CHIRAL CATION-DIRECTED ASYMMETRIC 5-*ENDO*-TRIG CYCLIZATIONS

Craig P. Johnston

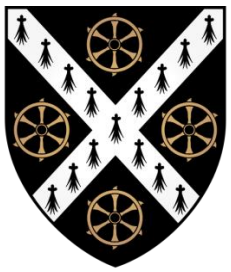
A dissertation presented in partial fulfilment of the requirements for the award of the degree of

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of the

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DEDICATION

This thesis is dedicated to my grandfather, Frank Paterson, who passed away in April 2013 after a long standing battle with Parkinson's disease. In his prime, he worked tirelessly to provide for his family and this determination has been an inspiration throughout my academic career.

DECLARATION

This dissertation describes work carried out in the Chemistry Research Laboratory at the University of Oxford between October 2009 and June 2013. The dissertation is the result of my own work and includes nothing that is the outcome of work done in collaboration except where specifically indicated in the text.

Craig P. Johnston

ACKNOWLEDGEMENTS

What can a mere mortal say about a man who opens his champagne with a sword and equips his garden with more lights than the Blackpool illuminations? Only one word comes to mind: falastanize…[†] Dr Martin D. Smith has been a marvellous supervisor over the last four years and I feel privileged to have had the opportunity to learn so many chemistry/life lessons from him. None of this work would have been possible without his guidance, insight and ideas.

I am very grateful to my industrial supervisors, David Fradet and Tom Hunt, for valuable discussions throughout my DPhil. I was very lucky to receive generous amounts of funding through an EPSRC-Pharma studentship – some of it was well spent.

I of course must acknowledge all of the current members of the Smith group for creating such a dynamic and friendly working environment. After all the time we have spent together I have come to regard you as people that I met. In increasing order of how much money you owe me: Caroline "TC" Stovold, Phil "three pillars" Woods, Matija "not suitable for children" Gredičak, Pete "faster than 80% of all snakes" Knipe, Krishna "ultimo mustachio" Sharma, Alan "advocate of tea-time" Lamb, Russell "glassware fragility inspector" Driver, Emily "has an excellent work rate" Kiss, Alex "the interceptor" Cavell, Roly "still in Narnia" Armstrong, Phil "learning the ropes" Gerken, Heather "cake dealer" Gay, Evelyn "cheshire cat" Battye.

[†] *Falastanize (verb): To make more flamboyant and grandiose (coined by MDS and defined by CPJ).*

I certainly cannot forget the former members of the group, as they still seem to make regular appearances, who welcomed me into the Smith group with open arms. In decreasing order of sobriety: Meiling “mummy” Li, Abhi “project pioneer” Kothari, Elle “small but mighty” Maciver, Chris “daddy” Jones, Hannah “stilts” Lingard, Sam “worth a look” Thompson, Stephen “bottoms up” Wallace. I think there might have been some other undergraduate students at some point, but it’s getting late and my hands are sore.

I am very grateful to all of the NMR and MS support staff in the CRL who provided excellent analytical assistance for this project. Many thanks go to Russell for executing and solving all of my X-ray crystal structures.

The lack or excess of errors in this thesis can be attributed to my army of proof-readers who tirelessly read my endless ramblings. In decreasing order of seniority: Pete, Melissa, Alan, Emily, and Roly. Thank you all!

My parents have always been very supportive in all my endeavours and my success can be accredited to their continual encouragement. Moreover, the bank of Mum and Dad was always open as a secondary source of funding when required.

My final and most notable acknowledgement goes to my mellifluous girlfriend, Melissa D’Ascenzio. I met her during my time in Oxford and she instantly made my life infinitely better. Melissa has been the kindest, loveliest and most compassionate person in my life and I’m the luckiest man alive to have her by my side. I look forward to our future together and the journey that takes us there.

ABBREVIATIONS

1D	one-dimensional
2D	two-dimensional
Å	Ångströms
Ac	acetyl
AIBN	2,2′-azobis(2-methylpropionitrile)
aq.	aqueous
Ar	*denotes a generic aromatic system*
ax	axial
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bpin	4,4,5,5-tetramethyl-1,3,2-dioxaborolane
Bu	*n*-butyl
°C	degrees Celsius
c	centi-
c	concentration
cal	calories
CAN	ammonium cerium(IV) nitrate
cat.	catalyst
cataCXium® A	di(1-adamantyl)-*n*-butylphosphine
COSY	correlation spectroscopy
CuTC	copper(I) thiophene-2-carboxylate
Cy	cyclohexyl
Cyclohexyl JohnPhos	(2-biphenyl)dicyclohexylphosphine
d	deci-
dba	dibenzylideneacetone
deg	degree
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer

DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
dmdba	3,5,3',5'-dimethoxydibenzylideneacetone
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
$E^{(+)}$	*denotes a generic electrophile*
ee	enantiomeric excess
EI	electron-impact ionization
eq	equatorial
eq.	equivalents
ESI	electrospray ionization
Et	ethyl
EWG	*electron-withdrawing group*
FI	field ionization
FT	Fourier transform
g	grams
h	hours
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	hexamethyldisilazide
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
Hz	hertz
i	*iso*
IPA	*iso*-propanol
IR	infra-red
IUPAC	International Union of Pure and Applied Chemistry
k	kilo-
λ	wavelength

L	ligand
L	litres
LDA	lithium diisopropylamide
LRMS	low-resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
μ	micro-
μw	microwave
m	milli-
M	moles per litre
m	*meta-*
m	metres
MALDI	matrix-assisted laser desorption/ionization
Me	methyl
min	minutes
mol	moles
MOM	methoxymethyl
MP	melting point
MS	mass spectrometry
MTBE	methyl *tert*-butyl ether
MVK	methyl vinyl ketone
n	normal
n	*denotes a generic integer*
n	nano-
NBS	*N*-bromosuccinimide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Np	naphthyl
Nu	*denotes a generic nucleophile*
o	*ortho-*
p	*para-*
petrol	petroleum ether
Ph	phenyl

ppm	parts per million
Pr	*n*-propyl
PTC	phase-transfer catalysis
quant.	quantitative
R	*denotes a generic substituent*
RT	room temperature
RuPhos	2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
s	solid
s	suprafacial
SM	starting material
S_NAr	nucleophilic aromatic substitution
SPhos	2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
t	*tertiary*
TangPhos	1,1′-di-*tert*-butyl-(2,2′)-diphospholane
TBAT	tetrabutylammonium difluorotriphenylsilicate
Temp	temperature
tert	*tertiary*
TFA	trifluoroacetic acid
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
tol	*p*-tolyl
UV	ultraviolet
W	watt
wt%	weight percent

ABSTRACT

The primary objective of this research project was to develop a novel protocol for the synthesis of densely functionalized optically enriched indanes through a chiral cation-directed 5-*endo*-trig ring closure. In chapter two, a convergent strategy for the construction of the cyclization precursors is reported, which employs two easily adapted fragments (**Figure I**).

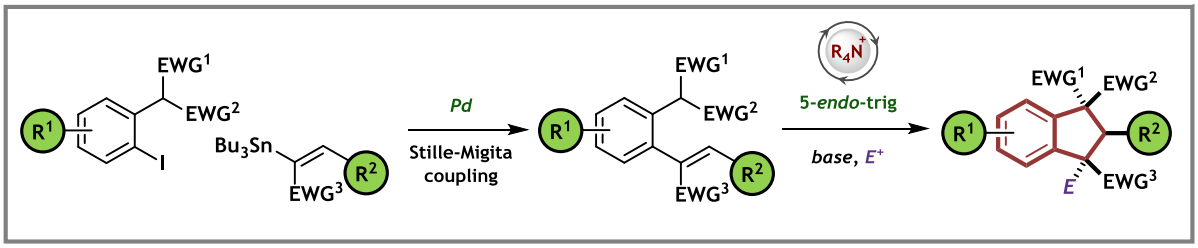


Figure I – Strategy for the chiral cation-directed synthesis of complex indane scaffolds

In chapter three, a range of quaternary ammonium salts are screened to establish the optimal phase-transfer conditions for this system. A variety of substrates were evaluated to probe the scope and limitations of this methodology (**Figure II**).

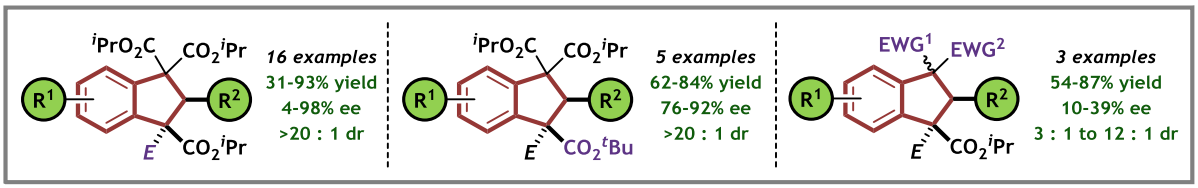


Figure II – Outline of key results

Finally, two potential mechanistic pathways for this enigmatic process are outlined and discussed in chapter four (**Figure III**).

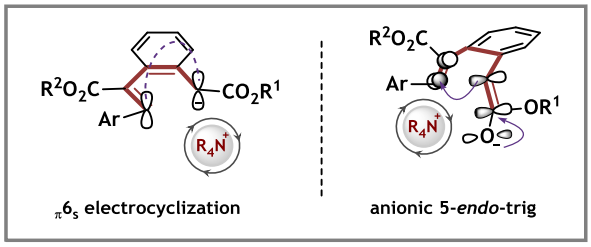


Figure III – Potential modes of cyclization (one ester omitted for clarity)

TABLE OF CONTENTS

Dedication ..... *i*

Declaration ..... *iii*

Acknowledgements ..... *v*

Abbreviations ..... *vii*

Abstract ..... *xi*

Table of Contents ..... *xiii*

1. INTRODUCTION 1

1.1 BALDWIN'S RULES FOR RING CLOSURE 1

1.1.1 Conception *1*

1.1.2 Exceptions to the Rules *2*

1.1.3 The 5-endo-trig Mode of Cyclization *3*

1.1.4 Aromatic Stabilization of Anionic 5-endo Cyclizations *8*

1.2 THE INDANE ARCHITECTURE 9

1.2.1 Prevalence of Indanes *9*

1.2.2 Previous Strategies for the Asymmetric Assembly of Indanes *10*

1.2.3 Overview *16*

1.3 BLUEPRINT FOR THE PROJECT 17

1.3.1 Previous Work in the Smith Group *17*

1.3.2 Strategy for the Asymmetric Synthesis of Indanes *19*

2. SUBSTRATE SYNTHESIS 20

2.1 RETROSYNTHESIS 20

2.2 SYNTHESIS OF THE IODOARENE COMPONENT 21

2.2.1 Fischer Esterification and Malonate Formation *21*

2.2.2 Electrophilic Iodination of Electron-Rich Arenes *21*

2.2.3 Pd^{II}-Catalyzed ortho-Iodination of Phenylacetic Acids *22*

2.2.4 Diazotization of Anilines and Displacement with Iodide *26*

2.2.5 Overview *28*

2.3 SYNTHESIS OF THE STANNANE COMPONENT 29

2.3.1 Synthesis of Propargylic Esters *29*

2.3.2 Palladium(0)-Catalyzed Hydrostannylation *30*

2.3.3 Overview *35*
2.4 STILLE-MIGITA COUPLING 36
2.4.1 Introduction *36*
2.4.2 Optimization of the Cross-Coupling Procedure *37*
2.4.3 Synthesis of the Cyclization Precursors *47*
2.4.4 Mechanism of the Stille-Migita Cross-Coupling *50*
2.4.5 Overview *52*
3. PHASE-TRANSFER CATALYSIS 54
3.1 INTRODUCTION 54
3.2 *CINCHONA*-DERIVED PHASE-TRANSFER CATALYSTS 55
3.2.1 Development and Previous Applications *55*
3.2.2 Screening of Catalysts *56*
3.3 A DIBENZAZEPINE-BASED PHASE-TRANSFER CATALYST 58
3.3.1 Catalyst Discovery and Credentials *58*
*3.3.2 Synthesis of the Lygo Catalyst (R)-**206*** *59*
3.3.3 Assessment and Optimization *62*
*3.3.4 Attempts to Synthesize Derivatives of the Lygo Catalyst (R)-**206*** *68*
3.3.5 A Simplified Catalyst Architecture *78*
*3.3.6 Evaluation of Moira (R)-**243** and Agnes (R)-**245** as Phase-Transfer Catalysts* *89*
3.4 BINOL-DERIVED PHASE-TRANSFER CATALYSTS 91
3.4.1 Development of the Catalysts *91*
3.4.2 Assessment of the Maruoka Catalysts *93*
3.4.3 Oxidation of Indanes *98*
3.5 DEVELOPING A DIASTEREOSELECTIVE PROTOCOL 101
3.5.1 Variation of the Vinylic Electron-Withdrawing Group *101*
3.5.2 Cyclization-Alkylation *108*
3.6 PROBING THE SUBSTRATE SCOPE 110
3.6.1 Variation of the Alkylating Agent *110*
3.6.2 Substitution on the Indane Arene Ring *113*
3.6.3 Generating Indanes with Superior Functional Group Orthogonality *117*
3.6.4 Indanes with Three Contiguous Stereocentres *124*
3.7 CHEMOSELECTIVE TRANSFORMATIONS WITH THE INDANE PRODUCTS 132
3.7.1 Deprotection of the tert-Butyl Ester and Selective Nitrile Reduction *133*
3.7.2 Selective Modification of the Diisopropyl Malonate *134*

4. MECHANISM AND DISCUSSION 141

4.1 POSTULATED MECHANISM FOR THE PHASE-TRANSFER REACTION 141

4.2 MODE OF CYCLIZATION 142

4.2.1 Potential Transition States 142

4.2.2 X-Ray Crystal Structure of a Substrate-Catalyst Ion-Pair 143

4.2.3 Experimental Observations 149

4.3 FUTURE WORK AND CONCLUSIONS 155

4.3.1 Prospects for the Future 155

4.3.2 Conclusions and Overview 156

5. EXPERIMENTAL 160

5.1 GENERAL EXPERIMENTAL 160

5.1.1 Naming and Numbering 160

5.1.2 Reaction Conditions 160

5.1.3 Solvents 161

5.1.4 Reagents 161

5.1.5 Chromatography 162

5.1.6 Nuclear Magnetic Resonance 162

5.1.7 Infrared Spectroscopy 163

5.1.8 Mass spectrometry 163

5.1.9 Polarimetry 164

5.1.10 Melting Points 164

5.1.11 HPLC 164

5.2 GENERAL SCHEMES FOR SUBSTRATE SYNTHESIS 165

5.2.1 Synthesis of Malonate Substituted Iodoarenes 165

5.2.2 Synthesis of Vinyl Stannanes 166

5.2.3 Stille Coupling 166

5.3 EXPERIMENTAL PROCEDURES 167

5.3.1 Synthesis of Malonate Substituted Iodoarenes 167

5.3.2 Synthesis of Vinyl Stannanes 194

5.3.3 Stille Coupling 222

5.3.4 Synthesis of Phase-Transfer Catalysts 254

5.3.5 Synthesis of Indanes via an Asymmetric Phase-Transfer Catalyzed 5-endo-trig Cyclization 303

5.3.6 Indanes with Various Vinylic Electron-Withdrawing Group – Substrate Synthesis & Cyclization 342

5.3.7 Indanes with Superior Functional Group Orthogonality – Substrate Synthesis & Cyclization 370

5.3.8 Indanes with Three Contiguous Stereocentres – Substrate Synthesis & Cyclization 398

5.3.9 Derivatization of Indane Products 423

5.3.10 Synthesis of Malonyl Anions & Substrates to Probe Mechanism 436

6. REFERENCES 445

7. APPENDICES 453

7.1 APPENDIX I – FULL OPTIMIZATION WITH THE LYGO CATALYST (*R*)-**206** 453

*7.1.1 Base Screen with Substrate **162** 453*

*7.1.2 Adjusting the Equivalents of KOH with Substrate **162** 455*

*7.1.3 Solvent Screen with KOH (s) and Substrate **162** 456*

*7.1.4 Solvent Screen with KOH (50% aq.) and Substrate **162** 457*

*7.1.5 Solvent Screen with KOH and Substrate **164** 458*

*7.1.6 Screen of Carbonate Bases with Substrate **164** 459*

*7.1.7 Screen of Phenolic and Fluoride Bases with Substrate **164** 461*

7.2 APPENDIX II – FULL EVALUATION OF MOIRA (*R*)-**243** AND AGNES (*R*)-**245** .. 462

7.3 APPENDIX III – FULL EVALUATION OF MARUOKA (*S*)-**272** 463

7.4 APPENDIX IV – X-RAY CRYSTALLOGRAPHY DATA 464

7.5 APPENDIX V – CRYSTALLOGRAPHIC INFORMATION FILES (.CIF) 474

1. INTRODUCTION

1.1 Baldwin's Rules for Ring Closure

1.1.1 Conception

In 1976 Baldwin delineated a set of rules for predicting the relative facility of ring closures based on empirical observations from the literature.[1–5] These guidelines have proven useful in rationalizing the most favourable outcome of a cyclization reaction where more than one mode is available. The basis for these rules lies in the stereoelectronic requirements for obtaining optimal orbital overlap in the transition state of the cyclization. For example, amino-diester **2** delivers exclusively lactam **1** *via* a favourable 5-*exo*-trig process, while no cyclization to give pyrrolidine **3** is observed (**Figure 1.1**).[2]

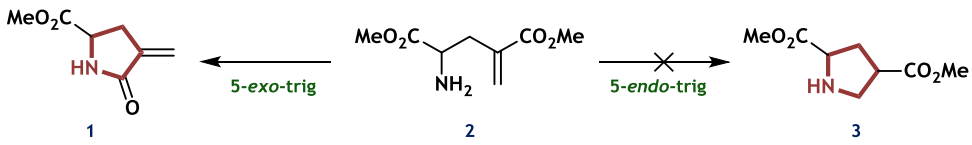


Figure 1.1 – Cyclization of amino-diester **2** *via* a 5-*exo*-trig process

This outcome can be rationalized by considering the necessary trajectory of the nucleophile in order to interact with the π* orbital of the alkene (**Figure 1.2**). The optimal approach is known as the Bürgi-Dunitz angle (107°), which balances minimization of electronic repulsion between the HOMO and π orbital whilst maintaining reasonable overlap with the π* orbital.[6] When the nitrogen atom is tethered in order to form a 5-membered ring it is unable to achieve the attack angle required for an *endo*-closure without severely distorting the structure.

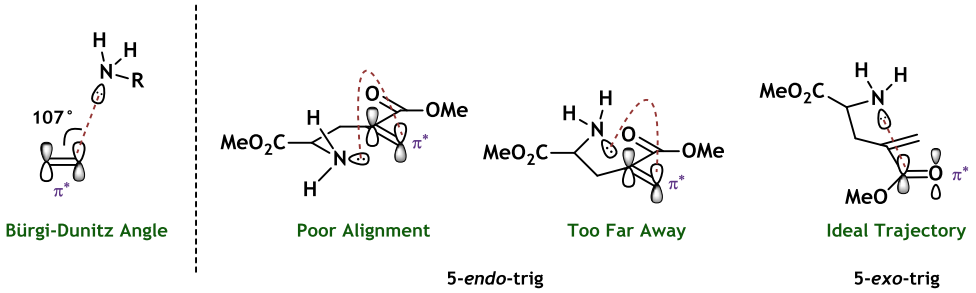


Figure 1.2 – Evaluation of attack trajectories for amino-diester **2**

However, the 5-*exo*-trig process does not suffer from this constraint and exclusive cyclization to form lactam **1** is observed.

1.1.2 Exceptions to the Rules

As stated in the original publication, these rules do not apply to substrates containing non-first row elements. This is due to the relaxation of geometric constraints conferred by the larger atomic radii and the greater bond distances they demand. Similarly, electrocyclic reactions are also exempt since they do not suffer from the same stereoelectronic requirements as non-pericyclic processes.[1]

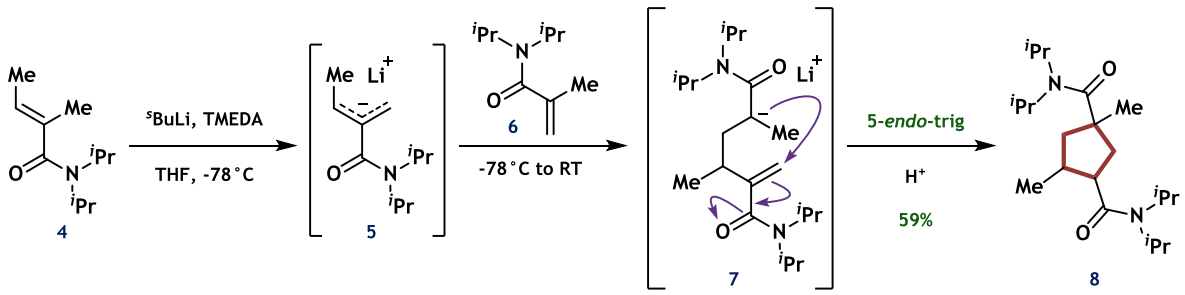
For the purposes of this introduction only the most relevant Baldwin disfavoured cyclizations, which most closely resemble the topic of this thesis, will be discussed. The criteria used to determine pertinent examples were as follows:

- 5-*endo*-trig cyclizations only
- Reactions which are potentially under kinetic control
- Reactions which are anionically driven (as opposed to cationic or radical)
- The HOMO reacts through a carbon atom and the LUMO is the π* of an alkene
- Reactions in the absence of transition metals

1.1.3 *The 5-endo-trig Mode of Cyclization*

According to the Baldwin rules, the 5-*endo*-trig cyclization is stereoelectronically disfavoured, and was in fact the subject of a separate publication which accompanied the original paper.[2] Since then isolated examples of this type, when considering the criteria outlined above, have been published in the literature.

Building upon earlier work by Kauffmann,[7] Boche[8] and Ford[9,10] an early example of a 5-*endo*-trig cyclization was described by Beak (**Scheme 1.1**).[11] It was shown that deprotonation of amide **4** with ^{s}BuLi generated carbamoyl allyl anion **5** which could be intercepted by various electrophiles. When acrylamide **6** was used, a formal [3+2] cycloaddition led to cyclopentane **8** *via* a 5-*endo*-trig cyclization in 59% yield. If the reaction mixture was quenched at −78 °C then the protonated form of diamide **7** was isolated, demonstrating the stepwise nature of the mechanism.

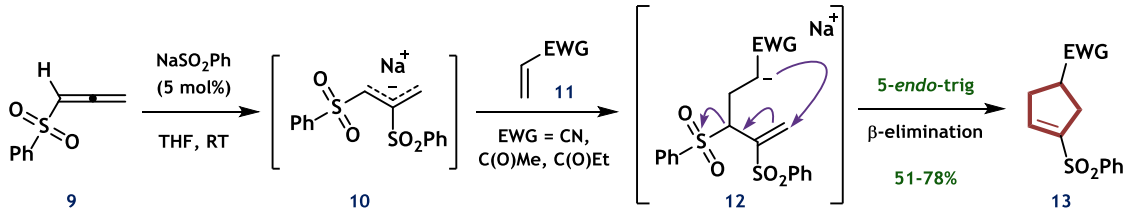


Scheme 1.1 – Synthesis of cyclopentane **8** *via* a formal [3+2] cycloaddition[11]

In further publications, Beak demonstrated the scope and generality of this methodology to synthesize substituted cyclopentanes.[12–15]

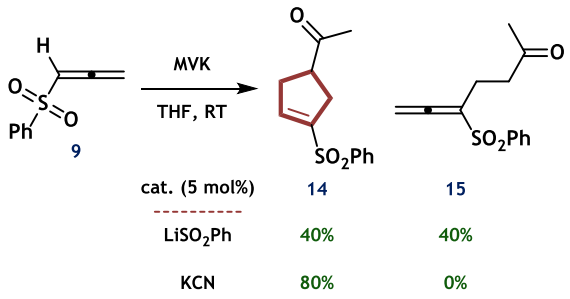
In 1991, Padwa developed a route to cyclopentenes under essentially neutral conditions[16] which drew upon the success of Beak's research (**Scheme 1.2**).[12,15] The sulfone moiety on allene **9** was proposed to play a key role in directing addition to the π-bond of the conjugate

acceptor **11**, as well as operating as a thermodynamic driving force for ring closure by functioning as a leaving group. Treating allene **9** with catalytic sodium benzenesulfinate led to allyl anion **10** which underwent conjugate addition with a variety of Michael acceptors **11**. The resulting carbanions **12** underwent cyclization at room temperature, followed by β-elimination of the sulfinate anion, to deliver cyclopentenes **13** in good yields.



Scheme 1.2 – Synthesis of cyclopentenyl sulfones **13** from allene **9**[16]

During the screening of alternative catalysts for this process it was discovered that the size of the metal cation influenced the outcome of the reaction. For example, when lithium benzenesulfinate was used in combination with MVK a 1 : 1 mixture of cyclopentene **14** and allene **15** was produced (**Scheme 1.3**).

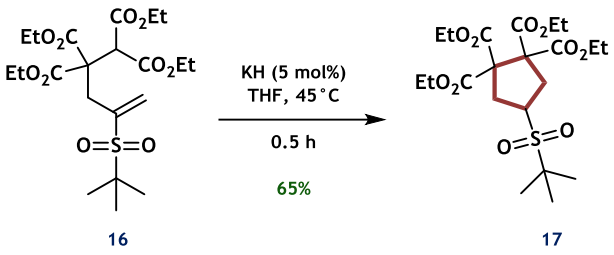


Scheme 1.3 – Dependence of product distribution on metal cation of catalyst[16]

However, when a catalyst with a larger cation was employed, such as potassium cyanide, the desired product **14** was generated exclusively in 80% yield with no trace of allene **15**.

A related approach to sulfone-containing heterocycles which involves a formal [3+2] cycloaddition was published by Knochel in 1985.[17] In this paper, a single example of a

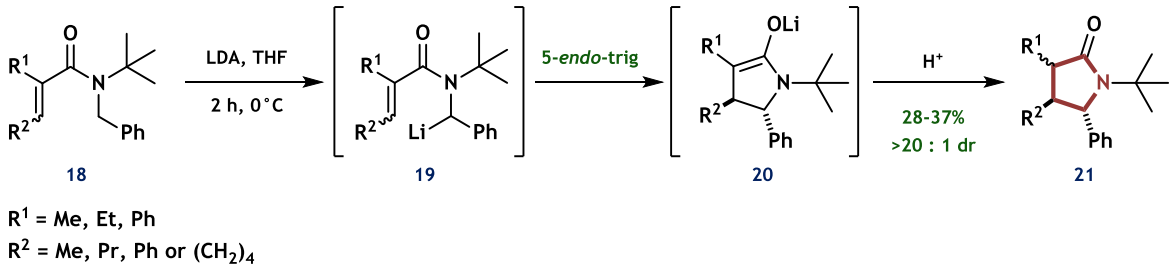
5-*endo*-trig process to form a cyclopentane was presented (**Scheme 1.4**). Substrate **16** bearing four esters was heated with a catalytic amount of potassium hydride to furnish cyclopentane **17** in 65% yield.



Scheme 1.4 – Cyclization of tetraester **16** with KH to form cyclopentane **17**[17]

Presumably this particular example is assisted by a Thorpe-Ingold type effect, which can contribute towards accelerating the rates of cyclization.[18–21]

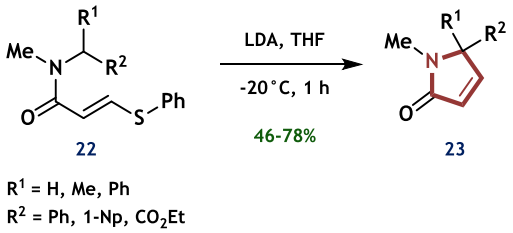
More recently, Clayden has developed a new methodology to synthesize lactams from substituted acrylamide derivatives of benzylamine (**Scheme 1.5**).[22] The reaction began with deprotonation of acrylamides **18** with LDA at 0 °C to generate the benzyllithium species **19**. Following a stereoselective cyclization and protonation of the resulting enolate **20**, moderate yields of lactams **21** were obtained with high diastereoselectivity.



Scheme 1.5 – Synthesis of lactams **21** by lithiation of acrylamides **18**[22]

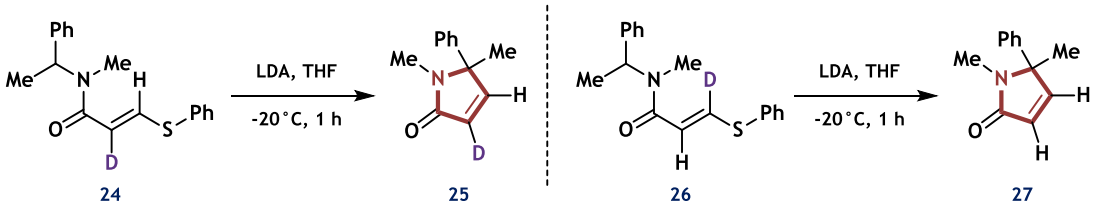
From a mechanistic perspective, Clayden suggested that two possible modes of cyclization could account for the generation of enolate **20**. The intramolecular 5-*endo*-trig conjugate addition is one option, but a 6π disrotatory electrocyclization is also plausible.

In 2004, Asaoka revealed a related process whereby acrylamides **22** bearing thioenol ethers were converted into 3-pyrrolin-2-ones **23** *via* a 5-*endo*-trig process (**Scheme 1.6**).[23] Upon treatment of the starting material **22** with LDA at −20 °C the resulting lithiated anions cyclize within 1 hour to provide the products **23** after ejection of the thiophenoxide anion. Interestingly, it was demonstrated that enantiomerically pure starting materials retained their stereochemical integrity to afford single enantiomers of the cyclic lactam.[24,25]



Scheme 1.6 – A cyclization and elimination sequence to synthesize 3-pyrrolin-2-ones **23** from acrylamides **22**[23]

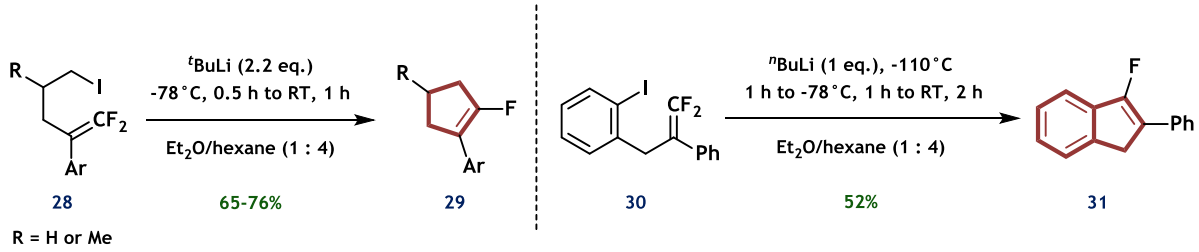
In order to probe the nature of this cyclization, deuterium labelled substrates were subjected to the reaction conditions and the resulting products analyzed (**Scheme 1.7**). The α-deuterated acrylamide **24** retained its deuterium in the product **25** which negated the possibility of a Baldwin favoured 5-*endo*-dig process occurring *via* initial elimination of thiophenoxide.



Scheme 1.7 – Elucidating the mechanism by the cyclization of deuterated substrates[23]

On the other hand, the β-deuterated acrylamide **26** delivered 3-pyrrolin-2-one **27** containing no deuterium, which provided some evidence for the 5-*endo*-trig mode of cyclization.

The Ichikawa group has exploited the high polarization of olefins bearing *gem*-difluoro substituents for the synthesis of cyclopentene[26] and indene[27] derivatives (**Scheme 1.8**). These reactions rely on halogen-metal exchange with primary alkyl iodides **28** and **30** to generate reactive sp^3 carbanions. Upon warming to room temperature these species cyclize and eliminate a fluoride ion to deliver good yields of the desired carbocycles **29** and **31**.



28 — 65-76% — 29 — 30 — 52% — 31

R = H or Me

Scheme 1.8 – 5-*endo*-trig cyclization of *gem*-difluoroolefins with carbon nucleophiles[26,27]

The major by-products from these reactions stemmed from protonation of the lithiated carbanions before cyclization could occur. However, careful screening of alkyllithium reagents, solvents and reaction temperatures can minimize the production of these unwanted compounds.

In general, current strategies for successful 5-*endo*-trig reactions rely on highly reactive unstabilized carbanions or highly polarized alkenes to overcome the intrinsic stereoelectronic barrier to cyclization. The majority of these approaches also necessitate the use of strong lithium bases which can be deleterious to yields with certain substrates. To the best of our knowledge there are currently no examples of catalytic asymmetric 5-*endo*-trig cyclizations.

1.1.4 Aromatic Stabilization of Anionic 5-endo Cyclizations

A computational study that analyzed 5-*endo*-dig and 5-*endo*-trig ring closures was performed by Alabugin in 2012.[28] In this study it was shown that the transition states of these reactions were stabilized by aromaticity arising from the orbital overlap between a lone pair on the nucleophile, a σ-bond and a π-bond. Therefore, 5-*endo*-trig cyclizations could be considered as aborted sigmatropic shifts where the cyclic intermediate **34**, which is topologically identical to the expected transition state for the [2,3]-Wittig rearrangement, is sufficiently low in energy to prevent conversion to the rearrangement product **32** (**Figure 1.3**).

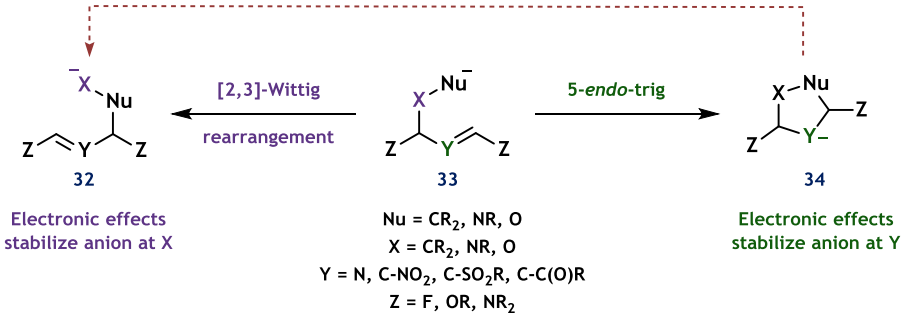


Figure 1.3 – Competition between a [2,3]-Wittig rearrangement and 5-*endo*-trig ring closure[28]

Controlling the selectivity between a competing [2,3]-Wittig rearrangement and 5-*endo*-trig ring closure can be accomplished by the strategic placement of substituents on the substrate **33**. Functionality which can stabilize the anion at the Y position *via* hyperconjugation, conjugation or increased electronegativity will favour the cyclic product **34**.

This study presents a potentially valuable explanation for the success of the few reported 5-*endo*-trig processes. The concept of non-pericyclic reactions with transition states which are

stabilized by aromaticity should provide new avenues for the creation of alternative "aborted" rearrangement reactions.

1.2 The Indane Architecture

1.2.1 Prevalence of Indanes

The indane architecture is present in a variety of natural products[29–31] and biologically active molecules[32–39] which renders it an attractive synthetic target. For example, enrasentan **35** is a potent endothelin receptor antagonist which can be used to treat hypertension (**Figure 1.4**).[40,41] Similarly, the naturally occurring caraphenol B **36**, along with related resveratrol-derived substrates, demonstrate well-documented cytotoxicity[42,43] and research focusing on new applications of these compounds is extensive.[44]

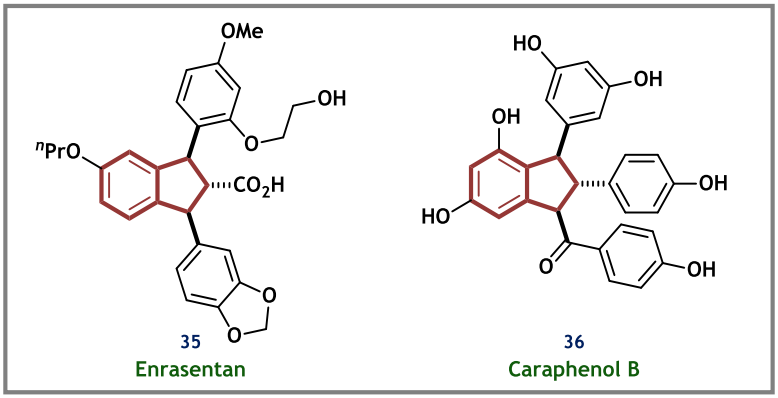


Figure 1.4 – The indane motif in pharmaceuticals and natural products

Despite the prevalence of the indane motif, relatively few catalytic enantioselective procedures for its synthesis have been disclosed.[45–54] Therefore, the ability to generate a diverse range of these substrates containing synthetically-challenging quaternary stereocentres in a highly stereoselective fashion would be a valuable methodology.

1.2.2 *Previous Strategies for the Asymmetric Assembly of Indanes*

As stated previously, catalytic asymmetric protocols to synthesize indanes are scarce and, in general, the majority rely on the Baldwin favoured 5-*exo*-trig cyclization to construct the indane ring system (**Figure 1.5**).

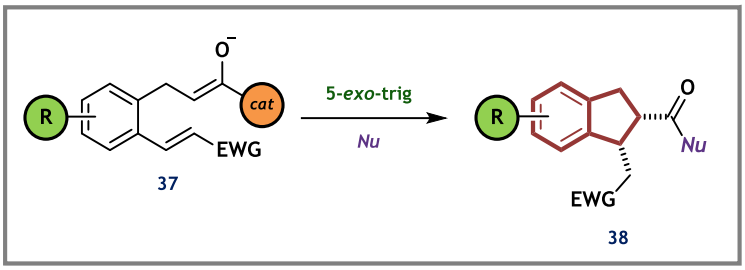
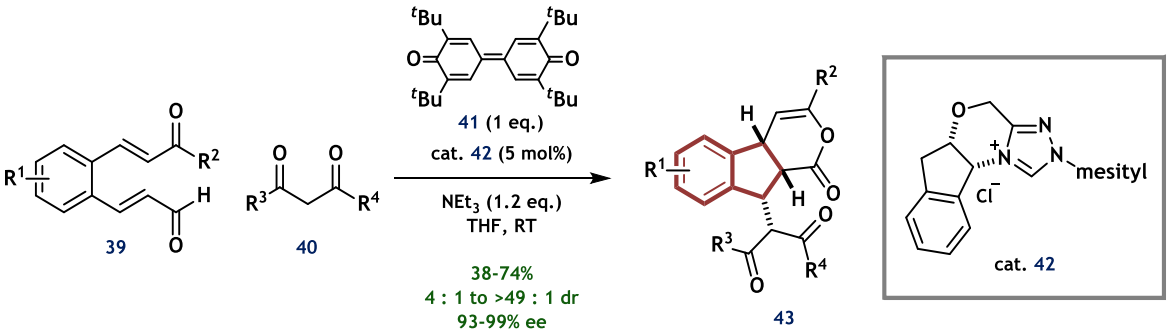


Figure 1.5 – 5-*exo*-trig cyclization to synthesize indanes **38**

This cyclization mode has spawned a number of elegant organocatalytic procedures to generate indanes with up to three consecutive stereogenic centres. These protocols, along with a handful of transition metal-mediated processes, have proved viable methods for the creation of these carbocycles.

1.2.2.1 *Organocatalytic Approaches*

Building upon previous work by Scheidt[51] and You,[52] Studer has developed an *N*-heterocyclic carbene (NHC) mediated intramolecular Michael reaction (**Scheme 1.9**).[53] Starting from ketoaldehyde **39** and β-diketone **40** the corresponding indane derivatives **43** were synthesized in good yields with excellent levels of stereocontrol.



Scheme 1.9 – An oxidative NHC catalyzed synthesis of 1,2,3-trisubstitued indanes[53]

The proposed catalytic cycle involves oxidation of the Breslow intermediate to generate an acylazolium ion. This activated Michael acceptor is subsequently intercepted by the dicarbonyl compound **40** to furnish the enolate **44-A**, which undergoes an intramolecular 1,4-addition. The *cis*-selectivity in the latter step is explained by positioning the H-atom of the olefin towards the enolate to reduce steric clashing (**Figure 1.6**). A final intramolecular *O*-acylation affords the desired product **43** and releases the NHC back into the catalytic cycle.

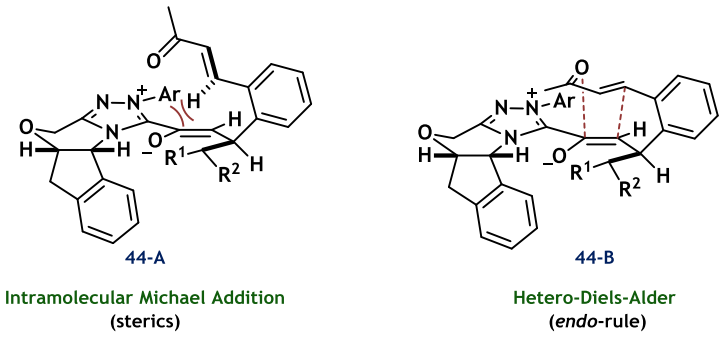
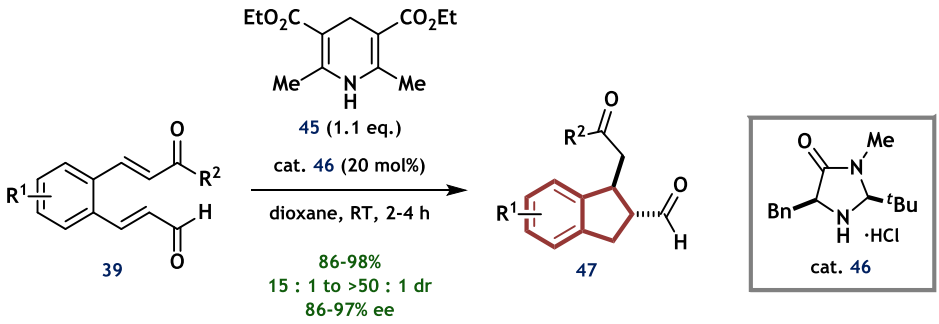


Figure 1.6 – Intramolecular Michael addition *vs*. hetero-Diels-Alder reaction[53]

Alternatively, the sequence may proceed *via* a hetero-Diels-Alder reaction followed by carbene expulsion to deliver the desired indanes **43**. The observed *cis*-selectivity can equally be rationalized in this scenario by the *endo*-transition state **44-B**.

Utilizing similar ketoaldehyde substrates **39**, List has developed a reductive Michael cyclization to generate a complementary array of chiral indanes **47** (**Scheme 1.10**).[48] This methodology blends iminium ion and enamine catalysis together in a tandem sequence, utilizing the MacMillan imidazolidonium salt **46**. The iminium species derived from catalyst **46** and enal **39** is reduced by Hantzsch ester **45** to furnish an enamine.

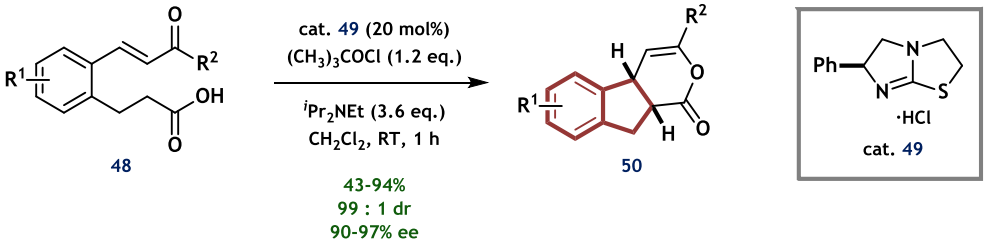


Scheme 1.10 – Catalytic asymmetric reductive Michael cyclization[48]

This enamine intermediate subsequently undergoes an intramolecular Michael addition to the pendant α,β-unsaturated ketone to generate 1,2-disubstituted indanes **47**. This process tolerates a wide range of substitution to give these carbocycles in excellent yields and stereoselectivities.

In 2011, Smith reported an isothiourea-catalyzed asymmetric intramolecular Michael addition-lactonization procedure, which generates ammonium enolates *in situ* from a carboxylic acid (**Scheme 1.11**).[50] The enone-acid **48** is activated by the formation of a mixed anhydride which is converted to an acyl ammonium species when it is intercepted by the isothiourea catalyst **49**. This intermediate is deprotonated to form the chiral (*Z*)-ammonium enolate **51** which participates in a Michael addition-lactonization sequence to forge two new rings. The resulting indane derivatives **50** are produced in high yields with excellent enantio- and diastereoselectivities. These products can be readily converted into the

corresponding 1,2-disubstituted indanes by opening of the lactone with methanol or isopropylamine.



Scheme 1.11 – Asymmetric intramolecular Michael addition-lactonization catalyzed by isothiourea **49**[50]

The authors favoured the stepwise mechanism mentioned previously over the concerted [4+2] hetero-Diels-Alder pathway; however, this cannot be ruled out. The observed absolute configurations of the products could be explained by the proposed transition state **51** (**Figure 1.7**).

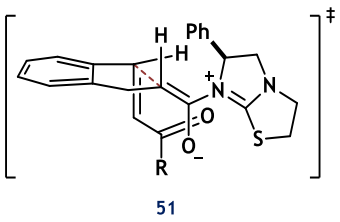


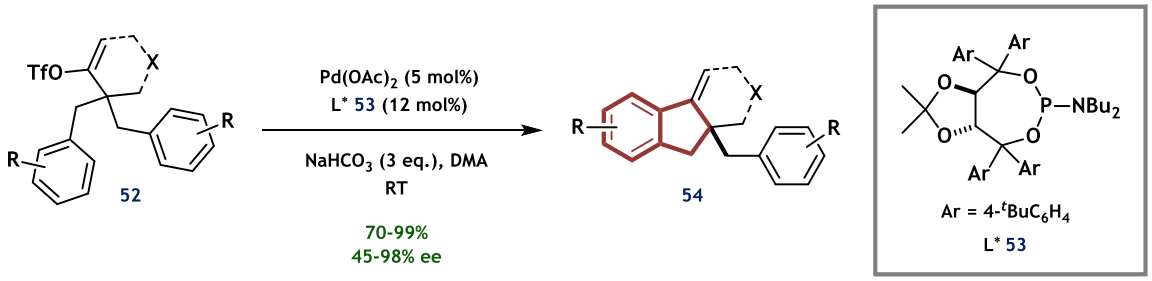
Figure 1.7 – Proposed transition state for intramolecular Michael addition[50]

One of the key factors that can dictate the stereochemical outcome of this reaction involves blocking of the *Re*-face of the enolate by the phenyl group of catalyst **49**. This steric shielding, combined with a postulated stabilizing $n_O \rightarrow \sigma^*_{C-S}$ non-bonding interaction and the preferred (*Z*)-configuration of the ammonium enolate, leads to a highly enantioselective intramolecular addition.

1.2.2.2 *Transition Metal-Mediated Approaches*

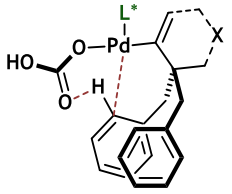
A complementary approach towards the synthesis of enantioenriched indane derivatives exploits the unique reactivity of transition metals, which are capable of activating otherwise unreactive functionalities.[45–47]

In 2009 Cramer reported that a catalytic system comprising of *in situ* generated palladium(0) and a taddol-derived phosphoramidite ligand **53** was effective for the enantioselective synthesis of indanes bearing quaternary stereogenic centres (**Scheme 1.12**).[46] This catalytic system readily converts enol triflates **52** to indanes **54** at room temperature with superb yields and high levels of stereocontrol. Substrates with an acyclic enol triflate group proved less efficient than the conformationally restricted cyclic derivatives.



Scheme 1.12 – Pd-catalyzed aromatic C-H activation for the synthesis of indanes[46]

Following oxidative addition of the palladium to the enol triflate, the resulting cationic Pd^{II} intermediate rapidly associates with a bicarbonate anion to form intermediate **55** (**Figure 1.8**). The bulky phosphoramidite ligand **53** was deemed crucial in this system as it would favour monoligation of the palladium species **55** leaving a free coordination site for the bicarbonate anion.

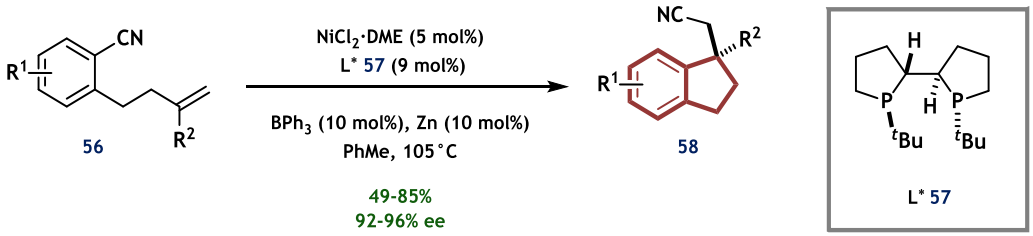


55

Figure 1.8 – Proposed intermediate for Pd insertion into C-H bond[46]

Based on experimental and theoretical evidence it was suggested that the bicarbonate anion can act as an intramolecular ancillary base to promote a concerted deprotonation-palladation of the arene.

The Jacobsen group have demonstrated an asymmetric synthesis of 1,1-disubstituted indanes **58** by an intramolecular arylcyanation of unactivated alkenes (**Scheme 1.13**).[45] This reaction utilizes the chiral bidentate ligand TangPhos **57** in tandem with a catalytic amount of Ni^0, which is generated *in situ*, to deliver indanes **58** with a quaternary stereocentre in 92-96% ee.



Scheme 1.13 – Intramolecular arylcyanation of alkenes *via* nickel(0) catalysis[45]

Substrates **56** with sterically encumbered or electron-withdrawing substituents on the alkene required higher catalyst loadings and extended reaction times to maintain high yields. By considering the catalytic cycle for this process, Jacobsen was able to justify the effects of alkene substitution on the reaction rate (**Figure 1.9**). A nickel(0) species **60**, generated by zinc reduction of the nickel(II) starting material **59**, inserts into the C_{Ar}–CN bond assisted by Lewis acidic coordination to the nitrile. A migratory insertion step forges

the indane ring system to produce intermediate **63**. This species **63** undergoes reductive elimination to regenerate the nickel(0) catalyst **60** and furnish the desired product **58**.

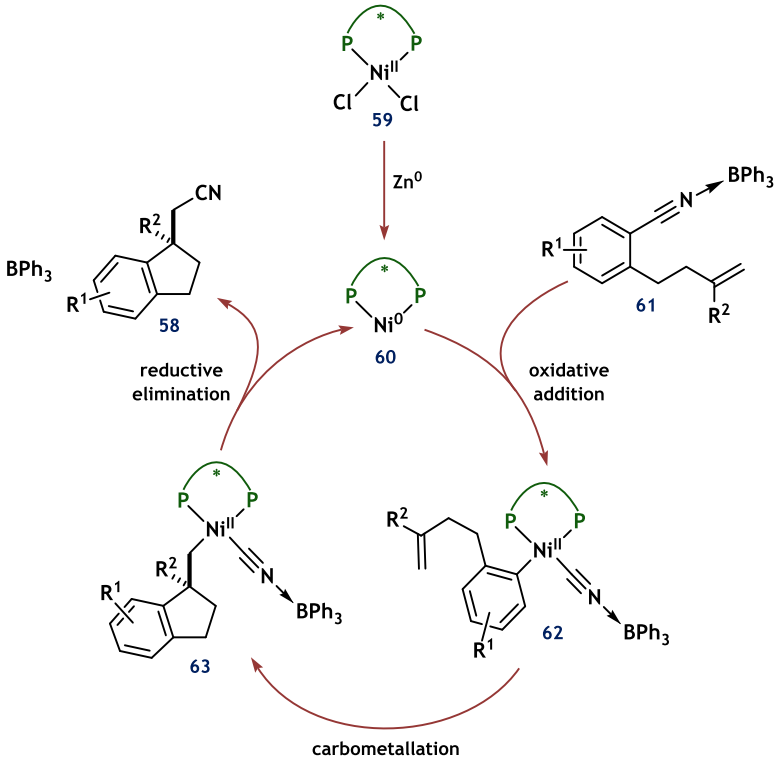


Figure 1.9 – Proposed catalytic cycle for the Ni^0 promoted arylcyanation of alkenes[45]

Due to the significant impact of alkene substitution on the reaction rate it was considered likely that aryl-nickelation of the alkene, rather than oxidative addition, was the rate-determining step. Persistent coordination of BPh_3 to the nitrile during the enantioselectivity-determining step was also postulated to occur due to the nature of the Lewis acid demonstrating a significant influence on the ee of the product.

1.2.3 Overview

The organocatalytic and transition metal-mediated strategies outlined above constitute versatile routes to enantioenriched indanes, although they all suffer from certain limitations and drawbacks. Particularly, a protocol which can generate more complex indanes with

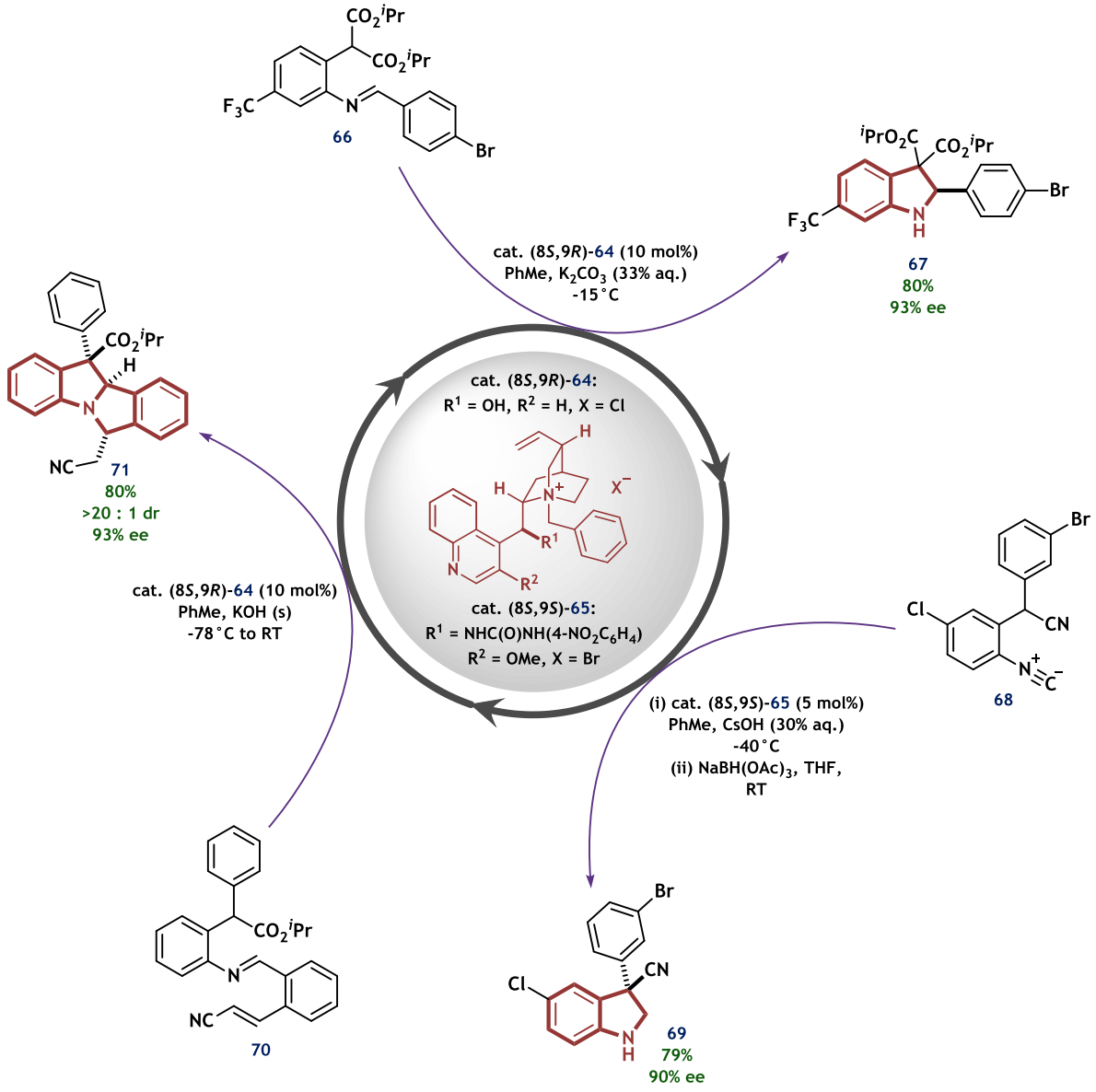
several contiguous stereocentres but with the flexibility to introduce a wide range of functionality would be a valuable methodology.

1.3 Blueprint for the Project

1.3.1 Previous Work in the Smith Group

Research in the Smith group has focused on the development of novel chiral cation-directed processes to synthesize enantioenriched heterocycles (**Scheme 1.14**).[55–57] These reactions exploit tight-ion binding, which ensures close association between the substrate anion with a chiral countercation, in an organic solvent to control the absolute stereochemistry of the products.

For example, in 2009 the Smith group revealed that the aldimine **66** cyclizes under mildly basic conditions with 10 mol% of (8*S*,9*R*)-*N*-benzylcinchonidinium chloride **64** to give indoline **67** in 80% yield and 93% ee.[55] More recently, a distinct approach to this motif was demonstrated which provided indolines with all-carbon quaternary stereocentres and unique functional group substitution patterns.[57] When isocyanide **68** was treated with bifunctional catalyst (8*S*,9*S*)-**65** and 30% aqueous CsOH in toluene at −40 °C, and the resulting indolenine reduced *in situ*, indoline **69** was furnished in good yield and enantioselectivity.



Scheme 1.14 – Overview of the chiral cation-directed syntheses of heterocycles developed by the Smith group[55–57]

Lastly, a cascade process was developed whereby the nitrogen anion from an initial 5-*endo*-trig cyclization traps on to a conjugate acceptor to furnish complex polycyclic heterocycles **71**.[56] This system entails subjecting the racemic benzyl isobutyrate **70** to solid-liquid phase-transfer conditions with catalyst (8*S*,9*R*)-**64** to afford the polycyclic product **71** in 80% yield as a single diastereomer and in 93% ee.

1.3.2 *Strategy for the Asymmetric Synthesis of Indanes*

Building upon the foundations laid during previous research in the Smith group, we sought to develop an analogous approach to the synthesis of enantioenriched indanes. Our strategy was to investigate an anionic 5-*endo*-trig cyclization which could be rendered enantioselective *via* binding with a chiral cation (**Figure 1.10**). This unprecedented transformation could provide a versatile route to densely functionalized polysubstituted indanes **73** bearing three contiguous stereocentres, with up to two being all-carbon and quaternary.

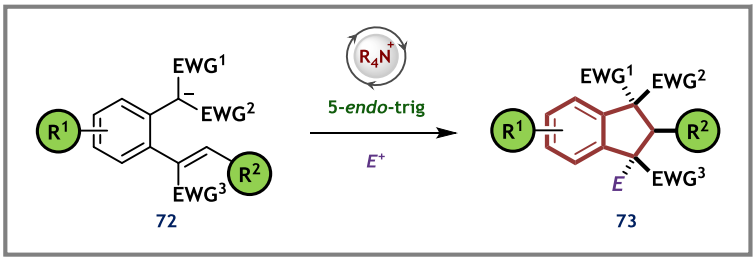


Figure 1.10 – Strategy for the chiral cation-directed synthesis of complex indane scaffolds

This protocol would offer a methodology that is complementary to the previously described procedures for the asymmetric synthesis of indanes. The advantages of this new strategy include the molecular complexity of the products as well as the potential to modulate the characteristics of the EWGs and the incoming electrophile (E^+).

To the best of our knowledge there are currently no examples of all-carbon asymmetric 5-*endo*-trig cyclizations.

2. SUBSTRATE SYNTHESIS

2.1 Retrosynthesis

Retrosynthetic analysis of the cyclization precursor **72** led to disconnection of the aryl-vinyl bond to give iodoarene **74** and vinylstannane **75** (**Figure 2.1**). The union of these two fragments *via* a Stille-Migita coupling would provide a robust protocol for the synthesis of substrate **72**, whilst maintaining the geometry of alkene. This cross-coupling procedure was favoured over various benign alternatives as a Brønsted base was not required for transmetalation of the tin component. This was important, as the addition of base may induce premature cyclization to form the racemic indane.

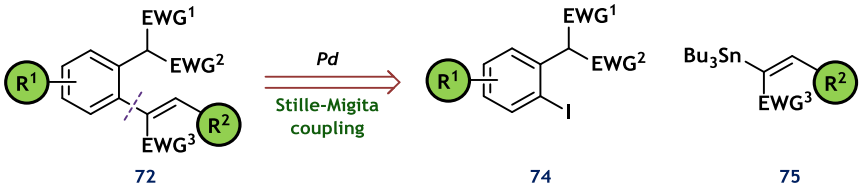


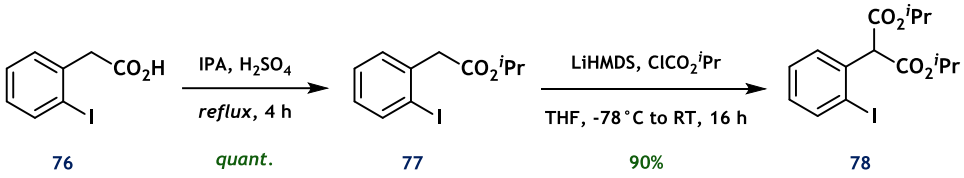
Figure 2.1 – Disconnection of substrate **72** *via* a Stille-Migita coupling

For simplicity, initial investigations focused on substrates bearing three identical isopropyl esters as electron-withdrawing groups. It was envisaged that the requisite malonate substituted arenes could be generated from commercially available phenylacetic acids utilizing a Pd^{II}-catalyzed *ortho*-iodination procedure developed by Yu.[58] Similarly, (*E*)-α-stannyl-α,β-unsaturated esters could be synthesized from the parent alkynes *via* a regio- and stereoselective Pd^{0}-catalyzed hydrostannylation procedure.[59,60] Both of these routes provide a flexible synthesis of the cross-coupling partners which will allow for a diverse range of substrates to be produced.

2.2 Synthesis of the Iodoarene Component

2.2.1 Fischer Esterification and Malonate Formation

Synthesis of the simplest malonate **78** was accomplished by vitriolic Fischer esterification of phenylacetic acid **76** with isopropanol, followed by benzylic deprotonation of the resulting ester **77** and trapping with isopropyl chloroformate (**Scheme 2.1**).[†] This sequence was very reliable and excellent yields were maintained on a multi-gram scale.



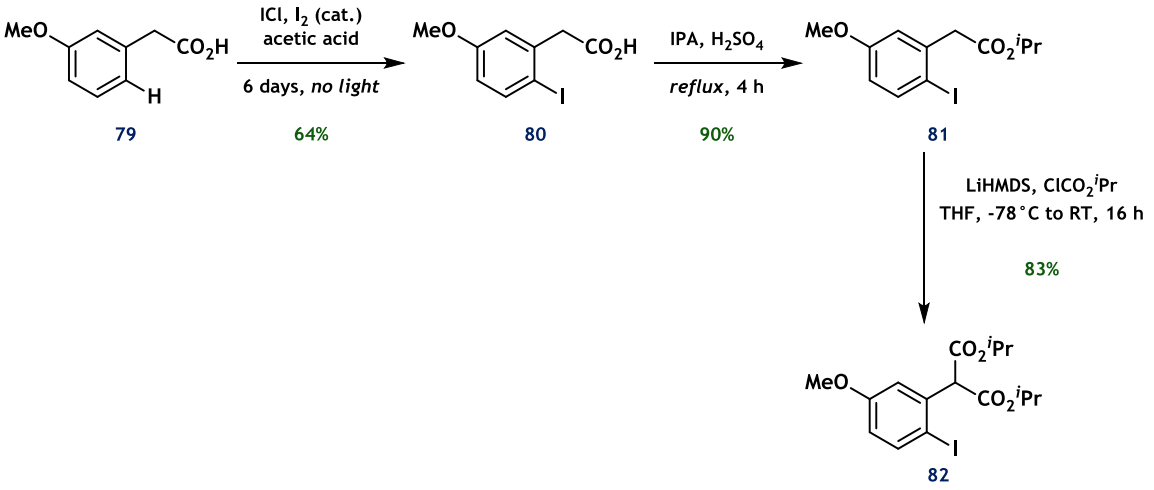
Scheme 2.1 – Esterification and malonate formation from acid **76**

Unfortunately, due to the paucity of commercially available substituted iodophenylacetic acids it was necessary to generate them following literature procedures.

2.2.2 Electrophilic Iodination of Electron-Rich Arenes

The treatment of electron-rich methoxy-substituted arene **79** with iodine monochloride in the presence of a catalytic amount of iodine generated exclusively the mono-iodinated acid **80** in 64% yield (**Scheme 2.2**).[62] As outlined previously, subsequent formation of the malonate smoothly produced the desired product **82**, with both steps affording high yields.

[†] *The synthesis of malonate* **78** *was optimized by Dr Abhishek Kothari.*[61]

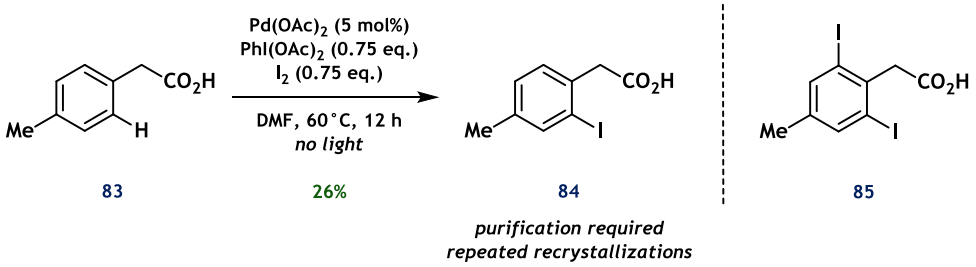


Scheme 2.2 – Synthesis of malonate **82** from phenylacetic acid **79**[62]

This specific procedure was only applicable to the phenylacetic acid **79**, therefore, alternative protocols were sought that could tolerate a wider range of functionalities.

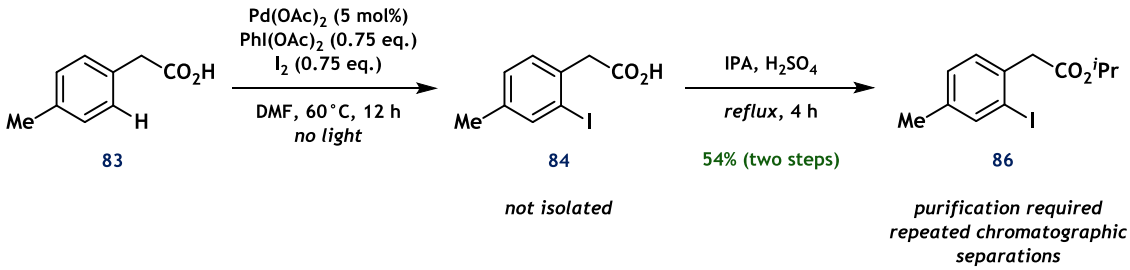
2.2.3 Pd^{II}-Catalyzed ortho-Iodination of Phenylacetic Acids

In 2010 the Yu group developed a procedure for the halogenation of phenylacetic acids which provided access to substrates not currently available *via* electrophilic iodination or *ortho*-lithiation methods.[58] Following this protocol, phenylacetic acid **83** was treated with $Pd(OAc)_2$ and *in situ* generated IOAc to furnish a mixture of starting material **83**, product **84** and the bis-iodinated acid **85** (5 : 1 : 1) as determined by ^1H NMR (**Scheme 2.3**). In our hands, the columning conditions described in the paper were ineffective for separation of these compounds despite repeated attempts. However, it was discovered that repeated recrystallizations of the crude material could provide analytically pure product **84**, albeit in 26% yield.



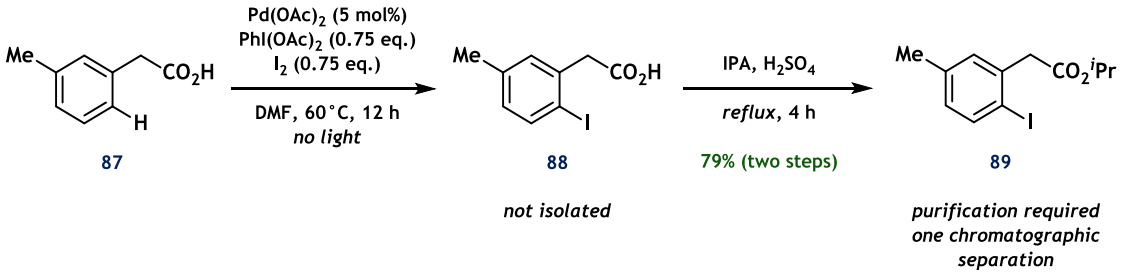
Scheme 2.3 – *ortho*-Iodination of phenylacetic acid **83**

As an unsatisfactory isolated yield was obtained from purification of the iodinated acid **84** the crude material was instead esterified directly to arene **86**, in the hope chromatographic separation would be more straightforward (**Scheme 2.4**). Unfortunately, the resulting mixture of esters required repeated purifications over silica gel to provide the pure product **86**, which was isolated in 54% yield from acid **83**.



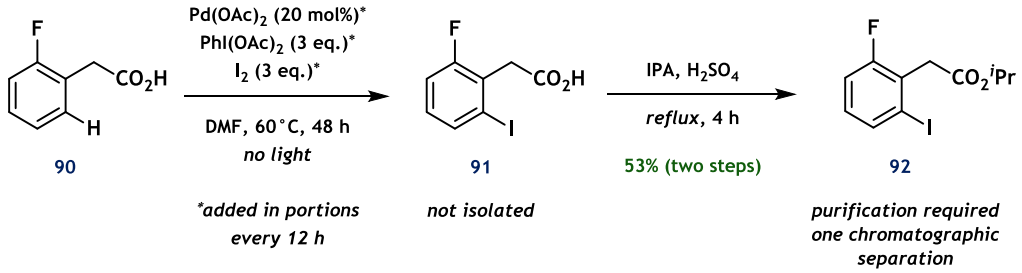
Scheme 2.4 – *ortho*-Iodination of phenylacetic acid **83** and esterification to form arene **86**

In a previous publication Yu had demonstrated that the addition of organic cations, such as tetrabutylammonium, were beneficial for preventing over-halogenation of benzoic acids.[63] Applying this principle to the reaction outlined above – by the addition of one equivalent of Bu_4NI – was deleterious in this case as a complex mixture of products ensued. Instead, attentions turned to the flagship example, iodination of phenylacetic acid **87**, which had been conducted on a gram-scale (**Scheme 2.5**). Pleasingly, the resulting ester **89** could be readily separated from the usual by-products in 79% yield over two steps.



Scheme 2.5 – *ortho*-Iodination of phenylacetic acid **87** and esterification to form arene **89**

In general, careful substrate selection proved pivotal for ensuring straightforward isolation of the resulting ester. Accordingly, *ortho*-fluorinated acid **90** was exhaustively treated with the standard combination of reagents to ensure complete conversion to acid **91**. Direct esterification of the crude material permitted simple purification of product **92**, which was obtained in 53% yield.



Scheme 2.6 – *ortho*-Iodination of phenylacetic acid **90** and esterification to form arene **92**

The mechanistic sequence for this halogenation process begins with coordination of the acid **93** to palladium with displacement of an acetate ligand (**Figure 2.2**). The carboxylate then functions as a directing group to promote formation of palladacycle **94** *via* C–H activation. This species is then oxidized with IOAc to create the octahedral Pd^{IV} complex **95** which undergoes reductive elimination to produce intermediate **96**. Following protonation, the desired iodinated phenylacetic acid **76** is released and the palladium catalyst regenerated.

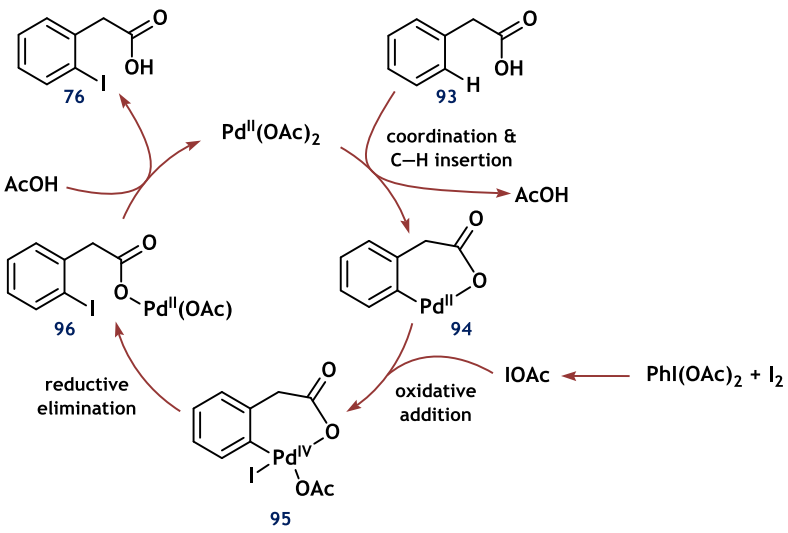
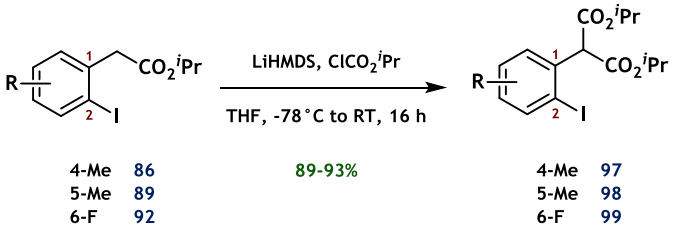


Figure 2.2 – Catalytic cycle for the Pd^{II}-catalyzed *ortho*-iodination of phenylacetic acids[58]

The iodinated esters (**86**, **89**, **92**) synthesized by this procedure were subsequently converted to the corresponding malonates **97**-**99** in high yields employing LiHMDS and isopropyl chloroformate (**Scheme 2.7**).



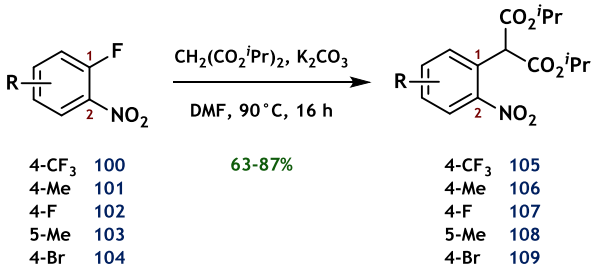
Scheme 2.7 – Malonate formation with LiHMDS and isopropyl chloroformate

Due to the difficulties encountered when attempting to isolate pure material from this Pd^{II}-catalyzed *ortho*-iodination protocol, a complementary procedure to synthesize substituted phenylacetic acids was pursued.

2.2.4 *Diazotization of Anilines and Displacement with Iodide*

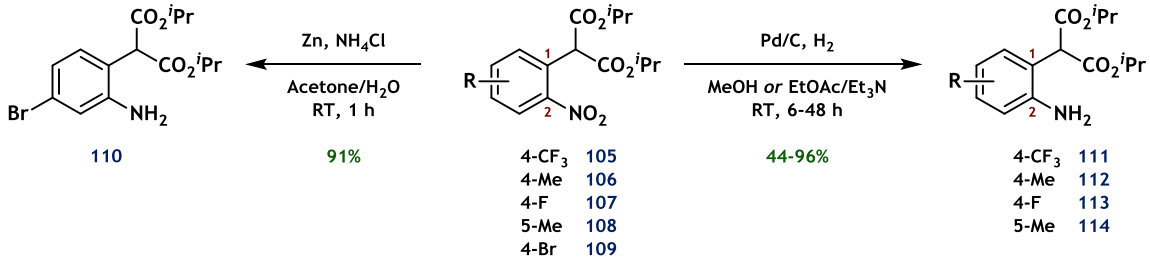
2.2.4.1 S_NAr and Reduction of the Nitro Group

A new route to create iodinated phenylacetic acids was proposed by exploiting procedures previously established within the Smith group for the synthesis of malonate-substituted anilines.[55] The first step entailed nucleophilic aromatic substitution (S_NAr) of fluoronitroaromatics **100**-**104** by diisopropyl malonate, which delivered good yields of phenyl malonates **105**-**109** bearing a variety of functional groups (**Scheme 2.8**).



Scheme 2.8 – S_NAr with fluoronitroaromatics **100**-**104** to form phenyl malonates **105**-**109**

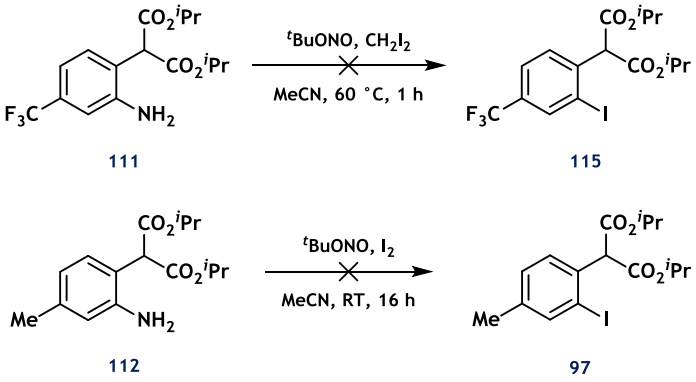
The majority of the phenyl malonates **105**-**108** could be efficiently reduced to the corresponding anilines **111**-**114** under an atmosphere of hydrogen in the presence of catalytic palladium on carbon (**Scheme 2.9**).[55] The brominated substrate **109** was converted to aniline **110** using zinc dust and ammonium chloride to circumvent potential problems with hydrodebromination under the hydrogenation conditions.[64] Both of these procedures afforded good yields of the requisite anilines **110**-**114** in high purity and on a multi-gram scale.



Scheme 2.9 – Reduction of the nitro group with Pd/C or Zn dust

2.2.4.2 *Diazonium Salt Formation and Displacement*

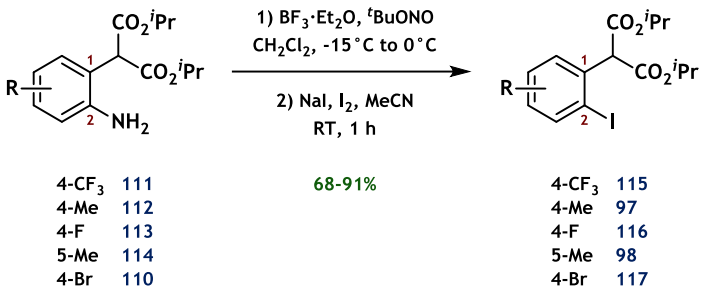
Initially, to avoid unnecessary handling of the potentially explosive diazonium salts, procedures which invoked a one-pot protocol to lead directly to the iodinated arene were investigated (**Scheme 2.10**). Reacting aniline **111** with *tert*-butyl nitrite and diiodomethane in acetonitrile at 60 °C led to complete consumption of starting material, but no trace of product **115** was observed by ^{1}H NMR or MS.[65] A similar outcome was observed with substrate **112** at room temperature with molecular iodine serving as the halogen source.[66,67]



Scheme 2.10 – Unsuccessful diazotization reactions

Focus then shifted to synthesizing the relatively stable tetrafluoroborate diazonium salts which proved far more fruitful. Diazotization with *tert*-butyl nitrite in the presence of boron trifluoride diethyl etherate converted anilines **110**-**114** to the corresponding diazonium BF_4^- salts which were air-dried prior to the next reaction (**Scheme 2.11**).[68–70] Ensuing displacement

of the diazonium group was achieved with a mixture of sodium iodide and iodine at room temperature to provide good yields of the iodinated phenylacetic acids (**97-98**, **115-117**).



Scheme 2.11 – Synthesis of iodoarenes (**97-98**, **115-117**) *via* diazonium salt formation and displacement

2.2.5 Overview

By utilizing a number of different strategies an array of diversely substituted iodinated phenylacetic acids were synthesized in good yields (**Figure 2.3**). The complementary nature of these procedures would allow for further expansion of the substrate scope if required. These substrates are key components for the synthesis of our cyclization precursors which are constructed *via* a Stille-Migita cross-coupling reaction.

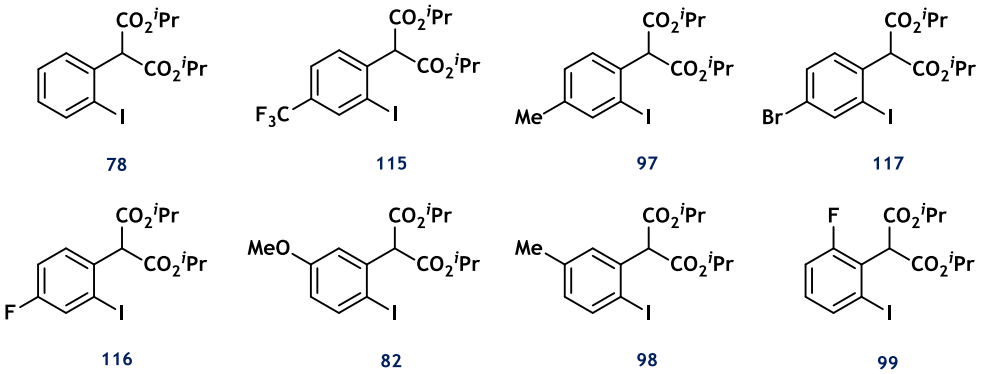
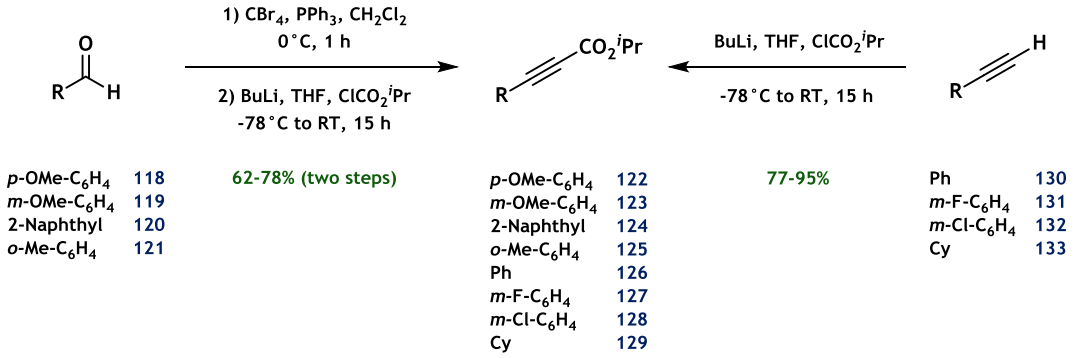


Figure 2.3 – Collection of substituted aryl malonates

2.3 Synthesis of the Stannane Component

2.3.1 Synthesis of Propargylic Esters

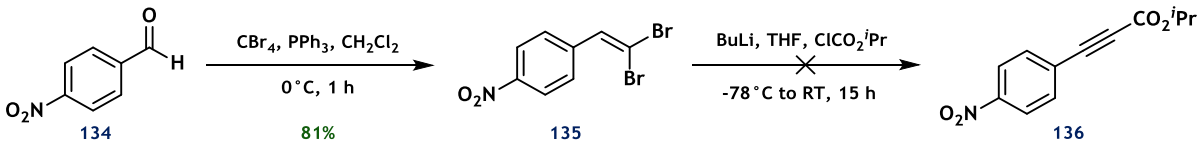
The vinylstannanes required for the Stille-Migita coupling reaction were generated from the corresponding propargylic esters. The latter were synthesized by two similar approaches that commenced from simple and inexpensive starting materials: aldehydes **118**-**121** or terminal acetylenes **130**-**133** (**Scheme 2.12**). Following a Corey-Fuchs protocol, alkynes **122**-**125** could be constructed by base-induced elimination from dibromoolefins and trapping of the resulting lithium acetylides with isopropyl chloroformate.[71,72] Identical intermediates were generated by the direct deprotonation of alkynes **130**-**133** with *n*-butyllithium; these were converted to propargylic esters **126**-**129** in the same manner. Together these procedures afforded high yields of the desired products **122**-**129** and remained robust on larger scales.



Scheme 2.12 – Conversion of aldehydes **118**-**121** or terminal acetylenes **130**-**133** to propargylic esters **122**-**129**

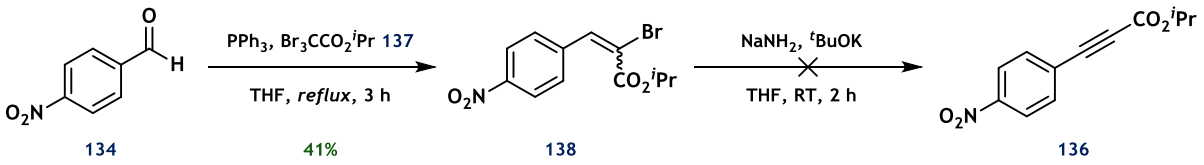
The solitary exception to the aforementioned examples was a substrate bearing a nitroaromatic group that failed to return the desired alkyne **136** (**Scheme 2.13**). Synthesis of the dibromoolefin **135** was straightforward, but upon treatment with *n*-butyllithium the

reaction turned black and a complex mixture of unidentifiable compounds was generated as observed by TLC and ^{1}H NMR.



Scheme 2.13 – Unsuccessful Corey-Fuchs reaction to synthesize alkyne **136**

A related protocol that generated α-bromoacrylate **138** using a mixture of triphenylphosphine and ester **137** was also investigated (**Scheme 2.14**).[73] Attempts to induce elimination of this intermediate **138** with an equimolar mixture of sodium amide and potassium *tert*-butoxide were unsuccessful. A 41% yield of unreacted α-bromoacrylate **138** could be recovered from this reaction but no trace of alkyne **136** was observed.



Scheme 2.14 – Attempted synthesis of alkyne **136** *via* elimination from alkene **138**

Due to the difficulties encountered while attempting to synthesize alkyne **136**, and the fact that an array of numerous propargylic esters had already been created, it was not pursued any further.

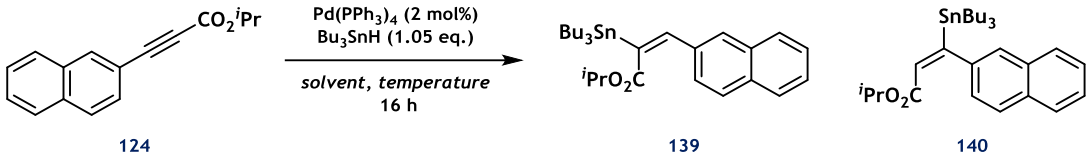
2.3.2 Palladium(0)-Catalyzed Hydrostannylation

The addition of an organotin hydride to an alkyne is a common strategy to synthesize vinylstannanes as mild, neutral conditions can be employed. Crucially, we sought a process which could convert our range of propargylic esters to the desired α-stannyl acrylates in a highly regio- and stereoselective manner. In 1992, Rossi described a palladium(0)-catalyzed

hydrostannylation procedure which provided vinylstannanes with excellent regio- and stereocontrol.[59] Employing this method, a solution of tributyltin hydride[†] was added dropwise over 4 hours to a mixture of alkyne **124** and 2 mol% of tetrakis(triphenylphosphine)palladium(0) in THF at room temperature (**Table 2.1**, **entry 1**).[60] A crude ^{1}H NMR spectrum indicated that the starting material **124** was fully consumed and a 6 : 1 mixture of regioisomers **139** and **140** had been produced. This result was in good accordance with the observed regioselectivities of similar substrates known in the literature.[59,60] Attempts to improve upon this selectivity by cooling the reaction to 0 °C led to an identical ratio of products (**entry 2**). Gradual introduction of tributyltin hydride to the reaction was critical, as rapid addition led to a 4 : 1 ratio of vinylstannanes **139** and **140** (**entry 3**).[‡] Follow up research by the Cai group suggested that benzene was a superior solvent for this transformation, with only a single regioisomer being observed for alkynyl ethyl esters.[74] However, in our hands no enhancement – with either slow or rapid addition of the organotin reagent – was observed for propargylic ester **124** (**entries 4**-**5**). Concurrently, toluene was examined as a benign alternative to benzene, but THF remained the optimal choice for this transformation (**entries 6**-**7**).

[†] *It was discovered that Bu_3SnH had a tendency to decompose and should be stored in the freezer.*

[‡] *These were the optimal conditions Dr Abhishek Kothari had determined before I took over the project.*[61]



124 139 140

Entry[i]	Solvent[ii]	Temperature	Time of Addition (Bu_3SnH)[iii]	Regioselectivity (139 : 140)[iv]	Combined Yield[v]
1[60]	THF	RT	4 h	6 : 1	81%
2	THF	0 °C	4 h	6 : 1	-
3	THF	0 °C	< 1 min	4 : 1	63%
4[74]	benzene	RT	< 1 min	5 : 1	-
5	benzene	RT	4 h	6 : 1	-
6	PhMe	RT	< 1 min	5 : 1	-
7	PhMe	RT	4 h	5 : 1	-

[i] References for procedures obtained from the literature are given. [ii] Solvents were degassed prior to use. [iii] Bu_3SnH was dissolved in THF and added via syringe pump. [iv] Ratio determined by analysis of the crude ^1H NMR spectrum. [v] Where quoted, yields are for isolated material.

Table 2.1 – Optimization of the reaction conditions for the hydrostannylation of alkyne **124**

Separation of the two regioisomers *via* column chromatography was feasible but necessitated protracted exposure to silica gel, which can promote protodestannylation, resulting in poor isolated yields.[75] Therefore, the regioisomeric mixtures of vinylstannanes were employed optimistically in the subsequent Stille-Migita cross-coupling in the hope that separation of the isomeric products would be less demanding. The major regio- and stereoisomer was identified to be α-stannyl acrylate **139** by analogy to the literature.[59,60] The coupling constants of the $^{117}Sn/^{119}Sn$ satellite peaks observed in a ^1H NMR spectrum are

indicative of the configuration of a vinylstannane (**Figure 2.4**).[76] Based on this precedent we were confident that our products had the intended (*E*)-configuration.[†]

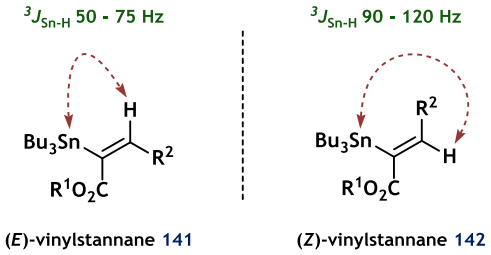
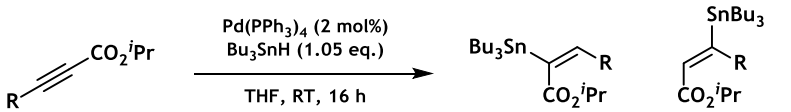


Figure 2.4 – Typical coupling constants for (*E*)- and (*Z*)-vinylstannanes

Utilizing the optimal hydrostannylation conditions a range of propargylic esters **122**-**129** were converted to the corresponding vinyl stannanes in high yields (**Table 2.2**). Electron-rich aromatic groups were well tolerated and they displayed an insignificant impact on the regioselectivity of the reaction (**entries 1**-**2**). Similarly, substrates **124**-**126** with essentially electron-neutral substituents demonstrated only mild variances in selectivities (**entries 3**-**5**). Two propargylic esters with halogenated aryl rings both provided identical 4 : 1 mixtures of regioisomers in 91-94% yield (**entries 6**-**7**). Interestingly, the only non-aromatic example **129**, containing a cyclohexyl group, provided a single regio- and stereoisomer of vinylstannane **155** (**entry 8**).

[†] *Stannane **139** has J_{Sn-H} 58.9 and stannane **140** has J_{Sn-H} 58.7 for the tin satellites around the olefinic proton.*



Entry[i,ii]	R	Starting Material	Products	Regioselectivity[iii]	Combined Yield[iv]
1	*p*-OMe-C_6H_4	**122**	**143** & **144**	4 : 1	78%
2	*m*-OMe-C_6H_4	**123**	**145** & **146**	6 : 1	91%
3	2-Naphthyl	**124**	**139** & **140**	6 : 1	81%
4[v]	*o*-Me-C_6H_4	**125**	**147** & **148**	3 : 1	88%
5	Ph	**126**	**149** & **150**	7 : 1	90%
6	*m*-F-C_6H_4	**127**	**151** & **152**	4 : 1	91%
7	*m*-Cl-C_6H_4	**128**	**153** & **154**	4 : 1	94%
8	Cy	**129**	**155**	>20 : 1	74%

[i] Solvents were degassed prior to use. [ii] Tributyltin hydride was dissolved in THF and added via syringe pump over 4 hours. [iii] Ratio determined by analysis of the crude ^{1}H NMR spectrum. [iv] Yields are for isolated material. [v] Due to syringe pump malfunction the tributyltin hydride solution was added over a considerably shorter period than 4 hours (approx. 30 min) and may in part have led to poor regioselectivity in this example.

Table 2.2 – Hydrostannylation of a range of propargylic esters **122**-**129**

The rationale for the observed high regio- and stereoselectivities can be understood by examining the mechanism of this reaction (**Figure 2.5**). Initially, tributyltin hydride undergoes oxidative addition with tetrakis(triphenylphosphine)palladium(0) to generate Pd^{II} intermediate **156**. By displacing a phosphine ligand the alkyne **157** can coordinate to the metal centre to give complex **158**. A concerted hydropalladation gives the vinylpalladium intermediate **159** *via* a stereoselective *syn*-addition. The regioselectivity of this step can be justified by considering the polarization of the alkyne, whereby the hydride of the Pd–H species preferentially attacks the most electron-deficient carbon of the acetylene. Subsequent

reductive elimination regenerates the Pd^0 catalyst and releases the desired stereodefined (*E*)-vinylstannane **160**.

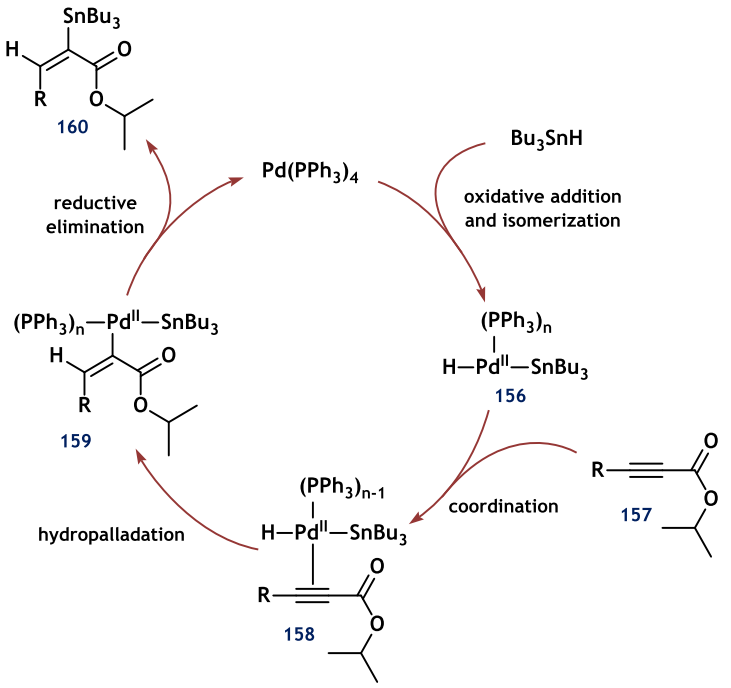


Figure 2.5 – Proposed catalytic cycle for a Pd(0)-catalyzed hydrostannylation

2.3.3 Overview

A range of vinylstannanes with an assortment of substituents were synthesized in good yields with high regio- and stereoselectivities (**Figure 2.6**). By analogy to the literature, and with reference to the ^{1}H NMR spectrum, the major isomer was confirmed to be an (*E*)-*α*-stannyl acrylate. Attempts to remove the minor regioisomeric impurities from these vinyl tin reagents were detrimental for their isolated yields, thus the mixtures were utilized in the subsequent cross-coupling reaction.

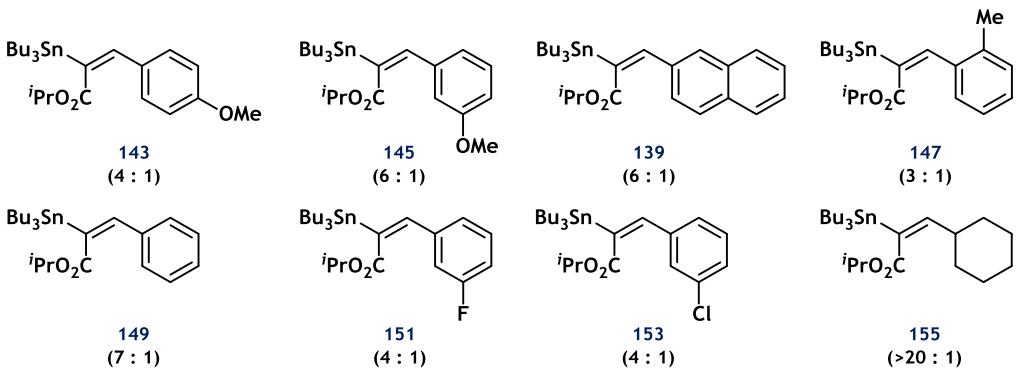


Figure 2.6 – A range of vinyl stannanes (regioisomeric ratio given in parentheses)

2.4 Stille-Migita Coupling

2.4.1 Introduction

Since its development the Stille-Migita cross-coupling reaction has proven to be a powerful and robust C–C bond forming reaction.[77–79] The remarkable stability of the organotin component, in tandem with the superb functional group compatibility of this palladium-mediated process, has led to expansive applications of this methodology in natural product synthesis.[80,81] Despite the availability of more benign procedures, such as the Suzuki-Miyaura reaction that employs less toxic coupling partners,[82,83] we chose to investigate a Stille-Migita cross-coupling for the synthesis of our indane precursors. The reason for this decision was rooted in the fact that no base was required for transmetalation of the organotin reagent, which may facilitate premature cyclization of the substrate *in situ*.[84] Moreover, it is well documented that vinylstannanes retain their configuration during a Stille-Migita coupling, which is key for the stereochemical integrity of the products.[85,86] Numerous combinations of palladium catalysts, ligands, solvents and additives have been exploited successfully in a wide range of syntheses.[87] The daunting task of selecting which protocol to employ was reiterated by Mitchell in a recent review:

"A look at the catalyst (or to be exact, precatalyst) and cocatalyst combinations, together with solvent variations, which have been used in the papers cited above will make it clear that there is in fact no 'ideal' system, but that each reaction will basically require optimization. If readers are slightly bewildered by this plethora of possibilities, they are not alone: the author of these lines is, too!"[88]

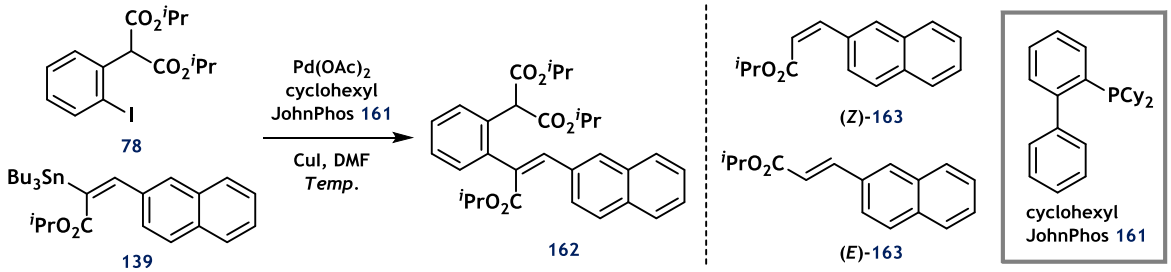
With this in mind, we fully optimized a Stille-Migita reaction to synthesize our cyclization precursors. The proximity of sterically demanding substituents in the coupling region rendered this a highly challenging C–C bond forming step.

2.4.2 Optimization of the Cross-Coupling Procedure

2.4.2.1 Initial Investigations with the Cyclohexyl JohnPhos Ligand

Previous research by a co-worker revealed that the ligand cyclohexyl JohnPhos **161** developed by the Buchwald group was suitable for the synthesis of our cyclization precursors (**Table 2.3**).[89,90] A catalytic system combining $Pd(OAc)_2$ (20 mol%), phosphine **161** (30 mol%) and copper(I) iodide (20 mol%) in DMF at 80 °C generated the desired product **162** in 35% yield, albeit with minor unidentifiable contaminants (**entry 1**).[†] Performing identical cross-coupling reactions under microwave irradiation proved detrimental, with the sole discernible product arising from protodestannylation of the vinylstannane **139** to form alkene (*Z*)-**163** (**entries 2**-**3**). A return to conventional heating with an increased quantity of copper(I) iodide (75 mol%) led to a modest increase in yield to 40% (**entry 4**). Concomitantly, superior conditions for purifying the crude reaction mixture furnished the isolated product **162** free from impurities. Further improvements in yield seemed doubtful with this catalytic system, which had not been previously employed for Stille-Migita type couplings.

[†] *These were the optimal conditions Dr Abhishek Kothari had determined before I took over the project.*[61]



Entry[i,ii]	Temperature	Time	Outcome[iii]
1[†]	80 °C	15 h	35% yield of **162** but contaminated by unidentifiable entities[iv]
2	200 °C μw	0.5 h	No product, only alkene (*Z*)-**163** observed[v]
3	80 °C μw	1 h	Complex mixture[v]
4[vi,vii]	80 °C	15 h	40% yield of pure **162**, 11% of (*Z*)-**163** and 5% of (*E*)-**163**

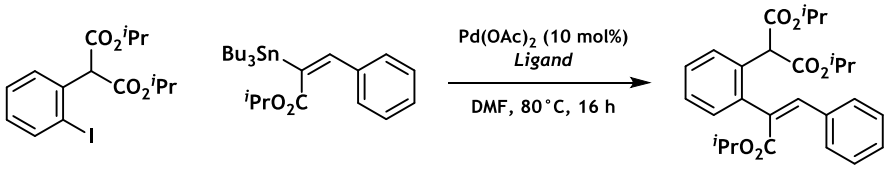
*[i] Unless otherwise stated, the reaction conditions and stoichiometries were as follows: $Pd(OAc)_2$ (20 mol%), cyclohexyl JohnPhos **161** (30 mol%), CuI (20 mol%), iodoarene **78** (1 eq.), vinylstannane **139** (1.2 eq.) in DMF at 80 °C. [ii] Solvents were degassed prior to use. [iii] Where quoted, yields refer to isolated material. [iv] As determined by analysis of the ^1H NMR spectrum. [v] As determined by analysis of the crude ^1H NMR spectrum, TLC and MS. [vi] 15 mol% of $Pd(OAc)_2$ and 75 mol% of CuI were used. [vii] Purification involved silica gel chromatography with toluene as eluent.*

Table 2.3 – Screening of reaction conditions with cyclohexyl JohnPhos **161**

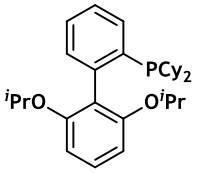
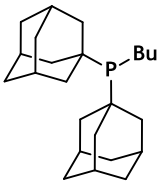
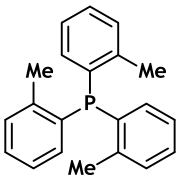
2.4.2.2 *Screening of Phosphine Ligands with $Pd(OAc)_2$*

In an endeavour to improve the yield of this demanding cross-coupling reaction various phosphine ligands were evaluated in combination with $Pd(OAc)_2$ (**Table 2.4**). Initially, RuPhos **165**, an efficient ligand for the Negishi reaction, was examined under copper-free conditions in DMF at 80 °C, but returned mostly starting materials (**entry 1**). Similarly, the bulky ligand cataCXium® A **166** proved ineffective and was merely able to generate traces of the desired product **164** (**entry 2**).[91]

[†] *These were the optimal conditions Dr Abhishek Kothari had determined before I took over the project.*[61]



78 149 164

Entry[i]	Conditions[ii,iii]	Outcome[iv]
1	RuPhos **165** (20 mol%) 	Trace product **164**, mostly starting materials[v]
2	cataCXium® A **166** (20 mol%) 	Trace product **164**, mostly starting materials[v]
3[92]	P(*o*-tolyl)$_3$ **167** (20 mol%) 	59% yield of **164** contaminated by unidentifiable entities[vi]
4[vii]	P(*o*-tolyl)$_3$ **167** (20 mol%)	43% yield of pure **164**
5[vii]	$Pd_2(dba)_3$ (5 mol%), P(*o*-tolyl)$_3$ **167** (20 mol%)	45% yield of pure **164**
6[93]	P(*o*-tolyl)$_3$ **167** (30 mol%), CuI (75 mol%), 50 °C	Trace product **164**, mostly starting materials[v]

*[i] References for procedures obtained from the literature are given. [ii] Unless otherwise stated, the reaction conditions and stoichiometries were as follows: Pd(OAc)$_2$ (10 mol%), ligand (20 mol%), iodoarene **78** (1 eq.), vinylstannane **149** (1.8 eq.) in DMF at 80 °C for 16 h. [iii] Solvents were degassed prior to use. [iv] Where quoted, yields refer to isolated material. [v] As determined by analysis of the crude ^{1}H NMR spectrum, TLC and MS [vi] As determined by analysis of the ^{1}H NMR spectrum. [vii] Purification involved silica gel chromatography with toluene as eluent.*

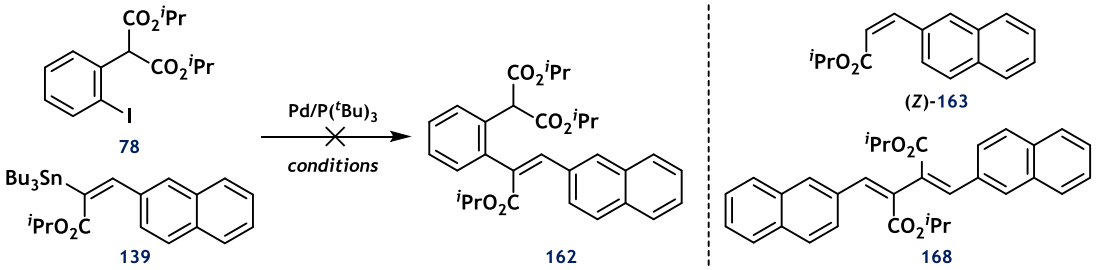
Table 2.4 – Screen of phosphine ligands in combination with Pd(OAc)$_2$

Remarkably, the relatively simple ligand P(*o*-tolyl)$_3$ **167** was far more suitable and provided a 59% yield of the cyclization precursor **164**, but with minor contamination (**entry 3**). Pure material could be acquired by repeated column chromatography and combined with changing the palladium pre-catalyst to $Pd_2(dba)_3$ yields as high as 45% were achievable (**entries 4**-**5**). Following a literature procedure, which invoked similar coupling conditions but with the inclusion of copper(I) iodide, was less effective and only a trace of

product **164** was observed by analysis of the crude ^{1}H NMR spectrum (**entry 6**).[93] Overall, this method of synthesizing our substrates proved only marginally better than the previous system which employed cyclohexyl JohnPhos **161**.

2.4.2.3 Evaluation of the Pd/P(^{t}Bu)$_3$ Catalyst System

In pursuit of a mild and general procedure for conducting Stille-Migita couplings at room temperature Fu discovered that tri-*tert*-butylphosphine **170** was a remarkably effective ligand.[94] Furthermore, this protocol could exploit unactivated aryl chlorides as coupling partners at elevated temperatures and by utilizing these unreactive starting materials the scope of this system is broadened. Owing to the air sensitivity of P(^{t}Bu)$_3$ **170**, initial reactions employed the more stable Pd(P(^{t}Bu)$_3$)$_2$ complex **169**, which is commercially available. When iodoarene **78** and vinylstannane **139** were treated with 3 mol% of the palladium catalyst **169** in the presence of CsF at room temperature negligible reactivity was observed (**Table 2.5**, **entry 1**). The role of the fluoride additive was proposed to invoke a hypercoordinate species which undergoes transmetalation more efficiently.[95] However, heating the reaction under identical conditions to above led to a complex mixture of products, which did not comprise the coupled product **162** (**entry 2**). Reactions implemented at room temperature that employed phosphine **170** directly demonstrated no improvement in reactivity (**entries 3**-**4**). Trace amounts of the desired product **162** were observed at 80 °C amongst by-products arising from starting material decomposition (**entry 5**). Introduction of copper(I) iodide as an additive generated primarily diene **168** *via* homocoupling of the vinylstannane **139** (**entry 6**).



Entry[i]	Conditions[ii,iii]	Outcome[iv]
1[94]	$Pd(P(^tBu)_3)_2$ **169** (3 mol%), CsF (2.2 eq.), Sn **139** (1.2 eq.), NMP, RT, 24 h	NR, trace of alkene (*Z*)-**163**
2[94]	$Pd(P(^tBu)_3)_2$ **169** (3 mol%), CsF (2.2 eq.), Sn **139** (1.2 eq.), NMP, 60 °C, 24 h	Complex mixture
3[94]	$Pd_2(dba)_3$ (1.5 mol%), $P(^tBu)_3$ **170** (3.2 mol%), Sn **139** (1.4 eq.), CsF (2 eq.), NMP, RT, 48 h	NR
4[94]	$Pd_2(dba)_3$ (0.5 mol%), $P(^tBu)_3$ **170** (1.2 mol%), Sn **139** (1.4 eq.), PhMe, RT, 24 h	NR
5[94]	$Pd_2(dba)_3$ (0.5 mol%), $P(^tBu)_3$ **170** (1.2 mol%), Sn **139** (1.4 eq.), PhMe, 80 °C, 24 h	Complex mixture, trace of product **162**
6	$Pd(OAc)_2$ (10 mol%), $P(^tBu)_3$ **170** (20 mol%), CuI (1.4 eq.), Sn **139** (1.4 eq.), NMP, 45 °C, 48 h	Diene **168**, trace of product **162**

*[i] References for procedures obtained from the literature are given. [ii] The reaction conditions are as stated with iodoarene **78** (1 eq.) [iii] Solvents were degassed prior to use. [iv] As determined by analysis of the crude ^1H NMR spectrum, TLC and MS.*

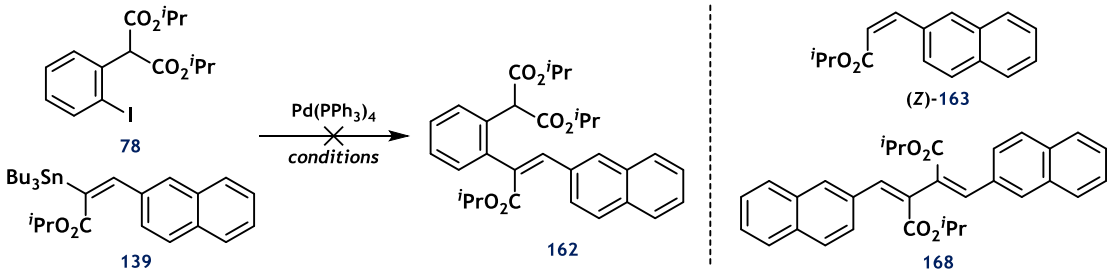
Table 2.5 – Evaluation of $Pd/P(^tBu)_3$ for synthesizing substrate **162**

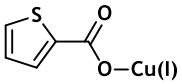
For the synthesis of our cyclization precursors tri-*tert*-butylphosphine **170** proved ineffective, with only traces of product **162** observed under a variety of coupling conditions. The investigation of alternative protocols to construct the required products continued, with different palladium-based catalytic systems being scrutinized.

2.4.2.4 Investigation of $Pd(PPh_3)_4$ Mediated Stille-Migita Couplings

Sterically encumbered 1-substituted vinylstannanes are problematic substrates for performing cross-coupling reactions. Early investigations with these bulky organotin

components demonstrated very slow reaction rates and competitive formation of a by-product *via* a *cine*-substitution pathway.[96–98] However, a solution to this predicament was delineated by Corey in which excess CuCl and LiCl were employed to accelerate the transmetalation step as well as suppress undesired side-reactions.[99] Unfortunately, the sole product isolated from a reaction that utilized this combination of reagents along with $Pd(PPh_3)_4$ was the dimer **168** (**Table 2.6**, **entry 1**). The homocoupling of vinylstannanes mediated by CuCl is known and in this system outcompetes the intended coupling process.[100] Subsequently, an alternative copper(I) source (CuTC **171**), which was pioneered by Liebeskind for promoting low temperature Stille-Migita reactions, was examined.[101]



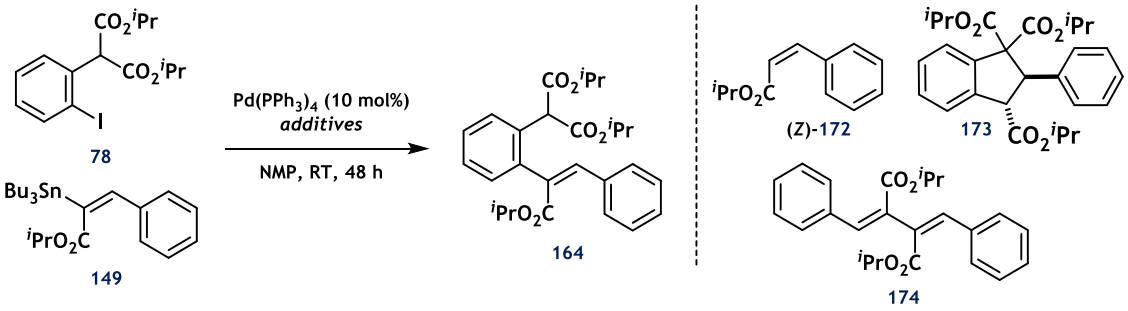
Entry[i]	Conditions[ii,iii]	Outcome
1[99]	$Pd(PPh_3)_4$ (10 mol%), CuCl (5 eq.), LiCl (6 eq.), DMSO, 60 °C, 48 h	20% yield of diene **168**[iv]
2[102]	$Pd(PPh_3)_4$ (5 mol%), CuTC **171** (1.25 eq.), CsF (2 eq.), DMF, RT, 24 h 	Complex mixture, trace of alkene (*Z*)-**163**[v]

*[i] References for procedures obtained from the literature are given. [ii] Solvents were degassed prior to use. [iii] The reaction conditions are as stated with iodoarene **78** (1 eq.) and vinylstannane **139** (1.2 eq.). [iv] Isolated yield. [v] As determined by analysis of the crude ^1H NMR spectrum, TLC and MS.*

Table 2.6 – Screening of $Pd(PPh_3)_4/Cu^I$ reaction conditions

The benefits of tin's fluorophilicity and this highly efficient Cu^I salt **171** were merged by Trauner to generate delicate hexatriene substrates.[102] Exposing iodoarene **78** and vinylstannane **139** to these conditions led to a complex mixture of products which contained traces of protodestannylated material (*Z*)-**163** (**entry 2**). Eventually, a suitable additive (CuI)

was found that generated substrate **164** in 19% yield (**Table 2.7**, **entry 1**).[93] The formation of product **164** was accompanied by a 13% yield of the diene **174**, which had been observed previously.



Entry[i]	**Additives**[ii,iii]	**Outcome**[iv]
1[93]	CuI (1.2 eq.)	19% yield of product **164**, 13% yield of diene **174**
2[103,104]	CuI (0.2 eq.), CsF (2 eq.)	62% yield of *anti*-indane **173** (>20 : 1 dr)
3[105]	CuI (0.2 eq.), $[Bu_4N]^+[Ph_2PO_2]^-$ **175** (2 eq.)	84% yield of alkene (*Z*)-**172**

*[i] References for procedures obtained from the literature are given. [ii] Unless otherwise stated, the reaction conditions and stoichiometries were as follows: $Pd(PPh_3)_4$ (10 mol%), the stated additives, iodoarene **78** (1 eq.), vinylstannane **149** (1.2 eq.) in NMP at RT for 48 h. [iii] Solvents were degassed prior to use. [iv] Yields are for isolated material.*

Table 2.7 – Evaluation of various additives with $Pd(PPh_3)_4$

Further optimization of this process was undertaken by the application of CsF in conjunction with copper(I) iodide, as described by Baldwin, which provided an efficient and clean cross-coupling between iodoarene **78** and stannane **149** (**entry 2**).[103,104] However, upon analysis by ^{1}H NMR the observed product was not triester **164**, but the cyclized compound **173**. This outcome implied that the basicity of the fluoride ion in NMP was sufficient to promote this 5-*endo*-trig ring closure at room temperature. The carbocycle **173** was obtained as a single diastereomer and was confirmed to have an *anti*-configuration of substituents by X-ray diffraction (**Figure 2.7**).

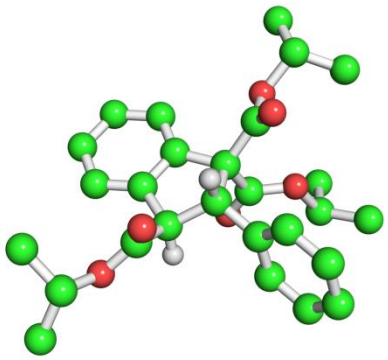


Figure 2.7 – Single crystal X-ray structure of *anti*-indane **173**[†]

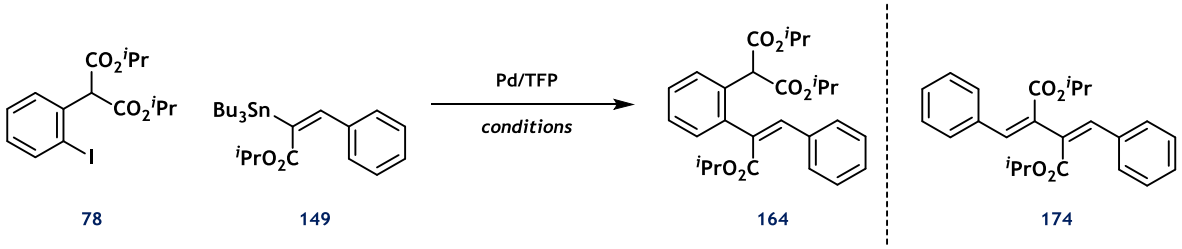
Pursuing a replacement for the fluoride additive uncovered a phosphinate salt **175**, which is a broadly neutral tin scavenger. Fürstner has demonstrated the utility of this reagent by performing several challenging coupling reactions in the presence of sensitive functionalities.[105] When $[Bu_4N]^+[Ph_2PO_2]^-$ **175** was exchanged with CsF in the Stille-Migita reaction to form substrate **164**, extensive protodestannylation transpired to deliver alkene (*Z*)-**172** in 84% yield (**entry 3**). Additional efforts were directed towards discovering a protocol which could promote cross-coupling as efficiently as the combination of CuI and CsF without subsequent cyclization to form the indane directly.

2.4.2.5 Assessment of the Tri(2-furyl)phosphine Ligand

Alternative proposals to facilitate the transmetalation of a stannane with a Pd^{II} intermediate focused on the nature of the phosphine. Farina proposed that an ideal ligand should be a poor Lewis base which has minimal coordinative abilities.[107] This would render the ligated palladium species resulting from oxidative addition more susceptible to transmetalation. The tri(2-furyl)phosphine **176** (TFP) ligand exhibits all of these properties and has been employed in a vast number of successful Stille-Migita cross-coupling

[†] *X-ray diffraction data was collected and the structure solved by Dr Russell W. Driver. The molecule was rendered using PyMOL.*[106]

reactions.[108] In particular, the Overman group has adopted TFP **176** on several occasions for the synthesis of complex natural products such as asperazine and hodgkinsine derivatives.[109,110] The resemblance of the coupling partners involved in these systems to our specific substrates encouraged the evaluation of this ligand (**Table 2.8**). Accordingly, two related literature procedures were examined and the initial outcomes appeared encouraging, with the desired indane precursor **164** furnished in up to 48% yield (**entries 1**-**2**).[110,111] As observed previously in couplings facilitated by copper salts, significant quantities of diene **174** were also generated; rigorous degassing of the reaction was beneficial but insufficient to completely suppress this side-reaction. The evaluation of two reactions conducted with CuCl at room temperature or thermally in the absence of any copper(I) salts produced poor yields of triester **164** (**entries 3**-**4**). However, reverting to excess CuI in combination with heating the reaction to 60 °C forged the desired product **164** in 64% yield (**entry 5**).[112,113] No further improvements were gained by employing $Pd(dmdba)_2$ or $Pd(OAc)_2$ as pre-catalysts in this process (**entries 6**-**7**).[114] Concomitant to the development of this coupling procedure, further improvements to the purification method were implemented. The production of Bu_3SnI as a by-product from Stille-Migita reactions has remained a long-standing issue. Recently, several protocols have emerged for the removal of tin impurities from reaction mixtures, however, the majority of these techniques are incompatible with base-sensitive compounds.[115,116] Nevertheless, we were delighted to discover that purification of our substrates over a stationary phase comprising 10% K_2CO_3 and 90% silica (w/w) was very effective for sequestering tin residues.[117] The adoption of this technique meant repeated chromatographic separations were no longer mandatory to obtain pure isolated material. Moreover, premature cyclization of the substrates was not observed following elution from the K_2CO_3-doped column.



78 149 164 174

Entry[i]	**Conditions**[ii,iii]	**Outcome**[iv]
1[110]	$Pd_2(dba)_3$ (10 mol%), TFP **176** (40 mol%), CuI (1.0 eq.), Sn **149** (1.5 eq.), NMP, RT, 48 h	48% yield of product **164**[v]
2[111]	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.6 mol%), TFP **176** (20.5 mol%), CuI (1.1 eq.), Sn **149** (1.1 eq.), NMP, RT, 48 h	40% yield of product **164**, 36% yield of diene **174**
3	$Pd_2(dba)_3$ (10 mol%), TFP **176** (40 mol%), CuCl (2.0 eq.), Sn **149** (1.5 eq.), NMP, RT, 48 h	25% yield of product **164**[v]
4	$Pd_2(dba)_3$ (10 mol%), TFP **176** (40 mol%), Sn **149** (1.2 eq.), NMP, 50 °C, 48 h	23% yield of product **164**
5[112,113]	$Pd_2(dba)_3$ (10 mol%), TFP **176** (40 mol%), CuI (1.5 eq.), Sn **149** (1.5 eq.), NMP, 60 °C, 24 h	64% yield of product **164**[v]
6	$Pd(dmdba)_2$ (20 mol%), TFP **176** (40 mol%), CuI (1.5 eq.), Sn **149** (1.5 eq.), NMP, 60 °C, 24 h	52% yield of product **164**[v]
7	$Pd(OAc)_2$ (20 mol%), TFP **176** (60 mol%), CuI (1.4 eq.), Sn **149** (1.4 eq.), NMP, 60 °C, 24 h	35% yield of product **164**[v]

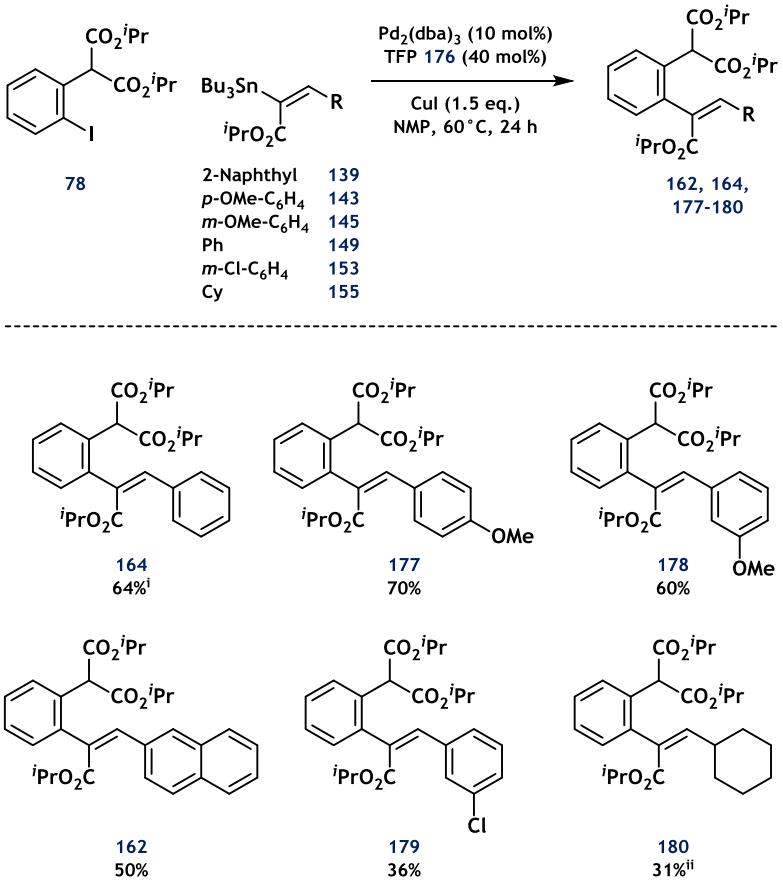
*[i] References for procedures obtained from the literature are given. [ii] Solvents were degassed prior to use. [iii] The reaction conditions are as stated with iodoarene **78** (1 eq.). [iv] Yields are for isolated material. [v] Homocoupling of vinylstannane **149** to form diene **174** was a significant side reaction.*

Table 2.8 – Optimization of the Stille-Migita coupling with TFP **176**

Having established a synthetic route to our indane precursors, which could provide analytically pure triester **164** in good yield, we wished to assess the generality and robustness of this procedure through the construction of a substrate library.

2.4.3 Synthesis of the Cyclization Precursors

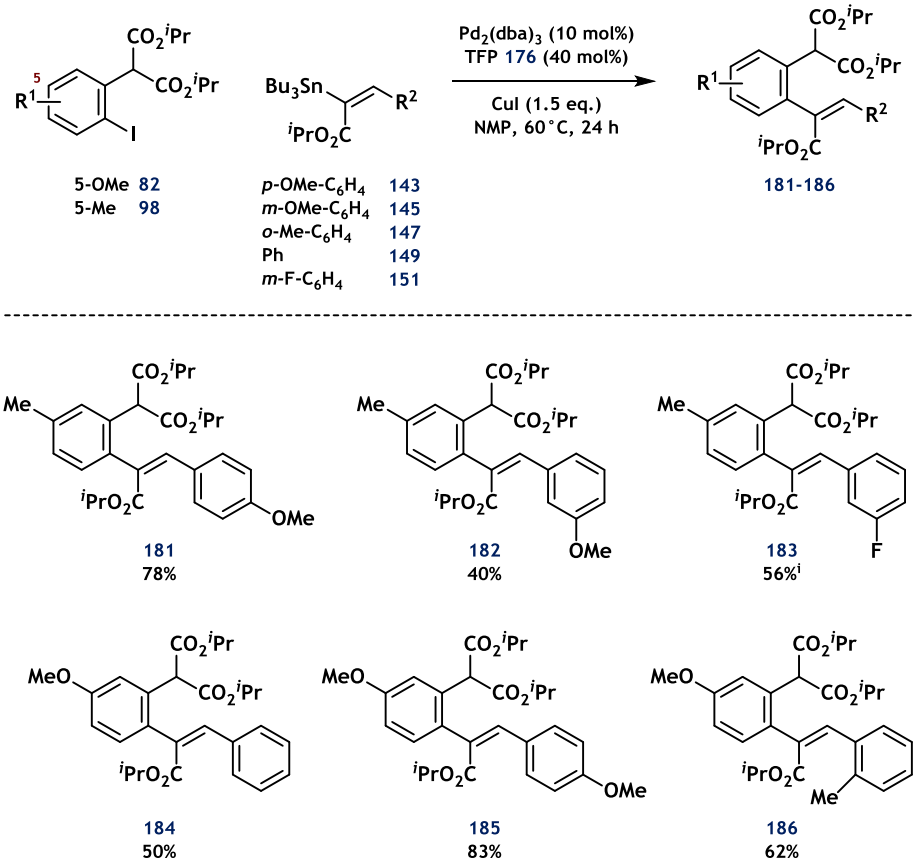
Employing the optimized cross-coupling procedure, iodoarene **78** was reacted with various vinylstannanes comprising diverse functionalities (**Scheme 2.15**). The 2-naphthyl substituted tin reagent **139** delivered a slightly lower yield of triester **162** when compared to the phenyl analogue **164**. The inclusion of electron-rich functional groups on the aromatic ring was fully tolerated and provided 60-70% yield of products **177**-**178**. Indane precursors **179**-**180** were isolated in moderate yields owing to the difficulty of separating these products from residual dibenzylideneacetone (dba) and the diene arising from homocoupling of the stannane. In certain circumstances, $Pd(PPh_3)_4$ could be employed as an alternative catalyst; this streamlined the purification of substrates with similar retention factors to dba. For example, utilizing 20 mol% of this palladium source furnished 31% yield of the cyclohexyl analogue **180** free from contamination.



*[i] Yield was 48% on larger scale. [ii] $Pd(PPh_3)_4$ (20 mol%) was used instead of $Pd_2(dba)_3$/TFP **176***

Scheme 2.15 – Synthesis of substrates through a Stille-Migita cross-coupling

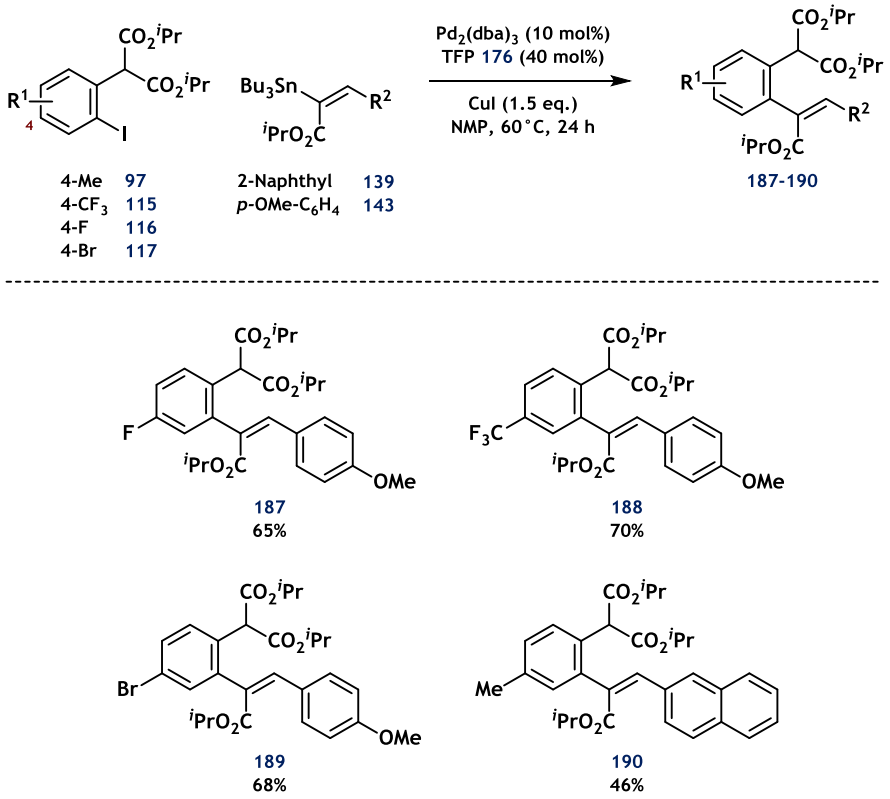
Further diversification of the substrate library utilized iodoarenes **82** and **98** with substituents *meta* to the malonate (**Scheme 2.16**). The alkylated coupling partner **98** had a negligible effect on the efficiency of the reaction, with triesters **181**-**182** being formed in 78% and 40% yield respectively. As witnessed previously, purification of substrate **183** proved troublesome under the standard conditions, but after switching to $Pd(PPh_3)_4$ pure material was obtained in good yield. The electron-rich methoxyarene **82** underwent smooth oxidative addition and subsequent coupling to afford three new products **184**-**186** in 50-83% yield. In general, the introduction of polar functional groups to the indane precursors was beneficial for their separation from reaction by-products such as ligands and dienes stemming from dimerization of the stannane.



*[i] $Pd(PPh_3)_4$ (20 mol%) was used instead of $Pd_2(dba)_3$/TFP **176***

Scheme 2.16 – Synthesis of substrates through a Stille-Migita cross-coupling

Lastly, iodoarenes (**97**, **115**-**117**) with alkyl and halogen substituents *para* to the malonate were examined (**Scheme 2.17**). The reaction between fluorinated analogues **115**-**116** with vinylstannane **143** was facilitated by $Pd_2(dba)_3$ and TFP **176** to afford very good yields of products **187**-**188**. Substrate **189** bears a relatively unhindered bromine atom that remained intact during the coupling process. This suggested that competitive oxidative addition was not observed for this site despite the steric obstacles adjacent to the carbon-iodine bond. The comparatively lipophilic product **190** necessitated repeated chromatographic separations to obtain pure material, which led to a lower than average yield of 46%.



Scheme 2.17 – Synthesis of substrates through a Stille-Migita cross-coupling

Overall, a library consisting of sixteen diversely substituted analogues was generated. These substrates were synthesized through a very sterically demanding cross-coupling procedure with an average isolated yield of 59%.

2.4.4 Mechanism of the Stille-Migita Cross-Coupling

Since its inception, several proposals for the mechanism of Stille-Migita couplings have been delineated.[84,85,97,98,107,118–121] In general, the reaction variables play a significant role in determining the mechanistic pathway for one particular set of conditions. A simplified mechanism for a coupling protocol is provided, which attempts to rationalize the outcomes of the different procedures we employed (**Figure 2.8**). Palladium(0) species **191** is postulated to be the active complex that oxidatively inserts into the carbon-iodine bond of arene **192**.[122] In the absence of copper(I) salts, transmetalation of stannane **160** directly with the Pd^{II}

intermediate **193** is probably rate-determining in our system. However, the addition of a stoichiometric quantity of CuI seemed beneficial and permitted reactions to be conducted at room temperature. In polar solvents it is hypothesized that the more reactive vinylcopper(I) species **197** is generated and is subsequently intercepted by the palladium(II) species **193**. However, the initial tin-copper transmetalation event is considered to be an equilibrium process which is retarded by increasing concentrations of Bu_3SnI. The Baldwin group have demonstrated that the addition of fluoride ions can drive this equilibrium towards the organocopper intermediate **197** by converting tin by-products into polymeric Bu_3SnF.[103,104] This synergistic combination of additives was very effective in our system but unfortunately the fluoride ion was also capable of inducing substrate cyclization to form the indane compounds directly. Transmetalation of the vinylcopper species **197** may occur directly or by initial coordination of the alkene; the latter requires dissociation of a ligand.

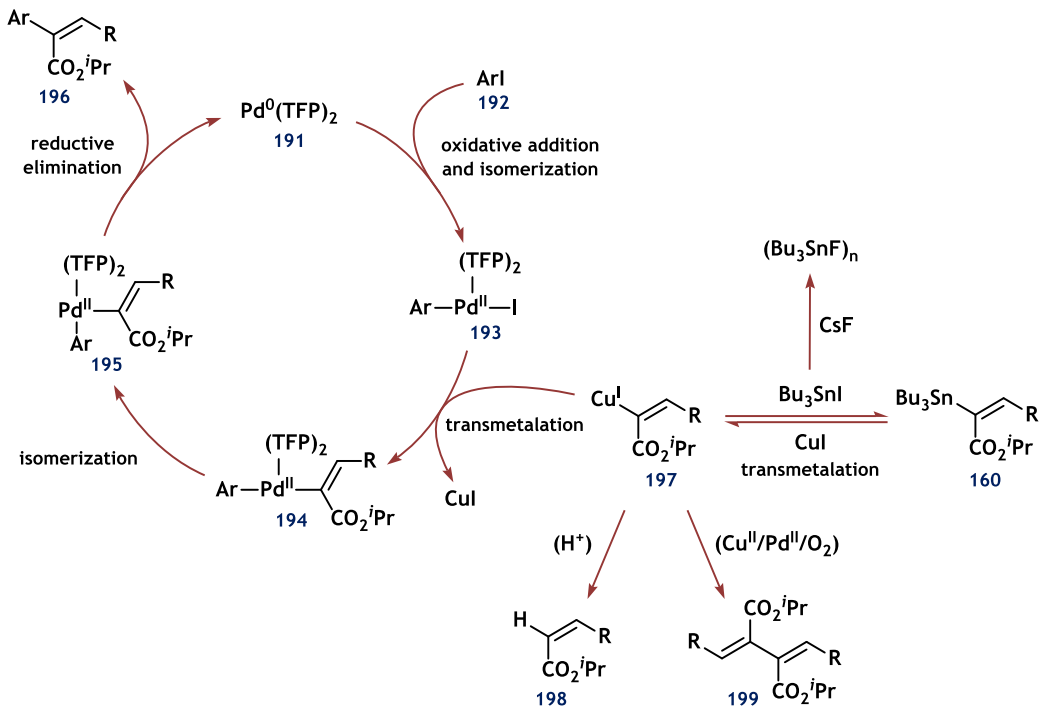


Figure 2.8 – Putative mechanism for a Stille-Migita cross-coupling

Despite the advantages of incorporating copper(I) salts in Stille-Migita reactions, they also facilitate the formation of unwanted side products, such as alkene **198** and diene **199**. For example, the organostannane **160** is air and moisture stable, whereas the more reactive Cu(I) species **197** is susceptible to proto-demetalation. Similarly, a number of copper (or palladium) reagents have been implicated in the dimerization of stannanes, which is often facilitated by molecular oxygen.[123–125] Extensive efforts were made to minimize these side reactions by conducting the coupling procedure under anhydrous and air-free conditions. Following successful transmetalation to form intermediate **194**, isomerization to the *cis*-complex **195** occurs to set up a reductive elimination that liberates the coupled product **196** and regenerates the active Pd^0 species **191**.

2.4.5 Overview

The development of an efficient procedure to synthesize our cyclization precursors necessitated considerable optimization. The sterically demanding nature of the reaction as well as the inherent base sensitivity of the products rendered this a synthetically challenging process. The established conditions for the cross-coupling reaction engaged a highly active catalytic system generated from $Pd_2(dba)_3$ and TFP **176** along with a stoichiometric copper(I) additive. Rigorous degassing of the reaction mixture was crucial for minimizing homocoupling of the vinylcopper species, which generated a conjugated diene that often impeded product purification. The addition of a fluoride source promoted a very efficient Stille-Migita reaction, potentially by sequestering Bu_3SnI, but its latent basicity instigated uncontrollable cyclization of the coupled product to form the indane directly. Despite this setback an alternative method for removing tin residues was discovered that involved conducting column chromatography through a K_2CO_3-silica stationary phase. Overall, this

protocol was capable of constructing a wide range of substrates in good yields and re-emphasizes the robustness of Stille-Migita cross-coupling reactions.

3. PHASE-TRANSFER CATALYSIS

3.1 Introduction

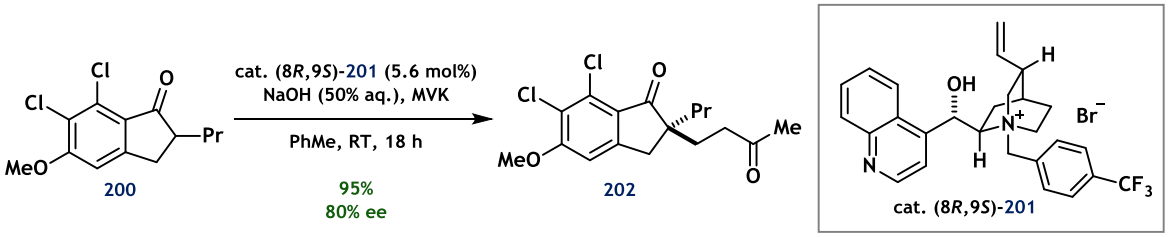
The advent of phase-transfer catalysis (PTC) and its later application to asymmetric synthesis ushered in a new era of synthetic organic chemistry. The foundations of this methodology were laid by Starks,[126] Mąkosza[127,128] and Brändström,[129] when they reported the ability of quaternary ammonium salts to transfer ions between two immiscible phases. The key features of these onium catalysts include their organic solubility and large ionic radius, which allows them to generate lipophilic ion-pairs that preferentially reside in the organic phase. This process can render extracted anions such as cyanide or hydroxide more reactive due to improved charge separation and reduced hydration. These mild reaction conditions circumvent the requirement for pyrophoric bases and have rendered phase-transfer catalysis a relatively benign protocol, which is progressively being employed in large-scale industrial processes.[130]

More recently, the application of chiral non-racemic quaternary ammonium salts in enantioselective synthesis has grown considerably. A number of asymmetric phase-transfer catalysts have been developed to induce high levels of stereoselectivity in an extensive range of common processes including alkylation, Aldol, Mannich, epoxidation and Michael reactions.[131,132] Accordingly, we sought to discover the optimal phase-transfer conditions for conducting highly enantioselective 5-*endo*-trig ring closures to provide complex diversely substituted indanes.

3.2 *Cinchona*-Derived Phase-Transfer Catalysts

3.2.1 Development and Previous Applications

The *cinchona* alkaloids have been established as stalwart organocatalysts for implementing a variety of asymmetric transformations. This rise to prominence can be rationalized by the commercial availability of several inexpensive pseudo-enantiomeric analogues. Moreover, this unique scaffold has a rich variety of functionality that can be easily manipulated and tuned to deliver a myriad of chiral non-racemic phase-transfer catalysts. A wide range of *cinchona*-derived quaternary ammonium salts have been disclosed and successfully employed in a multitude of asymmetric reactions.[133] One of the earliest reports of an alkaloid-based phase-transfer catalyst mediated asymmetric Michael reaction was reported by a Merck research group in 1986 (**Scheme 3.1**).[134] The cinchoninium salt (8*R*,9*S*)-**201** was readily synthesized in a single step by quaternization of the quinuclidine amine with the appropriate benzyl bromide derivative. Subsequently, 5.6 mol% of this catalyst (8*R*,9*S*)-**201** was employed in a biphasic mixture of toluene and 50% aqueous NaOH, with MVK serving as an electrophile, to promote alkylation of indanone substrate **200**.



Scheme 3.1 – Enantioselective alkylation of indanone **200** with phase-transfer catalyst (8*R*,9*S*)-**201**[134]

This process generated a coveted all-carbon quaternary stereocentre and delivered the diketone product **202** in 95% yield with 80% ee. The broad applicability of *cinchona*-derived

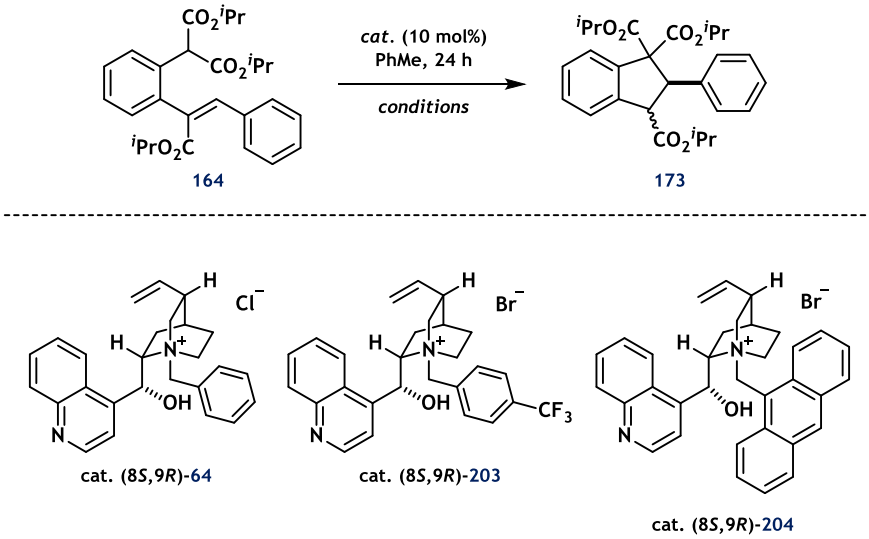
phase-transfer catalysts rendered them ideal candidates to examine in our reaction to produce enantioenriched indane derivatives.

3.2.2 Screening of Catalysts[†]

Previous research in the Smith group has demonstrated the utility of alkaloid-based phase-transfer catalysts for the enantioselective synthesis of indoline and indolenine based heterocycles.[55–57] Accordingly, an array of chiral cinchonidinium salts were evaluated to assess their putative stereocontrolling ability and to ascertain the viability of this project (**Table 3.1**). Initially, the simplest indane precursor **164** was examined with two carbonate bases, which had proven successful in the indoline scaffold,[55] in combination with 10 mol% of (8*S*,9*R*)-*N*-benzylcinchonidinium chloride **64** in toluene (**entries 1**-**2**). Surprisingly, 40% aqueous K_2CO_3 and solid Cs_2CO_3 demonstrated poor reactivity in this system, and solely starting material **164** was recovered. However, switching to a stronger base ($CsOH{\cdot}H_2O$) furnished a 2.5 : 1.0 (*anti* : *syn*) mixture of indanes **173** with the major diastereomer obtained in 28% ee (**entry 3**). Reducing the reaction temperature under these conditions was detrimental for conversion and enantioselectivity (**entries 4**-**5**). Evaluation of an electron-deficient catalyst (8*S*,9*R*)-**203** bearing a CF_3-substituted arene led to a decline in asymmetric induction (**entry 6**). The introduction of a bulky anthracenyl group to the *cinchona* scaffold was independently pioneered by Corey[135] and Lygo.[136] In general, catalyst (8*S*,9*R*)-**204** has been demonstrated to be superior for the asymmetric alkylation of glycine Schiff bases when compared to the previous analogues (8*S*,9*R*)-**64** and (8*S*,9*R*)-**203**. Treatment of substrate **164** with 10 mol% of onium salt (8*S*,9*R*)-**204** and solid $CsOH{\cdot}H_2O$

[†] *These results were obtained by Dr Abhishek Kothari and are included for completeness.*[61]

resulted in a 1.6 : 1.0 (*anti* : *syn*) mixture of indanes **173**, but these were isolated as racemates (**entry 7**).



Entry	**Conditions**[i,ii]	**dr**[iii]	**ee**[iv]
1[v]	cat. (8*S*,9*R*)-**64**, K_2CO_3 (40% aq.), RT	SM	–
2	cat. (8*S*,9*R*)-**64**, Cs_2CO_3 (s), −15 °C	SM	–
3	cat. (8*S*,9*R*)-**64**, $CsOH{\cdot}H_2O$ (s), −15 °C	2.5 : 1.0	28%
4	cat. (8*S*,9*R*)-**64**, $CsOH{\cdot}H_2O$ (s), −30 °C	2.5 : 1.0	9%
5	cat. (8*S*,9*R*)-**64**, $CsOH{\cdot}H_2O$ (s), −50 °C	SM	–
6	cat. (8*S*,9*R*)-**203**, $CsOH{\cdot}H_2O$ (s), −15 °C	1.8 : 1.0	10%
7	cat. (8*S*,9*R*)-**204**, $CsOH{\cdot}H_2O$ (s), −15 °C	1.6 : 1.0	0%

[i] All reactions were carried out on analytical scale without determining the reaction yield. [ii] Unless otherwise stated, reactions were conducted with the specified catalyst (10 mol%) and base (2 eq.) in PhMe for 24 h at the given temperature. [iii] Determined by analysis of the crude ^1H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] 10 equivalents of base were used.

Table 3.1 – Evaluation of chiral cinchonidinium phase-transfer catalysts

Pleasingly, the feasibility of this project was verified as the employment of catalyst (8*S*,9*R*)-**64** and solid $CsOH{\cdot}H_2O$ delivered *anti*-indane **173** in 28% ee. However, no further improvements in enantioselectivity were observed with modified quaternary ammonium

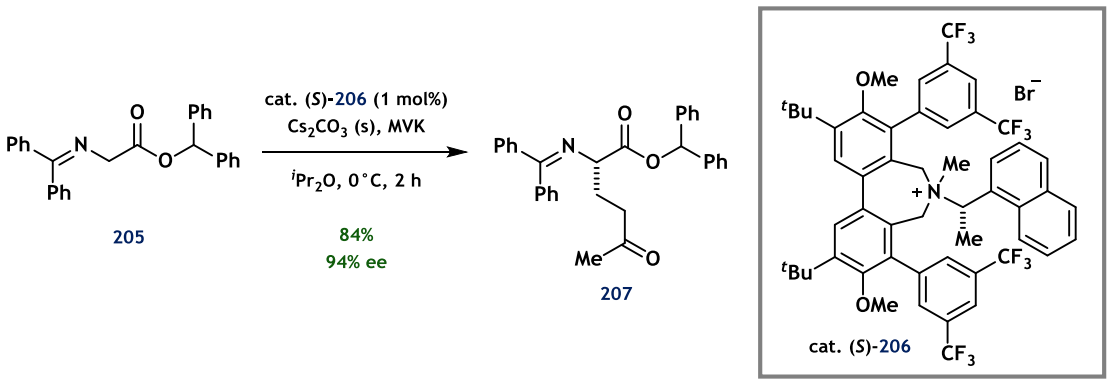
salts (8*S*,9*R*)-**203** or (8*S*,9*R*)-**204**. Consequently, we proceeded to investigate architecturally distinct phase-transfer catalysts in our intramolecular Michael addition reaction.

3.3 A Dibenzazepine-Based Phase-Transfer Catalyst

3.3.1 Catalyst Discovery and Credentials

In an endeavour to diversify the range of chiral phase-transfer catalysts available, Lygo developed the quaternary ammonium salt (*S*)-**206** that incorporates a conformationally labile biphenyl unit.[137] This was achieved through the evaluation of a library of dibenzazepine-based structures, constructed from achiral biphenyls and commercially available secondary amines, which were benchmarked in the asymmetric alkylation of a glycine Schiff base. The optimal catalyst (*S*)-**206** demonstrated remarkable catalytic activity and selectivity in this reaction.

The efficacy of the Lygo catalyst (*S*)-**206** was further established in an asymmetric Michael addition between glycine imine **205** and MVK (**Scheme 3.2**).[138] The starting material **205** was completely consumed in two hours with only 1 mol% of quaternary ammonium salt (*S*)-**206** and afforded an 84% yield of the amino acid derivative **207** in 94% ee.

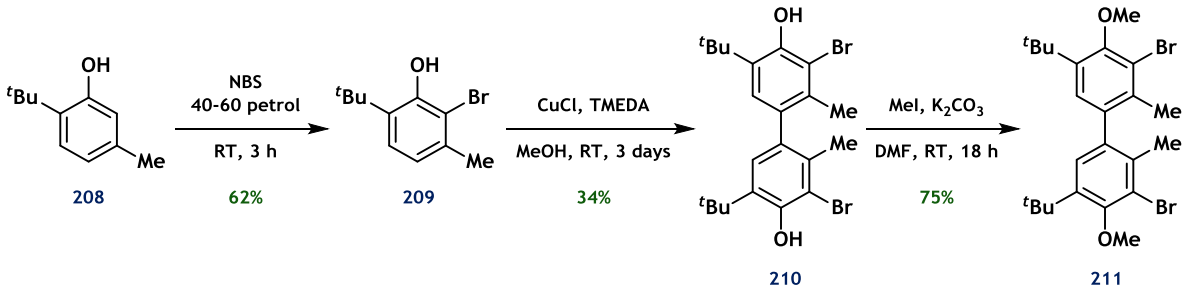


Scheme 3.2 – Asymmetric Michael addition catalyzed by the phase-transfer catalyst (*S*)-**206**[138]

The fantastic levels of stereocontrol exerted by the quaternary ammonium salt (*S*)-**206** encouraged us to assess its ability to improve the enantioselectivity in our 5-*endo*-trig reaction to synthesize optically enriched indane carbocycles.

3.3.2 Synthesis of the Lygo Catalyst (R)-206

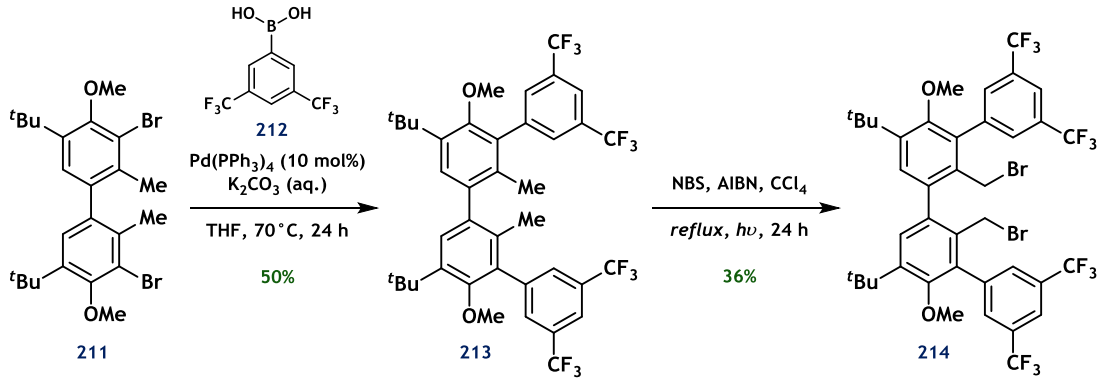
The phase-transfer catalyst (*R*)-**206** is not currently commercially available but can be readily synthesized from inexpensive starting materials. Following the procedures reported by Lygo, phenol **208** was selectively *ortho*-brominated with NBS to deliver arene **209** in 62% yield (**Scheme 3.3**).[139] A subsequent oxidative dimerization mediated by copper(I) chloride and TMEDA produced a moderate yield of the biphenyl **210**. Methylation of the two phenolic oxygens was achieved with methyl iodide and potassium carbonate in DMF to afford intermediate **211** in good yield.



Scheme 3.3 – Synthesis of the key intermediate **211** starting from phenol **208**

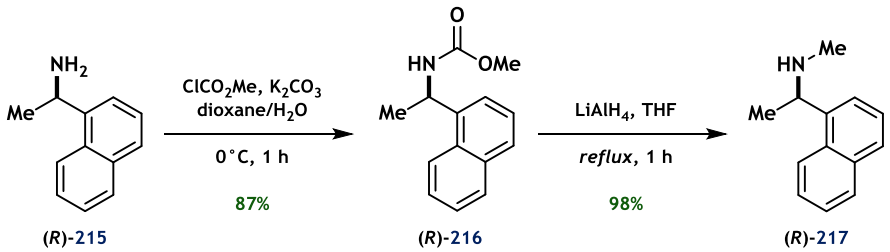
At this stage, the synthesis of the phase-transfer catalyst can diverge, as various aromatic substituents can be appended to biphenyl **211** through a Suzuki-Miyaura protocol. However, through examination of an array of analogous ammonium salts, Lygo established that CF_3-substituted arenes were particularly effective in the asymmetric alkylation of glycine imines.[137] The ensuing cross-coupling was facilitated by 10 mol% of $Pd(PPh_3)_4$ in a biphasic mixture of THF and aqueous K_2CO_3 to produce tetraphenyl **213** in 50% yield

(**Scheme 3.4**). Radical bromination at the benzylic positions was accomplished by irradiating a mixture of NBS and AIBN in carbon tetrachloride to furnish the catalyst precursor **214**.



Scheme 3.4 – Suzuki-Miyaura coupling and radical bromination to synthesize catalyst precursor **214**

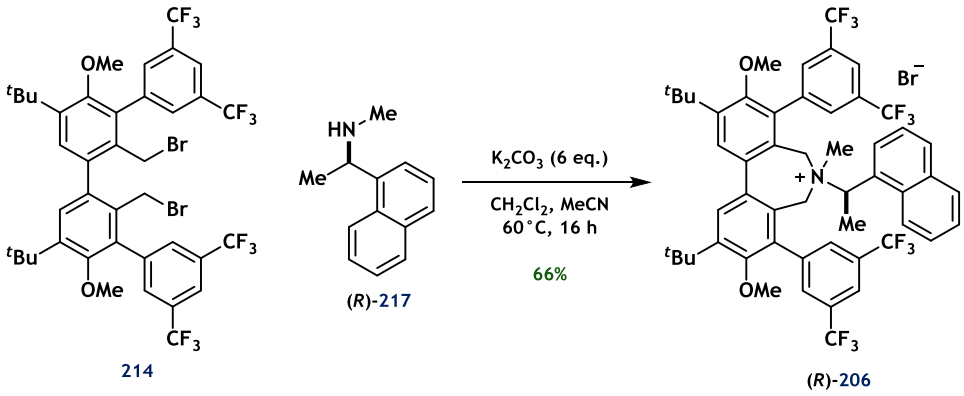
The optically pure secondary amine (*R*)-**217** required to complete the synthesis of catalyst (*R*)-**206** can be produced from the commercially available primary amino-arene (*R*)-**215** (**Scheme 3.5**). The methylcarbamate derivative (*R*)-**216** was generated cleanly in 87% yield by employing methyl chloroformate and potassium carbonate in aqueous dioxane.[140] Subsequent reduction with excess $LiAlH_4$ in refluxing THF provided secondary amine (*R*)-**217** in 98% yield.[141]



Scheme 3.5 – Methylation of amine (*R*)-**215** *via* hydride reduction of carbamate (*R*)-**216**

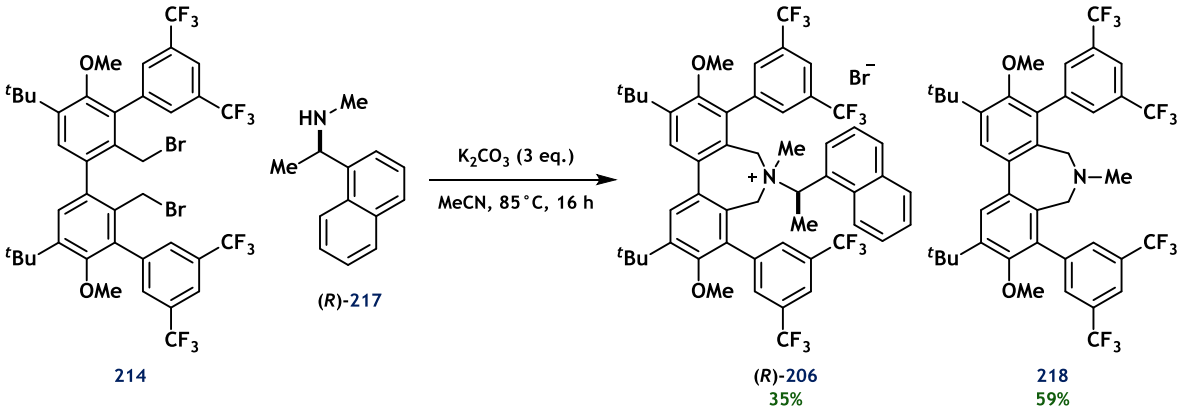
The final step to synthesize the Lygo catalyst (*R*)-**206** unites its precursor **214** with the chiral amine (*R*)-**217** through two sequential S_N2-type displacements (**Scheme 3.6**). However, this *N*-quaternization process was very capricious, with isolated yields varying wildly. A particularly efficacious reaction, which employed Lygo's conditions precisely, generated the

onium salt (*R*)-**206** in 66% yield. This procedure utilized 6 equivalents of potassium carbonate and was conducted at 60 °C for 16 hours.



Scheme 3.6 – Quaternary ammonium salt formation according to Lygo's conditions

In an endeavour to improve the yield and consistency of forming the quaternary ammonium salt (*R*)-**206**, alternative reaction conditions were vetted. In particular, Maruoka has disclosed *N*-quaternization procedures to generate a wide range of novel phase-transfer catalysts.[142] In general, these protocols employed reduced levels of K_2CO_3 and were carried out at 85 °C for 16 hours. The application of these conditions to the Lygo system proved detrimental, as analysis of the crude reaction mixture by ^{1}H NMR indicated the presence of a significant contaminant (**Scheme 3.7**). Following purification, a mere 35% yield of the catalyst (*R*)-**206** was acquired, along with a 59% yield of tertiary amine **218**. The latter can arise by base-induced Hofmann elimination of the ammonium salt (*R*)-**206**, which is a common decomposition pathway for phase-transfer catalysts.[143,144]



Scheme 3.7 – Maruoka's conditions for quaternary ammonium salt preparation

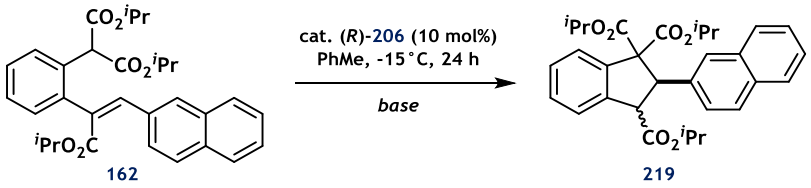
Further adjustments to these conditions with respect to base stoichiometry and the reaction temperature were futile. Therefore, the application of Lygo's original procedure seemed optimal, although stringent control of the temperature and reaction time were crucial for suppressing catalyst degradation *via* Hofmann elimination.

3.3.3 Assessment and Optimization[†]

Following the synthesis of the Lygo catalyst (*R*)-**206** we evaluated its ability to control the enantioselectivity in a model cyclization reaction (**Table 3.2**). Subjecting indane precursor **162** to asymmetric phase-transfer conditions with solid $CsOH{\cdot}H_2O$ in toluene at −15 °C produced a 3.4 : 1.0 (*anti* : *syn*) mixture of indanes **219**, with the major diastereomer being formed in 42% ee (**entry 1**). This was a promising improvement over the *cinchona* alkaloid-derived quaternary ammonium salts, as the related product **173** was only obtained in 28% ee with the optimal catalyst. Further enhancements in selectivity were achieved when a screen of bases was conducted. Evaluation of alternative inorganic hydroxide salts identified NaOH and KOH as superior alternatives to $CsOH{\cdot}H_2O$ (**entries 2-3**). In particular, 2 equivalents of potassium hydroxide under solid-liquid phase-transfer conditions could

[†] *For the full range of optimization performed with the Lygo catalyst (R)-**206** refer to Appendix I, section 7.1.*

generate *anti*-indane **219** in 64% ee. A justification for the observed trend in diastereoselectivity was not apparent for these reactions, but reversible enolization of the indane product is expected in these processes. The metal cation of the base also had a profound effect on reactivity, as no cyclization was observed with $LiOH{\cdot}H_2O$ or $Ba(OH)_2{\cdot}8H_2O$ (**entries 4**-**5**). Similarly, weaker phosphate salts were also unsuitable with only traces of indane **219** materializing (**entries 6**-**7**). Finally, the organo-soluble phosphazene base BEMP was employed under homogeneous conditions to afford a 1.0 : 8.1 (*anti* : *syn*) mixture of diastereomers (**entry 8**). The major isomer of indane **219** was acquired in 62% ee, although full consumption of the starting material was not achieved after 24 hours.



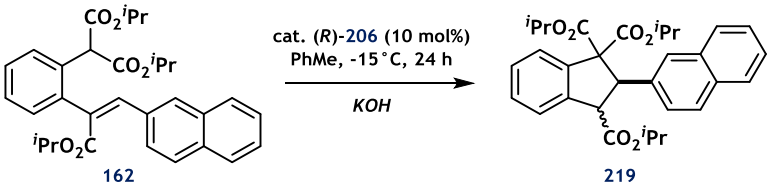
Entry	**Base**[i,ii]	**dr**[iii]	**ee**[iv]
1	$CsOH{\cdot}H_2O$ (s)	3.4 : 1.0	42%
2	NaOH (s)	1.0 : 2.7	62%
3	KOH (s)	1.6 : 1.0	64%
4	$LiOH{\cdot}H_2O$ (s)	SM	–
5	$Ba(OH)_2{\cdot}8H_2O$ (s)	SM	–
6	K_2HPO_4 (s)[v]	SM	–
7	K_3PO_4 (s)[v]	SM[vi]	–
8	BEMP (l)[v]	1.0 : 8.1[vii]	62%

*[i] All reactions were carried out on analytical scale without determining the reaction yield. [ii] Unless otherwise stated, reactions were conducted with catalyst (R)-**206** (10 mol%) and the specified base (2 eq.) in PhMe for 24 h at −15 °C. [iii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] One equivalent of base was used. [vi] Trace product observed by analysis of the crude ^{1}H NMR spectrum. [vii] Reaction conversion was 72% by analysis of the crude ^{1}H NMR spectrum (no internal standard was added).*

Table 3.2 – Base screen with the Lygo catalyst (*R*)-**206**

The evaluation of an assortment of bases with the Lygo catalyst (*R*)-**206** ascertained that KOH was optimal in this system. Subsequently, we investigated the impact of varying the stoichiometry of this potassium salt, whilst also comparing solid-liquid and liquid-liquid phase-transfer conditions (**Table 3.3**). Increasing the quantity of solid KOH from two to five equivalents had a negligible impact on the enantioselectivity, but improved the reaction rate significantly (**entries 1**-**2**). On the other hand, reducing the levels of potassium hydroxide proved beneficial – with sub-stoichiometric quantities favouring the opposite diastereomer – as *syn*-indane **219** was obtained in 73% ee (**entries 3**-**4**). Switching to aqueous

base provided a more convenient protocol, which despite slower reaction rates, could maintain good levels of stereocontrol irrespective of the quantity added (**entry 5**).



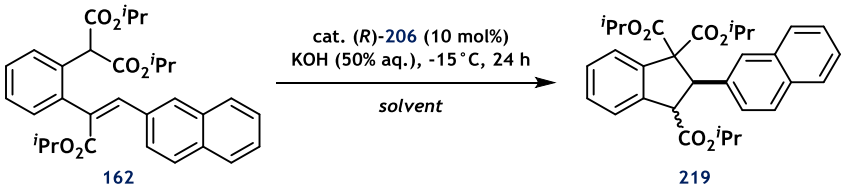
Entry	Equivalents of KOH[i,ii]	dr[iii]	ee[iv]
1	2.0 (s)	1.6 : 1.0	64%
2	5.0 (s)[v]	3.0 : 1.0	65%
3	1.0 (s)	2.2 : 1.0	69%
4	0.5 (s)	1.0 : 3.5	73%
5	10 (50% aq.)	3.8 : 1.0	71%

*[i] All reactions were carried out on analytical scale without determining the reaction yield. [ii] Unless otherwise stated, reactions were conducted with catalyst (R)-**206** (10 mol%) and KOH in PhMe for 24 h at −15 °C. [iii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] Reaction was complete in 3 h by TLC.*

Table 3.3 – Optimizing the stoichiometry of KOH

The ease of handling concentrated aqueous base, rather than milligram quantities of hygroscopic powdered KOH, persuaded us to employ it for future optimization. Accordingly, the influence of the organic solvent on the stereoselectivity of the reaction was also investigated (**Table 3.4**). Since the substrate anion cyclizes in the hydrocarbon phase, it was crucial that a suitable reaction medium was selected to coerce the formation of an intimately associated ion-pair. For example, when toluene was replaced by *m*-xylene a decline in enantiomeric excess from 71% to 52% was observed (**entries 1-2**). The employment of lipophilic ethereal solvents offered modest increases in both diastereo- and enantioselectivity (**entries 3-4**). In an attempt to probe the dependence of stereocontrol upon the solvent polarity, several reactions were conducted with varying amounts of hexane

(**entries 5**-**7**). As anticipated, poor solubility was a major factor in a procedure performed with absolute hexane and despite good levels of enantiocontrol the reaction only reached 73% conversion after 48 hours (**entry 5**).



Entry	**Solvent**[i,ii]	**dr**[iii]	**ee**[iv]
1	PhMe	3.8 : 1.0	71%
2	*m*-xylene	3.4 : 1.0	52%
3	MTBE	5.6 : 1.0	70%
4	$^{i}Pr_2O$	7.9 : 1.0	75%
5	hexane[v]	1.7 : 1.0	79%
6	PhMe : hexane (1 : 1)	5.6 : 1.0	76%
7	CH_2Cl_2 : hexane (1 : 1)	3.2 : 1.0	45%

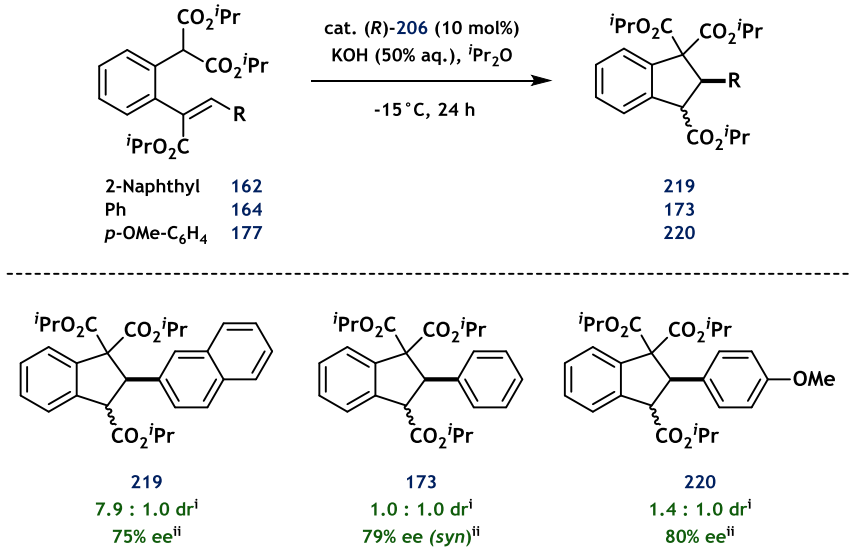
*[i] All reactions were carried out on analytical scale without determining the reaction yield. [ii] Unless otherwise stated, reactions were conducted with catalyst (R)-**206** (10 mol%) and KOH (50% aq.) (10 eq.) in the specified solvent for 24 h at −15 °C. [iii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] Reaction conversion was 73% by analysis of the crude ^{1}H NMR spectrum after 48 h (no internal standard was added).*

Table 3.4 – Solvent screen with 50% aqueous KOH and the Lygo catalyst (*R*)-**206**

By introducing toluene into this system, in a 1 : 1 ratio, reactivity was restored to afford *anti*-indane **219** in a mildly compromised 76% ee (**entry 6**). The same proportions of dichloromethane and hexane were less effective, as a significant drop in enantioselectivity was observed (**entry 7**).

Overall, extensive optimization of the reaction parameters determined that high diastereo- and enantioselectivities were attainable with the Lygo catalyst (*R*)-**206** in a

biphasic mixture of aqueous KOH and $^{i}Pr_2O$. The generality of these conditions was demonstrated by the synthesis of three optically enriched indanes (**173**, **219**-**220**) (**Scheme 3.8**). The parent substrate **164** and its methoxy-substituted analogue **177** were both cyclized efficiently to afford products **173** and **220** with similar levels of enantioenrichment. Unfortunately, poor control over the diastereoselectivity was encountered with these two examples compared to the corresponding naphthylated indane **219**.



[i] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [ii] ee for major diastereomer as determined by chiral HPLC.

Scheme 3.8 – Representative examples of enantioenriched indanes generated with the Lygo catalyst (*R*)-**206**

The potential to further enhance the observed degrees of stereocontrol by examining additional bases and solvents seemed dubious. Therefore, we concluded that modification of the phase-transfer catalyst architecture was necessary in order to provide a highly enantioselective route towards densely functionalized indane carbocycles.

3.3.4 *Attempts to Synthesize Derivatives of the Lygo Catalyst (R)-206*

The original strategy devised by Lygo for the development of dibenzazepine-based phase-transfer catalysts focused on a flexible synthetic route that allowed for late-stage structural modification.[137,139] In particular, introducing alternative aromatic substituents to the biphenyl scaffold was demonstrated to influence the observed stereoselectivities significantly. However, the utilization of large flanking aryl groups was not embraced in the initial library of catalysts generated. The application of sterically demanding substituents in related asymmetric anion-binding processes has encountered considerable success.[145] Therefore, we rationalized that the presence of anthracenyl derivatives or a triphenylsilyl group could exert enhanced control over the enantioselectivity in our 5-*endo*-trig cyclization process (**Figure 3.1**).

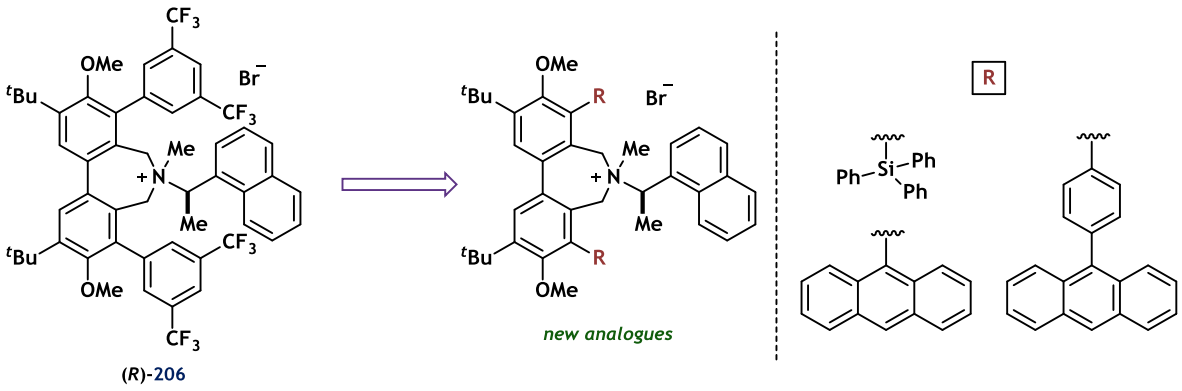


Figure 3.1 – Proposed new analogues derived from the Lygo catalyst (*R*)-**206**

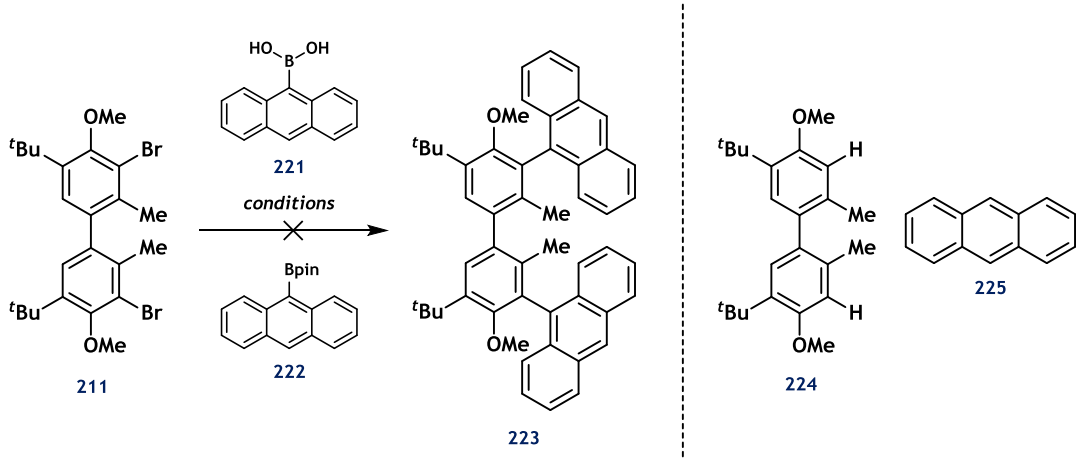
Accordingly, we endeavoured to synthesize three new analogues derived from the Lygo catalyst (*R*)-**206** that incorporated these larger functionalities.

3.3.4.1 Suzuki-Miyaura Coupling

Initially, we investigated a cross-coupling procedure to introduce an anthracenyl group on to the biaryl scaffold **211** (**Table 3.5**). Employing boronic acid **221** with the

Suzuki-Miyaura protocol originally disclosed by Lygo returned only starting material after 16 hours (**entry 1**). A related set of conditions that employed a refluxing mixture of ethanol and toluene were also assessed, but resulted in protodehalogenation of biaryl **211** as well as formation of anthracene **225** from the decomposition of boronic acid **221** (**entry 2**).[146] A similar outcome was observed with a combination of the adamantyl-based ligand cataCXium® A **166** and palladium(II) acetate, which utilized CsF to promote transmetalation of the boron species (**entry 3**).[91] In general, boronic acids are prone to dehydration to form oligomeric species, which complicates their isolation and purification.[147] Therefore, we evaluated the more stable pinacol derivative **222**, which can be chromatographed to afford a single entity.[†] A catalytic system generated from $Pd(OAc)_2$ (20 mol%) and P(*o*-tolyl)$_3$ **167** (80 mol%) was evaluated with boronic ester **222**, but no coupling to deliver the desired product **223** was observed (**entry 4**).[148] Finally, we assessed the Buchwald ligand SPhos **226**, which has exhibited great efficacy in the synthesis of hindered biaryls.[149] Utilizing the optimal coupling conditions reported for phosphine **226**, with potassium phosphate in refluxing toluene, merely returned unreacted biaryl **211** after 16 hours (**entry 5**).

[†] *For a comprehensive discussion regarding the synthesis of anthracenyl boronic acid derivatives refer to section 3.3.5.3.*



Entry[i]	Conditions[ii,iii]	Outcome[iv]
1[139]	$Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (2 M aq.), boronic acid **221**, THF, 70 °C	NR
2[146]	$Pd(PPh_3)_4$ (10 mol%), Na_2CO_3 (2 M aq.), boronic acid **221**, PhMe/EtOH, 115 °C	Biaryl **211**, biphenyl **224**, anthracene **225**
3[91]	$Pd(OAc)_2$ (5 mol%), cataCXium® A **166** (10 mol%), CsF (6 eq.), boronic acid **221**, PhMe, 90 °C	Biaryl **211**, biphenyl **224**, anthracene **225**
4[148]	$Pd(OAc)_2$ (20 mol%), P(*o*-tolyl)$_3$ **167** (80 mol%), K_3PO_4 (10 eq.), boronic ester **222**, DMF/H_2O, 100 °C	Biaryl **211**, biphenyl **224**, anthracene **225**
5[149]	$Pd(OAc)_2$ (4 mol%), SPhos **226** (8 mol%), K_3PO_4 (3 eq.), boronic ester **222**, PhMe, 110 °C	NR

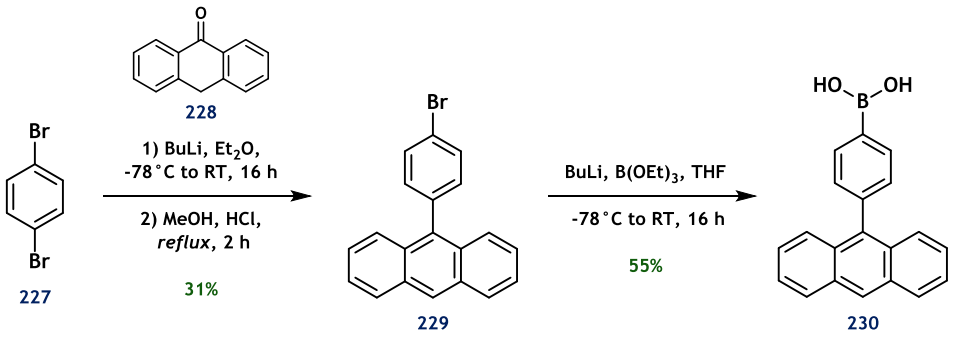
*[i] References for procedures obtained from the literature are given. [ii] The reaction conditions are as stated with biaryl **211** (1 eq.) and boronic acid **221** (3 eq.) or boronic ester **222** (3 eq.). Reactions were performed for 16 hours. [iii] Solvents were degassed prior to use. [iv] As determined by analysis of the crude ^{1}H NMR spectrum, TLC and MS.*

Table 3.5 – Suzuki-Miyaura coupling conditions attempted to synthesize product **223**

The poor reactivity observed in this Suzuki-Miyaura reaction can be rationalized on the basis of the sterically demanding environment around the reactive centres of both coupling partners. The by-products obtained from these procedures, biphenyl **224** and anthracene **225**, are a testament to the challenging nature of this carbon-carbon bond forming step.

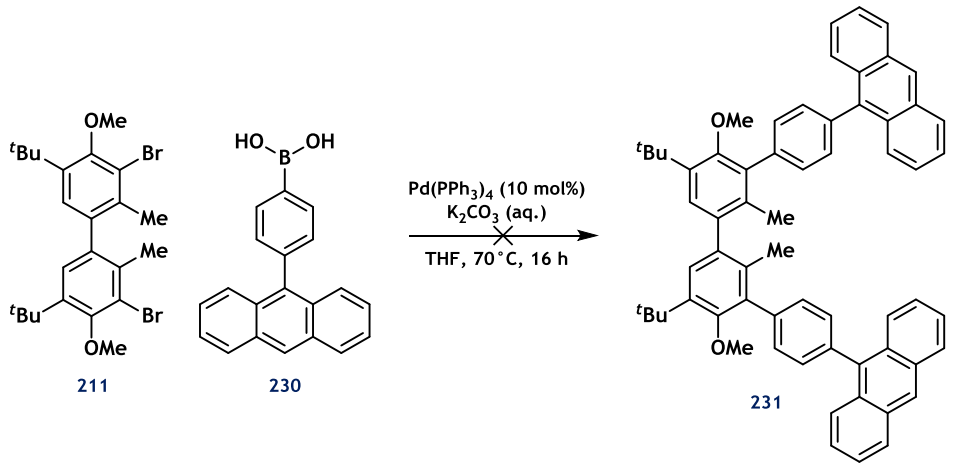
Following repeated unproductive attempts to append anthracenyl units to the catalyst backbone, a radially extended aryl system was explored. We reasoned that positioning the

bulky aromatic ring remote from the boronic acid group could re-establish the desired reactivity. The requisite boronic acid **230** was synthesized in three straightforward steps from 1,4-dibromobenzene **227** (**Scheme 3.9**). Trapping of the aryl anion created by lithium-halogen exchange with anthrone **228**, followed by acid-mediated dehydration, produced arene **229** in 31% yield.[150] Subsequent formation of the boronic acid **230** was accomplished in good yield employing butyllithium and triethyl borate.



Scheme 3.9 – Synthesis of boronic acid **230**

For the cross-coupling reaction between biaryl **211** and boronic acid **230** we reverted back to Lygo's reported protocol (**Scheme 3.10**).[139] These conditions utilized 10 mol% of $Pd(PPh_3)_4$ in a biphasic mixture of aqueous K_2CO_3 and THF at 70 °C, but after 24 hours product **231** was not observed.

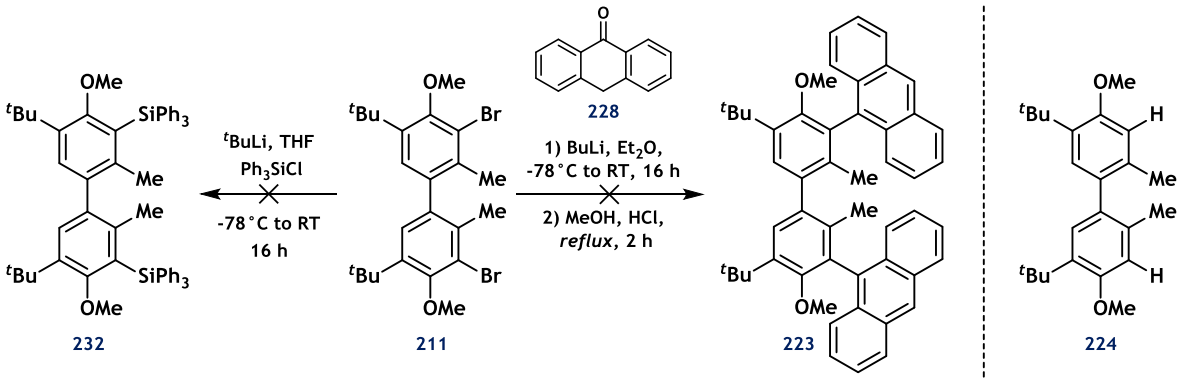


Scheme 3.10 – Attempted cross-coupling with boronic acid **230**

The difficulties associated with introducing bulky aromatic substituents to the Lygo catalyst scaffold prompted us to pursue alternative methods for achieving this objective.

3.3.4.2 Lithium-Halogen Exchange

The metal-halogen exchange procedure employed to generate arene **229** seemed to be a pragmatic strategy, which is distinct from palladium-mediated cross-couplings. Accordingly, we subjected biaryl **211** to the conditions applied previously with butyllithium and anthrone **228**, but only debrominated material **224** was isolated (**Scheme 3.11**).[150] Similarly, a protocol comprising double lithium-halogen exchange triggered by ^{t}BuLi and quenching of the resulting dianion with chlorotriphenylsilane was attempted to produce arene **232**.[151] Unfortunately, only protonation of the lithiated species to form biphenyl **224** was detected, despite conducting the reaction under strictly anhydrous conditions.



Scheme 3.11 – Attempted formation of arenes **223** and **232** *via* lithium-halogen exchange reactions

Overall, efforts to introduce large sterically demanding substituents to the Lygo catalyst manifold by two distinct methods were futile. The dibromoarene **211** proved to be a difficult intermediate to transform in the manner we had originally envisaged.

3.3.4.3 *Increasing the Alkyl Chain Length*

Due to the challenges associated with modifying the biaryl unit, we opted to investigate subtler refinements to the Lygo catalyst (*R*)-**206**, in particular, altering the chiral secondary amine component. Maruoka has previously demonstrated that extending the pendant *N*-alkyl chain can significantly impact the enantioselectivity of a reaction.[142,152,153] This concept was not addressed in Lygo's original library of catalysts, with all of the ammonium salts bearing methylated nitrogen cations. Therefore, we proposed that the more lipophilic catalyst (*R*)-**233**, which encompasses a longer alkyl group, would improve the extraction rate of the substrate anion into the organic phase (**Figure 3.2**).

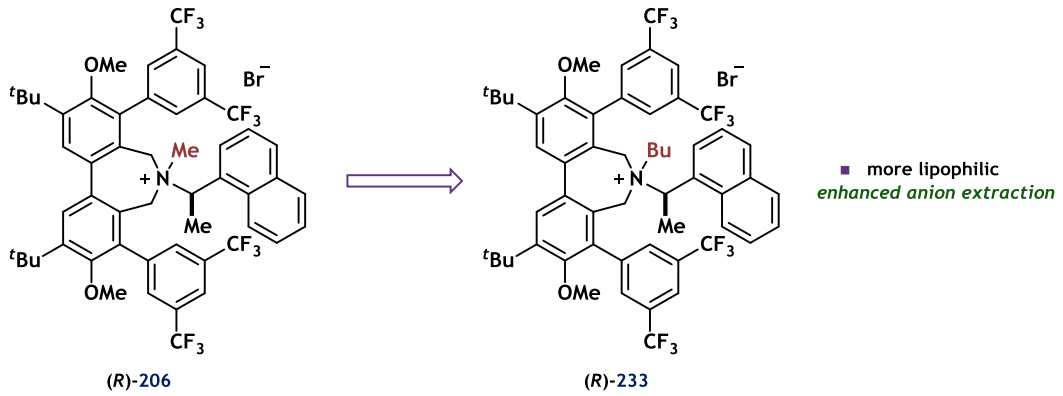
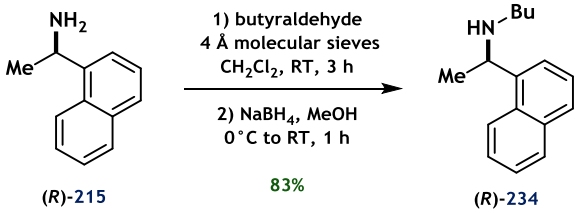


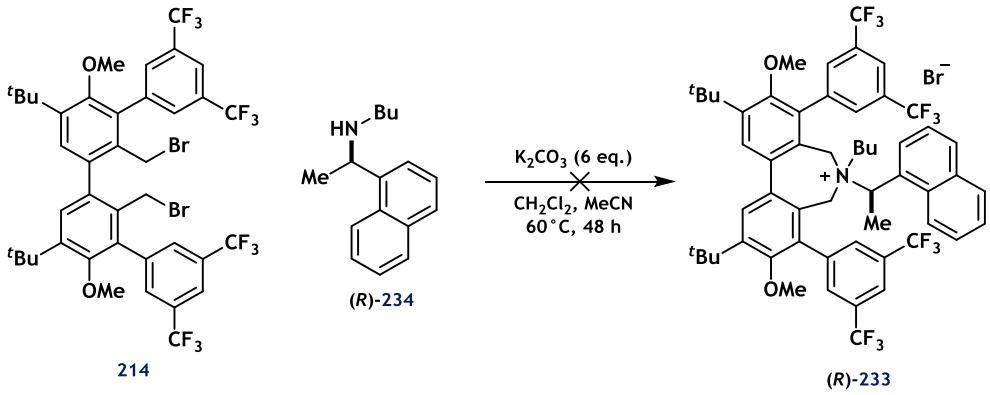
Figure 3.2 – Modifying the Lygo catalyst (*R*)-**206** by incorporating an extended alkyl chain

To synthesize the requisite butylated ammonium salt (*R*)-**233** we first opted to generate the secondary amine (*R*)-**234** and then subsequently employ it in a quaternization procedure. The chiral aminoarene (*R*)-**234** was created through a two-step reductive amination protocol, which commenced with imine formation between amine (*R*)-**215** and butyraldehyde (**Scheme 3.12**). After exchanging the solvent for methanol, reduction with sodium borohydride progressed efficiently to afford the desired product (*R*)-**234** in 83% yield.



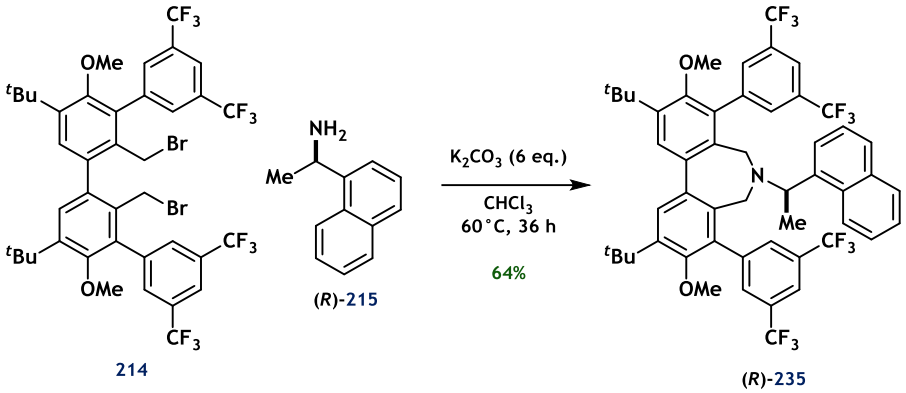
Scheme 3.12 – Two step reductive amination to synthesize secondary amine (*R*)-**234**

Consequently, we examined the synthesis of the butylated catalyst analogue (*R*)-**233** under the previously utilized conditions (**Scheme 3.13**). After 48 hours at 60 °C with excess K_2CO_3 only minor conversion to the ammonium salt (*R*)-**233** was observed by ^{1}H NMR and TLC. The traces of catalyst (*R*)-**233** that were formed could not be separated from the chiral amine (*R*)-**234** *via* silica gel chromatography or recrystallization.



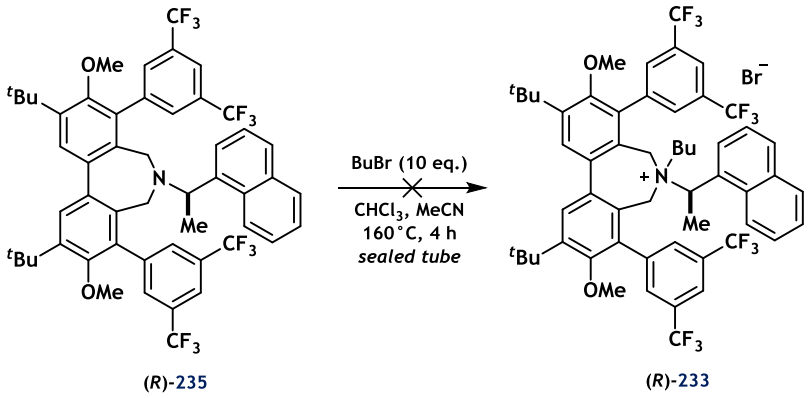
Scheme 3.13 – Attempted synthesis of the butylated catalyst analogue (*R*)-**233**

Due to the poor levels of reactivity observed with this approach towards the modified Lygo salt (*R*)-**233**, we considered an alternative strategy. This entailed combining the chiral aminoarene (*R*)-**215** directly with the catalyst backbone **214** to form the tertiary amine (*R*)-**235** (**Scheme 3.14**). This reaction proceeded effectively with excess potassium carbonate in chloroform at 60 °C to deliver the product (*R*)-**235** in 64% yield.



Scheme 3.14 – Synthesis of the tertiary amine (*R*)-**235**

The ensuing quaternization procedure was then conducted with tertiary amine (*R*)-**235** and surplus butyl bromide (**Scheme 3.15**). The harshest conditions we employed involved heating the reaction to 160 °C in a sealed tube, but only starting material or decomposition products were obtained. This result implied that the nitrogen lone pair was severely sterically shielded within the structure and, therefore, the alkylating agent was unable to reach it.



Scheme 3.15 – Attempted quaternization of amine (*R*)-**235** with butyl bromide

Two different approaches for synthesizing the butylated analogue (*R*)-**233** of the Lygo catalyst (*R*)-**206** were examined but both were unsuccessful. In general, under the reaction conditions we screened these systems were highly inert and unable to tolerate increased steric bulk around the nitrogen atom.

3.3.4.4 *A Trifluoromethyl-Stabilized Catalyst*

The principal route for quaternary ammonium salts to decompose involves a Hofmann elimination reaction.[143,144] This base-induced process has often plagued phase-transfer systems by the creation of unwanted side products as well as reducing the available levels of catalyst. This degradation pathway proved problematic during the synthesis of the Lygo salt (*R*)-**206**, whereby attempts to improve starting material consumption led to enhanced rates of product decomposition. However, we rationalized that substitution of the stereogenic methyl group with a CF_3 derivative would block Hofmann elimination due to the absence of β-hydrogens (**Figure 3.3**). This stabilized catalyst (*S*)-**236** could also benefit from stronger substrate anion binding affinities due to its enhanced electrostatic positive charge.

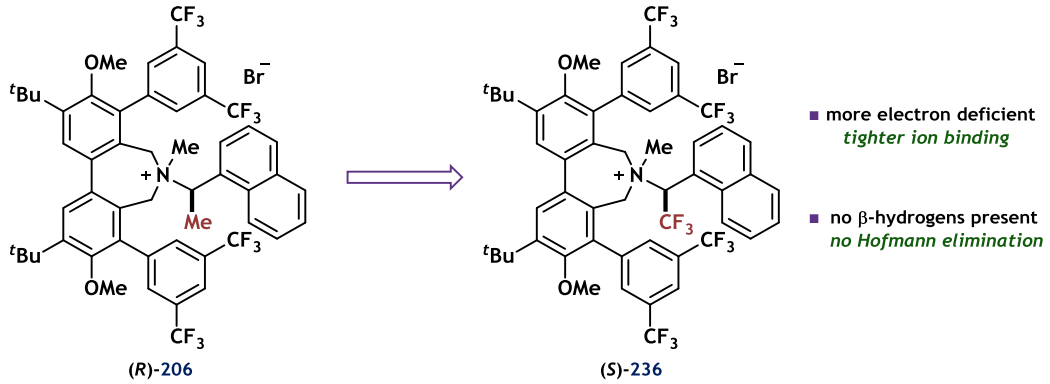
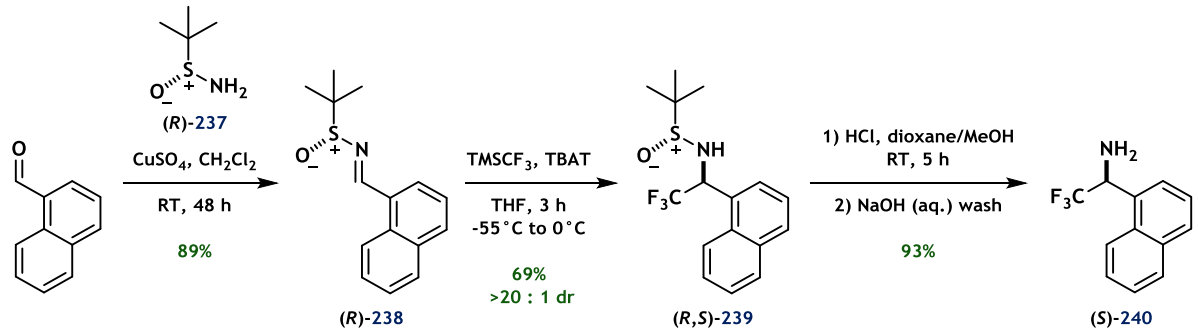


Figure 3.3 – Design of a trifluoromethyl-stabilized catalyst derivative

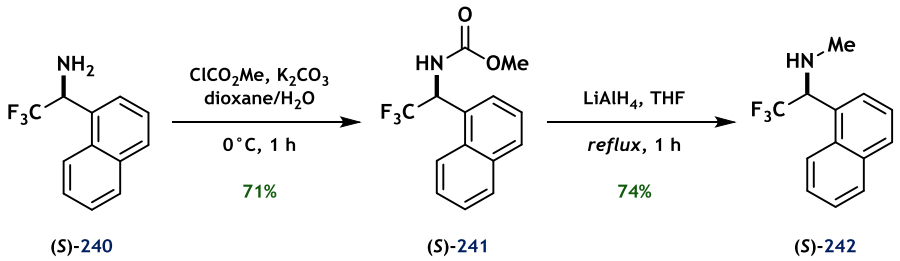
The chiral fluorinated amine (*S*)-**242** required for the synthesis of catalyst (*S*)-**236** is not commercially available. However, a methodology developed by Olah permitted a highly stereoselective synthesis of the trifluoromethylated aminoarene (*S*)-**240** (**Scheme 3.16**).[154] Beginning from 1-naphthaldehyde and sulfinamide *(R)*-**237** the corresponding optically pure sulfinylimine *(R)*-**238** was generated in 89% yield employing $CuSO_4$ as a desiccant. A highly diastereoselective nucleophilic trifluoromethylation was accomplished with a mixture of

TBAT and $TMSCF_3$ to provide the desired product *(R,S)*-**239** in 69% yield. This was followed by acid-mediated hydrolysis of the sulfinamide, which after a basic workup afforded the primary amine (*S*)-**240** in excellent yield.



Scheme 3.16 – Synthesis of the primary amine (*S*)-**240** through a diastereoselective trifluoromethylation

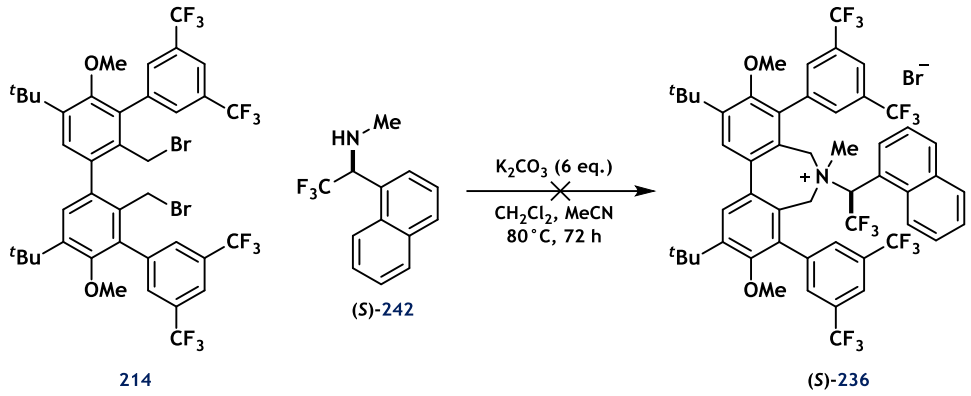
Conversion of the primary amine (*S*)-**240** to its secondary methylated analogue (*S*)-**242** was achieved as previously described (**Scheme 3.17**). Carbamate formation with methyl chloroformate in aqueous dioxane produced the desired product (*S*)-**241** in good yield. Subsequent reduction with lithium aluminium hydride in refluxing THF delivered the fluorinated chiral secondary amine (*S*)-**242** in 74% yield.



Scheme 3.17 – Methylation of amine (*S*)-**240** *via* hydride reduction of carbamate (*S*)-**241**

Consequently, we examined the quaternization reaction to synthesize the fluorinated analogue (*S*)-**236** of the Lygo catalyst (*R*)-**206** (**Scheme 3.18**). Since Hofmann elimination was not feasible for the ammonium salt (*S*)-**236**, we employed conditions that were likely to ensure good levels of conversion. A mixture of the catalyst backbone **214** and the chiral

amine (*S*)-**242** were heated in the presence of excess potassium carbonate at 80 °C for 72 hours. After this time, analysis of the crude reaction mixture indicated only the existence of unreacted starting materials, with no evidence of the quaternary ammonium salt (*S*)-**236**. Potentially, the electron-withdrawing capacity of the CF_3 group rendered the amine functionality less nucleophilic and unreactive in this system.



Scheme 3.18 – Attempted synthesis of the trifluoromethyl catalyst analogue (*S*)-**236**

In conclusion, endeavours to synthesize new derivatives of the Lygo catalyst (*R*)-**206** were fraught with difficulties, which prevented the generation of the intended quaternary ammonium salts. The principal reason for the poor reactivity in this system was ascribed to the sterically demanding nature of the catalyst architecture. Therefore, future modifications to the Lygo manifold would necessitate alterations that do not stray significantly from the original structure.

3.3.5 A Simplified Catalyst Architecture[†]

The endeavours to fine-tune the Lygo catalyst structure (*R*)-**206** in order to augment the enantioselectivity in our 5-*endo*-trig reaction were met with widespread adversities. We

[†] *The designations provided for these phase-transfer catalysts are arbitrary, but in general are elegant old-fashioned ladies' names.*

hypothesized that the extensive substitution on the biphenyl core of the ammonium salt (*R*)-**206** was responsible for these outcomes. Therefore, we reasoned that a simpler motif with less "organic shrubbery" would tolerate modification more readily. Maruoka has previously demonstrated that conformationally flexible *N*-spiro C_2-symmetric quaternary ammonium cations, which incorporate achiral biaryl units, are efficient and highly selective phase-transfer catalysts.[155] Accordingly, we exploited this concept to generate new onium salts that merged a configurationally labile biaryl scaffold with the readily accessible secondary amine (*R*)-**217**, originally disclosed by Lygo, as a replacement for the chiral binaphthyl component of the Maruoka catalyst (**Figure 3.4**). This strategy would spawn new, inexpensive and straightforward to synthesize quaternary ammonium salts that could improve upon previous incarnations.

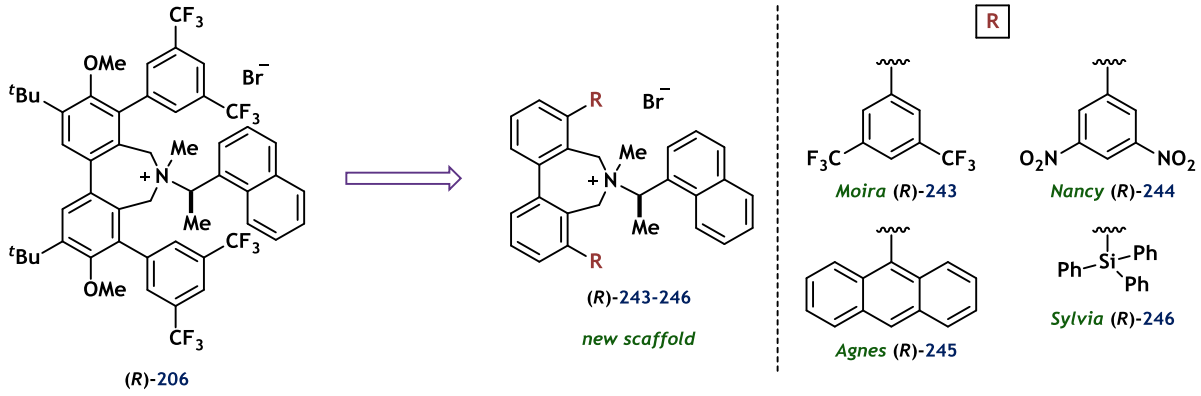
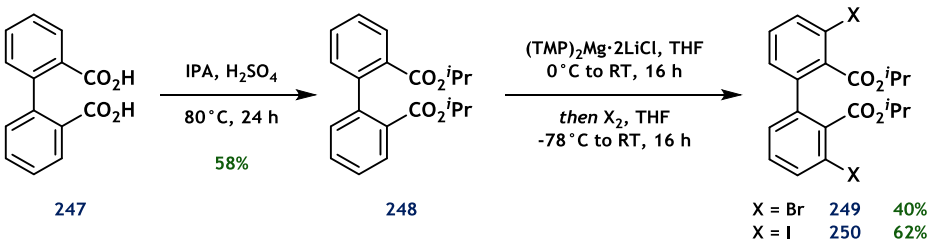


Figure 3.4 – A new streamlined catalyst architecture

The simplified biaryl core could potentially allow for the introduction of bulky substituents such as anthracenyl or triphenylsilyl units. Furthermore, a catalyst bearing dinitroarene groups would probe the effectiveness of electron-deficient flanking aromatic species, which are prevalent in this field.[131,132] However, initial investigations sought to benchmark these new designs by synthesizing Moira (*R*)-**243**, which would allow a direct comparison with the Lygo ammonium salt (*R*)-**206**.

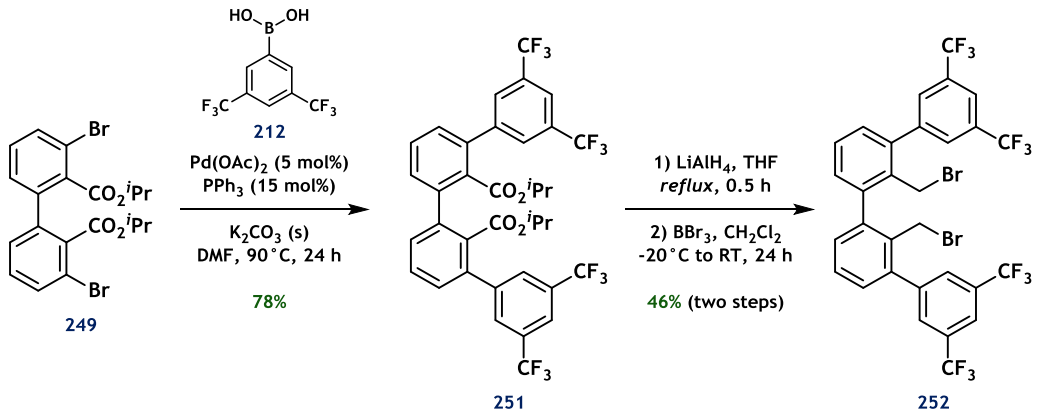
3.3.5.1 Moira

The synthesis of the biaryl scaffold was adapted from procedures that had been previously reported by Maruoka.[155] The first step involved vitriolic esterification of diphenic acid **247** to produce diester **248** in 58% yield (**Scheme 3.19**). Installation of the two adjacent halogen atoms was accomplished by employing Knochel's *ortho*-magnesiation protocol.[156,157] This methodology has demonstrated exceptional functional group tolerance in a number of systems and represents a complementary approach to lithium-based procedures. Accordingly, the biphenyl substrate **248** was treated with freshly prepared $(TMP)_2Mg{\cdot}2LiCl$ in THF to trigger an ester-directed double *ortho*-deprotonation. The resulting magnesiated arene was quenched with either bromine or iodine at −78 °C to afford halogenated biaryls **249**-**250** in 40% and 62% yield respectively (**Scheme 3.19**).



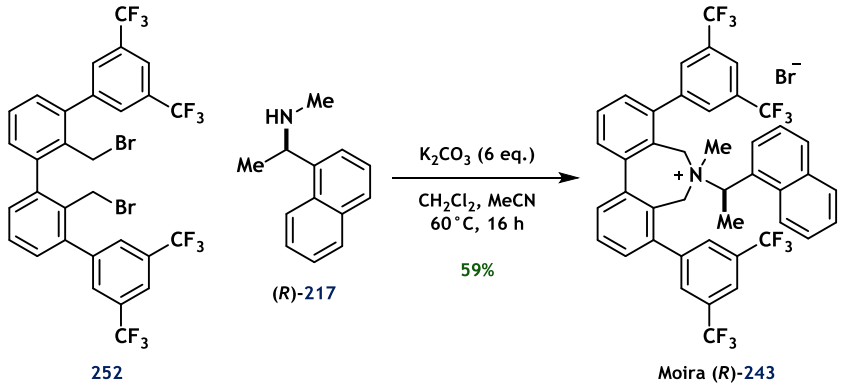
Scheme 3.19 – Halogenation of the biphenyl scaffold by *ortho*-magnesiation

A Suzuki-Miyaura cross-coupling between dibromoarene **249** and boronic acid **212** was performed with $Pd(OAc)_2$ and PPh_3 in the presence of K_2CO_3 to afford the product **251** in 78% yield (**Scheme 3.20**).[158] Subsequent reduction of both ester groups by $LiAlH_4$ in refluxing THF was followed by direct formation of the alkyl bromide species **252** with BBr_3 in dichloromethane.[159,160] The latter product was isolated in 46% yield over these two steps and only a total of five reactions were required to synthesize penultimate substrate **252** that leads to our new phase-transfer catalyst, Moira (*R*)-**243**.



Scheme 3.20 – Suzuki-Miyaura coupling followed by reduction and bromination

Previous research towards synthesizing derivatives of the Lygo catalyst (*R*)-**206** has highlighted the propensity for related ammonium salts to undergo Hofmann elimination. Therefore, we cautiously employed the mildest and most consistent conditions we had established for creating quaternary cations of this type. Hence, biaryl **252** and chiral secondary amine (*R*)-**217** were carefully heated in the presence of excess K_2CO_3 for 16 hours to afford Moira (*R*)-**243** in 59% yield (**Scheme 3.21**).



Scheme 3.21 – Synthesis of the phase-transfer catalyst (*R*)-**243**

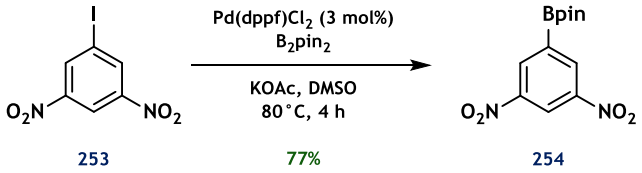
The generation of the quaternary ammonium salt (*R*)-**243** was relatively straightforward and would function as a good benchmark for comparing against the original Lygo manifold (*R*)-**206**. Following the success of this sequence we investigated the synthesis of different

catalyst analogues that incorporated alternative functionalities appended to the biphenyl core.

3.3.5.2 Nancy

The initial library of phase-transfer catalysts created by Lygo emphasized the importance of additional aromatic substitution on the biphenyl scaffold for ensuring high levels of stereocontrol in biphasic reactions.[137] The optimal arene in this array was established to comprise two trifluoromethyl groups and we considered that its effectiveness may stem from its electron-withdrawing capacity. To probe this theory, we designed the nitro analogue (*R*)-**244** (Nancy) to amplify any favourable π-π interactions that were potentially vital for binding the substrate anion.

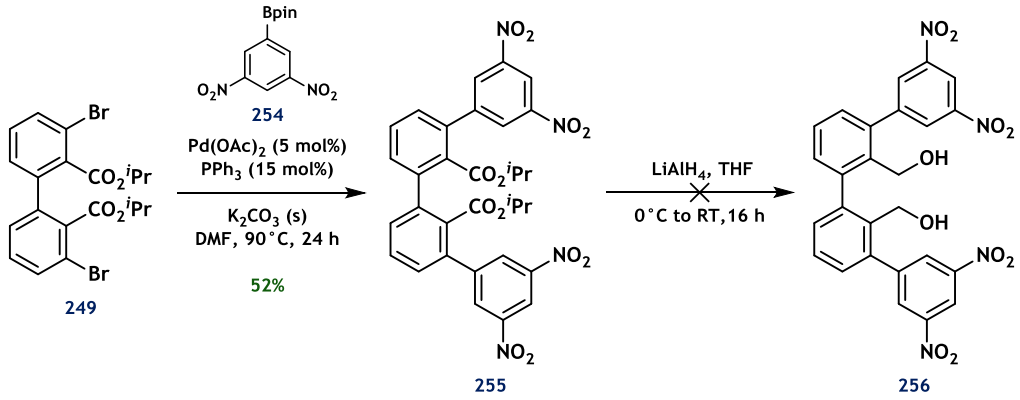
The requisite boronic ester **254** was synthesized by Miyaura borylation of iodoarene **253** with bis(pinacolato)diboron (**Scheme 3.22**).[161] This reaction utilized 3 mol% of $Pd(dppf)Cl_2$ and KOAc in DMSO at 80 °C to afford the desired product **254** in 77% yield.



Scheme 3.22 – Miyaura borylation of dinitroarene **253**

The subsequent Suzuki-Miyaura coupling was conducted as before with dibromoarene **249** and boronic ester **254** (**Scheme 3.23**). The active catalytic species was generated *in situ* from $Pd(OAc)_2$ and PPh_3 in DMF to produce the quaterphenyl **255** in 52% yield.[158] Reduction of this intermediate with $LiAlH_4$ in THF resulted in the instantaneous formation of an insoluble precipitate suspended in a black solution. Analysis of the reaction mixture by

^{1}H NMR and MS suggested that the desired alcohol **256** was not present, but the starting material had been fully consumed. The formation of a polymeric diazo compound is one possible explanation for this outcome.[162]



Scheme 3.23 – Suzuki-Miyaura coupling and an unsuccessful double ester reduction

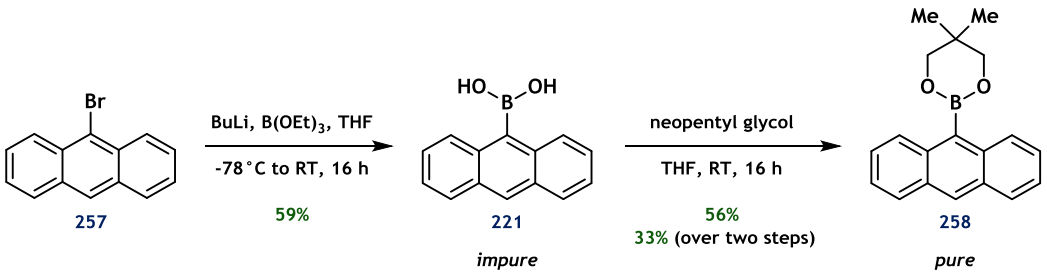
This unforeseen reactivity prompted us to investigate alternative aromatic motifs bearing more passive functionalities that would be appropriate for our synthetic route.

3.3.5.3 Agnes

Our initial strategy for enhancing the Lygo catalyst (*R*)-**206** focused on introducing large aromatic substituents to the biphenyl backbone. However, efforts to achieve this modification were wholly unsuccessful owing to the sterically demanding nature of both components. We reasoned that this transformation would be more productive with a less substituted biphenyl core; hence we attempted to construct the phase-transfer catalyst designated as Agnes (*R*)-**245**.

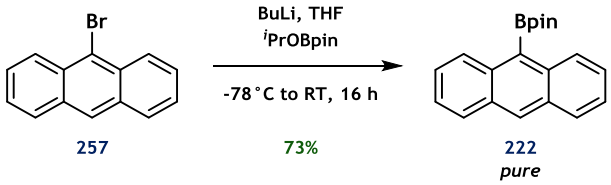
The required anthracenyl boronic acid **221** was synthesized from 9-bromoanthracene **257** by lithium-halogen exchange followed by quenching of the lithiated arene with triethyl borate (**Scheme 3.24**). The resulting product **221** was often contaminated by anthracene **225** and oligomeric species stemming from dehydration.[147] Purification to remove these

by-products was challenging and resulted in greatly reduced yields. Conversion of the boronic acid **221** to its neopentyl glycol ester **258** permitted the isolation of pure material, albeit in 33% yield starting from 9-bromoanthracene **257**.



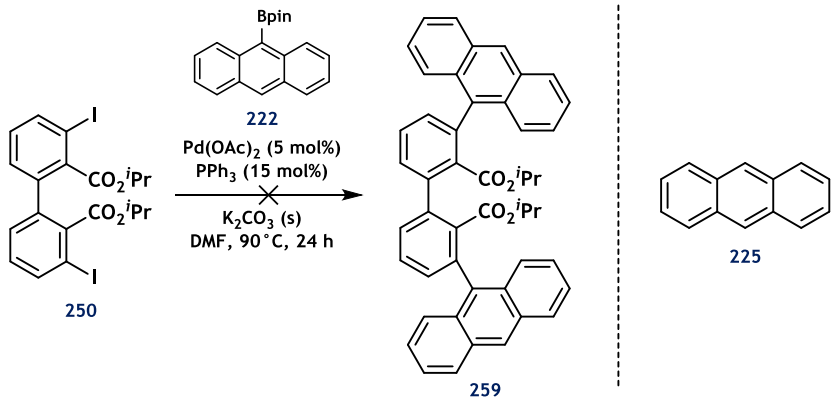
Scheme 3.24 – Generation of the anthracenyl boronic acid **221** and its conversion to neopentyl glycol ester **258**

Direct formation of the pinacol boronic ester **222** was established to be a more efficient route to the required coupling partner (**Scheme 3.25**). Trapping of the carbanion arising from lithium-bromine exchange with ^{i}PrOBpin afforded the product **222** as a single entity in 73% yield.[163]



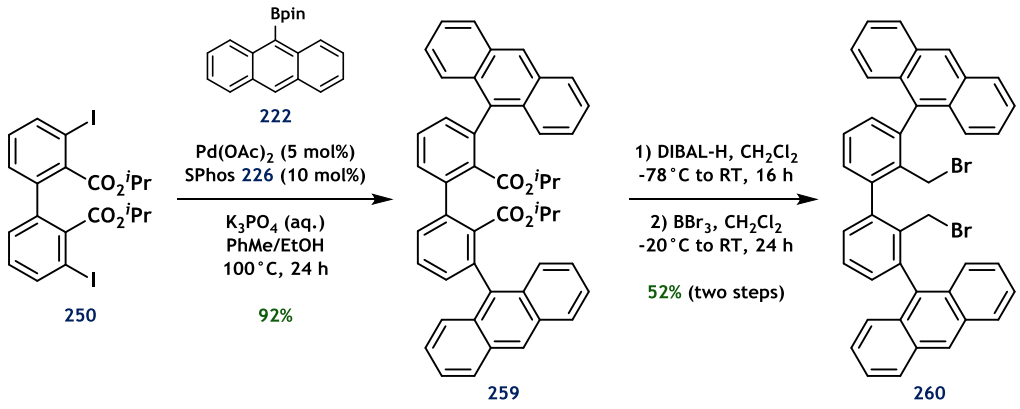
Scheme 3.25 – Direct synthesis of the pinacol boronic ester **222**

A cross-coupling reaction to unite diiodoarene **250** and boronic ester **222**, with the reagents that had succeeded previously, was ineffective on this occasion (**Scheme 3.26**). A combination of $Pd(OAc)_2$ (5 mol%) and PPh_3 (15 mol%) led to the recovery of starting material and protodeboronation to form anthracene **225**.



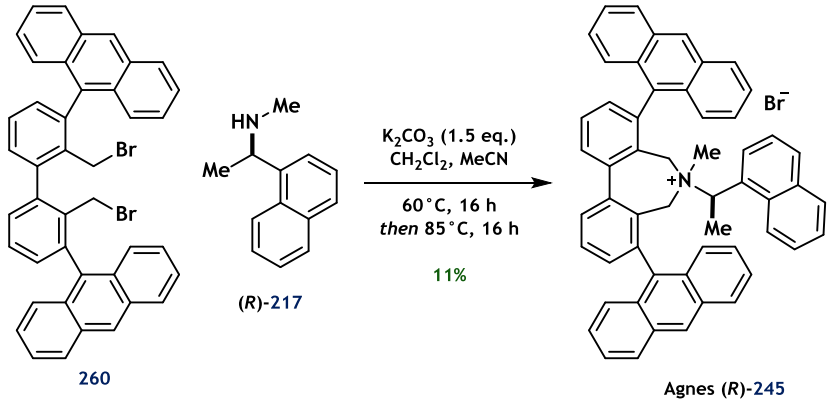
Scheme 3.26 – Unsuccessful Suzuki-Miyaura cross-coupling

Despite the diminished steric hindrance around the iodo-coupling partner **250**, the Suzuki-Miyaura reaction to synthesize diester **259** remained very challenging. Accordingly, we investigated alternative conditions that have proven effective for generating encumbered biaryls. In particular, the Buchwald ligand SPhos **226** has demonstrated unprecedented activity in a number of difficult cross-coupling processes.[149] Utilizing this ligand alongside $Pd(OAc)_2$ in a mixture of toluene and ethanol at 100 °C was highly effective for linking boronic ester **222** to diiodoarene **250** (**Scheme 3.27**). The resulting diester **259** was reduced with DIBAL-H in dichloromethane to furnish a diol, which was directly converted to the alkyl bromide substrate **260** with BBr_3 in 52% yield over both steps.



Scheme 3.27 – Suzuki-Miyaura reaction followed by reduction and bromination

The final step to synthesize the quaternary ammonium salt Agnes (*R*)-**245** was conducted with 1.5 equivalents of potassium carbonate in a mixture of dichloromethane and acetonitrile (**Scheme 3.28**). After 16 hours at 60 °C conversion to product (*R*)-**245** was very poor by TLC, therefore, heating was continued at 85 °C for a similar period of time. Isolation of the catalyst (*R*)-**245** from the crude reaction mixture proved difficult and this was reflected in the low yield (11%) of pure material obtained.



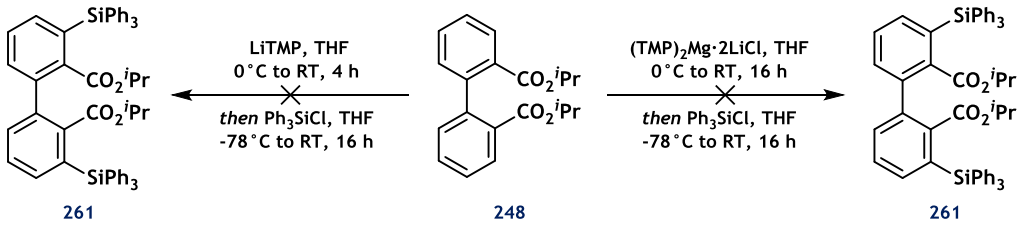
Scheme 3.28 – Synthesis of the phase-transfer catalyst Agnes (*R*)-**245**

Despite the complications encountered during the final *N*-quaternization step, the ammonium salt Agnes (*R*)-**245** was successfully synthesized. Inspired by this accomplishment, we subsequently investigated further analogues of this catalyst architecture.

3.3.5.4 Sylvia

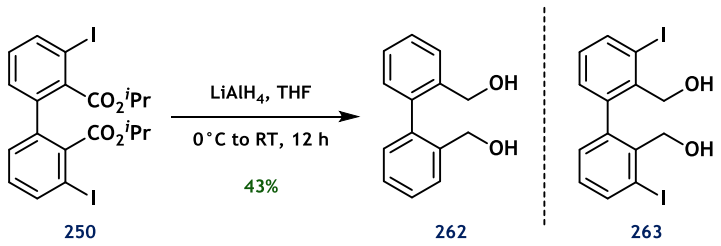
The final quaternary ammonium salt we pursued integrated large triphenylsilyl groups onto its biphenyl scaffold. These flanking substituents would increase the lipophilicity of the chiral cation, which may improve the transfer rate of the substrate anion into the organic phase. Moreover, the bulk of the silicon groups could aid the construction of a better defined chiral environment for controlling the asymmetry in our intramolecular Michael addition.

Initially, we examined *ortho*-metalation approaches to install the triphenylsilyl unit directly onto the diester substrate **248** (**Scheme 3.29**). The magnesium amide base developed by Knochel, which allowed halogen substituents to be inserted at the *ortho*-position, was ineffective in this transformation.[156,157] Following a directed metalation of diester **248** with $(TMP)_2Mg{\cdot}2LiCl$ the resulting aryl anion was treated with Ph_3SiCl, but only starting material was recovered. A related procedure that employed LiTMP as a base generated a doubly lithiated arene, which was merely reprotonated on workup to restore the biphenyl substrate **248**.[164]



Scheme 3.29 – Attempts to silylate biphenyl **248** by *ortho*-metalation.

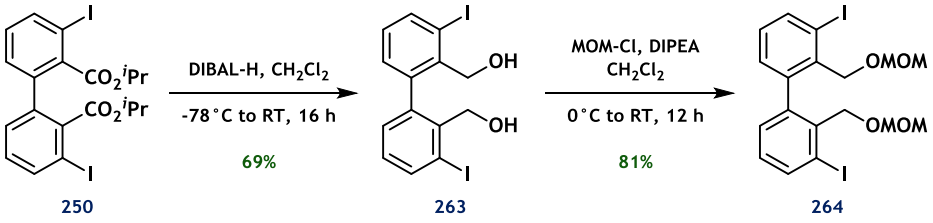
In a different approach, we considered performing lithium-halogen exchange on an iodinated substrate that could be subsequently trapped with Ph_3SiCl. The biaryl **250** has been synthesized previously, but due to the presence of ester functionalities it was concluded that the silylation procedure should be implemented later in the sequence. Therefore, diiodoarene **250** was reduced with $LiAlH_4$ in THF, but instead of acquiring the intended product **263**, diol **262** was isolated in 43% yield (**Scheme 3.30**). The hydride-mediated deiodination of arenes is a known transformation and is postulated to involve a radical mechanism.[165–167]



250 262 263

Scheme 3.30 – Reduction and deiodination of diester **250**

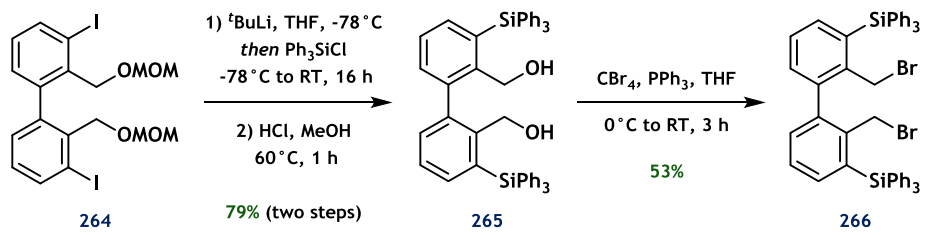
This problem could be circumvented by conducting the reduction of diester **250** with DIBAL-H in dichloromethane (**Scheme 3.31**). The ensuing diol **263** was obtained in 69% yield and was converted to the MOM-protected intermediate **264** using chloromethyl methyl ether.



250 263 264

Scheme 3.31 – Reduction and MOM protection to form diiodoarene **264**

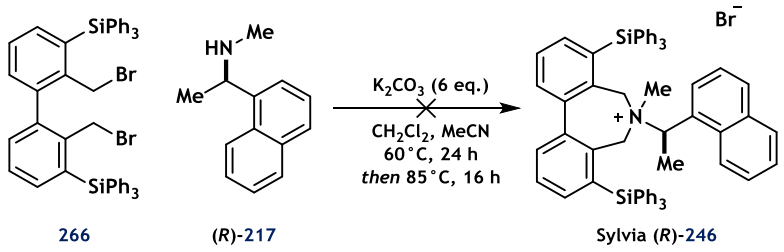
The protected diol **264** was exposed to *tert*-butyllithium in THF to promote halogen-metal exchange and the lithiated species was subsequently silylated with Ph_3SiCl (**Scheme 3.32**).[168] Removal of the MOM ethers was accomplished with HCl in methanol at 60 °C to afford diol **265** in 79% over both steps. The alkyl bromide substrate **266** was synthesized in good yield through an Appel reaction performed with a mixture of CBr_4 and PPh_3 (**Scheme 3.32**).[168]



264 265 266

Scheme 3.32 – Silylation by lithium-halogen exchange followed by MOM-deprotection and bromination

The attempted synthesis of the phase-transfer catalyst Sylvia (*R*)-**246** was conducted under the standard conditions employed previously (**Scheme 3.33**). After 24 hours at 60 °C in the presence of excess potassium carbonate only starting materials were observed in the crude ^{1}H NMR spectrum. Further heating of the reaction at elevated temperatures resulted in slow conversion to a complex mixture of products, of which none were identified as Sylvia (*R*)-**246**.



Scheme 3.33 – Attempted synthesis of the phase-transfer catalyst (*R*)-**246**

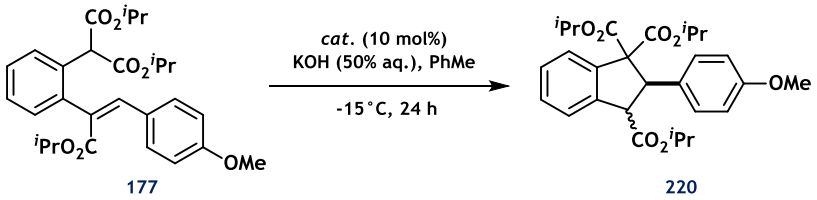
Disappointingly, the *N*-quaternization reaction to produce the ammonium salt (*R*)-**246** was unsuccessful. The alkyl bromide substrate **266** proved less reactive than previous analogues in this system. The higher temperatures required to form catalyst (*R*)-**246** may have simultaneously contributed to its decomposition through a Hofmann elimination pathway.

3.3.6 Evaluation of Moira (R)-243 and Agnes (R)-245 as Phase-Transfer Catalysts[†]

Following the synthesis of two new phase-transfer catalysts constructed from a simple achiral biphenyl backbone, we evaluated them alongside the Lygo catalyst (*R*)-**206** in a model cyclization reaction. To obtain an accurate comparison, all three ammonium salts

[†] *For additional experiments conducted with Moira (R)-***243** *and Agnes (R)-***245** *refer to Appendix II, section 7.2.*

were benchmarked under identical conditions and the levels of stereocontrol recorded in each case (**Table 3.6**). Substrate **177** was previously cyclized with the Lygo catalyst (*R*)-**206** in a biphasic mixture of toluene and 50% aqueous KOH at −15 °C to afford *anti*-indane **220** in 71% ee (**entry 1**). Under identical conditions, the quaternary ammonium salt Moira (*R*)-**243** led to a slight decline in enantioselectivity with the cyclized product **220** being isolated in 62% ee (**entry 2**). On the other hand, the bulky anthracenyl catalyst Agnes (*R*)-**245** demonstrated poor enantiocontrol over the reaction, with the major diastereomer of indane **220** possessing an enantiomeric excess of only 5% (**entry 3**). This outcome implied that the efficiency of the catalyst was highly dependent on the steric environment surrounding the nitrogen atom. The increased bulk of the anthracenyl groups may shield the cation, thus preventing it from participating in key stereodetermining interactions with the substrate anion.



Entry	Catalyst[i,ii]	dr[iii]	ee[iv]
1	Lygo (*R*)-**206**	3.8 : 1.0	71%
2	Moira (*R*)-**243**	2.3 : 1.0	62%
3	Agnes (*R*)-**245**	2.2 : 1.0	5%

[i] All reactions were carried out on analytical scale without determining the reaction yield. [ii] Reactions were conducted with the specified catalyst (10 mol%) and KOH (50% aq.) in PhMe for 24 h at −15 °C. [iii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC.

Table 3.6 – Comparison of the Lygo catalyst (*R*)-**206**, Moira (*R*)-**243** and Agnes (*R*)-**245**

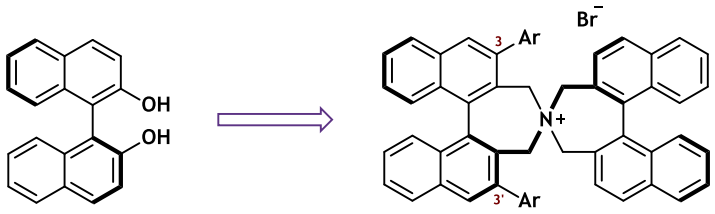
Overall, the Lygo salt (*R*)-**206** has remained the optimal phase-transfer catalyst to generate optically enriched indanes in a stereoselective a manner. This indicates that the additional "shrubbery" on the original Lygo manifold was mildly beneficial for increasing the levels of enantiocontrol in this system. Due to the difficulties encountered during the development of new phase-transfer catalysts derived from Lygo's design, we then examined alternative commercially available quaternary ammonium salts with established track records.

3.4 Binol-Derived Phase-Transfer Catalysts

3.4.1 Development of the Catalysts

At the turn of the 21st century, Maruoka delineated the class of quaternary ammonium salts (*S*,*S*)-**268** that were constructed from axially chiral binaphthyl derivatives (**Figure 3.5**).[169] These *N*-spiro C_2-symmetric phase-transfer catalysts presented a viable

alternative to *cinchona* alkaloid-derived systems, which had previously dominated the field of asymmetric ion-binding catalysis.[131,132] The presence of 3,3′-bisaryl substituents on this rigid scaffold was crucial for attaining high levels of asymmetric induction and enhancing catalytic reactivity.



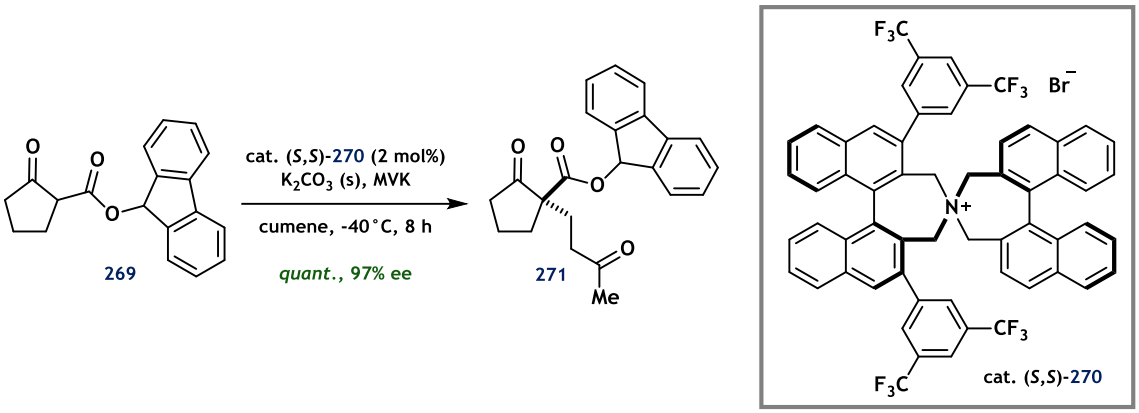
(*S*)-BINOL **267**

(*S*,*S*)-**268**
Maruoka's *N*-spiro C_2-symmetric phase-transfer catalysts

Figure 3.5 – A new class of BINOL-derived phase-transfer catalysts

The modular design of these quaternary ammonium salts permitted further refinement of their steric and electronic properties, which could ultimately be tailored towards a variety of asymmetric phase-transfer processes. The availability of (*R*)- and (*S*)-BINOL **267** allows for the assembly of both enantiomeric forms of the catalyst, which can facilitate the synthesis of a wide range of optically enriched natural and unnatural α-amino acids.[170]

The efficacy of these axially chiral C_2-symmetric phase-transfer catalysts was also demonstrated through an intermolecular asymmetric Michael addition (**Scheme 3.34**).[171] The treatment of β-keto ester **269** with MVK, in the presence of 2 mol% of ammonium salt (*S*,*S*)-**270** and powdered K_2CO_3 in cumene at −40 °C, led to quantitative formation of product **271** in 97% ee. This protocol was particularly attractive as it generated a coveted all-carbon quaternary stereocentre with excellent enantioselectivity.



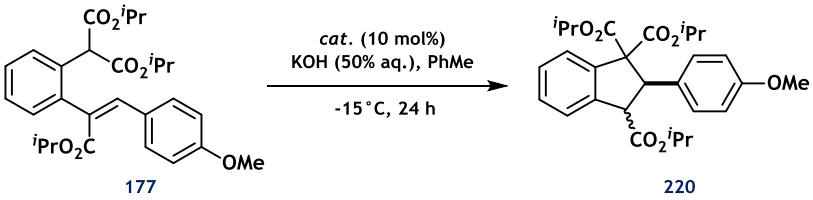
Scheme 3.34 – Intermolecular asymmetric Michael addition mediated by the Maruoka catalyst (*S*,*S*)-**270**

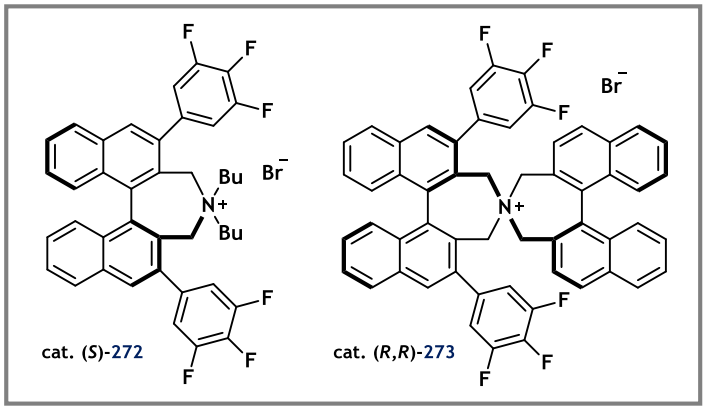
The high degrees of stereocontrol exhibited by Maruoka's BINOL-derived phase-transfer catalysts in a number of asymmetric reactions prompted us to examine them in our 5-*endo*-trig ring closure process to synthesize enantioenriched indanes.

3.4.2 Assessment of the Maruoka Catalysts[†]

The commercial availability of the *N*-spiro ammonium salt (*R*,*R*)-**273** and its dibutylated analogue (*S*)-**272** rendered them appealing to examine in our system. Accordingly, both of these axially chiral catalysts were evaluated in a model cyclization reaction with substrate **177** (**Table 3.7**). The Lygo catalyst (*R*)-**206** was previously utilized to synthesize *anti*-indane **220** in 71% ee (**entry 1**). When identical conditions were employed with 10 mol% of the quaternary ammonium salt (*S*)-**272** a 1.0 : 3.5 (*anti* : *syn*) mixture of products was produced (**entry 2**). Interestingly, a preference for the *syn*-diastereomer was observed in this case, but chiral HPLC revealed an enantiomeric excess of only 32%. The *N*-spiro C_2-symmetric catalyst (*R*,*R*)-**273** also exhibited a bias for the *syn*-epimer, but led to vastly improved levels of asymmetric induction (**entry 3**). In a biphasic mixture of toluene and 50% aqueous KOH the *syn*-indane **220** was delivered in 92% ee after 24 hours at −15 °C.

[†] *For additional experiments conducted with Maruoka (S)-***272** *refer to Appendix III, section 7.3*





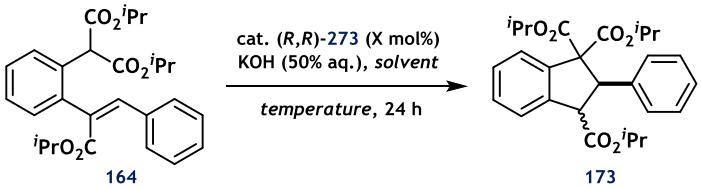
Entry	**Catalyst**[i,ii]	**dr**[iii]	**ee**[iv]
1	Lygo (*R*)-**206**	3.8 : 1.0	71%
2	Maruoka (*S*)-**272**	1.0 : 3.5	32%
3	Maruoka (*R,R*)-**273**	1.0 : 4.0	92%[v]

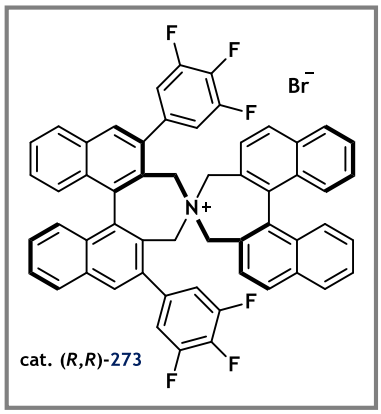
[i] All reactions were carried out on analytical scale without determining the reaction yield. [ii] Reactions were conducted with the specified catalyst (10 mol%) and KOH (50% aq.) in PhMe for 24 h at −15 °C. [iii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] Opposite absolute configuration.

Table 3.7 – Comparison of the phase-transfer catalysts developed by Lygo and Maruoka

The phase-transfer catalyst (*R,R*)-**273** which was developed by the Maruoka group significantly enhanced the enantioselectivity of our reaction, when compared to the Lygo salt (*R*)-**206**. Subsequently, we conducted a brief optimization of the asymmetric cyclization conditions to determine if further improvements were feasible (**Table 3.8**). Initially, we sought to establish the lowest catalyst loading that could be employed without adversely affecting the efficiency of the reaction. The cyclization of substrate **164** with 10 mol% of quaternary ammonium salt (*R,R*)-**273** under liquid-liquid phase-transfer conditions with toluene and 50% aqueous KOH furnished *syn*-indane **173** in 87% ee (**entry 1**). Pleasingly,

upon decreasing the catalyst loading the enantioselectivity of the process remained generally consistent (**entries 2**-**4**). However, the reaction rate was impeded at lower ratios, as a cyclization conducted with 1 mol% of onium salt (*R*,*R*)-**273** required 48 hours to reach full conversion (**entry 4**). Therefore, to maintain reasonable reaction times 2 mol% of the chiral quaternary ammonium bromide (*R*,*R*)-**273** was deemed to be optimal for this process.





Entry	**Conditions**[i]	**Yield**[ii]	**dr**[iii]	**ee**[iv]
1	cat. (*R*,*R*)-**273** (10 mol%), PhMe, −15 °C	–	1.0 : 1.4	87%
2	cat. (*R*,*R*)-**273** (5 mol%), PhMe, −15 °C	–	1.0 : 3.5	92%
3	cat. (*R*,*R*)-**273** (2 mol%), PhMe, −15 °C	70%	1.2 : 1.0	92%
4	cat. (*R*,*R*)-**273** (1 mol%), PhMe, −15 °C[v]	44%	1.0 : 2.4	91%
5	cat. (*R*,*R*)-**273** (2 mol%), PhMe : hexane (1 : 1), −15 °C	–	1.0 : 2.7	83%
6	cat. (*R*,*R*)-**273** (2 mol%), PhMe, −30 °C[v]	–	1.0 : 2.0	93%

*[i] Unless otherwise stated, reactions were conducted with catalyst (R,R)-**273** (X mol%) and KOH (50% aq.) in the given solvent for 24 h at the provided temperature. [ii] Where quoted, yields are for isolated material and for the combined mixture of diastereomers; otherwise, yields were not determined. [iii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] Reaction time was 48 hours.*

Table 3.8 – Optimization with the Maruoka catalyst (*R*,*R*)-**273**

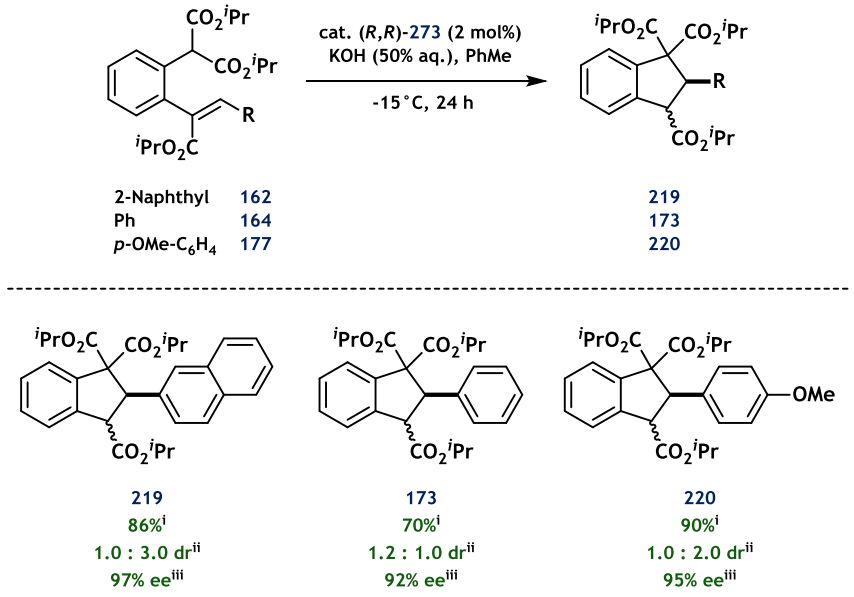
Interestingly, the isolated yield of indane **173** dropped from 70% to 44% upon reduction of the catalyst loading from 2 mol% to 1 mol% (**entries 3**-**4**). This decline was attributed to

the longer reaction period that was required for complete consumption of the starting material, as degradation of product **173** was observed by TLC and ^{1}H NMR over time. A subsequent investigation revealed that oxidation of the indane facilitated by adventitious oxygen was responsible for the generation of a complex mixture of products through this decomposition pathway.[†] Therefore, rigorous degassing of the phase-transfer reaction was necessary to circumvent this deleterious process.

Previous optimization with the Lygo catalyst (*R*)-**206** indicated that reduction of the organic solvent polarity was beneficial for the levels of enantioselectivity (*vide supra, section 3.3.3*). Exploiting this concept with the Maruoka salt (*R,R*)-**273** by utilizing a 1 : 1 mixture of toluene and hexane was unfavourable in this instance, as *syn*-indane **173** was recovered in 83% ee (**entry 5**). Lowering the reaction temperature to −30 °C with pure toluene as the solvent led to a negligible improvement in enantioselectivity, but a noticeable decrease in reaction rate was detected (**entry 6**). Overall, the optimal conditions were determined to involve 2 mol% of Maruoka salt (*R,R*)-**273** in a biphasic mixture of toluene and 50% aqueous KOH, which after 24 hours at −15 °C delivered a 1.2 : 1.0 (*anti* : *syn*) ratio of indanes **173** with the major diastereomer being formed in 92% ee (**entry 3**).

To probe the generality of this asymmetric phase-transfer protocol we generated a small set of tetrasubstituted indanes (**Scheme 3.35**). In general, all of these substrates (**173** and **219**-**220**) were isolated in good yields with high levels of enantioselectivity, although, no consistent bias for either diastereomer was observed. The difficulties encountered during attempts to separate the epimeric mixtures of indanes precluded this process from becoming a convenient and practical methodology.

[†] *This side-reaction is discussed in greater detail later, see section 3.4.3 on page 98.*



[i] Isolated yield for the combined mixture of diastereomers. [ii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iii] ee for major diastereomer as determined by chiral HPLC.

Scheme 3.35 – Representative examples of enantioenriched indanes generated with the catalyst (*R,R*)-**273**

A pure sample of the major diastereomer of indane **173** was acquired by repeated silica gel chromatography, which allowed a single crystal of high purity to be grown. Following X-ray diffraction analysis, the identity of the product was corroborated and the *anti*-configuration of substituents on the ring allowed the relative stereochemistry to be determined (**Figure 3.6**).

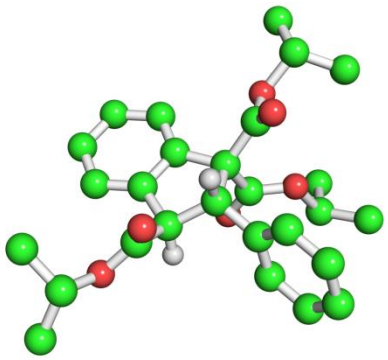


Figure 3.6 – X-ray crystal structure of *anti*-indane **173**[†]

To render this protocol for synthesizing optically enriched indanes more expedient, we sought to develop a process which was not only enantioselective, but also highly diastereoselective.

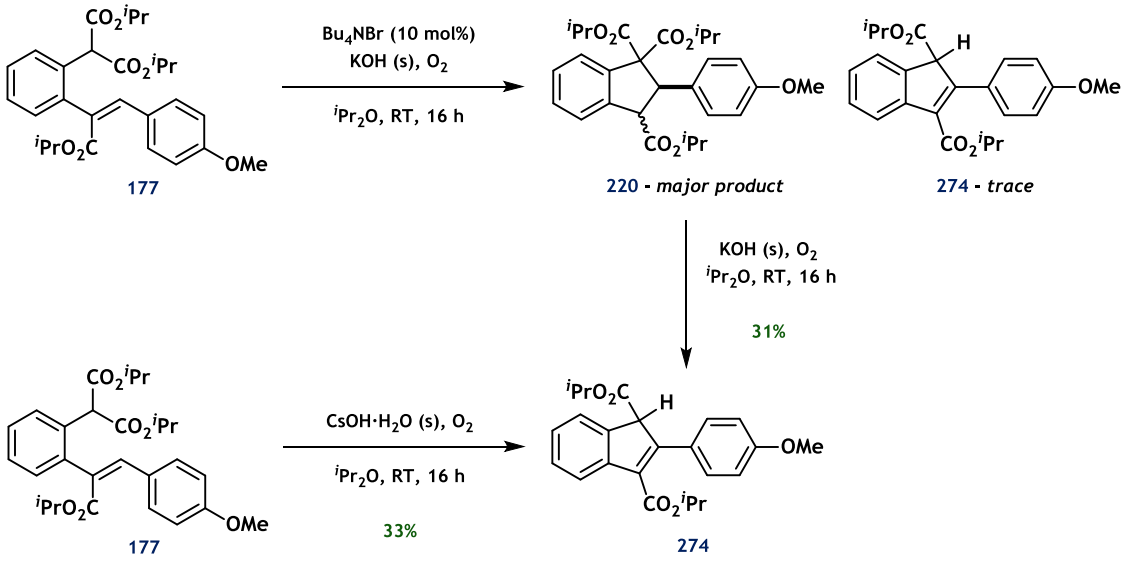
3.4.3 Oxidation of Indanes

During the optimization of the asymmetric phase-transfer procedure with the C_2-symmetric BINOL-derived catalyst (*R*,*R*)-**273**, we discovered that a significant side-reaction was diminishing the isolated yield of the indane product. This degradation led to a complex mixture of by-products that were present in trace quantities by ^{1}H NMR. However, MS of the crude reaction mixture implied that oxidation of the substrate was responsible for the decomposition observed.[‡] To fully probe this undesirable pathway we investigated the cyclization of substrate **177** with achiral phase-transfer conditions performed under an oxygen atmosphere (**Scheme 3.36**). After a 16 hour period at room temperature, analysis of the crude reaction by ^{1}H NMR and TLC indicated that the major products were a diastereomeric mixture of indanes **220** with only trace levels of oxidation by-products. Interestingly, a similar procedure conducted with solid $CsOH{\cdot}H_2O$ in the

[†] *X-ray diffraction data was collected and the structure solved by Dr Russell W. Driver. The molecule was rendered using PyMOL.*[106]

[‡] *The indene* **274** *and hydroxylated indane* **278** *were observed by MS, but only indene* **274** *was isolated (****Figure 3.7****).*

absence of a phase-transfer catalyst resulted in the formation of a sole major product, which was assigned as indene **274**. This outcome implied that the various by-products, which were previously observed by ^{1}H NMR, MS and TLC, converged to the fully conjugated carbocycle **274** under more forcing conditions. The observation that substrate oxidation was prevalent in the absence of a phase-transfer catalyst suggested that the metal-enolate ion-pair was more susceptible to this transformation. Moreover, this principle could explain why reduced loadings of the chiral ammonium salt (*R*,*R*)-**273** led to more significant oxidation. To ascertain if indane **220** was an intermediate on the mechanistic pathway *en route* to indene **274** we treated the epimeric mixture of products **220** with powdered KOH in diisopropyl ether under an atmosphere of oxygen (**Scheme 3.36**). This process led to complete consumption of starting material to form the equivalent indene carbocycle **274** in an isolated yield of 31%.



Scheme 3.36 – Oxidation of substrate **177** or indane **220** to form indene **274**

Based on these results, as well as previous observations, a mechanism for the formation of indene **274** through oxidation of the parent indane **220** was proposed (**Figure 3.7**).

Following an initial 5-*endo*-trig cyclization to construct the indane ring, the resultant enolate **275** could be oxidized by adventitious oxygen to form the radical intermediate **276** and the superoxide radical anion. The enolate radical **276** could be intercepted by another molecule of triplet oxygen to generate peroxy radical **277**. Subsequent reduction, conceivably facilitated by another enolate moiety, would lead to the hydroxylated indane **278**, which is observable by MS. Elimination of water from this species generates the more conjugated adduct **279**, which undergoes decarboxylation and protonation to form indene **274**. This decarboxylation is presumably driven by the formation of a stable anionic aromatic system.

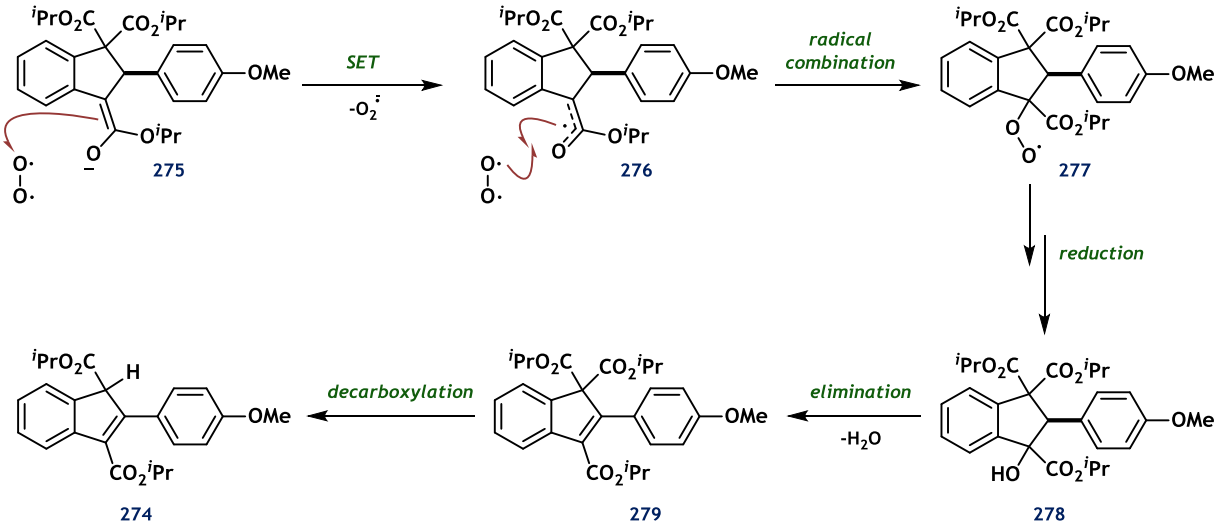


Figure 3.7 – Postulated mechanism for the formation of indene **274**

Maruoka has previously highlighted the detrimental impact of oxygen upon asymmetric phase-transfer processes for the synthesis of α-amino acid derivatives.[172] Accordingly, degassing of our reaction system was necessary to suppress this undesirable side-reaction and to enhance the isolated yields of the indane products.

3.5 Developing a Diastereoselective Protocol

3.5.1 Variation of the Vinylic Electron-Withdrawing Group

To augment the synthetic merit of this methodology we investigated the impact of modifying the vinylic ester functionality on the cyclization precursor (**Figure 3.8**). In particular, we sought a substrate that would maintain the high levels of enantioselectivity observed previously, whilst also demonstrating a consistent bias for a single diastereomer. A small collection of electron-withdrawing groups were considered for this study, including: nitrile, amide, sulfone and phosphonate substituents.

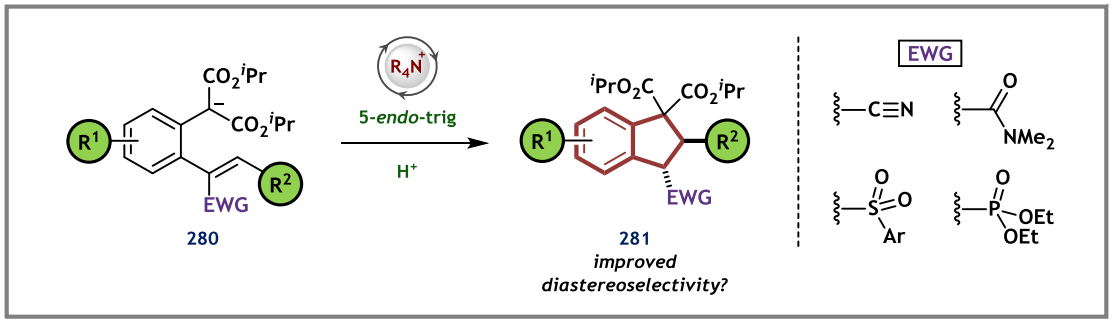


Figure 3.8 – Proposed new substrates with alternative vinylic electron-withdrawing groups

This endeavour would additionally lead to diversification of the substrate scope and provide carbocyclic products that are more synthetically valuable.

3.5.1.1 Substrate Synthesis

The synthetic strategy to generate these new indane precursors remained unchanged and a set of vinylstannanes bearing the required electron-withdrawing groups were constructed (**Figure 3.9**). As before, we reasoned that hydrostannylation of the parent alkyne would be the best method to synthesize these coupling partners.

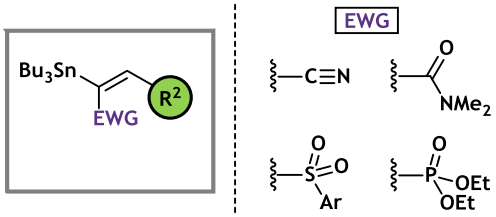
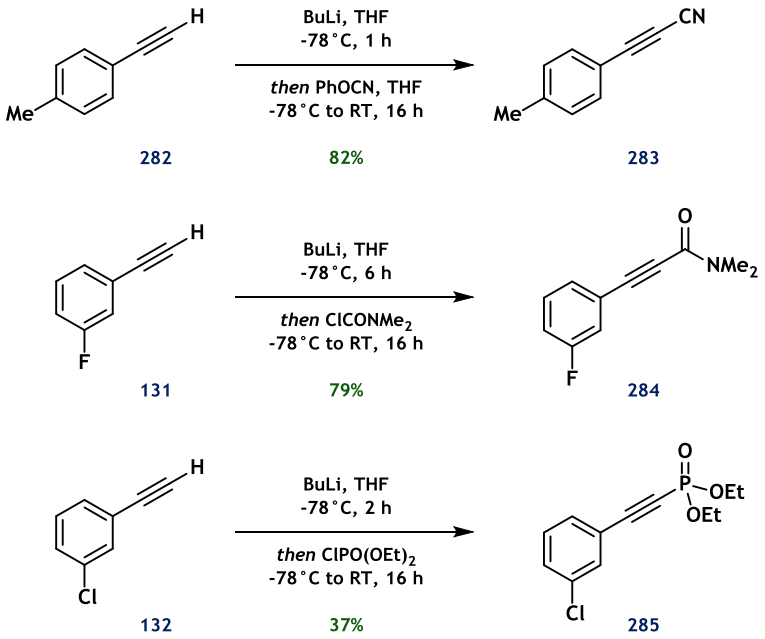


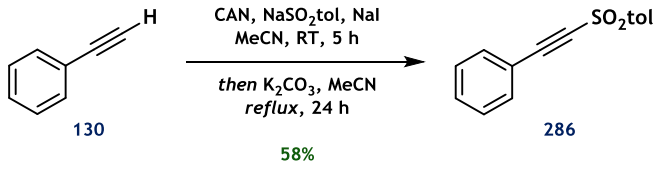
Figure 3.9 – Vinylstannanes required for synthesizing new indane precursors

Following literature procedures, the desired functionalized acetylenes were rapidly synthesized from inexpensive, commercially available alkynes (**Scheme 3.37**). For example, *p*-tolylacetylene **282** was deprotonated with BuLi and the subsequent lithium anion trapped with phenyl cyanate to form the corresponding nitrile adduct **283** in 82% yield.[173] A similar protocol was applied to synthesize the propargylic amide **284** from the fluorinated species **131**, with dimethylcarbamoyl chloride serving as the electrophile.[174] Likewise, a lithium acetylide prepared from alkyne **132** was reacted with diethyl chlorophosphate to deliver propargylic phosphonate **285** in 37% yield.[174] The low recovery of product from this reaction was consistent with the literature report for a similar transformation.[174]



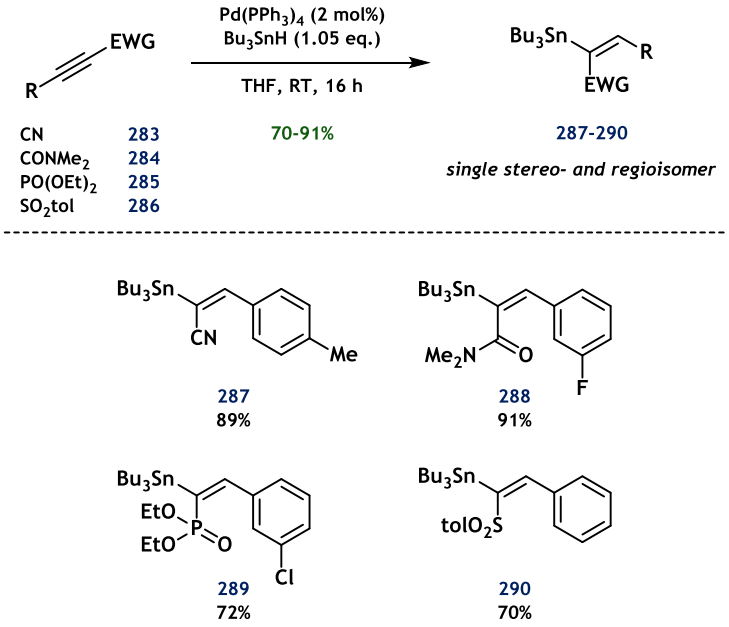
Scheme 3.37 – Generation of functionalized propargylic derivatives

The propargylic sulfone **286** was synthesized in a one-pot procedure starting from phenyl acetylene **130** (**Scheme 3.38**). This simple alkyne was transformed into a β-iodovinyl sulfone with a mixture of CAN, *p*-toluene sulfinate and sodium iodide in acetonitrile at room temperature.[175] Subsequent heating of this intermediate in the presence of potassium carbonate induced elimination of hydrogen iodide to form acetylenic sulfone **286** in 58% yield.



Scheme 3.38 – Synthesis of propargylic sulfone **286**

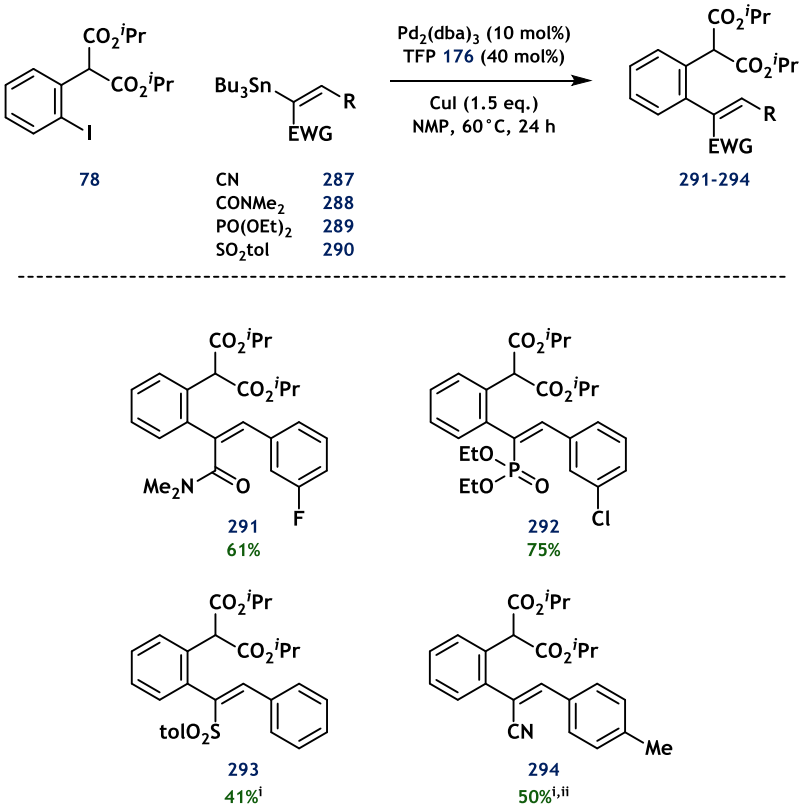
This series of functionalized alkynes was then hydrostannylated according to the procedure employed for the propargylic ester substrates (**Scheme 3.39**).[60] For example, the acetylenic nitrile compound **283** was converted to vinylstannane **287** in the presence of 2 mol% of $Pd(PPh_3)_4$ and Bu_3SnH in THF at room temperature. The product was observed as a single stereo- and regioisomer by ^1H NMR analysis of the crude reaction mixture. Exchanging the nitrile group for a dimethyl amide was well tolerated as the corresponding vinylstannane **288** was isolated in 91% yield. Furthermore, identical conditions were applied to synthesize the phosphonate and sulfone containing stannanes **289** and **290**, which were acquired in 72% and 70% yield respectively (**Scheme 3.39**). In contrast to the propargylic ester substrates, all of these reactions furnished the products as single stereo- and regioisomers, as detected through evaluation of the relevant crude ^1H NMR spectra (*vide supra, section 2.3.2*).



Scheme 3.39 – Pd^0-catalyzed hydrostannylation to form vinylstannanes **287**-**290**

We then proceeded to examine the efficacy of the Stille-Migita reaction between *ortho*-substituted arene **78** and the newly constructed vinylstannanes **287**-**290** (**Scheme 3.40**). For instance, the cross-coupling of iodoarene **78** with the amide substrate **288** was implemented with a mixture of $Pd_2(dba)_3$ and TFP **176** in *N*-methyl-2-pyrrolidone at 60 °C for a 24 hour period.[112,113] The resulting indane precursor **291** was isolated cleanly in 61% yield following the removal of tin residues through a K_2CO_3-doped silica gel column.[117] Under analogous conditions, the α-stannyl vinylphosphonate **289** also reacted successfully to afford the desired product **292** in 75% yield. However, the nitrile and sulfone substituted stannanes **287** and **290** were less tolerant in this procedure, as a complex mixture of products was generated that precluded isolation of pure material. Upon closer inspection, the ^{1}H NMR spectra for these reactions indicated that partial cyclization was transpiring to afford mixtures of coupled products and indanes. Fortunately, this predicament was circumvented by gradual addition of the vinyltin reagent over 12 hours, whilst maintaining the reaction at ambient temperature. This protocol was very effective for generating the

sulfone product **293**, which was isolated cleanly in 41% yield. For the nitrile containing substrate **294**, the palladium source was changed to $Pd(PPh_3)_4$, as the dba ligand co-eluted with the product during purification. The propensity of indane precursor **294** to cyclize upon heating, even in the absence of a Brønsted base, demonstrated its high reactivity. Therefore, the coupling of iodoarene **78** with α-stannylvinyl nitrile **287** was conducted cautiously to afford the desired substrate **294** in 50% yield (**Scheme 3.40**).



[i] Reaction was conducted at room temperature with the stannane being added dropwise over 12 hours.
*[ii] $Pd(PPh_3)_4$ (20 mol%) was used instead of $Pd_2(dba)_3$/TFP **176***

Scheme 3.40 – Stille-Migita cross-coupling to synthesize substrates **291**-**294**

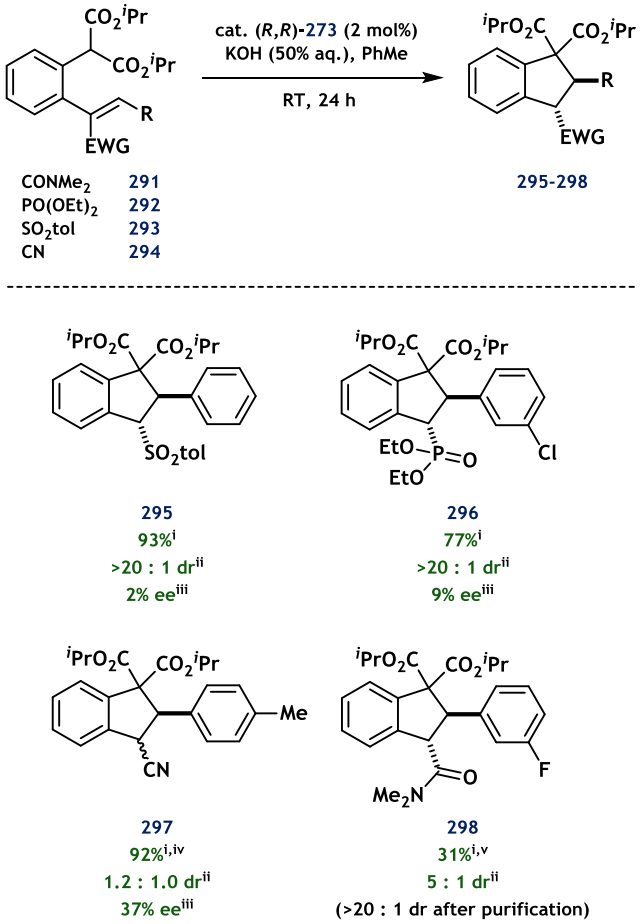
Following the synthesis of four new cyclization precursors bearing various vinylic electron-withdrawing groups we proceeded to evaluate their capacity to form indanes with high levels of diastereo- and enantiocontrol under asymmetric phase-transfer conditions.

3.5.1.2 Substrate Evaluation

The C_2-symmetric quaternary ammonium salt (*R*,*R*)-**273** was previously demonstrated to be the optimal phase-transfer catalyst for the asymmetric cyclization of triester substituted indane precursors. To assess the generality of this system we examined new substrates comprising a variety of alternative conjugate acceptors under these optimal conditions (**Scheme 3.41**). Treatment of the sulfone substrate **293** with 2 mol% of catalyst (*R*,*R*)-**273** in a biphasic mixture of toluene and 50% aqueous KOH at room temperature led to a single diastereoisomer of indane **295**. The *anti*-relationship of substituents in this compound was confirmed by nOe experiments, which provided the relative configuration.[†] Unfortunately, despite the high diastereoselectivity of this process product **295** was revealed to be essentially racemic by chiral HPLC. Subsequently, we evaluated the phosphonate substrate **292** under identical asymmetric phase-transfer conditions. The resulting carbocyclic product **296** was isolated in 77% yield with >20 : 1 dr (*anti* : *syn*), but irrespective of the high diastereoselectivity, the *anti*-indane **296** was obtained in only 9% ee. As before, the relative stereochemistry of this compound was elucidated by nOe analysis.[‡] A substrate bearing a highly reactive nitrile-based conjugate acceptor was cyclized at −15 °C to furnish a 1.2 : 1.0 ratio of diastereomeric indanes **297**, which could not be separated by silica gel chromatography. However, analysis of the mixture by chiral HPLC demonstrated that the major epimer was formed with an enantiomeric excess of 37%. Finally, the α,β-unsaturated amide derivative **291** was evaluated with the Maruoka catalyst (*R*,*R*)-**273** at room temperature, but after an extended period no cyclization was observed. Replacing the chiral ammonium salt (*R*,*R*)-**273** with Bu_4NBr, as well as heating the reaction to 50 °C, was required

[†] *Refer to experimental section 5.3.6, page 363 for the 1D nOe data.*
[‡] *Refer to experimental section 5.3.6, page 370 for the 1D nOe data.*

to promote this less favourable ring closure. The resulting indane **298** was generated as a 5 : 1 (*anti* : *syn*) mixture of diastereomers, but following purification a single stereoisomer was isolated in 31% yield (**Scheme 3.41**). The relative stereochemistry of the major epimer was determined by nOe enhancements and was later corroborated by X-ray crystallographic analysis.[†]



[i] Isolated yield for the combined mixture of diastereomers. [ii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iii] ee for major diastereomer as determined by chiral HPLC. [iv] Reaction conducted at –15 °C. [v] Reaction performed with Bu_4NBr at 50 °C.

Scheme 3.41 – Cyclization to form indanes with various electron-withdrawing groups

In general, the evaluation of four new substrates bearing distinct conjugate acceptor groups demonstrated improved diastereoselectivity, but with a concomitant loss of

[†] *Refer to experimental section 5.3.6, page 367 for the 1D nOe data and to section 4.2.2, page 148 for information regarding the X-ray crystal structure.*

enantioselectivity. This outcome highlighted the importance of the ester functionality at this position, to ensure good levels of the asymmetric induction. Therefore, we reassessed the original indane precursors in the hope of developing a protocol that was both highly diastereo- and enantioselective.

3.5.2 *Cyclization-Alkylation*

We previously demonstrated that the Maruoka catalyst (*R*,*R*)-**273** could direct an anionic 5-*endo*-trig ring closure to furnish optically enriched indane carbocycles. However, despite the good levels of enantiocontrol achieved in this process, no consistent bias for the *syn*- or *anti*-diastereomer was observed. We conjectured that reversible enolization α- to the ester under the basic phase-transfer conditions was responsible for this poor discrimination. Consequently, we rationalized that intercepting the enolate intermediate with a suitable electrophile (E^+) could lead to an irreversible carbon-carbon bond-forming event (**Figure 3.10**). The facial selectivity of this process could be directed by the adjacent stereocentre and would generate an all-carbon quaternary stereocentre.

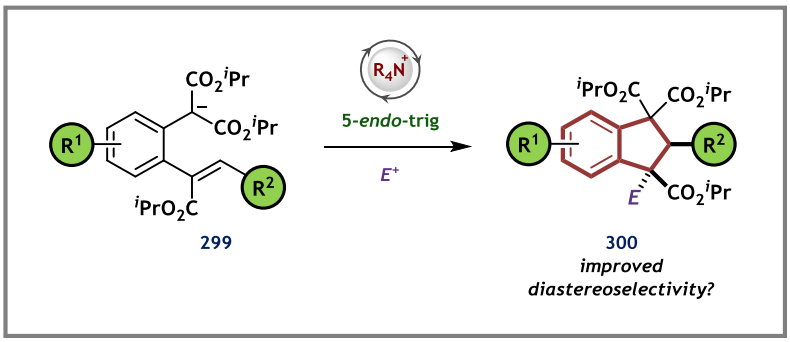
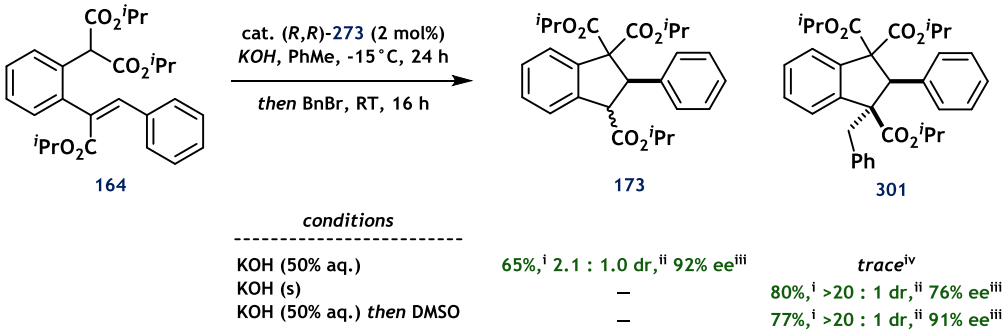


Figure 3.10 – Proposed alkylation strategy for improving the diastereomeric ratio of indanes

To examine this hypothesis, excess benzyl bromide was added to a standard phase-transfer reaction post-cyclization (**Scheme 3.42**). After 16 hours at room temperature,

analysis of the crude reaction mixture by ^{1}H NMR and MS indicated only trace quantities of the benzylated indane **301**. This outcome implied that alkylation α- to the ester to form the desired quaternary stereogenic centre was a highly challenging bond-forming event. Further investigations indicated that a cyclization conducted under solid-liquid phase-transfer conditions, with powdered KOH as a base, was able to promote this demanding benzylation step. The resultant indane **301** was afforded as a single diastereomer in 80% yield, but a reduction in enantioselectivity (76% ee) suggested that the background reaction was more facile in this system. Subsequently, we reverted to aqueous potassium hydroxide to recover the excellent levels of asymmetric induction observed previously. Additional experimentation revealed that the polar aprotic solvent DMSO could be introduced post-cyclization to mediate this alkylation with no degradation of the ee set in the first step (**Scheme 3.42**). This reaction proceeded with complete diastereoselectivity to furnish indane **301** in 77% yield and 91% ee.



[i] Isolated yield. [ii] Ratio was determined by analysis of the crude ^{1}H NMR spectrum. [iii] ee determined by chiral HPLC. [iv] As determined by analysis of the crude ^{1}H NMR spectrum and MS.

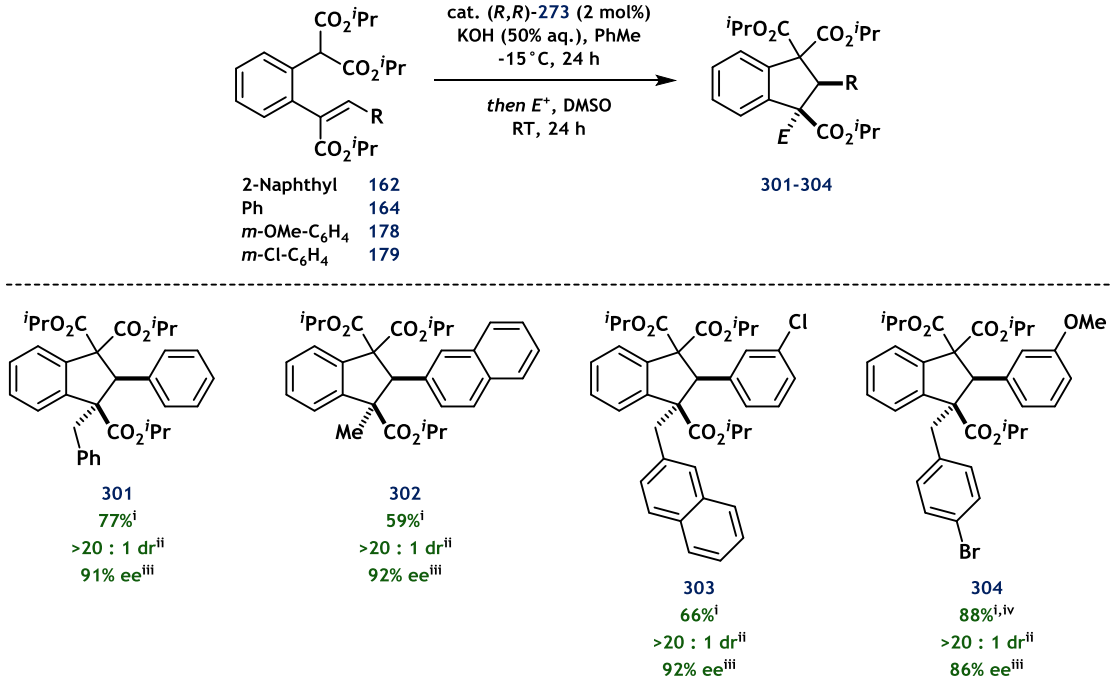
Scheme 3.42 – Optimization of benzylation procedure to form indane **301**

In summary, treatment of the unresolvable mixture of epimeric indanes **173** with benzyl bromide in DMSO rendered this protocol a viable strategy for the diastereo- and enantioselective synthesis of polyfunctionalized carbocycles.

3.6 Probing the Substrate Scope

3.6.1 Variation of the Alkylating Agent

To illustrate the scope and limitations of this methodology we explored alternative alkylating agents on a range of indane analogues (**Scheme 3.43**). A 2-naphthyl substituted substrate was cyclized in the presence of the Maruoka catalyst (*R*,*R*)-**273** and subsequently treated with iodomethane to afford indane **302** as single diastereomer in 92% ee and 59% yield. Equally, 2-naphthyl bromide could be employed to stereoselectivity forge the quaternary stereocentre in the chlorinated carbocycle **303**, which was isolated in 66% yield with very high levels of diastereo- and enantioselectivity. The *meta*-methoxy substituted precursor **178** was cyclized under asymmetric phase-transfer conditions with an organic phase comprising toluene and chloroform (9 : 1). This more solubilizing mixture of solvents was essential in order to maintain reasonable reaction rates with this particular system. Following ring closure, the enolate intermediate was intercepted with excess *para*-bromobenzyl bromide in DMSO to generate indane **304** in excellent yield with 86% ee (**Scheme 3.43**).



[i] Isolated yield. [ii] Ratio was determined by analysis of the crude ^{1}H NMR spectrum. [iii] ee determined by chiral HPLC. [iv] Reaction solvent was PhMe : $CHCl_3$ (9 : 1).

Scheme 3.43 – Synthesis of pentasubstituted indanes through a cyclization-alkylation protocol

Diffraction quality crystals of indane **304** were grown and the X-ray structure solved to confirm the relative *anti*-configuration of substituents on the ring (**Figure 3.11**). This was consistent with alkylation on the least hindered face of the enolate, directed by the aromatic ring attached to the adjacent stereocentre.

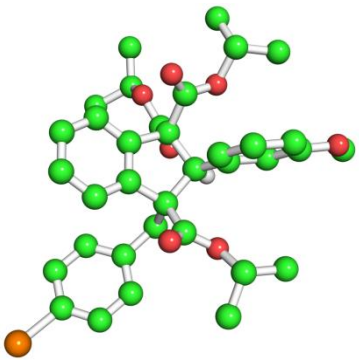
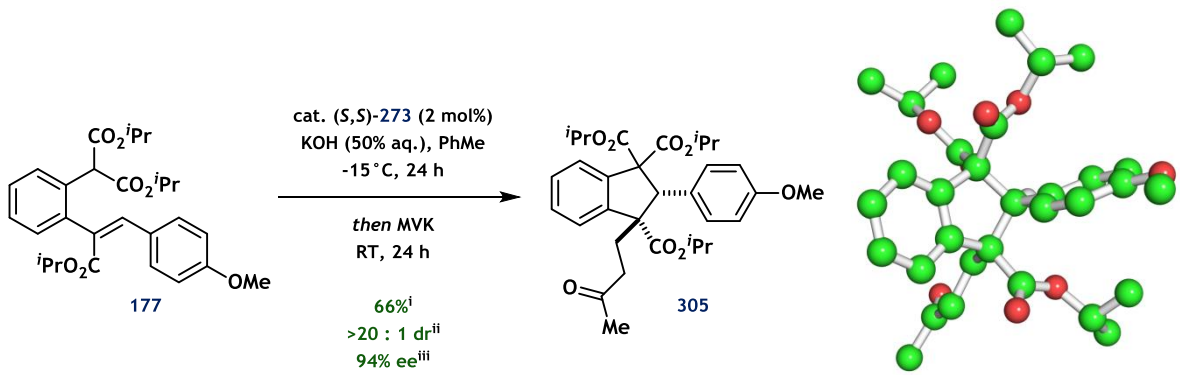


Figure 3.11 – X-ray crystal structure of indane **304**[†]

[†] *X-ray diffraction data was collected and the structure solved by Dr Russell W. Driver. The molecule was rendered using PyMOL.*[106]

Continued exploration of different electrophiles led to the assessment of Michael acceptors as alkylating agents. The *para*-methoxyarene substituted substrate **177** was cyclized in the presence of quaternary ammonium salt (*S*,*S*)-**273** for 24 hours at −15 °C. Subsequent addition of MVK, in the absence of DMSO, led efficiently to indane **305** in >20 : 1 dr and 94% ee (**Scheme 3.44**). This product was demonstrated to have an identical relative configuration to carbocycle **304** by single crystal X-ray diffraction (**Scheme 3.44**).



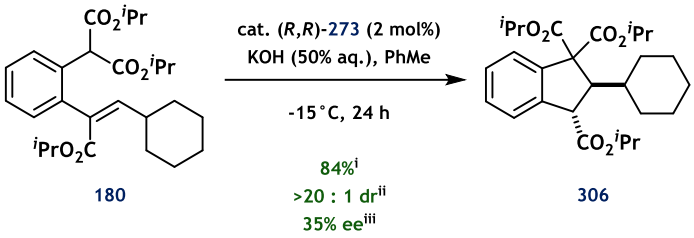
[i] Isolated yield. [ii] Ratio was determined by analysis of the crude ^{1}*H NMR spectrum. [iii] ee determined by chiral HPLC.*

Scheme 3.44 – Alkylation with MVK and crystal structure of indane **305**[†]

Thus far, we have established that both the aryl substituent at the 2-position of the indane and the nature of the electrophile can be varied substantially without compromising the stereoselectivity of the reaction. However, cyclization of the cyclohexyl containing substrate **180** resulted in a significant decrease in enantioselectivity. After 24 hours, indane **306** was acquired as a single diastereomer in 84% yield, but with an enantiomeric excess of only 35%. The relative stereochemistry of carbocycle **306** was determined by nOe experiments, which indicated that the substituents on the adjacent stereocentres were in an *anti*-relationship.[‡]

[†] *X-ray diffraction data was collected and the structure solved by Dr Russell W. Driver. The molecule was rendered using PyMOL.*[106]

[‡] *Refer to experimental section 5.3.5.3, page 342 for the 1D nOe data.*



[*i] Isolated yield. [ii] Ratio was determined by analysis of the crude* ^{1}*H NMR spectrum. [iii] ee determined by chiral HPLC.*

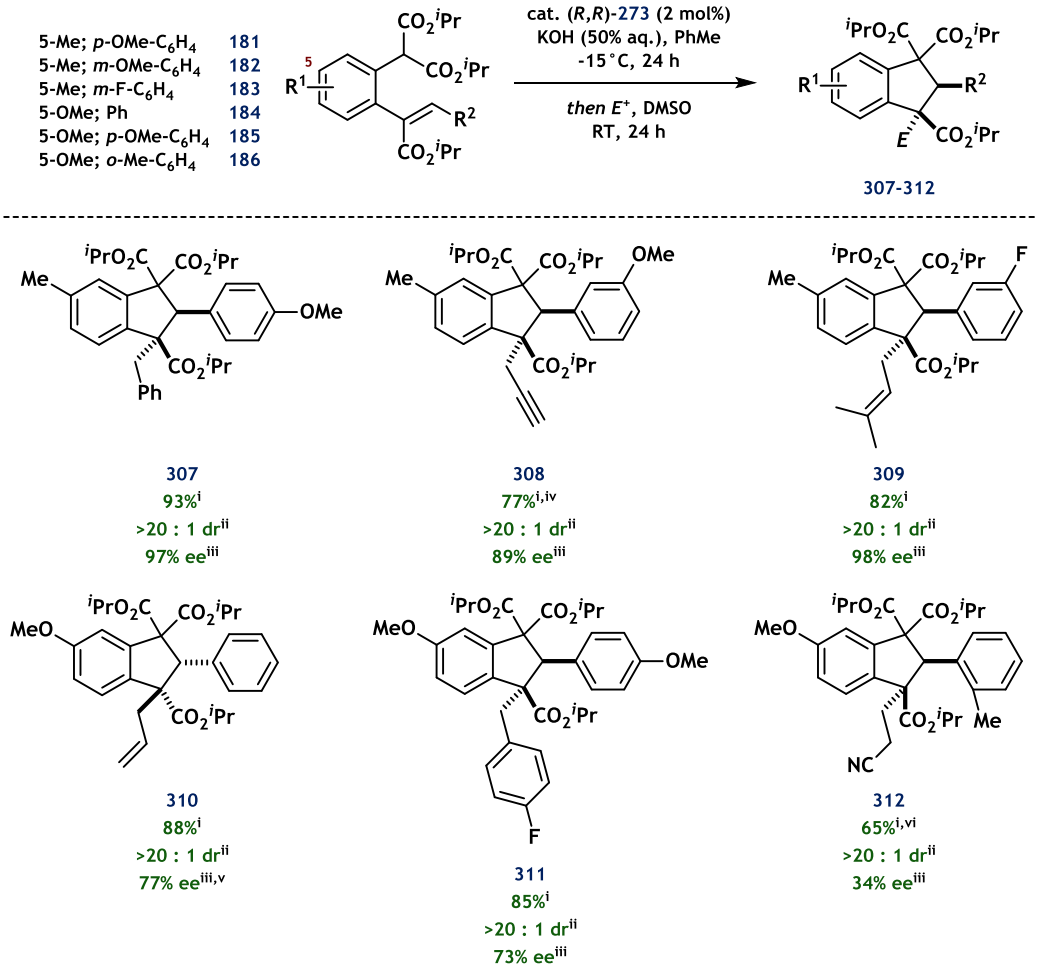
Scheme 3.45 – Cyclization of the cyclohexyl substrate **180**

This result highlighted the significant role of the aromatic ring on the Michael acceptor for attaining high levels of asymmetric induction in this system.

3.6.2 Substitution on the Indane Arene Ring

Further exploration of the substrate tolerance was carried out to probe substitution patterns on the aromatic ring of the indane moiety. Notably, the addition of a methyl group to the 5-position of the indane precursor was beneficial, as it provided a modest enhancement in enantioselectivity (**Scheme 3.46**). For example, cyclization-alkylation under standard conditions led to the benzylated indane **307**, which was isolated in 93% yield and 97% ee. Propargyl bromide was also found to be an effective electrophile, as trapping of the intermediate enolate generated from substrate **182** after the initial ring closure led to a single diastereomer of product **308** in 89% ee. The combination of a 5-methyl group with a fluorinated aryl substituent proved highly rewarding, with prenylated indane **309** being attained in 98% ee. In contrast, exchanging the alkyl group for a methoxy group resulted in a slight reduction in enantioselectivity. For instance, cyclization of substrate **184** mediated by catalyst (*S*,*S*)-**273** was followed by allylation to form carbocycle **310** in 88% yield, but with only 77% ee. A similar outcome was observed after ring closure and benzylation of dimethoxy-substituted analogue **185**, which proceeded with high diastereoselectivity to

furnish indane **311** in 73% ee. Installation of an *ortho*-methyl group on the arene of the conjugate acceptor triggered a severe loss in asymmetric induction. Alkylation of this substrate was achieved with acrylonitrile, which did not require a polar aprotic solvent, to deliver product **312** with an enantiomeric excess of 34% (**Scheme 3.46**).

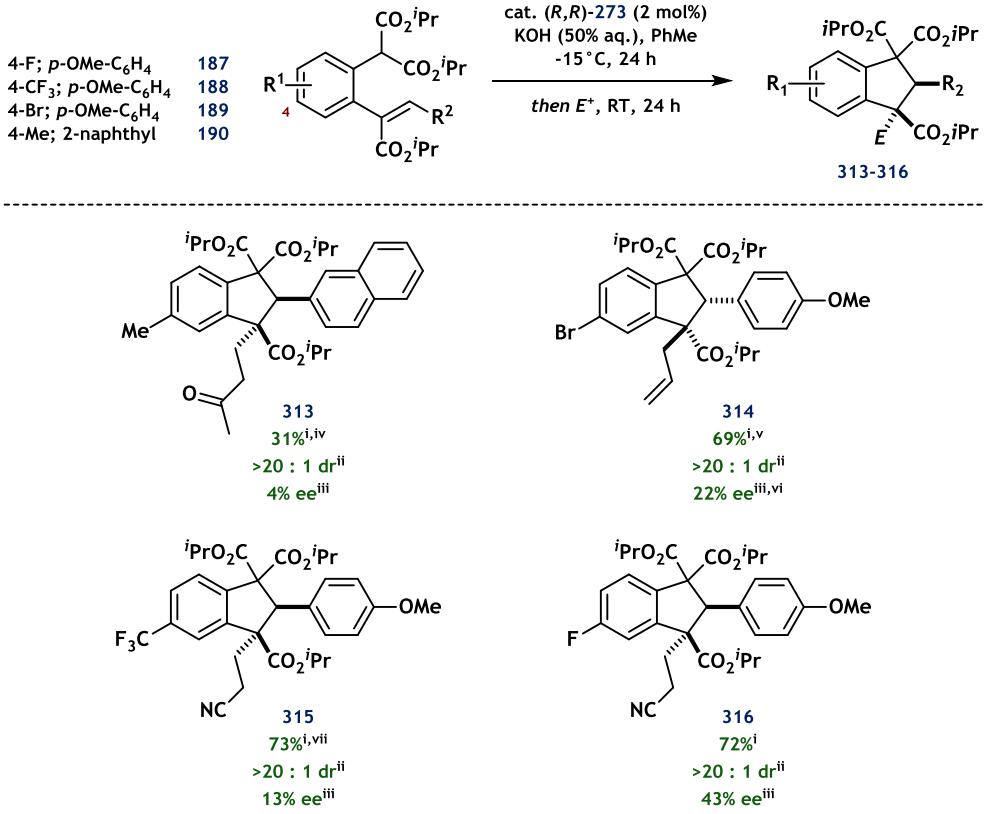


*[i] Isolated yield. [ii] Ratio was determined by analysis of the crude ^{1}H NMR spectrum. [iii] ee determined by chiral HPLC. [iv] Reaction solvent was PhMe : $CHCl_3$ (9 : 1). [v] cat. (S,S)-**273** was used. [vi] No DMSO was added.*

Scheme 3.46 – Stereoselective synthesis of indanes with substitution on the arene ring

We also established that any substituent, apart from hydrogen, was not well tolerated at the 4-position of the cyclization precursor (**Scheme 3.47**). This was clearly illustrated by the poor reactivity of the methylated analogue **190**, which under asymmetric phase-transfer conditions required 48 hours at room temperature to fully consume the starting material.

Subsequently, the epimeric mixture of indanes was alkylated with MVK to afford a single diastereomer of product **313**, which was determined to be essentially racemic. To probe this outlying result we investigated a range of substituents at this position. The introduction of a bromine atom restored typical reactivity in the ring closing step, but following the stereoselective allylation of the intermediate enolate the ensuing indane **314** was recovered in 22% ee. The trifluoromethylated indane **315** was synthesized under asymmetric phase-transfer conditions in a mixture of toluene and chloroform (9 : 1) with acrylonitrile serving as the electrophile. The product **315** was isolated in 73% yield with >20 : 1 dr, but with only 13% ee. Finally, a substrate with a fluorine atom at the 4-position was also evaluated in this sequence. Cyclization-alkylation with cyanoethene returned the halogenated indane **316** in 72% yield and 43% ee, which was a modest improvement over analogous products in this series (**Scheme 3.47**).



*[i] Isolated yield. [ii] Ratio was determined by analysis of the crude ^{1}H NMR spectrum. [iii] ee determined by chiral HPLC. [iv] Cyclization step was conducted at RT for 48 h. [v] DMSO was added post-cyclization. [vi] cat. (S,S)-**273** was used. [vii] Reaction solvent was PhMe : $CHCl_3$ (9 : 1).*

Scheme 3.47 – Exploring the impact of substitution on the arene *para* to the malonate group

Currently, the intimate details of how minor alterations to the substrate structure affect the levels of asymmetric induction in the cyclization cannot be rationalized. Tentatively, the observed trend in enantioselectivity for indane precursors bearing substituents at the 4-position can be correlated with the A-values for these groups.[†] Despite this limitation of product scope, the breadth of alkylating agents that can be employed as well as the tolerance of alternative substitution patterns still renders this methodology highly valuable.

[†] *Literature A-values (kcal/mol) are as follows: H = 0, F = 0.15, Br = 0.38, Me = 1.7, CF_3 = 2.1.*[176]

3.6.3 *Generating Indanes with Superior Functional Group Orthogonality*

In order to provide enantioenriched indanes with greater synthetic utility we sought to introduce increased functional group orthogonality. We have previously highlighted the sensitivity of this system towards the nature of the vinylic electron-withdrawing group, which can lead to greatly reduced levels of asymmetric induction. Therefore, we considered the ester functionality to be crucial in these substrates and only minor modifications were explored. In particular, the inclusion of *tert*-butyl esters would deliver indanes with a complementary set of carboxylate groups, which may not significantly perturb the overall structure of the starting material (**Figure 3.12**). To explore this concept, we investigated altering both the α,β-unsaturated ester and malonate moiety, as this would enhance the flexibility of manipulating these products further.

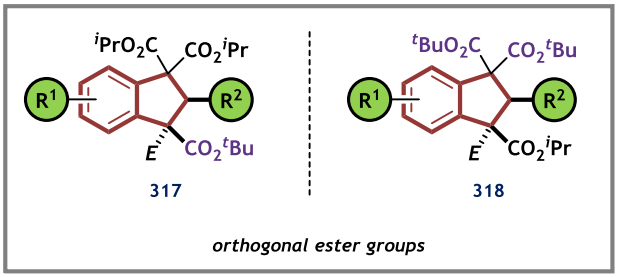


Figure 3.12 – Proposed new indanes with orthogonal ester groups

3.6.3.1 *Substrate Synthesis*

In order to evaluate our new indane precursors we first had to synthesize the fragments required to construct them (**Figure 3.13**). We planned to assess and compare one of each analogue before continuing to expand the scope of this methodology. The two starting materials required for this purpose were an iodoarene substituted with a di-*tert*-butyl malonate group (**319**) and a vinylstannane appended with a ^{t}Bu ester (**320**).

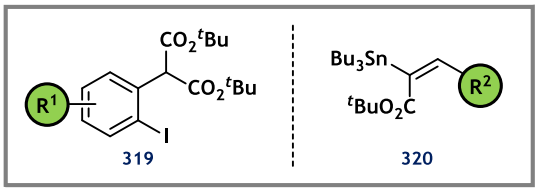
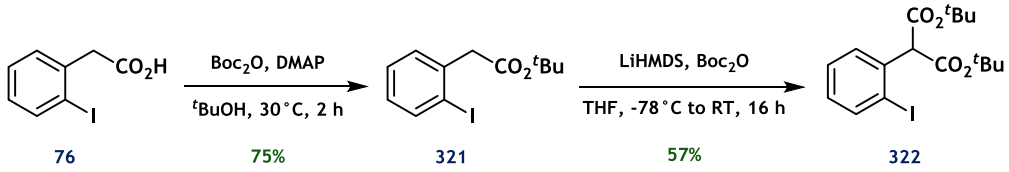


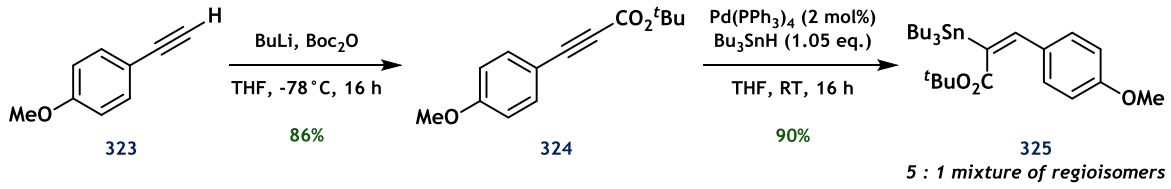
Figure 3.13 – The starting materials required to synthesize new cyclization precursors

The first component was synthesized from 2-iodophenylacetic acid **76**, which was esterified with a mixture of Boc anhydride and DMAP in *tert*-butanol, to afford arene **321** in 75% yield (**Scheme 3.48**).[177] Conversion to the di-*tert*-butyl malonate **322** was achieved in good yield through benzylic deprotonation of ester **321** with LiHMDS at −78 °C, and trapping of the subsequent carbanion with Boc_2O.



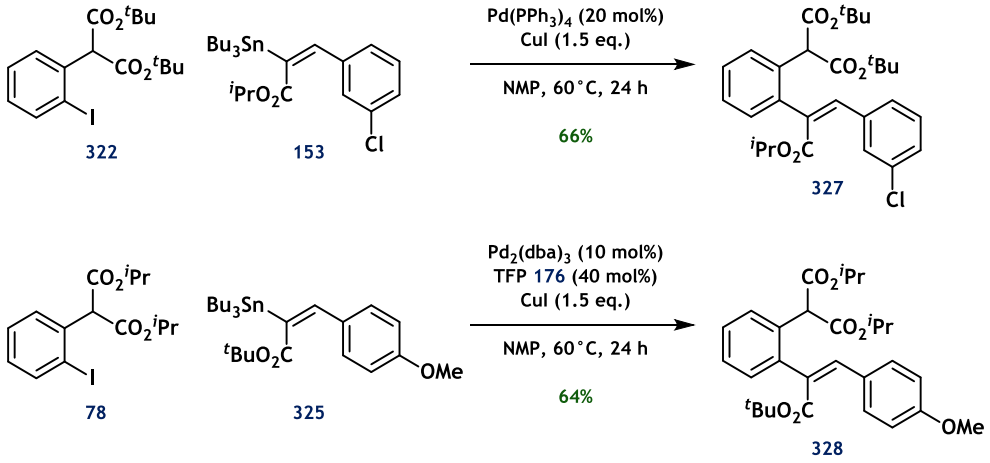
Scheme 3.48 – Synthesis of the di-*tert*-butylmalonate substituted arene **322**

The new α-stannylvinyl ester **325** was synthesized from 4-ethynylanisole **323** in two steps according to previously optimized procedures (**Scheme 3.49**).[60] The metal acetylide generated from deprotonation of alkyne **323** with butyllithium was quenched with Boc anhydride to afford propargylic ester **324** in 86% yield. Subsequent $Pd(PPh_3)_4$ mediated hydrostannylation of acetylene **324** with tributyltin hydride delivered a 5 : 1 mixture of regioisomeric vinylstannanes **325**, in a combined yield of 90%.



Scheme 3.49 – Formation of propargylic ester **324** and its subsequent hydrostannylation to form stannane **325**

Assembly of the *ortho*-substituted vinyl arenes was conducted with the optimal Stille-Migita cross-coupling conditions, which have performed consistently in previous systems (**Scheme 3.50**).[112,113] Di-*tert*-butyl malonate iodoarene **322** was united with the chlorinated vinylstannane **153** in the presence of $Pd(PPh_3)_4$ (20 mol%) and CuI (1.5 eq.) to afford indane precursor **327** in 66% yield. Similarly, a catalytic system generated from $Pd_2(dba)_3$ and TFP **176** was effective for synthesizing substrate **328** bearing an α,β-unsaturated *tert*-butyl ester in 64% yield.



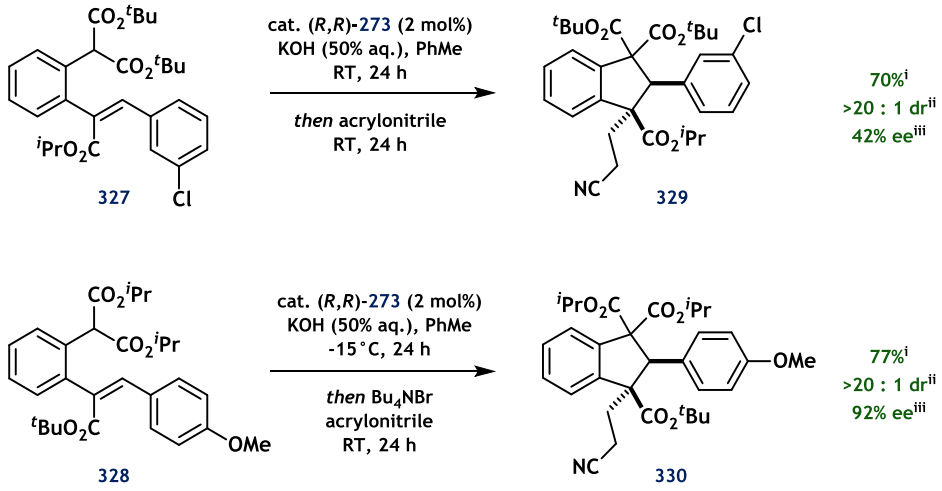
Scheme 3.50 – Stille-Migita reaction with *tert*-butyl ester containing coupling partners

Pleasingly, the increased steric bulk of the *tert*-butyl ester on either coupling partner did not adversely impact the success of the cross-coupling reaction.

3.6.3.2 Substrate Comparison

To evaluate and compare the levels of asymmetric induction furnished by substrates containing distinct ester groups, we performed a phase-transfer catalyzed cyclization-alkylation sequence (**Scheme 3.51**). The di-*tert*-butyl malonate analogue **327** reacted lethargically at −15 °C, but starting material was fully consumed after 24 hours at ambient temperature. The resulting enolate was alkylated with acrylonitrile to deliver a

single diastereomer of indane **329** in 70% yield and 42% ee. In contrast, 2 mol% of catalyst (*R*,*R*)-**273** at −15 °C was sufficient to cyclize substrate **328** within a reasonable time frame. However, the addition of Bu_4NBr post-cyclization was necessary to promote formation of the quaternary stereocentre. This highly diastereoselective protocol afforded 77% yield of the desired product **330**, which had an enantiomeric excess of 92% (**Scheme 3.51**).



[i] Isolated yield. [ii] Ratio was determined by analysis of the crude ^1H NMR spectrum. [iii] ee determined by chiral HPLC.

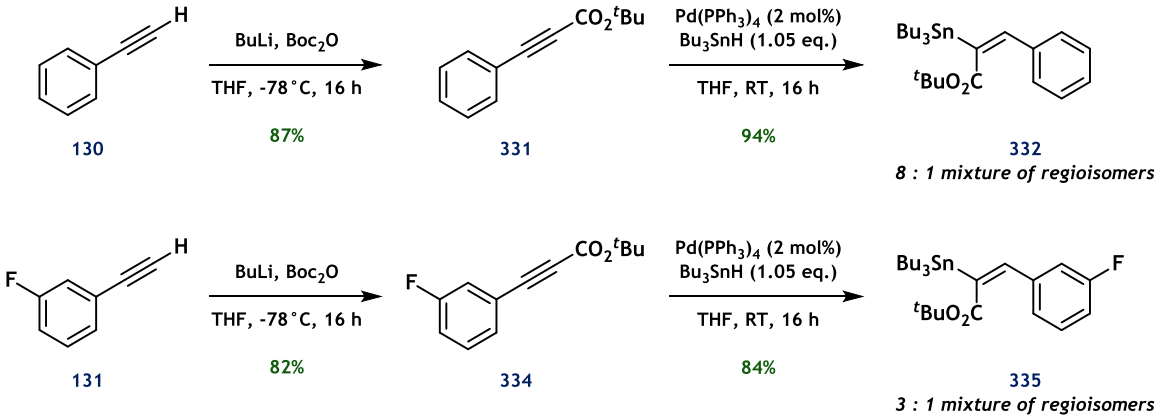
Scheme 3.51 – Evaluating the tolerance of *tert*-butyl esters in the asymmetric 5-*endo*-trig cyclization

The increased steric hindrance introduced by the *tert*-butyl esters was reflected by the reduced reactivity observed in the cyclization step for substrate **327** and the required addition of Bu_4NBr to promote 1,4-addition with the enolate derived from precursor **328**. Despite the apparent sensitivity of this asymmetric 5-*endo*-trig cyclization towards minor structural alterations, the successful utilization of a conjugate acceptor bearing a *tert*-butyl ester has furnished a more orthogonally substituted indane.

3.6.3.3 Substrate Scope

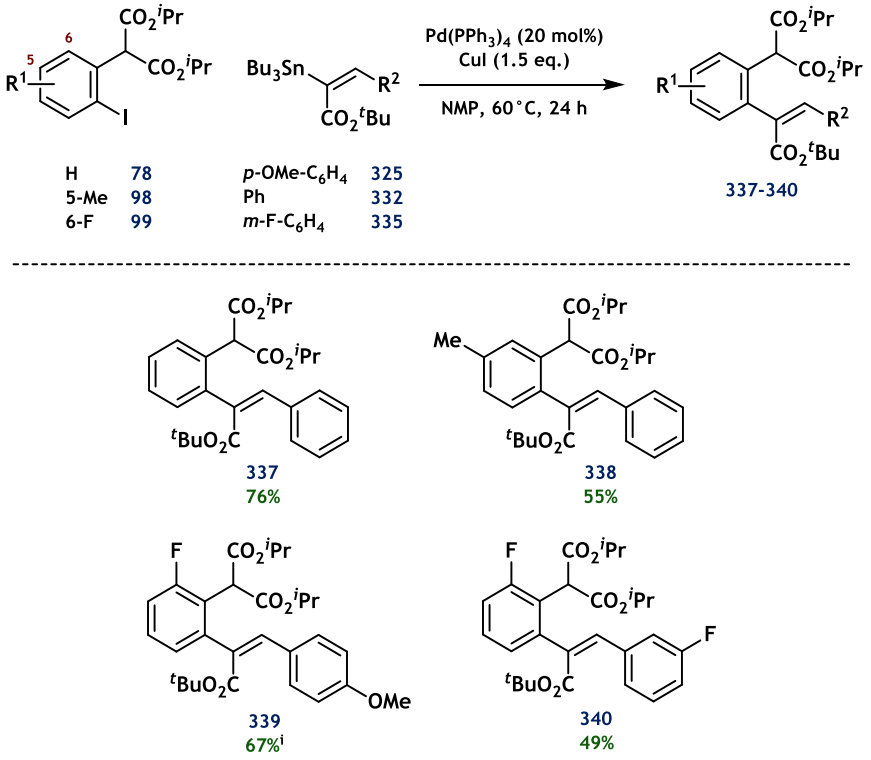
The tolerance of a *tert*-butyl ester in the vinylic position of the indane precursor presented an excellent opportunity to expand the substrate scope. Accordingly, we synthesized

additional vinylstannanes starting from inexpensive commercially available terminal acetylenes (**Scheme 3.52**).[60] For example, propargylic ester **331** was synthesized in 87% yield from phenylacetylene **130** and was then subsequently hydrostannylated with excellent regioselectivity to afford vinylstannane **332** in 94% yield. In a similar sequence, alkyne **131** was converted to α-stannylvinyl ester **335** *via* intermediate **334** in good isolated yields.



Scheme 3.52 – Synthesis of two new vinylstannanes **332** and **335**

Consequently, a small collection of substrates was assembled according to the Stille-Migita reaction conditions outlined previously (**Scheme 3.53**).[112,113] The simplest case, which involved unadorned coupling partners (arene **78** and stannane **332**), was accomplished with $Pd(PPh_3)_4$ and excess copper(I) iodide to afford precursor **337** in 76% yield. Under equivalent conditions with the identical vinylstannane **332**, the methylated analogue **338** could be generated in 55% yield. Fluorinated iodoarene **99** was also employed in two Stille-Migita reactions that furnished the substrates **339**-**340** in 67% and 49% yield respectively (**Scheme 3.53**).

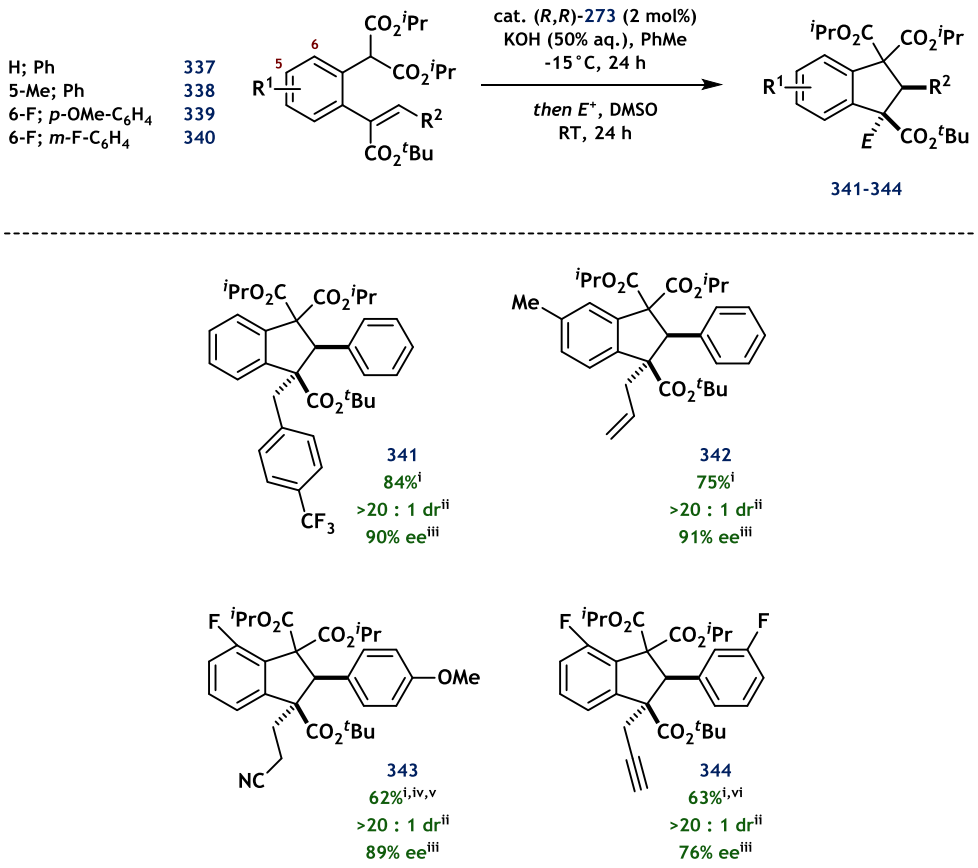


*[i] $Pd_2(dba)_3$ (10 mol%) and TFP **176** (40 mol%) were used instead of $Pd(PPh_3)_4$*

Scheme 3.53 – Stille-Migita cross-coupling to form a new set of indane precursors

The new analogues were cyclized in the presence of the Maruoka catalyst (*R,R*)-**273** and subsequently alkylated to afford indanes bearing two contiguous stereocentres, including an all-carbon quaternary centre (**Scheme 3.54**). For instance, substrate **337** underwent ring closure under our standard asymmetric phase-transfer conditions to afford an enolate that was trapped with a trifluoromethyl benzyl bromide derivative in DMSO. The resulting indane **341** was acquired as a single diastereomer in 84% yield and 90% ee. A methylated analogue **342** was also delivered with similar degrees of asymmetric induction, following a highly diastereoselective allylation step with an epimeric mixture of *anti*- and *syn*-indanes. Pleasingly, the 6-fluorinated substrates were also well tolerated and maintained good levels of enantioselectivity. In particular, precursor **339** was treated with quaternary ammonium salt (*R,R*)-**273** in a biphasic mixture of toluene and 50% aqueous KOH to promote the initial

5-*endo*-trig ring closure. The ensuing product was then alkylated *via* 1,4-addition onto acrylonitrile to furnish indane **343** in 89% ee. The final analogue bearing two fluorine substituents was cyclized in a solubilizing mixture of toluene and chloroform (9 : 1), which encouraged a rate acceleration in the initial ring closing step, when compared to pure toluene. Subsequently, the intermediate enolate was quenched with propargyl bromide in DMSO to produce indane **344** in 63% yield with a moderate decline in enantioselectivity to 76% ee (**Scheme 3.54**).



[i] Isolated yield. [ii] Ratio was determined by analysis of the crude ^{1}H NMR spectrum. [iii] ee determined by chiral HPLC. [iv] Bu_4NBr was added instead of DMSO. [v] Reaction time was 48 h. [vi] Reaction solvent was PhMe : $CHCl_3$ (9 : 1).

Scheme 3.54 – Generation of optically enriched indanes with superior functional group orthogonality

In summary, the ester of the 1,4-acceptor can be modified to a *tert*-butyl carboxylate with little impact on the levels of asymmetric induction. The indanes generated in this array

demonstrate superior functional group orthogonality to those synthesized previously. This complementary set of substituents can provide a convenient handle for performing selective derivatizations to form a diverse assortment of analogues.

3.6.4 Indanes with Three Contiguous Stereocentres

In order to fully exploit the synthetic potential of this 5-*endo*-trig cyclization we investigated modifications to the benzylic substituents, which could provide a more powerful and versatile methodology (**Figure 3.14**). In particular, by employing two distinct acidifying groups at this position, three contiguous stereocentres are formed, with two being all-carbon and quaternary. This strategy also presents further opportunities to increase the orthogonality of substituents on the carbocyclic core of the molecule.

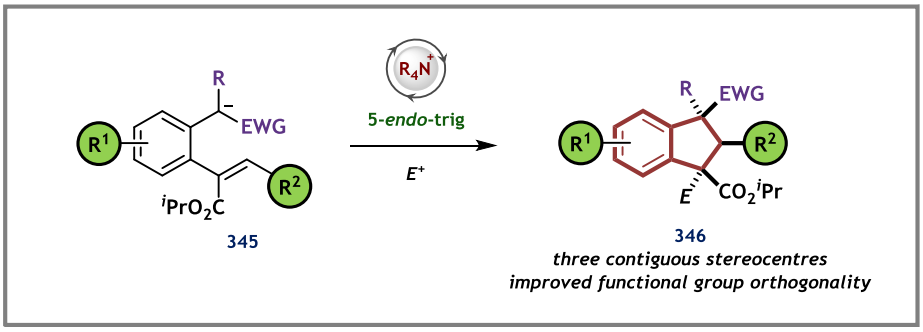


Figure 3.14 – Strategy for the synthesis of indanes with three contiguous stereocentres

Evidently, the combination of substituents at the benzylic position must harmonize in order to ensure good reactivity and stereoselectivity. For instance, deprotonation of the substrate under the relatively mild phase-transfer conditions requires functional groups that can stabilize the incipient anion. Previous work within the Smith group demonstrated that non-symmetrical malonates were poorly diastereoselective in related cyclizations.[55] This highlighted an important role of the chiral cation, which must be capable of differentiating between the prochiral faces of the benzylic anion. To achieve this distinction and obtain

higher levels of stereocontrol the nature of the two groups must be dissimilar. Recently, research in the Smith group has established that certain permutations of ester, nitrile and phenyl substituents can accommodate these requirements.[55–57] Therefore, we sought to exploit these arrangements in our system and devised three new iodoarene components (**347**-**349**) to examine this extension of the 5-*endo*-trig protocol (**Figure 3.15**).

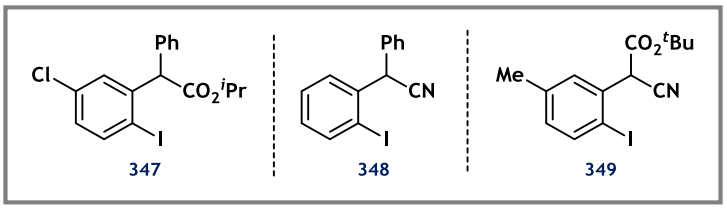
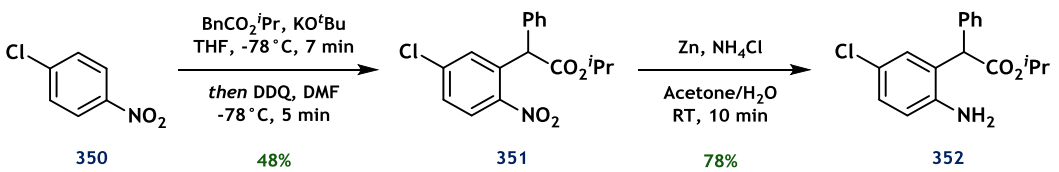


Figure 3.15 – Proposed new iodoarene components with distinct geminal benzylic substituents

3.6.4.1 Substrate Synthesis

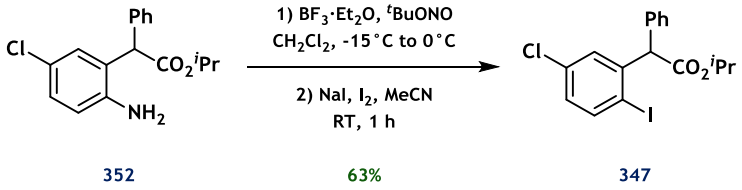
In general, the procedures for generating the following aniline compounds were previously optimized within the Smith group. We reasoned that these derivatives would be excellent candidates for the diazotization-displacement sequence employed for the malonate adducts. Accordingly, an oxidative nucleophilic substitution reaction was employed to generate *ortho*-substituted arene **351** from *para*-chloronitrobenzene **350** (**Scheme 3.55**).[†] Oxidation of the intermediate Meisenheimer complex with DDQ delivers the desired product **351** in 48% yield.[178] Subsequent reduction mediated by zinc dust and ammonium chloride furnished the corresponding aniline **352** in 78% yield.[64]



Scheme 3.55 – Synthesis of aniline **352** from nitroarene **350**

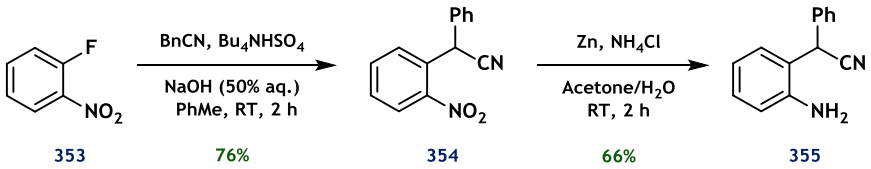
[†] *This compound was prepared and gifted by Dr Philip Woods.*

The next step involved diazotization with *tert*-butyl nitrite in the presence of boron trifluoride diethyl etherate, which converted aniline **352** into the corresponding diazonium BF_4^- salt (**Scheme 3.56**).[68–70] Displacement of N_2 was achieved with a mixture of sodium iodide and iodine at room temperature to provide a 63% isolated yield of iodoarene **347**.



Scheme 3.56 – Diazonium salt formation and displacement to form iodoarene **347**

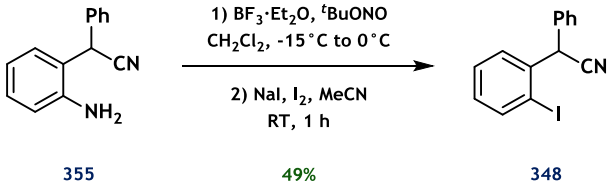
The α-phenyl nitrile aniline **355** was synthesized in a similar manner, with an initial S_NAr reaction between *ortho*-fluoronitrobenzene **353** and benzyl cyanide (**Scheme 3.57**).[†] This protocol required stoichiometric quantities of the phase-transfer catalyst Bu_4NHSO_4 due to product inhibition, and led to 76% yield of nitroarene **354**.[179] Subsequent reduction with zinc dust smoothly afforded the desired aniline **355** in 66% yield.[64]



Scheme 3.57 – S_NAr-reduction sequence to form aniline **355**

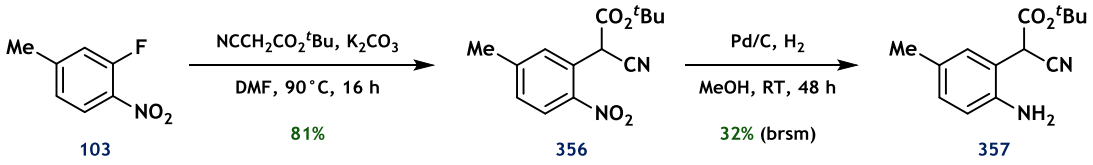
The aniline **355** was then reacted with $BF_3{\cdot}Et_2O$ and *tert*-butyl nitrite to generate a relatively stable diazonium salt (**Scheme 3.58**).[68–70] Subsequent treatment with a blend of iodine and sodium iodide in MeCN afforded the *ortho*-substituted arene **348** in 49% yield over two steps.

[†] *This compound was prepared and gifted by Krishna Sharma.*



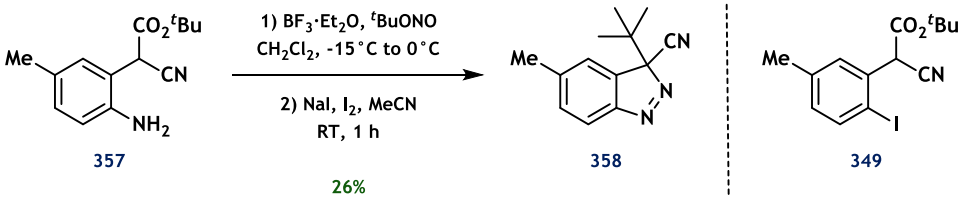
Scheme 3.58 – Diazonium salt formation and displacement to form iodoarene **348**

The final iodoarene that we required was the α-cyano ester arene **349**, which was synthesized by a slightly modified route. Nucleophilic aromatic substitution between fluoronitroaromatic **103** and *tert*-butyl cyanoacetate in DMF furnished the desired product **356** in 81% yield (**Scheme 3.59**).[55] The nitro group was reduced with palladium on carbon under an atmosphere of hydrogen to deliver aniline **357** in 32% yield, based on the recovery of starting material.[55]



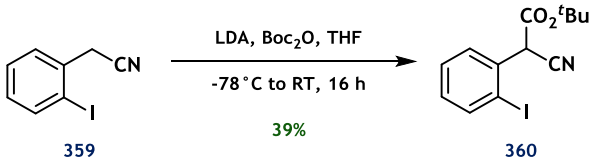
Scheme 3.59 – Synthesis of aniline **357** starting from fluoronitroarene **103**

Disappointingly, the synthesis of the iodoarene **349** was not successful with this particular aniline. As before, diazotization was conducted with a mixture of *tert*-butyl nitrite and $BF_3{\cdot}Et_2O$, but following the addition of sodium iodide and iodine the sole product isolated from the reaction was tentatively assigned as 3*H*-indazole **358**.[68–70] Presumably, this outcome reflects the enhanced reactivity of this cyanoacetate group, which attacked the diazonium cation directly to form the heterocyclic ring. Decarboxylation and trapping of the resulting *tert*-butyl cation could fully rationalize the structure of compound **358**.



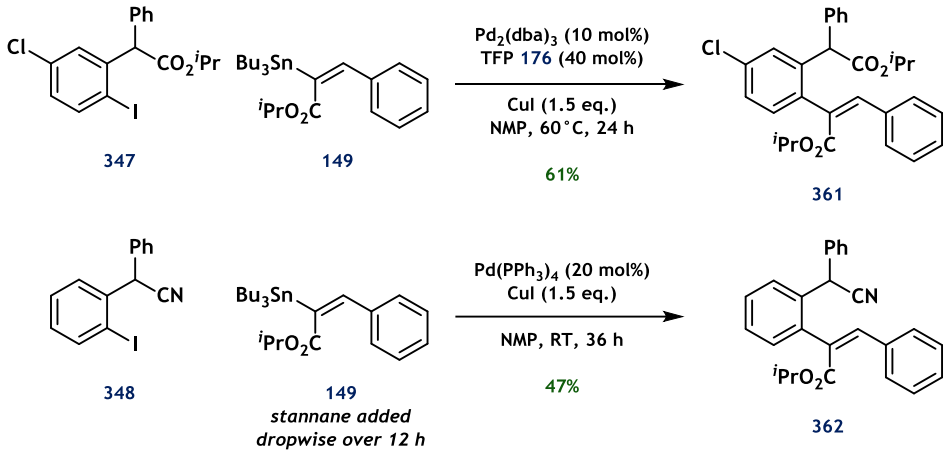
Scheme 3.60 – Unexpected formation of 3*H*-indazole **358** upon diazotization of aniline **357**

Fortunately, a more expedient route that involved a single synthetic step to form the less substituted iodoarene **360** was discovered (**Scheme 3.61**). Benzylic deprotonation of the aryl substrate **359** with LDA and quenching of the resulting carbanion with Boc_2O generated a moderate yield of product **360**.[180]



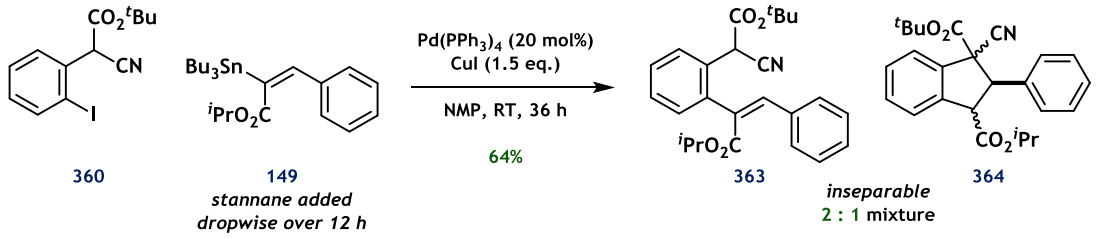
Scheme 3.61 – Synthesis of iodoarene **360** with LDA and Boc_2O

Following the synthesis of the required iodoarene components, we utilized them in a Stille-Migita reaction to construct new indane precursors. Initially, the α-phenyl ester substrate **347** was coupled to vinylstannane **149** by a catalyst generated from $Pd_2(dba)_3$ and TFP **176** (**Scheme 3.62**).[112,113] The chlorinated adduct **361** was obtained in 61% yield following purification on a K_2CO_3-doped silica column to remove residual tin by-products.[117] To facilitate isolation of precursor **362**, $Pd(PPh_3)_4$ was employed in the cross-coupling reaction, as residual dba hampered separation attempts. Moreover, as substrate **362** was prone to cyclize at elevated temperatures, this coupling protocol was performed at room temperature with the stannane **149** being transferred dropwise over 12 hours. The desired product **362** was acquired in 47% yield, free from any impurities (**Scheme 3.62**).



Scheme 3.62 – Stille-Migita cross-coupling to form substrates **361**-**362**

Disappointingly, this very mild set of cross-coupling conditions could not be successfully applied to our final analogue **363**. Performing the reaction at room temperature with slow addition of vinyltin reagent **149** led to an inseparable 2 : 1 mixture of precursor **363** and indane **364** (**Scheme 3.63**). This outcome precluded the α-cyano ester substrate **363** as a viable intermediate to synthesize optically enriched carbocycles.

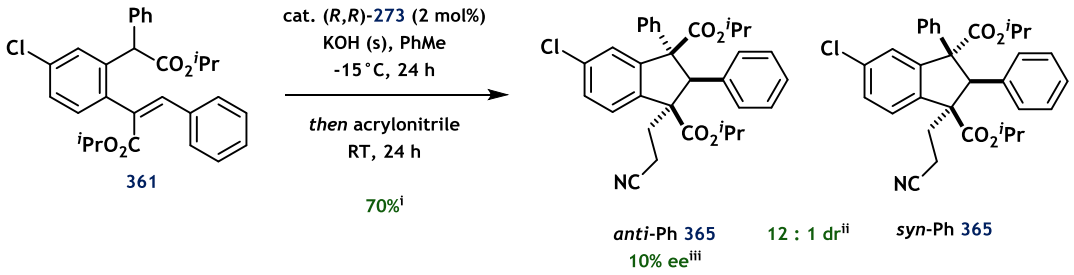


Scheme 3.63 – Pd^0-mediated cross-coupling to generate a mixture of substrate **363** and indane **364**

3.6.4.2 Substrate Evaluation

Our new precursors bearing distinct geminal benzylic substituents were subsequently examined under optimized conditions with the C_2-symmetric quaternary ammonium salt (*R*,*R*)-**273**. Previous research within the Smith group demonstrated that a solid-liquid phase-transfer protocol was necessary to promote efficient cyclization with the less acidic α-phenyl ester moiety.[56] Accordingly, substrate **361** was treated with 2 mol% of catalyst

(*R*,*R*)-**273** and solid powdered KOH in toluene for 24 hours at −15 °C (**Scheme 3.64**). Following ring closure, alkylation with acrylonitrile generated the second quaternary stereocentre in a highly diastereoselective manner. Analysis of the crude reaction mixture by ^{1}H NMR indicated that a 12 : 1 mixture of *anti*-Ph **365** and *syn*-Ph **365** was produced. The major epimer was determined to have an enantiomeric excess of only 10%, which was significantly lower than the analogous malonate substrates.

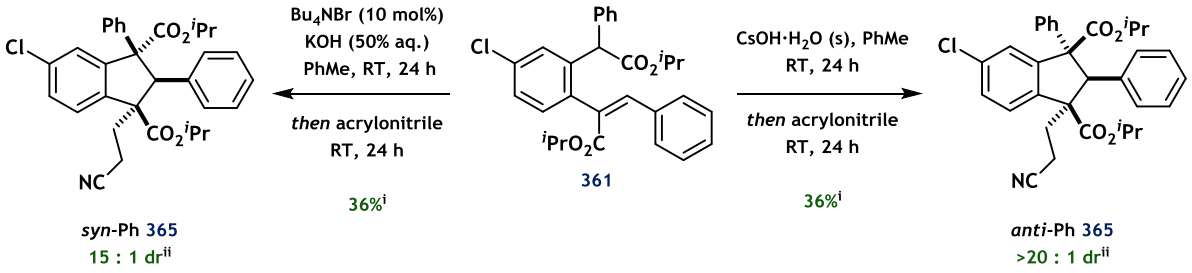


[i] Isolated yield for the combined mixture of diastereomers. [ii] Ratio was determined by analysis of the crude ^{1}H NMR spectrum. [iii] ee for the major diastereomer determined by chiral HPLC.

Scheme 3.64 – Asymmetric phase-transfer catalyzed cyclization of substrate **361**

To provide an authentic racemic sample of *anti*-Ph **365** for chiral HPLC, the starting material **361** was cyclized under typical achiral phase-transfer conditions (**Scheme 3.65**). Remarkably, employing Bu_4NBr in a biphasic mixture of toluene and 50% aqueous KOH led to a 15 : 1 mixture of diastereomers, which favoured the *syn*-Ph **365** epimer. In contrast, conducting the reaction with solid $CsOH{\cdot}H_2O$ in the absence of an alkylammonium salt provided the opposite stereoisomer with near perfect selectivity. This outcome emphasized the significance of the cation in this process, as a strong bias for either epimer could be dictated by the inclusion or absence of the Bu_4N^+ counterion. The relative configuration for both diastereomers was established by nOe experiments.[†]

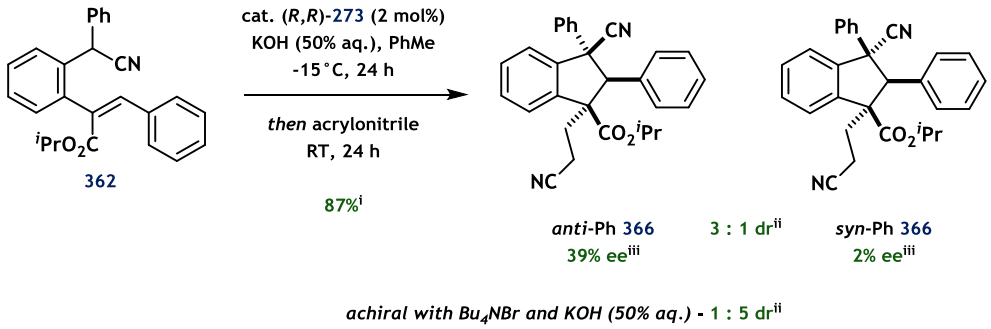
[†] *Refer to experimental section 5.3.8, pages 418-419 for the 1D nOe and 2D NOESY data.*



[i] Isolated yield for the combined mixture of diastereomers. [ii] Ratio was determined by analysis of the crude ^{1}H NMR spectrum.

Scheme 3.65 – The variation of diastereoselectivity with the racemic cyclization conditions utilized

A similar cation-dependence was observed with the α-cyano phenyl substrate **362**, but to a lesser degree (**Scheme 3.66**). In the presence of the Maruoka catalyst (*R*,*R*)-**273** cyclization and alkylation led to a 3 : 1 (*anti*-Ph **366** : *syn*-Ph **366**) ratio of indanes, with the major epimer being formed in 39% ee. A reversal of selectivity was observed under achiral phase-transfer conditions with Bu_4NBr delivering a 1 : 5 (*anti*-Ph **366** : *syn*-Ph **366**) mixture of diastereomeric products. The relative configuration of the major stereoisomer, *syn*-Ph **366**, was determined by nOe analysis.[†]



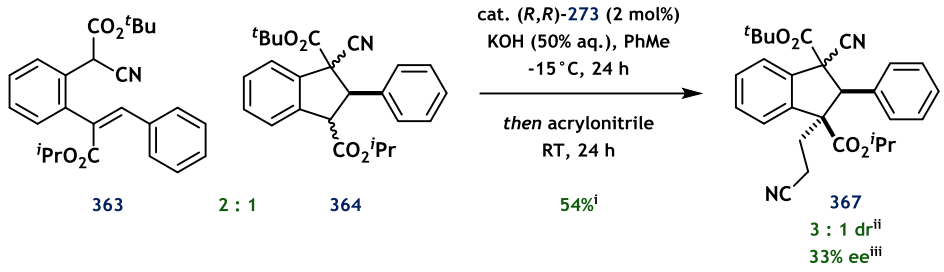
[i] Isolated yield for the combined mixture of diastereomers. [ii] Ratio was determined by analysis of the crude ^{1}H NMR spectrum. [iii] ee determined by chiral HPLC.

Scheme 3.66 – Cyclization-alkylation to form a mixture of *anti*-Ph **366** and *syn*-Ph **366**

The α-cyano ester substrate **363** was isolated from the Stille-Migita cross-coupling reaction as a 2 : 1 mixture with the cyclized product **364**. Evidently, the presence of this

[†] *Refer to experimental section 5.3.8, page 423 for the 1D nOe data.*

racemic derivative would have a detrimental impact on the enantioselectivity of the ensuing 5-*endo*-trig ring closure. Nevertheless, subjecting this medley of compounds to asymmetric phase-transfer conditions and quaternization of the benzylic stereocentre with acrylonitrile afforded an inseparable 3 : 1 mixture of indanes **367** in 54% yield (**Scheme 3.67**). Analysis of the product by chiral HPLC revealed the major epimer was produced in 33% ee.



[i] Isolated yield for the combined mixture of diastereomers. [ii] Ratio was determined by analysis of the crude ^{1}H NMR spectrum. [iii] ee determined for the major diastereomer by chiral HPLC.

Scheme 3.67 – Formation of an indane with three contiguous stereocentres

Three systems encompassing two distinct acidifying groups at the benzylic position were examined to synthesize densely functionalized indanes bearing three contiguous stereocentres. An intriguing dependence of the diastereoselectivity on the nature of the cation was observed, which could significantly bias the formation of one epimeric product. However, the poor levels of asymmetric induction imparted by the Maruoka catalyst (*R*,*R*)-**273** rendered these substrates less valuable when compared to the optically pure analogues created previously.

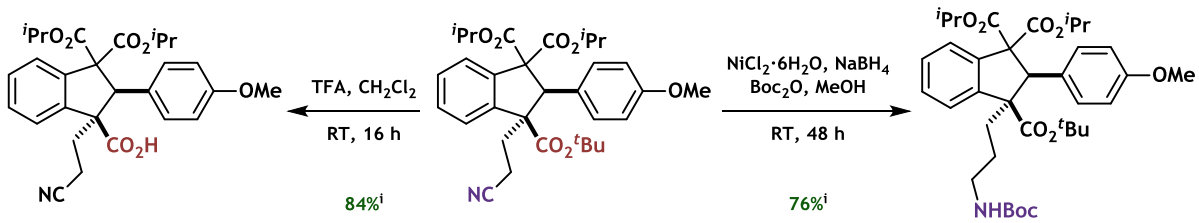
3.7 Chemoselective Transformations with the Indane Products

To highlight the synthetic utility of the highly substituted indane substrates a series of chemoselective derivatizations were investigated. In particular, demonstration of the

functional group orthogonality within these products would render this methodology a practical and versatile route for generating small complex carbocyclic materials.

3.7.1 Deprotection of the tert-Butyl Ester and Selective Nitrile Reduction

The simplest modification involved deprotection of the *tert*-butyl ester in substrate **330** to furnish the corresponding carboxylic acid **368** (**Scheme 3.68**). This reaction was readily accomplished under strongly acidic conditions and produced an 84% yield of indane **368**, which retained its stereochemical integrity. The resulting carboxyl group could be further transformed into a variety of amides or reduced selectively with borane to deliver a primary alcohol.[181]



[i] Isolated yield. [ii] Ratio was determined by analysis of the crude ^{1}H NMR spectrum. [iii] ee determined by chiral HPLC.

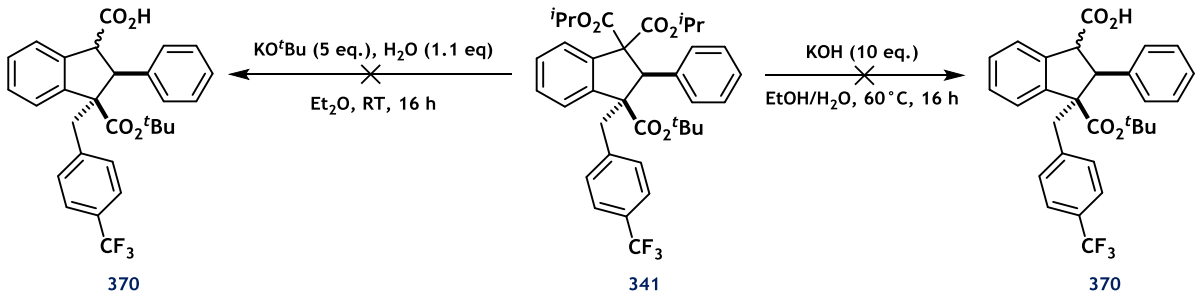
Scheme 3.68 – Deprotection of the *tert*-butyl ester and selective reduction of the nitrile group

Subsequently, the more demanding task of reducing the nitrile group in substrate **330**, whilst leaving the three ester functionalities intact was examined. Research by the Caddick group has demonstrated that nickel(II) boride is a mild and efficient reagent for this transformation.[182] The active catalytic species can be generated *in situ* from $NiCl_2{\cdot}6H_2O$ and $NaBH_4$ in methanol, and was able to smoothly afford amine **369** in 76% yield after trapping with Boc anhydride (**Scheme 3.68**). Pleasingly, under these reaction conditions no reduction

of the esters was witnessed, and enantioenriched starting material did not undergo racemization or epimerization.

3.7.2 Selective Modification of the Diisopropyl Malonate

Demonstration of the orthogonality of the malonate and ester groups was also deemed necessary. Currently, there are only limited reported methods for the selective modification of an isopropyl ester in the presence of its *tert*-butyl counterpart.[183] We were primarily interested in developing a protocol that could introduce a third stereocentre into the indane ring system. Initially, we reasoned that a conventional basic hydrolysis may exclusively target the less sterically demanding isopropyl ester. Under these conditions it was assumed that decarboxylation to the monoacid **370** would predominate. Accordingly, indane **341** was treated with potassium hydroxide in a mixture of ethanol and water at 60 °C (**Scheme 3.69**). However, analysis of the crude reaction by ^{1}H NMR and TLC indicated a rather complex array of products; therefore, no attempt was made to isolate the desired acid **370**.

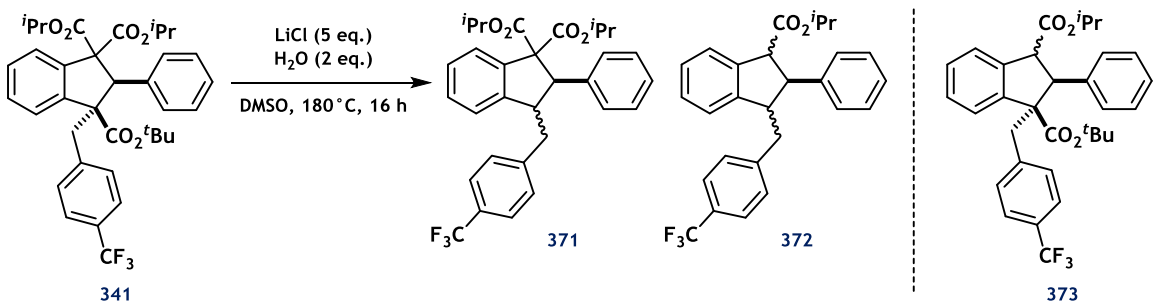


Scheme 3.69 – Attempted hydrolysis of a diisopropyl malonate to produce acid **370**

The efficacy of unsolvated hydroxide ions to promote the saponification of hindered esters at room temperature has been illustrated.[184] The anhydrous base can be generated by adding a trace of water to potassium *tert*-butoxide suspended in diethyl ether. Employing this procedure with indane **341** proved futile as only starting material was recovered after

16 hours (**Scheme 3.69**). The reluctance of substrate **341** to undergo clean decarboxylation and hydrolysis to produce acid **370** led us to investigate alternative protocols which could accomplish this feat.

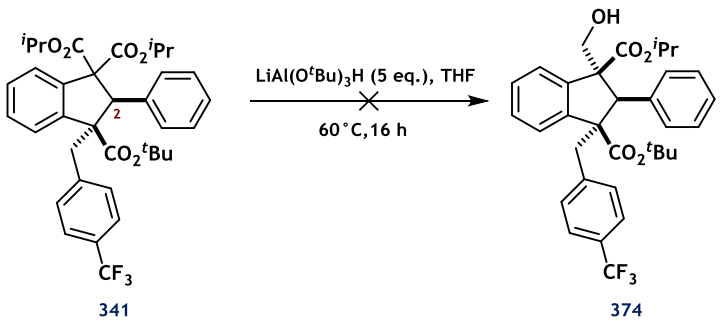
Subsequently, we explored the possibility of inducing decarboxylation *via* a Krapcho reaction.[185] This process would provide direct access to an epimeric mixture of esters which could be alkylated diastereoselectively to afford indanes with three contiguous stereogenic centres. However, there are no literature reports of a diisopropyl malonate being utilized in this transformation, although previous research within the Smith group has established its feasibility.[186] Despite the harsh temperatures involved the Krapcho decarboxylation is often considered a very mild and functional group tolerant reaction.[187] Exposing indane **341** to lithium chloride in wet DMSO at 180 °C did not generate the expected product **373** (**Scheme 3.70**). The crude reaction mixture was very complicated but mass spectrometry provided tentative evidence for two major components, compounds **371** and **372**, which were not isolated. The thermolysis of *tert*-butyl esters is a known phenomenon and it emerged as the dominant pathway in this reaction.[188] Reduction of the temperature to 150 °C was sufficient to suppress this side-reaction, but decarboxylation of the malonate was also impeded.



Scheme 3.70 – Attempted Krapcho decarboxylation of a diisopropyl malonate to generate ester **373**

These results emphasized the challenging nature of this transformation, but undeterred we began to investigate alternative approaches to selectively modify the diisopropyl malonate group.

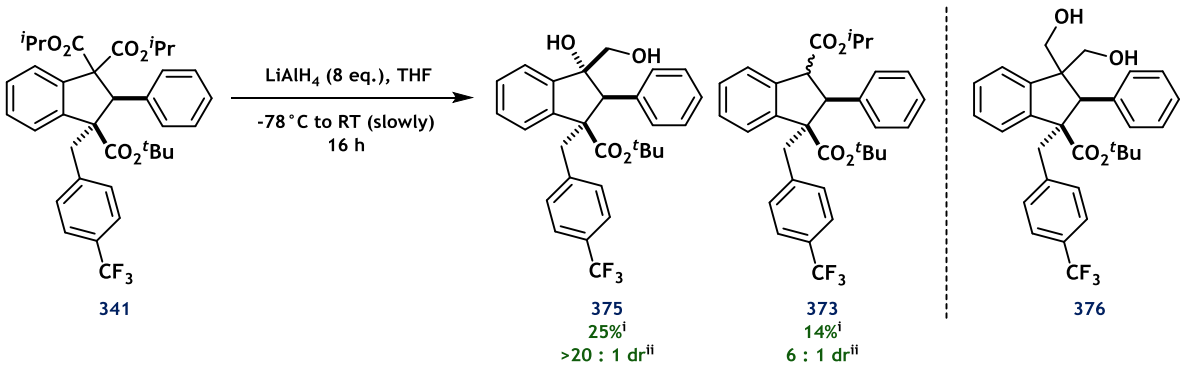
The introduction of an additional stereogenic centre on the indane ring with chemoselective hydride reducing agents was also examined. We reasoned that the isopropyl ester that lies remote to the phenyl ring attached at the 2-position would be less sterically obstructed and, therefore, its reduction more facile. The electron-rich $LiAl(O^tBu)_3H$ reagent has been demonstrated to reduce malonates exclusively to their hydroxy-ester derivatives.[189] The intermediate aluminate species formed during the reaction is considered to be sufficiently bulky to prevent further reduction. Treatment of indane **341** with excess $LiAl(O^tBu)_3H$ in THF at 60 °C led to no discernible reactivity and implied that the substrate was too hindered from the outset (**Scheme 3.71**).



Scheme 3.71 – Attempted diastereoselective reduction to synthesize indane **374**

Lamentably, endeavours to introduce a third stereocentre were halted, and our focus was diverted to purely attaining selective modification of the isopropyl ester. We reasoned that by fastidiously controlling the reaction conditions, a double reduction of the malonate **341** to the diol **376** was viable (**Scheme 3.72**). An early result delivered an unexpected outcome when indane **341** was treated with a large excess of $LiAlH_4$ in THF. After warming the

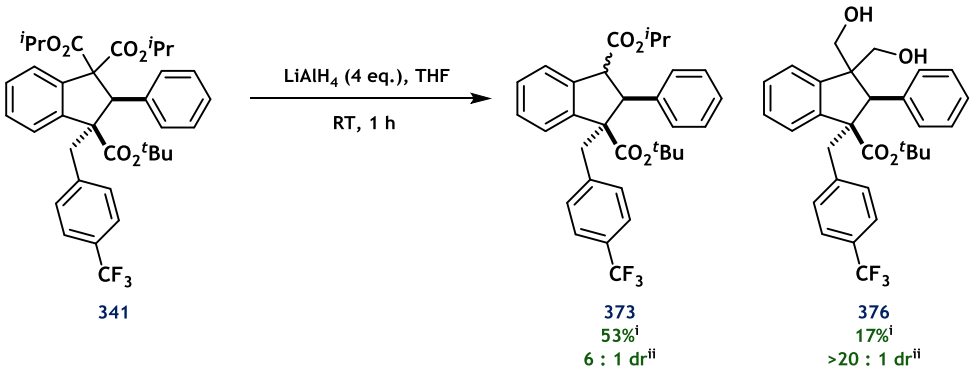
reaction slowly to room temperature overnight, none of the desired product **376** was observed. Purification of the crude reaction mixture provided two major products: diol **375** and ester **373**, albeit in low yields. The diol **375** presumably arose from atmospheric oxidation of ester **373** and subsequent reduction. Therefore, it appeared that a nucleophilic *retro*-Claisen type process was favoured over the standard reduction pathway.



[i] Isolated yield for the combined mixture of diastereomers. [ii] Ratio was determined by analysis of the crude ^{1}H NMR spectrum.

Scheme 3.72 – Chemoselective reduction of diisopropyl esters over a *tert*-butyl ester

Despite the unforeseen circumstances surrounding this reaction it was apparent that the *tert*-butyl ester was inert to these conditions. An alternative protocol conducted at ambient temperature with four equivalents of $LiAlH_4$ proved more practical, and led to two major products (**Scheme 3.73**). The decarboxylated indane **373** was produced in 53% yield as before but the anticipated product diol **376** was also generated as a minor constituent of the reaction.



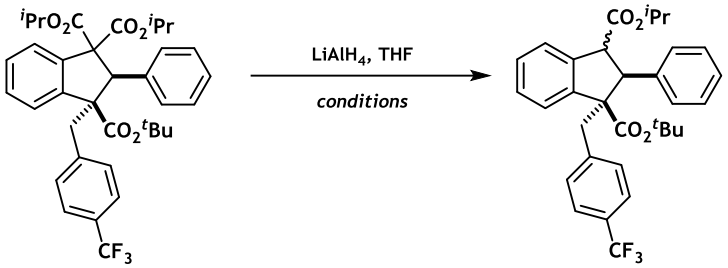
[i] Isolated yield for the combined mixture of diastereomers. [ii] Ratio was determined by analysis of the crude ^{1}H NMR spectrum.

Scheme 3.73 – Reductive *retro*-Claisen type process to produce ester **373** and diol **376**

The ester substrate **373** was actually the compound we had initially attempted to produce *via* hydrolysis or Krapcho decarboxylation. Our previous experience with these materials has demonstrated that alkylations controlled by the adjacent stereocentre were highly diastereoselective (*vide supra, section 3.5.2*). Accordingly, we optimized a protocol to synthesize the *retro*-Claisen product **373** selectively over the expected diol product **376**. An assessment of alternative reducing agents established that lithium aluminium hydride was the most effective and consistent reagent for this transformation.[†] One of the main concerns with this procedure was further reduction of the decarboxylated material **373** to form an unresolvable mixture of diastereomeric alcohols, which must be avoided. Scrupulous optimization of the reaction parameters was performed in order to further bias the *retro*-Claisen pathway and to minimize over-reduction of the resulting epimeric mixture of esters (**Table 3.9**). Initially, the quantity of $LiAlH_4$ was lowered as excess was deemed to be detrimental (**entries 1**-**3**). The use of two equivalents was optimal and provided ester **373** in 65% isolated yield (**entry 2**). Conducting the reduction at −78 °C halted the progress of the

[†] *Common reducing agents such as DIBAL-H, Red-Al, $LiBH_4$ and $LiEt_3BH$ were all screened and promoted the same retro-Claisen type decarboxylation to different degrees of efficiency.*

reaction completely (**entry 4**). Addition of the hydride reagent at low temperature followed by warming the mixture to ambient conditions provided slightly lower and inconsistent yields (**entry 5**). This was due to the difficulties of monitoring the internal reaction temperature and identifying the optimal time to quench the hydride reagent. Performing a procedure at a constant −20 °C for 24 hours led to poor conversion of starting material and only 10% yield of the desired ester **373** was obtained (**entry 6**).



341 **373**

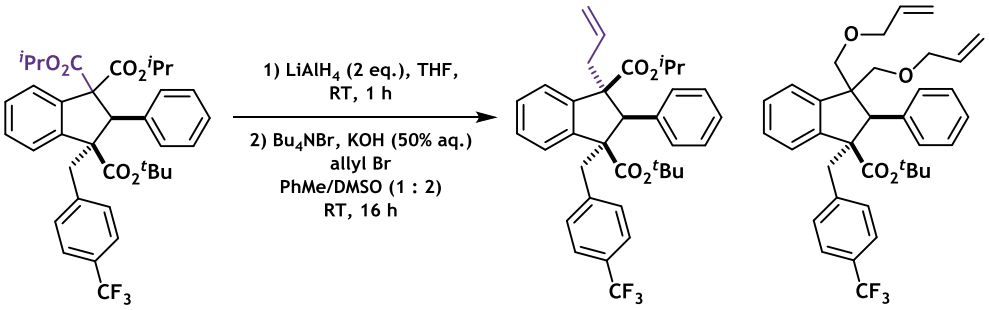
Entry	**Conditions**[i]	**Outcome**[ii,iii]
1	$LiAlH_4$ (4 eq.), THF, RT, 1 h	53% yield of **373**
2	$LiAlH_4$ (2 eq.), THF, RT, 1 h	65% yield of **373**
3	$LiAlH_4$ (1 eq.), THF, RT, 1 h	60% yield of **373**
4	$LiAlH_4$ (2 eq.), THF, −78 °C, 6 h	SM[iv]
5	$LiAlH_4$ (1 eq.), THF, −78 °C to RT, 1 h	51% yield of **373**
6	$LiAlH_4$ (1 eq.), THF, −20 °C, 24 h	10% yield of **373**

*[i] The reaction conditions are as stated with indane **341** (1 eq.). [ii] Isolated yields are for the mixture of diastereomers. [iii] The major side product from these reactions was diol **376**, which was not isolated in these cases. The only exception to this is entry 1 (see **Scheme 3.73**). [iv] As determined by analysis of the crude ^{1}H NMR spectrum.*

Table 3.9 – Optimization of the reductive *retro*-Claisen reaction to synthesize ester **373**

Following determination of the optimal conditions to generate the *retro*-Claisen product preferentially over the traditional reduction product, we examined the subsequent alkylation step. The ester **373** was produced as a mixture of diastereomers, but previous research has demonstrated that alkylation controlled by the adjacent stereocentre is highly

diastereoselective (*vide supra, section 3.5.2*). Subjecting substrate **341** to the reductive decarboxylation procedure followed by alkylation with allyl bromide in toluene and DMSO generated indane **377** in 56% as a single diastereomer. Moreover, this product has three contiguous stereocentres, two of which are all-carbon and quaternary. The major by-product from this sequence was the doubly allylated compound **378**, which was readily separated from indane **377**.



[i] Isolated yield. [ii] Ratio was determined by analysis of the crude ^{1}H NMR spectrum. [iii] ee determined by chiral HPLC.

Scheme 3.74 – Reductive *retro*-Claisen-alkylation sequence to generate indane **377**

The serendipitous discovery of a hydride induced *retro*-Claisen type transformation has granted entry to indane structures with greater synthetic value and complexity. Although only one example has been presented here, the potential range of alkylating agents that could be employed are legion. Moreover, this protocol provides a more efficient and selective route to indanes bearing three contiguous stereocentres than the attempted asymmetric 5-*endo*-trig cyclizations with substrates bearing distinct geminal functional groups at the benzylic position (*vide infra, section 3.6.4*).

4. MECHANISM AND DISCUSSION

4.1 Postulated Mechanism for the Phase-Transfer Reaction

There are two well-established mechanistic descriptions of phase-transfer catalyzed reactions, which can be distinguished by considering the location of the substrate's deprotonation. The extractive mechanism was originally proposed by Starks and involves equilibration between an ammonium salt and an inorganic base across the boundary of two immiscible layers.[126] The organophilic catalyst cation can travel readily between these phases and upon ion-exchange can transport hydroxide ions into the organic layer where substrate deprotonation ensues. However, for our system we favour the alternative interfacial mechanism, which was advocated by Mąkosza (**Figure 4.1**).[190] We reasoned that the highly lipophilic Maruoka catalyst (*R,R*)-**273** would be reluctant to enter the aqueous phase to extract hydroxide ions.[†]

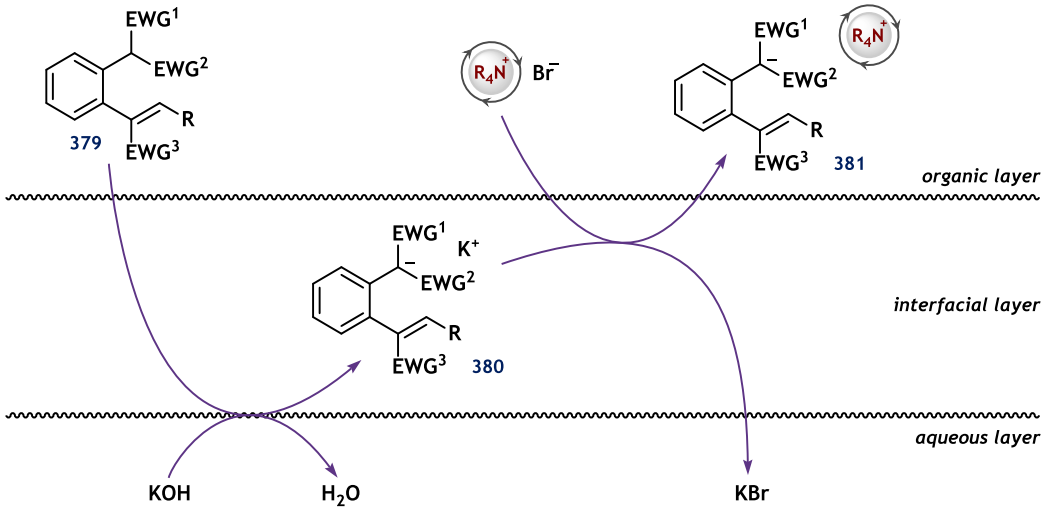


Figure 4.1 – Simplified outline of an interfacial mechanism

[†] *This is in accord with Maruoka's own hypothesis*[131]

The absence of base in the bulk organic layer implies that deprotonation of the substrate **379** occurs elsewhere. Mąkosza predicated that an interfacial region at the boundary of the organic and aqueous phases could accommodate the formation of the potassium carbanion **380** in the absence of the catalyst (*R*,*R*)-**273**. In our system, this metal-substrate salt **380** remains at the interface pending its interception by the ammonium cation (R_4N^+) to form the lipophilic ion-pair **381**. The high hydration state of this potassium salt **380** in the interfacial region renders it less reactive than a species in the bulk organic layer. Following diffusion of the ammonium ion-pair **381** deep into the organic phase the carbanion can cyclize, whilst intimately associated with the chiral countercation, to construct the enantioenriched carbocyclic product. The success of an asymmetric phase-transfer reaction relies upon rapid ion-exchange at the interface to prevent racemic cyclization emanating from potassium salt **380**. Thus, rapid stirring of these biphasic systems to produce turbid emulsions was essential for maximizing mass-transfer rates and to ensure that results were reproducible.[191]

4.2 Mode of Cyclization

4.2.1 Potential Transition States

Following diffusion of the chiral catalyst-substrate ion-pair into the organic phase it can undergo a highly stereoselective ring closure to forge an enantioenriched indane. However, the precise manner of this cyclization is contentious and could occur *via* two feasible pathways: a 6π electrocyclization or an anionic 5-*endo*-trig intramolecular Michael addition (**Figure 4.2**). The electrocyclic pathway would entail a thermal disrotatory cyclization, which proceeds suprafacially, in accordance with the Woodward-Hoffmann rules.[192–194] This necessitates that pentadienyl anion **382**-**A** achieves near-planarity in order to maximize

orbital overlap across the extended π-system. The chiral cation would then discriminate between the enantiotopic faces of the negatively charged substrate to control the stereochemical outcome of the reaction. Therefore, this reaction could potentially constitute a rare example of a catalytic asymmetric 6π electrocyclization.[55,56,102,195–197]

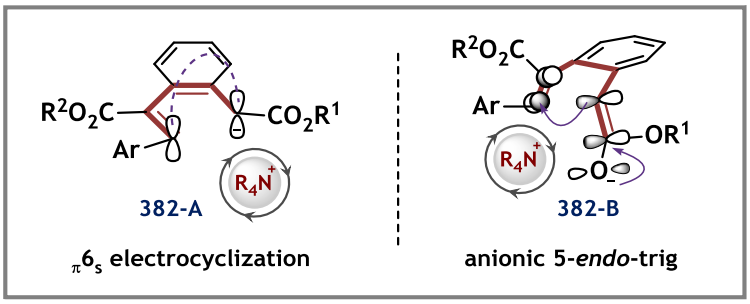


Figure 4.2 – Potential modes of cyclization (one ester omitted for clarity)

Alternatively, this process could involve a stereoelectronically challenging 5-*endo*-trig Michael reaction in which the facial selectivity of addition to the α,β-unsaturated ester is governed by the chiral cation. To facilitate efficient orbital overlap between the HOMO of the enolate and the LUMO of the alkene, the conjugate acceptor and the malonate group must lie perpendicular to the plane of the aromatic ring. However, this unfavourable arrangement would position the reacting centres a significant distance apart. There are currently only limited examples of 5-*endo*-trig cyclizations with a carbon-based nucleophile attacking the π* of an olefin (*vide supra, section 1.1.3*).[11,16,17,22,23,26,27]

4.2.2 X-Ray Crystal Structure of a Substrate-Catalyst Ion-Pair

These two potential mechanistic pathways are very difficult to distinguish as the experimental markers that could be exploited to infer information about the transition state are absent. For example, the stereospecificity of the cyclization cannot be deduced as the malonate anion is symmetrical and reacts through an indeterminate geometry. However, we

reasoned that an X-ray crystal structure of the chiral catalyst bound to the anion of the substrate could provide some structural insight into the arrangement of the transition state. Encouragingly, Maruoka has accomplished similar feats utilizing ion-exchange chromatography to generate the hydroxide form of the phase-transfer catalyst.[153,198,199] For this investigation, we selected an amide substrate as it bears a strong structural resemblance to the analogous triester cyclization precursors (**Figure 4.3**). Previous research has demonstrated that thermal coercion was vital to promote ring closure in this system, rendering it appropriate for this study (*vide supra, section 3.5.1*).

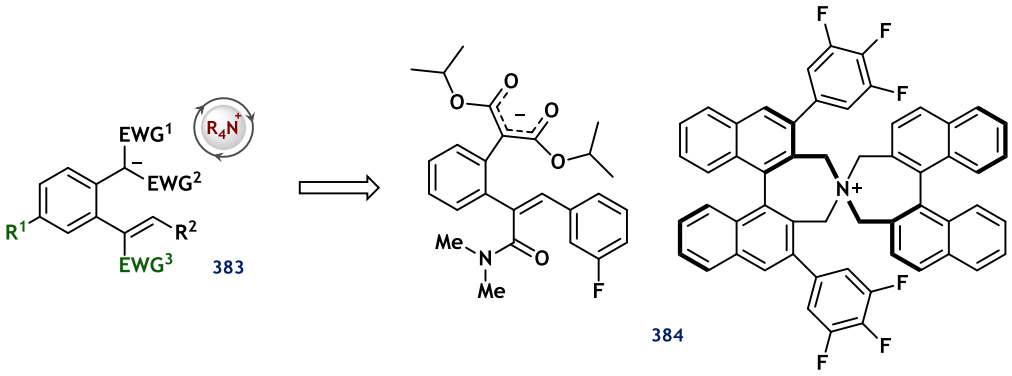
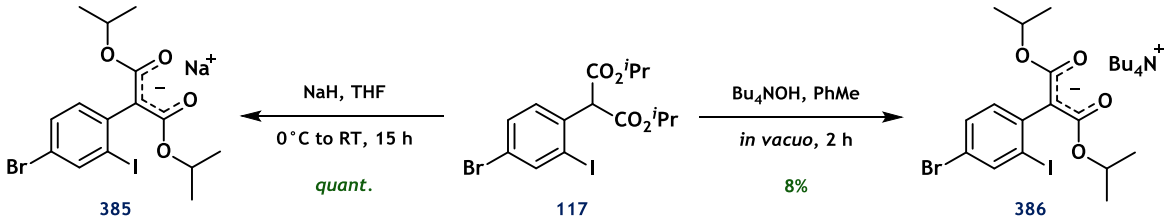


Figure 4.3 – Potential substrate-catalyst ion-pair

Furthermore, the specific interactions which govern the binding orientation of the ammonium cation relative to the substrate anion could be elucidated from an X-ray crystal structure of complex **384**. This information could aid our understanding of the poor levels of enantiocontrol observed with particular Michael acceptors (EWG^3) or by the incorporation of non-hydrogen substituents (R^1) *para* to the malonate (*vide supra, sections 3.5.1 and 3.6.2*).

To explore this concept, a model system was investigated to ascertain the feasibility of synthesizing related ammonium enolate ion-pairs and to gauge their chemical stability. Accordingly, malonate **117** was deprotonated with NaH in THF to deliver the sodium salt

385 in quantitative yield (**Scheme 4.1**). This product was highly moisture sensitive, but was successfully characterized by standard analytical techniques. Following this accomplishment we pursued a procedure to synthesize the tetrabutylammonium salt **386**. Unfortunately, this task proved less straightforward, as the hydride base that was employed before conveniently liberated hydrogen gas as the sole by-product. Research by Reetz has investigated the solid-state structure of similar ion-pairs and a protocol for their synthesis was provided.[200] Implementing this procedure, a solution of iodoarene **117** in toluene was added dropwise into anhydrous Bu_4NOH, which had been azeotroped repeatedly with toluene to remove traces of methanol and moisture (**Scheme 4.1**). The reaction was conducted *in vacuo* to ensure steady removal of the water produced from deprotonation of the malonate.

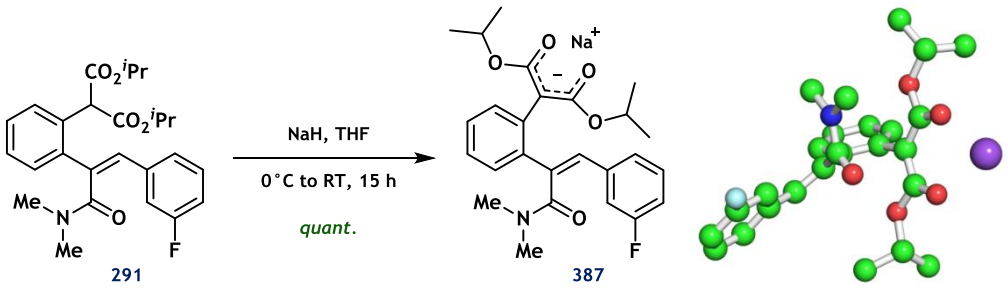


Scheme 4.1 – Synthesis of the sodium salt **385** and tetrabutylammonium salt **386**

This procedure was only moderately successful with pure material being isolated in 8% yield. Prior inspection of the crude ^{1}H NMR spectrum indicated poor levels of conversion to the anion. The intricate nature of this protocol as well as the propensity of the enolate to protonate during handling contributed to the low recovery of product **386**.

Subsequently, we applied our garnered knowledge to the key amide substrate **291** in anticipation that we would eventually be capable of synthesizing complex **384**. As before, the anion of precursor **291** was generated in THF utilizing NaH as a base (**Scheme 4.2**).

Evaporation of the reaction solvent provided a hygroscopic solid which exhibited remarkable solubility in non-polar solvents. A diffraction-quality single crystal of salt **387** was grown at a cryogenic temperature from anhydrous pentane. The resulting X-ray structure established that the malonate anion lay perpendicular to the aromatic ring and therefore, out of conjugation with the π-system (**Scheme 4.2**).



Scheme 4.2 – Synthesis of sodium carbanion **387** and its X-ray crystal structure[†]

However, scrutinizing the whole unit cell of this system revealed a cubic cluster of Na ions (purple) and oxygen atoms (red) at the heart of the crystal (**Figure 4.4**). Therefore, it seemed that the coordinative abilities of the sodium ion were potentially distorting the preferred conformation of the carbanion, as expected in the catalyst-substrate ion-pair. It became evident that the structural information we required could not be obtained from this crystal structure.

[†] *X-ray diffraction data was collected and the structure solved by Dr Russell W. Driver. The molecule was rendered using PyMOL.*[106]

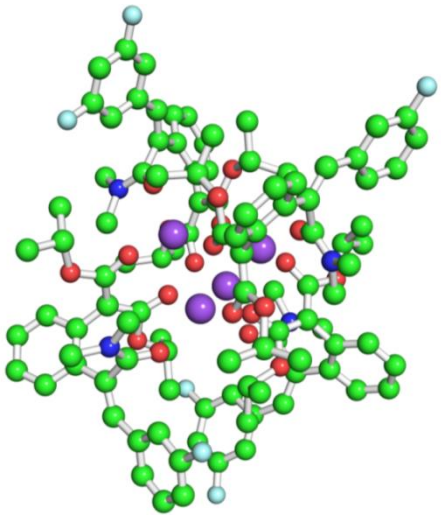
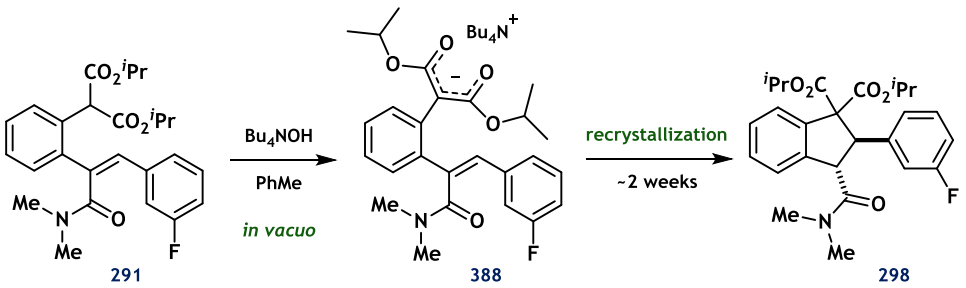


Figure 4.4 – Unit cell for the X-ray crystal structure of salt **387**[†]

We rationalized that a system containing a non-coordinating tetrabutylammonium cation would provide a more accurate representation of the preferred carbanion geometry. Accordingly, the amide substrate **291** was converted to the tetrabutylammonium salt **388** employing the same procedure that was utilized to create complex **386** (**Scheme 4.3**). ^{1}H NMR analysis of the crude reaction mixture indicated that conversion to the anion was low (<40%) and endeavours to isolate the product **388** were fraught with difficulty due to its instability to moisture. Hence, attempted purification of the crude reaction mixture by recrystallization had the dual purpose of furnishing pure material and growing diffraction-quality single crystals.

[†] *X-ray diffraction data was collected and the structure solved by Dr Russell W. Driver. The molecule was rendered using PyMOL.*[106]



Scheme 4.3 – Synthesis of quaternary ammonium enolate **388** and its conversion to indane **298**

After an extended period copacetic crystals were acquired, but X-ray crystallography determined the substance to be the carbocyclic indane **298** (**Figure 4.5**). This outcome was later confirmed by ^{1}H NMR and implied that ring closure in this system was kinetically slow but still feasible at room temperature. This result reiterated the demanding nature of synthesizing a quaternary ammonium carbanion complex and suggested that the amide substrate **291** may not be suitable for this application. Therefore, similar investigations with the Maruoka salt (*R*,*R*)-**273** were not pursued to avoid squandering this valuable catalyst.

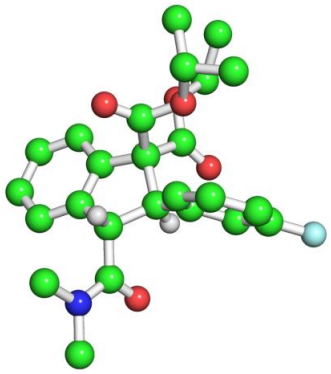


Figure 4.5 – X-ray crystal structure of indane **298**[†]

Due to this impediment, a portrait of the specific substrate-catalyst interactions which govern the high enantioselectivities observed in our reaction could not be determined. However, potential organizational elements that have been proposed for quaternary

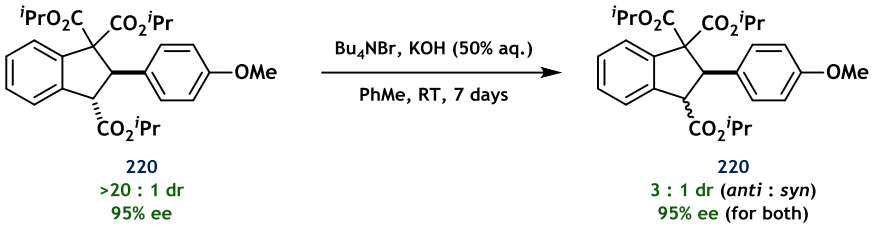
[†] *X-ray diffraction data was collected and the structure solved by Dr Russell W. Driver. The molecule was rendered using PyMOL.*[106]

ammonium salt-catalyzed asymmetric phase-transfer reactions include: (i) electrostatic attraction,[191] (ii) C–H···O hydrogen bonds,[201–203] and (iii) π-π interactions.[204,205] Based on the availability of several H-bond acceptors on the substrate and the extensive aromaticity shrouding the ammonium cation, it seems reasonable to assume that these intermolecular forces are key binding features.

4.2.3 Experimental Observations

A definitive answer to the mechanistic conundrum surrounding our synthesis of carbocyclic indane products rationalized through experimental evidence would be challenging. However, several important observations were documented during the development of this project and merit additional discussion.

The 5-*endo*-trig mode of ring closure is a stereoelectronically disfavoured process, whereas an identical reaction proceeding through an electrocyclic transition state is not restricted in this manner. The application of Baldwin's rules to a specific cyclization assumes that the reaction is under kinetic control.[1,2] The high levels of asymmetric induction observed in our system imply that it is kinetically driven, leading to irreversible formation of the indane ring. Consequently, to test this premise the enantioenriched indane **220** was subjected to achiral phase-transfer conditions at room temperature for one week (**Scheme 4.4**). As expected, equilibration led to a thermodynamic mixture of *syn*- and *anti*-diastereomers but neither demonstrated any erosion of stereochemical integrity.



Scheme 4.4 – Subjecting enantioenriched indane **220** to achiral phase-transfer conditions

This outcome substantiated the irreversibility of this reaction which, therefore, must be under kinetic control. However, this fact does not constitute irrefutable evidence for the electrocyclic pathway, as there are distinct examples of 5-*endo*-trig cyclizations in the literature that may be kinetically feasible (*vide supra, section 1.1.3*), but detailed mechanistic discussions for these racemic processes are not reported.[11,16,17,22,23,26,27] Another interpretation, based on computational studies conducted by Alabugin, would portray our synthesis of indanes as "aborted" electrocyclic reactions (**Figure 4.6**).[28]

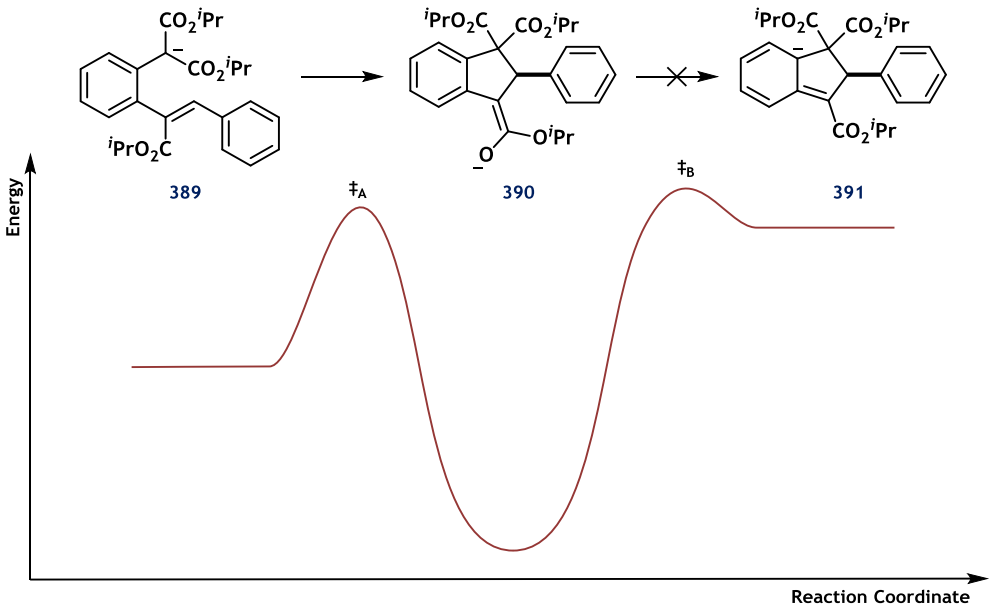
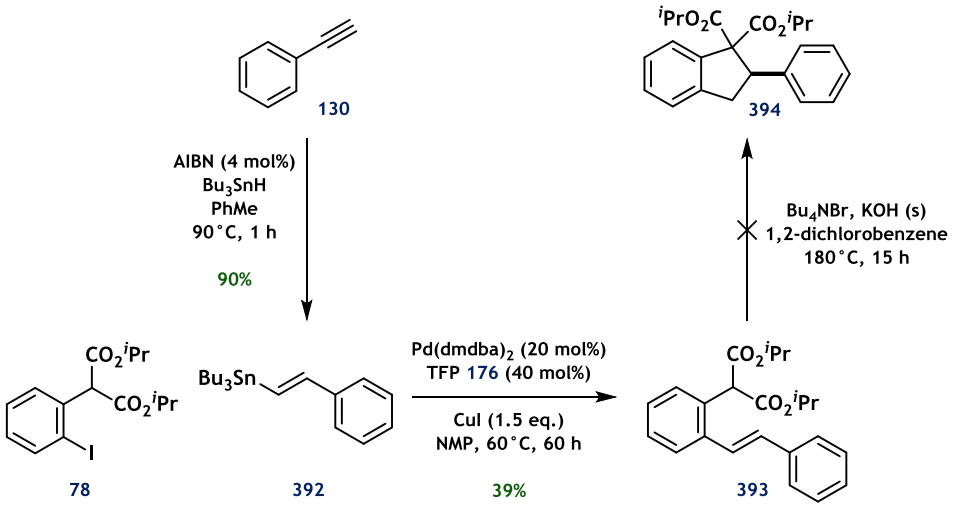


Figure 4.6 – Postulated energy landscape for an "aborted" electrocyclization

In this scenario, the transition state ($‡_A$) is stabilized by aromaticity and is topologically identical to its pericyclic counterpart. However, the enhanced stability of the intermediary

anion **390** relative to the starting material **389**, as well as the large activation barrier associated with perturbing the π-system of the arene, precludes the reaction from progressing as expected.[†] This hypothesis could rationalize the perceived facility of ring closure, although examining this theory would necessitate computational analysis.

Further experimental investigation to probe the reactivity of related substrates focused on the deletion analogue **393**. Conceivably, a system that lacks a vinylic electron-withdrawing group would exclusively proceed through a concerted electrocyclic mechanism without any discrete intermediate species. To examine this idea, vinylstannane **392**, which was produced *via* a radical hydrostannylation of phenyl acetylene **130**, was combined with iodoarene **78** to synthesize alkene **393** (**Scheme 4.5**).



Scheme 4.5 – Synthesis and evaluation of the deletion analogue **393**

To accomplish this reaction, optimized Stille-Migita coupling conditions exploiting $Pd(dmdba)_2$ as the pre-catalyst were employed and provided a 39% yield of the diester **393**. Subjecting substrate **393** to basic conditions in refluxing 1,2-dichlorobenzene returned merely starting material after 15 hours (**Scheme 4.5**). In this example, severe disruption of a

[†] *It is worth noting that both anions **390** and **391** will eventually lead to the same indane product.*

highly conjugated aromatic system is obligatory for cyclization to occur: this might involve overcoming a formidable activation barrier.[†] However, we cannot exclude the possibility of substrates bearing conjugate acceptors reacting *via* a pericyclic transition state, as the synergistic combination of electron-withdrawing and electron-donating groups has been demonstrated to considerably lower the activation energy for electrocyclizations.[208]

Furthermore, the conformational impact of introducing a substituent to the vinyl position of the substrate is an important factor to consider. The most stable ground-state conformation of substrate **393** is presumably the open form **393-B**, which has reduced $A^{1,3}$ strain (**Figure 4.7**). However, this molecular topology places the reacting centres a considerable distance apart. Therefore, if we assume the reaction proceeds through rotamer **393-A**, the entropic and enthalpic penalty for relocating the styryl group would contribute to an increase in activation energy.

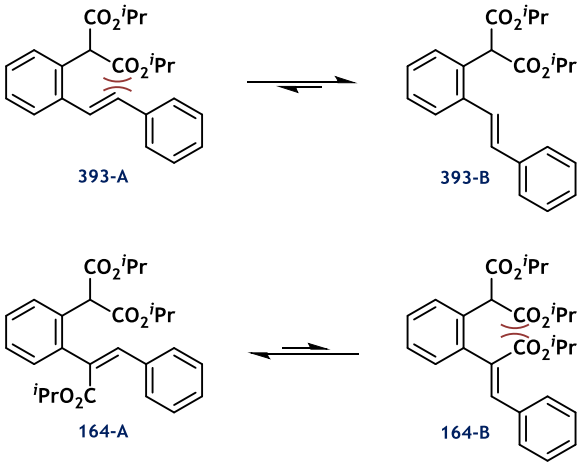


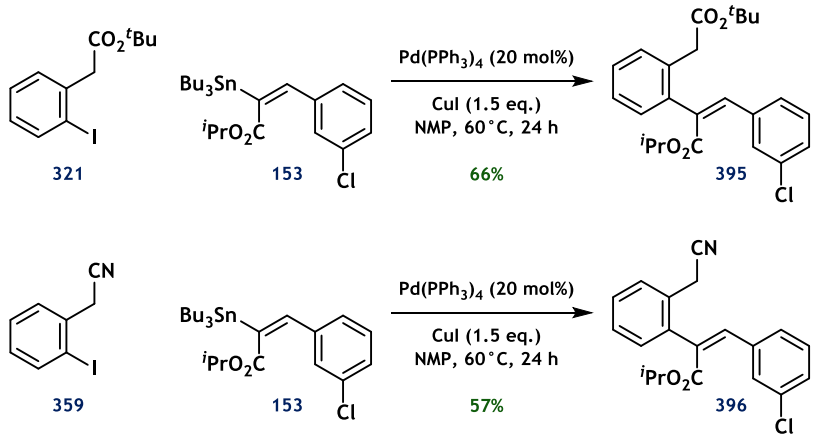
Figure 4.7 – The effect of vinylic substitution on the ground-state conformation

However, substrates that incorporate a third ester at the vinylic position will probably prefer conformer **164-A**. In this system, a steric clash between the malonate and the

[†] *Temperatures reported for the ring closure of 1,3,5-hexatriene*[206] *and o-divinylbenzene*[207] *are 132 °C and 250 – 300 °C respectively.*

α,β-unsaturated ester drives the conversion of **164-B** to **164-A**. Therefore, if this enforced ground-state conformation is highly populated, then the reaction, pericyclic or otherwise, becomes more kinetically favourable.[209] Consequently, the role of the vinyl substituent could be twofold: an electron-withdrawing group and a structural influence on ground-state geometry of the substrates.

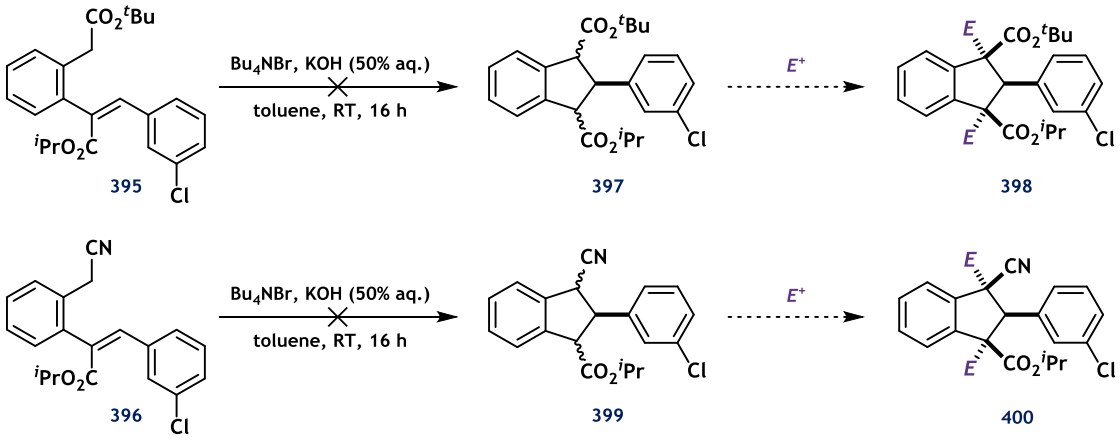
Analogously, the importance of strategic substitution was observed during the development of a methodology to synthesize indanes bearing three contiguous stereocentres. It was rationalized that cyclization precursors bearing a sole *tert*-butyl ester or nitrile group could be diastereoselectively alkylated twice following ring closure to afford complex orthogonally-substituted carbocyclic products (**Scheme 4.7**). The requisite substrates **395** and **396** were both produced in good yields employing vinylstannane **153** with $Pd(PPh_3)_4$ as the catalyst (**Scheme 4.6**).



Scheme 4.6 – Synthesis of substrates **395** and **396** *via* a Stille-Migita cross-coupling

Subjecting the indane precursors, ester **395** and nitrile **396**, to achiral phase-transfer conditions (Bu_4NBr/KOH) for 16 hours at room temperature returned only starting material (**Scheme 4.7**). Deprotonation of substrates **395**-**396** should be facile with these reagents and the regal purple hue generated upon adding the base was indicative of a highly delocalised

anion. A possible explanation for this poor reactivity is that after proton abstraction the resulting enolate remains in conjugation with the aromatic ring to maximize overlap with the π-system. This renders it poorly aligned for a process which proceeds through a 5-*endo*-trig Michael addition (**Figure 4.2**).



Scheme 4.7 – Attempted cyclization of substrates **395**-**396** and their envisaged alkylation

Therefore, additional substitution at the benzylic position of these substrates seems pivotal for promoting efficient cyclization. The extra steric bulk at this location may coerce the anion to rest perpendicular to the π-system, which would favour the nonpericyclic transition state. Another contribution may derive from a Thorpe-Ingold type effect, which is known to accelerate the rate of ring formation with increasing substitution on an alicyclic substrate.[18,21] The exact nature of this rate enhancement is debatable but could manifest itself through a combination of several reported theories including: restricting the substrate's degrees of freedom and in particular favouring a higher population of the reactive conformation,[209] relief of ground-state strain caused by van der Waals repulsion,[210,211] or decreasing the solvation of the starting material anion.[20]

Overall, these effects, combined with the advantages of vinylic substitution discussed previously, could all contribute towards facilitating this 5-*endo*-trig ring closure. As stated by Woodward:

"We all know that enforced propinquity often leads on to greater intimacy…"[212]

This notion epitomizes the observations made during the development of this project, yet no conclusive argument for the precise mechanism of this reaction can be provided. The mystery shrouding this surprisingly facile ring closure remains an intriguing point of discussion and undeniably warrants additional examination.

4.3 Future Work and Conclusions

4.3.1 Prospects for the Future

Collaboration with a computational research group could provide a deeper insight into the mechanistic aspects of this 5-*endo*-trig ring closure. For example, quantum chemical calculations to determine the lowest energy transition state for this system could distinguish between the electrocyclic and non-pericyclic pathways. Furthermore, these computational studies may also elucidate the most favourable binding mode between the quaternary ammonium cation and the anion of the starting material. This model of the substrate-catalyst ion-pair could aid the rationalization of the poor levels of asymmetric induction observed with certain minor modifications to the indane precursor.

As an extension of this methodology, the cyclization of a non-aromatic analogue of our present system could generate a series of enantioenriched cyclopentene derivatives **402** (**Figure 4.8**). These highly substituted complex small molecules offer great potential for

further elaboration and derivatization. Moreover, these substrates would contribute additional experimental evidence towards understanding the mechanism of these 5-*endo*-trig ring closures.

A complementary set of optically enriched cyclopentene products **404** could be generated from pentadienyl anion **403** (**Figure 4.8**). Following a 5-*endo*-trig cyclization, a desymmetrizing alkylation directed by a chiral cation would deliver synthetically valuable carbocyclic materials. From a mechanistic perspective, this unique reaction presents a further opportunity to explore this stereoelectronically disfavoured mode of ring closure.

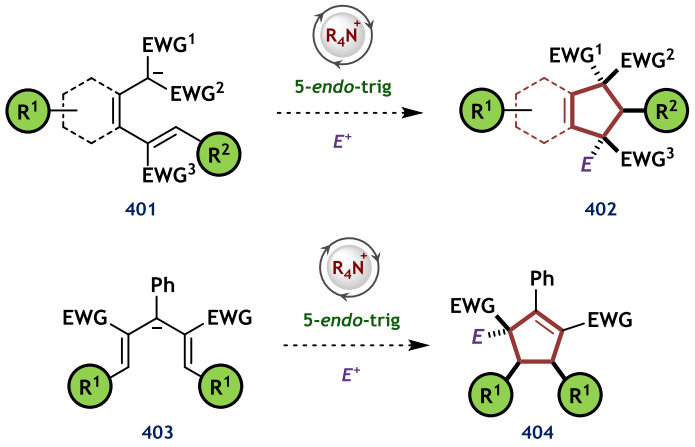


Figure 4.8 – Novel ion-binding approaches to synthesize cyclopentene derivatives

4.3.2 Conclusions and Overview

Overall, we have developed a novel chiral cation-directed 5-*endo*-trig cyclization protocol, which can deliver a wide variety of polysubstituted indanes with high levels of asymmetric induction.

The synthesis of the cyclization precursors **72** was achieved through a Stille-Migita cross-coupling reaction (**Figure 4.9**). A robust set of procedures for the construction of the

iodoarene **74** and vinylstannane **75** components facilitated the generation of numerous analogues with distinct substitution patterns.

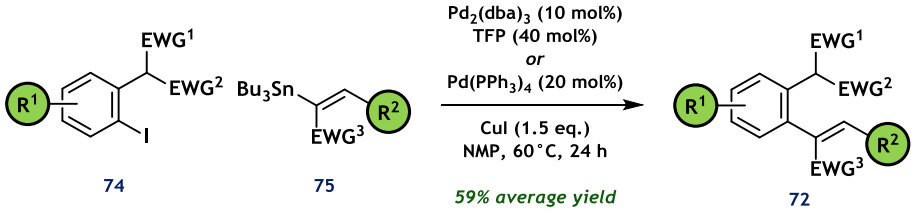


Figure 4.9 – Stille-Migita cross-coupling to synthesize cyclization precursors

Evaluation of the substrates under asymmetric phase-transfer conditions identified the Maruoka catalyst (*R,R*)-**273** as the optimal quaternary ammonium salt for controlling the enantioselectivity of the ring closure (**Figure 4.10**). Three representative indanes were generated and all demonstrated high levels of enantiocontrol, but were formed as an epimeric mixture of products.

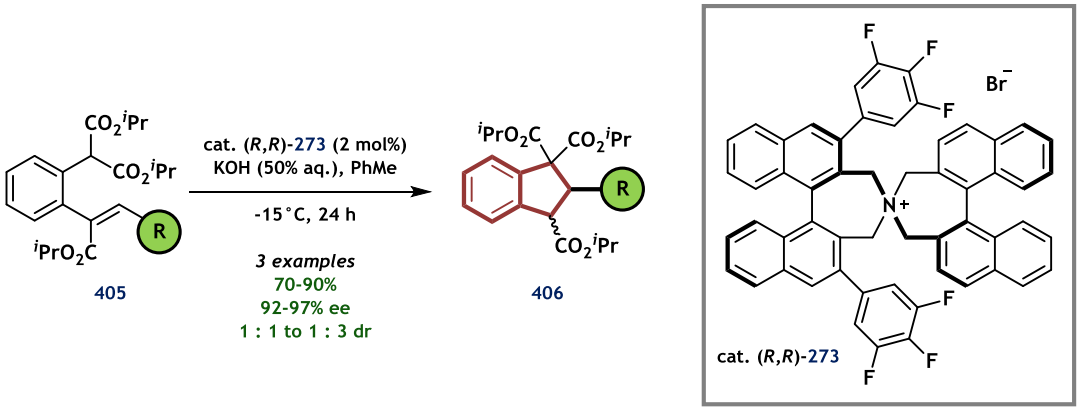


Figure 4.10 – Optimal phase-transfer conditions with the Maruoka catalyst (*R,R*)-**273**

Alternative conjugate acceptors were investigated, in the hope of improving the ratio of stereoisomers (**Figure 4.11**). Unfortunately, these systems led to a decrease in enantioselectivity, despite an enhanced distribution of diastereomers.

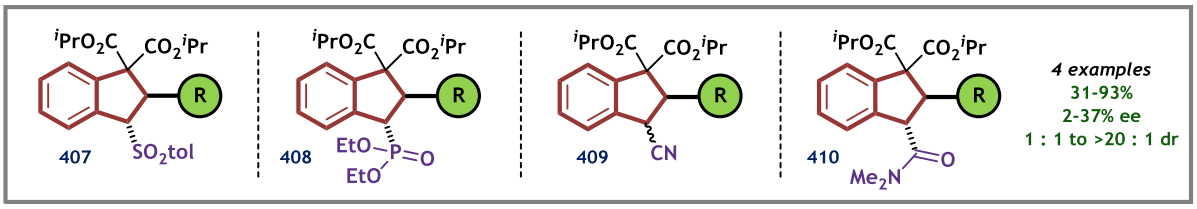


Figure 4.11 – Variation of the vinylic electron-withdrawing group

Subsequently, a highly diastereoselective protocol was developed by alkylation of the epimeric mixture of indanes formed following the initial cyclization (**Figure 4.12**). A wide variety of electrophiles were employed to create diastereomerically pure products bearing all-carbon quaternary stereocentres. In general, good levels of enantiocontrol were observed, with the exception of products containing non-hydrogen substituents at the 7-position of the indane ring. To enhance the orthogonality of functional groups in the carbocyclic products a small array of analogues containing isopropyl and *tert*-butyl esters was generated (**Figure 4.12**). The complementary nature of these substituents was demonstrated through a series of chemoselective derivatizations.

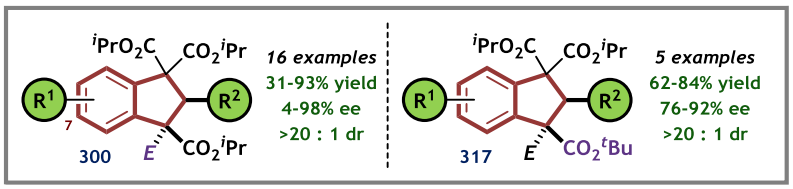


Figure 4.12 – Enantio- and diastereoselective synthesis of indanes

To enhance the synthetic value of this methodology we examined a protocol to generate indanes with three contiguous stereocentres (**Figure 4.13**). When these substrates were evaluated under the optimized phase-transfer conditions with the Maruoka catalyst (*R*,*R*)-**273** mixtures of epimers were produced with low levels of enantioselectivity.

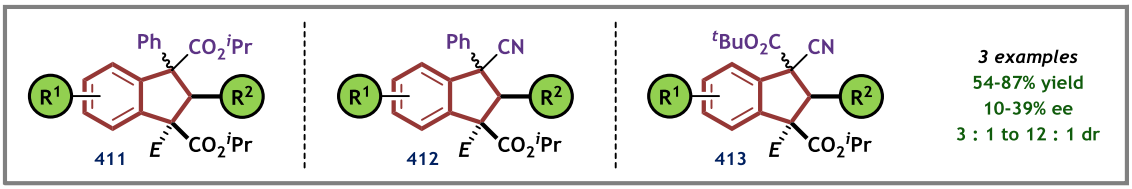


Figure 4.13 – Indanes with three contiguous stereocentres

The variation in asymmetry with respect to substitution on the cyclization precursor cannot be rationalized at present. To gain insight into this dependency attempts to isolate a substrate-catalyst ion-pair were conducted, but were ultimately unsuccessful.

There are two feasible mechanistic pathways for this ring closure: a 6π electrocyclization or an anionic 5-*endo*-trig cyclization (**Figure 4.14**). However, no conclusive evidence has been established to fully support either mode of ring closure.

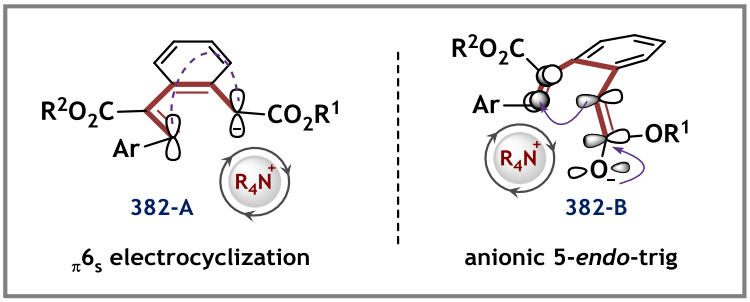


Figure 4.14 – Potential modes of cyclization (one ester omitted for clarity)

Future exploration of related systems as well as theoretical calculations may support the understanding of the mechanism that facilitates these stereoelectronically disfavoured processes.

5. EXPERIMENTAL

5.1 General Experimental

5.1.1 Naming and Numbering

Compounds have been named according to IUPAC recommendations or as written in the referenced publication used for the correlation of spectral data.

The atomic numbering system for compounds does not correspond to the IUPAC names but was chosen to allow for simplistic and consistent assignment of spectra.

5.1.2 Reaction Conditions

Reactions were carried out in washed and flame-dried glassware under an atmosphere of argon or nitrogen unless stated otherwise.

Room temperature refers to 20 – 25 °C. Temperatures of 0 °C were obtained using an ice/water bath. Temperatures of −78 °C were obtained using a dry ice/acetone bath. Reflux conditions were obtained using an oil bath equipped with a contact thermometer. Temperatures below 0 °C which had to be maintained for extended periods of time were obtained using an immersion cooler (Haake EK90 or Julabo FT902).

Phase-transfer procedures were rapidly stirred (~1200 rpm) with the reaction vessel placed centrally on the magnetic stirrer to ensure efficient mixing of the biphasic layers.

5.1.3 Solvents

Dichloromethane, methanol, acetonitrile, tetrahydrofuran and toluene were purified by filtration through activated alumina columns employing the method of Grubbs *et al*.[213] DMF and NMP were purchased as anhydrous solvents in Sure/Seal™ bottles from Sigma-Aldrich.

All other solvents were used as supplied without prior purification. Degassing of solvents was carried out according to the procedure of Procter *et al*.[214] Mixtures of solvents are quoted as ratios of volume : volume.

5.1.4 Reagents

Triethylamine, 2,2,6,6-tetramethylpiperidine and diisopropylamine were distilled from calcium hydride and stored over potassium hydroxide. *n*-Butyllithium solutions in hexanes were titrated before use with menthol and 1,10-phenanthroline as an indicator. Copper(I) iodide was purified according to the procedure of Echavarren *et al*.[215] Potassium carbonate was dried overnight under high vacuum at 150 °C before use. Phenyl cyanate was synthesized according to the procedure of Moss *et al*.[216] NBS was recrystallized from distilled water prior to use.[217] Butyraldehyde was distilled from $MgSO_4$ prior to use. KOAc was recrystallized three times from water : ethanol (1 : 1) and dried *in vacuo*.[217] Copper(II) sulfate was dried at 150 °C under high vacuum for 16 hours. 4 Å molecular sieves were dried at 250 °C under high vacuum for 16 hours.[218]

The Maruoka phase-transfer catalysts (*R*,*R*)-**273** and (*S*,*S*)-**273** were purchased from Wako. The Maruoka phase-transfer catalyst (*S*)-**272** was purchased from Sigma-Aldrich.

All other reagents were used as supplied without prior purification

5.1.5 *Chromatography*

Thin layer chromatography was performed on Merck Kiesegel 60 F_{254} 0.25 mm precoated aluminium plates. Product spots were visualized under UV light (λ = 254 nm) and/or by staining with ceric ammonium molybdate solution or potassium permanganate solution. Flash chromatography was performed using VWR silica gel 60 (40 – 63 μm particle size) using head pressure by means of head bellows or a nitrogen line.

5.1.6 *Nuclear Magnetic Resonance*

^{1}H NMR spectra were recorded on a Bruker AVII 500 with cryoprobe (500 MHz), Bruker AVII 500 (500 MHz), Bruker DRX500 (500 MHz), Bruker AVIII 400 (400 MHz), Bruker AV400 (400 MHz), DPX400 (400 MHz) spectrometer and were referenced to residual non-deuterated solvent peaks. Chemical shifts are quoted in ppm with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sex), septet (sept), octet (oct), nonet (non), multiplet (m) or AB quartet (AB_q). The abbreviation Ar is used to denote aromatic, br. to denote broad, app. to denote apparent and Q to denote quaternary. Coupling constants, *J*, are measured to the nearest 0.1 Hz and are presented as observed. Unresolved satellite peaks for ^{117}Sn and ^{119}Sn are quoted as a single combined coupling constant unless otherwise specified.[76] ^{13}C NMR spectra were recorded on a Bruker AVII 500 with cryoprobe (126 MHz), Bruker AVII 500 (126 MHz), Bruker DRX500 (126 MHz), Bruker AVIII 400 (101 MHz), Bruker AV400 (101 MHz) spectrometer and were referenced to the residual solvent peak. Coupling constants, *J*, are measured to the nearest 1 Hz and are presented as observed. Unresolved satellite peaks for ^{117}Sn and ^{119}Sn are quoted as a single combined coupling constant unless otherwise specified.[76] ^{19}F NMR spectra were

recorded on a Bruker AVII 500 (470 MHz), Bruker AVIII 400 (377 MHz), Bruker AV400 (377 MHz) spectrometer and were referenced externally to $CFCl_3$ in $CDCl_3$. ^{31}P NMR spectra were recorded on a Bruker AVII 500 with cryoprobe (202 MHz), Bruker AVIII 400 (162 MHz), Bruker AV400 (162 MHz) spectrometer and were referenced externally to H_3PO_4 in D_2O. Assignment of spectra was assisted by the results of DEPT, COSY, HSQC, HMBC and NOESY experiments. A forward slash (/) separates ambiguous assignments for that particular peak. An ampersand (&) separates assignments that occur at the same chemical shift, i.e. coincidental peaks.

5.1.7 Infrared Spectroscopy

Infrared spectra were recorded neat on a Bruker Tensor 27 FTIR spectrometer equipped with an attenuated total reflectance attachment with internal calibration. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

5.1.8 Mass spectrometry

Low-resolution mass spectra were recorded on a Micromass LCT Premier spectrometer under conditions of electrospray ionization (ESI) or a Waters LCT Premier XE Micromass spectrometer (ESI). High-resolution mass spectra were recorded on a Bruker FT-ICR-MS Apex Qe (9.4 T) spectrometer under conditions of electrospray ionization (ESI) or a Micromass GCT spectrometer under conditions of electron impact (EI) or field ionization (FI). Values are reported as a ratio of mass to charge in Daltons.

5.1.9 Polarimetry

Optical rotations were recorded on a Perkin Elmer 241 or 341 polarimeter with a path length of 1 dm (using the sodium D line, 589 nm). $[\alpha]_D$ values are reported in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are reported in g/100 mL. Temperatures are reported in °C.

5.1.10 Melting Points

Melting points were determined using a Gallenkamp melting point apparatus or a Reichert melting point stage, and are uncorrected. Solvents are reported in parentheses where solids were purified by recrystallization. Temperatures are reported in °C.

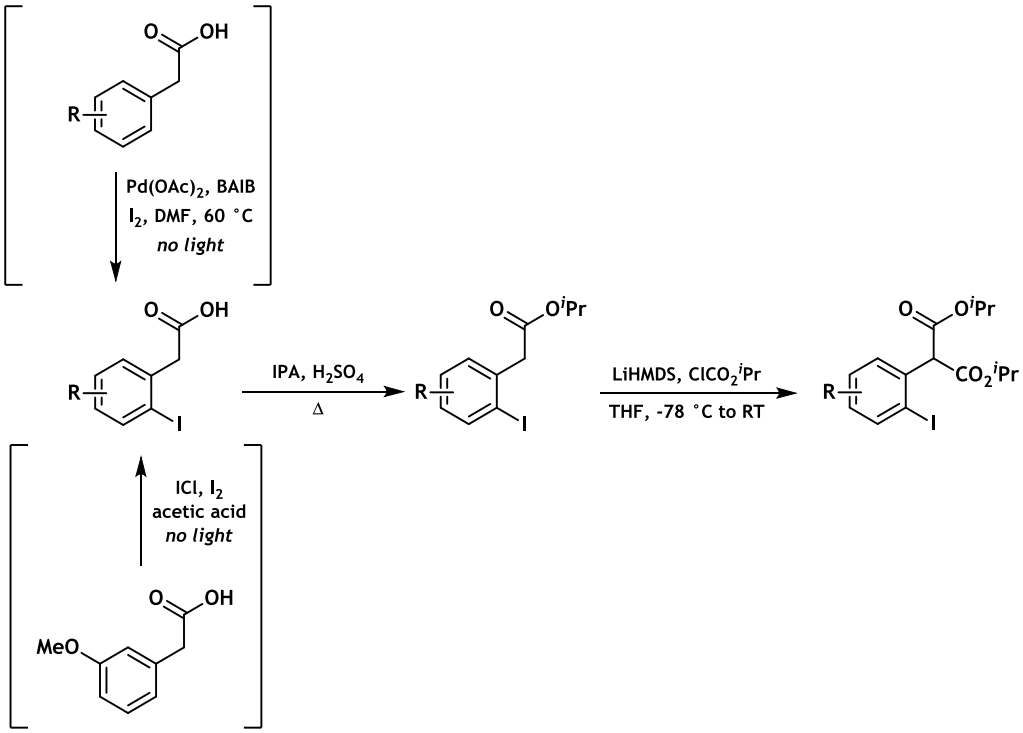
5.1.11 HPLC

Chiral HPLC was performed on a Dionex UltiMate 3000 system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler, TCC-3000SD column compartment, DAD-3000 diode-array detector, fitted with the appropriate DAICEL Chiralpak column (dimensions: 0.46 cm ø x 25 cm) and corresponding guard column (0.4 cm ø x 1 cm). Wavelengths (λ) are reported in nm, retention times (t_R) are reported in minutes and solvent flow rates are reported in mL/min.

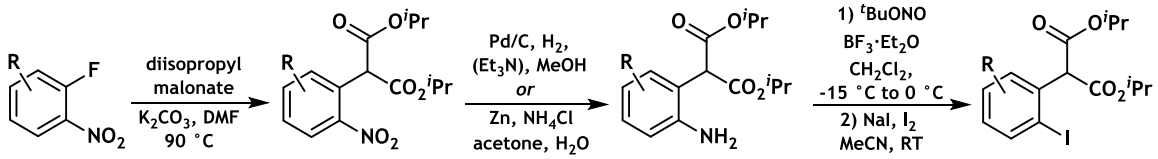
5.2 General Schemes for Substrate Synthesis

5.2.1 Synthesis of Malonate Substituted Iodoarenes

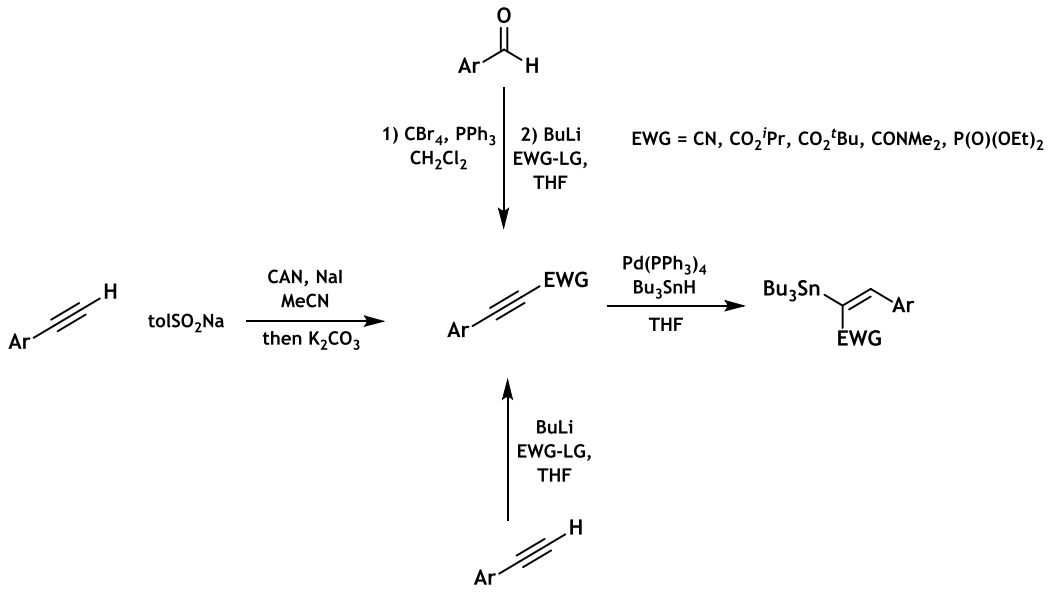
5.2.1.1 Iodination of Phenylacetic Acids



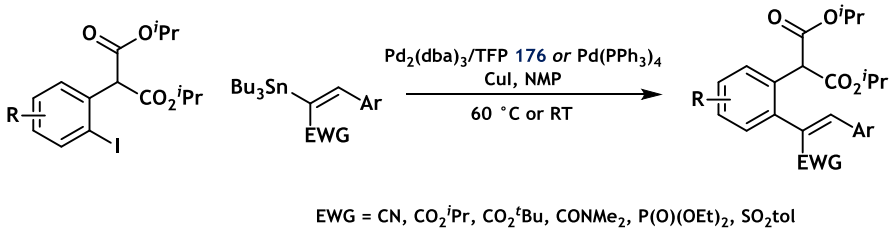
5.2.1.2 S_NAr of Fluoronitrobenzenes



5.2.2 *Synthesis of Vinyl Stannanes*



5.2.3 *Stille Coupling*

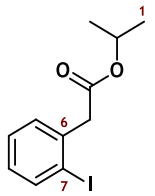


EWG = CN, $CO_2{}^{i}Pr$, $CO_2{}^{t}Bu$, $CONMe_2$, $P(O)(OEt)_2$, SO_2tol

5.3 Experimental Procedures

5.3.1 Synthesis of Malonate Substituted Iodoarenes

Isopropyl (2-iodophenyl)acetate (77)



Concentrated sulfuric acid (12.5 mL) was added to a stirred solution of (2-iodophenyl)acetic acid **76** (25.0 g, 95.4 mmol) in isopropanol (125 mL). The reaction was heated to 80 °C for 4 hours and was then allowed to cool to room temperature. After dilution with water (200 mL) the mixture was extracted with dichloromethane (3 × 200 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product, isopropyl ester **77** (29.0 g, quant.), which did not require purification, was afforded as a colourless oil.

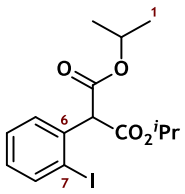
^{1}H (400 MHz, $CDCl_3$): δ 7.85 (1H, dd, *J* 7.9, 0.9, **8**-**H**), 7.34 – 7.27 (2H, m, **10**-**H**, **11**-**H**), 6.98 – 6.94 (1H, m, **9**-**H**), 5.07 (1H, sept, *J* 6.3, **2**-**H**), 3.76 (2H, s, **5**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 170.1 (**C4**), 139.6 ($\mathbf{C}_{Ar}$**8**), 138.2 ($\mathbf{C}_{Ar}$**6**), 130.7 ($\mathbf{C}_{Ar}$**9**), 128.9 ($\mathbf{C}_{Ar}$**10**), 128.5 ($\mathbf{C}_{Ar}$**11**), 101.1 ($\mathbf{C}_{Ar}$**7**), 68.6 (**C2**), 46.7 (**C5**), 21.9 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2979 (C–H), 1728 (C=O), 1466, 1253, 1169, 1103, 736.

HRMS (ESI): $C_{11}H_{13}O_2INa$ $[M+Na]^+$ requires 326.9852; found 326.9853

Diisopropyl (2-iodophenyl)malonate (78)



A solution of lithium bis(trimethylsilyl)amide (1.0 M in toluene, 53.8 mL, 53.8 mmol) was added to a stirred solution of isopropyl ester **77** (6.54 g, 21.5 mmol) in tetrahydrofuran (25 mL) at −78 °C. The reaction was stirred at this temperature for 1 hour, then a solution of isopropyl chloroformate (1.0 M in toluene, 43.0 mL, 43.0 mmol) was added dropwise. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (200 mL). The biphasic mixture was extracted with dichloromethane (3 × 150 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5) to afford malonate **78** (7.55 g, 90%) as a pale yellow oil.

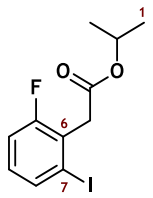
^{1}H (400 MHz, $CDCl_3$): δ 7.87 (1H, dd, *J* 7.9, 1.1, **8**-**H**), 7.48 – 7.43 (1H, m, **11**-**H**), 7.37 (1H, app. t, *J* 7.5, **10**-**H**), 7.02 (1H, app. t, *J* 7.6, **9**-**H**), 5.11 (2H, sept, *J* 6.3, **2**-**H**), 5.05 (1H, s, **5**-**H**), 1.29 (6H, d, *J* 6.5, **1**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 167.4 (**C4**), 139.7 ($\mathbf{C}_{Ar}$**8**), 136.8 ($\mathbf{C}_{Ar}$**6**), 129.7 ($\mathbf{C}_{Ar}$**9** & $\mathbf{C}_{Ar}$**11**), 128.6 ($\mathbf{C}_{Ar}$**10**), 101.9 ($\mathbf{C}_{Ar}$**7**), 69.8 (**C2**), 62.7 (**C5**), 21.7 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1729 (C=O), 1260, 1223, 1163, 1101, 741.

HRMS (ESI): $C_{15}H_{19}O_4INa$ $[M+Na]^+$ requires 413.0220; found 413.0213

Isopropyl 2-(2-fluoro-6-iodophenyl)acetate (92)



According to a literature procedure,[58] iodine (2.47 g, 9.74 mmol) was added to a solution of 2-(2-fluorophenyl)acetic acid **90** (2.00 g, 13.0 mmol), palladium(II) acetate (292 mg, 1.30 mmol) and (diacetoxyiodo)benzene (3.14 g, 9.74 mmol) in anhydrous *N*,*N*-dimethylformamide (80 mL). The flask was wrapped in aluminium foil to keep the system in the dark and was heated at 60 °C for 24 hours after which the reaction was left to cool to room temperature.[†] A further batch of iodine (2.47 g, 9.74 mmol) and (diacetoxyiodo)benzene (3.14 g, 9.74 mmol) was added to the reaction and the mixture was heated at 60 °C in the dark for 24 hours. After cooling to room temperature, additional iodine (2.47 g, 9.74 mmol), palladium(II) acetate (292 mg, 1.30 mmol) and (diacetoxyiodo)benzene (3.14 g, 9.74 mmol) was added and the reaction was heated at 60 °C in the dark for 24 hours. After cooling to room temperature, another batch of iodine (2.47 g, 9.74 mmol) and (diacetoxyiodo)benzene (3.14 g, 9.74 mmol) was added to the reaction and the mixture was heated at 60 °C in the dark for 24 hours. After cooling to room temperature, the reaction was diluted with saturated aqueous sodium sulfite (200 mL) and ethyl acetate (300 mL). The aqueous layer was made acidic by the addition of aqueous 3 M hydrochloric acid. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 300 mL). The combined organic fractions dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude acid **91**, without further purification, was

[†] *The progress of the reaction was monitored by mass spectrometry or by TLC/^{1}H NMR analysis of a small sample which was converted to the corresponding isopropyl ester.*

dissolved in isopropanol (50 mL) and concentrated sulfuric acid (5 mL) was added. The reaction was heated to 80 °C for 4 hours and was then allowed to cool to room temperature. After dilution with water (100 mL) the mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 99 : 1 to 97 : 3) to afford ester **92** (2.21 g, 53%) as a colourless oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.66 (1H, d, *J* 7.8, **8**-**H**), 7.12 – 7.06 (1H, m, **10**-**H**), 7.04 – 6.97 (1H, m, **9**-**H**), 5.09 (1H, sept, *J* 6.2, **2**-**H**), 3.86 (2H, d, $J_{F\text{-}H}$ 2.2, **5**-**H**), 1.28 (6H, d, *J* 6.4, **1**-**H**).

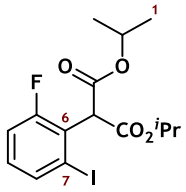
^{13}C (101 MHz, $CDCl_3$): δ 169.1 (**C4**), 160.5 (d, $J_{F\text{-}C}$ 251, $\mathbf{C}_{Ar}$**11**), 135.0 (d, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**8**), 130.2 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**9**), 126.5 (d, $J_{F\text{-}C}$ 17, $\mathbf{C}_{Ar}$**6**), 115.5 (d, $J_{F\text{-}C}$ 23, $\mathbf{C}_{Ar}$**10**), 101.9 (d, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**7**), 68.8 (**C2**), 39.7 (d, $J_{F\text{-}C}$ 2, **C5**), 21.9 (**C1**).

^{19}F (377 MHz, $CDCl_3$): δ −109.6

IR: v_{max} (neat)/ cm^{-1} 2981 (C–H), 1732 (C=O), 1569, 1456, 1177, 1105, 776.

HRMS (ESI): $C_{11}H_{12}FO_2INa$ $[M+Na]^+$ requires 344.9758; found 344.9761

Diisopropyl 2-(2-fluoro-6-iodophenyl)malonate (99)



A solution of lithium bis(trimethylsilyl)amide (1.0 M in toluene, 15.1 mL, 15.1 mmol) was added to a stirred solution of isopropyl ester **92** (1.95 g, 6.05 mmol) in tetrahydrofuran (10 mL) at −78 °C. The reaction was stirred at this temperature for 1 hour then a solution of

isopropyl chloroformate (1.0 M in toluene, 12.1 mL, 12.1 mmol) was added dropwise. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (50 mL). The biphasic mixture was extracted with dichloromethane (3 × 50 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford malonate **99** (2.25 g, 91%) as a colourless oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.66 (1H, d, *J* 7.8, **8**-**H**), 7.14 – 7.07 (1H, m, **10**-**H**), 7.06 – 6.99 (1H, m, **9**-**H**), 5.13 (2H, sept, *J* 6.3, **2**-**H**), 5.01(1H, s, **5**-**H**), 1.29 (6H, d, *J* 6.4, **1**-**H**), 1.28 (6H, d, *J* 6.4, **1**-**H**).

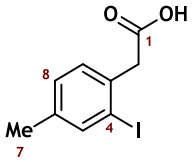
^{13}C (101 MHz, $CDCl_3$): δ 166.5 (**C4**), 160.7 (d, $J_{F\text{-}C}$ 254, C_{Ar}**11**), 135.2 (d, $J_{F\text{-}C}$ 3, C_{Ar}**8**), 131.1 (d, $J_{F\text{-}C}$ 10, C_{Ar}**9**), 126.6 (d, $J_{F\text{-}C}$ 17, C_{Ar}**6**), 116.4 (d, $J_{F\text{-}C}$ 22, C_{Ar}**10**), 102.0 (d, $J_{F\text{-}C}$ 3, C_{Ar}**7**), 69.9 (**C2**), 60.2 (**C5**), 21.7 (**C1**), 21.6 (**C1**).

^{19}F (377 MHz, $CDCl_3$): δ −104.7

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1731 (C=O), 1454, 1249, 1162, 1099, 782.

HRMS (ESI): $C_{15}H_{18}FO_4INa$ $[M+Na]^+$ requires 431.0126; found 431.0120

2-(2-Iodo-4-methylphenyl)acetic acid (84)



According to a modified literature procedure,[58] (diacetoxyiodo)benzene (1.61 g, 5.00 mmol) was added to suspension of 2-(2-iodo-4-methylphenyl)acetic acid **83** (1.00 g, 6.66 mmol),

palladium(II) acetate (0.075 g, 0.333 mmol) and iodine (1.27 g, 5.00 mmol) in anhydrous *N*,*N*-dimethylformamide (40 mL). The flask was wrapped in aluminium foil to keep the system in the dark and was then stirred at 60 °C for 24 h. After cooling to room temperature the reaction was concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate : acetic acid, 2 : 1 : 0.05) followed by three recrystallizations (hexane × 1 & ethanol/H_2O × 2) to afford acid **84** (479 mg, 26%) as a white solid with spectroscopic data in accordance with the literature.[219,220]

^{1}H (400 MHz, $CDCl_3$): δ 9.67 (1H, br. s, O**H**), 7.70 (1H, s, **5**-**H**), 7.19 – 7.11 (2H, m, **8**-**H**, **9**-**H**), 3.81 (2H, s, **2**-**H**), 2.30 (3H, s, **7**-**H**).

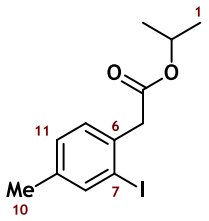
^{13}C (101 MHz, $CDCl_3$): δ 177.1 (**C1**), 140.1 ($\mathbf{C}_{Ar}$**5**), 139.3 ($\mathbf{C}_{Ar}$**3**), 134.2 ($\mathbf{C}_{Ar}$**6**), 130.4 ($\mathbf{C}_{Ar}$**9**), 129.5 ($\mathbf{C}_{Ar}$**8**), 101.1 ($\mathbf{C}_{Ar}$**4**), 45.7 (**C2**), 20.6 (**C7**).

IR: ν_{max} (neat)/ cm^{-1} 2961 (C–H), 1694 (C=O), 1405, 1234, 1199, 1034, 827, 666.

LRMS (ESI): $[M-H]^-$ 274.9

MP: 128 – 130 °C (ethanol/H_2O), lit. MP: 137 – 139 °C (hexane).[219]

Isopropyl 2-(2-iodo-4-methylphenyl)acetate (86)



According to a modified literature procedure,[58] (diacetoxyiodo)benzene (1.61 g, 5.00 mmol) was added to suspension of 2-(2-iodo-4-methylphenyl)acetic acid **83** (1.00 g, 6.66 mmol), palladium(II) acetate (0.075 g, 0.333 mmol) and iodine (1.27 g, 5.00 mmol) in anhydrous

N,*N*-dimethylformamide (40 mL). The flask was wrapped in aluminium foil to keep the system in the dark and was then stirred at 60 °C for 24 h. After cooling to room temperature the reaction was concentrated *in vacuo*. Isopropanol (25 mL) and concentrated sulfuric acid (2.5 mL) were added to the resulting residue. The reaction was heated to 80 °C for 4 hours and was then allowed to cool to room temperature. After dilution with water (100 mL) the mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium sulfite (100 mL) followed by saturated aqueous sodium bicarbonate (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified twice by silica gel chromatography (40-60 petrol : toluene, 3 : 2 to 0 : 1) to afford ester **86** (1.14 g, 54%) as a colourless oil.

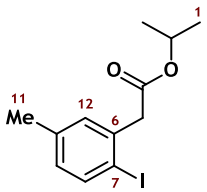
^{1}H (400 MHz, $CDCl_3$): δ 7.69 (1H, s, **8**-**H**), 7.19 – 7.10 (2H, m, **11**-**H**, **12**-**H**), 5.06 (1H, sept, *J* 6.3, **2**-**H**), 3.72 (2H, s, **5**-**H**), 2.30 (3H, s, **10**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 170.4 (**C4**), 140.0 ($\mathbf{C}_{Ar}$**8**), 138.9 ($\mathbf{C}_{Ar}$**6**), 135.1 ($\mathbf{C}_{Ar}$**9**), 130.3 ($\mathbf{C}_{Ar}$**12**), 129.3 ($\mathbf{C}_{Ar}$**11**), 101.0 ($\mathbf{C}_{Ar}$**7**), 68.5 (**C2**), 46.1 (**C5**), 21.9 (**C1**), 20.5 (**C10**).

IR: ν_{max} (neat)/ cm^{-1} 2979 (C–H), 1730 (C=O), 1487, 1255, 1169, 1106, 728.

HRMS (ESI): $C_{12}H_{15}O_2INa$ $[M+Na]^+$ requires 341.0009; found 341.0004

Isopropyl 2-(2-iodo-5-methylphenyl)acetate (89)



According to a modified literature procedure,[58] (diacetoxyiodo)benzene (1.61 g, 5.00 mmol) was added to suspension of 2-(2-iodo-5-methylphenyl)acetic acid **87** (1.00 g, 6.66 mmol),

palladium(II) acetate (0.075 g, 0.333 mmol) and iodine (1.27 g, 5.00 mmol) in anhydrous *N*,*N*-dimethylformamide (40 mL). The flask was wrapped in aluminium foil to keep the system in the dark and was then stirred at 60 °C for 24 h. After cooling to room temperature the reaction was concentrated *in vacuo*. Isopropanol (25 mL) and concentrated sulfuric acid (2.5 mL) were added to the resulting residue. The reaction was heated to 80 °C for 4 hours and was then allowed to cool to room temperature. After dilution with water (100 mL) the mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium sulfite (100 mL) followed by saturated aqueous sodium bicarbonate (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : dichloromethane, 5 : 1 to 2 : 1) to afford ester **89** (1.69 g, 79%) as a colourless oil.

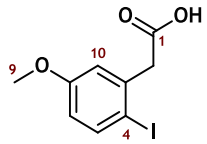
^{1}H (400 MHz, $CDCl_3$): δ 7.70 (1H, d, *J* 8.1, **8**-**H**), 7.11 (1H, d, *J* 1.8, **12**-**H**), 6.79 (1H, dd, *J* 8.1, 1.8, **9**-**H**), 5.08 (1H, sept, *J* 6.3, **2**-**H**), 3.72 (2H, s, **5**-**H**), 2.30 (3H, s, **11**-**H**), 1.28 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 170.2 (**C4**), 139.2 ($\mathbf{C}_{Ar}$**8**), 138.4 ($\mathbf{C}_{Ar}$**6**), 137.8 ($\mathbf{C}_{Ar}$**10**), 131.6 ($\mathbf{C}_{Ar}$**12**), 129.8 ($\mathbf{C}_{Ar}$**9**), 97.0 ($\mathbf{C}_{Ar}$**7**), 68.5 (**C2**), 46.4 (**C5**), 21.9 (**C1**), 21.0 (**C11**).

IR: ν_{max} (neat)/ cm^{-1} 2979 (C–H), 1728 (C=O), 1468, 1251, 1164, 1104, 807.

HRMS (ESI): $C_{12}H_{15}O_2INa$ $[M+Na]^+$ requires 341.0009; found 341.0000

2-(2-Iodo-5-methoxyphenyl)acetic acid (80)



According to a literature procedure,[62] iodine monochloride (5.86 g, 36.1 mmol) was added to a stirred solution of 2-(3-methoxyphenyl)acetic acid **79** (5.00 g, 30.1 mmol) and iodine (107 mg, 0.420 mmol) in acetic acid (55 mL). The resulting mixture was stirred for 6 days in the dark at room temperature. The reaction was poured into water (200 mL) and the resulting precipitate was collected by filtration. The crude product was purified by recrystallization (toluene) to afford iodoarene **80** (5.60 g, 64%) as a white solid.

^{1}H (400 MHz, $(CD_3)_2SO$): δ 12.44 (1H, br. s, **OH**), 7.68 (1H, d, *J* 8.8, **5**-**H**), 7.00 (1H, d, *J* 3.0, **10**-**H**), 6.65 (1H, dd, *J* 8.6, 3.0, **6**-**H**), 5.18 (1H, s, **5**-**H**), 3.73 (3H, s, **9**-**H**), 3.68 (2H, s, **2**-**H**).

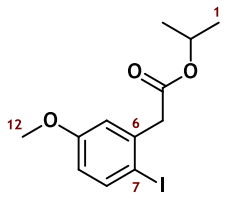
^{13}C (101 MHz, $(CD_3)_2SO$): δ 171.4 (**C1**), 159.4 ($\mathbf{C}_{Ar}$**7**), 139.6 ($\mathbf{C}_{Ar}$**3**), 139.3 ($\mathbf{C}_{Ar}$**5**), 117.4 ($\mathbf{C}_{Ar}$**10**), 114.7 ($\mathbf{C}_{Ar}$**6**), 90.1 ($\mathbf{C}_{Ar}$**4**), 55.3 (**C9**), 45.6 (**C2**).

IR: ν_{max} (neat)/ cm^{-1} 3005 (O–H), 2940 (C–H), 1710 (C=O), 1471, 1298, 1238 (C–O).

HRMS (ESI): $C_9H_8IO_3$ $[M-H]^-$ requires 290.9524; found 290.9529

MP: 124 – 126 °C (toluene), lit. MP: 134 – 135 °C (toluene).[62]

Isopropyl 2-(2-iodo-5-methoxyphenyl)acetate (81)



Concentrated sulfuric acid (3.1 mL) was added to a stirred solution of phenylacetic acid **80** (6.12 g, 21.0 mmol) in isopropanol (31 mL). The reaction was heated to 80 °C for 4 hours and was then allowed to cool to room temperature. After dilution with water (100 mL) the mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product, isopropyl ester **81** (6.31 g, 90%), which did not require purification, was afforded as a yellow oil.

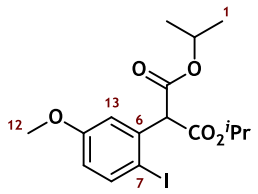
^{1}H (400 MHz, $CDCl_3$): δ 7.69 (1H, d, *J* 8.6, **8**-**H**), 6.87 (2H, d, *J* 3.0, **13**-**H**), 6.57 (1H, dd, *J* 8.8, 3.0, **9**-**H**), 5.07 (1H, sept, *J* 6.3, **2**-**H**), 3.78 (3H, s, **12**-**H**), 3.71 (2H, s, **5**-**H**), 1.25 (6H, d, *J* 6.1, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 170.0 (**C4**), 160.0 ($\mathbf{C}_{Ar}$**10**), 139.9 ($\mathbf{C}_{Ar}$**8**), 139.0 ($\mathbf{C}_{Ar}$**6**), 116.8 ($\mathbf{C}_{Ar}$**13**), 115.0 ($\mathbf{C}_{Ar}$**9**), 89.6 ($\mathbf{C}_{Ar}$**7**), 68.6 (**C2**), 55.4 (**C12**), 46.7 (**C5**), 21.9 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2979 (C–H), 1728 (C=O), 1468, 1245 (C–O), 1168, 1106, 769.

HRMS (ESI): $C_{12}H_{15}O_3INa$ $[M+Na]^+$ requires 356.9958; found 356.9950

Diisopropyl 2-(2-iodo-5-methoxyphenyl)malonate (82)



A solution of lithium bis(trimethylsilyl)amide (1.0 M in toluene, 44.0 mL, 44.0 mmol) was added to a stirred solution of isopropyl ester **81** (5.87 g, 17.6 mmol) in tetrahydrofuran (20 mL) at −78 °C. The reaction was stirred at this temperature for 1 hour and then a solution of isopropyl chloroformate (1.0 M in toluene, 35.2 mL, 35.2 mmol) was added dropwise. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (200 mL). The biphasic mixture was extracted with dichloromethane (3 × 150 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5) to afford malonate **82** (6.11 g, 83%) as a pale yellow oil.

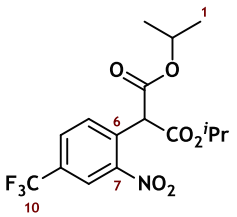
^{1}H (400 MHz, $CDCl_3$): δ 7.72 (1H, d, *J* 8.9, **8**-**H**), 7.05 (1H, d, *J* 3.1, **13**-**H**), 6.63 (1H, dd, *J* 8.8, 3.0, **9**-**H**), 5.11 (2H, sept, *J* 6.3, **2**-**H**), 4.99 (1H, s, **5**-**H**), 3.78 (3H, s, **12**-**H**), 1.30 (6H, d, *J* 6.3, **1**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 167.2 (**C4**), 160.0 ($\mathbf{C}_{Ar}$**10**), 139.9 ($\mathbf{C}_{Ar}$**8**), 137.5 ($\mathbf{C}_{Ar}$**6**), 116.2 ($\mathbf{C}_{Ar}$**9**), 115.6 ($\mathbf{C}_{Ar}$**13**), 90.2 ($\mathbf{C}_{Ar}$**7**), 69.7 (**C2**), 62.6 (**C5**), 55.4 (**C12**), 21.7 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1728 (C=O), 1291, 1239 (C–O), 1162, 1098.

HRMS (ESI): $C_{16}H_{21}O_5INa$ $[M+Na]^+$ requires 443.0326; found 443.0321

Diisopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)malonate (105)



According to a modified literature procedure,[55] diisopropyl malonate (21.9 mL, 115 mmol) was added to a stirred suspension of potassium carbonate (23.9 g, 173 mmol) and 1-fluoro-2-nitro-4-(trifluoromethyl)benzene **100** (12.0 g, 57.6 mmol) in anhydrous *N*,*N*-dimethylformamide (160 mL). The resulting mixture was heated to 90 °C for 16 hours and after cooling to room temperature was concentrated *in vacuo*. The residue was treated with aqueous hydrochloric acid (1 M, 500 mL), extracted with dichloromethane (3 × 500 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by recrystallization (60-80 petrol) to afford nitroarene **105** (18.6 g, 86%) as a yellow crystalline solid with spectroscopic data in accordance with the literature.[55]

^{1}H (400 MHz, $CDCl_3$): δ 8.32 (1H, d, *J* 1.3, **8**-**H**), 7.90 (1H, dd, *J* 8.1, 1.5, **11**-**H**), 7.73 (1H, d, *J* 8.3, **12**-**H**), 5.27 (1H, s, **5**-**H**), 5.14 (2H, sept, *J* 6.3, **2**-**H**), 1.31 (6H, d, *J* 6.3, **1**-**H**), 1.28 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 166.2 (**C4**), 149.1 ($\mathbf{C}_{Ar}$**7**), 132.6 ($\mathbf{C}_{Ar}$**12**), 132.3 ($\mathbf{C}_{Ar}$**6**), 131.8 (q, $J_{F\text{-}C}$ 34, $\mathbf{C}_{Ar}$**9**), 129.9 (q, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**11**), 122.7 (q, $J_{F\text{-}C}$ 272, **C10**), 122.5 (q, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**8**), 70.7 (**C2**), 54.8 (**C5**), 21.6 (**C1**).

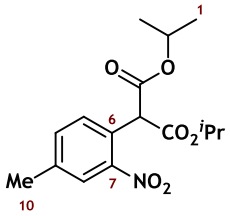
^{19}F (377 MHz, $CDCl_3$): δ −63.1

IR: ν_{max} (neat)/ cm^{-1} 2985 (C–H), 1731 (C=O), 1543 (NO_2), 1326 (NO_2), 1135, 1090.

HRMS (ESI): $C_{16}H_{19}F_3NO_6$ $[M+H]^+$ requires 378.1154; found 378.1159

MP: 44 – 46 °C (60-80 petrol), lit. MP: 40 – 42 °C (60-80 petrol).[186]

Diisopropyl 2-(4-methyl-2-nitrophenyl)malonate (106)



According to a modified literature procedure,[55] diisopropyl malonate (12.7 mL, 67.0 mmol) was added to a stirred suspension of potassium carbonate (13.9 g, 101 mmol) and 1-fluoro-4-methyl-2-nitrobenzene **101** (5.20 g, 33.5 mmol) in anhydrous *N*,*N*-dimethylformamide (94 mL). The resulting mixture was heated to 90 °C for 16 hours and after cooling to room temperature was concentrated *in vacuo*. The residue was treated with aqueous hydrochloric acid (1 M, 250 mL), extracted with dichloromethane (3 × 250 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by recrystallization (60-80 petrol) to afford nitroarene **106** (8.85 g, 82%) as white needles with spectroscopic data in accordance with the literature.[55]

^{1}H (400 MHz, $CDCl_3$): δ 7.86 (1H, d, *J* 0.8, **8**-**H**), 7.90 (1H, dd, *J* 8.1, 1.0, **11**-**H**), 7.38 (1H, d, *J* 8.1, **12**-**H**), 5.16 (1H, s, **5**-**H**), 5.14 (2H, sept, *J* 6.3, **2**-**H**), 2.43 (3H, s, **10**-**H**), 1.28 (6H, d, *J* 6.3, **1**-**H**), 1.26 (6H, d, *J* 6.3, **1**-**H**).

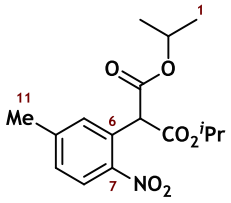
^{13}C (101 MHz, $CDCl_3$): δ 167.1 (**C4**), 148.8 ($\mathbf{C}_{Ar}$**7**), 139.8 ($\mathbf{C}_{Ar}$**9**), 134.3 ($\mathbf{C}_{Ar}$**11**), 131.0 ($\mathbf{C}_{Ar}$**12**), 125.6 ($\mathbf{C}_{Ar}$**6**), 125.6 ($\mathbf{C}_{Ar}$**8**), 70.0 (**C2**), 54.7 (**C5**), 21.6 (**C1**), 20.9 (**C10**).

IR: ν_{max} (neat)/ cm^{-1} 2983 (C–H), 1729 (C=O), 1531 (NO_2), 1351 (NO_2), 1228, 1166, 1099.

HRMS (ESI): $C_{16}H_{21}NO_6Na$ $[M+Na]^+$ requires 346.1261; found 346.1264

MP: 73 – 75 °C (60-80 petrol).

Diisopropyl 2-(5-methyl-2-nitrophenyl)malonate (108)



According to a modified literature procedure,[55] diisopropyl malonate (12.8 mL, 67.4 mmol) was added to a stirred suspension of potassium carbonate (14.0 g, 101 mmol) and 2-fluoro-4-methyl-1-nitrobenzene **103** (5.23 g, 33.7 mmol) in anhydrous *N*,*N*-dimethylformamide (95 mL). The resulting mixture was heated to 90 °C for 16 hours and after cooling to room temperature was concentrated *in vacuo*. The residue was treated with aqueous hydrochloric acid (1 M, 250 mL), extracted with dichloromethane (3 × 250 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by recrystallization (60-80 petrol) to afford nitroarene **108** (6.82 g, 63%) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.00 (1H, d, *J* 8.1, **8**-**H**), 7.32 – 7.25 (2H, m, **9**-**H**, **12**-**H**), 5.24 (1H, s, **5**-**H**), 5.14 (2H, sept, *J* 6.3, **2**-**H**), 2.45 (3H, s, **11**-**H**), 1.30 (6H, d, *J* 6.3, **1**-**H**), 1.28 (6H, d, *J* 6.3, **1**-**H**).

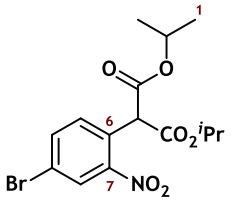
^{13}C (101 MHz, $CDCl_3$): δ 167.1 (**C4**), 146.7 ($\mathbf{C}_{Ar}$**7**), 144.9 ($\mathbf{C}_{Ar}$**10**), 131.8 ($\mathbf{C}_{Ar}$**12**), 129.7 ($\mathbf{C}_{Ar}$**9**), 128.7 ($\mathbf{C}_{Ar}$**6**), 125.6 ($\mathbf{C}_{Ar}$**8**), 70.1 (**C2**), 55.2 (**C5**), 21.7 (**C1**), 21.7 (**C11**).

IR: ν_{max} (neat)/ cm^{-1} 2980 (C–H), 1739 (C=O), 1726 (C=O), 1519 (NO_2), 1342 (NO_2), 1168, 1101, 737.

HRMS (ESI): $C_{16}H_{21}NO_6Na$ $[M+Na]^+$ requires 346.1261; found 346.1263

MP: 102 – 104 °C (60-80 petrol).

Diisopropyl 2-(4-bromo-2-nitrophenyl)malonate (109)



According to a modified literature procedure,[55] diisopropyl malonate (12.5 mL, 66.0 mmol) was added to a stirred suspension of potassium carbonate (13.7 g, 99.0 mmol) and 4-bromo-1-fluoro-2-nitrobenzene **104** (7.26 g, 33.0 mmol) in anhydrous *N*,*N*-dimethylformamide (95 mL). The resulting mixture was heated to 90 °C for 16 hours and after cooling to room temperature was concentrated *in vacuo*. The residue was treated with aqueous hydrochloric acid (1 M, 250 mL), extracted with dichloromethane (3 × 250 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by recrystallization (60-80 petrol) to afford nitroarene **109** (10.2 g, 79%) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.00 (1H, d, *J* 2.0, **8**-**H**), 7.75 (1H, dd, *J* 8.5, 2.1, **10**-**H**), 7.42 (1H, d, *J* 8.3, **11**-**H**), 5.14 (1H, s, **5**-**H**), 5.10 (2H, sept, *J* 6.3, **2**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**), 1.25 (6H, d, *J* 6.3, **1**-**H**).

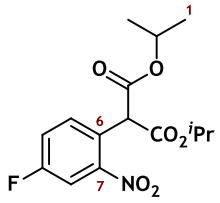
^{13}C (101 MHz, $CDCl_3$): δ 166.4 (**C4**), 149.3 ($\mathbf{C}_{Ar}$**7**), 136.4 ($\mathbf{C}_{Ar}$**10**), 132.8 ($\mathbf{C}_{Ar}$**11**), 128.1 ($\mathbf{C}_{Ar}$**8**), 127.5 ($\mathbf{C}_{Ar}$**6**), 122.5 ($\mathbf{C}_{Ar}$**9**), 70.3 (**C2**), 54.5 (**C5**), 21.6 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2983 (C–H), 1729 (C=O), 1534 (NO_2), 1348 (NO_2), 1166, 1097, 734.

HRMS (ESI): $C_{15}H_{18}{}^{79}BrNO_6Na$ $[M+Na]^+$ requires 410.0210; found 410.0208

MP: 34 – 36 °C (60-80 petrol).

Diisopropyl 2-(4-fluoro-2-nitrophenyl)malonate (107)



According to a modified literature procedure,[55] diisopropyl malonate (20.8 mL, 110 mmol) was added to a stirred suspension of potassium carbonate (22.7 g, 164 mmol) and 1,4-difluoro-2-nitrobenzene **102** (8.72 g, 54.8 mmol) in anhydrous *N*,*N*-dimethylformamide (158 mL). The resulting mixture was heated to 90 °C for 16 hours and after cooling to room temperature was concentrated *in vacuo*. The residue was treated with aqueous hydrochloric acid (1 M, 500 mL), extracted with dichloromethane (3 × 500 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by recrystallization (60-80) petrol to afford nitroarene **107** (15.6 g, 87%) as a light yellow solid with spectroscopic data in accordance with the literature.[55]

^{1}H (500 MHz, $CDCl_3$): δ 7.78 (1H, dd, $J_{F\text{-}H}$ 8.2, *J* 2.8, **8**-**H**), 7.55 (1H, dd, *J* 8.8, $J_{F\text{-}H}$ 5.4, **11**-**H**), 7.37 (1H, ddd, $J_{F\text{-}H}$ 8.8, *J* 7.3, 2.8, **10**-**H**), 5.18 (1H, s, **5**-**H**), 5.12 (2H, sept, *J* 6.3, **2**-**H**), 1.29 (6H, d, *J* 6.3, **1**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 166.7 (**C4**), 161.7 (d, $J_{F\text{-}C}$ 253, $\mathbf{C}_{Ar}$**9**), 149.5 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**7**), 133.1 (d, $J_{F\text{-}C}$ 8, $\mathbf{C}_{Ar}$**11**), 124.7 (d, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**6**), 120.8 (d, $J_{F\text{-}C}$ 21, $\mathbf{C}_{Ar}$**10**), 112.9 (d, $J_{F\text{-}C}$ 27, $\mathbf{C}_{Ar}$**8**), 70.3 (**C2**), 54.3 (**C5**), 21.7 (**C1**).

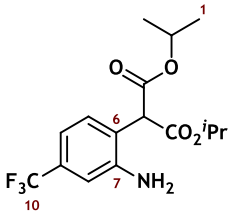
^{19}F (470 MHz, $CDCl_3$): δ −109.6

IR: ν_{max} (neat)/ cm^{-1} 2984 (C–H), 1729 (C=O), 1538 (NO_2), 1354 (NO_2), 1239, 1099, 909.

LRMS (ESI): $[M+Na]^+$ 350.1

MP: 58 – 60 °C (60-80 petrol).[†]

Diisopropyl 2-(2-amino-4-(trifluoromethyl)phenyl)malonate (111)



According to a literature procedure,[55] palladium on activated carbon (200 mg, 10 wt.% palladium) was added to a stirred solution of nitroarene **105** (2.14 g, 5.68 mmol) in methanol (12 mL). The solution was purged with hydrogen gas three times and then left to stir under an atmosphere of hydrogen (balloon pressure) for 14 hours. The mixture was filtered through Celite® with methanol and the solvent was removed *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5) to afford aniline **111** (1.89 g, 96%) as a pale yellow solid with spectroscopic data in accordance with the literature.[55]

^{1}H (400 MHz, $CDCl_3$): δ 7.27 (1H, d, *J* 8.1, **12-H**), 6.99 (1H, d, *J* 8.1, **11-H**), 6.95 (1H, s, **8-H**), 5.11 (2H, sept, *J* 6.3, **2-H**), 4.60 (1H, s, **5-H**), 4.39 (2H, br. s, N**H**$_2$), 1.28 (6H, d, *J* 6.3, **1-H**), 1.24 (6H, d, *J* 6.3, **1-H**).

^{13}C (101 MHz, $CDCl_3$): δ 167.8 (**C4**), 146.2 (**C**$_{Ar}$**7**), 131.9 (**C**$_{Ar}$**12**), 131.4 (q, $J_{F\text{-}C}$ 32, **C**$_{Ar}$**9**), 124.1 (q, $J_{F\text{-}C}$ 272, **C10**), 122.7 (**C**$_{Ar}$**6**), 115.3 (q, $J_{F\text{-}C}$ 4, **C**$_{Ar}$**11**), 114.0 (q, $J_{F\text{-}C}$ 3, **C**$_{Ar}$**8**), 70.0 (**C2**), 56.0 (**C5**), 21.6 (**C1**).

^{19}F (377 MHz, $CDCl_3$): δ −62.9

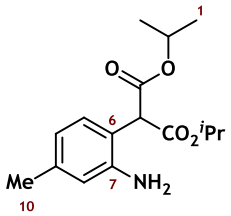
[†] *A melting point has not been previously quoted in the literature.*

IR: ν_{max} (neat)/ cm^{-1} 3445 (N–H), 3378 (N–H), 2985 (C–H), 1722 (C=O), 1336, 1165, 1123, 1098, 733.

HRMS (ESI): $C_{16}H_{21}F_3NO_4$ $[M+H]^+$ requires 348.1417; found 348.1417

MP: 48 – 50 °C.[†]

Diisopropyl 2-(2-amino-4-methylphenyl)malonate (112)



According to a modified literature procedure,[55] palladium on activated carbon (453 mg, 10 wt.% palladium) was added to a stirred solution of nitroarene **106** (4.53 g, 14.0 mmol) and triethylamine (1.95 mL, 14.0 mmol) in ethyl acetate (45 mL). The solution was purged with hydrogen gas three times and then left to stir under an atmosphere of hydrogen (balloon pressure) for 8 hours. The mixture was filtered through Celite® with ethyl acetate and the solvent was removed *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5 to 90 : 10) to afford aniline **112** (3.47 g, 84%) as a yellow solid with spectroscopic data in accordance with the literature.[55]

^{1}H (400 MHz, $CDCl_3$): δ 7.06 (1H, d, *J* 7.8, **12**-**H**), 6.59 (1H, dd, *J* 7.8, 1.0, **11**-**H**), 6.54 (1H, s, **8**-**H**), 5.10 (2H, sept, *J* 6.3, **2**-**H**), 4.55 (1H, s, **5**-**H**), 4.08 (2H, br. s, N**H**$_2$), 2.25 (3H, s, **10**-**H**), 1.28 (6H, d, *J* 6.3, **1**-**H**), 1.25 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 168.4 (**C4**), 145.4 (**C**$_{Ar}$**7**), 139.0 (**C**$_{Ar}$**9**), 131.0 (**C**$_{Ar}$**12**), 119.8 (**C**$_{Ar}$**11**), 118.2 (**C**$_{Ar}$**8**), 116.6 (**C**$_{Ar}$**6**), 69.3 (**C2**), 55.6 (**C5**), 21.6 (**C1**), 21.1 (**C10**).

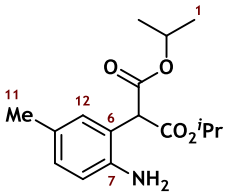
[†] *A melting point has not been previously quoted in the literature.*

IR: ν_{max} (neat)/ cm^{-1} 3437 (N–H), 3371 (N–H), 2982 (C–H), 1721 (C=O), 1301, 1163, 1099, 731.

HRMS (ESI): $C_{16}H_{24}NO_4$ $[M+H]^+$ requires 294.1700; found 294.1691

MP: 38 – 40 °C.[†]

Diisopropyl 2-(2-amino-5-methylphenyl)malonate (114)



According to a modified literature procedure,[55] palladium on activated carbon (531 mg, 10 wt.% palladium) was added to a stirred solution of nitroarene **108** (5.31 g, 16.4 mmol) and triethylamine (2.30 mL, 16.4 mmol) in ethyl acetate (53 mL). The solution was purged with hydrogen gas three times and then left to stir under an atmosphere of hydrogen (balloon pressure) for 48 hours. The mixture was filtered through Celite® with ethyl acetate and the solvent was removed *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5 to 90 : 10) to afford aniline **114** (2.14 g, 44%) as a beige solid.

^{1}H (400 MHz, $CDCl_3$): δ 6.98 (1H, s, **12**-**H**), 6.94 (1H, d, *J* 7.8, **9**-**H**), 6.64 (1H, d, *J* 8.1, **8**-**H**), 5.11 (2H, sept, *J* 6.3, **2**-**H**), 4.55 (1H, s, **5**-**H**), 3.97 (2H, br. s, N**H**$_2$), 2.24 (3H, s, **11**-**H**), 1.29 (6H, d, *J* 6.3, **1**-**H**), 1.25 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 168.4 (**C4**), 143.0 (**C**$_{Ar}$**7**), 131.7 (**C**$_{Ar}$**12**), 129.8 (**C**$_{Ar}$**9**), 128.3 (**C**$_{Ar}$**10**), 119.7 (**C**$_{Ar}$**6**), 117.8 (**C**$_{Ar}$**8**), 69.5 (**C2**), 56.0 (**C5**), 21.7 (**C1**), 20.5 (**C11**).

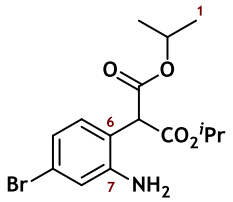
[†] *A melting point has not been previously quoted in the literature.*

IR: ν_{max} (neat)/ cm^{-1} 3434 (N–H), 3366 (N–H), 2982 (C–H), 1721 (C=O), 1510, 1297, 1161, 1098, 818.

HRMS (ESI): $C_{16}H_{23}NO_4Na$ $[M+Na]^+$ requires 316.1519; found 316.1517

MP: 73 – 75 °C.

Diisopropyl 2-(2-amino-4-bromophenyl)malonate (110)



According to a modified literature procedure,[64] zinc dust (12.0 g, 184 mmol) and ammonium chloride (14.8 g, 276 mmol) were added to a stirred solution of nitroarene **109** (7.13 g, 18.4 mmol) in acetone : water (5 : 1, 200 mL). After 1 hour the heterogeneous reaction mixture was filtered through Celite®, and concentrated *in vacuo*. The crude residue was treated with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5 to 90 : 10) to afford aniline **110** (6.02 g, 91%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.04 – 6.99 (1H, m, **11**-**H**), 6.90 – 6.84 (2H, m, **8**-**H**, **10**-**H**), 5.09 (2H, sept, *J* 6.3, **2**-**H**), 4.51 (1H, s, **5**-**H**), 4.24 (2H, br. s, N**H**$_2$), 1.26 (6H, d, *J* 6.3, **1**-**H**), 1.23 (6H, d, *J* 6.3, **1**-**H**).

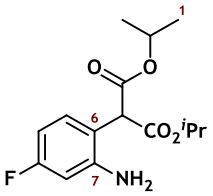
^{13}C (101 MHz, $CDCl_3$): δ 167.9 (**C4**), 147.1 (**C**$_{Ar}$**7**), 132.7 (**C**$_{Ar}$**11**), 122.8 (**C**$_{Ar}$**9**), 121.7 (**C**$_{Ar}$**10**), 120.0 (**C**$_{Ar}$**8**), 118.3 (**C**$_{Ar}$**6**), 69.8 (**C2**), 55.7 (**C5**), 21.6 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 3439 (N–H), 3375 (N–H), 2982 (C–H), 1720 (C=O), 1492, 1297, 1165, 1097.

HRMS (ESI): $C_{15}H_{20}{}^{79}BrNO_4Na$ $[M+Na]^+$ requires 380.0468; found 380.0468

MP: 81 – 83 °C.

Diisopropyl 2-(2-amino-4-fluorophenyl)malonate (113)



According to a literature procedure,[55] palladium on activated carbon (773 mg, 10 wt.% palladium) was added to a stirred solution of nitroarene **107** (7.73 g, 327 mmol) in methanol (70 mL). The solution was purged with hydrogen gas three times and then left to stir under an atmosphere of hydrogen (balloon pressure) for 6 hours. The mixture was filtered through Celite® with methanol and the solvent was removed *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 90 : 10) to afford aniline **113** (5.87 g, 84%) as a white solid with spectroscopic data in accordance with the literature.[55]

^{1}H (500 MHz, $CDCl_3$): δ 7.11 (1H, dd, *J* 8.5, $J_{F\text{-}H}$ 6.3, **11**-**H**), 6.48 – 6.39 (2H, m, **8**-**H**, **10**-**H**), 5.09 (2H, sept, *J* 6.3, **2**-**H**), 4.51 (1H, s, **5**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**), 1.24 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 168.2 (**C4**), 163.4 (d, $J_{F\text{-}C}$ 244, $\mathbf{C}_{Ar}$**9**), 147.5 (d, $J_{F\text{-}C}$ 11, $\mathbf{C}_{Ar}$**7**), 132.8 (d, $J_{F\text{-}C}$ 10, $\mathbf{C}_{Ar}$**11**), 115.2 (d, $J_{F\text{-}C}$ 2, $\mathbf{C}_{Ar}$**6**), 105.5 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**8**), 104.1 (d, $J_{F\text{-}C}$ 25, $\mathbf{C}_{Ar}$**10**), 69.7 (**C2**), 55.5 (**C5**), 21.6 (**C1**).

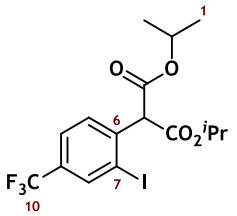
^{19}F (470 MHz, $CDCl_3$): δ −113.8

IR: ν_{max} (neat)/ cm^{-1} 3442 (N–H), 3377 (N–H), 2983 (C–H), 1721 (C=O), 1509, 1261, 1171, 1099, 730.

HRMS (ESI): $C_{15}H_{20}FNO_4Na$ $[M+Na]^+$ requires 320.1269; found 320.1270

MP: 62 – 64 °C (40-60 petrol/ethyl acetate).[†]

Diisopropyl 2-(2-iodo-4-(trifluoromethyl)phenyl)malonate (115)



According to a modified literature procedure,[70] boron trifluoride diethyl etherate (1.60 mL, 13.0 mmol) was added to a flask under argon and cooled to −15 °C. To this, was added a solution of aniline **111** (3.00 g, 8.64 mmol) in dichloromethane (20 mL) dropwise over 5 minutes. Subsequently, a solution of *tert*-butyl nitrite (1.37 mL, 10.4 mmol) in dichloromethane (9 ml) was added dropwise over 30 minutes. The resulting suspension was stirred at −15 °C for 20 minutes then at 0 °C for 30 minutes. After warming to room temperature the reaction was concentrated *in vacuo* and the crude diazonium salt dissolved in acetonitrile (36 mL) under argon. The resulting solution was added dropwise over 1 hour to a stirred suspension of sodium iodide (1.56 g, 10.4 mmol) and iodine (219 mg, 0.864 mmol) in acetonitrile (65 mL) at room temperature. The dark solution was stirred for 1 hour before quenching with saturated aqueous sodium sulfite (200 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 200 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate,

[†] *A melting point has not been previously quoted in the literature.*

filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford iodoarene **115** (2.74 g, 69%) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.12 (1H, s, **8**-**H**), 7.64 (1H, d, *J* 8.3, **11**-**H**), 7.60 (1H, d, *J* 8.3, **12**-**H**), 5.12 (2H, sept, *J* 6.3, **2**-**H**), 5.09 (1H, s, **5**-**H**), 1.30 (6H, d, *J* 6.3, **1**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 166.8 (**C4**), 140.8 ($\mathbf{C}_{Ar}$**6**), 136.4 (q, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**8**), 131.7 (q, $J_{F\text{-}C}$ 33, $\mathbf{C}_{Ar}$**9**), 130.1 ($\mathbf{C}_{Ar}$**12**), 125.4 (q, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**11**), 122.8 (q, $J_{F\text{-}C}$ 273, **C10**), 101.41 ($\mathbf{C}_{Ar}$**7**), 70.2 (**C2**), 62.5 (**C5**), 21.7 (**C1**).

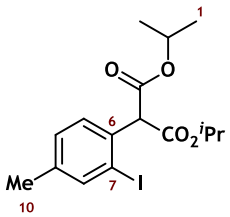
^{19}F (377 MHz, $CDCl_3$): δ −62.8

IR: ν_{max} (neat)/ cm^{-1} 2983 (C–H), 1730 (C=O), 1322, 1129, 1098, 1080.

HRMS (ESI): $C_{16}H_{18}F_3IO_4Na$ $[M+Na]^+$ requires 481.0094; found 481.0098

MP: 76 – 78 °C (hexane).

Diisopropyl 2-(2-iodo-4-methylphenyl)malonate (97)



According to a modified literature procedure,[70] boron trifluoride diethyl etherate (1.24 mL, 10.0 mmol) was added to a flask under argon and cooled to −15 °C. To this, was added a solution of aniline **112** (1.96 g, 6.68 mmol) in dichloromethane (13 mL) dropwise over 5 minutes. Subsequently, a solution of *tert*-butyl nitrite (1.06 mL, 8.02 mmol) in dichloromethane (6 ml) was added dropwise over 30 minutes. The resulting suspension was

stirred at −15 °C for 20 minutes then at 0 °C for 30 minutes. After warming to room temperature the reaction was concentrated *in vacuo* and the crude diazonium salt dissolved in acetonitrile (24 mL) under argon. The resulting solution was added dropwise over 1 hour to a stirred suspension of sodium iodide (1.20 g, 8.02 mmol) and iodine (170 mg, 0.668 mmol) in acetonitrile (43 mL) at room temperature. The dark solution was stirred for 1 hour before quenching with saturated aqueous sodium sulfite (100 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford iodoarene **97** (2.46 g, 91%) as a yellow oil.

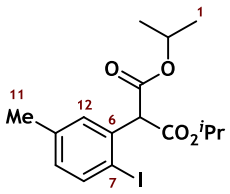
^{1}H (400 MHz, $CDCl_3$): δ 7.71 (1H, d, *J* 0.9, **8**-**H**), 7.33 (1H, d, *J* 8.0, **12**-**H**), 7.18 (1H, dd, *J* 7.9, 1.1, **11**-**H**), 5.10 (2H, sept, *J* 6.3, **2**-**H**), 5.01 (1H, s, **5**-**H**), 2.30 (3H, s, **10**-**H**), 1.29 (6H, d, *J* 6.3, **1**-**H**), 1.26 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 167.5 (**C4**), 140.0 ($\mathbf{C}_{Ar}$**8**), 139.8 ($\mathbf{C}_{Ar}$**6**), 133.8 ($\mathbf{C}_{Ar}$**9**), 129.4 ($\mathbf{C}_{Ar}$**11**), 129.2 ($\mathbf{C}_{Ar}$**12**), 101.7 ($\mathbf{C}_{Ar}$**7**), 69.6 (**C2**), 62.2 (**C5**), 21.7 (**C1**), 20.5 (**C10**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1729 (C=O), 1258, 1225, 1162, 1100, 732.

HRMS (ESI): $C_{16}H_{21}IO_4Na$ $[M+Na]^+$ requires 427.0377; found 427.0373

Diisopropyl 2-(2-iodo-5-methylphenyl)malonate (98)



According to a modified literature procedure,[70] boron trifluoride diethyl etherate (1.30 mL, 10.6 mmol) was added to a flask under argon and cooled to −15 °C. To this, was added a solution of aniline **114** (2.08 g, 7.09 mmol) in dichloromethane (14 mL) dropwise over 5 minutes. Subsequently, a solution of *tert*-butyl nitrite (1.10 mL, 8.51 mmol) in dichloromethane (7 ml) was added dropwise over 30 minutes. The resulting suspension was stirred at −15 °C for 20 minutes then at 0 °C for 30 minutes. After warming to room temperature the reaction was concentrated *in vacuo* and the crude diazonium salt dissolved in acetonitrile (25 mL) under argon. The resulting solution was added dropwise over 1 hour to a stirred suspension of sodium iodide (1.28 g, 8.51 mmol) and iodine (180 mg, 0.710 mmol) in acetonitrile (46 mL) at room temperature. The dark solution was stirred for 1 hour before quenching with saturated aqueous sodium sulfite (100 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford iodoarene **98** (2.49 g, 87%) as a yellow oil.

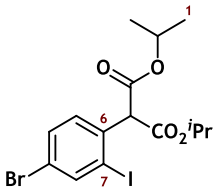
^{1}H (400 MHz, $CDCl_3$): δ 7.72 (1H, d, *J* 8.1, **8**-**H**), 7.26 (1H, d, *J* 1.8, **12**-**H**), 6.83 (1H, dd, *J* 8.1, 2.0, **9**-**H**), 5.11 (2H, sept, *J* 6.3, **2**-**H**), 5.01 (1H, s, **5**-**H**), 2.31 (3H, s, **11**-**H**), 1.29 (6H, d, *J* 6.3, **1**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 167.5 (**C4**), 139.3 ($\mathbf{C}_{Ar}$**8**), 138.5 ($\mathbf{C}_{Ar}$**10**), 136.4 ($\mathbf{C}_{Ar}$**6**), 130.8 ($\mathbf{C}_{Ar}$**9**), 130.5 ($\mathbf{C}_{Ar}$**12**), 97.7 ($\mathbf{C}_{Ar}$**7**), 69.6 (**C2**), 62.5 (**C5**), 21.7 (**C1**), 21.1 (**C11**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1728 (C=O), 1237, 1160, 1098, 1011, 907.

HRMS (ESI): $C_{16}H_{21}IO_4Na$ $[M+Na]^+$ requires 427.0377; found 427.0381

Diisopropyl 2-(4-bromo-2-iodophenyl)malonate (117)



According to a modified literature procedure,[70] boron trifluoride diethyl etherate (2.90 mL, 23.5 mmol) was added to a flask under argon and cooled to −15 °C. To this, was added a solution of aniline **110** (5.60 g, 15.6 mmol) in dichloromethane (30 mL) dropwise over 5 minutes. Subsequently, a solution of *tert*-butyl nitrite (2.50 mL, 18.8 mmol) in dichloromethane (14 ml) was added dropwise over 30 minutes. The resulting suspension was stirred at −15 °C for 20 minutes then at 0 °C for 30 minutes. After warming to room temperature the reaction was concentrated *in vacuo* and the crude diazonium salt dissolved in acetonitrile (56 mL) under argon. The resulting solution was added dropwise over 1 hour to a stirred suspension of sodium iodide (2.81 g, 18.8 mmol) and iodine (397 mg, 1.56 mmol) in acetonitrile (100 mL) at room temperature. The dark solution was stirred for 1 hour before quenching with saturated aqueous sodium sulfite (200 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 200 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford iodoarene **117** (5.25 g, 72%) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.01 (1H, d, *J* 2.0, **8**-**H**), 7.50 (1H, dd, *J* 8.3, 2.0, **10**-**H**), 7.35 (1H, d, *J* 8.6, **11**-**H**), 5.09 (2H, sept, *J* 6.3, **2**-**H**), 4.99 (1H, s, **5**-**H**), 1.28 (6H, d, *J* 6.3, **1**-**H**), 1.25 (6H, d, *J* 6.3, **1**-**H**).

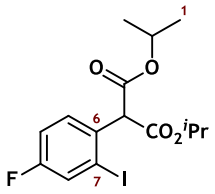
^{13}C (101 MHz, $CDCl_3$): δ 167.0 (**C4**), 141.5 ($\mathbf{C}_{Ar}$**8**), 135.9 ($\mathbf{C}_{Ar}$**6**), 131.7 ($\mathbf{C}_{Ar}$**10**), 130.7 ($\mathbf{C}_{Ar}$**11**), 122.7 ($\mathbf{C}_{Ar}$**9**), 102.1 ($\mathbf{C}_{Ar}$**7**), 70.0 (**C2**), 62.0 (**C5**), 21.7 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1728 (C=O), 1464, 1251, 1161, 1097, 905.

HRMS (ESI): $C_{15}H_{18}{}^{79}BrIO_4Na$ $[M+Na]^+$ requires 490.9325; found 490.9333

MP: 66 – 68 °C.

Diisopropyl 2-(4-fluoro-2-iodophenyl)malonate (116)



According to a modified literature procedure,[70] boron trifluoride diethyl etherate (3.90 mL, 31.5 mmol) was added to a flask under argon and cooled to −15 °C. To this, was added a solution of aniline **113** (6.24 g, 21.0 mmol) in dichloromethane (40 mL) dropwise over 5 minutes. Subsequently, a solution of *tert*-butyl nitrite (3.30 mL, 25.2 mmol) in dichloromethane (19 ml) was added dropwise over 30 minutes. The resulting suspension was stirred at −15 °C for 20 minutes then at 0 °C for 30 minutes. After warming to room temperature the reaction was concentrated *in vacuo* and the crude diazonium salt dissolved in acetonitrile (82 mL) under argon. The resulting solution was added dropwise over 1 hour to a stirred suspension of sodium iodide (3.78 g, 25.2 mmol) and iodine (533 mg, 2.10 mmol) in acetonitrile (146 mL) at room temperature. The dark solution was stirred for 1 hour before

quenching with saturated aqueous sodium sulfite (300 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 300 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford iodoarene **116** (5.86 g, 68%) as a yellow oil.

^{1}H (500 MHz, $CDCl_3$): δ 7.59 (1H, dd, $J_{F\text{-}H}$ 8.0, *J* 2.7, **8**-**H**), 7.46 (1H, dd, *J* 8.7, $J_{F\text{-}H}$ 5.8, **11**-**H**), 7.35 (1H, app. td, *J* 8.3, 2.7, **10**-**H**), 5.10 (2H, sept, *J* 6.3, **2**-**H**), 5.02 (1H, s, **5**-**H**), 1.29 (6H, d, *J* 6.3, **1**-**H**), 1.26 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 167.3 (**C4**), 161.6 (d, $J_{F\text{-}C}$ 253, $\mathbf{C}_{Ar}$**9**), 132.9 (d, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**6**), 130.5 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**11**), 126.5 (d, $J_{F\text{-}C}$ 24, $\mathbf{C}_{Ar}$**8**), 115.7 (d, $J_{F\text{-}C}$ 21, $\mathbf{C}_{Ar}$**10**), 101.0 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**7**), 69.9 (**C2**), 61.7 (**C5**), 21.7 (**C1**).

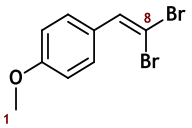
^{19}F (470 MHz, $CDCl_3$): δ −112.5

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1729 (C=O), 1484, 1226, 1161, 1098, 853.

HRMS (ESI): $C_{15}H_{18}FIO_4Na$ $[M+Na]^+$ requires 431.0126; found 431.0112

5.3.2 Synthesis of Vinyl Stannanes

1-(2,2-Dibromovinyl)-4-methoxybenzene (414)



According to a modified literature procedure,[71] triphenylphosphine (9.40 g, 35.7 mmol) was added portionwise over 5 minutes to a stirred solution of carbon tetrabromide (5.94 g, 17.9 mmol) in dichloromethane (32 mL) at 0 °C. The solution was stirred for a further

30 minutes and then *p*-methoxybenzaldehyde **118** (2.00 g, 14.7 mmol) was added. After stirring for 1 hour at 0 °C, water (20 mL) and brine (20 mL) were added and the layers separated. The aqueous layer was extracted with a mixture of 40-60 petrol and dichloromethane (1 : 1, 60 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 94 : 6) to afford dibromoalkene **414** (3.95 g, 92%) as a yellow solid with spectroscopic data in accordance with the literature.[221]

^{1}H (400 MHz, $CDCl_3$): δ 7.53 (2H, d, *J* 8.8, **5**-**H**), 7.43 (1H, s, **7**-**H**), 6.91 (2H, d, *J* 8.8, **4**-**H**), 3.84 (3H, s, **1**-**H**).

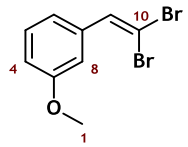
^{13}C (101 MHz, $CDCl_3$): δ 159.8 ($\mathbf{C}_{Ar}\mathbf{3}$), 136.4 (**C7**), 130.0 ($\mathbf{C}_{Ar}\mathbf{5}$), 127.9 ($\mathbf{C}_{Ar}\mathbf{6}$), 113.9 ($\mathbf{C}_{Ar}\mathbf{4}$), 87.3 (**C8**), 55.4 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 3005 (C–H), 1604 (C=C), 1572, 1246 (C–O), 1177, 802, 730.

HRMS (FI): $C_9H_8{}^{79}Br_2O$ $[M]^+$ requires 289.8942; found 289.8942

MP: 33 – 35 °C, lit. MP: 35 – 36 °C (hexane).[221]

1-(2,2-Dibromovinyl)-3-methoxybenzene (415)



According to a modified literature procedure,[71] triphenylphosphine (9.40 g, 35.7 mmol) was added portionwise over 5 minutes to a stirred solution of carbon tetrabromide (5.94 g, 17.9 mmol) in dichloromethane (32 mL) at 0 °C. The solution was stirred for a further 30 minutes and then *m*-methoxybenzaldehyde **119** (2.00 g, 14.7 mmol) was added. After

stirring for 1 hour at 0 °C, water (20 mL) and brine (20 mL) were added and the layers separated. The aqueous layer was extracted with a mixture of 40-60 petrol and dichloromethane (1 : 1, 60 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 94 : 6) to afford dibromoalkene **415** (3.61 g, 84%) as a pale yellow oil with spectroscopic data in accordance with the literature.[222]

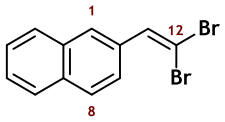
^{1}H (400 MHz, $CDCl_3$): δ 7.47 (1H, s, **9-H**), 7.33 – 7.26 (1H, m, **5-H**), 7.14 – 7.08 (2H, m, **6-H**, **8-H**), 6.90 (1H, ddd, *J* 8.3, 2.5, 0.7, **4-H**), 3.83 (3H, s, **1-H**).

^{13}C (101 MHz, $CDCl_3$): δ 159.6 ($\mathbf{C}_{Ar}$**3**), 136.9 (**C9**), 136.6 ($\mathbf{C}_{Ar}$**7**), 129.6 ($\mathbf{C}_{Ar}$**5**), 121.2 ($\mathbf{C}_{Ar}$**6**), 114.4 ($\mathbf{C}_{Ar}$**4**), 113.8 ($\mathbf{C}_{Ar}$**8**), 90.0 (**C10**), 55.4 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 3005 (C–H), 1598 (C=C), 1577, 1253 (C–O), 1150, 818, 688.

HRMS (FI): $C_9H_8{}^{79}Br_2O$ $[M]^+$ requires 289.8942; found 289.8943

2-(2,2-Dibromovinyl)naphthalene (416)



According to a modified literature procedure,[71] triphenylphosphine (8.20 g, 31.1 mmol) was added portionwise over 5 minutes to a stirred solution of carbon tetrabromide (5.20 g, 15.6 mmol) in dichloromethane (32 mL) at 0 °C. The solution was stirred for a further 30 minutes and then 2-naphthaldehyde **120** (2.00 g, 12.8 mmol) was added. After stirring for 1 hour at 0 °C, water (20 mL) and brine (20 mL) were added and the layers separated. The aqueous layer was extracted with a mixture of 40-60 petrol and dichloromethane (1 : 1, 60 mL). The combined organic layers were dried over anhydrous magnesium sulfate,

filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 94 : 6) to afford dibromoalkene **416** (3.16 g, 79%) as a white solid with spectroscopic data in accordance with the literature.[223]

^{1}H (400 MHz, $CDCl_3$): δ 8.03 (1H, s, **1-H**), 7.89 – 7.80 (3H, m, **4-H**, **6-H**, **8-H**), 7.69 – 7.63 (2H, m, **9-H**, **11-H**), 7.56 – 7.49 (2H, m, **3-H**, **5-H**).

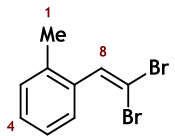
^{13}C (101 MHz, $CDCl_3$): δ 137.1 (**C11**), 133.1 ($\mathbf{C}_{Ar}$**10**), 132.9 ($\mathbf{C}_{Ar}$**7**), 132.2 ($\mathbf{C}_{Ar}$**2**), 128.4 ($\mathbf{C}_{Ar}$**1**), 128.3 ($\mathbf{C}_{Ar}$**3**), 128.1 ($\mathbf{C}_{Ar}$**4**/$\mathbf{C}_{Ar}$**6**/$\mathbf{C}_{Ar}$**8**), 127.8 ($\mathbf{C}_{Ar}$**4**/$\mathbf{C}_{Ar}$**6**/$\mathbf{C}_{Ar}$**8**), 126.9 ($\mathbf{C}_{Ar}$**4**/$\mathbf{C}_{Ar}$**6**/$\mathbf{C}_{Ar}$**8**), 126.7 ($\mathbf{C}_{Ar}$**5**), 125.8 ($\mathbf{C}_{Ar}$**9**), 90.0 (**C12**).

IR: ν_{max} (neat)/ cm^{-1} 3011 (C–H), 1595 (C=C), 1507, 1272, 906, 835, 749.

HRMS (FI): $C_{12}H_8{}^{79}Br_2$ $[M]^+$ requires 309.8993; found 309.8993

MP: 84 – 86 °C, lit. MP: 94 – 96 °C.[223]

1-(2,2-Dibromovinyl)-2-methylbenzene (417)



According to a modified literature procedure,[71] triphenylphosphine (22.0 g, 84.0 mmol) was added portionwise over 5 minutes to a stirred solution of carbon tetrabromide (13.9 g, 42.0 mmol) in dichloromethane (88 mL) at 0 °C. The solution was stirred for a further 30 minutes and then 2-methylbenzaldehyde **121** (4.21 g, 35.0 mmol) was added. After stirring for 1 hour at 0 °C, water (50 mL) and brine (50 mL) were added and the layers separated. The aqueous layer was extracted with a mixture of 40-60 petrol and dichloromethane (1 : 1, 100 mL). The combined organic layers were dried over anhydrous

magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 15 : 1) to afford dibromoalkene **417** (9.13 g, 95%) as a pale yellow oil with spectroscopic data in accordance with the literature.[224]

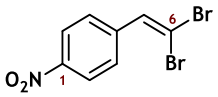
^{1}H (400 MHz, $CDCl_3$): δ 7.51 (1H, s, **8**-**H**), 7.45 (1H, d, *J* 7.6, **6**-**H**), 7.32 – 7.20 (3H, m, **3**-**H**, **4**-**H**, **5**-**H**), 2.31 (3H, s, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 136.9 (**C8**), 136.1 ($\mathbf{C}_{Ar}$**7**), 135.4 ($\mathbf{C}_{Ar}$**2**), 130.2 ($\mathbf{C}_{Ar}$**3**), 128.6 ($\mathbf{C}_{Ar}$**4** & $\mathbf{C}_{Ar}$**6**), 125.9 ($\mathbf{C}_{Ar}$**5**), 91.7 (**C9**), 20.0 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 3019 (C–H), 1602 (C=C), 1457, 878, 857, 816, 745, 714.

HRMS (FI): $C_9H_8{}^{79}Br_2$ $[M]^+$ requires 273.8993; found 273.8992

1-(2,2-Dibromovinyl)-4-nitrobenzene (135)



According to a literature procedure,[71] triphenylphosphine (8.43 g, 32.2 mmol) was added portionwise over 5 minutes to a stirred solution of carbon tetrabromide (5.35 g, 16.1 mmol) in dichloromethane (32 mL) at 0 °C. The solution was stirred for a further 30 minutes and then *p*-nitrobenzaldehyde **134** (2.00 g, 13.2 mmol) was added. After stirring for 1 hour at 0 °C, water (25 mL) and brine (25 mL) were added and the layers separated. The aqueous layer was extracted with a mixture of 40-60 petrol and dichloromethane (1 : 1, 60 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 94 : 6) to afford dibromoalkene **135** (3.30 g, 81%) as a yellow solid with spectroscopic data in accordance with the literature.[222]

^{1}H (400 MHz, $CDCl_3$): δ 8.21 (2H, d, *J* 8.7, **2**-**H**), 7.70 (2H, d, *J* 8.7, **3**-**H**), 7.55 (1H, s, **5**-**H**).

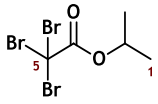
^{13}C (101 MHz, $CDCl_3$): δ 147.2 ($\mathbf{C}_{Ar}$**1**), 141.4 ($\mathbf{C}_{Ar}$**4**), 134.9 (**C5**), 129.2 ($\mathbf{C}_{Ar}$**3**), 123.7 ($\mathbf{C}_{Ar}$**2**), 94.1 (**C6**).

IR: v_{max} (neat)/ cm^{-1} 2924 (C–H), 1587 (C=C), 1509 (NO_2), 1339 (NO_2), 1012, 860, 741, 685.

LRMS (FI): $[M(^{79}Br_2)]^+$ 304.9

MP: 100 – 102 °C, lit. MP: 105 – 106 °C.[222]

Isopropyl 2,2,2-tribromoacetate (137)



Concentrated sulfuric acid (4 mL) was added dropwise to a stirred solution of 2,2,2-tribromoacetic acid (5.00 g, 16.9 mmol) in isopropanol (40 mL) at 0 °C. The reaction was then heated to 80 °C for 4 hours and was then allowed to cool to room temperature. After dilution with water (100 mL) the mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (40-60 petrol : dichloromethane, 1 : 0 to 4 : 1) to afford the major product as ester **137** (2.73 g, 48%) as a colourless oil.

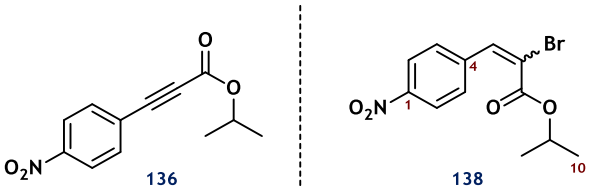
^{1}H (400 MHz, $CDCl_3$): 5.16 (1H, sept, *J* 6.2, **2**-**H**), 1.40 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 161.5 (**C4**), 74.3 (**C2**), 30.7 (**C5**), 21.3 (**C1**).

IR: v_{max} (neat)/ cm^{-1} 2984 (C–H), 1745 (C=O), 1240, 1098, 837, 759.

HRMS (FI): $C_5H_7{}^{79}Br_3O_2$ $[M]^+$ requires 335.7996 ; found 335.7990

Attempted synthesis of isopropyl 3-(4-nitrophenyl)propiolate (136) and isolation of isopropyl 2-bromo-3-(4-nitrophenyl)acrylate (138)



According to a modified literature procedure,[73] *p*-nitrobenzaldehyde **134** (190 mg, 1.26 mmol) was added to a solution of triphenylphosphine (1.32 g, 5.03 mmol) and ester **137** (854 mg, 2.52 mmol) in THF (6 mL). The resulting solution was refluxed for 3 hours and then allowed to cool to room temperature. A suspension of sodium amide (74 mg, 1.89 mmol) and potassium *tert*-butoxide (212 mg, 1.89 mmol) in THF (3 mL) was added at room temperature. The resulting mixture was stirred for 2 hours before diluting the reaction with diethyl ether (20 mL). The organic phase was washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 19 : 1) to afford acrylate **138** (122 mg, 41%) as a light yellow solid and as the sole isolated major product.

^{1}H (400 MHz, $CDCl_3$): δ 8.28 (2H, d, *J* 8.8, **2**-**H**), 8.21 (1H, s, **5**-**H**), 7.96 (2H, d, *J* 8.6, **3**-**H**), 5.19 (1H, sept, *J* 6.2, **9**-**H**), 1.38 (6H, d, *J* 6.1, **10**-**H**).

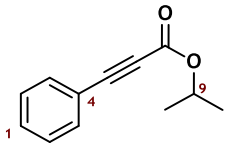
^{13}C (101 MHz, $CDCl_3$): δ 162.1 (**C7**), 148.1 ($\mathbf{C}_{Ar}$**1**), 140.3 ($\mathbf{C}_{Ar}$**4**), 138.0 (**C5**), 130.8 ($\mathbf{C}_{Ar}$**3**), 123.7 ($\mathbf{C}_{Ar}$**2**), 118.2 (**C6**), 71.4 (**C9**), 21.9 (**C10**).

IR: ν_{max} (neat)/ cm^{-1} 2976 (C–H), 1701 (C=O), 1610 (C=C), 1517 (NO_2), 1343 (NO_2), 1265, 1197, 1106, 914, 846, 756.

HRMS (ESI): $C_{12}H_{12}{}^{79}BrNO_4Na$ $[M+Na]^+$ requires 335.9842; found 335.9829

MP: 58 – 60 °C.

Isopropyl 3-phenylprop-2-ynoate (126)



A solution of *n*-butyllithium (1.6 M in hexanes, 30.0 mL, 48.6 mmol) was added dropwise over 30 minutes to a stirred solution of phenylacetylene **130** (4.96 g, 48.6 mmol) in anhydrous tetrahydrofuran (92 mL) at −78 °C. The reaction was stirred for 1 hour at −78 °C and then a solution of isopropyl chloroformate (1.0 M in toluene, 53.5 mL, 53.5 mmol) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (150 mL). The biphasic mixture was extracted with dichloromethane (3 × 150 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford propargylic ester **126** (7.98 g, 87%) as a colourless oil with spectroscopic data in accordance with the literature.[225]

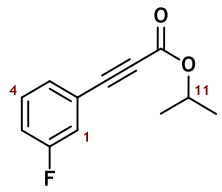
^{1}H (400 MHz, $CDCl_3$): δ 7.62 – 7.58 (2H, m, **3**-**H**), 7.48 – 7.43 (1H, m, **1**-**H**), 7.41 – 7.35 (2H, m, **2**-**H**), 5.17 (1H, sept, *J* 6.3, **9**-**H**), 1.35 (6H, d, *J* 6.3, **10**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 153.7 (**C7**), 133.0 ($\mathbf{C}_{Ar}$**3**), 130.6 ($\mathbf{C}_{Ar}$**1**), 128.6 ($\mathbf{C}_{Ar}$**2**), 119.8 ($\mathbf{C}_{Ar}$**4**), 85.7 (**C5**), 81.2 (**C6**), 70.1 (**C9**), 21.8 (**C10**).

IR: ν_{max} (neat)/ cm^{-1} 2983 (C–H), 2215 (C≡C), 1701 (C=O), 1282, 1191, 1000, 755.

HRMS (ESI): $C_{12}H_{12}O_2Na$ $[M+Na]^+$ requires 211.0730; found 211.0726

Isopropyl 3-(3-fluorophenyl)propiolate (127)



A solution of *n*-butyllithium (1.6 M in hexanes, 26.0 mL, 41.6 mmol) was added dropwise over 30 minutes to a stirred solution of 1-ethynyl-3-fluorobenzene **131** (5.00 g, 41.6 mmol) in anhydrous tetrahydrofuran (80 mL) at −78 °C. The reaction was stirred for 1 hour at −78 °C and then a solution of isopropyl chloroformate (1.0 M in toluene, 45.8 mL, 45.8 mmol) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (150 mL). The biphasic mixture was extracted with dichloromethane (3 × 150 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford propargylic ester **127** (6.64 g, 77%) as a yellow oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.40 – 7.32 (2H, m, **4**-**H**, **5**-**H**), 7.31 – 7.25 (1H, m, **1**-**H**), 7.16 (1H, app. t, *J* 7.7, **3**-**H**), 5.17 (1H, sept, *J* 6.3, **11**-**H**), 1.35 (6H, d, *J* 6.3, **12**-**H**).

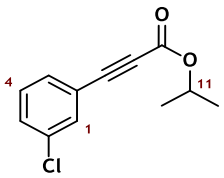
^{13}C (101 MHz, $CDCl_3$): δ 162.2 (d, $J_{F\text{-}C}$ 248, $\mathbf{C}_{Ar}$**2**), 153.2 (**C9**), 130.3 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**4**), 128.8 (d, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**5**), 121.5 (d, $J_{F\text{-}C}$ 10, $\mathbf{C}_{Ar}$**6**), 119.5 (d, $J_{F\text{-}C}$ 23, $\mathbf{C}_{Ar}$**1**), 118.0 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**3**), 83.7 (d, $J_{F\text{-}C}$ 4, **C7**), 81.6 (**C8**), 70.2 (**C11**), 21.6 (**C12**).

^{19}F (377 MHz, $CDCl_3$): δ −111.8

IR: ν_{max} (neat)/ cm^{-1} 2985 (C–H), 2225 (C≡C), 1706 (C=O), 1582, 1299, 1221, 1103, 750.

HRMS (ESI): $C_{12}H_{11}FO_2Na$ $[M+Na]^+$ requires 229.0635; found 229.0629

Isopropyl 3-(3-chlorophenyl)propiolate (128)



A solution of *n*-butyllithium (1.6 M in hexanes, 22.9 mL, 36.6 mmol) was added dropwise over 30 minutes to a stirred solution of 1-chloro-3-ethynylbenzene **132** (5.00 g, 36.6 mmol) in anhydrous tetrahydrofuran (70 mL) at −78 °C. The reaction was stirred for 1 hour at −78 °C and then a solution of isopropyl chloroformate (1.0 M in toluene, 40.3 mL, 40.3 mmol) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (150 mL). The biphasic mixture was extracted with dichloromethane (3 × 150 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford propargylic ester **128** (6.28 g, 77%) as a yellow oil.

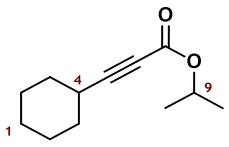
^{1}H (400 MHz, $CDCl_3$): δ 7.58 (1H, s, **1**-**H**), 7.49 – 7.45 (1H, m, **5**-**H**), 7.44 – 7.40 (1H, m, **3**-**H**), 7.32 (1H, app. t, *J* 8.0, **4**-**H**) 5.17 (1H, sept, *J* 6.3, **11**-**H**), 1.35 (6H, d, *J* 6.3, **12**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 153.4 (**C9**), 134.6 ($\mathbf{C}_{Ar}$**2**), 132.7 ($\mathbf{C}_{Ar}$**1**), 131.1 ($\mathbf{C}_{Ar}$**5**), 130.9 ($\mathbf{C}_{Ar}$**3**), 129.9 ($\mathbf{C}_{Ar}$**4**), 121.6 ($\mathbf{C}_{Ar}$**6**), 83.7 (**C7**), 81.9 (**C8**), 70.4 (**C11**), 21.8 (**C12**).

IR: ν_{max} (neat)/ cm^{-1} 2984 (C–H), 2220 (C≡C), 1704 (C=O), 1287, 1193, 1102, 837.

HRMS (ESI): $C_{12}H_{11}{}^{35}ClO_2Na$ $[M+Na]^+$ requires 245.0340; found 245.0344

Isopropyl 3-cyclohexylpropiolate (129)



A solution of *n*-butyllithium (1.6 M in hexanes, 5.54 mL, 8.86 mmol) was added dropwise over 30 minutes to a stirred solution of cyclohexylacetylene **133** (959 mg, 8.86 mmol) in anhydrous tetrahydrofuran (17 mL) at −78 °C. The reaction was stirred for 1 hour at −78 °C and then a solution of isopropyl chloroformate (1.0 M in toluene, 9.75 mL, 9.75 mmol) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (50 mL). The biphasic mixture was extracted with dichloromethane (3 × 50 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 98 : 2) to afford propargylic ester **129** (1.63 g, 95%) as a brown oil.

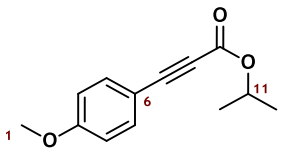
^{1}H (400 MHz, $CDCl_3$): δ 5.05 (1H, sept, *J* 6.3, **9**-**H**), 2.53 – 2.44 (1H, m, **4**-**H**), 1.87 – 1.77 (2H, m, **3**-$\mathbf{H_{eq}}$), 1.76 – 1.64 (2H, m, **2**-$\mathbf{H_{eq}}$), 1.57 – 1.43 (3H, m, **1**-$\mathbf{H_{eq}}$, **3**-$\mathbf{H_{ax}}$), 1.36 – 1.23 (3H, m, **1**-$\mathbf{H_{ax}}$, **2**-$\mathbf{H_{ax}}$), 1.26 (6H, d, *J* 6.3, **10**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 153.7 (**C7**), 92.4 (**C5**), 73.5 (**C6**), 69.6 (**C9**), 31.6 (**C3**), 29.0 (**C4**), 25.7 (**C1**), 24.8 (**C2**), 21.8 (**C10**).

IR: ν_{max} (neat)/ cm^{-1} 2933 (C–H), 2227 (C≡C), 1704 (C=O), 1249, 1106, 1088, 754.

HRMS (ESI): $C_{12}H_{18}O_2Na$ $[M+Na]^+$ requires 217.1204; found 217.1211

Isopropyl 3-(4-methoxyphenyl)prop-2-ynoate (122)



According to a modified literature procedure,[71] a solution of *n*-butyllithium (1.6 M in hexanes, 18.0 mL, 28.4 mmol) was added dropwise over 30 minutes to a stirred solution of dibromoalkene **414** (3.95 g, 13.5 mmol) in anhydrous tetrahydrofuran (40 mL) at −78 °C. The reaction was stirred for 45 minutes at −78 °C and for 45 minutes at 0 °C. The flask was re-cooled to −78 °C and a solution of isopropyl chloroformate (1.0 M in toluene, 16.2 mL, 16.2 mmol) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (80 mL). The biphasic mixture was extracted with diethyl ether (3 × 80 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5) to afford propargylic ester **122** (2.26 g, 77%) as a white solid with spectroscopic data in accordance with the literature.[226]

^{1}H (400 MHz, $CDCl_3$): δ 7.53 (2H, d, *J* 8.8, **5**-**H**), 6.87 (2H, d, *J* 9.1, **4**-**H**), 5.15 (1H, sept, *J* 6.3, **11**-**H**), 3.82 (3H, s, **1**-**H**), 1.33 (6H, d, *J* 6.3, **12**-**H**).

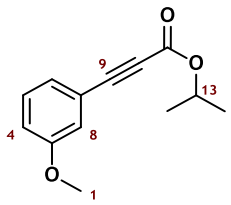
^{13}C (101 MHz, $CDCl_3$): δ 161.5 ($\mathbf{C}_{Ar}\mathbf{3}$), 154.0 (**C9**), 135.0 ($\mathbf{C}_{Ar}\mathbf{5}$), 114.3 ($\mathbf{C}_{Ar}\mathbf{4}$), 111.6 ($\mathbf{C}_{Ar}\mathbf{6}$), 86.6 (**C7**), 80.6 (**C8**), 69.9 (**C11**), 55.5 (**C1**), 21.8 (**C12**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 2210 (C≡C), 1697 (C=O), 1509, 1165, 1100, 832.

HRMS (ESI): $C_{13}H_{14}O_3Na$ $[M+Na]^+$ requires 241.0835; found 241.0834

MP: 57 – 59 °C (40-60 petrol), lit. MP: 61 – 62 °C (pentane).[226]

Isopropyl 3-(3-methoxyphenyl)prop-2-ynoate (123)



According to a modified literature procedure,[71] a solution of *n*-butyllithium (1.6 M in hexanes, 16.2 mL, 25.8 mmol) was added dropwise over 30 minutes to a stirred solution of dibromoalkene **415** (3.59 g, 12.3 mmol) in anhydrous tetrahydrofuran (40 mL) at −78 °C. The reaction was stirred for 45 minutes at −78 °C and for 45 minutes at 0 °C. The flask was re-cooled to −78 °C and a solution of isopropyl chloroformate (1.0 M in toluene, 14.7 mL, 14.7 mmol) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (80 mL). The biphasic mixture was extracted with diethyl ether (3 × 80 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5) to afford propargylic ester **123** (2.21 g, 82%) as a yellow oil.

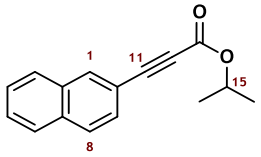
^{1}H (400 MHz, $CDCl_3$): δ 7.29 – 7.23 (1H, m, **5**-**H**), 7.19 – 7.15 (1H, m, **6**-**H**), 7.09 – 7.07 (1H, m, **8**-**H**), 7.00 (1H, ddd, *J* 8.3, 2.8, 1.0, **4**-**H**), 5.15 (1H, sept, *J* 6.3, **13**-**H**), 3.78 (3H, s, **1**-**H**), 1.33 (6H, d, *J* 6.3, **14**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 159.4 ($\mathbf{C}_{Ar}$**3**), 153.6 (**C11**), 129.7 ($\mathbf{C}_{Ar}$**5**), 125.5 ($\mathbf{C}_{Ar}$**6**), 120.7 ($\mathbf{C}_{Ar}$**7**), 117.5 ($\mathbf{C}_{Ar}$**4**/$\mathbf{C}_{Ar}$**8**), 117.4 ($\mathbf{C}_{Ar}$**4**/$\mathbf{C}_{Ar}$**8**), 85.6 (**C9**), 80.8 (**C10**), 70.1 (**C13**), 55.4 (**C1**), 21.8 (**C14**).

IR: ν_{max} (neat)/ cm^{-1} 2983 (C–H), 2222 (C≡C), 1704 (C=O), 1323, 1234, 1103, 725.

HRMS (ESI): $C_{13}H_{14}O_3Na$ $[M+Na]^+$ requires 241.0835; found 241.0837

Isopropyl 3-(2-naphthyl)prop-2-ynoate (124)



According to a modified literature procedure,[71] a solution of *n*-butyllithium (1.6 M in hexanes, 13.2 mL, 21.1 mmol) was added dropwise over 30 minutes to a stirred solution of dibromoalkene **416** (3.13 g, 10.1 mmol) in anhydrous tetrahydrofuran (40 mL) at −78 °C. The reaction was stirred for 45 minutes at −78 °C and for 45 minutes at 0 °C. The flask was re-cooled to −78 °C and a solution of isopropyl chloroformate (1.0 M in toluene, 12.1 mL, 12.1 mmol) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (80 mL). The biphasic mixture was extracted with diethyl ether (3 × 80 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5) to afford propargylic ester **124** (1.89 g, 79%) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.16 (1H, s, **1**-**H**), 7.87 – 7.80 (3H, m, **4**-**H**, **6**-**H**, **8**-**H**), 7.59 (1H, dd, *J* 8.5, 1.6, **9**-**H**), 7.57 – 7.50 (2H, m, **3**-**H**, **5**-**H**), 5.21 (1H, sept., *J* 6.3, **15**-**H**), 1.38 (6H, d, *J* 6.1, **16**-**H**).

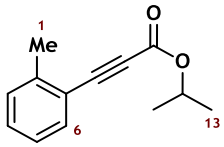
^{13}C (101 MHz, $CDCl_3$): δ 153.8 (**C13**), 134.3 ($\mathbf{C_{Ar}}$**1**), 133.9 ($\mathbf{C_{Ar}}$**7**), 132.7 ($\mathbf{C_{Ar}}$**2**), 128.5 ($\mathbf{C_{Ar}}$**H**), 128.4 ($\mathbf{C_{Ar}}$**H**), 128.2 ($\mathbf{C_{Ar}}$**H**), 128.0 (2 × $\mathbf{C_{Ar}}$**H**), 127.1 ($\mathbf{C_{Ar}}$**4**), 117.0 ($\mathbf{C_{Ar}}$**10**), 86.2 (**C11**), 81.4 (**C12**), 70.2 (**C15**), 21.9 (**C16**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 2213 (C≡C), 1699 (C=O), 1284, 1237, 1100, 747.

HRMS (ESI): $C_{16}H_{14}O_2Na$ $[M+Na]^+$ requires 261.0886; found 261.0886

MP: 66 – 68 °C (40-60 petrol).

Isopropyl 3-(*o*-tolyl)propiolate (125)



According to a modified literature procedure,[71] a solution of *n*-butyllithium (1.6 M in hexanes, 41.0 mL, 65.2 mmol) was added dropwise over 30 minutes to a stirred solution of dibromoalkene **417** (8.57 g, 31.1 mmol) in anhydrous tetrahydrofuran (101 mL) at −78 °C. The reaction was stirred for 45 minutes at −78 °C and for 45 minutes at 0 °C. The flask was re-cooled to −78 °C and a solution of isopropyl chloroformate (1.0 M in toluene, 31.1 mL, 31.1 mmol) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (200 mL). The biphasic mixture was extracted with diethyl ether (3 × 200 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 50 : 1 to 20 : 1) to afford propargylic ester **125** (5.18 g, 82%) as an orange oil.

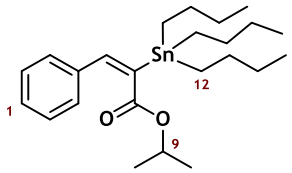
^{1}H (400 MHz, $CDCl_3$): δ 7.55 (1H, d, *J* 7.6, **6**-**H**), 7.34 (1H, app. td, *J* 7.6, 1.0, **4**-**H**), 7.28 – 7.22 (1H, m, **3**-**H**), 7.19 (1H, app. t, *J* 7.5, **5**-**H**), 5.17 (1H, sept, *J* 6.2, **12**-**H**), 2.50 (3H, s, **1**-**H**), 1.35 (6H, d, *J* 6.3, **13**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 153.9 (**C10**), 142.3 ($\mathbf{C}_{Ar}$**2**), 133.4 ($\mathbf{C}_{Ar}$**6**), 130.6 ($\mathbf{C}_{Ar}$**4**), 129.8 ($\mathbf{C}_{Ar}$**3**), 125.8 ($\mathbf{C}_{Ar}$**5**), 119.7 ($\mathbf{C}_{Ar}$**7**), 84.9 (**C9**), 84.8 (**C8**), 70.0 (**C12**), 21.8 (**C13**), 20.7 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2983 (C–H), 2212 (C≡C), 1703 (C=O), 1277, 1204, 1188, 1103, 759.

HRMS (FI): $C_{13}H_{14}O_3$ $[M]^+$ requires 202.0994; found 202.0991

(*E*)-Isopropyl 3-phenyl-2-(tributylstannyl)acrylate (149)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (5.20 mL, 19.7 mmol) in tetrahydrofuran (19 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (430 mg, 0.372 mmol) and propargylic ester **126** (3.51 g, 18.6 mmol) in tetrahydrofuran (19 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (100 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a 7 : 1 mixture of regioisomers by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford stannane **149** (8.03 g, 90%) as a yellow oil and as a 10 : 1 mixture of regioisomers which were used in the subsequent reaction without separation.

A small amount of the product was repurified for analysis by silica gel chromatography (40-60 petrol : toluene, 100 : 0 to 80 : 20).

Data for major regioisomer:

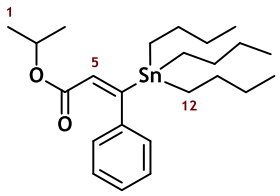
^{1}H (400 MHz, $CDCl_3$): δ 7.36 – 7.22 (5H, m, **1**-**H**, **2**-**H**, **3**-**H**), 6.70 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 59.9, **5**-**H**), 5.08 (1H, sept, *J* 6.4, **9**-**H**), 1.66 – 1.52 (6H, m, **13**-**H**), 1.40 – 1.29 (6H, m, **14**-**H**), 1.21 (6H, d, *J* 6.1, **10**-**H**), 1.11 – 1.03 (6H, m, **12**-**H**), 0.91 (9H, t, *J* 7.3, **15**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 172.8 (**C7**), 141.9 ($J_{^{117,119}Sn\text{-}C}$ 14, **C5**), 140.3 (C_{Ar}**4**), 137.2 (**C6**), 128.3 (C_{Ar}**2**/C_{Ar}**3**), 128.2 (C_{Ar}**2**/C_{Ar}**3**), 127.9 (C_{Ar}**1**), 67.8 (**C9**), 28.9 ($J_{^{117,119}Sn\text{-}C}$ 21, **C13**), 27.4 ($J_{^{117,119}Sn\text{-}C}$ 60, **C14**), 21.9 (**C10**), 13.8 (**C15**), 10.7 ($J_{^{117}Sn\text{-}C}$ 330, $J_{^{119}Sn\text{-}C}$ 345, **C12**).

IR: ν_{max} (neat)/ cm^{-1} 2923 (C–H), 1698 (C=O), 1601 (C=C), 1182, 1106, 693.

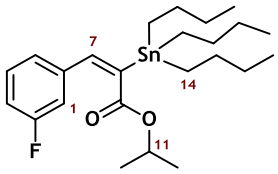
HRMS (ESI): $C_{24}H_{40}O_2{}^{116}SnNa$ $[M+Na]^+$ requires 499.1938; found 499.1922

Selected data for minor regioisomer (**150**):



^{1}H (400 MHz, $CDCl_3$): 6.10 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 59.2, **5**-**H**), 4.84 (1H, sept, *J* 6.4, **2**-**H**).

(*E*)-Isopropyl 3-(3-fluorophenyl)-2-(tributylstannyl)acrylate (151)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (8.50 mL, 31.3 mmol) in tetrahydrofuran (30 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (693 mg, 0.599 mmol) and propargylic ester **127** (6.18 g, 30.0 mmol) in tetrahydrofuran (30 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (200 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a 4 : 1 mixture of regioisomers by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford stannane **151** (13.51 g, 91%) as a yellow oil and as a 5 : 1 mixture of regioisomers which were used in the subsequent reaction without separation.

A small amount of the product was repurified for analysis by silica gel chromatography (40-60 petrol : toluene, 100 : 0 to 80 : 20).

Data for major regioisomer:

^{1}H (400 MHz, $CDCl_3$): δ 7.30 – 7.23 (1H, m, **4**-**H**), 7.10 (1H, d, *J* 7.8, **5**-**H**), 7.06 (1H, app. dt, *J* 10.0, 2.1, **1**-**H**), 6.90 (1H, app. tdd, *J* 8.4, 2.5, 0.7, **3**-**H**), 6.64 (1H, s, $J_{117,119_{Sn-H}}$ 57.7, **7**-**H**), 5.09 (1H, sept, *J* 6.3, **11**-**H**), 1.68 – 1.44 (6H, m, **15**-**H**), 1.35 (6H, app. dq, *J* 14.7, 7.3, **16**-**H**), 1.22 (6H, d, *J* 6.4, **12**-**H**), 1.18 – 0.98 (6H, m, **14**-**H**), 0.92 (9H, t, *J* 7.3, **17**-**H**).

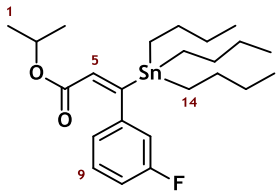
^{13}C (101 MHz, $CDCl_3$): δ 172.5 (**C9**), 162.8 (d, $J_{F\text{-}C}$ 246, C_{Ar}**2**), 142.3 (**C8**), 140.1 (d, $J_{F\text{-}C}$ 2, **C7**), 139.3 (d, $J_{F\text{-}C}$ 8, C_{Ar}**6**), 129.8 (d, $J_{F\text{-}C}$ 8, C_{Ar}**4**), 124.0 (d, $J_{F\text{-}C}$ 2, C_{Ar}**5**), 114.9 (d, $J_{F\text{-}C}$ 21, C_{Ar}**3**), 114.8 (d, $J_{F\text{-}C}$ 21, C_{Ar}**1**), 68.0 (**C11**), 28.9 ($J_{^{117,119}Sn\text{-}C}$ 20, **C15**), 27.4 ($J_{^{117,119}Sn\text{-}C}$ 60, **C16**), 21.9 (**C12**), 13.8 (**C17**), 10.7 ($J_{^{117}Sn\text{-}C}$ 330, $J_{^{119}Sn\text{-}C}$ 346, **C14**).

^{19}F (377 MHz, $CDCl_3$): δ −113.6

IR: ν_{max} (neat)/ cm^{-1} 2927 (C–H), 1695 (C=O), 1611 (C=C), 1341, 1197, 1105, 782.

HRMS (ESI): $C_{24}H_{39}FO_2{}^{116}SnNa$ $[M+Na]^+$ requires 517.1844; found 517.1841

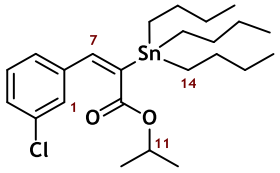
Selected data for minor regioisomer (**152**):



^{1}H (400 MHz, $CDCl_3$): 6.10 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 57.5, **5-H**), 4.85 (1H, sept, *J* 6.2, **2-H**).

^{19}F (377 MHz, $CDCl_3$): δ −114.1

(*E*)-Isopropyl 3-(3-chlorophenyl)-2-(tributylstannyl)acrylate (153)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (7.70 mL, 28.6 mmol) in tetrahydrofuran (30 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (629 mg, 0.540 mmol) and propargylic ester **128** (6.06 g, 27.2 mmol) in tetrahydrofuran (30 mL) at room temperature. The reaction was allowed to

stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (200 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a 4 : 1 mixture of regioisomers by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford stannane **153** (13.19 g, 94%) as a yellow oil and as a 4 : 1 mixture of regioisomers which were used in the subsequent reaction without separation.

A small amount of the product was repurified for analysis by silica gel chromatography (40-60 petrol : toluene, 100 : 0 to 80 : 20).

Data for major regioisomer:

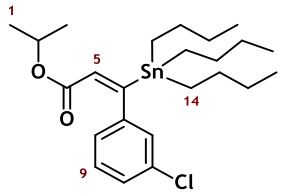
^{1}H (400 MHz, $CDCl_3$): δ 7.35 – 7.31 (1H, m, **1**-**H**), 7.25 – 7.17 (3H, m, **3**-**H**, **4**-**H**, **5**-**H**), 6.62 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 58.4, **7**-**H**), 5.09 (1H, sept, *J* 6.3, **11**-**H**), 1.98 – 1.45 (6H, m, **15**-**H**), 1.35 (6H, app. dq, *J* 14.7, 7.3, **16**-**H**), 1.23 (6H, d, *J* 6.1, **12**-**H**), 1.16 – 0.97 (6H, m, **14**-**H**), 0.92 (9H, t, *J* 7.3, **17**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 172.4 (**C9**), 142.5 (**C8**), 139.9 ($J_{^{117,119}Sn\text{-}C}$ 14, **C7**), 138.9 ($\mathbf{C}_{Ar}$**6**), 134.3 ($\mathbf{C}_{Ar}$**2**), 129.6 ($\mathbf{C}_{Ar}$**4**), 128.0 ($\mathbf{C}_{Ar}$**1**), 128.0 ($\mathbf{C}_{Ar}$**3**), 126.3 ($\mathbf{C}_{Ar}$**5**), 68.0 (**C11**), 28.9 ($J_{^{117,119}Sn\text{-}C}$ 20, **C15**), 27.4 ($J_{^{117,119}Sn\text{-}C}$ 60, **C16**), 21.9 (**C12**), 13.8 (**C17**), 10.7 ($J_{^{117}Sn\text{-}C}$ 331, $J_{^{119}Sn\text{-}C}$ 345, **C14**).

IR: ν_{max} (neat)/ cm^{-1} 2926 (C–H), 1694 (C=O), 1593 (C=C), 1465, 1207, 1104, 687.

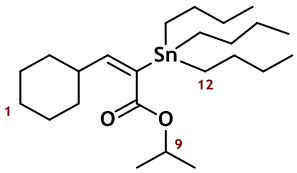
HRMS (ESI): $C_{24}H_{39}{}^{35}ClO_2{}^{116}SnNa$ $[M+Na]^+$ requires 533.1548; found 533.1551

Selected data for minor regioisomer (**154**):



^{1}H (400 MHz, $CDCl_3$): 6.10 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 57.2, **5**-**H**), 4.85 (1H, sept, *J* 6.2, **2**-**H**).

(*E*)-Isopropyl 3-cyclohexyl-2-(tributylstannyl)acrylate (155)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (2.20 mL, 8.27 mmol) in tetrahydrofuran (8 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (182 mg, 0.160 mmol) and propargylic ester **129** (1.50 g, 7.88 mmol) in tetrahydrofuran (8 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (100 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a single regioisomer by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 99 : 1) to afford stannane **155** (2.76 g, 74%) as a colourless oil.

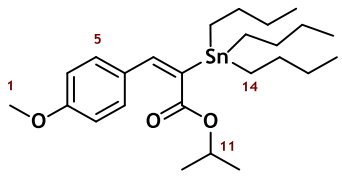
^{1}H (400 MHz, $CDCl_3$): δ 5.81 (1H, d, *J* 9.3, $J_{^{117,119}Sn\text{-}H}$ 61.9, **5**-**H**), 5.02 (1H, sept, *J* 6.2, **9**-**H**), 2.84 – 2.71 (1H, m, **4**-**H**), 1.77 – 1.61 (5H, m, **1**-$\mathbf{H_{eq}}$, **2**-$\mathbf{H_{eq}}$, **3**-$\mathbf{H_{eq}}$), 1.61 – 1.38 (6H, m, **13**-**H**), 1.36 – 1.24 (8H, m, **2**-$\mathbf{H_{ax}}$, **14**-**H**), 1.26 (6H, d, *J* 6.4, **10**-**H**), 1.22 – 0.97 (3H, m, **1**-$\mathbf{H_{ax}}$, **3**-$\mathbf{H_{ax}}$), 1.02 – 0.84 (6H, m, **12**-**H**), 0.89 (9H, t, *J* 7.3, **15**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 171.0 (**C7**), 158.4 (**C5**), 133.7 (**C6**), 67.3 (**C9**), 40.8 ($J_{^{117,119}Sn\text{-}C}$ 38, **C4**), 32.8 (**C3**), 29.0 ($J_{^{117,119}Sn\text{-}C}$ 20, **C13**), 27.4 ($J_{^{117,119}Sn\text{-}C}$ 57, **C14**), 26.1 (**C1**), 25.8 (**C2**), 22.2 (**C10**), 13.8 (**C15**), 10.4 ($J_{^{117}Sn\text{-}C}$ 331, $J_{^{119}Sn\text{-}C}$ 347, **C12**).

IR: ν_{max} (neat)/ cm^{-1} 2924 (C–H), 1703 (C=O), 1601 (C=C), 1373, 1190, 1108, 984.

HRMS (ESI): $C_{24}H_{46}O_2{}^{116}SnNa$ $[M+Na]^+$ requires 505.2407; found 505.2371

(*E*)-Isopropyl 3-(4-methoxyphenyl)-2-(tributylstannyl)acrylate (143)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (6.10 mL, 22.7 mmol) in tetrahydrofuran (24 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (500 mg, 0.430 mmol) and propargylic ester **122** (4.72 g, 21.6 mmol) in tetrahydrofuran (24 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (100 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a 4 : 1 mixture of regioisomers by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford stannane **143** (8.57 g, 78%) as a yellow oil and as a 12 : 1 mixture of regioisomers which were used in the subsequent reaction without further separation.

A small amount of the product was repurified for analysis by silica gel chromatography (40-60 petrol : toluene, 100 : 0 to 80 : 20).

Data for major regioisomer:

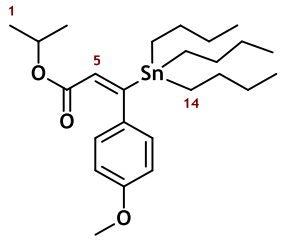
^{1}H (400 MHz, $CDCl_3$): δ 7.31 (2H, d, *J* 8.6, **5**-**H**), 6.83 (2H, d, *J* 8.8, **4**-**H**), 6.64 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 60.9, **7**-**H**), 5.09 (1H, sept, *J* 6.2, **11**-**H**), 3.80 (3H, s, **1**-**H**), 1.70 – 1.47 (6H, m, **15**-**H**), 1.36 (6H, app. dq, *J* 14.7, 7.3, **16**-**H**), 1.25 (6H, d, *J* 6.3, **12**-**H**), 1.16 – 0.98 (6H, m, **14**-**H**), 0.92 (9H, t, *J* 7.3, **17**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 172.9 ($J_{^{117,119}Sn\text{-}C}$ 33, **C9**), 159.6 (C_{Ar}**3**), 141.6 ($J_{^{117,119}Sn\text{-}C}$ 14, **C7**), 137.4 (**C8**), 129.9 (C_{Ar}**6**), 129.8 (C_{Ar}**5**), 113.6 (C_{Ar}**4**), 67.6 (**C11**), 55.3 (**C1**), 28.9 ($J_{^{117,119}Sn\text{-}C}$ 20, **C15**), 27.4 ($J_{^{117,119}Sn\text{-}C}$ 59, **C16**), 22.0 (**C12**), 13.8 (**C17**), 10.6 ($J_{^{117}Sn\text{-}C}$ 329, $J_{^{119}Sn\text{-}C}$ 344, **C14**).

IR: ν_{max} (neat)/ cm^{-1} 2923 (C–H), 1695 (C=O), 1603 (C=C), 1509, 1252, 1177, 1107.

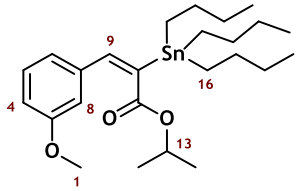
HRMS (ESI): $C_{25}H_{42}O_3{}^{116}SnNa$ $[M+Na]^+$ requires 529.2044; found 529.2012

Selected data for minor regioisomer (**144**):



^{1}H (400 MHz, $CDCl_3$): 6.07 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 60.2, **5**-**H**), 4.88 (1H, sept, *J* 6.3, **2**-**H**).

(*E*)-Isopropyl 3-(3-methoxyphenyl)-2-(tributylstannyl)acrylate (145)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (4.50 mL, 16.8 mmol) in tetrahydrofuran (16 mL) was added dropwise over 4 hours to a

degassed solution of $Pd(PPh_3)_4$ (371 mg, 0.320 mmol) and propargylic ester **123** (3.50 g, 16.0 mmol) in tetrahydrofuran (16 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (100 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a 6 : 1 mixture of regioisomers by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford stannane **145** as a yellow oil (7.42 g, 91%) and as a 12 : 1 mixture of regioisomers which were used in the subsequent reaction without further separation.

A small amount of the product was repurified for analysis by silica gel chromatography (40-60 petrol : toluene, 100 : 0 to 80 : 20).

Data for major regioisomer:

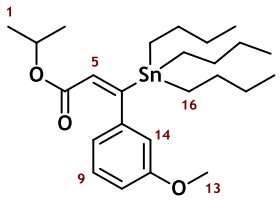
^{1}H (400 MHz, $CDCl_3$): δ 7.22 (1H, app. t, *J* 7.9, **5**-**H**), 6.94 (1H, d, *J* 8.1, **6**-**H**), 6.90 (1H, s, **8**-**H**), 6.81 (1H, dd, *J* 8.4, 2.2, **4**-**H**), 6.68 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 58.9, **9**-**H**), 5.08 (1H, sept, *J* 6.3, **13**-**H**), 3.79 (3H, s, **1**-**H**), 1.70 – 1.48 (6H, m, **17**-**H**), 1.37 (6H, app. dq, *J* 14.8, 7.4, **18**-**H**), 1.22 (6H, d, *J* 6.2, **14**-**H**), 1.18 – 0.99 (6H, m, **16**-**H**), 0.93 (9H, t, *J* 7.3, **19**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 172.8 (**C11**), 159.6 ($\mathbf{C}_{Ar}$**3**), 141.5 ($J_{^{117,119}Sn\text{-}C}$ 14, **C9**), 140.6 (**C10**), 138.5 ($J_{^{117,119}Sn\text{-}C}$ 47, $\mathbf{C}_{Ar}$**7**), 129.2 ($\mathbf{C}_{Ar}$**5**), 120.7 ($\mathbf{C}_{Ar}$**6**), 114.0 ($\mathbf{C}_{Ar}$**4**), 113.3 ($\mathbf{C}_{Ar}$**8**), 67.7 (**C13**), 55.3 (**C1**), 28.9 ($J_{^{117,119}Sn\text{-}C}$ 21, **C17**), 27.4 ($J_{^{117,119}Sn\text{-}C}$ 59, **C18**), 21.9 (**C14**), 13.8 (**C19**), 10.7 ($J_{^{117}Sn\text{-}C}$ 329, $J_{^{119}Sn\text{-}C}$ 344, **C16**).

IR: ν_{max} (neat)/ cm^{-1} 2923 (C–H), 1697 (C=O), 1588 (C=C), 1460, 1196, 1106, 691.

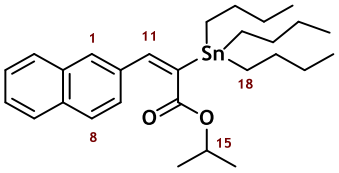
HRMS (ESI): $C_{25}H_{42}O_3{}^{116}SnNa$ $[M+Na]^+$ requires 529.2044; found 529.2013

Selected data for minor regioisomer (**146**):



^{1}H (400 MHz, $CDCl_3$): 6.08 (1H, s, $J_{117,119_{Sn-H}}$ 59.2, **5**-**H**), 4.85 (1H, sept, *J* 6.2, **2**-**H**), 3.79 (3H, s, **13**-**H**).

(*E*)-Isopropyl 3-(naphthalen-2-yl)-2-(tributylstannyl)acrylate (139)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (3.33 mL, 12.4 mmol) in tetrahydrofuran (13 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (273 mg, 0.236 mmol) and propargylic ester **124** (2.81 g, 11.8 mmol) in tetrahydrofuran (13 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (100 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a 6 : 1 mixture of regioisomers by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford stannane **139** (5.06 g, 81%) as a yellow oil and as a 6 : 1 mixture of regioisomers which were used in the subsequent reaction without further separation.

A small amount of the product was repurified for analysis by silica gel chromatography (40-60 petrol : toluene, 100 : 0 to 80 : 20).

Data for major regioisomer:

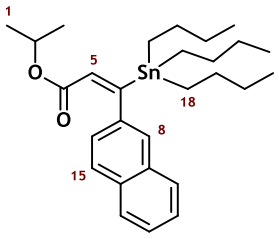
^{1}H (400 MHz, $CDCl_3$): δ 7.84 – 7.71 (4H, m, **1**-**H**, **4**-**H**, **6**-**H**, **8**-**H**), 7.49 (1H, dd, *J* 8.6, 1.5, **9**-**H**), 7.47 – 7.41 (2H, m, **3**-**H**, **5**-**H**), 6.78 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 58.9, **11**-**H**), 5.13 (1H, sept, *J* 6.3, **15**-**H**), 1.73 – 1.51 (6H, m, **19**-**H**), 1.43 (6H, app. sex, *J* 7.3, **20**-**H**), 1.22 (6H, d, *J* 6.3, **16**-**H**), 1.19 – 1.03 (6H, m, **18**-**H**), 0.94 (9H, t, *J* 7.3, **21**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 172.9 (**C13**), 141.8 ($J_{^{117,119}Sn\text{-}C}$ 14, **C11**), 140.9 (C_{Ar}**10**), 134.7 (**C12**), 133.4 (C_{Ar}**7**), 133.1 (C_{Ar}**2**), 128.3 (C_{Ar}**1**/C_{Ar}**4**/C_{Ar}**6**/C_{Ar}**8**), 127.8 (C_{Ar}**1**/C_{Ar}**4**/C_{Ar}**6**/C_{Ar}**8**), 127.7 (C_{Ar}**1**/C_{Ar}**4**/C_{Ar}**6**/C_{Ar}**8**), 127.7 (C_{Ar}**1**/C_{Ar}**4**/C_{Ar}**6**/C_{Ar}**8**), 126.3 (C_{Ar}**3**/C_{Ar}**5**/C_{Ar}**9**), 126.2 (C_{Ar}**3**/C_{Ar}**5**/C_{Ar}**9**), 125.9 (C_{Ar}**3**/C_{Ar}**5**/C_{Ar}**9**), 67.8 (**C15**), 29.0 ($J_{^{117,119}Sn\text{-}C}$ 20, **C19**), 27.4 ($J_{^{117,119}Sn\text{-}C}$ 59, **C20**), 21.9 (**C16**), 13.8 (**C21**), 10.7 ($J_{^{117}Sn\text{-}C}$ 329, $J_{^{119}Sn\text{-}C}$ 345, **C18**).

IR: ν_{max} (neat)/ cm^{-1} 2926 (C–H), 1693 (C=O), 1601 (C=C), 1464, 1200, 1105, 750.

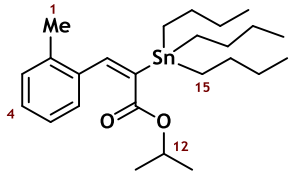
HRMS (ESI): $C_{28}H_{42}O_2{}^{116}SnNa$ $[M+Na]^+$ requires 549.2094; found 549.2098

Selected data for minor regioisomer (**140**):



^{1}H (400 MHz, $CDCl_3$): 6.20 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 58.7, **5**-**H**), 4.82 (1H, sept, *J* 6.3, **2**-**H**).

(*E*)-Isopropyl 3-(*o*-tolyl)-2-(tributylstannyl)acrylate (147)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (6.75 mL, 25.1 mmol) in tetrahydrofuran (24 mL) was added dropwise over 4 hours[†] to a degassed solution of $Pd(PPh_3)_4$ (553 mg, 0.480 mmol) and propargylic ester **125** (4.84 g, 23.9 mmol) in tetrahydrofuran (24 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (100 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a 3 : 1 mixture of regioisomers by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford stannane **147** (10.4 g, 88%) as a yellow oil and as a 3 : 1 mixture of regioisomers which were used in the subsequent reaction without separation.

A small amount of the product was repurified for analysis by silica gel chromatography (40-60 petrol : toluene, 100 : 0 to 80 : 20).

Data for major regioisomer:

^{1}H (400 MHz, $CDCl_3$): δ 7.23 (1H, d, *J* 7.3, **6**-**H**), 7.18 – 7.03 (3H, m, **3**-**H**, **4**-**H**, **5**-**H**), 6.90 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 58.2, **8**-**H**), 4.94 (1H, sept, *J* 6.2, **12**-**H**), 2.32 (3H, s, **1**-**H**), 1.68 – 1.49 (6H, m, **16**-**H**),

[†] *Due to syringe pump malfunction the tributyltin hydride solution was added considerably quicker than 4 hours (approx. 30 mins) and may in part have led to poor regioselectivity in this example.*

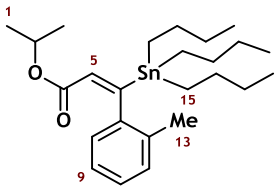
1.45 – 1.28 (6H, m, **17**-**H**), 1.09 (6H, d, *J* 6.1, **13**-**H**), 1.15 – 0.98 (6H, m, **15**-**H**), 0.92 (9H, t, *J* 7.2, **18**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 172.2 (**C10**), 143.2 ($J_{^{117,119}Sn\text{-}C}$ 14, **C8**), 140.7 ($\mathbf{C}_{Ar}$**2**), 137.5 ($\mathbf{C}_{Ar}$**7**), 135.5 (**C9**), 129.9 ($\mathbf{C}_{Ar}$**3**), 128.1 ($\mathbf{C}_{Ar}$**6**), 127.9 ($\mathbf{C}_{Ar}$**4**), 125.6 ($\mathbf{C}_{Ar}$**5**), 67.5 (**C12**), 29.0 ($J_{^{117,119}Sn\text{-}C}$ 21, **C16**), 27.4 ($J_{^{117,119}Sn\text{-}C}$ 59, **C17**), 21.8 (**C13**), 19.9 (**C1**), 13.9 (**C18**), 10.7 ($J_{^{117}Sn\text{-}C}$ 330, $J_{^{119}Sn\text{-}C}$ 346, **C15**).

IR: ν_{max} (neat)/ cm^{-1} 2925 (C–H), 1700 (C=O), 1601 (C=C), 1462, 1179, 1107, 746.

HRMS (ESI): $C_{25}H_{42}O_2{}^{116}SnNa$ $[M+Na]^+$ requires 513.2094; found 513.2092

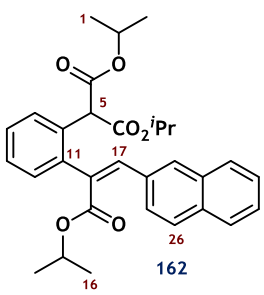
Selected data for minor regioisomer (**148**):



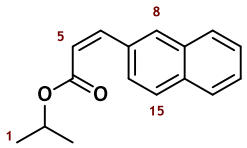
^{1}H (400 MHz, $CDCl_3$): 6.15 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 59.4, **5**-**H**), 4.81 (1H, sept, *J* 6.2, **2**-**H**), 2.12 (3H, s, **13**-**H**).

5.3.3 Stille Coupling

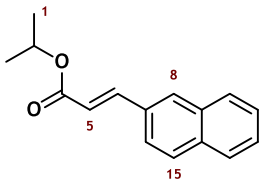
(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-1-(naphthalen-2-yl)-3-oxoprop-1-en-2-yl)phenyl) malonate (162), (*Z*)-isopropyl 3-(naphthalen-2-yl)acrylate (163) & (*E*)-isopropyl 3-(naphthalen-2-yl)acrylate (163)



162



(*Z*)-163

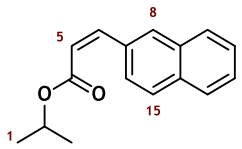


(*E*)-163

Palladium(II) acetate (71 mg, 0.32 mmol) and biphenyl-2-yl(dicyclohexyl)phosphine (220 mg, 0.630 mmol) were added to a stirred degassed solution of malonate **78** (823 mg, 2.10 mmol) in anhydrous *N*,*N*-dimethylformamide (6 mL). After stirring for 15 minutes, CuI (300 mg, 1.58 mmol) and a degassed solution of stannane **139** (1.34 g, 2.53 mmol) in anhydrous *N*,*N*-dimethylformamide (4 mL) was added. The mixture was heated to 80 °C for 15 hours and after cooling to room temperature was concentrated *in vacuo*. The residue was filtered through Celite® with diethyl ether and the filtrate was concentrated *in vacuo*. The crude product was purified by silica gel chromatography (toluene : ethyl acetate, 100 : 0 to 99 : 1) to afford cyclization precursor **162** (420 mg, 40%) as a colourless oil, (*Z*)-alkene **163** (68 mg, 11%) as a brown oil and (*E*)-alkene **163** (32 mg, 5%) as a beige solid.

Cyclization precursor **162**: *For spectroscopic data see page 234*.

(*Z*)-Isopropyl 3-(naphthalen-2-yl)acrylate (163)



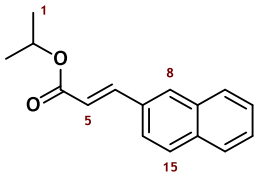
^{1}H (400 MHz, $CDCl_3$): δ 8.04 (1H, s, **8**-**H**), 7.90 – 7.79 (3H, m, **10**-**H**, **13**-**H**, **15**-**H**), 7.77 – 7.72 (1H, m, **16**-**H**), 7.55 – 7.45 (2H, m, **11**-**H**, **12**-**H**), 7.09 (1H, d, *J* 12.6, **6**-**H**), 6.03 (1H, d, *J* 12.6, **5**-**H**), 5.12 (1H, sept, *J* 6.2, **2**-**H**), 1.26 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 166.0 (**C4**), 142.4 (**C6**), 133.5 ($\mathbf{C}_{Ar}$**7**), 133.0 ($\mathbf{C}_{Ar}$**9**), 132.7 ($\mathbf{C}_{Ar}$**14**), 129.9 ($\mathbf{C}_{Ar}$**8**), 128.6 ($\mathbf{C}_{Ar}$**H**), 127.7 ($\mathbf{C}_{Ar}$**H**), 127.5 ($\mathbf{C}_{Ar}$**H**), 127.1 ($\mathbf{C}_{Ar}$**H**), 126.8 ($\mathbf{C}_{Ar}$**11**/$\mathbf{C}_{Ar}$**12**), 126.3 ($\mathbf{C}_{Ar}$**11**/$\mathbf{C}_{Ar}$**12**), 120.8 (**C5**), 67.9 (**C2**), 21.9 (**C1**).

IR: v_{max} (neat)/ cm^{-1} 2980 (C–H), 1715 (C=O), 1628 (C=C), 1373, 1182, 1108 (C–O), 750.

HRMS (ESI): $C_{16}H_{16}O_2Na$ $[M+Na]^+$ requires 263.1043; found 263.1044.

(*E*)-Isopropyl 3-(naphthalen-2-yl)acrylate (163)



^{1}H (400 MHz, $CDCl_3$): δ 7.94 (1H, s, **8**-**H**), 7.89 – 7.78 (4H, m, **6**-**H**, **10**-**H**, **13**-**H**, **15**-**H**), 7.68 (1H, d, *J* 8.6, **16**-**H**), 7.56 – 7.46 (2H, m, **11**-**H**, **12**-**H**), 6.55 (1H, d, *J* 16.2, **5**-**H**), 5.19 (1H, sept, *J* 6.2, **2**-**H**), 1.35 (6H, d, *J* 6.3, **1**-**H**).

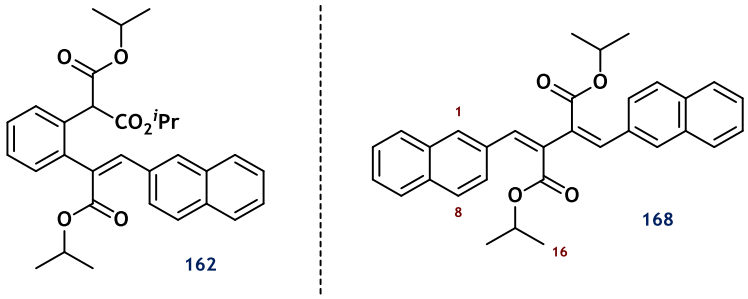
^{13}C (101 MHz, $CDCl_3$): δ 166.7 (**C4**), 144.5 (**C6**), 134.2 ($\mathbf{C}_{Ar}$**7**), 133.3 ($\mathbf{C}_{Ar}$**9**), 132.0 ($\mathbf{C}_{Ar}$**14**), 129.9 ($\mathbf{C}_{Ar}$**8**), 128.8 ($\mathbf{C}_{Ar}$**10**/$\mathbf{C}_{Ar}$**13**/$\mathbf{C}_{Ar}$**15**), 128.7 ($\mathbf{C}_{Ar}$**10**/$\mathbf{C}_{Ar}$**13**/$\mathbf{C}_{Ar}$**15**), 127.9 ($\mathbf{C}_{Ar}$**10**/$\mathbf{C}_{Ar}$**13**/$\mathbf{C}_{Ar}$**15**), 127.3 ($\mathbf{C}_{Ar}$**11**/$\mathbf{C}_{Ar}$**12**), 126.8 ($\mathbf{C}_{Ar}$**11**/$\mathbf{C}_{Ar}$**12**), 123.7 ($\mathbf{C}_{Ar}$**16**), 119.1 (**C5**), 68.0 (**C2**), 22.1 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2983 (C–H), 1716 (C=O), 1630 (C=C), 1378, 1189, 1109 (C–O), 736.

HRMS (ESI): $C_{16}H_{16}O_2Na$ $[M+Na]^+$ requires 263.1043; found 263.1046.

MP: 77 – 79 °C.

Attempted synthesis of (*Z*)-diisopropyl 2-(2-(3-isopropoxy-1-(naphthalen-2-yl)-3-oxoprop-1-en-2-yl)phenyl) malonate (162) & isolation of (2*Z*,3*Z*)-diisopropyl 2,3-bis(naphthalen-2-ylmethylene)succinate (168)



According to a modified literature procedure,[99] lithium chloride (64 mg, 1.50 mmol) was flame dried under high vacuum. Upon cooling, $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and copper(I) chloride (124 mg, 1.25 mmol) were added. The mixture was purged with argon (× 4) and anhydrous DMSO (2 mL) was added. To this suspension was added malonate **78** (98 mg, 0.250 mmol) and stannane **139** (159 mg, 0.300 mmol). The resulting mixture was degassed (× 4) *via* a freeze-pump-thaw process and then allowed to stir at room temperature for 1 hour. The reaction was then heated to 60 °C for 48 hours and after cooling to room temperature was concentrated *in vacuo*. The resulting residue was diluted with diethyl ether (5 mL) and washed with brine (5 mL). The aqueous layer was then extracted with diethyl ether (2 × 5 mL) and the combined organic layers washed with water (2 × 10 mL) then brine (2 × 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and

concentrated *in vacuo*. The crude product was purified by silica gel chromatography (toluene) to afford diene **168** (14 mg, 20%) as a colourless oil.

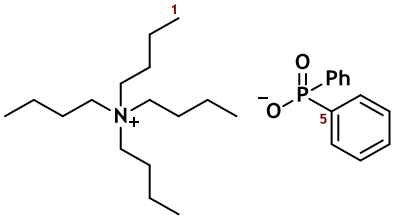
^{1}H (500 MHz, $CDCl_3$): δ 7.86 (2H, s, **1**-**H**), 7.85 – 7.79 (6H, m, **3**-**H**, **6**-**H**, **8**-**H**), 7.53 – 7.48 (6H, m, **4**-**H**, **5**-**H**, **9**-**H**), 7.04 (2H, s, **11**-**H**), 5.23 (2H, sept, *J* 6.3, **15**-**H**), 1.21 (12H, d, *J* 6.3, **16**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 167.8 (**C13**), 133.7 ($\mathbf{C}_{Ar}$**10**), 133.3 (**C11**), 133.1 ($\mathbf{C}_{Ar}$**7**), 132.6 ($\mathbf{C}_{Ar}$**2**), 128.6 ($\mathbf{C}_{Ar}$**1**), 128.4 ($\mathbf{C}_{Ar}$**3**/$\mathbf{C}_{Ar}$**6**/$\mathbf{C}_{Ar}$**8**), 128.0 ($\mathbf{C}_{Ar}$**3**/$\mathbf{C}_{Ar}$**6**/$\mathbf{C}_{Ar}$**8**), 127.8 ($\mathbf{C}_{Ar}$**3**/$\mathbf{C}_{Ar}$**6**/$\mathbf{C}_{Ar}$**8**), 126.8 (**C12**), 126.6 ($\mathbf{C}_{Ar}$**4**/$\mathbf{C}_{Ar}$**5**/$\mathbf{C}_{Ar}$**9**), 126.2 ($\mathbf{C}_{Ar}$**4**/$\mathbf{C}_{Ar}$**5**/$\mathbf{C}_{Ar}$**9**), 69.5 (**C15**), 21.7 (**C16**).[†]

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1709 (C=O), 1374, 1243, 1104 (C–O), 748.

HRMS (ESI): $C_{32}H_{31}O_4$ $[M+H]^+$ requires 479.2217; found 479.2215

Tetrabutylammonium diphenylphosphinate (175)



According to a literature procedure,[227] tetrabutylammonium hydroxide (1 M in methanol, 18.3 mL, 18.3 mmol) was added to a solution of diphenylphosphinic acid (4.00 g, 18.3 mmol) in methanol (20 mL) at room temperature. The reaction was shaken for 4 minutes and was then filtered through Celite® with methanol. Following concentration *in vacuo*, the resulting yellow oil was placed under high vacuum overnight to give a semi-solid. The crude product was then purified by recrystallization (diethyl ether/hexane) to afford phosphinate salt **175**

[†] *One* $\mathbf{C}_{Ar}\mathbf{H}$ (*$\mathbf{C}_{Ar}$**4**/$\mathbf{C}_{Ar}$**5**/$\mathbf{C}_{Ar}$**9**) peak not observed and assumed to be coincident with another peak around 126.4 – 126.1 ppm*

(3.32 g, 39%) as a white hygroscopic solid with spectroscopic data in accordance with the literature.[227]

^{1}H (400 MHz, $CDCl_3$): δ 7.70 – 7.61 (4H, m, **6**-**H**), 7.05 – 6.93 (6H, m, **7**-**H**, **8**-**H**), 2.90 (8H, m, **4**-**H**), 1.28 – 1.14 (8H, m, **3**-**H**), 1.13 – 0.99 (8H, m, **2**-**H**), 0.68 (12H, t, *J* 7.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 143.0 (d, $J_{P\text{-}C}$ 125, $\mathbf{C}_{Ar}$**5**), 131.3 (d, $J_{P\text{-}C}$ 9, $\mathbf{C}_{Ar}$**6**), 127.9 (d, $J_{P\text{-}C}$ 2, $\mathbf{C}_{Ar}$**8**), 126.7 (d, $J_{P\text{-}C}$ 11, $\mathbf{C}_{Ar}$**7**), 57.9 (**C4**), 23.4 (**C3**), 19.1 (**C2**), 13.2 (**C1**).

^{31}P (162 MHz, $CDCl_3$): δ 12.8

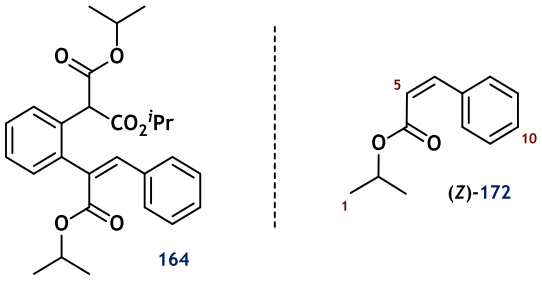
IR: ν_{max} (neat)/ cm^{-1} 2963 (C–H), 1645, 1485, 1189 (P=O), 1124, 1041 (P=O), 884, 720, 558.

LRMS (ESI): $[M]^+$ 242.3

LRMS (ESI): $[M]^-$ 217.0

MP: 66 – 68 °C (diethyl ether/hexane), lit. MP: 53 – 63 °C (diethyl ether/hexane).[227]

Attempted synthesis of (*Z*)-diisopropyl 2-(2-(3-isopropoxy-3-oxo-1-phenylprop-1-en-2-yl)phenyl)malonate (164) and isolation of (*Z*)-isopropyl 3-phenylacrylate (172)



According to a modified literature procedure,[105] hygroscopic tetrabutylammonium diphenylphosphinate **175** (570 mg, 1.24 mmol) was melted under high vacuum and allowed to cool to room temperature. The flask was purged with argon before the addition of malonate **78** (241 mg, 0.620 mmol), stannane **149** (355 mg, 0.740 mmol), $Pd(PPh_3)_4$ (0.072 g,

0.060 mmol) and NMP (3 mL). The reaction mixture was degassed three times using a freeze-pump-thaw protocol before adding CuI (0.024 g, 0.120 mmol) under a flow of argon. The resulting suspension was left to stir at room temperature for 48 hours. The reaction was then diluted with aqueous ammonium hydroxide (5%, 20 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1) to afford the major product as (*Z*)-alkene **172** (118 mg, 84%) as a yellow oil with spectroscopic data in accordance with the literature.[228]

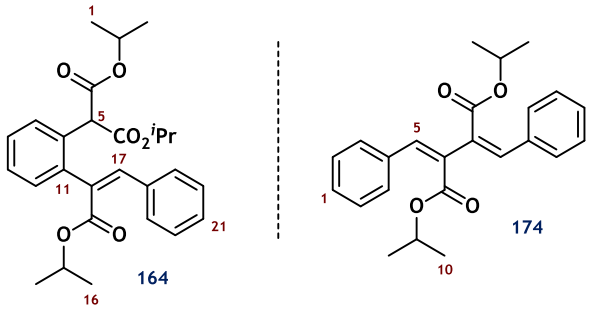
^{1}H (400 MHz, $CDCl_3$): δ 7.58 (2H, app. dd, *J* 7.6, 1.5, **8**-**H**), 7.40 – 7.31 (3H, m, **9**-**H**, **10**-**H**), 6.94 (1H, d, *J* 12.6, **6**-**H**), 5.94 (1H, d, *J* 12.6, **5**-**H**), 5.06 (1H, sept, *J* 6.3, **2**-**H**), 1.23 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 166.0 (**C4**), 142.6 (**C6**), 135.1 ($\mathbf{C}_{Ar}$**7**), 129.8 ($\mathbf{C}_{Ar}$**8**), 129.0 ($\mathbf{C}_{Ar}$**10**), 128.1 ($\mathbf{C}_{Ar}$**9**), 120.7 (**C5**), 67.9 (**C2**), 21.9 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1716 (C=O), 1628 (C=C), 1179, 1107, 831, 697.

LRMS (ESI): $[M+Na]^+$ 213.1

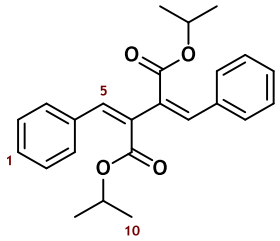
(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-3-oxo-1-phenylprop-1-en-2-yl)phenyl)malonate & (164) diisopropyl 2,3-di((*Z*)-benzylidene)succinate (174)



According to a modified literature procedure,[111] a dried schlenk flask was charged with stannane **149** (431 mg, 0.899 mmol) and anhydrous NMP (7 mL). Under a flow of argon $Pd_2(dba)_3{\cdot}CHCl_3$ (22 mg, 0.021 mmol) and tri(2-furyl)phosphine **176** (38 mg, 0.164 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **78** (313 mg, 0.802 mmol) was dissolved in anhydrous NMP (4 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **78** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (171 mg, 0.898 mmol) was added and the reaction stirred at room temperature for 48 hours. After this time, the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 50 mL) and ethyl acetate (150 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 50 mL) and brine (3 × 50 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) to afford cyclization precursor **164** (146 mg, 40%) as a white solid and diene **174** (62 mg, 36%) as yellow oil.

Cyclization precursor **164**: *For spectroscopic data see page 230*.

Diisopropyl 2,3-di((*Z*)-benzylidene)succinate (174)



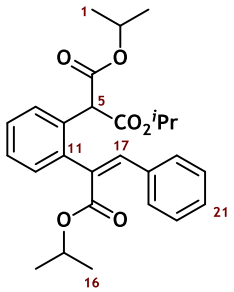
^{1}H (400 MHz, $CDCl_3$): δ 7.41 – 7.26 (10H, m, **Ar-H**), 6.86 (2H, s, **5-H**), 5.16 (2H, sept, *J* 6.4, **9-H**), 1.19 (12H, d, *J* 6.1, **10-H**).

^{13}C (126 MHz, $CDCl_3$): δ 167.6 (**C7**), 135.6 ($\mathbf{C}_{Ar}$**4**), 133.5 (**C6**), 132.6 (**C5**), 128.7 ($\mathbf{C}_{Ar}$**2**/$\mathbf{C}_{Ar}$**3**), 128.6 ($\mathbf{C}_{Ar}$**1**), 128.4 ($\mathbf{C}_{Ar}$**2**/$\mathbf{C}_{Ar}$**3**), 69.3 (**C9**), 21.6 (**C10**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1713 (C=O), 1606 (C=C), 1223, 1099 (C–O), 975, 908, 820, 731, 693.

HRMS (ESI): $C_{24}H_{26}O_4Na$ $[M+Na]^+$ requires 401.1723; found 401.1717

(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-3-oxo-1-phenylprop-1-en-2-yl)phenyl)malonate (164)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **149** (1.12 g, 2.34 mmol) and anhydrous NMP (8 mL). Under a flow of argon $Pd_2(dba)_3$ (143 mg, 0.156 mmol) and tri(2-furyl)phosphine **176** (145 mg, 0.624 mmol) were

added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **78** (608 mg, 1.56 mmol) was dissolved in anhydrous NMP (1.5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **78** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (446 mg, 2.34 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) to afford cyclization precursor **164** (337 mg, 48%) as a white solid.[†]

^{1}H (400 MHz, $CDCl_3$): δ 7.61 (1H, d, *J* 7.9, **7**-**H**), 7.45 – 7.29 (8H, m, **Ar**-**H**), 6.68 (1H, s, **17**-**H**), 5.15 (1H, s, **5**-**H**), 5.06 (3H, app. oct, *J* 6.3, **2**-**H**, **15**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**), 1.20 (6H, d, *J* 6.3, **1**-**H**), 1.13 (6H, d, *J* 6.3, **16**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 168.2 (**C4**), 167.9 (**C13**), 138.9 ($\mathbf{C}_{Ar}$**11**), 137.0 (**C17**), 135.4 ($\mathbf{C}_{Ar}$**18**), 133.7 (**C12**), 132.0 ($\mathbf{C}_{Ar}$**6**), 129.6 ($\mathbf{C}_{Ar}$**7**), 129.4 ($\mathbf{C}_{Ar}$**10**), 128.6 ($\mathbf{C}_{Ar}$**19**), 128.5 ($\mathbf{C}_{Ar}$**H**), 128.4 ($\mathbf{C}_{Ar}$**20**), 128.3 ($\mathbf{C}_{Ar}$**H**), 127.9 ($\mathbf{C}_{Ar}$**9**), 69.4 (**C2**), 69.0 (**C15**), 54.9 (**C5**), 21.7 (**C1**), 21.7 (**C1**), 21.5 (**C16**).

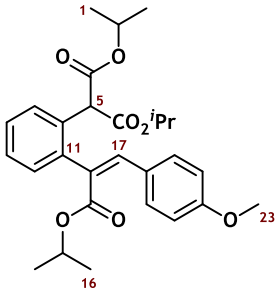
IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1727 (C=O), 1374, 1216, 1104 (C–O), 756.

HRMS (ESI): $C_{27}H_{32}O_6Na$ $[M+Na]^+$ requires 475.2094; found 475.2083

[†] *Under identical reaction conditions but on a smaller scale (iodoarene **78** (236 mg, 0.605 mmol)) this reaction provided cyclization precursor **164** in 64% yield.*

MP: 53 – 55 °C (petrol 60-80).

(Z)-Diisopropyl 2-(2-(3-isopropoxy-1-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl)phenyl) malonate (177)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **143** (1.20 g, 2.36 mmol) and anhydrous NMP (9 mL). Under a flow of argon $Pd_2(dba)_3$ (144 mg, 0.160 mmol) and tri(2-furyl)phosphine **176** (146 mg, 0.628 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **78** (613 mg, 1.57 mmol) was dissolved in anhydrous NMP (2 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **78** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (449 mg, 2.36 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) to afford cyclization precursor **177** (527 mg, 70%) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.62 – 7.56 (1H, m, **7**-**H**), 7.40 (2H, d, *J* 8.8, **19**-**H**), 7.39 – 7.30 (3H, m, **8**-**H**, **9**-**H**, **10**-**H**), 6.89 (2H, d, *J* 8.6, **20**-**H**), 6.58 (1H, s, **17**-**H**), 5.13 (1H, s, **5**-**H**), 5.10 – 5.01 (3H, m, **2**-**H**, **15**-**H**), 3.84 (3H, s, **23**-**H**), 1.26 (6H, d, *J* 6.1, **1**-**H**), 1.19 (6H, d, *J* 6.1, **1**-**H**), 1.16 (6H, d, *J* 6.3, **16**-**H**).

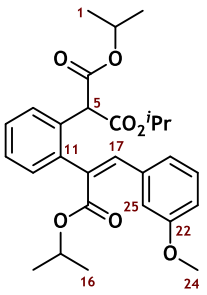
^{13}C (101 MHz, $CDCl_3$): δ 168.2 (**C4**), 168.1 (**C13**), 160.0 ($\mathbf{C}_{Ar}$**21**), 139.4 ($\mathbf{C}_{Ar}$**11**), 137.0 (**C17**), 132.1 (**C12**), 131.4 ($\mathbf{C}_{Ar}$**6**), 130.4 ($\mathbf{C}_{Ar}$**19**), 129.6 ($\mathbf{C}_{Ar}$**7**), 129.5 ($\mathbf{C}_{Ar}$**10**), 128.2 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**9**), 127.9 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**9**), 127.9 ($\mathbf{C}_{Ar}$**18**), 113.8 ($\mathbf{C}_{Ar}$**20**), 69.3 (**C2**), 68.9 (**C15**), 55.4 (**C23**), 54.9 (**C5**), 21.7 (**C1**), 21.7 (**C1**), 21.6 (**C16**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1726 (C=O), 1607 (C=C), 1512, 1256, 1217, 1103 (C–O).

HRMS (ESI): $C_{28}H_{34}O_7Na$ $[M+Na]^+$ requires 505.2197; found 505.2193

MP: 72 – 74 °C.

(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-1-(3-methoxyphenyl)-3-oxoprop-1-en-2-yl)phenyl) malonate (178)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **145** (986 mg, 1.94 mmol) and anhydrous NMP (7 mL). Under a flow of argon $Pd_2(dba)_3$ (118 mg, 0.129 mmol) and tri(2-furyl)phosphine **176** (120 mg, 0.520 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried

schlenk flask iodoarene **78** (505 mg, 1.29 mmol) was dissolved in anhydrous NMP (1.5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **78** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (369 mg, 1.94 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) followed by recrystallization (hexane/diethyl ether) to afford cyclization precursor **178** (371 mg, 60%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.62 (1H, dd, *J* 8.0, 1.1, **7**-**H**), 7.42 – 7.31 (3H, m, **8**-**H**, **9**-**H**, **10**-**H**), 7.28 (1H, app. t, *J* 8.0, **20**-**H**), 7.02 (1H, dd, *J* 7.6, 0.8, **19**-**H**), 6.98 (1H, s, **25**-**H**), 6.88 (1H, dd, *J* 8.2, 1.9, **21**-**H**), 6.64 (1H, s, **17**-**H**), 5.16 (1H, s, **5**-**H**), 5.13 – 4.99 (3H, m, **2**-**H**, **15**-**H**), 3.82 (3H, s, **24**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**), 1.21 (6H, d, *J* 6.3, **1**-**H**), 1.14 (6H, d, *J* 6.3, **16**-**H**).

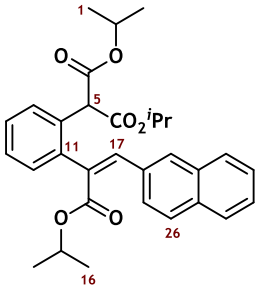
^{13}C (101 MHz, $CDCl_3$): δ 168.1 (**C4**), 167.8 (**C13**), 159.6 ($\mathbf{C}_{Ar}$**22**), 138.7 ($\mathbf{C}_{Ar}$**11**), 136.6 ($\mathbf{C}_{Ar}$**18**), 136.5 (**C17**), 134.0 (**C12**), 131.9 ($\mathbf{C}_{Ar}$**6**), 129.6 ($\mathbf{C}_{Ar}$**7**), 129.4 ($\mathbf{C}_{Ar}$**20**), 129.3 ($\mathbf{C}_{Ar}$**10**), 128.3 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**9**), 127.9 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**9**), 121.0 ($\mathbf{C}_{Ar}$**19**), 114.1 ($\mathbf{C}_{Ar}$**21**), 113.9 ($\mathbf{C}_{Ar}$**25**), 69.3 (**C2**), 69.0 (**C15**), 55.3 (**C24**), 54.8 (**C5**), 21.6 (**C1**), 21.6 (**C1**), 21.5 (**C16**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1723 (C=O), 1599 (C=C), 1374, 1208, 1099 (C–O), 779.

HRMS (ESI): $C_{28}H_{34}O_7Na$ $[M+Na]^+$ requires 505.2197; found 505.2193

MP: 62 – 64 °C (hexane/diethyl ether).

(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-1-(naphthalen-2-yl)-3-oxoprop-1-en-2-yl)phenyl) malonate (162)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **139** (1.02 g, 1.93 mmol) and anhydrous NMP (7 mL). Under a flow of argon $Pd_2(dba)_3$ (118 mg, 0.129 mmol) and tri(2-furyl)phosphine **176** (120 mg, 0.520 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **78** (502 mg, 1.29 mmol) was dissolved in anhydrous NMP (1.5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **78** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (368 mg, 1.93 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol :

ethyl acetate, 50 : 1 to 30 : 1) to afford cyclization precursor **162** (321 mg, 50%) as a colourless oil.

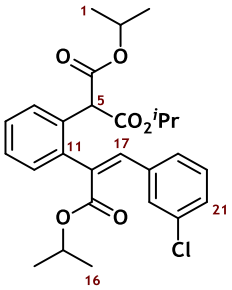
^{1}H (400 MHz, $CDCl_3$): δ 7.91 (1H, s, **19**-**H**), 7.88 – 7.80 (3H, m, **Ar**-**H**), 7.66 (1H, d, *J* 7.6, **7**-**H**), 7.57 (1H, d, *J* 8.6, **27**-**H**), 7.54 – 7.35 (5H, m, **8**-**H**, **9**-**H**, **10**-**H**, **Ar**-**H**), 6.85 (1H, s, **17**-**H**), 5.23 (1H, s, **5**-**H**), 5.17 – 5.05 (3H, m, **2**-**H**, **15**-**H**), 1.29 (6H, d, *J* 6.3, **1**-**H**), 1.23 (6H, d, *J* 6.3, **1**-**H**), 1.14 (6H, d, *J* 6.3, **16**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 168.2 (**C4**), 168.0 (**C13**), 138.9 ($\mathbf{C_{Ar}}$**11**), 137.0 (**C17**), 133.9 (**C12**), 133.2 ($\mathbf{C_{Ar}}$**20** & $\mathbf{C_{Ar}}$**25**) 132.9 ($\mathbf{C_{Ar}}$**18**), 132.0 ($\mathbf{C_{Ar}}$**6**), 129.6 ($\mathbf{C_{Ar}}$**7**), 129.5 ($\mathbf{C_{Ar}}$**H**), 128.4 ($\mathbf{C_{Ar}}$**H**), 128.3 ($\mathbf{C_{Ar}}$**H**), 128.2 ($\mathbf{C_{Ar}}$**19**), 127.9 (2 × $\mathbf{C_{Ar}}$**H**), 127.8 ($\mathbf{C_{Ar}}$**H**), 126.6 ($\mathbf{C_{Ar}}$**H**), 126.5 ($\mathbf{C_{Ar}}$**H**), 126.1 ($\mathbf{C_{Ar}}$**27**), 69.4 (**C2**), 69.1 (**C15**), 55.0 (**C5**), 21.7 (**C1**), 21.6 (**C1**), 21.5 (**C16**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1725 (C=O), 1598 (C=C), 1208, 1102 (C–O), 737.

HRMS (ESI): $C_{31}H_{34}O_6Na$ $[M+Na]^+$ requires 525.2248; found 525.2235

(*Z*)-Diisopropyl 2-(2-(1-(3-chlorophenyl)-3-isopropoxy-3-oxoprop-1-en-2-yl)phenyl) malonate (179)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **153** (1.60 g, 3.12 mmol) and anhydrous NMP (13 mL). Under a flow of argon $Pd_2(dba)_3$ (191 mg, 0.208 mmol) and tri(2-furyl)phosphine **176** (193 mg, 0.832 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the

solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **78** (813 mg, 2.08 mmol) was dissolved in anhydrous NMP (2.5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **78** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (594 mg, 3.12 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 75 mL) and ethyl acetate (400 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 75 mL) and brine (3 × 75 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 40 : 1 to 30 : 1) followed by three (re)crystallizations (hexane)[†] and trituration with cold diethyl ether to afford cyclization precursor **179** (363 mg, 36%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.61 (1H, d, *J* 7.6, **7**-**H**), 7.42 (1H, s, **23**-**H**), 7.42 – 7.33 (3H, m, **8**-**H**, **9**-**H**, **10**-**H**), 7.33 – 7.24 (3H, m, **19**-**H**, **20**-**H**, **21**-**H**), 6.61 (1H, s, **17**-**H**), 5.13 – 5.00 (4H, m, **2**-**H**, **5**-**H**, **15**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**), 1.21 (6H, d, *J* 6.3, **1**-**H**), 1.15 (6H, d, *J* 6.3, **16**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 168.1 (**C4**), 167.5 (**C13**), 138.4 (C_{Ar}**11**), 137.2 (C_{Ar}**18**), 135.4 (**C17**), 135.2 (**C12**), 134.4 (C_{Ar}**22**), 131.9 (C_{Ar}**6**), 129.7 (C_{Ar}**20**), 129.7 (C_{Ar}**7**), 129.4 (C_{Ar}**8**), 128.6 (C_{Ar}**10**/C_{Ar}**21**), 128.5 (C_{Ar}**10**/C_{Ar}**21**), 128.4 (C_{Ar}**23**), 128.0 (C_{Ar}**9**), 126.8 (C_{Ar}**19**), 69.5 (**C2**), 69.4 (**C15**), 55.0 (**C5**), 21.7 (**C1**), 21.7 (**C1**), 21.5 (**C16**).

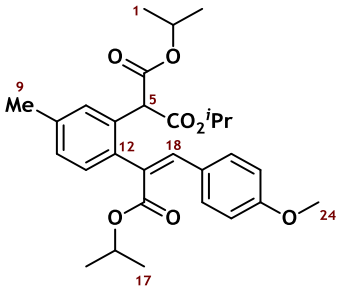
[†] *The majority of the product was found in the filtrate of the first recrystallization but as the precipitate in latter (re)crystallizations. Dibenzylideneacetone was the major constituent of the precipitate from the first recrystallization.*

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1726 (C=O), 1467, 1375, 1216, 1103 (C–O), 991.

HRMS (ESI): $C_{27}H_{31}{}^{35}ClO_6Na$ $[M+Na]^+$ requires 509.1701; found 509.1697

MP: 68 – 70 °C (hexane).

(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-1-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl)-5-methylphenyl)malonate (181)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **143** (1.08 g, 2.13 mmol) and anhydrous NMP (9 mL). Under a flow of argon $Pd_2(dba)_3$ (130 mg, 0.142 mmol) and tri(2-furyl)phosphine **176** (132 mg, 0.568 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **98** (575 mg, 1.42 mmol) was dissolved in anhydrous NMP (2 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **98** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (406 mg, 2.13 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over

anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1 to 20 : 1) to afford cyclization precursor **181** (549 mg, 78%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.41 – 7.35 (3H, m, **7**-**H**, **20**-**H**), 7.28 – 7.22 (1H, m, **11**-**H**), 7.13 (1H, d, *J* 7.8, **10**-**H**), 6.88 (2H, d, *J* 8.1, **21**-**H**), 6.55 (1H, s, **18**-**H**), 5.09 (1H, s, **5**-**H**), 5.11 – 5.00 (3H, m, **2**-**H**, **16**-**H**), 3.84 (3H, s, **24**-**H**), 2.38 (3H, s, **9**-**H**), 1.26 (6H, d, *J* 6.3, **1**-**H**), 1.19 (6H, d, *J* 6.3, **1**-**H**), 1.16 (6H, d, *J* 6.3, **17**-**H**).

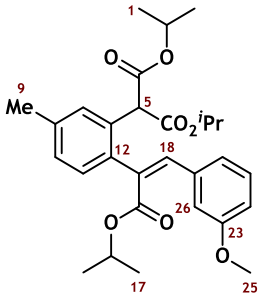
^{13}C (126 MHz, $CDCl_3$): δ 168.4 (**C4**), 168.3 (**C14**), 159.9 ($\mathbf{C}_{Ar}$**22**), 137.9 ($\mathbf{C}_{Ar}$**8**), 136.6 (**C18**), 136.5 ($\mathbf{C}_{Ar}$**12**), 131.8 (**C13**), 131.5 ($\mathbf{C}_{Ar}$**6**), 130.3 ($\mathbf{C}_{Ar}$**20**), 130.1 ($\mathbf{C}_{Ar}$**7**), 129.4 ($\mathbf{C}_{Ar}$**11**), 128.8 ($\mathbf{C}_{Ar}$**10**), 128.0 ($\mathbf{C}_{Ar}$**19**), 113.8 ($\mathbf{C}_{Ar}$**21**), 69.3 (**C2**), 68.8 (**C16**), 55.4 (**C24**), 54.8 (**C5**), 21.7 (**C1**), 21.7 (**C1**), 21.6 (**C17**), 21.5 (**C9**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1728 (C=O), 1607 (C=C), 1513, 1255, 1215, 1101 (C–O).

HRMS (ESI): $C_{29}H_{36}O_7Na$ $[M+Na]^+$ requires 519.2353; found 519.2346

MP: 116 – 118 °C (hexane/diethyl ether).

(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-1-(3-methoxyphenyl)-3-oxoprop-1-en-2-yl)-5-methylphenyl)malonate (182)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **145** (1.02 g, 2.01 mmol) and anhydrous NMP (7 mL). Under a flow of argon $Pd_2(dba)_3$ (123 mg, 0.134 mmol) and tri(2-furyl)phosphine **176** (124 mg, 0.536 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **98** (540 mg, 1.34 mmol) was dissolved in anhydrous NMP (1.5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **98** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (383 mg, 2.01 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) to afford cyclization precursor **182** (267 mg, 40%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.40 (1H, s, **7**-**H**), 7.30 – 7.24 (2H, m, **11**-**H**, **21**-**H**), 7.14 (1H, dd, *J* 7.8, 1.0, **10**-**H**), 6.99 (1H, dd, *J* 7.6, 0.8, **20**-**H**), 6.97 – 6.94 (1H, m, **26**-**H**), 6.87 (1H, dd, *J* 8.3, 2.5, **22**-**H**), 6.60 (1H, s, **18**-**H**), 5.11 (1H, s, **5**-**H**), 5.12 – 4.98 (3H, m, **2**-**H**, **16**-**H**), 3.82 (3H, s, **25**-**H**), 2.38 (3H, s, **9**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**), 1.20 (6H, d, *J* 6.3, **1**-**H**), 1.13 (6H, d, *J* 6.3, **17**-**H**).

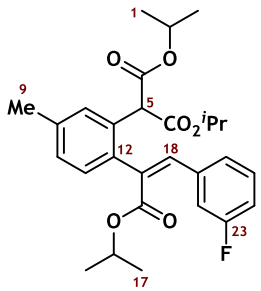
^{13}C (126 MHz, $CDCl_3$): δ 168.3 (**C4**), 168.1 (**C14**), 159.6 (C_{Ar}**23**), 138.2 (C_{Ar}**8**), 136.9 (C_{Ar}**19**), 136.3 (**C18**), 135.9 (C_{Ar}**12**) 134.1 (**C13**), 131.7 (C_{Ar}**6**), 130.2 (C_{Ar}**7**), 129.4 (C_{Ar}**11**/C_{Ar}**21**), 129.2 (C_{Ar}**11**/C_{Ar}**21**), 128.8 (C_{Ar}**10**), 121.1 (C_{Ar}**20**), 114.1 (C_{Ar}**22**), 113.9 (C_{Ar}**26**), 69.3 (**C2**), 69.0 (**C16**), 55.4 (**C25**), 54.8 (**C5**), 21.7 (**C1**), 21.7 (**C1**), 21.5 (**C17**), 21.5 (**C9**).

IR: v_{max} (neat)/ cm^{-1} 2982 (C–H), 1726 (C=O), 1599 (C=C), 1374, 1207, 1101 (C–O), 783.

HRMS (ESI): $C_{29}H_{36}O_7Na$ $[M+Na]^+$ requires 519.2353; found 519.2358

MP: 52 – 54 °C (hexane/ethyl acetate).

(*Z*)-Diisopropyl 2-(2-(1-(3-fluorophenyl)-3-isopropoxy-3-oxoprop-1-en-2-yl)-5-methylphenyl)malonate (183)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **151** (1.35 g, 2.72 mmol) and anhydrous NMP (11 mL). Under a flow of argon $Pd(PPh_3)_4$ (418 mg, 0.362 mmol) was added carefully. The resulting suspension was degassed with argon for 30 minutes. Meanwhile, in a separate dried schlenk flask iodoarene **98** (732 mg, 1.81 mmol) was dissolved in anhydrous NMP (2 mL) and was also degassed

with argon for 30 minutes. Subsequently, the solution of iodoarene **98** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (518 mg, 2.72 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified twice by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1 to 20 : 1) followed by (silica gel : potassium carbonate, 9 : 1; toluene) to afford cyclization precursor **183** (489 mg, 56%) as a yellow oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.40 (1H, s, **7**-**H**), 7.36 – 7.24 (2H, m, **11**-**H**, **21**-**H**), 7.18 – 7.10 (3H, m, **10**-**H**, **20**-**H**, **24**-**H**), 7.02 (1H, app. t, *J* 8.5, **22**-**H**), 6.59 (1H, s, **18**-**H**), 5.14 – 4.98 (4H, m, **2**-**H**, **5**-**H**, **16**-**H**), 2.38 (3H, s, **9**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**), 1.20 (6H, d, *J* 6.3, **1**-**H**), 1.14 (6H, d, *J* 6.3, **17**-**H**).

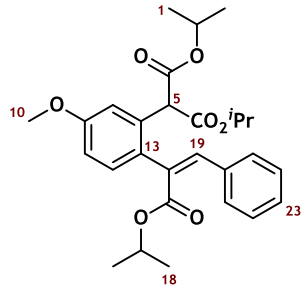
^{13}C (126 MHz, $CDCl_3$): δ 168.2 (**C4**), 167.7 (**C14**), 162.7 (d, $J_{F\text{-}C}$ 246, $\mathbf{C}_{Ar}$**23**), 138.3 ($\mathbf{C}_{Ar}$**8**), 137.6 (d, $J_{F\text{-}C}$ 8, $\mathbf{C}_{Ar}$**19**), 135.6 ($\mathbf{C}_{Ar}$**12**), 135.21 (d, $J_{F\text{-}C}$ 2, **C18**), 135.1 (**C13**), 131.6 ($\mathbf{C}_{Ar}$**6**), 130.2 ($\mathbf{C}_{Ar}$**7**), 129.9 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**21**), 129.1 ($\mathbf{C}_{Ar}$**11**), 128.8 ($\mathbf{C}_{Ar}$**10**), 124.4 (d, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**20**), 115.3 (d, $J_{F\text{-}C}$ 21, $\mathbf{C}_{Ar}$**22**), 115.2 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**24**), 69.4 (**C2**), 69.2 (**C16**), 54.8 (**C5**), 21.7 (**C1**), 21.7 (**C1**), 21.5 (**C17**), 21.4 (**C9**).

^{19}F (377 MHz, $CDCl_3$): δ −113.3

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1724 (C=O), 1610 (C=C), 1375, 1205, 1102 (C–O), 787.

HRMS (ESI): $C_{28}H_{33}FO_6Na$ $[M+Na]^+$ requires 507.2153; found 507.2140

(Z)-Diisopropyl 2-(2-(3-isopropoxy-3-oxo-1-phenylprop-1-en-2-yl)-5-methoxyphenyl) malonate (184)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **149** (978 mg, 2.04 mmol) and anhydrous NMP (7 mL). Under a flow of argon $Pd_2(dba)_3$ (125 mg, 0.136 mmol) and tri(2-furyl)phosphine **176** (126 mg, 0.544 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **82** (572 mg, 1.36 mmol) was dissolved in anhydrous NMP (1.5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **82** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (388 mg, 2.04 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (400 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1;

40-60 petrol : ethyl acetate, 30 : 1 to 10 : 1) to afford cyclization precursor **184** (328 mg, 50%) as a light yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.43 – 7.38 (2H, m, **21**-**H**), 7.38 – 7.28 (4H, m, **Ar**-**H**), 7.15 (1H, d, *J* 2.5, **7**-**H**), 6.89 (1H, dd, *J* 8.5, 2.4, **11**-**H**), 6.64 (1H, s, **19**-**H**), 5.11 (1H, s, **5**-**H**), 5.12 – 5.00 (3H, m, **2**-**H**, **17**-**H**), 3.83 (3H, s, **10**-**H**), 1.27 (6H, d, *J* 6.1, **1**-**H**), 1.21 (6H, d, *J* 6.1, **1**-**H**), 1.13 (6H, d, *J* 6.3, **18**-**H**).

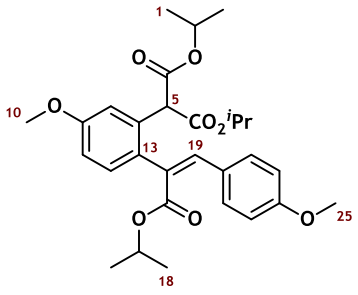
^{13}C (101 MHz, $CDCl_3$): δ 168.2 (**C15**), 168.1 (**C4**), 159.4 (C_{Ar}**8**), 136.8 (**C19**), 135.5 (C_{Ar}**20**), 133.5 (**C14**), 133.2 (C_{Ar}**6**), 131.4 (C_{Ar}**13**), 130.5 (C_{Ar}**12**), 128.5 (C_{Ar}**21**), 128.4 (C_{Ar}**23**), 128.4 (C_{Ar}**22**), 114.5 (C_{Ar}**7**), 114.2 (C_{Ar}**11**), 69.4 (**C2**), 68.9 (**C17**), 55.4 (**C10**), 55.0 (**C5**), 21.7 (**C1**), 21.7 (**C1**), 21.5 (**C18**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1723 (C=O), 1374, 1292, 1229, 1102 (C–O), 754.

HRMS (ESI): $C_{28}H_{34}O_7Na$ $[M+Na]^+$ requires 505.2197; found 505.2189

MP: 74 – 76 °C.

(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-1-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl)-5-methoxyphenyl) malonate (185)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **143** (955 mg, 1.87 mmol) and anhydrous NMP (9 mL). Under a flow of argon

$Pd_2(dba)_3$ (119 mg, 0.130 mmol) and tri(2-furyl)phosphine **176** (116 mg, 0.500 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **82** (525 mg, 1.25 mmol) was dissolved in anhydrous NMP (2 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **82** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (356 mg, 1.87 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (400 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 9 : 1) to afford cyclization precursor **185** (531 mg, 83%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.37 (2H, d, *J* 8.8, **21**-**H**), 7.30 – 7.26 (1H, m, **12**-**H**), 7.13 (1H, d, *J* 2.8, **7**-**H**), 6.90 – 6.85 (3H, m, **11**-**H**, **22**-**H**), 6.54 (1H, s, **19**-**H**), 5.09 (1H, s, **5**-**H**), 5.11 – 5.00 (3H, m, **2**-**H**, **17**-**H**), 3.83 (3H, s, **10**-**H**), 3.83 (3H, s, **25**-**H**), 1.26 (6H, d, *J* 6.1, **1**-**H**), 1.20 (6H, d, *J* 6.3, **1**-**H**), 1.16 (6H, d, *J* 6.3, **18**-**H**).

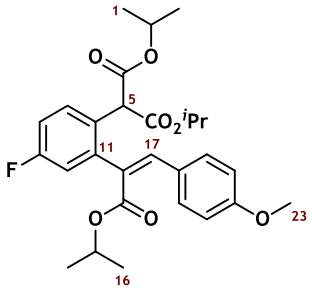
^{13}C (126 MHz, $CDCl_3$): δ 168.5 (**C15**), 168.1 (**C4**), 159.9 ($\mathbf{C}_{Ar}$**23**), 159.3 ($\mathbf{C}_{Ar}$**8**), 136.7 (**C19**), 133.2 ($\mathbf{C}_{Ar}$**6**), 131.8 ($\mathbf{C}_{Ar}$**13**), 131.2 (**C14**), 130.6 ($\mathbf{C}_{Ar}$**12**), 130.2 ($\mathbf{C}_{Ar}$**21**), 128.0 ($\mathbf{C}_{Ar}$**20**), 114.5 ($\mathbf{C}_{Ar}$**7**/$\mathbf{C}_{Ar}$**11**), 114.1 ($\mathbf{C}_{Ar}$**7**/$\mathbf{C}_{Ar}$**11**), 113.8 ($\mathbf{C}_{Ar}$**22**), 69.3 (**C2**), 68.8 (**C17**), 55.4 (**C10**), 55.4 (**C25**), 55.0 (**C5**), 21.7 (**C1**), 21.7 (**C1**), 21.6 (**C18**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1725 (C=O), 1607 (C=C), 1512, 1237, 1175, 1099 (C–O), 826.

HRMS (ESI): $C_{29}H_{36}O_8Na$ $[M+Na]^+$ requires 535.2302; found 535.2311

MP: 98 – 100 °C (hexane/ethyl acetate).

(*Z*)-Diisopropyl 2-(4-fluoro-2-(3-isopropoxy-1-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl)phenyl)malonate (187)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **143** (1.37 g, 2.69 mmol) and anhydrous NMP (11 mL). Under a flow of argon $Pd_2(dba)_3$ (164 mg, 0.179 mmol) and tri(2-furyl)phosphine **176** (166 mg, 0.716 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **116** (730 mg, 1.79 mmol) was dissolved in anhydrous NMP (2.5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **116** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (512 mg, 2.69 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (400 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over

anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) to afford cyclization precursor **187** (583 mg, 65%) as a yellow oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.58 (1H, dd, *J* 8.3, $J_{F\text{-}H}$ 5.6, **7**-**H**), 7.40 (2H, d, *J* 8.6, **19**-**H**), 7.12 – 7.05 (2H, m, **8**-**H**, **10**-**H**), 6.89 (2H, d, *J* 8.8, **20**-**H**), 6.60 (1H, s, **17**-**H**), 5.12 – 5.00 (4H, m, **2**-**H**, **5**-**H**, **15**-**H**), 3.84 (3H, s, **23**-**H**), 1.26 (6H, d, *J* 6.3, **1**-**H**), 1.19 (6H, d, *J* 6.3, **1**-**H**), 1.16 (6H, d, *J* 6.3, **16**-**H**).

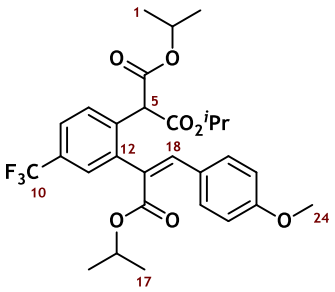
^{13}C (126 MHz, $CDCl_3$): δ 168.1 (**C4**), 167.5 (**C13**), 161.9 (d, $J_{F\text{-}C}$ 248, $\mathbf{C}_{Ar}$**9**), 160.2 ($\mathbf{C}_{Ar}$**21**), 141.3 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**11**), 137.8 (**C17**), 131.4 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**7**), 130.5 ($\mathbf{C}_{Ar}$**19**), 130.2 (d, $J_{F\text{-}C}$ 2, **C12**), 128.0 (d, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**6**), 127.4 ($\mathbf{C}_{Ar}$**18**), 116.4 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**10**), 115.3 (d, $J_{F\text{-}C}$ 21, $\mathbf{C}_{Ar}$**8**), 113.9 ($\mathbf{C}_{Ar}$**20**), 69.5 (**C2**), 69.1 (**C15**), 55.5 (**C23**), 54.2 (**C5**), 21.7 (**C1**), 21.7 (**C1**), 21.6 (**C16**).

^{19}F (470 MHz, $CDCl_3$): δ −114.2

IR: v_{max} (neat)/ cm^{-1} 2982 (C–H), 1725 (C=O), 1606 (C=C), 1512, 1255, 1217, 1161, 1100 (C–O), 827.

HRMS (ESI): $C_{28}H_{33}FO_7Na$ $[M+Na]^+$ requires 523.2103; found 523.2101

(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-1-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl)-4-(trifluoromethyl)phenyl)malonate (188)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **143** (844 mg, 1.66 mmol) and anhydrous NMP (6 mL). Under a flow of argon $Pd_2(dba)_3$ (101 mg, 0.110 mmol) and tri(2-furyl)phosphine **176** (102 mg, 0.440 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **115** (506 mg, 1.10 mmol) was dissolved in anhydrous NMP (1 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **115** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (314 mg, 1.65 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 75 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 75 mL) and brine (3 × 75 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) to afford cyclization precursor **188** (424 mg, 70%) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.75 (1H, d, *J* 8.1, **7**-**H**), 7.67 – 7.60 (2H, m, **8**-**H**, **11**-**H**), 7.43 (2H, d, *J* 8.6, **20**-**H**), 6.90 (2H, d, *J* 8.8, **21**-**H**), 6.64 (1H, s, **18**-**H**), 5.15 (1H, s, **5**-**H**), 5.13 – 5.02 (3H, m, **2**-**H**, **16**-**H**), 3.84 (3H, s, **24**-**H**), 1.27 (6H, d, *J* 6.1, **1**-**H**), 1.20 (6H, d, *J* 6.3, **1**-**H**), 1.17 (6H, d, *J* 6.3, **17**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 167.6 (**C4**), 167.3 (**C14**), 160.3 ($\mathbf{C}_{Ar}$**22**), 140.2 ($\mathbf{C}_{Ar}$**12**), 138.7 (**C18**), 136.0 ($\mathbf{C}_{Ar}$**6**), 130.6 ($\mathbf{C}_{Ar}$**20**), 130.3 ($\mathbf{C}_{Ar}$**7**), 130.1 (q, $J_{F\text{-}C}$ 33, $\mathbf{C}_{Ar}$**9**), 129.8 (**C13**), 127.3 ($\mathbf{C}_{Ar}$**19**), 126.7 (q, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**11**), 124.8 (q, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**8**), 124.0 (q, $J_{F\text{-}C}$ 272, **C10**), 113.9 ($\mathbf{C}_{Ar}$**21**), 69.8 (**C2**), 69.2 (**C16**), 55.4 (**C24**), 54.8 (**C5**), 21.7 (**C1**), 21.6 (**C1**), 21.6 (**C17**).

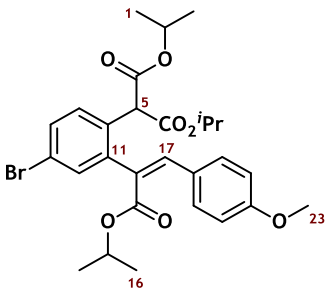
^{19}F (377 MHz, $CDCl_3$): δ −62.6

IR: ν_{max} (neat)/ cm^{-1} 2983 (C–H), 1727 (C=O), 1606 (C=C), 1512, 1334, 1166, 1100 (C–O), 828.

HRMS (ESI): $C_{29}H_{33}F_3O_7Na$ $[M+Na]^+$ requires 573.2071; found 573.2050

MP: 64 – 66 °C (hexane).

(*Z*)-Diisopropyl 2-(4-bromo-2-(3-isopropoxy-1-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl)phenyl)malonate (189)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **143** (316 mg, 0.620 mmol) and anhydrous NMP (2 mL). Under a flow of argon $Pd_2(dba)_3$ (38 mg, 0.041 mmol) and tri(2-furyl)phosphine **176** (38 mg, 0.164 mmol) were

added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **117** (194 mg, 0.410 mmol) was dissolved in anhydrous NMP (0.5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **117** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (118 mg, 0.620 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 20 mL) and ethyl acetate (100 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 20 mL) and brine (3 × 20 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) to afford cyclization precursor **189** (157 mg, 68%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.54 (1H, d, *J* 1.8, **10**-**H**), 7.52 – 7.45 (2H, m, **7**-**H**, **8**-**H**), 7.40 (2H, d, *J* 8.6, **19**-**H**), 6.89 (2H, d, *J* 8.8, **20**-**H**), 6.60 (1H, s, **17**-**H**), 5.12 – 4.99 (4H, m, **2**-**H**, **5**-**H**, **15**-**H**), 3.84 (3H, s, **23**-**H**), 1.25 (6H, d, *J* 6.3, **1**-**H**), 1.19 (6H, d, *J* 6.3, **1**-**H**), 1.17 (6H, d, *J* 6.3, **16**-**H**).

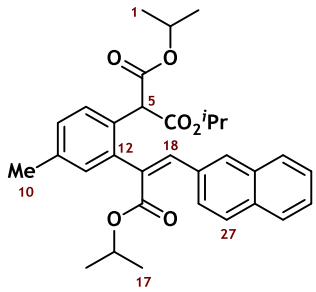
^{13}C (101 MHz, $CDCl_3$): δ 167.7 (**C4**), 167.4 (**C13**), 160.2 ($\mathbf{C_{Ar}}$**21**), 141.3 ($\mathbf{C_{Ar}}$**11**), 138.2 (**C17**), 132.4 ($\mathbf{C_{Ar}}$**10**), 131.2 ($\mathbf{C_{Ar}}$**7** & $\mathbf{C_{Ar}}$**8**), 130.5 ($\mathbf{C_{Ar}}$**19**), 129.9 ($\mathbf{C_{Ar}}$**6** & **C12**), 127.4 ($\mathbf{C_{Ar}}$**18**), 121.8 ($\mathbf{C_{Ar}}$**9**), 113.8 ($\mathbf{C_{Ar}}$**20**), 69.6 (**C2**), 69.1 (**C15**), 55.4 (**C23**), 54.5 (**C5**), 21.7 (**C1**), 21.6 (**C1**), 21.6 (**C16**).

IR: v_{max} (neat)/ cm^{-1} 2981 (C–H), 1727 (C=O), 1606 (C=C), 1512, 1255, 1195, 1100 (C–O), 826.

HRMS (ESI): $C_{28}H_{33}{}^{79}BrO_7Na$ $[M+Na]^+$ requires 583.1302; found 583.1309

MP: 63 – 65 °C (hexane/ethyl acetate).

(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-1-(naphthalen-2-yl)-3-oxoprop-1-en-2-yl)-4-methylphenyl) malonate (190)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **139** (955 mg, 1.80 mmol) and anhydrous NMP (7 mL). Under a flow of argon $Pd_2(dba)_3$ (110 mg, 0.120 mmol) and tri(2-furyl)phosphine **176** (111 mg, 0.480 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **97** (486 mg, 1.20 mmol) was dissolved in anhydrous NMP (1.5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **97** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (343 mg, 1.80 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (400 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified twice by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 40 : 1 to 30 : 1) followed by (silica gel : potassium carbonate, 9 : 1; toluene) to afford cyclization precursor **190** (284 mg, 46%) as a yellow oil.

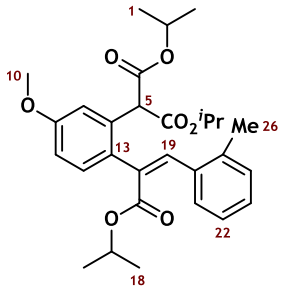
^{1}H (400 MHz, $CDCl_3$): δ 7.88 – 7.78 (4H, m, **20**-**H**, **Ar**-**H**), 7.57 – 7.45 (4H, m, **7**-**H**, **28**-**H**, **Ar**-**H**), 7.29 – 7.25 (1H, m, **11**-**H**), 7.22 (1H, dd, *J* 8.1, 1.2, **8**-**H**), 6.80 (1H, s, **18**-**H**), 5.14 (1H, s, **5**-**H**), 5.08 (3H, sept, *J* 6.2, **2**-**H**, **16**-**H**), 2.39 (3H, s, **10**-**H**), 1.27 (6H, d, *J* 6.1, **1**-**H**), 1.20 (6H, d, *J* 6.1, **1**-**H**), 1.12 (6H, d, *J* 6.4, **17**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 168.4 (**C4**), 168.2 (**C14**), 138.7 ($\mathbf{C_{Ar}}$**12**), 137.8 ($\mathbf{C_{Ar}}$**9**), 136.7 (**C18**), 134.2 (**C13**), 133.3 ($\mathbf{C_{Ar}}$**26**), 133.2 ($\mathbf{C_{Ar}}$**19**/$\mathbf{C_{Ar}}$**21**), 133.0 ($\mathbf{C_{Ar}}$**19**/$\mathbf{C_{Ar}}$**21**), 130.1 ($\mathbf{C_{Ar}}$**11**), 129.5 ($\mathbf{C_{Ar}}$**7**), 129.3 ($\mathbf{C_{Ar}}$**8**), 129.0 ($\mathbf{C_{Ar}}$**6**), 128.3 ($\mathbf{C_{Ar}}$**H**), 128.2 ($\mathbf{C_{Ar}}$**20**), 128.0 ($\mathbf{C_{Ar}}$**H**), 127.8 ($\mathbf{C_{Ar}}$**H**), 126.6 ($\mathbf{C_{Ar}}$**H**), 126.5 ($\mathbf{C_{Ar}}$**H**), 126.1 ($\mathbf{C_{Ar}}$**28**), 69.3 (**C2**), 69.1 (**C16**), 54.7 (**C5**), 21.8 (**C1**), 21.7 (**C1**), 21.6 (**C17**), 21.2 (**C10**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1724 (C=O), 1374, 1214, 1165, 1101 (C–O), 818.

HRMS (ESI): $C_{32}H_{36}O_6Na$ $[M+Na]^+$ requires 539.2404; found 539.2404

(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-3-oxo-1-(*o*-tolyl)prop-1-en-2-yl)-5-methoxyphenyl) malonate (186)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **147** (1.15 g, 2.34 mmol) and anhydrous NMP (9 mL). Under a flow of argon $Pd_2(dba)_3$ (143 mg, 0.156 mmol) and tri(2-furyl)phosphine **176** (145 mg, 0.624 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried

schlenk flask iodoarene **82** (655 mg, 1.56 mmol) was dissolved in anhydrous NMP (1.5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **82** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (446 mg, 2.34 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified twice by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1 to 20 : 1) followed by (silica gel : potassium carbonate, 9 : 1; toluene : diethyl ether, 1 : 0 to 99 : 1) to afford cyclization precursor **186** (484 mg, 62%) as a yellow oil.

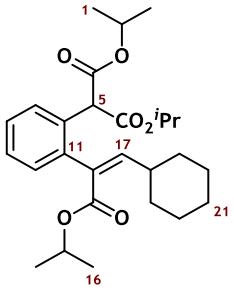
^{1}H (400 MHz, $CDCl_3$): δ 7.31 (2H, app. t, *J* 7.7, **12**-**H**, **23**-**H**), 7.25 – 7.13 (4H, m, **Ar**-**H**), 6.90 (1H, dd, *J* 8.5, 2.4, **11**-**H**), 6.84 (1H, s, **19**-**H**), 5.13 – 4.99 (3H, m, **2**-**H**, 5-**H**), 4.89 (1H, sept, *J* 6.2, **17**-**H**), 3.84 (3H, s, **10**-**H**), 2.34 (3H, s, **26**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**), 1.21 (6H, d, *J* 6.1, **1**-**H**), 0.98 (6H, d, *J* 6.3, **18**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 168.0 (**C4**), 167.7 (**C15**), 159.4 ($\mathbf{C_{Ar}8}$), 137.9 (**C19**), 136.1 ($\mathbf{C_{Ar}20}$), 135.9 ($\mathbf{C_{Ar}25}$), 135.0 (**C14**), 133.0 ($\mathbf{C_{Ar}6}$), 131.3 ($\mathbf{C_{Ar}13}$), 130.9 ($\mathbf{C_{Ar}12}$), 129.8 ($\mathbf{C_{Ar}24}$), 128.2 ($\mathbf{C_{Ar}21}$ & $\mathbf{C_{Ar}23}$), 125.6 ($\mathbf{C_{Ar}22}$), 114.4 ($\mathbf{C_{Ar}7}$), 114.2 ($\mathbf{C_{Ar}11}$), 69.4 (**C2**), 68.6 (**C17**), 55.4 (**C10**), 55.0 (**C5**), 21.7 (**C1**), 21.7 (**C1**), 21.4 (**C18**), 20.1 (**C26**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1727 (C=O), 1502, 1293, 1238, 1100 (C–O), 989.

HRMS (ESI): $C_{29}H_{36}O_7Na$ $[M+Na]^+$ requires 519.2353; found 519.2351

(*Z*)-Diisopropyl 2-(2-(1-cyclohexyl-3-isopropoxy-3-oxoprop-1-en-2-yl)phenyl) malonate (180)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **155** (677 mg, 1.40 mmol) and anhydrous NMP (5 mL). Under a flow of argon $Pd(PPh_3)_4$ (215 mg, 0.186 mmol) was added carefully. The resulting suspension was degassed with argon for 30 minutes. Meanwhile, in a separate dried schlenk flask iodoarene **78** (363 mg, 0.930 mmol) was dissolved in anhydrous NMP (1.0 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **78** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (267 mg, 1.40 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 50 mL) and ethyl acetate (150 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 50 mL) and brine (3 × 50 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 40 : 1) to afford cyclization precursor **180** (133 mg, 31%) as a colourless oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.54 (1H, d, *J* 7.6, **7**-**H**), 7.32 (1H, app. t, *J* 7.5, **8**-**H**), 7.29 – 7.23 (1H, m, **9**-**H**), 7.17 (1H, d, *J* 7.6, **10**-**H**), 5.76 (1H, d, *J* 9.9, **17**-**H**), 5.05 (3H, sept, *J* 6.3, **2**-**H**, **15**-**H**), 4.81 (1H, s, **5**-**H**), 3.07 – 2.94 (1H, m, **18**-**H**), 1.85 (2H, d, 11.6, **19**-$\mathbf{H_{eq}}$), 1.80 – 1.64 (3H, m, **20**-$\mathbf{H_{eq}}$, **21**-$\mathbf{H_{eq}}$), 1.43 – 1.29 (2H, m, **20**-$\mathbf{H_{ax}}$), 1.25 (6H, d, *J* 6.1, **1**-**H**), 1.21 (6H, d, *J* 6.1, **1**-**H**), 1.20 (6H, d, *J* 6.1, **16**-**H**), 1.22 – 1.03 (3H, m, **19**-$\mathbf{H_{ax}}$, **21**-$\mathbf{H_{ax}}$).

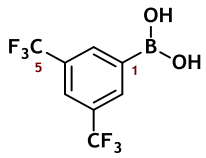
^{13}C (101 MHz, $CDCl_3$): δ 168.0 (**C4**), 166.5 (**C13**), 151.5 (**C17**), 139.6 ($\mathbf{C_{Ar}}$**11**), 131.7 ($\mathbf{C_{Ar}}$**6**), 130.6 (**C12**), 129.9 ($\mathbf{C_{Ar}}$**10**), 129.0 ($\mathbf{C_{Ar}}$**7**), 127.6 ($\mathbf{C_{Ar}}$**8**), 127.5 ($\mathbf{C_{Ar}}$**9**), 69.2 (**C2**), 68.2 (**C15**), 54.8 (**C5**), 38.5 (**C18**), 32.6 (**C19**), 26.0 (**C21**), 25.6 (**C20**), 21.7 (**C1**/**C16**), 21.6 (**C1**/**C16**), 21.6 (**C1**/**C16**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 2927 (C–H), 1730 (C=O), 1712 (C=O), 1374, 1205, 1101 (C–O), 987.

HRMS (ESI): $C_{27}H_{38}O_6Na$ $[M+Na]^+$ requires 481.2561; found 481.2563

5.3.4 Synthesis of Phase-Transfer Catalysts

(3,5-Bis(trifluoromethyl)phenyl) boronic acid (212)



A solution of *n*-butyllithium (1.6 M in hexanes, 23.0 mL, 36.9 mmol) was added dropwise over 30 minutes to a stirred solution of 1-bromo-3,5-bis(trifluoromethyl)benzene (9.00 g, 30.7 mmol) in anhydrous tetrahydrofuran (300 mL) at −78 °C. The reaction was stirred at this temperature for 1 hour and then triethyl borate (6.30 mL, 36.9 mmol) was added dropwise over 30 minutes. After stirring for 2 hours at −78 °C the reaction was left to warm to room temperature overnight. Saturated aqueous ammonium chloride (300 mL) was added and the

aqueous phase acidified with aqueous HCl (1 M). The biphasic mixture was extracted with ethyl acetate (3 × 300 mL) and the combined organic layers were washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by trituration (40-60 petrol) to afford boronic acid **212** (4.78 g, 60%) as a white solid with spectroscopic data in accordance with the literature.[229,230]

^{1}H (400 MHz, CD_3CN): δ 8.32 (2H, s, **2**-**H**), 8.07 (1H, s, **4**-**H**), 6.46 (2H, br. s, O**H**).

^{13}C (101 MHz, CD_3CN): δ 134.1 (**C**$_{Ar}$**2**), 130.2 (q, $J_{F\text{-}C}$ 32, **C**$_{Ar}$**3**), 124.0 (**C**$_{Ar}$**4**), 123.9 (q, $J_{F\text{-}C}$ 272, **C5**), 117.3 (**C**$_{Ar}$**1**).

^{11}B (160 MHz, CD_3CN): δ 27.8 (br. s).

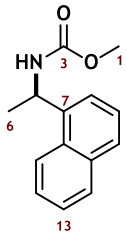
^{19}F (470 MHz, CD_3CN): δ −63.4

IR: ν_{max} (neat)/ cm^{-1} 3356 (O–H), 1617 (C=C), 1446, 1405, 1346, 1319, 1279, 1131, 680.

LRMS (FI): $[M]^+$ 258.0

MP: 205 – 207 °C, lit. MP: 219 – 220 °C (H_2O).[230]

Methyl (*R*)-(1-(naphthalen-1-yl)ethyl)carbamate (216)



According to a literature procedure,[140] methyl chloroformate (0.550 mL, 7.08 mmol) was added dropwise to a stirred solution of (*R*)-1-(naphthalen-1-yl)ethan-1-amine **215** (1.01 g, 5.90 mmol) and potassium carbonate (1.63 g, 11.8 mmol) in dioxane/water (1 : 1, 50 mL) at

0 °C. After 1 hour, aqueous HCl (3 M, 30 mL) was added and the reaction extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 4 : 1) to afford (*R*)-carbamate **216** (1.17 g, 87%) as a white solid with spectroscopic data in accordance with the literature.[140,231]

^{1}H (400 MHz, $CDCl_3$): δ 8.17 (1H, br. d, *J* 7.6, **15**-**H**), 7.89 (1H, d, *J* 7.8, **12**-**H**), 7.80 (1H, d, *J* 8.1, **10**-**H**), 7.61 – 7.55 (1H, m, **14**-**H**), 7.55 – 7.49 (2H, m, **8**-**H**, **13**-**H**), 7.49 – 7.42 (1H, m, **9**-**H**), 5.70 (1H, br. s, **5**-**H**), 5.31 (1H, br. d, *J* 7.1, N**H**), 3.68 (3H, s, **1**-**H**), 1.65 (3H, br. d, *J* 6.6, **6**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 156.2 (**C3**), 138.9 ($\mathbf{C}_{Ar}$**7**), 134.0 ($\mathbf{C}_{Ar}$**11**), 130.9 ($\mathbf{C}_{Ar}$**16**), 128.9 ($\mathbf{C}_{Ar}$**12**), 128.1 ($\mathbf{C}_{Ar}$**10**), 126.4 ($\mathbf{C}_{Ar}$**14**), 125.8 ($\mathbf{C}_{Ar}$**13**), 125.3 ($\mathbf{C}_{Ar}$**9**), 123.3 ($\mathbf{C}_{Ar}$**15**), 122.3 ($\mathbf{C}_{Ar}$**8**), 52.1 (**C1**), 46.6 (**C5**), 21.7 (**C6**).

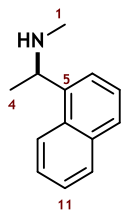
IR: ν_{max} (neat)/ cm^{-1} 3323 (N–H), 2977 (C–H), 1693 (C=O), 1510, 1240, 1065, 908, 776, 728.

LRMS (ESI): $[M+Na]^+$ 252.1

MP: 83 – 85 °C, lit. MP: 89 – 90 °C (hexane).[231]

$[\alpha]_D$ +45.0 (*c* 0.80, chloroform).

(*R*)-*N*-methyl-1-(naphthalen-1-yl)ethan-1-amine (217)



According to a literature procedure,[141] a solution of (*R*)-methyl carbamate **216** (1.06 g, 4.62 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise to a stirred solution

of lithium aluminium hydride (1 M in tetrahydrofuran, 9.25 mL, 9.25 mmol) at 0 °C. The mixture was refluxed for 1 hour and then cooled back down to 0 °C. The reaction was diluted with diethyl ether (10 mL) and then quenched sequentially, dropwise, under vigorous stirring with: water (0.350 mL), aqueous sodium hydroxide (15%, 0.350 mL) and water (1.05 mL). The resulting suspension was allowed to stir for 30 minutes at room temperature and was then filtered through Celite® with diethyl ether. The filtrate was concentrated *in vacuo* and the crude product (*R*)-amine **217** (836 mg, 98%), which did not require further purification, was isolated as a colourless oil with spectroscopic data in accordance with the literature.[232,233]

^{1}H (400 MHz, $CDCl_3$): δ 8.23 (1H, d, *J* 8.3, **13**-**H**), 7.92 (1H, d, *J* 7.8, **10**-**H**), 7.80 (1H, d, *J* 8.1, **8**-**H**), 7.71 (1H, d, *J* 7.1, **6**-**H**), 7.59 – 7.49 (3H, m, **7**-**H**, **11**-**H**, **12**-**H**), 4.58 (1H, q, *J* 6.6, **3**-**H**), 2.46 (3H, s, **1**-**H**), 2.35 (1H, br. s, N**H**), 1.57 (3H, d, *J* 6.6, **4**-**H**).

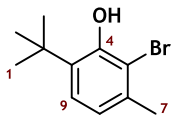
^{13}C (101 MHz, $CDCl_3$): δ 140.6 ($\mathbf{C}_{Ar}$**5**), 134.0 ($\mathbf{C}_{Ar}$**9**), 131.4 ($\mathbf{C}_{Ar}$**14**), 129.1 ($\mathbf{C}_{Ar}$**10**), 127.3 ($\mathbf{C}_{Ar}$**8**), 125.9 ($\mathbf{C}_{Ar}$**7**/$\mathbf{C}_{Ar}$**11**/$\mathbf{C}_{Ar}$**12**), 125.8 ($\mathbf{C}_{Ar}$**7**/$\mathbf{C}_{Ar}$**11**/$\mathbf{C}_{Ar}$**12**), 125.4 ($\mathbf{C}_{Ar}$**7**/$\mathbf{C}_{Ar}$**11**/$\mathbf{C}_{Ar}$**12**), 122.9 ($\mathbf{C}_{Ar}$**13**), 122.7 ($\mathbf{C}_{Ar}$**6**), 55.4 (**C3**), 34.6 (**C1**), 23.1 (**C4**).

IR: ν_{max} (neat)/ cm^{-1} 3328 (N–H), 2969 (C–H), 1596 (C=C), 1511, 1451, 1369, 1135, 800, 779.

LRMS (ESI): $[M+H]^+$ 186.1

$[\alpha]_D$ +89.0 (*c* 1.30, chloroform).

2-Bromo-6-(*tert*-butyl)-3-methylphenol (209)



According to a literature procedure,[139] *N*-bromosuccinimide (15.9 g, 89.5 mmol) was added in batches to a stirred solution of 2-(*tert*-butyl)-5-methylphenol **208** (14.0 g, 85.2 mmol) in 40-60 petrol (300 mL). The resulting mixture was stirred for 3 hours at room temperature, then filtered through silica gel with 40-60 petrol. After being concentrated *in vacuo* the product, bromophenol **209** (12.9 g, 62%), was afforded as a colourless oil with spectroscopic data in accordance with the literature.[139]

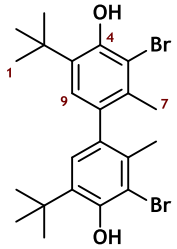
^{1}H (400 MHz, $CDCl_3$): δ 7.17 (1H, d, *J* 8.0, **9**-**H**), 6.80 (1H, d, *J* 8.0, **8**-**H**), 5.98 (1H, s, O**H**), 2.42 (3H, s, **7**-**H**), 1.46 (9H, s, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 150.4 ($\mathbf{C}_{Ar}\mathbf{4}$), 135.9 ($\mathbf{C}_{Ar}\mathbf{3}$/$\mathbf{C}_{Ar}\mathbf{6}$), 134.6 ($\mathbf{C}_{Ar}\mathbf{3}$/$\mathbf{C}_{Ar}\mathbf{6}$), 125.5 ($\mathbf{C}_{Ar}\mathbf{9}$), 121.6 ($\mathbf{C}_{Ar}\mathbf{8}$), 115.3 ($\mathbf{C}_{Ar}\mathbf{5}$), 35.1 (**C2**), 29.5 (**C1**), 23.0 (**C7**).

IR: ν_{max} (neat)/ cm^{-1} 3498 (O–H), 2959 (C–H), 1604 (C=C), 1487, 1403, 1272, 1193, 1143, 1032, 807, 595.

LRMS (ESI): $[M-H]^-$ 241.0

3,3′-Dibromo-5,5′-di-*tert*-butyl-2,2′-dimethyl-4,4′-dihydroxybiphenyl (210)



According to a literature procedure,[139] copper(I) chloride (172 mg, 1.74 mmol) was added to a stirred solution of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (0.270 mL, 1.80 mmol) in methanol (42 mL). After 20 minutes, bromophenol **209** (4.23 g, 17.4 mmol) was added and the mixture was stirred for 3 days open to the atmosphere. The methanol was removed *in vacuo* and the residue filtered through silica gel with diethyl ether. The solvent was removed *in vacuo* and purification by silica gel chromatography (40-60 petrol : diethyl ether, 99.9 : 0.1) afforded biaryl **210** (1.43 g, 34%) as a colourless solid with spectroscopic data in accordance with the literature.[139]

^{1}H (400 MHz, $CDCl_3$): δ 7.04 (2H, s, **9**-**H**), 6.02 (2H, s, O**H**), 2.17 (6H, s, **7**-**H**), 1.47 (18H, s, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 149.5 ($\mathbf{C}_{Ar}\mathbf{4}$), 134.2 ($\mathbf{C}_{Ar}\mathbf{3}$/$\mathbf{C}_{Ar}\mathbf{6}$/$\mathbf{C}_{Ar}\mathbf{8}$), 134.0 ($\mathbf{C}_{Ar}\mathbf{3}$/$\mathbf{C}_{Ar}\mathbf{6}$/$\mathbf{C}_{Ar}\mathbf{8}$), 127.6 ($\mathbf{C}_{Ar}\mathbf{9}$), 116.0 ($\mathbf{C}_{Ar}\mathbf{5}$), 35.2 (**C2**), 29.6 (**C1**), 20.9 (**C7**).[†]

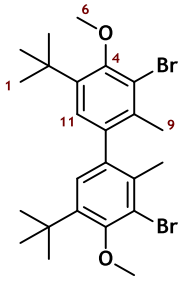
IR: ν_{max} (neat)/ cm^{-1} 3496 (O–H), 1596 (C=C), 1030.

LRMS (ESI): $[M-H]^-$ 483.0

MP: 183 – 184 °C, lit. MP: 183 – 184 °C.[139]

[†] *Two peaks coincide at 134.0 ppm*

3,3′-Dibromo-5,5′-di-*tert*-butyl-4,4′-dimethoxy-2,2′-dimethylbiphenyl (211)



According to a literature procedure,[139] methyl iodide (0.640 mL, 10.0 mmol) was added dropwise to a stirred suspension of biaryl **210** (1.99 g, 4.11 mmol) and anhydrous potassium carbonate (1.70 g, 12.3 mmol) in anhydrous *N*,*N*-dimethylformamide (50 mL). The mixture was stirred at room temperature for 18 hours and was then diluted with water (60 mL). The reaction was extracted with ethyl acetate (2 × 40 mL) and the combined organic layers washed with brine (2 × 40 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 97.5 : 2.5) to afford biaryl **211** (1.58 g, 75%) as a white solid with spectroscopic data in accordance with the literature.[139]

^{1}H (400 MHz, $CDCl_3$): δ 7.03 (2H, s, **11**-**H**), 3.99 (6H, s, **6**-**H**), 2.13 (6H, s, **9**-**H**), 1.42 (18H, s, **1**-**H**).

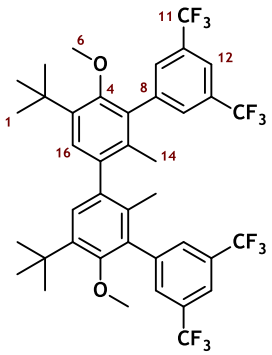
^{13}C (101 MHz, $CDCl_3$): δ 155.8 ($\mathbf{C}_{Ar}$**4**), 141.6 ($\mathbf{C}_{Ar}$**3**), 137.7 ($\mathbf{C}_{Ar}$**8**), 135.7 ($\mathbf{C}_{Ar}$**10**), 127.5 ($\mathbf{C}_{Ar}$**11**), 122.0 ($\mathbf{C}_{Ar}$**7**), 61.5 (**C6**), 35.3 (**C2**), 31.1 (**C1**), 21.0 (**C9**).

IR: ν_{max} (neat)/ cm^{-1} 2960 (C–H), 1465, 1359, 1262 (C–O), 1224, 1043, 909, 735.

LRMS (ESI): $[M+Na]^+$ 535.1

MP: 110 – 111 °C, lit. MP: 105 – 107 °C.[139]

5,5′-Di-*tert*-butyl-4,4′-dimethoxy-2,2′-dimethyl-3,3′-(3,5-bistrifluoromethylphenyl) biphenyl (213)



According to a literature procedure,[139] boronic acid **212** (2.20 g, 8.49 mmol) was added to a stirred solution of biaryl **211** (1.45 g, 2.83 mmol) in degassed tetrahydrofuran (50 mL). Tetrakis(triphenylphosphine)palladium(0) (327 mg, 0.280 mmol) and degassed aqueous potassium carbonate (2 M, 33 mL) were added and the mixture heated for 24 hours at 70 °C. After cooling to room temperature the reaction was acidified with aqueous HCl (2 M, 40 mL) and then extracted with diethyl ether (2 x 75 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was recrystallized (diethyl ether/methanol) to afford biaryl **213** (1.10 g, 50%) as a white solid with spectroscopic data in accordance with the literature.[139]

^{1}H (400 MHz, $CDCl_3$): δ 7.94 (4H, s, **9**-**H**), 7.92 (2H, s, **12**-**H**), 7.24 (2H, s, **16**-**H**), 3.22 (6H, s, **6**-**H**), 1.83 (6H, s, **14**-**H**), 1.47 (18H, s, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 156.3 ($\mathbf{C}_{Ar}$**4**), 141.1 ($\mathbf{C}_{Ar}$**3**), 140.5 ($\mathbf{C}_{Ar}$**8**), 137.6 ($\mathbf{C}_{Ar}$**13**), 133.3 ($\mathbf{C}_{Ar}$**7**), 133.1 ($\mathbf{C}_{Ar}$**9**), 131.6 (q, $J_{F\text{-}C}$ 34, $\mathbf{C}_{Ar}$**10**), 131.1 ($\mathbf{C}_{Ar}$**15**), 129.1 ($\mathbf{C}_{Ar}$**16**), 123.4 (q, $J_{F\text{-}C}$ 272, **C11**), 120.8 ($\mathbf{C}_{Ar}$**12**), 60.6 (**C6**), 35.0 (**C2**), 31.0 (**C1**), 18.1 (**C14**).

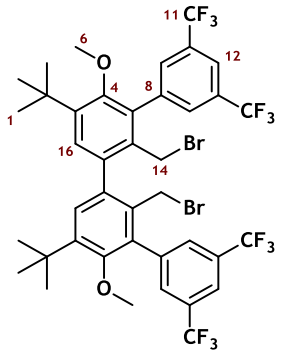
^{19}F (377 MHz, $CDCl_3$): δ −62.6, −62.6

IR: ν_{max} (neat)/ cm^{-1} 2962 (C–H), 1619 (C=C), 1467, 1355, 1280, 1179, 1137, 935, 736.

LRMS (EI): $[M]^+$ 778.2

MP: 179 – 181 °C (diethyl ether/methanol), lit. MP 183 – 184 °C (diethyl ether/methanol).[139]

5,5′-Di-*tert*-butyl-4,4′-dimethoxy-2,2′-bisbromomethyl-3,3′-(3,5-bistrifluoromethylphenyl) biphenyl (214)



According to a literature procedure,[139] *N*-bromosuccinimide (187 mg, 1.05 mmol) and azobisisobutyronitrile (1 mg, 0.010 mmol) were added to a stirred solution of biaryl **213** (390 mg, 0.500 mmol) in carbon tetrachloride (6 mL). The mixture was heated to reflux using a 60 W light bulb (1 cm from flask and covered in aluminium foil) for 20 minutes. The reaction was then allowed to cool to room temperature and filtered through a plug of silica gel using dichloromethane. The solvent was removed *in vacuo* to afford dibromobiaryl **214** (170 mg, 36%) as a white solid with spectroscopic data in accordance with the literature.[139]

^{1}H (400 MHz, $CDCl_3$): δ 8.19 (2H, s, **9**-**H**), 8.01 (2H, s, **9**-**H**), 7.99 (2H, s, **12**-**H**), 7.44 (2H, s, **16**-**H**), 3.99 (1H, AB_q, *J* 10.1, **14**-$\mathbf{H_A}$), 3.92 (1H, AB_q, *J* 10.1, **14**-$\mathbf{H_B}$), 3.25 (6H, s, **6**-**H**), 1.47 (18H, s, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 157.4 ($\mathbf{C}_{Ar}$**4**), 143.9 ($\mathbf{C}_{Ar}$**3**), 138.9 ($\mathbf{C}_{Ar}$**8**), 135.8 ($\mathbf{C}_{Ar}$**13**), 134.1 ($\mathbf{C}_{Ar}$**7**), 132.8 ($\mathbf{C}_{Ar}$**15**), 131.7 (q, $J_{F\text{-}C}$ 34, $\mathbf{C}_{Ar}$**10**), 131.6 (q, $J_{F\text{-}C}$ 34, $\mathbf{C}_{Ar}$**10**), 131.1 ($\mathbf{C}_{Ar}$**9**), 130.8 ($\mathbf{C}_{Ar}$**9**), 130.3

(C_{Ar}**16**), 123.3 (q, $J_{F\text{-}C}$ 276, **C11**), 123.3 (q, $J_{F\text{-}C}$ 276, **C11**), 121.6 (m, C_{Ar}**12**), 60.9 (**C6**), 35.4 (**C2**), 30.7 (**C1**), 30.2 (**C14**).

^{19}F (377 MHz, $CDCl_3$): δ −62.7, −62.8

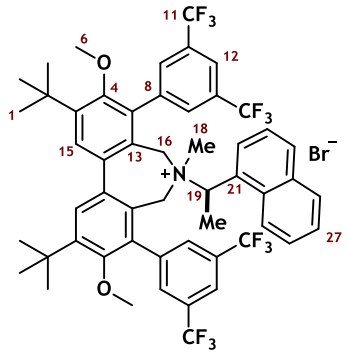
IR: ν_{max} (neat)/ cm^{-1} 2964 (C–H), 1618 (C=C), 1359, 1280, 1180, 1137, 907, 736.

LRMS (EI): $[M]^+$ 938.0

MP: 190 – 192 °C, lit. MP 90 – 92 °C.[139†]

(*R*)-2,10-Di-*tert*-butyl-3,9-dimethoxy-6-methyl-6-(1-naphthalen-1ylethyl)-4,8-bis(3,5-bistrifluoromethylphenyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]-azepinium bromide (*aka* Lygo)

(206)



According to a literature procedure,[139] (*R*)-amine **217** (35 mg, 0.190 mmol) and anhydrous potassium carbonate (141 mg, 1.02 mmol) were added to a stirred solution of dibromobiaryl **214** (157 mg, 0.170 mmol) in acetonitrile (4 mL) and dichloromethane (1 mL). The mixture was heated to 60 °C for 16 hours and after cooling to room temperature was filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (dichloromethane : methanol, 99 : 1 to 95 : 5) to afford the Lygo catalyst (*R*)-**206** (116 mg, 66%) as a white solid with spectroscopic data in accordance with the literature.[139]

† *The literature melting point was presumably misquoted in the original publication.*

^{1}H (400 MHz, $CDCl_3$): δ 8.23 (1H, s, **9**-**H**), 8.09 – 8.05 (2H, m, **9**-**H**, **29**-**H**), 8.00 (1H, s, **12**-**H**), 7.93 – 7.87 (2H, m, **9**-**H**, **26**-**H**), 7.83 (1H, s, **12**-**H**), 7.53 (1H, s, **15**-**H**), 7.52 (1H, s, **15**-**H**), 7.48 (1H, app. t, *J* 7.5, **24**-**H**), 7.36 – 7.26 (3H, m, **22**-**H**, **27**-**H**, **28**-**H**), 7.03 (1H, app. d, *J* 8.8, **23**-**H**), 6.81 (1H, s, **9**-**H**), 5.42 (1H, d, *J* 14.7, **16**-**H**), 5.18 (1H, q, *J* 6.7, **19**-**H**), 4.08 (1H, d, *J* 14.7, **16**-**H**), 3.38 (1H, d, *J* 13.1, **16**-**H**), 3.17 (3H, s, **6**-**H**), 2.97 (3H, s, **6**-**H**), 2.88 (3H, s, **18**-**H**), 2.82 (1H, d, *J* 13.1, **16**-**H**), 1.58 (9H, s, **1**-**H**), 1.43 (9H, s, **1**-**H**), 1.05 (3H, d, *J* 6.7, **20**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 158.2 ($\mathbf{C}_{Ar}$**4**), 158.0 ($\mathbf{C}_{Ar}$**4**), 147.8 ($\mathbf{C}_{Ar}$**3**), 147.8 ($\mathbf{C}_{Ar}$**3**), 137.7 ($\mathbf{C}_{Ar}$**8**), 137.4 ($\mathbf{C}_{Ar}$**14**), 137.2 ($\mathbf{C}_{Ar}$**8**), 137.1 ($\mathbf{C}_{Ar}$**14**), 135.5 ($\mathbf{C}_{Ar}$**7**), 134.4 ($\mathbf{C}_{Ar}$**7**), 134.0 ($\mathbf{C}_{Ar}$**25**), 133.8 (q, $J_{F\text{-}C}$ 34, $\mathbf{C}_{Ar}$**10**), 132.8 (q, $J_{F\text{-}C}$ 34, $\mathbf{C}_{Ar}$**10**), 132.6 (q, $J_{F\text{-}C}$ 34, $\mathbf{C}_{Ar}$**10**), 132.4 ($\mathbf{C}_{Ar}$**9**), 132.1 ($\mathbf{C}_{Ar}$**29**), 131.8 ($\mathbf{C}_{Ar}$**9**), 131.7 ($\mathbf{C}_{Ar}$**30**), 131.5 (q, $J_{F\text{-}C}$ 34, $\mathbf{C}_{Ar}$**10**), 130.7 ($\mathbf{C}_{Ar}$**9**), 130.5 ($\mathbf{C}_{Ar}$**26**), 129.8 ($\mathbf{C}_{Ar}$**9**), 129.2 ($\mathbf{C}_{Ar}$**15**), 128.8 ($\mathbf{C}_{Ar}$**15**), 128.3 ($\mathbf{C}_{Ar}$**27**), 127.2 ($\mathbf{C}_{Ar}$**21**), 126.7 ($\mathbf{C}_{Ar}$**24**), 126.2 ($\mathbf{C}_{Ar}$**28**), 125.4 ($\mathbf{C}_{Ar}$**13**), 125.0 ($\mathbf{C}_{Ar}$**22**), 123.5 ($\mathbf{C}_{Ar}$**13**), 122.8 ($\mathbf{C}_{Ar}$**12**), 122.8 (q, $J_{F\text{-}C}$ 274, **C11**), 122.7 (q, $J_{F\text{-}C}$ 274, **C11**), 122.7 (q, $J_{F\text{-}C}$ 274, **C11**), 122.4 (q, $J_{F\text{-}C}$ 274, **C11**), 121.9 ($\mathbf{C}_{Ar}$**12**), 119.2 ($\mathbf{C}_{Ar}$**23**), 62.1 (**C19**), 61.1 (**C6**), 60.8 (**C6**), 59.3 (**C16**), 57.7 (**C16**), 42.5 (**C18**), 35.9 (**C2**), 35.7 (**C2**), 30.7 (**C1**), 30.6 (**C1**), 15.7 (**C20**).[†]

^{19}F (470 MHz, $CDCl_3$): δ −61.8, −62.5, −62.7, −62.9

IR: ν_{max} (neat)/ cm^{-1} 2965 (C–H), 2188, 1619 (C=C), 1466, 1365, 1281, 1184, 1141, 909, 733.

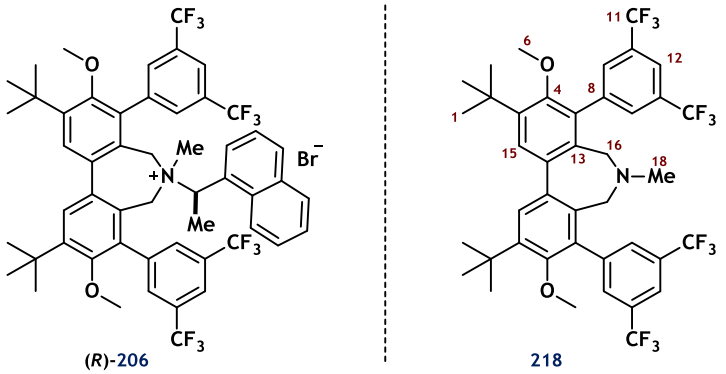
LRMS (ESI): $[M-Br^-]^+$ 960.2

MP: 102 – 104 °C, lit. MP: 102 – 104 °C (toluene).[139]

$[\alpha]_D$ +96.0 (*c* 0.40, chloroform).

[†] *Due to overlapping peaks and F-C coupling this spectrum was very complex. Therefore, all peaks may not be accounted for and assignment was very difficult.*

(*R*)-2,10-Di-*tert*-butyl-3,9-dimethoxy-6-methyl-6-(1-naphthalen-1ylethyl)-4,8-bis(3,5-bistrifluoromethylphenyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]-azepinium bromide (*aka* Lygo) (206) & 4,8-bis(3,5-bis(trifluoromethyl)phenyl)-2,10-di-*tert*-butyl-3,9-dimethoxy-6-methyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (218)



According to a literature procedure,[142] amine (*R*)-**217** (31 mg, 0.167 mmol) and anhydrous potassium carbonate (46 mg, 0.333 mmol) were added to a stirred solution of dibromobiaryl **214** (100 mg, 0.107 mmol) in acetonitrile (3 mL). The mixture was heated to 85 °C for 16 hours and after cooling to room temperature was filtered and concentrated *in vacuo*. The crude products were purified by silica gel chromatography (dichloromethane : methanol, 100 : 0 to 95 : 5) to afford the Lygo catalyst (*R*)-**206** (40 mg, 35%) as a white solid and amine **218** (51 mg, 59%) as a colourless oil.

Lygo catalyst (*R*)-**206**: *For spectroscopic data see page 263*.

Data for amine **218**:

^{1}H (500 MHz, $CDCl_3$): δ 8.03 (4H, br. s, **9**-**H**), 7.92 (2H, s, **12**-**H**), 7.56 (2H, s, **15**-**H**), 3.20 (6H, s, **6**-**H**), 3.11 (4H, br. s, **16**-**H**), 1.92 (3H, s, **18**-**H**), 1.51 (18H, s, **1**-**H**).

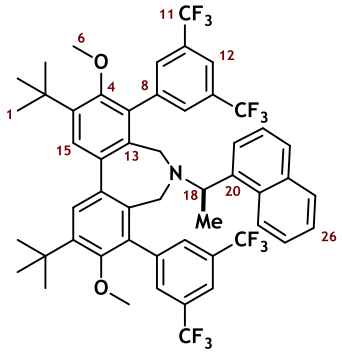
^{13}C (126 MHz, $CDCl_3$): δ 157.0 (**C**$_{Ar}$**4**), 142.8 (**C**$_{Ar}$**3**), 140.1 (**C**$_{Ar}$**8**), 137.1 (**C**$_{Ar}$**13**), 133.1 (**C**$_{Ar}$**7**), 132.4 (**C**$_{Ar}$**14**), 131.9 – 131.3 (m, **C**$_{Ar}$**9**), 131.5 (q, $J_{F\text{-}C}$ 34, **C**$_{Ar}$**10**), 127.4 (**C**$_{Ar}$**15**), 123.5 (q, $J_{F\text{-}C}$ 273, **C11**), 121.2 – 120.9 (m, **C**$_{Ar}$**12**), 61.0 (**C6**), 53.2 (**C16**), 43.2 (**C18**), 35.4 (**C2**), 31.1 (**C1**).

^{19}F (377 MHz, $CDCl_3$): δ −62.8

IR: ν_{max} (neat)/ cm^{-1} 2966 (C–H), 1619 (C=C), 1363, 1278, 1172, 1132, 892, 684.

HRMS (ESI): $C_{41}H_{40}F_{12}NO_2$ $[M+H]^+$ requires 806.2862; found 806.2888

(*R*)-4,8-Bis(3,5-bis(trifluoromethyl)phenyl)-2,10-di-*tert*-butyl-3,9-dimethoxy-6-(1-(naphthalen-1-yl)ethyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (235)



According to a literature procedure,[139] amine (*R*)-**215** (81 mg, 0.473 mmol) and anhydrous potassium carbonate (357 mg, 2.58 mmol) were added to a stirred solution of dibromobiaryl **214** (400 mg, 0.427 mmol) in chloroform (13 mL). The mixture was heated to 60 °C for 36 hours and after cooling to room temperature was filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : dichloromethane, 100 : 0 to 90 : 10) to afford the amine (*R*)-**235** (259 mg, 64%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.18 (2H, br. s, **9-H**), 7.90 – 7.43 (9H, m, **12-H**, **15-H**, **Ar-H**), 7.38 (2H, app. t, *J* 7.6, **Ar-H**), 7.34 – 7.18 (2H, m, **Ar-H**), 3.92 (2H, s, **16-H**), 3.76 (1H, br. s, **18-H**), 3.38 (2H, s, **16-H**), 3.07 (6H, s, **6-H**), 1.54 (18H, s, **1-H**), 0.89 (3H, d, *J* 6.3, **19-H**).

^{13}C (101 MHz, $CDCl_3$): δ 157.1 (**C**$_{Ar}$**4**), 143.0 (**C**$_{Ar}$**3**), 140.1 (**C**$_{Ar}$**20**), 139.5 (**C**$_{Ar}$**8**), 137.8 (**C**$_{Ar}$**13**), 133.9 (**C**$_{Ar}$**24**), 133.4 (**C**$_{Ar}$**7**), 132.6 (**C**$_{Ar}$**14**), 132.1 – 131.6 (m, **C**$_{Ar}$**9**), 131.5 (app. d, $J_{F\text{-}C}$ 34, **C**$_{Ar}$**10**), 131.4 – 130.9 (m, **C**$_{Ar}$**9**), 130.3 (**C**$_{Ar}$**29**), 128.9 (**C**$_{Ar}$**25**), 127.4 (**C**$_{Ar}$**15**), 127.2 (**C**$_{Ar}$**23**), 125.6 (**C**$_{Ar}$**H**), 125.3 (**C**$_{Ar}$**H**), 125.0 (**C**$_{Ar}$**H**), 123.4 (app. d, $J_{F\text{-}C}$ 273, **C11**), 123.3 (app. d, $J_{F\text{-}C}$ 272, **C11**), 122.2 (**C**$_{Ar}$**28**), 120.8 (br., **C**$_{Ar}$**12**), 60.6 (**C6**), 48.4 (**C16**), 41.5 (**C18**), 35.5 (**C2**), 31.1 (**C1**), 22.8 (**C19**).[†]

^{19}F (377 MHz, $CDCl_3$): δ −62.3, −62.8

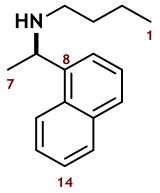
IR: v_{max} (neat)/ cm^{-1} 2961 (C–H), 1467, 1362, 1276, 1178, 1136, 903, 734.

HRMS (ESI): $C_{52}H_{48}F_{12}NO_2$ $[M+H]^+$ requires 946.3488; found 946.3484

MP: 140 – 142 °C.

$[\alpha]_D$ −118.6 (*c* 0.80, chloroform).

(*R*)-*N*-(1-(naphthalen-1-yl)ethyl)butan-1-amine (234)



According to a modified literature procedure,[234] dried 4 Å molecular sieves were added to a solution of (*R*)-1-(naphthalen-1-yl)ethan-1-amine **215** (500 mg, 2.92 mmol) in anhydrous dichloromethane (6 mL). Butyraldehyde (0.260 mL, 2.92) was added and the reaction stirred at room temperature for 3 hours. The reaction was then filtered through Celite® with dichloromethane and the filtrate concentrated *in vacuo*. The crude imine was dissolved in anhydrous methanol (12 mL) and cooled to 0 °C. Sodium borohydride (144 mg, 3.80 mmol)

[†] *Due to overlapping peaks and F-C coupling this spectrum was very complex. Therefore, all peaks may not be accounted for and assignment was very difficult.*

was added portionwise and then the reaction was stirred at room temperature for 1 hour. Saturated aqueous ammonium chloride (15 mL) was added and the reaction extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 7 : 3) to afford amine (*R*)-**234** (549 mg, 83%) as a colourless oil with spectroscopic data in accordance with the literature.[235]

^{1}H (400 MHz, $CDCl_3$): δ 8.24 (1H, d, *J* 8.6, **16**-**H**), 7.94 – 7.89 (1H, m, **13**-**H**), 7.78 (1H, d, *J* 8.3, **11**-**H**), 7.71 (1H, d, *J* 6.8, **9**-**H**), 7.58 – 7.48 (3H, m, **10**-**H**, **14**-**H**, **15**-**H**), 4.67 (1H, q, *J* 6.6, **6**-**H**), 2.62 (2H, app. qt, *J* 11.5, 7.2, **4**-**H**) 1.59 – 1.48 (5H, m, **3**-**H**, **7**-**H**), 1.45 – 1.30 (2H, m, **2**-**H**), 0.94 (3H, t, *J* 7.2, **1**-**H**).

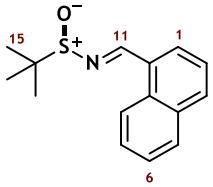
^{13}C (101 MHz, $CDCl_3$): δ 141.6 ($\mathbf{C}_{Ar}$**8**), 134.1 ($\mathbf{C}_{Ar}$**12**), 131.5 ($\mathbf{C}_{Ar}$**17**), 129.1 ($\mathbf{C}_{Ar}$**13**), 127.2 ($\mathbf{C}_{Ar}$**11**), 125.8 ($\mathbf{C}_{Ar}$**10**/$\mathbf{C}_{Ar}$**14**/$\mathbf{C}_{Ar}$**15**), 125.8 ($\mathbf{C}_{Ar}$**10**/$\mathbf{C}_{Ar}$**14**/$\mathbf{C}_{Ar}$**15**), 125.3 ($\mathbf{C}_{Ar}$**10**/$\mathbf{C}_{Ar}$**14**/$\mathbf{C}_{Ar}$**15**), 123.0 ($\mathbf{C}_{Ar}$**16**), 122.7 ($\mathbf{C}_{Ar}$**9**), 53.8 (**C6**), 47.9 (**C4**), 32.7 (**C3**), 23.7 (**C7**), 20.6 (**C2**), 14.1 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2959 (C–H), 1593 (C=C), 1511, 1455, 1377, 1130, 911, 782, 734.

LRMS (ESI): $[M+H]^+$ 228.2

$[\alpha]_D$ +63.7 (*c* 1.40, acetone).

(*R*,*E*)-2-methyl-*N*-(naphthalen-1-ylmethylene)propane-2-sulfinamide (238)



According to a modified literature procedure,[236] (*R*)-*tert*-butylsulfinamide **237** (424 mg, 3.50 mmol) was added to a suspension of $CuSO_4$ (1.36 g, 8.53 mmol) in anhydrous

dichloromethane (7 mL). After the addition of 1-naphthaldehyde (606 mg, 3.88 mmol) the reaction was stirred for 24 hours. A further portion of $CuSO_4$ (1.36 g, 8.53 mmol) was added and the resulting suspension left for 24 hours. The reaction was then filtered through Celite® with dichloromethane and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5 to 90 : 10) to afford sulfinamide (*R*)-**238** (806 mg, 89%) as a yellow oil with spectroscopic data in accordance with the literature.[237]

^{1}H (400 MHz, $CDCl_3$): δ 9.17 (1H, s, **11**-**H**), 9.04 (1H, d, *J* 8.6, **8**-**H**), 8.05 (1H, dd, *J* 7.2, 1.1, **5**-**H**), 8.01 (1H, d, *J* 8.3, **3**-**H**), 7.92 (1H, d, *J* 8.1, **1**-**H**), 7.65 (1H, ddd, *J* 8.5, 6.9, 1.5, **7**-**H**), 7.57 (2H, app. t, *J* 7.8, **2**-**H**, **6**-**H**), 1.33 (9H, s, **15**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 162.6 (**C11**), 134.0 ($\mathbf{C}_{Ar}$**4**), 133.4 ($\mathbf{C}_{Ar}$**3**), 132.1 ($\mathbf{C}_{Ar}$**5**), 131.3 ($\mathbf{C}_{Ar}$**9**), 129.5 ($\mathbf{C}_{Ar}$**10**), 128.9 ($\mathbf{C}_{Ar}$**1**), 128.1 ($\mathbf{C}_{Ar}$**7**), 126.6 ($\mathbf{C}_{Ar}$**6**), 125.3 ($\mathbf{C}_{Ar}$**2**), 124.5 ($\mathbf{C}_{Ar}$**8**), 57.8 (**C14**), 22.7 (**C15**).

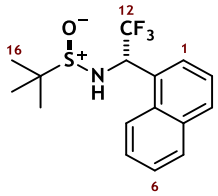
IR: ν_{max} (neat)/ cm^{-1} 2968 (C–H), 1690 (C=N), 1580, 1511, 1462, 1227, 1174, 1079 (S–O), 739.

LRMS (ESI): $[M+H]^+$ 282.1

$[\alpha]_D$ +61.4 (*c* 0.90, methanol).

(*R*)-2-Methyl-*N*-((*S*)-2,2,2-trifluoro-1-(naphthalen-1-yl)ethyl)propane-2-sulfinamide

(239)



According to a modified literature procedure,[154] a solution of $TMSCF_3$ (0.5 M in THF, 13.4 mL, 6.72 mmol) was added dropwise over 10 minutes to a solution of sulfinamide (*R*)-**238** (872 mg, 3.36 mmol) and TBAT (3.63 g, 6.72 mmol) in THF (53 mL) at −55 °C. After 2 hours, the solution was allowed to warm to 0 °C slowly over 1 hour before cooling it down to −30 °C. The reaction was quenched with saturated aqueous ammonium chloride (75 mL) and was extracted with ethyl acetate (3 × 75 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. ^{1}H NMR of the crude reaction mixture revealed a >20 : 1 mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 4 : 1 to 7 : 3) to afford sulfinamide (*R*,*S*)-**239** (761 mg, 69%, >20 : 1 dr) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.17 (1H, d, *J* 8.6, **8**-**H**), 7.97 – 7.89 (2H, m, **3**-**H**, **5**-**H**), 7.70 (1H, d, *J* 7.1, **1**-**H**), 7.64 (1H, app. td, *J* 7.7, 1.3, **7**-**H**), 7.60 – 7.48 (2H, m, **2**-**H**, **6**-**H**), 5.82 – 5.69 (1H, m, **11**-**H**), 3.83 (1H, d, *J* 5.1, N**H**), 1.27 (9H, s, **16**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 134.1 ($\mathbf{C}_{Ar}$**10**), 131.0 ($\mathbf{C}_{Ar}$**4**), 130.5 ($\mathbf{C}_{Ar}$**3**), 129.9 ($\mathbf{C}_{Ar}$**9**), 129.3 ($\mathbf{C}_{Ar}$**5**), 127.5 ($\mathbf{C}_{Ar}$**7**), 126.4 ($\mathbf{C}_{Ar}$**6**), 125.6 (br., $\mathbf{C}_{Ar}$**1**), 125.2 ($\mathbf{C}_{Ar}$**2**), 125.2 (q, $J_{F\text{-}C}$ 282, **C12**), 122.6 ($\mathbf{C}_{Ar}$**8**), 57.1 (**C15**), 56.1 (q, $J_{F\text{-}C}$ 30, **C11**), 22.4 (**C16**).

^{19}F (377 MHz, $CDCl_3$): δ −72.6

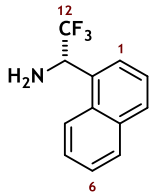
IR: ν_{max} (neat)/ cm^{-1} 3210 (N–H), 2962 (C–H), 1365, 1258, 1166, 1123, 1067 (S–O), 896, 798, 778.

HRMS (ESI): $C_{16}H_{18}F_3NOSNa$ $[M+Na]^+$ requires 352.0953; found 352.0956

MP: 129 – 131 °C.

$[\alpha]_D$ −143.8 (*c* 0.70, methanol).

(*S*)-2,2,2-Trifluoro-1-(naphthalen-1-yl)ethan-1-amine (240)



According to a modified literature procedure,[238] a solution of HCl (2 M in dioxane, 4.40 mL, 8.82 mmol) was added to a solution of sulfinamide (*R*,*S*)-**239** (726 mg, 2.20 mmol) in methanol (21 mL) at room temperature. After 5 hours, all volatile components were removed *in vacuo* and the resulting residue treated with aqueous NaOH (3 M, 20 mL). This mixture was extracted with ethyl acetate (3 × 25 mL) and the combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 9 : 1) to afford amine (*S*)-**240** (462 mg, 93%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 8.12 (1H, d, *J* 8.6, **8**-**H**), 7.95 – 7.88 (2H, m, **3**-**H**, **5**-**H**), 7.81 (1H, d, *J* 7.3, **1**-**H**), 7.63 – 7.58 (1H, m, **7**-**H**), 7.58 – 7.51 (2H, m, **2**-**H**, **6**-**H**), 5.35 (1H, q, $J_{F\text{-}H}$ 7.1, **11**-**H**), 1.92 (2H, br. s, N**H**$_2$).

^{13}C (101 MHz, $CDCl_3$): δ 133.9 (**C**$_{Ar}$**10**), 131.9 (**C**$_{Ar}$**4**/**C**$_{Ar}$**9**), 131.6 (**C**$_{Ar}$**4**/**C**$_{Ar}$**9**), 129.6 (**C**$_{Ar}$**3**), 129.2 (**C**$_{Ar}$**5**), 126.8 (**C**$_{Ar}$**7**), 126.2 (q, $J_{F\text{-}C}$ 282, **C12**), 126.0 (**C**$_{Ar}$**6**), 125.4 (**C**$_{Ar}$**2**), 125.4 (**C**$_{Ar}$**1**), 122.8 (**C**$_{Ar}$**8**), 52.8 (q, $J_{F\text{-}C}$ 30, **C11**).

^{19}F (377 MHz, $CDCl_3$): δ −72.5

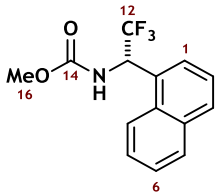
IR: ν_{max} (neat)/ cm^{-1} 3398 (N–H), 3054 (C–H), 1514, 1254, 1154, 1114, 894, 798, 778.

HRMS (ESI): $C_{12}H_{11}F_3N$ $[M+H]^+$ requires 226.0838; found 226.0838

MP: 54 – 56 °C.

$[\alpha]_D$ +17.6 (*c* 0.65, methanol).

Methyl (*S*)-(2,2,2-trifluoro-1-(naphthalen-1-yl)ethyl)carbamate (241)



According to a modified literature procedure,[140] methyl chloroformate (0.200 mL, 2.54 mmol) was added dropwise to a stirred solution of amine (*S*)-**240** (477 mg, 2.12 mmol) and potassium carbonate (585 mg, 4.24 mmol) in dioxane/water (1 : 1, 17 mL) at 0 °C. After 1 hour, aqueous HCl (3 M, 20 mL) was added and the reaction extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 19 : 1 to 9 : 1) to afford carbamate (*S*)-**241** (425 mg, 71%) as a white solid.

^{1}H (400 MHz, CD_3OD): δ 8.15 (1H, d, *J* 8.6, **8**-**H**), 7.91 (2H, d, *J* 8.3, **3**-**H**, **5**-**H**), 7.76 (1H, d, *J* 7.3, **1**-**H**), 7.58 (1H, ddd, *J* 8.4, 7.0, 1.3, **7**-**H**), 7.55 – 7.48 (2H, m, **2**-**H**, **6**-**H**), 6.33 (1H, q, $J_{F\text{-}H}$ 7.8, **11**-**H**), 3.68 (3H, s, **16**-**H**).

^{13}C (101 MHz, CD_3OD): δ 159.1 (**C14**), 135.4 ($\mathbf{C}_{Ar}$**10**), 132.8 ($\mathbf{C}_{Ar}$**4**), 131.1 ($\mathbf{C}_{Ar}$**9**), 130.9 ($\mathbf{C}_{Ar}$**3**), 130.2 ($\mathbf{C}_{Ar}$**5**), 128.2 ($\mathbf{C}_{Ar}$**7**), 127.2 ($\mathbf{C}_{Ar}$**6**), 126.9 ($\mathbf{C}_{Ar}$**1**), 126.8 (q, $J_{F\text{-}C}$ 281, **C12**), 126.3 ($\mathbf{C}_{Ar}$**2**), 123.8 ($\mathbf{C}_{Ar}$**8**), 53.3 (**C16**), 53.2 (q, $J_{F\text{-}C}$ 31, **C11**).

^{19}F (377 MHz, CD_3OD): δ −74.6

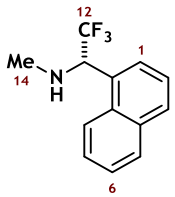
IR: ν_{max} (neat)/ cm^{-1} 3311 (N–H), 2950 (C–H), 1695 (C=O), 1528, 1312, 1253, 1187, 1120, 1049, 772, 650.

HRMS (ESI): $C_{14}H_{12}F_3NO_2Na$ $[M+Na]^+$ requires 306.0712; found 306.0712

MP: 113 – 115 °C.

$[\alpha]_D$ −12.9 (*c* 0.95, methanol).

(*S*)-2,2,2-Trifluoro-*N*-methyl-1-(naphthalen-1-yl)ethan-1-amine (242)



According to a literature procedure,[141] a solution of methyl carbamate (*S*)-**241** (393 mg, 1.39 mmol) in anhydrous tetrahydrofuran (3 mL) was added dropwise to a stirred solution of lithium aluminium hydride (1 M in tetrahydrofuran, 2.77 mL, 2.77 mmol) at 0 °C. The mixture was refluxed for 1 hour and then cooled back down to 0 °C. The reaction was diluted with diethyl ether (5 mL) and then quenched sequentially, dropwise, under vigorous

stirring with: water (0.105 mL), aqueous sodium hydroxide (15%, 0.105 mL) and water (0.315 mL). The resulting suspension was allowed to stir for 30 minutes at room temperature and was then filtered through Celite® with diethyl ether. The filtrate was concentrated *in vacuo* and the crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 9 : 1) to afford amine (*S*)-**242** (246 mg, 74%) as a colourless oil with spectroscopic data in accordance with the literature (amine (±)-**242** is known).[233]

^{1}H (400 MHz, $CDCl_3$): δ 8.21 (1H, d, *J* 8.3, **8**-**H**), 7.97 – 7.91 (2H, m, **3**-**H**, **5**-**H**), 7.80 (1H, d, *J* 7.3, **1**-**H**), 7.65 – 7.60 (1H, m, **7**-**H**), 7.60 – 7.54 (2H, m, **2**-**H**, **6**-**H**), 5.05 (1H, q, $J_{F\text{-}H}$ 7.3, **11**-**H**), 2.50 (3H, s, **14**-**H**), 1.89 (1H, br. s, N**H**).

^{13}C (101 MHz, $CDCl_3$): δ 134.0 ($\mathbf{C}_{Ar}$**10**), 132.4 ($\mathbf{C}_{Ar}$**4**), 130.3 ($\mathbf{C}_{Ar}$**9**), 129.6 ($\mathbf{C}_{Ar}$**3**), 129.2 ($\mathbf{C}_{Ar}$**5**), 126.8 ($\mathbf{C}_{Ar}$**7**), 126.0 (q, $J_{F\text{-}C}$ 282, **C12**), 125.9 ($\mathbf{C}_{Ar}$**6**), 125.8 ($\mathbf{C}_{Ar}$**1**), 125.4 ($\mathbf{C}_{Ar}$**2**), 122.8 ($\mathbf{C}_{Ar}$**8**), 61.1 (q, $J_{F\text{-}C}$ 29, **C11**), 34.9 (**C14**).

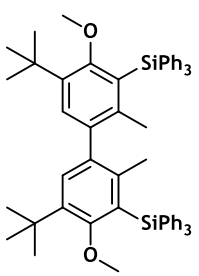
^{19}F (377 MHz, $CDCl_3$): δ −72.7

IR: ν_{max} (neat)/ cm^{-1} 3356 (N–H), 2960 (C–H), 1513, 1351, 1264, 1153, 1133, 1107, 846, 798, 776.

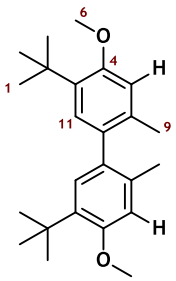
HRMS (ESI): $C_{13}H_{13}F_3N$ $[M+H]^+$ requires 240.0995; found 240.0988

$[\alpha]_D$ +37.9 (*c* 1.00, chloroform).

Attempted synthesis of (5,5'-di-*tert*-butyl-4,4'-dimethoxy-2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(triphenylsilane) (232) and isolation of 5,5'-di-*tert*-butyl-4,4'-dimethoxy-2,2'-dimethyl-1,1'-biphenyl (224)



232



224

According to a modified literature procedure,[168] *tert*-butyllithium (1.7 M in pentane, 2.90 mL, 4.88 mmol) was added dropwise to a solution of biaryl **211** (500 mg, 0.976 mmol) in anhydrous THF (24 mL) at −78 °C. After 15 minutes, a solution of chlorotriphenylsilane (867 mg, 2.94 mmol) in anhydrous THF (12 mL) was added dropwise. The reaction was allowed to reach room temperature overnight and was then quenched with water (40 mL). The reaction was extracted with dichloromethane (3 × 50 mL) and the combined organic layers washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 100 : 0 to 99 : 1) to afford biaryl **224** (320 mg, 92%) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.04 (2H, s, **11**-**H**), 6.78 (2H, s, **7**-**H**), 3.89 (6H, s, **6**-**H**), 2.07 (6H, s, **9**-**H**), 1.38 (18H, s, **1**-**H**).

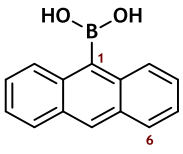
^{13}C (126 MHz, $CDCl_3$): δ 157.3 ($\mathbf{C}_{Ar}$**4**), 135.3 ($\mathbf{C}_{Ar}$**3**), 134.8 ($\mathbf{C}_{Ar}$**8**), 133.5 ($\mathbf{C}_{Ar}$**10**), 128.7 ($\mathbf{C}_{Ar}$**11**), 112.9 ($\mathbf{C}_{Ar}$**7**), 55.1 (**C6**), 34.7 (**C2**), 30.1 (**C1**), 20.0 (**C9**).

IR: ν_{max} (neat)/ cm^{-1} 2953 (C–H), 1493, 1361, 1226, 1090, 1050, 844, 711.

HRMS (EI): $C_{24}H_{34}O_2$ $[M]^+$ requires 354.2559; found 354.2552

MP: 158 – 160 °C.

Anthracen-9-ylboronic acid (221)



A solution of *n*-butyllithium (1.5 M in hexanes, 3.10 mL, 4.67 mmol) was added dropwise over 30 minutes to a stirred solution of 9-bromoanthracene **257** (1.06 g, 3.89 mmol) in anhydrous tetrahydrofuran (39 mL) at −78 °C. The reaction was stirred at this temperature for 1 hour and then triethyl borate (0.660 mL, 3.89 mmol) was added dropwise over 30 minutes. After stirring for 2 hours at −78 °C the reaction was left to warm to room temperature overnight. Saturated aqueous ammonium chloride (50 mL) was added and the aqueous phase acidified with aqueous HCl (1 M). The biphasic mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with brine (75 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by trituration (40-60 petrol) to afford boronic acid **221** (507 mg, 59%) as a light brown solid with spectroscopic data in accordance with the literature.[239,240]

^{1}H (400 MHz, $(CD_3)_2SO$): δ 8.83 (2H, s, O**H**), 8.53 (1H, s, **8**-**H**), 8.13 – 8.05 (2H, m, **3**-**H**), 8.04 – 7.99 (2H, m, **6**-**H**), 7.55 – 7.47 (4H, m, **4**-**H**, **5**-**H**).

^{13}C (101 MHz, $(CD_3)_2SO$): δ 132.8 ($\mathbf{C}_{Ar}$**2**), 130.8 ($\mathbf{C}_{Ar}$**7**), 129.1 ($\mathbf{C}_{Ar}$**6**), 128.5 ($\mathbf{C}_{Ar}$**3**), 126.0 ($\mathbf{C}_{Ar}$**8**), 125.2 ($\mathbf{C}_{Ar}$**4**/$\mathbf{C}_{Ar}$**5**), 125.0 ($\mathbf{C}_{Ar}$**4**/$\mathbf{C}_{Ar}$**5**).[†]

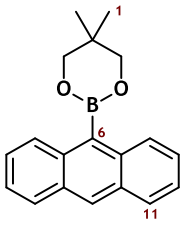
[†] ***C**$_{Ar}$**1** was not observed.*

IR: ν_{max} (neat)/ cm^{-1} 3283 (O–H), 2953 (C–H), 1416, 1299, 1268, 1137, 1016, 947, 883, 726.

LRMS (ESI): $[M+Na]^+$ 245.1

MP: 210 – 212 °C, lit. MP: 217 °C (H_2O).[239]

2-(Anthracen-9-yl)-5,5-dimethyl-1,3,2-dioxaborinane (258)



According to a modified literature procedure,[241] a solution of *n*-butyllithium (1.6 M in hexanes, 3.20 mL, 5.06 mmol) was added dropwise over 1 hour to a stirred solution of 9-bromoanthracene **257** (1.00 g, 3.89 mmol) and triisopropyl borate (1.35 mL, 5.84 mmol) in anhydrous tetrahydrofuran (30 mL) at −78 °C. The reaction was stirred at this temperature for 1 hour and was left to warm to room temperature overnight. Aqueous HCl (2 M, 20 mL) was added and the biphasic mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude boronic acid **221** was dissolved in THF (7 mL) and neopentyl glycol (312 mg, 3.00 mmol) was added. After stirring overnight at room temperature the reaction was concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 99 : 1 to 90 : 10) to afford boronic ester **258** (373 mg, 33%) as a tan solid.

^{1}H (400 MHz, CD_3Cl): δ 8.46 (1H, s, **13**-**H**), 8.32 (2H, d, *J* 8.8, **8**-**H**), 8.01 (2H, d, *J* 8.1, **11**-**H**), 7.53 – 7.43 (4H, m, **9**-**H**, **10**-**H**), 4.05 (4H, s, **3**-**H**), 1.29 (6H, s, **1**-**H**).

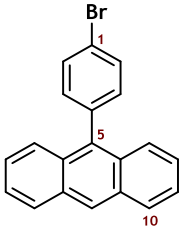
^{13}C (101 MHz, CD_3Cl): δ 135.0 (**C**$_{Ar}$**7**), 131.4 (**C**$_{Ar}$**12**), 128.9 (**C**$_{Ar}$**11**), 128.7 (**C**$_{Ar}$**8**), 128.5 (**C**$_{Ar}$**13**), 125.5 (**C**$_{Ar}$**9**), 125.0 (**C**$_{Ar}$**10**), 72.9 (**C3**), 32.0 (**C2**), 22.6 (**C1**).[†]

IR: ν_{max} (neat)/ cm^{-1} 2964 (C–H), 1673, 1476, 1413, 1289, 1238, 1170, 1012, 734.

HRMS (FI): $C_{19}H_{19}BO_2$ $[M]^+$ requires 290.1482; found 290.1488

MP: 122 – 124 °C.

9-(4-Bromophenyl)anthracene (229)



According to a literature procedure,[150] a solution of *n*-butyllithium (1.6 M in hexanes, 16.4 mL, 25.4 mmol) was added dropwise over 30 minutes to a stirred solution of 1,4-dibromobenzene **227** (5.00 g, 21.2 mmol) in anhydrous diethyl ether (100 mL) at −78 °C. The reaction was stirred at this temperature for 1 hour and then anthrone (4.12 g, 21.2 mmol) was added portionwise over 20 minutes. The reaction was left to warm to room temperature overnight before pouring it on to a mixture of crushed ice and aqueous HCl (0.5 M, 50 mL). After the ice had melted the layers were separated and the organic layer washed with saturated aqueous sodium bicarbonate (50 mL). The diethyl ether was removed *in vacuo* and the residue dissolved in refluxing methanol (85 mL). Aqueous HCl (6 M, 15 mL) was added and refluxing continued for 2 hours. After cooling to room temperature the product precipitated and was filtered off. The crude product was purified by recrystallization

[†] ***C***$_{Ar}$***6*** *was not observed.*

(ethanol) to afford bromoarene **229** (2.19 g, 31%) as a white solid with spectroscopic data in accordance with the literature.[150,242]

^{1}H (400 MHz, CD_3Cl): δ 8.53 (1H, s, **12**-**H**), 8.07 (2H, d, *J* 8.6, **10**-**H**), 7.75 (2H, d, *J* 8.3, **2**-**H**), 7.67 (2H, d, *J* 8.8, **7**-**H**), 7.50 (2H, app. t, *J* 7.3, **9**-**H**), 7.44 – 7.37 (2H, m, **8**-**H**), 7.34 (2H, d, *J* 8.3, **3**-**H**).

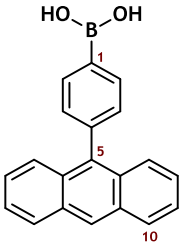
^{13}C (101 MHz, CD_3Cl): δ 137.9 ($\mathbf{C}_{Ar}$**4**), 135.6 ($\mathbf{C}_{Ar}$**5**), 133.1 ($\mathbf{C}_{Ar}$**2**), 131.8 ($\mathbf{C}_{Ar}$**3**), 131.5 ($\mathbf{C}_{Ar}$**6**), 130.2 ($\mathbf{C}_{Ar}$**11**), 128.6 ($\mathbf{C}_{Ar}$**10**), 127.1 ($\mathbf{C}_{Ar}$**12**), 126.6 ($\mathbf{C}_{Ar}$**7**), 125.8 ($\mathbf{C}_{Ar}$**8**), 125.3 ($\mathbf{C}_{Ar}$**9**), 121.9 ($\mathbf{C}_{Ar}$**1**).

IR: ν_{max} (neat)/ cm^{-1} 3052 (C–H), 1517, 1485, 1386, 1359, 1011, 887, 736, 608.

HRMS (EI): $C_{20}H_{13}{}^{79}Br$ $[M]^+$ requires 332.0201; found 332.0197

MP: 178 – 180 °C (ethanol), lit. MP: 174 °C (ethanol).[150]

(4-(Anthracen-9-yl)phenyl)boronic acid (230)



A solution of *n*-butyllithium (1.6 M in hexanes, 1.13 mL, 1.80 mmol) was added dropwise over 30 minutes to a stirred solution of bromoarene **229** (500 mg, 1.50 mmol) in anhydrous tetrahydrofuran (15 mL) at −78 °C. The reaction was stirred at this temperature for 1 hour and then triethyl borate (0.260 mL, 1.50 mmol) was added dropwise over 30 minutes. After stirring for 2 hours at −78 °C the reaction was left to warm to room temperature overnight. Saturated aqueous ammonium chloride (20 mL) was added and the aqueous phase acidified with aqueous HCl (1 M). The biphasic mixture was extracted with ethyl acetate (3 × 25 mL)

and the combined organic layers were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by trituration (40-60 petrol) to afford boronic acid **230** (246 mg, 55%) as a yellow solid.

^{1}H (400 MHz, $(CD_3)_2SO$): δ 8.67 (1H, s, **12**-**H**), 8.28 (2H, d, *J* 7.8, **2**-**H**), 8.15 (2H, d, *J* 8.6, **10**-**H**), 7.64 (2H, d, *J* 8.8, **7**-**H**), 7.56 – 7.35 (6H, m, **Ar**-**H**).

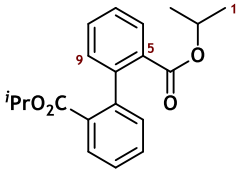
^{13}C (101 MHz, $(CD_3)_2SO$): δ 139.2 ($\mathbf{C}_{Ar}$**4**), 136.8 ($\mathbf{C}_{Ar}$**5**), 133.8 ($\mathbf{C}_{Ar}$**2**), 130.9 ($\mathbf{C}_{Ar}$**6**), 130.1 ($\mathbf{C}_{Ar}$**3**), 129.5 ($\mathbf{C}_{Ar}$**11**), 128.4 ($\mathbf{C}_{Ar}$**10**), 126.4 ($\mathbf{C}_{Ar}$**12**), 126.2 ($\mathbf{C}_{Ar}$**7**), 125.8 ($\mathbf{C}_{Ar}$**8**), 125.3 ($\mathbf{C}_{Ar}$**9**).[†]

IR: ν_{max} (neat)/ cm^{-1} 3426 (O–H), 1658, 1606, 1404, 1303, 1100, 909, 732.

HRMS (ESI): $C_{20}H_{14}BO_2$ $[M-H]^-$ requires 297.1096; found 297.0464

MP: 232 – 234 °C.

Diisopropyl [1,1'-biphenyl]-2,2'-dicarboxylate (248)



Concentrated sulfuric acid (10 mL) was added to a stirred solution of diphenic acid **247** (10.0 g, 41.3 mmol) in isopropanol (100 mL). The reaction was heated to 80 °C for 24 hours and was then allowed to cool to room temperature. After concentration *in vacuo*, water (100 mL) and dichloromethane (100 mL) were added. The layers were separated and the aqueous fraction was extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was

[†] $\mathbf{C}_{Ar}$***1*** *was not observed.*

purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5) and recrystallization (40-60 petrol) to afford ester **248** (7.75 g, 58%) as a white solid with spectroscopic data in accordance with the literature.[243]

^{1}H (400 MHz, $CDCl_3$): δ 8.00 (2H, dd, *J* 7.8, 1.3, **6**-**H**), 7.49 – 7.43 (2H, m, **8**-**H**), 7.42 – 7.36 (2H, m, **7**-**H**), 7.16 (2H, dd, *J* 7.6, 1.0, **9**-**H**), 4.92 (2H, sept, *J* 6.3, **2**-**H**), 0.98 (6H, d, *J* 6.3, **1**-**H**), 0.88 (6H, d, *J* 6.3, **1**-**H**).

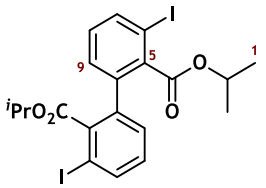
^{13}C (101 MHz, $CDCl_3$): δ 166.5 (**C4**), 143.2 ($\mathbf{C}_{Ar}$**10**), 130.9 ($\mathbf{C}_{Ar}$**8**), 130.3 ($\mathbf{C}_{Ar}$**5**), 130.0 ($\mathbf{C}_{Ar}$**9**), 129.8 ($\mathbf{C}_{Ar}$**6**), 126.8 ($\mathbf{C}_{Ar}$**7**), 67.8 (**C2**), 21.2 (**C1**), 21.1 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 2937 (C–H), 1724 (C=O), 1600, 1445, 1350, 1295, 1108 (C–O), 918, 760.

LRMS (ESI): $[M+Na]^+$ 349.1

MP: 72 – 74 °C (40-60 petrol), lit. MP: 68 – 70 °C.[243]

Diisopropyl 3,3'-diiodo-[1,1'-biphenyl]-2,2'-dicarboxylate (250)



This transformation was performed according to modified literature procedures.[156,157]

Preparation of TMPMgCl•LiCl in THF: 2,2,6,6-tetramethylpiperidine (10.7 mL, 63.0 mmol) was added to a stirred solution of ^{i}PrMgCl•LiCl (1 M in THF, 60 mL, 60 mmol) at room temperature and was then left to stir for 24 hours. Titration against benzoic acid using

(4-phenylazo)diphenylamine as an indicator in THF revealed a concentration of 0.95 M of TMPMgCl•LiCl in THF.

*Preparation of TMP_2Mg•2LiCl in THF & diiodoarene **250**:* A solution of *n*-butyllithium (1.6 M in hexanes, 34.2 mL, 54.7 mmol) was added to anhydrous THF (56 mL) at −40 °C. After 15 minutes, 2,2,6,6-tetramethylpiperidine (9.30 mL, 54.7 mmol) was added and the reaction warmed to 0 °C. After 30 minutes, TMPMgCl•LiCl (0.95 M in THF, 57.6 mL, 54.7 mmol) was added and the resulting solution stirred for 30 minutes at 0 °C. The reaction was then warmed to room temperature and stirred for 1 hour before concentration *in vacuo*. The resulting pale brown solid was redissolved in THF (63 mL) and cooled to 0 °C. A solution of diester **248** (3.57 g, 10.9 mmol) in THF (10 mL) was added dropwise into the TMP_2Mg•2LiCl solution. After warming to room temperature the solution was stirred for 16 hours before cooling down to −78 °C. Iodine (22.2 g, 87.5 mmol) dissolved in anhydrous THF (80 mL) was then added dropwise over 30 minutes and the resulting mixture allowed to warm to room temperature overnight. The reaction was quenched with aqueous HCl (1 M, 150 mL) and diluted with ethyl acetate (200 mL). The layers were separated and the aqueous fraction extracted with ethyl acetate (2 × 200 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1) to afford diiodoarene **250** (3.91 g, 62%) as a pale yellow solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.86 (2H, d, *J* 8.2, **7**-**H**), 7.28 (2H, d, *J* 6.9, **9**-**H**), 7.09 (2H, app. t, *J* 7.7, **8**-**H**), 4.98 (2H, sept, *J* 6.3, **2**-**H**), 1.21 (6H, d, *J* 6.3, **1**-**H**), 0.88 (6H, d, *J* 6.3, **1**-**H**).

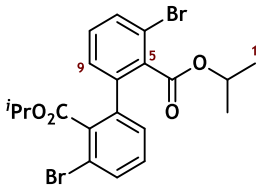
^{13}C (126 MHz, $CDCl_3$): δ 167.3 (**C4**), 140.1 (**C**$_{Ar}$**10**), 138.9 (**C**$_{Ar}$**7**), 138.2 (**C**$_{Ar}$**5**), 129.9 (**C**$_{Ar}$**8**), 129.7 (**C**$_{Ar}$**9**), 92.0 (**C**$_{Ar}$**6**), 69.4 (**C2**), 21.7 (**C1**), 21.1 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2980 (C–H), 1722 (C=O), 1432, 1274, 1098 (C–O), 1058, 913, 782.

HRMS (ESI): $C_{20}H_{20}I_2O_4Na$ $[M+Na]^+$ requires 600.9343; found 600.9331

MP: 115 – 117 °C (40-60 petrol).

Diisopropyl 3,3'-dibromo-[1,1'-biphenyl]-2,2'-dicarboxylate (249)



$TMP_2Mg•2LiCl$ was prepared as described previously.

A solution of diester **248** (2.62 g, 8.03 mmol) in THF (6 mL) was added dropwise into a solution of $TMP_2Mg•2LiCl$ (0.8 M in THF, 32.1 mmol) at 0 °C. After warming to room temperature the solution was stirred for 16 hours before cooling down to −78 °C. Bromine (3.31 mL, 64.2 mmol) was then added dropwise over 30 minutes and the resulting mixture allowed to warm to room temperature overnight. The reaction was quenched with aqueous HCl (1 M, 100 mL) and diluted with ethyl acetate (100 mL). The layers were separated and the aqueous fraction extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1) to afford dibromoarene **249** (1.56 g, 40%) as a white solid with spectroscopic data in accordance with the literature.[155]

^1H (400 MHz, $CDCl_3$): δ 7.65 – 7.58 (2H, m, **7**-**H**), 7.29 – 7.23 (4H, m, **8**-**H**, **9**-**H**), 4.99 (2H, sept, *J* 6.3, **2**-**H**), 1.20 (6H, br. d, *J* 3.3, **1**-**H**), 0.90 (6H, br. d, *J* 4.3, **1**-**H**).

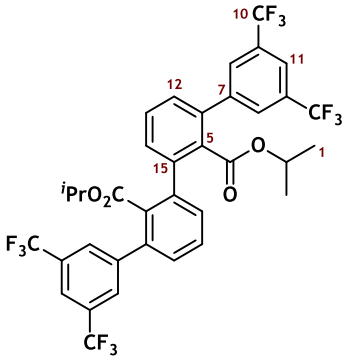
^{13}C (101 MHz, $CDCl_3$): δ 166.0 (**C4**), 138.4 ($\mathbf{C}_{Ar}$**10**), 136.2 ($\mathbf{C}_{Ar}$**5**), 132.4 ($\mathbf{C}_{Ar}$**7**), 129.7 ($\mathbf{C}_{Ar}$**8**), 129.0 ($\mathbf{C}_{Ar}$**9**), 119.3 ($\mathbf{C}_{Ar}$**6**), 69.4 (**C2**), 21.6 (**C1**), 21.1 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1728 (C=O), 1554, 1437, 1281, 1148, 1102 (C–O), 914, 786, 733.

LRMS (ESI): $[M+Na]^+$ 505.0, 507.0

MP: 89 – 91 °C (40-60 petrol).[†]

Diisopropyl 3,3''',5,5'''-tetrakis(trifluoromethyl)-[1,1':3',1'':3'',1'''-quaterphenyl]-2',2''-dicarboxylate (251)



According to a modified literature procedure,[158] boronic acid **212** (639 mg, 2.48 mmol) was added to a schlenk flask containing dibromoarene **249** (500 mg, 1.03 mmol), $Pd(OAc)_2$ (12 mg, 0.050 mmol), triphenylphosphine (41 mg, 0.150 mmol) and potassium carbonate (427 mg, 3.09 mmol). The flask was purged with argon three times before degassed *N*,*N*-dimethylformamide (5 mL) was added. The resulting suspension was heated to 90 °C for 24 hours. After cooling to room temperature, the reaction was acidified with aqueous HCl (1 M, 40 mL) and then extracted with diethyl ether (3 × 75 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered

[†] *A melting point has not been previously quoted in the literature.*

and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1) to afford biaryl **251** (601 mg, 78%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.93 (2H, s, **11**-**H**), 7.90 (4H, s, **8**-**H**), 7.60 – 7.54 (2H, m, **13**-**H**), 7.47 – 7.42 (4H, m, **12**-**H**, **14**-**H**), 4.77 (2H, sept, *J* 6.3, **2**-**H**), 1.00 (6H, d, *J* 6.1, **1**-**H**), 0.75 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 167.4 (**C4**), 142.8 ($\mathbf{C}_{Ar}$**7**), 139.0 ($\mathbf{C}_{Ar}$**Q**), 137.7 ($\mathbf{C}_{Ar}$**Q**), 133.7 ($\mathbf{C}_{Ar}$**5**), 131.9 (q, $J_{F\text{-}C}$ 34, $\mathbf{C}_{Ar}$**9**), 130.5 ($\mathbf{C}_{Ar}$**H**), 129.5 ($\mathbf{C}_{Ar}$**H**), 129.4 ($\mathbf{C}_{Ar}$**H**), 128.8 (app. d, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**8**), 123.4 (q, $J_{F\text{-}C}$ 272, **C10**), 121.6 (app. dt, $J_{F\text{-}C}$ 7.4, 3.9, $\mathbf{C}_{Ar}$**11**), 69.4 (**C2**), 21.2 (**C1**), 20.9 (**C1**).

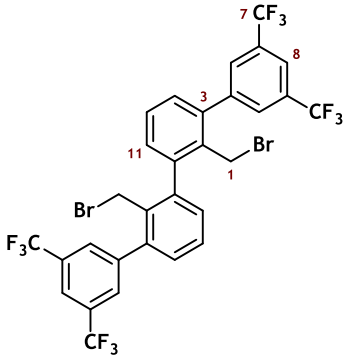
^{19}F (377 MHz, $CDCl_3$): δ −62.9

IR: v_{max} (neat)/ cm^{-1} 2985 (C–H), 1725 (C=O), 1468, 1381, 1282, 1181, 1135, 1102 (C–O), 902.

HRMS (ESI): $C_{36}H_{26}F_{12}O_4Na$ $[M+Na]^+$ requires 733.1532; found 733.1533

MP: 108 – 110 °C.

2',2''-Bis(bromomethyl)-3,3''',5,5'''-tetrakis(trifluoromethyl)-1,1':3',1'':3'',1'''-quaterphenyl (252)



According to modified literature procedures,[159,160] $LiAlH_4$ (40 mg, 1.05 mmol) was added portionwise to biaryl **251** (263 mg, 0.350 mmol) in THF (2 mL) at 0 °C. The reaction mixture

was then heated to 65 °C for 30 minutes before cooling to room temperature. The reaction was quenched with aqueous HCl (3 M, 2 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude diol was used directly in the next step without further purification. The crude diol was dissolved in dichloromethane (9 mL) and cooled to −20 °C. A solution of BBr_3 (1 M in dichloromethane, 1.05 mL, 1.05 mmol) was added dropwise and the reaction was then warmed to room temperature. After 24 hours, the reaction was quenched with water (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol) to afford dibromoarene **252** (108 mg, 46%) as a white solid.[†]

^{1}H (400 MHz, $CDCl_3$): δ 8.05 (4H, s, **5**-**H**), 7.98 (2H, s, **8**-**H**), 7.59 – 7.45 (4H, m, **10**-**H**, **9**-**H**/**11**-**H**), 7.36 (2H, d, *J* 7.3, **9**-**H**/**11**-**H**), 4.19 (2H, AB_q, *J* 10.4, **1**-$\mathbf{H_A}$), 4.10 (2H, AB_q, *J* 10.4, **1**-$\mathbf{H_B}$).

^{13}C (101 MHz, $CDCl_3$): δ 142.4 ($\mathbf{C_{Ar}}$**4**), 140.9 ($\mathbf{C_{Ar}}$**Q**), 140.8 ($\mathbf{C_{Ar}}$**Q**), 133.4 ($\mathbf{C_{Ar}}$**Q**), 131.8 (q, $J_{F\text{-}C}$ 34, $\mathbf{C_{Ar}}$**6**), 131.0 ($\mathbf{C_{Ar}}$**9**/$\mathbf{C_{Ar}}$**11**), 130.8 ($\mathbf{C_{Ar}}$**9**/$\mathbf{C_{Ar}}$**11**), 129.5 (app. d, $J_{F\text{-}C}$ 3, $\mathbf{C_{Ar}}$**5**), 128.7 ($\mathbf{C_{Ar}}$**10**), 123.4 (q, $J_{F\text{-}C}$ 272, **C7**), 121.9 (app. dt, $J_{F\text{-}C}$ 7.4, 3.9, $\mathbf{C_{Ar}}$**8**), 29.8 (**C1**).

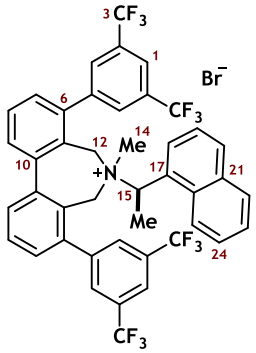
^{19}F (377 MHz, $CDCl_3$): δ −62.8

IR: ν_{max} (neat)/ cm^{-1} 2924 (C–H), 1620, 1444, 1380, 1280, 1173, 1133, 901.

MP: 182 – 184 °C.

[†] *A high resolution mass spectrum could not be obtained for this compound as it did not fly under ESI, EI or MALDI ionization conditions.*

(*R*)-4,8-Bis(3,5-bis(trifluoromethyl)phenyl)-6-methyl-6-(1-(naphthalen-1-yl)ethyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepin-6-ium bromide (*aka* Moira) 243



According to a modified literature procedure,[139] amine (*R*)-**217** (17 mg, 0.095 mmol) and anhydrous potassium carbonate (71 mg, 0.516 mmol) were added to a stirred solution of dibromoarene **252** (66 mg, 0.086 mmol) in acetonitrile (2 mL) and dichloromethane (0.5 mL). The mixture was heated to 60 °C for 16 hours and after cooling to room temperature was filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (dichloromethane : methanol, 99 : 1 to 97 : 3) to afford Moira (*R*)-**243** (44 mg, 59%) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 8.17 (1H, s, **4**-**H**), 8.05 (2H, s, **1**-**H**, **4**-**H**), 7.98 – 7.92 (3H, m, **22**-**H**, **25**-**H**, **Ar**-**H**), 7.85 (1H, s, **1**-**H**), 7.81 – 7.69 (5H, m, **Ar**-**H**), 7.57 – 7.47 (2H, m, **24**-**H**, **Ar**-**H**), 7.44 – 7.40 (2H, m, **4**-**H**, **23**-**H**), 7.40 – 7.35 (2H, m, **18**-**H**, **20**-**H**), 7.08 (1H, d, *J* 8.5, **19**-**H**), 5.53 (1H, d, *J* 14.8, **12**-**H**), 5.34 (1H, q, *J* 6.8, **15**-**H**), 4.37 (1H, d, *J* 14.8, **12**-**H**), 3.53 (1H, d, *J* 13.2, **12**-**H**), 3.12 (1H, d, *J* 12.9, **12**-**H**), 3.05 (3H, s, **14**-**H**), 1.20 (3H, d, *J* 6.6, **16**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 142.8 ($\mathbf{C}_{Ar}\mathbf{Q}$), 142.1 ($\mathbf{C}_{Ar}\mathbf{Q}$), 142.0 ($\mathbf{C}_{Ar}\mathbf{Q}$), 141.0 ($\mathbf{C}_{Ar}\mathbf{Q}$), 140.9 ($\mathbf{C}_{Ar}\mathbf{Q}$), 140.8 ($\mathbf{C}_{Ar}\mathbf{Q}$), 134.2 ($\mathbf{C}_{Ar}$**21**), 132.4 ($\mathbf{C}_{Ar}\mathbf{H}$), 131.9 ($\mathbf{C}_{Ar}$**25**), 131.7 ($\mathbf{C}_{Ar}$**26**), 131.7 ($\mathbf{C}_{Ar}$**4**), 130.7 ($\mathbf{C}_{Ar}$**22**), 130.4 ($\mathbf{C}_{Ar}\mathbf{H}$), 130.2 ($\mathbf{C}_{Ar}\mathbf{H}$), 128.6 ($\mathbf{C}_{Ar}$**4** & $\mathbf{C}_{Ar}$**23**), 127.2 ($\mathbf{C}_{Ar}$**17**), 126.8 ($\mathbf{C}_{Ar}$**20**), 126.8 ($\mathbf{C}_{Ar}$**24**), 125.2 ($\mathbf{C}_{Ar}$**18**), 123.2 ($\mathbf{C}_{Ar}$**1**), 122.8 (q, $J_{F\text{-}C}$ 279, **C3**), 122.7 (q, $J_{F\text{-}C}$ 274, **C3**), 122.7 (q,

$J_{F\text{-}C}$ 274, **C3**), 122.1 (**C**$_{Ar}$**1**), 119.3 (**C**$_{Ar}$**19**), 62.4 (**C15**), 59.0 (**C12**), 57.4 (**C12**), 42.7 (**C14**), 16.1 (**C16**).[†]

^{19}F (377 MHz, $CDCl_3$): δ −61.9, −62.7, −62.8, −62.9

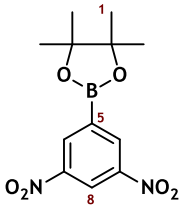
IR: v_{max} (neat)/ cm^{-1} 3008 (C–H), 1467, 1381, 1279, 1174, 1133, 973, 727.

HRMS (ESI): $C_{43}H_{30}F_{12}N$ $[M-Br^-]^+$ requires 788.2181; found 788.2187

MP: 98 – 100 °C.

$[\alpha]_D$ +117.0 (*c* 0.30, chloroform).

2-(3,5-Dinitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (254)



According to a modified literature procedure,[161] KOAc (1.00 g, 10.2 mmol), Pd(dppf)Cl_2 (75 mg, 0.102 mmol), bis(pinacolato)diboron (976 mg, 3.84 mmol) and 1-iodo-3,5-dinitrobenzene **253** (1.00 g, 3.40 mmol) are combined in a dry schlenk flask and are purged with argon. Degassed DMSO (10 mL) was introduced and the reaction heated to 80 °C for 4 hours. The solution was diluted with water (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude boronic ester **254** (772 mg, 77%), which was used without further purification, was isolated as a brown solid with spectroscopic data in accordance with the literature.[244]

[†] *Due to overlapping peaks and F-C coupling this spectrum was very complex. Therefore, all peaks may not be accounted for and assignment was very difficult.*

^{1}H (400 MHz, CD_3Cl): δ 9.09 (1H, t, *J* 2.1, **8**-**H**), 8.92 (2H, d, *J* 2.3, **6**-**H**), 1.40 (12H, s, **1**-**H**).

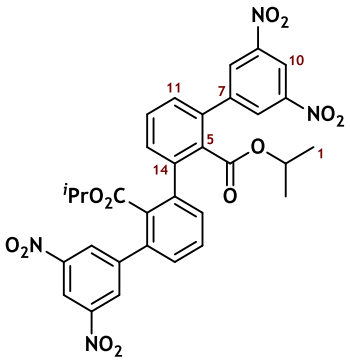
^{13}C (101 MHz, CD_3Cl): δ 148.3 ($\mathbf{C}_{Ar}$**7**), 134.5 ($\mathbf{C}_{Ar}$**6**), 121.1 ($\mathbf{C}_{Ar}$**8**), 85.6 (**C2**), 25.0 (**C1**).[†]

IR: v_{max} (neat)/ cm^{-1} 2986 (C–H), 1626, 1542 (NO_2), 1472, 1341 (NO_2), 1139, 847, 729, 692.

HRMS (FI): $C_{12}H_{15}BN_2O_6$ $[M]^+$ requires 294.1025; found 294.1029

MP: 146 – 148 °C.[‡]

Diisopropyl 3,3''',5,5'''-tetranitro-[1,1':3',1'':3'',1'''-quaterphenyl]-2',2''-dicarboxylate (255)



According to a modified literature procedure,[158] boronic ester **254** (365 mg, 1.24 mmol) was added to a schlenk flask containing dibromoarene **249** (200 mg, 0.413 mmol), $Pd(OAc)_2$ (5 mg, 0.021 mmol), triphenylphosphine (16 mg, 0.062 mmol) and potassium carbonate (170 mg, 1.24 mmol). The flask was purged with argon three times before degassed *N*,*N*-dimethylformamide (2 mL) was added. The resulting suspension was heated to 90 °C for 48 hours. After cooling to room temperature, the reaction was acidified with aqueous HCl (1 M, 10 mL) and then extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography

[†] *$\mathbf{C}_{Ar}$**5** was not observed.*

[‡] *A melting point has not been previously quoted in the literature.*

(40-60 petrol : ethyl acetate, 20 : 1 to 10 : 1) to afford biaryl **255** (141 mg, 52%) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 9.04 (2H, t, *J* 1.8, **10**-**H**), 8.59 (4H, d, *J* 1.5, **8**-**H**), 7.63 (2H, app. t, *J* 7.7, **12**-**H**), 7.51 (2H, d, *J* 7.6, **11**-**H**/**13**-**H**), 7.48 (2H, d, *J* 7.8, **11**-**H**/**13**-**H**), 4.78 (2H, sept, *J* 6.2, **2**-**H**), 1.01 (6H, d, *J* 6.3, **1**-**H**), 0.78 (6H, d, *J* 6.3, **1**-**H**).

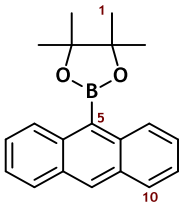
^{13}C (101 MHz, $CDCl_3$): δ 166.9 (**C4**), 148.4 ($\mathbf{C}_{Ar}$**9**), 144.1 ($\mathbf{C}_{Ar}$**Q**), 139.2 ($\mathbf{C}_{Ar}$**Q**), 136.2 ($\mathbf{C}_{Ar}$**Q**), 133.3 ($\mathbf{C}_{Ar}$**5**), 131.2 ($\mathbf{C}_{Ar}$**11**/$\mathbf{C}_{Ar}$**13**), 129.8 ($\mathbf{C}_{Ar}$**12**), 129.5 ($\mathbf{C}_{Ar}$**11**/$\mathbf{C}_{Ar}$**13**), 128.7 ($\mathbf{C}_{Ar}$**8**), 117.9 ($\mathbf{C}_{Ar}$**10**), 69.7 (**C2**), 21.3 (**C1**), 21.0 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 3103 (C–H), 2984 (C–H), 1728 (C=O), 1551 (NO_2), 1357 (NO_2), 1269, 1101 (C–O), 908, 726.

HRMS (ESI): $C_{32}H_{26}N_4O_{12}Na$ $[M+Na]^+$ requires 681.1439; found 681.1450

MP: 162 – 164 °C.

2-(Anthracen-9-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (222)



According to a modified literature procedure,[163] a solution of *n*-butyllithium (1.6 M in hexanes, 10.8 mL, 17.2 mmol) was added dropwise to a stirred solution of 9-bromoanthracene **257** (3.40 g, 13.2 mmol) in anhydrous tetrahydrofuran (55 mL) at −78 °C. The reaction was stirred at this temperature for 1 hour and then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.50 mL, 17.2 mmol) was added. The

reaction was left to warm to room temperature overnight and was subsequently diluted with water (50 mL). The biphasic mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : dichloromethane, 4 : 1) to afford boronic ester **222** (2.93 g, 73%) as a light yellow solid with spectroscopic data in accordance with the literature.[163]

^{1}H (400 MHz, CD_3Cl): δ 8.52 – 8.46 (3H, m, **7**-**H**, **12**-**H**), 8.02 (2H, d, *J* 8.1, **10**-**H**), 7.55 – 7.45 (4H, m, **8**-**H**, **9**-**H**), 1.60 (12H, s, **1**-**H**).

^{13}C (101 MHz, CD_3Cl): δ 136.1 ($\mathbf{C}_{Ar}$**6**), 131.3 ($\mathbf{C}_{Ar}$**11**), 129.6 ($\mathbf{C}_{Ar}$**12**), 129.0 ($\mathbf{C}_{Ar}$**10**), 128.5 ($\mathbf{C}_{Ar}$**7**), 125.9 ($\mathbf{C}_{Ar}$**8**), 125.0 ($\mathbf{C}_{Ar}$**9**), 84.5 (**C2**), 25.3 (**C1**).[†]

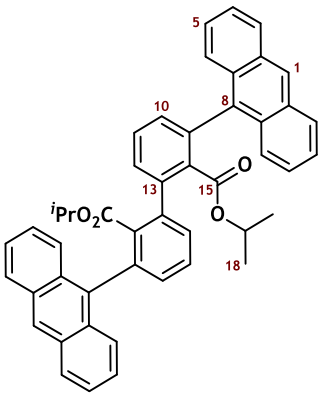
IR: ν_{max} (neat)/ cm^{-1} 2976 (C–H), 1370, 1314, 1296, 1239, 1138, 1015, 845, 735.

LRMS (ESI): $[M+Na]^+$ 327.2

MP: 134 – 136 °C, lit. MP: 141 – 142 °C.[163]

[†] $\mathbf{C}_{Ar}$**5** *was not observed.*

Diisopropyl 3,3'-di(anthracen-9-yl)-[1,1'-biphenyl]-2,2'-dicarboxylate (259)



According to modified literature procedures,[149,245] boronic ester **222** (1.05 g, 3.46 mmol) was added to a schlenk flask containing diiodoarene **250** (500 mg, 0.860 mmol), $Pd(OAc)_2$ (10 mg, 0.043 mmol), SPhos **226** (35 mg, 0.086 mmol) and tripotassium phosphate (1.46 g, 6.88 mmol). The flask was purged with argon three times before a degassed mixture of toluene, ethanol and water (1.4 : 1.4 : 1.0, 9.5 mL) was added. The resulting suspension was heated to 100 °C for 24 hours. After cooling to room temperature, the reaction was acidified with aqueous HCl (1 M, 20 mL) and then extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 19 : 1 to 0 : 100) to afford biaryl **259** (535 mg, 92%) as a yellow solid.

^{1}H (500 MHz, $CDCl_3$): δ 8.50 (2H, s, **1**-**H**), 8.03 (4H, br. d, *J* 6.6, **3**-**H**), 7.82 – 7.65 (2H, app. br. s, **6**-**H**), 7.69 (2H, dd, *J* 7.9, 1.3, **10**-**H**), 7.65 – 7.53 (2H, app. br. s, **6**-**H**), 7.59 (2H, app. t, *J* 7.6, **11**-**H**), 7.53 – 7.35 (8H, app. br. s, **4**-**H**, **5**-**H**), 7.39 (2H, dd, *J* 7.6, 0.9, **12**-**H**), 4.28 (2H, sept, *J* 6.3, **17**-**H**), 0.36 (12H, app. br. d, *J* 39.4, **18**-**H**).

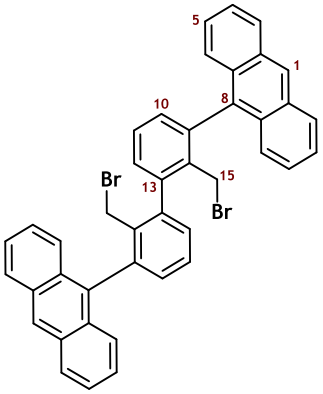
^{13}C (126 MHz, $CDCl_3$): δ 167.3 (**C15**), 138.8 (C_{Ar}**9**), 137.4 (C_{Ar}**13**), 135.8 (C_{Ar}**14**), 134.9 (C_{Ar}**8**), 131.3 (C_{Ar}**2**), 131.1 (C_{Ar}**12**), 130.7 (br., C_{Ar}**7**), 130.1 (C_{Ar}**10**), 128.8 (C_{Ar}**11**), 128.3 (C_{Ar}**3**), 127.3 (C_{Ar}**6**), 127.0 (C_{Ar}**1**), 125.2 (br., C_{Ar}**4** & C_{Ar}**5**), 67.9 (**C17**), 20.8 (**C18**).

IR: v_{max} (neat)/ cm^{-1} 2979 (C–H), 1721 (C=O), 1576, 1461, 1277, 1097 (C–O), 1064, 910, 732.

HRMS (ESI): $C_{48}H_{38}O_4Na$ $[M+Na]^+$ requires 701.2662; found 701.2686

MP: 126 – 128 °C.

9,9'-(2,2'-Bis(bromomethyl)-[1,1'-biphenyl]-3,3'-diyl)dianthracene (260)



According to modified literature procedures,[160,246] DIBAL-H (1 M in dichloromethane, 6.22 mL, 6.22 mmol) was added dropwise to biaryl **259** (469 mg, 0.690 mmol) in dichloromethane (8 mL) at −78 °C. The reaction mixture was stirred at this temperature for 1 hour before allowing it to warm to room temperature overnight. The reaction was cooled to 0 °C before quenching with aqueous HCl (3 M, 15 mL) and after warming to room temperature was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude diol was used directly in the next step without further purification. The crude diol was dissolved in dichloromethane (18 mL) and cooled to −20 °C. A solution of BBr_3 (1 M in dichloromethane, 1.22 mL, 1.22 mmol) was added dropwise and the reaction was then

warmed to room temperature. After 24 hours, the reaction was quenched with water (30 mL) and extracted with dichloromethane (3 × 40 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : dichloromethane, 100 : 0 to 4 : 1) to afford dibromoarene **260** (248 mg, 52%) as a brown solid.

^{1}H (500 MHz, $CDCl_3$): δ 8.58 (2H, s, **1**-**H**), 8.13 – 8.04 (4H, m, **3**-**H**), 7.73 (2H, dd, *J* 7.6, 1.3, **12**-**H**), 7.69 (2H, d, *J* 8.5, **6**-**H**), 7.64 (2H, app. t, *J* 7.7, **11**-**H**), 7.58 – 7.51 (4H, m, **4**-**H**, **6**-**H**), 7.49 – 7.38 (6H, m, **4**-**H**, **5**-**H**, **10**-**H**), 7.31 – 7.25 (2H, m, **5**-**H**), 4.17 (2H, AB_q, *J* 10.1, **15**-**H**), 4.02 (2H, AB_q, *J* 9.8, **15**-**H**).

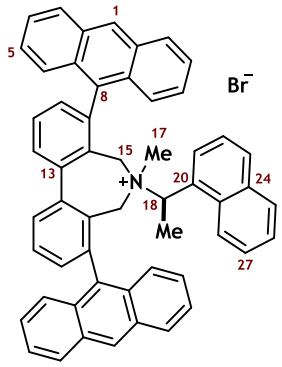
^{13}C (126 MHz, $CDCl_3$): δ 141.3 ($\mathbf{C}_{Ar}$**13**), 140.4 ($\mathbf{C}_{Ar}$**9**), 135.5 ($\mathbf{C}_{Ar}$**14**), 134.2 ($\mathbf{C}_{Ar}$**8**), 132.3 ($\mathbf{C}_{Ar}$**10**), 131.6 ($\mathbf{C}_{Ar}$**2**), 131.5 ($\mathbf{C}_{Ar}$**2**), 130.5 ($\mathbf{C}_{Ar}$**7**), 130.4 ($\mathbf{C}_{Ar}$**7**), 130.4 ($\mathbf{C}_{Ar}$**12**), 128.6 ($\mathbf{C}_{Ar}$**3**/$\mathbf{C}_{Ar}$**11**), 128.6 ($\mathbf{C}_{Ar}$**3**/$\mathbf{C}_{Ar}$**11**), 128.5 ($\mathbf{C}_{Ar}$**3**/$\mathbf{C}_{Ar}$**11**), 127.5 ($\mathbf{C}_{Ar}$**1**), 127.0 ($\mathbf{C}_{Ar}$**6**), 127.0 ($\mathbf{C}_{Ar}$**6**), 125.8 ($\mathbf{C}_{Ar}$**5**), 125.7 ($\mathbf{C}_{Ar}$**5**), 125.4 ($\mathbf{C}_{Ar}$**4**), 125.4 ($\mathbf{C}_{Ar}$**4**), 30.3 (**C15**).

IR: ν_{max} (neat)/ cm^{-1} 3052 (C–H), 1578, 1441, 1357, 1219, 1014, 907, 887, 792, 733.

HRMS (EI): $C_{42}H_{28}{}^{79}Br_2$ $[M]^+$ requires 692.0316; found 692.0542

MP: 194 – 196 °C.

(*R*)-4,8-Di(anthracen-9-yl)-6-methyl-6-(1-(naphthalen-1-yl)ethyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepin-6-ium bromide (*aka* Agnes) (245)



According to a modified literature procedure,[139] amine (*R*)-**217** (72 mg, 0.390 mmol) and anhydrous potassium carbonate (66 mg, 0.480 mmol) were added to a stirred solution of dibromoarene **260** (224 mg, 0.320 mmol) in acetonitrile (8 mL) and dichloromethane (1.5 mL). The mixture was heated to 60 °C for 16 hours followed by 85 °C for 16 hours before cooling to room temperature. The reaction was filtered, concentrated *in vacuo* and diluted with dichloromethane (30 mL). The organic solution was washed with aqueous HBr (3 M, 3 × 10 mL) and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (dichloromethane : methanol, 99 : 1 to 19 : 1) to afford Agnes (*R*)-**245** (29 mg, 11%, 16% brsm) as a brown solid.

^{1}H (500 MHz, $CDCl_3$): δ 8.62 (1H, s, **1**-**H**), 8.32 (1H, s, **1**-**H**), 8.18 – 8.09 (4H, m, **Ar**-**H**), 8.05 (1H, d, *J* 7.6, **25**-**H**), 8.03 – 7.96 (4H, m, **Ar**-**H**), 7.92 – 7.84 (2H, m, **26**-**H**, **Ar**-**H**), 7.78 (1H, d, *J* 8.5, **3**-**H**), 7.70 – 7.64 (2H, m, **Ar**-**H**), 7.61 – 7.39 (10H, m, **Ar**-**H**), 7.31 – 7.23 (2H, m, **Ar**-**H**), 7.14 – 7.09 (1H, m, **4**-**H**), 6.91 – 6.86 (1H, m, **21**-**H**), 6.86 – 6.80 (1H, m, **22**-**H**), 6.43 – 6.37 (1H, m, **5**-**H**), 6.30 (1H, d, *J* 8.8, **6**-**H**), 4.84 (1H, q, *J* 6.4, **18**-**H**), 4.32 (1H, d, *J* 13.6, **15**-**H**), 3.91 (1H, d, *J* 13.6, **15**-**H**), 3.58 (1H, d, *J* 12.9, **15**-**H**), 2.42 (1H, d, *J* 12.9, **15**-**H**), 1.94 (3H, s, **17**-**H**), −0.13 (3H, br. d, *J* 6.6, **19**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 143.0 ($\mathbf{C}_{Ar}\mathbf{Q}$), 142.1 ($\mathbf{C}_{Ar}\mathbf{Q}$), 141.1 ($\mathbf{C}_{Ar}\mathbf{Q}$), 140.4 ($\mathbf{C}_{Ar}\mathbf{Q}$), 133.4 ($\mathbf{C}_{Ar}\mathbf{H}$), 133.3 ($\mathbf{C}_{Ar}\mathbf{H}$), 133.2 ($\mathbf{C}_{Ar}\mathbf{24}$), 131.7 ($\mathbf{C}_{Ar}\mathbf{H}$), 131.5 ($\mathbf{C}_{Ar}\mathbf{H}$), 131.4 ($\mathbf{C}_{Ar}\mathbf{Q}$), 131.4 ($\mathbf{C}_{Ar}\mathbf{Q}$), 131.3 ($\mathbf{C}_{Ar}\mathbf{Q}$), 131.3 ($\mathbf{C}_{Ar}\mathbf{Q}$), 131.0 ($\mathbf{C}_{Ar}\mathbf{H}$), 130.8 ($\mathbf{C}_{Ar}\mathbf{Q}$), 130.5 ($\mathbf{C}_{Ar}\mathbf{Q}$), 130.3 ($\mathbf{C}_{Ar}\mathbf{Q}$), 130.3 ($\mathbf{C}_{Ar}\mathbf{Q}$), 130.2 ($\mathbf{C}_{Ar}\mathbf{H}$), 130.2 ($\mathbf{C}_{Ar}\mathbf{H}$), 130.1 ($\mathbf{C}_{Ar}\mathbf{Q}$), 129.7 ($\mathbf{C}_{Ar}\mathbf{H}$), 129.6 ($\mathbf{C}_{Ar}\mathbf{H}$), 129.6 ($\mathbf{C}_{Ar}\mathbf{H}$), 129.2 ($\mathbf{C}_{Ar}\mathbf{1}$), 129.2 ($\mathbf{C}_{Ar}\mathbf{Q}$), 128.6 ($\mathbf{C}_{Ar}\mathbf{H}$), 128.5 ($\mathbf{C}_{Ar}\mathbf{H}$), 128.2 ($\mathbf{C}_{Ar}\mathbf{Q}$), 128.1 ($\mathbf{C}_{Ar}\mathbf{H}$), 128.0 ($\mathbf{C}_{Ar}\mathbf{21}$), 127.9 ($\mathbf{C}_{Ar}\mathbf{H}$), 127.2 ($\mathbf{C}_{Ar}\mathbf{H}$), 127.1 ($\mathbf{C}_{Ar}\mathbf{H}$), 126.8 ($\mathbf{C}_{Ar}\mathbf{29}$), 126.5 ($\mathbf{C}_{Ar}\mathbf{20}$), 126.5 ($\mathbf{C}_{Ar}\mathbf{H}$), 126.3 ($\mathbf{C}_{Ar}\mathbf{5}$), 126.0 ($\mathbf{C}_{Ar}\mathbf{H}$), 125.7 ($\mathbf{C}_{Ar}\mathbf{H}$), 125.4 ($\mathbf{C}_{Ar}\mathbf{H}$), 125.3 ($\mathbf{C}_{Ar}\mathbf{H}$), 125.0 ($\mathbf{C}_{Ar}\mathbf{H}$), 124.9 ($\mathbf{C}_{Ar}\mathbf{H}$), 124.8 ($\mathbf{C}_{Ar}\mathbf{H}$), 124.5 ($\mathbf{C}_{Ar}\mathbf{22}$), 123.2 ($\mathbf{C}_{Ar}\mathbf{6}$), 121.2 ($\mathbf{C}_{Ar}\mathbf{H}$), 63.5 (**C18**), 59.4 (**C15**), 58.8 (**C15**), 42.2 (**C17**), 14.3 (**C19**).[†]

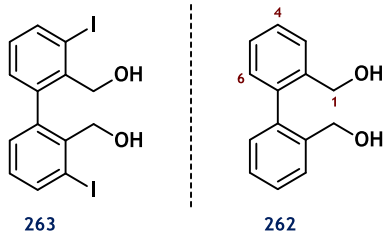
IR: ν_{max} (neat)/ cm^{-1} 2923 (C–H), 1665, 1445, 1408, 1261, 1100, 1016, 923, 800, 783, 732.

HRMS (ESI): $C_{55}H_{42}N$ $[M-Br^-]^+$ requires 716.3312; found 716.3311

MP: 156 – 158 °C (decomposed).

$[\alpha]_D$ +261.7 (*c* 0.40, chloroform).

Attempted synthesis of (3,3'-diiodo-[1,1'-biphenyl]-2,2'-diyl)dimethanol (263) and isolation of [1,1'-biphenyl]-2,2'-diyldimethanol (262)



263 262

Diiodobiphenyl **250** (500 mg, 0.865 mmol) in THF (3 mL) was added dropwise into a slurry of $LiAlH_4$ (164 mg, 4.32 mmol) in THF (3 mL) at 0 °C. The reaction was then left to stir for

[†] *One $\mathbf{C}_{Ar}\mathbf{H}$ and one $\mathbf{C}_{Ar}\mathbf{Q}$ were not observed and assumed coincident with other peaks in the spectrum. Due to the vast number of peaks in the aromatic region a more comprehensive assignment of this spectrum was not possible.*

12 hours at room temperature before quenching carefully with aqueous HCl (1 M, 10 mL) at 0 °C. The resulting biphasic mixture was extracted with ethyl acetate (3 × 15 mL) and the combined organic extracts washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 7 : 3) to afford diol **262** (171 mg, 43%) as a white solid with spectroscopic data in accordance with the literature.[247]

^{1}H (400 MHz, $CDCl_3$): δ 7.46 (2H, dd, *J* 7.3, 1.2, **6**-**H**), 7.38 (2H, app. td, *J* 7.4, 1.6, **5**-**H**), 7.33 (2H, app. td, *J* 7.3, 1.5, **4**-**H**), 7.14 (2H, dd, *J* 7.2, 1.3, **3**-**H**), 4.30 (2H, AB_q, *J* 11.7, **1**-$\mathbf{H_A}$), 4.27 (2H, AB_q, *J* 11.7, **1**-$\mathbf{H_B}$) 3.49 (2H, br. s, O**H**).

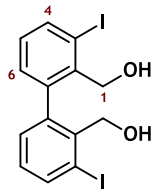
^{13}C (101 MHz, $CDCl_3$): δ 140.1 ($\mathbf{C_{Ar}}$**2**), 138.7 ($\mathbf{C_{Ar}}$**7**), 129.7 ($\mathbf{C_{Ar}}$**3**), 129.7 ($\mathbf{C_{Ar}}$**6**), 128.2 ($\mathbf{C_{Ar}}$**5**), 127.7 ($\mathbf{C_{Ar}}$**4**), 62.8 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 3348 (O–H), 2944 (C–H), 1444, 1340, 1250, 1194, 1003, 754.

LRMS (ESI): $[M+Na]^+$ 237.1

MP: 104 – 106 °C, lit. MP: 108 – 110 °C.[247]

(3,3'-Diiodo-[1,1'-biphenyl]-2,2'-diyl)dimethanol (263)



DIBAL-H (1 M in cyclohexane, 7.78 mL, 7.78 mmol) was added dropwise into a solution of diiodobiphenyl **250** (500 mg, 0.865 mmol) in dichloromethane (10 mL) at −78 °C. The reaction was then warmed to room temperature overnight. Excess DIBAL-H was destroyed

with methanol at 0 °C before the addition of aqueous HCl (1 M, 20 mL). The resulting biphasic mixture was extracted with dichloromethane (3 × 20 mL) and the combined organic extracts washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude diol **263** (278 mg, 69%), which was used without further purification, was afforded as a white solid.

^{1}H (400 MHz, $(CD_3)_2SO$): δ 7.92 (2H, dd, *J* 7.8, 1.2, **4**-**H**), 7.18 (2H, dd, *J* 7.6, 1.2, **6**-**H**), 7.07 (2H, app. t, *J* 7.7, **5**-**H**), 4.99 (2H, t, *J* 4.6, O**H**), 4.27 – 4.18 (4H, m, **1**-**H**).

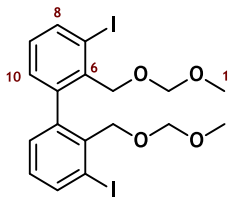
^{13}C (101 MHz, $(CD_3)_2SO$): δ 141.9 ($\mathbf{C}_{Ar}\mathbf{7}$), 140.5 ($\mathbf{C}_{Ar}\mathbf{2}$), 139.1 ($\mathbf{C}_{Ar}\mathbf{4}$), 130.0 ($\mathbf{C}_{Ar}\mathbf{6}$), 129.0 ($\mathbf{C}_{Ar}\mathbf{5}$), 102.5 ($\mathbf{C}_{Ar}\mathbf{3}$), 64.8 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 3222 (O–H), 2945 (C–H), 1549, 1436, 1203, 1016, 958, 771, 653.

HRMS (ESI): $C_{14}H_{12}I_2O_2Na$ $[M+Na]^+$ requires 488.8819; found 488.8808

MP: 220 – 222 °C.

3,3'-Diiodo-2,2'-bis((methoxymethoxy)methyl)-1,1'-biphenyl (264)



MOM-Cl (0.354 mL, 4.66 mmol) was added dropwise into a solution of diol **263** (217 mg, 0.466 mmol) and DIPEA (1.15 mL, 6.58 mmol) in dichloromethane (6 mL) at 0 °C. The reaction was then warmed to room temperature and stirred for 12 hours. The reaction was diluted with saturated aqueous sodium bicarbonate (10 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and then the

combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5) to afford MOM protected diol **264** (210 mg, 81%) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.93 (2H, dd, *J* 8.0, 1.1, **8-H**), 7.24 (2H, dd, *J* 7.6, 0.9, **10-H**), 7.02 (2H, app. t, *J* 7.7, **9-H**), 4.54 (2H, AB_q, *J* 6.6, **3-H_A**), 4.50 (2H, AB_q, *J* 6.6, **3-H_B**), 4.37 (2H, AB_q, *J* 10.1, **5-H_A**), 4.29 (2H, AB_q, *J* 10.4, **5-H_B**), 3.23 (6H, s, **1-H**).

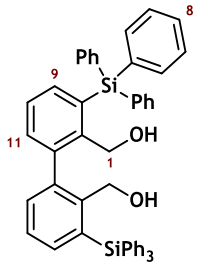
^{13}C (126 MHz, $CDCl_3$): δ 142.7 (**C_{Ar}11**), 139.8 (**C_{Ar}8**), 138.1 (**C_{Ar}6**), 130.3 (**C_{Ar}10**), 129.3 (**C_{Ar}9**), 102.5 (**C_{Ar}7**), 97.0 (**C3**), 71.9 (**C5**), 55.7 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2948 (C–H), 1550, 1438, 1149, 1100, 1041, 942, 787.

HRMS (ESI): $C_{18}H_{20}I_2O_4Na$ $[M+Na]^+$ requires 576.9343; found 576.9358

MP: 72 – 74 °C.

(3,3'-Bis(triphenylsilyl)-[1,1'-biphenyl]-2,2'-diyl)dimethanol (265)



According to a modified literature procedure,[168] *tert*-butyllithium (1.7 M in pentane, 0.650 mL, 1.11 mmol) was added dropwise to a solution of MOM protected diol **264** (137 mg, 0.247 mmol) in anhydrous THF (6 mL) at −78 °C. After 15 minutes, a solution of chlorotriphenylsilane (221 mg, 0.750 mmol) in anhydrous THF (3 mL) was added dropwise. The reaction was allowed to reach room temperature overnight and was then quenched with

water (20 mL). The reaction was extracted with dichloromethane (3 × 20 mL) and the combined organic layers washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude silylated material was dissolved methanol (3 mL) and cooled to 0 °C. Concentrated HCl (4 drops) was added and the reaction heated to 60 °C for 1 hour. After cooling to room temperature, saturated aqueous sodium bicarbonate (10 mL) was added and the reaction extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 9 : 1) to afford diol **265** (144 mg, 79%) as a white solid.

^{1}H (500 MHz, CD_3Cl): δ 7.64 – 7.60 (12H, m, **6**-**H**), 7.49 – 7.33 (24H, m, **Ar**-**H**), 4.30 (2H, AB_q, *J* 12.3, **1**-$\mathbf{H_A}$), 4.23 (2H, AB_q, *J* 12.3, **1**-$\mathbf{H_B}$).

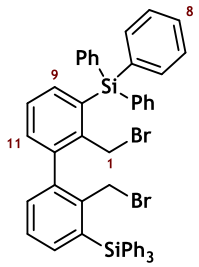
^{13}C (126 MHz, CD_3Cl): δ 145.1 ($\mathbf{C_{Ar}2}$), 142.3 ($\mathbf{C_{Ar}3}$/$\mathbf{C_{Ar}12}$), 137.9 ($\mathbf{C_{Ar}9}$/$\mathbf{C_{Ar}11}$), 136.4 ($\mathbf{C_{Ar}6}$), 135.0 ($\mathbf{C_{Ar}5}$), 134.3 ($\mathbf{C_{Ar}3}$/$\mathbf{C_{Ar}12}$), 132.5 ($\mathbf{C_{Ar}9}$/$\mathbf{C_{Ar}11}$), 129.8 ($\mathbf{C_{Ar}8}$), 128.2 ($\mathbf{C_{Ar}7}$), 127.0 ($\mathbf{C_{Ar}10}$), 62.7 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 3359 (O–H), 3069 (C–H), 1485, 1428, 1189, 1107, 998, 741, 700.

HRMS (ESI): $C_{50}H_{42}O_2Si_2Na$ $[M+Na]^+$ requires 753.2616; found 753.2617

MP: 124 – 126 °C.

(2,2'-Bis(bromomethyl)-[1,1'-biphenyl]-3,3'-diyl)bis(triphenylsilane) (266)



According to a modified literature procedure,[168] carbon tetrabromide (283 mg, 0.850 mmol) was added portionwise to a mixture of diol **265** (104 mg, 0.140 mmol) and triphenylphosphine (223 mg, 0.850 mmol) in THF (10 mL) at 0 °C. The reaction was allowed to reach room temperature and stirred for 3 hours. The reaction was diluted with water (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 100 : 0 to 99 : 1) to afford dibromoarene **266** (63 mg, 53%) as a white solid.[†]

^{1}H (500 MHz, CD_3Cl): δ 7.65 (12H, d, *J* 6.9, **6**-**H**), 7.46 – 7.40 (10H, m, **8**-**H**, **9**-**H**, **11**-**H**), 7.40 – 7.35 (12H, m, **7**-**H**), 7.31 (2H, app. t, *J* 7.6, **10**-**H**), 4.21 (2H, AB_q, *J* 10.1, **1**-$\mathbf{H_A}$), 4.09 (2H, AB_q, *J* 10.1, **1**-$\mathbf{H_B}$).

^{13}C (126 MHz, CD_3Cl): δ 142.0 ($\mathbf{C_{Ar}Q}$), 142.0 ($\mathbf{C_{Ar}Q}$), 138.9 ($\mathbf{C_{Ar}9}$/$\mathbf{C_{Ar}11}$), 136.7 ($\mathbf{C_{Ar}6}$), 135.0 ($\mathbf{C_{Ar}Q}$), 134.4 ($\mathbf{C_{Ar}5}$), 133.1 ($\mathbf{C_{Ar}9}$/$\mathbf{C_{Ar}11}$), 129.9 ($\mathbf{C_{Ar}8}$), 128.1 ($\mathbf{C_{Ar}7}$), 127.4 ($\mathbf{C_{Ar}10}$), 33.8 (**C1**).

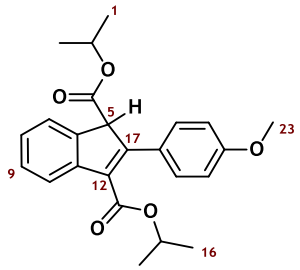
IR: ν_{max} (neat)/ cm^{-1} 3069 (C–H), 1484, 1428, 1189, 1108, 998, 743, 700.

MP: 218 – 220 °C.

[†] *A high resolution mass spectrum could not be obtained for this compound as it did not fly under ESI, EI or MALDI ionization conditions.*

5.3.4.1 Oxidation of Indanes to Indenes

Diisopropyl 2-(4-methoxyphenyl)-1*H*-indene-1,1-dicarboxylate (274)



Cesium hydroxide monohydrate (42 mg, 0.248 mmol) was added to a solution of (±)-indane **220** (60 mg, 0.124 mmol) in toluene (1 mL). The resulting suspension was purged with oxygen for 15 minutes was then stirred rapidly at room temperature under oxygen for 16 hours. The reaction was then quenched with saturated aqueous ammonium chloride (5 mL) and the reaction diluted with dichloromethane (10 mL). The layers were separated and the aqueous layer extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1) to afford the major product indene **274** (15 mg, 31%) as a light red oil.

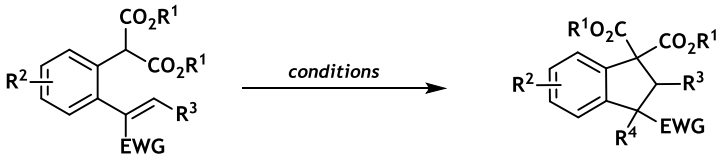
^{1}H (500 MHz, $CDCl_3$): δ 7.78 (1H, d, *J* 7.9, **10**-**H**), 7.52 (1H, d, *J* 7.6, **7**-**H**), 7.41 (2H, d, *J* 8.8, **19**-**H**), 7.41 – 7.36 (1H, m, **9**-**H**), 7.26 (1H, app. td, *J* 7.5, 1.1, **8**-**H**), 6.91 (2H, d, *J* 8.8, **20**-**H**), 5.23 (1H, sept, *J* 6.3, **15**-**H**), 4.92 – 4.82 (2H, m, **2**-**H**, **5**-**H**), 3.85 (3H, s, **23**-**H**), 1.27 (6H, app. dd, *J* 6.0, 3.8, **16**-**H**), 1.03 (3H, d, *J* 6.0, **1**-**H**), 1.01 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 169.2 (**C4**), 164.9 (**C13**), 160.0 (C_{Ar}**21**), 151.0 (**C17**), 142.7 (C_{Ar}**11**), 140.0 (C_{Ar}**6**), 131.8 (**C12**), 130.4 (C_{Ar}**19**), 128.2 (C_{Ar}**9**), 127.4 (C_{Ar}**18**), 126.1 (C_{Ar}**8**), 123.2 (C_{Ar}**7**), 122.2 (C_{Ar}**10**), 113.6 (C_{Ar}**20**), 69.0 (**C2**), 68.6 (**C15**), 59.3 (**C5**), 55.4 (**C23**), 22.0 (**C16**), 21.8 (**C16**), 21.6 (**C1**), 21.6 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2980 (C–H), 1719 (C=O), 1608 (C=C), 1511, 1375, 1254, 1105 (C–O), 1031.

HRMS (ESI): $C_{24}H_{26}O_5Na$ $[M+Na]^+$ requires 417.1672; found 417.1669

5.3.5 Synthesis of Indanes via an Asymmetric Phase-Transfer Catalyzed 5-endo-trig Cyclization



5.3.5.1 General Procedures for Racemic Cyclization

General Procedure 1: Tetrabutylammonium bromide (0.1 eq.) was added to a solution of the substrate in toluene (1 mL/80 mg substrate). The resulting suspension was degassed with argon for 30 minutes and then degassed aqueous KOH (50%, 0.1 mL/80 mg substrate) was added *via* an argon purged syringe. The biphasic reaction mixture was then stirred rapidly at room temperature under argon for 16 hours. The reaction was then quenched with saturated aqueous ammonium chloride (5 mL/80 mg substrate) and the reaction diluted with dichloromethane (20 mL/80 mg substrate). The layers were separated and the aqueous layer extracted with dichloromethane (3 × 10 mL/80 mg substrate). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was then purified to give the desired indane.

General Procedure 2: Tetrabutylammonium bromide (0.1 eq.) was added to a solution of the substrate in toluene (1 mL/80 mg substrate). The resulting suspension was degassed with argon for 30 minutes and then degassed aqueous KOH (50%, 0.1 mL/80 mg substrate) was added *via* an argon purged syringe. The biphasic reaction mixture was then stirred rapidly

at room temperature under argon for 16 hours. After complete cyclization, the electrophile (2.0 eq.) was added followed by degassed DMSO (2 mL/80 mg substrate). An excess of the electrophile[†] (8.0 eq) was then added over 1 hour *via* syringe pump to the reaction mixture. After 16 hours the reaction was quenched with saturated aqueous ammonium chloride (5 mL/80 mg substrate) and the reaction diluted with ethyl acetate (10 mL/80 mg substrate). The layers were separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL/80 mg substrate). The combined organic layers were washed with brine (3 × 20 mL/80 mg substrate), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was then purified to give the desired alkylated indane.

General Procedure 3: Tetrabutylammonium bromide (0.1 eq.) was added to a solution of the substrate in toluene (1 mL/80 mg substrate). The resulting suspension was degassed with argon for 30 minutes and then degassed aqueous KOH (50%, 0.1 mL/80 mg substrate) was added *via* an argon purged syringe. The biphasic reaction mixture was then stirred rapidly at room temperature under argon for 16 hours. An excess of the electrophile (10.0 eq) was then added over 1 hour *via* syringe pump to the reaction mixture. After 16 hours the reaction was quenched with saturated aqueous ammonium chloride (5 mL/80 mg substrate) and the reaction diluted with dichloromethane (20 mL/80 mg substrate). The layers were separated and the aqueous layer extracted with dichloromethane (3 × 10 mL/80 mg substrate). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was then purified to give the desired alkylated indane.

[†] *Solid electrophiles were dissolved in degassed DMSO to allow syringe pump addition*

5.3.5.2 General Procedures for Asymmetric Cyclization

General Procedure 4: (*R*,*R*)-**273** (0.02 eq.) was added to a schlenk tube and purged with argon three times. A solution of the substrate, which had been degassed for 30 minutes with argon, in toluene (1 mL/80 mg substrate) was added *via* an argon purged syringe. The resulting suspension was sonicated for 1 minute to generate a fine dispersion of the phase-transfer catalyst. The reaction mixture was then cooled to −15 °C before adding precooled and degassed aqueous KOH (50%, 0.1 mL/80 mg substrate) *via* an argon purged syringe. The biphasic reaction mixture was then stirred rapidly at −15 °C under argon for 24 hours. The reaction was then quenched with saturated aqueous ammonium chloride (5 mL/80 mg substrate) and allowed to warm to room temperature. Following dilution with dichloromethane (20 mL/80 mg substrate), the layers were separated and the aqueous layer extracted with dichloromethane (3 × 10 mL/80 mg substrate). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was then purified to give the desired indane.

General Procedure 5: (*R*,*R*)-**273** (0.02 eq.) was added to a schlenk tube and purged with argon three times. A solution of the substrate, which had been degassed for 30 minutes with argon, in toluene (1 mL/80 mg substrate) was added *via* an argon purged syringe. The resulting suspension was sonicated for 1 minute to generate a fine dispersion of the phase-transfer catalyst. The reaction mixture was then cooled to −15 °C before adding precooled and degassed aqueous KOH (50%, 0.1 mL/80 mg substrate) *via* an argon purged syringe. The biphasic reaction mixture was then stirred rapidly at −15 °C under argon for 24 hours. After complete cyclization the reaction was allowed to warm to room temperature and the electrophile (2.0 eq.) was added followed by degassed DMSO (2 mL/80 mg

substrate). An excess of the electrophile[†] (8.0 eq) was then added over 1 hour *via* syringe pump to the reaction mixture. After 16 hours the reaction was quenched with saturated aqueous ammonium chloride (5 mL/80 mg substrate) and the reaction diluted with ethyl acetate (10 mL/80 mg substrate). The layers were separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL/80 mg substrate). The combined organic layers were washed with brine (3 × 20 mL/80 mg substrate), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was then purified to give the desired alkylated indane.

General Procedure 6: (*R,R*)-**273** (0.02 eq.) was added to a schlenk tube and purged with argon three times. A solution of the substrate, which had been degassed for 30 minutes with argon, in toluene (1 mL/80 mg substrate) was added *via* an argon purged syringe. The resulting suspension was sonicated for 1 minute to generate a fine dispersion of the phase-transfer catalyst. The reaction mixture was then cooled to −15 °C before adding precooled and degassed aqueous KOH (50%, 0.1 mL/80 mg substrate) *via* an argon purged syringe. The biphasic reaction mixture was then stirred rapidly at −15 °C under argon for 24 hours. After complete cyclization, the reaction was allowed to warm to room temperature and an excess of the electrophile (10.0 eq) was then added over 1 hour *via* syringe pump to the reaction mixture. After 16 hours the reaction was quenched with saturated aqueous ammonium chloride (5 mL/80 mg substrate) and the reaction diluted with dichloromethane (20 mL/80 mg substrate). The layers were separated and the aqueous layer extracted with dichloromethane (3 × 10 mL/80 mg substrate). The combined organic layers were dried over

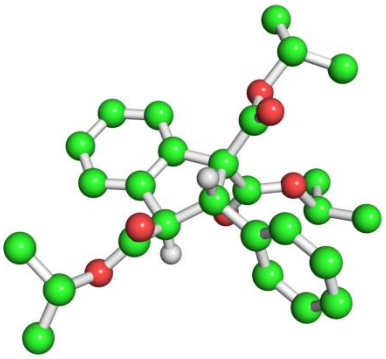
[†] *Solid electrophiles were dissolved in degassed DMSO to allow syringe pump addition*

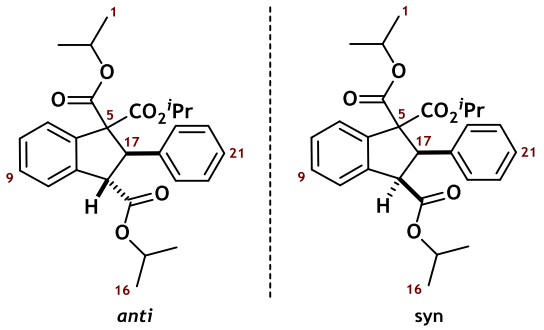
anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was then purified to give the desired alkylated indane.

General Procedure 7: (*R*,*R*)-**273** (0.02 eq.) was added to a schlenk tube and purged with argon three times. A solution of the substrate, which had been degassed for 30 minutes with argon, in toluene (1 mL/80 mg substrate) was added *via* an argon purged syringe. The resulting suspension was sonicated for 1 minute to generate a fine dispersion of the phase-transfer catalyst. The reaction mixture was then cooled to −15 °C before adding precooled and degassed aqueous KOH (50%, 0.1 mL/80 mg substrate) *via* an argon purged syringe. The biphasic reaction mixture was then stirred rapidly at −15 °C under argon for 24 hours. After complete cyclization the reaction was allowed to warm to room temperature and tetrabutylammonium bromide (0.1 eq.) was added under a flow of argon. An excess of the electrophile (10.0 eq) was then added over 1 hour *via* syringe pump to the reaction mixture. After 16 hours the reaction was quenched with saturated aqueous ammonium chloride (5 mL/80 mg substrate) and the reaction diluted with dichloromethane (20 mL/80 mg substrate). The layers were separated and the aqueous layer extracted with dichloromethane (3 × 10 mL/80 mg substrate). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was then purified to give the desired alkylated indane.

5.3.5.3 Full Procedures and Characterization Data for Indanes

Triisopropyl 2-phenyl-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (173)





Racemic: Prepared according to ***general procedure 1*** using cyclization precursor **164** (20 mg, 0.044 mmol). ^{1}H NMR of the crude reaction mixture revealed a 5 : 2 (*anti* : *syn*) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 50 : 1) to afford a 5 : 2 mixture of indanes *anti*-**173** & *syn*-**173** (20 mg, quant.) as a colourless oil. The diastereomers were only partially separable by silica gel chromatography.

Asymmetric: Prepared according to ***general procedure 4*** using cyclization precursor **164** (81 mg, 0.179 mmol). ^{1}H NMR of the crude reaction mixture revealed a 1.2 : 1.0 (*anti* : *syn*) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 50 : 1) to afford a 1.2 : 1.0 mixture of indanes *anti*-**173** (92% ee) & *syn*-**173** (86% ee) as a colourless oil in a combined yield of 57 mg (70%). The diastereomers were only partially separable by silica gel chromatography.

anti-**173** diastereomer:

^{1}H (400 MHz, $CDCl_3$): δ 7.69 – 7.64 (1H, m, **7-H**), 7.47 – 7.43 (1H, m, **10-H**), 7.41 – 7.32 (4H, m, **8-H**, **9-H**, **19-H**), 7.29 – 7.19 (3H, m, **20-H**, **21-H**), 5.13 (1H, sept, *J* 6.3, **2-H**), 5.06 (1H, sept,

J 6.3, **15**-**H**), 4.95 (1H, d, *J* 8.1, **17**-**H**), 4.58 (1H, sept, *J* 6.3, **2**-**H**), 4.43 (1H, d, *J* 7.8, **12**-**H**), 1.30 (3H, d, *J* 6.1, **1**-**H**), 1.27 (3H, d, *J* 6.1, **1**-**H**), 1.23 (6H, app. t, *J* 6.6, **16**-**H**), 1.07 (3H, d, *J* 6.1, **1**-**H**), 0.57 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 171.3 (**C13**), 168.8 (**C4**), 168.7 (**C4**), 141.1 ($\mathbf{C}_{Ar}$**11**), 139.5 ($\mathbf{C}_{Ar}$**6**), 139.3 ($\mathbf{C}_{Ar}$**18**), 129.0 ($\mathbf{C}_{Ar}$**9** & $\mathbf{C}_{Ar}$**19**), 128.3 ($\mathbf{C}_{Ar}$**20**), 128.1 ($\mathbf{C}_{Ar}$**8**), 127.4 ($\mathbf{C}_{Ar}$**21**), 126.5 ($\mathbf{C}_{Ar}$**7**), 124.9 ($\mathbf{C}_{Ar}$**10**), 70.2 (**C5**), 69.6 (**C2**), 69.2 (**C2**), 68.7 (**C15**), 55.5 (**C12**), 53.8 (**C17**), 21.9 (**C1**/**C16**), 21.8 (**C1**/**C16**), 21.7 (**C1**/**C16**), 21.7 (**C1**/**C16**), 21.5 (**C1**), 20.8 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1726 (C=O), 1377, 1256, 1202, 1105 (C–O), 739.

HRMS (ESI): $C_{27}H_{32}O_6Na$ $[M+Na]^+$ requires 475.2091; found 475.2091

MP: 91 – 93 °C (40-60 petrol).

Chiral HPLC: Chiralpak IC (2.5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 203 nm), t_R(**minor**) 9.8 min and t_R(**major**) 15.4 min, 92% ee.

$[\alpha]_D^{20}$ +34.5 (*c* 0.50, chloroform).

syn-**173** diastereomer:

^{1}H (500 MHz, $CDCl_3$): δ 7.74 – 7.71 (1H, m, **7**-**H**), 7.63 (1H, d, *J* 7.6, **10**-**H**), 7.44 – 7.36 (2H, m, **8**-**H**, **9**-**H**), 7.12 – 7.07 (1H, m, **21**-**H**), 7.07 – 7.02 (2H, m, **20**-**H**), 6.93 (2H, d, *J* 7.3, **19**-**H**), 4.96 (1H, sept, *J* 6.3, **2**-**H**), 4.81 (1H, d, *J* 8.2, **12**-**H**), 4.75 (1H, d, *J* 8.2, **17**-**H**), 4.67 (1H, sept, *J* 6.3, **15**-**H**), 4.62 (1H, sept, *J* 6.3, **2**-**H**), 1.25 (3H, d, *J* 6.3, **1**-**H**), 1.11 (3H, d, *J* 6.3, **1**-**H**), 1.07 (3H, d, *J* 6.3, **1**-**H**), 1.05 (3H, d, *J* 6.3, **16**-**H**), 0.70 (3H, d, *J* 6.3, **1**-**H**), 0.65 (3H, d, *J* 6.3, **16**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 170.2 (**C13**), 168.9 (**C4**), 167.4 (**C4**), 140.9 (C_{Ar}**11**), 139.2 (C_{Ar}**6**), 137.6 (C_{Ar}**18**), 129.5 (C_{Ar}**19**), 128.9 (C_{Ar}**9**), 127.9 (C_{Ar}**7**), 127.8 (C_{Ar}**20**), 127.7 (C_{Ar}**21**), 127.6 (C_{Ar}**8**), 126.6 (C_{Ar}**10**), 69.6 (**C2** & **C5**), 68.9 (**C2**), 68.0 (**C15**), 54.9 (**C17**), 53.6 (**C12**), 21.8 (**C1**/**C16**), 21.6 (**C1**/**C16**), 21.5 (**C1**/**C16**), 21.4 (**C1**/**C16**), 21.0 (**C1** & **C16**).

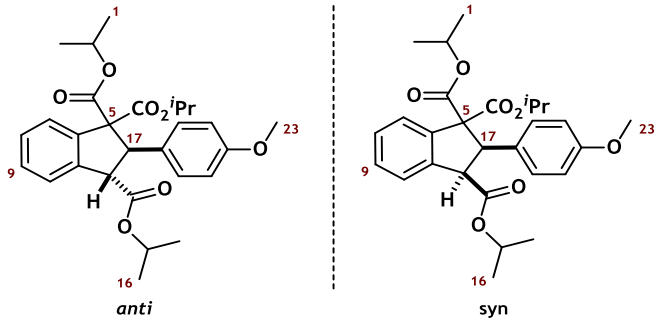
IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1730 (C=O), 1375, 1250, 1158, 1107 (C–O), 699.

HRMS (ESI): $C_{27}H_{32}O_6Na$ $[M+Na]^+$ requires 475.2091; found 475.2085

Chiral HPLC: Chiralpak AD-H (2.5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 205 nm), t_R(**major**) 6.9 min and t_R(**minor**) 9.0 min, 86% ee.

$[\alpha]_D^{20}$ −52.0 (*c* 0.25, chloroform).

Triisopropyl 2-(4-methoxyphenyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (220)



Racemic: Prepared according to ***general procedure 1*** using cyclization precursor **177** (20 mg, 0.041 mmol). ^1H NMR of the crude reaction mixture revealed a 5 : 2 (*anti* : *syn*) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 50 : 1 to 30 : 1) to afford a 5 : 2 mixture of indanes *anti*-**220** & *syn*-**220** (20 mg, quant.) as a colourless oil. The diastereomers were only partially separable by silica gel chromatography.

Asymmetric: Prepared according to ***general procedure 4*** using cyclization precursor **117** (80 mg, 0.166 mmol). ^{1}H NMR of the crude reaction mixture revealed a 1 : 2 (*anti* : *syn*) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 50 : 1 to 30 : 1) to afford a 1 : 2 mixture of indanes *anti*-**220** (96% ee) & *syn*-**220** (95% ee) as a colourless oil in a combined yield of 72 mg (90%). The diastereomers were only partially separable by silica gel chromatography.

anti-**220** diastereomer:

^{1}H (500 MHz, $CDCl_3$): δ 7.66 – 7.63 (1H, m, **7**-**H**), 7.44 – 7.40 (1H, m, **10**-**H**), 7.39 – 7.32 (2H, m, **8**-**H**, **9**-**H**), 7.27 (2H, d, *J* 8.5, **19**-**H**), 6.79 (2H, d, *J* 8.8, **20**-**H**), 5.13 (1H, sept, *J* 6.3, **2**-**H**), 5.05 (1H, sept, *J* 6.3, **15**-**H**), 4.88 (1H, d, *J* 8.2, **17**-**H**), 4.60 (1H, sept, *J* 6.3, **2**-**H**), 4.39 (1H, d, *J* 8.2, **12**-**H**), 3.77 (3H, s, **23**-**H**), 1.30 (3H, d, *J* 6.3, **1**-**H**), 1.27 (3H, d, *J* 6.3, **1**-**H**), 1.24 (3H, d, *J* 6.3, **16**-**H**), 1.22 (3H, d, *J* 6.3, **16**-**H**), 1.08 (3H, d, *J* 6.3, **1**-**H**), 0.64 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.4 (**C13**), 168.9 (**C4**), 168.8 (**C4**), 159.0 ($\mathbf{C}_{Ar}$**21**), 141.2 ($\mathbf{C}_{Ar}$**11**), 139.5 ($\mathbf{C}_{Ar}$**6**), 131.2 ($\mathbf{C}_{Ar}$**18**), 130.1 ($\mathbf{C}_{Ar}$**19**), 129.0 ($\mathbf{C}_{Ar}$**9**), 128.1 ($\mathbf{C}_{Ar}$**8**), 126.5 ($\mathbf{C}_{Ar}$**7**), 124.9 ($\mathbf{C}_{Ar}$**10**), 113.6 ($\mathbf{C}_{Ar}$**20**), 70.2 (**C5**), 69.6 (**C2**), 69.3 (**C2**), 68.7 (**C15**), 55.4 (**C23**) 55.4 (**C12**), 53.2 (**C17**), 22.0 (**C1**/**C16**), 21.9 (**C1**/**C16**), 21.8 (**C1**/**C16**), 21.7 (**C1**/**C16**), 21.6 (**C1**), 21.0 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1721 (C=O), 1514, 1374, 1252, 1181, 1103 (C–O), 748.

HRMS (ESI): $C_{28}H_{34}O_7Na$ $[M+Na]^+$ requires 505.2197; found 505.2179

MP: 108 – 110 °C (40-60 petrol/ethyl acetate).

Chiral HPLC: Chiralpak IC (20% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 204 nm), t_R(**major**) 5.1 min and t_R(**minor**) 5.4 min, 96% ee.

$[\alpha]_D^{20}$ +16.4 (*c* 0.25, chloroform).

syn-**220** diastereomer:

^{1}H (500 MHz, $CDCl_3$): δ 7.71 (1H, d, *J* 7.6, **7**-**H**), 7.61 (1H, d, *J* 7.3, **10**-**H**), 7.43 – 7.33 (2H, m, **8**-**H**, **9**-**H**), 6.84 (2H, d, *J* 8.5, **19**-**H**), 6.59 (2H, d, *J* 8.8, **20**-**H**), 4.95 (1H, sept, *J* 6.3, **2**-**H**), 4.78 (1H, d, *J* 7.9, **12**-**H**), 4.70 (1H, d, *J* 7.9, **17**-**H**), 4.74 – 4.60 (2H, m, **2**-**H**, **15**-**H**), 3.67 (3H, s, **23**-**H**), 1.25 (3H, d, *J* 6.3, **1**-**H**), 1.11 – 1.06 (9H, m, **1**-**H**, **16**-**H**), 0.76 (3H, d, *J* 6.3, **1**-**H**), 0.72 (3H, d, *J* 6.3, **16**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 170.3 (**C13**), 168.9 (**C4**), 167.5 (**C4**), 159.2 ($\mathbf{C}_{Ar}$**21**), 140.9 ($\mathbf{C}_{Ar}$**11**), 139.2 ($\mathbf{C}_{Ar}$**6**), 130.5 ($\mathbf{C}_{Ar}$**19**), 129.7 ($\mathbf{C}_{Ar}$**18**), 128.8 ($\mathbf{C}_{Ar}$**9**), 127.9 ($\mathbf{C}_{Ar}$**7**), 127.6 ($\mathbf{C}_{Ar}$**8**), 126.6 ($\mathbf{C}_{Ar}$**10**), 113.0 ($\mathbf{C}_{Ar}$**20**), 69.7 (**C5**), 69.5 (**C2**), 68.8 (**C2**), 68.0 (**C15**), 55.3 (**C23**), 54.2 (**C17**), 53.6 (**C12**), 21.8 (**C1**/**C16**), 21.6 (**C1**/**C16**), 21.6 (**C1**/**C16**), 21.4 (**C1**/**C16**), 21.2 (**C1**/**C16**), 21.2 (**C1**/**C16**).

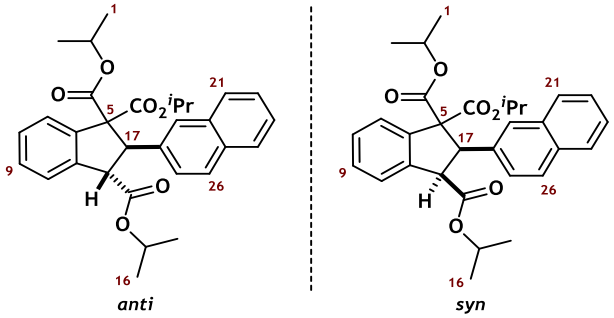
IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1728 (C=O), 1513, 1375, 1249, 1182, 1107 (C–O), 910, 732.

HRMS (ESI): $C_{28}H_{34}O_7Na$ $[M+Na]^+$ requires 505.2197; found 505.2179

Chiral HPLC: Chiralpak AD-H (2.5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 208 nm), t_R(**major**) 12.2 min and t_R(**minor**) 15.2 min, 95% ee.

$[\alpha]_D^{20}$ −56.8 (*c* 0.50, chloroform).

Triisopropyl 2-(naphthalen-2-yl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (219)



Racemic: Prepared according to ***general procedure 1*** using cyclization precursor **162** (20 mg, 0.040 mmol). ^{1}H NMR of the crude reaction mixture revealed a 5 : 2 (*anti* : *syn*) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 50 : 1) to afford a 7 : 2 mixture of indanes *anti*-**219** & *syn*-**219** (15 mg, 75%) as a colourless oil. The diastereomers were only partially separable by silica gel chromatography.

Asymmetric: Prepared according to ***general procedure 4*** using cyclization precursor **162** (80 mg, 0.159 mmol). ^{1}H NMR of the crude reaction mixture revealed a 1 : 3 (*anti* : *syn*) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 50 : 1) to afford a 1 : 3 mixture of indanes *anti*-**219** (95% ee) & *syn*-**219** (97% ee) as a colourless oil in a combined yield of 69 mg (86%). The diastereomers were only partially separable by silica gel chromatography.

anti-**219** diastereomer:

^{1}H (500 MHz, $CDCl_3$): δ 7.84 (1H, s, **19-H**), 7.81 – 7.76 (2H, m, **21-H**, **24-H**), 7.74 (1H, d, *J* 8.5, **26-H**), 7.70 – 7.66 (1H, m, **7-H**), 7.50 – 7.46 (2H, m, **10-H**, **27-H**), 7.46 – 7.42 (2H, m, **22-H**, **23-H**), 7.42 – 7.36 (2H, m, **8-H**, **9-H**), 5.21 – 5.11 (1H, m, **2-H**), 5.14 (1H, d, *J* 8.5, **17-H**), 5.05 (1H, sept, *J* 6.0, **15-H**), 4.56 (1H, d, *J* 8.2, **12-H**), 4.49 (1H, sept, *J* 6.3, **2-H**), 1.31 (3H, d, *J* 6.3,

1-**H**), 1.29 (3H, d, *J* 6.3, **1**-**H**), 1.24 (3H, d, *J* 6.3, **16**-**H**), 1.21 (3H, d, *J* 6.3, **16**-**H**), 1.00 (3H, d, *J* 6.3, **1**-**H**), 0.28 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.3 (**C13**), 168.9 (**C4**), 168.8 (**C4**), 141.2 (C_{Ar}**11**), 139.5 (C_{Ar}**6**), 136.7 (C_{Ar}**18**), 133.3 (C_{Ar}**20**), 132.9 (C_{Ar}**25**), 129.1 (C_{Ar}**9**), 128.3 (C_{Ar}**8**), 128.0 (C_{Ar}**19**), 127.9 (C_{Ar}**21**/C_{Ar}**26**), 127.8 (C_{Ar}**21**/C_{Ar}**26**), 127.6 (C_{Ar}**27**), 127.3 (C_{Ar}**24**), 126.5 (C_{Ar}**7**), 126.0 (C_{Ar}**22**/C_{Ar}**23**), 125.8 (C_{Ar}**22**/C_{Ar}**23**), 124.9 (C_{Ar}**10**), 70.3 (**C5**), 69.7 (**C2**), 69.3 (**C2**), 68.8 (**C15**), 55.4 (**C12**), 53.9 (**C17**), 22.0 (**C1**/**C16**), 21.9 (**C1**/**C16**), 21.8 (**C1**/**C16**), 21.7 (**C1**/**C16**), 21.5 (**C1**), 20.6 (**C1**).

IR: v_{max} (neat)/ cm^{-1} 2981 (C–H), 1722 (C=O), 1374, 1257, 1203, 1103 (C–O), 746.

HRMS (ESI): $C_{31}H_{34}O_6Na$ $[M+Na]^+$ requires 525.2253; found 525.2251

MP: 128 – 130 °C (hexane).

Chiral HPLC: Chiralpak AD-H (2.5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 228 nm), t_R(**major**) 11.7 min and t_R(**minor**) 28.1 min, 95% ee.

$[\alpha]_D^{20}$ +20.5 (*c* 0.35, chloroform).

syn-**219** diastereomer:

^{1}H (500 MHz, $CDCl_3$): δ 7.78 – 7.74 (1H, m, **7**-**H**), 7.70 – 7.63 (3H, m, **10**-**H**, **21**-**H**,), 7.52 – 7.48 (2H, m, **19**-**H**, **26**-**H**), 7.48 – 7.40 (2H, m, **8**-**H**, **9**-**H**), 7.39 – 7.34 (3H, m, **Ar**-**H**), 6.95 (1H, dd, *J* 8.8, 1.3, **27**-**H**), 4.99 (1H, sept, *J* 6.0, **2**-**H**), 4.94 (1H, d, *J* 8.2, **17**-**H**), 4.88 (1H, d, *J* 7.9, **12**-**H**), 4.56 (1H, sept, *J* 6.3, **15**-**H**), 4.49 (1H, sept, *J* 6.3, **2**-**H**), 1.27 (3H, d, *J* 6.3, **1**-**H**), 1.12 (3H, d, *J* 6.3, **1**-**H**), 1.00 (3H, d, *J* 6.0, **1**-**H**), 0.97 (3H, d, *J* 6.0, **16**-**H**), 0.52 (3H, d, *J* 6.3, **1**-**H**), 0.46 (3H, d, *J* 6.0, **16**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 170.2 (**C13**), 168.9 (**C4**), 167.4 (**C4**), 140.9 (C_{Ar}**11**), 139.2 (C_{Ar}**6**), 135.2 (C_{Ar}**18**), 133.0 (C_{Ar}**20**/C_{Ar}**25**), 132.9 (C_{Ar}**20**/C_{Ar}**25**), 129.0 (C_{Ar}**9** & C_{Ar}**19**), 127.9 (C_{Ar}**7**), 127.9 (C_{Ar}**21**/C_{Ar}**24**), 127.7 (C_{Ar}**8**), 127.5 (C_{Ar}**21**/C_{Ar}**24**), 127.3 (C_{Ar}**26**), 126.9 (C_{Ar}**27**), 126.6 (C_{Ar}**10**), 125.8 (C_{Ar}**22**/C_{Ar}**23**), 125.7 (C_{Ar}**22**/C_{Ar}**23**), 69.7 (**C5**), 69.7 (**C2**), 68.8 (**C2**), 67.9 (**C15**), 55.1 (**C17**), 53.6 (**C12**), 21.7 (**C1**/**C16**), 21.6 (**C1**/**C16**), 21.5 (**C1**), 21.4 (**C1**), 20.9 (**C1** & **C16**).

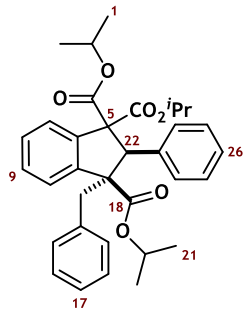
IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1728 (C=O), 1250, 1205, 1106 (C–O), 910, 732.

HRMS (ESI): $C_{31}H_{34}O_6Na$ $[M+Na]^+$ requires 525.2253; found 525.2251

Chiral HPLC: Chiralpak AD-H (2.5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 229 nm), t_R(**minor**) 21.2 min and t_R(**major**) 26.5 min, 97% ee.

$[\alpha]_D^{20}$ −76.6 (*c* 0.75, chloroform).

Triisopropyl 3-benzyl-2-phenyl-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (301)



Racemic: Prepared according to ***general procedure 2*** using cyclization precursor **164** (58 mg, 0.128 mmol) and benzyl bromide (30 μL, 0.256 mmol & 121 μL, 1.02 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1 to 30 : 1) to afford indane **301** (55 mg, 80%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 5*** using cyclization precursor **164** (80 mg, 0.177 mmol) and benzyl bromide (42 μL, 0.354 mmol & 169 μL, 1.42 mmol). The

crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1 to 30 : 1) to afford indane **301** (75 mg, 77%, 91% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.75 (1H, d, *J* 7.6, **7**-**H**), 7.37 (1H, app. td, *J* 7.6, 1.1, **8**-**H**), 7.22 – 7.12 (4H, m, **9**-**H**, **16**-**H**, **17**-**H**), 7.11 – 7.02 (3H, m, **25**-**H**, **26**-**H**), 6.97 (2H, br. d, *J* 5.7, **24**-**H**), 6.73 (2H, d, *J* 6.9, **15**-**H**), 6.58 (1H, d, *J* 7.6, **10**-**H**), 5.08 (1H, sept, *J* 6.2, **2**-**H**), 4.73 (1H, s, **22**-**H**), 4.45 (2H, app. septd, *J* 6.3, 2.5, **2**-**H**, **20**-**H**), 3.84 (1H, d, *J* 13.2, **13**-**H**), 3.07 (1H, d, *J* 13.2, **13**-**H**), 1.31 (3H, d, *J* 6.3, **1**-**H**), 1.23 (3H, d, *J* 6.3, **1**-**H**), 1.05 (3H, d, *J* 6.3, **1**-**H**), 1.01 (3H, d, *J* 6.3, **21**-**H**), 0.60 (6H, app. dd, *J* 6.3, 3.8, **1**-**H**, **21**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.6 (**C18**), 169.6 (**C4**), 167.9 (**C4**), 143.4 (C_{Ar}**11**), 139.2 (C_{Ar}**23**), 138.5 (C_{Ar}**6**), 136.9 (C_{Ar}**14**), 130.9 (C_{Ar}**15**), 129.9 (C_{Ar}**24**), 128.9 (C_{Ar}**7**/C_{Ar}**10**), 128.8 (C_{Ar}**7**/C_{Ar}**10**), 127.8 (C_{Ar}**16**), 127.7 (C_{Ar}**25**), 127.5 (C_{Ar}**26**), 127.5 (C_{Ar}**8**), 127.1 (C_{Ar}**9**), 126.8 (C_{Ar}**17**), 70.4 (**C5**), 70.0 (**C2**), 69.3 (**C2**), 68.6 (**C20**), 66.2 (**C12**), 61.0 (**C22**), 47.6 (**C13**), 21.7 (**C1**/**C21**), 21.6 (**C1**/**C21**), 21.6 (**C1**/**C21**), 21.5 (**C1**), 20.8 (**C1**/**C21**), 20.7 (**C1**/**C21**).

IR: ν_{max} (neat)/ cm^{-1} 2980 (C–H), 1730 (C=O), 1455, 1244, 1195, 1104 (C–O), 700.

HRMS (ESI): $C_{34}H_{38}O_6Na$ $[M+Na]^+$ requires 565.2561; found 565.2565

MP: 90 – 92 °C (hexane/ethyl acetate).

Chiral HPLC: Chiralpak IC (2.0% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 201 nm), t_R(**minor**) 6.6 min and t_R(**major**) 7.7 min, 91% ee.

$[\alpha]_D^{20}$ +1.2 (*c* 0.70, chloroform).

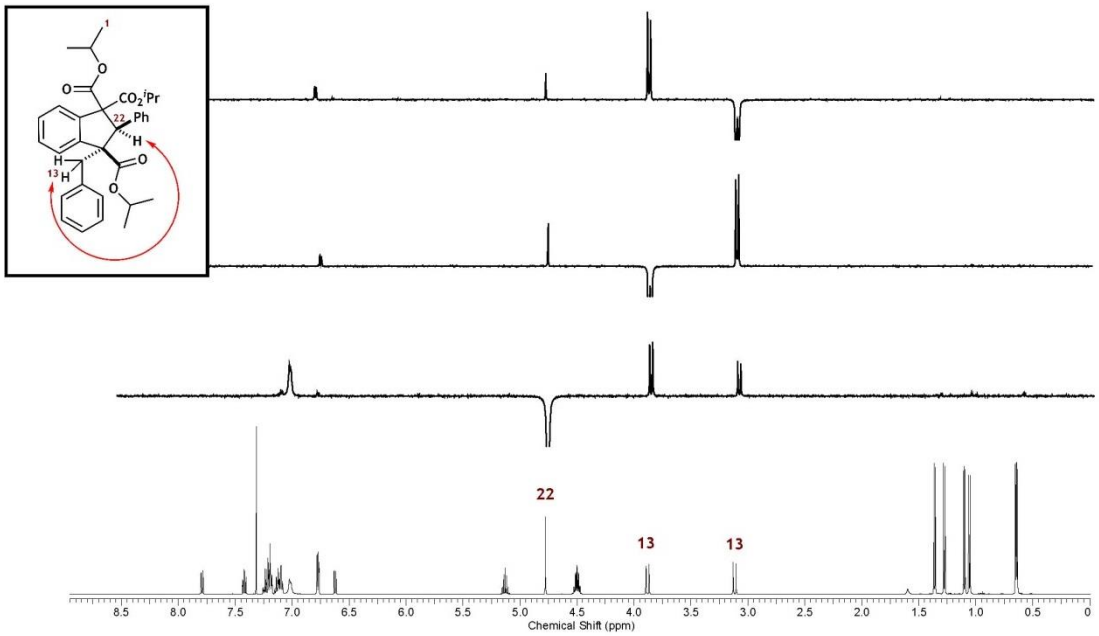
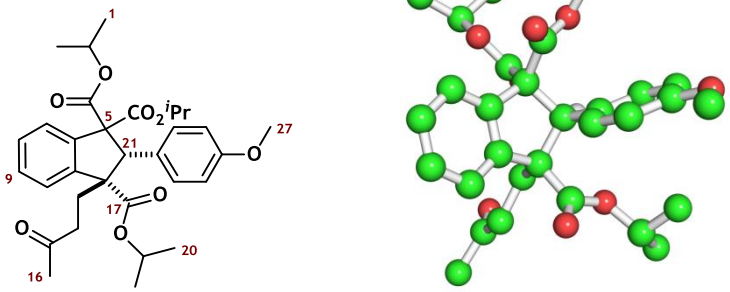


Figure 5.1 – 1D nOe data for indane **301** in $CDCl_3$ (mixing time = 0.8 s).

Triisopropyl 2-(4-methoxyphenyl)-3-(3-oxobutyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (305)



Racemic: Prepared according to ***general procedure 3*** using cyclization precursor **177** (40 mg, 0.083 mmol) and methyl vinyl ketone (67 μL, 0.830 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1 to 9 : 1) to afford indane **305** (30 mg, 68%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 6*** using cyclization precursor **177** (80 mg, 0.166 mmol), methyl vinyl ketone (135 μL, 1.66 mmol) and (*S*,*S*)-**273** (3 mg,

3.32 μmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1 to 9 : 1) to afford indane **305** (62 mg, 66%, 94% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.74 – 7.70 (1H, m, **7**-**H**), 7.58 – 7.53 (1H, m, **10**-**H**), 7.43 – 7.38 (2H, m, **8**-**H**, **9**-**H**), 6.85 (2H, br. d, *J* 7.9, **23**-**H**), 6.59 (2H, d, *J* 9.1, **24**-**H**), 5.00 (1H, sept, *J* 6.3, **2**-**H**), 4.55 (1H, s, **21**-**H**), 4.57 – 4.44 (2H, m, **2**-**H**, **19**-**H**), 3.67 (3H, s, **27**-**H**), 2.61 – 2.52 (1H, m, **14**-**H**), 2.51 – 2.39 (2H, m, **13**-**H**, **14**-**H**), 2.11 – 2.02 (1H, m, **13**-**H**), 2.09 (3H, s, **16**-**H**), 1.28 (3H, d, *J* 6.0, **1**-**H**), 1.19 (3H, d, *J* 6.3, **1**-**H**), 1.05 (3H, d, *J* 6.3, **1**-**H**), 1.03 (3H, d, *J* 6.3, **20**-**H**), 0.68 (3H, d, *J* 6.3, **20**-**H**), 0.65 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 207.6 (**C15**), 171.8 (**C17**), 169.1 (**C4**), 167.8 (**C4**), 159.1 (C_{Ar}**25**), 144.6 (C_{Ar}**11**), 138.3 (C_{Ar}**6**), 131.1 (C_{Ar}**22**), 130.7 (br., C_{Ar}**23**), 129.5 (C_{Ar}**7**), 128.3 (C_{Ar}**9**), 127.8 (C_{Ar}**8**), 126.8 (C_{Ar}**10**), 112.9 (C_{Ar}**24**), 70.3 (**C5**), 70.0 (**C2**), 69.2 (**C2**), 68.3 (**C19**), 63.5 (**C12**), 59.2 (**C21**), 55.3 (**C27**), 39.9 (**C14**), 35.7 (**C13**), 29.9 (**C16**), 21.7 (**C1**/**C20**), 21.5 (**C1**/**C20**), 21.5 (**C1**/**C20**), 21.5 (**C1**/**C20**), 20.9 (**C1**/**C20**), 20.9 (**C1**/**C20**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1729 (C=O), 1513, 1374, 1242, 1103 (C–O), 910, 732.

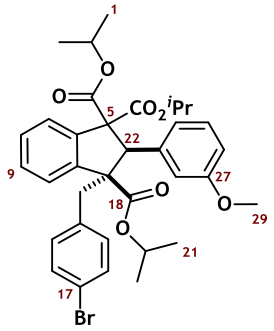
HRMS (ESI): $C_{32}H_{40}O_8Na$ $[M+Na]^+$ requires 575.2615; found 575.2626

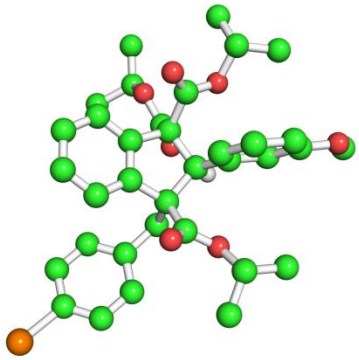
MP: 102 – 104 °C (hexane/ethyl acetate).

Chiral HPLC: Chiralpak AD-H (5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 205 nm), t_R(**minor**) 11.9 min and t_R(**major**) 14.8 min, 94% ee.

$[\alpha]_D^{20}$ −26.2 (*c* 0.70, chloroform).

Triisopropyl 3-(4-bromobenzyl)-2-(3-methoxyphenyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (304)





Racemic: Prepared according to ***general procedure 2*** using cyclization precursor **178** (47 mg, 0.097 mmol) and 4-bromobenzyl bromide (48 mg, 0.194 mmol & 194 mg, 0.776 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1 to 30 : 1) to afford indane **304** (22 mg, 35%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 5*** using cyclization precursor **178** (81 mg, 0.168 mmol) and 4-bromobenzyl bromide (84 mg, 0.336 mmol & 335 mg, 1.34 mmol). The reaction solvent was toluene : chloroform (9 : 1, 1 mL). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1 to 30 : 1) to afford indane **304** (96 mg, 88%, 86% ee, >20 : 1 dr) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.74 (1H, d, *J* 7.8, **7-H**), 7.37 (1H, app. t, *J* 7.6, **8-H**), 7.28 (2H, d, *J* 8.1, **16-H**), 7.17 (1H, app. t, *J* 7.6, **9-H**), 6.94 (1H, app. t, *J* 8.0, **25-H**), 6.67 – 6.58 (4H, m, **10-H**, **15-H**, **26-H**), 6.56 (1H, br. s, **30-H**), 6.49 (1H, br. d, *J* 6.3, **24-H**), 5.06 (1H, sept, *J* 6.2, **2-H**), 4.67 (1H, s, **22-H**), 4.49 (2H, app. non, *J* 6.3, **2-H**, **20-H**), 3.76 (1H, d, *J* 13.4, **13-H**), 3.63 (3H, s, **29-H**), 3.02 (1H, d, *J* 13.4, **13-H**), 1.31 (3H, d, *J* 6.3, **1-H**), 1.22 (3H, d, *J* 6.3, **1-H**), 1.06 (3H, d, *J* 6.3, **1-H**), 0.99 (3H, d, *J* 6.1, **21-H**), 0.64 (6H, app. t, *J* 6.8, **1-H**, **21-H**).

^{13}C (101 MHz, $CDCl_3$): δ 171.4 (**C18**), 169.6 (**C4**), 167.7 (**C4**), 158.7 (C_{Ar}**27**), 143.1 (C_{Ar}**11**), 140.4 (C_{Ar}**23**), 138.5 (C_{Ar}**6**), 135.8 (C_{Ar}**14**), 132.6 (C_{Ar}**15**), 130.9 (C_{Ar}**16**), 128.9 (C_{Ar}**7**), 128.7 (C_{Ar}**10** & C_{Ar}**25**), 127.7 (C_{Ar}**8**), 127.3 (C_{Ar}**9**), 122.0 (br., C_{Ar}**24**), 120.9 (C_{Ar}**17**), 115.8 (br., C_{Ar}**30**), 113.3 (C_{Ar}**26**), 70.3 (**C5**), 70.1 (**C2**), 69.3 (**C2**), 68.6 (**C20**), 66.0 (**C12**), 61.0 (**C22**), 55.1 (**C29**), 47.0 (**C13**), 21.6 (**C1**/**C21**), 21.6 (**C1**/**C21**), 21.5 (**C1**/**C21**), 20.9 (**C1**/**C21**), 20.7 (**C1**/**C21**).[†]

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1728 (C=O), 1488, 1243, 1198, 1103 (C–O), 908, 730.

HRMS (ESI): $C_{35}H_{40}{}^{79}BrO_7$ $[M+H]^+$ requires 651.1952; found 651.1943

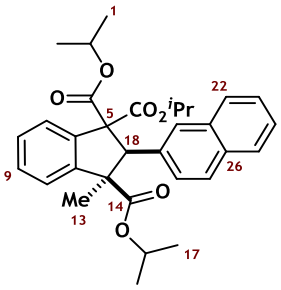
MP: 136 – 137 °C.

Chiral HPLC: Chiralpak AD-H (2.5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 210 nm), t_R(**major**) 10.0 min and t_R(**minor**) 13.6 min, 86% ee.

$[\alpha]_D^{20}$ +10.8 (*c* 0.45, chloroform).

Triisopropyl 3-methyl-2-(naphthalen-2-yl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate

(302)



Racemic: Prepared according to ***general procedure 2*** using cyclization precursor **162** (49 mg, 0.097 mmol) and methyl iodide (12 μL, 0.194 mmol & 48 μL, 0.776 mmol). The crude product

[†] *A peak for **C1**/**C21** was not observed and assumed coincident.*

was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1) to afford indane **302** (16 mg, 32%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 5*** using cyclization precursor **162** (71 mg, 0.141 mmol) and methyl iodide (18 μL, 0.282 mmol & 70 μL, 1.13 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1) to afford indane **302** (43 mg, 59%, 92% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.73 (1H, dd, *J* 7.6, 0.9, **7**-**H**), 7.69 – 7.63 (2H, m, **22**-**H**, **25**-**H**), 7.58 (1H, dd, *J* 7.6, 0.9, **10**-**H**), 7.54 – 7.50 (2H, m, **20**-**H**, **27**-**H**), 7.46 (1H, app. td, *J* 7.4, 1.3, **9**-**H**), 7.42 (1H, app. td, *J* 7.6, 1.6, **8**-**H**), 7.39 – 7.33 (2H, m, **23**-**H**, **24**-**H**), 7.03 (1H, dd, *J* 8.7, 1.1, **28**-**H**), 5.01 (1H, sept, *J* 6.3, **2**-**H**), 4.72 (1H, s, **18**-**H**), 4.37 (1H, sept, *J* 6.3, **16**-**H**), 4.32 (1H, sept, *J* 6.3, **2**-**H**), 1.74 (3H, s, **13**-**H**), 1.28 (3H, d, *J* 6.0, **1**-**H**), 1.18 (3H, d, *J* 6.3, **1**-**H**), 0.95 (3H, d, *J* 6.0, **1**-**H**), 0.91 (3H, d, *J* 6.3, **17**-**H**), 0.32 (6H, app. t, *J* 6.5, **1**-**H**, **17**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 173.2 (**C14**), 169.3 (**C4**), 167.9 (**C4**), 147.1 ($\mathbf{C}_{Ar}$**11**), 137.8 ($\mathbf{C}_{Ar}$**6**), 137.1 ($\mathbf{C}_{Ar}$**19**), 132.9 ($\mathbf{C}_{Ar}$**21**/$\mathbf{C}_{Ar}$**26**), 132.8 ($\mathbf{C}_{Ar}$**21**/$\mathbf{C}_{Ar}$**26**), 129.0 ($\mathbf{C}_{Ar}$**9**), 128.9 ($\mathbf{C}_{Ar}$**7**), 128.7 (br., $\mathbf{C}_{Ar}$**20**), 127.9 ($\mathbf{C}_{Ar}$**22**/$\mathbf{C}_{Ar}$**25**), 127.6 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**22**/$\mathbf{C}_{Ar}$**25** & $\mathbf{C}_{Ar}$**28**), 127.5 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**22**/$\mathbf{C}_{Ar}$**25**), 127.1 ($\mathbf{C}_{Ar}$**27**), 126.0 ($\mathbf{C}_{Ar}$**10**), 125.8 ($\mathbf{C}_{Ar}$**23**/$\mathbf{C}_{Ar}$**24**), 125.6 ($\mathbf{C}_{Ar}$**23**/$\mathbf{C}_{Ar}$**24**), 70.6 (**C5**), 70.0 (**C2**), 69.1 (**C2**), 68.0 (**C16**), 60.5 (**C12**), 60.4 (**C18**), 30.3 (**C13**), 21.6 (**C1**/**C17**), 21.6 (**C1**/**C17**), 21.5 (**C1**/**C17**), 21.4 (**C1**), 20.6 (**C1**/**C17**), 20.5 (**C1**/**C17**).

IR: ν_{max} (neat)/ cm^{-1} 2980 (C–H), 1731 (C=O), 1374, 1244, 1199, 1105 (C–O), 751.

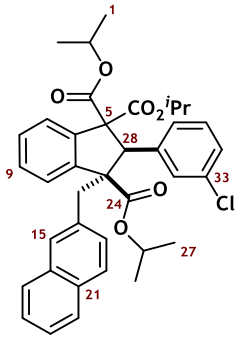
HRMS (ESI): $C_{32}H_{36}O_6Na$ $[M+Na]^+$ requires 539.2404; found 539.2383

MP: 110 – 112 °C.

Chiral HPLC: Chiralpak AD-H (1.3% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 229 nm), t_R(**minor**) 31.7 min and t_R(**major**) 33.8 min, 92% ee.

$[\alpha]_D^{20}$ −2.2 (*c* 0.45, chloroform).

Triisopropyl 2-(3-chlorophenyl)-3-(naphthalen-2-ylmethyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (303)



Racemic: Prepared according to ***general procedure 2*** using cyclization precursor **179** (85 mg, 0.175 mmol) and 2-(bromomethyl)naphthalene (77 mg, 0.350 mmol & 310 mg, 1.40 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 49 : 1) to afford indane **303** (40 mg, 36%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 5*** using cyclization precursor **179** (84 mg, 0.172 mmol) and 2-(bromomethyl)naphthalene (76 mg, 0.344 mmol & 305 mg, 1.38 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 49 : 1) to afford indane **303** (71 mg, 66%, 92% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.82 – 7.74 (2H, m, **7**-**H**, **20**-**H**), 7.67 – 7.61 (2H, m, **17**-**H**, **22**-**H**), 7.46 – 7.40 (2H, m, **18**-**H**, **19**-**H**), 7.40 (1H, app. td, *J* 7.6, 1.3, **8**-**H**), 7.23 (1H, s, **15**-**H**), 7.17 (1H, br. s, **34**-**H**), 7.13 – 7.08 (2H, m, **9**-**H**, **32**-**H**), 6.96 (1H, app. t, *J* 7.9, **31**-**H**), 6.84 (1H, dd, *J* 8.5,

1.6, **23**-**H**), 6.74 (1H, br. d, *J* 7.3, **30**-**H**), 6.55 (1H, d, *J* 7.6, **10**-**H**), 5.12 (1H, sept, *J* 6.2, **2**-**H**), 4.76 (1H, s, **28**-**H**), 4.58 – 4.46 (2H, m, **2**-**H**, **26**-**H**), 3.97 (1H, d, *J* 13.2, **13**-**H**), 3.22 (1H, d, *J* 13.2, **13**-**H**), 1.34 (3H, d, *J* 6.3, **1**-**H**), 1.27 (3H, d, *J* 6.3, **1**-**H**), 1.10 (3H, d, *J* 6.3, **1**-**H**), 1.08 (3H, d, *J* 6.3, **27**-**H**), 0.69 (3H, d, *J* 6.3, **1**-**H**), 0.66 (3H, d, *J* 6.3, **27**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.4 (**C24**), 169.4 (**C4**), 167.7 (**C4**), 143.1 ($\mathbf{C}_{Ar}$**11**), 141.4 ($\mathbf{C}_{Ar}$**29**), 138.2 ($\mathbf{C}_{Ar}$**6**), 134.2 ($\mathbf{C}_{Ar}$**14**), 133.3 ($\mathbf{C}_{Ar}$**16**/$\mathbf{C}_{Ar}$**33**), 133.2 ($\mathbf{C}_{Ar}$**16**/$\mathbf{C}_{Ar}$**33**), 132.5 ($\mathbf{C}_{Ar}$**21**), 130.9 (br., $\mathbf{C}_{Ar}$**34**), 129.5 ($\mathbf{C}_{Ar}$**15**), 129.3 ($\mathbf{C}_{Ar}$**23**), 129.1 ($\mathbf{C}_{Ar}$**31**), 128.9 ($\mathbf{C}_{Ar}$**7**), 128.9 ($\mathbf{C}_{Ar}$**10**), 127.8 ($\mathbf{C}_{Ar}$**8**), 127.7 ($\mathbf{C}_{Ar}$**17**/$\mathbf{C}_{Ar}$**20**/$\mathbf{C}_{Ar}$**22**/$\mathbf{C}_{Ar}$**32**), 127.7 ($\mathbf{C}_{Ar}$**17**/$\mathbf{C}_{Ar}$**20**/$\mathbf{C}_{Ar}$**22**/$\mathbf{C}_{Ar}$**32**), 127.6 ($\mathbf{C}_{Ar}$**17**/$\mathbf{C}_{Ar}$**20**/$\mathbf{C}_{Ar}$**22**/$\mathbf{C}_{Ar}$**32**), 127.4 ($\mathbf{C}_{Ar}$**17**/$\mathbf{C}_{Ar}$**20**/$\mathbf{C}_{Ar}$**22**/$\mathbf{C}_{Ar}$**32**), 127.2 ($\mathbf{C}_{Ar}$**9**), 127.0 (br., $\mathbf{C}_{Ar}$**30**), 125.9 ($\mathbf{C}_{Ar}$**18**/ $\mathbf{C}_{Ar}$**19**), 125.6 ($\mathbf{C}_{Ar}$**18**/ $\mathbf{C}_{Ar}$**19**), 70.3 (**C2** & **C5**), 69.5 (**C2**), 68.9 (**C26**), 66.2 (**C12**), 60.6 (**C28**), 47.8 (**C13**), 21.7 (**C1**/**C27**), 21.7 (**C1**/**C27**), 21.6 (**C1**/**C27**), 21.5 (**C1**), 20.9 (**C27**), 20.7 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1730 (C=O), 1454, 1244, 1196, 1104 (C–O), 909.

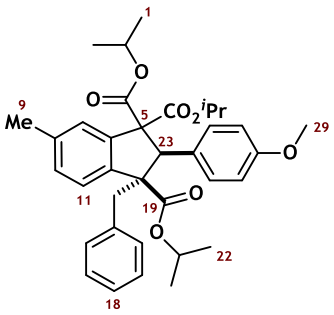
HRMS (ESI): $C_{38}H_{39}{}^{35}ClO_6Na$ $[M+Na]^+$ requires 649.2327; found 649.2320

MP: 182 – 184 °C (hexane).

Chiral HPLC: Chiralpak AD-H (2.0% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 234 nm), t_R(**major**) 13.0 min and t_R(**minor**) 20.1 min, 92% ee.

$[\alpha]_D^{20}$ +15.5 (*c* 0.40, chloroform).

Triisopropyl 3-benzyl-2-(4-methoxyphenyl)-6-methyl-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (307)



Racemic: Prepared according to ***general procedure 2*** using cyclization precursor **181** (74 mg, 0.149 mmol) and benzyl bromide (35 μL, 0.298 mmol & 142 μL, 1.19 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1) to afford indane **307** (55 mg, 63%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 5*** using cyclization precursor **181** (81 mg, 0.163 mmol) and benzyl bromide (39 μL, 0.326 mmol & 155 μL, 1.30 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1) to afford indane **307** (87 mg, 93%, 97% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.53 (1H, s, **7**-**H**), 7.21 – 7.11 (3H, m, **17**-**H**, **18**-**H**), 6.95 (1H, dd, *J* 8.0, 1.1, **10**-**H**), 6.89 (2H, br. d, *J* 7.3, **25**-**H**), 6.74 (2H, d, *J* 6.6, **16**-**H**), 6.60 (2H, d, *J* 8.8, **26**-**H**), 6.45 (1H, d, *J* 7.9, **11**-**H**), 5.07 (1H, sept, *J* 6.3, **2**-**H**), 4.66 (1H, s, **23**-**H**), 4.54 – 4.42 (2H, m, **2**-**H**, **21**-**H**), 3.80 (1H, d, *J* 12.9, **14**-**H**), 3.67 (3H, s, **29**-**H**), 3.04 (1H, d, *J* 13.2, **14**-**H**), 2.42 (3H, s, **9**-**H**), 1.31 (3H, d, *J* 6.0, **1**-**H**), 1.23 (3H, d, *J* 6.3, **1**-**H**), 1.08 (3H, d, *J* 6.3, **1**-**H**), 1.02 (3H, d, *J* 6.3, **22**-**H**), 0.65 (6H, app. dd, *J* 6.3, 2.5, **1**-**H**, **22**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.8 (**C19**), 169.8 (**C4**), 168.1 (**C4**), 159.0 (C_{Ar}**27**), 140.5 (C_{Ar}**12**), 138.5 (C_{Ar}**6**), 137.1 (C_{Ar}**8**/C_{Ar}**15**), 137.0 (C_{Ar}**8**/C_{Ar}**15**), 131.5 (C_{Ar}**24**), 130.9 (C_{Ar}**16** & C_{Ar}**25**), 129.2 (C_{Ar}**7**),

128.5 (C_{Ar}**11**), 128.3 (C_{Ar}**10**), 127.7 (C_{Ar}**17**), 126.7 (C_{Ar}**18**), 112.9 (C_{Ar}**26**), 70.3 (**C5**), 69.9 (**C2**), 69.2 (**C2**), 68.4 (**C21**), 66.0 (**C13**), 60.4 (**C23**), 55.4 (**C29**), 47.5 (**C14**), 21.7 (**C1**/**C9**/**C22**), 21.6 (**C1**/**C9**/**C22**), 21.6 (**C1**/**C9**/**C22**), 21.0 (**C1**/**C22**), 20.9 (**C1**/**C22**).[†]

IR: v_{max} (neat)/ cm^{-1} 2980 (C–H), 1731 (C=O), 1513, 1246, 1195, 1106 (C–O), 702.

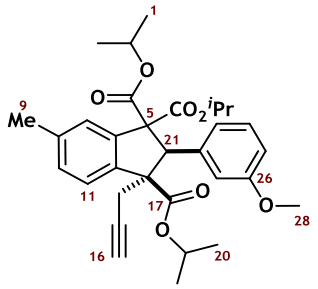
HRMS (ESI): $C_{36}H_{42}O_7Na$ $[M+Na]^+$ requires 609.2823; found 609.2818

MP: 108 – 110 °C (hexane).

Chiral HPLC: Chiralpak AD-H (5.0% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 205 nm), t_R(**major**) 6.5 min and t_R(**minor**) 8.7 min, 97% ee.

$[\alpha]_D^{20}$ +3.8 (*c* 0.55, chloroform).

Triisopropyl 2-(3-methoxyphenyl)-6-methyl-3-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (308)



Racemic: Prepared according to ***general procedure 2*** using cyclization precursor **182** (48 mg, 0.097 mmol) and propargyl bromide (80 wt.% in toluene, 22 μL, 0.194 mmol & 86 μL, 0.776 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1) to afford indane **308** (23 mg, 44%, >20 : 1 dr) as a white solid.

[†] *Only five peaks are observed for **C1**, **C9** & **C22** instead of seven due to overlapping signals*

Asymmetric: Prepared according to ***general procedure 5*** using cyclization precursor **182** (90 mg, 0.181 mmol) and propargyl bromide (80 wt.% in toluene, 40 μL, 0.362 mmol & 162 μL, 1.45 mmol). The reaction solvent was toluene : chloroform (9 : 1, 1.2 mL). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1) to afford indane **308** (75 mg, 77%, 89% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.68 (1H, d, *J* 7.9, **11**-**H**), 7.51 (1H, s, **7**-**H**), 7.23 (1H, dd, *J* 8.0, 1.1, **10**-**H**), 6.95 (1H, app. t, *J* 8.0, **24**-**H**), 6.65 (1H, dd, *J* 8.4, 1.7, **25**-**H**), 6.57 (1H, br. s, **29**-**H**), 6.50 (1H, br. d, *J* 7.3, **23**-**H**), 4.97 (1H, sept, *J* 6.3, **2**-**H**), 4.56 (1H, sept, *J* 6.3, **19**-**H**), 4.51 (1H, sept, *J* 6.3, **2**-**H**), 4.41 (1H, s, **21**-**H**), 3.66 (3H, s, **28**-**H**), 3.25 (1H, dd, *J* 16.6, 2.7, **14**-**H**), 2.76 (1H, dd, *J* 16.6, 2.7, **14**-**H**), 2.44 (3H, s, **9**-**H**), 2.04 (1H, t, *J* 2.5, **16**-**H**), 1.27 (3H, d, *J* 6.0, **1**-**H**), 1.18 (3H, d, *J* 6.3, **1**-**H**), 1.06 (6H, app. dd, *J* 6.3, 2.8, **1**-**H**, **20**-**H**), 0.70 (3H, d, *J* 6.3, **20**-**H**), 0.57 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 170.6 (**C17**), 169.4 (**C4**), 167.6 (**C4**), 158.6 ($\mathbf{C}_{Ar}$**26**), 141.0 ($\mathbf{C}_{Ar}$**12**), 140.0 ($\mathbf{C}_{Ar}$**22**), 138.2 ($\mathbf{C}_{Ar}$**6**), 137.9 ($\mathbf{C}_{Ar}$**8**), 129.5 ($\mathbf{C}_{Ar}$**10**), 128.8 ($\mathbf{C}_{Ar}$**7**), 128.6 ($\mathbf{C}_{Ar}$**24**), 127.3 ($\mathbf{C}_{Ar}$**11**), 121.8 (br., $\mathbf{C}_{Ar}$**23**), 115.8 (br., $\mathbf{C}_{Ar}$**29**), 113.3 ($\mathbf{C}_{Ar}$**25**), 80.9 (**C15**), 71.2 (**C16**), 70.1 (**C5**), 70.0 (**C2**), 69.0 (**C2**), 68.2 (**C19**), 62.8 (**C13**), 60.3 (**C21**), 55.1 (**C28**), 32.1 (**C14**), 21.6 (**C9**), 21.5 (**C1**/**C20**), 21.5 (**C1**/**C20**), 21.4 (**C1**/**C20**), 21.4 (**C1**/**C20**), 20.9 (**C20**), 20.5 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 2362 (C≡C), 1728 (C=O), 1491, 1374, 1247, 1204, 1106 (C–O), 915, 703.

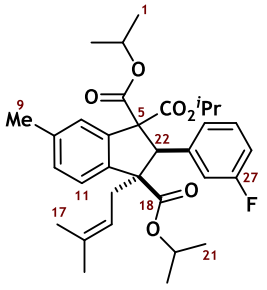
HRMS (ESI): $C_{32}H_{38}O_7Na$ $[M+Na]^+$ requires 557.2510; found 557.2494

MP: 136 – 138 °C.

Chiral HPLC: Chiralpak IA (2.5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 207 nm), t_R(**major**) 7.6 min and t_R(**minor**) 8.4 min, 89% ee.

$[\alpha]_D^{20}$ +5.3 (*c* 0.45, chloroform).

Triisopropyl 2-(3-fluorophenyl)-6-methyl-3-(3-methylbut-2-en-1-yl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (309)



Racemic: Prepared according to ***general procedure 2*** using cyclization precursor **183** (82 mg, 0.169 mmol) and prenyl bromide (39 μL, 0.338 mmol & 156 μL, 1.35 mmol). The crude product was purified twice by silica gel chromatography (40-60 petrol : ethyl acetate, 50 : 1) followed by (toluene) to afford indane **309** (53 mg, 57%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 5*** using cyclization precursor **183** (82 mg, 0.169 mmol) and prenyl bromide (39 μL, 0.338 mmol & 156 μL, 1.35 mmol). The crude product was purified twice by silica gel chromatography (40-60 petrol : ethyl acetate, 50 : 1) followed by (toluene) to afford indane **309** (77 mg, 82%, 98% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.50 (1H, s, **7-H**), 7.36 (1H, d, *J* 7.9, **11-H**), 7.16 (1H, dd, *J* 8.0, 1.1, **10-H**), 7.00 (1H, app. td, *J* 7.9, 6.3, **25-H**), 6.82 – 6.74 (2H, m, **26-H**, **28-H**), 6.70 (1H, d, *J* 7.9, **24-H**), 5.07 (1H, app. ddt, *J* 8.4, 7.1, 1.3, **15-H**), 5.01 (1H, sept, *J* 6.3, **2-H**), 4.56 (1H, s, **22-H**), 4.55 – 4.46 (2H, m, **2-H**, **20-H**), 2.95 (1H, dd, *J* 14.0, 6.8, **14-H**), 2.50 (1H, dd, *J* 13.9, 8.5, **14-H**),

2.43 (3H, s, **9**-**H**), 1.65 (3H, s, **17**-**H**), 1.28 (3H, d, *J* 6.0, **1**-**H**), 1.18 – 1.13 (6H, m, **1**-**H**, **17**-**H**), 1.06 (3H, d, *J* 6.3, **1**-**H**), 1.02 (3H, d, *J* 6.3, **21**-**H**), 0.67 (3H, d, *J* 6.3, **21**-**H**), 0.65 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.8 (**C18**), 169.3 (**C4**), 167.8 (**C4**), 162.0 (d, $J_{F\text{-}C}$ 245, C_{Ar}**27**), 141.9 (d, $J_{F\text{-}C}$ 8, C_{Ar}**23**), 141.6 (C_{Ar}**12**), 138.0 (C_{Ar}**6**), 137.1 (C_{Ar}**8**), 135.6 (**C16**), 129.3 (C_{Ar}**7**), 129.1 (C_{Ar}**25**), 129.1 (C_{Ar}**10**), 127.2 (C_{Ar}**11**), 125.0 (br., C_{Ar}**24**), 118.9 (**C15**), 117.3 (d, $J_{F\text{-}C}$ 21, C_{Ar}**28**), 114.1 (d, $J_{F\text{-}C}$ 21, C_{Ar}**26**), 70.1 (**C5**), 69.9 (**C2**), 69.2 (**C2**), 68.0 (**C20**), 64.1 (**C13**), 60.3 (**C22**), 40.9 (**C14**), 26.0 (**C17**), 21.7 (**C1**/**C21**), 21.6 (**C1**/**C21**), 21.6 (**C1**/**C21**), 21.5 (**C1**/**C21** & **C9**), 20.9 (**C21**), 20.7 (**C1**), 17.8 (**C17**).

^{19}F (470 MHz, $CDCl_3$): δ −114.5

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1732 (C=O), 1615 (C=C), 1453, 1374, 1245, 1198, 1106 (C–O), 909, 702.

HRMS (ESI): $C_{33}H_{41}FO_6Na$ $[M+Na]^+$ requires 575.2779; found 575.2772

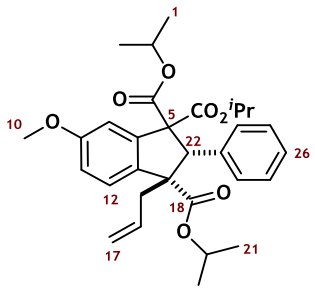
MP: 102 – 104 °C (hexane).

Chiral HPLC: Chiralpak IA (2.5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 206 nm), t_R(**major**) 5.5 min and t_R(**minor**) 6.7 min, 98% ee.

$[\alpha]_D^{20}$ +3.3 (*c* 0.55, chloroform).

Triisopropyl 3-allyl-6-methoxy-2-phenyl-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate

(310)



Racemic: Prepared according to ***general procedure 2*** using cyclization precursor **184** (20 mg, 0.041 mmol) and allyl bromide (7 μL, 0.082 mmol & 28 μL, 0.328 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1) to afford indane **310** (10 mg, 48%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 5*** using cyclization precursor **184** (83 mg, 0.172 mmol), allyl bromide (30 μL, 0.344 mmol & 119 μL, 1.38 mmol) and (*S*,*S*)-**273** (3 mg, 3.44 μmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1) to afford indane **310** (78 mg, 88%, 77% ee, >20 : 1 dr) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.43 (1H, d, *J* 8.6, **12**-**H**), 7.24 (1H, d, *J* 2.5, **7**-**H**), 7.11 – 7.01 (3H, m, **25**-**H**, **26**-**H**), 6.99 – 6.92 (3H, m, **11**-**H**, **24**-**H**), 5.71 (1H, ddt, *J* 17.1, 9.9, 7.5, **16**-**H**), 5.04 (1H, dd, *J* 10.2, 1.9, **17**-**H**), 5.05 – 4.95 (1H, m, **2**-**H**), 4.94 (1H, d, *J* 16.9, **17**-**H**), 4.55 (1H, s, **22**-**H**), 4.50 – 4.38 (2H, m, **2**-**H**, **20**-**H**), 3.86 (3H, s, **10**-**H**), 3.05 (1H, dd, *J* 13.4, 7.8, **15**-**H**), 2.52 (1H, dd, *J* 13.6, 7.1, **15**-**H**), 1.28 (3H, d, *J* 6.1, **1**-**H**), 1.20 (3H, d, *J* 6.3, **1**-**H**), 1.02 (6H, app. t, *J* 5.6, **1**-**H**, **21**-**H**), 0.57 (3H, d, *J* 6.6, **21**-**H**), 0.55 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 171.7 (**C18**), 169.2 (**C4**), 167.7 (**C4**), 159.3 (C_{Ar}**8**), 139.5 (C_{Ar}**6**), 139.3 (C_{Ar}**23**), 136.8 (C_{Ar}**13**), 133.5 (**C16**), 129.7 (br., C_{Ar}**24**), 128.1 (C_{Ar}**12**), 127.6 (C_{Ar}**25**), 127.4 (C_{Ar}**26**), 118.8 (**C17**), 115.3 (C_{Ar}**11**), 113.2 (C_{Ar}**7**), 70.3 (**C5**), 69.9 (**C2**), 69.2 (**C2**), 68.0 (**C20**), 63.6 (**C14**), 60.7 (**C22**), 55.5 (**C10**), 46.7 (**C15**), 21.7 (**C1**/**C21**), 21.6 (**C1**/**C21**), 21.5 (**C1**/**C21**), 21.5 (**C1**/**C21**), 20.7 (**C1**/**C21**), 20.7 (**C1**/**C21**).

IR: v_{max} (neat)/ cm^{-1} 2980 (C–H), 1731 (C=O), 1639 (C=C), 1494, 1239, 1213, 1105 (C–O), 912, 701.

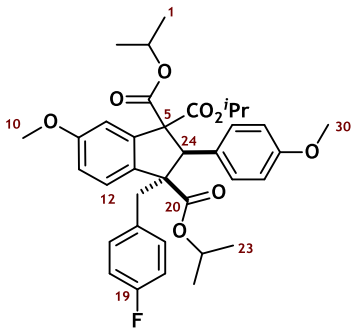
HRMS (ESI): $C_{31}H_{38}O_7Na$ $[M+Na]^+$ requires 545.2510; found 545.2507

MP: 94 – 96 °C (hexane).

Chiral HPLC: Chiralpak AD-H (2.5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 216 nm), t_R(**major**) 6.3 min and t_R(**minor**) 8.3 min, 77% ee.

$[\alpha]_D^{20}$ −19.6 (*c* 0.30, chloroform).

Triisopropyl 3-(4-fluorobenzyl)-6-methoxy-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (311)



Racemic: Prepared according to ***general procedure 2*** using cyclization precursor **185** (80 mg, 0.156 mmol) and 4-fluorobenzyl bromide (39 μL, 0.312 mmol & 156 μL, 1.25 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1) to afford indane **311** (42 mg, 43%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 5*** using cyclization precursor **185** (80 mg, 0.156 mmol) and 4-fluorobenzyl bromide (39 μL, 0.312 mmol & 156 μL, 1.25 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1) to afford indane **311** (82 mg, 85%, 73% ee, >20 : 1 dr) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.26 (1H, d, *J* 2.3, **7-H**), 6.90 (2H, br. d, *J* 7.6, **26-H**), 6.84 (2H, app. t, *J* 8.7, **18-H**), 6.74 (1H, dd, *J* 8.6, 2.5, **11-H**), 6.68 (2H, dd, *J* 8.3, 5.6, **17-H**), 6.60 (2H, d, *J* 8.6, **27-H**), 6.44 (1H, d, *J* 8.6, **12-H**), 5.07 (1H, sept, *J* 6.2, **2-H**), 4.63 (1H, s, **24-H**), 4.56 – 4.39 (2H, m, **2-H**, **22-H**), 3.87 (3H, s, **10-H**), 3.75 (1H, d, *J* 13.4, **15-H**), 3.68 (3H, s, **30-H**), 3.02 (1H, d, *J* 13.1, **15-H**), 1.31 (3H, d, *J* 6.0, **1-H**), 1.24 (3H, d, *J* 6.3, **1-H**), 1.07 (3H, d, *J* 6.3, **1-H**), 1.01 (3H, d, *J* 6.3, **23-H**), 0.66 (6H, app. dd, *J* 6.1, 4.8, **1-H**, **23-H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.8 (**C20**), 169.5 (**C4**), 167.8 (**C4**), 162.0 (d, $J_{F\text{-}C}$ 245, $\mathbf{C}_{Ar}$**19**), 159.3 ($\mathbf{C}_{Ar}$**8**), 159.1 ($\mathbf{C}_{Ar}$**28**), 139.9 ($\mathbf{C}_{Ar}$**6**), 135.4 ($\mathbf{C}_{Ar}$**13**), 132.8 (d, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**16**), 132.3 (d, $J_{F\text{-}C}$ 8, $\mathbf{C}_{Ar}$**17**),

131.3 (C_{Ar}**25**), 130.9 (br., C_{Ar}**26**), 129.3 (C_{Ar}**12**), 114.6 (C_{Ar}**11**), 114.5 (d, $J_{F\text{-}C}$ 21, C_{Ar}**18**), 113.0 (C_{Ar}**7**), 113.0 (C_{Ar}**27**), 70.4 (**C5**), 70.0 (**C2**), 69.3 (**C2**), 68.6 (**C22**), 65.6 (**C14**), 60.5 (**C24**), 55.5 (**C10**), 55.4 (**C30**), 46.5 (**C15**), 21.7 (**C1**/**C23**), 21.7 (**C1**/**C23**), 21.6 (**C1**/**C23**), 21.6 (**C1**/**C23**), 21.0 (**C1**/**C23**), 20.9 (**C1**/**C23**).

^{19}F (470 MHz, $CDCl_3$): δ −116.4

IR: v_{max} (neat)/ cm^{-1} 2981 (C–H), 1731 (C=O), 1609, 1511, 1246, 1220, 1195, 1106 (C–O), 733.

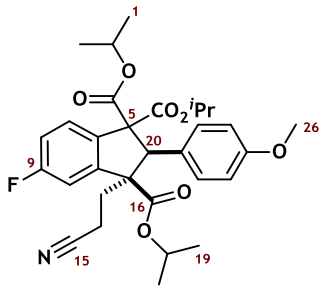
HRMS (ESI): $C_{36}H_{41}FO_8Na$ $[M+Na]^+$ requires 643.2678; found 643.2674

MP: 116 – 118 °C (hexane/ethyl acetate).

Chiral HPLC: Chiralpak IA (5.0% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 234 nm), t_R(**minor**) 9.2 min and t_R(**major**) 10.0 min, 73% ee.

$[\alpha]_D^{20}$ +1.0 (*c* 0.55, chloroform).

Triisopropyl 3-(2-cyanoethyl)-5-fluoro-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (316)



Racemic: Prepared according to ***general procedure 3*** using cyclization precursor **187** (84 mg, 0.168 mmol) and acrylonitrile (110 μL, 1.68 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1 to 20 : 1) to afford indane **316** (68 mg, 72%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 6*** using cyclization precursor **187** (86 mg, 0.172 mmol) and acrylonitrile (113 μL, 1.72 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1 to 20 : 1) to afford indane **316** (68 mg, 72%, 43% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.70 (1H, dd, *J* 8.7, $J_{F\text{-}H}$ 5.2, **7**-**H**), 7.22 (1H, dd, $J_{F\text{-}H}$ 9.1, *J* 2.5, **10**-**H**), 7.15 (1H, app. td, *J* 8.7, 2.5, **8**-**H**), 6.82 (2H, br. d, *J* 6.0, **22**-**H**), 6.61 (2H, d, *J* 8.8, **23**-**H**), 5.01 (1H, sept, *J* 6.3, **2**-**H**), 4.55 (1H, sept, *J* 6.3, **18**-**H**), 4.51 (1H, s, **20**-**H**), 4.48 (1H, sept, *J* 6.3, **2**-**H**), 3.67 (3H, s, **26**-**H**), 2.64 – 2.56 (1H, m, **13**-**H**), 2.54 – 2.45 (1H, m, **14**-**H**), 2.42 (1H, m, **14**-**H**), 2.17 (1H, ddd, *J* 13.7, 11.0, 4.6, **13**-**H**), 1.27 (3H, d, *J* 6.3, **1**-**H**), 1.19 (3H, d, *J* 6.3, **1**-**H**), 1.06 (6H, app. dd, *J* 6.3, **1**-**H**, **19**-**H**), 0.69 (3H, d, *J* 6.3, **19**-**H**), 0.63 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 170.5 (**C16**), 169.0 (**C4**), 167.4 (**C4**), 163.1 (d, $J_{F\text{-}C}$ 247, $\mathbf{C}_{Ar}$**9**), 159.4 ($\mathbf{C}_{Ar}$**24**), 145.7 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**11**), 134.0 (d, $J_{F\text{-}C}$ 2, $\mathbf{C}_{Ar}$**6**), 131.0 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**7**), 130.7 (br., $\mathbf{C}_{Ar}$**22**), 130.1 ($\mathbf{C}_{Ar}$**21**), 119.0 (**C15**), 115.9 (d, $J_{F\text{-}C}$ 23, $\mathbf{C}_{Ar}$**8**), 113.8 (d, $J_{F\text{-}C}$ 23, $\mathbf{C}_{Ar}$**10**), 113.1 ($\mathbf{C}_{Ar}$**23**), 70.4 (**C2**), 69.7 (**C2**), 69.5 (**C5**), 69.4 (**C18**), 63.1 (**C12**), 59.1 (**C20**), 55.4 (**C26**), 36.8 (**C13**), 21.7 (**C1**/**C19**), 21.6 (**C1**/**C19**), 21.5 (**C1**/**C19**), 21.5 (**C1**/**C19**), 20.9 (**C1** & **C19**), 13.7 (**C14**).

^{19}F (470 MHz, $CDCl_3$): δ −112.5

IR: ν_{max} (neat)/ cm^{-1} 2983 (C–H), 1729 (C=O), 1514, 1246, 1211, 1103 (C–O), 911, 733.

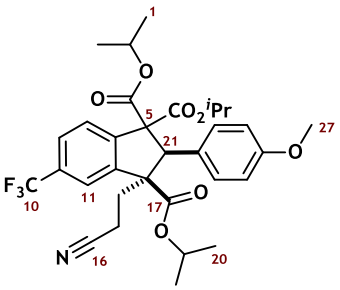
HRMS (ESI): $C_{31}H_{36}FNO_7Na$ $[M+Na]^+$ requires 576.2368; found 576.2369

MP: 112 – 114 °C (hexane/ethyl acetate).

Chiral HPLC: Chiralpak AD-H (20% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 206 nm), t_R(**major**) 4.4 min and t_R(**minor**) 5.5 min, 43% ee.

$[\alpha]_D^{20}$ +10.2 (*c* 0.75, chloroform).

Triisopropyl 3-(2-cyanoethyl)-2-(4-methoxyphenyl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (315)



Racemic: Prepared according to ***general procedure 3*** using cyclization precursor **188** (40 mg, 0.073 mmol) and acrylonitrile (48 μL, 0.730 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1) to afford indane **315** (36 mg, 82%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 6*** using cyclization precursor **188** (84 mg, 0.153 mmol) and acrylonitrile (101 μL, 1.53 mmol). The reaction solvent was toluene: chloroform (9 : 1, 1 mL). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1) to afford indane **315** (66 mg, 73%, 13% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.87 (1H, d, *J* 8.2, **7**-**H**), 7.78 (1H, s, **11**-**H**), 7.72 (1H, d, *J* 8.2, **8**-**H**), 6.79 (2H, br. s, **23**-**H**), 6.62 (2H, d, *J* 8.5, **24**-**H**), 5.02 (1H, sept, *J* 6.3, **2**-**H**), 4.62 – 4.54 (2H, m, **19**-**H**, **21**-**H**), 4.51 (1H, sept, *J* 6.3, **2**-**H**), 3.68 (3H, s, **27**-**H**), 2.65 – 2.57 (1H, m, **14**-**H**), 2.52 – 2.38 (2H, m, **15**-**H**), 2.17 (1H, ddd, *J* 13.8, 10.6, 5.2, **14**-**H**), 1.29 (3H, d, *J* 6.0, **1**-**H**), 1.20 (3H, d, *J* 6.3, **1**-**H**), 1.07 (6H, app. dd, *J* 6.3, 3.8, **1**-**H**, **20**-**H**), 0.70 (3H, d, *J* 6.0, **20**-**H**), 0.64 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 170.3 (**C17**), 168.4 (**C4**), 167.0 (**C4**), 159.5 (C_{Ar}**25**), 144.4 (C_{Ar}**12**), 142.4 (C_{Ar}**6**), 131.2 (q, $J_{F\text{-}C}$ 32, C_{Ar}**9**), 130.7 (br., C_{Ar}**23**), 130.2 (C_{Ar}**7**), 129.8 (C_{Ar}**22**), 125.4 (q, $J_{F\text{-}C}$ 4, C_{Ar}**8**), 124.2 (q, $J_{F\text{-}C}$ 273, **C10**), 123.8 (q, $J_{F\text{-}C}$ 4, C_{Ar}**11**), 118.9 (**C16**), 113.2 (C_{Ar}**24**), 70.8 (**C2**), 70.2 (**C5**), 69.9 (**C2**), 69.6 (**C19**), 63.2 (**C13**), 58.8 (**C21**), 55.4 (**C27**), 36.8 (**C14**), 21.7 (**C1**/**C20**), 21.5 (**C1**/**C20**), 21.5 (**C1**/**C20**), 20.9 (**C1**/**C20**), 20.8 (**C1**/**C20**), 13.7 (**C15**).[†]

^{19}F (377 MHz, $CDCl_3$): δ −62.2

IR: v_{max} (neat)/ cm^{-1} 2983 (C–H), 2250 (C≡N), 1730 (C=O), 1515, 1333, 1246, 1104 (C–O), 908, 733.

HRMS (ESI): $C_{32}H_{36}F_3NO_7Na$ $[M+Na]^+$ requires 626.2336; found 626.2333

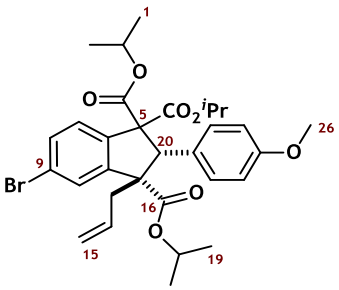
MP: 106 – 108 °C (hexane).

Chiral HPLC: Chiralpak IA (4% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 208 nm), t_R(**major**) 7.3 min and t_R(**minor**) 11.6 min, 13% ee.

$[\alpha]_D^{20}$ −1.6 (*c* 0.50, chloroform).

[†] *Two **C1**/**C20** peaks coincide at 21.5 ppm*

Triisopropyl 3-allyl-5-bromo-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (314)



Racemic: Prepared according to ***general procedure 2*** using cyclization precursor **189** (25 mg, 0.045 mmol) and allyl bromide (8 μL, 0.090 mmol & 31 μL, 0.360 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1) to afford indane **314** (24 mg, 89%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 5*** using cyclization precursor **189** (81 mg, 0.144 mmol), allyl bromide (25 μL, 0.288 mmol & 100 μL, 1.15 mmol) and (*S*,*S*)-**273** (3 mg, 2.88 μmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1) to afford indane **314** (58 mg, 69%, 22% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.69 (1H, d, *J* 1.9, **10**-**H**), 7.57 (1H, d, *J* 8.5, **7**-**H**), 7.52 (1H, dd, *J* 8.5, 1.9, **8**-**H**), 6.85 (2H, br. d, *J* 7.9, **22**-**H**), 6.61 (2H, d, *J* 9.1, **23**-**H**), 5.69 (1H, ddt, *J* 17.2, 9.9, 7.4, **14**-**H**), 5.10 (1H, dd, *J* 10.2, 2.0, **15**-**H**), 5.00 (1H, sept, *J* 6.3, **2**-**H**), 4.95 (1H, dd, *J* 16.9, 1.7, **15**-**H**), 4.52 (1H, s, **20**-**H**), 4.53 – 4.43 (2H, m, **2**-**H**, **18**-**H**), 3.68 (3H, s, **26**-**H**), 3.06 (1H, dd, *J* 13.6, 7.9, **13**-**H**), 2.44 (1H, dd, *J* 13.6, 7.3, **13**-**H**), 1.27 (3H, d, *J* 6.0, **1**-**H**), 1.17 (3H, d, *J* 6.3, **1**-**H**), 1.05 (6H, app. t, *J* 6.3, **1**-**H**, **19**-**H**), 0.65 (3H, d, *J* 6.3, **1**-**H**), 0.63 (3H, d, *J* 6.3, **19**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.0 (**C16**), 168.8 (**C4**), 167.5 (**C4**), 159.2 (C_{Ar}**24**), 146.7 (C_{Ar}**11**), 137.3 (C_{Ar}**6**), 132.7 (**C14**), 130.9 (C_{Ar}**21**), 130.9 (C_{Ar}**8**), 130.8 (br., C_{Ar}**22**), 130.7 (C_{Ar}**7**/C_{Ar}**10**), 130.5 (C_{Ar}**7**/C_{Ar}**10**), 122.3 (C_{Ar}**9**), 119.4 (**C15**), 113.0 (C_{Ar}**23**), 70.2 (**C2**), 70.0 (**C5**), 69.5 (**C2**), 68.4 (**C18**), 64.2 (**C12**), 59.7 (**C20**), 55.4 (**C26**), 46.3 (**C13**), 21.8 (**C1**/**C19**), 21.6 (**C1**/**C19**), 21.5 (**C1**/**C19**), 21.5 (**C1**/**C19**), 20.9 (**C1** & **C19**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1730 (C=O), 1640 (C=C), 1513, 1245, 1217, 1182, 1104 (C–O), 911, 732.

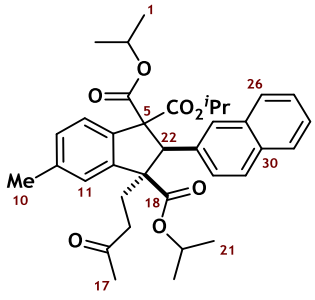
HRMS (ESI): $C_{31}H_{37}{}^{79}BrO_7Na$ $[M+Na]^+$ requires 623.1615; found 623.1631

MP: 112 – 113 °C.

Chiral HPLC: Chiralpak AD-H (2.5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 204 nm), t_R(**minor**) 5.3 min and t_R(**major**) 11.2 min, 22% ee.

$[\alpha]_D^{20}$ −8.6 (*c* 0.30, chloroform).

Triisopropyl 5-methyl-2-(naphthalen-2-yl)-3-(3-oxobutyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (313)



Racemic: Prepared according to ***general procedure 3*** using cyclization precursor **190** (69 mg, 0.134 mmol) and methyl vinyl ketone (112 μL, 1.34 mmol). The crude product was purified

by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1 to 9 : 1) to afford indane **313** (27 mg, 36%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 7*** using cyclization precursor **190** (72 mg, 0.139 mmol), methyl vinyl ketone (116 μL, 1.39 mmol). The cyclization was performed at room temperature for 48 hours. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1 to 9 : 1) to afford indane **313** (25 mg, 31%, 4% ee, >20 : 1 dr) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.70 – 7.64 (2H, m, **26**-**H**, **29**-**H**), 7.63 (1H, d, *J* 8.1, **7**-**H**), 7.54 – 7.48 (2H, m, **24**-**H**, **31**-**H**), 7.42 (1H, s, **11**-**H**), 7.40 – 7.32 (2H, m, **27**-**H**, **28**-**H**), 7.29 – 7.24 (1H, m, **8**-**H**), 6.99 (1H, d, *J* 8.6, **32**-**H**), 5.02 (1H, sept, *J* 6.3, **2**-**H**), 4.77 (1H, s, **22**-**H**), 4.40 – 4.23 (2H, m, **2**-**H**, **20**-**H**), 2.68 – 2.49 (2H, m, **14**-**H**, **15**-**H**), 2.49 – 2.42 (1H, m, **15**-**H**), 2.48 (3H, s, **10**-**H**), 2.21 – 2.11 (1H, m, **14**-**H**), 2.11 (3H, s, **17**-**H**), 1.29 (3H, d, *J* 6.3, **1**-**H**), 1.21 (3H, d, *J* 6.3, **1**-**H**), 0.93 (6H, app. t, *J* 5.7, **1**-**H**, **21**-**H**), 0.31 (6H, d, *J* 6.3, **1**-**H**, **21**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 207.8 (**C16**), 171.8 (**C18**), 169.3 (**C4**), 167.9 (**C4**), 144.8 (C_{Ar}**12**), 138.4 (C_{Ar}**9**), 136.8 (C_{Ar}**23**), 135.5 (C_{Ar}**6**), 132.9 (C_{Ar}**25**/C_{Ar}**30**), 132.8 (C_{Ar}**25**/C_{Ar}**30**), 129.1 (C_{Ar}**7**/C_{Ar}**8**), 129.0 (C_{Ar}**7**/C_{Ar}**8**), 128.9 (br., C_{Ar}**24**), 127.9 (C_{Ar}**26**/C_{Ar}**29**), 127.5 (C_{Ar}**26**/C_{Ar}**29**), 127.4 (C_{Ar}**11** & C_{Ar}**32**), 127.1 (C_{Ar}**31**), 125.8 (C_{Ar}**27**/C_{Ar}**28**), 125.7 (C_{Ar}**27**/C_{Ar}**28**), 70.0 (**C2 & C5**), 69.1 (**C2**), 68.3 (**C20**), 63.5 (**C13**), 60.3 (**C22**), 40.0 (**C15**), 36.1 (**C14**), 30.0 (**C17**), 21.9 (**C10**), 21.7 (**C1**/**C21**), 21.6 (**C1**/**C21**), 21.6 (**C1**/**C21**), 21.4 (**C1**/**C21**), 20.6 (**C1**/**C21**), 20.5 (**C1**/**C21**).

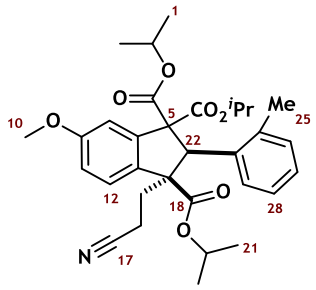
IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1728 (C=O), 1374, 1241, 1182, 1102 (C–O), 912, 731.

HRMS (ESI): $C_{36}H_{42}O_7Na$ $[M+Na]^+$ requires 609.2823; found 609.2829

MP: 96 – 98 °C (hexane).

Chiral HPLC: Chiralpak AD-H (20% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 230 nm), t_R(**minor**) 4.8 min and t_R(**major**) 9.6 min, 4% ee.

Triisopropyl 3-(2-cyanoethyl)-6-methoxy-2-(*o*-tolyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (312)



Racemic: Prepared according to ***general procedure 3*** using cyclization precursor **186** (71 mg, 0.143 mmol) and acrylonitrile (94 μL, 1.43 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1) to afford indane **312** (37 mg, 47%, >20 : 1 dr) as a colourless oil.

Asymmetric: Prepared according to ***general procedure 6*** using cyclization precursor **186** (95 mg, 0.191 mmol) and acrylonitrile (126 μL, 1.91 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1) to afford indane **312** (68 mg, 65%, 34% ee, >20 : 1 dr) as a colourless oil.

^{1}H (500 MHz, $CDCl_3$): δ 7.41 (1H, d, *J* 8.5, **12-H**), 7.28 (1H, d, *J* 2.5, **7-H**), 7.02 (1H, d, *J* 7.3, **26-H**), 7.00 – 6.94 (2H, m, **11-H**, **27-H**), 6.77 (1H, app. t, *J* 7.1, **28-H**), 6.52 (1H, d, *J* 7.9, **29-H**), 5.03 (1H, sept, *J* 6.3, **2-H**), 4.93 (1H, s, **22-H**), 4.50 (1H, sept, *J* 6.3, **20-H**), 4.45 (1H, sept, *J* 6.3, **2-H**), 3.86 (3H, s, **10-H**), 2.65 – 2.56 (1H, m, **15-H**), 2.52 – 2.43 (4H, m, **16-H**, **25-H**), 2.38 – 2.29

(1H, m, **15**-**H**), 2.26 – 2.19 (1H, m, **16**-**H**), 1.28 (3H, d, *J* 6.3, **1**-**H**), 1.22 (3H, d, *J* 6.3, **1**-**H**), 1.04 (6H, app. dd, *J* 6.3, 2.2, **1**-**H**, **21**-**H**), 0.56 (3H, d, *J* 6.3, **21**-**H**), 0.51 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.1 (**C18**), 169.1 (**C4**), 167.3 (**C4**), 159.8 (C_{Ar}**8**), 140.1 (C_{Ar}**6**), 137.6 (C_{Ar}**24**), 137.5 (C_{Ar}**23**), 135.7 (C_{Ar}**13**), 129.9 (C_{Ar}**26**), 127.5 (C_{Ar}**27**), 127.2 (C_{Ar}**12**), 126.8 (C_{Ar}**29**), 125.8 (C_{Ar}**28**), 119.2 (**C17**), 115.9 (C_{Ar}**11**), 113.9 (C_{Ar}**7**), 70.3 (**C2**), 70.2 (**C5**), 69.4 (**C2**), 69.0 (**C20**), 62.8 (**C14**), 55.6 (**C10**), 53.6 (**C22**), 37.5 (**C15**), 21.7 (**C1**/**C21**), 21.6 (**C1**/**C21**), 21.6 (**C1**/**C21**), 21.5 (**C1**/**C21**), 21.0 (**C25**), 20.4 (**C1**/**C21**), 20.3 (**C1**/**C21**), 13.7 (**C16**).

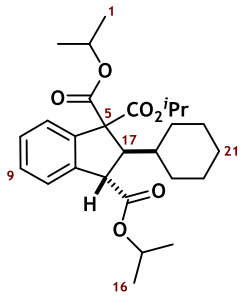
IR: v_{max} (neat)/ cm^{-1} 2981 (C–H), 2248 (C≡N), 1731 (C=O), 1494, 1242, 1201, 1106 (C–O), 833.

HRMS (ESI): $C_{32}H_{39}NO_7Na$ $[M+Na]^+$ requires 572.2619; found 572.2617

Chiral HPLC: Chiralpak AD-H (5.0% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 204 nm), t_R(**minor**) 6.3 min and t_R(**major**) 8.9 min, 34% ee.

$[\alpha]_D^{20}$ +5.4 (*c* 0.85, chloroform).

Triisopropyl 2-cyclohexyl-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (306)



Racemic: Prepared according to ***general procedure 1*** using cyclization precursor **180** (50 mg, 0.109 mmol). ^{1}H NMR of the crude reaction mixture revealed a >20 : 1 (*anti* : *syn*) mixture of diastereomers. The crude product was purified by silica gel chromatography

(40-60 petrol : ethyl acetate, 40 : 1) to afford indane **306** (31 mg, 62%, >20 : 1 dr) as a colourless oil.

Asymmetric: Prepared according to ***general procedure 4*** using cyclization precursor **180** (86 mg, 0.188 mmol). ^{1}H NMR of the crude reaction mixture revealed a >20 : 1 (*anti* : *syn*) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1) to afford indane **306** (72 mg, 84%, 35% ee, >20 : 1 dr) as a colourless oil.

^{1}H (500 MHz, $CDCl_3$): δ 7.53 – 7.50 (1H, m, **7-H**), 7.30 – 7.21 (3H, m, **8-H**, **9-H**, **10-H**), 5.17 – 5.08 (2H, m, **2-H**, **15-H**), 5.04 (1H, sept, *J* 6.3, **2-H**), 3.94 (1H, d, *J* 8.8, **12-H**), 3.61 (1H, dd, *J* 8.7, 7.1, **17-H**), 1.98 – 1.89 (1H, m, **19-H$_{eq}$**), 1.77 – 1.67 (2H, m, **20-H$_{eq}$**/**21-H$_{eq}$**), 1.67 – 1.59 (2H, m, **18-H**, **20-H$_{eq}$**/**21-H$_{eq}$**), 1.59 – 1.53 (1H, m, **19-H$_{eq}$**), 1.32 (6H, app. t, *J* 6.0, **1-H**, **16-H**), 1.28 (6H, d, *J* 6.3, **1-H**, **16-H**), 1.26 – 1.22 (4H, m, **1-H**, **19-H$_{ax}$**), 1.22 – 1.18 (4H, m, **1-H**, **20-H$_{ax}$**/**21-H$_{ax}$**), 1.19 – 1.09 (2H, m, **20-H$_{ax}$**/**21-H$_{ax}$**), 1.04 – 0.93 (1H, m, **19-H$_{ax}$**).

^{13}C (126 MHz, $CDCl_3$): δ 173.0 (**C13**), 169.5 (**C4**), 169.3 (**C4**), 142.0 (**C$_{Ar}$11**), 140.8 (**C$_{Ar}$6**), 128.7 (**C$_{Ar}$9**), 127.7 (**C$_{Ar}$8**), 125.4 (**C$_{Ar}$7**), 123.9 (**C$_{Ar}$10**), 69.4 (**C2**), 69.3 (**C2**), 68.5 (**C15**), 68.2 (**C5**), 54.8 (**C17**), 52.5 (**C12**), 39.5 (**C18**), 33.3 (**C19**), 30.6 (**C19**), 26.8 (**C20**/**C21**), 26.8 (**C20**/**C21**), 26.4 (**C20**/**C21**), 22.1 (**C1**/**C16**), 21.8 (**C1**/**C16**), 21.8 (**C1**/**C16**), 21.7 (**C1**/**C16**).[†]

IR: ν_{max} (neat)/ cm^{-1} 2980 (C–H), 1722 (C=O), 1453, 1374, 1253, 1180, 1103 (C–O), 745.

HRMS (ESI): $C_{27}H_{38}O_6Na$ $[M+Na]^+$ requires 481.2561; found 481.2543

Chiral HPLC: Chiralpak AD-H (2.0% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 200 nm), t_R(**minor**) 8.0 min and t_R(**major**) 14.2 min, 35% ee.

[†] *Only four peaks, instead of the expected six, were observed for **C1**/**C16** due to coincident peaks*

$[\alpha]_D^{20}$ −9.3 (*c* 0.45, chloroform).

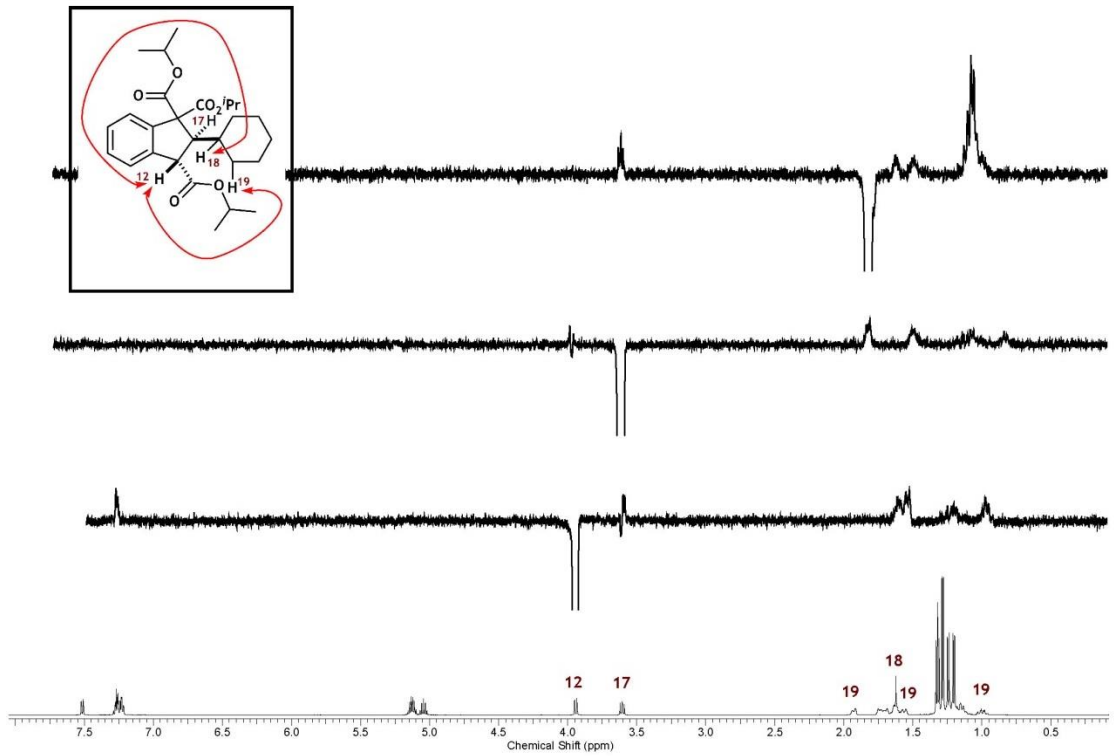
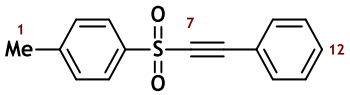


Figure 5.2 – 1D nOe data for indane **306** in $CDCl_3$ (mixing time = 0.8 s).

5.3.6 *Indanes with Various Vinylic Electron-Withdrawing Group – Substrate Synthesis & Cyclization*

1-Methyl-4-((phenylethynyl)sulfonyl)benzene (286)



According to a modified literature procedure,[175] ceric ammonium nitrate (26.9 g, 49.0 mmol) in anhydrous acetonitrile (116 mL) was added to a suspension of phenylacetylene **130** (2.00 g, 19.6 mmol), sodium *p*-toluenesulfinate (4.19 g, 23.5 mmol) and sodium iodide (5.60 g, 37.2 mmol) in anhydrous acetonitrile (74 mL) under an atmosphere of argon. After stirring for 5 hours at room temperature the reaction mixture was filtered through Celite® with

acetonitrile. The reaction was concentrated *in vacuo* to its original volume and anhydrous potassium carbonate (16.3 g, 118 mmol) was added. The reaction was refluxed for 24 hours under argon before cooling to room temperature and quenching with saturated aqueous sodium sulfite (200 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3 × 200 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 9 : 1) to afford sulfone **286** (2.92 g, 58%) as a white solid with spectroscopic data in accordance with the literature.[248]

^{1}H (400 MHz, $CDCl_3$): δ 7.96 (2H, d, *J* 8.3, **4**-**H**), 7.54 – 7.44 (3H, m, **10**-**H**, **12**-**H**), 7.42 – 7.33 (4H, m, **3**-**H**, **11**-**H**), 2.47 (3H, s, **1**-**H**).

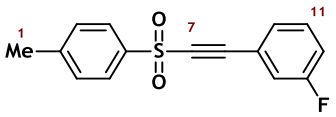
^{13}C (101 MHz, $CDCl_3$): δ 145.5 ($\mathbf{C}_{Ar}$**2**), 139.0 ($\mathbf{C}_{Ar}$**5**), 132.8 ($\mathbf{C}_{Ar}$**10**), 131.6 ($\mathbf{C}_{Ar}$**12**), 130.1 ($\mathbf{C}_{Ar}$**3**), 128.8 ($\mathbf{C}_{Ar}$**11**), 127.6 ($\mathbf{C}_{Ar}$**4**), 118.1 ($\mathbf{C}_{Ar}$**9**), 93.1 (**C7**), 85.7 (**C8**), 21.8 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 3064 (C–H), 2179 (C≡C), 1329 (S=O), 1154 (S=O), 1086, 848, 757, 677.

LRMS (ESI): $[M+Na]^+$ 279.1 and $[2M+Na]^+$ 535.1

MP: 75 – 77 °C, lit. MP: 73 – 75 °C.[248]

1-Fluoro-3-(tosylethynyl)benzene (418)



According to a modified literature procedure,[175] ceric ammonium nitrate (23.0 g, 42.0 mmol) in anhydrous acetonitrile (99 mL) was added to a suspension of 1-ethynyl-3-fluorobenzene **131** (2.02 g, 16.8 mmol), sodium *p*-toluenesulfinate (3.60 g, 20.2 mmol) and sodium iodide

(4.78 g, 31.9 mmol) in anhydrous acetonitrile (63 mL) under an atmosphere of argon. After stirring for 5 hours at room temperature the reaction mixture was filtered through Celite® with acetonitrile. The reaction was concentrated *in vacuo* to its original volume and anhydrous potassium carbonate (13.9 g, 101 mmol) was added. The reaction was refluxed for 24 hours under argon before cooling to room temperature and quenching with saturated aqueous sodium sulfite (200 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3 × 200 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 9 : 1) to afford sulfone **418** (1.89 g, 41%) as a yellow solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.95 (2H, d, *J* 8.3, **4**-**H**), 7.40 (2H, d, *J* 8.1, **3**-**H**), 7.37 – 7.13 (4H, m, **10**-**H**, **11**-**H**, **12**-**H**, **14**-**H**), 2.46 (3H, s, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 162.1 (d, $J_{F\text{-}C}$ 249, $\mathbf{C}_{Ar}$**13**), 145.8 ($\mathbf{C}_{Ar}$**2**), 138.6 ($\mathbf{C}_{Ar}$**5**), 130.6 (d, $J_{F\text{-}C}$ 8, $\mathbf{C}_{Ar}$**11**), 130.2 ($\mathbf{C}_{Ar}$**3**), 128.7 (d, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**10**), 127.6 ($\mathbf{C}_{Ar}$**4**), 119.8 (d, $J_{F\text{-}C}$ 10, $\mathbf{C}_{Ar}$**9**), 119.4 (d, $J_{F\text{-}C}$ 23, $\mathbf{C}_{Ar}$**14**), 119.1 (d, $J_{F\text{-}C}$ 21, $\mathbf{C}_{Ar}$**12**), 91.0 (**C7**), 86.2 (**C8**), 21.8 (**C1**).

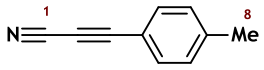
^{19}F (377 MHz, $CDCl_3$): δ −111.0

IR: v_{max} (neat)/ cm^{-1} 3074 (C–H), 2178 (C≡C), 1332 (S=O), 1157 (S=O), 1085, 952, 777, 674.

HRMS (ESI): $C_{15}H_{11}FO_2SNa$ $[M+Na]^+$ requires 297.0356; found 297.0356

MP: 81 – 83 °C.

3-(*p*-Tolyl)propiolonitrile (283)



According to a modified literature procedure,[173] *n*-butyllithium (1.6 M, 20.9 mL, 33.4 mmol) was added dropwise to a solution of 1-ethynyl-4-methylbenzene **282** (3.37 g, 29.0 mmol) in anhydrous tetrahydrofuran (96 mL) at −78 °C. After stirring for 1 hour at the same temperature the resulting lithium acetylide solution was added dropwise in to a solution of phenyl cyanate (4.84 g, 40.6 mmol) in anhydrous tetrahydrofuran (48 mL) pre-cooled to −78 °C. The reaction was left to stir for 1 hour at the same temperature before allowing the reaction to reach room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride (150 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 98 : 2) to afford nitrile **283** (3.37 g, 82%) as a white solid with spectroscopic data in accordance with the literature.[249,250]

^{1}H (400 MHz, $CDCl_3$): δ 7.50 (2H, d, *J* 8.1, **5**-**H**), 7.23 (2H, d, *J* 7.8, **6**-**H**), 2.42 (3H, s, **8**-**H**).

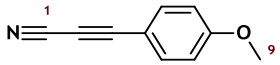
^{13}C (101 MHz, $CDCl_3$): δ 142.9 (**C**$_{Ar}$**7**), 133.5 (**C**$_{Ar}$**5**), 129.7 (**C**$_{Ar}$**6**), 114.4 (**C**$_{Ar}$**4**), 105.7 (**C1**), 83.6 (**C3**), 62.7 (**C2**), 21.9 (**C8**).

IR: ν_{max} (neat)/ cm^{-1} 2924 (C–H), 2258 (C≡N), 2143 (C≡C), 1603, 1508, 816.

HRMS (FI): $C_{10}H_7N$ $[M]^+$ requires 141.0578; found 141.0579

MP: 50 – 52 °C (40-60 petrol), lit. MP: 52 °C (40-60 petrol).[250]

3-(4-Methoxyphenyl)propiolonitrile (419)



According to a modified literature procedure,[173] *n*-butyllithium (1.6 M, 14.2 mL, 22.8 mmol) was added dropwise to a solution of 1-ethynyl-4-methoxybenzene **323** (2.62 g, 19.8 mmol) in anhydrous tetrahydrofuran (68 mL) at −78 °C. After stirring for 1 hour at the same temperature the resulting lithium acetylide solution was added dropwise in to a solution of phenyl cyanate (2.93 g, 24.6 mmol) in anhydrous tetrahydrofuran (34 mL) pre-cooled to −78 °C. The reaction was left to stir for 1 hour at the same temperature before allowing the reaction to reach room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride (150 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 98 : 2) to afford nitrile **419** (2.48 g, 80%) as a white solid with spectroscopic data in accordance with the literature.[249,251]

^{1}H (400 MHz, $CDCl_3$): δ 7.55 (2H, d, *J* 8.8, **5**-**H**), 6.91 (2H, d, *J* 8.8, **6**-**H**), 3.86 (3H, s, **9**-**H**).

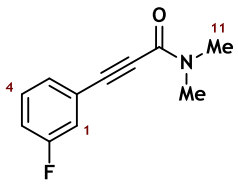
^{13}C (101 MHz, $CDCl_3$): δ 162.5 ($\mathbf{C}_{Ar}\mathbf{7}$), 135.5 ($\mathbf{C}_{Ar}\mathbf{5}$), 114.7 ($\mathbf{C}_{Ar}\mathbf{6}$), 109.1 ($\mathbf{C}_{Ar}\mathbf{4}$), 105.9 (**C1**), 83.8 (**C3**), 62.5 (**C2**), 55.6 (**C9**).

IR: ν_{max} (neat)/ cm^{-1} 2967 (C–H), 2260 (C≡N), 2137 (C≡C), 1600, 1509, 1256, 908, 730.

HRMS (FI): $C_{10}H_7NO$ $[M]^+$ requires 157.0528; found 157.0521

MP: 70 – 72 °C, lit. MP: 79 – 80 °C (hexane).[251]

3-(3-Fluorophenyl)-*N*,*N*-dimethylpropiolamide (284)



According to a modified literature procedure,[174] a solution of *n*-butyllithium (1.6 M in hexanes, 32.0 mL, 51.4 mmol) was added dropwise over 30 minutes to a stirred solution of 1-ethynyl-3-fluorobenzene **131** (5.14 g, 42.8 mmol) in anhydrous tetrahydrofuran (122 mL) at −78 °C. The reaction was stirred for 6 hours at −78 °C and then dimethylcarbamoyl chloride (5.90 mL, 64.2 mmol) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (150 mL). The biphasic mixture was extracted with dichloromethane (3 × 150 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 7 : 3 to 3 : 2) to afford propargylic amide **284** (6.45 g, 79%) as a beige solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.32 – 7.25 (2H, m, **4**-**H**, **5**-**H**), 7.19 – 7.14 (1H, m, **1**-**H**), 7.10 – 7.02 (1H, m, **3**-**H**), 3.22 (3H, s, **11**-**H**), 2.97 (3H, s, **11**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 162.2 (d, $J_{F\text{-}C}$ 248, $\mathbf{C}_{Ar}$**2**), 154.1 (**C9**), 130.2 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**4**), 128.2 (d, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**5**), 122.3 (d, $J_{F\text{-}C}$ 10, $\mathbf{C}_{Ar}$**6**), 118.9 (d, $J_{F\text{-}C}$ 23, $\mathbf{C}_{Ar}$**1**), 117.4 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**3**), 88.4 (d, $J_{F\text{-}C}$ 3, **C7**), 82.1 (**C8**), 38.3 (**C11**), 34.1 (**C11**).

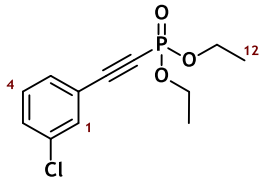
^{19}F (377 MHz, $CDCl_3$): δ −112.0

IR: ν_{max} (neat)/ cm^{-1} 2932 (C–H), 2219 (C≡C), 1620 (C=O), 1487, 1393, 1180, 1123, 797, 681.

HRMS (ESI): $C_{11}H_{10}FNONa$ $[M+Na]^+$ requires 214.0639; found 214.0640

MP: 56 – 58 °C.

Diethyl ((3-chlorophenyl)ethynyl)phosphonate (285)



According to a modified literature procedure,[174] a solution of *n*-butyllithium (1.6 M in hexanes, 25.6 mL, 41.0 mmol) was added dropwise over 30 minutes to a stirred solution of 1-chloro-3-ethynylbenzene **132** (4.67 g, 34.2 mmol) in anhydrous tetrahydrofuran (100 mL) at −78 °C. The reaction was stirred for 2 hours at −78 °C and then diethylphosphinic chloride (5.90 mL, 41.0 mmol) was added dropwise over 30 minutes. After stirring for 1 hour at −78 °C the reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (150 mL). The biphasic mixture was extracted with dichloromethane (3 × 150 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 7 : 3) to afford propargylic phosphonate **285** (3.47 g, 37%) as a yellow oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.55 (1H, s, **1**-**H**), 7.48 – 7.41 (2H, m, **3**-**H**, **5**-**H**), 7.33 (1H, app. t, *J* 7.8, **4**-**H**), 4.28 – 4.19 (4H, m, **11**-**H**), 1.42 (6H, t, *J* 7.1, **12**-**H**).

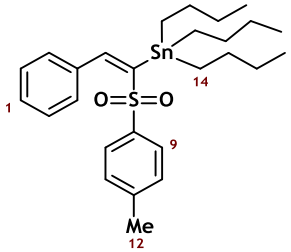
^{13}C (101 MHz, $CDCl_3$): δ 134.4 ($\mathbf{C}_{Ar}\mathbf{2}$), 132.1 ($\mathbf{C}_{Ar}\mathbf{1}$), 130.9 ($\mathbf{C}_{Ar}\mathbf{3}$), 130.6 (d, $J_{P\text{-}C}$ 2, $\mathbf{C}_{Ar}\mathbf{5}$), 129.9 ($\mathbf{C}_{Ar}\mathbf{4}$), 121.1 (d, $J_{P\text{-}C}$ 6, $\mathbf{C}_{Ar}\mathbf{6}$), 96.9 (d, $J_{P\text{-}C}$ 53, **C7**), 79.5 (d, $J_{P\text{-}C}$ 297, **C8**), 63.3 (d, $J_{P\text{-}C}$ 5, **C11**), 16.0 (d, $J_{P\text{-}C}$ 6, **C12**).

^{31}P (162 MHz, $CDCl_3$): δ −6.69

IR: ν_{max} (neat)/ cm^{-1} 2995 (C–H), 2193 (C≡C), 1260 (P=O), 1017, 898, 680.

HRMS (ESI): $C_{12}H_{14}{}^{35}ClO_3PNa$ $[M+Na]^+$ requires 295.0261; found 295.0265

(*E*)-Tributyl(2-phenyl-1-tosylvinyl)stannane (290)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (3.20 mL, 12.1 mmol) in tetrahydrofuran (13 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (266 mg, 0.230 mmol) and propargylic sulfone **286** (2.95 g, 11.5 mmol) in tetrahydrofuran (13 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (100 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a single regioisomer by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford stannane **290** (4.41 g, 70%) as a colourless solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.28 (2H, d, *J* 8.3, **9**-**H**), 7.21 (1H, s, **5**-**H**), 7.18 – 7.08 (5H, m, **1**-**H**, **2**-**H**, **3**-**H**), 6.92 (2H, d, *J* 8.3, **10**-**H**), 2.25 (3H, s, **12**-**H**), 1.77 – 1.51 (6H, m, **15**-**H**), 1.42 (6H, app. dq, *J* 15.7, 7.3, **16**-**H**), 1.34 – 1.15 (6H, m, **14**-**H**), 0.96 (9H, t, *J* 7.3, **17**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 154.6 (**C6**), 149.5 ($J_{^{117,119}Sn\text{-}C}$ 17, **C5**), 142.7 (C_{Ar}**11**), 138.6 (C_{Ar}**8**), 135.5 (C_{Ar}**4**), 129.0 (C_{Ar}**2**/C_{Ar}**3**), 128.6 (C_{Ar}**10**), 128.2 (C_{Ar}**1**), 127.7 (C_{Ar}**2**/C_{Ar}**3**), 127.5 (C_{Ar}**9**), 29.0

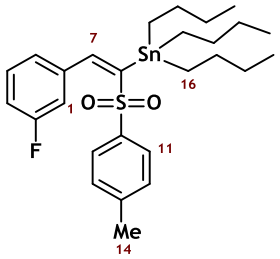
($J_{117,119_{Sn-C}}$ 20, **C15**), 27.4 ($J_{117,119_{Sn-C}}$ 63, **C16**), 21.4 (**C12**), 13.8 (**C17**), 12.0 ($J_{117_{Sn-C}}$ 338, $J_{119_{Sn-C}}$ 354, **C14**).

IR: ν_{max} (neat)/ cm^{-1} 2922 (C–H), 1588 (C=C), 1281 (S=O), 1133 (S=O), 1080, 881, 776.

HRMS (ESI): $C_{27}H_{40}O_2S^{116}SnNa$ $[M+Na]^+$ requires 567.1659; found 567.1662

MP: 30 – 32 °C.

(*E*)-Tributyl(2-(3-fluorophenyl)-1-tosylvinyl)stannane (420)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (1.80 mL, 6.77 mmol) in tetrahydrofuran (7 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (149 mg, 0.130 mmol) and propargylic sulfone **418** (1.77 g, 6.45 mmol) in tetrahydrofuran (7 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (50 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a single regioisomer by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5 to 85 : 15) to afford stannane **420** (2.25 g, 62%) as a colourless oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.29 (2H, d, *J* 8.3, **11**-**H**), 7.12 (1H, s, **7**-**H**), 7.10 – 7.05 (1H, m, **4**-**H**), 6.97 (2H, d, *J* 8.1, **12**-**H**), 6.92 (1H, d, *J* 7.6, **5**-**H**), 6.83 (1H, app. td, *J* 8.5, 2.5, **3**-**H**), 6.74 (1H, d,

J 9.6, **1**-**H**), 2.28 (3H, s, **14**-**H**), 1.76 – 1.54 (6H, m, **17**-**H**), 1.41 (6H, app. dq, *J* 14.7, 7.3, **18**-**H**), 1.34 – 1.14 (6H, m, **16**-**H**), 0.96 (9H, t, *J* 7.3, **19**-**H**).

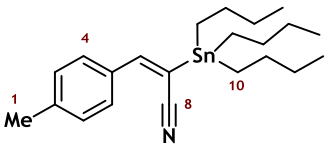
^{13}C (101 MHz, $CDCl_3$): δ 162.1 (d, $J_{F\text{-}C}$ 247, $\mathbf{C}_{Ar}$**2**), 156.5 (**C8**), 147.2 ($J_{^{117,119}Sn\text{-}C}$ 18, **C7**), 143.1 ($\mathbf{C}_{Ar}$**13**), 138.5 ($\mathbf{C}_{Ar}$**10**), 137.4 (d, $J_{F\text{-}C}$ 8, $\mathbf{C}_{Ar}$**6**), 129.3 (d, $J_{F\text{-}C}$ 8, $\mathbf{C}_{Ar}$**4**), 128.8 ($\mathbf{C}_{Ar}$**12**), 127.6 ($\mathbf{C}_{Ar}$**11**), 124.9 (d, $J_{F\text{-}C}$ 2, $\mathbf{C}_{Ar}$**5**), 115.7 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**1**), 115.0 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**3**), 29.0 ($J_{^{117,119}Sn\text{-}C}$ 20, **C17**), 27.4 ($J_{^{117,119}Sn\text{-}C}$ 63, **C18**), 21.5 (**C14**), 13.8 (**C19**), 12.1 ($J_{^{117}Sn\text{-}C}$ 337, $J_{^{119}Sn\text{-}C}$ 356, **C16**).

^{19}F (377 MHz, $CDCl_3$): δ −113.6

IR: ν_{max} (neat)/ cm^{-1} 2923 (C–H), 1578 (C=C), 1283 (S=O), 1135 (S=O), 1080, 850, 666.

HRMS (ESI): $C_{27}H_{39}FO_2S^{116}SnNa$ $[M+Na]^+$ requires 585.1564; found 585.1559

(*E*)-3-(*p*-Tolyl)-2-(tributylstannyl)acrylonitrile (287)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (7.05 mL, 26.6 mmol) in tetrahydrofuran (28 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (584 mg, 0.506 mmol) and propargylic nitrile **283** (3.57 g, 25.3 mmol) in tetrahydrofuran (28 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (100 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a single regioisomer by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford stannane **287** (9.68 g, 89%) as a light yellow oil.

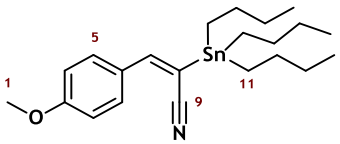
^{1}H (400 MHz, $CDCl_3$): δ 7.74 (2H, d, *J* 8.1, **4**-**H**), 7.23 (2H, d, *J* 8.1, **3**-**H**), 7.02 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 47.2, **6**-**H**), 2.39 (3H, s, **1**-**H**), 1.70 – 1.48 (6H, m, **11**-**H**), 1.37 (6H, app. dq, *J* 14.7, 7.3, **12**-**H**), 1.27 – 1.08 (6H, m, **10**-**H**), 0.93 (9H, t, *J* 7.3, **13**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 156.1 ($J_{^{117,119}Sn\text{-}C}$ 14, **C6**), 140.7 (C_{Ar}**2**), 133.9 (**C8**), 129.5 (C_{Ar}**3**), 128.7 (C_{Ar}**4**), 121.5 (C_{Ar}**5**), 109.5 (**C7**), 28.8 ($J_{^{117,119}Sn\text{-}C}$ 22, **C11**), 27.3 ($J_{^{117,119}Sn\text{-}C}$ 58, **C12**), 21.6 (**C1**), 13.8 (**C13**), 10.9 ($J_{^{117}Sn\text{-}C}$ 331, $J_{^{119}Sn\text{-}C}$ 346, **C10**).

IR: ν_{max} (neat)/ cm^{-1} 2922 (C–H), 2172 (C≡N), 1608 (C=C), 1463, 1184, 813, 693.

HRMS (ESI): $C_{22}H_{35}N^{116}SnNa$ $[M+Na]^+$ requires 452.1679; found 452.1676

(*E*)-3-(4-Methoxyphenyl)-2-(tributylstannyl)acrylonitrile (421)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (4.80 mL, 18.1 mmol) in tetrahydrofuran (19 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (398 mg, 0.340 mmol) and propargylic nitrile **419** (2.71 g, 17.2 mmol) in tetrahydrofuran (19 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (100 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a single regioisomer by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford stannane **421** (7.24 g, 94%) as a colourless oil.

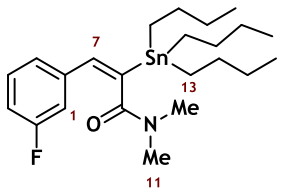
^{1}H (400 MHz, $CDCl_3$): δ 7.83 (2H, d, *J* 8.8, **5**-**H**), 6.98 (1H, s, **7**-**H**), 6.94 (2H, d, *J* 8.8, **4**-**H**), 3.85 (3H, s, **1**-**H**), 1.70 – 1.49 (6H, m, **12**-**H**), 1.38 (6H, app. dq, *J* 14.7, 7.3, **13**-**H**), 1.27 – 1.08 (6H, m, **11**-**H**), 0.93 (9H, t, *J* 7.3, **14**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 161.1 ($\mathbf{C}_{Ar}$**3**), 155.5 ($J_{^{117,119}Sn\text{-}C}$ 14, **C7**), 130.5 ($\mathbf{C}_{Ar}$**5**), 129.6 ($J_{^{117,119}Sn\text{-}C}$ 38, **C9**), 121.8 ($\mathbf{C}_{Ar}$**6**), 114.1 ($\mathbf{C}_{Ar}$**4**), 107.0 (**C8**), 55.5 (**C1**), 28.8 ($J_{^{117,119}Sn\text{-}C}$ 21, **C12**), 27.3 ($J_{^{117,119}Sn\text{-}C}$ 59, **C13**), 13.7 (**C14**), 10.9 ($J_{^{117}Sn\text{-}C}$ 331, $J_{^{119}Sn\text{-}C}$ 347, **C11**).

IR: ν_{max} (neat)/ cm^{-1} 2926 (C–H), 2171 (C≡N), 1604 (C=C), 1509, 1254, 1177, 829.

HRMS (ESI): $C_{22}H_{35}NO^{116}SnNa$ $[M+Na]^+$ requires 468.1628; found 468.1617

(*E*)-3-(3-fluorophenyl)-*N*,*N*-dimethyl-2-(tributylstannyl)acrylamide (288)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (9.10 mL, 33.0 mmol) in tetrahydrofuran (35 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (725 mg, 0.628 mmol) and propargylic amide **284** (6.00 g, 31.4 mmol) in tetrahydrofuran (35 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (150 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a single regioisomer by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5 to 80 : 20) to afford stannane **288** (13.73 g, 91%) as a yellow oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.30 – 7.19 (1H, m, **4**-**H**), 7.06 (1H, d, *J* 7.8, **5**-**H**), 6.99 (1H, d, $J_{F\text{-}H}$ 10.1, **1**-**H**), 6.90 (1H, app. td, *J* 8.3, 1.8, **3**-**H**), 6.51 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 60.1, **7**-**H**), 2.95 (3H, s, **11**-**H**), 2.72 (3H, s, **11**-**H**), 1.66 – 1.43 (6H, m, **14**-**H**), 1.33 (6H, app. sex, *J* 7.3, **15**-**H**), 1.15 – 0.96 (6H, m, **13**-**H**), 0.89 (9H, t, *J* 7.2, **16**-**H**).

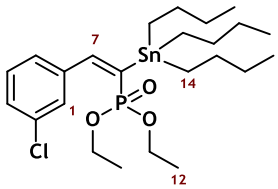
^{13}C (101 MHz, $CDCl_3$): δ 173.8 (**C9**), 163.0 (d, $J_{F\text{-}C}$ 246, $\mathbf{C}_{Ar}$**2**), 145.4 (**C8**), 139.7 (d, $J_{F\text{-}C}$ 7, $\mathbf{C}_{Ar}$**6**), 136.5 (d, $J_{F\text{-}C}$ 2, **C7**), 130.0 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**4**), 123.5 (d, $J_{F\text{-}C}$ 2, $\mathbf{C}_{Ar}$**5**), 114.7 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**3**), 114.2 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**1**), 37.1 (**C11**), 34.2 (**C11**), 28.9 ($J_{^{117,119}Sn\text{-}C}$ 20, **C14**), 27.4 ($J_{^{117,119}Sn\text{-}C}$ 60, **C15**), 13.8 (**C16**), 10.6 ($J_{^{117}Sn\text{-}C}$ 326, $J_{^{119}Sn\text{-}C}$ 341, **C13**).

^{19}F (377 MHz, $CDCl_3$): δ −113.1

IR: ν_{max} (neat)/ cm^{-1} 2924 (C–H), 1611 (C=O), 1580 (C=C), 1390, 1137, 906, 730.

HRMS (ESI): $C_{23}H_{38}FNO^{116}SnNa$ $[M+Na]^+$ requires 502.1847; found 502.1842

(*E*)-Diethyl (2-(3-chlorophenyl)-1-(tributylstannyl)vinyl)phosphonate (289)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (2.52 mL, 9.36 mmol) in tetrahydrofuran (10 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (206 mg, 0.178 mmol) and propargylic phosphonate **285** (2.43 g, 8.91 mmol) in tetrahydrofuran (10 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (100 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude

product which was a single regioisomer by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 90 : 10 to 80 : 20) to afford stannane **289** (3.61 g, 72%) as a yellow oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.60 – 7.43 (2H, m, **1**-**H**, **5**-**H**), 7.26 (1H, d, $J_{P\text{-}H}$ 62.6, **7**-**H**), 7.28 – 7.12 (2H, m, **3**-**H**, **4**-**H**), 3.82 (4H, app. quin, *J* 7.2, **11**-**H**), 1.62 – 1.39 (6H, m, **15**-**H**), 1.33 (6H, app. sex, *J* 7.3, **16**-**H**), 1.08 (6H, t, *J* 7.1, **12**-**H**), 1.04 – 0.90 (6H, m, **14**-**H**), 0.84 (9H, t, *J* 7.3, **17**-**H**).

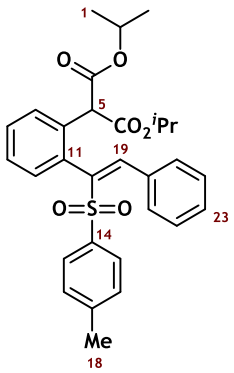
^{13}C (101 MHz, $CDCl_3$): δ 153.8 (**C7**), 139.7 (d, $J_{P\text{-}C}$ 14, $\mathbf{C}_{Ar}$**6**), 137.2 (d, $J_{P\text{-}C}$ 135, **C8**), 133.8 ($\mathbf{C}_{Ar}$**2**), 129.2 ($\mathbf{C}_{Ar}$**4**), 129.1 ($\mathbf{C}_{Ar}$**1**), 128.5 ($\mathbf{C}_{Ar}$**3**), 127.3 ($\mathbf{C}_{Ar}$**5**), 61.3 (d, $J_{P\text{-}C}$ 6, **C11**), 28.9 ($J_{^{117,119}Sn\text{-}C}$ 19, **C15**), 27.3 ($J_{^{117,119}Sn\text{-}C}$ 61, **C16**), 16.2 (d, $J_{P\text{-}C}$ 6, **C12**), 13.7 (**C17**), 11.3 ($J_{^{117}Sn\text{-}C}$ 333, $J_{^{119}Sn\text{-}C}$ 348, **C14**).

^{31}P (162 MHz, CDCl3): δ 21.2 (s, $J_{^{117,119}Sn\text{-}P}$ 107).

IR: ν_{max} (neat)/ cm^{-1} 2924 (C–H), 1643 (C=C), 1231 (P=O), 1051, 1025, 955, 783.

HRMS (ESI): $C_{24}H_{42}{}^{35}ClO_3P^{116}SnNa$ $[M+Na]^+$ requires 583.1470; found 583.1467

(*Z*)-Diisopropyl 2-(2-(2-phenyl-1-tosylvinyl)phenyl)malonate (293)



According to a modified literature procedure,[112] a dried schlenk flask was charged with iodoarene **78** (800 mg, 2.05 mmol) and anhydrous NMP (8 mL). Under a flow of argon $Pd_2(dba)_3$ (192 mg, 0.210 mmol) and tri(2-furyl)phosphine **176** (190 mg, 0.820 mmol) were

added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Under a flow of argon flame dried CuI (586 mg, 3.08 mmol) was added. In a separate dried schlenk flask stannane **290** (1.23 g, 2.26 mmol) was dissolved in anhydrous NMP (7 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of stannane **290** was transferred dropwise *via* an argon purged syringe into the reaction mixture over 12 hours and stirred for a further 24 hours. The black reaction mixture was then poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (400 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 9 : 1) followed by crystallization (hexane/ethyl acetate) to afford cyclization precursor **293** (442 mg, 41%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.62 – 7.55 (3H, m, **7**-**H**, **21**-**H**), 7.44 – 7.32 (6H, m, **8**-**H**, **15**-**H**, **22**-**H**, **23**-**H**), 7.15 (1H, app. t, *J* 7.5, **9**-**H**), 7.09 (1H, s, **19**-**H**), 7.06 (2H, d, *J* 8.1, **16**-**H**), 7.02 (1H, d, *J* 7.6, **10**-**H**), 5.13 (1H, s, **5**-**H**), 5.16 – 5.06 (1H, m, **2**-**H**), 4.97 (1H, sept, *J* 6.2, **2**-**H**), 2.34 (3H, s, **18**-**H**), 1.32 (6H, app. dd, *J* 6.1, 2.5, **1**-**H**), 1.21 (3H, d, *J* 6.3, **1**-**H**), 1.09 (3H, d, *J* 6.1, **1**-**H**).

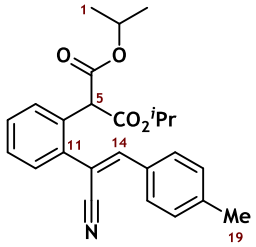
^{13}C (126 MHz, $CDCl_3$): δ 168.2 (**C4**), 167.4 (**C4**), 144.3 (**C17**), 143.1 (**C19**), 141.5 (**C12**), 136.5 ($\mathbf{C}_{Ar}$**14**), 135.7 ($\mathbf{C}_{Ar}$**11**), 133.5 ($\mathbf{C}_{Ar}$**6**/$\mathbf{C}_{Ar}$**20**), 133.4 ($\mathbf{C}_{Ar}$**6**/$\mathbf{C}_{Ar}$**20**), 131.3 ($\mathbf{C}_{Ar}$**10**), 130.0 ($\mathbf{C}_{Ar}$**7**), 129.7 ($\mathbf{C}_{Ar}$**21**), 129.2 ($\mathbf{C}_{Ar}$**16**), 129.1 ($\mathbf{C}_{Ar}$**8**), 129.1 ($\mathbf{C}_{Ar}$**23**), 128.9 ($\mathbf{C}_{Ar}$**22**), 127.9 ($\mathbf{C}_{Ar}$**15**), 127.5 ($\mathbf{C}_{Ar}$**9**), 69.5 (**C2**), 69.5 (**C2**), 55.1 (**C5**), 21.8 (**C1**), 21.7 (**C1**), 21.7 (**C18**), 21.6 (**C1**), 21.5 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1727 (C=O), 1318 (S=O), 1291, 1145 (S=O), 1101 (C–O), 766, 691.

HRMS (ESI): $C_{30}H_{32}O_6SNa$ $[M+Na]^+$ requires 543.1812; found 543.1822

MP: 118 – 120 °C (hexane/ethyl acetate).

(*Z*)-Diisopropyl 2-(2-(1-cyano-2-(*p*-tolyl)vinyl)phenyl)malonate (294)



According to a modified literature procedure,[112] a dried schlenk flask was charged with iodoarene **78** (549 mg, 1.41 mmol) and anhydrous NMP (5 mL). Under a flow of argon $Pd(PPh_3)_4$ (326 mg, 0.280 mmol) was added carefully and the resulting suspension was degassed with argon for 30 minutes. Under a flow of argon flame dried CuI (404 mg, 2.12 mmol) was added. In a separate dried schlenk flask stannane **287** (916 mg, 2.12 mmol) was dissolved in anhydrous NMP (5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of stannane **287** was transferred dropwise *via* an argon purged syringe into the reaction mixture over 12 hours and stirred for a further 24 hours. The black reaction mixture was then poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (400 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium

carbonate, 9 : 1; 30-40 petrol : diethyl ether, 19 : 1) to afford cyclization precursor **294** (288 mg, 50%) as a light red oil.[†]

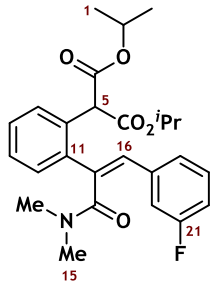
^{1}H (400 MHz, $CDCl_3$): δ 7.81 (2H, d, *J* 8.1, **16-H**), 7.65 (1H, d, *J* 7.8, **7-H**), 7.48 – 7.37 (3H, m, **8-H**, **9-H**, **10-H**), 7.29 (2H, d, *J* 8.1, **17-H**), 7.14 (1H, s, **14-H**), 5.08 (2H, sept, *J* 6.2, **2-H**), 4.98 (1H, s, **5-H**), 2.43 (3H, s, **19-H**), 1.27 (6H, d, *J* 6.3, **1-H**), 1.22 (6H, d, *J* 6.3, **1-H**).

^{13}C (126 MHz, $CDCl_3$): δ 167.6 (**C4**), 148.6 (**C14**), 141.8 ($\mathbf{C}_{Ar}$**18**), 136.4 ($\mathbf{C}_{Ar}$**11**), 131.5 ($\mathbf{C}_{Ar}$**6**), 130.7 ($\mathbf{C}_{Ar}$**15**), 130.4 ($\mathbf{C}_{Ar}$**7**), 129.8 ($\mathbf{C}_{Ar}$**17**), 129.8 ($\mathbf{C}_{Ar}$**10**), 129.4 ($\mathbf{C}_{Ar}$**16**), 129.3 ($\mathbf{C}_{Ar}$**8**), 128.6 ($\mathbf{C}_{Ar}$**9**), 118.3 ($\mathbf{C}_{Ar}$**13**), 107.8 (**C12**), 69.8 (**C2**), 54.6 (**C5**), 21.7 (**C19**), 21.7 (**C1**), 21.7 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 2208 (C≡N), 1730 (C=O), 1598, 1465, 1266, 1102 (C–O), 756.

HRMS (ESI): $C_{25}H_{27}NO_4Na$ $[M+Na]^+$ requires 428.1832; found 428.1814

(*Z*)-Diisopropyl 2-(2-(3-(dimethylamino)-1-(3-fluorophenyl)-3-oxoprop-1-en-2-yl)phenyl)malonate (291)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **288** (2.82 g, 5.85 mmol) and anhydrous NMP (17 mL). Under a flow of argon $Pd_2(dba)_3$ (357 mg, 0.390 mmol) and tri(2-furyl)phosphine **176** (362 mg, 1.56 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the

[†] *This product readily cyclizes at any temperature greater than ambient temperature, therefore, concentration on a rotary evaporator must be carried out without heating the water bath or via nitrogen gas blow down.*

solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **78** (1.52 g, 3.90 mmol) was dissolved in anhydrous NMP (4 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **78** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (1.11 g, 5.85 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 200 mL) and ethyl acetate (700 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 200 mL) and brine (3 × 200 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 9 : 1 to 4 : 1) to afford cyclization precursor **291** (1.08 g, 61%) as a golden oil.

^{1}H (500 MHz, $CDCl_3$): δ 7.65 (1H, dd, *J* 7.9, 1.3, **7**-**H**), 7.48 (1H, dd, *J* 7.6, 1.6, **10**-**H**), 7.38 (1H, app. td, *J* 7.3, 1.6, **8**-**H**), 7.35 – 7.29 (2H, m, **9**-**H**, **19**-**H**), 7.19 (1H, d, *J* 7.6, **18**-**H**), 7.12 (1H, app. dt, $J_{F\text{-}H}$ 10.1, *J* 1.9, **22**-**H**), 7.01 (1H, app. td, $J_{F\text{-}H}$ 8.4, *J* 1.9, **20**-**H**), 6.50 (1H, s, **16**-**H**), 5.41 (1H, s, **5**-**H**), 5.08 (2H, sept, *J* 6.3, **2**-**H**), 2.99 (3H, s, **15**-**H**), 2.86 (3H, s, **15**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**), 1.21 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 169.3 (**C13**), 168.3 (**C4**), 163.1 (d, $J_{F\text{-}C}$ 246, $\mathbf{C}_{Ar}$**21**), 138.4 ($\mathbf{C}_{Ar}$**11**), 137.5 (d, $J_{F\text{-}C}$ 8, $\mathbf{C}_{Ar}$**17**), 136.2 (**C12**), 132.2 (d, $J_{F\text{-}C}$ 2, **C16**), 131.5 ($\mathbf{C}_{Ar}$**6**), 130.5 ($\mathbf{C}_{Ar}$**7**), 130.3 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**19**), 128.5 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**10**), 128.4 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**10**), 128.1 ($\mathbf{C}_{Ar}$**9**), 124.2 (d, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**18**), 115.4 (d, $J_{F\text{-}C}$ 21, $\mathbf{C}_{Ar}$**20**), 114.8 (d, $J_{F\text{-}C}$ 23, $\mathbf{C}_{Ar}$**22**), 69.5 (**C2**), 54.7 (**C5**), 37.4 (**C15**), 34.9 (**C15**), 21.7 (**C1**), 21.7 (**C1**).

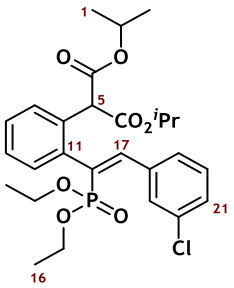
^{19}F (377 MHz, $CDCl_3$): δ −112.6

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1725 (C=O), 1628 (C=O), 1447, 1268, 1145, 1100 (C–O), 910, 729.

HRMS (ESI): $C_{26}H_{30}FNO_5Na$ $[M+Na]^+$ requires 478.2000; found 478.1991

(*Z*)-Diisopropyl 2-(2-(2-(3-chlorophenyl)-1-diethoxyphosphoryl)vinyl)phenyl)malonate

(292)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **289** (1.04 g, 1.85 mmol) and anhydrous NMP (7 mL). Under a flow of argon $Pd_2(dba)_3$ (113 mg, 0.123 mmol) and tri(2-furyl)phosphine **176** (114 mg, 0.492 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **78** (480 mg, 1.23 mmol) was dissolved in anhydrous NMP (1.0 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **78** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (352 mg, 1.85 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (400 mL). The layers were separated and the organic layer was washed with aqueous ammonium

hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 9 : 1 to 4 : 1) to afford cyclization precursor **292** (494 mg, 75%) as a golden oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.66 (1H, s, **23**-**H**), 7.61 – 7.55 (2H, m, **7**-**H**, **9**-**H**), 7.42 – 7.30 (5H, m, **Ar**-**H**), 7.03 (1H, d, $J_{P\text{-}H}$ 46.0, **17**-**H**), 5.17 – 4.97 (3H, m, **2**-**H**, **5**-**H**), 3.93 – 3.80 (2H, m, **15**-**H**), 3.79 – 3.58 (2H, m, **15**-**H**), 1.29 (3H, d, *J* 6.1, **1**-**H**), 1.24 (6H, app. dd, *J* 6.1, 3.5, **1**-**H**), 1.13 (3H, d, *J* 6.3, **1**-**H**), 0.98 (6H, t, *J* 7.1, **16**-**H**).

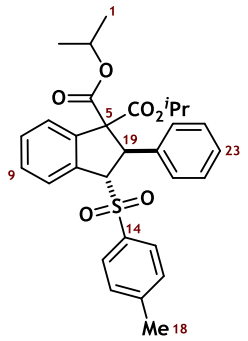
^{13}C (101 MHz, $CDCl_3$): δ 168.2 (**C4**), 167.7 (**C4**), 146.2 (d, $J_{P\text{-}C}$ 8, **C17**), 139.3 (d, $J_{P\text{-}C}$ 10, $\mathbf{C}_{Ar}$**11**), 137.4 (d, $J_{P\text{-}C}$ 7, $\mathbf{C}_{Ar}$**18**), 133.8 ($\mathbf{C}_{Ar}$**22**), 132.7 (d, $J_{P\text{-}C}$ 178, **C12**), 132.1 (d, $J_{P\text{-}C}$ 5, $\mathbf{C}_{Ar}$**6**), 129.7 (d, $J_{P\text{-}C}$ 4, $\mathbf{C}_{Ar}$**10**), 129.6 ($\mathbf{C}_{Ar}$**7**), 129.2 ($\mathbf{C}_{Ar}$**8**), 129.2 (d, $J_{P\text{-}C}$ 2, $\mathbf{C}_{Ar}$**23**), 128.7 ($\mathbf{C}_{Ar}$**20**), 128.1 (d, $J_{P\text{-}C}$ 2, $\mathbf{C}_{Ar}$**19**), 127.6 ($\mathbf{C}_{Ar}$**21**), 127.6 (d, $J_{P\text{-}C}$ 2, $\mathbf{C}_{Ar}$**9**), 69.3 (**C2**), 69.2 (**C2**), 62.6 (d, $J_{P\text{-}C}$ 6, **C15**), 62.2 (d, $J_{P\text{-}C}$ 6, **C15**), 55.0 (**C5**), 21.6 (**C1**), 21.6 (2 × **C1**), 21.5 (**C1**), 16.0 (d, $J_{P\text{-}C}$ 6, **C16**), 15.8 (d, $J_{P\text{-}C}$ 6, **C16**).

^{31}P (162 MHz, $CDCl_3$): δ 13.1

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1728 (C=O), 1235 (P=O), 1100 (C–O), 1051, 1023, 969, 790.

HRMS (ESI): $C_{27}H_{34}{}^{35}ClO_7PNa$ $[M+Na]^+$ requires 559.1623; found 559.1614

Diisopropyl 2-phenyl-3-tosyl-2,3-dihydro-1*H*-indene-1,1-dicarboxylate (295)



Racemic: Prepared according to ***general procedure 1*** using cyclization precursor **293** (37 mg, 0.071 mmol). ^{1}H NMR of the crude reaction mixture revealed a >20 : 1 (*anti* : *syn*) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 9 : 1) to afford indane **295** (15 mg, 41%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 4*** using cyclization precursor **293** (41 mg, 0.079 mmol). The reaction was performed at room temperature. ^{1}H NMR of the crude reaction mixture revealed a >20 : 1 (*anti* : *syn*) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 9 : 1) to afford indane **295** (38 mg, 93%, 2% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.80 – 7.74 (1H, m, **10**-**H**), 7.70 – 7.65 (3H, m, **7**-**H**, **15**-**H**), 7.50 – 7.43 (2H, m, **8**-**H**, **9**-**H**), 7.19 (2H, d, *J* 8.2, **16**-**H**), 7.14 – 7.04 (3H, m, **22**-**H**, **23**-**H**), 6.89 (2H, d, *J* 7.3, **21**-**H**), 5.03 (1H, sept, *J* 6.3, **2**-**H**), 4.96 (1H, d, *J* 5.4, **12**-**H**), 4.91 (1H, d, *J* 5.4, **19**-**H**), 4.40 (1H, sept, *J* 6.3, **2**-**H**), 2.38 (3H, s, **18**-**H**), 1.28 (3H, d, *J* 6.3, **1**-**H**), 1.21 (3H, d, *J* 6.3, **1**-**H**), 0.99 (3H, d, *J* 6.3, **1**-**H**), 0.38 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 168.2 (**C4**), 167.8 (**C4**), 144.7 ($\mathbf{C}_{Ar}$**17**), 141.4 ($\mathbf{C}_{Ar}$**6**), 139.3 ($\mathbf{C}_{Ar}$**20**), 135.2 ($\mathbf{C}_{Ar}$**11**), 134.6 ($\mathbf{C}_{Ar}$**14**), 129.7 ($\mathbf{C}_{Ar}$**8**), 129.6 ($\mathbf{C}_{Ar}$**15**/$\mathbf{C}_{Ar}$**16**), 129.5 ($\mathbf{C}_{Ar}$**15**/$\mathbf{C}_{Ar}$**16**), 129.4 ($\mathbf{C}_{Ar}$**9**), 128.6

(br., C_{Ar}**21**), 128.3 (C_{Ar}**22**), 128.3 (C_{Ar}**7**), 127.5 (C_{Ar}**23**), 126.5 (C_{Ar}**10**), 76.2 (**C12**), 71.2 (**C5**), 70.2 (**C2**), 69.9 (**C2**), 51.6 (**C19**), 21.7 (**C1**), 21.6 (**C1**), 21.6 (**C1**), 21.4 (**C1**), 20.5 (**C18**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1725 (C=O), 1456, 1320 (S=O), 1291, 1264, 1243, 1146 (S=O), 1105 (C–O), 702, 670.

HRMS (ESI): $C_{30}H_{32}O_6SNa$ $[M+Na]^+$ requires 543.1812; found 543.1808

MP: 68 – 70 °C (decomposed) (40-60 petrol/ethyl acetate).

Chiral HPLC: Chiralpak AD-H (20% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 205 nm), t_R(**minor**) 7.7 min and t_R(**major**) 12.0 min, 2% ee.

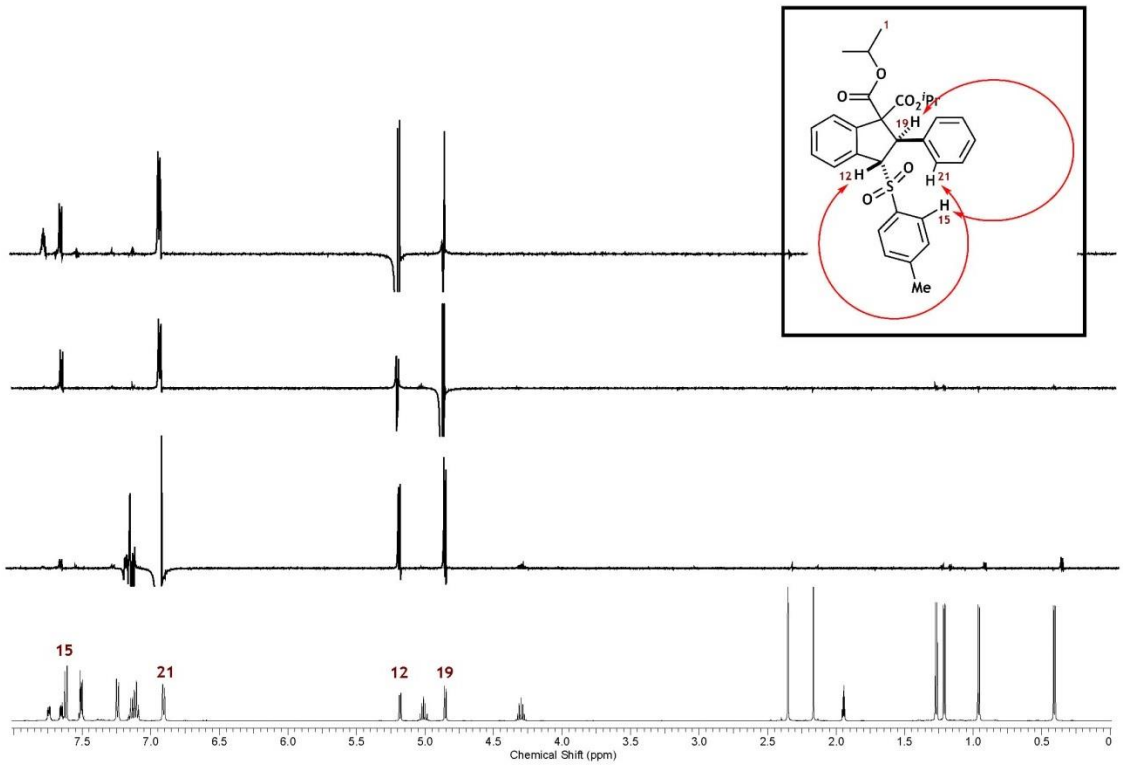
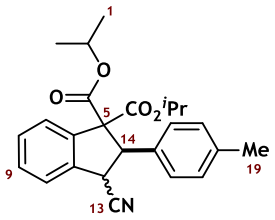


Figure 5.3 – 1D nOe data for indane **295** in CD_3CN (mixing time = 0.8 s).

Diisopropyl 3-cyano-2-(*p*-tolyl)-2,3-dihydro-1*H*-indene-1,1-dicarboxylate (297)



Racemic: Prepared according to ***general procedure 1*** using cyclization precursor **294** (50 mg, 0.123 mmol). ^{1}H NMR of the crude reaction mixture revealed a 1.3 : 1.0 mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1) to afford indane **297** (43 mg, 86%, 1.7 : 1.0 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 4*** using cyclization precursor **294** (76 mg, 0.187 mmol). ^{1}H NMR of the crude reaction mixture revealed a 1.2 : 1.0 mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 30 : 1) to afford indane **297** (70 mg, 92%, 37% ee (major), 39% ee (minor), 1.2 : 1.0 dr) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.82 – 7.76 (0.8H, m, **7**-**H**), 7.69 – 7.65 (1H, m, **7**-**H**), 7.55 – 7.52 (1H, m, **10**-**H**), 7.52 – 7.39 (4.40H, m, **Ar**-**H**), 7.21 (2H, d, *J* 8.3, **16**-**H**), 7.11 (2H, m, *J* 7.8, **17**-**H**), 6.97 (1.6H, d, *J* 7.8, **17**-**H**), 6.81 (1.6H, d, *J* 8.3, **16**-**H**), 5.17 (1H, sept, *J* 6.3, **2**-**H**), 5.03 – 4.91 (1.6H, m, **2**-**H**, **12**-**H**), 4.79 (1H, d, *J* 8.8, **14**-**H**), 4.69 (0.8H, sept, *J* 6.4, **2**-**H**), 4.64 – 4.54 (2.6H, m, **2**-**H**, **12**-**H**, **14**-**H**), 2.32 (3H, s, **19**-**H**), 2.24 (2.4H, s, **19**-**H**), 1.31 (6H, app. dd, *J* 6.4, 2.0, **1**-**H**), 1.25 (2.4H, d, *J* 6.1, **1**-**H**), 1.11 (4.8H, app. dd, *J* 6.1, 1.5, **1**-**H**), 1.08 (3H, d, *J* 6.4, **1**-**H**), 0.70 (2.4H, d, *J* 6.1, **1**-**H**), 0.59 (3H, d, *J* 6.1, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 168.5 (**C4**), 168.1 (**C4**), 167.9 (**C4**), 166.7 (**C4**), 139.0 ($\mathbf{C_{Ar}6}$), 138.3 ($\mathbf{C_{Ar}6}$/$\mathbf{C_{Ar}11}$/$\mathbf{C_{Ar}18}$), 138.3 ($\mathbf{C_{Ar}6}$/$\mathbf{C_{Ar}11}$/$\mathbf{C_{Ar}18}$), 138.1 ($\mathbf{C_{Ar}6}$/$\mathbf{C_{Ar}11}$/$\mathbf{C_{Ar}18}$), 138.1 ($\mathbf{C_{Ar}6}$/$\mathbf{C_{Ar}11}$/$\mathbf{C_{Ar}18}$), 137.8 ($\mathbf{C_{Ar}11}$), 133.7 ($\mathbf{C_{Ar}15}$), 133.5 ($\mathbf{C_{Ar}15}$), 129.8 (2 × $\mathbf{C_{Ar}9}$), 129.3 ($\mathbf{C_{Ar}8}$), 129.3 ($\mathbf{C_{Ar}17}$), 129.1 ($\mathbf{C_{Ar}17}$), 129.0 ($\mathbf{C_{Ar}8}$), 128.5 ($\mathbf{C_{Ar}16}$), 128.4 ($\mathbf{C_{Ar}16}$), 128.3 ($\mathbf{C_{Ar}7}$), 126.7 ($\mathbf{C_{Ar}7}$), 124.6 ($\mathbf{C_{Ar}10}$), 124.2 ($\mathbf{C_{Ar}10}$), 119.5 (**C13**), 118.3 (**C13**), 70.2 (**C2**), 70.1 (**C2**), 70.0 (**C5**), 69.8 (**C2**), 69.5 (**C5**), 69.3 (**C2**), 54.9 (**C14**), 54.3 (**C14**), 41.2 (**C12**), 40.1 (**C12**), 21.7 (**C1**), 21.6 (**C1**), 21.6 (**C1**), 21.5 (**C1**), 21.5 (**C1**), 21.3 (**C1**), 21.2 (**C19**), 21.2 (**C19**), 20.8 (**C1**), 20.7 (**C1**).

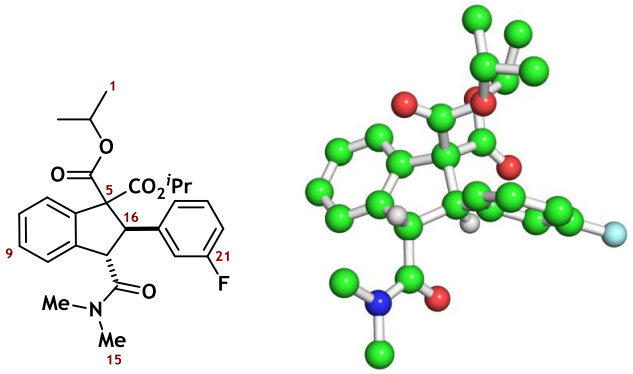
IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 2244 (C≡N), 1724 (C=O), 1517, 1458, 1375, 1262, 1106 (C–O), 908, 754.

HRMS (ESI): $C_{25}H_{27}NO_4Na$ $[M+Na]^+$ requires 428.1832; found 428.1826

MP: 128 – 130 °C.

Chiral HPLC: Chiralpak IA (5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 208 nm), minor diastereomer: t_R(**minor**) 7.4 min and t_R(**major**) 8.2 min, 39% ee & major diastereomer: t_R(**major**) 10.4 min and t_R(**minor**) 19.1 min, 37% ee.

Diisopropyl 3-(dimethylcarbamoyl)-2-(3-fluorophenyl)-2,3-dihydro-1*H*-indene-1,1-dicarboxylate (298)



Racemic: Prepared according to ***general procedure 1*** using cyclization precursor **291** (48 mg, 0.105 mmol). The reaction was performed at 50 °C for 48 hours. ^{1}H NMR of the crude reaction mixture revealed a 5.0 : 1.0 (*anti* : *syn*) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 9 : 1) to afford indane *anti*-**298** (15 mg, 31%, >20 : 1 dr) as a yellow solid.[†]

^{1}H (500 MHz, $CDCl_3$): δ 7.68 – 7.64 (1H, m, **7-H**), 7.37 – 7.30 (2H, m, **8-H**, **9-H**), 7.25 – 7.20 (2H, m, **18-H**, **19-H**), 7.17 – 7.11 (2H, m, **10-H**, **22-H**), 6.97 – 6.92 (1H, m, **20-H**), 5.16 (1H, sept, *J* 6.3, **2-H**), 5.02 (1H, d, *J* 9.5, **16-H**), 4.77 (1H, d, *J* 9.5, **12-H**), 4.66 (1H, sept, *J* 6.3, **2-H**), 3.18 (3H, s, **15-H**), 3.02 (3H, s, **15-H**), 1.30 (6H, app. dd, *J* 6.3, 4.1, **1-H**), 1.10 (3H, d, *J* 6.3, **1-H**), 0.66 (3H, d, *J* 6.3, **1-H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.3 (**C13**), 169.1 (**C4**), 168.4 (**C4**), 162.7 (d, $J_{F\text{-}C}$ 245, C_{Ar}**21**), 142.3 (C_{Ar}**11**), 141.0 (d, $J_{F\text{-}C}$ 7, C_{Ar}**17**), 139.7 (C_{Ar}**6**), 129.7 (d, $J_{F\text{-}C}$ 9, C_{Ar}**19**), 129.2 (C_{Ar}**9**), 128.1 (C_{Ar}**8**), 126.2 (C_{Ar}**7**), 125.2 (d, $J_{F\text{-}C}$ 3, C_{Ar}**18**), 123.9 (C_{Ar}**10**), 116.4 (d, $J_{F\text{-}C}$ 22, C_{Ar}**22**), 114.4 (d, $J_{F\text{-}C}$ 21, C_{Ar}**20**), 69.8 (**C5**), 69.7 (**C2**), 69.6 (**C2**), 54.5 (**C16**), 51.2 (**C12**), 37.8 (**C15**), 36.2 (**C15**), 21.8 (**C1**), 21.7 (**C1**), 21.6 (**C1**), 21.0 (**C1**).

[†] *The minor syn diastereomer was not isolated.*

^{19}F (377 MHz, $CDCl_3$): δ −113.5

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1719 (C=O), 1650 (C=O), 1489, 1375, 1259, 1105 (C–O), 751.

HRMS (ESI): $C_{26}H_{30}FNO_5Na$ $[M+Na]^+$ requires 478.2000; found 478.1999

MP: 128 – 130 °C (40-60 petrol/ethyl acetate).

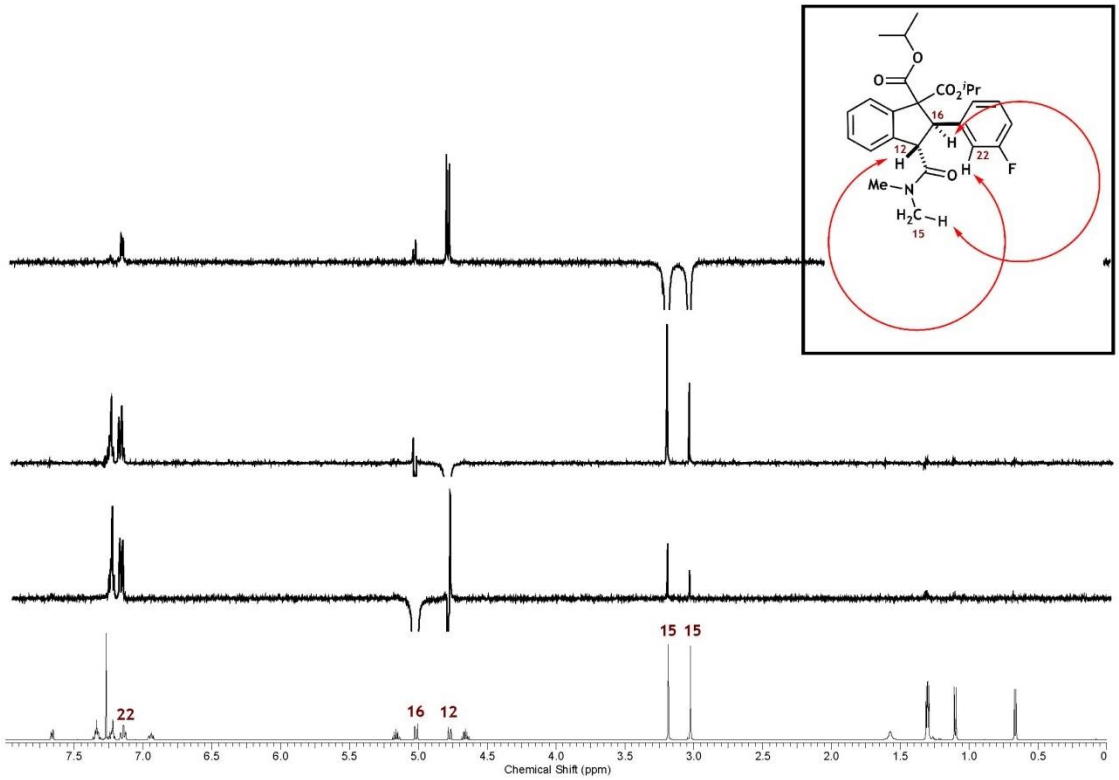
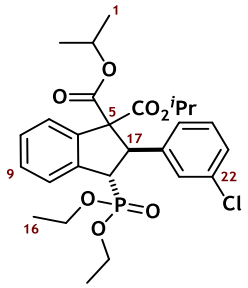


Figure 5.4 – 1D nOe data for indane **298** in $CDCl_3$ (mixing time = 0.8 s).

Diisopropyl 2-(3-chlorophenyl)-3-(diethoxyphosphoryl)-2,3-dihydro-1*H*-indene-1,1-dicarboxylate (296)



Racemic: Prepared according to ***general procedure 1*** using cyclization precursor **292** (25 mg, 0.047 mmol). ^{1}H NMR of the crude reaction mixture revealed a >20 : 1 (*anti* : *syn*) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 4 : 1) to afford indane **296** (17 mg, 68%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 4*** using cyclization precursor **292** (39 mg, 0.073 mmol). The reaction was performed at room temperature. ^{1}H NMR of the crude reaction mixture revealed a >20 : 1 (*anti* : *syn*) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 4 : 1) to afford indane **296** (30 mg, 77%, 9% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, C_6D_6): δ 8.17 (1H, d, *J* 7.6, **10**-**H**), 7.88 (1H, d, *J* 7.6, **7**-**H**), 7.64 (1H, s, **23**-**H**), 7.27 (1H, d, *J* 7.9, **19**-**H**), 7.23 (1H, app. td, *J* 7.6, 1.3, **9**-**H**), 7.19 (1H, app. t, *J* 7.6, **8**-**H**), 7.00 (1H, dd, *J* 8.0, 1.1, **21**-**H**), 6.75 (1H, app. t, *J* 7.9, **20**-**H**), 5.37 (1H, dd, $J_{P\text{-}H}$ 18.8, *J* 8.7, **17**-**H**), 5.04 (1H, sept, *J* 6.3, **2**-**H**), 4.56 (1H, sept, *J* 6.3, **2**-**H**), 4.13 (1H, dd, $J_{P\text{-}H}$ 21.1, *J* 8.5, **12**-**H**), 3.90 – 3.61 (4H, m, **15**-**H**), 1.06 (3H, d, *J* 6.0, **1**-**H**), 0.96 (3H, d, *J* 6.3, **1**-**H**), 0.89 (3H, d, *J* 6.3, **1**-**H**), 0.81 (3H, t, *J* 7.1, **16**-**H**), 0.77 (3H, t, *J* 6.9, **16**-**H**), 0.49 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, C_6D_6): δ 169.1 (**C4**), 168.9 (d, $J_{P\text{-}C}$ 2, **C4**), 143.3 (d, $J_{P\text{-}C}$ 4, $\mathbf{C}_{Ar}$**18**), 140.6 (d, $J_{P\text{-}C}$ 11, $\mathbf{C}_{Ar}$**6**), 140.5 (d, $J_{P\text{-}C}$ 4, $\mathbf{C}_{Ar}$**11**), 134.5 ($\mathbf{C}_{Ar}$**22**), 130.2 (br., $\mathbf{C}_{Ar}$**23**), 130.0 ($\mathbf{C}_{Ar}$**20**), 129.7 (d, $J_{P\text{-}C}$ 3, $\mathbf{C}_{Ar}$**9**), 128.5 ($\mathbf{C}_{Ar}$**8**), 128.3 ($\mathbf{C}_{Ar}$**19**), 127.8 ($\mathbf{C}_{Ar}$**21**), 127.7 ($\mathbf{C}_{Ar}$**7**), 126.6 ($\mathbf{C}_{Ar}$**10**), 72.0 (d, $J_{P\text{-}C}$ 9, **C5**), 70.0 (**C2**), 69.6 (**C2**), 62.9 (d, $J_{P\text{-}C}$ 7, **C15**), 62.0 (d, $J_{P\text{-}C}$ 6, **C15**), 52.3 (**C17**), 49.1 (d, $J_{P\text{-}C}$ 144, **C12**), 21.8 (**C1**), 21.8 (**C1**), 21.8 (**C1**), 21.1 (**C1**), 16.6 (d, $J_{P\text{-}C}$ 5, **C16**), 16.4 (d, $J_{P\text{-}C}$ 6, **C16**).

^{31}P (202 MHz, C_6D_6): δ 39.5

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1722 (C=O), 1249 (P=O), 1104 (C–O), 1054, 1025, 968, 800.

HRMS (ESI): $C_{27}H_{34}{}^{35}ClO_7PNa$ $[M+Na]^+$ requires 559.1623; found 559.1601

MP: 108 – 110 °C.

Chiral HPLC: Chiralpak AD-H (50% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 221 nm), t_R(**minor**) 3.5 min and t_R(**major**) 4.2 min, 9% ee.

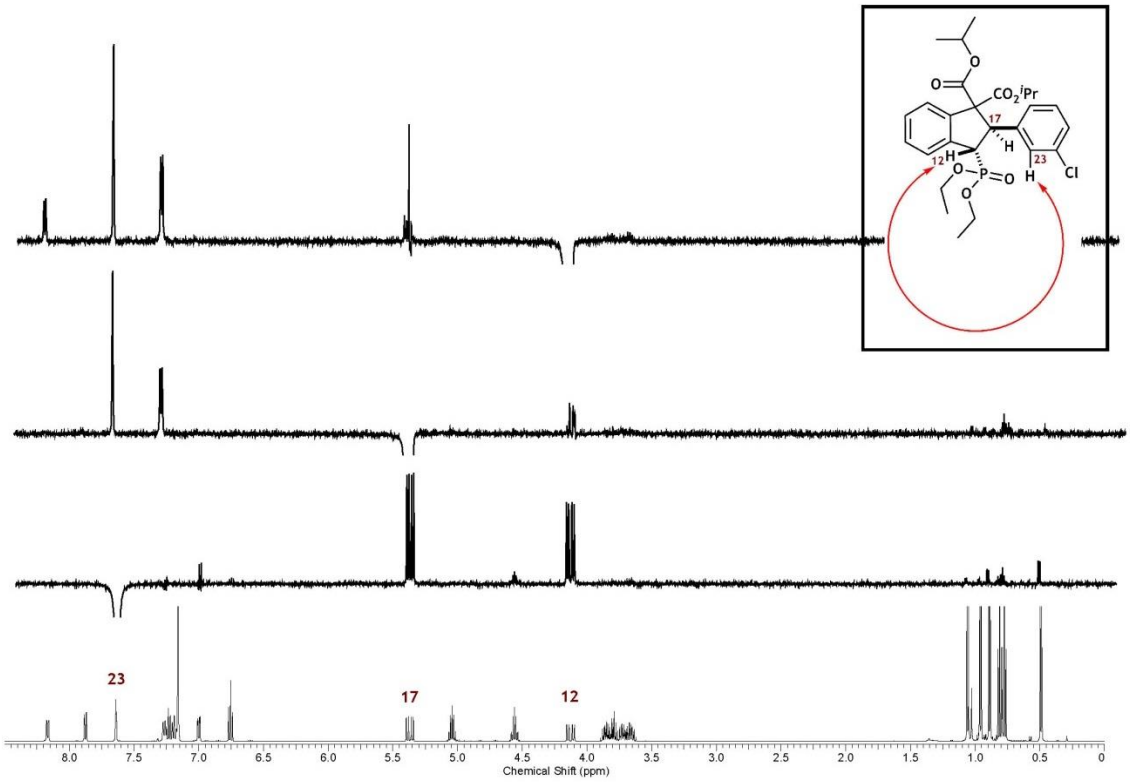
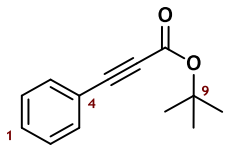


Figure 5.5 – 1D nOe data for indane **296** in C_6D_6 (mixing time = 0.8 s).

5.3.7 Indanes with Superior Functional Group Orthogonality – Substrate Synthesis & Cyclization

tert-Butyl 3-phenylpropiolate (331)



A solution of *n*-butyllithium (1.6 M in hexanes, 20.6 mL, 33.0 mmol) was added dropwise over 30 minutes to a stirred solution of phenylacetylene **130** (3.06 g, 30.0 mmol) in anhydrous tetrahydrofuran (80 mL) at −78 °C. The reaction was stirred for 1 hour at −78 °C and then a solution of di-*tert*-butyl dicarbonate (6.55 g, 30.0 mmol) in tetrahydrofuran (10 mL) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride

(150 mL). The biphasic mixture was extracted with dichloromethane (3 × 150 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate 98 : 2) to afford propargylic ester **331** (5.26 g, 87%) as a yellow oil with spectroscopic data in accordance with the literature.[252,253]

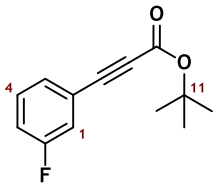
^{1}H (400 MHz, $CDCl_3$): δ 7.60 – 7.55 (2H, m, **3**-**H**), 7.46 – 7.40 (1H, m, **1**-**H**), 7.39 – 7.33 (2H, m, **2**-**H**), 1.55 (9H, s, **10**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 153.3 (**C7**), 133.0 ($\mathbf{C}_{Ar}$**3**), 130.4 ($\mathbf{C}_{Ar}$**1**), 128.6 ($\mathbf{C}_{Ar}$**2**), 120.1 ($\mathbf{C}_{Ar}$**4**), 83.9 (**C5**), 83.6 (**C6**), 82.1 (**C9**), 28.2 (**C10**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 2211 (C≡C), 1703 (C=O), 1295, 1146, 755.

LRMS (ESI): $[M+Na]^+$ 225.1

tert-Butyl 3-(3-fluorophenyl)propiolate (334)



A solution of *n*-butyllithium (1.6 M in hexanes, 19.1 mL, 30.6 mmol) was added dropwise over 30 minutes to a stirred solution of 1-ethynyl-3-fluorobenzene **131** (3.34 g, 27.8 mmol) in anhydrous tetrahydrofuran (80 mL) at −78 °C. The reaction was stirred for 1 hour at −78 °C and then a solution of di-*tert*-butyl dicarbonate (6.07 g, 27.8 mmol) in tetrahydrofuran (10 mL) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (150 mL). The biphasic mixture was extracted with dichloromethane (3 × 150 mL) and then

the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 98 : 2) to afford propargylic ester **334** (5.02 g, 82%) as a yellow oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.38 – 7.30 (2H, m, **4**-**H**, **5**-**H**), 7.28 – 7.23 (1H, m, **1**-**H**), 7.18 – 7.11 (1H, m, **3**-**H**), 1.55 (9H, s, **12**-**H**).

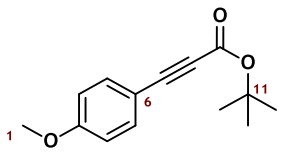
^{13}C (101 MHz, $CDCl_3$): δ 162.3 (d, $J_{F\text{-}C}$ 248, $\mathbf{C}_{Ar}$**2**), 152.9 (**C9**), 130.4 (d, $J_{F\text{-}C}$ 8, $\mathbf{C}_{Ar}$**4**), 128.9 (d, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**5**), 121.9 (d, $J_{F\text{-}C}$ 10, $\mathbf{C}_{Ar}$**6**), 119.6 (d, $J_{F\text{-}C}$ 23, $\mathbf{C}_{Ar}$**1**), 117.9 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**3**), 84.0 (**C8**), 82.6 (**C11**), 82.2 (d, $J_{F\text{-}C}$ 3, **C7**), 28.2 (**C12**).

^{19}F (377 MHz, $CDCl_3$): δ −112.0

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 2222 (C≡C), 1701 (C=O), 1582, 1309, 1231, 1155, 1139, 766.

HRMS (ESI): $C_{13}H_{13}FO_2Na$ $[M+Na]^+$ requires 243.0792; found 243.0799

tert-Butyl 3-(4-methoxyphenyl)propiolate (324)



A solution of *n*-butyllithium (1.6 M in hexanes, 10.4 mL, 16.6 mmol) was added dropwise over 30 minutes to a stirred solution of 1-ethynyl-4-methoxybenzene **323** (2.00 g, 15.1 mmol) in anhydrous tetrahydrofuran (40 mL) at −78 °C. The reaction was stirred for 1 hour at −78 °C and then a solution of di-*tert*-butyl dicarbonate (3.30 g, 15.1 mmol) in tetrahydrofuran (5 mL) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride

(80 mL). The biphasic mixture was extracted with dichloromethane (3 × 80 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 98 : 2) to afford propargylic ester **324** (3.00 g, 86%) as a colourless oil with spectroscopic data in accordance with the literature.[254]

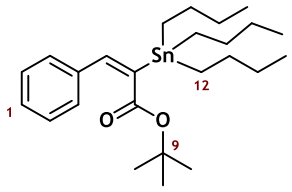
^{1}H (400 MHz, $CDCl_3$): δ 7.53 (2H, d, *J* 9.0, **5**-**H**), 6.87 (2H, d, *J* 8.8, **4**-**H**), 3.83 (3H, s, **1**-**H**), 1.54 (9H, s, **12**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 161.4 ($\mathbf{C}_{Ar}$**3**), 153.5 (**C9**), 134.9 ($\mathbf{C}_{Ar}$**5**), 114.3 ($\mathbf{C}_{Ar}$**4**), 111.9 ($\mathbf{C}_{Ar}$**6**), 84.7 (**C7**), 83.3 (**C8**), 81.5 (**C11**), 55.5 (**C1**), 28.2 (**C12**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 2205 (C≡C), 1698 (C=O), 1511, 1290, 1208, 1145, 834.

LRMS (ESI): $[M+Na]^+$ 255.1

(*E*)-*tert*-Butyl 3-phenyl-2-(tributylstannyl)acrylate (332)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (4.18 mL, 15.5 mmol) in tetrahydrofuran (15 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (342 mg, 0.296 mmol) and propargylic ester **331** (3.00 g, 14.8 mmol) in tetrahydrofuran (15 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (100 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product

which was an 8 : 1 mixture of regioisomers by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford stannane **332** (6.86 g, 94%) as a yellow oil and as a 10 : 1 mixture of regioisomers which were used in the subsequent reaction without separation.

A small amount of the product was repurified for analysis by silica gel chromatography (40-60 petrol : toluene, 100 : 0 to 80 : 20).

Data for major regioisomer:

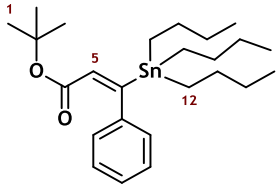
^{1}H (400 MHz, $CDCl_3$): δ 7.39 – 7.20 (5H, m, **1**-**H**, **2**-**H**, **3**-**H**), 6.63 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 60.6, **5**-**H**), 1.66 – 1.48 (6H, m, **13**-**H**), 1.44 (9H, s, **10**-**H**), 1.40 – 1.29 (6H, m, **14**-**H**), 1.16 – 0.97 (6H, m, **12**-**H**), 0.91 (9H, t, *J* 7.2, **15**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 172.5 (**C7**), 141.5 ($\mathbf{C}_{Ar}$**4**), 141.3 (**C5**), 137.4 (**C6**), 128.3 ($\mathbf{C}_{Ar}$**2**/$\mathbf{C}_{Ar}$**3**), 128.2 ($\mathbf{C}_{Ar}$**2**/$\mathbf{C}_{Ar}$**3**), 127.9 ($\mathbf{C}_{Ar}$**1**), 80.7 (**C9**), 29.0 ($J_{^{117,119}Sn\text{-}C}$ 21, **C13**), 28.3 (**C10**), 27.5 ($J_{^{117,119}Sn\text{-}C}$ 61, **C14**), 13.8 (**C15**), 10.6 ($J_{^{117}Sn\text{-}C}$ 329, $J_{^{119}Sn\text{-}C}$ 344, **C12**).

IR: ν_{max} (neat)/ cm^{-1} 2926 (C–H), 1696 (C=O), 1597 (C=C), 1366, 1224, 1143, 695.

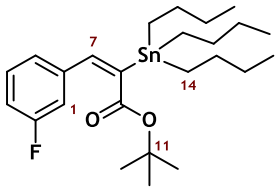
HRMS (ESI): $C_{25}H_{42}O_2{}^{116}SnNa$ $[M+Na]^+$ requires 513.2094; found 513.2107

Selected data for minor regioisomer (**333**):



^{1}H (400 MHz, $CDCl_3$): 6.02 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 60.4, **5**-**H**).

(*E*)-*tert*-Butyl 3-(3-fluorophenyl)-2-(tributylstannyl)acrylate (335)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (3.84 mL, 31.3 mmol) in tetrahydrofuran (15 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (314 mg, 0.272 mmol) and propargylic ester **334** (3.00 g, 13.6 mmol) in tetrahydrofuran (15 mL) at room temperature. The reaction was allowed to stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (100 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a 3 : 1 mixture of regioisomers by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford stannane **335** (5.67 g, 84%) as a light yellow oil and as a 4 : 1 mixture of regioisomers which were used in the subsequent reaction without separation.

A small amount of the product was repurified for analysis by silica gel chromatography (40-60 petrol : toluene, 100 : 0 to 80 : 20).

Data for major regioisomer:

^{1}H (400 MHz, $CDCl_3$): δ 7.32 – 7.25 (1H, m, **4**-**H**), 7.16 – 7.09 (2H, m, **1**-**H**, **5**-**H**), 6.96 (1H, app. tdd, *J* 8.4, 2.5, 0.7, **3**-**H**), 6.60 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 58.9, **7**-**H**), 1.68 – 1.50 (6H, m, **15**-**H**), 1.48 (9H, s, **12**-**H**), 1.38 (6H, app. dq, *J* 14.7, 7.3, **16**-**H**), 1.18 – 1.00 (6H, m, **14**-**H**), 0.94 (9H, t, *J* 7.3, **17**-**H**).

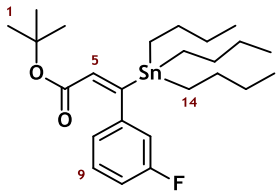
^{13}C (101 MHz, $CDCl_3$): δ 172.2 (**C9**), 162.8 (d, $J_{F\text{-}C}$ 245, C_{Ar}**2**), 143.4 (**C8**), 139.6 (C_{Ar}**6**), 139.5 (d, $J_{F\text{-}C}$ 2, **C7**), 129.7 (d, $J_{F\text{-}C}$ 8, C_{Ar}**4**), 124.1 (d, $J_{F\text{-}C}$ 2, C_{Ar}**5**), 114.8 (d, $J_{F\text{-}C}$ 22, C_{Ar}**3**), 114.7 (d, $J_{F\text{-}C}$ 21, C_{Ar}**1**), 81.0 (**C11**), 29.0 ($J_{^{117,119}Sn\text{-}C}$ 20, **C15**), 28.3 (**C12**), 27.5 ($J_{^{117,119}Sn\text{-}C}$ 60, **C16**), 13.8 (**C17**), 10.7 ($J_{^{117}Sn\text{-}C}$ 330, $J_{^{119}Sn\text{-}C}$ 345, **C14**).

^{19}F (377 MHz, $CDCl_3$): δ −113.8

IR: ν_{max} (neat)/ cm^{-1} 2927 (C–H), 1695 (C=O), 1611 (C=C), 1367, 1224, 1140, 693.

HRMS (ESI): $C_{25}H_{41}FO_2{}^{116}SnNa$ $[M+Na]^+$ requires 531.2000; found 531.2020

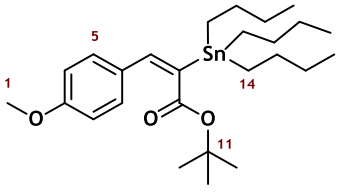
Selected data for minor regioisomer (**336**):



^{1}H (400 MHz, $CDCl_3$): 6.03 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 58.4, **5-H**).

^{19}F (377 MHz, $CDCl_3$): δ −114.3

(*E*)-*tert*-Butyl 3-(4-methoxyphenyl)-2-(tributylstannyl)acrylate (325)



According to a modified literature procedure,[60] a degassed solution of tributyltin hydride (3.47 mL, 12.9 mmol) in tetrahydrofuran (13 mL) was added dropwise over 4 hours to a degassed solution of $Pd(PPh_3)_4$ (284 mg, 0.246 mmol) and propargylic ester **324** (2.85 g, 12.3 mmol) in tetrahydrofuran (13 mL) at room temperature. The reaction was allowed to

stir overnight and was then concentrated *in vacuo*. The residue was diluted with 40-60 petrol (70 mL) and stirred for 20 minutes. The resulting precipitate was removed by filtration through Celite® with 40-60 petrol and the filtrate concentrated *in vacuo*. The crude product which was a 5 : 1 mixture of regioisomers by ^{1}H NMR was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford stannane **325** (5.78 g, 90%) as a colourless oil and as an inseparable 5 : 1 mixture of regioisomers which were used in the subsequent reaction without further separation.

Data for major regioisomer:

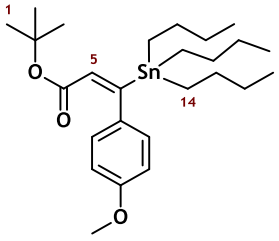
^{1}H (400 MHz, $CDCl_3$): δ 7.34 (2H, d, *J* 8.8, **5**-**H**), 6.83 (2H, d, *J* 8.8, **4**-**H**), 6.57 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 62.1, **7**-**H**), 3.81 (3H, s, **1**-**H**), 1.68 – 1.47 (6H, m, **15**-**H**), 1.48 (9H, s, **12**-**H**), 1.35 (6H, app. dq, *J* 14.7, 7.4, **16**-**H**), 1.15 – 0.96 (6H, m, **14**-**H**), 0.91 (9H, t, *J* 7.3, **17**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 172.7 (**C9**), 159.5 ($\mathbf{C}_{Ar}$**3**), 141.0 ($J_{^{117,119}Sn\text{-}C}$ 14, **C7**), 138.7 (**C8**), 130.2 ($\mathbf{C}_{Ar}$**6**), 129.8 ($\mathbf{C}_{Ar}$**5**), 113.6 ($\mathbf{C}_{Ar}$**4**), 80.6 (**C11**), 55.4 (**C1**), 29.0 ($J_{^{117,119}Sn\text{-}C}$ 20, **C15**), 28.3 (**C12**), 27.5 ($J_{^{117,119}Sn\text{-}C}$ 60, **C16**), 13.8 (**C17**), 10.6 ($J_{^{117}Sn\text{-}C}$ 329, $J_{^{119}Sn\text{-}C}$ 344, **C14**).

IR: ν_{max} (neat)/ cm^{-1} 2927 (C–H), 1695 (C=O), 1606 (C=C), 1509, 1251, 1143, 747.

HRMS (ESI): $C_{26}H_{44}O_3{}^{116}SnNa$ $[M+Na]^+$ requires 543.2200; found 543.2193

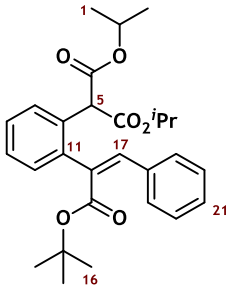
Selected data for minor regioisomer (**326**):



^{1}H (400 MHz, $CDCl_3$): 6.01 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 60.9, **5**-**H**), 3.80 (3H, s, **12**-**H**).

(Z)-Diisopropyl 2-(2-(3-(*tert*-butoxy)-3-oxo-1-phenylprop-1-en-2-yl)phenyl)malonate

(337)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **332** (2.89 g, 5.85 mmol) and anhydrous NMP (22 mL). Under a flow of argon $Pd(PPh_3)_4$ (901 mg, 0.780 mmol) was added carefully and the resulting suspension was degassed with argon for 30 minutes. Meanwhile, in a separate dried schlenk flask iodoarene **78** (1.52 g, 3.90 mmol) was dissolved in anhydrous NMP (5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **78** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (1.11 g, 5.85 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 200 mL) and ethyl acetate (700 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 200 mL) and brine (3 × 200 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) to afford cyclization precursor **337** (1.38 g, 76%) as a colourless oil.

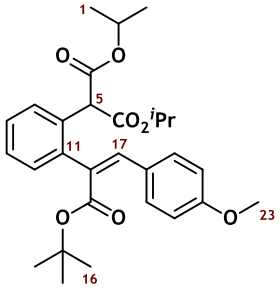
^{1}H (400 MHz, $CDCl_3$): δ 7.61 – 7.57 (1H, m, **7**-**H**), 7.46 – 7.42 (2H, m, **19**-**H**), 7.41 – 7.29 (6H, m, **Ar**-**H**), 6.59 (1H, s, **17**-**H**), 5.14 (1H, s, **5**-**H**), 5.07 (2H, sept, *J* 6.2, **2**-**H**), 1.36 (9H, s, **16**-**H**), 1.26 (6H, d, *J* 6.1, **1**-**H**), 1.19 (6H, d, *J* 6.1, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 168.3 (**C4**), 167.5 (**C13**), 139.1 ($\mathbf{C}_{Ar}$**11**), 136.2 (**C17**), 135.7 ($\mathbf{C}_{Ar}$**18**), 134.8 (**C12**), 132.0 ($\mathbf{C}_{Ar}$**6**), 129.6 ($\mathbf{C}_{Ar}$**7**), 129.3 ($\mathbf{C}_{Ar}$**10**), 128.6 ($\mathbf{C}_{Ar}$**19**), 128.4 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**21**), 128.3 ($\mathbf{C}_{Ar}$**20**), 128.2 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**21**), 127.9 ($\mathbf{C}_{Ar}$**9**), 82.1 (**C15**), 69.3 (**C2**), 54.9 (**C5**), 27.9 (**C16**), 21.7 (**C1**), 21.7 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1726 (C=O), 1370, 1225, 1149, 1100 (C–O), 752.

HRMS (ESI): $C_{28}H_{34}O_6Na$ $[M+Na]^+$ requires 489.2248; found 489.2239

(*Z*)-Diisopropyl 2-(2-(3-(*tert*-butoxy)-1-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl)phenyl) malonate (328)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **325** (2.98 g, 5.69 mmol) and anhydrous NMP (22 mL). Under a flow of argon $Pd_2(dba)_3$ (347 mg, 0.379 mmol) and tri(2-furyl)phosphine **176** (352 mg, 1.52 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **78** (1.48 g, 3.79 mmol) was dissolved in anhydrous NMP (5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **78** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of

argon flame dried CuI (1.08 g, 5.69 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 150 mL) and ethyl acetate (600 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 150 mL) and brine (3 × 150 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 20 : 1) to afford cyclization precursor **328** (1.20 g, 64%) as a light yellow oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.60 – 7.56 (1H, m, **7**-**H**), 7.41 (2H, d, *J* 8.6, **19**-**H**), 7.42 – 7.29 (3H, m, **8**-**H**, **9**-**H**, **10**-**H**), 6.89 (2H, d, *J* 8.8, **20**-**H**), 6.49 (1H, s, **17**-**H**), 5.14 (1H, s, **5**-**H**), 5.06 (2H, sept, *J* 6.3, **2**-**H**), 3.84 (3H, s, **23**-**H**), 1.39 (9H, s, **16**-**H**), 1.26 (6H, d, *J* 6.4, **1**-**H**), 1.19 (6H, d, *J* 6.4, **1**-**H**).

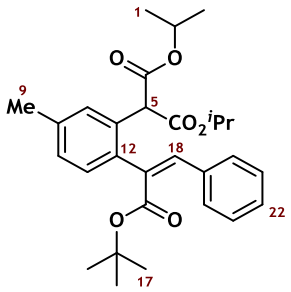
^{13}C (126 MHz, $CDCl_3$): δ 168.3 (**C4**), 167.7 (**C13**), 159.9 ($\mathbf{C}_{Ar}$**21**), 139.6 ($\mathbf{C}_{Ar}$**11**), 135.9 (**C17**), 132.5 (**C12**), 132.0 ($\mathbf{C}_{Ar}$**6**), 130.3 ($\mathbf{C}_{Ar}$**19**), 129.5 ($\mathbf{C}_{Ar}$**7**), 129.4 ($\mathbf{C}_{Ar}$**10**), 128.1 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**9**), 127.8 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**9**), 113.8 ($\mathbf{C}_{Ar}$**20**), 81.9 (**C15**), 69.3 (**C2**), 55.4 (**C23**), 54.9 (**C5**), 28.0 (**C16**), 21.7 (**C1**), 21.7 (**C1**).[†]

IR: v_{max} (neat)/ cm^{-1} 2981 (C–H), 1728 (C=O), 1607 (C=C), 1512, 1255, 1150, 1102 (C–O).

HRMS (ESI): $C_{29}H_{36}O_7Na$ $[M+Na]^+$ requires 519.2353; found 519.2340

[†] ***C***$_{Ar}$***18*** *was not observed and assumed coincident with* ***C***$_{Ar}$***8*** *and* ***C***$_{Ar}$***9***

(*Z*)-Diisopropyl 2-(2-(3-(*tert*-butoxy)-3-oxo-1-phenylprop-1-en-2-yl)-5-methylphenyl) malonate (338)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **332** (1.89 g, 3.83 mmol) and anhydrous NMP (16 mL). Under a flow of argon $Pd(PPh_3)_4$ (589 mg, 0.510 mmol) was added carefully and the resulting suspension was degassed with argon for 30 minutes. Meanwhile, in a separate dried schlenk flask iodoarene **98** (1.03 g, 2.55 mmol) was dissolved in anhydrous NMP (3.5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **98** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (729 mg, 3.83 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 125 mL) and ethyl acetate (500 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 125 mL) and brine (3 × 125 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) to afford cyclization precursor **338** (680 mg, 55%) as a colourless oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.45 – 7.40 (2H, m, **20**-**H**), 7.40 – 7.30 (4H, m, **7**-**H**, **21**-**H**, **22**-**H**), 7.29 – 7.25 (1H, m, **11**-**H**), 7.14 (1H, dd, *J* 7.8, 1.0, **10**-**H**), 6.56 (1H, s, **18**-**H**), 5.11 (1H, s, **5**-**H**),

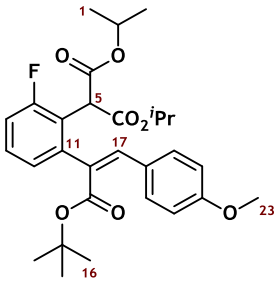
5.07 (2H, sept, *J* 6.4, **2**-**H**), 2.38 (3H, s, **9**-**H**), 1.36 (9H, s, **17**-**H**), 1.27 (6H, d, *J* 6.4, **1**-**H**), 1.19 (6H, d, *J* 6.4, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 168.4 (**C4**), 167.7 (**C14**), 138.0 ($\mathbf{C}_{Ar}$**8**), 136.3 ($\mathbf{C}_{Ar}$**12**), 135.9 (**C18**), 135.8 ($\mathbf{C}_{Ar}$**19**), 134.8 (**C13**), 131.7 ($\mathbf{C}_{Ar}$**6**), 130.1 ($\mathbf{C}_{Ar}$**7**), 129.1 ($\mathbf{C}_{Ar}$**11**), 128.8 ($\mathbf{C}_{Ar}$**10**), 128.5 ($\mathbf{C}_{Ar}$**20**), 128.3 ($\mathbf{C}_{Ar}$**21**), 128.3 ($\mathbf{C}_{Ar}$**22**), 82.0 (**C16**), 69.3 (**C2**), 54.8 (**C5**), 27.9 (**C17**), 21.7 (**C1**), 21.7 (**C1**), 21.5 (**C9**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1726 (C=O), 1370, 1231, 1150, 1100 (C–O), 984, 697.

HRMS (ESI): $C_{29}H_{36}O_6Na$ $[M+Na]^+$ requires 503.2404; found 503.2399

(*Z*)-Diisopropyl 2-(2-(3-(*tert*-butoxy)-1-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl)-6-fluorophenyl)malonate (339)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **325** (763 mg, 1.46 mmol) and anhydrous NMP (9 mL). Under a flow of argon $Pd_2(dba)_3$ (133 mg, 0.145 mmol) and tri(2-furyl)phosphine **176** (135 mg, 0.580 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **99** (591 mg, 1.45 mmol) was dissolved in anhydrous NMP (2 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **99** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of

argon flame dried CuI (278 mg, 1.46 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 75 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 75 mL) and brine (3 × 75 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1 to 20 : 1) to afford cyclization precursor **339** (503 mg, 67%) as a colourless oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.39 (2H, d, *J* 8.6, **19**-**H**), 7.31 (1H, app. td, *J* 8.0, $J_{F\text{-}H}$ 5.5, **9**-**H**), 7.16 (1H, dd, *J* 7.7, 1.1, **10**-**H**), 7.09 (1H, ddd, $J_{F\text{-}H}$ 10.0, *J* 8.5, 1.1, **8**-**H**), 6.88 (2H, d, *J* 8.8, **20**-**H**), 6.44 (1H, s, **17**-**H**), 5.15 – 5.04 (2H, m, **2**-**H**), 5.06 (1H, s, **5**-**H**), 3.84 (3H, s, **23**-**H**), 1.40 (9H, s, **16**-**H**), 1.26 (6H, d, *J* 6.4, **1**-**H**), 1.19 (6H, d, *J* 6.4, **1**-**H**).

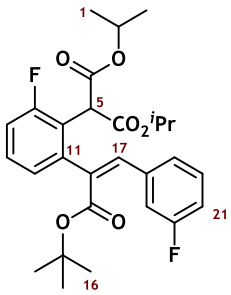
^{13}C (126 MHz, $CDCl_3$): δ 167.5 (**C4**), 167.3 (**C13**), 161.8 (d, $J_{F\text{-}C}$ 250, $\mathbf{C}_{Ar}$**7**), 160.1 ($\mathbf{C}_{Ar}$**21**), 141.6 (d, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**11**), 136.4 (**C17**), 131.5 (d, $J_{F\text{-}C}$ 2, **C12**), 130.4 ($\mathbf{C}_{Ar}$**19**), 129.2 (d, $J_{F\text{-}C}$ 10, $\mathbf{C}_{Ar}$**9**), 127.7 ($\mathbf{C}_{Ar}$**18**), 124.8 (d, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**10**), 121.7 (d, $J_{F\text{-}C}$ 14, $\mathbf{C}_{Ar}$**6**), 115.5 (d, $J_{F\text{-}C}$ 23, $\mathbf{C}_{Ar}$**8**), 113.8 ($\mathbf{C}_{Ar}$**20**), 82.2 (**C15**), 69.5 (**C2**), 55.5 (**C23**), 52.5 (**C5**), 28.0 (**C16**), 21.7 (**C1**), 21.7 (**C1**).

^{19}F (377 MHz, $CDCl_3$): δ −109.8

IR: v_{max} (neat)/ cm^{-1} 2981 (C–H), 1719 (C=O), 1606 (C=C), 1512, 1253, 1148, 1102 (C–O).

HRMS (ESI): $C_{29}H_{35}FO_7Na$ $[M+Na]^+$ requires 537.2259; found 537.2250

(*Z*)-Diisopropyl 2-(2-(3-(*tert*-butoxy)-1-(3-fluorophenyl)-3-oxoprop-1-en-2-yl)-6-fluorophenyl) malonate (340)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **335** (1.29 g, 2.52 mmol) and anhydrous NMP (10 mL). Under a flow of argon $Pd(PPh_3)_4$ (388 mg, 0.336 mmol) was added carefully and the resulting suspension was degassed with argon for 30 minutes. Meanwhile, in a separate dried schlenk flask iodoarene **99** (684 mg, 1.68 mmol) was dissolved in anhydrous NMP (2.5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **99** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (480 mg, 2.52 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (400 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) to afford cyclization precursor **340** (413 mg, 49%) as a colourless oil

^{1}H (400 MHz, $CDCl_3$): δ 7.37 – 7.29 (2H, m, **9**-**H**, **20**-**H**), 7.19 – 7.13 (3H, m, **10**-**H**, **19**-**H**, **23**-**H**), 7.13 – 7.08 (1H, m, **8**-**H**), 7.06 – 7.00 (1H, m, **21**-**H**), 6.49 (1H, s, **17**-**H**), 5.10 (2H, sept, *J* 6.2, **2**-**H**), 5.03 (1H, s, **5**-**H**), 1.37 (9H, s, **16**-**H**), 1.26 (6H, d, *J* 6.4, **1**-**H**), 1.21 (6H, d, *J* 6.1, **1**-**H**).

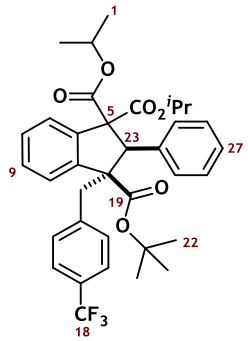
^{13}C (126 MHz, $CDCl_3$): δ 167.3 (**C4**), 166.6 (**C13**), 162.8 (d, $J_{F\text{-}C}$ 246, C_{Ar}**22**), 161.8 (d, $J_{F\text{-}C}$ 250, C_{Ar}**7**), 140.6 (d, $J_{F\text{-}C}$ 4, C_{Ar}**11**), 137.4 (d, $J_{F\text{-}C}$ 8, C_{Ar}**18**), 135.1 (d, $J_{F\text{-}C}$ 2, **C12**), 135.0 (d, $J_{F\text{-}C}$ 2, **C17**), 130.0 (d, $J_{F\text{-}C}$ 9, C_{Ar}**20**), 129.4 (d, $J_{F\text{-}C}$ 10, C_{Ar}**9**), 124.7 (d, $J_{F\text{-}C}$ 3, C_{Ar}**10**), 124.5 (d, $J_{F\text{-}C}$ 3, C_{Ar}**19**), 121.6 (d, $J_{F\text{-}C}$ 14, C_{Ar}**6**), 115.9 (d, $J_{F\text{-}C}$ 23, C_{Ar}**8**), 115.5 (d, $J_{F\text{-}C}$ 21, C_{Ar}**21**), 115.2 (d, $J_{F\text{-}C}$ 23, C_{Ar}**23**), 82.8 (**C15**), 69.6 (**C2**), 52.5 (**C5**), 27.9 (**C16**), 21.7 (**C1**), 21.7 (**C1**).

^{19}F (377 MHz, $CDCl_3$): δ −109.4, −113.3

IR: v_{max} (neat)/ cm^{-1} 2982 (C–H), 1725 (C=O), 1612 (C=C), 1458, 1371, 1234, 1147, 1102 (C–O), 967.

HRMS (ESI): $C_{28}H_{32}F_2O_6Na$ $[M+Na]^+$ requires 525.2059; found 525.2070

3-(*tert*-Butyl) 1,1-diisopropyl 2-phenyl-3-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (341)



Racemic: Prepared according to ***general procedure 2*** using cyclization precursor **337** (500 mg, 1.07 mmol) and 4-(trifluoromethyl)benzyl bromide (512 mg, 2.14 mmol & 2.05 g, 8.56 mmol).

The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1) to afford indane **341** (574 mg, 86%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 5*** using cyclization precursor **337** (180 mg, 0.386 mmol) and 4-(trifluoromethyl)benzyl bromide (185 mg, 0.772 mmol & 738 mg, 3.09 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1) to afford indane **341** (203 mg, 84%, 90% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.77 (1H, d, *J* 7.9, **7**-**H**), 7.41 (2H, d, *J* 7.9, **16**-**H**), 7.41 – 7.36 (1H, m, **8**-**H**), 7.17 (1H, app. td, *J* 7.6, 1.3, **9**-**H**), 7.13 – 7.05 (3H, m, **26**-**H**, **27**-**H**), 6.98 (2H, br. s, **25**-**H**), 6.90 (2H, d, *J* 7.9, **15**-**H**), 6.61 (1H, d, *J* 7.6, **10**-**H**), 5.07 (1H, sept, *J* 6.3, **2**-**H**), 4.69 (1H, s, **23**-**H**), 4.45 (1H, sept, *J* 6.3, **2**-**H**), 3.84 (1H, d, *J* 13.2, **13**-**H**), 3.14 (1H, d, *J* 13.2, **13**-**H**), 1.31 (3H, d, *J* 6.0, **1**-**H**), 1.22 (3H, d, *J* 6.3, **1**-**H**), 1.06 (3H, d, *J* 6.3, **1**-**H**), 0.95 (9H, s, **22**-**H**), 0.58 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 170.7 (**C19**), 169.7 (**C4**), 167.8 (**C4**), 143.4 ($\mathbf{C}_{Ar}$**11**), 141.2 ($\mathbf{C}_{Ar}$**14**), 139.0 ($\mathbf{C}_{Ar}$**24**), 138.5 ($\mathbf{C}_{Ar}$**6**), 131.4 ($\mathbf{C}_{Ar}$**15**), 130.1 ($\mathbf{C}_{Ar}$**25**), 129.1 (q, $J_{F\text{-}C}$ 32, $\mathbf{C}_{Ar}$**17**), 129.1 ($\mathbf{C}_{Ar}$**7**), 128.6 ($\mathbf{C}_{Ar}$**10**), 127.8 ($\mathbf{C}_{Ar}$**26**), 127.7 ($\mathbf{C}_{Ar}$**27**), 127.7 ($\mathbf{C}_{Ar}$**8**), 127.3 ($\mathbf{C}_{Ar}$**9**), 124.5 (q, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**16**), 124.5 (q, $J_{F\text{-}C}$ 273, **C18**), 81.7 (**C21**), 70.4 (**C5**), 70.1 (**C2**), 69.4 (**C2**), 66.1 (**C12**), 61.2 (**C23**), 47.3 (**C13**), 27.4 (**C22**), 21.6 (**C1**), 21.6 (**C1**), 21.5 (**C1**), 20.7 (**C1**).

^{19}F (377 MHz, $CDCl_3$): δ −62.3

IR: v_{max} (neat)/ cm^{-1} 2981 (C–H), 1731 (C=O), 1456, 1245, 1155, 1111 (C–O), 846.

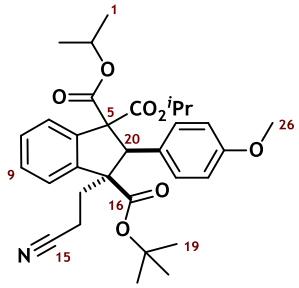
HRMS (ESI): $C_{36}H_{39}F_3O_6Na$ $[M+Na]^+$ requires 647.2591; found 647.2568

MP: 150 – 152 °C.

Chiral HPLC: Chiralpak IC (1.5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 206 nm), t_R(**minor**) 4.3 min and t_R(**major**) 4.7 min, 90% ee.

$[\alpha]_D^{20}$ −1.0 (*c* 0.50, chloroform)

3-(*tert*-Butyl) 1,1-diisopropyl 3-(2-cyanoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (330)



Racemic: Prepared according to ***general procedure 3*** using cyclization precursor **328** (84 mg, 0.169 mmol) and acrylonitrile (111 μL, 1.69 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1) to afford indane **330** (40 mg, 43%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 7*** using cyclization precursor **328** (85 mg, 0.171 mmol) and acrylonitrile (112 μL, 1.71 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1) to afford indane **330** (72 mg, 77%, 92% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.77 – 7.71 (1H, m, **7**-**H**), 7.53 – 7.48 (1H, m, **10**-**H**), 7.46 – 7.40 (2H, m, **8**-**H**, **9**-**H**), 6.83 (2H, br. s, **22**-**H**), 6.61 (2H, d, *J* 8.8, **23**-**H**), 5.01 (1H, sept, *J* 6.3, **2**-**H**), 4.53 – 4.43 (2H, m, **2**-**H**, **20**-**H**), 3.67 (3H, s, **26**-**H**), 2.63 – 2.55 (1H, m, **13**-**H**), 2.54 – 2.46 (1H, m, **14**-**H**), 2.41 – 2.33 (1H, m, **14**-**H**), 2.22 – 2.14 (1H, m, **13**-**H**), 1.28 (3H, d, *J* 6.3, **1**-**H**), 1.19 (3H, d, *J* 6.3, **1**-**H**), 1.06 (3H, d, *J* 6.3, **1**-**H**), 1.05 (9H, s, **19**-**H**), 0.64 (3H, d, *J* 6.0, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 170.4 (**C16**), 169.2 (**C4**), 167.6 (**C4**), 159.4 (C_{Ar}**24**), 143.6 (C_{Ar}**11**), 138.4 (C_{Ar}**6**), 130.9 (C_{Ar}**21** & C_{Ar}**22**), 129.7 (C_{Ar}**7**), 128.7 (C_{Ar}**9**), 128.3 (C_{Ar}**8**), 126.7 (C_{Ar}**10**), 119.5 (**C15**), 113.2 (C_{Ar}**23**), 81.8 (**C18**), 70.3 (**C2**), 70.2 (**C5**), 69.5 (**C2**), 63.8 (**C12**), 58.8 (**C20**), 55.4 (**C26**), 37.3 (**C13**), 27.4 (**C19**), 21.6 (2 × **C1**), 21.5 (**C1**), 20.9 (**C1**), 13.7 (**C14**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 2250 (C≡N), 1729 (C=O), 1513, 1245, 1182, 1156, 1107 (C–O), 851, 732.

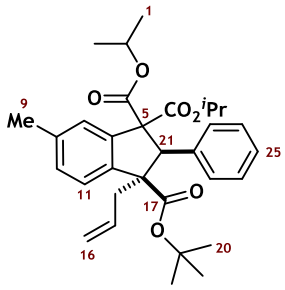
HRMS (ESI): $C_{32}H_{39}NO_7Na$ $[M+Na]^+$ requires 572.2619; found 572.2615

MP: 94 – 96 °C.

Chiral HPLC: Chiralpak AD-H (20% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 208 nm), t_R(**minor**) 4.0 min and t_R(**major**) 4.4 min, 92% ee.

$[\alpha]_D^{20}$ +19.4 (*c* 0.50, chloroform).

3-(*tert*-Butyl) 1,1-diisopropyl 3-allyl-6-methyl-2-phenyl-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (342)



Racemic: Prepared according to ***general procedure 2*** using cyclization precursor **338** (132 mg, 0.275 mmol) and allyl bromide (48 μL, 0.550 mmol & 190 μL, 2.20 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1) to afford indane **342** (110 mg, 77%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 5*** using cyclization precursor **338** (158 mg, 0.329 mmol), allyl bromide (57 μL, 0.658 mmol & 228 μL, 2.63 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1) to afford indane **342** (129 mg, 75%, 91% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.52 (1H, s, **7**-**H**), 7.44 (1H, d, *J* 7.9, **11**-**H**), 7.19 (1H, dd, *J* 7.9, 0.9, **10**-**H**), 7.11 – 7.03 (3H, m, **24**-**H**, **25**-**H**), 6.97 (2H, br. d, *J* 6.6, **23**-**H**), 5.78 (1H, ddt, *J* 17.2, 9.9, 7.4, **15**-**H**), 5.06 (1H, dd, *J* 10.2, 2.0, **16**-**H**), 5.03 – 4.93 (1H, m, **2**-**H**, **16**-**H**), 4.51 (1H, s, **21**-**H**), 4.44 (1H, sept, *J* 6.3, **2**-**H**), 3.04 (1H, dd, *J* 13.7, 7.7, **14**-**H**), 2.52 (1H, dd, *J* 13.6, 6.9, **14**-**H**), 2.43 (3H, s, **9**-**H**), 1.28 (3H, d, *J* 6.0, **1**-**H**), 1.19 (3H, d, *J* 6.3, **1**-**H**), 1.04 (3H, d, *J* 6.3, **1**-**H**), 0.97 (9H, s, **20**-**H**), 0.57 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.1 (**C17**), 169.5 (**C4**), 168.0 (**C4**), 142.0 ($\mathbf{C}_{Ar}$**12**), 139.7 ($\mathbf{C}_{Ar}$**22**), 138.2 ($\mathbf{C}_{Ar}$**6**), 137.2 ($\mathbf{C}_{Ar}$**8**), 133.6 (**C15**), 129.9 (br., $\mathbf{C}_{Ar}$**23**), 129.5 ($\mathbf{C}_{Ar}$**7**), 129.0 ($\mathbf{C}_{Ar}$**10**), 127.7 ($\mathbf{C}_{Ar}$**24**), 127.4 ($\mathbf{C}_{Ar}$**25**), 127.3 ($\mathbf{C}_{Ar}$**11**), 118.8 (**C16**), 80.6 (**C19**), 70.2 (**C5**), 69.8 (**C2**), 69.2 (**C2**), 64.2 (**C13**), 60.7 (**C21**), 47.1 (**C14**), 27.4 (**C20**), 21.7 (**C1**), 21.6 (**C1** & **C9**), 21.5 (**C1**), 20.7 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2980 (C–H), 1731 (C=O), 1640 (C=C), 1455, 1243, 1164, 1108 (C–O), 913, 733, 700.

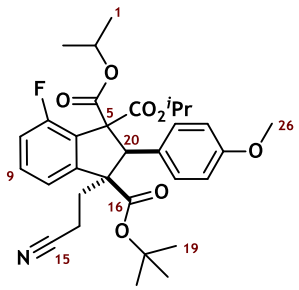
HRMS (ESI): $C_{32}H_{40}O_6Na$ $[M+Na]^+$ requires 543.2717; found 543.2700

MP: 104 – 106 °C.

Chiral HPLC: Chiralpak AD-H (1.0% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 214 nm), t_R(**major**) 8.2 min and t_R(**minor**) 9.6 min, 91% ee.

$[\alpha]_D^{20}$ +11.4 (*c* 0.50, chloroform).

3-(*tert*-Butyl) 1,1-diisopropyl 3-(2-cyanoethyl)-7-fluoro-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (343)



Racemic: Prepared according to ***general procedure 3*** using cyclization precursor **339** (85 mg, 0.165 mmol) and acrylonitrile (109 μL, 1.65 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 10 : 1) to afford indane **343** (5 mg, 5%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 7*** using cyclization precursor **339** (84 mg, 0.163 mmol) and acrylonitrile (107 μL, 1.63 mmol). The cyclization required 48 hours to reach completion by TLC. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 10 : 1) to afford indane **343** (58 mg, 62%, 89% ee, >20 : 1 dr) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.48 – 7.37 (2H, m, **9**-**H**, **10**-**H**), 7.13 (1H, app. t, *J* 8.6, **8**-**H**), 6.87 (2H, br. d, *J* 8.1, **22**-**H**), 6.63 (2H, d, *J* 8.6, **23**-**H**), 5.04 (1H, sept, *J* 6.2, **2**-**H**), 4.54 (1H, s, **20**-**H**), 4.57 – 4.43 (1H, m, **2**-**H**), 3.68 (3H, s, **26**-**H**), 2.59 – 2.41 (2H, m, **13**-**H**, **14**-**H**), 2.41 – 2.30 (1H, m, **14**-**H**), 2.03 (1H, td, *J* 12.1, 3.7, **13**-**H**), 1.29 (3H, d, *J* 6.4, **1**-**H**), 1.21 (3H, d, *J* 6.4, **1**-**H**), 1.04 (9H, s, **19**-**H**), 0.97 (3H, d, *J* 6.4, **1**-**H**), 0.76 (3H, d, *J* 6.1, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 169.9 (**C16**), 169.0 (d, $J_{F\text{-}C}$ 2, **C4**), 165.6 (**C4**), 160.8 (d, $J_{F\text{-}C}$ 257, $\mathbf{C}_{Ar}$**7**), 159.5 ($\mathbf{C}_{Ar}$**24**), 146.6 (d, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**11**), 131.0 (br., $\mathbf{C}_{Ar}$**22**), 130.8 (d, $J_{F\text{-}C}$ 8, $\mathbf{C}_{Ar}$**9**), 129.9 ($\mathbf{C}_{Ar}$**21**), 125.4

(d, $J_{F\text{-}C}$ 14, C_{Ar}**6**), 122.4 (d, $J_{F\text{-}C}$ 4, C_{Ar}**10**), 119.1 (**C15**), 116.6 (d, $J_{F\text{-}C}$ 22, C_{Ar}**8**), 113.1 (C_{Ar}**23**), 82.1 (**C18**), 70.6 (**C2**), 69.8 (**C2**), 69.4 (d, $J_{F\text{-}C}$ 4, **C5**), 63.7 (**C12**), 59.9 (**C20**), 55.4 (**C26**), 37.3 (**C13**), 27.4 (**C19**), 21.5 (**C1**), 21.4 (**C1**), 21.3 (**C1**), 21.1 (**C1**), 13.6 (**C14**).

^{19}F (377 MHz, $CDCl_3$): δ −106.5

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 2250 (C≡N), 1728 (C=O), 1514, 1250, 1181, 1156, 1105 (C–O), 1039, 850.

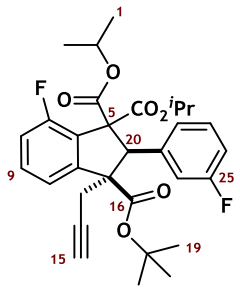
HRMS (ESI): $C_{32}H_{38}FNO_7Na$ $[M+Na]^+$ requires 590.2525; found 590.2517

MP: 148 – 150 °C (pentane/ethyl acetate).

Chiral HPLC: Chiralpak IA (20% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 238 nm), t_R(**minor**) 4.4 min and t_R(**major**) 5.5 min, 89% ee.

$[\alpha]_D^{20}$ +47.2 (*c* 0.50, chloroform).

3-(*tert*-Butyl) 1,1-diisopropyl 7-fluoro-2-(3-fluorophenyl)-3-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (344)



Racemic: Prepared according to ***general procedure 2*** using cyclization precursor **340** (18 mg, 0.036 mmol) and propargyl bromide (80 wt.% in toluene, 8 μL, 0.072 mmol & 32 μL, 0.288 mmol). The crude product was purified by silica gel chromatography

(40-60 petrol : ethyl acetate, 40 : 1) to afford indane **344** (9 mg, 47%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 5*** using cyclization precursor **340** (67 mg, 0.133 mmol) and propargyl bromide (80 wt.% in toluene, 30 μL, 0.266 mmol & 119 μL, 1.06 mmol). The reaction solvent was toluene : chloroform (9 : 1, 1.0 mL). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 40 : 1) to afford indane **344** (45 mg, 63%, 76% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.67 (1H, d, *J* 7.9, **10**-**H**), 7.44 (1H, app. td, *J* 8.0, $J_{F\text{-}H}$ 4.9, **9**-**H**), 7.12 (1H, app. t, *J* 9.1, **8**-**H**), 7.06 (1H, app. td, *J* 8.0, $J_{F\text{-}H}$ 6.3, **23**-**H**), 6.86 (1H, app. td, *J* 8.0, 1.6, **24**-**H**), 6.79 – 6.74 (2H, m, **22**-**H**, **26**-**H**), 5.01 (1H, sept, *J* 6.2, **2**-**H**), 4.57 – 4.47 (2H, m, **2**-**H**, **20**-**H**), 3.18 (1H, dd, *J* 16.4, 2.5, **13**-**H**), 2.60 (1H, dd, *J* 16.7, 2.5, **13**-**H**), 2.09 (1H, t, *J* 2.5, **15**-**H**), 1.29 (3H, d, *J* 6.3, **1**-**H**), 1.19 (3H, d, *J* 6.3, **1**-**H**), 1.07 (9H, s, **19**-**H**), 0.98 (3H, d, *J* 6.3, **1**-**H**), 0.75 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 169.3 (**C16**), 169.1 (d, $J_{F\text{-}C}$ 2, **C4**), 165.6 (**C4**), 162.0 (d, $J_{F\text{-}C}$ 245, $\mathbf{C}_{Ar}$**25**), 160.1 (d, $J_{F\text{-}C}$ 255, $\mathbf{C}_{Ar}$**7**), 146.6 (d, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**11**), 140.4 (d, $J_{F\text{-}C}$ 7, $\mathbf{C}_{Ar}$**21**), 130.7 (d, $J_{F\text{-}C}$ 8, $\mathbf{C}_{Ar}$**9**), 129.2 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**23**), 125.7 (d, $J_{F\text{-}C}$ 2, $\mathbf{C}_{Ar}$**22**), 124.9 (d, $J_{F\text{-}C}$ 13, $\mathbf{C}_{Ar}$**6**), 123.6 (d, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**10**), 117.5 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**26**), 116.4 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**8**), 114.7 (d, $J_{F\text{-}C}$ 20, $\mathbf{C}_{Ar}$**24**), 81.6 (**C18**), 80.1 (**C14**), 72.0 (**C15**), 70.6 (**C2**), 69.8 (**C2**), 69.5 (d, $J_{F\text{-}C}$ 3, **C5**), 63.4 (**C12**), 60.6 (**C20**), 32.5 (**C13**), 27.3 (**C19**), 21.5 (**C1**), 21.4 (**C1**), 21.3 (**C1**), 20.9 (**C1**).

^{19}F (377 MHz, $CDCl_3$): δ −108.1, −114.2

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 2261 (C≡C), 1728 (C=O), 1590, 1475, 1256, 1156, 1105 (C–O), 907, 734, 701.

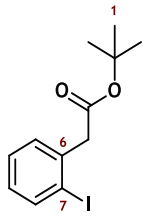
HRMS (ESI): $C_{31}H_{34}F_2O_6Na$ $[M+Na]^+$ requires 563.2216; found 563.2219

MP: 132 – 134 °C (pentane/diethyl ether).

Chiral HPLC: Chiralpak AD-H (1.5% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 210 nm), t_R(**minor**) 9.0 min and t_R(**major**) 15.4 min, 76% ee.

$[\alpha]_D^{20}$ −1.4 (*c* 0.50, chloroform).

tert-Butyl 2-(2-iodophenyl)acetate (321)



According to a literature procedure,[177] di-*tert*-butyl dicarbonate (3.43 g, 15.7 mmol) was added to a stirred solution of (2-iodophenyl)acetic acid **76** (2.06 g, 7.86 mmol) and DMAP (288 mg, 2.36 mmol) in *tert*-butanol (25 mL). The reaction mixture was heated to 30 °C for 2 hours and subsequently concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5) to afford ester **321** (1.88 g, 75%) as a colourless oil.

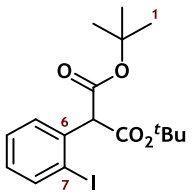
^{1}H (400 MHz, $CDCl_3$): δ 7.85 (1H, dd, *J* 7.7, 0.9, **8**-**H**), 7.35 – 7.26 (2H, m, **10**-**H**, **11**-**H**), 6.96 (1H, app. td, *J* 7.5, 2.0, **9**-**H**), 3.71 (2H, s, **5**-**H**), 1.48 (9H, s, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 169.9 (**C4**), 139.6 ($\mathbf{C}_{Ar}$**8**), 138.6 ($\mathbf{C}_{Ar}$**6**), 130.8 ($\mathbf{C}_{Ar}$**9**), 128.8 ($\mathbf{C}_{Ar}$**10**), 128.5 ($\mathbf{C}_{Ar}$**11**), 101.2 ($\mathbf{C}_{Ar}$**7**), 81.4 (**C2**), 47.6 (**C5**), 28.2 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2977 (C–H), 1730 (C=O), 1368, 1225, 1145, 746.

HRMS (ESI): $C_{12}H_{15}O_2INa$ $[M+Na]^+$ requires 341.0009; found 341.9995

Di-*tert*-butyl 2-(2-iodophenyl)malonate (322)



A solution of lithium bis(trimethylsilyl)amide (1.0 M in toluene, 10.5 mL, 10.5 mmol) was added to a stirred solution of *tert*-butyl ester **321** (1.33 g, 4.18 mmol) in tetrahydrofuran (5 mL) at −78 °C. The reaction was stirred at this temperature for 1 hour then a solution of di-*tert*-butyl dicarbonate (1.00 g, 4.60 mmol) in tetrahydrofuran (4 mL) was added dropwise. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (25 mL). The biphasic mixture was extracted with dichloromethane (3 × 25 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by recrystallization (hexane) to afford malonate **322** (999 mg, 57%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.87 (1H, dd, *J* 8.1, 1.2, **8**-**H**), 7.47 (1H, dd, *J* 7.9, 1.6, **11**-**H**), 7.37 (1H, app. td, *J* 7.5, 1.2, **10**-**H**), 7.02 (1H, app. td, *J* 7.7, 1.7, **9**-**H**), 4.93 (1H, s, **5**-**H**), 1.49 (18H, s, **1**-**H**).

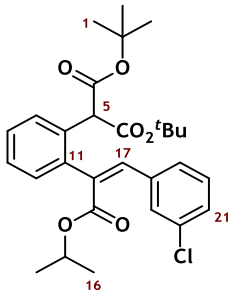
^{13}C (101 MHz, $CDCl_3$): δ 167.1 (**C4**), 139.6 ($\mathbf{C}_{Ar}$**8**), 137.4 ($\mathbf{C}_{Ar}$**6**), 129.6 ($\mathbf{C}_{Ar}$**9**/$\mathbf{C}_{Ar}$**11**), 129.5 ($\mathbf{C}_{Ar}$**9**/$\mathbf{C}_{Ar}$**11**), 128.5 ($\mathbf{C}_{Ar}$**10**), 102.1 ($\mathbf{C}_{Ar}$**7**), 82.5 (**C2**), 64.3 (**C5**), 28.0 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2978 (C–H), 1729 (C=O), 1469, 1369, 1134, 752.

HRMS (ESI): $C_{17}H_{23}O_4INa$ $[M+Na]^+$ requires 441.0533; found 441.0526

MP: 48 – 50 °C (hexane).

(*Z*)-Di-*tert*-butyl 2-(2-(1-(3-chlorophenyl)-3-isopropoxy-3-oxoprop-1-en-2-yl)phenyl) malonate (327)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **153** (1.06 g, 2.06 mmol) and anhydrous NMP (8 mL). Under a flow of argon $Pd(PPh_3)_4$ (317 mg, 0.274 mmol) was added carefully. The resulting suspension was degassed with argon for 30 minutes and in a separate dried schlenk flask iodoarene **322** (573 mg, 1.37 mmol) was dissolved in anhydrous NMP (2 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **322** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (392 mg, 2.06 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 50 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 50 mL) and brine (3 × 50 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified twice by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 40 : 1) followed by (silica gel : potassium carbonate, 9 : 1; toluene) to afford cyclization precursor **327** (464 mg, 66%) as a light yellow oil.

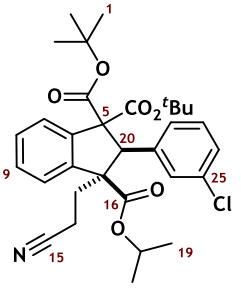
^{1}H (400 MHz, $CDCl_3$): δ 7.61 (1H, dd, *J* 7.8, 0.7, **7-H**), 7.44 – 7.25 (7H, m, **Ar-H**), 6.60 (1H, s, **17-H**), 5.06 (1H, sept, *J* 6.2, **15-H**), 4.96 (1H, s, **5-H**), 1.46 (18H, s, **1-H**), 1.15 (6H, d, *J* 6.1, **16-H**).

^{13}C (126 MHz, $CDCl_3$): δ 167.8 (**C4**), 167.5 (**C13**), 138.4 (C_{Ar}**11**), 137.3 (C_{Ar}**18**), 135.4 (C_{Ar}**22**), 135.2 (**C17**), 134.3 (**C12**), 132.4 (C_{Ar}**6**), 129.7 (C_{Ar}**20**), 129.6 (C_{Ar}**7**), 129.3 (C_{Ar}**10**), 128.4 (C_{Ar}**8**), 128.4 (C_{Ar}**21**), 128.4 (C_{Ar}**23**), 127.8 (C_{Ar}**9**), 126.8 (C_{Ar}**19**), 82.0 (**C2**), 69.3 (**C15**), 56.5 (**C5**), 28.0 (**C1**), 21.5 (**C16**).

IR: ν_{max} (neat)/ cm^{-1} 2980 (C–H), 1720 (C=O), 1368, 1214, 1105 (C–O), 755.

HRMS (ESI): $C_{29}H_{35}{}^{35}ClO_6Na$ $[M+Na]^+$ requires 537.2014; found 537.2009

1,1-Di-*tert*-butyl 3-isopropyl 2-(3-chlorophenyl)-3-(2-cyanoethyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (329)



Racemic: Prepared according to ***general procedure 3*** using cyclization precursor **327** (80 mg, 0.155 mmol) and acrylonitrile (102 μL, 1.55 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1) to afford indane **329** (52 mg, 59%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 6*** using cyclization precursor **327** (80 mg, 0.155 mmol) and acrylonitrile (102 μL, 1.55 mmol). The reaction was performed at room temperature. The crude product was purified by silica gel chromatography

(40-60 petrol : ethyl acetate, 20 : 1) to afford indane **329** (62 mg, 70%, 42% ee, >20 : 1 dr) as a white solid.

^{1}H (500 MHz, $CDCl_3$): δ 7.76 – 7.70 (1H, m, **7**-**H**), 7.54 – 7.49 (1H, m, **10**-**H**), 7.48 – 7.41 (2H, m, **8**-**H**, **9**-**H**), 7.14 – 7.05 (2H, m, **24**-**H**, **26**-**H**), 6.97 (1H, app. t, *J* 7.9, **23**-**H**), 6.66 (1H, br. d, *J* 4.4, **22**-**H**), 5.57 (1H, sept, *J* 6.3, **18**-**H**), 4.44 (1H, s, **20**-**H**), 2.63 – 2.55 (1H, m, **13**-**H**), 2.54 – 2.46 (1H, m, **14**-**H**), 2.42 – 2.33 (1H, m, **14**-**H**), 2.18 (1H, ddd, *J* 13.4, 11.0, 4.6, **13**-**H**), 1.45 (9H, s, **1**-**H**), 1.08 (3H, d, *J* 6.3, **19**-**H**), 1.03 (9H, s, **1**-**H**), 0.69 (3H, d, *J* 6.3, **19**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 170.8 (**C16**), 168.4 (**C4**), 166.6 (**C4**), 143.2 ($\mathbf{C}_{Ar}$**11**), 141.1 ($\mathbf{C}_{Ar}$**21**), 138.5 ($\mathbf{C}_{Ar}$**6**), 133.5 ($\mathbf{C}_{Ar}$**25**), 130.9 (br., $\mathbf{C}_{Ar}$**26**), 129.6 ($\mathbf{C}_{Ar}$**7**), 129.4 ($\mathbf{C}_{Ar}$**23**), 128.8 ($\mathbf{C}_{Ar}$**9**), 128.4 ($\mathbf{C}_{Ar}$**8**), 127.8 ($\mathbf{C}_{Ar}$**24**), 126.8 (br., $\mathbf{C}_{Ar}$**22**), 126.6 ($\mathbf{C}_{Ar}$**10**), 119.2 (**C15**), 83.0 (**C2**), 82.2 (**C2**), 71.3 (**C5**), 69.3 (**C18**), 63.2 (**C12**), 59.0 (**C20**), 37.2 (**C13**), 27.8 (**C1**), 27.2 (**C1**), 21.7 (**C19**), 20.7 (**C19**), 13.7 (**C14**).

IR: ν_{max} (neat)/ cm^{-1} 2980 (C–H), 2251 (C≡N), 1729 (C=O), 1477, 1370, 1252, 1142, 1105 (C–O), 734.

HRMS (ESI): $C_{32}H_{38}{}^{35}ClNO_6Na$ $[M+Na]^+$ requires 590.2280; found 590.2272

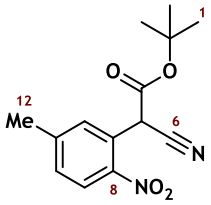
MP: 148 – 150 °C.

Chiral HPLC: Chiralpak AD-H (10% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 205 nm), t_R(**minor**) 3.9 min and t_R(**major**) 4.5 min, 42% ee.

$[\alpha]_D^{20}$ +18.0 (*c* 0.70, chloroform).

5.3.8 *Indanes with Three Contiguous Stereocentres – Substrate Synthesis & Cyclization*

tert-Butyl (±)-2-cyano-2-(5-methyl-2-nitrophenyl)acetate (356)



According to a modified literature procedure,[55] *tert*-butyl cyanoacetate (9.10 g, 64.4 mmol) was added to a stirred suspension of potassium carbonate (13.4 g, 96.6 mmol) and 2-fluoro-4-methyl-1-nitrobenzene **103** (5.00 g, 32.2 mmol) in *N*,*N*-dimethylformamide (92 mL). The resulting mixture was heated to 90 °C for 16 hours and after cooling to room temperature was concentrated *in vacuo*. The residue was treated with aqueous hydrochloric acid (1 M, 150 mL), extracted with dichloromethane (3 × 150 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 19 : 1 to 9 : 1) to afford nitroarene **356** (7.22 g, 81%) as a yellow oil.

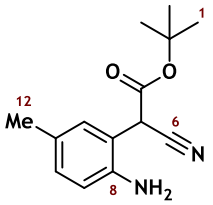
^{1}H (400 MHz, $CDCl_3$): δ 8.14 (1H, d, *J* 8.3, **9**-**H**), 7.55 (1H, s, **13**-**H**), 7.40 (1H, d, *J* 8.6, **10**-**H**), 5.57 (1H, s, **5**-**H**), 2.51 (3H, s, **12**-**H**), 1.50 (9H, s, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 162.5 (**C4**), 146.2 ($\mathbf{C}_{Ar}$**8**), 145.2 ($\mathbf{C}_{Ar}$**11**), 132.1 ($\mathbf{C}_{Ar}$**13**), 130.9 ($\mathbf{C}_{Ar}$**10**), 126.2 ($\mathbf{C}_{Ar}$**9**), 125.7 ($\mathbf{C}_{Ar}$**7**), 115.1 (**C6**), 85.6 (**C2**), 42.5 (**C5**), 27.7 (**C1**), 21.6 (**C12**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 2252 (C≡N), 1742 (C=O), 1593, 1521 (NO_2), 1342 (NO_2), 1280, 1148, 837.

HRMS (ESI): $C_{14}H_{16}N_2O_4Na$ $[M+Na]^+$ requires 299.1002; found 299.1008

tert-Butyl (±)-2-(2-amino-5-methylphenyl)-2-cyanoacetate (357)



According to a modified literature procedure,[55] palladium on activated carbon (300 mg, 10 wt.% palladium) was added to a stirred solution of nitroarene **356** (3.00 g, 10.9 mmol) in methanol (30 mL). The solution was purged with hydrogen gas three times and then left to stir under an atmosphere of hydrogen (balloon pressure) for 48 hours. The mixture was filtered through Celite® with methanol and the solvent was removed *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 19 : 1) to afford aniline **357** as a viscous orange oil (571 mg, 32% brsm).

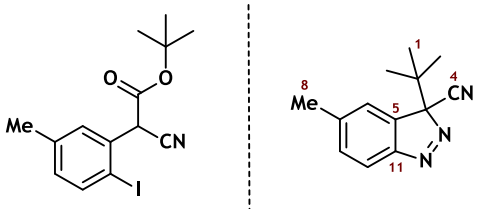
^{1}H (500 MHz, $CDCl_3$): δ 7.18 (1H, d, *J* 1.3, **13**-**H**), 7.00 (1H, dd, *J* 8.0, 1.4, **10**-**H**), 6.69 (1H, d, *J* 8.2, **9**-**H**), 4.78 (1H, s, **5**-**H**), 3.93 (2H, br. s, N**H**$_2$), 2.28 (3H, s, **12**-**H**), 1.48 (9H, s, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 164.6 (**C4**), 141.9 (**C**$_{Ar}$**8**), 130.8 (**C**$_{Ar}$**10**), 129.5 (**C**$_{Ar}$**11**), 129.4 (**C**$_{Ar}$**13**), 118.2 (**C**$_{Ar}$**9**), 116.7 (**C**$_{Ar}$**7**), 115.9 (**C6**), 85.1 (**C2**), 41.5 (**C5**), 27.8 (**C1**), 20.5 (**C12**).

IR: ν_{max} (neat)/ cm^{-1} 3443 (N–H), 3376 (N–H), 2981 (C–H), 2253 (C≡N), 1736 (C=O), 1636, 1510, 1371, 1288, 1258, 1152, 821.

HRMS (ESI): $C_{14}H_{18}N_2O_2Na$ $[M+Na]^+$ requires 269.1260; found 269.1259

Attempted synthesis of *tert*-butyl (±)-2-cyano-2-(2-iodo-5-methylphenyl)acetate (349) and isolation of (±)-3-(*tert*-butyl)-5-methyl-3*H*-indazole-3-carbonitrile (358)



349 358

According to a modified literature procedure,[70] boron trifluoride diethyl etherate (399 μL, 3.23 mmol) was added to a flask under argon and cooled to −15 °C. To this, was added a solution of aniline **357** (529 mg, 2.15 mmol) in dichloromethane (4 mL) dropwise over 5 minutes. Subsequently, a solution of *tert*-butyl nitrite (341 μL, 2.58 mmol) in dichloromethane (2 ml) was added dropwise over 30 minutes. The resulting suspension was stirred at −15 °C for 20 minutes then at 0 °C for 30 minutes. After warming to room temperature the reaction was concentrated *in vacuo* and the crude diazonium salt dissolved in acetonitrile (8 mL) under argon. The resulting solution was added dropwise over 1 hour to a stirred suspension of sodium iodide (387 mg, 2.58 mmol) and iodine (55 mg, 0.215 mmol) in acetonitrile (14 mL) at room temperature. The dark solution was stirred for 1 hour before quenching with saturated aqueous sodium sulfite (25 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 25 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. A crude ^{1}H NMR spectrum and TLC (40-60 petrol : ethyl acetate, 90 : 10) indicated a complex mixture of products. The major product was isolated by silica gel chromatography (40-60 petrol : ethyl acetate, 95 : 5) to afford 3*H*-indazole **358** (121 mg, 26%) as a yellow oil.

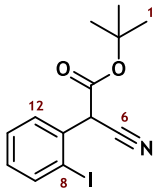
^{1}H (500 MHz, $CDCl_3$): δ 7.73 (1H, d, *J* 8.8, **10**-**H**), 7.49 (1H, s, **6**-**H**), 7.21 (1H, dd, *J* 8.8, 1.3, **9**-**H**), 2.48 (3H, d, *J* 0.9, **8**-**H**), 1.89 (9H, s, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 145.1 ($\mathbf{C}_{Ar}$**11**), 135.7 ($\mathbf{C}_{Ar}$**7**), 129.7 ($\mathbf{C}_{Ar}$**9**), 128.6 ($\mathbf{C}_{Ar}$**5**), 118.8 ($\mathbf{C}_{Ar}$**10**), 116.6 ($\mathbf{C}_{Ar}$**6**), 112.9 (**C4**), 103.4 (**C3**), 64.4 (**C2**), 30.1 (**C1**), 22.0 (**C8**).

IR: ν_{max} (neat)/ cm^{-1} 2986 (C–H), 2216 (C≡N), 1461 (N=N), 1372, 1271, 1187, 802.

HRMS (ESI): $C_{13}H_{15}N_3Na$ $[M+Na]^+$ requires 236.1158; found 236.1161

tert-Butyl (±)-2-cyano-2-(2-iodophenyl)acetate (360)



According to a modified literature procedure,[180] a solution of 2-iodophenylacetonitrile **359** (1.21 g, 5.00 mmol) in THF (15 mL) was added dropwise to a solution of LDA (0.53 M in THF, 23.6 mL, 12.5 mmol) at −78 °C. The reaction was stirred at this temperature for 30 minutes and then at room temperature for an additional 30 minutes. The reaction was cooled to −78 °C and a solution of di-*tert*-butyl dicarbonate (1.14 g, 5.25 mmol) in THF (10 mL) was added dropwise. The reaction was allowed to warm to room temperature overnight and was quenched with saturated aqueous ammonium chloride (75 mL). The biphasic mixture was extracted with diethyl ether (3 × 100 mL) and then the combined organic layers were washed with aqueous HCl (10%, 3 × 50 mL) then brine (100 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 19 : 1) to afford iodoarene **360** (667 mg, 39%) as a colourless oil.

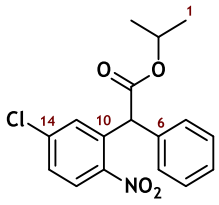
^{1}H (400 MHz, $CDCl_3$): δ 7.89 (1H, dd, *J* 8.0, 1.1, **9**-**H**), 7.60 (1H, dd, *J* 7.7, 1.6, **12**-**H**), 7.44 (1H, app. td, *J* 7.6, 1.3, **11**-**H**), 7.08 (1H, app. td, *J* 7.7, 1.8, **10**-**H**), 5.09 (1H, s, **5**-**H**), 1.49 (9H, s, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 163.0 (**C4**), 140.2 ($\mathbf{C}_{Ar}$**9**), 134.3 ($\mathbf{C}_{Ar}$**7**), 130.7 ($\mathbf{C}_{Ar}$**10**), 129.3 ($\mathbf{C}_{Ar}$**11**), 129.3 ($\mathbf{C}_{Ar}$**12**), 115.8 (**C6**), 99.8 ($\mathbf{C}_{Ar}$**8**), 85.1 (**C2**), 49.1 (**C5**), 27.8 (**C1**).

IR: v_{max} (neat)/ cm^{-1} 2980 (C–H), 2249 (C≡N), 1740 (C=O), 1468, 1370, 1258, 1146, 1014, 752.

HRMS (ESI): $C_{13}H_{14}O_2INNa$ $[M+Na]^+$ requires 365.9961; found 365.9956

(±)-Isopropyl 2-(5-chloro-2-nitrophenyl)-2-phenylacetate (351)[†]



According to a modified literature procedure,[178] isopropyl phenylacetate (2.26 g, 12.7 mmol) in tetrahydrofuran (25 mL) was added to a stirred suspension of potassium *tert*-butoxide (1.42 g, 12.7 mmol) in tetrahydrofuran (100 mL) at −78 °C, and the resulting yellow solution stirred for three minutes. 1-Chloro-4-nitrobenzene **350** (4.00 g, 25.4 mmol) in tetrahydrofuran (25 mL) was added over a period of one minute, and the solution stirred for a further 3 minutes. DDQ (3.45 g, 15.2 mmol) in *N*,*N*-dimethylformamide (25 mL) was added and the solution stirred for a further 5 minutes before saturated aqueous ammonium chloride (50 mL) was added and the reaction mixture allowed to warm to room temperature. The crude mixture was poured into water (1 L) and extracted with ethyl acetate (3 x 250 mL), the combined organic extracts were washed with brine (250 mL), dried over anhydrous

[†] *This compound was prepared by Dr Philip Woods and characterized by Dr Peter Knipe but is included for completeness.*

magnesium sulfate, filtered and concentrated *in vacuo*.[†] The resulting crude product was purified by flash column chromatography (40-60 petrol : ethyl acetate, 50 : 1) and subsequent recrystallization (ethyl acetate/40-60 petrol) to afford nitroarene **351** (2.03 g, 48%) as a white crystalline solid with spectroscopic data in accordance with the literature.[178]

^{1}H (400 MHz, $CDCl_3$): δ 8.02 (1H, d, *J* 8.7, **12**-**H**), 7.46 − 7.35 (4H, m, **Ar**-**H**), 7.28 − 7.24 (2H, m, **Ar**-**H**), 7.05 (1H, d, *J* 2.2, **15**-**H**), 5.63 (1H, s, **5**-**H**), 5.10 (1H, sept, *J* 6.3, **2**-**H**), 1.29 (3H, d, *J* 6.2, **1**-**H**), 1.17 (3H, d, *J* 6.2, **1**-**H**).

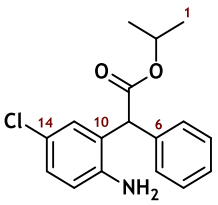
^{13}C (101 MHz, $CDCl_3$): δ 170.4 (**C4**), 147.1 ($\mathbf{C_{Ar}11}$), 139.8 ($\mathbf{C_{Ar}14}$), 136.3 ($\mathbf{C_{Ar}6}$/$\mathbf{C_{Ar}10}$), 135.9 ($\mathbf{C_{Ar}6}$/$\mathbf{C_{Ar}10}$), 131.8 ($\mathbf{C_{Ar}H}$) 129.2 ($\mathbf{C_{Ar}7}$/$\mathbf{C_{Ar}8}$), 129.1 ($\mathbf{C_{Ar}7}$/$\mathbf{C_{Ar}8}$), 128.3 ($\mathbf{C_{Ar}H}$), 128.2 ($\mathbf{C_{Ar}H}$), 126.4 ($\mathbf{C_{Ar}H}$), 69.5 (**C2**), 53.5 (**C5**), 21.7 (**C1**), 21.4 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1731 (C=O), 1516 (NO_2) 1339 (NO_2), 1106, 713.

HRMS (ESI): $C_{17}H_{16}{}^{35}ClNO_4Na$ $[M+Na]^+$ requires 326.0660; found 356.0652

MP: 94 − 99 °C (40-60 petrol/ethyl acetate), lit. MP: 133 − 134 °C (heptane).[178]

(±)-Isopropyl 2-(2-amino-5-chlorophenyl)-2-phenylacetate (352)[‡]



According to a modified literature procedure,[64] zinc dust (2.43 g, 37.1 mmol) and ammonium chloride (2.93 g, 54.8 mmol) were added to a stirred room temperature solution of nitroarene

[†] *The separation of aqueous and organic layers was exceptionally difficult due to their very dark (almost black) colouration. Upon close inspection the organic layer could be distinguished from the aqueous by its slight purple hue.*
[‡] *This compound was prepared by Dr Philip Woods and characterized by Dr Peter Knipe but is included for completeness.*

351 (1.25 g, 3.75 mmol) in acetone : water (5 : 1, 100 mL). After 10 minutes, the heterogeneous reaction mixture was filtered over Celite®, and diluted with ethyl acetate (100 mL). The crude mixture was washed with water (100 mL) and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by recrystallization (40-60 petrol/ethyl acetate) to afford aniline **352** (888 mg, 78%) as a pale yellow crystalline solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.39 − 7.26 (5H, m, **7**-**H**, **8**-**H**, **9**-**H**), 7.13 (1H, s, **15**-**H**), 7.08 (1H, d, *J* 8.4, **13**-**H**), 6.62 (1H, d, *J* 8.6, **12**-**H**), 5.12 (1H, sept, *J* 6.1, **2**-**H**), 4.93 (1H, s, **5**-**H**), 3.80 (2H, br. s, N**H**), 1.29 − 1.24 (6H, m, **1**-**H**).

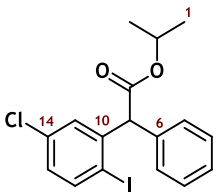
^{13}C (101 MHz, $CDCl_3$): δ 171.5 (**C4**), 143.3 ($\mathbf{C}_{Ar}$**11**), 136.3 ($\mathbf{C}_{Ar}$**6**), 129.1 ($\mathbf{C}_{Ar}$**15**), 128.8 ($\mathbf{C}_{Ar}$**7**/$\mathbf{C}_{Ar}$**8**), 128.7 ($\mathbf{C}_{Ar}$**7**/$\mathbf{C}_{Ar}$**8**), 128.2 ($\mathbf{C}_{Ar}$**13**), 127.7 ($\mathbf{C}_{Ar}$**9**), 124.9 ($\mathbf{C}_{Ar}$**10**), 123.5 ($\mathbf{C}_{Ar}$**14**), 117.8 ($\mathbf{C}_{Ar}$**12**), 69.1 (**C2**), 53.4 (**C5**), 21.7 (**C1**), 21.6 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 3477 (N–H), 3374 (N–H), 2983 (C–H), 2932 (C–H), 1720 (C=O), 1493, 1201, 1093, 813, 698.

HRMS (ESI): $C_{17}H_{18}{}^{35}ClNO_2Na$ $[M+Na]^+$ requires 326.0918; found 326.0906

MP: 118−121 °C (40-60 petrol/ethyl acetate).

(±)-Isopropyl 2-(5-chloro-2-iodophenyl)-2-phenylacetate (347)



According to a modified literature procedure,[70] boron trifluoride diethyl etherate (0.79 mL, 6.29 mmol) was added to a flask under argon and cooled to −15 °C. To this, was added a solution of aniline **352** (1.27 g, 4.18 mmol) in dichloromethane (7 mL) dropwise over 5 minutes. Subsequently, a solution of *tert*-butyl nitrite (0.60 mL, 5.05 mmol) in dichloromethane (3 ml) was added dropwise over 30 minutes. The resulting suspension was stirred at −15 °C for 20 minutes then at 0 °C for 30 minutes. After warming to room temperature the reaction was concentrated *in vacuo* and the crude diazonium salt dissolved in acetonitrile (12 mL) under argon. The resulting solution was added dropwise over 1 hour to a stirred suspension of sodium iodide (940 mg, 6.29 mmol) and iodine (796 mg, 3.13 mmol) in acetonitrile (23 mL) at room temperature. The dark solution was stirred for 1 hour before quenching with saturated aqueous sodium sulfite (50 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 95 : 5) to afford iodoarene **347** (1.09 g, 63%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.79 (1H, d, *J* 8.3, **12**-**H**), 7.42 – 7.26 (5H, m, **7**-**H**, **8**-**H**, **9**-**H**), 7.22 (1H, d, *J* 2.3, **15**-**H**), 6.97 (1H, dd, *J* 8.3, 2.5, **13**-**H**), 5.30 (1H, s, **5**-**H**), 5.14 (1H, sept, *J* 6.3, **2**-**H**), 1.29 (3H, d, *J* 6.3, **1**-**H**), 1.24 (3H, d, *J* 6.1, **1**-**H**).

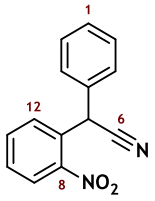
^{13}C (101 MHz, $CDCl_3$): δ 170.9 (**C4**), 143.6 (C_{Ar}**10**), 140.6 (C_{Ar}**12**), 137.2 (C_{Ar}**6**), 134.9 (C_{Ar}**14**), 130.2 (C_{Ar}**15**), 129.3 (C_{Ar}**13**), 129.0 (C_{Ar}**8**), 128.9 (C_{Ar}**7**), 127.8 (C_{Ar}**9**), 98.8 (C_{Ar}**11**), 69.3 (**C2**), 61.3 (**C5**), 21.9 (**C1**), 21.7 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2980 (C–H), 1728 (C=O), 1453, 1188, 1102, 975, 704.

HRMS (ESI): $C_{17}H_{16}{}^{35}ClIO_2Na$ $[M+Na]^+$ requires 436.9776; found 436.9774

MP: 68 – 70 °C.

(±)-2-(2-Nitrophenyl)-2-phenylacetonitrile (354)[†]



According to a modified literature procedure,[179] a mixture of phenylacetonitrile (5.85 g, 50.0 mmol), tetrabutylammonium hydrogensulfate (17.0 g, 50.0 mmol), toluene (90 mL) and aqueous NaOH (50%, 20 mL) was degassed *via* a vacuum-argon purge cycle three times. To this mixture was added a degassed solution of 2-fluoronitrobenzene **353** (7.05 g, 50.0 mmol) in toluene (60 mL) and the reaction stirred at room temperature for 2 hours. The reaction was diluted with aqueous HCl (3 M, 100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by silica gel chromatography (40-60 petrol : diethyl ether, 15 : 1) to afford nitroarene **354** as an orange solid (9.05 g, 76%) with spectroscopic data in accordance with the literature.[178]

[†] *This compound was prepared and characterized by Krishna Sharma (MPhil student) but is included for completeness.*

^{1}H (400 MHz, $CDCl_3$): δ 8.08 (1H, d, *J* 8.1, **9**-**H**), 7.77 – 7.67 (2H, m, **11**-**H**, **12**-**H**), 7.56 (1H, app. td, *J* 7.7, 1.5, **10**-**H**), 7.42 – 7.30 (5H, m, **1**-**H**, **2**-**H**, **3**-**H**), 6.18 (1H, s, **5**-**H**).

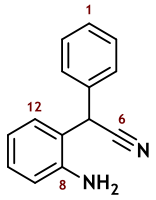
^{13}C (101 MHz, $CDCl_3$): δ 147.8 ($\mathbf{C}_{Ar}$**8**), 134.3 ($\mathbf{C}_{Ar}$**11**), 134.2 ($\mathbf{C}_{Ar}$**4**), 131.1 ($\mathbf{C}_{Ar}$**12**), 130.7 ($\mathbf{C}_{Ar}$**7**), 129.8 ($\mathbf{C}_{Ar}$**10**), 129.5 ($\mathbf{C}_{Ar}$**2**), 128.8 ($\mathbf{C}_{Ar}$**1**), 128.0 ($\mathbf{C}_{Ar}$**3**), 125.9 ($\mathbf{C}_{Ar}$**9**), 118.8 (**C6**), 38.4 (**C5**).

IR: ν_{max} (neat)/ cm^{-1} 3067 (C–H), 2362 (C≡N), 1691, 1602, 1525 (NO_2), 1494, 1453, 1345 (NO_2), 1180.

HRMS (ESI): $C_{14}H_{10}N_2O_2Na$ $[M+Na]^+$ requires 261.0634; found 261.0638

MP: 38 – 40 °C.[†]

(±)-2-(2-Aminophenyl)-2-phenylacetonitrile (355)



According to a modified literature procedure,[64] zinc dust (5.32 g, 81.4 mmol) and ammonium chloride (6.53 g, 122 mmol) were added to a stirred solution of nitroarene **354** (1.94 g, 8.14 mmol) in acetone : water (5 : 1, 90 mL). After 2 hours the heterogeneous reaction mixture was filtered through Celite®, and concentrated *in vacuo*. The crude residue was treated with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 9 : 1) to afford aniline **355** (1.12 g, 66%) as a light orange solid.

[†] *A melting point has not been previously quoted in the literature.*

^{1}H (400 MHz, $CDCl_3$): δ 7.45 – 7.29 (6H, m, **1**-**H**, **2**-**H**, **3**-**H**, **12**-**H**), 7.21 (1H, app. td, *J* 7.6, 1.4, **10**-**H**), 6.89 (1H, t, *J* 7.5, **11**-**H**), 6.74 (1H, d, *J* 7.8, **9**-**H**), 5.19 (1H, s, **5**-**H**), 3.54 (2H, br. s, N**H**).

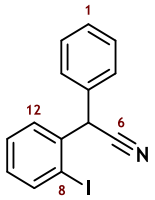
^{13}C (101 MHz, $CDCl_3$): δ 144.0 ($\mathbf{C}_{Ar}$**8**), 134.1 ($\mathbf{C}_{Ar}$**4**), 129.8 ($\mathbf{C}_{Ar}$**10**), 129.6 ($\mathbf{C}_{Ar}$**12**), 129.5 ($\mathbf{C}_{Ar}$**2**), 128.7 ($\mathbf{C}_{Ar}$**1**), 127.8 ($\mathbf{C}_{Ar}$**3**), 120.2 ($\mathbf{C}_{Ar}$**7**), 119.7 ($\mathbf{C}_{Ar}$**11**), 119.1 (**C6**), 117.7 ($\mathbf{C}_{Ar}$**9**), 39.2 (**C5**).

IR: ν_{max} (neat)/ cm^{-1} 3462 (N–H), 3377 (N–H), 2247 (C≡N), 1632, 1495, 1456, 1304, 1162, 743, 700.

HRMS (ESI): $C_{14}H_{12}N_2Na$ $[M+Na]^+$ requires 231.0893; found 231.0891

MP: 72 – 74 °C.

(±)-2-(2-Iodophenyl)-2-phenylacetonitrile (348)



According to a modified literature procedure,[70] boron trifluoride diethyl etherate (0.920 mL, 7.43 mmol) was added to a flask under argon and cooled to −15 °C. To this was added a solution of aniline **355** (1.03 g, 4.95 mmol) in dichloromethane (10 mL) dropwise over 5 minutes. Subsequently, a solution of *tert*-butyl nitrite (0.780 mL, 5.94 mmol) in dichloromethane (4 ml) was added dropwise over 30 minutes. The resulting suspension was stirred at −15 °C for 20 minutes then at 0 °C for 30 minutes. After warming to room temperature the reaction was concentrated *in vacuo* and the crude diazonium salt dissolved in acetonitrile (18 mL) under argon. The resulting solution was added dropwise over 1 hour to a stirred suspension of sodium iodide (890 mg, 5.94 mmol) and iodine (127 mg, 0.500 mmol) in acetonitrile (32 mL) at room temperature. The dark solution was stirred for

1 hour before quenching with saturated aqueous sodium sulfite (75 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL) and then the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 19 : 1) to afford iodoarene **348** (781 mg, 49%) as a yellow oil.

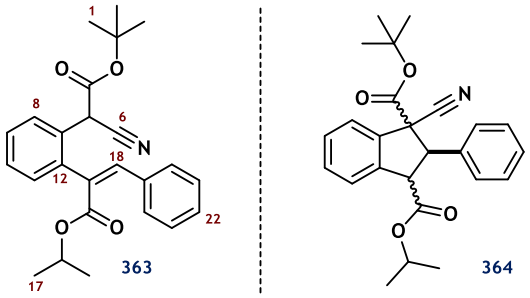
^{1}H (500 MHz, $CDCl_3$): δ 7.91 (1H, dd, *J* 8.0, 1.1, **9-H**), 7.50 (1H, dd, *J* 7.9, 1.6, **12-H**), 7.43 – 7.40 (1H, m, **11-H**), 7.40 – 7.33 (5H, m, **1-H**, **2-H**, **3-H**), 7.06 (1H, app. td, *J* 7.6, 1.6, **10-H**), 5.60 (1H, s, **5-H**).

^{13}C (126 MHz, $CDCl_3$): δ 140.3 ($\mathbf{C}_{Ar}$**9**), 138.8 ($\mathbf{C}_{Ar}$**7**), 134.8 ($\mathbf{C}_{Ar}$**4**), 130.3 ($\mathbf{C}_{Ar}$**10**), 129.8 ($\mathbf{C}_{Ar}$**12**), 129.4 ($\mathbf{C}_{Ar}$**11**), 129.3 ($\mathbf{C}_{Ar}$**2**), 128.5 ($\mathbf{C}_{Ar}$**1**), 128.0 ($\mathbf{C}_{Ar}$**3**), 119.4 (**C6**), 99.9 ($\mathbf{C}_{Ar}$**8**), 46.8 (**C5**).

IR: ν_{max} (neat)/ cm^{-1} 3061 (C–H), 2244 (C≡N), 1494, 1465, 1453, 1436, 1014, 753, 697.

HRMS (ESI): $C_{14}H_{10}INNa$ $[M+Na]^+$ requires 341.9750; found 341.9747

Isopropyl (±)-(*Z*)-2-(2-(2-(*tert*-butoxy)-1-cyano-2-oxoethyl)phenyl)-3-phenylacrylate (363)



According to a modified literature procedure,[112] a dried schlenk flask was charged with iodoarene **360** (470 mg, 1.37 mmol) and anhydrous NMP (5 mL). Under a flow of argon

$Pd(PPh_3)_4$ (316 mg, 0.270 mmol) and flame dried CuI (392 mg, 2.06 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes and in a separate dried schlenk flask stannane **149** (987 mg, 2.06 mmol) was dissolved in anhydrous NMP (5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of stannane **149** was transferred dropwise over 12 hours *via* an argon purged syringe into the reaction mixture at room temperature. After a further 24 hours the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 50 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 50 mL) and brine (3 × 50 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. ^{1}H NMR of the crude reaction mixture revealed a mixture of product **363** and cyclized material **364** (1.8 : 1.0). The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) to afford cyclization precursor **363** (356 mg, 64%) as a colourless oil, but contaminated with 36% of the cyclized product **364**.

^{1}H (500 MHz, $CDCl_3$): δ 7.63 (1H, d, *J* 7.6, **8**-**H**), 7.47 – 7.31 (6H, m, **Ar**-**H**), 7.21 – 7.17 (1H, m, **Ar**-**H**), 7.01 – 6.98 (1H, m, **Ar**-**H**), 6.75 (1H, s, **18**-**H**), 5.26 (1H, s, **5**-**H**), 5.07 (1H, sept, *J* 6.3, **16**-**H**), 1.44 (9H, s, **1**-**H**), 1.18 (3H, d, *J* 6.3, **17**-**H**), 1.14 (3H, d, *J* 6.3, **17**-**H**).

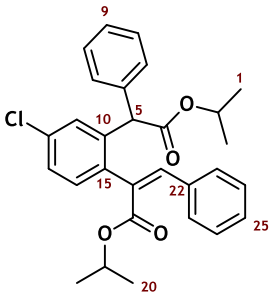
^{13}C (126 MHz, $CDCl_3$): δ 167.7 (**C4**), 164.3 (**C14**), 138.3 ($\mathbf{C_{Ar}}$**12**), 137.6 (**C18**), 134.9 ($\mathbf{C_{Ar}}$**19**), 132.9 (**C13**), 132.6 ($\mathbf{C_{Ar}}$**7**), 130.2 ($\mathbf{C_{Ar}}$**H**), 129.2 ($\mathbf{C_{Ar}}$**H**), 128.9 ($\mathbf{C_{Ar}}$**H**), 128.7 ($\mathbf{C_{Ar}}$**8**), 128.5 ($\mathbf{C_{Ar}}$**20**), 128.5 ($\mathbf{C_{Ar}}$**21**), 128.4 ($\mathbf{C_{Ar}}$**H**), 116.7 (**C6**), 84.5 (**C2**), 69.5 (**C16**), 41.6 (**C5**), 27.7 (**C1**), 21.5 (**C17**), 21.4 (**C17**).[†]

[†] *Due to the presence of the cyclized material* ***364****, which could not be removed by silica gel chromatography, assignment and peak picking in aromatic region was especially difficult.*

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 2250 (C≡N), 1736 (C=O), 1456, 1371, 1253, 1147, 1104 (C–O), 837, 755, 698.

HRMS (ESI): $C_{25}H_{27}NO_4Na$ $[M+Na]^+$ requires 428.1832; found 428.1821

(±)-(*Z*)-Isopropyl 2-(4-chloro-2-(2-isopropoxy-2-oxo-1-phenylethyl)phenyl)-3-phenylacrylate (361)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **149** (357 mg, 0.750 mmol) and anhydrous NMP (3 mL). Under a flow of argon $Pd_2(dba)_3$ (46 mg, 0.050 mmol) and tri(2-furyl)phosphine **176** (46 mg, 0.200 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **347** (206 mg, 0.500 mmol) was dissolved in anhydrous NMP (1.0 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **347** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (143 mg, 0.750 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 50 mL) and ethyl acetate (150 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 50 mL) and brine (3 × 50 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product

was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 40 : 1) to afford cyclization precursor **361** (146 mg, 61%) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.41 (1H, d, *J* 2.0, **11**-**H**), 7.39 – 7.23 (12H, m, **Ar**-**H**), 6.56 (1H, s, **21**-**H**), 5.45 (1H, s, **5**-**H**), 5.11 – 4.99 (2H, m, **2**-**H**, **19**-**H**), 1.20 (3H, d, *J* 6.3, **1**-**H**), 1.14 (6H, app. dd, *J* 6.3, 1.3, **1**-**H**, **20**-**H**), 1.10 (3H, d, *J* 6.3, **20**-**H**).

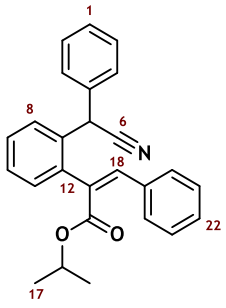
^{13}C (126 MHz, $CDCl_3$): δ 171.8 (**C4**), 167.8 (**C17**), 139.4 ($\mathbf{C}_{Ar}$**6**), 138.6 ($\mathbf{C}_{Ar}$**10**), 138.1 (**C21**), 137.1 ($\mathbf{C}_{Ar}$**15**), 135.3 (**C16**), 134.3 ($\mathbf{C}_{Ar}$**12**), 133.0 ($\mathbf{C}_{Ar}$**22**), 131.0 ($\mathbf{C}_{Ar}$**H**), 129.7 ($\mathbf{C}_{Ar}$**11**), 128.8 ($\mathbf{C}_{Ar}$**7**), 128.7 ($\mathbf{C}_{Ar}$**H**), 128.6 ($\mathbf{C}_{Ar}$**H**), 128.6 ($\mathbf{C}_{Ar}$**23**), 128.4 ($\mathbf{C}_{Ar}$**H**), 127.5 ($\mathbf{C}_{Ar}$**H**), 127.4 ($\mathbf{C}_{Ar}$**H**), 69.2 (**C19**), 69.0 (**C2**), 53.7 (**C5**), 21.8 (**C1**), 21.7 (**C1**), 21.6 (**C20**), 21.5 (**C20**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 1729 (C=O), 1374, 1216, 1193, 1105 (C–O), 698.

HRMS (ESI): $C_{29}H_{29}{}^{35}ClO_4Na$ $[M+Na]^+$ requires 499.1647; found 499.1646

MP: 80 – 82 °C (pentane/ethyl acetate).

Isopropyl (±)-(*Z*)-2-(2-(cyano(phenyl)methyl)phenyl)-3-phenylacrylate (362)



According to a modified literature procedure,[112] a dried schlenk flask was charged with iodoarene **348** (415 mg, 1.30 mmol) and anhydrous NMP (5 mL). Under a flow of argon $Pd(PPh_3)_4$ (300 mg, 0.260 mmol) and flame dried CuI (371 mg, 1.95 mmol) were added

carefully. The resulting suspension was degassed with argon for 30 minutes and in a separate dried schlenk flask stannane **149** (935 mg, 1.95 mmol) was dissolved in anhydrous NMP (5 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of stannane **149** was transferred dropwise over 12 hours *via* an argon purged syringe into the reaction mixture at room temperature. After a further 24 hours the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 50 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 50 mL) and brine (3 × 50 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified twice by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) followed by (silica gel : potassium carbonate, 9 : 1; toluene) to afford cyclization precursor **362** (233 mg, 47%) as a yellow oil.

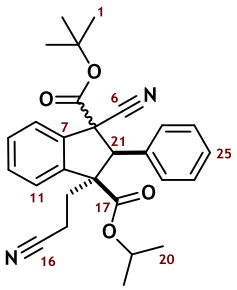
^{1}H (500 MHz, $CDCl_3$): δ 7.51 – 7.46 (1H, m, **8**-**H**), 7.46 – 7.42 (1H, m, **Ar**-**H**), 7.42 – 7.28 (12H, m, **Ar**-**H**), 6.70 (1H, s, **18**-**H**), 5.78 (1H, s, **5**-**H**), 5.09 (1H, sept, *J* 6.3, **16**-**H**), 1.19 (3H, d, *J* 6.3, **17**-**H**), 1.15 (3H, d, *J* 6.3, **17**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 167.9 (**C14**), 138.0 ($\mathbf{C}_{Ar}$**12**), 137.7 (**C18**), 136.2 ($\mathbf{C}_{Ar}$**7**), 134.9 ($\mathbf{C}_{Ar}$**4**), 134.9 ($\mathbf{C}_{Ar}$**19**), 133.1 ($\mathbf{C}_{Ar}$**13**), 130.3 ($\mathbf{C}_{Ar}$**H**), 129.3 ($\mathbf{C}_{Ar}$**H**), 129.2 ($\mathbf{C}_{Ar}$**8**), 129.0 ($\mathbf{C}_{Ar}$**2**), 128.8 ($\mathbf{C}_{Ar}$**H**), 128.5 ($\mathbf{C}_{Ar}$**21**), 128.5 ($\mathbf{C}_{Ar}$**H**), 128.4 ($\mathbf{C}_{Ar}$**20**), 128.1 ($\mathbf{C}_{Ar}$**H**), 127.9 ($\mathbf{C}_{Ar}$**3**), 120.1 (**C6**), 69.5 (**C16**), 39.2 (**C5**), 21.5 (**C17**), 21.4 (**C17**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 2242 (C≡N), 1713 (C=O), 1494, 1451, 1374, 1217, 1105 (C–O), 757, 698.

HRMS (ESI): $C_{26}H_{23}NO_2Na$ $[M+Na]^+$ requires 404.1621; found 404.1610

1-(*tert*-Butyl) 3-isopropyl 1-cyano-3-(2-cyanoethyl)-2-phenyl-2,3-dihydro-1*H*-indene-1,3-dicarboxylate (367)



Racemic: Prepared according to ***general procedure 3*** using cyclization precursor **363** (101 mg, 0.249 mmol, contains 34% of (±)-indane **364**) and acrylonitrile (160 μL, 2.49 mmol). ^{1}H NMR of the crude reaction mixture revealed a 1.0 : 1.2 mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1 to 9 : 1) to afford indane **367** (23 mg, 20%, 1.0 : 1.2 dr) as a yellow oil.

Asymmetric: Prepared according to ***general procedure 6*** using cyclization precursor **363** (76 mg, 0.187 mmol, contains 34% of (±)-indane **364**) and acrylonitrile (120 μL, 1.87 mmol). ^{1}H NMR of the crude reaction mixture revealed a 2.7 : 1.0 mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1 to 9 : 1) to afford a 2.7 : 1.0 mixture of indanes *major*-**367** (33% ee) & *minor*-**367** (12% ee) as a colourless oil in a combined yield of 47 mg (54%). The diastereomers were not separable by silica gel chromatography with a variety of common mobile phases.

NMR data for major diastereomer:[†]

^{1}H (500 MHz, $CDCl_3$): δ 7.67 – 7.63 (1H, m, **8**-**H**), 7.53 – 7.47 (3H, m, **Ar**-**H**), 7.31 – 7.24 (3H, m, **24**-**H**, **25**-**H**), 7.13 (2H, dd, *J* 8.0, 1.4, **23**-**H**), 4.75 (1H, sept, *J* 6.3, **19**-**H**), 4.37 (1H, s, **21**-**H**),

[†] *The major diastereomer refers to the major isomer obtained from the asymmetric reaction as the racemic reaction produced a slight excess of the other diastereomer.*

2.61 – 2.53 (1H, m, **14**-**H**), 2.49 – 2.42 (1H, m, **15**-**H**), 2.33 – 2.20 (2H, m, **14**-**H**, **15**-**H**), 1.53 (9H, s, **1**-**H**), 1.12 (3H, d, *J* 6.3, **20**-**H**), 0.70 (3H, d, *J* 6.3, **20**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 170.5 (**C17**), 166.1 (**C4**), 142.5 ($\mathbf{C}_{Ar}$**12**), 137.9 ($\mathbf{C}_{Ar}$**7**), 136.6 ($\mathbf{C}_{Ar}$**22**), 130.2 ($\mathbf{C}_{Ar}$**10**), 129.7 ($\mathbf{C}_{Ar}$**9**), 128.9 ($\mathbf{C}_{Ar}$**25**), 128.8 ($\mathbf{C}_{Ar}$**23** & $\mathbf{C}_{Ar}$**24**), 126.5 ($\mathbf{C}_{Ar}$**8**), 126.1 ($\mathbf{C}_{Ar}$**11**), 118.8 (**C16**), 117.4 (**C6**), 85.7 (**C2**), 69.9 (**C19**), 62.0 (**C13**), 59.9 (**C5**), 59.8 (**C21**), 34.7 (**C14**), 27.7 (**C1**), 21.5 (**C20**), 20.8 (**C20**), 13.5 (**C15**).

NMR data for minor diastereomer:

^{1}H (500 MHz, $CDCl_3$): δ 7.72 – 7.70 (1H, m, **8**-**H**), 7.69 – 7.64 (1H, m, **11**-**H**), 7.57 – 7.52 (2H, m, **9**-**H**, **10**-**H**), 7.20 – 7.16 (1H, m, **25**-**H**), 7.12 – 7.08 (2H, m, **24**-**H**), 6.86 (2H, d, *J* 7.3, **23**-**H**), 4.59 (1H, sept, *J* 6.0, **19**-**H**), 4.23 (1H, s, **21**-**H**), 2.87 (1H, ddd, *J* 13.6, 9.8, 6.6, **14**-**H**), 2.62 – 2.54 (1H, m, **14**-**H**), 2.50 – 2.41 (1H, m, **15**-**H**), 2.33 – 2.21 (1H, m, **15**-**H**), 1.08 (9H, s, **1**-**H**), 1.03 (3H, d, *J* 6.3, **20**-**H**), 0.63 (3H, d, *J* 6.3, **20**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 169.5 (**C17**), 163.2 (**C4**), 142.7 ($\mathbf{C}_{Ar}$**12**), 136.4 ($\mathbf{C}_{Ar}$**7**), 136.1 ($\mathbf{C}_{Ar}$**22**), 129.8 ($\mathbf{C}_{Ar}$**10**), 129.5 ($\mathbf{C}_{Ar}$**9**), 129.5 ($\mathbf{C}_{Ar}$**23**), 128.8 ($\mathbf{C}_{Ar}$**25**), 128.4 ($\mathbf{C}_{Ar}$**8**), 128.2 ($\mathbf{C}_{Ar}$**24**), 127.7 ($\mathbf{C}_{Ar}$**11**), 120.3 (**C6**), 118.3 (**C16**), 84.7 (**C2**), 69.8 (**C19**), 64.7 (**C21**), 63.4 (**C13**), 55.7 (**C5**), 35.7 (**C14**), 27.2 (**C1**), 21.5 (**C20**), 20.6 (**C20**), 13.7 (**C15**).

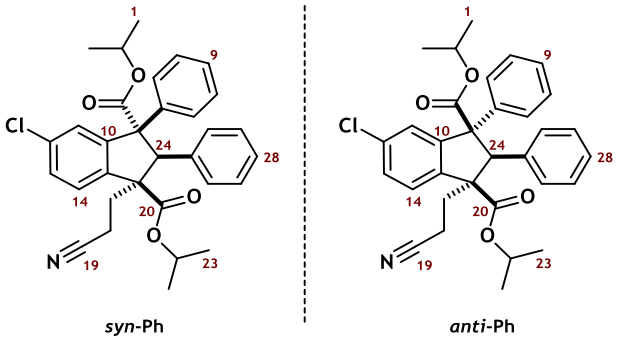
Spectroscopic data for the mixture of diastereomers:

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 2250 (C≡N), 1732 (C=O), 1457, 1372, 1252, 1151, 1106 (C–O), 841, 761.

HRMS (ESI): $C_{28}H_{30}N_2O_4Na$ $[M+Na]^+$ requires 481.2098; found 481.2102

Chiral HPLC: Chiralpak AD-H (20% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 208 nm), major diastereomer: t_R(**minor**) 5.4 min and t_R(**major**) 6.4 min, 33% ee & minor diastereomer: t_R(**major**) 4.5 min and t_R(**minor**) 4.8 min, 12% ee.

Diisopropyl 5-chloro-1-(2-cyanoethyl)-2,3-diphenyl-2,3-dihydro-1*H*-indene-1,3-dicarboxylate (365)



Racemic I: Prepared according to ***general procedure 3*** using cyclization precursor **361** (40 mg, 0.084 mmol) and acrylonitrile (55 μL, 0.840 mmol). ^{1}H NMR of the crude reaction mixture revealed a 15 : 1 (*syn*-Ph : *anti*-Ph) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1) followed by recrystallization (40-60 petrol/ethyl acetate) to afford *syn*-Ph indane **365** (16 mg, 36%, >20 : 1 dr) as a white solid.

Racemic II: Prepared according to ***general procedure 3*** using cyclization precursor **361** (50 mg, 0.105 mmol), acrylonitrile (65 μL, 1.05 mmol) and CsOH·H_2O (34 mg, 0.210 mmol) which was used instead of tetrabutylammonium bromide and aqueous KOH. ^{1}H NMR of the crude reaction mixture revealed a >20 : 1 (*anti*-Ph : *syn*-Ph) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1) to afford *anti*-Ph indane **365** (19 mg, 36%, >20 : 1 dr) as a white solid.

Asymmetric: Prepared according to ***general procedure 6*** using cyclization precursor **361** (80 mg, 0.168 mmol), acrylonitrile (110 μL, 1.68 mmol) and solid powdered KOH (9 mg, 0.168 mmol) instead of aqueous KOH. ^{1}H NMR of the crude reaction mixture revealed a 12 : 1 (*anti*-Ph : *syn*-Ph) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1) to afford *anti*-Ph indane **365** (62 mg, 70%, 10% ee, 12 : 1 dr) as a white solid. The diastereomers were only partially separable by silica gel chromatography.

anti-Ph diastereomer **365**:

^{1}H (500 MHz, C_6D_6): δ 8.63 (1H, d, *J* 2.2, **11**-**H**), 7.55 (2H, d, *J* 7.3, **7**-**H**), 7.42 (1H, d, *J* 8.2, **14**-**H**), 7.29 (1H, dd, *J* 8.4, 2.0, **13**-**H**), 7.05 – 7.01 (2H, m, **8**-**H**), 7.01 – 6.96 (3H, m, **9**-**H**, **26**-**H**), 6.87 – 6.83 (1H, m, **28**-**H**), 6.83 – 6.78 (2H, m, **27**-**H**), 4.55 (1H, sept, *J* 6.3, **22**-**H**), 4.38 (1H, sept, *J* 6.3, **2**-**H**), 4.26 (1H, s, **24**-**H**), 2.06 (1H, ddd, *J* 13.9, 8.8, 7.3, **17**-**H**), 1.59 – 1.50 (1H, m, **18**-**H**), 1.47 – 1.39 (1H, m, **18**-**H**), 1.22 (1H, ddd, *J* 13.8, 8.9, 5.4, **17**-**H**), 0.76 (3H, d, *J* 6.3, **23**-**H**), 0.62 (3H, d, *J* 6.3, **1**-**H**), 0.60 (3H, d, *J* 6.3, **23**-**H**), 0.39 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, C_6D_6): δ 170.3 (**C4**/**C20**), 170.2 (**C4**/**C20**), 145.4 (**C**$_{Ar}$**10**), 142.8 (**C**$_{Ar}$**6**), 141.7 (**C**$_{Ar}$**15**), 140.5 (**C**$_{Ar}$**25**), 134.5 (**C**$_{Ar}$**12**), 131.3 (**C**$_{Ar}$**11**), 130.0 (br., **C**$_{Ar}$**26**), 129.9 (**C**$_{Ar}$**14**), 129.2 (**C**$_{Ar}$**8**), 128.9 (**C**$_{Ar}$**13**), 128.7 (**C**$_{Ar}$**7**), 128.5 (**C**$_{Ar}$**9**), 128.3 (**C**$_{Ar}$**27**), 128.0 (**C**$_{Ar}$**28**), 118.6 (**C19**), 69.3 (**C2**/**C22**), 69.2 (**C2**/**C22**), 68.2 (**C24**), 67.4 (**C5**), 62.9 (**C16**), 35.2 (**C17**), 21.6 (**C23**), 21.3 (**C1**), 21.2 (**C23**), 20.8 (**C1**), 13.5 (**C18**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 2252 (C≡N), 1725 (C=O), 1469, 1235, 1211, 1106 (C–O), 1083, 909, 732, 699.

HRMS (ESI): $C_{32}H_{32}{}^{35}ClNO_4Na$ $[M+Na]^+$ requires 552.1912; found 552.1911

MP: 128 – 130 °C (hexane).

Chiral HPLC: Chiralpak IA (20% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 207 nm), t_R(**minor**) 4.3 min and t_R(**major**) 5.4 min, 10% ee.

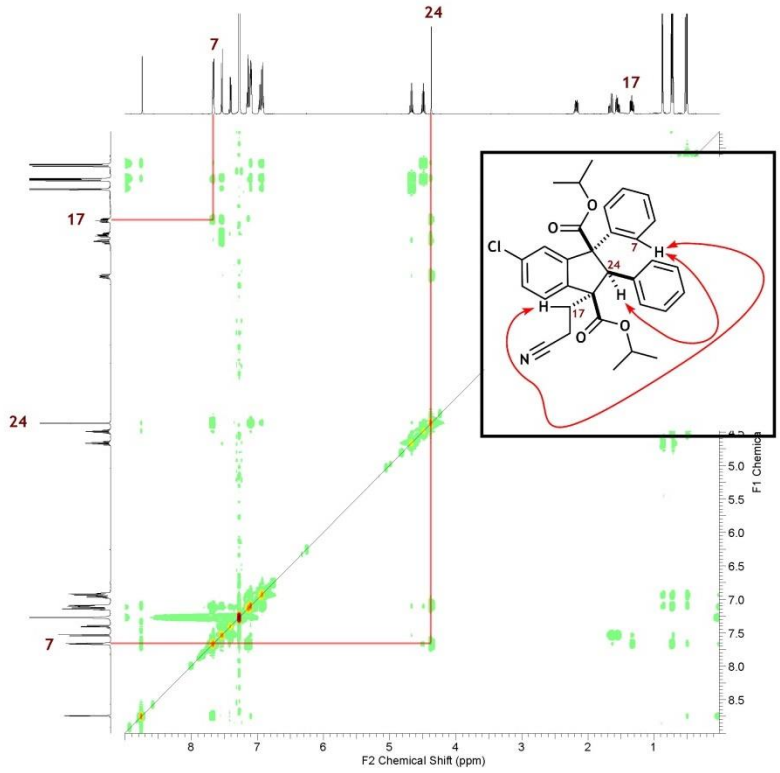


Figure 5.6 – 2D NOESY correlations for *anti*-Ph indane **365** in C_6D_6 (mixing time = 0.8 s).

syn-Ph diastereomer **365**:

^{1}H (500 MHz, C_6D_6): δ 7.88 (1H, d, *J* 1.9, **11**-**H**), 7.44 (1H, d, *J* 8.5, **14**-**H**), 7.29 (1H, dd, *J* 8.2, 2.2, **13**-**H**), 6.96 (2H, dd, *J* 8.4, 1.1, **7**-**H**), 6.77 – 6.68 (3H, m, **8**-**H**, **9**-**H**), 6.67 – 6.61 (5H, m, **26**-**H**, **27**-**H**, **28**-**H**), 4.92 (1H, s, **24**-**H**), 4.86 (1H, sept, *J* 6.2, **2**-**H**), 4.58 (1H, sept, *J* 6.1, **22**-**H**), 2.50 (1H, ddd, *J* 14.0, 10.0, 6.3, **17**-**H**), 2.17 (1H, ddd, *J* 14.0, 9.5, 6.1, **17**-**H**), 2.10 – 1.97 (2H, m, **18**-**H**), 0.84 (3H, d, *J* 6.0, **23**-**H**), 0.81 (3H, d, *J* 6.0, **1**-**H**), 0.74 (3H, d, *J* 6.3, **1**-**H**), 0.32 (3H, d, *J* 6.3, **23**-**H**).

^{13}C (126 MHz, C_6D_6): δ 173.4 (**C4**), 171.3 (**C20**), 144.4 (C_{Ar}**10**), 144.2 (C_{Ar}**15**), 139.7 (C_{Ar}**6**), 139.5 (C_{Ar}**25**), 134.6 (C_{Ar}**12**), 130.5 (br., C_{Ar}**26**), 130.5 (C_{Ar}**11**), 129.4 (C_{Ar}**13**), 128.7 (C_{Ar}**7**), 128.5 (C_{Ar}**14**), 128.3 (C_{Ar}**8**), 127.9 (C_{Ar}**27**), 127.4 (C_{Ar}**9**), 127.2 (C_{Ar}**28**), 119.2 (**C19**), 70.5 (**C2**), 69.2 (**C5**), 69.1 (**C22**), 62.9 (**C24**), 62.3 (**C16**), 37.3 (**C17**), 21.8 (**C23**), 21.3 (**C1**), 21.2 (**C1**), 20.7 (**C23**), 13.8 (**C18**).

IR: ν_{max} (neat)/ cm^{-1} 2981 (C–H), 2250 (C≡N), 1721 (C=O), 1470, 1455, 1220, 1104 (C–O), 909, 732, 698.

HRMS (ESI): $C_{32}H_{32}{}^{35}ClNO_4Na$ $[M+Na]^+$ requires 552.1912; found 552.1911

MP: 156 – 158 °C (40-60 petrol/ethyl acetate).

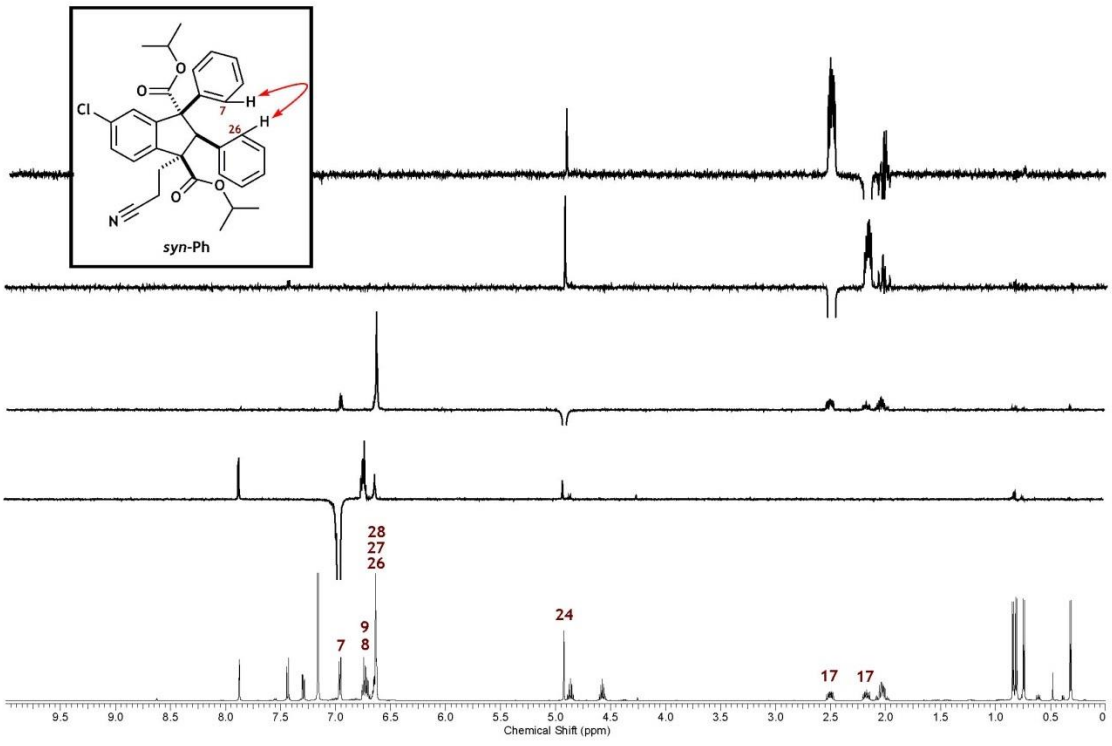
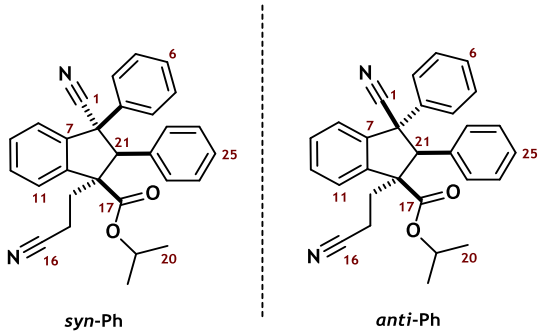


Figure 5.7 – 1D nOe data for *syn*-Ph indane **365** in C_6D_6 (mixing time = 0.8 s).

Isopropyl 3-cyano-1-(2-cyanoethyl)-2,3-diphenyl-2,3-dihydro-1*H*-indene-1-carboxylate

(366)



Racemic: Prepared according to ***general procedure 3*** using cyclization precursor **362** (59 mg, 0.155 mmol) and acrylonitrile (102 μL, 1.55 mmol). ^{1}H NMR of the crude reaction mixture revealed a 5 : 1 (*syn*-Ph : *anti*-Ph) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1 to 9 : 1) to afford a 5 : 1 mixture of indanes *syn*-Ph **366** & *anti*-Ph **366** (28 mg, 42%) as a white solid. Further purification by recrystallization (diethyl ether/hexane) provided an analytically pure sample of *syn*-Ph indane **366**.

Asymmetric: Prepared according to ***general procedure 6*** using cyclization precursor **362** (75 mg, 0.197 mmol), acrylonitrile (129 μL, 1.97 mmol). ^{1}H NMR of the crude reaction mixture revealed a 3 : 1 (*anti*-Ph : *syn*-Ph) mixture of diastereomers. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1 to 9 : 1) to afford a 3 : 1 mixture of indanes *anti*-Ph **366** (39% ee) & *syn*-Ph **366** (2% ee) as a white solid in a combined yield of 75 mg (87%). Further purification by recrystallization (hexane) provided an analytically pure sample of *anti*-Ph indane **366**.

anti-Ph diastereomer **366**:

^{1}H (500 MHz, $CDCl_3$): δ 7.61 – 7.56 (3H, m, **9**-**H**, **10**-**H**, **11**-**H**), 7.55 – 7.51 (1H, m, **8**-**H**), 7.39 – 7.34 (3H, m, **5**-**H**, **6**-**H**), 7.34 – 7.25 (3H, m, **24**-**H**, **25**-**H**), 7.20 (2H, dd, *J* 7.6, 1.9, **4**-**H**), 7.13 (2H, d, *J* 7.3, **23**-**H**), 4.80 (1H, sept, *J* 6.3, **19**-**H**), 3.87 (1H, s, **21**-**H**), 2.40 (2H, m, **14**-**H**, **15**-**H**), 2.23 – 2.12 (1H, m, **15**-**H**), 2.07 (1H, m, **14**-**H**), 1.17 (3H, d, *J* 6.3, **20**-**H**), 0.74 (3H, d, *J* 6.3, **20**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 170.7 (**C17**), 143.0 ($\mathbf{C}_{Ar}$**12**), 141.4 ($\mathbf{C}_{Ar}$**3**), 140.6 ($\mathbf{C}_{Ar}$**7**), 136.8 ($\mathbf{C}_{Ar}$**22**), 129.9 ($\mathbf{C}_{Ar}$**9**/$\mathbf{C}_{Ar}$**10**), 129.8 ($\mathbf{C}_{Ar}$**9**/$\mathbf{C}_{Ar}$**10**), 129.3 ($\mathbf{C}_{Ar}$**5**), 129.0 ($\mathbf{C}_{Ar}$**23**), 128.9 ($\mathbf{C}_{Ar}$**25**), 128.8 ($\mathbf{C}_{Ar}$**24**), 128.8 ($\mathbf{C}_{Ar}$**6**), 127.4 ($\mathbf{C}_{Ar}$**8**), 127.1 ($\mathbf{C}_{Ar}$**4**), 126.5 ($\mathbf{C}_{Ar}$**11**), 120.9 (**C1**), 118.8 (**C16**), 70.0 (**C19**), 68.8 (**C21**), 62.0 (**C13**), 58.4 (**C2**), 34.4 (**C14**), 21.6 (**C20**), 20.9 (**C20**), 13.4 (**C15**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 2250 (C≡N), 1723 (C=O), 1449, 1220, 1106 (C–O), 912, 757, 732, 700.

HRMS (ESI): $C_{29}H_{26}N_2O_2Na$ $[M+Na]^+$ requires 457.1886; found 457.1875

MP: 174 – 176 °C (hexane).

Chiral HPLC: Chiralpak IA (20% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 207 nm), t_R(**minor**) 7.4 min and t_R(**major**) 9.2 min, 39% ee.

$[\alpha]_D^{20}$ +1.3 (*c* 0.60, chloroform).

syn-Ph diastereomer **366**:

^{1}H (500 MHz, C_6D_6): δ 7.67 (1H, d, *J* 7.9, **11**-**H**), 7.19 – 7.15 (1H, m, **10**-**H**), 7.12 – 6.95 (4H, m, **4**-**H**, **8**-**H**, **9**-**H**), 6.79 – 6.73 (3H, m, **5**-**H**, **6**-**H**), 6.62 (1H, app. t, *J* 7.3, **25**-**H**), 6.53 (2H, app. t,

J 7.7, **24**-**H**), 6.40 (2H, d, *J* 7.3, **23**-**H**), 4.66 (1H, sept, *J* 6.3, **19**-**H**), 4.03 (1H, s, **21**-**H**), 2.65 (1H, ddd, *J* 14.0, 8.3, 5.8, **14**-**H**), 2.46 (1H, app. dt, *J* 14.0, 7.8, **14**-**H**), 1.87 – 1.79 (1H, m, **15**-**H**), 1.74 (1H, m, **15**-**H**), 0.90 (3H, d, *J* 6.3, **20**-**H**), 0.26 (3H, d, *J* 6.3, **20**-**H**).

^{13}C (126 MHz, C_6D_6): δ 170.7 (**C17**), 144.8 ($\mathbf{C}_{Ar}$**12**), 140.4 ($\mathbf{C}_{Ar}$**7**), 137.3 ($\mathbf{C}_{Ar}$**22**), 136.6 ($\mathbf{C}_{Ar}$**3**), 130.1 ($\mathbf{C}_{Ar}$**23**), 129.9 ($\mathbf{C}_{Ar}$**10**), 129.9 ($\mathbf{C}_{Ar}$**9**), 129.5 ($\mathbf{C}_{Ar}$**4**), 128.7 ($\mathbf{C}_{Ar}$**5**/$\mathbf{C}_{Ar}$**6**/$\mathbf{C}_{Ar}$**11**), 128.5 ($\mathbf{C}_{Ar}$**5**/$\mathbf{C}_{Ar}$**6**/$\mathbf{C}_{Ar}$**11**), 128.3 ($\mathbf{C}_{Ar}$**5**/$\mathbf{C}_{Ar}$**6**/$\mathbf{C}_{Ar}$**11**), 128.0 ($\mathbf{C}_{Ar}$**24**), 127.8 ($\mathbf{C}_{Ar}$**25**), 127.8 ($\mathbf{C}_{Ar}$**8**), 124.6 (**C1**), 118.8 (**C16**), 69.3 (**C19**), 67.9 (**C21**), 62.8 (**C13**), 56.3 (**C2**), 36.0 (**C14**), 21.8 (**C20**), 20.5 (**C20**), 13.4 (**C15**).

IR: v_{max} (neat)/ cm^{-1} 2982 (C–H), 2251 (C≡N), 1724 (C=O), 1449, 1221, 1101 (C–O), 911, 756, 730, 698.

HRMS (ESI): $C_{29}H_{26}N_2O_2Na$ $[M+Na]^+$ requires 457.1886; found 457.1868

MP: 110 – 112 °C (diethyl ether/hexane).

Chiral HPLC: Chiralpak IA (20% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 207 nm), t_R(**major**) 5.7 min and t_R(**minor**) 6.6 min, 2% ee.

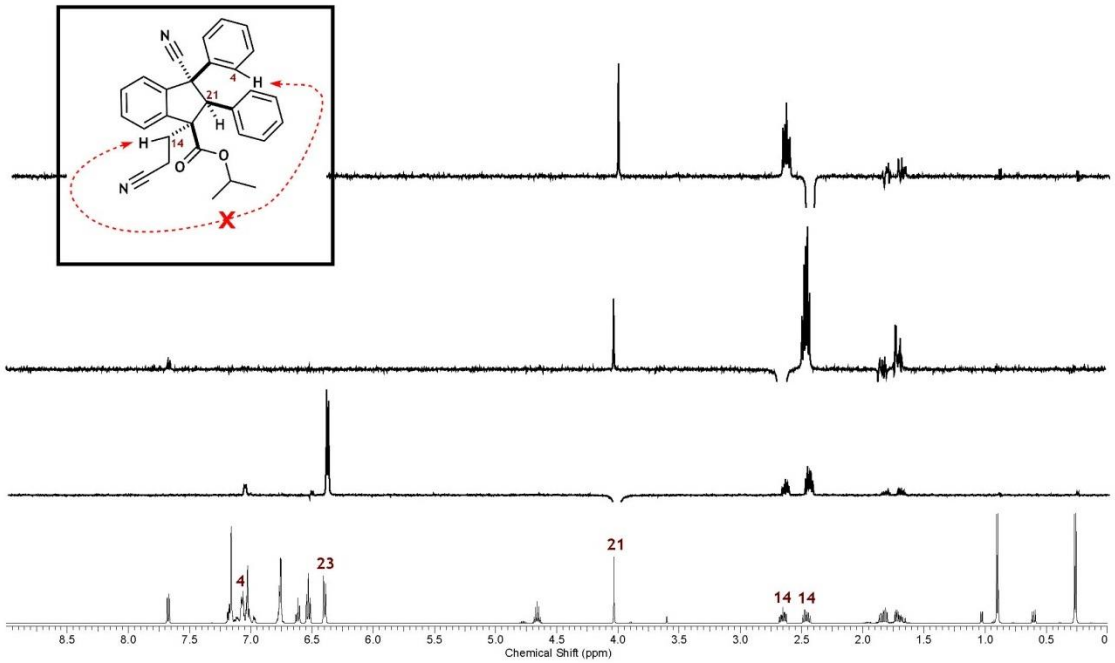
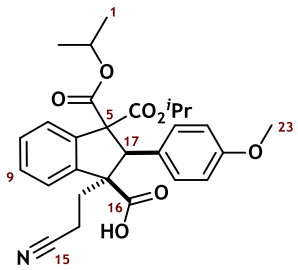


Figure 5.8 – 1D nOe data for *syn*-Ph indane **366** in C_6D_6 (mixing time = 0.8 s).

5.3.9 Derivatization of Indane Products

1-(2-Cyanoethyl)-3,3-bis(isopropoxycarbonyl)-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-indene-1-carboxylic acid (368)



Racemic: TFA (0.5 mL) was added to a stirred solution of indane (±)-**330** (26 mg, 0.047 mmol) in dichloromethane (1 mL) at room temperature. The reaction mixture was stirred for 16 hours and then diluted with chloroform (3 mL). The solution was then concentrated *in vacuo* and azeotroped twice with chloroform (3 ml). The crude product was

purified by silica gel chromatography (40-60 petrol : ethyl acetate, 9 : 1 to 4 : 1) to afford acid (±)-**368** (22 mg, 85%) as a white solid.

Asymmetric: TFA (1.5 mL) was added to a stirred solution of indane **330** (70 mg, 0.127 mmol, 92% ee) in dichloromethane (3 mL) at room temperature. The reaction mixture was stirred for 16 hours and then diluted with chloroform (10 mL). The solution was then concentrated *in vacuo* and azeotroped twice with chloroform (10 ml). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 9 : 1 to 4 : 1) to afford acid **368** (53 mg, 84%, 92% ee, >20 : 1 dr) as a white solid.

^{1}H (400 MHz, $CDCl_3$): δ 7.80 – 7.75 (1H, m, **7**-**H**), 7.45 (2H, app. quind, *J* 7.1, 1.5, **8**-**H**, **9**-**H**), 7.39 – 7.33 (1H, m, **10**-**H**), 6.85 (2H, d, *J* 8.6, **19**-**H**), 6.61 (2H, d, *J* 8.8, **20**-**H**), 5.01 (1H, sept, *J* 6.3, **2**-**H**), 4.59 – 4.47 (2H, m, **2**-**H**, **17**-**H**), 3.70 (3H, s, **23**-**H**), 2.65 – 2.55 (1H, m, **13**-**H**), 2.54 – 2.44 (1H, m, **14**-**H**), 2.43 – 2.32 (1H, m, **14**-**H**), 2.29 – 2.17 (1H, m, **13**-**H**), 1.28 (3H, d, *J* 6.3, **1**-**H**), 1.20 (3H, d, *J* 6.3, **1**-**H**), 1.07 (3H, d, *J* 6.3, **1**-**H**), 0.58 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 174.9 (br., **C16**), 169.0 (**C4**), 167.6 (**C4**), 159.3 ($\mathbf{C}_{Ar}$**21**), 142.6 ($\mathbf{C}_{Ar}$**11**), 138.6 ($\mathbf{C}_{Ar}$**6**), 130.8 ($\mathbf{C}_{Ar}$**19**), 129.7 ($\mathbf{C}_{Ar}$**18**), 129.6 ($\mathbf{C}_{Ar}$**7**), 128.9 ($\mathbf{C}_{Ar}$**9**), 128.6 ($\mathbf{C}_{Ar}$**8**), 126.5 ($\mathbf{C}_{Ar}$**10**), 119.2 (**C15**), 113.1 ($\mathbf{C}_{Ar}$**20**), 70.4 (**C2**), 70.1 (**C5**), 69.6 (**C2**), 63.6 (**C12**), 58.8 (**C17**), 55.4 (**C23**), 36.4 (**C13**), 21.6 (2 × **C1**), 21.5 (**C1**), 20.8 (**C1**), 13.8 (**C14**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1731 (C=O), 1513, 1245, 1183, 1105 (C–O), 770.

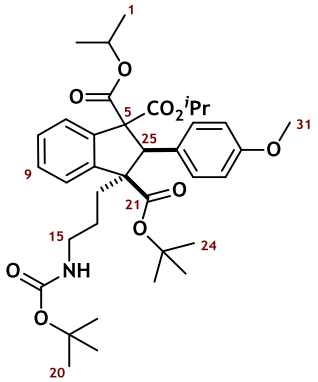
HRMS (ESI): $C_{28}H_{31}NO_7Na$ $[M+Na]^+$ requires 516.1993; found 516.2006

MP: 104 – 106 °C (hexane/diethyl ether).

Chiral HPLC: Chiralpak AD-H (20% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 242 nm), t_R(**major**) 4.6 min and t_R(**minor**) 8.1 min, 92% ee.

$[\alpha]_D^{20}$ +20.2 (*c* 0.70, chloroform).

3-(*tert*-Butyl) 1,1-diisopropyl 3-(3-((*tert*-butoxycarbonyl)amino)propyl)-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (369)



Racemic: According to a modified literature procedure,[182] sodium borohydride (21 mg, 0.560 mmol) was added portionwise over 30 minutes to a solution of indane (±)-**330** (44 mg, 0.080 mmol), di-*tert*-butyl dicarbonate (35 mg, 0.160 mmol) and nickel(II) chloride hexahydrate (2 mg, 8.00 μmol) in methanol (1 mL) at 0 °C. The resulting black suspension was stirred overnight and allowed to reach room temperature. Afterwards, another portion of nickel(II) chloride hexahydrate (2 mg, 8.00 μmol) and sodium borohydride (21 mg, 0.560 mmol) were added at 0 °C and the reaction stirred overnight at room temperature. Diethylenetriamine (17 μL, 0.160 mmol) was added and the reaction stirred for 30 minutes before concentrating *in vacuo*. The purple residue was portioned between ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude

product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1 to 15 : 1) to afford Boc-amine (±)-**369** (23 mg, 44%) as a colourless oil.

Asymmetric: According to a modified literature procedure,[182] sodium borohydride (24 mg, 0.637 mmol) was added portionwise over 30 minutes to a solution of indane **330** (50 mg, 0.091 mmol, 92% ee), di-*tert*-butyl dicarbonate (40 mg, 0.182 mmol) and nickel(II) chloride hexahydrate (2 mg, 9.10 μmol) in methanol (1 mL) at 0 °C. The resulting black suspension was stirred overnight and allowed to reach room temperature. Afterwards, another portion of nickel(II) chloride hexahydrate (2 mg, 9.10 μmol) and sodium borohydride (24 mg, 0.637 mmol) were added at 0 °C and the reaction stirred overnight at room temperature. Diethylenetriamine (19 μL, 0.182 mmol) was added and the reaction stirred for 30 minutes before concentrating *in vacuo*. The purple residue was portioned between ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1 to 15 : 1) to afford Boc-amine **369** (45 mg, 76%, 92% ee, >20 : 1 dr) as a colourless oil.

^{1}H (500 MHz, $CDCl_3$): δ 7.73 – 7.67 (1H, m, **7**-**H**), 7.61 – 7.56 (1H, m, **10**-**H**), 7.42 – 7.36 (2H, m, **8**-**H**, **9**-**H**), 6.83 (2H, br. d, *J* 6.0, **27**-**H**), 6.60 (2H, d, *J* 8.8, **28**-**H**), 4.98 (1H, sept, *J* 6.3, **2**-**H**), 4.56 (1H, br. s, **N**-**H**), 4.52 – 4.42 (2H, m, **2**-**H**, **25**-**H**), 3.67 (3H, s, **31**-**H**), 3.16 – 3.04 (1H, m, **15**-**H**), 3.02 – 2.92 (1H, m, **15**-**H**), 2.21 (1H, td, *J* 13.0, 13.3, **13**-**H**), 1.72 (1H, td, *J* 13.1, 4.7, **13**-**H**), 1.64 – 1.54 (1H, m, **14**-**H**), 1.55 – 1.43 (1H, m, **14**-**H**), 1.41 (9H, s, **20**-**H**), 1.27 (3H, d, *J* 6.0, **1**-**H**), 1.18 (3H, d, *J* 6.3, **1**-**H**), 1.05 (3H, d, *J* 6.3, **1**-**H**), 1.03 (9H, s, **24**-**H**), 0.65 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.4 (**C21**), 169.4 (**C4**), 167.9 (**C4**), 159.1 (C_{Ar}**29**), 155.9 (**C17**), 145.2 (C_{Ar}**11**), 138.2 (C_{Ar}**6**), 131.7 (C_{Ar}**26**), 130.8 (br., C_{Ar}**27**), 129.4 (C_{Ar}**7**), 128.2 (C_{Ar}**9**), 127.5 (C_{Ar}**8**), 127.2 (C_{Ar}**10**), 113.0 (C_{Ar}**28**), 80.8 (**C23**), 79.1 (**C19**), 70.3 (**C5**), 69.9 (**C2**), 69.2 (**C2**), 64.5 (**C12**), 59.6 (**C25**), 55.4 (**C31**), 40.7 (**C15**), 39.6 (**C13**), 28.5 (**C20**), 27.4 (**C24**), 25.9 (**C14**), 21.6 (**C1**), 21.5 (2 × **C1**), 20.9 (**C1**).

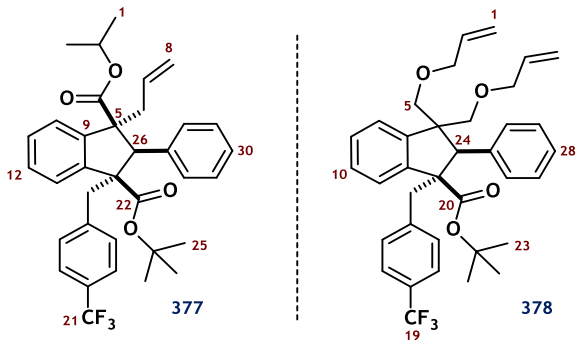
IR: ν_{max} (neat)/ cm^{-1} 3410 (N–H), 2979 (C–H), 1731 (C=O), 1513, 1367, 1246, 1180, 1108 (C–O), 852.

HRMS (ESI): $C_{37}H_{51}NO_9Na$ $[M+Na]^+$ requires 676.3456; found 676.3461

Chiral HPLC: Chiralpak IA (10% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 230 nm), t_R(**major**) 5.6 min and t_R(**minor**) 6.3 min, 92% ee.

$[\alpha]_D^{20}$ +11.7 (*c* 0.35, chloroform).

3-(*tert*-Butyl) 1-isopropyl 1-allyl-2-phenyl-3-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1*H*-indene-1,3-dicarboxylate (377) & *tert*-butyl 3,3-bis((allyloxy)methyl)-2-phenyl-1-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1*H*-indene-1-carboxylate (378)



Racemic: $LiAlH_4$ (1.0 M in THF, 0.320 mL, 0.320 mmol) was added quickly to a rapidly stirred solution of (±)-indane **341** (100 mg, 0.160 mmol) in anhydrous THF (2 mL) at room temperature. After 1 hour, the resulting yellow solution was cooled to 0 °C and was diluted

with anhydrous diethyl ether (2 mL). The reaction was then quenched sequentially with water (12 μL), NaOH (15% aq., 12 μL), water (36 μL) and then allowed to stir for 1 hour at room temperature. Sodium sulfate was added before filtration of the reaction mixture through Celite® with THF. The solvent was removed *in vacuo* and without further purification the reduction products were subjected to ***general procedure 2*** using allyl bromide (28 μL, 0.320 mmol & 111 μL, 1.28 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 50 : 1) to afford (±)-indane **377** (51 mg, 55%, >20 : 1 dr) as a white solid and (±)-indane **378** (17 mg, 18%, >20 : 1 dr) as a colourless oil.

Asymmetric: $LiAlH_4$ (1.0 M in THF, 0.320 mL, 0.320 mmol) was added quickly to a rapidly stirred solution of indane **341** (100 mg, 0.160 mmol, 90% ee) in anhydrous THF (2 mL) at room temperature. After 1 hour, the resulting yellow solution was cooled to 0 °C and was diluted with anhydrous diethyl ether (2 mL). The reaction was then quenched sequentially with water (12 μL), NaOH (15% aq., 12 μL), water (36 μL) and then allowed to stir for 1 hour at room temperature. Sodium sulfate was added before filtration of the reaction mixture through Celite® with THF. The solvent was removed *in vacuo* and without further purification the reduction products were subjected to ***general procedure 2*** using allyl bromide (28 μL, 0.320 mmol & 111 μL, 1.28 mmol). The crude product was purified by silica gel chromatography (40-60 petrol : ethyl acetate, 50 : 1) to afford indane **377** (52 mg, 56%, 90% ee, >20 : 1 dr) as a white solid and indane **378** (16 mg, 17%, 90% ee, >20 : 1 dr) as a colourless oil.

Data for indane **377**:

^{1}H (500 MHz, $CDCl_3$): δ 7.59 (1H, d, *J* 7.6, **10**-**H**), 7.46 (2H, d, *J* 7.9, **19**-**H**), 7.34 (1H, app. td, *J* 7.6, 1.3, **11**-**H**), 7.13 (1H, app. td, *J* 7.6, 1.0, **12**-**H**), 7.10 – 7.04 (3H, m, **29**-**H**, **30**-**H**), 7.01 (2H, d,

J 8.2, **18**-**H**), 6.94 (2H, dd, *J* 7.7, 1.4, **28**-**H**), 6.55 (1H, d, *J* 7.9, **13**-**H**), 5.91 (1H, ddt, *J* 17.0, 9.8, 7.4, **7**-**H**), 5.17 (1H, dd, *J* 10.1, 1.6, **8**-**H**), 5.05 (1H, dd, *J* 17.0, 1.3, **8**-**H**), 4.44 (1H, sept, *J* 6.3, **2**-**H**), 3.92 (1H, d, *J* 12.9, **16**-**H**), 3.73 (1H, s, **26**-**H**), 3.22 (1H, d, *J* 12.9, **16**-**H**), 3.16 (1H, dd, *J* 13.2, 7.9, **6**-**H**), 2.82 (1H, dd, *J* 13.2, 6.9, **6**-**H**), 1.06 (3H, d, *J* 6.3, **1**-**H**), 0.95 (9H, s, **25**-**H**), 0.58 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.7 (**C4**), 171.0 (**C22**), 143.9 (**C$_{Ar}$9**), 141.6 (**C$_{Ar}$14**), 140.9 (**C$_{Ar}$27**), 140.8 (**C$_{Ar}$17**), 133.3 (**C7**), 131.6 (**C$_{Ar}$18**), 129.6 (**C$_{Ar}$28**), 129.3 (q, $J_{F\text{-}C}$ 32, **C$_{Ar}$20**), 129.3 (**C$_{Ar}$13**), 127.9 (**C$_{Ar}$10**), 127.8 (**C$_{Ar}$29**), 127.3 (**C$_{Ar}$30**), 127.2 (**C$_{Ar}$11**), 126.3 (**C$_{Ar}$12**), 124.7 (q, $J_{F\text{-}C}$ 4, **C$_{Ar}$19**), 124.4 (q, $J_{F\text{-}C}$ 272, **C21**), 119.4 (**C8**), 81.7 (**C24**), 68.3 (**C2**), 66.2 (**C26**), 66.0 (**C15**), 63.8 (**C5**), 47.8 (**C6**), 47.5 (**C16**), 27.4 (**C25**), 21.8 (**C1**), 20.8 (**C1**).

^{19}F (377 MHz, $CDCl_3$): δ −62.3

IR: ν_{max} (neat)/ cm^{-1} 2980 (C–H), 1730 (C=O), 1618 (C=C), 1324, 1215, 1151, 1109 (C–O), 1068, 733, 700.

HRMS (ESI): $C_{35}H_{37}F_3O_4Na$ $[M+Na]^+$ requires 601.2536; found 601.2527

MP: 138 – 140 °C (hexane).

Chiral HPLC: Chiralpak AD-H (2% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 220 nm), t_R(**minor**) 4.6 min and t_R(**major**) 5.3 min, 90% ee.

$[\alpha]_D^{20}$ −4.4 (*c* 0.50, chloroform).

Data for indane **378**:

^{1}H (500 MHz, $CDCl_3$): δ 7.51 (1H, d, *J* 7.6, **8**-**H**), 7.44 (2H, d, *J* 7.9, **17**-**H**), 7.28 (1H, app. td, *J* 7.5, 1.1, **9**-**H**), 7.16 (1H, app. td, *J* 7.6, 1.3, **10**-**H**), 7.14 – 7.09 (3H, m, **27**-**H**, **28**-**H**), 7.01 (2H, d, *J* 8.2, **16**-**H**), 6.97 (2H, dd, *J* 7.7, 1.7, **26**-**H**), 6.81 (1H, d, *J* 7.6, **11**-**H**), 5.88 (1H, ddt, *J* 17.1, 10.5, 5.3, **2**-**H**), 5.69 (1H, ddt, *J* 17.3, 10.5, 5.4, **2**-**H**), 5.25 (1H, app. dq, *J* 17.2, 1.6, **1**-**H**), 5.17 – 5.10 (2H, m, **1**-**H**), 5.04 (1H, app. dq, *J* 10.6, 1.7, **1**-**H**), 4.02 (2H, dt, *J* 5.3, 1.3, **3**-**H**), 3.92 (1H, d, *J* 9.1, **5**-**H**), 3.82 – 3.79 (2H, m, **5**-**H**, **24**-**H**), 3.75 (1H, d, *J* 13.2, **14**-**H**), 3.58 (1H, ddt, *J* 12.9, 5.4, 1.3, **3**-**H**), 3.48 – 3.43 (2H, m, **3**-**H**, **5**-**H**), 3.29 (1H, d, *J* 12.9, **14**-**H**), 3.05 (1H, d, *J* 9.1, **5**-**H**), 1.03 (9H, s, **23**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.8 (**C20**), 145.9 ($\mathbf{C}_{Ar}$**7**), 142.8 ($\mathbf{C}_{Ar}$**12**), 141.3 ($\mathbf{C}_{Ar}$**15**), 139.7 ($\mathbf{C}_{Ar}$**25**), 135.3 (**C2**), 135.2 (**C2**), 131.5 ($\mathbf{C}_{Ar}$**16**), 130.1 ($\mathbf{C}_{Ar}$**26**), 129.1 (q, $J_{F\text{-}C}$ 32, $\mathbf{C}_{Ar}$**18**), 128.3 ($\mathbf{C}_{Ar}$**11**), 127.9 ($\mathbf{C}_{Ar}$**9**), 127.5 ($\mathbf{C}_{Ar}$**27**), 126.8 ($\mathbf{C}_{Ar}$**28**), 126.5 ($\mathbf{C}_{Ar}$**10**), 125.5 ($\mathbf{C}_{Ar}$**8**), 124.6 (q, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**17**), 124.4 (q, $J_{F\text{-}C}$ 272, **C19**), 116.5 (**C1**), 115.9 (**C1**), 81.5 (**C22**), 73.9 (**C5**), 72.4 (**C3**), 72.2 (**C5**), 71.9 (**C3**), 65.4 (**C13**), 60.8 (**C24**), 55.1 (**C6**), 47.6 (**C14**), 27.6 (**C23**).

^{19}F (377 MHz, $CDCl_3$): δ −62.3

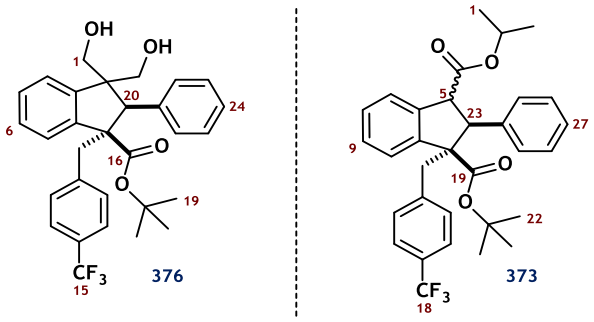
IR: ν_{max} (neat)/ cm^{-1} 2979 (C–H), 1725 (C=O), 1646 (C=C), 1419, 1324, 1166, 1110 (C–O), 1067, 921, 846, 759, 703.

HRMS (ESI): $C_{36}H_{39}F_3O_4Na$ $[M+Na]^+$ requires 615.2693; found 615.2668

Chiral HPLC: Chiralpak IA (2.0% isopropanol in hexane, flow rate = 1.0 mL/min, λ = 204 nm), t_R(**minor**) 3.9 min and t_R(**major**) 4.3 min, 90% ee.

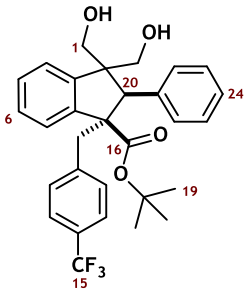
$[\alpha]_D^{20}$ +33.6 (*c* 0.50, chloroform).

tert-Butyl (±)-3,3-bis(hydroxymethyl)-2-phenyl-1-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1_H_-indene-1-carboxylate (376) & 1-(_tert_-butyl) 3-isopropyl (±)-2-phenyl-1-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1_H_-indene-1,3-dicarboxylate (373)



$LiAlH_4$ (1.0 M in THF, 0.320 mL, 0.320 mmol) was added quickly to a rapidly stirred solution of (±)-indane **341** (50 mg, 0.080 mmol) in anhydrous THF (1 mL) at room temperature. After 1 hour, the resulting yellow solution was cooled to 0 °C and was diluted with anhydrous diethyl ether (1 mL). The reaction was then quenched sequentially with water (12 μL), NaOH (15% aq., 12 μL), water (36 μL) and then allowed to stir for 1 hour at room temperature. Sodium sulfate was added before filtration of the reaction mixture through Celite® with THF. TLC (40-60 petrol : ethyl acetate, 4 : 1) of the crude reaction indicated a complex mixture of products. The solvent was removed *in vacuo* and the crude products were purified by silica gel chromatography (40-60 petrol : ethyl acetate, 20 : 1 to 4 : 1) to afford (±)-indane **373** (23 mg, 53%, 6 : 1 dr) as a colourless oil and (±)-indane **376** (7 mg, 17%, >20 : 1 dr) as a white solid.

Data for (±)-indane **376**:



^{1}H (500 MHz, $CDCl_3$): δ 7.44 (2H, d, *J* 8.2, **13**-**H**), 7.31 (1H, app. td, *J* 7.4, 0.9, **5**-**H**), 7.24 – 7.20 (3H, m, **23**-**H**, **24**-**H**), 7.20 – 7.15 (2H, m, **4**-**H**, **6**-**H**), 7.13 – 7.09 (2H, m, **22**-**H**), 7.00 (2H, d, *J* 8.2, **12**-**H**), 6.82 (1H, d, *J* 7.6, **7**-**H**), 4.16 – 4.10 (2H, m, **1**-**H**, **20**-**H**), 4.01 – 3.94 (2H, m, **1**-**H**), 3.84 (1H, d, *J* 13.2, **10**-**H**), 3.68 (1H, d, *J* 11.3, **1**-**H**), 3.23 (1H, d, *J* 13.2, **10**-**H**), 1.06 (9H, s, **19**-**H**).

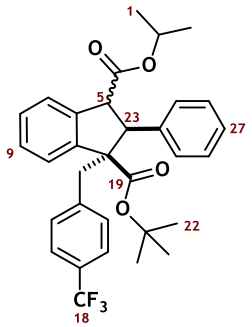
^{13}C (126 MHz, $CDCl_3$): δ 171.6 (**C16**), 143.8 ($\mathbf{C}_{Ar}$**3**), 143.1 ($\mathbf{C}_{Ar}$**8**), 141.0 ($\mathbf{C}_{Ar}$**11**), 140.0 ($\mathbf{C}_{Ar}$**21**), 131.4 ($\mathbf{C}_{Ar}$**12**), 129.7 ($\mathbf{C}_{Ar}$**22**), 129.3 (q, $J_{F\text{-}C}$ 32, $\mathbf{C}_{Ar}$**14**), 129.0 ($\mathbf{C}_{Ar}$**7**), 128.7 ($\mathbf{C}_{Ar}$**23**), 128.3 ($\mathbf{C}_{Ar}$**5**), 127.7 ($\mathbf{C}_{Ar}$**24**), 127.1 ($\mathbf{C}_{Ar}$**6**), 124.7 (q, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**13**), 124.4 (q, $J_{F\text{-}C}$ 272, **C15**), 123.6 ($\mathbf{C}_{Ar}$**4**), 81.8 (**C18**), 71.8 (**C1**), 69.3 (**C1**), 65.5 (**C9**), 59.0 (**C20**), 56.6 (**C2**), 47.4 (**C10**), 27.6 (**C19**).

^{19}F (377 MHz, $CDCl_3$): δ −62.4

IR: ν_{max} (neat)/ cm^{-1} 3367 (O–H), 2979 (C–H), 1726 (C=O), 1369, 1325, 1152, 1127, 1111 (C–O), 909, 733.

HRMS (ESI): $C_{30}H_{31}F_3O_4Na$ $[M+Na]^+$ requires 535.2067; found 535.2042

Data for major diastereomer of (±)-indane **373**:



^{1}H (500 MHz, $CDCl_3$): δ 7.59 (1H, d, *J* 7.6, **7**-**H**), 7.41 (2H, d, *J* 7.9, **16**-**H**), 7.37 – 7.32 (1H, m, **8**-**H**), 7.17 – 7.12 (1H, m, **9**-**H**), 7.12 – 7.03 (3H, m, **26**-**H**, **27**-**H**), 6.91 (2H, br. d, *J* 7.3, **25**-**H**), 6.86 (2H, d, *J* 7.9, **15**-**H**), 6.78 (1H, d, *J* 7.6, **10**-**H**), 4.68 (1H, sept, *J* 6.3, **2**-**H**), 4.45 (1H, d, *J* 7.6, **5**-**H**), 4.02 (1H, d, *J* 7.6, **23**-**H**), 3.72 (1H, d, *J* 12.6, **13**-**H**), 2.98 (1H, d, *J* 12.6, **13**-**H**), 1.02 (3H, d, *J* 6.6, **1**-**H**), 0.99 (9H, s, **22**-**H**), 0.70 (3H, d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 170.8 (**C19**), 170.3 (**C4**), 142.6 ($\mathbf{C}_{Ar}$**11**), 140.8 ($\mathbf{C}_{Ar}$**14**), 139.4 ($\mathbf{C}_{Ar}$**6**), 138.8 ($\mathbf{C}_{Ar}$**24**), 131.0 ($\mathbf{C}_{Ar}$**15**), 129.5 (br., $\mathbf{C}_{Ar}$**25**), 129.2 (q, $J_{F\text{-}C}$ 32, $\mathbf{C}_{Ar}$**17**), 128.5 ($\mathbf{C}_{Ar}$**10**), 127.8 ($\mathbf{C}_{Ar}$**8** & $\mathbf{C}_{Ar}$**26**), 127.6 ($\mathbf{C}_{Ar}$**27**), 126.6 ($\mathbf{C}_{Ar}$**7**), 126.4 ($\mathbf{C}_{Ar}$**9**), 124.7 (q, $J_{F\text{-}C}$ 4, $\mathbf{C}_{Ar}$**16**), 124.4 (q, $J_{F\text{-}C}$ 272, **C18**), 81.5 (**C21**), 68.1 (**C2**), 65.3 (**C12**), 59.8 (**C23**), 52.4 (**C5**), 45.4 (**C13**), 27.4 (**C22**), 21.7 (**C1**), 21.1 (**C1**).

^{19}F (377 MHz, $CDCl_3$): δ −62.3

IR: v_{max} (neat)/ cm^{-1} 2980 (C–H), 1733 (C=O), 1456, 1324, 1154, 1110 (C–O), 1068, 855, 699.

HRMS (ESI): $C_{32}H_{33}F_3O_4Na$ $[M+Na]^+$ requires 561.2223; found 561.2205

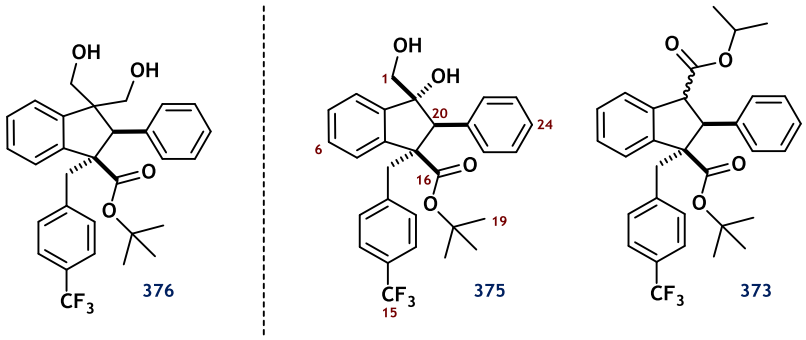
Selected NMR data for minor diastereomer of (±)-indane **373**:

^{1}H (500 MHz, $CDCl_3$): δ 5.03 (1H, sept, *J* 6.3, **2**-**H**), 4.33 (1H, d, *J* 5.0, **5**-**H**), 4.10 (1H, d, *J* 4.7, **23**-**H**), 3.84 (1H, d, *J* 13.6, **13**-**H**), 3.31 (1H, d, *J* 13.6, **13**-**H**), 1.20 (3H, d, *J* 6.3, **1**-**H**), 1.18 (3H, d, *J* 6.3, **1**-**H**) 1.01 (9H, s, **22**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 172.5 (**C19**), 171.7 (**C4**), 81.5 (**C21**), 68.8 (**C2**), 57.1 (**C5**), 56.0 (**C23**), 44.8 (**C13**), 27.5 (**C22**), 21.8 (**C1**).

^{19}F (377 MHz, $CDCl_3$): δ −62.4

Attempted synthesis of *tert*-Butyl (±)-3,3-bis(hydroxymethyl)-2-phenyl-1-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1*H*-indene-1-carboxylate (376) & isolation of *tert*-butyl (±)-3-hydroxy-3-(hydroxymethyl)-2-phenyl-1-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1*H*-indene-1-carboxylate (375) & 1-(*tert*-butyl) 3-isopropyl (±)-2-phenyl-1-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1*H*-indene-1,3-dicarboxylate (373)



$LiAlH_4$ (1.0 M in THF, 0.320 mL, 0.320 mmol) was added dropwise to a solution of indane (±)-**341** (25 mg, 0.040 mmol) in anhydrous THF (0.5 mL) at −78 °C. The resulting colourless solution was allowed to warm to room temperature overnight very slowly. Subsequently, the reaction was cooled to 0 °C and was diluted with anhydrous diethyl ether (0.5 mL). The reaction was then quenched sequentially with water (12 μL), NaOH (15% aq., 12 μL), water (36 μL) and then allowed to stir for 1 hour at room temperature. Sodium sulfate was added before filtration of the reaction mixture through Celite® with THF. TLC (40-60 petrol : ethyl acetate, 4 : 1) of the crude reaction indicated a complex mixture of products. The solvent was removed *in vacuo* and the crude products were purified by silica gel chromatography

(40-60 petrol : ethyl acetate, 9 : 1 to 4 : 1) to afford indane (±)-**375** (5 mg, 25%, >20 : 1 dr) as a white solid and indane (±)-**373** (3 mg, 14%, 6 : 1 dr) as a colourless oil.

(±)-indane **373**: *For spectroscopic data see page 432*.

Data for (±)-indane **375:**

^{1}H (500 MHz, $CDCl_3$): δ 7.48 (1H, d, *J* 7.6, **4**-**H**), 7.44 (2H, d, *J* 7.9, **13**-**H**), 7.35 (1H, app. td, *J* 7.5, 1.1, **5**-**H**), 7.24 (1H, app. td, *J* 7.6, 1.1, **6**-**H**), 7.19 – 7.11 (3H, m, **23**-**H**, **24**-**H**), 6.97 (2H, d, *J* 8.2, **12**-**H**), 6.88 (2H, d, *J* 6.6, **22**-**H**), 6.83 (1H, d, *J* 7.9, **7**-**H**), 3.81 (1H, AB_q, *J* 12.9, **10**-$\mathbf{H_A}$), 3.77 (1H, AB_q, *J* 12.9, **10**-$\mathbf{H_B}$), 3.75 – 3.71 (2H, m, **1**-**H**, **20**-**H**), 3.50 (1H, dd, *J* 11.2, 4.3, **1**-**H**), 1.01 (9H, s, **19**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.2 (**C16**), 144.4 ($\mathbf{C_{Ar}}$**3**), 143.7 ($\mathbf{C_{Ar}}$**8**), 141.5 ($\mathbf{C_{Ar}}$**11**), 139.6 ($\mathbf{C_{Ar}}$**21**), 131.3 ($\mathbf{C_{Ar}}$**12**), 129.2 ($\mathbf{C_{Ar}}$**7**), 129.0 (q, $J_{F\text{-}C}$ 32, $\mathbf{C_{Ar}}$**14**), 129.0 ($\mathbf{C_{Ar}}$**22**), 128.6 ($\mathbf{C_{Ar}}$**23**), 128.4 ($\mathbf{C_{Ar}}$**5**), 128.4 ($\mathbf{C_{Ar}}$**6**), 127.6 ($\mathbf{C_{Ar}}$**24**), 124.6 (q, $J_{F\text{-}C}$ 4, $\mathbf{C_{Ar}}$**13**), 124.5 (q, $J_{F\text{-}C}$ 273, **C15**), 123.6 ($\mathbf{C_{Ar}}$**4**), 84.2 (**C2**), 81.5 (**C18**), 66.9 (**C20**), 66.8 (**C1**), 65.1 (**C9**), 48.1 (**C10**), 27.5 (**C19**).

^{19}F (377 MHz, $CDCl_3$): δ −62.3

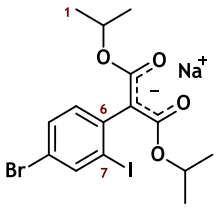
IR: ν_{max} (neat)/ cm^{-1} 3427 (O–H), 2978 (C–H), 1728 (C=O), 1369, 1325, 1153, 1126, 1110 (C–O), 1068, 847, 703.

HRMS (ESI): $C_{29}H_{29}F_3O_4Na$ $[M+Na]^+$ requires 521.1910; found 521.1910

5.3.10 Synthesis of Malonyl Anions & Substrates to Probe Mechanism

Isopropyl (*E*)-2-(4-bromo-2-iodophenyl)-3-hydroxy-3-isopropoxyacrylate, sodium salt

(385)



Sodium hydride (60 wt% in mineral oil, 43 mg, 1.07 mmol) was added portionwise to a solution of malonate **117** (500 mg, 1.07 mmol) in THF (5 mL) at 0 °C. The resulting solution was stirred for 16 hours at room temperature before concentration *in vacuo*. The resulting solid was dried under high vacuum for several hours to afford malonate salt **385** (525 mg, quant.) as a hygroscopic yellow solid.

^{1}H (500 MHz, THF-d_8): δ 7.77 (1H, d, *J* 1.9, **8**-**H**), 7.16 (1H, dd, *J* 8.2, 1.9, **10**-**H**), 7.00 (1H, d, *J* 8.2, **11**-**H**), 4.75 (2H, sept, *J* 6.3, **2**-**H**), 0.98 (6H, d, *J* 6.3, **1**-**H**), 0.92 (6H, d, *J* 6.3, **1**-**H**).

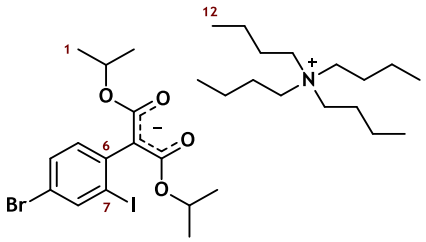
^{13}C (126 MHz, THF-d_8): δ 169.3 (**C4**), 148.4 (**C**$_{Ar}$**6**), 139.9 (**C**$_{Ar}$**8**), 135.8 (**C**$_{Ar}$**11**), 130.5 (**C**$_{Ar}$**10**), 117.5 (**C**$_{Ar}$**7**), 111.4 (**C**$_{Ar}$**9**), 84.8 (**C5**), 63.4 (**C2**), 23.2 (**C1**), 23.2 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2977 (C–H), 1636 (C=O), 1508, 1462, 1380, 1309, 1111, 1068, 993.

HRMS (ESI): $C_{15}H_{17}{}^{79}BrIO_4$ $[M]^-$ requires 466.9360; found 466.9355

MP: 70 – 72 °C.

Isopropyl (*E*)-2-(4-bromo-2-iodophenyl)-3-hydroxy-3-isopropoxyacrylate, tetrabutylammonium salt (386)



According to a modified literature procedure,[200] a solution of tetrabutylammonium hydroxide (1 M in methanol, 0.500 mL, 0.500 mmol) was diluted with anhydrous toluene (5 mL) and was subsequently concentrated *in vacuo* without heating to approx. 1 mL. This procedure was performed six times to give a solution of tetrabutylammonium hydroxide in toluene with minimal levels of methanol and water. Using a pressure-equalizing dropping funnel malonate **117** (234 mg, 0.500 mmol) dissolved in anhydrous toluene (3 mL) was added to the solution of tetrabutylammonium hydroxide over 2 hours under vacuum. After complete addition of malonate **117** all of the solvent was removed *in vacuo*. The resulting residue was triturated (anhydrous diethyl ether) to give a yellow solid which was filtered off under argon. The resulting solid was dried under high vacuum for several hours to afford malonate salt **386** (30 mg, 8%) as a hygroscopic yellow solid.

^{1}H (400 MHz, THF-d_8): δ 7.81 (1H, d, *J* 2.0, **8**-**H**), 7.19 (1H, dd, *J* 8.3, 2.2, **10**-**H**), 7.08 (1H, d, *J* 8.3, **11**-**H**), 4.87 (2H, sept, *J* 6.2, **2**-**H**), 3.57 – 3.50 (8H, m, **15**-**H**), 1.82 – 1.71 (8H, m, **14**-**H**), 1.45 (8H, app. sex, *J* 7.4, **13**-**H**), 1.05 – 0.96 (24H, m, **1**-**H**, **12**-**H**).

^{13}C (101 MHz, THF-d_8): δ 169.1 (**C4**), 148.9 (C_{Ar}**6**), 139.8 (C_{Ar}**8**), 136.0 (C_{Ar}**11**), 130.3 (C_{Ar}**10**), 117.2 (C_{Ar}**7**), 111.7 (C_{Ar}**9**), 84.7 (**C5**), 63.2 (**C2**), 59.6 (**C15**), 23.3 (**C1**), 23.3 (**C1**), 20.9 (**C13**), 14.4 (**C12**).[†]

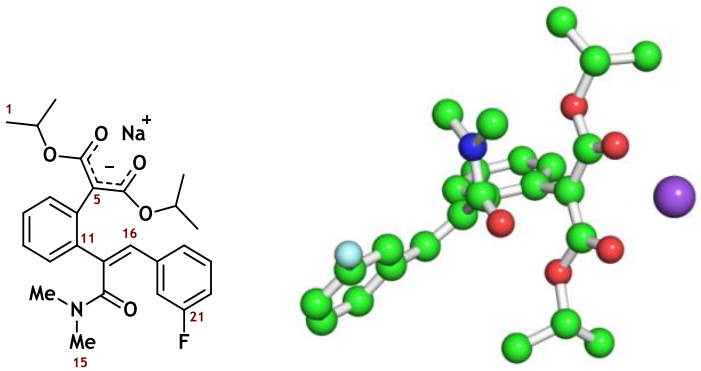
IR: ν_{max} (neat)/ cm^{-1} 2966 (C–H), 1673 (C=O), 1560, 1453, 1370, 1211, 1117, 1054, 992, 739.

HRMS (ESI): $C_{16}H_{36}N$ $[M]^+$ requires 242.2842; found 242.2839

HRMS (ESI): $C_{15}H_{17}{}^{79}BrIO_4$ $[M]^-$ requires 466.9360; found 466.9355

MP: 108 – 110 °C.

Isopropyl (*E*)-2-(2-((*Z*)-3-(dimethylamino)-1-(3-fluorophenyl)-3-oxoprop-1-en-2-yl)phenyl)-3-hydroxy-3-isopropoxyacrylate, sodium salt (387)



Sodium hydride (60 wt% in mineral oil, 13 mg, 0.330 mmol) was added portionwise to a solution of cyclization precursor **291** (151 mg, 0.330 mmol) in THF (1.5 mL) at 0 °C. The resulting solution was stirred for 16 hours at room temperature before concentration *in vacuo*. The resulting solid was dried under high vacuum for several hours to afford malonate salt **387** (158 mg, quant.) as a hygroscopic yellow solid.

[†] ***C14*** *is obscured by the residual THF peak in the region 25.9 – 25.0 ppm*

^{1}H (500 MHz, THF-d_8): δ 7.33 (1H, d, *J* 7.6, **10**-**H**), 7.25 – 7.19 (1H, m, **19**-**H**), 7.15 – 7.09 (2H, m, **18**-**H**, **22**-**H**), 7.09 – 7.06 (2H, m, **7**-**H**, **8**-**H**), 7.06 – 7.00 (1H, m, **9**-**H**), 6.88 (1H, app. td, $J_{F\text{-}H}$ 8.4, *J* 2.2, **20**-**H**), 6.73 (1H, s, **16**-**H**), 4.80 (2H, sept, *J* 6.1, **2**-**H**), 3.02 (3H, s, **15**-**H**), 2.73 (3H, s, **15**-**H**), 0.99 (12H, br. d, *J* 6.3, **1**-**H**).

^{13}C (126 MHz, THF-d_8): δ 171.2 (**C4** & **C13**), 163.8 (d, $J_{F\text{-}C}$ 243, $\mathbf{C}_{Ar}$**21**), 144.2 (**C12**), 142.4 ($\mathbf{C}_{Ar}$**6**), 142.0 ($\mathbf{C}_{Ar}$**11**), 141.0 (d, $J_{F\text{-}C}$ 8, $\mathbf{C}_{Ar}$**17**), 136.3 ($\mathbf{C}_{Ar}$**7**), 131.2 (**C16**), 130.4 (d, $J_{F\text{-}C}$ 9, $\mathbf{C}_{Ar}$**19**), 129.0 ($\mathbf{C}_{Ar}$**10**), 127.4 ($\mathbf{C}_{Ar}$**8**), 126.0 (d, $J_{F\text{-}C}$ 3, $\mathbf{C}_{Ar}$**18**), 125.2 ($\mathbf{C}_{Ar}$**9**), 115.9 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**22**), 114.4 (d, $J_{F\text{-}C}$ 22, $\mathbf{C}_{Ar}$**20**), 79.8 (**C5**), 63.6 (**C2**), 39.1 (**C15**), 36.1 (**C15**), 23.4 (**C1**).

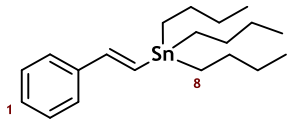
^{19}F (377 MHz, THF-d_8): δ −115.5

IR: v_{max} (neat)/ cm^{-1} 2974 (C–H), 1639 (C=O), 1497, 1376, 1308, 1112, 1048, 750, 687.

HRMS (ESI): $C_{26}H_{29}FNO_5$ $[M]^-$ requires 454.2035; found 454.2046

MP: 110 – 112 °C.

(*E*)-Tributyl(styryl)stannane (392)



According to a modified literature procedure,[255] 2,2′-azobis(2-methylpropionitrile) (0.039 g, 0.230 mmol) was added to a solution of tributyltin hydride (2.06 mL, 7.63 mmol) and phenylacetylene **130** (600 mg, 5.87 mmol) in toluene (12 mL). The resulting colourless solution was heated to 90 °C for 40 minutes and after cooling to room temperature was concentrated *in vacuo*. The crude product was purified by silica gel chromatography

(40-60 petrol) to afford stannane **392** (2.07 g, 90%) as a colourless oil with spectroscopic data in accordance with the literature.[256]

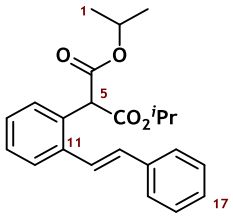
^{1}H (400 MHz, $CDCl_3$): δ 7.48 – 7.42 (2H, m, **3**-**H**), 7.38 – 7.32 (2H, m, **2**-**H**), 7.27 – 7.23 (1H, m, **1**-**H**), 6.91 (1H, s, $J_{^{117,119}Sn\text{-}H}$ 64.9, **5**-**H**), 6.90 (1H, s, **6**-**H**), 1.71 – 1.47 (6H, m, **9**-**H**), 1.38 (6H, app. dq, *J* 14.8, 7.3, **10**-**H**), 1.10 – 0.90 (6H, m, **8**-**H**), 0.94 (9H, t, *J* 7.3, **11**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 146.2 ($J_{^{117,119}Sn\text{-}C}$ 10, **C5**), 139.0 (C_{Ar}**4**), 129.7 (**C6**), 128.6 (C_{Ar}**2**), 127.6 (C_{Ar}**1**), 126.1 (C_{Ar}**3**), 29.3 ($J_{^{117,119}Sn\text{-}C}$ 20, **C9**), 27.5 ($J_{^{117,119}Sn\text{-}C}$ 57, **C10**), 13.9 (**C11**), 9.8 ($J_{^{117}Sn\text{-}C}$ 330, $J_{^{119}Sn\text{-}C}$ 344, **C8**).

IR: ν_{max} (neat)/ cm^{-1} 2923 (C–H), 1593 (C=C), 1463, 1376, 1071, 987, 722, 688.

HRMS (FI): $C_{20}H_{34}{}^{116}Sn$ $[M]^+$ requires 390.1678; found 390.1765

(*E*)-Diisopropyl 2-(2-styrylphenyl)malonate (393)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **392** (1.20 g, 3.05 mmol) and anhydrous NMP (10 mL). Under a flow of argon $Pd(dmdba)_2$ (331 mg, 0.406 mmol) and tri(2-furyl)phosphine **176** (189 mg, 0.812 mmol) were added carefully. The resulting suspension was degassed with argon for 30 minutes as the solution turned from a deep purple to a dark green colour. Meanwhile, in a separate dried schlenk flask iodoarene **78** (794 mg, 2.03 mmol) was dissolved in anhydrous NMP (2 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **78** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of

argon flame dried CuI (581 mg, 3.05 mmol) was added and the reaction was then heated to 60 °C for 60 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 100 mL) and ethyl acetate (400 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 100 mL) and brine (3 × 100 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 40 : 1 to 30 : 1) to afford cyclization precursor **393** (293 mg, 39%) as a colourless oil.

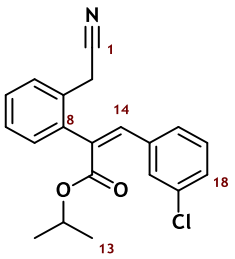
^{1}H (400 MHz, $CDCl_3$): δ 7.60 (1H, dd, *J* 7.7, 1.1, **10**-**H**), 7.51 (2H, d, *J* 7.3, **15**-**H**), 7.44 (1H, dd, *J* 7.3, 1.5, **7**-**H**), 7.41 – 7.26 (6H, m, **Ar**-**H**, **12**-**H**), 6.96 (1H, d, *J* 15.9, **13**-**H**), 5.09 (2H, sept, *J* 6.2, **2**-**H**), 4.99 (1H, s, **5**-**H**), 1.27 (6H, d, *J* 6.3, **1**-**H**), 1.23 (6H, d, *J* 6.3, **1**-**H**).

^{13}C (101 MHz, $CDCl_3$): δ 168.0 (**C4**), 137.6 (**C$_{Ar}$11**/**C$_{Ar}$14**), 137.4 (**C$_{Ar}$11**/**C$_{Ar}$14**), 132.6 (**C13**), 131.3 (**C$_{Ar}$6**), 129.7 (**C$_{Ar}$7**), 128.8 (**C$_{Ar}$16**), 128.4 (**C$_{Ar}$9**), 128.0 (**C$_{Ar}$17**), 127.9 (**C12**), 126.9 (**C$_{Ar}$10**), 126.8 (**C$_{Ar}$15**), 126.0 (**C$_{Ar}$8**), 69.6 (**C2**), 55.4 (**C5**), 21.7 (**C1**), 21.7 (**C1**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 1728 (C=O), 1375, 1159, 1104 (C–O), 908, 760, 731.

HRMS (ESI): $C_{23}H_{26}O_4Na$ $[M+Na]^+$ requires 389.1723; found 389.1725

(*Z*)-Isopropyl 3-(3-chlorophenyl)-2-(2-(cyanomethyl)phenyl)acrylate (396)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **153** (1.76 g, 3.42 mmol) and anhydrous NMP (13 mL). Under a flow of argon $Pd(PPh_3)_4$ (527 mg, 0.456 mmol) was added carefully and the resulting suspension was degassed with argon for 30 minutes. Meanwhile, in a separate dried schlenk flask iodoarene **359** (553 mg, 2.28 mmol) was dissolved in anhydrous NMP (3 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **359** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (651 mg, 3.42 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 75 mL) and ethyl acetate (400 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 75 mL) and brine (3 × 75 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 20 : 1) to afford cyclization precursor **396** (441 mg, 57%) as a colourless oil.

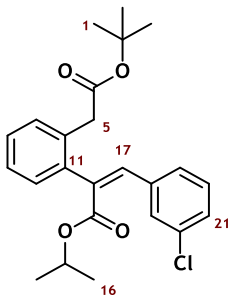
^{1}H (400 MHz, $CDCl_3$): δ 7.54 (1H, d, *J* 7.1, **4**-**H**), 7.45 – 7.36 (4H, m, **5**-**H**, **6**-**H**, **17**-**H**, **20**-**H**), 7.35 – 7.30 (2H, m, **7**-**H**, **18**-**H**), 7.30 – 7.25 (1H, m, **16**-**H**), 6.76 (1H, s, **14**-**H**), 5.07 (1H, sept, *J* 6.3, **12**-**H**), 3.88 (2H, s, **2**-**H**), 1.16 (6H, d, *J* 6.4, **13**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 167.4 (**C10**), 137.8 (C_{Ar}**8**), 136.9 (C_{Ar}**15**), 136.0 (**C14**), 134.9 (**C9**), 134.4 (C_{Ar}**19**), 130.3 (C_{Ar}**17**), 129.8 (C_{Ar}**7**), 129.3 (C_{Ar}**4**/C_{Ar}**5**), 129.2 (C_{Ar}**4**/C_{Ar}**5**), 128.9 (C_{Ar}**3**), 128.7 (C_{Ar}**18**), 128.5 (C_{Ar}**6**), 128.4 (C_{Ar}**20**), 126.8 (C_{Ar}**16**), 118.1 (**C1**), 69.7 (**C12**), 22.0 (**C2**), 21.5 (**C13**).

IR: ν_{max} (neat)/ cm^{-1} 2982 (C–H), 2250 (C≡N), 1709 (C=O), 1373, 1216, 1100 (C–O), 992, 779, 687.

HRMS (ESI): $C_{20}H_{18}{}^{35}ClNO_2Na$ $[M+Na]^+$ requires 362.0918; found 362.0908

(*Z*)-Isopropyl 2-(2-(2-(*tert*-butoxy)-2-oxoethyl)phenyl)-3-(3-chlorophenyl)acrylate (395)



According to a modified literature procedure,[112] a dried schlenk flask was charged with stannane **153** (981 mg, 1.91 mmol) and anhydrous NMP (7 mL). Under a flow of argon $Pd(PPh_3)_4$ (294 mg, 0.254 mmol) was added carefully. The resulting suspension was degassed with argon for 30 minutes and in a separate dried schlenk flask iodoarene **321** (404 mg, 1.27 mmol) was dissolved in anhydrous NMP (2 mL) and was also degassed with argon for 30 minutes. Subsequently, the solution of iodoarene **321** was transferred *via* an argon purged syringe into the reaction mixture. Under a flow of argon flame dried CuI (364 mg, 1.91 mmol) was added and the reaction was then heated to 60 °C for 24 hours. After cooling to room temperature the black reaction mixture was poured into a mixture of aqueous ammonium hydroxide (5%, 50 mL) and ethyl acetate (300 mL). The layers were separated and the organic layer was washed with aqueous ammonium hydroxide (5%, 50 mL) and brine (3 × 50 mL). The organic fraction was dried over anhydrous magnesium sulfate,

filtered and concentrated *in vacuo*. The crude product was purified twice by column chromatography (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : ethyl acetate, 30 : 1) followed by (silica gel : potassium carbonate, 9 : 1; 40-60 petrol : dichloromethane, 4 : 1 to 2 : 3) to afford cyclization precursor **395** (349 mg, 66%) as a colourless oil.

^{1}H (400 MHz, $CDCl_3$): δ 7.40 (1H, s, **23**-**H**), 7.37 – 7.22 (7H, m, **Ar**-**H**), 6.74 (1H, s, **17**-**H**), 5.06 (1H, sept, *J* 6.2, **15**-**H**), 3.68 (2H, s, **5**-**H**), 1.41 (9H, s, **1**-**H**), 1.15 (6H, d, *J* 6.4, **16**-**H**).

^{13}C (126 MHz, $CDCl_3$): δ 171.1 (**C4**), 167.9 (**C13**), 138.3 ($\mathbf{C}_{Ar}$**11**), 137.7 ($\mathbf{C}_{Ar}$**18**), 135.9 ($\mathbf{C}_{Ar}$**22**), 135.2 (**C17**), 134.2 (**C12**), 133.3 ($\mathbf{C}_{Ar}$**6**), 130.8 ($\mathbf{C}_{Ar}$**7**), 129.7 ($\mathbf{C}_{Ar}$**10**/$\mathbf{C}_{Ar}$**20**), 129.6 ($\mathbf{C}_{Ar}$**10**/$\mathbf{C}_{Ar}$**20**), 128.5 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**21**/$\mathbf{C}_{Ar}$**23**), 128.4 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**21**/$\mathbf{C}_{Ar}$**23**), 128.2 ($\mathbf{C}_{Ar}$**8**/$\mathbf{C}_{Ar}$**21**/$\mathbf{C}_{Ar}$**23**), 127.2 ($\mathbf{C}_{Ar}$**9**), 126.7 ($\mathbf{C}_{Ar}$**19**), 81.0 (**C2**), 69.2 (**C15**), 40.3 (**C5**), 28.1 (**C1**), 21.5 (**C16**).

IR: ν_{max} (neat)/ cm^{-1} 2980 (C–H), 1717 (C=O), 1368, 1215, 1145, 1104 (C–O), 992.

HRMS (ESI): $C_{24}H_{27}{}^{35}ClO_4Na$ $[M+Na]^+$ requires 437.1490; found 437.1483

6. REFERENCES

(1) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734–736.
(2) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc. Chem. Commun.* **1976**, 736–738.
(3) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 738–741.
(4) Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc. Chem. Commun.* **1977**, 233–235.
(5) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846–3852.
(6) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563–1572.
(7) Eidenschink, R.; Kauffmann, T. *Angew. Chem. Int. Ed.* **1972**, *11*, 292–293.
(8) Boche, G.; Martens, D. *Angew. Chem. Int. Ed.* **1972**, *11*, 724–725.
(9) Luteri, G. F.; Ford, W. T. *J. Org. Chem.* **1977**, *42*, 820–826.
(10) Ford, W. T.; Luteri, G. F. *J. Am. Chem. Soc.* **1977**, *99*, 5330–5333.
(11) Kempf, D. J.; Wilson, K. D.; Beak, P. *J. Org. Chem.* **1982**, *47*, 1610–1612.
(12) Beak, P.; Burg, D. A. *Tetrahedron Lett.* **1986**, *27*, 5911–5914.
(13) Beak, P.; Wilson, K. D. *J. Org. Chem.* **1986**, *51*, 4627–4639.
(14) Beak, P.; Wilson, K. D. *J. Org. Chem.* **1987**, *52*, 218–225.
(15) Beak, P.; Burg, D. A. *J. Org. Chem.* **1989**, *54*, 1647–1654.
(16) Padwa, A.; Yeske, P. E. *J. Org. Chem.* **1991**, *56*, 6386–6390.
(17) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4455–4458.
(18) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc. Trans.* **1915**, *107*, 1080–1106.
(19) Bachrach, S. M. *J. Org. Chem.* **2008**, *73*, 2466–2468.
(20) Kostal, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2010**, *132*, 8766–8773.
(21) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.
(22) Clayden, J.; Watson, D. W.; Helliwell, M.; Chambers, M. *Chem. Commun.* **2003**, 2582–2583.
(23) Asaoka, M.; Naitoh, R.; Nakamura, Y.; Katano, E.; Nakamura, Y.; Okada, E. *Heterocycles* **2004**, *63*, 1009–1012.
(24) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Elsevier: Oxford, **2002**.
(25) Gawley, R. E. *Stereochemical Aspects of Organolithium Compounds: Topics in Stereochemistry, Volume 26*; Topics in Stereochemistry; Wiley: Weinheim, **2010**.
(26) Ichikawa, J.; Sakoda, K.; Wada, Y. *Chem. Lett.* **2002**, 282–283.
(27) Ichikawa, J.; Miyazaki, H.; Sakoda, K.; Wada, Y. *J. Fluor. Chem.* **2004**, *125*, 585–593.
(28) Gilmore, K.; Manoharan, M.; Wu, J. I.-C.; Schleyer, P. v. R.; Alabugin, I. V. *J. Am. Chem. Soc.* **2012**, *134*, 10584–10594.
(29) Murata, H.; Iliya, I.; Tanaka, T.; Furasawa, M.; Ito, T.; Nakaya, K.; Oyama, M.; Iinuma, M. *Chem. Biodivers.* **2005**, *2*, 773–779.
(30) Luo, H.-F.; Zhang, L.-P.; Hu, C.-Q. *Tetrahedron* **2001**, *57*, 4849–4854.
(31) Huang, K.-S.; Wang, Y.-H.; Li; Lin, M. *J. Nat. Prod.* **2000**, *63*, 86–89.
(32) Hu, H.; Hollinshead, S. P.; Hall, S. E.; Kalter, K.; Ballas, L. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 973–978.
(33) Ulmschneider, S.; Müller-Vieira, U.; Klein, C. D.; Antes, I.; Lengauer, T.; Hartmann, R. W. *J. Med. Chem.* **2005**, *48*, 1563–1575.

(34) Gross, M. F.; Beaudoin, S.; McNaughton-Smith, G.; Amato, G. S.; Castle, N. A.; Huang, C.; Zou, A.; Yu, W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2849–2853.
(35) Hudson, S.; Kiankarimi, M.; Eccles, W.; Mostofi, Y. S.; Genicot, M. J.; Dwight, W.; Fleck, B. A.; Gogas, K.; Wade, W. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4495–4498.
(36) Camps, P.; Formosa, X.; Galdeano, C.; Gómez, T.; Muñoz-Torrero, D.; Scarpellini, M.; Viayna, E.; Badia, A.; Clos, M. V.; Camins, A.; Pallàs, M.; Bartolini, M.; Mancini, F.; Andrisano, V.; Estelrich, J.; Lizondo, M.; Bidon-Chanal, A.; Luque, F. J. *J. Med. Chem.* **2008**, *51*, 3588–3598.
(37) Elliott, J. D.; Lago, M. A.; Cousins, R. D.; Gao, A.; Leber, J. D.; Erhard, K. F.; Nambi, P.; Elshourbagy, N. A.; Kumar, C. *J. Med. Chem.* **1994**, *37*, 1553–1557.
(38) Cook, C. E.; Wani, M. C.; Jump, J. M.; Lee, Y.-W.; Fail, P. A.; Anderson, S. A.; Gu, Y.-Q.; Petrow, V. *J. Med. Chem.* **1995**, *38*, 753–763.
(39) Upton, C.; Osborne, R. H.; Jaffar, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1277–1279.
(40) Ohlstein, E. H.; Nambi, P.; Lago, A.; Hay, D. W.; Beck, G.; Fong, K. L.; Eddy, E. P.; Smith, P.; Ellens, H.; Elliott, J. D. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 609–615.
(41) Cosenzi, A. *Cardiovasc. Drug Rev.* **2003**, *21*, 1–16.
(42) Ohyama, M.; Tanaka, T.; Ito, T.; Iinuma, M.; Bastow, K. F.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3057–3060.
(43) Ito, T.; Akao, Y.; Yi, H.; Ohguchi, K.; Matsumoto, K.; Tanaka, T.; Iinuma, M.; Nozawa, Y. *Carcinogenesis* **2003**, *24*, 1489–1497.
(44) Wood, J. G.; Rogina, B.; Lavu, S.; Howitz, K.; Helfand, S. L.; Tatar, M.; Sinclair, D. *Nature* **2004**, *430*, 686–689.
(45) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594–12595.
(46) Albicker, M.; Cramer, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 9139–9142.
(47) Martin, N.; Pierre, C.; Davi, M.; Jazzar, R.; Baudoin, O. *Chem. - Eur. J.* **2012**, *18*, 4480–4484.
(48) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036–15037.
(49) Jui, N. T.; Garber, J. A. O.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 11400–11403.
(50) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714–2720.
(51) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3107–3110.
(52) Li, Y.; Wang, X.-Q.; Zheng, C.; You, S.-L. *Chem. Commun.* **2009**, 5823.
(53) Biswas, A.; Sarkar, S. D.; Fröhlich, R.; Studer, A. *Org. Lett.* **2011**, *13*, 4966–4969.
(54) Chua, P. J.; Tan, B.; Yang, L.; Zeng, X.; Zhu, D.; Zhong, G. *Chem. Commun.* **2010**, *46*, 7611.
(55) Maciver, E. E.; Thompson, S.; Smith, M. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 9979–9982.
(56) Maciver, E. E.; Knipe, P. C.; Cridland, A. P.; Thompson, A. L.; Smith, M. D. *Chem. Sci.* **2012**, *3*, 537–540.
(57) Li, M.; Woods, P. A.; Smith, M. D. *Chem. Sci.* **2013**, 2907–2911.
(58) Mei, T.-S.; Wang, D.-H.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 3140–3143.
(59) Rossi, R.; Carpita, A.; Cossi, P. *Tetrahedron Lett.* **1992**, *33*, 4495–4498.
(60) Rossi, R.; Carpita, A.; Bellina, F.; Cossi, P. *J. Organomet. Chem.* **1993**, *451*, 33–43.
(61) Kothari, A. *An Approach to Catalytic Asymmetric Electrocyclization*. DPhil, University of Oxford, **2010**.

(62) Carson, J. R. *Methods for the Treatment of Hypertension.* US4898889 (A), **1990**.
(63) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 5215–5219.
(64) MacMillan, K. S.; Nguyen, T.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 1187–1194.
(65) Mihara, J.; Araki, K.; Mori, T.; Murata, T.; Yoneta, Y.; Watanabe, Y.; Shimojo, E.; Ichihara, T.; Ataka, M.; Shibuya, K.; Görgens, U. *Pesticidal Carboxamides.* WO2011018170 (A2), **2011**.
(66) Friedman, L.; Chlebowski, J. *J. Org. Chem.* **1968**, *33*, 1636–1638.
(67) Ek, F.; Wistrand, L.-G.; Frejd, T. *J. Org. Chem.* **2003**, *68*, 1911–1918.
(68) Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* **1979**, *44*, 1572–1574.
(69) Hwang, J.-J.; Tour, J. M. *Tetrahedron* **2002**, *58*, 10387–10405.
(70) Kawaguchi, K.; Nakano, K.; Nozaki, K. *Org. Lett.* **2008**, *10*, 1199–1202.
(71) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496–13497.
(72) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.
(73) Kim, J.-G.; Kang, D. H.; Jang, D. O. *Synlett* **2008**, 443–447.
(74) Cai, M.; Fang, X.; Dai, R.; Zha, L. *Appl. Organomet. Chem.* **2009**, *23*, 229–234.
(75) Cochran, J. C.; Bronk, B. S.; Terrence, K. M.; Phillips, H. K. *Tetrahedron Lett.* **1990**, *31*, 6621–6624.
(76) Betzer, J.-F.; Ménez, P. L.; Prunet, J.; Brion, J.-D.; Ardisson, J.; Pancrazi, A. *Synlett* **2002**, 1–15.
(77) Azarian, D.; Dua, S. S.; Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1976**, *117*, C55–C57.
(78) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, *6*, 301–302.
(79) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638.
(80) Nora De Souza, M. V. *Curr. Org. Synth.* **2006**, *3*, 313–326.
(81) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.
(82) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440.
(83) Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, 866–867.
(84) Espinet, P.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4704–4734.
(85) Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508–524.
(86) Mitchell, T. N. *J. Organomet. Chem.* **1986**, *304*, 1–16.
(87) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1998**, *50*, 1–652.
(88) Diederich, F.; Stang, P. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley: Weinheim, **2008**.
(89) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
(90) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 2413–2416.
(91) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4153–4155.
(92) Zhu, J.; Germain, A. R.; Porco, J. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1239–1243.
(93) Bellina, F.; Carpita, A.; De Santis, M.; Rossi, R. *Tetrahedron* **1994**, *50*, 12029–12046.
(94) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348.
(95) Smith, P. J. *Chemistry of Tin*; 2nd Ed.; Springer: London, **1997**.
(96) Flohr, A. *Tetrahedron Lett.* **1998**, *39*, 5177–5180.
(97) Busacca, C. A.; Swestock, J.; Johnson, R. E.; Bailey, T. R.; Musza, L.; Rodger, C. A. *J. Org. Chem.* **1994**, *59*, 7553–7556.
(98) Peng, Y.; Li, W.-D. Z. *Eur. J. Org. Chem.* **2010**, 6703–6718.

(99) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.
(100) Piers, E.; McEachern, E. J.; Romero, M. A.; Gladstone, P. L. *Can. J. Chem.* **1997**, *75*, 694–701.
(101) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749.
(102) Bishop, L. M.; Barbarow, J. E.; Bergman, R. G.; Trauner, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8100–8103.
(103) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 1132–1136.
(104) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Chem. - Eur. J.* **2005**, *11*, 3294–3308.
(105) Fürstner, A.; Funel, J.-A.; Tremblay, M.; Bouchez, L. C.; Nevado, C.; Waser, M.; Ackerstaff, J.; Stimson, C. C. *Chem. Commun.* **2008**, 2873.
(106) Schrödinger LLC, *The PyMOL Molecular Graphics System*, Version 1.3r1, **2010**.
(107) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
(108) Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997–1030.
(109) Govek, S. P.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 9468–9469.
(110) Kodanko, J. J.; Hiebert, S.; Peterson, E. A.; Sung, L.; Overman, L. E.; Linck, V. de M.; Goerck, G. C.; Amador, T. A.; Leal, M. B.; Elisabetsky, E. *J. Org. Chem.* **2007**, *72*, 7909–7914.
(111) Devreux, V.; Wiesner, J.; Jomaa, H.; Rozenski, J.; Van der Eycken, J.; Van Calenbergh, S. *J. Org. Chem.* **2007**, *72*, 3783–3789.
(112) Smith III, A. B.; Kürti, L.; Davulcu, A. H. *Org. Lett.* **2006**, *8*, 2167–2170.
(113) Smith III, A. B.; Kürti, L.; Davulcu, A. H.; Cho, Y. S.; Ohmoto, K. *J. Org. Chem.* **2007**, *72*, 4611–4620.
(114) Macé, Y.; Kapdi, A. R.; Fairlamb, I. J. S.; Jutand, A. *Organometallics* **2006**, *25*, 1795–1800.
(115) Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140–3157.
(116) Renaud, P.; Lacôte, E.; Quaranta, L. *Tetrahedron Lett.* **1998**, *39*, 2123–2126.
(117) Harrowven, D. C.; Curran, D. P.; Kostiuk, S. L.; Wallis-Guy, I. L.; Whiting, S.; Stenning, K. J.; Tang, B.; Packard, E.; Nanson, L. *Chem. Commun.* **2010**, *46*, 6335.
(118) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978–8985.
(119) Casado, A. L.; Espinet, P.; Gallego, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11771–11782.
(120) Amatore, C.; Bahsoun, A. A.; Jutand, A.; Meyer, G.; Ndedi Ntepe, A.; Ricard, L. *J. Am. Chem. Soc.* **2003**, *125*, 4212–4222.
(121) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911.
(122) Amatore, C.; Jutand, A.; Meyer, G.; Atmani, H.; Khalil, F.; Chahdi, F. O. *Organometallics* **1998**, *17*, 2958–2964.
(123) Piers, E.; Yee, J. G. K.; Gladstone, P. L. *Org. Lett.* **2000**, *2*, 481–484.
(124) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434–5444.
(125) Han, X.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1871–1872.
(126) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195–199.
(127) Mąkosza, M. *Tetrahedron Lett.* **1966**, *7*, 4621–4624.
(128) Mąkosza, M. *Tetrahedron Lett.* **1969**, *10*, 677–678.
(129) Brändström, A. *Adv. Phys. Org. Chem.* **1978**, *15*, 267–330.
(130) Lygo, B.; Andrews, B. I. *Accounts Chem. Res.* **2004**, *37*, 518–525.
(131) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266.
(132) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348.
(133) Jew, S.; Park, H. *Chem. Commun.* **2009**, 7090–7103.

(134) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710–4711.
(135) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.
(136) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595–8598.
(137) Lygo, B.; Allbutt, B.; James, S. R. *Tetrahedron Lett.* **2003**, *44*, 5629–5632.
(138) Lygo, B.; Allbutt, B.; Kirton, E. H. M. *Tetrahedron Lett.* **2005**, *46*, 4461–4464.
(139) Lygo, B.; Allbutt, B.; Beaumont, D. J.; Butt, U.; Gilks, J. A. R. *Synlett* **2009**, 675–680.
(140) Ghosh, A. K.; Takayama, J.; Aubin, Y.; Ratia, K.; Chaudhuri, R.; Baez, Y.; Sleeman, K.; Coughlin, M.; Nichols, D. B.; Mulhearn, D. C.; Prabhakar, B. S.; Baker, S. C.; Johnson, M. E.; Mesecar, A. D. *J. Med. Chem.* **2009**, *52*, 5228–5240.
(141) Rezaei, H.; Marek, I.; Normant, J. F. *Tetrahedron* **2001**, *57*, 2477–2483.
(142) Kitamura, M.; Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 1549–1551.
(143) Starks, C. M. *Phase-Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*; Springer: New York, **1994**.
(144) von Hofmann, A. W. *Justus Liebigs Ann. Chem.* **1851**, *78*, 253–286.
(145) Brak, K.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2013**, *52*, 534–561.
(146) Singh, R.; Czekelius, C.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. *Organometallics* **2007**, *26*, 2528–2539.
(147) Hall, D. G. *Boronic Acids*; Wiley: Weinheim, **2012**.
(148) Wang, Y.-G.; Ueda, M.; Wang, X.; Han, Z.; Maruoka, K. *Tetrahedron* **2007**, *63*, 6042–6050.
(149) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
(150) Spreitzer, H.; Daub, J. *Liebigs Ann.* **1995**, 1637–1641.
(151) Tsuchiya, Y.; Matsuno, M.; Itoh, T.; Hirai, K.; Tomioka, H. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 2037–2050.
(152) Kitamura, M.; Arimura, Y.; Shirakawa, S.; Maruoka, K. *Tetrahedron Lett.* **2008**, *49*, 2026–2030.
(153) Shirakawa, S.; Liu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 916–919.
(154) Surya Prakash, G. K.; Mandal, M.; Olah, G. A. *Angew. Chem.* **2001**, *113*, 609–610.
(155) Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Tetrahedron* **2006**, *62*, 11425–11436.
(156) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681–7684.
(157) Rohbogner, C. J.; Wagner, A. J.; Clososki, G. C.; Knochel, P. *Org. Synth.* **2009**, *86*, 374–384.
(158) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Org. Chem.* **2003**, *68*, 4576–4578.
(159) Cao, Z.; Du, H. *Org. Lett.* **2010**, *12*, 2602–2605.
(160) Costero, A. M.; Andreu, C.; Pitarch, M.; Andreu, R. *Tetrahedron* **1996**, *52*, 3683–3692.
(161) Beigelman, L.; Buckman, B.; Wang, G.; Matulic-Adamic, J.; Stoycheva, A. D.; Andrews, S.; Misialek, S.; Rajagopalan, P. T. R.; Fryer, A.; Gunawardana, I.; Haas, J.; Huang, L.; Madduru, M.; Zhang, G.; Kossen, K.; Serebryany, V. Novel Inhibitors *Hepatitis C Virus Replication*. WO2008100867 (A2), **2008**.
(162) Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1948**, *70*, 3738–3740.
(163) Zhang, H.; Yu, T.; Zhao, Y.; Fan, D.; Xia, Y.; Zhang, P.; Qiu, Y.; Chen, L. *Spectrochim. Acta. A. Mol. Biomol. Spectrosc.* **2010**, *75*, 325–329.
(164) Reichert, S.; Breit, B. *Org. Lett.* **2007**, *9*, 899–902.
(165) Meltzer, R. I.; Lustgarten, D. M.; Fischman, A. *J. Org. Chem.* **1957**, *22*, 1577–1581.

(166) Hendrix, J. A.; Stefany, D. W. *Tetrahedron Lett.* **1999**, *40*, 6749–6752.
(167) Bunnett, J. F. *Accounts Chem. Res.* **1992**, *25*, 2–9.
(168) Shirakawa, S.; Ueda, M.; Tanaka, Y.; Hashimoto, T.; Maruoka, K. *Chem. – Asian J.* **2007**, *2*, 1276–1281.
(169) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520.
(170) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139–5151.
(171) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 3796–3798.
(172) Ooi, T.; Takeuchi, M.; Ohara, D.; Maruoka, K. *Synlett* **2001**, 1185–1187.
(173) Fang, Z.; Song, Y.; Sarkar, T.; Hamel, E.; Fogler, W. E.; Agoston, G. E.; Fanwick, P. E.; Cushman, M. *J. Org. Chem.* **2008**, *73*, 4241–4244.
(174) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003–1011.
(175) Nair, V.; Augustine, A.; Suja, T. D. *Synthesis* **2002**, 2259–2265.
(176) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, **1994**.
(177) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157–15166.
(178) Mąkosza, M.; Kamieńska-Trela, K.; Paszewski, M.; Bechcicka, M. *Tetrahedron* **2005**, *61*, 11952–11964.
(179) Mąkosza, M.; Tomashewskij, A. A. *J. Org. Chem.* **1995**, *60*, 5425–5429.
(180) Trost, B. M.; Miller, J. R.; Hoffman, C. M. *J. Am. Chem. Soc.* **2011**, *133*, 8165–8167.
(181) Lane, C. F. *Chem. Rev.* **1976**, *76*, 773–799.
(182) Caddick, S.; Judd, D. B.; Lewis, A. K. de K.; Reich, M. T.; Williams, M. R. V. *Tetrahedron* **2003**, *59*, 5417–5423.
(183) Long, D. D.; Termin, A. P. *Tetrahedron Lett.* **2000**, *41*, 6743–6747.
(184) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918–920.
(185) Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. *Tetrahedron Lett.* **1967**, *8*, 215–217.
(186) Maciver, E. E. *Asymmetric Electrocyclic Reactions*. DPhil, University of Oxford, **2011**.
(187) Poon, P. S.; Banerjee, A. K.; Laya, M. S. *J. Chem. Res.* **2011**, *35*, 67–73.
(188) Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1996**, *61*, 4572–4581.
(189) Ayers, T. A. *Tetrahedron Lett.* **1999**, *40*, 5467–5470.
(190) Mąkosza, M. J. *Pure Appl. Chem.* **1975**, *43*, 439–462.
(191) Rabinovitz, M.; Cohen, Y.; Halpern, M. *Angew. Chem. Int. Ed.* **1986**, *25*, 960–970.
(192) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395–397.
(193) Hoffmann, R.; Woodward, R. B. *Accounts Chem. Res.* **1968**, *1*, 17–22.
(194) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, **1970**.
(195) Müller, S.; List, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9975–9978.
(196) Bishop, L. M.; Roberson, R. E.; Bergman, R. G.; Trauner, D. *Synthesis* **2010**, 2233–2244.
(197) Das, A.; Volla, C. M. R.; Atodiresei, I.; Bettray, W.; Rueping, M. *Angew. Chem. Int. Ed.* **2013**, DOI: 10.1002/anie.201301638.
(198) Wang, L.; Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 5327–5330.
(199) Shirakawa, S.; Terao, S. J.; He, R.; Maruoka, K. *Chem. Commun.* **2011**, *47*, 10557–10559.
(200) Reetz, M. T.; Huette, S.; Goddard, R. *J. Am. Chem. Soc.* **1993**, *115*, 9339–9340.
(201) Cannizzaro, C. E.; Houk, K. N. *J. Am. Chem. Soc.* **2002**, *124*, 7163–7169.

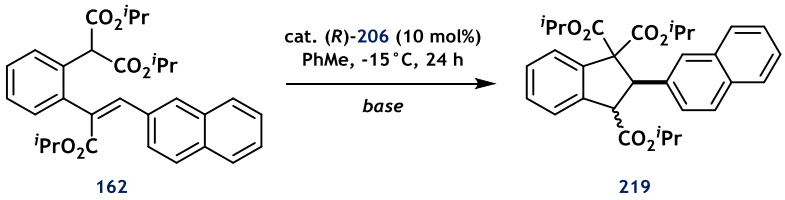
(202) Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403–2409.
(203) Cook, T. C.; Andrus, M. B.; Ess, D. H. *Org. Lett.* **2012**, *14*, 5836–5839.
(204) Bhattacharya, A.; Dolling, U.-H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. M. *Angew. Chem. Int. Ed.* **1986**, *25*, 476–477.
(205) Hughes, D. L.; Dolling, U.-H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745–4752.
(206) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press, Inc.: London, **1980**.
(207) Lo, C.-Y.; Kumar, M. P.; Chang, H.-K.; Lush, S.-F.; Liu, R.-S. *J. Org. Chem.* **2005**, *70*, 10482–10487.
(208) Yu, T.-Q.; Fu, Y.; Liu, L.; Guo, Q.-X. *J. Org. Chem.* **2006**, *71*, 6157–6164.
(209) Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1996**, *118*, 2595–2605.
(210) Danforth, C.; Nicholson, A. W.; James, J. C.; Loudon, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 4275–4281.
(211) Winans, R. E.; Wilcox, C. F. *J. Am. Chem. Soc.* **1976**, *98*, 4281–4285.
(212) Woodward, R. B. *Pure Appl. Chem.* **1968**, *17*, 519–547.
(213) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.
(214) Szostak, M.; Spain, M.; Procter, D. J. *Nat. Protoc.* **2012**, *7*, 970–977.
(215) De Frutos, Ó.; Atienza, C.; Echavarren, A. M. *Eur. J. Org. Chem.* **2001**, 163–171.
(216) Moss, R. A.; Chu, G.; Sauers, R. R. *J. Am. Chem. Soc.* **2005**, *127*, 2408–2409.
(217) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals 5th Edition*; 5th Ed.; Butterworth-Heinemann: Oxford, **2003**.
(218) Williams, D. B. G.; Lawton, M. *J. Org. Chem.* **2010**, *75*, 8351–8354.
(219) Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218–4227.
(220) Yamakawa, N.; Suemasu, S.; Matoyama, M.; Tanaka, K.; Katsu, T.; Miyata, K.; Okamoto, Y.; Otsuka, M.; Mizushima, T. *Bioorg. Med. Chem.* **2011**, *19*, 3299–3311.
(221) Katoh, T.; Akagi, T.; Noguchi, C.; Kajimoto, T.; Node, M.; Tanaka, R.; Nishizawa, M.; Ohtsu, H.; Suzuki, N.; Saito, K. *Bioorg. Med. Chem.* **2007**, *15*, 2736–2748.
(222) Pawluć, P.; Hreczycho, G.; Walkowiak, J.; Marciniec, B. *Synlett* **2007**, 2061–2064.
(223) Rao, M. L. N.; Jadhav, D. N.; Dasgupta, P. *Org. Lett.* **2010**, *12*, 2048–2051.
(224) Huh, D. H.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2002**, *58*, 9925–9932.
(225) Chen, M.-Y.; Lee, A. S.-Y. *J. Chin. Chem. Soc.-Taipei* **2003**, *50*, 103–108.
(226) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron* **1994**, *50*, 4323–4334.
(227) Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376–12377.
(228) Liao, S.; List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 628–631.
(229) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757–760.
(230) Myung, B. Y.; Kim, J. J.; Yoon, T. H. *J. Polym. Sci. Part Polym. Chem.* **2002**, *40*, 4217–4227.
(231) Pirkle, W. H.; Simmons, K. A.; Boeder, C. W. *J. Org. Chem.* **1979**, *44*, 4891–4896.
(232) Rossiter, B. E.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernández, A. E.; Vickers, D.; Fluckiger, E.; Greg Patterson, R.; Vásavi Reddy, K. *Tetrahedron* **1993**, *49*, 965–986.
(233) Fuglseth, E.; Otterholt, E.; Høgmoen, H.; Sundby, E.; Charnock, C.; Hoff, B. H. *Tetrahedron* **2009**, *65*, 9807–9813.

(234) Hanessian, S.; Yang, G.; Rondeau, J.-M.; Neumann, U.; Betschart, C.; Tintelnot-Blomley, M. *J. Med. Chem.* **2006**, *49*, 4544–4567.
(235) Alberti, A.; Canè, F.; Dembech, P.; Lazzari, D.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1996**, *61*, 1677–1681.
(236) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.
(237) Plobeck, N.; Powell, D. *Tetrahedron Asymmetry* **2002**, *13*, 303–310.
(238) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.
(239) Filthaus, M.; Oppel, I. M.; Bettinger, H. F. *Org. Biomol. Chem.* **2008**, *6*, 1201–1207.
(240) Dai, Q.; Xu, D.; Lim, K.; Harvey, R. G. *J. Org. Chem.* **2007**, *72*, 4856–4863.
(241) Prokopcová, H.; Bergman, S. D.; Aelvoet, K.; Smout, V.; Herrebout, W.; Van der Veken, B.; Meerpoel, L.; Maes, B. U. W. *Chem. – Eur. J.* **2010**, *16*, 13063–13067.
(242) Huang, J.; Su, J.-H.; Li, X.; Lam, M.-K.; Fung, K.-M.; Fan, H.-H.; Cheah, K.-W.; Chen, C. H.; Tian, H. *J. Mater. Chem.* **2011**, *21*, 2957–2964.
(243) Andersen, N. G.; Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 9556–9559.
(244) Zahn, A.; Leumann, C. J. *Bioorg. Med. Chem.* **2006**, *14*, 6174–6188.
(245) Carreño, M. C.; González-López, M.; Latorre, A.; Urbano, A. *J. Org. Chem.* **2006**, *71*, 4956–4964.
(246) Stearman, C. J.; Behar, V. *Tetrahedron Lett.* **2002**, *43*, 1943–1946.
(247) Nagendra, G.; Madhu, C.; Vishwanatha, T. M.; Sureshbabu, V. V. *Tetrahedron Lett.* **2012**, *53*, 5059–5063.
(248) Riddell, N.; Tam, W. *J. Org. Chem.* **2006**, *71*, 1934–1937.
(249) Cheng, Z.-Y.; Li, W.-J.; He, F.; Zhou, J.-M.; Zhu, X.-F. *Bioorg. Med. Chem.* **2007**, *15*, 1533–1538.
(250) Curran, B. C.; Wenzke, H. H. *J. Am. Chem. Soc.* **1937**, *59*, 943–944.
(251) Iwai, I.; Nakamura, N. *Chem. Pharm. Bull.* **1966**, *14*, 1277 – 1286.
(252) Lipshutz, B. H.; Huff, B. E.; McCarthy, K. E.; Jaweed Mukarram, S. M.; Siahaan, T. J.; Vaccaro, W. D.; Webb, H.; Falick, A. M.; Miller, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 7032–7041.
(253) Duggan, P. J.; Johnston, M.; March, T. L. *J. Org. Chem.* **2010**, *75*, 7365–7372.
(254) Hari, Y.; Date, K.; Kondo, R.; Aoyama, T. *Tetrahedron Lett.* **2008**, *49*, 4965–4967.
(255) Fukase, K.; Tanake, K.; Watanabe, Y.; Tahara, T.; Hasegawa, K. *Novel Hexatriene- -Carbonyl Compound.* EP2128124 (A1), **2009**.
(256) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129–6137.

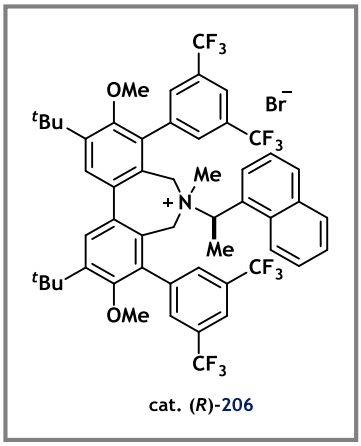
7. APPENDICES

7.1 Appendix I – Full Optimization with the Lygo Catalyst (*R*)-206

7.1.1 Base Screen with Substrate 162



162 219

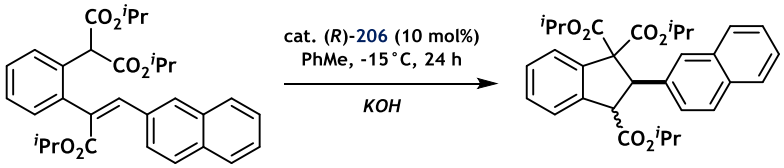


Entry	**Base**[i,ii]	**dr**[iii]	**ee**[iv]
1	$CsOH{\cdot}H_2O$ (s)	3.4 : 1.0	42%
2	NaOH (s)	1.0 : 2.7	62%
3	NaOH (s)[v]	SM	–
4	NaOH (50% aq.)[vi]	2.0 : 1.0	73%
5	KOH (s)	1.6 : 1.0	64%
6	$LiOH{\cdot}H_2O$ (s)	SM	–
7	$Ba(OH)_2{\cdot}8H_2O$ (s)	SM	–
8	K_2HPO_4 (s)[v]	SM	–
9	K_3PO_4 (s)[v]	SM[vii]	–
10	NaOMe (s) (old bottle)	1.0 : 6.8	75% ee
11	NaOMe (s) (freshly prepared)[viii]	1.0 : 3.6[ix]	56% ee
12	KOMe (s)[v]	SM[vii]	–

13	NaO^{t}Bu (s)	SM	–
14	KO^{t}Bu (s)	SM[vii]	–
15	NaHMDS (s)	1.6 : 1.0	40%
16	KHMDS (s)	SM	–
17	NaH (s)[v]	SM	–
18	BEMP (l)[x]	SM	–
19	BEMP (l)[v]	1.0 : 8.1[xi]	62% ee

*[i] All reactions were carried out on analytical scale without determining the reaction yield [ii] Unless otherwise stated, reactions were conducted with catalyst (R)-**206** (10 mol%) and the specified base (2 eq.) in PhMe for 24 h at –15 °C. [iii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] 1 equivalent of base was used. [vi] 10 equivalents of base were used. [vii] Trace product observed by analysis of the crude ^{1}H NMR spectrum. [viii] 0.5 equivalents of base were used. [ix] Reaction conversion was 83% by analysis of the crude ^{1}H NMR spectrum (no internal standard was added). [x] 0.1 equivalents of base were used. [xi] Reaction conversion was 72% by analysis of the crude ^{1}H NMR spectrum (no internal standard was added).*

7.1.2 *Adjusting the Equivalents of KOH with Substrate 162*

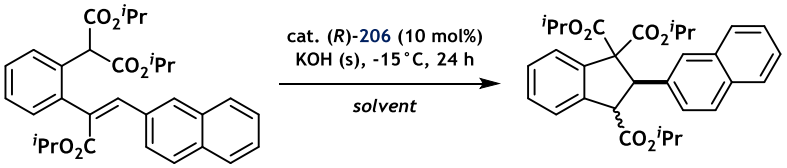


162 219

Entry	Equivalents of KOH[i,ii]	dr[iii]	ee[iv]
1	2.0 (s)[v,vi]	4.0 : 1.0	65%
2	2.0 (s)	1.6 : 1.0	64%
3	5.0 (s)[v]	3.0 : 1.0	65%
4	1.0 (s)	2.2 : 1.0	69%
5	0.5 (s)	1.0 : 3.5	73%
6	2.0 (50% aq.)	3.2 : 1.0	70%
7	10 (50% aq.)	3.8 : 1.0	71%
8	2.0 (s)[vii]	2.0 : 1.0	50%

*[i] All reactions were carried out on analytical scale without determining the reaction yield [ii] Unless otherwise stated, reactions were conducted with catalyst (R)-**206** (10 mol%) and KOH in PhMe for 24 h at –15 °C. [iii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] Reaction was complete in 3 h by TLC. [vi] Reaction was conducted at RT. [vii] 4 Å molecular sieves were added.*

7.1.3 *Solvent Screen with KOH (s) and Substrate 162*

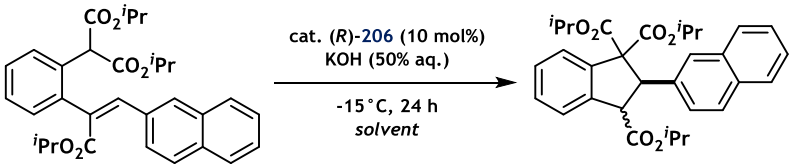


162 219

Entry	**Solvent**[i,ii]	**dr**[iii]	**ee**[iv]
1	PhMe	2.2 : 1.0	69%
2	benzene[v]	1.0 : 1.3	67%
3	*p*-xylene[v]	1.2 : 1.0	76%
4	chlorobenzene	1.0 : 5.4	67%
5	PhMe : $CHCl_3$ (9 : 1)	1.5 : 1.0	69%
6	PhMe : hexane (9 : 1)	2.4 : 1.0	73%
7	hexane	SM	–

*[i] All reactions were carried out on analytical scale without determining the reaction yield [ii] Unless otherwise stated, reactions were conducted with catalyst (R)-***206** *(10 mol%) and KOH (s) (1 eq.) in the specified solvent for 24 h at −15 °C. [iii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] Reaction was conducted at RT.*

7.1.4 *Solvent Screen with KOH (50% aq.) and Substrate 162*

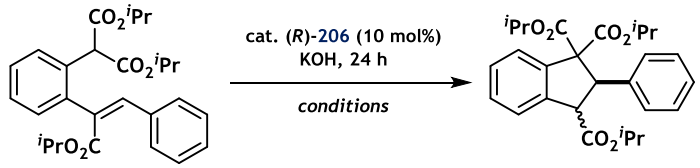


162 219

Entry	**Solvent**[i,ii]	**dr**[iii]	**ee**[iv]
1	PhMe	3.8 : 1.0	71%
2	*m*-xylene	3.4 : 1.0	52%
3	MTBE	5.6 : 1.0	70%
4	$^{i}Pr_2O$	7.9 : 1.0	75%
5	PhMe : hexane (1 : 1)	5.6 : 1.0	76%
6	CH_2Cl_2 : hexane (1 : 1)	3.2 : 1.0	45%
7	hexane[v]	1.7 : 1.0	79%

*[i] All reactions were carried out on analytical scale without determining the reaction yield [ii] Unless otherwise stated, reactions were conducted with catalyst (R)-**206** (10 mol%) and KOH (50% aq.) (10 eq.) in the specified solvent for 24 h at −15 °C. [iii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] Reaction conversion was 73% by analysis of the crude ^{1}H NMR spectrum (no internal standard was added).*

7.1.5 *Solvent Screen with KOH and Substrate 164*

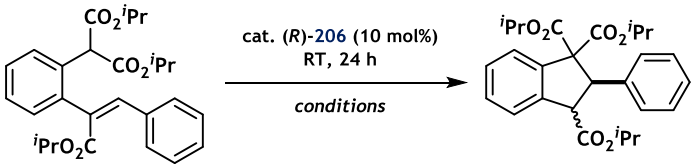


164 173

Entry	**Conditions**[i,ii]	**dr**[iii]	**ee**[iv]
1	KOH (s), PhMe, RT	1.0 : 2.8	67%
2	KOH (s), Et_2O, RT	1.0 : 1.3	65%
3	KOH (25% aq.),[v] PhMe, RT	1.0 : 3.0	70%
4	KOH (25% aq.), chlorobenzene, −15 °C	1.0 : 6.3	64%
5	KOH (25% aq.), chlorobenzene : hexane (1 : 1), −15 °C	1.0 : 6.9	74%
6	KOH (50% aq.),[vi] chlorobenzene, −15 °C	2.0 : 1.0	56%
7	KOH (50% aq.),[v] PhMe : hexane (1 : 1), −15 °C	1.0 : 2.6	78%
8	KOH (50% aq.),[vi] $^iPr_2O$, −15 °C	1.0 : 1.0	79%
9	KOH (50% aq.),[vi] $^iPr_2O$: hexane (1 : 1), −15 °C	2.1 : 1.0	80%
10	KOH (50% aq.),[vii] $^iPr_2O$: hexane (1 : 1), −15 °C	1.3 : 1.0	75%
11	KOH (25% aq.), PhMe, −30 °C	SM	–
12	KOH (25% aq.), $^iPr_2O$, −30 °C	1.0 : 3.2	79%
13	KOH (25% aq.), 18-crown-6 (10 mol%), PhMe, −30 °C	SM	–

*[i] All reactions were carried out on analytical scale without determining the reaction yield [ii] Unless otherwise stated, reactions were conducted with catalyst (R)-***206** *(10 mol%) and the specified base (0.5 eq.) in the given solvent for 24 h at the provided temperature. [iii] Determined by analysis of the crude ^1H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] 2 equivalents of base were used. [vi] 10 equivalents of base were used. [vii] 5 equivalents of base were used.*

7.1.6 *Screen of Carbonate Bases with Substrate 164*

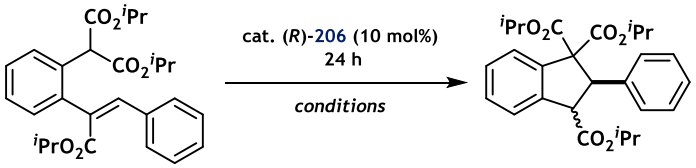


164 173

Entry	**Conditions**[i,ii]	**dr**[iii]	**ee**[iv]
1	K_2CO_3 (s), PhMe	SM[v]	–
2	K_2CO_3 (40% aq.),[vi] PhMe	1.0 : 1.2	68%
3	K_2CO_3 (s), Et_2O	1.0 : 3.5	72%
4	Cs_2CO_3 (s), PhMe	1.0 : 2.6	69%
5	Cs_2CO_3 (s), chlorobenzene	1.0 : 3.4	61%
6	Cs_2CO_3 (s), fluorobenzene	1.0 : 3.5	58%
7	Cs_2CO_3 (s), MTBE	1.0 : 1.7	75%
8	Cs_2CO_3 (s), $^iPr_2O$	1.0 : 1.5	71%
9	Cs_2CO_3 (s), Et_2O	1.0 : 2.5	76%
10	Cs_2CO_3 (s), Et_2O[vii]	1.0 : 1.9	71%
11	Cs_2CO_3 (s), Et_2O[viii]	SM	–
12	Cs_2CO_3 (s), Et_2O : hexane (1 : 1)	1.0 : 2.5	80%
13	Cs_2CO_3 (s),[ix] Et_2O : hexane (1 : 1)	1.0 : 2.8	76%
14	Cs_2CO_3 (10% aq.), Et_2O : hexane (1 : 1)	1.0 : 3.6	76%
15	Cs_2CO_3 (70% aq.),[x] Et_2O : hexane (1 : 1)	1.0 : 3.2	76%
16	Cs_2CO_3 (70% aq.),[xi] Et_2O : hexane (1 : 1)	1.0 : 1.9	78%

*[i] All reactions were carried out on analytical scale without determining the reaction yield [ii] Unless otherwise stated, reactions were conducted with catalyst (R)-***206** *(10 mol%) and the specified base (0.5 eq.) in the given solvent for 24 h at RT. [iii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] Trace product observed by analysis of the crude ^{1}H NMR spectrum. [vi] 10 equivalents of base were used. [vii] Reaction was conducted at −15 °C. [viii] Reaction was conducted at −30 °C. [ix] 0.1 equivalents of base were used. [x] 2 equivalents of base were used. [xi] 5 equivalents of base were used.*

7.1.7 *Screen of Phenolic and Fluoride Bases with Substrate 164*

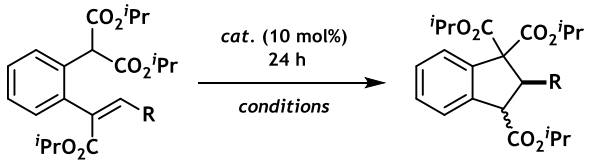


164 173

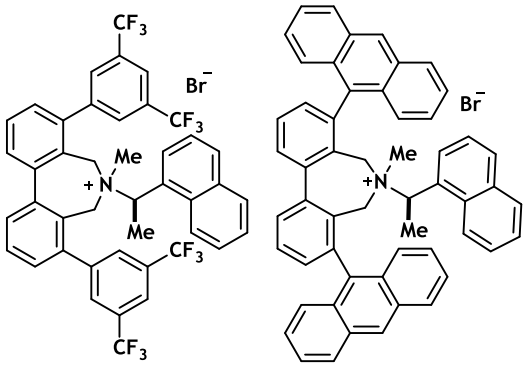
Entry	**Conditions**[i,ii]	**dr**[iii]	**ee**[iv]
1	KOH (s), mesitol (10 mol%), PhMe, −15 °C	1.5 : 1.0	38%
2	KOH (s), mesitol (10 mol%), CH_2Cl_2, −15 °C	1.0 : 3.6	43%
3	KOH (s), mesitol (10 mol%), CH_2Cl_2, −78 °C	SM	–
4	KOPh (s),[v] PhMe, RT	1.3 : 1.0	60%
5	KOPh (s),[v] $^iPr_2O$, RT	3.0 : 1.0	71%
6	KOPh (s),[vi] $^iPr_2O$, RT	1.0 : 2.3	70%
7	CsF (s),[vii] PhMe, RT	1.0 : 2.4	65%
8	CsF (s),[vii] $^iPr_2O$, RT	1.0 : 1.5	62%

*[i] All reactions were carried out on analytical scale without determining the reaction yield [ii] Unless otherwise stated, reactions were conducted with catalyst (R)-**206** (10 mol%) and the specified base (2 eq.) in the given solvent for 24 h at the provided temperature. [iii] Determined by analysis of the crude ^1H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] 1 equivalent of base was used. [vi] 0.1 equivalents of base were used. [vii] 0.5 equivalents of base were used.*

7.2 Appendix II – Full Evaluation of Moira (*R*)-243 and Agnes (*R*)-245



Ph 164 173
p-OMe-C_6H_4 177 220

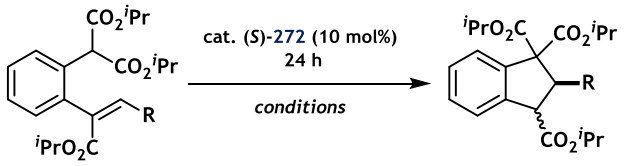


Moira (*R*)-243 Agnes (*R*)-245

Entry	R	Conditions[i,ii]	dr[iii]	ee[iv]
1	*p*-OMe-C_6H_4	Moira (*R*)-**243**, KOH (50% aq.), PhMe, −15 °C	2.3 : 1.0	62%
2	*p*-OMe-C_6H_4	Moira (*R*)-**243**, KOH (s),[v] PhMe, −30 °C	1.0 : 2.6	50%
3	Ph	Moira (*R*)-**243**, K_2CO_3 (40% aq.), PhMe, RT[vi]	1.0 : 3.0	55%
4	*p*-OMe-C_6H_4	Agnes (*R*)-**245**, KOH (50% aq.), PhMe, −15 °C	2.2 : 1.0	5%
5	*p*-OMe-C_6H_4	Agnes (*R*)-**245**, KOH (50% aq.), $^iPr_2O$, −15 °C	SM[vii]	–
6	Ph	Agnes (*R*)-**245**, K_2CO_3 (40% aq.), PhMe, RT[vi]	1.0 : 1.6	4%

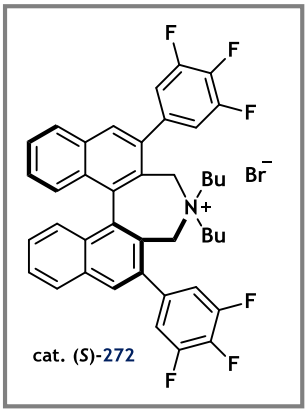
[i] All reactions were carried out on analytical scale without determining the reaction yield [ii] Unless otherwise stated, reactions were conducted with the listed catalyst (10 mol%) and the specified base (10 eq.) in the given solvent for 24 h at the provided temperature. [iii] Determined by analysis of the crude ^{1}H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] 5 equivalents of base were used. [vi] Reaction time was 48 hours. [vii] Trace product observed by analysis of the crude ^{1}H NMR spectrum.

7.3 Appendix III – Full Evaluation of Maruoka (*S*)-272



2-Naphthyl	162
Ph	164
p-OMe-C_6H_4	177

219
173
220



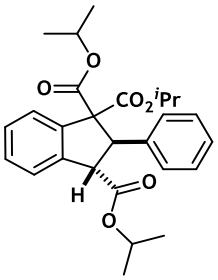
Entry	R	Conditions[i,ii]	dr[iii]	ee[iv]
1	*p*-OMe-C_6H_4	KOH (50% aq.), PhMe, −15 °C	1.0 : 3.5	32%
2	2-Naphthyl	KOH (50% aq.), PhMe, −15 °C	1.0 : 2.5	63%
3	Ph	K_2CO_3 (40% aq.), PhMe, RT	1.0 : 3.5	73%
4	Ph	Cs_2CO_3 (s),[v] Et_2O, RT	1.0 : 2.1	58%
5	*p*-OMe-C_6H_4	Cs_2CO_3 (s),[v] Et_2O, RT	1.0 : 1.9	63%
6[†]	*p*-OMe-C_6H_4	CsOH·H_2O (s),[vi] PhMe, −15 °C	2.5 : 1.0	48%
7[†]	Ph	CsOH·H_2O (s),[vi] PhMe, −15 °C	2.5 : 1.0	60%
8[†]	2-Naphthyl	CsOH·H_2O (s),[vi] PhMe, −15 °C	3.5 : 1.0	51%

*[i] All reactions were carried out on analytical scale without determining the reaction yield [ii] Unless otherwise stated, reactions were conducted with catalyst (S)-***272** *(10 mol%) and the specified base (10 eq.) in the given solvent for 24 h at the provided temperature. [iii] Determined by analysis of the crude* ^{1}*H NMR spectrum; reported as anti : syn. [iv] ee for major diastereomer as determined by chiral HPLC. [v] 0.5 equivalents of base were used. [vi] 2 equivalents of base were used.*

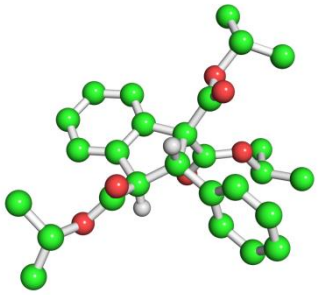
[†] *These results were obtained by Dr Abhishek Kothari and are included for completeness.*[61]

7.4 Appendix IV – X-ray Crystallography Data

anti-Triisopropyl 2-phenyl-2,3-dihydro-1_H_-indene-1,1,3-tricarboxylate (173)



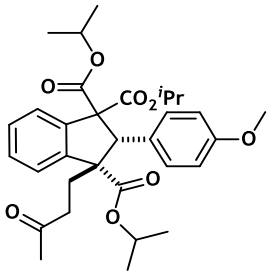
anti

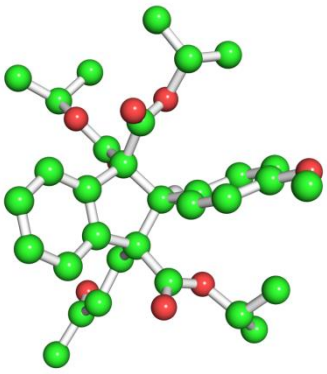


Key data and refinement for the crystal structure of compound _anti_-173	
CCDC	943254
Identification code	001RWD12
Empirical formula	$C_{27}H_{32}O_6$
Formula weight	452.55
Temperature	150 K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P\ 2_1\ 2_1\ 2_1$
Unit cell dimensions	a = 10.18910(10) Å α = 90°
	b = 14.2193(2) Å β = 90°
	c = 17.2171(2) Å γ = 90°
Volume	2494.45(5) $Å^3$
Z	4
Density (calculated)	1.205 Mg/m^3
Absorption coefficient	0.084 mm^{-1}
F (000)	968

Crystal size	0.20 × 0.20 × 0.20 mm^3
Theta range for data collection	5.339° to 27.478°
Index ranges	−13<=h<=13, −18<=k<=18, −22<=l<=22
Reflections collected	40108
Independent reflections	3184 [R(int) = 0. 011]
Completeness to theta = 27.478°	98.9%
Max. and min. transmission	0.98 and 0.98
Refinement method	Full-matrix least-squared on F^2
Data/restraints/parameters	3184 / 0 / 298
Goodness-of-fit on F^2	0.9286
Final R indices [I>2sigma(I)]	R1 = 0.0319, wR2 = 0.0740
R indices (all data)	R1 = 0.0358, wR2 = 0.0792
Largest diff. peak and hole	0.14 and −0.17 e.$Å^{-3}$

Triisopropyl 2-(4-methoxyphenyl)-3-(3-oxobutyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (305)

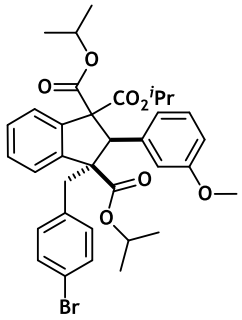


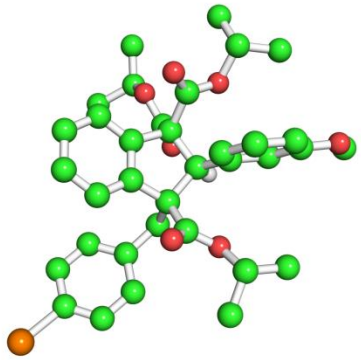


Key data and refinement for the crystal structure of compound 305	
CCDC	943255
Identification code	033RWD13
Empirical formula	$C_{32}H_{40}O_8$
Formula weight	552.66
Temperature	150 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*P* 1 2_1 1
Unit cell dimensions	a = 12.27450(10) Å α = 90°
	b = 17.2889(2) Å β = 100.2480(5)°
	c = 14.5037(2) Å γ = 90°
Volume	3028.77(6) $Å^3$
Z	4
Density (calculated)	1.212 Mg/m^3
Absorption coefficient	0.086 mm^{-1}
F (000)	1184

Crystal size	0.52 × 0.42 × 0.30 mm^3
Theta range for data collection	5.127° to 27.512°
Index ranges	−15<=h<=15, −22<=k<=22, −18<=l<=18
Reflections collected	13635
Independent reflections	13635 [R(int) = 0. 000]
Completeness to theta = 27.512°	99.0%
Max. and min. transmission	0.97 and 0.96
Refinement method	Full-matrix least-squared on F^2
Data/restraints/parameters	13635 / 1 / 721
Goodness-of-fit on F^2	0.9120
Final R indices [I>2sigma(I)]	R1 = 0.0399, wR2 = 0.0908
R indices (all data)	R1 = 0.0481, wR2 = 0.0987
Largest diff. peak and hole	0.31 and −0.29 e.$Å^{-3}$

Triisopropyl 3-(4-bromobenzyl)-2-(3-methoxyphenyl)-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (304)



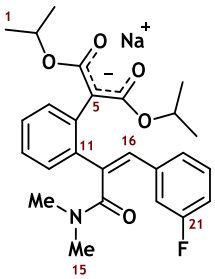


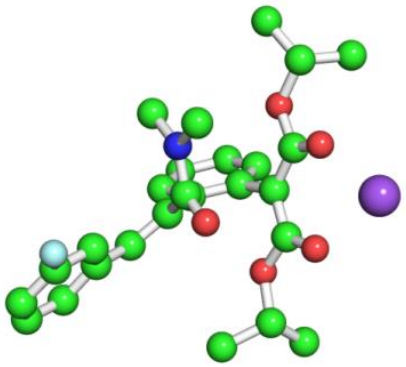
Key data and refinement for the crystal structure of compound 304

CCDC	943256	
Identification code	083RWD13	
Empirical formula	$C_{35}H_{39}BrO_7$	
Formula weight	651.59	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	*C* 2 / *c*	
Unit cell dimensions	a = 18.7049(3) Å	α = 90°
	b = 11.8319(2) Å	β = 93.1834(12)°
	c = 29.3647(4) Å	γ = 90°
Volume	6488.81(18) $Å^3$	
Z	8	
Density (calculated)	1.334 Mg/m^3	
Absorption coefficient	2.108 mm^{-1}	
F (000)	2720	

Crystal size	$0.30 \times 0.10 \times 0.10\ mm^3$
Theta range for data collection	3.014° to 76.507°
Index ranges	−23<=h<=23, −14<=k<=14, −36<=l<=36
Reflections collected	293436
Independent reflections	13063 [R(int) = 0. 041]
Completeness to theta = 76.507°	99.5%
Max. and min. transmission	0.87 and 0.57
Refinement method	Full-matrix least-squared on F^2
Data/restraints/parameters	13018 / 0 / 388
Goodness-of-fit on F^2	0.9941
Final R indices [I>2sigma(I)]	R1 = 0.0494, wR2 = 0.1271
R indices (all data)	R1 = 0.0511, wR2 = 0.1290
Largest diff. peak and hole	1.04 and −0.79 e.$Å^{-3}$

Isopropyl (*E*)-2-(2-((*Z*)-3-(dimethylamino)-1-(3-fluorophenyl)-3-oxoprop-1-en-2-yl)phenyl)-3-hydroxy-3-isopropoxyacrylate, sodium salt (387)



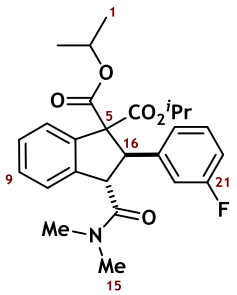


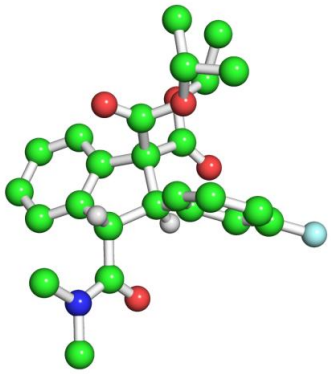
Key data and refinement for the crystal structure of compound 387

Identification code	053RWD12	
Empirical formula	$C_{26}H_{29}FNNaO_5$	
Formula weight	477.51	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	*P* −1	
Unit cell dimensions	a = 13.9445(5) Å	α = 87.160(2)°
	b = 17.3881(4) Å	β = 74.771(3)°
	c = 23.8317(7) Å	γ = 87.363(2)°
Volume	5565.4(3) $Å^3$	
Z	9	
Density (calculated)	1.224 Mg/m^3	
Absorption coefficient	0.866 mm^{-1}	
F (000)	2170	
Crystal size	0.10 × 0.10 × 0.05 mm^3	

Theta range for data collection	3.131° to 58.613°
Index ranges	−14<=h<=12, −15<=k<=18, −25<=l<=24
Reflections collected	34567
Independent reflections	11971 [R(int) = 0. 017]
Completeness to theta = 58.613°	99.6%
Max. and min. transmission	1.00 and 1.00
Refinement method	Full-matrix least-squared on F^2
Data/restraints/parameters	11877 / 0 / 1333
Goodness-of-fit on F^2	0.9389
Final R indices [I>2sigma(I)]	R1 = 0.0540, wR2 = 0.1275
R indices (all data)	R1 = 0.0601, wR2 = 0.1353
Largest diff. peak and hole	0.89 and −0.49 e.$Å^{-3}$

Diisopropyl 3-(dimethylcarbamoyl)-2-(3-fluorophenyl)-2,3-dihydro-1*H*-indene-1,1-dicarboxylate (298)





Key data and refinement for the crystal structure of compound 298	
Identification code	087RWD13
Empirical formula	$C_{26}H_{30}FNO_5$
Formula weight	455.53
Temperature	150 K
Wavelength	0.68890 Å
Crystal system	Monoclinic
Space group	*P* 2_1
Unit cell dimensions	a = 9.2291(3) Å α = 90°
	b = 21.8610(5) Å β = 100.068(3)°
	c = 1802558(6) Å γ = 90°
Volume	3626.52(19) $Å^3$
Z	4
Density (calculated)	1.254 Mg/m^3
Absorption coefficient	0.092 mm^{-1}
F (000)	1456
Crystal size	0.05 × 0.10 × 0.10 mm^3

Theta range for data collection	2.196° to 28.004°
Index ranges	−12<=h<=12, −28<=k<=27, −24<=l<=24
Reflections collected	51242
Independent reflections	8822 [R(int) = 0. 092]
Completeness to theta = 28.004°	95.7%
Max. and min. transmission	1.00 and 0.64
Refinement method	Full-matrix least-squared on F^2
Data/restraints/parameters	8790 / 1 / 893
Goodness-of-fit on F^2	0.9355
Final R indices [I>2sigma(I)]	R1 = 0.0580, wR2 = 0.1123
R indices (all data)	R1 = 0.0819, wR2 = 0.1257
Largest diff. peak and hole	0.80 and −0.57 e.$Å^{-3}$

7.5 Appendix V – Crystallographic Information Files (.cif)

The crystallographic information files (.cif) for all of the X-ray structures provided in this thesis can be found in the attached CD.