

Synthesis of Acyl Cyclohexenes *via* an Aluminium Mediated 1,5-Hydride Shift–Aldol Cascade



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Dedication

I would like to dedicate this thesis to the memory of my grandfather, who inspired my love of chemistry and whose example continues to guide me.

Declaration

The work described in this thesis is entirely my own, except where otherwise acknowledged, and has not been submitted previously for any other degree at this or any other university.

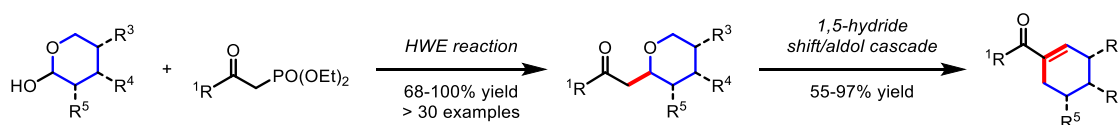
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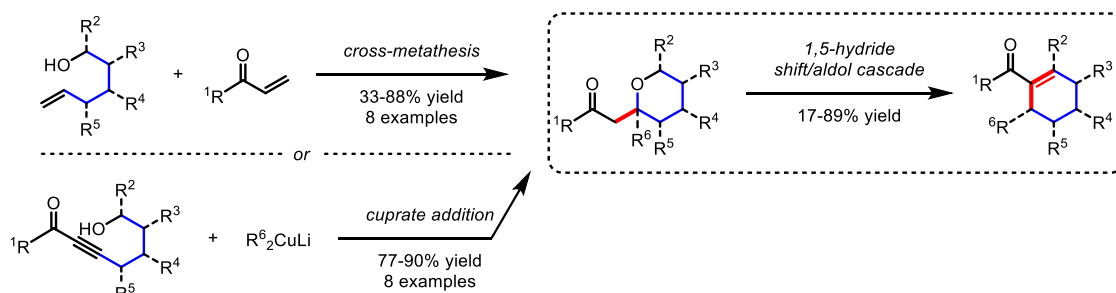
Abstract

Cyclohexenes and their derivatives are important intermediates in the preparation of natural products and medically relevant compounds. Many methodologies have been reported for the synthesis of such materials, including Diels–Alder cycloaddition, ring-closing metathesis and catalytic cyclotrimerisation. Recently, the Donohoe group has developed a new approach to the synthesis of cyclohexenes from readily accessible pyrans. This method employs inexpensive aluminium reagents to promote a 1,5-hydride shift–aldol cascade. By combining Horner–Wadsworth–Emmons (HWE) olefination with the aluminium-mediated 1,5-hydride shift developed, it was possible to selectively functionalise three of the five positions around the acyl cyclohexene core (**Scheme I**).



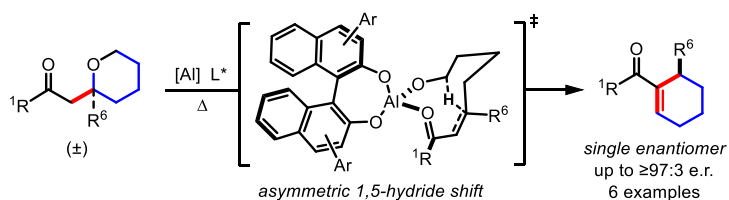
Scheme I Synthesis of cyclohexenes via HWE olefination followed by aluminium-mediated 1,5-hydride shift.

In this thesis, alternative strategies, including cross metathesis and cuprate addition were developed in **Chapter 2** to construct the intermediate tetrahydropyrans, thereby enabling functionalisation of all five positions around the acyl cyclohexene framework (**Scheme II**). To gain insight into the reaction mechanism of the aluminium-catalysed 1,5-hydride shift, detailed computational studies supported by experimental validation were conducted in **Chapter 3** to identify the nature of the active catalytic species and to determine the corresponding reaction pathway.



Scheme II Synthesis of cyclohexenes via cross-metathesis or cuprate addition followed by aluminium-mediated 1,5-hydride shift.

An asymmetric variant of the 1,5-hydride shift–aldol cascade was developed in **Chapter 4**, allowing the synthesis of enantioenriched cyclohexenes from racemic tetrahydropyran substrates in the presence of a chiral BINOL-derived ligand (**Scheme III**). Future directions include the single-step removal of the Ph* protecting group to afford a variety of carboxylic acid derivatives and the application of this transformation in natural product synthesis.



Scheme III An asymmetric variant of the aluminium-mediated 1,5-hydride shift–aldol cascade.

Acknowledgements

Firstly, I would like to thank Professor Tim Donohoe for giving me the opportunity to work as part of his research group. His supervision, guidance, and encouragement throughout this project have been invaluable. His office door has always been open for discussion, regardless of whether the results were good or bad, and I am deeply grateful for the insight and support he has so generously provided.

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A special thank you goes to Teddy and Andrew, who kindly took the time to proofread this thesis. I am very grateful for the time and effort they set aside to read and correct it – and for pointing out that my complaint about Doug Discovery sending us the wrong chemical probably shouldn't make the final version.

Thank you to all members of the Donohoe Group, past and present – they have all been a pleasure to work with. Thank you to Dana for being such a helpful and funny lab neighbour, despite the occasional out-of-nowhere swearing at her experiments. Thank you to Jess for always being so kind and talkative – even if it did mean hearing the same story six times. Thank you to Teddy for being such a great Part II student; supervising him has been a pleasure. Thank you to Andrew for troubleshooting the HPLC with me – which, most of the time, involved searching through a manual of more than a hundred pages for a solution. Thank you also to Tim Jenkins – the daily crossword sessions have definitely improved my vocabulary.

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Finally, I would like to thank my family – Mum, Dad and Yechen. The final year of my DPhil has been a challenging time for all of us, and I am deeply grateful for their love, understanding, constant support. Thank you for always telling me I'm the best when I doubted myself, and for believing in me even when I didn't. Lastly, I would like to thank my grandfather. I am grateful for everything he taught me; his love and wisdom continue to inspire me, and his memory will forever remain in my heart.

Table of Contents

Dedication	iii
Declaration	iv
Abstract	v
Acknowledgements	vii
Table of Contents	ix
Abbreviations	xi
Chapter 1: Introduction	1
1.1 Importance of Cyclohexenes	1
1.2 Preparation of Cyclohexenes	2
1.3 C–H Functionalisation	9
1.4 Overview of 1,5-Hydride Shifts in Organic Synthesis	11
1.5 Aluminium-Based Catalysis	14
1.6 Project Aims	16
Chapter 2: Synthesis of Acyl Cyclohexenes <i>via</i> an Aluminium Mediated 1,5-Hydride Shift–Aldol Cascade	18
2.1 Introduction and Preliminary Results	18
2.2 Metathesis Approach	19
2.2.1 Optimisation	19
2.2.2 Substrate Scope	21
2.3 Cuprate Addition Approach	32
2.4 Conclusion	35
Chapter 3: Mechanistic Investigations	37
3.1 Introduction	37
3.2 Computational Modelling Using Density Functional Theory	38
3.3 Reaction Kinetics	42
3.4 Constrained Model System	53
3.5 Double Label Crossover Experiment	55
3.6 Conclusion	58
Chapter 4: Asymmetric Hydride Shift Methodology	60
4.1 Introduction and Preliminary Results	60
4.2 Reaction Optimisation	62
4.2.1 TADDOL Derivatives	62
4.2.2 BINOL Derivatives	65
4.2.3 Catalytic Aluminium Species in the Hydride Shift	71

4.2.4 Synthesis of Ph* Substrate	75
4.2.5 Reproducibility Challenges at Low Catalyst Loading	83
4.3 Substrate Scope	84
4.4 Mechanistic Discussion	89
4.5 Conclusion and Future Work	91
Chapter 5: Experimental Section	93
5.1 General information	93
5.2 General Procedures	95
General Procedure 1 – Synthesis of Hydroalkenes by Grignard Addition	95
General Procedure 2 – Synthesis of Tetrahydropyrans by Cross Metathesis	95
General Procedure 3 – Synthesis of Weinreb Amides	96
General Procedure 4 – Synthesis of Ynones	96
General Procedure 5 – Synthesis of Cyclohexenes by Aluminium Catalysed 1,5-Hydride Shift	96
General Procedure 6 – Asymmetric Synthesis of Cyclohexenes by Aluminium Catalysed 1,5-Hydride Shift	97
5.3 Synthesis of Starting Materials	97
5.3.1 Synthesis of Cross Metathesis Precursors	97
5.3.2 Synthesis of Cuprate Addition Precursors	109
5.3.3 Miscellaneous	114
5.4 Synthesis of Diol Ligands	127
5.5 Synthesis of Tetrahydropyrans	132
5.6 Synthesis of Cyclohexenes	152
Chapter 6: References	172
Chapter 7: Appendices	178
7.1 ReactIR Experiments	178
7.2 ¹ H NMR Experiments	223
7.3 Mathematical Derivation of Aluminium Rate Orders	231
7.4 Double Label Crossover Experiment	233
7.5 Single Crystal X-Ray Structure Data	237

Abbreviations

δ	chemical shift
Δ	heat
ν	IR stretching frequency
Ac	acetyl
[Al]	aluminium species
Ar	aryl or denotes reaction under argon
ax	axial
BINOL	1,1'-bi-2-naphthol
br.	broad
<i>n</i> -Bu	<i>normal</i> -butyl
<i>t</i> -Bu	<i>tert</i> -butyl
°C	degree(s) Celcius
cataCXium® A	di(1-adamantyl)- <i>n</i> -butylphosphine
COD	1,5-cyclooctadiene
COSY	Correlation spectroscopy
Cp*	pentamethylcyclopentadienyl
d	doublet
DIBAL-H	diisobutylaluminium hydride
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
e.e.	enantiomeric excess
eq	equatorial
equiv.	equivalents

e.r.	enantiomeric ratio
ESI	Electrospray ionisation
Et	ethyl
EWG	electron-withdrawing group
g	gram(s)
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMBC	Heteronuclear multiple bond correlation
HPLC	High-performance liquid chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
<i>in situ</i>	In place (Latin)
<i>in vacuo</i>	In a vacuum (Latin)
IR	Infra-red spectroscopy
<i>J</i>	coupling constant (Hz)
LDA	lithium diisopropylamide
<i>m</i>	<i>meta-</i>
m	multiplet
M	molar (mol dm ⁻³)
Me	methyl
mg	milligram(s)
min	minute(s)
mL	millilitre(s)
mol	mole(s)

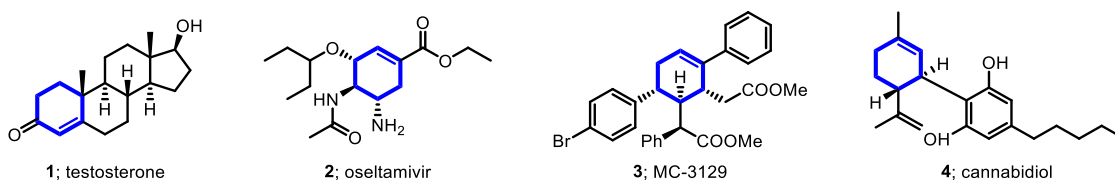
mol%	molar percentage
m.p.	melting point
m/z	mass to charge ratio
NMR	Nuclear Magnetic Resonance
nOe	nuclear Overhauser effect
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
Ph	phenyl
Ph*	pentamethylphenyl
ppm	part(s) per million
PPTS	pyridinium p-toluenesulfonate
<i>i</i>-Pr	<i>iso</i> -propyl
q	quartet
R	generic substituent
r.r.	regioisomeric ratio
RT	room temperature
s	second(s) or singlet
sat.	saturated
T	temperature
TADDOL	$\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	Thin-layer chromatography
t_r	retention time
Ts	tosyl

UV	ultraviolet
<i>via</i>	by way of (Latin)
w/v%	weight for volume percent
wt%	weight for weight percent
X	generic halide

Chapter 1: Introduction

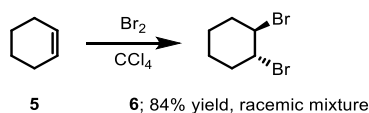
1.1 Importance of Cyclohexenes

Cyclohexenes represent a fundamentally important class of structural motifs in organic chemistry, valued for their versatility, reactivity and prevalence in both natural and synthetic compounds. As synthetic building blocks, cyclohexene derivatives play a crucial role in the construction of a wide range of biologically active molecules. Notably, they serve as key intermediates in the synthesis of pharmaceutically relevant compounds, including the steroid hormone testosterone **1**^[1], the antiviral agent oseltamivir **2**^[2], the antileukaemic agent MC-3129 **3**^[3] and the anticonvulsant cannabidiol **4**^[4] (**Scheme 1.1**).



Scheme 1.1 Selected examples of biologically active compounds containing a cyclohexenyl motif.

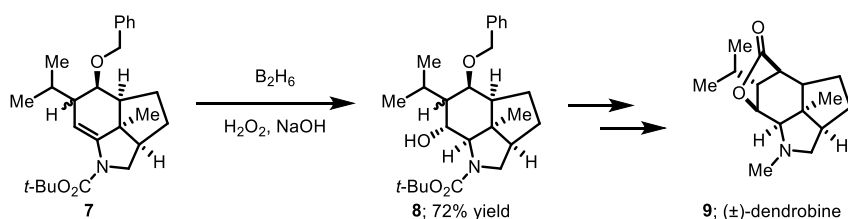
The presence of a carbon–carbon double bond within the six-membered ring of cyclohexenes makes them highly reactive towards electrophilic addition reactions. This reactivity is of particular significance in synthetic organic chemistry, as it enables the transformation of cyclohexenes into a wide variety of functionalised compounds. For example, cyclohexene **5** can be easily converted into vicinal dibromocyclohexane **6** upon treatment with molecular bromine (**Scheme 1.2**). This transformation proceeds *via* the formation of a three-membered bromonium ion intermediate,^[5] which enforces anti addition across the double bond, resulting in the two bromine atoms being installed on opposite faces of the ring.



Scheme 1.2 Bromination of cyclohexene **5**.

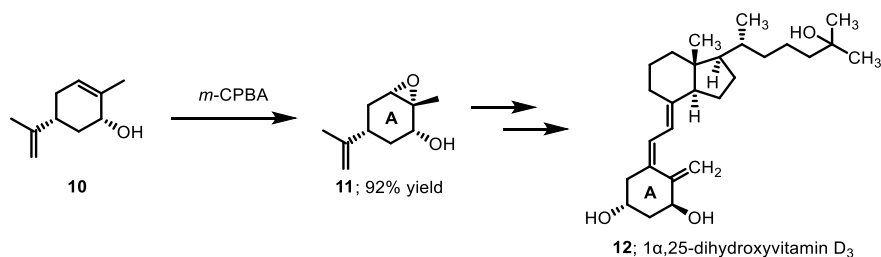
Similarly, hydroboration–oxidation enables the regioselective conversion of cyclohexene derivatives to cyclohexanols *via* the anti-Markovnikov addition of water across the double bond. This transformation was employed by Padwa and co-workers in their formal synthesis of (±)-

dendrobine **9**, an alkaloid originally isolated from the *Dendrobium* genus of orchids, particularly *Dendrobium nobile* (**Scheme 1.3**).^[6]



Scheme 1.3 Formal synthesis of (±)-dendrobine **9** via hydroboration–oxidation of cyclohexene derivative **7**.

Another noteworthy transformation is the Prilezhaev reaction, which involves the epoxidation of alkenes using peracids such as *meta*-chloroperbenzoic acid (*m*-CPBA). In 2010, Chen and Ju applied this reaction in the enantioselective synthesis of a key A-ring intermediate for the preparation of 1 α ,25-dihydroxyvitamin D₃ **12**,^[7] the hormonally active form of vitamin D₃ (**Scheme 1.4**). 1 α ,25-dihydroxyvitamin D₃ serves as a crucial immunoregulatory molecule that helps prevent the development of autoimmune diseases, including inflammatory bowel disease.^[8]

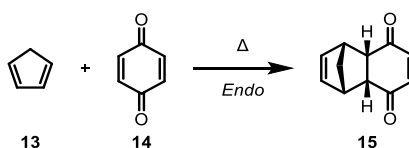


Scheme 1.4 Epoxidation of cyclohexene derivative **10** in the enantioselective synthesis of key A-ring intermediate **11** towards 1 α ,25-dihydroxyvitamin D₃ **12**.

1.2 Preparation of Cyclohexenes

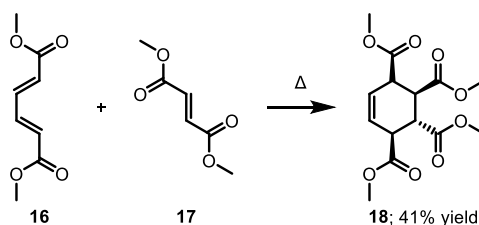
Several synthetic strategies have been developed for the preparation of functionalised cyclohexenes, each offering distinct advantages depending on the desired substitution pattern and functional group compatibility. Among these, the Diels–Alder cycloaddition reaction remains the most powerful and widely employed method for constructing the cyclohexene core (**Scheme 1.5**). First reported by Otto Diels and Kurt Alder in 1928,^[9] this pericyclic transformation represents a seminal advance in organic synthesis and was subsequently recognised with the Nobel Prize in Chemistry in 1950. The reaction proceeds *via* a concerted [4+2] cycloaddition

between a conjugated diene **13** and an electron-deficient alkene **14** or alkyne (dienophile), resulting in the formation of a six-membered ring **15**.



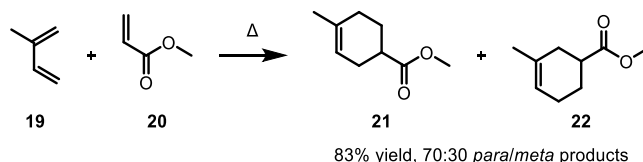
Scheme 1.5 The Diels–Alder cycloaddition between diene **13** and dienophile **14** to form cyclohexene ring **15**, as originally described by Otto Diels and Kurt Alder in 1928.

Despite its broad utility and historical significance, the Diels–Alder reaction is not without limitations. A primary constraint arises from the electronic requirements of the reacting partners: optimal reactivity generally requires pairing an electron-rich diene with an electron-deficient dienophile. When these conditions are not met, the reaction often proceeds sluggishly or affords low yields. For example, the cycloaddition of the electron-deficient diene (2*E*, 4*E*)-dimethyl hexa-2,4-dienedioate **16** with the electron-deficient dienophile dimethyl fumarate **17** required heating at 170 °C for 10 h, affording the corresponding adduct **18** in a modest 41% yield (**Scheme 1.6**).^[10] This example highlights the significant kinetic barrier arising from poor orbital alignment between similarly electron-deficient partners.



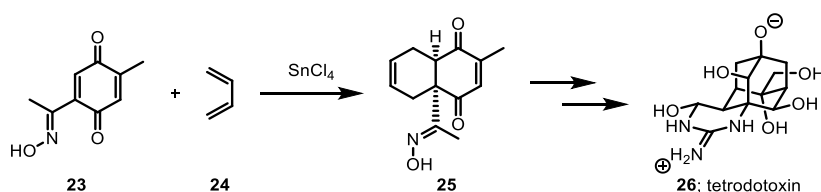
Scheme 1.6 Diels–Alder cycloaddition of electron-deficient diene **16** and electron-deficient dienophile **17**.

Another significant challenge associated with the Diels–Alder reaction is achieving high regioselectivity, particularly when unsymmetrical dienes and dienophiles are involved. In the absence of strong electronic directing effects, the reaction can lead to mixtures of regioisomeric products. This limitation was demonstrated by Hosomi and co-workers, who reported that the reaction of isoprene **19** with methyl acrylate **20** afforded a 70:30 mixture of *meta*- and *para*-substituted adducts, **21** and **22**, respectively (**Scheme 1.7**).^[11]



Scheme 1.7 Regioselective outcome of the Diels–Alder reaction between isoprene **19** and methyl acrylate **20**.

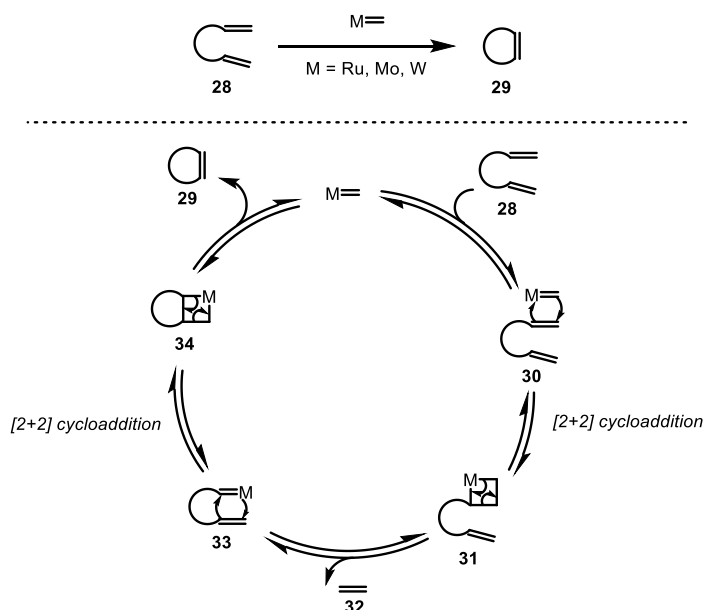
A classical strategy to enhance regioselectivity in the Diels–Alder reaction involves the use of Lewis acid catalysts. These catalysts lower the activation energy by decreasing the HOMO–LUMO energy gap and favour the formation of the *endo* product through secondary orbital interactions. It is worth noting that Lewis acids can also reverse the regiochemical preferences of the reaction, enabling access to products that are otherwise unattainable under thermal conditions. A representative example is found in Kishi’s total synthesis of tetrodotoxin **26**, where SnCl_4 catalysed a selective Diels–Alder cycloaddition by activating an oxime-containing dienophile **23** (Scheme 1.8).^[12] While oximes typically act as electron-donating substituents that deactivate the adjacent olefin towards cycloaddition, coordination to a Lewis acid withdraws electron density from the oxime, making the neighbouring olefin highly electron-deficient. In the absence of the Lewis acid, the alternative olefinic bond of the quinone preferentially undergoes the reaction.



Scheme 1.8 Synthesis of tetrodotoxin **26** via SnCl_4 -catalysed, regiospecific Diels–Alder cycloaddition of dienophile **23** and diene **24**.

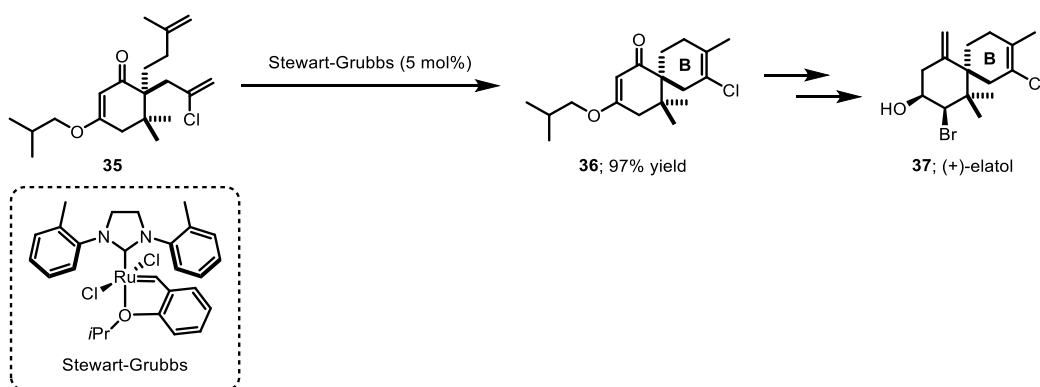
The second most commonly employed strategy for the synthesis of cyclohexenes is ring-closing metathesis (RCM), as illustrated in Scheme 1.9.^[13] This transformation involves the intramolecular metathesis of diene substrate **28**, bearing two alkene functionalities, and is typically catalysed by transition metal complexes, most notably those based on ruthenium,^[14] molybdenum,^[15] or tungsten.^[16] Proceeding *via* a reversible [2+2] cycloaddition mechanism, RCM affords the desired cycloalkene **29**, along with the elimination of ethylene gas **32** as a by-product. The continuous removal of ethylene from the reaction mixture provides a

thermodynamic driving force, shifting the equilibrium in favour of cyclisation and enhancing the overall yield of the reaction.



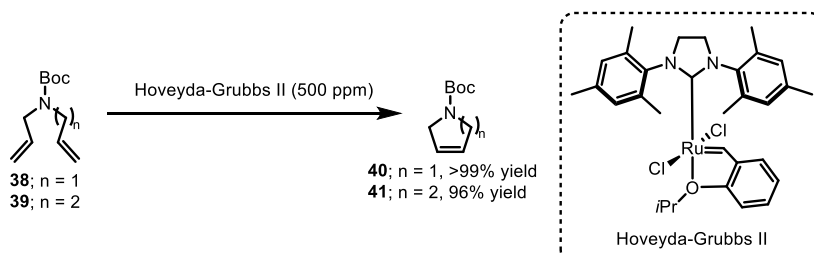
Scheme 1.9 Proposed catalytic cycle for ring-closing metathesis.

The synthetic utility of RCM has been particularly well demonstrated in the context of natural product synthesis, where the formation of six-membered systems often presents a challenge. A notable example is the work of Stoltz and co-workers in 2010, in which RCM was applied to the synthesis of members of the chamigrene subclass of sesquiterpenes.^[17] In this study, RCM enabled the efficient construction of tri- and tetrasubstituted cyclohexene B-rings, which are key structural features of the target molecules. Among the analogues synthesised, the tetrasubstituted chlorinated olefin **36** was obtained in an excellent yield of 97% (**Scheme 1.10**), exemplifying the power of RCM in forming sterically demanding, highly substituted cyclohexene frameworks with both high efficiency and selectivity.



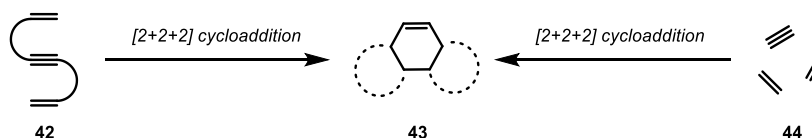
Scheme 1.10 Ring-closing metathesis of diene **35** in the enantioselective synthesis of (+)-elatol **37**, a representative member of the chamigrene subclass of sesquiterpenes.

In recent years, RCM has emerged as a powerful strategy for the synthesis of heterocycles, particularly five- to seven-membered rings containing heteroatoms such as oxygen^[18], nitrogen^[19], or sulphur^[20]. In 2010, Pederson and co-workers employed a high-throughput robotic platform using Symyx technology to identify the optimum reaction conditions for the formation of nitrogen-containing heterocycles.^[21] By using catalyst loadings as low as 500 parts per million (ppm), they achieved efficient synthesis of the cyclic amines **40** and **41**, which were obtained in yields of up to 99% (**Scheme 1.11**).



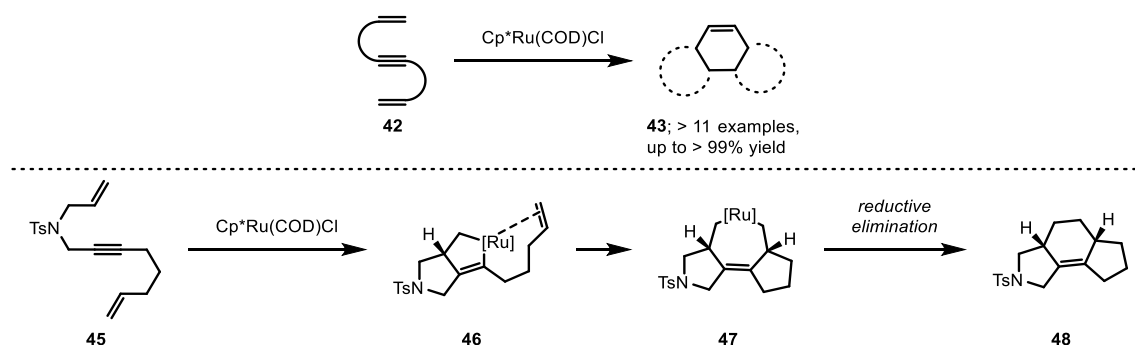
Scheme 1.11 Synthesis of pyrrolidine and piperidine derivatives **40** and **41** via ring-closing metathesis.

Cyclotrimerisation,^[22] specifically the [2+2+2] cycloaddition of two alkenes and an alkyne, is another well-established method for synthesising cyclohexene derivatives. This reaction is typically catalysed by transition metals such as cobalt^[23], nickel^[24], or rhodium^[25], which facilitate the formation of six-membered rings with high atom economy. Although both intramolecular and intermolecular variants have been developed, the intramolecular approach is often preferred due to its superior control over regio- and stereochemistry.



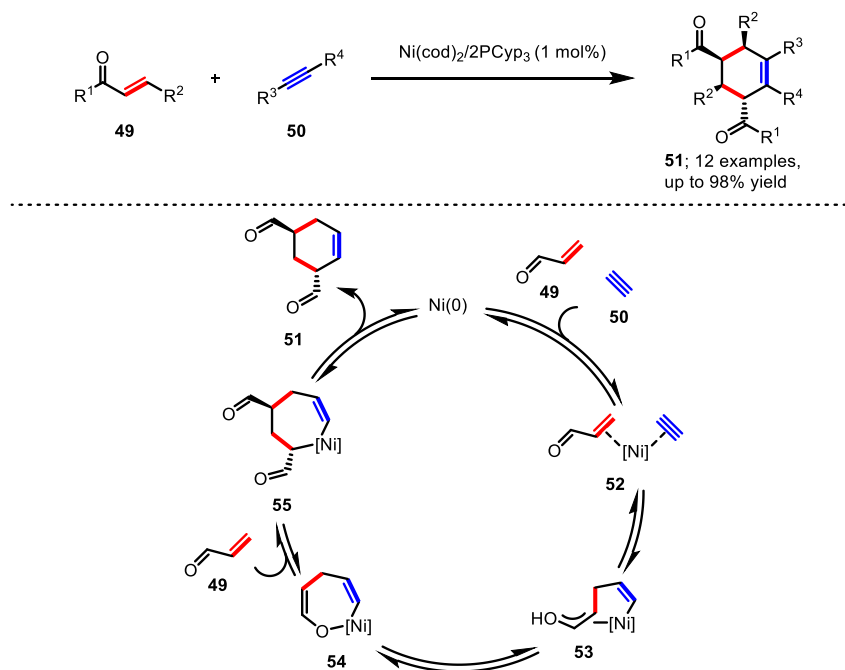
Scheme 1.12 Synthesis of cyclohexenes via [2+2+2] cyclotrimerisation.

Mori and co-workers demonstrated the intramolecular [2+2+2] cyclotrimerisation of tethered diene–yne substrates **42** using $\text{Cp}^*\text{Ru}(\text{COD})\text{Cl}$ as the catalyst (**Scheme 1.13**).^[26] The reaction proceeds *via* an initial oxidative cyclisation between an alkene and an alkyne to form a ruthenacyclopentene intermediate **46**. Subsequently, the remaining tethered alkene inserts into the metallacycle, generating a ruthenacycloheptene species **47**. Reductive elimination of this intermediate then yields the desired tricyclic product **48**.



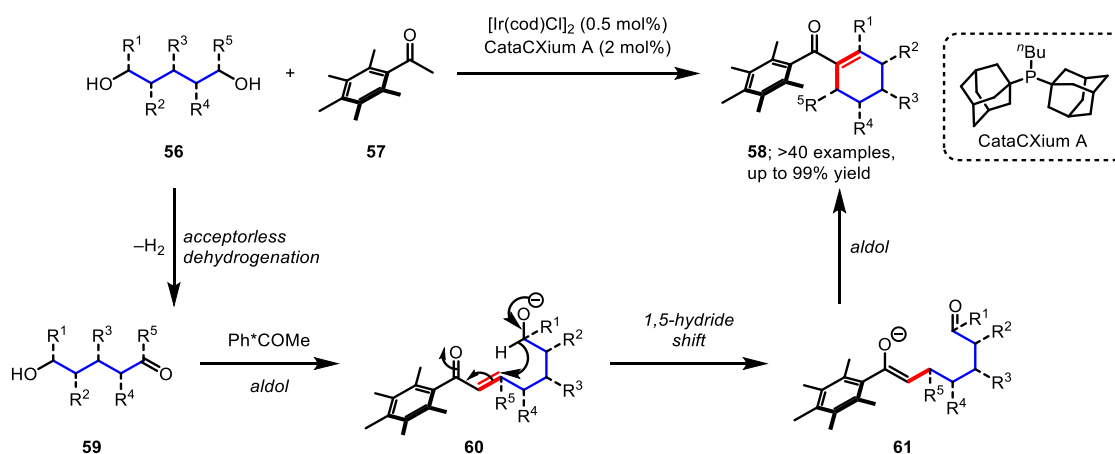
Scheme 1.13 Ruthenium-catalysed intramolecular [2+2+2] cycloaddition of tethered diene–yne **42**.

The first intermolecular example of this [2+2+2] cycloaddition reaction was reported by Ohashi and co-workers in 2010, in which two equivalents of enone **49** and one equivalent of alkyne **50** underwent coupling in the presence of a nickel catalyst (**Scheme 1.14**).^[27] Mechanistically, the transformation is proposed to proceed analogously to the previously described intramolecular variant. The catalytic cycle is initiated by an oxidative cyclisation between alkene **49** and alkyne **50**, resulting in the formation of an η^3 -oxallylnickel intermediate **53**. This species exists in equilibrium with a seven-membered η^1 -O-nickelenolate intermediate **54**, which subsequently reacts with a second equivalent of enone **49** to generate a nickelacycle **55**. The observed inversion of stereochemistry at the enone moiety is consistent with a mechanistic pathway involving the η^1 -coordinated nickelenolate **54**.^[28] The cycle concludes with reduction elimination from intermediate **55**, delivering the [2+2+2] cycloaddition product **51**.



Scheme 1.14 Nickel-catalysed intermolecular [2+2+2] cycloaddition of enone **49** (2.0 equiv.) with alkyne **50** (1.0 equiv.).

Finally, the Donohoe group recently reported a complementary intermolecular approach for the synthesis of multisubstituted cyclohexenes, employing pentamethylacetophenone **57** and 1,5-pentanediols **56** as starting materials (**Scheme 1.15**).^[29] The reaction was catalysed by $[\text{Ir}(\text{COD})\text{Cl}]_2$ in the presence of the sterically bulky alkyl phosphine ligand CataCXium® A. This ligand facilitated the acceptorless dehydrogenation of diol **56**, generating the corresponding hydroxyaldehyde **59**. Subsequent aldol condensation between hydroxyaldehyde **59** and pentamethylacetophenone **57** afforded the enone intermediate **60**, which then underwent a 1,5-hydride shift. A second aldol condensation furnished the final cyclohexene product **58**.

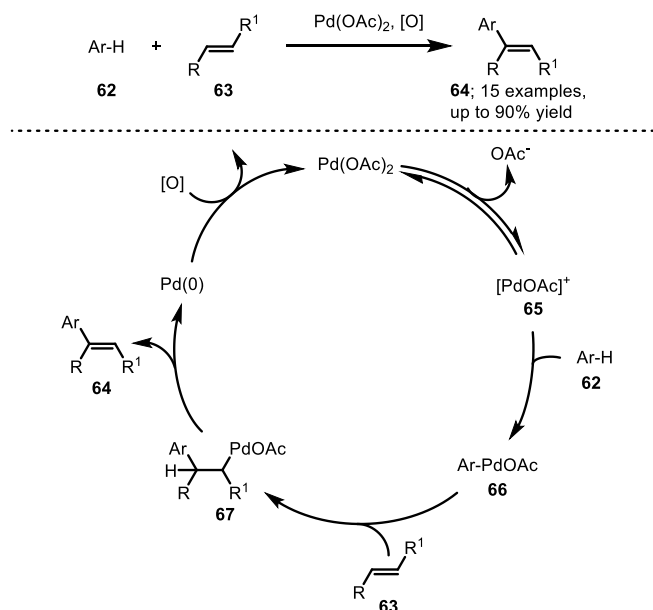


Scheme 1.15 Iridium-catalysed synthesis of multisubstituted cyclohexenes **58** via a tandem sequence involving acceptorless dehydrogenation and a 1,5-hydride shift.

1.3 C–H Functionalisation

The selective functionalisation of carbon–hydrogen (C–H) bonds has long been recognised as a significant challenge in organic chemistry. This is because C–H bonds are generally difficult to activate under mild reactions due to their high bond dissociation energies and non-polar character.^[30] Nevertheless, in recent decades, C–H functionalisation has emerged as a central objective in synthetic chemistry, driven by the growing demand for more sustainable and atom-economical methodologies. In response to this challenge, a diverse range of strategies has been developed, which can be broadly categorised into two mechanistic classes: oxidative and redox-neutral processes.^[31]

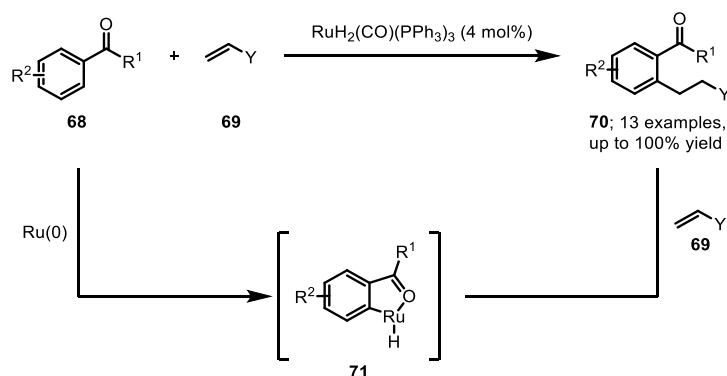
Oxidative pathways frequently involve transition metal catalysts in conjunction with external oxidants and typically proceed *via* high-valent metal intermediates. Notable early contributions in this area include the work of Fujiwara, who demonstrated the direct arylation of olefins using Pd(OAc)₂ in combination with oxidants such as Ag(I) Cu(II) (**Scheme 1.16**).^[32] The transformation involves the electrophilic substitution of aromatic C–H bonds by cationic [PdOAc]⁺ species **65**, leading to the formation of a σ -aryl-palladium complex **66**. This intermediate subsequently reacts with styrene **63** to afford the desired stilbene **64**. The reaction exhibits broad substrate scope, with a wide range of arenes, heteroarenes, and olefins, affording products in yields of up to 90%.



Scheme 1.16 Palladium-catalysed oxidative coupling of arene **62** with olefin **63** to afford stilbene derivative **64**.

In recent years, techniques such as photoredox catalysis,^[33] processes in which molecular oxygen serves as the terminal oxidant,^[34] and site-selective transition-metal-catalysed C–H oxygenation have further advanced the field,^[35] enabling the functionalisation of increasingly complex and diverse molecular frameworks.

In parallel, redox-neutral C–H functionalisation strategies have gained increasing attention due to their improved atom economy and alignment with green chemistry principles. Foundational work by Murai and co-workers demonstrated the efficient ruthenium-catalysed addition of aromatic C–H bonds to olefins, using RuH₂(CO)(PPh₃)₃ as the catalyst (**Scheme 1.17**).^[36] The method accommodates a wide range of acylbenzenes, acylated heteroarenes, and both mono- and di-substituted terminal olefins, with reported yields reaching up to quantitative levels. Equally noteworthy is the method's exceptional regioselectivity: in substrates possessing multiple reactive sites, the coupling consistently delivers a single regioisomer.



Scheme 1.17 Ruthenium-catalysed redox-neutral coupling of aromatic ketone **68** with olefin **69**.

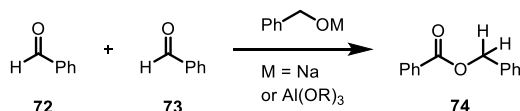
In addition to Murai-type transformations, several other redox-neutral C–H functionalisation strategies have been developed, including hydrogen borrowing methodologies^[37] and dehydrogenation of alkyl groups.^[38] Within this class of transformations, intramolecular hydride shifts offer a mechanistically distinct approach to C–H bond activation. These transformations proceed *via* the migration of a hydride from a donor carbon to a remote electrophilic acceptor site within the same molecule.

1.4 Overview of 1,5-Hydride Shifts in Organic Synthesis

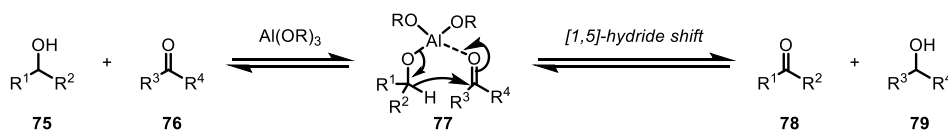
Among the various hydride shift processes, the 1,5-hydride shift is the most frequently encountered in organic synthesis due to its favourable six-membered transition state, which is both kinetically accessible and conformationally preferred. This transformation involves the intramolecular migration of a hydrogen atom to a carbon atom located five atoms away within the molecular framework. Mechanistically, the process results in the formal oxidation of the hydride donor and the corresponding reduction of the hydride acceptor. The earliest documented example of this transformation is now recognised as the Claisen–Tishchenko reaction (**Scheme 1.18A**).^[39, 40] Although originally proposed to proceed *via* a 1,3-hydride shift, subsequent mechanistic investigations by Kawasaki and co-workers established that the reaction instead follows a 1,5-hydride shift pathway.^[41] In this revised mechanism, Al³⁺ ions simultaneously coordinate to both the aldehyde and the deprotonated hemiacetal, thereby facilitating the formation of a pre-organised reactive conformation. Furthermore, a 1,3-hydride shift is considered unfavourable under the Woodward–Hoffmann rules, due to prohibitive

geometric constraints and the absence of appropriate orbital alignment necessary for effective overlap.^[42] By replacing the aldehyde functionality with an alcohol and a ketone, the analogous Meerwein–Ponndorf–Verley reduction is obtained,^[43] which proceeds *via* an identical Al^{3+} -coordinated, pre-organised 1,5-hydride shift mechanism (**Scheme 1.18B**).

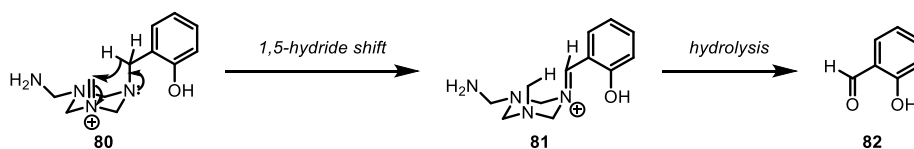
A. Claisen–Tishchenko reaction



B. Meerwein–Ponndorf–Verley reduction

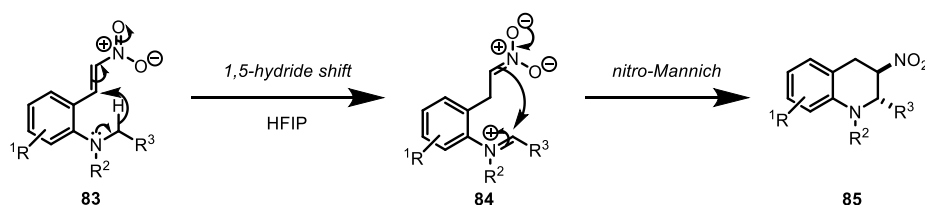
**Scheme 1.18** Representative early examples of 1,5-hydride shift reactions

The efficiency and feasibility of the 1,5-hydride shift are highly dependent on the electronic and structural characteristics of both the hydride donor and acceptor. In particular, the reaction is unlikely to proceed if the carbocation intermediate generated during the migration is insufficiently stabilised, or if the acceptor lacks sufficient electrophilicity. Substituents adjacent to the hydride donor, such as heteroatoms,^[44] aryl groups,^[45] and alkyl groups^[46] have been shown to facilitate hydride migration through stabilising electronic effects. Likewise, a broad range of electron-withdrawing groups can be employed to enhance the electrophilicity of the hydride acceptors.^[31] In 1941, Duff demonstrated that incorporation of a phenyl substituent and a nitrogen heteroatom adjacent to the hydride donor,^[47] in combination with the use of an iminium ion as the acceptor, significantly facilitated the 1,5-hydride shift of **80** to intermediate **81**, which subsequently underwent hydrolysis to furnish benzaldehyde **82** (**Scheme 1.19**).

**Scheme 1.19** Part of the Duff reaction mechanism showing the 1,5-hydride shift of **80** to **81** and subsequent hydrolysis to **82**.

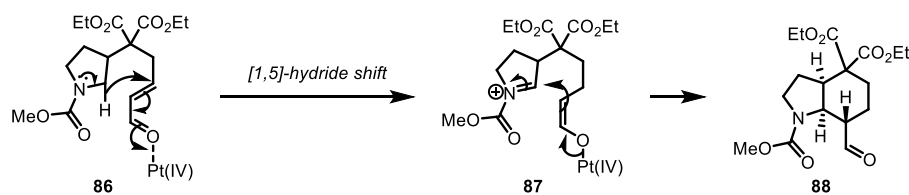
In many organic transformations, a 1,5-hydride shift serves not only as a key mechanistic step but also as a strategic trigger for subsequent bond-forming processes. This principle was

elegantly demonstrated by Ware and co-workers in the synthesis of tetrahydroquinolines *via* a 1,5-hydride shift–initiated nitro-Mannich reaction (**Scheme 1.20**).^[48] In this transformation, hydride migration is facilitated by electronic activation of the C–H bond, which is weakened through a hyperconjugative interaction between the σ^* orbital of the C–H bond and the lone pair of electrons on the adjacent nitrogen atom. Additionally, the nitro-olefin functions as a highly effective hydride acceptor due to the strong electron-withdrawing nature of the nitro group. The efficiency of the reaction is further enhanced by the use of hexafluoroisopropanol (HFIP) as the solvent. The high dielectric constant of HFIP stabilises the iminium cation intermediate formed during the hydride transfer, thereby lowering the activation energy of the process.^[49]



Scheme 1.20 Synthesis of tetrahydroquinolines via a 1,5-hydride shift–initiated nitro-Mannich reaction.

The 1,5-hydride shift often requires elevated temperatures to overcome the activation energy barrier. To address this limitation, both Lewis acids and Brønsted acids are frequently employed to increase the electrophilicity of the hydride acceptor, thereby facilitating the migration process. Representative catalysts such as $\text{Sc}(\text{OTf})_3$,^[50] $\text{BF}_3 \cdot \text{OEt}_2$,^[51] and PtBr_2 ^[52] have been shown to promote hydride shifts effectively under milder conditions. Building on this approach, Sames and co-workers developed catalytic strategies that enable 1,5-hydride shifts to proceed even at ambient temperature.^[45] They demonstrated that PtCl_4 acts as an effective catalyst for the hydroalkylation of α,β -unsaturated aldehydes by activating the hydride acceptor (**Scheme 1.21**). This transformation is of particular relevance to the present project, as it similarly employs an α,β -unsaturated carbonyl compound as the hydride acceptor, which subsequently undergoes an intramolecular cyclisation to afford a six-membered ring.

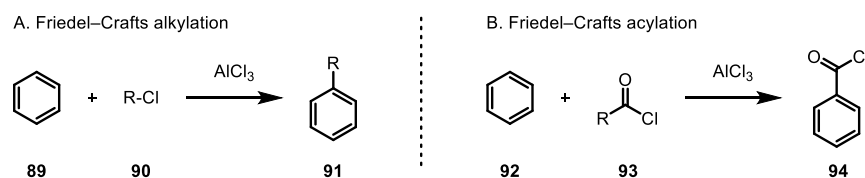


Scheme 1.21 PtCl_4 -catalysed hydroalkylation of α,β -unsaturated aldehydes.

1.5 Aluminium-Based Catalysis

The pursuit of sustainable, efficient, and environmentally friendly catalytic systems has driven increasing interest in main-group metals as viable alternatives to conventional transition metal catalysts.^[53] While transition metals have long dominated the field of catalysis due to their broad applicability and tunable reactivity, they are often associated with significant drawbacks, including high cost, limited natural abundance, and considerable toxicity. In contrast, aluminium, as a representative main group element, presents several compelling advantages. It is earth-abundant, economically accessible, and exhibits comparatively low toxicity, making it particularly attractive for catalytic processes aligned with the principles of green chemistry.

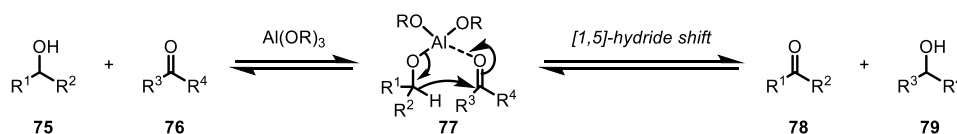
The catalytic utility of aluminium was first demonstrated in the pioneering work of Friedel and Crafts in 1877,^[54] where aluminium trichloride was employed as a Lewis acid to activate electrophiles for aromatic substitution reactions. In Friedel–Crafts alkylation, aluminium trichloride coordinates to the halogen atom of an alkyl halide, facilitating the formation of a carbocation or a carbocation-like intermediate, which subsequently undergoes electrophilic attack by an arene (**Scheme 1.22A**). In Friedel–Crafts acylation, a similar mechanism operates in which aluminium trichloride activates acyl halides to generate highly reactive acylium ions, leading to the formation of aryl ketones upon reaction with aromatic substrates (**Scheme 1.22B**).



Scheme 1.22 Classic Friedel–Crafts reactions.

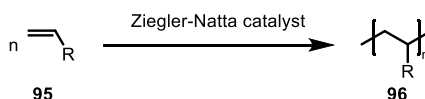
A second historically significant reaction involving aluminium is the Meerwein–Ponndorf–Verley reduction, which was discussed in **Chapter 1.4** as a representative example of a 1,5-hydride

shift.^[43] Beyond its mechanistic relevance, the MPV reaction is notable as the earliest documented example of an aluminium alkoxide functioning as a homogeneous catalyst (**Scheme 1.23**). In this process, a secondary or tertiary alcohol serves as the reductant, while an aldehyde or ketone acts as the oxidant. Both substrates are simultaneously coordinated to the aluminium centre, enabling hydride transfer *via* a six-membered transition state.^[55] This mechanism exemplifies the dual coordination ability of aluminium and underscores its potential as a Lewis acid catalyst.



Scheme 1.23 Generalised mechanism of the Meerwein–Ponndorf–Verley (MPV) reduction.

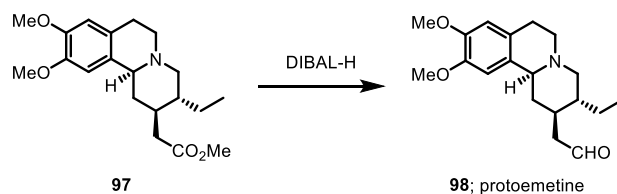
In the 1950s, a major breakthrough was achieved with the development of the Ziegler–Natta polymerisation, in which a combination of aluminium alkyls and titanium-based compounds was shown to catalyse the polymerisation of α -olefins with high linearity and stereoselectively (**Scheme 1.24**).^[56-58]



Scheme 1.24 Polymerisation of α -olefins using a Ziegler–Natta catalyst.

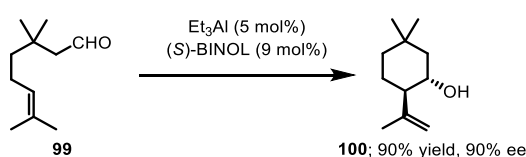
Around the same period, Ziegler and co-workers also explored the utility of triisobutylaluminium and diisobutylaluminium hydride (DIBAL-H) in hydroaluminium reactions.^[59] These transformations proceed *via* the addition of Al-H bonds across alkenes, generating organoaluminium intermediates that can subsequently undergo diverse functionalisation. Notably, DIBAL-H was later recognised for its distinctive chemoselective reducing properties.^[60] In contrast to conventional hydride reagents, DIBAL-H enables the partial reduction of esters, nitriles, and other carboxylic acid derivatives to their corresponding aldehydes under mild conditions and with high selectivity. This reactivity is particularly advantageous in the late stages of natural product synthesis, where preservation of sensitive functional groups and complex stereochemical features is essential. A representative example is found in the synthesis of

protoemetine, a key intermediate in the total synthesis of emetine, an isoquinoline alkaloid historically employed as an anti-protozoal agent and emetic (**Scheme 1.25**).^[61] In this context, DIBAL-H facilitated the partial reduction of ester functionalities to aldehydes without over-reduction to alcohols.



Scheme 1.25 Chemoselective reduction of ester **97** to aldehyde with DIBAL-H in the synthesis of protoemetine **98**.

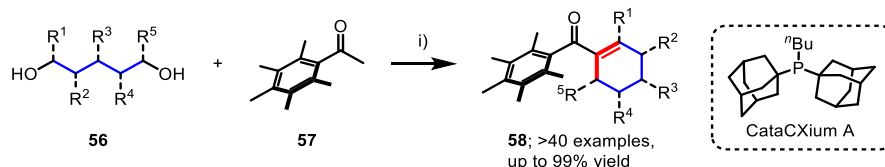
In recent years, significant progress has been made in extending aluminium-based catalysis into the realm of asymmetric synthesis.^[62] A noteworthy example was reported by Sakamoto and co-workers in 2015, who developed a highly enantioselective ring-closing ene reaction catalysed by aluminium complexes coordinated with chiral BINOL ligands (**Scheme 1.26**).^[63] The active catalytic species was generated *in situ* from triethylaluminium and (*S*)-BINOL, forming a chiral aluminium complex prior to substrate introduction. Upon addition of substrate **99**, the reaction proceeded smoothly to afford the (–)-enantiomer of product **100** in 90% yield and 90% ee. This work highlights the potential of aluminium complexes as effective and stereoselective Lewis acid catalysts in asymmetric transformations.



Scheme 1.26 Aluminium-catalysed enantioselective ring-closing ene reaction of substrate **99**.

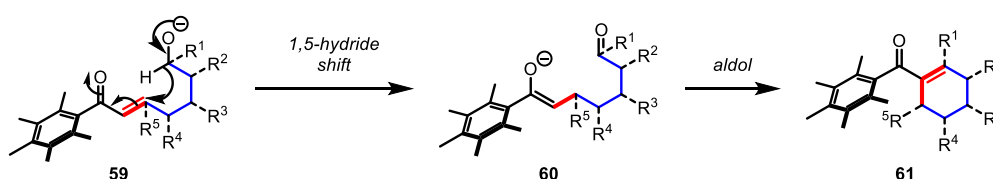
1.6 Project Aims

As previously discussed in **Chapter 1.2**, the Donohoe group has developed a novel approach to the synthesis of cyclohexenes *via* the iridium-catalysed cyclisation of 1,5-pentanediols **56** with pentamethylphenyl ketone **57** (**Scheme 1.27**).^[29] The use of pentamethylphenyl ketone is critical to the success of this transformation, as the *ortho*-methyl substituents of the Ph* group sterically hinder 1,2-addition to the adjacent carbonyl, thereby promoting selective cyclisation.



Scheme 1.27 Chemo- and regioselective synthesis of acyl cyclohexenes. Reagents and conditions: i) KOH (4.0 equiv.), [Ir(COD)Cl]₂ (0.5 mol%), CataCXium A (2 mol%), PhMe (0.25 M), 115 °C, 24 h.

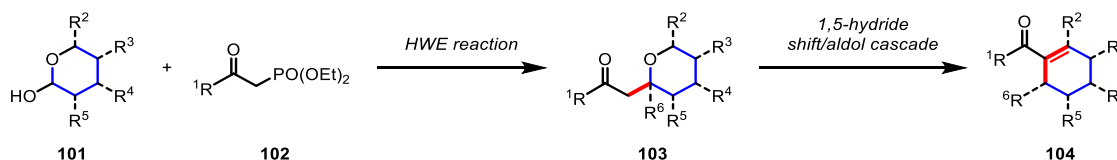
Although the annulation reaction was initially expected to proceed *via* a double hydrogen borrowing sequence, deuterium labelling and re-subjection experiments revealed that the transformation instead follows an unusual, transition metal-free 1,5-hydride shift–aldol cascade (**Scheme 1.28**).



Scheme 1.28 Proposed mechanism of the 1,5-hydride shift–aldol cascade.

Building upon this work by our group, Dr L. B. Smith initiated the development of a novel approach to cyclohexene synthesis *via* a tandem 1,5-hydride shift–aldol cascade (**Scheme 1.29**).^[64] He demonstrated that simple aluminium-based complexes, such as Al₂O₃ and Al(Ot-Bu)₃, are highly effective in promoting the hydride shift with complete regio- and enantiocontrol. In this strategy, the tetrahydropyran intermediates undergoing 1,5-hydride shift were primarily synthesised *via* the Horner–Wadsworth–Emmons (HWE) reaction.

The aim of the present work was to develop alternative synthetic methodologies that would enable expansion of the substrate scope, particularly by providing access to tetrahydropyrans that could not be efficiently prepared using the HWE protocol. In addition, mechanistic investigations were undertaken to gain deeper insight into the underlying reaction pathway.

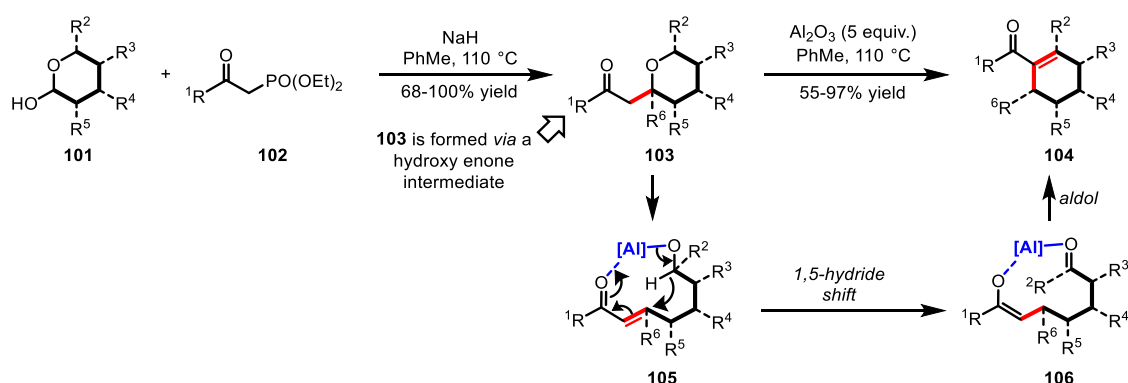


Scheme 1.29 Synthesis of cyclohexenes *via* a 1,5-hydride shift–aldol cascade.

Chapter 2: Synthesis of Acyl Cyclohexenes *via* an Aluminium Mediated 1,5-Hydride Shift–Aldol Cascade

2.1 Introduction and Preliminary Results

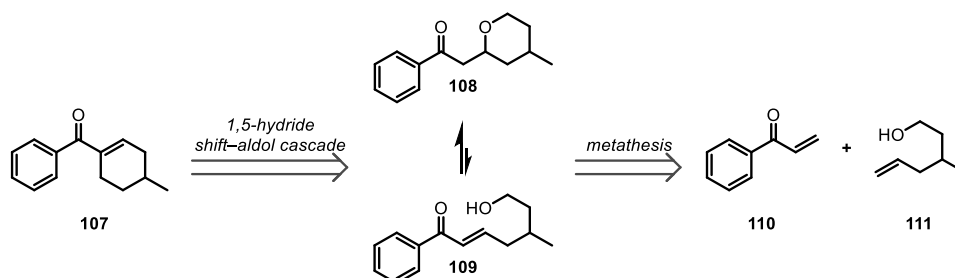
Cyclohexenes and their derivatives represent a valuable class of intermediates in the synthesis of natural products and pharmacologically active compounds. As outlined in the preceding chapter, numerous strategies have been developed for the construction of these structural motifs. Notably, the Donohoe group has recently reported a novel synthetic approach for the preparation of cyclohexenes **104** from readily available pyran substrates **103** (Scheme 2.1).^[64] This transformation is promoted by cost-effective aluminium-based reagents and proceeds *via* a 1,5-hydride shift followed by an intramolecular aldol condensation cascade.



Scheme 2.1 Synthesis of cyclohexenes **104** via a 1,5-hydride shift–aldol cascade. Note the reversible ring opening of the tetrahydropyran (THP) moiety.

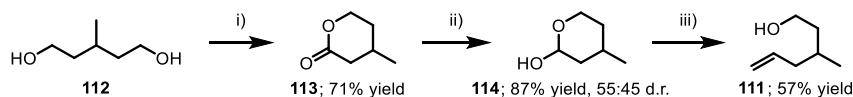
By using a combination of Horner–Wadsworth–Emmons (HWE) olefination followed by an aluminium-mediated 1,5-hydride shift, selective functionalisation of three out of the five positions around the acyl cyclohexene core (see R³, R⁴ and R⁵) was successfully achieved. However, access to δ -substituted lactols, which are key intermediates required for the synthesis of R² substituted cyclohexenes, remained limited. Moreover, the preparation of R⁶ substituted cyclohexenes through this cascade proved unfeasible, as ketones typically display significantly lower reactivity than aldehydes in HWE reactions and often lead to poor yields or complete reaction failure. Consequently, alternative synthetic strategies were explored for the preparation of the key tetrahydropyran intermediates, with the objective of enabling full functionalisation across all five positions of the acyl cyclohexene framework.

2.2 Metathesis Approach



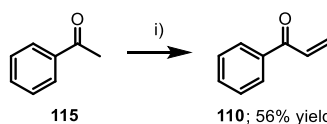
Scheme 2.2 Retrosynthetic analysis illustrating the strategic disconnection approach towards the synthesis of cyclohexene **107**.

Cyclohexene **107** was selected as the initial synthetic target due to its straightforward accessibility from tetrahydropyran **108/109** via a 1,5-hydride shift, a transformation previously developed within the group. It was envisaged that tetrahydropyran **108** could be assembled through a cross-metathesis (CM) reaction between phenylvinyl ketone **110** and hydroxyalkene **111**, followed by *in situ* cyclisation (**Scheme 2.2**). Hydroxyalkene **111** was synthesised via a three-step sequence starting from commercially available diol **112** (**Scheme 2.3**). The sequence commenced with oxidation of diol **112** to lactone **113**, obtained in 71% yield. Subsequent DIBAL-H reduction furnished the corresponding lactol **114** in 87% yield.



Scheme 2.3 Preparation of hydroxyalkene **111**. Reagents and conditions: i) copper chromite (2 mol%), air, 200 °C, 12 h; ii) DIBAL-H in hexanes (1.0 M, 1.4 equiv.), CH₂Cl₂ (0.5 M), -78 °C, 3 h; iii) MePh₃PBr (2.2 equiv.), *n*-BuLi (2.0 equiv.), THF (0.5 M), reflux, 12 h.

A Wittig reaction employing methyltriphenylphosphonium bromide afforded hydroxyalkene **115** in 57% yield. In parallel, phenylvinyl ketone **110** was synthesised in 56% yield via direct α -methylenation of acetophenone **115** (**Scheme 2.4**).



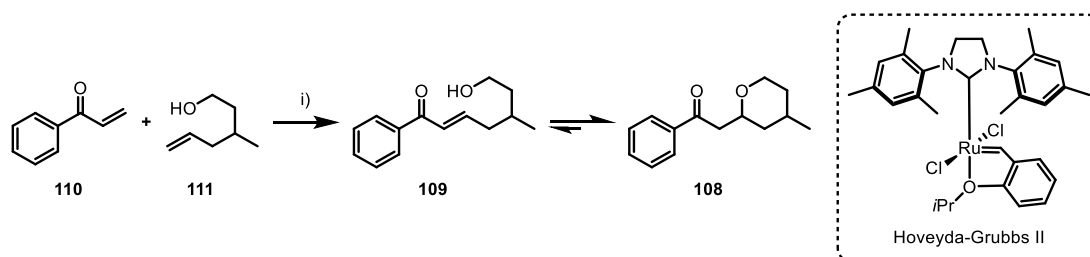
Scheme 2.4 Preparation of phenylvinyl ketone **110**. Reagents and conditions: i) (CH₂O)_n (4.0 equiv.), *i*-Pr₂NH:TFA (1.0 equiv.), TFA (10 mol%), THF (1.0 M), reflux, 12 h.

2.2.1 Optimisation

With both the desired hydroxyalkene **111** and phenylvinyl ketone **110** in hand, optimisation of the cross-metathesis (CM) reaction was undertaken (**Table 2.1**). The investigation commenced using literature-reported conditions developed by Sasaki and co-workers.^[65] Under these

conditions, the desired tetrahydropyran **108** (formed *via* **109**) was obtained in 64% isolated yield *via* a domino olefin cross-metathesis–cyclisation sequence employing the Hoveyda-Grubbs second-generation catalyst (**Entry 1**). In the product, formation of the ring-closed pyran **108** was favoured over the ring-opened hydroxyenone **109**, presumably due to the Thorpe–Ingold effect, wherein the presence of an additional methyl group promotes cyclisation.^[66]

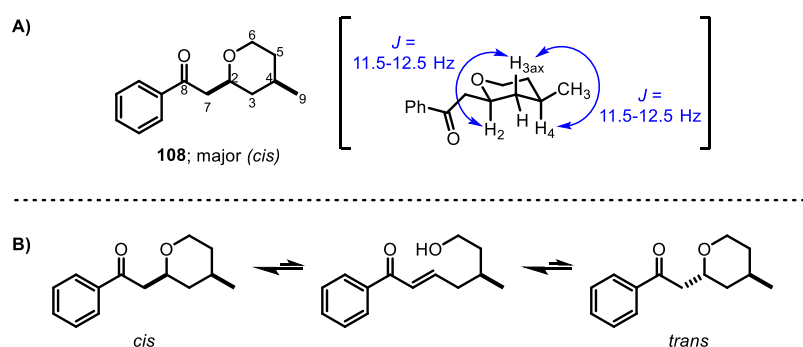
Substitution of the reaction solvent with a less polar alternative, such as toluene (PhMe), resulted in diminished reactivity and a reduced yield of 40% (**Entry 2**). Increasing the quantity of phenylvinyl ketone **110** to two equivalents improved the yield of 72%; however, further increasing the equivalents offered no additional benefit (**Entries 3 and 4**). A modest increase in yield was observed when the reaction temperature was raised 100 °C, affording the desired tetrahydropyran **108** in 76% (**Entry 5**). These investigations led to the identification of the optimal reaction conditions: two equivalents of phenylvinyl ketone **110** in 1,2-dichloroethane (ClCH₂CH₂Cl, 0.1 M) at 100 °C for 16 h.



Entry	110 (equiv.)	Solvent (0.1 M)	Temperature (°C)	Yield ^(a) (%)	d.r. (<i>cis:trans</i>) ^(b)
1	1.5	ClCH ₂ CH ₂ Cl	80	64	82:18
2	1.5	PhMe	110	(40)	84:16
3	2.0	ClCH ₂ CH ₂ Cl	80	72	83:17
4	3.0	ClCH ₂ CH ₂ Cl	80	(72)	84:16
5	2.0	ClCH ₂ CH ₂ Cl	100	76	82:18

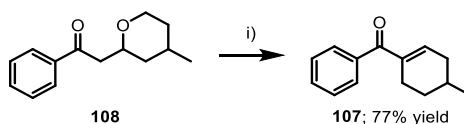
Table 2.1 Screening of conditions for the synthesis of tetrahydropyran **108** using cross-metathesis. Reagents and conditions: i) **111** (1.0 equiv.), Hoveyda–Grubbs II (10 mol%), 16 h. (a) Yield refers to isolated material after flash column chromatography, and conversion is reported in parentheses, which was determined by quantitative ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard. (b) Determined by quantitative ¹H NMR.

Tetrahydropyran **108** was obtained predominantly as the *cis*-diastereomer following the optimised metathesis reaction. The stereochemistry was confirmed by analysis of the ^1H NMR *J*-coupling constants, which revealed a quartet with a large coupling constant associated with the axial hydrogen H_3 . This observation is consistent with both the acyl and methyl substituents occupying equatorial positions (**Scheme 2.5A**). It is proposed that tetrahydropyran **108** undergoes reversible ring-opening, allowing equilibration to the thermodynamically favoured *cis* isomer (**Scheme 2.5B**).



Scheme 2.5 Stereochemical assignment of tetrahydropyran **108** and proposed rationalisation of the observed diastereoselectivity.

Finally, tetrahydropyran **108** was subjected to the optimised aluminium-promoted 1,5-hydride shift conditions, affording cyclohexene **107** in 77% isolated yield (**Scheme 2.6**). This outcome is considered highly satisfactory, reflecting both the efficiency and robustness of the developed 1,5-hydride shift transformation. With the metathesis strategy successfully optimised, subsequent efforts focused on evaluating the substrate scope for the synthesis of R^2 -substituted cyclohexenes.



Scheme 2.6 Synthesis of cyclohexene **107** via an aluminium-mediated 1,5-hydride shift–aldol cascade. Reagents and conditions: i) $\text{Al}(\text{O}t\text{-Bu})_3$ (1.0 equiv.), PhMe (0.2 M), 110°C , 16 h.

2.2.2 Substrate Scope

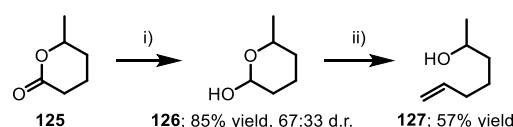
A series of hydroxyalkenes was prepared to enable access to R^2 -substituted cyclohexenes. These hydroxyalkene precursors were readily synthesised *via* Grignard addition to the corresponding aldehydes (**Table 2.2**). Using this approach, the pentyl-substituted hydroxyalkene **120** was obtained in 55% yield (**Entry 1**), while the phenyl-substituted analogue **122** was isolated in 57%

yield (**Entry 2**), the aldehyde bearing a thiophenyl substituent reacted efficiently to afford the corresponding hydroxyalkene **124** in 51% yield. (**Entry 3**).

Entry	Starting Material	Product	Yield (%)
1			55
2			57
3			51

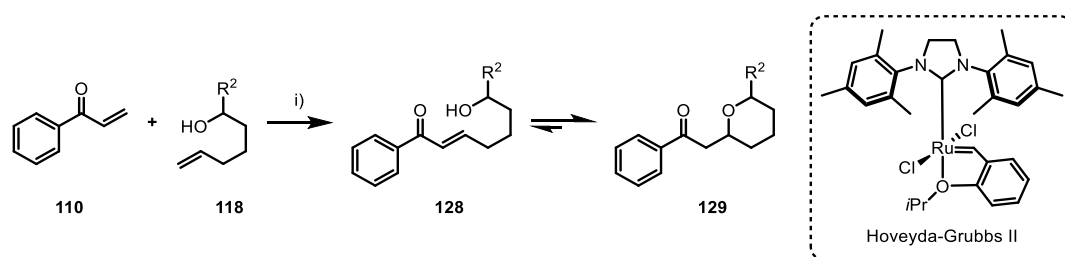
Table 2.2 Preparation of hydroxyalkenes via Grignard addition. Reagents and conditions: i) aldehyde (1.0 equiv.), 5-bromopent-1-ene (2.0 equiv.), Mg turnings (2.5 equiv.), THF (1.0 M), RT, 12 h.

The methyl-substituted hydroxyalkene **127** was synthesised *via* a two-step sequence starting from commercially available lactone **125** (**Scheme 2.7**). Initial reduction of the lactone using DIBAL-H afforded lactol **126** in 85% yield. Subsequent Wittig olefination with methyltriphenylphosphonium bromide furnished the desired hydroxyalkene **127** in 57% yield. Although this route requires two steps, it was preferred over direct Grignard addition to acetaldehyde, which is a highly volatile compound and classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC).



Scheme 2.7 Preparation of hydroxyalkene **117**. Reagents and conditions: i) DIBAL-H in hexanes (1.0 M, 1.4 equiv.), CH_2Cl_2 (0.5 M), -78°C , 3 h; ii) MePh_3PBr (2.2 equiv.), $n\text{-BuLi}$ (2.0 equiv.), THF (1.0 M), reflux, 12 h.

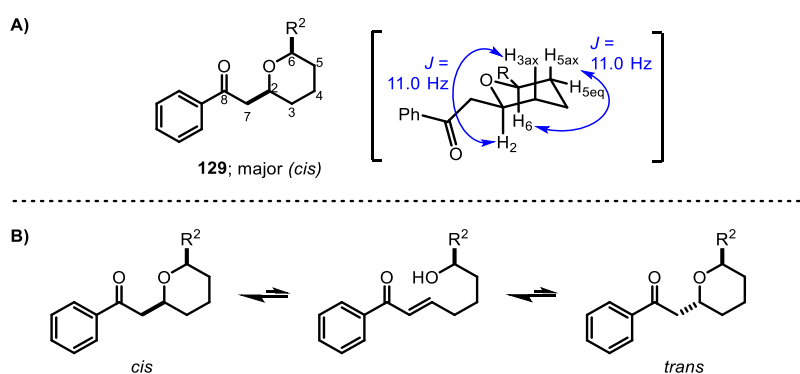
With a series of aromatic and aliphatic hydroxyalkenes in hand, their reactivity under the optimised metathesis conditions was evaluated (**Table 2.3**). The methyl-substituted tetrahydropyran **130** was obtained in 88% yield (**Entry 1**). The pentyl-substituted analogue **131** performed particularly well, affording the desired tetrahydropyran in 90% yield (**Entry 2**). The phenyl-substituted hydroxyalkene **122** also underwent smooth transformation with phenylvinyl ketone **110**, delivering tetrahydropyran **132** in 80% yield (**Entry 3**). Furthermore, the substrate bearing a thiophenyl substituent afforded the corresponding tetrahydropyran **133** in 75% yield (**Entry 4**).



Entry	Starting Material	Product	Yield (%)	d.r. (<i>cis:trans</i>) ^(a)
1			88	>95:5
2			90	>95:5
3			80	>95:5
4			75	88:12

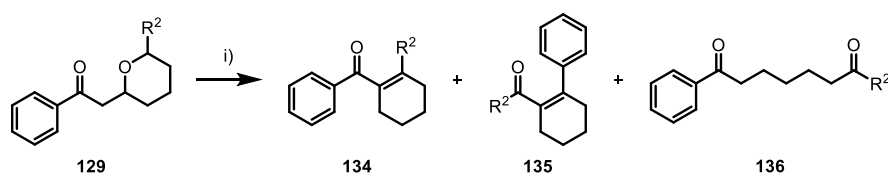
Table 2.3 Preparation of tetrahydropyrans **130-133**. Reagents and conditions: i) hydroxyalkene (1.0 equiv.), phenylvinyl ketone **110** (2.0 equiv), Hoveyda-Grubbs II (10 mol%), $\text{ClCH}_2\text{CH}_2\text{Cl}$ (0.1 M), 100 °C, 16 h. (a) Determined by quantitative ^1H NMR.

All of the tetrahydropyrans were obtained predominantly as the thermodynamically favoured *cis*-diastereomers. Stereochemical assignments were made based on *J*-coupling constant analysis (**Scheme 2.8**). Both axial protons, H₃ and H₅ appeared as triplets of doublets of doublets, consistent with two large vicinal couplings, one large geminal coupling, and one small vicinal coupling. The reversible nature of ring-opening process allows the tetrahydropyrans to equilibrate to the most stable conformation, minimising 1,3-diaxial interactions.



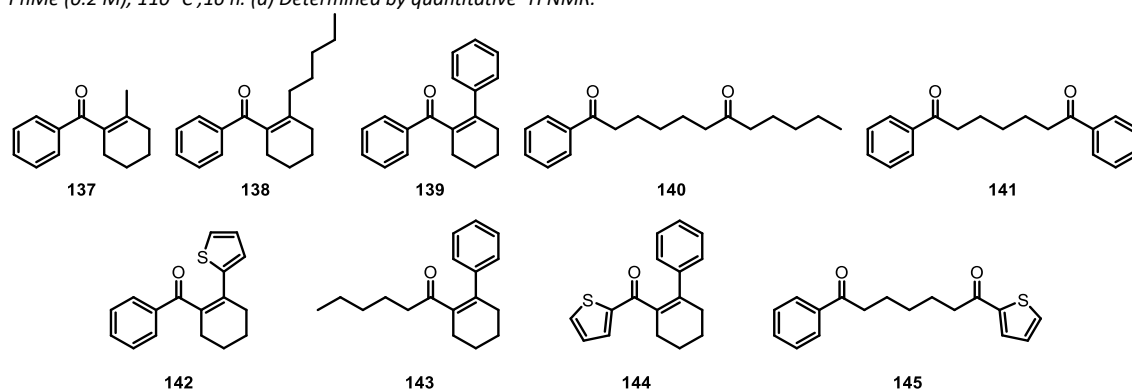
Scheme 2.8 Stereochemical assignment of R² tetrahydropyrans.

The reactivity of tetrahydropyrans **130-133** under the optimised aluminium-mediated 1,5-hydride shift–aldol cascade conditions was subsequently evaluated to investigate the influence of R² substitution (**Table 2.4**). The methyl-substituted tetrahydropyran **129** underwent efficient transformation, affording the corresponding cyclohexene in 80% yield with complete consumption of the starting material (**Entry 1**). Conversely, substrates bearing substituents larger than a methyl group resulted in complex mixtures comprising unreacted starting material, the uncyclised diketone intermediate, and two distinct aldol products (**Entries 2-4**).



Entry	Starting Material	129	Yield (%)	134:135	Yield (%)	r.r. ^(a)	136	Yield (%)
1		130	-	137	80	-	-	-
2		131	26	138:143	38	4:1	140	26
3		132	22	139	40	-	141	24
4		133	22	142:144	36	2:1	145	25

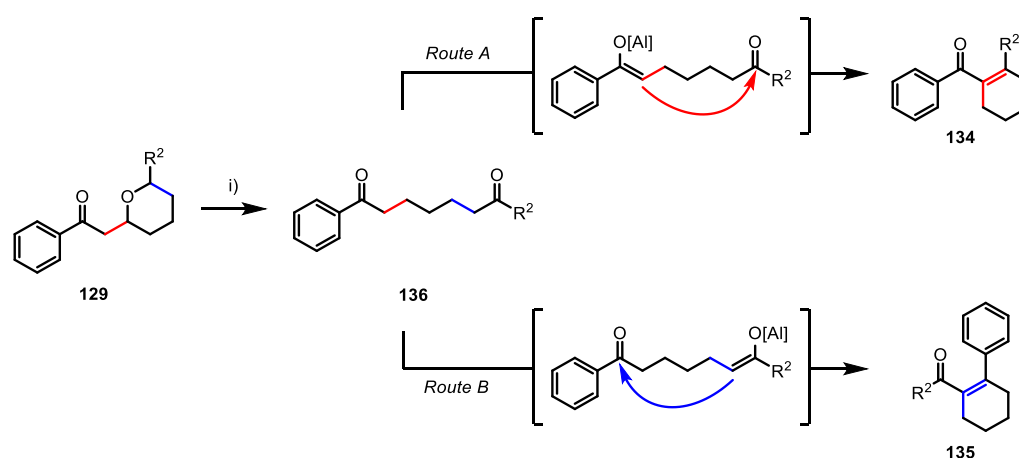
Table 2.4 Preparation of cyclohexenes **137-142**. Reagents and conditions: i) tetrahydropyran (1.0 equiv.), Al(Ot-Bu)₃ (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h. (a) Determined by quantitative ¹H NMR.



For R²-substituted tetrahydropyrans, the 1,5-hydrate shift delivers an unsymmetrical 1,5-diketone intermediate (**136**), in contrast to other substitution patterns that typically generate a ketone–aldehyde species. In ketone–aldehyde systems, the aldehyde carbonyl is more electrophilic than the ketone carbonyl and is therefore preferentially attacked by the enolate.

In the diketone system, however, the two ketone carbonyls exhibit comparable electrophilic character, providing no preference for nucleophilic addition at either site (**Scheme 2.9**). As a result, no single reaction pathway is favoured, and a mixture of regioisomeric products is formed.

Intramolecular aldol reactions involving two ketones are also more challenging due to the reduced electrophilicity of the carbonyl groups and the increased steric hindrance at the reaction sites. Consequently, intermediate **136** was detected, a species that had not been observed in previous studies.

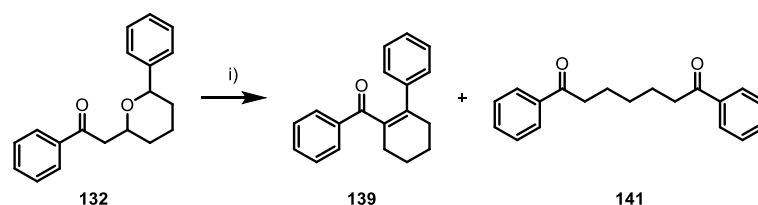


Scheme 2.9 Competing cyclisation pathways from diketone **136** leading to regioisomeric aldol products **134** and **135**. Reagents and conditions: *i)* **129** (1.0 equiv.), Al(Ot-Bu)₃ (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h.

Attempts to accomplish selective aldol cyclisation through variation of aluminium-based catalysts were explored; however, these efforts were largely unsuccessful. The phenyl-substituted tetrahydropyran **132** represents a notable exception (**Table 2.4, Entry 3**), as it generates a symmetrical 1,5-diketone intermediate in which both aldol pathways converge to a single cyclohexene product. Given this structural advantage, further optimisation efforts were directed towards this substrate.

To improve the yield of the cascade transformation for the phenyl-substituted tetrahydropyran substrate, the effect of varying the equivalents of Al(Ot-Bu)₃ was investigated (**Table 2.5**). When 1.0 equivalent of Al(Ot-Bu)₃ was employed, incomplete conversion was observed, with 22% of the starting material recovered. The desired cyclohexene product **139** was obtained in a

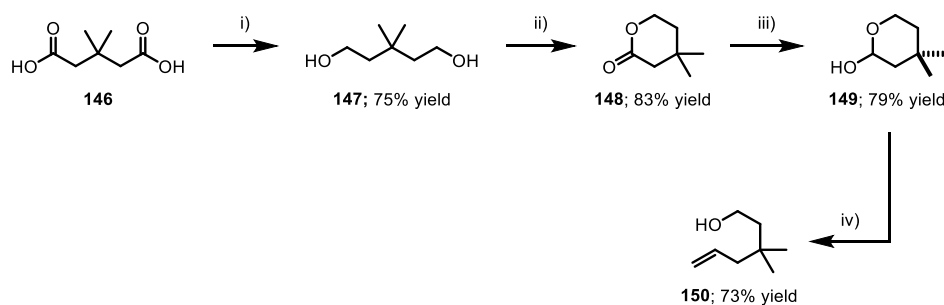
moderate yield of 40% yield, accompanied by the formation of the uncyclised diketone intermediate **141** in 24% yield. Increasing the loading to 2.0 equivalents led to full consumption of the starting material and afforded the highest yield of the target product **139** at 62%, while simultaneously reducing the accumulation of the diketone intermediate **141** to 11%. However, further increasing the catalyst loading to 3.0 equivalents did not improve the outcome, resulting in a slightly reduced yield of 55% for product **139**, and a corresponding increase in diketone **141** to 24%. No additional optimisation was undertaken, in order to preserve the generality of the established reaction conditions for broader substrate scope.



Entry	Al(Ot-Bu) ₃ (equiv.)	Yield (%)		
		132	139	141
1	1.0	22	40	24
2	2.0	-	62	11
3	3.0	-	55	24

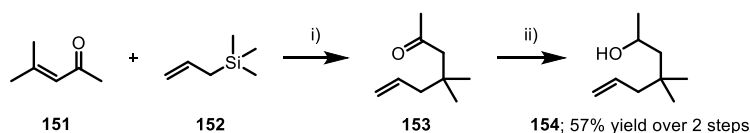
Table 2.5 Screening of equivalents of Al(Ot-Bu)₃ for the synthesis of cyclohexene **139**. Reagents and conditions: i) tetrahydropyran (1.0 equiv), PhMe (0.2 M), 110 °C, 16 h.

The metathesis approach was not limited to the synthesis of cyclohexenes bearing R² substitution. To further explore the substrate scope, an R⁴ substituted hydroxyalkene **150** was synthesised *via* a four-step sequence (**Scheme 2.10**). The sequence commenced with the reduction of commercially available diacid **146** using lithium aluminium hydride (LiAlH₄), affording the corresponding diol **147** in 75% yield. Oxidation of diol **147** provided lactone **148** in 83% yield, which was subsequently reduced with DIBAL-H to give lactol **149** in 79% yield. Finally, lactol **149** underwent Wittig olefination with methyltriphenylphosphonium bromide to furnish hydroxyalkene **150** in 73%.



Scheme 2.10 Preparation of hydroxyalkenes **149**. Reagents and conditions: i) LiAlH_4 (3.0 equiv.), THF (1.0 M), reflux, 12 h; ii) copper chromite (2 mol%), air, 200 °C, 12 h; iii) DIBAL-H in hexanes (1.0 M, 1.4 equiv.), CH_2Cl_2 (0.5 M), -78 °C, 3 h; iv) MePh_3PBr (2.2 equiv.), $n\text{-BuLi}$ (2.0 equiv.), THF (1.0 M), reflux, 12 h.

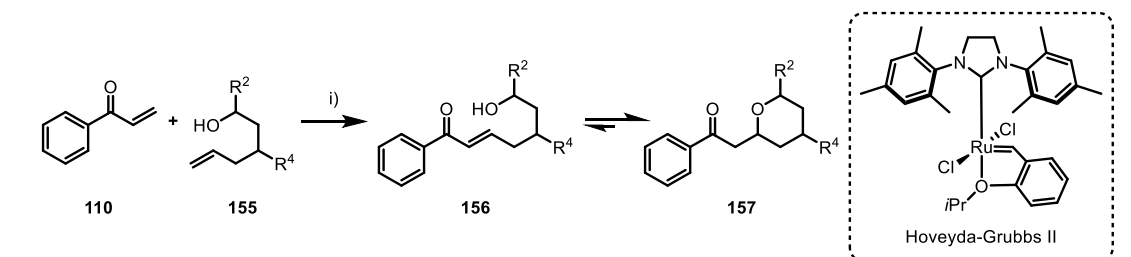
In addition to the R^4 -substituted hydroxyalkene, a disubstituted hydroxyalkene **154** bearing substituents at both the R^2 and R^4 positions was also prepared (**Scheme 2.11**). This compound was synthesised *via* a Sakurai reaction involving TiCl_4 -promoted allylation of α,β -unsaturated ketone **151** with allyltrimethylsilane **152** followed by reduction with sodium borohydride (NaBH_4). The desired hydroxyalkene **154** was obtained in 57% yield over two steps.



Scheme 2.11 Preparation of hydroxyalkene **154**. Reagents and conditions: i) TiCl_4 (1.0 equiv.), $\text{CH}_2=\text{CHCH}_2\text{SiMe}_3$ (1.3 equiv.) CH_2Cl_2 (0.5 M), -78 °C, 15 min; ii) NaBH_4 (1.5 equiv.), EtOH (0.2 M), RT, 12 h.

Next, using hydroxyalkenes **150**, **154**, and commercially available hex-5-en-1-ol **158**, tetrahydropyrans **159-161** were synthesised under the established metathesis conditions (**Table 2.6**). In comparison to the model substrate **108**, the yield decreased to 67% for tetrahydropyran **159** (**Entry 1**), which lacks substituents on the carbon backbone. Conversely, a significant increase in yield to 88% was observed for the corresponding dimethyl-substituted tetrahydropyran **160** (**Entry 2**). The presence of the gem-dimethyl groups facilitates cyclisation *via* the Thorpe–Ingold effect, effectively removing the ring-opened hydroxyenone **156** from the metathesis equilibrium and shifting the position of equilibrium towards the desired product. However, a notable reduction in yield to 44% was observed for tetrahydropyran **161**, bearing substituents at both the R^2 and R^4 positions (**Entry 3**), despite the presence of a gem-dimethyl group at the R^4 site. While the Thorpe–Ingold effect typically facilitates ring closure by promoting conformations that minimise steric strain, the combined steric bulk at R^2 and R^4 likely

overwhelms this effect. Additionally, the conformational constraints introduced by multiple substituents may interfere with the reversible THP ring-closing process, limiting access to the thermodynamically favoured product.



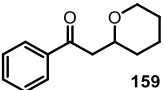
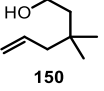
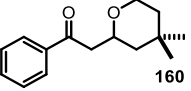
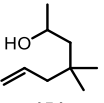
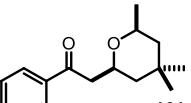
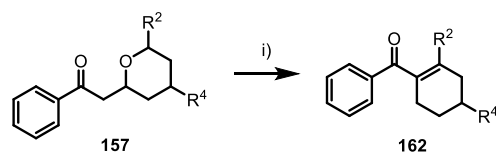
Entry	Starting Material	Product	Yield (%)	d.r. (<i>cis:trans</i>) ^(a)
1	 158	 159	67	-
2	 150	 160	88	-
3	 154	 161	44	>95:5

Table 2.6 Preparation of tetrahydropyrans **159–161**. Reagents and conditions: i) hydroxyalkene (1.0 equiv.), 1-phenylprop-2-en-1-one **110** (2.0 equiv.), Hoveyda-Grubbs II (10 mol%), $\text{ClCH}_2\text{CH}_2\text{Cl}$ (0.1 M), 100 °C, 16 h. (a) Determined by quantitative ^1H NMR.

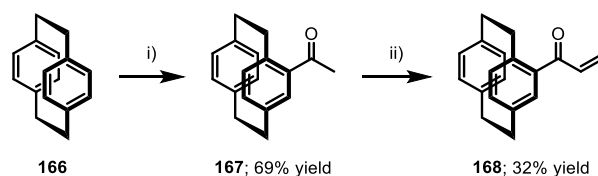
Following the synthesis of tetrahydropyrans **159–161**, each compound was subjected to the optimised aluminium-promoted 1,5-hydride shift conditions (**Table 2.4**). Pleasingly, the unsubstituted cyclohexene **163** was obtained in an excellent yield of 89%. A slight reduction in yield was observed for the dimethyl-substituted cyclohexene **164**, which was isolated in 78% yield. A further decrease in yield was noted for cyclohexene **165**, bearing substituents at both the R^2 and R^4 positions. In this case, the beneficial influence of the Thorpe–Ingold effect during the 1,5-hydride shift–aldol cascade, appears to be counteracted by the steric hindrance introduced by the substituents, which presumably hinders cyclisation and leads to a lower yield.



Entry	Starting Material	Product	Yield (%)
1			89
2			78
3			66

Table 2.7 Preparation of cyclohexenes **163–165**. Reagents and conditions: i) tetrahydropyran (1.0 equiv.), $\text{Al}(\text{Ot-Bu})_3$ (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h.

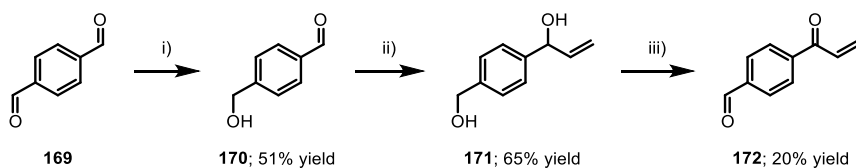
Having explored the scope of the hydroxyalkene partner, attention was next directed towards investigating the scope of the vinyl ketone partner. Vinyl ketone **168** was synthesised in two steps from commercially available paracyclophane **166** (Scheme 2.12). The sequence commenced with a Friedel–Crafts acylation of **166**, affording the corresponding aryl ketone **167** in 69% yield, followed by direct α -methylenation using paraformaldehyde to furnish the desired product.



Scheme 2.12 Preparation of vinyl ketone **168**. Reagents and conditions: i) AlCl_3 (1.8 equiv.), CH_3COCl (2.0 equiv.), CH_2Cl_2 (0.5 M), RT, 1 h; ii) $(\text{CH}_2\text{O})_n$ (4.0 equiv.), $i\text{-Pr}_2\text{NH}:\text{TFA}$ (1.0 equiv.), TFA (10 mol%), THF (1.0 M), reflux, 12 h.

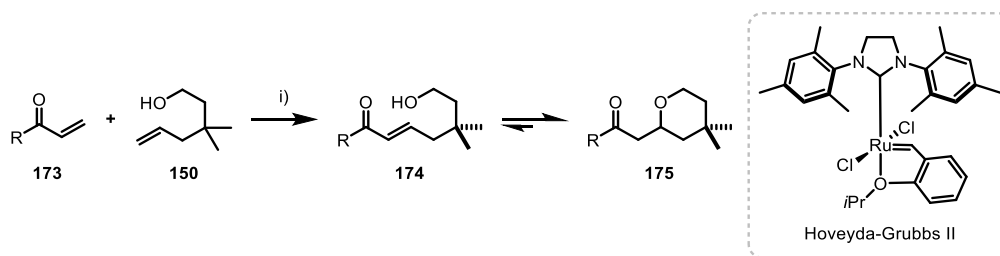
Subsequently, the feasibility of incorporating an aldehyde functionality onto the aryl ring was examined, given that carbonyl groups are not tolerated under the previously described HWE conditions. Vinyl ketone **172** was synthesised *via* a four-step sequence starting from commercially available terephthalaldehyde **169** (Scheme 2.13). Initial sodium borohydride reduction afforded the mono-reduced benzaldehyde **170** in 51%, which underwent nucleophilic

addition with vinylmagnesium bromide to provide diol **171** in 65% yield. Final oxidation of diol **171** using activated manganese dioxide yielded the desired vinyl ketone **172**.



Scheme 2.13 Preparation of hydroxyalkene **172**. Reagents and conditions: i) NaBH_4 (0.3 equiv.), EtOH (0.5 M), 0°C , 1 h; ii) $\text{CH}_2=\text{CHMgBr}$ (3.0 equiv.), THF (0.1 M), 0°C , 2 h; iii) activated MnO_2 (20 equiv.), air, CH_2Cl_2 (0.2 M), reflux, 12 h.

With vinyl ketone **168** and **172** in hand, the metathesis reaction was carried out using hydroxyalkene **150**, which had previously provided the highest yield in combination with phenyl vinyl ketone **110**. In this case, tetrahydropyran **176** was obtained in a modest yield of 33%, while tetrahydropyran **177** was isolated in 58% yield.



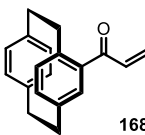
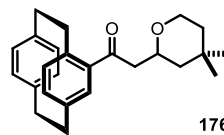
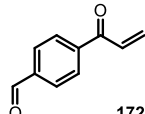
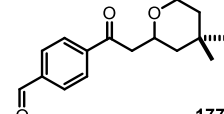
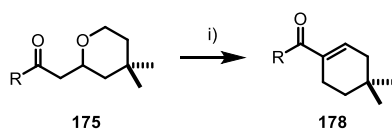
Entry	Starting Material	Product	Yield (%)
1	 168	 176	33
2	 172	 177	58

Table 2.8 Preparation of tetrahydropyrans **176-177**. Reagents and conditions: i) 3,3-dimethylhex-5-en-1-ol **150** (1.0 equiv.), vinyl ketone (2.0 equiv.), Hoveyda-Grubbs II (10 mol%), $\text{ClCH}_2\text{CH}_2\text{Cl}$ (0.1 M), 100°C , 16 h.

Finally, tetrahydropyrans **176** and **177** were subjected to the optimised aluminium-mediated 1,5-hydride shift conditions using $\text{Al}(\text{Ot-Bu})_3$. The paracyclophane-substituted cyclohexene **179** was successfully obtained in 68% yield, while the cyclohexene bearing an aldehyde functionality was isolated in 17%. Although the yield of the aldehyde-containing cyclohexene **180** was lower

than anticipated, the successful formation of the desired product demonstrates that aldehyde functionalities are tolerated to some degree under the 1,5-hydride shift conditions.

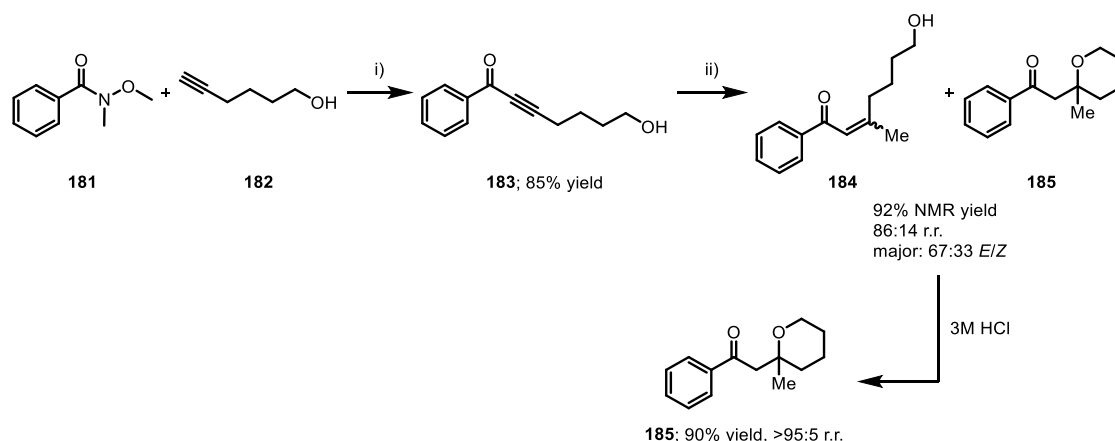


Entry	Starting Material	Product	Yield (%)
1	 176	 179	68
2	 177	 180	17

Table 2.9 Preparation of cyclohexenes **179–180**. Reagents and conditions: i) tetrahydropyran (1.0 equiv.), $\text{Al}(\text{Ot-Bu})_3$ (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h.

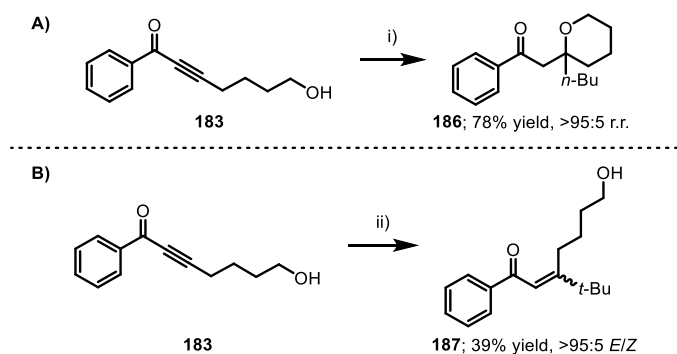
2.3 Cuprate Addition Approach

Finally, efforts were directed towards accessing the remaining substitution pattern of acyl cyclohexenes, namely those bearing an R^6 substituent. Tetrahydropyran **185** was synthesised in a two-step sequence from commercially available Weinreb amide **181** and hydroxyalkyne **182** (**Scheme 2.14**). Deprotonation of hydroxyalkyne **182** with *n*-butyllithium, followed by nucleophilic addition to the Weinreb amide, furnished ynone **183** in 85% yield. A Gilman cuprate, generated *in situ* from methyllithium and copper(I) iodide, was then added to ynone **183** in a 1,4-fashion. The introduction of a substituent adjacent to the alkene introduced significant steric hindrance, which prevented the spontaneous *in situ* cyclisation of the intermediate hydroxyenone **184** to tetrahydropyran **185** as a single product. Instead, a mixture of *E/Z* hydroxyenone **184** isomers and tetrahydropyran **185** was obtained, giving a total NMR yield of 92%. To simplify purification and ensure accurate yield determination, the crude mixture was treated with 3 M HCl, which facilitated complete conversion of both hydroxyenone isomers to tetrahydropyran **185** and affording the product in 90% isolated yield.



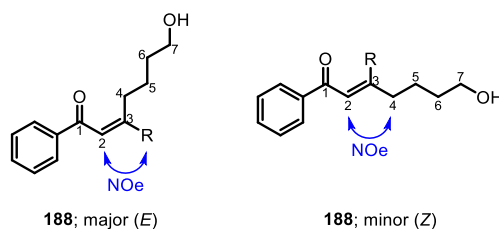
Scheme 2.14 Preparation of tetrahydropyran **185**. Reagents and conditions: i) *n*-BuLi (2.4 equiv.), THF (0.3 M), RT, 1 h; ii) MeLi (6.0 equiv.), CuI (3.0 equiv.), THF (0.3 M), $-78\ ^\circ\text{C}$, 30 min.

Following the same approach, organocuprates derived from *n*-butyllithium and *t*-butyllithium were reacted with ynone **182** (**Scheme 2.15**). In the case of the *n*-butyl cuprate, tetrahydropyran **186** was isolated in 78% yield. However, due to the steric bulk of the *t*-butyl group, no tetrahydropyran formation was observed in the crude mixture, and hydroxyenone **187** was isolated in 39% yield with an *E/Z* ratio greater than 95:5.



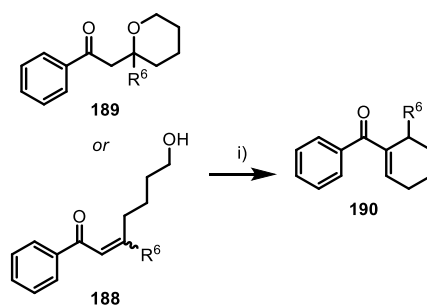
Scheme 2.15 Preparation of tetrahydropyran **186–187**. Reagents and conditions: i) *n*-BuLi (6.0 equiv.), CuI (3.0 equiv.), THF (0.3 M), $-78\ ^\circ\text{C}$, 30 min; ii) *t*-BuLi (6.0 equiv.), CuI (3.0 equiv.), THF (0.3 M), $-78\ ^\circ\text{C}$, 30 min.

The relative stereochemistry of the products was established by nuclear Overhauser effect (nOe) analysis (**Scheme 2.16**). A characteristic nOe correlation between H_2 and the hydrogen atom on the R group was observed for the *E*-isomers, whereas the *Z*-isomers exhibited a distinct correlation between H_2 and H_4 . These spatial interactions enabled confident differentiation between the two geometric isomers.



Scheme 2.16 Stereochemical assignment of hydroxyenones **188**.

With tetrahydropyrans **185** and **186**, and hydroxyenone **187** in hand, their reactivity under the optimised aluminium-mediated 1,5-hydride shift conditions was investigated. The methyl-substituted tetrahydropyran **185** underwent smooth conversion to the corresponding cyclohexene, affording the product in 83% yield. A clear trend was observed in which increasing the steric bulk of the R^6 substituent led to a progressive decrease in reaction efficiency. Specifically, the *n*-butyl- and *t*-butyl-substituted tetrahydropyrans **186** and **187** furnished the desired cyclohexenes in 67% and 65% yields, respectively. This reduction in yield could be attributed to the increase steric hindrance associated with larger R^6 groups, as the hydride shift occurs at the carbon bearing this substituent. Enhanced steric congestion at this position is likely to crowd and destabilise the transition state for the hydride migration, thereby reducing the overall efficiency of the transformation.



Entry	Starting Material	Product	Yield (%)
1	 185	 191	83
2	 186	 192	67
3	 187; >95:5 E/Z	 193	65

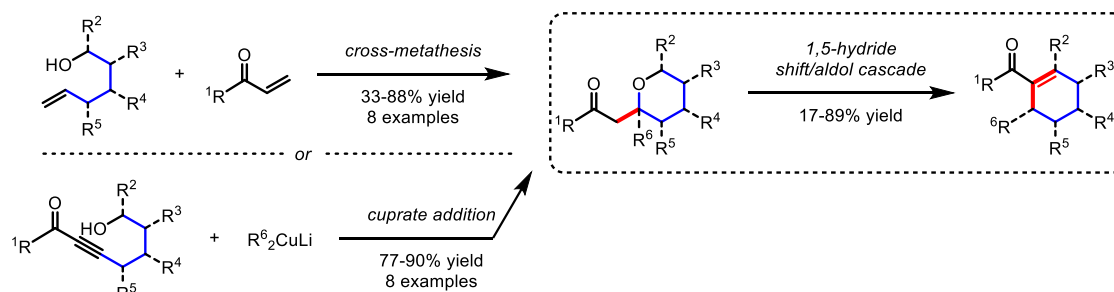
Table 2.10 Preparation of cyclohexenes **191-193**. Reagents and conditions: i) tetrahydropyran (1.0 equiv.), $Al(Ot-Bu)_3$ (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h.

2.4 Conclusion

To conclude, two alternative and complementary strategies for the synthesis of tetrahydropyrans have been successfully developed (**Scheme 2.17**). These methodologies provided access to structurally diverse starting materials that were previously challenging to obtain using the Horner-Wadsworth-Emmons approach. In particular, these strategies enabled the introduction of substitution at the R^2 and R^6 positions, substitutions patterns that had previously remained inaccessible, thereby expanding the substrate scope.

Subsequent applications of these tetrahydropyrans in the aluminium-promoted 1,5-hydride shift/aldol cascade successfully furnished the corresponding cyclohexene products. The R^2 -substituted tetrahydropyrans revealed limitations in regioselectivity due to the generation of

unsymmetrical 1,5-diketone intermediates that led to mixtures of aldol products. In contrast, R^6 -substituted substrates exhibited good reactivity under the optimised conditions, highlighting the compatibility of these systems with the cascade process.

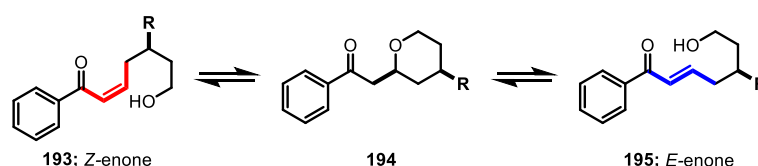


Scheme 2.17 Synthesis of cyclohexenes via cross-metathesis or cuprate addition followed by aluminium-mediated 1,5-hydride shift.

Chapter 3: Mechanistic Investigations

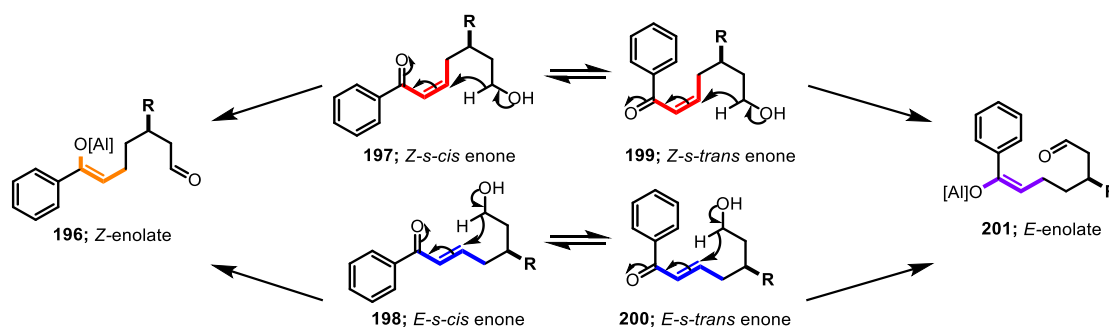
3.1 Introduction

Having developed an efficient strategy for the synthesis of acyl-substituted cyclohexenes, we proceeded to investigate the mechanism of the 1,5-hydride shift reaction. Several mechanistic pathways could potentially account for this transformation. It was recognised that ring opening of tetrahydropyran **194** could lead to the formation of either an *E*- or *Z*-configured enone (**193** or **195**) prior to the hydride shift (**Scheme 3.1**).



Scheme 3.1. Ring-opening of tetrahydropyran **194** to generate either *Z*- or *E*-configured enone intermediates.

Furthermore, each enone isomer can adopt either an *s-cis* or *s-trans* conformation. When *s-cis* conformers (**197** and **198**) undergo a 1,5-hydride shift, the resulting intermediate is a *Z*-enolate **196**, whereas the corresponding transformation from the *s-trans* conformers (**199** and **200**) gives rise to an *E*-enolate **201** (**Scheme 3.2**).



Scheme 3.2. Formation of *Z*- and *E*-enolate intermediates from *s-cis* and *s-trans* enones.

We were also interested in elucidating the role of aluminium in the 1,5-hydride shift—specifically, whether it interacts primarily with the alkoxide, the carbonyl group, or both. If a dual activation pathway is operative, analogous to that proposed for the Meerwein–Pondorff–Verley (MPV) reduction, this raises the question of whether a single aluminium centre simultaneously coordinates to both the alcohol and carbonyl functionalities.

To gain mechanistic insight into the preferred pathway for the 1,5-hydride shift and to clarify the role of aluminium in the key rearrangement step, four complementary approaches were pursued. First, density functional theory (DFT) calculations were conducted in collaboration with Prof. Duarte and her research team to model the potential transition states and associated energy profiles. Second, two geometrically constrained model systems were synthesised to evaluate the viability of distinct enone conformers in facilitating the hydride shift. Third, kinetic studies were undertaken using the method of initial rates to determine the reaction order with respect to $\text{Al}(\text{Ot-Bu})_3$. Finally, a deuterium-labelled tetrahydropyran substrate was prepared and subjected to a double-label crossover experiment with a non-deuterated analogue to assess the intramolecular nature of the hydride transfer.

3.2 Computational Modelling Using Density Functional Theory

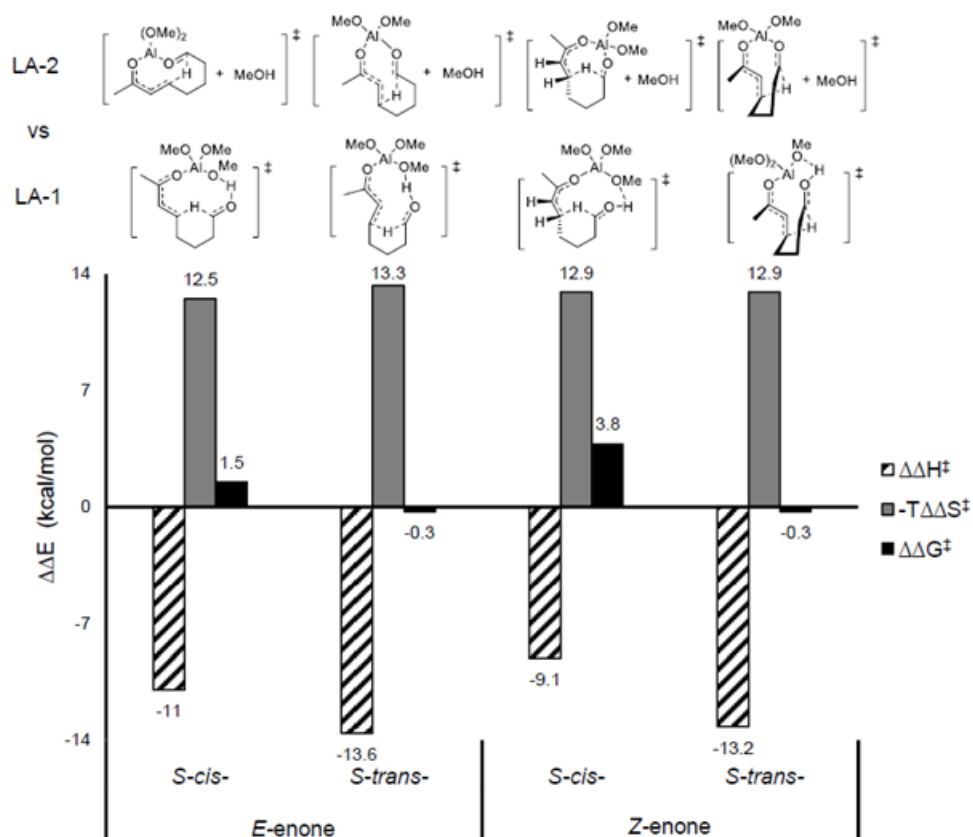
Our collaborator, Sze from the Duarte Group, carried out comprehensive computational modelling of all plausible transition states associated with the 1,5-hydride shift.^[67] This study employed a simplified model system comprising $\text{Al}_2(\text{OMe})_6$ and (*E*)-8-hydroxyoct-3-en-2-one. For the monomeric Lewis acid-promoted pathways, two chelation modes were considered: a singly chelated mode (LA-1), in which an alkoxy ligand on aluminium engages in hydrogen bonding with the alcohol; and a doubly chelated mode (LA-2), in which the aluminium centre acts as a bifunctional Lewis acid, coordinating to both the enone carbonyl and the alcohol.

The comparative thermodynamic parameters, namely enthalpy ($\Delta\Delta H^\ddagger$), entropy ($\Delta\Delta S^\ddagger$) and Gibbs free energy ($\Delta\Delta G^\ddagger$), for the two chelation modes were visualised as bar charts (**Scheme 3.3**). In this representation, positive values denote a preference for the LA-2 pathway, whereas negative values indicate favourability of the LA-1 pathway. The enthalpic profiles favoured the LA-1 transition states, primarily due to the presence of an additional O–H hydrogen bond. Furthermore, all LA-1 transition states form a [7.3.1]-bridged bicyclic system, which is less susceptible to ring strain. In contrast, the LA-2 transition states benefitted from favourable

entropic contributions, as this chelation mode results in the release of a methanol molecule into solution, thereby increasing the overall entropy of the system.

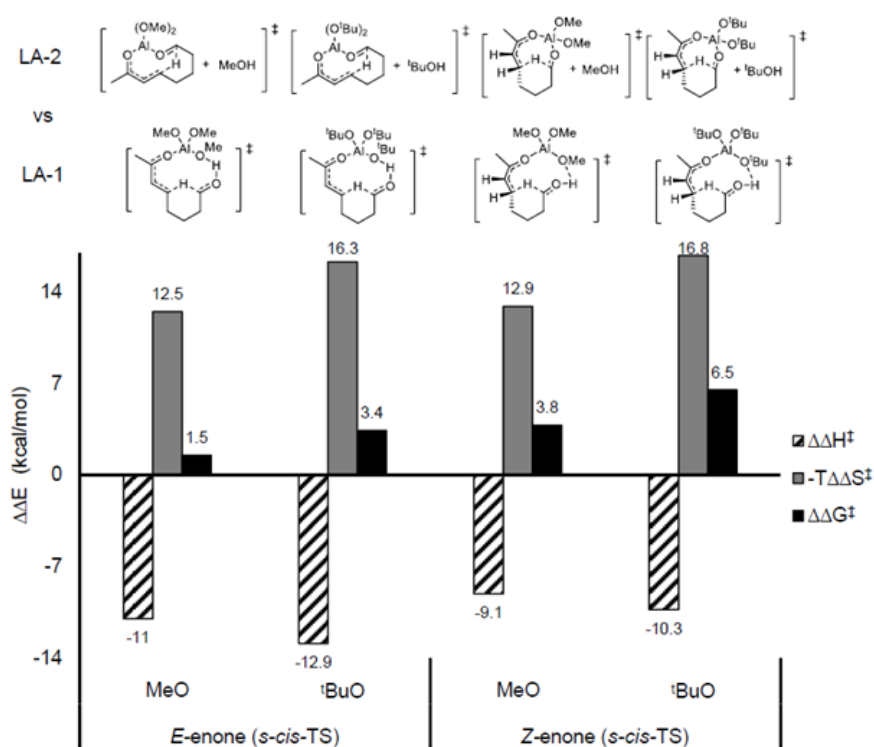
For the *s-trans* enone conformers, the computed free energy differences ($\Delta\Delta G^\ddagger$) between the LA-1 and LA-2 transition states were minimal, with values of -0.3 kcal/mol for both *E*- and *Z*-enones. In contrast, for the *s-cis* configured enones, the LA-2 transition states were significantly more favourable, with $\Delta\Delta G^\ddagger$ values of 1.5 kcal/mol for the *E*-enone and 3.8 kcal/mol for the *Z*-enone.

Although these calculations were performed using methoxide ligands, the experimental system employs bulkier *tert*-butoxide ligands. This substitution is expected to amplify steric interactions within the LA-1 coordination environment, as LA-1 transition states incorporate an additional alkoxide ligand relative to their LA-2 counterparts. Consequently, the LA-2 pathway is likely to be further favoured under the actual reaction conditions.



Scheme 3.3. Comparison of enthalpy, entropy, and Gibbs free energy for the 1,5-hydride shift transition states in monomeric Lewis acid-promoted pathways. Taken from M. K. Sze's Part II Thesis.^[67]

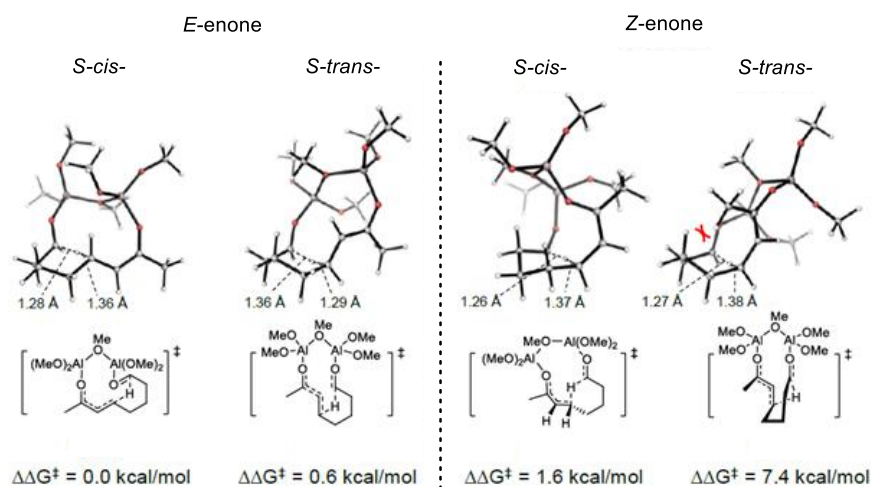
To verify this hypothesis, additional energy calculations were conducted by Sze, replacing methoxide with *tert*-butoxide ligands (**Scheme 3.4**). These results confirmed an enhanced preference for the LA-2 pathway, as reflected by the increased free energy differences. Specifically, for the *E-s-cis* enone, $\Delta\Delta G^\ddagger$ increased from 1.5 kcal/mol (OMe) to 3.4 kcal/mol (O^{*t*}Bu), while for the *Z-s-cis* enone, the corresponding value rose from 3.8 kcal/mol to 6.5 kcal/mol. Only the *s-cis* transition states were re-evaluated, as these had previously been identified as the more energetically favourable conformers.



Scheme 3.4 Comparison of enthalpy, entropy, and Gibbs free energy for *s-cis* transition states in monomeric Lewis acid-promoted pathways bearing either MeO or ^{*t*}BuO Ligands on aluminium. Taken from M. K. Sze's Part II Thesis.^[67]

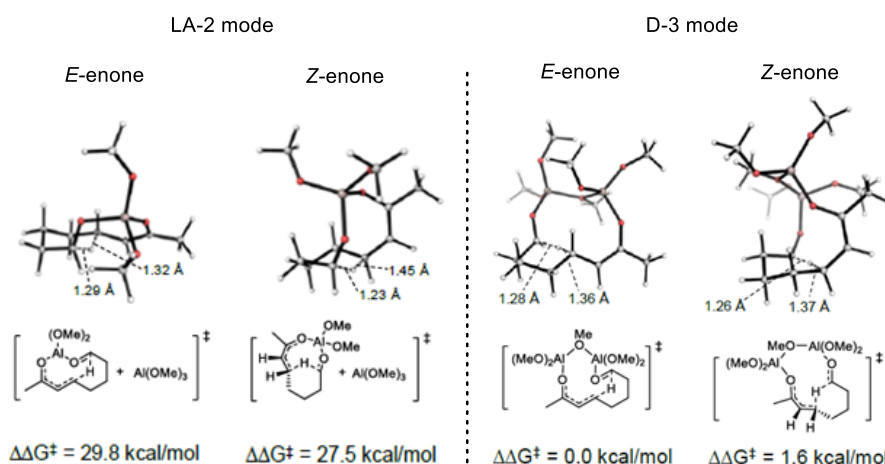
Focus was then directed toward dimeric Lewis acid-promoted pathways. Given the established preference for the di-chelated mode (LA-2) in the monomeric system, only the analogous di-chelated mode (D-3) was considered for the dimeric case, as shown in **Scheme 3.5**. Within this framework, the *s-cis* configurations were consistently more favourable than their *s-trans* counterparts, as indicated by lower Gibbs free energy ($\Delta\Delta G^\ddagger$) values. This preference is likely due to the increased ring strain associated with a *trans* enone.

Additionally, *Z*-configured enones were found to be significantly less stable than their *E*-configured counterparts in both *s-cis* and *s-trans* conformations, as reflected by higher $\Delta\Delta G^\ddagger$ values. This reduction in stability is likely due to transannular steric interactions. In the *Z-s-cis* transition state, an alkoxy ligand is directed into the concave face of the bicyclic structure, while in the *Z-s-trans* transition state, steric clash arises from the ketone's alkyl substituent. These steric effects are expected to be further intensified in the presence of *tert*-butoxide ligands, owing to their greater steric bulk.



Scheme 3.5. Gibbs free energies of the 1,5-hydride shift transition states for dimeric Lewis acid-promoted pathways. Taken from M. K. Sze's Part II Thesis.^[67]

Given that *s-cis* pathways were consistently identified as the lowest-energy routes for both monomeric and dimeric systems, a direct comparison was made between the LA-2 and D-3 transition states (**Scheme 3.6**). Among the four transition states evaluated, the dimeric (D-3) *E-s-cis* transition state exhibited the lowest overall Gibbs free energy. The substantial difference in free energy between the monomeric and dimeric pathways is attributed to the enthalpic penalty associated with the dissociation of dimeric $\text{Al}_2(\text{OMe})_6$ into monomeric $\text{Al}(\text{OMe})_3$ species. It is well established that $\text{Al}_2(\text{OMe})_6$ exists as a dimer in solid state, and a similar aggregation behaviour is reported for $\text{Al}(\text{O}t\text{-Bu})_3$.^[68] Although the monomeric pathway benefits entropically from the increased number of species in solution, these entropic gains are insufficient to compensate for the enthalpic stability of the dimeric system. As a result, the dimeric transition states are energetically more favourable overall.



Scheme 3.6. Comparison of the Gibbs free energies of *s-cis* transition states in monomeric and dimeric Lewis acid-promoted pathways. Taken from M. K. Sze's Part II Thesis.^[67]

In summary, the dimeric pathway (D-3) is energetically more favourable than the monomeric alternatives (LA-1 and LA-2). This preference is attributed to the substantial enthalpic cost associated with the dissociation of aluminium alkoxide dimers into monomeric species. Furthermore, for a given alkene geometry, the *s-cis* enone conformers are consistently lower in Gibbs free energy than their corresponding *s-trans* counterparts, a trend that arises from the reduction of ring strain in the *s-cis* geometry. Within the *s-cis* manifold, the *E*-enone is further stabilised relative to the *Z*-enone due to minimised transannular steric interactions. As a result, the D-3 *s-cis E*-enone was identified as the most favourable pathway overall.

3.3 Reaction Kinetics

DFT computational studies suggested that the key rearrangement step in the 1,5-hydride shift is most likely mediated by a dimeric, singly bridged aluminium complex. To experimentally validate this hypothesis, the rate order with respect to $\text{Al}(\text{Ot-Bu})_3$ was evaluated using the method of initial rates. In this approach, the instantaneous reaction rate is measured at the very beginning of the reaction for a series of experiments conducted at varying concentrations of a given reactant. The rate of reaction (v) is defined as the rate of consumption of the reactant or the rate of formation of the product.

$$v = -\frac{d[\text{S}]}{dt} = \frac{d[\text{P}]}{dt} \quad (3-1)$$

Suppose the rate law for the 1,5-hydride shift reaction with respect to $\text{Al}(\text{Ot-Bu})_3$ is given by:

$$v = k[\text{Al}]^a \quad (3-2)$$

Then the initial rate of the reaction, v_0 , will depend on the initial concentration of $\text{Al}(\text{Ot-Bu})_3$, $[\text{A}]_0$, as follows:

$$v_0 = k[\text{Al}]_0^a \quad (3-3)$$

Taking logarithms on both sides will give:

$$\log v_0 = \log(k[\text{Al}]_0^a) \quad (3-4)$$

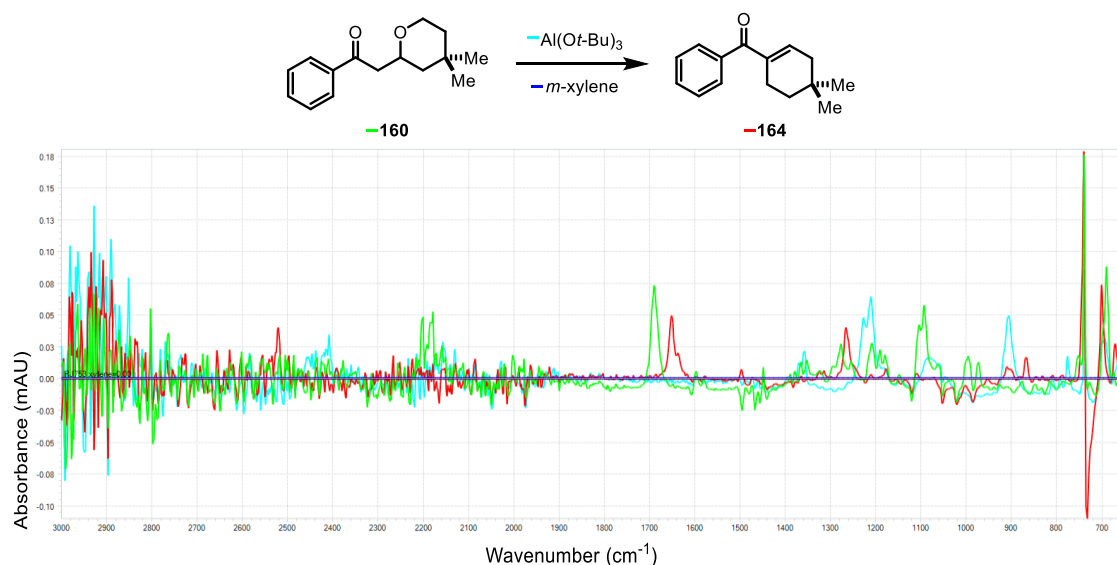
$$\log v_0 = \log k + a \log[\text{Al}]_0 \quad (3-5)$$

The equation now takes the form of a straight-line graph. When a plot of $\log v_0$ is constructed against $\log[\text{Al}]_0$, the gradient of the resulting line corresponds to the rate order a with respect to $\text{Al}(\text{Ot-Bu})_3$. The initial rates of the reaction, v_0 , were determined by monitoring either the formation of product or the consumption of starting material over time. Only the linear portion at the beginning of the reaction was considered, where changes in concentration are directly proportional to time, and the effects of substrate depletion and catalyst deactivation are negligible.

The first spectroscopic method explored for monitoring reaction progress was *in situ* Infrared (IR) spectroscopy, as it enabled the use of the same reaction vessel. This approach ensured consistent stirring and maintained reaction scale and conditions comparable to those employed in the reaction scope studies. However, heating the reaction mixture to 110 °C caused toluene to reach its boiling point, generating internal pressure within the sealed reaction vessel and posing a risk to the IR detection probe. To resolve this issue, the solvent was changed to *m*-xylene, which has a higher boiling point of 139 °C, thereby allowing safe operation at the required temperature.

A reference IR spectrum was recorded using a 2–5 mL Biotage[®] microwave vial containing 1.5 mL of *m*-xylene. Subsequently, 0.30 mmol of each tetrahydropyran **160**, cyclohexene **164** and $\text{Al}(\text{Ot-Bu})_3$ were dissolved individually in 1.5 mL of *m*-xylene, and three distinct IR spectra were

collected. Overlaying these spectra revealed clearly distinguishable absorptions bands at 1690 cm^{-1} and 1650 cm^{-1} , corresponding to tetrahydropyran **160** and cyclohexene **164**, respectively (**Scheme 3.7**).

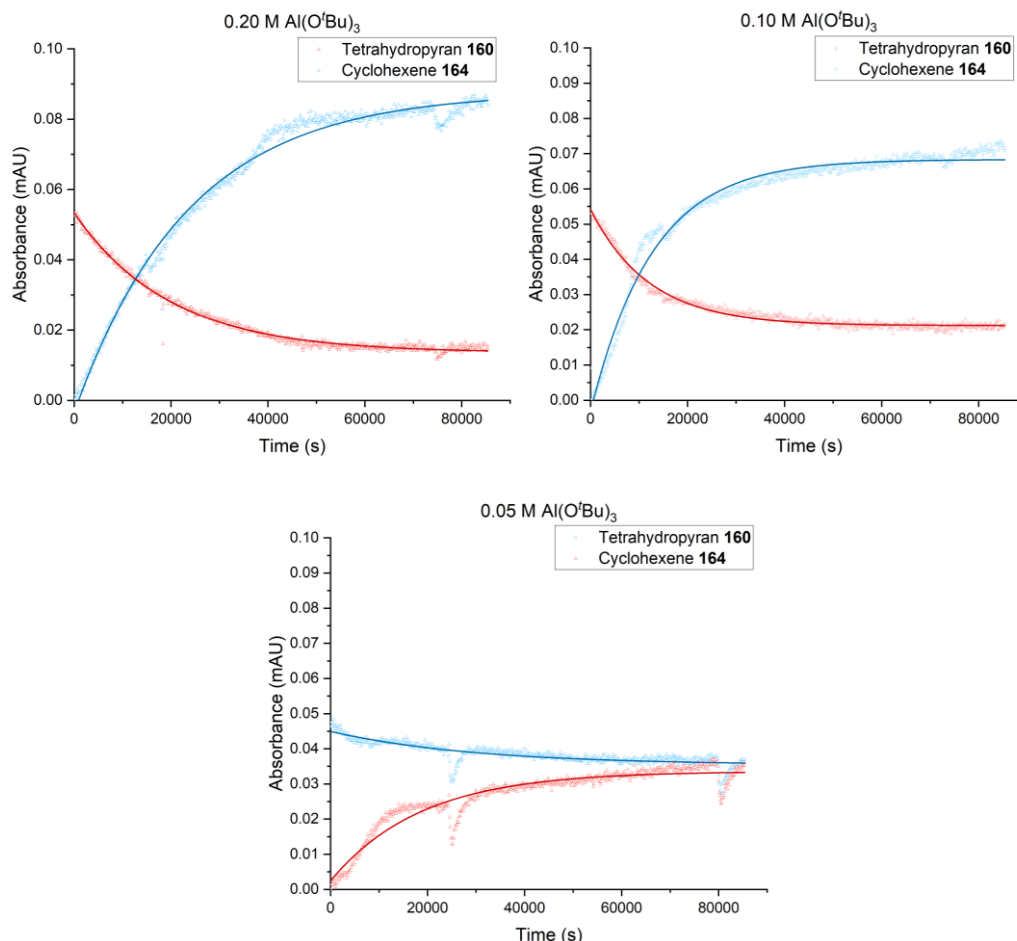


Scheme 3.7. Overlay of the IR spectra of tetrahydropyran **160**, cyclohexene **164**, and $\text{Al}(\text{Ot-Bu})_3$ in *m*-xylene.

With these reference bands established, a suspension of $\text{Al}(\text{Ot-Bu})_3$ in 1.0 mL of *m*-xylene was prepared in an oil bath preheated to 110 °C. The IR probe was then inserted, and the mixture was stirred for 15 min to ensure homogeneity. The reaction was initiated by injecting a stock solution containing tetrahydropyran **160**. Reaction mixtures containing varying concentrations of $\text{Al}(\text{Ot-Bu})_3$ were heated to 110 °C, and IR spectra were recorded over a 24-hour period. For each concentration of $\text{Al}(\text{Ot-Bu})_3$ (0.20, 0.10 and 0.05 M), graphs of time versus absorbance for both tetrahydropyran **160** and cyclohexene **164** were plotted, and curves of best fit were applied to both data sets (**Scheme 3.8**; for detailed experimental procedures and tabulated data, see **Chapter 7.1**).

In general, the data points closely followed the trend described by the curve of best fit, indicating strong overall agreement between the experimental measurements and the fitted model. However, more pronounced deviations were observed at lower concentrations of $\text{Al}(\text{Ot-Bu})_3$, which may be attributed to the increased relative influence of instrumental error under slower reaction conditions. One source of such error was the formation of aluminium-containing

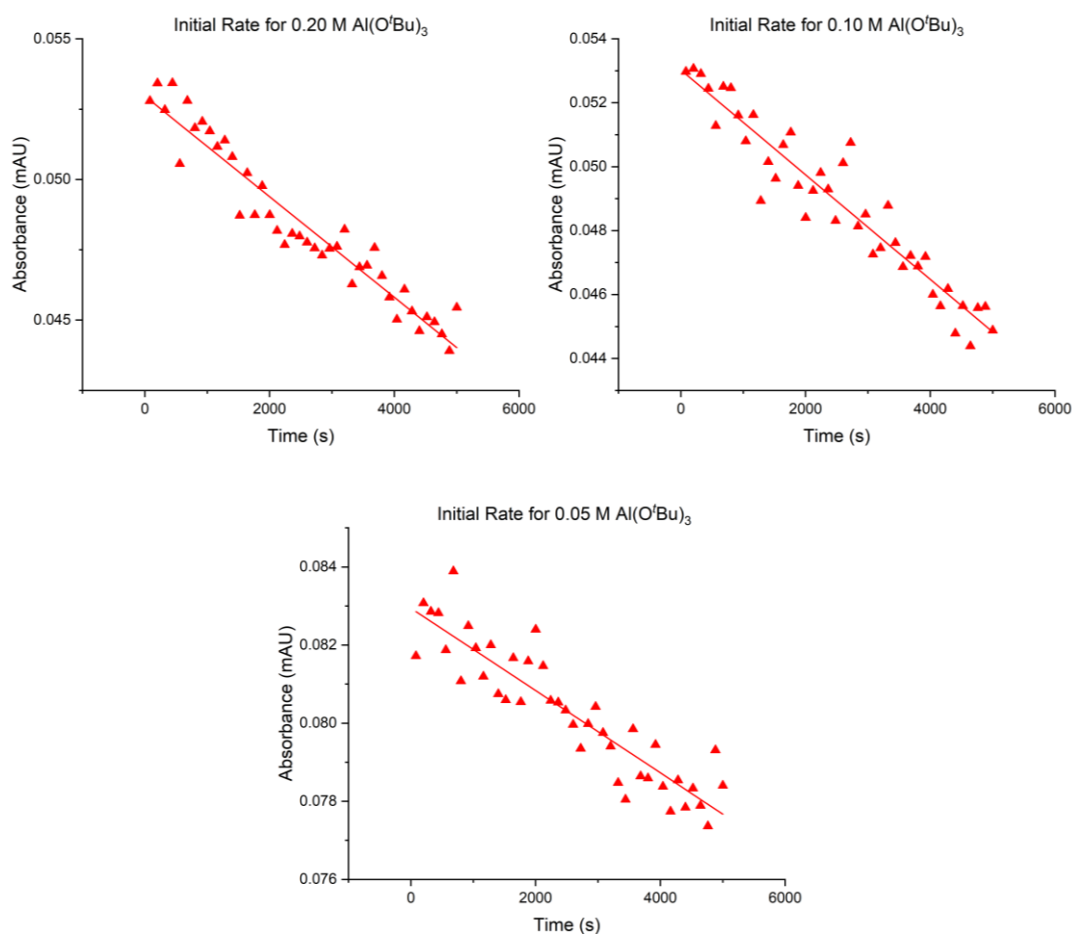
precipitates on the surface of the silicon detection probe upon completion of the reaction. This coating is suspected to interfere with signal transmission, leading to an underestimation of the absorbance values.



Scheme 3.8. Time versus absorbance plots for reactions conducted with 0.20 M, 0.10 M, and 0.05 M $\text{Al}(\text{O}t\text{-Bu})_3$, showing the consumption of tetrahydropyran **160** and the formation of cyclohexene **164** over 24 h.

For the purpose of calculating initial rates, time versus absorbance graphs for tetrahydropyran **160** were re-plotted, with analysis restricted to the first 5000 seconds following injection of the substrate stock solution (**Scheme 3.9**). This time window was sufficient to capture the linear portion of the reaction profile, where the rate remains constant and is not significantly affected by substrate depletion or catalyst deactivation. Data sets corresponding to the depletion of the starting material were used in preference to those for product formation, as they more closely followed the curves of best fit in the original plots. For each catalyst concentration, a line of best

fit was applied to the re-plotted data, and the negative gradients of these lines were taken as the initial rates of reaction. (**Table 3.1**).



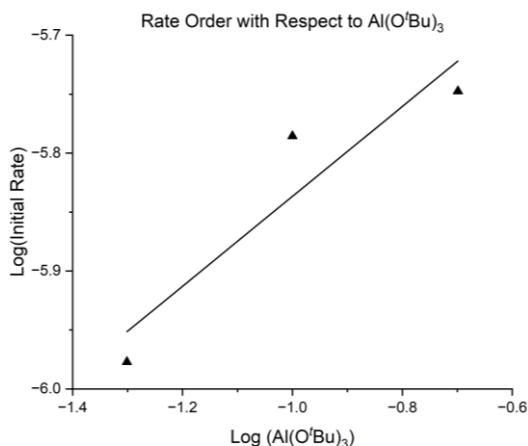
Scheme 3.9 Time versus absorbance plots showing the consumption of tetrahydropyran **160** over the first 5000 seconds for reactions conducted with 0.20 M, 0.10 M, and 0.05 M $\text{Al}(\text{Ot-Bu})_3$, used for initial rate determination.

Concentration of $\text{Al}(\text{Ot-Bu})_3$ (mol dm^{-3})	$\text{Log}[\text{Al}(\text{Ot-Bu})_3]$	Initial rate, v_0 (mAU s^{-1})	$\text{Log}(v_0)$
0.05	-1.3010	1.0542×10^{-6}	-5.9770
0.1	-1	1.6385×10^{-6}	-5.7856
0.2	-0.6990	1.7888×10^{-6}	-5.7474

Table 3.1 Initial rates determined over the first 5000 seconds at varying concentrations of $\text{Al}(\text{Ot-Bu})_3$, with corresponding logarithmic values used for rate order analysis.

A plot of the logarithm of the initial reaction rates against the logarithm of the corresponding concentrations of $\text{Al}(\text{Ot-Bu})_3$ was constructed to determine the reaction order with respect to the aluminium catalyst (**Scheme 3.10**). The gradient of the resulting line of best fit indicated a

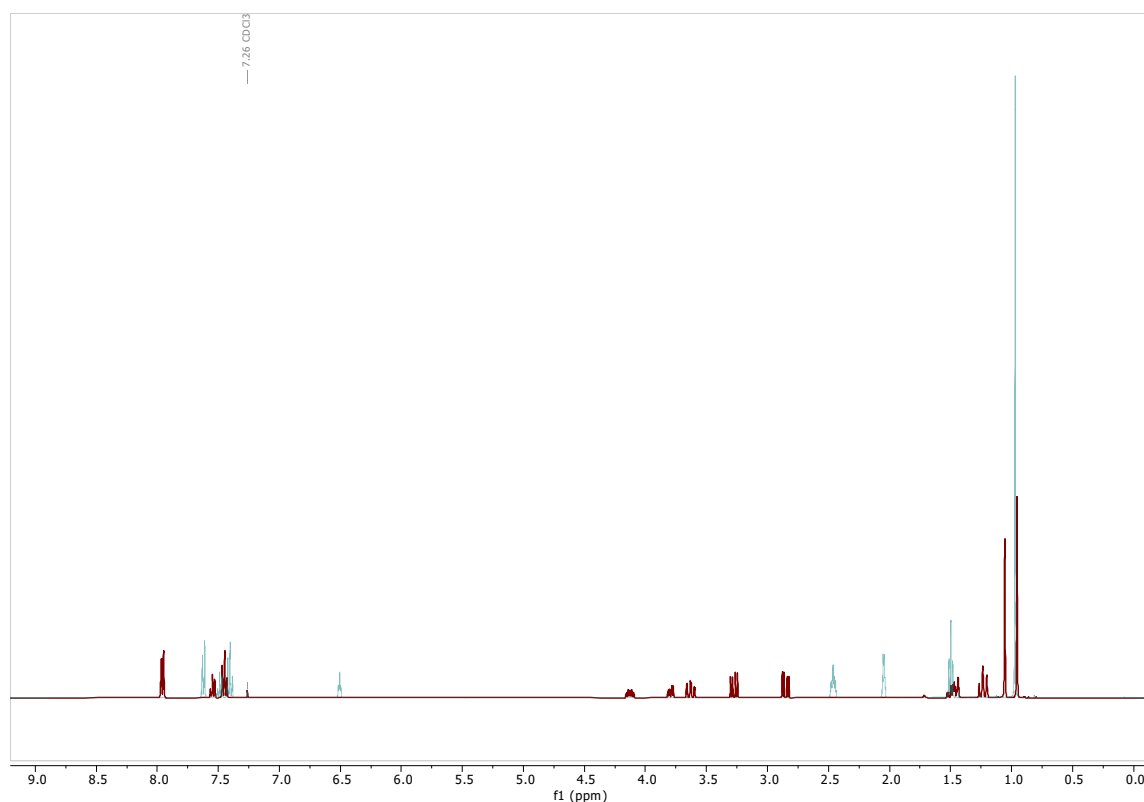
rate order of 0.381. However, this result was considered inconclusive due to significant deviations of the data points from the fitted line, suggesting a weak linear correlation. Furthermore, the use of only three data points was generally considered insufficient to reliably determine the order of a reaction.



Scheme 3.10 Plot of $\log v_0$ versus $\log[\text{Al}(\text{Ot-Bu})_3]$ for the determination of the reaction order with respect to $\text{Al}(\text{Ot-Bu})_3$.

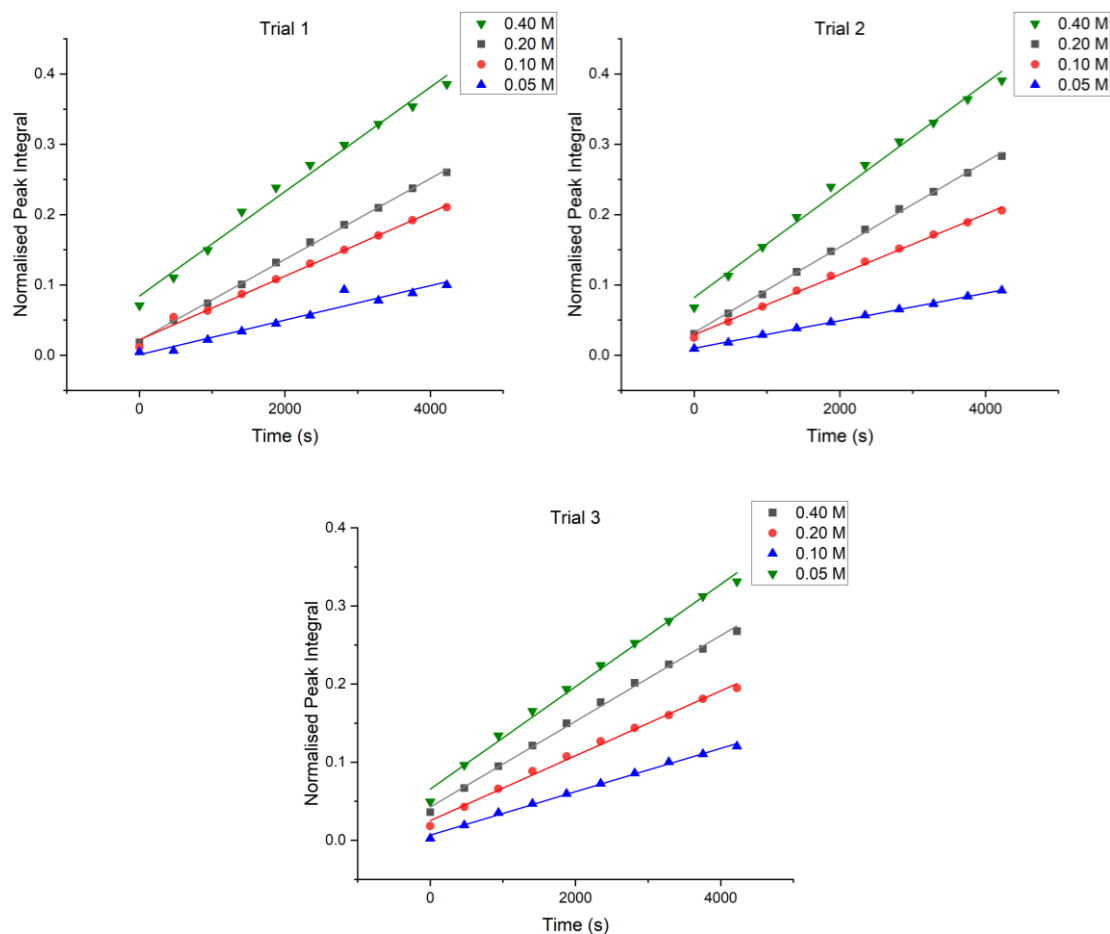
To obtain a more accurate value for the rate order with respect to $\text{Al}(\text{Ot-Bu})_3$, variable-temperature NMR spectroscopy was employed. This non-invasive technique enables the monitoring of reaction kinetics without direct contact with the reaction mixture, thereby eliminating instrumental errors such as catalyst deposition on detection surfaces or signal scattering.

Kinetic experiments were conducted in NMR tubes using *p*-xylene-*d*₁₀ as the solvent, with 1.0 equivalent of 1,3,5-trimethoxybenzene included as the internal standard. This compound was selected because its diagnostic proton signal at 6.08-6.32 ppm does not overlap with any resonances corresponding to either the reactant or the product (**Scheme 3.11**). The resonance at 6.32-6.45 ppm was used as the diagnostic signal for cyclohexene **164**.



Scheme 3.11 Overlay of the ^1H NMR spectra of tetrahydropyran **160** and cyclohexene **164**.

However, the cyclohexene signal was found to overlap with the downfield ^{13}C satellite peak of the 1,3,5-trimethoxybenzene signal at 6.59 ppm. To correct for this, the upfield ^{13}C satellite peak at 6.27 ppm was separately integrated and subtracted from the integral of the overlapping cyclohexene signal. Reaction mixtures containing varying concentrations of $\text{Al}(\text{Ot-Bu})_3$ were heated to 110 °C, and quantitative ^1H NMR spectra were recorded over a 70-minute period. Each experiment was repeated three times to ensure consistency and reproducibility of the data. For the purpose of calculating initial rates, plots of time versus normalised peak integrals for cyclohexene **164** were constructed (**Scheme 3.11**; for detailed experimental procedures and tabulated data, see **Chapter 7.2**). The gradients of the resulting lines of best fit were taken as the initial rates of reaction (**Tables 3.2–3.4**).



Scheme 3.12 Time versus normalised peak integral for the formation of cyclohexene **164** in reactions conducted with 0.40 M, 0.20 M, 0.10 M and 0.05 M $\text{Al}(\text{Ot-Bu})_3$, used for initial rate determination.

Concentration of $\text{Al}(\text{Ot-Bu})_3$ (mol dm^{-3})	$\text{Log}[\text{Al}(\text{Ot-Bu})_3]$	Initial rate, ν_0 (s^{-1})	$\text{Log}(\nu_0)$
0.05	-1.3010	2.7771×10^{-5}	-4.5564
0.10	-1.0000	4.1507×10^{-5}	-4.3819
0.20	-0.6990	5.4878×10^{-5}	-4.2606
0.40	-0.3979	7.4228×10^{-5}	-4.1294

Table 3.2 Initial rates determined for trial 1 at varying concentrations of $\text{Al}(\text{Ot-Bu})_3$, with corresponding logarithmic values used for rate order analysis.

Concentration of $\text{Al}(\text{Ot-Bu})_3$ (mol dm^{-3})	$\text{Log}[\text{Al}(\text{Ot-Bu})_3]$	Initial rate, v_0 (s^{-1})	$\text{Log}(v_0)$
0.05	-1.3010	2.2257×10^{-5}	-4.6525
0.10	-1.0000	4.2945×10^{-5}	-4.3671
0.20	-0.6990	6.0758×10^{-5}	-4.2164
0.40	-0.3979	7.6164×10^{-5}	-4.1182

Table 3.3 Initial rates determined for trial 2 at varying concentrations of $\text{Al}(\text{Ot-Bu})_3$, with corresponding logarithmic values used for rate order analysis.

Concentration of $\text{Al}(\text{Ot-Bu})_3$ (mol dm^{-3})	$\text{Log}[\text{Al}(\text{Ot-Bu})_3]$	Initial rate, v_0 (s^{-1})	$\text{Log}(v_0)$
0.05	-1.3010	2.4524×10^{-5}	-4.6104
0.10	-1.0000	4.5199×10^{-5}	-4.3449
0.20	-0.6990	5.7485×10^{-5}	-4.2404
0.40	-0.3979	6.5545×10^{-5}	-4.1835

Table 3.4 Initial rates determined for trial 3 at varying concentrations of $\text{Al}(\text{Ot-Bu})_3$, with corresponding logarithmic values used for rate order analysis.

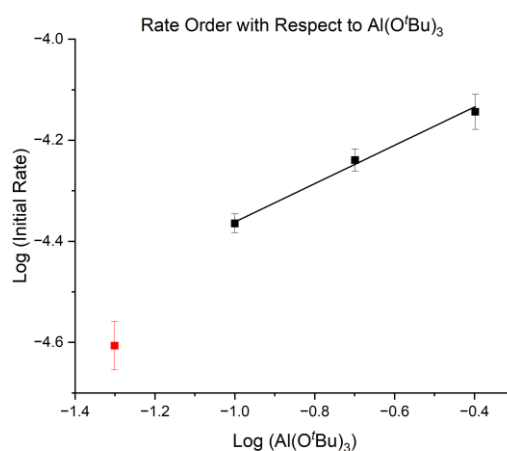
Concentration of $\text{Al}(\text{Ot-Bu})_3$ (mol dm^{-3})	$\text{Log}[\text{Al}(\text{Ot-Bu})_3]$	Mean log (initial rate)	Standard deviation
0.05	-1.3010	-4.6065	4.8189×10^{-2}
0.10	-1.0000	-4.3646	1.8627×10^{-2}
0.20	-0.6990	-4.2391	2.2132×10^{-2}
0.40	-0.3979	-4.1437	3.4872×10^{-2}

Table 3.5 Mean logarithmic values of the initial reaction rates at varying concentrations of $\text{Al}(\text{Ot-Bu})_3$, with associated standard deviations.

A plot of the mean logarithm of the initial reaction rates against the logarithms of the corresponding concentrations of $\text{Al}(\text{Ot-Bu})_3$ was constructed, with error bars calculated for each data point based on the standard deviation (**Scheme 3.13**). The red data point, corresponding to 0.05 M $\text{Al}(\text{Ot-Bu})_3$, was treated as an outlier and excluded from the gradient calculation, as it deviated significantly from the linear trend established by the remaining points. This data point

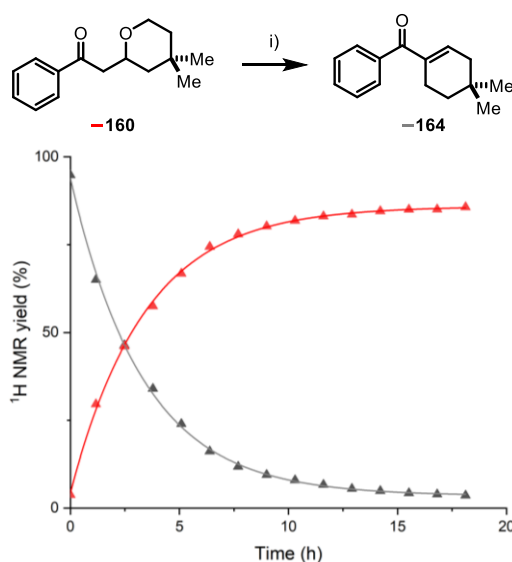
also exhibited a large error bar in the x-direction, indicating a high degree of uncertainty in its measurement. The observed deviation and associated uncertainty may be attributed to the increased relative impact of experimental uncertainty (e.g. mass measurement uncertainty) at lower concentrations. From the resulting plot, a rate order of 0.379 with respect to $\text{Al}(\text{Ot-Bu})_3$ was obtained, which closely matches the value independently derived from the ReactIR study.

Dr C.E. Lunt-Laurin subsequently derived the rate order with respect to $\text{Al}(\text{Ot-Bu})_3$ using a set of appropriate assumptions (for details, see **Chapter 7.3**). In this derivation, a rate order close to 0.5 implies the involvement of a single aluminium alkoxide species in the transition state (i.e. an active monomer in an equilibrium biased towards a dimer), which contrasts with computational predictions suggesting a dimeric active species. However, interpretation of the experimental data was complicated by the limited solubility of $\text{Al}(\text{Ot-Bu})_3$. At high concentrations, undissolved white solids were visible in the NMR tubes, which may have led to an underestimation of the effective catalyst concentration. In addition, water, a by-product of the subsequent intramolecular aldol condensation, reacts rapidly with $\text{Al}(\text{Ot-Bu})_3$ to form Al_2O_3 , which is itself capable of catalysing the 1,5-hydride shift. The presence of such secondary catalytic species introduces an additional variable that can influence the reaction kinetics, thereby challenging the validity of the original assumptions and potentially making the derived rate order unreliable.



Scheme 3.13. Plot of $\log v_0$ versus $\log[\text{Al}(\text{Ot-Bu})_3]$ for the determination of the reaction order with respect to $\text{Al}(\text{Ot-Bu})_3$.

To gain further insight into the reaction profile, the transformation was monitored over an extended period using ^1H NMR spectroscopy at an $\text{Al}(\text{Ot-Bu})_3$ concentration of 0.20 M (**Scheme 3.14**; for detailed experimental procedures and tabulated data, see **Chapter 7.2**). The reaction progress was followed over 18 h, during which a gradual decrease in the resonance corresponding to tetrahydropyran **160** was observed, accompanied by the formation of cyclohexene **164**. The reaction reached completion after approximately 14 h. Notably, no intermediate species were detected at any point during the reaction, suggesting that the intramolecular aldol condensation proceeds rapidly following the hydride shift, preventing the accumulation of the intermediate ketoaldehyde.



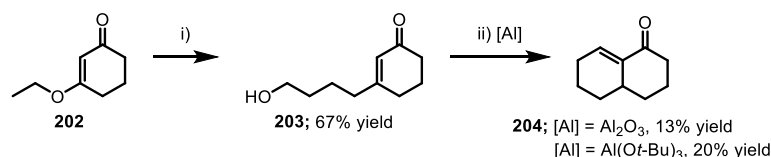
Scheme 3.14. Monitoring of the aluminium-mediated rearrangement by ^1H NMR spectroscopy. Reagents and conditions: i) $\text{Al}(\text{Ot-Bu})_3$ (1.0 equiv.), 1,3,5-(MeO) $_3\text{C}_6\text{H}_3$ (1.0 equiv.), *p*-xylene (0.2 M), 110 °C.

In conclusion, kinetic studies employing *in situ* ReactIR and variable-temperature NMR revealed a reaction order of approximately 0.38 with respect to $\text{Al}(\text{Ot-Bu})_3$, suggesting the possible involvement of a monomeric aluminium species in the rate-determining step. Although this finding is consistent across two independent experimental techniques, it contrasts with computational studies, which predict a dimeric species as the catalytically active form. The accuracy of the kinetic data may be affected by experimental limitations, such as the limited solubility of $\text{Al}(\text{OtBu})_3$ and the potential formation of secondary aluminium-containing species, either of which could perturb the measured reaction rates. Extended NMR monitoring

confirmed that the overall transformation proceeds cleanly, with no observable intermediates, thereby supporting a mechanism in which the intramolecular aldol condensation occurs rapidly following the 1,5-hydride shift.

3.4 Constrained Model System

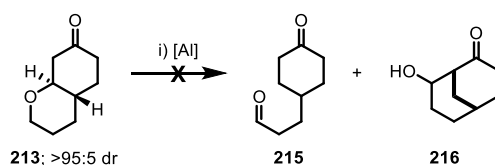
To support the DFT calculations, two geometrically constrained enones were synthesised. Enone **203** was prepared from commercially available 3-ethoxycyclohex-2-en-1-one **202** via Grignard addition followed by acidic work-up (**Scheme 3.15**). This enone was selected because it is conformationally locked in the *E-s-trans* geometry, which was predicted to possess the second-lowest free energy barrier for the 1,5-hydride shift. Pleasingly, subjecting enone **203** to the 1,5-hydride shift conditions in the presence of aluminium oxide afforded cyclohexene **204** in 13% yield, which improved to 20% upon switching to $\text{Al}(\text{Ot-Bu})_3$. Further investigation suggested that the low yields were likely due to the volatility of cyclohexene **204**. To address this issue, a modified enone **207** bearing gem-dimethyl substituents on the backbone was synthesised in an effort to reduce product volatility and thereby improve the overall yield of the transformation.



Scheme 3.15 Preparation and reactivity of *E-s-trans* enone **203**. Reagents and conditions: i) MeMgBr (1.5 equiv.), $\text{HO}(\text{CH}_2)_4\text{Cl}$ (1.5 equiv.), Mg turnings (2.0 equiv.), 0 °C, 1.5 h; ii) Al_2O_3 (5.0 equiv.) or $\text{Al}(\text{Ot-Bu})_3$ (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h.

Enone **207** was synthesised in two steps from commercially available dimedone **205** (**Scheme 3.16**). The first step involved the formation of enol ether **206** in 74% yield, facilitated by the use of a Dean-Stark apparatus to efficiently remove water, a crucial factor in achieving high conversion. In the second step, enol ether **206** underwent Grignard addition followed by acidic work-up, using the same protocol previously employed for the synthesis of enone **203**, to afford the desired enone **207** in 63% yield. The resulting enone **207** was then subjected to 1,5-hydride shift conditions using either Al_2O_3 or $\text{Al}(\text{Ot-Bu})_3$, affording cyclohexene **208** in 41% and 43% yield,

The absence of the desired product **216** could be attributed to the lack of a viable intramolecular aldol reaction pathway within the system. However, the uncyclised intermediate **215** was also not observed, providing further evidence that the hydride shift does not proceed through a *Z-s-trans* configured enone. This observation is consistent with computational predictions, which indicate that this conformation is associated with the highest energy barrier and is therefore not a viable pathway under the reaction conditions examined. An alternative explanation for the lack of reactivity may lie in the inability of bicyclic ketone **213** to undergo tetrahydropyran ring opening, as attempts to intercept the proposed intermediate **214** via an *in situ* Diels–Alder cycloaddition with pentamethylcyclopentadiene were unsuccessful.



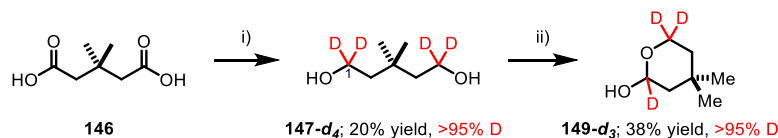
Scheme 3.18 Reactivity of *Z-s-trans* enone **213**. Reagents and conditions: i) Al_2O_3 (5.0 equiv.) or $\text{Al}(\text{Ot-Bu})_3$ (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h.

3.5 Double Label Crossover Experiment

Having established the role of $\text{Al}(\text{Ot-Bu})_3$ in the key rearrangement step, the investigation then turned to elucidating the nature of the hydride transfer process. In principle, this transformation could proceed *via* either an intermolecular Cannizzaro-type pathway or an intramolecular 1,5-hydride shift. To distinguish between these mechanistic possibilities, a double-label crossover experiment was designed.

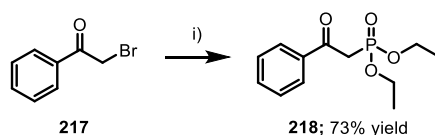
Dr R. J. Armstrong prepared deuterated lactol **149-*d*₃** from diacid **146** *via* a two-step sequence. In the first step, diacid **146** was reduced to diol **147-*d*₄** in 20% yield using deuterated borane, generated *in situ* from commercial NaBD_4 and iodine (**Scheme 3.19**). Quantitative ^1H NMR analysis of the product revealed an integral of 0.20 for H_1 across the four symmetrical positions, indicating greater than 95% deuterium incorporation at each site. This result was further confirmed by ^2H NMR spectroscopy, which showed a singlet at 3.70 ppm corresponding to deuterium at H_1 . Additionally, the ^{13}C NMR displayed a quintet for C_1 with a 1:2:3:2:1 splitting

pattern and a J -coupling constant of 21.0 Hz, consistent with two C–D couplings. Inspired by the precedent set by Corey and co-workers in 1995,^[70] diol **147-d₄** was successfully oxidised to lactol **149-d₃** in 38% yield.



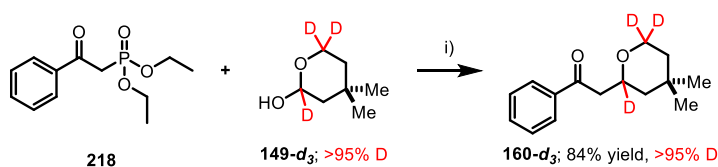
Scheme 3.19 Preparation of deuterated lactol **149-d₃** by Dr R. J. Armstrong. Reagents and conditions: i) NaBD₄ (3.0 equiv.), THF (0.2 M), then I₂ (1.2 equiv.), 0 °C to RT, 48 h; ii) 30% IBX with stabiliser (1.2 equiv.), 3:1 acetone/DMSO (0.1 M), RT, 5 h.

The Horner-Wadsworth-Emmons (HWE) coupling partner, phenyl phosphonate **218** was synthesised *via* an Arbuzov reaction by heating α -bromoketone **217** and triethyl phosphite under neat conditions (**Scheme 3.20**).



Scheme 3.20 Preparation of phenyl phosphonate **218**. Reagents and conditions: i) P(OEt)₃ (1.1 equiv.), 160 °C, 24 h.

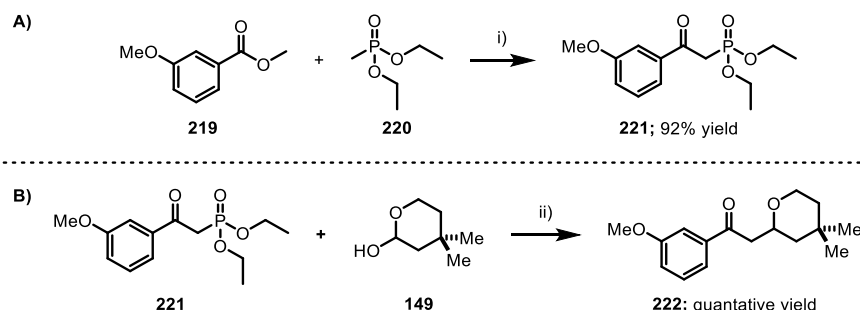
With deuterated lactol **149-d₃** and phenyl phosphonate **218** in hand, Dr R. J. Armstrong applied the optimised HWE reaction conditions, affording the desired deuterated tetrahydropyran **160-d₃** in 84% yield. Deuterium incorporation was subsequently assessed by quantitative ¹H, ²H, and ¹³C NMR spectroscopy, which confirmed greater than 95% incorporation at each labelled position (for further details, see **Chapter 6**).



Scheme 3.21 Preparation of deuterated tetrahydropyran **160-d₃** by Dr R. J. Armstrong. Reagents and conditions: i) NaH (1.2 equiv.), PhMe (0.2 M), 110 °C, 16 h.

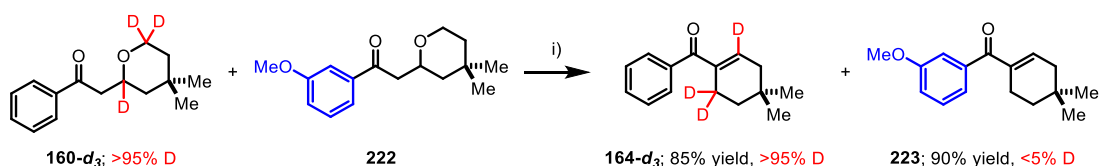
Tetrahydropyran **222** was selected as the non-deuterated substrate for the crossover experiment due to its structural similarity to deuterated tetrahydropyran **160-d₃**, differing only by the presence of a methoxy substituent. This minimal variation ensured that the two compounds would exhibit highly comparable ¹H NMR spectra, thereby facilitating accurate analysis of crossover products. Dr R. J. Armstrong synthesised phosphonate **221** by deprotonating methyl diethyl phosphonate **220** with LDA at 0 °C, followed by a Claisen-type

condensation with commercially available ester **219** (Scheme 3.22A). The resulting phosphonate **221** was then reacted with lactol **149** under standard HWE conditions to afford tetrahydropyran **222** in quantitative yield (Scheme 3.22B).



Scheme 3.22 Preparation of tetrahydropyran **222** by Dr R. J. Armstrong. Reagents and conditions: i) DIPA (2.3 equiv.), *n*-BuLi (2.2 equiv.), THF (0.2 M), 0 °C, 5 min; ii) NaH (1.2 equiv.), PhMe (0.2 M), 110 °C, 16 h.

When Dr R. J. Armstrong subjected a 1:1 mixture of deuterated tetrahydropyran **160-*d*₃** and non-deuterated tetrahydropyran **222** to the standard 1,5-hydride shift reaction conditions, the resulting products were identified as cyclohexene **164-*d*₃**, exhibiting greater than 95% deuterium incorporation, and cyclohexene **223**, with no detectable deuterium labelling. The extent and distribution of deuterium incorporation were confirmed by quantitative ¹H, ²H, and ¹³C NMR spectroscopy (for further details, see Chapter 7.4). These results strongly support the hypothesis that the hydride transfer proceeds *via* an intramolecular mechanism. If an intermolecular pathway were operative, significant hydrogen–deuterium exchange between the two substrates would be expected, leading to partial deuterium incorporation in both cyclohexene products. However, the complete retention of deuterium in cyclohexene **164-*d*₃** alongside its complete absence in cyclohexene **223**, clearly demonstrates that the hydride transfer occurs exclusively within a single molecule.



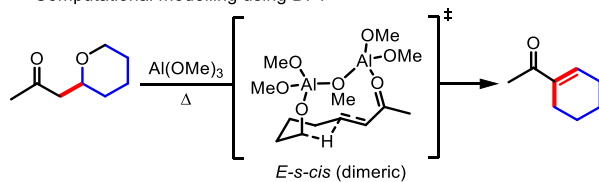
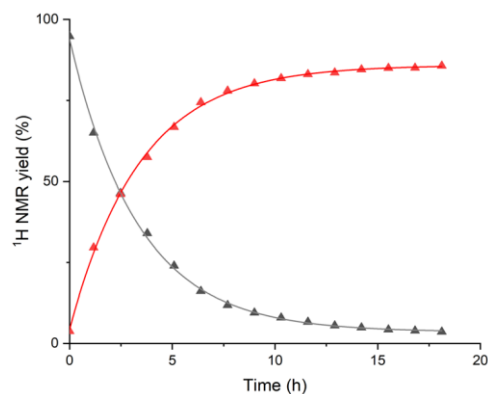
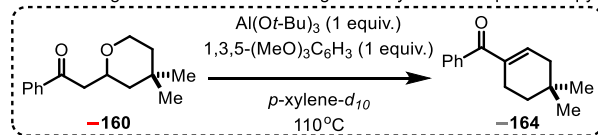
Scheme 3.23 Double label crossover experiment performed by Dr R. J. Armstrong. Reagents and conditions: i) Al(*O*-*t*-Bu)₃ (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h.

3.6 Conclusion

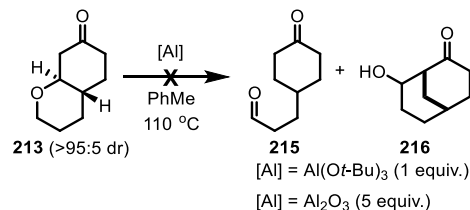
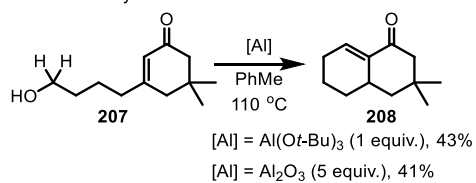
This chapter has explored the mechanistic and kinetic aspects of the aluminium-catalysed 1,5-hydride shift, combining computational predictions with experimental validation to elucidate the nature of the active catalytic species and the operative reaction pathway (**Scheme 3.24**). DFT calculations revealed a strong energetic preference for dimeric Lewis acid-promoted pathways, with the *E-s-cis* enone conformation identified as the most favourable transition state (**A**). In contrast, the *Z-s-trans* enone was predicted to be energetically inaccessible due to its high activation barrier, making it the least favourable of all conformers. This prediction was experimentally validated using a geometrically constrained *Z-s-trans* isomer, which was found to be unreactive under the standard reaction conditions (**C**); however, this lack of reactivity may arise from the absence of the initial ring-opening step required prior to the 1,5-hydride shift.

Kinetic studies employing both *in situ* ReactIR and variable-temperature ^1H NMR spectroscopy gave a reaction order of 0.38 with respect to $\text{Al}(\text{Ot-Bu})_3$, suggesting the possible involvement of a monomeric aluminium species. However, given the limitations associated with these experiments (such as solubility issues and potential secondary catalysis), the validity of this conclusion remains uncertain and should be interpreted with caution. A reaction profile was obtained using variable-temperature ^1H NMR spectroscopy, in which no intermediates were detected, indicating that the subsequent intramolecular aldol condensation occurs rapidly (**B**). Finally, a double-label crossover experiment conclusively demonstrated that the 1,5-hydride shift occurs exclusively *via* an intramolecular process, as no hydrogen–deuterium exchange was detected between deuterated and non-deuterated substrates (**D**).

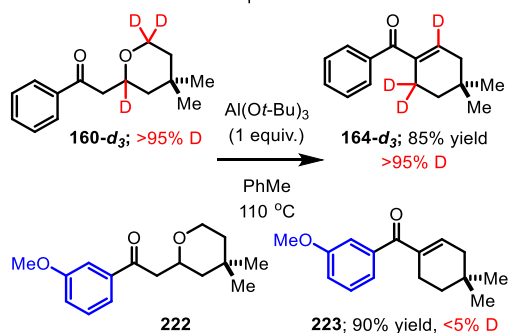
A. Computational modelling using DFT

B. Monitoring the Al-mediated rearrangement by ^1H -NMR spectroscopy

C. Geometrically constrained substrates



D. Double label crossover experiment

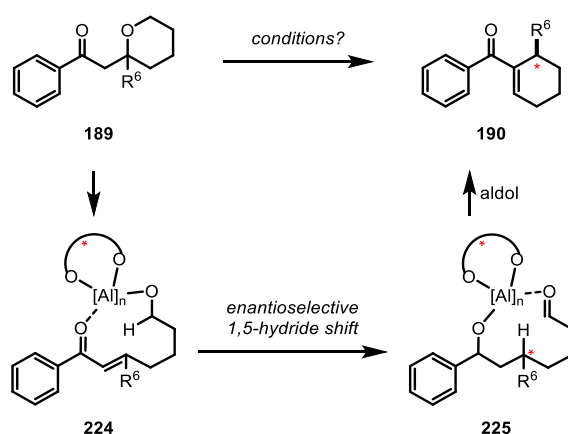


Scheme 3.24 Mechanistic investigations of the key 1,5-hydride shift step.

Chapter 4: Asymmetric Hydride Shift Methodology

4.1 Introduction and Preliminary Results

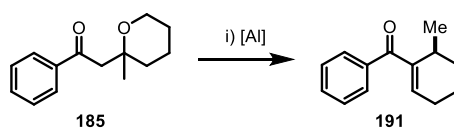
After establishing the mechanism of the 1,5-hydride shift reaction, attention was next directed towards developing an asymmetric variant of the 1,5-hydride shift–aldol cascade, with the aim of accessing enantioenriched cyclohexenes from racemic tetrahydropyran substrates. It was hypothesised that replacing two of the *tert*-butoxide ligands on aluminium with a chiral diol would introduce asymmetry into the transition state, thereby favouring the formation of a single enantiomer of the cyclohexene product (**Scheme 4.1**).



Scheme 4.1 Asymmetric synthesis of cyclohexene **190**.

For enantioinduction to occur during the 1,5-hydride shift, the open-chain enone intermediate must be substituted at the β -position. This key intermediate can be accessed from tetrahydropyrans bearing an R^6 substituent, a substitution pattern that has previously been achieved *via* cuprate addition methodologies. Upon ring opening, these tetrahydropyran derivatives are capable of generating either the *E*- or *Z*-configured enone. Precise control over the resulting alkene geometry is critical, as it directly influences the stereochemical outcome of the transformation and is therefore essential for achieving high levels of enantioselectivity.

Methyl-substituted tetrahydropyran **185** was selected as the model substrate owing to its straightforward preparation and the observation that the corresponding 1,5-hydride shift proceeded in excellent yield (83%). The synthesis of tetrahydropyran **185** was previously described in **Chapter 2.3 (Scheme 2.14)**.



Entry	Diol Ligand	Yield ^(a) (%)	e.r. ^(b)
1	226	12	57:43
2	227	15	52:48
3	228	0	N/A
4	229	0	N/A
5	230	20	51:49
6	231	26	55.5:45.5

Table 4.1 Screening of chiral diols for the asymmetric synthesis of cyclohexene **191** by Dr L. B. Smith. Reagents and conditions: i) chiral diol (1.0 equiv.), *t*-BuOH (1.0 equiv.), AlMe₃ (1.0 equiv.), tetrahydropyran **185** (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h. a) Determined by quantitative ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard. (b) Determined by chiral HPLC against a racemic standard; the absolute stereochemistry of the major enantiomer was not assigned.

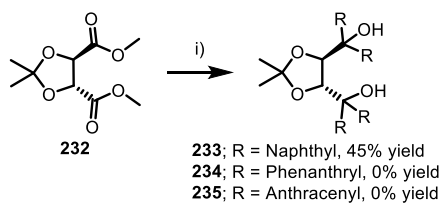
In preliminary studies, Dr L. B. Smith evaluated a small selection of commercially available diol ligands for the asymmetric 1,5-hydride shift–aldol cascade. In each case, the diol ligand was pre-

mixed with *tert*-butanol in toluene, followed by the addition of a solution of trimethylaluminium to generate the corresponding chiral aluminium complex *in situ*, which was then reacted with tetrahydropyran **185**. Reactions employing (*R*)-BINOL-derived ligands **226** and **227** (Entries **1** and **2**) afforded cyclohexene **191** in low yields (12-15%) and induced only a minor change in the enantiomeric ratio (determined by HPLC). Neither (*R,R*)-Jacobsen's ligand **228** (Entry **3**) nor (*R*)-VANOL ligand **229** (Entry **4**) catalysed the transformation, as no product formation was detected. The use of (*R*)-spirobiindane **230** (Entry **5**) resulted in a slightly improved yield of 20%, albeit with an essentially racemic product. Notably, (*R*)-TADDOL **231** (Entry **6**) delivered cyclohexene **191** in 26% yield and an enantiomeric ratio of 55.5:44.5. Among the ligands evaluated, (*R*)-TADDOL **231** provided the most favourable balance of yield and enantioselectivity and was therefore selected for further investigation.

4.2 Reaction Optimisation

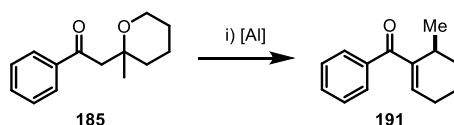
4.2.1 TADDOL Derivatives

Following established literature precedents,^[71] (*R*)-1-naphthyl-TADDOL **233** was successfully synthesised *via* direct Grignard addition to (*R*)-tartrate **232** (Scheme 4.2). Although no reported procedure exists for the preparation of phenanthryl- and anthracenyl-substituted TADDOLs **234** and **235**, we sought to extend this methodology, hypothesising that the same Grignard addition strategy would be applicable. However, both reactions failed to proceed as expected and instead yielded complex mixtures. This outcome is likely due to the increased steric bulk of the phenanthryl and anthracenyl Grignard reagents, which may hinder effective addition to the ester functionalities of the tartrate.



Scheme 4.2 Preparation of TADDOL-derived ligands **233-235**. Reagents and conditions: i) Mg turnings (8.5 equiv.), aryl bromide (8.0 equiv.), THF (0.2 M), 70 °C, 6 h.

Replacing the phenyl group on the TADDOL scaffold with a naphthyl substituent led to a significant improvement in both the yield and the enantiomeric ratio of the 1,5-hydride shift reaction (**Table 4.2**) The use of (*R*)-1-naphthyl-TADDOL **233** afforded cyclohexene **191** in 34% yield with an enantiomeric ratio of 65:35 (**Entry 1**). This improvement could be attributed to the greater steric bulk of the naphthyl substituent relative to the phenyl group, which could stabilise the aluminium complex and promote the formation of a more rigid and well-defined chiral environment.

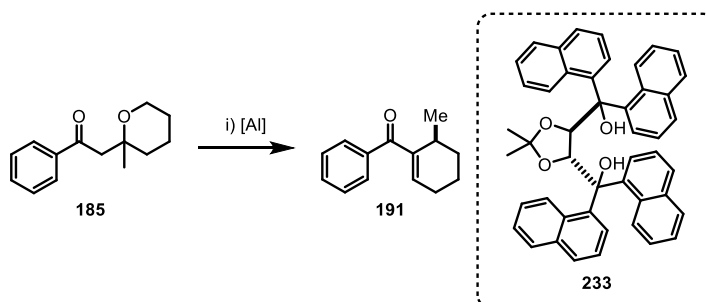


Entry	Diol Ligand	Yield ^(a) (%)	e.r. ^(b)
1	233	34	65:35

Table 4.2 Screening of chiral diols for the asymmetric synthesis of cyclohexene **191**. Reagents and conditions: i) chiral diol (1.0 equiv.), *t*-BuOH (1.0 equiv.), AlMe₃ (1.0 equiv.), tetrahydropyran **185** (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h. a) Determined by quantitative ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard. (b) Determined by chiral HPLC against a racemic standard; the absolute stereochemistry of the major enantiomer was not assigned.

The influence of the third coordination site on aluminium was next examined with respect to both the yield and enantiomeric ratio of cyclohexene **191** (**Table 4.3**). Replacing *tert*-butanol with a less sterically demanding ligand, such as 2-propanol (**Entry 1**), had a detrimental effect on the yield. Substitution with an electron-withdrawing phenol ligand (**Entry 2**) further reduced the yield to 7%. This result was somewhat unexpected, as the incorporation of an electron-withdrawing substituent was anticipated to increase the electron deficiency at the aluminium centre, thereby strengthening coordination strength and potentially improving catalytic activity. Interestingly, increasing the steric bulk around the phenyl ring by introducing methyl groups at both the *ortho*- and *para*-positions improved the yield to 28% (**Entry 3**), highlighting the

importance of steric effects in promoting reactivity. Despite these variations in yield, modifications at the third coordination site had no significant impact on the enantiomeric ratio.



Entry	Ligand	Yield ^(a) (%)	e.r. ^(b)
1	<i>i</i> -PrOH	17	64:36
2	PhOH	7	65:35
3	2,4,6-trimethylphenol	28	66:34

Table 4.3 Screening of alcohols for the asymmetric synthesis of cyclohexene **191**. Reagents and conditions: i) chiral diol **233** (1.0 equiv.), alcohol (1.0 equiv.), AlMe₃ (1.0 equiv.), tetrahydropyran **185** (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h. a) Determined by quantitative ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard. (b) Determined by chiral HPLC against a racemic standard; the absolute stereochemistry of the major enantiomer was not assigned.

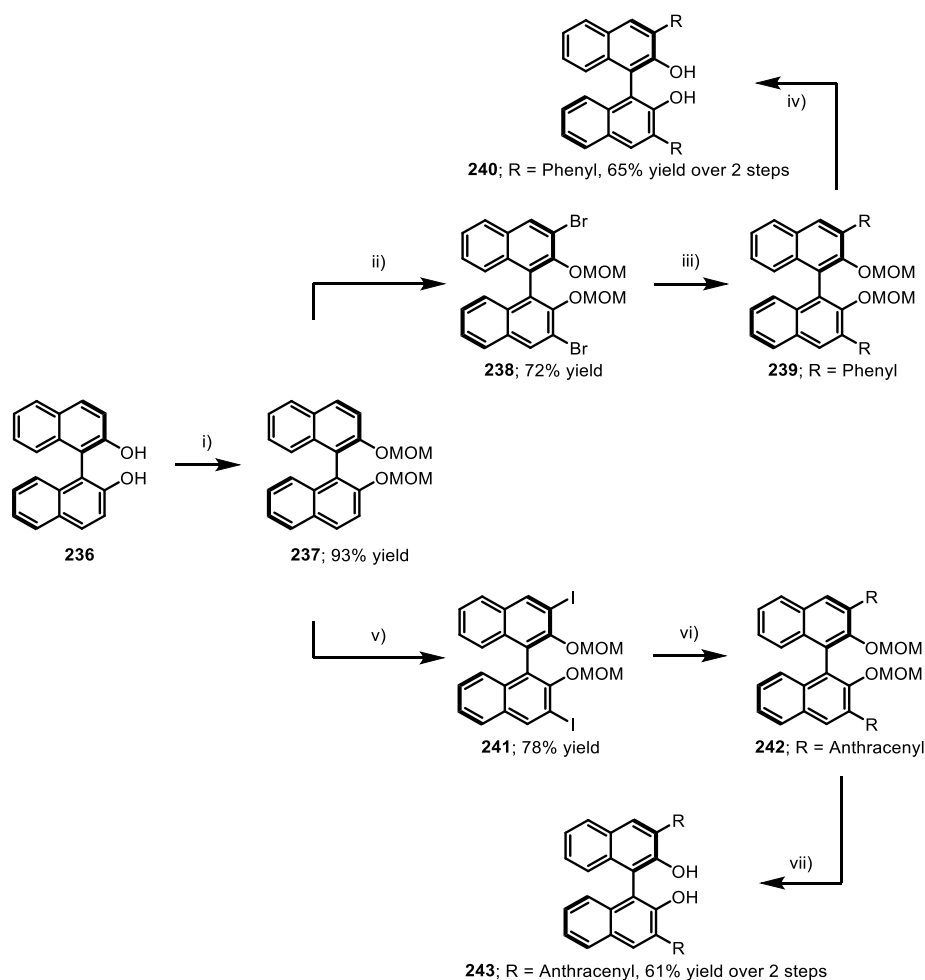
It is reasonable to conclude that increasing the steric bulk of the ligand improves both the yield and the enantiomeric ratio of cyclohexene **191**. However, previous attempts to introduce substituents larger than a naphthyl group onto the TADDOL framework (**Scheme 4.2**) were unsuccessful. As a result, rather than focusing exclusively on TADDOL-derived ligands, attention was redirected towards to BINOL-derived systems, which had also shown promising results in terms of yield and enantioselectivity in the preliminary studies (**Table 4.1, Entry 1**). The synthesis and application of BINOL-based ligands are well established in the literature, particularly due to their central role in the development of chiral phosphines and phosphoric acids, which have become widely employed in asymmetric catalysis over the past decade.

4.2.2 BINOL Derivatives

Following the work of Yamamoto and co-workers,^[72] (*R*)-6,6'-diphenyl-BINOL **240** was synthesised *via* a four-step sequence (**Scheme 4.3**). The process began with protection of (*R*)-BINOL **236** using bromomethyl methyl ether, affording the desired MOM-protected BINOL **237** in 93% yield. Directed *ortho*-lithiation using *n*-butyllithium, followed by electrophilic bromination, furnished the corresponding (*R*)-6,6'-dibromo-BINOL **238** in 72% yield. The resulting dibromo derivative **238** was then subjected to Suzuki cross-coupling with phenylboronic acid to provide MOM-protected (*R*)-6,6'-diphenyl-BINOL **239**. Due to difficulties in isolating compound **239** in analytically pure form, it was carried forward to the final step without further purification. Deprotection of the MOM groups using 12 M hydrochloric acid yielded the target (*R*)-6,6'-diphenyl-BINOL **240** in 65% yield over two steps.

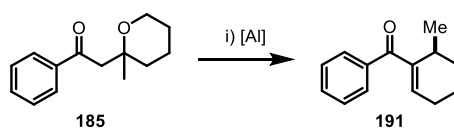
A slight modification was introduced for the preparation of (*R*)-6,6'-dianthracenyl-BINOL **243**.^[73] In this case, molecular iodine was used in place of a bromine source to afford (*R*)-6,6'-diiodo-BINOL **241** in 78% yield. The diiodo intermediate **241** was then subjected to Suzuki cross-coupling with anthracenylboronic acid to give MOM-protected (*R*)-6,6'-dianthracenyl-BINOL **242**, which was subsequently deprotected with 12 M HCl to yield the desired (*R*)-6,6'-dianthracenyl-BINOL **243** in 61% yield over two steps.

The diiodide is more effective than the corresponding dibromide in facilitating the Suzuki coupling with anthracenylboronic acid. This is because oxidative addition, which is the rate-determining step in the Suzuki–Miyaura catalytic cycle, occurs more readily with aryl iodides than with bromides due to their weaker C–I bonds and superior leaving ability.^[74] This increase in reactivity is particularly beneficial when coupling sterically demanding substrates such as anthracenyl derivatives, where less reactive electrophiles often result in poor yields or incomplete conversion.



Scheme 4.3 Preparation of BINOL-derived ligands **240** and **243**. Reagents and conditions: i) NaH (2.2 equiv.), MOMBr (2.2 equiv.), THF (0.5 M), 0 °C, 4 h; ii) *n*-BuLi (3.0 equiv.), C₂Br₂Cl₂ (3.0 equiv.), THF (0.3 M), RT, 2 h; iii) PhB(OH)₂ (2.4 equiv.), Pd(PPh₃)₄ (10 mol%), Na₂CO₃ (5.0 equiv.), DME (0.1 M), reflux, 12 h; iv) HCl (10 equiv.), dioxane (0.1 M), 80 °C, 6 h; v) *n*-BuLi (3.0 equiv.), I₂ (3.0 equiv.), THF (0.3 M), -78 °C, 2 h; vi) anthracenylboronic acid (2.4 equiv.), Pd(PPh₃)₄ (15 mol%), Ba(OH)₂ (5.0 equiv.), 3:1 dioxane:H₂O (0.1 M), 80 °C, 16 h; vii) 12 M HCl (10 equiv.), dioxane (0.1 M), 80 °C, 6 h.

Incorporation of a phenyl substituent at the *ortho*-position of the BINOL framework had little effect on the reaction yield but resulted in a modest improvement in enantioselectivity. The enantiomeric ratio has increased from 57:43 to 63:37 relative to the unsubstituted BINOL (**Table 4.4, Entry 1**). Replacement of the phenyl substituent with a bulkier anthracenyl group further enhanced the reaction outcome, affording a higher yield of 22% and a significantly improved enantiomeric ratio of 77.5:22.5 (**Entry 2**). In contrast, (*R*)-6,6'-diphenanthryl-BINOL **230**, synthesised by Dr N. Kratena using the same synthetic sequence, delivered a lower yield of 14% and a less favourable enantiomeric ratio of 40:60 (**Entry 3**).

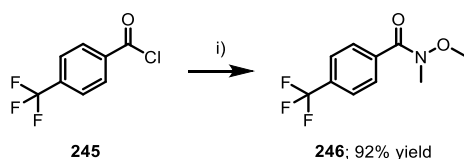


Entry	Diol Ligand	Yield ^(a) (%)	e.r. ^(b)
1	240	9	63:37
2	243	22	77.5:22.5
3	244	14	60:40

Table 4.4 Screening of chiral diols for the asymmetric synthesis of cyclohexene **191**. Reagents and conditions: i) chiral diol (1.0 equiv.), *t*-BuOH (1.0 equiv.), AlMe₃ (1.0 equiv.), tetrahydropyran **185** (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h. a) Determined by quantitative ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard. (b) Determined by chiral HPLC against a racemic standard; the absolute stereochemistry of the major enantiomer was not assigned.

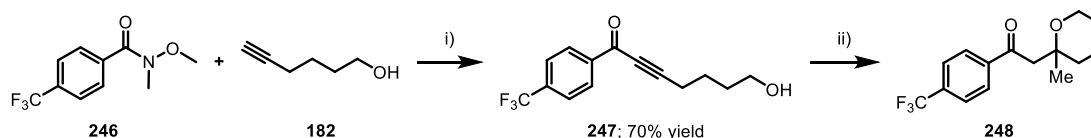
Although the enantiomeric ratio of product **191** improved significantly to 77.5:22.5, the overall reaction yield remained unsatisfactory. To address this limitation, the substrate was modified by introducing a trifluoromethyl (-CF₃) group onto the aryl ring. As a strongly electron-withdrawing group, the CF₃ substituent was expected to draw electron density away from the double bond, thereby enhancing its ability to accept the hydride, which we assumed was the rate determining step of the reaction. Unlike the phenyl-substituted Weinreb amide, the corresponding trifluoromethyl-substituted Weinreb amide **232** is not commercially available;

however, it can be readily synthesised in a single step from the corresponding acid chloride **231** (Scheme 4.4).



Scheme 4.4 Preparation of Weinreb amide **246**. Reagents and conditions: i) $\text{CH}_3\text{ONHCH}_3\cdot\text{HCl}$ (1.1 equiv.), Et_3N (3.0 equiv.), CH_2Cl_2 (0.3 M), RT, 16 h.

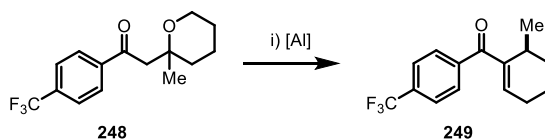
Following the same cuprate addition approach described in Chapter 2.3 (Scheme 2.14), hex-5-yn-1-ol **182** was deprotonated using *n*-butyllithium and subsequently reacted with Weinreb amide **246** to afford ynone **247** in 70% yield. The resulting ynone **247** was then subjected to conjugate addition with a methyl-substituted Gilman cuprate, furnishing tetrahydropyran **248** in 86% yield following *in situ* cyclisation.



Scheme 4.5 Preparation of tetrahydropyran **248**. Reagents and conditions: i) *n*-BuLi (2.4 equiv.), THF (0.3 M), RT, 1 h; ii) MeLi (6.0 equiv.), CuI (3.0 equiv.), THF (0.3 M), -78°C , 30 min.

The modified substrate **248** was then subjected to the standard conditions for the 1,5-hydride shift using both chiral diols **240** and **243** (Table 4.5). As predicted, the reaction yields improved with both ligands. However, the use of ligand **240** (Entry 1) led to a significant reduction in enantioselectivity, affording in a nearly racemic mixture. In contrast, ligand **243** (Entry 2) delivered the desired cyclohexene **249** in 61% yield with an enantiomeric ratio of 83:17. This improvement in both yield and enantioselectivity supported the continued use of ligand **243** in subsequent investigations.

Lowering the reaction temperature is a commonly employed strategy to enhance the enantioselectivity of asymmetric reactions. To examine this effect, the reaction temperature was lowered to 80°C (Entry 3). However, this adjustment resulted in a reduced yield of 30% and a diminished enantiomeric ratio of 76:24.

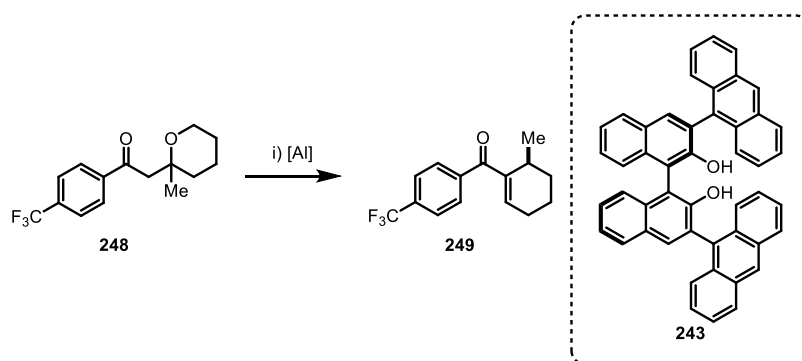


Entry	Diol Ligand	Temperature (°C)	Yield ^(a) (%)	e.r. ^(b)
1	240	110	22	51:49
2	243	110	(61)	83:17
3	243	80	30	76:24

Table 4.5 Screening of chiral diols for the asymmetric synthesis of cyclohexene **191**. Reagents and conditions: i) chiral diol (1.0 equiv.), *t*-BuOH (1.0 equiv.), AlMe₃ (1.0 equiv.), tetrahydropyran **185** (1.0 equiv.), PhMe (0.2 M), 16 h. a) Determined by quantitative ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard. (b) Determined by chiral HPLC against a racemic standard; the absolute stereochemistry of the major enantiomer was not assigned.

In this reaction, quantitative NMR analysis of the crude product showed a mass recovery of only 63%, with no detectable starting material or side products, suggesting potential instability of the product and/or the starting material under the reaction conditions. To assess the effect of reaction time on mass recovery, the reaction duration was first reduced to 4 h (**Table 4.6, Entry 1**). Interestingly, complete consumption of the starting material was observed, indicating that introduction of the trifluoromethyl group had significantly accelerated the reaction rate. Despite this, the mass recovery remained unsatisfactory. Further reductions in reaction time to

30 min (**Entry 2**) and 15 min (**Entry 3**) were subsequently explored. At 15 min, residual starting material was detected, indicating incomplete conversion; however, no significant improvement in mass recovery was observed. This unexpected outcome remained unresolved. Finally, performing the reaction at an elevated temperature of 130 °C in *m*-xylene for 15 min restored the yield to 66% and afforded the product with an enantiomeric ratio of 86:14.

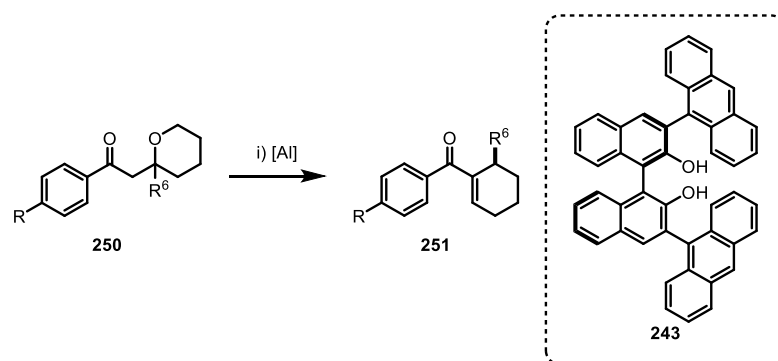


Entry	Modifications	Yield ^(a) (%)	e.r. ^(b)
1	4 h	(66)	84:16
2	30 min	(64)	83:17
3	15 min	(58)	82:18
4	130 °C in <i>m</i> -xylene, 15 min	66	86:14

Table 4.6 Screening of reaction temperature and reaction duration for the asymmetric synthesis of cyclohexene **249**. Reagents and conditions: i) chiral diol **243** (1.0 equiv.), *t*-BuOH (1.0 equiv.), AlMe₃ (1.0 equiv.), tetrahydropyran **248** (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h. (a) Yield refers to isolated material after flash column chromatography, and conversion is reported in parentheses, which was determined by quantitative ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard. (b) Determined by chiral HPLC against a racemic standard; the absolute stereochemistry of the major enantiomer was not assigned.

Having examined the available parameters for optimisation, attention was next directed towards evaluating different substrates to assess their reactivity under the established conditions. The synthesis of tetrahydropyrans **186** and **187** was previously discussed in **Chapter 2.3 (Scheme 2.14)** and these compounds were tested in the asymmetric reaction to investigate the influence of the β-substituent size on the enone. Heating tetrahydropyran **185** (**Entry 2**) with the pre-formed chiral aluminium complex at 130 °C resulted in a two-fold increase in the yield of cyclohexene **191** (compared to **Table 4.4. Entry 2**), while maintaining a comparable enantiomeric ratio. The yields for the *n*-butyl- (**Entry 3**) and *tert*-butyl-substituted cyclohexenes

(Entry 4) were 64% and 61%, respectively. Remarkably, both substrates afforded the products with high enantiomeric ratios of 96:4 and 96.5:3.5 – the highest observed so far. This outcome was both intriguing and unexpected: a relatively minor structural modification, involving replacement of a methyl group with a *n*-butyl substituent at the C₆ position, resulted in a substantial enhancement in enantioselectivity.



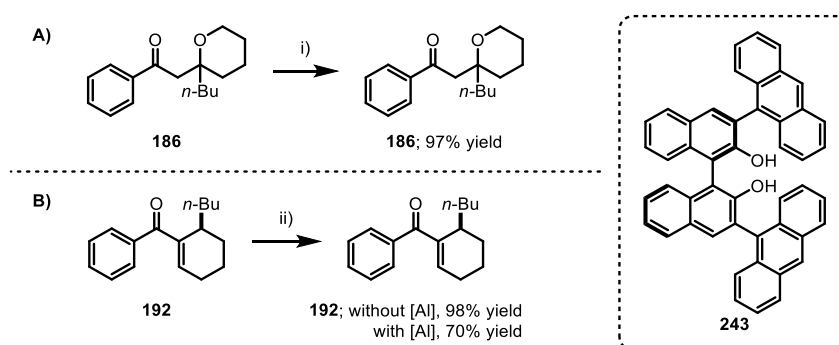
Entry	Starting Material	Product	Yield (%)	e.r. ^(a)
1 ^(b)	 248	 249	66	86:14
2	 185	 191	58	77:23
3	 186	 192	64	96:4
4	 187; >95:5 E/Z	 193	61	96.5:3.5

Table 4.7 Asymmetric synthesis of cyclohexene **191-193**. Reagents and conditions: i) chiral diol **243** (1.0 equiv.), *t*-BuOH (1.0 equiv.), AlMe₃ (1.0 equiv.), tetrahydropyran (1.0 equiv.), *m*-xylene (0.2 M), 130 °C, 16 h. (a) Determined by chiral HPLC against a racemic standard; the absolute stereochemistry of the major enantiomer was not assigned. (b) Reaction was heated for 15 min.

4.2.3 Catalytic Aluminium Species in the Hydride Shift

Quantitative NMR spectra for all four reactions described above showed only the desired product, with no detectable starting material or side products. Mediocre mass recovery has

been a persistent issue since the beginning this project, and neither lowering the reaction temperature nor shortening the reaction time had any significant effect on improving the overall mass recovery. To further investigate this problem, a series of control experiments was conducted. First, tetrahydropyran **186** (Scheme 4.6A) and cyclohexene **192** (Scheme 4.6B) were independently heated in *m*-xylene at 130 °C for 16 h in the absence of the chiral aluminium complex. In both cases, the compounds were efficiently recovered, indicating that both the starting material and the product are thermally stable. However, when cyclohexene **192** was subjected to the same conditions in the presence of the chiral aluminium complex, the recovery dropped to 70%.

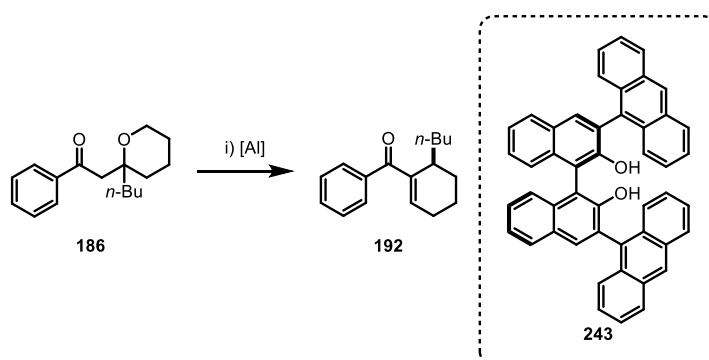


Scheme 4.6 Control experiment with tetrahydropyran **186** and cyclohexene **192**. Reagents and conditions: i) *m*-xylene (0.2 M), 130 °C, 16 h; ii) [Al] = chiral diol **243** (1.0 equiv.), *t*-BuOH (1.0 equiv.), AlMe₃ (1.0 equiv.); *m*-xylene (0.2 M), 130 °C, 16 h.

These findings suggest that the chiral aluminium complex not only facilitates the conversion of racemic tetrahydropyran **186** into enantioenriched cyclohexene **192** but may also contribute to product decomposition. To address this issue, the effect of using a sub-stoichiometric amount of the aluminium complex was investigated. This approach offered two potential advantages: first, reducing the quantity of aluminium complex lowers the overall consumption of chiral ligand, thereby decreasing the cost per reaction; and second, a reduced concentration of the aluminium species may suppress product degradation.

Using tetrahydropyran **186** as the model substrate, a series of optimisation studies were carried out to investigate the effect of aluminium catalyst loading (Table 4.8). Increasing the loading to 120 mol% (Entry 2) resulted in a decreased yield of 58%, while the enantiomeric ratio remained unchanged. This observation further supports the conclusion that an excess of aluminium

complex promotes product decomposition. Reducing the catalyst loading to 80 mol% (**Entry 3**) and 60 mol% (**Entry 4**) afforded yields and enantiomeric ratios comparable to those obtained at 100 mol%. However, at 40 mol% loading (**Entry 5**), both the yield and enantiomeric ratio declined, and residual starting material was detected. To address this, the reaction temperature was increased to 150 °C (**Entry 6**), which led to successful isolation of cyclohexene **192** in 73% yield with an enantiomeric ratio of 94:6. Further reduction of the catalyst loading to 30 mol% (**Entry 7**), led to a slight decrease in enantioselectivity, while at 20 mol% loading (**Entry 8**), a notable drop in yield was again observed.

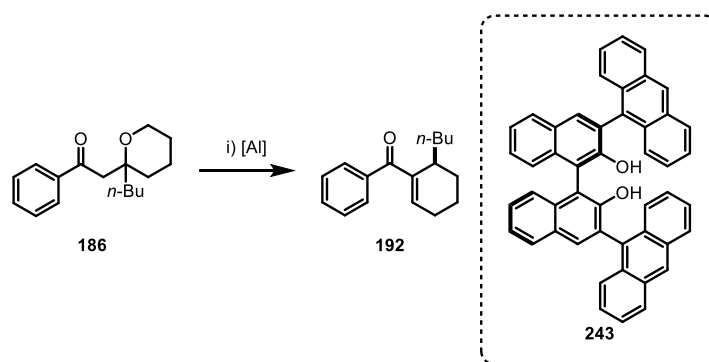


Entry	Temperature (°C)	[Al] loading (mol%)	Yield ^(a) (%)	e.r. ^(b)
1	130	100	64	96:4
2	130	120	(58)	95:5
3	130	80	(66)	95:5
4	130	60	(60)	94:6
5	130	40	(40)	90:10
6	150	40	73	94:6
7	150	30	74	91:9
8	150	20	(59)	87:13

Table 4.8 Screening of catalyst loading for the asymmetric synthesis of cyclohexene **192**. Reagents and conditions: i) chiral diol **243**, *t*-BuOH, AlMe_3 , tetrahydropyran **186** (1.0 equiv.), *m*-xylene (0.2 M), 130 °C, 16 h. (a) Yield refers to isolated material after flash column chromatography, and conversion is reported in parentheses, which was determined by quantitative ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. (b) Determined by chiral HPLC against a racemic standard; the absolute stereochemistry of the major enantiomer was not assigned.

We successfully reduced the aluminium complex loading to 40 mol% while maintaining both a good yield and enantiomeric ratio (**Table 4.8, Entry 6**). However, this optimisation did not

resolve the primary issue of poor mass recovery. Given that aluminium complexes are known to form strong dative coordinate bonds with carbonyl-containing compounds, attention was directed towards the quenching protocol. It was hypothesised that the product may chelate to the aluminium centre, thereby complicating isolation and contributing to the reduced mass recovery. The current quenching protocol involved dilution of the reaction mixture with approximately 30 mL of diethyl ether, followed by filtration through a short plug of silica. Alternative methods for aluminium complex removal were explored, including quenching with Rochelle's salt and the Fieser work-up (adapted from standard LiAlH_4 quenching protocols). However, both approaches resulted in lower yields relative to the established procedure (**Table 4.9**). The enantiomeric ratios for these reactions were not determined.

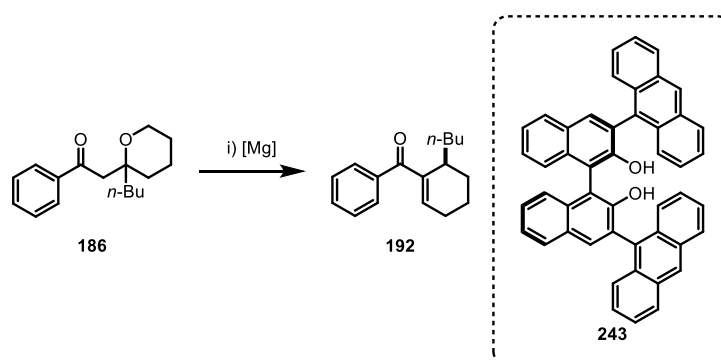


Entry	Quenching Protocol	Yield ^(a) (%)
1	Filter through silica plug	73
2	Rochelle's salt ($\text{C}_4\text{H}_4\text{O}_6\text{KNa} \cdot 4\text{H}_2\text{O}$) ^(b)	52
3	Fieser work-up ^(c)	66

Table 4.9 Screening of quenching protocols for the asymmetric synthesis of cyclohexene **192**. Reagents and conditions: i) chiral diol **243** (1.0 equiv.), *t*-BuOH (1.0 equiv.), AlMe_3 (1.0 equiv.), tetrahydropyran (1.0 equiv.), *m*-xylene (0.2 M), 130 °C, 16 h. (a) Determined by quantitative ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. (b) Reaction mixture was quenched with Rochelle's salt (2 mL/mmol tetrahydropyran), stirred vigorously and extracted with diethyl ether. (c) Reaction mixture diluted with diethyl ether and cooled to 0 °C; water (1 mL/g tetrahydropyran), 15% aqueous sodium hydroxide (1 mL/g tetrahydropyran), and water (3 mL/g tetrahydropyran) were then added sequentially. The reaction mixture was warmed to RT, stirred for 15 min, MgSO_4 was added, stirred for a further 15 min, and filtered to remove salts.

Next, we investigated the use of magnesium as a less chelating alternative to aluminium, motivated by its reported success in mild Lewis acid catalysis (**Table 4.10**).^[75] Owing to its lower charge density and larger ionic radius, magnesium is expected to form weaker interactions with

carbonyl groups, thereby reducing the likelihood of strong chelation and potentially simplifying product isolation. The chiral magnesium complex was prepared using the same protocol as its aluminium analogue: BINOL **243** was pre-mixed with *tert*-butanol in *m*-xylene, followed by the addition of a solution of di-*n*-butylmagnesium to generate the desired chiral complex. However, both stoichiometric (**Entry 1**) and sub-stoichiometric (40 mol%, **Entry 2**) loading resulted in poor outcomes. The reduced Lewis acidity of magnesium negatively impacted both the reaction yield and enantiomeric ratio, indicating that its catalytic activity was insufficient to promote the transformation effectively.



Entry	Temperature (°C)	[Mg] loading (mol%)	Yield ^(a) (%)	e.r. ^(b)
1	130	100	37	87:13
2	150	40	43	84:16

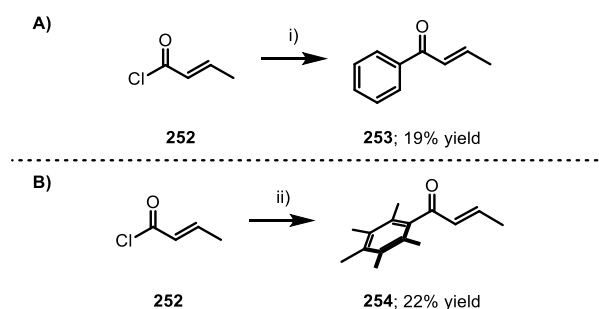
Table 4.10 Asymmetric synthesis of cyclohexene **186** with chiral magnesium complex. Reagents and conditions: i) chiral diol **243** (1.0 equiv.), *t*-BuOH (1.0 equiv.), (CH₃CH₂CH₂CH₂)₂Mg (1.0 equiv.), *m*-xylene (0.2 M), 16 h. (a) Determined by quantitative ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard. (b) Determined by chiral HPLC against a racemic standard; the absolute stereochemistry of the major enantiomer was not assigned.

4.2.4 Synthesis of Ph* Substrate

After several months of extensive optimisation of both the reaction conditions and catalyst systems without achieving the desired outcome, it was deemed necessary to re-evaluate the choice of substrate in order to identify potential limitations or structural features that might be impeding the reaction's success. All substrates examined up to this point had been aryl-substituted tetrahydropyrans bearing substituents at the C₆ position. Upon ring opening, these substrates generate enones with β-substitution – a structural feature known to hinder 1,4-

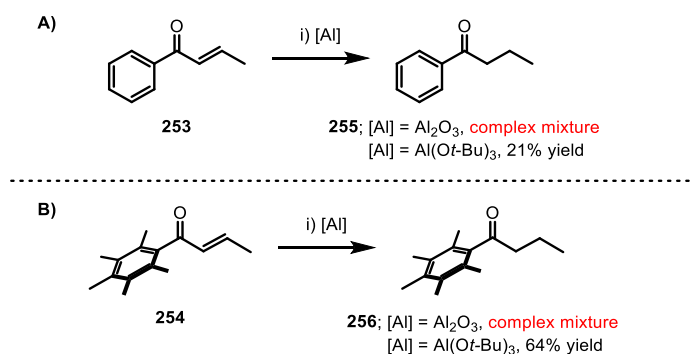
addition and shift selectivity towards 1,2-addition. We proposed that this structural characteristic may favour undesired side reactions and decomposition, thereby limiting the overall yield.

The Donohoe group has an extensive track record in the synthesis and application of Ph*-substituted ketones.^[76] Drawing inspiration from this precedent, we hypothesised that introducing a bulky Ph* group adjacent to the carbonyl could provide steric shielding, thereby suppress 1,2-addition pathways and reduce decomposition. To evaluate this hypothesis, two model substrates were synthesised: phenyl-substituted enone **253** (Scheme 4.7A) and Ph*-substituted enone **254** (Scheme 4.7B). Both enones were prepared *via* Friedel–Crafts acylation of crotonyl chloride **252** with the corresponding benzene derivative.



Scheme 4.7 Preparation of enone **253** and **254**. Reagents and conditions: i) AlCl_3 (1.5 equiv.), benzene (4.0 equiv.), 0 °C, 1 h; ii) AlCl_3 (1.2 equiv.), pentamethylbenzene (1.0 equiv.), CH_2Cl_2 (0.5 M), 0 °C, 2 h.

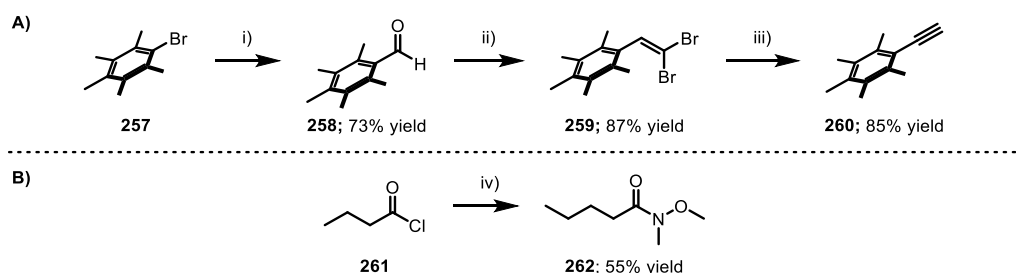
With both the phenyl-substituted enone **253** and the Ph*-substituted enone **254** in hand, each was subjected to heating at 110 °C in toluene with Al_2O_3 and $\text{Al}(\text{Ot-Bu})_3$, respectively (Scheme 4.8). While both enones gave complex mixtures when treated with aluminium oxide, an unexpected outcome was observed with $\text{Al}(\text{Ot-Bu})_3$: in both cases, the enones were converted into their corresponding reduced ketones. This transformation is unusual, as $\text{Al}(\text{Ot-Bu})_3$ does not possess reducing properties, making the underlying mechanism difficult to rationalise. In terms of isolated yields, the phenyl-substituted ketone **255** was obtained in 21% yield, whereas Ph*-substituted ketone **256** was obtained in 64% yield. Although the mechanistic basis remains unclear, these results are consistent with the hypothesis that incorporation of a Ph* group enhances substrate stability under the reaction conditions.



Scheme 4.8 Reactivity of enone **253** and **254** under 1,5-hydride shift conditions. Reagents and conditions: i) Al_2O_3 (5.0 equiv.) or $\text{Al}(\text{O}t\text{-Bu})_3$ (1.0 equiv.), PhMe (0.2 M), 110 °C, 16 h.

With the aim of accessing Ph^* -substituted tetrahydropyrans for further investigation, efforts were directed towards developing a suitable synthetic route. R^6 -substituted tetrahydropyrans are typically prepared *via* cuprate addition to an ynone intermediate, which is obtained through the nucleophilic addition of hex-5-yn-1-ol to a Weinreb amide. However, as a Ph^* Weinreb amide has not been reported in the literature, an alternative strategy was adopted. Ph^* acetylene **260** and *n*-butyl Weinreb amide **262** were synthesised independently and subsequently combined under nucleophilic addition conditions to afford the desired ynone intermediate.

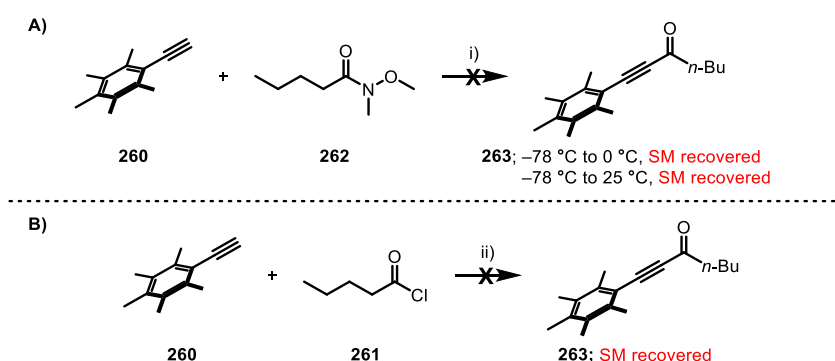
The synthesis of Ph^* acetylene **260** was accomplished through a three-step sequence involving lithium–halogen exchange, DMF quench, and the Corey-Fuchs reaction (**Scheme 4.9A**). Initially, pentamethylbromobenzene **257** was treated with *n*-butyllithium to induce lithium–bromide exchange, and the resulting organolithium species was quenched with DMF to afford the corresponding Ph^* -substituted aldehyde **258** in 73% yield. In the first step of the Corey-Fuchs protocol, aldehyde **258** was treated with carbon tetrabromide and triphenylphosphine to give dibromoalkene **259** in 85% yield. This intermediate was then treated with *n*-butyllithium to promote lithium–bromide exchange, followed by α -elimination to generate the reactive carbene species. A subsequent 1,2-shift yielded the desired terminal alkyne **260** in 88% yield. Separately, *n*-butyl Weinreb amide **262** was synthesised in a single step from the corresponding acid chloride **261** using *N,O*-dimethylhydroxylamine in the presence of triethylamine (**Scheme 4.9B**).



Scheme 4.9 Preparation of Ph* acetylene **260** and *n*-butyl Weinreb amide **262**. Reagents and conditions: i) *n*-BuLi (1.1 equiv.), DMF (2.0 equiv.), THF (0.5 M), RT, 16 h; ii) CBr₄ (2.0 equiv.), PPh₃ (4.0 equiv.), CH₂Cl₂ (0.5 M), RT, 4 h; iii) *n*-BuLi (2.0 equiv.), THF (0.2 M), RT, 1 h; iv) CH₃ONHCH₃·HCl (1.1 equiv.), Et₃N (3.0 equiv.), CH₂Cl₂ (0.3 M), RT, 16 h.

Next, Ph* acetylene **260** was treated with *n*-butyllithium for deprotonation, followed by the addition of *n*-butyl Weinreb amide **262** under standard nucleophilic addition conditions (**Scheme 4.10A**). However, no desired product (**263**) was obtained, and only unreacted starting material was recovered. It was anticipated that the significant steric bulk of the Ph* group might hinder nucleophilic attack at the carbonyl centre, thereby preventing the formation of ynone **263**.

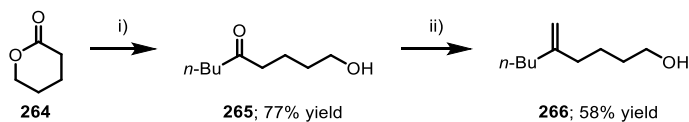
To address this, the temperature was raised to room temperature following deprotonation at $-78\text{ }^{\circ}\text{C}$, in an effort to facilitate the addition step; however, this modification had no effect on the reaction outcome. Subsequently, an alternative strategy was investigated, in which Ph* acetylene **260** was reacted with commercially available *n*-butyl acid chloride in the presence of a palladium (II) catalyst (**Scheme 4.10B**). Despite this change in approach, the reaction again failed to yield the desired product.



Scheme 4.10 Attempted preparation of ynone **263**. Reagents and conditions: i) *n*-BuLi (2.4 equiv.), THF (0.3 M), 1 h; ii) NEt₃ (1.0 equiv.), Pd(Ph₃)₂Cl₂ (2 mol%), CuI (4 mol%), THF (0.3 M), RT, 16 h.

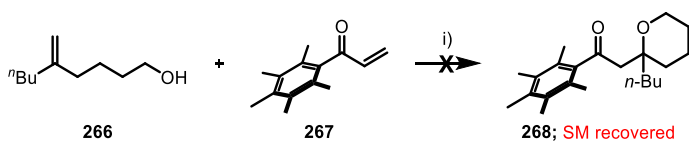
As described in **Chapter 2.2**, the successful synthesis of aryl-substituted tetrahydropyrans *via* cross metathesis prompted further investigation into an alternative route involving the synthesis of hydroxyalkene **266** and its subsequent coupling with Ph* vinyl ketone **267** to access the

desired substrate. Hydroxyalkene **266** was prepared through a two-step sequence (**Scheme 4.11**). The first step involved direct alkylation of δ -valerolactone with *n*-butyllithium, affording hydroxyketone **265** in 77% yield. This intermediate was then subjected to a Wittig olefination to introduce the alkene moiety, furnishing hydroxyalkene **266** in 58% yield.



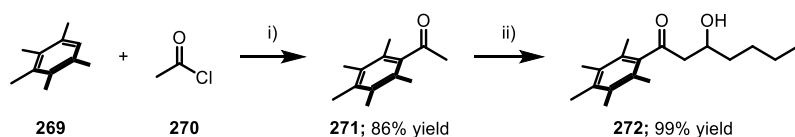
Scheme 4.11 Preparation of hydroxyalkene **266**. Reagents and conditions: i) *n*-BuLi (1.0 equiv.), -78°C , 3 h; ii) MePPh₃Br (3.0 equiv.), *n*-BuLi (3.0 equiv.), THF (0.2 M), reflux, 16 h.

Ph* vinyl ketone **267** and hydroxyalkene **266** were subsequently subjected to the cross-metathesis conditions optimised in Chapter 2.2 (**Scheme 4.12**). However, no product formation was observed, and only the starting materials were recovered. This lack of reactivity may be attributed to the use of disubstituted and/or electron-deficient alkenes, where increased steric hindrance around the double bond can impede catalyst approach and coordination, thereby diminishing the overall efficiency of the metathesis process.



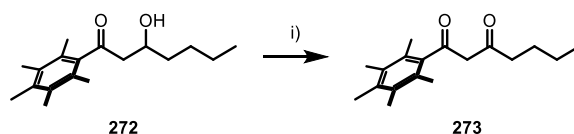
Scheme 4.12 Attempted preparation of Ph*-substituted tetrahydropyran **268**. Reagents and conditions: i) Hoveyda-Grubbs II (10 mol%), ClCH₂CH₂Cl (0.1 M), 100°C , 16 h.

Following an extensive review of the literature and the group's prior work, the aldol reaction emerged as the most promising strategy for alkylating a Ph*-substituted compound. Consequently, a new synthetic route was proposed (**Scheme 4.13**). Starting from pentamethylbenzene **269** and acetyl chloride **270**, the corresponding Ph* ketone was synthesised *via* Friedel–Crafts acylation in 81% yield. Alkylation of Ph* ketone **271** was achieved by deprotonation with ethylmagnesium bromide, followed by addition of pentanal, furnishing β -hydroxy ketone **272** in 79% yield.



Scheme 4.13 Preparation of β -hydroxy ketone **272**. Reagents and conditions: i) AlCl₃ (1.2 equiv.), CH₂Cl₂ (0.2 M), 25°C , 4 h; ii) EtMgBr (1.1 equiv.), CH₃CH₂CH₂CH₂CHO (1.2 equiv.), Et₂O (0.5 M), 40°C , 1 h.

The yield for the oxidation of the β -hydroxy ketone **272** appeared to be scale-dependent and sensitive to the choice of oxidant (**Table 4.11**). Oxidation of **272** with Dess–Martin Periodinane on a 1 g scale afforded the corresponding 1,3-dicarbonyl compound **273** in 96% yield (**Entry 1**). However, when the reaction was scaled up to 3 g, the yield dropped significantly to 44% (**Entry 2**). To improve efficiency on a larger scale, a Swern oxidation was employed, delivering dicarbonyl compound **273** in 87% yield on a 5 g scale and 82% yield on a 10 g scale.

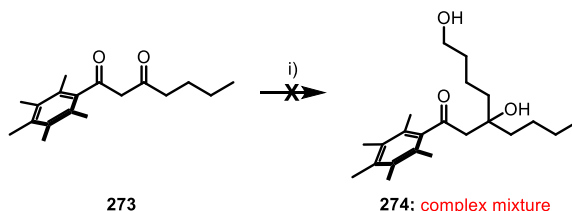


Entry	Oxidation Method	Scale (g)	Yield (%)
1	Dess-Martin Periodinane ^(a)	1	96
2	Dess-Martin Periodinane ^(a)	3	44
3	Swern oxidation ^(b)	5	87
4	Swern oxidation ^(b)	10	82

Table 4.11 Optimisation of the oxidation of β -hydroxy ketone **272** using different oxidants and reaction scales. (a) DMP (2.0 equiv.), NaHCO_3 (4.0 equiv.), CH_2Cl_2 (1.0 M), RT, 1 h. (b) CO_2Cl_2 (1.2 equiv.), DMSO (2.0 equiv.), NEt_3 (3.0 equiv.), CH_2Cl_2 (0.3 M), -78°C , 2 h.

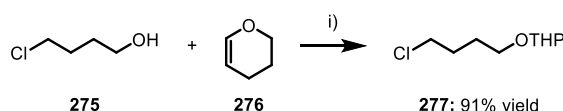
The next objective was to identify a method for the selective functionalisation of one carbonyl group in the 1,3-dicarbonyl compound (**273**) without affecting the other. Yuan and co-workers developed a strategy for the unilateral addition of Grignard reagents to β -diketones,^[77] which appeared well suited to the system. The presence of the bulky Ph^* group was also expected to act as a steric shield, potentially protecting one of the carbonyl functionalities from undesired 1,2-addition. However, an initial attempt did not afford the desired product (**Scheme 4.14**). It was hypothesised that the failure arose from the presence of multiple Grignard reagents in the reaction mixture, leading to competing side reactions. The reported protocol required three distinct Grignard reagents: one to promote enol–ketone equilibrium, one to deprotonate the hydroxyl group of the starting material and one to perform the nucleophilic addition. To reduce the number of reactive species in the system, the free alcohol was replaced with its

tetrahydropyranyl (THP)-protected analogue. A close examination of Yuan's work further revealed that the use of *i*-PrMgCl to promote enol-ketone formation was not essential for reactivity. Instead, employing four equivalents of the Grignard reagent intended for nucleophilic addition proved sufficient and furnished the desired product in 77% yield.



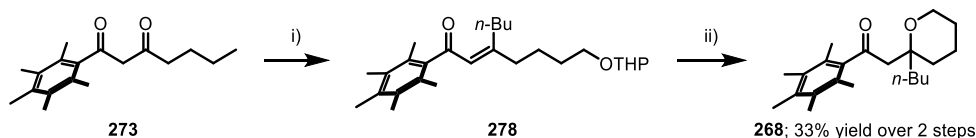
Scheme 4.14 Attempted preparation of ketone **259**. Reagents and conditions: i) *i*-PrMgCl (0.2 equiv.), MeMgCl (1.5 equiv.), ClCH₂CH₂CH₂CH₂OH (1.5 equiv.), Mg turnings (1.5 equiv.), THF (1.0 M), reflux, 16 h.

4-Chlorobutanol **275** was protected as its tetrahydropyranyl (THP) ether through reaction with 3,4-dihydro-2H-pyran, affording the corresponding THP-protected alcohol **277** in 91% yield. (**Scheme 4.15**).



Scheme 4.15 Preparation of THP-protected alcohol **277**. Reagents and conditions: i) PPTS (8 mol%), CH₂Cl₂ (0.3 M), RT, 16 h.

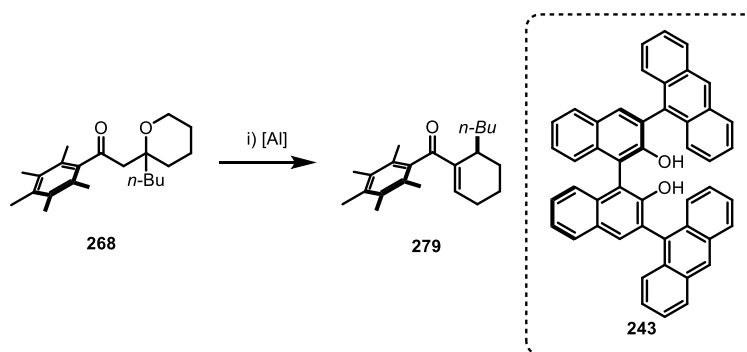
Treatment of this intermediate with magnesium turnings generated the corresponding Grignard reagent, which was subsequently added to dicarbonyl compound **273**, furnishing THP-protected enone **278** (**Scheme 4.16**). Notably, the unsaturated ketone was obtained as the major product rather than the expected diol **274**, likely due to dehydration of the initially formed tertiary alcohol under the reaction conditions. Despite repeated attempts at purification, enone **278** could not be cleanly isolated, even after two rounds of flash column chromatography, and was therefore carried forward to the next step without further purification. Finally, acidic deprotection of crude enone **278** using *p*-toluenesulphonic acid yielded the target tetrahydropyran **268** in 33% yield over 2 steps.



Scheme 4.16 Preparation of Ph*-substituted tetrahydropyran **268**. Reagents and conditions: i) THP-protected alcohol **277** (4.0 equiv.), Mg turnings (6.0 equiv.), THF (0.3 M), reflux, 16 h; ii) *p*-TsOH (2.0 equiv.), MeOH (0.1 M), RT, 16 h.

The reaction of key tetrahydropyran **268** with 100 mol% of the chiral aluminium complex derived from (*R*)-6,6'-dianthracenyl-BINOL **243** afforded cyclohexenes **279** in 67% yield with an enantiomeric ratio of 96:4 (**Table 4.12, Entry 1**). Disappointingly, this result showed no significant improvement in either yield or mass recovery when compared to the corresponding reaction involving the phenyl-substituted tetrahydropyran analogue. Reducing the catalyst loading to 40 mol% (**Entry 2**), in combination with elevated reaction temperatures, had a detrimental effect on both the yield and enantioselectivity, with unreacted starting material observed in the crude reaction mixture.

In an effort to improve conversion and reduce reaction time, Dr M.M. Amer proposed the use of microwave-assisted heating. This strategy was subsequently explored, as microwave irradiation has been reported to accelerate reaction rates and promote cleaner conversions in related catalytic systems. At the same temperature as **Entry 2** and using 40 mol% of the chiral aluminium complex, microwave irradiation furnished cyclohexene **279** in 70% yield within one hour, with an enantiomeric ratio of 90:10 (**Entry 3**). Further improvement was achieved when the reaction was conducted at a reduced temperature of 130 °C under microwave conditions, affording cyclohexene **279** in 86% yield with an enantiomeric ratio of 94:6 (**Entry 4**). However, this result proved irreproducible, as several subsequent attempts failed to reproduce the high yield. The best result obtained under identical conditions in the following week was a 73% yield, while the enantiomeric ratio of 94:6 remained consistent (**Entry 5**).

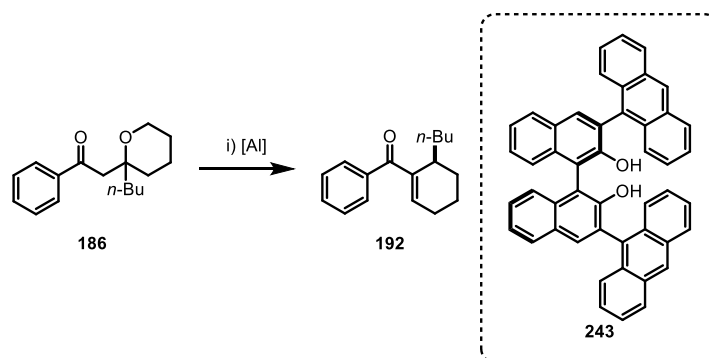


Entry	Temperature (°C)	Reaction time (h)	[Al] Loading (mol%)	Yield ^(a) (%)	e.r. ^(b)
1	130	16	100	67	96:4
2	150	16	40	(56)	90:10
3 ^(c)	150	1	40	70	90:10
4 ^(c)	130	1	40	86	94:6
5 ^{(c) (d)}	130	1	40	73	94:6

Table 4.12 Asymmetric synthesis of cyclohexene **279**. Reagents and conditions: i) chiral diol **243**, *t*-BuOH, AlMe₃, tetrahydropyran **268** (1.0 equiv.), *m*-xylene (0.2 M). (a) Yield refers to isolated material after flash column chromatography, and conversion is reported in parentheses, which was determined by quantitative ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard. (b) Determined by chiral HPLC against a racemic standard; the absolute stereochemistry of the major enantiomer was not assigned. (c) Reaction was heated by microwave irradiation. (d) Identical reaction was repeated after one week.

4.2.5 Reproducibility Challenges at Low Catalyst Loading

Throughout the optimisation process, the use of 40 mol% of the chiral aluminium complex was found to result in notable inconsistencies in both reaction yield and enantiomeric ratio. These variations were themselves irreproducible, with discrepancies of up to 29% observed between experiments conducted under identical conditions. Under the initially optimised conditions, the reaction of tetrahydropyran **186** with 40 mol% of the aluminium catalyst afforded cyclohexene **192** in 73% yield with an enantiomeric ratio of 94:6 (**Table 4.13, Entry 1**). However, when the reaction was repeated two weeks later under the same conditions, the yield dropped to 44%, and the enantiomeric ratio decreased to 90:10 (**Entry 2**). Notably, when the reaction was repeated using a freshly opened bottle of trimethylaluminium solution (**Entry 3**), both the yield and enantiomeric ratio returned to their original values. This observation suggests that degradation of the trimethylaluminium reagent over time (presumably by air and/or moisture) may have contributed to the variability in reaction outcomes.



Entry	Temp (°C)	[Al] Loading (mol%)	Yield ^(a) (%)	e.r. ^(b)
1	150	40	73	94:6
2 ^(c)	150	40	(44)	90:10
3 ^(d)	150	40	72	94:6

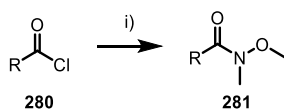
Table 4.13 Variations in yield and enantiomeric ratio for the asymmetric synthesis of cyclohexene **192**. Reagents and conditions: i) chiral diol (0.4 equiv.), t-BuOH (0.4 equiv.), AlMe₃ (0.4 equiv.), tetrahydropyran **186** (1.0 equiv.), m-xylene (0.2 M), 150 °C, 16 h. (a) Yield refers to isolated material after flash column chromatography, and conversion is reported in parentheses, which was determined by quantitative ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard. (b) Determined by chiral HPLC against a racemic standard; the absolute stereochemistry of the major enantiomer was not assigned. (c) Identical reaction was repeated after two weeks. (d) Identical reaction was repeated using a freshly opened bottle of trimethylaluminium solution.

However, this explanation did not account for the behaviour observed with Ph*-substituted tetrahydropyran **268**. Even when a freshly opened bottle of trimethylaluminium solution was used, the desired product was consistently obtained in reduced yield. Despite repeated efforts, the underlying cause of this discrepancy remained unresolved. It was suspected that distinct active catalytic species may have been responsible for the reactions that led to high versus low conversions. However, this could not be experimentally verified, as the chiral aluminium complex is highly sensitive to air and moisture, and the necessary equipment for its isolation and characterisation was not available. Notably, similar behaviour has been reported by Yamamoto and co-workers,^[72] who demonstrated that subtle changes in reaction conditions can led to the formation of structurally distinct aluminium-based catalytic species with differing reactivities.

4.3 Substrate Scope

While addressing the irreproducibility issues associated with the use of 40 mol% of the catalyst, the substrate scope was concurrently investigated under conditions employing 100 mol% of the

chiral aluminium complex. To facilitate this study, a series of Weinreb amides was synthesised from the corresponding acid chlorides *via* reaction with *N,O*-dimethylhydroxylamine hydrochloride in the presence of triethylamine. The acid chloride bearing strongly electron-withdrawing trifluoromethyl groups (**282**) afforded Weinreb amide **284** in 79% yield (**Table 4.14**, **Entry 1**). In contrast, the electron-donating methoxy-substituted aryl chloride **283** gave Weinreb amide **285** in a lower yield of 51% (**Entry 3**). It was observed that yields were sensitive to the age and handling of the acid chlorides, which are prone to hydrolysis to the corresponding carboxylic acids upon exposure to moisture. The substrates were carefully selected to evaluate the influence of electronic on the 1,5-hydride shift.



Entry	Starting Material	Product	Yield (%)
1	282	284	79
2	283	285	51

Table 4.14 Preparation of Weinreb amides **284-285**. Reagents and conditions: i) $\text{CH}_3\text{ONHCH}_3\cdot\text{HCl}$ (1.1 equiv.), Et_3N (3.0 equiv.), CH_2Cl_2 (0.3 M), RT, 16 h.

Subsequently, the reactivities of the synthesised Weinreb amides were evaluated under nucleophilic addition conditions (**Table 4.15**). Hex-5-yn-1-ol **182** was first treated with *n*-butyllithium to generate the corresponding organolithium species, which was then reacted with the Weinreb amides to afford the desired ynone products. Ynones bearing trifluoromethyl (**287**) and *n*-butyl substituents (**289**) were obtained in good yields of up to 70%. Ynone **288**,

derived from methoxy-substituted Weinreb amide **285** was synthesised in the highest yield of 89%, suggesting that electron-rich substrates are particularly favourable under these conditions.

Entry	Starting Material	Product	Yield (%)
1	 284	 287	67
2	 285	 288	89
3	 262	 289	70

Table 4.15 Preparation of ynone **287-289**. Reagents and conditions: i) *n*-BuLi (2.4 equiv.), THF (0.3 M), RT, 1 h.

The final step in the synthesis of the 1,5-hydride shift substrates involved the preparation of a *n*-butyl Gilman cuprate, generated *in situ* by the addition of *n*-butyllithium to copper (I) iodide. The resulting cuprate was then reacted with the ynone substrates under the established reaction conditions to furnish the corresponding tetrahydropyrans (**Table 4.16**). Substrates bearing electron-withdrawing trifluoromethyl groups afforded the products in more modest yields of 62% and 43% yields (**Entries 1 and 2**), respectively. In contrast, the electron-rich methoxy-substituted substrate **292** gave the desired tetrahydropyran in 93% yield, representing the highest yield in this series (**Entry 3**). The aliphatic ynone **289**, which lacks aryl substitution, delivered the corresponding product in 41% yield (**Entry 4**).

	286	290

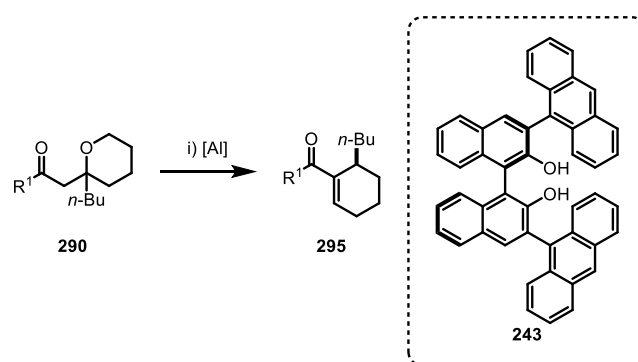
Entry	Starting Material	Product	Yield (%)
1	 247	 291	62
2	 287	 292	43
3	 288	 293	93
27	 289	 294	41

Table 4.16 Preparation of tetrahydropyrans **291-294**. Reagents and conditions: i) *n*-BuLi (6.0 equiv.), CuI (3.0 equiv.), THF (0.3 M), -78°C , 30 min.

The 1,5-hydride shift was carried out on the series of tetrahydropyrans described above. All substrates underwent cyclisation to afford the corresponding cyclohexenes in moderate to good yields, ranging from 61% to 68% (**Table 4.17**). Tetrahydropyrans bearing electron-withdrawing trifluoromethyl groups delivered the desired products in comparable yields of 60% and 64% (**Entries 1 and 2**), with the highest enantiomeric ratios of 3.5:96.5 and 3:97, respectively. However, the enantiomeric ratio measured for cyclohexene **297** is believed to overestimate the true value.

This discrepancy arises from the presence of a minor impurity, which exhibits a distinct UV absorption profile and co-elutes with the major enantiomer peak in the chiral HPLC trace.

Attempts to separate this impurity using available chiral stationary phases were unsuccessful. The electron-rich methoxy-substituted substrate **293** afforded the product in 64% with an enantiomeric ratio of 6:94 (**Entry 3**). Lastly, the aliphatic substrate gave the highest yield of 68%, albeit with the lowest enantioselectivity in the series (**Entry 4**). These results suggest that replacing the aryl group with an aliphatic substituent diminishes stereochemical control in the 1,5-hydride shift process.



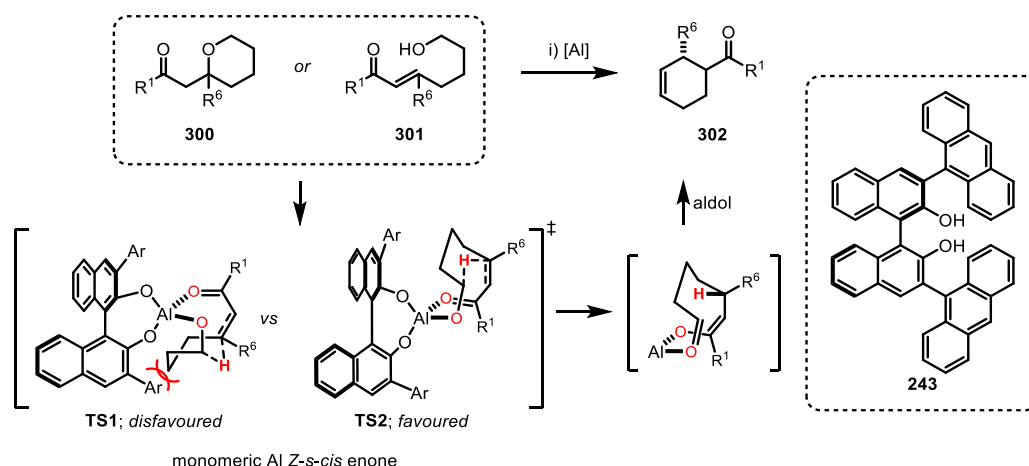
Entry	Starting Material	Product	Yield (%)	e.r. ^(a)
1^(b)			60	96.5:3.5
2			64	97:3 ^(c)
3			64	94:6
4			68	89:11

Table 4.17 Asymmetric synthesis of cyclohexene **296-299**. Reagents and conditions: i) chiral diol **243** (1.0 equiv.), *t*-BuOH (1.0 equiv.), AlMe₃ (1.0 equiv.), tetrahydropyran (1.0 equiv.), *m*-xylene (0.2 M), 130 °C, 16 h. (a) Determined by chiral HPLC against a racemic standard; the absolute stereochemistry of the major enantiomer was not assigned. (b) Reaction was heated for 15 min. (c) With overlapping impurity.

4.4 Mechanistic Discussion

In **Chapter 3**, the mechanistic features of the general 1,5-hydride shift mediated by $\text{Al}(\text{O}t\text{-Bu})_3$ were examined in detail. Computational studies suggest that this transformation proceeds through a pathway involving a dimeric Lewis acid species. This mechanistic proposal is consistent with the well-established solid-state structure of $\text{Al}(\text{O}t\text{-Bu})_3$, which predominantly exists in a dimeric form.^[68] The dissociation of these dimers into monomeric aluminium species is energetically demanding, thereby making monomeric pathways significantly less favourable under the reaction conditions employed.

In contrast, Yamamoto and co-workers have reported that aluminium complexes bearing sterically bulky ligands, such as methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) and aluminium tris(2,6-di-phenylphenoxide) (ATPH) exist mainly as monomeric species in organic solvents as steric congestion inhibits dimer formation.^[78] By analogy, it is reasonable to propose that the preformed catalyst employed in the asymmetric 1,5-hydride shift similarly adopts a monomeric structure, driven by the pronounced steric bulk of the chiral ligand **243**. Consequently, the energetic penalty associated with the dissociation of dimeric species is no longer significant, thereby making the monomeric catalytic pathways accessible. On this basis, it can be assumed that the asymmetric variant of the 1,5-hydride shift proceeds *via* a monomeric pathway. In this case, the *Z-s-cis* transition state is favoured, as computational analysis indicates that it corresponds to the lowest energy monomeric transition state (**Scheme 4.17**).



Scheme 4.17 The monomeric Z-s-cis transition state with anthracenyl-substituted BINOL ligand **243**. Reagents and conditions: i) chiral diol **243** (1.0 equiv.), t-BuOH (1.0 equiv.), AlMe₃ (1.0 equiv.), tetrahydropyran (1.0 equiv.), m-xylene (0.2 M), 130 °C, 16 h.

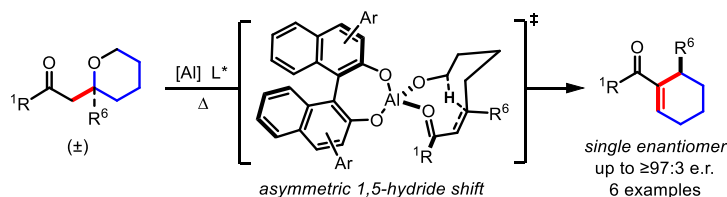
Coordination of the Z-s-cis-enone to the aluminium catalyst bearing the (*R*)-**243** ligand can give rise to two distinct transition states, each corresponding to a different facial approach of the hydride to the electrophilic enone. These transition states position the transferring hydride in distinct spatial orientations within the chiral environment of the catalyst. One conformation (**TS1**) is sterically disfavoured due to significant interactions between the substrate and the bulky anthracenyl group of the catalyst, whereas the alternative conformation (**TS2**) minimises such steric interactions and is therefore energetically favoured. As each conformation leads to the formation of opposite enantiomers of the aldol product, the favoured transition state dictates the enantiomeric outcome of the reaction. Based on this model, the major product is predicted to be the (*R*)-enantiomer. Unfortunately, at this point, crystalline material could not be obtained for any of the products as most of which were oils, thereby preventing confirmation of the stereochemical assignment by X-ray crystallography.

On the other hand, several experimental observations challenge the completeness of this transition-state model. In theory, the enantiomeric ratio of the product should remain invariant with respect to substituents R⁶ and R¹ if the proposed model were entirely accurate. Contrary to this expectation, experimentally increasing the size of R⁶ from a methyl to a *n*-butyl group resulted in an increase in the enantiomeric ratio from 23:77 to 4:96 (**Table 4.7**). Conversely, replacing the R¹ phenyl with a *n*-butyl group led to a decrease in enantiomeric ratio from 4:96

to 11:89 (**Table 4.17**). These findings suggest that the proposed transition-state model requires refinement to fully account for the observed substrate-dependent enantioselectivity.

4.5 Conclusion and Future Work

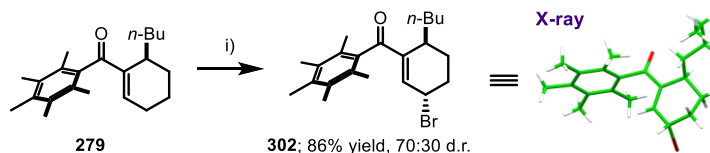
In conclusion, this chapter has outlined the development and optimisation of an asymmetric 1,5-hydride shift for the synthesis of enantioenriched cyclohexenes (**Scheme 4.18**). Using a chiral aluminium complex generated from anthracenyl-substituted BINOL and *tert*-butanol, the transformation proceeded in good yields and with high levels of enantioselectivity. A small series of cyclohexenes bearing electronically diverse substituents were synthesised, demonstrating that the reaction tolerates a broad range of functional groups. In parallel, efforts were made to achieve the transformation catalytically in aluminium. However, these attempts revealed significant challenges with reproducibility.



Scheme 4.18 An asymmetric variant of the aluminium-mediated 1,5-hydride shift–aldol cascade.

Further studies should focus on improving the robustness and reproducibility of the catalytic system. Preliminary work in this direction has been initiated by Dr M. M. Amer, who has begun exploring replacement of the *tert*-butanol ligand with an additional equivalent of anthracenyl-substituted BINOL. This modification aims to minimise the effects of uneven mixing and enhance the uniformity of the chiral aluminium complex formed *in situ*. While this thesis was in preparation, Dr M. M. Amer also tried to derivatise Ph*-substituted cyclohexene **279** by treating it with molecular bromine to effect an allylic bromination, affording **302** in 86% yield as a 70:30 mixture of diastereoisomers (**Scheme 4.19**). A single crystal of the major isomer was successfully grown, and X-ray diffraction data were collected and analysed by A. Mazeikaite. The crystallographic analysis revealed a *trans* relationship between the *n*-Bu group and the bromide substituent, thus establishing the relative stereochemistry. Furthermore, the analysis confirmed

that the absolute configuration of the *n*-Bu-bearing stereocentre corresponds to the (*R*)-enantiomer, consistent with our hypothesis based on the *Z*-*s-cis* transition-state model discussed in **Chapter 4.4**.



Scheme 4.19 Derivatisation of the cyclohexene product **279** by Dr M. M. Amer. Reagents and conditions: *i)* Br₂ (1.0 equiv.), CHCl₃ (0.1 M), RT, 3 h.

For completeness of the project, the cyclohexene core should also be further functionalised to yield cyclohexenone,^[79] cyclohexene oxide,^[7] and other synthetically useful derivatives. The Ph* protecting group could also be removed in a single step to afford a variety of carboxylic acid derivatives.^[80]

Chapter 5: Experimental Section

5.1 General information

Glassware: Microwave vials and vial caps (with resealing silicone/PTFE septa) were purchased from Kinesis (Cole-Parmer). All reactions were performed in glassware without flame-drying and under a nitrogen atmosphere, unless stated otherwise.

Temperature and Heating: Room temperature (RT) refers to 20–25 °C. A temperature of 0 °C was achieved using an ice-water bath, and –78 °C was obtained using a dry ice-acetone bath. Other temperatures below 0 °C were reached using a Julabo FT902 immersion cooler. Temperatures above 25 °C were obtained using a hot plate with an oil bath or DrySyn® heating blocks.

Reagents and Solvents: PhMe, CH₂Cl₂, Et₂O, tetrahydrofuran (THF), MeCN, and 1,4-dioxane were purified by filtration through activated alumina columns according to the method of Grubbs *et al.*^[1] Water was purified using an Elix® UV-10 system. All other solvents and reagents were used as received from commercial suppliers without further purification.

Chromatography: Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F₂₅₄, 0.25 mm pre-coated aluminium plates. TLC plates were visualised under UV light (λ = 254 nm) and/or by staining with aqueous potassium permanganate, phosphomolybdic acid, or vanillin. Flash column chromatography was carried out on VWR silica gel 60 (particle size 40 – 63 μ m or 15 – 40 μ m) using head pressure provided by a nitrogen line.

NMR Spectroscopy: NMR spectra were recorded on Bruker 400, 500, 600 (with helium-cooled broadband cryoprobe), or 700 MHz (with inverse TCI cryoprobe) spectrometers in the deuterated solvent stated, using the residual non-deuterated solvent signal as an internal reference. Chemical shifts (δ) are quoted in parts per million (ppm) to the nearest 0.01 ppm for ¹H spectra, and to the nearest 0.1 ppm for ¹³C, ³¹P and ¹⁹F spectra. For fluorine-containing

compounds, ^{13}C NMR spectra were acquired with ^{19}F decoupling. Coupling constants (J) are reported to the nearest 0.5 Hz. ^2H NMR spectra were recorded on a Bruker AVIII HD 500 (77 or 92 MHz) in non-deuterated solvent with a single drop of the corresponding deuterated solvent as an internal reference. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), sept (heptet), or m (multiplet). Unless otherwise stated, all NMR experiments were performed at 298 K. ^1H and ^{13}C NMR resonances for diastereomers were assigned as major or minor; if these could not be distinguished, peaks were assigned with a “,” (e.g. H_1 and $\text{H}_{1'}$, C_1 and $\text{C}_{1'}$). ^1H and ^{13}C NMR resonances for diastereotopic environments were assigned with subscripts “a” and “b” (e.g. H_a and H_b), or subscripts “ax.” (axial) and “eq.” (equatorial) where applicable. Assignments were made with the assistance of COSY, HSQC, HMBC or NOESY spectra. Quantitative NMR spectra were acquired on a Bruker AVIII400 spectrometer with a relaxation delay of 25 s between scans.

Chiral High-Performance Liquid Chromatography: Chiral HPLC separations were performed using an Agilent 1260 Infinity Series normal-phase HPLC system with HP Chemstation software. Chiralpak® columns (250 x 4.6 mm) fitted with matching Chiralpak® Guard Cartridges (10 x 4 mm) were used as specified in the text. Solvents were of HPLC grade (Fisher Scientific, Sigma Aldrich or Rathburn), and all eluent systems were run isocratically.

Compound Names and Atom Numbering: Systematic names were generated using ChemDraw 23.0.1 according to International Union of Pure and Applied Chemistry (IUPAC) guidelines. The atom numbering shown does not follow IUPAC conventions and therefore differs from that used in the compound names.

Melting Points and Infrared Spectroscopy: Melting points were determined using a Griffin melting point apparatus and are uncorrected. Infrared spectra were recorded neat or as a thin film on a Bruker Tensor 27 spectrometer equipped with an attenuated total reflectance

attachment, with internal calibration over the range 600–4000 cm^{-1} . Absorption maxima (λ_{max}) are reported in wavenumbers (cm^{-1}). The abbreviation “br.” denotes broad.

Optical rotations: Optical rotations were measured on a PerkinElmer 241 polarimeter at 25 °C in a 5 cm cell in the stated solvent. $[\alpha]_{\text{D}}$ values are reported in $10^{-1}\text{deg}\cdot\text{cm}^2\text{g}^{-1}$, with concentration (c) given in g/100 mL.

Mass Spectrometry: High-resolution mass spectrometry (HRMS) was performed using flow injection analysis on an ACQUITY I-Class PLUS UPLC System (Waters, Milford, MA, USA) coupled to an ACQUITY RDa mass spectrometer (Waters, Milford, MA, USA) equipped with an ESI probe and a TOF mass analyser. In positive ion mode, the flow rate was 0.300 mL/min with a 50% methanol(aq) + 0.1% formic acid eluent. Scan parameters were as follows: analyser mode, full scan; scan range, 50–2000 m/z; scan rate, 2 Hz; cone voltage, 30 V; capillary voltage, 1.5 kV; desolvation temperature, 550 °C; intelligent data capture, on.

5.2 General Procedures

General Procedure 1 – Synthesis of Hydroalkenes by Grignard Addition

5-Bromopent-1-ene (2.0 equiv.) was added dropwise to a suspension of magnesium turnings (2.5 equiv.) in THF (1.0 M) at RT and stirred for 1 h. The reaction mixture was cooled to 0 °C, and a solution of the aldehyde (1.0 equiv.) in THF (3.0 M) was added dropwise. The mixture was then warmed to RT and stirred for 12 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride and extracted with Et_2O . The combined organic phases were dried over MgSO_4 , filtered and concentrated *in vacuo*. For details of purification, see the experimental procedures.

General Procedure 2 – Synthesis of Tetrahydropyrans by Cross Metathesis

A 10–20 mL Biotage® microwave vial was charged with alkenyl alcohol (1.0 equiv.), vinyl ketone (2.0 equiv.), $\text{ClCH}_2\text{CH}_2\text{Cl}$ (0.1 M) and Hoveyda-Grubbs Catalyst® M720 (10 mol%). The vial was flushed with N_2 , sealed with a microwave vial cap containing a Reseal™ septum and heated at

100 °C for 16 h. The reaction was cooled to RT and concentrated *in vacuo*. For details of purification, see the experimental procedures.

General Procedure 3 – Synthesis of Weinreb Amides

Dimethylhydroxylamine hydrochloride (1.1 equiv.) was added to a solution of benzoyl chloride (1.0 equiv.) in CH₂Cl₂ (0.3 M). The reaction mixture was cooled to 0 °C, and triethylamine (3.0 equiv.) was added dropwise. The mixture was then warmed to RT and stirred overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride and extracted with CH₂Cl₂. The combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. For details of purification, see the experimental procedures.

General Procedure 4 – Synthesis of Ynones

n-BuLi in hexanes (2.4 equiv.) was added dropwise to a solution of 5-hexyn-1-ol (1.2 equiv.) in THF (0.3 M) at –78 °C. The reaction mixture was stirred for 1 h, after which a solution of Weinreb amide (1.0 equiv.) in THF (3.0 M) was added dropwise. The mixture was then warmed to RT and stirred for a further 1 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride and extracted with EtOAc. The combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. For details of purification, see the experimental procedures.

General Procedure 5 – Synthesis of Cyclohexenes by Aluminium Catalysed 1,5-Hydride Shift

A 2–5 mL Biotage® microwave vial was charged with the tetrahydropyran (1.0 equiv.), basic alumina (Brockmann I, 5.0 equiv.) or Al(*Ot*-Bu)₃ (1.0 equiv.) and PhMe (0.2 M). The vial was flushed with N₂, sealed with a microwave vial cap containing a Reseal™ septum, and heated at 110 °C for 16 h. The reaction was cooled to RT, diluted with Et₂O, filtered through a plug of silica gel, and concentrated *in vacuo*. For details of purification, see the experimental procedures.

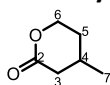
General Procedure 6 – Asymmetric Synthesis of Cyclohexenes by Aluminium Catalysed 1,5-Hydride Shift

A 2–5 mL Biotage[®] microwave vial was charged with (*R*)-3,3'-di(anthracen-9-yl)-[1,1'-binaphthalene]-2,2'-diol (1.0 equiv.), *tert*-butanol (1.0 equiv.) and *m*-xylene (0.2 M). The vial was degassed, backfilled with N₂, and a solution of AlMe₃ in PhMe (2.0 M, 1.0 equiv.) was added dropwise to the suspension. The mixture was stirred for 30 min, tetrahydropyran (1.0 equiv.) was added, and the vial was sealed with a microwave vial cap containing a Reseal[™] septum. The reaction was heated at 130 °C for 16 h, cooled to RT, diluted with Et₂O, filtered through a plug of silica gel, and concentrated *in vacuo*. For details of purification, see the experimental procedures.

5.3 Synthesis of Starting Materials

5.3.1 Synthesis of Cross Metathesis Precursors

4-Methyltetrahydro-2*H*-pyran-2-one 113



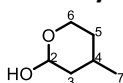
A 25 mL round-bottom flask fitted with an air condenser was charged with 3-methyl-1,5-pentanediol (10.0 g, 84.6 mmol, 1.0 equiv.) and copper chromite (526 mg, 1.69 mmol, 2 mol%). The reaction mixture was heated at 200 °C for 12 h open to air, then cooled to RT. The title compound was afforded after purification by FCC (20% EtOAc/pentane) as a colourless oil (6.87 g, 60.2 mmol, 71% yield).

¹H NMR (400 MHz, CDCl₃) δ 4.39 (ddd, *J* = 11.5, 5.0, 4.0 Hz, 1H, H_{6eq}), 4.24 (ddd, *J* = 11.5, 11.0, 4.0 Hz, 1H, H_{6ax}), 2.70 – 2.58 (m, 1H, H_{3a}), 2.15 – 2.02 (m, 2H, H_{3b} and H₄), 1.89 (dq, *J* = 14.0, 4.0, 2.0 Hz, 1H, H_{5eq}), 1.55 – 1.43 (m, 1H, H_{5ax}), 1.04 (d, *J* = 6.0 Hz, 3H, H₇ x 3).

¹³C NMR (101 MHz, CDCl₃) δ 174.4 (C₂), 77.5 (C₆), 38.3 (C₃), 32.0 (C₅), 26.0 (C₄), 21.5 (C₇).

The spectroscopic data matched that previously reported in the literature.^[81]

4-Methyltetrahydro-2*H*-pyran-2-ol 114



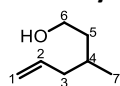
DIBAL-H in hexanes (1.0 M, 12.3 mL, 12.3 mmol, 1.4 equiv.) was added dropwise to a solution of 4-methyltetrahydro-2H-pyran-2-one **113** (1.00 g, 8.76 mmol, 1.0 equiv.) in CH₂Cl₂ (0.5 M, 18 mL) at -78 °C. The reaction mixture was stirred for 3 h, and aqueous Rochelle salt (2 mL/mmol lactone) was added dropwise. The mixture was warmed to RT, stirred vigorously, and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (30% Et₂O/pentane) as a colourless oil (890 mg, 7.66 mmol, 87% yield, 55:45 mixture of anomers by ¹H NMR).

¹H NMR (400 MHz, CDCl₃) δ 5.23 (t, *J* = 2.5 Hz, 1H, minor H₂), 4.62 (dd, *J* = 9.5, 2.0 Hz, 1H, major H₂), 4.44 (s, 1H, OH), 4.03 – 3.92 (m, 2H, major H_{6a}, minor H_{6a}), 3.82 (s, 1H, OH), 3.59 (ddd, *J* = 11.0, 4.5, 2.0 Hz, 1H, minor H_{6b}), 3.44 (td, *J* = 12.0, 2.5 Hz, 1H, major H_{6b}), 2.06 – 1.89 (m, 1H, minor H₄), 1.84 (ddt, *J* = 13.0, 4.0, 2.0 Hz, 1H, major H_{3a}), 1.75 – 1.50 (m, 3H, major H₄, minor H_{3a}, minor H_{5a}), 1.45 (ddd, *J* = 13.5, 4.0, 2.0 Hz, 1H, major H_{5a}), 1.32 – 1.14 (m, 3H, minor H_{3b}, major H_{5b}, minor H_{5b}), 1.07 – 0.98 (m, 1H, major H_{3b}), 0.93 (d, *J* = 6.5 Hz, 3H, major H₇ x 3), 0.87 (d, *J* = 6.5 Hz, 3H, minor H₇ x 3).

¹³C NMR (101 MHz, CDCl₃) δ 96.0 (major C₂), 91.3 (minor C₂), 65.5 (major C₆), 59.5 (minor C₆), 41.4 (major C₃), 38.7 (minor C₃), 34.0 (minor C₅), 33.5 (major C₅), 29.3 (major C₄), 23.5 (minor C₄), 22.0 (major C₇), 21.8 (minor C₇).

The spectroscopic data matched that previously reported in the literature.^[29]

3-Methylhex-5-en-1-ol **111**



n-BuLi in hexanes (1.6 M, 10.8 mL, 17.2 mmol, 2.0 equiv.) was added dropwise to a solution of MePh₃PBr (6.77 g, 18.9 mmol, 2.2 equiv.) in THF (0.5 M, 38 mL) at -78 °C. The reaction mixture was warmed to RT and stirred for 2 h, then a solution of 4-methyltetrahydro-2H-pyran-2-ol **114** (1.00 g, 8.61 mmol, 1.0 equiv.) in THF (3.0 M, 3 mL) was added dropwise. The mixture was heated under reflux for 12 h, cooled to RT, quenched by the addition of saturated aqueous ammonium

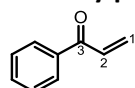
chloride (25 mL) and extracted with Et₂O (3 x 40 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% EtOAc/pentane) as a colourless oil (560 mg, 4.90 mmol, 57% yield).

¹H NMR (400 MHz, CDCl₃) δ 5.78 (ddt, *J* = 16.5, 10.5, 7.0 Hz, 1H, H₂), 5.06 – 4.95 (m, 2H, H₁ x 2), 3.77 – 3.61 (m, 2H, H₆ x 2), 2.15 – 2.03 (m, 1H, H_{3a}), 2.00 – 1.88 (m, 1H, H_{3b}), 1.76 – 1.56 (m, 2H, H₄, H_{5a}), 1.46 – 1.31 (m, 2H, H_{5b}, OH), 0.92 (d, *J* = 6.5 Hz, 3H, H₇ x 2).

¹³C NMR (101 MHz, CDCl₃) δ 137.3 (C₂), 116.1 (C₁), 61.3 (C₆), 41.6 (C₃), 39.5 (C₅), 29.6 (C₄), 19.6 (C₇).

The spectroscopic data matched that previously reported in the literature.^[82]

1-Phenylprop-2-en-1-one 110

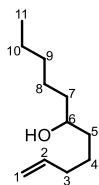


i-Pr₂NH:TFA (8.96 mg, 41.6 mmol, 1.0 equiv.) and trifluoroacetic acid (0.32 mL, 4.16 mmol, 10 mol%) were added sequentially to a suspension of acetophenone (5.00 g, 41.6 mmol, 1.0 equiv.) and paraformaldehyde (2.50 g, 83.2 mmol, 2.0 equiv.) in THF (1.0 M, 42 mL). The reaction mixture was heated under reflux for 2 h, after which a second portion of paraformaldehyde (2.50 g, 83.2 mmol, 2.0 equiv.) was added. The reaction was heated under reflux for a further 10 h, cooled to RT, diluted with Et₂O (20 mL), and washed successively with NaOH (1.0 M, 40 mL), HCl (1.0 M, 40 mL) and brine (40 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% EtOAc/pentane) as a colourless oil (3.08 g, 23.3 mmol, 56% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.00 – 7.91 (m, 2H, ArCH), 7.53 (m, 1H, ArCH), 7.53 – 7.42 (m, 2H, ArCH), 7.16 (dd, *J* = 17.0, 10.5 Hz, 1H, H₂), 6.44 (dd, *J* = 17.0, 1.5 Hz, 1H, H_{1a}), 5.94 (dd, *J* = 10.5, 1.5 Hz, 1H, H_{1b}).

¹³C NMR (101 MHz, CDCl₃) δ 191.2 (C₃), 137.4 (ArC), 133.1 (ArC), 132.5 (C₂), 130.4 (C₁), 128.9 (ArC x 2), 128.8 (ArC x 2).

The spectroscopic data matched that previously reported in the literature.^[83]

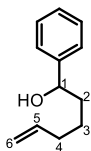
Undec-1-en-6-ol 120

5-Bromopent-1-ene (2.4 mL, 20.0 mmol, 2.0 equiv.), magnesium turnings (607 mg, 25.0 mmol, 2.5 equiv.), THF (1.0 M, 25 mL), and hexanal (1.00 g, 9.98 mmol, 1.0 equiv.) were subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (10% EtOAc/pentane) as a colourless oil (933 mg, 5.48 mmol, 55% yield).

^1H NMR (400 MHz, CDCl_3) δ 5.81 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H, H_2), 5.06 – 4.91 (m, 2H, $\text{H}_1 \times 2$), 3.60 (m, 1H, H_6), 2.08 (m, 2H, $\text{H}_3 \times 2$), 1.65 – 1.21 (m, 10H, $\text{H}_5 \times 2$, $\text{H}_7 \times 2$, $\text{H}_4 \times 2$, $\text{H}_8 \times 2$, $\text{H}_9 \times 2$), 0.94 – 0.84 (m, 3H, $\text{H}_{10} \times 3$).

^{13}C NMR (101 MHz, CDCl_3) δ 138.9 (C_2), 114.7 (C_1), 72.0 (C_6), 37.6 (C_5), 37.03 (C_7), 33.9 (C_3), 32.1 (C_{10}), 25.5 (C_8), 25.1 (C_4), 22.8 (C_9).

The spectroscopic data matched that previously reported in the literature ^[84].

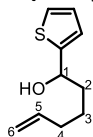
1-Phenylhex-5-en-1-ol 122

5-Bromopent-1-ene (2.2 mL, 18.8 mmol, 2.0 equiv.), magnesium turnings (573 mg, 23.6 mmol, 2.5 equiv.), THF (1.0 M, 24 mL), and benzaldehyde (1.00 g, 9.42 mmol, 1.0 equiv.) were subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (10% EtOAc/pentane) as a colourless oil (946 mg, 5.37 mmol, 57% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.20 (m, 5H, $\text{ArCH} \times 5$), 5.78 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H, H_5), 5.03 – 4.91 (m, 2H, $\text{H}_6 \times 2$), 4.68 (dd, J = 7.5, 5.5 Hz, 1H, H_1), 2.15 – 2.00 (m, 2H, $\text{H}_4 \times 2$), 1.89 – 1.66 (m, 3H, $\text{H}_2 \times 2$, OH), 1.53 (m, 1H, H_{3a}), 1.39 (m, 1H, H_{3b}).

^{13}C NMR (101 MHz, CDCl_3) δ 145.0 (ArC), 138.7 (C_5), 128.6 (ArC $\times 2$), 127.7 (ArC), 126.0 (ArC $\times 2$), 114.8 (C_6), 74.7 (C_1), 38.6 (C_2), 33.7 (C_4), 25.2 (C_3).

The spectroscopic data matched that previously reported in the literature. ^[85]

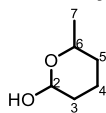
1-(Thiophen-2-yl)hex-5-en-1-ol 124

5-Bromopent-1-ene (3.0 mL, 25.6 mmol, 2.0 equiv.), magnesium turnings (778 mg, 32.0 mmol, 2.5 equiv.), THF (1.0 M, 25 mL), and 2-thiophenecarboxaldehyde (1.23 g, 12.8 mmol, 1.0 equiv.) were subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (10% EtOAc/pentane) as a colourless oil (1.20 g, 7.22 mmol, 51% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.28 – 7.19 (m, 1H, ArCH), 7.01 – 6.91 (m, 2H, ArCH x 2), 5.80 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H, H_5), 5.08 – 4.85 (m, 3H, H_6 x 2, H_1), 2.33 – 2.21 (m, 1H, OH), 2.14 – 2.05 (m, 2H, H_4 x 2), 1.96 – 1.75 (m, 2H, H_2 x 2), 1.66 – 1.34 (m, 2H, H_3 x 2).

^{13}C NMR (101 MHz, CDCl_3) δ 148.9 (ArCH), 138.5 (C_5), 126.7 (ArCH), 124.6 (ArCH), 123.8 (ArCH), 114.9 (C_6), 70.3 (C_1), 38.8 (C_2), 33.5 (C_4), 25.1 (C_3).

The spectroscopic data matched that previously reported in the literature.^[86]

6-Methyltetrahydro-2H-pyran-2-ol 126

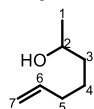
DIBAL-H in hexanes (1.0 M, 24.5 mL, 24.5 mmol, 1.4 equiv.) was added dropwise to a solution of δ -hexalactone (2.00 g, 17.5 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 M, 35 mL) at -78°C . The reaction mixture was stirred for 3 h, after which aqueous Rochelle salt (2 mL/mmol lactone) was added dropwise. The mixture was warmed to RT, stirred vigorously and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (30% Et_2O /pentane) as a colourless oil (1.73 g, 14.9 mmol, 85% yield, 67:33 mixture of anomers by ^1H NMR).

^1H NMR (400 MHz, CDCl_3) δ 5.31 – 5.16 (m, 1H minor, H_2), 4.78 – 4.57 (m, 1H major H_2), 4.19 – 3.96 (m, 1H, minor H_6), 3.86 – 3.62 (m, 1H, major OH), 3.59 – 3.47 (m, 1H major H_6), 3.24 – 3.00 (m, 1H, minor OH), 1.91 – 1.09 (m, 15H, minor H_3 x 2, minor H_4 x 2 and minor H_5 x 2, major H_7 x 3, major H_3 x 2, major H_4 x 2 and major H_5 x 2), 1.09 – 1.04 (m, 3H minor H_7 x 3).

^{13}C NMR (101 MHz, CDCl_3) δ 96.5 (minor C_2), 91.7 (major C_2), 72.6 (major C_6), 65.0 (minor C_6), 33.1 (major C_5), 32.4 (major C_4), 32.3 (minor C_5), 29.7 (minor C_4), 22.2 (major C_3), 21.7 (minor C_7), 21.6 (major C_7), 17.5 (minor C_3).

The spectroscopic data matched that previously reported in the literature.^[81]

Hept-6-en-2-ol 127



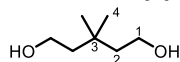
n-BuLi in hexanes (1.6 M, 10.8 mL, 17.2 mmol, 2.0 equiv.) was added dropwise to a solution of MePh_3PBr (6.77 g, 18.9 mmol, 2.2 equiv.) in THF (0.5 M, 38 mL) at -78°C . The reaction mixture was warmed to RT, stirred for 2 h, after which a solution of 6-methyltetrahydro-2*H*-pyran-2-ol **126** (1.00 g, 8.61 mmol, 1.0 equiv.) in THF (3.0 M, 3 mL) was added dropwise. The reaction was heated under reflux for 12 h, cooled to RT, quenched by the addition of saturated aqueous ammonium chloride (25 mL), and extracted with Et_2O (3 x 40 mL). The combined organic phases were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% EtOAc /pentane) as a colourless oil (558 mg, 4.89 mmol, 57% yield).

^1H NMR (400 MHz, CDCl_3) δ 5.81 (ddt, $J = 17.0, 10.0, 6.5$ Hz, 1H, H_6), 5.05 – 4.92 (m, 2H, $\text{H}_7 \times 2$), 3.81 (h, $J = 6.0$ Hz, 1H, H_2), 2.13 – 2.02 (m, 2H, $\text{H}_5 \times 2$), 1.51 – 1.39 (m, 4H, $\text{H}_f \times 2$, $\text{H}_3 \times 2$), 1.30 (s, 1H, OH), 1.19 (d, $J = 6.0$ Hz, 3H, $\text{H}_1 \times 3$).

^{13}C NMR (101 MHz, CDCl_3) δ 138.8 (C_6), 114.8 (C_7), 68.2 (C_2), 38.9 (C_3), 33.8 (C_5), 25.2 (C_4), 23.7 (C_1).

The spectroscopic data matched that previously reported in the literature.^[87]

3,3-Dimethylpentane-1,5-diol 147



A solution of 3,3-dimethylglutaric acid (6.00 g, 37.5 mmol, 1.0 equiv.) in THF (1.5 M, 2.5 mL) was added dropwise to a suspension of LiAlH_4 (4.30 g, 112 mmol, 3.0 equiv.) in THF (1.0 M, 112 mL) at 0°C . The reaction vessel was fitted with an air condenser and heated under reflux for 12 h. The mixture was cooled to 0°C , diluted with Et_2O (50 mL) and quenched by sequential addition

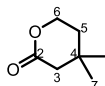
of water (1 mL/g of LiAlH_4), aq. NaOH (15% w/v, 5 mL), and water (3 mL/g of LiAlH_4). The reaction was stirred vigorously for 15 min, MgSO_4 was added, and stirred for a further 15 min. The mixture was then filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% MeOH/ CH_2Cl_2) as a colourless oil (3.72 g, 28.2 mmol, 75% yield).

^1H NMR (400 MHz, CDCl_3) δ 3.72 (t, $J = 7.0$ Hz, 4H, $\text{H}_1 \times 4$), 2.08 (s, 2H, OH $\times 2$), 1.57 (t, $J = 7.0$ Hz, 4H, $\text{H}_2 \times 4$), 0.94 (s, 6H, $\text{H}_4 \times 6$).

^{13}C NMR (101 MHz, CDCl_3) δ 60.5 ($\text{C}_1 \times 2$), 46.0 ($\text{C}_2 \times 2$), 31.8 (C_3), 28.2 ($\text{C}_4 \times 2$).

The spectroscopic data matched that previously reported in the literature.^[81]

4,4-Dimethyltetrahydro-2H-pyran-2-one **148**



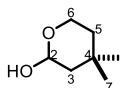
A 10 mL round-bottom flask fitted with an air condenser was charged with 3,3-dimethylpentane-1,5-diol **147** (3.72 g, 28.1 mmol, 1.0 equiv.) and copper chromite (175 mg, 0.563 mmol, 2 mol%). The reaction mixture was heated at 200 °C for 12 h open to air, then cooled to RT. The title compound was afforded after purification by FCC (20% EtOAc/Pentane) as a colourless oil (2.98 g, 23.3 mmol, 83% yield).

^1H NMR (400 MHz, CDCl_3) δ 4.37 (t, $J = 6.0$ Hz, 2H, $\text{H}_6 \times 2$), 2.32 (s, 2H, $\text{H}_3 \times 2$), 1.69 (t, $J = 6.0$ Hz, 2H, H_5), 1.09 (s, 6H, $\text{H}_7 \times 6$).

^{13}C NMR (101 MHz, CDCl_3) δ 171.8 (C_2), 66.6 (C_6), 44.2 (C_3), 36.0 (C_5), 29.9 (C_4), 28.9 ($\text{C}_7 \times 2$).

The spectroscopic data matched that previously reported in the literature.^[81]

4,4-Dimethyltetrahydro-2H-pyran-2-ol **149**



DIBAL-H in hexanes (1.0 M, 27.2 mL, 27.2 mmol, 1.4 equiv.) was added dropwise to a solution of 4,4-dimethyltetrahydro-2H-pyran-2-one **148** (2.56 g, 19.7 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 M, 39 mL) at -78 °C. The reaction mixture was stirred for 3 h, and aqueous Rochelle salt (2 mL/mmol lactone) was added dropwise. The mixture was warmed to RT, stirred vigorously, and extracted with CH_2Cl_2 (3 $\times$ 40 mL). The combined organic phases were dried over MgSO_4 , filtered, and

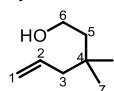
concentrated *in vacuo*. The title compound was afforded after purification by FCC (30% Et₂O/pentane) as a colourless oil (2.07 g, 15.9 mmol, 79% yield).

¹H NMR (400 MHz, CDCl₃) δ 4.92 (dd, *J* = 8.0, 2.5 Hz, 1H, H₂), 3.93 (dt, *J* = 12.0, 4.0 Hz, 1H, H_{6a}), 3.64 (ddd, *J* = 12.0, 10.5, 3.0 Hz, 1H, H_{6b}), 1.59 (ddd, *J* = 13.0, 3.0, 1.5 Hz, 1H, H_{5a}), 1.45 (ddd, *J* = 13.5, 10.5, 4.5 Hz, 1H, H_{5b}), 1.30 – 1.22 (m, 2H, H_{3a}, H_{3b}), 1.02 (s, 3H, H_{7a} x 3), 0.99 (s, 3H, H_{7b} x 3).

¹³C NMR (101 MHz, CDCl₃) δ 94.2 (C₂), 60.2 (C₆), 42.5 (C₃), 38.8 (C₅), 31.6 (C₄), 30.2 (C_{7a}), 28.5 (C_{7b}).

The spectroscopic data matched that previously reported in the literature.^[81]

3,3-Dimethylhex-5-en-1-ol **150**

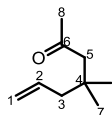


n-BuLi in hexanes (1.6 M, 9.6 mL, 15.4 mmol, 2.0 equiv.) was added dropwise to a solution of MePh₃PBr (6.03 g, 16.9 mmol, 2.2 equiv.) in THF (0.5 M, 34 mL) at –78 °C. The reaction mixture was warmed to RT, and stirred for 2 h, then a solution of 6-methyltetrahydro-2*H*-pyran-2-ol **149** (1.00 g, 7.68 mmol, 1.0 equiv.) in THF (3.0 M, 3 mL) was added dropwise. The mixture was heated under reflux for 12 h, cooled to RT, quenched by the addition of saturated aqueous ammonium chloride (25 mL), and extracted with Et₂O (3 x 40 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% EtOAc/pentane) as a colourless oil (718 mg, 5.60 mmol, 73% yield).

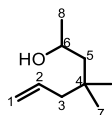
¹H NMR (400 MHz, CDCl₃) δ 5.82 (ddt, *J* = 17.0, 10.5, 7.5 Hz, 1H, H₂), 5.08 – 4.96 (m, 2H, H, H₁ x 2), 3.75 – 3.67 (m, 2H, H₆ x 2), 1.98 (m, 2H, H₃ x 2), 1.57 – 1.48 (m, 2H, H₅ x 2), 0.91 (s, 6H, H₇ x 6).

¹³C NMR (101 MHz, CDCl₃) δ 135.3 (C₂), 117.1 (C₁), 59.8 (C₆), 47.0 (C₃), 44.3 (C₅), 32.5 (C₄), 27.3 (C₇ x 2).

The spectroscopic data matched that previously reported in the literature.^[88]

4,4-Dimethylhept-6-en-2-one 153

TiCl_4 (neat, 2.2 mL, 20.0 mmol, 1.0 equiv.) and allyltrimethylsilane (4.1 mL, 26.0 mmol, 1.3 equiv.) were added sequentially, dropwise, to a solution of 4-methyl-3-penten-2-one (2.3 mL, 20.0 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 M, 40 mL) at -78°C . The reaction mixture was stirred for 15 min, then warmed to 0°C , and Et_3N (15 mL) and MeOH (5 mL) were added dropwise. The mixture was allowed to warm to RT, diluted with Et_2O (40 mL), washed successively with HCl (1.0 M, 40 mL) and saturated aqueous NaHCO_3 (40 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude product was taken onto the next step with no further purification.

4,4-Dimethylhept-6-en-2-ol 154

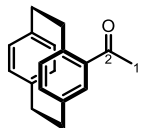
NaBH_4 (1.13 g, 30.0 mmol, 1.5 equiv.) was added to a solution of 4,4-dimethylhept-6-en-2-one **153** (2.80 g, 20.0 mmol, 1.0 equiv.) in EtOH (0.2 M, 100 mL) at 0°C . The reaction mixture was allowed to warm to RT and stirred for 12 h, then concentrated *in vacuo*. The residue was quenched by the addition of saturated aqueous ammonium chloride (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic phases were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (30% EtOAc/pentane) as a colourless oil (1.62 g, 11.4 mmol, 57% yield over 2 steps).

^1H NMR (400 MHz, CDCl_3) δ 5.83 (ddt, $J = 17.0, 10.5, 7.5$ Hz, 1H, H_2), 5.07 – 4.96 (m, 2H, $\text{H}_1 \times 2$), 3.99 (m, 1H, H_6), 2.10 – 1.96 (m, 2H, $\text{H}_3 \times 2$), 1.46 – 1.30 (m, 3H, $\text{H}_3 \times 2$, OH), 1.19 (d, $J = 6.0$ Hz, 3H, $\text{H}_8 \times 3$), 0.95 (s, 6H, $\text{H}_7 \times 2$).

^{13}C NMR (101 MHz, CDCl_3) δ 135.7 (C_2), 117.0 (C_1), 65.5 (C_6), 50.8 (C_5), 47.3 (C_3), 33.0 (C_4), 27.6 ($\text{C}_7 \times 2$), 26.1 (C_8).

HRMS: Acceptable ionisation could not be obtained by ESI, CI or EI methods.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3331, 2954, 2891, 1662, 1598, 1368.

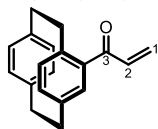
rac*-4-Acetyl[2.2]paracyclophane **167*

AlCl_3 (5.76 g, 43.2 mmol, 1.8 equiv.) was added in several portions to a solution of [2.2]Paracyclophane (5.00 g, 24.0 mmol, 1.0 equiv.) and acetyl chloride (3.4 mL, 48.0 mmol, 2.0 equiv.) in CH_2Cl_2 (0.5 M, 48 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 1 h, then poured onto crushed ice. The resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic phases were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% EtOAc/pentane) as a white solid (4.14 g, 16.5 mmol, 69% yield).

^1H NMR (400 MHz, CDCl_3) δ 6.93 (d, J = 2.0 Hz, 1H, ArCH), 6.66 (dd, J = 7.5, 2.0 Hz, 1H, ArCH), 6.59 – 6.44 (m, 4H, ArCH x 4), 6.38 (dd, J = 8.0, 2.0 Hz, 1H, ArCH), 4.03 – 3.92 (m, 1H, Paracyclophane- CH_2), 3.26 – 3.10 (m, 4H, Paracyclophane- CH_2 x 4), 3.10 – 2.96 (m, 2H, Paracyclophane- CH_2 x 2), 2.90 – 2.78 (m, 1H, Paracyclophane- CH_2), 2.47 (s, 3H, H_1 x 3).

^{13}C NMR (101 MHz, CDCl_3) δ 200.4 (C_2), 141.7 (ArC), 140.4 (ArC), 139.9 (ArC), 139.3 (ArC), 138.0 (ArC), 136.5 (ArC), 136.5 (ArC), 134.3 (ArC), 133.2 (ArC), 133.0 (ArC), 132.2 (ArC), 131.3 (ArC), 36.2 (Paracyclophane- CH_2), 35.3 (Paracyclophane- CH_2), 35.3 (Paracyclophane- CH_2), 35.0 (Paracyclophane- CH_2), 28.9 (C_1).

The spectroscopic data matched that previously reported in the literature.^[89]

1-(1,4(1,4)-Dibenzenacyclohexaphane-1²-yl)prop-2-en-1-one **168**

i-Pr₂NH:TFA (859 mg, 3.99 mmol, 1.0 equiv.) and trifluoroacetic acid (31 μL , 0.399 mmol, 10 mol%) were added sequentially to a suspension of *rac*-4-acetyl[2.2]paracyclophane **167** (1.00 g, 3.99 mmol, 1.0 equiv.) and paraformaldehyde (240 mg, 7.99 mmol, 2.0 equiv.) in THF (1.0 M, 4 mL). The reaction mixture was heated under reflux for 2 h, after which a second portion of paraformaldehyde (240 mg, 7.99 mmol, 2.0 equiv.) was added. The reaction was then heated

under reflux for a further 10 h, cooled to RT, diluted with Et₂O (2 mL), and washed successively with NaOH (1.0 M, 5 mL), HCl (1.0 M, 5 mL) and brine (5 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% EtOAc/pentane) as a white solid (339 mg, 1.29 mmol, 32% yield).

¹H NMR (400 MHz, CDCl₃) δ 6.83 (d, *J* = 2.0 Hz, 1H, ArH), 6.76 (dd, *J* = 17.5, 10.5 Hz, 1H, H₂), 6.66 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 6.62 – 6.49 (m, 4H, ArH x 4), 6.35 (dd, *J* = 8.5, 1.5 Hz, 1H, ArH), 6.19 (dd, *J* = 17.5, 1.5 Hz, 1H, H_{1a}), 5.84 (dd, *J* = 10.5, 1.5 Hz, 1H, H_{1b}), 3.68 (ddd, *J* = 12.5, 10.0, 2.0 Hz, 1H, Paracyclophane-CH₂), 3.29 – 2.95 (m, 6H, Paracyclophane-CH₂ x 6), 2.89 (ddd, *J* = 12.5, 10.0, 6.0 Hz, 1H, Paracyclophane-CH₂).

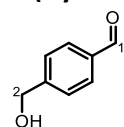
¹³C NMR (101 MHz, CDCl₃) δ 193.5 (C₃), 141.5 (ArC), 134.0 (ArC), 139.7 (ArC), 139.3 (ArC), 137.2 (ArC), 136.3 (ArC), 136.1 (ArC), 136.0 (C₂), 133.6 (ArC), 132.8 (ArC), 132.6 (ArC), 132.5 (ArC), 131.2 (ArC), 129.4 (C₁), 35.5 (Paracyclophane-CH₂), 35.4 (Paracyclophane-CH₂), 35.2 (Paracyclophane-CH₂), 35.1 (Paracyclophane-CH₂).

HRMS (ESI⁺): Found [M+H]⁺ = 263.1429; C₁₉H₁₉O requires 263.1430, Δ -0.37 ppm

IR (film) ν_{max}/cm⁻¹: 2980, 2888, 1664, 1602, 1473, 1462.

m.p.: 103-104 °C

4-(Hydroxymethyl)benzaldehyde 170



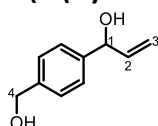
NaBH₄ (423 mg, 11.2 mmol, 0.3 equiv.) was added to a solution of terephthalaldehyde (5.00 g, 37.2 mmol, 1.0 equiv.) in EtOH (0.5 M, 74 mL) at 0 °C. The reaction mixture was stirred for 1 h, warmed to RT and concentrated *in vacuo*. The reaction was quenched by the addition of saturated aqueous ammonium chloride (40 mL) and extracted with EtOAc (3 x 40 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (2% MeOH/CH₂Cl₂) as a white solid (2.60 g, 19.1 mmol, 51% yield).

^1H NMR (400 MHz, CDCl_3) δ 10.01 (s, 1H, H_1), 7.92 – 7.84 (m, 2H, ArCH x 2), 7.53 (d, J = 8.0 Hz, 2H, ArCH x 2), 4.81 (s, 2H, H_2).

^{13}C NMR (101 MHz, CDCl_3) δ 192.1 (C_1), 147.9 (ArC), 135.9 (ArC), 130.2 (ArC x 2), 127.1 (ArC x 2), 64.7 (C_2).

The spectroscopic data matched that previously reported in the literature.^[90]

1-(4-(Hydroxymethyl)phenyl)prop-2-en-1-ol **171**



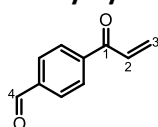
Vinylmagnesium bromide (1.0 M, 22.0 mL, 22.0 mmol, 3.0 equiv.) was added to a solution of 4-(hydroxymethyl)benzaldehyde **170** (1.00 g, 7.34 mmol, 1.0 equiv.) in THF (0.1 M, 73 mL) at 0 °C. The reaction mixture was stirred for 2 h, quenched by the addition of saturated aqueous ammonium chloride (40 mL), and extracted with EtOAc (3 x 40 mL). The combined organic phases were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (4% MeOH/ CH_2Cl_2) as a yellow solid (784 mg, 4.77 mmol, 65% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.32 (m, 4H, ArCH x 4), 6.04 (ddd, J = 17.0, 10.0, 6.0 Hz, 1H, H_2), 5.36 (dd, J = 17.0, 1.5 Hz, 1H, H_{3a}), 5.26 – 5.16 (m, 2H, H_1 , H_{3b}), 4.69 (d, J = 6.0 Hz, 2H, H_4 x 2), 1.96 (d, J = 3.5 Hz, 1H, OH), 1.67 (t, J = 6.0 Hz, 1H, OH).

^{13}C NMR (101 MHz, CDCl_3) δ 142.2 (ArC), 140.6 (ArC), 140.3 (C_2), 127.4 (ArC x 2), 126.7 (ArC x 2), 115.4 (C_3), 75.3 (C_1), 65.3 (C_4).

The spectroscopic data matched that previously reported in the literature.^[90]

4-Acryloylbenzaldehyde **172**



Activated MnO_2 (8.30 g, 95.5 mmol, 20 equiv.) was added to a solution of 1-(4-(hydroxymethyl)phenyl)prop-2-en-1-ol **171** (0.784 g, 4.77 mmol, 1.0 equiv.) in CH_2Cl_2 (0.2 M, 24 mL). The reaction mixture was heated under reflux for 12 h open to air, cooled to RT, filtered

through a pad of Celite, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (30% Et₂O/pentane) as a yellow solid (153 mg, 0.955 mmol, 20% yield).

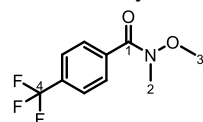
¹H NMR (400 MHz, CDCl₃) δ 10.12 (s, 1H, H₄), 8.11 – 8.04 (m, 2H, ArCH x 2), 8.04 – 7.94 (m, 2H, ArCH x 2), 7.14 (dd, *J* = 17.0, 10.5 Hz, 1H, H₂), 6.47 (dd, *J* = 17.0, 1.5 Hz, 1H, H_{3a}), 6.03 (dd, *J* = 10.5, 1.5 Hz, 1H, H_{3b}).

¹³C NMR (101 MHz, CDCl₃) δ 191.7 (C₄), 190.8 (C₁), 141.9 (ArC), 139.06 (ArC), 132.4 (C₂), 131.6 (C₃), 123.0 (ArC x 2), 129.3 (ArC x 2).

The spectroscopic data matched that previously reported in the literature.^[90]

5.3.2 Synthesis of Cuprate Addition Precursors

N-Methoxy-*N*-methyl-4-(trifluoromethyl)benzamide 246



Dimethylhydroxylamine hydrochloride (3.22 g, 33.0 mmol, 1.1 equiv.), CH₂Cl₂ (0.3 M, 100 mL), 4-(trifluoromethyl)benzoyl chloride (6.26 g, 30.0 mmol, 1.0 equiv.), and triethylamine (12.6 mL, 90.0 mmol, 3.0 equiv.) were subjected to **General Procedure 3**. The title compound was afforded after purification by FCC (20% EtOAc/pentane) as a colourless oil (6.42 g, 27.5 mmol, 92% yield).

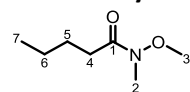
¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, *J* = 8.0 Hz, 2H, ArCH x 2), 7.66 (d, *J* = 8.0 Hz, 2H, ArCH x 2), 3.52 (s, 3H, H₃ x 3), 3.37 (s, 3H, H₂ x 3).

¹⁹F NMR (471 MHz, CDCl₃) δ -63.0.

¹³C NMR (126 MHz, CDCl₃) δ 168.6 (C₁), 137.7 (ArC), 132.3 (ArC), 128.7 (ArC x 2), 125.1 (ArC x 2), 122.8 (C₄), 61.4 (C₃), 33.4 (C₂).

The spectroscopic data matched that previously reported in the literature.^[91]

N-Methoxy-*N*-methylpentanamide 262



Dimethylhydroxylamine hydrochloride (2.17 g, 22.2 mmol, 1.1 equiv.), CH₂Cl₂ (0.3 M, 33 mL), valeroyl chloride (2.4 mL, 20.2 mmol, 1.0 equiv.), and triethylamine (4.4 mL, 60.7 mmol, 3.0

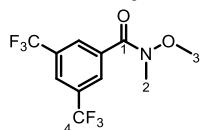
equiv.) were subjected to **General Procedure 3**. The title compound was afforded after purification by FCC (20% EtOAc/pentane) as a colourless oil (1.59 g, 11.0 mmol, 55% yield).

^1H NMR (400 MHz, CDCl_3) δ 3.67 (s, 3H, $\text{H}_3 \times 3$), 3.17 (s, 3H, $\text{H}_2 \times 3$), 2.41 (t, $J = 7.5$ Hz, 2H, $\text{H}_4 \times 2$), 1.66 – 1.54 (m, 2H, $\text{H}_5 \times 2$), 1.42 – 1.29 (m, 2H, $\text{H}_6 \times 2$), 0.92 (t, $J = 7.5$ Hz, 3H, $\text{H}_7 \times 3$).

^{13}C NMR (101 MHz, CDCl_3) δ 174.8, 61.3, 32.3, 31.7, 26.9, 22.7, 14.0.

The spectroscopic data matched that previously reported in the literature.^[92]

***N*-Methoxy-*N*-methyl-3,5-bis(trifluoromethyl)benzamide 284**



Dimethylhydroxylamine hydrochloride (1.07 g, 11.0 mmol, 1.1 equiv.), CH_2Cl_2 (0.3 M, 33 mL), 3,5-bis(trifluoromethyl)benzoyl chloride (2.77 g, 10.0 mmol, 1.0 equiv.), and triethylamine (4.2 mL, 30.0 mmol, 3.0 equiv.) were subjected to **General Procedure 3**. The title compound was afforded after purification by FCC (20% EtOAc/pentane) as a colourless oil (2.39 g, 7.94 mmol, 79% yield).

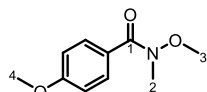
^1H NMR (500 MHz, CDCl_3) δ 8.21 – 8.17 (m, 2H, ArCH $\times 2$), 7.99 – 7.95 (m, 1H, ArCH), 3.55 (s, 3H, $\text{H}_3 \times 3$), 3.41 (s, 3H, $\text{H}_2 \times 3$).

^{19}F NMR (471 MHz, CDCl_3) δ -63.0.

^{13}C NMR (126 MHz, CDCl_3) δ 166.7 (C_1), 136.0 (ArC), 131.7 (ArC), 128.9 (ArC $\times 2$), 124.4 (ArC $\times 2$), 122.0 (C_4), 61.6 (C_3), 33.3 (C_2).

The spectroscopic data matched that previously reported in the literature.^[93]

***N*,4-Dimethoxy-*N*-methylbenzamide 285**



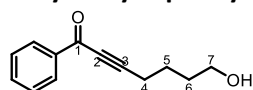
Dimethylhydroxylamine hydrochloride (1.61 g, 16.5 mmol, 1.1 equiv.), CH_2Cl_2 (0.3 M, 50 mL), 4-methoxybenzoyl chloride (2.56 g, 15.0 mmol, 1.0 equiv.), and triethylamine (6.3 mL, 45.0 mmol, 3.0 equiv.) were subjected to **General Procedure 3**. The title compound was afforded after purification by FCC (40% EtOAc/pentane) as a colourless oil (1.51 g, 7.73 mmol, 51% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.77 – 7.68 (m, 2H, ArCH x 2), 6.94 – 6.86 (m, 2H, ArCH x 2), 3.84 (s, 3H, H_4 x 3), 3.56 (s, 3H, H_3 x 3), 3.35 (s, 3H, H_2 x 3).

^{13}C NMR (101 MHz, CDCl_3) δ 169.5 (C_1), 161.6 (ArC), 130.7 (ArC x 2), 126.1 (ArC), 113.4 (ArC x 2), 61.0 (C_3), 55.4 (C_4), 34.0 (C_2).

The spectroscopic data matched that previously reported in the literature.^[94]

7-Hydroxy-1-phenylhept-2-yn-1-one **183**



n-BuLi in hexanes (23 mL, 2.5 M, 58.0 mmol, 2.4 equiv.), 5-hexyn-1-ol (2.83 g, 28.8 mmol, 1.2 equiv.), THF (0.3 M, 80 mL), and *N*-methoxy-*N*-methylbenzamide (3.96 g, 24.0 mmol, 1.0 equiv.) were subjected to **General Procedure 4**. The title compound was afforded after purification by FCC (20→40% EtOAc/Pentane) as a yellow oil (4.15 g, 20.5 mmol, 85% yield).

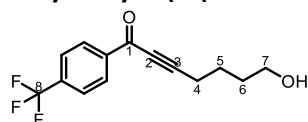
^1H NMR (400 MHz, CDCl_3) δ 8.17 – 8.07 (m, 2H, ArCH x 2), 7.64 – 7.54 (m, 1H, ArCH), 7.52 – 7.41 (m, 2H, ArCH x 2), 3.78 – 3.65 (m, 2H, H_7 x 2), 2.61 – 2.49 (m, 2H, H_4 x 2), 1.85 – 1.69 (m, 4H, H_5 x 2, H_6 x 2), 1.62 (s, 1H, OH).

^{13}C NMR (101 MHz, CDCl_3) δ 178.4 (C_1), 137.0 (ArC), 134.1 (ArC), 129.7 (ArC x 2), 128.7 (ArC x 2), 96.4 (C_3), 80.0 (C_2), 62.3 (C_7), 31.9 (C_6), 24.4 (C_5), 19.2 (C_4).

HRMS (ESI⁺): Found $[\text{M}+\text{H}]^+ = 203.1071$; $\text{C}_{13}\text{H}_{15}\text{O}_2$ requires 203. 1067 Δ 2.16 ppm

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3389, 2938, 2869, 2236, 2200, 1639.

7-Hydroxy-1-(4-(trifluoromethyl)phenyl)hept-2-yn-1-one **247**



n-BuLi in hexanes (19.2 mL, 2.5 M, 48.0 mmol, 2.4 equiv.), 5-hexyn-1-ol (2.35 g, 24.0 mmol, 1.2 equiv.), THF (0.3 M, 67 mL), and *N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide **246** (4.66 g, 20.0 mmol, 1.0 equiv.) were subjected to **General Procedure 4**. The title compound was afforded after purification by FCC (10→40% EtOAc/pentane) as a yellow oil (3.76 g, 13.9 mmol, 70% yield).

^1H NMR (500 MHz, CDCl_3) δ 8.23 (d, J = 8.0 Hz, 2H, ArCH x 2), 7.74 (d, J = 8.0 Hz, 2H, ArCH x 2), 3.73 (t, J = 6.0 Hz, 2H, H_7 x 2), 2.59 (t, J = 6.5 Hz, 2H, H_4 x 2), 1.86 – 1.71 (m, 4H, H_5 x 2, H_6 x 2), 1.39 (s, 1H, OH).

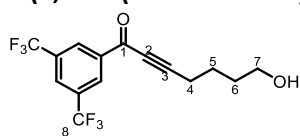
^{19}F NMR (471 MHz, CDCl_3) δ -63.1.

^{13}C NMR (126 MHz, CDCl_3) δ 177.0 (C_1), 139.5 (ArC), 135.2 (ArC), 129.9 (ArC x 2), 125.8 (ArC x 2), 123.7 (C_8), 97.9 (C_3), 79.8 (C_2), 62.3 (C_7), 31.9 (C_6), 24.4 (C_5), 19.2 (C_4).

HRMS (ESI $^+$): Found $[\text{M}+\text{H}]^+ = 271.0945$; $\text{C}_{14}\text{H}_{14}\text{F}_3\text{O}_2$ requires 271.0940 Δ 1.68 ppm

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3433, 2942, 2239, 2204, 1651, 1583.

1-(3,5-Bis(trifluoromethyl)phenyl)-7-hydroxyhept-2-yn-1-one **287**



n-BuLi in hexanes (7.2 mL, 2.5 M, 18.0 mmol, 2.4 equiv.), 5-hexyn-1-ol (884 mg, 9.00 mmol, 1.2 equiv.), THF (0.3 M, 25 mL), and *N*-methoxy-*N*-methyl-3,5-bis(trifluoromethyl)benzamide **284** (2.26 g, 7.50 mmol, 1.0 equiv.) were subjected to **General Procedure 4**. The title compound was afforded after purification by FCC (10 $\rightarrow$ 40% EtOAc/Pentane) as a yellow oil (1.69 g, 5.00 mmol, 67% yield).

^1H NMR (500 MHz, CDCl_3) δ 8.57 – 8.53 (m, 2H, ArCH x 2), 8.09 (s, 1H, ArCH), 3.74 (t, J = 6.0 Hz, 2H, H_7 x 2), 2.63 (t, J = 7.0 Hz, 2H, H_4 x 2), 1.88 – 1.72 (m, 4H, H_5 x 2, H_6 x 2), 1.46 (s, 1H, OH).

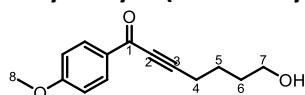
^{19}F NMR (471 MHz, CDCl_3) δ -63.00.

^{13}C NMR (126 MHz, CDCl_3) δ 175.0 (C_1), 138.4 (ArC), 132.5 (ArC), 129.5 (ArC x 2), 127.1 (ArC), 123.0 (C_8), 99.6 (C_3), 79.2 (C_2), 62.2 (C_7), 31.8 (C_6), 24.3 (C_5), 19.3 (C_4).

HRMS (ESI $^+$): Found $[\text{M}+\text{H}]^+ = 399.0806$; $\text{C}_{15}\text{H}_{13}\text{F}_6\text{O}_2$ requires 399.0814 Δ -2.44 ppm.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3366, 2980, 2211, 1660, 1615, 1459.

7-Hydroxy-1-(4-methoxyphenyl)hept-2-yn-1-one **288**



n-BuLi in hexanes (9.8 mL, 2.5 M, 24.6 mmol, 2.4 equiv.), 5-hexyn-1-ol (1.21 g, 12.3 mmol, 1.2 equiv.), THF (0.3 M, 34 mL) and *N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide **285** (2.00 g, 10.2 mmol, 1.0 equiv.) were subjected to **General Procedure 4**. The title compound was afforded after purification by FCC (20→60% EtOAc/Pentane) as a yellow oil (2.11 g, 9.08 mmol, 89% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.13 – 8.04 (m, 2H, ArCH x 2), 6.98 – 6.89 (m, 2H, ArCH x 2), 3.88 (s, 3H, H₈ x 3), 3.75 – 3.67 (m, 2H, H₇ x 2), 2.58 – 2.48 (m, 2H, H₄ x 2), 1.82 – 1.69 (m, 4H, H₅ x 2, H₆ x 2).

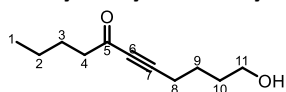
¹³C NMR (101 MHz, CDCl₃) δ 177.1 (C₁), 164.5 (ArC), 132.1 (ArC x 2), 130.4 (ArC), 113.9 (ArC x 2), 95.5 (C₃), 80.0 (C₂), 62.3 (C₇), 55.7 (C₈), 31.9 (C₆), 24.4 (C₅), 19.2 (C₄).

HRMS (ESI⁺): Found [M+H]⁺ = 233.1172; C₁₄H₁₇O₃ requires 233.1172 Δ -0.11 ppm.

m.p.: 43-44 °C.

IR (film) ν_{max}/cm⁻¹: 3421, 2980, 2238, 2203, 1636, 1598.

11-Hydroxyundec-6-yn-5-one **289**



n-BuLi in hexanes (14.4 mL, 2.5 M, 36.0 mmol, 2.4 equiv.), 5-hexyn-1-ol (1.77 g, 18.0 mmol, 1.2 equiv.), THF (0.3 M, 50 mL) and *N*-methoxy-*N*-methylpentanamide **262** (2.18 g, 15.0 mmol, 1.0 equiv.) were subjected to **General Procedure 4**. The title compound was afforded after purification by FCC (20→60% EtOAc/Pentane) as a yellow oil (1.92 g, 10.5 mmol, 70% yield).

¹H NMR (400 MHz, CDCl₃) δ 3.72 – 3.64 (m, 2H, H₁₁ x 2), 2.52 (t, *J* = 7.5 Hz, 2H, H₄ x 2), 2.47 – 2.37 (m, 2H, H₈ x 2), 1.75 – 1.56 (m, 6H, H₉ x 2, H₁₀ x 2, H₃ x 2), 1.46 (s, 1H, OH), 1.41 – 1.27 (m, 2H, H₂ x 2), 0.91 (t, *J* = 7.5 Hz, 3H, H₁ x 3).

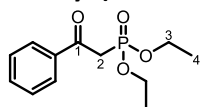
¹³C NMR (101 MHz, CDCl₃) δ 188.7 (C₅), 93.7 (C₇), 81.3 (C₆), 62.3 (C₁₁), 45.4 (C₄), 31.8 (C₁₀), 26.3 (C₃), 24.3 (C₉), 22.3 (C₂), 18.9 (C₈), 13.9 (C₁).

HRMS (ESI⁺): Found [M+H]⁺ = 183.1383; C₁₁H₁₉O₂ requires 183.1380 Δ 1.85 ppm

IR (film) ν_{max}/cm⁻¹: 3432, 2980, 2214, 1672, 1618, 1461.

5.3.3 Miscellaneous

Diethyl (2-oxo-2-phenylethyl)phosphonate 218



A 25 mL round-bottom flask fitted with an air condenser was charged with 2-bromoacetophenone (4.00 g, 20.0 mmol, 1.0 equiv.) and triethyl phosphite (3.60 g, 22.0 mmol, 1.1 equiv.). The reaction mixture was heated at 160 °C for 16 h and then cooled to RT. The title compound was afforded after purification by FCC (50→100% Et₂O/pentane) as a colourless oil (4.78 g, 18.7 mmol, 93% yield).

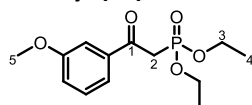
¹H NMR (400 MHz, CDCl₃) δ 8.07 – 8.00 (m, 2H, ArCH x 2), 7.65 – 7.56 (m, 1H, ArCH), 7.55 – 7.45 (m, 2H, ArCH x 2), 4.22 – 4.07 (m, 4H, H₃ x 4), 3.65 (d, *J* = 23.0 Hz, 2H, H₂ x 2), 1.30 (td, *J* = 7.0, 0.5 Hz, 6H, H₄ x 6).

³¹P NMR (162 MHz, CDCl₃) δ 19.9.

¹³C NMR (101 MHz, CDCl₃) δ 192.1 (d, *J* = 7.0 Hz, C₁), 136.7 (d, *J* = 1.5 Hz, ArC), 133.8 (ArC), 129.2 (ArC x 2), 128.7 (ArC x 2), 62.8 (d, *J* = 6.5 Hz, C₃ x 2), 38.6 (d, *J* = 130.0 Hz, C₂), 16.4 (d, *J* = 6.5 Hz, C₄ x 2).

The spectroscopic data matched that previously reported in the literature.^[95]

Diethyl (2-(3-methoxyphenyl)-2-oxoethyl)phosphonate 221



A 100 mL round-bottom flask under an argon atmosphere was charged with diisopropylamine (2.3 mL, 16.2 mmol, 2.25 equiv.) and THF (0.4 M, 41 mL), and the resulting stirred solution was cooled to 0 °C. *n*-BuLi in hexanes (2.5 M, 6.4 mL, 15.9 mmol, 2.20 equiv.) was added dropwise, and the mixture was stirred at 0 °C for 30 min. A separate 250 mL round-bottom flask under an argon atmosphere was charged with methyl 3-methoxybenzoate (1.20 g, 7.22 mmol, 1.00 equiv.), diethyl methylphosphonate (1.21 g, 7.94 mmol, 1.10 equiv.) and THF (0.2 M, 36 mL), and cooled to 0 °C. The LDA solution was added dropwise to this flask *via* cannula, and the

reaction mixture was stirred at 0 °C for 5 min. The mixture was diluted with HCl (3 M, 30 mL), warmed to RT, and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (50→100% EtOAc/pentane) as a colourless oil (1.90 g, 6.64 mmol, 92% yield).

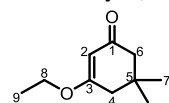
¹H NMR (400 MHz, CDCl₃) δ 7.58 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H, ArCH), 7.52 (dd, *J* = 2.5, 1.5 Hz, 1H, ArCH), 7.37 (t, *J* = 8.0 Hz, 1H, ArCH), 7.12 (ddd, *J* = 8.5, 2.5, 1.0 Hz, 1H, ArCH), 4.27 – 4.03 (m, 4H, H₃ x 4), 3.84 (s, 3H, H₅ x 3), 3.61 (d, *J* = 23.0 Hz, 2H, H₂ x 2), 1.27 (td, *J* = 7.0, 0.5 Hz, 6H, H₄ x 6).

³¹P NMR (162 MHz, CDCl₃) δ 19.9.

¹³C NMR (101 MHz, CDCl₃) δ 191.9 (d, *J* = 6.5 Hz), 159.9, 138.0 (d, *J* = 2.0 Hz), 129.7, 122.0, 120.5, 112.9, 62.8 (d, *J* = 6.5 Hz), 55.6, 38.7 (d, *J* = 130.0 Hz), 16.4 (d, *J* = 6.5 Hz).

The spectroscopic data matched that previously reported in the literature.^[64]

3-Ethoxy-5,5-dimethylcyclohex-2-en-1-one 206

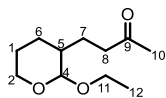


Ethanol (1.7 mL, 28.5 mmol, 2.0 equiv.) and *p*-toluenesulphonic acid (136 mg, 0.713 mmol, 5 mol%) were added to a solution of dimedone (2.00 g, 14.3 mmol, 1.0 equiv.) in toluene (0.4 M, 36 mL). The reaction mixture was fitted with a Dean-Stark apparatus and heated under reflux for 2 h, after which a second portion of ethanol (1.7 mL, 28.5 mmol, 2.0 equiv.) was added. The reaction was then heated under reflux for a further 10 h, cooled to RT, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (50% Et₂O/pentane) as a yellow oil (1.78 g, 10.6 mmol, 74% yield).

¹H NMR (400 MHz, CDCl₃) δ 5.32 (s, 1H, H₂), 3.89 (q, *J* = 7.0 Hz, 2H, H₈ x 3), 2.25 (s, 2H, H₄ x 2), 2.19 (s, 2H, H₆ x 2), 1.35 (t, *J* = 7.0 Hz, 3H, H₉ x 3), 1.06 (s, 6H, H₇ x 6).

¹³C NMR (101 MHz, CDCl₃) δ 199.7 (C₁), 176.3 (C₃), 101.6 (C₂), 64.3 (C₈), 50.9 (C₄), 43.1 (C₆), 32.6 (C₅), 28.4 (C₇ x 2), 14.2 (C₉).

The spectroscopic data matched that previously reported in the literature.^[96]

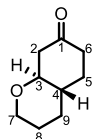
4-(2-Ethoxytetrahydro-2H-pyran-3-yl)butan-2-one 212

Methyl vinyl ketone (1.7 mL, 20.0 mmol, 2.0 equiv.), ethanol (1.2 mL, 20.0 mmol, 2.0 equiv.), and boron trifluoride diethyl etherate (0.6 mL, 0.005 mmol, 0.05 mol%) were added sequentially to a solution of 3,4-dihydro-2H-pyran (841 mg, 10.0 mmol, 1.0 equiv.) in nitromethane (1.0 M, 10 mL) at 0 °C. The reaction mixture was stirred for 30 min, then quenched by the addition of saturated aqueous NaHCO₃ (10 mL). The mixture was allowed to warm to RT, extracted with DCM (3 x 10 mL), and the combined organic phases were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (20% EtOAc/pentane) as a colourless oil (574 mg, 2.87 mmol, 29% yield).

¹H NMR (400 MHz, CDCl₃) δ 4.59 (d, *J* = 2.5 Hz, 1H, major H₄), 4.11 (d, *J* = 6.5 Hz, 1H, minor H₄), 3.98 – 3.80 (m, 2H, minor H_{2a}, minor H_{11a}), 3.79 – 3.64 (m, 2H, major H_{11a}, major H_{2a}), 3.55 – 3.34 (m, 4H, major H_{2b}, minor H_{11b}, minor H_{2b}, major H_{11b}), 2.50 (t, *J* = 7.5 Hz, 2H, minor H₈ x 2), 2.47 – 2.33 (m, 2H, major H₈ x 2), 2.14 (s, 6H, major H₁₀ x 3, minor H₁₀ x 3), 1.93 – 1.74 (m, 2H, major H_{6a}, minor H_{6a}), 1.71 – 1.33 (m, 11H, major H₅, major H₇ x 2, minor H₇ x 2, major H₁ x 2, minor H₁ x 2, minor H_{6b}, minor H₅), 1.26 – 1.16 (m, 7H, major H₁₂ x 3, minor H₁₂ x 3, major H_{6b}).

¹³C NMR (101 MHz, CDCl₃) δ 209.3 (major C₉, minor C₉), 104.8 (minor C₄), 98.9 (major C₄), 64.7 (minor C₂), 64.0 (minor C₁₁), 62.7 (major C₁₁), 59.6 (major C₂), 41.7 (minor C₈), 41.1 (major C₈), 39.8 (minor C₅), 39.3 (major C₅), 30.1 (minor C₁₀), 30.0 (major C₁₀), 27.5 (minor C₆), 25.9 (major C₆), 25.6 (major C₁ or C₇), 25.4 (minor C₁ or C₇), 24.5 (minor C₁ or C₇), 24.3 (major C₁ or C₇), 15.4 (minor C₁₂), 15.2 (major C₁₂).

The spectroscopic data matched that previously reported in the literature.^[69]

(4a*S*,8a*S*)-Octahydro-7H-chromen-7-one 213

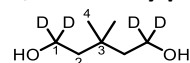
A 50 mL round-bottom flask was charged with 4-(2-ethoxytetrahydro-2H-pyran-3-yl)butan-2-one **212** (1.09 g, 5.44 mmol, 1.0 equiv.), HCl (3.0 M, 13.6 mL, 40.8 mmol, 7.5 equiv.) and CH₂Cl₂ (0.2 M, 28 mL). The reaction mixture was heated under reflux for 3 h, cooled to RT, and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10→20% Et₂O/pentane) as a white solid (270 mg, 1.75 mmol, 32% yield).

¹H NMR (400 MHz, CDCl₃) δ 4.03 – 3.95 (m, 1H, H_{7a}), 3.42 (td, *J* = 12.0, 2.5 Hz, 1H, H_{7b}), 3.12 (ddd, *J* = 12.0, 9.5, 5.0 Hz, 1H, H₃), 2.67 (ddt, *J* = 14.0, 5.0, 1.5 Hz, 1H, H_{2a}), 2.44 – 2.22 (m, 3H, H_{2b}, H₆ x 2), 1.97 – 1.48 (m, 5H, H_{8a}, H_{5a}, H₉ x 2, H₄), 1.34 – 1.12 (m, 2H, H_{5b}, H_{8b}).

¹³C NMR (101 MHz, CDCl₃) δ 208.9 (C₁), 79.6 (C₃), 68.2 (C₇), 48.3 (C₂), 41.2 (C₆), 40.7 (C₄), 29.8 (C₈), 28.2 (C₅), 26.2 (C₉).

The spectroscopic data matched that previously reported in the literature.^[69]

3,3-Dimethylpentane-1,1,5,5-*d*₄-1,5-diol **147-*d*₄**



Iodine (7.52 g, 29.6 mmol, 1.2 equiv.) in THF (0.2 M, 148 mL) was added dropwise *via* dropping funnel to a 1 L three-necked flask at 0 °C under an argon atmosphere containing with 3,3-dimethylglutaric acid (3.95 g, 24.7 mmol, 1.0 equiv.), NaBD₄ (3.10 g, 74.1 mmol, 3.0 equiv.) and THF (0.2 M, 124 mL). The reaction mixture was warmed to RT and stirred for 48 h. The reaction was quenched by the addition of MeOH (25 mL) at 0 °C and concentrated *in vacuo*. The residue was diluted with water (100 mL), extracted with EtOAc (3 x 200 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (100% EtOAc) as a yellow oil (666 mg, 4.89 mmol, 20% yield, 95% D incorporation by ¹H and ¹³C NMR).

¹H NMR (400 MHz, CDCl₃) δ 3.72 (t, *J* = 7.0 Hz, 0.2H, H₁), 2.06 (s, 2H, OH x 2), 1.56 (s, 4H, H₂ x 4), 0.94 (s, 6H, H₄ x 6). [N.B. In the absence of deuteration, the peak for H₁ would integrate to 4.00. The measured integral by quantitative ¹H NMR was 0.20, indicating that a total of 3.80

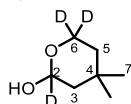
deuterium atoms were incorporated across the four equivalent positions, corresponding to 95% D incorporation at each site.]

^{13}C NMR (101 MHz, CDCl_3) δ 59.1 (1:2:3:2:1 quintet, $J = 21.0$ Hz, C_1), 44.1 (C_2), 31.8 (C_3), 28.2 ($\text{C}_4 \times 2$).

^2H NMR (92 MHz, $\text{CHCl}_3 + 1$ drop CDCl_3) δ 3.70 (s).

Apart from deuterium incorporation at C_1 , the spectral data for **147-*d*₄** were consistent with those of **147** prepared and reported previously.

4,4-Dimethyltetrahydro-2*H*-pyran-2,6-*d*₃-2-ol, **149-*d*₃**



A 50 mL round-bottom flask under an argon atmosphere was charged with IBX (30% wt. with stabilizer, 4.11 g, 4.41 mmol, 1.2 equiv.), dry DMSO (4.3 mL) and acetone (15.2 mL), and stirred for 40 min at RT. 3,3-dimethylpentane-1,1,5,5-*d*₄-1,5-diol, **147-*d*₄** (500 mg, 3.67 mmol, 1 equiv.) was then added, and the reaction mixture was stirred for 5 h, after which the reaction was diluted with water (15 mL) and filtered. The aqueous phase was extracted with Et_2O (4 x 50 mL), and the combined organic phases were washed with saturated aqueous Na_2CO_3 (20 mL), brine (20 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (50% Et_2O /pentane) as a colourless oil (187 mg, 1.40 mmol, 38% yield, >95% D incorporation by ^1H and ^{13}C NMR).

^1H NMR (400 MHz, CDCl_3) δ 3.69 (s, 1H, OH), 1.57 (dd, $J = 13.0$, 1.5 Hz, 1H, H_{3a}), 1.42 (d, $J = 13.0$ Hz, 1H, H_{5a}), 1.35 – 1.18 (m, 2H, H_{3b} and H_{5b}), 1.01 (s, 3H, $\text{H}_{7a} \times 3$), 0.98 (s, 3H, $\text{H}_{7b} \times 3$). [N.B. In the absence of deuteration, the peaks for H_2 , H_{6a} and H_{6b} would each integrate to 1.00. Integration of the quantitative

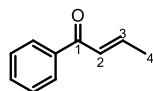
^1H NMR spectrum showed integrals of 0.02-0.03 for each of these peaks, indicating that 0.97-0.98 deuterium atoms were incorporated at each position.]

^{13}C NMR (101 MHz, CDCl_3) δ 92.9 (1:1:1 t, $J = 24.5$ Hz, C_2), 60.8 (1:2:3:2:1 quintet, $J = 21.5$ Hz, C_6), 45.1 (C_3), 37.9 (C_5), 31.7 (C_4), 29.8 (C_{7a}), 26.5 (C_{7b}).

^2H NMR (92 MHz, $\text{CHCl}_3 + 1$ drop CDCl_3) δ 4.91 (s, 1H, H_2), 3.90 (s, 1H, H_{6a}), 3.62 (s, 1H, H_{6b}).

Apart from deuterium incorporation at C_2 and C_6 , the spectral data for **149-*d*₃** were consistent with those of **149** prepared and reported previously.

(*E*)-1-Phenylbut-2-en-1-one **253**



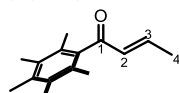
AlCl_3 (5.00 g, 37.5 mmol, 1.5 equiv.) was added in several portions to a solution of (*E*)-crotonoyl chloride (1.8 mL, 25.0 mmol, 1.0 equiv.) in benzene (8.9 mL, 100 mmol, 4.0 equiv.) at 0 °C. The reaction mixture was warmed to RT and stirred for 30 min, then poured onto crushed ice. The resulting solution was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic phases were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et_2O /pentane) as a colourless oil (695 mg, 4.75 mmol, 19% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.97 – 7.89 (m, 2H, ArH x 2), 7.59 – 7.51 (m, 1H, ArH), 7.50 – 7.42 (m, 2H, ArH x 2), 7.08 (dq, J = 15.5, 7.0 Hz, 1H, H_3), 6.91 (dq, J = 15.5, 1.5 Hz, 1H, H_2), 2.00 (dd, J = 6.5, 1.5 Hz, 3H, H_4 x 3).

^{13}C NMR (101 MHz, CDCl_3) δ 191.0 (C_1), 145.2 (C_3), 138.1 (ArC), 132.7 (ArC), 128.6 (ArC x 2), 127.7 (C_2), 18.7 (C_4).

The spectroscopic data matched that previously reported in the literature.^[97]

(*E*)-1-(2,3,4,5,6-Pentamethylphenyl)but-2-en-1-one **254**



AlCl_3 (3.72 g, 27.9 mmol, 1.2 equiv.) was added in several portions to a solution of (*E*)-crotonoyl chloride (2.0 mL, 27.9 mmol, 1.2 equiv.) and pentamethylbenzene (3.45 g, 23.3 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 M, 47 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h, then poured onto crushed ice. The resulting solution was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic phases were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The title

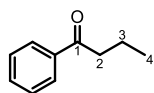
compound was afforded after purification by FCC (5% Et₂O/pentane) as a colourless oil (1.09 g, 5.04 mmol, 22% yield).

¹H NMR (400 MHz, CDCl₃) δ 6.48 (dq, *J* = 16.0, 6.5 Hz, 1H, H₃), 6.33 (dq, *J* = 15.5, 1.5 Hz, 1H, H₂), 2.24 (s, 3H, ArCH₃), 2.18 (s, 6H, ArCH₃ x 2), 2.06 (s, 6H, ArCH₃ x 2), 1.89 (dd, *J* = 6.5, 1.5 Hz, 3H, H₄ x 3).

¹³C NMR (101 MHz, CDCl₃) δ 203.1 (C₁), 148.0 (C₃), 138.2 (ArC), 135.4 (ArC), 134.8 (C₂), 132.9 (ArC x 2), 129.0 (ArC x 2), 18.6 (C₄), 17.5 (ArCH₃ x 2), 16.8 (ArCH₃), 16.1 (ArCH₃ x 2).

The spectroscopic data matched that previously reported in the literature.^[98]

1-Phenylbutan-1-one 255



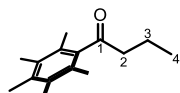
(*E*)-1-Phenylbut-2-en-1-one **253** (43.8 mg, 0.300 mmol, 1.0 equiv.), Al(*O**t*-Bu)₃ (74.1 mg, 0.300 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et₂O/pentane) as a colourless oil (9.3 mg, 0.063 mmol, 21% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.00 – 7.93 (m, 2H, ArH x 2), 7.60 – 7.51 (m, 1H, ArH), 7.50 – 7.41 (m, 2H, ArH x 2), 2.95 (t, *J* = 7.5 Hz, 2H, H₂ x 2), 1.78 (h, *J* = 7.5 Hz, 2H, H₃ x 2), 1.01 (t, *J* = 7.5 Hz, 3H, H₄ x 3).

¹³C NMR (101 MHz, CDCl₃) δ 200.6 (C₁), 137.3 (ArC), 133.0 (ArC), 128.7 (ArC x 2), 128.2 (ArC x 2), 40.7 (C₂), 17.9 (C₃), 14.0 (C₄).

The spectroscopic data matched that previously reported in the literature.^[99]

1-(2,3,4,5,6-Pentamethylphenyl)butan-1-one 256



(*E*)-1-(2,3,4,5,6-Pentamethylphenyl)but-2-en-1-one **254** (64.9 mg, 0.300 mmol, 1.0 equiv.), Al(*O**t*-Bu)₃ (74.1 mg, 0.300 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to

General Procedure 5. The title compound was afforded after purification by FCC (3% Et₂O/pentane) as a colourless oil (41.9 mg, 0.192 mmol, 64% yield).

¹H NMR (400 MHz, CDCl₃) δ 2.66 (t, *J* = 7.5 Hz, 2H, H₂ x 2), 2.23 (s, 3H, ArCH₃), 2.19 (s, 6H, ArCH₃ x 2), 2.10 (s, 6H, ArCH₃ x 2), 1.75 (h, *J* = 7.5 Hz, 2H, H₃ x 2), 1.01 (t, *J* = 7.5 Hz, 3H, H₄ x 3).

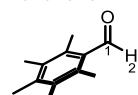
¹³C NMR (101 MHz, CDCl₃) δ 212.2 (C₁), 140.9 (ArC), 135.4 (ArC), 133.2 (ArC x 2), 127.5 (ArC x 2), 47.7 (C₂), 17.3 (ArCH₃ x 2), 16.8 (ArCH₃), 16.8 (C₃), 16.1 (ArCH₃ x 2), 13.9 (C₄).

HRMS (ESI⁺): Found [M+H]⁺ = 219.1740; C₁₅H₂₃O requires 219.1743, Δ −1.78 ppm.

m.p.: 60–62 °C.

IR (film) ν_{max}/cm^{−1}: 2980, 2927, 1695, 1658, 1457, 1381.

2,3,4,5,6-Pentamethylbenzaldehyde 258

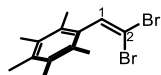


n-BuLi in hexanes (2.5 M, 9.7 mL, 24.2 mmol, 1.1 equiv.) was added dropwise to a solution of 1-bromo-2,3,4,5,6-pentamethylbenzene (5.00 g, 22.0 mmol, 1.0 equiv.) in THF (0.5 M, 44 mL) at −78 °C. The reaction mixture was stirred for 3 h, after which DMF (3.4 mL, 73.1 mmol, 2.0 equiv.) was added dropwise. The mixture was allowed to warm to RT, and stirred for 12 h, then quenched by the addition of saturated aqueous ammonium chloride (50 mL). The resulting solution was extracted with EtOAc (3 x 50 mL), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% EtOAc/pentane) as a white solid (2.85 g, 16.2 mmol, 73% yield).

¹H NMR (400 MHz, CDCl₃) δ 10.63 (s, 1H, H₂), 2.42 (s, 6H, ArCH₃ x 2), 2.29 (s, 3H, ArCH₃), 2.24 (s, 6H, ArCH₃ x 2).

¹³C NMR (101 MHz, CDCl₃) δ 196.6 (C₁), 140.2 (ArC), 134.6 (ArC x 2), 133.7 (ArC), 133.2 (ArC), 17.7 (ArCH₃), 16.2 (ArCH₃ x 2).

The spectroscopic data matched that previously reported in the literature.^[100]

1-(2,2-Dibromovinyl)-2,3,4,5,6-pentamethylbenzene 259

CBr_4 (9.41 g, 28.4 mmol, 2.0 equiv.) was added in one portion to a solution of PPh_3 (14.9 g, 56.7 mmol) in CH_2Cl_2 (1.0 M, 57 mL) at 0 °C. The dark red reaction mixture was stirred for 10 min, after which a solution of 2,3,4,5,6-pentamethylbenzaldehyde **258** (2.50 g, 14.2 mmol, 1.0 equiv.) in CH_2Cl_2 (0.4 M, 36 mL) was added dropwise. The dark brown mixture was allowed to warm to RT over 5 h, then transferred to a conical flask. Pentane (300 mL) was added, resulting in precipitation. The suspension was stirred vigorously for 1 min, filtered under suction, and concentration *in vacuo*. The title compound was afforded after purification by FCC (100 % pentane) as a white solid (3.99 g, 12.4 mmol, 87% yield).

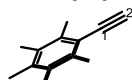
^1H NMR (400 MHz, CDCl_3) δ 7.46 (s, 1H, H_1), 2.26 – 2.21 (m, 9H, $\text{ArCH}_3 \times 3$), 2.19 (s, 6H, $\text{ArCH}_3 \times 2$).

^{13}C NMR (101 MHz, CDCl_3) δ 139.6 (C_1), 135.3 (ArC), 133.6 (ArC), 132.8 (ArC $\times 2$), 131.1 (ArC $\times 2$), 92.6 (C_2), 17.6 ($\text{ArCH}_3 \times 2$), 17.0 (ArCH_3), 16.6 ($\text{ArCH}_3 \times 2$).

HRMS (EI) Found $[\text{M}]^+ = 329.9626$; $\text{C}_{13}\text{H}_{16}^{79}\text{Br}_2$ requires 329.9629, $\Delta -2.28$ ppm.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2989, 2949, 2918, 2873, 2862, 1606.

m.p. = 75–77 °C.

1-Ethynyl-2,3,4,5,6-pentamethylbenzene 260

n-BuLi in hexanes (2.5 M, 9.9 mL, 24.8 mmol, 2.0 equiv.) was added dropwise to a solution of 1-(2,2-dibromovinyl)-2,3,4,5,6-pentamethylbenzene **259** (3.99 g, 12.4 mmol, 1.0 equiv.) in THF (0.2 M, 62 mL) at –78 °C. The reaction mixture was stirred for 40 min, warmed to RT over 1 h and quenched by the addition of water (80 mL). The resulting solution was extracted with Et_2O (3 $\times$ 80 mL), and the combined organic phases were dried over MgSO_4 , filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (100% pentane) as a white solid (1.81 g, 10.5 mmol, 85% yield).

^1H NMR (400 MHz, CDCl_3) δ 3.44 (s, 1H, H_2), 2.45 (s, 6H, $\text{ArCH}_3 \times 2$), 2.24 (s, 3H, ArCH_3), 2.21 (s, 6H, $\text{ArCH}_3 \times 2$).

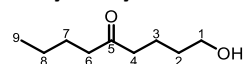
^{13}C NMR (CDCl_3 , 101 MHz) δ = 136.2 ($\text{ArC} \times 2$), 135.9 (ArC), 132.4 ($\text{ArC} \times 2$), 119.9 (ArC), 84.0 (C_2), 83.2 (C_1), 18.9 ($\text{ArCH}_3 \times 2$), 17.0 (ArCH_3), 16.7 ($\text{ArCH}_3 \times 2$).

HRMS (EI) Found $[\text{M}]^+ = 172.1248$; $\text{C}_{13}\text{H}_{16}$ requires 172.1248, $\Delta -0.86$ ppm.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3306, 2988, 2957, 2943, 2922, 2871.

m.p. = 88–91 °C.

1-Hydroxynonan-5-one **265**



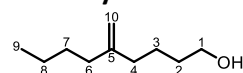
n-BuLi in hexanes (2.5 M, 20.0 mL, 49.9 mmol, 1.0 equiv.) was added dropwise to a solution of δ -valerolactone (5.00 g, 49.9 mmol, 1.0 equiv.) in Et_2O (0.5 M, 100 mL) at -78 °C. The reaction mixture was stirred for 2 h and quenched by the addition of saturated aqueous ammonium chloride (100 mL). The resulting solution was warmed to RT, extracted with Et_2O (3 x 100 mL), and the combined organic phases were dried over MgSO_4 , filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (20% EtOAc /pentane) as a colourless oil (6.08 g, 38.4 mmol, 77% yield).

^1H NMR (400 MHz, CDCl_3) δ 3.69 – 3.54 (m, 2H, $\text{H}_1 \times 2$), 2.49 – 2.36 (m, 4H, $\text{H}_4 \times 2$, $\text{H}_6 \times 2$), 1.74 – 1.47 (m, 6H, $\text{H}_3 \times 2$, $\text{H}_2 \times 2$, $\text{H}_7 \times 2$), 1.29 (q, $J = 7.5$ Hz, 2H, $\text{H}_8 \times 2$), 0.90 (t, $J = 7.5$ Hz, 3H, $\text{H}_9 \times 3$).

^{13}C NMR (100 MHz, CDCl_3) δ 211.8 (C_5), 62.4 (C_1), 42.7 (C_4 , C_6), 32.2 (C_2), 26.1 (C_7), 22.5 (C_8), 19.8 (C_3), 14.1 (C_9).

The spectroscopic data matched that previously reported in the literature.^[101]

5-Methylenenonan-1-ol **266**



n-BuLi in hexanes (2.5 M, 5.1 mL, 12.6 mmol, 2.0 equiv.) was added dropwise to a solution of MePh_3PBr (4.97 g, 13.9 mmol, 2.2 equiv.) in THF (0.5 M, 28 mL) at -78 °C. The reaction mixture was warmed to RT and stirred for 2 h, then a solution of 1-hydroxynonan-5-one **265** (1.00 g, 6.32

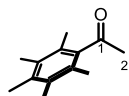
mmol, 1.0 equiv.) in THF (3.0 M, 2 mL) was added dropwise. The mixture was heated under reflux for 12 h, cooled to RT, quenched by the addition of saturated aqueous ammonium chloride (30 mL) and extracted with Et₂O (3 x 30 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (15% EtOAc/pentane) as a colourless oil (571 mg, 3.65 mmol, 58% yield).

¹H NMR (400 MHz, CDCl₃) δ 4.73 – 4.67 (m, 2H, H₁₀ x 2), 3.65 (t, *J* = 6.5 Hz, 2H, H₁ x 2), 2.07 – 1.96 (m, 4H, H₄ x 2, H₆ x 2), 1.63 – 1.23 (m, 8H, H₂ x 2, H₃ x 2, H₇ x 2, H₈ x 2), 0.90 (t, *J* = 7.0 Hz, 3H, H₉ x 3).

¹³C NMR (101 MHz, CDCl₃) δ 149.9 (C₅), 108.9 (C₁₀), 63.1 (C₁), 35.9 (C₄), 35.8 (C₆), 32.6 (C₂), 30.1 (C₇), 24.0 (C₃), 22.6 (C₈), 14.1 (C₉).

The spectroscopic data matched that previously reported in the literature.^[102]

1-(2,3,4,5,6-Pentamethylphenyl)ethan-1-one 271

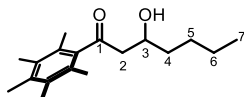


AlCl₃ (11.7 g, 87.7 mmol, 1.3 equiv.) was added in several portions to a solution of pentamethylbenzene (10.0 g, 67.5 mmol, 1.0 equiv.) and acetyl chloride (5.3 mL, 74.2 mmol, 1.1 equiv.) in CH₂Cl₂ (0.3 M, 225 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h, then poured onto crushed ice. The resulting solution was extracted with CH₂Cl₂ (3 x 100 mL), and the combined organic phases were dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5→10% Et₂O/pentane) as a white solid (11.1 g, 58.3 mmol, 86% yield).

¹H NMR (400 MHz, CDCl₃) δ 2.45 (s, 3H, H₂ x 3), 2.23 (s, 3H, ArCH₃), 2.19 (s, 6H, ArCH₃ x 2), 2.13 (s, 6H, ArCH₃ x 2).

¹³C NMR (101 MHz, CDCl₃) δ 210.2 (C₁), 141.1 (ArC), 135.5 (ArC), 133.2 (ArC x 2), 127.1 (ArC x 2), 33.3 (C₂), 17.2 (ArCH₃ x 2), 16.8 (ArCH₃), 16.1 (ArCH₃ x 2).

The spectroscopic data matched that previously reported in the literature.^[81]

3-Hydroxy-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one 272

EtMgBr in Et₂O (3.0 M, 17.7 mL, 53.2 mmol, 1.2 equiv.) was added dropwise to a solution of 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one **271** (8.44 g, 44.4 mmol, 1.0 equiv.) in Et₂O (0.5 M, 89 mL) at 0 °C. The reaction mixture was heated under reflux for 1 h, affording a white precipitate. Valeraldehyde (7.1 mL, 67.0 mmol, 1.5 equiv.) was added dropwise over 2 h *via* a syringe pump, and the mixture was maintained under reflux for a further 1 h. The reaction was cooled to RT and poured onto a mixture of ice/conc. HCl (45 g/9 mL). The resulting solution was extracted with Et₂O (3 x 80 mL) and the combined organic phases were dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5→10% Et₂O/pentane) as a white solid (12.1 g, 43.8 mmol, 99% yield).

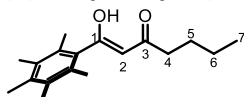
¹H NMR (400 MHz, CDCl₃) δ 4.29 – 4.19 (m, 1H, H₃), 2.91 – 2.70 (m, 2H, H₂ x 2), 2.24 (s, 3H, ArCH₃), 2.19 (s, 6H, ArCH₃ x 2), 2.12 (s, 6H, ArCH₃ x 2), 1.69 – 1.20 (m, 6H, H₄ x 2, H₅ x 2, H₆ x 2), 0.97 – 0.83 (m, 3H, H₇ x 3).

¹³C NMR (101 MHz, CDCl₃) δ 213.7 (C₁), 140.1 (ArC), 135.9 (ArC), 133.4 (ArC x 2), 127.3 (ArC x 2), 67.6 (C₃), 52.2 (C₂), 36.1 (C₄), 27.8 (C₅), 22.8 (C₆), 17.3 (ArCH₃ x 2), 16.8 (ArCH₃), 16.1 (ArCH₃ x 2), 14.2 (C₇).

HRMS (ESI⁺): Found [M+H]⁺ = 277.2166; C₁₈H₂₉O₂ requires 277.2162, Δ 1.41 ppm.

m.p.: 39–40 °C.

IR (film) ν_{max}/cm⁻¹: 3657, 3457, 2980, 2889, 1696, 1462.

(Z)-1-Hydroxy-1-(2,3,4,5,6-pentamethylphenyl)hept-1-en-3-one 273

DMSO (6.2 mL, 87.9 mmol, 2.0 equiv.) and a solution of 3-hydroxy-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one **272** (12.1 g, 43.8 mmol, 1.0 equiv.) in CH₂Cl₂ (3.0 M, 15 mL) were added sequentially dropwise to a solution of oxalyl chloride (4.4 mL, 52.5 mmol, 1.2 equiv.) in CH₂Cl₂ (0.3 M, 146 mL) at –78 °C. The reaction mixture was stirred for 1 h, and triethylamine

(18.3 mL, 131 mmol, 3.0 equiv.) was added dropwise. The reaction was stirred for 5 min, warmed to RT, and diluted with water (70 mL). The resulting solution was extracted with Et₂O (3 x 150 mL) and the combined organic phases were washed with HCl (1.0 M, 150 mL), saturated aqueous NaHCO₃ (150 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a white solid (9.91 g, 36.1 mmol, 82% yield).

¹H NMR (400 MHz, CDCl₃) δ 15.73 (s, 1H, OH), 5.61 (s, 1H, H₂), 2.40 – 2.34 (m, 2H, H₄ x 2), 2.25 (s, 3H, ArCH₃), 2.23 – 2.17 (m, 12H, ArCH₃ x 4), 1.70 – 1.58 (m, 2H, H₅ x 2), 1.38 (dq, *J* = 14.5, 7.5 Hz, 2H, H₆ x 2), 0.93 (t, *J* = 7.5 Hz, 3H, H₇ x 3).

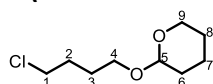
¹³C NMR (101 MHz, CDCl₃) δ 196.8 (C₃), 190.5 (C₁), 136.0 (ArC), 135.7 (ArC), 133.0 (ArC x 2), 129.6 (ArC x 2), 102.8 (C₂), 38.9 (C₄), 27.9 (C₅), 22.5 (C₆), 17.6 (ArCH₃ x 2), 16.9 (ArCH₃), 16.3 (ArCH₃ x 2), 14.0 (C₇).

HRMS (ESI⁺): Found [M+H]⁺ = 275.2014; C₁₈H₂₇O₂ requires 275.2006, Δ 3.05 ppm

m.p.: 39–41 °C.

R (film) ν_{max}/cm⁻¹: 3430, 3016, 2958, 2931, 2867, 1611.

2-(4-Chlorobutoxy)tetrahydro-2H-pyran 277



Pyridinium *p*-toluenesulfonate (703 mg, 2.80 mmol, 0.08 equiv.) was added to a mixture of 4-chlorobutan-1-ol (3.5 mL, 35.0 mmol, 1.0 equiv.) and dihydropyran (3.8 mL, 42.0 mmol, 1.2 equiv.) in CH₂Cl₂ (0.3 M, 117 mL). The reaction mixture was stirred at RT overnight and washed with water (60 mL). The resulting solution was extracted with Et₂O (3 x 120 mL) and the combined organic phases were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a colourless oil (5.73 g, 29.7 mmol, 85% yield).

¹H NMR (400 MHz, CDCl₃) δ 4.57 (dd, *J* = 4.5, 3.0 Hz, 1H, H₅), 3.85 (ddd, *J* = 11.0, 7.5, 3.5 Hz, 1H, H_{9a}), 3.77 (dt, *J* = 9.5, 6.5 Hz, 1H, H_{4a}), 3.58 (t, *J* = 6.5 Hz, 2H, H₁ x 2), 3.54 – 3.46 (m, 1H, H_{9b}), 3.42

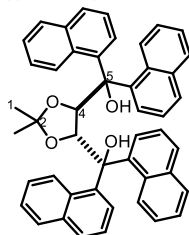
(dt, $J = 9.5, 6.0$ Hz, 1H, H_{4b}), 1.96 – 1.65 (m, 6H, $H_2 \times 2$, H_{7a} , $H_3 \times 2$, H_{6a}), 1.64 – 1.45 (m, 4H, H_{6b} , $H_8 \times 2$, H_{7b}).

^{13}C NMR (101 MHz, CDCl_3) δ 99.0 (C_5), 66.8 (C_4), 62.5 (C_9), 45.1 (C_1), 30.8 (C_6), 29.8 (C_2), 27.3 (C_3), 25.6 (C_8), 19.8 (C_7).

The spectroscopic data matched that previously reported in the literature.^[103]

5.4 Synthesis of Diol Ligands

((4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(di(naphthalen-1-yl)methanol) 221



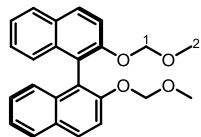
1-Bromonaphthalene (16.5 g, 79.9 mol, 8.0 equiv.) was added dropwise to a suspension of magnesium turnings (2.04 g, 83.9 mmol, 8.4 equiv.) in THF (3.5 M, 24 mL) at RT and stirred for 1 h. A solution of (4*R*, 5*R*)-diethyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (2.18 g, 9.99 mmol, 1.0 equiv.) in THF (0.2 M, 50 mL) was added dropwise and the mixture was heated under reflux for 6 h. The reaction was cooled to RT, quenched by the addition of saturated aqueous ammonium chloride (40 mL) and extracted with Et_2O (3 x 40 mL). The combined organic phases were dried over MgSO_4 , filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10→20% Et_2O /pentane) as a colourless oil (2.99 g, 4.49 mmol, 45% yield).

^1H NMR (400 MHz, DMSO) δ 8.51 (br s, 2H, $\text{ArH} \times 2$), 8.14 – 7.38 (br m, 18H, $\text{ArH} \times 18$), 7.24 (br s, 2H, $\text{ArH} \times 2$), 7.12 (br s, 2H, $\text{ArH} \times 2$), 6.96 (br s, 2H, $\text{ArH} \times 2$), 6.72 (br s, 2H, $\text{ArH} \times 2$), 5.18 (br s, 2H, $H_4 \times 2$), 0.05 (s, 6H, $H_1 \times 6$).

^{13}C NMR (101 MHz, DMSO) δ 142.2 ($\text{ArC} \times 2$), 140.3 ($\text{ArC} \times 2$), 134.2 ($\text{ArC} \times 2$), 133.8 ($\text{ArC} \times 2$), 132.2 ($\text{ArC} \times 2$), 131.3 ($\text{ArC} \times 2$), 128.8 ($\text{ArC} \times 2$), 128.4 ($\text{ArC} \times 2$), 127.9 ($\text{ArC} \times 4$), 127.0 ($\text{ArC} \times 2$), 126.4 ($\text{ArC} \times 2$), 126.1 ($\text{ArC} \times 2$), 125.1 ($\text{ArC} \times 4$), 124.7 ($\text{ArC} \times 6$), 123.9 ($\text{ArC} \times 2$), 123.3 ($\text{ArC} \times 2$), 120.9 (C_2), 80.9 ($C_4 \times 2$), 47.7 ($C_5 \times 2$), 25.9 ($C_1 \times 2$).

The spectroscopic data matched that previously reported in the literature.^[104]

(R)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthalene 237



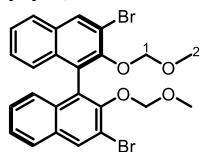
A solution of (*R*)-2,2'-dihydroxy-1,1'-binaphthyl (5.01 g, 17.5 mmol, 1.0 equiv.) in THF (0.5 M, 35 mL) was added to a stirring suspension of 60% wt. NaH (1.54 g, 28.5 mmol, 2.2 equiv.) in THF (0.5 M, 57 mL) at 0 °C. The reaction mixture was stirred for 1 h, warmed to RT, and stirred for a further 15 min. The mixture was cooled back to 0 °C, and bromomethyl methyl ether (3.1 mL, 28.5 mmol, 2.2 equiv.) was added dropwise. The reaction was then warmed to RT, stirred for 4 h, quenched by the addition of saturated aqueous ammonium chloride (50 mL). The solution was extracted with CH₂Cl₂ (3 x 50 mL), and the combined organic phases were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% EtOAc/pentane) as a white solid. (6.09 g, 16.3 mmol, 93% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.98 – 7.91 (m, 2H, ArH x 2), 7.87 (dt, *J* = 8.0, 1.0 Hz, 2H, ArH x 2), 7.57 (d, *J* = 9.0 Hz, 2H, ArH x 2), 7.34 (ddd, *J* = 8.0, 6.5, 1.5 Hz, 2H, ArH x 2), 7.22 (ddd, *J* = 8.0, 6.5, 1.5 Hz, 2H, ArH x 2), 7.15 (ddt, *J* = 8.5, 1.5, 1.0 Hz, 2H, ArH x 2), 5.08 (d, *J* = 7.0 Hz, 2H, H_{1a} x 2), 4.97 (d, *J* = 7.0 Hz, 2H, H_{1b} x 2), 3.14 (s, 6H, H₂ x 6).

¹³C NMR (101 MHz, CDCl₃) δ 152.8 (ArC x 2), 134.2 (ArC x 2), 130.0 (ArC x 2), 129.5 (ArC x 2), 128.0 (ArC x 2), 126.4 (ArC x 2), 125.7 (ArC x 2), 124.2 (ArC x 2), 121.5 (ArC x 2), 117.4 (ArC x 2), 95.4 (C₁ x 2), 56.0 (C₂ x 2).

The spectroscopic data matched that previously reported in the literature.^[105]

(R)-3,3'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene 238



n-BuLi in hexanes (2.5 M, 12.9 mL, 32.1 mmol, 3.0 equiv.) was added dropwise to a solution of (*R*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene **237** (4.01 g, 10.7 mmol, 1.0 equiv.) in THF (0.3

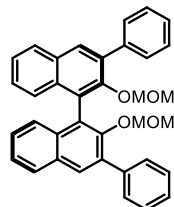
M, 36 mL) at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was then warmed to $0\text{ }^{\circ}\text{C}$ and stirred for 2 h. The mixture was cooled back to $-78\text{ }^{\circ}\text{C}$, and a solution of 1,2-dibromotetrachloroethane (10.5 g, 32.1 mmol, 3.0 equiv.) in THF (1.0 M, 32 mL) was added dropwise. The reaction was warmed to RT, stirred for 2 h, and quenched by the addition of saturated aqueous ammonium chloride (50 mL). The solution was extracted with EtOAc (3 x 50 mL), and the combined organic phases were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% EtOAc/pentane) as a white solid (4.09 g, 7.68 mmol, 72% yield).

^1H NMR (400 MHz, CDCl_3) δ 8.27 (s, 2H, ArH x 2), 7.84 – 7.77 (m, 2H, ArH x 2), 7.44 (ddd, $J = 8.0$, 7.0, 1.0 Hz, 2H, ArH x 2), 7.31 (ddd, $J = 8.0$, 7.0, 1.5 Hz, 2H, ArH x 2), 7.21 – 7.16 (m, 2H, ArH x 2), 4.86 – 4.78 (m, 4H, H_1 x 4), 2.57 (s, 6H, H_2 x 6).

^{13}C NMR (101 MHz, CDCl_3) δ 150.3 (ArC x 2), 133.2 (ArC x 2), 133.2 (ArC x 2), 131.6 (ArC x 2), 127.5 (ArC x 2), 127.0 (ArC x 4), 126.7 (ArC x 2), 126.2 (ArC x 2), 117.5 (ArC x 2), 99.3 (C_1 x 2), 56.4 (C_2 x 2).

The spectroscopic data matched that previously reported in the literature.^[105]

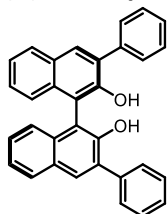
(*R*)-2,2'-Bis(methoxymethoxy)-3,3'-diphenyl-1,1'-binaphthalene 239



A 50 mL round-bottom flask was charged with (*R*)-3,3'-dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene **238** (1.00 g, 1.88 mmol, 1.0 equiv.), phenylboronic acid (550 mg, 4.51 mmol, 2.4 equiv.), $\text{Pd}(\text{PPh}_3)_4$ (217 mg, 0.188 mmol, 10 mol%), Na_2CO_3 (2 M, 4.7 mL, 9.39 mmol, 5.0 equiv.) and 1,2-dimethoxyethane (0.1 M, 19 mL). The reaction mixture was heated under reflux for 12 h, cooled to RT, passed through a pad of Celite and concentrated *in vacuo*. The residue was quenched by the addition of saturated aqueous ammonium chloride (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4 , filtered, and

concentrated *in vacuo*. The crude product was taken onto the next step with no further purification.

(R)-3,3'-Diphenyl-[1,1'-binaphthalene]-2,2'-diol 240



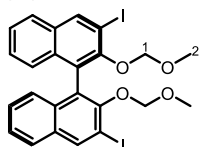
A 50 mL round-bottom flask was charged with (R)-2,2'-bis(methoxymethoxy)-3,3'-diphenyl-1,1'-binaphthalene **239** (989 mg, 1.88 mmol, 1.0 equiv.), HCl (12 M, 1.6 mL, 18.8 mmol, 10 equiv.) and dioxane (0.1 M, 19 mL). The reaction mixture was heated at 80 °C for 6 h, cooled to RT and concentrated *in vacuo*. The residue was quenched by the addition of saturated aqueous NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% EtOAc/pentane) as a white solid (532 mg, 1.21 mmol, 65% yield over 2 steps).

¹H NMR (400 MHz, CDCl₃) δ 8.03 (s, 2H, ArH x 2), 7.95 – 7.89 (m, 2H, ArH x 2), 7.77 – 7.70 (m, 4H, ArH x 4), 7.54 – 7.45 (m, 4H, ArH x 4), 7.45 – 7.36 (m, 4H, ArH x 4), 7.36 – 7.29 (m, 2H, ArH x 2), 7.27 – 7.21 (m, 2H, ArH x 2), 5.36 (s, 2H, OH x 2).

¹³C NMR (101 MHz, CDCl₃) δ 150.3 (ArC x 2), 137.6 (ArC x 2), 133.1 (ArC x 2), 131.5 (ArC x 2), 130.8 (ArC x 2), 129.8 (ArC x 4), 129.6 (ArC x 2), 128.6 (ArC x 4), 128.6 (ArC x 2), 127.9 (ArC x 2), 127.5 (ArC x 2), 124.5 (ArC x 2), 124.4 (ArC x 2), 112.5 (ArC x 2).

The spectroscopic data matched that previously reported in the literature.^[105]

(R)-3,3'-Diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene 241



n-BuLi in hexanes (2.5 M, 16.1 mL, 40.2 mmol, 3.0 equiv.) was added dropwise to a solution of (R)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene **237** (5.02 g, 13.4 mmol, 1.0 equiv.) in THF (0.3 M, 45 mL) at –78 °C. The reaction mixture was warmed to 0 °C and stirred for 2 h. The mixture

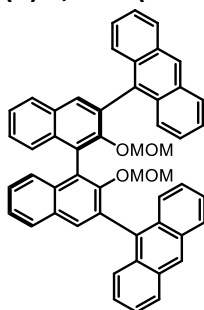
was cooled back to $-78\text{ }^{\circ}\text{C}$, and solid iodine (10.2 g, 40.2 mmol, 3.0 equiv.) was added in one portion. The reaction was warmed to RT, stirred for 2 h, and quenched by the addition of saturated sodium thiosulphate (50 mL). The solution was extracted with EtOAc (3 x 50 mL), and the combined organic phases were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% EtOAc/pentane) as a white solid (5.62 g, 8.97 mmol, 78% yield).

^1H NMR (400 MHz, CDCl_3) δ 8.54 (s, 2H, ArH x 2), 7.81 – 7.74 (m, 2H, ArH x 2), 7.43 (ddd, $J = 8.0$, 7.0, 1.0 Hz, 2H, ArH x 2), 7.30 (ddd, $J = 8.0$, 7.0, 1.0 Hz, 2H, ArH x 2), 7.21 – 7.13 (m, 2H, ArH x 2), 4.81 (d, $J = 5.5$ Hz, 2H, H_{1a} x 2), 4.69 (d, $J = 5.5$ Hz, 2H, H_{1b} x 2), 2.60 (s, 6H, H_2 x 6).

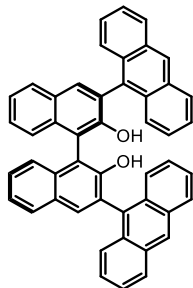
^{13}C NMR (101 MHz, CDCl_3) δ 152.3 (ArC x 2), 140.2 (ArC x 2), 134.0 (ArC x 2), 132.4 (ArC x 2), 127.3 (ArC x 2), 126.9 (ArC x 2), 126.7 (ArC x 2), 126.4 (ArC x 2), 126.0 (ArC x 2), 99.6 (ArC x 2), 92.6 (C_1 x 2), 56.7 (C_2 x 2).

The spectroscopic data matched that previously reported in the literature.^[106]

(*R*)-3,3'-Bis(9-anthracenyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene 242



A 100 mL round-bottom flask was charged with (*R*)-3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene **241** (3.76 g, 6.00 mmol, 1.0 equiv.), 9-anthracenylboronic acid (3.20 g, 14.4 mmol, 2.4 equiv.), $\text{Pd}(\text{PPh}_3)_4$ (1.04 g, 0.901 mmol, 15 mol%), $\text{Ba}(\text{OH})_2$ (5.14 g, 30.0 mmol, 5.0 equiv.) and a mixture of 3:1 dioxane: H_2O (0.1 M, 60 mL). The reaction mixture was heated at $80\text{ }^{\circ}\text{C}$ for 12 h, cooled to room temperature, and diluted with 1M AcOH and EtOAc until a homogeneous biphasic solution had formed. The solution was extracted with EtOAc (3 x 60 mL), and the combined organic phases were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was taken onto the next step with no further purification.

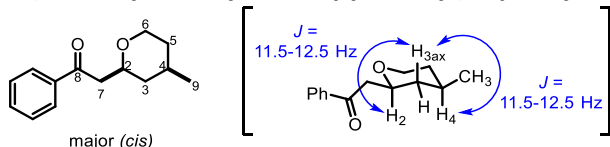
(R)-3,3'-Di(anthracen-9-yl)-[1,1'-binaphthalene]-2,2'-diol 243

A 100 mL round-bottom flask was charged with (R)-3,3'-bis(9-anthracenyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene **227** (4.36 g, 6.00 mmol, 1.0 equiv.), HCl (12 M, 5 mL, 60.0 mmol, 10 equiv.) and dioxane (0.1 M, 60 mL). The reaction mixture was heated at 80 °C for 6 h, cooled to RT and *concentrated in vacuo*. The residue was quenched by the addition of saturated aqueous NaHCO₃ (60 mL) and extracted with CH₂Cl₂ (3 x 60 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% EtOAc/pentane) as a yellow solid (2.34 g, 3.66 mmol, 61% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.58 (s, 2H, ArH x 2), 8.13 – 7.99 (m, 6H, ArH x 6), 7.95 – 7.90 (m, 2H, ArH x 2), 7.89 – 7.83 (m, 2H, ArH x 2), 7.70 – 7.64 (m, 2H, ArH x 2), 7.61 – 7.56 (m, 2H, ArH x 2), 7.54 – 7.39 (m, 10H, ArH x 10), 7.28 – 7.23 (m, 2H, ArH x 2), 5.08 (s, 2H, OH x 2).

¹³C NMR (101 MHz, CDCl₃) δ 151.2 (ArC x 2), 134.1 (ArC x 2), 133.2 (ArC x 2), 131.7 (ArC x 2), 131.6 (ArC x 2), 131.0 (ArC x 2), 130.9 (ArC x 2), 130.9 (ArC x 2), 129.4 (ArC x 2), 128.8 (ArC x 2), 128.7 (ArC x 2), 128.6 (ArC x 2), 127.9 (ArC x 2), 127.5 (ArC x 2), 127.3 (ArC x 2), 126.4 (ArC x 2), 126.3 (ArC x 4), 126.3 (ArC x 2), 125.5 (ArC x 4), 125.0 (ArC x 2), 124.4 (ArC x 2), 113.7 (ArC x 2).

The spectroscopic data matched that previously reported in the literature.^[106]

5.5 Synthesis of Tetrahydropyrans**2-(4-Methyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one 108**

3-Methylhex-5-en-1-ol **111** (103 mg, 0.902 mmol, 1.0 equiv.), 1-phenylprop-2-en-1-one **110** (238 mg, 1.80 mmol, 2.0 equiv.), $\text{ClCH}_2\text{CH}_2\text{Cl}$ (0.1 M, 9 mL), and Hoveyda–Grubbs Catalyst[®] M720 (56.5 mg, 0.0902 mmol, 10 mol%) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (5% Et_2O /pentane) as a yellow oil (150 mg, 0.687 mmol, 76% yield, 82:18 d.r.).

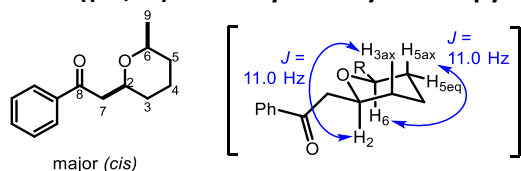
^1H NMR (400 MHz, CDCl_3) δ 7.99 – 7.93 (m, 4H, major ArCH x 2, major ArCH x 2), 7.60 – 7.51 (m, 2H, major ArCH, minor ArCH), 7.49 – 7.41 (m, 4H, major ArCH x 2, minor ArCH x 2), 4.30 (dtd, $J = 9.5, 6.5, 3.0$ Hz, 1H, minor H_2), 4.00 – 3.88 (m, 3H, major H_{6a} , major H_2), 3.72 (dd, $J = 7.5, 3.5$ Hz, 2H, minor $\text{H}_6 \times 2$), 3.45 (td, $J = 12.0, 2.5$ Hz, 1H, major H_{6b}), 3.36 – 3.24 (m, 2H, major H_{7a} , minor H_{7a}), 2.98 – 2.87 (m, 2H, major H_{7b} , minor H_{7b}), 2.06 (dt, $J = 7.5, 4.8$ Hz, 1H, minor H_4), 1.89 – 1.46 (m, 6H, minor H_{5a} , major H_{3eq} , major H_4 , minor $\text{H}_5 \times 2$, major H_{5a}), 1.32 – 1.14 (m, 2H, minor H_{5b} , major H_{5b}), 1.10 (d, $J = 7.1$ Hz, 2H, minor $\text{H}_9 \times 2$), 1.00 (dt, $J = 12.5, 11.5$ Hz, 1H, major H_{3ax}), 0.94 (d, $J = 6.5$ Hz, 3H major $\text{H}_9 \times 3$).

^{13}C NMR (101 MHz, CDCl_3) δ 80198.6 (minor C_8), 198.5 (major C_8), 137.4 (major ArC, minor ArC), 133.2 (major ArC, minor ArC), 128.7 (minor ArC x 2), 128.7 (major ArC x 2), 128.4 (major ArC x 2), 128.4 (minor ArC x 2), 74.2 (major C_2), 69.1 (minor C_2), 68.4 (major C_6), 62.9 (minor C_6), 45.4 (major C_7), 44.3 (minor C_7), 40.7 (major C_3), 37.7 (minor C_3), 34.6 (major H_5), 32.2 (minor H_5), 30.3 (major C_4), 25.1 (minor C_4), 22.4 (major C_9), 18.7 (minor C_9).

HRMS (ESI⁺): Found $[\text{M}+\text{H}]^+ = 219.1382$; $\text{C}_{14}\text{H}_{19}\text{O}_2$ requires 219.1380, Δ 1.12 ppm

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2978, 2842, 1683, 1597, 1489, 1382.

rac*-2-((2*S*,6*S*)-6-Methyltetrahydro-2*H*-pyran-2-yl)-1-phenylethan-1-one **130*



Hept-6-en-2-ol **127** (103 mg, 0.902 mmol, 1.0 equiv.), 1-phenylprop-2-en-1-one **110** (238 mg, 1.80 mmol, 2.0 equiv.), $\text{ClCH}_2\text{CH}_2\text{Cl}$ (0.1 M, 9 mL), and Hoveyda–Grubbs Catalyst[®] M720 (56.5 mg, 0.0902 mmol, 10 mol%) were subjected to **General Procedure 2**. The title compound was

afforded after purification by FCC (5% Et₂O/pentane) as a yellow oil (172 mg, 0.788 mmol, 88% yield, >95:5 d.r.).

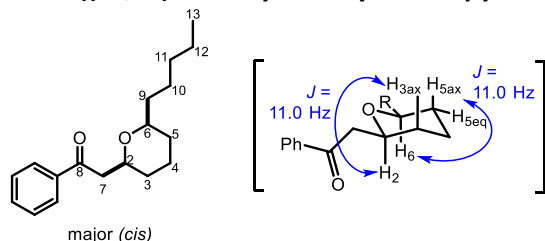
¹H NMR (400 MHz, CDCl₃) δ 8.03 – 7.92 (m, 2H, ArCH x 2), 7.59 – 7.51 (m, 1H, ArCH), 7.49 – 7.41 (m, 2H, ArCH x 2), 3.98 (dddd, *J* = 11.0, 6.5, 6.0, 2.0 Hz, 1H, H₂), 3.49 (dq, *J* = 11.0, 6.0, 2.0 Hz, 1H, H₆), 3.31 (dd, *J* = 16.0, 6.0 Hz, 1H, H_{7a}), 2.97 (dd, *J* = 16.0, 6.5 Hz, 1H, H_{7b}), 1.87 – 1.68 (m, 2H, H_{4a}, H_{3a}), 1.61 – 1.54 (m, 2H, H_{4b}, H_{5a}), 1.30 – 1.16 (m, 2H, H_{3b}, H_{5b}), 1.14 (d, *J* = 6.0 Hz, 3H, H₉ x 3).

¹³C NMR (101 MHz, CDCl₃) δ 198.6 (C₈), 137.5 (ArC), 133.1 (ArC), 128.6 (ArC x 2), 128.4 (ArC x 2), 74.3 (C₂), 74.2 (C₆), 45.8 (C₇), 33.3 (C₅), 31.6 (C₃), 23.7 (C₄), 22.3 (C₉).

HRMS (ESI⁺): Found [M+H]⁺ = 219.1381 ; C₁₄H₁₉O₂ requires 219.1380, Δ 0.66 ppm

IR (film) ν_{max}/cm⁻¹: 2931, 2860, 1686, 1597, 1580, 1449.

rac*-2-((2*S*,6*S*)-6-Pentyltetrahydro-2*H*-pyran-2-yl)-1-phenylethan-1-one **131*



Undec-1-en-6-ol **120** (153 mg, 0.898 mmol, 1.0 equiv.), 1-phenylprop-2-en-1-one **110** (238 mg, 1.80 mmol, 2.0 equiv.), ClCH₂CH₂Cl (0.1 M, 9 mL), and Hoveyda–Grubbs Catalyst[®] M720 (56.3 mg, 0.0898 mmol, 10 mol%) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a yellow oil (223 mg, 0.813 mmol, 90% yield, >95:5 d.r.).

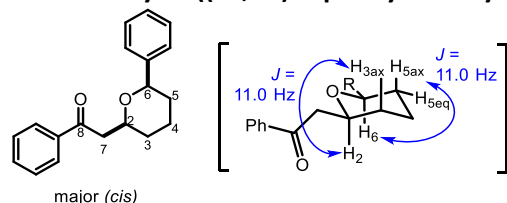
¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.92 (m, 2H, ArCH x 2), 7.59 – 7.50 (m, 1H, ArCH), 7.49 – 7.40 (m, 2H, ArCH x 2), 3.93 (dtd, *J* = 11.0, 6.5, 2.0 Hz, 1H, H₂), 3.36 – 3.23 (m, 2H, H₆, H_{7a}), 2.93 (dd, *J* = 15.5, 6.0 Hz, 1H, H_{7b}), 1.83 (m, 1H, H_{4a}), 1.77 – 1.68 (m, 1H, H_{3a}), 1.63 – 1.10 (m, 12H, H_{3b}, H_{4b}, H₅ x 2, H₉ x 2, H₁₀ x 2, H₁₁ x 2, H₁₂ x 2), 0.84 (t, *J* = 7.0 Hz, 3H, H₁₃ x 3).

^{13}C NMR (101 MHz, CDCl_3) δ 199.1 (C_8), 137.7 (ArC), 133.04 (ArC), 128.6 (ArC x 2), 128.5 (ArC x 2), 78.3 (C_6), 74.8 (C_2), 45.8 (C_7), 36.6 (C_5), 32.0 (C_3 , C_{11}), 31.6 (C_9), 25.3 (C_{10}), 23.7 (C_4), 22.7 (C_{12}), 14.2 (C_{13}).

HRMS (ESI⁺): Found $[\text{M}+\text{H}]^+ = 275.2006$; $\text{C}_{18}\text{H}_{27}\text{O}_2$ requires 275.2006, Δ 0.46 ppm

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2932, 2861, 1686, 1581, 1565, 1519.

rac*-1-Phenyl-2-((2*S*,6*R*)-6-phenyltetrahydro-2*H*-pyran-2-yl)ethan-1-one **132*



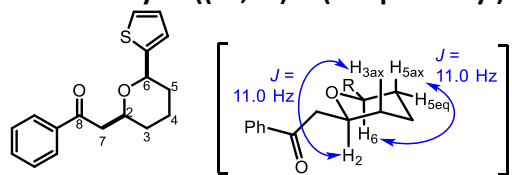
1-Phenylhex-5-en-1-ol **122** (159 mg, 0.902 mmol, 1.0 equiv.), 1-phenylprop-2-en-1-one **110** (238 mg, 1.80 mmol, 2.0 equiv.), $\text{ClCH}_2\text{CH}_2\text{Cl}$ (0.1 M, 9 mL), and Hoveyda–Grubbs Catalyst[®] M720 (56.5 mg, 0.0902 mmol, 10 mol%) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (5% Et_2O /pentane) as a yellow oil (202 mg, 0.720 mmol, 80% yield, >95:5 d.r.).

^1H NMR (400 MHz, CDCl_3) δ 7.95 – 7.85 (m, 2H, ArCH x 2), 7.50 – 7.41 (m, 1H, ArCH), 7.41 – 7.30 (m, 2H, ArCH x 2), 7.25 – 7.08 (m, 5H, ArCH x 5), 4.34 (dd, $J = 11.5$, 2.0 Hz, 1H, H_6), 4.09 (dtd, $J = 11.0$, 6.0, 2.0 Hz, 1H, H_2), 3.33 (dd, $J = 16.0$, 6.0 Hz, 1H, H_{7a}), 2.97 (dd, $J = 16.0$, 6.5 Hz, 1H, H_{7b}), 1.92 – 1.55 (m, 4H, H_4 x 2, H_{5a} , H_{3a}), 1.50 – 1.23 (m, 2H, H_{5b} , H_{3b}).

^{13}C NMR (101 MHz, CDCl_3) δ 198.6 (C_8), 143.2 (ArC), 137.5 (ArC), 133.0 (ArC), 128.5 (ArC x 2), 128.4 (ArC x 2), 128.2 (ArC), 127.2 (ArC x 2), 125.8 (ArC x 2), 79.8 (C_6), 75.0 (C_2), 45.6 (C_7), 33.3 (C_5), 31.4 (C_3), 23.9 (C_4).

HRMS (ESI⁺): Found $[\text{M}+\text{H}]^+ = 281.1536$; $\text{C}_{19}\text{H}_{21}\text{O}_2$ requires 281.1536, Δ 0.07 ppm

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2935, 1683, 1597, 1449, 1341, 1284.

rac*-1-Phenyl-2-((2*S*,6*R*)-6-(thiophen-2-yl)tetrahydro-2*H*-pyran-2-yl)ethan-1-one **133*major (*cis*)

1-(Thiophen-2-yl)hex-5-en-1-ol **124** (182 mg, 1.00 mmol, 1.0 equiv.), 1-phenylprop-2-en-1-one **110** (264 mg, 2.00 mmol, 2.0 equiv.), ClCH₂CH₂Cl (0.1 M, 10 mL) and Hoveyda–Grubbs Catalyst[®] M720 (62.7 mg, 0.100 mmol, 10 mol%) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a yellow solid (216 mg, 0.754 mmol, 75% yield, 88:12 d.r.).

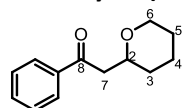
¹H NMR (400 MHz, CDCl₃) δ 8.04 – 7.94 (m, 2H, ArCH x 2), 7.60 – 7.51 (m, 1H, ArCH), 7.50 – 7.41 (m, 2H, ArCH x 2), 7.19 (dd, *J* = 4.5, 1.5 Hz, 1H, ArCH), 6.94 – 6.89 (m, 2H, ArCH x 2), 4.71 – 4.63 (m, 1H, H₆), 4.19 (dtd, *J* = 11.0, 6.5, 2.0 Hz, 1H, H₂), 3.42 (dd, *J* = 16.0, 6.0 Hz, 1H, H_{7a}), 3.03 (dd, *J* = 16.0, 6.5 Hz, 1H, H_{7b}), 2.09 – 1.92 (m, 2H, H_{5ax}, H_{4a}), 1.90 – 1.60 (m, 3H, H_{3eq}, H_{4b}, H_{5eq}), 1.45 – 1.33 (m, 1H, H_{3ax}).

¹³C NMR (101 MHz, CDCl₃) δ 198.6 (C8), 146.6 (ArC), 137.5 (ArC), 133.2 (ArC), 128.7 (ArC x 2), 128.5 (ArC x 2), 126.5 (ArC), 124.4 (ArC), 123.2 (ArC), 76.0 (C₆), 75.3 (C₂), 45.6 (C₇), 33.3 (C₅), 31.4 (C₃), 23.7 (C₄).

HRMS (ESI⁺): Found [M+H]⁺ = 287.1096; C₁₇H₁₉O₂S requires 287.1100, Δ −0.47 ppm.

IR (film) ν_{max}/cm^{−1}: 2943, 2859, 1686, 1597, 1504, 1449.

m.p.: 48–50 °C.

1-Phenyl-2-(tetrahydro-2*H*-pyran-2-yl)ethan-1-one **159**

Hex-5-en-1-ol (90.2 mg, 0.901 mmol, 1.0 equiv.), 1-phenylprop-2-en-1-one **110** (238 mg, 1.80 mmol, 2.0 equiv.), ClCH₂CH₂Cl (0.1 M, 9 mL), and Hoveyda–Grubbs Catalyst[®] M720 (56.5 mg, 0.0901 mmol, 10 mol%) were subjected to **General Procedure 2**. The title compound was

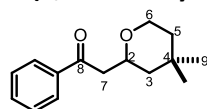
afforded after purification by FCC (5% Et₂O/pentane) as a yellow oil (123 mg, 0.602 mmol, 67% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.00 – 7.91 (m, 2H, ArCH x 2), 7.59 – 7.49 (m, 1H, ArCH), 7.49 – 7.39 (m, 2H, ArCH x 2), 4.00 – 3.89 (m, 2H, H₂, H_{6a}), 3.54 – 3.39 (m, 1H, H_{6b}), 3.28 (dd, *J* = 16.0, 6.5 Hz, 1H, H_{7a}), 2.91 (dd, *J* = 16.0, 6.0 Hz, 1H, H_{7b}), 1.82 (dddd, *J* = 11.0, 8.0, 4.5, 2.0 Hz, 1H, H_{4a}), 1.77 – 1.69 (m, 1H, H_{3a}), 1.64 – 1.44 (m, 3H, H_{4b}, H₅ x 2), 1.41 – 1.29 (m, 1H, H_{3b}).

¹³C NMR (101 MHz, CDCl₃) δ 198.4 (C8), 137.4 (ArC), 133.1 (ArC), 128.6 (ArC x 2), 128.3 (ArC x 2), 74.4 (C₂), 68.7 (C₆), 45.5 (C₇), 32.1 (C₃), 26.0 (C₅), 23.5 (C₄).

The spectroscopic data matched that previously reported in the literature.^[71]

2-(4,4-Dimethyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one **160**



Method A: 3,3-Dimethylhex-5-en-1-ol **150** (115 mg, 0.897 mmol, 1.0 equiv.), 1-phenylprop-2-en-1-one **110** (238 mg, 1.79 mmol, 2.0 equiv.), ClCH₂CH₂Cl (0.1 M, 9 mL), and Hoveyda–Grubbs Catalyst® M720 (56.2 mg, 0.0897 mmol, 10 mol%) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a yellow oil (184 mg, 0.792 mmol, 88% yield).

Method B: A 50 mL round-bottom flask fitted with an air condenser was charged with diethyl (2-oxo-2-phenylethyl)phosphonate **218** (1.04 g, 4.06 mmol, 1.4 equiv.) and evacuated/backfilled with N₂ three times. Toluene (0.2 M, 15 mL) was added, followed by 60% wt. NaH (140 mg, 3.48 mmol, 1.2 equiv.) in one portion [caution: vigorous release of H₂]. The suspension was stirred at RT for 30 min until a homogeneous solution had formed. 4,4-Dimethyltetrahydro-2H-pyran-2-ol **149** (378 mg, 2.90 mmol, 1.0 equiv.) was then added, and the reaction was heated at 110 °C for 15 h. The mixture was cooled to RT, diluted with Et₂O (30 mL), filtered through a plug of silica gel, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a yellow oil (626 mg, 2.69 mmol, 93% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.98 – 7.94 (m, 2H, ArCH x 2), 7.59 – 7.53 (m, 1H, ArCH), 7.49 – 7.43 (m, 2H, ArCH x 2), 4.18 – 4.07 (m, 1H, H_2), 3.80 (ddd, $J = 12.0, 5.0, 1.5$ Hz, 1H, $\text{H}_{6\text{eq}}$), 3.63 (ddd, $J = 13.0, 12.0, 2.5$ Hz, 1H, $\text{H}_{6\text{ax}}$), 3.28 (dd, $J = 16.0, 7.0$ Hz, 1H, $\text{H}_{7\text{a}}$), 2.86 (dd, $J = 16.0, 5.5$ Hz, 1H, $\text{H}_{7\text{b}}$), 1.54 – 1.43 (m, 2H, $\text{H}_{3\text{a}}$ and $\text{H}_{5\text{a}}$), 1.28 – 1.19 (m, 2H, $\text{H}_{3\text{b}}$ and $\text{H}_{5\text{b}}$), 1.06 (s, 3H, $\text{H}_{9\text{a}}$ x 3), 0.96 (s, 3H, $\text{H}_{9\text{b}}$ x 3).

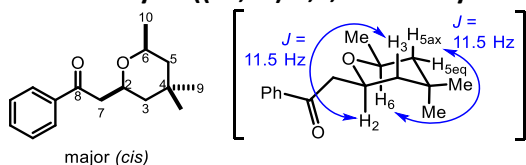
^1H NMR (500 MHz, *p*-Xylene- d_{10} , 298 K) δ 7.98 – 7.92 (m, 2H, ArCH x 2), 7.32 – 7.25 (m, 1H, ArCH), 7.22 (m, 2H, ArCH x 2), 4.21 (dtd, $J = 12.0, 6.0, 2.0$ Hz, 1H, H_2), 3.76 (ddd, $J = 11.5, 5.0, 1.5$ Hz, 1H, $\text{H}_{6\text{eq}}$), 3.55 (ddd, $J = 13.0, 11.5, 2.0$ Hz, 1H, $\text{H}_{6\text{ax}}$), 3.20 (dd, $J = 16.0, 6.5$ Hz, 1H, $\text{H}_{7\text{a}}$), 2.62 (dd, $J = 16.0, 6.0$ Hz, 1H, $\text{H}_{7\text{b}}$), 1.52 – 1.41 (m, 2H, $\text{H}_{3\text{a}}$ and $\text{H}_{5\text{eq}}$), 1.17 (dd, $J = 13.0, 11.5$ Hz, 1H, $\text{H}_{5\text{ax}}$), 1.07 – 1.01 (m, 2H, $\text{H}_{3\text{b}}$, $\text{H}_{9\text{a}}$ x 3), 0.97 (s, 3H, $\text{H}_{9\text{b}}$ x 3).

^{13}C NMR (101 MHz, CDCl_3) δ 198.5 (C_8), 137.5 (ArC), 133.2 (ArC), 128.7 (ArC x 2), 128.4 (ArC x 2), 70.2 (C_2), 64.6 (C_6), 45.5 (C_7), 45.1 (C_3), 38.8 (C_5), 33.3 ($\text{C}_{9\text{b}}$), 29.1 (C_4), 24.1 ($\text{C}_{9\text{a}}$).

HRMS (ESI $^+$): Found $[\text{M}+\text{H}]^+ = 233.1537$; $\text{C}_{15}\text{H}_{21}\text{O}_2$ requires 233.1536, Δ 0.48 ppm

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2952, 1685, 1449, 1382, 1277, 1210.

***rac*-1-Phenyl-2-((2*S*,6*S*)-4,4,6-trimethyltetrahydro-2*H*-pyran-2-yl)ethan-1-one 161**



4,4-Dimethylhept-6-en-2-ol **154** (128 mg, 0.900 mmol, 1.0 equiv.), 1-phenylprop-2-en-1-one **110** (238 mg, 1.80 mmol, 2.0 equiv.), $\text{ClCH}_2\text{CH}_2\text{Cl}$ (0.1 M, 9 mL), and Hoveyda–Grubbs Catalyst[®] M720 (56.4 mg, 0.0900 mmol, 10 mol%) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (5% Et_2O /pentane) as a yellow oil (98.1 mg, 0.398 mmol, 44% yield, >95:5 d.r.).

^1H NMR (400 MHz, CDCl_3) δ 8.01 – 7.92 (m, 2H, ArCH x 2), 7.59 – 7.51 (m, 1H, ArCH), 7.50 – 7.40 (m, 2H, ArCH x 2), 4.16 (dtd, $J = 11.5, 6.0, 2.0$ Hz, 1H, H_2), 3.66 (dq, $J = 11.5, 6.0, 2.0$ Hz, 1H, H_6), 3.31 (dd, $J = 16.0, 6.0$ Hz, 1H, $\text{H}_{7\text{a}}$), 2.91 (dd, $J = 16.0, 6.5$ Hz, 1H, $\text{H}_{7\text{b}}$), 1.46 (dt, $J = 13.0, 2.0$ Hz,

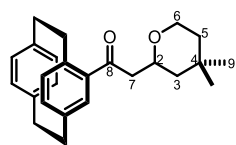
^1H , H_{3a}), 1.30 (dt, $J = 13.0, 2.0$ Hz, 1H, H_{5a}), 1.17 – 1.08 (m, 5H, H_{3b} , $\text{H}_{10} \times 3$, H_{5b}), 1.05 (s, 3H, $\text{H}_{9a} \times 3$), 0.93 (s, 3H, $\text{H}_{9b} \times 3$).

^{13}C NMR (101 MHz, CDCl_3) δ 198.7 (C_8), 137.6 (ArC), 133.1 (ArC), 128.6 (ArC $\times 2$), 128.4 (ArC $\times 2$), 70.2 (C_2), 69.7 (C_6), 46.6 (C_5), 45.7 (C_7), 44.7 (C_3), 33.2 (C_{9b}), 29.8 (C_4), 25.0 (C_{9a}), 22.2 (C_{10}).

HRMS (ESI⁺): Found $[\text{M}+\text{H}]^+ = 247.1693$; $\text{C}_{16}\text{H}_{23}\text{O}_2$ requires 247.1695, Δ 0.90 ppm.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2953, 2903, 1687, 1597, 1449, 1374.

1-(1,4(1,4)-Dibenzenacyclohexaphane-1²-yl)-2-(4,4-dimethyltetrahydro-2H-pyran-2-yl)ethan-1-one 176



3,3-dimethylhex-5-en-1-ol **150** (115 mg, 0.898 mmol, 1.0 equiv.), 1-(1,4(1,4)-dibenzenacyclohexaphane-1²-yl)prop-2-en-1-one **168** (472 mg, 1.80 mmol, 2.0 equiv.),

$\text{ClCH}_2\text{CH}_2\text{Cl}$ (0.1 M, 9 mL), and Hoveyda–Grubbs Catalyst[®] M720 (56.3 mg, 0.0898 mmol, 10 mol%) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (5% Et_2O /Pentane) as a yellow oil (107 mg, 0.295 mmol, 33% yield, 1:1 d.r.).

^1H NMR (400 MHz, CDCl_3) δ 7.01 (d, $J = 2.0$ Hz, 1H, ArCH), 6.89 (d, $J = 2.0$ Hz, 1H, ArCH), 6.63 (dd, $J = 7.5, 2.0$ Hz, 2H, ArCH $\times 2$), 6.58 – 6.44 (m, 8H, ArCH $\times 8$), 6.34 (ddd, $J = 8.5, 7.0, 2.0$ Hz, 2H, ArCH $\times 2$), 4.20 – 4.01 (m, 2H, H_2 and $\text{H}_{2'}$), 3.97 – 3.85 (m, 3H, Cyclophane- $\text{CH}_2 \times 2$ and H_{6a}), 3.79 (ddd, $J = 12.0, 5.0, 1.5$ Hz, 1H, $\text{H}_{6a'}$), 3.74 – 3.59 (m, 2H, H_{6b} and $\text{H}_{6b'}$), 3.30 – 2.94 (m, 14H, Cyclophane- $\text{CH}_2 \times 12$, H_{7a} and $\text{H}_{7a'}$), 2.89 – 2.80 (m, 2H, Cyclophane- $\text{CH}_2 \times 2$), 2.76 (dd, $J = 16.0, 5.5$ Hz, 1H, H_{7b}), 2.48 (dd, $J = 15.5, 5.0$ Hz, 1H, $\text{H}_{7b'}$), 1.61 – 1.32 (m, 4H, $\text{H}_5 \times 2$ and $\text{H}_{5'} \times 2$), 1.31 – 1.14 (m, 4H, $\text{H}_3 \times 2$ and $\text{H}_{3'} \times 2$), 1.08 (s, 3H, $\text{H}_{9a'} \times 3$), 1.07 (s, 3H, $\text{H}_{9a} \times 3$), 0.98 (s, 3H, $\text{H}_{9b} \times 3$), 0.96 (s, 3H, $\text{H}_{9b'} \times 3$).

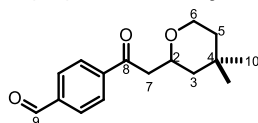
^{13}C NMR (101 MHz, CDCl_3) δ 201.1 (C_8), 200.6 (C_8'), 141.7 (ArC), 141.5 (ArC), 140.4 (ArC $\times 2$), 139.9 (ArC), 139.8 (ArC), 139.3 (ArC), 139.2 (ArC), 138.3 (ArC), 138.0 (ArC), 136.5 (ArC), 136.4 (ArC $\times 2$), 136.3 (ArC), 134.1 (ArC), 133.6 (ArC), 133.0 (ArC), 133.0 (ArC), 132.8 (ArC), 132.8 (ArC), 132.6 (ArC), 132.2 (ArC), 131.6 (ArC), 131.3 (ArC), 70.9 (C_2), 70.2 ($\text{C}_{2'}$), 64.6 (C_6), 64.5 ($\text{C}_{6'}$), 47.6

(C₇'), 47.5 (C₇), 45.1 (C₃), 45.0 (C_{3'}), 38.8 (C₅), 38.8 (C_{5'}), 36.1 (Paracyclophane-CH₂), 36.1 (Paracyclophane-CH₂), 35.3 (Paracyclophane-CH₂), 35.3 (Paracyclophane-CH₂), 35.2 (Paracyclophane-CH₂ x 2), 35.2 (Paracyclophane-CH₂), 35.1 (Paracyclophane-CH₂), 33.4 (C_{9b'}), 33.3 (C_{9b}), 29.2 (C₄), 29.1 (C_{4'}), 24.2 (C_{9a}), 24.1 (C_{9a'}).

HRMS (ESI⁺): Found [M-H]⁺ = 363.2320; C₂₅H₃₁O₂ requires 363.2319, Δ 0.30 ppm

IR (film) ν_{max}/cm⁻¹: 2951, 2925, 2854, 1674, 1593, 1552.

4-(2-(4,4-Dimethyltetrahydro-2H-pyran-2-yl)acetyl)benzaldehyde **177**



3,3-Dimethylhex-5-en-1-ol **150** (77 mg, 0.601 mmol, 1.0 equiv.), 4-acryloylbenzaldehyde **172** (192 mg, 1.20 mmol, 2.0 equiv.), ClCH₂CH₂Cl (0.1 M, 9 mL), and Hoveyda–Grubbs Catalyst[®] M720 (37.7 mg, 0.0601 mmol, 10 mol%) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (5% Et₂O/Pentane) as a yellow oil (91.0 mg, 0.350 mmol, 58% yield).

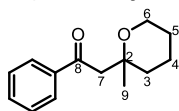
¹H NMR (400 MHz, CDCl₃) δ 10.10 (s, 1H, H₉), 8.14 – 8.07 (m, 2H, ArCH x 2), 8.01 – 7.93 (m, 2H, ArCH x 2), 4.12 (dddd, *J* = 12.0, 7.0, 5.0, 2.0 Hz, 1H, H₂), 3.79 (ddd, *J* = 12.0, 5.0, 1.5 Hz, 1H, H_{6a}), 3.62 (ddd, *J* = 13.0, 12.0, 2.5 Hz, 1H, H_{6b}), 3.30 (dd, *J* = 16.0, 7.5 Hz, 1H, H_{7a}), 2.86 (dd, *J* = 16.0, 5.0 Hz, 1H, H_{7b}), 1.50 – 1.41 (m, 2H, H_{5a}, H_{3a}), 1.32 – 1.19 (m, 2H, H_{3b}, H_{5b}), 1.06 (s, 3H, H_{10a} x 3), 0.97 (s, 3H, H_{10b} x 3).

¹³C NMR (101 MHz, CDCl₃) δ 198.3 (C₈), 191.8 (C₉), 141.8 (ArC), 139.1 (ArC), 129.9 (ArC x 2), 120.0 (ArC x 2), 70.3 (C₂), 64.6 (C₆), 46.0 (C₇), 45.1 (C₃), 38.7 (C₅), 33.3 (C_{10a}), 29.2 (C₄), 24.1 (C_{10b}).

HRMS (ESI⁺): Found [M+H]⁺ = 261.1484; C₁₆H₂₁O₃ requires 261.1485, Δ 0.26 ppm

IR (film) ν_{max}/cm⁻¹: 2965, 2876, 1787, 1643, 1567, 154

2-(2-Methyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one **185**



MeLi in Et₂O (1.6 M, 11.2 mL, 18.0 mmol, 6.0 equiv.) was added dropwise to a solution of CuI (1.72 g, 9.00 mmol, 3.0 equiv.) in THF (0.3 M, 25 mL) at –78 °C. The reaction mixture was warmed to 0 °C and stirred for 1 h, affording a colourless solution. The mixture was then cooled back to –78 °C, and a solution of 7-hydroxy-1-phenylhept-2-yn-1-one **183** (606 mg, 3.00 mmol, 1.0 equiv.) in THF (1.0 M, 3 mL) was added dropwise. The reaction was stirred for 30 min before being quenched with saturated aqueous ammonium chloride (30 mL) and warmed to RT. The mixture was treated with 35% aqueous ammonium hydroxide solution (30 mL), resulting in a clear blue aqueous phase. The solution was extracted with EtOAc (3 x 60 mL), and the combined organic phases were washed with HCl (1.0 M, 50 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a yellow oil (588 mg, 2.69 mmol, 90% yield).

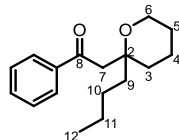
¹H NMR (400 MHz, CDCl₃) δ 8.02 – 7.94 (m, 2H, ArCH x 2), 7.59 – 7.50 (m, 1H, ArCH), 7.49 – 7.40 (m, 2H, ArCH x 2), 3.76 – 3.65 (m, 2H, H₆ x 2), 3.25 – 3.13 (m, 2H, H₇ x 2), 1.78 – 1.62 (m, 4H, H₃ x 2, H₄ x 2), 1.59 – 1.47 (m, 2H, H₅ x 2), 1.33 (s, 3H, H₉ x 3).

¹³C NMR (101 MHz, CDCl₃) δ 199.2 (C₈), 138.5 (ArC), 133.0 (ArC), 128.6 (ArC x 4), 73.5 (C₂), 61.8 (C₆), 48.1 (C₇), 35.1 (C₃), 25.9 (C₅), 23.4 (C₉), 19.5 (C₄).

HRMS (ESI⁺): Found [M+H]⁺ = 219.1373; C₁₄H₁₉O₂ requires 219.1380 Δ -3.01 ppm.

IR (film) ν_{max}/cm⁻¹: 2980, 1676, 1597, 1449, 1378, 1232.

2-(2-Butyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one **186**



n-BuLi in hexanes (2.5 M, 1.2 mL, 3.0 mmol, 6.0 equiv.) was added dropwise to a solution of CuI (285 mg, 1.5 mmol, 3.0 equiv.) in THF (0.3 M, 5 mL) at –78 °C. The reaction mixture was warmed to 0 °C and stirred for 1 h, during which a black precipitate formed. The mixture was then cooled back to –78 °C, and a solution of 7-hydroxy-1-phenylhept-2-yn-1-one **183** (101 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 M, 0.5 mL) was added dropwise. The reaction was stirred for 30 min, then

quenched with saturated aqueous ammonium chloride (10 mL) and warmed to RT. The mixture was treated with 35% aqueous ammonium hydroxide solution (10 mL), resulting in a clear blue aqueous phase. The solution was extracted with EtOAc (3 x 20 mL) and the combined organic phases were washed with HCl (1.0 M, 20 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a yellow oil (101 mg, 0.39 mmol, 78% yield).

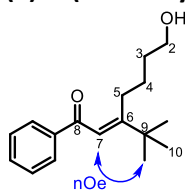
¹H NMR (400 MHz, CDCl₃) δ 8.00 – 7.93 (m, 2H, ArCH x 2), 7.58 – 7.50 (m, 1H, ArCH), 7.49 – 7.40 (m, 2H, ArCH x 2), 3.66 (dd, *J* = 6.0, 5.0 Hz, 2H, H₆ x 2), 3.24 (d, *J* = 15.5 Hz, 1H, H_{7a}), 3.14 (d, *J* = 15.5 Hz, 1H, H_{7b}), 1.91 – 1.56 (m, 6H, H₃ x 2, H₅ x 2, H₉ x 2), 1.55 – 1.45 (m, 2H, H₄ x 2), 1.41 – 1.13 (m, 4H, H₁₀ x 2, H₁₁ x 2), 0.86 (t, *J* = 7.0 Hz, 3H, H₁₂ x 3).

¹³C NMR (101 MHz, CDCl₃) δ 199.3 (C₈), 138.6 (ArC), 132.9 (ArC), 128.6 (ArC x 2), 128.4 (ArC x 2), 75.4 (C₂), 61.5 (C₆), 44.8 (C₇), 34.3 (C₉), 33.7 (C₃), 25.9 (C₅), 25.4 (C₁₀), 23.3 (C₁₁), 19.2 (C₄), 14.2 (C₁₂).

HRMS (ESI⁺): Found [M+H]⁺ = 261.1849; C₁₇H₂₅O₂ requires 261.1849 Δ -0.04 ppm

IR (film) ν_{max}/cm⁻¹: 2933, 2860, 1677, 1448, 1350, 1085.

(*E*)-3-(*tert*-Butyl)-7-hydroxy-1-phenylhept-2-en-1-one **187**



t-BuLi in pentane (1.7 M, 3.5 mL, 6.0 mmol, 6.0 equiv.) was added dropwise to a solution of CuI (572 mg, 3.0 mmol, 3.0 equiv.) in THF (0.1 M, 10 mL) at -78 °C. The reaction mixture was warmed to 0 °C and stirred for 1 h, during which a black precipitate formed. The mixture was then cooled back to -78 °C, and a solution of 7-hydroxy-1-phenylhept-2-yn-1-one **183** (202 mg, 1.0 mmol, 1.0 equiv.) in THF (1.0 M, 1 mL) was added dropwise. The reaction was stirred for 30 min, then quenched with saturated aqueous ammonium chloride (10 mL) and warmed to RT. The mixture was treated with 35% aqueous ammonium hydroxide solution, resulting in a clear blue aqueous

phase. The solution was extracted with EtOAc (3 x 30 mL), and the combined organic phases were dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (20→40% EtOAc/pentane) as a colourless oil (102 mg, 0.39 mmol, 39% yield, >95:5 *E/Z*).

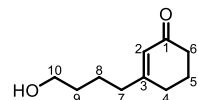
¹H NMR (400 MHz, CDCl₃) δ 7.95 – 7.88 (m, 2H, ArCH x 2), 7.59 – 7.49 (m, 1H, ArCH), 7.50 – 7.40 (m, 2H, ArCH x 2), 6.86 (s, 1H, H₇), 3.81 – 3.73 (m, 2H, H₂ x 2), 2.67 – 2.57 (m, 2H, H₄ x 2), 2.26 (s, 1H, OH), 1.73 – 1.55 (m, 4H, H₃ x 2, H₅ x 2), 1.22 (s, 9H, H₁₀ x 9).

¹³C NMR (101 MHz, CDCl₃) δ 192.2 (C₈), 173.5 (ArC), 140.1 (C₆), 132.4 (ArC), 128.6 (ArC x 2), 128.3 (ArC x 2), 117.1 (C₇), 61.4 (C₂), 39.0 (C₉), 32.7 (C₃), 29.5 (C₄), 29.0 (C₁₀ x 3), 26.3 (C₅).

HRMS (ESI⁺): Found [M+H]⁺ = 261.1848; C₁₇H₂₅O₂ requires 261.1849 Δ -0.59 ppm

IR (film) ν_{max}/cm⁻¹: 3503, 2958, 2871, 1703, 1658, 1599.

3-(4-Hydroxybutyl)cyclohex-2-en-1-one 203



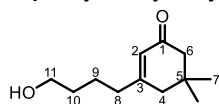
A solution of MeMgBr in THF (2.0 M, 18.8 mL, 37.5 mmol, 1.5 equiv.) was added to a solution of 4-chloro-1-butanol (4.07 g, 37.5 mmol, 1.5 equiv.) in THF (1.0 M, 38 mL) at -78 °C. The reaction mixture was then warmed to RT, and magnesium turnings (1.22 g, 50.0 mmol, 2.0 equiv.) were added. The reaction was heated under reflux for 3 h, cooled to 0 °C, after which a solution of 3-ethoxycyclohex-2-en-1-one (3.50 g, 25.0 mmol, 1.0 equiv.) in THF (3.0 M, 8 mL) was added dropwise. The mixture was stirred for 2 h, warmed to RT, and quenched by the addition of saturated aqueous ammonium chloride (40 mL). The resulting solution was diluted with HCl (3.0 M, 40 mL), extracted with Et₂O (3 x 80 mL), and the combined organic phases were dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a yellow oil (2.82 g, 16.8 mmol, 67% yield).

¹H NMR (400 MHz, CDCl₃) δ 5.605 – 5.72 (m, 1H, H₂), 3.79 – 3.56 (m, 2H, H₁₀ x 2), 2.37 (t, *J* = 6.5 Hz, 2H, H₆ x 2), 2.31 – 2.19 (m, 4H, H₄ x 2, H₇ x 2), 1.99 (p, *J* = 6.5 Hz, 2H, H₅ x 2), 1.89 – 1.47 (m, 5H, OH, H₈ x 2, H₉ x 2).

^{13}C NMR (101 MHz, CDCl_3) δ 200.5 (C_1), 166.9 (C_3), 125.8 (C_2), 62.4 (C_{10}), 37.8 (C_7), 37.4 (C_6), 32.2 (C_9), 29.7 (C_4), 23.3 (C_8), 22.8 (C_5).

The spectroscopic data matched that previously reported in the literature.^[107]

3-(4-Hydroxybutyl)-5,5-dimethylcyclohex-2-en-1-one **207**



A solution of MeMgBr in THF (2.0 M, 3.8 mL, 7.5 mmol, 1.5 equiv.) was added to a solution of 4-chloro-1-butanol (814 mg, 7.5 mmol, 1.5 equiv.) in THF (1.0 M, 8 mL) at $-78\text{ }^\circ\text{C}$. The reaction mixture was then warmed to RT, and magnesium turnings (243 mg, 10 mmol, 2.0 equiv.) were added. The reaction was heated under reflux for 3 h, cooled to $0\text{ }^\circ\text{C}$, after which a solution of 3-ethoxy-5,5-dimethylcyclohex-2-en-1-one **206** (841 mg, 5.00 mmol, 1.0 equiv.) in THF (3.0 M, 2 mL) was added dropwise. The reaction was stirred for 2 h, warmed to RT, and quenched by the addition of saturated aqueous ammonium chloride (10 mL). The resulting solution was diluted with HCl (3.0 M, 10 mL), extracted with Et_2O (3 x 20 mL), and the combined organic phases were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et_2O /pentane) as a yellow oil (621 mg, 3.16 mmol, 63% yield).

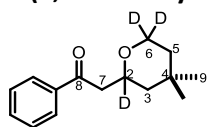
^1H NMR (400 MHz, CDCl_3) δ 5.91 – 5.84 (m, 1H, H_2), 3.70 – 3.63 (m, 2H, $\text{H}_{11} \times 2$), 2.26 – 2.15 (m, 6H, $\text{H}_8 \times 2$, $\text{H}_4 \times 2$, $\text{H}_6 \times 2$), 1.67 – 1.52 (m, 4H, $\text{H}_{10} \times 2$, $\text{H}_9 \times 2$), 1.41 (s, 1H, OH), 1.03 (s, 6H, $\text{H}_7 \times 6$).

^{13}C NMR (101 MHz, CDCl_3) δ 200.3 (C_1), 164.0 (C_3), 124.8 (C_2), 62.4 (C_{11}), 51.1 (C_4), 44.0 (C_6), 37.9 (C_8), 33.7 (C_5), 32.3 (C_{10}), 28.4 ($\text{C}_7 \times 2$), 23.2 (C_9).

HRMS (ESI⁺): Found $[\text{M}+\text{H}]^+ = 197.1537$; $\text{C}_{12}\text{H}_{21}\text{O}_2$ requires 197.1536, Δ 0.45 ppm

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3430 (broad), 2954, 1663, 1460, 1412, 1369.

2-(4,4-Dimethyltetrahydro-2H-pyran-2-yl-2,6,6- d_3)-1-phenylethan-1-one **160- d_3**



A 10 mL round-bottom flask fitted with an air condenser was charged with diethyl (2-oxo-2-phenylethyl)phosphonate **218** (269 mg, 1.05 mmol, 1.4 equiv.) and evacuated/backfilled with N_2

three times. Toluene (0.2 M, 5 mL) was added, followed by 60% wt. NaH (36 mg, 0.901 mmol, 1.2 equiv.) in one portion [caution: vigorous release of H₂]. The suspension was stirred at RT for 30 min, until a homogeneous solution had formed. 4,4-Dimethyltetrahydro-2H-pyran-2,6,6-*d*₃-2-ol **149-*d*₃** (100 mg, 0.751 mmol, 1.0 equiv.) was then added, and the reaction was heated at 110 °C for 15 h. The mixture was cooled to RT, diluted with Et₂O (30 mL), filtered through a plug of silica gel, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a yellow oil (148 mg, 0.629 mmol, 84% yield, >95% D incorporation by ¹H and ¹³C NMR).

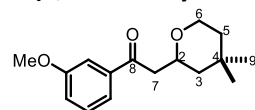
¹H NMR (400 MHz, CDCl₃) δ 7.98 – 7.94 (m, 2H, ArCH x 2), 7.58 – 7.52 (m, 1H, ArCH), 7.47 – 7.42 (m, 2H, ArCH x 2), 3.27 (d, *J* = 16.0 Hz, 1H, H_{7a}), 2.84 (d, *J* = 16.0 Hz, 1H, H_{7b}), 1.51 – 1.42 (m, 2H, H_{3a} and H_{5a}), 1.27 – 1.17 (m, 2H, H_{3b} and H_{5b}), 1.05 (s, 3H, H_{9a} x 3), 0.95 (s, 3H, H_{9b} x 3). [N.B. In the absence of deuteration, the peaks for H₂, H_{6a} and H_{6b} would each integrate to 1.00. Integration of the quantitative ¹H NMR spectrum showed integrals of 0.02-0.03 for each of these peaks, indicating that 0.97-0.98 deuterium atoms were incorporated at each position.]

¹³C NMR (101 MHz, CDCl₃) δ 198.4 (C₈), 137.3 (ArC), 133.0 (ArC), 128.5 (ArC x 2), 128.2 (ArC x 2), 69.6 (1:1:1 t, *J* = 21.4 Hz, C₂), 63.7 (1:2:3:2:1 quintet, *J* = 21.5 Hz, C₆), 38.4 (C₇), 33.2 (C_{9b}), 29.0 (C₄), 24.0 (C_{9a}).

²H NMR (92 MHz, CHCl₃ + 1 drop CDCl₃) δ 4.12 (s, 1H, H₂), 3.76 (s, 1H, H_{6a}), 3.61 (s, 1H, H_{6b}).

Apart from deuterium incorporation at C₂ and C₆, the spectral data for **160-*d*₃** were consistent with those of **160** prepared and reported previously.

2-(4,4-Dimethyltetrahydro-2H-pyran-2-yl)-1-(3-methoxyphenyl)ethan-1-one **222**



A 10 mL round-bottom flask fitted with an air condenser was charged with Diethyl (2-(3-methoxyphenyl)-2-oxoethyl)phosphonate **221** (360 mg, 1.26 mmol, 1.4 equiv.) and evacuated/backfilled with N₂ three times. Toluene (0.2 M, 6 mL) was added, followed by 60% wt. NaH (43.1 mg, 1.08 mmol, 1.2 equiv.) in one portion [caution: vigorous release of H₂]. The

suspension was stirred at RT for 30 min, until a homogeneous solution had formed. 4,4-Dimethyltetrahydro-2H-pyran-2-ol **149** (117 mg, 0.899 mmol, 1.0 equiv.) was then added, and the reaction was heated at 110 °C for 15 h. The mixture was cooled to RT, diluted with Et₂O (30 mL), filtered through a plug of silica gel, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% Et₂O/pentane) as a yellow oil (235 mg, 0.896 mmol, 100% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.54 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H, ArCH), 7.49 (dd, *J* = 2.5, 1.5 Hz, 1H, ArCH), 7.36 (t, *J* = 8.0 Hz, 1H, ArCH), 7.10 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, ArCH), 4.12 (dddd, *J* = 11.5, 7.0, 5.5, 2.0 Hz, 1H, H₂), 3.85 (s, 3H, OCH₃ × 3), 3.80 (ddd, *J* = 12.0, 5.0, 1.5 Hz, 1H, H_{6eq}), 3.63 (ddd, *J* = 13.0, 12.0, 2.5 Hz, 1H, H_{6ax}), 3.25 (dd, *J* = 16.0, 7.0 Hz, 1H, H_{7a}), 2.85 (dd, *J* = 16.0, 5.5 Hz, 1H, H_{7b}), 1.53 – 1.42 (m, 2H, H_{3a} and H_{5a}), 1.29 – 1.18 (m, 2H, H_{3b} and H_{5b}), 1.06 (s, 3H, H_{9a} × 3), 0.95 (s, 3H, H_{9b} × 3).

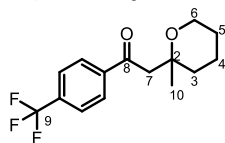
¹³C NMR (101 MHz, CDCl₃) δ 198.4, 159.9, 138.8, 129.7, 121.1, 119.8, 112.5, 70.3, 64.6, 55.6, 45.6, 45.1, 38.8, 33.3, 29.1, 24.1.

HRMS (ESI⁺): Found [M+H]⁺ = 263.1642; C₁₆H₂₃O₃ requires 263.1642, Δ 0.05 ppm

IR (film) ν_{max}/cm⁻¹: 2953, 1684, 1597, 1583, 1456, 1430.

m.p.: 36–38 °C

2-(2-Methyltetrahydro-2H-pyran-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-one **248**



MeLi in Et₂O (13.9 mL, 1.6 M, 22.2 mmol, 6.0 equiv.) was added dropwise to a solution of CuI (2.11 g, 11.1 mmol, 3.0 equiv.) in THF (0.3 M, 37 mL) at –78 °C. The reaction mixture was warmed to 0 °C and stirred for 1 h, affording a colourless solution. The mixture was cooled to –78 °C, and a solution of 7-hydroxy-1-(4-(trifluoromethyl)phenyl)hept-2-yn-1-one **247** (1.00 g, 3.70 mmol, 1.0 equiv.) in THF (1.0 M, 4 mL) was added dropwise and stirred for 30 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride (30 mL) and warmed to RT.

The mixture was treated with 35% aqueous ammonium hydroxide solution (30 mL), affording a clear blue aqueous phase. The solution was extracted with EtOAc (3 x 60 mL), and the combined organic phases were washed with HCl (1.0 M, 60 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a yellow oil (911 mg, 3.18 mmol, 86% yield).

¹H NMR (500 MHz, CDCl₃) δ 8.08 (d, *J* = 8.0 Hz, 2H, ArCH x 2), 7.71 (d, *J* = 8.0 Hz, 2H, ArCH x 2), 3.73 – 3.62 (m, 2H, H₆ x 2), 3.22 – 3.13 (m, 2H, H₇ x 2), 1.76 – 1.59 (m, 4H, H₃ x 2, H₄ x 2), 1.55 – 1.47 (m, 2H, H₅ x 2), 1.33 (s, 3H, H₁₀ x 3).

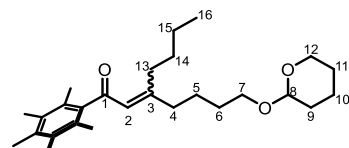
¹⁹F NMR (471 MHz, CDCl₃) δ -63.1.

¹³C NMR (126 MHz, CDCl₃) δ 198.4 (C₈), 141.1 (ArC), 134.1 (ArC), 129.0 (ArC x 2), 125.6 (ArC x 2), 122.7 (C₉), 73.5 (C₂), 61.8 (C₆), 49.1 (C₇), 35.1 (C₃), 25.8 (C₅), 22.9 (C₁₀), 19.4 (C₄).

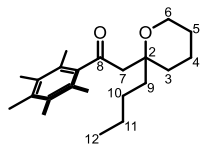
HRMS (ESI⁺): Found [M+H]⁺ = 287.1255; C₁₅H₁₈F₃O₂ requires 287.1253 Δ 0.54 ppm

IR (film) ν_{max}/cm⁻¹: 3660, 2980, 1677, 1597, 1449, 1378.

3-Butyl-1-(2,3,4,5,6-pentamethylphenyl)-7-((tetrahydro-2H-pyran-2-yl)oxy)hept-2-en-1-one 278



A solution of 2-(4-chlorobutoxy)tetrahydro-2H-pyran **277** (11.2 g, 58.3 mmol, 4.0 equiv.) in THF (2.0 M, 29 mL) was added to a suspension of magnesium turnings (2.13 g, 87.6 mmol, 6.0 equiv.) in THF (3.0 M, 29 mL). The reaction mixture was heated under reflux for 3 h, cooled to RT, and a solution of (Z)-1-hydroxy-1-(2,3,4,5,6-pentamethylphenyl)hept-1-en-3-one **273** (4.00 g, 14.6 mmol, 1.0 equiv.) in THF (1.0 M, 15 mL) was added dropwise. The reaction was heated under reflux for a further 16 h, cooled to RT, and poured onto a mixture of ice/conc. HCl (40 g/8 mL). The resulting solution was extracted with Et₂O (3 x 90 mL) and the combined organic phases were dried over MgSO₄, filtered, and concentrate *in vacuo*. The crude product was taken onto the next step with no further purification.

2-(2-Butyltetrahydro-2H-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one 268

A 250 mL round-bottom flask was charged with 3-butyl-1-(2,3,4,5,6-pentamethylphenyl)-7-((tetrahydro-2H-pyran-2-yl)oxy)hept-2-en-1-one **278** (6.05 g, 14.6 mmol, 1.0 equiv.), *p*-TsOH (5.02 g, 29.2 mmol, 2.0 equiv.) and MeOH (0.1 M, 146 mL). The reaction mixture was stirred at RT for 16 h, diluted with CH₂Cl₂ (70 mL), and washed with saturated aqueous NaHCO₃ (100 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (3% Et₂O/pentane) as a yellow solid (1.59 g, 4.81 mmol, 33% over 2 steps)

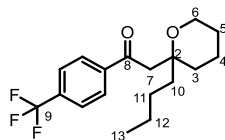
¹H NMR (400 MHz, CDCl₃) δ 3.70 – 3.49 (m, 2H, H₆ x 2), 3.09 – 2.89 (m, 2H, H₇ x 2), 2.23 (s, 3H, ArCH₃), 2.18 (s, 6H, ArCH₃ x 2), 2.15 (s, 6H, ArCH₃ x 2), 1.99 – 1.46 (m, 8H, H₉ x 2, H₃ x 2, H₄ x 2, H₅ x 2), 1.42 – 1.20 (m, 4H, H₁₀ x 2, H₁₁ x 2), 0.91 (t, *J* = 7.0 Hz, 3H, H₁₂ x 3).

¹³C NMR (101 MHz, CDCl₃) δ 209.7 (C₈), 141.2 (ArC), 135.4 (ArC), 133.2 (ArC x 2), 127.5 (ArC x 2), 74.7 (C₂), 61.3 (C₆), 50.9 (C₇), 34.6 (C₉), 33.2 (C₃), 25.9 (C₅), 25.4 (C₁₀), 23.4 (C₁₁), 19.2 (C₄), 17.3 (ArCH₃ x 2), 16.8 (ArCH₃), 16.1 (ArCH₃ x 2), 14.3 (C₁₂).

HRMS (ESI⁺): Found [M+H]⁺ = 331.2625; C₂₂H₃₅O₂ requires 331.2632 Δ -1.94 ppm.

IR (film) ν_{max}/cm⁻¹: 2980, 2935, 2869, 2244, 1703, 1446.

m.p.: 47–49 °C.

2-(2-Butyltetrahydro-2H-pyran-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-one 291

n-BuLi in hexanes (2.5 M, 8.9 mL, 22.2 mmol, 6.0 equiv.) was added dropwise to a solution of CuI (2.11 g, 11.1 mmol, 3.0 equiv.) in THF (0.3 M, 37 mL) at –78 °C. The reaction mixture was warmed to 0 °C and stirred for 1 h, affording a black precipitate. The mixture was cooled to –78 °C, and a solution of 7-hydroxy-1-(4-(trifluoromethyl)phenyl)hept-2-yn-1-one **247** (1.00 g, 3.70 mmol, 1.0 equiv.) in THF (1.0 M, 4 mL) was added dropwise and stirred for 30 min. The

reaction was quenched by the addition of saturated aqueous ammonium chloride (30 mL) and warmed to RT. The mixture was treated with 35% aqueous ammonium hydroxide solution (30 mL), affording a clear blue aqueous phase. The solution was extracted with EtOAc (3 x 60 mL) and the combined organic phases were washed with HCl (1.0 M, 60 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et_2O /pentane) as a yellow oil (755 mg, 2.30 mmol, 62% yield).

^1H NMR (500 MHz, CDCl_3) δ 8.07 (d, J = 8.0 Hz, 2H, ArCH x 2), 7.71 (d, J = 8.0 Hz, 2H, ArCH x 2), 3.68 – 3.58 (m, 2H, H_6 x 2), 3.26 (d, J = 15.0 Hz, 1H, H_{7a}), 3.07 (d, J = 15.0 Hz, 1H, H_{7b}), 1.83 (ddd, J = 14.0, 12.0, 4.0 Hz, 1H, H_{3a}), 1.77 – 1.56 (m, 4H, H_{10} x 2, H_4 x 2, H_{3b}), 1.48 (p, J = 5.5 Hz, 2H, H_5 x 2), 1.42 – 1.15 (m, 3H, H_{11a} , H_{12} x 2, H_{11b}), 0.88 (t, J = 7.0 Hz, 3H, H_{13} x 3).

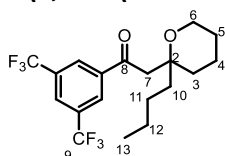
^{19}F NMR (471 MHz, CDCl_3) δ -63.1.

^{13}C NMR (126 MHz, CDCl_3) δ 198.6 (C_8), 141.3 (ArC), 134.1 (ArC), 128.9 (ArC x 2), 125.6 (ArC x 2), 123.8 (C_9), 75.5 (C_2), 61.5 (C_6), 45.8 (C_7), 34.0 (C_3), 33.4 (C_{10}), 25.7 (C_5), 25.5 (C_{11}), 23.3 (C_{12}), 19.2 (C_4), 14.2 (C_{13}).

HRMS (ESI⁺): Found $[\text{M}+\text{H}]^+ = 329.1714$; $\text{C}_{18}\text{H}_{24}\text{F}_3\text{O}_2$ requires 329.1723 Δ -2.72 ppm.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2980, 1685, 1582, 1511, 1461, 1408.

1-(3,5-Bis(trifluoromethyl)phenyl)-2-(2-butyltetrahydro-2H-pyran-2-yl)ethan-1-one **292**



n-BuLi in hexanes (2.5 M, 9.2 mL, 23.0 mmol, 6.0 equiv.) was added dropwise to a solution of CuI (2.19 g, 11.5 mmol, 3.0 equiv.) in THF (0.3 M, 38 mL) at -78°C . The reaction mixture was warmed to 0°C and stirred for 1 h, affording a black precipitate. The mixture was cooled to -78°C , and a solution of 1-(3,5-bis(trifluoromethyl)phenyl)-7-hydroxyhept-2-yn-1-one **287** (1.30 g, 3.84 mmol, 1.0 equiv.) in THF (1.0 M, 4 mL) was added dropwise and stirred for 30 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride (30 mL) and warmed to RT. The mixture was treated with 35% aqueous ammonium hydroxide solution (30

mL), affording a clear blue aqueous phase. The solution was extracted with EtOAc (3 x 60 mL) and the combined organic phases were washed with HCl (1.0 M, 60 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et_2O /pentane) as a yellow oil (648 mg, 1.63 mmol, 43% yield).

^1H NMR (500 MHz, CDCl_3) δ 8.48 – 8.44 (m, 2H, ArCH x 2), 8.03 (s, 1H, ArCH), 3.67 – 3.55 (m, 2H, H_6 x 2), 3.29 (d, J = 14.5 Hz, 1H, H_{7a}), 3.01 (d, J = 14.5 Hz, 1H, H_{7b}), 1.83 (ddd, J = 14.0, 12.0, 4.0 Hz, 1H, H_{3a}), 1.73 – 1.59 (m, 5H, H_{3b} , H_{10} x 2, H_4 x 2), 1.52 – 1.16 (m, 6H, H_5 x 2, H_{11a} , H_{12} x 2, H_{11b}), 0.91 (t, J = 7.0 Hz, 3H, H_{13} x 3).

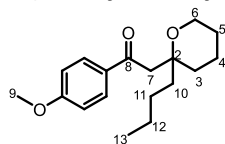
^{19}F NMR (471 MHz, CDCl_3) δ -63.0.

^{13}C NMR (126 MHz, CDCl_3) δ 197.0 (C_8), 140.0 (ArC), 132.0 (ArC x 2), 129.0 (ArC), 125.9 (ArC), 123.2 (C_9 x 2), 75.6 (C_2), 61.5 (C_6), 47.0 (C_7), 33.4 (C_3), 33.1 (C_{10}), 25.6 (C_5), 25.6 (C_{11}), 23.3 (C_{12}), 19.1 (C_4), 14.2 (C_{13}).

HRMS (ESI+): Found $[\text{M}+\text{H}]^+ = 397.1596$; $\text{C}_{19}\text{H}_{23}\text{F}_6\text{O}_2$ requires 397.1597 Δ -0.20 ppm.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2981, 2845, 1684, 1589, 1476, 1412.

2-(2-Butyltetrahydro-2H-pyran-2-yl)-1-(4-methoxyphenyl)ethan-1-one **293**



n-BuLi in hexanes (2.5 M, 7.2 mL, 18.1 mmol, 6.0 equiv.) was added dropwise to a solution of CuI (1.72 g, 9.03 mmol, 3.0 equiv.) in THF (0.3 M, 30 mL) at -78°C . The reaction mixture was warmed to 0°C and stirred for 1 h, affording a black precipitate. The mixture was cooled to -78°C and a solution of 7-hydroxy-1-(4-methoxyphenyl)hept-2-yn-1-one **288** (700 mg, 3.01 mmol, 1.0 equiv.) in THF (1.0 M, 3 mL) was added dropwise and stirred for 30 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride (30 mL) and warmed to RT. The mixture was treated with 35% aqueous ammonium hydroxide solution (30 mL), affording a clear blue aqueous phase. The solution was extracted with EtOAc (3 x 60 mL), and the combined organic phases were washed with HCl (1.0 M, 60 mL), dried over MgSO_4 , filtered, and

concentrated *in vacuo*. The title compound was afforded after purification by FCC (15% Et₂O/pentane) as a yellow oil (812 mg, 2.79 mmol, 93% yield).

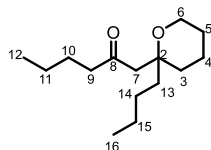
¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.91 (m, 2H, ArCH x 2), 6.96 – 6.88 (m, 2H, ArCH x 2), 3.86 (s, 3H, H₉ x 3), 3.70 – 3.61 (m, 2H, H₆ x 2), 3.19 (d, *J* = 15.0 Hz, 1H, H_{7a}), 3.08 (d, *J* = 15.0 Hz, 1H, H_{7b}), 1.87 – 1.58 (m, 6H, H₃ x 2, H₅ x 2, H₁₀ x 2), 1.54 – 1.44 (m, 2H, H₄ x 2), 1.39 – 1.17 (m, 4H, H₁₁ x 2, H₁₂ x 2), 0.87 (t, *J* = 7.0 Hz, 3H, H₁₃ x 2).

¹³C NMR (101 MHz, CDCl₃) δ 197.7 (C₈), 163.4 (ArC), 131.7 (ArC), 130.8 (ArC x 2), 113.7 (ArC x 2), 75.4 (C₂), 61.5 (C₆), 55.6 (C₉), 44.6 (C₇), 34.3 (C₁₀), 33.7 (C₃), 25.9 (C₅), 25.4 (C₁₁), 23.3 (C₁₂), 19.2 (C₄), 14.3 (C₁₃).

HRMS (ESI⁺): Found [M+H]⁺ = 291.1957; C₁₈H₂₇O₃ requires 291.1955 Δ 0.77 ppm

IR (film) ν_{max}/cm⁻¹: 2957, 2869, 1670, 1601, 1576, 1510.

1-(2-Butyltetrahydro-2H-pyran-2-yl)hexan-2-one **294**



n-BuLi in hexanes (2.5 M, 13.2 mL, 3.0 mmol, 6.0 equiv.) was added dropwise to a solution of CuI (3.13 g, 16.5 mmol, 3.0 equiv.) in THF (0.3 M, 55 mL) at –78 °C. The reaction mixture was warmed to 0 °C and stirred for 1 h, affording a black precipitate. The mixture was cooled to –78 °C and a solution of 11-hydroxyundec-6-yn-5-one **274** (1.00 g, 5.49 mmol, 1.0 equiv.) in THF (1.0 M, 4 mL) was added dropwise and stirred for 30 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride (50 mL) and warmed to RT. The reaction was treated with 35% aqueous ammonium hydroxide solution (50 mL), affording a clear blue aqueous phase. The solution was extracted with EtOAc (3 x 100 mL), and the combined organic phases were washed with HCl (1.0 M, 100 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a yellow oil (536 mg, 2.23 mmol, 41% yield).

^1H NMR (500 MHz, CDCl_3) δ 3.69 – 3.60 (m, 2H, $\text{H}_6 \times 2$), 2.60 (d, $J = 2.5$ Hz, 2H, $\text{H}_7 \times 2$), 2.47 (td, $J = 7.0, 1.0$ Hz, 2H, $\text{H}_9 \times 2$), 1.74 – 1.45 (m, 10H, $\text{H}_3 \times 2$, $\text{H}_4 \times 2$, $\text{H}_{13} \times 2$, $\text{H}_{10} \times 2$, $\text{H}_5 \times 2$), 1.38 – 1.10 (m, 6H, $\text{H}_{14} \times 2$, $\text{H}_{11} \times 2$, $\text{H}_{15} \times 2$), 0.94 – 0.84 (m, 6H, $\text{H}_{12} \times 3$, $\text{H}_{16} \times 3$).

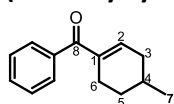
^{13}C NMR (126 MHz, CDCl_3) δ 210.5 (C_8), 74.9 (C_2), 61.5 (C_6), 49.2 (C_7), 44.7 (C_9), 35.1 (C_3), 33.4 (C_{13}), 25.9 (C_5 or C_{10}), 25.8 (C_5 or C_{10}), 25.4 (C_{14}), 23.3 (C_{15}), 22.4 (C_{11}), 19.2 (C_4), 14.2 (C_{12} or C_{16}), 14.0 (C_{12} or C_{16}).

HRMS (ESI $^+$): Found $[\text{M}+\text{H}]^+ = 241.2161$; $\text{C}_{15}\text{H}_{29}\text{O}_2$ requires 241.2162 Δ -0.34 ppm.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2957, 2871, 1709, 1460, 1379, 1284.

5.6 Synthesis of Cyclohexenes

(4-Methylcyclohex-1-en-1-yl)(phenyl)methanone **107**



2-(4-Methyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one **108** (65.5 mg, 0.300 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (74.1 mg, 0.300 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et_2O /pentane) as a colourless oil (46.2 mg, 0.23 mmol, 77% yield).

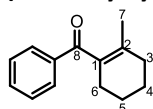
^1H NMR (400 MHz, CDCl_3) δ 7.66 – 7.59 (m, 2H, ArCH $\times 2$), 7.53 – 7.44 (m, 1H, ArCH), 7.45 – 7.36 (m, 2H, ArCH $\times 2$), 6.59 – 6.51 (m, 1H, H_2), 2.67 – 2.53 (m, 1H, H_{6a}), 2.42 – 2.22 (m, 2H, H_{3a} , H_{6b}), 1.94 – 1.80 (m, 2H, H_{3b} , H_{5a}), 1.82 – 1.66 (m, 1H, H_4), 1.30 (dtd, $J = 12.0, 10.0, 5.0$ Hz, 1H, H_{5b}), 1.02 (d, $J = 6.5$ Hz, 3H, $\text{H}_7 \times 3$).

^{13}C NMR (101 MHz, CDCl_3) δ 198.3 (C_8), 143.7 (C_2), 138.9 (C_1), 138.6 (ArC), 131.4 (ArC), 129.3 (ArC $\times 2$), 128.1 (ArC $\times 2$), 34.7 (C_6), 30.4 (C_5), 27.9 (C_4), 24.2 (C_3), 21.7 (C_7).

HRMS (ESI $^+$): Found $[\text{M}+\text{H}]^+ = 201.1275$; $\text{C}_{14}\text{H}_{17}\text{O}$ requires 201.1274, Δ 0.71 ppm.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3000, 2886, 1725, 1685, 1380, 1252.

(2-Methylcyclohex-1-en-1-yl)(phenyl)methanone **137**



rac-2-((2*S*,6*S*)-6-Methyltetrahydro-2*H*-pyran-2-yl)-1-phenylethan-1-one **130** (65.5 mg, 0.30 mmol, 1.0 equiv.), Al(*O**t*-Bu)₃ (74.1 mg, 0.30 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et₂O/pentane) as a colourless oil (48.0 mg, 0.24 mmol, 80% yield).

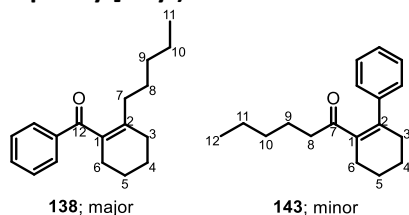
¹H NMR (400 MHz, CDCl₃) δ 7.93 – 7.84 (m, 2H, ArCH x 2), 7.59 – 7.50 (m, 1H, ArCH), 7.50 – 7.40 (m, 2H, ArCH x 2), 2.25 – 2.18 (m, 2H, H₆ x 2), 2.12 – 2.08 (m, 2H, H₃ x 2), 1.79 – 1.65 (m, 4H, H₅ x 2, H₄ x 2), 1.54 (tt, *J* = 2.0, 1.0 Hz, 3H, H₇ x 3).

¹³C NMR (101 MHz, CDCl₃) δ 201.7 (C₈), 137.1 (C₂), 134.9 (ArC), 133.1 (ArC), 132.5 (C₁), 129.4 (ArC x 2), 128.8 (ArC x 2), 31.3 (C₃), 27.6 (C₆), 22.7 (C₅), 22.4 (C₄), 21.3 (C₇).

HRMS (ESI⁺): Found [M+H]⁺ = 201.1276; C₁₄H₁₇O requires 201.1274, Δ 0.85 ppm

IR (film) ν_{max}/cm⁻¹: 2981, 2931, 1659, 1596, 1579, 1448.

(2-Pentylcyclohex-1-en-1-yl)(phenyl)methanone 138 and 1-(3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)hexan-1-one 143



2-((2*S*,6*S*)-6-Pentyltetrahydro-2*H*-pyran-2-yl)-1-phenylethan-1-one **127** (82.3 mg, 0.300 mmol, 1.0 equiv.), Al(*O**t*-Bu)₃ (74.1 mg, 0.300 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et₂O/pentane) as a yellow oil (29.1 mg, 0.113 mmol, 38% yield, 80:20 mixture of regioisomers by ¹H NMR).

¹H NMR (400 MHz, CDCl₃) δ 7.93 – 7.86 (m, 2H, major ArH x 2), 7.58 – 7.51 (m, 1H, major ArH), 7.49 – 7.42 (m, 2H, major ArH x 2), 7.36 – 7.22 (m, 3H, minor ArH x 3), 7.18 – 7.11 (m, 2H, minor ArH x 2), 2.40 (td, *J* = 6.0, 2.5 Hz, 2H, minor H₆ x 2), 2.34 (td, *J* = 6.0, 2.5 Hz, 2H, minor H₃ x 2), 2.25 – 2.17 (m, 2H, major H₆ x 2), 2.16 – 2.09 (m, 2H, major H₃ x 2), 1.95 – 1.82 (m, 4H, minor H₈ x 2, major H₇ x 2), 1.81 – 1.65 (m, 8H, minor H₅ x 2, major H₄ x 2, minor H₄ x 2, major H₅ x 2), 1.37

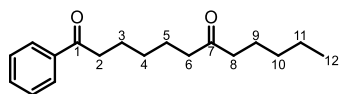
– 0.96 (m, 12H, major H₈ x 2, minor H₉ x 2, major H₉ x 2, minor H₁₀ x 2, major H₁₀ x 2, minor H₁₁ x 2), 0.74 (t, *J* = 7.5 Hz, 3H, major H₁₁ x 3), 0.69 (t, *J* = 7.5 Hz, 3H, minor H₁₂ x 3).

¹³C NMR (101 MHz, CDCl₃) δ 210.6 (minor C₇), 201.8 (major C₁₂), 142.7 (minor ArC), 140.9 (minor C₂), 138.5 (major C₂), 138.2 (minor C₁), 137.1 (major ArC), 133.1 (major ArC), 132.5 (major C₁), 129.4 (major ArC x 2), 128.7 (major ArC x 2), 128.5 (minor ArC x 2), 127.9 (minor ArC x 2), 127.8 (minor ArC), 42.6 (minor C₈), 34.9 (major C₇), 31.8 (minor C₆), 31.8 (major C₉), 31.3 (minor C₁₀), 30.3 (major C₈), 28.5 (major C₃), 27.8 (major C₆), 27.1 (minor C₃), 26.6 (minor C₉), 22.9 (minor C₄), 22.8 (major C₄), 22.7 (major C₁₀), 22.4 (major C₅), 22.3 (minor C₁₁), 22.2 (minor C₅), 13.9 (major C₁₁), 13.8 (minor C₁₂).

HRMS (ESI⁺): Found [M+H]⁺ = 257.1901; C₁₈H₂₅O requires 257.1900, Δ 0.22 ppm.

IR (film) ν_{max}/cm⁻¹: 2985, 2921, 1654, 1569, 1558, 1478.

1-Phenyldodecane-1,7-dione **140**



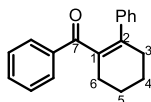
2-((2*S*,6*S*)-6-Pentyltetrahydro-2*H*-pyran-2-yl)-1-phenyl²than-1-one **131** (82.3 mg, 0.300 mmol, 1.0 equiv.), Al(*O**t*-Bu)₃ (74.1 mg, 0.300 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et₂O/pentane) as a yellow oil (21.4 mg, 0.0780 mmol, 26% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.99 – 7.92 (m, 2H, ArH x 2), 7.60 – 7.51 (m, 1H, ArH), 7.50 – 7.41 (m, 2H, ArH x 2), 2.97 (t, *J* = 7.5 Hz, 2H, H₂ x 2), 2.40 (dt, *J* = 12.5, 7.5 Hz, 4H, H₆ x 2, H₈ x 2), 1.81 – 1.68 (m, 2H, H₃ x 2), 1.68 – 1.48 (m, 4H, H₅ x 2, H₉ x 2), 1.44 – 1.18 (m, 6H, H₄ x 2, H₁₀ x 2, H₁₁ x 2), 0.90 (t, *J* = 7.5 Hz, 3H, H₁₂).

¹³C NMR (101 MHz, CDCl₃) δ 211.6 (C₁), 200.4 (C₇), 137.2 (ArC), 133.1 (ArC), 128.7 (ArC x 2), 128.2 (ArC x 2), 42.8 (C₆), 42.6 (C₈), 38.4 (C₂), 31.8 (C₁₀), 29.0 (C₄), 26.1 (C₉), 24.1 (C₃), 23.7 (C₅), 22.5 (C₁₁), 14.0 (C₁₂).

HRMS (ESI⁺): Found [M+H]⁺ = 275.2003; C₁₈H₂₇O₂ requires 275.2005, Δ -1.16 ppm.

IR (film) ν_{max}/cm⁻¹: 2934, 2869, 1654, 1708, 1684, 1450.

Phenyl(3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methanone 139

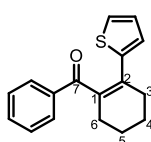
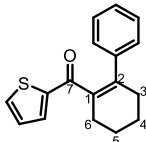
rac-1-Phenyl-2-((2*S*,6*R*)-4-phenyltetrahydro-2*H*-pyran-2-yl)ethan-1-one **132** (84.1 mg, 0.30 mmol, 1.0 equiv.), Al(*O**t*-Bu)₃ (74.1 mg, 0.30 mmol, 1.0 equiv.) and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et₂O/pentane) as a yellow oil (48.9 mg, 0.19 mmol, 62% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.71 – 7.65 (m, 2H, ArCH x 2), 7.36 – 7.29 (m, 1H, ArCH), 7.24 – 7.18 (m, 2H, ArCH x 2), 7.12 – 6.96 (m, 5H, ArCH x 5), 2.54 – 2.44 (m, 4H, H₆ x 2, H₃ x 2), 1.95 – 1.78 (m, 4H, H₅ x 2, H₄ x 2).

¹³C NMR (101 MHz, CDCl₃) δ 201.5 (C₇), 142.0 (ArC), 140.0 (ArC), 137.0 (C₂), 135.5 (ArC), 132.5 (C₁), 129.3 (ArC x 2), 128.1 (ArC x 2), 128.0 (ArC x 4), 127.3 (ArC), 31.0 (C₆), 28.2 (C₃), 23.0 (C₅), 22.2 (C₄).

HRMS (ESI⁺): Found [M+H]⁺ = 263.1431; C₁₉H₁₉O requires 263.1430, Δ 0.21 ppm.

IR (film) ν_{max}/cm⁻¹: 2980, 1650, 1597, 1579, 1447, 1383.

Phenyl(2-(thiophen-2-yl)cyclohex-1-en-1-yl)methanone 142 and (3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)(thiophen-2-yl)methanone 144**142; major****144; minor**

rac-1-Phenyl-2-((2*S*,6*R*)-6-(thiophen-2-yl)tetrahydro-2*H*-pyran-2-yl)ethan-1-one **133** (57.3 mg, 0.200 mmol, 1.0 equiv.), Al(*O**t*-Bu)₃ (49.3 mg, 0.200 mmol, 1.0 equiv.) and PhMe (0.2 M, 1.0 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et₂O/pentane) as a yellow oil (19.3 mg, 0.719 mmol, 36% yield, 80:20 mixture of regioisomers by ¹H NMR)

Major 142:

¹H NMR (400 MHz, CDCl₃) δ 7.83 – 7.76 (m, 2H, ArH x 2), 7.48 – 7.37 (m, 1H, ArH), 7.34 – 7.27 (m, 2H, ArH x 2), 7.03 (dd, *J* = 5.0, 1.0 Hz, 1H, ArH), 6.77 (dd, *J* = 3.5, 1.0 Hz, 1H, ArH), 6.69 (dd, *J*

= 5.0, 3.5 Hz, 1H, ArH), 2.58 (tt, J = 6.0, 2.5 Hz, 2H, $H_6 \times 2$), 2.44 (tt, J = 6.0, 2.5 Hz, 2H, $H_3 \times 2$), 1.94 – 1.85 (m, 2H, $H_5 \times 2$), 1.85 – 1.77 (m, 2H, $H_4 \times 2$).

^{13}C NMR (101 MHz, CDCl_3) δ 201.4 (C_7), 143.8 (ArC), 136.2 (ArC), 135.9 (C_2), 133.0 (ArC), 131.4 (C_1), 129.3 (ArC $\times 2$), 128.4 (ArC $\times 2$), 126.9 (ArC), 126.7 (ArC), 125.3 (ArC), 31.4 (C_6), 28.7 (C_3), 22.9 (C_5), 22.0 (C_4).

Minor **144**:

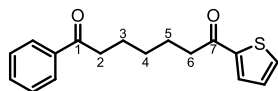
^1H NMR (400 MHz, CDCl_3) δ 7.42 (dd, J = 5.0, 1.0 Hz, 1H, ArH), 7.35 (dd, J = 4.0, 1.0 Hz, 1H, ArH), 7.20 – 7.02 (m, 5H, ArH $\times 5$), 6.88 – 6.81 (m, 1H, ArH), 2.57 – 2.44 (m, 4H, $H_6 \times 2$, $H_3 \times 2$), 1.93 – 1.76 (m, 4H, $H_5 \times 2$, $H_4 \times 2$).

^{13}C NMR (101 MHz, CDCl_3) δ 193.7 (C_7), 144.2 (ArC), 141.9 (ArC), 139.4 (C_2), 135.9 (C_1), 134.0 (ArC), 133.9 (ArC), 128.2 (ArC $\times 2$), 128.0 (ArC $\times 2$), 127.7 (ArC), 127.4 (ArC), 30.8 (C_6), 28.2 (C_3), 23.0 (C_5), 22.2 (C_4).

HRMS (ESI+): Found $[\text{M}+\text{H}]^+ = 269.0988$; $\text{C}_{17}\text{H}_{17}\text{OS}$ requires 269.0995, Δ -2.29 ppm.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2980, 1659, 1597, 1580, 1448, 1382.

1-Phenyl-7-(thiophen-2-yl)heptane-1,7-dione **145**



rac-1-Phenyl-2-((2*S*,6*R*)-6-(thiophen-2-yl)tetrahydro-2*H*-pyran-2-yl)ethan-1-one **133** (57.3 mg, 0.200 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (49.3 mg, 0.200 mmol, 1.0 equiv.) and PhMe (0.2 M, 1.0 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et_2O /pentane) as a white solid (14.9 mg, 0.0520 mmol, 26% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.98 – 7.92 (m, 2H, ArH $\times 2$), 7.71 (d, J = 4.0 Hz, 1H, ArH), 7.62 (d, J = 5.0 Hz, 1H, ArH), 7.58 – 7.52 (m, 1H, ArH), 7.50 – 7.42 (m, 2H, ArH $\times 2$), 7.16 – 7.09 (m, 1H, ArH), 3.03 – 2.88 (m, 4H, $H_6 \times 2$, $H_2 \times 2$), 1.87 – 1.74 (m, 4H, $H_3 \times 2$, $H_5 \times 2$), 1.55 – 1.43 (m, 2H, $H_4 \times 2$).

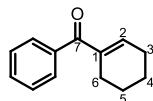
^{13}C NMR (101 MHz, CDCl_3) δ 200.4 (C_1), 193.4 (C_7), 144.6 (ArC), 137.2 (ArC), 133.5 (ArC), 133.1 (ArC), 131.9 (ArC), 128.7 (ArC $\times 2$), 128.2 (ArC), 128.2 (ArC $\times 2$), 39.3 (C_2), 38.4 (C_6), 29.1 (C_4), 24.6 (C_3), 24.1 (C_5).

HRMS (ESI⁺): Found $[M+H]^+ = 287.1093$; $C_{17}H_{19}O_2S$ requires 287.1100, Δ -2.59 ppm.

IR (film) $\nu_{\max}/\text{cm}^{-1}$: 2981, 1651, 1597, 1580, 1446, 1382.

m.p.: 42–44 °C.

Cyclohex-1-en-1-yl(phenyl)methanone **163**



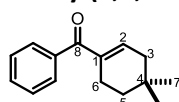
1-Phenyl-2-(tetrahydro-2*H*-pyran-2-yl)ethan-1-one **159** (61.2 mg, 0.30 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (74.1 mg, 0.30 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et_2O /pentane) as a yellow oil (50.0 mg, 0.27 mmol, 89% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.66 – 7.57 (m, 2H, ArCH x 2), 7.53 – 7.45 (m, 1H, ArCH), 7.44 – 7.36 (m, 2H, ArCH x 2), 6.58 (tt, $J = 4.0, 1.5$ Hz, 1H, H_2), 2.47 – 2.38 (m, 2H, H_6 x 2), 2.31 – 2.22 (m, 2H, H_3 x 2), 1.79 – 1.62 (m, 4H, H_5 x 2, H_4 x 2).

^{13}C NMR (101 MHz, CDCl_3) δ 198.4 (C_7), 144.2 (ArC), 138.9 (ArC, C_1), 131.4 (ArC), 129.3 (ArC), 128.1 (ArC), 26.3 (C_3), 24.1 (C_6), 22.2 (C_5), 21.8 (C_4).

The spectroscopic data matched that previously reported in the literature.^[108]

Phenyl(2,4,4-trimethylcyclohex-1-en-1-yl)methanone **164**



2-(4,4-Dimethyltetrahydro-2*H*-pyran-2-yl)-1-phenylethan-1-one **160** (70 mg, 0.30 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (74.1 mg, 0.30 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et_2O /pentane) as a colourless oil (50 mg, 0.23 mmol, 78% yield).

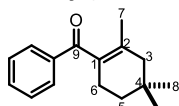
^1H NMR (400 MHz, CDCl_3) δ 7.66 – 7.59 (m, 2H, ArCH x 2), 7.53 – 7.45 (m, 1H, ArCH), 7.45 – 7.36 (m, 2H, ArCH x 2), 6.51 (tt, $J = 4.0, 1.5$ Hz, 1H, H_2), 2.46 (ttd, $J = 6.5, 2.5, 1.5$ Hz, 2H, H_6 x 2), 2.05 (dt, $J = 4.5, 2.5$ Hz, 2H, H_3 x 2), 1.50 (t, $J = 6.5$ Hz, 2H, H_5 x 2), 0.97 (s, 6H, H_7 x 6).

^{13}C NMR (101 MHz, CDCl_3) δ 198.2 (C_8), 143.2 (C_2), 138.9 (ArC), 137.6 (C_1), 131.4 (ArC), 129.2 (ArC x 2), 128.1 (ArC x 2), 40.2 (C_3), 35.0 (C_5), 28.7 (C_4), 28.3 (C_7), 21.9 (C_6).

HRMS (ESI+): Found $[\text{M}-\text{H}]^+ = 215.1431$; $\text{C}_{15}\text{H}_{19}\text{O}$ requires 215.1430, Δ 0.40 ppm

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2981, 1644, 1598, 1578, 1446, 1381.

Phenyl(2,4,4-trimethylcyclohex-1-en-1-yl)methanone **165**



rac-1-Phenyl-2-((2*S*,6*S*)-4,4,6-trimethyltetrahydro-2*H*-pyran-2-yl)ethan-1-one **161** (74.0 mg, 0.30 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (74.1 mg, 0.30 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et_2O /pentane) as a colourless oil (44.9 mg, 0.20 mmol, 66% yield).

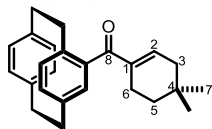
^1H NMR (400 MHz, CDCl_3) δ 7.90 – 7.83 (m, 2H, ArCH x 2), 7.59 – 7.50 (m, 1H, ArCH), 7.50 – 7.40 (m, 2H, ArCH x 2), 2.27 (th, $J = 6.0, 2.0$ Hz, 2H, H_6 x 2), 1.89 (br s, H_3 x 2), 1.52 (tt, $J = 2.0, 1.0$ Hz, 3H, H_7 x 3), 1.46 (t, $J = 6.5$ Hz, 2H, H_5 x 2), 1.01 (s, 6H, H_8 x 6).

^{13}C NMR (101 MHz, CDCl_3) δ 201.7 (C_9), 137.4 (C_2), 134.1 (ArC), 133.1 (ArC), 131.1 (C_1), 129.3 (ArC x 2), 128.8 (ArC x 2), 45.4 (C_3), 35.1 (C_5), 29.3 (C_4), 28.5 (C_8 x 2), 25.5 (C_6), 21.5 (C_7).

HRMS (ESI+): Found $[\text{M}+\text{H}]^+ = 229.1587$; $\text{C}_{16}\text{H}_{21}\text{O}$ requires 229.1587, Δ 0.15 ppm.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2951, 2915, 2866, 1661, 1596, 1580.

1,4(1,4)-Dibenzenacyclohexaphane-1²-yl(4,4-dimethylcyclohex-1-en-1-yl)methanone **179**



1-(1,4(1,4)-Dibenzenacyclohexaphane-1²-yl)-2-(4,4-dimethyltetrahydro-2*H*-pyran-2-yl)ethan-1-one **176** (109 mg, 0.301 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (74.1 mg, 0.301 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et_2O /pentane) as a yellow solid (70.6 mg, 0.205 mmol, 68% yield).

^1H NMR (400 MHz, CDCl_3) δ 6.77 (dd, $J = 8.0, 1.5$ Hz, 1H, ArCH), 6.62 – 6.51 (m, 4H, ArCH x 4), 6.45 (d, $J = 8.0$ Hz, 1H, ArCH), 6.35 (dd, $J = 8.0, 1.5$ Hz, 1H, ArCH), 6.16 (tt, $J = 4.0, 1.5$ Hz, 1H, H_2),

3.32 – 2.79 (m, 8H, Paracyclophane-CH₂ x 8), 2.57 – 2.35 (m, 2H, H₆ x 2), 1.90 (tt, J = 4.0, 2.5 Hz, 2H, H₃ x 2), 1.48 (t, J = 6.5 Hz, 2H, H₅ x 2), 0.94 (s, 3H, H_{7a} x 3), 0.92 (s, 3H, H_{7b} x 3).

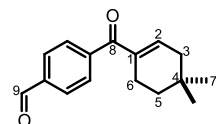
¹³C NMR (101 MHz, CDCl₃) δ 198.2 (C₈), 143.4 (C₂), 140.3 (ArC), 139.8 (ArC), 139.3 (ArC), 139.2 (ArC), 139.2 (ArC x 2), 136.8 (C₁), 135.3 (ArC), 135.2 (ArC x 2), 133.1 (ArC), 132.9 (ArC), 132.6 (ArC), 132.2 (ArC), 131.6 (ArC), 40.2 (C₃), 35.7 (Paracyclophane-CH₂), 35.3 (Paracyclophane-CH₂), 35.2 (C₅), 35.1 (Paracyclophane-CH₂), 34.9 (Paracyclophane-CH₂), 28.7 (C₄), 28.5 (C_{7a}), 28.1 (C_{7b}), 21.6 (C₆).

HRMS (ESI⁺): Found $[M+H]^+$ = 345.2214; C₂₅H₂₉O requires 345.2213, Δ 0.42 ppm.

IR (film) $\nu_{\max}/\text{cm}^{-1}$: 2980, 1638, 1462, 1383, 1262, 1152.

m.p.: 100–101 °C.

4-(4,4-Dimethylcyclohex-1-ene-1-carbonyl)benzaldehyde **180**



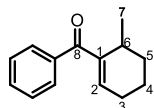
4-(2-(4,4-Dimethyltetrahydro-2H-pyran-2-yl)acetyl)benzaldehyde **177** (78.3 mg, 0.301 mmol, 1.0 equiv.), Al(O*t*-Bu)₃ (74.1 mg, 0.301 mmol, 1.0 equiv.) and dry PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et₂O/pentane) as a colourless oil (12.4 mg, 0.0512 mmol, 17% yield).

¹H NMR (400 MHz, CDCl₃) δ 10.08 (s, 1H, H₉), 7.97 – 7.89 (m, 2H, ArCH x 2), 7.76 – 7.69 (m, 2H, ArCH x 2), 6.55 – 6.50 (m, 1H, H₂), 2.52 – 2.42 (m, 2H, H₆ x 2), 2.12 – 2.04 (m, 2H, H₃ x 2), 1.51 (t, J = 6.5 Hz, 2H, H₅ x 2), 0.98 (s, 6H, H₇ x 6).

¹³C NMR (101 MHz, CDCl₃) δ 198.3 (C₈), 191.8 (C₉), 145.2 (C₂), 144.3 (ArC), 137.8 (C₁), 131.1 (ArC), 129.6 (ArC x 2), 129.5 (ArC x 2), 40.4 (C₃), 34.9 (C₅), 28.7 (C₄), 28.3 (C₇ x 2), 21.7 (C₆).

HRMS (ESI⁺): Found $[M+H]^+$ = 243.1382; C₁₆H₁₉O₂ requires 243.1380, Δ 0.65 ppm.

IR (film) $\nu_{\max}/\text{cm}^{-1}$: 2962, 2920, 1748, 1666, 1582, 1359.

(6-Methylcyclohex-1-en-1-yl)(phenyl)methanone 191

Racemic: 2-(2-Methyltetrahydro-2*H*-pyran-2-yl)-1-phenylethan-1-one **185** (65.4 mg, 0.30 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (73.9 mg, 0.30 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et_2O /pentane) as a colourless oil (50.2 mg, 0.25 mmol, 83% yield).

Enantioenriched: (*R*)-3,3'-Di(anthracen-9-yl)-[1,1'-binaphthalene]-2,2'-diol **243** (128 mg, 0.20 mmol, 1.0 equiv.), *tert*-butanol (14.8 mg, 0.20 mmol, 1.0 equiv.), *m*-xylene (1.0 mL, 0.2 M), AlMe_3 in PhMe (2.0 M, 0.1 mL, 0.20 mmol, 1.0 equiv.) and 2-(2-methyltetrahydro-2*H*-pyran-2-yl)-1-phenylethan-1-one **185** (43.7 mg, 0.20 mmol, 1.0 equiv.) were subjected to **General Procedure 6**. The title compound was afforded after purification by FCC (3% Et_2O /pentane) as a colourless oil (23.2 mg, 0.12 mmol, 58% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.73 – 7.62 (m, 2H, ArCH x 2), 7.55 – 7.47 (m, 1H, ArCH), 7.45 – 7.37 (m, 2H, ArCH x 2), 6.40 (td, J = 4.0, 1.5 Hz, 1H, H_2), 3.09 – 2.88 (m, 1H, H_6), 2.37 – 2.05 (m, 2H, H_3 x 2), 1.86– 1.50 (m, 4H, H_4 x 2, H_5 x 2), 1.07 (d, J = 7.0 Hz, 3H, H_7 x 3).

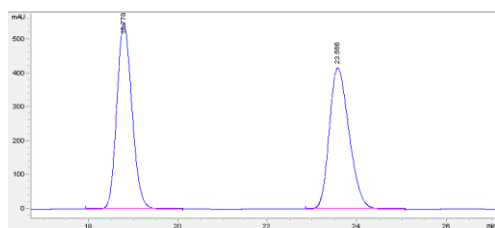
^{13}C NMR (101 MHz, CDCl_3) δ 198.6 (C_8), 144.1 (C_1), 141.8 (C_2), 139.2 (ArC), 131.7 (ArC), 129.5 (ArC x 2), 128.2 (ArC x 2), 30.2 (C_5), 28.1 (C_6), 26.3 (C_3), 19.9 (C_7), 18.6 (C_4).

HRMS (ESI⁺): Found $[\text{M}+\text{H}]^+ = 201.1273$; $\text{C}_{14}\text{H}_{17}\text{O}$ requires 201.1274 Δ -0.45 ppm.

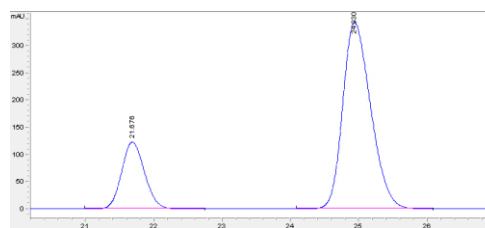
IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2933, 2870, 1649, 1598, 1579, 1447.

$\alpha_{25}^{\text{D}} = +5.34$ (c = 1.0, CHCl_3).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IG column (99.5:0.5 hexane:IPA, 1.0 mL min⁻¹, 254 nm, room temperature); t_r (minor) = 21.7 min, t_r (major) = 24.9 min, 77:23 e.r.

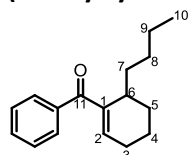


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	18.778	BB	12977.7	549.7	0.3675	50.244	0.825
2	23.566	BB	12851.6	418.5	0.4782	49.756	0.709



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	21.676	BB	2887.8	123.7	0.3645	22.794	0.857
2	24.93	BB	9781.3	344	0.4398	77.206	0.701

(6-Butylcyclohex-1-en-1-yl)(phenyl)methanone **192**



Racemic: 2-(2-Butyltetrahydro-2*H*-pyran-2-yl)-1-phenylethan-1-one **186** (52.1 mg, 0.20 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (49.3 mg, 0.20 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.0 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (5% Et_2O /pentane) as a colourless oil (32.6 mg, 0.13 mmol, 67% yield).

Enantioenriched: (*R*)-3,3'-Di(anthracen-9-yl)-[1,1'-binaphthalene]-2,2'-diol **243** (128 mg, 0.20 mmol, 1.0 equiv.), *tert*-butanol (14.8 mg, 0.20 mmol, 1.0 equiv.), *m*-xylene (1.0 mL, 0.2 M), AlMe_3 in PhMe (2.0 M, 0.1 mL, 0.20 mmol, 1.0 equiv.), and 2-(2-Butyltetrahydro-2*H*-pyran-2-yl)-1-phenylethan-1-one **186** (52.1 mg, 0.20 mmol, 1.0 equiv.) were subjected to **General Procedure 6**. The title compound was afforded after purification by FCC (3% Et_2O /pentane) as a colourless oil (31.0 mg, 0.13 mmol, 64% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.73 – 7.64 (m, 2H, ArCH x 2), 7.54 – 7.46 (m, 1H, ArCH), 7.46 – 7.36 (m, 2H, ArCH x 2), 6.38 (td, J = 4.0, 1.0 Hz, 1H, H_2), 3.08 – 2.75 (m, 1H, H_6), 2.39 – 2.02 (m, 2H, H_3 x 2), 1.80 – 1.54 (m, 4H, H_4 x 2, H_5 x 2), 1.53 – 1.39 (m, 1H, H_{7a}), 1.42 – 1.13 (m, 5H, H_{7b} , H_8 x 2, H_9 x 2), 0.85 (t, J = 7.0 Hz, 3H, H_{10} x 3).

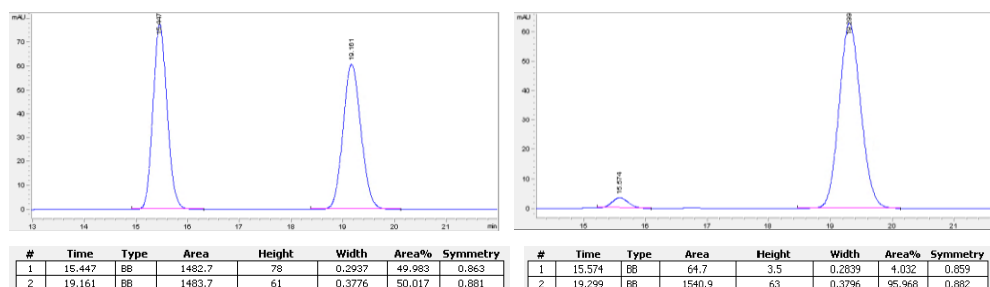
^{13}C NMR (101 MHz, CDCl_3) δ 198.6 (C_{11}), 143.7 (C_1), 141.8 (C_2), 139.0 (ArC), 131.8 (ArC), 129.6 (ArC x 2), 128.2 (ArC x 2), 33.5 (C_7), 32.8 (C_6), 29.8 (C_9), 26.4 (C_5), 26.3 (C_3), 22.9 (C_8), 18.4 (C_4), 14.2 (C_{10}).

HRMS (ESI⁺): Found $[\text{M}+\text{H}]^+ = 243.1741$; $\text{C}_{17}\text{H}_{23}\text{O}$ requires 243.1743 Δ -0.82 ppm.

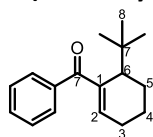
IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2980, 2970, 2931, 1650, 1598, 1579, 1447.

$\alpha_{25}^D = +9.80$ ($c = 1.0$, CHCl_3).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IG column (99.5:0.5 hexane:IPA, 1.0 mL min^{-1} , 254 nm, room temperature); t_r (minor) = 15.6 min, t_r (major) = 19.3 min, 96:4 e.r.



6-(*tert*-Butyl)cyclohex-1-en-1-yl)(phenyl)methanone **193**



Racemic: (*E*)-3-(*tert*-Butyl)-7-hydroxy-1-phenylhept-2-en-1-one **187** (78.1 mg, 0.30 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (73.9 mg, 0.30 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (3% Et_2O /Pentane) as a colourless oil (47.0 mg, 0.194 mmol, 65% yield).

Enantioenriched: (*R*)-3,3'-di(anthracen-9-yl)-[1,1'-binaphthalene]-2,2'-diol **243** (128 mg, 0.20 mmol, 1.0 equiv.), *tert*-butanol (14.8 mg, 0.20 mmol, 1.0 equiv.), *m*-xylene (1.0 mL, 0.2 M), AlMe_3 in PhMe (2.0 M, 0.1 mL, 0.20 mmol, 1.0 equiv.), and (*E*)-3-(*tert*-Butyl)-7-hydroxy-1-phenylhept-2-en-1-one **187** (52.1 mg, 0.30 mmol, 1.0 equiv.) were subjected to **General Procedure 6**. The title compound was afforded after purification by FCC (3% Et_2O /pentane) as a colourless oil (29.6 mg, 0.12 mmol, 61% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.87 – 7.81 (m, 2H, ArCH x 2), 7.57 – 7.49 (m, 1H, ArCH), 7.48 – 7.39 (m, 2H, ArCH x 2), 6.44 (ddd, $J = 4.5, 3.5, 1.0$ Hz, 1H, H_2), 3.09 – 2.95 (m, 1H, H_6), 2.32 – 2.05 (m, 2H, H_3 x 2), 2.00 – 1.78 (m, 2H, H_{4a} , H_{5a}), 1.77 – 1.60 (m, 1H, H_{5b}), 1.57 – 1.47 (m, 1H, H_{4b}), 0.93 (s, 9H, H_9 x 9).

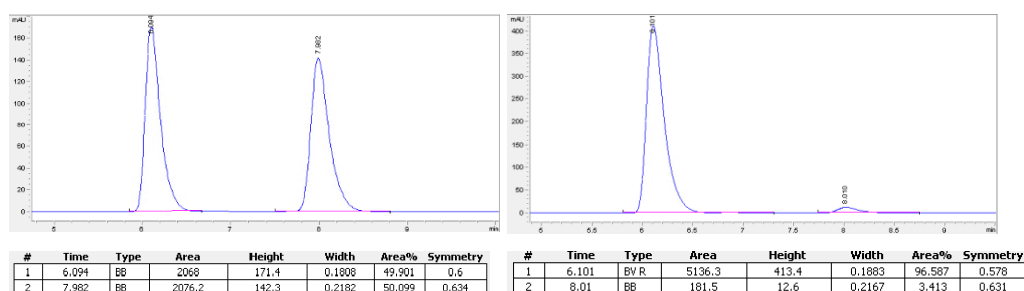
^{13}C NMR (101 MHz, CDCl_3) δ 198.9 (C_7), 142.5 (C_1), 142.0 (C_2), 137.7 (ArC), 132.2 (ArC), 130.2 (ArC x 2), 128.3 (ArC x 2), 41.9 (C_6), 35.9 (C_8), 29.5 (C_9 x 3), 25.5 (C_3), 24.5 (C_5), 20.3 (C_4).

HRMS (ESI+): Found $[\text{M}+\text{H}]^+ = 243.1741$; $\text{C}_{17}\text{H}_{23}\text{O}$ requires 243.1743 Δ -0.82 ppm.

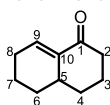
IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2980, 1655, 1598, 1579, 1448.

$\alpha_{25}^{\text{D}} = -8.20$ ($c = 1.0$, CHCl_3).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® OD column (99.5:0.5 hexane:IPA, 1.0 mL min^{-1} , 230 nm, room temperature); t_r (major) = 6.1 min, t_r (minor) = 8.0 min, 96.5:3.5 e.r.



3,4,4a,5,6,7-hexahydronaphthalen-1(2H)-one **204**



Method A: 3-(4-Hydroxybutyl)cyclohex-2-en-1-one **203** (50.5 mg, 0.300 mmol, 1 equiv.), basic alumina (Brockmann I, 153 mg, 1.50 mmol, 5.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (5% Et_2O /Pentane) as a colourless oil (5.8 mg, 0.039 mmol, 13% yield).

Method B: 3-(4-Hydroxybutyl)cyclohex-2-en-1-one **203** (50.1 mg, 0.298 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (73.4 mg, 0.298 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (5% Et_2O /Pentane) as a colourless oil (9.1 mg, 0.061 mmol, 20% yield).

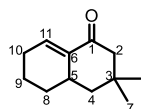
^1H NMR (400 MHz, CDCl_3) δ 6.71 – 6.62 (m, 1H, H_9), 2.49 (ddt, $J = 17.5, 4.7, 2.0$ Hz, 1H, H_8), 2.34 – 2.08 (m, 4H, H_2 x 2, H_5 , H_8), 1.96 – 1.79 (m, 3H, H_4 , H_6 , H_7), 1.77 – 1.61 (m, 2H, H_3 , H_7), 1.44 (dtdd, $J = 16.5, 13.5, 6.5, 3.0$ Hz, 1H, H_3), 1.29 – 1.09 (m, 2H, H_4 , H_6).

^{13}C NMR (101 MHz, CDCl_3) δ 201.3 (C_1), 140.1 (C_{10}), 136.0 (C_9), 40.4 (C_8), 38.0 (C_5), 31.7 (C_4 or C_6), 30.5 (C_4 or C_6), 26.3 (C_2), 22.7 (C_7), 21.6 (C_3).

HRMS (ESI+): Found $[\text{M}+\text{H}]^+ = 151.1117$; $\text{C}_{10}\text{H}_{15}\text{O}$ requires 151.1117 Δ -0.31 ppm

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3023, 2925, 1656, 1617, 1452, 1262.

3,3-Dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-1(2H)-one **208**



Method A: 3-(4-Hydroxybutyl)-5,5-dimethylcyclohex-2-en-1-one **207** (58.9 mg, 0.300 mmol, 1.0 equiv.), basic alumina (Brockmann I, 153 mg, 1.50 mmol, 5.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (5% Et_2O /Pentane) as a colourless oil (22.1 mg, 0.124 mmol, 41% yield).

Method B: 3-(4-Hydroxybutyl)-5,5-dimethylcyclohex-2-en-1-one **207** (59.2 mg, 0.302 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (74.3 mg, 0.302 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (5% Et_2O /Pentane) as a colourless oil (23.3 mg, 0.131 mmol, 44% yield).

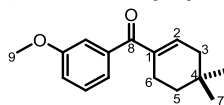
^1H NMR (400 MHz, CDCl_3) δ 6.68 – 6.61 (m, 1H, H_{11}), 2.57 – 2.41 (m, 1H, H_5), 2.34 – 2.09 (m, 4H, H_{2a} , $\text{H}_{10} \times 2$, H_{2b}), 1.91 – 1.76 (m, 2H, H_{8a} , H_{9a}), 1.71 – 1.46 (m, 2H, H_{4a} , H_{9b}), 1.35 – 1.13 (m, 2H, H_{4b} , H_{8b}), 1.02 (s, 3H, $\text{H}_{7a} \times 3$), 0.98 (s, 3H, $\text{H}_{7b} \times 3$).

^{13}C NMR (101 MHz, CDCl_3) δ 202.0 (C_1), 139.2 (C_6), 135.5 (C_{11}), 54.0 (C_2), 44.9 (C_4), 33.6 (C_5), 32.0 (C_{7a}), 32.0 (C_3), 30.5 (C_8), 26.3 (C_{7b}), 26.3 (C_{10}), 21.8 (C_9).

HRMS (ESI+): Found $[\text{M}+\text{H}]^+ = 179.1432$; $\text{C}_{12}\text{H}_{19}\text{O}$ requires 179.1430, Δ 0.86 ppm.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2955, 1689, 1621, 1423, 1368, 1316

(4,4-Dimethylcyclohex-1-en-1-yl)(3-methoxyphenyl)methanone **223**



2-(4,4-Dimethyltetrahydro-2H-pyran-2-yl)-1-(3-methoxyphenyl)ethan-1-one **222** (79 mg, 0.30 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (73 mg, 0.30 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.5 mL) were

subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a colourless oil (63 mg, 0.26 mmol, 86% yield).

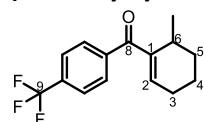
¹H NMR (400 MHz, CDCl₃) δ 7.31 (t, *J* = 7.8 Hz, 1H, ArCH), 7.21 – 7.15 (m, 2H, ArCH x 2), 7.03 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, ArCH), 6.53 (tt, *J* = 4.0, 1.5 Hz, 1H, H₂), 3.84 (s, 3H, OCH₃ x 3), 2.45 (tq, *J* = 6.5, 2.5 Hz, 2H, H₆ x 2), 2.04 (dt, *J* = 4.5, 2.5 Hz, 2H, H₃ x 2), 1.49 (t, *J* = 6.5 Hz, 2H, H₅ x 2), 0.97 (s, 6H, H₇ x 6).

¹³C NMR (101 MHz, CDCl₃) δ 197.9, 159.5, 143.3, 140.2, 137.6, 129.1, 121.8, 117.5, 114.0, 55.5, 40.2, 35.0, 28.7, 28.3, 22.0.

HRMS (ESI⁺): Found [M+H]⁺ = 245.1537; C₁₆H₂₁O₂ requires 245.1536, Δ 0.33 ppm.

IR (film) ν_{max}/cm⁻¹: 2953, 1645, 1579, 1429, 1271, 1044.

(6-Methylcyclohex-1-en-1-yl)(4-(trifluoromethyl)phenyl)methanone **249**



Racemic: 2-(2-Methyltetrahydro-2*H*-pyran-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-one **248**

(57.3 mg, 0.20 mmol, 1.0 equiv.), Al(*O**t*-Bu)₃ (49.3 mg, 0.20 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.0 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a colourless oil (38.9 mg, 0.14 mmol, 72% yield).

Enantioenriched: (*R*)-3,3'-di(anthracen-9-yl)-[1,1'-binaphthalene]-2,2'-diol **243** (128 mg, 0.20 mmol, 1.0 equiv.), *tert*-butanol (14.8 mg, 0.20 mmol, 1.0 equiv.), *m*-xylene (1.0 mL, 0.2 M), AlMe₃ in PhMe (2.0 M, 0.1 mL, 0.20 mmol, 1.0 equiv.), and 2-(2-Methyltetrahydro-2*H*-pyran-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-one **248** (57.3 mg, 0.20 mmol, 1.0 equiv.) were subjected to **General Procedure 6**. The title compound was afforded after purification by FCC (3% Et₂O/pentane) as a colourless oil (35.4 mg, 0.13 mmol, 66% yield).

¹H NMR (500 MHz, CDCl₃) δ 7.73 (d, *J* = 8.0 Hz, 2H, ArCH x 2), 7.67 (d, *J* = 8.0 Hz, 2H, ArCH x 2), 6.43 (td, *J* = 4.0, 1.0 Hz, 1H, H₂), 3.04 – 2.94 (m, 1H, H₆), 2.34 – 2.23 (m, 1H, H_{3a}), 2.22 – 2.10 (m, 1H, H_{3b}), 1.83 – 1.68 (m, 2H, H₄ x 2), 1.68 – 1.54 (m, 2H, H₅ x 2), 1.09 (d, *J* = 7.0 Hz, 3H, H₇ x 3).

^{19}F NMR (471 MHz, CDCl_3) δ -63.0.

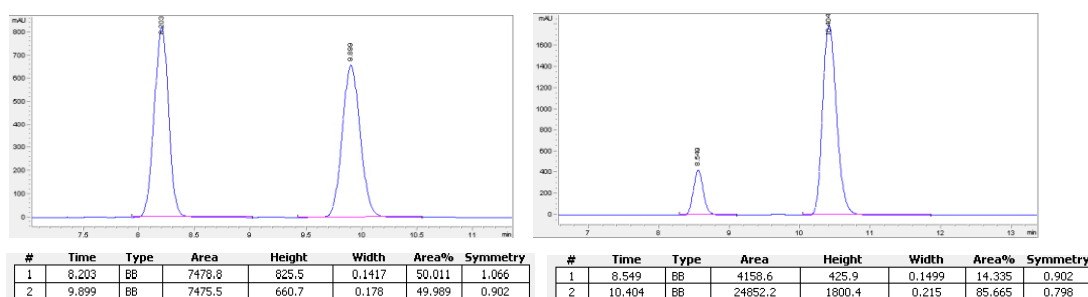
^{13}C NMR (126 MHz, CDCl_3) δ 197.1 (C_8), 144.0 (ArC), 143.9 (C_2), 142.4 (C_1), 133.1 (ArC), 129.5 (ArC x 2), 125.2 (ArC x 2), 123.9 (C_9), 29.9 (C_5), 27.8 (C_6), 26.5 (C_3), 19.9 (C_7), 18.2 (C_4).

HRMS (ESI⁺): Found $[\text{M}+\text{H}]^+ = 269.1143$; $\text{C}_{15}\text{H}_{16}\text{F}_3\text{O}$ requires 269.1148 Δ -1.60 ppm.

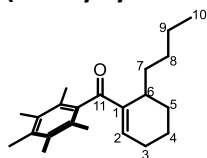
IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2937, 2873, 1654, 1579, 1512, 1457.

$\alpha_{25}^{\text{D}} = +4.84$ ($c = 1.0$, CHCl_3).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak[®] IC column (99.5:0.5 hexane:IPA, 1.0 mL min⁻¹, 230 nm, room temperature); t_r (minor) = 8.5 min, t_r (major) = 10.4 min, 86:14 e.r.



(6-Butylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone **279**



Racemic: 2-(2-Butyltetrahydro-2H-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one

268 (66.1 mg, 0.20 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (49.3 mg, 0.20 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.0 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (5% Et_2O /pentane) as a colourless oil (45.9 mg, 0.15 mmol, 73% yield).

Enantioenriched: (*R*)-3,3'-di(anthracen-9-yl)-[1,1'-binaphthalene]-2,2'-diol **243** (128 mg, 0.20 mmol, 1.0 equiv.), *tert*-butanol (14.8 mg, 0.20 mmol, 1.0 equiv.), *m*-xylene (1.0 mL, 0.2 M), AlMe_3 in PhMe (2.0 M, 0.1 mL, 0.20 mmol, 1.0 equiv.), and 2-(2-butyltetrahydro-2H-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one **268** (66.1 mg, 0.20 mmol, 1.0 equiv.) were subjected to **General Procedure 6**. The title compound was afforded after purification by FCC (3% Et_2O /pentane) as a colourless oil (41.6 mg, 0.13 mmol, 67% yield).

^1H NMR (400 MHz, CDCl_3) δ 6.46 (t, J = 4.0 Hz, 1H, H_2), 2.90 – 2.80 (m, 1H, H_6), 2.24 (s, 3H, ArCH_3), 2.21 – 2.08 (m, 8H, $\text{ArCH}_3 \times 2$, $\text{H}_3 \times 2$), 2.02 (d, J = 9.5 Hz, 6H, $\text{ArCH}_3 \times 2$), 1.92 – 1.71 (m, 2H, H_{8a} , H_{7a}), 1.70 – 1.55 (m, 2H, $\text{H}_4 \times 2$), 1.55 – 1.22 (m, 6H, H_{8b} , $\text{H}_5 \times 2$, $\text{H}_9 \times 2$, H_{7b}), 0.94 (t, J = 7.0 Hz, 3H, $\text{H}_{10} \times 3$).

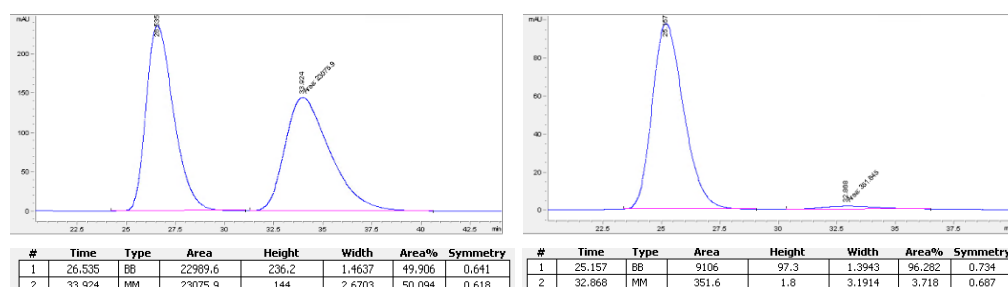
^{13}C NMR (101 MHz, CDCl_3) δ 202.9 (C_{11}), 146.1 (C_2), 145.1 (C_1), 138.4 (ArC), 134.9 (ArC), 132.6 (ArC), 132.6 (ArC), 129.4 (ArC), 129.2 (ArC), 32.7 (C_7), 31.1 (C_6), 30.2 (C_5), 26.6 (C_3), 25.0 (C_8), 22.9 (C_9), 17.5 (ArCH_3), 17.3 (ArCH_3), 17.1 (C_4), 16.8 (ArCH_3), 16.1 (ArCH_3), 16.0 (ArCH_3), 14.3 (C_{10}).

HRMS (ESI⁺): Found $[\text{M}+\text{H}]^+ = 313.2521$; $\text{C}_{22}\text{H}_{33}\text{O}$ requires 313.2526 Δ -1.55 ppm.

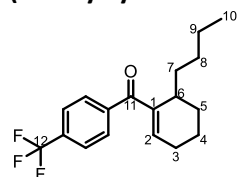
IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2928, 2859, 1650, 1631, 1601, 1456.

$\alpha_{25}^D = -8.38$ ($c = 1.0$, CHCl_3).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IG column (99.5:0.5 hexane:IPA, 1.0 mL min^{-1} , 210 nm, room temperature); t_r (major) = 25.1 min, t_r (minor) = 32.9 min, 96:4 e.r.



(6-Butylcyclohex-1-en-1-yl)(4-(trifluoromethyl)phenyl)methanone **296**



Racemic: 2-(2-Butyltetrahydro-2H-pyran-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-one **291**

(65.7 mg, 0.20 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (49.3 mg, 0.20 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.0 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (5% Et_2O /pentane) as a colourless oil (40.6 mg, 0.13 mmol, 65% yield).

Enantioenriched: (*R*)-3,3'-di(anthracen-9-yl)-[1,1'-binaphthalene]-2,2'-diol **243** (128 mg, 0.20 mmol, 1.0 equiv.), *tert*-butanol (14.8 mg, 0.20 mmol, 1.0 equiv.), *m*-xylene (1.0 mL, 0.2 M), AlMe_3

in PhMe (2.0 M, 0.1 mL, 0.20 mmol, 1.0 equiv.), and 2-(2-Butyltetrahydro-2*H*-pyran-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-one **291** (65.7 mg, 0.20 mmol, 1.0 equiv.) were subjected to **General Procedure 6**. The title compound was afforded after purification by FCC (3% Et₂O/pentane) as a colourless oil (37.2 mg, 0.12 mmol, 60% yield).

¹⁹F NMR (471 MHz, CDCl₃) δ -63.0.

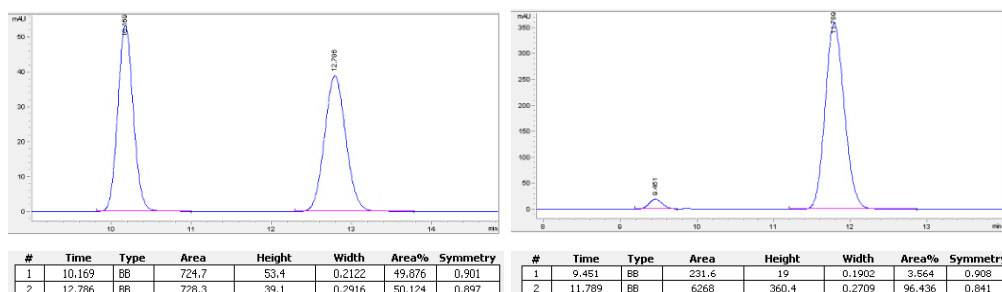
¹³C NMR (126 MHz, CDCl₃) δ 197.1 (C₁₁), 143.7 (ArC), 143.7 (C₂), 142.3 (C₁), 133.1 (ArC), 129.6 (ArC x 2), 125.2 (ArC x 2), 123.9 (C₁₂), 33.4 (C₇), 32.5 (C₆), 29.8 (C₈), 26.4 (C₃), 26.2 (C₅), 22.9 (C₉), 18.1 (C₄), 14.2 (C₁₀).

HRMS (ESI⁺): Found [M+H]⁺ = 311.1612; C₁₈H₂₂F₃O requires 311.1617 Δ -1.72 ppm.

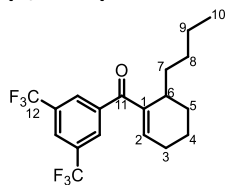
IR (film) ν_{max}/cm⁻¹: 2935, 2861, 1655, 1510, 1459, 1407.

α₂₅^D = +8.16 (c = 1.0, CHCl₃).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IC column (99.5:0.5 hexane:IPA, 1.0 mL min⁻¹, 254 nm, room temperature); t_r (minor) = 9.5 min, t_r (major) = 11.8 min, 96.5:3.5 e.r.



(3,5-Bis(trifluoromethyl)phenyl)(6-butylcyclohex-1-en-1-yl)methanone **297**



Racemic: 2-(2-Butyltetrahydro-2*H*-pyran-2-yl)-1-(4-methoxyphenyl)ethan-1-one **292** (58.1 mg, 0.20 mmol, 1.0 equiv.), Al(*O**t*-Bu)₃ (49.3 mg, 0.20 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.0 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (5% Et₂O/pentane) as a colourless oil (50.2 mg, 0.13 mmol, 66% yield).

Enantioenriched: (*R*)-3,3'-di(anthracen-9-yl)-[1,1'-binaphthalene]-2,2'-diol **243** (128 mg, 0.20 mmol, 1.0 equiv.), *tert*-butanol (14.8 mg, 0.20 mmol, 1.0 equiv.), *m*-xylene (1.0 mL, 0.2 M), AlMe₃ in PhMe (2.0 M, 0.1 mL, 0.20 mmol, 1.0 equiv.), and 2-(2-Butyltetrahydro-2*H*-pyran-2-yl)-1-(4-methoxyphenyl)ethan-1-one **292** (58.1 mg, 0.20 mmol, 1.0 equiv.) were subjected to **General Procedure 6**. The title compound was afforded after purification by FCC (3% Et₂O/pentane) as a colourless oil (34.9 mg, 0.13 mmol, 64% yield).

¹H NMR (500 MHz, CDCl₃) δ 8.07 (s, 2H, ArCH x 2), 8.00 (s, 1H, ArCH), 6.42 (t, *J* = 4.0 Hz, 1H, H₂), 2.90 (q, *J* = 4.5 Hz, 1H, H₆), 2.42 – 2.09 (m, 2H, H₃ x 2), 1.82 – 1.59 (m, 4H, H₄ x 2, H₅ x 2), 1.55 – 1.41 (m, 1H, H_{7a}), 1.41 – 1.24 (m, 3H, H_{7b}, H₈ x 2, H₉ x 2), 0.88 (t, *J* = 6.5 Hz, 3H, H₁₀).

¹⁹F NMR (471 MHz, CDCl₃) δ -62.9.

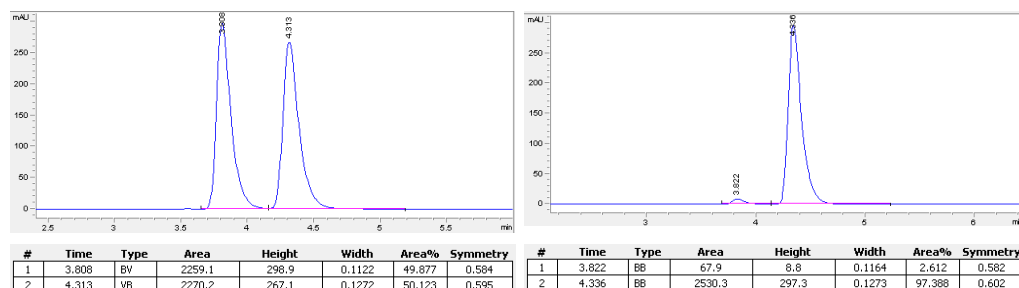
¹³C NMR (126 MHz, CDCl₃) δ 194.9 (C₁₁), 144.7 (C₂), 143.5 (C₁), 140.9 (ArC), 131.9 (ArC), 129.3 (ArC x 2), 125.0 (ArC), 123.1 (ArC), 33.4 (C₇), 32.6 (C₆), 29.9 (C₈), 26.6 (C₃), 26.0 (C₄), 22.9 (C₉), 18.0 (C₅), 14.2 (C₁₀).

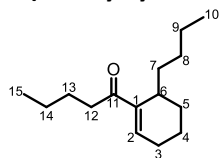
HRMS (ESI⁺): Found [M+H]⁺ = 379.1488; C₁₉H₂₁F₆O requires 379.1491 Δ -0.89 ppm.

IR (film) ν_{max}/cm⁻¹: 2980, 2889, 1731, 1661, 1461, 1382.

α_D²⁵ = +7.90 (c = 1.0, CHCl₃).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® OD column (99.5:0.5 hexane:IPA, 1.0 mL min⁻¹, 254 nm, room temperature); t_r (minor) = 3.82 min, t_r (major) = 4.34 min, 97:3 e.r.



1-(6-Butylcyclohex-1-en-1-yl)pentan-1-one 299

Racemic: 1-(2-Butyltetrahydro-2*H*-pyran-2-yl)hexan-2-one **294** (48.1 mg, 0.200 mmol, 1.0 equiv.), $\text{Al}(\text{O}t\text{-Bu})_3$ (49.3 mg, 0.200 mmol, 1.0 equiv.), and PhMe (0.2 M, 1.0 mL) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (5% Et_2O /pentane) as a colourless oil (32.2 mg, 0.145 mmol, 72% yield).

Enantioenriched: (*R*)-3,3'-di(anthracen-9-yl)-[1,1'-binaphthalene]-2,2'-diol **243** (128 mg, 0.200 mmol, 1.0 equiv.), *tert*-butanol (14.8 mg, 0.200 mmol, 1.0 equiv.), *m*-xylene (1.0 mL, 0.2 M), AlMe_3 in PhMe (2.0 M, 0.1 mL, 0.200 mmol, 1.0 equiv.), and 1-(2-butyltetrahydro-2*H*-pyran-2-yl)hexan-2-one **294** (48.1 mg, 0.200 mmol, 1.0 equiv.) were subjected to **General Procedure 6**. The title compound was afforded after purification by FCC (3% Et_2O /pentane) as a colourless oil (30.1 mg, 0.135 mmol, 68% yield).

^1H NMR (400 MHz, CDCl_3) δ 6.78 (s, 1H, H_2), 2.70 – 2.50 (m, 3H, H_6 , $\text{H}_{12} \times 2$), 2.31 – 2.10 (m, 2H, $\text{H}_3 \times 2$), 1.77 – 1.67 (m, 1H, H_{5a}), 1.67 – 1.53 (m, 4H, $\text{H}_4 \times 2$, $\text{H}_{13} \times 2$), 1.51 – 1.06 (m, 9H, H_{5b} , $\text{H}_7 \times 2$, $\text{H}_8 \times 2$, $\text{H}_9 \times 2$, $\text{H}_{14} \times 2$), 0.95 – 0.84 (m, 6H, $\text{H}_{10} \times 3$, $\text{H}_{15} \times 3$).

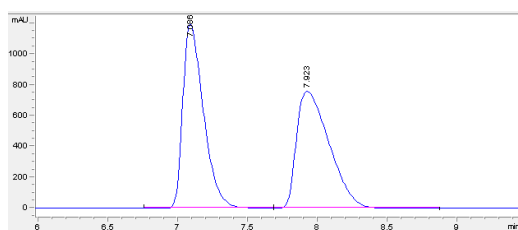
^{13}C NMR (101 MHz, CDCl_3) δ 202.1 (C_{11}), 144.4 (C_1), 138.9 (C_2), 37.5 (C_{12}), 33.3 (C_7), 31.6 (C_6), 30.1 (C_8), 27.2 (C_{13}), 26.2 (C_3), 25.4 (C_5), 22.9 (C_{14} or C_9), 22.7 (C_{14} or C_9), 17.3 (C_4), 14.2 (C_{15} or C_{10}), 14.1 (C_{15} or C_{10}).

HRMS (ESI⁺): Found $[\text{M}+\text{H}]^+ = 223.2054$; $\text{C}_{15}\text{H}_{27}\text{O}$ requires 223.2056 $\Delta -1.16$ ppm.

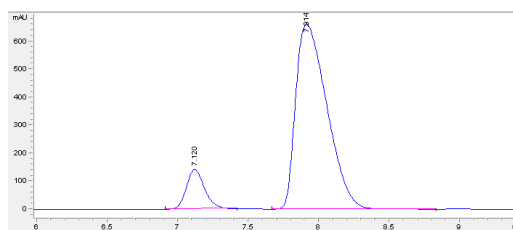
IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2957, 2933, 2872, 1671, 1464, 1381.

$\alpha_{25}^{\text{D}} = -5.86$ ($c = 1.0$, CHCl_3).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IG column (99.5:0.5 hexane:IPA, 1.0 mL min⁻¹, 230 nm, room temperature); t_r (minor) = 7.12 min, t_r (major) = 7.91 min, 11:89 e.r.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.086	BB	12230.4	1189.1	0.158	49.954	0.538
2	7.923	BB	12253	755.2	0.2573	50.046	0.452



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.12	BB	1268.4	141.8	0.1384	11.045	0.786
2	7.914	BB	10215.5	664.3	0.2454	88.955	0.506

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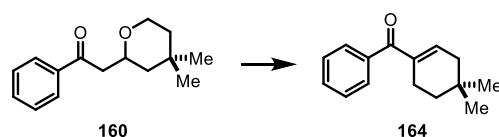
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Chapter 7: Appendices

7.1 ReactIR Experiments



Reaction monitoring by *in situ* infrared spectroscopy was conducted with a Mettler Toledo ReactIR 15 equipped with a 6.3 mm silicon composite probe. An oven-dried 5 mL volumetric flask was charged with tetrahydropyran **160** (69.7 mg, 0.600 mmol) and the volume was made up to 1 mL with *m*-xylene. An oven-dried 2-5 mL Biotage[®] microwave vial containing Al(*O**t*-Bu)₃ (73.9 mg, 0.300 mmol, 1.0 equiv.) and *m*-xylene (1 mL) was placed in an oil bath preheated to 110 °C. The silicon probe was lowered into the reaction mixture, after which stirring and data acquisition were initiated. After 15 min, 0.5 mL of the above stock solution (1.0 equiv. of **160**) was added *via* syringe. The reaction mixture was stirred for 24 h, with IR spectra recorded every 120 s.

The same experiment procedure was repeated using Al(*O**t*-Bu)₃ (36.9 mg, 0.15 mmol, 0.50 equiv.) and Al(*O**t*-Bu)₃ (18.5 mg, 0.075 mmol, 0.25 equiv.).

The following diagnostic signals were used to generate the time versus absorbance plots:

Tetrahydropyran **160**: $\nu_{\text{max}} = 1690 \text{ cm}^{-1}$ (C=O)

Cyclohexene **164**: $\nu_{\text{max}} = 1650 \text{ cm}^{-1}$ (C=O)

7.1.1 For 0.20 M Al(*O**t*-Bu)₃

Time (s)	Absorbance for tetrahydropyran 160 (1690 cm ⁻¹)	Absorbance for cyclohexene 164 (1650 cm ⁻¹)
82	0.0527929	0.0002809
202	0.0534222	0.0015429
322	0.0524752	0.0007628
442	0.0534304	0.0020109
562	0.0505568	0.0012915
682	0.0528044	0.0032791
802	0.0518307	0.0024370
922	0.0520569	0.0021679

1042	0.0517212	0.0022920
1162	0.0511634	0.0021426
1282	0.0513934	0.0042367
1402	0.0508048	0.0021244
1522	0.0487209	0.0049746
1642	0.0502359	0.0028463
1762	0.0487373	0.0030366
1882	0.0497741	0.0060137
2002	0.0487366	0.0042276
2122	0.0481818	0.0045072
2242	0.0476812	0.0058546
2362	0.0480735	0.0065629
2482	0.0479843	0.0077530
2602	0.0477664	0.0073672
2722	0.0475592	0.0067864
2842	0.0473023	0.0079329
2962	0.0475454	0.0082959
3082	0.0476129	0.0089730
3202	0.0482234	0.0079341
3322	0.0462769	0.0092096
3442	0.0468849	0.0081049
3562	0.0469448	0.0091597
3682	0.0475743	0.0116319
3802	0.0465774	0.0109551
3922	0.0458088	0.0106081
4042	0.0450267	0.0110443
4162	0.0460957	0.0128242
4282	0.0453131	0.0128549
4402	0.0446166	0.0118370
4522	0.0451124	0.0148068
4642	0.0449329	0.0129354
4762	0.0444983	0.0140681
4882	0.0439054	0.0144370
5002	0.0454497	0.0146691
5122	0.0448976	0.0146189
5242	0.0434157	0.0135202
5362	0.0422718	0.0162010
5482	0.0434162	0.0161339
5602	0.0435735	0.0167336
5722	0.0426725	0.0153032
5842	0.0431079	0.0173974
5962	0.0420259	0.0158566
6082	0.0422680	0.0180042
6202	0.0435263	0.0165869
6322	0.0421641	0.0190186
6442	0.0434303	0.0179154
6562	0.0413041	0.0183242
6682	0.0427379	0.0192694
6802	0.0417774	0.0209342

6922	0.0417834	0.0196021
7042	0.0408765	0.0201095
7162	0.0411827	0.0213502
7282	0.0412944	0.0219151
7402	0.0408504	0.0217083
7522	0.0415261	0.0224865
7642	0.0416976	0.0224383
7762	0.0420710	0.0211920
7882	0.0415564	0.0223955
8002	0.0405533	0.0234106
8122	0.0393478	0.0236865
8242	0.0388780	0.0234298
8362	0.0399788	0.0234499
8482	0.0389908	0.0230170
8602	0.0393841	0.0240770
8722	0.0388313	0.0252030
8842	0.0378495	0.0242936
8962	0.0391795	0.0240177
9082	0.0401597	0.0265553
9202	0.0387009	0.0246160
9322	0.0381250	0.0270202
9442	0.0391697	0.0279906
9562	0.0384194	0.0271873
9682	0.0375843	0.0277268
9802	0.0391489	0.0272540
9922	0.0374799	0.0283602
10042	0.0367715	0.0278620
10162	0.0376383	0.0288027
10282	0.0370364	0.0289938
10402	0.0383596	0.0289511
10522	0.0366071	0.0290863
10642	0.0366912	0.0296116
10762	0.0351629	0.0305451
10882	0.0366507	0.0296346
11002	0.0367791	0.0299362
11122	0.0379327	0.0318930
11242	0.0368600	0.0320512
11362	0.0366085	0.0316365
11482	0.0358544	0.0313956
11602	0.0354361	0.0321895
11722	0.0348065	0.0324725
11842	0.0373002	0.0322894
11962	0.0362083	0.0328636
12082	0.0357218	0.0338424
12202	0.0346093	0.0334640
12322	0.0342524	0.0331500
12442	0.0347600	0.0333533
12562	0.0353511	0.0348313
12682	0.0345324	0.0334414

12802	0.0342549	0.0357101
12922	0.0337021	0.0334068
13042	0.0340201	0.0354053
13162	0.0346910	0.0356627
13282	0.0344738	0.0378817
13402	0.0348414	0.0358942
13522	0.0337753	0.0374608
13642	0.0344280	0.0360298
13762	0.0340636	0.0354446
13882	0.0337230	0.0357265
14002	0.0336703	0.0382131
14122	0.0329823	0.0374221
14242	0.0328057	0.0377079
16062	0.0326144	0.0382047
14482	0.0337935	0.0377740
14602	0.0340496	0.0397545
16422	0.0327170	0.0384894
14842	0.0335705	0.0416470
14962	0.0324558	0.0389245
15082	0.0319299	0.0400542
15202	0.0328791	0.0388430
15322	0.0319254	0.0402969
15442	0.0298086	0.0378832
15562	0.0302297	0.0366410
15682	0.0306116	0.0378567
15802	0.0302054	0.0373739
15922	0.0312171	0.0370023
16042	0.0308309	0.0379652
16162	0.0308473	0.0383351
16282	0.0316818	0.0381721
16402	0.0306093	0.0386067
16522	0.0310088	0.0381741
16642	0.0305174	0.0384248
16762	0.0310204	0.0389739
16882	0.0308285	0.0403537
17002	0.0304573	0.0399443
17122	0.0313593	0.0402699
17242	0.0297486	0.0423231
17362	0.0309327	0.0399207
17482	0.0303201	0.0414581
17602	0.0296805	0.0404670
17722	0.0307757	0.0420533
17842	0.0310311	0.0398204
17962	0.0300470	0.0431402
18082	0.0291383	0.0421235
18202	0.0259551	0.0402332
18322	0.0161069	0.0259176
18442	0.0273698	0.0401458
18562	0.0292571	0.0440058

18682	0.0300378	0.0440597
18802	0.0295529	0.0430152
18922	0.0291313	0.0437912
19042	0.0290704	0.0446840
19162	0.0295503	0.0463620
19282	0.0285673	0.0458972
19402	0.0274558	0.0463398
19522	0.0292322	0.0467975
19642	0.0293320	0.0471610
19762	0.0293770	0.0482101
19882	0.0296050	0.0463076
20002	0.0282288	0.0471776
20122	0.0280361	0.0464669
20242	0.0270488	0.0487161
20362	0.0274108	0.0496004
20482	0.0274832	0.0475635
20602	0.0282771	0.0490471
20722	0.0276150	0.0477429
20842	0.0278805	0.0479406
20962	0.0272881	0.0485799
21082	0.0283064	0.0518580
21202	0.0270391	0.0497065
21322	0.0283226	0.0520666
21442	0.0286738	0.0500604
21562	0.0269982	0.0503866
21682	0.0283173	0.0493452
21802	0.0267242	0.0501008
21922	0.0263227	0.0502299
22042	0.0272776	0.0507051
22162	0.0272502	0.0507621
22282	0.0274758	0.0529731
22402	0.0263807	0.0520283
22522	0.0269608	0.0527505
22642	0.0265065	0.0516091
22762	0.0270865	0.0525401
22882	0.0255440	0.0518674
23002	0.0252810	0.0529968
23122	0.0265091	0.0513728
23242	0.0245235	0.0519397
23362	0.0262577	0.0530276
23482	0.0261640	0.0511713
23602	0.0255637	0.0513599
23722	0.0259784	0.0529423
23842	0.0255983	0.0524887
23962	0.0265373	0.0540748
24082	0.0264731	0.0546658
24202	0.0264776	0.0534938
24322	0.0250343	0.0548877
24442	0.0259037	0.0540597

24562	0.0259135	0.0553255
24682	0.0254319	0.0543829
24802	0.0250431	0.0545173
24922	0.0241918	0.0536380
25042	0.0241390	0.0550159
25162	0.0254912	0.0560087
25282	0.0244160	0.0559991
25402	0.0243478	0.0556932
25522	0.0242098	0.0549722
25642	0.0242844	0.0565256
25762	0.0245476	0.0547205
25882	0.0248644	0.0549505
26002	0.0255160	0.0544183
26122	0.0247070	0.0564165
26242	0.0244374	0.0588196
26362	0.0242667	0.0568887
26482	0.0254708	0.0577632
26602	0.0241425	0.0595512
26722	0.0244289	0.0571117
26842	0.0238627	0.0571394
26962	0.0243370	0.0553152
27082	0.0236241	0.0567875
27202	0.0244805	0.0587556
27322	0.0246291	0.0576388
27442	0.0238897	0.0587465
27562	0.0244625	0.0591981
27682	0.0248134	0.0596944
27802	0.0242814	0.0575473
27922	0.0243725	0.0589002
28042	0.0232963	0.0583060
28162	0.0231735	0.0592492
28282	0.0234883	0.0573630
28402	0.0231203	0.0607386
28522	0.0235139	0.0600400
28642	0.0238614	0.0591092
28762	0.0233446	0.0599527
28882	0.0226997	0.0588350
29002	0.0225015	0.0586167
29122	0.0231333	0.0604852
29242	0.0236379	0.0608945
29362	0.0217354	0.0585545
29482	0.0231731	0.0605598
29602	0.0218707	0.0608874
29722	0.0230664	0.0628068
29842	0.0230985	0.0611213
29962	0.0229660	0.0603817
30082	0.0232729	0.0607070
30202	0.0226446	0.0608221
30322	0.0228568	0.0615425

30442	0.0222573	0.0631869
30562	0.0227973	0.0619172
30682	0.0230023	0.0615983
30802	0.0212680	0.0623746
30922	0.0228745	0.0623244
31042	0.0228615	0.0621633
31162	0.0224046	0.0612512
31282	0.0223234	0.0623026
31402	0.0226131	0.0638209
31522	0.0218986	0.0633933
31642	0.0226855	0.0623472
31762	0.0215428	0.0636759
31882	0.0226729	0.0616095
32002	0.0213423	0.0624762
32122	0.0208025	0.0620794
32242	0.0207004	0.0632101
32362	0.0218394	0.0645857
32482	0.0218386	0.0610643
32602	0.0217291	0.0642323
32722	0.0215867	0.0634130
32842	0.0220962	0.0634798
32962	0.0208384	0.0634138
33082	0.0216031	0.0660572
33202	0.0216989	0.0627757
33322	0.0213666	0.0639040
33442	0.0204555	0.0650031
33562	0.0213754	0.0644499
33682	0.0224302	0.0651491
33802	0.0217752	0.0657737
33922	0.0213622	0.0669817
34042	0.0205248	0.0646812
34162	0.0214556	0.0662685
34282	0.0200112	0.0669392
34402	0.0212789	0.0662272
34522	0.0201793	0.0646203
34642	0.0210742	0.0674196
34762	0.0194225	0.0644264
34882	0.0194427	0.0645990
35002	0.0207843	0.0651191
35122	0.0199869	0.0666222
35242	0.0204038	0.0656189
35362	0.0204788	0.0665369
35482	0.0209690	0.0658484
35602	0.0209602	0.0659598
35722	0.0203388	0.0684483
35842	0.0193298	0.0680215
35962	0.0199804	0.0664586
36082	0.0206656	0.0668373
36202	0.0209175	0.0674982

36322	0.0209230	0.0687936
36442	0.0198986	0.0672000
36562	0.0197096	0.0688377
36682	0.0199442	0.0677012
36802	0.0197776	0.0691013
36922	0.0197965	0.0712085
37042	0.0195375	0.0677352
37162	0.0202119	0.0700614
37282	0.0202474	0.0697012
37402	0.0192380	0.0702532
37522	0.0198371	0.0697776
37642	0.0198478	0.0705705
37762	0.0194396	0.0703599
37882	0.0199425	0.0717578
38002	0.0184877	0.0721288
38122	0.0185472	0.0718479
38242	0.0190958	0.0727072
38362	0.0190853	0.0721697
38482	0.0190603	0.0723967
38602	0.0184567	0.0723579
38722	0.0195325	0.0738023
38842	0.0196576	0.0717696
38962	0.0183938	0.0711899
39082	0.0189708	0.0753903
39202	0.0184411	0.0745950
39322	0.0188874	0.0737286
39442	0.0181078	0.0737381
39562	0.0186629	0.0739727
39682	0.0193302	0.0754392
39802	0.0181715	0.0745912
39922	0.0184333	0.0767716
40042	0.0195770	0.0742906
40162	0.0184502	0.0763078
40282	0.0184750	0.0748917
40402	0.0185849	0.0742653
40522	0.0178517	0.0742425
40642	0.0178819	0.0757485
40762	0.0185741	0.0757380
40882	0.0182186	0.0771251
41002	0.0179519	0.0759695
41122	0.0182987	0.0756720
41242	0.0184702	0.0770109
41362	0.0182964	0.0768278
41482	0.0174449	0.0770142
41602	0.0177853	0.0782226
41722	0.0176321	0.0766080
41842	0.0172184	0.0768492
41962	0.0179180	0.0761465
42082	0.0176213	0.0761872

42202	0.0167173	0.0738561
42322	0.0170036	0.0768692
42442	0.0181518	0.0780805
42562	0.0184285	0.0779632
42682	0.0169236	0.0775387
42802	0.0178285	0.0779648
42922	0.0176470	0.0772760
43042	0.0169211	0.0744361
43162	0.0176163	0.0757809
43282	0.0171464	0.0743394
43402	0.0169332	0.0796522
43522	0.0178567	0.0778396
43642	0.0160021	0.0771699
43762	0.0169348	0.0764952
43882	0.0164502	0.0781863
44002	0.0179025	0.0779175
44122	0.0174378	0.0780199
44242	0.0177679	0.0767675
44362	0.0167658	0.0775752
44482	0.0176740	0.0778145
44602	0.0159015	0.0784757
44722	0.0172783	0.0782819
44842	0.0176134	0.0779990
44962	0.0167517	0.0759902
45082	0.0171690	0.0769336
45202	0.0172566	0.0772187
45322	0.0173619	0.0780123
45442	0.0161511	0.0794749
45562	0.0166544	0.0799266
45682	0.0172668	0.0787124
45802	0.0172160	0.0780561
45922	0.0170255	0.0797391
46042	0.0158619	0.0765328
46162	0.0168205	0.0781946
46282	0.0164351	0.0780766
46402	0.0172605	0.0775977
46522	0.0159114	0.0797115
46642	0.0163378	0.0810673
46762	0.0169562	0.0796404
46882	0.0170693	0.0807405
47002	0.0182184	0.0786178
47122	0.0149540	0.0796411
47242	0.0142263	0.0784264
47362	0.0150173	0.0797354
47482	0.0159605	0.0797712
47602	0.0162247	0.0783961
47722	0.0171055	0.0790222
47842	0.0159623	0.0780213
47962	0.0153683	0.0781183

48082	0.0167653	0.0792225
48202	0.0160041	0.0779119
48322	0.0165751	0.0795615
48442	0.0159236	0.0819686
48562	0.0154786	0.0790152
48682	0.0160025	0.0804160
48802	0.0164346	0.0802372
48922	0.0167579	0.0823297
49042	0.0151716	0.0790067
49162	0.0167520	0.0797724
49282	0.0157325	0.0796303
49402	0.0158827	0.0795694
49522	0.0168542	0.0797120
49642	0.0158462	0.0803769
49762	0.0161529	0.0806910
49882	0.0165060	0.0816109
50002	0.0162043	0.0790918
50122	0.0171996	0.0792157
50242	0.0155113	0.0795501
50362	0.0158741	0.0804996
50482	0.0159429	0.0784374
50602	0.0152989	0.0789293
50722	0.0164156	0.0811006
50842	0.0160008	0.0793557
50962	0.0151059	0.0795164
51082	0.0169037	0.0794939
51202	0.0172671	0.0805926
51322	0.0165177	0.0799397
51442	0.0158935	0.0806895
51562	0.0160675	0.0800659
51682	0.0163334	0.0785643
51802	0.0171806	0.0799032
51922	0.0157461	0.0800125
52042	0.0160513	0.0794506
52162	0.0156208	0.0814142
52282	0.0161936	0.0811291
52402	0.0155121	0.0789958
52522	0.0152295	0.0788703
52642	0.0144544	0.0784722
52762	0.0166888	0.0813811
52882	0.0149916	0.0807834
53002	0.0156295	0.0805070
53122	0.0161805	0.0791017
53242	0.0158858	0.0802291
53362	0.0159907	0.0786490
53482	0.0154220	0.0788213
53602	0.0155723	0.0817883
53722	0.0157071	0.0791222
53842	0.0155979	0.0795944

53962	0.0159247	0.0798522
54082	0.0157596	0.0818145
54202	0.0149206	0.0799088
54322	0.0146477	0.0789690
54442	0.0157272	0.0800188
54562	0.0148789	0.0783723
54682	0.0144083	0.0784383
54802	0.0159610	0.0816527
54922	0.0155694	0.0810208
55042	0.0150031	0.0807421
55162	0.0159123	0.0802512
55282	0.0155419	0.0811091
55402	0.0157221	0.0797527
55522	0.0157903	0.0810138
55642	0.0156302	0.0802657
55762	0.0156125	0.0803650
55882	0.0154144	0.0792956
56002	0.0162700	0.0823022
56122	0.0159651	0.0803299
56242	0.0155961	0.0801318
56362	0.0159080	0.0804897
56482	0.0157169	0.0815592
56602	0.0151163	0.0806008
56722	0.0159186	0.0799320
56842	0.0154277	0.0815216
56962	0.0145801	0.0791893
57082	0.0160193	0.0797921
57202	0.0142818	0.0793321
57322	0.0149927	0.0792812
57442	0.0163575	0.0802980
57562	0.0154649	0.0821345
57682	0.0142602	0.0803182
57802	0.0150065	0.0807552
57922	0.0152879	0.0805275
58042	0.0153043	0.0796426
58162	0.0164091	0.0811560
58282	0.0161392	0.0809240
58402	0.0150242	0.0812300
58522	0.0157223	0.0800698
58642	0.0150215	0.0794854
58762	0.0160966	0.0811591
58882	0.0146574	0.0793168
59002	0.0162786	0.0793740
59122	0.0149567	0.0813798
59242	0.0146617	0.0826827
59362	0.0151860	0.0811841
59482	0.0151886	0.0801779
59602	0.0163912	0.0803270
59722	0.0156518	0.0795366

59842	0.0156215	0.0815832
59962	0.0164580	0.0804190
60082	0.0162161	0.0802496
60202	0.0151532	0.0814902
60322	0.0153760	0.0780767
60442	0.0154446	0.0812399
60562	0.0150966	0.0816159
60682	0.0153497	0.0791218
60802	0.0157261	0.0809853
60922	0.0146468	0.0800075
61042	0.0150759	0.0805352
61162	0.0146976	0.0809445
61282	0.0144321	0.0797815
61402	0.0152530	0.0809006
61522	0.0151017	0.0807109
61642	0.0149077	0.0810303
61762	0.0154342	0.0810118
61882	0.0164959	0.0806868
62002	0.0158912	0.0821017
62122	0.0150770	0.0821400
62242	0.0146881	0.0812344
62362	0.0149288	0.0805741
62482	0.0151520	0.0808422
62602	0.0140306	0.0796472
62722	0.0149605	0.0819066
62842	0.0157931	0.0802847
62962	0.0156781	0.0805340
63082	0.0140033	0.0806320
63202	0.0161878	0.0802317
63322	0.0148653	0.0819405
63442	0.0146995	0.0788022
63562	0.0158452	0.0815555
63682	0.0149728	0.0827996
63802	0.0154270	0.0829357
63922	0.0151560	0.0808215
64042	0.0150831	0.0804517
64162	0.0157394	0.0806795
64282	0.0157356	0.0803900
64402	0.0142343	0.0811242
64522	0.0141091	0.0822562
64642	0.0152375	0.0806329
64762	0.0137702	0.0817984
64882	0.0151562	0.0811604
65002	0.0144967	0.0811145
65122	0.0144122	0.0807569
65242	0.0146121	0.0808682
65362	0.0144627	0.0815943
65482	0.0149407	0.0828457
65602	0.0146835	0.0804011

65722	0.0150807	0.0811372
65842	0.0148205	0.0813705
65962	0.0146584	0.0818091
66082	0.0156881	0.0842159
66202	0.0164209	0.0807601
66322	0.0152561	0.0812203
66442	0.0164430	0.0832099
66562	0.0150030	0.0828727
66682	0.0140857	0.0811308
66802	0.0152266	0.0826811
66922	0.0158347	0.0841606
67042	0.0164448	0.0817235
67162	0.0150873	0.0818553
67282	0.0156299	0.0809662
67402	0.0152401	0.0817156
67522	0.0142936	0.0824361
67642	0.0156064	0.0835898
67762	0.0154988	0.0809908
67882	0.0156509	0.0817561
68002	0.0142205	0.0826799
68122	0.0164759	0.0808815
68242	0.0148237	0.0823092
68362	0.0157386	0.0816658
68482	0.0171535	0.0842560
68602	0.0150848	0.0825699
68722	0.0145598	0.0818805
68842	0.0157504	0.0828561
68962	0.0157528	0.0826331
69082	0.0160637	0.0825638
69202	0.0159317	0.0822504
69322	0.0146939	0.0827730
69442	0.0158019	0.0834151
69562	0.0156169	0.0827218
69682	0.0140809	0.0806181
69802	0.0164868	0.0823001
69922	0.0150099	0.0832062
70042	0.0159889	0.0833959
70162	0.0140623	0.0820025
70282	0.0155423	0.0821232
70402	0.0157196	0.0835050
70522	0.0152854	0.0835085
70642	0.0155169	0.0832035
70762	0.0156894	0.0830193
70882	0.0142266	0.0828116
71002	0.0146577	0.0832924
71122	0.0160929	0.0811728
71242	0.0168832	0.0827651
71362	0.0163223	0.0826466
71482	0.0150325	0.0820994

71602	0.0164944	0.0823434
71722	0.0150452	0.0830160
71842	0.0164046	0.0827382
71962	0.0149380	0.0820576
72082	0.0157995	0.0847027
72202	0.0142136	0.0814844
72322	0.0159544	0.0831199
72442	0.0152999	0.0823915
72562	0.0146217	0.0848022
72682	0.0160164	0.0824863
72802	0.0151199	0.0817370
72922	0.0140452	0.0825272
73042	0.0160156	0.0833899
73162	0.0160678	0.0848803
73282	0.0146784	0.0826647
73402	0.0150479	0.0837413
73522	0.0148209	0.0828064
73642	0.0153105	0.0849132
73762	0.0164706	0.0838706
73882	0.0144342	0.0823599
74002	0.0144280	0.0826473
74122	0.0153988	0.0838793
74242	0.0145704	0.0829674
74362	0.0154368	0.0829398
74482	0.0160513	0.0810070
74602	0.0139322	0.0802163
74722	0.0135295	0.0788893
74842	0.0119270	0.0773227
74962	0.0116075	0.0780510
75082	0.0123660	0.0791156
75202	0.0123438	0.0779600
75322	0.0124687	0.0783817
75442	0.0122882	0.0784125
75562	0.0128666	0.0773130
75682	0.0125532	0.0781516
75802	0.0128700	0.0766780
75922	0.0140243	0.0781741
76042	0.0132663	0.0783735
76162	0.0154397	0.0783901
76282	0.0133379	0.0785045
76402	0.0160434	0.0784093
76522	0.0136173	0.0784592
76642	0.0137731	0.0794812
76762	0.0137849	0.0779883
76882	0.0139526	0.0794374
77002	0.0146969	0.0798674
77122	0.0164326	0.0798970
77242	0.0151492	0.0801783
77362	0.0164471	0.0823877

77482	0.0142213	0.0797388
77602	0.0152645	0.0808915
77722	0.0162556	0.0806924
77842	0.0144090	0.0818043
77962	0.0151573	0.0804359
78082	0.0159328	0.0819477
78202	0.0159982	0.0801243
78322	0.0142345	0.0842356
78442	0.0150154	0.0817780
78562	0.0146684	0.0832146
78682	0.0149790	0.0813094
78802	0.0146567	0.0818975
78922	0.0141823	0.0820906
79042	0.0160188	0.0839998
79162	0.0142355	0.0824201
79282	0.0157823	0.0829728
79402	0.0150557	0.0828586
79522	0.0142951	0.0820594
79642	0.0149362	0.0816060
79762	0.0157817	0.0835550
79882	0.0157327	0.0818653
80002	0.0136164	0.0845070
80122	0.0146140	0.0831548
80242	0.0157634	0.0810449
80362	0.0152788	0.0857073
80482	0.0148311	0.0842047
80602	0.0141224	0.0834044
80722	0.0167612	0.0840458
80842	0.0164555	0.0847324
80962	0.0159153	0.0861204
81082	0.0149078	0.0848900
81202	0.0153292	0.0841270
81322	0.0150530	0.0843127
81442	0.0142123	0.0848516
81562	0.0141301	0.0837139
81682	0.0156008	0.0848370
81802	0.0155158	0.0857410
81922	0.0149958	0.0829180
82042	0.0156638	0.0862855
82162	0.0158459	0.0850885
82282	0.0151604	0.0864578
82402	0.0149322	0.0827869
82522	0.0158212	0.0850230
82642	0.0156002	0.0869941
82762	0.0144150	0.0856104
82882	0.0152503	0.0856228
83002	0.0160902	0.0854387
83122	0.0150205	0.0835760
83242	0.0156360	0.0850057

83362	0.0155603	0.0854011
83482	0.0149171	0.0844970
83602	0.0161402	0.0855719
83722	0.0152412	0.0843864
83842	0.0142338	0.0850141
83962	0.0149052	0.0844542
84082	0.0151948	0.0836635
84202	0.0142036	0.0838136
84322	0.0146712	0.0848072
84442	0.0162625	0.0857372
84562	0.0161589	0.0852075
84682	0.0156932	0.0857490
84802	0.0158997	0.0848340
84922	0.0140353	0.0866212
85042	0.0156871	0.0864673
85162	0.0144823	0.0855874
85282	0.0146720	0.0854733
85402	0.0155295	0.0839988

7.1.2 For 0.10 M Al(Ot-Bu)₃

The initial absorbance at $\nu_{\max} = 1650 \text{ cm}^{-1}$ for cyclohexene **160** was found to be less than zero. To correct for this, the difference between the absorbance at $\nu_{\max} = 1650 \text{ cm}^{-1}$ for 0.20 M and 0.10 M Al(Ot-Bu)₃ was calculated ($0.0002809 + 0.0087366 = 0.0090175$), and this value was added to all absorbance measurements at $\nu_{\max} = 1650 \text{ cm}^{-1}$. This adjustment constitutes a zero-error correction.

Time (s)	Absorbance for tetrahydropyran 160 (1690 cm^{-1})	Absorbance for cyclohexene 164 (1650 cm^{-1})	Corrected absorbance for cyclohexene 164 (1650 cm^{-1})
82	0.0529716	-0.0087366	0.0002809
202	0.0530649	-0.0085772	0.0004403
322	0.0529039	-0.0093379	-0.0003204
442	0.0524422	-0.0083432	0.0006743
562	0.0512777	-0.0065863	0.0024312
682	0.0525061	-0.0070527	0.0019648
802	0.0524651	-0.0076086	0.0014089
922	0.0516097	-0.0061724	0.0028451
1042	0.0507983	-0.0058266	0.0031909
1162	0.0516253	-0.0055698	0.0034477
1282	0.0489327	-0.0065513	0.0024662
1402	0.0501556	-0.0050768	0.0039407
1522	0.0496288	-0.0039036	0.0051139
1642	0.0506826	-0.0044591	0.0045584
1762	0.0510727	-0.0035666	0.0054509
1882	0.0494053	-0.0039815	0.0050360
2002	0.0484041	-0.0030230	0.0059945

2122	0.0492529	-0.0032469	0.0057707
2242	0.0498109	-0.0026065	0.0064110
2362	0.0492930	-0.0025117	0.0065059
2482	0.0483079	-0.0011351	0.0078824
2602	0.0501164	-0.0009475	0.0080700
2722	0.0507519	-0.0016773	0.0073402
2842	0.0481342	0.0003831	0.0094006
2962	0.0485110	-0.0005404	0.0084771
3082	0.0472554	0.0016886	0.0107061
3202	0.0474591	0.0002997	0.0093172
3322	0.0487822	0.0020165	0.0110340
3442	0.0476217	0.0008770	0.0098945
3562	0.0468654	0.0022266	0.0112441
3682	0.0472150	0.0030142	0.0120317
3802	0.0468869	0.0034577	0.0124752
3922	0.0471810	0.0034581	0.0124756
4042	0.0459988	0.0039413	0.0129588
4162	0.0456362	0.0041124	0.0131299
4282	0.0461778	0.0041398	0.0131573
4402	0.0447848	0.0060034	0.0150209
4522	0.0456464	0.0064243	0.0154418
4642	0.0443850	0.0053072	0.0160247
4762	0.0455832	0.0064653	0.0154828
4882	0.0456228	0.0068243	0.0158418
5002	0.0448795	0.0065223	0.0155398
5122	0.0448995	0.0083057	0.0173232
5242	0.0434319	0.0081921	0.0172096
5362	0.0445875	0.0099486	0.0189661
5482	0.0435025	0.0079333	0.0169508
5602	0.0419420	0.0101553	0.0191728
5722	0.0424841	0.0096783	0.0186958
5842	0.0428947	0.0108327	0.0198502
5962	0.0419904	0.0107297	0.0197472
6082	0.0418294	0.0107035	0.0197210
6202	0.0415007	0.0121601	0.0211606
6322	0.0421501	0.0120640	0.0210815
6442	0.0401824	0.0134754	0.0224929
6562	0.0407893	0.0126551	0.0216726
6682	0.0399554	0.0126575	0.0216750
6802	0.0408759	0.0136243	0.0226418
6922	0.0392294	0.0146935	0.0237110
7042	0.0404763	0.0160941	0.0251116
7162	0.0395851	0.0149987	0.0240162
7282	0.0382487	0.0176095	0.0266270
7402	0.0406348	0.0172101	0.0262276
7522	0.0370224	0.0190392	0.0280567
7642	0.0376535	0.0182903	0.0273078
7762	0.0379107	0.0205949	0.0296124
7882	0.0382495	0.0217421	0.0307596

8002	0.0372455	0.0223463	0.0313638
8122	0.0376135	0.0232836	0.0323011
8242	0.0362650	0.0239330	0.0329505
8362	0.0368377	0.0255434	0.0345609
8482	0.0352123	0.0265514	0.0355689
8602	0.0364496	0.0268332	0.0358507
8722	0.0352728	0.0283607	0.0373782
8842	0.0354545	0.0283250	0.0373425
8962	0.0353665	0.0303738	0.0393913
9082	0.0349506	0.0304468	0.0394643
9202	0.0343502	0.0302853	0.0393028
9322	0.0347835	0.0316084	0.0404559
9442	0.0343886	0.0317809	0.0407984
9562	0.0346058	0.0306869	0.0397044
9682	0.0348429	0.0328110	0.0418285
9802	0.0343206	0.0339943	0.0430118
9922	0.0353362	0.0335127	0.0425302
10042	0.0340905	0.0354289	0.0444464
10162	0.0338736	0.0346434	0.0436609
10282	0.0340429	0.0337386	0.0427561
10402	0.0345898	0.0356132	0.0446307
10522	0.0330862	0.0347391	0.0437566
10642	0.0326046	0.0337664	0.0427839
10762	0.0341130	0.0355113	0.0445288
10882	0.0332096	0.0351986	0.0442161
11002	0.0349267	0.0368322	0.0458497
11122	0.0339432	0.0373750	0.0463925
11242	0.0340730	0.0377654	0.0467829
11362	0.0334416	0.0373489	0.0463664
11482	0.0327271	0.0377972	0.0468164
11602	0.0328700	0.0379842	0.0470017
11722	0.0338007	0.0369599	0.0459774
11842	0.0320287	0.0380227	0.0470402
11962	0.0306931	0.0358324	0.0448499
12082	0.0304057	0.0374535	0.0464710
12202	0.0314933	0.0361339	0.0451514
12322	0.0307880	0.0386229	0.0476404
12442	0.0309134	0.0370927	0.0461102
12562	0.0303814	0.0365800	0.0455975
12682	0.0319772	0.0380176	0.0470351
12802	0.0310593	0.0389769	0.0479944
12922	0.0306289	0.0372146	0.0462321
13042	0.0312309	0.0381668	0.0471843
13162	0.0302897	0.0383449	0.0473624
13282	0.0301452	0.0384949	0.0475124
13402	0.0306559	0.0392880	0.0483055
13522	0.0305263	0.0387279	0.0477454
13642	0.0304252	0.0395155	0.0485330
13762	0.0307547	0.0385771	0.0475946

13882	0.0313595	0.0400090	0.0490265
14002	0.0304895	0.0409349	0.0499524
14122	0.0305714	0.0394415	0.0484590
14242	0.0305574	0.0396829	0.0487004
16062	0.0305855	0.0400723	0.0490898
14482	0.0305241	0.0396015	0.0486190
14602	0.0299439	0.0395086	0.0485261
16422	0.0306279	0.0403897	0.0494072
14842	0.0296942	0.0382848	0.0473023
14962	0.0284559	0.0380568	0.0470743
15082	0.0280078	0.0374606	0.0464781
15202	0.0277217	0.0370386	0.0460561
15322	0.0282950	0.0380361	0.0470536
15442	0.0290866	0.0371866	0.0462041
15562	0.0282501	0.0366883	0.0457058
15682	0.0282517	0.0381011	0.0471186
15802	0.0290763	0.0367253	0.0457428
15922	0.0285641	0.0386806	0.0476981
16042	0.0285758	0.0372265	0.0462440
16162	0.0285225	0.0389921	0.0480096
16282	0.0286170	0.0380500	0.0470675
16402	0.0287991	0.0380850	0.0471025
16522	0.0278064	0.0389546	0.0479721
16642	0.0297750	0.0399098	0.0489273
16762	0.0288364	0.0405265	0.0495440
16882	0.0289261	0.0397484	0.0487659
17002	0.0292278	0.0412394	0.0502569
17122	0.0286116	0.0390261	0.0480436
17242	0.0274191	0.0418103	0.0508278
17362	0.0291644	0.0406339	0.0496514
17482	0.0287004	0.0403417	0.0493592
17602	0.0298133	0.0416958	0.0507133
17722	0.0278418	0.0410090	0.0500265
17842	0.0282846	0.0410616	0.0500791
17962	0.0290103	0.0416632	0.0506807
18082	0.0295759	0.0420104	0.0510279
18202	0.0286729	0.0413664	0.0503839
18322	0.0278001	0.0429565	0.0519740
18442	0.0284268	0.0417857	0.0508032
18562	0.0288516	0.0430567	0.0520742
18682	0.0286999	0.0429337	0.0519512
18802	0.0291714	0.0451157	0.0541332
18922	0.0289409	0.0423811	0.0513986
19042	0.0273463	0.0436425	0.0526600
19162	0.0274232	0.0438629	0.0528804
19282	0.0284429	0.0427898	0.0518073
19402	0.0286463	0.0446831	0.0537006
19522	0.0274451	0.0438645	0.0528820
19642	0.0282306	0.0457392	0.0547567

19762	0.0276575	0.0442486	0.0532661
19882	0.0277391	0.0440554	0.0530729
20002	0.0283314	0.0447103	0.0537278
20122	0.0277787	0.0436499	0.0526674
20242	0.0273504	0.0439086	0.0529261
20362	0.0274141	0.0454827	0.0545002
20482	0.0276586	0.0447996	0.0538171
20602	0.0283706	0.0459760	0.0549935
20722	0.0275989	0.0458916	0.0549091
20842	0.0278562	0.0458267	0.0548442
20962	0.0270950	0.0453768	0.0543943
21082	0.0276888	0.0459786	0.0549961
21202	0.0273710	0.0447735	0.0537910
21322	0.0277870	0.0456212	0.0546387
21442	0.0278692	0.0467224	0.0557399
21562	0.0279842	0.0470784	0.0560959
21682	0.0285041	0.0464614	0.0554789
21802	0.0271705	0.0463713	0.0553888
21922	0.0264103	0.0453631	0.0543806
22042	0.0277920	0.0475744	0.0565919
22162	0.0275421	0.0458693	0.0548868
22282	0.0266295	0.0475065	0.0565240
22402	0.0272536	0.0469912	0.0560087
22522	0.0272274	0.0458361	0.0548536
22642	0.0274044	0.0470531	0.0560706
22762	0.0271490	0.0464027	0.0554202
22882	0.0280157	0.0463336	0.0553511
23002	0.0270098	0.0462058	0.0552233
23122	0.0267730	0.0477726	0.0567901
23242	0.0267037	0.0459861	0.0550036
23362	0.0262438	0.0470734	0.0560909
23482	0.0273444	0.0484749	0.0574924
23602	0.0263184	0.0477038	0.0567213
23722	0.0256383	0.0483740	0.0573915
23842	0.0260701	0.0470166	0.0560341
23962	0.0264299	0.0471136	0.0561311
24082	0.0269547	0.0473708	0.0563883
24202	0.0260356	0.0476440	0.0566615
24322	0.0261228	0.0462370	0.0552545
24442	0.0254098	0.0475782	0.0565957
24562	0.0251000	0.0477826	0.0568001
24682	0.0266015	0.0483631	0.0573806
24802	0.0263208	0.0480522	0.0570697
24922	0.0253391	0.0471661	0.0561836
25042	0.0268917	0.0492413	0.0582588
25162	0.0255057	0.0474973	0.0565148
25282	0.0262994	0.0480510	0.0570685
25402	0.0259788	0.0490015	0.0580190
25522	0.0263041	0.0494357	0.0584532

25642	0.0250025	0.0488578	0.0578753
25762	0.0253572	0.0477104	0.0567279
25882	0.0252734	0.0476852	0.0567027
26002	0.0249284	0.0469694	0.0559869
26122	0.0251246	0.0487409	0.0577584
26242	0.0258585	0.0501727	0.0591902
26362	0.0266792	0.0487283	0.0577458
26482	0.0261689	0.0484442	0.0574617
26602	0.0250089	0.0486872	0.0577047
26722	0.0256186	0.0481229	0.0571404
26842	0.0263942	0.0492304	0.0582479
26962	0.0261581	0.0493055	0.0583230
27082	0.0249825	0.0484994	0.0575169
27202	0.0251697	0.0493780	0.0583955
27322	0.0256451	0.0497951	0.0588126
27442	0.0258544	0.0488641	0.0578816
27562	0.0245837	0.0504309	0.0594484
27682	0.0270810	0.0502618	0.0592793
27802	0.0245695	0.0490141	0.0580316
27922	0.0253545	0.0496510	0.0586685
28042	0.0240562	0.0485847	0.0576022
28162	0.0260500	0.0504071	0.0594246
28282	0.0255261	0.0493877	0.0584052
28402	0.0248386	0.0500058	0.0590233
28522	0.0255379	0.0492571	0.0582746
28642	0.0247429	0.0505651	0.0595826
28762	0.0250698	0.0499123	0.0589298
28882	0.0247139	0.0506617	0.0596792
29002	0.0243741	0.0491418	0.0581593
29122	0.0249099	0.0516903	0.0607078
29242	0.0257406	0.0514696	0.0604871
29362	0.0239824	0.0513871	0.0604046
29482	0.0248431	0.0504170	0.0594345
29602	0.0245591	0.0498628	0.0588803
29722	0.0255371	0.0520377	0.0610552
29842	0.0244396	0.0512463	0.0602638
29962	0.0245280	0.0500965	0.0591140
30082	0.0232128	0.0499418	0.0589593
30202	0.0249524	0.0497413	0.0587588
30322	0.0251500	0.0514172	0.0604347
30442	0.0246705	0.0516671	0.0606846
30562	0.0244661	0.0505566	0.0595741
30682	0.0245022	0.0508066	0.0598241
30802	0.0251646	0.0519593	0.0609768
30922	0.0245410	0.0502776	0.0592951
31042	0.0247358	0.0513869	0.0604044
31162	0.0244028	0.0518881	0.0609056
31282	0.0239582	0.0514029	0.0604204
31402	0.0248061	0.0516086	0.0606261

31522	0.0249396	0.0531930	0.0622105
31642	0.0251093	0.0538562	0.0628737
31762	0.0241701	0.0513754	0.0603929
31882	0.0241907	0.0512278	0.0602453
32002	0.0246469	0.0508871	0.0599046
32122	0.0242286	0.0520826	0.0611001
32242	0.0246660	0.0524278	0.0614453
32362	0.0251060	0.0516830	0.0607005
32482	0.0236019	0.0512323	0.0602498
32602	0.0245243	0.0524630	0.0614805
32722	0.0246290	0.0520926	0.0611101
32842	0.0259469	0.0528161	0.0618336
32962	0.0240793	0.0517038	0.0607213
33082	0.0240887	0.0520324	0.0610499
33202	0.0241166	0.0531794	0.0621969
33322	0.0249717	0.0515758	0.0605933
33442	0.0225001	0.0525687	0.0615862
33562	0.0250155	0.0533348	0.0623523
33682	0.0239813	0.0519128	0.0609303
33802	0.0240641	0.0523654	0.0613829
33922	0.0248577	0.0519634	0.0609809
34042	0.0232270	0.0530572	0.0620747
34162	0.0234683	0.0519261	0.0609436
34282	0.0236364	0.0523771	0.0613946
34402	0.0234738	0.0523738	0.0613913
34522	0.0234916	0.0528759	0.0618934
34642	0.0253556	0.0545858	0.0636033
34762	0.0240290	0.0530372	0.0620547
34882	0.0234793	0.0526062	0.0616237
35002	0.0233873	0.0550873	0.0641048
35122	0.0247248	0.0544487	0.0634662
35242	0.0233165	0.0533546	0.0623721
35362	0.0239413	0.0535021	0.0625196
35482	0.0235720	0.0545039	0.0635214
35602	0.0238210	0.0544289	0.0634464
35722	0.0242544	0.0540961	0.0631136
35842	0.0239805	0.0524592	0.0616467
35962	0.0238460	0.0552088	0.0642263
36082	0.0227803	0.0540175	0.0630350
36202	0.0240099	0.0546352	0.0636527
36322	0.0240438	0.0524441	0.0614616
36442	0.0240252	0.0538205	0.0628380
36562	0.0231053	0.0525067	0.0615242
36682	0.0246631	0.0531239	0.0621414
36802	0.0222680	0.0531489	0.0621664
36922	0.0234373	0.0527513	0.0617688
37042	0.0237099	0.0535039	0.0625214
37162	0.0227827	0.0537915	0.0628090
37282	0.0233837	0.0536876	0.0627051

37402	0.0236997	0.0539057	0.0629232
37522	0.0240549	0.0550356	0.0640531
37642	0.0226687	0.0536454	0.0626629
37762	0.0228714	0.0528443	0.0618618
37882	0.0245048	0.0554390	0.0644565
38002	0.0224422	0.0532549	0.0622724
38122	0.0240222	0.0548721	0.0638896
38242	0.0242538	0.0546932	0.0637107
38362	0.0237268	0.0547894	0.0638069
38482	0.0237552	0.0536894	0.0627069
38602	0.0240226	0.0554740	0.0644915
38722	0.0240895	0.0552774	0.0642949
38842	0.0229689	0.0549418	0.0639593
38962	0.0242638	0.0540225	0.0630400
39082	0.0244990	0.0541914	0.0632089
39202	0.0248492	0.0553072	0.0643247
39322	0.0229114	0.0533387	0.0623562
39442	0.0227985	0.0552688	0.0642863
39562	0.0232339	0.0537380	0.0627555
39682	0.0238998	0.0539850	0.0630025
39802	0.0231858	0.0554735	0.0644910
39922	0.0229818	0.0551206	0.0641381
40042	0.0240175	0.0542024	0.0632199
40162	0.0222619	0.0551002	0.0641177
40282	0.0230778	0.0537846	0.0628021
40402	0.0236303	0.0549668	0.0639843
40522	0.0221029	0.0537537	0.0627712
40642	0.0228635	0.0551798	0.0641973
40762	0.0229161	0.0552454	0.0642629
40882	0.0235319	0.0555089	0.0645264
41002	0.0219184	0.0551519	0.0641694
41122	0.0229234	0.0544471	0.0634646
41242	0.0234483	0.0553688	0.0643863
41362	0.0230019	0.0552618	0.0642793
41482	0.0225351	0.0542165	0.0632340
41602	0.0220325	0.0546341	0.0636516
41722	0.0226617	0.0562315	0.0652490
41842	0.0212791	0.0545073	0.0635248
41962	0.0224588	0.0548377	0.0638552
42082	0.0218248	0.0554011	0.0644186
42202	0.0232006	0.0545017	0.0635192
42322	0.0222726	0.0542382	0.0632557
42442	0.0234671	0.0562632	0.0652807
42562	0.0227786	0.0543186	0.0633361
42682	0.0222519	0.0553261	0.0643436
42802	0.0224996	0.0556010	0.0646185
42922	0.0214419	0.0555933	0.0646108
43042	0.0206905	0.0551547	0.0641722
43162	0.0226819	0.0551556	0.0641731

43282	0.0224313	0.0556614	0.0646789
43402	0.0215991	0.0546616	0.0636791
43522	0.0227960	0.0558967	0.0649142
43642	0.0212531	0.0543718	0.0633893
43762	0.0220333	0.0551949	0.0642124
43882	0.0221098	0.0553141	0.0643316
44002	0.0217022	0.0559939	0.0650114
44122	0.0225476	0.0563795	0.0653970
44242	0.0228818	0.0548061	0.0638236
44362	0.0221867	0.0556061	0.0646236
44482	0.0220021	0.0547574	0.0637749
44602	0.0223413	0.0558410	0.0648585
44722	0.0226841	0.0555245	0.0645420
44842	0.0235550	0.0563987	0.0654162
44962	0.0224854	0.0553952	0.0644127
45082	0.0222388	0.0565285	0.0655460
45202	0.0224473	0.0563259	0.0653434
45322	0.0245926	0.0572734	0.0662909
45442	0.0218423	0.0560942	0.0651117
45562	0.0220295	0.0565201	0.0655376
45682	0.0228493	0.0564135	0.0654310
45802	0.0222140	0.0559462	0.0649637
45922	0.0216836	0.0567579	0.0657754
46042	0.0223107	0.0557771	0.0647946
46162	0.0229666	0.0562023	0.0652198
46282	0.0233200	0.0572415	0.0662590
46402	0.0220416	0.0561290	0.0651465
46522	0.0216248	0.0562655	0.0652830
46642	0.0212195	0.0556907	0.0647082
46762	0.0232273	0.0569811	0.0659986
46882	0.0227111	0.0561225	0.0651400
47002	0.0202670	0.0552559	0.0642734
47122	0.0227639	0.0566532	0.0656707
47242	0.0228270	0.0564866	0.0655041
47362	0.0217068	0.0549476	0.0639651
47482	0.0215807	0.0550457	0.0640632
47602	0.0219540	0.0561224	0.0651399
47722	0.0216715	0.0569229	0.0659404
47842	0.0218194	0.0567297	0.0657472
47962	0.0239479	0.0572055	0.0662230
48082	0.0221811	0.0568659	0.0658834
48202	0.0233116	0.0568107	0.0658282
48322	0.0217197	0.0562728	0.0652903
48442	0.0217152	0.0573075	0.0663250
48562	0.0221132	0.0573555	0.0663730
48682	0.0228133	0.0581061	0.0671236
48802	0.0222045	0.0574546	0.0664721
48922	0.0227161	0.0557660	0.0647835
49042	0.0222414	0.0570409	0.0660584

49162	0.0229191	0.0563239	0.0653414
49282	0.0230320	0.0554808	0.0644983
49402	0.0216919	0.0558866	0.0649041
49522	0.0210902	0.0559050	0.0649225
49642	0.0232096	0.0584476	0.0674651
49762	0.0218155	0.0565365	0.0655540
49882	0.0218221	0.0568036	0.0658211
50002	0.0217591	0.0574076	0.0664251
50122	0.0214970	0.0569390	0.0659565
50242	0.0212101	0.0572331	0.0662506
50362	0.0206776	0.0568491	0.0658666
50482	0.0206296	0.0566118	0.0656293
50602	0.0217917	0.0565521	0.0655696
50722	0.0226595	0.0573156	0.0663331
50842	0.0211367	0.0552139	0.0642314
50962	0.0207447	0.0549070	0.0639245
51082	0.0222004	0.0573871	0.0664046
51202	0.0203875	0.0555266	0.0645441
51322	0.0210907	0.0565202	0.0655377
51442	0.0205185	0.0553924	0.0644099
51562	0.0209345	0.0570389	0.0660564
51682	0.0214223	0.0565284	0.0655459
51802	0.0212482	0.0577771	0.0667946
51922	0.0215364	0.0556964	0.0647139
52042	0.0226245	0.0577210	0.0667385
52162	0.0220742	0.0581829	0.0672004
52282	0.0211186	0.0574866	0.0665041
52402	0.0218365	0.0578642	0.0668817
52522	0.0204395	0.0559761	0.0649936
52642	0.0219707	0.0578491	0.0668666
52762	0.0215693	0.0571631	0.0661806
52882	0.0205765	0.0564461	0.0654636
53002	0.0220605	0.0577305	0.0667480
53122	0.0222848	0.0568026	0.0658201
53242	0.0227394	0.0564479	0.0654654
53362	0.0194892	0.0559258	0.0649433
53482	0.0216036	0.0579272	0.0669447
53602	0.0227025	0.0582618	0.0672793
53722	0.0211784	0.0580757	0.0670932
53842	0.0209598	0.0568328	0.0658503
53962	0.0208460	0.0561426	0.0651601
54082	0.0216944	0.0571675	0.0661850
54202	0.0199263	0.0566699	0.0656874
54322	0.0217000	0.0578117	0.0668292
54442	0.0220434	0.0593337	0.0683512
54562	0.0210904	0.0571107	0.0661282
54682	0.0212345	0.0570265	0.0660440
54802	0.0200114	0.0565140	0.0655315
54922	0.0213337	0.0582127	0.0672302

55042	0.0209694	0.0565035	0.0655210
55162	0.0201727	0.0571780	0.0661955
55282	0.0228431	0.0565271	0.0655446
55402	0.0220574	0.0561112	0.0651287
55522	0.0216055	0.0568511	0.0658686
55642	0.0213859	0.0580537	0.0670712
55762	0.0218876	0.0586892	0.0677067
55882	0.0214435	0.0585269	0.0675444
56002	0.0208321	0.0571897	0.0662072
56122	0.0208991	0.0571319	0.0661494
56242	0.0204994	0.0575646	0.0665821
56362	0.0217071	0.0594500	0.0684675
56482	0.0219924	0.0580754	0.0670929
56602	0.0210356	0.0565593	0.0655768
56722	0.0207734	0.0571962	0.0662137
56842	0.0217477	0.0584304	0.0674479
56962	0.0213847	0.0577831	0.0668006
57082	0.0215950	0.0577886	0.0668061
57202	0.0209799	0.0583649	0.0673824
57322	0.0203568	0.0585403	0.0675578
57442	0.0215719	0.0576190	0.0666365
57562	0.0218317	0.0564218	0.0654393
57682	0.0214522	0.0580840	0.0671015
57802	0.0204091	0.0570339	0.0660514
57922	0.0202959	0.0577458	0.0667633
58042	0.0205940	0.0565736	0.0655911
58162	0.0211316	0.0569770	0.0659945
58282	0.0216913	0.0584378	0.0674553
58402	0.0209070	0.0578286	0.0668461
58522	0.0213526	0.0590797	0.0680972
58642	0.0211926	0.0577929	0.0668104
58762	0.0227548	0.0579437	0.0669612
58882	0.0221070	0.0602942	0.0693117
59002	0.0220945	0.0580392	0.0670567
59122	0.0210771	0.0584846	0.0675021
59242	0.0210073	0.0577858	0.0668033
59362	0.0214481	0.0585801	0.0675976
59482	0.0211592	0.0572513	0.0662688
59602	0.0203486	0.0572899	0.0663074
59722	0.0217546	0.0587525	0.0677700
59842	0.0217888	0.0578435	0.0668610
59962	0.0213992	0.0593131	0.0683306
60082	0.0218874	0.0591786	0.0681961
60202	0.0205722	0.0579547	0.0669722
60322	0.0215008	0.0573596	0.0663771
60442	0.0214895	0.0583542	0.0673717
60562	0.0212433	0.0574899	0.0665074
60682	0.0214270	0.0592013	0.0682188
60802	0.0215525	0.0581378	0.0671553

60922	0.0215208	0.0597075	0.0687250
61042	0.0216293	0.0574354	0.0664529
61162	0.0213095	0.0572307	0.0662482
61282	0.0217474	0.0583028	0.0673203
61402	0.0200808	0.0589678	0.0679853
61522	0.0211654	0.0590234	0.0680409
61642	0.0213988	0.0584323	0.0674498
61762	0.0206471	0.0580305	0.0670480
61882	0.0207789	0.0592543	0.0682718
62002	0.0207828	0.0593078	0.0683253
62122	0.0211102	0.0593421	0.0683596
62242	0.0202286	0.0607133	0.0697308
62362	0.0188851	0.0583581	0.0673756
62482	0.0207208	0.0582677	0.0672852
62602	0.0216026	0.0583640	0.0673815
62722	0.0218036	0.0579506	0.0669681
62842	0.0215014	0.0587027	0.0677202
62962	0.0214094	0.0607510	0.0697685
63082	0.0213352	0.0598635	0.0688810
63202	0.0214812	0.0595160	0.0685335
63322	0.0201962	0.0594889	0.0685064
63442	0.0217506	0.0586983	0.0677158
63562	0.0214581	0.0586667	0.0676842
63682	0.0215451	0.0572673	0.0662848
63802	0.0210076	0.0596087	0.0686262
63922	0.0202718	0.0587155	0.0677330
64042	0.0210955	0.0578897	0.0669072
64162	0.0200778	0.0588100	0.0678275
64282	0.0210539	0.0594870	0.0685045
64402	0.0209755	0.0606611	0.0696786
64522	0.0207019	0.0600907	0.0691082
64642	0.0215907	0.0600164	0.0690339
64762	0.0217051	0.0605227	0.0695402
64882	0.0204733	0.0590854	0.0681029
65002	0.0206529	0.0612109	0.0702284
65122	0.0212002	0.0603568	0.0693743
65242	0.0208128	0.0602214	0.0692389
65362	0.0200653	0.0586736	0.0676911
65482	0.0203339	0.0586226	0.0676401
65602	0.0226579	0.0594140	0.0684315
65722	0.0207234	0.0588453	0.0678628
65842	0.0212492	0.0601340	0.0691515
65962	0.0216651	0.0599229	0.0689404
66082	0.0210357	0.0602257	0.0692432
66202	0.0214544	0.0601656	0.0691831
66322	0.0218059	0.0602469	0.0692644
66442	0.0215642	0.0595574	0.0685749
66562	0.0231139	0.0611763	0.0701938
66682	0.0208471	0.0608499	0.0698674

66802	0.0202195	0.0596247	0.0686422
66922	0.0210972	0.0603035	0.0693210
67042	0.0198857	0.0583916	0.0674091
67162	0.0218813	0.0612687	0.0702862
67282	0.0216475	0.0613400	0.0703575
67402	0.0206848	0.0602224	0.0692399
67522	0.0222328	0.0598312	0.0688487
67642	0.0208283	0.0614111	0.0704286
67762	0.0200710	0.0578562	0.0668737
67882	0.0204715	0.0586274	0.0676449
68002	0.0216075	0.0607153	0.0697328
68122	0.0199427	0.0591198	0.0681373
68242	0.0201739	0.0587703	0.0677878
68362	0.0208436	0.0600760	0.0690935
68482	0.0217287	0.0597332	0.0687507
68602	0.0203017	0.0605221	0.0695396
68722	0.0218273	0.0598473	0.0688648
68842	0.0205058	0.0605005	0.0695180
68962	0.0208961	0.0594269	0.0684444
69082	0.0213917	0.0598000	0.0688175
69202	0.0210447	0.0598316	0.0688491
69322	0.0214970	0.0602095	0.0692270
69442	0.0200477	0.0592435	0.0682610
69562	0.0218227	0.0607341	0.0697516
69682	0.0204372	0.0600583	0.0690758
69802	0.0212502	0.0599742	0.0689917
69922	0.0217042	0.0599022	0.0689197
70042	0.0206449	0.0599883	0.0690058
70162	0.0207393	0.0596201	0.0686376
70282	0.0216477	0.0595204	0.0685379
70402	0.0204801	0.0599429	0.0689604
70522	0.0208295	0.0596001	0.0686176
70642	0.0213841	0.0609688	0.0699863
70762	0.0206246	0.0602925	0.0693100
70882	0.0204259	0.0592075	0.0682250
71002	0.0215662	0.0598396	0.0688571
71122	0.0196174	0.0589925	0.0680100
71242	0.0191124	0.0589673	0.0679848
71362	0.0200769	0.0592875	0.0683050
71482	0.0197524	0.0594818	0.0684993
71602	0.0207112	0.0598226	0.0688401
71722	0.0200498	0.0607020	0.0697195
71842	0.0195404	0.0594537	0.0684712
71962	0.0209604	0.0586164	0.0676339
72082	0.0201879	0.0594310	0.0684485
72202	0.0209642	0.0603762	0.0693937
72322	0.0212849	0.0601295	0.0691640
72442	0.0212017	0.0597939	0.0688114
72562	0.0220971	0.0601821	0.0691996

72682	0.0196414	0.0573512	0.0663687
72802	0.0200091	0.0571290	0.0661465
72922	0.0190262	0.0572317	0.0662492
73042	0.0195289	0.0590580	0.0680755
73162	0.0207914	0.0583850	0.0674025
73282	0.0202368	0.0575599	0.0665774
73402	0.0200723	0.0579632	0.0669807
73522	0.0193803	0.0587819	0.0677994
73642	0.0217998	0.0587902	0.0678077
73762	0.0202272	0.0591917	0.0682092
73882	0.0211621	0.0588995	0.0679170
74002	0.0204241	0.0594428	0.0684603
74122	0.0210366	0.0607185	0.0697360
74242	0.0187881	0.0589460	0.0679635
74362	0.0203477	0.0579729	0.0669904
74482	0.0206890	0.0586989	0.0677164
74602	0.0203090	0.0602489	0.0692664
74722	0.0215070	0.0612992	0.0703167
74842	0.0205188	0.0597376	0.0687551
74962	0.0216114	0.0597511	0.0687686
75082	0.0210899	0.0617365	0.0707540
75202	0.0198409	0.0607853	0.0698028
75322	0.0207309	0.0605120	0.0695295
75442	0.0205885	0.0601708	0.0691883
75562	0.0210931	0.0615645	0.0705820
75682	0.0208199	0.0594785	0.0684960
75802	0.0215653	0.0617850	0.0708025
75922	0.0217686	0.0615358	0.0705533
76042	0.0211445	0.0623922	0.0714097
76162	0.0205520	0.0612585	0.0702760
76282	0.0211622	0.0608471	0.0698646
76402	0.0196176	0.0601051	0.0691226
76522	0.0219499	0.0612077	0.0702252
76642	0.0199053	0.0604162	0.0694337
76762	0.0221294	0.0606100	0.0696275
76882	0.0214102	0.0619927	0.0710102
77002	0.0216185	0.0622779	0.0712954
77122	0.0209161	0.0603220	0.0693395
77242	0.0230306	0.0627133	0.0717308
77362	0.0211286	0.0612901	0.0703076
77482	0.0206048	0.0607910	0.0698085
77602	0.0206908	0.0606758	0.0696933
77722	0.0219616	0.0612216	0.0702391
77842	0.0210570	0.0613860	0.0704035
77962	0.0215131	0.0615014	0.0705189
78082	0.0208687	0.0616475	0.0704950
78202	0.0205928	0.0617929	0.0708104
78322	0.0196495	0.0606118	0.0696293
78442	0.0212767	0.0598638	0.0688813

78562	0.0218510	0.0607870	0.0698045
78682	0.0216197	0.0612150	0.0702325
78802	0.0207914	0.0603288	0.0693463
78922	0.0206907	0.0605375	0.0695550
79042	0.0210196	0.0621917	0.0712092
79162	0.0206793	0.0607527	0.0697702
79282	0.0206455	0.0610883	0.0701058
79402	0.0215608	0.0621246	0.0711421
79522	0.0208687	0.0613898	0.0704073
79642	0.0200334	0.0618752	0.0708927
79762	0.0215130	0.0618071	0.0708246
79882	0.0211585	0.0615463	0.0705638
80002	0.0211687	0.0615636	0.0705811
80122	0.0208858	0.0619985	0.0710160
80242	0.0210259	0.0635539	0.0725714
80362	0.0218532	0.0629423	0.0719598
80482	0.0217115	0.0624559	0.0716434
80602	0.0200895	0.0618909	0.0709084
80722	0.0211989	0.0604903	0.0695078
80842	0.0205417	0.0611400	0.0701575
80962	0.0207926	0.0617557	0.0707732
81082	0.0213119	0.0624112	0.0714287
81202	0.0216160	0.0632075	0.0722250
81322	0.0208314	0.0626929	0.0717104
81442	0.0218200	0.0618891	0.0709066
81562	0.0200998	0.0634412	0.0724587
81682	0.0211767	0.0620850	0.0711025
81802	0.0203602	0.0612832	0.0703007
81922	0.0203659	0.0618225	0.0708400
82042	0.0203472	0.0616357	0.0706532
82162	0.0202990	0.0639971	0.0730146
82282	0.0211923	0.0625087	0.0715262
82402	0.0218085	0.0619833	0.0710008
82522	0.0216788	0.0620369	0.0710544
82642	0.0202095	0.0631650	0.0721825
82762	0.0203556	0.0604179	0.0694354
82882	0.0200220	0.0616684	0.0706859
83002	0.0205815	0.0609473	0.0699648
83122	0.0208488	0.0620045	0.0710220
83242	0.0210094	0.0605317	0.0695492
83362	0.0213239	0.0637650	0.0727825
83482	0.0215172	0.0635830	0.0726005
83602	0.0224246	0.0639353	0.0729528
83722	0.0226811	0.0641731	0.0731906
83842	0.0216524	0.0639763	0.0729938
83962	0.0198986	0.0618312	0.0708487
84082	0.0201148	0.0632953	0.0723128
84202	0.0205407	0.0626232	0.0716407
84322	0.0226172	0.0645711	0.0735886

84442	0.0208737	0.0641729	0.0731904
84562	0.0211162	0.0641081	0.0731256
84682	0.0212299	0.0640699	0.0730874
84802	0.0213201	0.0632557	0.0722732
84922	0.0208079	0.0624115	0.0714290
85042	0.0205569	0.0633112	0.0723287
85162	0.0216047	0.0617424	0.0707599
85282	0.0209094	0.0623924	0.0714099
85402	0.0217630	0.0638917	0.0729092

7.1.3 For 0.05 M Al(Ot-Bu)₃

The initial absorbance at $\nu_{\max} = 1690 \text{ cm}^{-1}$ for tetrahydropyran **160** was found to differ significantly from the values obtained with 0.20 M and 0.05 M Al(Ot-Bu)₃. To correct for this, the difference between the absorbance at $\nu_{\max} = 1690 \text{ cm}^{-1}$ for 0.20 M and 0.05 M Al(Ot-Bu)₃ was calculated ($0.0817224 - 0.0527929 = 0.0289295$), and this value was subtracted from all absorbance measurements at $\nu_{\max} = 1690 \text{ cm}^{-1}$. This adjustment constitutes a zero-error correction.

The initial absorbance at $\nu_{\max} = 1650 \text{ cm}^{-1}$ for cyclohexene **164** was also found to be non-zero. To correct for this, the difference between the absorbance at $\nu_{\max} = 1650 \text{ cm}^{-1}$ for 0.20 M and 0.05 M Al(Ot-Bu)₃ was calculated ($0.0354672 - 0.0002809 = 0.0351863$), and this value was subtracted from all absorbance measurements at $\nu_{\max} = 1650 \text{ cm}^{-1}$. This adjustment constitutes a zero-error correction.

Time (s)	Absorbance for tetrahydropyran 160 (1690 cm^{-1})	Corrected absorbance for tetrahydropyran 160 (1690 cm^{-1})	Absorbance for cyclohexene 164 (1650 cm^{-1})	Corrected absorbance for cyclohexene 164 (1650 cm^{-1})
82	0.0817224	0.0527929	0.0354672	0.0002809
202	0.0830766	0.0541641	0.0368105	0.0016242
322	0.0828583	0.0539288	0.0370964	0.0019101
442	0.0828200	0.0538905	0.0377165	0.0025302
562	0.0818733	0.0529438	0.0368223	0.0016360
682	0.0838919	0.0549624	0.0383462	0.0031599
802	0.0810798	0.0521503	0.0379365	0.0027502
922	0.0824881	0.0535586	0.0376531	0.0024668
1042	0.0819232	0.0529937	0.0362257	0.0010394
1162	0.0811979	0.0522684	0.0370896	0.0019033
1282	0.0819993	0.0530698	0.0372575	0.0020712

1402	0.0807475	0.0518180	0.0390408	0.0038545
1522	0.0805951	0.0516656	0.0394911	0.0043048
1642	0.0816688	0.0527393	0.0385278	0.0033415
1762	0.0805451	0.0516156	0.0382203	0.0030340
1882	0.0815881	0.0526586	0.0384381	0.0032518
2002	0.0823975	0.0534680	0.0397365	0.0045502
2122	0.0814675	0.0525380	0.0395094	0.0043231
2242	0.0805782	0.0516487	0.0396095	0.0044232
2362	0.0805322	0.0516027	0.0390629	0.0038766
2482	0.0803294	0.0513999	0.0392112	0.0040249
2602	0.0799601	0.0510306	0.0404208	0.0052345
2722	0.0793487	0.0504192	0.0396221	0.0044358
2842	0.0799824	0.0510529	0.0396475	0.0044612
2962	0.0804221	0.0514926	0.0402637	0.0050774
3082	0.0797525	0.0508230	0.0402314	0.0050451
3202	0.0794080	0.0504785	0.0396636	0.0044773
3322	0.0784744	0.0495449	0.0386403	0.0034540
3442	0.0780467	0.0491172	0.0395103	0.0043240
3562	0.0798505	0.0509210	0.0403729	0.0051866
3682	0.0786411	0.0497116	0.0404555	0.0052692
3802	0.0785940	0.0496645	0.0409363	0.0057500
3922	0.0794454	0.0505159	0.0407366	0.0055503
4042	0.0783798	0.0494503	0.0409399	0.0057536
4162	0.0777435	0.0488140	0.0407379	0.0055516
4282	0.0785411	0.0496116	0.0417524	0.0065661
4402	0.0778425	0.0489130	0.0424870	0.0073007
4522	0.0783316	0.0494021	0.0428244	0.0076381
4642	0.0778899	0.0489604	0.0433584	0.0081721
4762	0.0773666	0.0484371	0.0425791	0.0073928
4882	0.0793111	0.0503816	0.0429812	0.0077949
5002	0.0784027	0.0494732	0.0446909	0.0095046
5122	0.0779019	0.0489724	0.0446316	0.0094453
5242	0.0776996	0.0487701	0.0442499	0.0090636
5362	0.0769207	0.0479912	0.0445212	0.0093349
5482	0.0777592	0.0488297	0.0440413	0.0088550
5602	0.0785400	0.0496105	0.0447879	0.0096016
5722	0.0778416	0.0489121	0.0451702	0.0099839
5842	0.0774324	0.0485029	0.0445519	0.0093656
5962	0.0775496	0.0486201	0.0457605	0.0105742
6082	0.0776381	0.0487086	0.0454699	0.0102836
6202	0.0762262	0.0472967	0.0467737	0.0115874
6322	0.0784707	0.0495412	0.0465441	0.0113578
6442	0.0768331	0.0479036	0.0464516	0.0112653
6562	0.0777770	0.0488475	0.0474986	0.0123123
6682	0.0772585	0.0483290	0.0478594	0.0126731
6802	0.0774649	0.0485354	0.0481613	0.0129750
6922	0.0783825	0.0494530	0.0479241	0.0127378
7042	0.0780507	0.0491212	0.0477691	0.0125828
7162	0.0773135	0.0483840	0.0483751	0.0131888

7282	0.0787632	0.0498337	0.0490905	0.0139042
7402	0.0774513	0.0485218	0.0495466	0.0160603
7522	0.0787469	0.0498174	0.0492840	0.0140977
7642	0.0775591	0.0486296	0.0510707	0.0158844
7762	0.0774491	0.0485196	0.0486942	0.0135079
7882	0.0773274	0.0483979	0.0497290	0.0145427
8002	0.0771077	0.0481782	0.0507502	0.0155639
8122	0.0762435	0.0473140	0.0493203	0.0141340
8242	0.0771841	0.0482546	0.0512632	0.0160769
8362	0.0758747	0.0469452	0.0523009	0.0171146
8482	0.0762581	0.0473286	0.0494680	0.0142817
8602	0.0766502	0.0477207	0.0511548	0.0159685
8722	0.0765686	0.0476391	0.0508214	0.0156351
8842	0.0781456	0.0492161	0.0524021	0.0172158
8962	0.0766774	0.0477479	0.0538116	0.0186253
9082	0.0773124	0.0483829	0.0510339	0.0158476
9202	0.0771447	0.0482152	0.0520354	0.0168491
9322	0.0768918	0.0479623	0.0525109	0.0173246
9442	0.0776107	0.0486812	0.0529479	0.0177616
9562	0.0770720	0.0481425	0.0530850	0.0178987
9682	0.0775446	0.0486151	0.0536447	0.0184584
9802	0.0777241	0.0487946	0.0540858	0.0188995
9922	0.0772258	0.0482963	0.0545436	0.0193573
10042	0.0767017	0.0477722	0.0543475	0.0191612
10162	0.0769365	0.0480070	0.0546721	0.0194858
10282	0.0782188	0.0492893	0.0548632	0.0196769
10402	0.0765902	0.0476607	0.0542416	0.0190553
10522	0.0775880	0.0486585	0.0559220	0.0207357
10642	0.0786617	0.0497322	0.0555050	0.0203187
10762	0.0780369	0.0491074	0.0548989	0.0197126
10882	0.0771551	0.0482256	0.0556503	0.0204640
11002	0.0778063	0.0488768	0.0548385	0.0196522
11122	0.0775052	0.0485757	0.0557870	0.0206007
11242	0.0776420	0.0487125	0.0552586	0.0200723
11362	0.0773618	0.0484323	0.0572373	0.0220510
11482	0.0778769	0.0489474	0.0557462	0.0205599
11602	0.0777428	0.0488133	0.0571896	0.0220033
11722	0.0776895	0.0487600	0.0554725	0.0202862
11842	0.0775098	0.0485803	0.0549013	0.0197150
11962	0.0770783	0.0481488	0.0566225	0.0216062
12082	0.0771555	0.0482260	0.0570691	0.0218828
12202	0.0772851	0.0483556	0.0572811	0.0220948
12322	0.0773999	0.0484704	0.0581465	0.0229602
12442	0.0775199	0.0485904	0.0574158	0.0222295
12562	0.0783846	0.0494551	0.0565961	0.0214098
12682	0.0773929	0.0484634	0.0562150	0.0210287
12802	0.0769708	0.0480413	0.0575833	0.0223970
12922	0.0774539	0.0485244	0.0568562	0.0216699
13042	0.0776328	0.0487033	0.0575757	0.0223894

13162	0.0772396	0.0483101	0.0579191	0.0227328
13282	0.0784500	0.0495205	0.0580227	0.0228364
13402	0.0776510	0.0487215	0.0570265	0.0218402
13522	0.0775021	0.0485726	0.0570683	0.0218820
13642	0.0781170	0.0491875	0.0578320	0.0226457
13762	0.0772575	0.0483280	0.0583381	0.0231518
13882	0.0775179	0.0485884	0.0581064	0.0229201
14002	0.0772663	0.0483368	0.0598209	0.0246346
14122	0.0775274	0.0485979	0.0574331	0.0222468
14242	0.0771135	0.0481840	0.0585252	0.0233389
16062	0.0767304	0.0478009	0.0573127	0.0221264
14482	0.0766960	0.0477665	0.0581513	0.0229650
14602	0.0762708	0.0473413	0.0592340	0.0240477
16422	0.0773912	0.0484617	0.0583803	0.0231940
14842	0.0778784	0.0489489	0.0577962	0.0226099
14962	0.0783252	0.0493957	0.0586629	0.0234766
15082	0.0766892	0.0477597	0.0583980	0.0232117
15202	0.0778642	0.0489347	0.0598393	0.0246530
15322	0.0778322	0.0489027	0.0588376	0.0236513
15442	0.0771299	0.0482004	0.0581831	0.0229968
15562	0.0766313	0.0477018	0.0587945	0.0236082
15682	0.0787050	0.0497755	0.0583032	0.0231169
15802	0.0775160	0.0485865	0.0581391	0.0229528
15922	0.0778854	0.0489559	0.0585941	0.0234078
16042	0.0767601	0.0478306	0.0591196	0.0239333
16162	0.0765970	0.0476675	0.0582743	0.0230880
16282	0.0774798	0.0485503	0.0574797	0.0222934
16402	0.0762484	0.0473189	0.0598153	0.0246290
16522	0.0769707	0.0480412	0.0593967	0.0242104
16642	0.0770981	0.0481686	0.0593283	0.0241420
16762	0.0759255	0.0469960	0.0594080	0.0242217
16882	0.0761266	0.0471971	0.0583857	0.0231994
17002	0.0766046	0.0476751	0.0594413	0.0242550
17122	0.0771170	0.0481875	0.0583144	0.0231281
17242	0.0756121	0.0466826	0.0588415	0.0236552
17362	0.0765088	0.0475793	0.0587752	0.0235889
17482	0.0767060	0.0477765	0.0590425	0.0238562
17602	0.0769387	0.0480092	0.0595054	0.0243191
17722	0.0768164	0.0478852	0.0587628	0.0235765
17842	0.0765499	0.0476204	0.0591503	0.0239640
17962	0.0769736	0.0480441	0.0589157	0.0237294
18082	0.0768463	0.0479168	0.0598776	0.0246913
18202	0.0756034	0.0466739	0.0594824	0.0242961
18322	0.0766632	0.0477337	0.0592170	0.0240307
18442	0.0751357	0.0462062	0.0592256	0.0240393
18562	0.0762469	0.0473174	0.0588021	0.0236158
18682	0.0759261	0.0469966	0.0595791	0.0243928
18802	0.0763806	0.0474511	0.0593479	0.0241616
18922	0.0765512	0.0476217	0.0581743	0.0229880

19042	0.0761032	0.0471737	0.0573006	0.0221160
19162	0.0755663	0.0466368	0.0590791	0.0238928
19282	0.0760771	0.0471646	0.0599920	0.0248057
19402	0.0765678	0.0476383	0.0597020	0.0245157
19522	0.0780581	0.0491286	0.0595594	0.0243731
19642	0.0770653	0.0481358	0.0594415	0.0242552
19762	0.0756044	0.0466749	0.0588969	0.0237106
19882	0.0751735	0.0462440	0.0590285	0.0238422
20002	0.0758501	0.0469206	0.0599801	0.0247938
20122	0.0763858	0.0474563	0.0591333	0.0239470
20242	0.0768970	0.0479675	0.0588832	0.0236969
20362	0.0761210	0.0471915	0.0586611	0.0234748
20482	0.0765064	0.0475769	0.0600514	0.0248651
20602	0.0768590	0.0479295	0.0589536	0.0237673
20722	0.0759684	0.0470389	0.0591331	0.0239468
20842	0.0752695	0.0463400	0.0589863	0.0238000
20962	0.0760514	0.0471219	0.0596026	0.0244163
21082	0.0766726	0.0477431	0.0598891	0.0247028
21202	0.0755654	0.0466359	0.0591447	0.0239584
21322	0.0755362	0.0466067	0.0595863	0.0244000
21442	0.0756827	0.0467532	0.0592404	0.0240541
21562	0.0758328	0.0469033	0.0600946	0.0249083
21682	0.0754296	0.0465001	0.0593806	0.0241943
21802	0.0752537	0.0463242	0.0593233	0.0241370
21922	0.0752351	0.0463056	0.0584812	0.0232949
22042	0.0758587	0.0469292	0.0593801	0.0241938
22162	0.0756084	0.0466789	0.0598917	0.0247054
22282	0.0755436	0.0466141	0.0573638	0.0221775
22402	0.0753794	0.0464499	0.0606088	0.0254225
22522	0.0749624	0.0460329	0.0589865	0.0238002
22642	0.0751183	0.0461888	0.0594704	0.0242841
22762	0.0750567	0.0461272	0.0577487	0.0225624
22882	0.0752526	0.0463231	0.0591173	0.0239310
23002	0.0761303	0.0472008	0.0589505	0.0237642
23122	0.0751266	0.0461971	0.0605655	0.0253792
23242	0.0756324	0.0467029	0.0583376	0.0231513
23362	0.0736828	0.0447533	0.0584713	0.0232850
23482	0.0749068	0.0459773	0.0592369	0.0240506
23602	0.0757778	0.0468483	0.0597810	0.0245947
23722	0.0748704	0.0459409	0.0593678	0.0241815
23842	0.0748688	0.0459393	0.0589832	0.0237969
23962	0.0750572	0.0461277	0.0594546	0.0242683
24082	0.0752417	0.0463122	0.0594867	0.0243004
24202	0.0755546	0.0466251	0.0596818	0.0244955
24322	0.0735605	0.0446310	0.0591844	0.0239981
24442	0.0767723	0.0478428	0.0623289	0.0271426
24562	0.0718304	0.0429009	0.0559481	0.0207618
24682	0.0680200	0.0390905	0.0532495	0.0180632
24802	0.0665081	0.0375786	0.0500457	0.0148594

24922	0.0673979	0.0384684	0.0502886	0.0151023
25042	0.0661832	0.0372537	0.0482049	0.0130186
25162	0.0660641	0.0371346	0.0485159	0.0133296
25282	0.0665245	0.0375950	0.0499615	0.0164752
25402	0.0668394	0.0379099	0.0500659	0.0148796
25522	0.0667221	0.0377926	0.0523999	0.0172136
25642	0.0681269	0.0391974	0.0523540	0.0171677
25762	0.0696459	0.0407164	0.0529801	0.0177938
25882	0.0689067	0.0399772	0.0537380	0.0185517
26002	0.0706084	0.0416789	0.0539324	0.0187461
26122	0.0715415	0.0426120	0.0551780	0.0199917
26242	0.0703654	0.0416059	0.0544511	0.0192648
26362	0.0721091	0.0431796	0.0545650	0.0193787
26482	0.0721050	0.0431755	0.0560885	0.0209022
26602	0.0720268	0.0430973	0.0578356	0.0226493
26722	0.0722737	0.0433442	0.0563512	0.0211649
26842	0.0718263	0.0428968	0.0575537	0.0223674
26962	0.0729043	0.0439748	0.0577362	0.0225499
27082	0.0724884	0.0435589	0.0577774	0.0225911
27202	0.0723180	0.0433885	0.0588206	0.0236343
27322	0.0742017	0.0452722	0.0577891	0.0226028
27442	0.0743509	0.0454214	0.0586508	0.0234645
27562	0.0745582	0.0456287	0.0591656	0.0239793
27682	0.0740390	0.0451095	0.0597907	0.0246044
27802	0.0739784	0.0450489	0.0595531	0.0243668
27922	0.0747071	0.0457776	0.0599709	0.0247846
28042	0.0739571	0.0450276	0.0599129	0.0247266
28162	0.0739475	0.0450180	0.0599257	0.0247394
28282	0.0745867	0.0456572	0.0598587	0.0246724
28402	0.0748883	0.0459588	0.0616386	0.0264523
28522	0.0759550	0.0470255	0.0594187	0.0242324
28642	0.0757497	0.0468202	0.0608055	0.0256192
28762	0.0745448	0.0456153	0.0612253	0.0260390
28882	0.0748812	0.0459517	0.0617140	0.0265277
29002	0.0749121	0.0459826	0.0612208	0.0260345
29122	0.0751731	0.0462436	0.0613762	0.0261899
29242	0.0741098	0.0451803	0.0618061	0.0266198
29362	0.0747656	0.0458361	0.0616091	0.0262528
29482	0.0747731	0.0458436	0.0611986	0.0260123
29602	0.0748268	0.0458973	0.0612371	0.0260508
29722	0.0749801	0.0460506	0.0606362	0.0254499
29842	0.0740041	0.0450746	0.0622369	0.0270506
29962	0.0754739	0.0465444	0.0636036	0.0284173
30082	0.0752971	0.0463676	0.0631969	0.0280106
30202	0.0761291	0.0471996	0.0619120	0.0267257
30322	0.0758131	0.0468836	0.0612272	0.0260409
30442	0.0750747	0.0461452	0.0621154	0.0269291
30562	0.0756242	0.0466947	0.0625156	0.0273293
30682	0.0752455	0.0463160	0.0623547	0.0271684

30802	0.0754885	0.0465590	0.0621765	0.0269902
30922	0.0742892	0.0453597	0.0632122	0.0280259
31042	0.0746862	0.0457567	0.0632551	0.0280688
31162	0.0754860	0.0465565	0.0635586	0.0283723
31282	0.0743826	0.0454531	0.0625876	0.0274013
31402	0.0755242	0.0465947	0.0636354	0.0284491
31522	0.0760935	0.0471640	0.0640710	0.0288847
31642	0.0750073	0.0460778	0.0631883	0.0280020
31762	0.0751534	0.0462239	0.0638795	0.0286932
31882	0.0745576	0.0456281	0.0634535	0.0282672
32002	0.0750409	0.0461114	0.0620698	0.0268835
32122	0.0757020	0.0467725	0.0639601	0.0287738
32242	0.0747636	0.0458341	0.0640132	0.0288269
32362	0.0750202	0.0460907	0.0621765	0.0269902
32482	0.0753490	0.0464195	0.0627298	0.0275435
32602	0.0748435	0.0459140	0.0637862	0.0285999
32722	0.0747745	0.0458450	0.0648267	0.0296404
32842	0.0747092	0.0457797	0.0630649	0.0278786
32962	0.0753805	0.0464510	0.0637051	0.0285188
33082	0.0751029	0.0461734	0.0647560	0.0295697
33202	0.0749635	0.0460340	0.0632961	0.0281098
33322	0.0756377	0.0467082	0.0636156	0.0284293
33442	0.0748876	0.0459581	0.0629409	0.0277546
33562	0.0751714	0.0462419	0.0654063	0.0302200
33682	0.0751027	0.0461732	0.0648226	0.0296363
33802	0.0743709	0.0454414	0.0636883	0.0285020
33922	0.0742160	0.0452865	0.0632688	0.0280825
34042	0.0747414	0.0458119	0.0639070	0.0287207
34162	0.0744449	0.0455154	0.0644044	0.0292181
34282	0.0741872	0.0452577	0.0640469	0.0288606
34402	0.0752920	0.0463625	0.0645011	0.0293148
34522	0.0751690	0.0462395	0.0635975	0.0284112
34642	0.0757375	0.0468080	0.0633111	0.0281248
34762	0.0743697	0.0454402	0.0644959	0.0293096
34882	0.0746247	0.0456952	0.0634942	0.0283079
35002	0.0731663	0.0442368	0.0642341	0.0290478
35122	0.0748457	0.0459162	0.0636324	0.0284461
35242	0.0745909	0.0456614	0.0633929	0.0282066
35362	0.0741010	0.0451715	0.0647117	0.0295254
35482	0.0728862	0.0439567	0.0636979	0.0285116
35602	0.0747842	0.0458547	0.0638585	0.0286722
35722	0.0737656	0.0448361	0.0628694	0.0276831
35842	0.0749102	0.0459807	0.0644528	0.0292665
35962	0.0741226	0.0451931	0.0654134	0.0302271
36082	0.0748567	0.0459272	0.0646043	0.0294180
36202	0.0736528	0.0447233	0.0654683	0.0302820
36322	0.0749490	0.0460195	0.0630965	0.0279102
36442	0.0746554	0.0457259	0.0630325	0.0278462
36562	0.0743096	0.0453801	0.0632777	0.0280914

36682	0.0751112	0.0461817	0.0634521	0.0282658
36802	0.0744817	0.0455522	0.0647348	0.0295485
36922	0.0731610	0.0442315	0.0645274	0.0293411
37042	0.0730272	0.0440977	0.0638389	0.0286526
37162	0.0747403	0.0458108	0.0637675	0.0285812
37282	0.0735620	0.0446325	0.0644841	0.0292978
37402	0.0753949	0.0464654	0.0653281	0.0301418
37522	0.0739535	0.0450240	0.0645807	0.0293944
37642	0.0742503	0.0453208	0.0642345	0.0290482
37762	0.0744320	0.0455025	0.0636999	0.0285136
37882	0.0742637	0.0453342	0.0649196	0.0297333
38002	0.0745691	0.0456396	0.0640958	0.0289095
38122	0.0738606	0.0449311	0.0645438	0.0293575
38242	0.0742424	0.0453129	0.0637960	0.0286097
38362	0.0747093	0.0457798	0.0650856	0.0298993
38482	0.0734811	0.0445516	0.0633186	0.0281323
38602	0.0745246	0.0455951	0.0647136	0.0295273
38722	0.0742068	0.0452773	0.0650701	0.0298838
38842	0.0746845	0.0457550	0.0655620	0.0303757
38962	0.0737443	0.0448148	0.0646421	0.0294558
39082	0.0749192	0.0459897	0.0644192	0.0292329
39202	0.0743431	0.0454136	0.0651633	0.0299770
39322	0.0742456	0.0453161	0.0643393	0.0291530
39442	0.0742822	0.0453527	0.0655126	0.0303263
39562	0.0733566	0.0444271	0.0645670	0.0293807
39682	0.0741648	0.0452183	0.0658486	0.0306623
39802	0.0732436	0.0443141	0.0654311	0.0302448
39922	0.0756180	0.0466885	0.0637088	0.0285225
40042	0.0735720	0.0446425	0.0648252	0.0296389
40162	0.0731206	0.0441911	0.0652019	0.0300156
40282	0.0751786	0.0462491	0.0644941	0.0293078
40402	0.0739043	0.0449748	0.0647897	0.0296034
40522	0.0736158	0.0446863	0.0654922	0.0303059
40642	0.0731991	0.0442696	0.0649864	0.0298001
40762	0.0742117	0.0452822	0.0646484	0.0294621
40882	0.0741219	0.0451924	0.0646299	0.0294436
41002	0.0741507	0.0452212	0.0652367	0.0300504
41122	0.0736441	0.0447146	0.0650095	0.0298232
41242	0.0739881	0.0450586	0.0650327	0.0298464
41362	0.0733356	0.0444061	0.0639906	0.0288043
41482	0.0738448	0.0449153	0.0646989	0.0295126
41602	0.0730492	0.0441197	0.0645628	0.0293765
41722	0.0736727	0.0447432	0.0650991	0.0299128
41842	0.0734567	0.0445272	0.0651870	0.0300007
41962	0.0722876	0.0433581	0.0646684	0.0294821
42082	0.0738832	0.0449537	0.0648311	0.0296448
42202	0.0733015	0.0443720	0.0656503	0.0304640
42322	0.0732991	0.0443696	0.0656828	0.0304965
42442	0.0738421	0.0449126	0.0663877	0.0312014

42562	0.0731521	0.0442226	0.0657745	0.0305882
42682	0.0741814	0.0452519	0.0648264	0.0296401
42802	0.0732493	0.0443198	0.0661587	0.0309724
42922	0.0741344	0.0452049	0.0654256	0.0302393
43042	0.0741951	0.0452656	0.0654172	0.0302309
43162	0.0736920	0.0447625	0.0652281	0.0300418
43282	0.0738374	0.0449079	0.0651583	0.0299720
43402	0.0739825	0.0450530	0.0659116	0.0307253
43522	0.0728267	0.0438972	0.0647613	0.0295750
43642	0.0728032	0.0438737	0.0646260	0.0294397
43762	0.0725954	0.0436659	0.0655220	0.0303357
43882	0.0730373	0.0441078	0.0654068	0.0302205
44002	0.0741007	0.0451712	0.0662552	0.0310689
44122	0.0738193	0.0448898	0.0654648	0.0302785
44242	0.0734890	0.0445595	0.0661174	0.0309311
44362	0.0738989	0.0449694	0.0656970	0.0305107
44482	0.0729603	0.0440308	0.0659533	0.0307670
44602	0.0730875	0.0441580	0.0655335	0.0303472
44722	0.0735951	0.0446656	0.0661699	0.0309836
44842	0.0748328	0.0459033	0.0671071	0.0319208
44962	0.0742355	0.0453060	0.0665075	0.0313212
45082	0.0732312	0.0443017	0.0656437	0.0304574
45202	0.0736477	0.0447182	0.0659907	0.0308044
45322	0.0742024	0.0452729	0.0651456	0.0299593
45442	0.0736274	0.0446979	0.0650932	0.0299069
45562	0.0727508	0.0438213	0.0636705	0.0284842
45682	0.0729690	0.0440395	0.0661173	0.0309310
45802	0.0740623	0.0451328	0.0653585	0.0301722
45922	0.0732701	0.0443406	0.0657063	0.0305200
46042	0.0735286	0.0445991	0.0660671	0.0308808
46162	0.0729817	0.0440522	0.0655384	0.0303521
46282	0.0736205	0.0446910	0.0652217	0.0300354
46402	0.0723529	0.0434234	0.0656319	0.0304456
46522	0.0727910	0.0438615	0.0658725	0.0306862
46642	0.0727808	0.0438513	0.0654215	0.0302352
46762	0.0733640	0.0444345	0.0670146	0.0318283
46882	0.0728786	0.0439491	0.0667736	0.0315873
47002	0.0731006	0.0441711	0.0658901	0.0307038
47122	0.0734767	0.0445472	0.0653106	0.0301243
47242	0.0732602	0.0443307	0.0660932	0.0309069
47362	0.0742885	0.0453590	0.0655164	0.0303284
47482	0.0734823	0.0445528	0.0668450	0.0316587
47602	0.0735068	0.0445773	0.0650664	0.0298801
47722	0.0734425	0.0445130	0.0668281	0.0316418
47842	0.0726801	0.0437506	0.0657600	0.0305737
47962	0.0727356	0.0438061	0.0652449	0.0300586
48082	0.0729978	0.0440683	0.0658168	0.0306305
48202	0.0738446	0.0449151	0.0651040	0.0299177
48322	0.0723925	0.0434630	0.0654807	0.0302944

48442	0.0724699	0.0435404	0.0659815	0.0307952
48562	0.0723785	0.0434490	0.0667256	0.0315393
48682	0.0731207	0.0441912	0.0659427	0.0307564
48802	0.0730689	0.0441394	0.0677696	0.0325833
48922	0.0732498	0.0443203	0.0660102	0.0308239
49042	0.0721217	0.0431922	0.0658444	0.0306581
49162	0.0722786	0.0433491	0.0669315	0.0317452
49282	0.0734912	0.0445617	0.0666082	0.0314219
49402	0.0735080	0.0445785	0.0666153	0.0314290
49522	0.0726806	0.0437511	0.0652987	0.0301124
49642	0.0733551	0.0444256	0.0650173	0.0298310
49762	0.0730151	0.0440856	0.0662957	0.0311094
49882	0.0729199	0.0439904	0.0670467	0.0318604
50002	0.0722824	0.0433529	0.0659631	0.0307768
50122	0.0723487	0.0434192	0.0659869	0.0308006
50242	0.0729565	0.0440270	0.0648376	0.0296513
50362	0.0721069	0.0431774	0.0671652	0.0319789
50482	0.0724541	0.0435246	0.0668000	0.0316137
50602	0.0730339	0.0441044	0.0653696	0.0301833
50722	0.0722245	0.0432950	0.0664599	0.0312736
50842	0.0724869	0.0435574	0.0656385	0.0304522
50962	0.0731516	0.0442221	0.0661517	0.0309654
51082	0.0721332	0.0432037	0.0659282	0.0307419
51202	0.0720594	0.0431299	0.0663505	0.0311642
51322	0.0727187	0.0437892	0.0662012	0.0310149
51442	0.0724637	0.0435342	0.0672286	0.0320423
51562	0.0721317	0.0432022	0.0663881	0.0312018
51682	0.0721773	0.0432478	0.0661860	0.0309997
51802	0.0718653	0.0429358	0.0669386	0.0317523
51922	0.0720687	0.0431392	0.0655067	0.0303204
52042	0.0720716	0.0431421	0.0674565	0.0322702
52162	0.0725977	0.0436682	0.0666117	0.0314254
52282	0.0732020	0.0442725	0.0668933	0.0317070
52402	0.0727559	0.0438264	0.0668343	0.0316480
52522	0.0725733	0.0436438	0.0657680	0.0305817
52642	0.0739955	0.0450660	0.0669864	0.0318001
52762	0.0730836	0.0441541	0.0666943	0.0315080
52882	0.0713527	0.0424232	0.0662639	0.0310776
53002	0.0730309	0.0441014	0.0674616	0.0322753
53122	0.0724328	0.0435033	0.0679589	0.0327726
53242	0.0712030	0.0422735	0.0676879	0.0325016
53362	0.0728815	0.0439520	0.0666917	0.0315054
53482	0.0718906	0.0429611	0.0666356	0.0314493
53602	0.0728665	0.0439370	0.0679515	0.0327652
53722	0.0727072	0.0437777	0.0671837	0.0319974
53842	0.0720876	0.0431581	0.0669875	0.0318012
53962	0.0725984	0.0436689	0.0664555	0.0312692
54082	0.0723487	0.0434192	0.0660400	0.0308537
54202	0.0729265	0.0439970	0.0647650	0.0295787

54322	0.0732883	0.0443588	0.0655308	0.0303445
54442	0.0734858	0.0445563	0.0672359	0.0320496
54562	0.0729049	0.0439754	0.0675617	0.0323754
54682	0.0726064	0.0436769	0.0676635	0.0324772
54802	0.0721648	0.0432353	0.0676195	0.0324332
54922	0.0718954	0.0429659	0.0675985	0.0324122
55042	0.0718401	0.0429106	0.0664289	0.0312426
55162	0.0731805	0.0442510	0.0673499	0.0321636
55282	0.0720487	0.0431192	0.0672288	0.0320425
55402	0.0731002	0.0441707	0.0682218	0.0330355
55522	0.0723293	0.0433998	0.0659923	0.0308060
55642	0.0721629	0.0432334	0.0660506	0.0308643
55762	0.0712130	0.0422835	0.0653905	0.0302042
55882	0.0718965	0.0429670	0.0671765	0.0319902
56002	0.0729328	0.0440033	0.0669332	0.0317469
56122	0.0727852	0.0438557	0.0668558	0.0316695
56242	0.0738900	0.0449605	0.0675797	0.0323934
56362	0.0715403	0.0426108	0.0670514	0.0318651
56482	0.0739743	0.0450448	0.0686105	0.0334242
56602	0.0722278	0.0432983	0.0683647	0.0331784
56722	0.0735139	0.0445844	0.0662175	0.0310312
56842	0.0724981	0.0435686	0.0681325	0.0329462
56962	0.0721285	0.0431990	0.0693056	0.0341193
57082	0.0722204	0.0432909	0.0668171	0.0316308
57202	0.0727720	0.0438425	0.0674880	0.0323017
57322	0.0733786	0.0444491	0.0681757	0.0329894
57442	0.0731576	0.0442281	0.0668714	0.0316851
57562	0.0727502	0.0438207	0.0666226	0.0316063
57682	0.0728657	0.0439362	0.0668979	0.0317116
57802	0.0723860	0.0434565	0.0683500	0.0331637
57922	0.0726892	0.0437597	0.0664354	0.0312491
58042	0.0733133	0.0443838	0.0675325	0.0323462
58162	0.0725694	0.0436399	0.0681852	0.0329989
58282	0.0720626	0.0431331	0.0677661	0.0325798
58402	0.0738178	0.0448883	0.0677160	0.0325280
58522	0.0731427	0.0442132	0.0683718	0.0331855
58642	0.0726460	0.0437165	0.0678956	0.0327093
58762	0.0727084	0.0437789	0.0688260	0.0336397
58882	0.0732575	0.0443280	0.0680432	0.0328569
59002	0.0718634	0.0429339	0.0680991	0.0329128
59122	0.0719450	0.0430155	0.0691511	0.0339648
59242	0.0726005	0.0436710	0.0686850	0.0334987
59362	0.0723979	0.0434684	0.0676675	0.0324812
59482	0.0726385	0.0437090	0.0669366	0.0317503
59602	0.0711642	0.0422347	0.0674878	0.0323015
59722	0.0712717	0.0423422	0.0680370	0.0328507
59842	0.0720485	0.0431190	0.0678728	0.0326865
59962	0.0717765	0.0428470	0.0676337	0.0324474
60082	0.0718305	0.0429010	0.0676938	0.0325075

60202	0.0713030	0.0423735	0.0677952	0.0326089
60322	0.0723613	0.0434318	0.0688357	0.0336494
60442	0.0727219	0.0437924	0.0679402	0.0327539
60562	0.0718891	0.0429596	0.0681171	0.0329308
60682	0.0730215	0.0440920	0.0688771	0.0336908
60802	0.0722966	0.0433671	0.0676074	0.0324211
60922	0.0717355	0.0428060	0.0678701	0.0326838
61042	0.0719790	0.0430495	0.0681421	0.0329558
61162	0.0719760	0.0430465	0.0678403	0.0326540
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61762	0.0712106	0.0422811	0.0664412	0.0312549
61882	0.0715549	0.0426254	0.0684091	0.0332228
62002	0.0714087	0.0424792	0.0686901	0.0335038
62122	0.0721981	0.0432686	0.0679317	0.0327454
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62362	0.0726656	0.0437361	0.0682764	0.0330901
62482	0.0710300	0.0421005	0.0674663	0.0322800
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63082	0.0727603	0.0438308	0.0679234	0.0327371
63202	0.0713339	0.0424044	0.0694107	0.0342244
63322	0.0722462	0.0433167	0.0686081	0.0334218
63442	0.0726144	0.0436849	0.0686654	0.0334791
63562	0.0724207	0.0434912	0.0682505	0.0330642
63682	0.0717326	0.0428031	0.0688520	0.0336657
63802	0.0712018	0.0422723	0.0686054	0.0334191
63922	0.0720010	0.0430715	0.0695211	0.0343348
64042	0.0711042	0.0421747	0.0675731	0.0323868
64162	0.0724452	0.0435157	0.0678651	0.0326788
64282	0.0725482	0.0436187	0.0696432	0.0344569
64402	0.0718979	0.0429684	0.0692153	0.0340290
64522	0.0722807	0.0433512	0.0698611	0.0346748
64642	0.0731607	0.0442312	0.0680237	0.0328374
64762	0.0732250	0.0442955	0.0670188	0.0318325
64882	0.0718778	0.0429483	0.0686298	0.0334435
65002	0.0735442	0.0446164	0.0693022	0.0341159
65122	0.0718853	0.0429558	0.0680077	0.0328214
65242	0.0723074	0.0433779	0.0692307	0.0340444
65362	0.0714054	0.0424759	0.0690395	0.0338532
65482	0.0726540	0.0437245	0.0684969	0.0333106
65602	0.0709123	0.0419828	0.0683909	0.0332046
65722	0.0722025	0.0432730	0.0687953	0.0336090
65842	0.0724653	0.0435358	0.0677938	0.0326075
65962	0.0726162	0.0436867	0.0697864	0.0346001

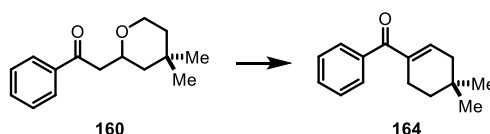
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66442	0.0725075	0.0435780	0.0687061	0.0335198
66562	0.0712062	0.0422767	0.0696451	0.0344588
66682	0.0727822	0.0438527	0.0694018	0.0342155
66802	0.0719670	0.0430375	0.0695033	0.0343170
66922	0.0724703	0.0435408	0.0685597	0.0333734
67042	0.0718007	0.0428712	0.0685451	0.0333588
67162	0.0729052	0.0439757	0.0696182	0.0344319
67282	0.0723247	0.0433952	0.0699385	0.0347522
67402	0.0725744	0.0436449	0.0699167	0.0347304
67522	0.0737563	0.0448268	0.0692242	0.0340379
67642	0.0726923	0.0437628	0.0700660	0.0348797
67762	0.0723372	0.0434077	0.0689375	0.0337512
67882	0.0733580	0.0444285	0.0701303	0.0349440
68002	0.0734204	0.0444909	0.0687542	0.0335679
68122	0.0719423	0.0430128	0.0693480	0.0341617
68242	0.0722693	0.0433398	0.0703054	0.0351191
68362	0.0727922	0.0438627	0.0691732	0.0339869
68482	0.0726074	0.0436779	0.0685266	0.0333403
68602	0.0712138	0.0422843	0.0693665	0.0341802
68722	0.0724946	0.0435651	0.0693947	0.0342084
68842	0.0730888	0.0441593	0.0686586	0.0334723
68962	0.0728847	0.0439552	0.0683700	0.0331837
69082	0.0721024	0.0431729	0.0697550	0.0345687
69202	0.0740037	0.0450742	0.0701781	0.0349918
69322	0.0722452	0.0433157	0.0699559	0.0347696
69442	0.0731326	0.0442031	0.0691008	0.0339145
69562	0.0726585	0.0437290	0.0696421	0.0344558
69682	0.0725961	0.0436666	0.0708829	0.0356966
69802	0.0731608	0.0442313	0.0701765	0.0349902
69922	0.0728293	0.0438998	0.0707454	0.0355591
70042	0.0724723	0.0435428	0.0700654	0.0348791
70162	0.0721326	0.0432031	0.0708132	0.0356269
70282	0.0731132	0.0441837	0.0705302	0.0353439
70402	0.0731100	0.0441805	0.0703031	0.0351168
70522	0.0725197	0.0435902	0.0699169	0.0347306
70642	0.0737928	0.0448633	0.0708358	0.0356495
70762	0.0731345	0.0442050	0.0693213	0.0341350
70882	0.0722629	0.0433334	0.0716357	0.0364494
71002	0.0734200	0.0444905	0.0702033	0.0350170
71122	0.0734391	0.0445096	0.0694097	0.0342234
71242	0.0724035	0.0434740	0.0700693	0.0348830
71362	0.0723127	0.0433832	0.0701863	0.0350000
71482	0.0723618	0.0434323	0.0689517	0.0337654
71602	0.0722802	0.0433507	0.0698660	0.0346797
71722	0.0709003	0.0419708	0.0702469	0.0350606
71842	0.0732148	0.0442853	0.0680745	0.0328882

71962	0.0727148	0.0437853	0.0698038	0.0346175
72082	0.0727002	0.0437707	0.0692253	0.0340390
72202	0.0729458	0.0440163	0.0697906	0.0346043
72322	0.0732031	0.0442736	0.0694766	0.0342903
72442	0.0719538	0.0430243	0.0695719	0.0343856
72562	0.0722826	0.0433531	0.0686372	0.0334509
72682	0.0721852	0.0432557	0.0698595	0.0346732
72802	0.0710027	0.0420732	0.0709435	0.0357572
72922	0.0714822	0.0425527	0.0712629	0.0360766
73042	0.0725072	0.0435777	0.0703706	0.0351843
73162	0.0725979	0.0436684	0.0688512	0.0336649
73282	0.0720949	0.0431654	0.0697894	0.0346031
73402	0.0725759	0.0436464	0.0699432	0.0347569
73522	0.0716945	0.0427650	0.0697749	0.0345886
73642	0.0721755	0.0432460	0.0697738	0.0345875
73762	0.0724671	0.0435376	0.0701176	0.0349313
73882	0.0711779	0.0422484	0.0695294	0.0343431
74002	0.0718929	0.0429634	0.0703858	0.0351995
74122	0.0718867	0.0429572	0.0705504	0.0353641
74242	0.0713957	0.0424662	0.0688933	0.0337070
74362	0.0716485	0.0425490	0.0695625	0.0343762
74482	0.0725095	0.0435800	0.0698155	0.0346292
74602	0.0728707	0.0439412	0.0700775	0.0348912
74722	0.0724896	0.0435601	0.0694935	0.0343072
74842	0.0711342	0.0422047	0.0701070	0.0349207
74962	0.0715030	0.0425735	0.0715289	0.0363426
75082	0.0731319	0.0442024	0.0699388	0.0347525
75202	0.0722044	0.0432749	0.0702519	0.0350656
75322	0.0730370	0.0441075	0.0711820	0.0359957
75442	0.0714270	0.0424975	0.0710987	0.0359124
75562	0.0730981	0.0441686	0.0698208	0.0346345
75682	0.0710134	0.0420839	0.0708910	0.0357047
75802	0.0716778	0.0427483	0.0695569	0.0343706
75922	0.0724284	0.0434989	0.0699354	0.0347491
76042	0.0730554	0.0441259	0.0705812	0.0353949
76162	0.0722956	0.0433661	0.0703505	0.0351642
76282	0.0721262	0.0431967	0.0720751	0.0368888
76402	0.0728815	0.0439520	0.0712311	0.0360448
76522	0.0719793	0.0430498	0.0705624	0.0353761
76642	0.0720317	0.0431022	0.0709161	0.0357298
76762	0.0723252	0.0433957	0.0701610	0.0349747
76882	0.0719576	0.0430281	0.0708921	0.0357058
77002	0.0727517	0.0438222	0.0709193	0.0357330
77122	0.0724445	0.0435150	0.0711094	0.0359231
77242	0.0723314	0.0434019	0.0697983	0.0346120
77362	0.0725528	0.0436233	0.0707161	0.0355298
77482	0.0719875	0.0430580	0.0705012	0.0353149
77602	0.0724546	0.0435251	0.0712066	0.0360203
77722	0.0736258	0.0446963	0.0710121	0.0358258

77842	0.0725305	0.0436010	0.0696018	0.0344155
77962	0.0727537	0.0438242	0.0706496	0.0354633
78082	0.0713169	0.0423874	0.0718323	0.0366460
78202	0.0733037	0.0443742	0.0718493	0.0366630
78322	0.0715741	0.0426446	0.0710302	0.0358439
78442	0.0741568	0.0452273	0.0711779	0.0359916
78562	0.0730699	0.0441404	0.0722938	0.0371075
78682	0.0722109	0.0432814	0.0708673	0.0356810
78802	0.0726560	0.0437265	0.0725211	0.0373348
78922	0.0731505	0.0442210	0.0708993	0.0357130
79042	0.0731767	0.0442472	0.0716672	0.0364809
79162	0.0719797	0.0430502	0.0721013	0.0369150
79282	0.0722283	0.0432988	0.0724689	0.0372826
79402	0.0732290	0.0442995	0.0712693	0.0360830
79522	0.0728909	0.0439614	0.0706602	0.0354739
79642	0.0735420	0.0446125	0.0717312	0.0365449
79762	0.0726344	0.0437049	0.0717987	0.0366124
79882	0.0713437	0.0424142	0.0704060	0.0352197
80002	0.0679499	0.0390204	0.0664183	0.0312320
80122	0.0657009	0.0367714	0.0630703	0.0278840
80242	0.0651952	0.0362657	0.0622559	0.0270696
80362	0.0637117	0.0347822	0.0607701	0.0255838
80482	0.0626879	0.0337584	0.0598755	0.0246892
80602	0.0626533	0.0337238	0.0599194	0.0247331
80722	0.0628230	0.0338935	0.0614674	0.0262811
80842	0.0659858	0.0370563	0.0613070	0.0261207
80962	0.0655706	0.0366411	0.0617697	0.0265834
81082	0.0655125	0.0365830	0.0622054	0.0270191
81202	0.0669066	0.0379771	0.0632173	0.0280310
81322	0.0664786	0.0375491	0.0644466	0.0292603
81442	0.0675741	0.0386446	0.0654896	0.0303033
81562	0.0668532	0.0379237	0.0643419	0.0291556
81682	0.0677875	0.0388580	0.0656470	0.0304607
81802	0.0679081	0.0389786	0.0640209	0.0288346
81922	0.0685289	0.0395994	0.0657728	0.0305865
82042	0.0684485	0.0395190	0.0667700	0.0315837
82162	0.0695156	0.0405861	0.0652731	0.0300868
82282	0.0694878	0.0405583	0.0666573	0.0316410
82402	0.0698791	0.0409496	0.0672441	0.0320578
82522	0.0702239	0.0412944	0.0678905	0.0327042
82642	0.0703029	0.0413734	0.0683838	0.0331975
82762	0.0708456	0.0419161	0.0670140	0.0318277
82882	0.0699765	0.0410470	0.0677421	0.0325558
83002	0.0702379	0.0413084	0.0683440	0.0331577
83122	0.0691758	0.0402463	0.0678915	0.0327052
83242	0.0707426	0.0418131	0.0680348	0.0328485
83362	0.0710197	0.0420902	0.0700824	0.0348961
83482	0.0706848	0.0417553	0.0699065	0.0347202
83602	0.0711545	0.0422250	0.0699972	0.0348109

83722	0.0705514	0.0416219	0.0687648	0.0335785
83842	0.0711586	0.0422291	0.0701591	0.0349728
83962	0.0702261	0.0412966	0.0696891	0.0345028
84082	0.0710290	0.0420995	0.0690402	0.0338539
84202	0.0704974	0.0415679	0.0718292	0.0366429
84322	0.0711700	0.0422405	0.0705253	0.0353390
84442	0.0718134	0.0428839	0.0707320	0.0355457
84562	0.0709781	0.0420486	0.0696996	0.0345133
84682	0.0725743	0.0436448	0.0701515	0.0349652
84802	0.0722432	0.0433137	0.0699073	0.0347210
84922	0.0722980	0.0433685	0.0710228	0.0358365
85042	0.0724464	0.0435169	0.0706368	0.0354505
85162	0.0714556	0.0425261	0.0706065	0.0354202
85282	0.0713429	0.0424134	0.0707754	0.0355891
85402	0.0723850	0.0434555	0.0715366	0.0363503

7.2 ^1H NMR Experiments



An oven-dried 5 mL volumetric flask was charged with tetrahydropyran **160** (232 mg, 1.00 mmol) and 1,3,5-trimethoxybenzene (168 mg, 1.00 mmol), and the volume was made up to 5 mL with *p*-xylene- d_{10} . An oven-dried S400 NMR tube was charged with $\text{Al}(\text{Ot-Bu})_3$ (24.6 mg, 0.100 mmol, 1.0 equiv.) and 0.5 mL of the above stock solution (1.0 equiv. of **160** and 1.0 equiv. 1,3,5-trimethoxybenzene) was added *via* syringe. The NMR tube was purged with argon, capped and placed in a 500 MHz NMR spectrometer preheated to 110 °C. Once the sample was locked and shimmed (< 5 min), it was analysed by recording ^1H NMR spectra every 7 min for 70 min (8 scans, relaxation delay = 25 s).

The same experiment procedure was repeated using $\text{Al}(\text{Ot-Bu})_3$ (36.9 mg, 0.150 mmol, 0.50 equiv.) and $\text{Al}(\text{Ot-Bu})_3$ (18.5 mg, 0.075 mmol, 0.25 equiv.). The experiment was repeated three times at each concentration.

The following diagnostic signals were integrated to generate the time versus normalised peak integral plots:

1,3,5-trimethoxybenzene: $\delta = 6.08\text{--}6.32$ ppm (ArCH)

Tetrahydropyran **160**: $\delta = 3.12\text{--}3.34$ ppm (H_{7a})

Cyclohexene **164**: $\delta = 6.32\text{--}6.45$ ppm (H_2)

The cyclohexene **160** signal at $\delta = 6.32\text{--}6.45$ ppm was found to overlap with the downfield ^{13}C -satellite peak of the 1,3,5-trimethoxybenzene resonance at $\delta = 6.38$ ppm. To correct for this, the upfield ^{13}C -satellite peak of 1,3,5-trimethoxybenzene ($\delta = 6.02\text{--}6.08$ ppm) was integrated separately, and the corresponding value was subtracted from the cyclohexene integral. As the diagnostic signal for 1,3,5-trimethoxybenzene corresponds to three protons, the corrected integral was subsequently normalised by dividing by the integral of the standard peak at $\delta = 6.08\text{--}6.32$ ppm and multiplying by three.

7.2.1 For 0.40 M $\text{Al}(\text{O}t\text{-Bu})_3$

Trial 1:

Time (min)	Integral for tetrahydropyran 160 (3.12–3.34 ppm)	Integral for cyclohexene 164 (6.32–6.45 ppm)	Integral standard (6.08–6.32 ppm)	Integral standard satellite (6.02–6.08 ppm)	Normalised integral for tetrahydropyran 160	Normalised integral for cyclohexene 164
0	8.7689	1.0000	30.5307	0.2788	0.8616	0.0709
470	8.2490	1.4380	30.5872	0.3115	0.8091	0.1105
939	7.7496	1.8382	30.5924	0.3144	0.7600	0.1494
1408	7.1828	2.3063	30.4562	0.2328	0.7075	0.2042
1878	6.8242	2.6803	30.5174	0.2561	0.6709	0.2383
2347	6.4235	3.0145	30.4851	0.2637	0.6321	0.2707
2816	6.1337	3.3375	30.5577	0.2885	0.6022	0.2993
3286	5.7315	3.6309	30.5631	0.2800	0.5626	0.3289
3755	5.4240	3.8991	30.5966	0.2901	0.5318	0.3539
4225	5.1782	4.2210	30.6478	0.2837	0.5069	0.3854

Trial 2:

Time (min)	Integral for tetrahydropyran 160 (3.12-3.34 ppm)	Integral for cyclohexene 164 (6.32-6.45 ppm)	Integral standard (6.08-6.32 ppm)	Integral standard satellite (6.02-6.08 ppm)	Normalised integral for tetrahydropyran 160	Normalised integral for cyclohexene 164
0	9.0039	1.0000	30.7935	0.3016	0.8772	0.0680
470	8.4012	1.4698	30.6944	0.3154	0.8211	0.1128
939	7.8784	1.8885	30.6649	0.3139	0.7708	0.1541
1408	7.4517	2.3203	30.7004	0.3100	0.7282	0.1964
1878	7.1128	2.7614	30.7473	0.3077	0.6940	0.2394
2347	6.6835	3.0808	30.7019	0.3126	0.6531	0.2705
2816	6.3455	3.4283	30.7142	0.3150	0.6198	0.3041
3286	5.9603	3.6835	30.6238	0.3077	0.5839	0.3307
3755	5.7238	4.0397	30.6520	0.3195	0.5602	0.3641
4225	5.2628	4.2437	30.5172	0.2703	0.5174	0.3906

Trial 3:

Time (min)	Integral for tetrahydropyran 160 (3.12-3.34 ppm)	Integral for cyclohexene 164 (6.32-6.45 ppm)	Integral standard (6.08-6.32 ppm)	Integral standard satellite (6.02-6.08 ppm)	Normalised integral for tetrahydropyran 160	Normalised integral for cyclohexene 164
0	10.6288	1.0000	36.3704	0.4003	0.8767	0.0680
470	9.8773	1.5267	36.2044	0.3636	0.8185	0.1128
939	9.5154	2.0326	36.5446	0.4004	0.7811	0.1541
1408	9.1278	2.4365	36.6485	0.4159	0.7472	0.1964
1878	8.7085	2.8062	36.6950	0.4378	0.7120	0.2394
2347	8.2924	3.1889	36.7440	0.4424	0.6770	0.2705
2816	7.9198	3.5426	36.7628	0.4487	0.6463	0.3041
3286	7.5844	3.8989	36.8073	0.4545	0.6182	0.3307
3755	7.3428	4.2946	36.8872	0.4537	0.5972	0.3641
4225	7.0020	4.5487	36.9171	0.4709	0.5690	0.3906

7.1.2 For 0.20 M Al(Ot-Bu)₃

Trial 1:

Time (min)	Integral for tetrahydropyran 160 (3.12-3.34 ppm)	Integral for cyclohexene 164 (6.32-6.45 ppm)	Integral standard (6.08-6.32 ppm)	Integral standard satellite (6.02-6.08 ppm)	Normalised integral for tetrahydropyran 160	Normalised integral for cyclohexene 164
0	20.1588	1.0000	62.8445	0.6165	0.0183	0.9623
470	19.4575	1.6191	62.8397	0.5724	0.0500	0.9289
939	18.7440	2.1823	62.8929	0.6328	0.0739	0.8941
1408	18.0192	2.7511	62.8555	0.6419	0.1007	0.8600
1878	17.2746	3.3685	62.7782	0.6081	0.1319	0.8255
2347	16.6520	3.9877	62.8301	0.6215	0.1607	0.7951
2816	15.9292	4.4779	62.6962	0.5984	0.1856	0.7622
3286	15.3634	5.0001	62.6385	0.6226	0.2097	0.7358
3755	14.7043	5.5339	62.5558	0.5829	0.2374	0.7052
4225	14.1469	6.0255	62.5439	0.6000	0.2602	0.6786

Trial 2:

Time (min)	Integral for tetrahydropyran 160 (3.12-3.34 ppm)	Integral for cyclohexene 164 (6.32-6.45 ppm)	Integral standard (6.08-6.32 ppm)	Integral standard satellite (6.02-6.08 ppm)	Normalised integral for tetrahydropyran 160	Normalised integral for cyclohexene 164
0	21.4676	1.1236	68.2268	0.4293	0.9440	0.0305
470	20.7050	1.7972	68.2082	0.4442	0.9107	0.0595
939	19.9469	2.4451	68.1097	0.4800	0.8786	0.0866
1408	19.1013	3.1414	67.9305	0.4575	0.8436	0.1185
1878	18.3169	3.7919	67.7675	0.4515	0.8109	0.1649
2347	17.6344	4.4816	67.5801	0.4484	0.7828	0.1790
2816	16.9370	5.1184	67.4917	0.4404	0.7528	0.2079
3286	16.1914	5.6485	67.2641	0.4316	0.7221	0.2327
3755	15.6213	6.2655	67.1550	0.4566	0.6978	0.2595
4225	15.0232	6.8005	67.1527	0.4586	0.6712	0.2833

Trial 3:

Time (min)	Integral for tetrahydropyran 160 (3.12-3.34 ppm)	Integral for cyclohexene 164 (6.32-6.45 ppm)	Integral standard (6.08-6.32 ppm)	Integral standard satellite (6.02-6.08 ppm)	Normalised integral for tetrahydropyran 160	Normalised integral for cyclohexene 164
0	15.1806	1.0000	49.0080	0.4101	0.9293	0.0361
470	14.6090	1.5123	49.0471	0.4172	0.8936	0.0670
939	14.0335	1.9876	49.0683	0.4336	0.8580	0.0950
1408	13.5032	2.4286	49.1024	0.4428	0.8250	0.1213
1878	12.9726	2.8887	49.0957	0.4361	0.7927	0.1499
2347	12.4939	3.3212	49.1105	0.4266	0.7632	0.1768
2816	12.0116	3.7234	49.0885	0.4247	0.7341	0.2016
3286	11.6207	4.1200	49.1644	0.4269	0.7091	0.2253
3755	11.2399	4.4640	49.2015	0.4468	0.6853	0.2449
4225	10.8283	4.8158	49.1516	0.4284	0.6609	0.2678

7.1.3 For 0.10 M Al(Ot-Bu)₃

Trial 1:

Time (min)	Integral for tetrahydropyran 160 (3.12-3.34 ppm)	Integral for cyclohexene 164 (6.32-6.45 ppm)	Integral standard (6.08-6.32 ppm)	Integral standard satellite (6.02-6.08 ppm)	Normalised integral for tetrahydropyran 160	Normalised integral for cyclohexene 164
0	30.4907	1.0000	93.1051	0.6418	0.9825	0.0115
470	28.9909	1.9884	92.7441	0.3121	0.9378	0.0542
939	28.6999	2.5637	92.7290	0.6032	0.9285	0.0634
1408	27.9116	3.2804	92.4952	0.5966	0.9053	0.0870
1878	27.1701	3.9430	92.2344	0.6250	0.8837	0.1079
2347	26.4534	4.6076	92.0399	0.6120	0.8622	0.1302
2816	25.7784	5.2199	91.7672	0.6332	0.8427	0.1499
3286	25.0400	5.8172	91.4617	0.6297	0.8213	0.1702
3755	24.3630	6.4349	91.1826	0.5959	0.8016	0.1921
4225	23.7749	6.9899	91.0003	0.6037	0.7838	0.2105

Trial 2:

Time (min)	Integral for tetrahydropyran 160 (3.12-3.34 ppm)	Integral for cyclohexene 164 (6.32-6.45 ppm)	Integral standard (6.08-6.32 ppm)	Integral standard satellite (6.02-6.08 ppm)	Normalised integral for tetrahydropyran 160	Normalised integral for cyclohexene 164
0	22.7971	1.0000	70.4294	0.4119	0.9711	0.0250
470	22.1859	1.5414	70.3416	0.4221	0.9462	0.0477
939	21.6024	2.0517	70.2057	0.4331	0.9231	0.0692
1408	20.9965	2.5819	70.0422	0.4343	0.8993	0.0920
1878	20.4362	3.0658	69.8744	0.4393	0.8774	0.1128
2347	19.9168	3.5391	69.7001	0.4423	0.8572	0.1333
2816	19.4320	3.9714	69.5827	0.4529	0.8378	0.1517
3286	18.9447	4.4280	69.4958	0.4537	0.8178	0.1716
3755	18.4836	4.8238	69.4207	0.4541	0.7988	0.1888
4225	18.0507	5.2249	69.3640	0.4658	0.7807	0.2058

Trial 3:

Time (min)	Integral for tetrahydropyran 160 (3.12-3.34 ppm)	Integral for cyclohexene 164 (6.32-6.45 ppm)	Integral standard (6.08-6.32 ppm)	Integral standard satellite (6.02-6.08 ppm)	Normalised integral for tetrahydropyran 160	Normalised integral for cyclohexene 164
0	16.2211	0.72937	49.9394	0.422555	0.9744	0.0184
470	15.7706	1.14697	49.986	0.435926	0.9465	0.0427
939	15.3349	1.54553	49.9943	0.445996	0.9202	0.0660
1408	14.9164	1.9167	49.9575	0.442539	0.8957	0.0885
1878	14.5293	2.24611	49.9842	0.456295	0.8720	0.1074
2347	14.1874	2.56685	49.9671	0.45252	0.8518	0.1269
2816	13.8773	2.86484	50.0044	0.464541	0.8326	0.1440
3286	13.5577	3.13892	49.9172	0.471002	0.8148	0.1603
3755	13.2132	3.44808	49.8608	0.439798	0.7950	0.1810
4225	12.9551	3.69654	49.8652	0.455938	0.7794	0.1950

7.1.4 For 0.05 M Al(Ot-Bu)₃

Trial 1:

Time (min)	Integral for tetrahydropyran 160 (3.12-3.34 ppm)	Integral for cyclohexene 164 (6.32-6.45 ppm)	Integral standard (6.08-6.32 ppm)	Integral standard satellite (6.02-6.08 ppm)	Normalised integral for tetrahydropyran 160	Normalised integral for cyclohexene 164
0	16.2211	0.72937	49.9394	0.422555	0.9744	0.0184
470	15.7706	1.14697	49.986	0.435926	0.9465	0.0427
939	15.3349	1.54553	49.9943	0.445996	0.9202	0.0660
1408	14.9164	1.9167	49.9575	0.442539	0.8957	0.0885
1878	14.5293	2.24611	49.9842	0.456295	0.8720	0.1074
2347	14.1874	2.56685	49.9671	0.45252	0.8518	0.1269
2816	13.8773	2.86484	50.0044	0.464541	0.8326	0.1440
3286	13.5577	3.13892	49.9172	0.471002	0.8148	0.1603
3755	13.2132	3.44808	49.8608	0.439798	0.7950	0.1810
4225	12.9551	3.69654	49.8652	0.455938	0.7794	0.1950

Trial 2:

Time (min)	Integral for tetrahydropyran 160 (3.12-3.34 ppm)	Integral for cyclohexene 164 (6.32-6.45 ppm)	Integral standard (6.08-6.32 ppm)	Integral standard satellite (6.02-6.08 ppm)	Normalised integral for tetrahydropyran 160	Normalised integral for cyclohexene 164
0	32.8650	1.0000	100.7570	0.6844	0.9785	0.0094
470	32.4736	1.3431	100.2510	0.7408	0.9718	0.0180
939	32.0121	1.7013	99.7634	0.7309	0.9626	0.0292
1408	31.6130	2.0315	99.3616	0.7588	0.9545	0.0384
1878	31.2722	2.3380	98.9488	0.7891	0.9481	0.0470
2347	30.8426	2.6447	98.5753	0.7772	0.9387	0.0568
2816	30.4943	2.9497	98.2806	0.8046	0.9308	0.0655
3286	30.0652	3.1851	97.7854	0.8036	0.9224	0.0731
3755	29.7070	3.5002	97.4189	0.7785	0.9148	0.0838
4225	29.3698	3.7825	97.1244	0.7983	0.9072	0.0922

Trial 3:

Time (min)	Integral for tetrahydropyran 160 (3.12-3.34 ppm)	Integral for cyclohexene 164 (6.32-6.45 ppm)	Integral standard (6.08-6.32 ppm)	Integral standard satellite (6.02-6.08 ppm)	Normalised integral for tetrahydropyran 160	Normalised integral for cyclohexene 164
0	42.2389	1.0000	127.0430	0.8944	0.9974	0.0025
470	41.3101	1.6705	126.5640	0.8442	0.9792	0.0196
939	40.4998	2.3259	126.4180	0.8370	0.9611	0.0353
1408	39.9072	2.8610	126.2920	0.8827	0.9480	0.0470
1878	39.2410	3.4352	126.1050	0.9241	0.9335	0.0597
2347	38.5575	3.9834	125.9040	0.9356	0.9187	0.0726
2816	37.9519	4.5309	125.6920	0.9328	0.9058	0.0859
3286	37.2369	5.0738	125.3600	0.8823	0.8911	0.1003
3755	36.8250	5.5319	125.1490	0.9250	0.8827	0.1104
4225	36.2484	5.9617	124.9310	0.9511	0.8704	0.1203

7.1.5 Monitoring the reaction by ^1H NMR

The reaction time was extended to 18 h, and ^1H NMR spectra were recorded every 70 min over this period. (8 scans, relaxation delay = 25 s).

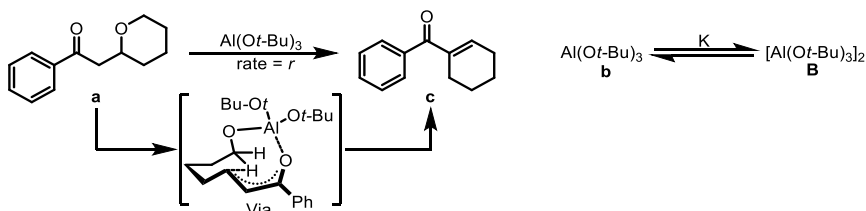
The integral for 1,3,5-trimethoxybenzene (δ = 6.08-6.32 ppm) was set to 300. The cyclohexene **160** signal at δ = 6.32-6.45 ppm was found to overlap with the downfield ^{13}C -satellite peak of the 1,3,5-trimethoxybenzene resonance at δ = 6.38 ppm. To correct for this, the upfield ^{13}C -satellite peak of 1,3,5-trimethoxybenzene (δ = 6.02-6.08 ppm) was integrated separately, and the corresponding value was subtracted from the cyclohexene integral.

Time (h)	Integral standard (6.08-6.32 ppm)	Integral for tetrahydropyran 160 (3.12-3.34 ppm)	Integral for cyclohexene 164 (6.32-6.45 ppm)	Integral standard satellite (6.02-6.08 ppm)	Corrected integral for cyclohexene 164
0.00	300.00	94.80	6.45	2.69	3.76
1.17	300.00	65.05	32.03	2.41	29.62
2.48	300.00	46.41	48.70	2.66	46.04
3.78	300.00	33.99	60.42	2.93	57.49
5.09	300.00	23.96	69.94	3.17	66.76
6.39	300.00	16.17	77.81	3.41	74.40
7.69	300.00	11.82	81.53	3.54	77.98
9.00	300.00	9.47	83.74	3.51	80.23
10.30	300.00	7.94	85.42	3.56	81.85
11.60	300.00	6.67	86.61	3.54	83.07
12.91	300.00	5.53	87.31	3.74	83.58
14.21	300.00	4.91	88.2 0	3.62	84.58
15.52	300.00	4.29	88.69	3.70	84.99
16.82	300.00	3.94	88.77	3.72	85.06
18.12	300.00	3.62	89.36	3.68	85.67

7.3 Mathematical Derivation of Aluminium Rate Orders

Derived by Dr C. E. Lunt-Laurin

Assume One Aluminium is in the Bridge. Aluminium species are in equilibrium.



$$\text{Rate} = r[a][b], K = \frac{[B]}{[b]^2} \text{ and } [b]_0 = [b] + 2[B]$$

Where $[b]_0$ is the initial input concentration.

$$\text{Then } [b]_0 = 2K[b]^2 + [b]$$

Using the quadratic formula.

$$[b] = \frac{(1 + 8K[b]_0)^{0.5} - 1}{4K}$$

If $1 \gg 8K[b]_0$ i.e. The equilibrium heavily favours the aluminium dimer.

Then $(1 + 8K[b]_0)^{0.5} - 1 \approx 8K[b]_0^{0.5}$ inserting this back in the rate equation.

$$\text{Rate} \approx \frac{2^{0.5}r[a][b]_0^{0.5}}{2K^{0.5}}, \text{ Order 0.5}$$

Physically this corresponds to dimer formation, which increasingly inhibits the reaction.

If $1 < 8K[b]_0$ i.e. The equilibrium heavily favours the aluminium monomer.

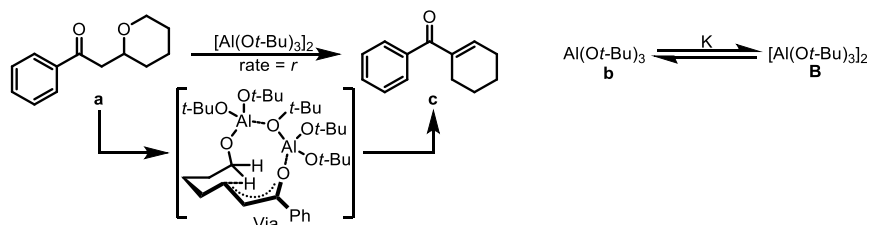
Then using a Taylor expansion $(1 + 8K[b]_0)^{0.5} \approx 1 + 4k[b]_0 + \dots$

$[b] \approx [b]_0$ inserting this back in the rate equation.

$\text{Rate} \approx r[a][b]_0$, **Order 1**

Physically this intuitively indicates that if the dimer doesn't form, these terms disappear.

Assume Two Aluminiums are in the Bridge. Aluminium species are in equilibrium.



$\text{Rate} = r[a][B]$, $K = \frac{[B]}{[b]^2}$ and $[b]_0 = [b] + 2[B]$

Then $[b]_0 = 2[B] + K^{-0.5}[B]^{0.5}$ or $K^{0.5}[b]_0 = 2K^{0.5}[B] + [B]^{0.5}$

Using the quadratic formula.

$$[B]^{0.5} = \frac{(1 + 8K[b]_0)^{0.5} - 1}{4K^{0.5}}$$

If $1 \gg 8K[b]_0$ i.e. The equilibrium heavily favours the aluminium dimer.

Then $(1 + 8K[b]_0)^{0.5} - 1 \approx 8K[b]_0^{0.5}$

$[B]^{0.5} \approx 2^{-0.5}[b]_0^{0.5}$ inserting this back in the rate equation.

$\text{Rate} \approx \frac{r[a][b]_0}{2}$, **Order 1**

Physically this corresponds to the amount of dimer being equal to half the monomer added.

If $1 \ll 8K[b]_0$ i.e. The equilibrium heavily favours the aluminium monomer.

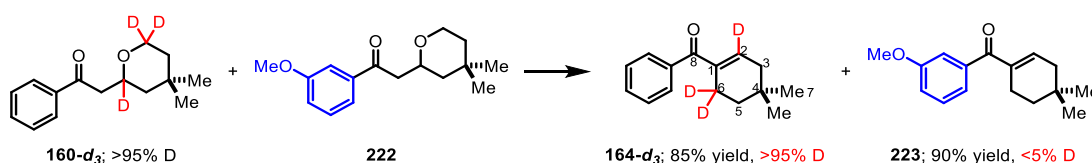
Then using a Taylor expansion $(1 + 8K[b]_0)^{0.5} \approx 1 + 4K[b]_0 + \dots$

$[B]^{0.5} \approx K^{0.5}[b]_0$ inserting this back in the rate equation.

$\text{Rate} \approx rK[a][b]_0^2$, **Order 2**

Physically this corresponds to an independent 3 component transition state.

7.4 Double Label Crossover Experiment



A 2–5 mL flame dried Biotage[®] microwave vial was charged with tetrahydropyran **160-*d*₃** (47 mg, 0.20 mmol, 1 equiv.), tetrahydropyran **222** (52 mg, 0.20 mmol, 1 equiv.), Al(*O**t*-Bu)₃ (99 mg, 0.40 mmol, 2 equiv.), and toluene (2.0 mL). The headspace was briefly purged with N₂ and the reaction vessel was sealed with a microwave vial cap (containing a Reseal[™] septum) and heated at 110 °C for 16 h. The reaction was then cooled to RT, diluted with Et₂O (50 mL), filtered through a plug of silica gel and concentrated *in vacuo*. Purification via FCC (3-6% Et₂O/pentane) afforded **164-*d*₃** as a colourless oil (37 mg, 0.17 mmol, 85% yield) and **223** as a colourless oil (44 mg, 0.18 mmol, 90% yield).

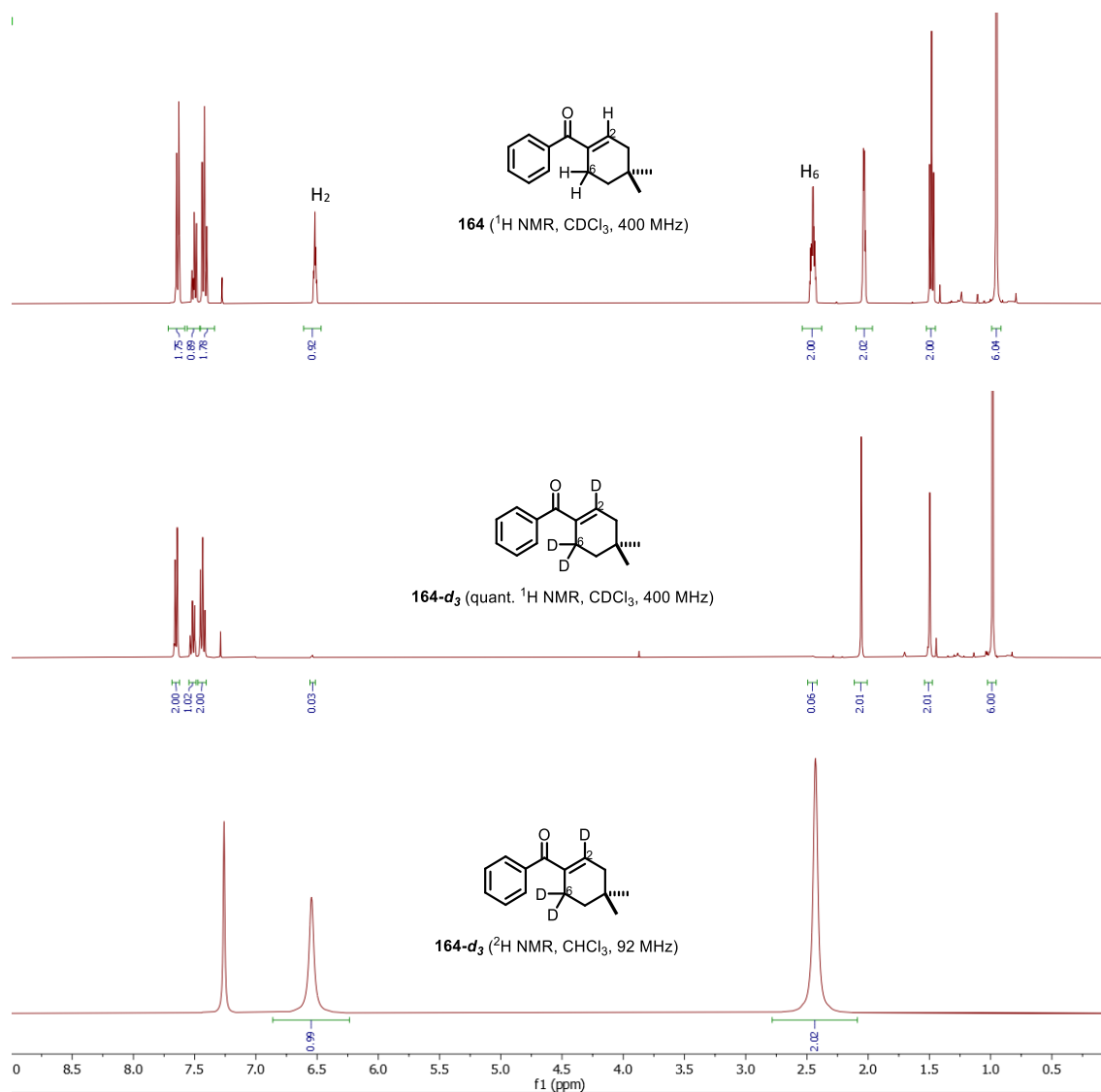
Data for **164-*d*₃** from crossover experiment:

¹H NMR (400 MHz, CDCl₃) δ 7.66 – 7.59 (m, 2H, ArCH x 2), 7.51 – 7.46 (m, 1H, ArCH), 7.44 – 7.38 (m, 2H, ArCH x 2), 2.04 (s, 2H, H₃ x 2), 1.48 (s, 2H, H₅ x 2), 0.97 (s, 6H, H₇ x 6). The peaks at δ = 6.51 ppm (H₂) and 2.43 ppm (H₆) integrate to 3% and 6% respectively, implying 97% D incorporation at each position (i.e. for H₆, 97% D for each hydrogen of the methylene group).

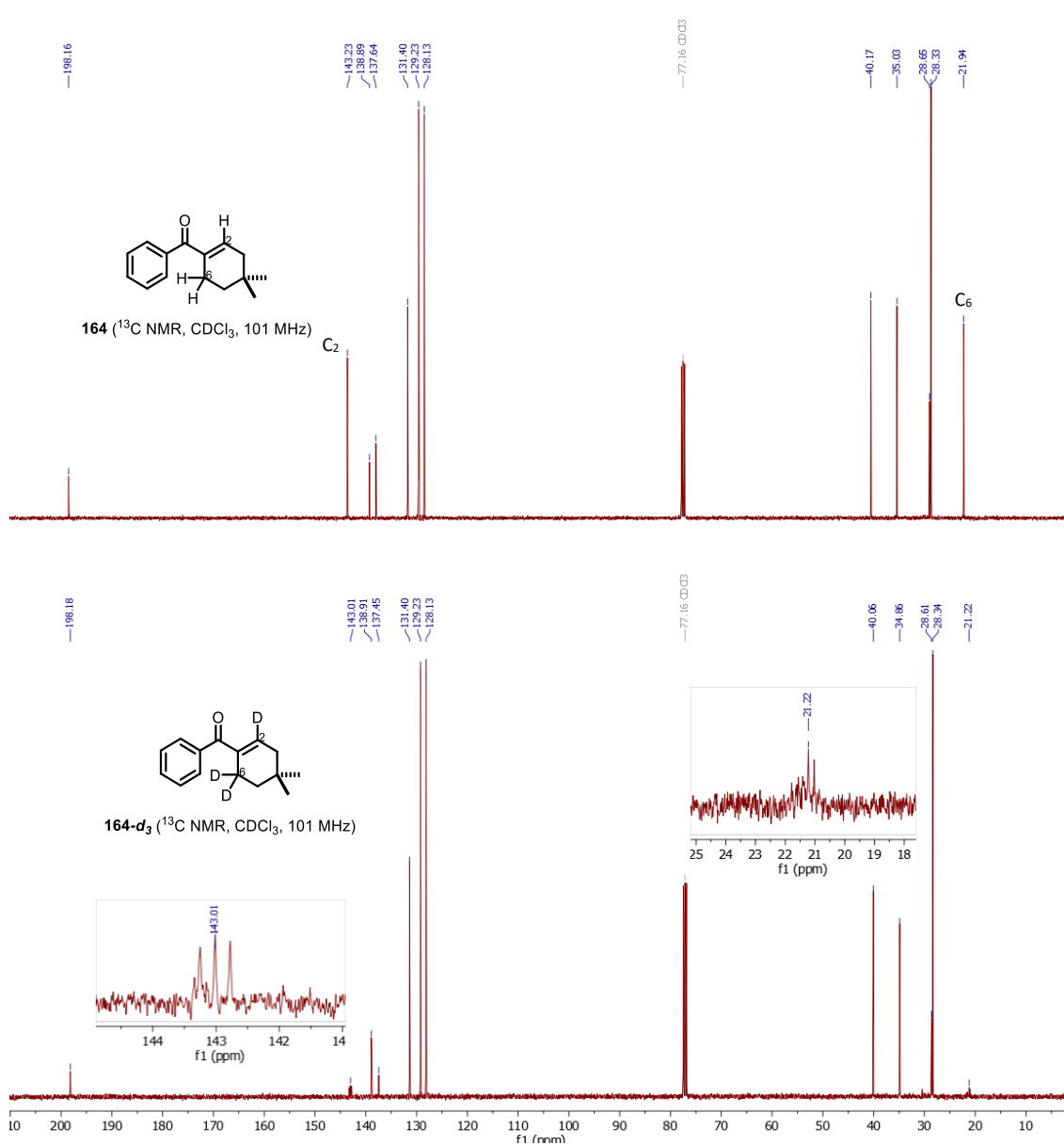
¹³C NMR (101 MHz, CDCl₃) δ 198.2 (C₈), 160.0 (1:1:1 triplet, *J* = 23.5 Hz, C₂), 138.9 (ArC), 137.4 (C₁), 131.4 (ArC), 129.2 (ArC x 2), 128.1 (ArC x 2), 40.1 (C₃), 34.9 (C₅), 28.6 (C₄), 28.3 (C₇), 21.9 (m, C₆). The ¹³C peaks corresponding to C₆ and C₂ displayed reduced intensity due to ²*J*_{CD} coupling.

²H NMR (92 MHz, CHCl₃ + 1 drop CDCl₃) δ 6.55 (s, 1H, H₂), 2.43 (s, 2H, H₆).

Stack plot showing reference ^1H NMR spectrum of **164** along with quantitative ^1H NMR and ^2H NMR spectra of **164-*d*₃** from crossover experiment:



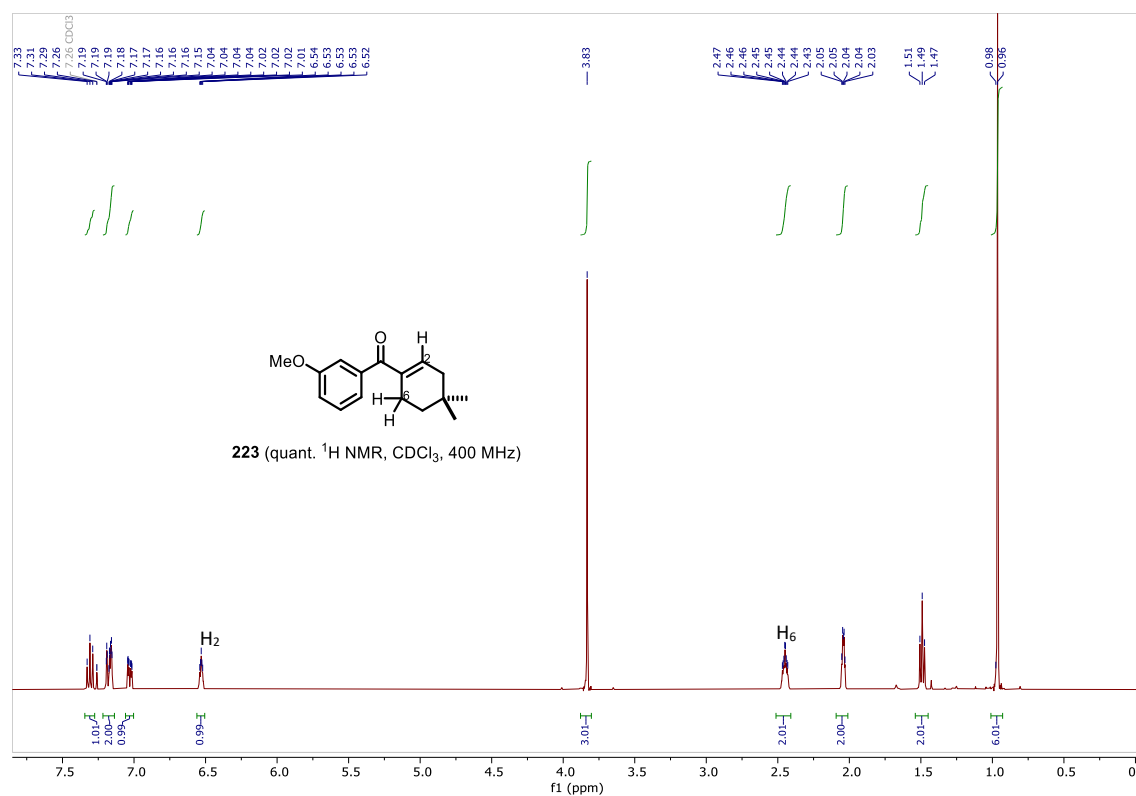
Stack plot showing reference ^{13}C NMR spectrum of **164** along with ^{13}C NMR spectrum of **164-*d*₃** from crossover experiment. Expansions show key regions for C₂ and C₆.



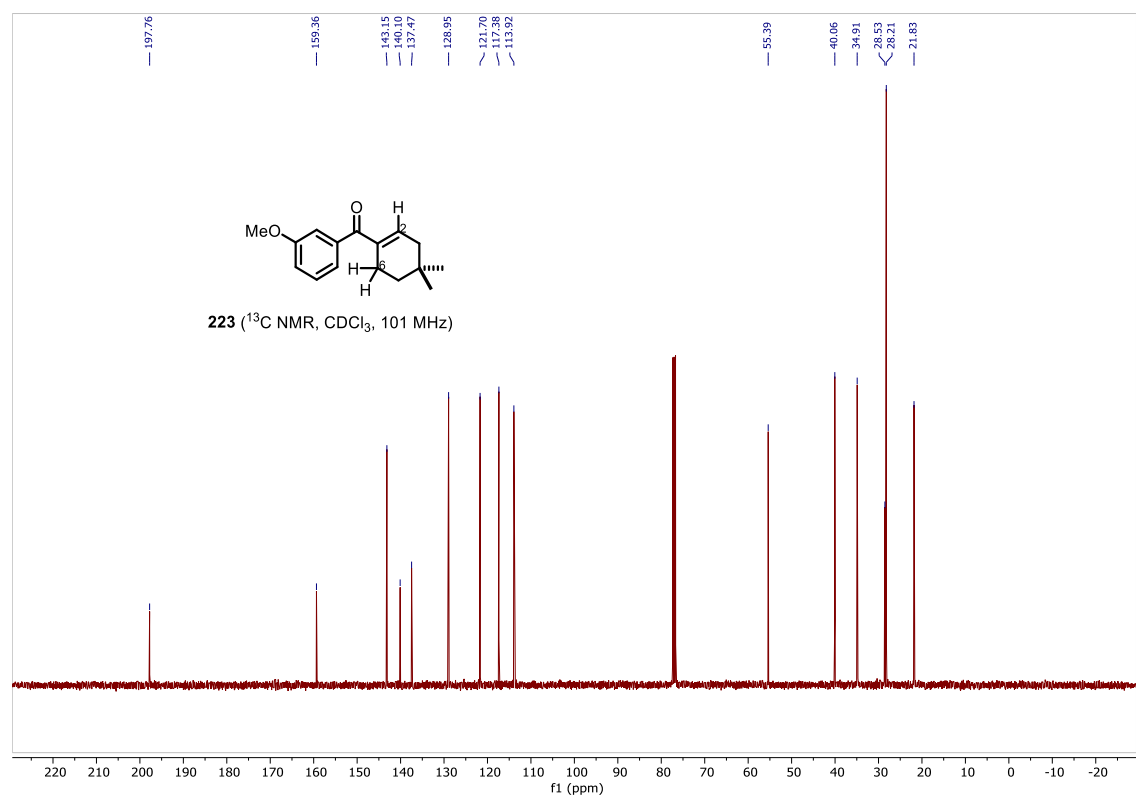
Data for **223** from crossover experiment:

<5% D incorporation at the 2- and 6-positions by quantitative ^1H NMR and ^{13}C NMR.

The ^1H NMR data was identical to that described above for non-deuterated **223** and the peaks corresponding to H₂ and H₆ integrated to >95% implying <5% D incorporation at these positions:



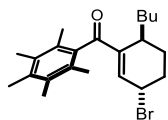
The ^{13}C NMR data was identical to that described above and showed no CD coupling:



7.5 Single Crystal X-Ray Structure Data

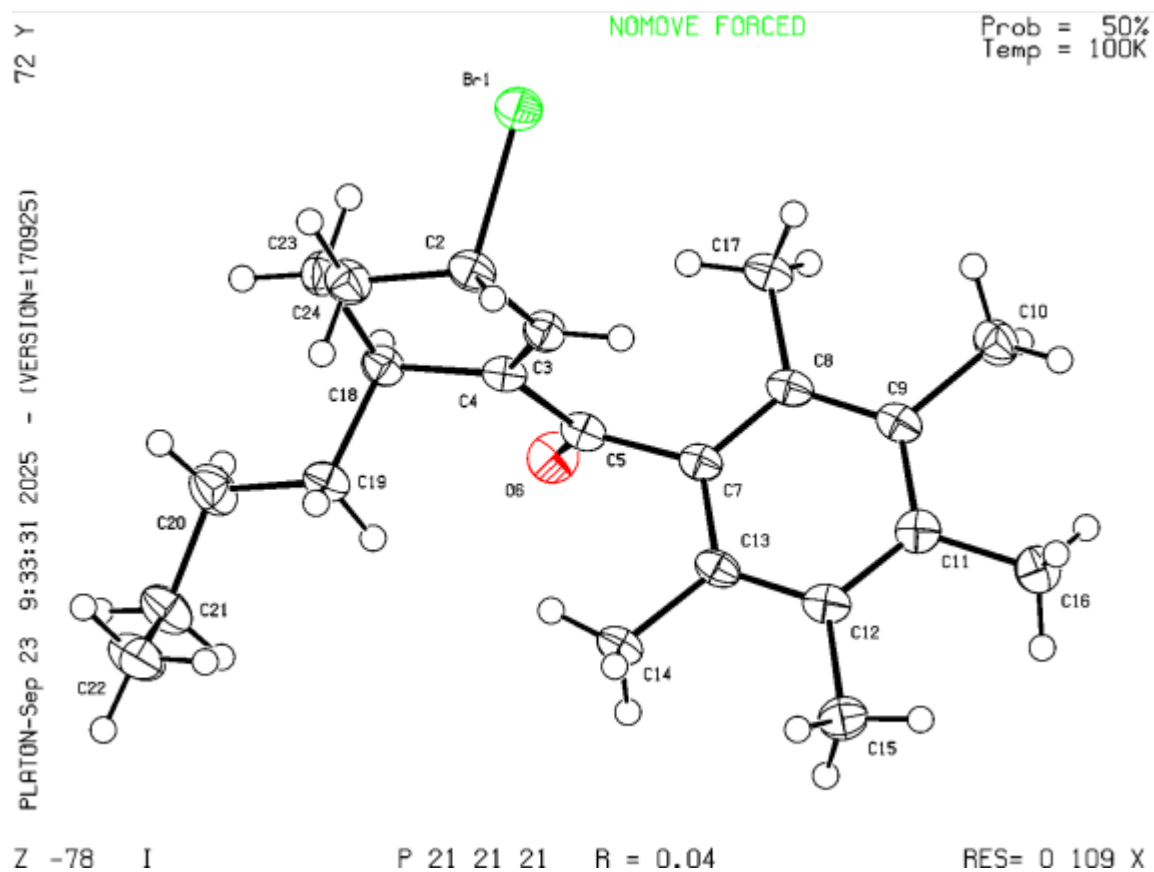
((3S,6S)-3-Bromo-6-butylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 302

Recrystallised *via* vapour diffusion using DCM/EtOH/DMSO.



Formula: C₂₂H₃₁BrO

Crystal class	orthorhombic	Space group	P2 ₁ 2 ₁ 2 ₁
a	7.3986(1)	alpha	90
b	8.6217(1)	beta	90
c	31.2132(2)	gamma	90
Volume	1991.04(4)	Z	4
Radiation type	Cu K α	Wavelength	1.54184
Dx	1.306	Mr	391.39
Mu	2.833	Temperature (K)	100
Size	0.014 $\times$ 0.071 $\times$ 0.086		
Colour	Clear pale colourless	Shape	plate
Cell from	75898 reflections	Theta range	3 to 76
Diffractometer type	multi-scan	Scan type	OMEGA
Absorption type	multi-scan	Transmission range	0.74 – 0.96
Rint	0.063	Independent reflections	4132
Hmin, Hmax	-9, 9	Theta max	76.078
Kmin, Kmax	-10, 9		
Lmin, Lmax	-38, 39		
Refinement on Fsqd			
R-factor	0.0351	Weighted R-factor	0.0965
Max shift/su	0.0007464		
Delta Rho min	-0.33	Delta Rho max	0.62
Reflections used	4132	sigma(I) limit	-3.00
Number of parameters	218	Goodness of fit	1.0017
Flack parameter	-0.021(5)		



Thermal ellipsoids are drawn at the 50% probability level.