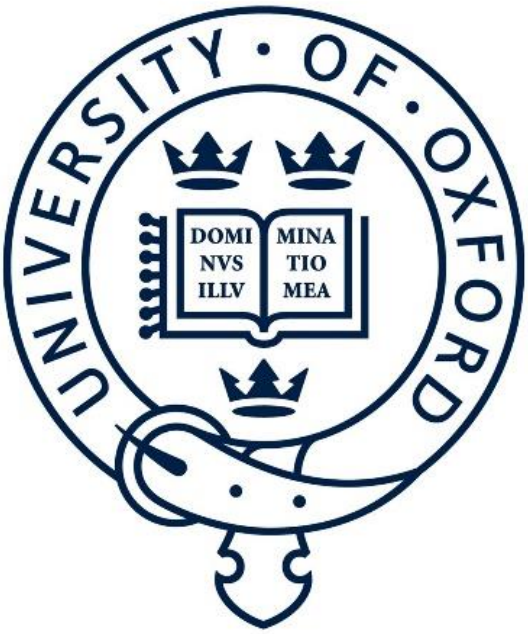
Asymmetric Rhodium Catalysed Arylation: From Ligand Design to Application



Alexander Marc Laurin Hell

Lincoln College

University of Oxford

A thesis submitted in partial fulfilment of the requirements for the degree of *Doctor of Philosophy*

Michaelmas Term 2020

Declaration of Authorship

This thesis describes work carried out in the Chemistry Research Laboratory, University of Oxford, between October 2016 and September 2020 under the supervision of Professor Stephen P. Fletcher. This thesis is the result of my own work, except when stated otherwise, and has not been submitted for any other degree at this or any other university.

The work described in Chapter 3: *Rhodium Catalysed Desymmetrization of meso Bisphosphates* has been performed in collaboration with Reece Jacques. Parts of the content of Chapter 3 have been included in a thesis submitted by Reece Jacques and accepted by the University of Oxford for the degree of a Doctor of Philosophy in Trinity term 2019.

Compounds and results shown in Table 4, Figure 10, and Scheme 39, including all starting materials, have been synthesised by Reece Jacques. Parts of the content of Chapter 3 have been published with shared first authorship in R. Jacques, A. M. L. Hell, R. D. C. Pullin, S. P. Fletcher, *Tetrahedron* **2019**, *75*, 130560.

In Chapter 4: *Rhodium Catalysed Asymmetric Arylation of Cyclobutenes*, selected examples shown in Scheme 56 were contributed by F. Wieland Goetzke. At the time of writing, the content of Chapter 4 is included in the accepted manuscript for F. W. Goetzke, A. M. L. Hell, L. van Dijk, S. P. Fletcher, *Nat. Chem.* **2021**, *accepted*.

Alexander M. L. Hell

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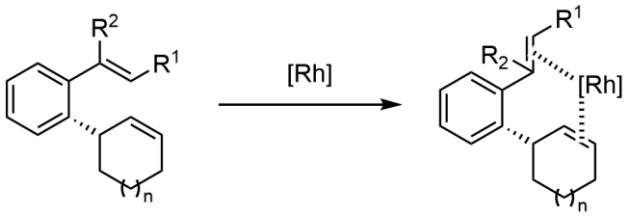
A final thanks goes to my master's studies mentor Dr. Tim den Hartog, without whom I would have never dreamed of coming to Oxford.

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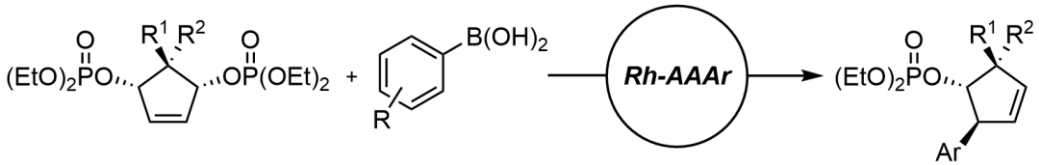
Abstract

This thesis focuses on the development of highly enantioselective rhodium catalysed arylation reactions on small, unsaturated carbocycles and on work towards the development of novel scaffolds for diene ligands applicable in asymmetric rhodium catalysis.

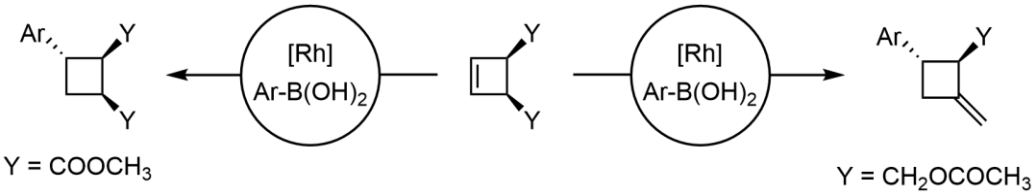
The synthesis and evaluation of a new type of diene ligand, which is based on a structure obtained as the product of a rhodium catalysed allylic arylation of racemic halides, is reported. Two different prototype ligands were designed, synthesised, and evaluated for their ability to coordinate to rhodium complexes. Successful coordination could be demonstrated for one of the prototype ligands by ^{1}H-NMR spectroscopy; however, catalytic activity in benchmarking reactions could not be achieved.



Moving on to the development of rhodium catalysed arylation reactions, an asymmetric allylic arylation was employed in the desymmetrization of a cyclic 5-membered *meso* bisphosphate. Despite being limited in scope and furnishing only satisfactory yields, this transformation proved to be highly enantioselective and illustrated the value of new rhodium catalysed transformations in an otherwise well-established field.



Exploring rhodium catalysed arylation reactions further, a method for the enantioselective generation of arylated cyclobutanes from functionalised cyclobutenes was developed. Cyclobutenes containing electron-withdrawing substituents were found to undergo a Heck-type arylation, while substrates with appropriate leaving groups achieved products arising from a remote homoallylic substitution mechanism.



Abbreviations

º	Degrees
*	Undefined stereocentre
α	Alpha
AAA	Asymmetric allylic alkylation
AAAr	Asymmetric allylic arylation
Ac	Acetyl
ACA	Asymmetric conjugate addition
Ar	Aryl
β	Beta
BINOL	1,1´-Bi-2-naphthol
BINAP	(2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl)
BIPHEP	2,2'-Bis(diphenylphosphino)biphenyl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
bpy	2,2′-Bipyridine
γ	Gamma
C	Centigrade
Cbz	Carboxybenzyl
cee	Conservation of enantiomeric excess
cm^{-1}	per centimetre, wavenumber
cod	1,5-Cyclooctadiene
coe	*cis*-Cyclooctene
COSY	Correlation spectroscopy
Cp	Cyclopentyl
Cy	Cyclohexyl
δ	Delta
d	Doublet (NMR)
dd	Doublet of doublets
ddd	Doublet of doublets of doublets

DCE	1,2-Dichloroethane
DIOP	2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DM-SEGPHOS	5,5′−Bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereomeric ratio
DTBM-SEGPHOS	5,5′-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
DYKAT	Dynamic kinetic asymmetric transformation
ε	Epsilon
E	Entgegen
ee	Enantiomeric excess
EI	Electron ionisation
ent	Opposite enantiomer
equiv	Equivalents
Et	Ethyl
er	Enantiomeric ratio
ESI	Electrospray ionization
FDA	United States Food and Drug Administration
GC	Gas chromatography
η	Eta
HMDS	Hexamethyldisilazane
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation spectroscopy
*i*Bu	Isobutyl
*i*Pr	Isopropyl

IR	Infrared
J	Coupling constant in Hertz
Josiphos	2-((Diphenylphosphino)ferrocenyl)ethyldicyclohexylphosphine
L	Ligand
LRMS	Low-resolution mass spectrometry
M	Molarity
m	Multiplet or Medium (IR)
Me	Methyl
MIDA	Methyliminodiacetic acid
mmol	Millimoles
m.p.	Melting Point
Ms	Methanesulfonyl
MTBE	Methyl *tert*-butyl ether
m/z	Mass to charge ratio
nbd	Norbornadiene
neopentyl	2,2-dimethylpropan-1-ol
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
OA	Oxidative addition
π	Pi
p	Pentet
Pin	Pinacol
PG	Protecting group
Ph	Phenyl
pH	Potential of hydrogen
P-Phos	2,2′,6,6′-Tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridine
ppm	Parts per million
q	Quartet
R	Rectus

rac	Racemic
RE	Reductive elimination
rr	Regioisomeric ratio
σ	Sigma
S	Sinister
s	Singlet or Strong (IR)
SEGPHOS	5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
SFC	Supercritical fluid chromatography
S_N2	Bimolecular nucleophilic substitution
S_N2'	Bimolecular nucleophilic substitution with allylic rearrangement
sp^2	Orbital hybridisation p:s character = 2:1
sp^3	Orbital hybridisation p:s character = 3:1
t	Triplet (NMR)
TADDOL	α,α,α',α'-Tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
*t*Bu	tert-Butyl
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
tfb	Tetrafluorobenzobarrelene
THF	Tetrahydrofuran
THAB	Tetrahexylammonium benzoate
TM	Transmetalation
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl
w	Weak (IR)
Xyl-P-Phos	2,2′,6,6′-Tetramethoxy-4,4′-bis(di(3,5-xylyl)phosphino)-3,3′-bipyridine
Z	Zusammen

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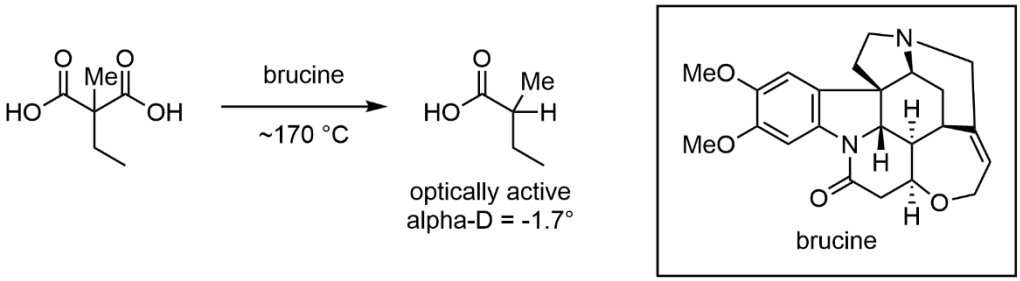
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1. Introduction

1.1 Historical Remarks

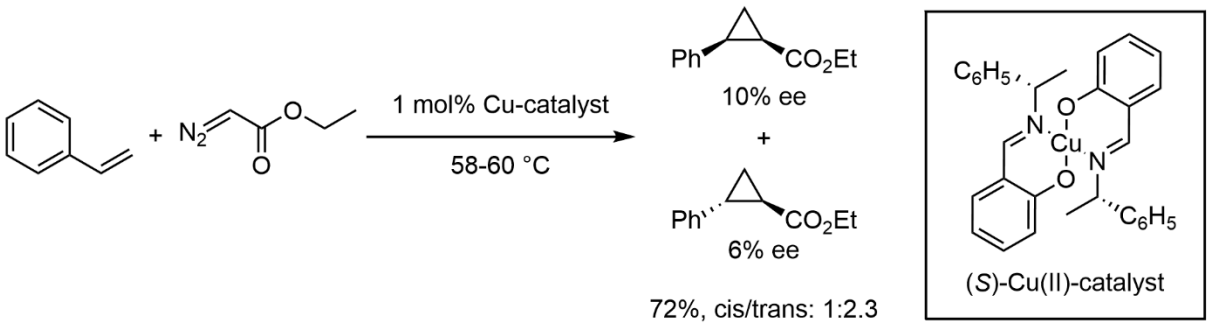
About 60 years after chemistry had emerged as a 'modern' science from the laboratory of Antoine-Laurent de Lavoisier,[1] the resolution of racemic sodium ammonium (±)-tartrate led to the discovery of 'molecular chirality' as the cause for the optical activity of asymmetric compounds by Louis Pasteur in 1848.[2] For a long time, of course, these technical terms were yet to be conceived – it is not exactly retraceable when Lord Kelvin introduced the term chirality, or 'cheirality' from Greek *kheir*: hand;[3] 'chirality' was defined in the context of published lectures in 1904.[4] A debate whether the optical activity of chemical compounds isolated from biological organisms originated from an unspecified 'vital force' and therefore could not artificially be achieved purely by chemical means was ongoing at that time. In light



Scheme 1: Decarboxylation of a substituted malonic acid derivative, the first intended synthesis of an optically active compound. According to the publication, the experiment was conducted 'quite arbitrarily,' but nevertheless was an important contribution to the understanding of organic molecules at the time.[5]

of this debate, the first deliberate asymmetric synthesis of a chemical compound was achieved by Willy Marckwald in 1904 with the enantioselective decarboxylation of 2-ethyl-2-methylmalonic acid, catalysed by the alkaloid brucine (Scheme 1).[5] While this transformation was of academic importance on the journey to reach a more holistic understanding of the role which chemistry – and organic chemistry in particular – plays in biological systems, it would take a plethora of scientific discoveries and technological innovations before the asymmetric synthesis of chiral compounds became a widespread subject of academic research and even longer until the first industrial applications would emerge. After the discovery by Marckwald,

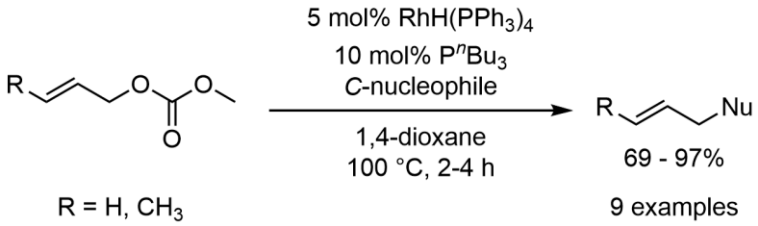
it took another nearly 90 years until the FDA adjusted its guidelines to require the enantiopure synthesis of pharmaceutically active compounds wherever possible in 1992.[6] One significant milestone in this development was the advent of asymmetric transformations catalysed by transition-metal based organometallic complexes.[7] This form of asymmetric catalysis was first encountered by Noyori and co-workers in 1966 during their studies of carbenoid chemistry, which resulted in the development of a Cu-catalysed asymmetric cyclopropanation of alkenes using diazomethane (Scheme 2).[8-9] At the same time, organometallic rhodium complexes were found to possess catalytic activity in the homogeneous hydrogenation of olefins by the group of Wilkinson,[10] and the first homogeneous asymmetric hydrogenation was reported in 1968 by Knowles and co-workers, who used enantioenriched (–)-methylpropylphenylphosphine as monodentate chiral ligand.[11] The generality of this asymmetric hydrogenation led to the rapid development of a range of ligands for Rh-catalysed asymmetric hydrogenations, which quickly converged onto chiral diphosphine-ligands as a privileged ligand class to facilitate this transformation, with DIOP as its first representative.[12-14] In the context of these findings, the axially chiral BINAP ligand (structure shown in Scheme 4) was designed by Noyori and co-workers as a ligand for asymmetric Rh-catalysed hydrogenations in 1980.[15] This ligand would hold significant potential outside the field of asymmetric hydrogenations and, in fact, constituted the foundation for atropoisomeric diphosphine-ligands, which are widely used in asymmetric catalysis today. While this discovery eventually would facilitate the emergence of powerful Rh-catalysed transformations other than asymmetric hydrogenations, particularly



Scheme 2: Cu-catalysed asymmetric cyclopropanation using a chiral Schiff-base type organometallic complex with modest enantioinduction.[8-9]

C–C-bond forming reactions, the field of C–C and C–O-bond formation was long dominated by Pd-catalysed transformations.

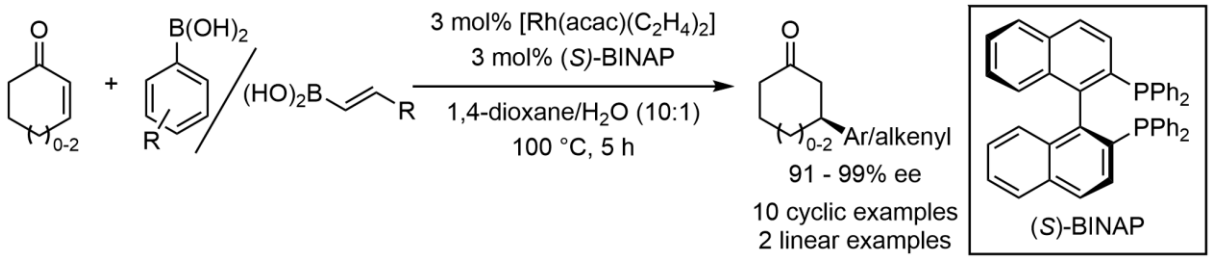
The first Rh-catalysed decarboxylative allylic substitution of allylic carbonates was reported by the group of Tsuji in 1984 (Scheme 3), introducing Rh-catalysis as a viable alternative to Pd-catalysed systems based on the possibility of neutral and often less sensitive reaction conditions.[16-18] However, the development of Rh-catalysed allylic alkylations remained somewhat stagnant.[19] This was the case until 1997, when Miyaura and co-workers reported the conjugate addition of aryl- and 1-alkenylboronic acids to enones, thus pioneering Rh-catalysed 1,4-addition reactions, which will be discussed in more detail in the following sub-chapter.[20]



Scheme 3: As an early example for Rh-catalysed C–C-bond formations, this allylic substitution reaction was developed by Tsuji and co-workers.[16]

1.2 Rh-Catalysed Asymmetric Conjugate Addition Reactions

Building on this first report of a Rh-catalysed 1,4-addition to enones, the groups of Hayashi and Miyaura developed a highly efficient asymmetric variant of this transformation, using (*S*)-BINAP as ligand to induce enantioselectivity (Scheme 4).[21] To achieve this breakthrough, several modifications of Miyaura's original publication were required. Notably, the rhodium



Scheme 4: First reported Rh-catalysed highly enantioselective 1,4-addition of boronic acids to *α,β*-unsaturated carbonyl compounds. 2-Cyclohexenone has been established as benchmark substrate for similar Rh-catalysed 1,4-additions.[21]

precursor complex was changed from [Rh(acac)$(CO)_2$] to [Rh(acac)$(C_2H_4)_2$] to facilitate the ligand exchange with the diphosphine BINAP in order to access the catalytically active species [Rh(acac)(*S*)-BINAP].[20-22] Following this report, the asymmetric conjugate addition of phenylboronic acid to 2-cyclohexenone has been used as a model reaction in the development of various catalytic systems in the field of Rh-catalysed 1,4-additions, to which the group of Hayashi made significant contributions. Among others,[23] diphosphine, bis-sulfoxide, diene, and their hybrid-ligands have been employed in these systems and exemplary transformations shall be briefly discussed in this section, with the exception of diene ligand based systems, which will be examined in more detail in chapter 2.1.[24-25]

Investigating the mechanism of the 1,4-addition of phenylboronic acid to 2-cyclohexenone, Hayashi found that, instead of [Rh(acac)(*S*)-BINAP], the catalytically more active [Rh(OH)(*S*)-BINAP] allowed for the reaction to be carried out at lower temperatures of 35 °C, thus increasing the obtained enantiomeric excess and partially suppressing the

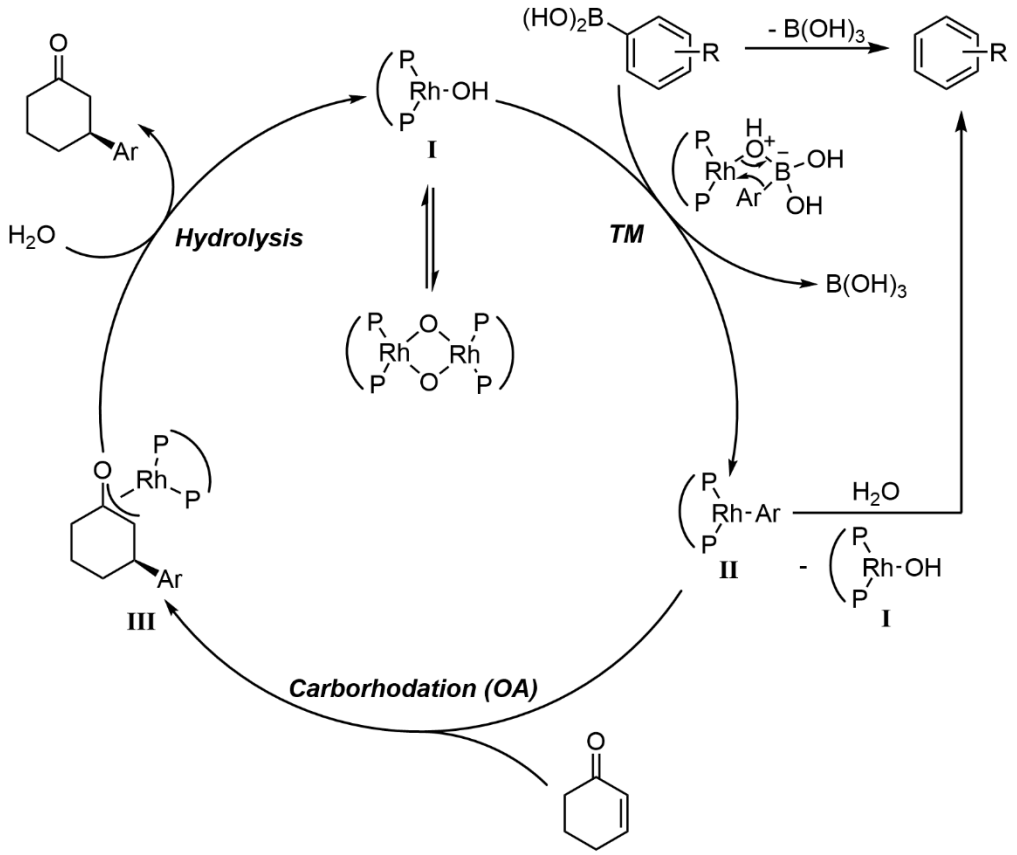


Figure 1: General mechanistic pathway of a Rh-catalysed 1,4-addition with the chiral rhodium-hydroxide complex Rh-**I** as active species. The Rh-catalysed protodeboronation pathway is abbreviated for simplicity.[24, 26]

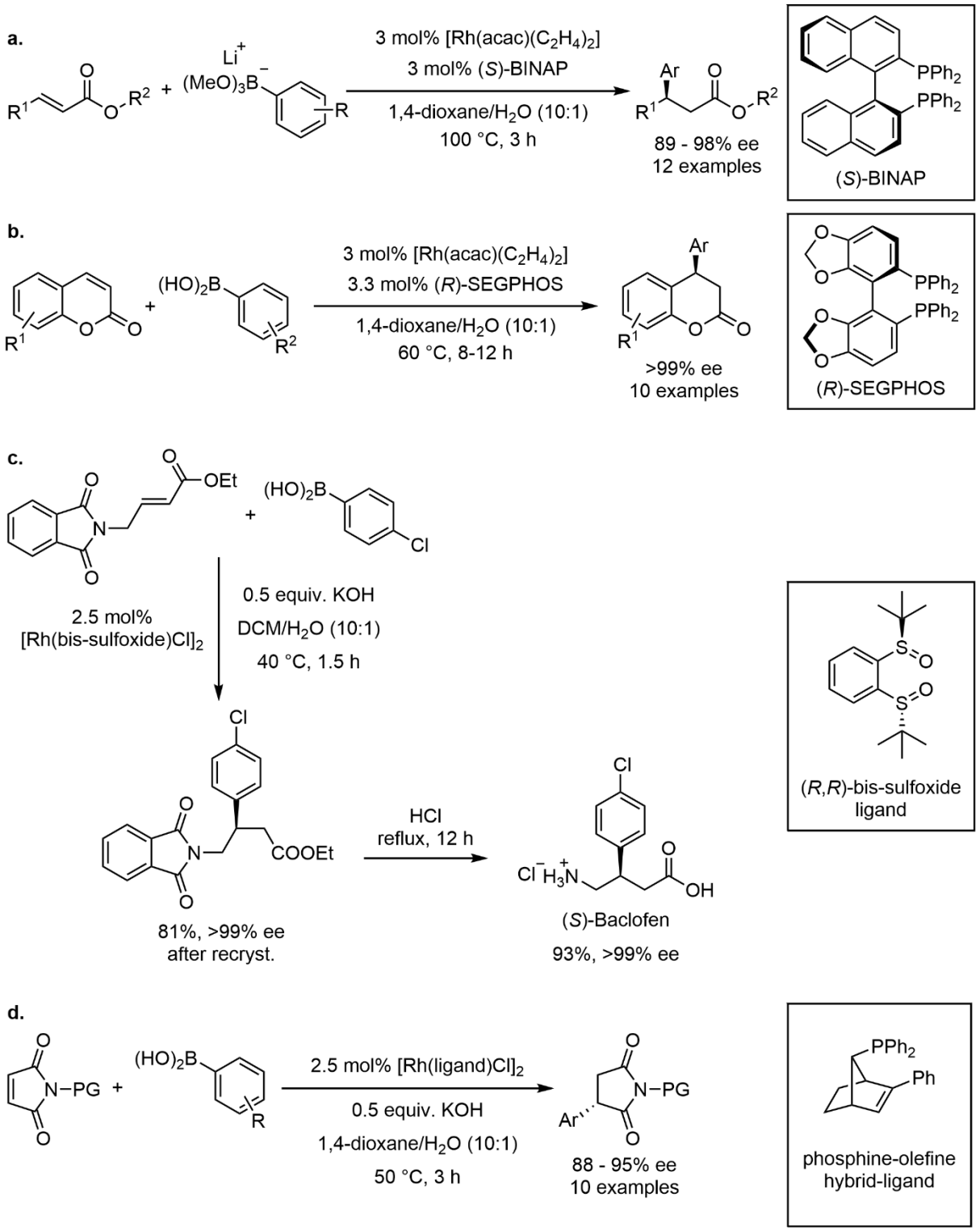
protodeboronation of the arylboronic acid.[26] This rhodium-hydroxido-complex **I** undergoes transmetalation (TM) with an arylboronic acid to form aryl-rhodium-complex **II**, followed by an insertion of the C–C-double-bond of the enone to achieve the oxa-π-allyl complex **III**. In a last step, hydrolysis of **III** liberates the 1,4-addition product and regenerates the active catalyst **I** (Figure 1).[24, 26] However, one major side reaction that potentially occurs when using boronic acids, and particularly (hetero)arylboronic acids, is the protodeboronation to the corresponding (hetero)arene derivative.[21]

1.2.1 Carbonyl electrophiles

Having demonstrated that the asymmetric Rh/BINAP catalysed 1,4-addition of aryl- and alkenylboronic acids avoids an undesired 1,2-addition as side reaction for both cyclic and acyclic ketones,[21] further carbonyl-based substrate classes were applied in this transformation.[27]

For this purpose, α,β-unsaturated esters proved suitable for the asymmetric conjugate addition of arylboronic acids; however, due to the reduced reactivity of acyclic α,β-unsaturated esters, more reactive lithiumborates were shown to be more efficient nucleophiles for such substrates (Scheme 5, a).[28] The corresponding α,β-unsaturated γ- and δ-lactones did not require this modification to achieve excellent yields and enantioselectivities,[28] and Hayashi and co-workers successfully expanded this methodology on α,β-unsaturated δ-lactones to less reactive coumarins (Scheme 5, b).[29] The synthetic utility of the asymmetric 1,4-addition to acyclic α,β-unsaturated esters was demonstrated by Helmchen and co-workers in the synthesis of γ-aminobutyric acid (GABA) analogue (*R*)-Baclofen.[30-31] In a later study, a bis-sulfoxide ligand with chirality originating from its sulfur centres was used to reproduce this synthesis, obtaining (*S*)-Baclofen in enantiomerically pure fashion (Scheme 5, c).[32]

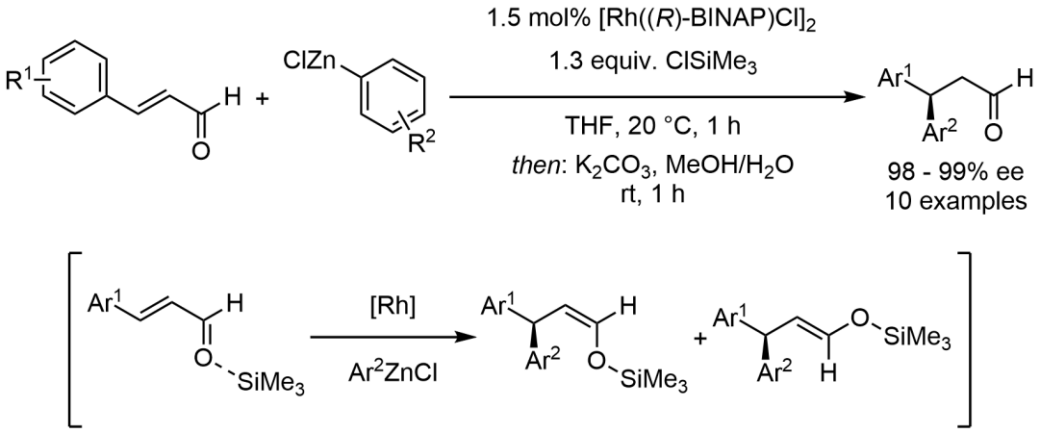
Despite their further reduced reactivity, both *α*,*β*-unsaturated acyclic amides[33] and *δ*-lactams[34] were demonstrated to undergo the 1,4-addition of arylboronic acids with high enantioselectivities, even though appropriate protection of the *N*-heteroatom is required to



Scheme 5: **a.** *α*,*β*-unsaturated esters as suitable substrates for a Rh-catalysed 1,4-addition, requiring lithium borate salts as more reactive nucleophiles;[28] **b.** Coumarin derivatives as example for *δ*-lactone substrates which readily undergo 1,4-addition with arylboronic acids;[29] **c.** Highly enantioselective synthesis of GABA analogue (*S*)-Baclofen;[32] **d.** Rh-catalysed 1,4-addition to protected, less reactive maleimides, using a hybrid ligand featuring both a phosphine and alkene coordinating to rhodium.[35]

obtain good yields. In a notable example for this substrate class, the application of a chiral phosphine-olefin hybrid ligand enabled the efficient 1,4-addition to a selection of *N*-protected maleimides, significantly improving results obtained with more conventional BINAP based ligand systems (Scheme 5, d).[24, 35]

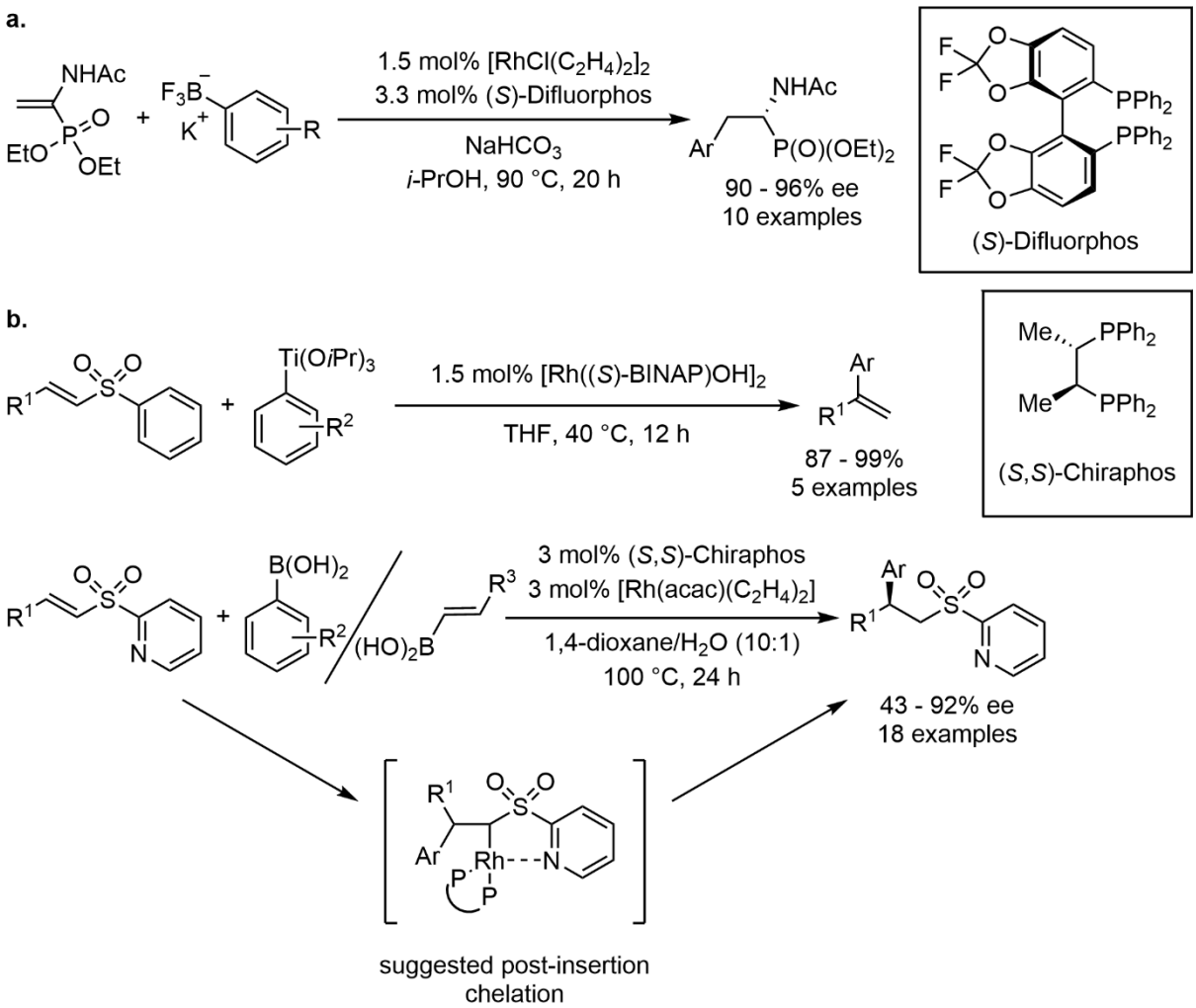
Among the series of α,β-unsaturated carbonyl compounds, aldehydes have been much more challenging substrates due to their innate reactivity to undergo an undesired 1,2-addition side reaction, which is additionally promoted by phosphine ligands coordinated to a rhodium catalyst.[36] Hence, the first successful Rh-catalysed asymmetric 1,4-addition of arylboronic acids to enals, as reported by the group of Carreira, avoided the use of phosphine ligands and instead employed a chiral diene ligand (see chapter 2.1.1, Scheme 19, c).[37] However, in combination with over-stoichiometric equivalents of chloro(trimethyl)silane as Lewis-acidic additive and arylzinc chlorides as nucleophiles, a Rh/BINAP catalyst was found to outperform the Rh/diene ligand system as well as an alternative Pd/Chiraphos system developed by Miyaura and co-workers (for Chiraphos ligand, see Scheme 7, b).[38-39] The underlying cause for the effect of chloro(trimethyl)silane still requires further investigation, but a Lewis-acidic interaction with the aldehyde was suggested as the activation mechanism (Scheme 6).[38]



Scheme 6: Highly enantioselective Rh-catalysed 1,4-addition to α,β-unsaturated aldehydes using arylzinc chlorides as nucleophiles. The additive TMS chloride is suggested to act as Lewis-acid to further activate the aldehyde. The regioselectivity of 1,4-addition versus 1,2-addition is governed by the transition-metal aryl nucleophile.[38]

1.2.2 Non-carbonyl electrophiles

Moving away from carbonyl compounds, other functionalities have been utilised to activate alkene substrates. Apart from nitroalkenes,[40] conjugated phosphonate esters have successfully been employed as substrates despite their lower reactivity as compared to carbonyl activated alkenes.[41] From a synthetic perspective, α-amino phosphonate esters constitute important building blocks for target molecules in the pharmaceutical and agrochemical industry. Hence, the enantioselective formation of α-amino phosphonate esters using a straightforward asymmetric 1,4-addition is an interesting example for the application of α,β-unsaturated phosphonates in this transformation (Scheme 7, a).[42] Perhaps surprisingly, phenyl-substituted α,β-unsaturated sulfones do not undergo a conjugate addition but rather eliminate the sulfone



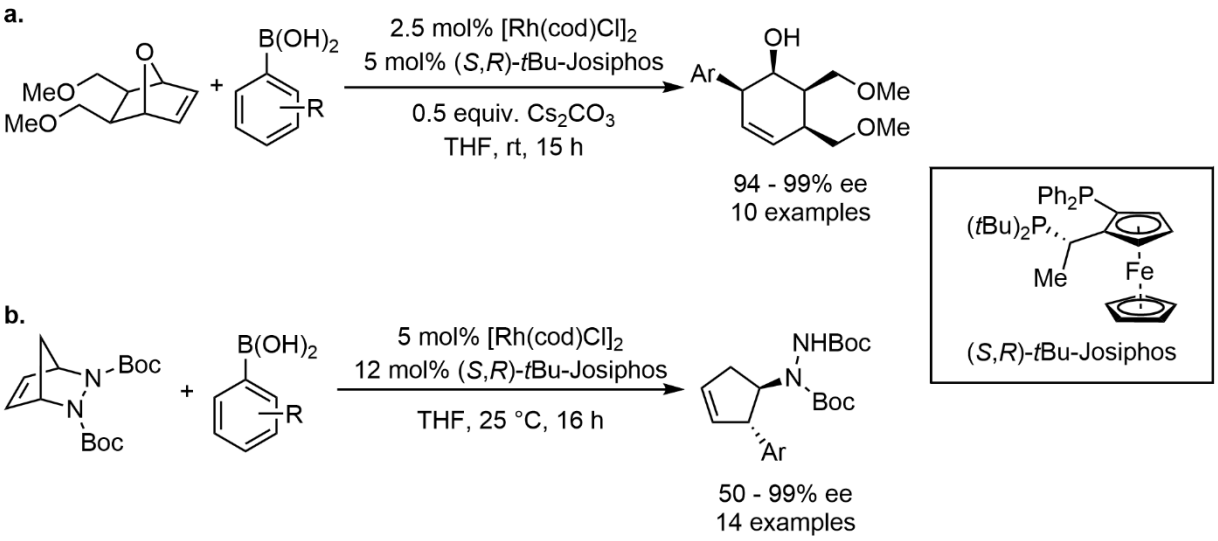
Scheme 7: **a.** Phosphonate-activated alkenes undergo 1,4-addition in the presence of protected amine groups, offering a pathway to the asymmetric synthesis of α-substituted amino phosphonates;[42] **b.** Top: Elimination of the sulfonyl moiety is suggested to be caused by a Rh-1,2-shift instead of a hydrolysis leading to the 1,4-addition product;[43] Bottom: Alternative substrate design to enable a successful 1,4-addition using a chelating 2-pyridyl moiety to prevent elimination.[44-45]

moiety in a Rh-catalysed S_N2-type substitution (Scheme 7, b, top).[43] Exploiting the chelating effect of a 2-pyridyl substituent on the sulfone moiety, the reaction occurs without further elimination, as the chelation prevents a Rh-1,2-shift and elimination pathway (Scheme 7, b, bottom).[44-45]

1.2.3 Strain-activated alkenes as electrophiles

Electron-deficiency achieved *via* a conjugated electron-withdrawing group is the most common strategy to generate activated alkenes suitable for 1,4-addition reactions. Alternatively, an alkene can be activated by the ring-strain present in mono- and bicyclic carbocycles, which can elegantly be released by ring-opening or by hydro-functionalisation of the unsaturated carbocycle. Such ring-opening reactions are mechanistically distinct from standard 1,4-addition reactions, but they do not proceed *via* a typical allylic substitution mechanism either (see chapter 1.3, Figure 2).

Lautens and co-workers developed the enantio- and diastereoselective ring-opening of oxa-bicyclic alkenes, which proceeds *via* a *β*-oxygen elimination step (Scheme 8, a).[46] This step triggers the ring-opening of the strained bicycle and therefore constitutes neither a 1,4-addition



Scheme 8: **a.** Rh-catalysed asymmetric ring-opening of oxa-bicycles, leading to all-*syn*-products *via* a *β*-O-elimination step;[46] **b.** Asymmetric ring-opening of diazabicycles *via* a *β*-N-elimination step. Alternative reaction conditions lead to the asymmetric hydroarylation of the diazabicycles instead of the ring-opening.[47]

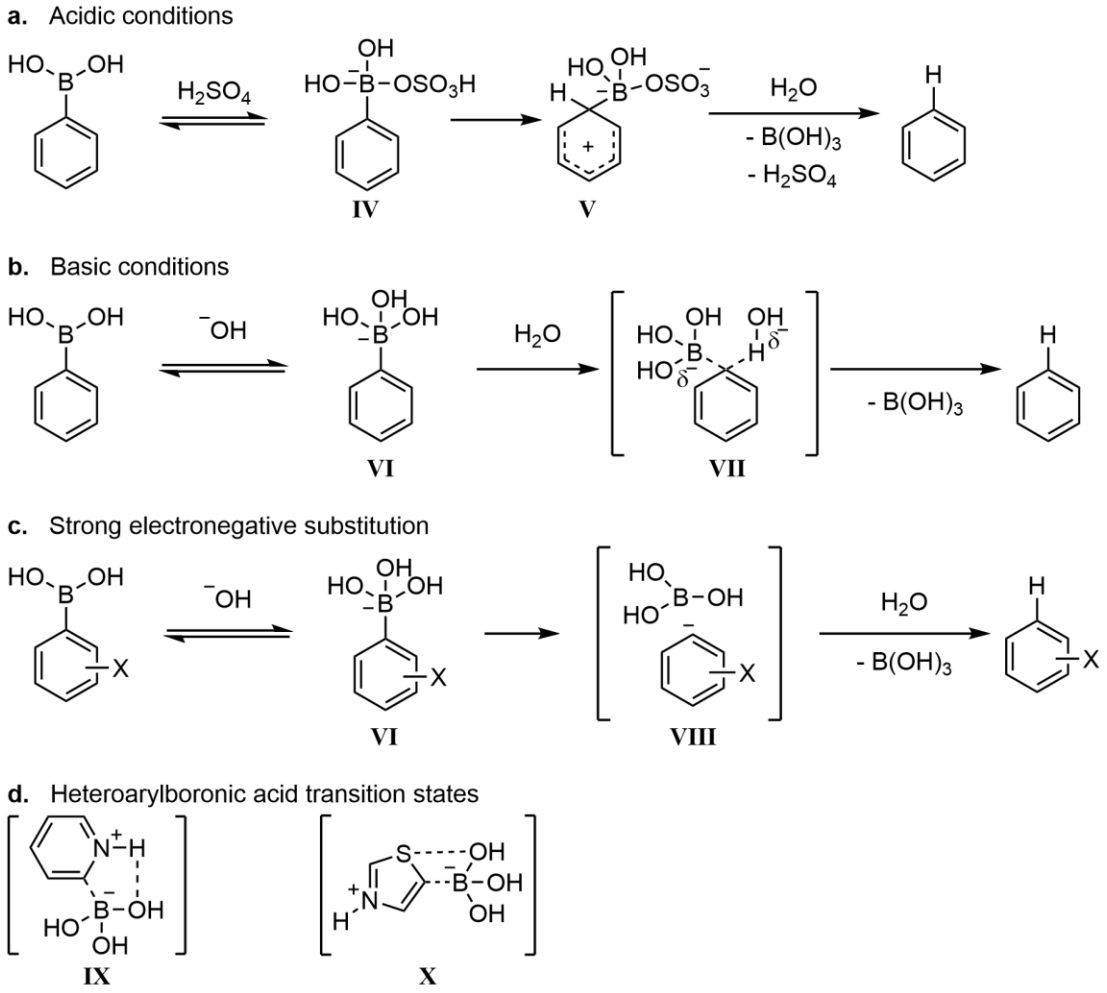
with the formation of an oxa-π-allyl complex prior to the hydrolysis of the catalyst, nor a classic allylic substitution *via* the formation of an η^3-allyl complex. Further, similar reactivity was discovered in diazabicycles which undergo β-nitrogen elimination to release ring-strain and the mechanism was shown to be ligand controlled, as the chemoselectivity could be switched to a Rh-catalysed hydroarylation process instead of the ring-opening by changing the ligand (Scheme 8, b).[47]

1.2.4 Aromatic nucleophiles – Boronic acids and protodeboronation

Due to their accessibility and their air and moisture stability, as well as their generally low toxicity, boronic acids frequently serve as highly practical nucleophiles in a wide range of transition-metal catalysed reactions. However, one disadvantage of these organometallic reagents is their ability to undergo protodeboronation, in which they form usually unreactive side products and therefore require excess equivalents of boronic acids to be used efficiently.

One possible pathway for Rh-catalysed protodeboronation is *via* hydrolysis of aryl-rhodium-complex **II** (Figure 1).[48-49] Depending on the electronic properties of the (hetero)arylboronic acids and the reaction conditions in protic (co-)solvents, the stability of boronic acids is particularly affected by an acid- or base-catalysed protodeboronation, which warrants consideration when examining the scope of a catalytic system or choosing a model reaction for optimisation studies.[50-51] The mechanism for this type of protodeboronation has been shown to be dependent on the pH of the reaction medium, as well as on the effects of heteroatoms in heteroarylboronic acids.[50-51] Initial kinetic studies in acidic conditions found an acid-catalysed protodeboronation mechanism *via* the formation of boronate **IV**, followed by the intramolecular protonation of the *ipso* position, leading to the formation of the zwitterionic σ-complex **V** and subsequent cleavage of the C–B-bond (Scheme 9, a).[52] This stepwise mechanism has recently been shown by the group of Lloyd-Jones not to apply to the base-catalysed protodeboronation

of slightly electron-deficient and electron-rich arylboronic acids.[50] For these systems, the most likely protodeboronation pathway was determined to include the concerted protonolysis step **VII** instead of a stepwise S_EAr-type mechanism (Scheme 9, b). With increasing electron-deficiency of the aromatic boronic acids, a dissociative anionic mechanism becomes more competitive as the resulting aryl anion **VIII** is stabilized more efficiently. Particularly, *ortho*-fluoro-substituents facilitate this process by enabling an additional orbital delocalisation of the free electron pair of the aryl anion, thus rendering the boronic acid less stable.[50] Protonation of this aryl anion species outcompetes a possible re-association with boric acid and other cations or the formation of an aryne side product (Scheme 9, c).[53] While the diverse electronic properties of heteroarylboronic acids impede the identification of clear trends, the



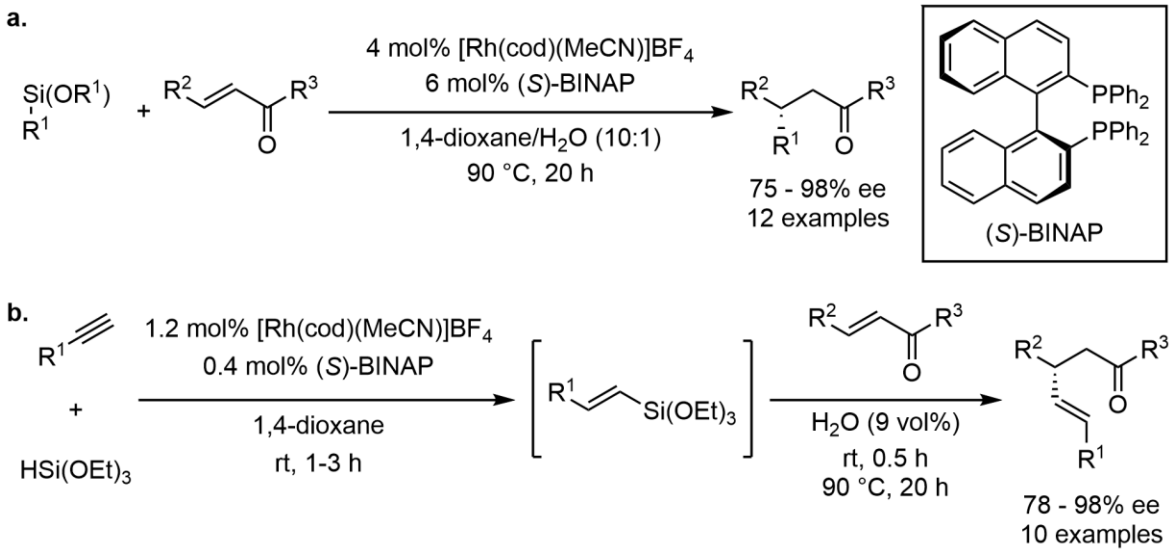
Scheme 9: **a.** Proposed mechanism for the acid-catalysed protodeboronation of arylboronic acids in the presence of sulfuric acid, which cannot be extrapolated to basic conditions;[52] **b.** Concerted hydrolysis of electron-rich aryl borates **VI** in a basic environment;[50] **c.** Dissociation mechanism for electron-deficient aryl borates **VI** *via* a stabilised aryl anion **VIII**;[53] **d.** Examples of alternative stabilisation mechanisms which accelerate protodeboronation in heteroarylboronic acids over a range of pH-values.[51]

protodeboronation mechanisms of heteroarylboronic acids can include a zwitterionic or orbital stabilisation of boronates such as **IX** and **X** (Scheme 9, d). In addition, autocatalytic protodeboronation processes in the presence of both boronic acid and boronate have been observed, as well as the disproportionation to boranes and borinic acid.[51]

1.2.5 Aromatic nucleophiles – Further organometallic reagents

Despite this potential for protodeboronation, (hetero)arylboronic acids are the most common nucleophiles for Rh-catalysed asymmetric 1,4-addition reactions. However, organometallic substrates other than boronic acids and their derivatives, such as boronic pinacol- or MIDA-esters and potassium trifluoroboronates, have been reported for this transformation.[24, 54-55]

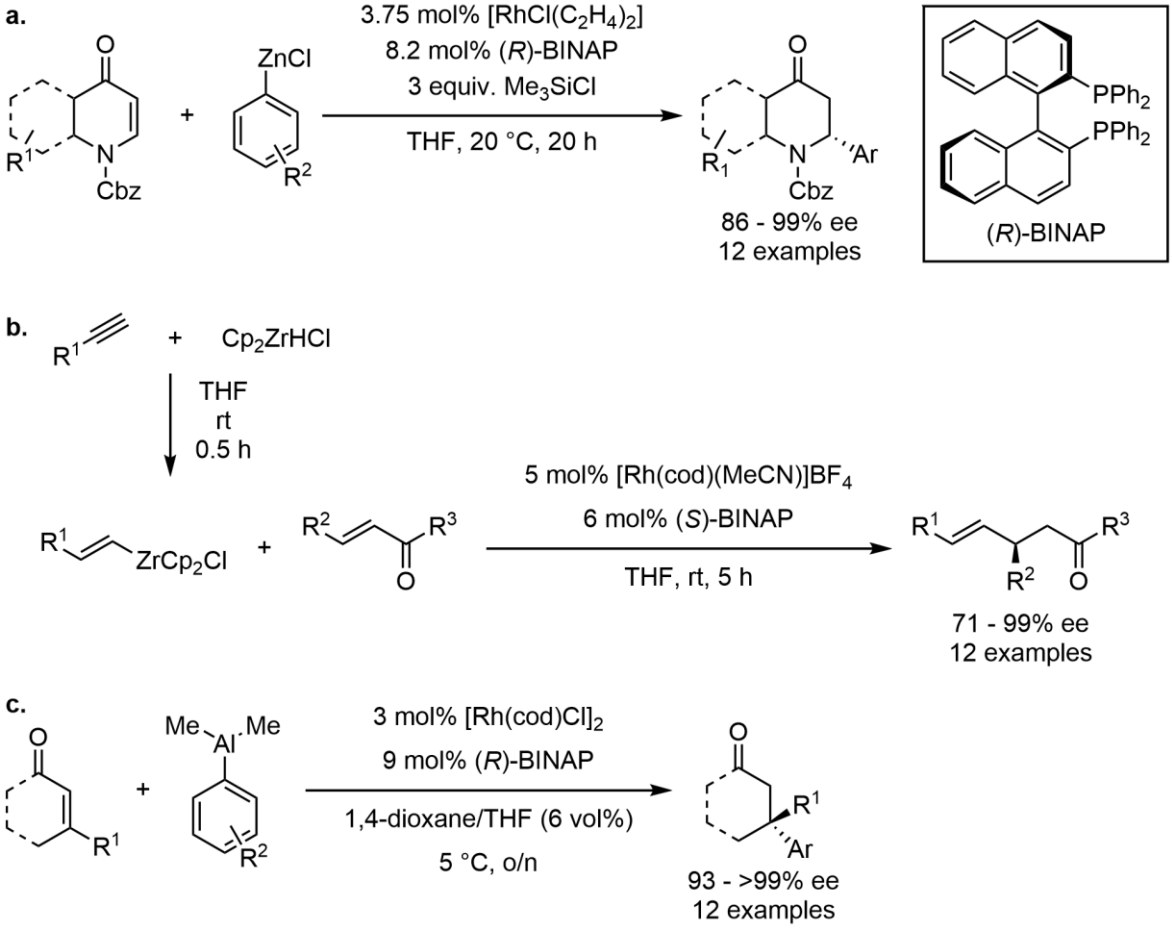
Oi and co-workers employed aryl- and alkenyl-siloxanes in their asymmetric 1,4-addition reaction to various cyclic and acyclic *α*,*β*-unsaturated carbonyl compounds, including a range of esters and amides (Scheme 10, a).[56-57] This strategy is sufficiently robust to allow for the development of a one-pot hydrosilylation of alkynes and the subsequent asymmetric 1,4-addition of the resulting alkenyl siloxanes to *α*,*β*-unsaturated ketones (Scheme 10, b).[58] Tetraorgano-silanes have also been identified as viable reagents, as long as their substituents



Scheme 10: **a.** Rh-catalysed 1,4-addition of siloxanes to *α*,*β*-unsaturated enones;[56] **b.** One-pot procedure combining a Rh-catalysed hydrosilylation and 1,4-addition of alkenyl-siloxanes to *α*,*β*-unsaturated enones.[58]

allow for an intramolecular formation of a siloxane during the transmetalation process (cf. chapter 2.1.1, Scheme 20, c).[59-60] Lacking the availability of this pathway, silanes are less prone to undergo transmetalation with rhodium, as Rh-catalysed alkynylation reactions that use sterically encumbered silyl-acetylenes as inert termini for the alkynylation have been reported.[61-63]

Expanding the Rh-catalysed asymmetric 1,4-addition to protected 2,3-dihydro-4-pyridones and quinolones, Hayashi and co-workers demonstrated the utility of arylzinc chlorides as nucleophiles in mild conditions and in the presence of excess equivalents of chloro(trimethyl)-silane (Scheme 11, a).[64-65] Further organometallic nucleophiles for the asymmetric 1,4-addition to *α,β*-unsaturated ketones comprise alkenyl zirconocene chlorides – obtained *via* the hydrozirconation of alkynes with Schwartz' reagent (Cp_2ZrHCl) (Scheme 11, b)[66] – as well



Scheme 11: **a.** Asymmetric 1,4-addition of arylzinc chlorides to pyridinones and quinolones; for the latter an excess of TMS-chloride is required as an additive;[65] **b**. Sequence of hydrozirconation of a terminal alkyne with Schwartz' reagent, followed by the Rh-catalysed 1,4-addition of the alkenyl zirconocene species to *α,β*-unsaturated enones;[66] **c.** Highly enantioselective construction of all-carbon quaternary centres *via* the asymmetric 1,4-addition of aryl alanes to *β*-substituted cyclic and acyclic enones.[70]

as aryl(trialkoxy) titanium reagents,[43, 67] and organo-stannanes.[68-69] Organo-aluminium species can be used as nucleophiles as demonstrated by the group of Alexakis, which employed aryl-alanes in the enantioselective formation of quaternary centres, using α,β-unsaturated, β-substituted enones (Scheme 11, c).[70]

1.3 Rh-Catalysed Allylic Substitution with *C*-Nucleophiles

Allylic substitution reactions are typically associated with Pd-catalysed transformations of allylic carbonates or acetates – the classic Tsuji-Trost reaction – with stabilised nucleophiles, resulting in the substitution of a leaving group with the nucleophile to give products either resembling an S_N2-type or S_N2'-type reaction.[71] A short time after reporting the Pd-catalysed allylic substitution, the group of Tsuji developed a Rh-catalysed intramolecular variant of this reaction in 1984.[17] While the mechanism of the typical Pd-catalysed allylic substitution is well

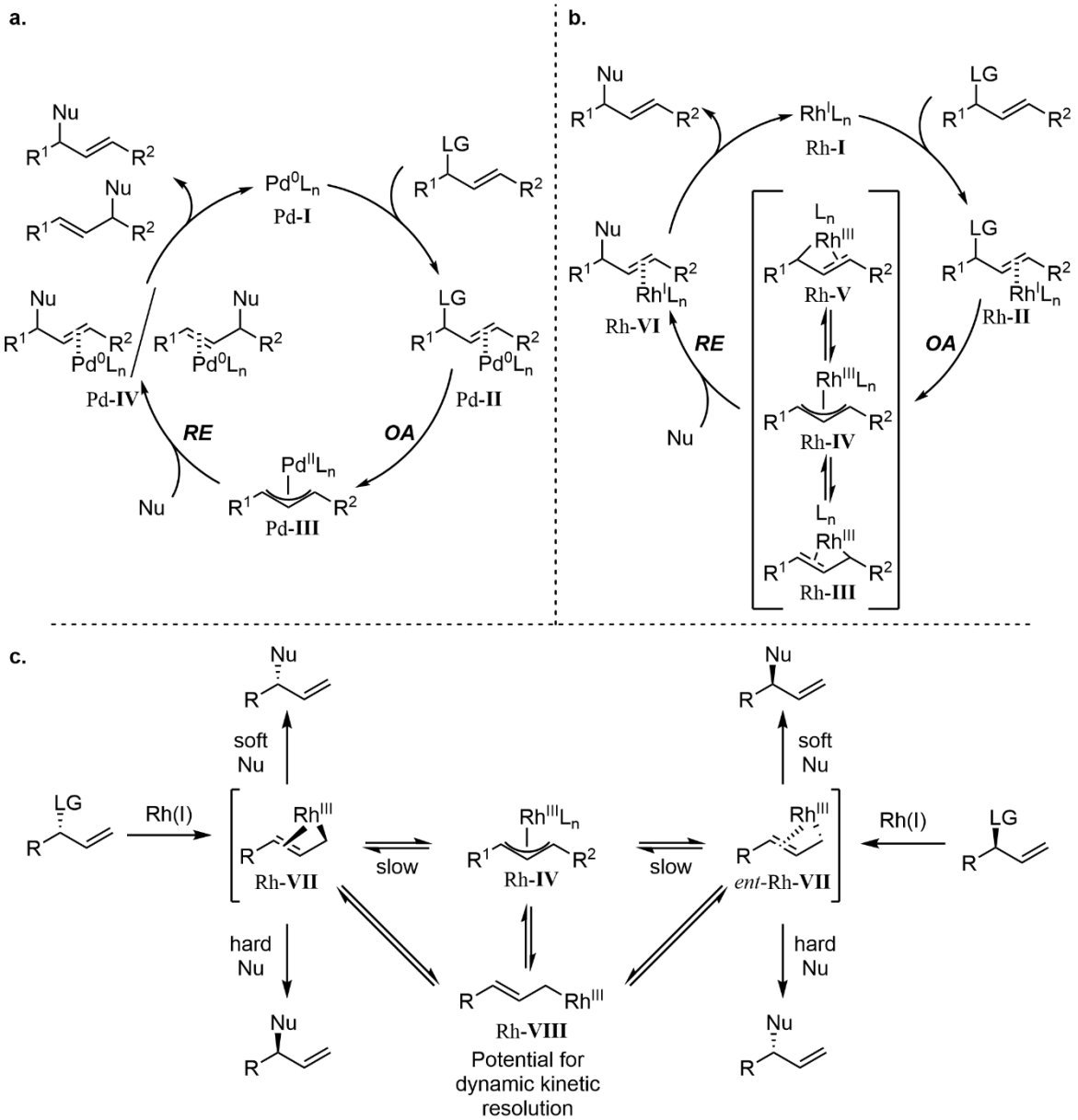


Figure 2: **a.** Typical mechanism for a Pd-catalysed allylic substitution *via* a π-allyl-complex; **b.** Mechanistic proposal for Rh-catalysed allylic substitutions, centred on a π-allyl-complex with strong σ-component (σ+π-complex); **c.** Model explaining both regio- and stereospecificity of Rh-catalysis, including a pathway for a dynamic kinetic resolution enabling enantioselective allylic substitutions.[72]

understood (Figure 2, a), the mechanistic details of the corresponding Rh-catalysed transformation are not completely analogous to the Pd-mediated catalytic cycle and require a brief introduction (Figure 2, b).[72]

In the generally accepted mechanism for an allylic substitution, the Pd(0)-catalyst (Figure 2, a, Pd-**I**) coordinates to the allylic alkene (Pd-**II**) and undergoes oxidative addition to form the delocalised Pd(II)-π-allyl complex Pd-**III**, cleaving the C–'R'-bond of an appropriate leaving group in the process. A suitable nucleophile then attacks the π-allyl complex to form a new C–C-bond, and the catalyst reductively eliminates to Pd-**IV**.[73] As there are two possible termini available for this nucleophilic attack, two regioisomeric products are accessible for non-C_2-symmetric allyl fragments. The ratio of these regioisomers depends on which terminus of the π-allyl complex is more electrophilic or less sterically hindered, or which catalyst system is employed in the specific transformation. In contrast, Rh-catalysed allylic substitution reactions are especially prone to a nucleophilic attack at the carbon centre connected to the leaving group.[74] While investigating this anomaly, Evans and co-workers postulated a mechanistic model involving a distorted π-allyl complex (Figure 2, b, Rh-**III**) that features a significant σ-component and could be interpreted as a σ+π-complex.[74] This intermediate can undergo a σ-π-σ isomerisation to Rh-**V** *via* a more conventional π-allyl complex Rh-**IV**. The preferred substitution at the position of the former leaving group is thus rationalised by assuming that this isomerisation process is slow compared to the nucleophilic attack that gives Rh-**VI**.[74]

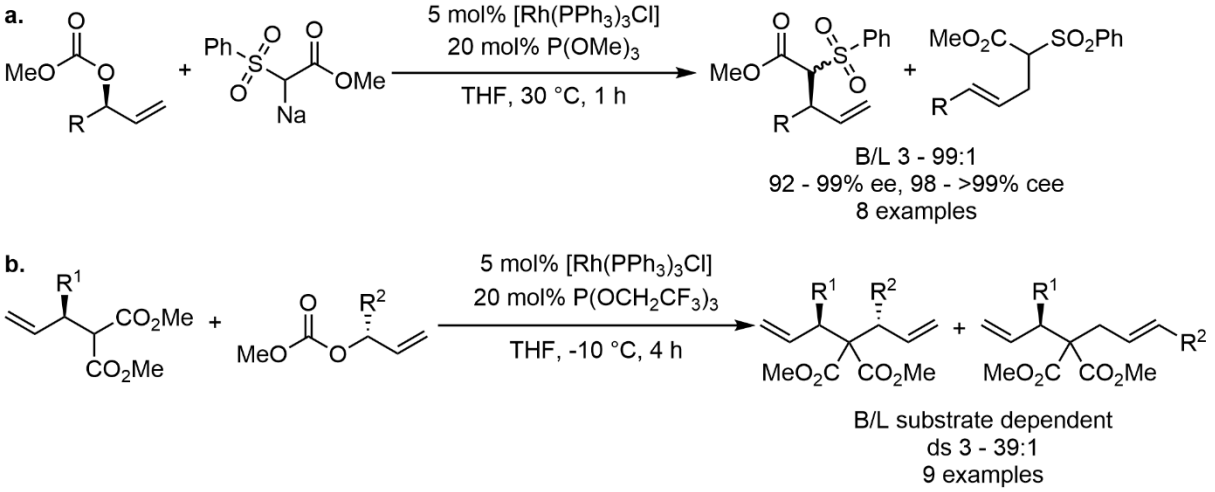
The intermolecular Rh-catalysed allylic alkylation using non-C_2-symmetric allylic carbonates was first reported by Tsuji and co-workers with regioselectivities up to 9:1 in favour of branched products.[16] However, this area of catalysis did not advance with the same dynamics as the Pd-catalysed allylic substitutions with C_2-symmetric electrophiles.[75] While Pd-catalysed systems prove particularly powerful for stabilised (soft) nucleophiles, examples for the use of unstabilised (hard) nucleophiles are scarce.[19] In contrast, Rh-catalysed allylic substitutions exhibit a higher versatility and tolerate unstabilised, as well as stabilised, nucleophiles.[76] Both

unstabilised and stabilised nucleophiles exhibit a strong tendency to undergo Rh-catalysed allylic substitutions in a stereospecific fashion, further complicating the development of widely applicable stereoselective Rh-catalysed allylic transformations.[73]

Conceptually, stabilised nucleophiles are expected to attack the allyl fragment of an enantiomerically enriched Rh-complex (Figure 2, c, Rh-**VII**) with an inversion of configuration, resulting in the overall retention of the configuration of the electrophile. However, unstabilised nucleophiles undergo coordination or transmetalation at the rhodium centre, triggering a reductive elimination from the same face as the catalyst, which leads to an inversion of the original configuration of the electrophile. Thus, this stereospecific nucleophilic attack, in combination with a slow interconversion of Rh-**VII** and *ent*-Rh-**VII**, poses a significant challenge for the development of highly enantioselective Rh-catalysed allylic substitutions.[73]

1.3.1 Enantiospecific Rh-catalysed allylic alkylation

Evans and co-workers developed a regioselective and enantiospecific allylic alkylation of enantioenriched carbonates with stabilised sodium methyl sulfonylacetates, which exhibits excellent levels of conservation of enantiomeric excess (cee) (Scheme 12, a).[77] Introducing enantioenriched nucleophiles to a similar catalytic system enabled the diastereospecific



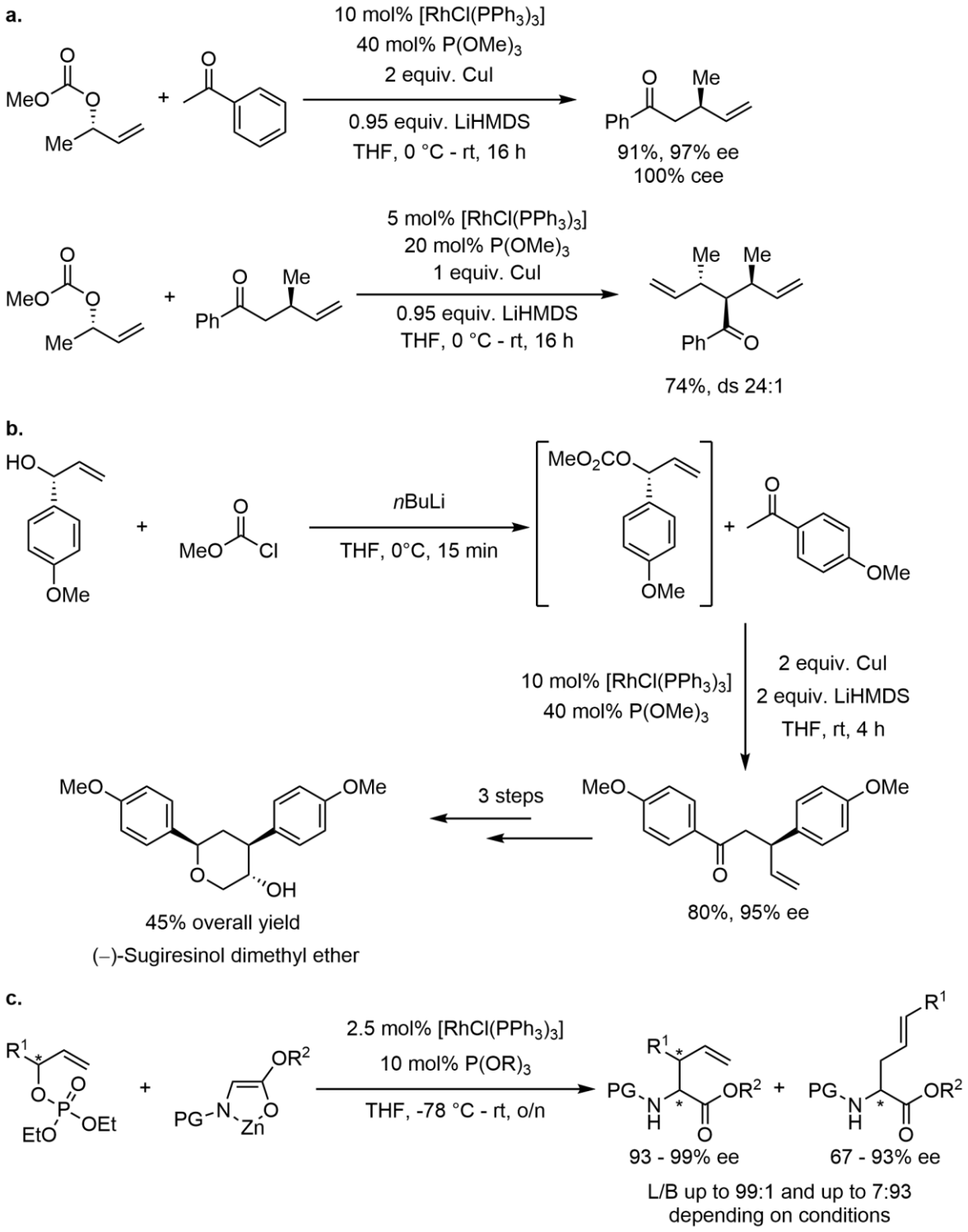
Scheme 12: **a.** Enantiospecific Rh-catalysed allylic alkylation using sulfonyl acetate as a soft nucleophile after deprotonation with NaH;[77] **b.** Enantiospecific allylic alkylation of malonates with enantioenriched electrophiles to give 1,3-disubstituted products in moderate to excellent diastereoselectivity.[78]

formation of *anti*-configured 1,3-substituted compounds, which are synthetically useful building blocks to access highly substituted small carbocycles or lactones (Scheme 12, b).[78] This example also highlights the effect of electronic tuning of the mono-phosphite ligands employed in this transformation, as the regioselectivity of the reaction improves with increasing electronegativity of the ligand.[78]

An important class of nucleophiles recurring across organic synthesis and catalysis are enolisable carbonyl compounds, which offer a pathway to establishing a new C–C or C–heteroatom-bond in α-position to the carbonyl moiety. Despite the early disclosure of cyclic silyl-enolate examples in the initial reports of Rh-catalysed allylic alkylations by the group of Tsuji,[16] a regioselective and enantiospecific catalytic system using enolates was first developed by Evans and co-workers in 2003 (Scheme 13, a).[79] Investigating lithium bases for the enolate formation and Cu(I)-halides for a subsequent transmetalation to obtain 'softer' Cu-enolates, it was found that the combination of a lithium-base and Cu(I)-salt was crucial for achieving both high yields and regioselectivities.[79] Further, the halide anion of the Cu(I)-salt significantly influenced both the enantiospecificity and regioselectivity of the reaction.[79] To showcase its synthetic utility, this transformation was applied in the first step of a 4-step synthesis of (–)-Sugiresinol dimethyl ester, a compound with antifungal activity (Scheme 13, b).[80]

Another highly useful example was developed by the group of Kazmaier, who re-designed an originally Pd-catalysed allylic substitution which exhibited unsatisfactory regioselectivity (Scheme 13, c).[81] By switching to a Rh-catalysed system, the regioselectivity was significantly improved and could be controlled by choosing appropriate reaction conditions. The nucleophile in this case is an amino ester enolate which is formed by the chelation of zinc chloride.[81] The synthesis of exclusively linear amino esters with high diastereo- and enantiospecificity allows for the construction of wide arrays of substituted amino acids that can be accessed through a

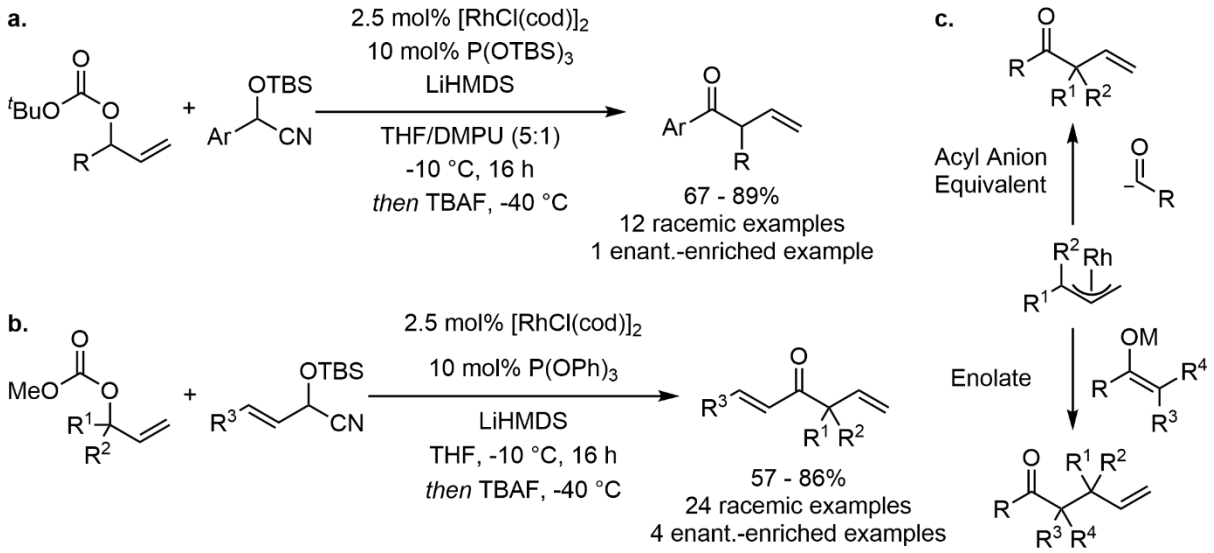
straightforward deprotection of both the amine and ester moieties. Further, this reaction demonstrates a remarkable regioselectivity controlled by the electronic and steric properties of both the amine-protecting group and the ester moiety of the nucleophile, thereby overwriting



Scheme 13: **a.** Two examples for the enantiospecific allylic alkylation of benzaldehyde (top) and an enantioenriched aryl ketone (bottom), which require a combination of Li-base and Cu(I)-salt to achieve high regio-and stereospecificity;[79] **b.** First two steps of the synthesis of antifungal agent (–)-Sugiresinol dimethyl ether, illustrating the utility of an enantiospecific allylic substitution of a substituted benzaldehyde nucleophile;[80] **c.** An amino ester enolate chelating Zn is a suitable nucleophile for the formation of substituted amino esters which are easily hydrolysed to the corresponding amino acids.[81]

the generally favoured substitution at the carbon centre of the leaving group in Rh-catalysed allylic alkylations.[81]

The α-substitution of the carbonyl compounds, obtained as products of allylic alkylation reactions outlined in the paragraph above, is governed by the substitution pattern of the enolate nucleophiles. In a reversion of this approach, Evans and co-workers employed acyl anion surrogates to install a carbonyl moiety directly on a functionalised allyl fragment (Scheme 14, c).[73] This approach enables the enantiospecific formation of tertiary and quaternary centres in α-position to the carbonyl moiety (Scheme 14, a and b).[82-85] This methodology is based on the use of protected cyanohydrins as pronucleophiles for acyl anions, which are 'activated' by a deprotonation in the presence of a lithium base, thereby rendering the tertiary carbon centre of the cyanohydrin nucleophilic. Following the nucleophilic attack on a Rh-π-allyl complex, a deprotection of the tertiary alcohol with subsequent elimination of the nitrile-group generates the α-substituted carbonyl moiety (Scheme 14, a).[82] This transformation was shown to elegantly access all-carbon quaternary centres in α-position to ketones in a stereospecific fashion, which is a non-trivial target motif (Scheme 14, b).[73, 84]



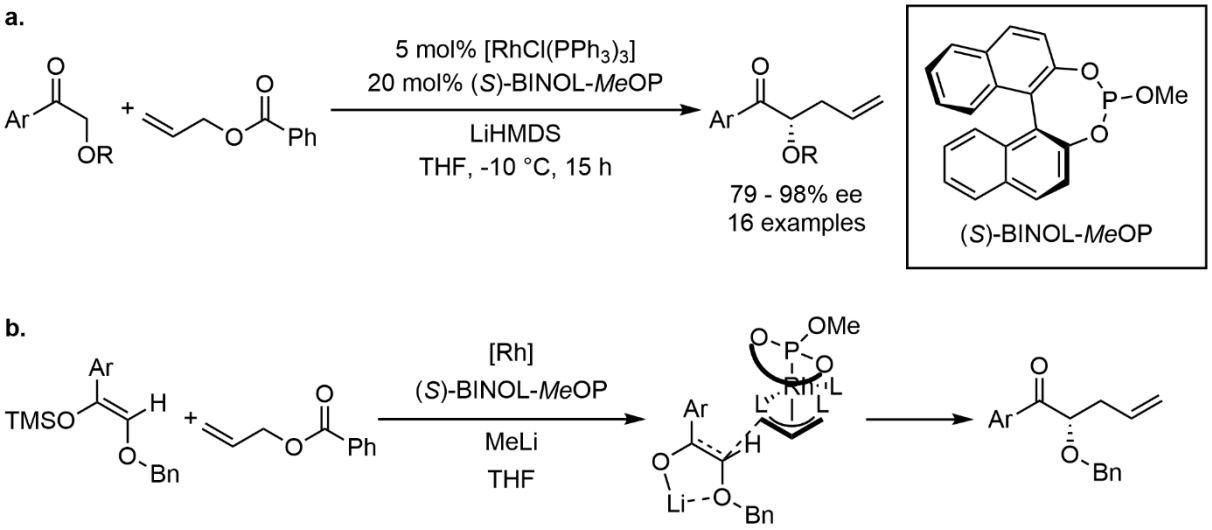
Scheme 14: **a.** Aryl cyanohydrins serve as acyl anion surrogates to achieve tertiary carbon centres in α-position to the carbonyl moiety of the allylic substitution product;[82] **b.** Formation of all-carbon quaternary centres using the same cyanohydrin strategy, the deprotection of the carbonyl is performed as one-pot procedure;[84] **c.** Conceptual approaches to α-functionalisation of the carbonyl moiety in allylic substitution reactions; acyl anions allow for the introduction of these substituents as part of the allylic substitution reaction.[73]

Similar strategies have been developed using 1-phenylsulfonyl-1-nitroethane as acyl anion equivalent and *N*,*N*-dialkylhydrazones as surrogates for formyl anions.[86-87]

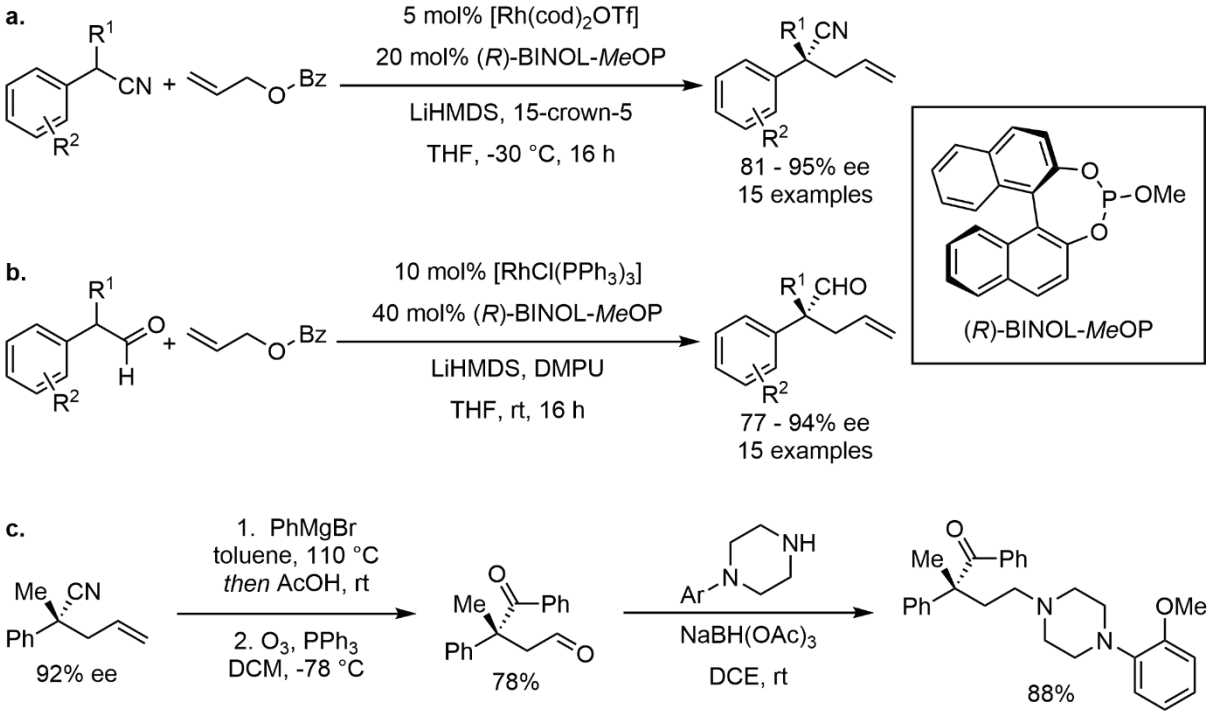
1.3.2 Enantioselective Rh-catalysed allylic alkylation

Having discussed systems for the enantiospecific allylic alkylation of predominantly linear electrophiles with a range of carbon-nucleophiles, the question remains how enantio*selectivity* can be achieved in allylic substitutions. Rendering these transformations enantioselective requires a modification of the active catalyst to overwrite or circumvent the enantiospecific attack of (un)stabilised nucleophiles, and a selection of successful strategies will be briefly introduced in this section.

Approaching the 'enantioselectivity challenge,' the group of Evans developed a strategy based on the well-established concept of facial discrimination of two enantiotopic faces during a nucleophilic attack, which is facilitated by a chiral catalyst (Scheme 15, a).[88] In this system, an α-alkoxy aryl ketone is deprotonated to form a lithium-enolate, which acts as nucleophile and attacks a chiral Rh-π-allyl complex in enantioselective fashion. Control experiments with potassium as the chelated cation resulted in racemic product, indicating that a comparatively small cation is required to achieve a stabilised transition state geometry (Scheme 15, b).[88]



Scheme 15: **a.** Enantioselective Rh-catalysed allylic alkylation of a prochiral enolisable carbonyl nucleophile; **b.** Proposed role of the Li-base in determining the nucleophile geometry after the enolate formation.[88]

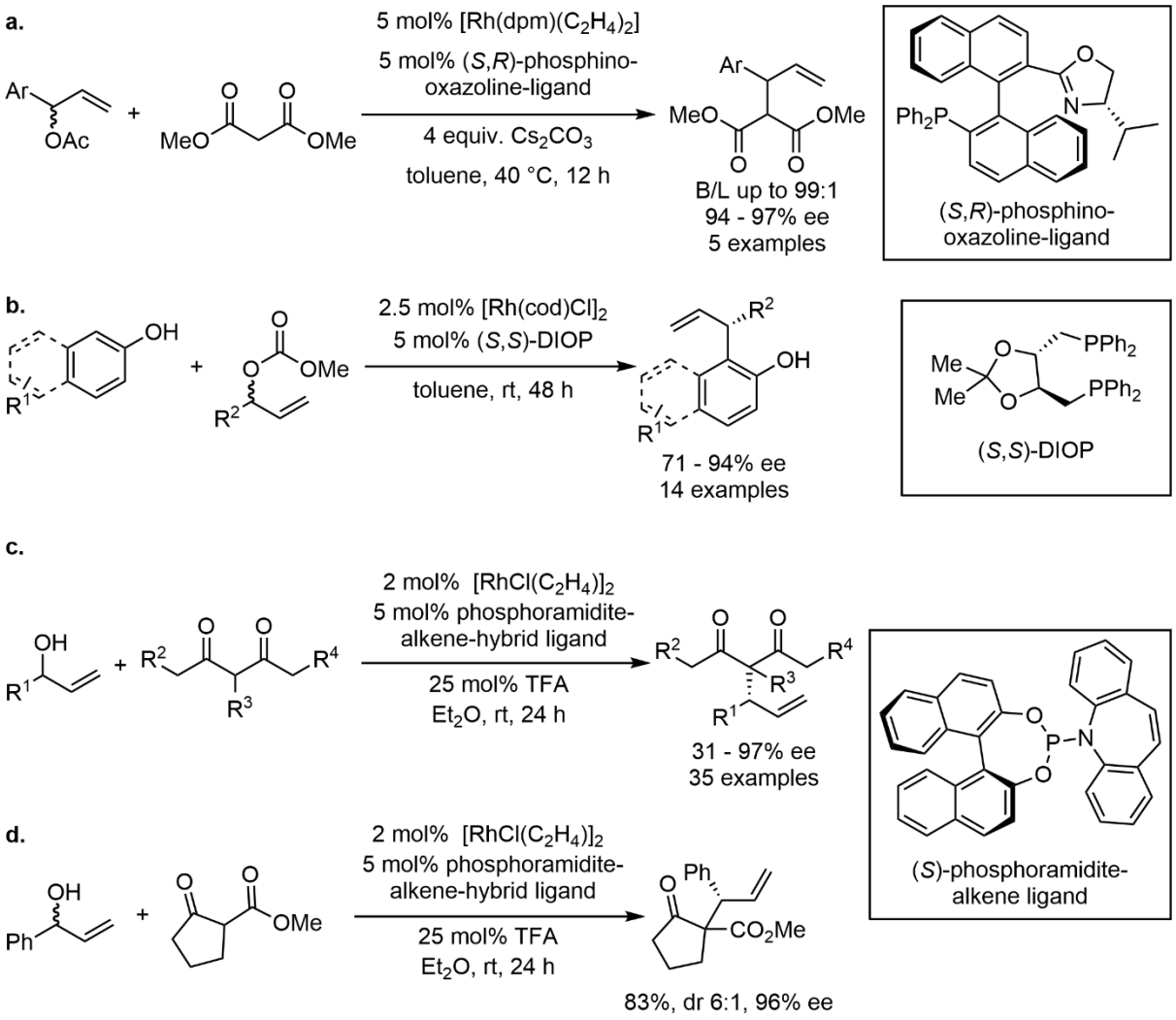


Scheme 16: **a.** Application of prochiral benzyl nitrile nucleophiles in the Rh-catalysed enantioselective allylic alkylation using a Li-base to activate the nucleophile;[89] **b.** Extension of this strategy to aldehydes to obtain synthetically useful *α,α*'-functionalised ketals;[90] **c.** Synthesis of a serotonin antagonist, demonstrating the utility of the enantioenriched *α,α*'-functionalised nitrile as a synthetic handle.[89]

Since exclusively C_2-symmetric allylic fragments were selected in this study, a potential racemisation of the Rh-*π*-allyl complex is not relevant for the selectivity of the product formation.[88] This strategy – generating prochiral nucleophiles by exposing suitable pronucleophiles to a lithium base – was subsequently expanded to *α*-substituted benzyl nitriles and benzaldehydes, with the former effectively acting as a nitrile anion while the latter is used as an enolate nucleophile (Scheme 16, a and b).[89-90] Using the same BINOL-derived monodentate phosphite ligand (*R*)-BINOL-*Me*OP, both nucleophiles allow for the enantioselective formation of all-carbon quaternary stereocentres in *α*-position to a versatile synthetic handle, and this advantage was showcased in the synthesis of a serotonin antagonist with the key motif of an *α,α*'-difunctionalised carbonyl moiety (Scheme 16, c).[89]

The complementary strategy to the outlined enantioinduction *via* a face-selective nucleophilic attack is based on the dynamic kinetic resolution of a non-C_2-symmetrical, substituted racemic allyl fragment by a Rh-catalyst. In this case, the attack of an achiral nucleophile is ligand-controlled, and enantioenriched products can be obtained. Early observations of moderate

enantioinduction of a Rh-catalysed allylic alkylation of racemic electrophiles were reported by Pregosin and co-workers.[91] However, the group of Hayashi is credited for developing a highly regio- and enantioselective Rh-catalysed allylic alkylation using racemic allylic acetals (Scheme 17, a).[92] Employing an axially chiral phosphino-oxazoline hybrid ligand, this catalytic system enables the racemisation of the distorted Rh-π-allyl complex, thereby changing the mechanism from an enantiospecific substrate-controlled to an enantioselective ligand-controlled pathway.[73] This equilibration potentially occurs *via* an η^1-Rh-allyl complex, which would remove the previous stereoinformation of the allyl fragment (see Figure 2, Rh-**VIII**), as suggested by Breit and co-workers.[93-94] While working on the allylic substitution of phenols

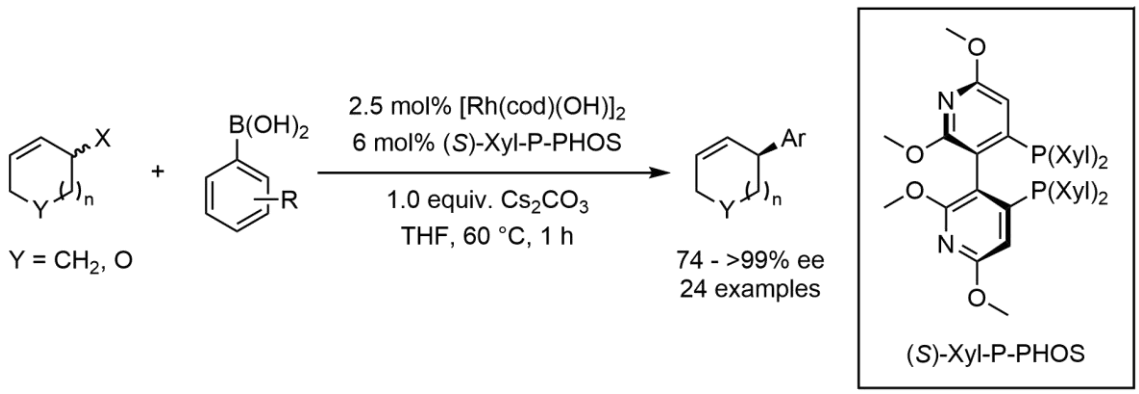


Scheme 17: **a.** Rh-catalysed enantioselective allylic alkylation of dimethyl malonate *via* a dynamic kinetic resolution of a racemic allyl acetate as electrophile;[92] **b.** Csp^2–Csp^3-bond formation in *ortho*-position of phenols using racemic allyl carbonates;[94] **c.** Enantioselective formation of all-carbon quaternary centres by Rh-catalysed allylic alkylation of 1,3-diketones using allyl alcohols; activation of the leaving group is achieved by the acidic additive TFA;[95] **d.** Rare example of the enantioselective allylic alkylation of a prochiral nucleophile and a racemic allyl-fragment, resulting in the diastereoselective formation of two adjacent stereocentres.[95]

with racemic allylic carbonates, they discovered a pathway for the intermolecular enantioselective formation of a C–C-bond in *ortho*-position to the phenolic hydroxy substituent (Scheme 17, b).[94] Using (*S*,*S*)-DIOP as ligand, a range of 2-naphthols and substituted phenols were susceptible to the transformation in satisfactory-to-good yields and enantiomeric ratios. The proposed mechanism is centred on the suggested Rh-η^1-allyl complex as a resting state (see Figure 2, Rh-**VIII**), in which the stereoinformation of the substrate is removed.[94] The following C–C, C–O, or C–N-bond formation is controlled by a chiral ligand and thus determines the enantioselectivity of the allylic substitution.[94]

The examples discussed so far require activated alkenes – that is, leaving groups in allylic position – to allow for a successful oxidative addition of a transition metal catalyst. Recently, the group of You achieved a highly regio- and enantioselective allylic alkylation of otherwise non-activated allylic alkyl and aryl alcohols in combination with stabilised 1,3-dicarbonyl nucleophiles (Scheme 17, c).[95] To compensate for the lack of electronegativity of the leaving hydroxy moiety, the reaction requires 25 mol% of trifluoroacetic acid to facilitate the formation of a Rh-π-allyl complex. Further, the potential of this transformation is demonstrated by the allylic alkylation of a prochiral β-ketoester with good diastereo- and excellent enantiocontrol, resulting in two adjacent asymmetrically substituted carbon centres (Scheme 17, d).[95] This represents, to the best of the author's knowledge, the first example of both an non-C_2-symmetric allyl fragment and a prochiral nucleophile undergoing a Rh-catalysed allylic alkylation in an enantioselective fashion.

While Rh-catalysed enantiospecific allylic substitutions have seen significant advances, asymmetric allylic alkylations have only gained wider attention much more recently. The related Rh-catalysed asymmetric allylic arylation has been reported once in enantiospecific fashion,[96] and our group developed an enantioselective arylation of racemic cyclic allyl chlorides (Scheme 18).[97-98] This underlines that the field of Rh-catalysed enantioselective allylic substitution reactions, particularly asymmetric allylic arylations, requires substantial further development.



Scheme 18: Rare example of a Rh-catalysed asymmetric allylic arylation of a racemic starting material, operating *via* a DYKAT mechanism.[97-98]

2. Towards New Scaffolds for Chiral Diene Ligands

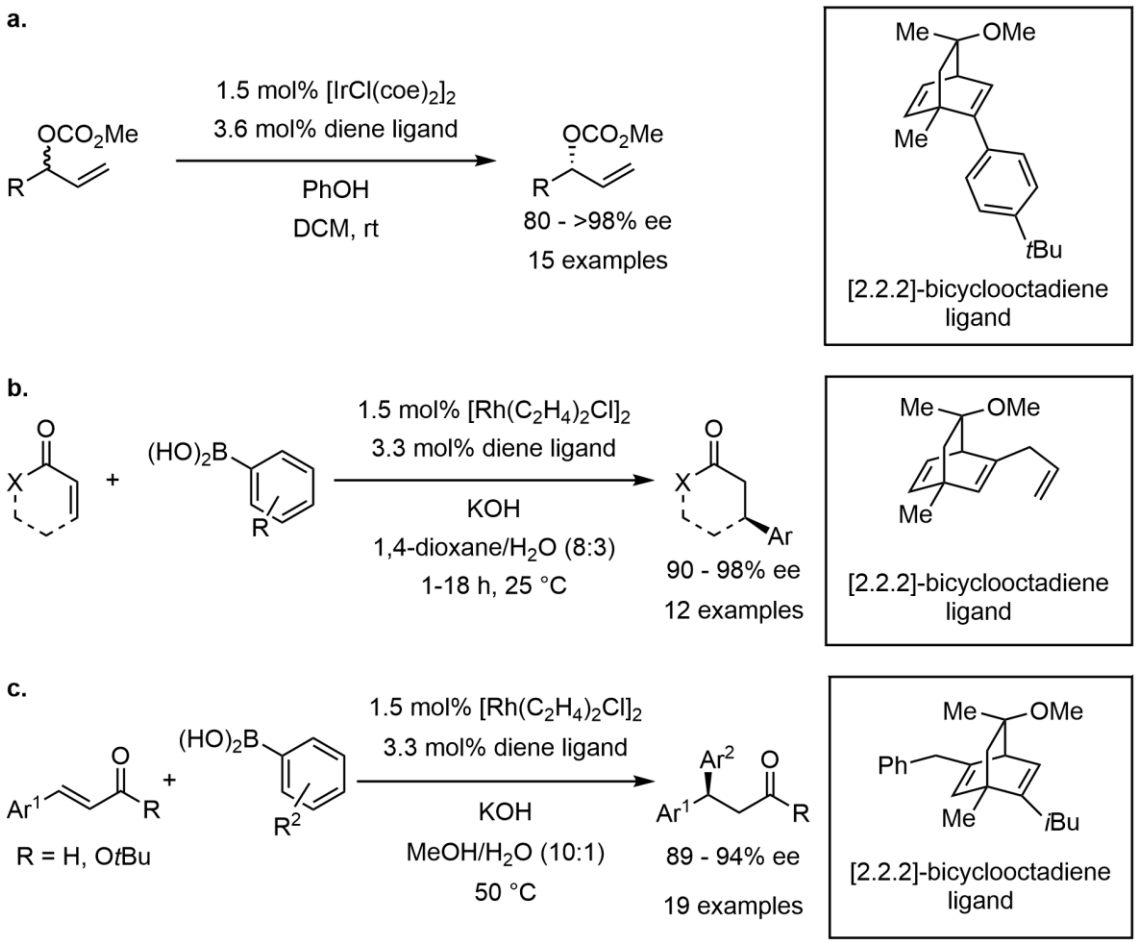
2.1 Introduction

Homogeneous asymmetric transition metal catalysis often relies on chiral ligands from a few classes of privileged structures which can coordinate to a metal centre and form catalytically active, chiral complexes. Such privileged ligands classes are predominantly diphosphine ligands, diol ligands, NHC-ligands, diamine ligands, mixed *P*,*N*-ligands, and diene ligands, the last of which will be introduced here in greater detail.

Even though the first report of a transition metal-alkene complex by Zeise dates back to 1830,[99] the independent development of diene ligands for asymmetric catalysis by the groups of Hayashi and Carreira is a much more recent advancement.[100-101] From the abundance of transformations using diene ligands that have been developed since, a selection illustrating the major aspects of the field will be introduced in this section.

2.1.1 Structurally rigid diene ligands

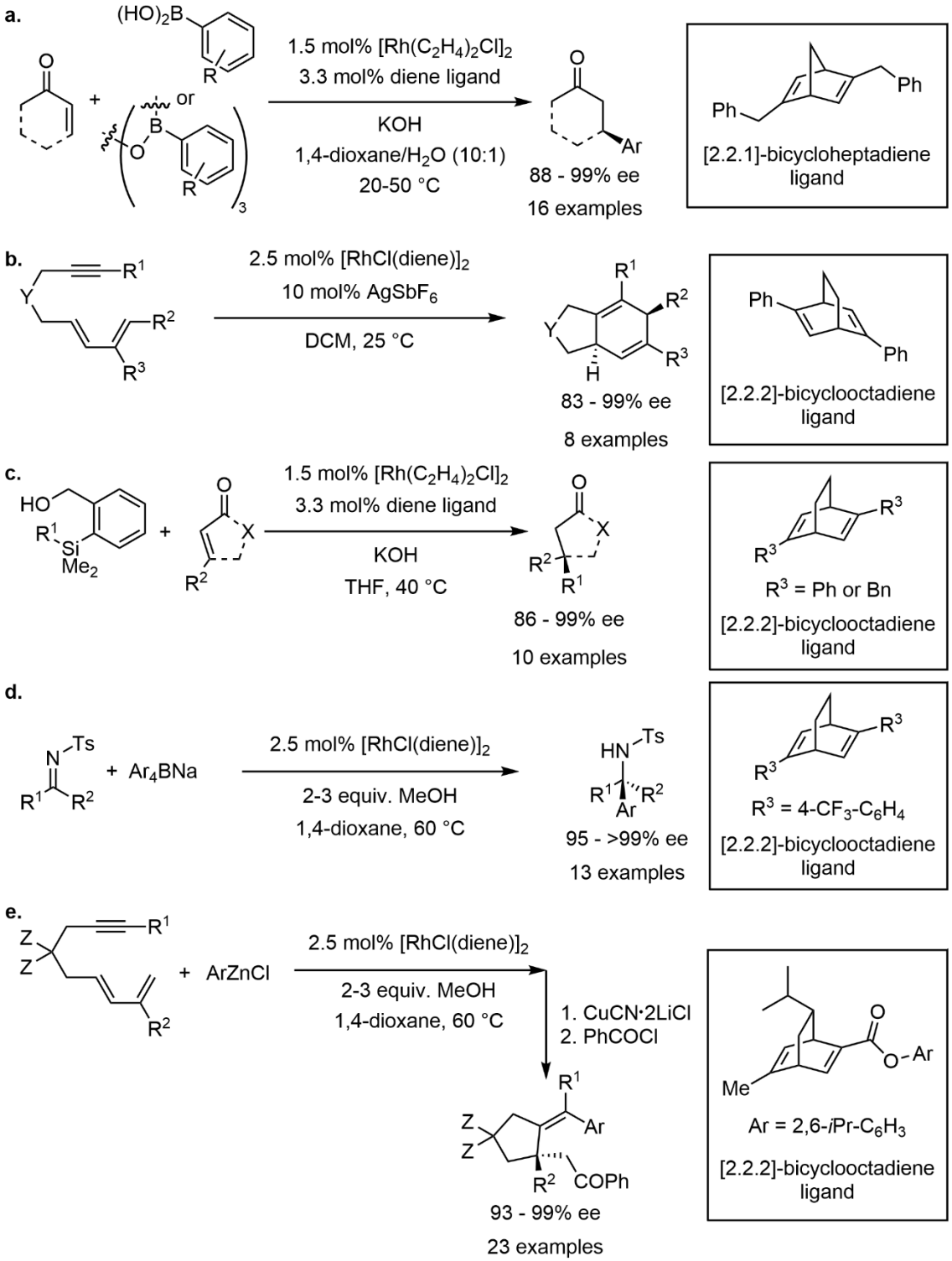
Carreira and co-workers first reported the Ir-catalysed kinetic resolution of allyl carbonates using a C_1-symmetric diene ligand derived from [2.2.2]-bicyclooctadiene (Scheme 19, a).[101] This ligand system was modified for the utilisation in Rh-catalysed transformations, most prominently in asymmetric 1,4-addition reactions of arylboronic acids to a range of *α*,*β*-unsaturated carbonyl compounds, achieving very high enantioselectivities (Scheme 19, b and c).[37, 102-103] Concurrently, the group of Hayashi developed a similar, C_2-symmetric norbornene-based diene ligand and demonstrated its utility in the asymmetric 1,4-addition of aryl- and alkenylboronic acids and boroxines to *α*,*β*-unsaturated ketones and esters (Scheme 20, a).[100] Among a wide range of applications,[104] this C_2-symmetric diene ligand system was expanded to reactions such as intramolecular [4+2] cycloadditions[105] and 1,2-additions to imines and ketimines,[106-108] as well as to less frequently used boronate salts



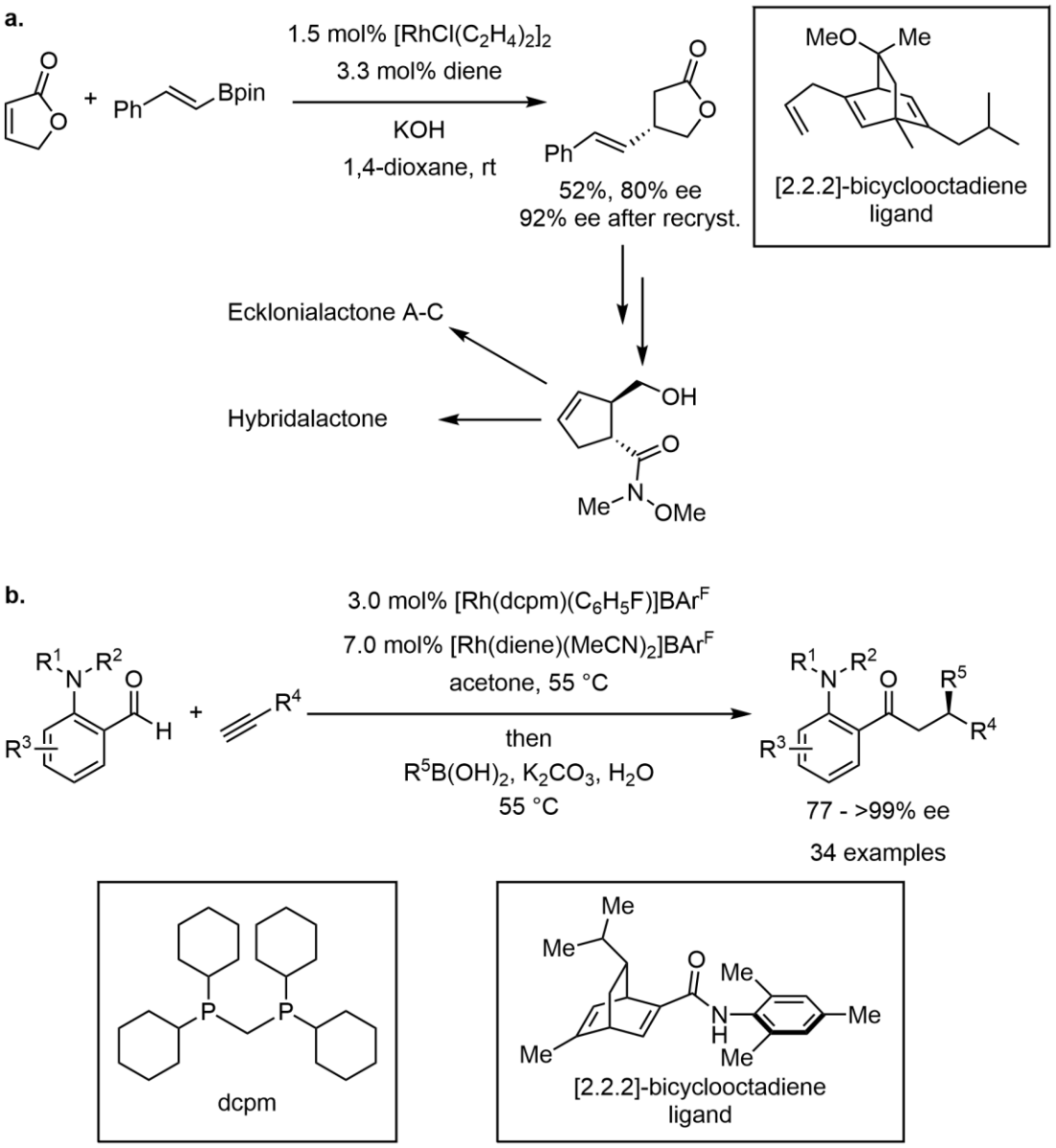
Scheme 19: **a.** First report for Ir/bicyclooctadiene catalysed kinetic resolution of allylic carbonates;[101] **b.** Rh/bicyclooctadiene catalysed asymmetric 1,4-addition of arylboronic acids to *α,β*-unsaturated cyclic carbonyl compounds;[37] **c.** Asymmetric 1,4-addition of arylboronic acids to *α,β*-unsaturated acyclic carbonyl compounds, including enals.[102-103]

and silanes as nucleophiles (Scheme 20, b-d).[59, 109-110] More recently, Hayashi and co-workers demonstrated the efficiency of a C_1-symmetric ligand in an enantioselective intramolecular cyclisation of 1,6-enynes triggered by an arylation of the alkyne.[111] In this transformation, a transient alkyl-rhodium species is trapped by transmetalation with zinc, followed by a functionalisation of the relatively stable alkyl-zinc intermediate (Scheme 20, e).[111]

Illustrating its synthetic utility, a Rh/diene ligand catalyst was employed in the conjugated alkenylation of 2-furanone in the total synthesis of macrocyclic lactones Hybridalactone and Ecklonialactones A-C (Scheme 21, a).[112] Further, a related diene ligand was used by Willis and co-workers to enhance the enantioselectivity of the 1,4-addition of arylboronic acids in a sequential asymmetric alkyne hydroacylation-1,4-addition-cascade, employing two different Rh-complexes for optimised performance (Scheme 21, b).[113]

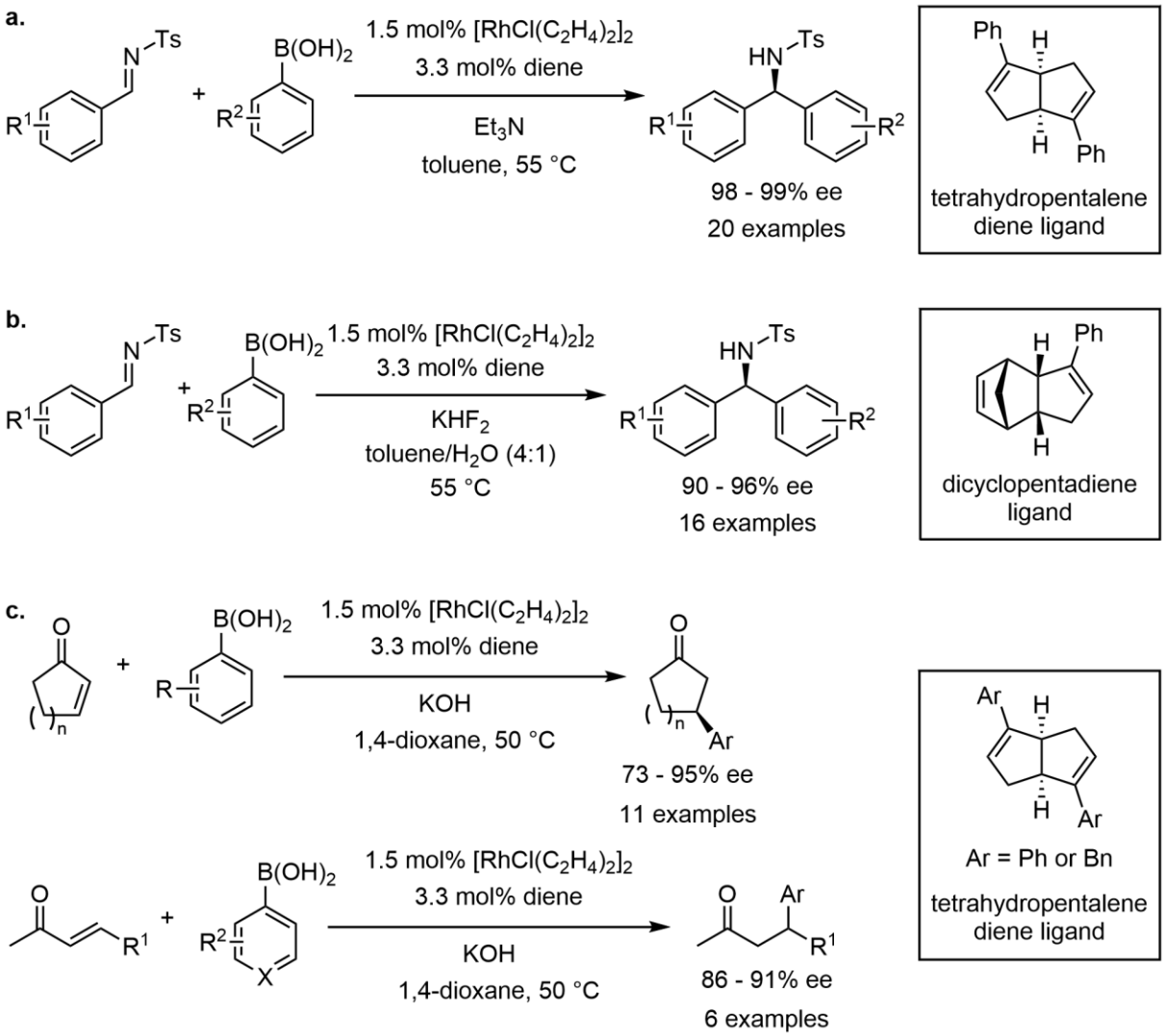


Scheme 20: **a.** First report of a Rh/bicycloheptadiene catalysed 1,4-addition reaction of arylboronic acids and boroxines to cyclic enones;[100] **b.** [4+2] cycloaddition of 1,6 enynes catalysed by a preformed Rh/diene ligand complex;[105] **c.** 1,4-addition of silanes as alternative nucleophiles to *α,β*-unsaturated carbonyls;[110] **d.** Rh/bicyclooctadiene catalysed 1,2-addition to protected ketimines using sodium tetraaryl boronates as nucleophiles;[108] **e.** Cyclisation of 1,6-enynes with trapping of an alkyl-rhodium intermediate by transmetalation to zinc and subsequent functionalisation.[111]



Scheme 21: **a.** Rh/diene catalysed 1,4-addition of alkenylboronic ester as first step towards a common platform intermediate in the total syntheses of several macrolactones;[112] **b.** Sequential hydroacylation and 1,4-addition using a Rh/diene complex to improve enantioselectivity of the 1,4-addition step.[113]

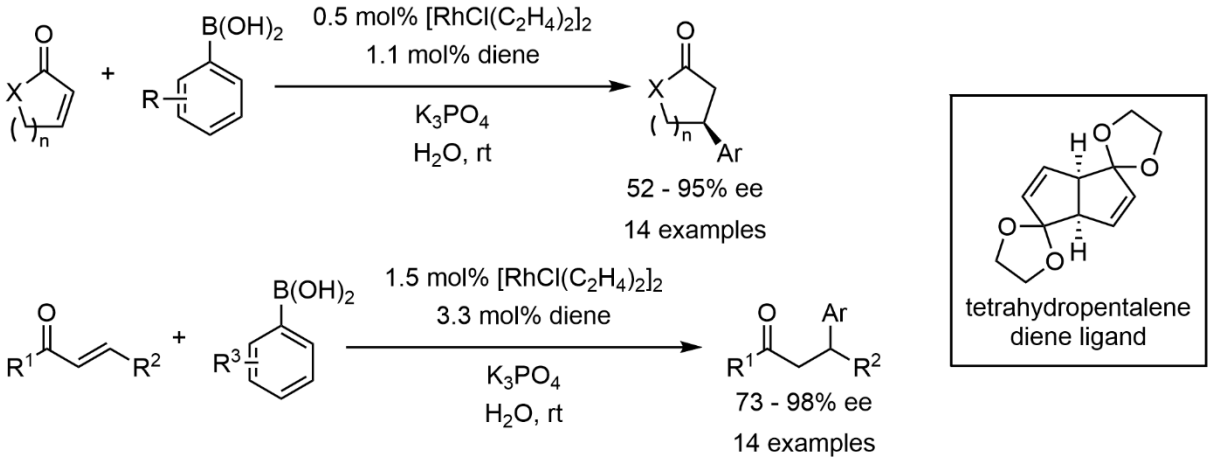
A second major scaffold of rigid diene ligands is constituted by chiral dicyclopentadiene and tetrahydropentalene ligands. These structures were first reported as efficient and highly enantioselective ligands in conjunction with a Rh-dimer for the asymmetric 1,2-addition of arylboronic acids to *N*-tosylaryl imines by Lin and co-workers (Scheme 22, a and b) and simultaneously by the group of Laschat for a 1,4-addition of arylboronic acids to *α,β*-unsaturated carbonyl compounds (Scheme 22, c).[114-116] A water soluble modification of this tetrahydropentalene ligand furnished high yields and enantioselectivities in 1,4-addition



Scheme 22: **a.** Rh/diene catalysed 1,2-addition of arylboronic acids to protected aldimines;[114] **b.** The higher yielding variant of the same transformation using a rigid dicyclopentadiene ligand;[115] **c.** The tetrahydropentalene diene ligands developed by Laschat, benchmarked with the Rh-catalysed 1,4-addition of arylboronic acids to *α,β*-unsaturated carbonyl compounds.[116]

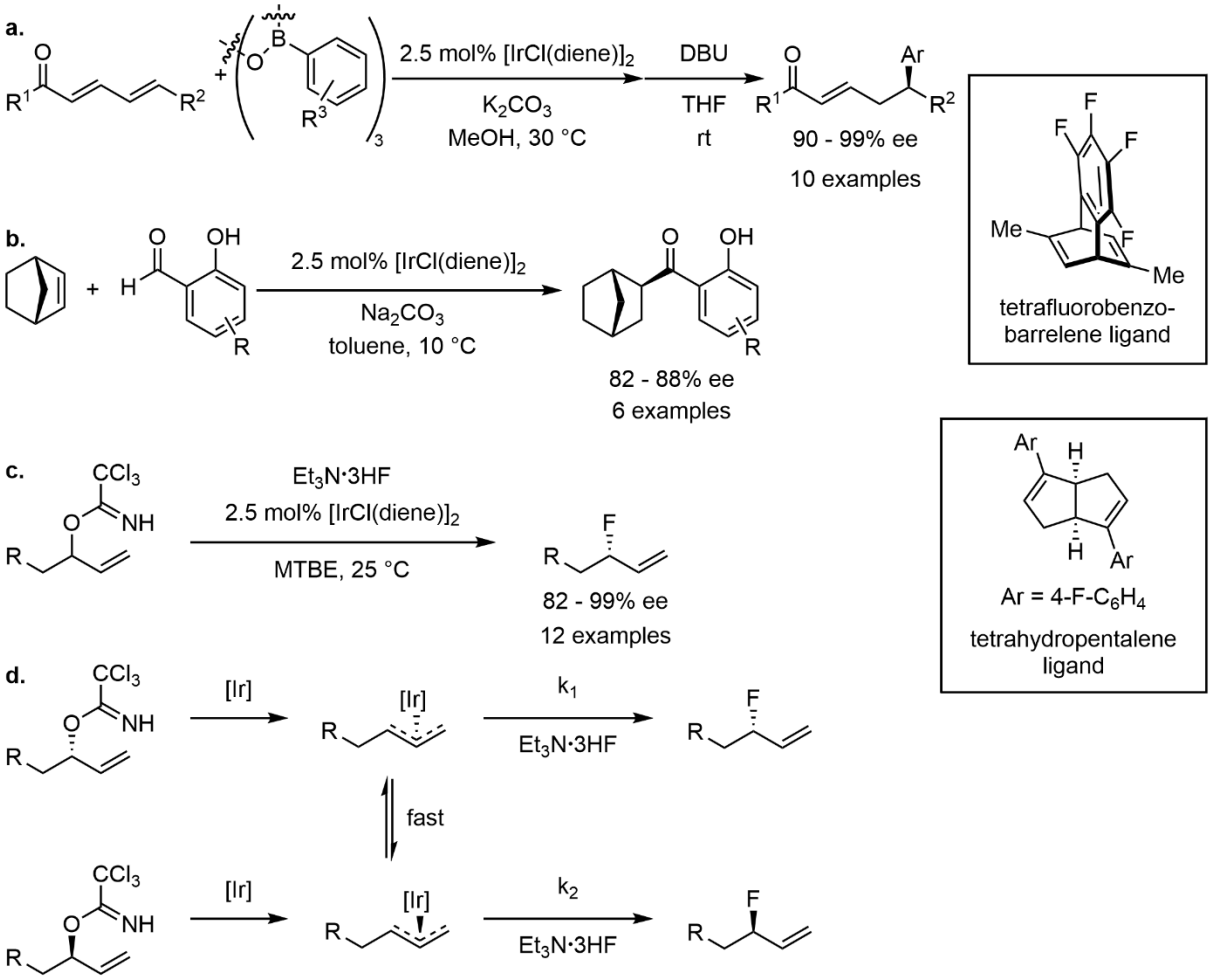
reactions of arylboronic acids to both cyclic and acyclic *α,β*-unsaturated carbonyl compounds in water without any organic co-solvents (Scheme 23).[117]

While the rigid diene ligand systems are developed for or benchmarked with Rh-catalysed 1,4-addition reactions to *α,β*-unsaturated carbonyls or 1,2-additions to protected aryl imines, they have also been demonstrated to be useful ligands in Ir-catalysed transformations apart from the initial report on the kinetic resolution of allyl carbonates (Scheme 19, a).[101] Exploiting the difference in reactivity, a catalytic system for the asymmetric 1,6-addition of arylboroxines to *α,β-γ,δ*-unsaturated carbonyl compounds was developed using a tetrafluorobenzobarrelene based diene as ligand (Scheme 24, a).[118] After a base mediated isomerization of the double



Scheme 23: Modification of the tetrahydropentalene ligand to render it hydrophilic and to perform a 1,4-addition of arylboronic acids to *α,β*-unsaturated carbonyl compounds in water.[117]

bond of the possible 1,6-addition products, the resulting *α,β*-unsaturated carbonyls were afforded with excellent enantioselectivity, and a further optimisation of the electronic ligand properties additionally improved the obtained yield.[119] Another example for the use of the

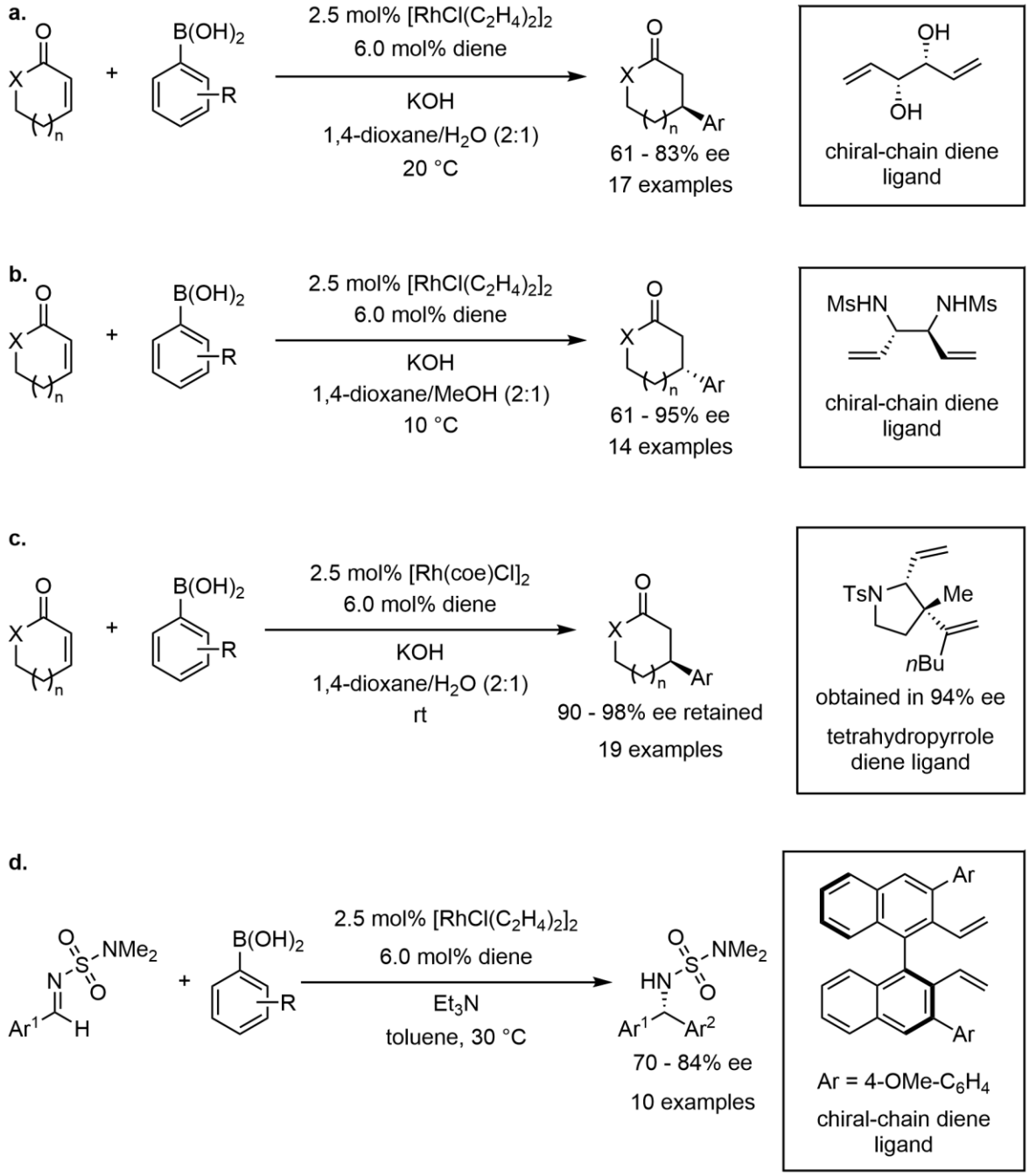


Scheme 24: **a.** Ir/tfb catalysed 1,6-addition of arylboroxines to *α,β-γ,δ*-unsaturated carbonyls, exploiting the chemoselectivity of the Ir/diene complex to avoid a 1,4-addition as a side reaction;[118] **b.** Asymmetric hydroacylation of [2.2.1]-bicycloheptene catalysed by the same Ir/tfb complex;[120] **c.** Ir/diene-catalysed DYKAT of allylic trichloroacetimides to achieve an enantioselective fluorination *via* the mechanism shown in **d**.[121]

same tetrafluorobenzobarrelene diene ligand in an Ir-catalysed transformation was reported with the asymmetric hydroacylation of 2-norbornene with 2-hydroxybenzaldehydes (Scheme 24, b).[120] Further, Nguyen and co-workers employed a tetrahydropentalene ligand in their Ir-catalysed dynamic kinetic asymmetric transformation of racemic allylic trichloroacetimidates to achieve an enantioselective fluorination with excellent regioselectivity (Scheme 24, c and d).[121]

2.1.2 Chiral-chain diene ligands

As an alternative to the described structurally rigid diene ligands, Du and co-workers developed chiral-chain diene ligands, which have a greater structural flexibility compared to their bicyclic counterparts.[122] Using the established Rh-catalysed 1,4-addition of arylboronic acids to *α,β*-unsaturated carbonyl compounds as a benchmark experiment, it was shown that 1,5-hexadiene exhibits significant catalytic activity, and the application of the simple chiral (3*R*,4*R*)-hexa-1,5-diene-3,4-diol rendered this catalytic system moderately enantioselective (Scheme 25, a).[123] Reducing the flexibility of the chiral chain by introducing a more restrictive cyclic backbone did not significantly improve the enantioselectivity,[124] but exchanging the diol for a mesylate protected diamine increased the efficiency and selectivity of the catalyst (Scheme 25, b).[125] For the same benchmark reaction, a different diene ligand – which is structurally based on a tetrahydropyrrole – is able to outcompete the chiral-chain diene ligands in terms of enantioselectivity (Scheme 25, c).[126] Further, it should be noted that the concept of a chiral-chain diene ligand was combined with the well-established axially chiral binaphthyl-backbone to facilitate the asymmetric arylation of protected aldimines, exhibiting only moderate reactivity and selectivity (Scheme 25, d).[127]



Scheme 25: **a.** Rh-catalysed asymmetric 1,4-addition of boronic acids employing a simple chiral-chain diene ligand;[123] **b.** Modification of the chiral-chain diene to improve enantioselectivity;[125] **c.** Highly enantioselective tetrahydropyrrole based diene ligand for the Rh-catalysed 1,4-addition of arylboronic acids to *α,β*-unsaturated carbonyl compounds;[126] **d.** BINAP backbone to provide axial chirality to a chiral-chain-type diene ligand for a Rh-catalysed 1,2-addition reaction to sulfonyl aldimines.[127]

2.2 Objective of the Project

In light of the potential for chiral diene ligands in Rh- and Ir-catalysed asymmetric transformations, we became interested in designing a new scaffold for diene ligands. The development of such a scaffold would allow for the benchmarking of its potential catalytic activity by applying the ligand in established Rh/diene-catalysed reaction systems. Based on the previously reported asymmetric allylic arylation of racemic halides (see chapter 1.3.2, Scheme 18),[97] a first prototype structure (Figure 3) was envisioned, which is covered by neither the rigid bicyclic nor the more flexible chiral-chain diene ligand scaffolds and thus expands the field of diene ligands to new structural features.

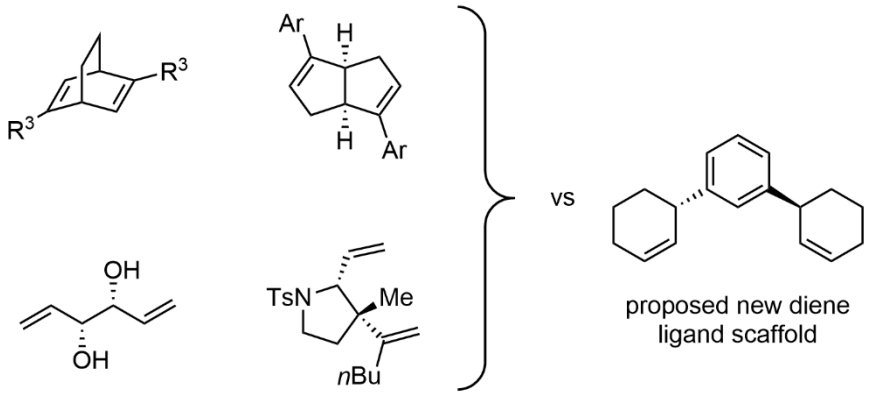


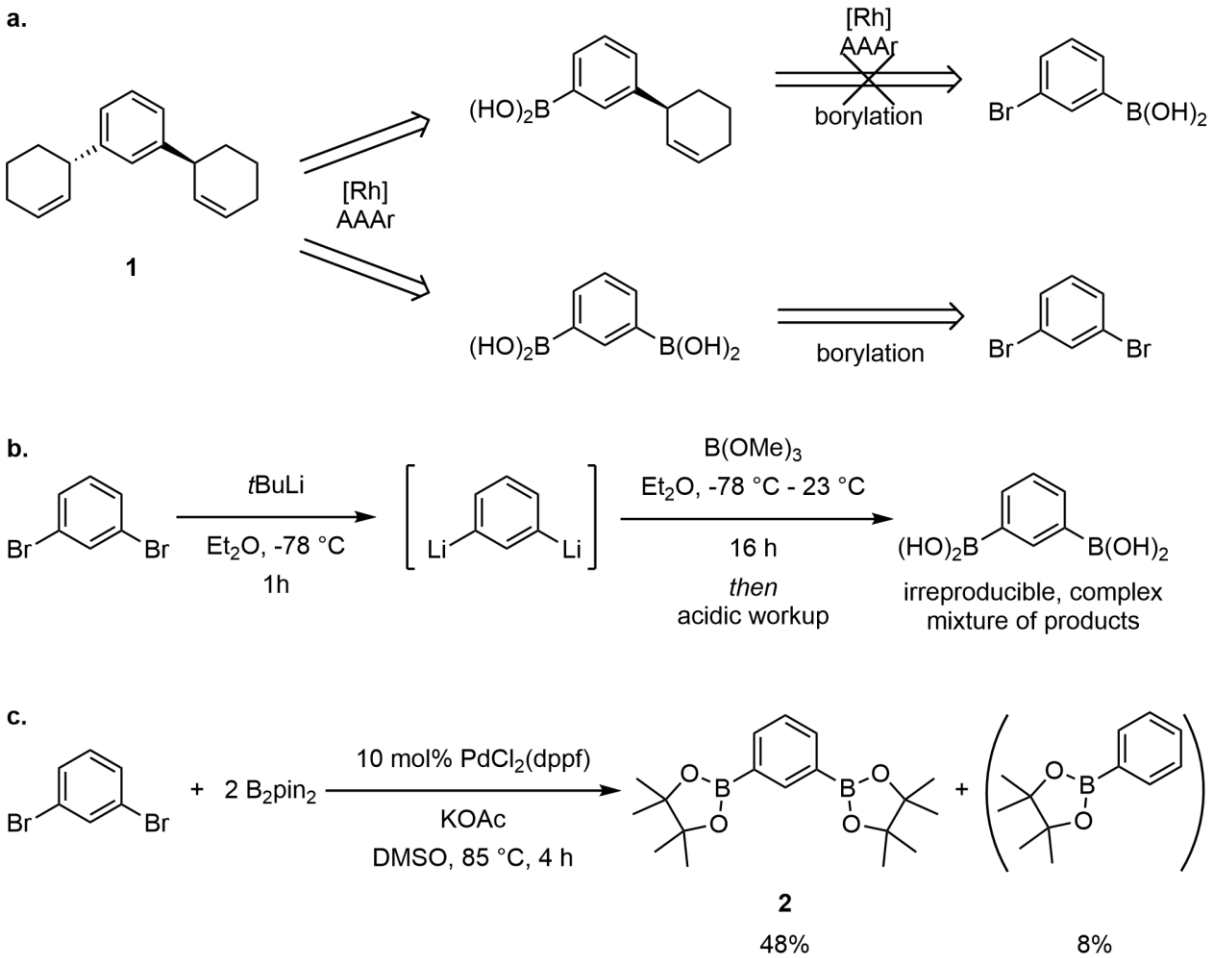
Figure 3: Established rigid (top left) and chiral-chain (bottom left) diene ligands in comparison to the proposed structure of a new diene ligand scaffold.

2.3 Results and Discussion

2.3.1 Approach to ligand synthesis using double AAAr

Initial experiments to access **1** from 3-bromophenylboronic acid, in a sequence of a Rh-catalysed asymmetric allylic arylation (AAAr) with 3-chlorocyclohexene and a subsequent lithiation-borylation of the resulting aryl bromide, indicated that this approach was not a feasible synthetic route (Scheme 26, a).

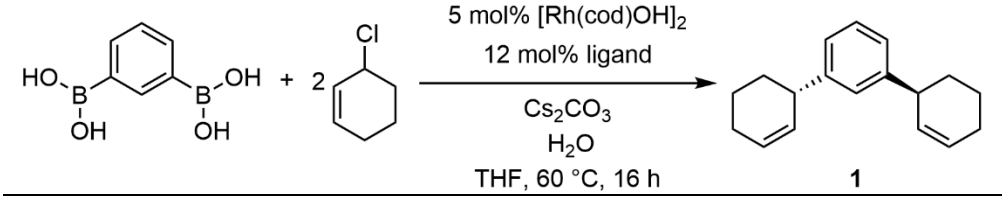
As an alternative starting point, we envisioned a two-step strategy based on a Rh-catalysed simultaneous 'double' AAAr using 1,3-phenylenediboronic acid, which in turn was anticipated to be accessible from 1,3-dibromobenzene (Scheme 26, a). However, after identifying conditions harsh enough to achieve a double lithiation of 1,3-dibromobenzene, the lithiation-



Scheme 26: **a.**Top: Bottom: envisioned synthetic strategy to obtain **1** from a 1,3-dibromobenze and Rh-catalysed double AAAr; **b.** Unsuccessful attempt to synthesise 1,3-phenylenediboronic acid *via* a lithiation-borylation sequence; **c.** Pd-catalysed double Miyaura borylation to achieve **2**, with a contamination of phenylboronic acid pinacol ester.

borylation sequence proved irreproducible and afforded a complex mixture of mono-, double-, and protodeboronation (Scheme 26, b). Hence, a well-established Pd-catalysed Miyaura borylation was employed to obtain 1,3-benzenediboronic acid bis(pinacol) ester **2** in 48 % yield with an inseparable impurity of phenylboronic pinacol ester as a side product (Scheme 26, c). It was assumed that this impurity would not hinder the subsequent AAAr to obtain proof of concept. Based on previous reports of the Rh-catalysed AAAr of racemic allyl halides,[97-98] a re-optimisation of the reaction conditions was necessary to adapt the procedure for the use of 1,3-phenylenediboronic acid (Table 1).

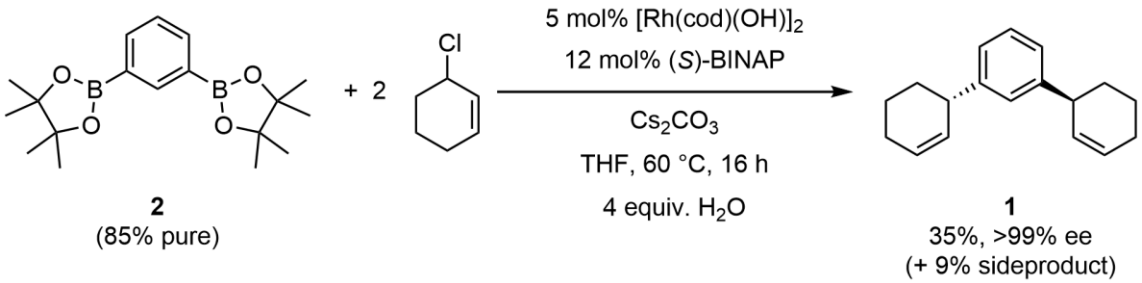
Table 1: Selected optimisation results for the double AAAr using 3-cyclohexenyl chloride and 1,3-phenylenediboronic acid.



Entry[a]	Ligand	equiv. H_2O	yield [%]	ee [%] (d.r.)
1	(*S*)-Xyl-P-PHOS	0	9	-
2	(*S*)-Xyl-P-PHOS	2	29	>99 (>20:1)
3	(*S*)-Xyl-P-PHOS	4	36	>99 (>20:1)
4[b]	(*S*)-Xyl-P-PHOS	4	51	>99 (>20:1)
5	(*S*)-BINAP	4	22	>99 (>20:1)
6	(*S*)-SEGPHOS	4	-	-
7[c]	(*S*)-BINAP	4	45	>99 (>20:1)

a. *Reaction conditions*: 1,3-phenylenediboronic acid (0.4 mmol, 1.0 equiv.), 3-cyclohexenyl chloride (0.8 mmol, 2.0 equiv.), Cs_2CO_3 (0.8 mmol, 2.0 equiv.), $[Rh(cod)OH]_2$ (0.02 mmol, 0.05 equiv.), ligand (0.048 mmol, 0.12 equiv.), in 4 mL anhydrous THF and specified equiv. H_2O, stirred at 60 °C for 16 h under argon atmosphere; **b.** Reaction performed in 1,4-dioxane at 80 °C; **c.** Reaction performed at 1.6 mmol scale of 1,3-phenylenediboronic acid.

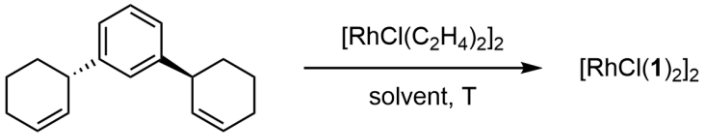
This optimisation was carried out with commercially available 1,3-phenylenediboronic acid. Most strikingly, a requirement for additional equivalents of water was identified (Table 1, entries 1-3), which proved essential in obtaining **1** in moderate yields. It can be speculated that this previously unreported, pronounced effect could be caused by the ability of boronic acids to undergo a condensation to boroxines.[128] Thus, due to its two boronic acid moieties, 1,3-phenylenediboronic acid could form aggregates or oligomeric structures which are not feasible transmetalation reagents for the Rh-catalysed AAAr but which readily hydrolyse in the presence of water to the desired diboronic acid. Despite moderate yields, **1** was obtained in



Scheme 27: Rh-catalysed double AAAr using **2** in re-optimised conditions to access **1**, albeit with an inseparable impurity originating from the contaminated **2**.

excellent enantio- and diastereoselectivity irrespective of specific reaction conditions. It should be noted that a higher reaction temperature of 80 °C provided a 15 % increase in yield (Table 1, entry 4), and that (*S*)-Segphos did not show any reactivity (entry 6). Upon upscale, (*S*)-BINAP performed comparably to (*S*)-Xyl-P-Phos (Table 1, entries 3, 5, and 7) and thus was chosen as the more cost-efficient option for a potential further upscale operation. With these conditions in hand, the double AAAr of **2** was attempted, and **1** was obtained with excellent enantioselectivity in 35 % yield, albeit suffering from a 9 % impurity which probably stems from the 'mono' boronic pinacol ester contamination of **2** (Scheme 27). Nevertheless, in an attempt to secure proof of concept, **1** was subjected to a range of conditions known to facilitate its coordination to $[RhCl(C_2H_4)_2]_2$, a common precursor in Rh-catalysed transformations (Table 2). Unfortunately, no coordination was observed in either dichloromethane, 1,4-dioxane, or toluene at various temperatures and, therefore, the prototype diene ligand was redesigned.

Table 2: Selected coordination experiments using **1**.



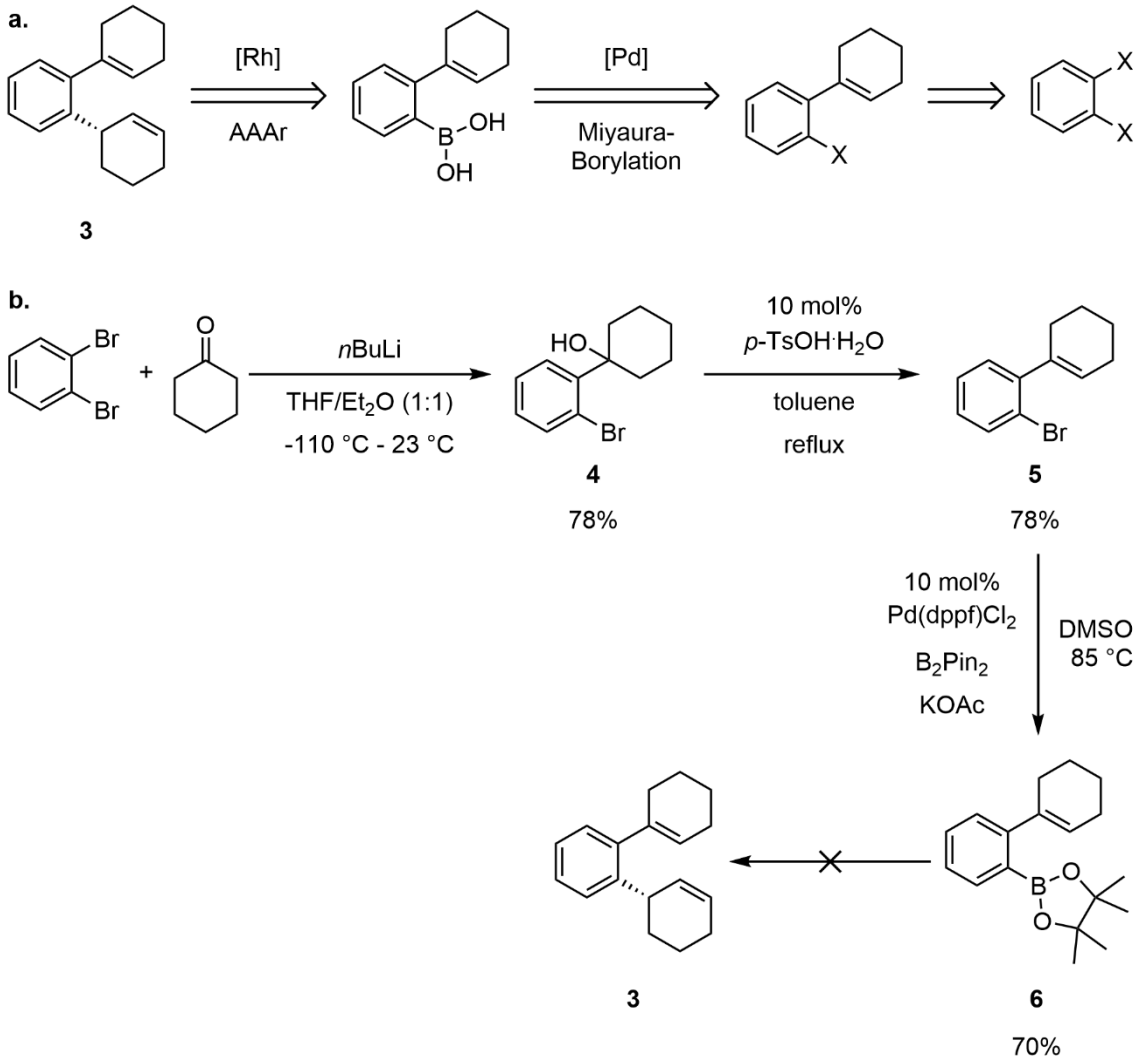
1

Entry[a]	Solvent	T [°C]	t [h]	Coordination[b]
1	DCM	23	16	no
2	1,4-dioxane	60	1	no
3	toluene	23	0.5	no
4	toluene	50	0.5	no
5	benzene	23	0.5	no
6	benzene	50	0.5	no
7	toluene	100	16	no

a. *Reaction conditions*: **1** (0.06 mmol, 1.0 equiv.), $[RhCl(C_2H_4)]_2$ (0.027 mmol, 0.45 equiv.), 1 mL solvent, reaction performed under argon atmosphere; **b.** Qualitatively determined by ^{1}H-NMR spectroscopy.

2.3.2 Alternative approach to ligand synthesis

Based on a preliminary, computational structural optimisation carried out by a member of the group,[129] the redesigned ligand prototype was predicted to require a 1,2-substitution pattern on the benzene 'backbone' to achieve a successful simultaneous coordination of both alkene moieties to a rhodium centre. For this purpose, a C_1-symmetric ligand prototype (**3**) was designed and projected to be accessible using the established Rh-catalysed AAAr to instal the 3-cyclohexenyl ring. This approach relies on a spectator role of the trisubstituted double bond of the 2-cyclohexenyl substituent which is introduced prior to the AAAr (Scheme 28, a).

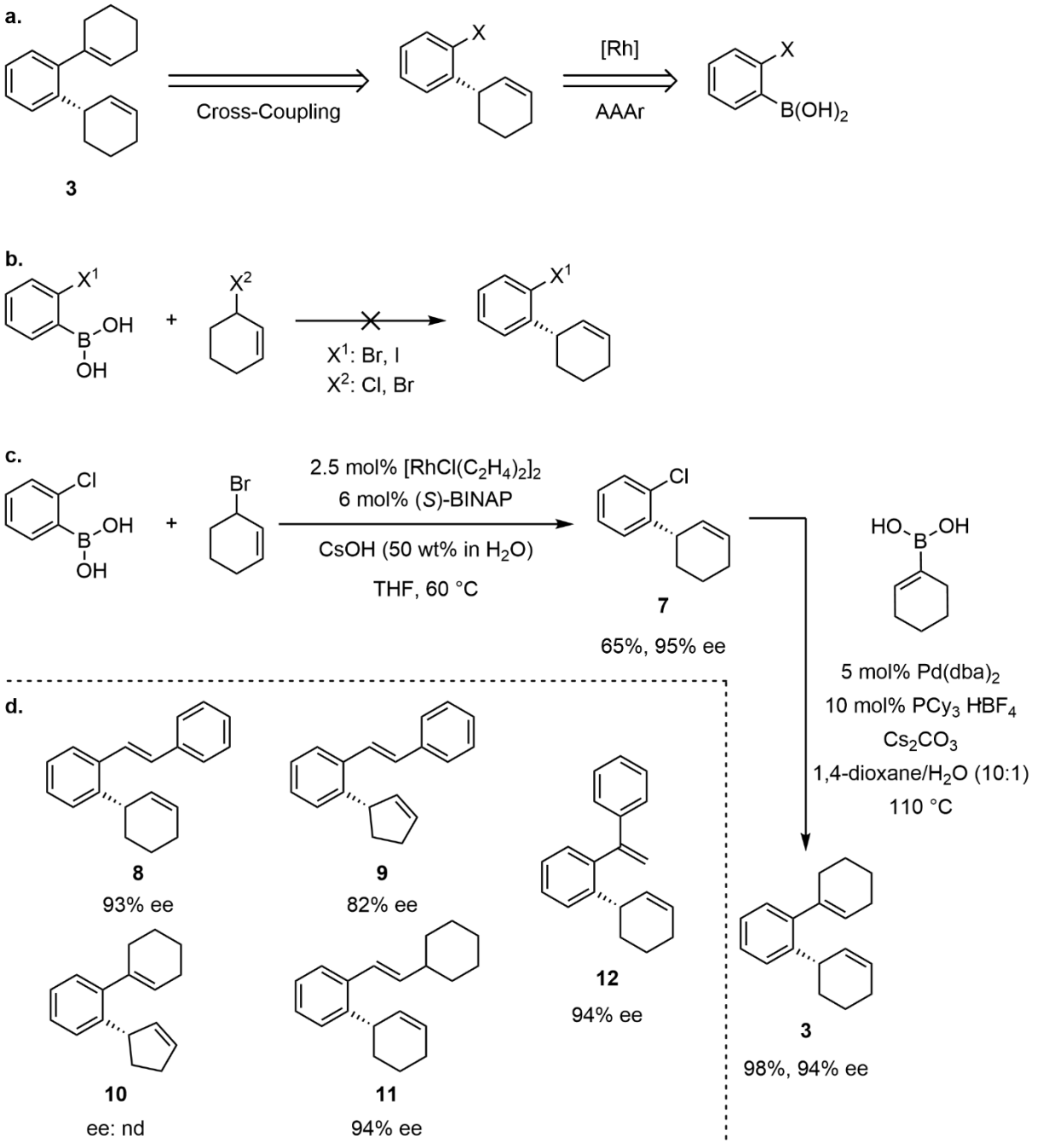


Scheme 28: **a.** Synthesis strategy for the assembly of the re-designed diene prototype **3**, with the installation of the 1-cyclohexenyl moiety prior to the Rh-catalysed AAAr; **b.** Attempted synthesis of **3**, *via* formation of tertiary alcohol **4** and subsequent elimination, followed by a Miyaura borylation to obtain **6**; the Rh-catalysed AAAr does not proceed successfully.

Implementing this synthesis strategy, the mono-lithiation of 1,2-dibromobenzene followed by a nucleophilic addition to cyclohexanone afforded tertiary alcohol **4** in 78 % yield (Scheme 28, b). It is noteworthy that this mono-lithiation proceeded smoothly, in contrast to the attempted double-lithiation of 1,3-dibromobenzene in the context of the double AAAr synthesis strategy discussed in section 2.3.1. The acid-catalysed elimination of the tertiary hydroxy moiety yields **5** in 78 % yield, which is then subjected to a Miyaura borylation to afford the desired boronic acid pinacol ester **6** in 70 % yield. Unfortunately, efforts to obtain **3** *via* the envisioned Rh-catalysed AAAr with 3-chlorocyclohexene did not prove successful (Scheme 28, b). However, encouraged by the relative success of modifying a sterically encumbered position on the core of the target structure, we hypothesised that an inverted strategy for the assembly of the prototype ligand might be more fruitful (Scheme 29, a).

Ortho-substituted arylboronic acids are known to pose challenging substrates for the Rh-catalysed AAAr, which constitutes the first step in this inverted approach. Hence, several possible combinations of arylboronic acids and allylic cyclohexenyl halides were screened and, to our delight, the combination of 2-chlorophenylboronic acid and 3-bromocyclohexene proved compatible and afforded **7** in 65 % yield and 95 % ee (Scheme 29, b and c). The catalytic system used for this transformation is a variation of the previously reported system,[130] as a stronger base was required to improve reactivity (Scheme 29, c). The application of (*S)*-BINAP most likely rendered the active catalyst sterically less demanding, thus improving the transmetalation of the *ortho*-substituted arylboronic acid at the expense of a minor reduction in enantioselectivity. This combination of substrates stood out as the only reactive reaction system, as both 3-chloro- and 3-bromocyclohexene did not exhibit reactivity in the presence of other *ortho*-halide substituted arylboronic acids (Scheme 29, b). As the chloride substituent is the least sterically demanding halide in this series, this could also indicate a steric interference of the larger bromo- and iodo-substituents that impedes the transformation. Intermediate **7** resisted all attempts to convert the aryl chloride in a boronic acid or pinacol ester and remained

unreactive even in harsh conditions in the presence of *t*BuLi, perhaps unsurprisingly as aryl chlorides are less reactive compared to synthetically more mendable aryl bromides and iodides.[131] Using **7** as the aryl halide component in a modified Pd-catalysed Suzuki cross-coupling with 1-cyclohexenylboronic acid instead, gave the desired prototype diene ligand **3** in 98 % yield and with near complete conservation of the enantiomeric excess of the previously



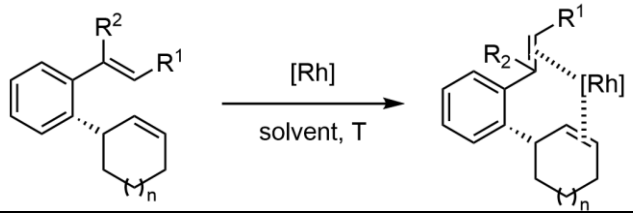
Scheme 29: **a.** Inverted synthetic strategy for **3** with the Rh-catalysed AAAr as first step, followed by the functionalisation of the *ortho* position; **b.** Selection of unreactive halide combinations for the AAAr; **c.** Synthetic pathway to **3** with a modified Rh-catalysed AAAr followed by a Suzuki cross-coupling between the aryl chloride **7** and 1-cyclohexenylboronic acid; **d.** Further potential diene ligands synthesised according to the above procedure.

introduced 3-cyclohexenyl ring (Scheme 29, c). For this transformation to be successful, the presence of water as a co-solvent is key, as initial attempts using only anhydrous 1,4-dioxane as solvent resulted in a 4 % yield, which correlates to one turnover of the Pd-catalyst. Based on this strategy, five variants of the prototype diene ligand were synthesised to investigate the coordination behaviour of such dienes by altering the ring size of the 3-cyclohexenyl moiety and by providing a more accessible disubstituted alkene as the second coordination site (Scheme 29, d).

2.3.3 Coordination experiments and approach to Rh-complex formation

To assess which of the synthesised prototype diene ligands exhibits potential for a coordination to rhodium and to form new Rh-diene complexes, the synthesised dienes **3** and **8**-**12** were subjected to a range of Rh-precursor complexes in conditions designed to facilitate the exchange of labile ligands with a diene ligand. After initial attempts with the dimeric $[RhCl(C_2H_4)_2]_2$ precursor did not yield positive results, $[Rh(C_2H_4)_2(acac)]$ was chosen as a more soluble and monomeric alternative precursor (Table 3).

Table 3: Selected coordination experiments with **3** and **8**-**12** and various Rh complexes.



Entry[a]	Diene	Rh precursor	Solvent	T [°C]	t [h]	Coordination[b]
1	3	$[RhCl(C_2H_4)_2]$	DCM	23	16	no
2	8	$[RhCl(C_2H_4)_2]$	DCM	23	16	no
3	3	$[Rh(C_2H_4)_2(acac)]$	toluene	23 and 80	16	no
4	8	$[Rh(C_2H_4)_2(acac)]$	toluene	23 and 80	16	yes
5	8	$[Rh(C_2H_4)_2(acac)]$	hexane	23	16	yes
6	10	$[Rh(C_2H_4)_2(acac)]$	toluene	23 and 80	16	no
7	11	$[Rh(C_2H_4)_2(acac)]$	hexane	23 and 50	16	yes
8	12	$[Rh(C_2H_4)_2(acac)]$	toluene	23 and 80	16	no
9	8	$[Rh(cod)(MeCN)_2][BF_4]$	hexane	23	16	no
10	8	$[RhCl(PPh_3)_3]$	hexane	23	16	no

a. *Reaction conditions*: diene (0.026 mmol, 1.0 equiv.), for monomeric Rh precursor (0.03 mmol, 1.2 equiv.), for dimeric Rh precursor (0.15 equiv.), 1 mL solvent, reaction performed under argon atmosphere at 23 °C and at elevated temperatures where indicated; **b.** Qualitatively determined by ^{1}H-NMR spectroscopy.

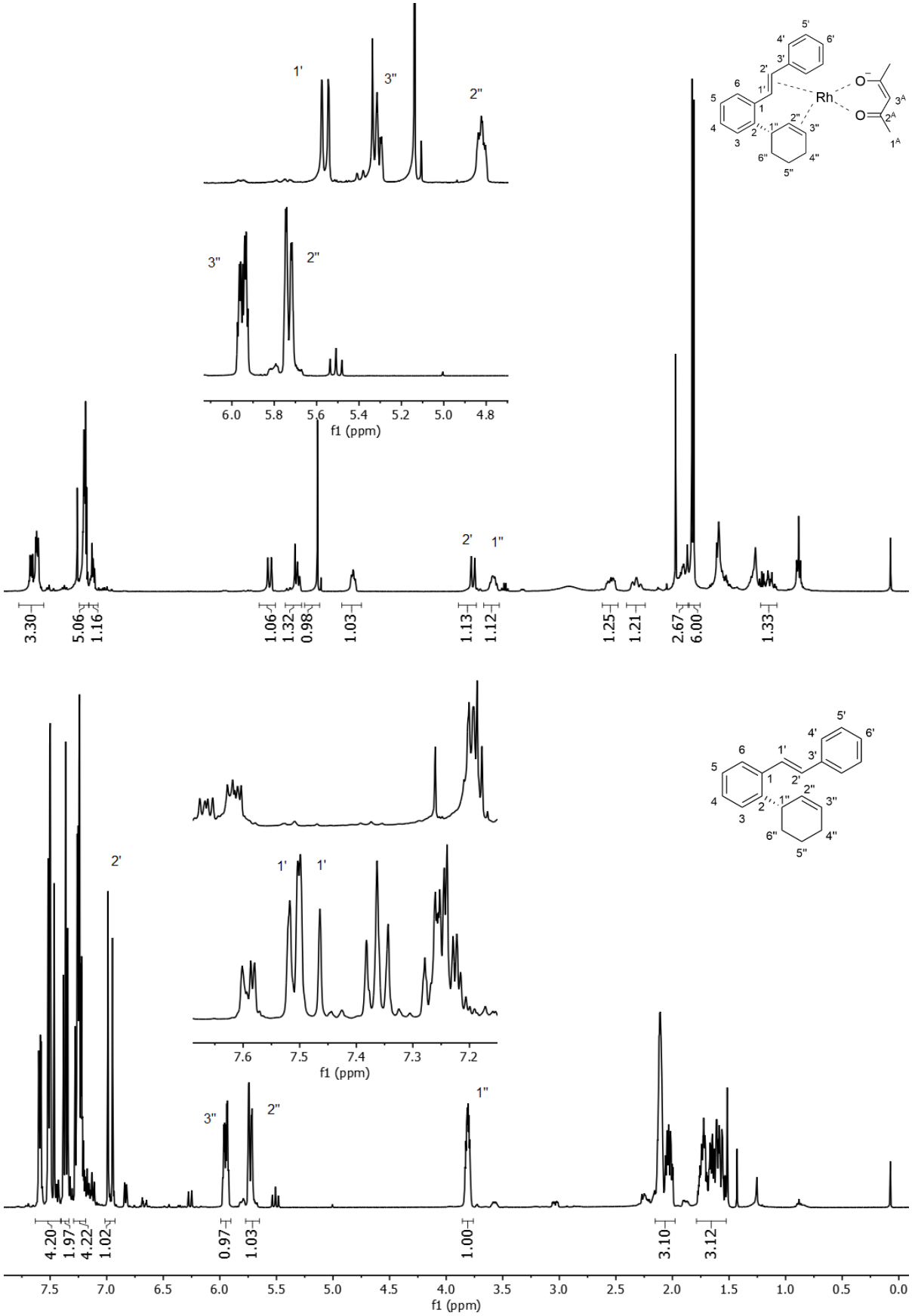


Figure 4: ^{1}H-NMR spectra of [Rh(**8**)(acac)] (top) and free **8** (bottom) with alkene signals for C(1')–H and C(2´) –H significantly shifted up-field, and less significant shifts for C(2´') –H and C(3'') –H.

Using qualitative ^{1}H-NMR spectroscopy, two potential diene ligands, **8** and **11,** showed clear evidence of coordination to rhodium to form [Rh(diene)(acac)]. This coordination was identified by the significant up-field shift observed for the protons of the Csp^2–Csp^2-bond vinylic to the benzene 'backbone.' A less significant up-field shift for the protons of the 3-cyclohexenyl Csp^2–Csp^2-bond and the stereogenic centre of the 3-cyclohexenyl ring was observed as well (Figure 4). Further, the terminal CH_3 moieties of the acac-ligand split into two singlets, indicating a different electronic environment that would be expected in a C_1-symmetric complex. As **11** exhibited a coordination to rhodium as well (see experimental information, Figure S 1), it could be shown that the position of the vinylic Csp^2–Csp^2-bond was key to a successful coordination and that it was not caused by the presence of a stilbene motif, which is known to act as a ligand for various transition metals, including rhodium.[132-133] It should be noted that structure **11** did not coordinate entirely to the Rh-precursor, as free **11** was found as a ~1:2 mixture with the desired [Rh(**11**)(acac)] complex (Figure S 1). Unfortunately, apart from these coordination experiments, the complex could neither be isolated in pure form nor crystallised to obtain a crystal structure. To move forward and determine the feasibility of the synthesised dienes in Rh-catalysed reactions, **8** was assessed in the 1,4-addition of phenylboronic acid to 2-cyclohexenone (for conditions, see Scheme 20, a). However, even with modifications to improve the *in situ* formation of the desired [Rh(**8**)(acac)] complex – such as bubbling argon through the reaction mixture to remove free ethylene – no reactivity was observed in several attempts, while a reference reaction with a commercially available diene ligand (for the type of diene ligand used, see Scheme 20, e, Ar = naphthyl), afforded the 1,4-addition product in 40 % and 93 % ee. It can be speculated that the inactivity of the [Rh(**8**)(acac)] complex might be caused by a more labile coordination of the diene ligand **8** to rhodium in comparison to its acetylacetonate counterpart or a more rigid bicyclic diene ligand. A free coordination site required for any interaction with a substrate would likely be made

available by a partial or complete de-coordination of the diene ligand, thus rendering the complex catalytically inactive.

2.4 Conclusion and Future Work

A prototype for a new diene ligand scaffold was synthesised, consisting of a unique combination of an asymmetric 3-cyclohexenyl moiety and a vinylic Csp^2–Csp^2-bond, connected by a simple benzene backbone. It was shown that two variations of this prototype successfully participate in a ligand exchange and coordinate to [Rh(C_2H_4)$_2$(acac)], although it proved not possible to isolate or crystallise such a new complex for further characterisation. Attempts to employ this novel Rh-diene ligand *in situ*, in a benchmark 1,4-addition reaction with 2-cyclohexenone and phenylboronic acid, remained fruitless.

Future investigation would have to start with the identification of a feasible Rh-precursor to form the desired Rh-diene complex while allowing for catalytic activity driven by the diene ligand. Once such a system is established and a reaction system is identified which can serve as a benchmark, modifications regarding the substitution patterns of the Csp^2–Csp^2-bonds, as well as expanding the ring size of the cyclic alkene introduced by AAAr, would provide further avenues for investigation.

3. Rhodium Catalysed Desymmetrization of *Meso* Bisphosphates

3.1 Introduction

In essence, desymmetrization operations are based on the reduction of the number of symmetry elements found in a molecule, such as the removal of inversion centres, mirror planes or other axes of improper symmetry.

In asymmetric catalysis, the enantioselective desymmetrization is one of the most common transformations as it allows for pro- or achiral compounds to be rendered chiral by introducing or exchanging a single substituent in a stereo-controlled fashion.[134] For prochiral compounds bearing a quaternary or tetrasubstituted centre, such desymmetrization reactions can form several stereocentres and are well-developed, often exploiting a regio- and stereoselective symmetry-breaking functionalization of a Csp^2–Csp^2 double bond (Figure 5, b).[134-135] The opportunity to rapidly create more than one defined stereocentre in a single transformation is especially advantageous when applied to substrates with quaternary pro-stereogenic centres, as although quaternary centres are important synthetic target structures, they are challenging to access asymmetrically.[135]

As the plethora of developed desymmetrization strategies exceeds the scope of this discussion, this introductory section will be limited to a selection of desymmetrization approaches which

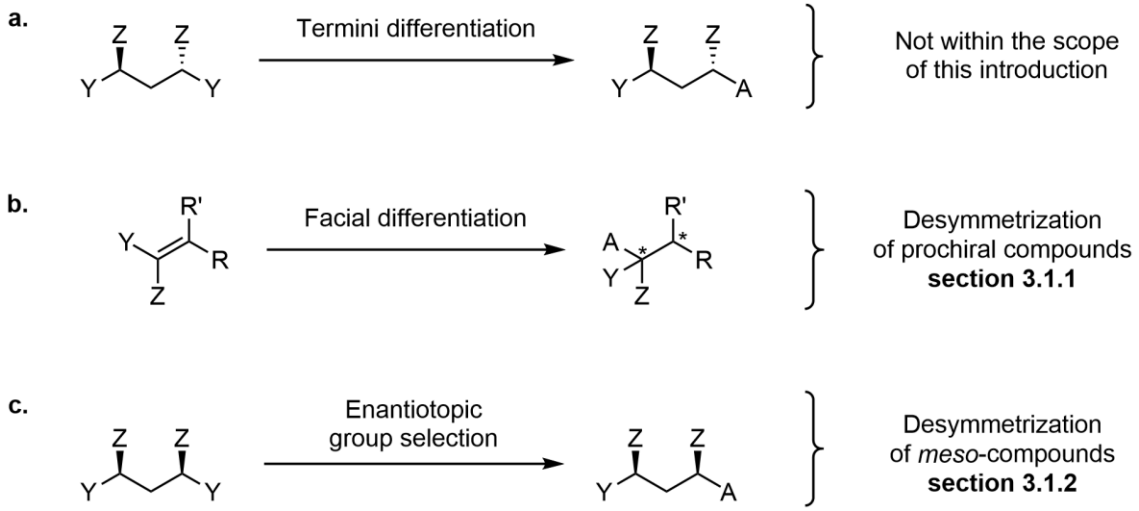
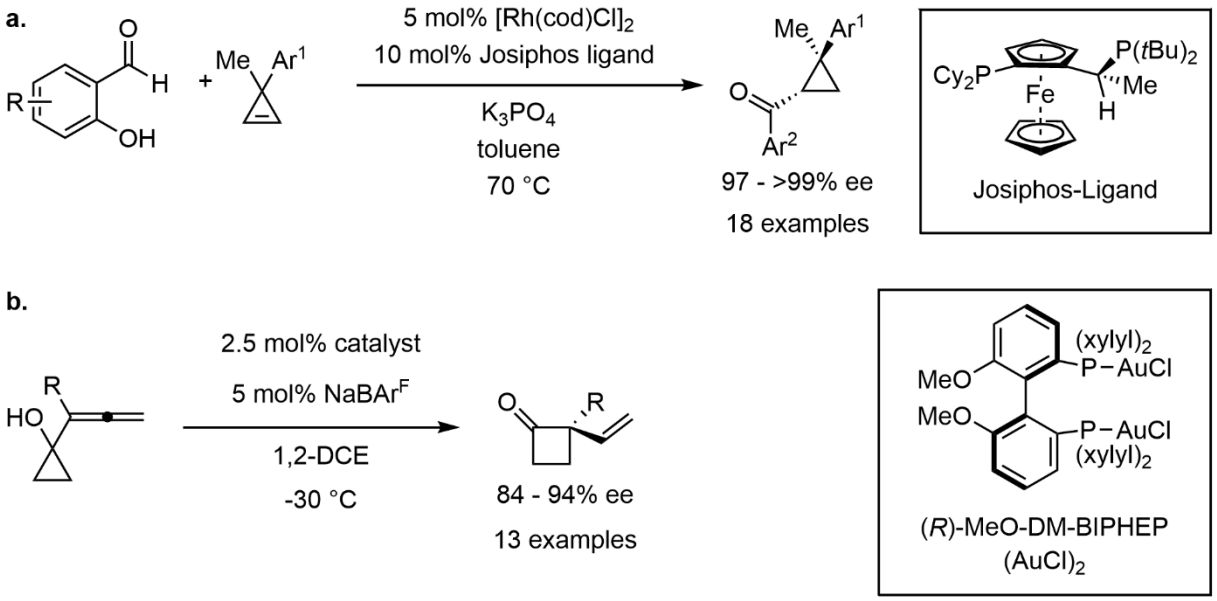


Figure 5: General approaches to desymmetrization; **a.** Differentiation of termini of C_2-symmetric compounds; **b.** Facial differentiation of a prochiral compound, illustrated by the functionalisation of a double bond yielding two stereocentres; **c.** Enantioselective desymmetrization of *meso* compounds.[134, 136]

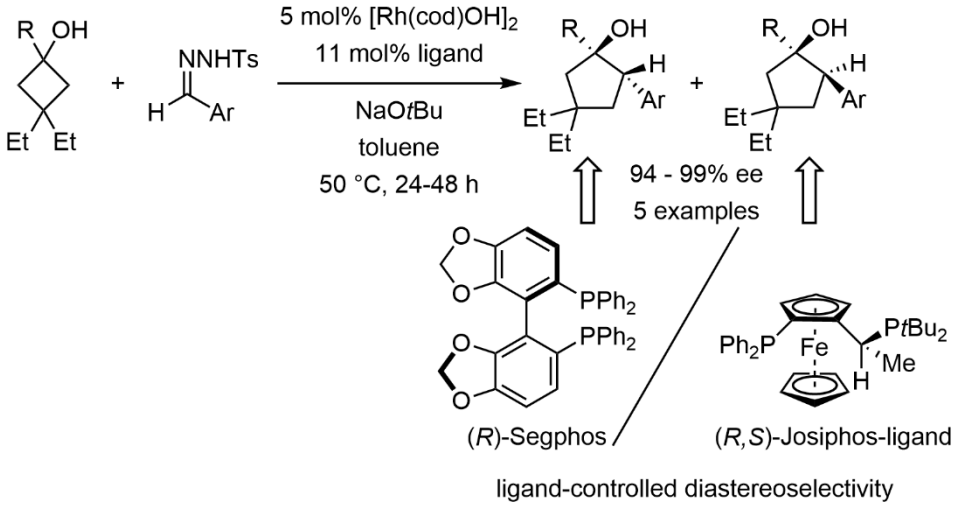
feature the asymmetric formation or 'revelation' of quaternary stereocentres in small carbocyclic systems. This area will be subdivided in the desymmetrization of prochiral compounds without prostereogenic centres (Figure 5, b) and *meso* compounds (Figure 5, c), while termini differentiating methodologies of C_2-symmetric compounds will not be discussed here (Figure 5, a).[136]

3.1.1 Desymmetrization of prochiral compounds

Focusing on prochiral compounds with preformed all-carbon quaternary centres, cyclopropenes are of specific interest. As long as the sp^3-configured carbon atom in a cyclopropene has at least one substituent, a face-selective desymmetrization targeting the double bond will automatically lead to the formation of two adjacent stereocentres, which often pose a significant challenge in synthesis.[137] The group of Dong has showcased this approach using cyclopropenes featuring all-carbon quaternary stereocentres (Scheme 30, a).[138] Alternatively, cyclopropanes can be desymmetrized *via* a ring expansion, and this has been shown to enable access to other asymmetrically substituted small carbocycles (Scheme 30, b).[139]



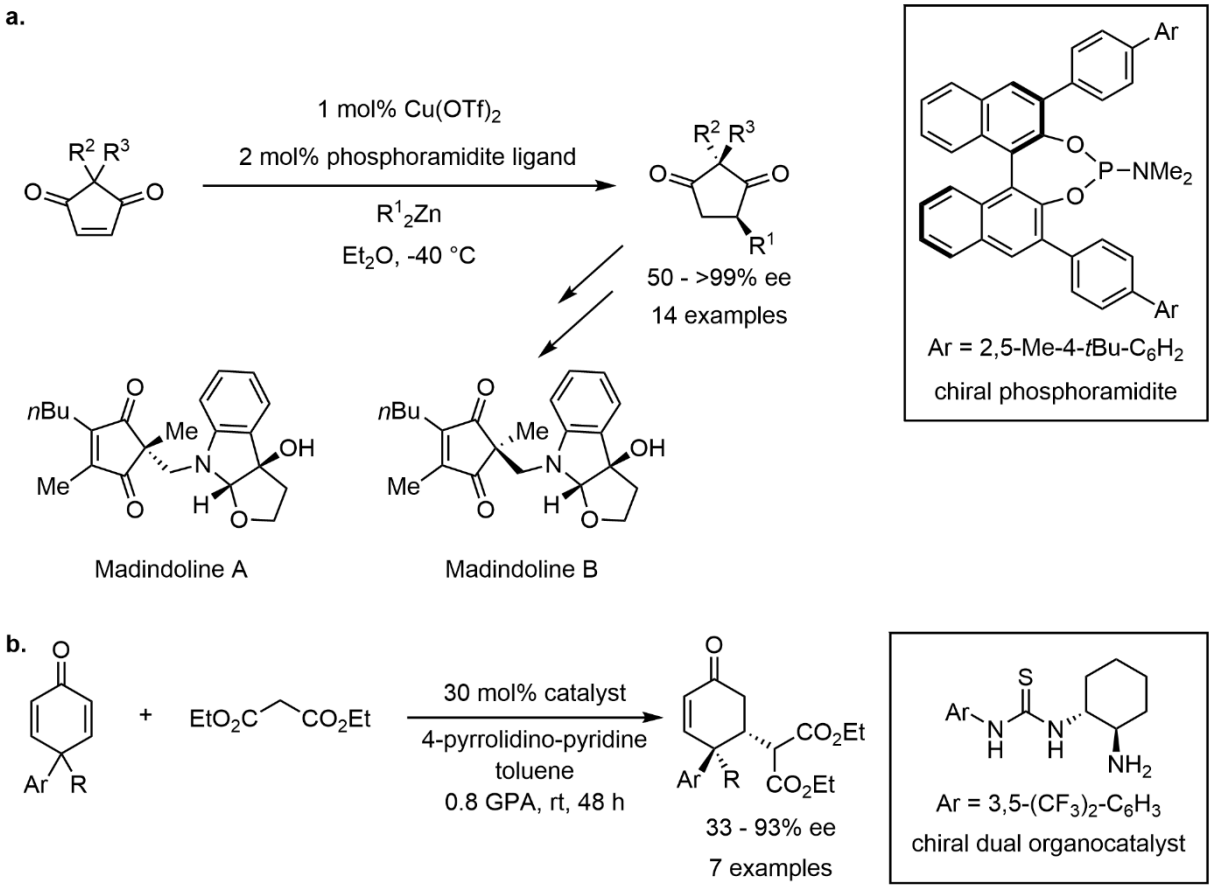
Scheme 30: **a.** Rh-catalysed desymmetrization of prochiral cyclopropenes by enantioselective hydroacylation;[138] **b.** Digold(I)-catalysed formation of a quaternary stereocentre by enantioselective ring-expansion of cyclopropanes.[139]



Scheme 31: Rh-catalysed ring expansion by enantioselective insertion of a carbenoid in which both diastereomers are selectively obtained by the choice of a chiral ligand.[140]

A similar carbenoid insertion and ring-expansion approach was developed by Murakami and co-workers, extending this strategy to the desymmetrization of cyclobutanols (Scheme 31).[140] In this case, two adjacent stereogenic centres on a cyclopentane ring are formed, one of which is a tetrasubstituted stereocentre.[140] While this example underlines the potential of desymmetrizing ring-expansion processes to rapidly generate stereoinformation, a more established approach to achieve enantioenriched cyclopentane structures is the desymmetrization of prochiral cyclopentenes (Scheme 32, a).[141] This strategy has been used, for example, in the formal total synthesis of Madindoline A and B, as reported by Mikami and co-workers (Scheme 32, a).[141] Comparing these two approaches to asymmetrically substituted cyclopentane products, it becomes clear that, to form contiguous stereogenic centres *via* desymmetrization of prochiral (non-*meso*) substrates, elaborate starting materials are required, which are often difficult to access.

Among others,[142-143] an elegant example for such a transformation, which avoids complex starting materials, is the intermolecular Michael-addition of diethyl malonate to substituted cyclohexadienones.[144] This reaction uses a dual organocatalyst to activate both substrates independently and yields the desymmetrized product with contiguous stereogenic centres (Scheme 32, b).[144]



Scheme 32: **a.** Cu(I)-catalysed enantioselective desymmetrization of prochiral cyclopentene-1,3-diones, a key transformation in the formal total synthesis of Madindoline A and B;[141] **b.** Dual organocatalysis affording two adjacent stereocentres by desymmetrization of prochiral cyclohexadienones.[144]

3.1.2 Desymmetrization of meso compounds

Other than by asymmetric transformations on prochiral substrates with prostereogenic centres, enantioenriched products can also be obtained by a kinetic resolution of chiral, yet racemic, compounds. This approach is by its nature limited to a theoretical yield of 50 %. This limitation can be mitigated in dynamic kinetic asymmetric transformations (DYKAT), which typically rely on a fast racemisation of a substrate in combination with a resolution of the preferred enantiomer. However, a powerful alternative to access complex enantioenriched molecules is the enantioselective desymmetrization of achiral *meso* compounds, which has been a well-established synthetic strategy for more than two decades.[145]

IUPAC defines a *meso* compound as 'the achiral member(s) of a set of diastereoisomers which also includes one or more chiral members,'[146] but it can be useful to further distinguish *meso*

compounds into two types based on the presence of further prostereogenic centres, as suggested by Bressy (Figure 6, a).[147] In addition to breaking its symmetry, desymmetrizing a 'type 2´ *meso* compound 'reveals' the stereoinformation embedded in a prostereogenic centre and allows for the rapid generation of multiple stereocentres using a single transformation. In particular, this strategy allows for access to contiguous stereocentres, including tetrasubstituted centres which pose challenging targets for direct asymmetric Csp^3–Csp^3 or Csp^3–heteroatom-bond formation reactions (Figure 6, b).[148] Comparing this strategy to the desymmetrization of other prochiral substrates discussed in section 3.1.1, the challenge of obtaining contiguous stereocentres is more easily addressed with *meso* compounds. The desymmetrizing transformation in a suitably designed *meso* compound does not need to occur next to a prostereogenic centre but instead can 'reveal' all stereocentres in one step.[147] However, enantioselective desymmetrizations 'revealing' all-carbon quaternary centres are less well developed.[148] Focusing on small carbocyclic systems, the scarcity of these 'type 2´ transformations becomes even more pronounced, in contrast to a wealth of desymmetrization

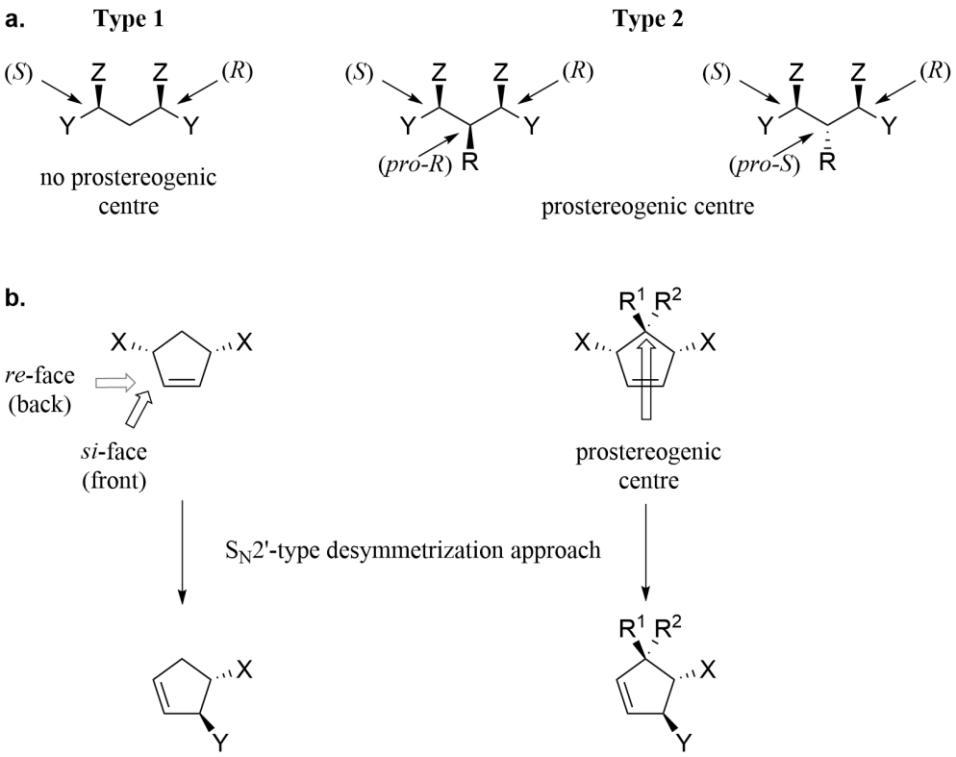
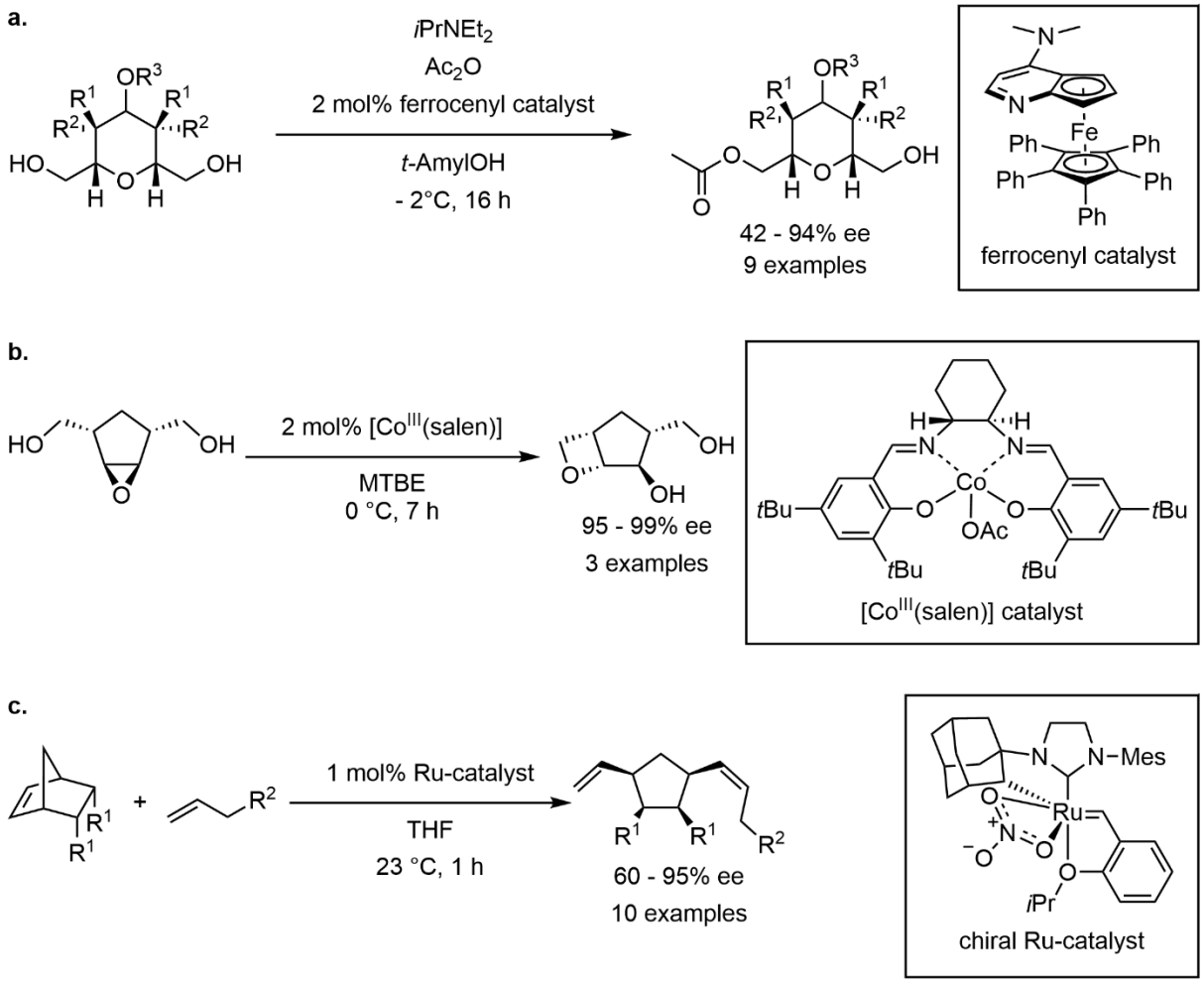


Figure 6: **a.** Generalised structures of *meso* compounds with (type 2) and without (type 1) an additional prostereogenic centre;[147] **b.** Adaptation of this concept to *meso* cyclopentene derivatives and potential products of an S_N2'-type desymmetrization.[148]

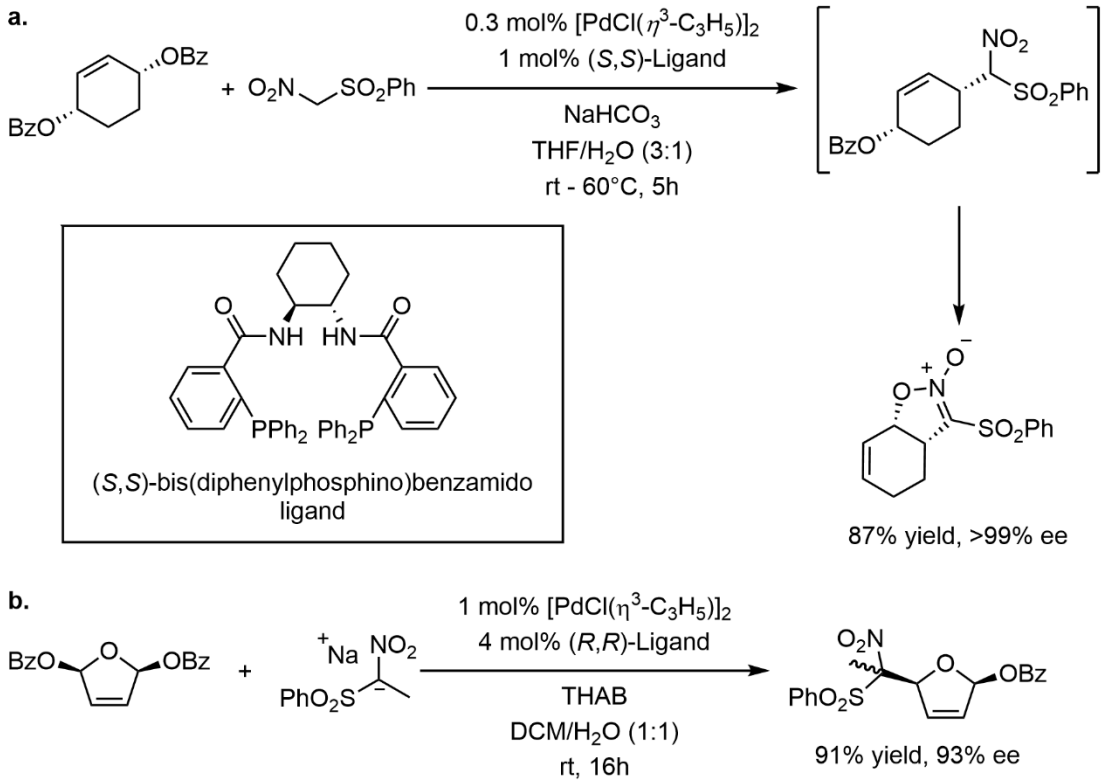
strategies within the 'type 1' category.[149] In the following paragraph, a selection of approaches to the desymmetrization of small carbocycles will be discussed, focussing on examples which exploit 'hidden' prostereogenic centres to elegantly form stereochemically complex carbocycles.

One strategy, applicable to the desymmetrization of all *meso* compounds, is the differentiation of termini, that is the selective functionalisation of one out of two relevant moieties to break the symmetry of the *meso* compound. Although the scope of this introductory section is restricted to small carbocyclic substrates, the desymmetrization of highly substituted tetrahydropyrans *via* a selective acetylation of a primary hydroxy moiety warrants mentioning (Scheme 33, a).[150] Developed by Bressy and co-workers, this system is a rare example of a



Scheme 33: **a.** Selective acetylation of a primary alcohol 'reveals' five contiguous stereocentres in a highly functionalised tetrahydropyrane;[150] **b.** Co(III)-catalysed intramolecular cyclisation of *meso* epoxy diols;[151] **c.** Desymmetrization of norbornene-derived bicyclic *meso* compounds by enantioselective and *Z*-selective ring-opening cross-metathesis to access highly functionalised cyclopentanes.[152]

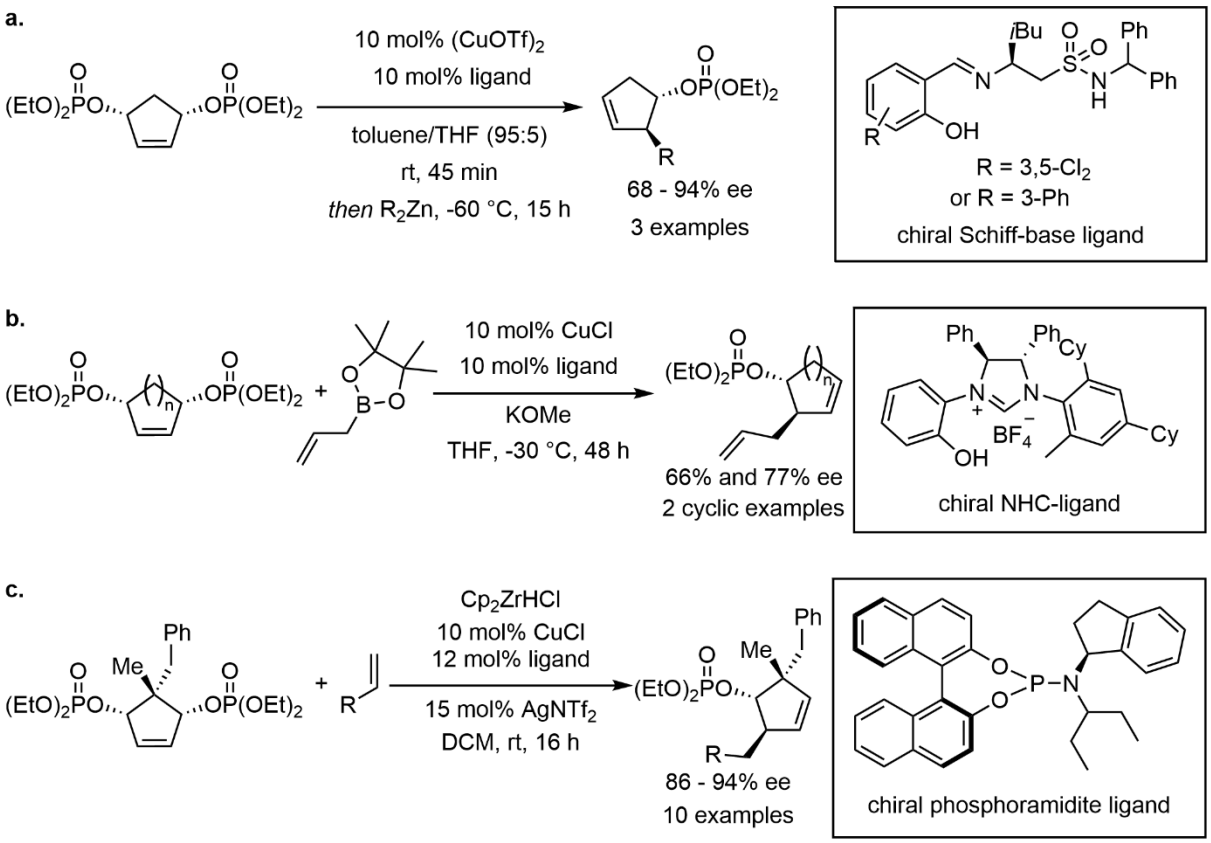
non-enzymatic enantioselective catalytic desymmetrization of stereochemically complex primary and unprotected diols.[150] Another example for the use of primary diols is the desymmetrization of *meso* epoxy diols *via* a cyclisation and epoxide opening (Scheme 33, b).[151] Even though there are only few examples reported, this transformation convincingly illustrates that the desymmetrization of *meso* compounds is a powerful tool to access highly substituted cyclopentanes with several contiguous stereocentres.[151] Admittedly not strictly a 'type 2´ desymmetrization, this reaction serves as an example for the application of a desymmetrization strategy *via* cyclisation reactions for *meso* compounds. More recently, the enantioselective ring-opening cross-metathesis of norbornene derived *meso* compounds and terminal alkenes enabled access to highly functionalised cyclopentanes with up to four all-carbon stereocentres (Scheme 33, c).[152] In this case, the desymmetrizing transformation forms two stereogenic centres, and also 'reveals' a set of two pro-stereogenic centres in a single step. Despite these efforts, however, widely applicable methodologies to desymmetrize cyclic 'type 2´ *meso* compounds, especially smaller carbocycles, remain underdeveloped.



Scheme 34: **a.** Desymmetrization of a 6-membered 'type 1' diol derivative by a Pd-catalysed allylic alkylation with a subsequent S_N2'-type intramolecular allylic substitution;[149] **b.** Desymmetrization of a furan diol derivative by an allylic alkylation using a stabilised nucleophile.[153]

This lack of structural diversity is further illustrated by the numerous desymmetrizations of 5- and 6-membered unsaturated diol derivatives for which the group of Trost in particular developed powerful methods in the context of numerous natural product syntheses (Scheme 34).[149, 153-154] In their strategies, a Pd-catalysed asymmetric allylic alkylation using a suitable leaving group in allyl-position to a Csp^2–Csp^2 double bond breaks the symmetry of the substrate (Scheme 34, a). These asymmetric allylic alkylation strategies commonly use 'type 1' *meso* compounds which are limited in structural complexity and are further restricted by requiring nucleophiles that form stabilised carbanions (Scheme 34, b).[149, 155]

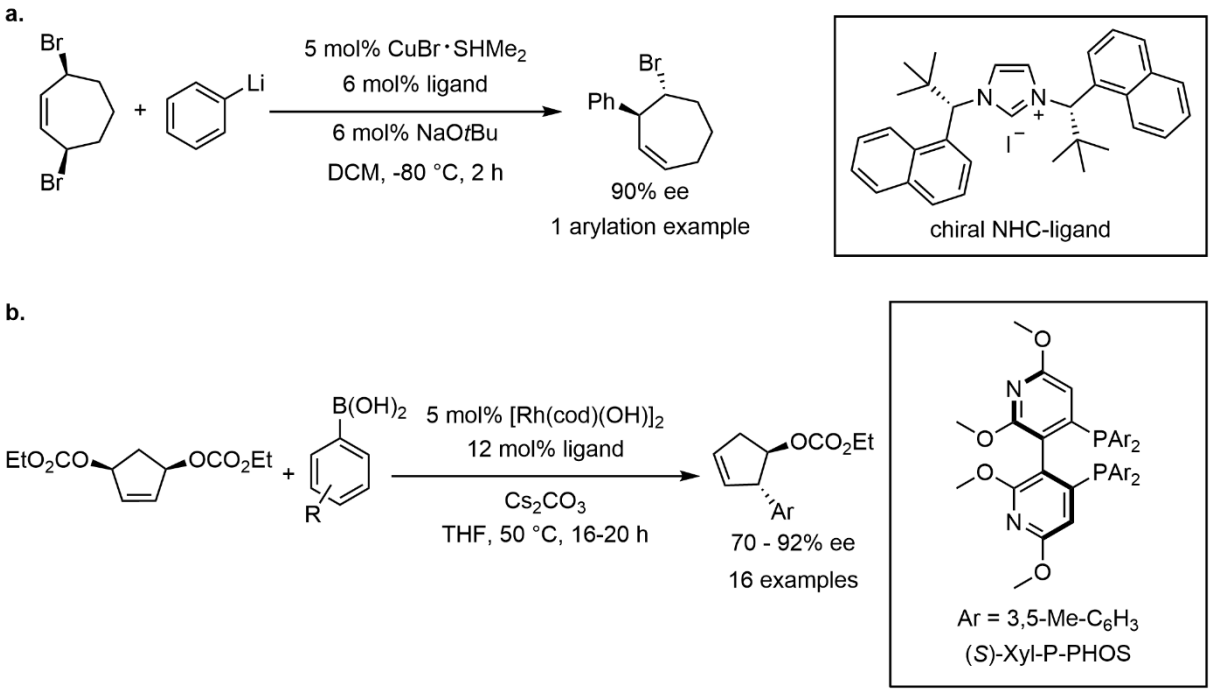
The use of non-stabilised nucleophiles in the desymmetrization of cyclic *meso* compounds *via* allylic substitutions is significantly more limited, but the groups of Gennari and Feringa developed a Cu(I)-catalysed alkylation of unfunctionalised 'type 1' *meso* bisphosphates using simple alkyl-zinc reagents (Scheme 35, a).[156-157] More recently, Sawamura and co-workers



Scheme 35: a. Cu(I)-catalysed desymmetrization of a cyclic *meso* bisphosphate by addition of simple alkyl- and arylzinc reagents;[156-157] **b.** Cu(I)-catalysed allyl-allyl coupling using allylic boronates, however, among numerous acyclic allylic phosphates only two cyclic examples were reported;[158] **c.** Cu(I)-catalysed asymmetric allylic alkylation to desymmetrize 'type 2′ *meso* bisphosphates containing a quaternary stereocentre.[159]

employed allylic boronic acid pinacol esters as nucleophiles for the desymmetrization of similar cyclic *meso* bisphosphates (Scheme 35, b).[158] In contrast to these comparably simple substrate structures, a rare case of the desymmetrization of cyclic 'type 2´ *meso* bisphosphates with unstabilised alkenes was recently published by our group (Scheme 35, c).[159] This method closes the gap for a widely applicable allylic alkylation of stereochemically complex cyclic 'type 2´ *meso* compounds.

Instead of desymmetrizing small *meso* carbocycles using asymmetric allylic alkylations, a complementary approach employing asymmetric allylic *arylation* strategies has been developed, though few examples are known. The briefly described transformation developed by Gennari and co-workers (Scheme 35, a) exhibited a moderate yield and enantioselectivity for the single aromatic nucleophile in the study.[156] Similarly, a Cu(I)-catalysed desymmetrization of *meso* dibromocycloalkenes has been developed by Feringa and co-workers, and only one example for a successful asymmetric allylic arylation was reported (Scheme 36, a).[160] As an alternative catalytic system, the Rh-catalysed desymmetrization of

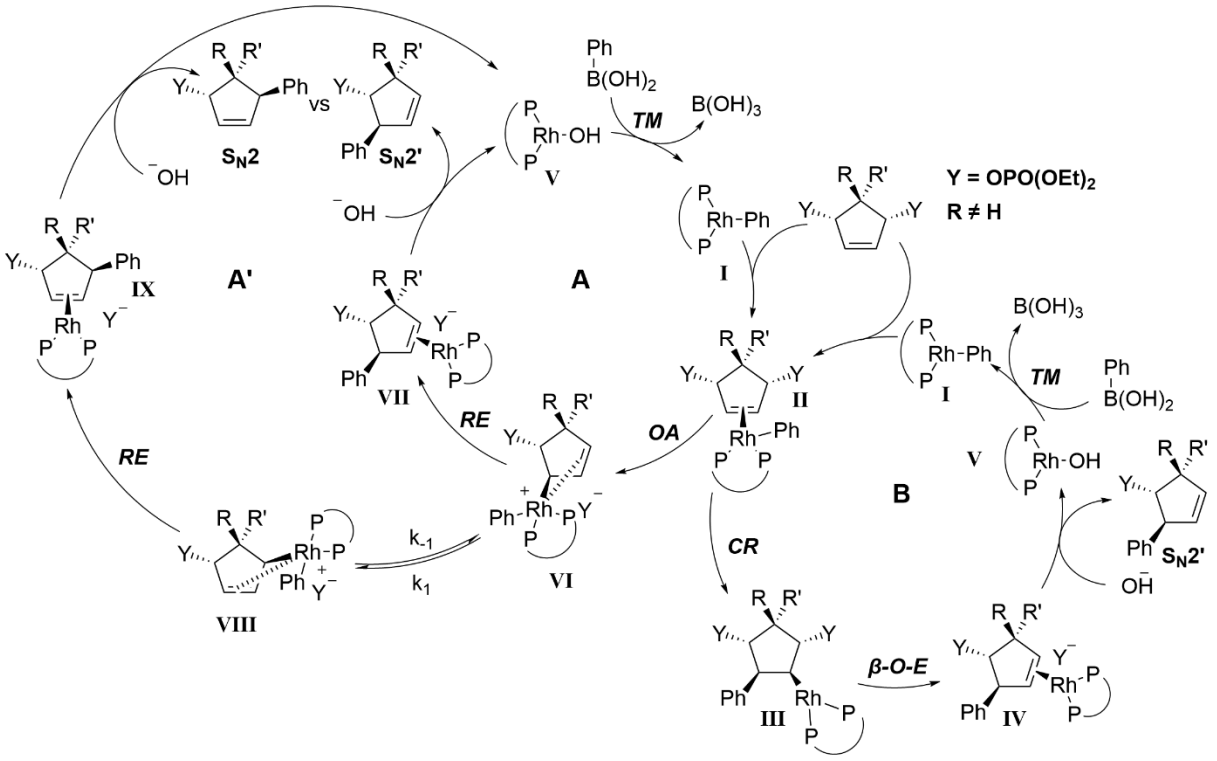


Scheme 36: a. Cu-catalysed desymmetrization of cyclic *meso* dibromides by an asymmetric allylic substitution in which only a single arylation product is reported;[160] **b.** Rh-catalysed enantioselective allylic arylation of 'type 1' *meso* cyclopentene-1,4-diethyl carbonate.[161-162]

cyclic ‘type 1’ *meso* diol derivatives has been developed with a broader scope of arylboronic acids as unstabilised nucleophiles (Scheme 36, b).[161-162] However, the range of cyclic *meso* compounds shown to be desymmetrized using this approach is limited, lacks structural diversity and is restricted to the use of *meso* cyclopentenes.[161]

The general mechanism of Rh-catalysed allylic substitutions has been discussed in the introduction of this thesis (chapter 1.3, Figure 2). As the efficient desymmetrization of cyclic *meso* compounds *via* an asymmetric allylic substitution requires a regio-, diastereo-, and enantioselective transformation, a more detailed discussion of possible mechanistic pathways is necessary.

Lautens and co-workers demonstrated that the regioselectivity in systems using *meso* cyclopentenes is dependent on the choice of ligand, and postulated the co-existence of two major pathways (Scheme 37, A/A´ vs B).[162] Following transmetalation (**I**), pathway B suggests a carborhodation step followed by *β*-O-elimination (**III** to **IV**) to give $S_N2´$-type products. This



Scheme 37: Postulated mechanistic system for the Rh-catalysed asymmetric allylic substitution of cyclic *meso* compounds: direct evidence for pathway B was not obtained, but not correlating enantiomeric ratios between $S_N2´$ and S_N2-products indicate the simultaneous occurrence of pathways A/A´ and B.[162]

does not explain the observed formation of the regioisomeric S_N2-type products, and although mechanism B cannot be excluded, an alternative set of pathways (pathway A/A´) needs to be considered. Oxidative addition of the Rh-aryl-complex (**II**) (provided that transmetalation occurs rapidly) to the cyclopentene *via* an enantioselective ionisation leads to a Rh(III)-*σ*-*π*-enyl-complex **VI**, which can undergo isomerization to **VIII**.[74, 163] Reductive elimination of the catalyst from intermediates **VII** and **IX**, respectively, affords either the $S_N2´$-type or the S_N2-type product. However, the formation of a *π*-*σ*-*π*-complex as result of the oxidative addition instead of the formation of **VI** cannot be ruled out. This alternative equally leads to both S_N2 and $S_N2´$ products, depending on the site of reductive elimination. Based on inconsistencies in the enantiomeric excess of both regioisomers, Lautens and co-workers thus concluded that both mechanisms have to be active in their system, with pathway B being potentially less enantioselective.[162]

3.2 Objective of the Project

The desymmetrization of *meso* compounds *via* a Rh-catalysed asymmetric allylic arylation (Rh-AAAr) is limited to simple 'type 1' structures, and there is only one report of a Rh-catalysed arylation of prochiral compounds bearing a pro-quaternary centre.[164]

Based on our expertise in Rh-catalysed asymmetric allylic substitution reactions, the known desymmetrization of cyclic *meso* dicarbonates using Rh-catalysis, and the recently reported successful desymmetrization of 'type 2´ *meso* bisphosphate **13** *via* allylic alkylation,[159] we envisaged that we could desymmetrize **13** *via* an asymmetric allylic *arylation*. This would enable access to highly functionalised cyclopentene derivatives using readily available boronic acids. Further, it would allow for the incorporation of heteroaryl moieties and would yield structures with three contiguous stereocentres.

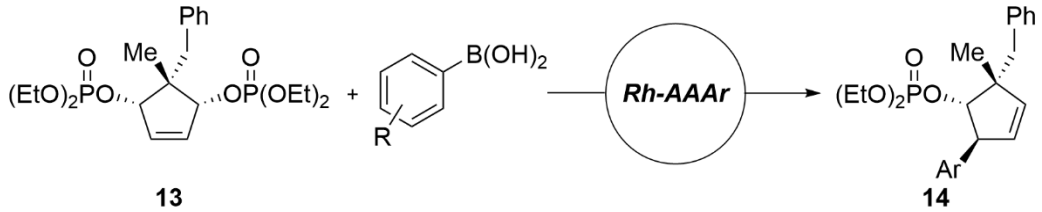


Figure 7: Envisaged development of an asymmetric allylic arylation reaction to desymmetrize complex *meso* cyclopentenes.

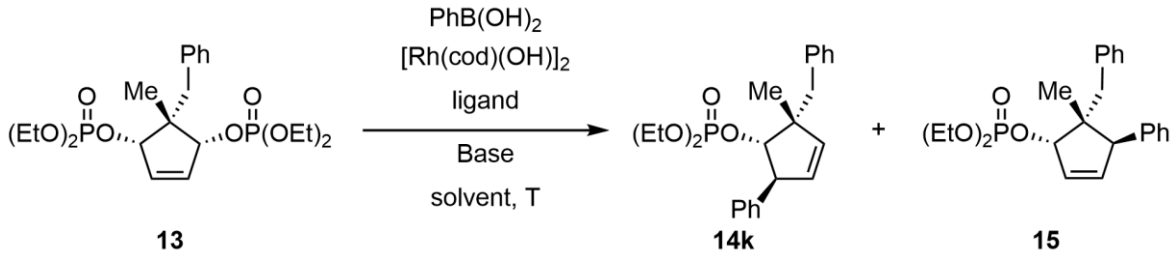
3.3 Results and Discussion

This project was carried out in collaboration with Reece Jacques, who performed the experimental work for sections 3.3.1 and 3.3.3. The author performed the experimental work for section 3.3.2 and made non-experimental contributions to sections 3.3.1 and 3.3.3.

3.3.1 Optimisation of desymmetrization reaction

Initial reaction conditions were adapted from a previously developed Rh-catalysed AAAr, and optimisation of reaction conditions was performed by Reece Jacques.[98] Further, the starting point for the optimisation is similar to conditions reported by Lautens for the desymmetrization of *meso* dicarbonates.[162] Using (*S*)-BINAP as ligand and Cs_2CO_3 as base resulted in 10 % conversion of the starting material to a separable mixture of S_N2':S_N2 regioisomers (**14k**:**15**) in a ratio of 3:1 (Table 4, entry 1). Encouragingly, the desired S_N2' regioisomer **14k** was obtained in 48 % ee, and, more significantly, as a single *anti* diastereomer. This indicates that the face-selectivity of the addition of Rh-aryl species to the alkene is not notably influenced by the steric demand of the pro-quaternary centre, and that it occurs *anti* to the diethyl phosphate leaving groups as previously proposed in related chemistry (Scheme 37).[162] Changing the base from Cs_2CO_3 to an aqueous solution of CsOH (50 wt%), which is a privileged base in previously reported Rh-catalysed AAAr,[98, 165] improved both the yield and enantiomeric excess to 40 % and >99 % ee, respectively (Table 4, entry 2). This finding suggests that the presence of water and a base with higher solubility might assist the regeneration of the active catalyst after the reductive elimination or potentially facilitate the formation of the active aryl boronate species from the boronic acid, prior to transmetalation.[166] The yield could not be significantly improved by increasing the reaction temperature to 80 °C in either THF or Me-THF, and the ratio of **14k**:**15** did not exceed 6.3:1 (Table 4, entries 3-5). Consequently, the effect of the ligand

Table 4: Optimisation of reaction conditions for the asymmetric allylic arylation of *meso* bisphosphate **13**.[a,†]



13 **14k** **15**

Entry	Ligand	Solvent	T [°C]	Conv. [%][b]	ee [%][c]	14k:15
1[d]	(*S*)-BINAP	THF	60	10	48	3:1
2	(*S*)-BINAP	THF	60	40	>99	4.3:1
3	(*S*)-BINAP	THF	80	36	>99	4:1
4	(*S*)-BINAP	2-Me-THF	60	36	>99	6.3:1
5	(*S*)-BINAP	2-Me-THF	80	49	>99	4.3:1
6	(*R*)-TOL-BINAP	THF	60	51	>-99	3.3:1
7	(*S*)-P-Phos	THF	60	60	>99	15.5:1
8	(*S*)-Xyl-P-Phos	THF	60	55	>99	9.1:1
9	(*S*)-SEGPHOS	THF	60	79	>99	7.6:1
10	(*S*)-DM-SEGPHOS	THF	60	>99	>99	8.7:1
11[e]	(*S*)-DM-SEGPHOS	THF	60	89 (84)	>99	8.1:1
12[e,f]	**(*S*)-DM-SEGPHOS**	**THF**	**60**	**95 (86)**	**>99**	**8.9:1**
13	(*S*)-DTBM-SEGPHOS	THF	60	2	n.d.	4:1

a. *Reaction conditions*: 0.2 mmol **13** (1.0 equiv.), 0.4 mmol phenylboronic acid (2.0 equiv.), 5 µmol $[Rh(cod)(OH)]_2$ (0.025 equiv., 5 mol% Rh), 0.012 mmol ligand (0.06 equiv.) 0.2 mmol CsOH (1.0 equiv.) in 2 mL THF (0.1 M); **b.** Determined by ^{1}H-NMR spectroscopy, isolated yield in parentheses; **c.** Referring to $S_N2´$regioisomer and determined by SFC; **d.** Cs_2CO_3 used as base instead of $CsOH_{(aq)}$; **e.** Scale-up to 0.4 mmol **13** (1.0 equiv.); **f.** Concentration at 0.2 M; † Experiments performed by Reece Jacques.

was explored (Table 4, entries 7-14; for structures, see Figure 8), with (*S*)-P-Phos yielding **14k** in a ratio of 15.5:1 and 60 % conversion (Table 4, entry 7). However, (*S*)-DM-Segphos demonstrated superior reactivity, furnishing the desired product in an 8.7:1 ratio at 99 %

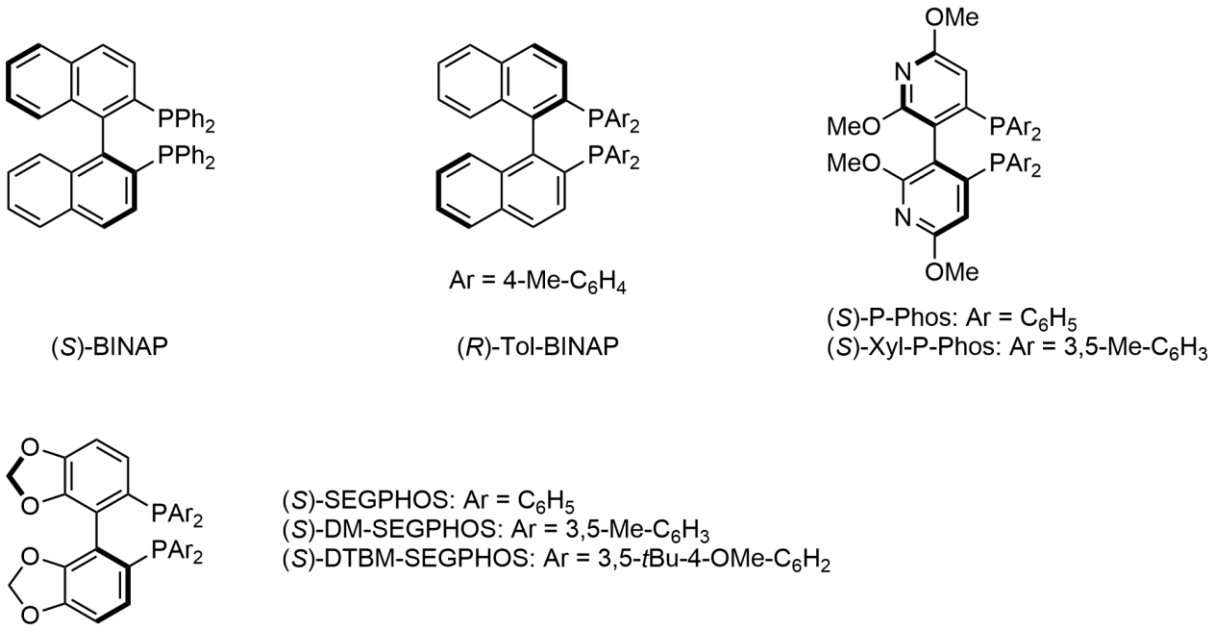


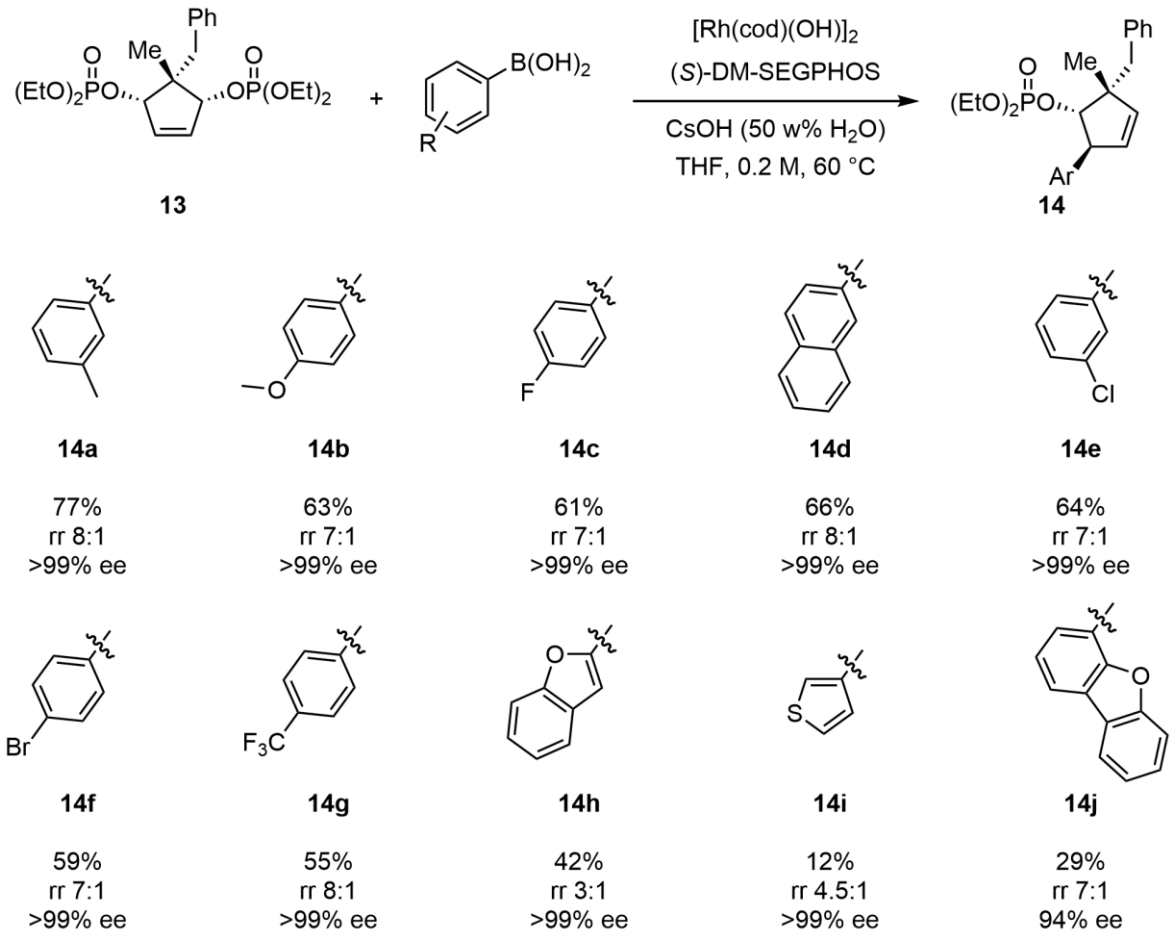
Figure 8: Chiral diphosphine-ligands used in the optimisation of the asymmetric allylic arylation of *meso* bisphosphate **13**.

conversion (Table 4, entry 10). Interestingly, (*S*)-DTBM-Segphos showed little reactivity and was not pursued any further (Table 4, entry 13). The attempted upscale of the conditions using (*S*)-DM-Segphos to 0.4 mmol resulted in an isolated yield of only 84 % (Table 4, entry 11). This result was slightly improved by increasing the concentration from 0.1 M to 0.2 M, which led to an isolated yield of 86 %, >99 % ee, and a regioisomeric ratio of 8.9:1 (Table 4, entry 12). With these conditions in hand, both the influence of modified prostereogenic quaternary centres and of a range of boronic acid nucleophiles was examined.

3.3.2 Scope of nucleophiles

Bisphosphate **13** was subjected to the optimised reaction conditions using a range of (hetero)arylboronic acids as nucleophiles (Scheme 38). A methyl substituent in the 3-position (**14a**) gave 77 % yield, and the regioisomeric ratio of 8:1 in favour of the $S_N2´$ type product is comparable to the rr achieved with the unsubstituted phenylboronic acid (Table 4, entry 12). The more electron-donating 4-methoxy-substitution (**14b**) resulted in a yield of 63 % and a rr of 7:1. Halo-substituted boronic acids were equally well tolerated, 4-fluoro- (**14c**) and 4-bromophenylboronic acid (**14f**) gave 61 % and 59 % yield, respectively, while a 3-chloro-substitution (**14e**) resulted in a 64 % yield. The regioisomeric ratio obtained with these halo-substituted arylboronic acids was 7:1 $S_N2´$:S_N2, and the enantiomeric excess remained excellent throughout. 2-naphthylboronic acid (**14d**) was tolerated, giving the desired product in 66 % yield and a rr of 8:1. Demonstrating that strongly electron-withdrawing groups are compatible with this system, 4-(trifluoromethyl)phenylboronic acid (**14g**) gave a 55 % yield, a rr of 8:1, and ee of >99 %. While maintaining excellent ee for this example is delightful, the slightly decreased yield could be the result of a protodeboronation of the starting material, as this process has been shown to be more significant in electron-deficient arylboronic acids (see chapter 1.2.4, Scheme 9).[50]

Further, a set of heteroarylboronic acids (**14h-j**) was examined. Heteroarylboronic acids are more challenging substrates in Rh-catalysed AAAr, probably due to a higher rate of the competing protodeboronation or the coordination of heteroatoms to the catalyst, leading to lower activity. This is reflected in the yields obtained for 2-benzofurylboronic acid (**14h**, 42 %, rr of 3:1), 3-thiopheneboronic acid (**14i**, 12 %, rr of 4.5:1), and 4-dibenzo[*b,d*]-furanylboronic acid (**14j**, 29 %, rr of 7:1). The ee obtained for **14j** is with 94 % lower than the ee found for all other successful boronic acids. As a general trend, the regioisomeric ratio is stable between 7:1-8:1 in favour of the desired S_N2' type product with the notable exception of **14h** and **14i**, which show decreased regioselectivity. As the electronic properties of these two heteroarylboronic acids are estimated to be similar to those of the range of arylboronic acids **14a**-**14g**, this might indicate a steric influence of the boronic acid on the equilibrium of the two possible *σ*-*π*-enyl-



Scheme 38: Scope in respect to (hetero)arylboronic acids, yield, regioisomeric ratio, and enantiomeric excess remain largely unaffected with the exception of **14h** and **14i**. *Reaction conditions*: 0.4 mmol **13**, 0.8 mmol arylboronic acid, 2.5 mol% Rh precursor (5 mol% Rh), 6 mol% (*S*)-DM-Segphos, THF, 0.2 M, 60 °C for 4 h.

intermediates or on the regioselectivity of the reductive elimination of the alternative π-σ-π-complex.

However, the applicability of heteroaryl boronic acids in this transformation appears to be limited. Apart from substitutions in the 2-position, which appear to be generally challenging motifs due to their steric demands and likely hinder transmetalation with the Rh-catalyst, heteroarylboronic acids containing nitrogen heteroatoms are known to be often unreactive as well. One example that proved feasible in earlier studies, (6-chloro-3-pyridinyl)boronic acid,[167] only provided trace amounts of product and was not pursued further. A range of more sophisticated heteroarylboronic acids kindly provided by Vertex Pharmaceuticals – including three cyclic sp^3-hybridised boronic acids – all failed to react under the outlined reactions conditions (Figure 9).

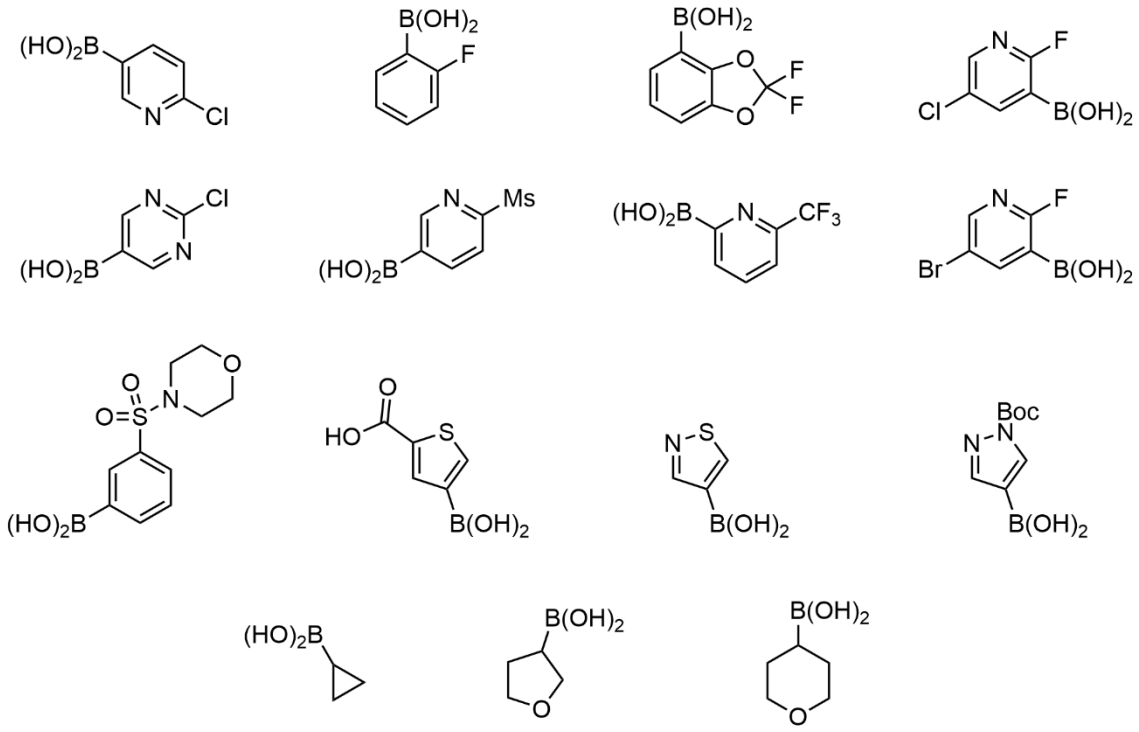
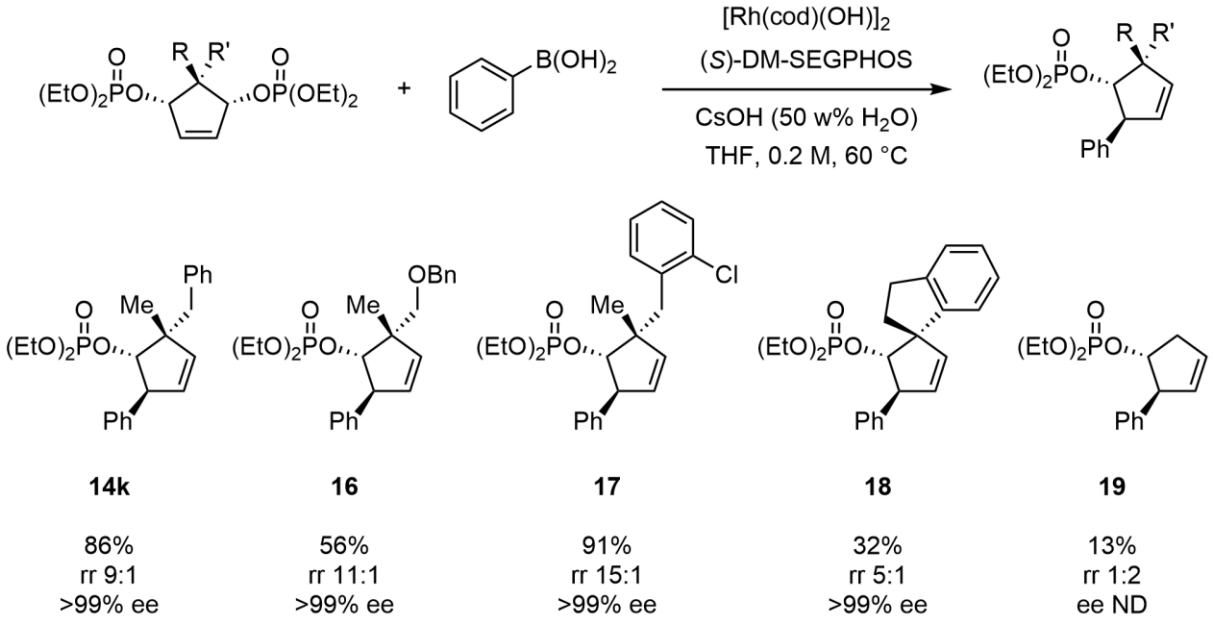


Figure 9: Unsuccessful boronic acids, which did not provide any or only trace amounts of the desired product.

3.3.3 Scope of electrophiles

As the second part of this study, Reece Jacques examined the applicability of different prostereogenic quaternary centres in this system. (Scheme 39). Compared to *meso* bisphosphate **14k,** which served as the model compound for the optimisation and nucleophile scope, both the yield and regioisomeric ratio are affected by variations of the quaternary centre. Exchanging the benzyl substituent for a benzyloxymethyl moiety (**16**) increases the rr to 11:1 in favour of the $S_N2´$ type product and chloro-substituted **17** gives a rr of 15:1 in 91 % yield. This underlines the hypothesis that, after oxidative addition, the steric interaction of the Rh- σ-π-enyl-complex with the quaternary centre is a key factor to influence the equilibrium of intermediates **VI** and **VIII** (Scheme 37) and therefore shifts the regioselectivity towards the desired $S_N2´$ type product. The diminished rr of 5:1 obtained with **18** would consequently arise from the sterically less demanding, yet more rigid spirodihydroindene moiety. The enantioselectivity of the transformation does not appear to be affected for any of the examined *meso* bisphosphates. However, the lack of a quaternary centre, as shown in **19**, leads to an inverted regioselectivity with a rr of 2:1 in favour of the undesired S_N2 type product, further highlighting the impact of the quaternary centre on the regioselectivity of this system. This mixture of *syn*/*anti*



Scheme 39: Scope in respect to the all-carbon quaternary stereocentre which is 'revealed' in the desymmetrization process. *Reaction conditions*: 0.4 mmol *meso* bisphosphate, 0.8 mmol phenylboronic acid, 2.5 mol% Rh precursor (5 mol% Rh), 6 mol% (*S*)-DM-Segphos, THF, 0.2 M, 60 °C for 4h; Experiments were performed by Reece Jacques.

diastereomers could no longer be separated, and thus a reliable characterisation of the enantiomeric excess using HPLC or SFC was not possible. As the desymmetrization of unfunctionalised dicarbonates, analogous to **19**, has already been developed by the group of Lautens,[161] further optimisation on this substrate was not carried out. The variation of the ring-size (Figure 10, a, **20** and **21**) provided improved yields, except for the incorporation of an oxygen heteroatom to obtain dihydrooxepine **22**, however, the regioisomeric ratios remained unsatisfactory. Notably, *meso* bisphosphates designed with the more sterically demanding substituent of the quaternary centre *anti* to both phosphate moieties proved unreactive, as did a more sterically complex bicyclic bisphosphate and the azepine analogue of **22** (Figure 10, b).

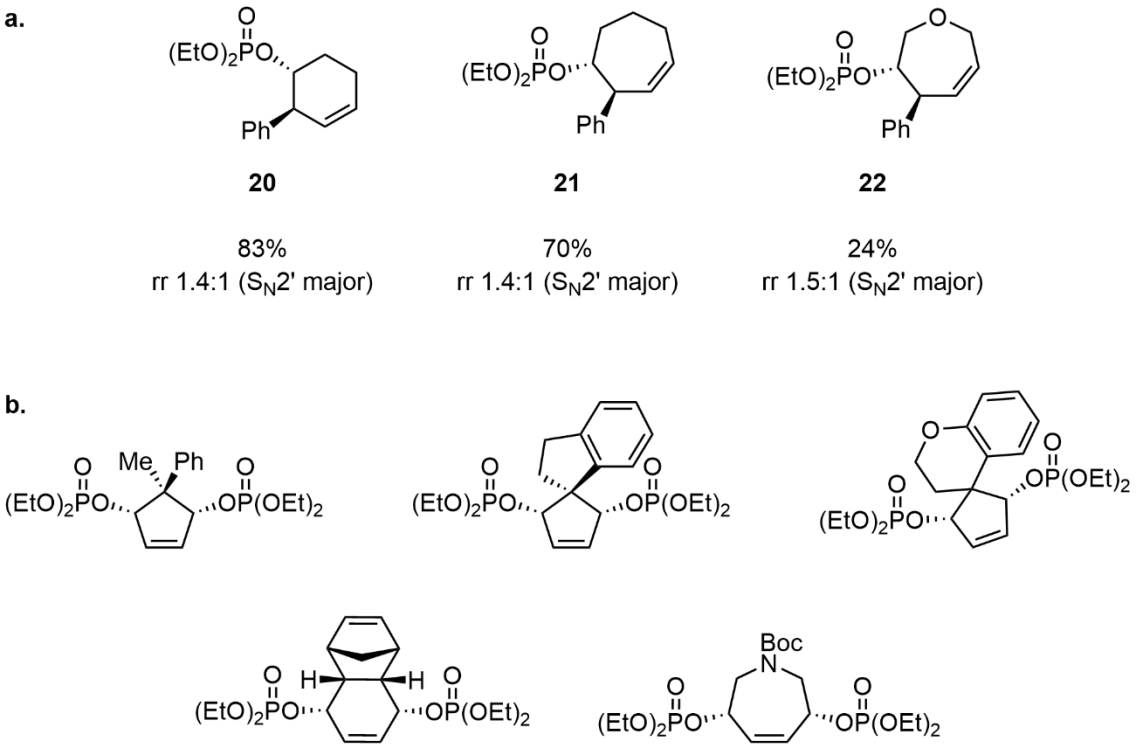


Figure 10: **a.** Variation of ring size of *meso* bisphosphates, leading to significantly reduced regioisomeric ratios; **b.** Unreactive *meso* bisphosphates exhibiting steric shielding *anti* to the phosphate moieties; *Reaction conditions*: 0.4 mmol *meso* bisphosphate, 0.8 mmol phenylboronic acid, 2.5 mol% Rh precursor (5 mol% Rh), 6 mol% (*S*)-DM-Segphos, THF, 0.2 M, 60 °C for 4h; Experiments were performed by Reece Jacques.

3.4 Conclusion and Future Work

A highly diastereo- and enantioselective Rh-catalysed AAAr strategy was developed for the desymmetrization of functionalised *meso* bisphosphates. The incorporation of a prostereogenic quaternary centre allows for the rapid assembly of highly functionalised 5-membered carbocycles bearing three continuous stereocentres, one of which is an all-carbon quaternary centre. This transformation proceeded with excellent enantioselectivity and moderate-to-good yields for a range of (hetero)arylboronic acids, with heteroarylboronic acids being generally less well tolerated. Further, variations of the prostereogenic quaternary centre led to significant changes in regioselectivity, while sterically more demanding *meso* bisphosphates remained unreactive. These results demonstrate that this strategy is a viable, yet sensitive, approach to the desymmetrization of highly functionalised *meso* bisphosphates, complementary to the recently reported Cu(I)-catalysed allylic alkylation strategy.

A future investigation of this system could focus on diversifying the applicable leaving groups, as *meso* bromides have already been used in similar Cu-catalysed transformations,[160] as well as *meso* carbonates.[161] Other oxygen-based leaving groups would therefore present themselves as possible candidates to expand the synthetic utility of this desymmetrization reaction.

The limitations of this methodology highlight the need for the development of transition-metal catalysed transformations that tolerate more complex heteroarylboronic acids or substrates containing heteroatoms.

4. Rhodium Catalysed Asymmetric Arylation of Cyclobutenes

4.1 Introduction

Highly substituted cyclobutanes are one of the structural features often found in natural products[168-169] and drug candidates[170-171], as a cyclobutane core provides a rigid backbone for more complex target molecules (Figure 11, a).[172] While cyclobutanes are therefore synthetic targets themselves, their inherent ring-strain additionally renders these structures intermediate platforms for further transformations,[173-174] including strain-release driven reactions.[175] Consequently, there has been interest in developing synthetic strategies to obtain cyclobutanes such as [2+2]-cycloaddition,[176] ring expansion,[177] and 1,4-cyclisation.[178-179] Another strategy is the desymmetrization of photo-catalytically obtained *meso* cyclobutanes in target synthesis,[180-182] but only recently advances have been made to directly access cyclobutanes enantioselectively. Cyclobutanes featuring an aromatic substituent on the carbocycle are motifs which are present in potential drug candidates (Figure 11, a) but, as of yet, there are no widely applicable methods to asymmetrically synthesise such aryl-substituted cyclobutanes. Therefore, an enantioselective, modular, or hydroarylation-type strategy to achieve these motifs is

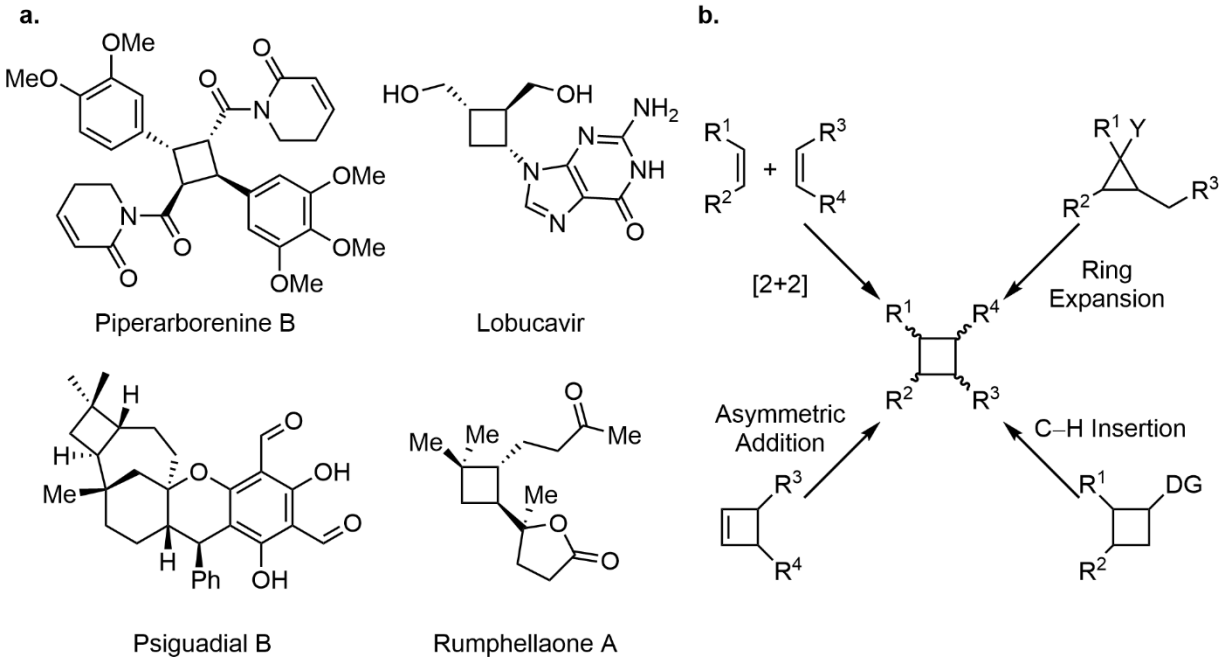
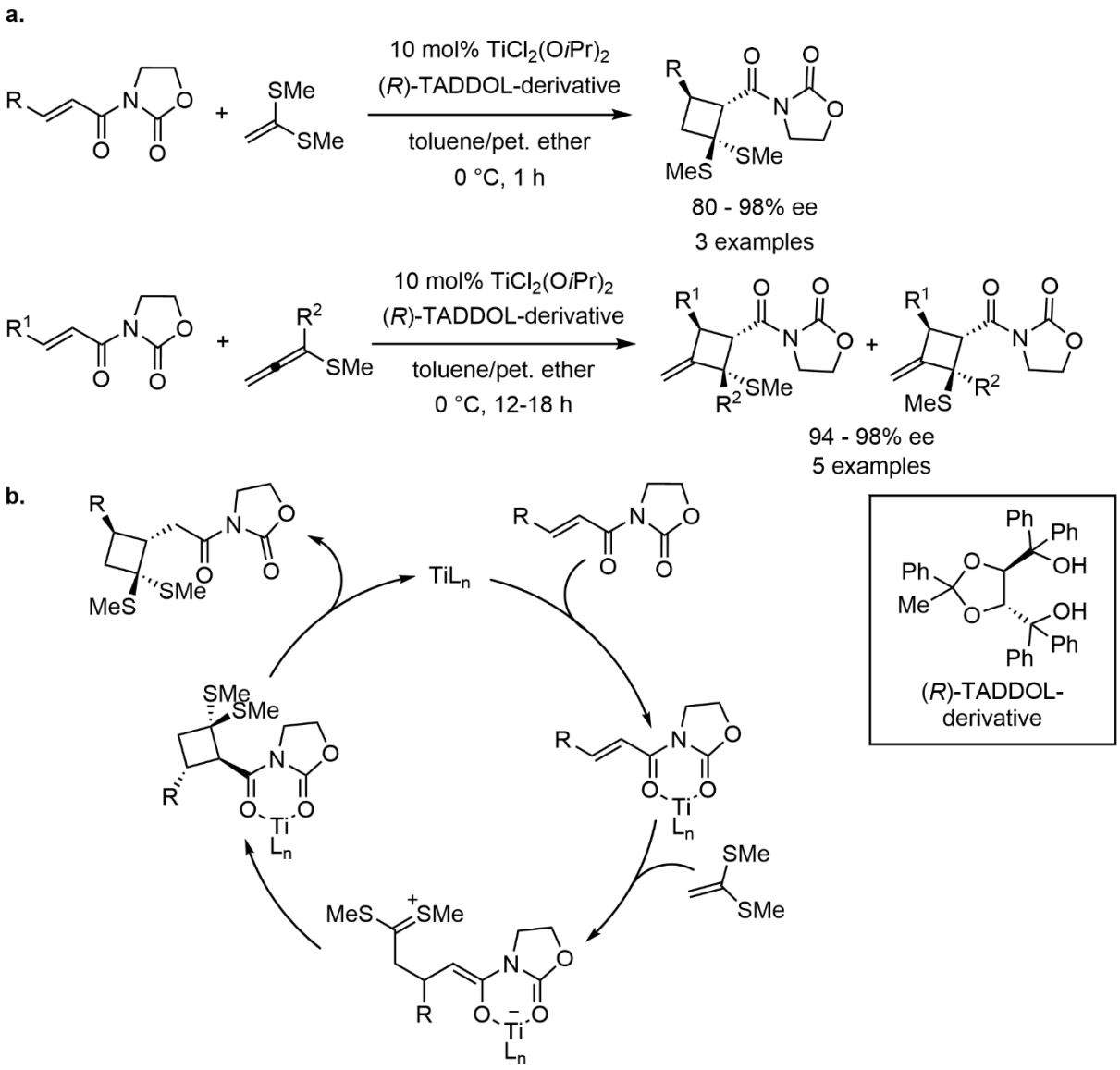


Figure 11: **a.** Selection of cyclobutanes found in natural products and biologically active compounds;[172, 243] **b.** General methodologies to access substituted cyclobutanes; carbometallation processes, such as asymmetric additions, are very scarce for cyclobutenes.[177]

desirable as it would enable the direct preparation of such cyclobutane motifs and their derivatives.

4.1.1 Cyclobutanes via [2+2]-cycloaddition

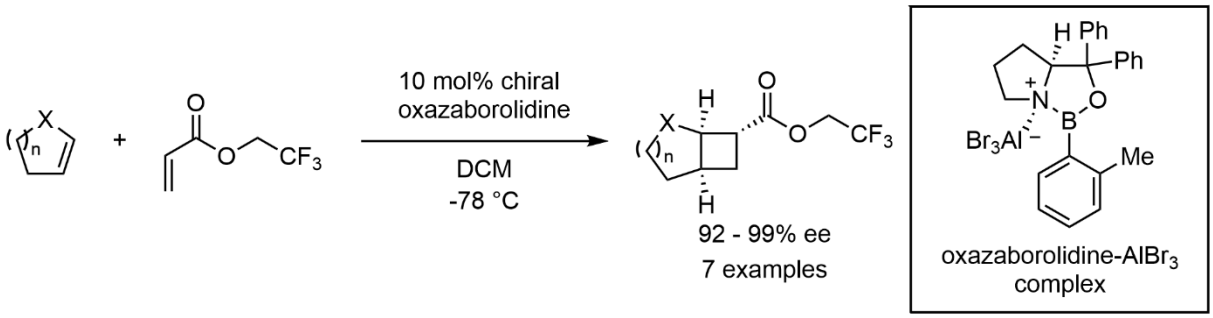
An intuitive option for accessing cyclobutanes is the [2+2]-cycloaddition of two alkene moieties.[183] As a consequence, large scale photosensitised processes using flow cells combined with tailored irradiation are emerging.[184] Other than photocatalysed [2+2]-cycloadditions, thermal [2+2]-cycloadditions are the second option to achieve cyclobutanes.



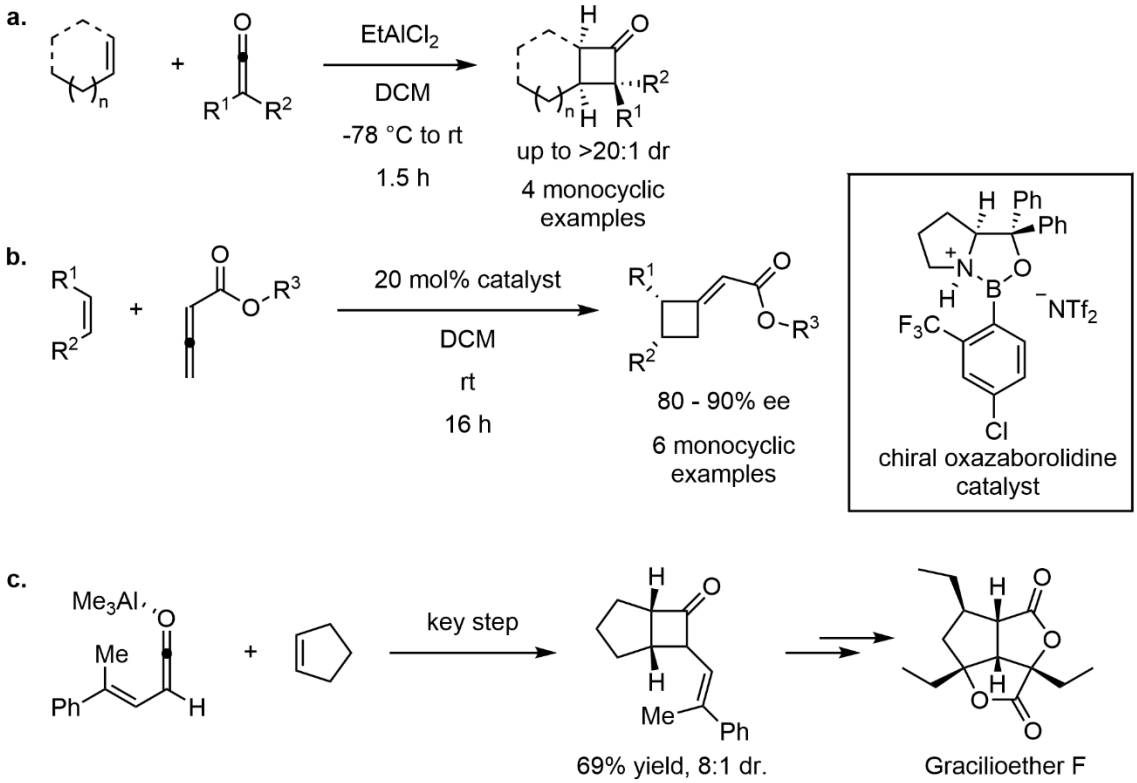
Scheme 40: **a.** First enantioselective Lewis-acid catalysed [2+2]-cyclisation to access functionalised cyclobutanes, including examples with an *exo*-cyclic double bond;[188-189] **b.** Proposed stepwise mechanism for this transformation *via* a zwitterionic intermediate.[176]

However, due to the formation of either highly reactive or sufficiently long-lived intermediates, both processes are inherently prone to stereochemical equilibration.[177] Hence, the enantio- or diastereoselective synthesis of functionalised cyclobutanes *via* [2+2]-cycloadditions requires other catalytic approaches.[176] Here, selective non-photochemical strategies will be discussed first, followed by recent developments in the enantioselective photocatalytic formation of cyclobutanes.

Examples of diastereoselective but non-enantioselective Brønsted acid and Lewis acid catalysed [2+2]-cycloadditions to obtain substituted cyclobutanes have long been known.[185-187] Highly enantioselective catalytic systems have also been reported, starting with the titanium catalysed [2+2]-cycloaddition of oxazolidinones with dimethyl dithioacetals and allenyl-sulfides in 1989 and 1992 by Narasaka (Scheme 40, a).[188-189] The mechanism for this transformation has been suggested to proceed stepwise *via* a zwitterionic species,[189] and, based on a separate mechanistic study of the Ti/TADDOL catalyst system in the [2+2]-cyclisation of benzoquinones,[190] Brown and co-workers suggested the mechanism shown in Scheme 40, b.[176] Another example is the highly enantio- and diastereoselective [2+2]-cycloaddition of trifluoroethyl acrylates with various enol ethers such as dihydrofuran reported by Corey and co-workers (Scheme 41).[191] The effective chiral oxazaborolidine $AlBr_3$-complex used for this transformation also achieves excellent yields and selectivities in asymmetric Diels-Alder reactions for which it was originally designed.[192] While these strategies result in highly



Scheme 41: [2+2]-Cycloaddition between highly activated terminal alkenes and enol ethers, catalysed by a Lewis-acidic chiral oxazaborolidinone complex, which was developed by Corey and co-workers.[191]

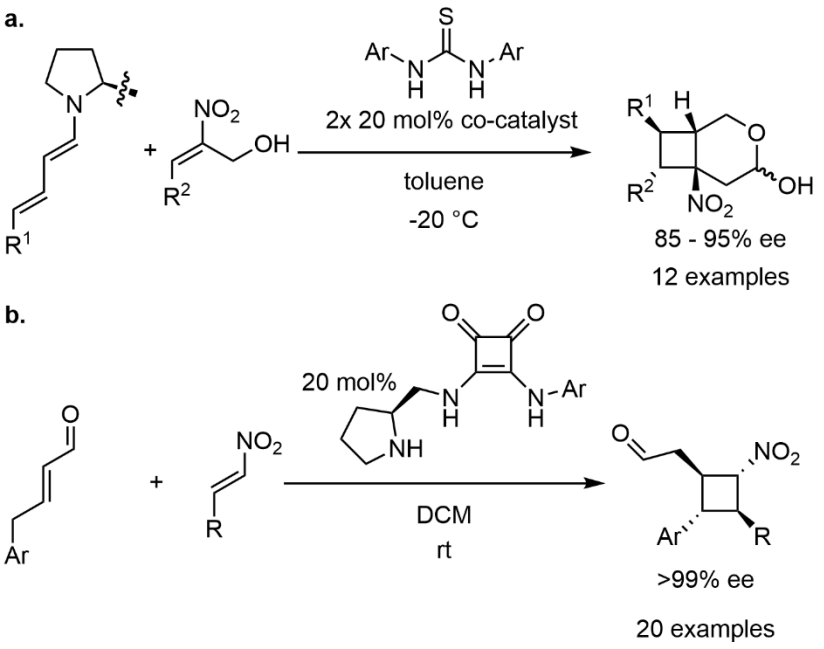


Scheme 42: **a.** Diastereoselective [2+2]-cycloaddition between non-activated alkenes and ketenes;[193] **b.** Enantioselective Lewis-acid catalysed [2+2]-cycloaddition between non-activated alkenes and allenoates;[194] **c.** Diastereoselective key [2+2]-cycloaddition in the synthesis of Gracilioether F.[196]

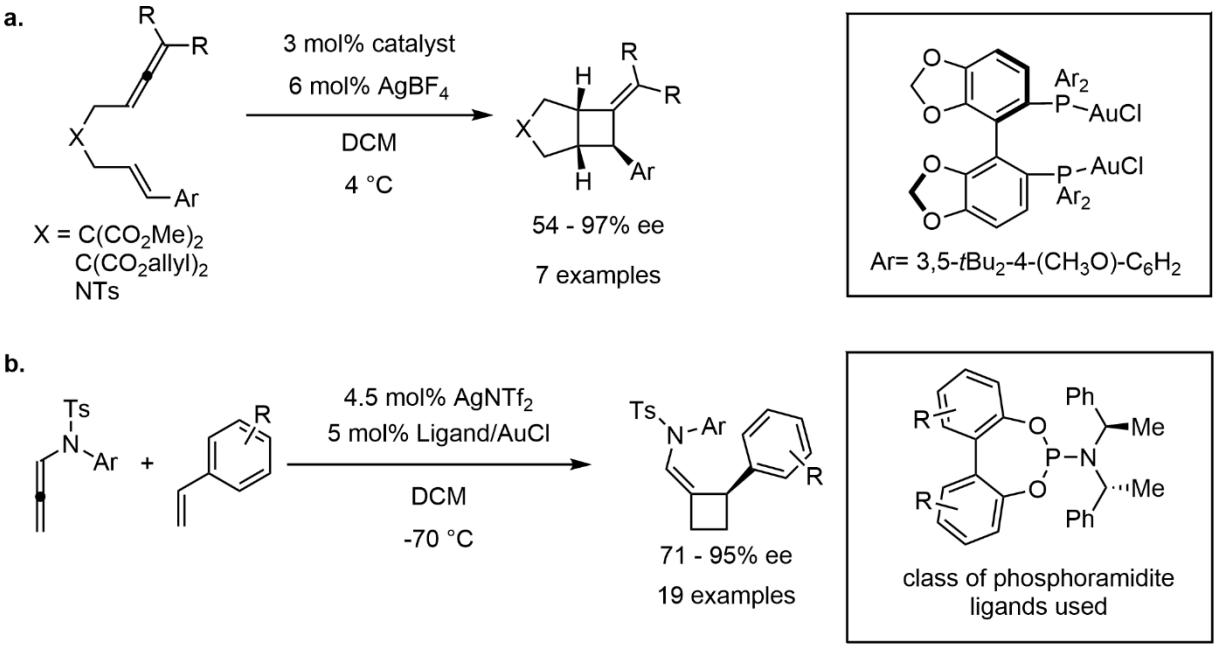
enantioenriched substituted cyclobutanes, they are limited to strongly polarised alkenes, and an *α,β*-unsaturated carbonyl moiety is required to interact with the Lewis acid catalyst.

Brown and co-workers developed a mechanistically different, Lewis acid catalysed approach which still requires an *α,β*-unsaturated carbonyl moiety for catalytic activation. However, this system utilises ketenes or allenoates as cyclisation partners and expands the scope of applicable substrates to non-activated alkenes (Scheme 42, a and b).[193-194] The use of $EtAlCl_2$ as a simple Lewis acid enables the generation of cyclobutanones in generally good diastereoselectivity from a wide range of non-activated alkenes (Scheme 42, a).[193] An enantioselective variation is the alkene-allenoate [2+2]-cycloaddition using a chiral oxazaborolidine as Lewis-acidic catalyst, leading to functionalised cyclobutanes featuring an exocyclic double-bond (Scheme 42, b).[194] This approach also enables access to non-asymmetric 1,3-disubstituted cyclobutanes.[195] It should be mentioned that the alkene-ketene cycloaddition strategy has been shown to be a useful synthetic tool in the total synthesis of Gracilioether F

(Scheme 42, c).[196] The limitation to activated carbonyl compounds is somewhat mitigated in alternative organocatalytic strategies using H-bonding assisted dienamine catalysis for formal [2+2]-cycloadditions (Scheme 43),[197-199] but the requirement for activated alkenes restricts the applicability of this approach. The dependency on polarised unsaturated carbonyls can be avoided by employing Au(I)-catalysts as Lewis acids in the [2+2]-cycloaddition of allenes and alkenes as demonstrated by the group of Toste (Scheme 44, a).[200-201] This approach is not limited to intramolecular reactions but enables the generation of



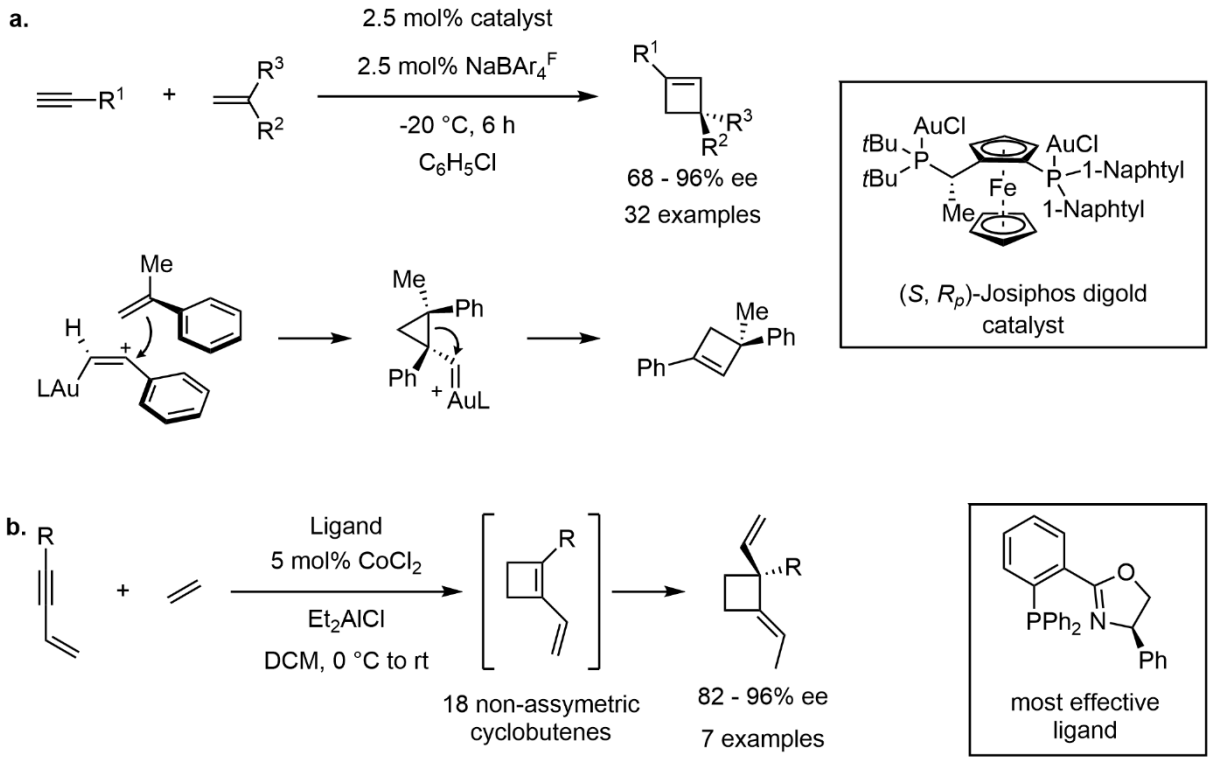
Scheme 43: **a.** H-bonding assisted dienamine catalysis for a formal [2+2]-cycloaddition using a thiourea based co-catalyst;[199] **b.** Combination of both required amine functionalities in one organocatalyst.[198]



Scheme 44: **a.** Au(I)-catalysed intramolecular [2+2]-cycloaddition between allenes and alkenes to form bicyclic cyclobutanes;[200] **b.** Au(I) catalysed intermolecular [2+2]-cycloaddition between activated allenamides and styrene derivatives.[202]

cyclobutanes from allenamides and styrene derivatives (Scheme 44, b), the latter constituting a restricting requirement for this Au-catalysed strategy.[202][203]

For the synthesis of related cyclobutenes, a catalytic system has been developed by Echavarren and co-workers utilising a [2+2]-cycloaddition of alkynes and alkenes to obtain substituted enantioenriched cyclobutenes (Scheme 45, a).[204-205] A similar approach has been chosen by the group of RajanBabu, who disclosed the enantioselective synthesis of cyclobutenes using a Co(I)-complex as catalyst.[206] In addition, this method allows for the subsequent Co(I)-catalysed asymmetric hydrovinylation of the obtained cyclobutenes, in the form of tandem catalysis, to provide enantioenriched cyclobutanes featuring an exocyclic double-bond and an all-carbon stereocentre (Scheme 45, b).[207] This approach requires terminal enynes as starting materials, and it appears not to tolerate any functional groups with heteroatoms, thus limiting its synthetic potential. It should be noted that the formation of cyclobutenes by a regioselective but non-asymmetric [2+2]-cycloaddition of terminal alkynes and alkenes has been reported previously.[208]

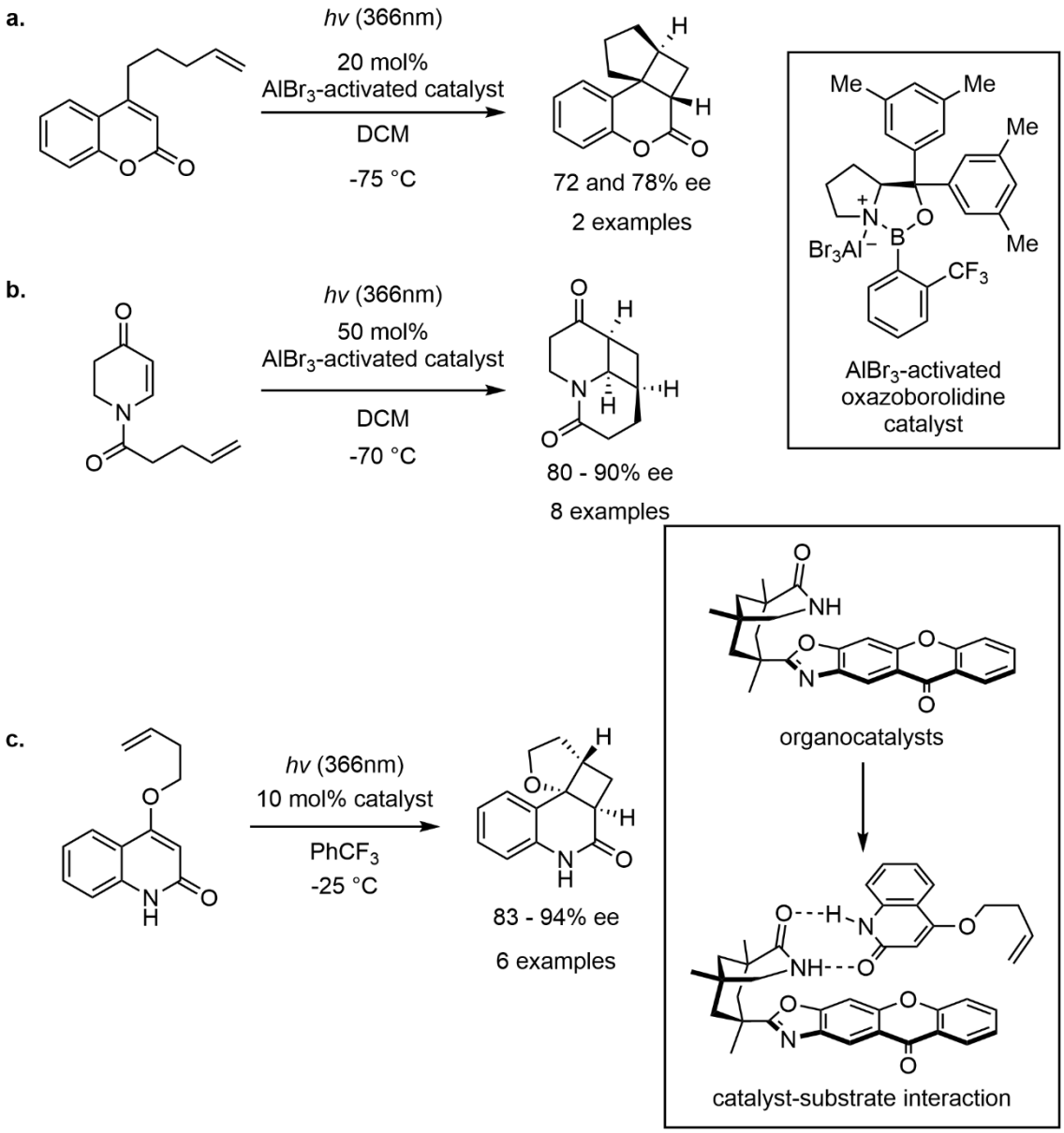


Scheme 45: **a.** Digold(I)-catalysed [2+2]-cycloaddition to access enantioenriched cyclobutenes and the suggested mechanism;[204] **b.** Co(I)-catalysed tandem [2+2]-cycloaddition and vinylation to achieve enantioenriched cyclobutanes featuring a quaternary stereocentre.[207]

A caveat of Lewis acid catalysed diastereo- or enantioselective [2+2]-cycloadditions is a potential competition with alternative, uncatalysed thermal reaction pathways which are less stereoselective.[209] A photocatalytic approach to the enantioselective synthesis of cyclobutanes circumvents this hurdle. In exchange, enantioselective photocatalysis is required to outcompete inherently racemic background and side reactions, which occur due to the formation of highly reactive radical intermediates that are challenging to subdue and exploit in a stereoselective fashion.[210-211] Against this backdrop, it is worth briefly discussing strategies which were developed to address this challenge.

Photocatalysed asymmetric [2+2]-cycloadditions have been known for several decades,[212-213] with the first intermolecular asymmetric photochemical [2+2]-cycloaddition being reported by Tolbert and Ali in 1982.[214] To achieve enantioinduction in these early intermolecular systems, chiral substituents, such as chiral esters, were used, albeit with moderate selectivity.[213] This approach is reminiscent of hydrolysable chiral linkers which were previously developed for asymmetric *intra*molecular [2+2]-cycloadditions.[215] These chiral-auxiliary based strategies were pioneering in the field of asymmetric photochemical [2+2]-cycloadditions but remained synthetically underdeveloped due to their often limited applicability and moderate selectivities.

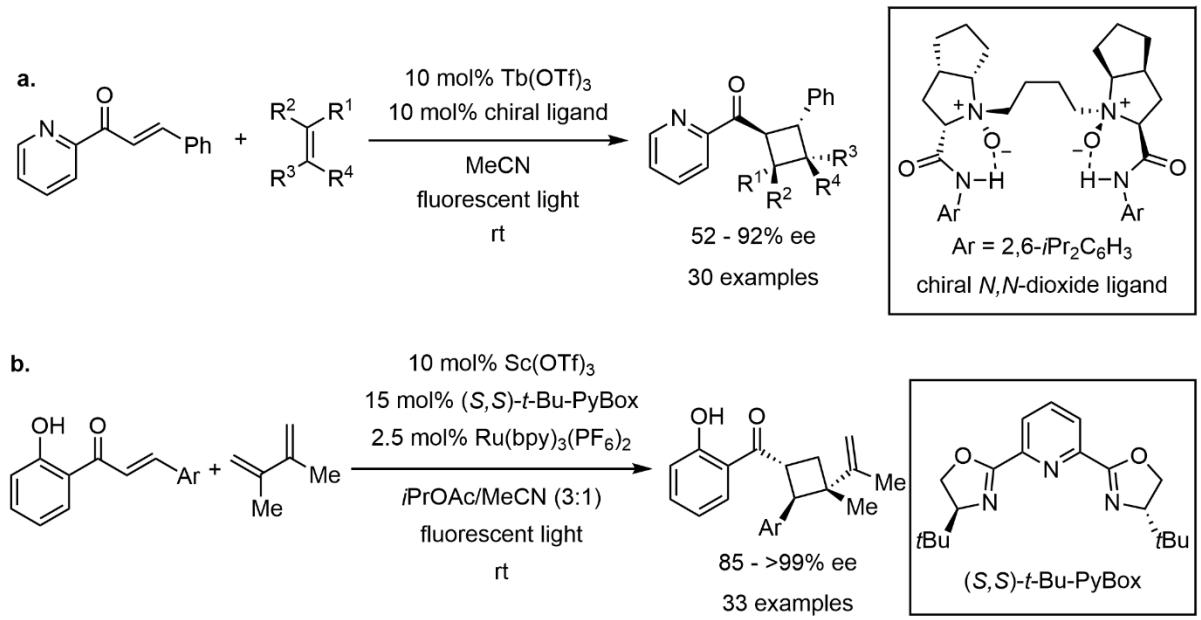
Using a different concept, the more recent and significant advances in photochemical asymmetric [2+2]-cycloadditions employ chiral Lewis acids as catalysts in combination with various photosensitisers. This type of catalysis originated in the field of asymmetric radical additions[216] and was first reported by Sato in 1995, before being adapted in photocatalytic reactions.[216-217] Bach and co-workers demonstrated that the use of a cationic oxazaborolidine (Scheme 46, a, catalyst) facilitates the photochemical enantioselective intramolecular [2+2]-cycloaddition of functionalised coumarins with an enantiomeric excess of up to 82 % ee (Scheme 46, a).[218] The same approach allows for the intramolecular [2+2]-cycloaddition of enone-motifs with good enantiomeric excess.[219] This reaction is enabled by a >50 nm



Scheme 46: **a.** Enantioselective intramolecular [2+2]-photocycloaddition of coumarins;[218] **b.** Enantioselective intramolecular [2+2]-photocycloaddition of cyclic enones, both catalysed by the chiral Lewis-acidic oxazaborolidine shown (top right);[219] **c.** Enantioselective intramolecular [2+2]-photocycloaddition facilitated by a supramolecular interaction with an organocatalyst.[220]

bathochromic shift of the absorption maximum of the substrate upon coordination to the Lewis acid catalyst, thus enabling the selective excitation of the substrate-catalyst complex and suppressing an undesired non-catalytic racemic background reaction (Scheme 46, b).[219] Alternatively, chiral metal-free photosensitisers are able to facilitate this transformation with good-to-very-good enantioselectivities. However, such organocatalytic approaches require specific motifs to be present in the substrate as these methods rely on supramolecular interactions, specifically the formation of hydrogen-bonds.[220] In addition, these systems are

limited to intramolecular, and therefore particularly fast, [2+2]-cycloadditions as reported by Bach (Scheme 46, c) and later by Sibi and Sivaguru.[220-223]



Scheme 47: **a.** Enantioselective intermolecular [2+2]-photocyclisation using a Lewis-acid/chiral ligand combination;[225] **b.** A dual catalysis approach with a Lewis-acid/chiral ligand and a ruthenium-based photosensitiser.[227]

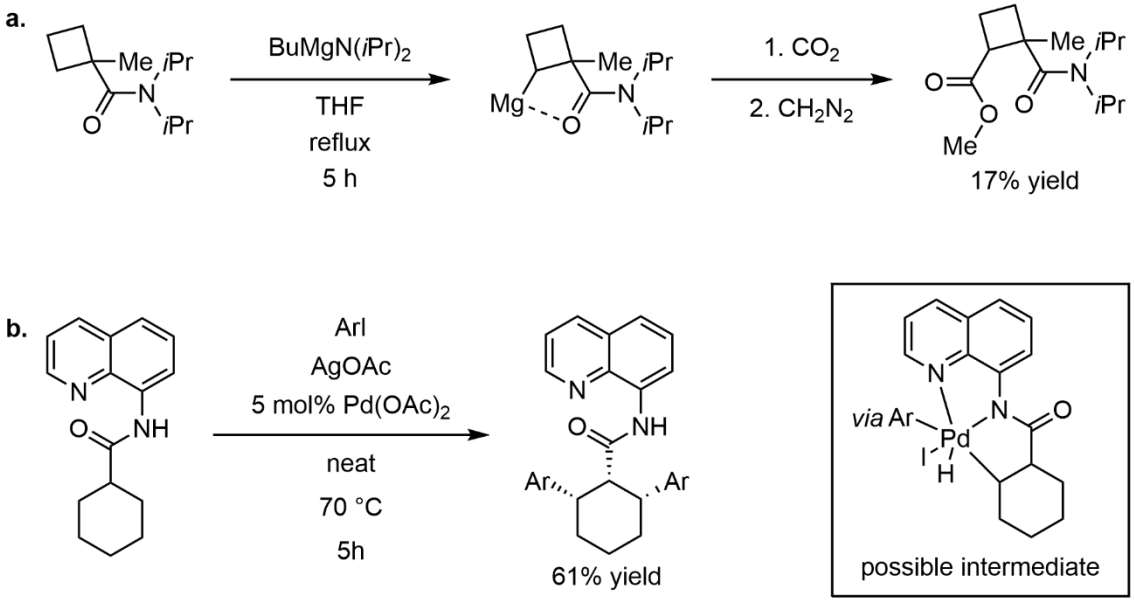
Using an Ir(III) based photosensitiser, Yoon and co-workers achieved an intramolecular [2+2]-cycloaddition of styrene motifs resulting in bicyclic products with an aromatic substituent directly connected to the cyclobutane ring.[224] This approach was extended to Tb(II) based photosensitisers by the group of Feng in 2018, who were able to achieve the enantioselective intermolecular [2+2]-cycloaddition of alkenes and 2-alkenoylpyridines or 2´-hydroxychalcones (Scheme 47, a).[225] In combining these two concepts in a dual catalysis approach, Yoon and co-workers developed a method for intermolecular enantioselective [2+2]-photocycloadditions which yield functionalised cyclobutanes,[226] including more diverse structures with an aryl moiety as a substituent on the formed cyclobutane ring (Scheme 47, b).[227-228] The same group demonstrated very recently that Brønsted acids are viable co-catalysts for this reaction as well.[229] Finally, it should be noted that both the intra- and intermolecular photochemical [2+2]-cycloadditions without enantiocontrol have been reported for the synthesis of aryl-substituted 3-azabicyclo[3.2.0]heptanes.[230-231]

While these contributions have significantly advanced the field of selective [2+2]-cycloaddition, only very few methods allow for enantioselective intermolecular transformations, and most strategies are generally restricted to specific substrate structures. Therefore, the introduction of aryl moieties directly connected to the cyclobutane scaffold remains challenging.

4.1.2 Cyclobutanes via C–H-bond activation

Another option to access aryl-substituted cyclobutanes is the arylation of preformed cyclobutanes *via* C–H-bond activation.

The activation of a C–H-bond in a cyclobutane by an oxidative addition of the Rh-Hydride complex [Cp*(PMe_3)Rh(neopentyl)(H)] has been reported with a rate constant of 2.7 ± 0.2 relative to cyclohexane by Periana and Bergman in 1986, which is faster than the comparable C–H-bond activation in cyclopropane with a relative rate constant of 2.3 ± 0.1.[232] A striking difference between the C–H-bond activation of cyclopropanes and cyclobutanes with Rh-complexes is a competing C–C-bond insertion to form a metallacycle.[233] While re-examining the Rh-catalysed C–H-bond activation of cyclobutanes in 1998, it was confirmed that, unlike in cyclopropanes, a C–C-bond insertion and the formation of a metallacycle does not occur.[233]

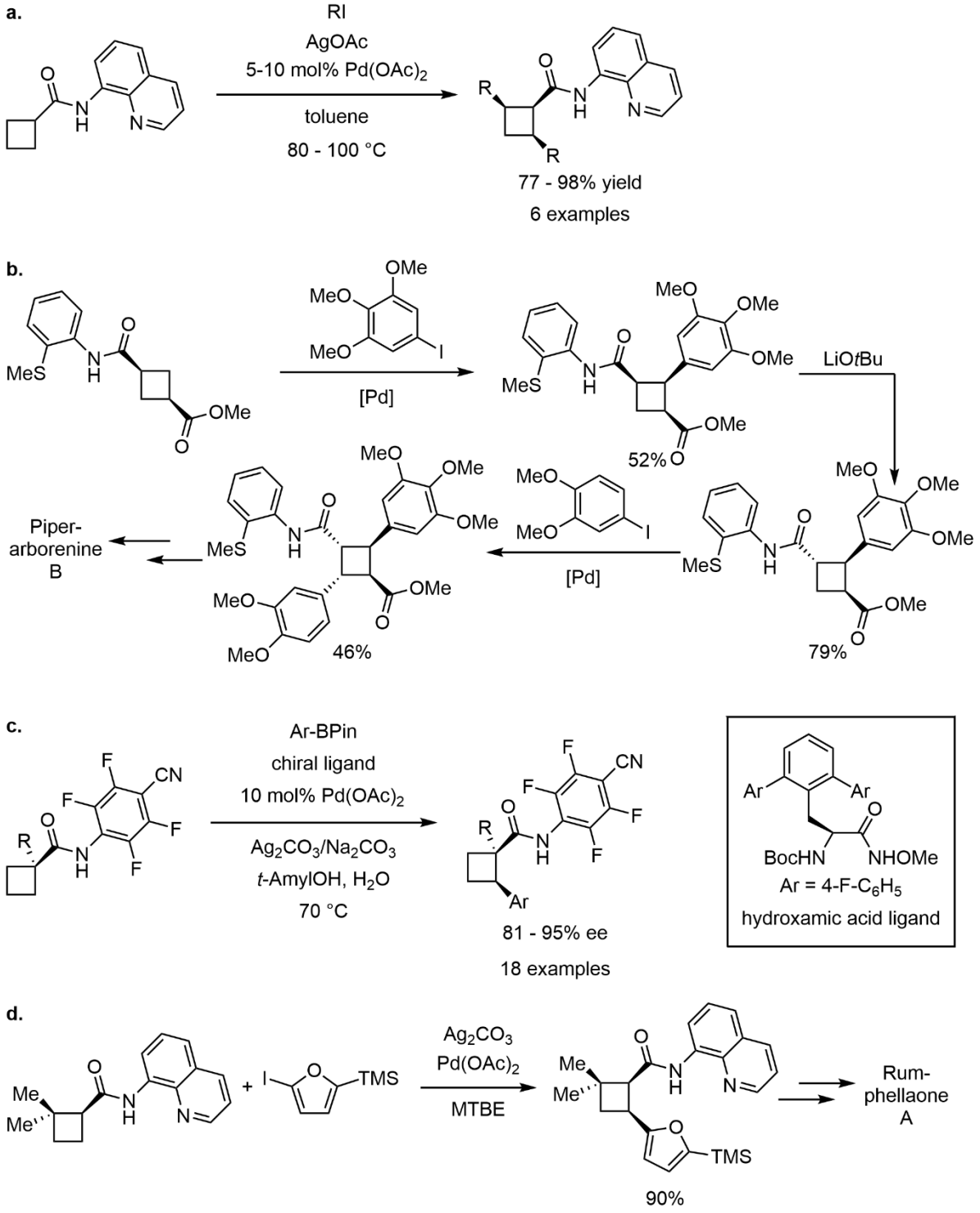


Scheme 48: **a.** C–H-bond activation of a cyclobutene *via* a magnesiation approach;[234] **b.** C–H-bond activation on a cyclohexane moiety to achieve double arylation using aminoquinoline amides as the directing group.[240]

Attempting to move to synthetically more useful systems, Eaton and co-workers developed a magnesiation strategy for cyclobutane amides, which requires harsh conditions and offers only limited options for functionalisation (Scheme 48, a).[234-235] Due to these challenges, the C–H-bond activation of small carbocycles focused predominantly on cyclopropanes. The group of Yu demonstrated the feasibility of this C–H-bond activation for synthetic applications with several examples of cyclopropanes,[236-238] but the functionalisation of a cyclobutane was shown only once.[239] Further illustrating the lack of a widely applicable methodology, only one example of a C–H-bond activation of a less strained cyclohexyl derivative was reported by Daugulis and co-workers, using Pd(II) acetate as a catalyst and an aminoquinoline amide moiety as a directing group (Scheme 48, b).[240]

Pioneering the C–H-arylation of cyclobutanes, Gutekunst and Baran applied an amide moiety derived from Daugulis' system in their synthesis of pseudo-symmetrical Piperarborenine B (Scheme 49, a and b).[180-182] This approach provides fully functionalised cyclobutanes after an arylation or vinylation at both β-positions to the directing group, making the introduction and potential removal of the amide directing groups the necessary hurdle to overcome for devising a synthetic strategy. Further, the stereoselectivity of the C–H-arylation is dependent on the stereochemistry of the directing group, which in turn is determined in the synthesis of a (pseudo)-symmetrical precursor and thus might necessitate further epimerization.[180] Building on this amide directed C–H-arylation approach, Yu and co-workers developed the mono-arylation of cyclobutanes with good-to-very-good enantioselectivities by incorporating a pre-installed quaternary stereocentre (Scheme 49, c).[241] In fact, the pre-installed quaternary stereocentre in α-position to the directing group is required for an efficient arylation, but this limitation was later remedied by moving to a chiral oxazoline ligand which also enabled the enantioselective mono-vinylation of cyclobutanes.[242]

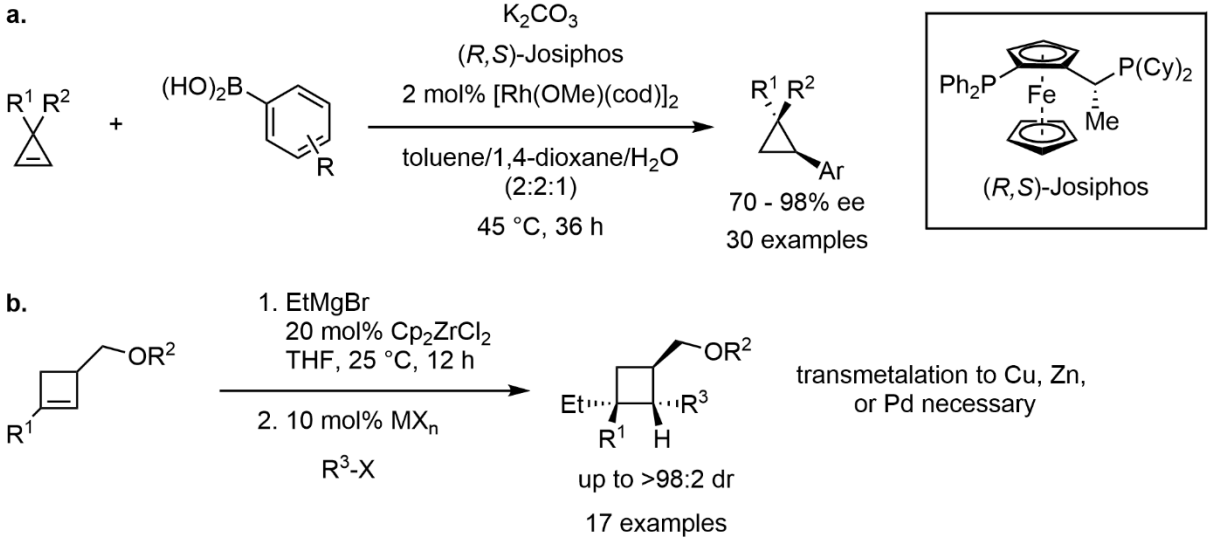
Despite the restrictions caused by the directing groups, this approach for the functionalisation of cyclobutanes has proven successful in further synthetic applications, as the group of Reisman recently utilised the C–H-arylation approach in their strategy to synthesise Rumphellaone A (Scheme 49, d) and other synthetic targets.[243-245]



Scheme 49: **a.** Double arylation/vinylation *via* Pd(II) catalysed C–H-bond activation;[182] **b.** Application of this strategy in the synthesis of pseudo-symmetrical Piperarborenine B;[180] **c.** Pd(II)-catalysed arylation of cyclobutenes with quaternary stereocentres using a similar directing group;[241] **d.** Pd(II)-catalysed mono-arylation in total synthesis of Rumphellaone A.[243]

4.1.3 Functionalisation based on carbometalation of cyclobutenes

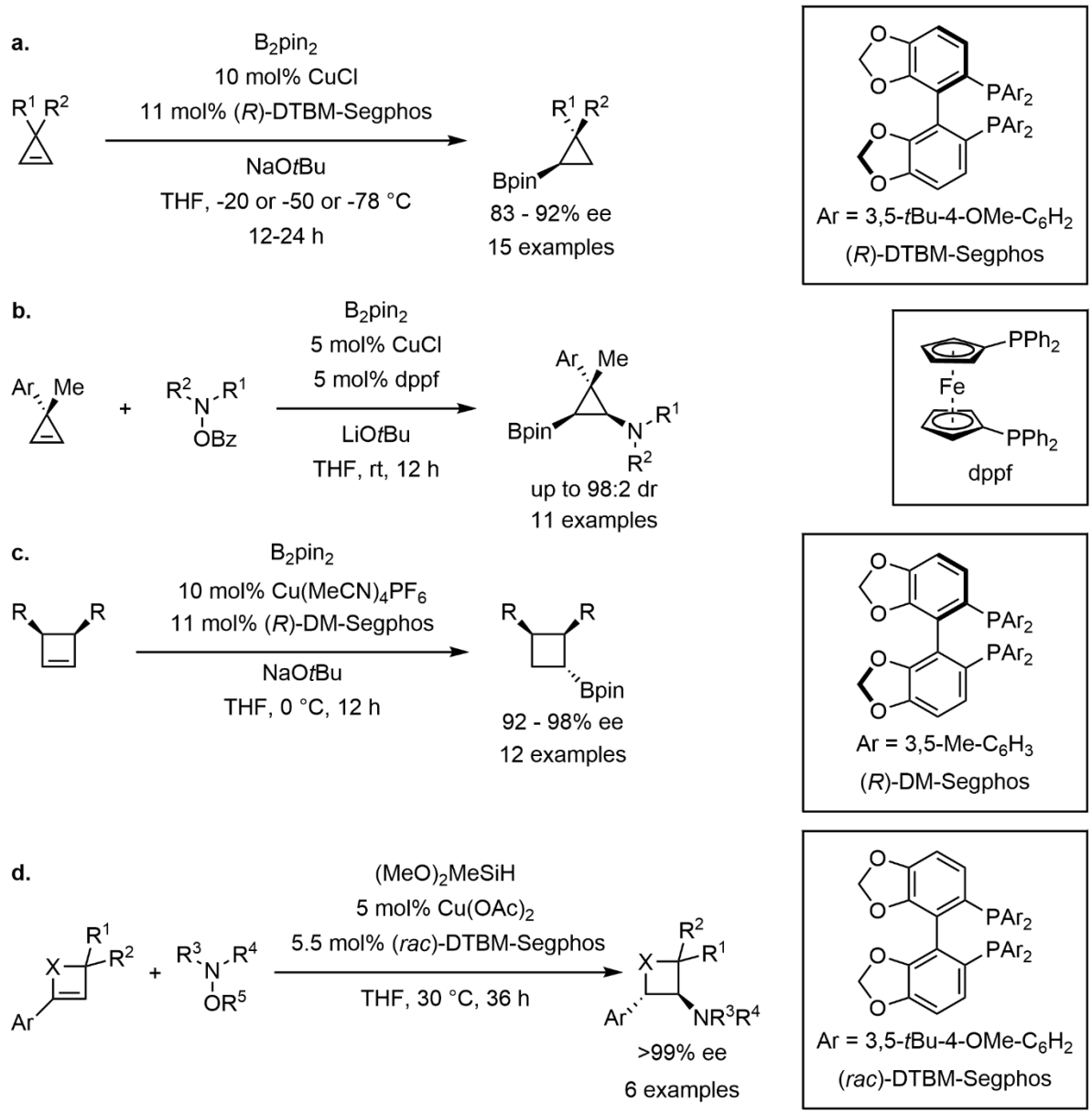
The concept of ring-strain in carbocycles was postulated by von Baeyer in 1885[246] and, particularly for small carbocycles, the release of ring-strain has been shown to be a significant driving force in transformations.[174] Apart from ring-expansion reactions, strain-release can also be exploited for the functionalisation of small unsaturated carbocycles, particularly cyclopropenes and cyclobutenes, if the substrate's Csp^2–Csp^2 double bond is converted to its corresponding Csp^3–Csp^3 single bond in the process. While the difference in strain energy of cyclobutene (28.4 kcal/mol) and cyclobutane (26.5 kcal/mol) is comparably small, the strain-release achieved by converting cyclopropene to cyclopropane (Δ 27.7 kcal/mol) can be more readily harnessed for strategies to obtain functionalised cyclopropanes.[247] Consequently, a wealth of enantioselective transition metal catalysed methodologies for the direct functionalization of the cyclopropene double bond has been developed,[248-249] including a Rh- and Cu-catalysed hydroboration,[250-252] Rh-catalysed asymmetric hydroformylation[253] and hydrostannation,[254] and Cu-catalysed hydroallylation.[255] The enantioselective direct arylation of cyclopropenes has been reported by Marek and co-workers in one example in which 4-bromoacetophenone undergoes Cu-catalysed asymmetric carbozincation.[256] A more general Rh-catalysed asymmetric hydroarylation of functionalised cyclopropenes with very good



Scheme 50: **a.** Rh-catalysed arylation of substituted cyclopropenes *via* carborhodation and subsequent hydrolysis;[257] **b.** Zr-catalysed diastereoselective difunctionalisation of cyclobutenes *via* transmetalation to various transition metals.[258]

diastereo- and enantioselectivities was reported by the same group in 2018 (Scheme 50, a).[257] However, transition metal-catalysed hydrofunctionalisations of cyclobutenes have been scarce. Marek and co-workers reported a Zr-catalysed carbomagnesiation of cyclobutenes, which allows for further arylation after additional transmetalation to Cu, Zn, or Pd (Scheme 50, b).[258]

Following up on their reported Cu-catalysed hydro- and aminoboration of cyclopropenes (Scheme 51, a and b),[259] Tortosa and co-workers developed a Cu(I)/(*R*)-DM-SEGPHOS system for the enantioselective hydro- and aminoboration of cyclobutenes (Scheme 51, c).[260]



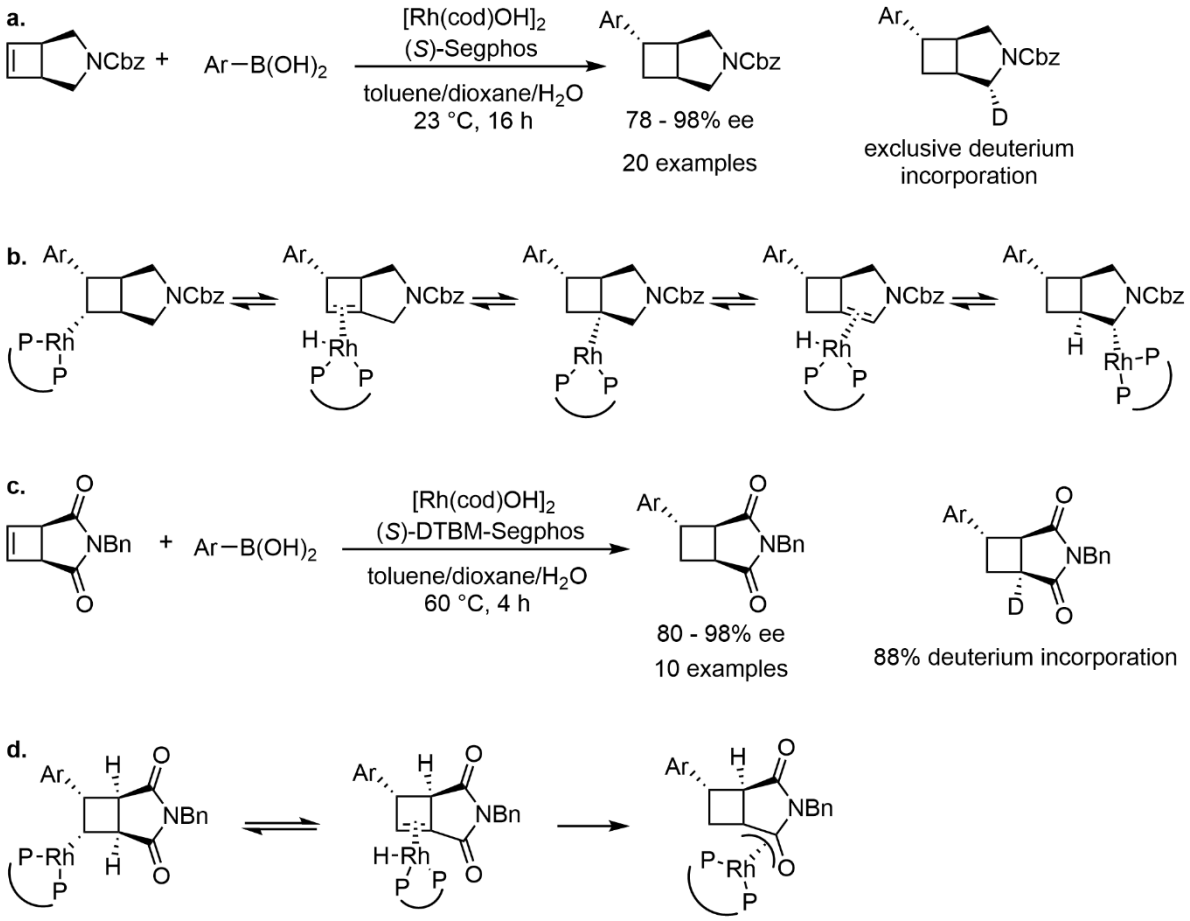
Scheme 51: **a.** Cu(I)-catalysed enantioselective hydroboration of cyclopropenes;[259] **b.** Diastereoselective aminoboration of cyclopropenes;[259] **c.** Cu(I)-catalysed enantioselective hydroboration of *meso* cyclobutenes;[260] **d.** CuH-catalysed regio- and diastereoselective hydroamination of 1-arylcyclobutenes.[261]

More recently, the CuH-catalysed hydroamination of 1-arylcyclobutenes has been reported as well (Scheme 51, d).[261]

Overall, there is a striking scarcity of reports for direct and convenient asymmetric functionalisation of cyclobutenes to achieve enantioenriched cyclobutanes, and this highlights the necessity for developing a general catalytic enantioselective strategy to harness the potential reactivity of cyclobutenes.

4.1.4 Rh-catalysed asymmetric arylation of bicyclic cyclobutenes

The Rh-catalysed asymmetric arylation of bicyclic cyclobutenes to afford functionalised cyclobutanes developed in our lab (Scheme 52, a) is, to the best of the author's knowledge, the



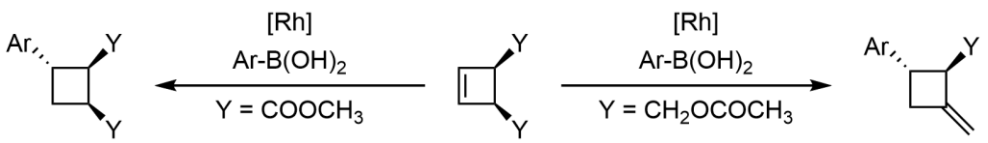
Scheme 52: **a.** Reductive Heck-type arylation of bicyclic cyclobutenes and deuterium labelling (right); **b.** The suggested mechanism *via* chain-walking across the bridgehead of the bicycle resulting in a remote hydrolysis; **c.** Asymmetric 1,5-addition of (hetero)arylboronic acids and the corresponding deuterium labelling (right); **d.** Suggested mechanism of the 1,5-addition *via* formation of an oxa-π-allyl complex.[262]

first example of a Csp^2–Csp^3 bond formation exploiting the release of ring-strain in bicyclic cyclobutenes and this system is a rare example of a metalation of the cyclobutene Csp^2–Csp^2 bond.[262] Depending on the functionalisation of the carbocycle fused to the cyclobutene moiety, the reaction was found to proceed *via* two distinct mechanistic pathways. Following carborhodation, protected 3-azabicylico[3.2.0]-6-heptenes exhibited an unusual chain-walking mechanism of the Rh-catalyst across the bridgehead of the bicycle (Scheme 52, a). The catalyst is regenerated by hydrolysis in the α-position to the nitrogen heteroatom (Scheme 52, b). This mechanism amounts to a reductive Heck-arylation including a remote hydrolysis of the catalyst. Changing the substrate to the related 2,4-dione (Scheme 52, c), the reaction proceeds *via* a 1,5-addition pathway in which the catalyst undergoes a β-hydride elimination and subsequent formation of an oxa-π-allyl complex prior to hydrolysis of the catalyst (Scheme 52, d).

4.2 Objective of the Project

Over the past decade, significant progress has been made in the fields of enantioselective [2+2]-cycloaddition and C–H-bond functionalisation to gain access to asymmetrically functionalised cyclobutane structures. However, these strategies usually require specifically designed substrates or directing groups and therefore often exhibit a lack of generality. A possible third approach to rapidly access asymmetrically functionalised cyclobutanes is *via* carbometalation of the Csp^2–Csp^2 double bond of the corresponding cyclobutene, which has been extensively demonstrated in various systems developed for the asymmetric functionalisation of cyclopropenes. The development of such transformations for bicyclic cyclobutenes and initial experiments using monocyclic variations of these substrates indicated the potential of such a carbometalation approach.

This project aims to address the lack of a widely applicable asymmetric functionalisation strategy by employing rhodium catalysis to develop an enantioselective direct arylation of simple monocyclic cyclobutenes.



Scheme 53: Two possible pathways based on substrate classes to be developed in this project.

4.3 Results and Discussion

4.3.1 Hydroarylation of non-bicyclic cyclobutenes with Michael acceptors

Based on preliminary results obtained in early optimisation studies of the hydroarylation of bicyclic cyclobutenes, our attention was drawn to non-bicyclic cyclobutene diesters. This substrate class is both structurally and electronically similar to previously investigated bicyclic cyclobutenes, while lacking the rigidity and added ring-strain of these bicyclic systems (Figure 12, a). (1*R*, 2*S*)-cyclobut-3-ene-1,2-dicarboxylate (**23**) was selected as a model substrate for an envisioned class of diester derivatives (Figure 12, b). The dicarboxylate **23** was accessed through a series of three synthetic steps (Scheme 54), starting with the photocatalytic [2+2]-cyclisation of maleic anhydride with a mixture of *cis*- and *trans*-1,2-dichloroethene to obtain **24** in a total yield of 71 % over two batches after trituration. Subsequently, **24** was reduced in the presence of zinc to acid anhydride **25**, in only 38 % yield due to losses in the purification step, followed by the acid-catalysed opening and esterification of anhydride **25** to obtain *meso* dimethyl dicarboxylate **23** in 42 % yield.

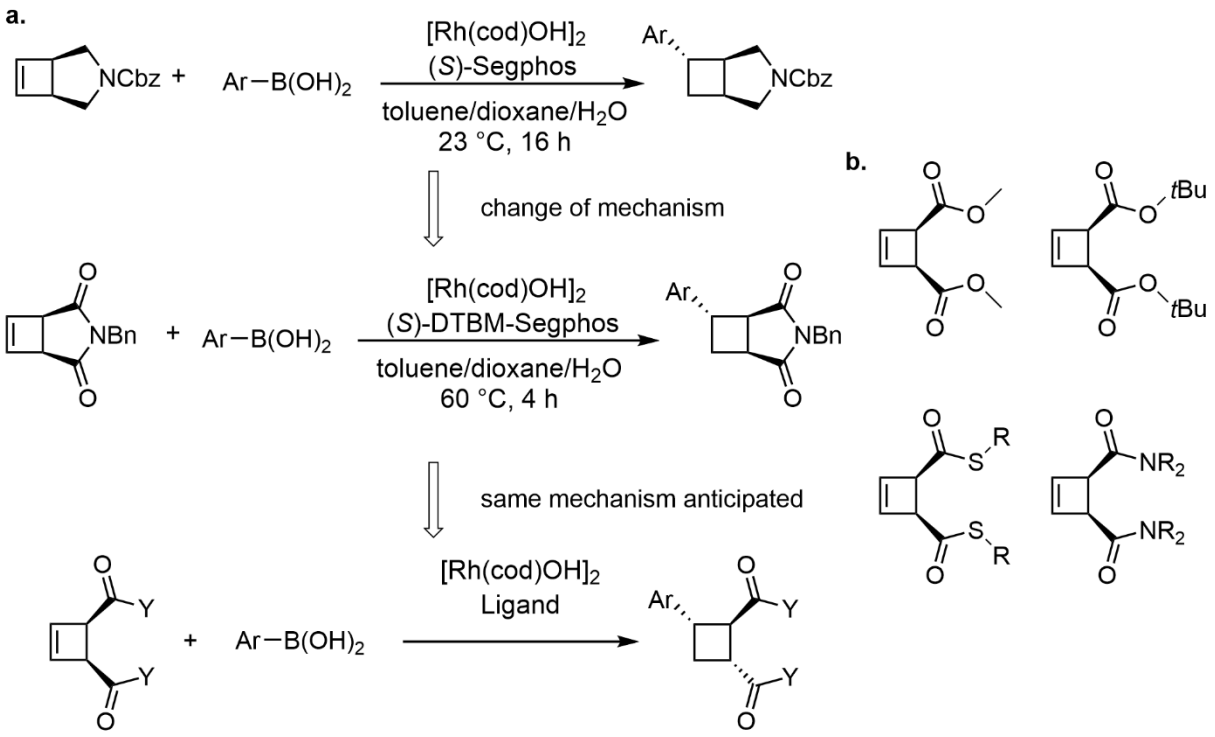
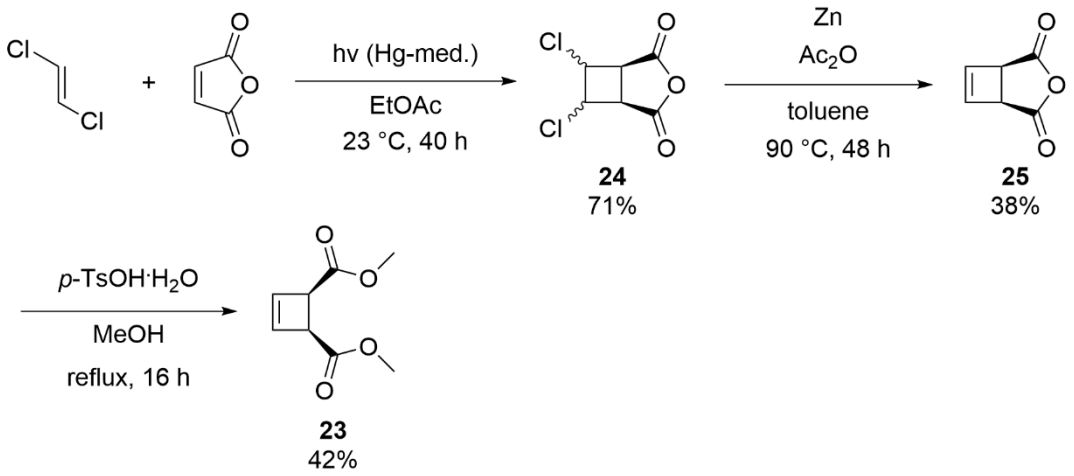


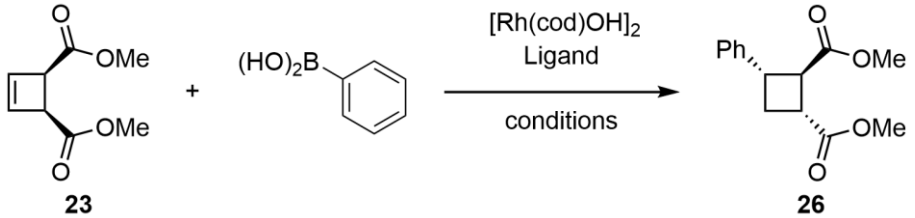
Figure 12: **a.** Previously developed reductive Heck arylation (top), carbometallation triggered 1,5-addition (middle) of fused cyclobutenes, and hypothesised reactivity of monocyclic cyclobutenes for 1,5-addition of arylboronic acids (bottom); **b.** Envisioned starting materials of which only the dimethyl dicarboxylate was synthetically accessible.



Scheme 54: Synthesis of monocyclic, non-conjugated cyclobutene **23** as starting material for Rh-catalysed 1,5-addition reactions with arylboronic acids.

To our delight, in the first attempt at the hydroarylation of **23** with phenylboronic acid, the product was obtained in 32 % yield (Table 5, entry 1), although incomplete conversion was observed and 15 % starting material was recovered. Due to this early success, and since (*S*)-DTBM-Segphos had proven optimal in the development of the 1,5-addition to bicyclic cyclobutenes, a ligand screening was not carried out. Instead, subsequent optimisation focused on modifying the composition of the solvent mixture, as its significant influence on reactivity and selectivity was previously reported for a similar system,[263] and this observation was reiterated in the optimisation of bicyclic cyclobutenes. Even though the addition of a base is known to improve Rh-based catalytic cycles by accelerating the regeneration of the active catalyst, the addition of CsF (Table 5, entry 3) and CsOH (entry 4) did not provide the desired results. After adapting the solvent system optimised for bicyclic cyclobutenes, an isolated yield of 49 % was obtained at room temperature in base free conditions (entry 5), which improved to 74 % yield at 60 °C (entry 6). The enantioselectivity appears to be primarily dependent on the reaction temperature, with room temperature being optimal in respect to enantiomeric excess. Eventually, changing the ligand to (*S*)-Segphos allowed for the isolation of the major diastereomer in 66 % yield and 94 % ee (entry 7), while (*S*)-DTBM-Segphos provided mixture of three diastereomers, of which only the two major diastereomers were separable.

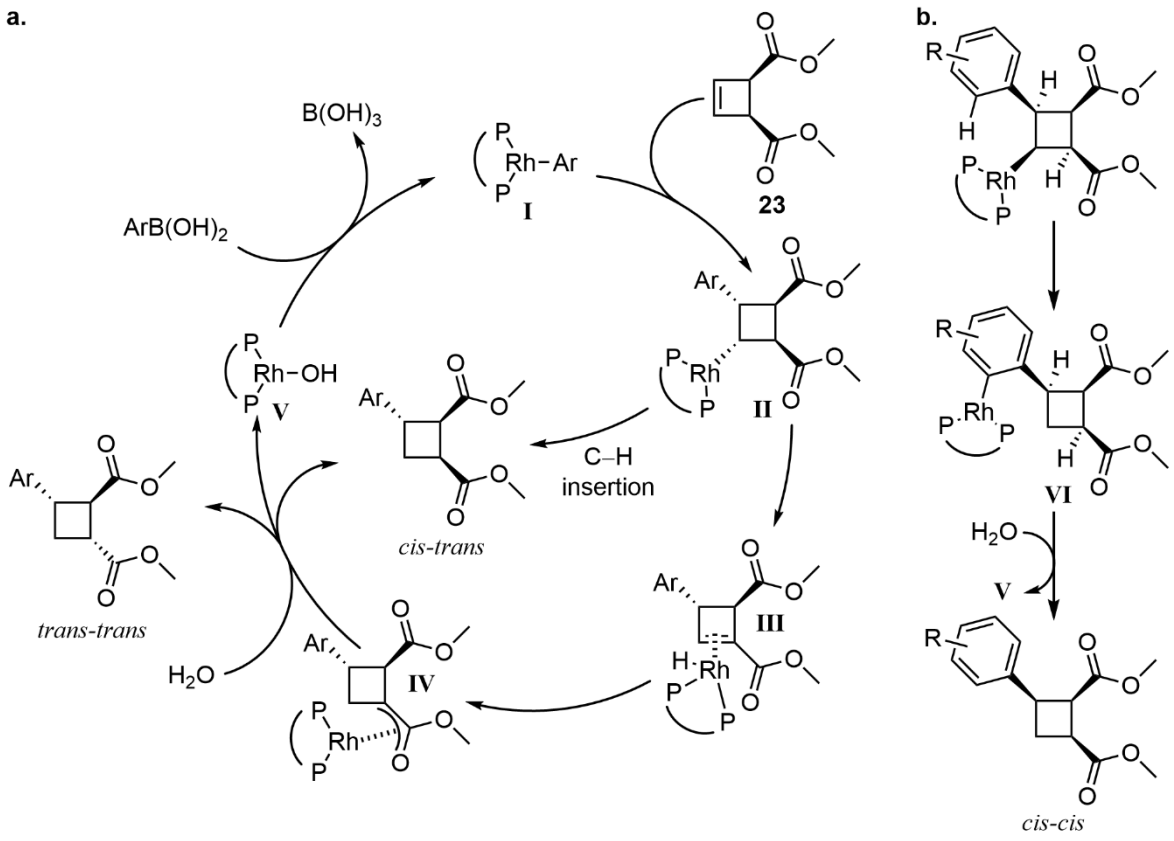
Table 5: Screening of reaction conditions for the 1,5-addition of phenylboronic acid to **23**.



23 **26**

Entry[a]	Solvent system	Base	Ligand	T [°C]	t [h]	Yield [%]	ee [%]
1	1-4 dioxane/toluene/H_2O (2:12:1)	-	(S)-DTBM-Segphos	40	16	32	nd
2	1,4-dioxane/H_2O (9:1)	-	(S)-DTBM-Segphos	60	16	58	86
3	1,4-dioxane/H_2O (9:1)	CsF[b]	(S)-DTBM-Segphos	60	16	46	89
4	1-4 dioxane/toluene/H_2O (25:25:1)	CsOH	(S)-DTBM-Segphos	23	16	10	nd
5	1-4 dioxane/toluene/H_2O (25:25:1)	-	(S)-DTBM-Segphos	23	16	49	93
6	1-4 dioxane/toluene/H_2O (25: 25:1)	-	(S)-DTBM-Segphos	60	4	74	87
7[c,†]	1-4 dioxane/toluene/H_2O (25: 25:1)	-	(S)-Segphos	60	4	66	94

a. Reactions performed with 0.1 mmol **23** (entries 1-4), 0.2 mmol (entry 5), or 0.4 mmol (entries 6 and 7); ee refers to major diastereomer; **b.** 1.25 mol% AcOH was added in an attempt to suppress C–H-insertion; **c.** Yield refers only to major diastereomer; † Experiment performed by F. Wieland Goetzke.



Scheme 55: **a.** Proposed mechanism for the 1,5 addition of arylboronic acids to monocyclic, non-conjugated dicarboxylates; **b.** Potential pathway for non-isolated minor *cis-cis*-diastereomer.

Based on the mechanism we suggest for this transformation (Scheme 55, a), the carborhodation of the double bond (**II**) is followed by *β*-hydride elimination at the *α*-position to the carboxyl group (**III**). A subsequent 1,2-hydride shift with formation of an oxa-*π*-allyl complex (**IV**) allows for the epimerization of the *cis*-dimethylester to the thermodynamically more stable *trans-trans*-dimethylester, which is consequently obtained as the major diastereomer. The *trans-trans*- and *cis-trans*-diastereomers constitute the two predominantly obtained product diastereomers, which were confirmed by ^{1}H-^{1}H-NOE analysis (Figure 13). In addition, a third minor diastereomer was observed and determined to likely be the *cis-cis*-product (Scheme 55, b). Unfortunately, this diastereomer could not be isolated, and hence a confirmation by ^{1}H-^{1}H-NOE analysis could not reliably be carried out.

Having proposed a mechanistic pathway for the formation of the main diastereomers *trans-trans* and *cis-trans*, the formation of the *cis-cis*-diastereomer cannot be rationalised in the same way. It can be speculated that this diastereomer arises from an approach of the catalyst from the face shielded by the methyl carboxylate groups (Scheme 55, b). In this scenario, a mechanistic pathway *via β*-hydride elimination is not available and the reaction most likely proceeds *via* a C–H-insertion at the *ortho*-position of the introduced aryl substituent (Scheme 55, b, **VI**), followed by a de-rhodation *via* hydrolysis and regeneration of the active catalyst species. This alternative termination pathway *via* C–H-bond insertion is also available if the carborhodation occurs from the opposite face of the methyl carboxylate groups as outlined in the pathway leading to the *trans-trans*- and *cis-trans*-diastereomers. A termination *via* C–H-insertion would circumvent the pathway *via β*-hydride elimination and epimerisation *via* the oxa-*π*-allyl complex (Scheme 55, a, **III** and **IV**). Given

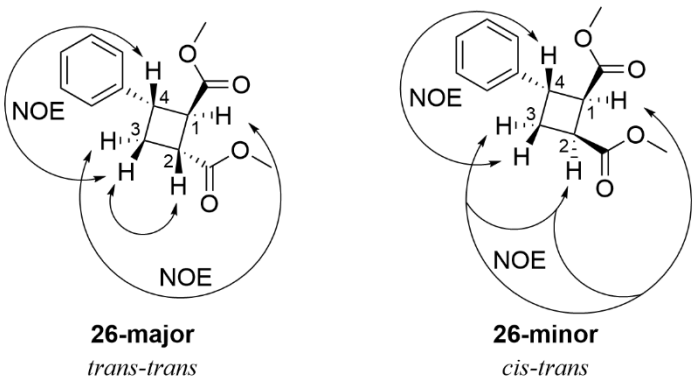
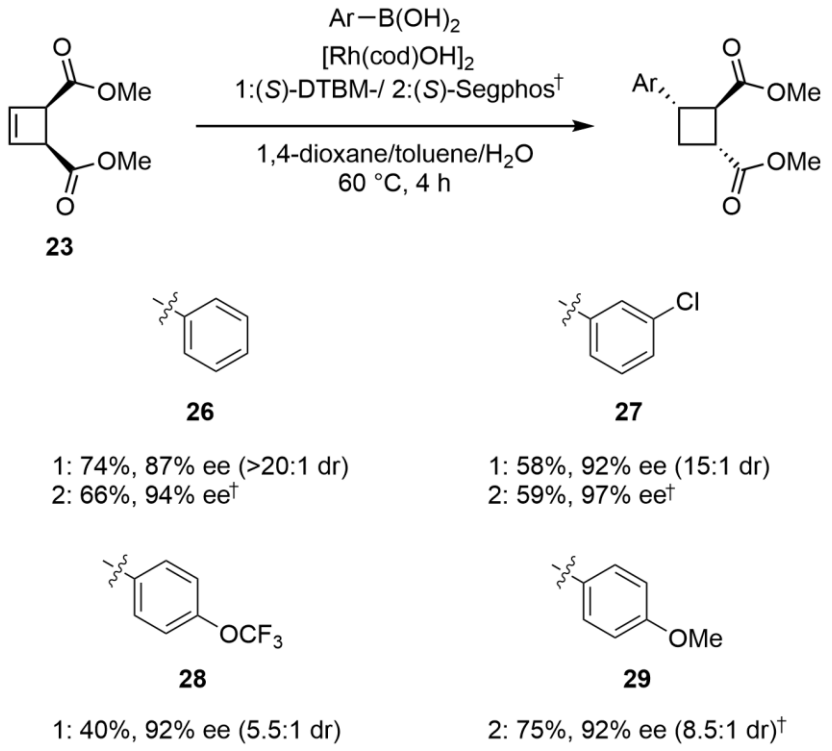


Figure 13: Major (left) and minor (right) diastereomers as determined by ^{1}H-^{1}H-NOE experiments.

that the oxa-π-allyl complex **IV** is required for the formation of the thermodynamically more stable *trans-trans*-diastereomer, the alternative C–H-bond insertion pathway explains an observed decrease in diastereoselectivity for electron-deficient boronic acids, as these boronic acids promote the C–H-bond insertion at the *ortho*-position to the cyclobutyl substituent. This decrease in diastereoselectivity in respect to the *trans-trans*- and *cis-trans*-diastereomers was observed when using 3-chlorophenylboronic acid (**27**, crude ^{1}H-NMR: 5:2 dr. *trans-trans* to *cis-trans*) and (4-trifluoromethoxy)-phenylboronic acid (**28,** crude ^{1}H-NMR: 1:1 dr. *trans-trans* to *cis-trans*) as nucleophiles. For these two examples, the minor *cis-trans*-diastereomer was isolated (see chapter 5.5 for compounds **S2** and **S3**).

Understanding the decrease of the diastereoselectivity as a result of the alternative C–H-bond insertion pathway, this indicates that the electronic properties of the boronic acid nucleophiles bear little influence over the face-selectivity of the carbo-rhodation step. However, the preference *via* which termination pathway the catalytic cycle completes a turnover sequence is dependent on the electronic properties of the boronic acid used, and this affects the diastereoselectivity between the two dominant diastereomers (*trans-trans* vs *cis-trans*). To our delight, this effect could be mitigated by changing the properties of the ligand by employing (*S*)-Segphos instead of (*S*)-DTBM-Segphos, which allowed for



Scheme 56: Scope of arylboronic acids for the 1,5-addition to **23**; *Reaction conditions*: 0.4 mmol **23**, 0.8 mmol arylboronic acid, 2.5 mol% Rh precursor (5 mol% Rh), 6 mol% ligand, 1,4-dioxane/toluene/H_2O (25:25:1), 0.1 M, 60 °C for 4 h; dr refers to isolated major diastereomer; † Experiments were performed by F. Wieland Goetzke.

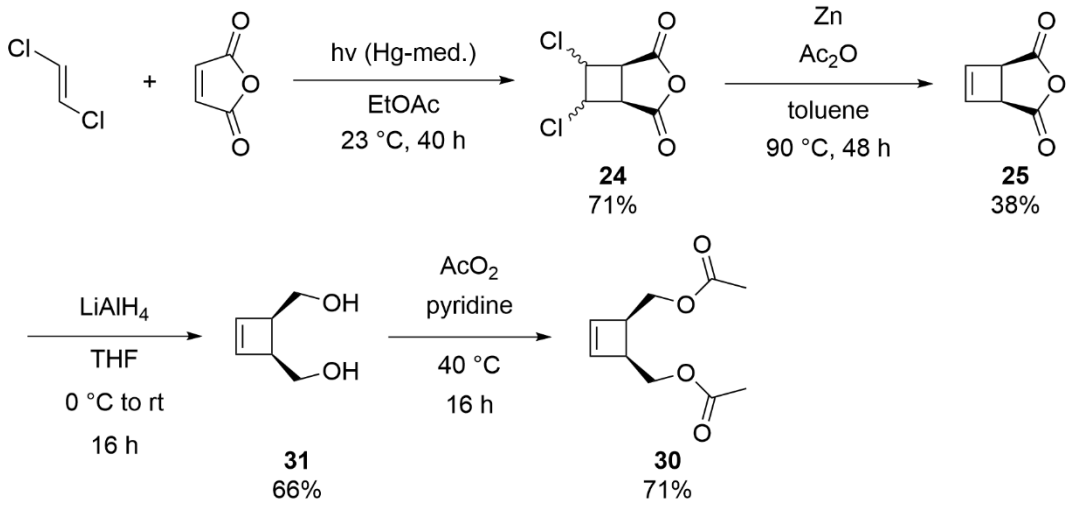
the isolation of the major *trans*-*trans*-diastereomer without diastereomeric impurities (Scheme 56, **26** and **27**).

Attempts to access diamide derivatives as starting materials did not yield the desired product, but instead a complex mixture was obtained using diethyl amine. In the case of benzylamine, the primary product was identified as 3-benzyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione, which has been used as model compound in the 1,5-arylation of bicyclic cyclobutenes (Figure 12, a, middle). This undesired cyclisation is likely the result of an intramolecular attack of the newly formed amide nitrogen lone pair at the *cis* carboxyl group which is easily accessible for a nucleophilic attack. The reported diamide syntheses for similar systems rely on *trans* configured carboxyl moieties or norbonene derived structures to avoid the intramolecular cyclisation.[264] In anticipation of the same reactivity leading to the corresponding intramolecular cyclisation products, modifications such as the synthesis of thioesters and sterically more demanding *tert*-butyl esters were not pursued further.

4.3.2 Optimisation of remote $S_N2´$ functionalisation of cyclobutenes with leaving groups

Having demonstrated the feasibility of the 1,5-addition of arylboronic acids to monocyclic *meso* cyclobutene carboxylates, we became interested in whether a substitution reaction would provide a sufficient driving force for the arylation of a monocyclic cyclobutene. Based on the mechanistic understanding gathered thus far, we speculated that *meso* diacetate **30** would be a promising candidate for an initial investigation. **30** can be synthesised in two steps from **25** by first reducing the anhydride to the corresponding monocyclic *meso* diol **31** in 66 % yield, which is then protected with acetic anhydride in the presence of pyridine to access the desired *meso* diacetate in 71 % yield (Scheme 57).

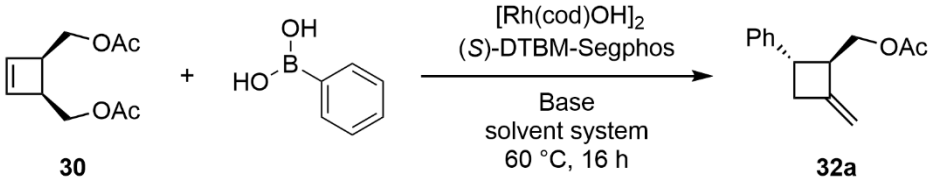
A preliminary ligand screening performed by F. Wieland Goetzke revealed that a catalytic system containing rhodium and (*S*)-DTBM-Segphos enables this highly enantioselective



Scheme 57: Synthesis of *meso* diacetate **30** as standard substrate for the remote homo-allylic substitution of monocyclic cyclobutenes.

transformation. After performing initial test reactions, it could be shown that, in contrast to previously described systems, a base is required to achieve full conversion of the starting material **30** to the substitution product **32** (Table 6, entries 1-3). This finding is in line with other Rh-catalysed substitution reactions such as the allylic arylation of *meso* bisphosphates[265] (see chapter 3) and cross-coupling-type reactions of boronic acids and mono- and bicyclic racemic allyl chlorides.[97, 165] Since a base is required to regenerate the active catalyst species, an exchange of the base is expected, and in fact was observed, to have a significant influence

Table 6: Selected results of the optimisation of the base component of the remote homo-allylic substitution of **30** and phenylboronic acid.

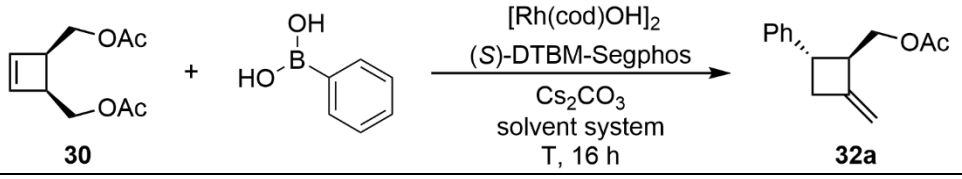


30 **32a**

Entry[a]	Solvent system	Base	Yield [%]	ee[%]
1[b]	1,4-dioxane/H_2O (9:1)	-	26	94
2[c]	1,4-dioxane/H_2O (9:1)	CsOH	61	87
3[c]	1,4-dioxane/H_2O (9:1)	CsF	41	93
4	1,4-dioxane/toluene/H_2O (25:25:1)	CsF	53	95
5[c]	1,4-dioxane/toluene/H_2O (25:25:1)	K_2CO_3	52	93
6[c]	1,4-dioxane/toluene/H_2O (25:25:1)	Cs_2CO_3	74	91

a. Reactions performed with 0.1 mmol **30** at 0.1 M, 2.0 equiv. phenylboronic acid, 2.5 mol% $[Rh(cod)OH]_2$, 6 mol% (*S*)-DTBM Segphos, 1.0 equiv. base, and stirred at 60 °C for 16 h; **b.** Only 50 % conversion observed; **c.** Isolated product contained ~5-10 % impurities.

Table 7: Selected results of the optimisation of the solvent system of the remote homo-allylic substitution of **30** and phenylboronic acid.

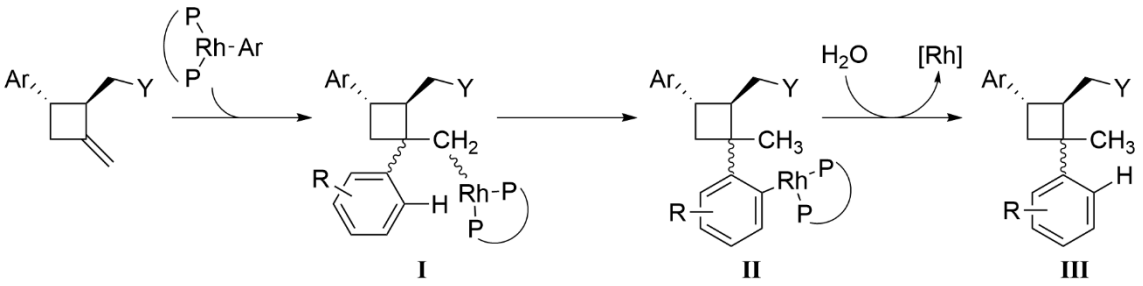


30 **32a**

Entry[a]	Solvent system	Concentration	T [°C]	Yield [%]	ee[%]
1[b]	toluene/H_2O (50:1)	0.1 M	60	57	95
2[b]	1,4-dioxane /H_2O (50:1)	0.1 M	40	70	92
3[b]	1,4-dioxane/toluene (25:25)	0.1 M	60	38	92
4[b]	1,4-dioxane/toluene/H_2O (12.5:37.5:1)	0.1 M	60	67	94
5[b]	1,4-dioxane/toluene/H_2O (37.5:12.5:1)	0.1 M	60	81	91
6[b]	1,4-dioxane/toluene/H_2O (45: 5:1)	0.1 M	60	83	91
7	1,4-dioxane/toluene/H_2O (25:25:1)	0.1 M	40	73	95
8[c]	**1,4-dioxane/toluene/H_2O (25:25:1)**	**0.1 M**	**23**	**79**	**97**

a. Reactions performed with 0.1 mmol **30** at a concentration of 0.1 M, 2.0 equiv. phenylboronic acid, 2.5 mol% $[Rh(cod)OH]_2$, 6 mol% (*S*)-DTBM Segphos, 1.0 equiv. Cs_2CO_3; **b.** Isolated product contained ~5-10 % impurities; **c.** Reaction was performed with 0.4 mmol **30**.

on the yield of the reaction (Table 6, entries 2-6). Based on previous experience, Cs_2CO_3 was projected to contribute to a high performance in this system (entry 6). In a combination with a homogeneous solvent mixture of 1,4-dioxane, toluene, and H_2O in a ratio of 25:25:1, and (*S*)-DTBM-Segphos as ligand, an initial set of conditions was identified which provided the basis for a further optimisation of the solvent composition and reaction temperature of this catalytic system (Table 7). The optimisation of this solvent system reiterated the superior performance of a tertiary solvent system comprising 1,4-dioxane, toluene, and water compared to binary solvent mixtures (Table 7, entries 1-3). Further, it was shown that water is a crucial co-solvent to achieve satisfactory yields, as it likely helps to dissolve the inorganic base and to promote catalyst turnover (Table 7, entry 3). A higher ratio of 1,4-dioxane increased the yield of the reaction (entries 5-6), while a higher ratio of toluene improved its enantioselectivity slightly (entry 4). After closely re-assessing these initial results, we observed ~5-10 % of impurities in the product mixture which could mostly be remedied by optimising the purification of earlier intermediates in the synthesis of **30** (Scheme 57). However, among these

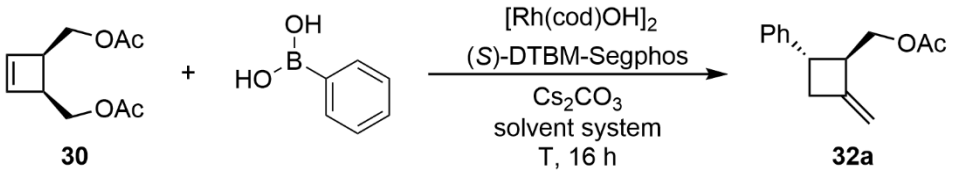


Scheme 58: Proposed mechanism for the reductive Heck-type arylation of the exocyclic double-bond discovered as a follow-up reaction during the optimisation study.

impurities, a side product of the remote homo-allylic substitution was identified by ^{1}H-NMR spectroscopy to be the hydroarylation product of the exocyclic double-bond of the desired substitution product (Scheme 58, **III**). It is proposed that this additional hydroarylation exhibits a termination mechanism *via* C–H-bond insertion into the aryl moiety (Scheme 58, **II**), followed by hydrolysis and regeneration of the active catalyst. This mechanism would be consistent with the C–H-bond insertion discussed in chapter 4.3.1 and there is no indication that the C–C-bond formation occurs at the terminal methyl group.

The formation of this side product was limited by quenching the reaction with hexane after 16 h, thereby controlling the exposure of the desired product to an active catalyst even if an immediate workup was not conducted. Intrigued by this side reaction, we briefly investigated the effect of an increase in boronic acid to determine if the hydroarylation of the *exo*-double

Table 8: Selected results of variation of phenylboronic acid equivalents for the remote homo-allylic substitution of **30**.



30 **32a**

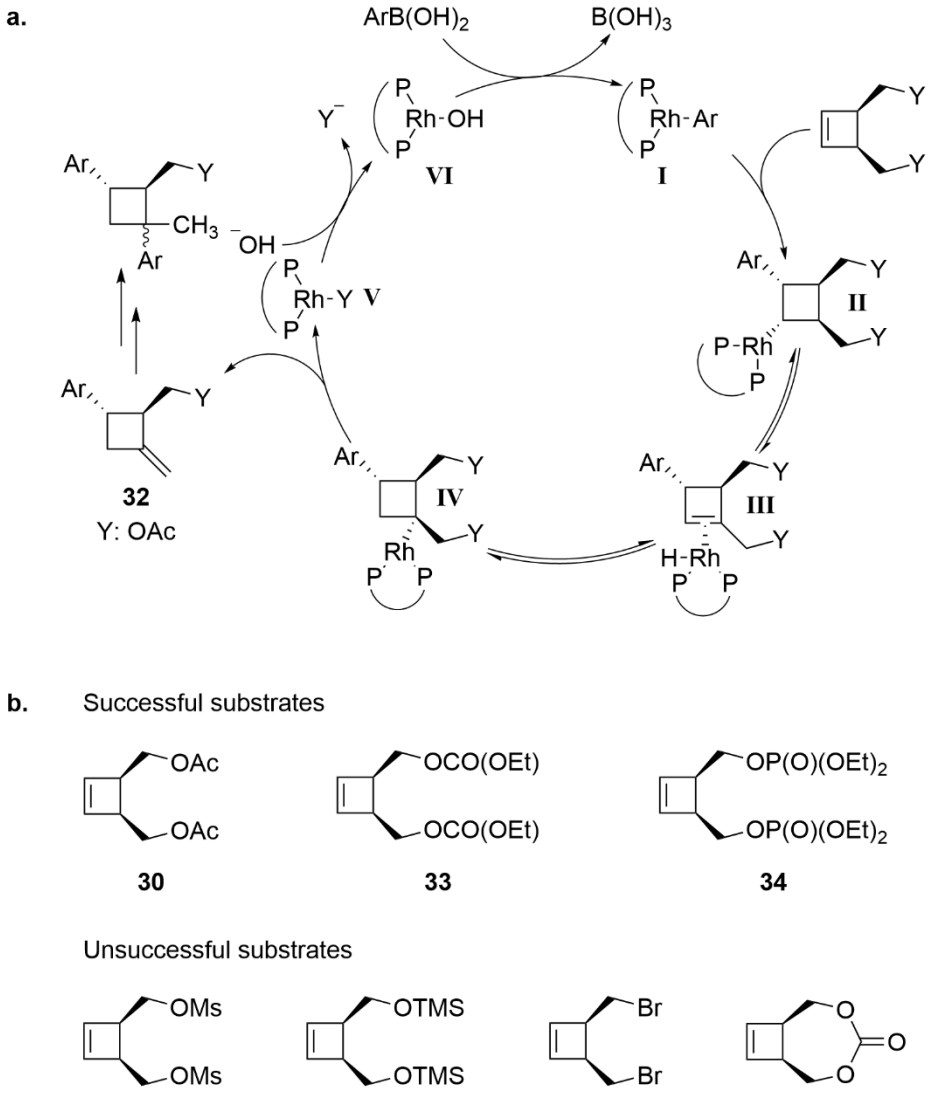
Entry[a]	Solvent system	equiv. $PhB(OH)_2$	T [°C]	Yield [%]	ee[%]
1	1,4-dioxane/toluene/H_2O (30:20:1)	2.0	40	77	95
2	1,4-dioxane/toluene/H_2O (30:20:1)† 1.5 eq	1.5	40	78	95
3	1,4-dioxane/toluene/H_2O (30:20:1)† 2 eq	2.0	60	76	92
4	1,4-dioxane/toluene/H_2O (30:20:1)† 3.0 eq	3.0	60	73	92
5	1,4-dioxane/toluene/H_2O (30:20:1)† 3.0 eq	3.0	23	76	97

a. Reactions performed with 0.4 mmol **30** at a concentration of 0.1 M, 2.5 mol% $[Rh(cod)OH]_2$, 6 mol% (*S*)-DTBM Segphos, 1.0 equiv. Cs_2CO_3.

bond is dependent on the concentration of the boronic acid without affording notably different results (Table 8). Hence, an optimal set of conditions was identified with a solvent system (0.1 M) consisting of 1,4-dioxane/toluene/H_2O (25:25:1) at 23 °C using two equivalents of arylboronic acid (Table 7, entry 8).

4.3.3 Scope of electrophiles for remote $S_N2´$ functionalisation

Based on the data obtained in the optimisation study of this system (Table 6 and Table 7) a potential mechanism for this transformation can be proposed which is different from both a



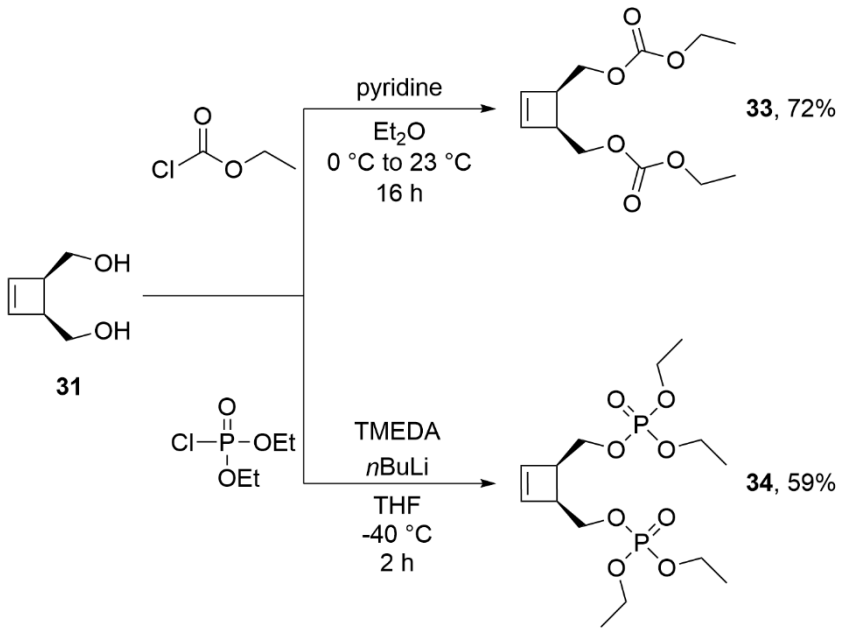
Scheme 59: **a.** Proposed mechanism for the carborhodation of monocyclic *meso* cyclobutenes with subsequent remote homo-allylic substitution of a leaving group; **b.** Successful leaving groups (top) and unsuccessful leaving groups (bottom) showing either no or very limited reactivity. Synthesis of the cyclic carbonate was not successful.

reductive Heck-type and a 1,5-addition reaction and which constitutes a homo-allylic remote substitution mechanism (Scheme 59).

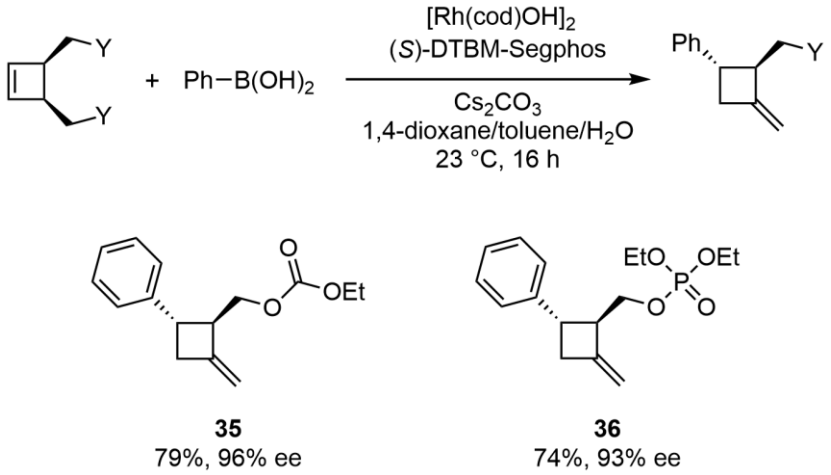
Following transmetalation with an arylboronic acid (**I**), the carborhodation occurs from the face of the cyclobutene that is not shielded by the methylene acetate moieties (**II**). This intermediate undergoes *β*-hydride elimination to **III**, but the formed Rh-hydride complex re-inserts *via* hydrorhodation, thus effectively facilitating a 1,2-hydride shift (**IV**). The elimination of the Rh-complex occurs *via* a *β*-oxygen elimination step, furnishing the product with an *exo*-cyclic double bond (**32**). The regeneration of the active catalyst species from **V** requires a base in an aqueous medium, which is consistent with the results of our optimisation study (Table 6).

We envisioned that alternative leaving groups would be suitable to undergo the same transformation (Scheme 59, b). Focusing on commonly used leaving groups, diethyl biscarbonate **33** and bis(diethyl) phosphate **34** were prepared in one step from *meso* diol **31** in 59 % yield and 72 % yield, respectively (Scheme 60).

To our delight, both alternative starting materials afforded good yields and high enantioselectivities under standard conditions (Scheme 61) and thus demonstrate the robustness



Scheme 60: Synthesis of diethyl biscarbonate **33** (top route) and bis(diethyl) phosphate **34** (bottom route) from diol **31**.



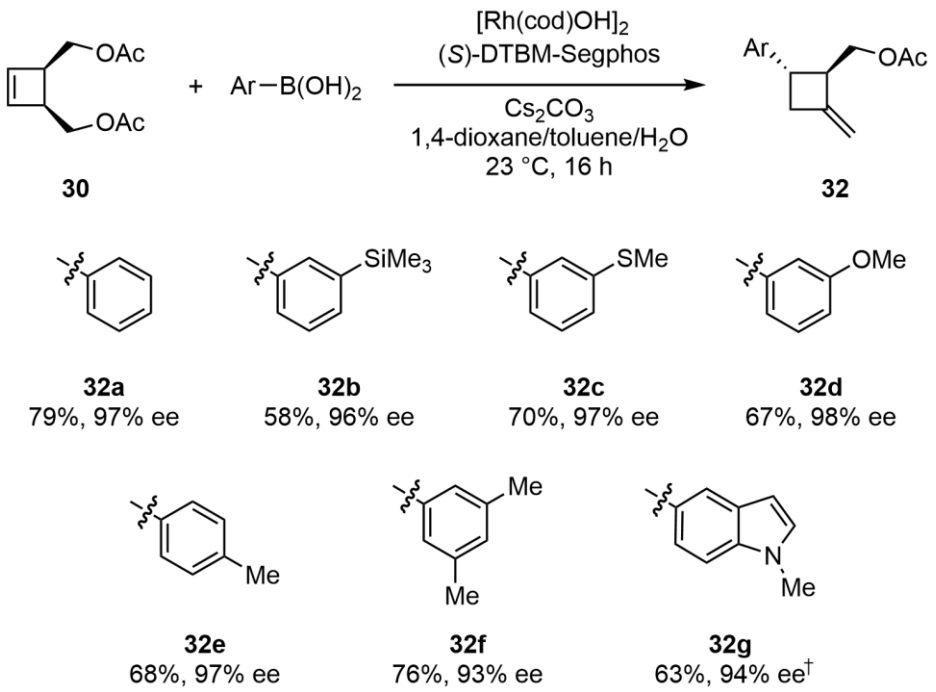
Scheme 61: Remote homo-allylic substitution with diethyl biscarbonate **33** and bis(diethyl) phosphate **34** as feasible alternative leaving groups. *Reaction conditions*: 0.4 mmol **33**/**34**, 0.8 mmol phenylboronic acid, 2.5 mol% Rh precursor (5 mol% Rh), 6 mol% (*S*)-DTBM-Segphos, 1,4-dioxane/toluene/H_2O (25:25:1), 0.1 M, 23 °C for 16 h.

of the developed catalytic system in respect to potential leaving groups. In contrast, subjecting a *meso* dimesylate **(**Scheme 59, b**)** to the reaction conditions powerfully underlined the requirement for the presence of a sufficiently strong base. Using Cs_2CO_3, only ~5 % conversion to the desired product and otherwise unreacted starting material was observed by ^{1}H-NMR spectroscopy, which indicates that the catalyst completes only a single turnover. To regenerate the active catalyst species after *β*-oxygen elimination and assumed coordination of the free mesylate to the Rh-complex, aqueous CsOH was tested and resulted in increased consumption of the starting material. However, the reaction furnished a complex mixture of at least two inseparable species, neither of which was the desired product. Unfortunately, using a dibromide instead of a diol derivative did not result in any desired product, and a protection of the diol with trimethylsilyl groups did not result in a suitable substrate either, as it afforded a complex product mixture as well (Scheme 59, b). We speculated that a cyclic carbonate derivative would overcome these limitations, as early experiments indicated a potential for a ring-opening of such a carbonate. Despite appearing to be a straightforward synthetic target, this cyclic carbonate proved inaccessible, most likely due to its high volatility (Scheme 59, b).

4.3.4 Scope of nucleophiles for remote $S_N2´$ functionalisation

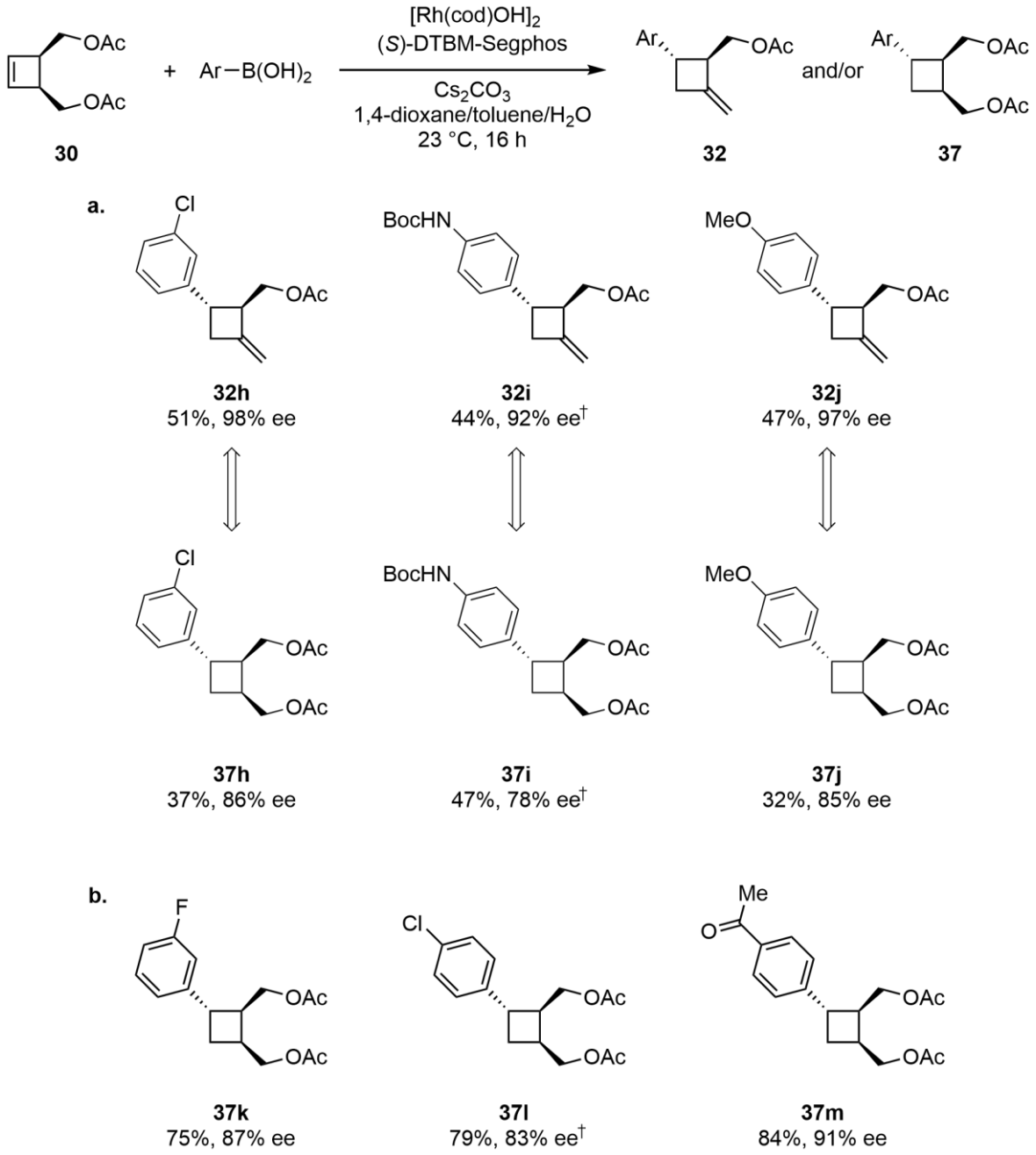
While exploring the feasibility of a range of arylboronic acids in the developed remote homo-allylic substitution reaction using **30** as a model substrate, it was found that electron-rich aryl boronic acids were generally well tolerated and demonstrated very-high-to-excellent enantioselectivity (Scheme 62). Substitution at the *meta* position appears to increase the yield slightly (**32f**), and heteroarylboronic acids, such as methyl indole **32g**, appear to be appropriate nucleophiles as well, expanding the usefulness of this catalytic system for synthetic applications. The investigation of more electron-deficient arylboronic acids revealed that the electronic properties of the arylboronic acid influence the chemoselectivity of this system, which allows for two competing mechanistic pathways to be exploited to select for one of two distinct products.

While electron-rich boronic acids only afford the **32**-type product as the result of the remote substitution mechanism (Scheme 62), electron-deficient arylboronic acids can promote a C–H-bond insertion of the catalyst in the *ortho*-position of the newly introduced aryl



Scheme 62: Remote homo-allylic substitution of **30** using electron-rich (hetero)arylboronic acids; *Reaction conditions*: 0.4 mmol **30**, 0.8 or 1.2 mmol arylboronic acid, 2.5 mol% Rh precursor (5 mol% Rh), 6 mol% (*S*)-DTBM-Segphos, 1,4-dioxane/toluene/H_2O (25:25:1), 0.1 M, 23 °C for 16 h; † Performed at 60 °C.

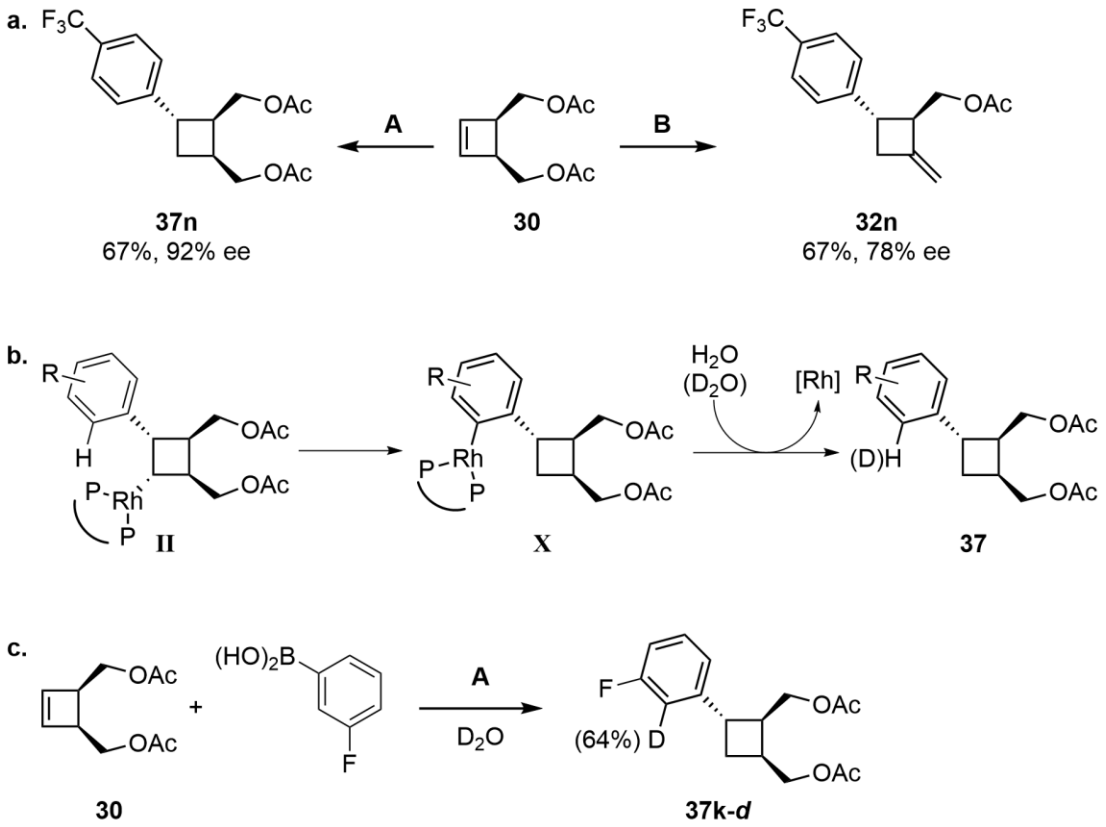
substituent, furnishing **37**-type products instead (Scheme 63, b). These two mechanisms are not mutually exclusive and can occur in parallel, with neither of the two pathways being dominant. In these 'middle ground' cases, both the remote substitution product and the reductive Heck-type product are obtained in significant amounts (Scheme 63, a), pushing the combined yields into a range between 79 % for **32/37j** and 91 % for **32/37i**. However, with increasing electron-deficiency, the C–H-bond insertion pathway appears to outcompete the remote substitution and,



Scheme 63: **a.** Both isolated products obtained from the remote homo-allylic substitution and C–H-bond insertion pathways; **b.** Reductive Heck-type arylation of **30** using significantly electron-deficient arylboronic acids; *Reaction conditions*: 0.4 mmol **30**, 0.8 mmol arylboronic acid, 2.5 mol% Rh precursor (5 mol% Rh), 6 mol% (*S*)-DTBM-Segphos, 1,4-dioxane/toluene/H_2O (25:25:1), 0.1 M, 23 °C for 16 h; † Performed at 60 °C.

eventually, the reductive Heck-type product is obtained exclusively (Scheme 63, b). It should be noted that the enantioselectivity for this process is more moderate in comparison to the remote substitution reaction, with the highest enantiomeric excess of 91 % ee obtained for **37m**.

Clarification of the termination mechanism of this reductive Heck-type reaction was carried out by using D_2O instead of H_2O in a deuterium-labelling study to determine the position at which the hydrolysis of the Rh-complex occurs. It was found that deuterium was incorporated in 64 % exclusively at the *ortho*-position of the introduced 3-fluorophenyl substituent (Scheme 64, c). Thus, it could be established that the reductive Heck-arylation occurs *via* C–H-bond insertion (to form intermediate **X**) following the formation of the common intermediate **II** by carborhodation (Scheme 64, b). Hydrolysis of **X** leads to the observed reductive Heck-type product and regenerates the active catalyst species **VI** as efficiently as the remote substitution pathway, since the yields for both mechanistic pathways are comparable (Scheme 62 and



Scheme 64: **a.** Ligand-switch induced inversion of chemoselectivity between the reductive Heck-arylation (**A**) and the remote homo-allylic substitution (**B**); **A**: Standard conditions using (*S*)-DTBM-Segphos; **B**: Standard conditions using (*S*)-Segphos; **b.** Proposed mechanism for reductive Heck-type arylation *via* C–H-bond insertion prior to hydrolysis; **c.** Deuterium labelling study for a reaction undergoing a reductive Heck-arylation as primary reaction.

Scheme 63, b). The trend of increasing reductive Heck-type arylation with increasing electron-deficiency of the arylboronic acid nucleophile can be rationalised, as electron-deficient arylboronic acids facilitate a potential C–H-bond insertion through increased electron-density *ortho* to the original transmetalation site. Hence, both products can be obtained in significant quantities for mildly electron-deficient arylboronic acids (Scheme 63, a).

Based on experience gained during the optimisation of the reductive Heck-type arylation of bicyclic cyclobutenes (conducted by F. Wieland Goetzke), we speculated that changing the electronic and steric properties of the ligand would provide an option to mitigate the C–H-bond insertion pathway. Gratefully, changing the ligand from (*S*)-DTBM-Segphos to (*S*)-Segphos allowed for the selective synthesis of the remote substitution product **32n** in 67 % yield and 78 % ee, under standard conditions, while (*S*)-DTBM-Segphos provided the reductive Heck-type arylation product **37n** in 67 % yield and 92 % ee. This illustrates that a change of ligand enables the inversion of chemoselectivity in this system (Scheme 64, a).

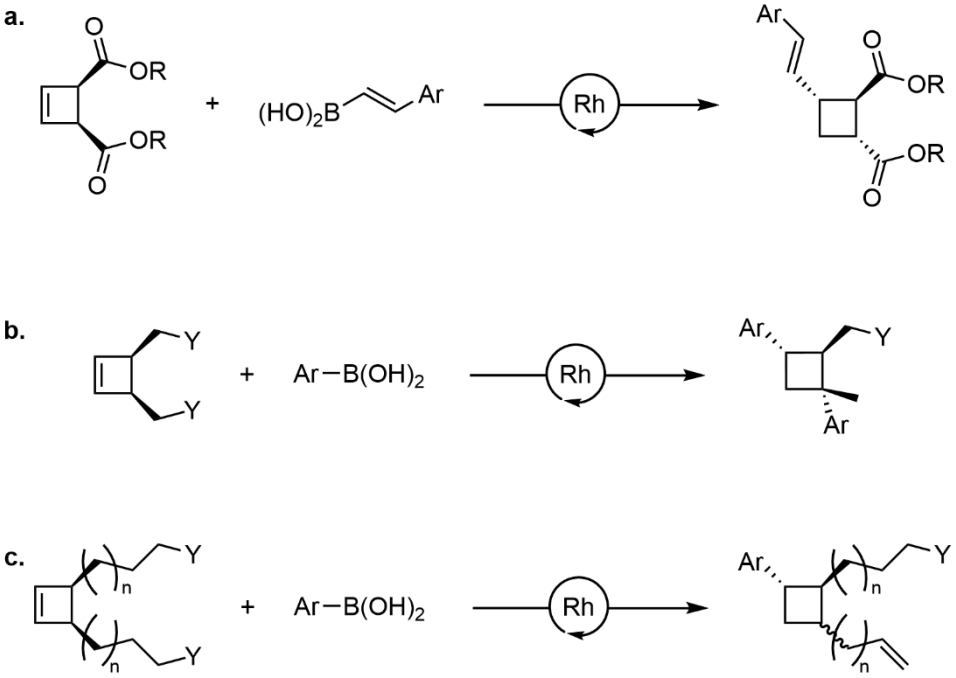
It is important to note that a possible dimerization *via* insertion of **X** in a second molecule of **30** was not observed in this system. This might be explained by a lower ring-strain of the monocyclic cyclobutene, which results in a lower reactivity towards carborhodation. In contrast, such a dimerization process has been observed for the reductive Heck-type arylation of bicyclic cyclobutenes *via* chain-walking (Figure 12, a) and posed significant challenges for the related regioselective reductive Heck-type arylation of spirocyclic cyclobutenes.

4.4 Conclusion and Future Work

In summary, a general method for the direct functionalisation of monocyclic *meso* cyclobutenes was developed. This functionalisation is initiated by a carbometallation process, which was almost unknown for cyclobutenes. Depending on the structural properties of the explored

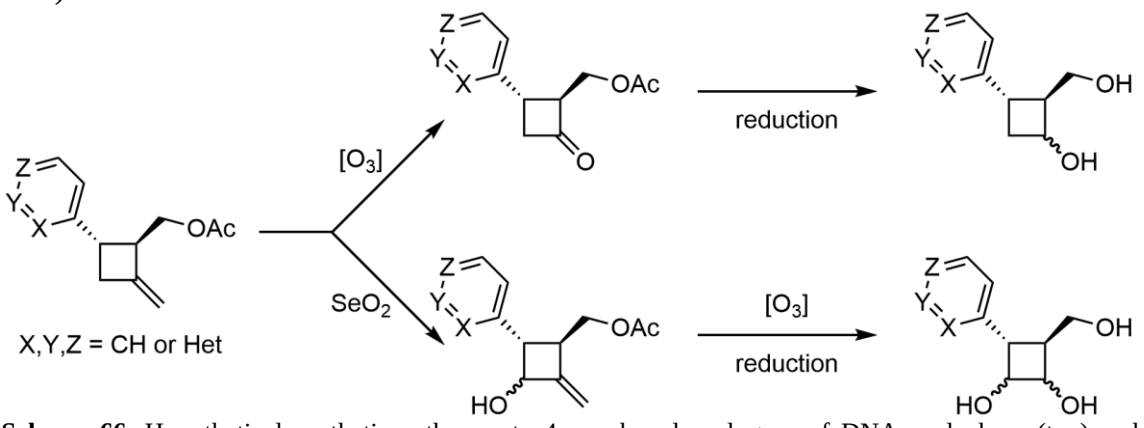
cyclobutenes, the reaction proceeds either *via* an oxa-π-allyl complex to furnish 1,5-addition products with three continuous stereocentres or, if using oxygen-based leaving groups, the reaction effectively undergoes a remote homo-allylic substitution process. In addition, it was found that this system also allows for a reductive Heck-type arylation *via* C–H-bond insertion depending on the electronic properties of the introduced aryl substituent. Further, this nucleophile based chemoselectivity was tailored using a simple ligand switch to avoid a reductive Heck-type arylation and to obtain products arising from the remote substitution process instead.

Moving forward, the feasibility of both the 1,5 addition and the remote substitution process should be investigated for non-(hetero)aryl boronic acids, especially vinyl boronic acids, or other nucleophiles known to undergo transmetalation with rhodium (Scheme 65, a). In particular, the remote substitution process lends itself to future expansion. A possible approach to such an investigation is the reductive Heck-type arylation of the exocyclic double-bond, which occurs as undesired follow-up reaction. Instead, it could be harnessed in a multi-step cascade reaction to develop an enantioselective and diastereoselective double arylation strategy



Scheme 65: **a.** Expansion of potential nucleophiles for 1,5-addition such as vinyl boronic acids; **b.** Potential exploitation of the reductive Heck-type arylation of the exocyclic double-bond in a tandem reaction, **c.** Exploration of chain-walking abilities to achieve remote substitution over larger distances.

and access highly functionalised cyclcobutanes with a quaternary stereocentre (Scheme **65**, b). The functionalisation of an exocyclic double-bond in cyclobutanes, while established for some decades, has been largely focused on hydrogenation or Rh-catalysed cyclopropanation. The arylation to form a quaternary stereocentre has so far only been reported as a non-asymmetric transformation on an unsubstituted cyclobutane[266] and as non-catalytic post-functionalisation with varying degrees of diastereoselectivity.[194-195] Thus, although the general feasibility of such a reaction has been demonstrated, this area appears to be significantly underdeveloped given the potential for accessing highly functionalised small carbocycles. Combining the ability of the catalyst to chain-walk, as demonstrated in the reductive Heck-type arylation of bicyclic cyclobutenes (Scheme 54, a) with a *β*-O-elimination process to serve as irreversible thermodynamic sink, one could hypothesise that a 'more remote' substitution process on a side chain of a monocyclic cyclobutene could be designed. Such a process would offer more fundamental insight into the mechanism of remote substitution reactions and explore the limits of such processes (Scheme 65, c). From a synthetic point of view, the product obtained by the remote substitution can be used as a key intermediate to access 4-membered analogues of DNA- or RNA-nucleobase structures, which may exhibit biological activity. Such a proposal would utilise the exocyclic double-bond as a handle to either form an exocyclic carbonyl moiety which is then reduced further (Scheme 66, top), or it could exploit the potential for an allylic oxidation to introduce a second hydroxy moiety to access 4-membered RNA type analogues (Scheme 66, bottom).



Scheme 66: Hypothetical synthetic pathways to 4-membered analogues of DNA-nucleobase (top) and RNA-nucleobase structures (bottom).

5. Experimental Information

5.1 General Information

All procedures were carried out in flame-dried flasks and in anhydrous solvents under an anhydrous argon atmosphere using standard Schlenk techniques. Heating was performed either using a sand bath or DrySyn heating blocks, both with digital thermometers to control temperature. Precoated, glass-backed plates (Silica Gel 60 F254; Merck) were used for analytical thin-layer chromatography and visualisation was facilitated by using a combination of UV light (254 nm) and cerium ammonium molybdate (CAM) solution or an aqueous basic potassium permanganate solution. Manual flash-column chromatography was performed using Apollo Scientific silica gel 60 (0.040 – 0.063 nm), Merck 60 Å silica gel, and Sigma Aldrich silica gel. Pressure was applied at the column head by flow of nitrogen as required and the silica gel was gelled in the relevant organic eluent mixture prior to use. Automated medium-pressure chromatography was performed on a CombiFlash Next Gen 100 system.

NMR spectroscopy measurements were recorded in solution and at room temperature. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and ^{31}P NMR spectroscopy experiments were carried out using a Bruker AVIII HD 400 (400/100 MHz) or a Bruker AVIII HD 500 (500/125 MHz) spectrometer. 2D-experiments, namely COSY, HSQC, and NOESY experiments, were carried out on the same spectrometers and the resulting spectra were used as guidance for the determination of assignments. Chemical shifts (δ) are reported in ppm relative to a normalised residual solvent peak, with coupling constants (*J*) in hertz (Hz). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and combinations thereof.

Chiral SFC (supercritical fluid chromatography) analyses were conducted on a Waters Acquity UPC^{2} system using Waters Empower software. Chiralpak® columns IA-IG (150x3 mm, particle size 3 μm) were used at 30 °C with the gradients specified in the experimental details. Solvents were of HPLC grade (Fisher Scientific, Sigma Aldrich or Rathburn).

High resolution mass spectrometry was performed by the internal characterisation service at the University of Oxford. Electron spray ionisation (ESI) spectra were recorded on a Fisons Platform II. Electron ionisation (EI) spectra were recorded on an Agilent 7200 quadrupole time of flight (Q-ToF) instrument equipped with a direct insertion probe supplied by Scientific instrument Manufacturer (SIM) GmbH. Indicative low-resolution mass spectra were recorded on an Agilent 6120 bench-top single quadrupole spectrometer with liquid chromatography loop injection mode.

Optical rotations $[\alpha]_{25}^{D}$ in 10^{-1} degree·cm^2·g^{-1} were recorded using a PerkinElmer 241 polarimeter in a 10 cm cuvette at 25 °C. Concentrations (*c*) are reported in g/100 mL chloroform.

Infrared spectra (neat or thin film) were recorded on a Bruker Tensor 27 FT–IR spectrometer with an internal calibration range of 4000–600 cm^{-1}. Absorption maxima are reported with the corresponding relative intensities described as br (broad), s (strong), m (medium), and w (weak) in cm^{-1}.

Photochemical reactions were performed in a 400 mL quartz immersion well reactor equipped with water cooling and a 400-watt medium-pressure Hg lamp from *Photochemical Reactors Ltd.*

5.2 Chemicals

Commercially available reagents and ligands were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics, Fluorochem, Apollo Scientific, Strem Chemicals, and Tokyo Chemical Industriy UK and unless otherwise stated were used without further purification. $[Rh(cod)OH]_2$ was purchased from Sigma Aldrich. All aryl and heteroarylboronic acids were used without additional purification. All chemicals were stored under exclusion of light and under argon

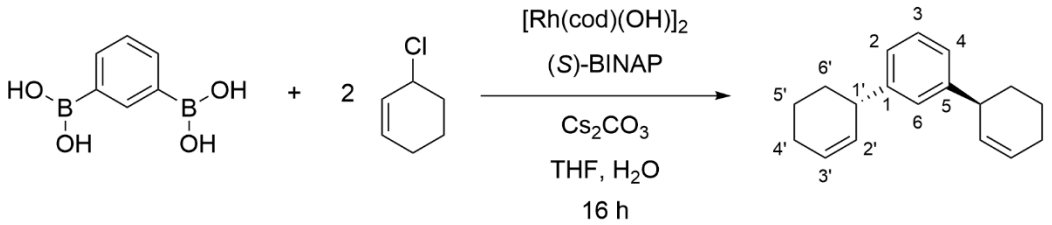
atmosphere and, if required, at -2 °C. Dry solvents were collected fresh from an mBraun SPS–800 solvent purification system after having passed through anhydrous alumina columns and were degassed with argon prior to usage. If required, dry solvents were stored under exclusion of light over activated 3 Å molecular sieves under argon. Deuterated solvents were purchased from Sigma Aldrich.

5.3 Experimental Information for Chapter 2

Assignment of absolute configuration

The absolute configuration of compounds in this section has been assigned according to the sign of optical rotation and in analogy to structures reported in: M. Sidera, S. P. Fletcher, *Nat. Chem.* **2015**, *7*, 935-939.

*Synthesis of (S,S)-1,3-bis(2-cyclohexenyl)benzene (**1**)*



Adapting a procedure reported by Sidera and Fletcher,[130] $[Rh(cod)(OH)]_2$ (36.8 mg, 0.08 mmol, 0.05 equiv.), (*S*)-BINAP (119.5 mg, 0.192 mmol, 0.12 equiv.), and Cs_2CO_3 (1042.0 mg, 3.20 mmol, 2.00 equiv.) were stirred in 8 mL anhydrous THF at 60 °C for 0.5 h. A solution of 1,3-phenylenediboronic acid (265.2 mg, 1.60 mmol, 1.00 equiv.), 3-chlorocyclohexene* (359.6 μL, 3.20 mmol, 2.00 equiv.), and distilled H_2O (115.2 μL, 6.4 mmol, 4.0 equiv.) in 8 mL THF was added to the catalyst mixture and the reaction was stirred at 60 °C for 16 h. The reaction was allowed to cool to room temperature and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography using silica-gel (100 % hexane) to give the corresponding product in a 45 % yield (171 mg) as a colourless oil. SFC analysis indicated an enantiomeric ratio of >99.5:0.5 and a diastereomeric ratio >20:1.

* 3-chlorocyclohexene was permanently stored under exclusion of light in a freezer at -2 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.26 – 7.20 (m, 1H, arom. C(6) –H), 7.06 (dt, J = 4.9, 1.8 Hz, 3H, arom. C(2) –H, arom. C(3) –H, arom. C(4) –H), 5.92 – 5.84 (m, 2H, 2x C(3') –H), 5.76 – 5.68 (m, 2H, 2x C(2') –H), 3.39 (ddt, J = 8.3, 5.6, 2.9 Hz, 2H, 2x C(1') –H), 2.13 – 1.96

(m, 6H, 4x C(4') $-H_2$, 2x C(6') $-H_2$), 1.82 – 1.70 (m, 2H, 2x C(5') $-H_2$), 1.69 – 1.51 (m, 4H, 2x C(5') $-H_2$, 2x C(6') $-H_2$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 146.8 (C(1), C(5)), 130.5 (2x C(2')), 128.34 (2x C(3')), 128.26 (C(6)), 127.4 (C(3)), 125.5 (C(2), C(4)), 42.1 (2x C(1')), 32.8 (2x C(6')), 25.2 (2x C(4')), 21.5 (2x C(5')).

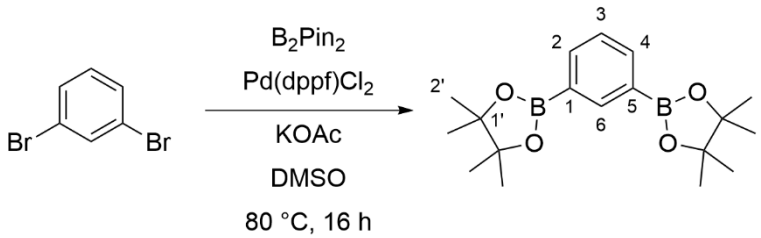
SFC: Chiralpak® ID; 1500 psi, 30 °C; flow: 0.5 mL/min, 0 % MeOH over 10 min; >99.5:0.5 er., >20:1 dr. (major enantiomer t_R = 3.43 min; minor enantiomer t_R: 6.16 min; *meso* diastereomer t_R = 4.17 min).

HRMS (EI): m/z calcd for $C_{18}H_{22}$ [M^+]: 238.1716, found: 238.1727.

IR ($CHCl_3$ film): 3380 (w), 3019 (m), 2929 (s), 2857 (m), 2836 (m), 2357 (w), 1648 (w), 1603 (w), 1484 (w), 1445 (w), 1299 (w), 1219 (w), 1134 (w), 1073 (w), 877 (w), 792 (m), 774 (m), 725 (m), 707 (m), 668 (w) cm^{-1}.

$[\alpha]^{25}_D$ = - 126.3 (c = 0.98, $CHCl_3$).

*Synthesis of 1,3-di(pinacolboryl)benzene (**2**)*



Adapting a procedure reported by Feng et al.,[267] 1,3-dibromobenzene (434.7 μL, 3.60 mmol, 1.00 equiv.), B_2Pin_2 (2011.5 mg, 7.92 mmol, 2.20 equiv.), $Pd(dppf)Cl_2$ (262.8 mg, 0.36 mmol, 0.10 equiv.), and KOAc (2119.5 mg, 21.60 mmol, 6.00 equiv.) were stirred in 18 mL anhydrous DMSO at 80 °C for 16 h. The reaction was allowed to cool to room temperature and 10 mL H_2O was added to the black product mixture which was extracted with 5x 10 mL EtOAc. While

the organic layer remained black, the aqueous layer contained a fluffy black precipitate. The combined organic layer was washed with 10 mL brine, dried over $MgSO_4$, concentrated under reduced pressure. The crude was purified by a flash column chromatography using silica-gel (hexane:EtOAc 10/1) to give a mixture of two products as a colourless oil. The desired product was obtained in a corrected yield of 48 % and the side product in 8 % yield. Both substances could not be separated and were used as mixture in any further reaction.

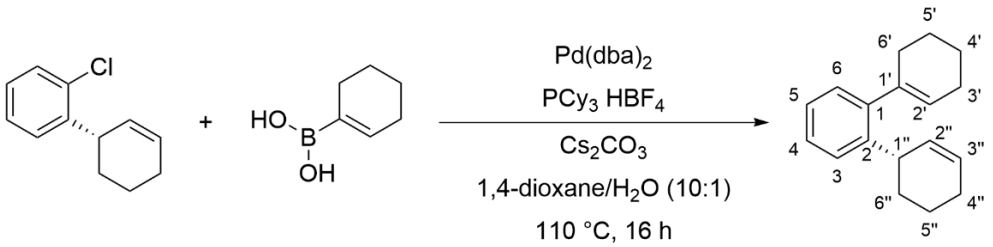
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.34 – 8.24 (m, 1H, arom. C(6) –H), 7.91 (dd, *J* = 7.4, 1.4 Hz, 2H, arom. C(2) –H, arom. C(4) –H), 7.38 (td, *J* = 7.5, 0.7 Hz, 1H, arom C(3) –H), 1.34 (s, 24H, 8x C(2') $-H_3$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 141.4 (C(6)), 137.8 (C(2), C(4)), 127.2 (C(3)), 83.9 (4x C(1')), 25.01 (8x C(2')).

HRMS (EI): m/z calcd for $C_{18}H_{28}B_2O_4$ [M^+]: 330.2175 for ^{11}B-isotopologue, found: 330.2170.

IR ($CHCl_3$ film): 2979 (m), 2925 (m), 2854 (m), 1245 (w), 1603 (m), 1467 (w), 1371 (s), 1345 (s), 1330 (s), 1307 (s), 1271 (m), 1216 (w), 1143 (s), 1089 (w), 1077 (w), 966 (m) 878 (w), 846 (w), 773 (m), 710 (m), 686 (m), 668 (w), 647 (w) cm^{-1}.

*Synthesis of (S)-3-(2-(1-cyclohexenyl)phenyl)cyclohexene (**3**)*



Adapting a procedure reported by Qian et al.,[268] (*S*)-3-(2-chlorophenyl)cyclohexene (**7**) (154.2 mg, 0.8 mmol, 1.00 equiv.), 1-cyclohexenylboronic acid (201.6 mg, 1.6 mmol, 2.00 equiv.), $Pd(dba)_2$ (23.0 mg, 0.04 mmol, 0.05 equiv.), $PCy_3{\cdot}HBF_4$ (29.5 mg, 0.08 mmol, 0.10 equiv.), and Cs_2CO_3 (651.6 mg, 2.0 mmol, 2.50 equiv.) were stirred in a flame-dried and

capped microwave vial in 4.4 mL of 1,4-dioxane/H_2O (10:1) at 110 °C for 16 h. The reaction was allowed to cool to room temperature and the clear orange product mixture was filtered through a Celite plug using ethyl acetate as eluent and solvents were removed under reduced pressure. The yellow crude was purified by a flash column chromatography using silica-gel (hexane:Et_2O 99:1) to give the product in 98 % yield (186 mg) as a colourless oil. SFC analysis indicated an enantiomeric ratio of 97.0:3.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.21 (qd, *J* = 7.8, 1.9 Hz, 2H, arom. C(4) –H, arom. C(6) –H), 7.14 (td, *J* = 7.1, 2.1 Hz, 1H, arom. C(3) –H), 7.05 (dd, *J* = 7.4, 1.4 Hz, 1H, arom. C(5) –H), 5.91 – 5.80 (m, 1H, C(3'') –H), 5.61 (dd, *J* = 10.1, 2.5 Hz, 1H, C(2'') –H), 5.55 (dt, *J* = 3.7, 1.9 Hz, 1H, C(2') –H), 3.69 – 3.55 (m, 1H, C(1'') –H), 2.23 – 2.01 (m, 6H, C(3') –H_2, C(6') –H_2, C(4'') –H_2), 2.00 – 1.90 (m, 1H, 1x C(6'') –H_2), 1.85 – 1.56 (m, 6H, C(4') –H_2, C(5') –H_2, C(5'') –H_2), 1.54 – 1.43 (m, 1H, 1x C(6'') –H_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 144.36 (C(2)), 143.96 (C(1)), 138.7 (C(1')), 131.7 (C(2'')), 128.7 (C(5)), 127.8 (C(6)), 127.7 (C(3'')), 126.8 (C(4)), 125.93 (C(2')), 125.70 (C(3)), 38.3 (C(1'')), 33.0 (C(6'')), 31.7 (C(4'')), 25.50 (C(6')), 25.11 (C(3')), 23.3 (C(5'')), 22.3 (C(5')), 22.1 (C(4')).

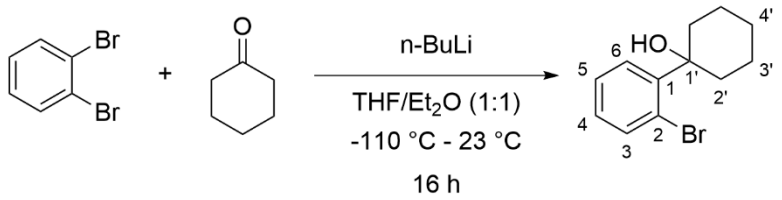
SFC: Chiralpak® IB, 1500 psi, 30 °C; flow: 1.0 mL/min; 0 % MeOH for 3 min, 0 % to 10 % MeOH over 5 min, 97.0:3.0 er (major enantiomer t_R = 3.13 min, minor enantiomer t_R = 3.03 min).

HRMS (EI): m/z calcd for $C_{18}H_{22}$ [M^+]: 238.1716, found: 238.1711.

IR ($CHCl_3$ film): 3018 (w), 2926 (s), 2855 (m), 2835 (m), 2360 (w), 1482 (w), 1444 (m), 1136 (w), 1076 (w), 982 (w), 919 (w), 899 (w), 881 (w), 848 (w), 803 (w), 754 (s), 721 (m), 680 (w), 648 (w) cm^{-1}.

$[\alpha]^{25}_D$ = - 61.5 (c = 0.91, $CHCl_3$).

*Synthesis of 1-(2-bromophenyl)cyclohexan-1-ol (**4**)*



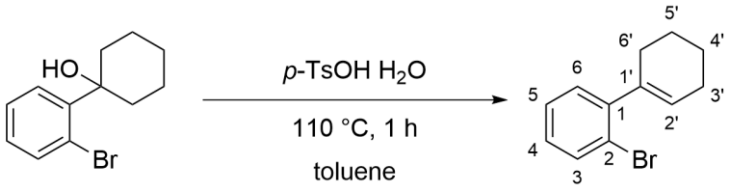
Following a procedure reported in literature,[269] a solution of 1,2-dibromobenzene (0.72 mL, 6.00 mmol, 1.00 equiv.) in anhydrous THF/Et_2O (18 mL/ 18 mL) was stirred in a 50 mL round-bottom flask and cooled down to -110 °C using a cooling bath of ethanol and liquid N_2. At this temperature, n-BuLi (2.28 mL, 2.50 M solution in hexane, 5.70 mmol, 0.95 equiv.) was slowly added to the solution over 15 min and the mixture was stirred at -110 °C for 1 h. Cyclohexanone (0.60 mL, 5.70 mmol, 0.95 equiv.) was added to the cooled reaction mixture, which was subsequently allowed to warm to room temperature over 16 h. The dark yellow mixture was treated with saturated $NH_4Cl_{(aq)}$, the organic layer was separated, and the aqueous layer was extracted with 3x10 mL hexane/EtOAc (5:1). The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography using silica-gel (hexane:EtOAc, 10/1) to give the corresponding product in 78 % yield (1.130 g) as colourless oil.

The characterisation data is in agreement with the literature.[269]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.64 (dd, *J* = 8.0, 1.7 Hz, 1H, arom. C(6) –H), 7.58 (dd, *J* = 7.9, 1.4 Hz, 1H, arom. C(3) –H), 7.30 (ddd, *J* = 8.0, 7.3, 1.4 Hz, 1H, arom. C(5) –H), 7.09 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H, arom. C(4) –H), 2.66 (s, 1H, C(1') –OH), 2.23 – 2.11 (m, 2H, 2x C(2') –H_2), 2.04 – 1.96 (m, 2H, 2x C(2') –H_2), 1.84 (tt, *J* = 13.0, 3.5 Hz, 2H, 2x C(3') –H_2), 1.79 – 1.70 (m, 1H, 1x C(4') –H_2), 1.70 – 1.62 (m, 2H, 2x C(3') –H_2), 1.31 (qt, *J* = 12.3, 3.3 Hz, 1H, 1x C(4') –H_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 146.2 (C(1)), 135.5 (C(3)), 128.6 (C(4)), 127.7 (C(6)), 127.6 (C(5)), 120.91 (C(2)), 74.3 (C(1')), 35.9 (2x C(2')), 25.4 (C(4')), 22.1 (2x C(3')).

*Synthesis of 1-bromo-2-(cyclohex-1-enyl) benzene (**5**)*



Following a procedure reported in literature,[269] a solution of 1-(2-bromophenyl)cyclohexan-1-ol (**4**) (1129.8 mg, 4.43 mmol, 1.00 equiv.) and *p*-TsOH·H_2O (84.3 mg, 0.443 mmol, 0.10 equiv.) in 8 mL anhydrous toluene was refluxed in a 50 mL round-bottom flask at 110 °C for 1 h. The reaction was allowed to cool to room temperature and the solvent was removed under reduced pressure. Purification by flash column chromatography using silica-gel (100 % hexane) gave the product in 94 % yield (89 mg) as a colourless oil.

The characterisation data is in agreement with the literature.[269]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.53 (dd, *J* = 8.0, 1.2 Hz, 1H, arom. C(3) –H), 7.28 – 7.20 (m, 1H, arom. C(5) –H), 7.15 (dd, *J* = 7.6, 1.9 Hz, 1H, arom. C(6) –H), 7.08 (ddd, *J* = 7.9, 7.2, 1.8 Hz, 1H, arom. C(4) –H), 5.62 (tt, *J* = 3.8, 1.8 Hz, 1H, C(2') –H), 2.27 (tq, *J* = 6.2, 2.1 Hz, 2H, C(6') –H_2), 2.18 (dtd, *J* = 8.0, 3.8, 2.0 Hz, 2H, C(3') –H_2), 1.81 – 1.73 (m, 2H, C(5') –H_2), 1.73 – 1.65 (m, 2H, C(4') –H_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.6 (C(1)) [5], 139.3 (C(1')), 132.7 (C(3)), 130.2 (C(6)), 128.1 (C(4)), 127.3 (C(5)), 127.2 (C(2')), 122.7 (C(2)), 29.5 (C(6')), 25.4 (C(3')), 23.0 (C(5')), 22.1 (C(4')).

*Synthesis of (2-(1-cyclohexenyl)phenyl)boronic acid pinacol ester (**6**)*



In a flame-dried 50 mL round-bottom flask, a mixture of 1-bromo-2-(cyclohex-1-enyl)benzene (**5**) (840.0 mg, 3.54 mmol, 1.00 equiv.), B_2Pin_2 (1978.5 mg, 7.79 mmol, 2.20 equiv.), $Pd(dppf)Cl_2$ (258.4 mg, 0.35 mmol, 0.10 equiv.), and KOAc (2085.2 mg, 21.25 mmol, 6.00 equiv.) were stirred in 20 mL anhydrous DMSO at 85 °C for 16 h. The reaction was allowed to cool to room temperature and 10 mL H_2O was added to the black product mixture which was extracted with 5x10 mL EtOAc. While the organic layer remained black, the aqueous layer contained a fluffy black precipitate. The combined organic layer was washed with 20 mL brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash column chromatography using silica-gel (hexane: Et_2O 10/1) to give the product in 70 % yield (707 mg) as a colourless oil.

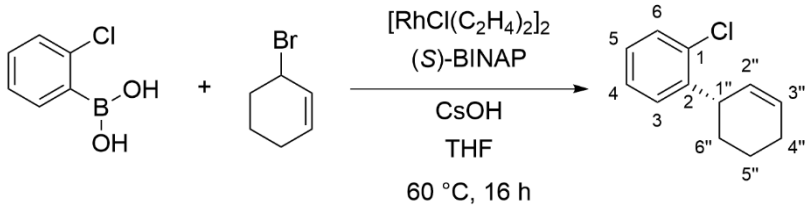
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.61 (ddd, *J* = 7.3, 1.6, 0.6 Hz, 1H, arom. C(3) –H), 7.33 (td, *J* = 7.5, 1.5 Hz, 1H, arom. C(5) –H), 7.21 (td, *J* = 7.4, 1.3 Hz, 1H, arom. C(6) –H), 7.17 (ddd, *J* = 7.6, 1.3, 0.6 Hz, 1H, C(2) –H), 5.53 (tt, *J* = 3.7, 1.8 Hz, 1H, C(2') –H), 2.33 (dtd, *J* = 6.2, 3.2, 2.6, 1.6 Hz, 2H, C(6') –H_2), 2.14 (ddt, *J* = 7.4, 6.1, 3.1 Hz, 2H, C(3') –H_2), 1.81 – 1.72 (m, 2H, C(5') –H_2), 1.67 (qd, *J* = 6.0, 2.5 Hz, 2H, C(4') –H_2), 1.32 (s, 12H, 4x C(2'') –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 150.8 (C(1')), 141.0 (C(1)), 134.4 (C(3)), 129.9 (C(5)), 127.2 (C(4)), 125.80 (C(6)), 125.40 (C(2')), 83.6 (C(1'')), 30.7 (C(6')), 25.8 (C(3')), 25.0 (4x C(2'')), 23.3 (C(5')), 22.2 (C(4')).

HRMS (EI): m/z calcd for $C_{18}H_{25}BO_2$ [M^+]: 283.1978, found: 283.1969.

IR ($CHCl_3$ film): 2979 (m), 2928 (m), 2833 (w), 2350 (w), 1595 (w), 1484 (w), 1439 (w), 1379 (m), 1350 (s), 1312 (m), 1266 (w), 1215 (w), 1146 (m), 1115 (w), 1078 (w), 1037 (w), 963 (w), 862 (w), 762 (w), 699 (w), 678 (w), 662 (w) cm^{-1}.

*Synthesis of (S)-3-(2-chlorophenyl)cyclohexene (**7**)*



Adapting a procedure reported by Sidera and Fletcher,[130] $[RhCl(C_2H_4)_2]_2$ (31.2 mg, 0.08 mmol, 0.025 equiv.), (S)-BINAP (119.7 mg, 0.192 mmol, 0.06 equiv.), and $CsOH_{(aq)}$ (557.6 μL, 50:50 w/w, 3.2 mmol, 1.00 equiv.) were stirred in 32 mL anhydrous THF at 60 °C in a 100 mL round-bottom flask for 0.5 h. A solution of 2-chlorophenylboronic acid (1000.8 mg, 6.4 mmol, 2.00 equiv.) and 3-bromocyclohexene (368.0 μL, 3.2 mmol, 1.00 equiv.) in 32 mL anhydrous THF was added to this catalyst mixture and the reaction was stirred at 60 °C for 16 h. The reaction was allowed to cool to room temperature and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography using silica-gel (100 % hexane) to give the product in 65 % yield (399 mg) as a colourless oil. SFC analysis indicated an enantiomeric ratio of 97.0:3.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.35 (dd, *J* = 7.8, 1.4 Hz, 1H, arom. C(6) –H), 7.27 (dd, *J* = 7.6, 1.8 Hz, 1H, arom. C(3) –H), 7.21 (td, *J* = 7.5, 1.4 Hz, 1H, arom. C(4) –H), 7.14 (td, *J* = 7.5, 1.9 Hz, 1H, arom. C(5) –H), 5.96 (dtd, *J* = 9.9, 3.7, 2.3 Hz, 1H, C(3'') –H), 5.66 (dq, *J* = 10.2, 2.4 Hz, 1H, C(2'') –H), 3.89 (ddt, *J* = 8.1, 5.5, 2.8 Hz, 1H, C(1'') –H), 2.15 – 2.01 (m, 3H, C(4'') –H_2, 1x C(6'') –H_2), 1.76 – 1.57 (m, 2H, C(5'') –H_2), 1.54 – 1.46 (m, 1H, 1x C(6'') –H_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 143.5 (C(2)), 133.8 (C(1)), 129.52 (C(6)), 129.37 (C(3)), 129.34 (C(2''), C(3'')), 127.3 (C(5)), 126.8 (C(4)), 38.1 (C(1'')), 30.1 (C(6'')), 25.2 (C(4'')), 20.9 (C(5'')).

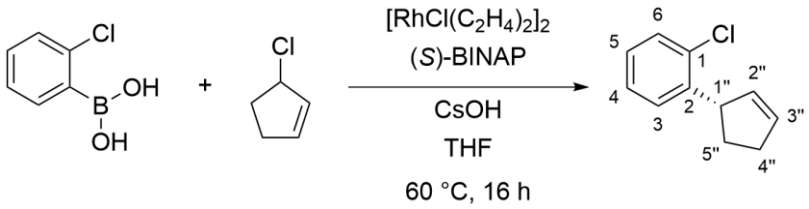
SFC: Chiralpak® ID, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 97.0:3.0 er (major enantiomer t_R = 0.89 min, minor enantiomer t_R = 1.00 min).

HRMS (EI): m/z calcd for $C_{12}H_{13}Cl$ [M^+]: 192.0700, found: 192.0699.

IR ($CHCl_3$ film): 3020 (w), 2930 (m), 2858 (w), 2836 (w), 1570 (w), 1471 (m), 1439 (m), 1124 (w), 1052 (m), 1033 (m), 984 (w), 882 (w), 751 (s), 733 (w), 714 (w), 670 (w), 655 (w) cm^{-1}.

$[\alpha]^{25}_D$ = - 30.8 (c = 1.0, $CHCl_3$).

*Synthesis of (S)-3-(2-chlorophenyl)cyclopentene (**S1**)*



Adapting a procedure reported by Sidera and Fletcher,[130] $[RhCl(C_2H_4)_2]_2$ (7.8 mg, 0.02 mmol, 0.025 equiv.), (*S*)-BINAP (29.8 mg, 0.048 mmol, 0.06 equiv.), and $CsOH_{(aq)}$ (139.4 μL, 50:50 w/w, 0.8 mmol, 1.00 equiv.) were stirred in 4 mL anhydrous THF at 60 °C for 0.5 h. A solution of 2-chlorophenylboronic acid (250.2 mg, 1.6 mmol, 2.00 equiv.) and 3-chlorocyclopentene* (0.8 mL, 1.0 M solution in THF, 0.8 mmol, 1.00 equiv.) in 4 mL anhydrous THF was added to the catalyst mixture and the reaction was stirred for 16 h at 60 °C. The reaction was allowed to cool to room temperature and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography using silica-gel (100 % hexane) to give the product in a 62 % yield (89 mg) as a colourless oil. SFC analysis indicated an enantiomeric ratio of 94.0:6.0.

*3-chlorocyclopentene was distilled prior to use and was permanently stored at -78 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.35 (dt, *J* = 7.8, 1.1 Hz, 1H, arom C(6) –H), 7.23 – 7.16 (m, 2H, arom. C(3) –H, arom. C(4) –H), 7.13 (ddd, *J* = 7.8, 5.3, 3.6 Hz, 1H, arom. C(5) –H), 6.01 (dq, *J* = 5.7, 2.3 Hz, 1H, C(3'') –H), 5.76 (dq, *J* = 5.7, 2.1 Hz, 1H, C(2'') –H), 4.35 (ddt, *J* = 8.9, 6.6, 2.4 Hz, 1H, C(1'') –H), 2.58 – 2.36 (m, 3H, C(4'') –H_2, 1x C(5'') –H_2), 1.67 – 1.57 (m, 1H, 1x C(5'') –H_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 143.9 (C(2)), 133.7 (C(1)), 133.1 (C(2'')), 132.9 (C(3'')), 129.4 (C(6)), 127.98 (C(3)), 127.31 (C(5)), 127.00 (C(4)), 47.8 (C(1'')), 32.36 (C(4'')), 32.31 (C(5'')).

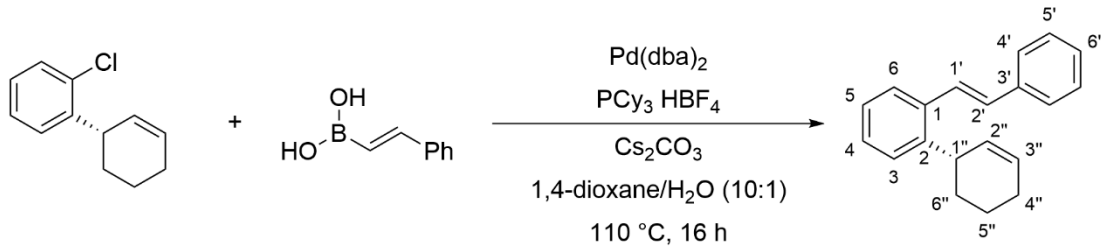
SFC: Chiralpak® ID, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 94.0:6.0 er (major enantiomer t_R = 0.82 min, minor enantiomer t_R = 0.90 min).

HRMS (EI): m/z calcd for $C_{11}H_{11}Cl$ [M^+]: 178.0544, found: 178.0541.

IR ($CHCl_3$ film): 3057 (w), 2970 (m), 2360 (m), 2340 (m), 1471 (w), 1442 (w), 1380 (w), 1219 (w), 1125 (w), 1052 (w), 1036 (w), 943 (w), 773 (s), 752 (m), 670 (w) cm^{-1}.

$[\alpha]^{25}_D$ = - 21.7 (c = 0.7, $CHCl_3$).

*Synthesis of (S)-3-(2-(2-phenylvinyl)phenyl)cyclohexene (**8**)*



Adapting a procedure reported by Qian et al.,[268] (*S*)-3-(2-chlorophenyl)cyclohexene (**7**) (77.1 mg, 0.4 mmol, 1.00 equiv.), 2-phenylvinylboronic acid (118.4 mg, 0.8 mmol, 2.00 equiv.), $Pd(dba)_2$ (11.5 mg, 0.02 mmol, 0.05 equiv.), $PCy_3{\cdot}HBF_4$ (14.7 mg, 0.04 mmol, 0.10 equiv.), and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.50 equiv.) were stirred in a flame-dried and capped microwave vial in 2.2 mL of 1,4-dioxane/H_2O (10:1) at 110 °C for 16 h. The reaction was allowed to cool to room temperature and the clear orange product mixture was filtered through a Celite plug using EtOAc as eluent and all solvents were removed under reduced pressure. The yellow crude was purified by flash column chromatography using silica-gel (hexane:Et_2O, 99/1) to give the corresponding product in 86 % yield (89 mg) as a colourless oil. SFC analysis indicated an enantiomeric ratio of 96.5:3.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.63-7.54 (m, 1H, arom. C(5) –H), 7.54-7.41 (m, 3H, C(1') –H, 2x arom. C(4') –H, 7.36 (dd, *J* = 8.4 Hz, 6.8 Hz, 2H, 2x arom. C(5') –H), 7.29-7.18 (m, 4H, arom. C(3) –H, arom. C(4) –H, arom. C(6) –H, arom. C(6') –H), 6.97 (d, *J* = 16.0 Hz, 1H, C(2') –H), 5.99-5.90 (m, 1H, C(3'') –H), 5.73 (dd, *J* = 10.2, 2.5 Hz, 1H, C(2'') –H), 3.81 (ddt, *J* = 8.3, 5.5, 2.8 Hz, 1H, C(1'') –H), 2.15-1.98 (m, 3H, C(4'') –H_2, 1x C(6'') –H_2), 1.79-1.53 (m, 3H, C(5'') –H_2, 1x C(6'') –H_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 143.9 (C(2)), 137.9 (C(3')), 136.0 (C(1)), 130.69 (C(2')), 130.39 C(C(2'')), 128.82 (2x C(5')), 128.71 (C(3'')), 128.25 (C(6')), 127.75 (C(6)), 127.69 (C(3)), 126.67 (2x C(4')), 126.55 (C(1')), 126.44 (C(4)), 126.26 (C(5)), 38.2 (C(1'')), 31.4 (C(6'')), 25.2 (C(4'')), 21.3 (C(5'')).

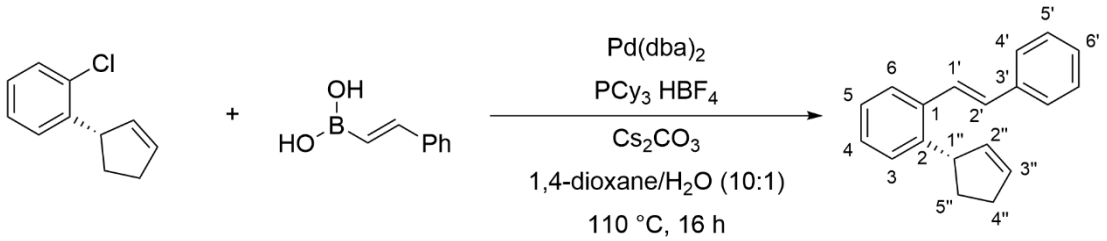
SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 96.5:3.5 er (major enantiomer t_R = 3.02 min, minor enantiomer t_R = 2.79 min).

HRMS (EI): m/z calcd for $C_{20}H_{20}$ [M^+]: 260.1560, found: 260.1559.

IR ($CHCl_3$ film): 3022 (m), 2930 (m), 2358 (w), 2339 (w), 1598 (w), 1494 (w), 1447 (w), 1383 (w), 1220 (w), 1073 (w), 960 (m), 772 (s), 762 (s), 722 (w), 691 (m) cm^{-1}.

$[\alpha]^{25}_D$ = + 27.2 (c = 1.0, $CHCl_3$).

*Synthesis of (S)-3-(2-(2-phenylvinyl)phenyl)cyclopentene (**9**)*



Adapting a procedure reported by Qian et al.,[268] (*S*)-3-(2-chlorophenyl)cyclopentene (**S1**) (71.5 mg, 0.40 mmol, 1.00 equiv.), 2-phenylvinylboronic acid (118.4 mg, 0.80 mmol, 2.00 equiv.), $Pd(dba)_2$ (11.5 mg, 0.02 mmol, 0.05 equiv.), $PCy_3{\cdot}HBF_4$ (14.7 mg, 0.04 mmol, 0.10 equiv.), and Cs_2CO_3 (325.8 mg, 0.845 mmol, 2.50 equiv.) were stirred in a flame-dried and capped microwave vial in 2.2 mL of 1,4-dioxane/H_2O (10:1) at 110 °C for 16 h. The reaction was allowed to cool to room temperature and the clear orange product mixture was filtered through a Celite plug using EtOAc as eluent and all solvents were removed under reduced pressure. The yellow crude product was purified by flash column chromatography using silica-gel (hexane: Et_2O 99/1) to give the product in 44 % yield (43 mg) as a colourless oil. SFC analysis indicated an enantiomeric ratio of 91.5:8.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.65 – 7.59 (m, 1H, arom. C(5) –H), 7.58 – 7.51 (m, 3H, C(1') –H, 2x arom. C(4') –H), 7.44 – 7.37 (m, 2H, (2x C(5') –H), 7.33 – 7.20 (m, 4H, arom. C(3) –H, arom. C(4) –H, arom. C(6) –H, arom. C(6') –H), 7.01 (d, *J* = 16.1 Hz, 1H, C(2') –H), 6.03 (dq, *J* = 5.8 Hz, 2.3 Hz, 1H, C(3'') –H), 5.85 (dq, *J* = 5.8, 2.1 Hz, 1H, C(2'') –H), 4.38 – 4.29 (m, 1H, C(1'') –H), 2.60 – 2.40 (m, 3H, C(4'') –H_2, 1x C(5'') –H_2), 1.82 – 1.67 (m, 1H, 1x C(5'') –H_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 144.1 (C(2)), 137.9 (C(3')), 136.0 (C(1)), 133.9 (C(2'')), 132.4 (C(3'')), 130.6 (C(2')), 128.8 (2x C(5')), 127.96 (C(6')), 127.71 (C(6)), 126.93 (C(4)), 126.82 (C(3)), 126.68 (2x C(4')), 126.41 (C(1')), 126.08 (C(5)), 47.6 (C(1'')), 33.3 (C(5'')), 32.6 (C(4'')).

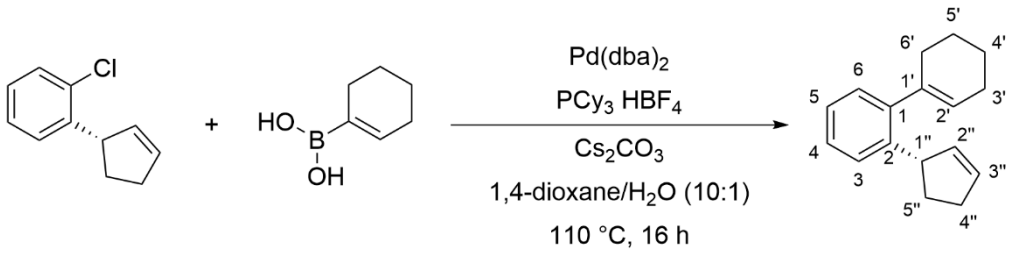
SFC: Chiralpak® IF 1500 psi, 30 °C; flow: 1.0 mL/min; 0 % MeOH for 3 min, 0 % to 10 % MeOH over 5 min, 91.5:8.5 er (major enantiomer t_R = 7.28 min, minor enantiomer t_R = 7.10 min).

HRMS (EI): m/z calcd for $C_{19}H_{18}$ [M^+]: 246.1403, found: 246.1394.

IR ($CHCl_3$ film): 3056 (w), 3025 (w), 2938 (w), 2848 (w), 1598 (w), 1493 (w), 1448 (w) 1073 (w), 960 (m), 915 (w), 760 (s), 691 (s) cm^{-1}.

$[\alpha]^{25}_D$ = + 107.0 (c = 1.0, $CHCl_3$).

*Synthesis of (S)-3-(2-(1-cyclohexenyl)phenyl)cyclopentene (**10**)*



Adapting a procedure reported by Qian et al.,[268] (*S*)-3-(2-chlorophenyl)cyclopentene (**S1**) (89.3 mg, 0.5 mmol, 1.00 equiv.), 1-cyclohexenylboronic acid (125.9 mg, 1.0 mmol, 2.00 equiv.), $Pd(dba)_2$ (14.4 mg, 0.025 mmol, 0.05 equiv.), $PCy_3{\cdot}HBF_4$ (18.4 mg, 0.05 mmol, 0.10 equiv.), and Cs_2CO_3 (407.3 mg, 1.25 mmol, 2.50 equiv.) were stirred in a flame-dried and capped microwave vial in 2.2 mL of 1,4-dioxane/H_2O (10:1) at 110 °C for 16 h. The reaction was allowed to cool to room temperature and the clear orange product mixture was filtered through a Celite plug using EtOAc as eluent and all solvents were removed under reduced pressure. The yellow crude product was purified by a flash column chromatography using silica-gel (hexane:Et_2O, 99/1) to give the corresponding product in a 75 % yield (84 mg) as a colourless oil. Determination of the enantiomeric excess by SFC and HPLC was attempted, but adequate separation could not be achieved.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.24 – 7.08 (m, 3H, arom. C(3) –H, arom. C(4) –H, arom. C(6) –H), 7.05 (dd, *J* = 7.5, 1.6 Hz, 1H, arom. C(5) –H), 5.92 (dt, *J* = 5.7, 2.3 Hz, 1H, C(3'') –H), 5.68 (dq, *J* = 6.2, 2.1 Hz, 1H, C(2'') –H), 5.56 (dt, *J* = 3.8, 1.9 Hz, 1H, C(2') –H), 4.14 – 4.04 (m, 1H, C(1'') –H), 2.57 – 2.30 (m, 3H, C(4'') –H_2, 1x C(5'') –H_2), 2.26 – 2.12 (m, 4H, C(3') –H_2, C(6') –H_2), 1.81 – 1.73 (m, 2H, C(5') –H), 1.73 – 1.62 (m, 3H, C(4') –H_2, 1x C(5'') –H_2).

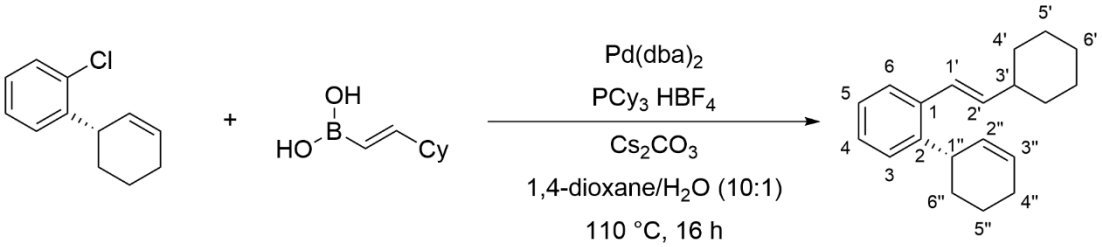
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 144.17 (C(2)), 143.95 (C(1)), 135.3 (C(2'')), 134.8 (C(1')) [7], 131.5 (C(3'')), 128.4 (C(5)), 127.00 (C(4), C(6)), 126.1 (C(3)), 125.6 (C(2')), 47.5 (C(1'')), 34.6 (C(5'')), 32.7 (C(4'')), 31.5 (C(6')), 25.5 (C(3')), 23.3 (C(5')), 22.3 (C(4')).

HRMS (EI): m/z calcd for $C_{17}H_{20}$ [M^+]: 224.1560, found: 224.1551.

IR ($CHCl_3$ film): 3053 (w), 3019 (w), 2929 (s), 2854 (m), 2360 (w), 2341 (w), 1483 (w), 1443 (w), 1347 (w), 1220 (w), 1136 (w), 1050 (w), 1005 (w), 917 (w), 847 (w), 803 (w), 755 (s), 722 (w) cm^{-1}.

$[\alpha]^{25}_D$ = - 48.6 (c = 1.0, $CHCl_3$) for unknown enantiomeric excess.

*Synthesis of (S)-3-(2-(2-cyclohexylvinyl)phenyl)cyclohexene (**11**)*



Adapting a procedure reported by Qian et al.,[268, 270] (*S*)-3-(2-chlorophenyl)cyclopentene (**7**) (77.1 mg, 0.40 mmol, 1.00 equiv.), 2-phenylvinylboronic acid (118.4 mg, 0.80 mmol, 2.00 equiv.), $Pd(dba)_2$ (11.5 mg, 0.02 mmol, 0.05 equiv.), $PCy_3{\cdot}HBF_4$ (14.7 mg, 0.04 mmol, 0.10 equiv.), and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.50 equiv.) were stirred in a flame-dried and capped microwave vial in 2.2 mL of 1,4-dioxane/H_2O (10:1) at 110 °C for 16 h. The reaction was allowed to cool to room temperature and the clear orange product mixture was filtered through a celite plug using EtOAc as eluent and all solvents were removed under reduced pressure. The yellow crude product was purified by flash column chromatography using silica-gel (hexane:Et_2O 99/1) to give the corresponding product in an 80 % yield (85 mg) as a colourless oil. SFC analysis indicated an enantiomeric ratio of 97.0:3.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.41 (dd, *J* = 6.9, 2.0 Hz, 1H, arom. C(3) –H), 7.23 – 7.11 (m, 3H, arom. C(3) –H, arom. C(4) –H, arom. C(6) –H), 6.66 (dd, *J* = 15.7, 1.2 Hz, 1H, C(1') –H), 6.01 (dd, *J* = 15.7, 7.0 Hz, 1H, C(2') –H), 5.92 (ddt, *J* = 9.9, 3.6, 1.8 Hz, 1H, C(3'') –H), 5.74 – 5.65 (m, 1H, C(2'') –H), 3.72 (ddt, *J* = 8.2, 5.5, 2.8 Hz, 1H, C(1'') –H), 2.21 – 2.06 (m, 3H, C(3') –H, C(4'') –H_2), 2.03 – 1.94 (m, 1H, 1x C(6'') –H_2), 1.86 – 1.73 (m, 4H, 2x C(4')

–H_2, 2x C(5') –H_2), 1.73 – 1.57 (m, 3H, 1x C(6') –H_2, C(5'') –H_2), 1.57 – 1.46 (m, 1H, 1x C(6'') –H_2), 1.40 – 1.12 (m, 5H, 2x C(4') –H_2, 2x C(5') –H_2, 1x C(6') –H_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 143.1 (C(2)), 139.1 (C(2')), 136.8 (C(1)), 130.6 (C(2'')), 128.5 (C(3'')), 127.9 (C(5)), 126.90 (C(4)), 126.28 (C(3)), 126.21 (C(6)), 124.9 (C(1')), 41.6 (C(3')), 37.8 (C(1'')), 33.2 (2x C(4')), 31.1 (C(6'')), 26.33 (C(6')), 26.19 (2x C(5')), 25.3 (C(4'')), 21.3 (C(5'')).

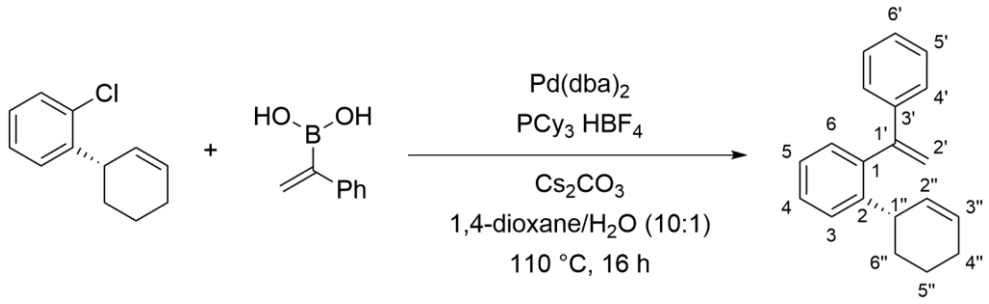
SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 97.0:3.0 er (major enantiomer t_R = 1.76 min, minor enantiomer t_R = 1.62 min).

HRMS (EI): m/z calcd for $C_{20}H_{26}$ [M^+]: 266.2029, found: 266.2021.

IR ($CHCl_3$ film): 3020 (w), 2923 (s), 2851 (m), 1480 (w), 1447 (m), 964 (m), 891 (w), 751 (m), 722 (w), 675 (w) cm^{-1}.

$[\alpha]^{25}_D$ = - 1.7 (c = 1.0, $CHCl_3$).

*Synthesis of (S)-3-(2-(1-phenylvinyl)phenyl)cyclohexene (**12**)*



Adapting a procedure reported by Qian et al.,[268] (*S*)-3-(2-chlorophenyl)cyclohexene (**7**) (77.1 mg, 0.40 mmol, 1.00 equiv.), 2-phenylvinylboronic acid (118.4 mg, 0.80 mmol, 2.00 equiv.), $Pd(dba)_2$ (11.5 mg, 0.02 mmol, 0.05 equiv.), $PCy_3{\cdot}HBF_4$ (14.7 mg, 0.04 mmol, 0.10 equiv.), and Cs_2CO_3 (325.8 mg, 1.00 mmol, 2.50 equiv.) were stirred in a flame-dried and capped microwave vial in 2.2 mL of 1,4-dioxane/H_2O (10:1) at 110 °C for 16 h. The reaction

was allowed to cool to room temperature and the clear orange product mixture was filtered through a Celite plug using EtOAc as eluent and all solvents were removed under reduced pressure. The yellow crude product was purified by flash column chromatography using silica-gel (hexane:Et_2O, 99/1) to give the corresponding product in 57 % yield (60 mg) as a colourless oil. SFC analysis indicated an enantiomeric ratio of 97.0:3.0, but sufficient separation could not be achieved.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.34 – 7.14 (m, 9H, arom. C(3) –H, arom. C(4) –H, arom. C(5) –H, arom. C(6) –H, 2x arom. C(4') –H, 2x arom. C(5') –H, arom. C(6') –H), 5.80 (d, *J* = 1.4 Hz, 1H, 1x C(2') –H_2), 5.76 (ddt, *J* = 10.0, 4.9, 2.8 Hz, 1H, C(3'') –H), 5.48 (dd, *J* = 10.0, 2.4 Hz, 1H, C(2'') –H), 5.19 (d, *J* = 1.4 Hz, 1H, 1x C(2') –H_2), 3.39 (dq, *J* = 5.9, 2.9 Hz, 1H, C(1'') –H), 2.10 – 1.88 (m, 2H, C(4'') –H_2), 1.74 – 1.62 (m, 2H, 1x C(5'') –H_2, 1x C(6'') –H_2), 1.47 – 1.31 (m, 2H, 1x C(5'') –H_2, 1x C(6'') –H_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 148.9 (C(1')), 144.8 (C(3')), 141.10 (C(2)), 141.04 (C(1)), 131.1 (C(2'')), 130.2 (C(5)), 128.40 (2x C(5')), 128.07 (C(6)), 127.83 (2x C(4')), 127.77 (C(3'')), 126.56 (C(3), C(4)), 125.9 (C(6')), 115.2 (C(2')), 38.5 (C(1'')), 32.2 (C(6'')), 25.0 (C(4')), 21.8 (C(5'')).

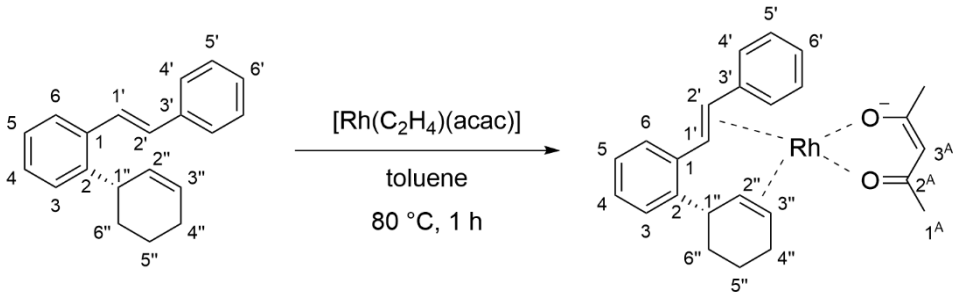
SFC: Chiralpak® IF; 1500 psi, 30 °C; flow: 0.5 mL/min, 0 % MeOH over 10 min; >97.0:3.0 er., insufficient separation. (major enantiomer t_R = 4.05 min; minor enantiomer t_R: 3.89 min).

HRMS (EI): m/z calcd for $C_{20}H_{20}$ [M^+]: 260.1560, found: 260.1559.

IR ($CHCl_3$ film): 3057 (w), 3019 (m), 2981 (m), 2930 (m), 2857 (m), 2835 (w), 2349 (w), 1615 (w), 1574 (w), 1493 (m), 1445 (m), 1386 (w), 1322 (w), 1251 (w), 1220 (w), 1136 (w), 1067 (w), 1028 (w), 982 (w), 902 (m), 771 (s), 757 (s), 709 (m), 664 (w) cm^{-1}.

$[\alpha]^{25}_D$ = - 41.3 (c = 1.0, $CHCl_3$).

*Synthesis of complex [Rh(**8**)(acac)]*



In a flame dried 5 mL round-bottom flask, **8** (6.73 mg, 0.026 mmol, 1.00 equiv.) and [Rh(C_2H_4)(acac)] (8.00 mg, 0.03 mmol, 1.20 equiv.) were stirred in 1 mL anhydrous toluene at 80 °C for 1 h. The solvent was removed under reduced pressure and the crude complex was dried in vacuo as a yellow oil. Further treatment with hexane at -78 °C led to small amounts of free **20** without any observed precipitation. An isolated yield could not be determined.

The complexation using **11** was performed analogously and is summarized in Figure S 1. The complex was observed in a 2:1 mixture with free ligand **11**.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.78 – 7.56 (m, 3H, arom. C(6) –H, 2x arom. C(4') –H), 7.24 – 7.16 (m, 5H, arom. C(3) –H, arom. C(5) –H, 2x arom. C(5') –H, arom. C(6') –H), 7.12 (dd, *J* = 5.6, 3.5 Hz, 1H, arom. C(4) –H), 5.56 (dd, *J* = 12.4, 1.6 Hz, 1H, C(1') –H), 5.42 – 5.28 (m, 1H, C(3'') –H), 5.14 (s, 1H, C(3^A) –H), 4.92 – 4.75 (m, 1H, C(2'') –H), 3.89 – 3.73 (m, 1H, C(2') –H), 3.67 – 3.53 (m, 1H, C(1'') –H), 2.62 – 2.48 (m, 1H, 1x C(4'') –H_2), 2.32 (t, *J* = 15.1 Hz, 1H, 1x C(4'') –H_2), 1.96 – 1.85 (m, 3H, C(5'') –H_2, 1x C(6'') –H_2), 1.82 (d, *J* = 6.5 Hz, 6H, 2x C(1^A) –H_3), 1.22 – 1.08 (m, 1H, 1x C(6'') –H_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 186.0 (d, *J* = 58.3 Hz, 2x C(2^A)), 142.7 (C(2)), 139.65 (C(3')), 139.31 (C(1)), 130.9 (C(4)), 130.3 (C(6)), 127.99 (2x C(5')), 127.41 (2x C(4')), 126.56 (C(5)), 126.55 (C(6')) 125.8 (C(3)), 99.1 (C(3^A)), 78.6 (C(3'')), 74.9 (C(2'')), 70.1 (C(1')), 59.7 (C(2')), 42.4 (C(1'')), 33.4 (C(6'')), 27.3 (d, *J* = 12.7 Hz, 2x C(1^A)), 25.6 (C(4'')), 23.9 (C(5'')).

IR ($CHCl_3$ film): 3020 (w), 2928 (w), 2361 (w), 1575 (s), 1519 (s), 1386 (m), 1271 (w), 1026 (w), 960 (w), 758 (m), 692 (m) cm^{-1}.

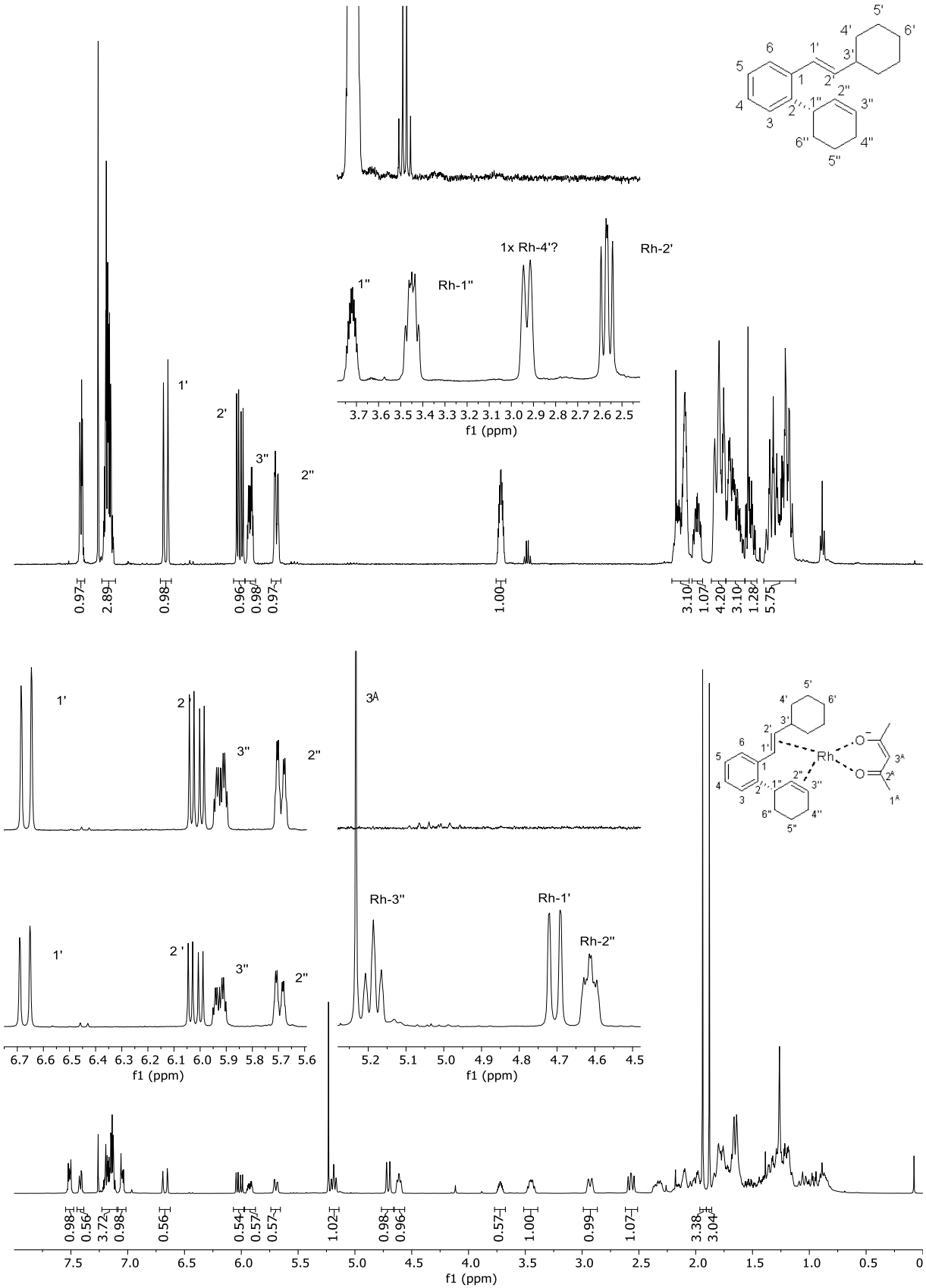


Figure S 1: Comparison of free ligand **11** (top) vs. free ligand and complex [Rh(**11**)(acac)] (~1:2 ratio) (bottom), showing signals for C(1')–H and C(2') –H significantly shifted up-field, and less significant shifts for C(2'') –H and C(3'') –H. The particularly strong shift for C(2') –H compared to complexation of **8** is due to the lack of aromaticity in the cyclohexene substituent.

5.4 Experimental Information for Chapter 3

Synthesis of Starting Materials

The synthesis and characterisation of *meso* bisphosphate **13** and the synthesis of *meso* bisphosphates corresponding to **16**-**22** was carried out by Reece Jacques and is therefore not included in this experimental section. The experimental details have been published in: R. Jacques, A. M. L. Hell, R. D. C. Pullin, S. P. Fletcher, *Tetrahedron* **2019**, *75*, 130560.

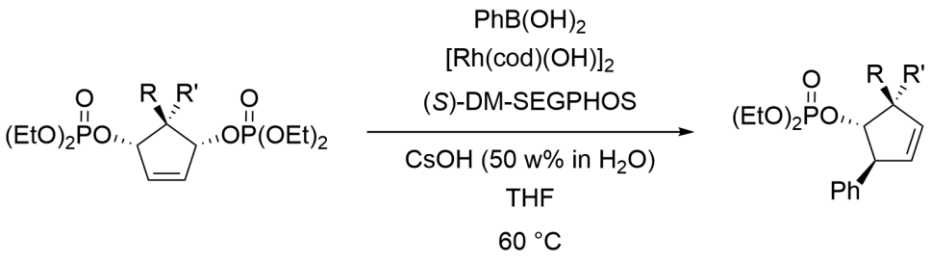
Desymmetrization Products

The synthesis and characterisation of allylic arylation products **14k**, **16**-**22** was carried out by Reece Jacques and is therefore not included in this experimental section. The experimental details have been published in: R. Jacques, A. M. L. Hell, R. D. C. Pullin, S. P. Fletcher, *Tetrahedron* **2019**, *75*, 130560.

Assignment of absolute configuration

The absolute configuration of compounds in this section has been assigned according to the sign of optical rotation and in analogy to structures reported in R. Jacques, R. D. C. Pullin, S. P. Fletcher, *Nat. Commun.* **2019**, *10*, 21.

General procedure 1: Asymmetric allylic arylation products with quaternary centres

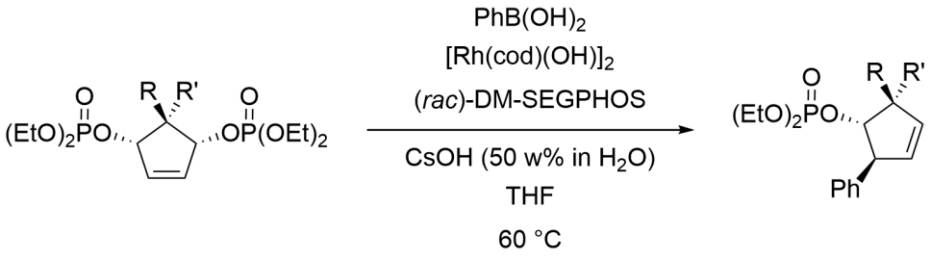


Flask **A**: A flame-dried 5 mL round-bottomed-flask was charged with (*S*)-DM-SEGPHOS (17.3 mg, 0.024 mmol, 0.06 equiv.) and $[Rh(cod)(OH)]_2$ (4.6 mg, 0.010 mmol, 0.025 equiv.) in this order and the solids were dissolved in 1.0 mL dry THF. An aqueous solution (50 wt. % in H_2O) of CsOH (70 µL, 0.4 mmol, 1.0 equiv.) was added to this mixture which was subsequently stirred at 60 °C for 30 min.

Flask **B**: A flame-dried 5 mL round-bottomed-flask was charged with bisphosphate **13** (190.4 mg, 0.4 mmol, 1.0 equiv.) and a boronic acid (0.8 mmol, 2.0 equiv.) in this order. The mixture was stirred in 0.8 mL dry THF for 30 min at room temperature.

After both mixtures in Flask **A** and **B** were stirred for 30 min, the contents of flask **B** were transferred into flask **A** *via* syringe. Flask **B** was rinsed with 0.2 mL dry THF which was transferred into flask **A** in the same way. The reaction was stirred at 60 °C for 4 hours and then allowed to cool down to room temperature. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography using silica gel and pentane/ethyl acetate (3:2) as eluent system to give the product.

Racemic allylic arylation products

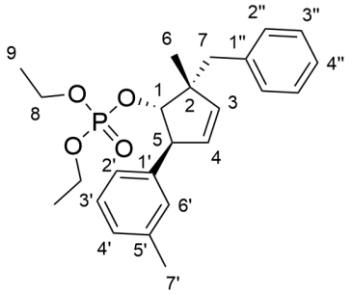


Flask **A**: A flame-dried 5 mL round-bottomed-flask was charged with (*rac*)-SEGPHOS (7.3 mg, 0.012 mmol, 0.06 equiv.) and $[Rh(cod)(OH)]_2$ (2.3 mg, 0.005 mmol, 0.025 equiv.) in this order and the solids were dissolved in 1.0 mL dry THF. An aqueous solution (50 wt. % in H_2O) of CsOH (35 µL, 0.2 mmol, 1.0 equiv.) was added to this mixture which was subsequently stirred at 60 °C for 30 min.

Flask **B**: A flame-dried 5 mL round-bottomed-flask was charged with bisphosphate **13** (95.2 mg, 0.2 mmol, 1.0 equiv.) and a boronic acid (0.4 mmol, 2.0 equiv.) in this order. The mixture was stirred in 0.8 mL dry THF for 30 min at room temperature.

After both mixtures in Flask **A** and **B** were stirred for 30 min, the contents of flask **B** were transferred into flask **A** *via* syringe. Flask **B** was rinsed with 0.2 mL dry THF which was transferred into flask **A** in the same way. The reaction was stirred at 60 °C overnight and then allowed to cool down to room temperature. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography using silica gel and pentane/ethyl acetate (3:2) as eluent system to give the racemic product.

***(**1S,2R,5S)-2-benzyl-2-methyl-5-(m-tolyl)cyclopent-3-en-1-yl diethyl phosphate (**14a**)*



The corresponding compound was prepared following *General procedure 1*, using (**13**) and 3-methylphenylboronic acid to give the product as a yellow oil in 77 % yield (128 mg). SFC analysis indicated an enantiomeric ratio of >99.5:0.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.31 – 7.26 (m, 2H, 2x arom. C(2'') –H), 7.25 – 7.17 (m, 4H, arom. C(3') –H, arom. C(6') –H, 2x arom. C(3'') –H), 7.07 – 7.02 (m, 3H, arom. C(2') –H, arom. C(4') –H, arom. C(4'') –H), 5.61 (dt, *J* = 6.2, 1.4 Hz, 1H, C(4) –H), 5.52 (dd, *J* = 6.2, 2.5 Hz, 1H, C(3) –H), 4.55 (dd, *J* = 8.6, 7.8 Hz, 1H, C(1) –H), 4.11 – 3.98 (m, 1H, 1x C(8) –H_2), 3.93 (dt, *J* = 7.8, 2.1 Hz, 1H, C(5) –H), 3.90 – 3.70 (m, 3H, 3x C(8) –H_2), 2.99 (d, *J* = 13.0 Hz, 1H, 1x C(7) –H_2), 2.74 (d, *J* = 13.0 Hz, 1H, 1x C(7) –H_2), 2.33 (s, 3H, C(7') –H_3), 1.26 – 1.22 (m, 3H; 3x C(9) –H_3), 1.21 (s, 3H, C(6) –H_3), 1.12 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 141.9 (C(1')), 138.9 (C(3)), 138.8 (C(1'')), 138.1 (C(5')), 131.0 (2x C(3'')), 130.1 (C(4)), 128.9 (C(4')), 128.5 (C(3')), 127.9 (2x C(2'')), 127.8 (C(4'')), 126.1 (C(6')), 125.3 (C(2')), 93.7 (d, *J* = 7.1 Hz, C(1)), 63.77 (d, *J* = 6.0 Hz, 1x C(8)), 63.63 (d, *J* = 6.1 Hz, 1x C(8)), 56.1 (d, *J* = 5.9 Hz, C(5)), 50.9 (d, *J* = 3.1 Hz, C(2)), 41.0 (C(7)), 24.4 (C(6)), 21.5 (C(7')), 16.22 (d, *J* = 7.1 Hz, 1x C(9)), 16.07 (d, *J* = 7.2 Hz, 1x C(9)).

^{31}P NMR{^{1}H} ($CDCl_3$, 162 MHz): δ (ppm) -1.86 (s, $PO(OR)_3$).

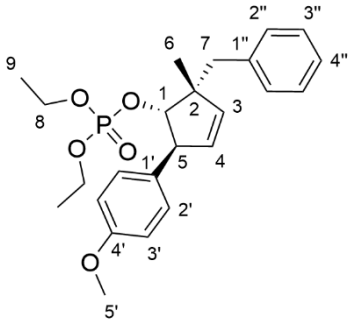
SFC: Chiralpak® IF; 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, >99.5:0.5 er (major enantiomer t_R = 3.25 min, minor enantiomer t_R = 3.15 min).

HRMS (ESI): m/z calcd for $C_{24}H_{32}O_4P$ $[M+H]^+$: 415.20437, found: 415.20340.

IR ($CHCl_3$ film): 2980 (w), 1606 (w), 1494 (w), 1454 (w), 1369 (w), 1265 (m), 1166 (w), 1025 (s), 974 (m), 901 (w), 786 (w), 750 (m), 703 (m) cm^{-1}.

$[\alpha]^{25}_D$ =-159.5 (c=1.0, $CHCl_3$).

*(1S,2R,5S)-2-benzyl-5-(4-methoxyphenyl)-2-methylcyclopent-3-en-1-yl diethyl phosphate **(14b)***



The corresponding compound was prepared following *General procedure 1*, using (**13**) and (4-methoxyphenyl)boronic acid to give the product as a yellow oil in 63% yield (109 mg). SFC analysis indicated an enantiomeric ratio of >99.5:0.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.30 – 7.12 (m, 7H, 2x arom. C(2') –H, 2x arom. C(2'') –H, 2x arom. C(3'') –H, arom. C(4'') –H), 6.88 – 6.82 (m, 2H, 2x arom. C(3') –H), 5.59 (dt, *J* = 6.3, 1.3 Hz, 1H, C(4) –H), 5.51 (dd, *J* = 6.2, 2.5 Hz, 1H, C(3) –H), 4.52 (dd, *J* = 8.6, 7.7 Hz, 1H, C(1) –H), 4.08 – 3.99 (m, 1H, 1x C(8) –H_2), 3.93 (dt, *J* = 7.3, 2.4, 1.7 Hz, 1H, C(5) –H), 3.91 – 3.80 (m, 2H, 2x C(8) –H_2), 3.79 (s, 3H, C(5') –H_3), 3.78 – 3.74 (m, 1H, 1x C(8) –H_2), 2.98 (d, *J* = 13.0 Hz, 1H, 1x C(7) –H_2), 2.74 (d, *J* = 13.0 Hz, 1H,1x C(7) –H_2), 1.27 – 1.22 (m, 3H, 3x C(9) –H_3), 1.20 (s, 3H, C(6) –H_3), 1.14 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 158.8 (C(4')), 138.8 (C(3)), 134.1 (C(1')), 131.0 (2x C(3'')), 130.3 (C(4)), 129.1 (2x C(2')), 127.8 (2x C(2'')), 126.1 (C(4'')), 114.0 (2x C(3')), 93.8 (d, *J* = 7.0 Hz, C(1)), 63.79 (d, *J* = 5.6 Hz, 1x C(8)), 63.67 (d, *J* = 6.0 Hz, 1x C(8)), 55.45

(C(5')), 55.42 (d, *J* = 7.1 Hz, C(5)), 50.9 (d, *J* = 3.2 Hz, C(2)), 41.0 (C(7)), 24.4 (C(6)), 16.25 (d, *J* = 7.2 Hz, 1x C(9)), 16.13 (d, *J* = 7.2 Hz, 1x C(9)).

^{31}P NMR{^{1}H} ($CDCl_3$, 162 MHz): δ (ppm) -1.79 (s, $PO(OR)_3$).

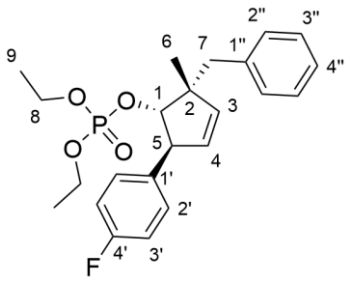
SFC: Chiralpak® IG; 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, >99.5:0.5 er (major enantiomer t_R = 3.71 min, minor enantiomer t_R = 3.56 min).

HRMS (ESI): m/z calcd for $C_{24}H_{32}O_5P$ $[M+H]^+$: 431.19819, found: 431.19830.

IR ($CHCl_3$ film): 3282 (w), 2983 (w), 2850 (w), 2360 (w), 1588 (m), 1513 (m), 1492 (m), 1479 (m), 1372 (w), 1258 (s), 1141 (m), 1082 (m), 1027 (s), 977 (m), 841 (m), 742 (m), 716 (m), 646 (w) cm^{-1}.

$[\alpha]^{25}_D$ = -133.0 (c=1.0, $CHCl_3$).

*(1S,2R,5S)-2-benzyl-5-(4-fluorophenyl)-2-methylcyclopent-3-en-1-yl diethyl phosphate (**14c**)*



The corresponding compound was prepared following *General procedure 1*, using (**13**) and 4-fluorophenylboronic acid to give the product as colourless crystals in 61 % yield (101 mg). SFC analysis indicated an enantiomeric ratio of >99.5:0.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.31 – 7.17 (m, 7H, 2x arom. C(2') –H, 2x arom. C(2'') –H, 2x arom. C(3'') –H**,** arom. C(4'') –H)), 7.04 – 6.97 (m, 2H, 2x arom. C(3') –H), 5.58 (dt, *J* = 6.4, 1.2 Hz, 1H, C(4) –H), 5.54 (dd, *J* = 6.3, 2.5 Hz, 1H, C(3) –H), 4.50 (dd, *J* = 8.7, 7.7 Hz, 1H, C(1) –H), 4.11 – 4.00 (m, 1H, 1x C(8) $–H_2$), 3.98 – 3.75 (m, 4H, C(5) –H, 3x C(8) $–H_2$), 2.98 (d, *J* = 13.0 Hz, 1H, 1x C(7) $–H_2$), 2.73 (d, *J* = 13.0 Hz, 1H, 1x C(7) $–H_2$), 1.26 (td, *J*

= 7.0, 1.1 Hz, 3H, 3x C(9) –H_3), 1.20 (s, 3H, C(6) –H_3), 1.15 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 148.0 (d, *J* = 6.0 Hz, C(4')), 139.3 (C(3)), 138.6 (C(1')), 131.0 (2x C(3'')), 129.73 (C(1'')), 129.60 (d, *J* = 8.0 Hz, 2x C(2')), 127.9 (2x C(2'')), 126.2 (C(4'')), 115.4 (d, *J* = 21.1 Hz, 2x C(3')), 93.6 (d, *J* = 7.4 Hz, C(1)), 63.79 (d, *J* = 8.2 Hz, 1x C(8)), 63.66 (d, *J* = 5.1 Hz, 1x C(8)), 55.5 (d, *J* = 5.7 Hz, C(5)), 51.0 (d, *J* = 2.9 Hz, C(2)), 41.0 (C(7)), 24.4 (C(6)), 16.25 (d, *J* = 7.1 Hz, 1x C(9)), 16.12 (d, *J* = 7.1 Hz, 1x C(9)).

^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): δ (ppm) -1.72 (s, $PO(OR)_3$).

^{19}F{^{1}H} NMR ($CDCl_3$, 376 MHz): δ (ppm) -116.22 (s, C(4') –F).

SFC: Chiralpak® IG; 1500 psi, 30 °C; flow: 1.0 mL/min; 0 % MeOH for 3 min, 0 % to 10 % MeOH over 5 min, 10 % to 50 % MeOH over 1 min, >99.5:0.5 er (major enantiomer t_R = 8.88 min, minor enantiomer t_R = 8.68 min).

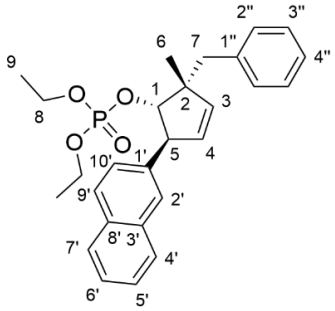
HRMS (ESI): m/z calcd for $C_{23}H_{29}O_4FP$ $[M+H]^+$: 419.17820, found: 419.17913.

IR ($CHCl_3$ film): 2982 (w), 1604 (w), 1510 (m), 1454 (w), 1370 (w), 1265 (m), 1224 (m), 1159 (w), 1025 (s), 974 (m), 904 (w), 863 (w), 831 (w), 750 (m), 704 (m), 626 (w) cm^{-1}.

$[\alpha]^{25}_D$ = -139.1 (c=1.0, $CHCl_3$).

m.p.: 74.9 °C

*(1S,2R,5S)-2-benzyl-2-methyl-5-(naphthalen-2-yl)cyclopent-3-en-1-yl diethyl phosphate (**14d**)*



The corresponding compound was prepared following *General procedure 1*, using (**13**) and naphthalen-2-ylboronic acid to give the product as colourless crystals in 66 % yield (120 mg). SFC analysis indicated an enantiomeric ratio of >99.5:0.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.87 – 7.74 (m, 3H, arom. C(4') –H , arom. C(7') –H , arom. C(9') –H), 7.70 (s, 1H, arom. C(2') –H), 7.51 – 7.36 (m, 3H; arom. C(5') –H, arom. C(6') –H, arom. C(10') –H), 7.32 – 7.27 (m, 2H, 2x arom. C(2'') –H), 7.26 – 7.20 (m, 3H, 2x arom C(3'') –H, arom. C(4'') –H), 5.70 (dt, *J* = 6.2, 1.3 Hz, 1H, C(4) –H), 5.60 (dd, *J* = 6.3, 2.5 Hz, 1H, C(3) –H), 4.67 (dd, *J* = 8.7, 7.7 Hz, 1H, C(1) –H), 4.14 (dt, *J* = 7.7, 2.1 Hz, 1H, C(5) –H), 4.07 – 3.92 (m, 1H, 1x C(8) –H_2), 3.89 – 3.78 (m, 1H, 1x C(8) –H_2), 3.78 – 3.60 (m, 2H, 2x C(8) –H_2), 3.04 (d, *J* = 13.0 Hz, 1H, 1x C(7) –H_2), 2.78 (d, *J* = 13.0 Hz, 1H, 1x C(7) –H_2), 1.25 (s, 3H, C(6) 1x C(6) –H_3), 1.13 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) –H_3), 0.95 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 139.3 (C(1')), 139.2 (C(1'')), 138.7 (C(3)), 133.6 (C(3')), 132.8 (C(8')), 131.0 (2x C(3'')), 129.9 (C(4)), 128.4 (C(7')), 127.9 (2x C(2'')), 127.8 (C(4')), 127.7 (C(9')), 126.9 (C(2')), 126.24 (C(10')), 126.21 (C(5')), 126.19 (C(4'')), 125.70 (C(6')), 93.4 (d, *J* = 7.1 Hz, C(1)), 63.80 (d, *J* = 6.0 Hz, 1x C(8)), 63.65 (d, *J* = 6.2 Hz, 1x C(8)), 56.4 (d, *J* = 5.7 Hz, C(5)), 51.1 (d, *J* = 3.1 Hz, C(2)), 41.0 (C(7)), 24.4 (C(6)), 16.1 (d, *J* = 7.3 Hz, 1x C(9)), 15.9 (d, *J* = 7.8 Hz, 1x C(9)).

^{31}P NMR {^{1}H} ($CDCl_3$, 162 MHz,) δ (ppm): -1.79 (s, $PO(OR)_3$).

SFC: Chiralpak® IA, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min; >99.5:0.5 er (major enantiomer, t_R = 3.47 min, minor enantiomer, t_R = 3.30 min).

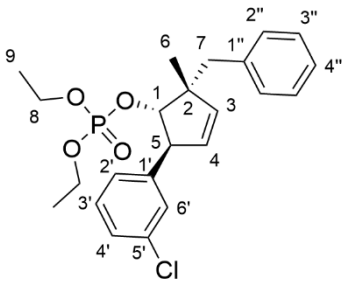
HRMS (ESI): m/z calcd for $C_{27}H_{31}O_4{}^{23}NaP$ $[M+Na]^+$: 473.18631, found: 473.18524.

IR ($CHCl_3$ film): $CHCl_3$: 2981 (w), 1602 (w), 1495 (w), 1454 (w), 1370 (w), 1264 (m), 1165 (w), 1026 (s), 974 (m), 901 (w), 819 (m), 749 (m), 704 (m) cm^{-1}.

$[\alpha]^{25}_D$ = -201.0 (c=1.0, $CHCl_3$).

m.p.: 79.5 °C

*(1S,2R,5S)-2-benzyl-5-(3-chlorophenyl)-2-methylcyclopent-3-en-1-yl diethyl phosphate (**14e**)*



The corresponding compound was prepared following *General procedure 1*, using (**13**) and 3-chlorophenylboronic acid to give the product as a dark yellow oil in 64 % yield (111 mg). SFC analysis indicated an enantiomeric ratio of >99.5:0.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.31 – 7.11 (m, 9H, arom. C(2') –H, arom. C(3') –H, arom. C(4') –H, arom. C(6') –H, 2x arom. C(2'') –H, 2x arom. C(3'') –H, arom. C(4'') –H), 5.63 – 5.54 (m, 2H, C(3) –H, C(4) –H), 4.51 (dd, *J* = 8.7, 7.8 Hz, 1H, C(1) –H), 4.13 – 4.00 (m, 1H, 1x C(8) –H_2), 4.00 – 3.77 (m, 4H, C(5) –H, 3x C(8) –H_2), 2.97 (d, *J* = 13.0 Hz, 1H, 1x C(7) –H_2), 2.74 (d, *J* = 13.0 Hz, 1H, 1x C(7) –H_2), 1.26 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) –H_3), 1.21 (s, 3H, C(6) –H_3), 1.16 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 144.2 (C(1')), 139.7 (C(3)), 138.5 (C(1'')), 134.4 (C(5')), 131.0 (2x C(3'')), 129.9 (C(3')), 129.2 (C(4)), 128.4 (C(4')), 127.9 (2x C(2'')), 127.2 (C(4'')), 126.3 (C(6')), 126.2 (C(2')), 93.3 (d, *J* = 7.1 Hz, C(1)), 63.92 (d, *J* = 6.2 Hz, 1x C(8)),

63.79 (d, *J* = 5.7 Hz, 1x C(8)), 55.9 (d, *J* = 5.7 Hz, C(5)), 51.1 (d, *J* = 3.1 Hz, C(2)), 41.0(C(7)), 24.4 (C(6)), 16.24 (d, *J* = 7.2 Hz, 1x C(9)), 16.10 (d, *J* = 6.9 Hz, 1x C(9)).

$^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz): δ (ppm) -1.75 (s, $PO(OR)_3$).

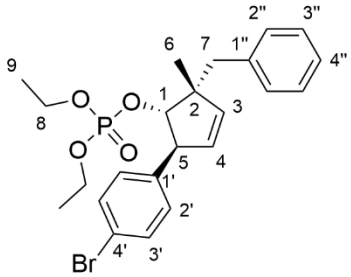
SFC: Chiralpak® IG; 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, >99.5:0.5 er (major enantiomer t_R = 3.40 min, minor enantiomer t_R = 3.20 min).

HRMS (ESI): m/z calcd for $C_{23}H_{29}O_4{}^{35}ClP$ $[M+H]^+$: 435.14865, found: 435.14816.

IR ($CHCl_3$ film): 2981 (w), 1598 (w), 1454.0 (w), 1393 (w), 1265 (m), 1165 (w), 1026 (s), 973 (m), 786 (w), 750 (m), 722 (w), 703 (w) cm^{-1}.

$[\alpha]^{25}_D$ = -84.2 (c=1.0, $CHCl_3$).

*(1S,2R,5S)-2-benzyl-5-(4-bromophenyl)-2-methylcyclopent-3-en-1-yl diethyl phosphate (**14f**)*



The corresponding compound was prepared following *General procedure 1*, using (**13**) and 4-bromophenylboronic acid to give the product as yellow crystals in 59 % yield (114 mg). SFC analysis indicated an enantiomeric ratio of >99.5:0.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.47 – 7.40 (m, 2H, 2x arom. C(3') –H), 7.30 – 7.17 (m, 5H, 2x arom. C(2') –H, 2x C(3'') –H, arom. C(4'') –H), 7.16 – 7.11 (m, 2H, 2x arom. C(2'') –H), 5.60 – 5.52 (m, 2H, C(3) –H, C(4) –H), 4.50 (dd, *J* = 8.7, 7.7 Hz, 1H, C(1) –H), 4.05 (dp, *J* = 10.1, 7.1 Hz, 1H, 1x C(8) $–H_2$), 3.98 – 3.75 (m, 4H, C(5) –H, 3x C(8) $–H_2$), 2.97 (d, *J* = 13.0 Hz, 1H, 1x C(7) $–H_2$), 2.73 (d, *J* = 13.1 Hz, 1H, 1x C(7) $–H_2$), 1.25 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) $–H_3$), 1.20 (s, 3H, C(6) $–H_3$), 1.15 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) $–H_3$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 141.1 (C(1')), 139.6 (C(3)), 138.5 (C(1'')), 131.6 (2x C(3')), 131.0 (2x C(3'')), 129.9 (2x C(2'')), 129.4 (C(4)), 127.9 (2x C(2')), 126.2 (C(4'')), 120.9 (C(4')), 93.4 (d, *J* = 6.8 Hz, C(1)), 63.91 (d, *J* = 5.9 Hz, 1x C(8)), 63.78 (d, *J* = 6.2 Hz, 1x C(8)), 55.7 (d, *J* = 5.6 Hz, C(5)), 51.1 (d, *J* = 3.0 Hz, C(2)), 41.0 (C(7)), 24.4 (C(6)), 16.24 (d, *J* = 7.0 Hz, 1x C(9)), 16.10 (d, *J* = 7.1 Hz, 1x C(9)).

^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): δ (ppm) -1.74 (s, $PO(OR)_3$).

SFC: Chiralpak® IG; 1500 psi, 30 °C; flow: 0.5 mL/min; 1 % to 30 % MeOH over 15 min, >99.5:0.5 er (major enantiomer t_R = 9.66 min, minor enantiomer t_R = 9.41 min).

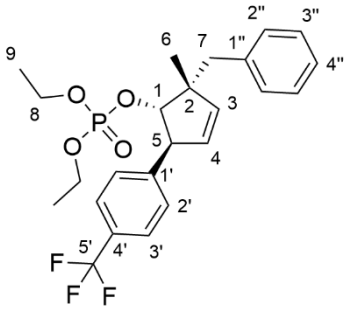
HRMS (ESI): m/z calcd for $C_{23}H_{29}O_4{}^{79}BrP$ $[M+H]^+$:479.09813, found: 479.09805.

IR ($CHCl_3$ film): 2981 (w), 1489 (w), 1454 (w), 1393.2 (w), 1265 (m), 1165 (w), 1025 (s), 973 (m), 903 (w), 818 (m), 750 (m), 704 (m) cm^{-1}.

$[\alpha]^{25}_D$ = -146.6 (c=1.0, $CHCl_3$).

m.p.: 78.6 °C

*(1S,2R,5S)-2-benzyl-2-methyl-5-(4-(trifluoromethyl)phenyl)cyclopent-3-en-1-yl diethyl phosphate (**14g**)*



The corresponding compound was prepared following *General procedure 1*, using (**13**) and (4-(trifluoromethyl)phenyl)boronic acid to give the product as dark red crystals in 55 % yield (104 mg). SFC analysis indicated an enantiomeric ratio of >99.5:0.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.58 (d, *J* = 8.0 Hz, 2H, 2x arom. C(3') –H), 7.38 (d, *J* = 8.0 Hz, 2H, 2x arom. C(2') –H), 7.32 –7.17 (m, 5H, 2x arom. C(2'') –H, 2x arom. C(3'') –H, arom. C(4'') –H), 5.60 (d, *J* = 0.9 Hz, 2H, C(3) –H, C(4) –H), 4.54 (dd, *J* = 8.7, 7.8 Hz, 1H; C(1) –H), 4.10 – 3.99 (m, 2H, 1x C(8) –H, C(1) –H), 3.96 – 3.72 (m, 3H,3x C(8) –H_2), 2.99 (d, *J* = 13.0 Hz, 1H, 1x C(7) –H_2), 2.74 (d, *J* = 13.0 Hz, 1H, 1x C(7) –H_2), 1.28 – 1.20 (m, 6H, C(6) –H_3, 3x C(9) –H_3), 1.11 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 146.2 (C(1')), 139.9 (C(3)), 138.4 (C(1'')), 131.0 (2x C(3'')) 129.6 (d, *J* = 8.4 Hz, C(4')), 129.0 (C(4)), 128.6 (2x C(2')), 127.9 (2x C(2'')), 126.3 (C(4'')), 125.52 (2x C(3')), 125.50 (q, *J* = 3.5 Hz, C(5')), 93.2 (d, *J* = 7.1 Hz, C(1)), 63.93 (d, *J* = 5.8 Hz, 1x C(8)), 63.77 (d, *J* = 5.6 Hz, 1x C(8)), 56.0 (d, *J* = 5.5 Hz, C(5)), 51.2 (d, *J* = 3.0 Hz, C(2)), 41.0 (C(7)), 24.4 (C(6)), 16.19 (d, *J* = 6.7 Hz, 1x C(9)), 16.01 (d, *J* = 7.3 Hz, 1x C(9)).

^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): δ (ppm) -1.74 (s, $PO(OR)_3$).

^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) -62.47 (s, C(5') –F_3).

SFC: Chiralpak® IC; 1500 psi, 30 °C; flow: 0.5 mL/min; 1 % MeOH for 4 min, 1 % to 5 % MeOH over 1 min, hold 5 % MeOH for 8 min, >99.5:0.5 er (major enantiomer t_R = 11.06 min, minor enantiomer t_R = 10.70 min).

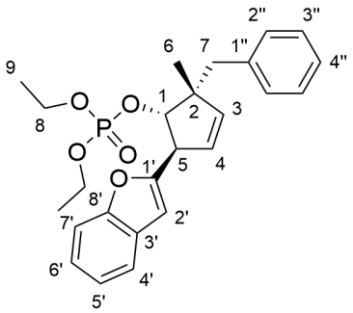
HRMS (ESI): m/z calcd for $C_{24}H_{29}O_4F_3P$ $[M+H]^+$: 469.17501, found: 469.17484.

IR ($CHCl_3$ film): 2981 (w), 1619 (w), 1454 (w), 1421 (w), 1326 (s), 1266 (m), 1165 (m), 1124 (m), 1068 (m), 1026 (s), 973 (m), 905 (w), 832 (w), 751 (m), 704 (m) cm^{-1}.

$[\alpha]^{25}_D$ = -113.8 (c=1.0, $CHCl_3$).

m.p.: 58.2 °C

*(1S,2R,5R)-5-(benzofuran-2-yl)-2-benzyl-2-methylcyclopent-3-en-1-yl diethyl phosphate (**14h**)*



The corresponding compound was prepared following *General procedure 1*, using (**13**) and benzofuran-2-ylboronic acid to give the product as colourless crystals in 42 % yield (73 mg). SFC analysis indicated an enantiomeric ratio of >99.5:0.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.52 – 7.47 (m, 1H, arom. C(4') –H), 7.41 (dt, *J* = 8.3, 0.9 Hz, 1H, C(7') –H)), 7.31 – 7.16 (m, 7H, arom. C(5') –H, arom. C(6') –H, 2x arom. (C2'') –H, 2x arom. C(3'') –H, arom. C(4) –H)), 6.60 (br t, *J* = 0.8 Hz, 1H, arom. C(2') –H)), 5.72 (ddd, *J* = 6.2, 1.8 Hz, 0.9 Hz 1H, C(4) –H), 5.58 (dd, *J* = 6.3, 2.6 Hz, 1H, C(3) –H), 4.92 (dd, *J* = 8.8, 7.6 Hz, 1H, C(1) –H), 4.19 – 3.86 (m, 5H, C(5) –H, 2x C(8) –H_2), 2.99 (d, *J* = 13.1 Hz, 1H, 1x C(7) –H_2), 2.76 (d, *J* = 13.0 Hz, 1H, 1x C(7) –H_2), 1.30 – 1.18 (m, 6H, C(6) –H_3, 3x C(9) –H_3), 1.12 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 157.7 (C(1')), 155.1 (C(8')), 139.5 (C(3)), 138.4 (C(1'')), 131.0 (2x C(3'')), 128.8 (C(3')), 127.9 (C(2'')), 127.0 (C(4)), 126.3 (C(4'')), 123.8 (C(6')), 122.8 (C(5')), 120.8 (C(4')), 111.1 (C(7')), 103.3 (C(2')), 89.4 (d, *J* = 7.1 Hz, C(1)), 64.02 (d, *J* = 5.7 Hz, 1x C(8)), 63.91 (d, *J* = 6.0 Hz, 1x C(8)), 51.0 (d, *J* = 3.2 Hz, C(2)), 50.4 (d, *J* = 5.6 Hz, C(5)), 41.0 (C(7)), 24.4 (C(6)), 16.18 (d, *J* = 7.1 Hz, 1x C(9)), 16.02 (d, *J* = 7.2 Hz, 1x C(9)).

^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): δ (ppm) -1.73 (s, $PO(OR)_3$).

SFC: Chiralpak® IG; 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, >99.5:0.5 er (major enantiomer t_R = 3.91 min, minor enantiomer t_R = 3.61 min).

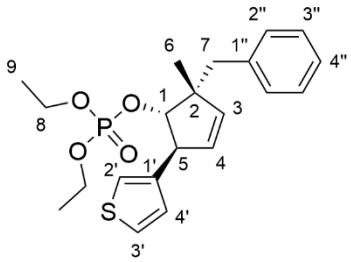
HRMS (ESI): m/z calcd for $C_{25}H_{30}O_5P$ $[M+H]^+$: 441.18254, found: 441.18256.

IR ($CHCl_3$ film): 2981 (w), 1602 (w), 1455 (m), 1256 (m), 1166 (w), 1025 (s), 973 (m), 901 (w), 803 (w), 750 (m), 704 (m) cm^{-1}.

$[\alpha]^{25}_D$ = -214.8 (c=1.0, $CHCl_3$).

m.p.: 81.3 °C

*(1S,2R,5S)-2-benzyl-2-methyl-5-(thiophen-3-yl)cyclopent-3-en-1-yl diethyl phosphate (**14i**)*



The corresponding compound was prepared following *General procedure 1*, using (**13**) and thiophen-3-ylboronic acid to give the product as an orange oil in 12 % yield (20 mg). SFC analysis indicated an enantiomeric ratio of 99.0:1.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.31 – 7.15 (m, 6H, arom. C(2') –H, 2x arom. C(2'') –H, 2x arom. C(3'') –H, arom. C(4'') –H), 7.11 (dd, *J* = 3.0, 1.2 Hz, 1H, arom. C(3') –H), 7.03 (dd, *J* = 5.0, 1.3 Hz, 1H, arom. C(4') –H), 5.64 (dt, *J* = 6.2, 1.3 Hz, 1H, C(4) –H), 5.50 (dd, *J* = 6.2, 2.5 Hz, 1H, C(3) –H), 4.61 (dd, *J* = 8.5, 7.5 Hz, 1H, C(1) –H), 4.15 – 4.03 (m, 2H, (5) –H, 1x C(8) $–H_2$), 4.02 – 3.83 (m, 3H, 3x C(8) $–H_2$), 2.97 (d, *J* = 13.0 Hz, 1H, 1x C(7) $–H_2$), 2.73 (d, *J* = 13.0 Hz, 1H, 1x C(7) $–H_2$), 1.29 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) $–H_3$), 1.24 – 1.16 (m, 6H, 3x C(9) $–H_3$, C(6) $–H_3$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 142.7 (C(1')), 138.63 (C(1'')), 138.57 (C(3)), 131.0 (2x C(3'')), 129.6 (C(4)), 127.9 (2x C(2'')), 127.4 (C(4')), 126.2 (C(3')), 125.9 (C(4'')), 121.4 (C(2')), 92.6 (d, *J* = 7.1 Hz, C(1)), 63.88 (d, *J* = 6.0 Hz, 1x C(8)), 63.78 (d, *J* = 6.1 Hz, 1x C(8)),

51.5 (d, *J* = 6.3 Hz, C(5)), 50.9 (d, *J* = 3.1 Hz, C(2)), 40.9 (C(7)), 24.5 (C(6)), 16.31 (d, *J* = 7.1 Hz, 1x C(9)), 16.19 (d, *J* = 7.1 Hz, 1x C(9)).

$^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz): δ (ppm) -1.71 (s, $PO(OR)_3$).

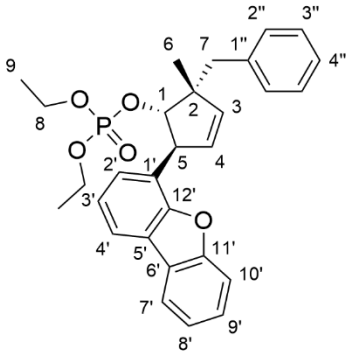
SFC: Chiralpak® IF; 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 99.0:1.0 er (major enantiomer t_R = 3.42 min, minor enantiomer t_R = 3.31 min).

HRMS (ESI): m/z calcd for $C_{21}H_{27}O_4{}^{23}NaP^{32}S$ $[M+Na]^+$: 429.12599, found: 429.12607.

IR ($CHCl_3$ film): 2981 (w), 1496 (w), 1454 (w), 1392 (w), 1260 (m), 1166 (w), 1031 (s), 987 (s), 777 (w), 753 (w), 704 (m) cm^{-1}.

$[\alpha]^{25}_D$ = -36.3 (c=1.0, $CHCl_3$).

*(1S,2R,5S)-2-benzyl-5-(dibenzo[b,d]furan-4-yl)-2-methylcyclopent-3-en-1-yl diethyl phosphate (**14j**)*



The corresponding compound was prepared following *General procedure 1*, using (**13**) and dibenzo[*b,d*] furan-4-ylboronic acid to give the product as an orange oil in 29 % yield (57 mg). SFC analysis indicated an enantiomeric ratio of 97.0:3.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.95 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H, arom. C(7') –H), 7.85 (dd, *J* = 7.0, 1.9 Hz, 1H, arom. C(4') –H), 7.57 (dt, *J* = 8.3, 0.9 Hz, 1H, arom. C(10') –H), 7.46 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H, arom. C(4'') –H), 7.38 – 7.21 (m, 8H, arom. C(2') –H, arom. C(3') –H, C(8') –H, C(9') –H, 2x arom. C(2'') –H, 2x arom. C(3'') –H), 5.71 (ddd, *J* = 6.2, 1.7,

1.0 Hz, 1H, C(4) –H), 5.59 (dd, *J* = 6.2, 2.6 Hz, 1H, C(3) –H), 4.90 (dd, *J* = 8.9, 8.1 Hz, 1H, C(1) –H), 4.72 (ddd, *J* = 8.1, 2.6, 1.7 Hz, 1H, C(5) –H), 3.98 (dp, *J* = 10.0, 7.1 Hz, 1H, 1x C(8) –H_2), 3.81 (ddq, *J* = 10.1, 7.9, 7.1 Hz, 1H, 1x C(8) –H_2), 3.64 – 3.44 (m, 2H, 2x C(8) –H_2), 3.12 (d, *J* = 12.9 Hz, 1H, 1x C(7) –H_2), 2.83 (d, *J* = 13.0 Hz, 1H, 1x C(7) –H_2), 1.29 (s, 3H, C(6) –H_3), 1.15 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) –H_3), 0.78 (td, *J* = 7.1, 1.1 Hz, 3H, 3x C(9) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 156.2 (C(11')), 155.0 (C(12')), 139.2 (C(3)), 138.8 (C(1'')), 131.0 (2x C(3'')), 129.5 (C(4)), 127.9 (2x C(2'')), 127.3 (C(4'')), 126.22 (C(9')), 126.20 (C(8')), 126.07(C(1')), 124.5 (C(6')), 124.2 (C(5')), 123.3 (C(2')), 122.8 (C(3')), 120.9 (C(7')), 119.2 (C(4')), 111.8 (C(10')), 92.4 (d, *J* = 6.7 Hz, C(1)), 63.8 (d, *J* = 6.2 Hz, 1x C(8)), 63.4 (d, *J* = 6.0 Hz, 1x C(8)), 50.9 (d, *J* = 3.1 Hz, C(2)), 50.0 (d, *J* = 5.7 Hz, C(5)), 41.0 (C(7)), 24.2 (C(6)), 16.1 (d, *J* = 7.1 Hz, 1x C(9)), 15.7 (d, *J* = 7.2 Hz, 1x C(9)).

^{31}P {^{1}H} NMR ($CDCl_3$, 162 MHz): δ (ppm) -1.86 (s, $PO(OR)_3$).

SFC: Chiralpak® ID; 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 97.0:3.0 er (major enantiomer t_R = 4.00 min, minor enantiomer t_R = 4.33 min).

HRMS (ESI): m/z calcd for $C_{29}H_{32}O_5P$ $[M+H]^+$: 491.19819, found: 491.19809.

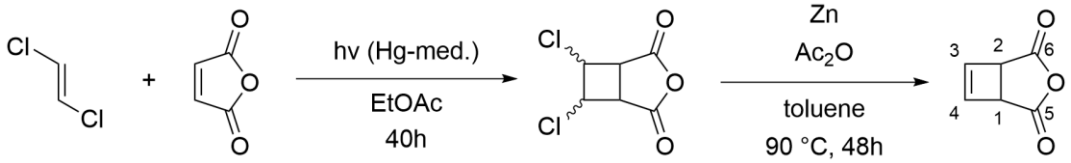
IR ($CHCl_3$ film): 2979 (w), 1495 (w), 1452 (m), 1425 (w), 1269 (m), 1186 (m), 1025 (s), 973 (m), 899 (w), 845 (w), 754 (m), 704 (m) cm^{-1}.

$[\alpha]^{25}_D$ = -114.9 (c=1.0, $CHCl_3$).

5.5 Experimental Information for Chapter 4

Synthesis of Starting Materials

*Synthesis of cis-cyclobut-3-ene-1,2-dicarboxylic anhydride (**25**) via (**24**)*



Adapting a reported procedure,[271] a 500 mL photochemical reactor equipped with a quartz immersion well was charged with maleic anhydride (20.0 g, 203.95 mmol, 1.0 equiv.) and benzophenone (3.7 g, 20.4 mmol, 0.1 equiv.) in ethyl acetate (400 mL). The solution was degassed with argon, then *E*-1,2-dichloroethylene (39.2 mL, 510 mmol, 2.5 equiv.) was added. The mixture was irradiated (400 W, medium-pressure Hg lamp) under cooling of the immersion well with a water flow for 40 h. After transferring the reaction mixture out of the photochemical reactor, remaining solid residues were taken up in ethyl acetate and added to the crude mixture. The solvents were removed under reduced pressure and the brown crude product was triturated with diethyl ether (ca. 200 mL) to obtain the product **24** as a mixture of diastereomers as a pale beige solid in two batches in 71 % yield. The mixture was taken forward without further purification.

Adapting a reported procedure,[271] a flame-dried 250 mL round-bottom flask was charged with 3,4-Dichlorocyclobutane-1,2-dicarboxylic Anhydride (10.2 g, 52.2 mmol, 1.0 equiv.) and acetic anhydride (61.7 mL, 625.5 mmol, 12.5 equiv.) in 110 mL anhydrous toluene. This mixture was vigorously stirred and heated to 90 °C, then activated Zn-powder (85.3 g, 1305 mmol, 25.0 equiv.) was added in one portion and the reaction was stirred at 90 °C for 48 h. The reaction was allowed to cool down to room temperature and filtered through a plug of Celite. The Zn-residue was washed several times with toluene (ca. 150 mL) in the sintered funnel until the filtrate did not show any significant yellow colouring. The organic solvents were removed under reduced pressure and the crude was transferred into a 50 mL round-bottom

flask for distillation. The crude was distilled *in vacuo* using a micro-distillation apparatus and the collection flask was cooled in an ice bath. Remaining solvent residues were removed at a head temperature of 40-50 °C (bottom temp. 85 °C), the product was distilled at a head temperature ranging from 85 °C to 105 °C (bottom temp. 150 °C). The collected product fraction was redistilled under the same conditions to obtain the product as pale-yellow crystals in 38 % yield.

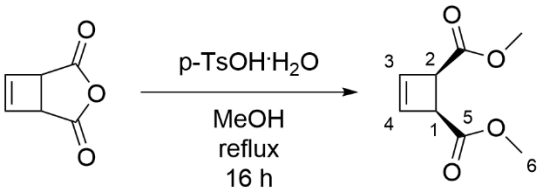
Spectroscopic data is in agreement with literature.[271]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.49 (s, 2H, C(3) –H, C(4) –H), 4.05 (s, 2H, C(1) –H, C(2) –H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 167.8 (C(5), C(6)), 139.5 (C(3), C(4)), 47.8 (C(1), C(2)).

m.p.: 88-89 °C

*Synthesis of cis-dimethyl cyclobut-3-ene-1,2-dicarboxylate (**23**)*



A flame-dried 10 mL round-bottom flask was charged with **25** (496.4 mg, 4.0 mmol, 1.0 equiv.) in 5 mL anhydrous MeOH. To this solution, *p*-TsOH monohydrate (22.8 mg, 0.12 mmol, 0.03 equiv.) was added and the reaction was stirred at reflux overnight for 16 h. Then, the reaction was allowed to cool down to room temperature, the solvent was removed under reduced pressure and the residue was taken up in CH_2Cl_2. This organic layer was neutralised with saturated $NaHCO_3$ solution and washed with brine three times, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The crude was purified by automated medium pressure liquid chromatography (hexane/EtOAc 90/10 to 50/50) to obtain the product in 42 % yield as a yellow oil.

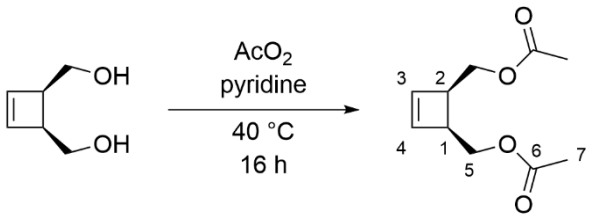
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.26 (s, 2H, C(3)–H, C(4)–H), 3.93 (s, 2H, C(1)–H, C(2)–H), 3.69 (s, 6H, 2x C(6)–H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.3 (2x C(5)), 136.8 (C(3), C(4)), 52.1 (2x C(6)), 49.1 (C(1), C(2)).

HRMS (ESI): m/z calcd for $C_8H_{10}O_4Na^+$ $[M+Na]^+$ 193.0471; found 193.0474.

IR ($CHCl_3$ film): 3648 (w), 2981 (m), 1731 (s), 1436 (m), 1338 (m), 1268 (m), 1198 (m), 1165 (s), 1112 (m), 1031 (m), 956 (w), 793 (m), 772 (m), 668 (w) cm^{-1}.

*Synthesis of cis-Cyclobut-3-ene-1,2-diylbis(methylene) diacetate (**30**)*



Adapting a reported procedure,[272] a 10 mL round-bottom flask was charged with **31** (1.14 g, 10.0 mmol, 1.0 equiv.), acetic anhydride (2.84 mL, 30.0 mmol, 3.0 equiv.), and pyridine (3.2 mL, 40.0 mmol, 4.0 equiv.). The reaction was stirred neat overnight for 16 h at room temperature. Then, the reaction was diluted with a solution 30 % 2-propanol/CH_2Cl_2 (5 mL), quenched by addition of saturated $NaHCO_3$ solution (ca. 5 mL) until organic layer indicates pH 6-7 on pH-paper, extracted with 30 % 2-propanol/CH_2Cl_2 (20 mL), the combined organic layers were washed once with a 1 M HCl solution (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by automated medium pressure liquid chromatography (hexane/Et_2O = 100/0 to 40/60) to yield the product in 71 % (1.41 g) as a colourless oil.

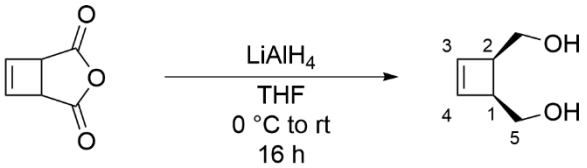
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.12 (s, 2H, C(3) –H, C(4) –H), 4.24 – 4.18 (m, 4H, 2x C(5) –H_2), 3.30 – 3.21 (m, 2H, C(1) –H, C(2) –H), 2.05 (s, 6H, 2x C(7) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.1 (2x C(6)), 138.0 (C(3), C(4)), 64.1 (2x C(5)), 44.5 (C(1), C(2)), 21.1 (2x C(7)).

HRMS (ESI): m/z calcd for $C_{10}H_{14}O_4Na^+$ $[M+Na]^+$ 221.0784; found 221.0786.

IR ($CHCl_3$ film): 2904 (w), 1738 (s), 1385 (w), 1365 (w), 1227 (s), 1033 (m), 973 (w), 740 (w) cm^{-1}.

*Synthesis of cis-cyclobut-3-ene-1,2-dimethanol (**31**)*



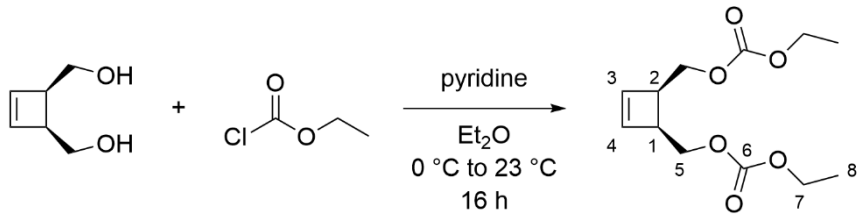
A flame dried 250 mL round-bottom flask was charged with $LiAlH_4$ (10.0 mL, 24.0 mmol, 2.4 M in THF, 1.1 equiv.) in 60 mL anhydrous THF and stirred at 0 °C. To this solution, **25** (2.7 g, 21.8 mmol, 1.0 equiv.) in 10 mL anhydrous THF was added *dropwise* and the reaction was allowed to warm up to room temperature while stirring overnight for 16 h. The reaction was cooled down to 0 °C and *carefully* quenched with 0.9 mL H_2O, 0.9 mL 15 w% NaOH solution, and 2.7 mL H_2O (Fieser workup), stirred at room temperature for 30 min. The precipitate was filtrated off and stirred in 40 mL THF at 40 °C for 2 h and subsequently filtrated again, the combined organic solvents were dried over $MgSO_4$, filtrated, and removed under reduced pressure. The crude was purified by automated medium pressure liquid chromatography (hexane/Et_2O = 50/50 to 0/100) to give the product in 66 % yield as a colourless oil.

Spectroscopic data is in agreement with literature.[273]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.04 (s, 2H, C(3) –H, C(4) –H), 3.85 (broad d, J = 11.4 Hz, 2H, 2x C(5) –H,, 3.73 (broad t, J = 11.0 Hz, 2H, 2x C(5) –H), 3.28 – 3.20 (m, 2H, C(1) –H, C(2) –H), 3.00 (broad s, 2H, 2x O–H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 137.5 (C(3), C(4)), 62.2 (2x C(5)), 48.4 (C(1), C(2)).

*Synthesis of cis-cyclobut-3-ene-1,2-diylbis(methylene) diethyl bis(carbonate) (**33**)*



A flame-dried 25 mL round-bottom flask was charged with **31** (171.2 mg, 1.5 mmol, 1.0 equiv.) in 10 mL anhydrous Et_2O and cooled to 0 °C. To this solution, pyridine (0.48 mL, 6.0 mmol, 4.0 equiv.) was added and the reaction was stirred for 15 min at 0 °C. Then, ethyl chloroformate (0.43 mL, 4.5 mmol, 3.0 equiv.) was added *dropwise* at 0 °C and the reaction was allowed to warm to room temperature while stirring overnight for 16 h. The reaction mixture, which formed colourless precipitate, was diluted with Et_2O (20 mL), washed with 1M HCl solution (2x15 mL) and H_2O (20mL), the combined organic layers were dried over $MgSO_4$, filtrated, and removed under reduced pressure. The crude was purified by automated medium pressure liquid chromatography (hexane/Et_2O = 100/0 to 50/50) to give the product in 72 % yield as a colourless oil.

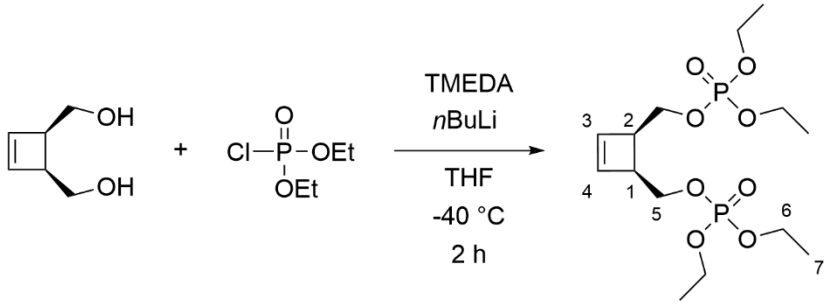
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.15 (s, 2H, C(3) –H, C(4) –H), 4.33 – 4.23 (m, 4H, 2x C(5) –H_2), 4.19 (q, J = 7.1 Hz, 4H, 2x C(7) –H_2), 3.35 – 3.27 (m, 2H, C(1) –H, C(2) –H), 1.31 (t, J = 7.1 Hz, 6H, 2x C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 155.2 (2x C(6)), 138.0 (C(3), C(4)), 67.3 (2x C(5)), 64.2 (2x C(7)), 44.4 (C(1), C(2)), 14.4 (2x C(8)).

HRMS (ESI): m/z calcd for $C_{12}H_{18}O_6Na^+$ $[M+Na]^+$ 281.0996; found 281.0997.

IR ($CHCl_3$ film): 2984 (w), 1744 (s), 1468 (w), 1385 (w), 1367 (w), 1247 (s), 1009 (m), 876 (w), 790 (w), 743 (w) cm^{-1}.

*Synthesis of cis-cyclobut-3-ene-1,2-diylbis(methylene) tetraethyl bis(phosphate) (**34**)*



A flame-dried 25 mL round-bottom flask was charged with **31** (228.3 mg, 2.0 mmol, 1.0 equiv.) and TMEDA (3.0 mL) in 12 mL anhydrous THF. The solution was cooled down to -40 °C using a MeCN/CO_2 cooling bath, n-Buli (2.0 mL, 5.0 mmol, 2.5 equiv. 2.5 M in hexanes) was added *dropwise*, and the reaction was stirred at -40 °C for 10 min. Then, diethyl chlorophosphate (0.87 mL, 6.0 mmol, 3.0 equiv.) was added *dropwise* to the reaction, which was stirred at -40 °C for 2 h and was then allowed to warm to room temperature. The reaction was *carefully* quenched with approx. 2 mL brine and was subsequently poured over 10 mL H_2O. The aqueous phase was extracted with CH_2Cl_2 (3x15 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The crude was purified by automated medium pressure liquid chromatography (EtOAc/MeOH =100/0 to 97/3) to give the product in 59 % yield as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.19 (s, 2H, C(3)–H, C(4)–H), 4.23 – 4.14 (m, 4H, 2x C(5)–H_2), 4.14 – 4.06 (m, 8H, 4x C(6)–H_2), 3.36 – 3.27 (m, 2H, C(1) –H, C(2) –H), 1.34 (t, J = 7.1 Hz, 12H, 4x C(7) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 138.7 (C(3), C(4)), 67.3 (2x C(5)), 63.9 (4x C(6), 45.5 (C(1), C(2)), 16.3 (4x C(7), C(12)).

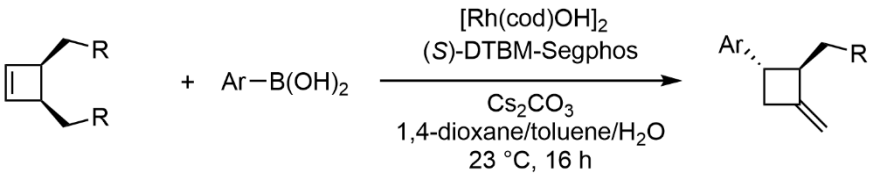
^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm): -0.94 (s, 2x $P(O)(OR)_3$).

HRMS (ESI): m/z calcd for $C_{14}H_{28}O_8P_2Na^+$ $[M+Na]^+$ 409.1152; found 409.1153.

IR ($CHCl_3$ film): 3492 (w), 2987 (w), 2909 (w), 1394 (w), 1264 (m), 1166 (w), 1025 (s), 819 (w), 744 (w), 607 (w) cm^{-1}.

Procedures for Rhodium Catalysed Reactions

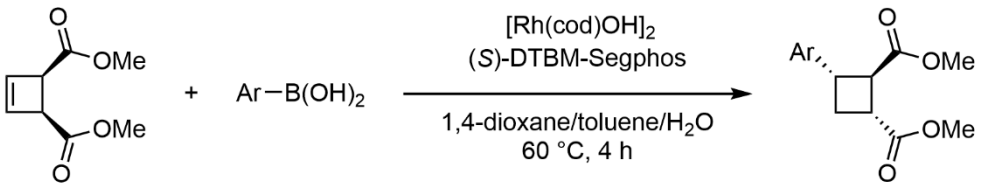
General Procedure 2: Asymmetric remote homo-allylic substitution reaction



A stock solution of the rhodium hydroxy phosphine complex was prepared in a flame-dried 10 mL round-bottom flask by stirring a solution of $[Rh(cod)(OH)]_2$ (15.96 mg, 0.035 mmol, 2.5 mol%) and (*S*)-DTBM-Segphos (99.1 mg, 0.084 mmol, 6.0 mol%) in anhydrous 1,4-dioxane (7.0 mL) under an Argon atmosphere at 60 °C for 30 min. (*This solution was used for three asymmetric reactions on 0.4 mmol scale*.)

A portion of the resulting dark red solution (2.0 mL; 0.05 equiv. [Rh]) was transferred *via* syringe to a flame-dried 10 mL round-bottom flask, containing a mixture of boronic acid (0.80 mmol, 2.0 equiv.), Cs_2CO_3 (130.3 mg, 0.4 mmol, 1.0 equiv.) and alkene (0.4 mmol, 1.0 equiv.) in anhydrous toluene (2.0 mL) and H_2O (0.080 mL). The resulting mixture was stirred at 23 °C for 16 h. Then, the reaction was quenched by addition of 2 mL hexane under ambient atmosphere and concentrated under reduced pressure. The crude mixture was directly loaded on a silica gel column and was purified by automated medium pressure liquid chromatography eluted with the indicated solvent mixtures to afford the desired product.

General procedure 3: Asymmetric 1,5-addition reaction



The experiment was performed as in *General procedure 2*, but without addition of Cs_2CO_3 to the alkene mixture. Instead at 23 °C for 16 h, the reaction was stirred at 60 °C for 4 h.

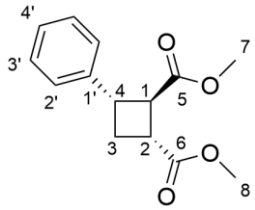
Racemates of remote substitution and 1,5-addition products

Racemic samples were synthesized using (±)-BINAP or (±)-Segphos on 0.1 mmol scale according to either *General Procedure 2* or *3* at 60 °C for 16 h.

Assignment of absolute configuration

The absolute configuration of compounds in this section has been assigned according to the sign of optical rotation and in analogy to structures reported in G. Steiner, R. Munschauer, G. Klebe, L. Siggel, *Heterocycles* **1995**, *40*, 319-330. Experiments to synthesise comparable bicyclic structures were carried out by F. Wieland Goetzke.

*Synthesis of dimethyl (1R,2R,3S)-3-phenylcyclobutane-1,2-dicarboxylate (**26**)*



The corresponding compound was prepared following *General procedure 3* using phenylboronic acid and *cis*-dimethyl cyclobut-3-ene-1,2-dicarboxylate **23** as starting materials, with the following modification: After addition of the catalyst solution, the resulting mixture was stirred at 60 °C for 4 h.

Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a yellow oil in a combined 74 % yield (73 mg, dr. >20:1). SFC analysis for the major diastereomer indicated an enantiomeric ratio of 93.5:6.5. An additional minor diastereomer was observed but could not be isolated in pure form. For this diastereomer, SFC analysis indicated an enantiomeric ratio of 84.5:15.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.36 – 7.26 (m, 4H, 2x arom. C(2') –H, 2x arom. C(3') –H), 7.26 – 7.21 (m, 1H, arom. C(4') –H), 3.72 (d, J = 1.6 Hz, 6H, C(7) –H_3, C(8) –H_3), 3.64 (q, J = 9.5 Hz, 1H, C(4) –H), 3.50 (t, J = 9.6 Hz, 1H, C(1) –H), 3.44 – 3.35 (m, 1H, C(2) –H), 2.62 (dtd, J = 10.8, 8.5, 0.7 Hz, 1H, 1x C(3) –H), 2.34 (dt, J = 10.9, 10.0 Hz, 1H, 1x C(3) –H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.75 (C(6)), 173.26 (C(5)), 142.3 (C(1')), 128.7 (2x C(3')), 127.0 (C(4')) 126.7 (2x C(2')), 52.2 (d, J = 2.4 Hz, C(7), C(8)), 47.8 (C(1)), 39.8 (C(4)), 37.0 (C(2)), 29.5 (C(3)).

SFC: Major diastereomer: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 94.0:6.0 er (major enantiomer t_R = 2.22 min, minor enantiomer t_R = 2.13 min).

Minor diastereomer: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 84.5:15.5 er (major enantiomer t_R = 3.35 min, minor enantiomer t_R = 2.98 min).

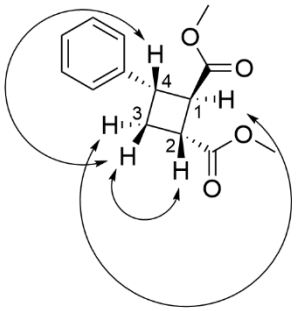
HRMS (ESI): m/z calcd for $C_{14}H_{16}O_4Na^+$ $[M+Na]^+$ 271.0941; found 271.0942.

IR ($CHCl_3$ film): 2953 (w), 1731 (s), 1497 (w), 1436 (m), 1391 (w), 1323 (w), 1233 (m), 1203 (m), 1174 (m), 1030 (w), 754 (w), 700 (w) cm^{-1}.

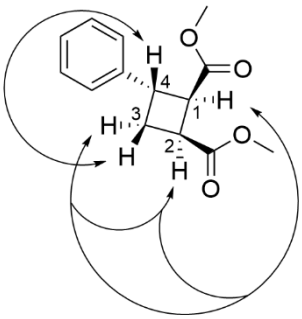
$[\alpha]^{25}_D$ = +34.0 (c = 1.0, $CHCl_3$).

Relative Stereochemistry *via* NOEs:

Major diastereomer:



Minor diastereomer:



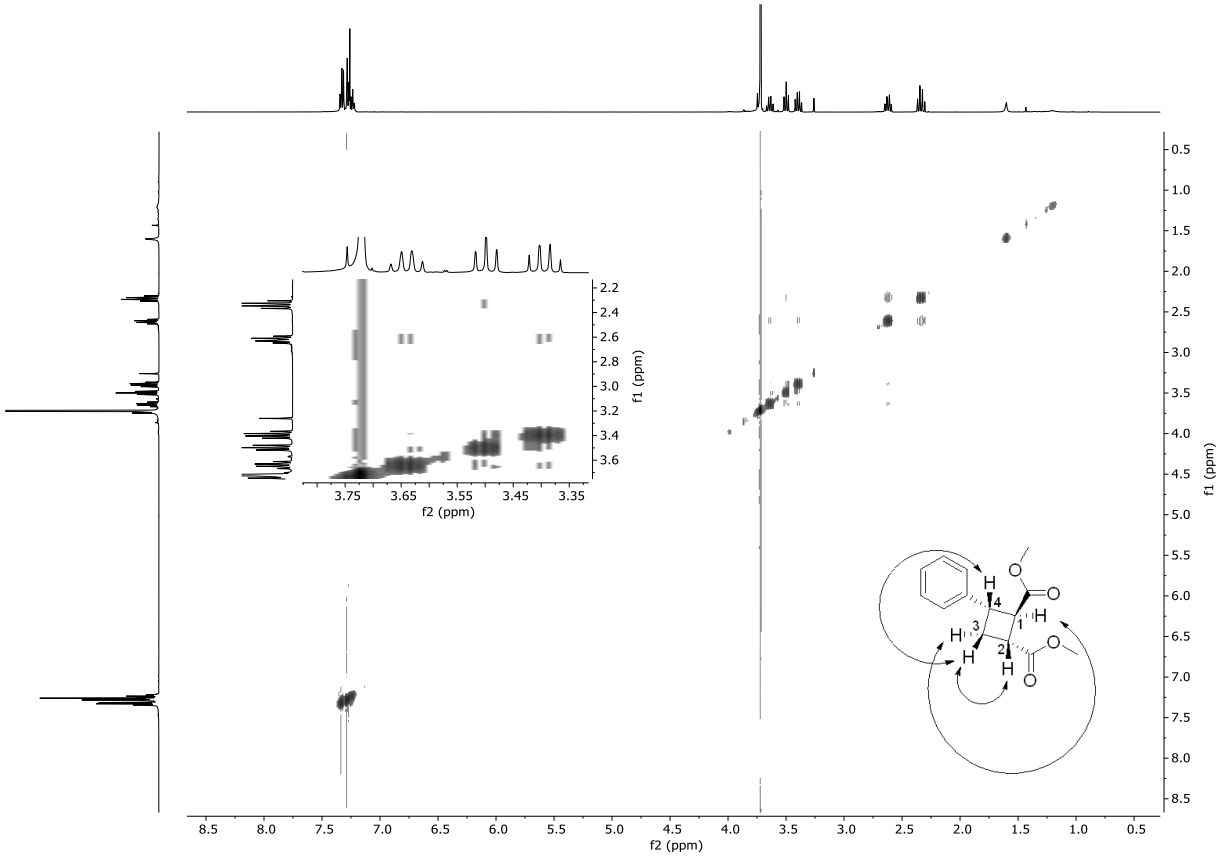


Figure S 2: ^{1}H-^{1}H-NOE (500 MHz, $CDCl_3$) spectra of **26-major diastereomer** recorded at 298 K.

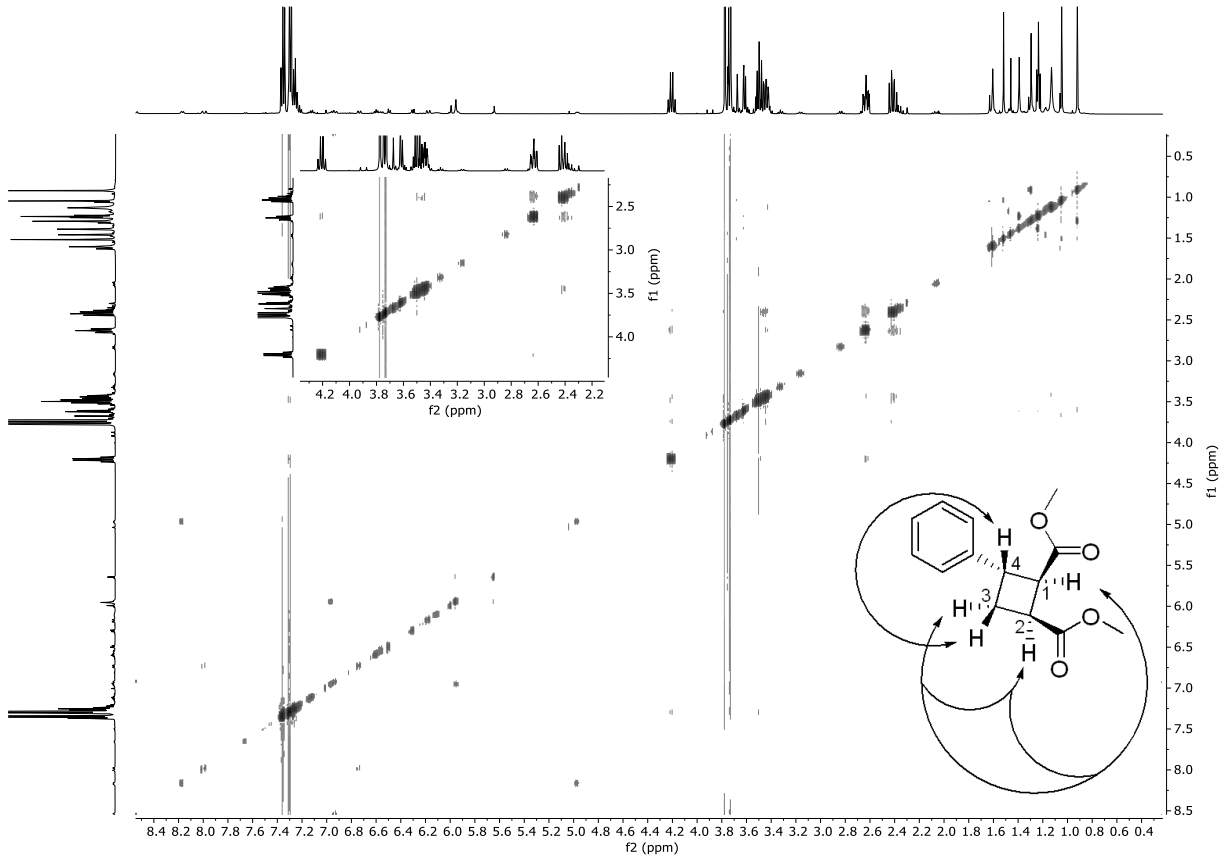
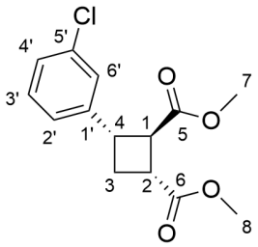


Figure S 3: ^{1}H-^{1}H-NOE (500 MHz, $CDCl_3$) spectra of **26-minor diastereomer** recorded at 298 K.

*Synthesis of dimethyl (1R,2R,3S)-3-(3-chlorophenyl)cyclobutane-1,2-dicarboxylate (**27**)*



The corresponding compound was prepared following *General procedure 3* using (3-chlorophenyl)boronic acid and *cis*-dimethyl cyclobut-3-ene-1,2-dicarboxylate **23** as starting materials, with the following modification: After addition of the catalyst solution, the resulting mixture was stirred at 60 °C for 4 h.

Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a pale-yellow oil in a combined 58 % yield (66 mg, dr. 15:1). SFC analysis for the major diastereomer indicated an enantiomeric ratio of 96.0:4.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.28 – 7.23 (m, 2H, C(3') –H, C(4') –H), 7.21 (dt, J = 8.2, 1.7 Hz, 1H, C(6') –H), 7.16 (ddt, J = 7.7, 2.3, 1.1 Hz, 1H, C(2') –H), 3.73 (d, J = 1.1 Hz, 6H, C(7) –H_3, C(8) –H_3), 3.61 (q, J = 9.4 Hz, 1H, C(4) –H), 3.47 (t, J = 9.4 Hz, 1H, C(1) –H), 3.42 – 3.34 (m, 1H, C(2) –H), 2.65 – 2.57 (m, 1H, 1x C(3) –H), 2.36 – 2.25 (m, 1H, 1x C(3) –H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.5 (C(6)), 172.9 (C(5)), 144.4 (C(1')), 134.6 (C(5')), 130.0 (C(3')), 127.17 (C(6')), 126.95 (C(4')), 124.9 (C(2')), 52.28 (d, J = 5.2 Hz, C(7), C(8)), 47.6 (C(1)), 39.3 (C(4)), 36.9 (C(2)), 29.3 (C(3)).

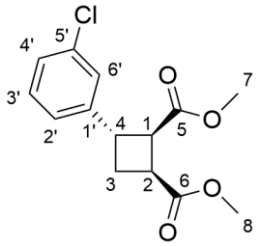
SFC: Chiralpak® ID, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % MeOH isocratic for 5 min, 96.0:4.0 er (major enantiomer t_R = 3.12 min, minor enantiomer t_R = 3.54 min).

HRMS (ESI): m/z calcd for $C_{14}H_{15}ClO_4Na^+$ $[M+Na]^+$ 305.0551; found 305.0551.

IR ($CHCl_3$ film): 2953 (w), 1731 (s), 1598 (w), 1572 (w), 1436 (m), 1388 (w), 1319 (w), 1234 (m), 1203 (m), 1083 (w), 1031 (w), 909 (w), 786 (w), 732 (w), 692 (w) cm^{-1}.

$[\alpha]^{25}_{D}$ = +42.4 (c = 1.0, $CHCl_3$).

*Synthesis of dimethyl (1S,2R,3S)-3-(3-chlorophenyl)cyclobutane-1,2-dicarboxylate (**S2**)*



The corresponding compound was prepared following *General procedure 2* using (3-chlorophenyl)boronic acid and *cis*-dimethyl cyclobut-3-ene-1,2-dicarboxylate **23** as starting materials, with the following modification: After addition of the catalyst solution, the resulting mixture was stirred at 60 °C for 4 h.

Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 21 % yield (24 mg). SFC analysis for the indicated an enantiomeric ratio of 92.5:7.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.28 – 7.22 (m, 2H, C(3') –H, C(4') –H), 7.22 – 7.17 (m, 1H, C(6') –H), 7.17 – 7.11 (m, 1H, C(2') –H), 4.22 – 4.12 (m, 1H, C(4) –H), 3.74 (s, 3H, C(8) –H_3), 3.71 (s, 3H, C(7) –H_3), 3.48 – 3.36 (m, 2H, C(1) –H, C(2) –H), 2.63 – 2.53 (m, 1H, 1x C(3) –H), 2.41 – 2.31 (m, 1H, 1x C(3) –H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 174.1 (C(6)), 172.3 (C(5)), 145.0 (C(1')), 134.6 (C(5')), 129.9 (C(3')), 127.0 (C(6')), 126.7 (C(4')), 124.8 (C(2')), 52.25 (C(6)), 52.12 (C(5)), 47.0 (C(1)), 40.3 (C(4)), 38.2 (C(2)), 28.2 (C(3)).

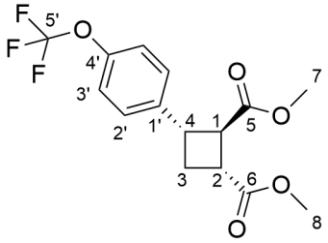
SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 92.5:7.5 er (major enantiomer t_R = 3.60 min, minor enantiomer t_R = 3.13 min).

HRMS (ESI): m/z calcd for $C_{14}H_{15}ClO_4Na^+$ $[M+Na]^+$ 305.0551; found 305.0551.

IR ($CHCl_3$ film): 2952 (w), 1736 (s), 1598 (w), 1571 (w), 1478 (w), 1436 (m), 1364 (m), 1204 (m), 1166 (m), 1072 (w), 1035 (w), 784 (w), 693 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +70.6 (c = 1.0, $CHCl_3$).

*Synthesis of dimethyl (1R,2R,3S)-3-(4-(trifluoromethoxy)phenyl)cyclobutane-1,2-dicarboxylate (**28**)*



The corresponding compound was prepared following *General procedure 3* using (4-(trifluoromethoxy)phenyl)boronic acid and *cis*-dimethyl cyclobut-3-ene-1,2-dicarboxylate **23** as starting materials, with the following modification: After addition of the catalyst solution, the resulting mixture was stirred at 60 °C for 4 h.

Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a pale-yellow oil in a combined 40 % yield (53 mg, dr. 5.5:1). SFC analysis for the major diastereomer indicated an enantiomeric ratio of 96.0:4.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.33 – 7.27 (m, 2H, 2x arom. C(2') –H), 7.20 – 7.13 (m, 2H, 2x arom. C(3') –H), 3.73 (d, J = 0.8 Hz, 6H, C(7) –H_3, C(8) –H_3), 3.64 (q, J = 9.3 Hz, 1H, C(4) –H), 3.50 – 3.35 (m, 2H, C(1) –H, C(2) –H), 2.69 – 2.58 (m, 1H, 1x C(3) –H), 2.31 (dt, J = 10.9, 10.0 Hz, 1H, 1x C(3) –H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.61 (C(6)), 172.98 (C(5)), 148.2 (d, J = 1.6 Hz, C(4')), 141.1 (C(1')), 128.1 (2x C(2')), 124.9 (d, J = 805.1 Hz, C(5')), 121.2 (2x C(3')), 52.3 (d, J = 4.3 Hz, C(7), C(8)), 47.8 (C(1)), 39.1 (C(4)), 36.9 (C(2)), 29.5 (C(3)).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -57.92 (s, C(5') $–F_3$), minor diastereomer: -57.97 (s, C(5') $–F_3$).

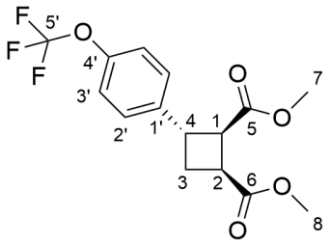
SFC: Chiralpak® IC, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % MeOH isocratic for 5 min, 96.0:4.0 er (major enantiomer t_R = 1.80 min, minor enantiomer t_R = 2.01 min).

HRMS (ESI): m/z calcd for $C_{15}H_{15}F_3O_5Na^+$ $[M+Na]^+$ 355.0764; found 355.0764.

IR ($CHCl_3$ film): 2955 (w), 1732 (s), 1511 (w), 1438 (w), 1259 (s), 1203 (s), 1162 (s), 1113 (w), 1019 (w), 922 (w), 854 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +28.2 (c = 1.0, $CHCl_3$).

*Synthesis of dimethyl (1S,2R,3S)-3-(4-(trifluoromethoxy)phenyl)cyclobutane-1,2-dicarboxylate (**S3**)*



The corresponding compound was prepared following *General procedure 3* using (4-(trifluoromethoxy)phenyl)boronic acid and cis-dimethyl cyclobut-3-ene-1,2-dicarboxylate **23** as starting materials, with the following modification: After addition of the catalyst solution, the resulting mixture was stirred at 60 °C for 4 h.

Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 38 % yield (50 mg). SFC analysis indicated an enantiomeric ratio of 96.0:4.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.32 – 7.25 (m, 2H, 2x arom. C(2') –H), 7.21 – 7.11 (m, 2H, 2x arom. C(3') –H), 4.25 – 4.14 (m, 1H, C(4) –H), 3.74 (s, 3H, C(8) $–H_3$), 3.70 (s, 3H, C(7)

–H_3), 3.47 – 3.36 (m, 2H, C(1) –H, C(2) –H), 2.58 (ddd, J = 11.3, 9.3, 2.1 Hz, 1H, 1x C(3) –H), 2.41 – 2.30 (m, 1H, 1x C(3) –H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 174.1 (C(6)), 172.3 (C(5)), 148.0 (d, J = 1.9 Hz, C(4')), 141.7 (C(1')), 127.9 (2x C(2')), 121.2 (2x C(3')), 120.6 (d, J = 256.8 Hz, C(5')), 52.20 (C(8)), 52.05 (C(7)), 47.2 (C(1)), 40.1 (C(4)), 38.2 (C(2)), 28.3 (C(3)).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -57.95 (s, C(5') –F_3).

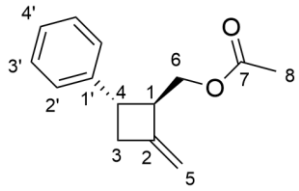
SFC: Chiralpak® IF, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % MeOH isocratic for 5 min, 96.0:4.0 er (major enantiomer t_R = 3.20 min, minor enantiomer t_R = 2.99 min).

HRMS (ESI): m/z calcd for $C_{15}H_{15}F_3O_5Na^+$ $[M+Na]^+$ 355.0764; found 355.0764.

IR ($CHCl_3$ film): 2954 (w), 1737 (s), 1510 (w), 1437 (w), 1365 (w), 1261 (s), 1202 (s), 1163 (s), 1072 (w), 1020 (w), 967 (w), 922 (w), 840 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +48.3 (c = 1.0, $CHCl_3$).

*Synthesis of ((1R,4S)-2-methylene-4-phenylcyclobutyl)methyl acetate (**32a**)*



The corresponding compound was prepared following *General procedure 2* using phenylboronic acid and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a pale-yellow oil in 79 % yield (68 mg). SFC analysis indicated an enantiomeric ratio of 98.5:1.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.37 – 7.26 (m, 4H, 2x arom. C(2') –H, 2x arom. C(3') –H), 7.25 – 7.18 (m, 1H, arom. C(4') –H), 4.96 – 4.89 (m, 2H, C(5) –H_2), 4.35 – 4.22 (m, 2H, C(6) –H_2), 3.39 – 3.27 (m, 2H, C(1) –H, C(4) –H), 3.05 (ddt, J = 15.2, 6.1, 1.9 Hz, 1H, 1x C(3) –H), 2.84 (ddt, J = 15.1, 7.6, 2.7 Hz, 1H, 1x C(3) –H), 2.03 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.2 (C(7)), 146.3 (C(2)), 144.1 (C(1')), 128.6 (2x C(3')), 126.75 (2x C(2')), 126.45 (C(4')), 106.1 (C(5)), 65.8 (C(6)), 50.8 (C(1)), 39.9 (C(4)), 37.2 (C(3)) 21.0 (C(8)).

SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 98.5:1.5 er (major enantiomer t_R = 1.57 min, minor enantiomer t_R = 1.67 min).

HRMS (ESI): m/z calcd for $C_{12}H_{13}^+$ $[M\text{-}OAc^-]^+$ 157.1012; found 157.1013.

IR ($CHCl_3$ film): 2956 (w), 1740 (s), 1679 (w), 1603 (w), 1496 (w), 1454 (w), 1382 (w), 1365 (w), 1234 (s), 1033 (m), 883 (w), 752 (m), 699 (m) cm^{-1}.

$[\alpha]^{25}_D$ = +66.3 (c = 1.0, $CHCl_3$).

Relative Stereochemistry *via* NOEs:

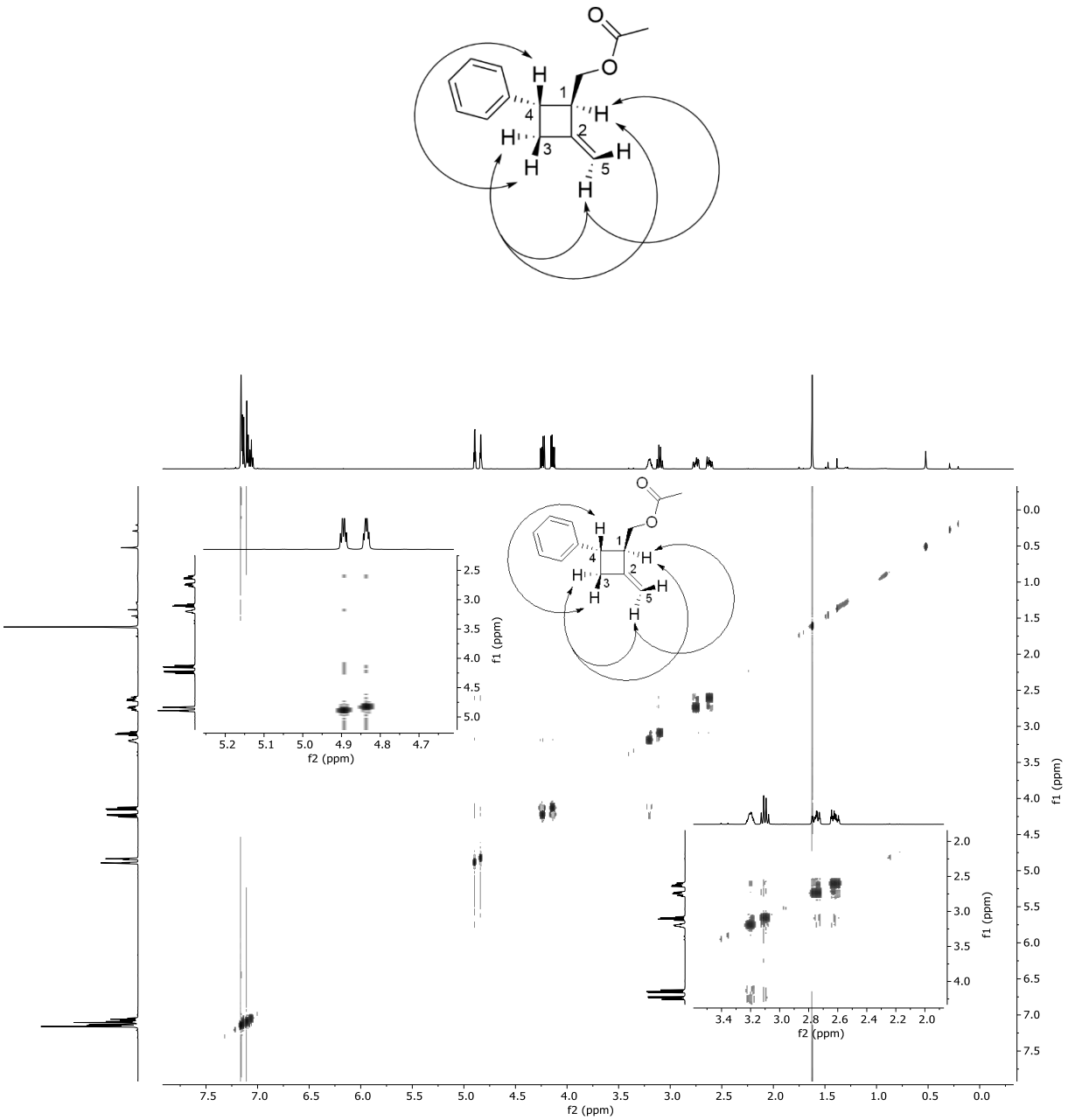
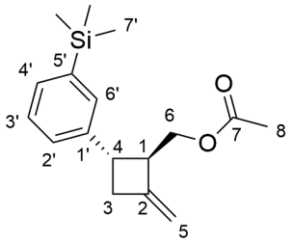


Figure S 4: ^{1}H-^{1}H-NOE (500 MHz, C_6D_6) spectra of **32a** recorded at 298 K.

*Synthesis of (1R,4S)-2-methylene-4-(3-(trimethylsilyl)phenyl)cyclobutyl methyl acetate (**32b**)*



The corresponding compound was prepared following *General procedure 2* using (3-(trimethylsilyl)phenyl)boronic acid and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 58 % yield (67 mg). SFC analysis indicated an enantiomeric ratio of 98.0:2.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.42 – 7.36 (m, 2H, arom. C(2') –H, arom. C(4') –H), 7.35 – 7.30 (m, 1H, arom. C(3') –H), 7.28 (dt, J = 7.6, 1.6 Hz, 1H, arom. C(6') –H), 4.96 – 4.90 (m, 2H, C(5) –H_2), 4.35 – 4.23 (m, 2H, C(6) –H_2), 3.41 – 3.27 (m, 2H, C(1) –H, C(4) –H), 3.06 (ddt, J = 15.1, 6.2, 2.2 Hz, 1H, 1x C(3) –H), 2.86 (ddt, J = 15.0, 7.6, 2.8 Hz, 1H, 1x (C(3) –H), 2.03 (s, 3H, C(8) –H_3), 0.28 (s, 9H, 3x (C(7') –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.2 (C(7)), 146.4 (C(2)), 143.2 (C(1')), 140.8 (C(5')), 131.69 (C(2')), 131.49 (C(4')), 128.0 (C(3')), 127.2 (C(6')), 106.1 (C(5)), 65.9 (C(6)), 50.8 (C(1)), 40.0 (C(4)), 37.2 (C(3)), 21.1 (C(8)), -0.9 (3x C(7')).

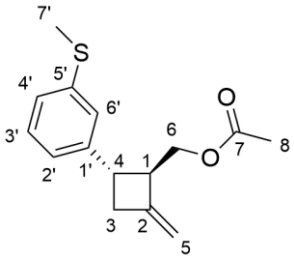
SFC: Chiralpak® IF, 1500 psi, 30 °C; flow: 0.5 mL/min; 0 % MeOH for 4 min, 0 % to 1 % MeOH over 9 min, 98.0:2.0 er (major enantiomer t_R = 12.73 min, minor enantiomer t_R = 12.27 min).

HRMS (ESI): m/z calcd for $C_{17}H_{24}O_2SiNa^+$ $[M+Na]^+$ 311.1438; found 311.1438.

IR ($CHCl_3$ film): 2955 (w), 1742 (s), 1678 (w), 1383 (w), 1364 (w), 1234 (s), 1120 (w), 1034 (m), 838 (s), 790 (w), 753 (m), 693 (w), 621 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +50.2 (c = 1.0, $CHCl_3$).

*Synthesis of (1R,4S)-2-methylene-4-(3-(methylthio)phenyl)cyclobutyl)methyl acetate (**32c**)*



The corresponding compound was prepared following *General procedure 2* using (3-(methylthio)phenyl)boronic acid and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 70 % yield (73 mg). SFC analysis indicated an enantiomeric ratio of 98.5:1.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.24 (t, J = 7.6 Hz, 1H, arom. C(3') –H), 7.18 (broad t, J = 1.8 Hz, 1H, arom. C(6')–H), 7.11 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H, arom. C(4') –H), 7.05 (dt, J = 7.6, 0.9 Hz, 1H, arom. C(2') –H), 4.97 – 4.88 (m, 2H, C(5) –H_2), 4.34 – 4.22 (m, 2H, C(6) –H_2), 3.38 – 3.24 (m, 2H, C(1) –H, C(4) –H), 3.09 – 3.00 (m, 1H, 1x C(3) –H), 2.88 – 2.78 (m, 1H, 1x C(3) –H), 2.49 (s, 3H, C(7') –H_3), 2.04 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.2 (C(7)), 146.0 (C(2)), 144.8 (C(5')), 138.7 (C(1')), 129.1 (C(3')), 125.2 (C(6')), 124.6 (C(4')), 123.6 (C(2')), 106.3 (C(5)), 65.7 (C(6)), 50.7 (C(1)), 39.9 (C(4)), 37.0 (C(3)), 21.0 (C(8)), 16.0 (C(7')).

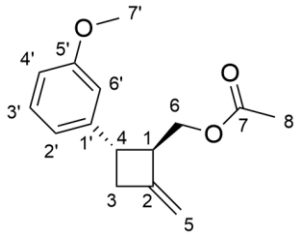
SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 98.5:1.5 er (major enantiomer t_R = 2.51 min, minor enantiomer t_R = 2.39 min).

HRMS (ESI): m/z calcd for $C_{13}H_{15}S^+$ $[M\text{-}OAc^-]^+$ 203.0889; found 203.0892.

IR ($CHCl_3$ film): 2921 (w), 1738 (s), 1678 (w), 1591 (w), 1571 (w), 1436 (w), 1382 (w), 1364 (w), 1235 (s), 1088 (w), 1034 (m), 883 (m), 779 (m), 695 (m) cm^{-1}.

$[\alpha]^{25}_D$ = +50.6 (c = 1.0, $CHCl_3$).

*Synthesis of (1R,4S)-2-(3-methoxyphenyl)-4-methylenecyclobutylmethyl acetate (**32d**)*



The corresponding compound was prepared following *General procedure 2* using (3- methoxyphenyl)boronic acid and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 67 % yield (66 mg). SFC analysis indicated an enantiomeric ratio of 99.0:1.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.24 (t, J = 7.8 Hz, 1H, C(3') –H), 6.90 – 6.80 (m, 2H, arom. C(2') –H, arom. C(6') –H), 6.76 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H, C(4') –H), 4.95 – 4.89 (m, 2H, C(5) –H_2), 4.34 – 4.22 (m, 2H, C(6) –H_2), 3.81 (s, 3H, C(7') –H_3), 3.38 – 3.25 (m, 2H, C(1) –H, C(4) –H), 3.09 – 2.98 (m, 1H, 1x C(3) –H), 2.89 – 2.78 (m, 1H, 1x C(3) –H), 2.04 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.2 (C(7)), 159.9 (C(5')), 146.2 (C(2)), 145.8 (C(1')), 129.6 (C(3')), 119.1 (C(2')), 112.7 (C(6')), 111.6 (C(4')), 106.2 (C(5)), 65.7 (C(6)), 55.3 (C(7')), 50.7 (C(1)), 39.9 (C(4)), 37.1 (C(3)), 21.1 (C(8)).

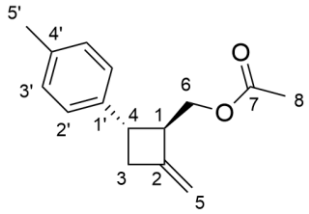
SFC: Chiralpak® IB, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 99.0:1.0 er (major enantiomer t_R = 1.56 min, minor enantiomer t_R = 1.70 min).

HRMS (ESI): m/z calcd for $C_{15}H_{18}O_3Na^+$ $[M+Na]^+$ 269.1148; found 269.1150.

IR ($CHCl_3$ film): 2950 (w), 1738 (s), 1678 (w), 1601 (w), 1584 (w), 1490 (w), 1454 (w) 1435 (w), 1382 (w), 1364 (w), 1289 (w), 1235 (s), 1159 (w), 1036 (m), 882 (w), 779 (w), 696 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +61.6 (c = 1.0, $CHCl_3$).

*Synthesis of (1R,4S)-2-methylene-4-(4-tolyl)cyclobutyl)methyl acetate (**32e**)*



The corresponding compound was prepared following *General procedure 2* using (4-methylphenyl)boronic acid and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 68 % yield (63 mg). SFC analysis indicated an enantiomeric ratio of 98.5:1.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.20 – 7.08 (m, 4H, 2x arom. C(2') –H, 2x arom. C(3') –H), 4.96 – 4.88 (m, 2H, C(5) –H_2), 4.34 – 4.21 (m, 2H C(6) –H_2), 3.36 – 3.22 (m, 2H, C(1) –H, C(4) –H), 3.07 – 2.98 (m, 1H, 1x C(3) –H), 2.86 – 2.77 (m, 1H, 1x C(3) –H), 2.33 (s, 3H, C(5') –H_3), 2.03 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.2 (C(7)), 146.5 (C(2)), 141.1 (C(4')), 136.0 (C(1')), 129.2 (2x C(3')), 126.6 (2x C(2')), 106.0 (C(5)), 65.8 (C(6)), 50.9 (C(1)), 39.5 (C(4)), 37.3 (C(3)), 21.1 (C(5')), 21.1 (C(8)).

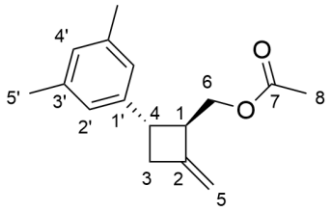
SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 98.5:1.5 er (major enantiomer t_R = 1.72 min, minor enantiomer t_R = 1.85 min).

HRMS (ESI): m/z calcd for $C_{15}H_{18}O_2Na^+$ $[M+Na]^+$ 253.1199; found 253.1201.

IR ($CHCl_3$ film): 3022 (w), 2921 (w), 1740 (s), 1678 (w), 1516 (w), 1433 (w), 1364 (w), 1234 (s), 1034 (m), 882 (m), 809 (m) cm^{-1}.

$[\alpha]^{25}_D$ = +62.8 (c = 1.0, $CHCl_3$).

*Synthesis of (1R,2S)-2-(3,5-dimethylphenyl)-4-methylenecyclobutylmethyl acetate (**32f**)*



The corresponding compound was prepared following *General procedure 2* using (3,5-dimethylphenyl)boronic acid and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 76 % yield (74 mg). SFC analysis indicated an enantiomeric ratio of 97.5:2.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.96 – 6.80 (m, 3H, 2x arom. C(2') –H, arom. C(4') –H), 4.96 – 4.88 (m, 2H, C(5) –H_2), 4.35 – 4.20 (m, 2H, C(6) –H_2), 3.36 – 3.20 (m, 2H, C(1) –H, C(4) –H), 3.01 (ddtd, J = 15.0, 8.4, 2.3, 1.6 Hz, 1H, 1x C(3) –H), 2.88 – 2.77 (m, 1H, 1x C(3) –H), 2.31 (d, J = 0.8 Hz, 6H, 2x C(5') –H_3), 2.04 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.2 (C(7)), 146.6 (C(2)), 144.0 (2x C(3'), 138.1 (C(1')), 128.1 (C(4')), 124.6 (2x C(2')), 106.0 (C(5)), 65.7 (C(6)), 50.7 (C(1)), 39.7 (C(4)), 37.1 (C(3)), 21.5 (2x C(5'), 21.0 (C(8)).

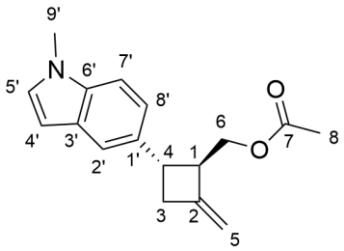
SFC: Chiralpak® IF, 1500 psi, 30 °C; flow: 1.0 mL/min; 0 % MeOH for 4 min, 0 % to 1 % MeOH over 9 min, 97.5:2.5 er (major enantiomer t_R = 9.14 min, minor enantiomer t_R = 8.90 min).

HRMS (ESI): m/z calcd for $C_{16}H_{20}O_2Na^+$ $[M+Na]^+$ 267.1356; found 267.1358.

IR ($CHCl_3$ film): 2918 (w), 1740 (s), 1678 (w), 1678 (w), 1604 (w), 1459 (w), 1381 (w), 1364 (w), 2333 (s), 1034 (m), 881 (s), 844 (s), 700 (s) cm^{-1}.

$[\alpha]^{25}_D$ = +66.4 (c = 1.0, $CHCl_3$).

*Synthesis of (1R,2S)-2-(1-methyl-5-indolyl)-4-methylenecyclobutylmethyl acetate (**32g**)*



The corresponding compound was prepared following a modification of *General procedure 2* using 1-methyl-5-indolyl boronic acid (*210.0 mg, 1.2 mmol, 3.0 equiv.*) and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials at 60 °C. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 63 % yield (68 mg). SFC analysis indicated an enantiomeric ratio of 97.0:3.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.54 – 7.50 (m, 1H, arom. C(2') –H), 7.28 (d, J = 8.5 Hz, 1H, arom. C(8') –H), 7.16 (dd, J = 8.4, 1.7 Hz, 1H. arom. C(7) –H), 7.04 (d, J = 3.0 Hz, 1H, arom C(5') –H), 6.44 (dd, J = 3.1, 0.8 Hz, 1H, arom. C(4') –H), 5.00 – 4.87 (m, 2H, C(5) –H_2), 4.40 – 4.22 (m, 2H, C(6) –H_2), 3.79 (s, 3H, C(9') –H_3), 3.47 – 3.33 (m, 2H, C(1) –H, C(4) –H), 3.07 (dddd, J = 12.6, 8.5, 4.2, 2.1 Hz, 1H, 1x C(3) –H), 2.90 (ddt, J = 15.5, 8.4, 2.8 Hz, 1H, 1x C(3) –H), 2.03 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.3 (C(7)), 147.0 (C(2)), 135.7 (C(6')), 135.0 (C(1')), 129.3 (C(5')), 128.7 (C(3'), 120.8 (C(7')), 118.5 (C(2')), 109.3 (C(8')), 105.7 (C(2)), 100.8 (C(4')), 65.9 (C(6)), 51.3 (C(1)), 40.0 (C(4)), 37.8 (C(3)), 33.0 (C(9')), 21.1 (C(8)).

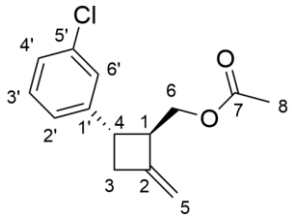
SFC: Chiralpak® ID, 1500 psi, 30 °C; flow: 1.0 mL/min; 0 % MeOH for 3 min, 0 % to 10 % MeOH over 5 min, 97.0:3.0 er (major enantiomer t_R = 7.95 min, minor enantiomer t_R = 8.17 min).

HRMS (ESI): m/z calcd for $C_{17}H_{20}O_2N^+$ $[M+H]^+$ 270.1489; found 270.1489.

IR ($CHCl_3$ film): 2984 (w), 1736 (s), 1677 (w), 1513 (w), 1493 (m), 1447 (w), 1423 (w), 1382 (w), 1363 (m), 1237 (s), 1081 (w), 1033 (m), 978 (w), 882 (m), 798 (m), 762 (w), 720 (m), 632 (w) cm^{-1}.

$[\alpha]^{25}_{D}$ = +81.8 (c = 1.0, $CHCl_3$).

*Synthesis of (1R,2S)-2-(3-chlorophenyl)-4-methylenecyclobutylmethyl acetate (**32h**)*



The corresponding compound was prepared following a modification of *General procedure 2* using (3-chlorophenyl)boronic acid (*187.6 mg, 1.2 mmol, 3.0 equiv*.) and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a pale-yellow oil in 52 % yield (52 mg). SFC analysis indicated an enantiomeric ratio of 99.0:1.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.27 (q, J = 2.0 Hz, 1H, arom. C(6') –H), 7.24 (d, J = 7.5 Hz, 1H, arom. C(3') –H), 7.19 (ddd, J = 7.9, 2.1, 1.3 Hz, 1H, C(4') –H), 7.14 (dt, J = 7.5, 1.5 Hz, 1H, C(2') –H), 4.96 – 4.90 (m, 2H, C(5) –H_2), 4.28 (dd, J = 6.2, 1.9 Hz, 2H, C(6) –H_2), 3.37 – 3.25 (m, 2H, C(1) –H, C(4) –H), 3.05 (ddt, J = 15.2, 5.9, 2.0 Hz, 1H, 1x C(3) –H), 2.82 (ddt, J = 15.3, 7.5, 2.8 Hz, 1H, C(3) –H), 2.04 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.2 (C(7)), 146.2 (C(2)), 145.4 (C(5')), 134.4 (C(1')), 129.8 (C(3')), 127.1 (C(6')), 126.6 (C(4')), 124.9 (C(2')), 106.6 (C(5)), 65.6 (C(6)), 50.8 (C(1)), 39.8 (C(4)), 36.9 (C(3)), 21.0 (C(8)).

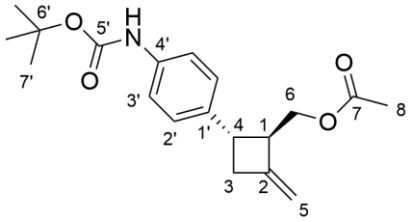
SFC: Chiralpak® IF, 1500 psi, 30 °C; flow: 1.0 mL/min; 0 % MeOH for 3 min, 0 % to 10 % MeOH over 5 min, 99.0:1.0 er (major enantiomer t_R = 6.18 min, minor enantiomer t_R = 6.12 min).

HRMS (ESI): m/z calcd for $C_{12}H_{12}Cl^+$ $[M\text{-}OAc^-]^+$ 191.0622; found 191.0624.

IR ($CHCl_3$ film): 2956 (w), 1739 (s), 1679 (w), 1597 (w), 1571 (w), 1478 (w), 1435 (w), 1383 (w), 1365 (w), 1234 (s), 1080 (w), 1034 (m), 885 (m), 780 (m), 692 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +55.6 (c = 1.0, $CHCl_3$).

*Synthesis of (1R,2S)-2-(4-((tert-butoxycarbonyl)amino)phenyl)-4-methylenecyclobutylmethyl acetate (**32i**)*



The corresponding compound was prepared following a modification of *General procedure 2* using (4-((tert-butoxycarbonyl)amino)phenyl)boronic acid (*284.5 mg, 1.2 mmol, 3.0 equiv.*) and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials at 60 °C. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100), followed by Kugelrohr distillation (2 h, 90 °C) to remove unreacted starting material, afforded the product as a colourless crystalline solid in 44 % yield (58 mg). SFC analysis indicated an enantiomeric ratio of 96.0:4.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.30 (d, J = 8.4 Hz, 2H, 2x arom. C(3') –H), 7.19 (d, J = 8.5 Hz, 2H, 2x arom. C(2') –H), 6.44 (br s, 1H, N–H), 4.95 – 4.87 (m, 2H, C(5) –H_2), 4.32 – 4.19 (m, 2H, C(6) –H_2), 3.32 – 3.21 (m, 2H, C(1) –H, C(4) –H), 3.01 (ddt, J = 15.2, 6.0, 2.1 Hz, 1H, 1x C(3) –H), 2.79 (ddt, J = 15.1, 7.6, 2.8 Hz, 1H, C(3) –H), 2.02 (s, 3H, C(8) –H_3), 1.51 (s, 9H, 3x C(7') –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.2 (C(7)), 153.0 (C(5')), 146.3 (C(2)), 138.9 (C(1')), 136.7 (C(4')), 127.3 (2x C(2')), 118.9 (2x C(3')), 106.1 (C(5)), 80.6 (C(6')), 65.8 (C(6)), 51.0 (C(1)), 39.5 (C(4)), 37.3 (C(3)), 28.5 (3x (C(7')), 21.0 (C(8)).

SFC: Chiralpak® IB, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 96.0:4.0 er (major enantiomer t_R = 3.24 min, minor enantiomer t_R = 2.97 min).

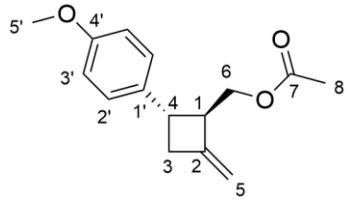
HRMS (ESI): m/z calcd for $C_{19}H_{25}NO_4Na^+$ $[M+Na]^+$ 354.1676; found 354.1675.

IR ($CHCl_3$ film): 3338 (w), 2979 (w), 1724 (s), 1595 (w), 1525 (s), 1411 (w), 1391 (m), 1366 (m), 1316 (m), 1235 (s), 1160 (s), 1052 (m), 1031 (m), 882 (w), 832 (w), 773 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +50.0 (c = 1.0, $CHCl_3$).

m.p.: 72-73 °C

*Synthesis of (1R,2S)-2-(4-methoxyphenyl)-4-methylenecyclobutyl)methyl acetate (**32j**)*



The corresponding compound was prepared following *General procedure 2* using (4-methoxyphenyl)boronic acid and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless solid in 47 % yield (46 mg). SFC analysis indicated an enantiomeric ratio of 99.0:1.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.23 – 7.16 (m, 2H, 2x arom. C(2') –H), 6.90 – 6.83 (m, 2H, 2x arom. C(3') –H), 4.95 – 4.88 (m, 2H, C(5) $–H_2$), 4.33 – 4.20 (m, 2H, C(6) $–H_2$), 3.80 (s, 3H, C(5') $–H_3$), 3.33 – 3.20 (m, 2H, C(1) –H, C(4) –H), 3.06 – 2.97 (m, 1H, 1x C(3) –H), 2.84 – 2.75 (m, 1H, 1x C(3) –H), 2.02 (s, 3H, C(8) $–H_3$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.2 (C(7)), 158.3 (C(4')), 146.4 (C(2)), 136.3 (C(1')), 127.7 (2x C(2')), 114.0 (2x C(3')), 106.0 (C(5)), 65.8 (C(6)), 55.5 (C(5')), 51.1 (C(1)), 39.3 (C(4)), 37.4 (C(3)), 21.1 (C(8)).

SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 99.0:1.0 er (major enantiomer t_R = 2.34 min, minor enantiomer t_R = 2.53 min).

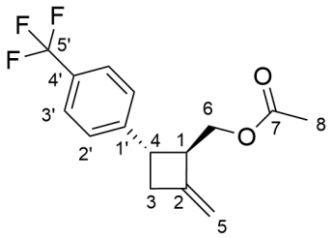
HRMS (ESI): m/z calcd for $C_{15}H_{18}O_3Na^+$ $[M+Na]^+$ 269.1148; found 269.1149.

IR ($CHCl_3$ film): 2950 (w), 2836 (w), 1738 (s), 1678 (w), 1613 (w), 1514 (s), 1464 (w), 1364 (w), 1244 (s), 1179 (w), 1035 (m), 883 (w), 827 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +70.1 (c = 1.0, $CHCl_3$).

m.p.: 32.9 °C

*Synthesis of (1R,4S)-2-methylene-4-(4-(trifluoromethyl)phenyl)cyclobutylmethyl acetate (**32n**)*



The corresponding compound was prepared following a modified *General procedure 2* using (4-(trifluoromethyl)phenyl)boronic acid and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials and (*S*)-SEGPHOS as ligand. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 67 % yield (77 mg). SFC analysis indicated an enantiomeric ratio of 89.5:10.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (pm) 7.57 (d, J = 8.1 Hz, 2H, 2x arom. C(3') –H), 7.39 (d, J = 8.4 Hz, 2H, 2x arom. C(2') –H), 4.95 (p, J = 2.3 Hz, 2H, C(5) –H_2), 4.35 – 4.24 (m, 2H, C(6) –H_2), 3.43 – 3.30 (m, 2H, C(1) –H, C(4) –H), 3.14 – 3.04 (m, 1H, 1x C(3) –H), 2.84 (ddt, J = 15.6, 8.1, 2.8 Hz, 1H, 1x C(3) –H), 2.03 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.1 (C(7)), 148.2 (C(1')), 145.3 (C(2)), 128.8 (d, J = 32.4 Hz, C(5')), 127.1 (2x C(2')), 125.5 (q, J = 3.7 Hz, 2x C(3')), 123.0 (C(4')), 106.8 (C(5)), 65.6 (C(6)), 50.8 (C(1)), 39.9 (C(4)), 37.1 (C(3)), 21.0 (C(8)).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -62.38 (s, C(5')-F_3).

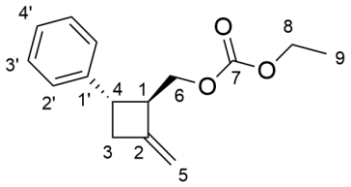
SFC: Chiralpak® IF, 1500 psi, 30 °C; flow: 1.0 mL/min; 1 % MeOH for 2 min, 1 % to 5 % MeOH over 1 min, hold 5 % MeOH for 5 min, 89.5:10.5 er (major enantiomer t_R = 2.13 min, minor enantiomer t_R = 2.34 min).

HRMS (EI/APCI): not found.

IR ($CHCl_3$ film): 2981 (w), 1741 (m), 1680 (w), 1619 (w), 1366 (w), 1325 (s), 1235 (m), 1163 (m), 1121 (m), 1068 (m), 1035 (w), 1018 (w), 886 (w), 834 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +40.5 (c = 1.0, $CHCl_3$).

*Synthesis of ethyl (1R,4S-(2-methylene-4-phenylcyclobutyl)methyl) carbonate (**35**)*



The corresponding compound was prepared following *General procedure 2* using phenylboronic acid and *cis*-cyclobut-3-ene-1,2-diylbis(methylene) diethyl bis(carbonate) **33** as starting materials. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a pale-yellow oil in 79 % yield (78 mg). SFC analysis indicated an enantiomeric ratio of 98.0:2.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.36 – 7.26 (m, 4H, 2x arom. C(2') –H, 2x arom. C(3') –H), 7.24 – 7.18 (m, 1H, arom. C(4') –H), 4.95 (dq, J = 12.0, 2.4 Hz, 2H, C(5) –H_2), 4.41 – 4.28 (m, 2H, C(6) –H_2), 4.18 (q, J = 7.1 Hz, 2H, C(8) –H_2), 3.43 – 3.32 (m, 2H, C(1) –H, C(4) –H), 3.12 – 3.00 (m, 1H, 1x C(3) –H), 2.84 (ddt, J = 15.4, 7.6, 2.8 Hz, 1H, 1x C(3) –H), 1.29 (t, J = 7.1 Hz, 3H, C(9) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 155.4 (C(7)), 145.9 (C(2)), 143.9 (C(1')), 128.6 (2x C(3')), 126.76 (2x C(2')), 126.47 (C(4')), 106.4 (C(5)), 68.8 (C(6)), 64.1 (C(8)), 50.8 (C(1)), 39.5 (C(4)), 37.2 (C(3)), 14.4 (C(9)).

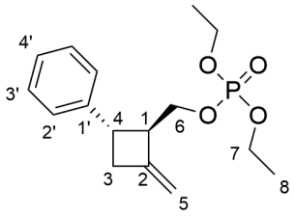
SFC: Chiralpak® IC, 1500 psi, 30 °C; flow: 0.75 mL/min; 1 % 2-propanol for 2 min, 1 % to 10 % 2-propanol over 14 min, 98.0:2.0 er (major enantiomer t_R = 4.86 min, minor enantiomer t_R = 4.65 min).

HRMS (ESI): m/z calcd for $C_{15}H_{18}O_3Na^+$ $[M+Na]^+$ 269.1148; found 269.1149.

IR ($CHCl_3$ film): 2985 (w), 1744 (s), 1680 (w), 1454 (w), 1382 (w), 1254 (s), 1007 (w), 879 (w), 791 (w), 753 (w), 699 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +58.3 (c = 1.0, $CHCl_3$).

*Synthesis of diethyl (1R,4S-(2-methylene-4-phenylcyclobutyl)methyl) phosphate (**36**)*



The corresponding compound was prepared following *General procedure 2* using phenylboronic acid and *cis*-cyclobut-3-ene-1,2-diylbis(methylene) tetraethyl bis(phosphate) **34** as starting materials. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 60/40 to 0/100) afforded the product as a yellow oil in 74 % yield (92 mg). SFC analysis indicated an enantiomeric ratio of 97.5:2.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.34 – 7.27 (m, 4H, 2x arom. C(2') –H, 2x arom. C(3') –H), 7.20 (m, 1H, arom. C(4') –H), 4.95 (dq, J = 13.9, 2.5 Hz, 2H, C(5) –H_2), 4.29 – 4.17 (m, 2H, C(6) –H_2), 4.12 – 3.99 (m, 4H, 2x C(7) –H_2), 3.42 – 3.33 (m, 2H, C(1) –H, C(4) –H), 3.05 (ddt, J = 15.4, 6.0, 2.0 Hz, 1H, 1x C(3) –H), 2.83 (ddt, J = 15.5, 7.6, 2.7 Hz, 1H, 1x C(3) –H), 1.29 (tdd, J = 7.1, 1.9, 1.0 Hz, 6H, 2x C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.54 (C(2)), 144.05 (C(1')), 128.6 (2x C(3')), 126.85 (2x C(2')), 126.45 (C(4')), 106.6 (C(5)), 68.6 (d, J = 6.0 Hz, C(6)), 63.9 (d, J = 5.8 Hz, 2x C(7)), 51.9 (d, J = 7.6 Hz, C(1)), 39.6 (C(4)), 37.2 (C(3)) 16.3 (d, J = 6.7 Hz, 2x C(8)).

^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm): -0.87 (s, $P(O)(OR)_3$).

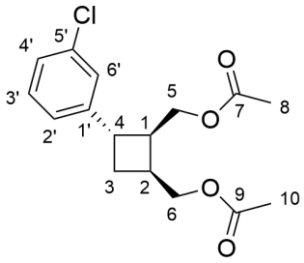
SFC: Chiralpak® IC, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 97.5:2.5 er (major enantiomer t_R = 2.99 min, minor enantiomer t_R = 2.93 min).

HRMS (ESI): m/z calcd for $C_{16}H_{23}O_4PNa^+$ $[M+Na]^+$ 333.1226; found 333.1227.

IR ($CHCl_3$ film): 2985 (w), 1678 (w), 1454 (w), 1393 (w), 1264 (m), 1166 (w), 1019 (s), 980 (m), 883 (w), 803 (w), 753 (w), 700 (m) cm^{-1}.

$[\alpha]^{25}_D$ = +30.6 (c = 1.0, $CHCl_3$).

Synthesis of ((1S,2R,3S)-3-(3-chlorophenyl)cyclobutane-1,2-diyl)bis(methylene) diacetate (37h)



The corresponding compound was prepared following a modification of *General procedure 2* using (3-chlorophenyl)boronic acid (*187.6 mg, 1.2 mmol, 3.0 equiv.*) and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 37 % yield (46 mg). SFC analysis indicated an enantiomeric ratio of 93.0:7.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.31 – 7.23 (m, 2H, arom. C(3') –H, arom. C(4') –H), 7.23 – 7.18 (m, 1H, arom. C(6') –H), 7.13 (ddd, J = 6.9, 1.8, 0.8 Hz, 1H, arom. C(2') –H), 4.42 – 4.29 (m, 2H, C(6) –H_2), 4.29 – 4.20 (m, 2H, C(5) –H_2), 3.45 (q, J = 9.2 Hz, 1H, C(4) –H), 2.89 (ddd, J = 15.8, 8.9, 7.1 Hz, 1H, C(1) –H), 2.83 – 2.72 (m, 1H, C(2) –H), 2.29 (dt, J = 11.8, 9.1 Hz, 1H, 1x C(3) –H), 2.15 (ddd, J = 12.0, 9.2, 3.3 Hz, 1H, 1x C(3) –H), 2.10 (s, 3H, C(10) –H_3), 2.01 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.12 (C(9)), 170.94 (C(7)), 145.9 (C(5')), 134.4 (C(1')), 129. 8 (C(3')), 126.90 (C(4')), 126.57 (C(6')), 124.8 (C(2')), 64.6 (C(6)), 63.9 (C(5)), 42.4 (C(1)), 40.6 (C(4)), 31.9 (C(2)), 28.3 (C(3)), 21.05 (C(10)), 20.91 (C(8)).

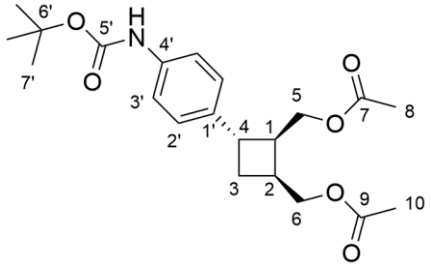
SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 93.0:7.0 er (major enantiomer t_R = 2.92 min, minor enantiomer t_R = 3.02 min).

HRMS (ESI): m/z calcd for $C_{16}H_{19}O_4ClNa^+$ $[M+Na]^+$ 333.0864; found 333.0864.

IR ($CHCl_3$ film): 2945 (w), 1739 (s), 1597 (w), 1571 (w), 1478 (w), 1367 (m), 1237 (s), 1034 (m), 780 (w), 724 (w), 691 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +34.4 (c = 1.0, $CHCl_3$).

*Synthesis of ((1S,2R,3S)-3-(4-((tert-butoxycarbonyl)amino)phenyl)cyclobutane-1,2-diyl)bis(methylene) diacetate (**37i**)*



The corresponding compound was prepared following a modification of *General procedure 2* using (4-((tert-butoxycarbonyl)amino)phenyl)boronic acid (*284.5 mg, 1.2 mmol, 3.0 equiv.*) and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials at 60 °C. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 47 % yield (69 mg). SFC analysis indicated an enantiomeric ratio of 90.0:10.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.29 (d, J = 8.4 Hz, 2H, 2x arom. C(3') –H), 7.15 (d, J = 8.5 Hz, 2H, 2x arom. C(2') –H), 6.45 (br s, 1H, N–H), 4.40 – 4.25 (m, 2H, C(6) –H_2), 4.25 – 4.15 (m, 2H, C(5) –H_2), 3.37 (q, J = 9.2 Hz, 1H, C(4) –H), 2.83 (ddd, J = 15.7, 8.8, 6.8 Hz, 1H, C(1) –H), 2.78 – 2.67 (m, 1H, C(2) –H), 2.23 (dt, J = 11.8, 9.0 Hz, 1H, 1x C(3) –H), 2.14 – 2.08 (m, 1H, 1x C(3) –H), 2.07 (s, 3H, C(10) –H_3), 1.97 (s, 3H, C(8) –H_3), 1.51 (s, 9H, 3x C(7') –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.26 (C(9)), 171.08 (C(7)), 153.0 (C(5')), 138.5 (C(1')), 136.8 (C(4')), 127.2 (2x C(2')), 118.8 (2x C(3')), 80.6 (C(6')), 64.82 (C(6)), 64.09 (C(5)), 42.7 (C(1)), 40.3 (C(4)), 31.9 (C(2)), 28.68 (C(3)), 28.49 (3x C(7')), 21.12 (C(10)), 21.02 (C(8)).

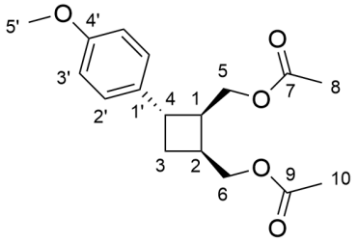
SFC: Chiralpak® IB, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 90.0:10.0 er (major enantiomer t_R = 3.58 min, minor enantiomer t_R = 3.27 min).

HRMS (ESI): m/z calcd for $C_{21}H_{29}NO_6Na^+$ $[M+Na]^+$ 414.1887; found 414.1888.

IR ($CHCl_3$ film): 3344 (w), 2975 (w), 1722 (s), 1595 (w), 1526 (m), 1415 (w), 1392 (w), 1367 (m), 1316 (w), 1236 (s), 1160 (s), 1032 (m), 832 (w), 773 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +32.5 (c = 1.0, $CHCl_3$).

*Synthesis of ((1S,2R,3S)-3-(4-methoxyphenyl)cyclobutane-1,2-diyl)bis(methylene) diacetate (**37j**)*



The corresponding compound was prepared following *General procedure 2* using (4-methoxyphenyl)boronic acid and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless solid in 32 % yield (39 mg). SFC analysis indicated an enantiomeric ratio of 92.5:7.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.18 – 7.12 (m, 2H, 2x arom C(2') –H), 6.88 – 6.82 (m, 2H, 2x arom. C(3') –H), 4.40 – 4.25 (m, 2H, C(6) –H_2), 4.25 – 4.15 (m, 2H, C(5) –H_2), 3.78 (s, 3H, C(5') –H_3), 3.36 (q, J = 9.2 Hz, 1H, C(4) –H), 2.83 (ddd, J = 15.7, 8.8, 6.9 Hz, 1H, C(1) –H), 2.73 (dtt, J = 13.6, 8.4, 4.4 Hz, 1H, C(2) –H), 2.23 (dt, J = 11.7, 9.1 Hz, 1H,1x C(3) –H), 2.13 – 2.07 (m, 1H, 1x C(3) –H), 2.06 (s, 3H, C(10) –H_3), 1.96 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.17 (C(9)), 170.98 (C(7)), 158.3 (C(4')), 135.8 (C(1')), 127.6 (2x C(2')), 113.9 (2x (C3')), 64.78 (C(6)), 64.01 (C(5)), 55.4 (C(5')), 42.8 (C(1)), 40.1 (C(4)), 31.9 (C(2)), 28.8 (C(3)), 21.05 (C(10)), 20.94 (C(8)).

SFC: Chiralpak® IF, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 92.5:7.5 er (major enantiomer t_R = 2.99 min, minor enantiomer t_R = 3.22 min).

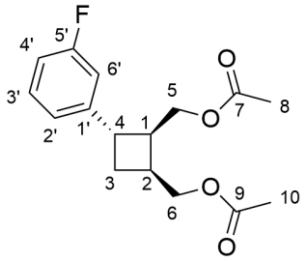
HRMS (ESI): m/z calcd for $C_{17}H_{22}O_5Na^+$ $[M+Na]^+$ 329.1359; found 329.1360.

IR ($CHCl_3$ film): 2942 (w), 1737 (s), 1611 (w), 1514 (m), 1465 (w), 1367 (w), 1244 (s), 1179 (w), 1034 (m), 828 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +40.9 (c = 1.0, $CHCl_3$).

m.p.: 40.3 °C

*Synthesis of ((1S,2R,3S)-3-(3-fluorophenyl)cyclobutane-1,2-diyl)bis(methylene) diacetate (**37k**)*



The corresponding compound was prepared following *General procedure 2* using (3-fluorophenyl)boronic acid and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 75 % yield (88 mg). SFC analysis indicated an enantiomeric ratio of 93.5:6.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.26 (td, J = 7.9, 6.1 Hz, 1H, arom. C(3') –H), 7.03 – 6.86 (m, 3H, arom. C(2') –H, arom. C(4') –H, arom. C(6') –H), 4.40 – 4.26 (m, 2H, C(6) –H_2), 4.26 – 4.17 (m, 2H, C(5) –H_2), 3.44 (q, J = 9.3 Hz, 1H, C(4) –H), 2.87 (ddd, J = 15.8, 8.9, 7.0 Hz, 1H, C(1) –H), 2.81 –2.69 (m, 1H, C(2) –H), 2.26 (dt, J = 11.8, 9.1 Hz, 1H, 1x C(3) –H), 2.13 (ddd, J = 12.1, 9.2, 3.2 Hz, 1H, 1x C(3) –H), 2.07 (s, 3H, C(10) –H_3), 1.98 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.22 (C(9)), 171.02 (C(7)), 163.2 (d, J = 245.6 Hz, C(5')), 146.5 (d, J = 7.0 Hz, C(1')), 130.0 (d, J = 8.4 Hz, C(3')), 122.3 (d, J = 2.8 Hz, C(2')),

113.59 (d, J = 21.2 Hz, C(6')), 113.33 (d, J = 21.0 Hz, C(4')), 64.66 (C(6)), 63.99 (C(5)), 42.5 (C(1)), 40.7 (d, J = 1.9 Hz, C(4)), 31.9 (C(2)), 28.5 (C(3)), 21.11 (C(10)), 20.97 (C(8)).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -113.32 (ddd, J = 10.3, 8.7, 6.1 Hz, C(5') –F).

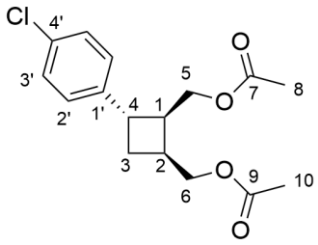
SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 93.5:6.5 er (major enantiomer t_R = 2.43 min, minor enantiomer t_R = 2.59 min).

HRMS (ESI): m/z calcd for $C_{16}H_{19}FO_4Na^+$ $[M+Na]^+$ 317.1160; found 317.1159.

IR ($CHCl_3$ film): 2946 (w), 1737 (s), 1615 (w), 1587 (w), 1490 (w), 1442 (w), 1367 (m), 1233 (s), 1149 (w), 1033 (m), 978 (w), 868 (w), 786 (w), 692 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +46.6 (c = 1.0, $CHCl_3$).

*Synthesis of ((1S,2R,3S)-3-(4-chlorophenyl)cyclobutane-1,2-diyl)bis(methylene) diacetate (**37l**)*



The corresponding compound was prepared following a modification of *General procedure 2* using 1-methyl-5-indolyl boronic acid (*187.6 mg, 1.2 mmol, 3.0 equiv.*) and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials at 60 °C. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 79 % yield (98 mg). SFC analysis indicated an enantiomeric ratio of 91.5:8.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.30 – 7.25 (m, 2H,2x arom C(3') –H), 7.19 – 7.13 (m, 2H, 2x arom C(2') –H), 4.40 – 4.27 (m, 2H, C(6) –H_2), 4.27 – 4.17 (m, 2H, C(5) –H_2), 3.40 (q, J = 9.2 Hz, 1H, C(4) –H), 2.85 (ddd, J = 15.7, 8.8, 6.7 Hz, 1H, C(1) –H), 2.80 – 2.69 (m, 1H,

C(2) –H), 2.23 (dt, J = 11.8, 9.0 Hz, 1H, 1x C(3) –H), 2.17 – 2.09 (m, 1H, 1x C(3) –H), 2.07 (s, 3H, C(10) –H_3), 1.97 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.18 (C(9)), 170.98 (C(7)), 142.3 (C(1')), 132.2 (C(4')), 128.67 (C(3')), 128.06 (C(2')), 64.66 (C(6)), 63.99 (C(5)), 42.6 (C(1)), 40.4 (C(4)), 32.0 (C(2)), 28.6 (C(3)), 21.11 (C(10)), 20.97 (C(8)).

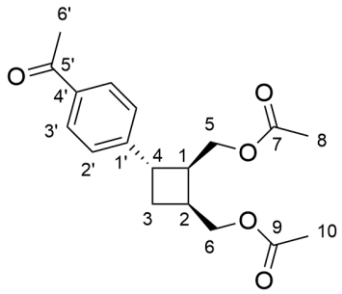
SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 91.5:8.5 er (major enantiomer t_R = 3.09 min, minor enantiomer t_R = 3.27 min).

HRMS (ESI): m/z calcd for $C_{16}H_{19}ClO_4Na^+$ $[M+Na]^+$ 333.0864; found 333.0865.

IR ($CHCl_3$ film): 2945 (w), 1737 (s), 1493 (w), 1367 (w), 1234 (s), 1092 (w), 1033 (m), 1014 (w), 978 (w), 821 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +50.8 (c = 1.0, $CHCl_3$).

*Synthesis of ((1S,2R,3S)-3-(4-acetylphenyl)cyclobutane-1,2-diyl)bis(methylene) diacetate **(37m)***



The corresponding compound was prepared following a modification of *General procedure 2* using (4-acetylphenyl)boronic acid (*196.8 mg, 1.2 mmol, 3.0 equiv.*) and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials *(rigorous stirring required due to heterogeneous reaction mixture*). Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 84 % yield (106 mg). SFC analysis indicated an enantiomeric ratio of 96.5:3.5.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.90 (d, J = 8.3 Hz, 2H, 2x arom. C(3') –H), 7.32 (d, J = 8.2 Hz, 2H, 2x arom. C(2') –H), 4.41 – 4.27 (m, 2H, C(6) –H_2), 4.27 – 4.18 (m, 2H, C(5) –H_2), 3.49 (q, J = 9.2 Hz, 1H, C(4) –H), 2.91 (ddd, J = 15.9, 8.9, 7.0 Hz, 1H, C(1) –H), 2.77 (dtt, J = 11.9, 7.1, 3.8 Hz, 1H, C(2) –H), 2.58 (s, 3H, C(6') –H_3), 2.29 (dt, J = 11.8, 9.1 Hz, 1H, 1x C(3) –H), 2.16 (ddd, J = 12.1, 9.3, 3.2 Hz, 1H, 1x C(3) –H), 2.07 (s, 3H, C(10) –H_3), 1.96 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) δ 197.8 (C(5')), 171.17(C(9)), 170.96 (C(7)), 149.4 (C(1')), 135.6 (C(4')), 128.7 (2x C(3')), 126.9 (2x C(2')), 64.6 (C(6)), 64.0 (C(5)), 42.4 (C(1)), 40.9 (C(4)), 32.0 (C(2)), 28.4 (C(3)), 26.7 (C(6')), 21.10 (C(10)), 20.96 (C(8)).

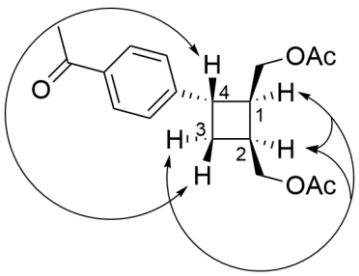
SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 96.5:3.5 er (major enantiomer t_R = 4.75 min, minor enantiomer t_R = 5.34 min).

HRMS (ESI): m/z calcd for $C_{15}H_{22}O_5Na^+$ $[M+Na]^+$ 341.1359; found 341.1360.

IR ($CHCl_3$ film): 2944 (w), 1736 (s), 1681 (s), 1606 (m), 1365 (w), 1236 (s), 1033 (m), 958 (w), 828 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +58.8 (c = 1.0, $CHCl_3$).

Relative Stereochemistry *via* NOEs:



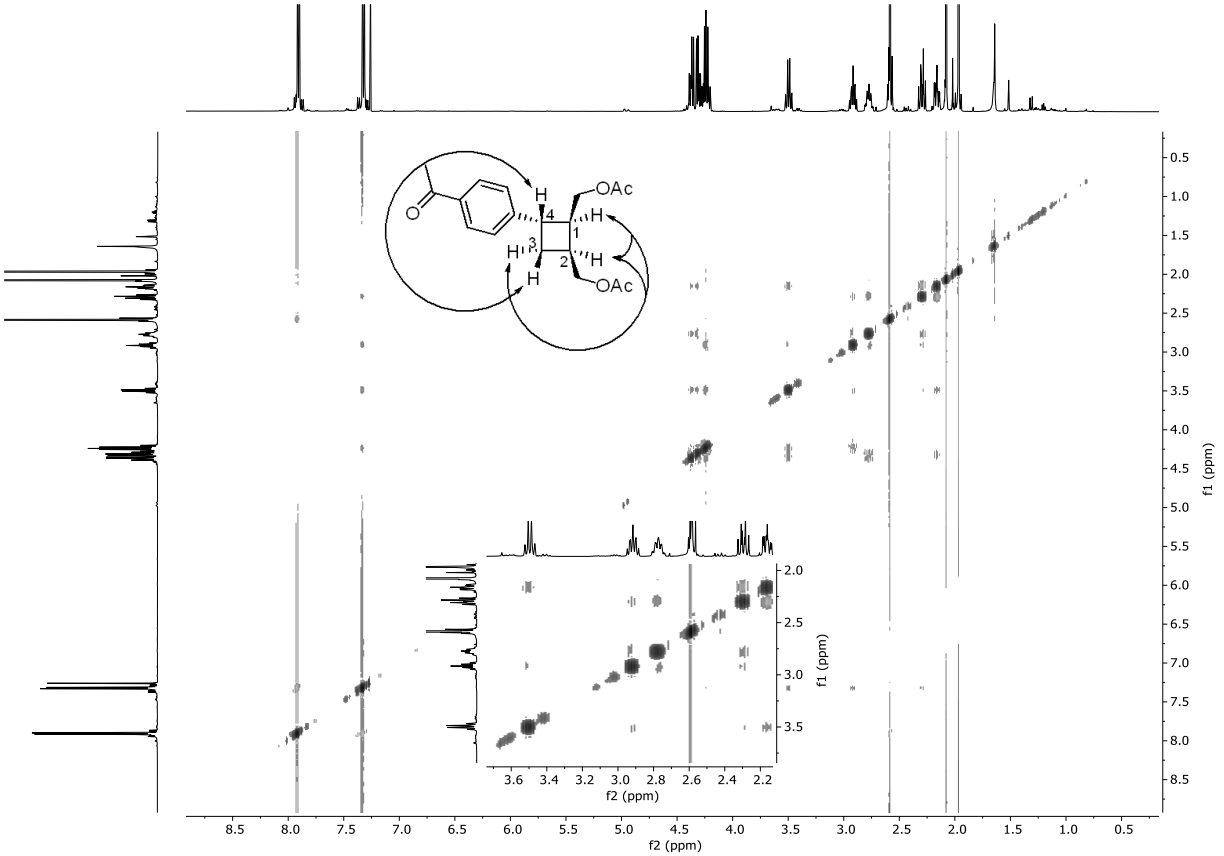
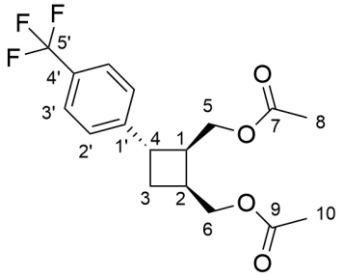


Figure S 5: ^{1}H-^{1}H-NOE (500 MHz, $CDCl_3$) spectra of **37m** recorded at 298 K.

*Synthesis of ((1S,2R,3S)-3-(4-(trifluoromethyl)phenyl)cyclobutane-1,2-diyl)bis(methylene) diacetate (**37n**)*



The corresponding compound was prepared following *General procedure 2* using (4-(trifluoromethyl)phenyl)boronic acid and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials. Purification by automated medium-pressure chromatography (hexane/Et_2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 67 % yield (93 mg). SFC analysis indicated an enantiomeric ratio of 96.0:4.0.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.56 (d, J = 8.1 Hz, 2H, 2x arom. C(3') –H), 7.34 (d, J = 8.3 Hz, 2H, 2x arom. C(2') –H), 4.42 – 4.28 (m, 2H, C(6) –H_2), 4.28 – 4.19 (m, 2H, C(5) –H_2), 3.50 (q, J = 9.2 Hz, 1H, C(4) –H), 2.91 (ddd, J = 15.8, 8.9, 7.0 Hz, 1H, C(1) –H), 2.84 – 2.72 (m, 1H, C(2) –H), 2.29 (dt, J = 11.8, 9.1 Hz, 1H, 1x C(3) –H), 2.17 (ddd, J = 12.0, 9.3, 3.1 Hz, 1H, 1x C(3) –H), 2.08 (s, 3H, C(10) –H_3), 1.97 (s, 3H, C(8) –H_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.18 (C(9)), 170.97 (C(7)), 147.8 (C(1')), 128.8 (d, J = 32.3 Hz, C(5')), 127.0 (2x (C(2')), 125.5 (q, J = 3.8 Hz, 2x C(3')), 123.0 (C(4')), 64.6 (C(6)), 64.0 (C(5)), 42.4 (C(1)), 40.7 (C(4)), 32.0 (C(2)), 28.5 (C(3)), 21.10 (C(10)), 20.95 (C(8)).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -62.39 (C(5')-F_3).

SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1 % to 30 % MeOH over 5 min, 96.0:4.0 er (major enantiomer t_R = 1.92 min, minor enantiomer t_R = 2.04 min).

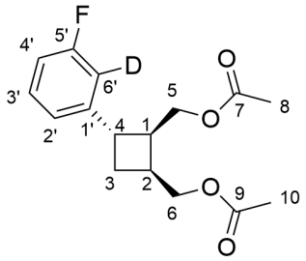
HRMS (ESI): m/z calcd for $C_{15}H_{16}O_2F_3^+$ $[M-^-OAc]^+$ 285.1097; found 285.1099.

IR ($CHCl_3$ film): 2946 (w), 1738 (s), 1618 (w), 1368 (w), 1326 (s), 1234 (s), 1163 (m), 1120 (s), 1068 (m), 1034 (m), 1017 (m), 979 (m), 836 (w) cm^{-1}.

$[\alpha]^{25}_D$ = +50.5 (c = 1.0, $CHCl_3$).

Mechanistic Studies

Deuterium labelling for C–H-bond insertion mechanism



The corresponding compound was prepared following *General procedure 2* using (3-fluorophenyl)boronic acid and cis-cyclobut-3-ene-1,2-diylbis(methylene) diacetate **30** as starting materials and D_2O instead of H_2O (0.2 mmol scale). Purification by automated medium-pressure chromatography (hexane/Et2O = 100/0 to 80/20 to flush at 0/100) afforded the product as a colourless oil in 60 % yield (35 mg) with 64% D-incorporation at the C(6')-position.

^{1}H NMR (CD_2Cl_2, 400 MHz, quantitative): 7.32 – 7.24 (m, 1H, arom. C(3') –H), 7.04 (d, J = 7.6 Hz, 1H, arom. C(2') –H), 6.98 (dt, J = 10.3, 2.2 Hz, 0.36H, arom. C(6') –H), 6.90 (td, J = 8.5, 1.2 Hz, 1H, arom. C(4') –H), 4.39 – 4.24 (m, 2H, C(6) –H), 4.21 (d, J = 6.8 Hz, 2H, C(5) –H), 3.46 (q, J = 9.2 Hz, 1H, C(4) –H), 2.86 (ddd, J = 15.8, 9.0, 7.1 Hz, 1H, C(1) –H), 2.80 – 2.68 (m, 1H, C(2) –H), 2.26 (dt, J = 11.8, 9.1 Hz, 1H, 1x C(3) –H), 2.18 – 2.10 (m, 1H, 1x C(3) –H), 2.05 (s, 3H, C(10) –H_3), 1.96 (s, 3H, C(8) –H_3).

HRMS (ESI): m/z calcd for $C_{16}H_{18}DFO_4Na^+$ $[M+Na]^+$ 318.1222; found 318.1223.

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