Rhodium-Catalysed Enantio- and Diastereoselective $C(sp^2)$-$C(sp^3)$ Cross-Coupling Reactions

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Declaration

This thesis describes work carried out in the Chemistry Research Laboratory, University of Oxford, between October 2017 and September 2021 under the supervision of Prof. Stephen P. Fletcher. This thesis is a result of my own work, except when otherwise stated, and has not been submitted for any other degree at this or any other university.

F. Wieland Goetzke

In memory of

François Diederich

Acknowledgements

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This thesis would not have been possible without the continuous support of the people I love and I feel loved by. The following chapters are each dedicated to the important people in my life and in particular during the last four years in Oxford.

Abstract

In this thesis, we describe a series of Rhodium-catalysed enantio- and diastereoselective C(sp^2)–C(sp^3) cross-coupling reactions and perform brief mechanistic studies in order to understand their underlying mechanisms.

In **Chapter 1**, cross-coupling reactions are introduced and recent developments in catalytic asymmetric Suzuki–Miyaura type cross-coupling reactions are summarised.

In **Chapter 2**, a series of asymmetric Rh-catalysed Suzuki–Miyaura type cross-coupling reactions between racemic allyl chlorides and aryl- and alkenylboronic acids are presented. These dynamic kinetic transformations (DYKATs) proceed via the stereoselective formation of *pseudo-meso* Rh-π-allyl complex, followed by enantiodetermining reductive elimination. This allows for the control of multiple stereogenic centres in a single reaction step. Synthetic applicability of this method was demonstrated with a concise synthesis of the prostaglandin analogue Tafluprost.

In **Chapter 3**, we contribute to the long-standing problem of asymmetric cyclobutane synthesis and present Rh-catalysed cross-coupling reactions between cyclobutenes and arylboronic acids. After an initial asymmetric carbometallation step, the Rh-cyclobutyl intermediates can undergo chain-walking or C–H insertion enabling reductive Heck reactions, 1,5-additions and homo-allylic substitution reactions. The synthetic applicability of these highly enantioselective transformations is demonstrated with formal syntheses of the drug candidates Belaperidone and PF-04862853. This work represents the first asymmetric carbometallation of cyclobutenes, which occurs despite a very small release in olefinic strain.

In **Chapter 4**, an asymmetric hydroacylation of cyclobutenes with salicylaldehydes is presented. Acyl cyclobutanes can be obtained with excellent enantio- and diastereoselectivity. Further, this reaction serves as a proof-of-concept that Rh-catalysed hydrometallation of cyclobutenes is feasible and will likely guide the development of other Rh-catalysed hydrofunctionalisation reactions.

List of Abbreviations

9-BNN	9-Borabicyclo(3.3.1)nonane
Ac	Acetyl or acetate
acac	Acetylacetone
Amyl	Pentyl
a.q.	Aqueous
atm	Atmosphere
$[BAr^F_4]^-$	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BBN	9-Borabicyclo[3.3.1]nonane
BINAP	(2,2‘–Bis(diphenylphosphino)-1,1‘-binaphthyl)
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BRSM	Based on recovered starting material
Bu	Butyl
BQ	1,4-Benzoquinone
Cbz	Carboxybenzyl
CDI	1,1’−-Carbonyldiimidazole
Cl-MeO-BIPHEP	5,5’-Dichloro-2,2’-bis(diphenylphosphino)-6,6’-dimethoxy-1,1’-biphenyl
cod	1,5-Cyclooctadiene
conc.	Concentrated
COSY	Correlation spectroscopy
Cy	Cyclohexyl
d	Doublet (NMR)
DBA	Dibenzylideneacetone
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DFB	Difluorobenzene
DG	Directing group
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylpyridine
DME	1,2-Dimethoxyethane

DMP	Dess–Martin periodinane (1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one)
DM-SEGPHOS	5,5’−Bis[di(3,5-xylyl)phosphino]-4,4’-bi-1,3-benzodioxole
DMSO	Dimethyl sulfoxide
dppf	1,1’–Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
DTBM	3,5-Di-*tert*-butyl-4-methoxypheny)phosphino
DTBM-SEGPHOS	5,5’−Bis[di(3,5-di-*tert*-butyl-4-methoxypheny)phosphino]-4,4’-bi-1,3-benzodioxole
DYKAT	Dynamic kinetic asymmetric transformation
E	Entgegen
ee	Enantiomeric excess
eq or equiv.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
FAAH	Fatty acid amide hydrolase
FDA	Food and Drug Administration
GC	Gas chromatography
HMBC	Heteronuclear multiple bond correlation spectroscopy
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation spectroscopy
IR	Infrared
J	Coupling constant (Hz)
KHMDS	Potassium bis(trimethylsilyl)amide
M	Molarity
m	Multiplet (NMR)
mac	*cis*-1,2-Dimethyl-1,2-dihydroacenaphthylene-1,2-bis(olate)
Me	Methyl
MeDuphos	1,2-Bis[-2,5-dimethylphospholano]benzene
mmol	millimoles
Ms	Methanesulfonyl

m/z	Mass to charge ratio
n	Normal
Napht	Naphthyl
NCS	*N*-Chlorosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
p	Pentet (or quintet) (NMR)
Ph	Phenyl
Pin	Pinacolato
Pr	Propyl
pyr	Pyridine
q	Quartet (NMR)
quant.	Quantitative
rr	Regioisomeric ratio
s	Singlet (NMR) 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	Orbital hybridisation: 1:1 p:s character
sp^2	Orbital hybridisation: 2:1 p:s character
sp^3	Orbital hybridisation: 3:1 p:s character
t	Triplet (NMR)
t	Tertiary
TBAF	*n*–Tetrabutylammonium fluoride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMB	Trimethoxybenzene
Tol	4-Tolyl
Tol-BINAP	2,2’-*p*-Tolyl-phosphino-1,1’-binaphthyl

Ts	4-Toluenesulfonyl
Tf	Triflate
UHP	Urea hydrogen peroxide
Xyl	3,5-Xylyl
Xyl-P-Phos	2,2’,6,6’-Tetramethoxy-4,4′-bis(di(3,5-xylyl)phosphino)-3,3’-bipyridine
Z	Zusammen

Table of Contents

Chapter 1: Asymmetric Cross-Coupling Reactions

Dedicated to my parents Ulla and Hans Jürgen for their unconditional love and support.

Chapter 1 of this thesis introduces cross-coupling reactions. **Chapter 1.1** gives a brief introduction on traditional cross-coupling reactions with a focus on the Suzuki–Miyaura reaction, highlighting its importance for the pharmaceutical industry. **Chapter 1.2** describes the different strategies for catalytic asymmetric Suzuki–Miyaura cross-coupling reactions that have been developed over the last 20 years.

1.1 Catalytic Cross-Coupling Coupling Reaction

1.1.1. Pd-Catalysed C(sp^2)–C(sp^2) Cross-Couplings

Carbon-carbon bond forming reactions are arguably the most powerful tools to generate molecular complexity.[1,2] Metal-catalysed cross-coupling reactions allow the coupling of two fragments – typically an organic (*pseudo*-)halide and an organometallic species or an alkene (Figure 1-1).[3] Palladium catalysts are historically the most employed catalysts in cross-coupling reactions and are especially useful and well developed for the formation of C(sp^2)–C(sp^2) bonds.[4]

Catalytic cross-coupling reactions have had a profound impact on the synthesis of pharmaceuticals, agrochemicals and organic materials,[5,6] and by that have deeply affected our modern lives and society.

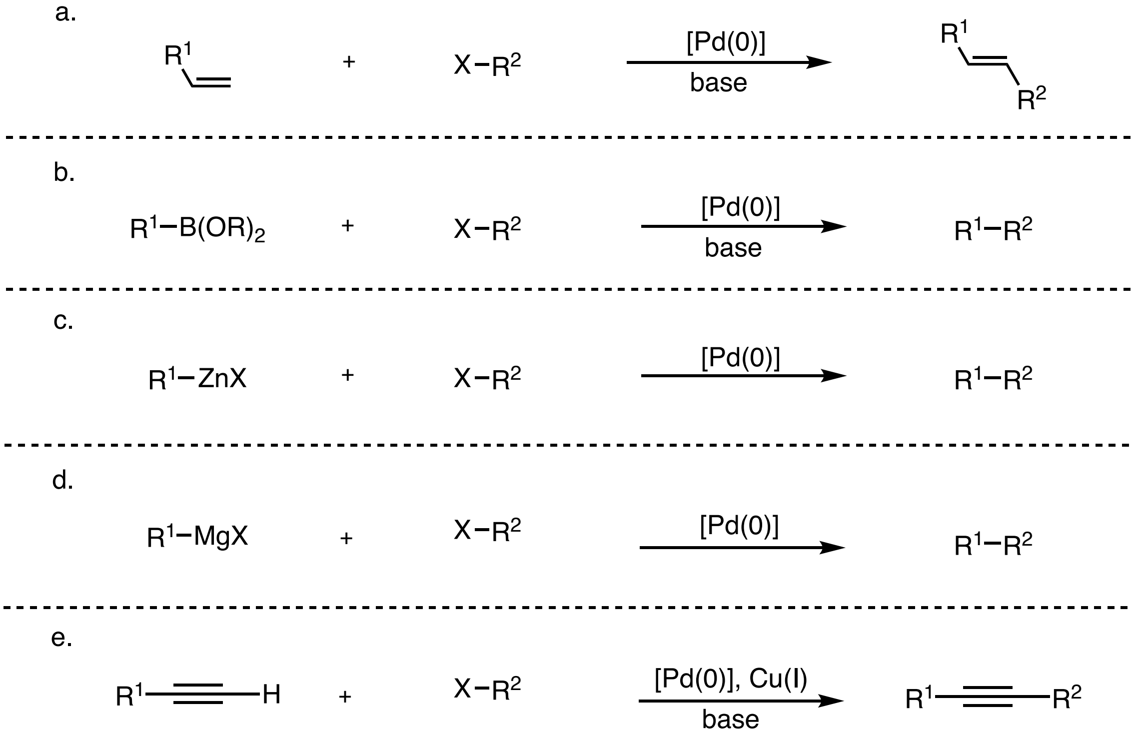


Figure 1-1: Classical Pd-catalysed C(sp^2)–C(sp^2) cross-couplings: Mizoroki–Heck reaction (a), Suzuki–Miyaura coupling (b), Negeshi coupling (c), Kumada coupling (d) and Sonogashira coupling (e). (X = (*pseudo*-)halide)

1.1.2. Pd-Catalysed Suzuki–Miyaura Couplings

Among all cross-coupling reactions, the Pd-catalysed Suzuki–Miyaura coupling between arylboronic acids and (*pseudo-*) aryl halides (Figure 1-1b) is the most frequently applied carbon-carbon bond forming reaction in the pharmaceutical industries.[7,8] (Hetero-) Arylboronic acids and their derivatives are almost ideal coupling partners as they are generally not sensitive to air and moisture, are bench-stable and have low toxicity.[9] They are also easy to synthesise and are now widely commercially available. The experimental convenience of organoboron compounds and the good and predictable chemoselectivity of Pd-catalysed Suzuki–Miyaura reactions have largely contributed to its wide success, which ultimately resulted in the recognition of Akira Suzuki's ground-breaking work with part of Nobel Prize in Chemistry in 2010.[10]

A generic mechanism for Pd-catalysed Suzuki–Miyaura couplings is depicted in Figure 1-2.[11] Oxidative addition of a (*pseudo-*)aryl halide to a palladium(0) complex gives an aryl palladium(II) intermediate. Base assisted transmetallation of the organoboron compound give a diaryl palladium(0) complex. However, the exact mechanism of transmetallation is still not fully elucidated.[12] Final reductive elimination liberates the biaryl product and simultaneously regenerates the active palladium(0) catalyst.

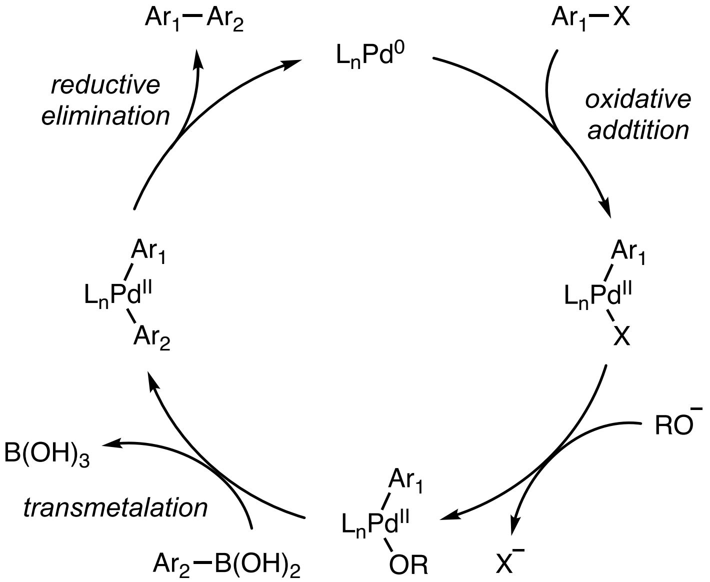
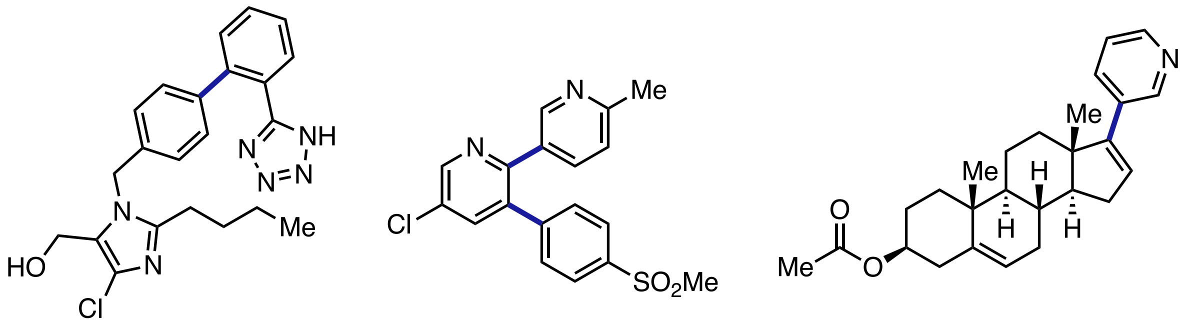


Figure 1-2: Generic catalytic cycle of a Pd-catalysed Suzuki–Miyaura reaction.

The prevalence of the flat (hetero-)biaryl motif in many approved drugs, spanning various applications (Figure 1-3)[8] is closely associated to the abundant use of Suzuki–Miyaura coupling between aryl halides and aryl organoboron compounds in medicinal chemistry.[13] This cross-coupling reaction has arguably become the most strategic carbon-carbon forming reaction in medicinal chemistry. However, this could be to the detriment of human health, as drug candidates with low saturation and the absence of stereogenic centres have reduced chance of success in all stages of drug discovery.[13–15]



Losartan
(FDA approved)

Etoricoxib
(FDA approved)

Abiraterone acetate
(FDA approved)

Figure 1-3: Suzuki–Miyaura coupling used for the synthesis of pharmaceuticals. *(Bonds constructed in Suzuki–Miyaura couplings highlighted in blue).*

In order to circumvent the drawback of classical Suzuki–Miyaura reactions generating “flat”, C(sp^2)-rich scaffolds, developing enantioselective C(sp^2)–C(sp^3) and C(sp^3)–C(sp^3) cross-coupling reactions has become a vibrant area of chemical research. Especially methods that give rigid scaffolds and therefore avoid the conformational entropy penalty of target binding[16] and methods that allow for the coupling of saturated heterocycles[17] are highly desirable for applications in medicinal chemistry.

Recent progress in asymmetric Suzuki–Miyaura couplings is described in the next sections of **Chapter 1**. The Fletcher group’s contribution to this research is presented in **Chapter 2**.

1.2. Catalytic Asymmetric Suzuki–Miyaura Couplings

Chapter 1.2. is based on the following book chapter publication:
Goetzke, F. W.; Dijk, L.; Fletcher, S. P. Catalytic Asymmetric Suzuki–Miyaura Couplings. In *PATAI'S Chemistry of Functional Groups*; Gandelman, M., Marek, I., Eds.; Wiley: Chichester, 2019; 1–54.

I contributed to the publication by joint planning of the book chapter with Lucy van Dijk, and Stephen P. Fletcher and by writing the book chapter with Lucy van Dijk with editing from Stephen P. Fletcher. In the book chapter, Lucy van Dijk wrote the section covering enantioselective C(sp^2)–C(sp^2) Suzuki-Miyaura reactions giving axially chiral biaryl compounds.

1.2.1. Enantioselective C(sp^2)–C(sp^2) Suzuki-Miyaura Reactions

Axially chiral biaryl compounds

Atropisomers are conformers that cannot interconvert efficiently due to hindered rotation about a C–C single bond and thereby display axial chirality.[18] Atropisomeric biaryl compounds can be found in natural products, drugs (e.g. vancomycin) and ligands (e.g. BINAP) for asymmetric synthesis.[19–22] Besides auxiliary-based approaches and resolution-based strategies, the catalytic asymmetric formation of the C–C single bond with hindered rotation has emerged as a practically useful strategy for the enantioselective synthesis of axially chiral biaryls over the last two decades.[23] As the classical Suzuki–Miyaura coupling is arguably the most powerful method for biaryl synthesis, many of these catalytic approaches have relied on asymmetric Suzuki–Miyaura reactions.

The groups of Cammidge and Buchwald independently pioneered Pd-catalysed enantioselective cross-coupling reactions with arylboron compounds to give chiral biaryls. Cammidge and Crepy showed that disubstituted binaphthalenes could be obtained in good enantioselectivities using a chiral ferrocene based ligand **L1-1** (Figure 1-4a).[24] The mechanism of this these transformations is likely similar to the general mechanism of Suzuki–Miyaura reactions depicted in Figure 1-2.

Buchwald and Yin developed enantioselective Pd-catalysed Suzuki–Miyaura reactions between 2-substituted arylboronic acids and a naphthylphosphonate bromide with the bulky phosphine ligand KenPhos (**L1-2**) (Figure 1-4b).[25] Subsequent computational studies suggest that phosphonate group is crucial for recognition in the enantio-determining reductive elimination step.[26]

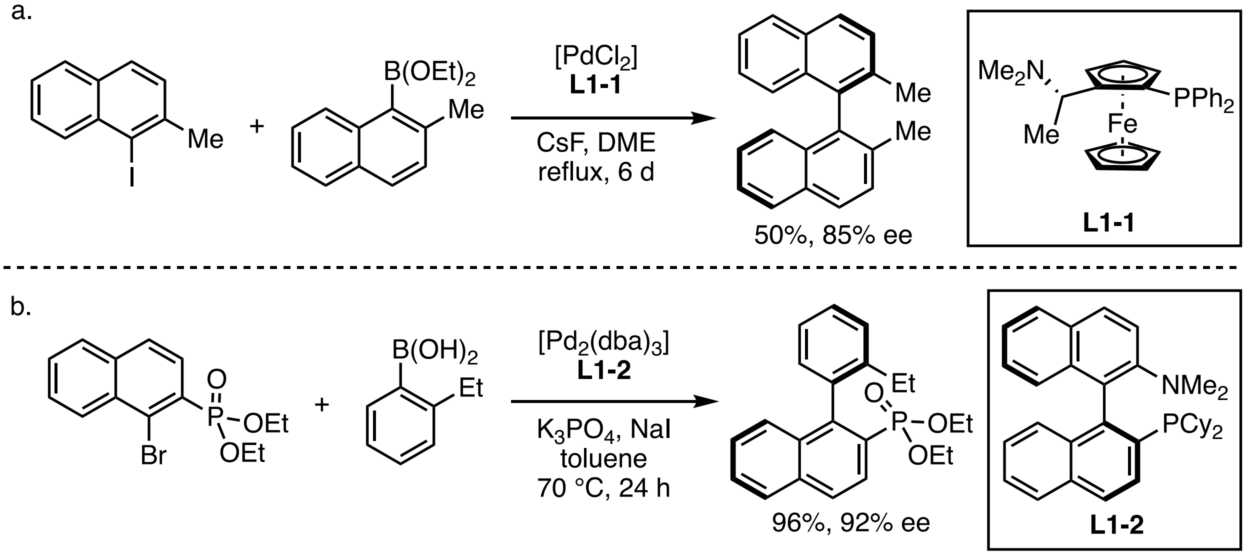


Figure 1-4: Enantioselective C(sp^2)–C(sp^2) Suzuki-Miyaura coupling giving axially chiral biaryls by Cammidge and Crepy (a) and Buchwald and Yin (b).

Most asymmetric C(sp^2)–C(sp^2) Suzuki-Miyaura coupling reactions have built extensively on Cammidge and Buchwald's pioneering work.[27] A conceptionally different approach was developed by Lassaletta and co-workers.[28] Here, a racemic mixture of biaryl triflate is converted into a highly enantioenriched atropisomeric coupling product in >50% yield (Figure 1-5).

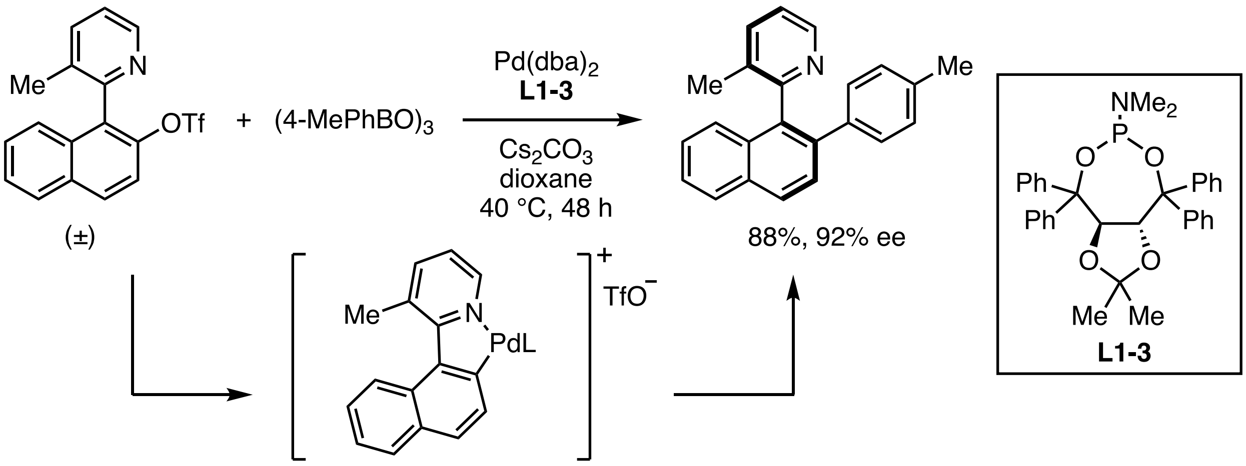


Figure 1-5: Dynamic Kinetic asymmetric Suzuki-Miyaura coupling for the synthesis of axially chiral biaryls.

In the oxidative addition, a configurationally labile palladacycle is formed, which facilitates de-racemisation. A more detailed description of reactions with racemic substrates and dynamic kinetic transformations can be found in **Chapter 2.1.2**.

Planar chirality

Kündig and co-workers introduced planar chirality into a chromium metallocene complex in a Pd-catalysed C(sp^2)–C(sp^2) Suzuki–Miyaura coupling reaction with a tricarbonyl chromium 1,4-dibromonaphthalene complex (Figure 1-6).[29] The enantioselectivity is likely set in the oxidative addition step, and the bulky phosphoramidite ligand **L1-4** induced excellent stereoselectivity and was crucial for minimising undesired bisarylation of the starting material.

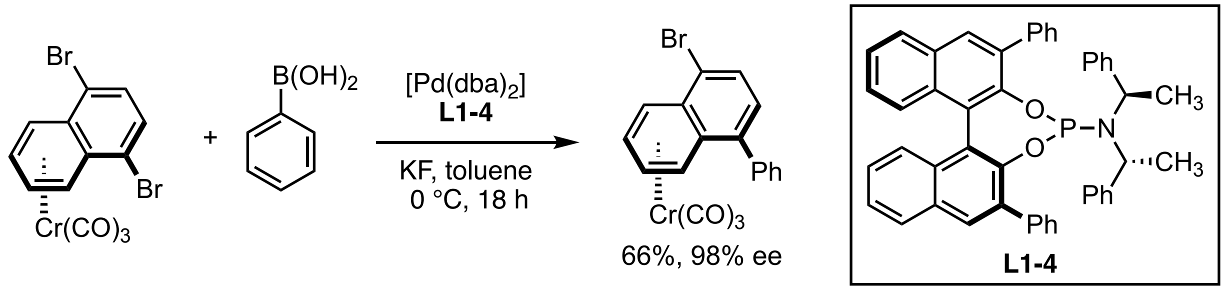


Figure 1-6: Enantioselective C(sp^2)–C(sp^2) Suzuki-Miyaura coupling giving a compound with planar chirality.

Desymmetrisation with a pro-stereogenic centre

Willis and co-workers showed that prochiral bis-triflates could be used in enantioselective C(sp^2)–C(sp^2) Suzuki–Miyaura reactions (Figure 1-7).[30] Here, a pro-stereogenic C(sp^3)-quaternary centre is desymmetrised. Moderate to good enantioselectivities were obtained for a range of different, functionalised arylboronic acids.

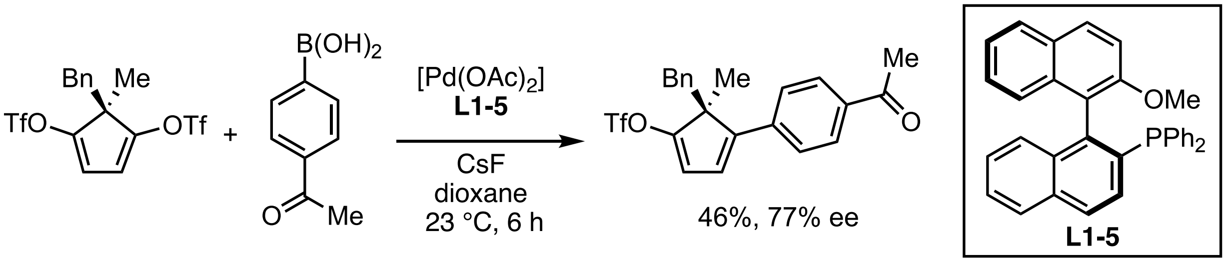


Figure 1-7: Desymmetrisation of ditriflate with an enantioselective C(sp^2)–C(sp^2) Suzuki-Miyaura coupling.

1.2.2. Enantioselective C(sp^2)–C(sp^3) and C(sp^3)–C(sp^3) Suzuki-Miyaura Reactions

Pd-catalysed cross-couplings with alkyl halides or alkyl boron compounds have proven to be significantly more challenging than the corresponding C(sp^2)−C(sp^2) coupling reactions.[31] Slower oxidative addition of alkyl halides to Pd-complexes and competitive β-hydride elimination pathways have likely delayed their development.[32]

Chapter 1.2.2 describes catalytic Suzuki–Miyaura coupling reactions that introduce one stereogenic centre in an enantioselective C(sp^2)–C(sp^3) or C(sp^3)–C(sp^3) bond forming reaction employing different transition metal catalysts. Several of these cross-couplings reactions between (*pseudo*-)halides and organoboron compounds can also be classified as typical asymmetric addition-type reactions – e.g. allylic substitution reactions. Further, a range of powerful stereospecific transformations have been developed with enantioenriched organoboron compounds, which are not discussed in this section.[33,34]

Palladium-catalysed asymmetric C(sp^2)–C(sp^3) and C(sp^3)–C(sp^3) couplings

The reactions presented in this section on Pd-catalysed couplings likely follow mechanisms in which oxidative addition of an organic halide to a Pd^0-complex is followed by transmetallation with an organoboron compound followed by reductive elimination (see Figure 1-2).

Miyaura and co-workers developed a Pd-catalysed asymmetric allylation reaction of aryl and alkenyl bromides with allyl potassium trifluoroborate salts (Figure 1-8a).[35] Excellent yields, good enantioselectivities and good to excellent regioselectivities were achieved for a range of different bromides with Josiphos ligand **L1-6**. The high regioselectivities likely arise from a mechanism in which base assisted transmetallation of the allyl boron species to an aryl Pd^{II}-complex is followed by a fast reductive elimination, prior to isomerisation of the Pd-allyl complex or undesired β-hydride elimination.[36]

Morken and co-workers developed an intramolecular variant of this coupling with tethered aryl chlorides using the phosphoramidite ligand **L1-7** (Figure 1-8b).[37] Here, the enantioselectivity was highly dependent on the length of the tether and lower enantioselectivities were achieved with longer tethers. Unlike in Miyaura's intermolecular coupling, the authors propose a mechanism in which a fast isomerisation of the Pd-allyl complex after transmetallation is crucial, and the enantioselectivity is set in the reductive elimination step.

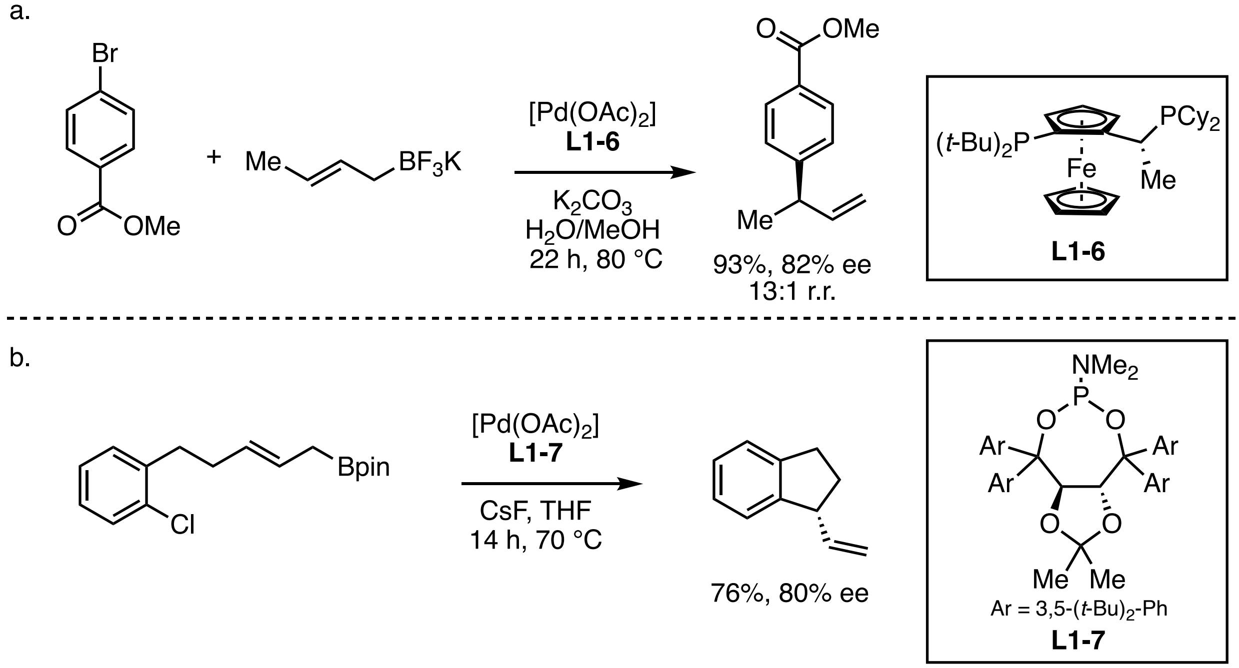


Figure 1-8: Intermolecular (a) and intramolecular (b) Pd-catalysed asymmetric allylation of aryl halides.

The Morken group has also pioneered a range of enantiotopic-group-selective cross-couplings of geminal bis(boronates) and aryl iodides[38] (Figure 1-9), or alkenyl halides[39]. A Pd-phosphoramidite (**L1-8**) complex discriminates between the two enantiotopic boronates in the enantiodetermining transmetallation step. The enantioenriched alkyl boronic esters can be used in subsequent cross-coupling reactions[40] as demonstrated in an asymmetric synthesis of the drug tolterodine.[38] A similar desymmetrisation reaction was reported by Hall and co-workers shortly after.[41]

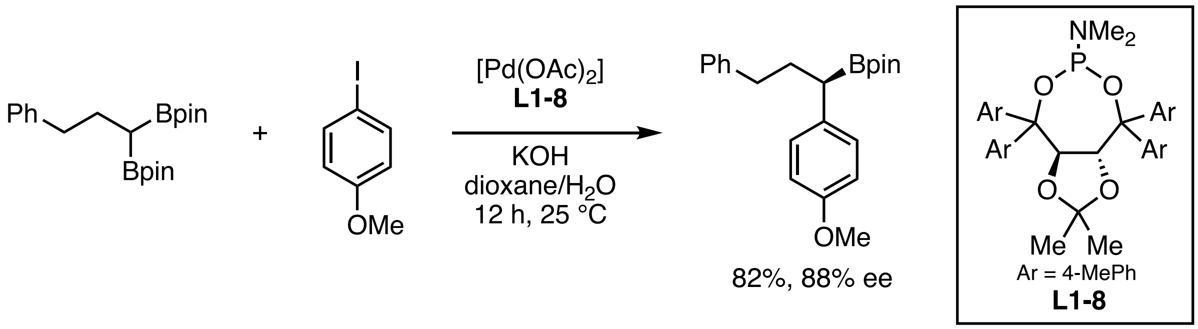


Figure 1-9: Pd-catalysed enantiotopic-group-selective cross-coupling of geminal bis(boronates).

A rare example of a C(sp^3)-coupling with arylboronic acids was developed by Tang and co-workers (Figure 1-10).[42,43] Racemic α-bromocarboxamides undergo enantioselective Suzuki–Miyaura reactions to give aryl carboxamides. Good enantioselectivities could only be achieved with specific α- and *N*-substitution on the starting material. The authors propose that oxidative addition of the halide gives an acyl palladium intermediate which is in fast equilibrium with an *O*-bound Pd-enolate complex, which facilitates de-racemisation.

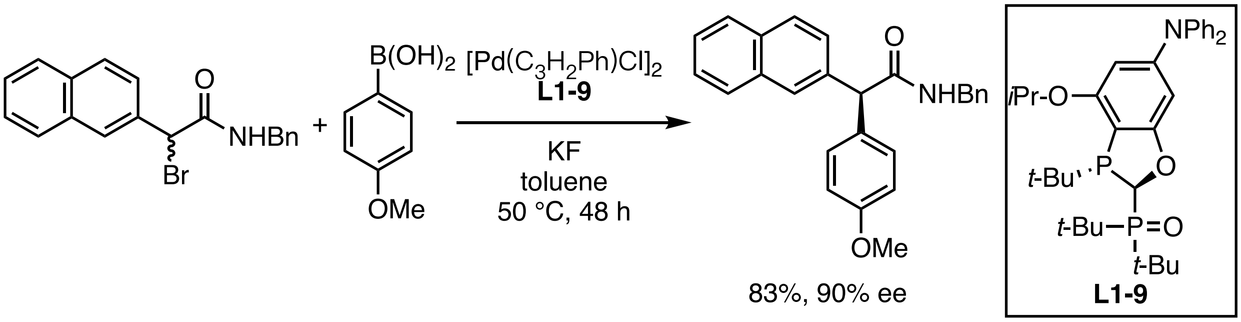


Figure 1-10: Pd-catalysed asymmetric cross-coupling reactions between α-bromocarboxamides and aryl boronic acids.

Inspired by Miyaura's work on couplings with allyl boronates (Figure 1-8a), Morken and co-workers also developed a few highly enantioselective C(sp^3)–C(sp^3) couplings with different substituted (*pseudo*-)halides and allylboronates (Figure 1-11).[44–47]

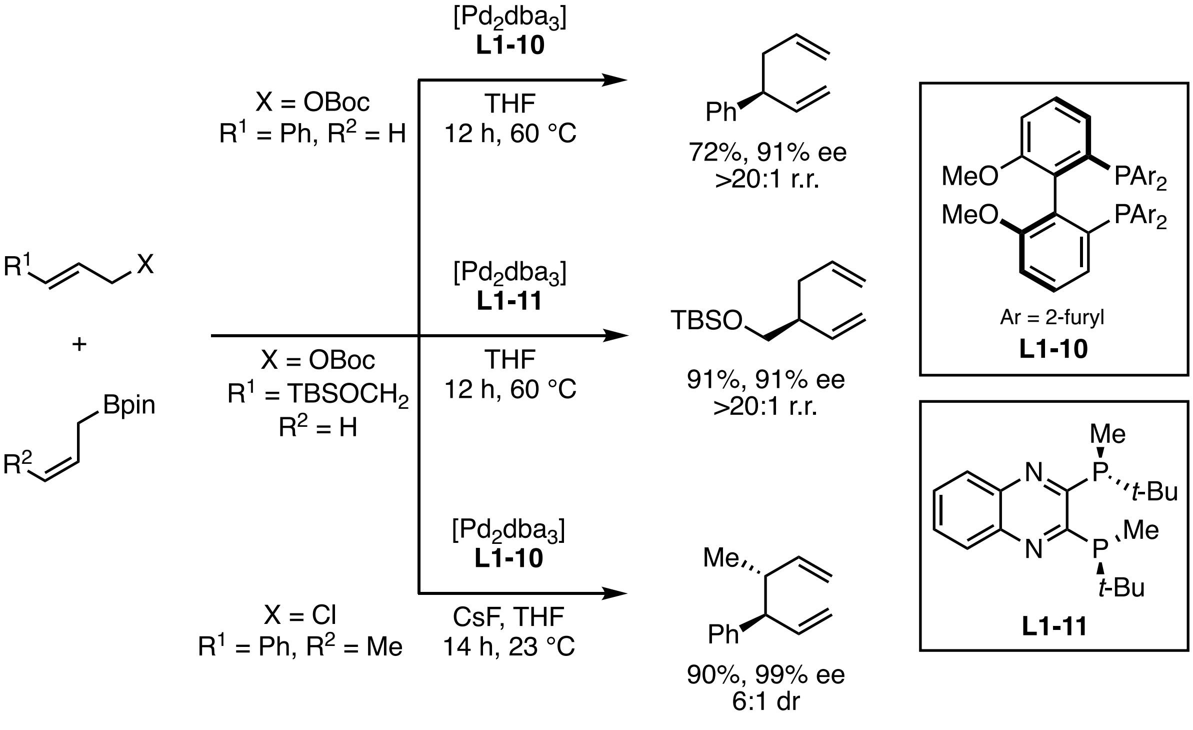


Figure 1-11: Pd-catalysed asymmetric allyl-allyl cross-couplings.

In these couplings, racemic branched or linear allylic carbonates (depicted) are both suitable substrates for the same transformation, suggesting that these transformations proceed via a common Pd-π-allyl complex.

Nickel-catalysed asymmetric C(sp^2)–C(sp^3) and C(sp^3)–C(sp^3) couplings

Nickel-catalyst are among the most common alternatives to palladium in conventional Suzuki–Miyaura reactions, especially in C(sp^2)–C(sp^3) couplings.[48] In an early example, Uemura and co-workers reported nickel-catalysed enantioselective cross-coupling reactions of racemic allylic acetates with arylboronic acids (Figure 1-12). Good yields but low enantioselectivities (all <60% ee) were obtained with cyclic and acyclic acetates using an oxazolinylferrocenyl-phosphine ligand (**L1-12**). Despite the low enantioinduction, this work confirms that de-racemisation in Ni-catalysed cross-couplings with organoboron compounds is feasible.

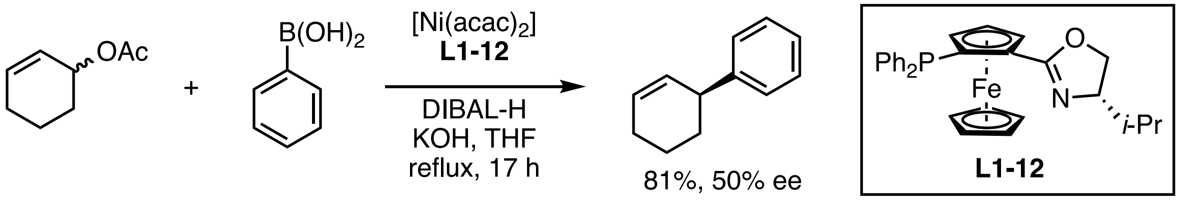


Figure 1-12: Ni-catalysed allylic arylation with boronic acids.

Other groups have reported good levels of enantioinduction in other Ni-catalysed transformations with racemic substrates. Fu and Lundin developed an enantioselective Ni-catalysed cross-coupling between racemic α-chlorocarboxamides and *B*-phenyl-9-borabicyclo[3.3.1]nonane (Ph–BBN) (Figure 1-13a).[49] This protocol gives α-arylcarboxamides in good yields and enantioselectivities, which can be converted to free carboxylic acids or benzylic alcohols without erosion of enantiomeric excess. Experiments with enantioenriched starting materials show that the enantiomeric excess of the product is independent of the stereoisomeric composition of the starting material, suggesting that the de-racemisation is fast compared to the enantiodetermining step.

A strategy to install trifluoromethoxylated stereogenic centres in a Ni-catalysed C(sp^2)–C(sp^3) cross-coupling was reported by Shen and co-workers (Figure 1-13b).[50] Couplings with α-trifluoromethoxylated benzyl bromides proceeded in good yields and enantioselectivities for a range of different aryl lithium organoborates. The choice for a more reactive lithium organoborate over an arylboronic acid was crucial in order to achieve transmetallation below room temperature, resulting in good enantioselectivities. This work was later extended to α-trifluoromethylated benzyl halides using zinc salts as additives in order to accelerate transmetallation.[51]

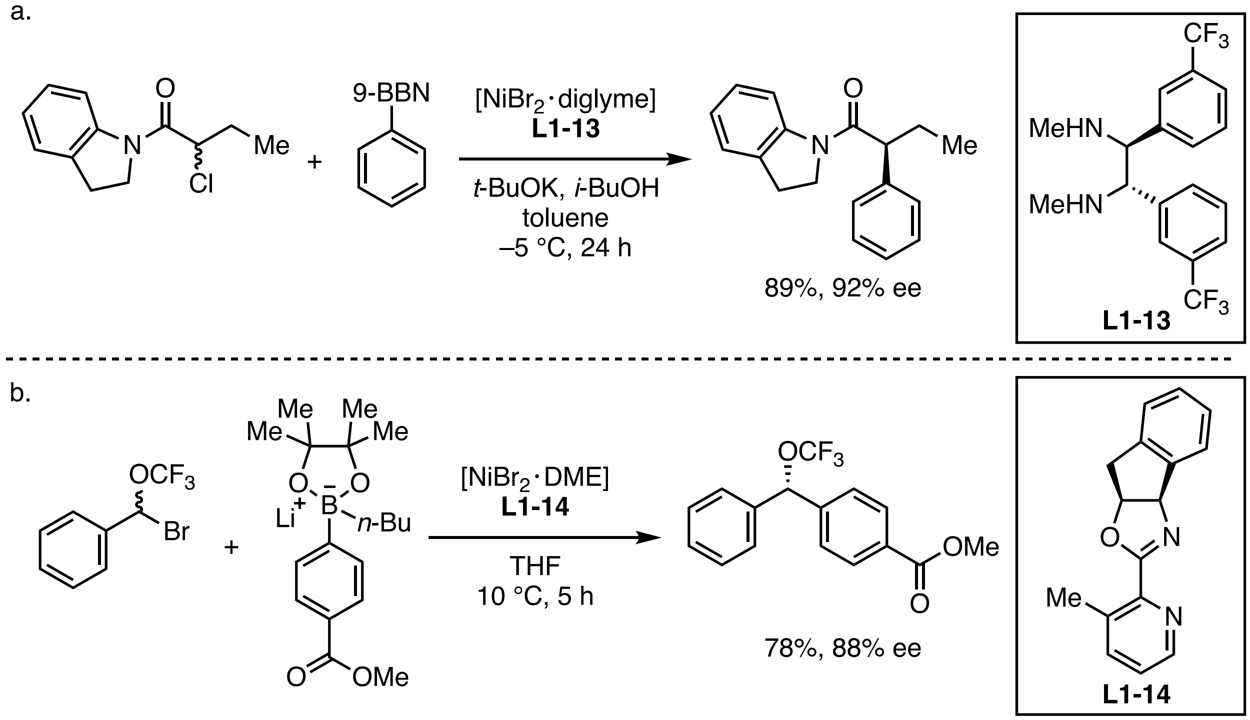


Figure 1-13: Ni-catalysed asymmetric cross-coupling reactions between α-chlorocarboxamides (a) or α-trifluoromethoxylated benzyl bromides (b) and (activated) arylboronic esters.

The Fu group pioneered a range of different Ni-catalysed asymmetric C(sp^3)–C(sp^3) cross-coupling reactions of electronically unactivated secondary alkyl halides bearing directing groups and alkylboron compounds (Figure 1-14). Nickel diamine complexes induced good to excellent enantioselectivities. Fu and Saito reported the first asymmetric alkylation of racemic homobenzylic bromides and alkyl-(9-BBN) species.[52] These C(sp^3)–C(sp^3) couplings were later extended to β-halohydrins[53], β-haloamines[54], γ-chloroamides[55], carbamate-protected amines, sulfamides and sulfones[56] (Figure 1-14).

For the β-haloamines, Fu and co-workers propose a mechanism in which transmetalation of the boronate to a Ni^{I}-complex is followed by a single-electron transfer oxidative addition as the enantiodetermining step. However, density-functional-theory (DFT) calculations by Kozlowski and co-workers suggest that oxidative addition is reversible, and the reductive elimination is enantiodetermining (level of theory: SMD-water-(U)M06/6-311+G(d,p)//B3LYP/6-31G).[57]

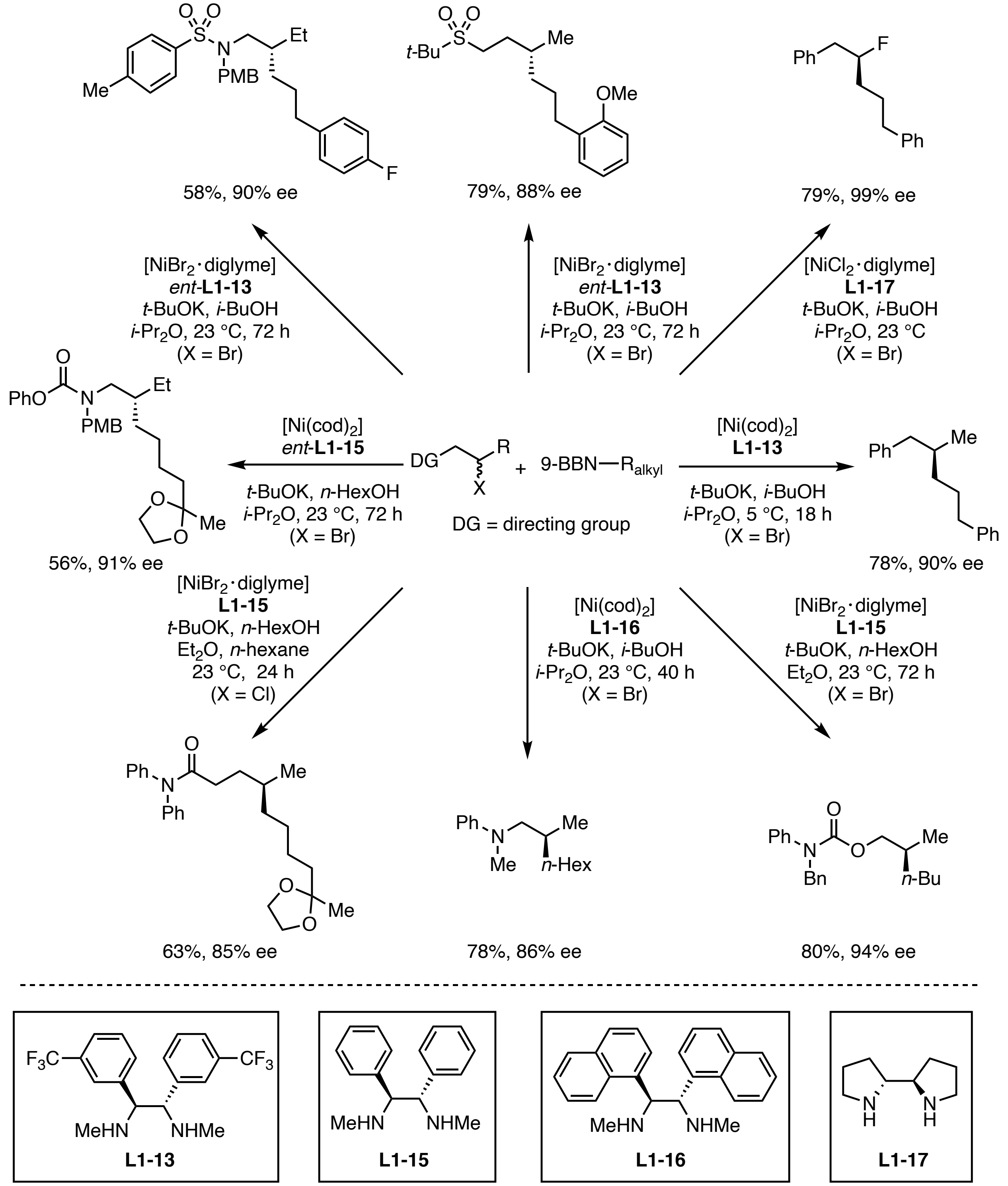


Figure 1-14: Directing group facilitated Ni-catalysed C(sp^2)–C(sp^3) Suzuki-Miyaura couplings.

Gandelman and co-workers reported related enantioselective nickel-catalysed alkylations of unactivated 1-fluoro-1-haloalkanes with various directing groups with moderate to excellent enantioselectivities (Figure 1-14).[58,59]

Cobalt-catalysed asymmetric C(sp^2)–C(sp^3) couplings

A rare example of cobalt-catalysed asymmetric C(sp^2)–C(sp^3) coupling was reported by Shen and co-workers.[60] Similar to the Shen group's work on Ni-catalysed Suzuki–Miyuara couplings (see Figure 1-13b), racemic mixtures of α-fluoro benzyl bromide were de-racemised using a cobalt-bisoxazoline (**L1-18**) complex and zinc salts as additives (Figure 1-15).

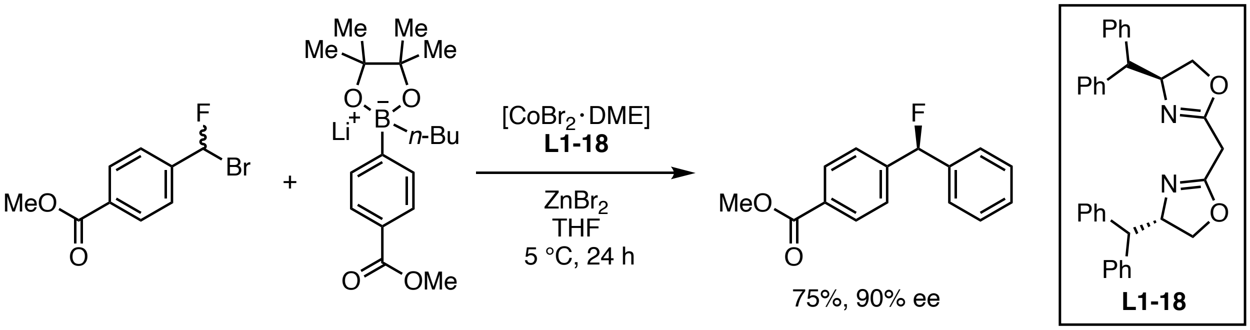


Figure 1-15: Co-catalysed asymmetric cross-coupling between a benzyl bromide and arylboron species.

Rhodium-catalysed asymmetric C(sp^2)–C(sp^3) couplings

Rh-catalysed asymmetric arylation reactions of activated alkenes are among the most powerful and versatile methods for enantioselective C(sp^2)–C(sp^3) bond formation.[61] A few of these reactions could be classified as asymmetric Suzuki–Miyaura couplings. Lautens and co-workers reported allylic arylation reactions with *meso*-biscarbonates.[62,63] Depending on the choice of the chiral ligand, either the 1,2-substituted (Figure 1-16; left) or the 1,4-substituted (Figure 1-16; right) aryl cyclopentenes were obtained. These reactions proceed in good yields and high stereoselectivities with a range of functionalised boronic acids. Recently, the Fletcher group extended this work to the desymmetrisation of five-membered *meso*-bisphosphates with a pro-stereogenic quaternary centre.[64] Further, a few asymmetric allylic arylations with acyclic substrates and arylboronic acids are also known.[65–67]

Gong and co-workers presented highly enantioselective cross-couplings between racemic 2-nitrocyclohex-2-enol acetate and arylboronic acids using BINAP (**L1-21**) as the chiral ligand (Figure 1-17).[68,69] Likely, this reaction proceeds via a stepwise mechanism consisting of conjugate addition to the Michael acceptor followed by β-oxygen elimination, which overall results in a substitution reaction. This method allowed for a concise synthesis of the alkaloid γ-lycorane.

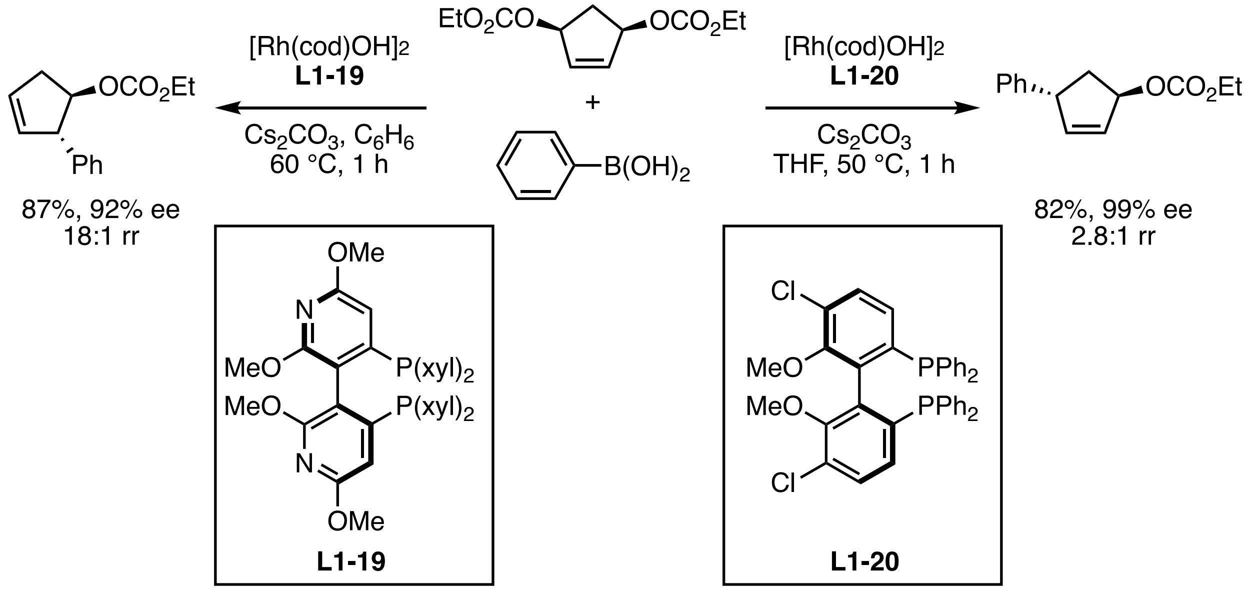


Figure 1-16: Rh-catalysed asymmetric allylic arylation of *meso*-biscarbonates.

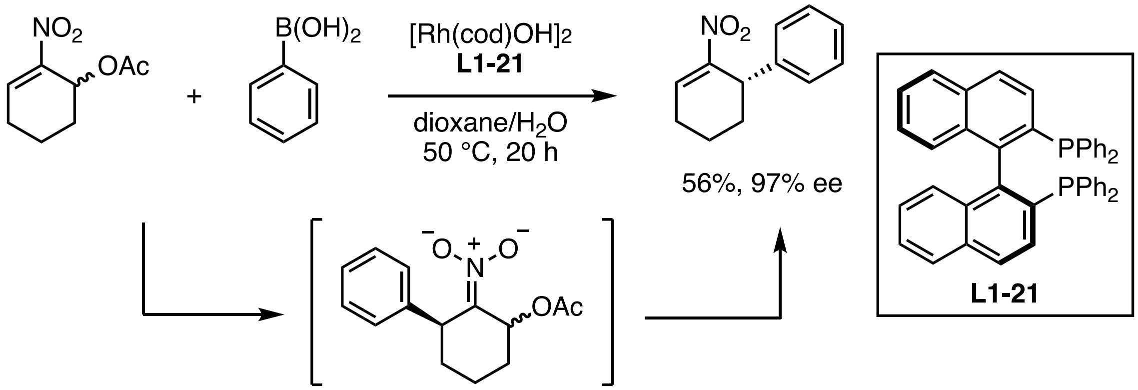


Figure 1-17: Rh-catalysed asymmetric allylic arylation of racemic 2-nitrocyclohex-2-enol acetate.

The Fletcher group has developed a range of cross-coupling reactions between racemic allyl halides and arylboronic acids, which are described and discussed in **Chapter 2** of this thesis.[70]

Iridium-catalysed asymmetric C(sp)–C(sp^3), C(sp^2)–C(sp^3) and C(sp^3)–C(sp^3) couplings

Iridium catalysts show typically high regioselectivity for the branched product in asymmetric allylic substitution reactions with acyclic substrates.[71] A few highly enantioselective allylic substitution reactions with organoboron compounds are known.

Carreira and co-workers reported the Ir-*P*,*N*-olefin (**L1-22**) catalysed alkenylation[72] (Figure 1-18; right) and alkynylation (Figure 1-18; left) of racemic allylic alcohols with the corresponding potassium trifluoroborate salts.[73] In these reactions, the allylic alcohol is activated with a Brønsted acid and the organoboron compound with a fluoride source. These allylic transformations were used as the key enantioselective step in concise syntheses of the natural products nyasol and hinokiresinol and the GPR40 agonist AMG 837.

Yang and co-workers reported an asymmetric C(sp^3)–C(sp^3) coupling using allyl borates and the same ligand used in the examples above (Figure 1-18; bottom).[74] Here, activation of the allylic alcohol was achieved with zinc triflate as the Lewis acid.

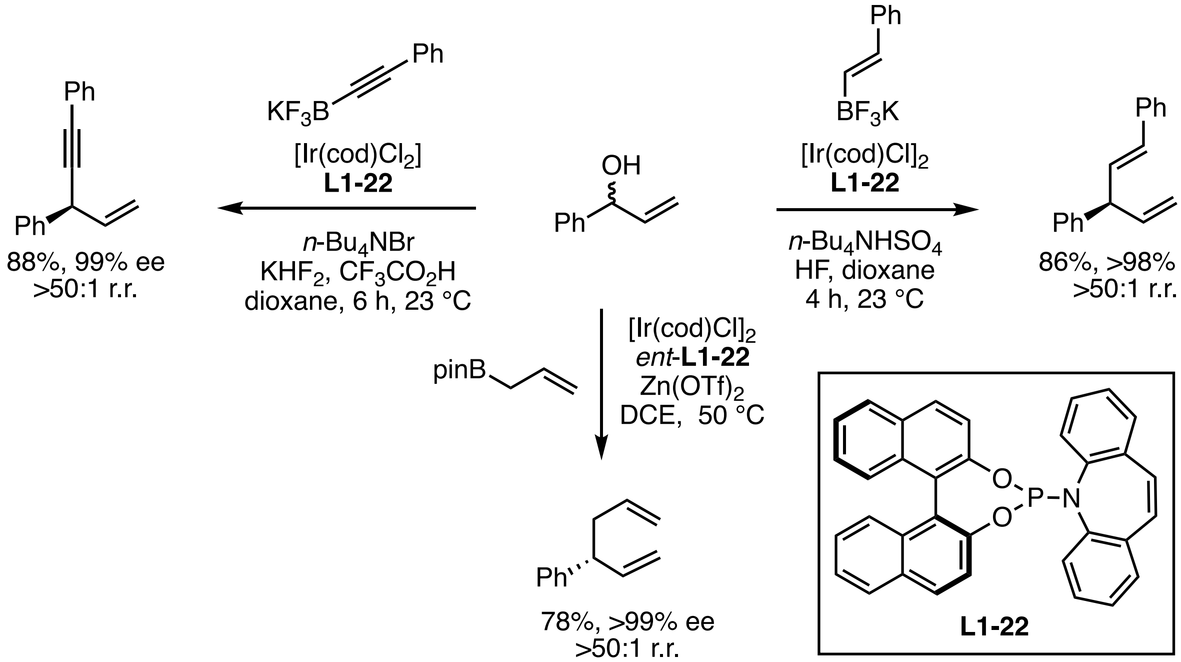


Figure 1-18: Ir-catalysed asymmetric allylic alkynylation, alkenylation and allylation.

Further, the asymmetric allylic alkylation with bis[(pinacolato)boryl]methane to give homoallylic boronic esters is known (Figure 1-19).[75] Phosphoramidite ligand **L1-22** induced good levels of enantioselectivity, and silver additives were used in order to promote transmetallation.

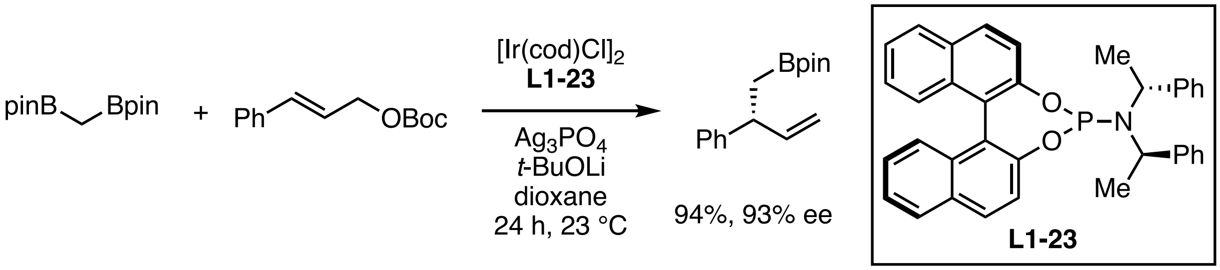


Figure 1-19: Ir-catalysed asymmetric allylic alkylation with bis[(pinacolato)boryl]methane.

Copper-catalysed C(sp^2)–C(sp^3) and C(sp^3)–C(sp^3) couplings

The groups of Hayashi and Hoveyda independently reported several Cu-catalysed allylic substitution reactions of allyl phosphates with organoboron compounds over the last decade. Shintani, Hayashi, and co-workers reported asymmetric allylic substitution reactions of prochiral allyl phosphates with aryl- and alkenyl boronic esters (Figure 1-20; right).[76] A Cu/NHC complex with **L1-24** allowed for high yielding couplings with good enantioselectivities. A related method resulting in the formation of quaternary centres was also developed (Figure 1-20; bottom).[77]

Hoveyda and co-worker reported related alkenylation reactions using a sulfonate-bridged bidentate NHC ligand **L1-25** (Figure 1-20; left).[78] While high enantioselectivities could only be achieved with substituents at the *ortho*-position of the aromatic ring, a more general protocol based on a different ligand, which is suitable for a range of alkenyl coupling partner including *E*-, or *Z*-disubstituted alkenyl- or 1,1-disubstituted alkenyl boronates was reported later.[79]

The same group also developed highly enantioselective allenylation reactions[80] (Figure 1-20; top) and alkynylation reactions[81] with organoboronic esters. Related C(sp^3)–C(sp^3) couplings between acyclic alkyl chlorides and alkylboronic acids have been reported by the group of Sawamura.[82–84]

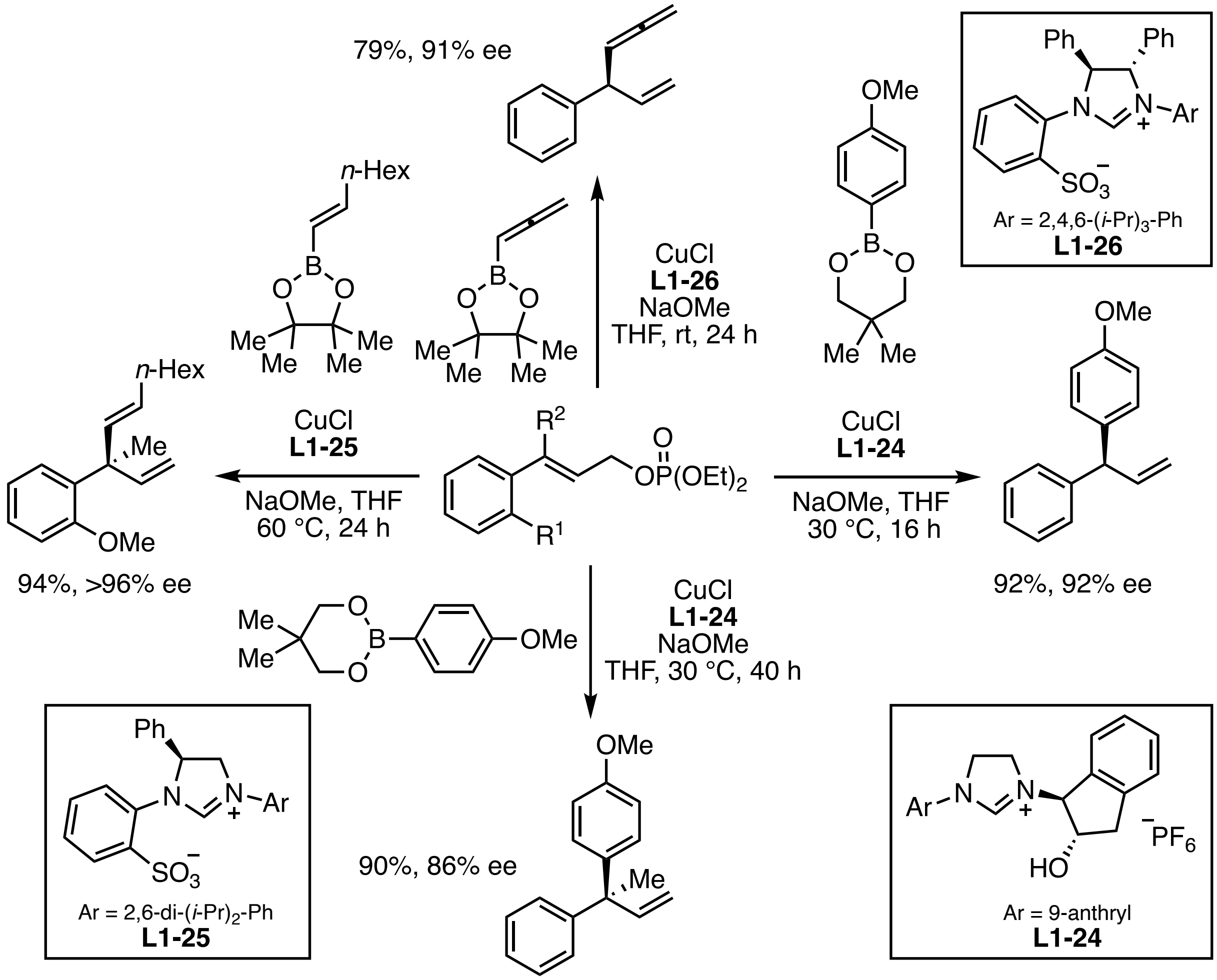


Figure 1-20: Cu-catalysed asymmetric allylic arylation, alkenylation and allenylation.

In a recent example, Li, Liu and co-worker reported copper catalysed Suzuki–Miyaura reactions between secondary benzyl or propargylic bromides and methylated acenaphthoquinone-derived arylboronates (Figure 1-21).[85] Good yields and enantioselectivities were obtained using a cinchona alkaloid-derived *N*,*N*,*P*-ligand **L1-27**. The authors propose a radical mechanism, which accounts for the deracemisation process.

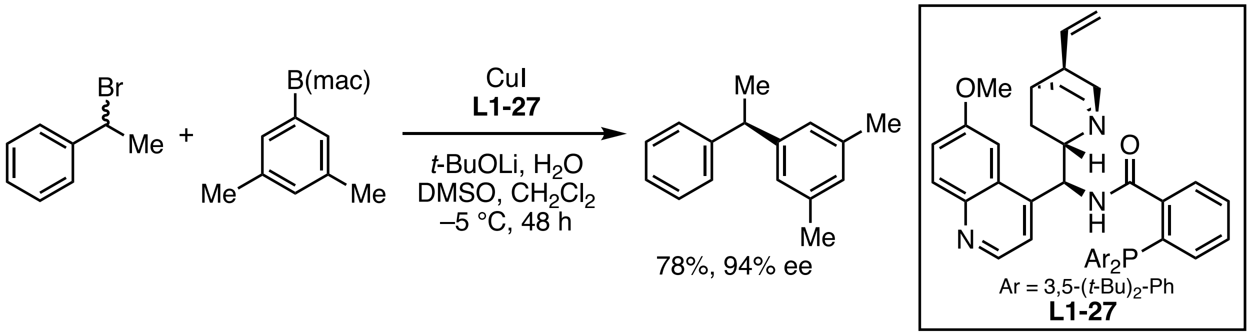


Figure 1-21: Cu-catalysed asymmetric cross-coupling between a benzyl bromide and arylboron species.

Iron-catalysed C(sp^2)–C(sp^3) couplings

There have also been reports of iron catalysed Suzuki–Miyaura couplings, which is the first time iron has been used for this type of asymmetric transformation. Recently, C(sp^2)–C(sp^3) Suzuki-couplings have been reported with racemic α-chlorocarboxylic esters[86] and secondary benzylic chlorides[87] (Figure 1-22). For the α-chlorocarboxylic esters (Figure 1-22a), highly reactive lithium alkylborates in combination with magnesium additives were used. Remarkably, for secondary benzylic esters (Figure 1-22b), lithium amide bases coupled with a cyanobis(oxazoline) ligand (**L1-29**) provided sufficient reactivity using boronic esters. However, in both reports the obtained enantioselectivities were moderate to low.

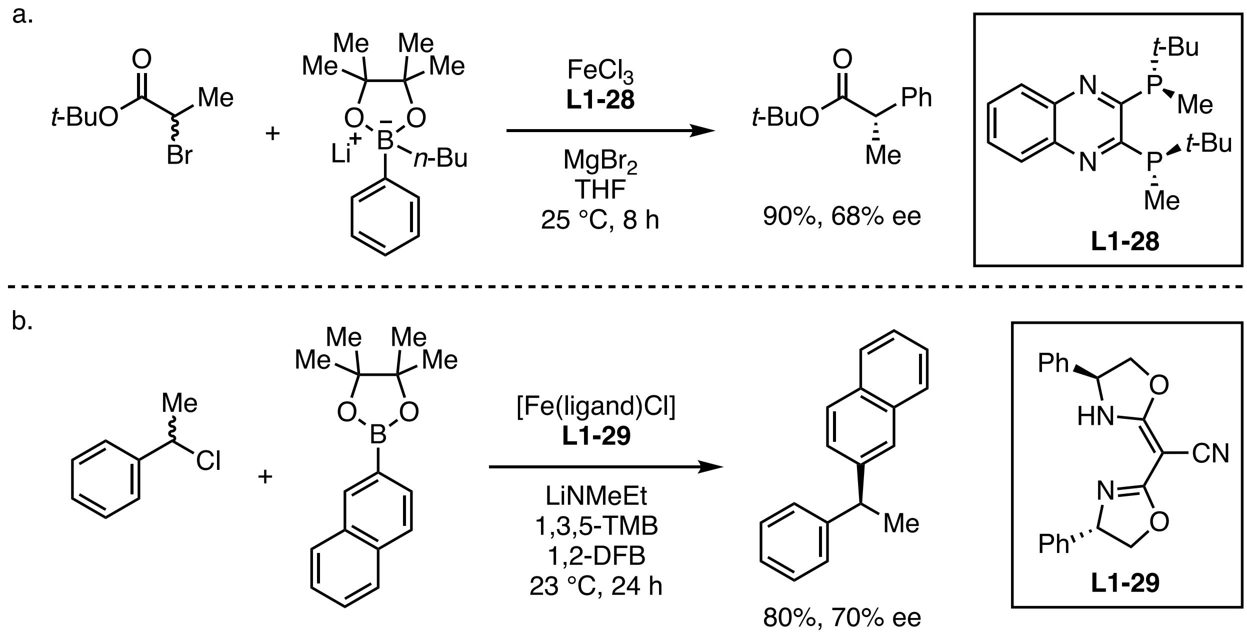


Figure 1-22: Fe-catalysed asymmetric cross-coupling reactions between α-chlorocarboxylic esters (a) or benzyl chlorides (b) and (activated) aryl boronic esters.

Outlook for C(sp^2)–C(sp^3) and C(sp^3)–C(sp^3) couplings

Over the last two decades, a range of powerful and highly enantioselective C(sp^2)–C(sp^3) and C(sp^3)–C(sp^3) Suzuki–Miyaura couplings have been developed with different metal catalysts. However, the development of most of these reactions still focuses on simple benchmark substrates, and many protocols are limited to specific functional groups on either coupling partner. Developing generally applicable enantioselective C(sp^2)–C(sp^3) and C(sp^3)–C(sp^3) cross-couplings offers exciting opportunities for the future.

Chapter 2: Asymmetric Suzuki–Miyaura Cross-Coupling Reactions

Dedicated to my siblings Oda Christiane, Hanns Hagen and Carl Christoph
for their love and support in all times.

Chapter **2** of this thesis deals with catalytic asymmetric Suzuki–Miyaura cross-coupling reactions between allyl halides and boronic acids. **Chapter 2.1** gives an overview over asymmetric addition reactions to racemic cyclic allyl halides with a focus on methods developed in the laboratory of Stephen Fletcher and introduces the rhodium-catalysed coupling of racemic allyl halides with aryl- and alkenylboronic acids. In **Chapter 2.2.**, we develop a de-racemisation of fused bicyclic allyl halides *via* formation of *pseudo*-meso Rh-π-allyl complexes. In **Chapter 2.3**, we demonstrate that the approach shown in **Chapter 2.2** can be applied in complex molecule synthesis – showcased in the synthesis of the prostaglandin analogue Tafluprost. In **Chapter 2.4**, we look at current challenges in rhodium-catalysed Suzuki-Miyaura reactions and propose some future directions of this research programme.

2.1. Additions to Racemates: A Strategy for Developing Asymmetric Cross-Coupling Reactions

Chapter 2.1. is based on the following invited account:

Goetzke, F. W.; Fletcher, S. P. Additions to Racemates: A Strategy for Developing Asymmetric Cross-Coupling Reactions. *Synlett* **2021**, *32*, 1816-1825.

I contributed to this chapter by joint planning of the manuscript with Stephen P. Fletcher and by writing the manuscript for publication with contributions from Stephen P. Fletcher.

2.1.1. Motivation

In order to circumvent the drawback of classical Suzuki–Miyaura reactions generating C(sp^2)-rich scaffolds without stereogenic centres (Figure 2-1a; see **Chapter 1.1**), the Fletcher group and many other laboratories are working on equipping medicinal chemists with generally applicable enantioselective C(sp^2)–C(sp^3) and C(sp^3)–C(sp^3) bond-forming reactions, which share the highly desirable features of established cross-coupling reactions. Our group identified cross-coupling reactions with racemic electrophiles as suitable substrates for the construction of C(sp^3)-rich, chiral scaffolds (Figure 2-1b). The use of racemic substrates is very attractive as it circumvents limitation of using only very simple, prochiral or *meso*-substrates, but mechanistically very challenging to realise.

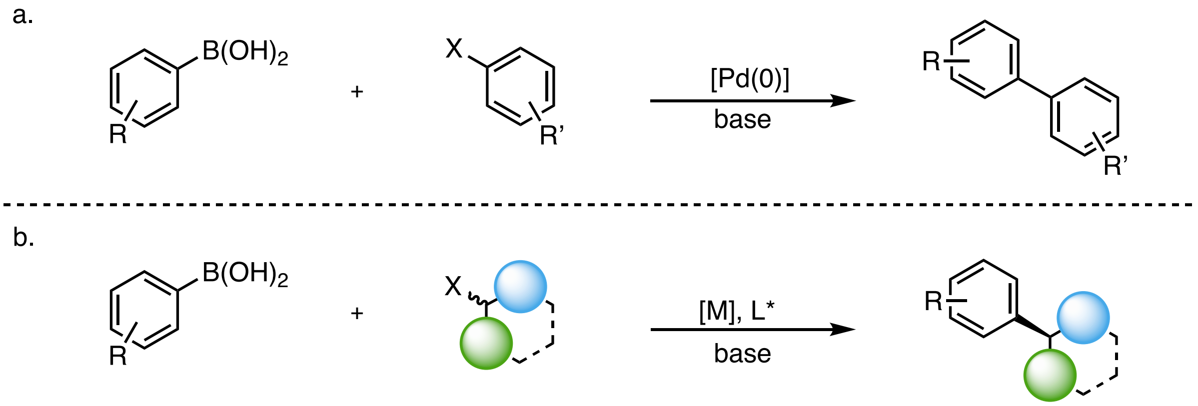


Figure 2-1: The classical Suzuki–Miyaura (a) and a schematic representation of an asymmetric C(sp^2)–C(sp^3) coupling (b).

2.1.2. Dynamic Kinetic Transformations

Dynamic kinetic transformations (DyKAT) or dynamic kinetic resolutions (DKR) are useful strategies to convert both enantiomers of a racemic mixture of starting material into highly enantioenriched reaction products.[88] They overcome the intrinsic drawback of kinetic resolutions (KR) where yields are limited to 50%.[89] In DyKATs, de-racemisation is facilitated via rapid racemisation of diastereomeric catalytic intermediates (Figure 2-2a; type I) or via formation of *pseudo*-achiral intermediates (Figure 2-2b; type II). The term *pseudo*-achiral implies that the chiral environment of the catalyst is still present, but the chiral element of the substrate is lost.

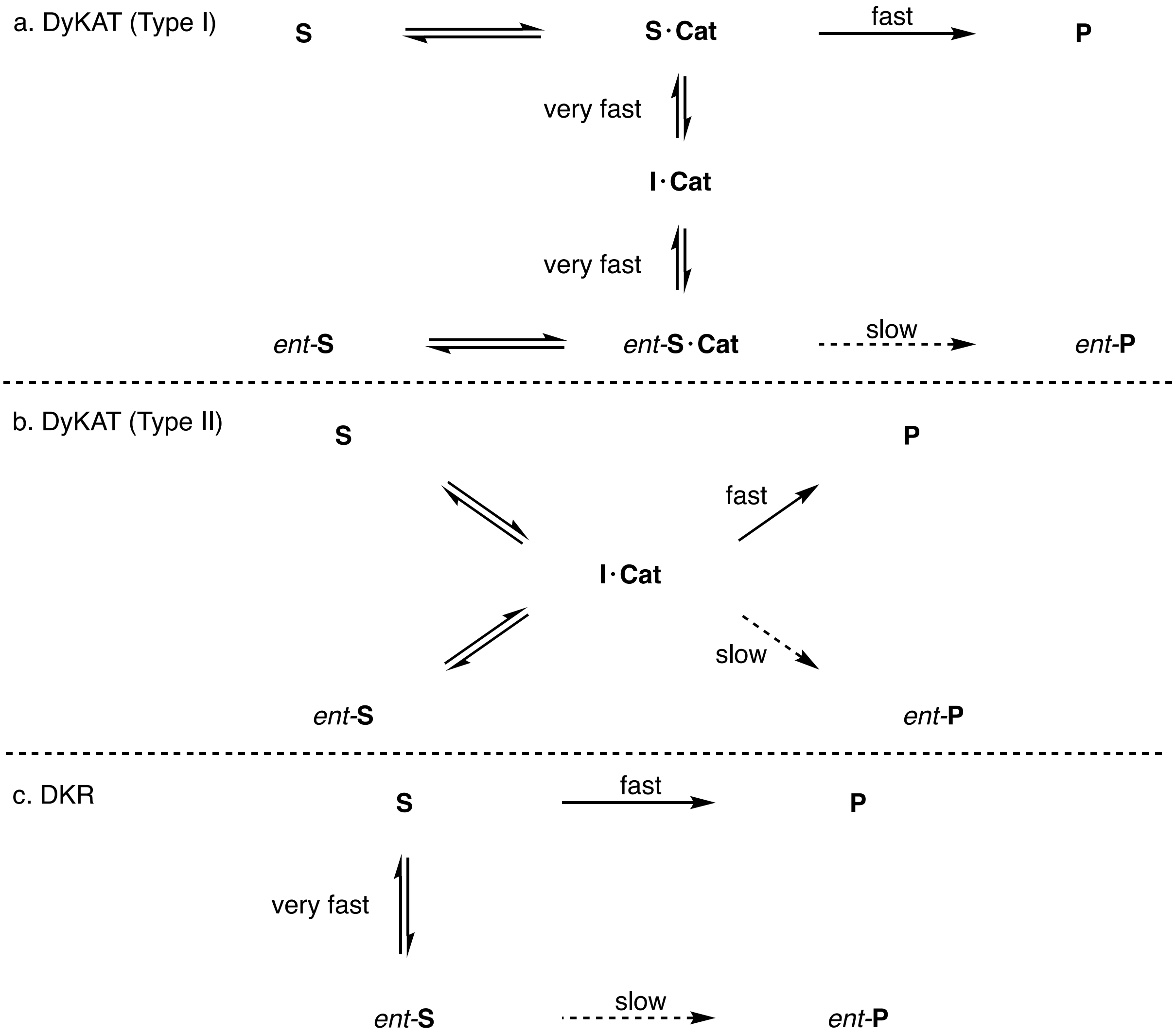


Figure 2-2: Dynamic kinetic transformation (a and b) and dynamic kinetic resolution (c).

In a dynamic kinetic resolution, racemisation occurs independent of the chiral catalyst.[88] In a kinetic resolution, a chiral catalyst selects one of the two enantiomers for a stereospecific reaction. In a DKR, an external and rapid racemisation of the starting material is coupled to a kinetic resolution, allowing for yields >50% of enantioenriched products (Figure 2-2c).

2.2.3. Pd-Catalysed Allylic Substitution with Stabilised Nucleophiles

Pd-catalysed asymmetric allylic substitution reactions – commonly also termed Tsuji–Trost reactions – have emerged as one of the few widely applicable de-racemisation processes.[90–92] In these reactions, de-racemisation occurs via formation of *pseudo*-prochiral Pd-π-allyl complexes from both enantiomers of an activated allylic species (e.g. allyl carbonate), followed by an enantioselective, outer-sphere attack of a stabilised nucleophile (Figure 2-3).[90] Stabilised nucleophiles have a corresponding pK_a <25, which includes many heteroatom nucleophiles and some stabilised α-carbonyl carbon nucleophiles.

As opposed to this, non-stabilised nucleophiles (pK_a >25) follow a distinct inner-sphere mechanism. After the initial oxidative addition, the organometal species attacks the metal centre. This transmetalation is then followed by enantiodetermining reductive elimination.[93] Non-stabilised nucleophiles are generally not suitable coupling partner in asymmetric Tsuji–Trost reactions, but a few noteworthy enantioselective exceptions are known.[94–96]

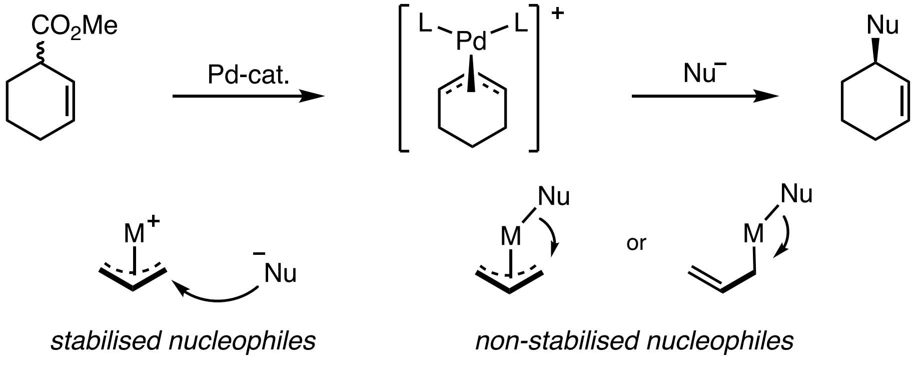


Figure 2-3: Stabilised and non-stabilised nucleophiles in metal-catalysed allylic substitution reactions.

2.2.4. Cu-Catalysed Allylic Substitution with Non-Stabilised Nucleophiles

Unlike palladium, copper is known to lack efficient σ-π-σ isomerisation in allylic substitution reactions, but pioneering work by Norinder and Bäckvall on enantiospecific allylic substitution reactions with Grignard reagents occurred under erosion of enantiomeric excess, suggesting that Cu-π allyl complexes could be formed transiently.[97] Several laboratories tried to harness the transient formation of Cu-π allyl complexes as de-racemisation strategy and Langlois and Alexakis developed an asymmetric alkylation of racemic, cyclic allylic bromides.[98] However, subsequent mechanistic work showed that the reaction proceeded via enantiodivergent oxidative addition of both enantiomers of the bromide rather than via the formation of a common Cu-π allyl complex.[99]

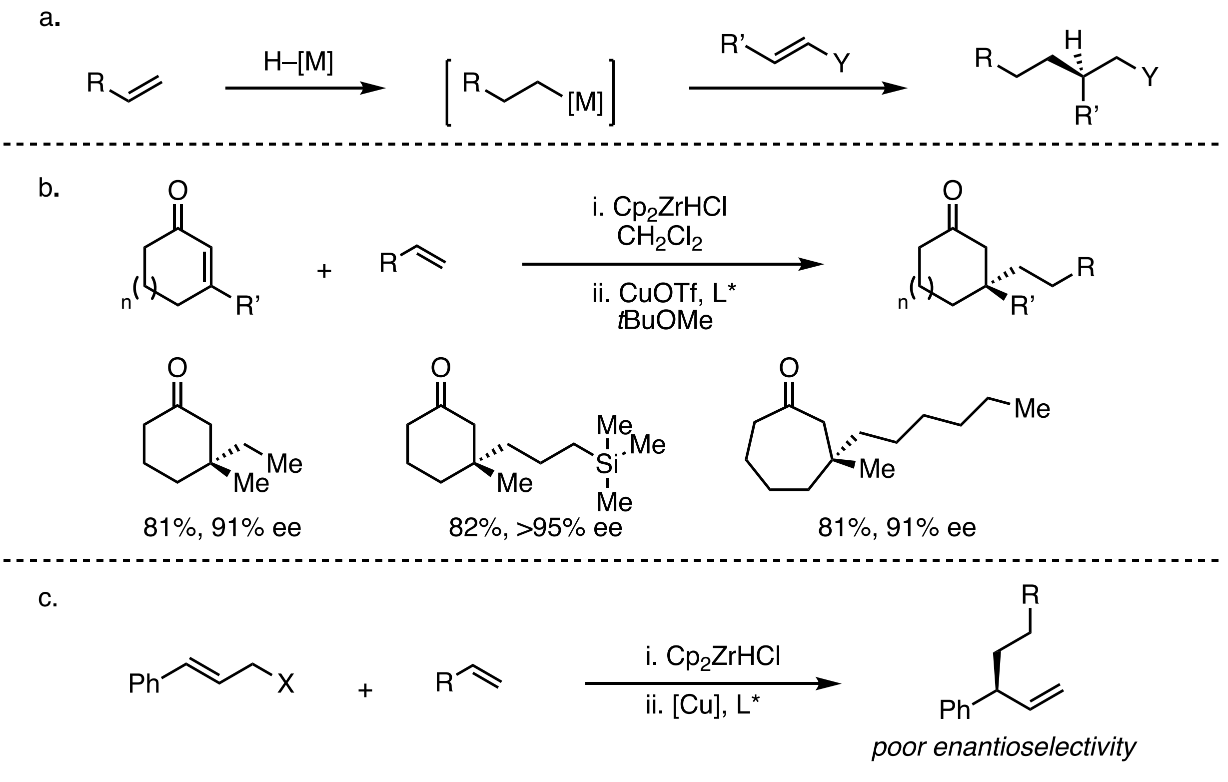


Figure 2-4: Asymmetric hydrometallation (a) and its application in conjugate addition (a, b) and attempted allylic substitution (c).

The Fletcher group has long standing interest in developing new metal-catalysed asymmetric carbon-carbon bond forming reactions. Earlier work by our group shows that alkyl zirconium reagents can be generated via hydrometallation of alkenes with the Schwartz's reagent (Cp_2ZrHCl) (Figure 2-4a). The *in situ* generated alkyl zirconium species can be used in Cu-catalysed asymmetric conjugate addition (ACA) reactions with cyclic and acyclic Michael acceptors (Figure 2-4b).[100–102] The use of alkyl zirconium nucleophiles, compared to other organometallic species like organomagnesium or organolithium compounds, is very attractive as they are less reactive towards a range of functional groups and can be used under non-cryogenic conditions.[103] Initial efforts were focussed on extending this work to asymmetric allylic alkylation (AAA) reactions with terminal, prochiral allyl halides (Fig 2-4c). Those reactions turned out to be challenging to optimise,[104] and during these studies cyclic, racemic allyl halides were investigated.

Cyclic, racemic allyl chlorides undergo highly enantioselective and high yielding asymmetric allylic alkylation (AAA) reactions under a unique set of optimised reaction parameters (Figure 2-5).[105] The use of chloride as the leaving group and the choice for a catalyst generated *in situ* from CuI and a phosphoramidite ligand proved to be crucial for effective reactions.

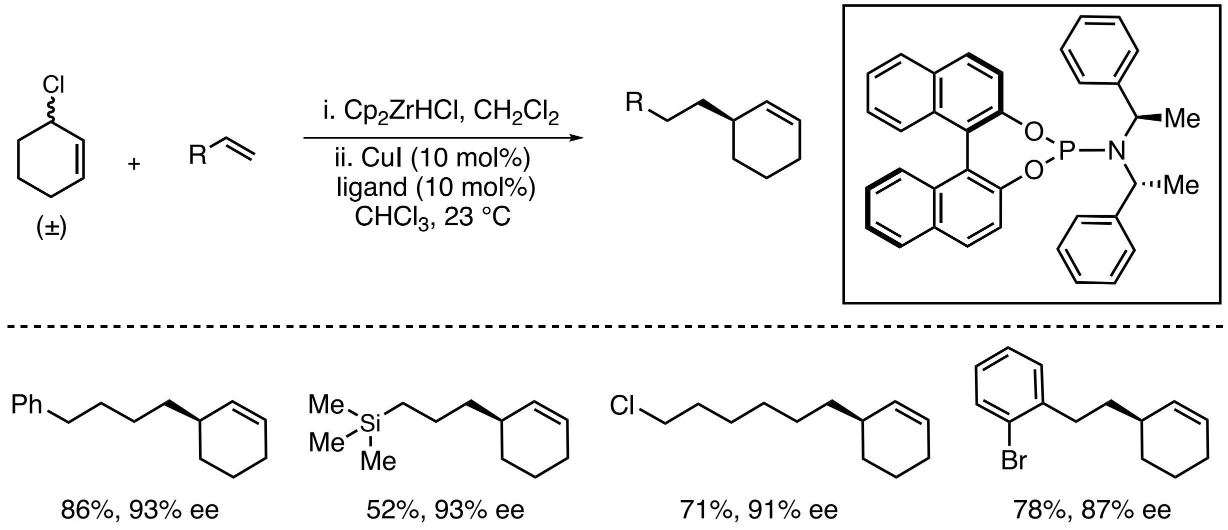


Figure 2-5: Copper-catalysed allylic alkylation with *in situ* generated alkyl zirconium species.

A key feature of this reaction is its underlying deracemisation mechanism, which allows for highly enantioenriched alkylation products with yields larger than 50%. *In situ* ^{1}H and EXSY NMR studies showed that an allyl iodide is formed reversibly (Figure 2-6a), which racemises rapidly on the NMR timescale.[105,106] The interconversion of allylic chlorides and iodides occurs via a catalyst-mediated *syn* S_N2' halide transfer (Figure 2-6b). A likely dimeric copper complex selects one of the allylic chloride enantiomers for enantioselective alkylation reaction.[106] Kinetic studies and determination of rate constants suggest that racemisation is >10^2 faster than the enantiodetermining carbon-carbon bond-formation.

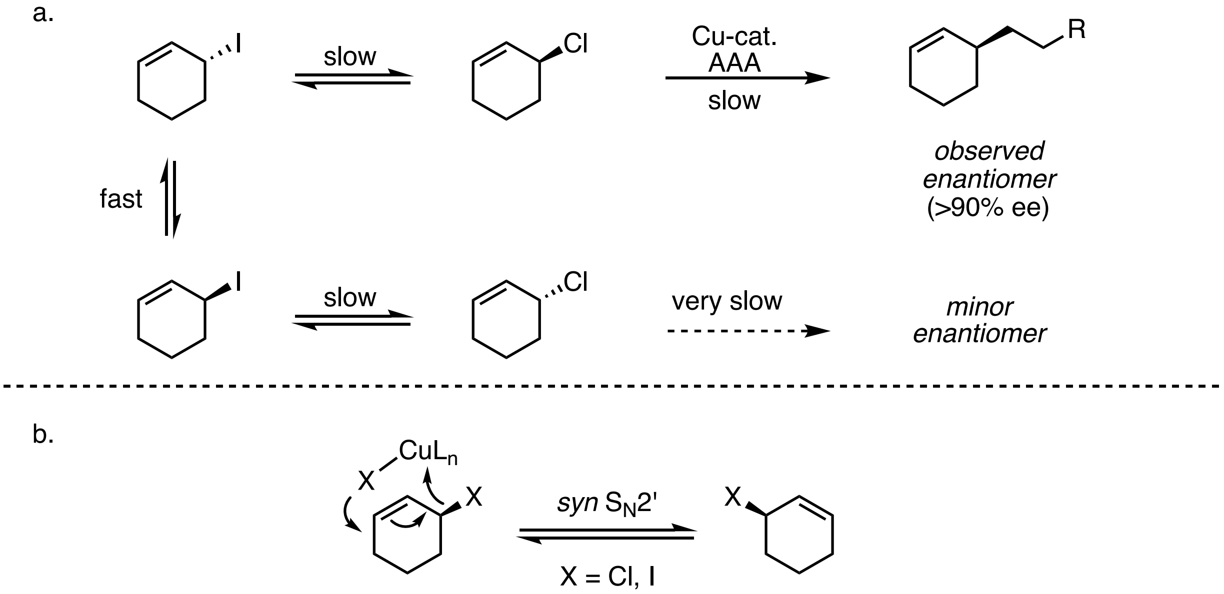


Figure 2-6: De-racemisation mechanism of allyl chlorides with CuI (a) and Cu-mediated *syn* S$_N$2' racemisation (b).

Lee, Tan and co-workers managed to harness a related racemisation mechanism for the asymmetric alkynylation of cyclic, racemic allyl bromides.[107] In this system, a (guanidine)copper bromide complex is likely to facilitate deracemisation.

While the reaction is highly enantioselective for 5 to 7-membered all-carbon allyl chlorides, heterocyclic allyl halides including 3-chloro-3,6-dihydro-2H-pyran have proven difficult to optimise and so far, no highly enantioselective conditions have been found.[108] Instead of a dynamic kinetic transformation, an unexpected kinetic resolution occurred with a tetrahydropyridine derived allyl chloride (Figure 2-7).[109] The kinetic resolution gives access to configurationally stable, enantioenriched allyl chlorides, which can be used as substrates in stereospecific substitution reactions.

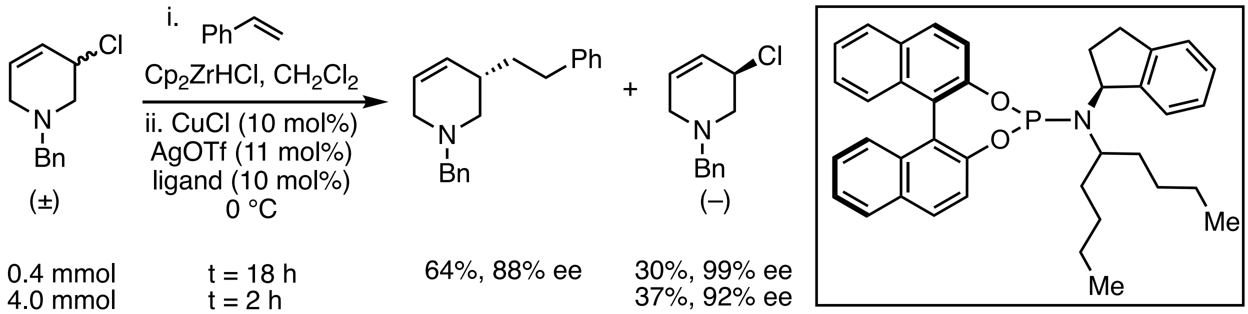


Figure 2-7: Kinetic resolution of a tetrahydropyridine allyl chloride.

Despite extensive optimisation, extending the same deracemisation mechanism to C(sp^2)-nucleophiles generated *in situ* from alkynes gave only low enantioselectivities on simple model substrates (Figure 2-8).[110] Probably, this Cu-catalysed alkenylation proceeds via a different mechanism.

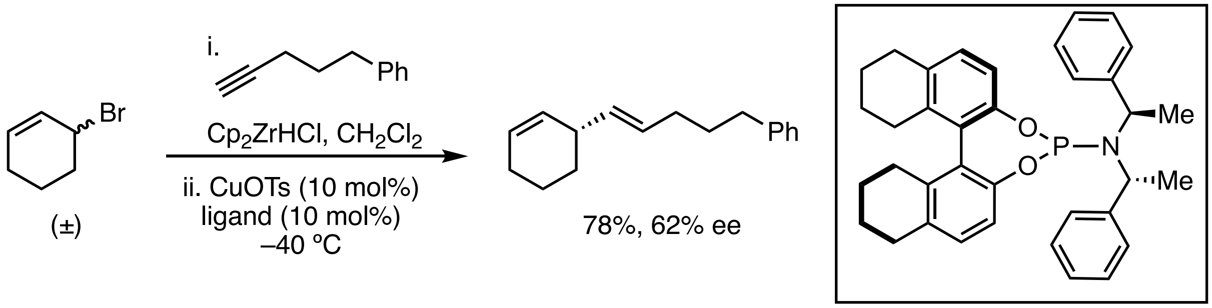


Figure 2-8: Copper-catalysed allylic alkenylation with *in situ* generated alkenyl zirconium species.

2.2.5. Rh-Catalysed Asymmetric Suzuki–Miyaura Couplings

Grounded by the poor results with C(sp^2) alkenyl nucleophiles, the Fletcher group aimed to develop alternative metal-catalysed C(sp^2)–C(sp^3) cross-coupling reactions, and an asymmetric variant of the Suzuki–Miyaura coupling between allyl chlorides and arylboronic acids was identified as a useful and attractive transformation (see **Chapter 1**).[27] Arylboronic acids had been previously used as nucleophiles in highly enantioselective Rh-catalysed addition reactions to Michael acceptors and other electron-deficient alkenes.[61,111,112] Inspired by the pioneering work of Hayashi, racemic allyl halides were investigates as coupling partner in Rh-catalysed arylations.

A range of conditions that were reported for asymmetric 1,4-addition reactions did not afford the desired cross-coupling products with racemic allyl chlorides. However, conditions that Lautens and co-workers used in Rh-catalysed desymmetrisation reactions of *meso*-cyclic allylic dicarbonates gave immediately excellent results (see Figure 1-16).[62,63,113] This reaction system consisting of a catalyst generated from $[Rh(cod)OH]_2$ and the bidentate phosphine (*S*)-Xyl-P-Phos with Cs_2CO_3 as a base gives consistently excellent stereoselectivity (generally >94% ee), is applicable to allyl chlorides of various ring sizes, and tolerates a broad range of functionality in the arylboronic acid coupling partner (Scheme 2-9). In some cases, with challenging boronic acids (e.g. *ortho*-substituted), better results can be achieved by using the allylic bromide instead of the chloride. In a related Hiyama protocol, siloxanes can be used instead of arylboronic acids upon activation with a fluoride source.[114]

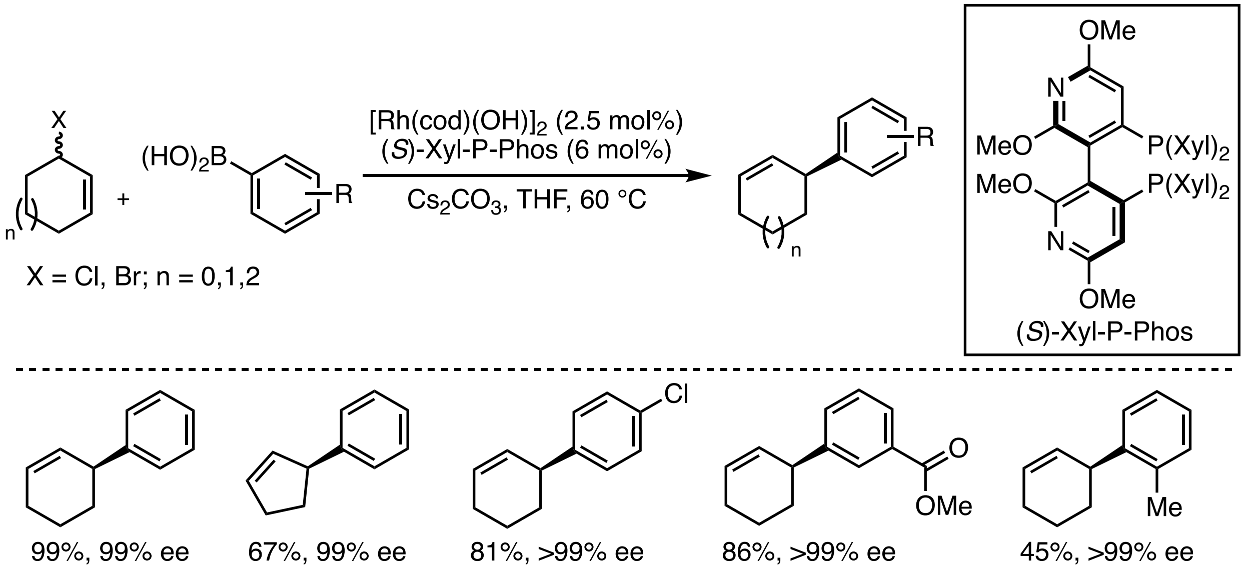


Figure 2-9: Asymmetric Rh-catalysed Suzuki–Miyaura coupling between racemic allyl chlorides and arylboronic acids.

Extensive mechanistic studies including natural abundance kinetic isotope effects, determination of rate constants, deuterium-labelled substrates, competition experiments and DFT studies showed that the underlaying deracemisation mechanism is very different from the one previously observed for Cu-catalysed allylic alkylation reaction.[115]

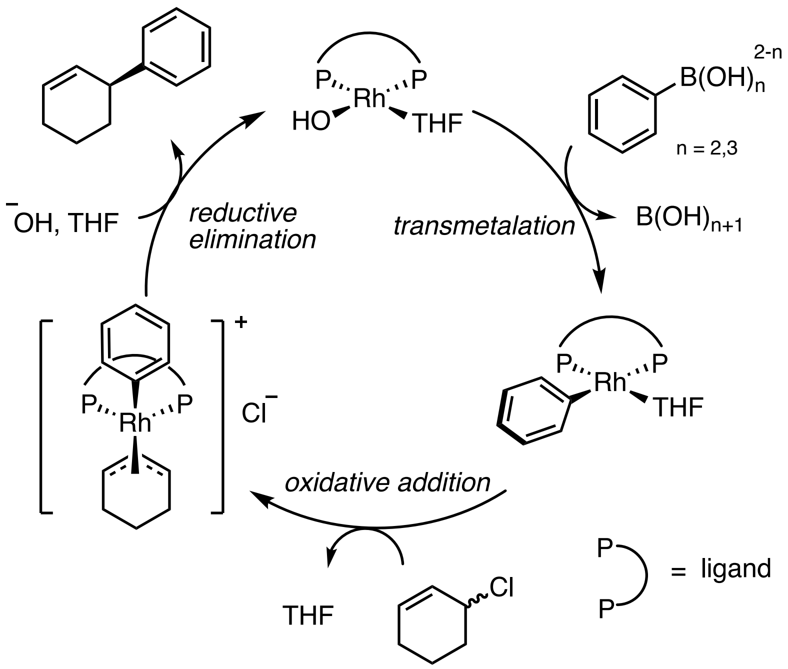


Figure 2-10: Mechanism of the Rh-catalysed Suzuki–Miyaura coupling.

The following mechanism is consistent with the obtained data (Figure 2-10). Fast and irreversible transmetallation of arylboronic acids to a Rh-hydroxide complex is followed by oxidative addition of both enantiomers of the allyl chloride to give a common η^3-allylic complex. The experiments with 5-phenyl-3-chlorocyclohex-1-ene as diastereomeric probe suggest that oxidative addition occurs *anti* (Figure 2-11).[113] Final enantiodetermining reductive elimination liberates the product and regenerates the active catalyst.[115]

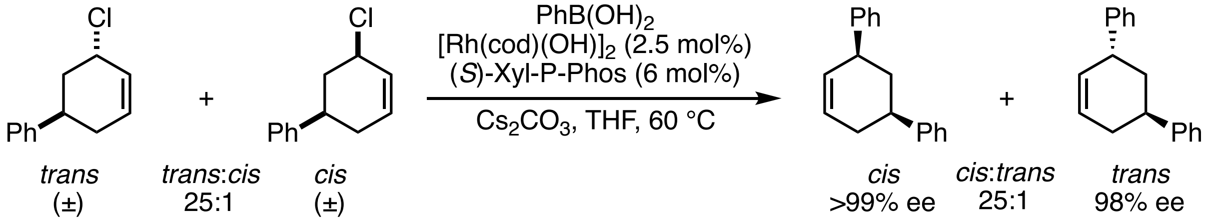


Figure 2-11: Diastereoselective Rh-catalysed Suzuki–Miyaura coupling with stereochemical probe.

Alkenylboronic acids can be challenging substrates in Rh-catalysed addition reactions due to different steric and electronics compared to arylboronic acids. Several (*E*)-styryl- and alkenylboronic gave good result using BINAP as the chiral ligand (Figure 2-12).[116] Sometimes superior results can be obtained with Xyl-P-Phos but the underlying trends for this behaviour are unclear (see Scheme 2-12, (*E*)-(2-fluorostyryl)boronic acid and (*E*)-(4-fluorostyryl)boronic acid).

One of the features of the classical Suzuki–Miyaura coupling, which made it so popular in medicinal chemistry, is that it allows for the coupling of one or two heterocycles.[17] This Rh-catalysed Suzuki–Miyaura coupling also tolerates heterocycles in either coupling partner.[116] Several heterocyclic boronic acids of different ring-sizes gave moderate to good yields with consistently excellent levels of enantioinduction (Figure 2-12). Fine tuning of the reaction conditions is often required to achieve optimal result with a specific boronic acid, and some nitrogen containing heterocycles can be challenging. While pyridylboronic acids inhibit the catalytic cycle, 2-halopyridines can be used as pyridine surrogates. The halide can be used for downstream reactions or can be cleaved under reductive conditions. This strategy was employed in an asymmetric synthesis of the natural product (+)-Isoanabasine.[116,117]

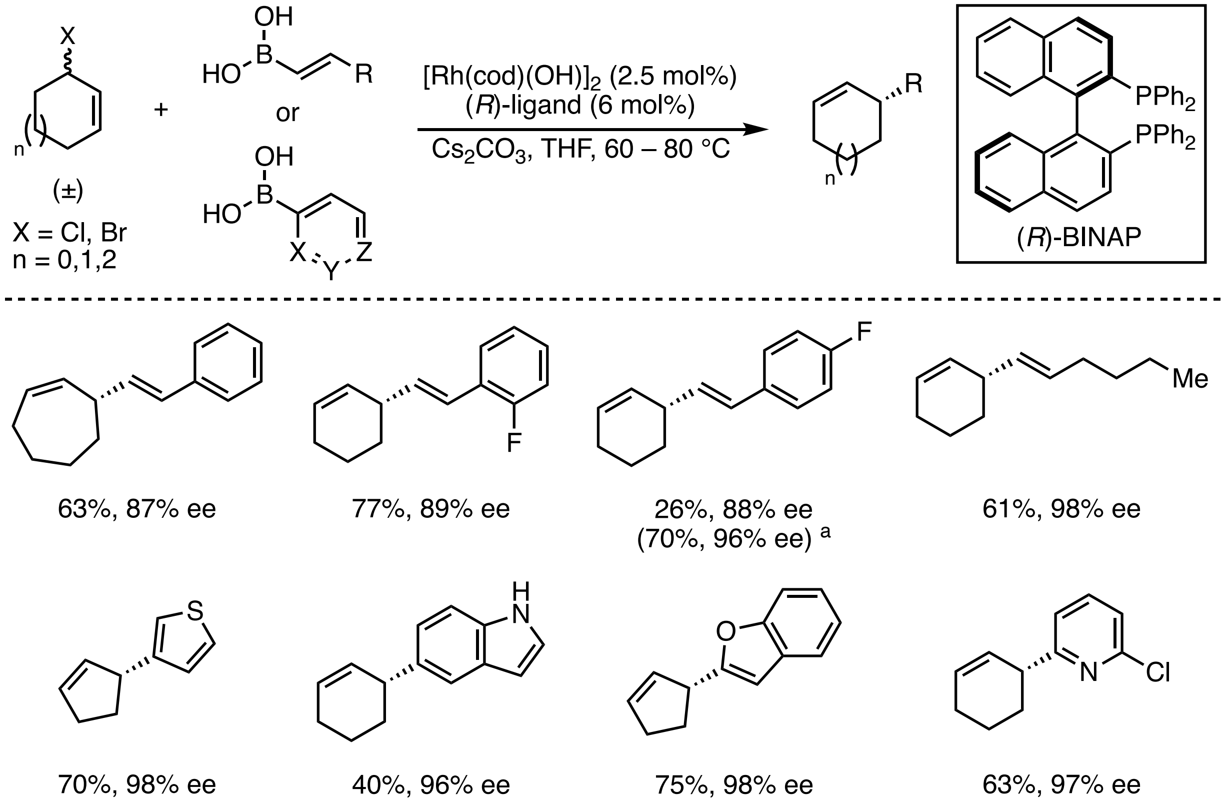


Figure 2-12: Asymmetric Rh-catalysed Suzuki–Miyaura coupling between racemic allyl chlorides and alkenyl- and heteroarylboronic acids. [a] Xyl-P-Phos used instead of BINAP.

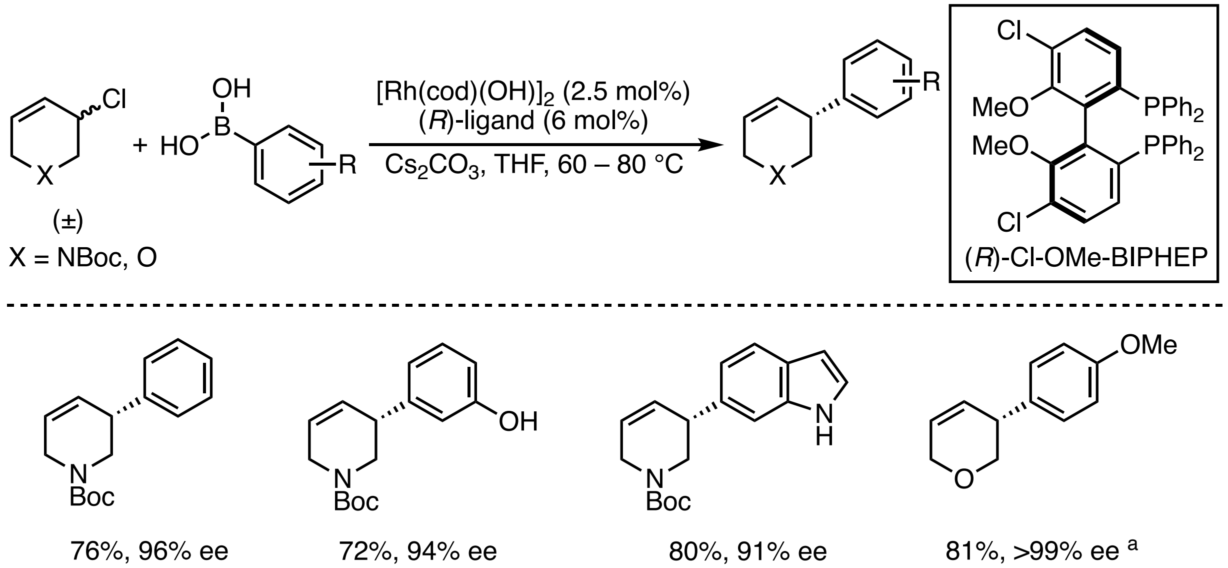


Figure 2-13: Asymmetric Rh-catalysed Suzuki–Miyaura coupling with racemic, heterocyclic allyl chlorides. [a] Xyl-P-Phos used instead of Cl-OMe-BIPHEP.

Heterocyclic allyl chlorides *N*-Boc protected 3-chloro-1,2,3,6-tetrahydropyridine and 3-chloro-3,6-dihydro-2H-pyran undergo high yielding cross-coupling reactions with various boronic acids under optimised conditions (Figure 2-12).[113,116] Importantly, this method allows for a C(sp^2)–C(sp^3) bond forming reaction between two heterocyclic coupling partner.

Rh-catalysed Suzuki–Miyaura reactions are well suited for the target synthesis of bioactive compounds. Niraparib (Zejula, MK-4827) is a poly-ADP ribose polymerase (PARB) inhibitor for the treatment of ovarian cancer.[118] Niraparib was discovered by Merck Sharp and Dohme and developed by Tesaro and gained FDA approval in 2017. Reported process routes rely on chiral resolution or biocatalytic cyclisation to obtain the enantioenriched piperidine core.[119] Our group showed that Niraparib can be synthesised via three different Rh-catalysed arylation reactions, followed by reduction of the tetrahydropyridine with Wilkinson's catalyst (Figure 2-14, only two depicted).[116] Upon re-optimisation of the reaction conditions with 4-bromophenylboronic acids, we found that better, highly reproducible and scalable results could be obtained with the pinacol ester instead of the free boronic acid in combination with aqueous CsOH as base.[120]

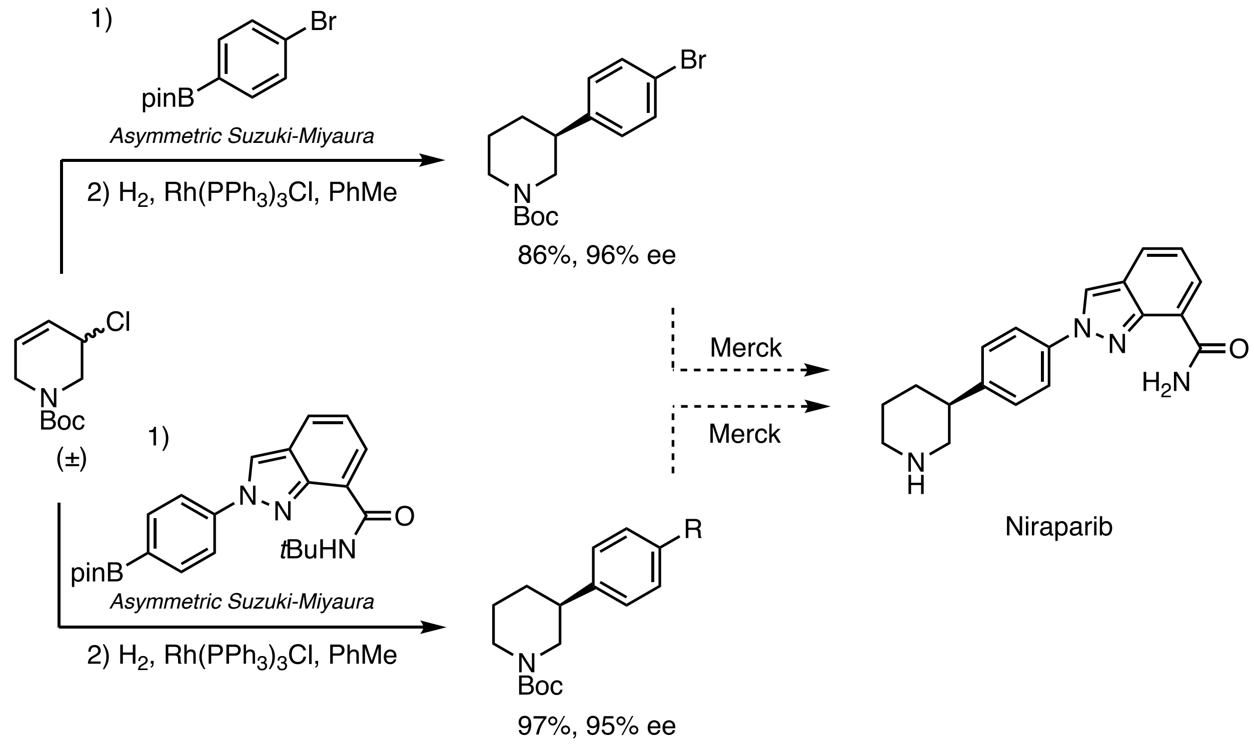


Figure 2-14: Asymmetric Rh-catalysed syntheses of Niraparib.

All asymmetric allylic alkylation and arylation reactions presented in this section allow for the formation of one stereogenic centre in a single reaction step. The following sections of **Chapter 2** describe strategies to obtain more stereochemically complex coupling products and their use for target synthesis.

2.2. Asymmetric Suzuki–Miyaura Coupling with Racemic Bicycles

Chapter 2.2. is based on the following publication:
Goetzke, F. W., Mortimore, M. & Fletcher, S. P. Enantio- and Diastereoselective Suzuki-Miyaura Coupling with Racemic Bicycles. *Angew. Chem Int. Ed.* **2019**, *58*, 12128–12132

I performed all experiments in **Chapter 2.2**. Further, I contributed to this chapter by joint project conception with Stephen P. Fletcher, and by writing the manuscript for publication with contributions from Stephen P. Fletcher. Stephen P. Fletcher and Mike Mortimore guided the research. Experimental procedures and characterisation data for experiments in **Chapter 2.2** can be found in **Chapter 5.2**.

2.2.1. Introduction

Over the last three decades, the development of catalytic asymmetric methods has been overly focussed on simple bench-mark substrates – typically introducing one stereogenic centre in a single step.[17] Methods that can be applied in complex settings or methods that generate a lot of complexity in a single step are rare but highly desirable. In this context, rigid and saturated bi- and polycyclic structures with multiple stereogenic centres are attractive and underexplored targets.

In 2018, Baran and co-workers reported a modular approach towards bridged bicyclic structures via a cycloaddition, desymmetrisation and cross-coupling sequence (Figure 2-15a).[121] Lautens and co-worker reported asymmetric hydroarylation reaction with strained alkenes (Figure 2-15b).[122] In both approaches, *meso*-starting materials are desymmetrised and multiple stereogenic centres are controlled in the desymmetrisation step. Methods that deracemise complex, racemic starting materials are rare,[70,123] but intrinsically attractive as they circumvent the problem of being limited to the use of prochiral and *meso* starting materials.[88] While our group's previous work with racemic starting materials enabled the synthesis of rather simple coupling products bearing only one stereogenic centre,[113,116] we wondered if multiple stereogenic centres could be controlled in a coupling with a racemic, bicyclic precursor, and we aimed to harness a related deracemisation mechanism via the formation of Rh-π-allyl complexes.

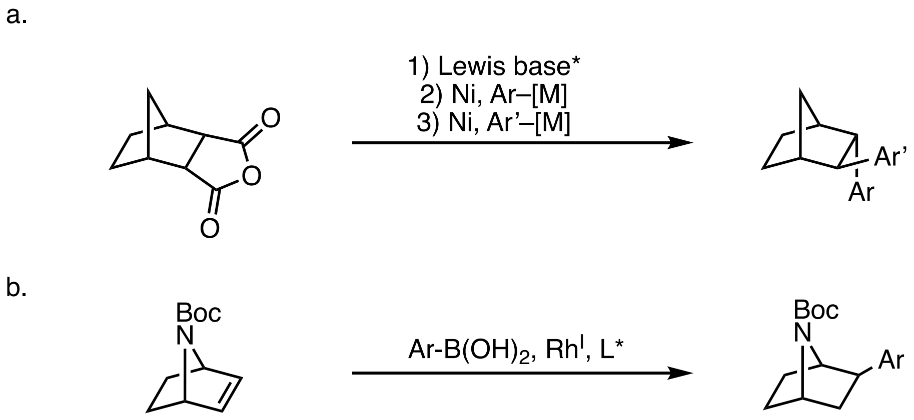


Figure 2-15: Desymmetrisation, cross-coupling sequence by Baran and co-workers (a.) and desymmetrisation of a bicyclic strained alkene by Lautens and co-worker (b.).

Asymmetric addition reactions to bicyclic allylic systems are non-trivial and challenging due to their high steric congestion,[124] and only three reports of related reactions with heteroatom nucleophiles have been reported using Pd-catalysis.[125–127]

2.2.2. Objective of the Project

In **Chapter 2.2**, we explore if enantio- and diastereoselective Rh-catalysed cross-coupling reactions between racemic allyl chlorides and arylboronic acids can be developed. A diastereoselective oxidative addition step of a *pseudo*-symmetric allyl chloride would give a *pseudo*-meso Rh-π-allyl complex (Figure 2-16; Pathway A or B) and set the relative stereochemistry in the product. Subsequent enantioselective reductive elimination would control the absolute stereochemical configuration of contiguous stereogenic centres in highly substituted coupling products. Depending on the mechanism of the oxidative addition, the *cis-cis* or the *cis-trans* product could be obtained.

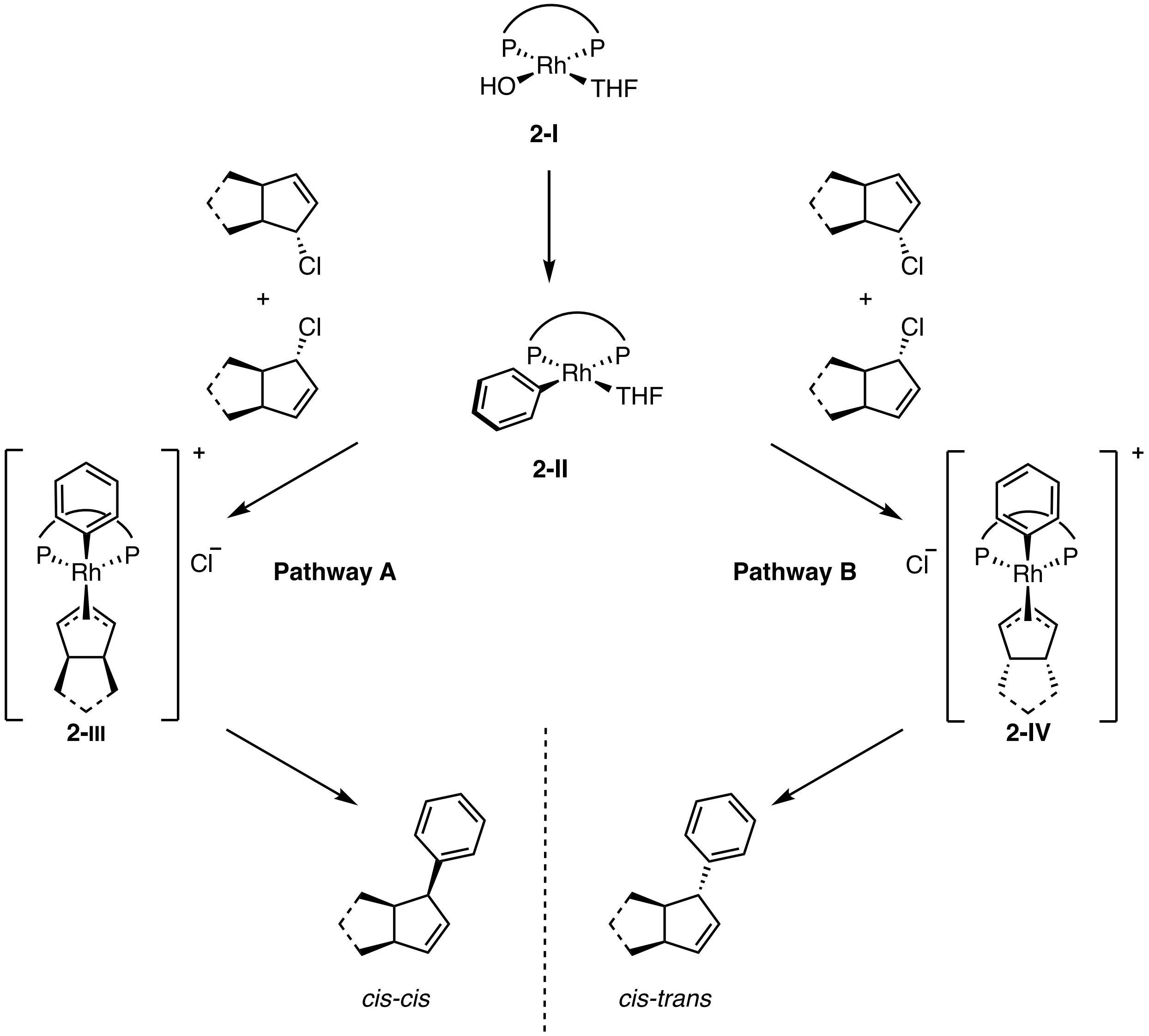


Figure 2-16: Stereoselective formation of *pseudo*-meso Rh-π-allyl complexes.

2.2.3. Results and Discussion

Synthesis of the model allyl chloride

We chose bicyclic allyl chloride (±)-**2-6a** as a sugar-like model substrate. The allylic alcohol (±)-**2-5** was obtained in 4 previously reported synthetic steps from cyclopentadiene (Figure 2-17).[125] Allylic chlorination under Appel conditions gave (±)-**2-6a** as a single *cis-trans* isomer.

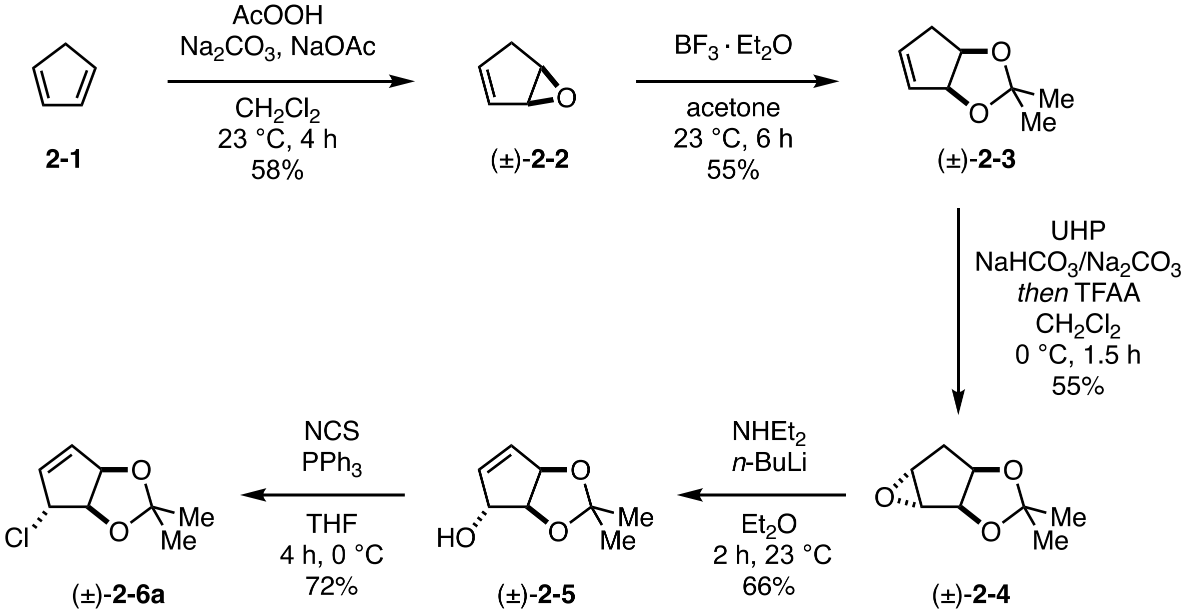


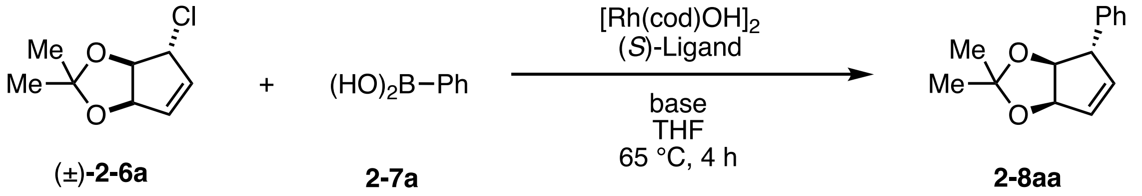
Figure 2-17: Synthesis of allyl chloride (±)-**2-6a**.

Reaction optimisation

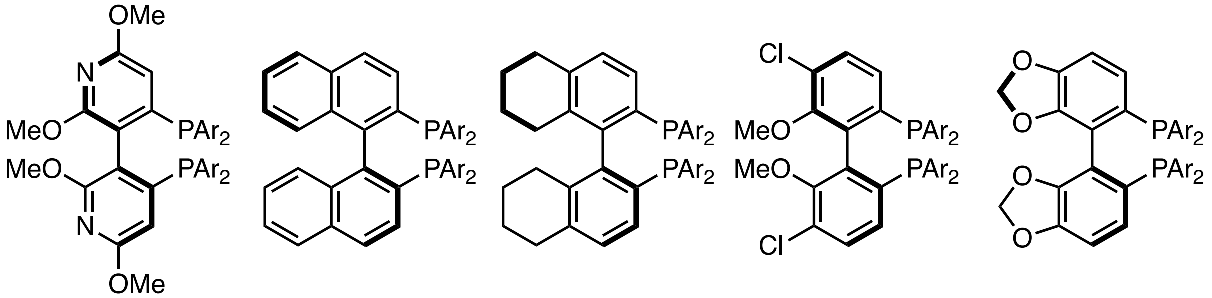
Having gram-quantities of (±)-**2-6a** in hand, we started our optimisation with phenylboronic acid (**2-7**) with conditions closely related to those previously reported by our group.[113,116] A catalyst generated *in situ* from $[Rh(cod)OH]_2$ in combination with **L2-1** or **L2-2** in THF afforded the single *cis-trans* diastereomer (dr >20:1) **2-8aa** in moderate yields and moderate enantioselectivity (Table 2-1; entries 1, 2). Changing the base from Cs_2CO_3 to aqueous solution of CsOH (50 wt%) improved conversion and yield without affecting the enantioselectivity (Table 2-1; entry 3). We subsequently explored different *C2*-symmetric bisphosphine ligands (Table 2-1; entries 4-11). Ligands with a 4,4'-bi-1,3-benzodioxole core (Segphos (**L2-8**), DM-Segphos (**L2-9**)) induced high levels of enantioinduction. Only with **L2-7**, we observed a significant formation of the minor *cis-cis* diastereoisomer (dr 12:1). Segphos was chosen for further experiments, and we observed that more reproducible results were obtained by increasing the concentration from 0.10

to 0.25 M upon changing the reaction scale from 0.2 to 0.4 mmol. We attributed this effect to changes in the effective concentration in the reaction flask at temperatures close to the boiling point of the solvent.

Table 2-1: Selected optimisation experiments for the coupling of (±)-**2-6a** with **2-7a**.



Entry	Ligand	Base	Yield [a]	Enantiomeric excess [b]
1	(*S*)-**L2-1**	Cs_2CO_3	62%	78%
2	(*S*)-**L2-2**	Cs_2CO_3	65%	76%
3	(*S*)-**L2-2**	aq. CsOH	74%	76%
4	(*S*)-**L2-3**	aq. CsOH	76%	82%
5	(*S*)-**L2-4**	aq. CsOH	92%	84%
6	(*S*)-**L2-5**	aq. CsOH	95%	84%
7	(*S*)-**L2-6**	aq. CsOH	75%	80%
8	(*S*)-**L2-7**	aq. CsOH	62%[c]	86%
9	(*S*)-**L2-8**	aq. CsOH	91%	95%
10	(*S*)-**L2-9**	aq. CsOH	88%	96%
11	(*S*)-**L2-10**	aq. CsOH	<20%	68%



(*S*)-**L2-1** Ar = Xyl
(*S*)-**L2-3** Ar = Ph

(*S*)-**L2-2** Ar = Ph
(*S*)-**L2-4** Ar = Xyl
(*S*)-**L2-5** Ar = Tol

(*S*)-**L2-6** Ar = Ph

(*S*)-**L2-7** Ar = Ph

(*S*)-**L2-8** Ar = Ph
(*S*)-**L2-9** Ar = Xyl
(*S*)-**L2-10** Ar = DTBM

Conditions: (±)-**2-6a** (0.4 mmol), **2-7a** (0.8 mmol), $[Rh(cod)OH]_2$ (2.5 mol%), (*S*)-Ligand (6 mol%), base (0.2 mmol), THF (0.1 M), 65 °C, 4 h.

[a] Isolated yields of the *cis-trans* diastereoisomer (>20:1 dr).

[b] Enantiomeric ratios were determined by SFC using a chiral non-racemic stationary phase.

[c] Isolated yield with dr of 12:1.

Asymmetric Suzuki–Miyaura coupling with different boronic acids

With optimised conditions, we investigated the scope of the boronic acid coupling partner (Figure 2-18a). Various *meta*- and *para*-substituted arylboronic acids gave the desired coupling products in good yields and excellent enantioselectivities. The reaction tolerates various electron-withdrawing (e.g. **2-8ah**) and donating (e.g. **2-8ai**) functional groups on the arene, including halides (**2-8ad-ag**) and also more challenging functionality including an acetyl group (**2-8ak**), a styrene (**2-8al**) and a cyano group (**2-8am**), albeit with only moderate yields for the latter. Like other asymmetric addition reactions with arylboronic acids,[62,113,128] *ortho*-substituted arylboronic acids (2-methyl or 2-chloro) showed very poor reactivity and enantioselectivity under our optimised reaction conditions. Steric factors are likely the driving factor for this behaviour, so that small 2-fluoro (**2-8ad**) and a 4-dibenzofuryl (**2-8ap**) substituents gave good results. The allyl halide (±)-**2-6a** is stable under the reaction conditions and almost exclusively undergoes the desired arylation reaction. The boronic acid coupling partner, which is used in excess, underwent decomposition pathways (protodeborylation),[129,130] so that significant quantities of unreacted **2-6a** were observed in the lower yielding reactions.

Heterocycles are key structural components of many small-molecule drugs.[131] Methods that tolerate a wide range of heterocycles are rare but highly desired for medicinal chemistry.[17] Key challenges associated with catalytic reactions with unsaturated heterocycles arise from the presence of basic sides and the different steric and electronics compared to simple arenes. Importantly, our method is compatible with a range of structurally and electronically different heteroarylboronic acids (**2-8ap-at**) with good to excellent enantioselectivities but sometimes moderate yields likely due to protodeborylation of the boronic acid (Figure 2-18b).

(*E*)-Alkenyl- and (*E*)-stryrenylboronic acids initially behaved poorly under our standard conditions, but a simple ligand change from Segphos to BINAP gave improved results with good enantiomeric excesses (**2-8au-aw**) (Figure 2-18c).

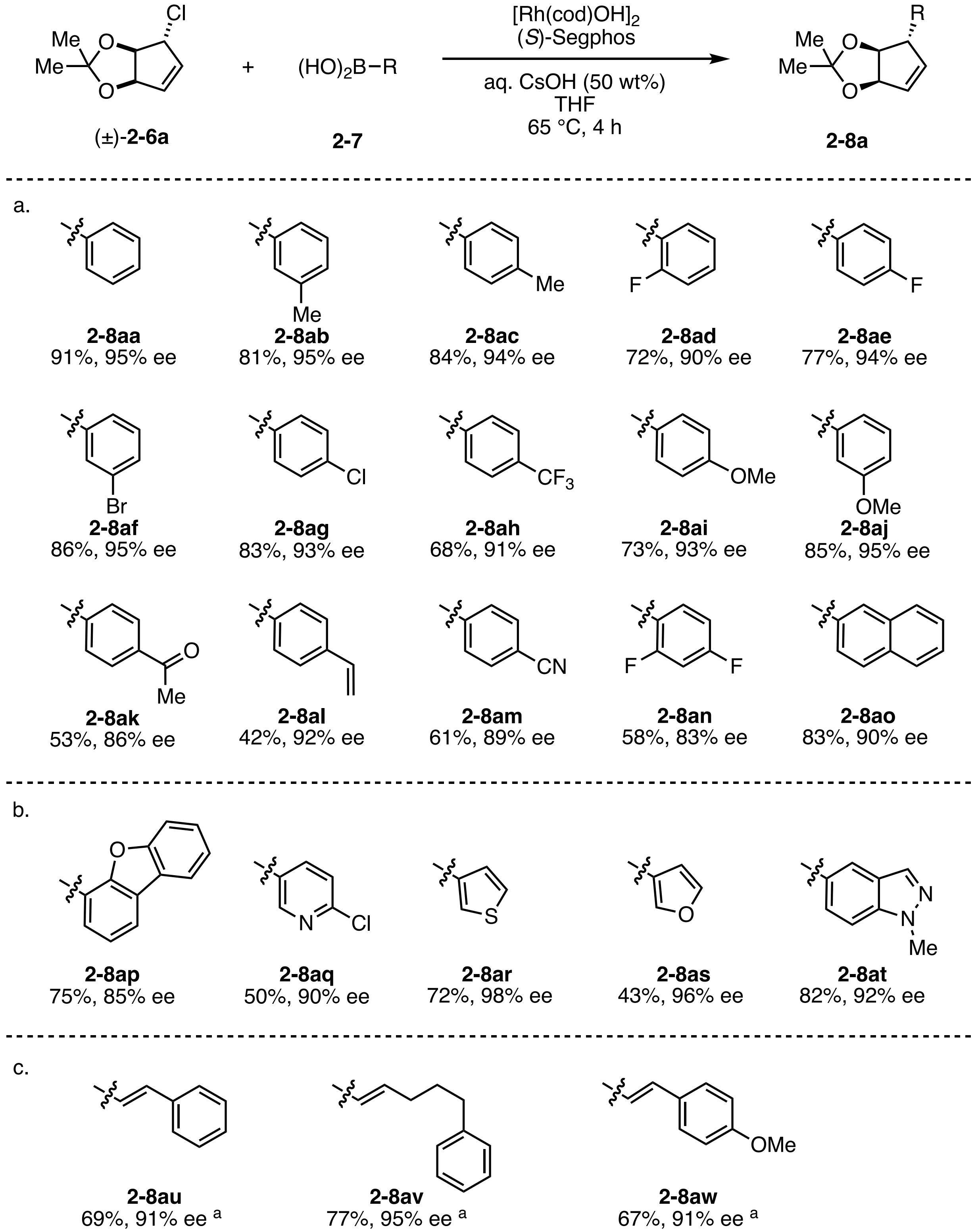


Figure 2-18: Cross-coupling of allyl chloride (±)-**2-6a** with arylboronic acids (a), heteroarylboronic acids (b) and alkenylboronic acids (c).

Conditions: (±)-**2-6a** (0.4 mmol), **2-7** (0.8 mmol), [Rh(cod)OH]$_2$ (2.5 mol%), (*S*)-Segphos (6 mol%), aq. CsOH (50 wt%, 0.4 mmol), THF (0.25 M), 65 °C, 4 h. [a] BINAP used instead of Segphos.

Asymmetric Suzuki–Miyaura coupling with different allyl acids

Subsequently, we explored three different *pseudo*-symmetric allyl chlorides as coupling partners. *Pseudo*-symmetric allyl chlorides are those with corresponding *meso* and therefore achiral carbocations upon dissociation of the halide ion. (±)-**2-6b**, (±)-**2-6c** and (±)-**2-6d** were synthesised from a suitable alkene via an allylic oxidation with stochiometric SeO_2, followed by allylic chlorination (Figure 2-19). While alkene (±)-**2-9** is commercially available, (±)-**2-11** was synthesised via a reported oxidative amination,[132] and (±)-**2-15** was obtained from commercial **2-13** in three synthetic steps.

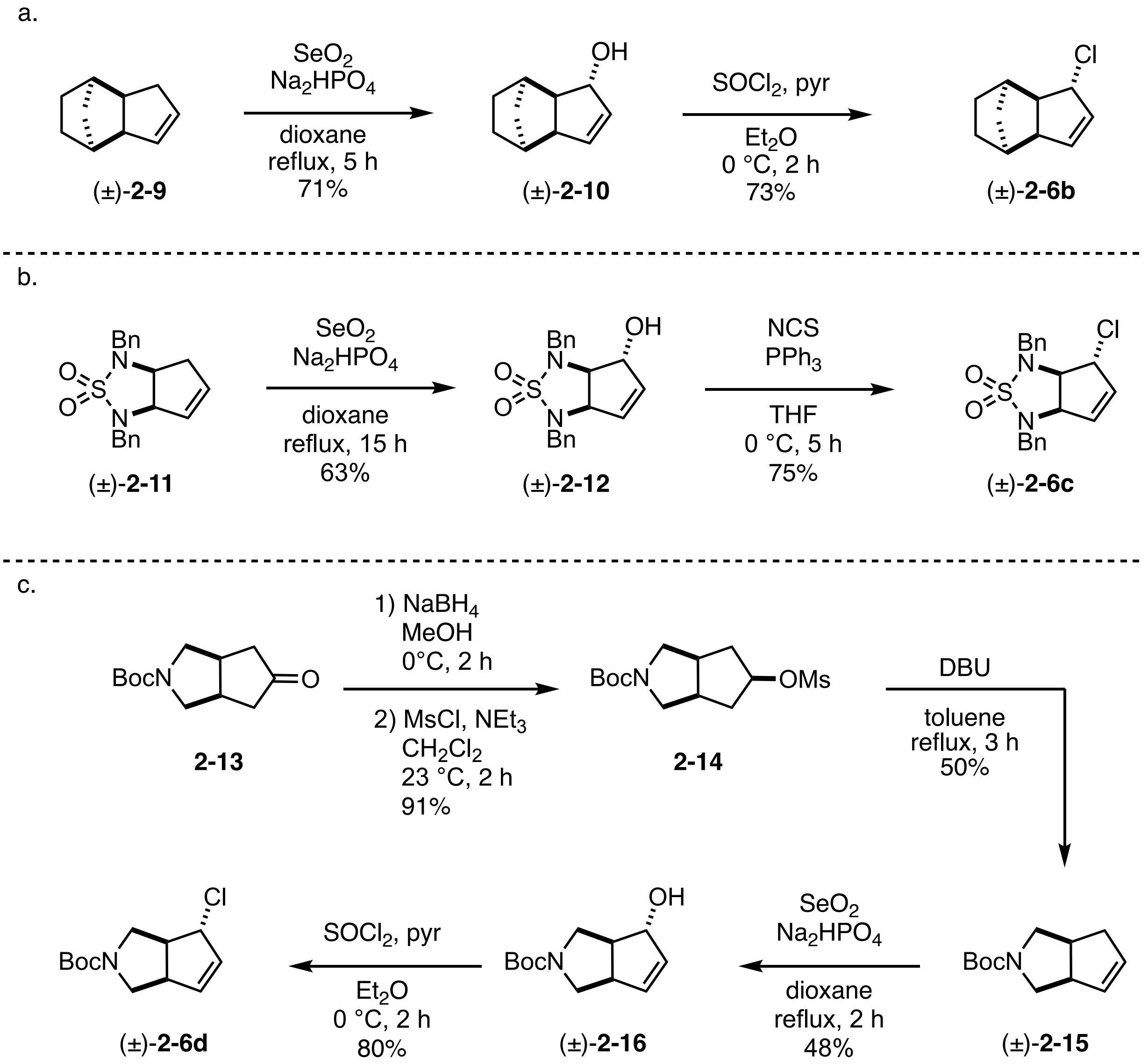


Figure 2-19: Synthesis of bicyclic allyl halides (±)-**2-6b**, (±)-**2-6c** and (±)-**2-6d**.

Only minor modifications from the standard conditions were required in order to achieve excellent results with a small set of aryl-, heteroaryl- and alkenylboronic acids for the three allyl chlorides (Figure 2-20). In all cases, the *cis-trans* isomer was obtained in high ratios (dr >20:1) and in most cases excellent enantioselectivity of 98 or 99% ee were achieved.

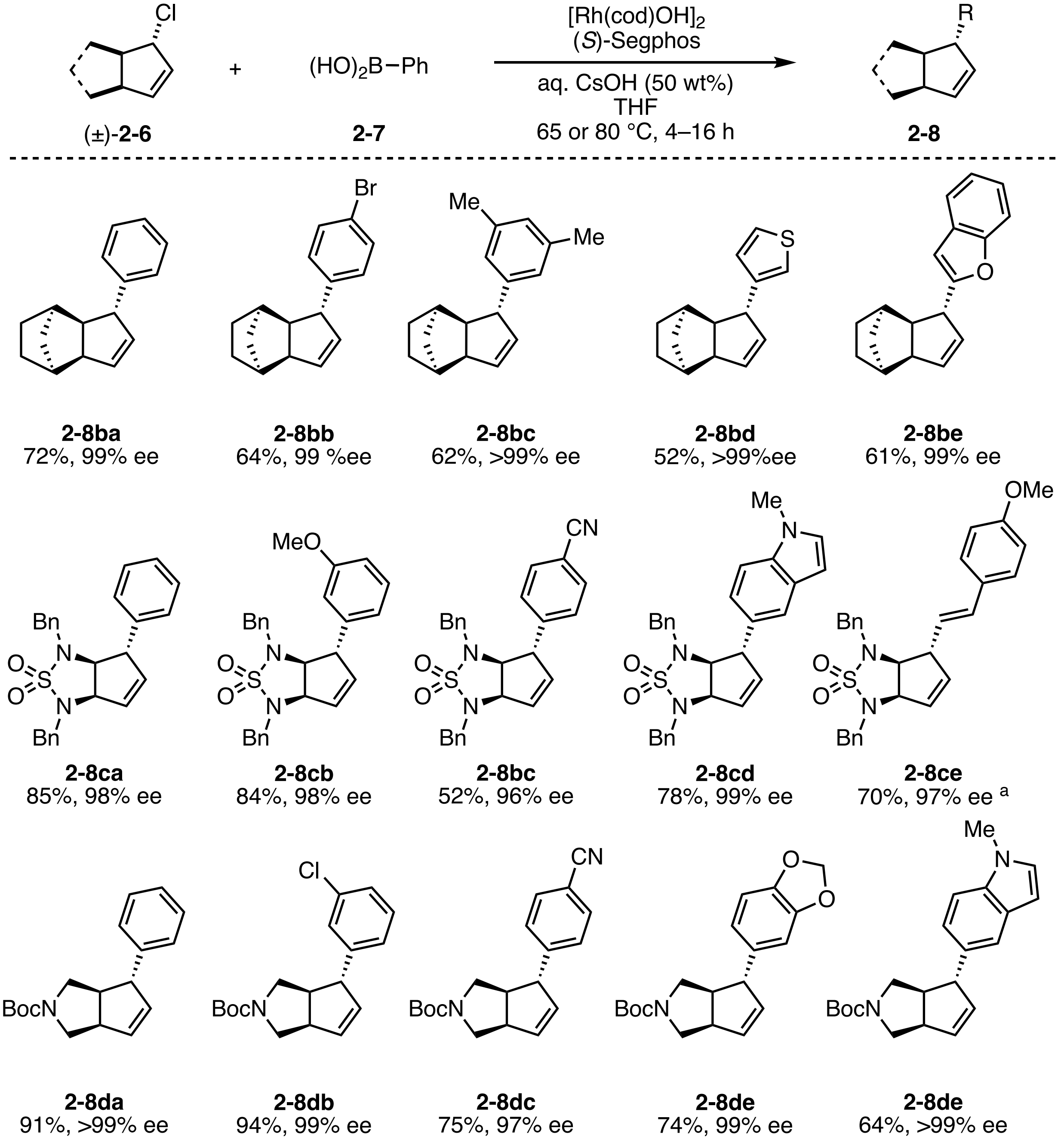
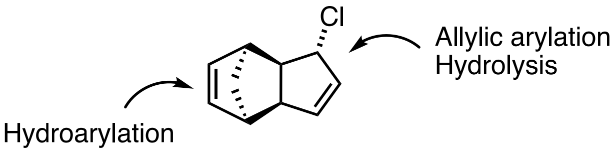


Figure 2-20: Cross-coupling of different bicyclic racemic allyl chlorides with boronic acids.

Conditions: (±)-**2-6** (0.4 mmol), **2-7** (0.8 mmol), [Rh(cod)OH]$_2$ (2.5 mol%), (*S*)-Segphos (6 mol%), aq. CsOH (50 wt%, 0.4 mmol), THF (0.25 M), 65 or 80 °C, 4–16 h. [a] BINAP used instead of Segphos.

The all-carbon allyl chloride (±)-**2-6b** underwent competitive hydrolysis to give the allylic alcohol (~10% determined by ^{1}H NMR for **2-8ba**), but the desired cross-coupling products were obtained in good to moderate yields. A related bicyclo[2.2.1]heptene derived allyl chloride (±)-**2-6b'** (Fig. 2-21), which was synthesized according to a literature procedure,[133] afforded complex mixtures of products due to an additional hydroarylation reaction on the strained alkene (compare **Chapter 3.2**). Nitrogen containing allyl chlorides (±)-**2-6c** and (±)-**2-6d** required heating to 80 °C (in a sealed flask) in order to obtain full conversion with phenylboronic acid (Fig. 2-20).



2-6b'

Figure 2-21: Unsuccessful substrate in a cross-coupling reaction with phenylboronic acid due to competitive hydroarylation of the strained alkene.

Upscale and derivatisation of the coupling products

The reaction between (±)-**2-6a** and **2-7a** proceeded with almost identical results at 6.0 mmol as at 0.4 mmol scale to give 1.21 g of the coupling product **2-8aa** (Figure 2-22a).

Subsequently, we explored derivatisations of the bicyclic cyclopentene cores. The acetonide group of **2-8aa** was cleaved under acidic conditions and the sulfamide of **2-8ca** was removed under reductive conditions yielding cyclopentenes bearing vicinal diols (**2-17**) and diamines (**2-18**) (Figure 2-22b), demonstrating how a bicyclic protecting group can be used strategically in a synthetic sequence. Furthermore, dihydroxylation of **2-8aa** gave a cyclopentane with 5 contiguous stereogenic centres (**2-19**).

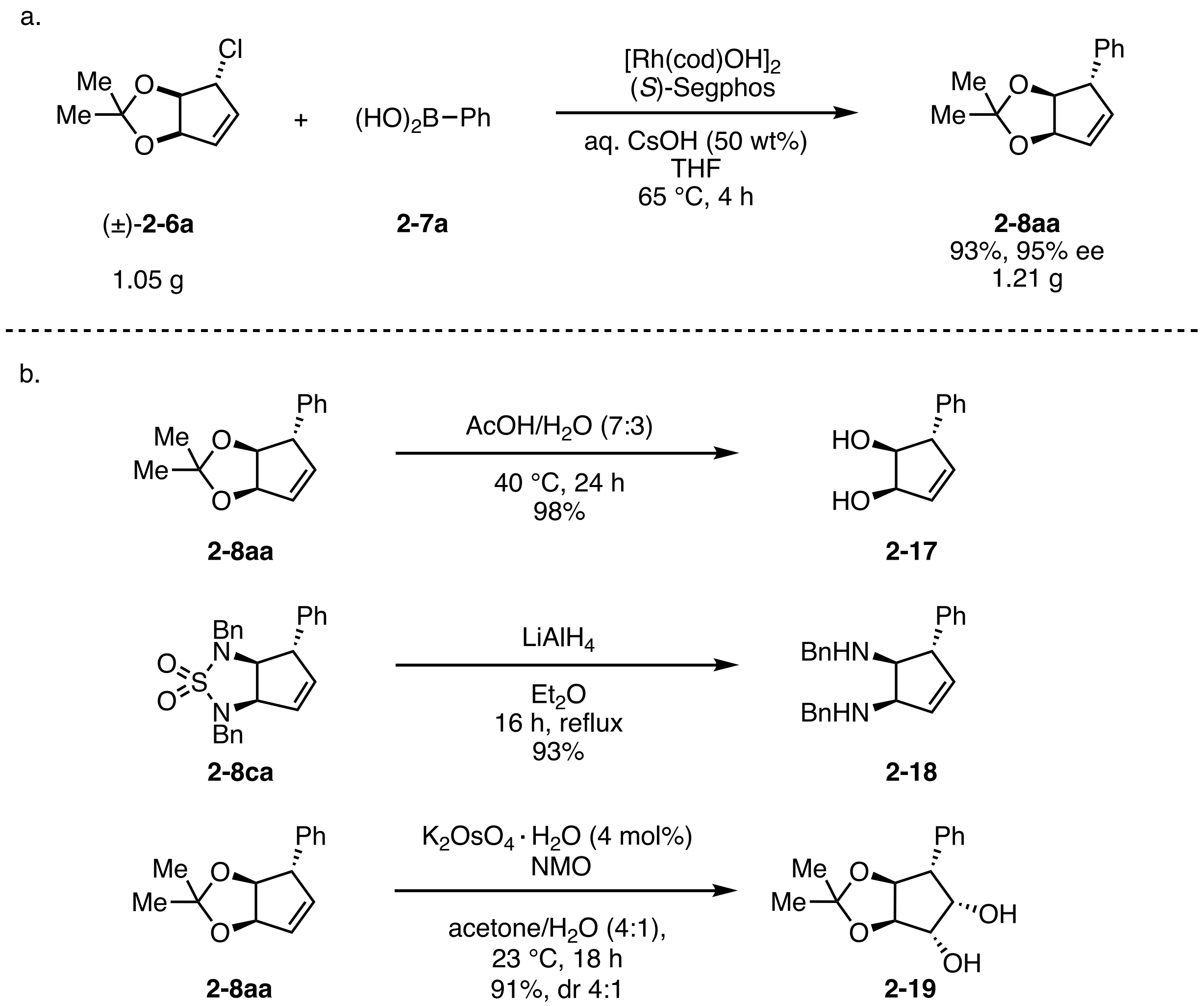


Figure 2-22: Gram-scale cross-coupling between (±)-**2-6a** and **2-7a** (a) and derivatisation of the bicyclic cyclopentenes (b).

Regiodivergent reaction on a racemic mixture

While chlorides (±)-**2-6a-d** are all *pseudo*-symmetric about the allylic unit, we were interested to see how a racemic mixture of an allyl chloride without *pseudo*-symmetry would behave in a Rh-catalysed arylation reaction. In the absence of an efficient racemisation mechanism (formation of a common π-allyl complex), two distinct pathways are possible. Either the reaction is under substrate control and a single regioisomer of a racemic coupling product is obtained, or the reaction is under catalyst control and single enantiomer of regioisomeric mixture is obtained. A combination of these two cases would also be possible.

We prepared a single regioisomer of (±)-**2-6e** (for details see experimental **Chapter 5.2**). Under our standard conditions we obtained almost a 1:1 mixture of highly enantioenriched **2-8ea** and its also highly enantioenriched regioisomer **2-8ea*** (Figure 2-23), which were separated by flash column chromatography. This is regiodivergent reaction on racemic mixture in which enantiomers of the starting material diverge into different regioisomeric products (Figure 2-23).[134] The reaction is under almost perfect catalyst control, and the absence of matched/mismatched effects for both isomers is quite remarkable.[135] Regiodivergent reactions on racemic mixture a practical alternative to kinetic resolutions as they do not require stopping the reaction at exactly 50% conversion in order to achieve high enantioselectivity for the product.

The coupling experiment with **2-6e** is less diastereoselective than the previously described reactions hinting that steric factors are likely responsible for achieving excellent levels of diastereoselectivity observed for (±)-**2-6a-d** (dr >20:1).

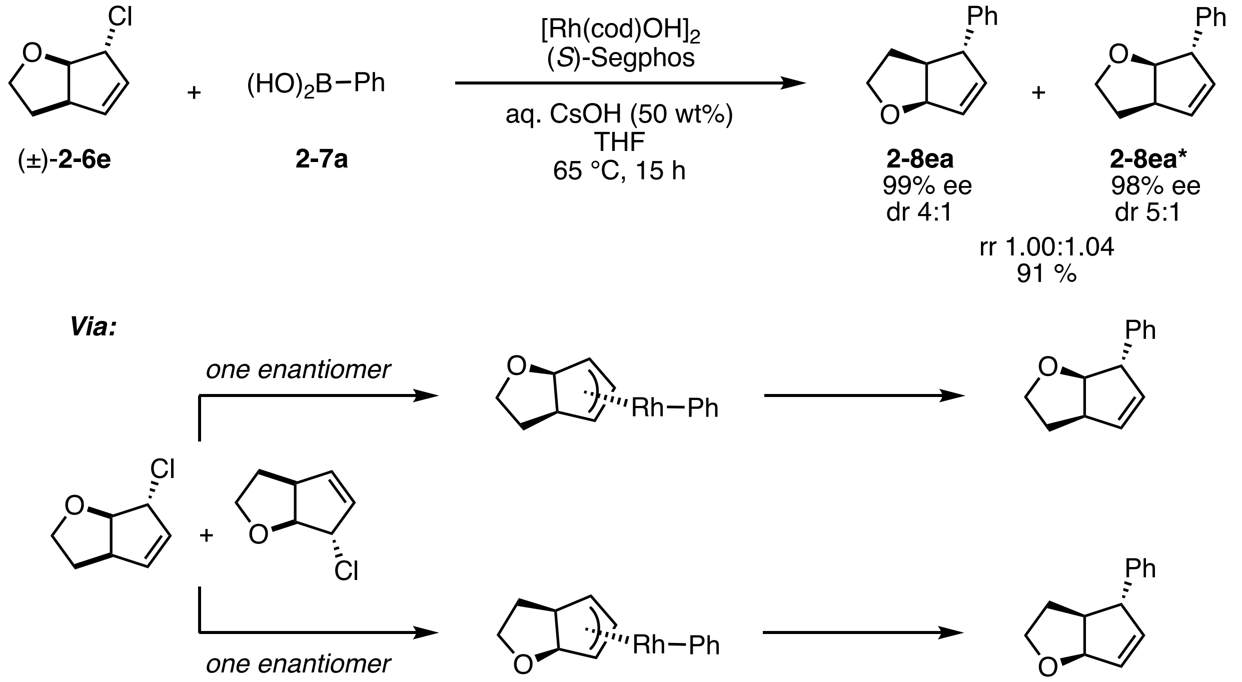


Figure 2-23: Regiodivergent reaction on a racemic mixture of an allyl chloride.

Conditions: (±)-**2-6e** (0.4 mmol), **2-7a** (0.8 mmol), [Rh(cod)OH]₂ (2.5 mol%), (*S*)-Segphos (6 mol%), aq. CsOH (50 wt%, 0.4 mmol), THF (0.25 M), 65 °C, 15 h.

Kinetics and proposed reaction mechanism

In order to obtain a better mechanistic understanding of reactions with racemic bicycles, we monitored the enantiomeric excesses of product and starting material over time (Figure 2-24). As the coupling between **2-6a** with **2-7a** is fast (>80% conversion within the first 10 minutes), we performed this kinetic experiment at 40 °C. Both enantiomers of **2-6a** reacted to give the same product. Despite that, we observed a kinetic resolution of **2-6a**, so that after approximately 75% conversion enantiopure **2-6a** is present, indicating that both enantiomers react at different rate. A selectivity (*s*)-factor of $s = k_{\mathbf{2\text{-}8aa}}/k_{ent\text{-}\mathbf{2\text{-}8aa}} \approx 6$ was determined (for calculation see **Chapter 5.2**).[89] As there is no obvious change in conversion upon enantioenrichment of the starting material, it is unlikely that oxidative addition is rate limiting. The ee of **2-8aa** is constant over the entire reaction, which is characteristic for a reaction of a racemic mixture that proceeds via a common intermediate.

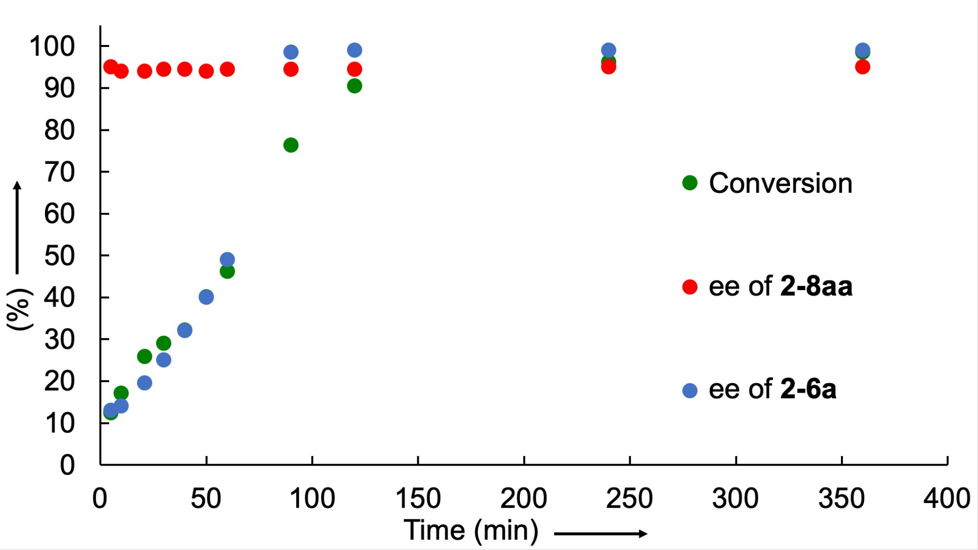


Figure 2-24: Product formation with kinetic resolution of **2-6a** with **2-7a** at 40 °C.

Previous mechanistic studies by our group suggested that 5-substituted cyclohex-1-enyl chlorides follow *anti* oxidative addition, leading to an overall inversion of the relative stereochemsitry.[113] In contrast, the exclusive formation of the *cis-trans* isomer in most coupling reactions suggests that *syn* oxidative addition is favoured in bicyclic systems (Figure 2-25) – likely due to steric reasons as later confirmed by computational studies from our group.[115]

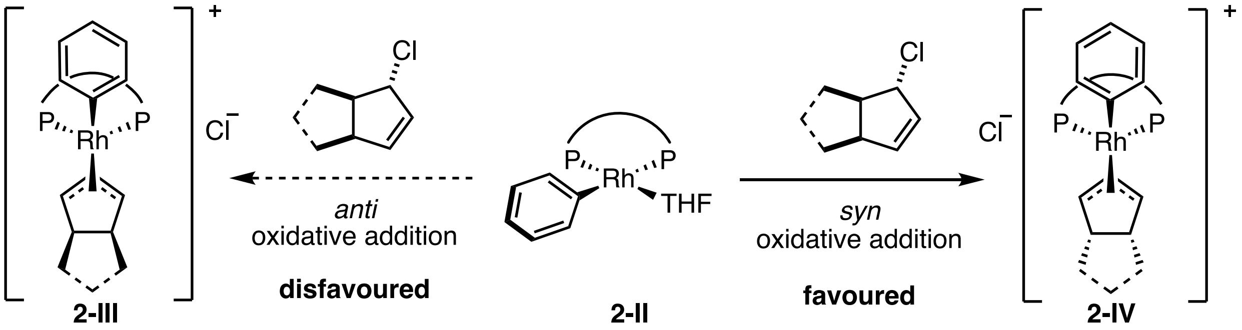


Figure 2- 25: Favoured *syn* oxidative addition.

A complete, plausible mechanistic cycle is depicted in Figure 2-26. Fast transmetallation of the arylboronic acid to Rh-hydroxide complex (**2-I**) gives aryl-Rh complex **2-II**. Both enantiomers of the allyl chloride undergo *syn* oxidative addition at different relative rates to set the relative stereochemistry in the product. Final reductive elimination from *pseudo*-meso Rh-π-allyl complex **2-IV** sets the absolute stereochemistry in the product and regenerates the active catalyst.

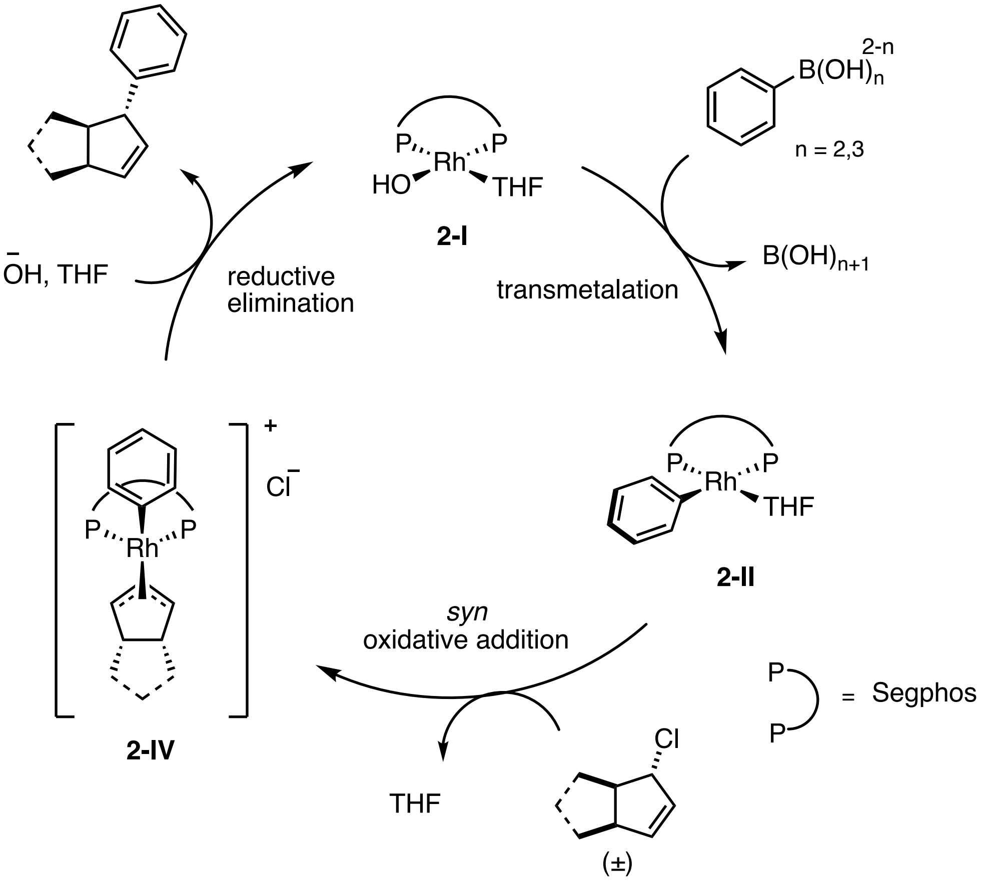


Figure 2-26: Mechanistic cycle for the arylation of racemic, bicyclic allyl chlorides.

2.2.4. Conclusion

In **Chapter 2.2**, we show that racemic, bicyclic allyl halides are suitable substrates in Rh-catalysed asymmetric Suzuki–Miyaura reactions and perform preliminary mechanistic experiments. These cross-coupling reactions are highly enantio- and diastereoselective, and are compatible with a range of aryl-, heteroaryl- and alkenylboronic acids. The reaction conditions are robust and scalable, making them ideal for applications in medicinal chemistry and target synthesis.

The formation of *pseudo*-meso Rh-π-allyl serves as an efficient de-racemisation mechanism for *pseudo*-meso allyl chlorides, so that highly enantioenriched products can be obtained from racemic mixtures of the starting material in yields >50%. A substrate without *pseudo*-symmetry undergoes a highly enantioselective regiodivergent reaction on a racemic mixture. The diastereoselectivity of the described coupling reactions is high and under strong substrate control, so that in most cases exclusively *cis-trans* diastereomers were obtained.

Our work shows that the mode in oxidative addition can be influenced based on steric factors in Rh-catalysed allylic substitution reactions, which can guide exploration of future substrate scope of related reactions.

2.3. An Asymmetric Suzuki–Miyaura Approach to Prostaglandins: Synthesis of Tafluprost

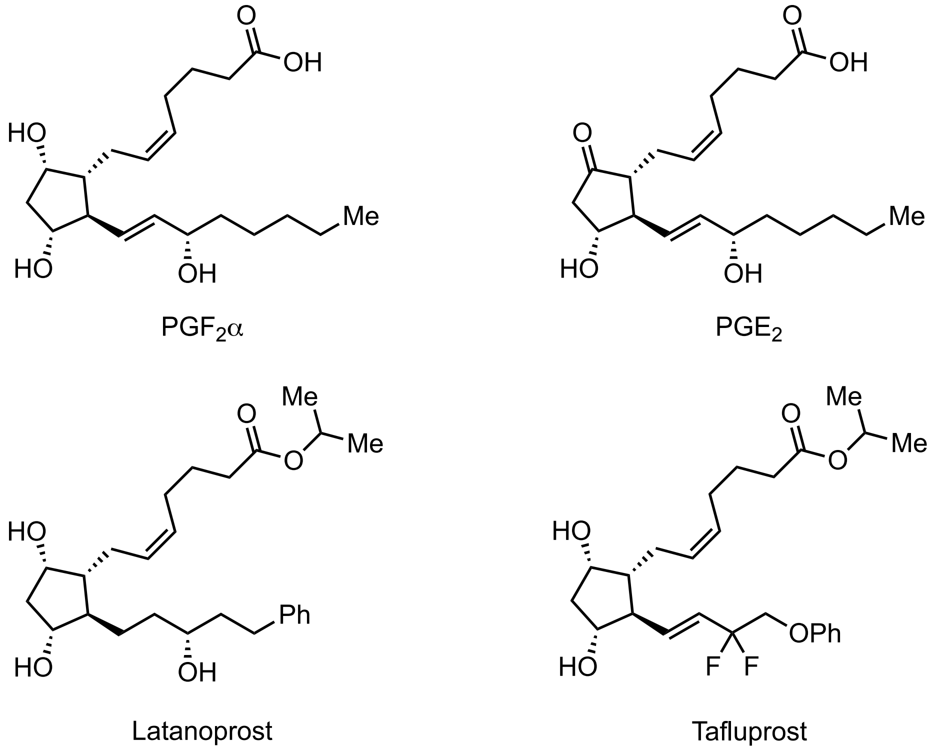
Chapter 2.3. is based on the following publication:
Kučera, R.; Goetzke, F. W.; & Fletcher, S. P. An Asymmetric Suzuki–Miyaura Approach to Prostaglandins: Synthesis of Tafluprost. *Org. Lett.* **2020**, *22*, 2991–2994.

The experiments in **Chapter 2.3** were performed by Roman Kučera as part of his SBM CDT rotation. I contributed to this chapter by joint project conception with Stephen P. Fletcher, by co-supervision, planning and analysing of experiments with Roman Kučera and by writing the manuscript for publication with contributions from Stephen P. Fletcher. Stephen P. Fletcher guided the research. Experimental procedures and characterisation data can be found in the online version of this article: https://pubs.acs.org/doi/abs/10.1021/acs.orglett.0c00745.

2.3.1. Introduction

Prostaglandins are a class of lipid compounds that have hormone like functions as they play a role in inflammation, fever, pain, sleep and other regulatory functions in humans and many animals.[136] They are synthesised enzymatically from arachidonic acid.[137] Prostaglandins have 20 carbon atoms with a five-membered core and two side chains but differ in the oxidation state of the cyclopentane core and in the saturation of the side chains (Figure 2-27; e.g. PGE_2 and $PGF_2\alpha$). Many prostaglandins and their analogues are used for clinical purposes (Figure 2-27; all four), and the development of new synthetic strategies to access these compounds has been a vibrant area of chemical research.[138,139]

The first syntheses of PGE_2 and $PGF_2\alpha$ five decades ago by E. J. Corey and co-workers can be considered as true landmarks in complex molecule synthesis (Figure 2-28a),[140–142] and even many contemporary routes to prostaglandins and their derivatives still rely on some of the same intermediates and synthetic strategies.[138] Building on Corey's work, developing higher yielding, more efficient and more modular synthetic routes to prostaglandins has been a long-standing challenge in asymmetric synthesis. While many approaches to prostaglandins are stereospecific or diastereoselective, catalytic asymmetric syntheses in which the asymmetry is controlled by a chiral catalyst are rare (Figure 2-28) and most powerful approaches have just been reported during the last twenty years.



$PGF_2\alpha$ PGE_2

Latanoprost Tafluprost

Figure 2-27: Prostaglandins and prostaglandin analogues in therapeutic use.

Aggarwal and co-workers reported an extremely concise, seven step synthesis of $PGF_2\alpha$.[143] The key step is an enantioselective organocatalysed aldol cascade between two molecules of succinaldehyde to obtain a structurally related intermediate to the Corey lactone (Figure 2-28b). The same strategy can be applied for asymmetric syntheses of the prostaglandin analogues Latanoprost and Bimatoprost.[144] The drawback of this approach is the low yield of the key succinaldehyde dimerisation step, but subsequent work of the same group shows that this step can be improved.[145]

In a related strategy, Hayashi and co-worker reported an asymmetric synthesis of PGE_1 methyl ester (Figure 2-28c).[146] The cyclopentane core was constructed via an enantioselective, organocatalytic Michael reaction-Henry reaction cascade. Key feature of this work is the high pot-economy,[147] so that only 3 pots and 9 synthetic steps are required for the completion of the synthesis.

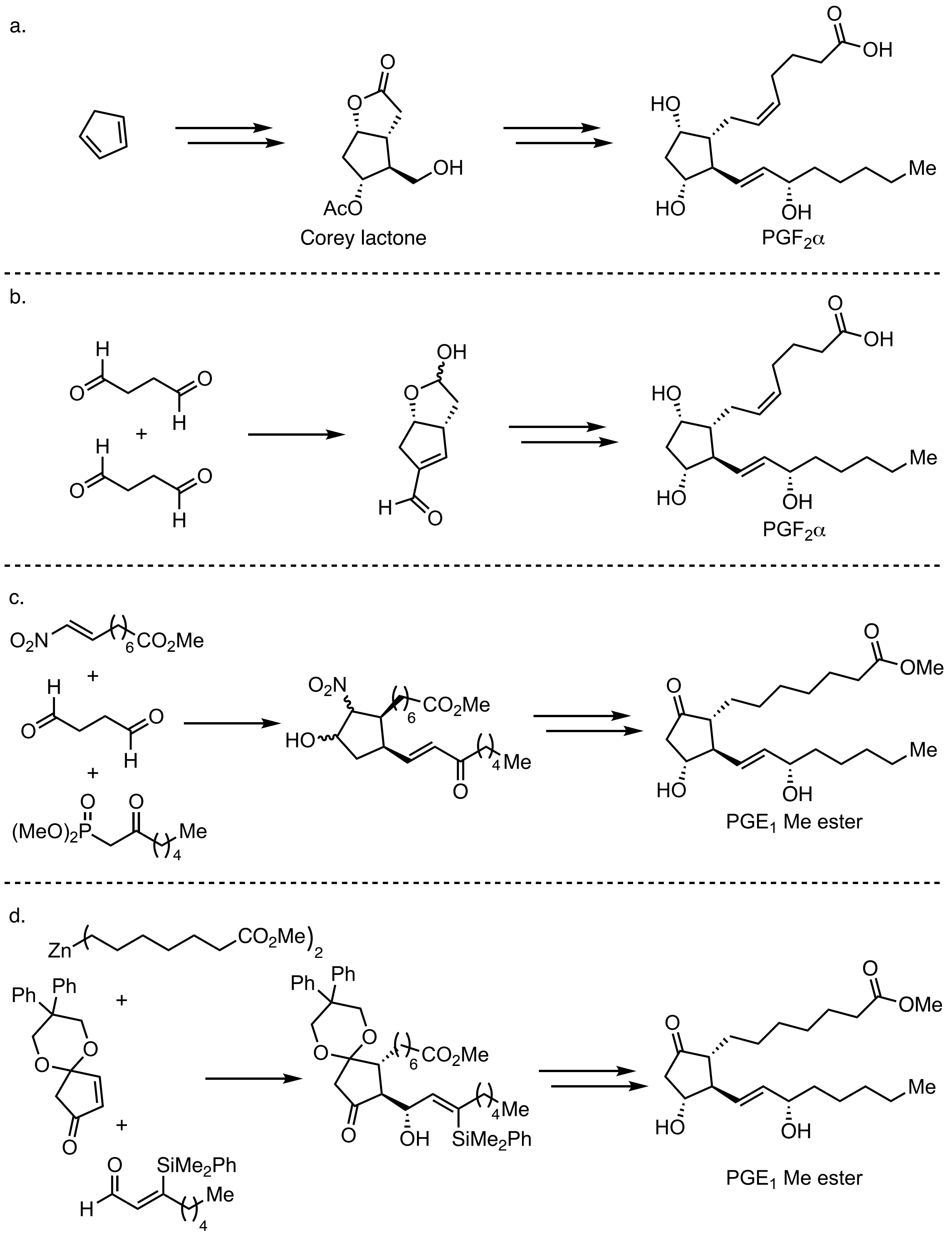


Figure 2-28: Catalytic asymmetric prostaglandin syntheses by the laboratories of Corey (a), Aggarwal (b), Hayashi (c) and Feringa (d).

Building on closely related diastereoselective work by the laboratories of Stork and Noyori,[148,149] Feringa and co-workers developed a Cu-catalysed enantioselective 1,4-addition, followed by enolate tapping approach for the synthesis of PGE_1 methyl ester (Figure 2-28d).[150] Nicolaou and co-workers' synthesis Δ_{12}-J_3, in which an enantioselective Tsuji–Trost reaction was used to introduce the asymmetry, represents a rare example of a catalytic asymmetric synthesis of a prostaglandin from a racemic precursor (not depicted).[151]

Tafluprost is Merck Sharp & Dohme and Santen Pharmaceutical Co.‘s prostaglandin $PGF_2\alpha$ analogue for the treatment of intraocular pressure in open-angle glaucoma and ocular hypertension (Figure 2-27).[152] Tafluprost was initially developed by Asahi Glass Co., Ltd., and Santen Pharmaceutical Co., and previous syntheses have relied on the functionalisation Corey aldehyde benzoate.[153,154]

2.3.2. Objective of the Project

In **Chapter 2.3**, we explore if enantio- and diastereoselective Rh-catalysed cross-couplings can be applied in the target synthesis of a complex, bioactive molecule. The high structural similarity of bicyclic **2-8av (**see **Chapter 2.2)** and the functionalised cyclopentane core of prostaglandins sparked our interest if these natural products could be synthesised from bicyclic allyl halides and alkenylboronic acids.[155]Prostaglandins and their analogues are extensively used as clinical drugs, but there is still a demand for efficient and modular, asymmetric syntheses. We chose the prostaglandin analogue Tafluprost as our first target as it elicits an uncommon and complex side chain. We envisioned that an asymmetric Suzuki–Miyaura coupling of a suitable racemic allyl chloride could facilitate the construction of one of the key carbon-carbon bonds and set the absolute and relative stereochemistry of the cyclopentene core (Figure 2-29). The second carbon chain could be introduced via a Pd-catalysed regio- and diastereoselective allylic substitution.

This cross-coupling approach would represent a very modular synthesis of prostaglandins and could also enable the synthesis of new analogues that would be difficult to make with existing methods. Further, it would demonstrate the robustness of Rh-catalysed asymmetric Suzuki–Miyaura coupling reactions in complex molecule settings.

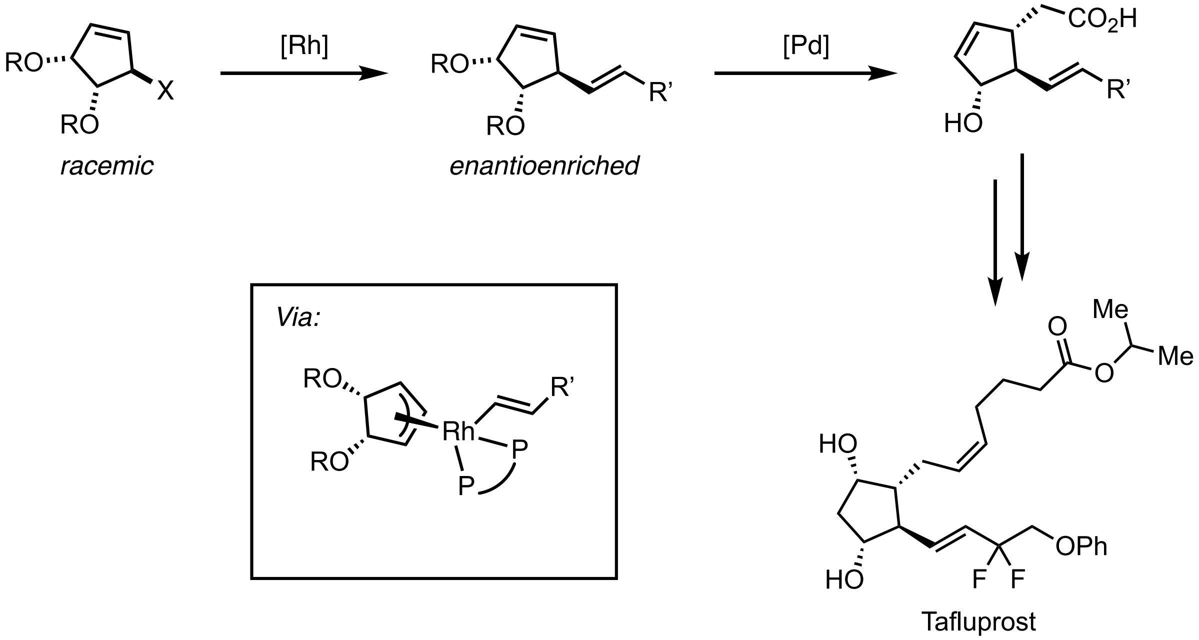


Figure 2-29: Strategy for the synthesis of Tafluprost.

2.3.3. Results and Discussion

Synthesis of the alkenyl fragment

The allylic halide (±)-**2-6a** was prepared from cyclopentadiene in 5 linear steps according to the method depicted in **Chapter 2.2.**[155] Alkenylboronic acid **2-25** was synthesised from 2-phenoxyethanol (**2-20**) according to literature procedures in overall 37% yield over 8 linear steps (Figure 2-30).[156] A sequence of Swern oxidation, alkynylation, oxidation with Dess-Martin-periodinane (DMP) and bisfluorination with XtalFluor-E® afforded alkyne **2-24**. Hydroboration of **2-24**, followed by treatment with aqueous formaldehyde afforded crude boronic acid **2-25**. For purification reasons, **2-25** was converted into the highly crystalline potassium trifluoroborate salt, and subsequently hydrolysed to obtain pure boronic acid.

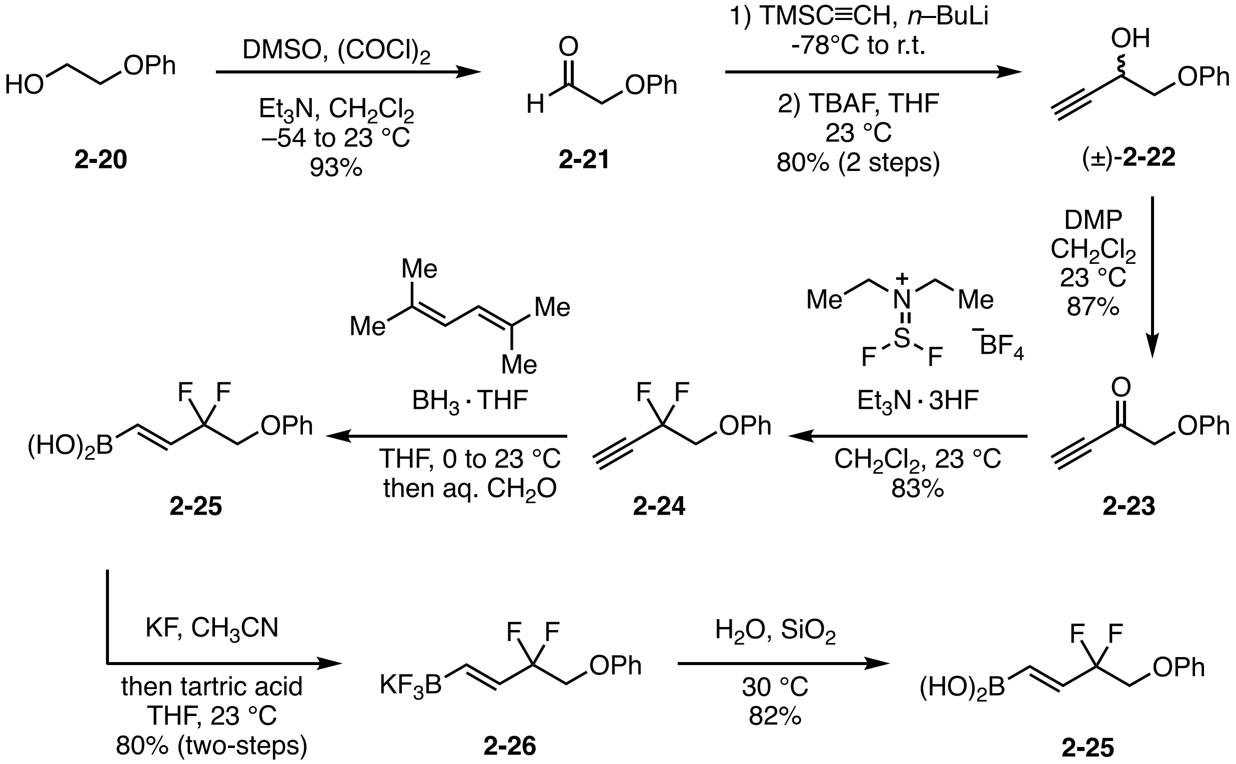
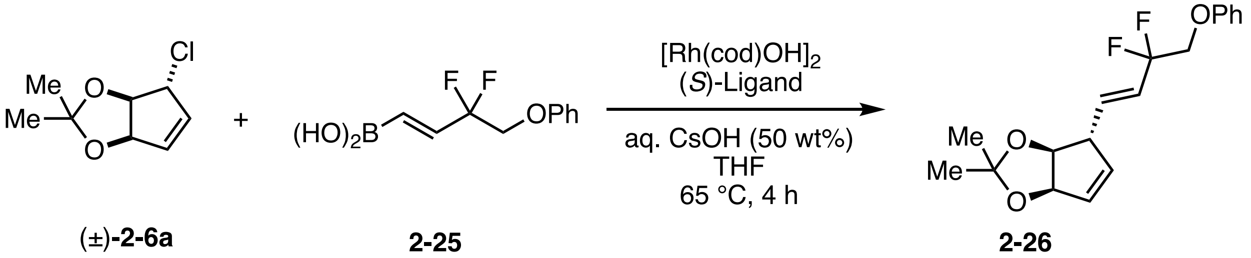


Figure 2-30: Synthesis of alkenyl fragment of Tafluprost. *(Experiments performed by Roman Kučera)*

Optimisation of the Rh-catalysed Suzuki-Miyaura coupling

Having prepared both coupling partners, we investigated the Rh-catalysed cross-coupling between the two fragments (±)-**2-6a** and **2-25**.[157] This reaction set the absolute stereochemical configuration of the cyclopentene core. BINAP was a superior ligand in terms of enantioselectivity for the alkenylboronic acids investigated in **Chapter 2.2**, but under the same conditions **2-26** was obtained in excellent yield and diastereoselectivity, albeit with moderate enantioselectivity (Table 2-2, entry 1).[155] Changing the ligand to Segphos type ligands Segphos (**L2-8**) and DM-Segphos (**L2-9**) improved the enantioselectivity to 90% ee at a slight expense on diastereoselectivity (Table 2-2, entries 2,3). This reaction sets the absolute stereochemistry of the cyclopentene core.

Table 2-2: Selected optimisation experiments for the coupling between (±)-**2-6a** and **2-25**.



Entry	Ligand	Yield [a]	Enantiomeric excess [b]	Diastereomeric ratio [c]
1	(*S*)-**L2-3**	87%	77%	>20:1
2	(*S*)-**L2-8**	79%	90%	7:1
3 [d]	(*S*)-**L2-9**	80%	90%	7:1

Conditions: (±)-**1a** (0.2 mmol), **3** (0.3 mmol), [Rh(cod)OH]$_2$ (2.5 mol%), (*S*)-Ligand (6 mol%), aq. CsOH (50 wt%, 0.2 mmol), THF (0.25 M), 65 °C, 4 h. *(Experiments performed by Roman Kučera)*

[a] Isolated yields of the *cis-trans* diastereoisomer (>20:1 dr).

[b] Enantiomeric ratios were determined by SFC using a chiral non-racemic stationary phase.

[c] Determined by ^{1}H NMR of the unpurified reaction mixture.

[d] Performed on 1.9 mmol scale.

Completion of the synthesis

The acetal protected allylic alcohol was then converted in two steps in an allylic carbonate in 80% yield (over two steps) (Figure 2-31). In the next step, Pd-catalysed Tsuji–Trost reaction with diethyl malonate afforded **2-28** as the major regioisomer with overall retention of the relative stereochemistry in 89% yield.[157] The cyclic carbonate serves as a traceless activation group, so that after rapid decarboxylation **2-28** cannot undergo a second allylic substitution reaction. Base mediated hydrolysis, and decarboxylation with 1,1'-carbonyldiimidazole (CDI) afforded the free carboxylic acid **2-29**.[158] Then, the second hydroxy group of the cyclopentane core was installed via an iodolactonisation (73% yield over three steps).[140]

The next steps are well precedented steps in the prostaglandin literature and have been also reported for Tafluprost,[153,157] but a lack of analytical data required us to complete the synthesis of Tafluprost. Deiodination with Bu_3SnH and catalytic AIBN gave the lactone **2-30** in 79% yield (Figure 2-31).

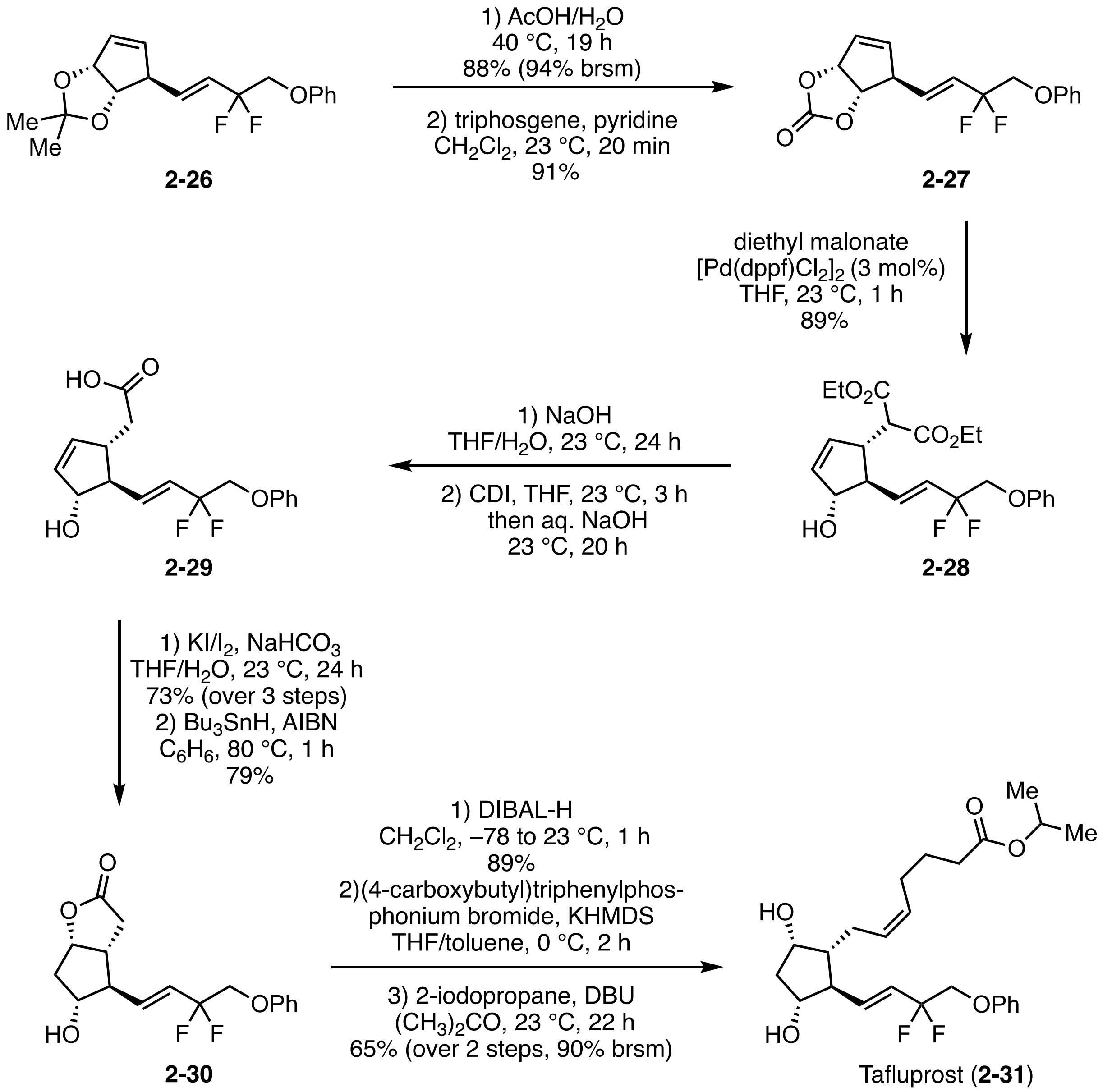


Figure 2-31: Synthesis of Tafluprost from cross-coupling product **2-26**. *(Experiments performed by Roman Kučera)*

Then, lactone **2-30** was reduced to the lactol with DIBAL-H in 89% yield. The synthesis of Tafluprost was completed with a Wittig reaction with (4-carboxybutyl)triphenylphosphonium bromide, followed by esterification 2-iodopropane (65% over two steps). The analytical data of our sample of Tafluprost matches optical rotation and ^{1}H and ^{13}C NMR data of previously described syntheses.[153,154]

2.3.4. Conclusion

In **Chapter 2.3**, we present the asymmetric synthesis of the prostaglandin analogue Tafluprost. The synthesis was accomplished in 19 steps over the longest linear sequence in 6.7% overall yield. Key feature of this synthesis is an enantio- and diastereoselective Suzuki–Miyaura coupling with a racemic allyl chloride to introduce the alkenyl chain and a regio- and diastereoselective Pd-catalysed allylic substitution with an enolate surrogate to introduce the second carbon chain.

We demonstrate that asymmetric Suzuki–Miyaura reactions can be applied in a complex molecule setting, and likely other bioactive molecules and especially prostaglandins and new prostaglandin analogues could be synthesised using related strategies.

2.4. Future Work

Over the last 20 years, many research laboratories have aimed to develop modern asymmetric C(sp^3) variants of the Suzuki–Miyaura cross-coupling (**Chapter 1.3**). However, general methods are still elusive. Inspired by the vision to provide the synthetic organic chemistry community with general C(sp^2)–C(sp^3) cross-coupling reactions, a main research focus of our research group is developing Rh-catalysed asymmetric cross-coupling reactions between racemic allyl halides and C(sp^2)-hybridised boronic acids. Highlights of this chemistry are applications in the synthesis of pharmaceutically relevant molecules like the PARP inhibitor Niraparib (Figure 2-32).[120]

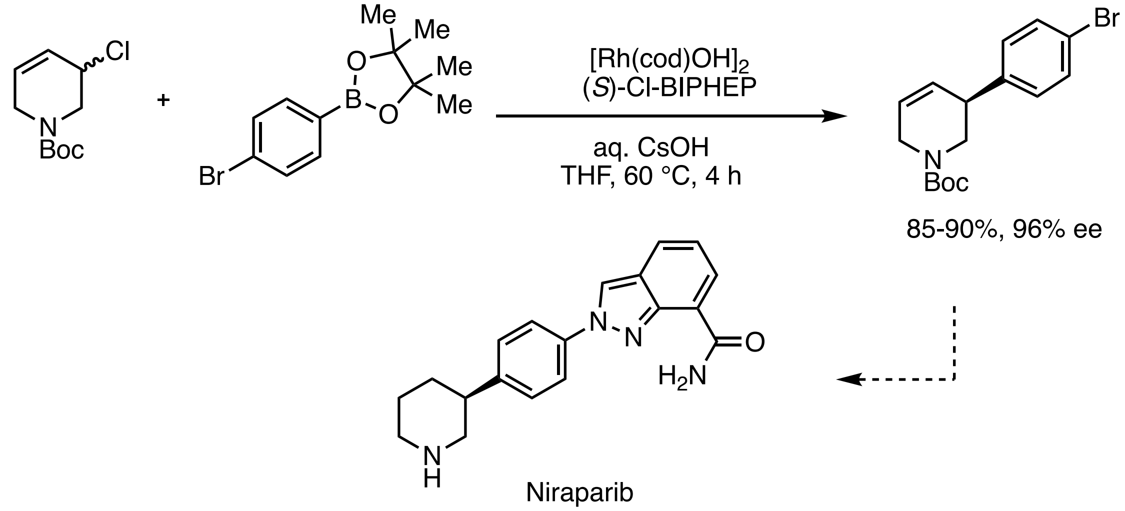


Figure 2-32: Asymmetric synthesis of the PARP inhibitor Niraparib.

We are currently working on expanding the repertoire of enantio- and diastereoselective Suzuki–Miyaura reactions and are aiming to expand the approach developed in **Chapter 2.2** from fused bicyclic to bridged bicyclic structures. Bridged bicyclic compounds are common motifs in medical drugs and natural products (Figure 2-33a),[131,159,160] but catalytic asymmetric syntheses are underexplored.[161,162] Rh-catalysed Suzuki–Miyaura reactions could enable the stereocontrolled synthesis of compounds with an 8-azabicyclo[3.2.1]octane or a 6,6-dimethylbicyclo[3.1.1]-heptane core, and suitable *pseudo*-symmetric allyl chloride are depicted in Figure 2-33b and c.

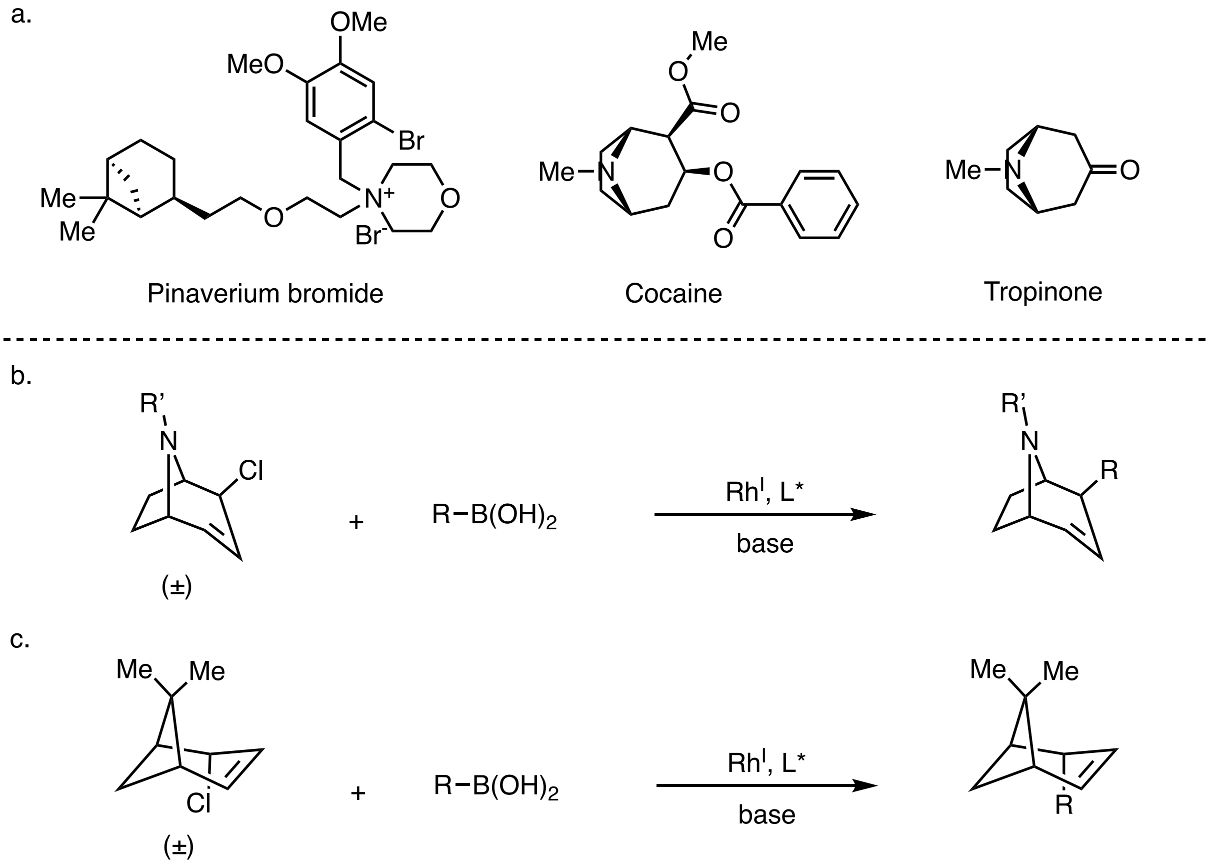


Figure 2-33: Selected natural products or bioactive compounds with a bicyclic core (a) and bicyclic allyl chlorides as potential substrates in enantio- and diastereoselective Suzuki–Miyaura reactions (b, c).

As a main limitation, racemic allyl halides with two or more stereogenic centres require *pseudo*-symmetry in order to achieve >50% yield for a single isomer in a rhodium-catalysed asymmetric cross-coupling reaction. Nevertheless, substrates without *pseudo*-symmetry can undergo highly stereoselective regiodivergent reactions (see **Chapter 2.2**) providing access to a much larger area of chiral chemical space.

Accessing all possible stereoisomers in a given reaction represents a formidable challenge in asymmetric catalysis.[163] While the bicyclic cyclopentenes in **Chapter 2.2** elicit strong preference for a *cis-trans* diastereoisomer, the synthesis of the *cis-cis* diastereoisomer requires an alternative strategy. We propose that using non-cyclic protecting groups for the allyl chloride could give access to the other diastereoisomer (Figure 2-34a), as our group has previously shown that *anti* oxidative addition can be favoured in a mono-cyclic system.[113]

Alternatively, all stereoisomers of a cyclopentane could be accessed by hydrogenation of the cross-coupling products, and by a sequence of metal-catalysed alkene isomerisation, followed by substrate controlled diastereoselective hydrogenation (Figure 2-34b).

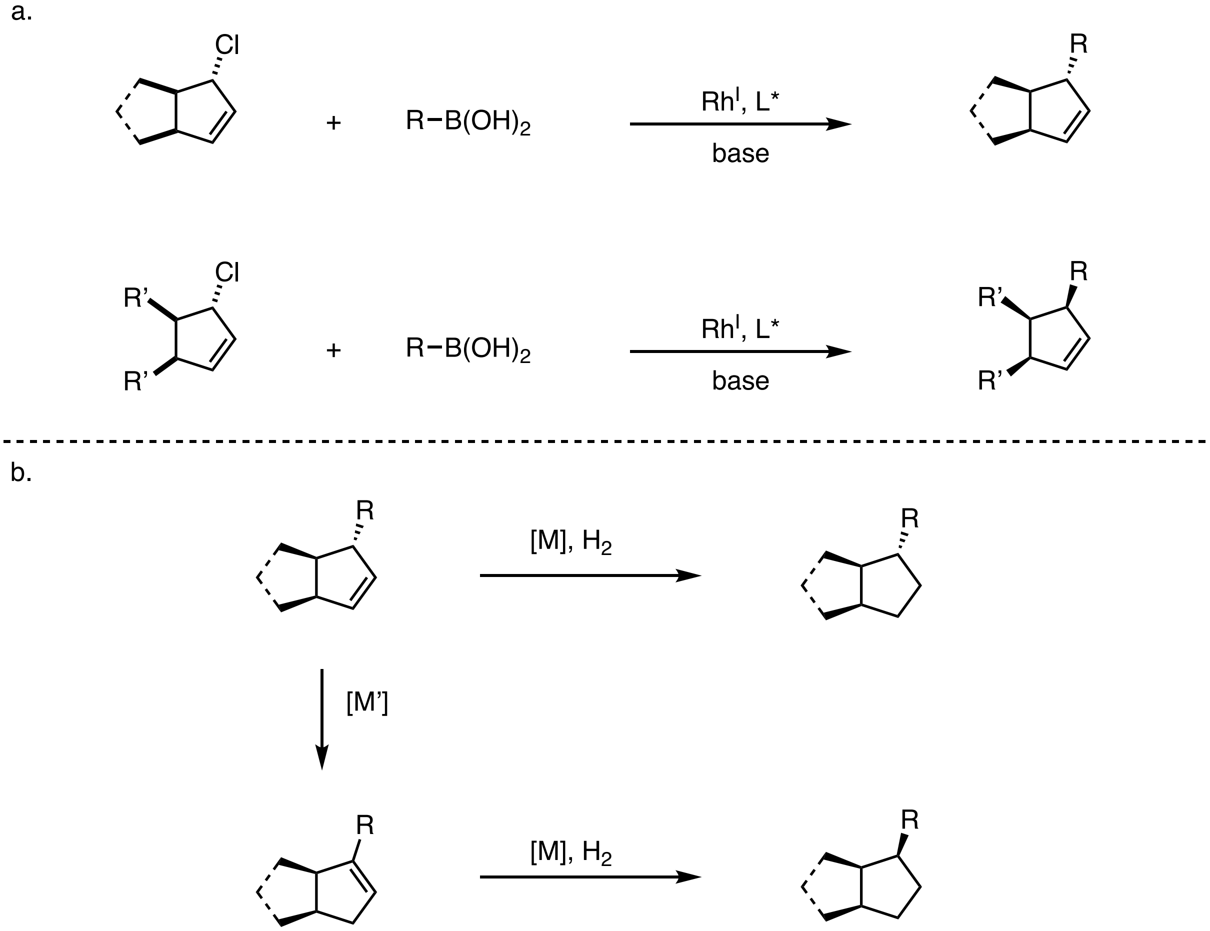


Figure 2-34: Proposed strategy for the diastereodivergent synthesis of cyclopentenes and cyclopentanes

Asymmetric Suzuki–Miyaura reactions are still in their infancy and some of the approaches to expand on this, and new applications in target synthesis are currently on-going in our laboratory.

Chapter 3: Catalytic Asymmetric Carbometallation of Cyclobutenes

Dedicated to the many amazing friends I made in Oxford. You have been the source of so much energy I put in this work – it is no surprise that the idea for Chapter 3 of this thesis was born in the Hall of our College. Special gratitude is directed towards Christiaan, Elisabeth, Karishma and Simon for becoming my first close friends here, to Giulia, Eleanor, Maria, and Giorgia for all the fun in College, to my German friends Malina, Rob, Bernd and Dennis, and to Kat.

Chapter 3 of this thesis deals with catalytic asymmetric synthesis of cyclobutanes. **Chapter 3.1** introduces the cyclobutane scaffold and describes the different strategies for catalytic asymmetric synthesis of 4-membered rings and their limitations. **Chapter 3.2** presents our solution to this long-standing problem in synthesis. We describe the first catalytic asymmetric carbometallation of cyclobutenes with arylboronic acids. The carbometallation reaction can trigger uncommon reactivity including reductive Heck, 1,5-additions and homo-allylic substitutions. **Chapter 3.3** describes future directions of this cyclobutene functionalisation approach.

3.1. Catalytic Asymmetric Synthesis of Cyclobutanes

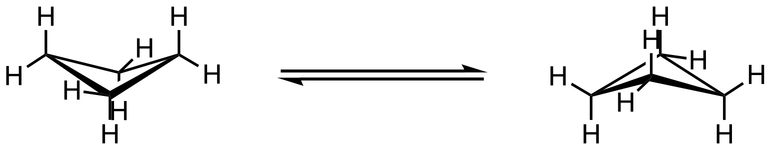
Chapter 3.1 is based on some sections from the following publications:

Goetzke, F. W.; Hell, A. M. L; van Dijk, L.; Fletcher, S. P. A catalytic asymmetric cross-coupling approach to the synthesis of cyclobutanes. *Nat. Chem.* **2021**, *13*, 880–886.

Goetzke, F. W.; Sidera, M.; Fletcher, S. P. Catalytic Asymmetric Hydrometallation of Cyclobutenes with Salicylaldehydes. *Manuscript submitted*.

3.1.1 Motivation

Cyclobutanes are small all-carbon rings, that exhibit a large amount of ring strain (26.5 kcal/mol) compared to larger homologous rings.[164] These 4-membered scaffolds are not flat, but rigid puckered conformations with dihedral angles of around 30° are generally preferred (Figure 3-1).[165–167]

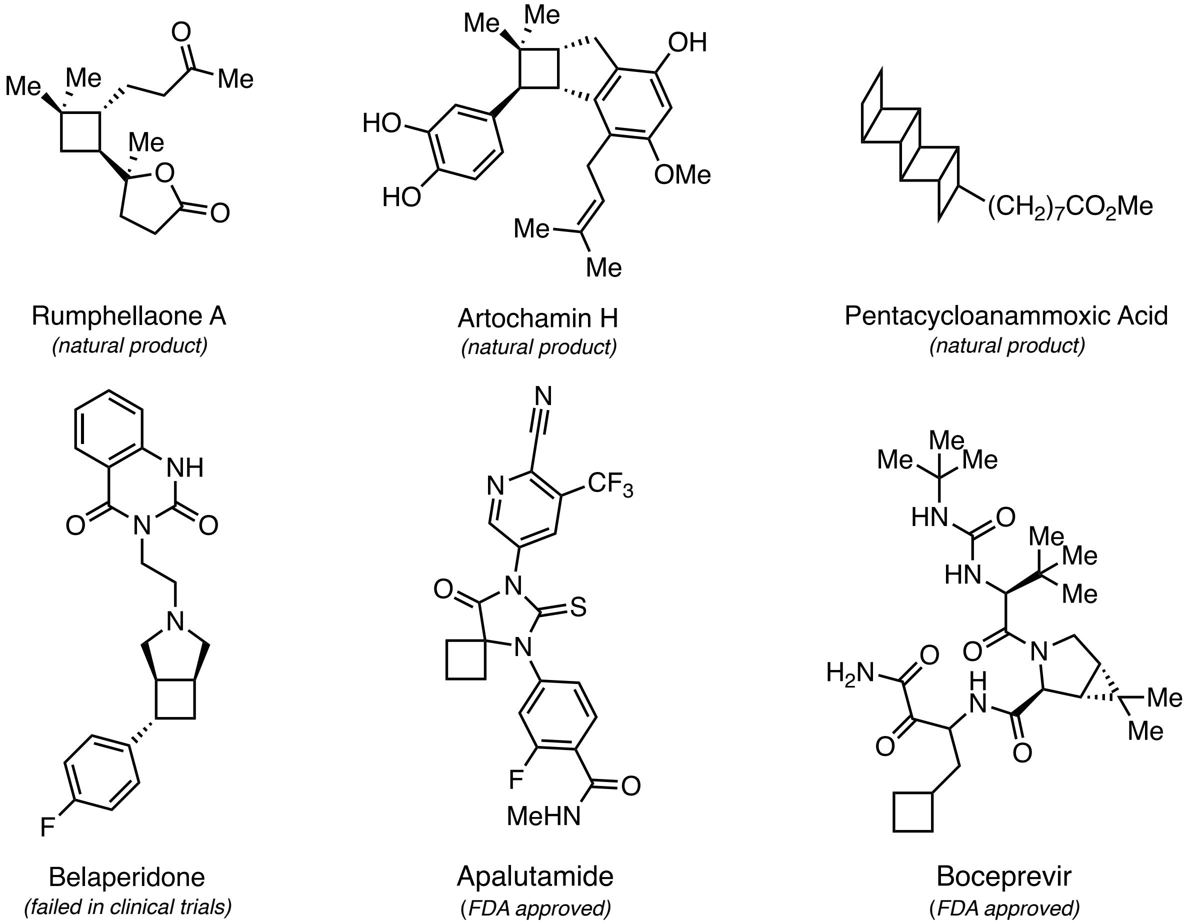


- puckered conformation
- rigid scaffold
- 30 ° dihedral angle
- 26.5 kcal/mol ring strain

Figure 3- 1: The puckered conformation of cyclobutane.

Substituted, stereochemically complex cyclobutanes can be found in many natural products (Figure 3-2),[168–171] and due to their inherent ring strain, they are also strategically important intermediates in organic synthesis.[172,173]

Over the last years, the cyclobutane motif has also received increased attention as a rigid scaffold, building block and isostere in medicinal chemistry.[174] In drug discovery programs, the substitution of alkyl chains with cyclobutane rings can be used as a strategy to increase hydrophobic interactions with a protein or to minimise free rotation.[174] So far 8 compounds that bear a cyclobutane ring have been approved by the FDA.[175] But their cyclobutyl rings are generally simply substituted like in the drugs Boceprevir or Apalutamide (Figure 3-2). None of the cyclobutanes bear any stereogenic centres.[156] Only a few compounds containing stereogenic cyclobutyl rings, including the D4/5-HT2 antagonist Belaperidone[176] (Figure 3-2) and the antiviral compound Lobucavir[177], have entered clinical trials.



Rumphellaone A
(natural product)

Artochamin H
(natural product)

Pentacycloanammoxic Acid
(natural product)

Belaperidone
(failed in clinical trials)

Apalutamide
(*FDA approved)*

Boceprevir
(*FDA approved)*

Figure 3-2: Stereochemically complex cyclobutane containing natural products and bioactive molecules with cyclobutane rings.

Previously developed synthetic strategies towards chiral cyclobutanes have relied heavily on multistep ring-contraction and expansion strategies.[172] Also a few asymmetric catalytic methods that use ring-closure or functionalisation reactions of pre-formed 4-membered rings have been developed, however, the latter methods are generally only applicable to specific substrates and substitution patterns. The synthesis of complex, chiral cyclobutanes is a largely unsolved problem, and there is a lack of general and modular synthetic methods to access these scaffolds.

Likely, the scarcity of generally useful synthetic methods has led to their underrepresentation in drug development.[178] The upcoming section describes some of the catalytic methods that have been developed over the last decade and discusses their limitations.

3.1.2 Catalytic Asymmetric Ring-Closure

[2+2] Cycloadditions

Photochemical, polar and transition metal mediated [2+2] cycloaddition addition reactions between two alkenes (or one alkene and one alkyne) are powerful tools for the synthesis of cyclobutanes (or cyclobutenes). However, developing asymmetric variants of photochemical cycloadditions is associated with the major challenge of outcompeting a racemic background reaction.[179] Two selected examples are described below.

Bach and co-workers pioneered chiral Lewis acid catalysed intramolecular [2+2] cycloaddition reactions (Figure 3-3a).[180] A bathochromic shift upon binding of a Lewis acid to an enone allows for the selective excitation of the substrate-catalyst complex over the unbound enone with a monochromatic light source, and thereby circumvents the non-catalysed, racemic pathway. This reaction requires very high catalyst loadings in order to achieve good levels of enantioinduction. Yoon and co-workers developed dual catalytic visible light mediated [2+2] cycloadditions (Figure 3-3b).[181] Here, visible light is used for excitation of a photosensitiser. The same group reasons that the photosensitiser catalyses single-electron transfer to an enone/Lewis acid adduct which undergoes subsequent [2+2] reaction with a different enone substrate.

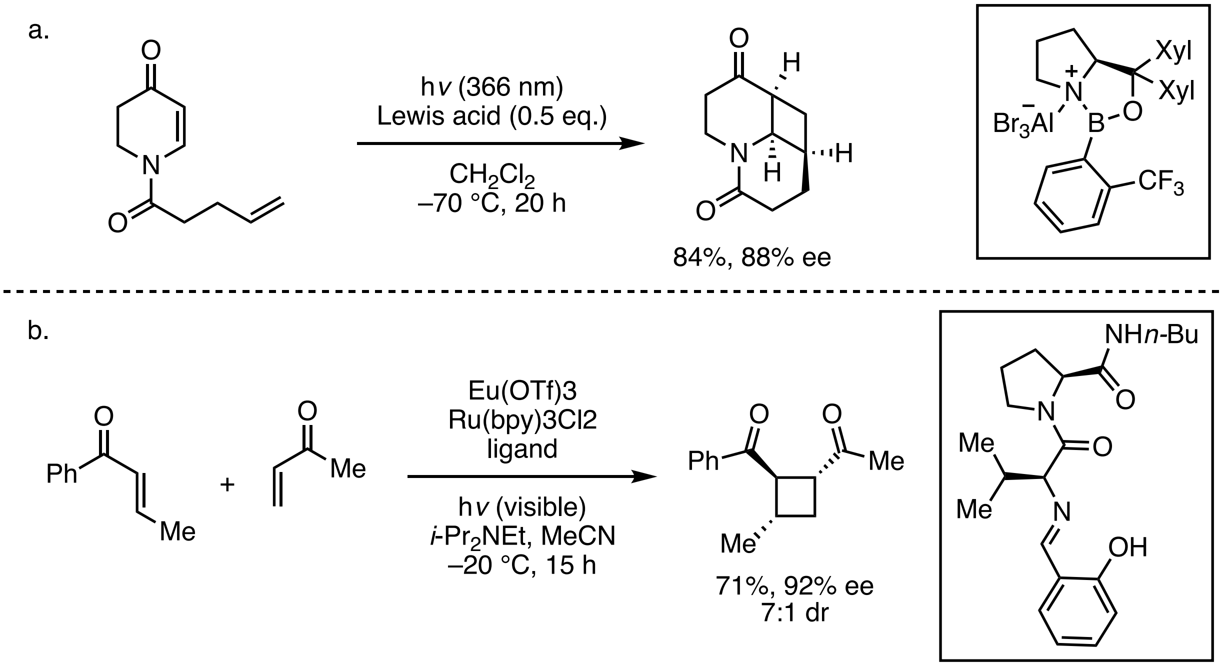


Figure 3-3: Intramolecular Lewis acid sensitised [2+2] cycloaddition (a) and visible light mediated dual catalytic intermolecular [2+2] cycloaddition (b).

A strategy to avoid the use of photoexcitation can be achieved by performing polarised cycloaddition reactions, including Lewis acid or amine catalysed reactions.[179] Echavarren and co-workers reported an asymmetric gold-catalysed [2+2] cycloaddition reaction between alkynes and alkenes (Figure 3-4), which was applied in an enantioselective synthesis of the *gem*-dimethylcyclobutane natural product rumphellaone A (Figure 3-2).[182] The linear geometry of gold(I) complex makes inducing excellent enantioselectivities in such a process very challenging. High-throughput experimentation guided the group to non-*C2* symmetric digold catalysts, which were able to induce good enantioselectivities, albeit only for disubstituted alkenes.

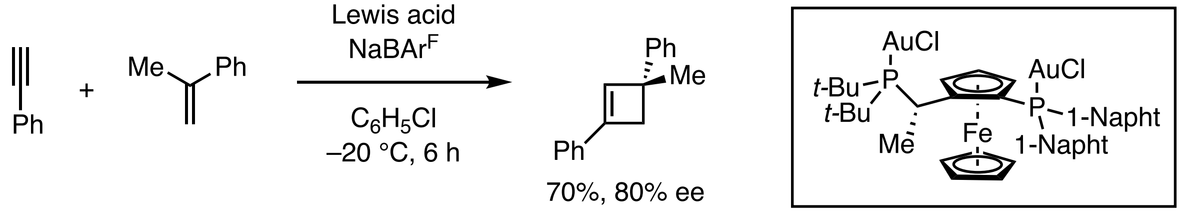


Figure 3-4: Au-catalysed [2+2] cycloaddition between terminal alkynes and alkenes.

A transition metal-catalysed method to construct complex cyclobutanes in a single step was developed by Pagar and RajanBabu. Cobalt complexes catalysed tandem reactions between 1,3-enynes and ethylene, followed by a second enantioselective addition of ethylene to the intermediary vinylcyclobutenes (Figure 3-5).[183] RajanBabu and co-workers also developed cobalt-catalysed cycloadditions between alkynes and functional alkenes in order to obtain enantioenriched cyclobutenes.[184]

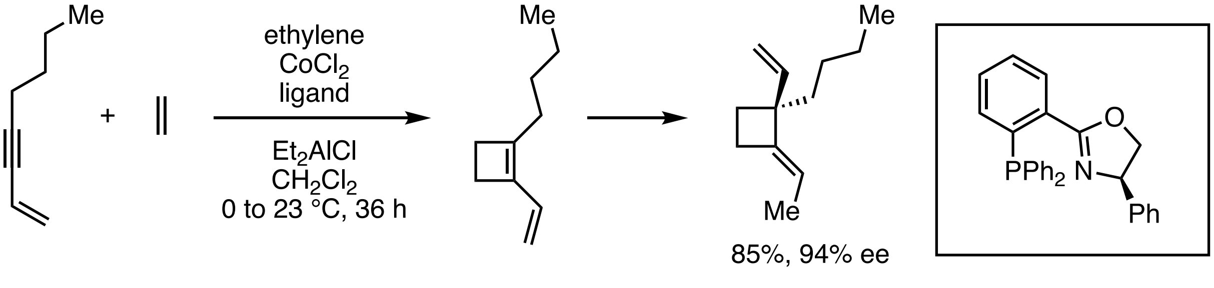


Figure 3-5: Tandem cobalt-catalysed couplings between ethylene and enynes.

The different activation principles of these [2+2] cycloaddition reactions require specific functional groups which thereby limits these approaches to specific substrate classes and substitution patterns.

Intramolecular cyclisation reactions

In the above cycloadditions, two carbon-carbon bonds are formed in one reaction. In an alternative strategy, intramolecular cyclisation reactions result in the formation of only one carbon-carbon bond. Enantioselective cyclisation reactions can allow for the synthesis of enantioenriched cyclobutane rings.

Buchwald and co-worker developed an asymmetric copper-catalysed cyclisation reaction with halide-tethered styrenes and a silane reductant (Figure 3-6).[185] With homoallylic halides, chiral 1,2-disubstituted cyclobutanes were obtained in excellent enantioselectivities. This reaction is mediated by a copper hydride species that it generated in situ with the silane reductant. An enantioselective and regioselective *syn*-hydrocupration is followed by the C–C bond and ring forming substitution reaction with the halide.

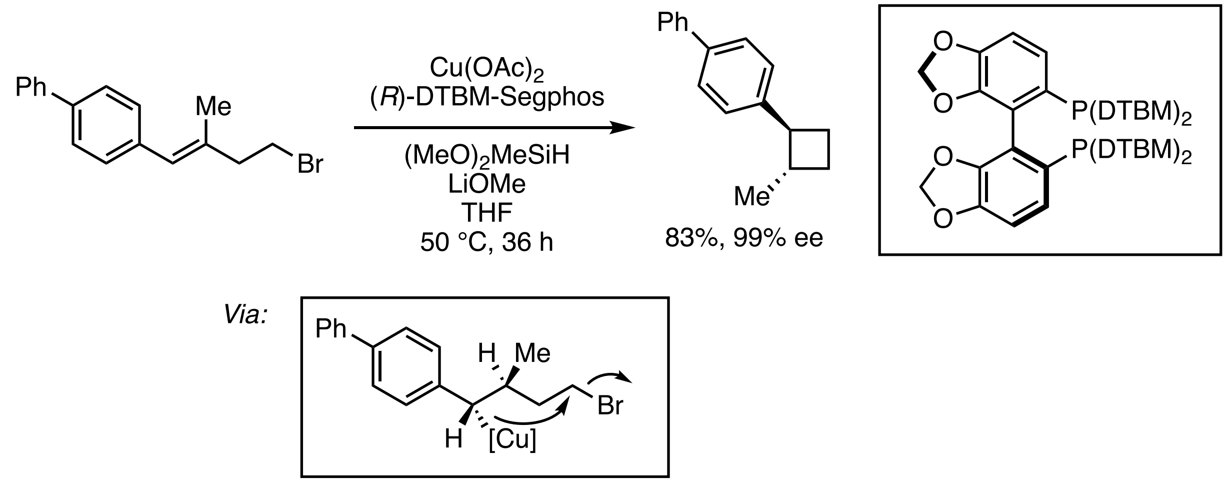


Figure 3-6: Enantioselective Cu–H mediated cyclisation reaction.

Dong and co-workers reported an enantioselective intramolecular hydroacylation reaction of pent-4-enals with earth-abundant cobalt as the catalyst (Figure 3-7).[186] A range of cyclobutanes with two stereogenic centres were obtained in good to excellent enantioselectivities. In a typical mechanism for a hydroacylation reaction, the acyl cobalt hydride intermediate can differentiate between the two enantiotopic allyl groups in the enantiodetermining olefin insertion step, which is followed by C–C bond forming reductive elimination.

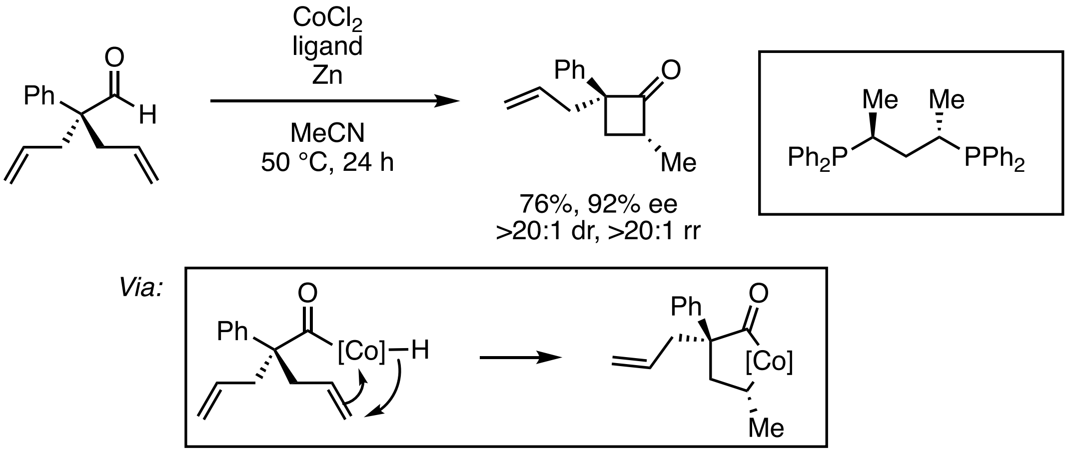


Figure 3-7: Co-catalysed intramolecular hydroacylation with pent-4-enals.

As diversification needs to occur before the cyclisation step and requires (multi-step) linear synthesis, intramolecular cyclisation reactions are intrinsically not ideal for building libraries of structurally related compounds.

3.1.3 Catalytic Asymmetric Functionalisation of Pre-formed Rings

Addition reactions to cyclobutanes

As many methods for the non-enantioselective synthesis of 4-membered rings exist, the enantioselective functionalisation of pre-formed rings represents a useful and complementary strategy for the asymmetric synthesis of cyclobutanes. These include asymmetric α-functionalisation reactions of cyclobutanones.[187]

The use of directing groups can facilitate the functionalisation of otherwise unactivated C(sp^3)−H bonds. Yu and co-workers developed an amide directed, Pd-catalysed enantioselective cross-coupling reaction of the C(sp^3)–H methylene groups of the cyclobutane with an arylboronic ester (Figure 3-8).[188] A chiral mono-*N*-protected α-amino-*O*-methylhydroxamic acid ligand induced good enantioselectivities, and benzoquinone (BQ) was used as the oxidant for the cross-coupling. This cross-coupling reaction gives a modular entry to a range of different aryl cyclobutanes. However, the necessity of a directing group limits the scope of this reaction to 1,2-difunctionalised cyclobutanes, and it can be challenging to remove or modify the directing group in a subsequent synthetic sequence.

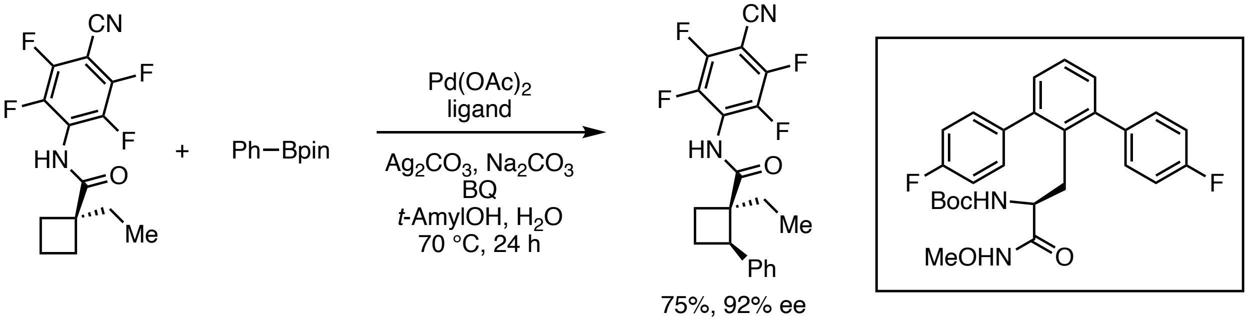


Figure 3-8: Enantioselective Pd^{II}-catalysed $C(sp^3)$−H cross-coupling of cyclobutyl carboxylic acid derivatives with arylboronic esters.

Addition reactions to cyclobutenes

Enantioselective addition reactions to cyclobutenes are a complementary method to direct cyclobutane functionalisations. Most of these reactions are triggered by activating groups like carbonyl groups or leaving groups in the allylic position. Conjugate additions or allylic substitution reactions with cyclobutenyl substrates typically operate under similar conditions as those that are applied with larger rings.

Feng, Lin and co-workers developed Rh-catalysed enantio- and diastereoselective 1,4-addition reactions of arylboronic acids to cyclobut-1-ene-1-carboxylates.[189] A bulky group on the ester was required to induce excellent stereoselectivities, and a strong ligand effect was observed for the diastereoselectivity of this transformation. Some asymmetric copper-catalysed addition reactions to substituted cyclobutenones are also known.[190,191]

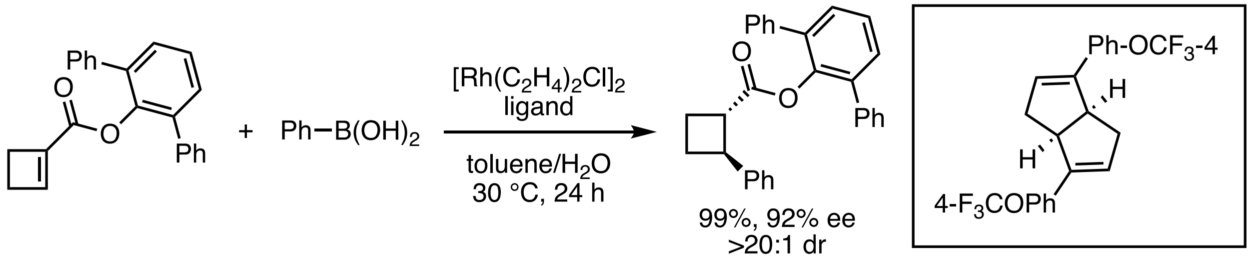


Figure 3-9: Enantio- and diastereoselective Rh-catalysed 1,4-additions to cyclobut-1-ene-1-carboxylates with arylboronic acids.

The Maulide group pioneered a few enantio- and diastereoselective Pd-catalysed allylic substitution reactions with cyclobutenes with leaving groups in the allylic position.[96,192–195]

Direct enantioselective functionalisation reactions with other unactivated cyclobutenes are scarce but highly attractive as they offer a modular entry to functionalised cyclobutanes. The alkene serves as traceless activating group, and such a reaction would generally not be limited to specific substitution patterns and activating or directing groups in the reaction products.

Tortosa and co-workers reported copper-catalysed asymmetric hydroboration reactions of *meso*-cyclobutenes (Figure 3-10a).[196] Several *trans-cis* cyclobutyl borates can be obtained in excellent enantioselectivities. The synthetic applicability if this transformation was demonstrated with a concise synthesis of the chiral ligand FlexiphosO and a formal synthesis of HIV protease inhibitor GRL-06579A. Recently, the same group also reported asymmetric bis-borylation of spirocyclic cyclobutenes.[197]

The Buchwald group applied copper-hydride chemistry to the asymmetric hydroamination of 1-substituted cyclobutenes (Figure 3-10b).[198] The use of tri-substituted alkenes in a hydrometallation process is quite remarkable in this study, however the reaction has a very limited substrate scope, requiring a bis-benzyl group on the amine.

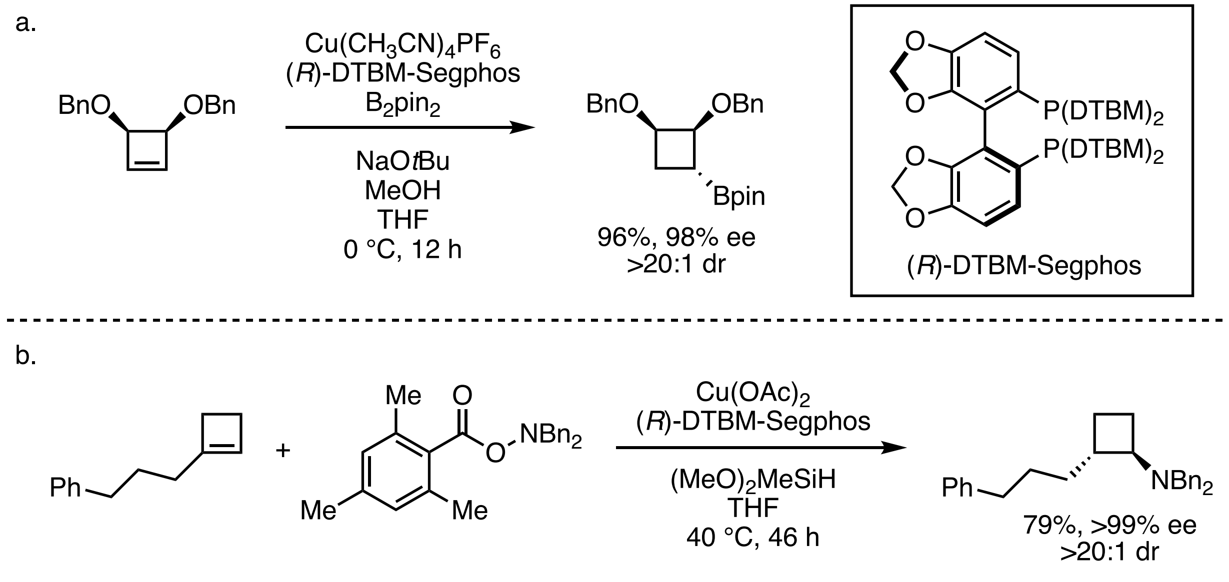


Figure 3-10: Cu-catalysed asymmetric hydroboration (a) and hydroamination (b) of cyclobutenes.

Both of these reactions proceed via hydrometallation mechanisms, and the asymmetric carbometallation has remained elusive.

3.2. A Catalytic Asymmetric Cross-Coupling Approach to the Synthesis of Cyclobutanes

Chapter 3.2 is based on the following publication:

Goetzke, F. W.; Hell, A. M. L; van Dijk, L.; Fletcher, S. P. A catalytic asymmetric cross-coupling approach to the synthesis of cyclobutanes. *Nat. Chem.* **2021**, *13*, 880–886.

This project was carried out in collaboration with Alexander M. L. Hell and Lucy van Dijk, who performed experimental work (optimisation and investigation of the scope). Experiments performed by Alexander M. L. Hell (A.M.L.H.) or Lucy van Dijk (L.v.D.) are indicated throughout the text. I conceived the project, discovered the different reactivity patterns described in this chapter, and performed all other experiments. Further, I contributed to this chapter by writing the manuscript for publication with Stephen P. Fletcher and contributions from Alexander M. L. Hell and Lucy van Dijk. Experimental procedures and characterisation data for experiments in **Chapter 3.2** can be found in **Chapter 5.3**.

3.2.1. Introduction

Rhodium-catalysed addition reactions to alkenes with arylboronic acids have emerged as some of the most powerful reactions for the enantioselective formation of C(sp^2)–C(sp^3) bonds.[61] The use of boronic acids and their derivatives as organometallic reagents is highly attractive, due to their widespread availability.[9] Also, their ease of handling has largely contributed to their frequent use in drug discovery programs.[7]

Rh-catalysed arylations can be triggered by electron-withdrawing groups in the allylic position. Hayashi and co-workers' pioneered enantioselective 1,4-addition reactions of arylboronic acids to α,β-unsaturated carbonyl compounds (Figure 3-11a).[111] Building on this work, numerous asymmetric addition reactions to Michael acceptors and other electron-deficient alkenes[61] and allylic substitution reactions (Figure 3-11b)[113] have been developed.

Another strategy to trigger addition reactions to alkenes relies on the release of olefinic strain in the carbometallation step. In this context, asymmetric Rh-catalysed addition reactions of boronic acids to cyclopropenes (Figure 3-11c)[199] and some bicyclic species including (di)azanorbornene[122,200] have been developed. Further, the hydroarylation of *N*-sulfonyl-3-pyrrolines is also known (Figure 3-11d).[201]

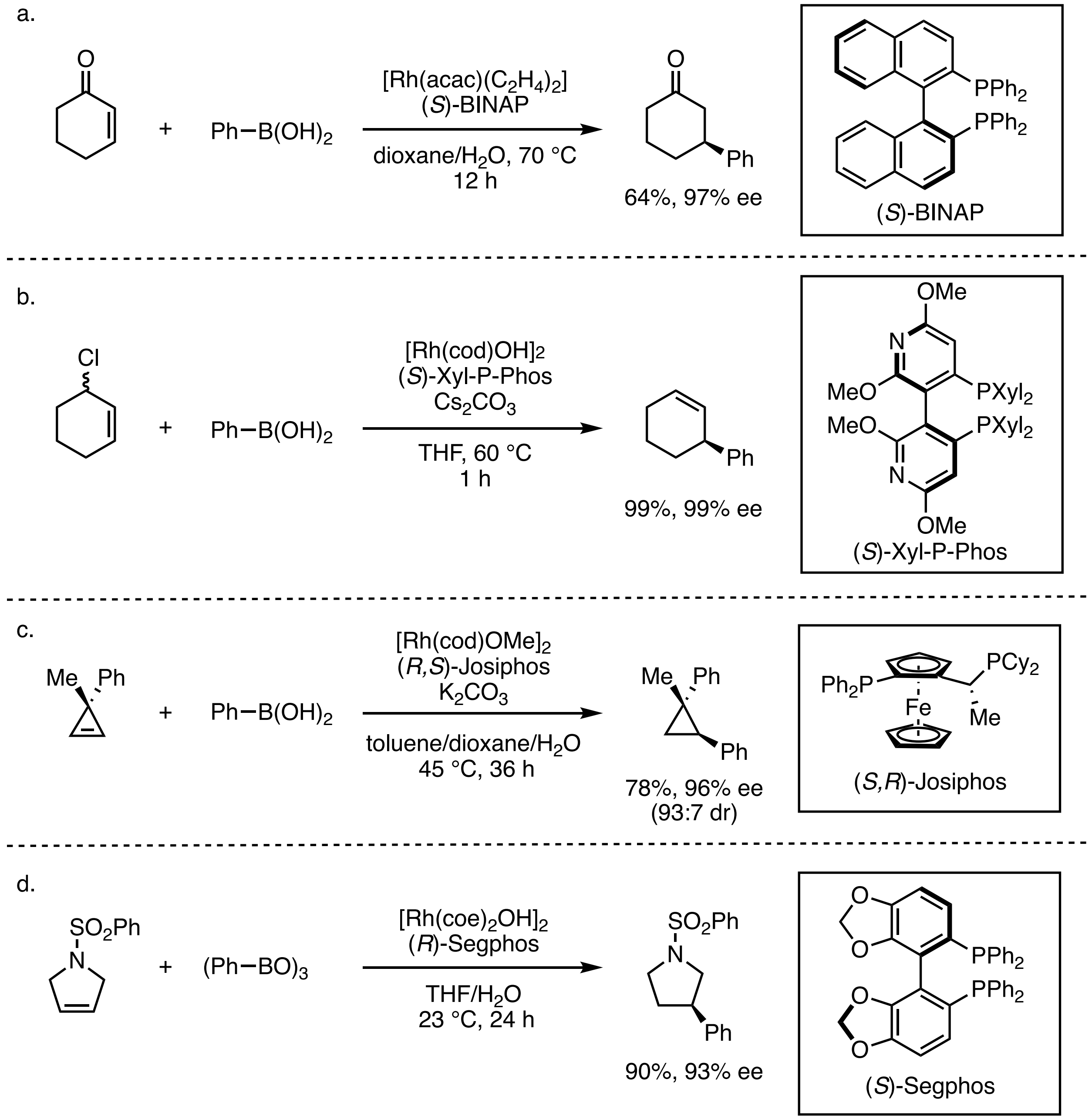


Figure 3-11: Asymmetric Rh-catalysed arylation of α,β-unsaturated carbonyl compounds (a), allyl halides (b), cyclopropenes (c) and 3-pyrrolines (d).

Cyclobutanes are – similarly like cyclopropanes or some bicyclic species – highly strained molecules Figure 3-12a), but unlike cyclopropenes (27.8 kcal/mol) or some unsaturated bicycles, the reduction (or carbometallation) of cyclobutenes is associated with a very small release in olefinic strain (1.9 kcal/mol) (Figure 3-12b).[164]

Rh-catalysed addition reactions to unfunctionalised cyclobutenes have remained elusive but would represent a major contribution to the long-standing problem of asymmetric cyclobutane synthesis (see **Chapter 3.1**).

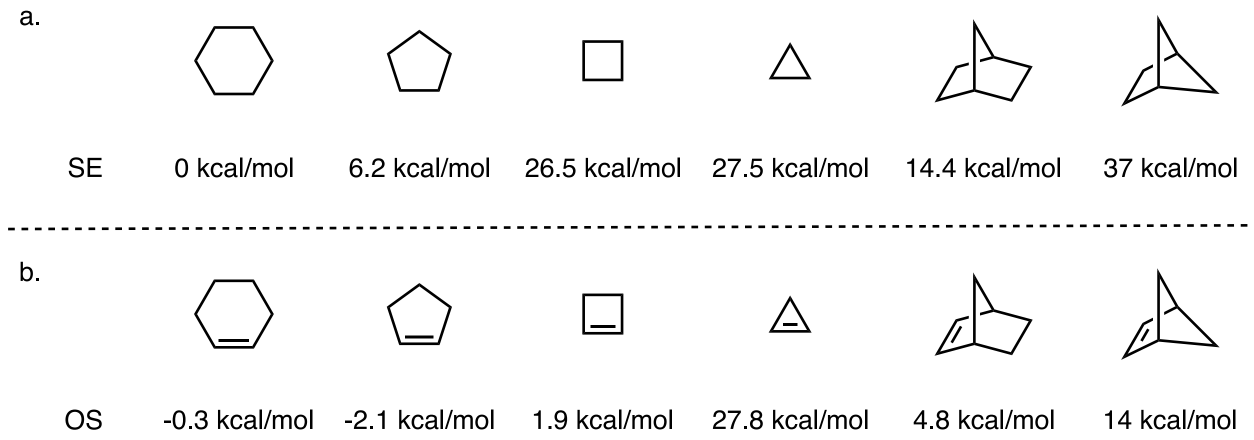


Figure 3-12: Strain energy (SE) of cyclic molecules (a) and their olefinic strain (OS) (b).[164]

3.2.2. Objective of the Project

In **Chapter 3.2**, we explore if the small olefinic strain of cyclobutenes (1.9 kcal/mol) is sufficient to enable enantioselective carbometallation reactions using arylboronic acids and Rh-catalysis (Figure 3-13). This would represent the first example of an asymmetric carbometallation of cyclobutenes. Even racemic carbometallations of cyclobutenes are scarce,[202] and established carbometallation approaches that work for more strained species like cyclopropenes (27.8 kcal/mol) generally do not translate to cyclobutenes.[203]

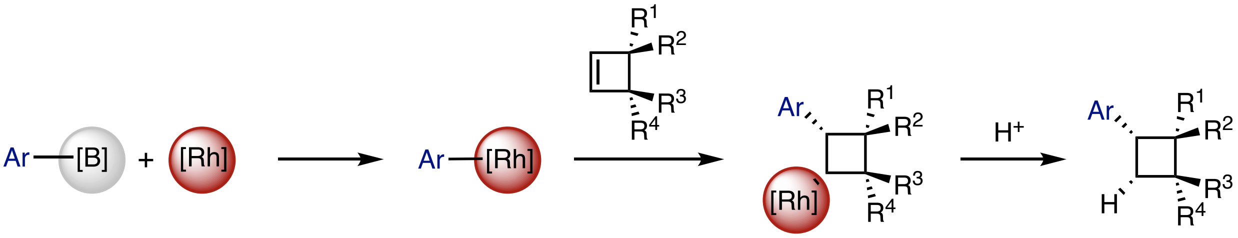


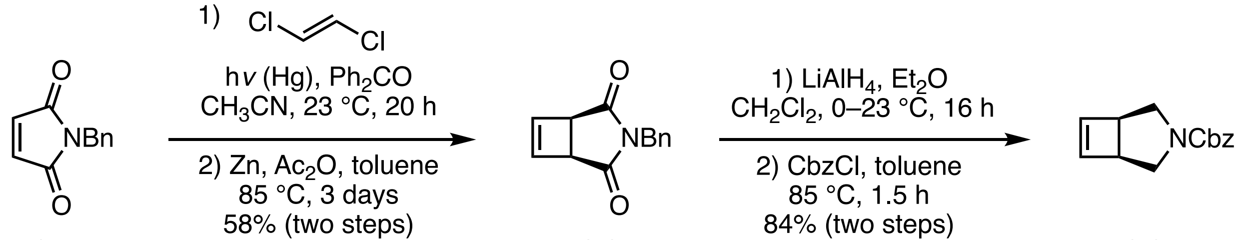
Figure 3-13: Asymmetric carbometallation with cyclobutenes.

The carbometallation could enable a range of enantio- and diastereoselective Rh-catalysed cross-coupling reactions between cyclobutenes and arylboronic acids and would give a modular entry to stereochemically complex cyclobutanes. Further, this approach would avoid the limitation to specific substitution patterns on the cyclobutane that many existing catalytic methods have (see **Chapter 3.1**).

3.2.3. Results and Discussion

Synthesis of bicyclic cyclobutenes

We chose the *N*-carbamate protected **3-3** as our model system as its hydroarylation would provide an entry to the bicyclic core of Belaperidone (see Figure 3-2). **3-3** was obtained after 4 synthetic steps in 49% overall yield and two purifications via automated medium pressure liquid chromatography (Figure 3-14). In the initial photoinduced [2+2] reaction, highly flammable acetylene was avoided and replaced by 1,2-dichloroethylene, followed by reduction with zinc and acetic anhydride to give cyclobutene **3-2**.[204] Best results were obtained in the cycloaddition using 10 mol% of the photosensitiser benzophenone under irradiation with a 400 W medium-pressure mercury lamp in a batch reactor.[205,206] Reduction of the imide to the pyrrolidine with lithium aluminium hydride was followed by swapping the *N*-benzyl group to the corresponding benzyl carbamate **3-3**. This sequence allows for the synthesis of 2–3 g of **3-3** in one synthetic cycle.



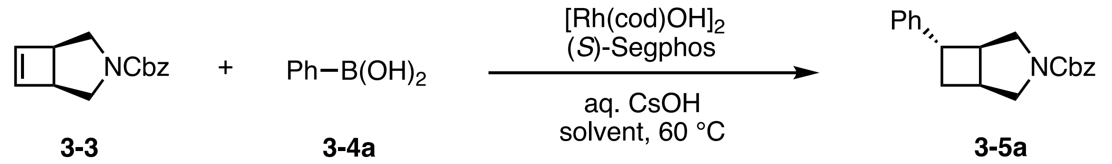
3-1 **3-2** **3-3**

Figure 3-14: Synthesis of *N*-containing bicyclic cyclobutenes.

Optimisation studies for the reductive Heck of a bicyclic cyclobutene

We started our optimisation for the coupling of cyclobutene **3-3** with phenylboronic acid (**3-4a**) under typical conditions for Rh-catalysed asymmetric 1,4-additions using the ligand Segphos (**L3-1**) – the ligand of choice for Rh-catalysed arylations with racemic bicyclic allyl chlorides.[61,155] Under these conditions, we obtained the desired *cis-trans* isomer **3-5a** (>20:1 dr) with promising levels of enantioselectivity, albeit in low yields (Table 3-1; entries 1-2). A change of the solvent to a mixture of toluene/dioxane/H_2O (7.2:1) led to a drastic increase in yield and an improvement in enantioselectivity (Table 3-1; entry 3).

Table 3-1: Selected initial experiments for the coupling of **3-3** with **3-4a**.



3-3 **3-4a** **3-5a**

Entry	Solvent	Time	Yield [a]	Enantiomeric excess [b]
1	dioxane/H_2O (9:1)	15 h	19%	89%
2	THF/H_2O (9:1)	15 h	36%	90%
3	toluene/dioxane/H_2O (7:2:1)	2 h	77%	94%

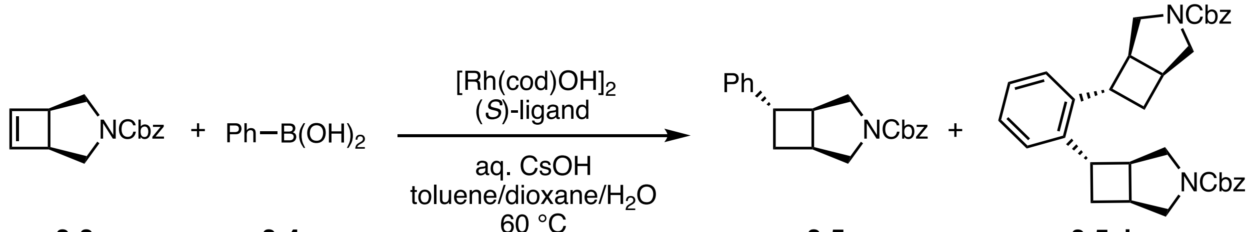
Conditions: (±)-**3-3** (0.2 mmol), **3-4a** (0.4 mmol), $[Rh(cod)OH]_2$ (2.5 mol%), (*S*)-Segphos (6 mol%), aq. CsOH (50 wt%, 0.2 mmol), solvent (0.1 M), 60 °C.

[a] Isolated yields of the *cis*-*trans* diastereoisomer (>20:1 dr).

[b] Enantiomeric ratios were determined by SFC using a chiral non-racemic stationary phase.

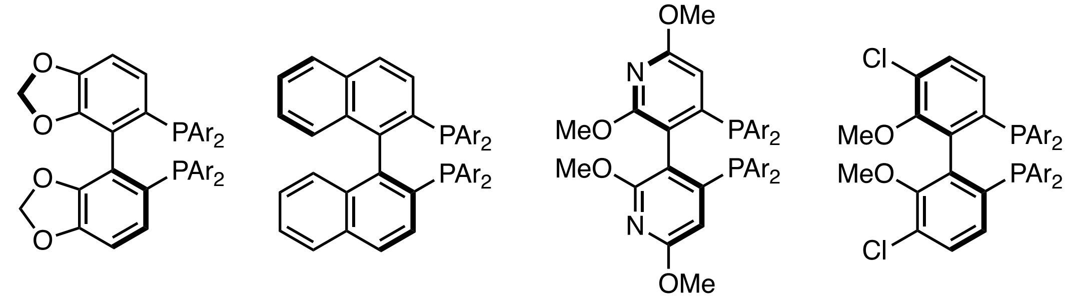
Encouraged by this result, we investigated the influence of the ligand on the reaction outcome. A careful analysis of the reaction mixture revealed the formation of a dimeric (and sometimes even trimeric) side-product **3-5a'** – typically as mixtures of diastereoisomers. As no other side-products were formed in significant quantities and full conversion of the cyclobutene was achieved in 1–2 h, the weighted ratio of **3-5a** to **3-5a'** served as a good approximation for isolated yields (compare Table 3-1; entry 3 and Table 3-2; entry 1). Several C_2-symmetric bidentate phosphine ligands were screened, which were all efficient ligands for this transformation with varying levels of enantioselectivity and dimer-formation (Table 3-2; entries 1-8). Among all investigated ligands, DTBM-Segphos (**L3-3**) gave the best enantioselectivity, albeit at the expense of increased dimer formation (Table 3-2; entry 3). Segphos (**L3-1**) provided a good compromise between enantioinduction and **3-5a** to **3-5a'** ratio (Table 3-2; entry 1) and was therefore chosen for further optimisation reactions.

Table 3-2: Selected ligand screening experiments for the coupling of **3-3** with **3-4a**.



3-3 **3-4a** **3-5a** **3-5a'**

Entry	Ligand	Weighted ratio 3-5a/3-5a' [a]	Enantiomeric excess [b]
1	(*S*)-**L3-1**	78/22	94%
2	(*S*)-**L3-2**	68/32	84%
3	(*S*)-**L3-3**	48/52	96%
4	(*S*)-**L3-4**	69/31	88%
5	(*S*)-**L3-5**	54/46	60%
6	(*S*)-**L3-6**	76/24	94%
7	(*S*)-**L3-7**	70/30	84%
8	(*S*)-**L3-8**	76/24	82%



(*S*)-**L3-1** Ar = Ph
(*S*)-**L3-2** Ar = Xyl
(*S*)-**L3-3** Ar = DTBM

(*S*)-**L3-4** Ar = Ph
(*S*)-**L3-5** Ar = Xyl

(*S*)-**L3-6** Ar = Ph
(*S*)-**L3-7** Ar = Xyl

(*S*)-**L3-8** Ar = Ph

Conditions: **3-3** (0.2 mmol), **3-4a** (0.4 mmol), [Rh(cod)OH]$_2$ (2.5 mol%), (*S*)-ligand (6 mol%), aq. CsOH (50 wt%, 0.2 mmol), toluene/dioxane/H$_2$O (0.1 M; 7:2:1), 60 °C, 1–2 h.

[a] Weighted ratio of monomeric to dimeric product determined by ^{1}H NMR of the unpurified reaction mixture. *(Under the approximation that trimer formation is minimal.)*

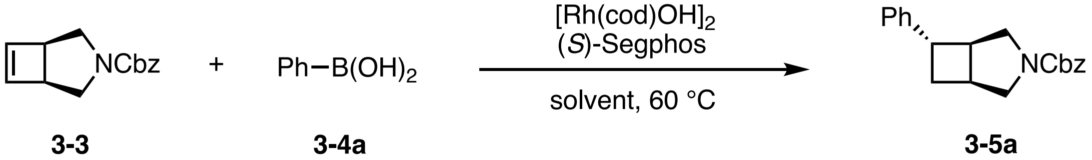
[b] Enantiomeric ratios were determined by SFC using a chiral non-racemic stationary phase.

During a screening of bases, we observed that the presence of the base CsOH had a negligible effect on the reaction outcome (Table 3-3; entries 1-2). Performing the reaction in a more diluted solvent system slightly improved the yield of the desired product but resulted in a lower enantioselectivity (Table 3-3; entry 3).

Ultimately, we realised that the presence of base in our initial experiments was responsible for the poor yields using dioxane/H_2O and THF/H_2O mixtures (Table 3-1; entries 1-2), and significantly better results were obtained without base (Table 3-3; entries 4-5).

This is likely because the presence of base slows down the protonation event, which is required to complete the catalytic cycle of the hydroarylation reaction (see Figure 3-17a). A similar behaviour was observed in Hayashi and co-workers hydroacylation of 3-pyrrolines.[201] We hypothesise that the biphasic nature of the toluene/dioxane/water (7:2:1) mixture led to a phase separation of the base and reagents, which allowed the reaction to proceed effectively in presence of the base (Table 3-3; entry 1).

Table 3-3: Selected solvent screening experiments for the coupling of **3-3** with **3-4a** at 60 °C.



Entry	Solvent	Yield [a]	Enantiomeric excess [b]
1	toluene/dioxane/H_2O (7:2:1) [c]	77%	94%
2	toluene/dioxane/H_2O (7:2:1)	75%	94%
3	toluene/dioxane/H_2O (7:2:1) [d]	82%	92%
4	THF/H_2O (9:1)	68%	92%
5	dioxane/H_2O (9:1)	74%	93%
6	dioxane/H_2O (9:1) [e]	90%	86%

Conditions: (±)-**3-3** (0.2 mmol), **3-4a** (0.4 mmol), $[Rh(cod)OH]_2$ (2.5 mol%), (*S*)-Segphos (6 mol%), solvent (0.1 M), 60 °C, 1–2 h.

[a] Isolated yields of the *cis*-*trans* diastereoisomer (>20:1 dr).

[b] Enantiomeric ratios were determined by SFC using a chiral non-racemic stationary phase.

[c] With aq. CsOH (50 wt%, 0.2 mmol).

[d] Performed at 0.05 M concentration.

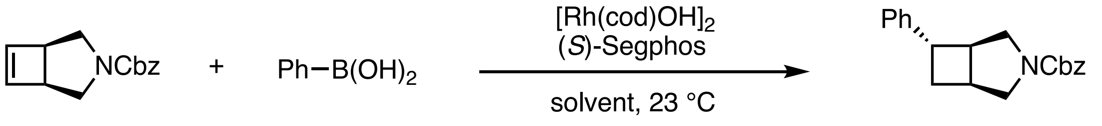
[e] Slow addition of the reagents over 1 h.

In order to reduce the formation of the dimeric side-product, we attempted slow addition of the reagents to the catalyst – in order to keep the concentration of the cyclobutene in the reaction mixture low. Indeed, an improved yield was obtained upon slow addition of the reagents over 1 h with a syringe pump, albeit at the cost of enantioinduction (Table 3-3; entry 6).

Some selected repeats from the initial ligand screening suggested that the selectivities observed under the conditions in Table 3-2 were comparable to those in a homogenous and base-free reaction mixture.

The reaction does not require heating and proceeds comparably at room temperature (23 °C) giving excellent enantioselectivities (98% ee) (Table 3-4). Reducing the amount of water from 10 to 2% did not affect the reaction outcome (Table 3-4; entries 1-2). A mixture of toluene/dioxane (1:1) gave slightly improved monomeric product formation than in dioxane (Table 3-4; entries 3-4), and we settled for the monophasic solvent system toluene/dioxane/H_2O (49:49:2) for the exploration of the reaction scope with different boronic acids.

Table 3-4: Selected solvent screening experiments for the coupling of **3-3** with **3-4a** at room temperature.



3-3 **3-4a** **3-5a**

Entry	Solvent	Weighted ratio 3-5a/3-5a' [a]	Enantiomeric excess [b]
1	dioxane/H_2O (90:10)	76/24	98%
2	dioxane/H_2O (98:2)	76/24	98%
3	toluene/dioxane/H_2O (45:45:10)	78/22	98%
4	toluene/dioxane/H_2O (49:49:2)	78/22	98%

Conditions: (±)-**3-3** (0.2 mmol), **3-4a** (0.4 mmol), $[Rh(cod)OH]_2$ (2.5 mol%), (*S*)-Segphos (6 mol%), solvent (0.1 M), r.t. (23 °C), 16 h.

[a] Weighted ratio of monomeric to dimeric product determined by ^1H NMR of the unpurified reaction mixture. *(Under the approximation that trimer formation is minimal.)*

[b] Enantiomeric ratios were determined by SFC using a chiral non-racemic stationary phase.

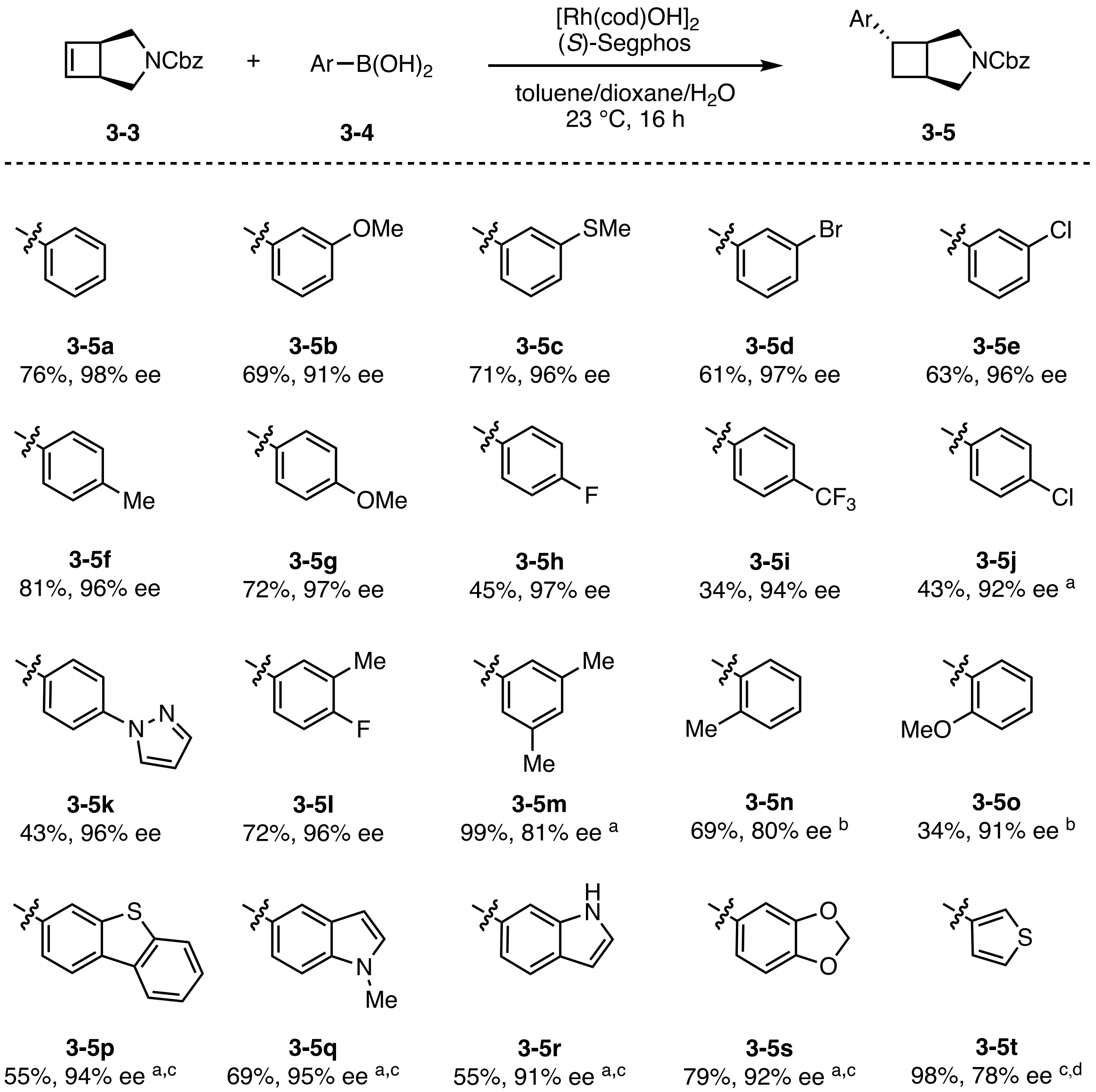
Asymmetric reductive Heck reactions with bicyclic cyclobutenes and boronic acids

Cross-coupling reactions with several different *meta*- and *para*-substituted arylboronic acids gave the desired aryl cyclobutanes – typically with excellent enantio- and diastereoselectivity and in good to moderate yields (Figure 3-15). The reaction proceeds effectively in the presence of a range of functional groups, including halides (**3-5d-e**, **3-5j**), (thio-)alkoxy groups (**3-5b-c**, **3-5g**) and a pyrazole (**3-5k**). Unfortunately, the yields were lower for electron-deficient *para*-substituted boronic acids (**3-5h-k**) due to increased formation of dimeric side-products. Full conversion of the cyclobutene was achieved in all cases, and no other side-products were formed in significant quantities. Di-substituted boronic acids gave good yields (**3-5l-m**).

Ortho-substituted boronic acids can be often challenging substrates in asymmetric arylation reaction.[128] With 2-methylphenylboronic acid, we obtained low enantioselectivity using our standard conditions involving (*S*)-Segphos (52% ee for **3-5n**), but a simple change of the ligand to (*S*)-BINAP gave improved results (80% ee for **3-5n**).

A small set of electron-rich bicyclic heteroarylboronic acids gave good yields and enantioselectivity (**3-5p-s**). Here, heating of the reaction mixture to 60 °C was required in order to achieve high conversion, and a change of the ligand to (*S*)-DTBM-Segphos was necessary for obtaining good levels of enantioinduction, albeit at the expense of slightly increased dimer formation. Electron-deficient (halo-) pyridyl and pyrimidyl boronic acids did not afford the coupling products (<5% yield). The 5-membered 3-thiopheneboronic acid gave only moderate enantioselectivity (78% ee) but quantitative yield, and low enantioselectivities were obtained with furan-derived boronic acids (e.g. 2-furylboronic acid; 14% ee), showing the limitations of our current catalytic system.

Further, two other bicyclic cyclobutenes with complementary *N*-protecting groups, a fused cyclopentanone and a fused sulfolane were used as substrates in the coupling with phenylboronic acid (see experimental **Chapter 5.3** for their synthesis). The coupling products were isolated in good yields and enantioselectivities (Figure 3-16).



3-3 + **3-4** → **3-5**

3-5a 76%, 98% ee

3-5b 69%, 91% ee

3-5c 71%, 96% ee

3-5d 61%, 97% ee

3-5e 63%, 96% ee

3-5f 81%, 96% ee

3-5g 72%, 97% ee

3-5h 45%, 97% ee

3-5i 34%, 94% ee

3-5j 43%, 92% ee [a]

3-5k 43%, 96% ee

3-5l 72%, 96% ee

3-5m 99%, 81% ee [a]

3-5n 69%, 80% ee [b]

3-5o 34%, 91% ee [b]

3-5p 55%, 94% ee [a,c]

3-5q 69%, 95% ee [a,c]

3-5r 55%, 91% ee [a,c]

3-5s 79%, 92% ee [a,c]

3-5t 98%, 78% ee [c,d]

Figure 3-15: Enantio- and diastereoselective reductive Heck of a bicyclic cyclobutene with different aryl- and heteroarylboronic acids.

Conditions: **3-3** (0.4 mmol), **3-4** (0.8 mmol), [Rh(cod)OH]$_2$ (2.5 mol%), (*S*)-Segphos (6 mol%), toluene/dioxane/H$_2$O (49:49:2; 0.1 M), r.t. (23 °C), 16 h. [a] Performed at 60 °C. [b] (*S*)-BINAP used instead of (*S*)-Segphos. [c] (*S*)-DTBM-Segphos used instead of (*S*)-Segphos. [d] 3 equivalents instead of 2 equivalents of boronic acid.

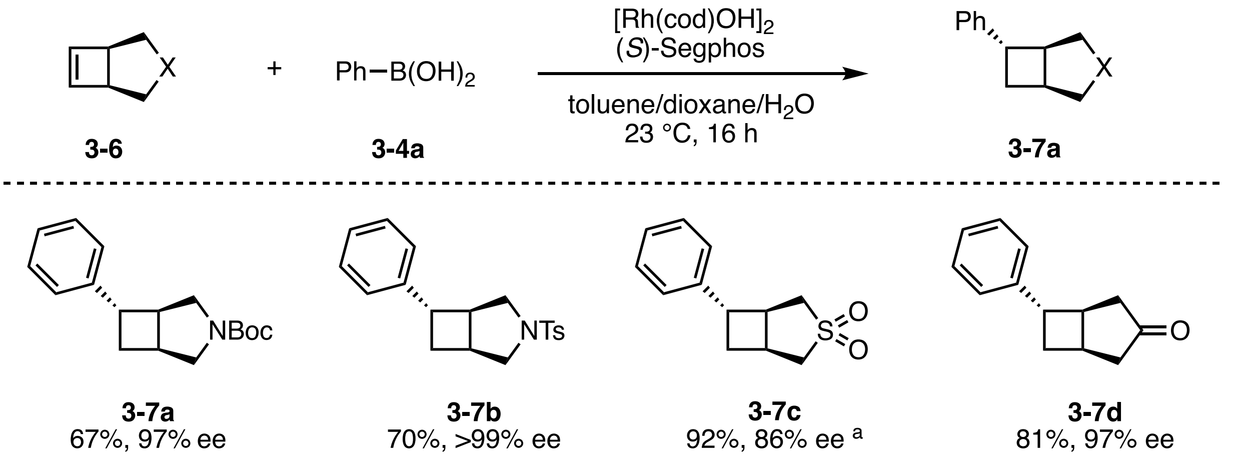


Figure 3-16: Enantio- and diastereoselective reductive Heck of bicyclic cyclobutenes with phenylboronic acid.

Conditions: **3-6** (0.4 mmol), **3-4a** (0.8 mmol), $[Rh(cod)OH]_2$ (2.5 mol%), (*S*)-Segphos (6 mol%), toluene/dioxane/H_2O (49:49:2; 0.1 M), r.t. (23 °C), 16 h. [a] Performed at 60 °C.

Proposed reaction mechanism for the hydroarylation of bicyclic cyclobutenes

In order to obtain a better mechanistic understanding of the hydroarylation of cyclobutene **3-3**, a reaction with D_2O instead of H_2O was performed. Deuterium incorporation occurs exclusively and in a stereospecific manner at the C(2) position next to *N*-carbamate (Figure 3-17a). We propose the following mechanism to explain product formation, deuterium incorporation and formation of dimeric side-products (**3-5a’**) (Figure 3-17a,b). Transmetallation of the boronic acid to Rh-hydroxide complex (**3-I**) gives a Rh-aryl intermediate (**3-II**).[112,115] Then, cyclobutene **3-3** undergoes carbometallation with **3-II** to give a Rh-cyclobutyl complex (**3-III**). This step sets the absolute and relative stereochemistry in the product. Complex **3-III** can engage in two different pathways, resulting in product and side-product formation. A series of reversible β-hydride eliminations and hydride-reinsertions gives the Rh-complex **3-IV** (Figure 3-17b; 1,2-hydride shift).[201,207] Alternatively, a 1,3-hydride shift from **3-VI** to **3-VIII** could occur, which does not involve intermediate **3-VII**. Remarkably, the chain-walking occurs over the bridgehead of the bicycle. Stereoselective protonation or deuteration with H_2O or D_2O completes the catalytic cycle and regenerates complex **3-1**. In the alternative pathway, **3-III** inserts into the *ortho*-C–H bond of the aromatic ring to give Rh-aryl complex **3-V** (Figure 3-17a).[208,209] Cyclobutene **3-3** can also undergo carbometallation with Rh-aryl complex **3-V** to form the dimeric side-product. The dimer **3-5’** was obtained as a mixture of diastereoisomers (2.2:1 dr). This behaviour is consistent with the observation that *ortho*-substituted boronic acids give poor enantioselectivities under our standard conditions, as the second addition corresponds to an addition with an *ortho*-substituted boronic acid. As no deuterium incorporation was observed at the aromatic C(2’) position, we reasoned that **3-5a** is not formed by protonation in the C–H insertion pathway. Using 3,5-dimethylphenylboronic acid resulted in quantitative product formation of **3-5m** (Figure 3-15), likely by slowing down C–H insertion for steric reasons and thereby completely suppressing dimer formation.

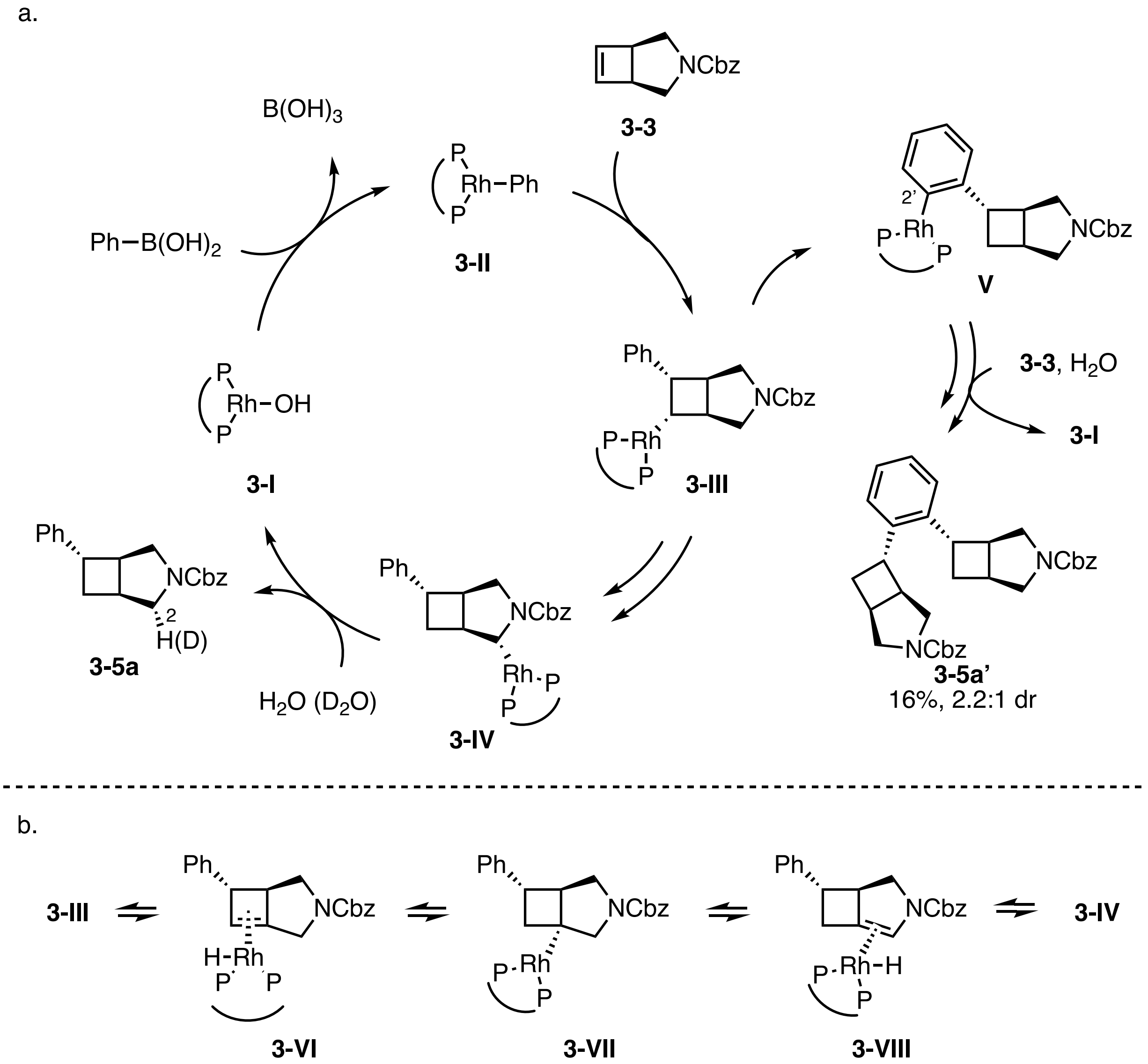


Figure 3-17: Mechanism of Rh-catalysed arylations of cyclobutenes (a) and chain-walking mechanism based on deuterium incorporation (b).

Rh-catalysed 1,5-additions to β,γ-unsaturated carbonyl compounds

Intrigued by the chain-walking mechanism, followed by protonation of an alkyl Rh-complex, we were motivated to investigate other substrate classes and to develop alternative protonation mechanism. We hypothesised that if the chain-walking had a stronger thermodynamic driving force, the formation of dimeric side-products could be suppressed. We investigated this hypothesis with an asymmetric 1,5-addition to the β,γ-unsaturated dicarbonyl compound **3-2**. For this reaction, heating of the reaction mixture to 60 °C was required in order to achieve full conversion of the cyclobutene, and a change of the ligand from (*S*)-Segphos to (*S*)-DTBM-Segphos resulted in excellent enantioselectivities. Good to excellent yields were obtained with a range of different *meta*- and *para*-substituted boronic acids with different electronics and functional groups (Figure 3-18).

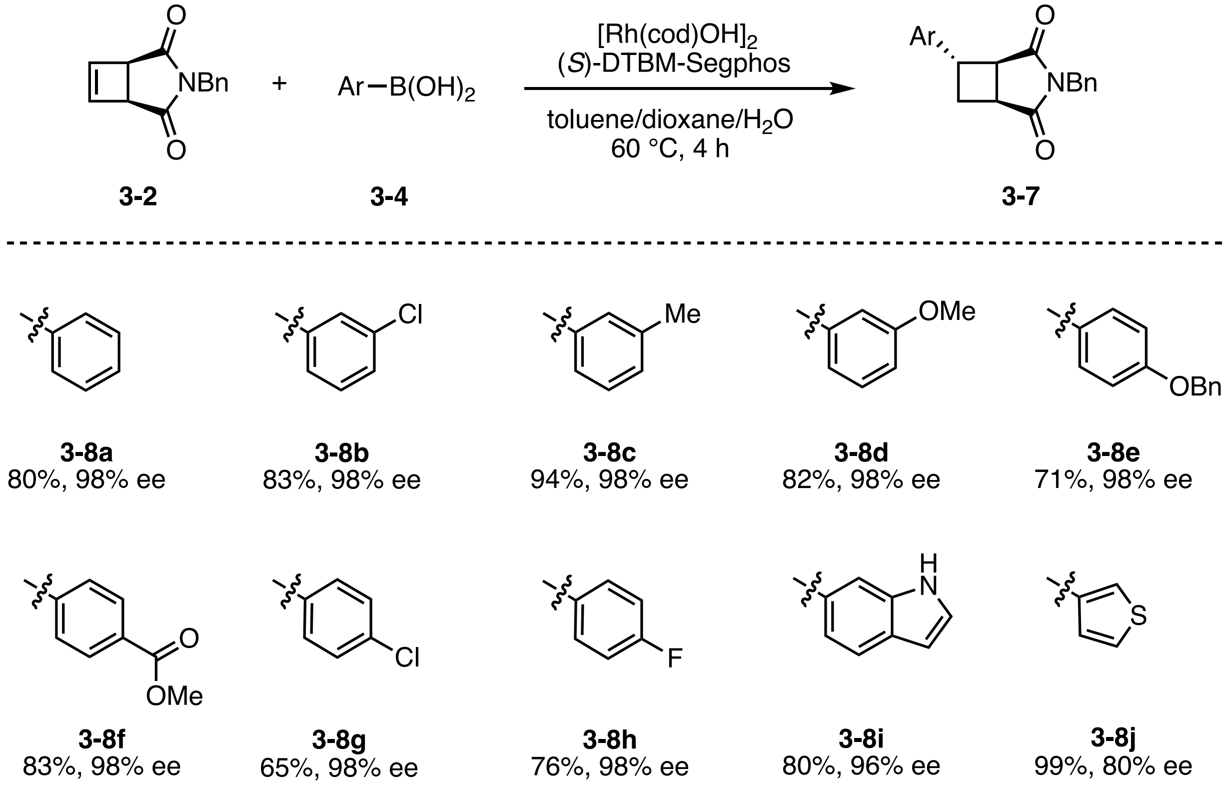


Figure 3-18: Enantio- and diastereoselective 1,5-additions to a bicyclic β,γ-unsaturated carbonyl compound with different aryl- and heteroarylboronic acids.

Conditions: **3-2** (0.4 mmol), **3-4** (0.8-1.2 mmol), [Rh(cod)OH]$_2$ (2.5 mol%), (*S*)-DTBM-Segphos (6 mol%), toluene/dioxane/H$_2$O (49:49:2; 0.1 M), 60 °C, 4 h.

Using D_2O instead of H_2O results in exclusive deuterium-incorporation at the bridgehead (Figure 3-19). This suggest the presence of an oxa-π-allyl Rh-complex **(3-XI)**,[112] which is formed from the cyclobutyl Rh-complex **3-IX** in a related chain-walking process. Likely, the oxa-π-allyl Rh-complex acts as a strong thermodynamic sink, which suppresses dimer formation and makes the product yields independent of the electronics of the boronic acid (Figure 3-18).

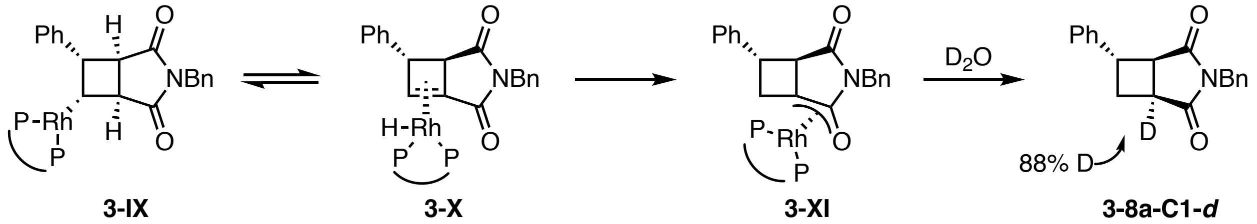


Figure 3-19: Mechanism of Rh-catalysed 1,5-additions of a bicyclic β,γ-unsaturated carbonyl compound based on deuterium incorporation.

Likely, ring-fusion controls the diastereoselective protonation to give the *cis*-fused bicycle **3-7**. We wondered how the protonation of a monocyclic oxa-π-allyl Rh-complex would occur. Asymmetric 1,5-addition to the β,γ-unsaturated dicarbonyl compound **3-9**[204,210] gives the *trans-trans* diastereoisomer as the major product for a small set of boronic acids (Figure 3-20), demonstrating that 1,5-additions allow for remote stereocontrol (Figure 3-21).

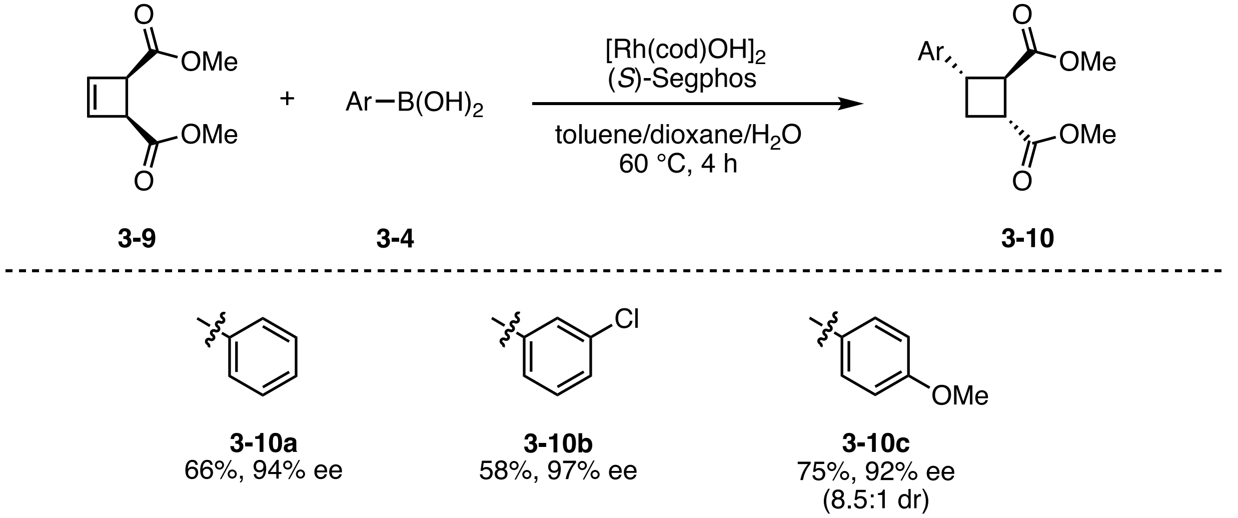


Figure 3-20: Enantio- and diastereoselective 1,5-additions to a monocyclic β,γ-unsaturated dicarbonyl compound with different arylboronic acids.

Conditions: **3-9** (0.4 mmol), **3-4** (0.8 mmol), $[Rh(cod)OH]_2$ (2.5 mol%), (*S*)-Segphos (6 mol%), toluene/dioxane/H_2O (49:49:2; 0.1 M), 60 °C, 4 h.

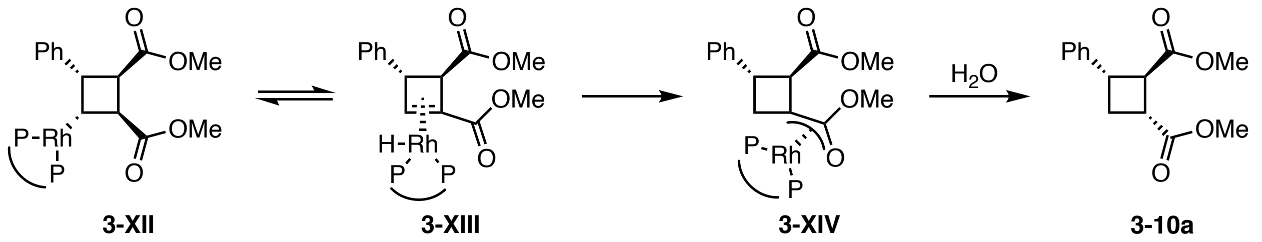


Figure 3-21: Mechanism of remote stereocontrol in Rh-catalysed 1,5-additions of a monocyclic of a β,γ-unsaturated carbonyl compound based on deuterium incorporation.

While cyclobutenes **3-3**, **3-5**, **3-2** and **3-9** are *meso*-achiral, we wondered how a racemic mixture of an unsymmetrically substituted cyclobutene would behave and prepared lactam (±)-**3-11** via mono-reduction of imide **3-2** (for details see experimental **Chapter 5.3**). The racemic mixture (±)-**3-11** gives a 1:1 mixture of the enantioenriched regioisomeric products **3-12** and **3-12'**, which could be separated easily via automated medium-pressure liquid chromatography (Figure 3-22).

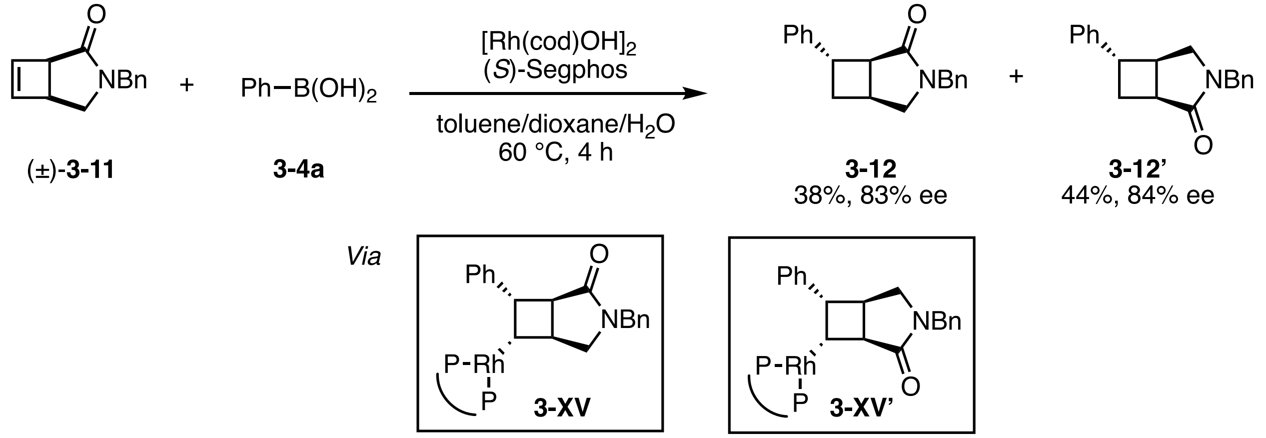


Figure 3-22: Regiodivergent reaction on a racemic mixture of bicyclic cyclobutene.

Conditions: (±)-**3-11** (0.4 mmol), **3-4a** (0.8 mmol), [Rh(cod)OH]$_2$ (2.5 mol%), (*S*)-Segphos (6 mol%), toluene/dioxane/H$_2$O (49:49:2; 0.1 M), 60 °C, 4 h.

Asymmetric syntheses of Belaperidone

In order to demonstrate the applicability of this chemistry, we developed two different asymmetric catalytic routes for the formal synthesis of the D4/5-HT2 antagonist Belaperidone (Figure 3-23), which was previously investigated in clinical studies as a treatment against Schizophrenia.[211] The first synthetic route relied on a highly enantioselective but only moderate yielding reductive Heck reaction with cyclobutene **3-3** (Figure 3-15; **3-5h**). Pd(OH)$_2$ mediated reduction with H_2 gave the previously reported intermediate **3-13**.[212,213] The absolute stereochemistry of the cross-coupling products was assigned via comparison with the known optical rotation of **3-13**.[212] In the second route, a higher yielding asymmetric 1,5-addition to **3-3** was used for the key C–C bond forming step (Figure 3-15; **3-8h**). Upon performing the reaction at 6 mmol scale, we managed to lower the catalyst loading to 0.5% dimeric $[Rh(cod)OH]_2$ and obtained >1 g of the desired coupling product. Two subsequent reductions gave the same free amine intermediate **3-13**. This represents the first catalytic asymmetric syntheses of the 3-azabicyclo[3.2.0]heptane core, while previously known routes to this enantioenriched scaffold have relied on kinetic resolution[212] or diastereoselective cycloaddition reactions with a chiral auxiliary[214].

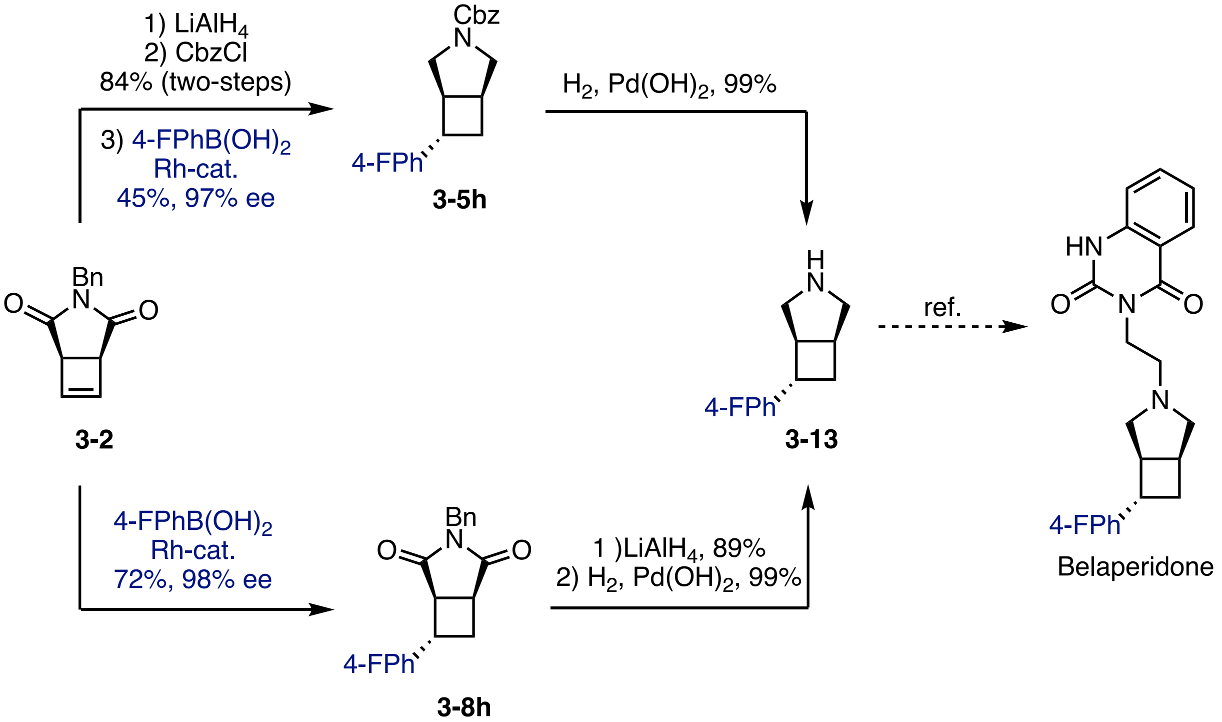


Figure 3-23: Two enantioselective approaches to synthesise the bicyclic core of Belaperidone using Rh-catalysed arylation reactions.

Regioselective reductive Heck reactions

We wondered how an unsymmetrically substituted, prochiral cyclobutene would behave in Rh-catalysed arylation reactions, where two different regioisomers could be formed in the rhodo-arylation step (Figure 3-24).

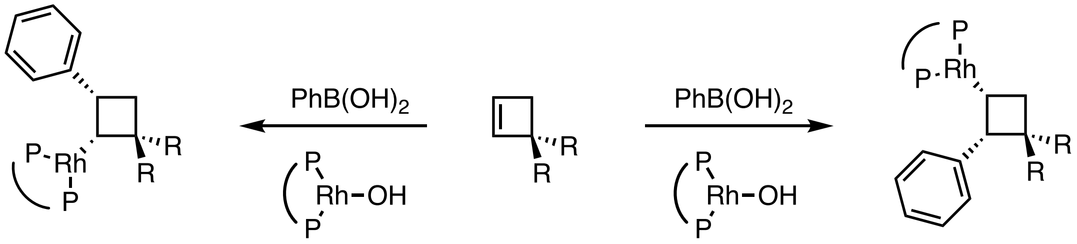


Figure 3-24: Regioselective arylation of a prochiral, unsymmetrically substituted cyclobutene.

We chose **3-14** as the model substrate, which synthesised in three steps from commercially available *tert*-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (see experimental **Chapter 3.3**). Simultaneously, Tortosa's group independently developed Cu-catalysed bis-borylation and mono-borylation reactions with the same substrate **3-14**.[197,215] A first reaction with phenylboronic acids and (±)-BINAP resulted in the regioselective formation of achiral product **3-15**, albeit in low yields due to extensive dimer formation. From here on, Lucy van Dijk continued the optimisation study on this substrate.[216] An optimal catalytic system can be generated in situ from $[Rh(cod)OH]_2$ and achiral 1,1'-bis(diphenylphosphino)-ferrocene (dppf). The addition of CsOH as base was required in order to reach high levels of conversion. Increasing the H_2O content from 2% to 10% led to reduced dimer formation. The coupling of **3-14** with different boronic acids was jointly investigated by Lucy van Dijk and me. Good to excellent yields were obtained with a range of functionalised boronic acids (Figure 3-25). Moderate yields were obtained with 2-methylphenylboronic acid and 4-benzyloxyphenylboronic acid due to incomplete conversion of the cyclobutene – likely caused by competitive protodeborylation.

This allowed us to develop a formal synthesis of the fatty acid amide hydrolase (FAAH) inhibitor PF-04862853 (Figure 3-26).[217–219] Here, an increase of the catalyst loading was required in order to obtain a good yield in the reductive Heck reaction with boronic acid **3-4k**, showing that small modifications of the reaction conditions can deliver improved results with challenging substrates.

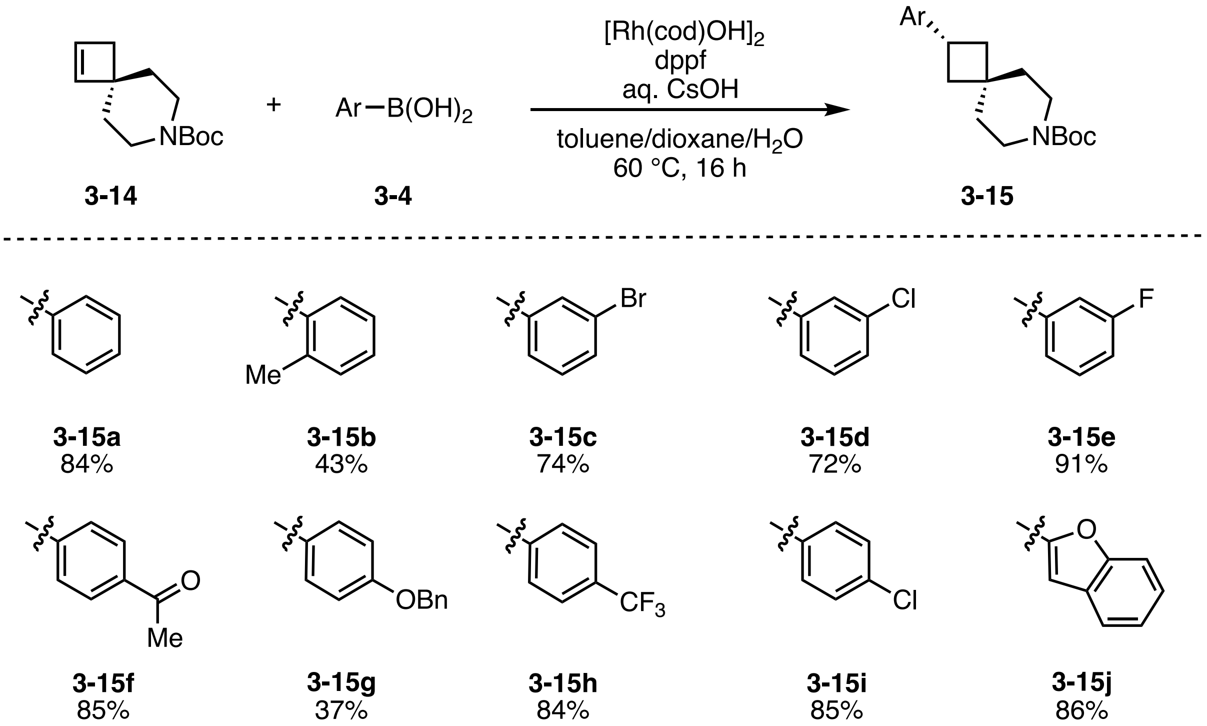


Figure 3-25: Regioselective reductive Heck of a spirocyclic cyclobutene with different aryl- and heteroarylboronic acids. *(Examples **3-7a-d**, **f**, **h** and **i** performed by Lucy van Dijk)*

Conditions: **3-14** (0.4 mmol), **3-4** (1.2 mmol), [Rh(cod)OH]$_2$ (2.5 mol%), dppf (6 mol%), aq. CsOH (50 wt%, 0.4 mmol), toluene/dioxane/H$_2$O (4.5:4.5:1; 0.1 M), 60 °C, 16 h.

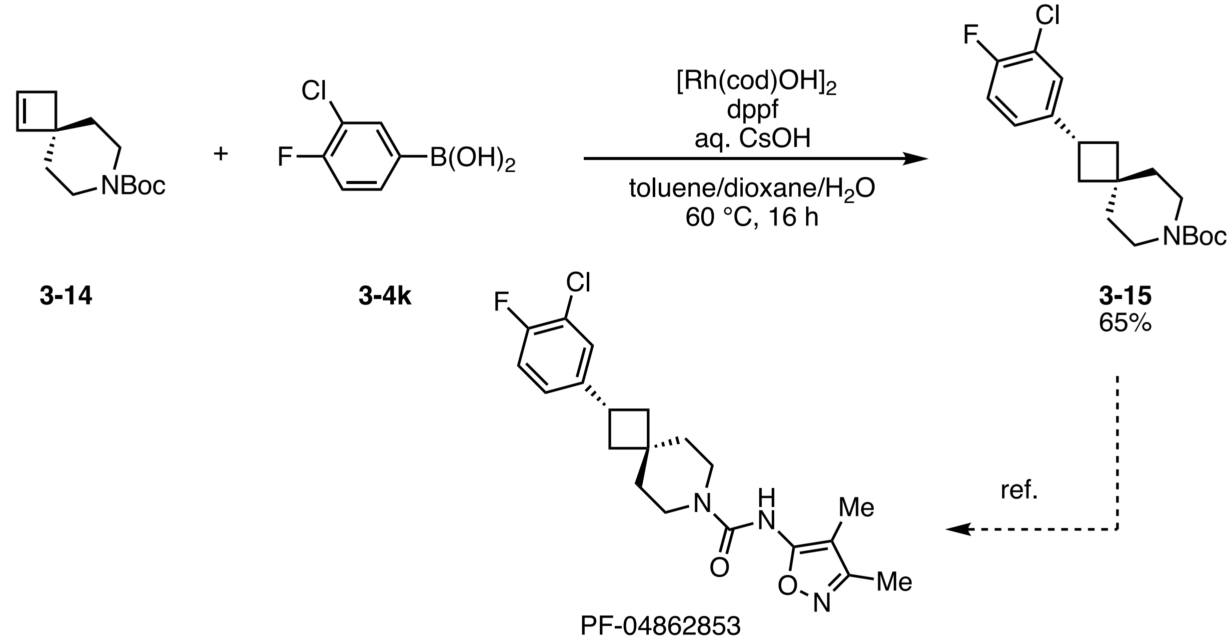
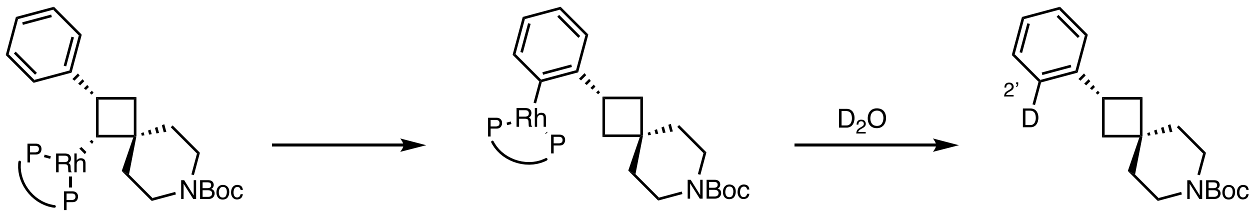


Figure 3-26: Regioselective Rh-catalysed synthesis of the FAAH inhibitor PF-04862853.

Conditions: **3-14** (0.4 mmol), **3-4k** (1.2 mmol), [Rh(cod)OH]$_2$ (5.0 mol%), dppf (12 mol%), aq. CsOH (50 wt%, 0.4 mmol), toluene/dioxane/H$_2$O (4.5:4.5:1; 0.1 M), 60 °C, 16 h.

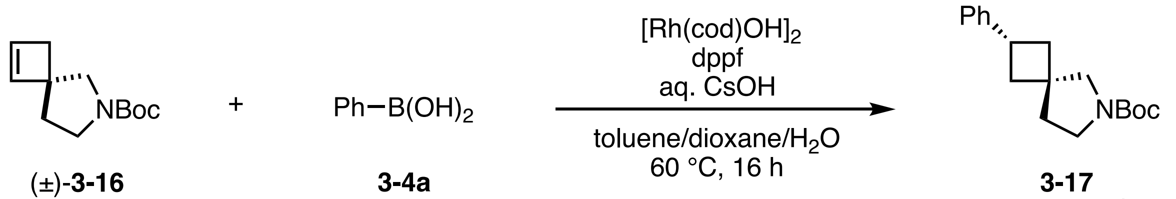
Performing the reaction in D_2O (and $CsOH \cdot H_2O$ in D_2O) resulted in the exclusive deuterium-incorporation at the C(2') position (Figure 3-27) *(experiment performed by L.v.D.)*. This suggests that chiral intermediate **3-XVI** is formed in the carbometallation step, and the subsequent C–H insertion gives achiral **3-XVII** (Figure 3-27).



3-XVI **3-XVII** **3-15-C2'-*d***

Figure 3-27: Mechanism of the regioselective reductive Heck of a spirocyclic of cyclobutene based on deuterium incorporation. *(Experiment performed by Lucy van Dijk)*

A regioselective reductive Heck reaction with racemic (±)-**3-16** afforded **3-17** as the major diastereoisomer, suggesting that other diastereoselective addition reactions to 3,3'-disubstituted cyclobutenes could be developed (Figure 3-28) (*experiment performed by L.v.D.).*



(±)-**3-16** **3-4a** **3-17**

65%, 4:1 dr

Figure 3-28: Regio- and diastereoselective reductive Heck of a racemic spirocyclic cyclobutene with phenylboronic acids. *(Experiment performed by Lucy van Dijk)*

Conditions: (±)-**3-16** (0.4 mmol), **3-4a** (1.2 mmol), $[Rh(cod)OH]_2$ (2.5 mol%), dppf (6 mol%), aq. CsOH (50 wt%, 0.4 mmol), toluene/dioxane/H_2O (4.5:4.5:1; 0.1 M), 60 °C, 16 h.

Homo-allylic substitution reactions

While all previously described addition reactions to cyclobutenes have relied on a remote protonation event to give products and complete the catalytic cycle, we wondered if other terminating mechanisms, like a selective heteroatom-elimination could be developed. The homoallylic diacetate **3-18** was prepared according to re-optimised literature procedures.[204,220,221]

Initial test reactions with **3-18** gave the homoallylic substitution product **3-19** bearing an exocyclic double bond. An initial ligand screening revealed that (*S*)-DTBM-Segphos induced excellent levels of enantioinduction for this transformation.

From here on, Alexander M. L. Hell continued the optimisation study on this substrate as the well as exploration of scope of this transformation.[222]

The optimal conditions were found to consist of a catalytic system generated in situ from $[Rh(cod)OH]_2$ and (*S*)-DTBM-Segphos and with cesium carbonate as the base, which was found to significantly improve conversion. These optimal conditions were applied to different boronic acids in order to explore the scope of this transformation. (Figure 3-29). With electron-donating boronic acids, the remote substitution product **3-19** was obtained in good yields and excellent enantioselectivities (Figure 3-29a). A phosphate or carbonate could serve as alternative leaving groups (Figure 3-30).

However, the reductive Heck product **3-20** was obtained as the major products, when electron deficient boronic acids were employed (Figure 3-29b). Using 3-Chloro-, 4-methoxy- and 4-(*N*-Boc-amino)phenylboronic acids resulted in the formation of mixtures of the remote substitution and the reductive Heck product (Figure 3-29). Here, the reductive Heck products were generally obtained in slightly lower enantioselectivities.

We propose a mechanism in which two pathways can occur after the initial carbometallation step (Figure 3-31). In the first pathway, β-hydride elimination, followed by reinsertion and β-oxygen elimination delivers the homoallylic substitution product **3-19**. In cases where C–H insertion is fast, e.g. with electron-deficient boronic acids, the reductive Heck product **3-20** is formed after protonation or deuteration at the C(2’) position (*D-labelling experiment performed by A.M.L.H.).*

While the enantioselectivity is set in the initial carbometallation step, a matched/mismatched effect between remote substitution and the reductive Heck pathway seems to predominate for each enantiomer[209], leading to different enantioselectivities for both products with the same boronic acid (Figure 3-29; **3-19e,g,h**, **3-20e,g,h**).

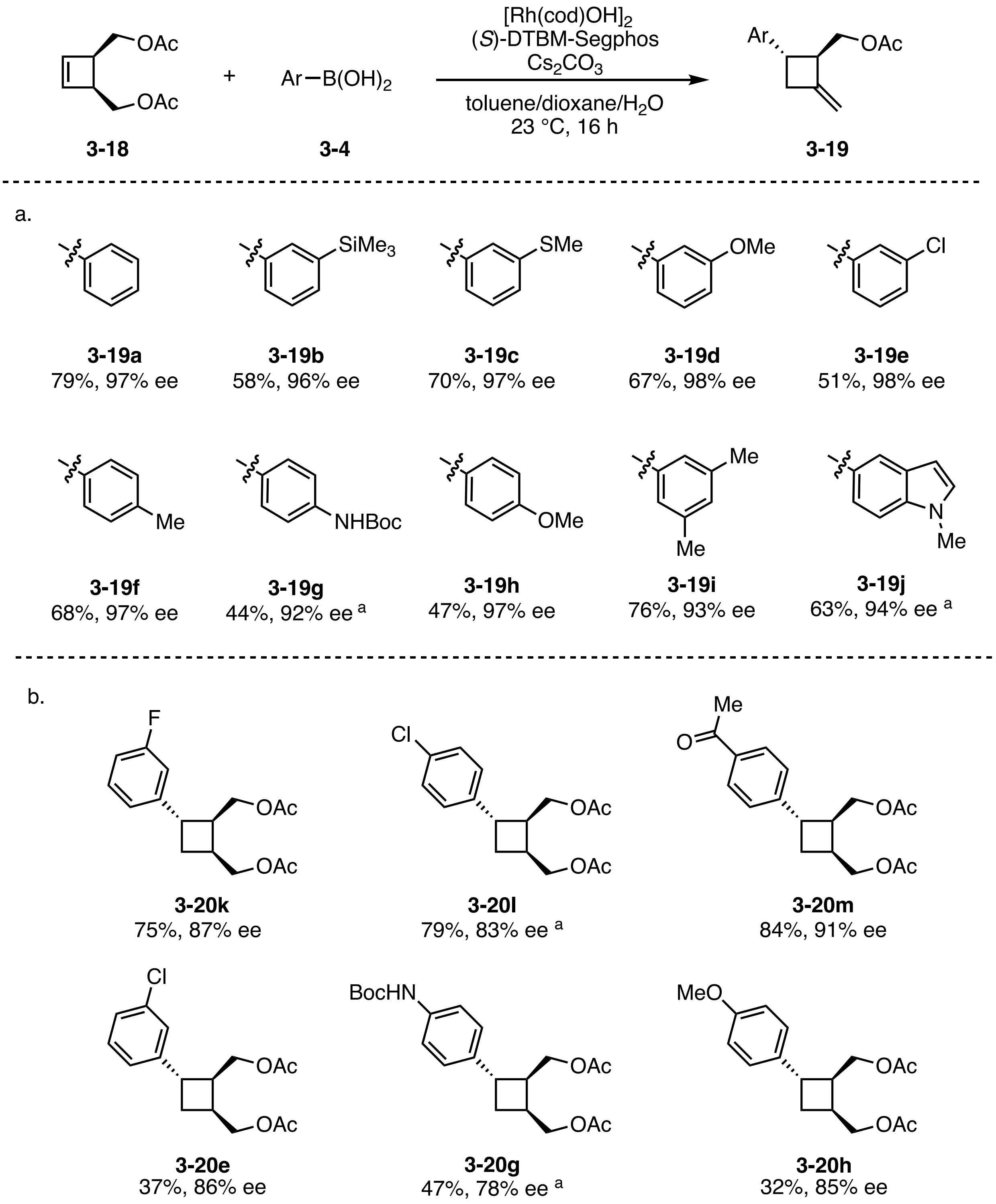
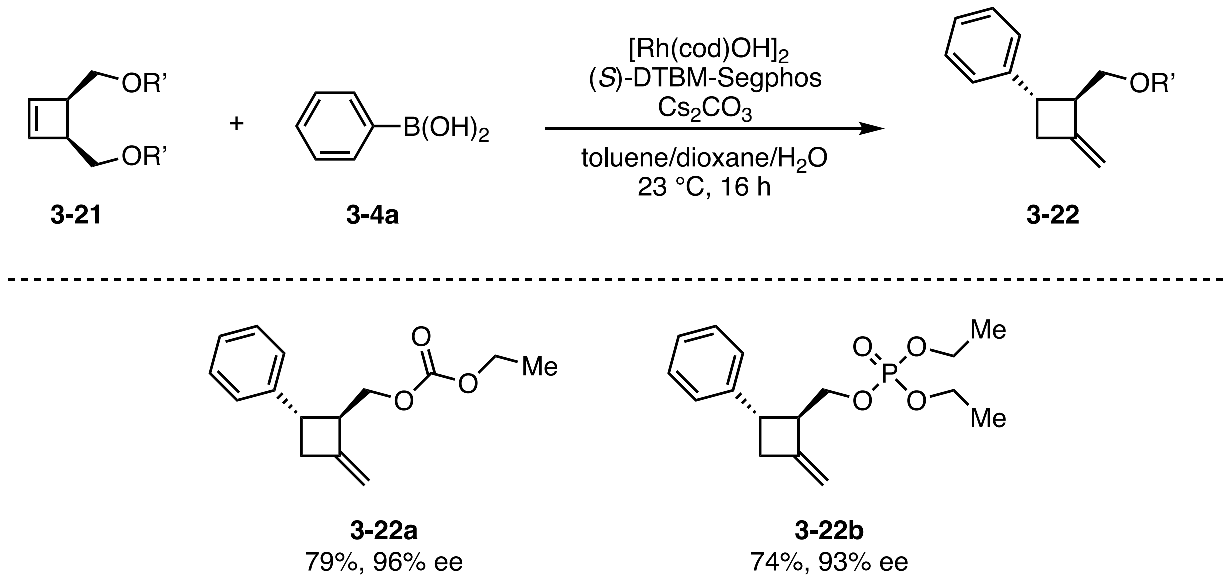


Figure 3-29: Enantio- and diastereoselective Rh-catalysed homo-allylic substitution with aryl- and heteroarylboronic acids (a) and reductive Heck reaction with electron-deficient boronic acids (b). *(Examples performed by Alexander M. L. Hell)*

Conditions: **3-18** (0.4 mmol), **3-4** (0.8-1.2 mmol), $[Rh(cod)OH]_2$ (2.5 mol%), (*S*)-DTBM-Segphos (6 mol%), Cs_2CO_3 (0.4 mmol), toluene/dioxane/H_2O (49:49:2; 0.1 M), r.t. (23 °C), 16 h. [a] Performed at 60 °C.



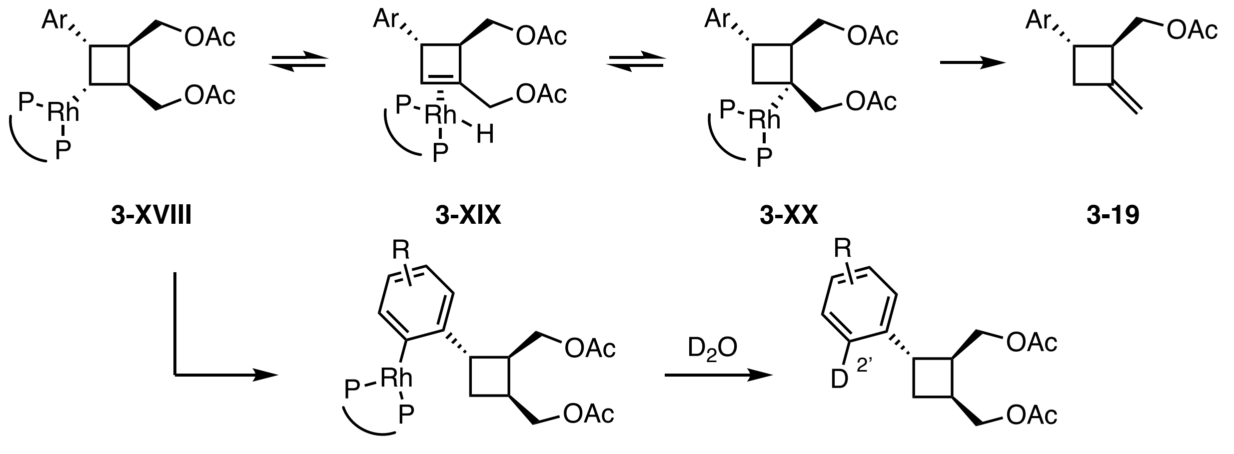
3-21 **3-4a** **3-22**

3-22a
79%, 96% ee

3-22b
74%, 93% ee

Figure 3-30: Enantio- and diastereoselective Rh-catalysed homo-allylic substitution with phenylboronic acids using alternative leaving groups. *(Examples performed by Alexander M. L. Hell)*

Conditions: **3-21** (0.4 mmol), **3-4a** (0.8 mmol), [Rh(cod)OH]$_2$ (2.5 mol%), (*S*)-DTBM-Segphos (6 mol%), Cs_2CO_3 (0.4 mmol), toluene/dioxane/H_2O (49:49:2; 0.1 M), r.t. (23 °C), 16 h

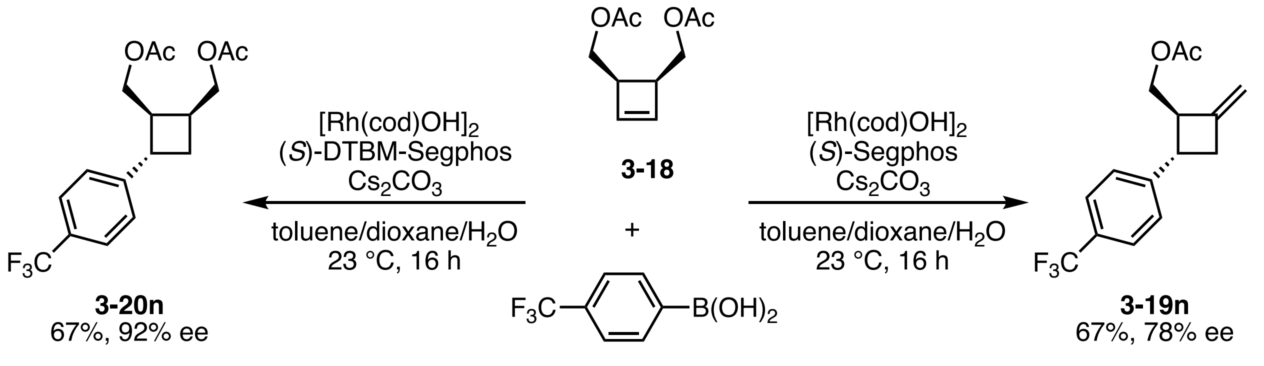


3-XVIII **3-XIX** **3-XX** **3-19**

3-XXI **3-20**

Figure 3-31: Mechanism of the chemodivergence in the Rh-catalysed remote substitution and hydroarylation based on deuterium incorporation. *(Experiment performed by Alexander M. L. Hell)*

The chemoselectivity of Rh-catalysed remote substitution and hydroarylation is both dependant on the electronic nature of the boronic acid and the Rh-complex. While the reductive Heck product **3-20n** was obtained as the major product using 4-trifluoromethylphenylboronic acid under our standard conditions, the remote-substitution product **3-19n** was obtained as the major product using the ligand (*S*)-Segphos (Figure 3-32) (*experiment performed by A.M.L.H.).*



3-4n

Figure 3-32: Catalyst controlled switching between reductive Heck and remote substitution selectivity. *(Experiments performed by Alexander M. L. Hell)*

Conditions: **3-18** (0.4 mmol), **3-4n** (0.8 mmol), [Rh(cod)OH]$_2$ (2.5 mol%), (*S*)-DTBM-Segphos or (*S*)-Segphos (6 mol%), Cs$_2$CO$_3$ (0.4 mmol), toluene/dioxane/H$_2$O (4.5:4.5:1; 0.1 M), r.t. (23 °C), 16 h.

3.2.4. Conclusion

Chapter 3.2 describes Rh-catalysed cross-coupling reactions between cyclobutenes and arylboronic acids.[223] This work represents the first asymmetric catalytic carbometallation of cyclobutenes, which proceeds despite the relatively small release in olefinic strain and does not require activating or directing groups. The carborhodation can trigger a range of different reaction pathways including chain-walking or C–H insertion, followed by remote protonation or heteroatom-elimination (Figure 3-33). Overall, a range of stereochemically complex, diverse aryl cyclobutanes can be obtained. Likely, other metal-catalysed asymmetric carbometallation reactions are possible, and some of these are currently under investigation in the Fletcher group.

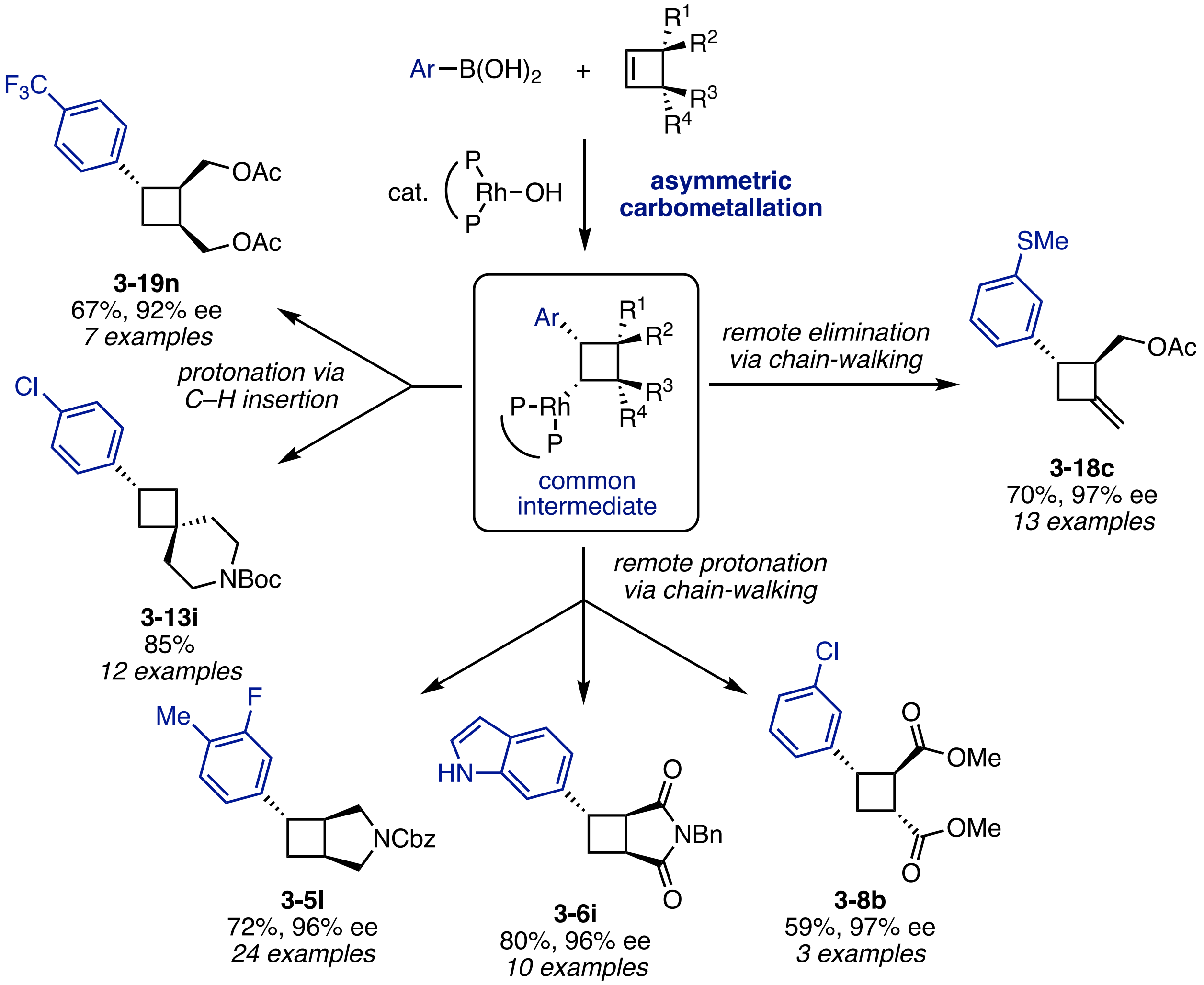


Figure 3-33: Overview of Rh-catalysed cyclobutene functionalisation reactions that can be triggered by asymmetric carbometallation.

3.3. Future Work

Having shown that the asymmetric carbometallation of cyclobutenes with boronic acids is feasible, we are aiming to expand on this work in several directions and apply related strategies to the synthesis of small stained, cyclic molecules. Here, we focus on the development of new Rh-catalysed transformations. Other Rh-catalysed cyclobutene functionalisation reactions – beyond the carbometallation approach presented in **Chapter 3** – are possible. They are presented and discussed in **Chapter 4**.

The carbometallation of cyclobutenes offers exciting opportunities to address synthetic problems which would be hard to solve with other methods. In this context, the conjugate addition of arylboronic acids to cyclobutenone would result in the formation of achiral 3-aryl cyclobutanones (Figure 3-34a). As Rh-catalysed arylation reactions with boronic acids generally proceed in the presence of water, which hydrolysed the Rh-oxa-π-allyl intermediate, trapping reactions for the synthesis of α,β-bisfunctionalised carbonyl compounds are challenging to implement.[224] Further, cyclobutenone is not bench-stable and can only be stored for short periods – even at –78 °C.[225] In order to avoid the use of unstable cyclobutanone, we propose that the asymmetric carbometallation of an α,β-unsaturated acetal would occur regioselectively (see **Chapter 3.2**) and would be followed by fast β-oxygen elimination to give chiral enol ethers (Figure 3-34b). The obtained enol ethers could be used for the subsequent α-functionalisation reactions with various electrophiles. A conceptually related cyclobutane bisfunctionalisation – in a system that avoids protonation of the metal intermediate – has been reported using 3-aryl cyclobutenones using copper catalysis.[191]

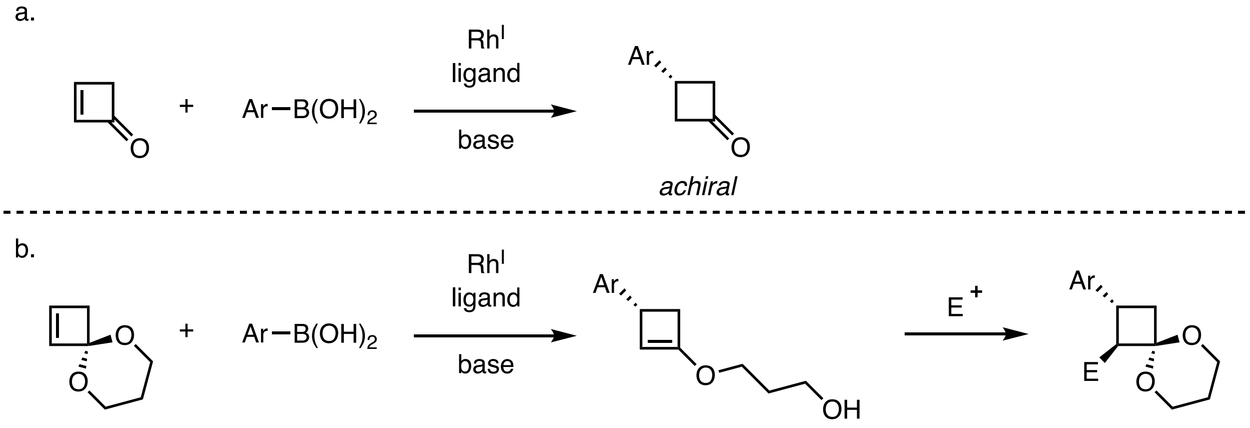


Figure 3-34: Rh-catalysed 1,4-addition to cyclobutanone (a) and asymmetric synthesis of α,β-bisfunctionalised cyclobutanones via a carborhodation approach (b).

Complex, polycyclic scaffold could be obtained via intramolecular trapping reactions of the Rh-cyclobutyl intermediate. One potential strategy is depicted in Figure 3-35 using 2-cyanophenylboronic acid. Unlike the hydroarylation reactions with spirocyclic cyclobutenes (see **Chapter 3.2**), the chirality of the cyclobutyl rhodium would not be lost in the protonation step but maintained in the tandem 1,2-addition step. Related strategies have been previously applied using alkynes and strained bicycles and Rh-catalysis.[226,227]

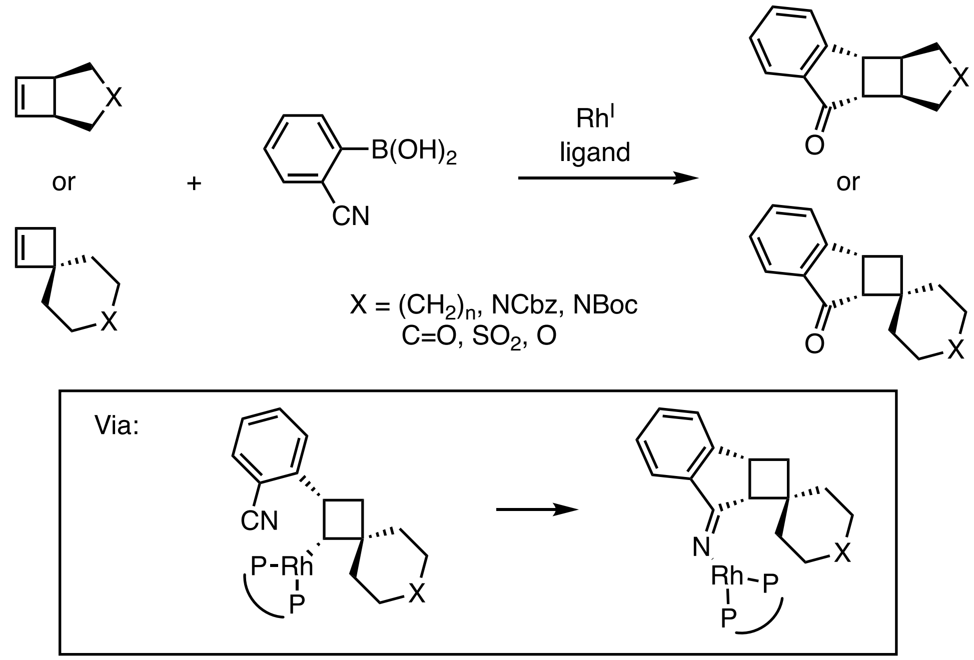


Figure 3-35: Intermolecular trapping of cyclobutyl rhodium intermediates with 2-functionalised arylboronic acids.

Currently, our method is limited to cyclobutenes with unsubstituted double-bonds. Extending the arylation protocol to 1-substituted cyclobut-1-enes[198] would represent a major challenge with two different regiochemical pathways.

Further, we are aiming to extend our methodology to other 4-membered ring scaffolds including 2-azetines[228] (Figure 3-36a) or 1,2-diazetines[229]. Azetidines can be found a numerous bioactive compounds,[230] including the FDA approved drugs Ezetimibe[231] and Siponimod[232] (Figure 3-36b). In the addition reaction with 2-azetines, either the achiral 3-substituted or the chiral 2-substituted azetidine could be formed (Figure 3-36a). The choice of the ligand and the *N*-protecting group could potentially favour both reaction outcomes.

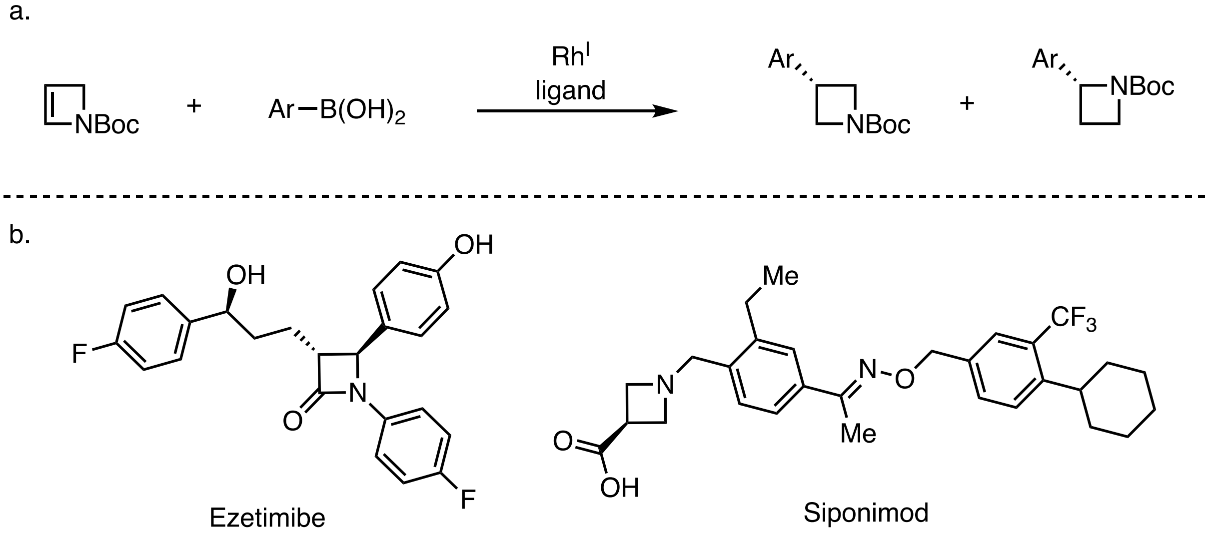


Figure 3-36: Regioselective (asymmetric) synthesis of aryl azetidines (a) and two examples of FDA approved drugs with an azetidine core (b).

We are also aiming to expand the carbometallation approach to other nucleophiles including alkenyl and alkynyl nucleophiles (Figure 3-37). Initial experiments for the alkenylation of cyclobutenes showed that good to very good enantioselectivity could be obtained with DTBM-Segphos as ligand and (*E*)-styryl and (*E*)-alkenyl boronic acids, albeit with only moderate conversion for latter. Asymmetric addition reactions of alkenyl boronic acids could be applied to the enantioselective synthesis of ladderane natural products (Figure 3-38).[233]

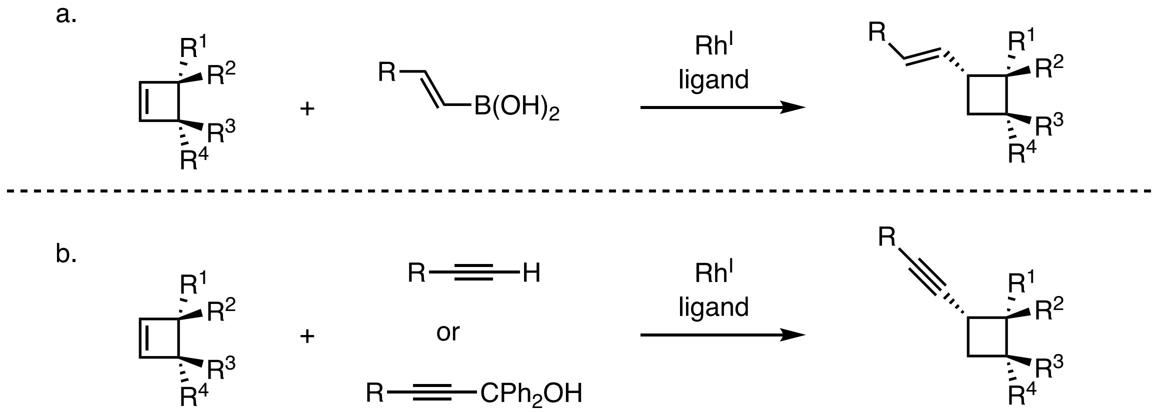


Figure 3-37: Rh-catalysed asymmetric alkenylation (a) and alkynylation of cyclobutenes.

Complementary to this, Rh-catalysed asymmetric alkynylation reactions could be developed (Figure 3-37b). Terminal alkynes are prone to undergo dimerisation under Rh-catalysis and therefore challenging substrates for Rh-catalysed 1,4-additions, but it has been previously shown that the use of bulky silyl groups on the alkyne and the choice for bulky phosphine ligand can suppress this undesired side-reaction.[234] Initial experiments using diphenyl[(triisopropylsilyl)ethynyl]methanol[235] as alkynylating agent show that the Rh-catalysed asymmetric alkynylation of cyclobutenes is possible, but so far limited to moderate levels of enantioselectivity.

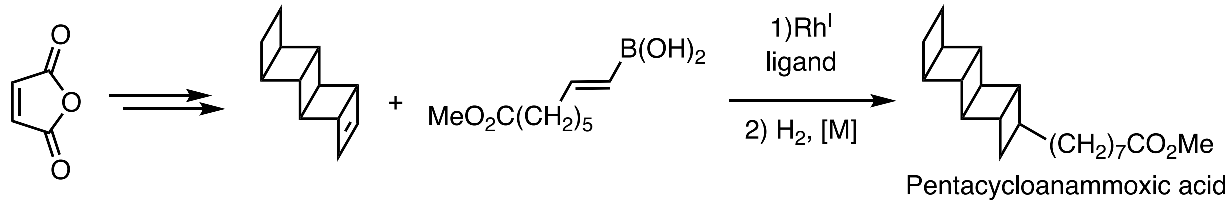


Figure 3-38: Asymmetric synthesis of a ladderane natural products.

Beyond the opportunities for the Rh-catalysed synthesis of small 4-membered rings, asymmetric carbometallation reactions of cyclobutenes are likely also possible with other metal catalysts and nucleophiles. These could include palladium[236], iridium[237,238], iron[239] or cobalt[240]. Developing and investigating these reactions could deliver selectivities different from those obtained with rhodium and could also help to uncover additional useful reactivity patterns.

Chapter 4: Catalytic Asymmetric Hydrometallation of Cyclobutenes

Dedicated to my two teammates Steffen and Jordan, and to Irene – I am really glad that we spent 2020/2021 together and grateful that our friendship brought so much fun into my last year at Oxford.

Chapter 4 of this thesis deals with the catalytic asymmetric hydrometallation of cyclobutenes. **Chapter 4.1** presents a Rh-catalysed hydrometallation of cyclobutenes with salicylaldehydes to give acyl cyclobutanes. These reactions serve as proof-of-concept that the addition of Rh-hydride, followed by reductive elimination is an effective and feasible strategy for the hydrofunctionalisation of cyclobutenes. In **Chapter 4.2**, future work on the hydrometallation of cyclobutenes is discussed.

4.1. Asymmetric Hydrometallation of Cyclobutenes with Salicylaldehydes

Chapter 4.1 is based on the following publication:

Goetzke, F. W.; Sidera, M.; Fletcher, S. P. Catalytic Asymmetric Hydrometallation of Cyclobutenes with Salicylaldehydes. *Manuscript submitted.*

I performed all experiments in **Chapter 4.1** and conceived the project. Further, I contributed to this chapter by writing the manuscript for publication with contributions from Mireia Sidera and Stephen P. Fletcher. Stephen P. Fletcher and Mireia Sidera guided the research. Experimental procedures and characterisation data for experiments in **Chapter 4.1** can be found in **Chapter 5.4**.

4.1.1. Introduction

Metal-catalysed hydroacylation of alkenes (and alkynes) represents one of the most powerful and atom economical methods for the synthesis of ketones (Figure 4-1a).[241] The hydroacylation reaction can be considered as the 'little brother' of the hydroformylation of alkenes with H_2 and CO for the synthesis of aldehydes (Figure 4-1b), which is among the most frequently applied reactions in the fine chemical industries.[242] Rhodium and cobalt catalyst are generally considered as the most active catalyst for hydroformylation and hydroacylation reactions, and have been applied in several industrial processes.[241–243] Both reactions are also mechanistically closely related and proceed via hydrometallation of the alkene, followed by carbon-carbon bond forming reductive elimination (for a typical mechanism of the hydroacylation see **Chapter 4.1.3**).

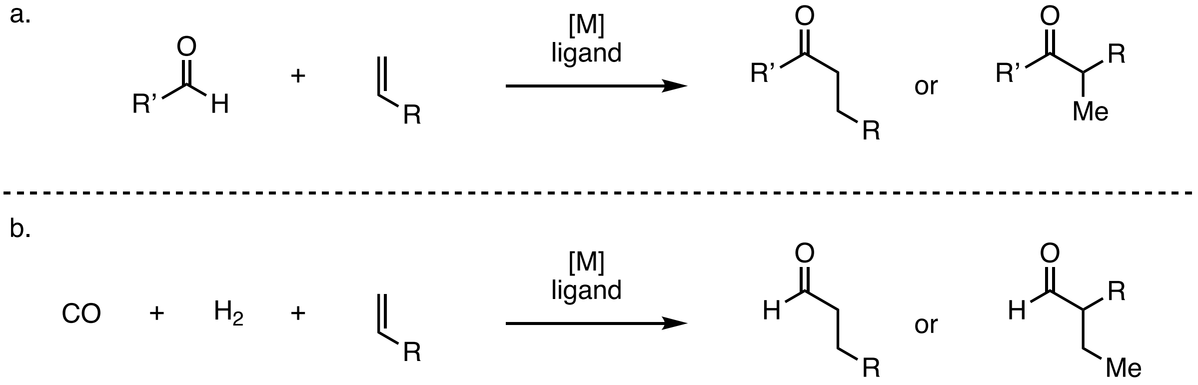


Figure 4-1: Metal-catalysed hydroacylation (a) and hydroformylation (b) of terminal alkenes.

The intramolecular Rh-catalysed hydroacylation is well established,[244–246] and asymmetric variants of this reaction have been reported for several ring-sizes.[247–252]

The intermolecular Rh-catalysed hydroacylation is often associated with fast and undesirable reductive decarbonylation side-reactions.[253] Many specific solutions for this problem have been developed using chelating groups on the aldehyde component including phosphines,[254] alcohols,[255] sulfides,[256] and amines.[257] The use of *ortho*-hydroxybenzaldehydes (salicylaldehydes) represents one of these strategies and several useful (asymmetric) reactions with terminal alkenes have been reported.[258–260]

Internal alkenes are significantly more challenging substrates for Rh-catalysed hydroacylation, but a few asymmetric hydroacylations of *Z*-alkenes, which operate via the release of ring strain are known.[251] Stemmler and Bolm developed enantio- and diastereoselective hydroacylation reactions of norbornadienes with salicylaldehydes (Figure 4-2a).[261] Despite extensive optimisation studies, only low to moderate enantioselectivities were obtained, and the stereoselectivity of this reaction was dependent on specific salicylaldehydes. Dong and co-workers reported the enantio- and diastereoselective desymmetrisation of different prochiral cyclopropenes with salicylaldehydes (Figure 4-2b).[262] Excellent stereoselectivities were obtained for a range of different cyclopropenes and salicylaldehydes using a Josiphos ligand.

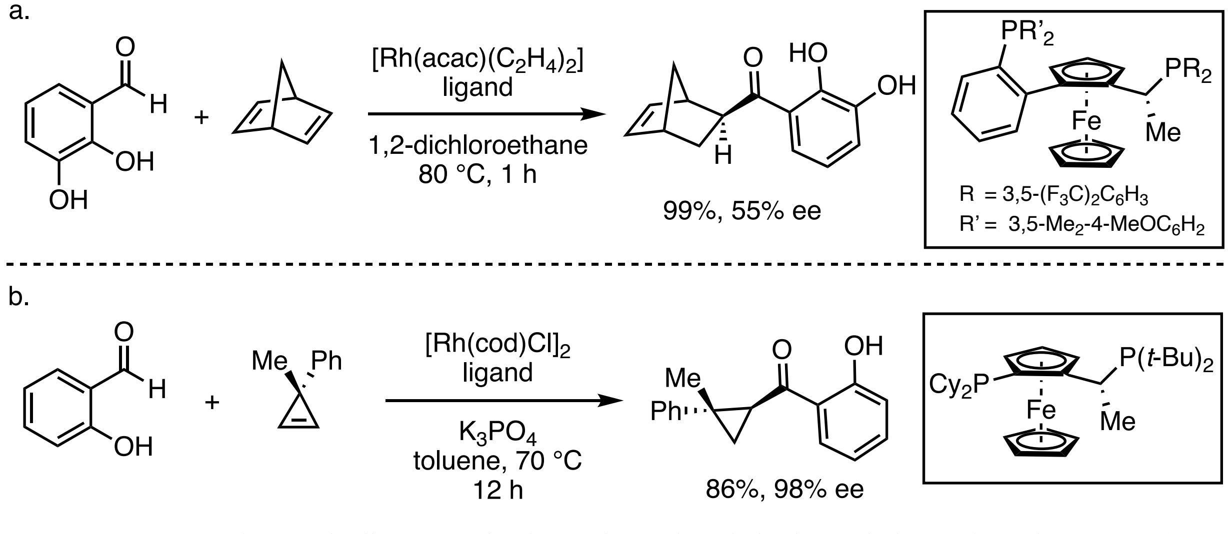


Figure 4-2: Enantio- and diastereoselective Rh-catalysed hydroacylation of norbornenes (a) and cyclopropenes (b) with salicylaldehydes.

As described in **Chapter 3**, cyclobutanes are useful reactive intermediates for organic synthesis,[173] and more recently, have been used as building blocks in medicinal chemistry with often beneficial properties.[174] Nevertheless, robust and efficient methods for their enantioselective synthesis are still scarce. An asymmetric hydroacylation reaction of cyclobutenes would add to the ‘tool-box’ of modular methods for the synthesis of densely functionalised, stereochemically complex cyclobutanes, and its development and scope is described in the next sections of **Chapter 4.1**.

4.1.2. Objective of the Project

In **Chapter 4.1**, we explore if mechanistically distinct asymmetric carbon-carbon forming reactions with cyclobutenes could be developed. The approach described in **Chapter 3.2** proceeds via an asymmetric carbometallation, followed by a remote protonation (Figure 4-3a). We hypothesised that a related asymmetric hydrometallation approach, followed by reductive elimination could serve as a viable strategy (Figure 4-3b).

An enantio- and diastereoselective rhodium-catalysed hydroacylation reaction with salicylaldehydes is investigated, which would allow for a modular access to valuable, chiral acyl cyclobutanes. Furthermore, this reaction would serve as a proof-of-concept that the addition of Rh-hydride to weakly activated cyclobutenes (1.9 kcal/mol) is feasible,[164] which could be extended to a range of asymmetric addition reactions to 4-membered rings.

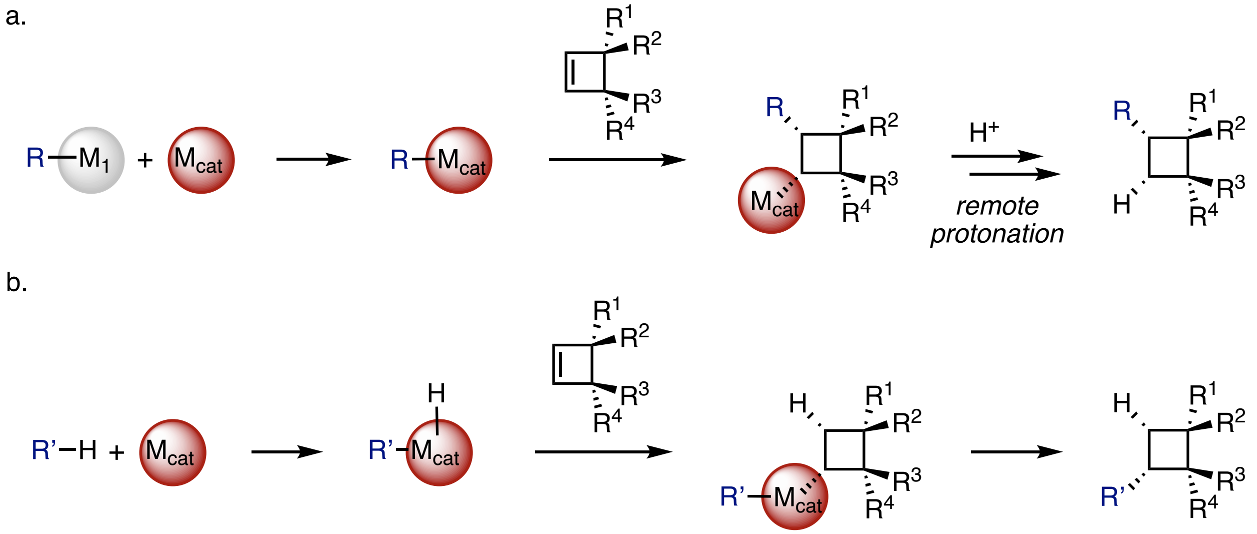


Figure 4-3: Asymmetric carbometallation followed by protonation (a) and hydrometallation followed by C–C formation (b) of cyclobutenes.

4.1.3. Results and Discussion

Optimisation of reaction conditions

Cyclobutenes were synthesised according to the methods presented in **Chapter 3.2**[223] and salicylaldehydes were purchased from commercial suppliers and used without further purification.

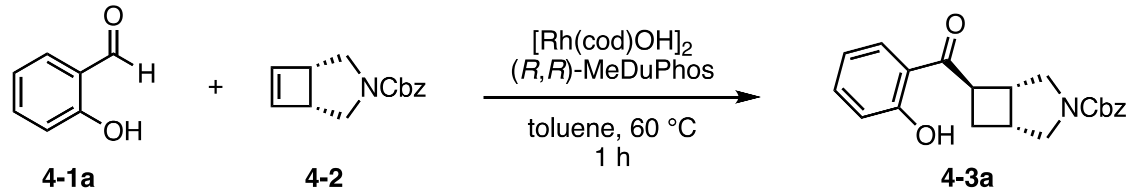
We chose the hydroacylation of **4-2** with salicylaldehyde (**4-1a**) as the model reaction. In these reactions, the hydroacylation occurred with high selectivity for the *cis-trans* diastereoisomer. A catalytic system generated *in situ* from $[Rh(cod)OH]_2$ and MeDuphos in toluene gave excellent levels of enantioselectivity and good yields of the major diastereoisomer (Table 4-1; entry 1). As the peaks in ^1H NMR spectra of **4-3a** are broad due to rotameric broadening, we approximated diastereomeric ratios via integration of the (non-calibrated) SFC chromatograms. A slight decrease in diastereomeric ratio was observed upon prolonged reaction times – possibly due to catalyst mediated epimerisation of the α-carbonyl stereogenic centre.

Experiments with a small set of different salicylaldehydes showed that a slight excess (1.5 equivalents) of the cyclobutene was beneficial in order to achieve high conversion for all salicylaldehydes under the optimised reaction parameters.[263] Under these conditions, salicylaldehyde **4-1a** was fully consumed, and decarbonylation of the aldehydes served as the major side-reaction (indicated by the disappearance of CHO peaks in the ^1H NMR).[253]

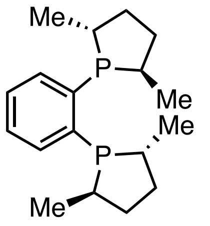
The reaction did not proceed in the absence of Rh (Table 4-1; entry 2) or the phosphine ligand (Table 4-1; entry 3). Other ligand scaffolds provided only poor to moderate levels of enantiocontrol (Table 4-1; entries 4-6). THF as solvent gave slightly lower diastereoselectivity and yield than toluene (Table 4-1; entry 7).

Using benzaldehyde instead of salicylaldehyde did not result in any hydroacylation of cyclobutene (Table 4-1; entry 8). This highlights the importance of chelating groups in order to avoid decarbonylation.[251]

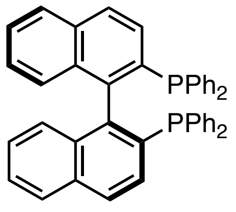
Table 4-1: Deviation from standard conditions for the hydroacylation of **4-2** with **4-1a**.



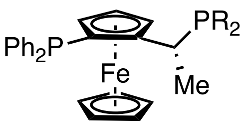
Entry	Deviation from standard conditions	Time	Yield [a]	Enantiomeric excess [b]	Diastereomeric ratio [c]
1	none [d]	1 h	81%	98%	9:1
2	no Rh	20 h	0%	-	-
3	no Ligand	20 h	≤1%	-	-
4	**L4-2** instead of **L4-1**	20 h	86%	32%	>20:1
5	**L4-2** instead of **L4-1**	2 h	86%	-74%	>20:1
6	**L4-3** instead of **L4-1**	20 h	31%	-12%	>20:1
7	THF instead of PhMe	1 h	72%	98%	7:1
8	PhCHO instead of **4-1a**	20 h	0%	-	-



L4-1
(*R*,*R*)-MeDuphos



L4-2
(*S*)-BINAP



L4-3 (R = Cy)
L4-4 (R = *t*-Bu)

Conditions: **4-1a** (0.4 mmol), **4-2** (0.6 mmol), [Rh(cod)OH]$_2$ (2.5 mol%), (*R,R*)-MeDuphos (6 mol%), toluene (0.2 M), 60 °C, 1–20 h.

[a] Isolated yields of the *cis-trans* diastereoisomer (>20:1 dr).

[b] Enantiomeric ratios were determined by SFC using a chiral non-racemic stationary phase.

[c] The dr values were estimated by non-calibrated SFC analysis of the unpurified reaction mixture.

[d] Performed on 0.4 mmol scale.

Asymmetric hydroacylation with different salicylaldehydes

Having an optimised set of reaction conditions in hand, we investigated different substituted salicylaldehydes as substrates for the hydroacylation of cyclobutene **4-2** (Figure 4-4). The reaction tolerates 3, 4, 5, and 6-substituted salicylaldehydes, different halides and electron-donating and withdrawing functional groups. In all cases excellent levels of enantioselectivity were achieved and the major *cis-trans* diastereomer was isolated in pure form.

In case of electron-withdrawing functional groups, we observed incomplete conversion under our standard conditions (**4-3c**, **4-3d**, **4-3g-h**) – likely due to increased catalyst deactivation via the decarbonylation pathway (see Figure 4-8). Here, full conversion and better yields could be achieved by doubling the catalyst loading. Remarkably, our reaction shows high chemoselectivity for the hydroacylation of the cyclobutene over a terminal olefin (**4-3b**).[260]

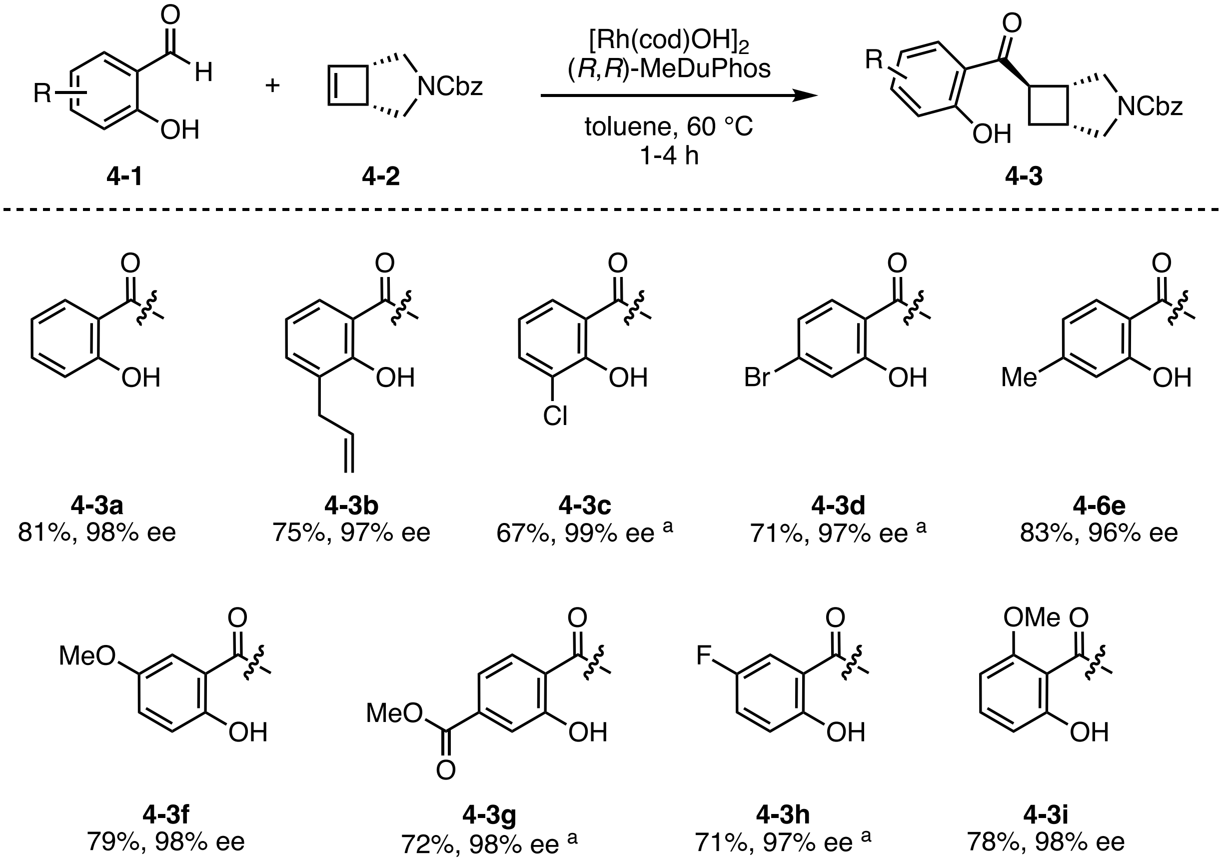
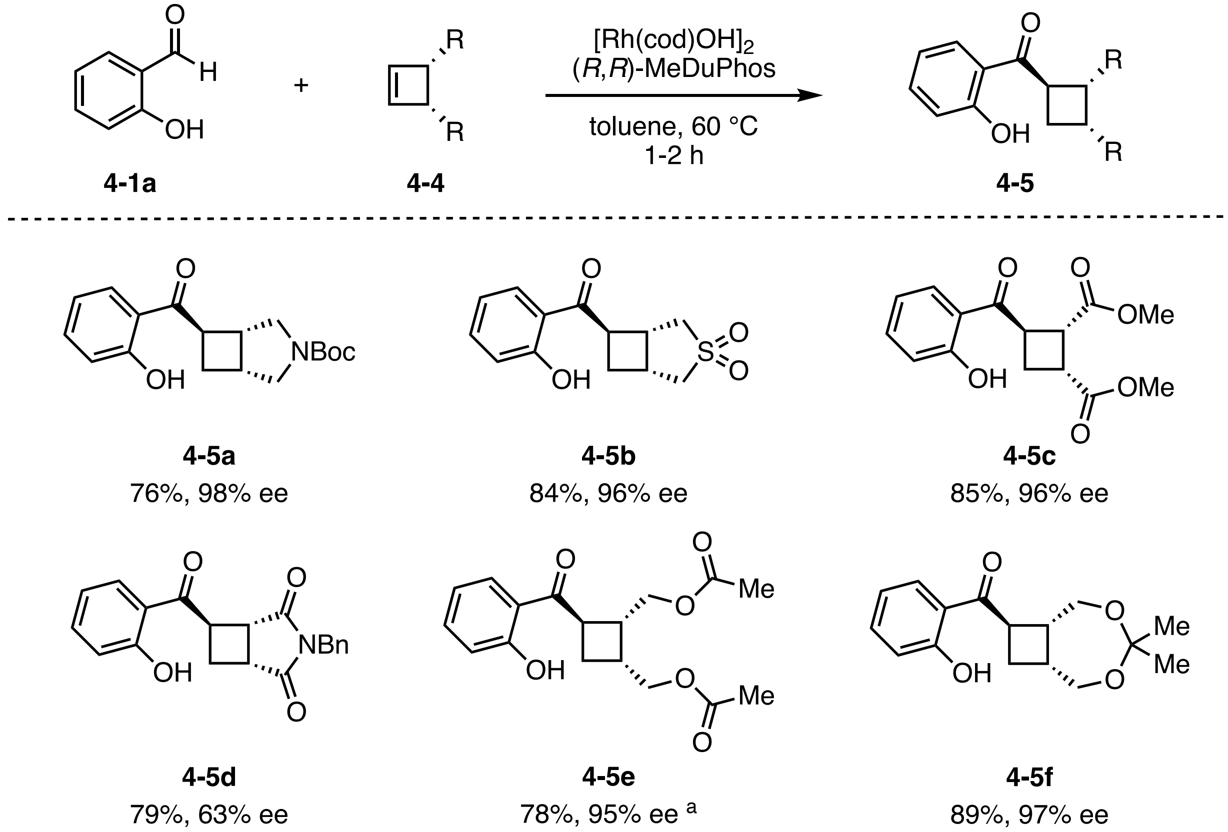


Figure 4-4: Enantio- and diastereoselective Rh-catalysed hydroacylation of a bicyclic cyclobutene with different salicylaldehydes.

Conditions: **4-1** (0.4 mmol), **4-2** (0.6 mmol), [Rh(cod)OH]$_2$ (2.5 mol%), (*R,R*)-MeDuphos (6 mol%), toluene (0.2 M), 60 °C, 1–4 h. [a] Increased catalyst loading of [Rh(cod)OH]$_2$ (5 mol%) and (*R,R*)-MeDuphos (12 mol%).

Asymmetric hydroacylation with different *meso*-cyclobutenes

A range of different *meso*-cyclobutenes underwent highly enantioselective hydroacylation reactions with salicylaldehyde (**4-1a**), and good yields and good to excellent diastereoselectivity were obtained throughout (for details see **Chapter 5.4**) (Figure 4-5). Low enantioselectivity was only observed for acyl cyclobutane **4-5d**, but we cannot rationalise this behaviour. While *cis*-cyclobut-3-ene-1,2-diyl)bis(methylene) diacetate (**4-4e**) underwent homo-allylic substitution reactions instead of reductive Heck reactions with arylboronic acids (see **Chapter 3-2**), here, we see exclusively hydroacylation to give **4-5e**.[223] Instead of the *trans-trans* reductive Heck product with arylboronic acids, the hydroacylation of *cis*-diester **4-4c** resulted in the *cis-trans* product **4-5c** (see **Chapter 3.2**).[223]



4-5a 76%, 98% ee

4-5b 84%, 96% ee

4-5c 85%, 96% ee

4-5d 79%, 63% ee

4-5e 78%, 95% ee [a]

4-5f 89%, 97% ee

Figure 4-5: Enantio- and diastereoselective Rh-catalysed hydroacylation of *meso*-cyclobutenes with salicylaldehyde.

Conditions: **4-1a** (0.4 mmol), **4-4** (0.6 mmol), [Rh(cod)OH]$_2$ (2.5 mol%), (*R,R*)-MeDuphos (6 mol%), toluene (0.2 M), 60 °C, 1–2 h. [a] Increased catalyst loading of [Rh(cod)OH]$_2$ (5 mol%) and (*R,R*)-MeDuphos (12 mol%).

These two reactions highlight the mechanistic difference between a carbometallation/protonation and hydrometallation/reductive elimination sequence, which can result in distinct overall reaction outcomes.

Regioselective hydroacylation with a spirocyclic cyclobutene

The hydroacylation of **4-6** gave the achiral acyl cyclobutane **4-7** under similar conditions that were used for *meso*-cyclobutenes **4-2** and **4-4**, where achiral 1,1'-bis(diphenylphosphino)-ferrocene (dppf) was used instead of chiral MeDuphos as the ligand.[215] The regioselectivity is set in the initial hydrometallation step and likely proceeds under steric control. Even though different catalytic steps control the regioselectivity of addition, overall the regiochemical outcome of this hydroacylation and the arylation using aryboronic acids (see **Chapter 3.2**) is the same with this substrate.

Further, good yields were obtained with a small set of functionalised salicylaldehydes with different substitution pattern (Figure 4-6). Electron-deficient 2-fluorosalicylaldehyde required an increased catalyst loading in order to achieve full conversion and to obtain **4-7** in 58% yield.

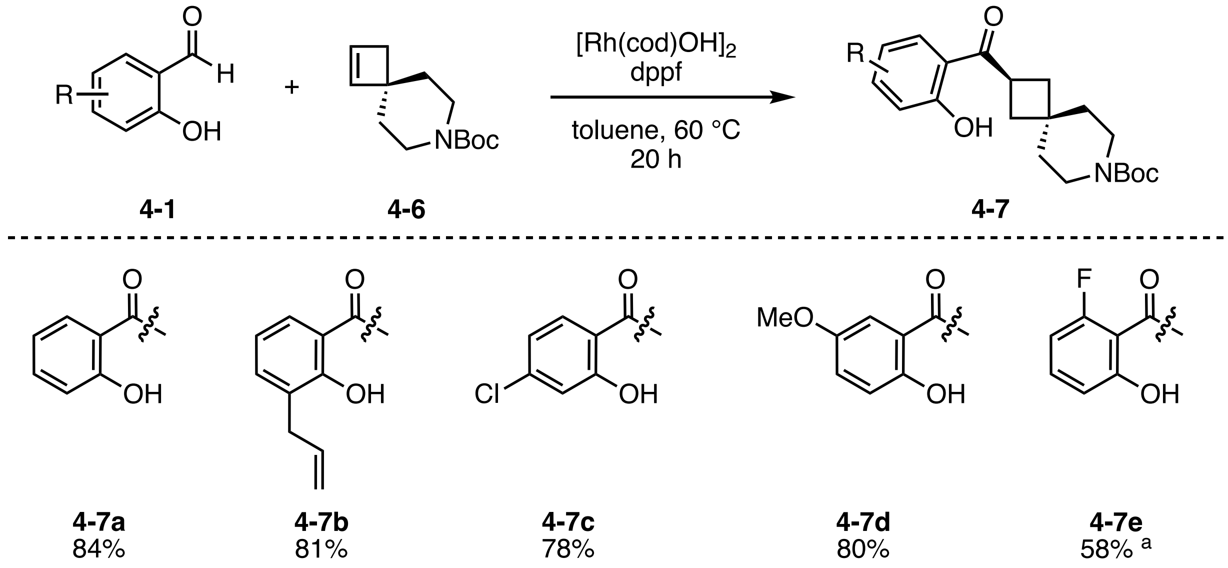


Figure 4-6: Regioselective hydroacylation of a spirocyclic cyclobutene with different salicylaldehydes.

Conditions: **4-1** (0.4 mmol), **4-5** (0.6 mmol), $[Rh(cod)OH]_2$ (2.5 mol%), dppf (6 mol%), toluene (0.2 M), 60 °C, 20 h. [a] Increased catalyst loading of $[Rh(cod)OH]_2$ (5 mol%) and dppf (12 mol%).

Upscale and derivatisation of the hydroacylation products

The hydroacylation of **4-2** with **4-1a** (Figure 4-7a) was scaled up to 4.0 mmol to give >1 g of highly enantioenriched **4-3a** (98% ee). Upon upscale, the excess of cyclobutene was lowered from 1.5 to 1.2 equivalents, which can be recovered (0.17 of 0.2 equivalents) after automated medium-pressure liquid chromatography.

In order to demonstrate the synthetic utility of the 2-hydroxybenzoyl core, we modified both the 2-hydroxyphenyl moiety (Figure 4-7b) and the benzoyl group (Figure 4-7c). The hydroxy group of **4-3a** was converted to the corresponding triflate **4-8a** with *N*-2-pyridylbis(trifluoromethanesulfonimide) and catalytic 4-dimethylaminopyridine (DMAP). Then, **4-8a** could be used for subsequent cross-coupling reactions – for example a Suzuki–Miyaura coupling to give **4-8b**.

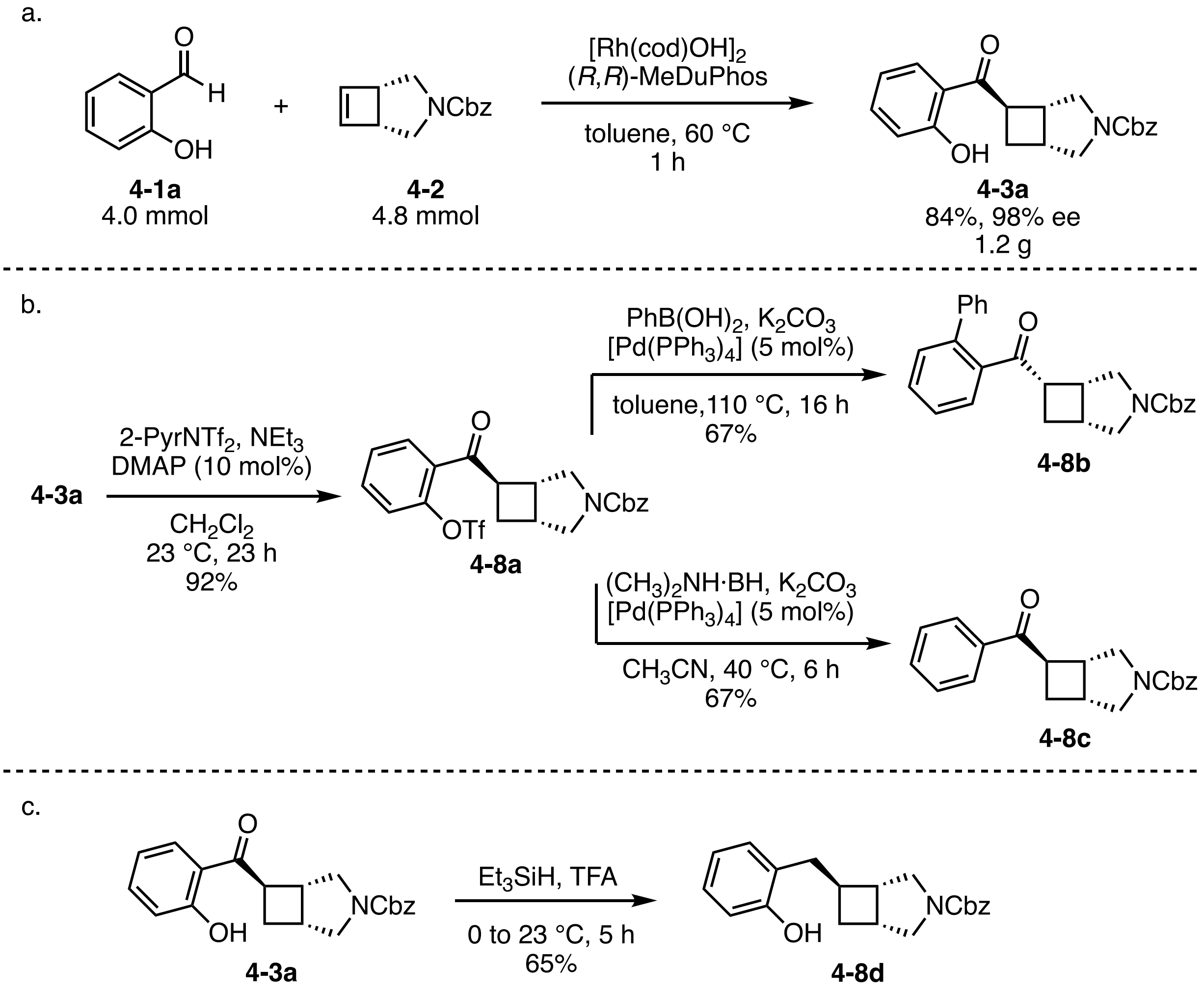


Figure 4-7: Up-scale to gram-scale (a), functionalisation of the phenol moiety (b) and functionalisation of the benzoyl group (c).

Alternatively, the triflate was cleaved using dimethylamine borane complex and catalytic $[Pd(PPh_3)_4]$ to give **4-8c**. The benzoyl group can also be reduced using triethylsilane in trifluoroacetic acid to give access to benzyl cyclobutanes (**4-8d**).

Proposed reaction mechanism

A plausible reaction mechanism is depicted in Figure 4-8. Oxidative addition of salicylaldehyde to rhodium complex **4-I** gives the chelated acyl rhodium hydride complex **4-II**. $[Rh(cod)OH]_2$ is an active pre-catalyst for this transformation and likely serves as catalytic internal base.[264] Coordination of the cyclobutene (**4-III**), followed by migratory insertion sets the absolute and relative stereochemistry in **4-IV**. Reductive elimination liberates the product. Catalyst deactivation and decomposition of the starting material could occur via a reductive decarbonylation (**4-II** to **4-V** to **4-VI**) to give phenol (**4-9**) or related decarbonylation products (**4-9'**).[253,263]

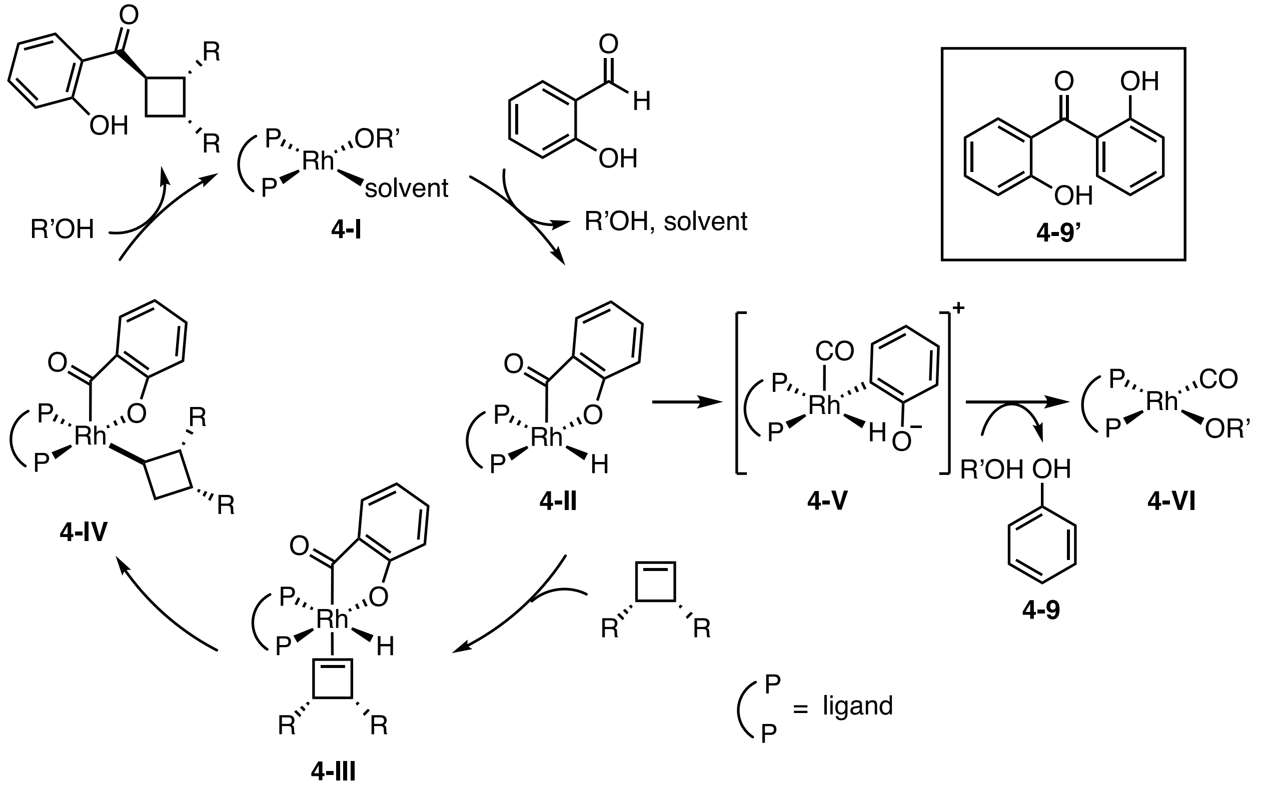


Figure 4-8: Plausible mechanism for the Rh-catalysed hydroacylation with salicylaldehydes.

4.1.4. Conclusion

In summary, we have developed a modular hydroacylation reaction with cyclobutenes and salicylaldehydes. The requirement for this reaction is the presence of a 2-hydroxy substituent on the benzaldehyde. *Meso*-cyclobutenes undergo highly enantioselective hydroacylation reactions, which proceed with good levels of diastereocontrol and give stereochemically complex acyl cyclobutanes in good yields. A prochiral, spirocyclic cyclobutene undergoes regioselective hydroacylation reactions to give achiral acyl cyclobutanes.

This reaction shows that the addition of Rh-hydride to weakly activated cyclobutenes occurs despite little release of olefinic strain. Likely, other Rh-catalysed hydrofunctionalisation reactions with cyclobutenes are possible and will be investigated in the future.

4.2. Future Work

In **Chapter 4.1**, we present the first asymmetric hydroacylation reaction of cyclobutenes with salicylaldehydes. The scope of this reaction could be extended in the several different directions. Cyclobutenes with different substitution patterns could be used as substrates. e.g. Racemic *trans*-disubstituted cyclobutenes could be resolved with a chiral catalyst, or enantioenriched *trans*-disubstituted cyclobutenes, for which some enantioselective preparations are known,[265] could be used in stereospecific acylation reactions (Figure 4-9a). Furthermore, other 4-membered rings beyond cyclobutenes like 2-azetine could be investigated (Figure 4-9b).[266]

All the examples in **Chapter 4.1** use a phenolic group in order to minimise decarbonylation and catalyst deactivation. Alternative chelating groups including phosphines, sulfides or amines, that are known to promote hydroacylation using rhodium catalysis, are likely also suitable acyl donors for the acylation of cyclobutenes.[251] Ultimately, hydroacylation reactions of cyclobutenes that do not require chelating groups and would thus be applicable to aliphatic aldehydes would be highly desirable. Potential solutions to this problem could be provided by other metal catalyst including cobalt, ruthenium and iridium, and other acyl donors beyond aldehydes.[267]

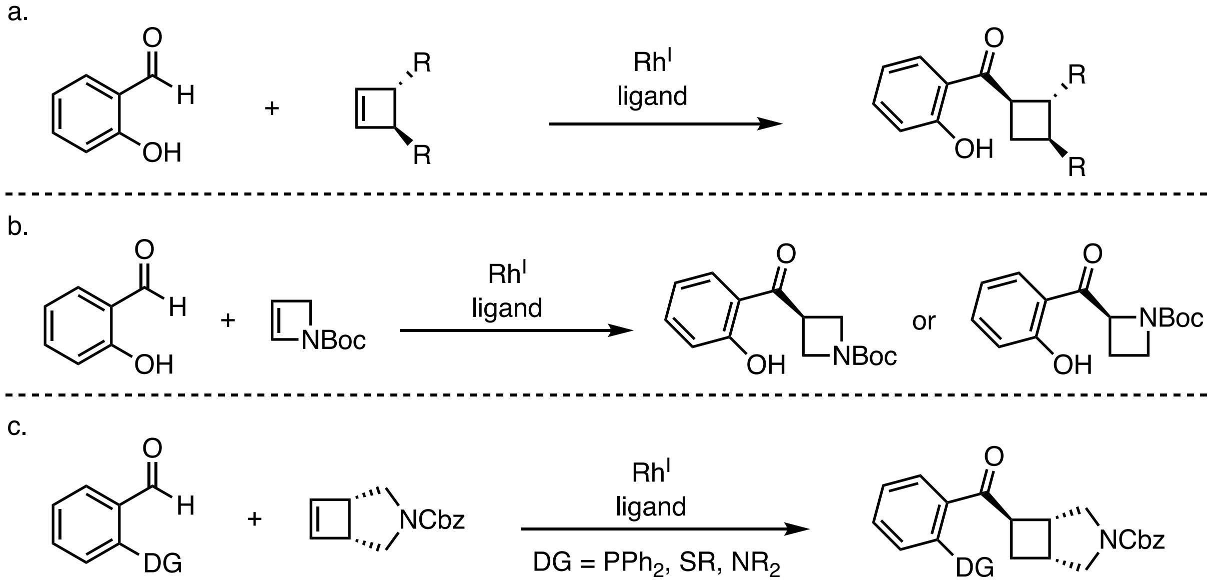


Figure 4-9: Expansion of Rh-catalysed hydroacylation to stereospecific hydroacylations (a), hydroacylations of 2-azetine and other chelating groups (c).

The hydroacylation reactions described in **Chapter 4.1** proceed under strong substrate control resulting in the formation of the *cis-trans* isomer as the major product. Methods that give access to the other diastereoisomers would be desirable. We propose that deprotonation, followed by kinetic protonation from the less hindered side would give the kinetic product *cis-cis* product (Figure 4-10).[268] Subsequent reduction would also give access to *cis-cis* benzyl cyclobutanes.

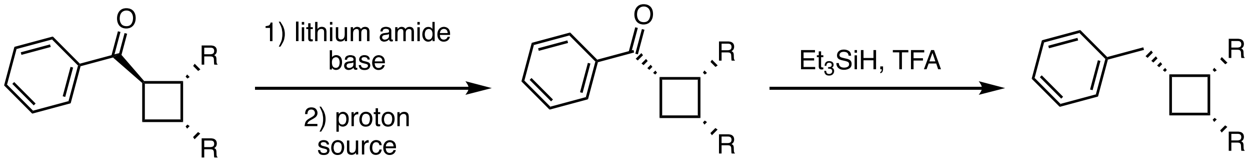


Figure 4-10: Synthesis of *cis*-*cis* acyl and benzyl cyclobutanes via kinetic protonation.

The Rh-catalysed hydroacylation in **Chapter 4.1** serves as a proof-of-concept that the addition of rhodium-hydride to cyclobutenes, followed by reductive elimination is possible. We propose that the reductive elimination could also occur with other heteroatom nucleophiles (Figure 4-11a). In this context, rhodium-catalysed asymmetric hydrofunctionalisation reactions with cyclopropenes and/or strained bicyclic species have been reported with thiols,[269] diselenides,[270] stannanes,[271] silanes[272] and boranes[273] have been reported. Related reaction conditions could serve as a starting point for developing new Rh-catalysed hydrofunctionalisations of cyclobutenes (Figure 4-11b).

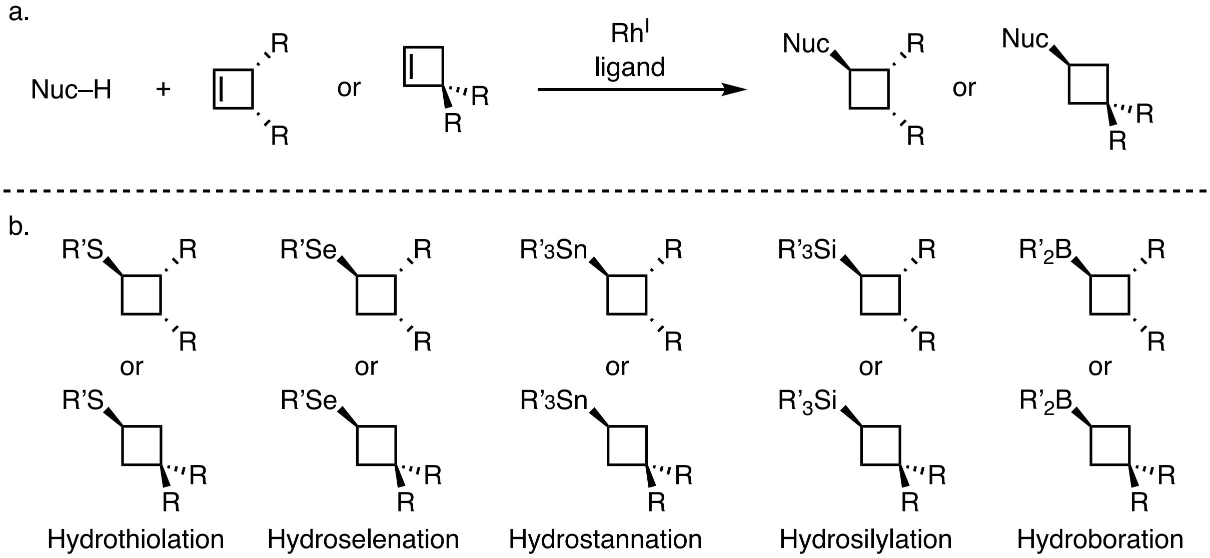


Figure 4-11: Rh-catalysed hydrofunctionalisation reactions with cyclobutenes based on asymmetric or regioselective hydrometallation.

Chapter 5: Experimental Procedures

5.1. General Methods

All reactions were carried out in anhydrous solvents with continuous magnetic stirring under an inert argon atmosphere. Heating was performed using DrySyn heating blocks.

Nuclear magnetic resonance (NMR) spectroscopy measurements were carried out at room temperature. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, COSY, HSQC, HMBC and NOESY experiments were carried out using Bruker AVIII HD 400 (400/101 MHz) or AVIII HD 500 (500/126 MHz) spectrometers. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak with corresponding coupling constants (*J*) in Hertz (Hz) and multiplicities (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet and combinations of these and app.: apparent multiplicities). Assignment follows HSQC, COSY, HMBC or/and NOESY spectra, chemical shift and coupling constant analysis.

Optical rotations ($[\alpha]_{25}^{D}$) were recorded using a Perkin Elmer-241 Polarimeter. Concentrations (*c*) are reported in g/100 mL.

Infrared (IR, neat or thin film): spectroscopy was carried out on a Bruker Tensor 27 FT–IR spectrometer with an internal calibration range of 4000–600 cm^{-1}. The samples are reported as absorption maxima in cm^{-1} with corresponding relative intensities described as br (broad), s (strong), m (medium), and w (weak).

Chiral SFC (supercritical fluid chromatography) separations were conducted on a Waters Acquity UPC2 system using Waters Empower software. Chiralpak® columns (150x3 mm, particle size 3 μm) were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Aldrich or Rathburn).

Chiral GC measurements were conducted on an Agilent 7820A GC (He as a vector gas) with the stated column in the characterization. Temperature programs are described as follows: initial temperature (°C) – initial time (min) – temperature gradient (°C/min) – final temperature (°C) – holding time (min). Flow rate is given in mL/min and retention times (t_R) are given in min.

High Resolution Mass spectra were carried out by internal service at the University of Oxford. (1) Electron spray ionisation (ESI^+) was recorded on a Fisons Platform II. (2) Electron ionisation (EI)/Chemical ionisation (CI): Analyses were performed on an Agilent 7200 quadrupole time of flight (Q-ToF) instrument equipped with a direct insertion probe supplied by Scientific instrument Manufacturer (SIM) GmbH. (3) Atmospheric pressure chemical ionisation ($APCI^+$): Analyses were performed using a Thermo Exactive mass spectrometer equipped with Waters Acquity liquid chromatography system.

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.*

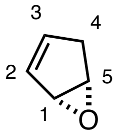
Commercially available reagents and ligands were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics, Fluorochem and Strem Chemicals and unless otherwise stated were used without further purification. $[Rh(cod)OH]_2$ was bought from Sigma Aldrich or Strem Chemicals. Dry solvents were collected fresh from an mBraun SPS–800 solvent purification system after having passed through anhydrous alumina columns and were degassed with argon prior to usage. Deuterated solvents were purchased from Sigma Aldrich.

Medium-pressure chromatography was performed on a CombiFlash Next Gen 100 system.

5.2. Procedures for Chapter 2

5.2.1. Synthesis of the Starting Materials

(±)-2-2[274]

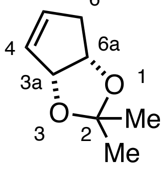


Similar to a procedure by Jung *et. al.* [274], Na_2CO_3 (99.4 g, 0.94 mol) and NaOAc (1.90 g, 23.2 mmol) were added to a solution of freshly cracked cyclopentadiene (**2-1**) (30 mL, 424 mmol) in CH_2Cl_2 (470 mL). Peracetic acid (40 wt% in acetic acid; 64 mL, 380 mmol) was added dropwise over 1 h at 0 °C under an open atmosphere. The reaction mixture was then allowed to reach 23 °C and stirring was continued for additional 3 h. The mixture was then filtered under reduced pressure, the residue was rinsed with CH_2Cl_2 and the filtrate was carefully concentrated under reduced pressure at 15 °C (the product is volatile). Vacuum distillation (25mbar, up to 80 °C) afforded the product (±)-**2-2** as a colourless oil containing CH_2Cl_2 (estimated yield: 16.9 g, 58%). The spectroscopic data are in agreement with the literature.[274]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.14 (dtd, *J* = 5.6, 2.2, 1.1 Hz, 1H, C(2)–H), 5.98 (dp, *J* = 6.3, 2.1 Hz, 1H, C(3)–H), 3.91 (ddd, *J* = 3.5, 2.9, 2.1 Hz, 1H, C(5)–H), 3.81 (dtd, *J* = 3.0, 1.9, 1.1 Hz, 1H, C(1)–H), 2.63 (dq, *J* = 19.1, 2.2 Hz, 1H, 1x C(4)–H_2), 2.39 (ddt, *J* = 19.1, 3.5, 2.1 Hz, 1H, 1x C(4)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 138.0 (C(3)), 131.4 (C(2)), 59.3 (C(1)), 57.0 (C(5)), 35.7 (C(4)).

(±)-2-3[125]

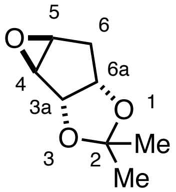


According to procedure by Trost *et. al.*[125], $BF_3·Et_2O$ (1.2 mL, 9.7 mmol) was added dropwise to a solution of 6-oxabicyclo[3.1.0]hex-2-ene ((±)-**2-2**) (8.00 g, 97.4 mmol) in dry acetone (60 mL) at 0 °C under an argon atmosphere. The reaction mixture was allowed to reach 23 °C and stirred for 6 h. The reaction mixture was concentrated under reduced pressure, dissolved in Et_2O (100 mL), washed with an aq. sat. solution of $NaHCO_3$ (2x 30 mL) and with an aq. sat. solution of NH_4Cl (2x 30 mL) and dried over Na_2SO_4. Purification by flash chromatography (pentane/Et_2O = 100/0 to 90/10) afforded the product (±)-**2-3** as a colourless volatile oil (7.55 g, 55% yield). The spectroscopic data are in agreement with the literature.[125]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.85 – 5.81 (m, 1H, C(5)–H), 5.78 (dq, *J* = 5.9, 1.9 Hz, 1H, C(4)–H), 5.11 (d, *J* = 5.9 Hz, 1H, C(3a)–H), 4.76 (t, *J* = 5.7 Hz, 1H, C(6a)–H), 2.57 – 2.53 (m, 2H, C(6)–H_2), 1.41 (s, 3H, CH_3), 1.35 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 132.5 (C(5)), 130.9 (C(4)), 109.9 (C(2)), 85.6 (C(3a)), 77.9 (C(6a)), 39.0 (C(6)), 27.6 (CH_3), 25.8 (CH_3).

(±)-2-4[125]

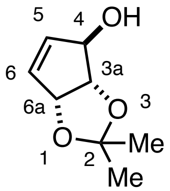


According to procedure by Trost *et. al.*[125], $NaHCO_3$ (1.89 g, 22.5 mmol), Na_2CO_3 (7.16 g, 67.5 mmol) and urea hydrogen peroxide (UHP) (10.6 g, 113 mmol) were added to a solution of (±)-**2-3** (3.15 g, 22.5 mmol) in CH_2Cl_2 (225 mL) under an argon atmosphere. A solution of trifluoroacetic anhydride (7.8 mL, 56.3 mmol) in CH_2Cl_2 (105 mL) was added dropwise at 0 °C. The mixture was stirred for 3 h, washed with an aq. sat. solution of $NaHCO_3$ (3x 50 mL) and dried over Na_2SO_4. Purification by flash chromatography (pentane/Et_2O = 90/10 to 70/30) afforded the product (±)-**2-4** as a colourless volatile oil (1.94 g, 55% yield) as single diastereomer (dr >20:1). The spectroscopic data are in agreement with the literature.[125]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.57 (d, *J* = 5.5 Hz, 1H, C(3a)–H), 4.53 (ddt, *J* = 6.4, 4.6, 1.0 Hz, 1H, C(6a)–H), 3.68 – 3.47 (m, 2H, C(4)–H, C(5)–H), 2.28 (dd, *J* = 15.4, 6.0 Hz, 1H, C(6)–*H_2*), 1.95 (dt, *J* = 15.3, 2.0 Hz, 1H, C(6)–*H_2*), 1.46 (s, 3H, CH_3), 1.31 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 111.95 (C(2)), 81.5 (C(6a)), 80.1 (C(3a)), 59.1, 58.9 (C(4), C(5)), 35.7 (C(6)), 27.3 (CH_3), 24.8 (CH_3).

(±)-**2-5**[125]

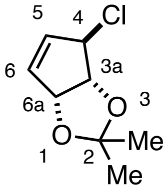


According to procedure by Trost *et. al.*[125], *n*–butyl lithium (2.5 M in hexane; 9.8 mL, 25 mmol was added slowly to a solution of diethylamine (2.6 mL, 26 mmol) in Et_2O (14 mL) at 0 °C under an argon atmosphere. After 30 min, a solution of (±)-**2-4** (1.90 g, 12.4 mmol) in Et_2O (14 mL) was added and the mixture was slowly allowed to reach 23 °C. After 2 h, additional Et_2O (30 mL) was added. The organic layer was washed with an aq. sat. solution of NH_4Cl (3x 15 mL) and dried over $MgSO_4$. Purification by flash chromatography (hexane/EtOAc = 70/30 to 50/50) afforded the product (±)-**2-5** as a colourless oil (1.26 g, 66 % yield) as single diastereomer (dr >20:1). The spectroscopic data are in agreement with the literature.[125]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.03 (dt, *J* = 5.8, 1.4 Hz, 1H, C(6)–H), 5.90 (ddd, *J* = 5.8, 2.2, 1.1 Hz, 1H, C(5)–H), 5.28 (dd, *J* = 5.6, 1.0 Hz, 1H, C(6a)–H), 4.79 (d, *J* = 5.1 Hz, 1H, C(4)–H), 4.52 (dd, *J* = 5.6, 0.8 Hz, 1H, C(3a)–H), 1.91 (d, *J* = 6.0 Hz, 1H, OH), 1.40 (s, 3H, CH_3), 1.35 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 135.8 (C(6)), 134.8 (C(5)), 111.9 (C(2)), 86.1 (C(3a)), 84.4 (C(6a)), 81.2 (C(4)), 27.5 (CH_3), 25.9 (CH_3).

(±)-**2-6a**



Triphenylphosphane (5.77 g, 22.1 mmol) followed by *N*-chlorosuccinimide (NCS) (3.18 g, 23.6 mmol) was added to a solution of (±)-**2-5** (2.30 g, 14.7 mmol) in THF (23 mL) at 0 °C under an argon atmosphere. After 1 h, the mixture was allowed to reach 23 °C and was stirred for additional 4 h. Et_2O (50 mL) was added and the mixture was filtered over Celite®. Purification by flash chromatography (hexane/CH_2Cl_2 = 90/10 to 0/100) afforded the product (±)-**2-6a** as a colourless volatile oil (1.85 g, 72% yield) as single diastereomer (dr >20:1).

Determination of the relative stereochemistry:

- Strong NOE of C(2)–CH_3 with C(4)–H (weaker NOE of C(2)–CH_3 with C(3a)–H and C(6a)–H) and NOE of C(2)–CH_3' with C(3a)–H and C(6a)–H indicate *trans* stereochemistry between C(3a)–H and C(4)–H.
- The dihedral angle between C(3a)–H and C(4)–H is close to 90°, therefore a small *J*-coupling is expected. The dihedral angle between C(3a)–H and C(6a)–H is close to zero, therefore a larger *J*-coupling is expected. The observed *J*-coupling between C(3a)–H and C(6a)–H is 5.5 Hz. C(4)–H (app. t, *J* = 1.4 Hz) has a significantly smaller *J*-coupling to C(3a)–H, therefore also supporting the *trans* stereochemistry between C(3a)–H and C(4)–H.

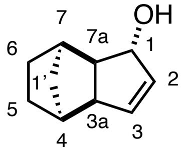
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.05 – 5.99 (m, 1H, C(6)–H), 5.92 (m, 1H, C(5)–H), 5.34 (dd, *J* = 5.5, 1.3 Hz, 1H, C(6a)–H), 4.82 (app. t, *J* = 1.4 Hz, 1H, C(4)–H), 4.80 (d, *J* = 5.5 Hz, 1H, C(3a)–H), 1.40 (s, 3H, CH_3), 1.36 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 135.7 (C(6)), 133.6 (C(5)), 112.3 (C(2)), 86.1 (C(3a)), 84.4 (C(6a)), 65.1 (C(4)), 27.6 (CH_3), 26.3 (CH_3).

IR (neat): 2983 (m), 2939 (w), 1374 (w), 1257 (m), 1207 (s), 1158 (m), 1079 (s), 1052 (s), 1004 (w), 869 (s), 771 (s), 718 (w) cm^{-1}.

HRMS (GC-MS EI): m/z calcd for $C_5H_6{}^{37}ClO^+$ $[M - (CH_3)_2CO + H]^+$ 117.0102 found 117.0098.

(±)-**2-10**[275]

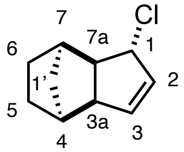


A flask equipped with a reflux condenser was charged with *endo*-5,6-dihydrodicyclopentadiene ((±)-**2-9**) (6.00 g, 44.8 mmol), selenium dioxide (9.90 g, 89.6 mmol), Na_2HPO_4 (6.44 g, 44.8 mmol), quartz sand (1.6 g) and dry dioxane (80 mL). The mixture was heated to reflux for 5 h under an argon atmosphere and then filtered over silica and rinsed with EtOAc. The filtrate was concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc = 90:10 to 70:30) afforded the product (±)-**2-10** as a yellow oil (4.76 g, 71% yield) as single diastereomer (dr >20:1). The spectroscopic data are broadly consistent with the literature.[275]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.91 (ddt, *J* = 5.6, 2.0, 0.9 Hz, 1H, C(3)–H), 5.80 (dt, *J* = 5.6, 2.1 Hz, 1H, C(2)–H), 4.67 (s, 1H, C(1)–H), 3.13 (ddp, *J* = 9.2, 4.2, 2.1 Hz, 1H, C(3a)–H), 2.52 – 2.35 (m, 1H, C(7)–H), 2.35 – 2.29 (m, 1H, C(4)–H), 2.25 (ddt, *J* = 8.6, 4.7, 1.7 Hz, 1H, C(7a)–H), 1.52 (dp, *J* = 9.4, 1.9 Hz, 1H, 1x C(1')–H_2), 1.46 (dt, *J* = 9.4, 1.7 Hz, 1H, 1x C(1')–H_2), 1.37 (s, 1H, OH), 1.33 – 1.03 (m, 4H, C(5)–H_2, C(6)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 139.4 (C(3)), 133.2 (C(2)), 77.8 (C(1)), 54.5 (C(7a)), 52.1 (C(3a)), 41.6 (C(1')), 39.8 (C(7)), 39.2 (C(4)), 24.9, 23.4 (C(5), C(6)).

(±)-2-6b[276]



Thionyl chloride (2.0 mL, 28 mmol) was added to solution of (±)-**2-10** (2.23 g, 15.0 mmol) in Et$_2$O (30 mL) 0 °C under an argon atmosphere. After stirring the mixture for 1 h, pyridine (4.1 mL) was added and stirring was continued for 1 h. Then Et$_2$O (30 mL) was added, the organic layer was washed with H$_2$O (2x 20 mL) and brine (20 mL), and dried over MgSO$_4$. The mixture was concentrated under reduced pressure at 40 °C. Vacuum distillation (approx. 1 mbar, up to 80 °C) afforded the product (±)-**2-6b** as a colourless oil (1.84 g, 73% yield) with a dr 20:1. The spectroscopic data are in agreement with the literature.[276]

Determination of the relative stereochemistry:

- Strong NOE of C(1)–H with C(5)–H$_2$/C(6)–H$_2$.

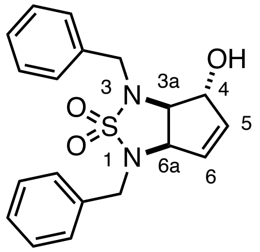
^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 5.93 (ddt, J = 5.6, 2.0, 0.9 Hz, 1H, C(3)–H), 5.80 (dt, J = 5.6, 2.1 Hz, 1H, C(2)–H), 4.93 (dq, J = 2.7, 1.4 Hz, 1H, C(1)–H), 3.23 (dddt, J = 6.8, 5.2, 3.8, 1.9 Hz, 1H, C(3a)–H), 2.74 (ddt, J = 9.1, 4.8, 1.7 Hz, 1H, C(7a)–H), 2.42 (t, J = 4.6 Hz, 1H, C(7)–H), 2.36 – 2.35 (m, 1H, C(4)–H), 1.53 (dt, J = 9.6, 1.9 Hz, 1H, 1x C(1')–H_2), 1.47 (dt, J = 9.6, 1.7 Hz, 1H, 1x C(1')–H_2), 1.37 – 1.02 (m, 4H, C(5)–H$_2$, C(6)–H$_2$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 139.7 (C(3)), 132.1 (C(2)), 66.2 (C(1)), 55.2 (C(7a)), 52.2 (C(3a)), 41.4 (C(1')), 40.0 (C(7)), 39.4 (C(4)), 25.1, 22.8 (C(5), C(6)).

IR (neat): 2952 (s), 2874 (m), 1472 (w), 1453 (w), 1386 (w), 1355 (w), 1126 (w), 1036 (w), 952 (w), 839 (m), 812 (m), 792 (m), 766 (s), 748 (m), 684 (w), 658 (w) cm^{-1}.

HRMS (GC-MS EI): m/z calcd for $C_{10}H_{13}{}^{37}Cl^+$ 168.0706 [M]$^+$ found 168.0698.

(±)-2-12



(±)-**2-11** was prepared according to a literature procedure by McDonald *et al.*[132]. A flask equipped with a reflux condenser was charged with selenium dioxide (4.62 g, 41.7 mmol), Na_2HPO_4 (3.00 g, 20.9 mmol), quartz sand (700 mg), dry dioxane (40 mL) and (±)-**2-11** (7.10 g, 20.9 mmol). The stirred mixture was heated to reflux for 15 h under an argon atmosphere, before being allowed to cool to room temperature and then filtered over Celite®. The filtrate was concentrated under reduced pressure and then diluted with EtOAc (100 mL). The organic layer was washed with an aq. sat. solution of NH_4Cl (3x 30 mL), an aq. sat. solution of $NaHCO_3$ (3x 30 mL) and dried over $MgSO_4$. Purification by flash chromatography (hexane/EtOAc = 80/20 to 50/50) afforded the product (±)-**2-12** as a highly viscous orange oil that solidified upon standing (4.66 g, 63% yield) as single diastereomer (dr >20:1).

Determination of the relative stereochemistry:

- The dihedral angle between C(3a)–H and C(4)–H is close to 90°, therefore a small *J*-coupling is expected. The dihedral angle between C(3a)–H and C(6a)–H is close to zero, therefore a larger *J*-coupling is expected. The observed *J*-coupling between C(3a)–H and C(6a)–H is 7.9 Hz. C(3a)–H has a significantly smaller *J*-coupling to C(4)–H, therefore also supporting the *trans* stereochemistry between C(3a)–H and C(4)–H.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.52 – 7.30 (m, 10H, 10x C_{Ar}–H), 5.75 (dt, *J* = 5.9, 1.6 Hz, 1H, C(5)–H), 5.32 (dt, *J* = 5.9, 1.7 Hz, 1H, C(6)–H), 4.61 (d, *J* = 13.8 Hz, 1H, 1x PhCH_2), 4.58 (dd, *J* = 5.0, 3.1 Hz, 1H, C(4)–H), 4.46 (d, *J* = 14.0 Hz, 1H, 1x PhCH_2), 4.34 (dq, *J* = 7.8, 1.8 Hz, 1H, C(6a)–H), 4.15 (d, *J* = 13.8 Hz, 1H, 1x PhCH_2), 4.10 (d, *J* = 14.0 Hz, 1H, 1x PhCH_2), 3.57 (dd, *J* = 7.9, 2.2 Hz, 1H, C(3a)–H), 1.17 (d, *J* = 5.7 Hz, 1H, OH).

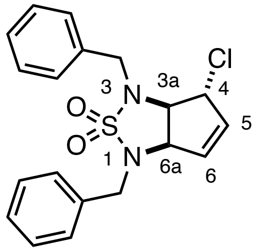
^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 136.7 (C(5)), 135.3 , 135.1 (2x C_{quart}), 131.5 (C(6)), 129.6, 129.10, 129.09, 128.9, 128.8, 128.4 (10x C_{Ar}–H), 81.1 (C(4)), 67.0 (C(3a)), 65.2 (C(6a)), 50.6, 50.5 (2x $PhCH_2$).

IR ($CHCl_3$ film): 3486 (br. w), 3031 (w), 2917 (s), 1495 (w), 1453 (w), 1296 (m), 1209 (w), 1152 (s), 1095 (m), 1032 (m), 965 (w), 873 (w), 811 (w), 747 (s), 698 (s) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{19}H_{20}O_3N_2NaS^+$ $[M + Na]^+$ 379.10868 found 379.10846.

m.p.: 70 – 72 °C.

(±)-2-6c



Triphenylphosphane (3.96 g, 15.1 mmol) and then *N*-chlorosuccinimide (2.02 g, 15.1 mmol) were added to solution of (±)-**2-12** (4.50 g, 12.6 mmol) in THF (20 mL) at 0 °C under an argon atmosphere®. Purification by flash chromatography (hexane/CH_2Cl_2 = 50/50 to 30/70) followed by a second purification by flash chromatography (hexane/EtOAc = 90/10 to 80/20) afforded the product (±)-**2-6c** as a colourless solid (3.55 g, 75% yield) as single diastereomer (dr >20:1).

Determination of the relative stereochemistry:

- Strong NOE of C(4)–H with PhC*H*$_2$ and C(5)–H_2 and a weaker NOE of C(4)–H with C(3a)–H do not allow for an unambiguous assignment, however are in agreement with *trans* stereochemistry between C(3a)–H and C(4)–H.
- The dihedral angle between C(3a)–H and C(4)–H is close to 90°, therefore a small *J*-coupling is expected. The dihedral angle between C(3a)–H and C(6a)–H is close to zero,

therefore a larger *J*-coupling is expected. The observed *J*-coupling between C(3a)–H and C(6a)–H is 7.4 Hz. C(4)–H (dt, *J* = 3.1, 1.6 Hz) has a significantly smaller *J*-coupling to C(3a)–H, therefore indicating the *trans* stereochemistry between C(3a)–H and C(4)–H.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.51 – 7.44 (m, 2H, 2x C_{Ar}–H), 7.43 – 7.32 (m, 8H, 8x C_{Ar}–H), 6.02 – 5.76 (m, 1H, C(5)–H), 5.53 (ddd, *J* = 5.8, 1.9, 1.2 Hz, 1H, C(6)–H), 4.68 (dt, *J* = 3.1, 1.6 Hz, 1H, C(4)–H), 4.53 (d, *J* = 14.4 Hz, 1H, 1x PhC*H*$_2$), 4.42 (d, *J* = 13.9 Hz, 1H, 1x PhC*H*$_2$), 4.41 (dq, *J* = 7.1, 1.8 Hz, 1H, C(6a)–H) 4.29 (d, *J* = 14.4 Hz, 1H, 1x PhC*H*$_2$), 4.18 (d, *J* = 13.9 Hz, 1H, 1x PhC*H*$_2$), 4.01 (dd, *J* = 7.7, 1.8 Hz, 1H, C(3a)–H).

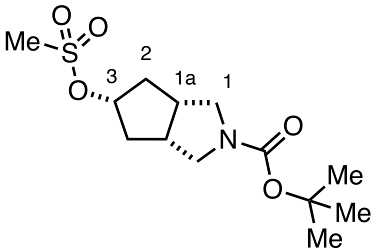
^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 135.0 (C(5)), 134.7, 134.6 (2x C_{quart}), 131.9 (C(6)), 129.4, 129.1, 129.03, 128.98, 128.63, 128.58 (10x C_{Ar}–H), 67.1 (C(3a)), 64.7 (C(6a)), 64.3 (C(1)), 50.8 , 50.5 (2x $PhCH_2$).

IR ($CHCl_3$ film): 3032 (w), 1496 (w), 1454 (w), 1310 (m), 1208 (w), 1160 (s), 1093 (m), 1066 (m), 1029 (w), 964 (w), 814 (m), 745 (s), 699 (s) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{19}H_{19}O_2N_2{}^{37}ClNaS^+$ $[M + Na]^+$ 397.07480 found 397.07472.

m.p.: 106 – 107 °C.

2-14



Sodium borohydride (832 mg, 22.0 mmol) was added into a stirred and cooled (0 °C, ice bath) solution of *cis*-*tert*-butyl 5-oxohexahydrocyclopenta[c]pyrrole-2(1*H*)-carboxylate (**2-13**) (4.50 g, 20.0 mmol) in MeOH (135 mL) under an open atmosphere. After stirring the reaction mixture for 2 h, a sat. aq. solution of NH_4Cl (1 mL) was added dropwise, and the mixture was concentrated under reduced pressure. H_2O (50 mL) was added, and the mixture was extracted with EtOAc (3x 100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and directly used in the next step without any further purification.

The crude product was dissolved in CH_2Cl_2 (50 mL) under an argon atmosphere and triethylamine (5.5 mL, 40 mmol) was added. Mesityl chloride (2.3 mL, 30 mmol) was added dropwise at 0 °C. After stirring the reaction mixture for 2 h at 23 °C, H_2O (50 mL) and EtOAc (200 mL) were added. The organic layer was separated, and the aq. layer was extracted with EtOAc (2x 100 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. Purification by flash chromatography (hexane/EtOAc = 70/30 to 30/70) afforded the product **2-14** as a pale-yellow solid (5.54 g, 91% yield) with dr of 14:1.

^{1}H NMR ($CDCl_3$, 400 MHz; major diastereomer): δ (ppm) 5.08 (tt, J = 6.8, 5.6 Hz, 1H, C(3)–H), 3.55 (br. s, 2H, 2x C(1)–H_2), 3.36 (s, 2H, 2x C(1)–H_2), 2.98 (s, 3H, SCH_3), 2.68 (br s, 2H, 2x C(1a)–H), 2.30 (ddd, J = 14.7, 8.3, 6.7 Hz 2H, 2x C(2)–H_2), 1.83 (dt, J = 14.4, 5.5 Hz, 2H, 2x C(2)–H_2), 1.43 (s, 9H, $C(CH_3)_3$)

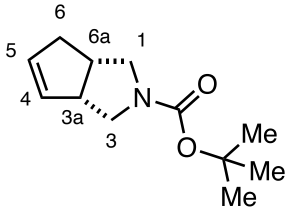
^{13}C NMR ($CDCl_3$, 101 MHz; major diastereomer): δ (ppm) 154.5 (C=O), 83.0 (C(3)), 79.4 ($C(CH_3)_3$), 51.8, 51.6 (rot.; 2x C(1)), 41.2, 40.3 (rot.; 2x C(1a)), 38.6 (SCH_3), 38.5 (2x C(2)), 28.6 (3x $C(CH_3)_3$).

IR ($CHCl_3$ film): 2974 (w), 1685 (m), 1480 (w), 1402 (m), 1351 (m), 1248 (w), 1168 (s), 1123 (m), 969 (m), 880 (m), 773 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{13}H_{23}O_5NNaS^+$ $[M + Na]^+$ 328.11891 found 328.11885.

m.p.: 52 – 53 °C.

(±)-2-15



1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) (8.0 mL, 54 mmol) was added to a stirred solution of **2-14 (**5.40 g, 17.7 mmol) in toluene (40 mL) under an argon atmosphere. The mixture was heated to reflux for 3 h, and then cooled and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc = 80/20 to 70/30) afforded the product (±)-**2-15** as a colourless oil (1.85 g, 50% yield).

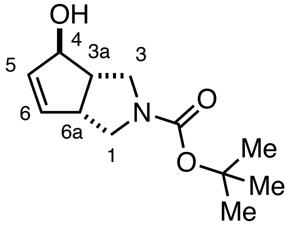
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.68 – 5.64 (m, 1H, C(5)–H), 5.58 (br. s, 1H, C(4)–H), 3.61 (br. s, 1H, 1x C(3)–H_2), 3.47 (br. s, 1H, 1x C(1)–H_2), 3.41 – 3.27 (m, 2H, C(3a)–H, 1x C(1)–H_2), 2.95 (br. s, 1H, 1x C(3)–H_2), 2.84 (app. t p, J = 7.4 Hz, 1H, C(6a)–H), 2.48 (ddq, J = 16.6, 7.3, 2.5 Hz, 1H, 1x C(6)–H_2), 2.13 (br. d, J = 16.1 Hz, 1H, 1x C(6)–H_2), 1.37 (s, 9H, 3x CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 154.5 (C=O), 133.6, 133.2 (rot.; 2x C(4)), 130.5, 130.2 (rot.; 2x C(5)), 79.1 ($C(CH_3)_3$), 52.8, 52.5 (rot.; 2x C(3)), 50.6, 50.3 (rot.; 2x C(1)), 50.2, 49.3 (rot.; 2x C(3a)), 40.6, 39.7 (rot.; 2x C(6a)), 38.4 (C(6)), 28.6 (3x CH_3).

IR ($CHCl_3$ film): 2974 (w), 1693 (s), 1478 (w), 1397 (s), 1365 (m), 1338 (w), 1249 (w), 1167 (m), 1109 (m), 881 (w), 772 (w), 684 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{12}H_{19}O_2NNa^+$ $[M + Na]^+$ 232.13080 found 232.13087.

(±)-2-16



A flask equipped with a reflux condenser was charged with selenium dioxide (1.62 g, 16.2 mmol), Na_2HPO_4 (1.05 g, 8.12 mmol), quartz sand (300 mg), dry dioxane (20 mL) and (±)-**2-15** (1.70 g, 8.12 mmol). The mixture was heated to reflux for 2 h under an argon atmosphere, before being allowed to cool to room temperature and then filtered over Celite®. The filtrate was concentrated under reduced pressure and then diluted with EtOAc (100 mL). The organic layer was washed with an aq. sat. solution of NH_4Cl (2x 30 mL), an aq. sat. solution of $NaHCO_3$ (2x 30 mL) and dried over $MgSO_4$. Purification by flash chromatography (hexane/EtOAc = 50/50 to 30/70) afforded the product (±)-**2-16** as a yellow oil (883 mg, 48% yield) as single diastereomer (dr >20:1).

Determination of the relative stereochemistry:

- Strong NOE of C(4)–H with C(3)–H_2 indicates *trans* stereochemistry between C(3a)–H and C(4)–H.

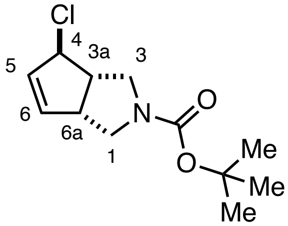
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.89 (br. d, *J* = 4.6 Hz, 1H, C(5)–H), 5.83 (dt, *J* = 5.1, 2.1 Hz, 1H, C(6)–H), 4.59 (s, 1H, C(4)–H), 3.57 (t, *J* = 9.7 Hz, 1H, 1x C(3)–H_2), 3.52 – 3.47 (br. m, 1H, C(6a)–H), 3.41 (d, *J* = 8.6 Hz, 2H, 2x C(1)–H_2), 3.18 (br. s, 1H, 1x C(3)–H_2), 2.72 (dd, *J* = 8.4, 6.5 Hz, 1H, C(3a)–H), 1.87 (br. s, 1H, OH), 1.43 (s, 9H, 3x CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 154.7 (C=O), 138.7 (C(5)), 133.0 (C(6)), 82.6 (C(4)), 79.5 (*C*(CH_3)$_3$), 50.9 (rot.; C(3a)), 49.7 (rot.; C(1), C(3)), 48.6, 47.8 (rot.; 2x C(6a)), 28.6 (3x CH_3).

IR ($CHCl_3$ film): 3395 (br. s), 2975 (w), 2878 (w), 1670 (s), 1479 (w), 1409 (s), 1365 (m), 1251 (w), 1168 (s), 1117 (m), 1062 (w), 1031 (w), 928 (w), 878 (w), 771 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{12}H_{19}O_3NNa^+$ $[M + Na]^+$ 248.12571 found 248.12576.

(±)-2-6d



Thionyl chloride (430 µL, 6.1 mmol) was added to solution of (±)-**2-16** (855 mg, 3.79 mmol) in Et_2O (7.0 mL) 0 °C under an argon atmosphere. After stirring the mixture for 1 h, pyridine (910 µL) was added and stirring was continued for 1 h. Then Et_2O (50 mL) was added, the organic layer was washed with H_2O (2x 10 mL) and brine (10 mL), and dried over $MgSO_4$. Purification by flash chromatography (hexane/EtOAc = 70/30) afforded the product (±)-**2-6d** as a colourless solid (743 mg, 80% yield) as single diastereomer (dr >20:1).

Determination of the relative stereochemistry:

- NOE of C(4)–H with C(3a)–H and C(3)–H_2 indicates *trans* stereochemistry between C(3a)–H and C(4)–H.
- *J* coupling analysis was due to rotameric broadening of the peaks difficult.
- High temperature (363 K) NMR in $C_6D_5CD_3$ allowed for *J* coupling analysis. The dihedral angle between C(3a)–H and C(4)–H is close to 90°, therefore a small *J*-coupling is expected. The dihedral angle between C(3a)–H and C(6a)–H is close to zero, therefore a larger *J*-coupling is expected. The observed *J*-coupling between C(3a)–H and C(6a)–H is 6.0 Hz. C(3a)–H has a significantly smaller *J*-coupling to C(4)–H (not resolved), therefore also supporting the *trans* stereochemistry between C(3a)–H and C(4)–H.

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 5.90 (br. d, *J* = 5.6 Hz, 1H, C(6)–H), 5.86 (dt, *J* = 5.3, 2.3 Hz, 1H, C(5)–H), 4.76 (s, 1H, C(4)–H), 3.64 – 3.56 (m, 2H, 1x C(3)–H_2, C(6a)–H), 3.51 – 3.40 (m, 2H, 2x C–H_2), 3.15 – 3.07 (m, 2H, 1x C(3)–H_2, (3a)–H), 1.43 (s, 9H, 3x CH_3).

^{1}H NMR ($C_6D_5CD_3$, 500 MHz; 363 K): 5.46 (dt, *J* = 4.8, 2.2 Hz, 1H, C(5)–H), 5.36 (dd, *J* = 5.6, 2.0 Hz, 1H, C(6)–H), 4.32 (s, 1H, C(4)–H), 3.29 (dd, *J* = 11.6, 9.4 Hz, 1H, 1x C(3)–H_2), 3.26 – 3.20 (m, 1H, 1x C(1)–H_2), 3.09 (dd, *J* = 10.9, 7.8 Hz, 1H, 1x C(1)–H_2), 3.05 – 3.01 (m, 1H, C(6a)–H), 2.96 (dd, J = 11.6, 5.8 Hz, 1H, 1x C(3)–H_2), 2.69 (dt, J = 9.4, 6.0 Hz, 1H, C(3a)–H), 1.42 (s, 9H, 3x CH_3).

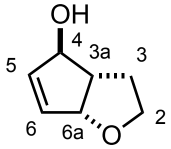
^{13}C NMR ($CDCl_3$, 126 MHz): δ (ppm) 154.4 (C=O), 139.1, 138.9 (2x rot.; C(6)), 132.1, 131.8 (2x rot.; C(5)), 79.7 (*C*(CH_3)$_3$), 68.3 (C(4)), 51.9, 50.9 (2x rot.; C(3a)), 50.1, 49.9 (2x rot.; CH_2), 49.4, 49.0 (2x rot.; CH_2), 48.9, 48.1 (2x rot.; C(6a)), 28.6 (3x CH_3).

IR ($CHCl_3$ film): 2973 (w), 2987 (w), 1691 (s), 1471 (w), 1397 (s), 1240 (w), 1167 (m), 1115 (m), 876 (w), 767 (m), 693 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{12}H_{19}O_2NCl^+$ [M + H]$^+$ 244.10988 found 244.10981.

m.p.: 42 – 43 °C.

(±)-S2-1



(±)-**S2-1** was prepared according to a literature procedure by Rönn *et al.*.[277] A flask equipped with a reflux condenser was charged with selenium dioxide (4.33 g, 39.0 mmol), Na_2HPO_4 (2.77 g, 19.5 mmol), quartz sand (1.0 g), dry dioxane (40 mL) and (±)-*cis*-3,3a,4,6a-tetrahydro-2H-cyclopenta[*b*]furan (2.15 g, 19.5 mmol). The mixture was stirred for 2 h under reflux under an argon atmosphere and then filtered over Celite®. The filtrate was concentrated under reduced pressure and then diluted with EtOAc (100 mL). The organic layer was washed with an aq. sat. solution of NH_4Cl (2x 30 mL), an aq. sat. solution of $NaHCO_3$ (2x 30 mL), and dried over $MgSO_4$. Purification by flash chromatography (hexane/EtOAc = 50/50 to 0/100) afforded the product (±)-**S2-1** as a yellow oil (540 mg, 22% yield) as single diastereomer (dr >20:1).

Determination of the relative stereochemistry:

- The dihedral angle between C(3a)–H and C(4)–H is close to 90°, therefore a small *J*-coupling is expected. The dihedral angle between C(3a)–H and C(6a)–H is close to zero, therefore a larger *J*-coupling is expected. The observed *J*-coupling between C(3a)–H and C(6a)–H is 6.6 Hz. C(4)–H (s) has a significantly smaller *J*-coupling to C(3a)–H, therefore indicating the *trans* stereochemistry between C(3a)–H and C(4)–H.

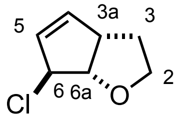
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.98 (ddd, *J* = 5.7, 2.3, 0.9 Hz, 1H, C(6)–H), 5.89 (ddd, *J* = 5.6, 2.0, 1.0 Hz, 1H, C(5)–H), 5.27 (dd, *J* = 6.6, 2.1 Hz, 1H, C(6a)–H), 4.61 (s, 1H, C(4)–H), 3.81 (ddd, *J* = 8.7, 7.3, 3.5 Hz, 1H, 1x C(2)–H_2), 3.50 (td, *J* = 9.0, 5.8 Hz, 1H, 1x C(2)–H_2), 2.66 (dddd, *J* = 9.8, 6.5, 3.3, 1.5 Hz, 1H, C(3a)–H), 2.05 (dtd, *J* = 12.5, 9.5, 7.3 Hz, 1H, 1x C(3)–H_2), 1.77 – 1.71 (m, 2H, OH, 1x C(3)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 136.8 (C(6)), 135.2 (C(5)), 87.6 (C(6a)), 83.5 (C(4)), 66.3 (C(2)), 50.7 (C(3a)), 32.0 (C(3)).

IR (neat): 3362 (br. w), 2944 (w), 2866 (w), 1448 (w), 1357 (m), 1256 (w), 1110 (w), 1057 (s), 1034 (s), 991 (s), 911 (s), 851 (w), 805 (w), 771 (m), 722 (w), 611 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_7H_{10}O_2^+$ $[M]^+$ 126.0675 found 126.0671.

(±)-2-6e



Thionyl chloride (540 µL, 7.4 mmol) was added to solution of (±)-**S2-1** (500 mg, 3.96 mmol) in Et_2O (8.0 mL) 0 °C under an argon atmosphere. After stirring the mixture for 1 h, pyridine (1.0 mL) was added and stirring was continued for 1 h. Then Et_2O (50 mL) was added, the organic layer was washed with H_2O (10 mL) and brine (10 mL), and dried over $MgSO_4$. Purification by flash chromatography (pentane/Et_2O = 90/10 to 80/20) afforded the product (±)-**2-**

6e as a volatile colourless oil (306 mg, 53% yield) as single diastereomer (dr >20:1) and regioisomer. The minor regioisomer was separated by flash chromatography and obtained as a 4:1 mixture of diastereoisomers (66 mg, 12% yield of mixed diastereoisomers) and not characterised.

Determination of the relative stereochemistry:

- The dihedral angle between C(6)–H and C(6a)–H is close to 90°, therefore a small *J*-coupling is expected. The dihedral angle between C(3a)–H and C(6a)–H is close to zero, therefore a larger *J*-coupling is expected. The observed *J*-coupling between C(3a)–H and C(6a)–H is 5.5 Hz. C(6)–H (s) has a significantly smaller *J*-coupling to C(6a)–H, therefore indicating the *trans* stereochemistry between C(6a)–H and C(6)–H.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.88 (dtd, *J* = 4.8, 2.4, 0.8 Hz, 1H, C(5)–H), 5.82 (dd, *J* = 5.6, 2.0 Hz, 1H, C(4)–H), 4.75 (t, *J* = 2.0 Hz, 1H, C(6)–H), 4.67 (d, *J* = 5.5 Hz, 1H, C(6a)–H), 3.86 (ddd, *J* = 8.4, 7.5, 2.4 Hz, 1H, 1x C(2)–H_2), 3.62 – 3.51 (m, 2H, 1x C(2)–H_2, C(3a)–H), 2.01 (ddt, *J* = 12.4, 10.4, 8.0 Hz, 1H, 1x C(3)–H_2), 1.79 (ddt, *J* = 12.4, 5.4, 2.0 Hz, 1H, 1x C(3)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 137.6 (C(4)), 132.1 (C(5)), 89.6 (C(3a)), 67.9 (C(6)), 67.5 (C(2)), 49.0 (C(6a)), 30.3 (C(3)).

IR (neat): 2948 (w), 2868 (w), 1610 (w), 1480 (w), 1448 (w), 1362 (w), 1325 (w), 1273 (w), 1201 (w), 1176 (w), 1092 (m), 1070 (s), 1020 (w), 954 (w), 922 (m), 867 (w), 842 (s), 807 (m), 764 (s), 704 (w), 636 (w) cm^{-1}.

HRMS (GC-MS EI): m/z calcd for $C_7H_9{}^{37}ClO^+$ $[M]^+$ 144.0336 found 144.0299.

5.2.2. Asymmetric Suzuki–Miyaura Couplings

Boronic acid were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics, Fluorochem, and Tokyo Chemical Industry and were used without further purification.

All reactions were carried out under an inert argon atmosphere using standard Schlenk techniques with all reagents weighed open to air.

General Procedure 2-1

$[Rh(cod)OH]_2$ (4.6 mg, 0.010 mmol, 2.5 mol%) and (*S*)-Segphos (14.6 mg, 0.02**4** mmol, 6.0 mol%) were added to a flame dried 5 mL round bottom flask, sealed with a rubber septum under an argon atmosphere, dissolved in THF (0.70 mL) and stirred at room temperature. CsOH (50 wt% aq. solution, 70 µL, 0.40 mmol, 1.00 eq**.**) was added and the mixture was heated to 65 °C. After 30 min, a solution (or suspension) of boronic acid (0.80 mmol, 2.0 eq) and allylic chloride (0.40 mmol, 1.0 eq) in THF (0.7 mL) was added via syringe and the flask was rinsed with THF (0.2 mL). The resulting mixture was then stirred at 65 °C or 80 °C for the period of time indicated. The mixture was then cooled to room temperature and diluted with Et_2O (2 mL) or petrolium ether (2 mL) before SiO_2 (50 mg) was added and the solvents were removed in vacuo. Purification by flash chromatography afforded the desired product.

Liquid allylic chlorides were added via syringe (for (±)-**2-6a** and (±)-**2-6b**: 0.4 mmol ≙ 62 µL).

Modification to General Procedure 2-1*

A suspension of the boronic acid was added to the reaction mixture followed by the addition of the neat allyl chloride to the reaction mixture.

General procedure 2-2

The experiment was performed as in general procedure 2-1 using (*S*)-BINAP instead of (*S*)-Segphos.

Upscale

Larger-scale experiments were performed in direct analogy to general procedure 2-1.

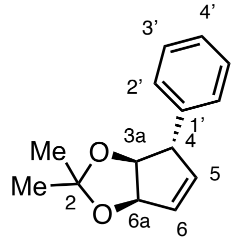
Racemates

Racemic samples were synthesized with (±)-BINAP instead of (*S*)-Segphos on 0.2 mmol scale.

Comment on relative and absolute stereochemistry

The absolute stereochemistry of the enantioenriched compounds was assigned by analogy to previous examples of rhodium-catalysed allylic arylation,[113,116] and confirmed with asymmetric synthesis of Tafluprost.92 The absolute stereochemistry of the enantioenriched compounds was assigned by analogy to previous examples of rhodium catalysed allylic arylation. The relative stereochemistry of the allyl chlorides (±)-**2-6a**, (±)-**2-6b**, (±)-**2-6c**, (±)-**2-6d** and (±)-**2-6e** and of the coupling products **2-8aa**, **2-8ba**, **2-8ca**, **2-8da**, **2-8ea** and **2-8aea*** was assigned by *J* coupling and 1D NOEs. The absolute and relative stereochemistry of all compounds was assigned by analogy to **2-8aa**, **2-8ba**, **2-8ca**, **2-8da**, **2-8ea** and **2-8ea***.

2-8aa



The corresponding compound was prepared following general procedure 2-1 using phenylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et$_2$O = 100/0 to 80/20) afforded the product **2-8aa** as a colourless oil (78 mg, 91% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 95%.

Determination of the relative stereochemistry:

- The dihedral angle between C(3a)–H and C(4)–H is close to 90°, therefore a small *J*-coupling is expected. The dihedral angle between C(3a)–H and C(6a)–H is close to zero, therefore a larger *J*-coupling is expected. The observed *J*-coupling between C(3a)–H and

C(6a)–H is 5.8 Hz. C(4)–H (d, *J* = 2.1 Hz) has a significantly smaller *J*-coupling to C(3a)–H, therefore indicating the *trans* stereochemistry between C(3a)–H and C(4)–H.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.37 – 7.29 (m, 2H, 2x C(3')–H), 7.26 – 7.21 (m, 1H, C(4')–H), 7.17 – 7.05 (m, 2H, 2x C(2')–H), 6.00 (dt, *J* = 5.7, 1.8 Hz, 1H, C(6)–H), 5.97 – 5.82 (m, 1H, C(5)–H), 5.31 (dq, *J* = 5.9, 1.4 Hz, 1H, C(6a)–H), 4.54 (d, *J* = 5.7 Hz, 1H, C(3a)–H), 4.04 (d, *J* = 2.1 Hz, 1H, C(4)–H), 1.49 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 141.6 (C(1')), 135.8 (C(5)), 131.9 (C(6)), 128.8 (2x C(3')), 127.7 (2x C(2')), 127.0 (C(4')), 110.5 (C(2)), 86.1 (C(6a)), 85.5 (C(3a)), 58.0 (C(4)), 27.6 (CH_3), 25.8 (CH_3).

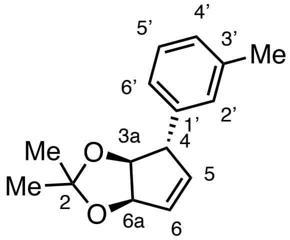
IR ($CHCl_3$ film): 3060 (w), 3028 (w), 2985 (m), 2931 (w), 1493 (w), 1454 (w), 1373 (m), 1255 (m), 1212 (s), 1159 (m), 1072 (s), 1049 (s), 885 (m), 755 (m), 701 (m) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{11}H_{11}O^+$ $[M – (CH_3)_2CO + H]^+$ 159.08044 found 159.08041.

SFC Chiralpak® ID; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 97.5:2.5 er (major enantiomer t_R = 1.25 min; minor enantiomer t_R = 1.43 min).

$[\alpha]^{25}_{D}$ = –244.3 (*c* = 1.0, $CHCl_3$).

2-8ab



The corresponding compound was prepared following general procedure 2-1 using 3-methylphenylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (petrol ether/Et_2O = 100/0 to 70/30) afforded the product **2-8ab** as a pale-yellow oil (75 mg, 81% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 95%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.20 (t, *J* = 7.5 Hz, 1H, C(5')–H), 7.05 (d, *J* = 7.5 Hz, 1H, C(6')–H), 6.96 – 6.87 (overlapping s and d, 2H, C(2')–H, C(4')–H), 5.99 (dt, *J* = 5.7, 1.8 Hz, 1H, C(6)–H), 5.94 – 5.87 (m, 1H, C(5)–H), 5.47 – 5.17 (m, 1H, C(6a)–H), 4.53 (d, *J* = 5.6 Hz, 1H, C(3a)–H), 4.00 (s, 1H, C(4)–H), 2.33 (s, 3H, C(3')–CH_3), 1.49 (s, 3H, C(CH_3)$_2$), 1.34 (s, 3H, C(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 141.6 (C(1')), 138.5 (C(3')), 135.9 (C(5)), 131.8 (C(6)), 128.7 (C(5')), 128.4 (C(2')), 127.8 (C(4'), 124.7 (C(6')), 110.5 (C(2)), 86.1 (C(6a)), 85.5 (C(3a)), 58.0 (C(4)), 27.6 (C(CH_3)$_2$), 25.8 (C(CH_3)$_2$), 21.5 (C(3')–CH_3).

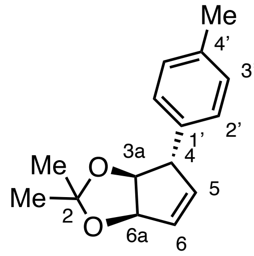
IR ($CHCl_3$ film): 3055 (w), 2984 (m), 2923 (m), 1373 (m), 1283 (w), 1247 (m), 1212 (m), 1159 (m), 1073 (m), 1049 (s), 867 (m), 781 (m), 704 (m) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{12}H_{13}O^+$ $[M – (CH_3)_2CO + H]^+$ 173.09609 found 173.09610.

SFC Chiralpak® ID; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 97.5:2.5 er (major enantiomer t_R = 1.19 min; minor enantiomer t_R = 1.44 min).

$[\alpha]^{25}_D$ = –229.8 (*c* = 1.0, $CHCl_3$).

2-8ac



The corresponding compound was prepared following general procedure 2-1 using 4-methylphenylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (petrol ether/Et_2O = 100/0 to 70/30) afforded the product **2-8ac** as a colourless oil (77 mg, 84% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 94%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.12 (d, *J* = 7.9 Hz, 2H, 2x C(2')–H), 7.02 (d, *J* = 8.0 Hz, 2H, 2x C(3')–H), 5.98 (dt, *J* = 5.7, 1.8 Hz, 1H, C(6)–H), 5.93 – 5.84 (m, 1H, C(5)–H), 5.30 (dq, *J* = 5.7, 1.4 Hz, 1H, C(6a)–H), 4.51 (d, *J* = 5.6 Hz, 1H, C(3a)–H), 4.00 (d, *J* = 2.2 Hz, 1H, C(4)–H), 2.33 (s, 3H, C(4')–CH_3), 1.48 (s, 3H, C(CH_3)$_2$), 1.34 (s, 3H, C(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 138.6 (C(1')), 136.6 (C(5)), 135.9 (C(4')), 131.7 (C(4')), 129.5 (2x C(3')), 127.6 (2x C(2')), 110.4 (C(2)), 86.2 (C(6a)), 85.5 (C(3a)), 57.6 (C(4)), 27.6 (C(CH_3)$_2$), 25.8 (C(CH_3)$_2$), 21.1 (C(4')–CH_3).

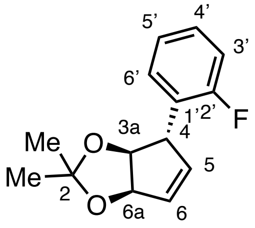
IR (neat): 3052 (w), 2985 (m), 2923 (m), 1513 (m), 1456 (w), 1373 (m), 1254 (m), 1212 (m), 1158 (m), 1073 (m), 1049 (s), 887 (m), 866 (m), 776 (w), 731 (w) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{12}H_{13}O^+$ $[M - (CH_3)_2CO + H]^+$ 173.09609 found 173.09603.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 97:3 er (minor enantiomer t_R = 1.96 min; major enantiomer t_R = 2.07 min).

$[\alpha]^{25}_D$ = –245.2 (*c* = 1.0, $CHCl_3$).

2-8ad



The corresponding compound was prepared following general procedure using 2-fluorophenylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 100/0 to 80/20) afforded the product **2-8ad** as a colourless oil (67 mg, 72% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 90%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.22 (dddd, *J* = 8.1, 7.3, 5.2, 1.9 Hz, 1H, C(4')–H), 7.09 – 7.03 (m, 2H, C(3')–H, C(6')–H), 7.00 (app. td, *J* = 7.7, 2.0 Hz, 1H, C(5')–H), 6.01 (dt, *J* = 5.7, 1.9 Hz, 1H, C(6)–H), 5.86 (ddt, *J* = 5.7, 2.5, 0.9 Hz, 1H, C(5)–H), 5.33 – 5.29 (m, 1H, C(6a)–H), 4.59 (dt, *J* = 5.7, 0.7 Hz, 1H, C(3a)–H), 4.27 (dt, *J* = 3.6, 1.9 Hz, 1H, C(4)–H), 1.49 (s, 3H, CH_3), 1.35 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 161.2 (d, *J* = 246.5 Hz, C(2')), 134.3 (C(5)), 132.6 (C(6)), 128.9 (d, *J* = 4.4 Hz, C(5')), 128.7 (d, *J* = 8.2 Hz, C(4')) 128.6 (d, *J* = 14.7 Hz, C(3')), 124.3 (d, *J* = 3.6 Hz, C(6')), 115.8 (d, *J* = 21.9 Hz, C(3')), 110.7 (C(2)), 85.6 (C(6a)), 85.1 (C(3a)), 51.5 (d, *J* = 2.1 Hz, C(4)), 27.7 (CH_3), 25.9 (CH_3).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -92.21 – -128.33 (m; C–F).

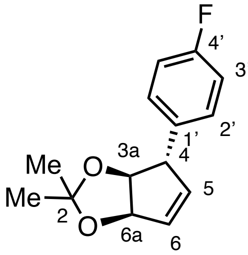
IR ($CHCl_3$ film) 3063 (w), 2987 (w), 2933 (w), 1585 (w), 1490 (m), 1456 (m), 1373 (m), 1212 (s), 1159 (m), 1098 (w), 1073 (m), 1049 (s), 866 (w), 841 (w), 758 (s), 731 (w) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{11}H_{10}OF^+$ 177.07102 $[M – (CH_3)_2CO + H]^+$ found 177.07105.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 95:5 er (major enantiomer t_R = 1.46 min; minor enantiomer t_R = 1.76 min).

$[\alpha]^{25}_D$ = –215.5 (*c* = 1.0, $CHCl_3$).

2-8ae



The corresponding compound was prepared following general procedure 2-1 using 4-fluorophenylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 100/0 to 70/30) afforded the product **2-8ae** as a yellow oil (73 mg, 77% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 94%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.16 – 7.05 (m, 2H, 2x C(2')–H), 7.04 – 6.93 (m, 2H, 2x C(3')–H), 6.01 (dt, *J* = 5.6, 1.8 Hz, 1H, C(6)–H), 5.90 (m, 1H, C(5)–H), 5.30 (dq, *J* = 5.7, 1.4 Hz, 1H, C(6a)–H), 4.49 (d, *J* = 5.6 Hz, 1H, C(3a)–H), 4.02 (s, 1H, C(4)–H), 1.49 (s, 3H, CH_3), 1.35 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 162.0 (d, *J* = 245.1 Hz, C(4')), 137.4 (d, *J* = 3.4 Hz, 2x C(1')), 135.7 (C(5)), 132.2 (C(6)), 129.2 (d, *J* = 8.1 Hz, 2 xC(2')), 115.7 (d, *J* = 21.4 Hz, 2x (C(3')), 110.7 (C(2)), 86.2 (C(6a)), 85.5 (C(3a)), 57.4 (C(4)), 27.7 (CH_3), 25.9 (CH_3).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -116.08 (tt, *J* = 8.6, 5.4 Hz; C–F).

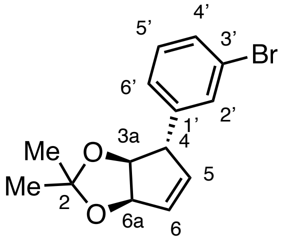
IR ($CHCl_3$ film): 2980 (s), 1604 (w), 1509 (s), 1459 (w), 1375 (m), 1218 (s), 1159 (m), 1074 (m), 1050 (s), 956 (w), 887 (w), 833 (m), 773 (w) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{11}H_{10}OF^+$ $[M - (CH_3)_2CO + H]^+$ 177.07102 found 177.07102.

SFC Chiralpak® ID; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 97:3 er (major enantiomer t_R = 1.09 min; minor enantiomer t_R = 1.24 min).

$[\alpha]^{25}_D$ = –207.7 (*c* = 1.0, $CHCl_3$).

2-8af



The corresponding compound was prepared following general procedure 2-1 using 3-bromophenylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 100/0 to 80/20) afforded the product **2-8af** as a colourless oil that solidified upon standing (103 mg, 86% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 95%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.37 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1H, C(4')–H), 7.25 (app. t, *J* = 1.8 Hz, 1H, C(2')–H), 7.18 (app. t, *J* = 7.8 Hz, 1H, C(5')–H), 7.07 (dt, *J*=7.6, 1.4 Hz, 1H, C(6')–H), 6.02 (dt, *J* = 5.7, 1.8 Hz, 1H, C(6)–H), 5.89 (ddt, *J* = 5.7, 2.5, 0.9 Hz, 1H, C(5)–H), 5.29 (ddd, *J* = 5.8, 1.6, 1.0 Hz, 1H, C(6a)–H), 4.50 (d, *J* = 5.7 Hz, 1H, C(3a)–H), 3.99 (d, *J* = 2.2 Hz, 1H, C(4)–H), 1.47 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 144.1 (C(1')), 135.1 (C(5)), 132.6 (C(6)), 130.7 (C(2'), 130.4 (C(5')), 130.2 (C(4')), 126.5 (C(6')), 123.0 (C(3')), 110.7 (C(2)), 85.8 (C(6a)), 85.3 (C(3a)), 57.7 (C(4)), 27.5 (CH_3), 25.8 (CH_3).

IR ($CHCl_3$ film): 3059 (w), 2986 (w), 2930 (w), 1592 (w), 1567 (w), 1474 (w), 1426 (w), 1373 (m), 1252 (w), 1211 (w), 1158 (m), 1073 (m), 1049 (s), 865 (m), 781 (m), 743 (w), 696 (m) cm^{-1}.

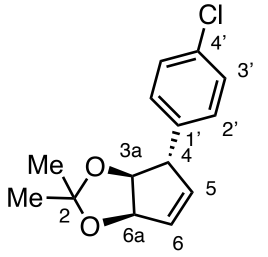
HRMS (APCI): m/z calcd for $C_{11}H_{10}O^{79}Br^+$ $[M – (CH_3)_2CO + H]^+$ 236.99095 found 236.99099.

SFC Chiralpak® ID; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 97.5:2.5 er (major enantiomer t_R = 1.39 min; minor enantiomer t_R = 1.98 min).

m.p.: 57 – 58 °C.

$[\alpha]^{25}_D$ = –210.4 (*c* = 1.0, $CHCl_3$).

2-8ag



The corresponding compound was prepared following general procedure 2-1 using 4-chlorophenylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 100/0 to 70/30) afforded the product **2-8ag** as a colourless solid (83 mg, 83% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 93%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.38 – 7.19 (m, 2H, 2x C(3')–H), 7.15 – 6.91 (m, 2H, 2x C(2')–H), 6.02 (dt, *J* = 5.7, 1.8 Hz, 1H, C(6)–H), 5.94 – 5.65 (m, 1H, C(5)–H), 5.30 (dq, *J* = 5.6, 1.4 Hz, 1H, C(6a)–H), 4.49 (d, *J* = 5.6 Hz, 1H, C(3a)–H), 4.01 (d, *J* = 2.2 Hz, 1H, C(4)–H), 1.48 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 140.1 (C(1')), 135.4 (C(5)), 132.8 (C(4')), 132.3 (C(6)), 129.0 (2x C(2')), 128.9 (2x C(3')), 110.7 (C(2)), 86.0 (C(6a)), 85.4 (C(3a)), 57.5 (C(4)), 27.6 (CH_3), 25.8 (CH_3).

IR ($CHCl_3$ film): 2986 (w), 2929 (w), 1492 (m), 1373 (m), 1254 (w), 1212 (m), 1158 (w), 1073 (m), 1050 (s), 1013 (w), 886 (m), 824 (m), 772 (w) cm^{-1}.

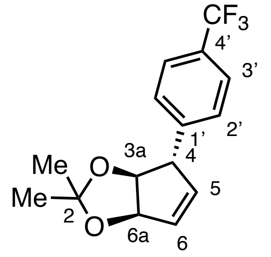
HRMS (APCI): m/z calcd for $C_{11}H_{10}O^{37}Cl^+$ $[M - (CH_3)_2CO + H]^+$ 195.03852 found 195.03871.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 96.5:3.5 er (minor enantiomer t_R = 2.09 min; major enantiomer t_R = 2.45 min).

m.p.: 61 – 62 °C.

$[\alpha]^{25}_D$ = –238.7 (*c* = 1.0, $CHCl_3$).

2-8ah



The corresponding compound was prepared following general procedure 2-1 using 4-trifluoromethylphenylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 100/0 to 70/30) afforded the product **2-8ah** as a colourless oil (78 mg, 68% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 91%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.56 (d, *J* = 8.0 Hz, 2H, 2x C(3')–H), 7.24 (d, *J* = 8.3 Hz, 2H, 2x C(2')–H), 6.05 (dt, *J* = 5.7, 1.8 Hz, 1H, C(6)–H), 5.92 – 5.90 (m, 1H, C(5)–H), 5.32 – 5.30 (m, 1H, C(6a)–H), 4.51 (d, *J* = 5.7 Hz, 1H, C(3a)–H), 4.09 (s, 1H, C(4)–H), 1.48 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 145.8 (C(1')), 135.0 (C(5)), 132.7 (C(6)), 129.39 (q, *J* = 32.4 Hz, C(4')), 128.1 (2x C(2')), 125.8 (weak q, *J* = 3.8 Hz, 2x C(3')), 124.3 (weak q, *J* = 271.8 Hz, just two peaks detected, CF_3), 110.8 (C(2)), 85.8 (C(6a)), 85.4 (C(3a)), 57.9 (C(4)), 27.6 (CH_3), 25.8 (CH_3).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -62.46 (br. s; CF_3).

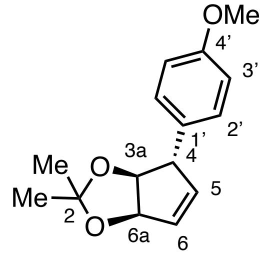
IR ($CHCl_3$ film): 2988 (w), 2934 (w), 1619 (w), 1419 (w), 1375 (w), 1326 (s), 1257 (w), 1213 (m), 1164 (m), 1127 (m), 1068 (m), 1051 (m), 953 (w), 887 (w), 837 (w), 773 (w) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{12}H_{10}OF_3^+$ $[M – (CH_3)_2CO + H]^+$ 227.06783 found 227.06787.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 95.5:4.5 er (minor enantiomer t_R = 1.20 min; major enantiomer t_R = 1.38 min).

$[\alpha]^{25}_{D}$ = –176.4 (*c* = 1.0, $CHCl_3$).

2-8ai



The corresponding compound was prepared following general procedure 2-1 using 4-methoxyphenylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (petrol ether/Et_2O = 100/0 to 60/40) afforded the product **2-8ai** as a colourless oil that solidified upon standing (71 mg, 73% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 93%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.12 – 6.98 (m, 2H, 2x C(2')–H), 6.88 – 6.82 (m, 2H, 2x C(3')–H), 6.00 – 5.94 (m, 1H, C(6)–H), 5.91 – 5.88 (m, 1H, C(5)–H), 5.35 – 5.17 (m, 1H, C(6a)–H), 4.54 – 4.43 (m, 1H, C(3a)–H), 3.98 (d, *J* = 2.1 Hz, 1H, C(4)–H), 3.79 (s, 3H, OCH_3), 1.48 (s, 3H, $C(CH_3)_2$), 1.33 (s, 3H, $C(CH_3)_2$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 158.7 (C(4')), 136.0 (C(5)), 133.6 (C(1')), 131.6 (C(6)), 128.6 (2x C(2')), 114.2 (2x C(3')), 110.4 (C(2)), 86.2 (C(6a)), 85.4 (C(3a)), 57.1 (C(4)), 55.4 (OCH_3), 27.6 ($C(CH_3)_2$), 25.8 ($C(CH_3)_2$).

IR ($CHCl_3$ film): 3059 (w), 2987 (w), 2932 (w), 2836 (w), 1611 (w), 1512 (s), 1461 (w), 1373 (m), 1251 (s), 1212 (m), 1179 (m), 1073 (m), 1044 (s), 887 (w), 823 (m), 777 (w), 727 (w) cm^{-1}.

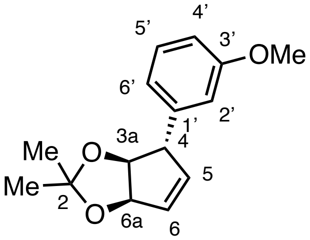
HRMS (APCI): m/z calcd for $C_{12}H_{13}O_2^+$ $[M – (CH_3)_2CO + H]^+$ 189.09101 found 189.09092.

SFC Chiralpak® IF; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 96.5:3.5 er (major enantiomer t_R = 2.25 min; minor enantiomer t_R = 2.55 min).

m.p.: 44 – 45 °C.

$[\alpha]^{25}_D$ = –228.8 (*c* = 1.0, $CHCl_3$).

2-8aj



The corresponding compound was prepared following general procedure 2-1 using 3-methoxyphenylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (petrol ether/Et_2O = 90/10 to 70/30) afforded the product **2-8aj** as a colourless oil (84 mg, 85% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 95%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.23 (app. t, *J* = 7.9 Hz, 1H, C(5')–H), 6.78 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H, C(4')–H), 6.72 (dt, *J* = 7.6, 1.4 Hz, 1H, C(6')–H), 6.67 (dd, *J* = 2.6, 1.6 Hz, 1H, C(2')–H), 6.09 – 5.96 (m, 1H, C(6)–H), 5.91 (ddt, *J* = 5.7, 2.4, 0.9 Hz, 1H, C(5)–H), 5.36 – 5.23 (m, 1H, C(5a)–H), 4.53 (d, *J* = 5.7 Hz, 1H, C(3a)–H), 4.00 (d, *J* = 2.1 Hz, 1H, C(4)–H), 3.79 (s, 3H, OCH_3), 1.48 (s, 3H, C(CH_3)$_2$), 1.34 (s, 3H, C(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 160.1 (C(3')), 143.3 (C(1')), 135.6 (C(5)), 132.0 (C(6)), 129.9 (C(5')), 120.0 (C(5')), 113.5 (C(2')), 112.2 (C(4')), 110.5 (C(2)), 86.0 (C(6a)), 85.5 (C(3a)), 58.1 (C(4)), 55.3 (OCH_3), 27.6 (C(CH_3)$_2$), 25.8 (C(CH_3)$_2$).

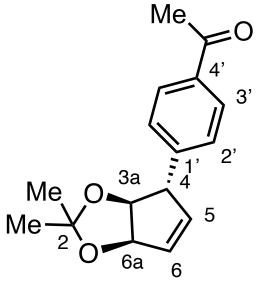
IR ($CHCl_3$ film): 2987 (w), 2933 (w), 1601 (m), 1489 (m), 1458 (w), 1373 (m), 1317 (m), 1261 (w), 1214 (m), 1157 (m), 1073 (m), 1048 (s), 866 (m), 774 (m), 699 (w) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{12}H_{13}O_2^+$ $[M - (CH_3)_2CO + H]^+$ 189.09101 found 189.09124.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 97.5:2.5 er (major enantiomer t_R = 2.19 min; minor enantiomer t_R = 3.67 min).

$[\alpha]^{25}_D$ = –221.9 (*c* = 1.0, $CHCl_3$).

2-8ak



The corresponding compound was prepared following general procedure 2-1 using 4-acetylphenylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et$_2$O = 90/10 to 40/60) afforded the product **2-8ak** as a pale-yellow oil (55 mg, 53% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 86%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.90 (d, *J* = 8.3 Hz, 2H, 2x C(2')–H), 7.21 (d, *J* = 8.2 Hz, 2H, 2x C(3')–H), 6.04 (ddd, *J* = 5.7, 2.6, 1.1 Hz, 1H, C(6)–H), 6.00 – 5.80 (m, 1H, C(5)–H), 5.31 (ddd, *J* = 5.7, 2.5, 1.5 Hz, 1H, C(6a)–H), 4.52 (dt, *J* = 5.7, 1.1 Hz, 1H, C(3a)–H), 4.09 (d, *J* = 1.8 Hz, 1H, C(4)–H), 2.58 (s, 3H, C(O)CH$_3$), 1.48 (s, 3H, C(*CH$_3$*)$_2$), 1.34 (s, 3H, C(*CH$_3$*)$_2$).

^{13}C NMR (CDCl$_3$, 101 MHz) δ (ppm) 197.7 (C=O), 147.2 (C(1')), 136.1 (C(4')), 135.1 (C(5)), 132.6 (C(6)), 129.0 (2x C(2')), 127.9 (2x C(3')), 110.8 (C(2)), 85.8 (C(6a)), 85.4 (C(3a)), 58.1 (C(4)), 27.6 (C(*CH$_3$*)$_2$), 26.7 (C(O)*CH$_3$*), 25.9 (C(*CH$_3$*)$_2$).

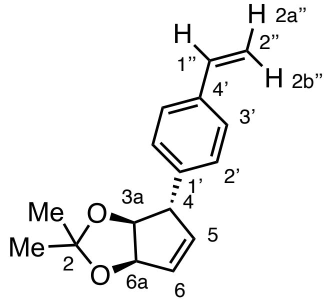
IR (CHCl$_3$ film) 2987 (w), 2931 (w), 1684 (s), 1606 (m), 1414 (w), 1363 (m), 1267 (s), 1211 (m), 1159 (w), 1073 (m), 1050 (s), 959 (w), 887 (w), 864 (w), 831 (w) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{13}H_{13}O_2^+$ [M – (CH$_3$)$_2$CO + H]$^+$ 201.09101 found 201.09112 and m/z calcd for $C_{16}H_{19}O_3^+$ [M + H]$^+$ 259.13287 found 259.13308.

SFC Chiralpak® ID; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 93:7 er (major enantiomer t_R = 2.85 min; minor enantiomer t_R = 3.35 min).

$[\alpha]^{25}_D$ = –251.1 (*c* = 1.0, CHCl$_3$).

2-8al



The corresponding compound was prepared following general procedure 2-1 using 4-vinylphenyl-boronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 100/0 to 80/20) afforded the product **2-8al** as a colourless oil that solidified upon standing (41 mg, 42% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 92%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.35 (d, *J* = 8.2 Hz, 2H, 2x C(3')–H), 7.08 (d, *J* = 8.2 Hz, 2H, 2x C(2')–H), 6.69 (dd, *J* = 17.6, 10.9 Hz, 1H, C(1'')–H), 6.00 (dt, *J* = 5.7, 1.8 Hz, 1H, C(6)–H), 5.91 (ddd, *J* = 4.8, 2.4, 1.2 Hz, 1H, C(5)–H), 5.72 (dd, *J* = 17.5, 0.9 Hz, 1H, C(2b'')–H), 5.31 (dd, *J* = 5.7, 1.3 Hz, 1H, C(6a)–H), 5.23 (dd, *J* = 10.9, 0.9 Hz, 1H, C(2a'')–H), 4.52 (d, *J* = 5.7 Hz, 1H, C(3a)–H), 4.02 (s, 1H, C(4)–H), 1.48 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 141.3 (C(1')), 136.5 (C(1''), 136.5 (2x C(4')), 135.7 (C(5)), 132.0 (C(6)), 127.9 (C(2')), 126.7 (C(2')), 113.8 (2x C(2'')), 110.6 (C(2)), 86.1 (C(6a)), 85.5 (C(3a)), 57.8 (C(4)), 27.6 (CH_3), 25.9 (CH_3).

IR ($CHCl_3$ film): 3053 (w), 2986 (w), 2929 (w), 1511 (w), 1373 (m), 1254 (w), 1211 (m), 1159 (w), 1073 (m), 1049 (s), 887 (w), 837 (m), 774 (w) cm^{-1}.

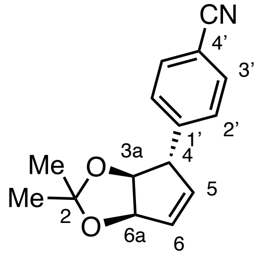
HRMS (APCI): m/z calcd for $C_{13}H_{12}O^+$ 184.0883 $[M – (CH_3)_2CO + H]^+$ found 184.0883.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 96:4 er (minor enantiomer t_R = 2.31 min; major enantiomer t_R = 2.64 min).

m.p.: 45 – 47 °C.

$[\alpha]^{25}_D$ = –288.3 (*c* = 1.0, $CHCl_3$).

2-8am



The corresponding compound was prepared following general procedure 2-1 using 4-cyanophenyl-boronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et$_2$O = 90/10 to 60/40) afforded the product **2-8am** as a colourless oil (59 mg, 61% yield) as a single diastereomer (d.r. >20:1). SFC analysis showed an enantiomeric excess of 89%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.68 – 7.53 (m, 2H, 2x C(3')–H), 7.25 – 7.20 (m, 2H, 2x C(2')–H), 6.06 (dt, *J* = 5.7, 1.8 Hz, 1H, C(6)–H), 5.89 (ddt, *J* = 5.8, 2.5, 0.9 Hz, 1H, C(5)–H), 5.30 (dq, *J* = 5.8, 1.5 Hz, 1H, C(6a)–H), 4.49 (dt, *J* = 5.6, 1.1 Hz, 1H, C(3a)–H), 4.08 (d, *J* = 2.0 Hz, 1H, C(4)–H), 1.48 (s, 3H, CH$_3$), 1.34 (s, 3H, CH$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 147.3 (C(4')), 134.6 (C(5)), 133.2 (C(6)), 132.7 (2x C(3')), 128.5 (2x C(2')), 118.9 (CN), 111.7 (C(2)), 111.0 (C(4')), 85.7 (C(6a)), 85.3 (C(3a)), 58.3 (C(4)), 27.6 (CH$_3$), 25.8 (CH$_3$).

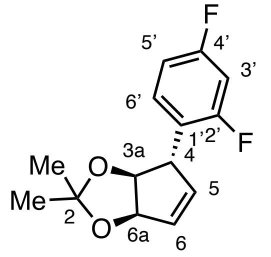
IR (CHCl$_3$ film): 2984 (m), 2932 (w), 2229 (m), 1608 (w), 1504 (w), 1375 (m), 1256 (m), 1211 (s), 1158 (m), 1074 (s), 1050 (s), 886 (m), 864 (m), 835 (m), 771 (w) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{15}H_{16}O_2N^+$ $[M + H]^+$ 242.11756 found 242.11742 and calcd for $C_{12}H_{10}ON^+$ $[M – (CH_3)_2CO + H]^+$ 184.07569 found 184.07561.

SFC Chiralpak® IC; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 94.5:5.5 er (major enantiomer t_R = 2.25 min; minor enantiomer t_R = 2.33 min).

$[\alpha]^{25}_D$ = –268.9 (*c* = 1.0, CHCl$_3$).

2-8an



The corresponding compound was prepared following general procedure 2-1 using 2,4-difluorophenylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 100/0 to 80/20) afforded the product **2-8an** as a colourless oil (59 mg, 58% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 83%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.96 (td, *J* = 8.7, 6.3 Hz, 1H, C(6')–H), 6.87 – 6.75 (m, 2H, C(3')–H and C(5')–H), 6.02 (dt, *J* = 5.7, 1.8 Hz, 1H, C(6)–H), 5.84 (ddt, *J* = 5.7, 2.5, 0.9 Hz, 1H, C(5)–H), 5.30 (ddt, *J* = 5.9, 2.2, 1.2 Hz, 1H, C(6a)–H), 4.57 – 4.50 (m, 1H, C(3a)–H), 4.23 (s, 1H, C(4)–H), 1.49 (s, 3H, CH_3), 1.36 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 162.8 (dd, *J* = 122.7, 11.9 Hz, C(2')), 160.3 (dd, *J* = 124.2, 11.8 Hz, C(4')), 134.0 (C(5)), 132.9 (C(6)), 129.5 (dd, *J* = 9.6, 6.0 Hz, C(6')), 124.6 (dd, *J* = 14.9, 3.8 Hz, C(1')), 111.3 (dd, *J* = 21.0, 3.8 Hz, C(5')), 110.8 (C(2)), 104.2 (app. t, *J* = 25.6 Hz, C(3')), 85.5 (C(6a)), 85.0 (C(3a)), 51.1 (d, *J* = 1.7 Hz, C(4)), 27.6 (CH_3), 25.9 (CH_3).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -111.19 – -112.28 (m, 1F), -112.51 – -114.51 (m; C–F).

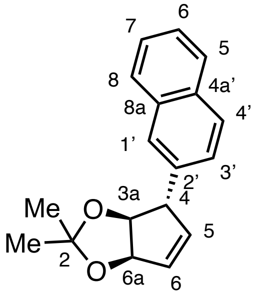
IR ($CHCl_3$ film): 2989 (w), 2932 (w), 1530 (s), 1350 (s), 1243 (w), 1211 (m), 1159 (w), 1075 (m), 1050 (m), 868 (w), 739 (m), 689 (w) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{11}H_{19}OF_2^+$ [M – $(CH_3)_2CO$ + H]$^+$ 195.06160 found 195.06192.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 91.5:8.5er (major enantiomer t_R = 1.23 min; minor enantiomer t_R = 1.48 min).

$[\alpha]^{25}_D$ = –206.7 (*c* = 1.0, $CHCl_3$).

2-8ao



The corresponding compound was prepared following general procedure 2-1 using 2-naphtylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 100/0 to 80/20) afforded the product **2-8ao** as a colourless solid (89 mg, 83% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 90%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.85 – 7.71 (m, 3H, 3x C_{Ar}–H), 7.59 – 7.54 (m, 1H, C_{Ar}–H), 7.51 – 7.37 (m, 2H, 2x C_{Ar}–H), 7.33 – 7.18 (m, 1H, C_{Ar}–H), 6.07 (dt, *J* = 5.7, 1.8 Hz, 1H, C(6)–H), 6.03 – 6.00 (m, 1H, C(5)–H), 5.37 (dq, *J* = 5.6, 1.3 Hz, 1H, C(6a)–H), 4.61 (d, *J* = 5.7 Hz, 1H, C(3a)–H), 4.21 (t, *J* = 2.2 Hz, 1H, C(4)–H), 1.52 (s, 3H, CH_3), 1.36 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 139.1 (C_{quart}), 135.7 (C(5)), 133.7 (C_{quart}), 132.6 (C_{quart}), 132.2 (C(6)), 128.6 , 127.8, 126.4, 126.2, 125.9, 125.8 (6x C_{Ar}–H), 110.6 (C(2)), 86.0 (C(5a)), 85.6 (C(3a)), 58.2 (C(4), 27.7 (CH_3), 25.9 (CH_3).

IR ($CHCl_3$ film): 2976 (m), 2924 (m), 2867 (w), 1375 (w), 1213 (w), 1053 (s), 1012 (m), 861 (w), 823 (w), 773 (w), 747 (w) cm^{-1}.

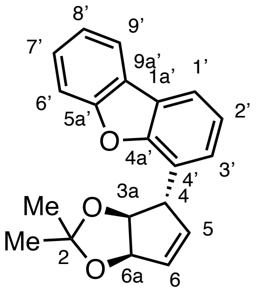
HRMS (APCI): m/z calcd for $C_{15}H_{13}O^+$ $[M – (CH_3)_2CO + H]^+$ 209.09609 found 209.09620.

SFC Chiralpak® IC; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 95:5 er (minor enantiomer t_R = 1.95 min; major enantiomer t_R = 2.10 min).

m.p.: 123 – 124 °C.

$[\alpha]^{25}_D$ = –294.0 (*c* = 1.0, $CHCl_3$).

2-8ap



The corresponding compound was prepared following general procedure 2-1 using 4-(dibenzofuranyl)boronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 95/0 to 70/30) afforded the product **2-8ap** as a colourless oil (92 mg, 75% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 85%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.95 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H, C(9')–H), 7.84 (dd, *J* = 7.7, 1.3 Hz, 1H, C(3')–H), 7.62 (d, *J* = 8.3 Hz, 1H, C(6')–H), 7.47 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 1H, C(7')–H), 7.35 (app. td, *J* = 7.5, 1.0 Hz, 1H, C(8')–H), 7.27 (app. t, *J* = 7.6 Hz, 1H, C(2')–H), 7.10 (dd, *J* = 7.4, 1.2 Hz, 1H, C(1')–H), 6.09 (dt, *J* = 5.8, 1.8 Hz, 1H, C(6)–H), 5.98 (ddt, *J* = 4.8, 2.6, 1.0 Hz, 1H, C(5)–H), 5.57 – 5.36 (m, 1H, C(6a)–H), 4.76 (dd, *J* = 5.6, 0.7 Hz, 1H, C(3a)–H), 4.63 (d, *J* = 2.2 Hz, 1H, C(4)–H), 1.55 (s, 3H, CH_3), 1.38 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 156.3 (C(5a')), 154.3 (C(4a')), 134.4 (C(5)), 132.6 (C(6)), 127.3 (C(7')), 125.7 (C(1')), 125.6 (C(4')), 124.5 (C(1a')), 124.5 (C(9a')), 123.0 (C(2')), 122.9 (C(8')), 120.8 (C(9')), 119.4 (C(3')), 112.1(C(6')), 110.7 (C(2)), 85.9 (C(5a)), 85.0 (C(3a)), 52.3 (C(4)), 27.8 (CH_3), 26.1 (CH_3).

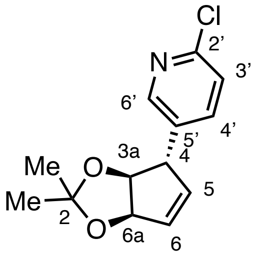
IR ($CHCl_3$ film): 3059 (w), 2984 (w), 2932 (w), 1451 (m), 1423 (w), 1374 (w), 1253 (m), 1210 (s), 1187 (w), 1049 (m), 866 (w), 753 (s) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{17}H_{13}O_2^+$ $[M – (CH_3)_2CO + H]^+$ 249.09101 found 249.09062.

SFC Chiralpak® IF; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 92.5:7.5 er (minor enantiomer t_R = 2.85 min; major enantiomer t_R = 3.31 min).

$[\alpha]^{25}_D$ = –120.9 (*c* = 1.0, $CHCl_3$).

2-8aq



The corresponding compound was prepared following general procedure 2-1 using 6-chloro-3-pyridinylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et$_2$O = 90/10 to 50/50 afforded the product **2-8aq** as a colourless oil (50 mg, 50 % yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 90%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 8.21 (d, *J* = 2.5 Hz, 1H, C(6')–H), 7.38 (dd, *J* = 8.2, 2.5 Hz, 1H, C(4')–H), 7.28 (d, *J* = 8.2 Hz, 1H, C(3')–H), 6.07 (dt, *J* = 5.9, 1.7 Hz, 1H, C(6)–H), 5.89 (ddd, *J* = 5.7, 2.5, 1.0 Hz, 1H, C(5)–H), 5.31 (dq, *J* = 5.7, 1.4 Hz, 1H, C(6a)–H), 4.49 (d, *J* = 5.7 Hz, 1H, C(3a)–H), 4.04 (s, 1H, C(4)–H), 1.48 (s, 3H, CH$_3$), 1.35 (s, 3H, CH$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 150.3 (C(2')), 149.1 (C(6')), 137.9 (C(4')), 136.1 (C(4')), 134.3 (C(5)), 133.3 (C(5)), 124.4 (C(3')), 111.1 (C(2), 85.6 (C(3a)), 85.3 (C(3a)), 55.0 (C(4)), 27.6 (CH$_3$), 25.9 (CH$_3$).

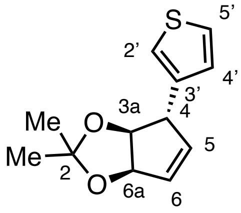
IR (CHCl$_3$ film): 3054 (w), 2990 (w), 2932 (w), 1584 (w), 1564 (w), 1458 (m), 1376 (m), 1246 (w), 1211 (m), 1158 (w), 1106 (m), 1075 (m), 1050 (s), 886 (m), 864 (w), 834 (w), 773 (w), 743 (w), 708 (w) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{13}H_{15}O_2NCl^+$ $[M + H]^+$ 252.07858 found 252.07822.

SFC Chiralpak® IF; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 95:5 er (minor enantiomer t_R = 3.84 min; major enantiomer t_R = 3.99 min).

$[\alpha]^{25}_D$ = –214.5 (*c* = 1.0, CHCl$_3$).

2-8ar



The corresponding compound was prepared following general procedure 2-1 using 3-thienylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 100/0 to 80/20 afforded the product **2-8ar** as a colorless oil (64 mg, 72% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.29 (dd, J = 5.0, 3.0 Hz, 1H, C(5')–H), 6.95 – 6.93 (m, 1H, C(2')–H), 6.91 (dd, J = 5.0, 1.3 Hz, 1H, C(4')–H) 5.96 (app. s, 2H, C(5)–H, C(6)–H), 5.28 (d, J = 5.7 Hz, 1H, C(6a)–H), 4.54 (d, J = 5.7 Hz, 1H, C(3a)–H), 4.11 (s, 1H, C(4)–H), 1.47 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 142.4 (C(3')), 135.4 (C(5)), 131.7 (C(6)), 127.3 (C(4')), 126.4 (C(5')), 120.8 (C(2')), 110.6 (C(2)), 85.3 (C(6a)), 85.3 (C(3a)), 52.9 (C(4)), 27.6 (CH_3), 25.9 (CH_3).

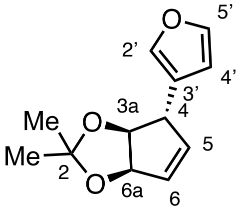
IR ($CHCl_3$ film): 3101 (w), 3060 (w), 2985 (w), 2930 (w), 1373 (m), 1246 (w), 1211 (m), 1158 (m), 1073 (m), 1049 (s), 871 (m), 851 (m), 777 (m), 660 (w) cm^{-1}.

HRMS (APCI): m/z calcd for $C_9H_9OS^+$ $[M - (CH_3)_2CO + H]^+$ 165.03686 found 165.03687.

SFC Chiralpak® ID; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99:1 er (major enantiomer t_R = 1.45 min; minor enantiomer t_R = 1.60 min).

$[\alpha]^{25}_D$ = –230.7 (c = 1.0, $CHCl_3$).

(–)-3as



The corresponding compound was prepared following general procedure 2-1 using 3-furanylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 100/0 to 90/10 afforded the product **2-8as** as a colourless oil (35 mg, 43% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 96%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.38 (app. t, *J* = 1.7 Hz, 1H, C(5’)–H), 7.18 (dt, *J* = 1.7, 0.9 Hz, 1H, C(2’)–H), 6.24 (dd, *J* = 1.9, 0.9 Hz, 1H, C(4’)–H), 6.10 – 5.70 (m, 2H, C(5)–H and C(6)–H), 5.25 (dq, *J* = 5.8, 1.3 Hz, 1H, C(6a)–H), 4.53 (dq, *J* = 5.7, 0.8 Hz, 1H, C(3a)–H), 3.89 (s, 1H, C(4)–H), 1.46 (s, 3H, CH_3), 1.35 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 143.6 (C(5’)), 139.0 (C(2’)), 135.0 (C(5)), 131.7 (C(6)), 125.7 (C(3’)), 110.6 (C(2)), 110.1 (C(4’)) , 85.3 (C(6a)), 85.1 (C(3a)), 48.3 (C(4)), 27.6 (CH_3), 25.9 (CH_3).

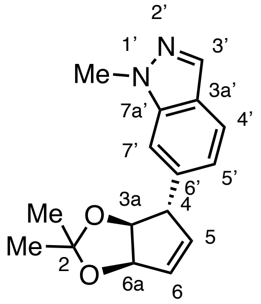
IR ($CHCl_3$ film) 2987 (w), 2931 (w), 1502 (w), 1374 (m), 1247 (w), 1212 (m), 1158 (m), 1072 (s), 1050 (s), 1027 (m), 873 (s), 777 (m), 728 (w), 665 (w) cm^{-1}.

HRMS (APCI): m/z calcd for $C_9H_9O_2^+$ $[M – (CH_3)_2CO + H]^+$ 149.05971 found 149.05995.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 98:2 er (major enantiomer t_R = 1.43 min; minor enantiomer t_R = 1.52 min).

$[\alpha]^{25}_D$ = –170.4 (*c* = 1.0, $CHCl_3$).

2-8at



The corresponding compound was prepared following general procedure 2-1 using 1-methyl-1*H*-indazole-6-boronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 60/40 to 30/70 afforded the product **2-8at** as a colourless solid (88 mg, 82% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 92%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.93 (d, *J* = 0.9 Hz, 1H, (C(3')–H), 7.66 (dd, *J* = 8.3, 0.8 Hz, 1H, C(4')–H), 7.12 (d, *J* = 0.8 Hz, 1H, C(5')–H), 6.93 (dd, *J* = 8.4, 1.4 Hz, 1H, C(7')–H), 6.07 (dt, *J* = 5.7, 1.8 Hz, 1H, C(6)–H), 5.99 (ddt, *J* = 5.7, 2.5, 0.9 Hz, 1H, C(5)–H), 5.34 (dq, *J* = 5.6, 1.4 Hz, 1H, C(6a)–H), 4.58 (d, *J* = 5.7 Hz, 1H, C(3a)–H), 4.19 (d, *J* = 2.3 Hz, 1H, C(4)–H), 4.04 (s, 3H, NCH_3), 1.51 (s, 3H, $C(CH_3)_2$), 1.35 (s, 3H, $C(CH_3)_2$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 140.4 (C(7a')), 140.3 (C(6')), 135.6 (C(5)), 132.7 (C(3')), 132.4 (C(6)), 123.3 (C(3a)), 121.5 (C(4')), 120.9 (C(7')), 110.7 (C(2)), 107.4 (C(5')), 86.2 (C(6a)), 85.5 (C(3a)), 58.6 (C(4)), 35.6 (NCH_3), 27.6 ($C(CH_3)_2$), 25.8 ($C(CH_3)_2$).

IR ($CHCl_3$ film): 2980 (m), 2934 (m), 1740 (w), 1623 (w), 1475 (w), 1374 (m), 1255 (m), 1213 (m), 1158 (m), 1073 (m), 1048 (s), 962 (m), 882 (m), 840 (m), 772 (w), 629 (w) cm^{-1}.

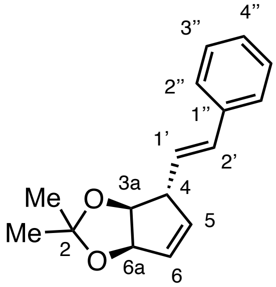
HRMS (APCI): m/z calcd for $C_{16}H_{18}O_2N_2O^+$ $[M + H]^+$ 271.14410 found 271.14374.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 96:4 er (major enantiomer t_R = 3.20 min; minor enantiomer t_R = 3.61 min).

m.p.: 100 – 102 °C.

$[\alpha]^{25}_D$ = –263.3 (*c* = 1.0, $CHCl_3$).

2-8au



The corresponding compound was prepared following general procedure 2-2 using (*E)*-styrylboronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et$_2$O = 100/0 to 70/30 afforded the product **2-8au** as a pale-yellow oil (66 mg, 69 % yield; containing minor impurities) as a single diastereomer (dr >20:1, ~33:1). SFC analysis showed an enantiomeric excess of 91%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.37 – 7.27 (m, 4H, 2x C(2’’)–H, 2x C(3’’)–H), 7.25 – 7.19 (m, 1H, C(4’’)–H), 6.41 (dd, *J* = 15.9, 1.2 Hz, 1H, C(2’)–H), 6.14 (dd, *J* = 15.9, 7.8 Hz, 1H, C(1’)–H), 5.92 (dt, *J* = 5.7, 1.7 Hz, 1H, C(6)–H), 5.86 (ddt, *J* = 5.8, 2.4, 0.9 Hz, 1H, C(5)–H), 5.23 (dq, *J* = 6.1, 1.4 Hz, 1H, C(6a)–H), 4.54 (dd, *J* = 5.7, 1.2 Hz, 1H, C(3a)–H), 3.62 (ddt, *J* = 7.8, 2.7, 1.3 Hz, 1H, C(4)–H), 1.46 (s, 3H, CH$_3$), 1.36 (s, 3H, CH$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 137.1 (C(1’’)), 135.3 (C(5)), 131.9 (C(6)), 131.1 (C(2’)), 129.9 (C(1’)), 128.7 (C(3’’)), 127.6 (C(4’’)), 126.3 (C(2’’)), 110.4 (C(2)), 85.2 (C(6a)), 84.0 (C(3a)), 54.8 (C(4)), 27.6 (CH$_3$), 25.9 (CH$_3$)

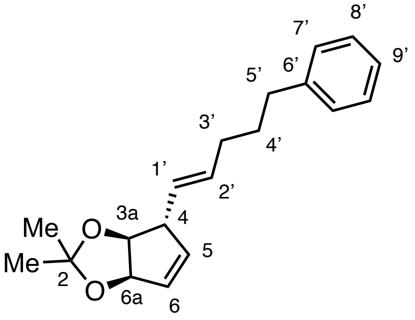
IR (CHCl$_3$ film): 3026 (w), 2984 (w), 2931 (w), 1494 (w), 1452 (w), 1373 (m), 1246 (w), 1210 (m), 1158 (m), 1048 (s), 997 (m), 869 (m), 770 (w), 745 (m), 695 (m) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{13}H_{13}O^+$ $[M – (CH_3)_2CO + H]^+$ 185.09609 found 185.09628.

SFC Chiralpak® IB; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 95.5:4.5 er (major enantiomer t_R = 1.58 min; minor enantiomer t_R = 1.76 min).

$[\alpha]^{25}_D$ = –265.3 (*c* = 1.0, CHCl$_3$).

2-8av



The corresponding compound was prepared following general procedure 2-2 using (*E*)-(5-phenylpent-1-en-1-yl)boronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 100/0 to 80/20 afforded the product **2-8av** as a pale-yellow oil (88 mg, 77% yield) as a single diastereomer (dr >20:1; ~25:1). SFC analysis showed an enantiomeric excess of 95%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.34 – 7.24 (m, 2H, 2x C(8’)–H), 7.18 (m, 3H, 2x C(7’)–H, C(9’)–H), 5.82 (dt, *J* = 5.7, 1.7 Hz, 1H, C(6)–H), 5.76 (dd, *J* = 5.7, 2.3 Hz, 1H, C(5)–H), 5.49 (dtd, *J* =15.5, 6.6, 1.0 Hz, 1H, C(2’)–H), 5.35 (ddt, *J* = 15.4, 7.6, 1.4 Hz, 1H, C(1’)–H), 5.16 (dd, *J* = 5.8, 1.1 Hz, 1H, C(6a)–H), 4.42 (d, *J* = 5.7 Hz, 1H, C(3a)–H), 3.40 (d, *J* = 7.7 Hz, 1H, C(4)–H), 2.89 – 2.50 (app. t, *J* = 7.6 Hz, 1H, C(5’)–H_2), 2.04 (app. q, *J* = 7.1 Hz, 1H, C(3’)–H_2), 1.85 – 1.63 (app. p, *J* = 7.6 Hz, 1H, C(4’)–H_2), 1.43 (s, 3H, C(CH_3)$_2$), 1.34 (s, 3H, C(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 142.5 (C(6’)), 136.0 (C(5)), 131.7 (C(2’)), 131.0 (C(6)), 130.3 (C(1’)), 128.6 (C(7’)), 128.4 (C(8’)), 125.8 (C(9’)), 110.2 (C(2)), 85.2 (C(6a)), 84.2 (C(3a)), 54.6 (C(4)), 35.5 (C(5’)), 32.1 (C(3’)), 31.1 (C(4’)), 27.6 (C(CH_3)$_2$), 25.9 (C(CH_3)$_2$).

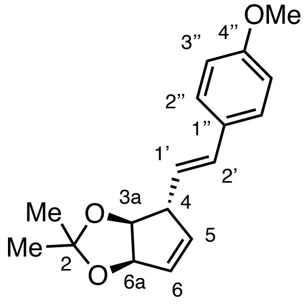
IR ($CHCl_3$ film): 2987 (w), 2927 (m), 1602 (w), 1495 (w), 1451 (w), 1372 (m), 1212 (m), 1159 (w), 1054 (s), 970 (m), 869 (m), 744 (m), 700 (m) cm^{-1}.

HRMS (APCI): m/z calcd for $C_{16}H_{19}O^+$ $[M – (CH_3)_2CO + H]^+$ 227.14304 found 227.14350.

SFC Chiralpak® ID; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 97.5:2.5 er (major enantiomer t_R = 1.78 min; minor enantiomer t_R = 2.09 min).

$[\alpha]^{25}_D$ = –167.9 (*c* = 1.0, $CHCl_3$).

2-8aw



The corresponding compound was prepared following general procedure 2-2 using (*E)*-(4-methoxy-styryl)boronic acid. The mixture was stirred at 65 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 100/0 to 70/30 afforded the product **2-8aw** as a colourless solid (73 mg, 67% yield) as a single diastereomer (dr >20:1; ~40:1). SFC analysis showed an enantiomeric excess of 91%.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.31 – 7.07 (m, 2H, 2x C(2'')–H), 6.91 – 6.73 (m, 2H, 2x C(3'')–H), 6.34 (d, *J* = 15.8 Hz, 1H, C(2')–H), 5.98 (dd, *J* = 15.9, 7.9 Hz, 1H, C(1')–H), 5.89 (dt, *J* = 5.7, 1.7 Hz, 1H, C(6)–H), 5.85 (ddt, *J* = 5.8, 2.4, 0.9 Hz, 1H, C(5)–H), 5.22 (dq, 1H, *J* = 5.7, 1.6 Hz, C(6a)–H), 4.52 (d, *J* = 5.7 Hz, 1H, C(3a)–H), 3.79 (s, 3H, C(4'')OCH_3), 3.59 (ddt, *J* = 7.9, 2.7, 1.3 Hz, 1H, C(4)–H), 1.45 (s, 3H, C(CH_3)$_2$), 1.35 (s, 3H, C(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 159.2 (C(4'')), 135.5 (C(5)), 131.7 (C(6)), 130.4 (C(2')), 129.9 (C(1'')), 127.7 (C(1')), 127.4 (2x C(2'')), 114.1 (2x C(3'')), 110.4 (C(2)), 85.2 (C(6a)), 84.1 (C(3a)), 55.4 (C(4'')OCH_3), 54.8 (C(4)), 27.6 (C(CH_3)$_2$), 25.9 (C(CH_3)$_2$).

IR ($CHCl_3$ film): 2985 (w), 2933 (w), 1607 (m), 1511 (s), 1462 (m), 1373 (m), 1293 (w), 1248 (s), 1209 (m), 1177 (m), 1044 (s), 968 (m), 869 (m), 848 (m), 809 (m), 751 (w) cm^{-1}.

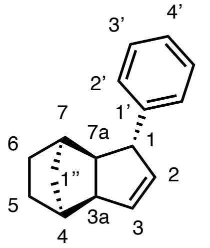
HRMS (APCI): m/z calcd for $C_{14}H_{15}O_2^+$ [M – $(CH_3)_2CO$ + H]$^+$ 215.10658 found 215.10658.

SFC Chiralpak® IA; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 95.5:4.5 er (minor enantiomer t_R = 2.55 min; minor enantiomer t_R = 2.75 min).

m.p.: 51 – 52 °C.

$[\alpha]^{25}_D$ = –273.1 (*c* = 1.0, $CHCl_3$).

2-8ba[278]



The corresponding compound was prepared following general procedure 2-1 using phenylboronic acid. The mixture was stirred at 65 °C for 14 h. Purification by flash chromatography (hexane) afforded the product **2-8ba** as a colorless oil (61 mg, 72% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 99%. The spectroscopic data are in agreement with the literature.[278]

Determination of the relative stereochemistry:

- NOE of C(1)–H with overlapping C(1'')–H_2 and C(5)–H_2/C(6)–H_2 is not unambiguous. Weak NOE between C(1)–H and C(7a)–H indicates *trans* stereochemistry between C(1)–H and C(7a)–H.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.31 – 7.23 (m, 2H, 2x C(3')–H), 7.18 – 7.09 (m, 3H, 2x C(2')–H) and C(4')–H), 5.84 – 5.73 (m, 1H, C(3)–H), 5.69 (dt, *J* = 5.6, 2.1 Hz, 1H, C(2)–H), 3.69 (p, *J* = 2.5 Hz, 1H, C(1)–H), 3.17 (dddq, *J* = 10.4, 5.2, 3.5, 1.8 Hz, 1H, C(3a)–H), 2.44 – 2.22 (m, 3H C(4)–H, C(7)–H and C(7a)–H), 1.43 (s, 2H, C(1'')–H_2), 1.41 – 1.19 (m, 4H, C(5)–H_2, C(6)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 147.8 (C(1')), 134.3 (C(2)), 134.1 (C(3)), 128.5 (2x C(3')), 127.5 (2x C(2')), 125.9 (C(4')), 54.4 (C(7a)), 52.9 (C(3a)), 51.4 (C(1)), 41.2 (C(7)), 41.1 (C(1'')), 39.3 (C(4)), 25.3, 23.0 (C(5), C(6)).

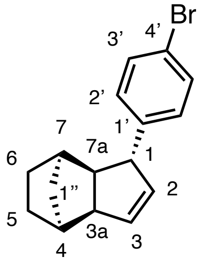
IR ($CHCl_3$ film): 2976 (s), 2949 (s), 2873 (m), 1493 (w), 1451 (w), 1385 (w), 1251 (w), 1153, 1074 (w), 955 (w), 763 (m), 745 (m), 698 (m) cm^{-1}.

HRMS (GC-MS EI): m/z calcd for $C_{18}H_{18}^+$ $[M]^+$ 210.1403 found 210.1400.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99.5:0.5 er (major enantiomer t_R = 1.84 min; minor enantiomer t_R = 2.02 min).

$[\alpha]^{25}_{D}$ = –324.1 (*c* = 1.0, $CHCl_3$).

2-8bb



The corresponding compound was prepared following general procedure 2-1 using 4-bromophenylboronic acid. The mixture was stirred at 65 °C for 14 h. Purification by flash chromatography (hexane) afforded the product **2-8bb** as a colourless oil (74 mg, 64% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 99%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.43 – 7.33 (m, 2H, 2x C(3')–H), 7.16 – 6.83 (m, 2H, 2x C(2')–H), 5.91 – 5.73 (m, 1H, C(3)–H), 5.66 (dt, *J* = 5.6, 2.2 Hz, 1H, C(2)–H), 3.66 (m, 1H, C(1)–H), 3.19 – 3.13 (m, 1H, C(3a)–H), 2.38 – 2.26 (m, 3H, C(4)–H, C(7)–H, C(7a)–H), 1.45 (s, 2H, C(1'')–H_2), 1.43 – 1.22 (m, 4H, C(5)–H_2, C(6)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 146.8 (C(1')), 134.9 (C(3)), 133.5 (C(2)), 131.5 (C(3')), 129.2 (C(2')), 119.6 (C(4')), 54.3 (C(7a)), 52.8 (C(3a)), 50.9 (C(1)), 41.2 (C(7)), 41.1 (C(1'')), 39.2 (C(4)), 25.3, 22.9 (C(5), C(6)).

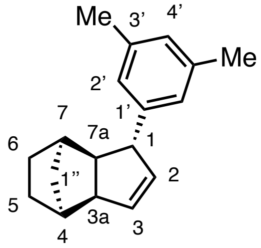
IR ($CHCl_3$ film): 3041 (w), 2948 (s), 2872 (m), 1484 (m), 1073 (w), 1010 (w), 863 (w), 845 (w), 822 (w), 800 (w), 758 (w), 654 (w) cm^{-1}.

HRMS (GC-MS EI): m/z calcd for $C_{13}H_{17}{}^{79}Br^+$ $[M]^+$ 288.0508 found 288.0512.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99.5:0.5 er (minor enantiomer t_R = 2.84 min; major enantiomer t_R = 3.64 min).

$[\alpha]^{25}_D$ = –287.0 (*c* = 1.0, $CHCl_3$).

2-8bc



The corresponding compound was prepared following general procedure 2-1* using 3,5-dimethylphenylboronic acid. The mixture was stirred at 65 °C for 14 h. Purification by flash chromatography (hexane) afforded the product **2-8bc** as a colourless oil (59 mg, 62% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of >99%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.86 (s, 1H, C(4')–H), 6.79 (s, 2H, 2x C(2')–H), 5.79 (dtd, J = 5.6, 2.0, 0.8 Hz, 1H, C(3)–H), 5.73 (dt, J = 5.6, 2.1 Hz, 1H, C(2)–H), 3.68 (p, J = 2.5 Hz, 1H, C(1)–H), 3.22 (ddq, J = 10.1, 5.1, 1.7 Hz, 1H, C(3a)–H), 2.44 – 2.34 (m, 3H, C(4)–H, C(7)–H and C(7a)–H), 2.33 (app. d, J = 0.7 Hz, 6H, 2x CH_3), 1.48 (s, 2H, C(1'')–H_2), 1.47 – 1.20 (m, 4H, C(5)–H_2, C(6)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 147.7 (C(1')), 138.0 (2x C(3')), 134.3 (C(3)), 134.1 (C(2)), 127.6 (C(4')), 125.3 (C(2')), 54.3 (C(7a)), 52.9 (C(3a)), 51.2 (C(1)), 41.2 (C(7)), 41.1 (C(1'')), 39.3 (C(4)), 25.3, 23.0 (C(5), C(6)), 21.5 (2x CH_3).

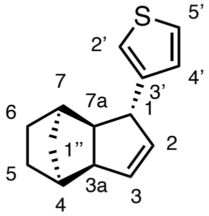
IR ($CHCl_3$ film): 3040 (w), 3014 (w), 2947 (s), 2921 (m), 2871 (m), 1603 (m), 1470 (w), 1451 (w), 851 (w), 764 (m), 700 (w) cm^{-1}.

HRMS (GC-MS EI): m/z calcd for $C_{18}H_{22}^+$ [M]$^+$ 238.1716 found 238.1722.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; >99.5:0.5 er (major enantiomer t_R = 1.46 min; minor enantiomer t_R = 1.90 min).

$[\alpha]^{25}_D$ = –298.6 (c = 1.0, $CHCl_3$).

2-8bd



The corresponding compound was prepared following general procedure 2-1 using 3-thiopheneboronic acid. The mixture was stirred at 65 °C for 14 h. Purification by flash chromatography (hexane) afforded the product **2-8bd** as a colourless solid (45 mg, 52% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of >99%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.24 (dd, *J* = 4.8, 3.0 Hz, 1H, C(5')–H), 6.95 – 6.85 (m, 2H, C(2')–H and C(4')–H), 5.73 (app. s, 2H, C(3)–H and C(2)–H), 3.82 – 3.80 (m, 1H, C(1)–H), 3.19 – 3.14 (m, 1H, C(3a)–H), 2.41 – 2.37 (m, 1H, C(7a)–H), 2.36 – 2.25 (m, 2H, C(4)–H and C(7)–H), 1.45 (s, 2H, C(1'')–H_2), 1.42 – 1.15 (m, 4H, C(5)–H_2, C(6)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 148.5 (C(1')), 134.1 (C(2)), 133.6 (C(3)), 127.5 (C(4')), 125.6 (C(5')), 118.9 (C(2')), 53.2 (C(7a)), 52.6 (C(3a)), 46.3 (C(1)), 41.1 (C(7), C(1'')), 39.3 (C(4)), 25.3, 22.9 (C(5), C(6)).

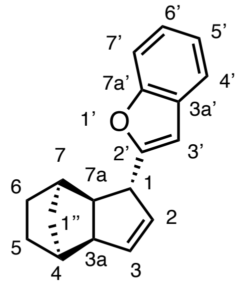
IR ($CHCl_3$ film): 3042 (w), 2947 (s), 2871 (m), 1451 (w), 842 (m), 765 (s), 679 (w), 642 (w) cm^{-1}.

HRMS (GC-MS EI): m/z calcd for $C_{14}H_{16}S^+$ $[M]^+$ 216.0967 found 216.0973.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; >99.5:0.5 er (minor enantiomer t_R = 2.47 min; major enantiomer t_R = 2.53 min).

$[\alpha]^{25}_D$ = –294.8 (*c* = 1.0, $CHCl_3$).

2-8be



The corresponding compound was prepared following general procedure 2-1 using 2-benzofuranylboronic acid. The mixture was stirred at 65 °C for 14 h. Purification by flash chromatography (hexane/CH_2Cl_2 = 100/0 to 95/5) afforded the product **2-8be** as a colourless solid (61 mg, 61% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 99%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.49 – 7.44 (m, 1H, C(4')–H), 7.42 – 7.40 (m, 1H, C(7')–H), 7.24 – 7.10 (m, 2H, C(5')–H, C(6')–H), 6.32 (s, 1H, C(3')–H) 5.84 (dtd, *J* = 5.0, 2.1, 0.7 Hz, 1H, (C(3)–H), 5.78 (dt, *J* = 5.7, 2.1 Hz, 1H, C(2)–H), 4.03 – 3.73 (m, 1H, C(1)–H), 3.23 – 3.17 (m, 1H, C(3a)–H), 2.65 (m, 1H, C(7a)–H), 2.40 – 2.38 (m, 1H, C(7)–H), 2.36 (tt, *J* = 3.5, 1.2 Hz, 1H, C(4)–H), 1.52 – 1.46 (m, 2H, C(1'')–H_2), 1.45 – 1.25 (m, 4H, C(5)–H_2, C(6)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 163.2 (C(2)), 155.0 (C(7a')), 136.1 (C(3)), 130.1 (C(2)), 129.1 (C(3a'), 123.2 (C(6')), 122.5 (C(5')), 120.4 (C(4')), 110.9 (C(7')), 100.7 (C(3')), 52.8 (C(3a)), 50.5 (C(7a)), 44.9 (C(1)), 41.1 (C(7)), 41.1 (C(1'')), 39.3 (C(4)), 25.3, 22.9 (C(5) and C(6)).

IR ($CHCl_3$ film): 3045 (w), 2949 (s), 2872 (m), 1585 (w), 1453 (s), 1253 (m), 1163 (w), 955 (w), 930 (w), 852 (w), 794 (m), 768 (m), 745 (s), 684 (w) cm^{-1}.

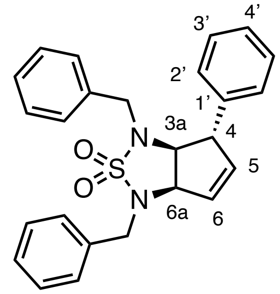
HRMS (GC-MS EI): m/z calcd for $C_{18}H_{18}O^+$ $[M]^+$ 250.1352 found 250.1361.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99.5:0.5 er (minor enantiomer t_R = 3.15 min; major enantiomer t_R = 3.64 min).

m.p.: 68 – 69 °C.

$[\alpha]^{25}_D$ = –322.4 (*c* = 1.0, $CHCl_3$).

2-8ca



The corresponding compound was prepared following general procedure 2-1 using phenylboronic acid. The mixture was stirred at 80 °C for 4 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 70/30) afforded the product **2-8ca** as a colourless solid (142 mg, 85% yield) as a single diastereomer (d.r. >20:1). SFC analysis showed an enantiomeric excess of 98%.

Determination of the relative stereochemistry:

- The dihedral angle between C(3a)–H and C(4)–H is close to 90°, therefore a small *J*-coupling is expected. The dihedral angle between C(3a)–H and C(6a)–H is close to zero, therefore a larger *J*-coupling is expected. The observed *J*-coupling between C(3a)–H and C(6a)–H is 7.9 Hz. C(4)–H (app. p, *J* = 2.3 Hz) has a significantly smaller *J*-coupling to C(3a)–H, therefore indicating the *trans* stereochemistry between C(3a)–H and C(4)–H.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.47 – 7.30 (m, 5H, 5x C_{Ar}–H), 7.28 – 7.21 (m, 5H, 5x C C_{Ar}–H), 7.19 – 7.10 (m, 3H, 3x C_{Ar}–H), 6.84 – 6.52 (m, 2H, 2x C_{Ar}–H), 5.80 (ddd, *J* = 5.8, 2.4, 1.1 Hz, 1H, C(5)–H), 5.52 (dt, *J* = 5.8, 2.1 Hz, 1H, C(6)–H), 4.51 (d, *J* = 14.7 Hz, 1H, 1x $PhCH_2$), 4.43 (d, *J* = 14.1 Hz, 1H, 1x $PhCH_2$), 4.43 – 4.40 (m, 1H, C(6a)–H), 4.23 (d, *J* = 14.0 Hz, 1H, 1x $PhCH_2$), 4.16 (d, *J* = 14.6 Hz, 1H, 1x $PhCH_2$), 3.98 (app. p, *J* = 2.3 Hz, 1H, C(4)–H), 3.78 (dd, *J* = 7.9, 2.9 Hz, 1H, C(3a)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 141.4 (C(1''), 138.1 (C(5)), 135.3, 135.3 (2x C_{quart}), 129.1, 129.0, 128.9, 128.8, 128.7, 128.4, 128.2, 128.1, 127.5, 127.2 (15x C_{Ar}–H, C(6)), 66.9 (C(6a)), 65.9 (C(3a)), 56.7 (C(4)), 50.7, 50.4 (2x $PhCH_2$).

IR ($CHCl_3$ film): 3030 (w) 2913 (w), 1495 (w), 1453 (w) 1306 (m), 1208 (w), 1159 (s), 1095 (m), 1068 (m), 1030 (w), 961 (w), 912 (w), 866 (w), 801 (w), 748 (w), 700 (s) cm^{-1}.

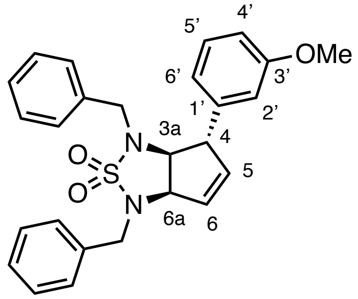
HRMS (ESI): m/z calcd for $C_{25}H_{24}O_2N_2NaS^+$ $[M + Na]^+$ 439.14507 found 439.14550.

SFC Chiralpak® IG; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99:1 er (major enantiomer t_R = 5.77 min; minor enantiomer t_R = 6.00 min).

m.p.: 96 – 97 °C.

$[\alpha]^{25}_D = -124.9$ (c = 1.0, $CHCl_3$).

2-8cb



The corresponding compound was prepared following general procedure 2-1 using 3-methoxyphenyl-boronic acid. The mixture was stirred at 80 °C for 4 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 70/30) afforded the product **2-8cb** as an off-white solid (150 mg, 84% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.46 – 7.33 (m, 5H, 5x C_{Ar}–H), 7.28 (s, 5H, 5x C_{Ar}–H), 7.12 (dd, J = 8.3, 7.6 Hz, 1H, C(5')–H), 6.72 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H, C(4')–H), 6.36 (dt, J = 7.6, 1.3 Hz, 1H, C(6')–H), 6.30 (dd, J = 2.6, 1.6 Hz, 1H, C(2')–H), 5.81 (ddd, J = 5.9, 2.4, 1.1 Hz, 1H, C(5)–H), 5.54 (dt, J = 5.8, 2.0 Hz, 1H, C(6)–H), 4.54 (d, J = 14.7 Hz, 1H, 1x $PhCH_2$), 4.45 (d, J = 14.0 Hz, 1H, 1x $PhCH_2$), 4.45 – 4.41 (m, 1H, C(6a)–H), 4.25 (d, J = 14.1 Hz, 1H, 1x $PhCH_2$), 4.19 (d, J = 14.7 Hz, 1H, 1x $PhCH_2$), 3.97 (app. p, J = 2.3 Hz, 1H, C(4)–H), 3.82 (dd, J = 7.9, 2.8 Hz, 1H, C(3a)–H), 3.72 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 159.9 (C(3’)), 142.9 (C(5)), 137.8 (C(1’)), 135.3, 135.3 (2x C_{quart}), 129.8 (C(5’)), 129.0, 128.9, 128.7, 128.3, 128.2, 128.1 (10x C_{Ar}–H, C(6)), 119.8 (C(6’’)), 113.4 (C(2’)), 112.3 (C(4’)), 66.8 (C(6a)), 65.9 (C(3a)), 56.6 (C(4)), 55.3 (CH_3), 50.7, 50.3 (2x $PhCH_2$).

IR ($CHCl_3$ film): 2914 (w), 1602 (w), 1491 (w), 1455 (w), 1307 (m), 1264 (m), 1156 (s), 104 (w), 1068, 1048 (w), 963 (w), 777 (w), 748 (m), 700 cm^{-1}.

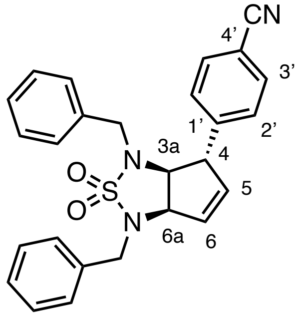
HRMS (ESI): m/z calcd for $C_{26}H_{26}O_3N_2NaS^+$ $[M + Na]^+$ 469.15563 found 469.15560.

SFC Chiralpak® IA; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99:1 er (minor enantiomer t_R = 4.61 min; major enantiomer t_R = 4.77 min).

m.p. 83 – 84 °C.

$[\alpha]^{25}_D$ = –115.3 (*c* = 1.0, $CHCl_3$).

2-8cc



The corresponding compound was prepared following general procedure 2-1 using 4-cyanophenylboronic acid. The mixture was stirred at 80 °C for 4 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 70/30) afforded the product **2-8cc** as an off-white solid (93 mg, 52% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 96%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.49 – 7.33 (m, 7H, 5x C_{Ar}–H, 2x C(3')–H), 7.32 – 7.20 (m, 5H, 5x C_{Ar}–H), 6.77 – 6.68 (m, 2H, 2x C(2')–H), 5.76 (ddd, *J* = 5.9, 2.3, 1.2 Hz, 1H, C(5)–H), 5.61 (dt, *J* = 5.9, 2.1 Hz, 1H, C(6)–H), 4.58 (d, *J* = 14.4 Hz, 1H, 1x PhC*H*$_2$), 4.46 (ddd, *J* = 8.1, 3.2, 1.9 Hz, 1H, C(6a)–H), 4.42 (d, *J* = 14.0 Hz, 1H, 1x PhC*H*$_2$), 4.28 (d, *J* = 14.0 Hz, 1H, 1x PhC*H*$_2$), 4.04 (d, *J* = 14.4 Hz, 1H, 1x PhC*H*$_2$), 4.00 (app. p, *J* = 2.4 Hz, 1H, C(4)–H), 3.72 (dd, *J* = 8.1, 3.1 Hz, 1H, C(3a)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 146.8 (C(1')), 136.9 (C(5)), 135.1, 135.0 (2x $C(Ar)_{quart}$), 132.5 (C(3')), 129.2, 129.1, 129.0, 128.9, 128.5, 128.4 (10x C(Ar)–H and C(5)), 128.2 (C(2')), 118.6 (CN), 111.1 (C(4')), 66.9 (C(6a)), 65.7 (C(3a)), 57.1 (C(4)), 51.7, 50.2 (2x $PhCH_2$).

IR ($CHCl_3$ film): 3033 (w), 2917 (w), 2227 (w), 1607 (w), 1499 (w), 1454 (w), 1308 (m), 1208 (w), 1160 (s), 1095 (w), 1068 (w), 1028 (w), 962 (w), 869 (w), 835 (w), 748 (m), 700 cm^{-1}.

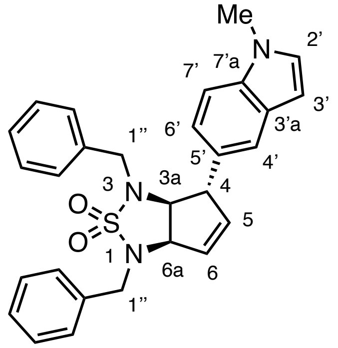
HRMS (ESI): m/z calcd for $C_{26}H_{23}O_2N_3NaS^+$ $[M + Na]^+$ 464.14032 found 464.14066.

SFC Chiralpak® IB; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 98:2 er (minor enantiomer t_R = 4.46 min; major enantiomer t_R = 4.56 min).

m.p.: 121 – 122 °C.

$[\alpha]^{25}_D$ = –162.9 (*c* = 1.0, $CHCl_3$).

2-8cd



The corresponding compound was prepared following general procedure 2-1 using (1-methyl-1*H*-indol-5-yl)boronic acid. The mixture was stirred at 80 °C for 4 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 70/30) afforded the product **2-8cd** as an off-white foam (147 mg, 78 % yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 99%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.51 – 7.35 (m, 5H, 5x C(Ar)–H), 7.34 – 7.27 (m, 5H, 5x C(Ar)–H), 7.14 (d, *J* = 8.4 Hz, 1H, C(7')–H), 7.03 (d, *J* = 3.1 Hz, 1H, C(2')–H), 6.95 (d, *J* = 1.7 Hz, 1H, C(4')–H), 6.60 (dd, *J* = 8.4, 1.7 Hz, 1H, C(6')–H), 6.35 (dd, *J* = 3.1, 0.9 Hz, 1H, C(3')–H), 5.86 (ddd, *J* = 5.9, 2.4, 1.1 Hz, 1H, C(5)–H), 5.52 (dt, *J* = 5.8, 2.0 Hz, 1H, C(6)–H), 4.59 (d, *J* = 14.8 Hz, 1H, 1x PhC*H*$_2$), 4.48 (dq, *J* = 7.8, 1.9 Hz, 1H, C(6a)–H), 4.46 (d, *J* = 13.8 Hz, 1H, 1x PhC*H*$_2$), 4.26 (d, *J* = 14.1 Hz, 1H, 1x PhC*H*$_2$), 4.18 (d, *J* = 14.8 Hz, 1H, 1x PhC*H*$_2$), 4.08 (p, *J* = 2.3 Hz, 1H, C(4)–H), 3.86 (dd, *J* = 7.9, 2.5 Hz, 1H, C(3a)–H), 3.75 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 138.7 (C(5)), 136.0, 135.7, 135.5, 132.1 (4x C_{quart}), 129.6, 129.1, 128.9, 128.8, 128.7, 128.3, 128.1, 127.4 (10x C_{Ar}–H, C(2'), C_{quart}), 121.1 (C(6')), 119.6 (C(4')), 109.5 (C(7')), 100.9 (C(3')), 67.6 (C(6a)), 66.0 (C(3a)), 56.9 (C(4)), 50.2, 50.3 (2x $PhCH_2$), 33.0 (CH_3).

IR ($CHCl_3$ film): 3031 (w), 2918 (w), 1513 (w), 1494 (w), 1455 (w), 1305 (m), 1246 (w), 1155 (s), 1094 (w), 1070 (w), 1028 (w), 963 (w), 801 (w), 749 (m), 726 (m), 699 cm^{-1}.

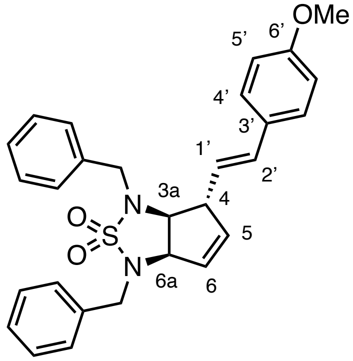
HRMS (ESI): m/z calcd for $C_{28}H_{28}O_2N_3S^+$ $[M + H]^+$ 470.18967 found 470.18955.

SFC Chiralpak® IB; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 99.5:0.5 er (major enantiomer t_R = 5.35 min; minor enantiomer t_R = 5.96 min).

m.p.: 107 – 108 °C.

$[\alpha]^{25}_D$ = –129.1 (c = 1.0, CHCl$_3$).

2-8ce



The corresponding compound was prepared following general procedure 2-2 using (*E*)-(4-methoxystyryl)boronic acid. The mixture was stirred at 80 °C for 4 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 70/30) afforded the product **2-8ce** as a brown viscous oil (138 mg, 70% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.52 – 7.28 (m, 10H, 10x C$_{Ar}$–H), 7.16 – 7.04 (m, 2H, 2x C(4')–H), 6.96 – 6.75 (m, 2H, 2x C(5')–H), 5.98 (d, J = 15.8 Hz, 1H, C(2')–H), 5.74 (ddd, J = 5.8, 2.4, 1.1 Hz, 1H, C(5)–H), 5.49 (dd, J = 15.8, 8.2 Hz, 1H, C(1')–H), 5.40 (dt, J = 5.9, 2.0 Hz, 1H, C(6)–H), 4.54 (d, J = 14.4 Hz, 1H, 1x PhCH_2), 4.44 (d, J = 14.1 Hz, 2H, 2x PhCH_2), 4.34 (dtd, J = 8.0, 1.9, 1.1 Hz, 1H, C(6a)–H), 4.22 (d, J = 14.2 Hz, 1H, 1x PhCH_2), 3.80 (s, 3H), 3.67 (dd, J = 8.0, 3.0 Hz, 1H, C(3a)–H), 3.53 (dddd, J = 8.2, 3.0, 2.1, 0.9 Hz, 1H, C(4)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 159.4 (C(6')), 137.5 (C(5)), 135.4, 135.3 (2x C_{quart}), 130.9 (C(2')), 129.5 (C(3')), 129.4, 129.1, 128.9, 128.8, 128.3 (10x C_{Ar}–H), 128.0 (C(6)), 127.5 (C(4')), 126.9 (C(1')), 114.1 (C(5')), 65.7 (C(6a)), 64.6 (C(3a)), 55.4 (CH_3), 53.7 (C(4)), 50.5, 50.5 (2x $PhCH_2$).

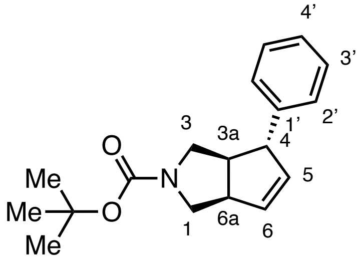
IR ($CHCl_3$ film): 3032 (w), 2910 (w), 1607 (m), 1511 (s), 1496 (w), 1456 (w), 1299 (m), 1249 (s), 1208 (w), 1158 (s), 1096 (m), 1068 (m), 1029 (m), 966 (m), 849 (w), 803 (m), 742 (m), 700 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{28}H_{29}O_3N_2S^+$ $[M + H]^+$ 473.18934 found 473.18967.

SFC Chiralpak® IB; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min; 98.5:1.5 er (major enantiomer t_R = 5.11 min; minor enantiomer t_R = 5.26 min).

$[\alpha]^{25}_D$ = –163.9 (*c* = 1.0, $CHCl_3$).

2-8da



The corresponding compound was prepared following general procedure 2-1 using phenylboronic acid. The mixture was stirred at 80 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 90/10 to 70/30) afforded the product **2-8da** as a colourless oil that solidified in the freezer (104 mg, 91% yield) as a single diastereomer (dr >20:1) containing small amounts (~2-3%) of unreacted starting material. SFC analysis showed an enantiomeric excess of >99%.

Determination of the relative stereochemistry:

- Overlapping peaks and the rotameric broadening of the peaks makes assignment of the relative stereochemistry difficult.
- High temperature (353 K) NMR in $C_6D_5CD_3$ allowed for *J* coupling analysis. The dihedral angle between C(3a)–H and C(4)–H is close to 90°, therefore a small *J*-coupling is expected. The dihedral angle between C(3a)–H and C(6a)–H is close to zero, therefore a larger *J*-coupling is expected. The observed *J*-coupling between C(3a)–H and C(6a)–H is 7.0 Hz. C(3a)–H has a significantly smaller *J*-coupling to C(4)–H (not resolved), therefore also supporting the *trans* stereochemistry between C(3a)–H and C(4)–H.

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.30 (t, *J* = 7.5 Hz, 2H, 2x C(3')–H), 7.21 (app. t, *J* = 7.3, 1.3 Hz, 1H, C(4')–H), 7.16 (dd, *J* = 8.2, 1.4 Hz, 2H, 2x C(2')–H), 5.82 (br. s, 1H, C(6)–H), 5.80 – 5.76 (br. m, 1H, C(5)–H), 3.76 – 3.64 (br. m, 2H, C(4)–H, 1x C–H_2), 3.58 – 3.23 (br. m, 4H, C(6a)–H, 3x C–H_2), 2.77 (br. s, 1H, C(3a)–H), 1.47 (s, 9H, 3x CH_3).

^{1}H NMR ($C_6D_5CD_3$, 500 MHz; 353 K; aromatic peaks due to overlap not reported): δ (ppm) 5.48 (q, *J* = 2.6 Hz, 1H, C(5)–H), 5.44 (dq, *J* = 3.6, 1.5 Hz, 1H, C(6)–H), 3.53 (dd, *J* = 9.1, 6.0 Hz, 1H, 1x C(3)–H_2), 3.42 (br. s, 1H, C(4)–H), 3.36 – 3.20 (br. m, 3H, 3x C–H_2), 3.06 – 2.95 (m, 1H, C(6a)–H), 2.43 (dtd, *J* = 8.1, 6.8 Hz, 2.5 Hz, 2.8 Hz, 1H, C(3a)–H), 1.47 (s, 9H, 3x CH_3).

^{13}C NMR (CDCl$_3$, 101 MHz) δ (ppm): 154.6 (C=O), 144.3 (C(1’)), 134.4, 134.3 (2x rot.; C(6)), 134.1, 133.9 (2x rot.; C(5)), 128.7 (2x C(3’)), 127.3 (2x C(2’)), 126.6 (C(4’)), 79.3 (*C*(CH$_3$)$_3$), 57.9 (C(4)), 52.5, 52.1 (2x rot.; CH$_2$), 51.0, 50.3 (2x rot.; C(3a)), 49.9, 49.7 (2x rot.; CH$_2$), 48.8 (C(6a)), 28.7 (3x CH$_3$).

IR (CHCl$_3$ film): 3055 (w), 2876 (w), 1694 (s), 1479 (w), 1453 (w), 1400 (m), 1365 (w), 1169 (m), 1114 (m), 1039 (w), 1027 (w), 980 (w), 772 (w), 717 (w), 700 (w) cm^{-1}.

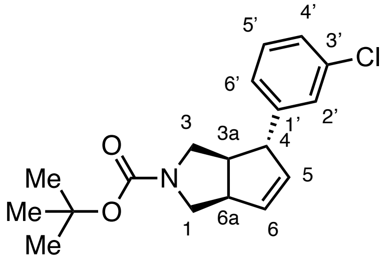
HRMS (ESI): m/z calcd for $C_{18}H_{23}O_2NNa^+$ [M + Na]$^+$ 308.1620 found 308.16238.

SFC Chiralpak® IE; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; >99.5:0.5 er (major enantiomer t_R = 2.99 min; minor enantiomer t_R = 3.12 min).

m.p.: 47 – 48 °C.

[α]^{25}$_D$ = –275.7 (*c* = 1.0, CHCl$_3$).

2-8db



The corresponding compound was prepared following general procedure 2-1 using 3-chlorophenylboronic acid. The mixture was stirred at 80 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 90/10 to 60/40) afforded the product **2-8db** as a pale-yellow oil (121 mg, 94% yield) as a single diastereomer (dr >20:1) containing small amounts (~2-3%) of unreacted starting material. SFC analysis showed an enantiomeric excess of 99%.

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.22 (app. t, *J* = 7.7 Hz, 1H, C(5')–H), 7.18 (app. dt, *J* = 8.0, 1.6 Hz, 1H, C(6')–H), 7.13 (app. t, *J* = 1.9 Hz, 1H, C(2')–H), 7.04 (dt, *J* = 7.4, 1.6 Hz, 1H, C(4')–H), 5.85 (br. s, 1H, C(6)–H), 5.75 – 5.73 (br. m, 1H, C(5)–H), 5.74 (br. ddd, *J* = 5.5, 2.6, 1.2 Hz, 1H, C(6)–H), 3.72 – 3.64 (br. m, 2H, C(4)–H, 1x C–H_2), 3.58 – 3.07 (br. m, 4H, C(6a)–H, 3x C–H_2), 2.74 (br. s, 1H, C(3a)–H), 1.46 (s, 9H, 3x CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): δ (ppm) 154.6 (C=O), 146.4 (C(1')), 135.2, 134.8 (2x rot.; C(6)), 134.6 (C(3')), 133.6, 133.2 (2x rot.; C(5)), 130.0 (C(5')), 127.4 (C(2')), 126.8 (C(6')), 125.5 (C(4')), 79.5 ($C(CH_3)_3$), 57.5 (C(4)), 52.4, 52.0 (2x rot.; CH_2), 50.9, 50.1 (2x rot.; C(3a)), 49.8, 49.6 (2x rot.; CH_2), 48.7 (C(6a)), 28.7 (3x CH_3).

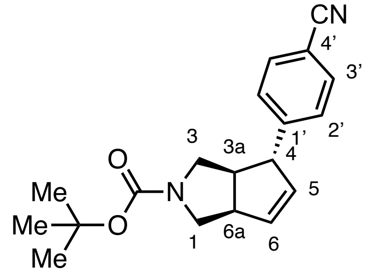
IR ($CHCl_3$ film): 2973 (w), 1693 (s), 1585 (w), 1474 (w), 1401 (s), 1247 (w), 1170 (m), 1114 (m), 880 (w), 776 (w), 694 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{18}H_{22}O_2NClNa^+$ $[M + Na]^+$ 342.12313 found 342.12326.

SFC Chiralpak® ID; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99.5:0.5 er (major enantiomer t_R = 2.44 min; minor enantiomer t_R = 2.75 min).

$[\alpha]^{25}_D$ = –255.1 (*c* = 1.0, $CHCl_3$).

2-8dc



The corresponding compound was prepared following general procedure 2-1 using 4-cyanophenylboronic acid. The mixture was stirred at 80 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 90/10 to 30/70) afforded the product **2-8dc** as a colourless oil (93 mg, 75% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.58 (d, *J* = 8.3 Hz, 2H, 2x C(3’)–H), 7.26 (d, *J* = 8.3 Hz, 2H, 2x C(2’)–H), 5.89 (br. s, 1H, C(6)–H), 5.79 – 5.65 (br. m, 1H, C(5)–H), 3.76 (br. s, 1H, C(4)–H), 3.69 (dd, *J* = 11.3, 8.7 Hz, 1H, 1x C–H_2), 3.58 – 3.23 (br. m, 4H, C(6a)–H, 3x C–H_2), 2.73 (br. s, 1H, C(3a)–H), 1.46 (s, 9H, 3x CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): δ (ppm) 154.6 (C=O), 149.8 (C(1’)), 135.8, 135.5 (2x rot.; C(6)), 133.0 (1x rot.; C(5)), 132.6 (1x rot.; C(5), 2x C(3’)), 128.1 (2x C(2’)), 119.0 (CN), 110.6 (C(4’)), 79.6 (*C*(CH_3)$_3$), 57.9 (C(4)), 52.3, 52.0 (2x rot.; CH_2), 50.8, 50.1 (2x rot.; C(3a)), 49.7 (rot.; CH_2), 48.8 (rot.; C(6a)), 28.6 (3x CH_3).

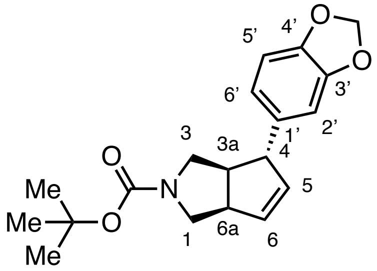
IR ($CHCl_3$ film): 2975 (w), 2227 (w), 1691 (s), 1607 (w), 1503 (w), 1478 (w), 1454 (w), 1400 (m), 1365 (m), 1250 (w), 1168 (m), 1116 (m), 884 (w), 830 (w), 771 (w), 702 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{19}H_{22}O_2N_2Na^+$ $[M + Na]^+$ 333.15735 found 333.15709.

SFC Chiralpak® IC; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 98.5:1.5 er (major enantiomer t_R = 4.64 min; minor enantiomer t_R = 4.80 min).

$[\alpha]^{25}_D$ = –343.2 (*c* = 1.0, $CHCl_3$).

2-8dd



The corresponding compound was prepared following general procedure 2-1 using benzo[*d*][1,3] dioxol-5-ylboronic acid. The mixture was stirred at 80 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 90/10 to 70/30) afforded the product **2-8dd** as a colourless oil (98 mg, 74% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 99%.

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 6.73 (d, *J* = 7.6 Hz, 1H, C(2')–H), 6.63 – 6.61 (m, 2H, C(3')–H, C(6')–H), 5.92 (s, 2H, CH_2O_2), 5.80 (br. s, 1H, C(6)–H), 5.73 (dt, *J* = 5.5, 1.7 Hz, 1H, C(5)–H), 3.77 – 3.56 (br. m, 2H, C(4)–H, 1x C–H_2), 3.55 – 3.18 (br. m, 4H, C(6a)–H, 3x C–H_2), 2.70 (br. s, 1H, C(3a)–H), 1.46 (s, 9H, 3x CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): δ (ppm) 154.6 (C=O), 148.0 (C(5')), 146.3 (C(4')), 138.3 (C(1')), 134.4, 134.1 (C(5), C(6)), 120.1 (C(2')), 108.3 (C(6')), 107.6 (C(3')), 101.0 (CH_2O_2), 79.4 (*C*(CH_3)$_3$), 57.6 (C(4)), 52.4, 52.0 (2x rot.; CH_2), 51.2, 50.4 (2x rot.; C(3a)), 50.2, 49.8 (2x rot.; CH_2), 49.6, 48.6 (2x rot.; C(6a)), 28.7 (3x CH_3).

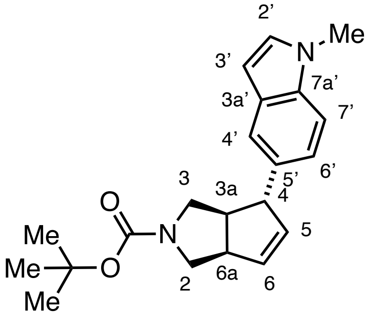
IR ($CHCl_3$ film): 2975 (w), 2880 (w), 1693 (s), 1503 (w), 1487 (m), 1441 (w), 1400 (m), 1365 (w), 1246 (m), 1170 (m), 1114 (m), 1039 (m), 937 (w), 881 (w), 802 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{19}H_{23}O_4NNa^+$ $[M + Na]^+$ 352.15193 found 352.15154.

SFC Chiralpak® IC; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99.5:0.5 er (major enantiomer t_R = 3.46 min; minor enantiomer t_R = 3.70 min).

$[\alpha]^{25}_D$ = –284.2 (*c* = 1.0, $CHCl_3$).

2-8de



The corresponding compound was prepared following general procedure 2-1 using (1-methyl-1*H*-indol-5-yl)boronic acid. The mixture was stirred at 80 °C for 4 h. Purification by flash chromatography (hexane/Et_2O = 90/10 to 30/70) afforded the product **2-8de** as a colourless oil that solidified at –20 °C (86 mg, 64% yield) as a single diastereomer (dr >20:1). SFC analysis showed an enantiomeric excess of 99%.

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.41 (d, *J* = 1.7 Hz, 1H, C(4')–H), 7.26 (d, *J* = 8.4 Hz, 1H, C(7')–H), 7.07 – 7.01 (m, 2H, C(2')–H, C(6')–H), 6.43 (dd, *J* = 3.0, 0.9 Hz, 1H, C(3')–H), 5.83 (br. s, 2H, C(6)–H, C(5)–H), 3.82 (br. s, 1H, C(4)–H), 3.78 (s, 3H, NCH_3), 3.70 (dd, *J* = 11.2, 8.7 Hz, 1H, 1x C–H_2), 3.58 – 3.23 (br. m, 4H, C(6a)–H, 3x C–H_2), 2.81 (br. s, 1H, C(3a)–H), 1.48 (s, 9H, 3x CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): δ (ppm) 154.7 (C=O), 135.8 (C(3a')), 135.2 (2x rot.; C(6), C(5')), 134.8 (1x rot.; C(6)), 133.7 (1x rot.; C(6)), 133.4 (2x rot.; C(5)), 129.3 (C(6')), 128.8 (C(3')), 121.3 (C(2')), 118.9 (C(4')), 109.4 (C(7')), 100.8 (C(7a')), 79.3 (*C*(CH_3)$_3$), 58.0 (C(4)), 52.6, 52.2 (2x rot.; CH_2), 51.6, 50.9 (2x rot.; C(3a)), 50.4, 50.0 (2x rot.; CH_2), 49.7, 48.7 (2x rot.; C(6a)), 33.0 (NCH_3), 28.7 (3x CH_3).

IR ($CHCl_3$ film): 2969 (w), 1691 (s), 1484 (w), 1401 (s), 1247 (w), 1170 (m), 1114 (m), 881 (w), 767 (w), 725 (w) cm^{-1}.

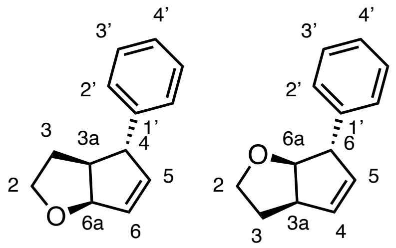
m.p.: 82 – 84 °C.

HRMS (ESI): m/z calcd for $C_{21}H_{27}O_2N_2^+$ [M + H]$^+$ 339.20670 found 339.20646.

SFC Chiralpak® IF; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min; 99.5:0.5 er (major enantiomer t_R = 4.54 min; minor enantiomer t_R = 5.23 min).

$[\alpha]^{25}_D$ = –293.7 (c = 1.0, $CHCl_3$).

2-8ea and 2-8ea*



The corresponding compound was prepared following general procedure 2-1 using phenylboronic acid. The mixture was stirred at 65 °C for 15 h. The unpurified reaction mixture showed a regioisomeric ratio of **2-8ea** (dr 4:1) and **2-8ea*** (dr 5:1) of 1.00:1.04. Purification by flash chromatography (hexane/Et_2O = 90/10 to 70/30) first afforded the product **2-8ea*** (28 mg, 37% yield) as single diastereomer (dr >20:1) and later fractions gave a mixture of **2-8ea** and the minor diastereomer of (–)-**3ea*** (ratio 1.00:0.30:0.25) (40 mg, 54% yield) as a colourless oil. SFC analysis showed an enantiomeric excess of 98% for **2-8ea*** and 99% for **2-8ea***.

Analytical data for Fraction 1 (2-8ea*)

Determination of the relative stereochemistry:

- The dihedral angle between C(6a)–H and C(6)–H is close to 90°, therefore a small *J*-coupling is expected. The dihedral angle between C(3a)–H and C(6a)–H is close to zero, therefore a larger *J*-coupling is expected. The observed *J*-coupling between C(3a)–H and C(6a)–H is 6.0 Hz. C(6)–H (s) has a significantly smaller *J*-coupling to C(6a)–H, therefore also supporting the *trans* stereochemistry between C(6a)–H and C(6)–H.

- Consequently, the minor diastereomer shows for C(6a)–H similar *J* coupling to C(3a)–H and C(6)–H (app. t, $J = 5.9$ Hz), therefore supporting the *cis* stereochemistry between C(6a)–H and C(6)–H.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.34 – 7.27 (m, 2H, 2x C(3')–H), 7.24 – 7.18 (m, 1H, C(4')–H), 7.18 – 7.11 (m, 2H, 2x C(2')–H), 5.82 (dt, $J = 4.9$, 2.3 Hz, 1H, C(5)–H), 5.76 (dt, $J = 5.7$, 1.9 Hz, 1H, C(6)–H), 4.42 (d, $J = 6.0$ Hz, 1H, C(6a)–H), 3.89 (s, 1H, C(6)–H), 3.83 (ddd, $J = 8.2$, 7.4, 3.5 Hz, 1H, 1x C(2)–H_2), 3.75 (td, $J = 8.8$, 5.8 Hz, 1H, 1x C(2)–H_2), 3.51 (ddq, $J = 8.3$, 6.1, 2.1 Hz, 1H, C(3a)–H), 2.01 (dtd, $J = 12.1$, 8.9, 7.4 Hz, 1H, 1x C(3)–H_2), 1.80 (ddt, $J = 11.9$, 5.8, 3.1 Hz, 1H, 1x C(3)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 143.0 (C(1')), 133.6 (C(5)), 133.4 (C(5)), 128.7 (2x C(3')), 127.6 (2x C(2')), 126.6 (C(4')), 90.2 (C(6a)), 67.1 (C(2)), 59.6 (C(6)), 49.9 (C(3a)), 31.2 (C(3)).

IR ($CHCl_3$ film): 3040 (w), 2936 (m), 2861 (m), 1600 (w), 1491 (w), 1450 (w), 1209 (w), 1069 (s), 1020 (w), 928 (w), 871 (w), 756 (m), 700 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{13}H_{15}O^+$ $[M + H]^+$ 187.11174 found 187.11202.

SFC Chiralpak® IC; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99:1 er (minor enantiomer $t_R = 1.72$ min; major enantiomer $t_R = 2.23$ min).

$[\alpha]^{25}_D$ = –315.8 ($c = 0.5$, $CHCl_3$).

Analytical data for Fraction 2 (2-8ea with minor diastereomers)

Determination of the relative stereochemistry:

- The dihedral angle between C(6a)–H and C(4)–H is close to 90°, therefore a small *J*-coupling is expected. The dihedral angle between C(3a)–H and C(6a)–H is close to zero, therefore a larger *J*-coupling is expected. The observed multiplicity for C(3a)–H is a ddq ($J = 8.3$, 6.1, 2.1 Hz). The *J*-coupling between C(3a)–H and C(6a)–H is 6.1 Hz. The *J* coupling between C(3a)–H and C(3)–H is 8.3 Hz. The *J* coupling between C(3a)–H and C(4)–H is significantly smaller, therefore also supporting the *trans* stereochemistry between C(3a)–H and C(4)–H.

^{1}H NMR ($CDCl_3$, 500 MHz; major diastereomer): δ (ppm) 7.33 – 7.28 (m, 2H, 2x C(3')–H), 7.25 – 7.19 (m, 1H, C(4')–H), 7.17 – 7.10 (m, 2H, C(2')–H), 5.95 (dd, *J* = 5.8, 2.3 Hz, 1H, C(5)–H), 5.87 (dt, *J* = 5.6, 2.1 Hz, 1H, C(6)–H), 5.30 (dt, *J* = 7.0, 2.2 Hz, 1H, C(6a)–H), 3.85 (ddd, *J* = 8.5, 6.9, 3.8 Hz, 1H, 1x C(2)–H_2), 3.76 – 3.63 (m, 2H, 1x C(2)–H_2, C(4)–H), 2.80 – 2.72 (m, 1H, C(3a)–H), 2.15 – 2.02 (m, 1H, 1x C(3)–H_2), 1.84 (ddt, *J* = 12.5, 5.6, 3.6 Hz, 1H, 1x C(3)–H_2).

^{13}C NMR ($CDCl_3$, 126 MHz; major diastereomer) δ (ppm) 145.0 (C(1')), 138.4 (C(5)), 131.2 (C(6)), 128.8 (2x C(3')), 127.2 (2x C(2')), 126.6 (C(4')), 88.8 (C(6a)), 66.3 (C(2)), 59.2 (C(4)), 50.5 (C(3a)), 34.6 (C(3)).

IR ($CHCl_3$ film) 3058 (w), 3026 (w), 2940 (w), 2862 (w), 1602 (w), 1492 (w), 1453 (w), 1360 (w), 1058 (m), 1031 (w), 928 (w), 906 (w), 867 (w), 770 (m), 748 (m), 700 (s) cm^{-1}.

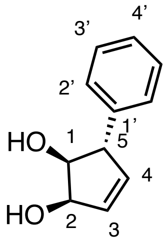
HRMS (ESI): m/z calcd for $C_{13}H_{15}O^+$ $[M + H]^+$ 187.11174 found 187.11197.

SFC Chiralpak® IC; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99.5:0.5 er (major enantiomer t_R = 1.96 min; minor enantiomer t_R = 2.02 min).

$[\alpha]^{25}_D$ = –210.8 (*c* = 0.5, $CHCl_3$).

5.2.3. Functionalisation Reactions of the Products

2-17



A solution of **2-8aa** (492 mg, 2.00 mmol) in AcOH (4.4 mL) and H_2O (1.9 mL) was stirred for 24 h at 40 °C. The reaction mixture was concentrated under reduced pressure and purification by flash chromatography (cyclohexane/EtOAc = 70/30 to 0/100) afforded the product **2-17** as a colourless solid (347 mg, 98% yield) as a single diastereomer (dr >20:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.38 – 7.29 (m, 2H, 2x C(3')–H), 7.28 – 7.22 (m, 1H, C(4')–H), 7.22 – 7.15 (m, 2H, 2x C(2')–H), 6.14 – 5.83 (m, 2H, C(3)–H and C(4)–H), 4.69 (tt, *J* = 5.8, 1.5 Hz, 1H, C(2)–H), 4.03 (dt, *J* = 7.1, 5.3 Hz, 1H, C(1)–H), 3.85 (dd, *J* = 4.9, 1.3 Hz, 1H, C(5)–H), 2.79 (d, *J* = 7.1 Hz, 1H, C(1)–OH), 2.27 (d, *J* = 6.0 Hz, 1H, C(2)–OH).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 141.8 (C(1')), 138.3 (C(4)), 132.1 (C(3)), 128.8 (2x C(3')), 127.4 (2x C(2')), 127.0 (2x C(4')), 79.9 (C(1)), 75.4 (C(2)), 57.1 (C(5)).

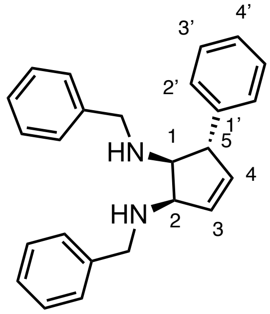
IR ($CHCl_3$ film): 3341 (br. s), 3060 (m), 2916 (m) 1600 (w), 1494 (w), 1443 (w), 1417 (w), 1318 (m), 1207 (m), 1105 (s), 1033 (m), 965 (w), 857 (w), 755 (s), 700 (s) cm^{-1}.

m.p.: 45 – 47 °C.

HRMS (ESI): m/z calcd for $C_{11}H_{12}O_2Na^+$ $[M + Na]^+$ 199.07295 found 199.07305.

$[\alpha]^{25}_D$ = –282.1 (*c* = 1.0, $CHCl_3$).

2-18



A round bottom flask equipped with a reflux condenser was charged with **2-8ca** (63 mg, 150 µmol) and Et_2O (1.8 mL). A solution of lithium aluminium hydride (4.0 M; 250 µL, 900 µmol) was added and the reaction mixture was stirred while heating to reflux for 16 h. H_2O (40 µL), an aq. sol. of NaOH (1N; 80 µL) and again H_2O (40 µL) were added subsequently. The mixture was concentrated under reduced pressure and purification by flash chromatography (EtOAc/MeOH = 98/2) afforded the product **2-18** as a pale-yellow oil (49 mg, 93% yield) as a single diastereomer (dr >20:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.37 – 7.13 (m, 15H, 15x C_{Ar}–H), 6.06 (dt, *J* = 5.9, 2.3 Hz, 1H, C(3)–H), 5.87 (ddd, *J* = 5.9, 2.0, 0.9 Hz, 1H, C(4)–H), 3.86 (d, *J* = 13.1 Hz, 1H, 1x PhC*H*$_2$), 3.80 – 3.74 (m, 2H, 1x PhC*H*$_2$, C(2)–H), 3.73 – 3.69 (m, 2H, 1x PhC*H*$_2$, C(5)–H), 3.66 (d, *J* = 13.4 Hz, 1H, 1x PhC*H*$_2$), 3.10 (app. t, *J* = 6.5 Hz, 1H, C(1)–H), 1.93 (s, 2H, 2x NH).

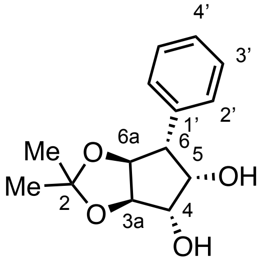
^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 143.4, 141.0, 140.7 (3x C_{quart}), 136.0 (C(4)), 133.8 (C(3)), 128.6, 128.5, 128.4, 128.1, 127.7, 127.0, 126.9, 126.6 (15x C_{Ar}–H), 68.8 (C(1)), 62.7 (C(5)), 56.8 (C(2)), 52.9 2x $PhCH_2$), 52.8 (2x $PhCH_2$).

IR ($CHCl_3$ film): 3305 (w), 3029 (w), 2915 (w), 2845 (w), 1959 (w), 1491 (w), 1452 (m), 1202 (w), 1137 (w), 1134 (w), 1081 (w), 1029 (w), 980 (w), 741 (s), 664 (s) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{25}H_{27}N_2^+$ $[M + H]^+$ 355.21688 found 355.21656.

$[\alpha]^{25}_D$ = –216.4 (*c* = 0.5, $CHCl_3$).

2-19



N-Methylmorpholine *N*-oxide (70.2 mg, 600 µmol) and $K_2OsO_6{\cdot}H_2O$ (5.9 mg, 16 µmol) were added to a solution of **2-8aa** (86.4 mg, 400 µmol) in acetone (650 µL) and H_2O (160 µL) and the mixture was stirred for 18 h at 23 °C. A sat. solution of $Na_2S_2O_3$ (2 mL) was added. After stirring the mixture for 20 min, the aqueous layer was extracted with EtOAc (3x 5 mL) and the combined organic layer was dried over $MgSO_4$. Purification by flash chromatography (hexane/EtOAc = 30/70) afforded the product **2-19** as a yellow oil (91 mg, 91% yield) with a dr of 4:1.

Determination of the relative stereochemistry:

- *Cis* stereochemistry between C(6a)–H and C(3a)–H and was set in the previous reaction step.
- *Trans* stereochemistry between C(6a)–H and C(6)–H was set in the previous reaction step.
- Strong NOE between C(4)–H and C(5)–H indicates *cis* stereochemistry between C(4)–H and C(5)–H.
- Strong NOE between C(6)–H and C(5)–H indicates *cis* stereochemistry between C(6)–H and C(5)–H.
- Very weak NOE between C(3a)–H and C(4)–H indicates *trans* stereochemistry between C(3a)–H and C(4)–H.
- For the minor diastereomer: Absence of NOE C(6)–H and C(5)–H indicates *trans* stereochemistry between C(6)–H and C(5)–H and NOE between C(3a)–H and C(4)–H indicates *cis* stereochemistry between C(3a)–H and C(4)–H

^{1}H NMR ($CDCl_3$, 500 MHz; major diastereomer): δ (ppm) 7.38 (app. d, *J* = 4.4 Hz, 4H, 2x C(3')–H, 2x C(2')–H), 7.32 – 7.25 (m, 1H, C(4')–H), 5.06 (t, *J* = 7.0 Hz, 1H, (C(6a)–H), 4.67 (dt, *J* = 7.3, 3.8 Hz, 1H, C(3a)–H), 4.40 (dt, *J* = 6.3, 3.0 Hz, 1H, C(5)–H), 4.25 (q, *J* = 4.2 Hz, 1H, C(4)–H), 3.27 (dd, $J = 6.5$, 4.0 Hz, 1H, C(6)–H), 3.01 (t, $J = 4.4$ Hz, 1H, OH), 2.45 (d, $J = 3.0$ Hz, 1H, OH), 1.54 (s, 3H, CH_3), 1.36 (s, 3H, CH_3)

^{13}C NMR ($CDCl_3$, 101 MHz; major diastereomer): δ (ppm) 137.3 (C(1’)), 128.8, 128.7 (2x C(2’), 2x C(3’)), 127.2 (C(4’)), 113.2 (C(2)), 86.1 (C(3a)), 83.2 (C(6a)), 79.2 (C(4)), 78.0 (C(5)), 54.3 (C(6)), 27.3 (CH_3), 24.7 (CH_3).

IR ($CHCl_3$ film): 3428 (br. m), 2980 (s), 1494 (w), 1457 (w), 1381 (s), 1259 (m), 1209 (m), 1155 (m), 1063 (s), 955 (m), 866 (w), 749 (w), 700 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{14}H_{18}O_4Na^+$ $[M + Na]^+$ 273.10973 found 273.10972.

$[\alpha]^{25}_D$ = –55.1 (*c* = 1.0, $CHCl_3$).

5.2.4. Mechanistic Studies

$[Rh(cod)OH]_2$ (9.2 mg, 0.020 mmol, 2.5 mol%) and (*S*)-Segphos (29.4 mg, 4.8 mmol 6.0 mol%) were added to a flame dried, septum sealed, 10 mL round bottom flask under an argon atmosphere and dissolved in THF (1.4 mL). CsOH (50 wt% aq. sol., 140 µL, 0.80 mmol, 1.00 eq) was added and the mixture was stirred while hearting at 65 °C. After 30 min the mixture was then cooled to 40 °C at heating and stirring was maintained at 40 °C. A solution of phenylboronic acid (196 mg, 1.60 mmol, 2.00 eq) and allylic chloride (±)-**2-6a** (122 µL, 0.80 mmol, 1.00 eq) in THF (1.8 mL) was added via syringe. Samples of (~50 µL) were taken *via* syringe, then diluted with hexane (1 mL), filtered, concentrated in vacuo (200 mbar, 40 ºC) and then analyzed by ^{1}H NMR spectroscopy (without internal standard), followed by SFC, followed by GC.

The conversion was determined by integration and taking the mean of the two protons C(3a)–H and C(4)–H in the starting material and the product and calculating the ratio [**2-8aa**]/([**2-6a**]+[**2-8aa**]).
(As we do not see any significant side-products derived from ***2-6a*** *during the reaction, we believe that this is a good approximation for conversion.)*

The ee of the product **2-8aa** was determined by super critical super fluid chromatography (SFC): Chiralpak® IF; 1500 psi, 30°C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; (major enantiomer t_R = 1.58 min; minor enantiomer t_R = 1.64 min).

The ee of the allylic chloride (±)-**2-6a** was determined by gas chromatography (GC):
Lipodex E column; initial temperature 60 °C, initial hold time 0 min, progress rate 1 °C/min, final temperature 190 °C; flow rate 2.8 mL/min; minor enantiomer t_R = 12.83 min; major enantiomer t_R = 13.53 min).

The *s*-factor was determined using the following formula (1) (*C*: Conversion; ee: ee of the starting material) for two data points:[89]

$$s = \frac{\ln[(1-C)(1-\mathrm{ee})]}{\ln[(1-C)(1+\mathrm{ee})]} \quad (1)$$

$$s\,(C = 0.17,\ \mathrm{ee} = 0.14) \approx 6.09 \quad (2)$$

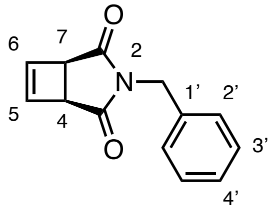
$$s\,(C = 0.46,\ \mathrm{ee} = 0.49) \approx 5.93 \quad (3)$$

5.3. Procedures for Chapter 3

5.3.1. Synthesis of the Starting Materials

3-oxabicyclo[3.2.0]hept-6-ene-2,4-dione was prepared according to a modified procedure using a 400 W medium-pressure Hg lamp and benzophenone (10 mol%) as photosensitizer[204] and bicyclo[3.2.0]hept-6-en-3-one was prepared according to a literature procedure[279].

3-2



A 500 mL photochemical reactor equipped with a quartz immersion well was charged with *N*-benzyl maleimide (7.48 g, 40.0 mmol), benzophenone (729 mg, 4.0 mmol) and acetonitrile (400 mL). The mixture was degassed with argon before *trans*-dichloroethylene (7.7 mL, 100 mmol) was added. The mixture was irradiated (400 W, medium-pressure Hg lamp) under cooling of the immersion well with a water flow for 20 h. The solvents were removed under reduced pressure and a crude yellow solid was obtained. ^{1}H NMR spectroscopy of the mixture showed >95% conversion and the solid was used in the next step without any purification.

Toluene (125 mL) and Ac_2O (48 mL) were added to the crude product from the previous step. Activated zinc powder (65.4 g, 1.00 mol) was added and the mixture was stirred at 85 °C under an argon atmosphere. After 3 days, the reaction mixture was cooled to room temperature, filtered over Celite® and the solvents were removed *in vacuo*. Purification by automated medium-pressure liquid chromatography (hexane:EtOAc 90:10 to 30:70) followed by trituration with hexane/Et_2O afforded **3-2** (4.95 g, 58% over two steps) as a colourless to pale-yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.40 – 7.22 (m, 5H; 5x C_{Ar}–H), 6.44 (d, J = 0.7 Hz, 2H; C(5)–H, C(6)–H), 4.62 (s, 2H; CH_2Ph), 3.81 (d, J = 0.8 Hz, 2H; C(4)–H and C(7)–H).

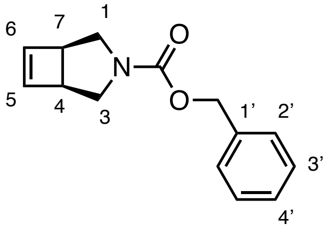
^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 174.3 (2x C=O), 139.5 (C(5), C(6)), 135.9 (C(1')), 128.8 (2x C(2')/C(3')), 128.7 (2x C(2')/C(3')), 128.0 (C(4')), 47.8 (C(4), C(7)), 42.4 (CH_2Ph).

IR ($CHCl_3$ film): 2980 (w), 1768 (w), 1694 (s), 1496 (w), 1455 (w), 1428 (w), 1387 (m), 1341 (m), 1312 (w), 1250 (w), 1154 (m), 936 (w), 890 (w), 832 (w), 754 (w), 697 (m), 652 (w), 611 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{13}H_{12}O_2N^+$ $[M + H]^+$ 214.0863 found 214.0866.

m.p.: 108 – 109 ºC.

3-3



A solution of $LiAlH_4$ (1.0 M in Et_2O; 37.5 mL, 37.5 mmol) was added slowly to a stirred solution of **3-2** (2.00 g, 9.38 mmol) in CH_2Cl_2 (85 mL) cooled in an ice water bath to 0 ºC under an argon atmosphere. The reaction mixture was then allowed to reach room temperature (23 °C) and was stirred for 16 h. H_2O (1.7 mL), aq. NaOH sol. (15%, 1.7 mL) and H_2O (4.9 mL) followed by $MgSO_4$ were added subsequently at 0 ºC. The mixture was filtered over a short plug of silica and rinsed with copious amounts of EtOAc. The solvents were removed under reduced pressure and a crude colourless to pale-yellow oil was obtained which was used in the next step without any purification.

Toluene (40 mL) and CbzCl (1.7 mL, 11 mmol) were added to the crude product from the previous step and the mixture was stirred at 80 °C. After 1 h, additional CbzCl (1.1 mL, 7.5 mmol) was added and heating was maintained for an additional 30 min. The solvents were removed under reduced pressure and purification by automated medium-pressure liquid chromatography (hexane:EtOAc 90:10 to 30:70) afforded **3-3** (1.80 g, 84% over two steps) as a colourless oil.

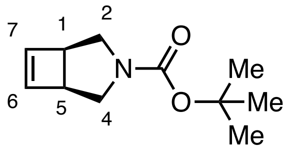
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.41 – 7.32 (m, 4H; 4x C_{Ar}–H), 7.33 – 7.27 (m, 1H; C(4')–H), 6.01 (d, *J* = 8.1 Hz, 1H; C(5)–H, C(6)–H), 5.14 (d, *J* = 3.6 Hz, 2H; CH_2Ph), 3.77 (dd, *J* = 26.1, 11.8 Hz, 2H; 2x CH_2N), 3.34 (d, *J* = 6.3 Hz, 2H; C(4)–H, C(7)–H), 3.11 – 2.62 (m, 2H; 2x CH_2N).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 156.7 (C=O), 139.2, 138.7 (rot. C(5), C(6)), 137.2 (C(1')), 128.6 (2x C(3')), 127.98 (C(4')), 127.89 (2x C(2')), 66.8 (CH_2Ph), 47.1, 46.8, 46.7, 46.2 (rot.; C(1), C(3), C(4) and C(7)).

IR ($CHCl_3$ film): 3036 (w), 2952 (w), 2866 (w), 1696 (s), 1479 (w), 1419 (s), 1358 (m), 1323 (m), 1265 (w), 1223 (s), 1152 (m), 1101 (s), 1075 (m), 1028 (w), 1007 (w), 965 (w), 915 (w), 881 (w), 835 (w), 765 (s), 735 (m), 696 (s) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{14}H_{15}O_2NNa^+$ $[M + Na]^+$ 252.09950 found 252.09955.

3-6a



A solution of HBr (33 wt% in AcOH, 2.5 mL) was added slowly to **3-3** (229 mg, 1.00 mmol) at room temperature (23 °C) under an open atmosphere. The reaction mixture was then stirred for 1 h. The solvents were removed under reduced pressure, and the residue was co-distilled with EtOAc (3x 5 mL). A crude beige solid was obtained which was used in the next step without any purification.

Dioxane was added (8.0 mL) and the mixture was cooled to 0 °C. Aq. KOH (1.0 M, 5.0 mL, 5.0 mmol) was added slowly, followed by Boc_2O (327 mg, 1.50 mmol) under an argon atmosphere. The reaction mixture was allowed to reach room temperature (23 °C) and stirring was continued for 18 h. H_2O (10 mL) and Et_2O (20 mL) were added, the organic layer was separated, and the aqueous layer was extracted with Et_2O (2x 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO4, and the solvents were removed under reduced pressure. Purification by automated medium-pressure liquid chromatography (hexane:EtOAc 10:0 to 0:10) afforded **3-6a** (123 mg, 63% over two steps) as a colourless oil.

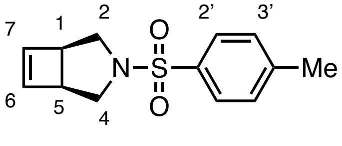
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.01 (s, 2H, C(6)–H, C(7)–H), 3.82 – 3.43 (rot. m, 2H; 1x C(2)–H_2, 1x C(4)–H_2), 3.31 (d, J = 6.0 Hz, 2H; C(1)–H, C(5)–H), 2.90 (dd, J = 12.0, 6.5 Hz, 2H, 1x C(2)–H_2, 1x C(4)–H_2), 1.45 (s, 9H; $C(CH_3)_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 156.5 (C=O), 139.2, 138.8 (rot.; C(6), C(7)), 79.2 ($C(CH_3)_3$), 47.1, 47.0, 46.3 (rot.; C(1), C(2), C(4), C(5)), 28.7 ($C(CH_3)_3$).

IR ($CHCl_3$ film): 3043 (w), 2949 (w), 2860 (w), 1693 (s), 1471 (s), 1365 (m), 1264 (m), 1223 (m), 1175 (s), 1152 (s), 883 (w), 781 (w), 758 (m), 704 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{11}H_{17}O_2NNa^+$ $[M + Na]^+$ 218.1152 found 218.1153.

3-6b



A solution of HBr (33 wt% in AcOH, 2.5 mL) was added slowly to **4-3** (229 mg, 1.00 mmol) at room temperature (23 °C) under an open atmosphere. The reaction mixture was then stirred for 1 h. The solvents were removed under reduced pressure, and the residue was co-distilled with

EtOAc (3x 5 mL). A crude beige solid was obtained which was used in the next step without any purification.

CH_2Cl_2 (10 mL) and NEt_3 (0.68 mL, 5.0 mmol) were added to the crude product from the previous step under an argon atmosphere. The mixture was cooled to 0 °C and TsCl (285 mg, 1.50 mmol) was added. The reaction mixture was allowed to reach room temperature (23 °C) and stirring was continued for 2 h. The solvents were removed under reduced pressure and purification by automated medium-pressure liquid chromatography (hexane:EtOAc 10:0 to 70:30) afforded **3-6b** (178 mg, 71% over two steps) as a colourless solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.72 – 7.61 (m, 2H; 2x C(2')–H), 7.35 – 7.27 (m, 2H; 2x C(3')–H), 5.97 (s, 2H; C(6)–H, C(7)–H), 3.49 (d, *J* = 10.5 Hz, 2H; 1x C(2)–H_2, 1x C(4)–H_2), 3.30 – 3.23 (m, 2H; C(1)–H, C(5)–H), 2.46 (ddd, *J* = 10.2, 4.9, 1.2 Hz, 2H; 1x C(2)–H_2, 1x C(4)–H_2), 2.43 (s, 3H; CH_3).

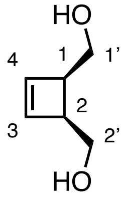
^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 143.5 (C(1')), 137.9 (C(6), C(7)), 133.4 (C(4')), 129.6 (2x C(3')), 128.0 (2x C(2')), 48.5 (C(2), C(4)), 46.7 (C(1), C(5)), 21.7 (CH_3).

IR (solid): 2925 (w), 2853 (w), 1595 (m), 1508 (w), 1458 (w), 1343 (s), 1323 (m), 1303 (m), 1275 (s), 1205 (m), 1162 (s), 1124 (s), 1083 (m), 1055 (m), 1022 (m), 1010 (m), 911 (w), 834 (w), 816 (m), 748 (m), 708 (w), 661 (s) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{13}H_{15}O_2NNaS^+$ $[M + Na]^+$ 272.0716 found 272.0715.

m.p.: 132 – 133 °C.

3-S1[221]

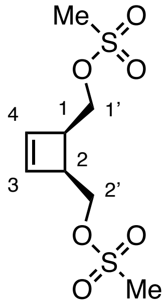


A solution of *cis*-cyclobut-3-ene-1,2-dicarboxylic anhydride (3.10 g, 25.0 mmol) in dry THF (10 mL) was added dropwise to a stirred mixture of $LiAlH_4$ (2.4 M in THF; 11.0 mL, 26.4 mmol) and dry THF (70 mL) at 0 °C under an argon atmosphere. After 30 min, the reaction mixture was allowed to reach room temperature (23 °C) and stirring was continued for 16 h. The reaction was cooled to 0 °C, and H_2O (1.0 mL), aq. NaOH sol. (15%, 1.0 mL) and H_2O (3.1 mL) were added slowly. The precipitate was filtrated off and washed with THF (25 mL). The residue was suspended in THF (50 mL), stirred for 2 h at 50 °C, and then filtered. The combined filtrates were concentrated under reduced pressure. Purification by automated medium pressure liquid chromatography (hexane/EtOAc = 100/0 to 30/70) afforded **3-S1** as a pale-yellow oil (1.95 g, 69%). The analytical data are in agreement with the literature.[221]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.04 (s, 2H; C(3)–H, C(4)–H), 3.84 (dd, J = 11.5, 3.8 Hz, 1H; C(1')–H_2, C(2')–H_2), 3.72 (t, J = 11.1 Hz, 2H; C(1')–H_2, C(2')–H_2), 3.41 – 2.97 (m, 4H; 2 OH, C(1)–H, C(2)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 137.5 (C(3), C(4)), 62.1 (C(1'), C(2')), 48.3 (C(1), C(2)).

3-S2[210]

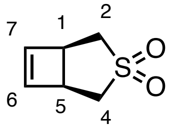


Triethylamine (1.5 mL, 10.5 mmol) was added slowly to a mixture of **3-S1** (571 mg, 5.00 mmol) in CH_2Cl_2 (25 mL) and mesityl chloride (0.79 mL, 10.3 mmol) at –5 °C under an argon atmosphere. After 10 min, the reaction mixture was allowed to reach room temperature (23 °C) and stirring was continued for 1 h. Aq. HCl (15 mL) was added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (2x 25 mL), and the combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. Purification by automated medium-pressure liquid chromatography (hexane/EtOAc = 70/30 to 30/70) afforded **3-S2** as a pale-yellow solid (1.21 g, 90%). The analytical data are in agreement with the literature.[210]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.17 (s, 2H; C(3)–H, C(4)–H), 4.65 – 4.05 (m, 4H; 2x C(1')–*H*$_2$, 2x C(2')–*H*$_2$), 3.42 (ddt, *J* = 6.4, 4.6, 2.1 Hz, 2H; C(1)–H, C(2)–H), 3.04 (s, 6H; 2x CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 137.6 (C(3), C(4)), 68.7 (C(1'), C(2')), 44.6 (C(1), C(2)), 37.6 (2x CH_3).

3-6c



A mixture of **3-S2** (810 mg, 3.00 mmol) and Na_2S·9 H_2O (936 mg, 3.90 mmol) in EtOH (4.2 mL) and H_2O (1.8 mL) was stirred under reflux for 15 h. H_2O (10 mL) and Et_2O (10 mL) were added, and the organic layer was separated. The aqueous layer was extracted with Et_2O (2x 10 mL), and the combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. The mixture was concentrated at 30 °C to an approximate volume of ~5 mL. MeOH (7.5 mL) and H_2O (7.5 mL) were added, followed by addition of Oxone® (2.29 mg, 9.0 mmol) at –5 °C. The mixture was stirred for 4 h while maintaining the temperature below 5 °C. H_2O (20 mL) and CH_2Cl_2 (30 mL) were added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2x 300 mL), and the combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Purification by automated medium-pressure liquid chromatography (hexane/EtOAc = 100/0 to 0/100) afforded **3-6c** as a colourless solid (259 mg, 60%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.22 (s, 2H; C(6)–H, C(7)–H), 3.98 – 3.54 (m, 2H; C(1)–

H, C(5)–H), 3.34 – 3.09 (m, 2H; C(2)–H_2, C(4)–H_2), 3.00 (ddd, *J* = 13.6, 2.9, 1.1 Hz, 2H; C(2)–H_2, C(4)–H_2).

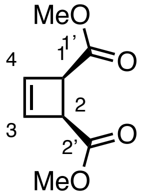
^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 139.7 (C(6), C(7)), 52.5 (C(2), C(4)), 41.6 (C(1), C(5)).

IR (CHCl$_3$ film): 3053 (w), 2997 (w), 2943 (w), 1407 (w), 1294 (s), 1226 (m), 1139 (s), 1122 (s), 984 (w), 808 (w), 750 (m), 726 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_6H_8O_2SNa^+$ $[M + Na]^+$ 167.0137 found 167.0139.

m.p.: 69 – 79 °C.

3-9[210]



Conc. sulfuric acid (0.05 mL) was added to a mixture of *cis*-cyclobut-3-ene-1,2-dicarboxylic anhydride (774 mg, 6.24 mmol) in MeOH (15 mL) at room temperature (23 °C) under an open atmosphere. After stirring the reaction mixture for 15 h at 50 °C, CH$_2$Cl$_2$ (40 mL) was added. The mixture was washed with brine (2x 10 mL) and dried over MgSO$_4$. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 50/50) afforded the product **3-9** as a yellow oil (684 mg, 65% yield). The analytical data are in agreement with the literature.[210]

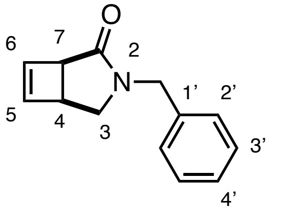
^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 6.26 (s, 2H; C(3)–H, C(4)–H), 3.93 (s, 2H; C(1)–H, C(2)–H), 3.69 (s, 6H; 2x C(6)–H$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 171.3 (2x C=O), 136.8 (C(3), C(4)), 52.1 (2x OCH$_3$), 49.1 (C(1), C(2)).

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}.

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

(±)-3-11



A solution of DIBAL–H (1 M in CH_2Cl_2; 4.0 mL, 4.0 mmol) was added dropwise to a solution of **3-2** (426 mg, 2.0 mmol) in CH_2Cl_2 (16 mL) at –78 °C under an argon atmosphere. After stirring the reaction mixture for 90 min, aq. 0.5 M HCl (20 mL) and CH_2Cl_2 (10 mL) were added and the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2x 20 mL). The combined organic layers were washed with an aq. sat. solution of $NaHCO_3$ (20 mL) and brine (20 mL) and dried over $MgSO_4$. A crude colourless solid was obtained which was used in the next step without any purification.

The crude product was suspended in CH_2Cl_2 (15 mL) and cooled to –78 °C under an argon atmosphere. Et_3SiH (3.2 mL, 20 mmol) was added followed by dropwise addition of $BF_3{\cdot}Et_2O$ (0.74 mL, 6.0 mmol). The reaction was slowly allowed to reach room temperature over night and was stirred for 20 h. H_2O (20 mL) and CH_2Cl_2 (20 mL) were added, and the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 0/100) afforded the product (±)-**3-11** as a yellow oil (289 mg, 72% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.35 – 7.24 (m, 3H; 2x C(3')–H, C(4')–H), 7.24 – 7.17 (m, 2H: 2x C(2')–H), 6.41 (d, $J = 2.6$ Hz, 1H; C(6)–H), 6.24 (d, $J = 2.6$ Hz, 1H; C(5)–H), 4.48 (d, $J =$

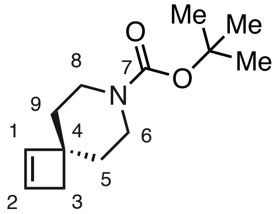
14.8 Hz, 1H; CH$_2$Ph), 4.37 (d, *J* = 14.8 Hz, 1H; CH$_2$Ph), 3.63 (ddt, *J* = 2.9, 2.1, 1.0 Hz, 1H; C(7)–H), 3.37 – 3.21 (m, 2H; C(4)–H, C(3)–H), 3.18 – 3.04 (m, 1H; C(3)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 173.6 (C=O), 141.1 (C(5)), 140.7 (C(6)), 136.5 (C(1’)), 128.8 (2x C(3’)), 128.1 (2x C(2’)), 127.6 (C(4’)), 50.4 (C(7)), 46.99, 46.95 (C(3) and CH$_2$Ph), 37.6 (C(4)).

IR (CHCl$_3$ film): 3051 (w), 2959 (w), 2915 (w), 1695 (s), 1486 (w), 1429 (m), 1281 (m), 1258 (w), 805 (w), 771 (w), 739 (m), 695 (s), 643 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{13}H_{14}ON^+$ $[M + H]^+$ 200.1070 found 200.1071.

3-14



(Experiment performed by L. van Dijk)

NaBH$_4$ (0.567 g, 15.0 mmol) was added in small portions to a solution of *tert*-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (3.00 g, 12.5 mmol) in MeOH (30 mL) at 0 °C under an open atmosphere. The reaction mixture was allowed to reach room temperature (23 °C) and stirred at that temperature for 2.5 h. The solvent was removed under reduced pressure to an approximate volume of ~5 mL. EtOAc (30 mL) and aq. NH$_4$Cl sol. (10 mL) were added. The layers were separated, and the aqueous layer extracted with EtOAc (2x 20 mL). The combined organic layers were washed with brine (50 mL) and dried over MgSO$_4$. The solvent was removed under reduced pressure and a crude colourless solid was obtained which was used in the next step without further purification.

This crude solid product was dissolved in pyridine (18 mL) and *p*-toluenesulfonyl chloride (2.62 g, 13.8 mmol) was added at 0 °C under an argon atmosphere. The reaction mixture was allowed to reach room temperature (23 °C) and stirred at this temperature. After 20 h, EtOAc (20 mL) followed by aq. 1 M HCl (20 mL) were added to reaction mixture at 0 °C. The layers were separated, and the organic layer was again washed with aq. 1 M HCl (20 mL), followed by brine (20 mL) and then dried over $MgSO_4$. The solvents were removed under reduced pressure. The crude oil was then dissolved in toluene (5 mL) and the solvents were again removed under reduced pressure. A crude colourless solid was obtained which was used in the next step without further purification.

DMSO (90 mL) was added to a mixture of potassium *tert*-butoxide (1.95 g, 17.4 mmol) and the crude product from the previous step at 0 °C under an argon atmosphere. The reaction was allowed to reach room temperature (23 °C) and stirring was continued for 16 h. EtOAc (180 mL) was added followed by brine (120 mL) at 0 °C. The layers were separated, and the aqueous layer extracted with EtOAc (2x 120 mL). The combined organic layers were washed with brine (200 mL) and dried over $MgSO_4$. Purification by automated medium-pressure liquid chromatography (hexane:EtOAc = 100/0 to 80/20) afforded **3-14** (1.90 g, 68% over 3 steps) as a colourless oil.

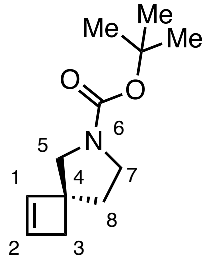
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.22 (d, J = 2.9 Hz, 1H; C(1)–H), 6.12 (dd, J = 2.6, 1.3 Hz, 1H; C(2)–H), 3.62 – 3.48 (m, 2H; 1x C(6)–H_2, 1x C(8)–H_2), 3.30 – 3.16 (m, 2H; 1x C(6)–H_2, 1x C(8)–H_2), 2.26 (d, J = 0.9 Hz, 2H; C(3)–H_2), 1.64 – 1.52 (m, 4H; C(9)–H_2, C(5)–H_2), 1.43 (s, 9H; $C(CH_3)_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.1 (C=O), 143.4 (C(1)), 134.3 (C(2)), 79.3 ($\mathit{C}(CH_3)_3$), 47.6 (C(4)), 42.4 (C(6), C(8)), 41.6 (C(3)), 35.4 (C(5), C(9)), 28.5 ($C(\mathit{C}H_3)_3$).

IR ($CHCl_3$ film): 3046 (w), 2976 (w), 2915 (w), 2842 (w), 1694 (s), 1457 (m), 1417 (s), 1365 (m), 1275 (m) 1244 (m), 1173 (m), 1131 (s), 1012 (w), 973 (w), 864 (w), 711 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{13}H_{21}NO_2Na^+$ $[M + Na]^+$ 246.1465 found 246.1465.

(±)-3-16



(Experiment performed by L. van Dijk)

$NaBH_4$ (0.151 g, 4.00 mmol) was added in small portions to a solution of *tert*-butyl 2-oxo-6 azaspiro[3.4]octane-6-carboxylate (0.750 g, 3.33 mmol) in MeOH (8 mL) at 0 °C under an open atmosphere. The reaction mixture was allowed to reach room temperature (23 °C) and stirred at that temperature for 2.5 h. The solvent was removed under reduced pressure to an approximate volume of ~1 mL. EtOAc (8 mL) and aq. NH_4Cl sol. (2.5 mL) were added. The layers were separated, and the aqueous layer extracted with EtOAc (2x 5 mL). The combined organic layers were washed with brine (5mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and a crude colourless solid was obtained which was used in the next step without further purification.

This crude solid product was dissolved in pyridine (4.8 mL) and *p*-toluenesulfonyl chloride (0.69 g, 3.6 mmol) was added at 0 °C under an argon atmosphere. The reaction mixture was allowed to reach room temperature (23 °C) and stirred at this temperature. After 20 h, EtOAc (5 mL) followed by aq. 1 M HCl (5 mL) were added to reaction mixture at 0 °C. The layers were separated, and the organic layer was again washed with aq. 1 M HCl (5 mL), followed by brine (5 mL) and then dried over $MgSO_4$. The solvents were removed under reduced pressure. The crude oil was then dissolved in toluene (1 mL) and the solvents were again removed under reduced pressure. A crude colourless solid was obtained which was used in the next step without further purification.

DMSO (25 mL) was added to a mixture of potassium *tert*-butoxide (0.56 g, 4.95 mmol) and the crude product from the previous step at 0 °C under an argon atmosphere. The reaction was allowed to reach room temperature (23 °C) and stirring was continued for 16 h. EtOAc (50 mL) was added followed by brine (30 mL) at 0 °C. The layers were separated, and the aqueous layer extracted with EtOAc (2x 30 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. Purification by automated medium-pressure liquid chromatography (hexane:EtOAc = 100/0 to 80/20) afforded (±)-**3-16** (0.27 g, 39% over 3 steps) as a colourless oil.

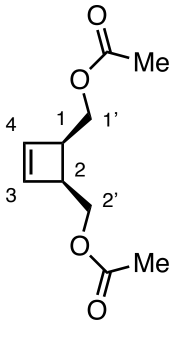
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.13 (dt, *J* = 2.8, 1.0 Hz, 1H; C(2)–H), 6.04 (d, *J* = 2.8 Hz, 1H; C(1)–H), 3.52 – 3.29 (m, 4H; C(5)–H_2, C(7)–H_2), 2.50 (dt, *J* = 13.1, 0.9 Hz, 1H; C(3)–H), 2.41 (dt, *J* = 13.2, 0.9 Hz, 1H; C(3)–H), 2.03 – 1.83 (m, 2H; C(8)–H_2), 1.46 (s, 9H; $C(CH_3)_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm): 154.8 (C=O), 139.4 (C(1)), 135.7 (C(2)), 79.2 (*C*$(CH_3)_3$), 53.7 (C(5)), 53.3 (C(4)), 45.1 (C(7)), 43.4 (C(3)), 34.9 (C(8)), 28.7 (C(*C*$H_3)_3$).

IR ($CHCl_3$ film): 3050 (w), 2973 (w), 2921 (w), 2866 (w), 1696 (s), 1476 (w), 1400 (s), 1365 (m), 1255 (w), 1164 (m), 1101 (m), 974 (w), 934 (w), 879 (w), 772 (w), 715 (w) cm^{-1}.

HRMS: m/z calcd for $C_{12}H_{19}NO_2Na^+$ $[M + Na]^+$ 232.1309 found 232.1308.

3-18[220]



(Experiment performed by A. M. L. Hell)

A mixture of **3-S1** (1.14 g, 10.0 mmol), acetic anhydride (2.8 mL, 30 mmol) and pyridine (3.2 mL, 40 mmol) was stirred at room temperature (23 °C) for 16 h under an argon atmosphere. Then, the reaction was diluted with 2-propanol/CH_2Cl_2 (3/7; 5 mL), followed by addition of saturated aqueous $NaHCO_3$ solution (~5 mL; pH 6-7). The organic layer was separated, and the aqueous layer was extracted with 2-propanol/CH_2Cl_2 (3/7; 2x 20 mL). The combined organic layers were washed with aq. 1 M HCl (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by automated medium-pressure liquid chromatography (hexane/Et_2O = 100/0 to 40/60) afforded **3-18** (1.41 g, 71%) as a colourless oil. The analytical data are in agreement with the literature.[220]

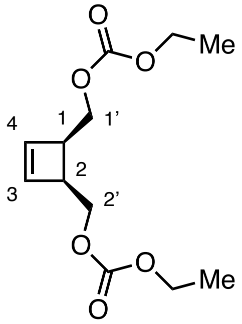
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.12 (s, 2H; C(3)–H, C(4)–H), 4.24 – 4.18 (m, 4H; C(1')–H_2, C(2')–H_2), 3.30 – 3.21 (m, 2H; C(1)–H, C(2)–H), 2.05 (s, 6H; 2x CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.1 (2x C=O), 138.0 (C(3), C(4)), 64.1 (C(1'), C(2')), 44.5 (C(1), C(2)), 21.1 (2x CH_3).

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

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

3-21a



Pyridine (0.48 mL, 6.0 mmol), followed by ethyl chloroformate (0.43 mL, 4.5 mmol) was added to a solution of **3-S1** (171 mg, 1.50 mmol) in anhydrous Et_2O (10 mL) at 0 °C under an argon atmosphere. After stirring for 15 min at 0 °C, the reaction mixture was allowed to reach room temperature (23 °C) and stirring was continued for 16 h. Et_2O (20 mL) was added, and the mixture washed with aq. 1 M HCl (2x 5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, and the solvents were removed under reduced pressure. Purification by automated medium-pressure liquid chromatography (hexane/EtOAc = 100/0 to 70/30) afforded **3-21a** (333 mg, 86%) as a colourless oil.

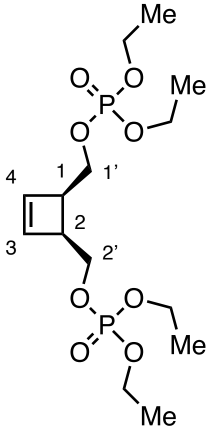
^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 6.15 (s, 2H; C(3)–H, C(4)–H), 4.33 – 4.23 (m, 4H; C(1')–H$_2$, C(2')–H$_2$), 4.19 (q, J = 7.1 Hz, 4H; 2x CH_2CH$_3$), 3.35 – 3.27 (m, 2H; C(1)–H, C(2)–H), 1.31 (t, J = 7.1 Hz, 6H; 2x CH$_2$CH_3).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 155.2 (2x C=O), 138.0 (C(3), C(4)), 67.3 (C(1'), C(2')), 64.2 (2x CH$_2$CH$_3$)), 44.4 (C(1), C(2)), 14.4 (2x CH$_2$$CH_3$).

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}.

HRMS (ESI): m/z calcd for C$_{12}$H$_{18}$O$_6$Na$^+$ [M + Na]$^+$ 281.0996 found 281.0997.

3-21b



(Experiment performed by A. M. L. Hell)

A solution of *n*-BuLi (2.5 M in hexane; 2.0 mL, 5.0 mmol) was added dropwise to a solution of **3-S1** (228 mg, 2.0 mmol) and tetramethylethylenediamine (3.0 mL) in anhydrous THF (12 mL) at –40 °C (MeCN/dry ice) under an argon atmosphere. After stirring the mixture for 10 min, diethyl chlorophosphate (0.87 mL, 6.0 mmol) was added dropwise to the mixture and stirring was continued for 2 h. The reaction mixture was then allowed to reach room temperature (23 °C), and brine (~2 mL) and H$_2$O (10 mL) were added slowly. The mixture was extracted with CH$_2$Cl$_2$ (3x 15 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. Purification by automated medium-pressure liquid chromatography (EtOAc/MeOH =100/0 to 97/3) afforded **3-21b** (458 mg, 59 %) 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; C(1')–H_2, C(2')–H_2), 4.14 – 4.06 (m, 8H; 4x CH_2CH_3), 3.36 – 3.27 (m, 2H; C(1)–H, C(2)–H), 1.34 (t, *J* = 7.1 Hz, 12H; 4x CH_2CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 138.7 (C(3), C(4)), 67.3 (C(1'), C(2')), 63.9 (2x CH_2CH_3), 45.5 (C(1), C(2)), 16.3 (4x CH_2CH_3).

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

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}.

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

5.3.2. Rhodium–Catalysed Cyclobutene Arylation Reactions

Boronic acid were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics, Fluorochem, and Tokyo Chemical Industry and were used without further purification.

All reactions were carried out under an inert argon atmosphere using standard Schlenk techniques with all reagents weighed open to air.

General Procedure 3-1

A stock solution of the rhodium hydroxy phosphine complex was prepared by stirring a solution of $[Rh(cod)OH]_2$ (20.5 mg, 0.045 mmol, 2.5 mol%) and (*S*)-Segphos (65.9 mg, 0.108 mmol, 6.0 mol%) in dry dioxane (9.0 mL) under an argon atmosphere at 60 °C for 30 min. When the addition reaction was performed at room temperature (23 °C), the rhodium hydroxy phosphine complex was allowed to reach room temperature (23 °C) over 5–10 min. (*This solution was used for four asymmetric reactions on 0.4 mmol scale and was always used within the next 15 min.)*

A portion of the resulting orange-red solution (2.0 mL; 0.05 equiv. [Rh]) was added to a 10 mL round-bottom flask containing a mixture of boronic acid (0.80 mmol, 2.0 equiv.) and cyclobutene (0.40 mmol, 1.0 equiv.) in toluene (2 mL) and H_2O (0.080 mL) *via* syringe under an argon atmosphere. The resulting mixture was then stirred at room temperature (23 °C) or 60 °C for a specified time. Then, the mixture was diluted with hexane (1 mL) and concentrated *in vacuo*. The crude mixture was directly loaded on a silica gel flash column and eluted with the indicated solvent mixture to afford the desired product.

General procedure 3-2

The experiment was performed as in general procedure 3-1 using (*S*)-BINAP instead of (*S*)-Segphos.

General procedure 3-3

The experiment was performed as in general procedure 3-1 using (*S*)-DTBM-Segphos instead of

(*S*)-Segphos.

General procedure 3-4

The experiment was performed as in general procedure 3-1 using dppf instead of (*S*)-Segphos (1.8 mL dioxane). In addition, aq. CsOH (50 wt%; 0.4 mmol, 1.0 equiv.) and an increased volume of H_2O (0.4 mL) was added to the round-bottom flask containing a mixture of boronic acid (1.20 mmol) and cyclobutene (0.40 mmol) in toluene (1.8 mL).

General procedure 3-5

The experiment was performed as in general procedure 3-1 using (*S*)-DTBM-Segphos instead of (*S*)-Segphos. In addition, Cs_2CO_3 (0.4 mmol, 1.0 equiv.) was added to the round-bottom flask containing a mixture of boronic acid and cyclobutene.

Comment: Minor alterations of the reaction conditions are specified in the section for individual substrates.

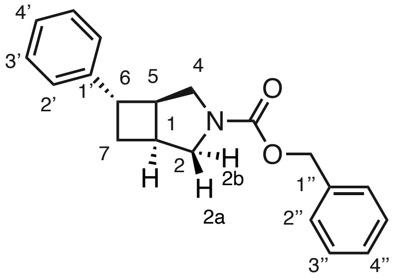
Racemates

Racemic samples were synthesized with (±)-BINAP, (±)-DTBM-Segphos or (±)-Segphos on 0.1 mmol scale at 60 °C.

Absolute stereochemistry

The absolute stereochemistry of all compounds was assigned by comparison of the optical rotation of **3-7b** and **3-13** with reported literature values.[212,214] The absolute configuration of compound **3-13** was previously assigned via X-ray diffraction analysis and of **3-7b** via X-ray diffraction analysis of a related compound. The relative stereochemistry of **3-5a**, **3-10a**, **3-17**, **3-19a** and **3-20m** was assigned by 2D NOEs. The absolute and relative stereochemistry of all other compounds was assigned by analogy.

3-5a



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-3** and phenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **3-5a** as a colourless solid (94 mg, 76% yield). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.54 – 7.29 (m, 7H; 7x C$_{Ar}$–H), 7.25 – 7.18 (m, 3H; 3x C$_{Ar}$–H), 5.21 (s, 2H; CH$_2$Ph), 3.77 (rot. s, 2H; CH$_2$N), 3.54 (rot. s, 1H; C(2)–H$_b$), 3.42 – 3.22 (m, 2H; CH$_2$N, C(6)–H), 3.04 – 2.94 (m, 2H; C(1)–H, C(5)–H), 2.37 (dt, *J* = 12.2, 8.5 Hz, 1H; C(7)–H), 2.19 (br. rot. s, 1H; C(7)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 155.6 (C=O), 145.1 (C(1')), 137.2 (C(1'')), 128.6 (2x C(3')), 2x C(3'')), 128.1 (C(4'')), 128.0 (2x C(2'')), 126.5 (2x C(2')), 126.3 (C(4')), 67.0 (CH$_2$Ph), 52.8 (rot.; 2x CH$_2$N), 46.7, 45.9 (rot.; 2x C(5)), 42.8 (C(6)), 34.7, 33.7 (rot.; 2x C(1)), 32.3 (C(7)).

IR (CHCl$_3$ film): 3028 (w), 2962 (w), 2868 (w), 1701 (s), 1496 (w), 1447 (w), 1414 (m), 1358 (m), 1228 (w), 1142 (w), 1097 (m), 768 (w), 748 (m), 698 (w) cm^{-1}.

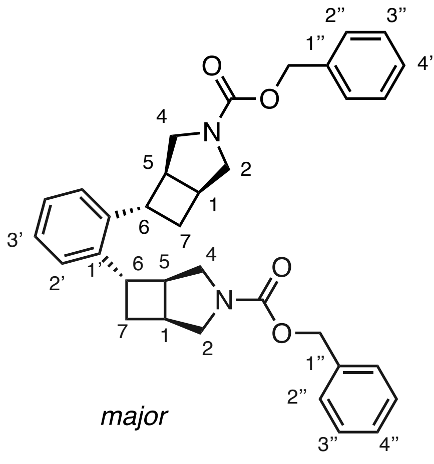
HRMS (ESI): m/z calcd for $C_{20}H_{21}O_2NNa^+$ $[M + Na]^+$ 330.14645 found 330.14648.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99:1 e.r. (minor enantiomer t_R = 4.77 min; major enantiomer t_R = 4.93 min).

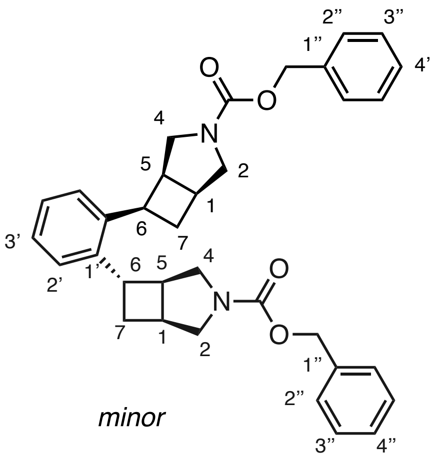
$[\alpha]^{25}_D$ = +73.8 (*c* = 1.0, CHCl$_3$).

m.p.: 40 – 41 °C.

3-5a’



major



minor

The following mixture of compounds was isolated as a side-product of **3-5a**. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **3-5a’** as a colourless oil (17 mg, 16% yield). Quantitative ^{1}H and ^{13}C NMR spectroscopy (*d*8-toluene) at 363 K showed a diastereomeric ratio of 2.2:1. The two diastereomers were assigned in analogy to the selectivity observed for *ortho*-substituted boronic acids.

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.50 – 7.31 (m, 12H; C_{Ar}–H), 7.28 – 7.24 (m, 2H; 2x C_{Ar}–H), 5.32 – 5.10 (m, 4H; 2x CH_2Ph), 3.94 – 3.67 (m, 4H; 4x CH_2N), 3.63 – 3.50 (br. rot. m, 2H; 2x CH_2N), 3.46 – 3.30 (br. rot. m, 4H; 2x C(6)–H, 2x CH_2N), 3.25 – 3.07 (br. rot. m, 2H; 2x C(5)–H), 2.97 (br. s, 2H; 2x C(1)–H), 2.49 – 1.98 (br. rot. m, 4H; 4x C(7)–H).

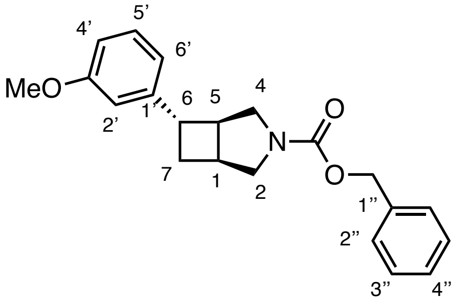
^{13}C NMR ($CDCl_3$, 126 MHz; * non-overlapping signal of the minor diastereomer): δ (ppm) 155.6 (2x C=O), 142.2 (2x C(1’)), 137.1 (2x C(1’’)), 128.6 (4x C(3’’)), 128.1 (4x C(4’’) and (2x C(4’’)), 126.6, 125.8 (C(2’) and C(3’)), 67.0 (2x CH_2Ph), 53.1, 52.9, 52.8, 52.6, 52.3 (rot.; 4x CH_2N), 45.2, 44.4, 43.9 (rot; 2x C(5)), 39.6 (C(6)*), 39.3 (C(6)), 34.5 (rot.; 2x C(1)), 33.9 (C(7)), 33.5 (rot.; 2x C(1)), 33.3 (C(7)*).

IR ($CHCl_3$ film): 3030 (w), 2959 (w), 2868 (w), 1699 (s), 1414 (m), 1358 (m), 1229 (w), 1143 (w), 1097 (m), 715 (w), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{34}H_{37}O_4N_2Na^+$ $[M + Na]^+$ 537.2748 found 537.2745.

$[\alpha]^{25}_{D}$ = +23.6 (*c* = 1.0, $CHCl_3$).

3-5b



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-3** and 3-methoxyphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 70/30) afforded the product **3-5b** as a colourless oil (93 mg, 69% yield). SFC analysis showed an enantiomeric excess of 91%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.45 – 7.28 (m, 5H; 5x C_{Ar}–H), 7.26 – 7.20 (m, 1H; C(5’)–H), 6.82 (d, *J* = 7.6 Hz, 1H; C(6’)–H), 6.77 – 6.70 (m, 2H; C(2’)–H, C(4’)–H), 5.20 (s, 2H; CH_2Ph), 3.81 (s, 3H; CH_3), 3.75 (s, 2H; rot. s, 2H; CH_2N), 3.53 (rot. s, 1H; CH_2N), 3.34 (dd, *J* = 11.6, 5.9 Hz, 1H; CH_2N), 3.30 – 3.18 (m, 1H; C(6)–H), 3.05 – 2.88 (m, 2H; C(1)–H, C(5)–H), 2.36 (dt, *J* = 12.2, 8.5 Hz, 1H; C(7)–H), 2.17 (br. rot. s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 159.9 (C(3’)), 155.6 (C=O), 146.9 (C(1’)), 137.1 (C(1’’)), 129.6 (C(5’)), 128.6 (2x C(3’’)), 128.1 (C(4’’)), 128.0 (2x C(2’’)), 118.8 (C(6’)), 112.5 (C(2’)), 111.4 (C(4’)), 67.0 (CH_2Ph), 55.3 (CH_3), 52.9 (rot.; CH_2N), 46.6, 45.9 (rot.; 2x C(5)), 42.9 (C(6)), 34.7, 33.6 (rot.; 2x C(1)), 32.2 (C(7)).

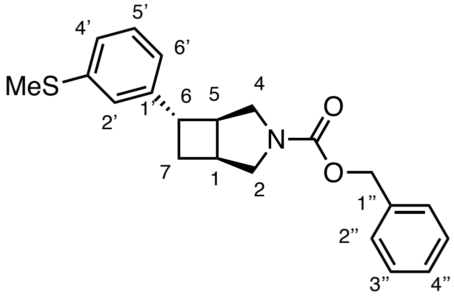
IR ($CHCl_3$ film): 2980 (m), 2883 (w), 1701 (s), 1601 (w), 1490 (w), 1475 (w), 1455 (w), 1416 (m), 1358 (m), 1229 (w), 1157 (m), 1097 (m), 1044 (w), 955 (w), 771 (m), 697 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{24}O_3NNa^+$ $[M + Na]^+$ 360.15701 found 360.15668.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 95.5:4.5 e.r. (minor enantiomer t_R = 6.02 min; major enantiomer t_R = 6.31 min).

$[\alpha]^{25}_{D}$ = +71.1 (*c* = 1.0, $CHCl_3$).

3-5c



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-3** and 3-thiomethoxyphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by flash chromatography (hexane/EtOAc = 100/0 to 60/40) afforded the product **3-5c** as a colourless oil (100 mg, 71% yield). SFC analysis showed an enantiomeric excess of 96%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.45 – 7.29 (m, 5H; 5x C_{Ar}–H), 7.24 (app. t, *J* = 7.5 Hz, 1H; C(5')–H), 7.14 – 7.07 (m, 2H; C(2')–H, C(4')–H), 7.00 (d, *J* = 7.6 Hz, 1H; C(6')–H), 5.20 (s, 2H; CH_2Ph), 3.89 – 3.67 (br. rot. m, 2H; 2x CH_2N), 3.62 – 3.43 (br. rot. m, 1H; CH_2N), 3.34 (dd, *J* = 11.6, 6.0 Hz, 1H; CH_2N), 3.28 – 3.19 (m, 1H; C(6)–H), 3.14 – 2.82 (m, 2H; C(1)–H, C(5)–H), 2.49 (s, 3H; SCH_3), 2.36 (dt, *J* = 12.2, 8.3 Hz, 1H; C(7)–H), 2.18 (s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.6 (C=O), 145.8 (C(1')), 138.7 (C(3')), 137.1 (C(1'')), 129.1 (C(5')), 128.6 (2x C(3'')), 128.1 (C(4'')), 128.0 (2x C(2'')), 124.9 (C(2')/C(4')), 124.4 (C(2')/C(4')), 123.3 (C(6')), 67.0 (CH_2Ph), 52.7 (rot.; CH_2N), 46.6, 45.8 (rot.; 2x C(5)), 42.7 (C(6)), 34.7, 33.6 (rot.; 2x C(1)), 32.2 (C(7)), 16.0 (SCH_3).

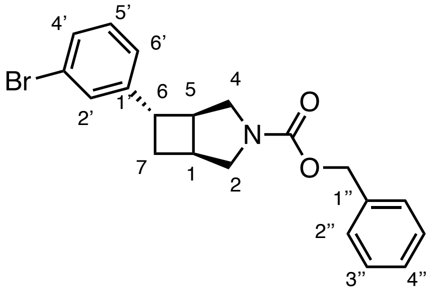
IR ($CHCl_3$ film): 2961 (w), 2867 (w), 1699 (s), 1590 (w), 1560 (w), 1414 (m), 1358 (m), 1097 (m), 770 (w), 696 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{24}O_2NS^+$ $[M + H]^+$ 354.1522 found 354.1523.

SFC Chiralpak® IA 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 98:2 e.r. (minor enantiomer t_R = 4.79 min; major enantiomer t_R = 5.06 min).

$[\alpha]^{25}_D$ = +82.8 (*c* = 1.0, $CHCl_3$).

3-5d



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-3** and 3-bromophenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 70/30) afforded the product **3-5d** as a colourless oil (94 mg, 61% yield). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.45 – 7.28 (m, 7H; 7x C_{Ar}–H), 7.18 (app. t, *J* = 7.7 Hz, 1H; C(5’)–H), 7.12 (d, *J* = 7.7 Hz, 1H; C(6’)–H), 5.20 (s, 2H; CH_2Ph), 3.76 (br. s, 2H; CH_2N), 3.52 (br. s, 1H; CH_2N), 3.34 (dd, *J* = 11.6, 5.7 Hz, 1H; CH_2N), 3.30 – 3.21 (m, 1H; C(6)–H), 3.01 – 2.92 (m, 2H; C(1)–H, C(5)–H), 2.42 – 2.28 (m, 1H; C(7)–H), 2.19 (br. rot. s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.6 (C=O) 147.5 (C(1’)), 137.1 (C(1’’)), 130.2 (C(5’)), 129.6 (C(2’)), 129.4 (C(4’)), 128.6 (2x C(3’’)), 128.1 (C(4’’)), 128.0 (2x C(2’’)), 125.2 (C(6’)), 122.8 (C(3’)), 67.1 (CH_2Ph), 52.7 (rot.; 2x CH_2N), 46.5, 45.7 (rot.; 2x C(5)), 42.4 (C(6)), 34.6, 33.9 (rot.; 2x C(1)), 32.1 (C(7)).

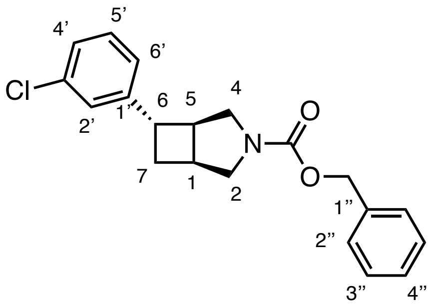
IR ($CHCl_3$ film): 3063 (w), 3032 (w), 2963 (w), 2869 (w), 1700 (s), 1596 (w), 1563 (w), 1498 (w), 1475 (w), 1445 (w), 1415 (m), 1358 (m), 1229 (w), 1157 (w), 1143 (w), 1098 (m), 770 (w), 746 (w), 663 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{20}H_{20}O_2N^{79}BrNa^+$ $[M + Na]^+$ 408.05696 found 408.05688.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 98.5:1.5 e.r. (minor enantiomer t_R = 5.69 min; major enantiomer t_R = 6.08 min).

$[\alpha]^{25}_D$ = +72.4 (*c* = 1.0, $CHCl_3$).

3-5e



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-3** and 3-chlorophenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 70/30) afforded the product **3-5e** as a colourless oil (86 mg, 63% yield). SFC analysis showed an enantiomeric excess of 96%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.47 – 7.28 (m, 5H; 5x C$_{Ar}$–H), 7.28 – 7.13 (m, 3H; 3x C$_{Ar}$–H), 7.08 (dt, *J* = 7.5, 1.6 Hz, 1H; C(6')–H), 5.20 (s, 2H; CH$_2$Ph), 3.91 – 3.67 (br. rot. m, 2H; CH$_2$N), 3.57 – 3.43 (br. rot. m, 1H; CH$_2$N), 3.34 (dd, *J* = 11.7, 5.6 Hz, 1H; CH$_2$N), 3.30 – 3.20 (m, 1H; C(6)–H), 3.01 – 2.86 (m, 2H; C(1)–H, C(5)–H), 2.43 – 2.26 (m, 1H; C(7)–H), 2.19 (br. rot. s, 1H; C(7)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 155.6 (C=O), 147.2 (C(1')), 137.1 (C(1'')), 134.5 (C(3')), 129.9 (C(5')), 128.6 (2x C(3'')), 128.1 (C(4'')), 128.0 (2x C(2'')), 126.7 (C(2')/C(4')), 126.4 (C(2')/C(4')), 124.7 (C(6')), 67.0 (CH$_2$Ph), 52.7 (rot.; 2x CH$_2$N), 46.5, 45.7 (rot.; 2x C(5)), 42.4 (C(6)), 34.7, 33.6 (rot.; 2x C(1)), 32.1 (C(7)).

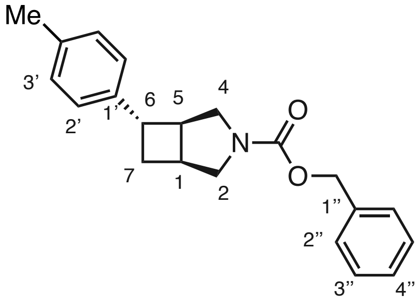
IR (CHCl$_3$ film): 2963 (w), 2869 (w), 1702 (s), 1597 (w), 1571 (w), 1498 (w), 1477 (w), 1415 (m), 1358 (m), 1228 (w), 1143 (w), 1099 (m), 769 (w), 694 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{20}H_{20}O_2N^{35}ClNa^+$ [M + Na]$^+$ 364.10748 found 364.10764.

SFC Chiralpak® IA 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 98:2 e.r. (minor enantiomer t$_R$ = 4.03 min; major enantiomer t$_R$ = 4.23 min).

$[\alpha]^{25}_D$ = +81.3 (*c* = 1.0, CHCl$_3$).

3-5f



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-3** and 4-methylphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 80/20) afforded the product **3-5f** as a colourless solid (104 mg, 81% yield). SFC analysis showed an enantiomeric excess of 96%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.44 – 7.29 (m, 5H; 5x C_{Ar}–H), 7.13 (s, 4H; 2x C(2')–H, 2x C(3')–H), 5.20 (s, 2H; CH_2Ph), 3.86 – 3.74 (rot. m, 2H; CH_2N), 3.62 – 3.46 (br. rot. m, 1H; CH_2N), 3.34 (dd, *J* = 11.6, 5.6 Hz, 1H; CH_2N), 3.28 – 3.15 (rot. m, 1H; C(6)–H), 3.00 – 2.90 (br. rot. m, 2H; C(1)–H, C(5)–H) 2.54 – 2.24 (m, s, 4H; CH_3, C(7)–H), 2.17 (br. rot. s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.6 (C=O), 142.1 (C(1')) , 137.2 (C(1'')), 135.9 (C(4')), 129.3 (2x C(3')), 128.6 (2x C(3'')), 128.1 (C(4'')), 128.0 (2x C(2'')), 126.4 (2x C(2')), 67.0 (CH_2Ph), 53.0, 52.8 (rot.; 2x CH_2N), 42.5 (C(6)), 34.6, 33.6 (rot.; 2x C(1)), 32.4 (C(7)), 21.1 (CH_3).

IR ($CHCl_3$ film): 2968 (w), 2868 (w), 1701 (s), 1515 (w), 1446 (w), 1414 (m), 1357 (m), 1228 (w), 1142 (w), 1096 (m), 811 (w), 769 (w), 698 (w) cm^{-1}.

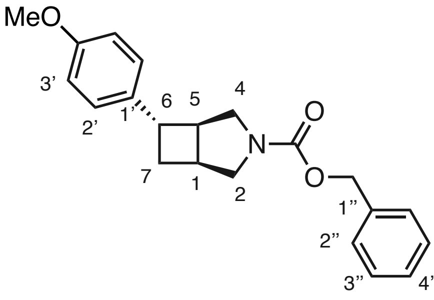
HRMS (ESI): m/z calcd for $C_{21}H_{23}O_2NNa^+$ $[M + Na]^+$ 344.16210 found 344.16217.

SFC Chiralpak® IG 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 98:2 e.r. (minor enantiomer t_R = 5.93 min; major enantiomer t_R = 6.29 min).

$[\alpha]^{25}_D$ = +84.9 (*c* = 1.0, $CHCl_3$).

m.p.: 92 – 93 °C.

3-5g



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-3** and 4-methoxyphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 70/30) afforded the product **3-5g** as a colourless solid (97 mg, 72% yield). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.48 – 7.30 (m, 5H; 5x C_{Ar}–H), 7.14 (d, J = 8.5 Hz, 2H; 2x C(2')–H), 6.86 (d, J = 8.7 Hz, 2H; 2x C(3')–H), 5.20 (s, 2H; CH_2Ph), 3.80 (s, 3H; OCH_3), 3.76 (rot. s, 2H; CH_2N), 3.54 (rot. s, 1H; CH_2N), 3.33 (dd, J = 11.6, 5.5 Hz, 1H; CH_2N), 3.24 (s, 1H; C(6)–H), 2.94 (rot. s, 2H; C(1)–H, C(5)–H), 2.32 (qd, J = 8.8, 3.1 Hz, 1H; C(7)–H), 2.17 (rot. s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 158.2 (C(4')), 155.6 (C=O), 137.3, 137.2 (C(1'), C(1'')), 128.6 (2x C(3'')), 128.1 (C(4'')), 128.0 (2x C(2'')), 127.5 (2x C(2')), 114.0 (2x C(3')), 67.0 (CH_2Ph), 55.5 (OCH_3), 52.8, 52.4 (rot.; 2x CH_2N), 47.0, 46.2 (rot.; 2x C(5)), 42.2 (C(6)), 34.6, 33.5 (rot.; 2x C(1)), 32.6 (C(7)).

IR ($CHCl_3$ film): 2957 (w), 2869 (w), 1699 (s), 1611 (w), 1512 (m), 1443 (w), 1414 (m), 1357 (m), 1358 (m), 1302 (w), 1244 (m), 1178 (w), 1096 (w), 1033 (w), 769 (w), 698 (w) cm^{-1}.

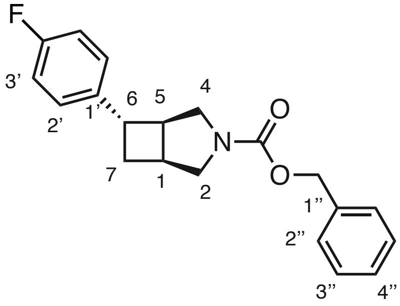
HRMS (ESI): m/z calcd for $C_{21}H_{23}O_3NNa^+$ $[M + Na]^+$ 360.15701 found 360.15710.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 98.5:1.5 e.r. (major enantiomer t_R = 5.93 min; minor enantiomer t_R = 6.07 min).

$[\alpha]^{25}_D$ = +84.1 (c = 1.0, $CHCl_3$).

m.p.: 78 – 79 °C.

3-5h



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-3** and 4-fluorophenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 80/20) afforded the product **3-5h** as a colourless solid (59 mg, 45% yield). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.49 – 7.28 (m, 5H; 5x C_{Ar}–H), 7.17 (dd, *J* = 8.5, 5.6 Hz, 2H; 2x C(2')–H), 7.05 – 6.96 (m, 2H; 2x C(3')–H), 5.20 (s, 2H; CH_2Ph), 3.97 – 3.66 (rot. m, 2H; CH_2N), 3.53 (br. rot. s, 1H; CH_2N), 3.43 – 3.30 (rot. m, 1H; CH_2N), 3.27 (br. rot. s, 1H; C(6)–H), 3.04 – 2.80 (m, 2H; C(1)–H and C(5)–H), 2.45 – 2.24 (m, 1H; C(7)–H), 2.19 (br. rot. s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 161.51 (d, *J* = 244.2 Hz; C(4')), 155.6 (C=O), 140.8 (C(1')), 137.1 (C(1'')), 128.6 (2x C(3'')), 128.1 (C(4'')), 128.0 (2x C(2'')), 127.9 (d, *J* = 7.8 Hz; 2x C(2')), 115.3 (d, *J* = 21.1 Hz; 2x C(3')), 67.0 (CH_2Ph), 52.7 (rot.; 2x CH_2N), 42.2 (C(6)), 34.6, 33.6 (rot.; 2x C(1)), 32.5 (C(7)).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) –117.10 (tt, *J* = 8.8, 5.6 Hz; C–F).

IR ($CHCl_3$ film): 2976 (w), 2871 (w), 1700 (w), 1510 (m), 1446 (w), 1414 (m), 1358 (w), 1223 (m), 1157 (w), 1143 (w), 1099 (w), 952 (w) cm^{-1}.

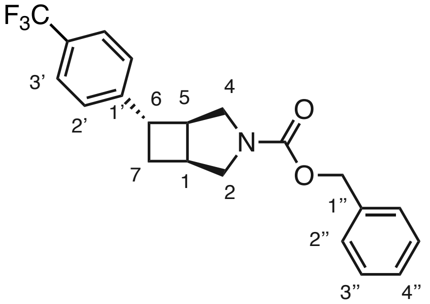
HRMS (ESI): m/z calcd for $C_{20}H_{20}O_2NFNa^+$ $[M + Na]^+$ 348.13703 found 348.13702.

SFC Chiralpak® IG 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 98.5:1.5 e.r. (minor enantiomer t_R = 5.20 min; major enantiomer t_R = 5.50 min).

$[\alpha]^{25}_D$ = +69.3 (*c* = 1.0, $CHCl_3$).

m.p.: 75 – 76 °C.

3-5i



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-3** and 4-trifluoromethylphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 80/20) afforded the product **3-5i** as a colourless solid (51 mg, 34% yield). SFC analysis showed an enantiomeric excess of 94%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.57 (d, *J* = 8.1 Hz, 2H; C(2')–H), 7.45 – 7.29 (m, 7H; 7x C_{Ar}–H), 5.21 (s, 2H; CH_2Ph), 3.92 – 3.70 (rot. m, 2H; CH_2N), 3.61 – 3.47 (rot. m, 1H; CH_2N), 3.36 (dd, *J* = 11.5, 5.7 Hz, 2H; CH_2N, C(6)–H), 3.06 – 2.85 (m, 2H; C(1)–H, C(5)–H), 2.37 (dt, *J* = 12.3, 8.8 Hz, 1H; C(7)–H), 2.24 (br. rot. s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.6 (C=O), 149.1 (C(1')), 137.1 (C(1'')), 128.6 (d, *J* = 32.6 Hz; C(4')), 128.6 (2x C(3'')), 128.1 (C(4'')), 128.0 (2x C(2'')), 126.8 (2x C(2')), 125.6 (q, *J* = 3.8 Hz; C(3'), 124.4 (q, *J* = 271.8 Hz; CF_3), 67.1 (CH_2Ph), 52.7 (rot.; 2x CH_2N), 46.5, 45.7 (rot.; 2x C(5)), 42.5 (C(6)), 34.7, 33.7 (rot.; 2x C(1)), 32.1 (C(7)).

^{19}**F NMR** ($CDCl_3$, 377 MHz): δ (ppm) –62.33 (s; CF_3).

IR ($CHCl_3$ film): 2965 (w), 2871 (w), 1702 (s), 1618 (w), 1446 (w), 1414 (m), 1358 (w), 1325 (s), 1229 (w), 1161 (m), 1113 (m), 1068 (m), 1017 (w), 955 (w), 830 (w), 697 (w), 768 (w) cm^{-1}.

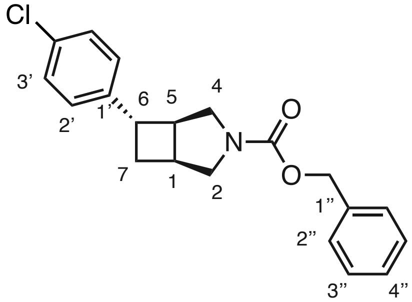
HRMS (ESI): m/z calcd for $C_{21}H_{20}O_2NF_3Na^+$ $[M + Na]^+$ 398.13383 found 398.13376.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; hold 1% MeOH for 2.0 min, then from 1% to 5% MeOH in 1 min, then hold 5% MeOH for 5.0 min, then from 5% to 30% MeOH in 5 min; 97:3 e.r. (major enantiomer t_R = 9.37 min; minor enantiomer t_R = 9.64 min).

[α]^{25}$_D$ = +71.1 (*c* = 1.0, $CHCl_3$).

m.p.: 60 – 61 °C.

3-5j



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-3** and 4-chlorophenylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure chromatography (hexaneEt$_2$O = 100/0 to 50/50) afforded the product **3-5j** as a colourless solid (58 mg, 43% yield). SFC analysis showed an enantiomeric excess of 92%.

^{1}**H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 7.43 – 7.29 (m, 5H; 5x C_{Ar}–H), 7.29 – 7.23 (m, 2H; 2x

C(3’’)–H), 7.13 (d, *J* = 8.4 Hz, 2H; 2x C(3’’)–H), 5.19 (s, 2H; CH_2Ph), 3.75 (br. rot. s, 2H; CH_2N), 3.63 – 3.47 (m, 1H; CH_2N), 3.44 – 3.28 (m, 1H; CH_2N), 3.27 – 3.17 (m, 1H; C(6)–H), 2.94 (br. s, 2H; C(1)–H, C(5)–H), 2.31 (dt, *J* = 12.2, 8.9 Hz, 1H; C(7)–H), 2.22 – 2.14 (m, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155. 6 (C=O), 143.6 (C(1’), 137.1 (C(1’’)), 132.0 (C(4’), 128.7 (2x C(2’)), 128.6 (2x C(3’’)), 128.1 (C(4’’)), 128.0 (2x C(2’’)), 127.8 (2x C(2’)), 67.0 (CH_2Ph), 53.0, 52.7, 52.4 (rot.; 2x CH_2N), 46.6, 45.9 (rot.; 2x C(5)), 42.2 (C(6)), 34.6, 33.6 (rot.; 2x C(1)), 32.3 (C(7)).

IR ($CHCl_3$ film): 2962 (w), 2868 (w), 1699 (s), 1492 (w), 1413 (m), 1358 (w), 1229 (w), 1092 (m), 1013 (w), 818 (w), 769 (w), 743 (w), 698 (w) cm^{-1}.

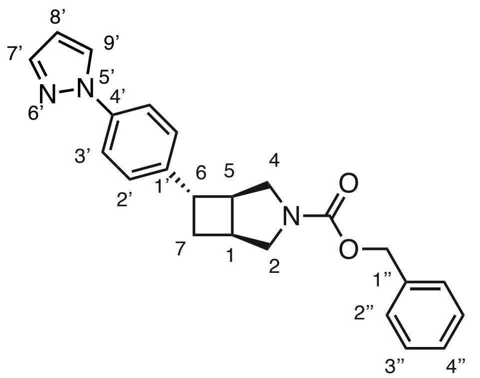
HRMS (ESI): m/z calcd for $C_{20}H_{21}O_2N^{35}Cl^+$ $[M + H]^+$ 342.1255 found 342.1257.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; hold 7.5% MeOH for 15 min; 96:4 e.r. (major enantiomer t_R = 12.13 min; minor enantiomer t_R = 12.77 min).

$[\alpha]^{25}_D$ = +86.3 (*c* = 1.0, $CHCl_3$).

m.p.: 97 – 98 °C.

3-5k



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-3** and (4-(1H-pyrazol-1-yl)phenyl)boronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 60/40) afforded the product **3-5k** as a colourless solid (64 mg, 43%). SFC analysis showed an enantiomeric excess of 96%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.90 (dd, *J* = 2.4, 0.6 Hz, 1H; C(9')–H), 7.71 (dd, *J* = 1.8, 0.6 Hz, 1H; C(7')–H), 7.68 – 7.60 (m, 2H: 2x C_{Ar}–H), 7.50 – 7.27 (m, 7H; 7x C_{Ar}–H), 6.46 (dd, *J* = 2.5, 1.8 Hz, 1H; C(8')–H), 5.21 (s, 2H; CH_2Ph), 3.92 – 3.69 (m, 2H; 2x CH_2N), 3.55 (s, 1H; CH_2N), 3.44 – 3.28 (m, 2H; CH_2N, C(6)–H), 3.14 – 2.92 (m, 2H; C(1)–H, C(5)–H), 2.45 – 2.32 (m, 1H; C(7)–H), 2.22 (rot. s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 155.6 (C=O), 143.5 (C(1')), 141.1 (C(7')), 138.7 (C(4')), 137.1 (C(1'')), 128.6 (2x C(3'')), 128.1 (2x C(2'')), 128.0 (C(4'')), 127.5 (2x C(2')), 126.8 (C(9')), 119.5 (2x C(3')), 107.6 (C(8')), 67.0 (CH_2Ph), 52.7 (rot.; 2x CH_2N), 46.8, 46.1 (rot.; 2x C(5)), 42.3 (C(8)), 34.7, 33.7 (rot.; 2x C(1)), 32.3 (C(7)).

IR ($CHCl_3$ film): 3034 (w), 2962 (w), 2869 (w), 1697 (s), 1524 (s), 1413 (s), 1395 (m), 1358 (m), 1334 (w), 1229 (w), 1097 (m), 1046 (w), 1031 (w), 937 (w), 828 (w), 750 (m), 698 (w) cm^{-1}.

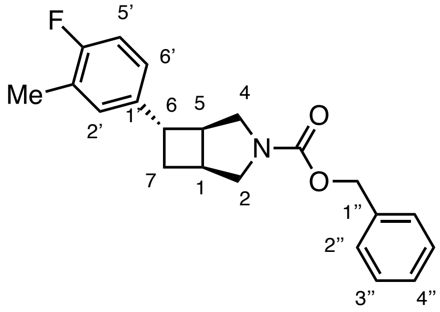
HRMS (ESI): m/z calcd for $C_{23}H_{24}O_2N_3^+$ $[M + H]^+$ 374.1863 found 374.1863.

SFC Chiralpak® IA 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 50% MeOH in 7 min, then hold 50% MeOH for 2 min; 98:2 e.r. (major enantiomer t_R = 6.83 min; minor enantiomer t_R = 7.44 min).

$[\alpha]^{25}_D$ = +96.4 (*c* = 1.0, $CHCl_3$).

m.p.: 109 °C.

3-5l



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-3** and 4-fluoro-3-methylphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 70/30) afforded the product **3-5l** as a colourless oil (98 mg, 72% yield). SFC analysis showed an enantiomeric excess of 96%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.52 – 7.29 (m, 5H; 5x C$_{Ar}$–H), 7.08 – 6.97 (m, 2H; 2x C$_{Ar}$–H), 6.96 – 6.90 (m, 1H; 1x C$_{Ar}$–H), 5.20 (s, 2H; CH$_2$Ph), 3.75 (br. s, 2H; rot. s, 2H; CH$_2$N), 3.53 (br. s, 1H; CH$_2$N), 3.33 (dd, *J* = 11.7, 5.5 Hz, 1H; CH$_2$N), 3.23 (br. s, 1H; C(6)–H), 2.95 (br. rot. s, 2H; C(1)–H, C(5)–H), 2.39 – 2.29 (m, 1H; C(7)–H), 2.26 (d, *J* = 2.0 Hz, 3H; CH$_3$), 2.17 (br. rot. s, 1H; C(7)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 160.0 (d, *J* = 243.0 Hz; C(4')), 155.6 (C=O), 140.5 (d, *J* = 3.5 Hz; C(1')), 137.2 (C(1'')), 129.5 (d, *J* = 5.0 Hz; C(2')), 128.6 (2x C(3'')), 128.1 (C(4'')), 128.0 (2x C(2'')), 125.1 (d, *J* = 7.8 Hz; C(6')), 124.8 (d, *J* = 17.1 Hz; C(3')), 115.0 (d, *J* = 22.2 Hz; C(5')), 67.0 (CH$_2$Ph), 52.8 (2x rot.; CH$_2$N), 46.9, 46.2 (rot.; 2x C(5)), 42.2 (C(6)), 34.6, 33.6 (rot.; 2x C(1)), 32.5 (C(7)), 14.7 (d, *J* = 3.6 Hz; CH$_3$).

^{19}F NMR (CDCl$_3$, 377 MHz): δ (ppm) –119.70 – –127.51 (m; C–F).

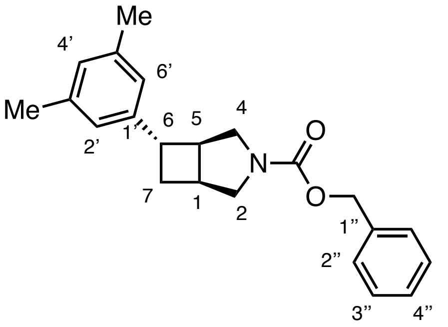
IR (CHCl$_3$ film): 2970(w), 2871 (w), 1702 (s), 1502 (m), 1414 (m), 1358 (m), 1229 (m), 1213 (m), 1147 (w), 1118 (m), 1098 (m), 954 (w), 817 (w), 756 (w), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{22}O_2NFNa^+$ [M + Na]$^+$ 362.1527 found 362.1525.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 98:2 e.r. (minor enantiomer t_R = 4.24 min; major enantiomer t_R = 4.45 min).

$[\alpha]^{25}_{D}$ = +72.0 (*c* = 1.0, $CHCl_3$).

3-5m



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-3** and 3,5-dimethylphenylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 80/20) afforded the product **3-5m** as a colourless oil (134 mg, 99%). SFC analysis showed an enantiomeric excess of 81%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.48 – 7.29 (m, 5H; 5x C_{Ar}–H), 6.85 (app. d, *J* = 4.5 Hz, 3H; 2x C(2')–H, C(4')–H), 5.20 (s, 2H; CH_2Ph), 3.89 – 3.66 (rot. m, 2H; CH_2N), 3.55 (br. rot. s, 1H; CH_2N), 3.34 (dd, *J* = 11.5, 5.7 Hz, 1H; CH_2N), 3.28 – 3.18 (m, 1H; C(6)–H), 3.05 – 2.91 (m, 2H; C(1)–H, C(5)–H), 2.38 – 2.33 (m, 1H; C(7)–H), 2.31 (s, 6H; 2x CH_3), 2.15 (s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.6 (C=O), 145.1 (C(1')), 138.2 (2x C(3')), 137.2 (C(1'')), 128.6 (2x C(3'')), 128.1 (C(4'')), 128.0 (2x C(2'')), 127.9 (C(4')), 124.3 (2x C(2')), 67.0 (CH_2Ph), 53.2, 52.9, 52.6 (rot.; 2x CH_2N), 46.8, 45.9 (rot.; 2x C(5)), 42.7 (C(6)), 34.7, 33.7 (rot.; 2x C(1)), 32.2 (C(7)), 21.5 (2x CH_3).

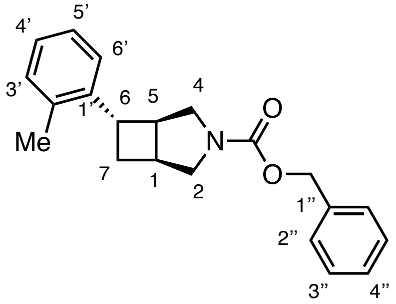
IR ($CHCl_3$ film): 3030 (w), 2962 (w), 2866 (w), 1702 (s), 1603 (w), 1447 (w), 1413 (m), 1357 (m), 1227 (w), 1156 (w), 1141 (w), 1097 (m), 840 (w), 768 (w), 698 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{22}H_{25}O_2NNa^+$ $[M + Na]^+$ 358.17775 found 358.17737.

SFC Chiralpak® ID 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 90.5:9.5 e.r. (minor enantiomer t_R = 3.44 min; major enantiomer t_R = 3.58 min).

$[\alpha]^{25}_D$ = +60.2 (*c* = 1.0, $CHCl_3$).

3-5n



The corresponding compound was prepared following general procedure 3-2 using cyclobutene **3-3** and 2-methylphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **3-5n** as a colourless oil (89 mg, 69%). SFC analysis showed an enantiomeric excess of 80%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.45 – 7.29 (m, 6H; 6x C_{Ar}–H), 7.22 (td, *J* = 7.8, 6.9, 2.6 Hz, 1H; C(3’)–H), 7.16 – 7.09 (m, 2H; C(4’)–H, C(5’)–H), 5.21 (br. s, 2H; CH_2Ph), 3.90 – 3.66 (br. m, 1H; 2x CH_2N), 3.54 (rot. s, 1H; CH_2N), 3.49 – 3.31 (m, 2H; C(6)–H, CH_2N), 3.11 (br. s, 1H; C(5)–H), 2.94 (br. s, 1H; C(1)–H), 2.41 – 2.25 (m, 1H; C(7)–H), 2.21 (s, 4H; C(7)–H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.6 (C=O), 137.2 (C(1’’)), 135.9 (C(1’) and C(2’)), 130.4 (C(3’)), 128.6 (2x C(3’’)), 128.1 (C(4’’)), 128.0 (2x C(2’’)), 126.20, 126.19 (C(4’), C(5’)), 125.1 (C(6’)), 66.9 (CH_2Ph), 53.2, 52.7 (rot.; 2x CH_2N), 44.7, 44.0 (rot.; C(5)), 39.9 (C(6)), 34.3, 33.3 (rot.; 2x C(1)), 32.0 (C(7)), 20.1 (CH_3).

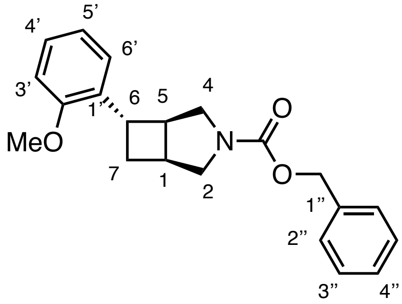
IR ($CHCl_3$ film): 3031 (w), 2958 (w), 2866 (w), 1701 (s), 1446 (w), 1412 (m), 1357 (m), 1229 (w), 1144 (w), 1091 (m), 751 (m), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{24}O_2N^+$ $[M + H]^+$ 322.1802 found 322.1803.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; hold 1% MeOH for 2 min, then from 1% to 2.5% MeOH in 1 min, then hold from 2.5% MeOH for 5 min, then from 2.5% to 30% MeOH in 5 min, then hold from 2.5% MeOH for 5 min; 90:10 e.r. (minor enantiomer t_R = 12.04 min; major enantiomer t_R = 12.15 min).

$[\alpha]^{25}_D$ = +69.4 (*c* = 1.0, $CHCl_3$).

3-5o



The corresponding compound was prepared following general procedure 3-2 using cyclobutene **3-3** and 2-methoxyphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 50/50) afforded the product **3-5o** as a colourless oil (46 mg, 34%). SFC analysis showed an enantiomeric excess of 91%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.48 – 7.29 (m, 5H), 7.25 – 7.12 (m, 2H; C(5')–H, C(6')–H), 6.95 (app. td, *J* = 7.4, 1.1 Hz, 1H; C(4')–H), 6.84 (dd, *J* = 8.6, 1.1 Hz, 1H; C(3')–H), 5.24 – 5.17 (rot. m, 2H; CH_2Ph)), 4.06 – 3.67 (m, 2H; 2x CH_2N), 3.80 (s, 3H, OCH_3), 3.65 – 3.46 (rot. m, 2H; CH_2N, C(6)–H), 3.35 (br. s, 1H; CH_2N), 3.12 – 2.77 (m, 2H; C(1)–H, C(5)–H), 2.45 (q, *J* = 9.9 Hz, 1H; C(7)–H), 2.26 – 2.01 (m, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 156.4 (C(2')), 155.6 (C=O), 137.4 (C(1'')), 132.7 (C(1')), 128.6 (2x C(3'')), 128.0 (2x C(2'')), 127.9 (C(4'')), 127.2 (C(5')/C(6')), 126.5 (C(5')/C(6')), 120.4 (C(4')), 110.2 (C(3')), 66.8 (CH_2Ph), 55.2 (OCH_3), 53.0, 52.5 (rot.; 2x CH_2N), 46.0, 45.3 (rot.; 2x C(5)), 38.0 (rot.; C(6)), 34.6, 33.6 (rot.; 2x C(1)), 30.1 (rot. C(7)).

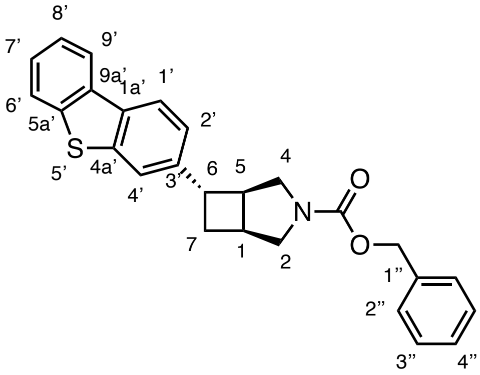
IR ($CHCl_3$ film): 2959 (w), 2868 (w), 1700 (s), 1603 (w), 1599 (w), 1492 (w), 1414 (m), 1358 (w), 1242 (w), 1149 (w), 1097 (w), 1029 (w), 752 (m), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{24}O_3N^+$ $[M + H]^+$ 338.1751 found 338.1752.

SFC Chiralpak® IG 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 95.5:4.5 e.r. (minor enantiomer t_R = 5.54 min; major enantiomer t_R = 5.78 min).

$[\alpha]^{25}_D$ = +63.9 (*c* = 1.0, $CHCl_3$).

3-5p



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-3** and 3-dibenzothienylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure liquid chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **3-5p** as a pale-yellow highly viscous oil (94 mg, 55%). SFC analysis showed an enantiomeric excess of 94%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 8.28 – 8.11 (m, 1H; C$_{Ar}$–H), 7.98 (d, *J* = 1.8 Hz, 1H; C(4')–H), 7.89 – 7.80 (m, 1H; C$_{Ar}$–H), 7.80 (d, *J* = 8.3 Hz, 1H; C$_{Ar}$–H), 7.57 – 7.30 (m, 7H; 8x C$_{Ar}$–H), 5.23 (s, 2H; CH$_2$Ph), 4.02 – 3.74 (m, 2H; 2x CH$_2$N), 3.64 – 3.55 (m, 1H; CH$_2$N), 3.51 – 3.46 (m, 1H; CH$_2$N), 3.40 (dd, *J* = 11.6, 6.0 Hz, 1H; C(6)–H), 3.19 – 2.92 (m, 2H; C(1)–H, C(5)–H), 2.48 (dt, *J* = 12.1, 8.5 Hz, 1H; C(7)–H), 2.29 (rot. s, 1H; C(7)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 155.6 (C=O), 141.6 (C$_{quart}$), 140.0 (C$_{quart}$), 137.4 (C$_{quart}$), 137.1 (C(1'')), 135.8 (C$_{quart}$), 135.5 (C$_{quart}$), 128.6 (2x C(3'')), 128.1 (C(4'')), 128.0 (2x C(2'')), 126.8 (C$_{Ar}$–H), 125.6 (C$_{Ar}$–H), 124.4 (C$_{Ar}$–H), 123.0 (C$_{Ar}$–H), 122.9 (C$_{Ar}$–H), 121.7 (C$_{Ar}$–H), 119.2 (C(4')), 67.0 (CH$_2$Ph), 53.2, 52.8, 52.6 (rot.; 2x CH$_2$N), 47.1, 46.3 (rot.; 2x C(5)), 42.9 (C(8)), 34.7, 33.7 (rot.; 2x C(1)), 32.6 (C(7)).

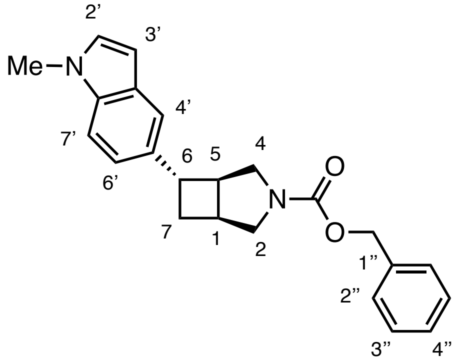
IR (CHCl$_3$ film): 2960 (w), 2868 (w), 1699 (s), 1469 (w), 1414 (m), 1357 (m), 1228 (m), 1157 (w), 1097 (m), 764 (m), 734 (m), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{26}H_{24}O_2NS^+$ $[M + H]^+$ 414.1522 found 414.1521.

SFC Chiralpak® ID 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 50% MeOH in 7 min, then hold 50% MeOH for 2 min; 97:3 e.r. (minor enantiomer t_R = 6.95 min; major enantiomer t_R = 7.59 min).

$[\alpha]^{25}_{D}$ = +78.9 (*c* = 1.0, $CHCl_3$).

3-5q



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-3** and *N*-methylindole-5-boronic acid. The mixture was stirred at 60 °C for 16 h. Purification by flash chromatography (hexane/EtOAc = 80/20 to 60/40) afforded the product **3-5q** as a pale-yellow oil (99 mg, 69%). SFC analysis showed an enantiomeric excess of 95%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.48 (s, 1H; C(4')–H), 7.45 – 7.31 (m, 5H; 5x C_{Ar}–H), 7.28 (d, *J* = 8.4 Hz, 1H; C(7')–H), 7.11 (dd, *J* = 8.4, 1.7 Hz, 1H; C(6')–H), 7.04 (d, *J* = 3.1 Hz, 1H; C(2')–H), 6.44 (dd, *J* = 3.1, 0.9 Hz, 1H; C(3')–H), 5.22 (s, 2H; CH_2Ph), 3.88 – 3.72 (s, 5H; 2x CH_2N, NCH_3), 3.57 (s, 1H; CH_2N), 3.46 – 3.31 (m, 2H; CH_2N, C(6)–H), 3.14 – 2.93 (m, 2H; C(1)–H, C(5)–H), 2.44 (dt, *J* = 12.1, 8.5 Hz, 1H; C(7)–H), 2.23 (s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.6 (C=O), 137.3 (C(1'')), 136.1, 135.7 (C(5') and C(7a')), 129.3 (C(2')), 128.7 (C(3a')), 128.6 (2x C(3'')), 128.03 (C(4'')), 127.98 (2x C(2'')), 120.6 (C(6')), 118.1 (C(4')), 109.3 (C(7')), 100.8 (C(3')), 66.9 (CH_2Ph), 53.3, 53.0, 52.5 (rot.; 2x

CH_2N), 47.4, 46.7 (rot.; 2x C(5)), 43.1 (C(8)), 34.7, 33.6 (rot.; 2x C(1)), 33.0 (NCH_3), 32.9 (C(7)).

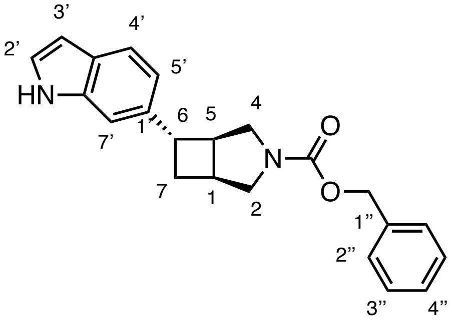
IR ($CHCl_3$ film): 2958 (w), 2870 (w), 1698 (s), 1512 (w), 1492 (s), 1446 (w), 1414 (m(, 1342 (m), 1229 (w), 1155 (w), 1097 (m), 799 (w), 768 (w), 721 (w), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{23}H_{25}O_2N_2^+$ $[M + H]^+$ 361.1911 found 361.1908.

SFC Chiralpak® ID 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 97.5:2.5 e.r. (minor enantiomer t_R = 5.92 min; major enantiomer t_R = 6.28 min).

$[\alpha]^{25}_D$ = +88.5 (*c* = 1.0, $CHCl_3$).

3-5r



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-3** and 6-indoylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 30/70) afforded the product **3-5r** as a brown viscous oil (76 mg, 55%). SFC analysis showed an enantiomeric excess of 91%

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.16 (s, 1H; NH), 7.60 (d, *J* = 8.1 Hz, 1H; C(5')–H), 7.46 – 7.29 (m, 5H; 5x C_{Ar}–H), 7.22 (s, 1H; C(7')–H), 7.17 (dd, *J* = 3.2, 2.4 Hz, 1H; C(2')–H), 7.03

(d, *J* = 8.1 Hz, 1H; C(4')–H), 6.52 (ddd, *J* = 3.1, 2.0, 1.0 Hz, 1H; C(3')–H), 5.22 (s, 2H; CH_2Ph), 3.94 – 3.72 (m, 2H; 2x CH_2N), 3.57 (s, 1H; CH_2N), 3.44 –3.34 (m, 2H; CH_2N and C(6)–H), 3.15 – 2.93 (m, 2H; C(1)–H and C(5)–H), 2.43 (dt, *J* = 12.0, 8.5 Hz, 1H; C(7)–H), 2.22 (s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.7 (C=O), 139.2 (C_{quart}), 137.2 (C(1'')), 136.2 (C_{quart}), 128.6 (2x C(3'')), 128.1 (C(4'')), 128.0 (2x C(2'')), 126.5 (C_{quart}), 124.2 (C(2')), 120.9 (C(5')), 118.9 (C(4')), 108.7 (C(7')), 102.6 (C(3')), 67.0 (CH_2Ph), 52.9 (rot.; 2x CH_2N), 47.3, 46.6 (rot.; 2x C(5)), 43.3 (C(8)), 34.7, 33.6 (rot.; 2x C(1)), 32.8 (C(7)).

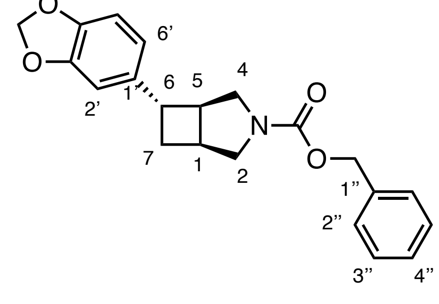
IR ($CHCl_3$ film): 3402 (br. w), 3322 (br. w), 2961 (w), 2931 (w), 2870 (w),1682 (s), 1454 (m), 1421 (m), 1358 (m), 1231 (w), 1100 (w), 809 (w), 768 (w), 726 (w), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{22}H_{23}O_2N_2^+$ $[M + H]^+$ 347.1754 found 347.1755.

SFC Chiralpak® ID 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 95.5:4.5 e.r. (minor enantiomer t_R = 5.63 min; major enantiomer t_R = 5.83 min).

$[\alpha]^{25}_D$ = +86.4 (*c* = 1.0, $CHCl_3$).

3-5s



The corresponding compound was prepared following general procedure 3-3 using cyclobutene

3-3 and 3,4-dioxolephenylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure liquid chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **3-5s** as a yellow oil (111 mg, 79%). SFC analysis showed an enantiomeric excess of 92%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.70 – 7.30 (m, 5H; 2x C(2'')–H, 2x C(3'')–H, C(4'')–H), 6.75 (d, *J* = 8.0 Hz, 1H; C(5')–H), 6.73 (br. s, 1H; C(2')–H), 6.64 (d, *J* = 8.0 Hz; C(6')–H), 5.93 (s, 2H; CH$_2$O$_2$), 5.19 (s, 2H; CH$_2$Ph), 3.89 – 3.65 (br. rot. m, 2H; 2x CH$_2$N), 3.52 (br. rot. s, 1H; CH$_2$N), 3.32 (dd, *J* = 11.4, 5.1 Hz, 1H; C(6)–H), 3.21 (br. rot. s, 1H; CH$_2$N), 2.93 (br. rot. s, 2H; C(1)–H, C(5)–H), 2.41 – 2.24 (m, 1H; C(7)–H), 2.15 (rot. s, 1H; C(7)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 155.6 (C=O), 147.9 (C(3')), 146.0 (C(4')), 139.2 (C(1')), 137.1 (C(1'')), 128.6 (2x C(3'')), 128.1 (C(4'')), 128.0 (2x C(2'')), 119.3 (C(6')), 108.2 (C(5')), 107.0 (C(2')), 101.0 (CH$_2$O$_2$), 67.0 (CH$_2$Ph), 53.0, 52.8, 52.4 (rot.; 2x CH$_2$N), 47.1, 46.2 (rot.; 2x C(5)), 42.7 (C(8)), 34.6, 33.5 (rot.; 2x C(1)), 32.6 (C(7)).

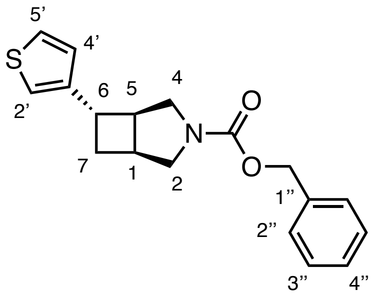
IR (CHCl$_3$ film): 2961 (w), 2873 (w), 1699 (s), 1503 (m), 1490 (m), 1415 (m), 1358 (m), 1231 (m), 1098 (m), 1038 (m), 934 (w), 809 (w), 769 (w), 742 (w), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{22}O_4N^+$ $[M + H]^+$ 352.1543 found 352.1545.

SFC Chiralpak® IA 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min; 96.5:3 e.r. (minor enantiomer t_R = 4.99 min; major enantiomer t_R = 5.29 min).

$[\alpha]^{25}_D$ = +77.1 (*c* = 1.0, CHCl$_3$).

3-5t



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-3** and 3-thiopheneboronic acid (3.0 eq). The mixture was stirred at room temperature (23 °C) for 16 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 80/20) afforded the product **3-5t** as a colourless oil (123 mg, 98%). SFC analysis showed an enantiomeric excess of 78%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.45 – 7.32 (m, 5H; 5x C_{Ar}–H), 7.29 (dd, *J* = 5.0, 3.0 Hz, 1H; C(5')–H), 6.99 (dd, *J* = 5.0, 1.3 Hz, 1H; C(4')–H), 6.97 (d, *J* = 2.4 Hz, 1H; C(2')–H), 5.20 (s, 2H; CH_2Ph), 3.90 – 3.64 (rot. m, 2H; CH_2N), 3.61 – 3.44 (m, 1H; CH_2N), 3.37 – 3.27 (m, 2H; CH_2N, C(6)–H), 3.10 – 2.75 (m, 2H; C(1)–H, C(5)–H), 2.46 – 2.26 (m, 1H; C(7)–H), 2.18 (s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.6 (C=O), 146.3 (C(1')), 137.1 (C(1'')), 128.6 (2x C(3'')), 128.1 (C(4'')), 128.0 (2x C(2'')), 126.6 (C(4')), 126.2 (C(5')), 119.2 (C(2')), 67.0 (CH_2Ph), 53.1, 52.7, 52.4 (rot.; 2x CH_2N), 46.8, 46.0 (rot.; 2x C(5)), 38.6 (C(6)), 34.8, 33.8 (rot.; 2x C(1)), 32.6 (C(7)).

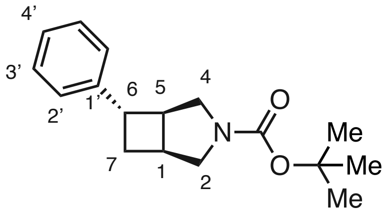
IR ($CHCl_3$ film): 2964 (w), 2867 (w), 1698 (s), 1414 (m), 1358 (m), 1228 (w), 1155 (w), 1141 (w), 1097 (m), 844 (w), 769 (m), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{18}H_{19}O_2NNaS^+$ $[M + Na]^+$ 336.10287 found 336.10266.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 89:11 e.r. (major enantiomer t_R = 5.83 min; minor enantiomer t_R = 6.01 min).

$[\alpha]^{25}_D$ = +58.0 (*c* = 1.0, $CHCl_3$).

3-7a



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-6a** and phenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by flash chromatography (hexane/EtOAc = 90/10) afforded the product **3-7a** as colourless oil (73 mg, 67%). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) δ 7.36 – 7.28 (m, 2H; 2x C(3')–H), 7.25 – 7.17 (m, 3H; 2x C(2')–H, C(4')–H), 3.66 (br. rot. s, 2H; 2x CH_2N), 3.46 (s, 1H; CH_2N), 3.37 – 3.21 (m, 2H; CH_2N, C(6)–H), 3.06 – 2.80 (m, 2H; C(1)–H, C(5)–H), 2.35 (dt, *J* = 12.2, 8.5 Hz, 1H; C(7)–H), 2.19 (t, *J* = 8.8 Hz, 2H; C(7)–H), 1.51 (s, 9H; $C(CH_3)_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.4 (C=O), 145.4 (C(1')), 128.6 (2x C(3')), 126.5 (2x C(2')), 126.2 (C(4')), 79.5 ($\mathit{C}(CH_3)_3$), 52.7 (rot.; 2x CH_2N), 46.7 (rot. C(5)), 42.8, (C(8)) 34.6, 33.7 (rot.; 2x C(1)), 32.3 (C(7)), 28.7 (3x $C(\mathit{C}H_3)_3$).

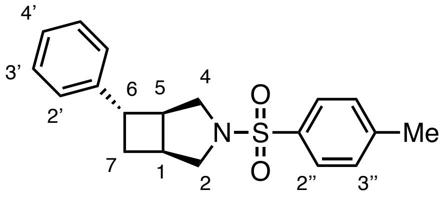
IR ($CHCl_3$ film): 2971 (w), 2931 (w), 2864 (w), 1694 (s), 1478 (w), 1454 (w), 1392 (m), 1365 (w), 1242 (w), 1178 (w), 1156 (w), 1100 (w), 875 (w), 773 (w), 749 (w), 699 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{17}H_{23}O_2NNa^+$ $[M + Na]^+$ 296.1621 found 296.1622.

SFC Chiralpak® IC 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 98.5:1.5 e.r. (major enantiomer t_R = 2.90 min; minor enantiomer t_R = 2.95 min).

$[α]^{25}_D$ = +77.2 (*c* = 1.0, $CHCl_3$).

3-7b[214]



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-6b** and phenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by flash chromatography (hexane/EtOAc = 80/20) afforded the product **3-7b** as a colourless solid (92 mg, 70%). SFC analysis showed an enantiomeric excess of >99%. The analytical data are in agreement with the literature.[214]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) δ 7.78 – 7.66 (m, 2H; 2x C(2'')–H), 7.47 – 7.27 (m, 4H; 2x C(3')–H and 2x C(3'')–H), 7.24 – 7.15 (m, 3H; 2x C(2')–H, C(4')–H), 3.60 (d, *J* = 9.8 Hz, 1H; 1x CH_2N), 3.55 (d, *J* = 9.7 Hz, 1H; 1x CH_2N), 3.40 (ddd, *J* = 9.8, 7.8, 4.3 Hz, 1H; C(6)–H), 2.92 – 2.79 (m, 2H; C(1)–H, C(5)–H), 2.75 (dd, *J* = 9.7, 6.4 Hz, 1H; 1x CH_2N), 2.67 (dd, *J* = 9.8, 5.4 Hz, 1H; 1x CH_2N), 2.44 (s, 3H; CH_3), 2.39 – 2.23 (m, 2H; C(7)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 145.5 (C(1'')), 143.7 (C(1')), 132.2 (C(4'')), 129.7 (2x C(3'')), 128.7 (2x C(3')), 128.3 (2x C(2'')), 126.5 (2x C(2')), 126.3 (C(4')), 54.6, 54.5 (C(2), C(4)), 45.8 (C(5)), 42.1 (C(6)), 34.2 (C(1)), 31.9 (C(7)), 21.7 (CH_3).

IR ($CHCl_3$ film): 3025 (w), 2934 (w), 2851 (w), 1598 (w), 1494 (w), 1470 (w), 1454 (w), 1343 (s), 1216 (w), 1171 (s), 1157 (s), 1094 (m), 1046 (w), 1012 (m), 812 (m), 751 (s), 700 (m) cm^{-1}.

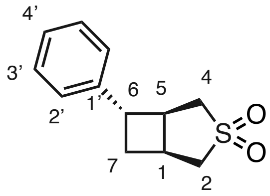
HRMS (ESI): m/z calcd for $C_{19}H_{21}O_2NNa^+$ $[M + Na]^+$ 350.1185 found 350.1184.

SFC Chiralpak® ID 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; >99.5:0.5 e.r. (major enantiomer t_R = 4.93 min; minor enantiomer t_R = 5.81 min).

$[\alpha]^{25}_D$ = –1.3 (*c* = 1.0, $CHCl_3$) (Lit.: $[\alpha]^{25}_D$ = –2.14 (*c* = 0.28, $CHCl_3$); *ent*-**3-5b** $[\alpha]^{25}_D$ = +1.45 (*c* = 0.60, $CHCl_3$)[214].

m.p.: 141 – 142 °C.

3-7c



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-6c** and phenylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure liquid chromatography (hexane/EtOAc = 100/0 to 50/50) afforded the product **3-7c** as colourless solid (81 mg, 92%). SFC analysis showed an enantiomeric excess of 86%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) δ 7.39 – 7.31 (m, 2H; 2x C(3')–H), 7.27 – 7.14 (m, 3H; 2x C(2')–H, C(4')–H), 4.03 – 3.57 (m, 1H; C(5)–H), 3.41 – 3.29 (m, 2H; C(2)–H_2, C(4)–H_2), 3.28 – 3.13 (m, 4H; C(2)–H_2, C(4)–H_2, C(1)–H, C(6)–H), 2.73 – 2.34 (m, 2H; C(7)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 143.4 (C(1')), 128.9 (2x C(3')), 127.0 (C(4')), 126.4 (2x C(2')), 56.1 (C(2)), 55.6, (C(4)) 43.8 (C(5)), 40.9 (C(6)), 32.2 (C(7)), 30.3 (C(1)).

IR ($CHCl_3$ film): 3028 (w), 2986 (w), 1414 (w), 1297 (s), 1234 (m), 1146 (m), 1123 (m) 1068 (w), 923 (w), 761 (w), 748 (w), 698 (m), 670 (w) cm^{-1}.

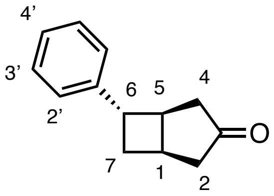
HRMS (ESI): m/z calcd for $C_{12}H_{14}O_2SNa^+$ $[M + Na]^+$ 245.0607 found 245.0609.

SFC Chiralpak® ID 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min; 93:7 e.r. (minor enantiomer t_R = 3.56 min; major enantiomer t_R = 3.67 min).

$[\alpha]^{25}_D$ = +87.7 (*c* = 1.0, $CHCl_3$)

m.p.: 133 – 134 °C.

3-5d



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-6d** and phenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by medium-pressure liquid chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-7d** as colourless oil (60 mg, 81%). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.37 – 7.30 (m, 2H; 2x C(3')–H), 7.26 – 7.17 (m, 3H; 2x C(2')–H, C(4')–H), 3.28 – 3.10 (m, 2H; C(6)–H, C(5)–H), 3.06 – 2.95 (m, 1H; C(1)–H), 2.68 (ddd, *J* = 19.5, 10.1, 2.2 Hz, 1H; 1x C(2)–H$_2$), 2.58 – 2.46 (m, 2H; 1x C(4)–*H*$_2$, 1x C(7)–*H*$_2$), 2.43 – 2.31 (m, 2H; 1x C(2)–*H*$_2$, 1x C(4)–*H*$_2$), 2.19 (ddd, *J* = 11.8, 8.6, 2.8 Hz, 1H; 1x C(7)–*H*$_2$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 221.1 (C=O), 144.6 (C(1')), 128.6 (2x C(3')), 126.5 (2x C(2')), 126.4 (C(4')), 45.2 (C(4)), 44.5 (2x C; C(6), C(2)), 43.1 (C(5)), 33.9 (C(7)), 30.7 (C(1)).

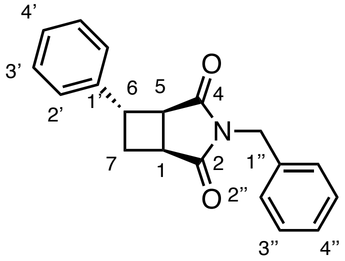
IR (CHCl$_3$ film): 3027 (w), 2958 (w), 1736 (s), 1602 (w) 1495 (w), 1454 (w), 1402 (w), 1258 (w) 1156 (w), 1138 (w), 753 (w), 699 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{13}H_{14}ONa^+$ $[M + H]^+$ 209.0937 found 209.0939.

SFC Chiralpak® ID 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 98.5:1.5 e.r. (major enantiomer t_R = 4.23 min; minor enantiomer t_R = 4.52 min).

$[\alpha]^{25}_D$ = +55.7 (*c* = 1.0, CHCl$_3$).

3-8a



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-2** and phenylboronic acid. The mixture was stirred at 60 °C for 4 h. Purification by automated medium-medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **3-8a** as a colourless solid (93 mg, 80%). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.48 – 7.42 (m, 2H; 2x C$_{Ar}$–H), 7.40 – 7.23 (m, 8H; 8x C$_{Ar}$–H), 4.76 (s, 2H; CH$_2$Ph), 3.62 (td, *J* = 8.5, 5.2 Hz, 1H; C(6)–H), 3.47 – 3.39 (m, 1H; C(5)–H), 3.32 (dddd, *J* = 10.6, 6.8, 3.7, 1.1 Hz, 1H; C(1)–H), 2.86 – 2.73 (m, 1H; C(7)–H), 2.64 (dddd, *J* = 12.9, 9.2, 3.8, 0.8 Hz, 1H; C(7)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 179.3 (N–C=O), 178.3 (N–C=O), 142.3 (C(1')), 136.1 (C(1'')), 128.93 (2x C(3')), 128.88 (2x C(2'')/C(3'')), 128.83 ((2x C(2'')/C(3'')), 128.1 (C(4'')), 127.2 (C(4')), 126.4 (2x C(2')), 46.6 (C(5)), 42.7 (CH$_2$Ph), 41.9 (C(6)), 35.9 (C(1)), 29.9 (C(7)).

IR (CHCl$_3$ film): 3031 (w), 2947 (w), 1769 (w), 1701 (s), 1496 (w), 1429 (w), 1391 (m), 1342 (w), 1159 (w), 931 (w), 757 (w), 642 (w) cm^{-1}.

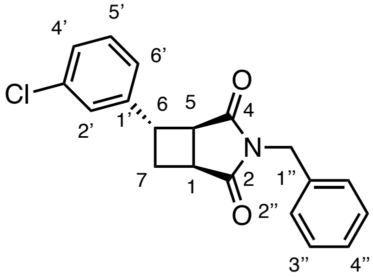
HRMS (ESI): m/z calcd for $C_{19}H_{18}O_2N^+$ $[M + H]^+$ 292.1112 found 292.1113.

SFC Chiralpak® IA 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99.5:0.5 e.r. (major enantiomer t_R = 4.09 min; minor enantiomer t_R = 4.80 min).

$[\alpha]^{25}_D$ = +99.5 (*c* = 1.0, CHCl$_3$).

m.p.: 94 – 95 °C.

3-8b



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-2** and 3-chlorophenylboronic acid (3.0 equiv.). The mixture was stirred at 60 °C for 4 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **3-8b** as a colourless oil (108 mg, 83%). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.49 – 7.40 (m, 2H; 2x C_{Ar}–H), 7.38 – 7.27 (m, 4H; 4x C_{Ar}–H), 7.26 – 7.21 (m, 1H; 1x C_{Ar}–H), 7.17 – 7.10 (m, 1H; 1x C_{Ar}–H), 4.74 (s, 2H; CH_2Ph), 3.57 (td, *J* = 8.5, 5.2 Hz, 1H; C(6)–H), 3.44 – 3.35 (m, 1H; C(5)–H), 3.32 (dddd, *J* = 10.6, 6.9, 3.7, 1.0 Hz, 1H; C(1)–H), 2.75 (ddd, *J* = 12.8, 10.4, 8.0 Hz, 1H); C(7)–H, 2.63 (dddd, *J* = 12.8, 9.2, 3.8, 0.8 Hz, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 178.9 (N–C=O), 177.9 (N–C=O), 144.3 (C(1')), 136.0 (C(1'')), 134.9 (C(3')), 130.2 (C(5')), 128.92 (2x C(2'')/C(3'')), 128.86 (2x C(2'')/C(3'')), 128.2 (C(4'')), 127.4, 126.7, 124.7 (C(2'), C(4') and C(6')), 46.4 (C(5)), 42.8 (CH_2Ph), 41.5 (C(6)), 35.9 (C(1)), 29.7 (C(7)).

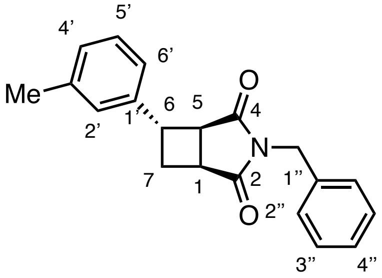
IR ($CHCl_3$ film): 2981 (w), 1770 (w), 1699 (s), 1598 (w), 1573 (w), 1429 (w), 1390 (m), 1341 (w), 1163 (w), 1084 (w), 936 (w), 785 (w), 750 (w), 696 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{19}H_{17}O_2N^{35}Cl^+$ $[M + H]^+$ 326.0942 found 326.0943.

SFC Chiralpak® IA 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99:1 e.r. (major enantiomer t_R = 4.41 min; minor enantiomer t_R = 4.73 min).

$[\alpha]^{25}_D$ = +99.9 (*c* = 1.0, $CHCl_3$).

3-8c



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-2** and 3-methylphenylboronic acid. The mixture was stirred at 60 °C for 4 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 70/30) afforded the product **3-8c** as a yellow oil (115 mg, 94%). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.46 – 7.40 (m, 2H; 2x C$_{Ar}$–H), 7.37 – 7.20 (m, 4H; 4x C$_{Ar}$–H), 7.08 (s, 2H; 2x C$_{Ar}$–H), 7.06 (s, 1H; 1x C$_{Ar}$–H), 4.75 (s, 2H; CH$_2$Ph), 3.58 (td, *J* = 8.5, 5.2 Hz, 1H; C(6)–H), 3.45 – 3.35 (m, 1H; C(5)–H), 3.31 (dddd, *J* = 10.6, 6.8, 3.7, 1.1 Hz, 1H; C(1)–H), 2.78 (ddd, *J* = 12.8, 10.6, 7.9 Hz, 1H; C(7)–H), 2.61 (dddd, *J* = 12.8, 9.2, 3.7, 0.8 Hz, 1H; C(7)–H), 2.36 (s, 3H; CH$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 179.3 (N–C=O), 178.3 (N–C=O), 142.3 (C(1’)), 138.6 (C(3’)), 136.1 (C(1’’)), 128.87 (2x C(2’’)/C(3’’)), 128.82 (2x C(2’’)/C(3’’), C$_{Ar}$–H), 128.1 (C(4’’)), 127.9 (C$_{Ar}$–H), 127.2 (C$_{Ar}$–H), 123.3 (C$_{Ar}$–H), 46.6 (C(1)), 42.7 (CH$_2$Ph), 41.9 (C(6)), 36.0 (C(5)), 29.8 (C(7)), 21.6 (CH$_3$).

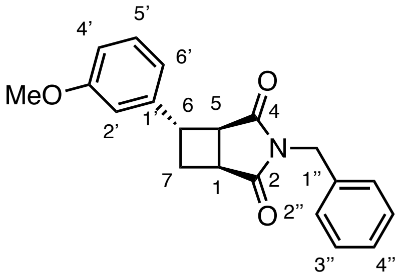
IR (CHCl$_3$ film): 2946 (w), 1769 (w), 1701 (s), 1429 (w), 1390 (m), 1342 (w), 1166 (w), 937 (w), 780 (w), 701 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{20}H_{20}O_2N^+$ $[M + H]^+$ 306.1489 found 306.1489.

SFC Chiralpak® ID 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99:1 e.r. (major enantiomer t_R = 3.42 min; minor enantiomer t_R = 3.60 min).

$[\alpha]^{25}_D$ = +99.8 (*c* = 1.0, CHCl$_3$).

3-8d



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-3** and 3-methoxyphenylboronic acid. The mixture was stirred at 60 °C for 4 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 70/30) afforded the product **3-8d** as a colourless solid (106 mg, 82%). SFC analysis showed an enantiomeric excess of 98%.

^{1}**H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 7.47 – 7.40 (m, 2H; 2x C_{Ar}–H), 7.37 – 7.27 (m, 4H; C(5')–H and 3x C_{Ar}–H), 6.86 (ddt, *J* = 7.6, 1.7, 0.9 Hz, 1H; C(6')–H), 6.83 – 6.78 (m, 2H; C(2')–H and C(4')–H), 4.74 (s, 2H; CH_2Ph), 3.82 (s, 3H, OCH_3), 3.58 (td, *J* = 8.5, 5.2 Hz, 1H; C(6)–H), 3.45 – 3.38 (m, 1H; C(5)–H), 3.31 (dddd, *J* = 10.6, 6.8, 3.8, 1.1 Hz, 1H; C(1)–H), 2.77 (ddd, *J* = 12.9, 10.6, 7.9 Hz, 1H; C(7)–H), 2.61 (dddd, *J* = 12.9, 9.2, 3.8, 0.8 Hz, 1H; C(7)–H).

^{13}**C NMR** ($CDCl_3$, 101 MHz): δ (ppm) 179.2 (N–C=O), 178.2 (N–C=O), 160.1 (C(3')), 144.0 (C(1')), 136.1 (C(1'')) 130.0 (C(5'), 128.89 (2x C(2'')/C(3'')), 128.84 (2x C(2'')/C(3'')), 128.1 (C(4'')), 118.7 (C(6')), 112.5 (C(2')/C(4')), 112.3 (C(2')/C(4')), 55.4 (OCH_3), 46.6 (C(1)), 42.7 (CH_2Ph), 41.9 (C(6)), 35.9 (C(5)), 29.8 (C(7)).

IR ($CHCl_3$ film): 2981 (w), 1769 (w), 1698 (s), 1602 (w), 1584 (w), 1493 (w), 1455 (w), 1431 (w), 1390 (m), 1340 (w), 1312 (w), 1291 (w), 1153 (m), 1048 (w), 939 (w), 780 (w), 755 (w), 645 (w) cm^{-1}.

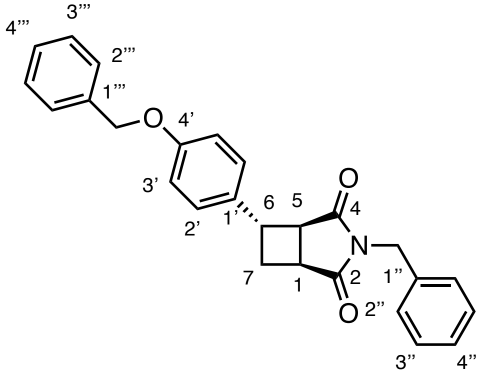
HRMS (ESI): m/z calcd for $C_{20}H_{19}O_3NNa^+$ $[M + Na]^+$ 344.1257 found 344.1256.

SFC Chiralpak® IE 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 99:1 e.r. (major enantiomer t_R = 5.54 min; minor enantiomer t_R = 5.99 min).

$[\alpha]^{25}_D$ = +100.8 (*c* = 1.0, $CHCl_3$).

m.p.: 140 – 141 °C.

3-8e



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-2** and (4-(benzyloxy)phenyl)boronic acid. The mixture was stirred at 60 °C for 4 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **3-8e** as a colourless solid (113 mg, 71%). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.51 – 7.27 (m, 9H; 9x C_{Ar}–H), 7.23 – 7.12 (m, 2H; 2x C(2')–H), 7.06 – 6.88 (m, 2H; 2x C(3')–H), 5.07 (s, 2H; OCH_2Ph), 4.74 (s, 2H; CH_2Ph), 3.55 (td, *J* = 8.5, 4.9 Hz, 1H; C(6)–H), 3.35 (ddd, *J* = 6.7, 5.1, 1.0 Hz, 1H; C(5)–H), 3.29 (dddd, *J* = 10.5, 6.8, 3.6, 0.9 Hz, 1H; C(1)–H), 2.80 – 2.68 (m, 1H; C(7)–H), 2.65 – 2.52 (m, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 179.3 (N–C=O), 178.3 (N–C=O), 158.0 (C(4')), 137.0 (C(1''')), 136.1 (C(1'')), 134.7 (C(1')), 128.88 (2x C(2'')/C(3'')), 128.83 (2x C(2'')/C(3'')), 128.75 (2x C_{Ar}–H), 128.14 (C(4''')), 128.11 (C(4''), 127.57 (2x C_{Ar}–H), 127.55 (2x C_{Ar}–H), 115.3 (2x C(3')), 70.3 (OCH_2Ph), 47.0 (C(1)), 42.7 (CH_2Ph), 41.5 (C(6)), 35.8 (C(5)), 30.1

(C(7)).

IR ($CHCl_3$ film): 3033 (w), 2945 (w), 1768 (w), 1700 (s), 1512 (m), 1453 (w), 1428 (w), 1389 (m), 1342 (w), 1310 (w), 1244 (m), 1174 (w), 1022 (w), 929 (w), 827 (w), 743 (w), 700 (w) cm^{-1}.

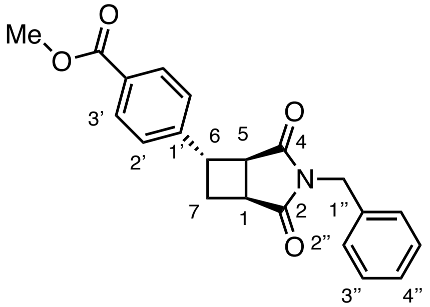
HRMS (ESI): m/z calcd for $C_{26}H_{24}O_3N^+$ $[M + H]^+$ 398.1751 found 398.1752.

SFC Chiralpak® IC 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 99:1 e.r. (major enantiomer t_R = 5.81 min; minor enantiomer t_R = 6.05 min).

$[\alpha]^{25}_D$ = +98.7 (*c* = 1.0, $CHCl_3$).

m.p.: 93 – 94 °C.

3-8f



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-2** and 4-methoxycarbonylphenylboronic acid. The mixture was stirred at 60 °C for 4 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 50/50) afforded the product **3-8f** as a colourless solid (117 mg, 83%). SFC analysis showed an enantiomeric ratio of 99:1.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.03 (d, *J* = 8.4 Hz, 1H; 2x C(3')–H), 7.49 – 7.39 (m, 2H; 2x C_{Ar}–H), 7.37 – 7.27 (m, 5H; 3x C_{Ar}–H and 2x C(2')–H), 4.75 (s, 2H; CH_2Ph), 3.92 (s, 3H;

OCH_3), 3.65 (td, *J* = 8.5, 5.6 Hz, 1H; C(6)–H), 3.47 – 3.37 (m, 1H; C(5)–H), 3.34 (dddd, *J* = 10.6, 6.9, 3.8, 1.1 Hz, 1H; C(1)–H), 2.89 – 2.74 (m, 1H; C(7)–H), 2.66 (dddd, *J* = 12.9, 9.2, 3.8, 0.8 Hz, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 178.9 (N–C=O), 177.93 (N–C=O), 166.8 (*C*O_2CH_3), 147.3 (C(1')), 136.0 (C(1'')), 130.3 (C(3')), 129.2 (C(2')), 128.91 (2x C(2'')/C(3'')), 128.86 (2x C(2'')/C(3'')), 128.2 (C(4'')), 126.5 (C(4')), 52.3 (OCH_3), 46.3 (C(1)), 42.8 (CH_2Ph), 41.8 (C(6)), 35.9 (C(4)), 29.7 (C(7)).

IR ($CHCl_3$ film): 2951 (w), 1770 (w), 1701 (s), 1610 (w), 1434 (w), 1391 (w), 1342 (w), 1281 (m), 1161 (w), 1112 (w), 768 (w), 703 (w) cm^{-1}.

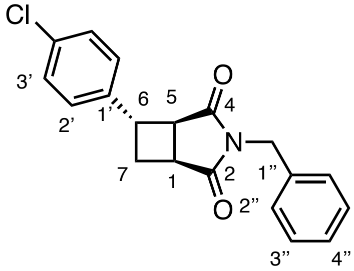
HRMS (ESI): m/z calcd for $C_{21}H_{20}O_4N^+$ $[M + H]^+$ 350.1387 found 350.1390.

SFC Chiralpak® IC 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 99:1 e.r. (major enantiomer t_R = 5.47 min; minor enantiomer t_R = 5.75 min).

$[\alpha]^{25}_D$ = +106.2 (*c* = 1.0, $CHCl_3$).

m.p.: 112 – 113 °C.

3-8g



The corresponding compound was prepared following general procedure 3-3 using cyclobutene

3-2 and 4-chlorophenylboronic acid. The mixture was stirred at 60 °C for 4 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **3-8g** as a colourless solid (85 mg, 65%). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.46 – 7.40 (m, 2H; 2x C(2')–H), 7.38 – 7.27 (m, 5H; 5x C$_{Ar}$–H), 7.23 – 7.14 (m, 2H; 2x C(3')–H), 4.74 (s, 2H; CH$_2$Ph), 3.57 (ddd, *J* = 9.1, 6.8, 2.8 Hz, 1H; C(6)–H), 3.45 – 3.26 (m, 2H; C(5)–H and C(1)–H), 2.73 (dddd, *J* = 12.9, 9.7, 7.9, 1.0 Hz, 1H; C(7)–H), 2.68 – 2.57 (m, 1H; C(7)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 179.0 (N–C=O), 178.0 (N–C=O), 140.7 (C(1')), 136.2 (C(1'')), 133.1 (C(4')), 129.1 (2x C(2'')/C(3'')), 128.91 (2x C(2')), 128.85 (2x C(2'')/C(3'')), 128.2 (C(4'')), 127.8 (2x C(3')), 46.6 (C(1)), 42.8 (CH$_2$Ph), 41.4 (C(6)), 35.8 (C(5)), 29.8 (C(7)).

IR (CHCl$_3$ film): 3032 (w), 2947 (w), 1770 (w), 1493 (w), 1455 (w), 1428 (w), 1390 (m), 1340 (w), 1291 (w), 1157 (w), 1092 (w), 820 (w), 701 (w) cm^{-1}.

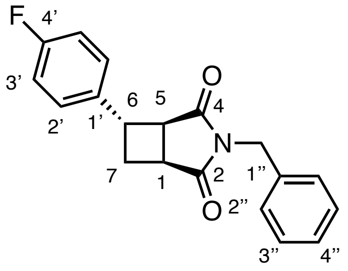
HRMS (ESI): m/z calcd for $C_{19}H_{17}O_2N^{35}Cl^+$ $[M + H]^+$ 326.0942 found 326.0943.

SFC Chiralpak® ID 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 99:1 e.r. (major enantiomer t_R = 4.18 min; minor enantiomer t_R = 5.39 min).

$[\alpha]^{25}_D$ = +118.1 (*c* = 1.0, CHCl$_3$).

m.p.: 60 – 61 °C.

3-8h



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-2** and 4-fluorophenylboronic acid (3.0 equiv.). The mixture was stirred at 60 °C for 4 h. Purification by automated medium-medium pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **3-8h** as a colourless oil (94 mg, 76%). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.45 – 7.39 (m, 2H; 2x C_{Ar}–H), 7.37 – 7.27 (m, 3H; 3x C_{Ar}–H), 7.25 – 7.20 (m, 2H; 2x C(2')–H), 7.10 – 7.00 (m, 2H; 2x C(3')–H), 4.74 (s, 2H; CH_2Ph), 3.65 – 3.52 (m, 1H; C(6)–H), 3.38 – 3.34 (m, 1H; C(5)–H), 3.34 – 3.26 (m, 1H; C(1)–H), 2.74 (dddd, *J* = 12.9, 9.8, 8.0, 0.9 Hz, 1H; C(7)–H), 2.68 – 2.53 (m, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 179.1 (N–C=O), 178.1 (N–C=O), 161.9 (d, *J* = 245.7 Hz: C(4')), 138.0 (d, *J* = 3.2 Hz; C(1')), 136.0 (C(1'')), 128.90 (2x C(2'')/C(3'')), 128.85 (2x C(2'')/C(3'')), 128.16 (2x C(2'')/C(3'')), 128.01 (d, *J* = 8.2 Hz; 2x C(2')), 115.8 (d, *J* = 21.5 Hz; 2x C(2')), 46.8 (C(1)), 42.8 (CH_2Ph), 41.4 (C(6)), 35.8 (C(5)), 29.0 (C(7)).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -115.40 – -115.51 (m) (m; C–F).

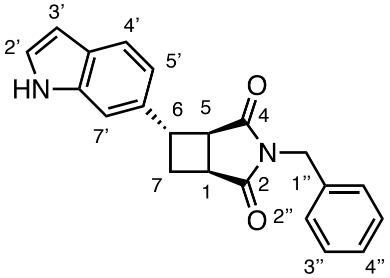
IR ($CHCl_3$ film): 2948 (w), 1769 (w), 1700 (s), 1604 (w), 1511 (m), 1429 (w), 1391 (m), 1342 (w), 1226 (w), 1158 (w), 933 (w), 831 (w), 704 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{19}H_{17}O_2NF^+$ $[M + H]^+$ 310.1238 found 310.1238.

SFC Chiralpak® ID 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99:1 e.r. (major enantiomer t_R = 3.42 min; minor enantiomer t_R = 3.92 min).

$[\alpha]^{25}_D$ = +84.5 (*c* = 1.0, $CHCl_3$).

3-8i



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-2** and 6-indoylboronic acid The mixture was stirred at 60 °C for 4 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 50/50) afforded the product **3-5i** as a colourless foam (106 mg, 80%). SFC analysis showed an enantiomeric excess of 96%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.22 (br. s, 1H; NH), 7.63 (d, *J* = 8.2 Hz, 1H; C(4')–H), 7.50 – 7.42 (m, 2H; 2x C_{Ar}–H), 7.39 – 7.27 (m, 3H; 3x C_{Ar}–H), 7.25 – 7.23 (m, 1H; C(7')–H), 7.18 (dd, *J* = 3.3, 2.3 Hz, 1H; C(2')–H), 7.04 (dd, *J* = 8.2, 1.7 Hz, 1H; C(5')–H), 6.53 (ddd, *J* = 3.2, 2.0, 1.0 Hz, 1H; C(3')–H), 4.77 (s, 2H; CH_2Ph), 3.72 (td, *J* = 8.6, 5.1 Hz, 1H; C(6)–H), 3.46 – 3.39 (m, 1H; C(5)–H), 3.32 (dddd, *J* = 10.6, 6.8, 3.7, 1.2 Hz, 1H; C(1)–H), 2.84 (ddd, *J* = 12.7, 10.6, 7.9 Hz, 1H; C(7)–H), 2.65 (dddd, *J* = 12.8, 9.2, 3.7, 1.0 Hz, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 179.5 (N–C=O), 178.6 (N–C=O), 136.3, 136.2 (C(3'$_a$), C(7'$_a$)), 136.0 (C(1'')), 128.88 (2x C(2'')/C(3'')), 128.80 (2x C(2'')/C(3'')), 128.10 (C(4''), 127.0 (C(6')), 124.8 (C(2')), 121.3 (C(5')), 118.3 (C(4')), 108.9 (C(7')), 102.7 (C(3')), 47.3 (C(1)), 42.7 (CH_2Ph), 42.5 (C(6)), 36.0 (C(4)), 30.2 (C(7)).

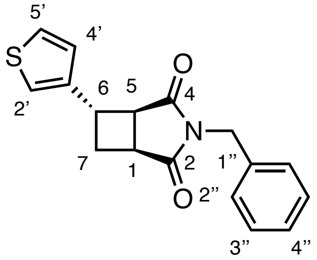
IR ($CHCl_3$ film): 3042 (br. w), 3032 (w), 2945 (w), 1766 (w), 1693 (s), 1455 (w), 1430 (w), 1392 (m), 1346 (m), 1166 (w), 812 (w) 755 (w), 723 (w), 701 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{18}O_2N_2Na^+$ $[M + Na]^+$ 353.1260 found 353.1260.

SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 98:2 e.r. (major enantiomer t_R = 5.92 min; minor enantiomer t_R = 6.19 min).

$[\alpha]^{25}_D$ = +124.4 (*c* = 1.0, $CHCl_3$).

3-8j



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-2** and 3-thiopheneboronic acid. The mixture was stirred at 60 °C for 4 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 60/40) afforded the product **3-8j** as a beige solid (119 mg, 99%). SFC analysis showed an enantiomeric excess of 80%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.49 – 7.38 (m, 2H; 2x C$_{Ar}$–H), 7.37 – 7.27 (m, 4H; 3x C$_{Ar}$–H, C(4')–H), 7.07 (dt, *J* = 3.0, 1.2 Hz, 1H; C(2')–H), 7.03 (dd, *J* = 5.0, 1.3 Hz, 1H; C(5')–H), 4.74 (s, 2H; CH$_2$Ph), 3.66 – 3.55 (m, 1H; C(6)–H), 3.40 – 3.25 (m, 2H; C(5)–H, C(1)–H), 2.74 (dddd, *J* = 14.2, 10.6, 7.6, 2.1 Hz, 1H; C(7)–H, 2.66 – 2.47 (m, 1H; C(7)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 179.2 (N–C=O), 178.0 (N–C=O), 143.4 (C(1')), 136.1 (C(1'')), 128.89 (2x C(2'')/C(3'')), 128.83 (2x C(2'')/C(3'')), 128.1 (C(4'')), 127.1 (C(4')), 126.2 (C(5')), 120.5 (C(2')), 46.7 (C(1)), 42.7 (CH$_2$Ph), 37.7 (C(6)), 35.6 (C(5)), 30.3 (C(7)).

IR (CHCl$_3$ film): 2946 (w), 1768 (w), 1698 (s), 1428 (w), 1390 (m), 1343 (w), 1167 (w), 780 (w), 701 (w) cm^{-1}.

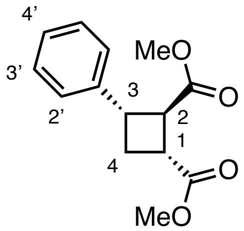
HRMS (ESI): m/z calcd for $C_{17}H_{16}O_2NS^+$ $[M + H]^+$ 298.0896 found 298.0898.

SFC Chiralpak® ID 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 90:10 e.r. (major enantiomer t$_R$ = 4.42 min; minor enantiomer t$_R$ = 5.42 min).

$[\alpha]^{25}_D$ = +86.6 (*c* = 1.0, CHCl$_3$).

m.p.: 77 – 79 °C.

3-10a



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-9** and phenylboronic acid. The mixture was stirred at 60 °C for 4 h. ^{1}H NMR spectroscopy of the reaction mixture showed a diastereomeric ratio of ~75:17:8. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-10a** as a colourless oil (66 mg, 66%). SFC analysis showed an enantiomeric excess of 94%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.38 – 7.30 (m, 2H; 2x C(3')–H), 7.30 – 7.26 (m, 2H; 2x C(2')–H), 7.23 (td, *J* = 6.6, 3.2 Hz, 1H; C(4')–H), 3.72 (s, 3H; CO_2CH_3), 3.72 (s, 3H; CO_2CH_3), 3.68 – 3.56 (m, 1H; C(3)–H), 3.50 (td, *J* = 9.4, 0.9 Hz, 1H; C(2)–H), 3.39 (dt, *J* = 9.9, 8.9 Hz, 1H; C(1)–H), 2.62 (dtd, *J* = 10.9, 8.5, 0.7 Hz, 1H; C(4)–H), 2.34 (dt, *J* = 11.0, 10.0 Hz, 1H; C(4)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 173.7 (C=O), 173.2 (C=O), 142.3 (C(1')), 128.7 (2x C(3')), 127.0 (C(4')), 126.7 (2x C(2')), 52.18 ($CO_2\mathit{C}H_3$), 52.16 ($CO_2\mathit{C}H_3$), 47.7 (C(2)), 39.8 (C(3)), 36.9 (C(1)), 29.5 (C(4)).

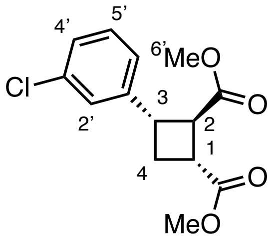
IR ($CHCl_3$ film): 2995 (w), 2953 (w), 1731 (s), 1436 (w), 1323 (w), 1234 (m), 1221 (m), 1174 (m), 1030 (w), 754 (w), 700 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{14}H_{16}O_4Na^+$ $[M + Na]^+$ 271.0941 found 271.0943.

SFC Chiralpak® IG 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 97:3 e.r. (minor enantiomer t_R = 2.12 min; major enantiomer t_R = 2.21 min).

$[\alpha]^{25}_D$ = +43.0 (*c* = 1.0, $CHCl_3$).

3-10b



The corresponding compound was prepared following general procedure 3-1 using cyclobutene **3-9** and 3-chlorophenylboronic acid. The mixture was stirred at 60 °C for 4 h. ^{1}H NMR spectroscopy of the reaction mixture showed a diastereomeric ratio of ~69:18:13. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-10b** as a colourless oil (67 mg, 59%). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.29 – 7.24 (m, 2H; C(2')–H, C(5')–H), 7.21 (dt, *J* = 8.0, 1.7 Hz, 1H; C(4')–H), 7.16 (ddt, *J* = 7.0, 1.6, 0.7 Hz, 1H; C(6')–H), 3.73 (s, 3H; CO$_2$CH$_3$), 3.73 (s, 3H; CO$_2$CH$_3$), 3.62 (ddd, *J* = 10.2, 9.4, 8.5 Hz, 1H; C(1)–H), 3.48 (td, *J* = 9.3, 0.6 Hz, 1H; C(2)–H), 3.39 (dt, *J* = 9.8, 8.8 Hz, 1H; C(1)–H), 2.62 (dtd, *J* = 10.9, 8.5, 0.7 Hz, 1H; C(4)–H), 2.31 (dt, *J* = 10.9, 9.9 Hz, 1H; C(4)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 173.5 (C=O), 172.9 (C=O), 144.3 (C(1')), 134.5 (C(3')), 129.9 (C(5')), 127.1 (C(4')), 126.9 (C(2')), 124.9 (C(6')), 52.27 (CO$_2$*C*H$_3$), 52.22 (CO$_2$*C*H$_3$), 47.5 (C(2)), 39.2 (C(3)), 36.9 (C(1)), 29.3 (C(4)).

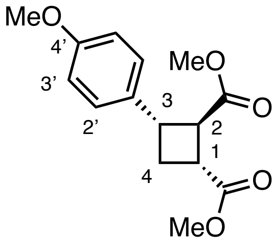
IR (CHCl$_3$ film): 2995 (w), 2953 (w), 1731 (s), 1598 (w), 1572 (w), 1436 (w), 1388 (w), 1321 (w), 1234 (m), 1203 (m), 1083 (w), 1031 (w), 786 (w), 732 (w), 692 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{14}H_{16}{}^{35}ClO_4^+$ $[M + H]^+$ 283.0732 found 283.0734.

SFC Chiralpak® ID 1500 psi, 30 °C; flow: 1.5 mL/min; hold 1% MeOH for 5 min; 98.5:1.5 e.r. (major enantiomer t_R = 3.16 min; minor enantiomer t_R = 3.56 min).

$[\alpha]^{25}_D$ = +49.7 (*c* = 1.0, CHCl$_3$).

3-10c



The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-9** and 4-methoxyphenylboronic acid. The mixture was stirred at 60 °C for 4 h. ^{1}H NMR spectroscopy of the reaction mixture showed a diastereomeric ratio of ~74:16:10. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-10c** in a diastereomeric ratio of 89.5:0:10.5 as a colourless oil (84 mg, 75%). SFC analysis showed an enantiomeric excess of 92%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.22 – 7.17 (m, 2H; 2x C(2')–H), 6.94 – 6.84 (m, 2H; 2x C(3')–H), 3.79 (s, 3H; OCH$_3$), 3.72 (s, 3H; CO$_2$CH$_3$), 3.70 (s, 3H; CO$_2$CH$_3$), 3.56 (ddd, *J* = 10.1, 9.2, 8.3 Hz, 1H; C(3)–H), 3.43 (t, *J* = 9.2 Hz, 1H; C(1)–H), 3.40 – 3.32 (m, 1H; C(4)–H), 2.62 – 2.53 (m, 1H; C(4)–H), 2.39 – 2.22 (m, 1H; C(4)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 173.8 (C=O), 173.3 (C=O), 158.7 (C(4')), 134.5 (C(1')), 127.8 (2x C(3')), 114.0 (2x C(2')), 55.4 (OCH$_3$), 52.1 (2x CO$_2$*C*H$_3$), 48.2 (C(2)), 39.4 (C(3)), 36.8 (C(1)), 29.8 (C(4)).

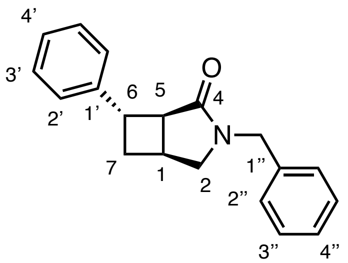
IR (CHCl$_3$ film): 2997 (w), 2953 (w), 2838 (w), 1731 (s), 1613 (w), 1515 (m), 1437 (w), 1489 (w), 1305 (w), 1249 (s), 1177 (m), 1114 (m), 1034 (m), 829 (w) cm^{-1}.

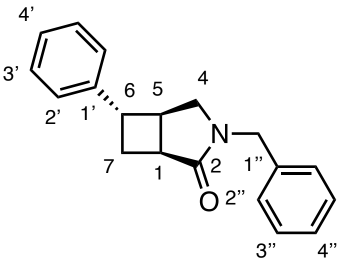
HRMS (ESI): m/z calcd for $C_{15}H_{19}O_5^+$ [M + H]$^+$ 279.1227 found 279.1228.

SFC Chiralpak® IG 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 96:4 e.r. (minor enantiomer t$_R$ = 2.96 min; major enantiomer t$_R$ = 3.16 min).

[α]^{25}$_D$ = +51.2 (*c* = 1.0, CHCl$_3$).

3-12 and **3-12’**





The corresponding compound was prepared following general procedure 3-1 using cyclobutene (±)-**3-11** and phenylboronic acid. The mixture was stirred at 60 °C for 4 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 20/80) afforded the product **3-12** as a colourless solid (42 mg, 38%) and **3-12’** as a colourless oil (49 mg, 44%). SFC analysis showed an enantiomeric excess of 83% for **3-12** and 84% for **3-12’**.

Analytical data for 3-12:

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.42 – 7.28 (m, 9H; 9x C_{Ar}–H), 7.25 – 7.20 (m, 1H; 1x C_{Ar}–H), 4.68 (d, J = 14.6 Hz, 1H; 1x CH_2Ph), 4.43 (d, J = 14.6 Hz, 1H; 1x CH_2Ph), 3.81 – 3.65 (m, 1H; C(6)–H), 3.51 (dd, J = 10.2, 7.8 Hz, 1H; C(2)–H), 3.32 – 3.15 (m, 2H; C(2)–H and C(5)–H), 3.07 – 2.93 (m, 1H; C(1)–H), 2.51 (dddd, J = 12.7, 9.0, 5.6, 2.0 Hz, 1H; C(7)–H), 2.33 (dddd, J = 12.5, 9.2, 5.6, 1.0 Hz, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 176.2 (C=O), 144.7 (C(1’)), 136.8 (C(1’’)), 128.9 (2x C_{Ar}–H), 128.7 (2x C_{Ar}–H), 128.3 (2x C_{Ar}–H), 127.8 (C_{Ar}–H), 126.6 (2x C_{Ar}–H), 126.5 (C_{Ar}–H), 53.3 (C(2)), 48.6 (C(5)), 46.9 (CH_2Ph), 42.9 (C(6)), 33.9 (C(7)), 27.5 (C(1)).

IR ($CHCl_3$ film): 3061 (w), 3027 (w), 2971 (w), 2928 (w), 1678 (s), 1493 (w), 1444 (w), 1427 (m), 1288 (w), 756 (w), 700 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{19}H_{20}ON^+$ $[M + H]^+$ 278.1540 found 278.1539.

SFC Chiralpak® IA 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 91.5:8.5 e.r. (major enantiomer t_R = 4.76 min; minor enantiomer t_R = 6.01 min).

$[\alpha]^{25}_D$ = +48.7 (*c* = 1.0, $CHCl_3$).

m.p.: 82 – 83 °C.

Analytical data for 3-12':

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.41 – 7.27 (m, 7H; 7x C_{Ar}–H), 7.24 – 7.13 (m, 3H; 3x C_{Ar}–H), 4.66 (d, *J* = 14.6 Hz, 1H; 1x CH_2Ph), 4.47 (d, *J* = 14.6 Hz, 1H; 1x CH_2Ph), 3.48 (dd, *J* = 10.3, 6.6 Hz, 1H; C(4)–H), 3.36 (td, *J* = 9.0, 6.5 Hz, 1H; C(6)–H), 3.20 (d, *J* = 10.3 Hz, 1H; C(4)–H), 3.14 – 3.07 (m, 1H; C(1)–H), 3.00 (dt, *J* = 7.7, 6.7 Hz, 1H; C(5)–H), 2.67 (dddd, *J* = 11.2, 8.8, 2.5, 0.9 Hz, 1H; C(4)–H), 2.58 (dt, *J* = 12.0, 9.4 Hz, 1H; C(4)–H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 177.0 (C=O), 143.9 (C(1')), 136.7 (C(1'')), 128.9 (2x C_{Ar}–H), 128.7 (2x C_{Ar}–H), 128.4 (2x C_{Ar}–H), 127.8 (C_{Ar}–H), 126.6 (C_{Ar}–H), 126.4 (2x C_{Ar}–H), 52.5 (C(4)), 47.1 (CH_2Ph), 44.7 (C(6)), 38.9 (C(5)), 38.1 (C(1)), 31.7 (C(7)).

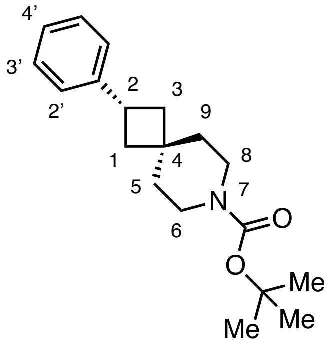
IR ($CHCl_3$ film): 3060 (w), 3027 (w), 2940 (w), 2865 (w), 1678 (s), 1494 (w), 1445 (w), 1426 (w), 1302 (w), 1263 (w), 749 (w), 700 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{19}H_{20}ON^+$ $[M + H]^+$ 278.1540 found 278.1541.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 92:8 e.r. (major enantiomer t_R = 5.05 min; minor enantiomer t_R = 5.39 min).

$[\alpha]^{25}_D$ = +80.0 (*c* = 1.0, $CHCl_3$).

3-15a



(Experiment performed by L. van Dijk)

The corresponding compound was prepared following general procedure 3-4 using cyclobutene **3-14** and phenylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-15a** as a colourless solid (102 mg, 84%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.36 – 7.26 (m, 2H; 2x C(3')–H), 7.24 – 7.14 (m, 3H; 2x C(2')–H), C(4')–H), 3.52 (p, *J* = 9.1 Hz, 1H; C(2)–H), 3.45 – 3.38 (m, 2H; 2x C(6)–H/C(8)–H), 3.34 – 3.25 (m, 2H; 2x C(6)–H/C(8)–H), 2.35 – 2.24 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.95 – 1.85 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.74 – 1.68 (m, 2H; 2x C(5)–H/C(9)–H), 1.54 – 1.48 (m, 2H; 2x C(5)–H/C(9)–H), 1.47 (s, 9H; $C(CH_3)_3$).

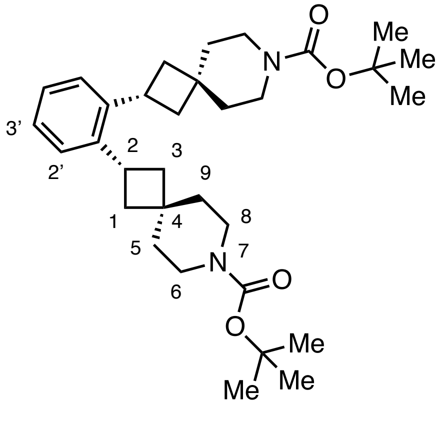
^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.1 (C=O), 146.2 (C(1')), 128.4 (2x C(3')), 126.5 (2x C(2')), 125.9 (C(4')), 79.4 ($\mathit{C}(CH_3)_3$), 41.1 (C(6)/C(8)), 40.8 (C(6)/C(8)), 39.3 (C(5)/C(9)), 39.2 (C(1), C(3)), 36.0 (C(5)/C(9)), 34.0 (C(4)), 33.6 (C(2)), 28.6 ($C(\mathit{C}H_3)_3$).

IR ($CHCl_3$ film): 2970 (w), 2921 (w), 2860 (w), 1677 (s), 1477 (m), 1425 (s), 1366 (m), 1271 (m), 1242 (s), 1177 (m), 1149 (s). 1110 (m), 1076 (m), 975 (m), 868 (w), 747 (w), 702 (w), 633 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{14}H_{20}N^+$ $[M + H – CO_2 – CH_2{=}C(CH_3)_2]^+$ 202.1590 found 202.1592.

m.p.: 91 – 92 °C.

3-15a’



(Experiment performed by L. van Dijk)

The following compound was isolated as a side-product of **3-15a**. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **3-15a’** as a colourless solid (24 mg, 11%).

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.30 – 7.23 (m, 2H; 2x C(2’)–H), 7.23 – 7.17 (m, 2H; 2x C(3’)–H,), 3.57 (p, *J* = 9.1 Hz, 2H; 2x C(2)–H)), 3.49 – 3.38 (m, 4H; 4x C(6)–H/C(8)–H)), 3.36 – 3.24 (m, 4H; 4x C(6)–H/C(8)–H)), 2.31 – 2.19 (m, 4H; 2x C(1)–H, 2x C(3)–H), 1.90 (td, *J* = 9.5, 2.4 Hz, 4H; 2x C(1)–H, 2x C(3)–H), 1.77 – 1.66 (m, 4H; 4x C(5)–H/C(9)–H), 1.52 – 1.47 (m, 4H; 4x C(5)–H/C(9)–H), 1.46 (s, 18H; C(CH$_3$)$_3$).

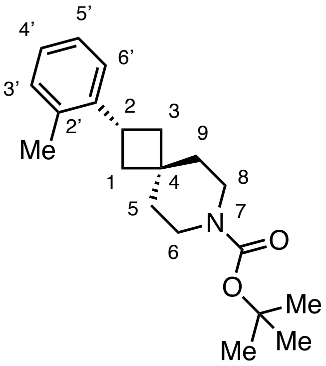
^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 155.1 (2x C=O), 143.1 (2x C(1’)), 126.1 (2x C(3’)), 125.8 (2x C(2’)), 79.4 (2x *C*(CH$_3$)$_3$), 41.1 (2x C(6)/C(8)), 40.8 (2x C(6)/C(8)), 39.4 (2x C(5)/C(9)), 38.8 (2x C(1), C(3)), 36.1 (2x C(5)/C(9)), 33.8 (2x C(4)), 31.0 (2x C(2)), 28.6 (6x CH$_3$).

IR (CHCl$_3$ film): 2974 (w), 2921 (w), 2850 (w), 1690 (s), 1477 (m), 1421 (m), 1364 (s), 1270 (m), 1243 (s), 1175 (m), 1147 (s). 1113 (m), 975 (w), 864 (w), 753 (w), 732 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{32}H_{48}N_2NaO_4^+$ $[M + Na]^+$ 547.3506 found 547.3505.

m.p.: 120 – 122 °C.

3-15b



(Experiment performed by L. van Dijk)

The corresponding compound was prepared following general procedure 3-4 using cyclobutene **3-14** and 2-methylphenylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-15b** as a colourless solid (55 mg, 43%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.24 (d, *J* = 7.8 Hz, 1H; C(6’)–H), 7.21 – 7.16 (m, 1H; C(3’)–H), 7.14 – 7.07 (m, 2H; C(4’)–H, C(5’)–H), 3.62 (p, *J* = 9.1 Hz, 1H; C(2)–H), 3.51 – 3.42 (m, 2H; 2x C(6)–H/C(8)–H), 3.36 – 3.14 (m, 2H; 2x C(6)–H/C(8)–H), 2.39 – 2.26 (m, 2H; 1x C(1)–H, 1x C(3)–H), 2.24 (s, 3H; CH_3), 1.92 (td, *J* = 9.5, 2.5 Hz, 2H; 1x C(1)–H, 1x C(3)–H), 1.77 – 1.70 (m, 2H; 2x C(5)–H/C(9)–H), 1.52 – 1.48 (m, 2H; 2x C(5)–H/C(9)–H), 1.47 (s, 9H; $C(CH_3)_3$)

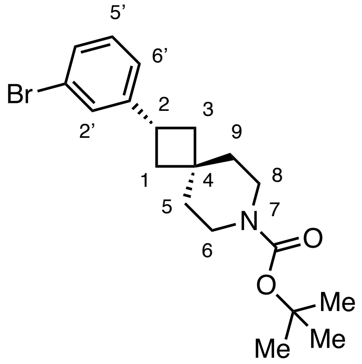
^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 155.1 (C=O), 143.5 (C(1’)), 136.1 (C(2’)), 130.2 (C(3’)), 126.0 (C(4’), C(5’)), 125.3 (C(6’)), 79.4 ($\mathit{C}(CH_3)_3$), 41.0 (rot.; C(6), C(8)), 39.5 (C(5)/C(9)), 38.0 (C(1), C(3)), 36.1 (C(5)/C(9)), 33.9 (C(4)), 31.6 (C(2)), 28.6 ($C(\mathit{C}H_3)_3$), 19.8 (CH_3).

IR ($CHCl_3$ film): 2972 (w), 2920 (w), 1691 (s), 1461 (m), 1420 (m), 1365 (m), 1270 (m), 1242 (s), 1175 (m), 1147 (s), 1111 (m), 973 (w), 865 (w), 750 (w), 721 (w), 635 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{15}H_{22}N^+$ $[M + H –CO_2–CH_2=C(CH_3)_2]^+$ 216.1747 found 216.1748.

m.p.: 86 – 87 °C.

3-15c



(Experiment performed by L. van Dijk)

The corresponding compound was prepared following general procedure 3-4 using cyclobutene **3-14** and 3-bromophenylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-15c** as a colourless oil (112 mg, 74%).

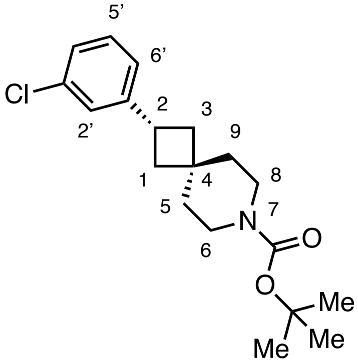
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.27 – 7.25 (m, 1H; C(2')–H), 7.24 – 7.21 (m, 1H; C(4')–H), 7.08 (t, *J* = 7.6 Hz, 1H; C(5)–H), 7.03 (dtd, *J* = 7.7, 1.5, 0.7 Hz, 1H; C(6')–H), 3.47 (p, *J* = 9.2 Hz, 1H; C(2)–H), 3.43 – 3.37 (m, 2H; 2x C(6)–H/C(8)–H), 3.32 – 3.19 (m, 2H; 2x C(6)–H/C(8)–H), 2.38 – 2.17 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.87 (td, *J* = 9.5, 2.5 Hz, 2H; 1x C(1)–H, 1x C(3)–H), 1.71 – 1.66 (m, 2H; 2x C(5)–H/C(9)–H), 1.52 – 1.47 (m, 2H; 2x C(5)–H/C(9)–H), 1.46 (s, 9H; $C(CH_3)_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.1 (C=O), 148.5 (C(1')), 130.0 (C(5')), 129.7 (C(2')), 129.0 (C(4')), 125.2 (C(6')), 122.6 (C(3')), 79.4 (*C*$(CH_3)_3$), 41.0 (C(6)/C(8)), 40.7 (C(6)/C(8)), 39.3 (C(5)/C(9)), 39.1 (C(1), C(3)), 35.9 (C(5)/C(9)), 34.1 (C(4)), 33.3 (C(2)), 28.6 (C(*C*$H_3)_3$).

IR ($CHCl_3$ film): 2973 (w), 2924 (w), 2848 (w), 1692 (s), 1595 (w), 1476 (w), 1422 (m), 1365 (w), 1270 (w), 1243 (m), 1148 (w), 1110 (m), 997 (w), 954 (w), 865 (w), 778 (w), 691 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{19}H_{26}O_2{}^{79}BrNNa^+$ $[M + Na]^+$ 402.1039 found 402.1039.

3-15d



(Experiment performed by L. van Dijk)

The corresponding compound was prepared following general procedure 3-4 using cyclobutene **3-14** and 3-chlorophenylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-15c** as a colourless solid (97 mg, 72%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.21 (app. t, J = 7.7 Hz, 1H; C(5')–H), 7.17 – 7.09 (m, 2H; C(2')–H, C(4')–H), 7.06 (ddt, J = 7.6, 1.9, 0.9 Hz, 1H, 1H; C(6')–H), 3.48 (p, J = 9.1 Hz, 1H; C(2)–H), 3.45 – 3.37 (m, 2H; 2x C(6)–H/C(8)–H), 3.33 – 3.25 (m, 2H; 2x C(6)–H/C(8)–H), 2.36 – 2.21 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.97 – 1.79 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.73 – 1.65 (m, 2H; 2x C(5)–H/C(9)–H), 1.53 – 1.46 (m, 2H; 2x C(5)–H/C(9)–H), 1.46 (s, 9H; $C(CH_3)_3$).

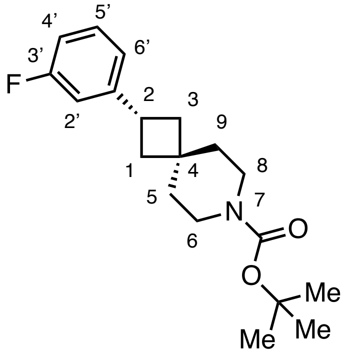
^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.0 (C=O), 148.2 (C(1')), 134.2 (C(3')), 129.6 (C(5')), 126.7 (C(2')), 126.0 (C(4')), 124.7 (C(6')), 79.4 ($\mathit{C}(CH_3)_3$), 41.0 (C(6)/C(8)), 40.7 (C(6)/C(8)), 39.3 (C(5)/C(9)), 39.0 (C(1)), C(3)), 35.9 (C(5)/C(9)), 34.0 (C(4)), 33.2 (C(2)), 28.6 ($C(\mathit{C}H_3)_3$).

IR ($CHCl_3$ film): 2923 (w), 2848 (w), 1677 (s), 1478 (m), 1420 (m), 1365 (s), 1270 (m), 1242 (s), 1175 (m), 1146 (s), 1079 (m), 955 (w), 866 (w), 780 (m), 702 (w), 692 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{14}H_{19}{}^{35}ClN^+$ $[M + H - CO_2 - CH_2{=}C(CH_3)_2]^+$ 236.1201 found 236.1202.

m.p.: 71 – 72 °C.

3-15e



The corresponding compound was prepared following general procedure 3-4 using cyclobutene **3-14** and 3-fluorophenylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-15e** as a colourless solid (119 mg, 91%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.24 (td, *J* = 7.9, 6.0 Hz, 1H; C(5')–H), 6.96 (d, *J* = 7.6 Hz, 1H; C(6')–H), 6.93 – 6.79 (m, 2H; C(2')–H, C(4')–H), 3.50 (p, *J* = 9.2 Hz, 1H; C(2)–H), 3.44 – 3.38 (m, 2H; 2x C(6)–H/C(8)–H), 3.34 – 3.22 (m, 2H; 2x C(6)–H/C(8)–H), 2.29 (td, *J* = 8.9, 2.6 Hz, 2H; 2x C(5)–H/C(9)–H), 1.87 (td, *J* = 9.5, 2.4 Hz, 2H; 2x C(5)–H/C(9)–H), 1.77 – 1.64 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.50 (dd, *J* = 6.8, 4.6 Hz, 2H; 1x C(1)–H, 1x C(3)–H), 1.46 (s, 9H; $C(CH_3)_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 163.1 (d, *J* = 245.6 Hz; C(3'')), 155.1 (C=O), 148.9 (d, *J* = 6.8 Hz; C(1'')), 129.8 (d, *J* = 8.3 Hz; C(5')), 122.1 (d, *J* = 2.8 Hz; C(6')), 113.3 (d, *J* = 21.1 Hz; C(2')), 112.7 (d, *J* = 21.1 Hz; C(4')), 79.4 ($\mathit{C}(CH_3)_3$), 40.9 (rot.; C(6), C(8)), 39.3 (C(5)/C(9)), 39.1 (C(1), C(3)), 35.9 (C(5)/C(9)), 34.0 (C(4)), 33.3 (d, *J* = 2.0 Hz; C(2)), 28.6 ($C(\mathit{C}H_3)_3$).

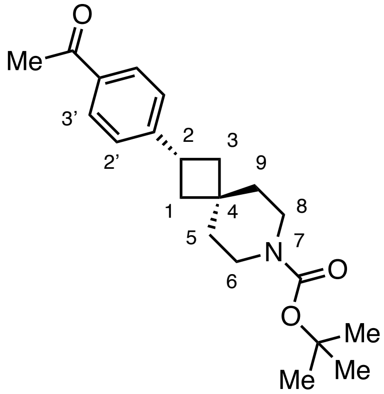
^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -113.65 (td, *J* = 9.5, 9.0, 6.0 Hz; C–F).

IR ($CHCl_3$ film): 2980 (w), 2926 (w), 1690 (s), 1588 (w), 1421 (m), 1365 (m), 1270 (m), 1243 (m), 1175 (m), 1145 (s), 1108 (m), 962(w), 862 (w), 780 (w), 691 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{14}H_{19}NF^+$ $[M+H–CO_2–CH_2=C(CH_3)_2]^+$ 220.1496 found 220.1498.

m.p.: 89 – 90 °C

3-15f



(Experiment performed by L. van Dijk)

The corresponding compound was prepared following general procedure 3-4 using cyclobutene **3-14** and 4-acetylphenylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-15f** as a colourless solid (117 mg, 85%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.94 – 7.87 (m, 2H; 2x C(3')–H), 7.32 – 7.25 (m, 2H; 2x C(2')–H), 3.58 (p, *J* = 9.1 Hz, 1H; C(2)–H), 3.47 – 3.39 (m, 2H; 2x C(6)–H/C(8)–H), 3.34 – 3.27 (m, 2H; 2x C(6)–H/C(8)–H), 2.58 (s, 3H; CH_3), 2.39 – 2.28 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.98 – 1.87 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.76 – 1.68 (m, 2H; 2x C(5)–H/C(9)–H), 1.57 – 1.49 (m, 2H; 2x C(5)–H/C(9)–H), 1.47 (s, 9H; $C(CH_3)_3$).

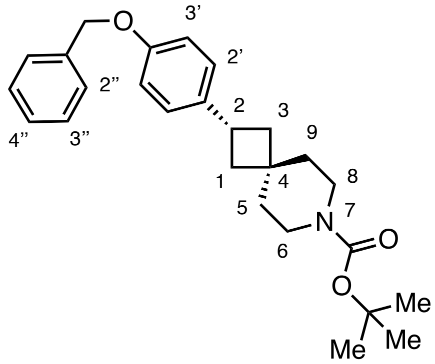
^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 197.8 ((*C*=O)CH_3), 155.0 (C=O), 151.8 (C(1')), 135.1 (C(4')), 128.6 (2x C(3')), 126.6 (2x C(2')), 79.4 (*C*$(CH_3)_3$), 41.0 (C(6)/C(8)), 40.7 (C(6)/C(8)), 39.2 (C(5)/C(9)), 39.0 (C(1), C(3)), 35.9 (C(5)/C(9)), 34.1 (C(4)), 33.6 (C(2)), 28.5 (3x CH_3), 26.6 (CH_3).

IR ($CHCl_3$ film): 2923 (w), 2851 (w), 1680 (s), 1605 (m), 1421 (m), 1364, (m), 1268 (m), 1243 (m), 1175 (m), 1146 (m), 1111 (m), 976 (w), 820 (w), 769 (w), 638 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{29}NNaO_3^+$ $[M + Na]^+$ 366.2040 found 366.2040.

m.p.: 79 – 81 °C

3-15g



The corresponding compound was prepared following general procedure 3-4 using cyclobutene **3-14** and 4-benzyloxyphenylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-15g** as a colourless solid (60 mg, 37%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.47 – 7.42 (m, 2H; 2x C(2'')–H), 7.41 – 7.36 (m, 2H; 2x C(3'')–H), 7.35 – 7.29 (m, 1H; (4'')–H), 7.18 – 7.07 (m, 2H; 2x C(2')–H), 7.04 – 6.84 (m, 2H; 2x C(3')–H), 5.05 (s, 2H, OCH_2Ph), 3.48 (p, *J* = 9.1 Hz, 1H; C(2)–H), 3.42 (dd, *J* = 6.7, 4.6 Hz, 2H; 2x C(6)–H/C(8)–H), 3.36 – 3.25 (m, 2H; 2x C(6)–H/C(8)–H), 2.27 (ddt, *J* = 10.4, 8.8, 1.5 Hz, 2H; 1x C(1)–H, 1x C(3)–H), 1.86 (td, *J* = 9.5, 2.5 Hz, 2H; 1x C(1)–H, 1x C(3)–H), 1.70 (t, *J* = 5.7 Hz, 2H; 2x C(5)–H/C(9)–H), 1.51 (dd, *J* = 6.5, 4.6 Hz, 2H; 2x C(5)–H/C(9)–H), 1.47 (s, 9H; $C(CH_3)_3$)

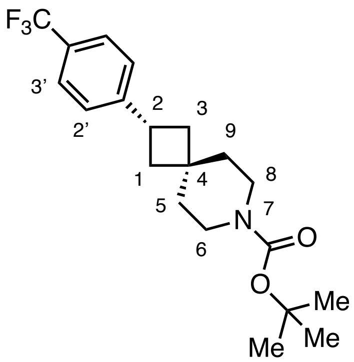
^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 157.1 (C(4')), 155.1 (C=O), 138.6 (C(1')), 137.3 (C(1'')), 128.7 (C(3'')), 128.0 (C(4'')), 127.6, 127.5 (2x C(2') and 2x C(2'')), 114.8 (2x C(3')), 79.3 ($\mathit{C}(CH_3)_3$), 70.2 (OCH_2Ph), 41.0 (rot.; C(6), C(8)), 39.5 (C(1), C(3)), 39.4 (C(5)/C(9)), 36.0 (C(5)/C(9)), 33.8 (C(4)), 32.9 (C(2)), 28.6 ($C(\mathit{C}H_3)_3$).

IR ($CHCl_3$ film): 2911 (w), 2852 (w), 1677 (s), 1609 (w), 1511 (m), 1467 (w), 1454 (w), 1424 (m), 1387 (w), 1270(m), 1243 (s), 1178 (m), 1148 (m), 1021 (w), 866 (w), 820 (w), 760 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{26}H_{33}O_3NNa^+$ $[M + Na]^+$ 430.2353 found 430.2352.

m.p.: 152 – 154 °C.

3-15h



(Experiment performed by L. van Dijk)

The corresponding compound was prepared following general procedure 3-4 using cyclobutene **3-14** and (4-(trifluoromethyl)phenyl)boronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-15h** as a colourless solid (124 mg, 84%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.58 – 7.50 (m, 2H; 2x C(3')–H), 7.33 – 7.26 (m, 2H; 2x C(2')–H), 3.57 (p, *J* = 9.1 Hz, 1H; C(2)–H), 3.46 – 3.40 (m, 2H; 2x C(6)–H/C(8)–H), 3.34 – 3.26 (m, 2H; 2x C(6)–H/C(8)–H), 2.38 – 2.27 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.98 – 1.83 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.75 – 1.65 (m, 2H; 2x C(5)–H/C(9)–H), 1.53 – 1.47 (m, 2H; 2x C(5)–H/C(9)–H), 1.46 (s, 9H; $C(CH_3)_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) δ 155.1 (C=O), 150.2 (C(1')), 128.2 (q, *J* = 31.9; C(4')) 126.8 (2x C(2')), 125.4 (q, *J* = 3.8; 2x C(3')) 124.5 (q, *J* = 271.4; CF_3), 79.5 ($\mathit{C}(CH_3)_3$), 41.1 (C(6)/C(8)), 40.7 (C(6)/C(8)), 39.3 (C(5)/C(9)), 39.1 (C(1), C(3)), 36.0 (C(5)/C(9)), 34.2 (C(4)), 33.4 (C(2)), 28.6 ($C(\mathit{C}H_3)_3$).

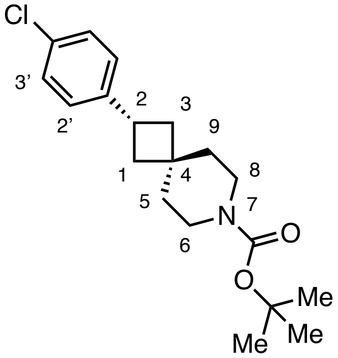
^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -62.29 (s; CF_3).

IR ($CHCl_3$ film): 2926 (w), 2855 (w), 1682 (s), 1424 (m), 1365 (m), 1322 (m), 1244 (w), 1151 (m), 1111 (s), 1064 (m), 977 (w), 860 (w), 825 (w), 768 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{15}H_{19}F_3N^+$ $[M + H - CO_2 - CH_2{=}C(CH_3)_2]^+$ 270.1464 found 270.1465.

m.p.: 88 – 90 °C.

3-15i



(Experiment performed by L. van Dijk)

The corresponding compound was prepared following general procedure 3-4 using cyclobutene **3-14** and 4-chlorophenylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-15i** as a colourless solid (114 mg, 85%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.32 – 7.22 (m, 2H; 2x C(3')–H), 7.16 – 7.10 (m, 2H; 2x C(2')–H), 3.48 (p, *J* = 9.1 Hz, 1H; C(2)–H), 3.45 – 3.39 (m, 2H; 2x C(6)–H/C(8)–H), 3.34 – 3.28 (m, 2H; 2x C(6)–H/C(8)–H), 2.37 – 2.23 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.86 (td, *J* = 9.5, 2.5 Hz, 2H; 1x C(1)–H, 1x C(3)–H), 1.77 – 1.66 (m, 2H; 2x C(5)–H/C(9)–H)), 1.55 – 1.49 (m, 2H; 2x C(5)–H/C(9)–H), 1.46 (s, 9H; $C(CH_3)_3$).

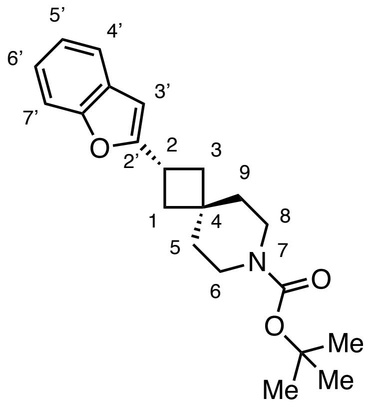
^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.1 (C=O), 144.6 (C(1')), 131.5 (C(4')), 128.4 (2x C(3')), 127.9 (2x C(2')), 79.4 ($\mathit{C}(CH_3)_3$), 41.0 (C(6)/C(8)), 40.7 (C(6)/C(8)), 39.3 (C(5)/C(9)), 39.2 (C(1), C(3)), 35.9 (C(5)/C(9)), 34.0 (C(4)), 33.0 (C(2)), 28.6 ($C(\mathit{C}H_3)_3$).

IR ($CHCl_3$ film): 2973(w), 2923 (w), 12851 (w), 1680 (s), 1491 (w), 1420 (m), 1365 (m), 1270 (m), 1243 (m), 1174 (m), 1147 (s), 1090 (m), 1034 (w), 976 (w), 908 (w), 814 (w) 731 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{14}H_{19}{}^{35}ClN^+$ $[M + H - CO_2 - CH_2{=}C(CH_3)_2]^+$ 236.1201 found 236.1202.

m.p.: 112 – 114 °C.

3-15j



The corresponding compound was prepared following general procedure 3-4 using cyclobutene **3-14** and 2-benzofuranylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-15j** as a pale-yellow solid (117 mg, 86%). *Note: The product is contaminated with a small amount (~5%) of an impurity which is likely the minor regioisomeric cyclobutane.*

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.55 – 7.44 (m, 1H; C(4')–H), 7.45 – 7.38 (m, 1H; C(7')–H), 7.24 – 7.19 (m, 1H; C(6')–H), 7.19 – 7.15 (m, 1H; C(5')–H), 6.39 (t, J = 0.8 Hz, 1H; C(3')–H), 3.62 (p, J = 8.7 Hz, 1H; C(2)–H), 3.45 – 3.37 (m, 2H; 2x C(6)–H/C(8)–H), 3.37 – 3.20 (m, 2H; 2x C(6)–H/C(8)–H), 2.40 – 2.19 (m, 2H; 1x C(1)–H, 1x C(3)–H), 2.19 – 2.06 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.71 – 1.66 (m, 2H; 2x C(5)–H/C(9)–H), 1.60 (td, J = 5.6, 5.0, 2.4 Hz, 2H; 2x C(5)–H/C(9)–H), 1.47 (s, 9H; $C(CH_3)_3$).

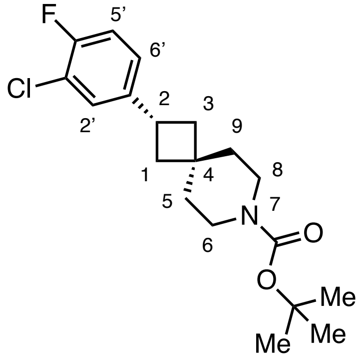
^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 162.2 (C(2')), 155.1 (C=O), 154.9 (C(7a')), 129.0 (C(3a')), 123.4 (C(6')), 122.6 (C(5')), 120.4 (C(4')), 110.9 (C(7')), 101.0 (C(3')), 79.4 ($C(CH_3)_3$), 40.9 (rot.; C(6) and C(8)), 38.9 (C(5)/C(9)), 37.2 (C(1), C(3)), 36.3 (C(5)/C(9)), 34.6 (C(4)), 28.6 ($C(CH_3)_3$), 27.4 (C(2)).

IR ($CHCl_3$ film): 2968 (w), 2927 (w), 2849 (w), 1689 (s), 1599 (w), 1455 9m), 1421 (m), 1365 (m), 1270 (m), 1243 (s), 1174 (m), 1146 (s), 1115 (w), 890 (w), 863 (w), 795 (w), 751 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{27}O_3NNa^+$ $[M + Na]^+$ 364.1883 found 364.1884.

m.p.: 59 – 61 °C.

3-15k



The corresponding compound was prepared following general procedure 3-4 using cyclobutene **3-14** and 3-chloro-4-fluorophenylboronic acid with an increased loading of [Rh(cod)OH]$_2$ (5.0 mol%) and dppf (12.0 mol%). The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-15k** as a colourless solid (92 mg, 65%).

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.20 (ddt, *J* = 7.1, 1.8, 0.8 Hz, 1H; C(2')–H), 7.10 – 6.94 (m, 2H; C(5')–H, C(6')–H), 3.47 (p, *J* = 9.1 Hz, 1H; C(2)–H), 3.44 – 3.37 (m, 2H; 2x C(6)–H/C(8)–H), 3.32 – 3.14 (m, 2H; 2x C(6)–H/C(8)–H), 2.45 – 2.11 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.84 (td, *J* = 9.4, 2.5 Hz, 2H; 1x C(1)–H, 1x C(3)–H), 1.75 – 1.66 (m, 2H; 2x C(5)–H/C(9)–H), 1.55 – 1.48 (m, 2H; 2x C(5)–H/C(9)–H), 1.46 (s, 9H; C(CH$_3$)$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 156.5 (d, *J* = 246.4 Hz; C(4')), 155.1 (C=O), 143.2 (d, *J* = 3.8 Hz; C(1')), 128.6 (C(2')), 126.1 (d, *J* = 6.9 Hz; C(6')), 120.7 (d, *J* = 17.6 Hz; C(3')), 116.3 (d, *J* = 20.7 Hz; C(5')), 79.5 (*C*(CH$_3$)$_3$), 40.8 (rot.; C(6), C(8)), 39.34 (C(5)/C(9)), 39.26 (C(1), C(3)), 35.9 (C(5)/C(9)), 34.0 (C(4)), 32.8 (C(2)), 28.6 (C(*C*H$_3$)$_3$).

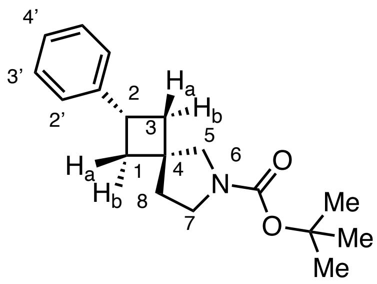
^{19}F NMR (CDCl$_3$, 377 MHz): δ (ppm) -119.73 – -120.59 (m; C–F).

IR (CHCl$_3$ film): 2977 (w), 2924 (w), 2852 (w), 1689 (s), 1501 (s), 1478 (m), 1466 (m), 1422 (m), 1365 (m), 1269 (m), 1244 (s), 1175 (m), 1148 (s). 1121 (w), 1059 (w), 983 (w), 957 (w), 908 (w), 864 (w), 815 (w), 801 (w), 769 (w), 731 (m), 617 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{14}H_{17}ClFN^+$ [M + H – CO$_2$ – CH$_2$=C(CH$_3$)$_2$]$^+$ 254.1106 found 254.1107.

m.p.: 71 – 72 °C.

3-17



(Experiment performed by L. van Dijk)

The corresponding compound was prepared following general procedure 3-4 using cyclobutene (±)-**3-16** and phenylboronic acid. The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-17** in a diastereomeric ratio of 4:1 as a colourless oil (75 mg, 65%).

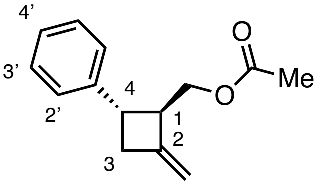
^{1}H NMR (CDCl$_3$, 400 MHz; major diastereomer): δ (ppm) 7.36 – 7.28 (m, 2H; 2x C(3’)–H), 7.23 – 7.10 (m, 3H; 2x C(2’)–H, C(4’)–H), 3.59 – 3.46 (m, 1H; C(2)–H), 3.41 (t, *J* = 6.8 Hz, 2H; C(7)–H$_2$), 3.26 (s, 2H; C(5)–H$_2$), 2.38 – 2.26 (m, 2H; C(1)–H$_a$, C(3)–H$_a$), 2.24 – 2.14 (m, 2H; C(1)–H$_b$, C(3)–H$_b$), 2.02 (t, *J* = 6.8 Hz, 1H; C(8)–H$_2$), 1.46 (s, 9H; C(CH$_3$)$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz; major diastereomer): δ (ppm) 154.7 (C=O), 145.4 (C(1’)), 128.4 (2x C(3’)), 126.4 (2x C(2’)), 126.1 (C(4’)), 79.2 (*C*(CH$_3$)$_3$), 57.7 (C(5)), 44.8 (C(7)), 39.0 (C(3)), 36.8 (C(8)), 34.1 (C(4)), 28.7 (C(*C*H$_3$)$_3$).

IR (CHCl$_3$ film): 2974 (w), 2924 (w), 2866 (w), 1697 (s), 1476 (w), 1455 (w), 1401 (s), 1365 (w), 1298 (w), 1255 (w), 1226 (w), 1164 (m), 1102 (m), 974 (w), 934 (w), 879 (w), 772 (w), 716 (w) cm^{-1}.

HRMS (ESI): m/z calcd for C$_{18}$H$_{25}$NNaO$_2$$^+$ [M + Na]$^+$ 310.1778 found 310.1778.

3-19a



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and phenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20) afforded the product **3-19a** as a pale-yellow oil (68 mg, 79%). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.37 – 7.26 (m, 4H; 2x C(2')–H; 2x C(3')–H), 7.25 – 7.18 (m, 1H; C(4')–H), 4.96 – 4.89 (m, 2H; C=CH_2), 4.32 (dd, *J* = 11.2, 6.5 Hz, 1H; 1x CH_2O), 4.25 (dd, *J* = 11.2, 5.7 Hz, 1H; 1x CH_2O), 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=O)CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.2 (C=O), 146.3 (C(2)), 144.1 (C(1')), 128.6 (2x C(3')), 126.8 (2x C(2')), 126.5 (C(4')), 106.1 (C=*C*H_2), 65.8 (CH_2O), 50.8 (C(1)), 39.9 (C(4)), 37.2 (C(3)) 21.0 ((C=O)*C*H_3).

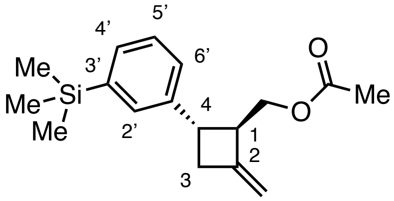
IR ($CHCl_3$ film): 2956 (w), 1740 (s), 1679 (w), 1603 (w), 1496 (w), 1454 (w), 1382 (w), 1365 (w), 1234 (s), 1033 (m), 883 (w), 752 (m), 699 (m) cm^{-1}.

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

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

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

3-19b



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and 3-trimethylsilylphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20) afforded the product **3-19b** as a colourless oil (67 mg, 58%). SFC analysis showed an enantiomeric excess of 96%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.41 (s, 1H; C(2')–H), 7.38 (dt, *J* = 7.0, 1.4 Hz, 1H; C(4')–H), 7.33 (app. t, *J* = 7.3 Hz, 1H; C(5')–H), 7.28 (dt, *J* = 7.6, 1.6 Hz, 1H; C(6')–H), 4.96 – 4.90 (m, 2H; C=CH_2), 4.32 (dd, *J* = 11.2, 6.6 Hz, 1H; 1x CH_2O), 4.26 (dd, *J*=11.2, 5.8 Hz, 1H; 1x CH_2O), 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=O)CH_3), 0.28 (s, 9H; Si(CH_3)$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.2 (C=O), 146.4 (C(2)), 143.2 (C(3')), 140.8 (C(1')), 131.7 (C(2')), 131.5 (C(4')), 128.0 (C(5')), 127.2 (C(6')), 106.1 (C=*C*H_2), 65.9 (CH_2O), 50.8 (C(1)), 40.0 (C(4)), 37.2 (C(3)), 21.1 ((C=O)*C*H_3), -0.9 (Si(CH_3)$_3$).

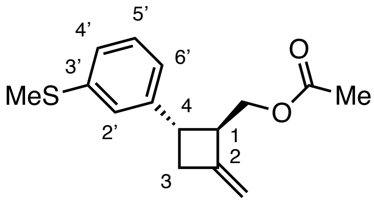
IR ($CHCl_3$ film): 2955 (w), 1742 (s), 1678 (w), 1383 (w), 1364 (w), 1234 (s), 1120 (w), 1034 (m), 838 (s), 790 (w), 753 (m), 693 (w), 621 (w) cm^{-1}.

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

SFC: Chiralpak® IF, 1500 psi, 30 °C; flow: 0.5 mL/min; 0% MeOH for 4 min, 0% to 1% MeOH over 9 min, 98:2 e.r. (minor enantiomer t_R = 12.73 min, major enantiomer t_R = 12.27 min).

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

3-19c



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and 3-thiomethoxyphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20) afforded the product **3-19c** as a colourless oil (73 mg, 70%). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.24 (app. t, *J* = 7.6 Hz, 1H; C(5')–H), 7.18 (t, *J* = 1.8 Hz, 1H; C(2')–H), 7.11 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H; C(4')–H), 7.05 (dt, *J* = 7.6, 0.9 Hz, 1H; C(2')–H), 4.97 – 4.88 (m, 2H; C=CH_2), 4.30 (dd, *J* = 11.2, 6.7 Hz, 1H; 1x CH_2O), 4.25 (dd, *J* = 11.2, 5.7 Hz, 1H; 1x CH_2O), 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; SCH_3), 2.04 (s, 3H, (C=O)CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.2 (C=O), 146.0 (C(2)), 144.8 (C(3')), 138.7 (C(1')), 129.1 (C(5')), 125.2 (C(2')), 124.6 (C(4')), 123.6 (C(2')), 106.3 (C=*C*H_2), 65.7 (CH_2O), 50.7 (C(1)), 39.9 (C(4)), 37.0 (C(3)), 21.0 ((C=O)*C*H_3), 16.0 (SCH_3).

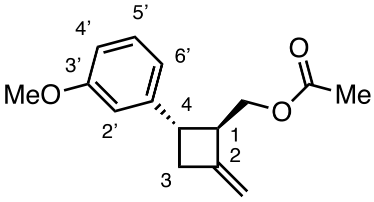
IR ($CHCl_3$ film): 2921 (w), 1738 (s), 1678 (w), 1591 (w), 1571 (w), 1436 (w), 1382 (w), 1364 (w), 1235 (s), 1088 (w), 1034 (m), 883 (m), 779 (m), 695 (m) cm^{-1}.

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

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

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

3-19d



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and 3-methoxyphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20) afforded the product **3-19d** as a colourless oil (66 mg, 67%). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.24 (app. t, *J* = 7.8 Hz, 1H; C(5’)–H), 6.87 (ddd, *J* = 7.6, 1.7, 0.8 Hz, 1H; C(6’)–H), 6.83 (app. t, *J* = 2.1 Hz, 1H; C(2’)–H), 6.76 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H; C(4’)–H), 4.95 – 4.89 (m, 2H, C=CH_2), 4.31 (dd, *J* = 11.2, 6.6 Hz, 1H; 1x CH_2O), 4.25 (dd, *J* = 11.2, 5.7 Hz, 1H; 1x CH_2O), 3.81 (s, 3H; OCH_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=O)CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.2 (C=O), 159.9 (C(3’)), 146.2 (C(2)), 145.8 (C(1’)), 129.6 (C(5’)), 119.1 (C(6’)), 112.7 (C(2’)), 111.6 (C(4’)), 106.2 (C=*C*H_2), 65.7 (CH_2O), 55.3 (OCH_3), 50.7 (C(1)), 39.9 (C(4)), 37.1 (C(3)), 21.1 ((C=O)*C*H_3).

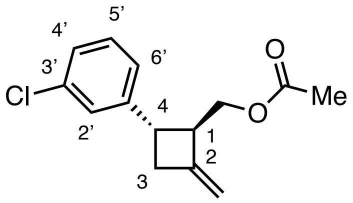
IR ($CHCl_3$ film): 2950 (w), 1738 (s), 1678 (w), 1601 (w), 1584 (w), 1490 (w), 1454 (w) 1435 (w), 1382 (w), 1364 (w), 1289 (w), 1235 (s), 1159 (w), 1036 (m), 882 (w), 779 (w)cm^{-1}.

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

SFC: Chiralpak® IB, 1500 psi, 30 °C; flow: 1.5 mL/min; 1% to 30% MeOH over 5 min, 99:1 e.r. (major enantiomer t_R = 1.56 min, minor enantiomer t_R = 1.70 min).

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

3-19e



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and 3-chlorophenylboronic acid (3.0 equiv.). The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20 to 0/100) afforded the product **3-19e** as a colourless oil (51 mg, 51%). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.27 (t, *J* = 1.9 Hz, 1H; C(2')–H), 7.25 (app. t, *J* = 7.6 Hz, 1H; C(5')–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(6')–H), 4.96 – 4.90 (m, 2H, C=CH_2), 4.32 – 4.23 (m, 1H; CH_2O), 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=O)CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.2 (C=O), 146.2 (C(2)), 145.4 (C(1')), 134.4 (C(3')), 129.8 (C(5')), 127.1 (C(2')), 126.6 (C(4')), 124.9 (C(6')), 106.6 (C=*C*H_2), 65.6 (CH_2O), 50.8 (C(1)), 39.8 (C(4)), 36.9 (C(3)), 21.0 ((C=O)*C*H_3).

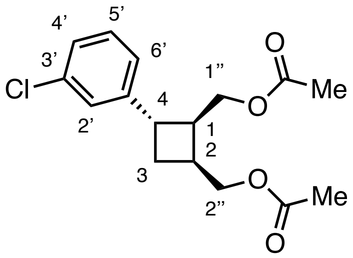
IR ($CHCl_3$ film): 2956 (w), 1739 (s), 1679 (w), 1597 (w), 1571 (w), 1478 (w), 1435 (w), 1383 (w), 1365 (w), 1234 (s), 1080 (w), 1034 (m), 885 (m), 780 (m), 692 (w) cm^{-1}.

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

SFC: Chiralpak® IF, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% MeOH for 3 min, 0% to 10% MeOH over 5 min, 99:1 e.r. (minor enantiomer t_R = 6.12 min, major enantiomer t_R = 6.18 min).

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

3-20e



(Experiment performed by A. M. L. Hell)

The following compound was isolated as a side-product of **3-20**. Purification by automated medium-pressure flash chromatography (hexane/Et$_2$O = 100/0 to 80/20 to 0/100) afforded the product **3-20e** as a colourless oil (47 mg, 37%). SFC analysis showed an enantiomeric excess of 86%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.30 – 7.26 (m, 2H; C(2’)–H, C(5’)–H), 7.20 (dt, *J* = 8.1, 1.5 Hz, 1H; C(4’)–H), 7.13 (dt, *J* = 8.0, 1.9 Hz, 1H; C(6’)–H), 4.38 (dd, *J* = 11.3, 8.1 Hz, 1H; 1x C(2’’)–H), 4.31 (dd, *J* = 11.2, 6.7 Hz, 1H; 1x C(2’’)–H), 4.23 (dd, *J* = 11.5, 6.9 Hz, 1H; 1x C(1’’)–H), 4.27 (dd, *J* = 11.4, 6.6 Hz, 1H; 1x C(1’’)–H), 3.45 (dt, *J* = 9.2, 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=O)CH$_3$), 2.01 (s, 3H; (C=O)CH$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 171.1 (C=O), 170.9 (C=O), 145.9 (C(1’)), 134.4 (C(3’)), 129.8 (C(5’)), 126.9 (C(2’)), 126.6 (C(4’)), 124.8 (C(6’)), 64.6 (C(2’’)), 63.9 (C(1’’)), 42.4 (C(1)), 40.6 (C(4)), 31.9 (C(2)), 28.3 (C(3)), 21.1 ((C=O)*C*H$_3$), 20.9 ((C=O)*C*H$_3$).

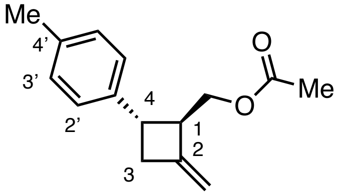
IR (CHCl$_3$ film): 2945 (w), 1739 (s), 1597 (w), 1571 (w), 1478 (w), 1367 (m), 1237 (s), 1034 (m), 780 (w), 724 (w), 691 (w) cm^{-1}.

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

SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1% to 30% MeOH over 5 min, 93:7 e.r. (major enantiomer t_R = 2.92 min, minor enantiomer t_R = 3.02 min).

$[\alpha]^{25}_D$ = +34.4 (c = 1.0, CHCl$_3$).

3-19f



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and 4-methylphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20) afforded the product **3-19f** as a colourless oil (63 mg, 68%). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.20 – 7.08 (m, 4H; 2x C(2')–H, 2x C(3')–H), 4.96 – 4.88 (m, 2H; C=CH_2), 4.30 (dd, *J* = 11.2, 6.5 Hz, 1H; 1x CH_2O), 4.24 (dd, *J* = 11.2, 5.7 Hz, 1H; 1x CH_2O), 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; CH_3), 2.03 (s, 3H, (C=O)CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.2 (C=O), 146.5 (C(2)), 141.1 (C(1')), 136.0 (C(4')), 129.2 (2x C(3')), 126.6 (2x C(2')), 106.0 (C=*C*H_2), 65.8 (CH_2O), 50.9 (C(1)), 39.5 (C(4)), 37.3 (C(3)), 21.1 (CH_3), 21.1 ((C=O)*C*H_3).

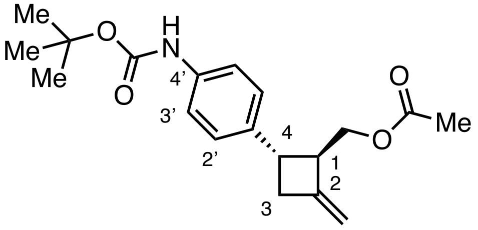
IR ($CHCl_3$ film): 3022 (w), 2921 (w), 1740 (s), 1678 (w), 1516 (w), 1433 (w), 1364 (w), 1234 (s), 1034 (m), 882 (m), 809 (m) cm^{-1}.

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

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

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

3-19g



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and 4-((tert-butoxycarbonyl)amino)phenylboronic acid (3.0 equiv.). The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20 to 0/100), followed by Kugelrohr distillation (2h, 90 °C; ~1 mbar) to remove unreacted starting material **3-18**, afforded the product **3-19g** as a colourless solid (58 mg, 44%). SFC analysis showed an enantiomeric excess of 92%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.30 (d, *J* = 8.4 Hz, 2H; 2x C(3')–H), 7.19 (d, *J* = 8.5 Hz, 2H; 2x C(2')–H), 6.44 (br. s, 1H; NH), 4.95 – 4.87 (m, 2H; C=CH_2), 4.28 (dd, *J* = 11.2, 6.6 Hz, 1H; 1x CH_2O), 4.23 (dd, *J* = 11.3, 5.6 Hz, 1H; 1x CH_2O), 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; 1x C(3)–H), 2.02 (s, 3H; (C=O)CH_3), 1.51 (s, 9H; $C(CH_3)_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.2 (C(7)), 153.0 (NH(C=O)O), 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=*C*H_2), 80.6 (*C*(CH_3)), 65.8 (CH_2O), 51.0 (C(1)), 39.5 (C(4)), 37.3 (C(3)), 28.5 (C(*C*H_3)$_3$), 21.0 ((C=O)CH_3).

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}.

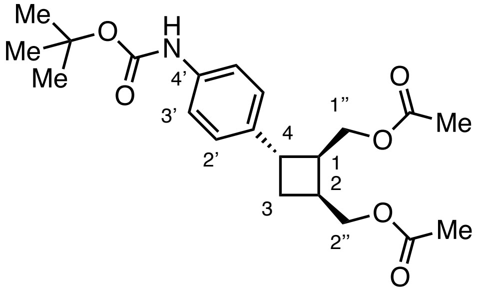
HRMS (ESI): m/z calcd for $C_{19}H_{25}NO_4Na^+$ $[M + Na]^+$ 354.1676 found 354.1675.

SFC: Chiralpak® IB, 1500 psi, 30 °C; flow: 1.5 mL/min; 1% to 30% MeOH over 5 min, 96:4 e.r. (minor enantiomer t_R = 3.24 min, major enantiomer t_R = 2.97 min).

[α]$^{25}_{D}$ = +50.0 (c = 1.0, $CHCl_3$).

m.p.: 72 – 73 °C.

3-20g



(Experiment performed by A. M. L. Hell)

The following compound was isolated as a side-product of **3-19g**. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20 to 0/100) afforded the product **3-20g** as a colourless oil (69 mg, 47%). SFC analysis showed an enantiomeric excess of 78%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.29 (d, J = 8.4 Hz, 2H; 2x C(3')–H), 7.15 (d, J = 8.5 Hz, 2H; 2x C(2')–H), 6.45 (br. s, 1H; NH), 4.35 (dd, J = 11.3, 8.0 Hz, 1H; 1x C(2'')–H), 4.29 (dd, J = 11.3, 6.9 Hz, 1H; 1x C(2'')–H), 4.22 (dd, J = 11.5, 6.6 Hz, 1H; 1x C(1'')–H), 4.22 (dd, J = 11.5, 7.2 Hz, 1H; 1x C(1'')–H), 3.37 (dt, J = 9.2, 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=O)CH_3), 1.97 (s, 3H; (C=O)CH_3), 1.51 (s, 9H; C(CH_3)$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.3 (C=O), 171.1 (C=O), 153.0 (NH(C=O)O), 138.5 (C(1')), 136.8 (C(4')), 127.2 (2x C(2')), 118.8 (2x C(3')), 80.6 (*C*(CH_3)$_3$), 64.8 (C(2'')), 64.1 (C(1'')), 42.7 (C(1)), 40.3 (C(4)), 31.9 (C(2)), 28.7 (C(3)), 28.5 (C(CH_3)$_3$), 21.1 ((C=O)*C*H_3), 21.0 ((C=O)*C*H_3).

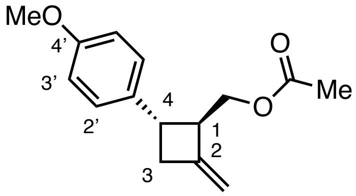
IR ($CHCl_3$ film): 3344 (w), 2975 (w), 1722 (s), 1595 (w), 1526 (m), 1415 (w), 1392 (w), 1367 (m), 1316 (w), 1236 (s), 1160 (s), 1032 (m), 832 (w), 773 (w) cm^{-1}.

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

SFC: Chiralpak® IB, 1500 psi, 30 °C; flow: 1.5 mL/min; 1% to 30% MeOH over 5 min, 89:11 e.r. (minor enantiomer t_R = 3.58 min, major enantiomer t_R = 3.27 min).

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

3-19h



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and 4-methoxyphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20 to 0/100) afforded the product **3-19h** as a colourless solid (46 mg, 47%). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.23 – 7.16 (m, 2H; 2x C(2')–H), 6.90 – 6.83 (m, 2H; 2x C(3')–H), 4.95 – 4.88 (m, 2H; C=CH_2), 4.30 (dd, *J* = 11.2, 6.5 Hz, 1H; 1x CH_2O), 4.24 (dd, *J* = 11.2, 5.7 Hz, 1H; 1x CH_2O), 3.80 (s, 3H; OCH_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=O)CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.2 (C=O), 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=*C*H_2), 65.8 (CH_2O), 55.5 (OCH_3), 51.1 (C(1)), 39.3 (C(4)), 37.4 (C(3)), 21.1 ((C=O)*C*H_3).

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}.

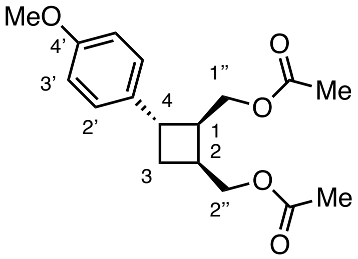
HRMS (ESI): m/z calcd for $C_{15}H_{18}O_3Na^+$ $[M + Na]^+$ 269.1148 found 269.1149.

SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1% to 30% MeOH over 5 min, 98.5:1.5 e.r. (major enantiomer t_R = 2.34 min, minor enantiomer t_R = 2.53 min).

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

m.p.: 33 °C.

3-20h



(Experiment performed by A. M. L. Hell)

The following compound was isolated as a side-product of **3-19h**. Purification by automated medium-pressure flash chromatography (hexane/Et$_2$O = 100/0 to 80/20 to 0/100) afforded the product **3-20h** as a colourless solid (39 mg, 32%). SFC analysis showed an enantiomeric excess of 85%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.18 – 7.12 (m, 2H; 2x C(2')–H), 6.88 – 6.82 (m, 2H; 2x C(3')–H), 4.36 (dd, *J* = 11.2, 8.1 Hz, 1H; 1x C(2'')–H), 4.29 (dd, *J* = 11.2, 6.9 Hz, 1H; 1x C(2'')–H), 4.22 (dd, *J* = 11.4, 6.5 Hz, 1H; 1x C(1'')–H), 4.19 (dd, *J* = 11.5, 7.2 Hz, 1H; 1x C(1'')–H), 3.78 (s, 3H; OCH$_3$), 3.36 (dt, *J* = 9.2, 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=O)CH$_3$), 1.96 (s, 3H; (C=O)CH$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 171.2 (C=O), 171.0 (C=O), 158.3 (C(4')), 135.8 (C(1')), 127.6 (2x C(2')), 113.9 (2x (C3')), 64.8 (C(2'')), 64.0 (C(1'')), 55.4 (OCH$_3$), 42.8 (C(1)), 40.1 (C(4)), 31.9 (C(2)), 28.8 (C(3)), 21.1 ((C=O)*C*H$_3$), 20.9 ((C=O)*C*H$_3$).

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}.

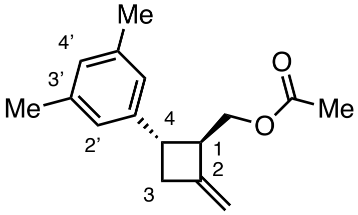
HRMS (ESI): m/z calcd for $C_{17}H_{22}O_5Na^+$ $[M + Na]^+$ 329.1359 found 329.1360.

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

$[\alpha]^{25}_D$ = +40.9 (c = 1.0, CHCl$_3$).

m.p.: 40 – 41 °C

3-19i



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and 3,5-dimethylphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20 to 0/100) afforded the product **3-19i** as a colourless oil (74 mg, 74%). SFC analysis showed an enantiomeric excess of 93%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.89 (s, 2H; 2x C(2')–H), 6.86 (s, 2H; C(4')–H), 4.96 – 4.88 (m, 2H, C=CH_2), 4.31 (dd, *J* = 11.2, 6.7 Hz, 1H; 1x CH_2O), 4.24 (dd, *J* = 11.2, 6.0 Hz, 1H; 1x CH_2O), 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 (2x s, 6H; 2x CH_3), 2.04 (s, 3H; (C=O)CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.2 (C=O), 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=CH_2), 65.7 (CH_2O), 50.7 (C(1)), 39.7 (C(4)), 37.1 (C(3)), 21.5 (2x CH_3), 21.0 ((C=O)CH_3).

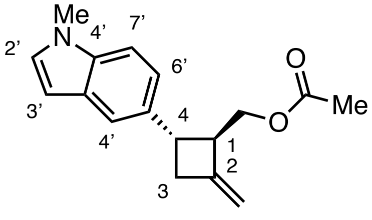
IR ($CHCl_3$ film): 2918 (w), 1740 (s), 1678 (w), 1678 (w), 1604 (w), 1459 (w), 1381 (w), 1364 (w), 2333 (s), 1034 (m), 881 (s), 844 (s), 700 (s) cm^{-1}.

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

SFC: Chiralpak® IF, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% MeOH for 4 min, 0% to 1% MeOH over 9 min, 96.5:3.5 e.r. (minor enantiomer t_R = 9.14 min, major enantiomer t_R = 8.90 min).

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

3-19j



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and *N*-methylindole-5-boronic acid (3.0 equiv.). The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20) afforded the product **3-19j** as a colourless oil (68 mg, 63%). SFC analysis showed an enantiomeric excess of 94%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.54 – 7.50 (m, 1H; C(4')–H), 7.28 (d, *J* = 8.5 Hz, 1H; C(7')–H), 7.16 (dd, *J* = 8.4, 1.7 Hz, 1H; C(6')–H), 7.04 (d, *J* = 3.0 Hz, 1H; C(2')–H), 6.44 (dd, *J* = 3.1, 0.8 Hz, 1H; C(3')–H), 5.00 – 4.87 (m, 2H; C=CH_2), 4.35 (dd, *J* = 11.2, 6.3 Hz, 1H; 1x CH_2O), 4.27 (dd, *J* = 11.2, 5.8 Hz, 1H; 1x CH_2O), 3.79 (s, 3H; NCH_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=O)CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.3 (C=O), 147.0 (C(2)), 135.7 (C(7a')), 135.0 (C(1')), 129.3 (C(2')), 128.7 (C(3a')), 120.8 (C(5')), 118.5 (C(4')), 109.3 (C(7')), 105.7 (C=CH_2), 100.8 (C(3')), 65.9 (CH_2O), 51.3 (C(1)), 40.0 (C(4)), 37.8 (C(3)), 33.0 (NCH_3), 21.1 ((C=O)*C*H_3).

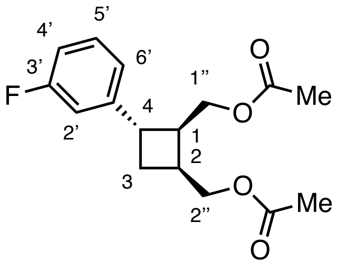
IR ($CHCl_3$ film): 2984 (w), 1736 (s), 1677 (w), 1513 (w), 1493 (m), 1447 (w), 1423 (w), 1382 (w), 1363 (m), 1237 (s), 1081 (w), 1033 (m), 978 (w), 882 (m), 798 (m), 762 (w), 720 (m), 632 (w) cm^{-1}.

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

SFC: Chiralpak® ID, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% MeOH for 3 min, 0% to 10% MeOH over 5 min, 97:3 e.r. (major enantiomer t_R = 7.89 min, minor enantiomer t_R = 8.13 min).

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

3-20k



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and 3-fluorophenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et$_2$O = 100/0 to 80/20) afforded the product **3-20k** as a colourless oil (88 mg, 75%). SFC analysis showed an enantiomeric excess of 87%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.26 (app. td, *J* = 7.9, 6.1 Hz, 1H; C(5')–H), 6.99 (ddt, *J* = 7.7, 1.6, 0.8 Hz, 1H; C(6')–H), 6.95 (dt, *J* = 10.2, 2.2 Hz, 1H; C(2')–H), 6.89 (tdd, *J* = 8.3, 2.6, 1.0 Hz, 1H; C(4')–H), 4.36 (dd, *J* = 11.3, 8.0 Hz, 1H; 1x C(2'')–H), 4.29 (dd, *J* = 11.2, 6.8 Hz, 1H; 1x C(2'')–H), 4.25 (dd, *J* = 11.4, 6.5 Hz, 1H; 1x C(1'')–H), 4.21 (dd, *J* = 11.5, 7.0 Hz, 1H; 1x C(1'')–H), 3.44 (dt, *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=O)CH$_3$), 1.98 (s, 3H; (C=O)CH$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 171.2 (C=O), 171.0 (C=O), 163.2 (d, *J* = 245.6 Hz; C(3')), 146.5 (d, *J* = 7.0 Hz; C(1')), 130.0 (d, *J* = 8.4 Hz; C(5')), 122.3 (d, *J* = 2.8 Hz; C(6')), 113.6 (d, *J* = 21.2 Hz; C(2')), 113.3 (d, *J* = 21.0 Hz, C(4')), 64.7 (C(2'')), 64.0 (C(1'')), 42.5 (C(1)), 40.7 (d, *J* = 1.9 Hz; C(4)), 31.9 (C(2)), 28.5 (C(3)), 21.1 ((C=O)*C*H$_3$), 21.0 ((C=O)*C*H$_3$).

^{19}F NMR (CDCl$_3$, 377 MHz): δ (ppm) -113.32 (ddd, *J* = 10.3, 8.7, 6.1 Hz; C–F).

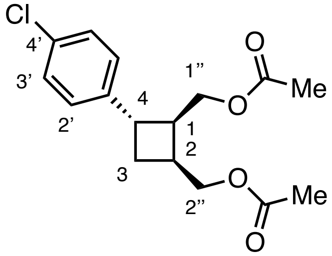
IR (CHCl$_3$ film): 2946 (w), 1737 (s), 1615 (w), 1587 (w), 1490 (w), 1442 (w), 1367 (m), 1233 (s), 1149 (w), 1033 (m), 978 (w), 868 (w), 786 (w), 692 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{16}H_{19}FO_4Na^+$ $[M + Na]^+$ 317.1160 found 317.1161.

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

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

3-20l



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and 4-chlorophenylboronic acid (3.0 equiv.). The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20) afforded the product **3-20l** as a colourless oil (98 mg, 79%). SFC analysis showed an enantiomeric excess of 83%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.30 – 7.25 (m, 2H; 2x C(3')–H), 7.19 – 7.13 (m, 2H; 2x C(2')–H), 4.36 (dd, *J* = 11.3, 7.9 Hz, 1H; 1x C(2'')–H), 4.29 (dd, *J* = 11.3, 6.8 Hz, 1H; 1x C(2'')–H), 4.24 (dd, *J* = 10.5, 5.6 Hz, 1H; 1x C(1'')–H), 4.20 (dd, *J* = 10.5, 6.0 Hz, 1H; 1x C(2'')–H), 3.40 (dt, *J* = 9.2, 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=O)CH_3), 1.97 (s, 3H; (C=O)CH_3).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 171.2 (C=O), 170.1 (C=O), 142.3 (C(1’)), 132.2 (C(4’)), 128.7 (C(3’)), 128.1 (C(2’)), 64.7 (C(2’’)), 64.0 (C(1’’)), 42.6 (C(1)), 40.4 (C(4)), 32.0 (C(2)), 28.6 (C(3)), 21.10 ((C=O)*C*H$_3$), 20.1 ((C=O)*C*H$_3$).

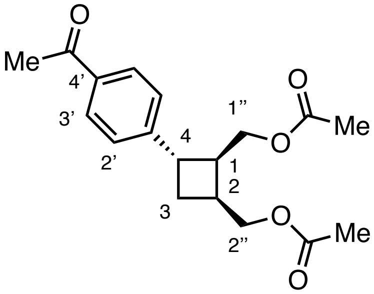
IR (CHCl$_3$ film): 2945 (w), 1737 (s), 1493 (w), 1367 (w), 1234 (s), 1092 (w), 1033 (m), 1014 (w), 978 (w), 821 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{16}H_{19}{}^{35}ClO_4Na^+$ [M + Na]$^+$ 333.0864 found 333.0865.

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

[α]$^{25}_{D}$ = +50.8 (c = 1.0, CHCl$_3$).

3-20m



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and 4-acetylphenylboronic acid (3.0 equiv.). The mixture was stirred at room temperature (23 °C) for 16 h (rigorous stirring required due to heterogeneous reaction mixture). Purification by automated medium-pressure flash chromatography (hexane/Et$_2$O = 100/0 to 80/20 to 0/100) afforded the product **3-20m** as a colourless oil (106 mg, 84%). SFC analysis showed an enantiomeric excess of 91%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.90 (d, *J* = 8.3 Hz, 2H; 2x C(3')–H), 7.32 (d, *J* = 8.2 Hz, 2H; 2x C(2')–H), 4.37 (dd, *J* = 11.3, 8.0 Hz, 1H; 1x C(2'')–H), 4.30 (dd, *J* = 11.3, 6.7 Hz, 1H; 1x C(2'')–H), 4.26 (dd, *J* = 10.9, 6.0 Hz, 1H; 1x C(1'')–H), 4.21 (dd, *J* = 11.0, 6.5 Hz, 1H; 1x C(1'')–H), 3.49 (dt, *J* = 9.2, 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(4')(C=O)*C*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=O)CH$_3$), 1.96 (s, 3H; (C=O)CH$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) δ 197.8 (C(4')(C=O)CH$_3$), 171.2 (C=O), 171.0 (C=O), 149.4 (C(1')), 135.6 (C(4')), 128.7 (2x C(3')), 126.9 (2x C(2')), 64.6 (C(3'')), 64.0 (C(1'')), 42.4 (C(1)), 40.9 (C(4)), 32.0 (C(2)), 28.4 (C(3)), 26.7 (C(4')(C=O)*C*H$_3$), 21.1 ((C=O)*C*H$_3$), 21.0 ((C=O)*C*H$_3$).

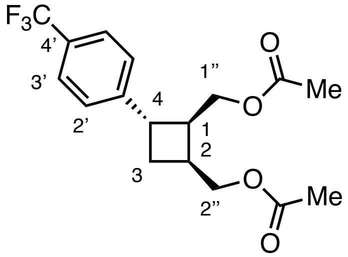
IR (CHCl$_3$ film): 2944 (w), 1736 (s), 1681 (s), 1606 (m), 1365 (w), 1236 (s), 1033 (m), 958 (w), 828 (w) cm^{-1}.

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

SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1% to 30% MeOH over 5 min, 95.5:4.5 e.r. (major enantiomer t_R = 4.75 min, minor enantiomer t_R = 5.34 min).

$[\alpha]^{25}_D$ = +58.8 (c = 1.0, CHCl$_3$).

3-20n



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and 4-trifluoromethylphenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20 to 0/100) afforded the product **3-20n** as a colourless oil (93 mg, 67%). SFC analysis showed an enantiomeric excess of 92%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.56 (d, *J* = 8.1 Hz, 2H; 2x C(3')–H), 7.34 (d, *J* = 8.3 Hz, 2H; 2x C(2')–H), 4.37 (dd, *J* = 11.3, 8.0 Hz, 1H; 1x C(2'')–H), 4.31 (dd, *J* = 11.4, 6.8 Hz, 1H; 1x C(2'')–H), 4.26 (dd, *J* = 11.8, 6.8 Hz; 1x C(1'')–H), 4.22 (dd, *J* = 11.5, 7.0 Hz, 1H; 1x C(1'')–H), 3.50 (dt, *J* = 9.2, 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=O)CH_3), 1.97 (s, 3H; (C=O)CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.2 (C=O), 171.0 (C=O), 147.8 (C(1')), 128.8 (d, *J* = 32.3 Hz; 2x C(4')), 127.0 (2x (C(2')), 125.7 (d, *J* = 271.8 Hz; CF_3), 125.5 (q, *J* = 3.8 Hz; 2x C(3')), 64.6 (C(2'')), 64.0 (C(1'')), 42.4 (C(1)), 40.7 (C(4)), 32.0 (C(2)), 28.5 (C(3)), 21.1 ((C=O)CH_3), 21.0 ((C=O)CH_3).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -62.39 (s; CF_3).

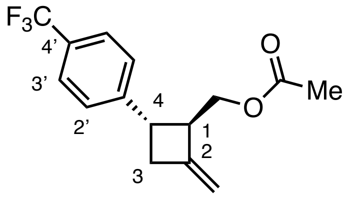
IR ($CHCl_3$ film): 2946 (w), 1738 (s), 1618 (w), 1368 (w), 1326 (s), 1234 (s), 1163 (m), 1120 (s), 1068 (m), 1034 (m), 1017 (m), 979 (m), 836 (w) cm^{-1}.

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

SFC: Chiralpak® IG, 1500 psi, 30 °C; flow: 1.5 mL/min; 1% to 30% MeOH over 5 min, 96:4 e.r. (major enantiomer t_R = 1.92 min, minor enantiomer t_R = 2.04 min).

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

3-19n



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** and 4-trifluoromethylphenylboronic acid with (*S*)-Segphos instead of (*S*)-DTBM-Segphos. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20) afforded the product **3-19n** as a colourless oil (77 mg, 67%). SFC analysis showed an enantiomeric excess of 78%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (pm) 7.57 (d, *J* = 8.1 Hz, 2H; 2x C(3')–H), 7.39 (d, *J* = 8.4 Hz, 2H; 2x C(2')–H), 4.31 (dd, *J* = 11.2, 6.7 Hz, 1H; 1x CH_2O), 4.27 (dd, *J* = 11.3, 5.4 Hz, 1H; 1x CH_2O), 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=O)CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 171.1 (C=O), 148.2 (C(1')), 145.3 (C(2)), 128.8 (q, *J* = 32.4 Hz, C(4')), 127.1 (2x C(2')), 125.7 (q, *J* = 272.0 Hz; CF_3), 125.5 (q, *J* = 3.7 Hz; 2x C(3')), 106.8 (C=*C*H_2), 65.6 (CH_2O), 50.8 (C(1)), 39.9 (C(4)), 37.1 (C(3)), 21.0 ((C=O)CH_3).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -62.38 (s; CF_3).

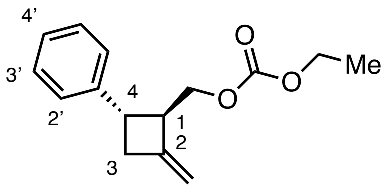
IR ($CHCl_3$ film): 2981 (w), 1741 (m), 1680 (w), 1619 (w), 1366 (w), 1325 (s), 1235 (m), 1163 (m), 1121 (m), 1068 (m), 1035 (w), 1018 (w), 886 (w), 834 (w) cm^{-1}.

HRMS (ESI/APCI): not found.
Note: We were not able to detect the molecular ion or a characteristic fragment for this molecule.

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, 89:11 e.r. (major enantiomer t_R = 2.13 min, minor enantiomer t_R = 2.34 min).

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

3-22a



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-21a** and phenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure flash chromatography (hexane/Et_2O = 100/0 to 80/20 to 0/100) afforded the product **3-22a** as a pale-yellow oil (78 mg, 79%). SFC analysis showed an enantiomeric excess of 96%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.36 – 7.26 (m, 4H; 2x C(2')–H, 2x C(3')–H), 7.24 – 7.18 (m, 1H; C(4')–H), 4.97 (q, *J* = 2.5 Hz, 1H; 1x C=CH_2), 4.94 (q, *J* = 2.4 Hz, 1H; 1x C=CH_2), 4.38 (dd, *J* = 11.0, 6.0 Hz, 1H; 1x CH_2O), 4.31 (dd, *J* = 11.1, 5.5 Hz, 1H; 1x CH_2O), 4.18 (q, *J* = 7.1 Hz, 2H; $\mathit{CH_2}CH_3$), 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; $CH_2\mathit{CH_3}$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.4 (C=O), 145.9 (C(2)), 143.9 (C(1')), 128.6 (2x C(3')), 126.8 (2x C(2')), 126.5 (C(4')), 106.4 (C=CH_2), 68.8 (CH_2O), 64.1 ($\mathit{C}H_2CH_3$), 50.8 (C(1)), 39.5 (C(4)), 37.2 (C(3)), 14.4 ($CH_2\mathit{C}H_3$).

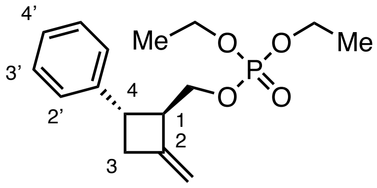
IR ($CHCl_3$ film): 2985 (w), 1744 (s), 1680 (w), 1454 (w), 1382 (w), 1254 (s), 1007 (w), 879 (w), 791 (w), 753 (w), 699 (w) cm^{-1}.

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

SFC: Chiralpak® IC, 1500 psi, 30 °C; flow: 0.75 mL/min; 1% 2-PrOH for 2 min, 1% to 10% 2-PrOH over 14 min, 98:2 e.r. (minor enantiomer t_R = 4.86 min, major enantiomer t_R = 4.65 min).

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

3-21b



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-21b** and phenylboronic acid. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 60/40 to 0/100) afforded the product **3-22b** as a pale-yellow oil (92 mg, 74%). SFC analysis showed an enantiomeric excess of 93%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.34 – 7.27 (m, 4H; 2x C(2')–H, 2x C(3')–H), 7.20 (m, 1H; C(4')–H), 4.93 (q, *J* = 2.6 Hz, 1H; 1x C=CH_2), 4.90 (q, *J* = 2.5 Hz, 1H; 1x C=CH_2), 4.29 – 4.17 (m, 2H, CH_2O), 4.12 – 3.99 (m, 4H; 2x $\mathit{CH_2}CH_3$), 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 $CH_2\mathit{CH_3}$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 145.5 (C(2)), 144.1 (C(1')), 128.6 (2x C(3')), 126.9 (2x C(2')), 126.5 (C(4')), 106.6 (C=CH_2), 68.6 (d, *J* = 6.0 Hz; CH_2O), 63.9 (d, *J* = 5.8 Hz; 2x $\mathit{CH_2}CH_3$), 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 $CH_2\mathit{CH_3}$).

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

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}.

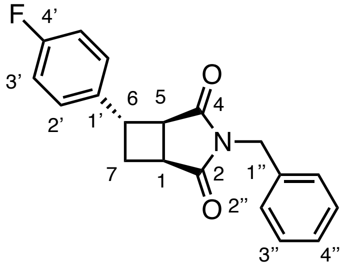
HRMS (ESI): m/z calcd for $C_{16}H_{23}O_4PNa^+$ $[M + Na]^+$ 333.1226; found 333.1227.

SFC: Chiralpak® IC, 1500 psi, 30 °C; flow: 1.5 mL/min; 1% to 30% MeOH over 5 min, 96.5:3.5 e.r. (minor enantiomer t_R = 2.99 min, major enantiomer t_R = 2.93 min).

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

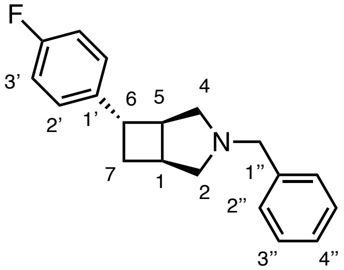
5.3.3. Formal Synthesis of Belaperidone

Gram-scale synthesis of 3-8h



The rhodium hydroxy phosphine complex was prepared by stirring a solution of $[Rh(cod)OH]_2$ (13.8 mg, 0.03 mmol, 0.5 mol%) and (*S*)-DTBM-Segphos (84.9 mg, 0.072 mmol, 1.2 mol%) in dry dioxane (6.0 mL) under an argon atmosphere at 60 °C for 30 min. The resulting dark red solution was added to a 25 mL round-bottom flask containing a mixture of 4-fluorophenylboronic acid (12.0 mmol, 2.0 eq) and cyclobutene **3-2** (6.00 mmol, 1.0 eq) in toluene (6 mL) and H_2O (1.2 mL) *via* syringe. The resulting mixture was then stirred at 60 °C for 16 h. The mixture was then cooled to room temperature and concentrated *in vacuo*. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 60/40) afforded the product **3-8h** as a pale-yellow oil (1.34 g, 72%). SFC analysis showed an enantiomeric excess of 99:1. For analytical data see above.

3-S3



A solution of $LiAlH_4$ (1.0 M in Et_2O; 4.4 mL, 4.4 mmol) was added slowly to a solution of **3-8h** (339 mg, 1.10 mmol) in CH_2Cl_2 (5.5 mL) at 0 °C under an argon atmosphere. The reaction mixture was then allowed to reach 23 °C and was stirred for 16 h. H_2O (0.2 mL), aq. NaOH

(15%, 0.2 mL) and H_2O (0.5 mL), followed by $MgSO_4$ were added subsequently. The mixture was filtered and rinsed with EtOAc (~50 mL). Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **3-S3** as a colourless oil (275 mg, 89%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.50 – 7.42 (m, 2H; 2x C(2'')–H), 7.35 (app. t, *J* = 7.4 Hz, 2H; 2x C(3'')–H), 7.31 – 7.23 (m, 1H; C(4'')–H), 7.23 – 7.16 (m, 2H; 2x C(2')–H), 7.06 – 6.92 (m, 2H; 2x C(3')–H), 3.77 (d, *J* = 13.3 Hz, 1H; $PhCH_2N$), 3.73 (d, *J* = 13.2 Hz, 1H; $PhCH_2N$), 3.36 (ddd, *J* = 9.0, 7.2, 3.9 Hz, 1H; C(6)–H), 2.95 (app. t, *J* = 9.0 Hz, 2H; 2x CH_2N), 2.85 – 2.70 (m, 2H; C(1)–H and C(5)–H), 2.36 – 1.96 (m, 4H; 2x C(7)–H and 2x CH_2N).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 161.22 (d, *J* = 243.1 Hz; C(4')), 143.06 (d, *J* = 3.1 Hz; C(1')), 140.1 (C(1'')), 128.8 (2x C(2'')), 128.3 (2x C(3'')), 127.9 (d, *J* = 7.7 Hz; 2x C(2')), 126.9 (C(4'')), 115.1 (d, *J* = 21.0 Hz; 2x C(3')), 60.35 (CH_2N), 60.31 (CH_2N), 59.8 ($PhCH_2N$), 46.2 (C(5)), 42.0 (C(6)), 34.1 (C(1)), 32.7 (C(7)).

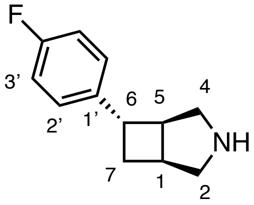
^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -118.12 (tt, *J* = 8.9, 5.4 Hz; C–F).

IR ($CHCl_3$ film): 2936 (w), 2784 (w), 1603 (w), 1509 (s), 1454 (w), 1345 (w), 1223 (m), 1158 (w), 1116 (w), 855 (w), 826 (m), 740 (w), 699 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{19}H_{21}NF^+$ $[M + H]^+$ 282.1653 found 282.1653.

$[\alpha]^{25}_D$ = +101.3 (*c* = 1.0, $CHCl_3$).

3-13



Route I:

A solution of **3-S3** (56.2 mg, 0.2 mmol) in MeOH (1.5 + 0.5 mL) was added slowly to a suspension of Pd(OH)$_2$/C (20 wt%, 15 mg) in MeOH (0.5 mL) at 23 °C under an argon atmosphere. The reaction mixture was then stirred under H$_2$ (1 atm) for 16 h. The reaction mixture was then filtered over Celite® and rinsed with EtOAc. The solvents were removed under reduced pressure and **3-13** was obtained as a pale-yellow oil (38 mg, quant.) containing trace impurities.

An analytical sample can be obtained by forming the hydrochloride salt followed by liberation of the free base. Aq. HCl (1 N; 5 mL) was added to **3-13** and the aqueous layer was washed with Et$_2$O (2 x 5 mL). The aqueous layer was then made alkaline with aq. NaOH (15 wt%) and the aqueous layer was extracted with CH$_2$Cl$_2$ (5x 5 mL). The combined organic layers were dried over MgSO$_4$ and the solvents were removed under reduced pressure.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 7.23 – 7.13 (m, 2H; 2x C(2’)–H), 7.04 – 6.87 (m, 2H; 2x C(3’)–H), 3.17 – 2.97 (m, 3H; 2x CH$_2$N, C(6)–H), 2.92 – 2.72 (m, 4H; 2x CH$_2$N, C(1)–H, C(5)–H), 2.68 (s, 1H; NH), 2.25 (dddd, *J* = 12.6, 9.7, 7.2, 1.4 Hz, 1H; C(7)–H), 2.10 – 1.76 (m, 1H; C(7)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 161.3 (d, *J* = 243.5 Hz; C(4’)), 142.4 (d, *J* = 3.2 Hz; C(1’’)), 127.9 (d, *J* = 7.7 Hz; 2x C(2’’)), 115.16 (d, *J* = 21.1 Hz; 2x C(3’’)), 53.87 (CH$_2$N), 53.84 (CH$_2$N), 47.2 (C(5)), 41.4 (C(6)), 34.9 (C(1)), 32.0 (C(7)).

^{19}F NMR (CDCl$_3$, 377 MHz): δ (ppm) -117.74 (tt, *J* = 8.7, 5.4 Hz; C–F).

IR ($CHCl_3$ film): 3375 (br. w), 2959 (w). 2853 (w), 1603 (w), 1509 (s), 1412 (m), 1343 (w), 1222 (m), 1159 (w), 825 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{12}H_{15}NF^+$ $[M + H]^+$ 192.1183 found 192.1184.

$[\alpha]^{25}_D$ = +101.5 (*c* = 1.0, EtOH) (Lit.: $[\alpha]^{25}_D$ = +97.8 (*c* = 1.08, EtOH).[212]

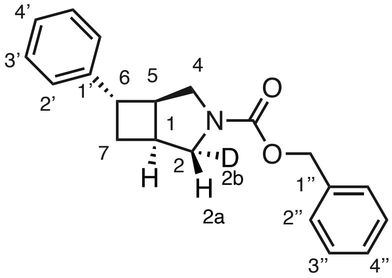
Route II:

A solution of **3-5h** (32.5 mg, 0.1 mmol) in MeOH (1.5 + 0.5 mL) was added slowly to a suspension of $Pd(OH)_2/C$ (20 wt%, 7.1 mg) in MeOH (0.5 mL) at 23 °C under an argon atmosphere. The reaction mixture was then stirred under H_2 (1 atm) for 5 h. The reaction mixture was then filtered over Celite® and rinsed with EtOAc. The solvents were removed under reduced pressure and **3-13** was obtained a colourless oil (18 mg, 94%). For analytical data see above.

$[\alpha]^{25}_D$ = +103.5 (*c* = 1.0, EtOH) (Lit.: $[\alpha]^{25}_D$ = +97.8 (*c* = 1.08, EtOH)[212].

5.3.4. Deuterium-Labelling Experiments

3-5a-C2-*d*

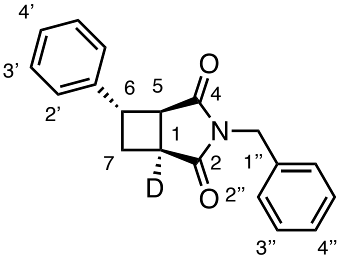


The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-4** (0.2 mmol), phenylboronic acid (0.4 mmol) and D_2O (0.040 mL) instead of H_2O. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by flash chromatography (hexane/EtOAc = 90/10 to 70/30) afforded the product **3-5a-C2-*d*** as a colourless oil (46 mg, 75% yield) with 88% D incorporation at the C(2) position.

^{1}H NMR ($CDCl_3$, 400 MHz; quantitative): δ (ppm) 7.43 – 7.26 (m, 7H; 7x C_{Ar}–H), 7.24 – 7.18 (m, 3H; 3x C_{Ar}–H), 5.21 (s, 2H; CH_2Ph), 3.83 – 3.76 (rot. m, 2H; CH_2N), 3.54 (rot. s, 0.12H; CH_2N), 3.37 – 3.29 (m, 2H; CH_2N and C(6)–H), 3.02 – 2.95 (m, 2H; C(1)–H and C(5)–H), 2.39 (dt, *J* = 12.2, 8.5 Hz, 1H; C(7)–H), 2.19 (br. rot. s, 1H; C(7)–H).

HRMS (ESI): m/z calcd for $C_{20}H_{20}DO_2NNa^+$ $[M + Na]^+$ 331.1527 found 331.1524.

3-8a-C1-*d*



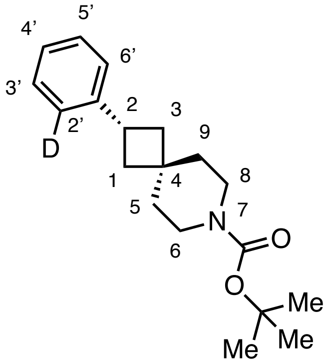
The corresponding compound was prepared following general procedure 3-3 using cyclobutene **3-2**, phenylboronic acid and D_2O instead of H_2O. The mixture was stirred at 60 °C for 4 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **3-8a-C1-*d*** as a colourless oil (85 mg, 72% yield) with 87% D incorporation at the C(1) position.

^{1}H NMR ($CDCl_3$, 400 MHz; quantitative): δ (ppm) 7.49 – 7.42 (m, 2H; 2x C_{Ar}–H), 7.39 – 7.21 (m, 8H; 8x C_{Ar}–H), 4.75 (s, 2H; CH_2Ph), 3.61 (td, *J* = 8.6, 5.3 Hz, 1H; C(6)–H), 3.40 (d, *J* = 5.3 Hz, 1H; C(5)–H), 3.35 – 3.27 (m, 0.12H; C(1)–H), 2.78 (dd, *J* = 12.9, 7.9 Hz, 1H; C(7)–H), 2.62 (ddd, *J* = 12.9, 9.2, 0.9 Hz, 1H; C(7)–H).

^{1}H NMR (CD_2Cl_2, 500 MHz; quantitative): 7.44 – 7.32 (m, 6H; 6x C_{Ar}–H), 7.32 – 7.20 (m, 4H; 4x C_{Ar}–H), 4.73 (s, 2H; CH_2Ph), 3.62 (td, *J* = 8.5, 5.4 Hz, 1H; C(6)–H), 3.39 (d, *J* = 5.4 Hz, 1H; C(5)–H), 3.34 – 3.26 (m, 0.12H; C(1)–H), 2.85 – 2.72 (m, 1H; C(7)–H), 2.61 (dd, *J* = 12.8, 9.2 Hz, 1H; C(7)–H).

HRMS (ESI): m/z calcd for $C_{19}H_{17}DO_2N^+$ $[M + H]^+$ 293.1395 found 293.1395.

3-15a-C2’-*d*



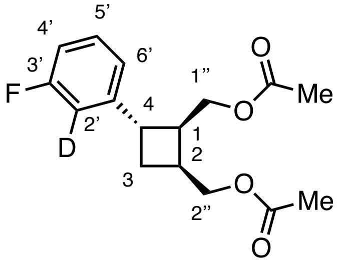
(Experiment performed by L. van Dijk)

The corresponding compound was prepared following general procedure 3-4 using cyclobutene **3-14** and phenylboronic acid with D_2O (0.40 mL) instead of H_2O and a solution of $CsOH{\cdot}H_2O$ in D_2O (70 μL; 0.4 mmol, 1.0 equiv.). The mixture was stirred at 60 °C for 16 h. Purification by automated medium-pressure flash chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **3-15a-C2’-*d*** as a colourless solid (65 mg, 54%) with 80% D incorporation at the C(2’) position.

^{1}H NMR (CDCl$_3$, 400 MHz; quantitative): δ (ppm) 7.35 – 7.27 (m, 2H; 2x C(3')–H), 7.25 – 7.14 (m, 2.20 H; 2x C(2')–H, C(4')–H), 3.53 (p, *J* = 9.1 Hz, 1H; C(2)–H), 3.47 – 3.39 (m, 2H; 2x C(6)–H/C(8)–H), 3.35 – 3.25 (m, 2H; 2x C(6)–H/C(8)–H), 2.37 – 2.23 (m, 2H 1x C(1)–H, 1x C(3)–H), 1.97 – 1.84 (m, 2H; 1x C(1)–H, 1x C(3)–H), 1.76 – 1.67 (m, 2H), 1.55 – 1.49 (m, 2H; 2x C(5)–H/C(9)–H), 1.48 (s, 9H; C(CH$_3$)$_3$).

HRMS (ESI): m/z calcd for $C_{19}H_{26}DNNaO_2^+$ [M + Na]$^+$ 325.1997 found 325.1997.

3-20k-C2'-*d*



(Experiment performed by A. M. L. Hell)

The corresponding compound was prepared following general procedure 3-5 using cyclobutene **3-18** (0.2 mmol), 3-fluorophenylboronic acid (0.4 mmol) and D$_2$O (0.040 mL) instead of H$_2$O. The mixture was stirred at room temperature (23 °C) for 16 h. Purification by automated medium-pressure chromatography (hexane/Et$_2$O = 100/0 to 80/20 to 0/100) afforded the product **3-20k-C2'-*d*** as a colourless oil (35 mg, 60% yield) with 64% D incorporation at the C(2') position.

^{1}H NMR (CD$_2$Cl$_2$, 400 MHz, quantitative): 7.32 – 7.24 (m, 1H; C(5')–H), 7.04 (d, *J* = 7.6 Hz, 1H, C(6')–H), 6.98 (dt, *J* = 10.3, 2.2 Hz, 0.36H; C(2')–H), 6.90 (td, *J* = 8.5, 1.2 Hz, 1H; C(4') – H), 4.35 (dd, *J* = 11.3, 8.0 Hz, 1H; 1x C(2'')–H), 4.27 (dd, *J* = 11.3, 6.8 Hz, 1H; 1x C(2'')–H), 4.21 (app. d, *J* = 6.8 Hz, 2H; 2x C(1'')–H), 3.46 (dt, *J* = 9.2, 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=O)CH$_3$), 1.96 (s, 3H;(C=O)CH$_3$).

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

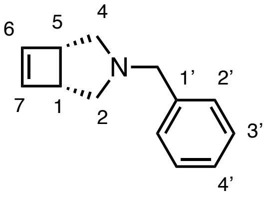
5.4. Procedures for Chapter 4

5.4.1. Synthesis of the Starting Materials

Cyclobutenes **4-2** (≡ **3-3**), **4-4b** (≡ **3-6d**), **4-4c** (≡ **3-9**), **4-4d** (≡ **3-2**), **4-4e** (≡ **3-18**) and **4-6** (≡ **3-14**) were synthesised according to our reported procedures.[223] All salicylaldehydes were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics, and Fluorochem were used without further purification. *Cis*-cyclobut-3-ene-1,2-diyl)dimethanol was prepared according to reported procedures.[204,223]

All reactions were carried out under an inert argon atmosphere using standard Schlenk techniques with all reagents weighed open to air.

4-S1



A solution of $LiAlH_4$ in Et_2O (1.0 M, 8.0 mL, 8.0 mmol) was added to a solution of **3-2/4-4d** (426 mg, 2.0 mol) in CH_2Cl_2 (18 mL) at 0 °C under an argon atmosphere. The reaction mixture was allowed to reach room temperature (23 °C) over night and was stirred for 16 h. Then, H_2O (0.4 mL), an aq. solution of NaOH (15 wt%, 0.4 mL), additional H_2O (1.0 mL), followed by $MgSO_4$ were added slowly at 0 °C. The mixture was filtered, and solvents were removed *in vacuo*. Purification by automated medium-pressure chromatography (EtOAc) afforded the product **4-S1** as a yellow oil (328 mg, 88% yield).

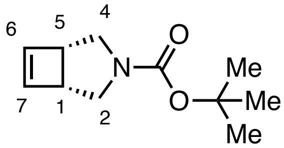
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.38 – 7.27 (m, 4H; 2x C(2')–H, 2x C(3')–H), 7.26 – 7.20 (m, 1H; C(4')–H), 6.05 (d, J = 0.7 Hz, 1H; C(6)–H, C(7)–H), 3.70 (s, 2H; CH_2Ph), 3.28 – 3.22 (m, 2H; C(1)–H, C(5)–H), 2.89 (d, J = 9.9 Hz, 2H; 1x C(2)–H_2, 1x C(4)–H_2), 1.88 (ddd, J = 9.9, 5.0, 1.1 Hz, 2H; 1x C(2)–H_2, 1x C(4)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 138.9 (C(1')), 138.0 (C(6), C(7)), 129.0, 128.1, 126.7 (C(4')), 59.6 (CH_2Ph), 53.8 (C(1), C(5)), 47.0 (C(2), C(4)).

IR (neat): 3033 (w), 2941 (w), 2777 (w), 1453 (w), 1345 (w), 1265 (w), 1172 (w), 1157 (w), 864 (w), 758 (s), 735 (m), 697 (s), 631 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{13}H_{16}N^+$ $[M + H]^+$ 186.1277 found 186.1279.

4-4a (≡ **3-6a**)



1-Chloroethyl chloroformate (220 µL, 2.0 mmol) was added to a solution of **4-S1** (278 mg, 1.50 mmol) in CH_2Cl_2 (15 mL) under an argon atmosphere. The mixture was stirred under reflux for 2 h. Then, the solvent was removed under reduced pressure.

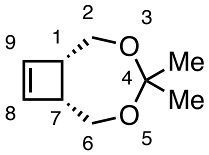
MeOH (15 mL) was added, and the mixture was stirred under reflux for 1.5 h. The solvent was removed under reduced pressure.

Dioxane (7 mL) was added, and the mixture was cooled to at 0 °C. An aq. solution of KOH (1 M, 7 mL), followed by Boc_2O were added, and the reaction mixture was allowed to reach room temperature (23 °C) over night and was stirred for 18 h. The mixture was diluted with Et_2O (20 mL) and H_2O (20 mL). The organic layer was separated, and aqueous layer was extracted with Et_2O (2x 20 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 80/10) afforded the product **4-4a** as a colourless oil (230 mg, 78% yield). The analytical data are in agreement with the literature.[223]

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 6.01 (s, 2H, C(6)–H and C(7)–H), 3.67 (rot. s, 2H; 1x C(2)–*H*$_2$, 1x C(4)–*H*$_2$), 3.30 (d, *J* = 6.0 Hz, 2H; C(1)–H, C(5)–H), 2.89 (dd, *J* = 12.0, 6.5 Hz, 2H, 1x C(2)–H$_2$, 1x C(4)–*H*$_2$), 1.45 (s, 9H; C(CH$_3$)$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 156.6 (C=O), 139.2, 138.7 (rot.; C(6), C(7)), 79.2 (*C*(CH$_3$)$_3$), 44.9, 46.3 (rot.; C(1), C(2), C(4), C(5)), 28.7 (C(*C*H$_3$)$_3$).

4-4f



A mixture of *cis*-cyclobut-3-ene-1,2-diyl)dimethanol (456 mg, 4.0 mmol) and *p*-toluenesulfonic acid (15.2 mg, 2.0 mol%) was dissolved in CH$_2$Cl$_2$ (15 mL) under an argon atmosphere. 2-Methoxypropene (0.77 mL, 8.0 mmol) The mixture was stirred at room temperature (23 °C) for 24 h. Purification by automated medium-pressure chromatography (pentane/Et$_2$O = 100/0 to 70/30) afforded the product **4-4f** as a yellow oil (348 mg, 56% yield).

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 6.12 (s, 2H; C(8)–H, C(9)–H), 3.99 – 3.82 (m, 1H; 1x C(2)–H$_2$, 1x C(6)–H$_2$), 3.81 – 3.70 (m, 2H; 1x C(2)–H$_2$, 1x C(6)–H$_2$), 3.20 – 3.10 (m, 2H; C(1)–H, C(7)–H), 1.40 (s, 3H; CH$_3$), 1.39 (s, 3H; CH$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 138.1 (C(8), C(9)), 102.1 (C(4)), 63.3 (C(2), C(6)), 47.7 (C(1), C(7)), 25.0 (rot.; CH$_3$), 24.5 (rot.; CH$_3$).

IR (neat): 2992 (w), 2935 (w), 1381 (w), 1368 (w), 1215 (m), 1151 (m), 1075 (s), 1036 (m), 993 (m), 829 (w), 797 (m), 737 (m), 710 (s) cm^{-1}.

HRMS (ESI/APCI): m/z not found.

Note: We were not able to detect the molecular ion or a characteristic fragment for this molecule.

5.4.2. Catalytic Hydroacylation Reactions

All reactions were carried out under an inert argon atmosphere using standard Schlenk techniques with all reagents weighed open to air.

General procedure 4-1

Flask I: A solution of cyclobutene (0.6 mmol) and salicylaldehyde (0.4 mol) in dry toluene (0.7 mL) was prepared under an argon atmosphere.

Flask II: A resulting (slightly turbid) solution of $[Rh(cod)OH]_2$ (4.6 mg, 2.5 mol%) and (*R*,*R*)-MeDuphos (7.3 mg, 6.0 mol%) was stirred in dry toluene (1.0 mL) under an argon atmosphere at room temperature (23 °C) for 15 min. Then, the solution of *Flask I* was added to *Flask II*, and *Flask I* was rinsed with dry toluene (0.3 mL). The reaction mixture was stirred 60 °C for 20 h. The reaction mixture was then concentrated *in vacuo* and purified by automated liquid chromatography.

General procedure 4-2

Flask I: A solution of cyclobutene (0.6 mmol) and salicylaldehyde (0.4 mol) in dry toluene (0.7 mL) was prepared under an argon atmosphere.

Flask II: A resulting (clear) solution of $[Rh(cod)OH]_2$ (5.5 mg, 3.0 mol%) and dppf (13.3 mg, 6.0 mol%) was stirred in dry toluene (1.0 mL) under an argon atmosphere at room temperature (23 °C) for 15 min. Then, the solution of *Flask I* was added to *Flask II*, and *Flask I* was rinsed with dry toluene (0.3 mL). The reaction mixture was stirred 60 °C for 20 h. The reaction mixture was then concentrated *in vacuo* and purified by automated liquid chromatography.

Racemates

Racemic samples were synthesized with (±)-BINAP or dppf.

Epimerisation of (±)-4-3

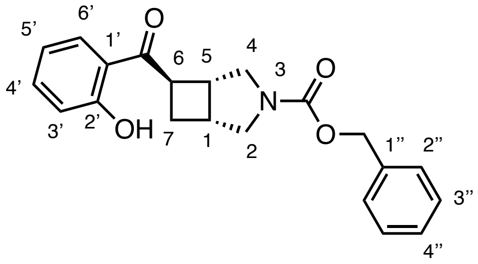
A mixture of (±)-**4-3** (0.5 mg) and a tip of a spatula of K_2CO_3 in MeOH (0.5 mL) was stirred for 16 h at room temperature (23 °C). The mixture was filtered and analysed by super critical fluid chromatography.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; (minor diast. t_R = 5.97 min; major diast. t_R = 6.07 min, minor diast. t_R = 6.21 min; major diast. t_R = 6.49 min).

Determination of absolute and relative stereochemistry

The absolute stereochemistry of **4-5b** was assigned via X-ray crystallographic analysis by Dr. Curtis Moore (Ohio State University). The structure was deposited on the Cambridge Crystallographic Data Centre (CCDC deposition number 2116804). The relative stereochemistry of **4-3a'**, **4-5b**, **4-5c**, **4-5d**, **4-5e** and **4-5f** was assigned by NOESY spectroscopy. The absolute and relative stereochemistry of all other compounds was assigned by analogy. A determination via x-Ray diffraction is ongoing.

4-3a



The corresponding compound was prepared following general procedure 4-1 using salicylaldehyde and cyclobutene **4-2**. The mixture was stirred at 60 °C for 1 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-3a** as a colourless solid (113 mg, 81% yield). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 12.26 (s, 1H; OH), 7.48 – 7.28 (m, 7H; 2x C(2'')–H, 2x C(3'')–H, C(4'')–H, C(6')–H, C(4')–H), 6.99 (dd, *J* = 8.6, 1.2 Hz, 1H; C(3')–H), 6.87 (td, *J* = 7.6, 1.2 Hz, 1H; C(5')–H), 5.21 (s, 2H; CH$_2$Ph), 4.07 – 3.67 (m, 3H; 2x CH$_2$N, C(6)–H), 3.45 – 3.31 (m, 3H; 2x CH$_2$N, C(5)–H), 2.96 – 2.84 (m, 1H; C(1)–H), 2.58 (br. s, 1H; C(7)–H), 2.11 (br. s, 1H; C(7)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 206.0 (C=O), 163.0 (C(2')), 155.7 (CO$_2$N), 136.9 (C(1'')), 136.5 (C(4')), 129.8 (C(6')), 128.7 (2x C(3'')), 128.2 (C(4'')), 128.1 (2x C(2'')), 119.1 (C(5')), 118.8 (C(3')), 117.8 (C(1')), 67.2 (CH$_2$Ph), 52.7, 52.3 (rot.; 2x CH$_2$N), 44.3 (C(6)), 39.6 (rot.; C(5)), 34.8, 33.9 (rot.; 2x C(1)), 29.2, 28.4 (rot.; 2x C(7)).

IR (CHCl$_3$ film): 2980 (w), 2872 (w), 1702 (s), 1634 (m), 1486 (w), 1447 (m), 1416 (m), 1358 (m), 1295 (w), 1229 (m), 1209 (m), 1158 (m), 1098 (m), 757 (m), 698 (w) cm^{-1}.

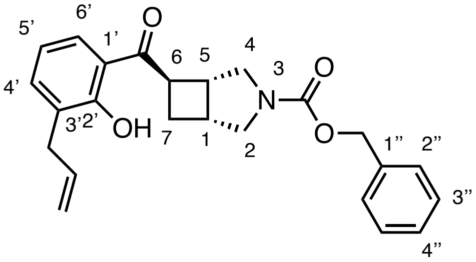
HRMS (ESI): m/z calcd for C$_{21}$H$_{21}$O$_4$NNa$^+$ [M + Na]$^+$ 374.1363 found 374.1362.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 99:1 e.r. (minor enantiomer t$_R$ = 6.10 min; major enantiomer t$_R$ = 6.46 min).

[α]^{25}$_{D}$ = –109.6 (*c* = 1.0, CHCl$_3$).

m.p.: 60 – 62 °C.

4-3b



The corresponding compound was prepared following general procedure 4-1 using 3-allylsalicylaldehyde and cyclobutene **4-2**. The mixture was stirred at 60 °C for 3 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-3b** as a pale-yellow oil (117 mg, 75% yield). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 12.61 (s, 1H; OH), 7.45 – 7.30 (m, 7H; 2x C(2’’)–H, 2x C(3’’)–H, C(4’’)–H, C(6’)–H, C(4’)–H), 6.82 (app. t, *J* = 7.7 Hz, 1H; C(5’)–H), 6.07 – 5.94 (m, 1H; C*H*=CH$_2$), 5.21 (s, 2H; CH$_2$Ph), 5.10 (dq, *J* = 7.2, 1.5 Hz, 1H; CH=C*H*$_2$), 5.07 (app. t, *J* = 1.5 Hz, 1H; CH=C*H*$_2$), 4.05 – 3.64 (m, 3H; 2x CH$_2$N, C(6)–H), 3.50 – 3.29 (m, 5H; 2x CH$_2$N, C(5)–H, C*H*$_2$CH=CH$_2$), 2.97 – 2.87 (m, 1H; C(1)–H), 2.59 (br. s, 1H; C(7)–H), 2.10 (br. s, 1H; C(7)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 206.2 (C=O), 161.0 (C(2’)), 155.7 (CO$_2$N), 137.0 (C(1’’)), 136.5 (C(4’)), 136.2 (CH$_2$*C*H=CH$_2$), 129.8 (C(3’)), 128.6 (2x C(3’’)), 128.2 (C(4’’)), 128.1 (2x C(2’’)), 127.9 (C(6’)), 118.6 (C(5’)), 117.4 (C(1’)), 116.2 (CH$_2$CH=*C*H$_2$), 67.1 (CH$_2$Ph), 52.8, 52.2 (rot.; 2x CH$_2$N), 44.4 (C(6)), 39.7 (rot.; C(5)), 34.7, 33.9 (rot.; 2x C(1)), 33.6 (*C*H$_2$CH=CH$_2$), 29.2, 28.4 (rot.; 2x C(7)).

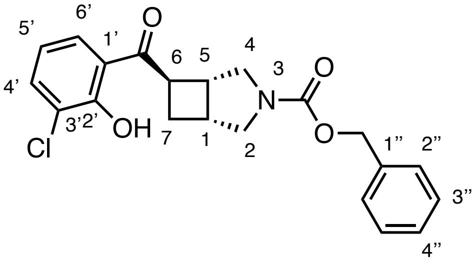
IR ($CHCl_3$ film): 2973 (w), 2871 (w), 1703 (s), 1628 (m), 1498 (m), 1426 (m), 1358 (m), 1295 (w), 1230 (m), 1158 (w), 1098 (m), 1028 (w), 915 (w), 769 (w), 753 (m), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{24}H_{26}O_4N^+$ $[M + H]^+$ 392.1856 found 392.1857.

SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 98.5:1.5 e.r. (major enantiomer $t_R = 3.92$ min; minor enantiomer $t_R = 4.07$ min).

$[\alpha]^{25}_D = -90.2$ ($c = 1.0$, $CHCl_3$).

4-3c



The corresponding compound was prepared following general procedure 4-1 using 3-chlorosalicylaldehyde and cyclobutene **4-2** with an increased catalyst loading of $[Rh(cod)OH]_2$ (5.0 mol%) and (*R*,*R*)-MeDuphos (12 mol%). The mixture was stirred at 60 °C for 4 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-3c** as a colourless solid (103 mg, 67 % yield). SFC analysis showed an enantiomeric excess of 99%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 12.85 (s, 1H; OH), 7.56 (dd, $J = 7.9$, 1.5 Hz, 1H; C(6')–H), 7.47 – 7.29 (m, 6H; 2x C(2'')–H, 2x C(3'')–H, C(4'')–H, C(4')–H), 6.83 (app. t, $J = 7.9$ Hz, 1H; C(5')–H), 5.21 (s, 2H; CH_2Ph), 4.05 – 3.62 (m, 3H; 2x CH_2N, C(6)–H), 3.48 – 3.26 (m, 3H; 2x CH_2N, C(5)–H), 2.97 – 2.85 (m, 1H; C(1)–H), 2.58 (br. s, 1H; C(7)–H), 2.11 (br. s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 205.9 (C=O), 158.7 (C(2’)), 155.7 (CO_2N), 136.9 (C(1’’)), 136.4 (C(6’)), 128.6 (2x C(3’’)), 128.22, 128.19 (C(4’’), C(4’)), 128.1 (2x C(2’’)), 123.3 (C(3’)), 119.2 (C(5’)), 118.8 (C(1’)), 67.2 (CH_2Ph), 52.8, 52.2 (rot.; 2x CH_2N), 44.4 (C(6)), 39.6 (rot.; C(5)), 34.9, 33.9 (rot.; 2x C(1)), 29.1, 28.4 (rot.; 2x C(7)).

IR ($CHCl_3$ film): 2980 (w), 2872 (w), 1702 (s), 1637 (m), 1433 (s), 1359 (m), 1229 (m), 1150 (m), 1099 (w), 743 (w) cm^{-1}.

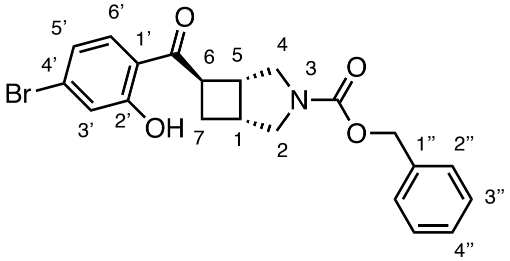
HRMS (ESI): m/z calcd for $C_{21}H_{19}O_4N^{35}Cl^+$ $[M - H]^-$ 384.1008 found 384.1001.

SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min; 99.5:0.5 e.r. (major enantiomer t_R = 4.73 min; minor enantiomer t_R = 5.13 min).

$[\alpha]^{25}_D$ = –115.5 (*c* = 1.0, $CHCl_3$).

m.p.: 112 – 113 °C.

4-3d



The corresponding compound was prepared following general procedure 4-1 using 4-bromosalicylaldehyde and cyclobutene **4-2** with an increased catalyst loading of $[Rh(cod)OH]_2$ (5.0 mol%) and (*R*,*R*)-MeDuphos (12 mol%). The mixture was stirred at 60 °C for 4 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-3d** as a yellow oil (124 mg, 71 % yield). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 12.35 (s, 1H; OH), 7.47 – 7.29 (m, 6H; 2x C(2'')–H, 2x C(3'')–H, C(4'')–H, C(6')–H), 7.19 (d, *J* = 1.9 Hz, 1H; C(3')–H), 7.00 (dd, *J* = 8.5, 2.0 Hz, 1H; C(6')–H), 5.21 (s, 2H; CH$_2$Ph), 4.00 – 3.58 (br. m, 3H; 2x CH$_2$N, C(6)–H), 3.50 – 3.27 (m, 3H; 2x CH$_2$N, C(5)–H), 2.92 (dd, *J* = 8.6, 4.8 Hz, 1H; C(1)–H), 2.55 (br. s, 1H; C(7)–H), 2.10 (br. s, 1H; C(7)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 205.5 (C=O), 163.4 (C(2')), 155.7 (CO$_2$N), 136.9 (C(1'')), 130.9 (C(4')), 130.7 (C(6')), 128.7 (2x C(3'')), 128.2 (C(4')), 128.1 (2x C(2'')), 122.7 (C(3')), 122.0 (C(5')), 116.7 (C(1')), 67.2 (CH$_2$Ph), 52.7, 52.1 (rot.; 2x CH$_2$N), 44.3 (C(6)), 39.3 (rot.; C(5)), 34.8, 33.4 (rot.; 2x C(1)), 28.8, 28.3 (rot.; 2x C(7)).

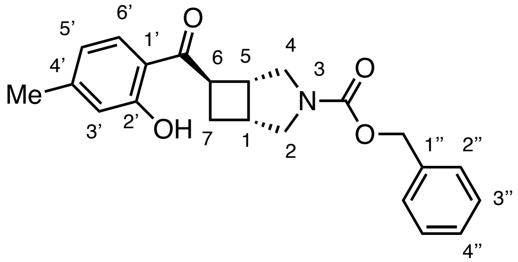
IR (CHCl$_3$ film): 2981 (w), 1699 (m), 1634 (m), 1416 (w), 1359 (w), 1229 (w), 1099 (w), 901 (w), 754 (s), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{19}O_4N^{79}Br^+$ $[M - H]^-$ 428.0503 found 428.0499.

SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; hold 1% MeOH for 2 min, then from 1% to 2.5% MeOH in 1 min, then hold 2.5% MeOH for 5 min, then from 2.5% to 35% MeOH in 7 min; 98.5:1.5 e.r. (major enantiomer t_R = 12.34 min; minor enantiomer t_R = 12.56 min).

$[\alpha]^{25}_D$ = –96.3 (*c* = 1.0, CHCl$_3$).

4-3e



The corresponding compound was prepared following general procedure 4-1 using 4-methylsalicylaldehyde and cyclobutene **4-2**. The mixture was stirred at 60 °C for 3 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-3e** as a yellow oil (121 mg, 83% yield). SFC analysis showed an enantiomeric excess of 96%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 12.29 (s, 1H; OH), 7.48 – 7.28 (m, 6H; 2x C(2'')–H, 2x C(3'')–H, C(4'')–H, C(6')–H), 6.80 (dd, *J* = 1.8, 0.9 Hz, 1H; C(3')–H), 6.67 (dd, *J* = 8.2, 1.7 Hz, 1H; C(5')–H), 5.21 (s, 2H; CH_2Ph), 4.03 – 3.64 (br. m, 3H; 2x CH_2N, C(6)–H), 3.45 – 3.25 (m, 3H; 2x CH_2N, C(5)–H), 2.91 (dq, *J* = 11.5, 6.8 Hz, 1H; C(1)–H), 2.57 (br. s, 1H; C(7)–H), 2.34 (s, 3H; CH_3), 2.08 (br. s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 205.3 (C=O), 163.1 (C(2')), 155.7 (CO_2N), 148.1 (C(4')), 136.9 (C(1'')), 129.7 (C(6')), 128.6 (2x C(3'')), 128.2 (C(4'')), 128.1 (2x C(2'')), 120.4 (C(5')), 118.8 (C(3')), 115.6 (C(1')), 67.1 (CH_2Ph), 52.7, 52.2 (rot.; 2x CH_2N), 44.1 (C(6)), 39.7 (rot.; C(5)), 33.5 (rot.; C(1)), 29.2, 28.3 (rot.; 2x C(7)), 22.1 (CH_3).

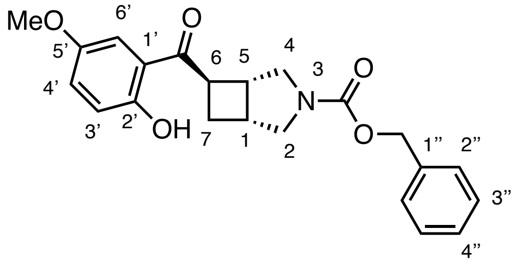
IR ($CHCl_3$ film): 2980 (w), 1702 (s), 1635 (m), 1415 (m), 1229 (m), 1211 (m), 1098 (w), 770 (w), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{22}H_{24}O_4N^+$ $[M + H]^+$ 366.1700 found 366.1700.

SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; hold 1% MeOH for 2 min, then from 1% to 2.5% MeOH in 1 min, then hold 2.5% MeOH for 5 min, then from 2.5% to 35% MeOH in 7 min; 98:2 e.r. (major enantiomer t_R = 10.88 min; minor enantiomer t_R = 11.04 min).

$[\alpha]^{25}_D$ = –109.4 (*c* = 1.0, $CHCl_3$).

4-3f



The corresponding compound was prepared following general procedure 4-1 using 5-methoxysalicylaldehyde and cyclobutene **4-2**. The mixture was stirred at 60 °C for 2 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 50/50) afforded the product **4-3f** as a yellow oil (121 mg, 79% yield). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 11.86 (s, 1H; OH), 7.44 – 7.29 (m, 5H; 2x C(2'')–H, 2x C(3'')–H, C(4'')–H), 7.10 (dd, *J* = 9.0, 3.1 Hz, 1H; C(4')–H), 6.94 (d, *J* = 9.1 Hz, 1H; C(3')–H), 6.90 (br. s, 1H; C(6')–H), 5.21 (s, 2H; CH_2Ph), 4.07 – 3.55 (br. m, 6H; 2x CH_2N, C(6)–H, OCH_3), 3.46 – 3.25 (m, 3H; 2x CH_2N, C(5)–H), 2.91 (p, *J* = 6.6 Hz, 1H; C(1)–H), 2.59 (dt, *J* = 12.4, 8.2 Hz, 1H; C(7)–H), 2.12 (br. s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 205.4 (C=O), 157.3 (C(2')), 155.7 (CO_2N), 151.9 (C(5')), 136.9 (C(1'')), 128.6 (2x C(3'')), 128.2 (C(4'')), 128.1 (2x C(2'')), 124.4 (C(4')), 119.7 (C(3')), 117.2 (C(1')), 112.3 (C(6')), 67.2 (CH_2Ph), 56.1 (OCH_3), 52.8, 52.3 (rot.; 2x CH_2N), 44.4 (C(6)), 39.8, 39.4 (rot.; 2x C(5)), 34.8, 33.9 (rot.; 2x C(1)), 28.9, 28.3 (rot.; 2x C(7)).

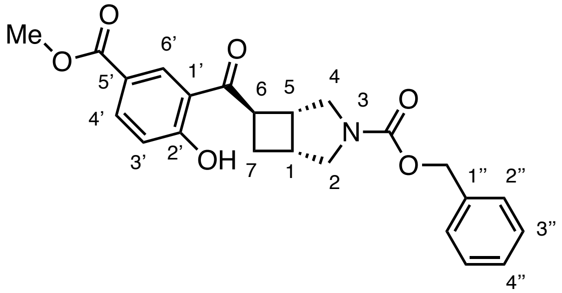
IR ($CHCl_3$ film): 2980 (w), 1702 (s), 1640 (w), 1614 (w), 1486 (s), 1417 (m), 1359 (m), 1285 (m), 1229 (m), 1176 (m), 1098 (w), 770 (w), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{22}H_{23}O_5NNa^+$ $[M + Na]^+$ 404.1468 found 404.1473.

SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 8 min; 99:1 e.r. (minor enantiomer t_R = 7.70 min; major enantiomer t_R = 7.82 min).

$[\alpha]^{25}_D$ = –93.8 (*c* = 1.0, $CHCl_3$).

4-3g



The corresponding compound was prepared following general procedure 4-1 using 5-methoxycarbonylsalicylaldehyde and cyclobutene **4-2** with an increased catalyst loading of $[Rh(cod)OH]_2$ (5.0 mol%) and (*R*,*R*)-MeDuphos (12 mol%). The mixture was stirred at 60 °C for 4 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-3g** as a colourless oil (118 mg, 72% yield). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 12.66 (s, 1H; OH), 8.22 (d, *J* = 2.1 Hz, 1H; C(6')–H), 8.12 (dd, *J* = 8.8, 2.1 Hz, 1H; C(4')–H), 7.46 – 7.29 (m, 5H; 2x C(2'')–H, 2x C(3'')–H, C(4'')–H), 7.03 (d, *J* = 8.8 Hz, 1H; C(3')–H), 5.22 (s, 2H; CH_2Ph), 4.02 – 3.72 (m, 6H; 2x CH_2N, C(6)–H, OCH_3), 3.48 – 3.30 (m, 3H; 2x CH_2N, C(5)–H), 2.94 (tt, *J* = 11.4, 5.6 Hz, 1H; C(1)–H), 2.55 (dt, *J* = 12.4, 8.2 Hz, 1H; C(7)–H), 2.21 (ddd, *J* = 12.9, 10.0, 4.2 Hz, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 206.11 (C=O), 166.5 (C(2')), 165.9 (CO_2CH_3), 155.7 (CO_2N), 137.2 (C(4')), 136.9 (C(1'')), 132.2 (C(6')), 128.6 (2x C(3'')), 128.2 (C(4'')), 128.1 (2x C(2'')), 121.3 (C(5')), 119.0 (C(3')), 117.2 (C(1')), 67.2 (CH_2Ph), 52.3 (2x CH_2N, OCH_3), 44.4 (C(6)), 39.7 (rot.; C(5)), 34.7 (rot.; C(1)), 29.1 (C(7)).

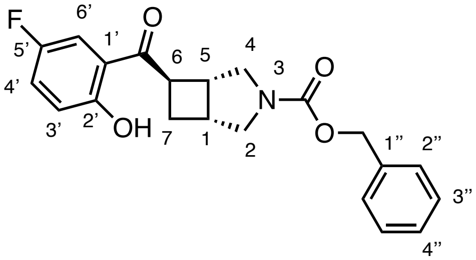
IR ($CHCl_3$ film): 2953 (w), 1706 (s), 1638 (m), 1419 (m), 1358 (m), 1278 (s), 1227 (s), 1108 (m), 769 (w), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{23}H_{24}O_6N^+$ $[M + H]^+$ 410.1598 found 410.1579.

SFC Chiralpak® IE 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 99:1 e.r. (major enantiomer t_R = 6.60 min; minor enantiomer t_R = 7.03 min).

$[\alpha]^{25}_D$ = –81.3 (*c* = 1.0, $CHCl_3$).

4-3g



The corresponding compound was prepared following general procedure 4-1 using 5-fluorosalicylaldehyde and cyclobutene **4-2** with an increased catalyst loading of $[Rh(cod)OH]_2$ (5.0 mol%) and (*R*,*R*)-MeDuphos (12 mol%). The mixture was stirred at 60 °C for 2 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-3g** as a colourless oil (105 mg, 71% yield). SFC analysis showed an enantiomeric excess 97%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 11.98 (s, 1H; OH), 7.47 – 7.29 (m, 5H; 2x C(2'')–H, 2x C(3'')–H, C(4'')–H), 7.20 (ddd, *J* = 9.1, 7.7, 3.1 Hz, 1H; C(4')–H), 7.12 (dd, *J* = 8.8, 3.1 Hz, 1H; C(6')–H), 6.96 (dd, *J* = 9.1, 4.5 Hz, 1H; C(3')–H), 5.21 (s, 2H; CH_2Ph), 3.97 – 3.72 (m, 2H; 2x CH_2N), 3.64 (t, *J* = 7.9 Hz, 1H; C(6)–H), 3.54 – 3.27 (m, 3H; 2x CH_2N, C(5)–H), 2.98 – 2.87 (m, 1H; C(1)–H), 2.59 – 2.48 (m, 1H; C(7)–H), 2.14 (br. s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 205.1 (d, *J* = 2.6 Hz; C=O), 159.16 (d, *J* = 1.5 Hz; C(2')), 155.7 (CO_2N), 154.93 (d, *J* = 239.1 Hz; C(5')), 128.6 (2x C(3'')), 128.2 (C(4'')), 128.1 (2x C(2'')), 124.1 (d, *J* = 23.6 Hz; C(4')), 120.1 (d, *J* = 7.2 Hz; C(3')), 117.3 (d, *J* = 6.0 Hz; C(1')), 114.6 (d, *J* = 23.0 Hz; C(6’)), 67.2 (CH_2Ph), 52.7, 52.1 (rot.; 2x CH_2N), 44.4, 39.4 (C(6)), 38.9 (rot.; 2x C(5)), 34.9, 34.0 (rot.; 2x C(1)), 29.0 (rot.; C(7)).

^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -123.59 (app. t, *J* = 9.9 Hz; C–F).

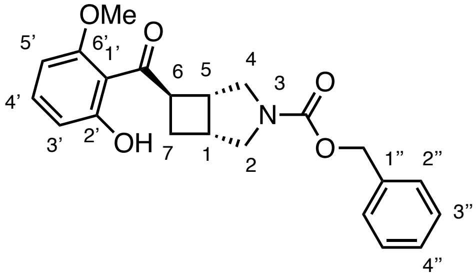
IR ($CHCl_3$ film): 2960 (w), 2872 (w), 1702 (s), 1643 (w), 1482 (m), 1418 (m), 1359 (m), 1283 (w), 1246 (m), 1229 (w), 1172 (m), 1099 (w), 830 (w), 788 (w), 769 (w), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{20}O_4FNNa^+$ $[M + Na]^+$ 392.1269 found 392.1268.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 98.5:1.5 e.r. (minor enantiomer t_R = 5.56 min; major enantiomer t_R = 6.23 min).

$[\alpha]^{25}_D$ = –109.3 (*c* = 1.0, $CHCl_3$).

4-3j



The corresponding compound was prepared following general procedure 4-1 using 6-methoxysalicylaldehyde and cyclobutene **4-2**. The mixture was stirred at 60 °C for 2 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 60/40) afforded the product **4-3j** as a pale-yellow oil (119 mg, 78% yield). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 13.07 (s, 1H; OH), 7.45 – 7.28 (m, 6H; 2x C(2’’)–H, 2x C(3’’)–H, C(4’’)–H, C(4‘)–H), 6.58 (dd, *J* = 8.4, 1.0 Hz, 1H; C(3‘)–H), 6.35 (d, *J* = 8.3 Hz, 1H; C(5‘)–H), 5.22 (d, *J* = 12.7 Hz, 1H; 1x CH_2Ph), 5.19 (d, *J* = 12.7 Hz, 1H; 1x CH_2Ph), 4.11 – 3.62 (br. m, 6H; 2x CH_2N, C(6)–H, OCH_3), 3.52 – 3.10 (m, 3H; 2x CH_2N, C(5)–H), 2.86 (s, 1H; C(1)–H), 2.57 (br. s, 1H; C(7)–H), 2.02 (br. s, 1H; C(7)–H).

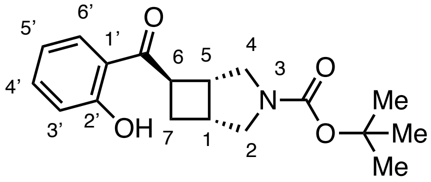
^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 206.7 (C=O), 165.0 (C(2’)), 161.0 (C(6’)), 155.6 (CO_2N), 137.0 (C(1’’)), 136.2 (C(4’)), 128.6 (2x C(3’’)), 128.1 (C(4’’)), 128.0 (2x C(2’’)), 111.0 (C(3’)), 110.2 (C(1’)), 101.3 (C(5’)), 67.0 (CH_2Ph), 55.8 (OCH_3), 53.1, 52.6, 52.2 (rot.; 3x CH_2N), 49.6 (C(6)), 40.3 (C(5)), 34.6, 33.4 (rot.; 2x C(1)), 28.7, 27.9 (rot.; 2x C(7)).

IR ($CHCl_3$ film): 2942 (w), 2869 (w), 1700 (s), 1623 (m), 1594 (m), 1456 (m), 1437 (m), 1419 (m), 1359 (m), 1236 (s), 1184 (w), 1093 (s), 746 (w), 699 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{22}H_{23}O_5NNa^+$ $[M + Na]^+$ 404.1468 found 404.1473.

SFC Chiralpak® IA 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 99:1 e.r. (major enantiomer t_R = 4.71 min; minor enantiomer t_R = 4.98 min).

4-5a



The corresponding compound was prepared following general procedure 4-1 using salicylaldehyde and cyclobutene **4-4a**. The mixture was stirred at 60 °C for 1 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **4-5a** as a colourless oil (98 mg, 76% yield). SFC analysis showed an enantiomeric excess of 98%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 12.28 (s, 1H; OH), 7.51 (dd, *J* = 8.0, 1.7 Hz, 1H; C(6')–H), 7.46 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H; C(4')–H), 6.99 (dd, *J* = 8.4, 1.2 Hz, 1H; C(3')–H), 6.87 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H; C(5')–H), 3.83 – 3.72 (m, 2H; 1x CH$_2$N, C(6)–H), 3.70 – 3.55 (m, 1H; 1x CH$_2$N), 3.39 – 3.24 (m, 3H; 2x CH$_2$N, C(5)–H), 2.89 (dddd, *J* = 11.7, 8.9, 6.6, 3.7 Hz, 1H; C(1)–H), 2.58 (dt, *J* = 12.5, 8.2 Hz, 1H; C(7)–H), 2.12 (ddd, *J* = 13.3, 10.0, 4.4 Hz, 1H; C(7)–H), 1.51 (s, 9H; C(CH$_3$)$_3$)

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 206.2 (C=O), 163.0 (C(2')), 155.5 (CO$_2$N), 136.4 (C(4')), 129.8 (C(6')), 119.1 (C(5')), 118.8 (C(3')), 117.9 (C(1')), 79.8 (*C*(CH$_3$)$_3$) , 52.7 (CH$_2$N), 52.1 (CH$_2$N), 44.4 (C(6)), 39.7 (C(5)), 34.4 (C(1)), 28.7 (C(*C*H$_3$)$_3$, C(7)).

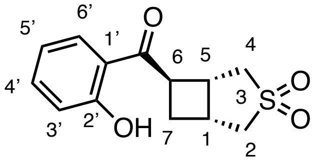
IR (CHCl$_3$ film): 2980 (m), 2882 (w), 1695 (s), 1635 (m), 1486 (w), 1448 (w), 1365 (s), 1349 (m), 1295 (w), 1238 (m), 1158 (s), 1100 (w), 758 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{18}H_{23}O_4NNa^+$ $[M + Na]^+$ 340.1519 found 340.1519.

SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from30% to 50% MeOH in 0.5 min; 99:1 e.r. (major enantiomer t_R = 2.23 min; minor enantiomer t_R = 2.38 min).

$[\alpha]^{25}_D$ = –119.1 (*c* = 1.0, CHCl$_3$).

4-5b



The corresponding compound was prepared following general procedure 4-1 using salicylaldehyde and cyclobutene **4-4b**. The mixture was stirred at 60 °C for 2 h. ^{1}H NMR analysis of the unpurified reaction mixture showed a diastereomeric ratio of 8:1. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 40/60) afforded the product **4-5b** as a colourless solid (89 mg, 84% yield). SFC analysis showed an enantiomeric excess of 96%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 12.08 (s, 1H; OH), 7.53 – 7.42 (m, 2H; C(6')–H, C(4')–H), 7.10 – 6.96 (m, 1H; C(3')–H), 6.96 – 6.74 (m, 1H; C(5')–H), 4.37 – 4.24 (m, 1H; C(6)–H), 3.87 (tdd, *J* = 8.4, 6.2, 2.1 Hz, 1H; C(5)–H), 3.38 – 3.18 (m, 3H; 2x CH_2SO_2, C(1)–H), 3.17 – 3.01 (m, 2H; 2x CH_2SO_2), 2.72 – 2.53 (m, 2H; C(7)–H_2).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 204.7 (C=O), 163.0 (C(2')), 136.9 (C(6')), 129.8 (C(5')), 119.3 (C(5')), 118.9 (C(3')), 117.5 (C(1')), 55.4 (CH_2SO_2), 55.0 (CH_2SO_2), 43.6 (C(6)), 33.3 (C(5)), 30.2 (C(1)), 29.6 (C(7)).

IR ($CHCl_3$ film): 2982 (w), 1634 (s), 1447 (m), 1415 (w), 1304 (s), 1273 (s), 1211 (m), 1140 (s), 1082 (w), 874 (w), 755 (s), 672 (m) cm^{-1}.

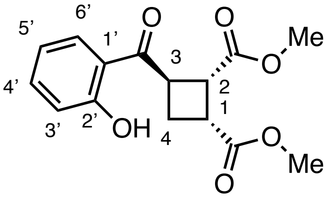
HRMS (ESI): m/z calcd for $C_{13}H_{13}O_4S^+$ $[M – H]^-$ 265.0540 found 265.0537.

SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 98:2 e.r. (major enantiomer t_R = 3.67 min; minor enantiomer t_R = 4.12 min).

$[\alpha]^{25}_D$ = –138.2 (*c* = 1.0, $CHCl_3$).

m.p.: 172 – 174°C.

4-5c



The corresponding compound was prepared following general procedure 4-1 using salicylaldehyde and cyclobutene **4-4c**. The mixture was stirred at 60 °C for 2 h. ^{1}H NMR analysis of the unpurified reaction mixture showed a diastereomeric ratio of >20:1:1. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 80/20) afforded a mixture of **4-4c** and **4-4c**. **4-4c** was removed under reduced pressure (approx. 0.1 mbar) at 50 °C and a colourless solid (101 mg, 84% yield) contaminated with 3% unreacted **4-5c** was obtained. SFC analysis showed an enantiomeric excess of 96%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 12.08 (s, 1H; OH), 7.69 (dd, *J* = 8.0, 1.6 Hz, 1H; C(6')–H), 7.48 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H; C(4')–H), 6.99 (dd, *J* = 8.4, 1.2 Hz, 1H; C(3')–H), 6.91 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H; C(5')–H), 4.63 – 4.55 (m, 1H; C(3)–H), 3.98 (ddd, *J* = 9.5, 8.3, 1.0 Hz, 1H; C(2)–H), 3.75 (s, 3H; OCH$_3$), 3.70 (s, 3H; OCH$_3$), 3.41 (dddd, *J* = 10.1, 9.2, 4.1, 1.2 Hz, 1H; C(1)–H), 2.70 – 2.60 (m, 1H; C(4)–H), 2.43 (dt, *J* = 11.7, 8.9 Hz, 1H; C(4)–H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 204.2 (C=O), 173.8 (CO$_2$CH$_3$), 171.8 (CO$_2$CH$_3$), 163.0 (C(2')), 136.9 (C(4')), 130.2 (C(6')), 119.3 (C(5')), 118.7 (C(3')), 117.8 (C(1')), 52.33 (OCH$_3$), 52.27 (OCH$_3$), 41.9 (C(3)), 40.2 (C(2)), 38.0 (C(1)), 26.8 (C(4)).

IR (CHCl$_3$ film): 2953 (w), 1736 (s), 1634 (s), 1487 (w), 1437 (m), 1308 (m), 1272 (m), 1205 (s), 1160 (m), 1034 (w), 955 (w), 758 (m) cm^{-1}.

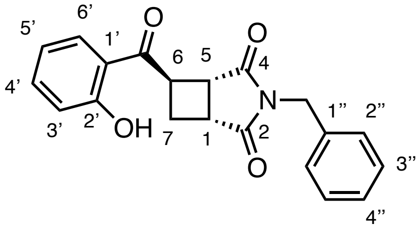
HRMS (ESI): m/z calcd for $C_{15}H_{16}O_6Na^+$ [M + Na]$^+$ 315.0839 found 315.0840.

SFC Chiralpak® IG 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30 to 50% in 0.5 min; 98:2 e.r. (minor enantiomer t_R = 4.03 min; major enantiomer t_R = 5.35 min).

[α]^{25}$_{D}$ = –98.9 (*c* = 1.0, $CHCl_3$).

m.p.: 83 – 85 °C.

4-5d



The corresponding compound was prepared following general procedure 4-1 using salicylaldehyde and cyclobutene **4-4d**. The mixture was stirred at 60 °C for 2 h. ^{1}H NMR analysis of the unpurified reaction mixture showed a diastereomeric ratio of >5:1. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-5d** as a colourless solid (106 mg, 79% yield). SFC analysis showed an enantiomeric excess of 63%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 11.93 (s, 1H; OH), 7.66 (dd, *J* = 8.0, 1.6 Hz, 1H; C(6')–H), 7.50 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H; C(3')–H), 7.47 – 7.41 (m, 2H; 2x C(2'')–H), 7.39 – 7.28 (m, 3H; 2x C(3'')–H, C(4'')–H), 7.02 (dd, *J* = 8.5, 1.1 Hz, 1H; C(3')–H), 6.93 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H; C(5')–H), 4.76 (s, 2H; CH_2Ph), 4.04 (dddd, *J* = 9.6, 6.5, 4.5, 1.1 Hz, 1H; C(6)–H), 3.73 (ddt, *J* = 6.7, 4.6, 1.0 Hz, 1H; C(5)–H), 3.30 (dddd, *J* = 10.7, 6.9, 4.6, 1.0 Hz, 1H; C(1)–H), 3.05 (dddd, *J* = 13.2, 10.8, 6.5, 1.0 Hz, 1H; C(7)–H), 2.48 (dddd, *J* = 13.2, 9.6, 4.6, 0.9 Hz, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 202.2 (C=O), 178.3 (CON), 177.7 (CON), 163.2 (C(2')), 137.2 (C(4')), 135.8 (C(1'')), 130.0 (C(6')), 129.0 (2x C(2''), 2x C(3'')), 128.3 (C(4'')), 119.6 (C(5')), 119.0 (C(3')), 117.1 (C(1')), 43.0 (CH_2Ph), 42.5 (C(6)), 40.8 (C(5)), 36.1 (C(1)), 25.9 (C(7)).

IR ($CHCl_3$ film): 2981 (w), 1771 (w), 1698 (s), 1637 (m), 1487 (w), 1148 (w), 1391 (m), 1342 (m), 1277 (m), 1159 (m), 756 (m), 670 (w) cm^{-1}.

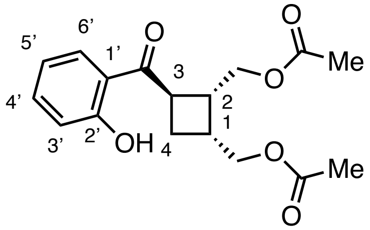
HRMS (ESI): m/z calcd for $C_{20}H_{17}O_4NNa^+$ $[M + Na]^+$ 358.1050 found 358.1053.

SFC Chiralpak® IA 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 81.5:18.5 e.r. (minor enantiomer t_R = 4.56 min; major enantiomer t_R = 6.33 min).

$[\alpha]^{25}_D$ = –81.2 (*c* = 1.0, $CHCl_3$).

m.p.: 144 – 154 °C.

4-5e



The corresponding compound was prepared following general procedure 4-1 using salicylaldehyde and cyclobutene **4-4e** with an increased catalyst loading of $[Rh(cod)OH]_2$ (5.0 mol%) and (*R*,*R*)-MeDuphos (12 mol%). The mixture was stirred at 60 °C for 2 h. ^{1}H NMR analysis of the unpurified reaction mixture showed a diastereomeric ratio of approximately 6:1. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-5e** as a colourless oil (99 mg, 78% yield). SFC analysis showed an enantiomeric excess of 95%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 12.25 (s, 1H; OH), 7.60 (dd, *J* = 8.1, 1.7 Hz, 1H; C(6')–H), 7.46 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H; C(4')–H), 6.99 (dd, *J* = 8.4, 1.2 Hz, 1H; C(3')–H), 6.88 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H; C(5')–H), 4.31 – 4.20 (m, 4H; 2x CH_2O), 3.95 (dtd, *J* = 9.0, 7.8, 1.1 Hz, 1H; C(3)–H), 3.46 – 3.02 (m, 1H; C(2)–H), 2.83 – 2.73 (m, 1H; C(1)–H), 2.44 (dddd, *J* = 11.8, 8.8, 7.9, 0.7 Hz, 1H; C(4)–H), 2.17 (dddd, *J* = 11.9, 9.8, 4.8, 0.9 Hz, 1H; C(4)–H), 2.07 (s, 3H; CH_3), 2.00 (s, 3H; CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 205.5 (C=O), 171.1 (CH_3CO_2), 170.9 (CH_3CO_2), 163.0 (C(2’)), 136.6 (C(4’)), 129.9 (C(6’)), 119.0 (C(5’)), 118.8 (C(3’)), 118.2 (C(1’)), 64.5 (CH_2O), 63.6 (CH_2O), 42.2 (C(3)), 36.6 (C(2)), 32.2 (C(1)), 26.4 (C(4)), 21.0 (CH_3), 20.9 (CH_3).

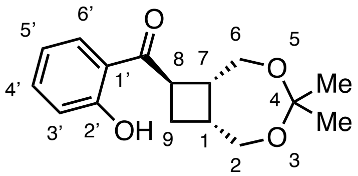
IR ($CHCl_3$ film): 2982 (s), 2971 (s), 2889 (w), 1740 (m), 1635 (m), 1382 (m), 1239 (m), 1035 (w), 957 (w), 758 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{17}H_{20}O_6Na^+$ $[M + Na]^+$ 343.1152 found 343.1153.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 97.5:2.5 e.r. (minor enantiomer t_R = 2.19 min; major enantiomer t_R = 2.42 min).

$[\alpha]^{25}_D$ = –56.6 (*c* = 1.0, $CHCl_3$).

4-5f



The corresponding compound was prepared following general procedure 4-1 using salicylaldehyde and cyclobutene **4-4f**. The mixture was stirred at 60 °C for 2 h. ^{1}H NMR analysis of the unpurified reaction mixture showed a diastereomeric ratio of >20:1. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 80/20) afforded the product **4-5f** as a colourless oil which solidified at –20 °C (98 mg, 89% yield). SFC analysis showed an enantiomeric excess of 97%.

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 12.38 (s, 1H; OH), 7.70 (dd, *J* = 8.0, 1.7 Hz, 1H; C(6')–H), 7.46 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H; C(4')–H), 6.98 (dd, *J* = 8.4, 1.1 Hz, 1H; C(3')–H), 6.91 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H; C(5')–H), 4.30 – 4.22 (m, 1H; C(8)–H), 4.00 – 3.90 (m, 2H; CH$_2$O), 3.81 (dd, *J* = 12.5, 6.1 Hz, 1H; 1x CH$_2$O), 3.55 (dd, *J* = 13.5, 3.0 Hz, 1H; 1x CH$_2$O), 2.81 (tt, *J* = 8.6, 2.9 Hz, 1H; C(7)–H), 2.62 – 2.50 (m, 1H; C(1)–H), 2.41 (ddd, *J* = 11.2, 8.9, 8.1 Hz, 1H; C(9)–H), 1.89 (ddd, *J* = 11.3, 8.6, 2.7 Hz, 1H; C(9)–H), 1.46 (s, 3H; CH$_3$), 1.39 (s, 3H; CH$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 206.6 (C=O), 162.9 (C(2')), 136.4 (C(4')), 130.4 (C(6')), 119.1 (C(5')), 118.8 (C(3')), 118.6 (C(1')), 102.6 (C(4)), 63.4 (CH$_2$O), 61.8 (CH$_2$O), 41.4 (C(8)), 40.8 (C(7)), 34.9 (C(1)), 25.7 (CH$_3$), 25.2 (C(9)), 24.1 (CH$_3$).

IR (CHCl$_3$ film): 2982 (s), 1633 (s), 1612 (m), 1487 (m), 1447 (m), 1382 (m), 1286 (m), 1239 (m), 1214 (s), 1151 (s), 1059 (m), 850 (w), 757 (m) cm^{-1}.

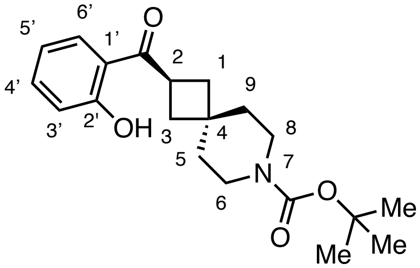
HRMS (ESI): m/z calcd for $C_{16}H_{19}O_4^-$ [M – H]$^-$ 275.1289 found 275.1286.

SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 98.5:1.5 e.r. (minor enantiomer t_R = 3.39 min; major enantiomer t_R = 3.95 min).

$[\alpha]^{25}_D$ = –113.0 (*c* = 1.0, CHCl$_3$).

m.p.: 56 – 58 °C

4-7a



The corresponding compound was prepared following general procedure 4-2 using salicylaldehyde and cyclobutene **4-6**. The mixture was stirred at 60 °C for 20 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-7a** as a colourless oil (116 mg, 84% yield).

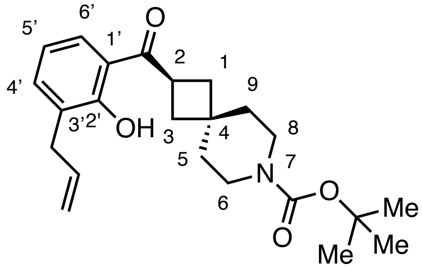
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 12.32 (s, 1H; OH), 7.57 (dd, *J* = 8.0, 1.7 Hz, 1H; C(6')–H), 7.45 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H; C(4')–H), 6.99 (dd, *J* = 8.4, 1.1 Hz, 1H; C(3')–H), 6.87 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H; C(5')–H), 3.97 (tt, *J* = 9.4, 8.1 Hz, 1H; 1x C(2)–H), 3.45 – 3.37 (m, 2H; 1x C(6)–H_2, 1x C(8)–H_2), 3.32 – 3.13 (m, 2H; 1x C(6)–H_2, 1x C(8)–H_2), 2.29 – 2.20 (m, 2H; 1x C(1)–H_2, 1x C(3)–H_2), 2.20 – 2.12 (m, 2H; 1x C(1)–H_2, 1x C(3)–H_2), 1.72 – 1.66 (m, 2H; 1x C(5)–H_2, 1x C(9)–H_2), 1.53 – 1.48 (m, 2H; 1x C(5)–H_2, 1x C(9)–H_2), 1.45 (s, 9H; $C(CH_3)_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 207.3 (C=O), 162.8 (C(2')), 155.0 (NCO_2), 136.3 (C(4')), 129.9 (C(6')), 118.9 (C(5')), 118.7 (C(3')), 118.1 (C(1')), 79.5 ($\mathit{C}(CH_3)_3$), 40.6 (rot. br.; C(2), C(8)), 38.2 (C(5)/C(9)), 36.9 (C(5)/C(9)), 35.8 (C(2)), 34.7 (C(1), C(3)), 34.4 (C(4)), 28.6 ($C(\mathit{C}H_3)_3$).

IR ($CHCl_3$ film): 3008 (w), 2974 (w), 2927 (w), 2848 (w), 1682 (m), 1635 (m), 1485 (w), 1391 (m), 1365 (m), 1273 (m), 1241 (s), 1206 (m), 1174 (m), 1147 (s), 968 (m), 892 (w), 750 (s), 649 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{20}H_{27}O_4NNa^+$ $[M + Na]^+$ 368.1832 found 368.1833.

4-7b



The corresponding compound was prepared following general procedure 4-2 using 3-allylsalicylaldehyde and cyclobutene **4-6**. The mixture was stirred at 60 °C for 20 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-7a** as a pale-yellow oil (124 mg, 81% yield).

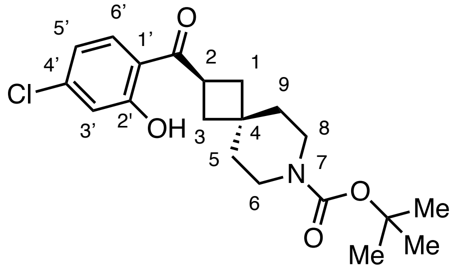
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 12.67 (s, 1H; OH), 7.46 (dd, *J* = 8.1, 1.6 Hz, 1H; C(6')–H), 7.33 (dd, *J* = 7.4, 1.6 Hz, 1H; C(4')–H), 6.81 (t, *J* = 7.7 Hz, 1H; C(5')–H), 6.07 – 5.94 (m, 1H; C*H*=CH$_2$), 5.12 – 5.08 (m, 1H; 1x CH=C*H*$_2$), 5.07 (q, *J* = 1.2 Hz, 1H; 1x CH=C*H*$_2$), 3.97 (app. p, *J* = 8.8 Hz, 1H; C(2)–H), 3.43 (d, *J* = 6.7 Hz, 2H; 1x C(6)–H$_2$, 1x C(8)–H$_2$), 3.45 – 3.36 (m, 2H; 1x C(6)–H$_2$, 1x C(8)–H$_2$), 3.33 – 3.24 (m, 2H; 1x C(1)–H$_2$, 1x C(3)–H$_2$), 2.30 – 2.20 (m, 2H; 1x C(1)–H$_2$, 1x C(3)–H$_2$), 2.20 – 2.11 (m, 2H), 1.68 (t, *J* = 5.7 Hz, 2H; 1x C(5)–H$_2$, 1x C(9)–H$_2$), 1.49 (t, *J* = 5.7 Hz, 2H; 1x C(5)–H$_2$, 1x C(9)–H$_2$), 1.45 (s, 9H; C(CH$_3$)$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 207.5 (C=O), 160.8 (C(2')), 155.0 (NCO$_2$), 136.3, 136.2 (C(4') and CH$_2$*C*H=CH$_2$), 129.7 (C(3')), 128.0 (C(6')), 118.5 (C(5')), 117.7 (C(1')), 116.1 (CH$_2$CH=*C*H$_2$), 79.5 (*C*(CH$_3$)$_3$), 40.6 (rot. br.; C(2), C(8)), 38.2 (C(5)/C(9)), 36.9 (C(5)/C(9)), 35.9 (C(2)), 34.8 (C(1), C(3)), 34.4 (C(4)), 33.6 (*C*H$_2$CH=CH$_2$), 28.6 (C(*C*H$_3$)$_3$).

IR ($CHCl_3$ film): 3007 (w), 2975 (w), 2926 (w), 2847 (w), 1685 (m), 1629 (m), 1426 (m), 1392 (m), 1271 (m), 1242 (m), 1174 (m), 1147 (m), 983 (m), 916 (w), 750 (s), 665 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{23}H_{31}O_4NNa^+$ [M + Na]$^+$ 408.2145 found 408.2143.

4-7c



The corresponding compound was prepared following general procedure 4-2 using 4-chlorosalicylaldehyde and cyclobutene **4-6**. The mixture was stirred at 60 °C for 20 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-7a** as a colourless solid (118 mg, 78% yield).

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 12.45 (s, 1H; OH), 7.49 (d, *J* = 8.6 Hz, 1H; C(6’)–H), 7.00 (d, *J* = 2.0 Hz, 1H; C(3’)–H), 6.84 (dd, *J* = 8.6, 2.1 Hz, 1H; C(5’)–H), 3.91 (tt, *J* = 9.4, 8.1 Hz, 1H; C(2)–H), 3.43 – 3.36 (m, 2H; 1x C(6)–H$_2$, 1x C(8)–H$_2$), 3.33 – 3.25 (m, 2H; 1x C(6)–H$_2$, 1x C(8)–H$_2$), 2.27 – 2.20 (m, 2H; 1x C(1)–H$_2$, 1x C(3)–H$_2$), 2.19 – 2.10 (m, 2H; 1x C(1)–H$_2$, 1x C(3)–H$_2$), 1.70 – 1.65 (m, 2H; 1x C(5)–H$_2$, 1x C(9)–H$_2$), 1.49 (dd, *J* = 6.8, 4.6 Hz, 2H; 1x C(5)–H$_2$, 1x C(9)–H$_2$), 1.45 (s, 9H; C(CH$_3$)$_3$).

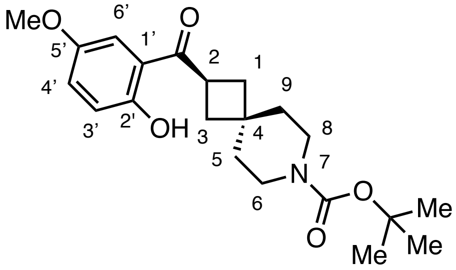
^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 206.5 (C=O), 163.5 (C(2’)), 155.0 (NCO$_2$), 142.0 (C(1’)), 130.9 (C(6’)), 119.6 (C(5’)), 118.8 (C(3’)), 116.7 (C(1’)), 79.6 (*C*(CH$_3$)$_3$), 40.7 (rot. br.; C(6), C(8)), 38.2 (C(5)/C(9)), 36.9 (C(5)/C(9)), 35.8 (C(2)), 34.7 (C(1), C(3)), 34.4 (C(4)), 28.6 (C(*C*H$_3$)$_3$).

IR (CHCl$_3$ film): 2975 (w), 2973 (w), 1684 (m), 1634 (m), 1422 (m), 1364 (m), 1270(m), 1241 (s), 1175 (s), 1145 (s), 1080 (m), 970 (m), 937 (m), 861 (m), 796 (m), 754 (s) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{20}H_{26}O_4N^{35}ClNa^+$ [M + Na]$^+$ 402.1443 found 402.1444.

m.p.: 103 – 104 °C.

4-7d



The corresponding compound was prepared following general procedure 4-2 using 5-methoxysalicylaldehyde and cyclobutene **4-6**. The mixture was stirred at 60 °C for 20 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-7d** as a yellow oil (122 mg, 80% yield).

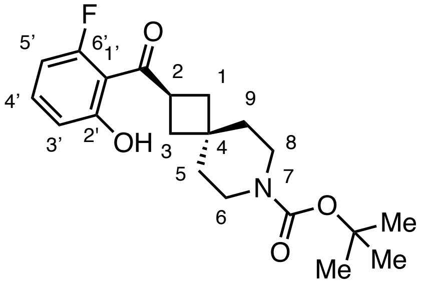
^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 11.89 (s, 1H; OH), 7.09 (dd, *J* = 9.0, 3.1 Hz, 1H; C(4')–H), 7.02 (d, *J* = 3.1 Hz, 1H; C(6')–H), 6.93 (d, *J* = 9.0 Hz, 1H; C(3')–H), 3.92 (tt, *J* = 9.4, 8.0 Hz, 1H; C(2)–H), 3.78 (s, 3H; OCH$_3$), 3.42 – 3.37 (m, 2H; 1x C(6)–H$_2$, 1x C(8)–H$_2$), 3.33 – 3.26 (m, 2H; 1x C(6)–H$_2$, 1x C(8)–H$_2$), 2.30 – 2.21 (m, 2H; 1x C(1)–H$_2$, 1x C(3)–H$_2$), 2.20 – 2.12 (m, 2H; 1x C(1)–H$_2$, 1x C(3)–H$_2$), 1.70 – 1.65 (m, 2H; 1x C(5)–H$_2$, 1x C(9)–H$_2$), 1.49 (dd, *J* = 6.7, 4.7 Hz, 2H; 1x C(5)–H$_2$, 1x C(9)–H$_2$), 1.45 (s, 9H; C(CH$_3$)$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 206.8 (C=O), 157.2 (C(2')), 155.0 (NCO$_2$), 151.8 (C(5')), 123.6 (C(4')), 119.5 (C(3')), 117.7 (C(1')), 113.3 (C(6')), 79.5 (*C*(CH$_3$)$_3$), 56.2 (OCH$_3$), 40.5 (rot. br.; C(2), C(8)), 38.2 (C(5)/C(9)), 36.9 (C(5)/C(9)), 35.9 (C(2)), 34.7 (C(1), C(3)), 34.4 (C(4)), 28.6 (C(*C*H$_3$)$_3$).

IR (CHCl$_3$ film): 2926 (w), 2846 (w), 1687 (m), 1641 (w), 1614 (w), 1485 (m), 1392 (m), 1364 (m), 1243 (s), 1174 (s), 1146 (s), 1119 (s), 970 (m), 772 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{29}O_5NNa^+$ [M + Na]$^+$ 398.1938 found 398.1938.

4-7e



The corresponding compound was prepared following general procedure 4-2 using 6-fluorosalicylaldehyde and cyclobutene **4-6** with an increased catalyst loading of [Rh(cod)OH]$_2$ (5.0 mol%) and dppf (12 mol%). The mixture was stirred at 60 °C for 20 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-7e** as a colourless solid (84 mg, 58% yield).

^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 12.81 (s, 1H; OH), 7.37 (td, *J* = 8.3, 6.4 Hz, 1H; C(4')–H), 6.78 (dt, *J* = 8.4, 1.0 Hz, 1H; C(3')–H), 6.57 (ddd, *J* = 11.7, 8.2, 1.1 Hz, 1H; C(5')–H), 3.90 (ttd, *J* = 9.3, 7.9, 3.4 Hz, 1H; C(2)–H), 3.40 – 3.35 (m, 2H; 1x C(6)–H$_2$, 1x C(8)–H$_2$), 3.32 – 3.25 (m, 2H; 1x C(6)–H$_2$, 1x C(8)–H$_2$), 2.26 – 2.10 (m, 4H; C(1)–H$_2$, C(3)–H$_2$), 1.68 – 1.62 (m, 2H; 1x C(5)–H$_2$, 1x C(9)–H$_2$), 1.51 – 1.46 (m, 2H; 1x C(5)–H$_2$, 1x C(9)–H$_2$), 1.45 (s, 9H; C(CH$_3$)$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ (ppm) 206.11 (d, *J* = 4.3 Hz; C=O), 164.4 (d, *J* = 5.2 Hz; C(2'))), 163.01 (d, *J* = 256.0 Hz; C(6')), 155.1 (NCO$_2$), 136.1 (d, *J* = 13.1 Hz; C(4')), 114.5 (d, *J* = 3.2 Hz; C(3')), 108.8 (d, *J* = 14.7 Hz; C(1')), 106.2 (d, *J* = 24.6 Hz; C(5')), 79.5 (*C*(CH$_3$)$_3$), 40.4 (d, *J* = 11.1 Hz; C(2)), 38.2 (C(5)/C(9)), 37.0 (C(5)/C(9)), 34.0 (d, *J* = 4.0 Hz; C(1), C(3)), 33.8 (C(4)), 28.6 (C(*C*H$_3$)$_3$)

^{19}F NMR (CDCl$_3$, 377 MHz): δ (ppm) -107.13 (br. s; C–F).

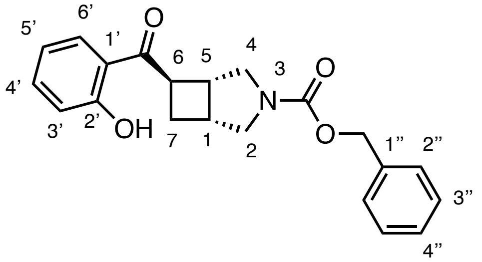
IR (CHCl$_3$ film): 2978 (w), 2927 (w), 2848 (w), 1689 (s), 1638 (s), 1615 (m), 1451 (s), 1421 (s), 1364 (s), 1242 (s), 1222 (s), 1200 (s), 1174 (s), 1146 (s), 1121 (m), 1027 (s), 965 (m), 796 (s), 744 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{20}H_{26}O_4FNNa^+$ $[M + Na]^+$ 386.1738 found 386.1737.

m.p.: 65 – 67 °C.

5.4.3. Upscale and Derivatisation of Acyl Cyclobutanes

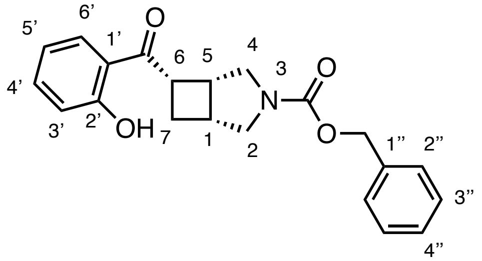
Gram-scale synthesis of 4-3a



The corresponding compound was prepared in direct analogy to general procedure 4-1 using salicylaldehyde (4.0 mmol) and cyclobutene **4-2** (4.8 mmol). The mixture was stirred at 60 °C for 1 h. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-3a** as a colourless solid (1.18 g, 84% yield). SFC analysis showed an enantiomeric excess of 98%.

Along with **4-3a**, unreacted cyclobutene **4-2** (156 mg, 0.68 mmol) was recovered and the minor diastereoisomer **4-3a’** (158 mg, 11%) was isolated as a colourless oil. SFC analysis of **4-3a’** showed an enantiomeric ratio of 99:1. The absolute stereochemistry of **4-3a’** was not assigned.

For analytical data of ***4-3a’****:*



^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm) 12.45 – 12.07 (m, 1H; OH), 7.56 (dd, *J* = 8.1, 1.7 Hz, 1H; C(6’)–H), 7.45 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H; C(4)–H), 7.37 – 7.28 (m, 5H; 2x C(2’’)–H, 2x C(3’’)–H, C(4’’)–H), 7.00 (dd, *J* = 8.4, 1.2 Hz, 1H; C(3’)–H), 6.87 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H; C(5’)–H), 5.12 (rot. s, 2H; CH$_2$Ph), 4.07 (q, *J* = 8.7 Hz, 1H; C(6)–H), 3.73 – 3.55 (m, 1H; 1x CH$_2$N), 3.53 – 3.41 (m, 2H; 1x CH$_2$N, C(5)–H), 3.35 – 3.16 (m, 3H; 2x CH$_2$N), 3.04 (p, *J* = 7.4 Hz, 1H; C(1)–H), 2.55 (dt, *J* = 12.7, 8.1 Hz, 1H; C(7)–H), 2.41 – 2.19 (m, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 204.7 (C=O), 162.8 (C(2')), 155.0 (CO_2N), 137.0 (C(1'')), 136.4 (C(4')), 129.6 (C(6')), 128.5 (2x C(4'')), 128.0 (C(4'')), 127.9 (2x C(2'')), 119.1 (C(5')), 119.0 (C(3')), 118.6 (C(1')), 66.9 (CH_2Ph), 51.9, 51.7 (rot.; 2x CH_2N), 47.8, 47.1 (rot.; 2x CH_2N), 44.0, 43.1 (rot.; 2x C(5)), 41.1, 40.8 (rot.; 2x C(6)), 35.4, 34.5 (rot.; 2x C(1)), 24.9, 24.6 (rot.; 2x C(7)).

IR ($CHCl_3$ film): 2972 (w), 2874 (w), 1699 (s), 1633 (m), 1486 (w), 1446 (m), 1418 (m), 1361 (m), 1277 (m), 1240 (m), 1212 (m), 758 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{22}O_4N^+$ $[M + H]^+$ 352.1543 found 352.1540.

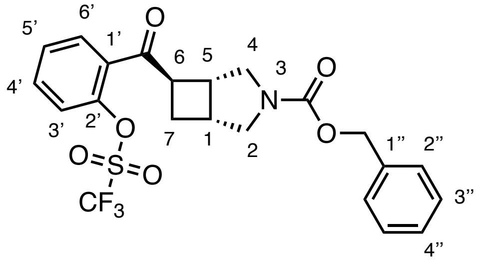
SFC Chiralpak® IF 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min, then from

30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min; 99:1 e.r. (minor enantiomer t_R = 5.97 min; major enantiomer t_R = 6.19 min).

$[\alpha]^{25}_D$ = –140.2 (*c* = 1.0, $CHCl_3$).

m.p.: 89 – 91 °C.

4-8a



Triethylamine (280 µL, 2.0 mmol), *N*-(2-pyridyl)bis(trifluoromethanesulfonimide) (537 mg, 1.50 mmol) followed by 4-dimethylaminopyridine (12.2 mg, 100 µmol) were added to a solution of **4-3a** (351 mg, 1.00 mmol) in CH_2Cl_2 (5.0 mL) under an argon atmosphere at room temperature (23 °C). After stirring the mixture for 22 h, additional triethylamine (70 µL, 0.50 mmol), *N*-(2-

pyridyl)bis(trifluoromethanesulfonimide) (178 mg, 0.50 mmol) were added, and stirring was continued for 1 h. The solvents were removed under reduced pressure. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 60/40) afforded the product **4-8a** as a pale-yellow oil (445 mg, 92% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.65 – 7.56 (m, 2H; C(4')–H, C(6')–H), 7.46 (app. td, *J* = 7.6, 1.2 Hz, 1H; C(5')–H), 7.42 – 7.29 (m, 6H; 2x C(2'')–H, 2x C(3'')–H, C(4'')–H, C(3')–H), 5.19 (s, 2H; CH_2Ph), 3.75 (rot. s, 2H; 2x CH_2N), 3.62 (s, 1H; C(6)–H), 3.47 – 3.25 (m, 3H; 2x CH_2N, C(5)–H), 2.91 (s, 1H; C(1)–H), 2.56 (br. s, 1H; C(7)–H), 2.03 (br. s, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 199.2 (C=O), 155.7 (CO_2N), 147.3 (C(2')), 136.9 (C(1'')), 133.9 (C(4')), 130.6 (C(2')), 130.3 (C(6')), 128.7 (C(5')), 128.6 (2x C(3'')), 128.14 (C(4'')), 128.05 (2x C(2'')), 123.2 (C(3')) 118.8 (q, *J* = 320.3 Hz; CF_3), 67.1 (CH_2Ph), 53.0 , 52.4 (rot.; 2x CH_2N), 46.5 (C(6)), 40.2 (rot.; C(5)), 34.6, 33.6 (rot.; 2x C(1)), 28.5, 28.0 (rot.; 2x C(7)).

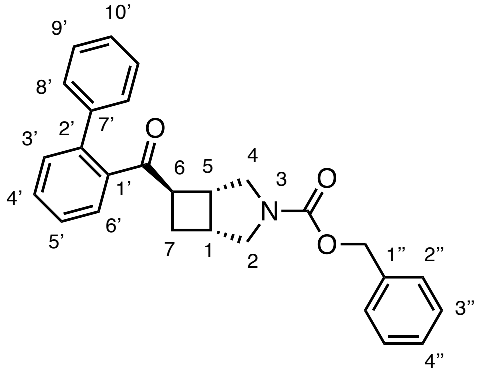
^{19}F NMR ($CDCl_3$, 377 MHz): δ (ppm) -73.34 (s; CF_3).

IR ($CHCl_3$ film): 2944 (w), 1694 (s). 1605 (w), 1423 (s), 1359 (m), 1211 (s), 1139 (m), 1113 (m) 903 (m), 769 (w), 698 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{22}H_{21}O_6NF_3S^+$ $[M + H]^+$ 484.1036 found 484.1036.

$[\alpha]^{25}_D$ = –58.2 (*c* = 1.0, $CHCl_3$).

4-8b



K_2CO_3 (34.6 mg, 250 μmol) and [Pd(PPh_3)$_4$] (5.8 mg, 5.0 μmol) were added to a solution of **4-8a** (48.4 mg, 100 μmol) and phenylboronic acid (24.4 mg, 200 μmol) in toluene (1.0 mL) under an argon atmosphere. The mixture was stirred for 16 h at 110 °C. The mixture was then filtered over a short plug of silica, rinsed with EtOAc, and the solvents were removed under reduced pressure. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-8b** as a colourless oil (28 mg, 67% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.51 (app. td, *J* = 7.3, 1.7 Hz, 1H; 1x C_{Ar}–H), 7.47 – 7.19 (m, 13H; 13x C_{Ar}–H), 5.10 (s, 2H; CH_2Ph), 3.46 (rot. s, 1H; 1x CH_2N), 3.22 (dd, *J* = 11.7, 7.5 Hz, 1H; 1x CH_2N), 3.08 – 2.63 (br. rot. m, 5H; 2x CH_2N, C(1)–H , C(5)–H, C(6)–H), 2.25 (dt, *J* = 12.3, 8.4 Hz, 1H; C(7)–H), 1.54 (br. s, 1H; C(7)–H).

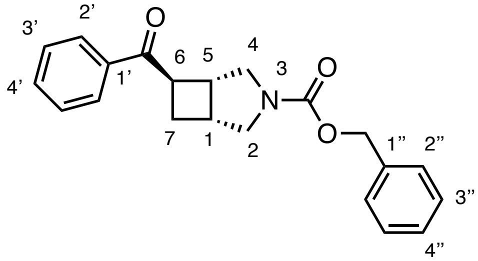
^{13}C NMR ($CDCl_3$, 101 MHz; C=O not detected): δ (ppm) 155.3 (CO_2N), 140.5 (C_{quart}), 140.1 (C_{quart}), 137.0 (C(1’’)), 130.8, 130.3, 128.9, 128.9, 128.6, 128.10, 128.08, 128.0, 127.9, 127.6 (14x C_{Ar}–H, C_{quart}), 66.8 (CH_2Ph), 52.7, 51.7 (rot.; 2x CH_2N), 48.0 (C(6)), 41.3, 40.8 (rot.; 2x C(5)), 33.3 (rot.; C(1)), 28.9, 28.7 (rot.; 2x C(7)).

IR ($CHCl_3$ film): 2971 (w), 2869 (w), 1702 (w), 1416 (m), 1358 (m), 1229 (m), 1211 (m) 1158 (w), 1098 (m), 954 (w), 746 (m), 699 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{27}H_{26}O_3N^+$ $[M + H]^+$ 412.1907 found 412.1913.

$[\alpha]^{25}_D$ = –40.6 (*c* = 1.0, $CHCl_3$).

4-8c



Acetonitrile (1.0 mL) was added to mixture of **4-8a** (48.4 mg, 100 µmol), K_2CO_3 (13.8 mg, 100 µmol), $(CH_3)_2NH·BH_3$ (6.5 mg, 110 µmol) and $[Pd(PPh_3)_4]$ (5.8 mg, 5.0 µmol) under an argon atmosphere. The mixture was stirred at 40 °C for 6 h, then filtered over a short plug of silica, rinsed with EtOAc, and the solvents were removed under reduced pressure. Purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-8c** as a pale-yellow oil (22 mg, 67% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.90 – 7.78 (m, 2H; 2x C(2')–H), 7.58 – 7.51 (m, 1H; C(4')–H), 7.48 – 7.28 (m, 7H; 2x C(2'')–H, 2x C(3'')–H, C(4'')–H, 2x C(3')–H), 5.21 (s, 2H; CH_2Ph), 4.04 – 3.61 (m, 3H; 2x CH_2N, C(6)–H), 3.45 – 3.22 (m, 3H; 2x CH_2N, C(5)–H), 2.96 – 2.83 (m, 1H; C(1)–H), 2.54 (br. s, 1H; C(7)–H), 2.07 (br. s, 1H; C(7)–H).

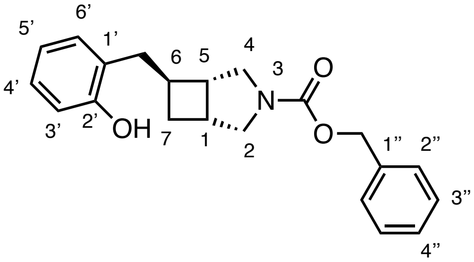
^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 199.9 (C=O), 155.7 (CO_2N), 137.0 (C(1'')), 135.3 (C(1')), 133.3 (C(4')), 128.8 (2x C(3')), 128.6 (2x C(3'')), 128.4 (2x C(2')), 128.1 (C(4'')), 128.0 (2x C(2'')), 67.1 (CH_2Ph), 52.9, 52.3 (rot.; 2x CH_2N), 44.5 (C(6)), 39.8 (rot.; C(5)), 34.7, 34.0 (rot.; 2x C(1)), 28.9, 28.4 (rot.; 2x C(7)).

IR ($CHCl_3$ film): 2970 (w), 2870 (w), 1701 (s), 1678 (s), 1148 (w), 1416 (m), 1359 (m), 1217 (m), 1098 (m), 769 (w), 696 (m) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{24}O_3N^+$ $[M + H]^+$ 338.1751 found 338.1746.

$[\alpha]^{25}_D$ = –91.4 (*c* = 1.0, $CHCl_3$).

4-8d



Trifluoroacetic acid (310 µL, 4.0 mmol) was added to **4-3a** (70 mg, 0.20 mmol) at 0 °C under an argon atmosphere. Et_3SiH (130 µL, 0.80 mmol) was then added dropwise. The mixture was then allowed to reach room temperature (23 °C) and stirring was maintained for 5 h. The solvent was removed under reduced pressure, and purification by automated medium-pressure chromatography (hexane/EtOAc = 100/0 to 70/30) afforded the product **4-8d** as a colourless oil (44 mg, 65% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.43 – 7.28 (m, 5H; 2x C(2'')–H, 2x C(3'')–H, C(4'')–H), 7.10 – 6.98 (m, 2H; C(4')–H, C(6')–H), 6.82 (td, *J* = 7.4, 1.2 Hz, 1H; C(5')–H), 6.77 (dd, *J* = 7.8, 1.2 Hz, 1H; C(3')–H), 6.12 (br. s, 1H; OH), 5.18 (s, 2H; CH_2Ph), 3.68 – 3.51 (m, 2H; 2x CH_2N), 3.42 (dd, *J* = 11.6, 7.7 Hz, 1H; 1x CH_2N), 3.25 (dd, *J* = 11.5, 6.8 Hz, 1H; 1x CH_2N), 2.87 (qt, *J* = 8.8, 3.5 Hz, 1H, C(5)–H), 2.81 – 2.71 (m, 2H; C(6)HCH_2Ar), 2.66 (q, *J* = 6.6 Hz, 1H, C(5)–H), 2.42 (q, *J* = 7.2 Hz, 1H; C(1)–H), 2.00 – 1.90 (m, 1H; C(7)–H), 1.84 (ddd, *J* = 12.3, 8.7, 4.0 Hz, 1H; C(7)–H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (ppm) 155.8 (CO_2N), 154.2 (C(2')), 137.0 (C(1'')), 130.4 (C(6')), 128.6 (2x C(3'')), 128.0 (C(4'')), 127.9 (2x C(2'')), 127.3 (C(4')), 126.6 (C(1'')), 120.3 (C(5')), 115.3 (C(3')), 67.0 (CH_2Ph), 53.1, 52.7 (rot.; 2x CH_2N), 43.9, 43.1 (rot.:; 2x C(5)), 38.0 (C(1)), 36.2 (C(6)H*C*H_2Ar), 34.5, 33.8 (rot.: 2x C(6)), 30.8 (C(7)).

IR ($CHCl_3$ film): 3306 (br. w), 2959 (w), 1673 (s), 1594 (w), 1455 (s), 1428 m), 1360 (m), 1240 (m), 1154 (w), 1107 (m), 753 (m), 697 (w) cm^{-1}.

HRMS (ESI): m/z calcd for $C_{21}H_{22}O_3N^+$ $[M + H]^+$ 336.1594 found 336.1594.

$[\alpha]^{25}_D$ = –23.9 (*c* = 1.0, $CHCl_3$).

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