Enantioselective Synthesis of Chiral Building Blocks with Non-stabilized Nucleophiles



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Declaration

This thesis describes work carried out in the Chemistry Research Laboratory, University of Oxford, between November 2013 and January 2017 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.

Philipp Schäfer

Abstract

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Wolfson College D.Phil. Thesis

This thesis describes the combination of non-stabilized nucleophiles and prochiral/racemic electrophiles in transition metal catalyzed asymmetric transformations. These enantioselective reactions have tremendous potential for the formation of chiral building blocks and new structural motifs that can be found in a variety of natural products and their derivatives.

The first part of the thesis focuses on the synthetic approach towards anti-cancer active diterpenoid structures. The two key steps involve a Cu-catalyzed asymmetric conjugate addition of alkylzirconocenes to enones and an intramolecular oxidative cyclisation. Particular investigations into the cyclisation are made with organocatalysis, transition metal catalysis and electrochemistry for the formation of these tricyclic scaffolds.

In the second part this work builds on the Rh-catalyzed asymmetric Suzuki–Miyaura coupling of benzeneboronic acids and cyclic allyl chlorides, which has been developed in our group. Here, the main point is to use more challenging coupling partners, such as heteroaromatic boronic acids, which are coupled to racemic cyclic allyl halides. The utility of this method is demonstrated by performing further transformations and an asymmetric synthesis of the natural product (+)-isoanabasine.

The last chapter describes the development of a new asymmetric Hiyama coupling of arylsiloxanes with racemic cyclic allyl chloride. Attempts are made to generate substrates that are not accessible via the asymmetric Suzuki–Miyaura reaction. After extensive optimisation a variety of arylsiloxanes is generated and tested with the best conditions to prove its utility in comparison to the asymmetric Suzuki–Miyaura coupling.

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Abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
A	Ampere
Å	Ångstrom
AAA	Asymmetric allylic alkylation
ACA	Asymmetric conjugate addition
acac	Acetylacetonate
Ac	Acetyl
anti	*ἀντί* (Greek) opposite
aq	Aqueous
Ar	Any aryl
Ar–C	Aryl carbon
Ar–H	Aryl hydrogen
ATR	Attenuated total reflection
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	Broadened (NMR)
Bu	Butyl
c	Concentration
C	Celsius
CALB	*Candida antarctica* lipase B
calc	Calculated
CAN	Cerium ammonium nitrate
CDDO	2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid
Cl-MeO-BIPHEP	(5,5′-Dichloro-6,6′-dimethoxy-1,1′-biphenyl)-2,2′-diyl-bis(diphenyl-phosphine)
cod	1,5-Cyclooctadiene
coe	Cyclooctene
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
CV	Cyclic voltammetry
d	Doublet (NMR)
D	Dexter
DCC	*N,N*′-Dicyclohexylcarbodiimide

DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless enhancement by polarization transfer spectroscopy
DET	Direct enantioconvergent transformation
DIBAL	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine, Hünig's base
DKR	Dynamic kinetic resolution
DMAP	4-Dimethylamino pyridine
DME	1,2-Dimethoxyethane
DMEDA	1,2-Dimethylethylenediamine
DMF	*N*,*N*-Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOSY	Diffusion-ordered spectroscopy
d.r.	Diastereomeric ratio
DTBM-SEGPHOS	5,5′-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
DYKAT	Dynamic kinetic asymmetric transformation
E	Electrochemical potential, or entgegen (stereochemistry)
ee	Enantiomeric excess
EI	Electron impact ionisation
e.g.	*Exempli gratia* (Latin) for example
e.r.	Enantiomeric ratio
Et	Ethyl
eq, equiv	Equivalents
ESI	Electron impact ionisation
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
et al.	*Et alia* (Latin) and others
etc.	*Et cetera* (Latin) and other things
EXSY	Exchange spectroscopy
FI	Field ionisation (HRMS)
FT	Fourier transformation
g	Gram

GC	Gas chromatography
GGPP	Geranylgeranyl pyrophosphate
Grubbs I	Grubbs' first generation catalyst
Het	Any heteroaryl group
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMDS	Bis(trimethylsilyl)amide
HMTS	Hexamethylenetetramine
HOMSi	(2-(Hydroxymethyl)phenyl)dimethylsilane
HSQC	heteronuclear single quantum correlation
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
i	Iso
I	Electrical current
i.e.	*Id est* (Latin) that is
IPA	Isopropyl alcohol
IR	Infrared
J	coupling constant (NMR)
k	Reaction rate coefficent
l	large (IR)
L	Litre
LAH	Lithium aluminum hydride
LG	Leaving group
LRMS	Low resolution mass spectrometry
m	Milli, meter or medium (IR)
m	meta
M	Molar
M	Mega
m/z	mass-to-charge ratio
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeO-MOP	2-(Diphenylphosphino)-2′-methoxy-1,1′-binaphthyl
MeOH	Methanol
MIDA	6-Methyl-1,3,6,2-dioxazaborocane-4,8-dione
MOPF	Monophosphine ferrocene
mp	Melting point

MS	Molecular sieves
MTBE	Methyl *tert*-butyl ether
n	Generic integer
NBS	*N*-Bromosuccinimide
NCME	*N*-Acetyl colchinol-*O*-methyl ether
NCS	*N*-Chlorosuccinimide
NHE	Standard hydrogen electrode
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
NQ	Naphthoquinone
Nu	Nucleophile
o	Ortho
o.n.	Overnight
P	Product
p	Para
Pa	Pascal
Ph	Phenyl
pH	Potential of hydrogen
Ph-BPE	1,2-Bis(2,5-diphenylphospholano)ethane
phen	1,10-Phenanthroline
pin	Pinacol
Piv	Pivaloyl
pK_a	Logarithmic acid dissociation constant
ppm	Parts per million
Pr	Propyl
q	Quartet (NMR)
QuinoxP	2,3-Bis(tert-butylmethylphosphino)quinoxaline
QPHOS	1,2,3,4,5-Pentaphenyl-1′-(di-tert-butylphosphino)ferrocene
R	Any group
R	Rectus
r.t.	Room temperature
s	Singlet (NMR), or short (IR)
S	Sinister
sat.	Saturated
SM	Starting material
S_N2	Bimolecular nucleophilic substitution

S_N2'	Bimolecular nucleophilic substitution with allylic rearrangement
SOMO	Singly occupied molecular orbital
sp^2	Orbital hybridisation: 33% s and 67% p character
sp^3	Orbital hybridisation: 25% s and 75% p character
SPHOS	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
t	Triplet (NMR)
t	Tert
T	Temperature
TASF	Tris(diethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBAT	Tetra-*n*-butylammonium triphenyldifluorosilicate
TBE-31	A specific acetylenic tricyclic bis(cyano enone)
TBS	*tert*-Butyldimethylsilyl
TC	Thiophene-2-carboxylate
TCA	Trichloroacetic acid
TeSADH	*Thermoanaerobacter ethanolicus* secondary alcohol dehydrogenase
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMG	1,1,3,3-Tetramethylguanidine
TMS	Trimethylsilyl
TLC	Thin layer chromatography
t_R	Retention time
Ts	Toluenesulfonyl
UHP	Urea hydrogen peroxide
UV	Ultraviolet
V	Volt
Vis	Visible
W	Watt
w/w	Mass fraction
Xyl-P-PHOS	2,2′,6,6′-Tetramethoxy-4,4′-bis(di(3,5-xylyl)phosphino)-3,3′-bipyridine
Z	Zusammen
δ	Chemical shift (NMR)
λ	Wavelength (HPLC)
ν	Wavenumber (IR)

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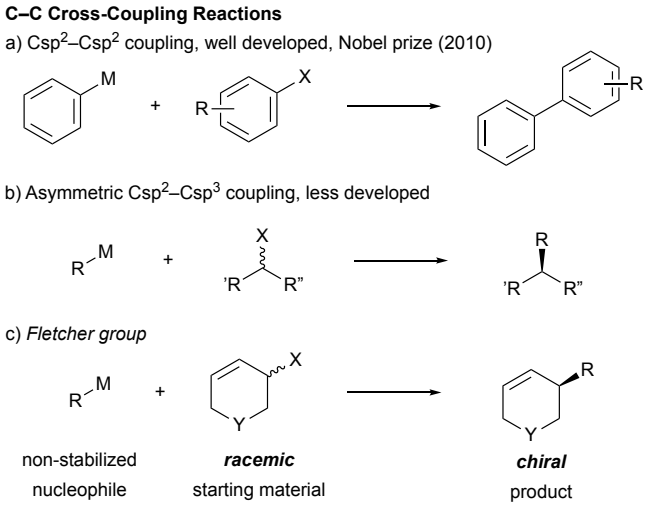
1 Non-stabilized Nucleophiles in Asymmetric Catalysis – An Introduction

This chapter is part of a published Feature Article in *Chem. Commun.*[1]

Transition-metal catalyzed cross-coupling reactions are some of the most important methods ever developed, with Suzuki–Miyaura coupling being arguably the most strategically important transformation used in industry.[2] The discovery and development of these transformations resulted in the 2010 Nobel prize being awarded to Suzuki, Heck and Negishi (Scheme 1.1a).[3,4] Transition metal complexes reliably form Csp^2–Csp^2 bonds by coupling aryl and alkenyl (pseudo)halides (X = Cl, Br, I, OTf, etc.) with unsaturated organometallic species (M = B, Si, Zn, Zr, Sn) and have been extensively developed to be highly tolerant of functional groups.

Efforts to develop asymmetric Csp^2–Csp^3 or Csp^3–Csp^3 cross-couplings have not yet yielded general solutions useful for complex molecule synthesis (Scheme 1.1b).[2,5] The preparation of enantiomerically pure molecules still often relies on chiral pool strategies, but asymmetric reactions to prochiral substrates have also been widely developed.[6] Methods involving racemic starting materials which undergo dynamic processes to give single enantiomer products are highly desirable as racemic substrates are far more abundant than *meso* or prochiral compounds.[7,8]

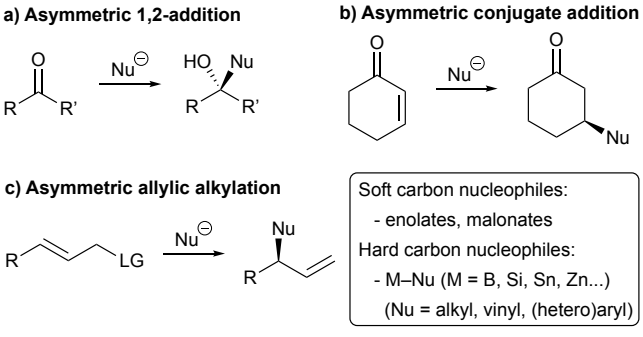
This introduction discusses recent advances in asymmetric C–C bond formation using metal catalyzed dynamic asymmetric transformations which convert racemic starting materials into highly enantioenriched products.



Scheme 1.1 Cross-coupling reactions and enantioselective approaches.

1.1 Use of Prochiral Electrophiles

Prior to catalytic asymmetric methods, chiral auxiliaries and stoichiometric reagents were often used to control absolute stereochemistry.[9] The development of asymmetric 1,2- (Scheme 1.2a) and 1,4-additions (Scheme 1.2b) to prochiral substrates represented major achievements for the field.[9] Another powerful method to form C–C bonds (Scheme 1.2c) is asymmetric allylic alkylation (AAA).[10–14] AAAs to prochiral allylic substrates are important processes as addition to the internal carbon atom provided chiral products featuring an alkene for further elaboration, but regio- as well as stereoselectivity is often difficult to control.



Scheme 1.2 Asymmetric additions to prochiral substrates.

1.2 Asymmetric Allylic Alkylation (AAA)

1.2.1 AAA with Stabilized Nucleophiles

Highly enantioselective AAA methods with racemic starting materials have been extensively developed using palladium catalysts and stabilized nucleophiles.[10,14–17] It is generally understood that both enantiomers of the substrate react with the palladium catalyst to form a common pseudo-prochiral π-allyl intermediate and the product is formed during stereoselective attack of the nucleophile.[18,19]

Stabilized or soft nucleophiles are generally defined as having a pK_a of < 25, and include carbonyl derivatives (for example malonates) as well as many heteroatom nucleophiles. With these nucleophiles the key bond-breaking and -forming events normally occur outside the coordination sphere of the metal (Fig. 1.1, left), and enantioselectivity is obtained by controlled attack of the nucleophile at allylic carbons of the π-metal complex.

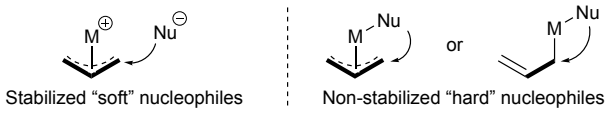
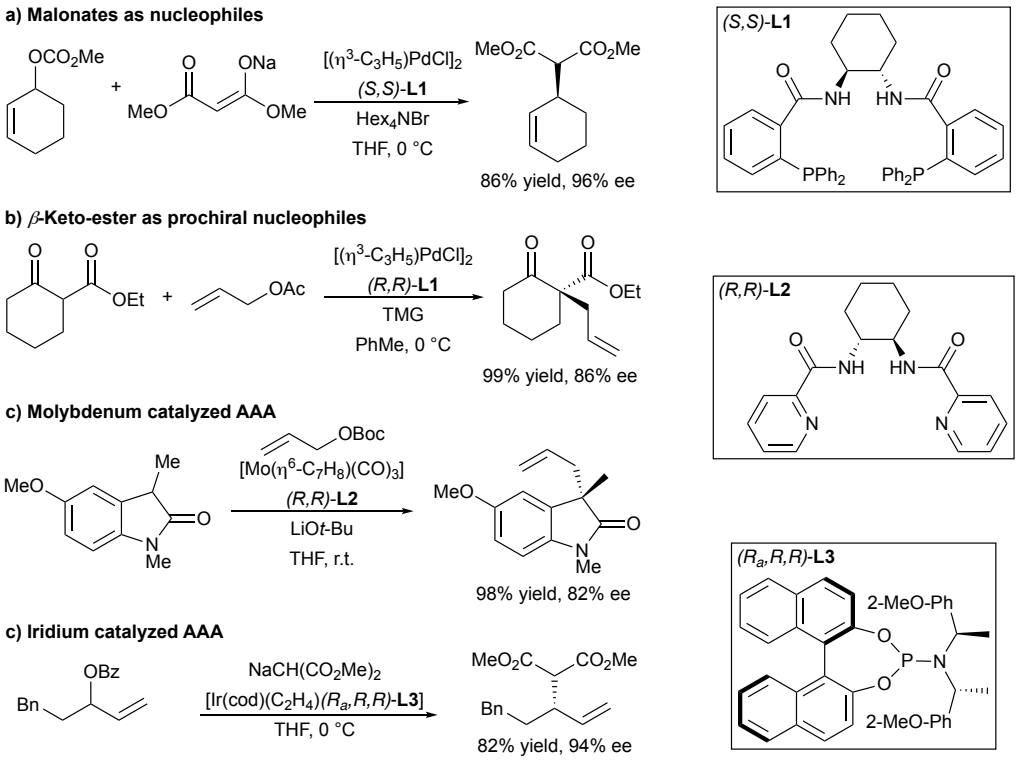


Figure 1.1 Mechanistic pathways of stabilized and non-stabilized nucleophiles.

A wide variety of stabilized nucleophiles have been employed in these processes (Scheme 1.3a).[20] As well as using racemic electrophiles, racemic nucleophiles can undergo resolutions in which one enantiomer reacts faster than the other, for example with β-ketoesters where the catalyst differentiates between two faces of the prochiral enolate (Scheme 1.3b).[21] As well as Pd, other transition metals such as molybdenum[22,23] and iridium[24–26] have seen extensive investigations in AAAs (Scheme 1.3c,d).

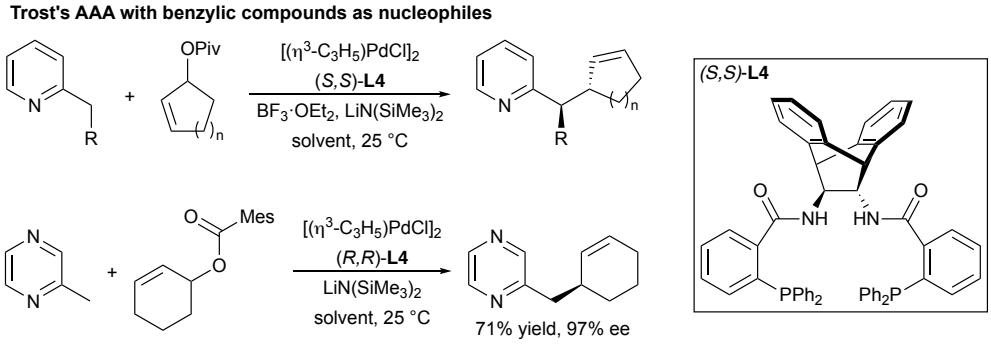


Scheme 1.3 Asymmetric allylic alkylations using soft nucleophiles.

1.2.2 AAA with Non-stabilized Nucleophiles

Non-stabilized nucleophiles ($pK_a > 25$), a huge category of structures including most alkyl, benzylic and (hetero)aromatic groups, undergo Pd-catalyzed Tsuji-Trost type allylic chemistry using different mechanistic pathways. These more reactive coupling partners generally attack at the metal centre (Fig. 1.1, right), and then the product is formed by a reductive elimination type process.

While AAA procedures with stabilized nucleophiles and racemic substrates are well established, the use of non-stabilized nucleophiles in these enantioselective reactions is far less developed but not unknown. For example, Trost and co-workers developed highly enantioselective Pd-catalyzed procedures using less-stabilized nucleophiles such as benzylic pyridines[27,28] and other nitrogen rich heterocycles[29] (Scheme 1.4).

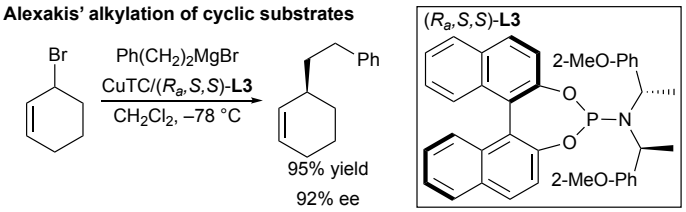


Scheme 1.4 Pd-catalyzed AAA of benzylic nitrogen-rich heterocycles.

1.2.3 Cu-catalyzed AAAs with Grignard reagents

The use of alkyl nucleophiles in asymmetric catalysis often relies on Cu-catalysis.[30,31] It is generally accepted that Cu-catalyzed AAAs occur via regiospecific *anti*-addition where an S_N2' oxidative addition is the rate-determining step. In contrast with Pd-catalysis, Cu-allyl intermediates lack an efficient σ- to π-isomerization, so if the reductive elimination is fast, racemic starting materials are expected to lead to racemic products.[32]

Alexakis and co-workers used Grignard reagents in a copper-catalyzed AAA with a racemic allyl bromide (Scheme 1.5).[33] However, the authors found the reaction scope to be limited, and further investigations showed that the reaction involved a direct enantioconvergent process whereby each enantiomer of the starting material followed a different mechanistic pathway to the same enantiomer of the product.[34]



Scheme 1.5 Cu-catalyzed AAA of Grignard reagents.

1.2.4 Cu-catalyzed AAA with Alkylzirconium Reagents

In 2015, our group developed new highly enantioselective conjugate addition reactions with alkylzirconium reagents.[35–38] *In situ* hydrozirconated alkenes can also be used in AAAs to racemic cyclic allylic halides[39] using the combination of CuI and phosphoramidite ligand **L5**[40] (Fig. 1.2).

The scope of the nucleophile ranges from gaseous, short-chained alkenes to more complex alkenes bearing stereogenic centers. A variety of functional groups are tolerated including protected alcohols, silanes and halides and the method can easily be scaled to grams of product (Scheme 1.6a). Good results were obtained with five-membered ring allyl chlorides, which is noteworthy considering that five-membered electrophiles are challenging substrates in asymmetric transformations because their transition states are relatively flat in comparison to six-membered ring systems. Alkylation products can be converted to more complex structures (Scheme 1.6b) and were used to make cyclopentene-containing antituberculosis and antileprosy agents hydnocarpic acid, chaulmoogric acid and anthelminthicin C (Scheme 1.6c). In a follow-up study we investigated the use of oxygen containing electrophiles. 3,6-Dihydro-2*H*-pyranyl chloride undergoes asymmetric alkylation albeit with low yields despite extensive screening.[41]

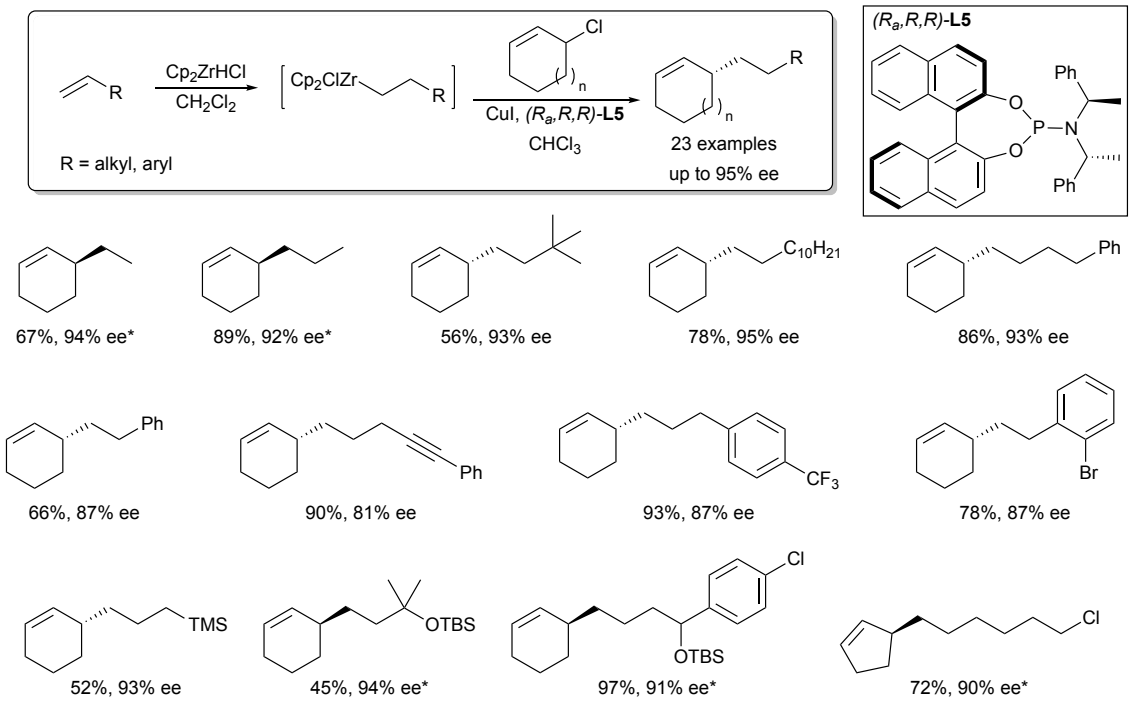
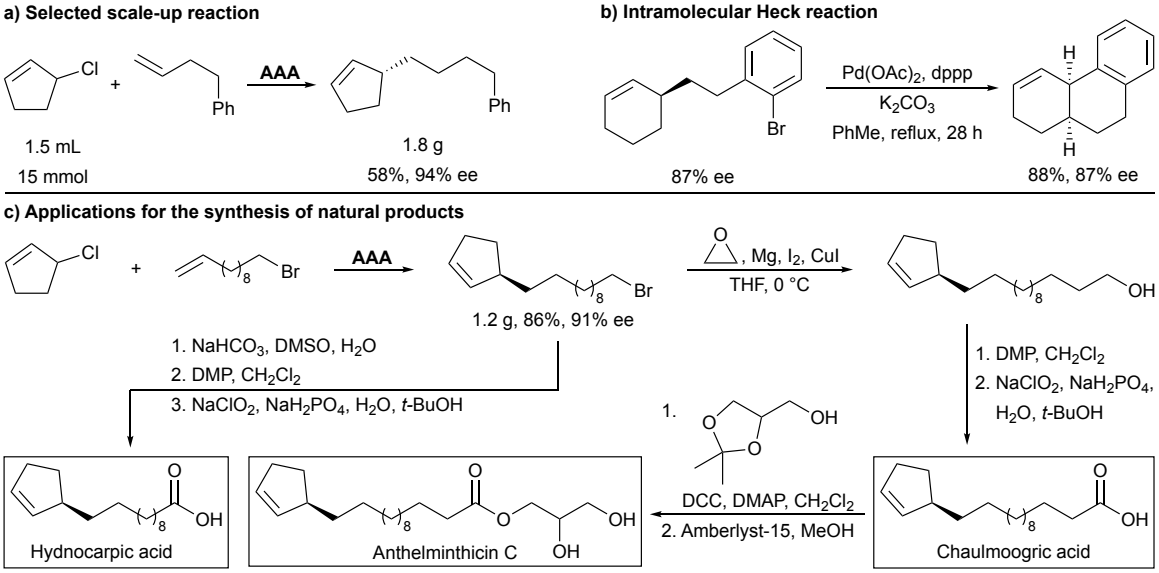
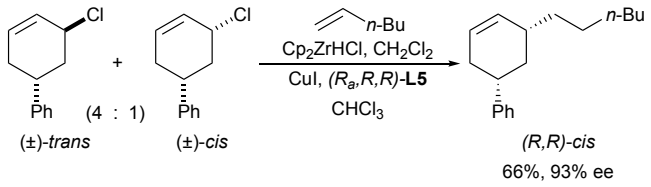


Figure 1.2 Cu-catalyzed AAA of alkylzirconium species and cyclic allyl chlorides, showing selected examples featuring a variety of functional groups. *In these experiments (*Sa,S,S*)-**L5** was used.



Scheme 1.6 a) Scale-up reaction; b) Intramolecular Heck reaction; c) Use of the AAA as key step for the synthesis of cyclopentene containing natural products.

In the case of starting materials with certain substitution patterns it is possible to resolve mixtures of racemic diastereoisomers (Scheme 1.7). For example, addition of 4-phenyl-1-butene to a mixture of racemic *cis*- and *trans*-5-phenyl allyl chloride (4:1) resulted in a single enantioenriched product with the *cis* configuration (66% yield, 93% ee).



Scheme 1.7 Cu-catalyzed conversion of a mixture of two racemic allyl chlorides to a single enantioenriched product.

1.2.5 Mechanistic studies

In order to understand how the reaction works we performed extensive NMR studies. Kinetics obtained by ^{1}H-NMR spectroscopy showed clean conversion of the allyl chloride to product along with the constant presence of an allyl iodide in small (~3%) amounts. NMR EXSY experiments suggest that this allyl halide interconverts or racemizes on the NMR timescale (Fig. 1.3a), and further experiments using allyl bromide starting materials demonstrated that allyl halide interconversion is mediated by the CuI-**L5** complex and occur via S_N2' pathways. Later, our group

was able to quantify the rate of allyl iodide interconversion as 0.10 ± 0.01 s^{-1}, using three related NMR spectroscopy methods. It is assumed that the allyl iodide formation is a key part of a mechanism for allyl chloride racemization (Fig. 1.3b). When CuCl or CuBr are used instead of CuI, the reaction works but is less enantioselective (49% ee and 73% ee respectively) – presumably halides that are better nucleophiles and leaving groups facilitate the rate of halide interconversion/ racemization.[42]

Evidence that AAA occurs via the catalyst selecting one enantiomer of a rapidly isomerizing mixture was obtained by following the ee of these reactions in time using different copper sources. When CuCl is used the reaction is faster but the ee decreases in time (from 82% at 10 min to 54% ee at completion). EXSY experiments did not show isomerisation of the allyl chloride with the CuCl-based catalyst on the NMR timescale and it is likely that as the reaction progresses the least preferred enantiomer of the substrate starts reacting. Supporting this, SM recovered during the reaction becomes enantioenriched (7% ee after 1 h, >11% ee after 2 h).

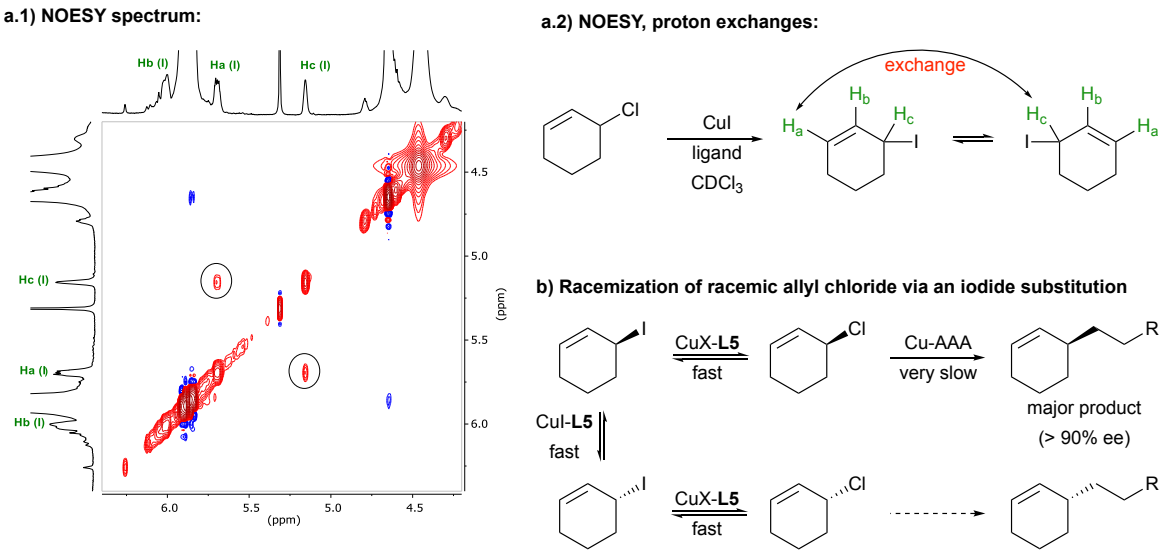


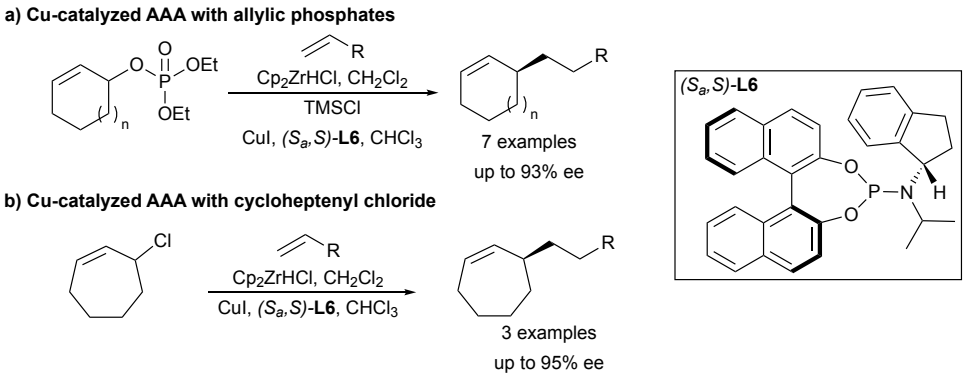
Figure 1.3 a) EXSY spectrum shows the exchanging protons of the allyl iodide; b) Proposed mechanism: racemization of starting material via an allyl iodide intermediate and selective reaction of one enantiomer of starting material

Most surprisingly, when using CuI, the ee of the reaction was found to increase over time (from 85% ee at 10 min to 95% ee at completion). *In situ* ^{1}H-NMR spectroscopy was used to collect kinetic data which was fitted to a model, and this data along with EXSY and DOSY experiments suggested that the catalyst evolves in time to become more efficient and more enantioselective.

The initial catalyst is believed to be dimeric, i.e. Cu_2I_2**L5**$_2$, but as the reaction progresses and Cl^- is released from the substrate a more selective catalytic complex containing both I and Cl anions, such as Cu_2ICl**L5**$_2$, is produced which is 3 times faster than the original catalyst.

1.2.6 Cu-catalyzed AAA of Allylic Phosphates

Our group aimed to use less reactive electrophiles in this process, which would be less prone to isomerization during preparation and manipulation, and to aid in mechanistic studies. Allylic phosphates gave promising results, and after optimisation the best results were obtained using CuI, ligand **L6** and TMSCl as an additive (Scheme 1.8a). In the absence of TMSCl the yields and ee's were both lower and the results were variable from one experiment to another. It should be noted that the allyl chloride system is superior to the phosphates in terms of robustness and generality. Ligand **L6** was found to be useful in all of these AAAs, generally providing higher levels of ee, and is necessary to get effective reactions with seven-membered rings (Scheme 1.8b).



Scheme 1.8 a) Cu-catalyzed AAA with isomerisation stable allylic phosphates, using ligand **L6**; b) Cu-catalyzed AAA to seven-membered rings.

In situ ^{1}H-NMR spectroscopy using the allyl phosphate and the optimised conditions with TMSCl (Fig. 1.4a) shows that the starting material is rapidly and entirely consumed to give an allyl chloride intermediate. Presumably the chloride is produced from reaction of the starting material with TMSCl. The allyl iodide in this system is seen to form very fast and reach a maximum concentration of ~10% in 2 min and then it appears to be consumed within 30 min. Although signals characteristic of allyl halide isomerization were never observed by *in situ* NMR EXSYs

during this AAA, it seems likely that once the allyl chloride is formed here it also undergoes racemization via the allyl iodide. Kinetic modelling indicated that the allyl chloride reacts 20 times faster than the phosphate and formation of the allyl chloride is 5 times faster than AAA.

Unexpectedly, when no TMSCl is used with allyl phosphate (Fig. 1.4b) the reaction still proceeds via an allyl chloride intermediate. In the absence of TMSCl, the allyl chloride is likely initially generated from adventitious Cl^- from reaction components ($Cp_2ZrClEt$ or CH_2Cl_2). As the reaction progresses Cl^- is also released from the substrate. Given how commonly allyl phosphates are used as electrophiles, and the apparent ease of which the allyl chloride forms, it seems likely that *in situ* allyl chloride formation is involved in the mechanism of other chemical reactions.

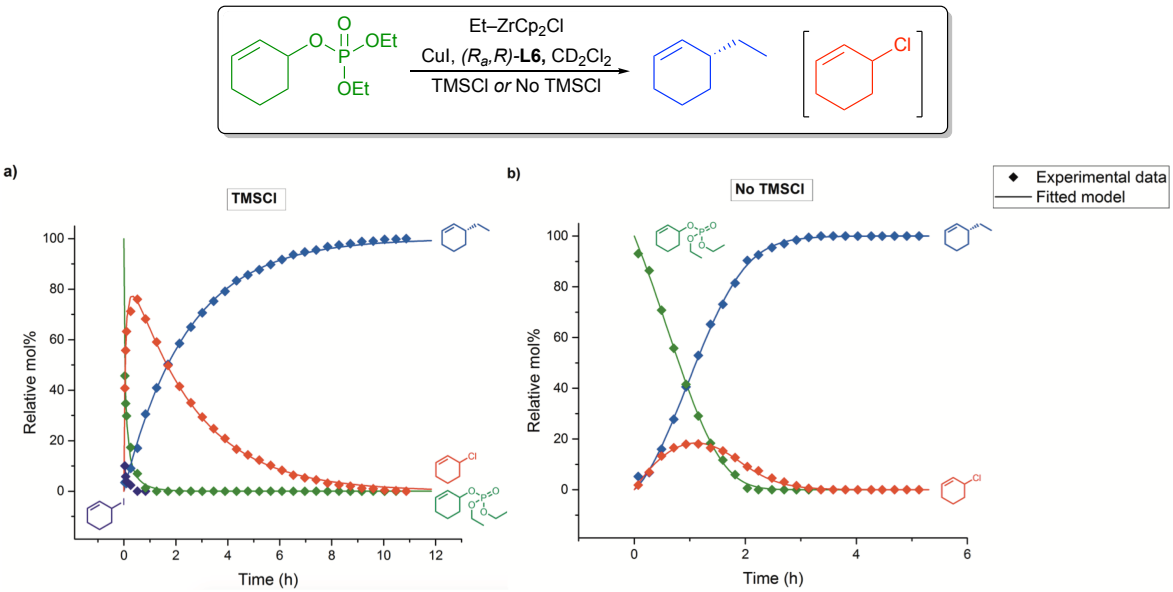
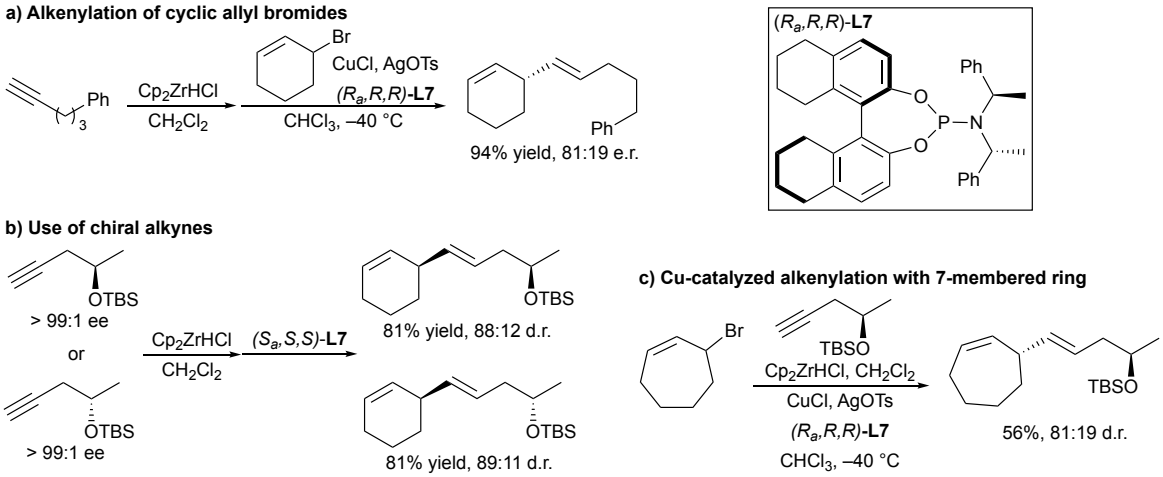


Figure 1.4 Results of the kinetic experiments obtained by ^{1}H-NMR spectra of the Cu-catalyzed AAA of racemic allyl phosphates (a) with and (b) without TMSCl.

1.2.7 Cu-catalyzed Asymmetric Allylic Alkenylation

The successful development of a system capable of adding alkyl nucleophiles encouraged us to explore DYKAT processes with sp^2-hybridised nucleophiles (Scheme 1.9a).[43] Alkenyl-zirconocenes were explored and found that reaction optimisation to be non-trivial. After extensive exploration CuOTs (prepared *in situ* from CuCl and AgOTs) in combination with allyl bromides gave the best results, although the enantioselectivity was low. In order to assist with determining

the stereoselectivity with which the dienes formed, enantiomerically pure alkynes featuring a TBS-protected alcohol were used so that the diastereomeric ratio could be determined by NMR spectroscopy (Scheme 1.9b). Coupling to 7-membered cyclic allyl bromide gave a product in 56% yield with a diasteromeric ratio of 81:19 d.r. (Scheme 1.9c).



Scheme 1.9 Asymmetric alkenylation with racemic cyclic allyl bromides.

2 Enantioselective Synthesis of Abietane Anti-cancer Type Structures

2.1 Introduction

2.1.1 Betulinic Acid and Other Anti-Cancer Active Derivatives

Natural products and their synthetic derivatives are privileged molecules in medicinal chemistry and pharmacy. They can both inspire and encourage the search for synthetic ways to access new structures. Nowadays the fight against cancer becomes more urgent than ever and the discovery of small molecules and drugs for its treatment is a vital part in the research and development sector.[44] Numerous natural products have been found to be anti-cancer active and are considered for clinical applications.[45–47] An important class amongst these are polycyclic terpenes. Such a pentacyclic triterpene is betulinic acid, which has been isolated from tropic plants[48] and was found to be active against multiple types of human cancers including breast, colon, lung, ovarian, prostate and others (Fig. 2.1).[49–51] One important way betulinic acid and other related antitumor active molecules work is via selective caspase activation.[52–54] Caspases are a family of specific cysteic proteases that have been found in a variety of species, including mammals. Over a dozen caspases are known and they are all expressed as inactive proenzymes which, once activated, lead finally to cell death, i.e. apoptosis. The caspase-activated apoptosis is a complex cascade and involves multiple chain reactions such as DNA degradation and chromatin condensation.

Important betulinic acid related structures are the phytochemical diterpene ferruginol[55,56] and the triterpene 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO).[57–59] Structure-activity relationships of the triterpenoid CDDO showed that only the core structure was required for anticancer activity. This led to the development of the synthetic derivative TBE-31.[60–62]

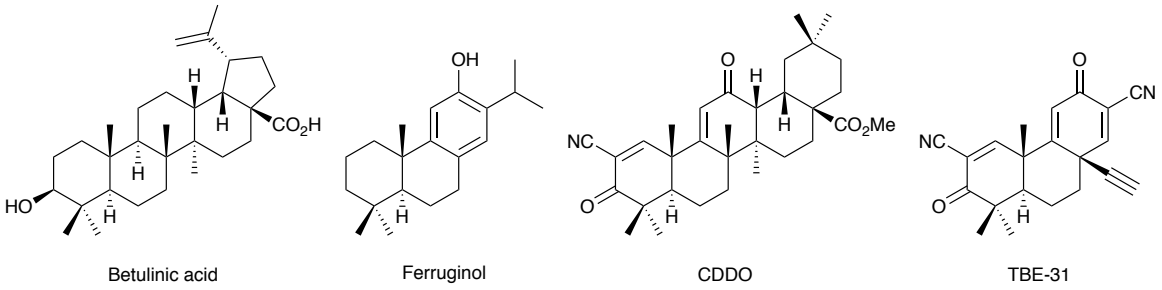
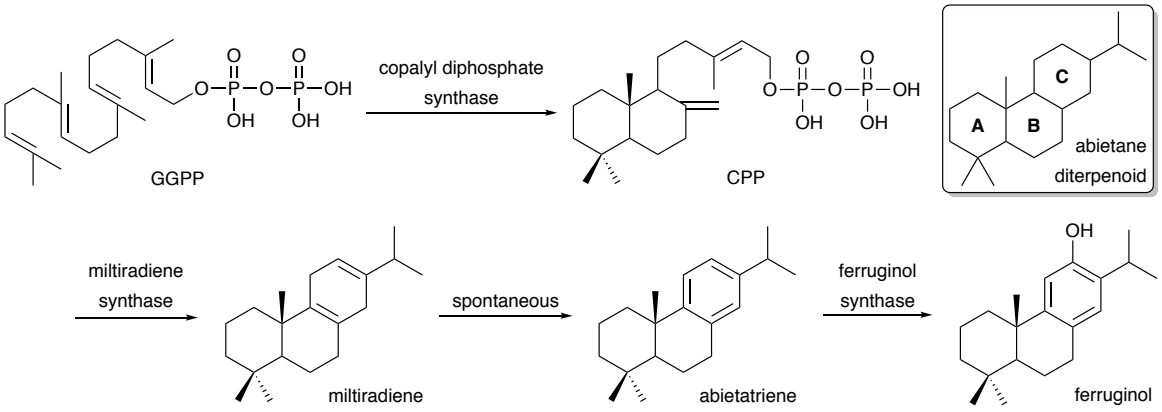


Figure 2.1 Structures of the natural products betulinic acid and ferruginol and two structurally related synthetic molecules (CDDO and TBE-31).

Nature's biosynthesis of these valuable diterpenoid structures is based on an enzymatic cascade that transforms geranylgeranyl pyrophosphate (GGPP) into ferruginol, which is a relevant structure for further synthesis of abietane-like diterpenoids (Scheme 2.1).[63] Many groups have adopted this biosynthetic cyclisation cascade approach for the total synthesis of a vast number of diterpenoids.[64]



Scheme 2.1 Biosynthetic pathway to abietane-like diterpenoids in *Rosmarinus officinali*.

2.1.2 Asymmetric Conjugate Addition (ACA)

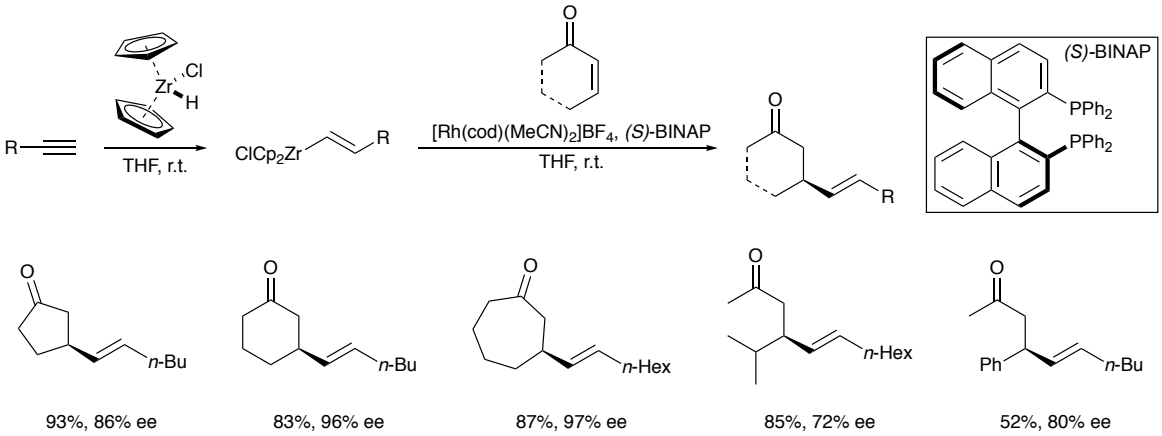
The synthesis of polycyclic terpene structures often requires long synthetic routes including inefficient protection and deprotection steps. The development of efficient routes to these core motifs is therefore necessary. Asymmetric conjugate addition reactions (ACA), i.e. the enantioselective addition to prochiral molecules, have been developed and applied into a variety of total syntheses catalyzed by different transition metals such as Pd, Rh, Ni, and copper.[65–68]

Cu-catalyzed conjugate additions give access to numerous enantioenriched small building blocks.[69–71] A major advantage of Cu-catalyzed asymmetric reactions is the use of a variety of non-

stabilized nucleophiles such as alkyl aluminium (AlR_3),[72,73] dialkylzinc (ZnR_2),[74,75] organolithium (RLi)[76] and Grignard reagents (MgBrR).[30] Especially the latter is considered to be attractive due to better availability and ability to transfer aryl and alkyl groups compared to other premade organometallic compounds.

However, the *in situ* preparation of organometallics can preclude the addition of structures with sensitive functional groups.[36] In addition, the majority of non-stabilized nucleophiles in Cu-catalyzed reactions require very specific conditions in order to obtain high yields and enantioselectivities, e.g. cryogenic temperatures, which can be problematic in large-scale processes.

In 2004, Oi and Inoue reported a Rh-catalyzed ACA of nonfunctionalized linear alkenes to cyclic and acyclic ketones.[77] Alkenylzirconocenes were generated *in situ* from alkenes with Schwartz's reagent, a commercial zirconocene used for hydrometalation.[78] Despite limited scope the products were obtained in good yield and enantioselectivities at ambient temperatures.



Scheme 2.2 Rh-catalyzed asymmetric 1,4-addition of alkenes to *α,β*-unsaturated enones with *in situ* generated alkenylzirconium reagents.

In 2012, our group combined the use of copper-catalysis and organozirconium reagents (Fig. 2.2).[35] This asymmetric conjugate addition uses a variety of terminal alkenes that upon hydrometalation undergo an asymmetric addition to cyclic enones at ambient temperatures. A variety of different functional groups, such as alkenes, halides and protected alcohols are tolerated. The reaction is catalyzed by a premade copper phosphoramidite trifluorosulfonate complex **L5***. The use of phosphoramidites, which are long known as intermediates in polynucleotide synthesis,

are nowadays a valuable class of ligands used in Cu-catalyzed ACA and other enantioselective transformations.[40,79] Recently, experimental and computational studies on these ligands gave the opportunity to gain insight into steric and electronic influences of these privileged structures. It was found that the phosphoramidite backbone defines the configuration of the product of the ACA, while amine substituents can be achiral but influences the degree of stereoselectivity (e.g. **L8** in Scheme 2.3).[80]

The developed ACA was also applied to the synthesis of **1**, a natural product isolated from *Balantiopsis rosea* (Fig. 2.2).[81,82] Further investigation of the method to different cyclic and substituted cyclic enones proved successful to form tertiary centres.[83]

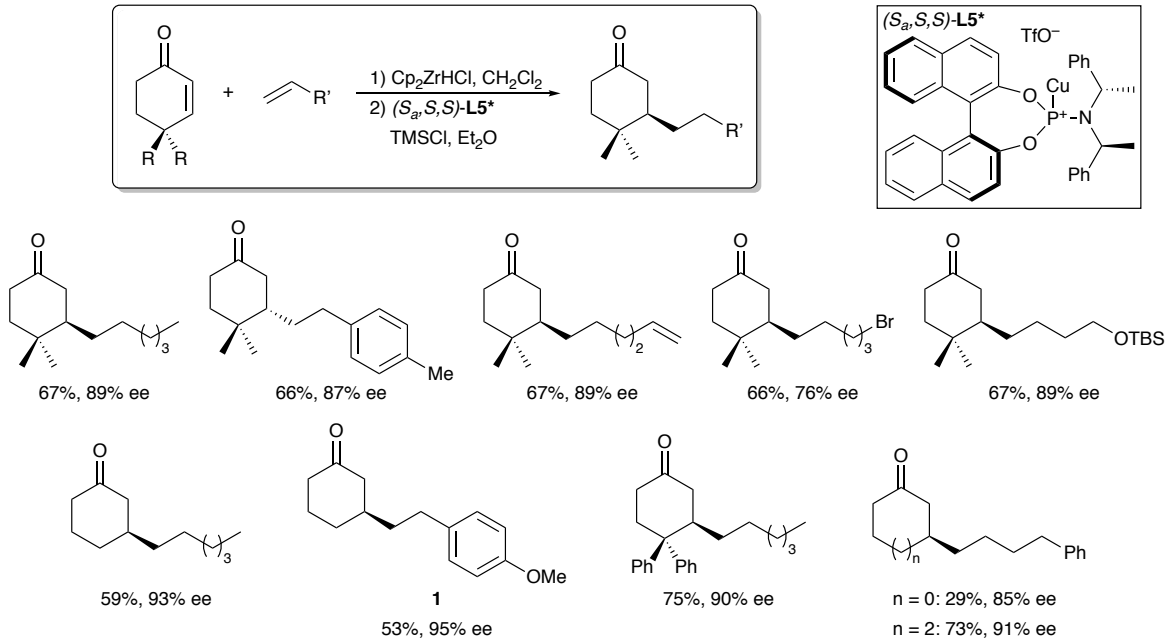
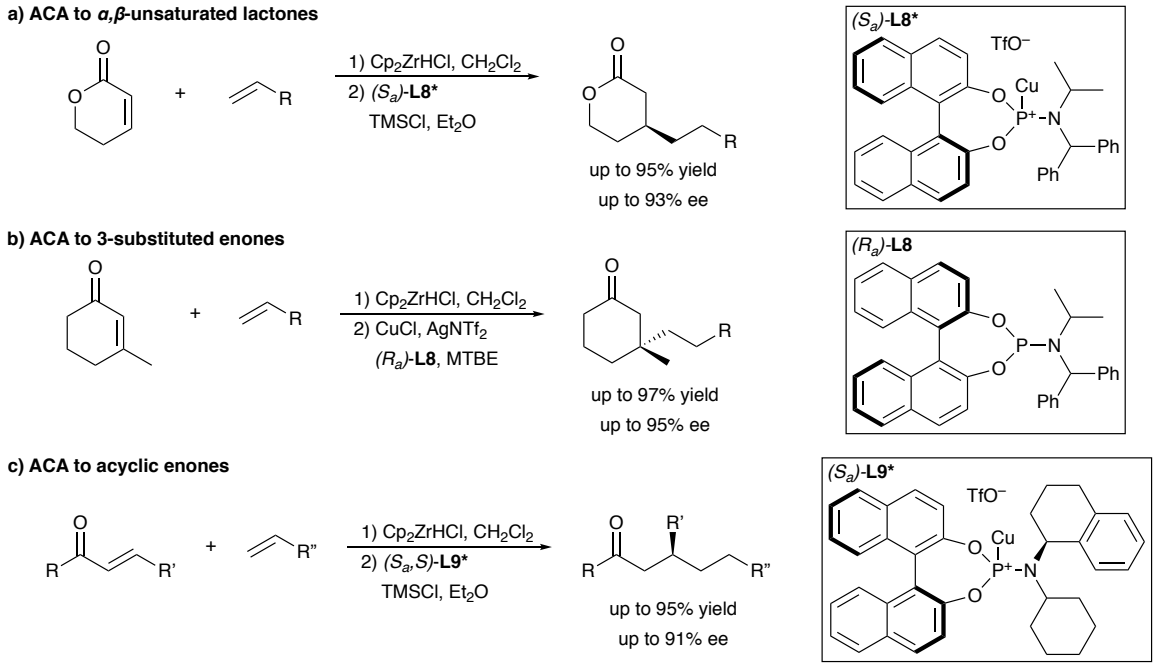


Figure 2.2 Enantioselective 1,4-addition of simple and functionalized alkenes.

Our group was interested into the generality of this method regarding other electrophiles with different electronic properties and found that lactones[84] as well as 3-methyl substituted enones[38,85] can be used (Scheme 2.3a,b). The latter transformation is a convenient way to obtain all-carbon quarternary centres, which are common motifs in many natural products.[68] It was also shown that the copper source and phosphoramidite ligand could be used to form the catalytic species *in situ*, which can be useful for the screening of different ligands to improve conditions for difficult substrates.

Extension to the more configurationally labile acyclic enones has been achieved with optimised catalyst systems for the formation of both tertiary[86,87] and quartenary centres (Scheme 2.3c).[37]



Scheme 2.3 Asymmetric 1,4-additions of alkylzirconium reagents to different electrophiles.

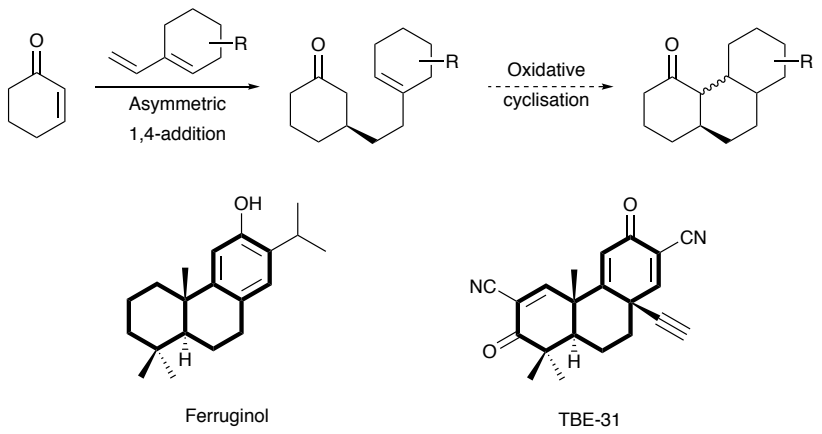
During the optimisation of the reaction it was observed that the reaction shows high tolerance to a number of halogenated and ethereal solvents at ambient temperatures.[35] Together with *in situ* hydrometalation of functionalized alkenes – which overcomes some of the limitations of pre-made organometallics – the Cu-catalyzed ACA has high potential for asymmetric organic synthesis and potentially scale-up processes.

2.2 Project Aims

With a variety of functionalized alkenes available as nucleophiles, we envisaged that ACA could be a useful tool for the synthesis of more complex structures and natural products. The key introduction of the first stereocenter can dictate the outcome of subsequent stereoselective reactions.

Once the asymmetric step is established investigations into oxidative coupling reactions should provide access to tricyclic frameworks of abietane-like structures, e.g. TBE-31 and ferruginol (Scheme. 2.4). This could be realized by a number of different oxidative cyclisation techniques, e.g. organocatalysis or anodic oxidation using electrochemical devices.

The main goals of the work were therefore to (a) develop a catalytic asymmetric tandem strategy, i.e. ACA and cyclisation, to access the tricyclic cores of medicinally relevant compounds, (b) optimise key steps for yield/enantioselectivity and scale up to gram-scale and (c) explore biocatalytic/electrochemical oxidation routes to compounds of pharmaceutical interest and extend the strategy to access homologues with other ring sizes



Scheme 2.4 Proposed synthetic sequence for the synthesis of the tricyclic core of natural products such as ferruginol and TBE-31.

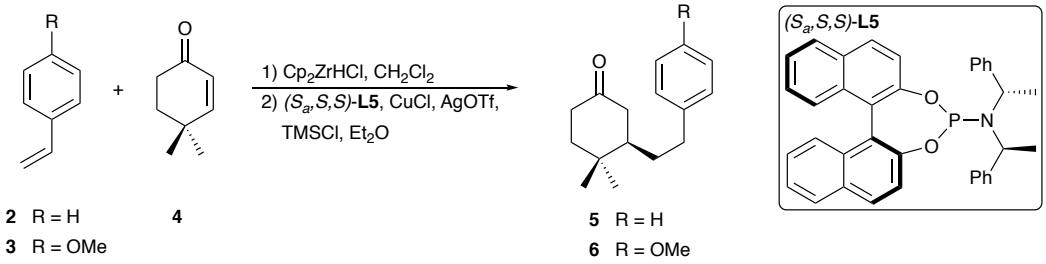
2.3 Results and Discussion

2.3.1 Asymmetric 1,4-Addition

Using chemistry developed in the Fletcher group, we investigated the catalytic asymmetric 1,4-addition of styrene **2** and 4-vinylanisol **3** to 4,4-dimethyl-2-cyclohexen-1-one **4** with phosphoramidite ligand **L5** (Table 2.1).

Based on previously reported conditions different parameters were screened in order to improve both the yield and the enantiomeric excess of products **5** and **6**. The highest ee values were obtained when the reaction was performed at 0 °C (entries 5 and 6). In all cases the purification of the products proved difficult due to the formation of a number of by-products.

Table 2.1 Optimisation of the asymmetric 1,4-addition of two different styrenes.



2 R = H
3 R = OMe

4

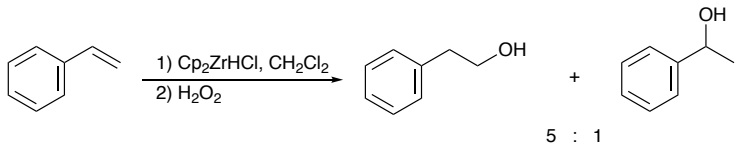
5 R = H
6 R = OMe

Entry	Alkene	Scale enone [mmol]	*T*	Yield (%)	ee (%)
1	**2**	1.0	r.t.	40	80
2	**2**^{a}	1.0	r.t.	38	78
3	**2**^{b}	1.0	r.t.	45	80
4	**2**	0.4	40 °C	30	26
5	**2**	0.4	0 °C	28	89
6	**3**	0.4	0 °C	55	92

Amounts used in this procedure: enone (1.0 eq), alkene (2.5 eq.), Cp_2ZrHCl (2.0 eq.), (*Sa,S,S*)-**L5** (0.10 eq.), CuCl (0.10 eq.), AgOTf (0.11 eq.), TMSCl (5.0 eq.); *a*: Alkene/Cp_2ZrHCl ratio: 3.0/2.3; *b*: distilled before use.

We tried to understand the formation of some of the by-products and in an independent experiment the hydrozirconated alkene was trapped by oxidation with hydrogen peroxide. We observed that

the hydrozirconation with styrene gave two products, with the Zr at either the terminal or benzylic position (ratio ≈ 5:1*).

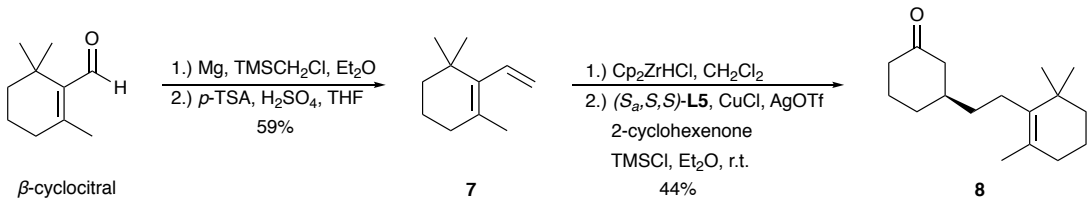


Scheme 2.5 Hydrozirconation and oxidation of styrene provides a mixture of products.

Based on preliminary data this would be consistent with the formation of the branched product 4,4-dimethyl-3-(1-phenylethyl)cyclohexanone which could be isolated in one case but other minor products were generated during the asymmetric reaction that could not be identified.

Synthesis of the racemic products using only CuBr·Me_2S gave notably higher yields (*rac*-**5**: 83%; *rac*-**6**: 92%).

We further investigated the use of alkenes and found **7** to be a suitable motif for abietane-like structures (Scheme 2.5). Diene **7** can be generated easily from the commercially available *β*-cyclocitral. Subsequent asymmetric conjugate addition to afford **8** was achieved with conditions similar to those used for vinylarenes. Unfortunately the enantiomeric excess could not be determined at this stage by either chromatographic methods or ketone derivatisation (see SI). Nonetheless we focused on this substrate as a proof of concept for further modifications.



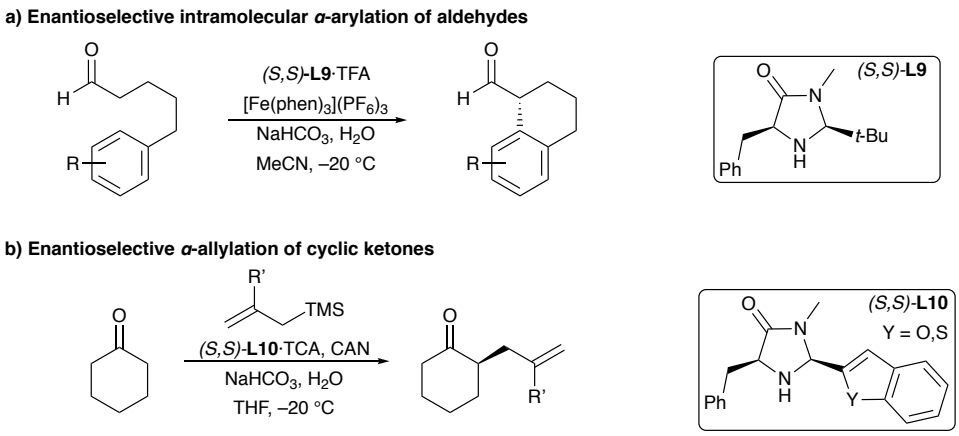
Scheme 2.6 Formation of cyclic diene **7** and subsequent asymmetric 1,4-addition with 2-cyclohexenone.

2.3.2 Oxidative Cyclisation

Once the asymmetric 1,4-addition was established, we investigated the coupling step. To our knowledge, the intramolecular coupling reaction of an unfunctionalized aryl group to the *α*-

* Measured by ^{1}H-NMR spectroscopy

position of a ketone is currently unknown. However, Nicolaou[88,89] and MacMillan[90] reported an analogous coupling between aldehydes and electron-rich aromatics using singly occupied molecular orbital (SOMO) organocatalysis (Scheme 2.6a).[91] In a subsequent report MacMillan showed that the α-allylation of the less reactive ketones can be successfully achieved by using cerium ammonium nitrate (CAN) as oxidant and modified catalysts (Scheme 2.6b).[92]

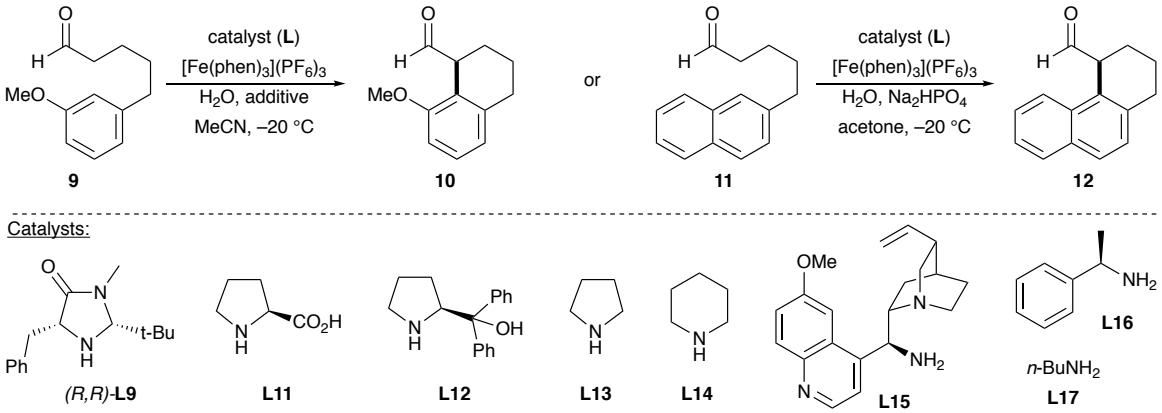


Scheme 2.7 MacMillan's enantioselective α-arylation and allylation of carbonyl compounds via SOMO catalysis.

In order to confirm the efficiency of the reported oxidative coupling[90] we repeated the synthesis of two different α-arylated aldehydes (Scheme 2.7). The imidazolidinone-based catalyst **L9** catalyzed the conversion of substrate **9** to the arylated compound **10** with 45% yield and 85% ee (Lit[90]: 61%, 92% ee) (Table 2.2, entry 1). We hypothesized that other cyclic amines would be able to catalyse product formation based on the literature set of conditions. Various amines **L11–L17** that are known for enamine formation were examined under different conditions. Neither chiral nor achiral amines provided the product with good results. In addition, no trend was observed when primary (entries 2–7) or secondary amines (entries 8–10) were used and only pyrrolidine **L13** and *n*-butylamine **L17** gave traces of racemic product **10** (entries 4,10). In contrast to the literature conditions, additional pivalic acid was not benefitial for the yield.

A second substrate was tested to evaluate a second set of conditions for the coupling reaction. Reaction of aldehyde **11** to **12** with $[Fe(phen)_3](PF_6)_3$ as oxidant in acetone yielded 56% of the coupling product (Lit[90]: 83%, 93% ee), the ee value was not determined.

Table 2.2 Yields and ee values for different reaction conditions with a variety of amines as catalysts.



Entry	Substrate	Catalyst	Additives	Yield % (%ee)
1	**9**	**L9**·TFA	$NaHCO_3$	45 (85)
2	**9**	**L9**	$NaHCO_3$	9 (85)
3	**9**	**L13**·TFA	$NaHCO_3$, PivOH	trace
4[a]	**9**	**L13**	–	trace
5	**9**	**L11**·TFA	$NaHCO_3$,PivOH	0
6	**9**	**L12**·TFA	$NaHCO_3$,PivOH	0
7	**9**	**L14**·TFA	$NaHCO_3$,PivOH	0
8	**9**	**L15**·3HCl	$NaHCO_3$	0
9	**9**	**L16**	$NaHCO_3$	0
10	**9**	**L17**	$NaHCO_3$	trace
11	**11**	**L9**·TfOH	$NaHCO_3$,PivOH	26 (n.d.)
12[b]	**11**	**L9**·TfOH	Na_2HPO_4	56 (n.d.)

Amounts used in this procedure: substrate (1.0 eq.), catalyst (0.3 eq.), $NaHCO_3$ (5.0 eq.), PivOH (0.3 eq.), H_2O (1.5 eq.); *a*: CAN and dimethoxyethane were used; *b*: reaction was carried out at –30 °C

Taking the best conditions, we applied them to racemic 1,4-addition products **5, 6** as well as diene **7**. TfOH and TFA salts of imidazolidinone catalyst **L9** and pyrrolidine **L13** respectively were used to achieve the oxidative coupling. However, over a range of different temperatures (–20, –10, 0 °C, r.t.) neither $[Fe(phen)_3](PF_6)_3$ nor CAN promoted the reaction.

Given the failure of these attempts, we looked for related catalysts which might successfully promote the formation of the C–C bond. MacMillan reported the α-allylation of ketones with modified imidazolidinone catalysts **L10** and **L17** (Figure 2.3).[92]

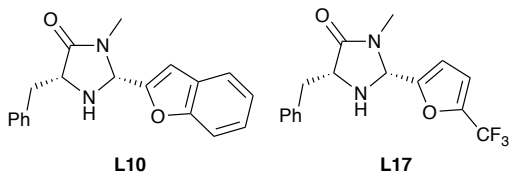
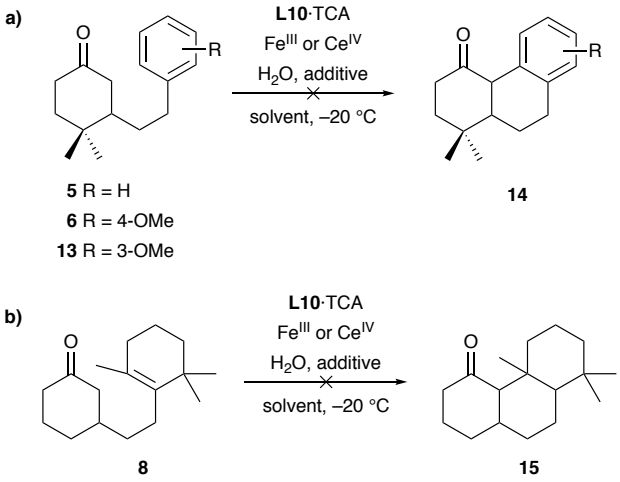


Figure 2.3 Structures of oxidation stable catalysts.

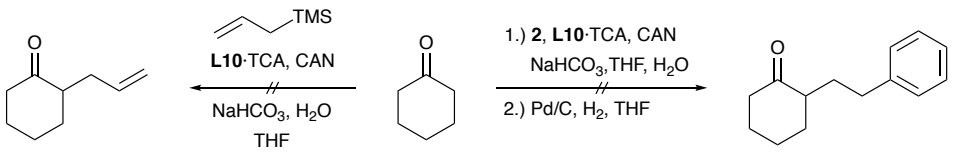
In addition racemic ketone **13**, which has an aromatic group similar to aldehydes used in the literature and examined in Scheme 2.7,[88,90] was synthesized in order to control for directing group effects in the aromatic ring. Imidazolidinone-based catalyst **L10** was prepared and examined in both α-arylation (Scheme 2.8a) and alkylation (Scheme 2.8b).

The combination of ketone **13** and catalyst **L10**, amongst other catalysts, did not provide to the desired coupling products. In most cases unreacted starting material was recovered.



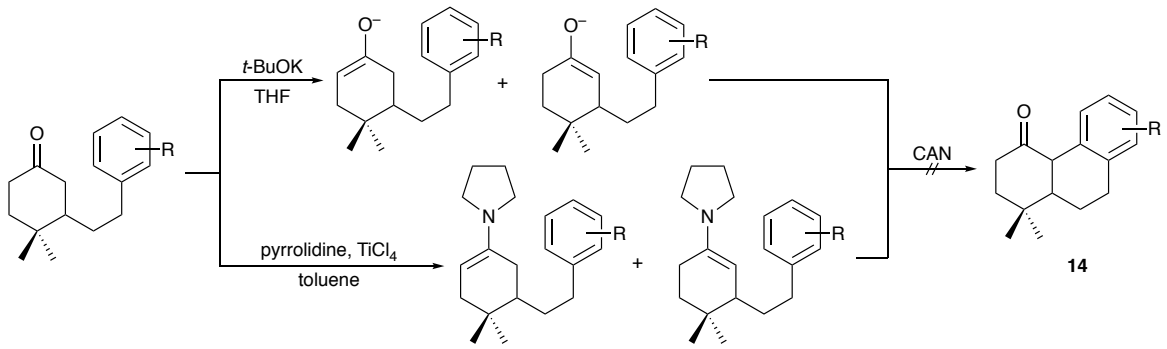
Scheme 2.8 Attempts for intramolecular a) α-arylation to 4,4-dimethylketone with different aromatic groups and b) α-alkylation to unsubstituted ketone.

We also used catalyst **L10** to reproduce and verify two different α-alkylations of cyclohexanone with either styrene **2** or allyltrimethylsilane reported in the literature (Scheme 2.9).[92] In our hands starting material remained unreacted in both cases using the reported reaction conditions.



Scheme 2.9 Reported asymmetric *α*-allylation and alkylation did not provide product.

We attempted to modify the desired arylation procedure using a number of simplified approaches, for example, deprotonation-oxidation (using *t*-BuOK) or stoichiometric enamine formation and subsequent oxidation did not provide the desired product **14** (Scheme 2.10). Subsequent oxidation with CAN also failed in our hands and starting was recovered unreacted.



Scheme 2.10 Two-step approaches to performing the oxidative coupling reaction.

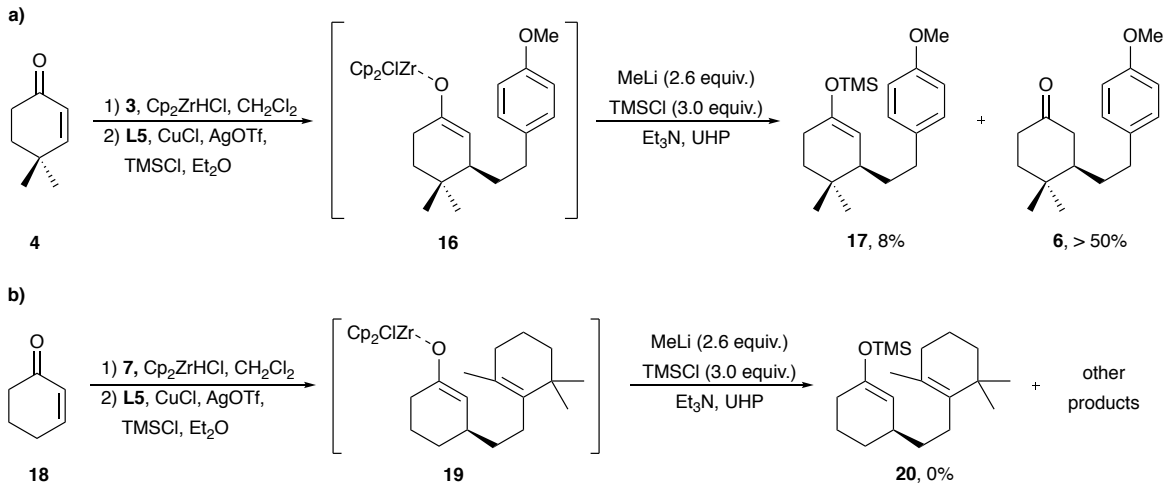
Another approach to overcome this problem involved the use of intermediate enolate **16** formed during the asymmetric 1,4-addition (Scheme 2.11a). Adding an oxidant following asymmetric addition was hoped to allow the desired oxidative coupling. However, addition of various oxidants, i.e. CAN, $Mn(OAc)_3$ or $[Fe(phen)_3](PF_6)_3$, to the enolate did not lead to C–C bond formation. Other attempts to form an *α*-haloketone with either NXS (X = Cl, Br, I), Br_2 or I_2 from the zirconium enolate were not successful.

However, trapping intermediate **16** regioselectively as a trimethylsilyl enol ether **17** (using MeLi followed by TMSCl) was successful. Von Zezschwitz *et al.* reported this kind of enolate trapping procedure for a Rh-catalyzed 1,4-addition of alkenylzirconocenes to cyclic enones.[93] The authors also noted that adding TMSCl before MeLi (as opposed to after) inhibited the trapping reaction. Here MeLi was added to the conjugate addition reaction already containing TMSCl to give **17** (Scheme 2.11a).

Unfortunately compound **17** is not stable to silica gel column chromatography, and even adding up to 3% v/v triethylamine to the eluent led to decomposition of TMS enolate **17**. We tried to modify

the procedure by replacing TMSCl with TBSCl. TBS ethers are known to be more acid stable but use of TBSCl did not provide the 1,4-addition product in the first place.

Applying von Zezwschitz's procedure to 1,4-addition intermediate **19** resulted in a number of products which could not be isolated (Scheme 2.11b). The desired TMS enolate **20** could not be detected.

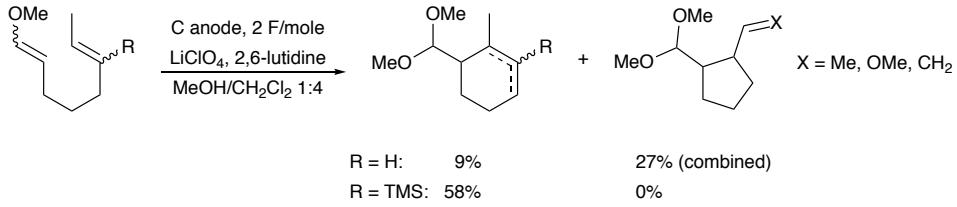


Scheme 2.11 Trapping of the Zr intermediate as a trimethylsilyl enol ether with MeLi and TMSCl.

2.3.3 Electrochemical Approach

The use of electrochemical processes in organic chemistry is a growing field. The replacement of stoichiometric oxidants with electrons in synthetic transformations makes electrochemistry a green alternative and hence very attractive for large scale processes.[94]

Baran[94] and Moeller[95–97] have developed valuable synthetic transformations that include intramolecular ring closures, various oxidations and C–H activations. For example, Moeller demonstrated the intramolecular electrocyclisation of alkenes with TMS substituted substrates (Scheme 2.12).[98]



Scheme 2.12 Moeller's intramolecular electrocyclisation of alkenes.

In many cases research groups do not have the required knowledge and/or equipment to use electrochemistry as an alternative method in organic synthesis. In addition, successful approaches on a small and often analytical scale may be problematic on larger scale due to concentration and/or electrode poisoning.

We attempted to use electrochemistry to better understand the coupling step. On studying the redox potential of the different species involved we can obtain information about their behaviour and oxidative stability in solution. The redox potential of the oxidants are known with $E(\text{Fe(phen)}_3^{\text{II/III}}) \approx 1.15$ V and $E(\text{CAN, Ce}^{\text{III/IV}}) \approx 1.72$ V vs. NHE.[99] However the oxidation potentials of the substrates and intermediates were unknown. Hence, the next step was to measure these potentials by cyclic voltammetry (CV).

In order to measure the redox potential of the different species we collaborated with the Richard G. Compton group. We measured the different potentials using a potentiostat, keeping in mind that applying a potential to a chemical compound affects the functional group with the lowest oxidation potential.

The potentials were measured under anhydrous conditions in an inert atmosphere (Fig. 2.4). Acetonitrile was used as a solvent together with tetraethylammonium *p*-toluenesulfonate (Et_4NOTs, 0.1 M), a common electrolyte in organic electrochemistry.[95] A glassy carbon electrode (working electrode), a carbon rod electrode (counter electrode) and a silver wire (reference electrode) were used for the experiments.[100] In this way we measured oxidation potentials for several key compounds involved in the oxidation step. The enamine **23** formed with pyrrolidine, has the lowest oxidation potential. Forming enolate **21** (using LiHMDS) or the trimethylsilyl enol ether **22** (using TMSOTf and triethylamine) lowered the oxidation potential slightly compared to the ketone.

With these results in hand, the application of electrochemical methods in substrates **5**, **6** and **13** seemed feasible, encouraging us to pursue the synthesis of the tricyclic core by applying a constant potential to the reaction.

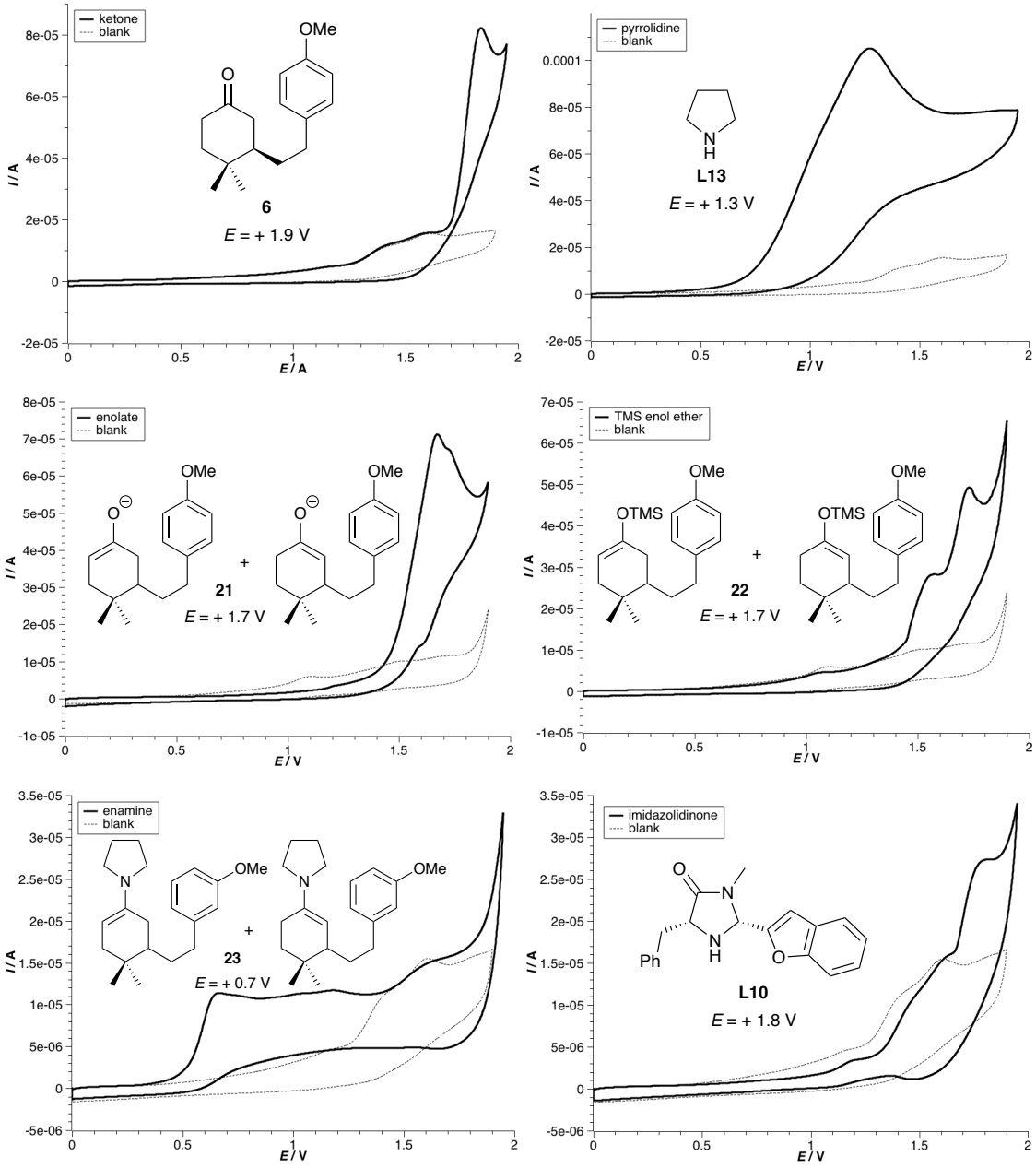


Figure 2.4 Cyclic voltammograms and oxidation potentials vs. Ag wire of relevant compounds in acetonitrile. The generated enolates and enamine structures were not formed regioselectively.

We designed a feasible apparatus for the electrochemical synthesis (Figure 2.5), comprising a 6 V lantern battery, two carbon rod electrodes, and an ammeter to measure the current *I*. This set up

was successful in cyclization reactions and coupling reactions to aromatic groups used in the literature.[95,101,102]

Throughout these experiments we made some general observations. Dichloromethane and THF have, in general, low conductivity ($I \approx 0.3$ mA) whereas *n*-Bu_4NBF_4 in acetonitrile showed the highest conductivity ($I \approx 10$ mA). Even though the electrochemical synthesis was set up as a constant current experiment we measured a decreasing current over time. It appears that the current decreases over time because a residue forms on the surface of the anode. A side effect of reduced current is a compensation effect where the potential increases, which can lead to overoxidation of the compounds in solution.

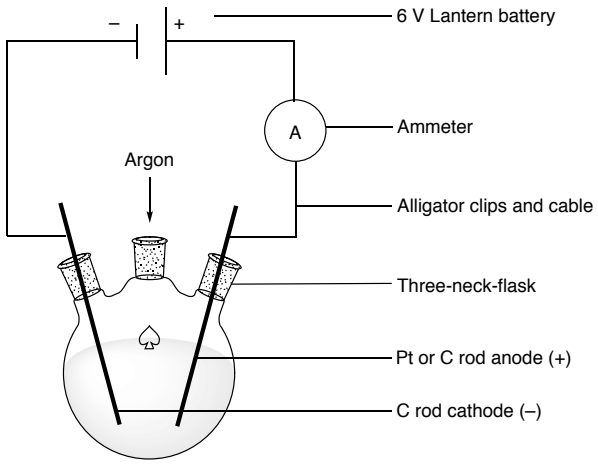
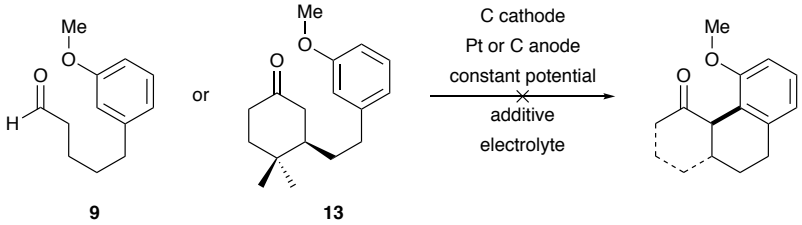


Figure 2.5 Sketch of the reaction apparatus for electrochemical synthesis.

The results of screening various conditions are shown in Table 2.3. Repeating MacMillan's procedure[90] electrochemically, i.e. using anodic oxidation instead adding an external oxidant, was not successful (entry 1). No product could be obtained when the electrolyte and other conditions were varied. Using aqueous electrolyte mixtures reduced **9** to the alcohol (entry 3). Assuming that the carbon rod electrode may be the problem, we replaced the anode with a platinum sheet, but obtained similar results (entry 5).

Using ketone **13** the desired product could not be isolated, but the reaction gave rise to a mixture of inseparable products (entries 6–10). Larger-scale reactions gave too little conversion to allow identification of any by-products presumably because of residue formation on the surface of the electrodes.

Table 2.3 Screening of catalysts, electrolytes and additives for the oxidative electrocyclisation.



9 **13**

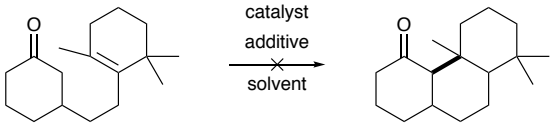
Entry	Substrate	Catalyst	Electrolyte	Additive
1	**9**	**L9**	$NaHCO_3$[b]	TCA, H_2O
2	**9**	**L9**	Et_4NOTs[c]	TFA, H_2O
3	**9**	**L11**	$NaHCO_3$[d]	–
4	**9**	**L9**	NaOAc/AcOH[b]	–
5[a]	**9**	**L9**	*n*-Bu_4NBF_4[c]	TCA
6	**13**	**L11**	Et_4NOTs[b]	–
7	**13**	**L11**	Et_4NOTs[c]	LiHMDS
8	**13**	–	*n*-Bu_4NBF_4[e]	TMSOTf[f]
9	**13**	–	$LiClO_4$	LiHMDS[g]
10	**13**	**L12**	*n*-Bu_4NBF_4[c]	TCA

a: Pt anode; *b*: 0.1 M in MeCN; *c*: 0.03 M in MeCN; *d*: 0.1 M in H_2O/MeCN 1:1; *e*: 0.03 M in CH_2Cl_2; *f*: additional 2,6-lutidine; *g*: 1.0 M in THF

2.3.4 Other Transition Metal Cyclisations

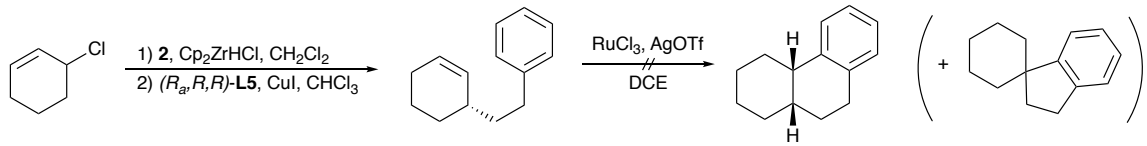
Alongside studying the intramolecular cyclisation via single electron transfer we considered a variety of transition metals for the coupling step (Table 2.4).[103–106] Reaction conditions reported for other inter- and/or intramolecular cyclisations were tested on our substrate but the cyclised product was never obtained. Reasons for the unsuccessful reaction might be the substrate itself, i.e. in contrast to majorly terminal alkenes that have been used, substrate **8** is tetra-substituted alkene and hence rather hindered. In some cases TMS substituted alkenes facilitate the coupling reaction (Scheme 2.12). However, such further modifications of the substrates, would not be suitable for the desired coupling motif.

Table 2.4 Screening of various transition metal catalysts to achieve cyclisation.



Entry[Ref.]	Catalyst	Additive or oxidant	Solvent
1[103]	$Pd(OAc)_2$, QPHOS	LiHMDS	THF
2[104]	$PdCl_2(MeCN)_2$, $CuCl_2$	HCl	dioxane
3[105]	$Cu(OTf)_2$	DDQ	MeCN, H_2O
4[106]	$Mn(OAc)_2$ or $Mn(OAc)_3$	air	AcOH

We also considered Ru-catalyzed hydroarylation as described by Sames.[107] This procedure describes the coupling of electron-rich arenes with trisubstituted alkenes and has advantages over other cross couplings, e.g. the Heck-coupling, which requires additional modification, such as an arylhalide.[39] The starting material can easily be obtained via AAA with styrene. However, the subsequent hydroarylation step did not provide any product, while Sames reported to obtain a mixture of products with 63% yield (Scheme 2.13).[107]

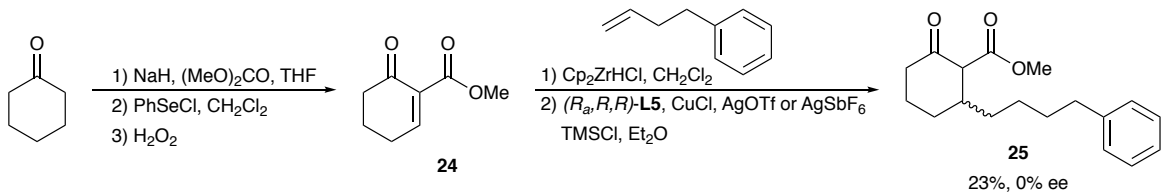


Scheme 2.13 AAA and subsequent Ru-catalyzed cyclisation.

2.3.5 Approaches with Modified Starting Materials

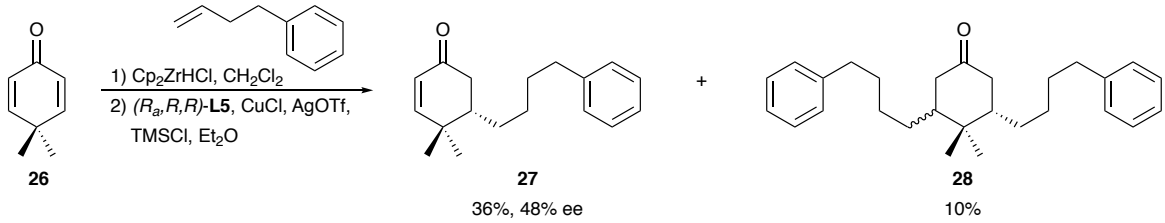
Since all previous attempts for oxidative ring closure were unsuccessful, we reconsidered the structure of the starting material. In order to activate the less hindered α-position of the ketone regioselectivily we synthesized of methoxycarbonyl substituted enone **24**. We presumed that the β-ketoester would form the enolate in the desired position for a subsequent oxidative cyclisation. A test reaction was performed with 4-phenylbut-1-ene but only racemic product was obtained (Scheme 2.14). Substitution in the 2-position of the enone seems to have considerable impact on

the enantioselectivity of the reaction and further optimisation would be required. In addition, the formed *β*-ketoester **25** might replace the chiral phosphoramidite ligand on Cu,[108] which results in a racemic catalytic species.



Scheme 2.14 Synthesis of methoxycarbonyl substituted enone **24** and subsequent 1,4-addition of 4-phenylbut-1-ene.

In addition, dienone **26** was used as electrophile for the asymmetric conjugate addition of 4-phenylbut-1-ene (Scheme 2.15). A test reaction gave the desired product **27** in 36% yield and 48% ee. During this reaction we observed the formation of bisalkylated product in 10% yield. The nucleophile is always used in excess (2.0 equiv) and further optimisation would be needed to increase yield and to prevent the double alkylation.



Scheme 2.15 ACA of substituted 2,5-dienone **26**.

2.4 Summary

The asymmetric 1,4-addition of styrene and 4-vinylanisol to **5** and **6** gave good yields and ees. A procedure for the intramolecular *α*-arylation of aldehydes, via the formation of enamines, could be reproduced from the literature. However, any variation of the reaction conditions failed. In the case of the *α*-arylation of ketones neither the modified ketone **13** nor an oxidation-stable catalyst **L10** gave any product. An alternative route based on anodic oxidation using electrochemical synthesis also failed. Cyclic voltammetry experiments suggested that the use of electrodes for the *α*-arylation

would be feasible, but this resulted either in a complex mixture of products or in low conversion presumably due to the formation of residues which reduce the active surface on the electrodes.

The use of electrochemistry seems to generate a number of products. Performing the experiments with constant potential rather than a constant current could help us to understand the formation of the different products.

Another approach to desired molecular frameworks involved the use of nucleophiles with aliphatic core structures. However similar approaches for the coupling steps failed with these substrates. The coupled alkene allowed further investigations into transition metal catalyzed cyclisation reactions but were not successful. A reliable zirconium enolate trapping protocol with different reagents could not be developed due to either harsh conditions (MeLi) or reactivity of the zirconium intermediate.

In order to minimize regioselectivity problems two different alternative electrophiles were generated. Methoxycarbonylester **24** and 2,5-dienone **26** would allow activation of the desired α-position in order to perform the oxidative cyclisation regioselectively. The latter showed good initial results (48% ee) and if double-addition of the alkylzirconium species could be minimised then this might give access to a more reliable protocol.

The addition of alkylzirconium nucleophiles to 2,5-dienones requires optimisation and the developed conditions could be applicable to different styrenes and diene structures. The subsequent addition step is more restricted and could be achieved regioselectively. Once the coupling step is achieved further variations of the substrates can be made to access other structural motifs. In addition, post functionalization of the desired products can be performed, e.g. with cytochrome P450 mutants or with electrochemical oxidation.

3 Asymmetric Suzuki–Miyaura Cross-coupling

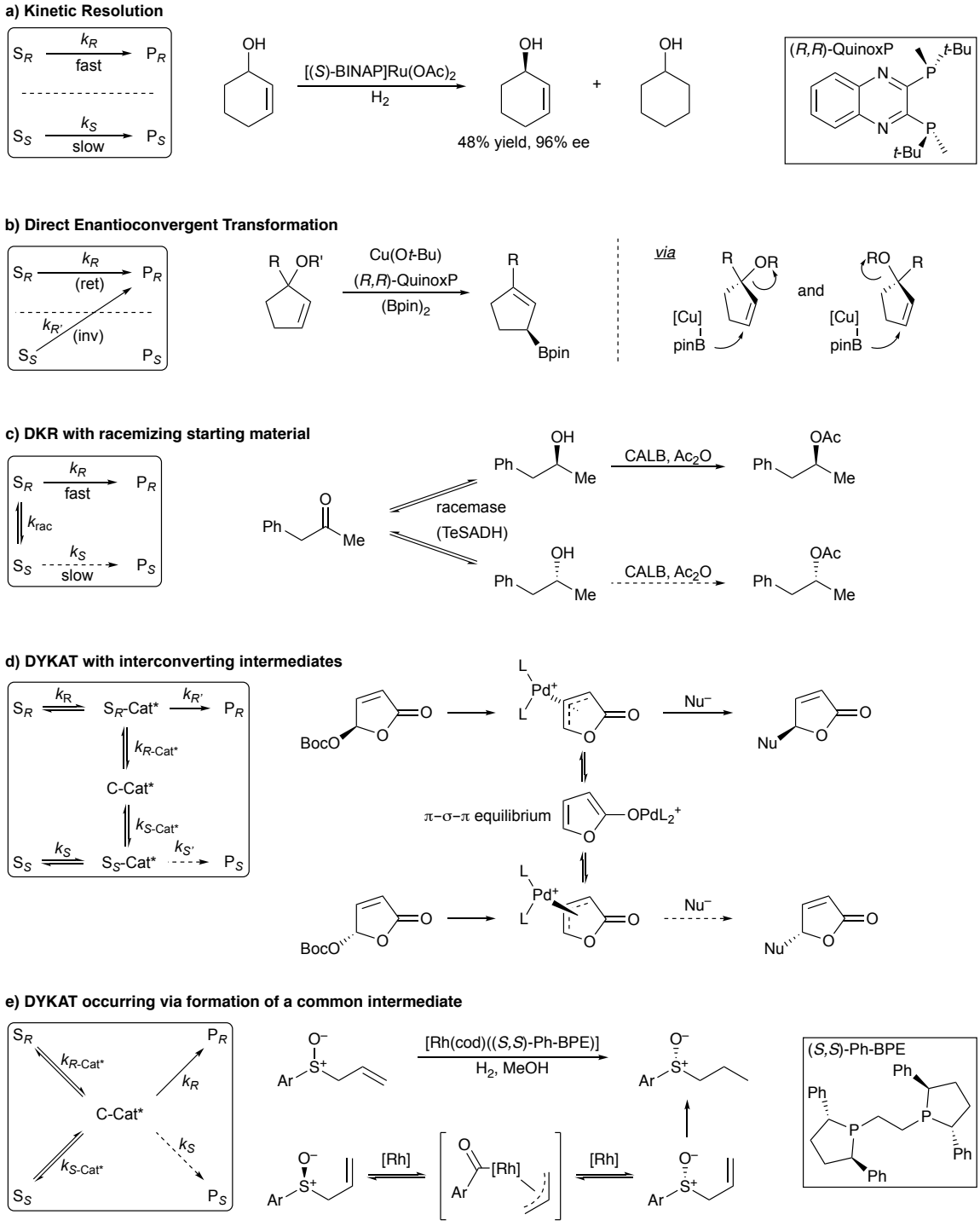
Sections of this chapter are published in *Nat. Commun.*[109] and in a Feature Article in *Chem. Commun.*[1].

3.1 Introduction

3.1.1 Resolutions, Kinetic Resolutions and Related Dynamic Processes

A classical way to obtain single enantiomeric products, still widely used today, is resolution of racemic mixtures. In a kinetic resolution one enantiomer of the starting material is transformed to product faster than the other, thus providing access to enantioenriched products, but with a maximum yield of 50% (Scheme 3.1a).[110,111]

Many efforts have been directed towards developing processes with over 50% yield in which both enantiomers are being transformed into a single stereoisomer.[112,113] Direct enantioconvergent transformations (DET) are fairly rare and presumably difficult to design processes where the two enantiomers of starting material follow separate mechanistic pathways to yield a common enantiomer of the product (Scheme 3.1b).[7,114,115] A more generally useful approach is to develop dynamic processes, where the starting material racemizes either during the reaction, or is recovered after the reaction, racemized and resubmitted to the reaction conditions, thus overcoming the 50% maximum yield problem. In a dynamic kinetic resolution (DKR) both enantiomers of the substrate interconvert *in situ* and $k_{rac} >> k_R >> k_S$ allowing one enantiomer to react faster than the other and a single product to be obtained (Scheme 3.1c).[7,114,116,117]



Scheme 3.1 Schematic representations and examples for kinetic resolutions and related processes.

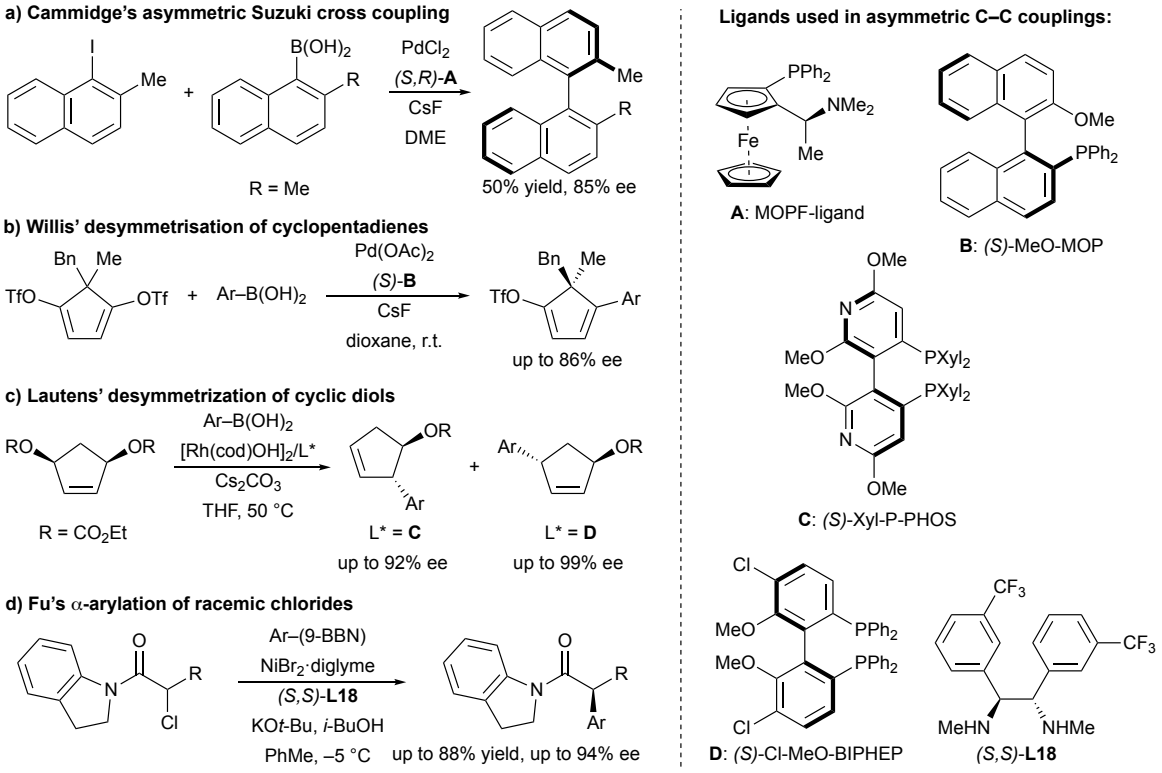
A related scenario is the dynamic kinetic asymmetric transformation (DYKAT) where there is no resolution, but both enantiomers of the starting material are converted into a single enantiomer product. These have been previously classified according to their mechanism. In a type I DYKAT the substrate reacts with a chiral catalyst to form a mixture of diastereomeric intermediates, one of which is favoured to give the product (Scheme 3.1d).[,118–120] In a DYKAT type II the catalyst

desymmetrizes the substrate to form an enantiomeric intermediate that preferentially affords one product (Scheme 3.1e).[121]

De-epimerisation reactions[7,114] and other de-racemization reactions, e.g. stereoablative transformations[122,123] are also known but not discussed here.

3.1.2 Asymmetric Cross-couplings

Since Suzuki and Miyaura reported the cross-coupling of Csp^2-hybridised boronic acids with aryl halides in 1979,[124] several strategies to achieve stereospecific Suzuki–Miyaura transformations have emerged.[125] Starting from either single enantiomer alkylboronic acids[126–130] or alkyl halides[131–133] enantioenriched cross-coupling products can be formed with high enantiomeric excess via processes exhibiting either stereo-retention or -inversion at the initial stereogenic centre.



Scheme 3.2 Asymmetric Suzuki–Miyaura coupling reactions.

In 2000, the synthesis of axially chiral biaryls via Pd-catalyzed coupling of boronic acids and aryl halides was reported independently by the Cammidge (Scheme 3.2a)[134] and Buchwald groups,[135] and many efforts have built upon these works to access atropisomeric products.[136,137]

Another asymmetric Suzuki–Miyaura strategy involves desymmetrization of meso compounds.[138] Willis reported asymmetric Pd-catalyzed reactions with bis-vinyltriflates featuring a prochiral quarternary centre (Scheme 3.2b).[139,140] Lautens has developed Rh-catalyzed asymmetric arylation of cyclopenten-1,4-diol derivatives (Scheme 3.2c),[141,142] as well as related desymmetrizations which ring-open oxabicyclic alkenes.[143,144]

More recently Fu and co-workers have reported a series of Ni-catalyzed alkylations and arylations of racemic alkyl halides using boranes (Scheme 3.2d),[145–147] as well as asymmetric decarboxylative Csp^3–Csp^2 cross-coupling by merging photoredox and nickel catalysis.[148]

3.1.3 Rh-catalyzed Asymmetric Allylic Arylation

Given the difficulty in developing an asymmetric addition using sp^2-hybridised zirconium nucleophiles our group considered the use of boronic acid nucleophiles. These have been extensively explored in enantioselective conjugate additions using Rh catalysts,[149] although the use of Rh in asymmetric allylic substitutions is far less known.[141–144,150–152] Suzuki–Miyaura couplings to synthesize enantioenriched compounds are known but most procedures involve enantiopure starting materials[125] or deracemization reactions,[138,141] though there are notable exceptions.[145,148] And it remains a long standing challenge to find methods to form Csp^2–Csp^3 that can serve as a useful synthetic tool in medicinal chemistry and drug-discovery.[153–155]

Our group tested numerous conditions for an enantioselective Suzuki–Miyaura reaction and after an extensive optimisation found that arylboronic acids can be added to racemic cyclic allyl halides using $[Rh(cod)OH]_2$ and *(S)*-Xyl-P-PHOS (Fig. 3.1).[156] Generally, highly enantioenriched products are obtained in excellent yields with both electron-deficient and -rich arylboronic acids. Later experiments revealed that different ligands could be used with similar levels of enantioselectivity and that allyl bromides can also be used.

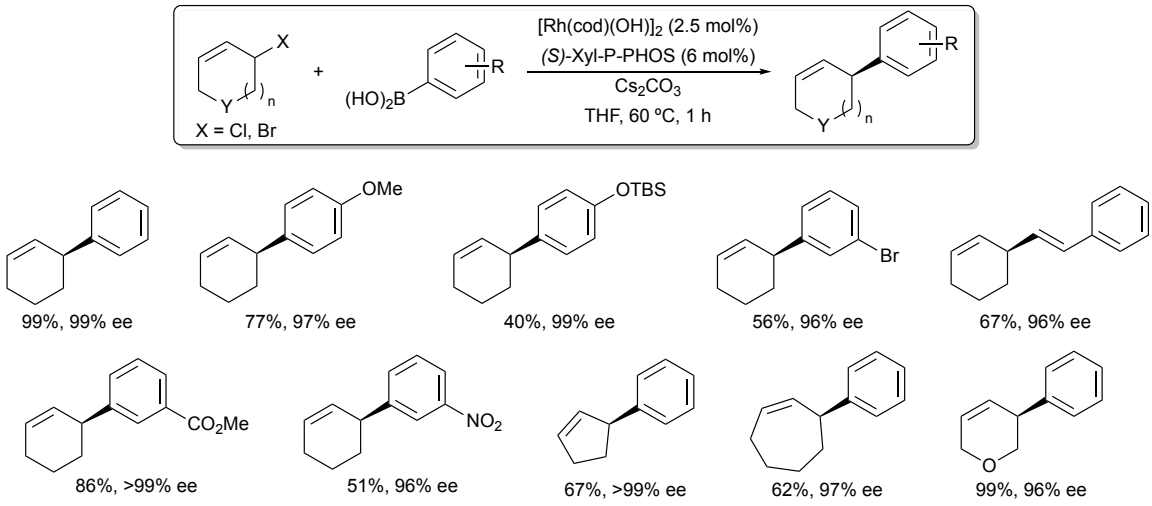


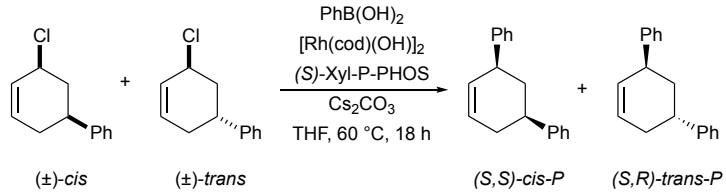
Figure 3.1 Selected examples for the Rh-catalyzed asymmetric allylic arylation of racemic allyl halides.

Different *cis*/*trans* mixtures of 5-phenyl substituted allyl chlorides were prepared and examined in order to determine the (Table 3.1). The performed experminent showed that in contrast to the stereoselectivity observed in the Cu(I)-catalyzed system, here a DYKAT mechanism occurs with overall inversion of configuration.

When using a 1:25 *cis*/*trans* ratio of diastereomeric starting materials, the *cis*-product is the major product in a 25:1 ratio. When the ratio of substrate is 1:5.3 in favour of *trans*, the *cis* product is again major with complete inversion.

When the *cis* starting material is in excess (6.1:1 ratio) the *trans* product is favoured although with a slightly altered (1:5.3) ratio. This latter reaction, when the reaction was stopped before completion (84% conversion) gave a lower ratio of 1:4.5, with recovered allyl chloride having a >50:1 ratio in favour of *cis*. These observations suggest that the *trans* allyl chloride reacts faster, and it is suggested that there is a partial *cis*-to-*trans* isomerization during the reaction.

Table 3.1 Stereoselectivity of allylic Arylation.



Entry	SM cis:trans	Conversion	Remaining SM *cis:trans*[a]	P *cis:trans*[a]	*cis*-P ee[b] (%)	*trans*-P ee[b] (%)
1	1:25	100	–	25:1	>99	98
2	1:5.3	100	–	5.3:1	>99	>99
3	6.1:1	100	–	1:5.3	98	>99
4[c]	6.1:1	84	>50:1	1:4.5	60	45 (89)

Conditions: 3-chloro-5-phenylcyclohex-1-ene (1.0 eq), benzeneboronic acid (2.0 eq), $[Rh(cod)(OH)]_2$ (2.5 mol%), *(S)*-Xyl-P-PHOS (6 mol%), Cs_2CO_3 (1.0 eq) in THF at 60 °C stirring for 18 h. *a*: Determined by ^{1}H-NMR spectroscopy. *b*: Determined by chiral HPLC. *c*: Reaction stopped after 3 h.

These results encouraged our group to explore more challenging coupling partners.[109] The asymmetric Suzuki–Miyaura coupling proved extremely robust and we found that a number of bidentate phosphine ligands can be employed with comparable results. BINAP – and in some cases Xyl-P-PHOS – is generally the best ligand for the majority of transformations involving vinyl- and *β*-styrenylboronic acids (Fig. 3.2).

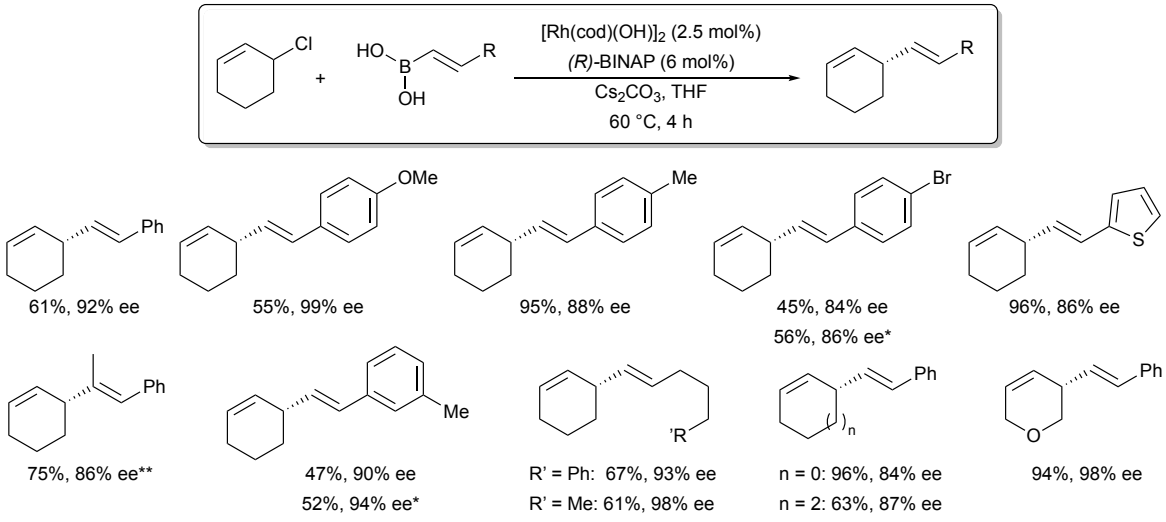
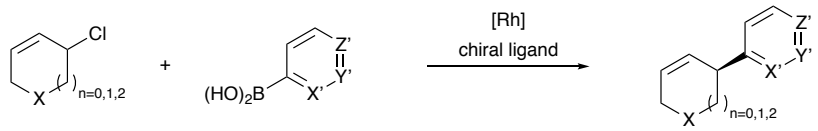


Figure 3.2 Asymmetric Suzuki–Miyaura coupling with a variety of vinylboronic acids. *In these experiments Xyl-P-PHOS was used instead of BINAP. ** Reaction performed at room temperature over two days.

3.2 Project Aims

The results of the asymmetric Suzuki–Miyaura coupling with benzeneboronic acids and vinylboronic acids was encouraging enough to investigate other important chemical motifs. In particular, despite their vital role in biologically active molecules, there is a lack of generally useful ways to prepare enantiopure heterocycles.[5,157,158] Heteroarylboronic acids are challenging substrates regarding their synthesis and use in coupling reactions.[159] Rhodium has been found to be promising for the coupling reaction with benzeneboronic acids and might also be used for the coupling with heterocycles or other more stable nucleophiles, such as boronic esters.

This project involves the application of the developed Suzuki–Miyaura coupling to heteroarylboronic acids. Different coupling partners will be examined which are expected to require optimisation of the reaction conditions. Protected boronic acids might prove to be a better choice when the free boronic acid is not stable under optimised conditions.



Scheme 3.3 General reaction scheme for the asymmetric Suzuki–Miyaura coupling with heterocycles.

We further aim to use heteroarylboronic acids with different functional groups that allow further transformations and might provide access to medicinal relevant compounds and new structural motifs.

3.3 Results and Discussion

3.3.1 Protected Boronic Acids

Our first aim was to establish whether the coupling reaction of 3-chlorocyclohexene could be performed with protected boronic acids (Figure 3.3). Compared to the coupling product with the free benzeneboronic acid (45%, 99% ee, Lit.: 99%, 99% ee)[156] limitations were observed when boronic acid derivatives were applied. Pinacol and 1,2-propanediol esters **29** and **30** provided the product under these conditions in somewhat low yield and decreased enantioselectivity in contrast to neopentyl ester **31**, MIDA ester **32** and trifluoroborate salt **33**, where the starting material remained unreacted.

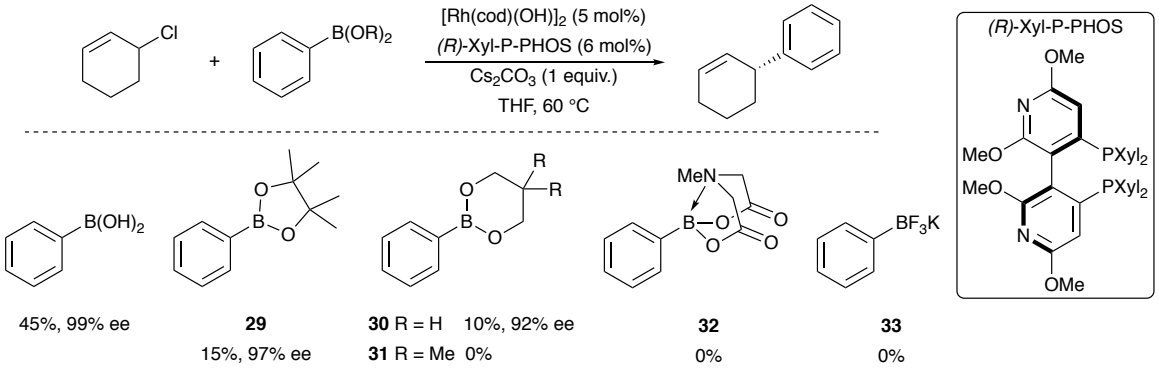


Figure 3.3 Asymmetric coupling with (protected) phenylboronic acids.

We assume that the free boronic acid plays an important role under our conditions and in the first step of the mechanistic cycle (Fig. 3.4). The active catalyst Rh–OH undergoes transmetalation and boric acid $B(OH)_3$ is released. After oxidative addition of the allyl chloride the Rh^{III}-intermediate is generated, which is in equilibrium with its diastereomeric isomer, probably via a suprafacial 1,3-isomerisation, suggesting to a DYKAT type I like mechanism. Upon reductive elimination the favoured stereoisomer of the product is formed. We assume that the additional caesium carbonate as a base regenerates not only the active catalytic species Rh–OH but also prevents the drop of the pH due to the formation of $B(OH)_3$.

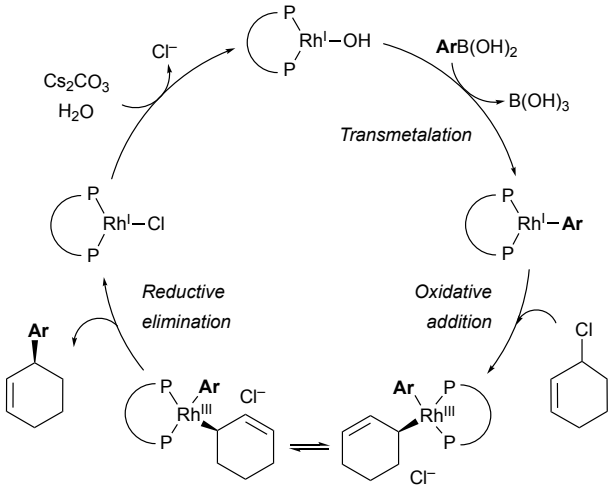


Figure 3.4 Proposed mechanism for the asymmetric allylic arylation of racemic allyl chlorides.

3.3.2 Application to O-, S- and N-Heteroaromatics

Heteroaryl boronic acids are often problematic due to rapid protodeboronation.[160,161] Using commercially available heteroarylboronic acids with previously reported conditions[156] we were pleased to see the majority worked with good results (Fig. 3.5).

From the range of *O*-heteraromatics, benzofuranylboronic acid **36** performed well under the shown conditions. In some cases the use of allyl bromide was superior to allyl chloride (**38**, **39**). In addition to (benzyl)thiophene boronic acids **39**–**43** we found that boronic acids of *N*-protected pyrrole **44**, indole **45** and indazole **46** are moderate coupling partners. Coupling products from furanyl- (**34**, **35)** or pyridinylboronic acids could not be observed in most cases under the current set of conditions. We generally observed the formation of the unfunctionalized heterocycle due to protodeboronation. Unfortunately, larger heterocyclic structures, such as dibenzofuranylboronic acid, gave inseparable mixtures of product and the heterocyclic by-product. Many attempts to separate this mixture, e.g. via chromatographic methods or trituration, remained unsuccessful. Overall, the majority of heteroarylboronic acids were good coupling partners under the current reaction conditions and we obtained a variety of coupling products with high enantioselectivities but low yields.

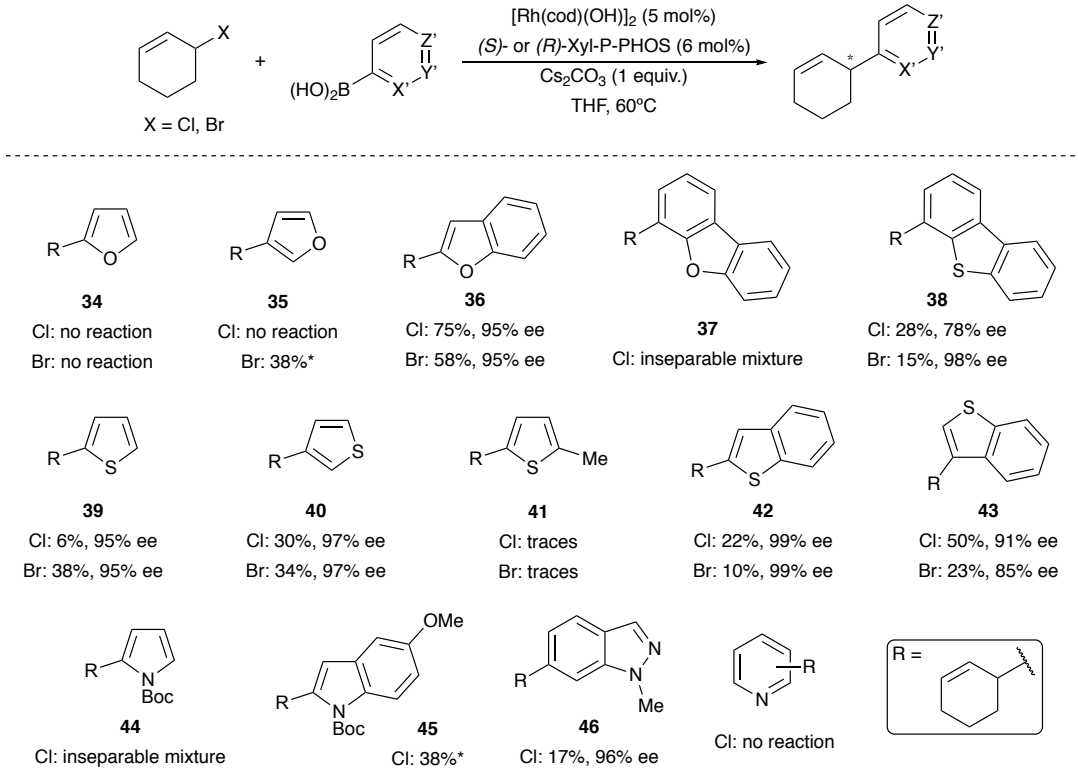


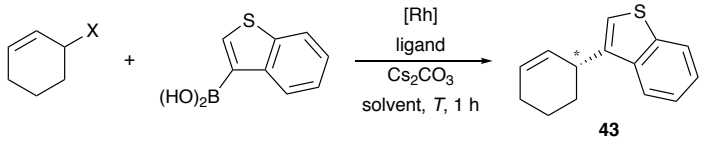
Figure 3.5 Exploration of the scope with commercially available heteroarylboronic acids under previously reported conditions. *Enantiomeric excess could not be determined.

We observed that one of the lowest enantioselectivities was found with using 3-benzo-[*b*]-thienylboronic acid **43** (<91% ee). In addition, benzo-[*b*]-thiophene was a common by-product which could never be completely removed from the desired product.

With the aim of improving this particular result, and ideally finding a more generally useful procedure that could be applied to a broad variety of heteroaryl boronic acids we further optimised the reaction, starting with 3-benzo-[*b*]-thienylboronic acid (Table 3.2). Higher temperatures and greater excess of boronic acid successfully improved the results and the best combination involved three equivalents of heteroarylboronic acid, BINAP as ligand, and THF at reflux (Table 3.2, entry 16). In some cases we obtained **43** with high ee's (>96%) albeit low yields (entries 7, 10, 11-14). Allyl bromide seemed to perform equally well compare to allyl chloride at higher temperatures but no obvious trend regarding yield and enantioselectivity could be observed. Performing the reaction at room temperature for 1 h gave only traces of product (entry 17).

However, in all cases we observed formation of the heterocyclic by-product benzo-[*b*]-thiophene, which prevented a full characterisation of the product.

Table 3.2 Optimisation table for the arylation with 3-benzo-[*b*]-thienylboronic acid.



43

Entry	X	L*	Rh(I)	Solvent	*T* [°C]	Yield % (%ee)
1	Cl	*(R)*-Xyl-P-PHOS	$[Rh(cod)(OH)]_2$	THF	60	17 (84)
2[a]	Cl	*(S)*-Xyl-P-PHOS	$[Rh(cod)(OH)]_2$	THF	60	50 (–91)
3	Br	*(S)*-Xyl-P-PHOS	$[Rh(cod)(OH)]_2$	THF	60	23 (–85)
4	Cl	*(R)*-BINAP	$[Rh(cod)(OH)]_2$	THF	60	45 (89)
5	Cl	*(R)*-BINAP	$Rh(acac)(C_2H_4)_2$	THF	60	16 (75)
6	Br	*(R)*-BINAP	$[Rh(cod)(OH)]_2$	THF	60	32 (93)
7	Br	*(R)*-BINAP	$Rh(acac)(C_2H_4)_2$	THF	60	35 (97)
8[b]	Br	*(R)*-BINAP	$Rh(acac)(C_2H_4)_2$	THF	60	>30 (95)
9	Br	*(R)*-BINAP	$Rh(acac)(C_2H_4)_2$	THF	reflux	60 (95)
10	Br	*(R)*-BINAP	$Rh(acac)(C_2H_4)_2$	dioxane	80	29 (97)
11	Br	*(R)*-BINAP	$Rh(acac)(C_2H_4)_2$	dioxane	reflux	60 (87)
12[c]	Cl	*(R)*-BINAP	$[Rh(cod)(OH)]_2$	THF	reflux	53 (97)
13[c]	Cl	*(R)*-BINAP	$[Rh(cod)(OH)]_2$	dioxane	80	56 (98)
14[c]	Cl	*(R)*-BINAP	$[Rh(cod)(OH)]_2$	dioxane	reflux	31 (96)
15[c,d]	Cl	*(R)*-BINAP	$[Rh(cod)(OH)]_2$	dioxane	80	40 (92)
16[c,d]	Cl	*(R)*-BINAP	$[Rh(cod)(OH)]_2$	THF	reflux	<80 (94)
17	Cl	*(R)*-BINAP	$[Rh(cod)(OH)]_2$	THF	r.t.	traces

Conditions: substrate (1.0 equiv.), boronic acid (2.0 equiv.), [Rh] (5 mol% Rh), ligand (6 mol%); *a*: 4 equiv. of boronic acids were used; *b*: aqueous reaction work-up; *c*: reaction time 2 h; *d*: 3 equiv. of boronic acid were used.

We were pleased to see that the reaction could be improved. Having these results in hand we looked again at the scope of the reaction (Fig. 3.6)[†]. The optimised conditions provided good results regarding yield and enantioselectivity for a number of heterocyclic products. *N*-Boc

[†] These compounds were tested against cancer cell lines MCF-7 and H460. No activity was observed.

protected pyrrole **44** had to be deprotected in order to achieve good separation from its protodeboronated by-product (Table 3.3).

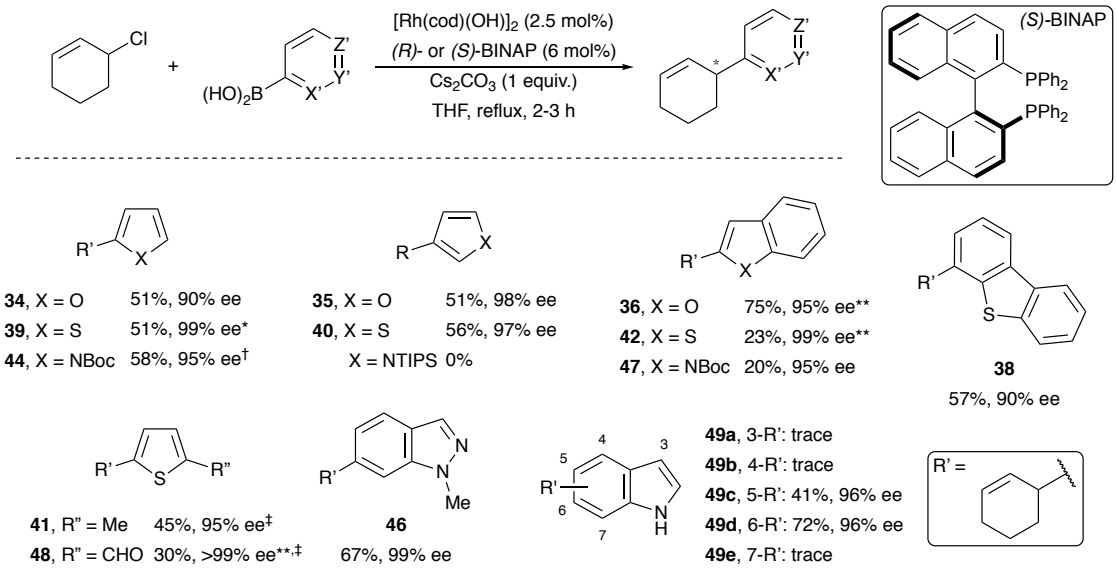
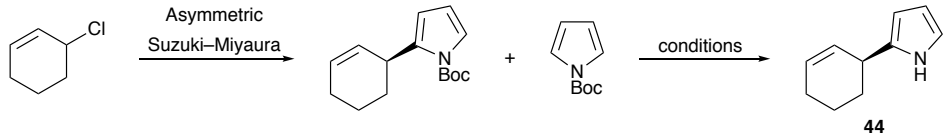


Figure 3.6 Scope of the asymmetric Suzuki-Miyaura coupling with the optimised conditions for heteroarylboronic acids. *3-bromocyclohexene was used as electrophile; **Xyl-P-PHOS was used instead of BINAP; †after deprotection; ‡Reaction was performed overnight at room temperature.

From a variety of the deprotection methods, i.e. TBAF,[162] AcOH, iodine,[163] NaOMe,[164] we found K_2CO_3 in MeOH (entry 5) to be most suitable and the 2-substituted free pyrrole was obtained in 58% over two steps.

Table 3.3 Attempts for *N*-Boc deprotection of pyrrole to afford **44** with yields given over two steps.



Entry	Reagent	Solvent	*T* [°C]	Yield %
1	NaOMe	MeOH	r.t.	traces
2	CH_3COCl	MeOH	r.t.	0%
3	I_2	CH_2Cl_2	r.t.	0%
4	TBAF	THF	60	traces
5	K_2CO_3	MeOH	60	58%

Initially we observed poor results for 5-substituted thienylboronic acids **41** and **48** but we were able to achieve reasonable yields by performing the reaction at room temperature overnight.

We also attempted the coupling reaction of several substituted indolylboronic acids. Only the boronic acids in 5- and 6-position **49c,d** gave satisfying results. 4-Substituted indole **49b** provided only small amounts of product, likely due to competitive protodeboronation. Indol-7-ylboronic acid[165] **49e** and *N*-TBS[166] (or *N*-SO_2Ph[167]) protected indol-3-ylboronic acid **49a** had to be synthesised but also performed poorly under the reaction conditions.

The use of the other commercially available *N*-heteroarylboronic acids shown in Fig 3.7 were unsuccessful, allyl chloride remained unreacted.

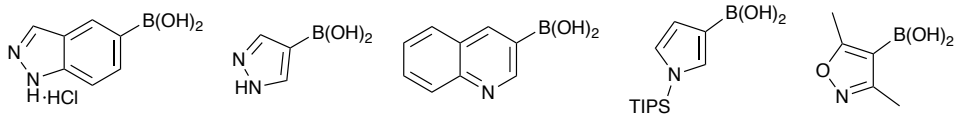


Figure 3.7 *N*-Heteroarylboronic acids that did not perform the asymmetric Suzuki–Miyaura reactions under the optimised conditions.

In addition, we successfully employed a variety of different electrophiles using heterocyclic boronic acids (Fig. 3.8)‡. Optimised conditions found for 3-chlorocyclohexene were less applicable for seven membered rings. Purification of dibenzofuran and benzo-[*b*]-thiophene coupled products was problematic with allyl chloride (**37**, **43**) but could be easily separated from protodeboronated heterocycle when coupled with 3-chloro-3,6-dihydro-2*H*-pyran to give **52** and **55**, despite low yields.

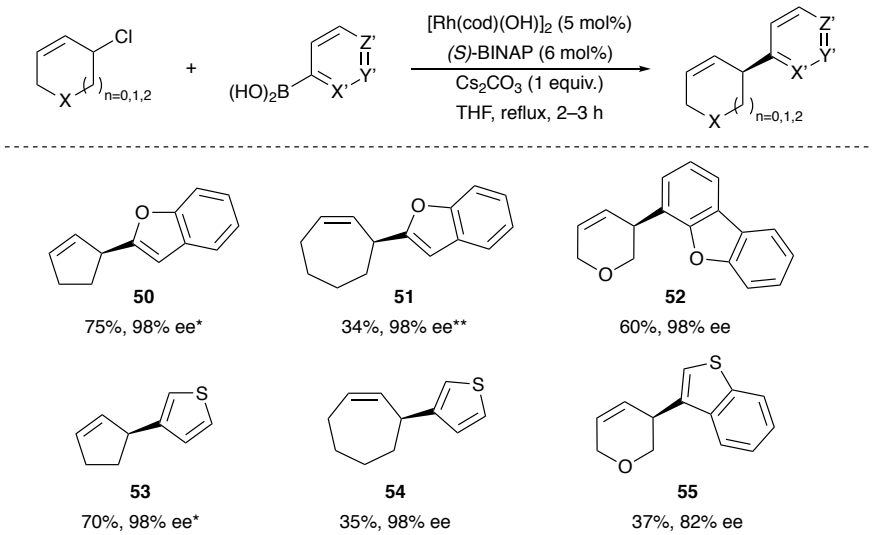


Figure 3.8 Asymmetric Suzuki–Miyaura coupling with different cyclic electrophiles. *In these experiments 5 mol% $[Rh(cod)(OH)]_2$ and 12 mol% ligand was used and the reaction stirred for four hours at reflux while protected from light; **Xyl-P-PHOS was used instead of BINAP.

‡ These compounds were tested against cancer cell lines MCF-7 and H460. No activity was observed.

3.3.3 Pyridinylboronic Acids

One of the most important heterocycles in catalysis, drugs and other bioactive compounds are pyridines and its derivatives.[157] When pyridinylboronic acids were applied to our system no product was observed. Extensive studies were performed by using either different conditions, e.g. additional water, and/or pyridinylboronates, but remained unsuccessful (Fig. 3.9).

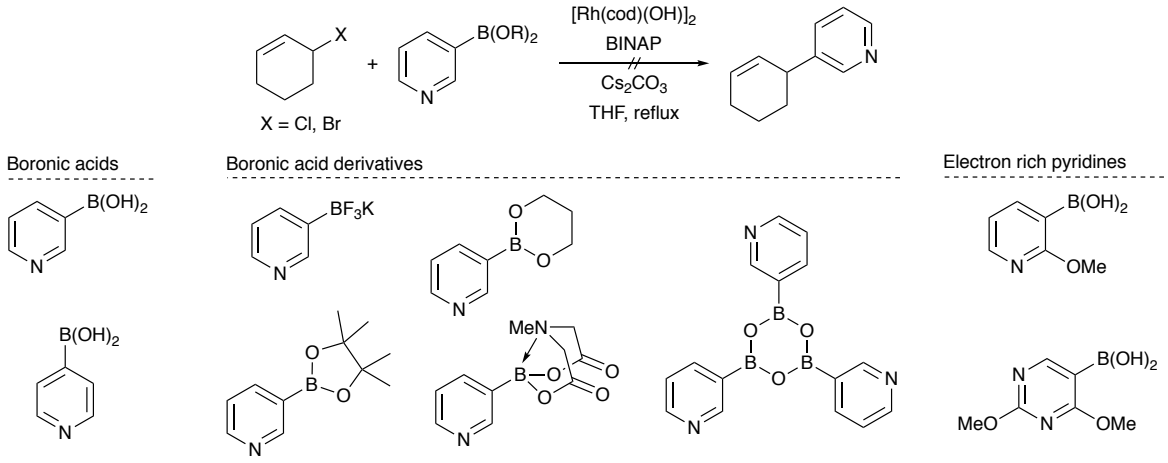


Figure 3.9 Reaction screening with shown pyridinylboronic acids and derivatives were unsuccessful.

Stability and reactivity problems are known with these substrates and changing the electronic properties can sometimes overcome issues.[168] The application of electron rich pyridines failed but we were pleased to see that 2-chloro and 2-fluoropyridines provided the desired product in only moderate yields (50-60%) but excellent enantioselectivities (99% ee) (Fig. 3.10)[§]. All regioisomers of the 2-chloropyridine **56a–d** were obtained with overall high enantioselectivities (>97%). Dihydropyran **58** was successfully coupled under the present conditions but other ring sizes **59–62** only gave low yields (<30%) and moderate stereoselectivity (80–85% ee), depending on the heterocycle.

[§] These compounds were tested against cancer cell lines MCF-7 and H460. No activity was observed.

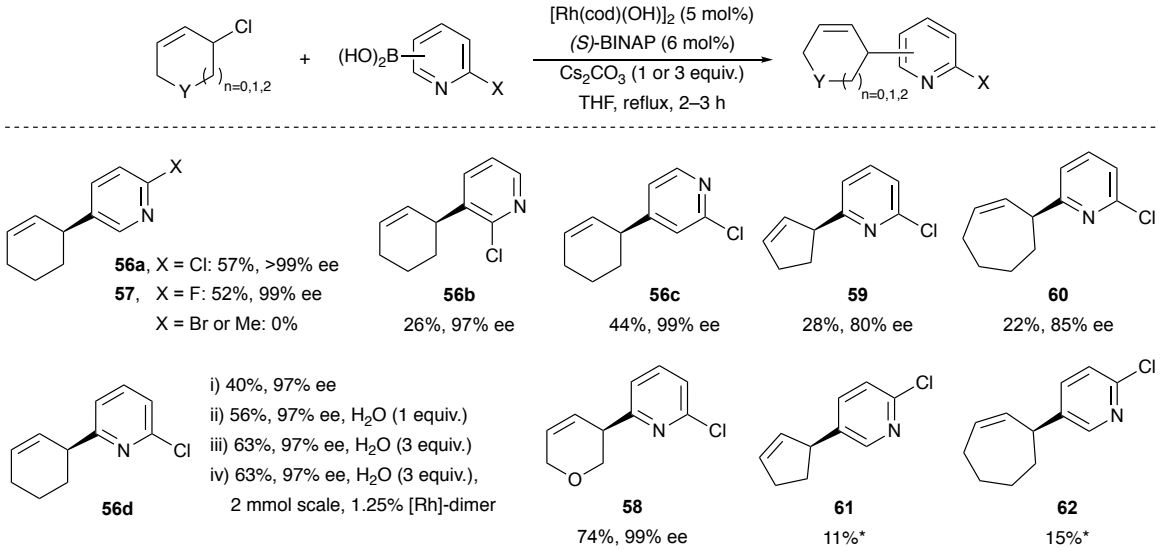
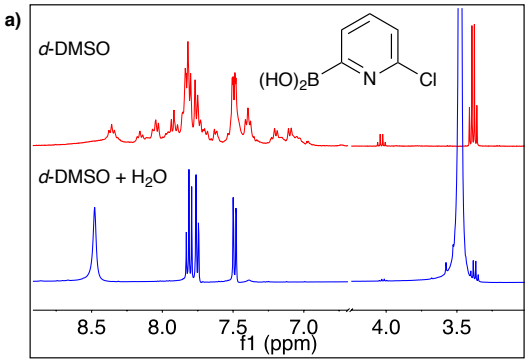


Figure 3.10 Asymmetric Suzuki–Miyaura coupling with 2-halopyridinylboronic acids; *For this product enantiomeric excess was not determined.

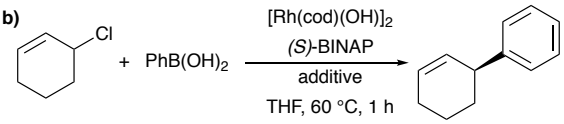
We chose **56d** as a substrate for further modifications and decided to synthesize 6-chloropyridin-2-ylboronic acid. Both repeating the asymmetric coupling and performing the scale up reaction on a 2 mmol scale gave variable results. We further investigated this problem and found that additional water (3 equiv.) increased the yield from 40% to a reproducible 63% without compromising enantioselectivity compared to dry conditions.

^{1}H-NMR spectroscopy studies suggest that the synthesised boronic acid forms a mixture of aggregates (Fig. 3.11a). Additional water may not only break up the aggregates and releases the free boronic acid but also help to regenerate the active Rh–OH species (see Fig. 3.4). Applying this finding to other heterocyclic coupling products with poor results did not achieve improvement.

We also tried to understand the failure of the pyridinylboronic acids (Fig 3.11b). By performing the asymmetric coupling of allyl chloride with benzeneboronic acid under standard conditions without further additives the product was obtained in 35% and 99% ee. The addition of pyridine completely inhibits the reaction, whereas additional 2-chloropyridine does not seem to influence the reaction and provides the coupling product with similar results compare to the unaltered reaction. 3-Chloropyridine only gives the product in 5% and lower ee and additives that might prevent the interaction of pyridine through coordination did not succeed. These results suggest that with both increased electron density and pK_a (2-Cl-py ~ 0.7, 3-Cl-py ~ 2.8 and py ~ 5.2)[169] the lone pair of the nitrogen interferes with rhodium and ultimately interrupts the catalytic cycle.



b)



Additive (2 equiv.)		Yield %	(% ee)
none		35	(99)
	R = H	0	–
	R = 2-Cl	48	(99)
	R = 3-Cl	5	(92)
	R = H, $CuSO_4$	0	–
	R = H, $BF_3{\cdot}Et_2O$	0	–

Figure 3.11 a) ^{1}H-NMR spectra of 6-chloropyridin-2-ylboronic acid in dry and wet *d*-DMSO; b) Reaction performance under standard conditions with different pyridines added.

3.3.4 Cross-coupling with Piperidenes

During these studies Thomas Palacin investigated aliphatic *N*-heterocyclic piperidene as suitable coupling partner. Piperidine and its derivatives are privileged structural motifs in bioactive compounds and drugs.[170] Cross-coupling reactions for the synthesis of chiral (dehydro)piperidine products are rare and relevant examples are either limited to the α-position or enantiospecific couplings.[171,172] The extension of the asymmetric Suzuki–Miyaura towards 5-substituted piperidenes **63**–**68** has been successfully achieved with slight alterations of the reaction conditions and using Cl-MeO-BIPHEP as ligand (Fig. 3.12).** Coupling products with aryl- and vinylboronic acids were obtained with overall high yields and enantioselectivities.[109]

Generally a variety of heterocyclic boronic acids were suitable coupling partners but *N*-Boc-pyrrole **69** did perform poorly. Trying to optimise the results failed for this product mainly due to incomplete conversion of the piperidene allyl chloride. Even though extensive screening was performed, i.e. longer reaction times, higher catalyst loading, using a microwave heating set at 80 °C, more equivalents of boronic acid etc., bisprotected pyrrolylpiperidene could only be obtained in 17% yield. The results for the coupling reaction with 2-chloropyridine **70** were again less reproducible, in this case highly depending on the water content from 40%, 95% ee (1 equiv. H_2O) to 59% yield and 90% ee (5 equiv. H_2O).

** Reactions and optimisation were performed by Thomas Palacin.

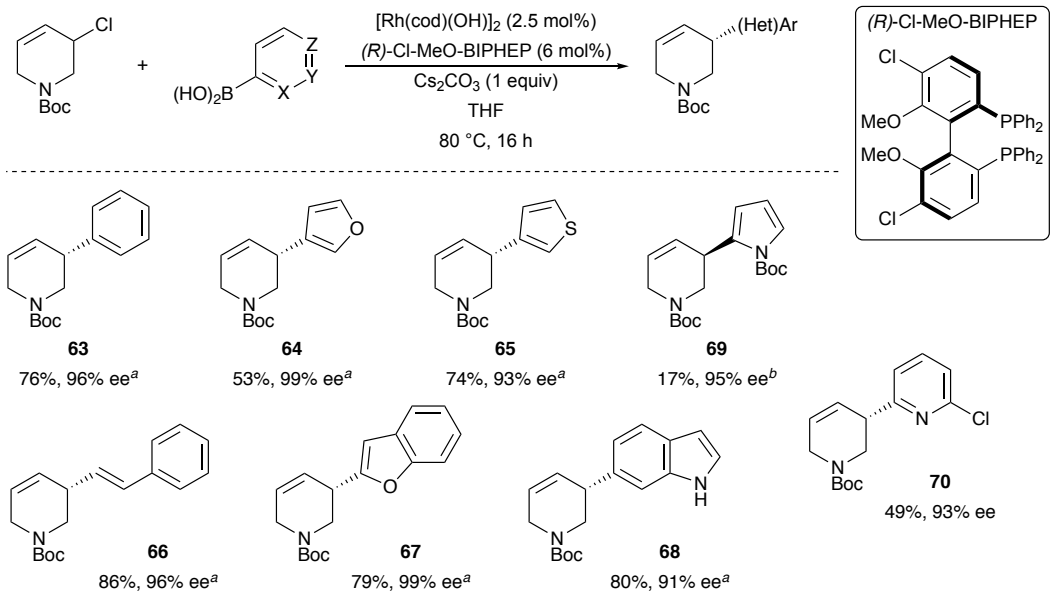


Figure 3.12 Extension of asymmetric Suzuki–Miyaura coupling towards piperidenes; *a*: Experiments performed by Thomas Palacin and Mireia Sidera; *b*: In this experiment *(S)*-BINAP was used instead of *(R)*-Cl-MeO-BIPHEP.

3.3.5 Further Synthetic Transformations and Synthesis of a Natural Product

Having explored the chemical scope of the asymmetric transformation we were trying to further demonstrate the synthetic potential of the coupling products. 2-Chloropyridines, which were essential for the successful coupling with cyclic allyl chlorides, can undergo diverse transformation reactions (Scheme 3.4).

(a) When **56a** was subjected to Buchwald–Hartwig conditions the oxazolidinone product **71** was obtained with 53% yield. Stoichiometric amounts of copper were necessary in order to achieve a reasonable conversion of **56a**.

(b) The Pd-catalyzed Suzuki–Miyaura cross-coupling with benzene boronic acid gave **72** in 68% yield while maintaining the ee.

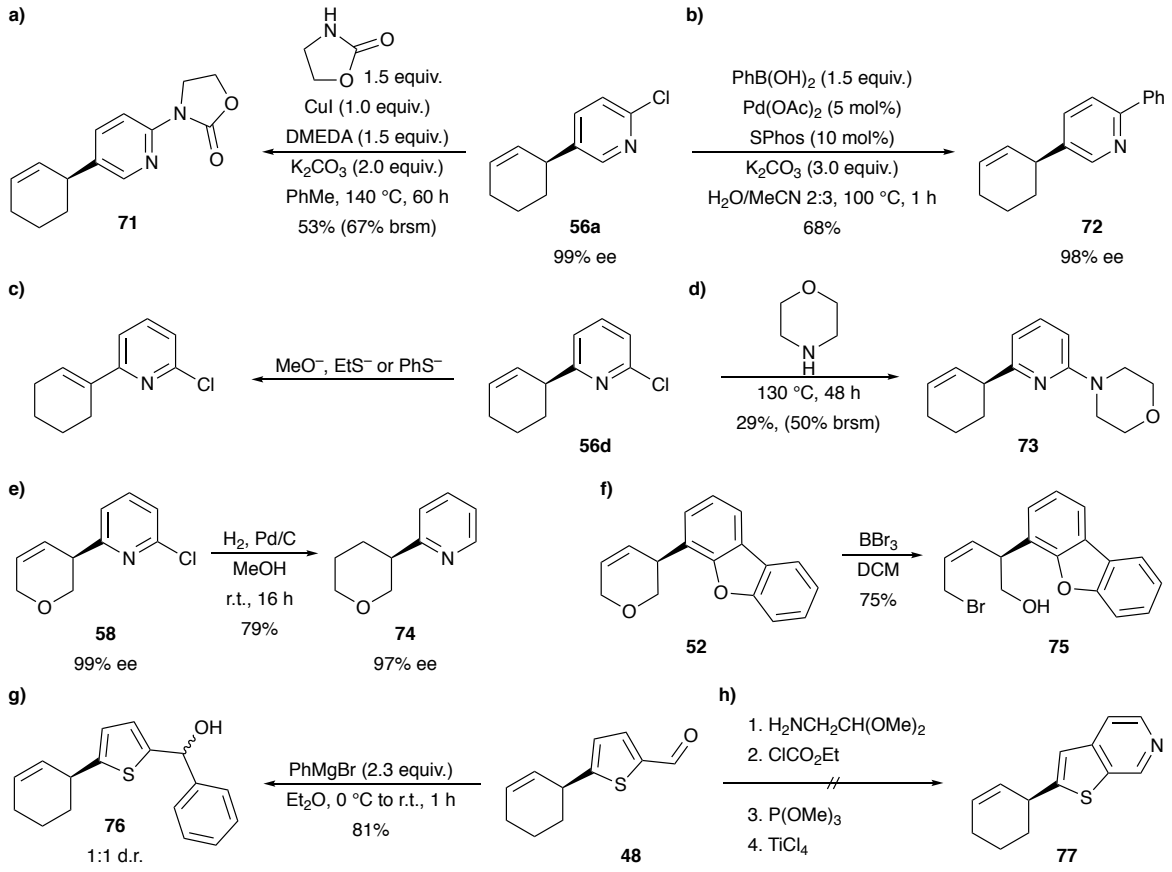
(c) Using **56d** for further transformations was more problematic. The proton in both benzylic and allylic position is acidic enough that subjecting **56d** to slightly basic conditions resulted in the loss of the stereocenter due to isomerisation of the starting material.

(d) Nucleophilic aromatic substitution with morpholine was achieved in 29% albeit incomplete conversion.

(e) Concomitant reduction of the dihydropyran and dechlorination of the pyridine unit led to **74** using H_2 and Pd/C, with a slight loss of ee. This can be a result of impurities of Pd^{II} which catalyses the isomerisation of the double bond[173] prior to reduction.

(f) We also attempted to perform ring opening of 3,6-dihydro-2*H*-pyrane **58** with BBr_3 but starting material decomposed under these conditions. However, we were pleased to see that **52** performed well and provided **75** in 75% yield.

(g) The Grignard addition to thienylcarbaldehyde **48** led to alcohol **76** in a 1:1 diastereomeric mixture.



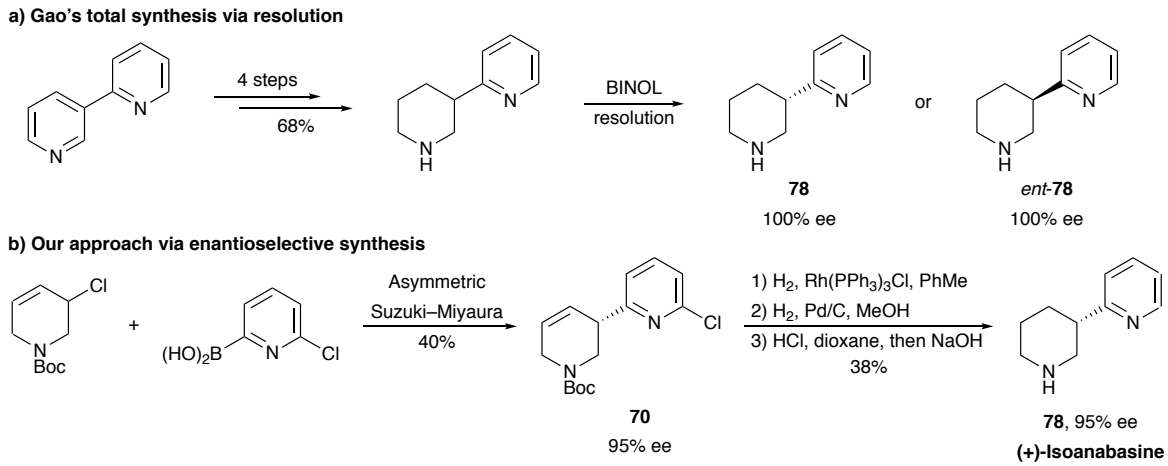
Scheme 3.4 Cross coupling reactions and functional group interconversions.

(h) In addition, we chose **48** as a suitable candidate for the synthesis of more challenging heteroaromatic structures such as thieno[2,3-*c*]pyridines.[174] Unfortunately, subjecting **48** to the

Hendrickson variation of the Pomeranz–Fritsch reaction to failed to give cyclohexenyl substituted heterocycle **77**.

We further attempted the enantioselective total synthesis of the natural product (+)-isoanabasine. Isoanabasine is found in *Anabasis aphylla* L. and is a structural isomer of the tobacco alkaloid anabasine. These pyridyl piperidines have therapeutic potential due to their activity as nicotinic acetylcholine receptors (AChRs).[175] To our knowledge, the only asymmetric synthesis of isoanabasine was achieved by hydrogenation of a 2,3'-bipyridine and multiple resolutions with stoichiometric BINOL to generate both enantiomers of isoanabasine **78** and *ent*-**78** (Scheme 3.5a).[176,177]

The asymmetric coupling product, and precursor of isoanabasine, was formed with good results (40%, 95% ee). Initial attempts to reduce both the double bond and the 2-chloride with Pd/C resulted in depletion of the ee due to the reactivity of the allyl group in the presence of Pd^{II} impurities. However, stepwise reduction, first of the double bond with first Wilkinson's catalyst then with Pd/C succeeded. Without further purification Boc protecting group was removed under acidic conditions providing (+)-isonanabasine **78** with 15% yield and 95% ee over 4 steps (Scheme 3.5b).



Scheme 3.5 Asymmetric syntheses of the natural product isoanabasine.

3.4 Summary

In this work we were able to apply the asymmetric Suzuki–Miyaura coupling to a variety of heteroarylboronic acids. Initial attempts to apply the reaction to protected boronic acids gave poor results. However, free boronic acids of *O*-, *S*- and *N*-heterocycles were coupled to cyclic allyl chlorides with good yields and high enantioselectivities (>90%). After optimisation, many commercially available heterocycles were found to be suitable coupling partners. A number of nitrogen rich heteroaromatics as well as pyridine were unsuccessful.

We found electron-deficient pyridines, i.e. 2-halopyridines, were able to afford the desired coupling products in good yield and excellent enantioselectivities. The 2-chloro substituent not only allowed further transformations but could also be used to formally introduce a pyridine moiety when reduced with Pd/C. The coupling with *N*-Boc protected piperidene afforded the first asymmetric synthesis of the natural product (+)-isoanabasine.

During the studies with (hetero)arylboronic acids and piperidenes Thomas Palacin and Mireia Sidera performed asymmetric syntheses of the drugs preclamol and niraparib.[109]

We showed that water can influence the quality of the asymmetric coupling reaction in terms of both yield and enantioselectivity. This is not yet fully understood and gaining insight into the mechanism with spectroscopic methods might provide a better understanding about active catalytic species and the role of additives in the reaction.

In addition, we explored symmetric cyclic allyl chlorides that contain heteroatoms. Studies on the regioselectivity of the asymmetric Suzuki–Miyaura coupling should certainly further explored with the goal of allowing highly enantioselective coupling to non-symmetrical and acyclic substrates in order to get access to new structural motifs.

4 Asymmetric Hiyama Cross-coupling

4.1 Introduction

4.1.1 Silicon – An Alternative to Boron

In the previous chapter we highlighted the important role of the Suzuki–Miyaura reaction as a one of the most ubiquitous C–C coupling reaction in natural product syntheses and the R&D sector (see previous chapter).[178] However, boronic acids are often associated with stability issues due to undesired aggregation or protodeboronation. Organoboranes and boronate esters provide better stability and are also suitable coupling partners although they are less reactive.[179] In addition, a recent study reveals the possible genotoxicity of a variety of boronic acids and its precursors based on the Ames test, supported by computational data.[180] The lability and toxicity of boron compounds can sometimes be problematic for application purposes and hence alternative coupling partners such as organosilicon reagents have been investigated.[181–184]

Silicon is the second most abundant element of the earth crust and silicon compounds are generally considered environmentally benign, non-toxic stable and easy to handle. Chemists made use of silicon a few decades ago and nowadays organosilicon species are versatile and valuable compounds that find use in material science, e.g. as polysilanes, polysiloxanes (silicones), etc., as well as in organic and organometallic chemistry.[185] In the field of organometallic chemistry the use of organosilicon species can enable a variety of cross-coupling reactions and asymmetric addition reactions and therefore provide a valuable alternative to boronic acids and other organometallics.[184] Their advantages include stability and availability, which makes them suitable groups to carry through a reaction compared to boron or tin, but they usually need to be activated by bases or fluoride sources.[186]

4.1.2 Silicon in Cross-coupling Reactions

The most prominent reaction amongst silicon-based cross-couplings is the Hiyama coupling. In this Pd-catalyzed reaction aryl (or vinyl) halides and aryl (or vinyl) silanes form a Csp^2–Csp^2 bond (Fig. 4.1). The mechanism of this coupling shows similarity to the Suzuki–Miyaura coupling. First the halide undergoes an oxidative addition to palladium, which then transmetalates with the activated hypervalent silane. The product is released upon reductive elimination and Pd^0–L_2 is regenerated.

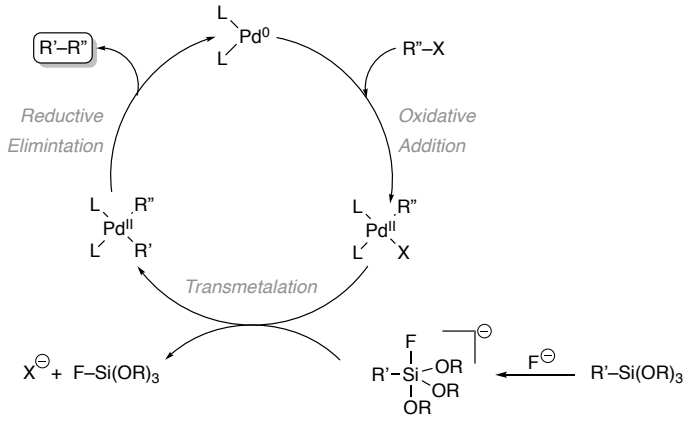
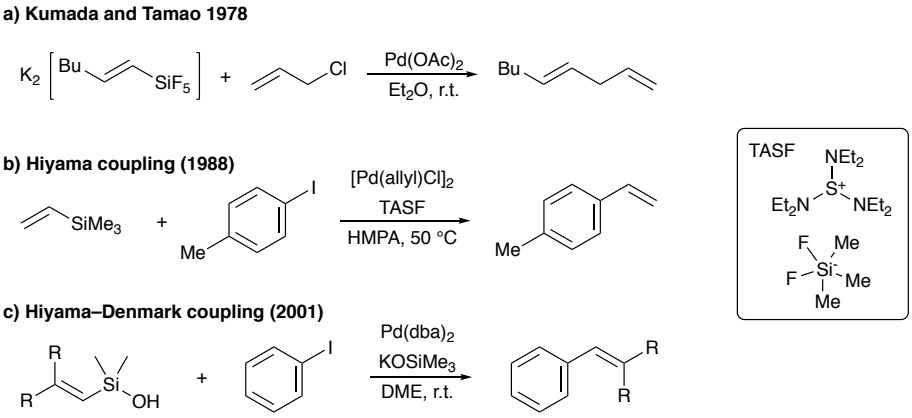


Figure 4.1 General mechanism for the Hiyama coupling with siloxanes.

Early work on the reactivity of organosilanes by Kumada and Tamao in 1978 showed that hexavalent pentafluoro(vinyl)silanes can be coupled with allylic chlorides in the presence of palladium (Scheme 4.1a).[187] It was not until a decade later that Hiyama reported the Pd-catalyzed cross-coupling of trialkyl(vinyl)silanes with aryl iodides (Scheme 4.1b).[188] In this case the silane is activated by tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) which acts as a fluoride source. Despite the success of the Hiyama-coupling the widespread use of this method is hindered by the need of fluoride sources, which precludes synthetic transformations of molecules that bear other silanes or silyl ether protecting groups. Another problem with F^- sources, such as tetrabutylammonium fluoride (TBAF), is the amount of water that comes with it. Even though anhydrous TBAF can be prepared,[189] commercial sources (solution in THF or solid hydrate) are usually the reagents of choice. Furthermore, the water in TBAF generates a basic solution that can be neutralized with acetic acid, but exact quantities are needed for this.[190] Alternative fluoride sources such as HF·pyridine, TASF or tetrabutylammonium triphenyldifluorosilicate (TBAT) can be corrosive or need to be prepared freshly which limits use in large-scale applications.

Other modes of activation have been investigated since and silanols (R–$SiMe_2OH$) were reported as suitable coupling partners, originally in the presence of silver(I) oxide[191,192] or TBAF[193] as activating agents. Denmark reported a Pd-catalyzed fluoride free cross-coupling reaction shortly after (Scheme 4.1c).[194] This kind of cross-coupling – known as Hiyama–Denmark coupling – uses Brønsted bases as activating agents and hence provides an attractive alternative to fluoride activation.

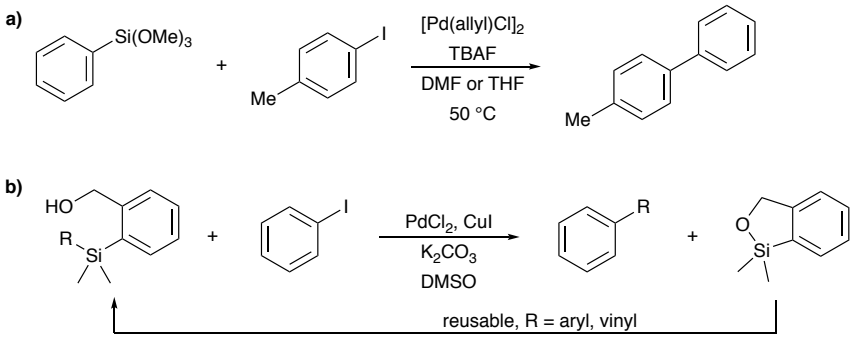


Scheme 4.1 Development of the Pd-catalyzed Hiyama coupling of silanes and the Hiyama–Denmark coupling of silanols.

Furthermore, the aryltrialkoxysilanes have been proved to be valuable coupling partners (Scheme 4.2a).[195] Their ease of handling and air/moisture stability is an attractive feature for a variety of applications in cross-couplings and asymmetric additions.[196] These siloxanes are generally used in combination with a fluoride source, although Brønsted bases and base-free conditions have been explored as well.[197,198] Another interesting group for cross-couplings is heptamethyltrisiloxane ($(TMSO)_2MeSi$–, HMTS), which also has been successfully used for a variety of cross-couplings.[199,200]

The reactivity of both the organosilanes and the palladium catalyst can be tuned in order to achieve the desired results under mild reaction conditions. For example organo-(2-(hydroxymethyl)-phenyl)dimethylsilanes (organo-HOMSi, Scheme 4.2b) can be activated with weak bases[201] or be used in cross-coupling without any additive.[202] The by-product is a cyclic silylether and can be used for the regeneration of the organo-HOMSi species. Despite being attractive coupling partners, organo-HOMSi species are not commercially available. With the exception of arylation via

Grignard reagents, no other useful synthetic routes have emerged to provide a large structural diversity of these organosilanes.



Scheme 4.2 a) Cross-coupling with siloxanes; b) Cross-coupling with organo-HOMSi.

Over the years a variety of different organosilicon reagents have emerged (Fig. 4.2), featuring different stabilities and advantages in cross-coupling reactions.[203]

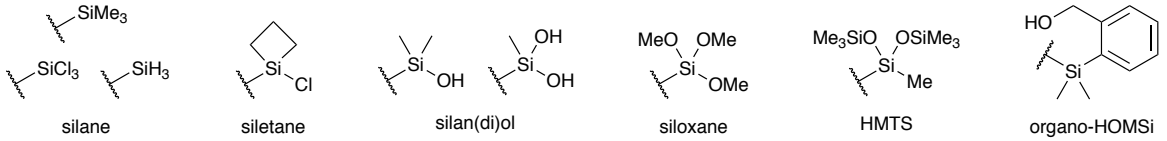
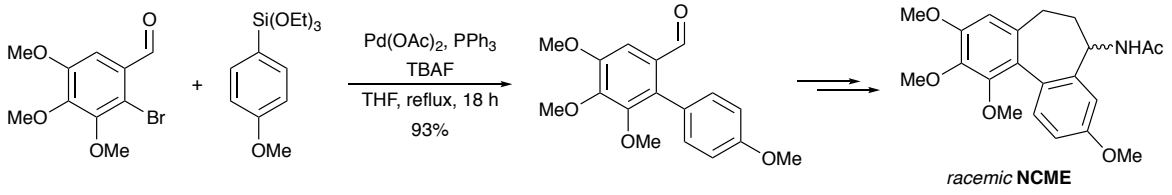
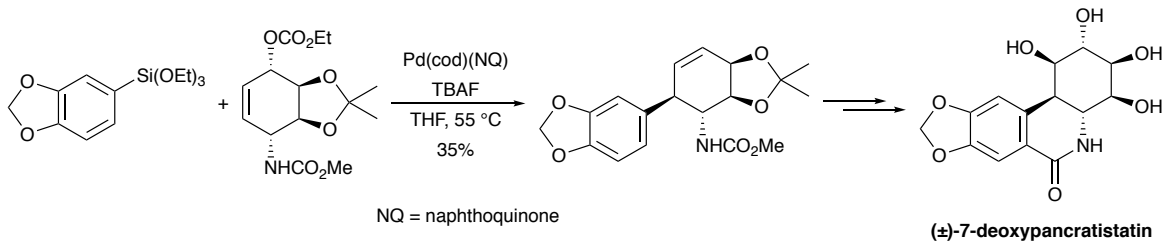


Figure 4.2 Overview of different organosilicon reagents used in cross-coupling reactions.

It is worth mentioning that organosilanes have been successfully applied in the synthesis of a variety of bioactive compounds and drugs.[186,204] For example, 4-(triethoxysilyl)anisole has been used by DeShong for cross-coupling in the total synthesis of a racemic *N*-acetyl colchinol-*O*-methyl ether (NCME, Scheme 4.3).[205] The synthesized structure belongs to the family of *Colchicum* alkaloids that show activity as tubulin inhibitors.



Scheme 4.3 Hiyama coupling in the total synthesis of a racemic allocolchicinoid derivative.

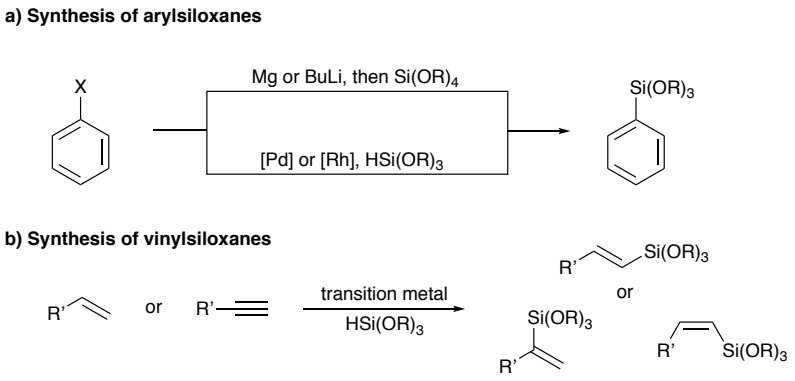


Scheme 4.4 Stereoselective arylation of siloxanes in the formal total synthesis of (±)-7-deoxypancratistatin and derivatives.

Stereoselective allylic arylation of a siloxane was used as a key step for the synthesis of (±)-7-deoxypancratistatin, an anticancer active Amaryllidaceae alkaloid (Scheme 4.4).[206] Despite a low yield (35%) the Pd(cod)(NQ) complex (NQ: naphthoquinone) was able to facilitate the reaction of the siloxane without the generation of undesired by-products.

4.1.3 Synthesis of Organosiloxanes

Siloxanes or trialkoxysilanes can be generated via various procedures (Scheme 4.5). Aryl halides are treated with either Mg or BuLi and subsequently with tetraalkyl orthosilicates to generate the desired siloxane.[207,208] In these protocols substituted (hetero)arenes are generated while $Si(OEt)_4$ seems to be a better electrophile than $Si(OMe)_4$. However, these transformations must be performed carefully at low temperatures because fast addition and increased temperatures lead to bis- and trisarylation of the silane. As the functional group tolerance is limited (e.g. esters and ketones are incompatible), other protocols have been developed with the aim of broadening the substrate scope.



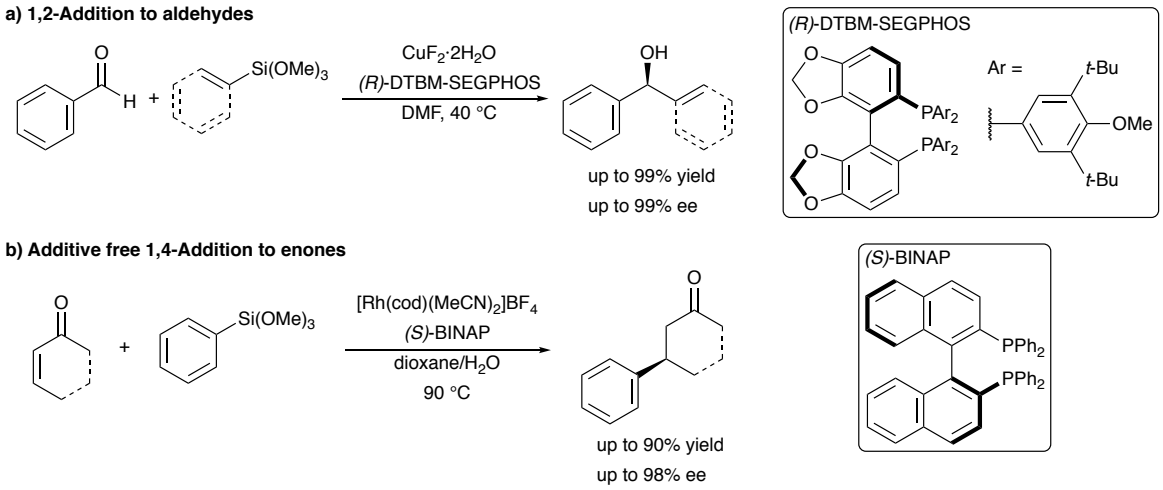
Scheme 4.5 Reported procedures for the synthesis of trialkoxysilanes.

Thus, Pd- and Rh-catalyzed silylations with trialkoxysilanes as electrophiles have been reported but also show only limited substrate scope regarding substituents or heteroaromatics.[209,210] A variety of (hetero)arylsiloxanes substrates have been generated but chemists still lack a general method for the synthesis of siloxanes, especially on a preparative scale with higher functional group tolerance. Broader scope is available for the generation of vinylsilanes, which is typically accomplished by hydrosilylation or Heck-type procedures.[211,212]

4.1.4 Asymmetric Cross-Couplings and Addition Reactions with Organosiloxanes

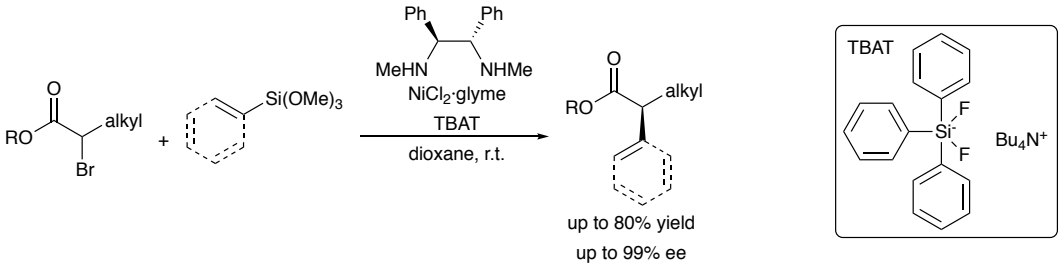
The development of stereoselective reactions is currently a highly active topic in organic synthesis. In this regard, new cross-coupling reactions that allow the preparation of molecules in a stereocontrolled manner have emerged over the last two decades. Regarding transition metal catalyzed addition reactions and cross-couplings the majority of processes that involve organosilanes are allylation reactions (Hosomi-Sakurai) to carbonyl compounds or imines.[213] Amongst other silicon-based asymmetric reactions siloxanes and silanols have been found to be the most suitable nucleophiles in organocatalytic procedures.[195,196,202]

A Cu-catalyzed asymmetric 1,2-addition of substituted trimethoxy(vinyl)silanes under mild conditions has been reported by Kanai and Shibasaki (Scheme 4.6a).[214] Addition of aromatic groups is limited to phenyl but the products are generally obtained in good yield and enantioselectivities. In 2003, Oi and Inoue developed a Rh-catalyzed asymmetric 1,4-addition of siloxanes to α,β-unsaturated enones, esters and acrylamides (Scheme 4.6b).[215] The substrate scope regarding vinyl- and arylsiloxane is limited but generally good yields and enantioselectivities are achieved, using BINAP as chiral bisphosphine ligand.



Scheme 4.6 Different approaches for asymmetric C–C bond formation using Csp^2-hybridised siloxanes.

To our knowledge, there are no known asymmetric allylic transformations of siloxanes to racemic starting materials. In addition, the only asymmetric Hiyama cross-coupling with racemic secondary α-bromoesters has been reported by Fu (Scheme 4.7).[216] The ester group as well as the fluoride source had considerable influence on the outcome of the reaction.



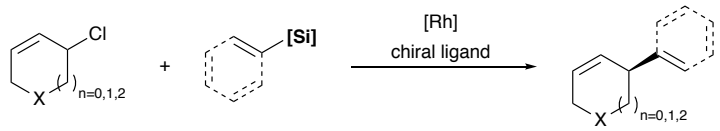
Scheme 4.7 Fu's asymmetric Hiyama coupling with siloxanes.

4.2 Project Aims

Good results in coupling reactions with (hetero)arylboronic acids encouraged us to explore other substrates as coupling partners as stability and protodeboronation are still common problems with boronic acids. Organosilicon compounds, even though less reactive, have a variety of advantages over boronic acids and we considered organosilanes as suitable coupling partners for an asymmetric cross-coupling approach.

The aim of this project was to develop an enantioselective Csp^2–Csp^3 coupling with organosilanes. Once the coupling reaction is established it should allow the coupling of structural motifs that are not accessible with boronic acids, e.g. vinylation. A variety of phenyl-substituted organosilanes are commercially available. Further derivatives can be accessed via reported procedures.

In addition, we envisage to overcome problems in the previous coupling with heterocyclic structures that either failed or only gave poor results when boronic acids where used.



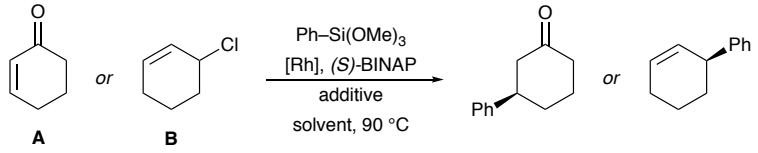
Scheme 4.8 General approach for an asymmetric Hiyama coupling with cyclic allyl chlorides.

4.3 Results and Discussion

4.3.1 Allylic Arylation with Trimethoxyphenylsilane

With an initial starting point provided by Oi and Inuoe's report of asymmetric 1,4-addition of trimethoxysilanes to α,β-unsaturated enones[215] (Scheme 4.6b) we subjected 3-chlorocyclohexene to these conditions without success (Table 4.1, entries 1,2). Also using trimethoxyphenylsilane with the conditions used with boronic acids (see chapter 3) did not provide any product (entries 3–5).

Table 4.1 Reproducing results and application to allyl chloride.



Entry	substrate	[Rh]	Additive	Solvent	Yield % (%ee)
1	**B**	$[Rh(cod)(MeCN)_2]BF_4$	–	dioxane/H_2O	0
2	**B**	$[Rh(cod)OH]_2$	Cs_2CO_3	THF[c]	0
3	**A**	$[Rh(cod)OH]_2$	Cs_2CO_3	THF[c]	0
4	**A**	$[Rh(cod)OH]_2$	Cs_2CO_3	dioxane	0
5	**A**	$[Rh(cod)(MeCN)_2]BF_4$	–	dioxane/H_2O	0
6	**A**	$[Rh(cod)Cl]_2$	$AgBF_4$	dioxane/H_2O	0
7	**A**	$[Rh(cod)(MeCN)_2]BF_4$	–	dioxane/H_2O[d]	33 (20)
8[a]	**A**	$[Rh(cod)(MeCN)_2]BF_4$	–	dioxane/H_2O	43 (73)
9[a]	**A**	$[Rh(cod)(MeCN)_2]BF_4$	–	dioxane/H_2O[d]	62 (63)
10[a]	**A**	$[Rh(cod)(MeCN)_2]BF_4$	–	dioxane/H_2O[e]	17 (92)
11[a]	**A**	$[Rh(cod)(MeCN)_2]BF_4$	TBAF[b]	dioxane/H_2O	78 (12)
12[a]	**A**	$[Rh(cod)(MeCN)_2]BF_4$	ZnF	dioxane/H_2O	38 (88)

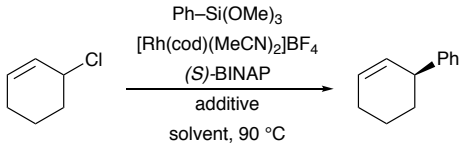
Conditions: substrate (1.0 equiv.), $PhSi(OMe)_3$ (2.0 equiv.), [Rh] (5 mol% Rh), *(S)*-BINAP (7.5 mol%), additive (1.0 equiv.), dioxane/H_2O 10:1; *a*: $PhSi(OMe)_3$ supplier was switched from Alfa Aesar to Sigma Aldrich; *b*: 1 M in THF; *c*: reaction performed at 60 °C, *d*: degassed mixture with three freeze-pump-thaw cycles before heating; *e*: using pre-degassed solvent.

In addition, we aimed to reproduce Oi's procedures but found formation of the 1,4-product gave variable results with both yield and enantioselectivity. Prior degassing of the solvents or additional fluoride sources did not improve the results significantly.

According to the suggested mechanism of this procedure water seems to play an essential role in the activation of the siloxane. Our next focus was to subject the allyl chloride to a combination of different bases in dioxane or dioxane/H_2O mixtures (Table 4.2). Earlier experiments showed that the cyclic allyl chloride is not stable in conditions that contain larger amounts of water but running the experiment with TBAF (1 M in THF) we were surprised to obtain product in 14% yield and excellent enantioselectivity (Table 4.2, entry 5). Caesium carbonate as a base is highly beneficial in

coupling reactions with some organosilanols[217] and boronic acids (cf chapter 3.2) but completely inhibits the reactivity in the present reaction (Table 4.2, entry 6).

Table 4.2 Influence of the additive.



Entry	Additive	Solvent	Yield % (%ee)
1	–	dioxane/H_2O	0
2	Et_3N	dioxane/H_2O	0
3	ZnF_2	dioxane	0
4	CsF	dioxane/H_2O	0
5	TBAF	dioxane	14 (99)
6	TBAF, Cs_2CO_3	dioxane	0

Conditions: allyl chloride (1.0 equiv.), $PhSi(OMe)_3$ (2.0 equiv.), [Rh] (5 mol%), *(S)*-BINAP (7.5 mol%), additive (1.0 equiv.) dioxane/H_2O 10:1, degassed mixture with three freeze-pump-thaw cycles before heating.

Parallel to these experiments we were trying to see if other organosilanes or silanols would perform the coupling reaction with allyl chloride under Oi's conditions (Fig. 4.3). A range of commercially available alkyl and alkoxysilanes were used but no substrate was able to provide the desired coupling product.

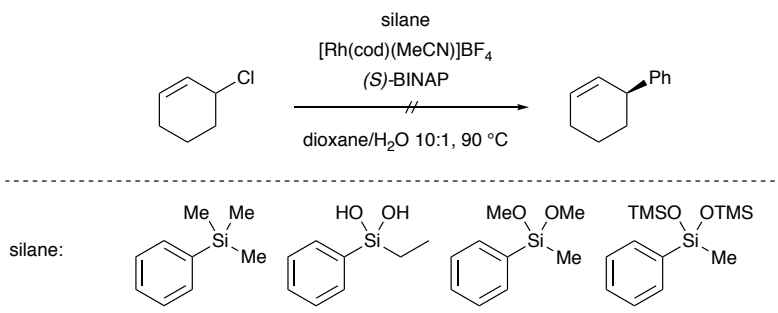
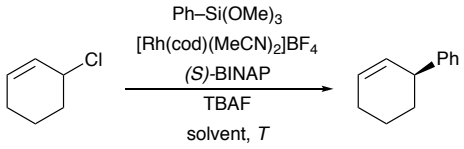


Figure 4.3 Reaction failed with other organosilanes. *Conditions*: allyl chloride (1.0 equiv.), organosilane (2.0 equiv.), [Rh] (5 mol%), *(S)*-BINAP (7.5 mol%).

However, with a successful starting point (Table 5, entry 5) in hand we tried to optimise the yield while maintaining BINAP as the preferred ligand. Assuming, that the reaction would work in a variety of ethereal solvents other than dioxane we found that THF gave the most promising results (Table 4.3, entry 5). TBAF is already used as a solution in THF and an additional ethereal solvent does not improve the yield for the reaction.

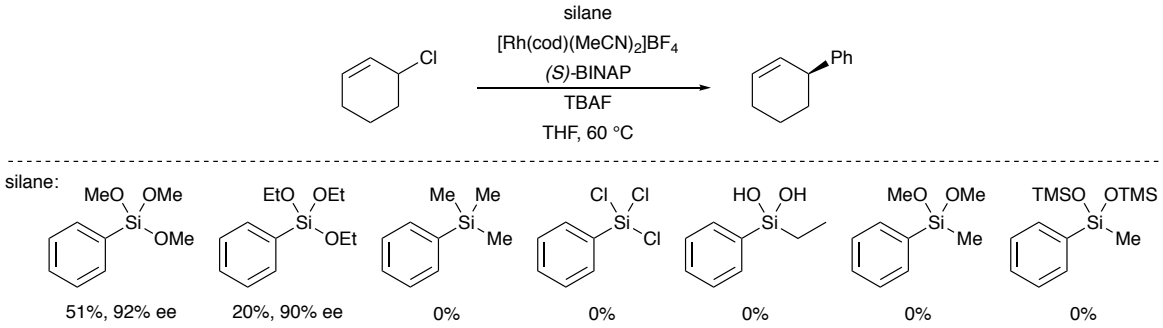
Table 4.3 Reaction screening with different ethereal solvents.



Entry	Solvent	*T* [°C]	Yield % (%ee)
1	dioxane	50	30 (95)
2	dioxane	80	20 (98)
3	DME	80	19 (96)
4	MTBE	60	24 (99)
5	THF	60	43 (99)
6	2-MeTHF	80	29 (98)

Conditions: allyl chloride (1.0 equiv.), $PhSi(OMe)_3$ (2.0 equiv.), [Rh] (5 mol%), *(S)*-BINAP (7.5 mol%), TBAF (1.0 equiv.).

Having fairly good conditions for the enantioselective Hiyama coupling we investigated the substrate scope for this reaction (Fig. 4.9). Under the current conditions, electron rich silanes, i.e. tri(m)ethoxyphenylsilane, provide the product in good yield, using two equivalents of both the siloxane and TBAF. However, other less electron rich silanes and trichlorophenylsilane were not effective.



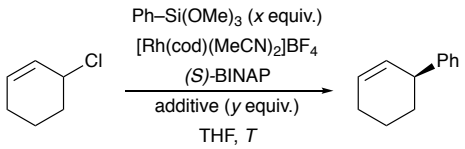
Scheme 4.9 Further optimised reaction with different silanes. *Conditions*: allyl chloride (1.0 equiv.), silane (2.0 equiv.), [Rh] (5 mol%), *(S)*-BINAP (7.5 mol%), TBAF (2.0 equiv.).

Other fluoride sources known to promote coupling reactions of organosilanes did not work in our case (Table 4.4, entries 1–3). 3-Bromocyclohexene only provided the product in 19% yield (entry 4). By changing temperatures and siloxane/TBAF ratios we were able to obtain the coupling product in 65% and 99% ee (entry 8), at 2.5 h[††]. Degassing the solvent prior to the reaction improved the result only by a negligible amount (entry 9). The use of a water-free alternative, i.e. tetrabutylammoniumhydrogen difluoride $TBAHF_2$,[218] did not provide better results (entry 10).

An independent experiment was performed in the absence of siloxane and decomposition of the starting material was observed. Using ^{1}H-NMR experiments we did not observe the formation of any 3-fluorocyclohexene under the present conditions. In order to decrease the amount of decomposition we performed experiments in which either 3-chlorohexene or TBAF was added last, but these experiments did not provide better results.

[††] Reaction monitored with ^{1}H-NMR spectroscopy.

Table 4.4 Influence of the additive in THF.

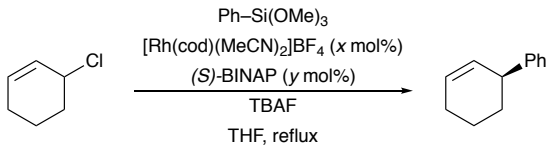


Entry	$PhSi(OMe)_3$ (*x* equiv.)	Additive (*y* equiv.)	*T* [°C]	Yield % (%ee)
1	2.0	KF (2.0)	60	0
2	2.0	AgF (2.0)	60	0
3	2.0	CsF (2.0)	60	0
4[a]	2.0	TBAF (2.0)	60	19 (99)
5[b]	2.0	TBAF (2.0)	60	57 (99)
6	2.0	TBAF (3.0)	60	48 (97)
7[b,c]	2.0	TBAF (2.0)	60	61 (99)
8	2.0	TBAF (2.0)	reflux	65 (99)
9[d]	2.0	TBAF (2.0)	reflux	67 (99)
10	2.0	$TBAHF_2$ (2.0)	reflux	48 (99)
11	1.2	TBAF (1.2)	60	33 (88)
12	3.0	TBAF (3.0)	60	60 (99)
13[d]	1.5	TBAF (1.5)	reflux	58 (99)
14	3.0	TBAF (3.0)	reflux	66 (99)

Conditions: allyl chloride (1.0 equiv.), [Rh] (5 mol%), *(S)*-BINAP (7.5 mol%); *a*: 3-bromocyclohexene was used instead of 3-chlorocyclohexene; *b*: reaction was stirred for 20 h; *c*: TBAF was added last to the reaction; *d*: THF was priorly degassed.

We further investigated different catalyst concentrations and loadings as well as rhodium/ligand ratios but no improved results were obtained (Table 4.5). A larger ligand to rhodium ratio (1.5:1)[215] was necessary for good results compared to the developed asymmetric Suzuki–Miyaura coupling (ligand/[Rh], 1.2:1).

Table 4.5 Influence of the catalyst loading and concentration.



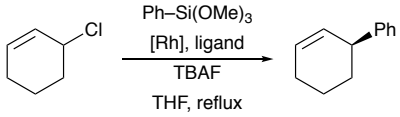
Entry	[Rh]/BINAP (x mol%/y mol%)	V_{tot} THF [mL]	T [°C]	Yield % (%ee)
Ref.	5/7.5	2.0	reflux	65 (99)
1	5/6	2.0	60	45 (99)
2	5/10	2.0	60	58 (99)
3	5/6	2.0	reflux	55 (99)
4	5/6	1.0	reflux	53 (99)
5	5/6	4.0	reflux	22 (99)
6	10/15	2.0	reflux	64 (99)

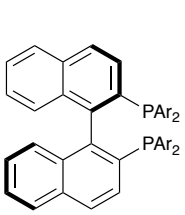
Conditions: allyl chloride (1.0 equiv.), $PhSi(OMe)_3$ (2.0 equiv.), TBAF (2.0 equiv.).

Different bisphosphine ligands that were available in our laboratory were screened from which BINAP performed best (Table 4.6, entries 1–5). Diene ligands that are known to facilitate Rh-catalyzed ACAs[219] did not work for our substrate (entry 6). We were surprised to see that a variety of different rhodium sources were successful in our hands, but unfortunately these were also inferior to the already established conditions (entries 7–13).

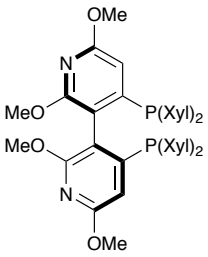
We were interested to see whether other, non-ethereal solvents can be used for the coupling reaction (Table 4.7). Polar and non-polar solvents were able to provide the coupling product with high ees. As already mentioned THF is a co-solvent in this reaction due to TBAF. Performing the reaction in the absence of THF only gave poor results (entries 5,6). Also larger amounts of water effect the outcome of the coupling negatively (entries 7,8).

Table 4.6 Screening of different rhodium sources and ligands.

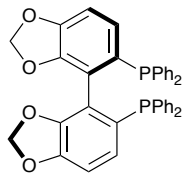




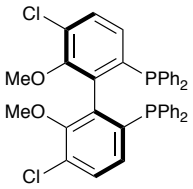
L19: Ar = *p*-Tolyl
L20: Ar = 3,5-Xylyl



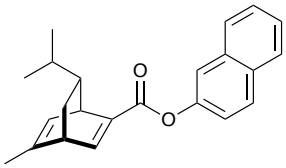
(S)-Xyl-P-PHOS



(R)-SEGPHOS



(S)-Cl-MeO-BIPHEP

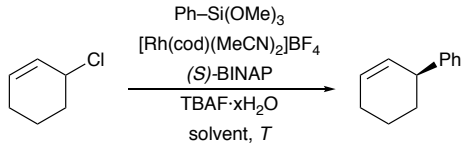


L21
diene ligand

Entry	[Rh]	*ligand*	Yield % (%ee)
Ref.[a]	$[Rh(cod)(MeCN)_2]BF_4$	*(S)*-BINAP	55 (99)
1[a]	$[Rh(cod)(MeCN)_2]BF_4$	**L19**	48 (99)
2[a]	$[Rh(cod)(MeCN)_2]BF_4$	**L20**	48 (99)
3[a]	$[Rh(cod)(MeCN)_2]BF_4$	*(S)*-Xyl-P-PHOS	17 (99)
4[a]	$[Rh(cod)(MeCN)_2]BF_4$	*(R)*-SEGPHOS	56 (–99)
5[a]	$[Rh(cod)(MeCN)_2]BF_4$	(S)-Cl-MeO-BIPHEP	45 (99)
6[a]	$[Rh(cod)(MeCN)_2]BF_4$	**L21**	0[b]
7	$[Rh(cod)(OH)]_2$	*(S)*-BINAP	34 (90)
8	$[Rh(cod)Cl]_2$	*(S)*-BINAP	34 (84)
9	$[Rh(coe)Cl]_2$	*(S)*-BINAP	25 (95)
10	$[RhCl(C_2H_4)_2]_2$	*(S)*-BINAP	55 (99)
11	$[RhClCp^*]_2$	*(S)*-BINAP	13 (99)
12	$Rh(acac)(C_2H_4)_2$	*(S)*-BINAP	11 (99)
13	$Rh(cod)_2OTf$	*(S)*-BINAP	22 (99)

Conditions: allyl chloride (1.0 equiv.), $PhSi(OMe)_3$ (2.0 equiv.), [Rh] (5 mol% Rh), ligand (7.5 mol%), TBAF (2.0 equiv.); *a*: ligand (6 mol%); *b*: major product was phenylbenzene.

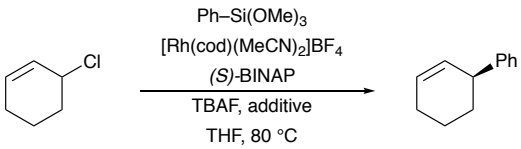
Table 4.7 Reaction screening with different TBAF sources in different solvents.



Entry	TBAF·xH_2O	Solvent	*T* [°C]	Yield % (%ee)
1	TBAF	PhMe	80	45 (93)
2	TBAF	DMF	60	9 (99)
3	TBAF	MeCN	60	42 (99)
4	TBAF	DCE	60	49 (99)
5	TBAF·3H_2O	MeCN	60	15 (99)
6	TBAF·3H_2O	DCE	60	17 (98)
7	TBAF·3H_2O	THF	60	50 (99)
8	TBAF (75% w/w in H_2O)	THF	60	13 (99)

Conditions: allyl chloride (1.0 equiv.), $PhSi(OMe)_3$ (2.0 equiv.), [Rh] (5 mol%), *(S)*-BINAP (7.5 mol%), TBAF source (2.0 equiv.).

Table 4.8 Reaction screening with additional additives.



Entry	Additive	Yield % (%ee)
1	CsOH	traces
2	DIPEA	46 (99)
3	Ag_2O	–
4	$AgBF_4$	–
5	$LiBF_4$	31 (99)
6	$TBABF_4$	43 (99)

Conditions: allyl chloride (1.0 equiv.), $PhSi(OMe)_3$ (2.0 equiv.), [Rh] (5 mol%), *(S)*-BINAP (7.5 mol%), TBAF (1.0 equiv.), additive (1.0 equiv.).

We found that in the presence of additional bases, e.g. caesium hydroxide or caesium carbonate, the reaction does not work (Table 4.2, entry 6 and Table 4.8, entry 1). However, weak basic additives such as Hünig's base gave the coupling product in moderate yield compared to the optimised conditions (Table 4.8, entry 2). Silver(I) oxide[220] was highly detrimental in our case and $AgBF_4$ resulted mostly in oxidative homocoupling to give phenylbenzene. Other tetrafluoroborate salts did not improve the reaction (entries 5,6).

At this point the reaction could not be further optimised and we decided to continue with the application of different arylsiloxanes.

4.3.2 Application to Other Aryltrimethoxysilanes

Our next focus was trying to apply the developed coupling procedure to other aromatic groups. Since only a few siloxanes are commercially available we tried to prepare most of the examples on a preparative scale (Fig. 4.4). The main approach for the generation of aryltrimethoxysilanes **79**–**85** was lithiation or Grignard formation and subsequent treatment with tetramethyl orthosilicate as the electrophile. The yields were mostly moderate but enough material was made in order to perform the reactions. In the case of 2-tolyl- **80b** and 4-fluorophenylsiloxane **85b** we were also able to isolate the bisarylated species. The synthesis of 4-bromophenyl- **86** and 4-trifluoromethylphenylsiloxane **87** was not successful. We considered the alternative synthesis via rhodium activation[210] but the synthesis failed on a preparative scale.

We then subjected the generated substrates to the optimised reaction conditions for the asymmetric Hiyama coupling (Fig. 4.5). We were pleased to see that the majority of the results were comparable to the ones reported with the boronic acids regarding enantioselectivity.[156] The coupling with trimethoxy(naphthalen-2-yl)silane **89** found to have superior enantioselectivity (99% ee) compare to the 89% ee, achieved with boronic acids. 2-Methyl substituted product **92** gave only traces of product, probably due to steric effects. The yields were expected to be generally lower and in the case of anisole siloxanes **93** and **96** some protodesylilated starting material could not be separated from the product.

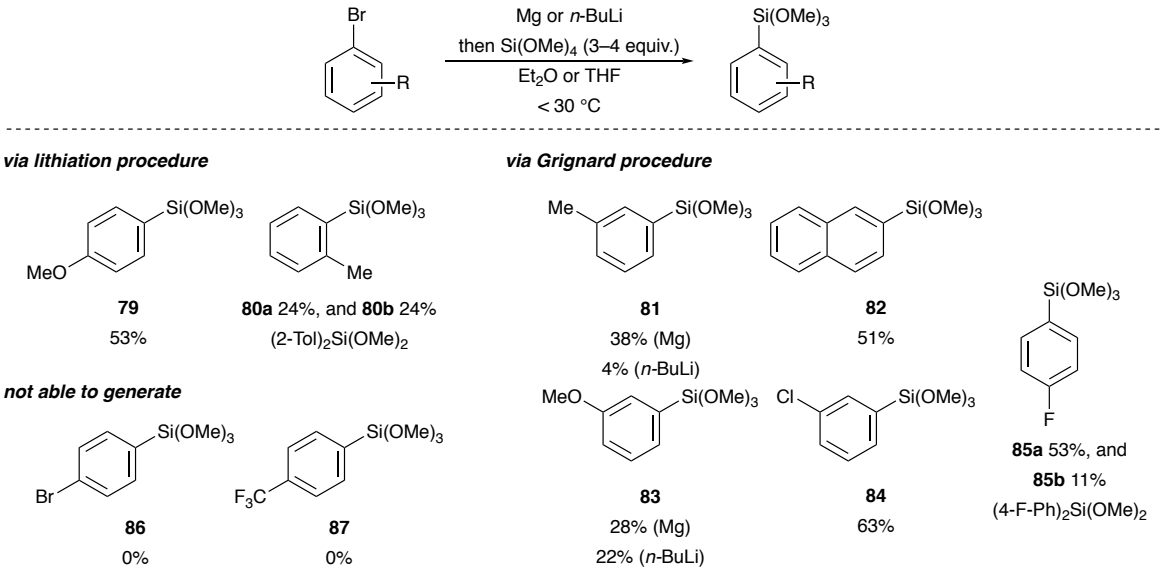


Figure 4.4 Syntheses of aryltrimethoxysilanes via Mg activation or lithiation.

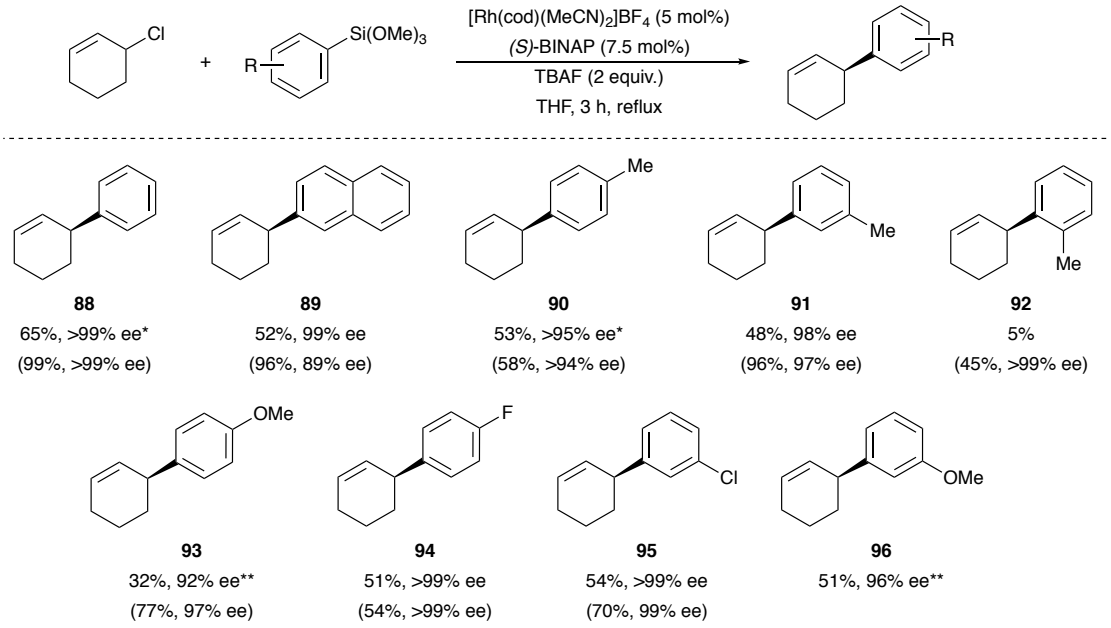
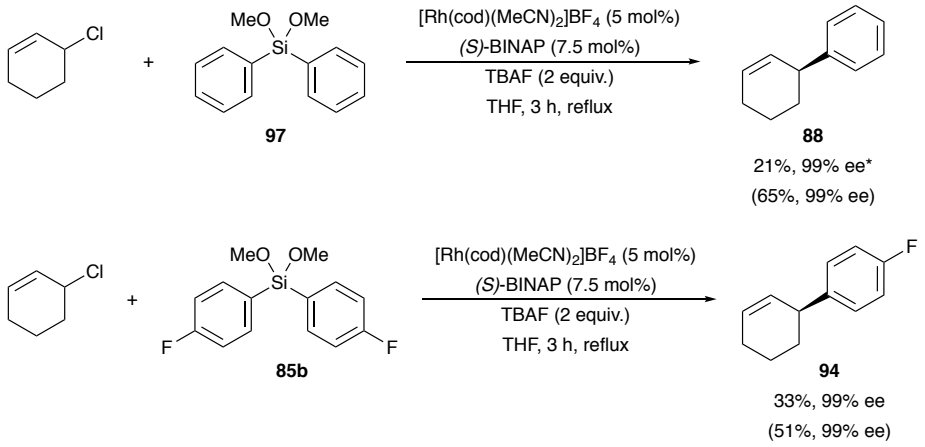


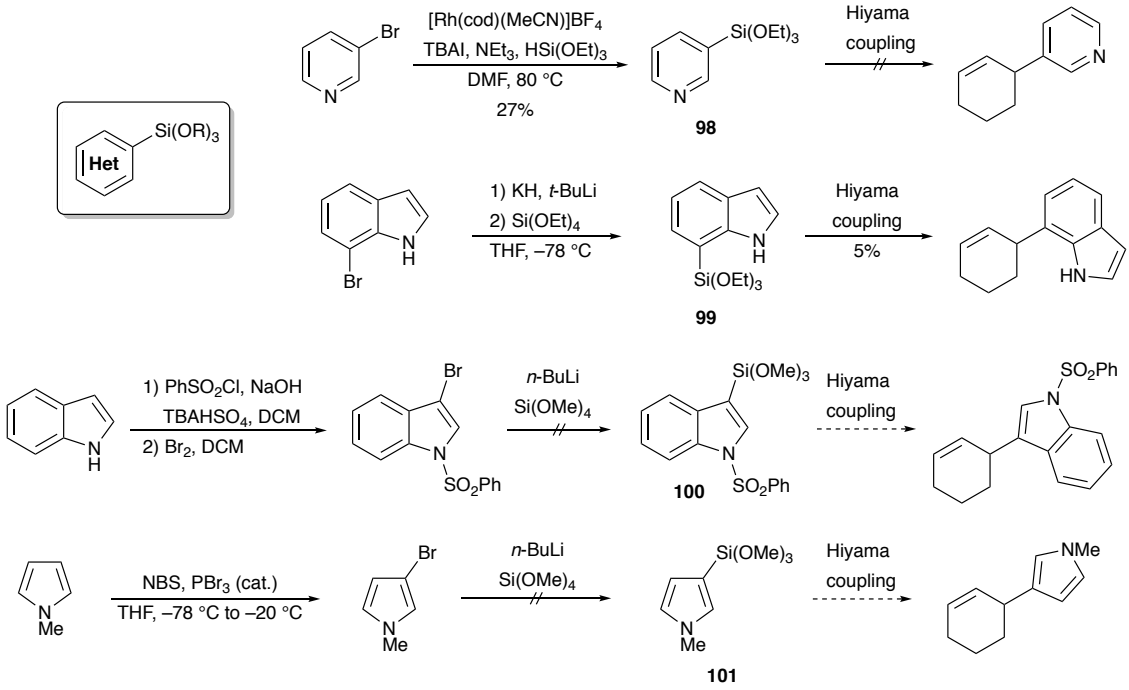
Figure 4.5 Asymmetric Hiyama coupling with a variety of aryltrimethoxysilanes. Results of the asymmetric coupling with arylboronic acids[156] are shown in brackets. *In this experiment the organosilane was commercially available. **Product contains impurities of anisole.

During the preparation of siloxanes we observed bisarylated species that might also able to undergo the coupling reaction (Scheme 4.10).[214,221] The bis(2-methylphenyl)siloxane **80b** was not considered due to the poor results with the monomeric species (Fig. 4.5). Other bisarylated dimethoxysilanes **97** and **85b** did undergo the asymmetric Hiyama coupling with excellent enantioselectivity but decreased yield.



Scheme 4.10 Asymmetric arylation with bisaryldimethoxysilanes. *Diphenyldimethoxysilane was commercially available.

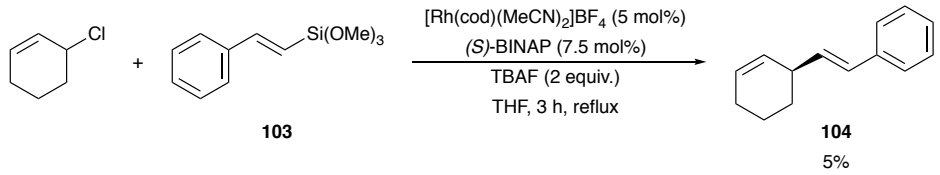
We then investigated some more challenging substrates (Scheme 4.11), particularly *N*-heterocycles that did not work or gave poor results when subjected to conditions of the asymmetric Suzuki–Miyaura coupling (cf Fig 3.6). We synthesized triethoxy(pyridin-3-yl)silane **98** but – similar to when pyridin-3-ylboronic acid was used – no product could be obtained when subjected to the subsequent coupling procedure. In case of 7-substituted indole **99** the siloxane was easier to handle regarding stability but similar to the Suzuki coupling only traces of product were obtained. 3-Substituted indole[222] **100** and pyrrole[223] **101** we were unable to form the siloxane upon lithiation-silylation.



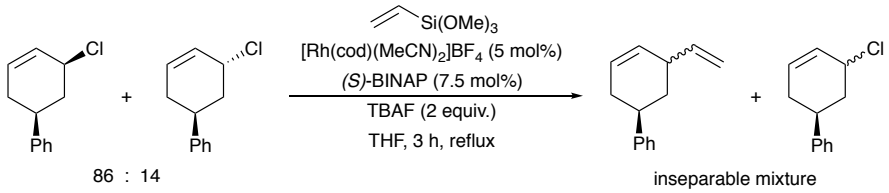
Scheme 4.11 Application to the coupling of *N*-heteroaryltrialkoxysilanes.

4.3.3 Asymmetric Addition of Trimethoxy(vinyl)silanes

Well developed synthetic procedures are known for the synthesis of vinylsiloxanes which makes them superior to their vinylboronic acid counterparts.[211] We also envisaged vinylsiloxanes and derivatives as suitable coupling partners for the asymmetric Hiyama coupling. Subjecting (*E*)-*β*-(trimethoxysilyl)styrene **102** to our optimised conditions provided small amounts of product **103** but mostly solidified material (Scheme 4.12). The latter was likely due to polymerisation of the starting material. The addition of trimethoxy(vinyl)siloxane to cyclic allyl chloride did not provide any product under the present conditions. Whether this poor result was a matter of reactivity, stability of the product, or the chosen reaction conditions, could not be confirmed at this stage. Hence we decided the coupling reaction with the 5-phenyl substituted cyclic allyl chloride (Scheme 4.13). Unfortunately the reaction gave a mixture of four inseparable compounds. ^{1}H-NMR spectroscopy indicates that the product was formed but yield and selectivity could not be determined.



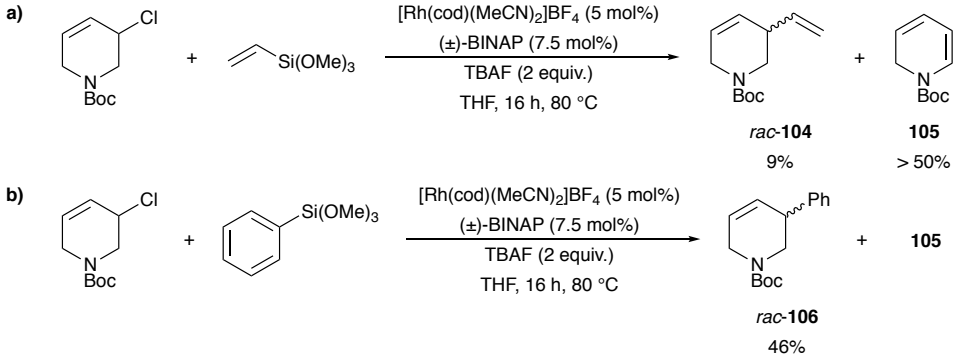
Scheme 4.12 Asymmetric alkenylation with trimethoxy(styrenyl)silane.



Scheme 4.13 Attempt for a vinylation of 5-phenyl substituted cyclic allyl chloride.

Another suitable substrate for the vinylation was considered to be *N*-Boc-5-chloro-3-piperidene. An initial experiment showed formation of a product that could not be isolated. Despite several optimisation attempts only 9% (~ two catalyst turnovers) of the desired product **104** were isolated (Scheme 4.14a). Careful isolation and characterisation attempts suggest that the major by-product is *N*-Boc protected 2*H*-pyridine **105**. A control experiment with phenylsiloxane provided the

product **106** in 46% yield in addition to the by-product, which has been formed in considerable amounts (Scheme 4.14b).



Scheme 4.14 Hiyama coupling of *N*-Boc protected piperidene.

These results suggest that trimethoxy(vinyl)silane is less reactive than its aryl counterpart. The formation of the by-product can be rationalised by a different pathway in the catalytic cycle (Fig. 4.6). First, we can assume that active Rh–X undergoes transmetalation with the siloxane fluoride ate complex. Upon oxidative addition the Rh^{III}-intermediate is formed in which the configuration is set. Reductive elimination releases the product and the Rh-catalyst is regenerated (Fig. 4.6, **A**)

However, in an alternative pathway (Fig. 4.6, **B**) the oxidative addition can occur prior to transmetalation and subsequent *β*-hydride elimination forms the undesired by-product. This may be possible if a) the vinylsiloxane is less reactive and/or b) the active Rh–X for pathway **A** is not sufficiently active, or the catalytically active Rh species is not regenerated. Hence, after at least one catalytic cycle the undesired pathway **B** would be preferred.

Changing rhodium counterions or ligands might also be able to change the preference of pathway **A** over **B**. Attempts to optimise the reaction regarding different additives (bases), counterions (e.g. BF_4^-) and siloxane/substrate ratios did not succeed.

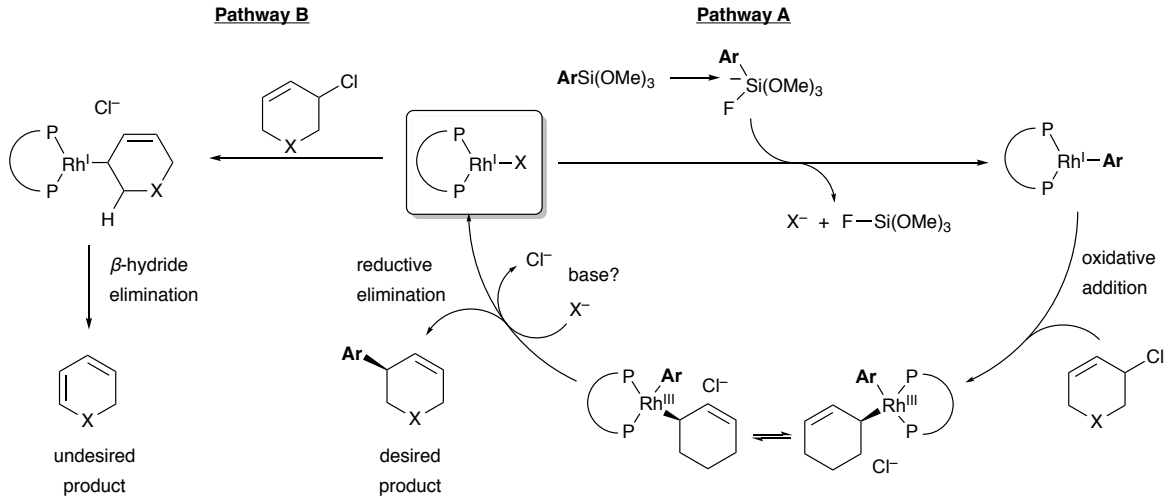


Figure 4.6 Suggested mechanism for asymmetric Hiyama coupling.

4.4 Summary

We were successful in the development of an asymmetric Hiyama coupling of aryltrimethoxysilanes with 3-chlorocyclohexene. Trialkoxysilanes and bisarylated siloxanes $Ar_2Si(OMe)_2$ were the only functional group(s) that worked under the optimised conditions with TBAF as an activation agent.

Despite intensive screening the coupling with a phenyl group only afforded the coupling product in 67% yield, but with excellent enantioselectivity (99% ee). Different phenylboronic acids were coupled with good yields and bisarylsiloxanes also provided the coupling products, all with excellent enantioselectivities.

The majority of the siloxanes were generated via Grignard formation (or lithiation) and silylation with tetraalkyl orthosilicate. Only few arylsiloxanes are commercially available and even though a number of procedures for the synthesis of arylsiloxanes have been reported, a reliable and general method has not been found yet.

The attempt to perform the vinylation of allylic species did not succeed. The desired product was formed but the performed experiments suggest that vinylsiloxanes are less reactive under the current conditions.

Using organosilanes is so far inferior to the use of boronic acids and requires further improvement. The developed conditions work for some substrates but other organosilanes might also conceivably be suitable coupling partners, as the screened reaction conditions are far from exhausted. Other desirable organosilanes, such as HMTS or organosilanols, have potential and have been not extensively described in the literature yet. However, rhodium has different electronic properties than, for example, palladium and it is possible that other transition metals improve the results found for this reaction.

5 Conclusions

During the course of this work new protocols for transition metal catalyzed asymmetric transformations of prochiral/racemic electrophiles and non-stabilized nucleophiles have been developed.

The first aim was to provide a general protocol for the synthesis of a nature derived tricyclic core structure using an asymmetric 1,4-addition of alkylzirconocenes as the first key step. SOMO-catalysis, electrochemical oxidation and other transition-metal catalysts did not perform the subsequent oxidative α-coupling of ketones with unsubstituted aromatic groups. Preliminary results in the regioselective coupling of dienones might give access to these desired motifs in further studies.

An asymmetric Suzuki–Miyaura cross-coupling of heteroarylboronic acids with racemic allyl halides was successfully developed and provided small chiral heterocyclic molecules with good yields and excellent enantioselectivities. Products of furanes, thiophenes, 2-pyrrole and indoles in 5- and 6-position were obtained in high yields and enantioselectivities. Pyridylboronic acids require electron withdrawing groups, e.g. Cl^-, to give access to pyridine structures. Using piperidenyl chloride as electrophile the method was applied to the natural product synthesis of (–)-isoanabasine with 15% yield and 95% ee.

With the attempt of replacing boronic acids with organosilanes an asymmetric Hiyama cross-coupling of trimethoxyarylsilanes and racemic allyl chlorides has been developed. Aryl- and bisarylsiloxanes were successfully used and provided products with high enantioselectivities albeit moderate yields. With the current set of conditions the addition of complex aryl moieties is so far limited by the synthesis of these organosilanes but the method is far from exhausted.

6 Experimental Information

6.1 General Information

All reactions were carried out in glassware which was flame dried under vacuum, in anhydrous solvents with continuous magnetic stirring in an inert argon atmosphere. Cooling to 0 °C was achieved using an ice/water bath and cooling to –78 °C with a dry ice/acetone bath. If needed, other temperatures were obtained using a Julabo FT902 immersion cooler. Heating was performed using DrySyn heating blocks.

Thin-layer chromatography was performed on plates with glass backing (Silica Gel 60 F_{254}, Merck) and visualised with UV light (254 nm) and aqueous stains. Column chromatography was performed by using Merck 60 Å silica gel and increased pressure of nitrogen.

Unless stated otherwise, nuclear magnetic resonance (NMR) spectroscopy measurements were carried out at room temperature. ^{1}H-NMR, ^{13}C-NMR, DEPT-135, COSY, HSQC and HMBC experiments were carried out using Bruker DPX-200, AVB-400, AVF-400, AVG-400, AVH-400 and/or AVB-500. Chemical shifts δ are reported in ppm from the residual solvent peak with corresponding coupling constants *J* in Hz and multiplicities (s: singlet, d: doublet, t: triplet, m: multiplet). Indices a and b of diastereotopic protons refer to the more upfield and more downfield signals respectively in the corresponding spectrum.

Infrared (IR, neat, thin film) spectroscopy was carried out in with the Bruker Tensor 27 FT-IR spectrometer with an internal calibration in the range of 4000–600 cm^{-1}.

Low-resolution mass spectra were recorded out using a Walters LCT premier XE. High-resolution mass spectrometry (HRMS) was carried using a Bruker MicroTOF spectrometer by the internal service at the University of Oxford. The values of mass over charge *m/z* in Th indicate the most

intense peak. Specific optical rotations $[\alpha]^{20}_{589}$ were recorded using a Perkin-Elmer 241 Polarimeter. Concentrations *c* are reported in g/100 mL.

HPLC unit and HP Chemstation software. Chiralpak® columns (250 × 4.6 mm), fitted with matching Chiralpak® Guard Cartridges (10 × 4 mm), were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Alrich or Rathburn); all eluent systems were isocratic.

Chiral GC measurements were conducted on a HP6890 (H_2 as vector gas) or HP6850 (H_2 as 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) –[certain temperature – holding time – temperature gradient (°C/min)]– final temperature (°C) – holding time. Retention times (t_R) are given in min.

Low-resolution mass spectra were recorded using a Walters LCT premier XE. High-resolution mass spectra (EI and ESI) were recorded using a Bruker MicroTOF spectrometer by the internal service at the University of Oxford.

6.2 Chemicals

Commercially available reagents were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics, Fluorochem, TCI Chemicals and Strem Chemicals. Dry solvents were collected fresh from an mBraun SPS-800 solvent purification system after having passed through anhydrous alumina columns. Deuterated solvents were purchased from Sigma Aldrich. All other solvents were purchased from Rathburn, Fisher or Sigma Aldrich. Hexane (HPLC grade) and petrol ether (40–60 °C) and were used without further purification.

Unless stated otherwise, chemicals were purchased from Acros Organics, Alfa Aesar and Sigma Aldrich. Phosphoramidite ligand **L5**,[224] Schwartz's reagent (Cp_2ZrHCl)[225], $[Fe(phen)_3](PF_6)_3$[226] and 3-chloro-3,6-dihydro-2*H*-pyran[227] were prepared according to the literature. The racemic HPLC traces of the enantioselective Hiyama coupling products were provided by Mireia Sidera.

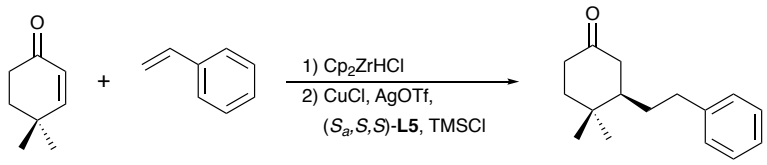
6.3 Experimental Procedures for Chapter 2

6.3.1 Asymmetric 1,4-Addition

Synthesis of the racemic products

A modified of procedure of Wipf *et al.* was used for the 1,4-addition of the racemic products.[35,78] The alkene (1.0 mmol, 2.50 eq) was added at room temperature to a solution of Cp_2ZrHCl (206 mg, 0.80 mmol, 2.00 eq) in dichloromethane (3.0 mL). After stirring for about 20 min $CuBr{\cdot}Me_2S$ (82 mg, 0.40 mmol, 1.00 eq) was added to the clear solution. After stirring for additional 10 min 4,4-dimethyl-2-cyclohexen-1-one **4** (53 µL, 0.40 mmol, 1.00 eq) was added and the dark solution was allowed to stir for 16 h at room temperature. The reaction mixture was diluted with diethyl ether (*ca* 3 mL) and quenched with NH_4Cl (1 M aq., *ca* 1.5 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with $NaHCO_3$ (sat. aq., 15 mL), dried ($NaSO_4$), filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica (petrol/Et_2O) gave the desired cyclic ketone.

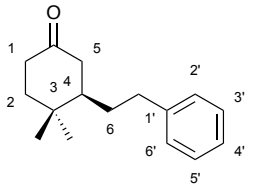
(–)-(*R*)-4,4-Dimethyl-3-(2-phenylethyl)cyclohexan-1-one 5[81]



Styrene **2** (0.12 mL, 1.0 mmol, 2.50 eq) was added at room temperature to a solution of Cp_2ZrHCl (206 mg, 0.80 mmol, 2.00 eq) in dichloromethane (0.4 mL) and was allowed to stir for about 20 min (I). In a second flask, a solution of CuCl (4.0 mg, 40 µmol, 0.10 eq) and *(S_a,S,S)*-**L5** (21.6 mg, 40 µmol, 0.10 eq) in diethyl ether (2.0 mL) was prepared at room temperature. After 1 h AgOTf (11.3 mg, 44 µmol, 0.11 eq) was added and the resulting mixture was allowed to stir for additional 15 min before it was added at 0 °C dropwise via syringe and filter to solution I. After 15 min 4,4-dimethyl-2-cyclohexen-1-one **4** (53 µL, 0.40 mmol, 1.00 eq) and trimethylsilyl chloride (0.25 mL, 2.0 mmol, 5.00 eq) were added and the solution was allowed to stir for 16 h at 0 °C. The

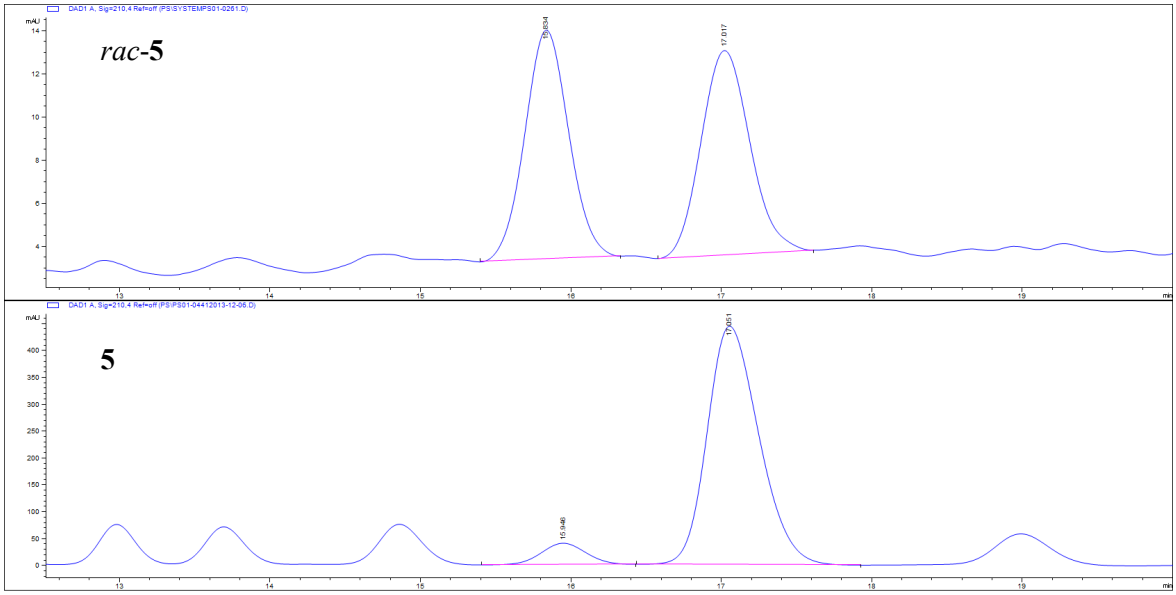
reaction mixture was diluted with diethyl ether (ca. 3 mL) and quenched with NH_4Cl (1 M aq., ca. 1.5 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with $NaHCO_3$ (sat. aq., 15 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica (petrol/Et_2O 9:1) to give (–)-(*R*)-4,4-dimethyl-3-(2-phenylethyl)cyclohexan-1-one as a yellow oil in 28% yield (26 mg, 0.11 mmol).

HPLC analysis indicated an enantiomeric excess of 89% [Chiralpak® IC; flow: 1.5 mL/min; hexane/*i*-PrOH 99:1; $\lambda = 210$ nm; minor enantiomer $t_R = 15.9$ min; major enantiomer $t_R = 17.1$ min].

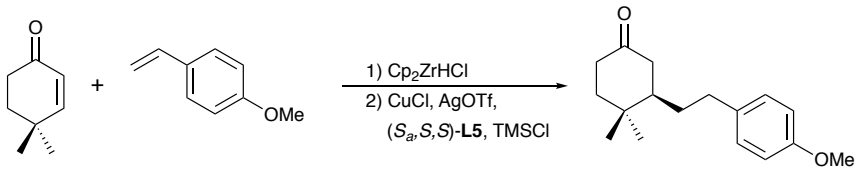


^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 1.23 – 1.31 (m, 1 H, H-6_a), 1.45 – 1.56 (m, 2 H, H-2_a, H-4), 1.63 (ddd, $J = 13.6, 6.1, 3.7$ Hz, 1 H, H-2_b), 1.82 (dddd, $J = 13.3, 10.6, 6.9, 2.4$ Hz, 1 H, H-6_b), 2.07 (ddd, $J = 14.3, 12.5, 1.0$ Hz, 1 H, H-5_a), 2.21 (dddd, $J = 15.0, 5.2, 3.6, 2.1$ Hz, 1 H, H-1_a), 2.31 - 2.38 (m, 2 H, H-1_b, $PhCH_{2a}$), 2.46 (ddd, $J = 14.8, 4.4, 2.1$ Hz, 1 H, H-5_b), 2.65 (ddd, $J = 13.8, 10.3, 5.1$ Hz, 1 H, $PhCH_{2b}$), 7.07 – 7.14 (m, 3 H, H-2', H-4', H-6'), 7.18 – 7.23 (m, 2 H, H-3', H-5'); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 18.5 (CH_3), 27.6 (CH_3), 31.7 (C6), 32.7 ($PhCH_2$), 37.3 (C-1), 39.3 (C-2), 41.8 (C-5), 45.3 (C-4), 124.9 (C-4'), 127.3, 127.4 (C-2', C-3', C-5', C-6'), 141.0 (C-1'), 211.0 (C=O); $[\alpha]^{20}_{589} = -33.5°$ (*c* 1.0, $CHCl_3$); **IR** ν_{max} /cm^{-1} = 2959br, 2361s, 1713l, 1495s, 1454s, 1389s, 1150s, 750s, 700m; **HRMS** (ESI): *m*/*z* calc. for $C_{16}H_{22}NaO^+$ $[M+Na]^+$: 253.1563, found: 253.1571.

HPLC traces for 5:



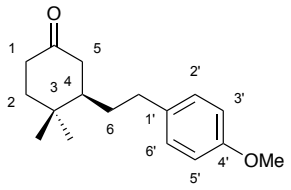
(–)-(*R*)-4,4-Dimethyl-3-(2-(4-methoxyphenyl)ethyl)cyclohexan-1-one 6[81]



4-Vinylanisole **3** (0.14 mL, 1.0 mmol, 2.50 eq) was added at room temperature to a solution of Cp_2ZrHCl (206 mg, 0.80 mmol, 2.00 eq) in dichloromethane (0.4 mL) and was allowed to stir for about 20 min (I). In a second flask, a solution of CuCl (4.0 mg, 40 µmol, 0.10 eq) and (*S*$_a$,*S*,*S*)-**L5** (21.6 mg, 40 µmol, 0.10 eq) in diethyl ether (2.0 mL) was prepared at room temperature. After 1 h AgOTf (11.3 mg, 44 µmol, 0.11 eq) was added and the resulting mixture was allowed to stir for additional 15 min before it was added at 0 °C dropwise via syringe and filter to solution I. After 15 min 4,4-dimethyl-2-cyclohexen-1-one **4** (53 µL, 0.40 mmol, 1.00 eq) and trimethylsilyl chloride (0.25 mL, 2.0 mmol, 5.00 eq) were added and the solution was allowed to stir for 16 h at 0 °C. The reaction mixture was diluted with diethyl ether (ca. 3 mL) and quenched with NH_4Cl (1 M aq., ca. 1.5 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with $NaHCO_3$ (sat. aq., 15 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica

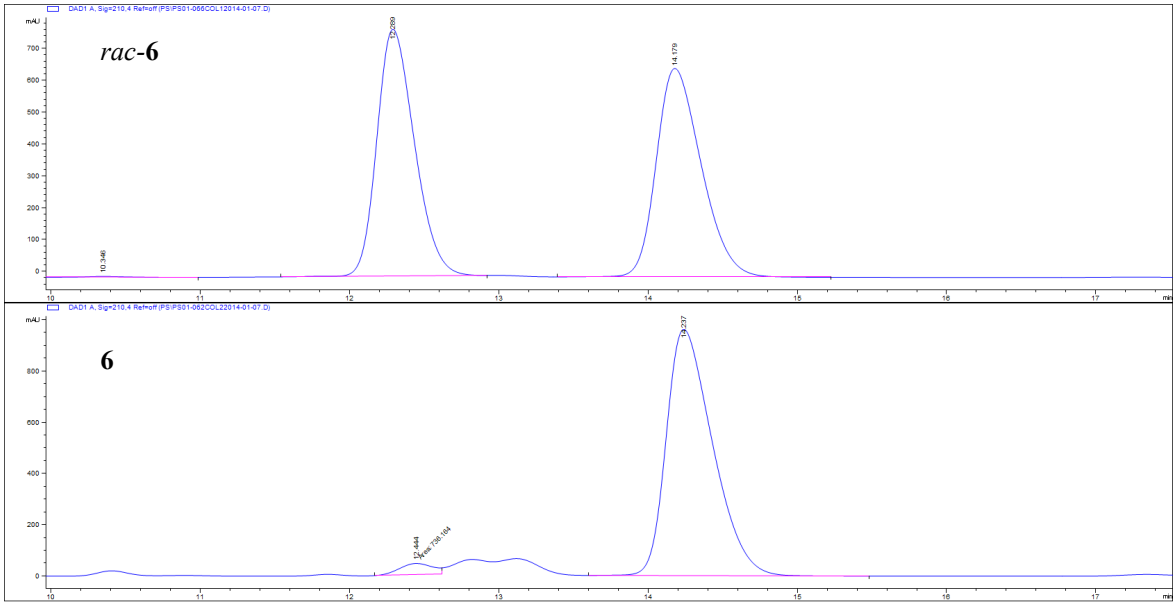
(petrol/Et_2O 4:1) to afford (–)-(*R*)-4,4-dimethyl-3-(2-(4-methoxyphenyl)ethyl)cyclohexan-1-one as a colourless oil in 55% yield (57 mg, 0.22 mmol).

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® IC; flow: 1.5 mL/min; hexane/*i*-PrOH 93:7; $\lambda = 210$ nm; minor enantiomer $t_R = 12.64$ min; major enantiomer $t_R = 14.43$ min].

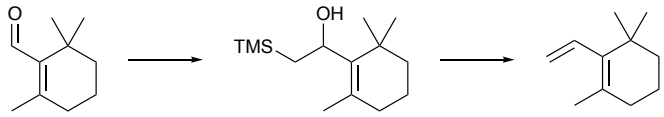


^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.02 (s, 6 H, $2CH_3$), 1.28 – 1.39 (m, 1 H, H-6_a), 1.51 – 1.66 (m, 2 H, H-2_a, H-4), 1.73 (ddd, $J = 13.6$, 6.1, 3.7 Hz, 1 H, H-2_b), 1.88 (dddd, $J = 13.5$, 10.3, 6.7, 2.3 Hz, 1 H, H-6_b), 2.16 (ddd, $J = 14.7$, 12.1, 1.0 Hz, 1 H, H-5_a), 2.25 – 2.50 (m, 3 H, H-1_a, H-1_b, $PhCH_{2a}$), 2.55 (ddd, $J = 14.8$, 4.4, 2.1 Hz, 1 H, H-5_b), 2.69 (ddd, $J = 14.1$, 10.2, 4.7 Hz, 1 H), 3.81 (s, 3 H, OCH_3), 6.86 (d, $J = 8.6$ Hz, 2 H, H-3', H-5'), 7.11 (d, $J = 8.6$ Hz, 2 H, H-2', H-6'); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 19.6 (CH_3), 28.7 (CH_3), 32.8 ($PhCH_2$), 32.9 (C-6), 38.3 (C-1), 40.4 (C-2), 42.8 (C-5), 46.2 (C-4), 55.3 (OCH_3), 113.8 (C-3', C-5'), 129.2 (C-2', C-6'), 134.1 (C-1'), 157.8 (C-4'), 212.1 (C=O); $[\alpha]^{20}_{589} = -39.3°$ (*c* 1.0, $CHCl_3$); **IR** ν_{max} /cm^{-1} = 2956br, 1713l, 1612s, 1512l, 1456s, 1300s, 1246l, 1178s, 1036s, 822s; **HRMS** (ESI): *m*/*z* calc. for $C_{16}H_{22}NaO^+$ $[M+Na]^+$: 283.1669, found: 283.1677.

HPLC traces for 6:



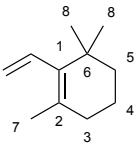
1-Vinyl-2,6,6-trimethylcyclohexene 7



A modified procedure of Ley[228] *et al.* was used for the synthesis of **7**. To a solution of magnesium (1.53 g, 63.8 mmol, 1.70 eq) and a crystal of iodine in diethyl ether (37 mL) (chloromethyl)trimethylsilane (7.7 mL, 55.6 mmol, 1.50 eq) was added under reflux. The reaction mixture was stirred for 15 min at room temperature *β*-cyclocitral (6.0 mL, 37.1 mmol, 1.00 eq) was added dropwise, and stirred for additional 1 h. The resulting mixture was transferred to an ice-saturated NH_4Cl solution (*ca* 150 mL). The organic phase was washed with NH_4Cl (sat. aq., 50 mL) and H_2O (50 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to provide the crude product in 92% yield (8.24 g, 34.3 mmol).

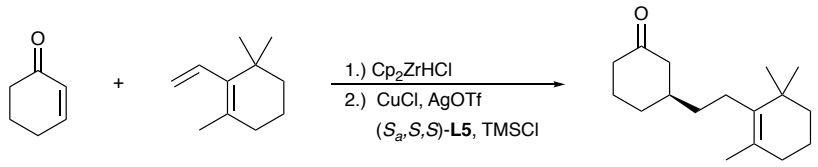
A solution of the crude alcohol (8.24 g, 34.3 mmol, 1.00 eq) in tetrahydrofuran (60 mL) was added to a solution *p*-toluenesulfonic acid monohydrate (19.57 g, 103 mmol, 3.00 eq) and conc. H_2SO_4 (1.83 mL, 34.3 mmol, 1.00 eq) in tetrahydrofuran (50 mL) and stirred vigorously for 5 min at room temperature. The reaction mixture was transferred to an ice-saturated $NaHCO_3$ solution (*ca* 250 mL). The mixture was extracted with pentane (4 × 70 mL) and the combined organic layers

were dried ($MgSO_4$) filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica (petrol/EtOAc 98:2) to afford 1-vinyl-2,6,6-trimethylcyclohexene as a colourless liquid in 59% yield over two steps (3.03 g, 21.9 mmol).



^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.91 (s, 6 H, H-8), 1.33 – 1.39 (m, 2 H, H-5), 1.48 – 1.55 (m, 2 H, H-4), 1.60 (d, J = 0.6 Hz, 3 H, H-7), 1.89 (t, J = 6.3 Hz, 2 H, H-3), 4.87 (dd, J = 17.8, 2.7 Hz, 1 H, CH=C$H_{2,trans}$), 5.14 (dd, J = 11.2, 2.7 Hz, 1 H, CH=C$H_{2,cis}$), 6.12 (ddd, J = 17.7, 11.3, 0.9 Hz, 1 H, CH=CH_2); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 20.4 (C-4), 22.5 (C-7), 29.8 (2C, C-8), 33.8 (C-3), 34.8 (C-6), 40.6 (C-5), 119.0 (CH=CH_2), 129.6 (C-2), 136.53 (CH=CH_2), 139.4 (C-2); **HRMS** (EI/FI$^+$) m/z calc. for $C_{11}H_{18}^+$ $[M]^+$: 150.1409, found 150.1409. The spectral data is in accordance with literature.[228]

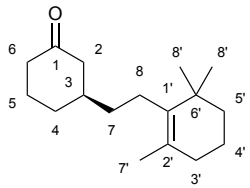
(+)-(*R*)-3-(2-(2,6,6-Trimethylcyclohex-1-en-1-yl)ethyl)cyclohexan-1-one 8



1-Vinyl-2,6,6-trimethylcyclohexene **7** (1.53 g, 10.0 mmol, 2.50 eq) was added at room temperature to a solution of Cp_2ZrHCl (2.06 g, 8.0 mmol, 2.00 eq) in dichloromethane (10 mL) and was allowed to stir for about 24 h at 40 °C (I). In a second flask a solution of CuCl (40.0 mg, 0.40 mmol, 0.10 eq) and (*S*$_a$,*S*,*S*)-**L5** (216 mg, 0.40 mmol, 0.10 eq) in diethyl ether (20 mL) was prepared at room temperature. After 1 h AgOTf (113 mg, 0.44 mmol, 0.11 eq) was added and the resulting mixture was allowed to stir for additional 15 min before it was added at at room temperature dropwise via syringe and filter to solution I. After 15 min 2-cyclohexen-1-one (0.38 mL, 4.0 mmol, 1.00 eq) and trimethylsilyl chloride (2.50 mL, 20.0 mmol, 5.0 eq) were added and the solution was allowed to stir for 24 h at room temperature. The reaction mixture was diluted with diethyl ether (20 mL) and quenched with NH_4Cl (1 M aq., *ca.* 10 mL). The aqueous phase was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were washed with $NaHCO_3$ (sat. aq., 75 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The resulting residue

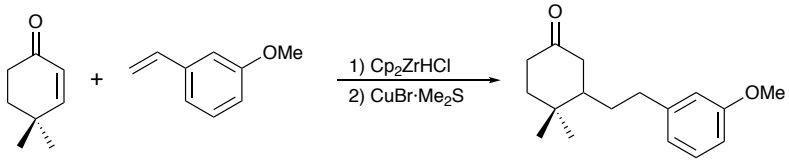
was purified by column chromatography over silica (petrol/Et_2O 88:12) to give (+)-(*R*)-3-(2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethyl)cyclohexan-1-one as a yellow oil in 44% yield (436 mg, 4.4 mmol).

Neither using the procedure from Alexakis and co-workers[72] nor epoxidation of the alkene with *m*-CPBA aided the determination the enantiomeric excess of the product.



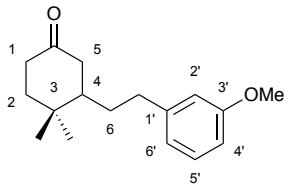
^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 3 H, H-8'), 0.97 (s, 3 H, H-8'), 1.29 – 1.48 (m, 5 H, H-4_a, H-7_a, H-7_b, H-$5'_a$, H-$5'_b$), 1.51 – 1.59 (m, 5 H, H-$4'_a$, H-$4'_b$, H-7'), 1.59 – 1.72 (m, 1 H, H-5_a), 1.72 – 1.83 (m, 1 H, H-3), 1.85 – 1.91 (m, 2 H, H-$3'_a$, H-$3'_b$), 1.91 – 2.01 (m, 3 H, H-4_b, H-8_a, H-8_b), 2.01 – 2.10 (m, 2 H, H-2_a, H-5_b), 2.19 – 2.31 (m, 1 H, H-6_a), 2.31 – 2.40 (m, 1 H, H-6_b), 2.41 – 2.51 (m, 1 H, H-2_b); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 19.50 (C-4'), 19.77 (C-7'), 25.36 (C-5), 25.90 (C-8), 28.59 (2 C, C-8'), 31.17 (C-4), 32.73 (C-3'), 34.91 (C-6'), 37.12 (C-7), 39.81 (C-5'), 40.13 (C-3), 41.51 (C-6), 48.14 (C-2), 126.93 (C-2'), 136.97 (C-1'), 211.87 (C=O); **IR** (ATR) ν_{max} /cm^{-1} = 2928m, 2864m, 2829s, 1713l, 1473s, 1447s, 1430s, 1360s, 1224s; **$[\alpha]^{20}_{589}$** = +2.4° (*c* 1.0, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{17}H_{29}O^+$ $[M+H]^+$: 249.2213, found: 249.2212.

4,4-Dimethyl-3-(2-(3-methoxyphenyl)ethyl)cyclohexanone 13[81]



3-Vinylanisole (0.40 mL, 2.9 mmol, 2.90 eq) was added at room temperature to a solution of Cp_2ZrHCl (593 mg, 2.3 mmol, 2.30 eq) in dichloromethane (6.0 mL). After stirring for about 20 min $CuBr{\cdot}Me_2S$ (206 mg, 1.0 mmol, 1.00 eq) was added to the clear solution. After stirring for additional 10 min 4,4-dimethyl-2-cyclohexen-1-one (0.13 mL, 1.0 mmol, 1.00 eq) was added and the dark solution was allowed to stir for 16 h at room temperature. The reaction mixture was diluted with diethyl ether (*ca* 6 mL) and quenched with NH_4Cl (1 M aq., *ca* 3 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL) and the combined organic layers were washed

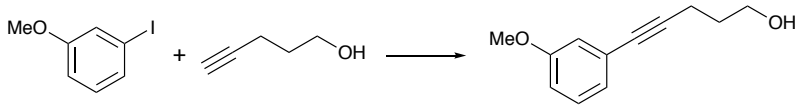
with $NaHCO_3$ (sat. aq., 20 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica (petrol/Et_2O 4:1) to afford 4,4-dimethyl-3-(2-(3-methoxyphenyl)ethyl)cyclohexanone as a yellow oil in 89% yield (231 mg, 0.89 mmol).



^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.00 (s, 3 H, CH_3), 1.01 (s, 3 H, CH_3), 1.26 – 1.44 (m, 1 H, H-6_a), 1.50 – 1.66 (m, 2 H, H-2_a, H-4), 1.71 (ddd, J = 13.6, 6.1, 3.7 Hz, 1 H, H-2_b), 1.90 (dddd, J = 13.2, 10.7, 6.7, 2.4 Hz, 1 H, H-6_b), 2.14 (ddd, J = 14.8, 12.0, 0.9 Hz, 1 H, H-5_a), 2.28 (dddd, J = 15.0, 5.3, 3.8, 2.1 Hz, 1 H, H-1_a), 2.35 – 2.48 (m, 2 H, H-1_b, $PhCH_{2a}$), 2.53 (ddd, J = 14.8, 4.4, 2.1 Hz, 1 H, H-5_b), 2.71 (ddd, J = 13.7, 10.5, 5.0 Hz, 1 H, $PhCH_{2b}$), 3.80 (s, 3 H, OCH_3), 6.68 – 6.82 (m, 3 H, H-2', H-4', H-6'), 7.21 (t, J = 7.7 Hz, 1 H, H-5'); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 19.5 (CH_3), 28.6 (CH_3), 32.5 (C-6), 32.8 (C-3), 33.7 ($PhCH_2$), 38.2 (C-1), 40.2 (C-2), 42.7 (C-5), 46.2 (C-4), 55.1 (OCH_3), 111.0, 114.1, 120.7 (C-2', C-4', C-6'), 129.3 (C-5'), 143.6 (C-1'), 159.6 (C-3'), 211.8 (C=O); **IR** (ATR) ν_{max} /cm^{-1} = 2955br, 1712l, 1584s, 1488s, 1259m, 1151m, 1043m, 780m, 696m; **HRMS** (ESI): *m*/*z* calc. for $C_{16}H_{22}NaO^+$ $[M+Na]^+$: 283.1669, found: 283.1663.

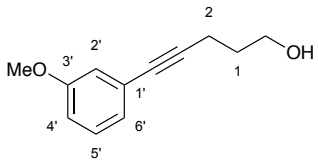
6.3.2 Oxidative Cyclisation

5-(3-Methoxyphenyl)pent-4-yn-1-ol[90]



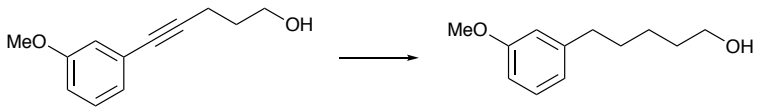
A solution of 3-iodoanisole (1.20 mL, 10.0 mmol, 1.00 eq) and 4-pentyn-1-ol (1.02 mL, 11.0 mmol, 1.10 eq) in acetonitrile (40 mL) was degassed at room temperature by evacuating and back filling with argon five times. CuI (152 mg, 0.80 mmol, 0.08 eq) and $Pd(PPh_3)_2Cl_2$ (140 mg, 0.20 mmol, 0.02 eq) were added and the reaction mixture was cooled down to 0 °C. After Et_3N was added the ice bath was removed and the reaction mixture was allowed to stir for 48 h. The reaction was filtered over Florisil®, washed with ethyl acetate (3 × 20 mL) and concentrated *in*

vacuo. The resulting crude was purified by column chromatography (petrol/EtOAc 3:2) to afford 5-(3-methoxyphenyl)pent-4-yn-1-ol as yellow oil in 83% yield (1.58 g, 8.31 mmol).

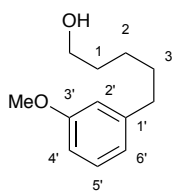


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.48 (br, 1 H, OH), 1.80 (tt, *J* = 6.9, 6.2 Hz, 2 H, H-1), 2.47 (t, *J* = 6.9 Hz, 2 H, *CH*$_2$OH), 3.72 (s, 3 H, OCH_3), 3.75 (t, *J* = 6.2 Hz, 2 H, H-2), 6.77 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1 H, H-4'), 6.85 (dd, *J* = 2.6, 1.4 Hz, 1 H, H-2'), 6.92 (dt, *J* = 7.6, 1.2 Hz, 1 H, H-6'), 7.12 (dd, *J* = 8.3, 7.6 Hz, 1 H, H-5'); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 16.0 (C-1), 31.4 (C-2), 55.3 (OCH_3), 61.9 (CH_2OH), 81.1 (Ar–*C*≡C), 89.2 (Ar–C≡*C*), 114.3 (C-4'), 116.4 (C-2'), 124.1 (C-6'), 124.7 (C-1'), 129.3 (C-5'), 159.3 (C-3'); **LRMS** (ESI): *m*/*z* calc. for $C_{12}H_{14}NaO_2^+$ $[M+Na]^+$: 213.1, found: 213.1.

5-(3-Methoxyphenyl)pentan-1-ol[90]



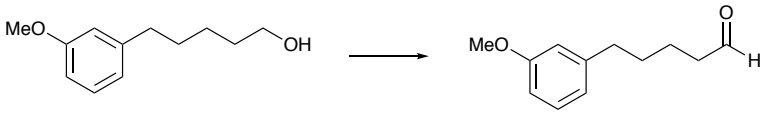
5-(Methoxyphenyl)pent-4-yn-1-ol (1.58 g, 8.3 mmol, 1.00 eq) was dissolved in methanol (20 mL) at room temperature and the solution was degassed by evacuating and back filling with argon five times. Against a positive pressure of argon Pd (10% on carbon, 182 mg, 0.17 mmol, 0.02 eq) was added and the solution was allowed to stir for 24 h under a hydrogen atmosphere (1 bar) and followed by TLC. Then the reaction mixture was filtered through Celite®, washed with ethyl acetate (3 × 20 mL) and concentrated *in vacuo*. Purification by column chromatography (petrol/EtOAc 3:2) provided 5-(3-methoxyphenyl)pentan-1-ol a colourless oil in 88% yield (1.44 g, 7.42 mmol).



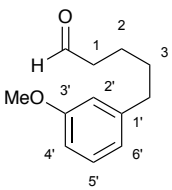
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.31 (t, *J* = 4.5 Hz, 1 H, OH), 1.37 – 1.46 (m, 2 H, H-2), 1.56 – 1.71 (m, 4 H, H-1, H-3), 2.61 (t, *J* = 7.8 Hz, 2 H, $ArCH_2$), 3.65 (td, *J* = 6.5, 4.2 Hz, 2 H, CH_2OH), 3.81 (s, 3 H, OCH_3), 6.72 - 6.76 (m, 2 H, H-2', H-4'), 6.78 (d, *J* = 7.8 Hz, 1 H, H-6'), 7.21 (dd, *J* = 8.8, 7.6 Hz, 1 H, H-5'); **^{13}C-**

NMR (101 MHz, $CDCl_3$): δ 25.4 (C-2), 31.2 (C-3), 32.7 (C-1), 36.0 ($ArCH_2$), 55.1 (OCH_3), 62.9 (CH_2OH), 110.9 (C-4'), 114.2 (C-6'), 120.9 (C-2'), 129.2 (C-5'), 144.2 (C-1'), 159.6 (C-3'); **LRMS** (ESI): *m*/*z* calc. for $C_{12}H_{18}NaO_2^+$ $[M+Na]^+$: 217.1, found: 217.1.

5-(3-Methoxyphenyl)pentanal 9

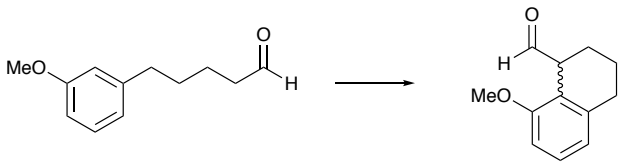


Dimethyl sulfoxide (1.09 mL, 7.4 mmol, 1.00 eq) in dichloromethane (1.8 mL) was added to a solution of oxalyl chloride (0.71 mL, 8.3 mmol, 1.12 eq) in dichloromethane (18 mL) at –78 °C. After stirring for 20 min a solution of 5-(3-methoxyphenyl)pentan-1-ol (1.44 g, 7.4 mmol, 1.00 eq) in dichloromethane (7 mL) was added. The reaction mixture was allowed to stir for 1 h at –78 °C before Et_3N (4.9 mL, 35 mmol, 4.73 eq) was added dropwise. The reaction warmed up to room temperature over 45 min and H_2O (8 mL) was added. The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by column chromatography (petrol/Et_2O 4:1) gave 5-(3-methoxyphenyl)pentanal as a colourless oil in 87% yield (1.23 g, 6.41 mmol).



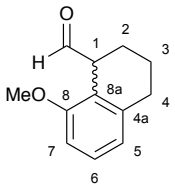
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.66 – 1.74 (m, 4 H, H-2, H-3), 2.48 (ttd, *J* = 7.0, 3.4, 1.8 Hz, 2 H, H-1), 2.65 (tdd, *J* =7.1, 2.0, 2.0 Hz, 2 H, $ArCH_2$) 3.83 (s, 3 H, OCH_3), 6.74 – 6.78 (m, 2 H, H-2', H-4'), 6.80 (d, *J* = 7.7 Hz, 1 H, H-6'), 7.23 (dd, *J* = 8.8, 7.6 Hz, 1 H, H-5'), 9.79 (t, *J* = 1.8 Hz, 1 H, CHO); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 21.7, 30.7 (C-2, C-3) 35.7 ($ArCH_2$), 43.8 (C-1), 55.1 (OCH_3), 111.1 (C-4'), 114.2 (C-2'), 120.8 (C-6'), 129.3 (C-5'), 143.6 (C-1'), 159.7 (C-3'), 202.5 (CHO); **LRMS** (ESI): *m*/*z* calc. for $C_{12}H_{16}NaO_2^+$ $[M+Na]^+$: 215.1, found: 215.1.

(+)-8-Methoxy-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde 10[90]



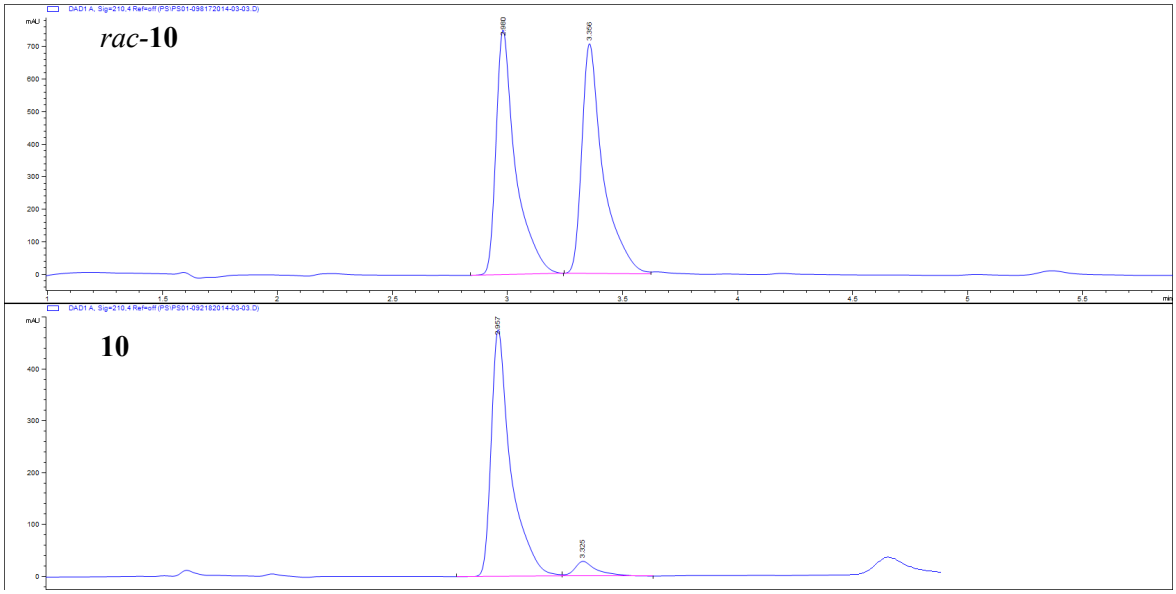
$[Fe(phen)_3](PF_6)_3$ (645 mg, 0.63 mmol, 2.50 eq) and $NaHCO_3$ (105 mg, 1.25 mmol, 5.00 eq) were added at –78 °C to a solution of (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one **L9** (18 mg, 0.08 mmol, 0.30 eq) and trifluoroacetic acid (6 µL, 0.08 mmol, 0.30 eq) in acetonitrile (0.1 mL). A solution of 5-(3-methoxyphenyl)pentanal **9** (49 mg, 0.25 mmol, 1.00 eq) and a drop of water in acetonitrile (1.9 mL) was added. The resulting mixture was degassed by evacuation and refilling with argon five times. The flask was transferred into a cooling bath (cryostat, –20 °C) and the reaction mixture was allowed to stir for 4 h. Adding Et_2O (10 mL) under vigorous stirring lead to the precipitation of a red solid. Then the mixture was filtered over silica and evaporated *in vacuo*. Purification by column chromatography (petrol/Et_2O 9:1) provided 8-methoxy-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde as a colourless oil in 45% yield (21 mg, 0.11 mmol). The racemic product was obtained in traces using pyrrolidine (7 µl, 0.08 mmol, 0.30 eq) instead of **L9**.

HPLC analysis indicated an enantiomeric excess of 85% [Chiralpak® IA; flow: 2.0 mL/min; hexane/*i*-PrOH 99:1; λ = 210 nm; t_R = 3.0 min and 3.4 min].

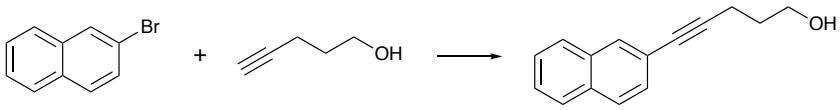


^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.67 – 1.79 (m, 2 H, H-3_a, H-3_b), 1.79 – 1.88 (m, 1 H, H-2_a), 2.13 – 2.22 (m, 1 H, H-2_b), 2.74 – 2.81 (m, 2 H, H-4_a, H-4_b), 3.76 – 3.81 (m, 1 H, H-1), 3.82 (s, 3 H, OCH_3), 6.75 (d, *J* = 8.2 Hz, 1 H, H-7), 6.79 (d, *J* = 7.7 Hz, 1 H, H-5), 7.20 (dd, *J* = 8.2, 7.7 Hz, 1 H, H-6), 9.61 (d, *J* = 1.9 Hz, 1 H, CHO); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 20.3 (C-3), 23.3 (C-2), 29.3 (C-4), 46.5 (C-1), 55.4 (OCH_3), 107.5 (C-7), 121.1 (C-8a), 121.9 (C-5), 127.7 (C-6), 139.5 (C-4a), 157.4 (C-8), 203.0 (CHO); $[\alpha]^{20}_{589}$ = +75.6° (*c* 1.0 $CHCl_3$); **LRMS** (ESI): *m*/*z* calc. for $C_{12}H_{14}NaO_2^+$ $[M+Na]^+$: 213.1, found: 213.1.

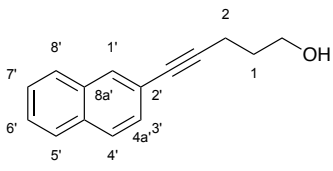
HPLC traces for 10:



5-(Naphthalen-2-yl)pent-4-yn-1-ol[229]



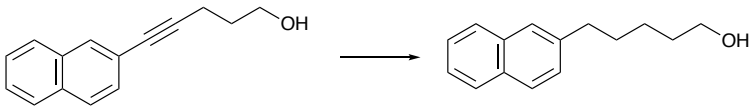
PPh_3 (26 mg, 0.1 mmol, 0.02 eq) and $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol, 0.01 eq) were added at room temperature to a solution of 2-bromonaphthalene (1.04 g, 5.0 mmol, 1.00 eq) and 4-pentyn-1-ol (0.70 mL, 7.5 mmol, 1.50 eq) in NEt_3 (7.0 mL) by evacuating and back filling with argon five times. The flask was heated up to 40 °C, CuI (19 mg, 0.1 mmol, 0.02 eq) was added and the mixture stirred for 15 min. Then the reaction mixture was heated up to 80 °C and was allowed to stir for 48 h. After cooling down the flask to room temperature the reaction was filtered over Florisil®, washed with ethyl acetate (3 × 15 mL) and concentrated *in vacuo*. The resulting crude was purified by column chromatography (petrol/EtOAc 3:2) and gave 5-(naphthalen-2-yl)pent-4-yn-1-ol as a white solid in 71% yield (745 mg, 3.54 mmol).



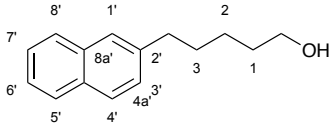
***T*$_{mp}$** = 37.8 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.52 (t, *J* = 5.0 Hz, 1 H, OH), 1.92 (tt, *J* = 6.5 Hz, 2 H, H-1), 2.61 (t, *J* = 6.9 Hz, 2 H, CH_2OH), 3.88 (q, *J* = 5.5 Hz, 2 H, H-2), 7.42 - 7.52 (m, 3 H, Ar-H),

7.73 - 7.84 (m, 3 H, Ar-H), 7.92 (s, 1 H, H-1'); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 16.1 (C-1), 31.4 (C-2), 61.9 (CH_2OH), 81.5 (Ar–*C*≡C), 89.7 (Ar–C≡*C*), 121.1 (C-2'), 126.3, 126.4, 127.6, 127.7, 127.8, 128.6 (C-3', C-4', C-5', C-6', C-7', C-8'), 131.1 (C-1'), 132.5, 133.0 (C-4a', C-8a'); **LRMS** (ESI): *m*/*z* calc. for $C_{15}H_{14}NaO^+$ $[M+Na]^+$: 233.1, found: 233.1.

5-(Naphthalen-2-yl)pentan-1-ol[90]

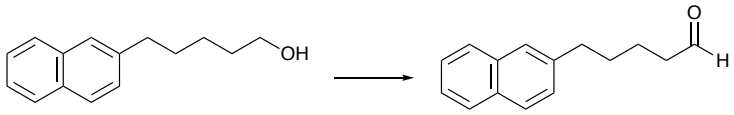


5-(Naphthalen-2-yl)pent-4-yn-1-ol (640 mg, 3.0 mmol, 1.00 eq) was dissolved in ethyl acetate (45 mL) at room temperature and the solution was degassed by evacuating and back filling with argon five times. Against a positive pressure of argon Pd (5% on carbon, 135 mg, 0.06 mmol, 0.02 eq) was added and the solution was allowed to stir for 24 h under a hydrogen atmosphere (1 bar) and followed by TLC. Then the reaction mixture was filtered through Celite®, washed with ethyl acetate (3 × 20 mL) and concentrated *in vacuo*. Purification by crystallization (≈ 2% EtOAc in hexane) provided 5-(naphthalen-2-yl)pentan-1-ol as a white solid in 61% yield (390 mg, 1.82 mmol).

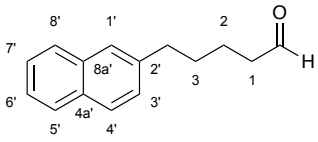


***T*$_{mp}$** = 45.2 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.29 (br, 1 H, OH), 1.38 – 1.52 (m, 2 H, H-2), 1.57 - 1.69 (m, 2 H, H-1), 1.70 – 1.82 (m, 2 H, H-3), 2.81 (t, *J* = 7.7 Hz, 2 H, $ArCH_2$), 3.66 (t, *J* = 6.6 Hz, 2 H, CH_2OH), 7.35 (dd, *J* = 8.4, 1.8 Hz, 1 H, H-3'), 7.39 – 7.50 (m, 2 H, H-6', H-7'), 7.63 (s, 1 H, H-1'), 7.78 (d, *J* = 8.3 Hz, 1 H, H-4) 7.78 – 7.83 (m, 2 H, H-5', H-8'); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 25.5 (C-2), 31.2 (C-3), 32.7 (C-1), 36.1 ($ArCH_2$), 63.0 (CH_2OH), 125.1, 125.9 (C-6', C-7'), 126.4 (C-1'), 127.4, 127.4, 127.6, 127.8 (C-3', C-4', C-5', C-8'), 132.0, 133.6 (C-4a', C-8a'), 140.1 (C-2'); **LRMS** (ESI): *m*/*z* calc. for $C_{12}H_{14}NaO_2^+$ $[M+Na]^+$: 237.1, found: 237.1.

5-(Naphthalen-2-yl)pentan-1-al 11

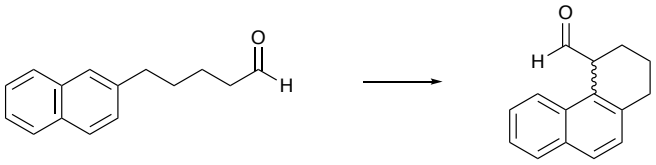


A solution of 5-(3-naphthalen-2-yl)pentan-1-ol (125 mg, 0.59 mmol, 1.00 eq) in dichloromethane (6 mL) was added at room temperature to Dess-Martin periodinane (400 mg, 0.94 mmol, 1.60 eq) and $NaHCO_3$ (500 mg, 5.95 mmol, 10 eq). After a drop of water was added the resulting mixture was allowed to stir for 1 h. The reaction mixture was quenched with NaS_2O_3 (1 M aq., 10 mL). The aqueous phase was extracted with dichloromethane (3 × 15 mL) and the combined organic layers was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica (petrol/Et_2O 4:1) and gave 5-(naphthalen-2-yl)pentan-1-al as a colourless oil in 73% yield (92 mg, 0.43 mmol).



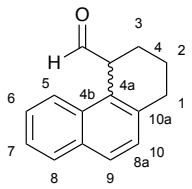
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.67 – 1.84 (m, 4 H, H-1, H-2), 2.48 (td, J = 7.0, 1.7 Hz, 2 H, H-1), 2.77 – 2.87 (t, J = 7.3 Hz, 2 H, $ArCH_2$), 7.33 (d, J = 8.4 Hz, 1 H, H-3'), 7.41 – 7.50 (m, 2 H, H-6', H-7'), 7.62 (s, 1 H, H-1'), 7.74 – 7.86 (m, 3 H, H-4', H-5', H-8'), 9.77 (t, J = 1.8 Hz, 1 H, CHO); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 21.7, 30.7 (C-2, C-3), 35.8 ($ArCH_2$), 43.7 (C-1), 125.1, 125.9 (C-6', C-7'), 126.4 (C-1'), 127.2 (C-3'), 127.4, 127.6, 127.9 (C-4', C-5', C-8'), 132.0, 133.6 (C-4a', C-8a'), 139.4 (C-2'), 202.5 (CHO); **LRMS** (ESI): *m/z* calc. for $C_{15}H_{17}O$ $[M+H]^+$: 213.1, found: 213.1. The spectral data is in accordance with literature.[88]

1,2,3,4-Tetrahydrophenanthrene-4-carbaldehyde 12[90]



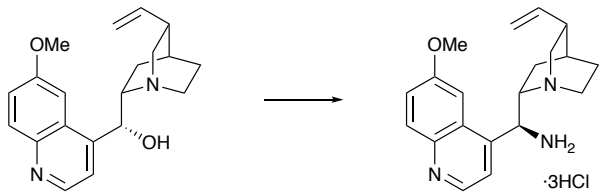
$[Fe(phen)_3](PF_6)_3$ (413 mg, 0.40 mmol, 2.00 eq) and Na_2HPO_4 (28 mg, 0.4 mmol, 2.00 eq) were added at –78 °C to a solution of (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one **L9** (10.0 mg, 0.04 mmol, 0.10 eq) and trifluoroacetic acid (6 µL, 0.04 mmol, 0.10 eq) in acetonitrile

(0.08 mL). A solution of 5-(3-methoxyphenyl)pentanal **11** (42 mg, 0.20 mmol, 1.00 eq) and a drop of water in acetone (1.0 mL) was added. The resulting mixture was degassed by evacuation and refilling with argon (5 ×). The flask was transferred into a cooling bath (cryostat, –20 °C) and the reaction mixture was allowed to stir for 24 h. Adding Et_2O (6 mL) under vigorous stirring lead to the precipitation of a red solid. Then the mixture was filtered over silica and evaporated *in vacuo*. Purification by column chromatography (petrol/Et_2O 9:1) provided 1,2,3,4-tetrahydrophenanthrene-4-carbaldehyde as a colourless oil in 56% yield (23 mg, 0.11 mmol).



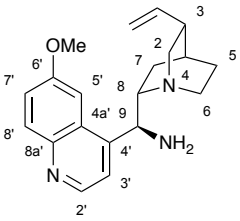
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.78 – 2.08 (m, 3 H, H-2_a, H-2_b, H-3_a), 2.48 (dddd, *J* = 13.5, 5.4, 3.2, 3.2 Hz, 1 H, H-3_b), 2.99 (app. dd, *J* = 7.8, 4.9 Hz, 2 H, H-1_a, H-1_b), 4.27 (ddd, *J* = 5.6, 2.8, 2.8 Hz, 1 H, H-4), 7.29 (d, *J* = 8.3 Hz, 1 H, H-10), 7.44 – 7.56 (m, 2 H, H-6, H-7), 7.74 (d, *J* = 8.6 Hz, 1 H, H-9), 7.79 – 7.89 (m, 2 H, H-5, H-8), 9.79 (d, *J* = 2.0 Hz, 1 H, CHO); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 19.8 (C-2), 24.0 (C-3), 30.0 (C-1), 47.9 (C-4), 122.7 (C-5 or C-8), 125.1 (C-6 or C-7), 126.2 (3C, C-4a, C-4b, C-8a or C-10a), 126.6 (C-6 or C-7), 127.7 (C-9), 128.2 (C-10), 128.8 (C-5 or C-8), 132.4, 132.5, 136.3 (C-4a, C-4b, C-8a or C-10a), 202.8 (CHO); **LRMS** (ESI): *m*/*z* calc. for $C_{15}H_{14}NaO^+$ $[M+Na]^+$: 233.1, found: 233.1.

9-Amino-(9-deoxy)*epi*-quinine·3HCl L15[230,231]



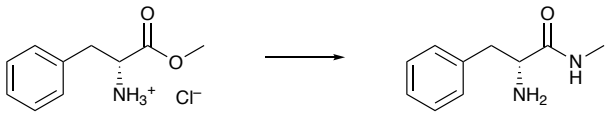
A solution of quinine (0.50 g, 1.54 mmol, 1.00 eq) and triphenylphosphine (404 mg, 1.54 mmol, 1.00 eq) in tetrahydrofuran (5 mL) was cooled down to 0 °C and diisopropyl azodicarboxylate (0.36 mL, 1.85 mmol, 1.20 eq) was added dropwise. After stirring for 10 min diphenylphosphoryl azide (0.40 mL, 1.85 mmol, 1.20 eq) was added dropwise. The reaction mixture was stirred for 4 h at room temperature and 2 h at 45 °C before triphenylphosphine (485 mg, 1.85 mmol, 1.20 eq) was added. The resulting mixture was stirred for 2 h at 45 °C, water (0.5 mL) was added and it was

stirred for further 16 h at room temperature. The reaction mixture was concentrated and diluted with dichloromethane (5 mL) and HCl (2 M, 4 mL). The aqueous phase was washed with dichloromethane (5 mL) and the combined organic layers were concentrated. Recrystallization of the crude yellow solid from EtOAc/MeOH 1:1 provided 9-amino-(9-deoxy)*epi*-quinine·3HCl as a pale yellow solid in 39% yield (262 mg, 0.61 mmol).

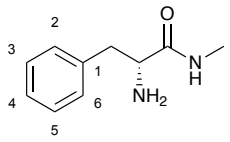


***T*$_{mp}$** = 179.8 °C; **^{1}H-NMR** (500 MHz, DMSO): δ 0.83 – 0.93 (m, 1 H, H-7$_a$), 1.46 – 1 .56 (m, 1 H, H-7$_b$), 1.80 – 1.93 (m, 3 H, H-4, H-5$_a$, H-5$_b$), 2.76 (br, 1 H, H-3), 3.31 – 3.44 (m, 2 H, H-2$_a$, H-6$_a$), 3.74 (dd, *J* = 12.6, 10.8 Hz, 1 H, H-2$_b$), 4.06 (s, 3 H, OCH_3), 4.07 - 4.18 (m, 1 H, H-6$_b$), 4.69 – 4.82 (m, 1 H, H-8), 5.15 (d, *J* = 10.5 Hz, 1 H, *cis*CH_2=CH), 5.29 (d, *J* = 17.2 Hz, 1 H, *trans*CH_2=CH), 5.88 (ddd, *J* = 17.3, 10.6, 6.6 Hz, 1 H, CH_2=C*H*), 5.97 (d, *J* = 10.1 Hz, 1 H, H-9), 7.73 (dd, *J* = 9.3, 2.3 Hz, 1 H, H-7'), 7.98 (d, *J* = 2.1 Hz, 1 H, H-5'), 8.30 (d, *J* = 9.2 Hz, 1 H, H-8'), 8.35 (d, *J* = 5.2 Hz, 1 H, H-2' or H-3'), 9.11 (d, *J* = 5.2 Hz, 1 H, H-2' or H-3'), 9.66 (br, 2 H, NH_2); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 23.4, 23.5, 25.5, 35.9, 41.7, 47.8, 51.9, 56.6, 58.7, 103.0, 116.7, 121.4, 124.9, 127.6, 128.5, 138.2, 139.3, 142.2, 144.7, 159.3; **LRMS** (ESI): *m*/*z* calc. for $C_{20}H_{26}N_3O^+$ $[M+H]^+$: 324.2, found: 324.2.

D-Phenylalanine *N*-methylamide[232,233]

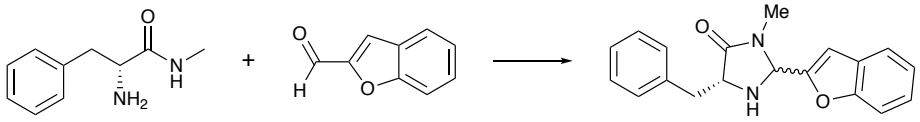


D-Phenylalanine methyl ester hydrochloride (1.00 g, 4.7 mmol, 1.0 eq) was added to methyl amine (33 wt.% solution in ethanol, 2.9 mL, 23.5 mmol, 5.3 eq) and was stirred for 4 d at room temperature. The reaction mixture was concentrated, dissolved in $NaHCO_3$ (sat. aq., 20 mL) and extracted with chloroform (4 × 10 mL). The solution was dried (Na_2SO_4), filtered and evaporated *in vacuo* to provide D-phenylalanine *N*-methylamide as a colourless solid in 99% yield (828 mg, 4.7 mmol).



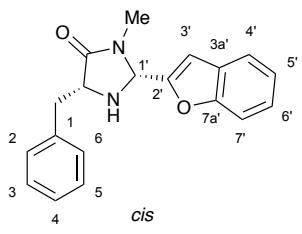
***T*$_{mp}$** = 65.8 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.33 (br, 3H, NH_2, NH), 2.68 (dd, *J* = 13.7, 9.5 Hz, 1 H, $ArCH_{2a}$), 2.83 (d, *J* = 5.0 Hz, 3 H, CH_3), 3.30 (dd, *J* = 13.8, 4.0 Hz, 1 H, $ArCH_{2b}$), 3.61 (dd, *J* = 9.4, 3.9 Hz, 1 H, CH), 7.20 – 7.26 (m, 3 H, H-2, H-4, H-6), 7.29 – 7.36 (m, 2 H, H-3, H-5); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 16.0 (C-1), 25.8 (CH_3), 41.0 ($ArCH_2$), 56.5 (CH), 126.8 (C-4), 128.7 (C-3, C-5), 129.2 (C-2, C-6), 138.0 (C-1), 174.8 (C=O); **[*α*]$^{20}_{589}$** = +90.2° (*c* 1.0, $CHCl_3$); **LRMS** (ESI): *m*/*z* calc. for $C_{10}H_{15}N_2O^+$ $[M+H]^+$: 179.1, found: 179.1.

(2*R*,5*R*)-2-(Benzofuran-2-yl)-5-benzyl-3-methyl-imidazolidin-4-one *cis*-L10 and (2*S*,5*R*)-2-(benzo-furan-2-yl)-5-benzyl-3-methyl-imidazolidin-4-one *trans*-L10 [92]



2-Benzofurancarboxaldehyde (108 µL, 0.89 mmol, 1.00 eq) and D-Phenylalanine *N*-methylamide (200 mg, 1.12 mmol, 1.25 eq) were added consecutively to a solution of ytterbium triflate (800 mg, 1.29 mmol, 1.45 eq) and powdered 4 Å molecular sieve (350 mg) in tetrahydrofuran (24 mL) and the reaction mixture was stirred for 4 d at room temperature. The yellow mixture was filtered through a pad of silica, washed with ethyl acetate (3 × 20 mL) and concentrated. The remaining residue was diluted with dichloromethane (20 mL), washed with $NaHCO_3$ (sat. aq., 20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica eluting with a gradient of 25%, 50% and 75% EtOAc/hexane to give *cis*-**L10** (26%, 72 mg, 0.23 mmol) and *trans*-**L10** (26%, 71 mg, 0.23 mmol) as yellow solids.

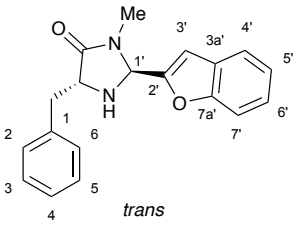
Analytical data of *cis*-**L10**:



***T*$_{mp}$** = 107.5 °C **TLC** R_f = 0.22 (hexane/EtOAc 1:4); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 2.74 (s, 3 H, NCH_3), 3.15 (dd, *J* = 14.2, 7.9 Hz, 1 H, $PhCH_{2a}$), 3.31 (dd, *J* = 14.2, 4.0 Hz, 1 H, $PhCH_{2b}$), 3.90 (dd, *J* = 7.9, 4.2 Hz, 1 H, COCH), 5.45 (d, *J* = 1.1 Hz, 1 H, H-1'), 6.64 (d,

J = 0.8 Hz, 1 H, H-3'), 7.23 – 7.37 (m, 7 H, H-2, H-3, H-4, H-5, H-6, H-5', H-6'), 7.43 (dd, *J* = 8.2, 0.8 Hz, 1 H, H-4'), 7.56 (d, *J* = 7.7 Hz, 1 H, H-7'); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 27.3 (NCH_3), 37.9 ($PhCH_2$), 60.3 (CO*C*H), 71.3 (C-1'), 106.7 (C-3'), 111.6 (C-4'), 121.5 (C-7'), 123.3, 125.2, 126.8 (3C, ArCH), 127.5 (ArC), 128.8, 129.5 (2C, ArCH), 137.2 (C-1), 153.2, 155.1 (ArC), 173.8 (C=O); **$[\alpha]^{20}_{589}$** = +141.1° (*c* 0.6, $CHCl_3$); **LRMS** (ESI): *m*/*z* calc. for $C_{19}H_{19}N_2O_2^+$ $[M+H]^+$: 307.1, found: 307.1.

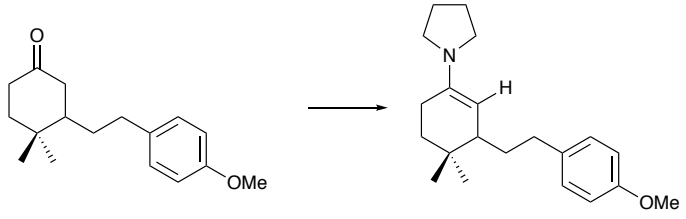
Analytical data of *trans*-**L10**:



***T*$_{mp}$** = 108.2 °C **TLC** R_f = 0.46 (hexane/EtOAc 1:4); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 2.45 (br, 1 H, NH), 2.77 (s, 3 H, NCH_3), 3.03 (dd, *J* = 13.7, 7.5 Hz, 1 H, $PhCH_{2a}$), 3.23 (dd, *J* = 13.8, 4.0 Hz, 1 H, $PhCH_{2b}$), 4.16 (dd, *J* = 7.0, 4.8 Hz, 1 H, COCH), 5.22 (d, *J* = 1.5 Hz, 1 H, H-1'), 6.73 (d, *J* = 0.8 Hz, 1 H, H-3'), 7.24 – 7.37 (m, 7 H, H-2, H-3, H-4, H-5, H-6, H-5', H-6'), 7.46 (dd, *J* = 8.2, 0.6 Hz, 5 H, H-4'), 7.57 (d, *J* = 7.6 Hz, 1 H, H-7'); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 27.2 (NCH_3), 38.2 ($PhCH_2$), 59.5 (CO*C*H), 71.1 (C-1'), 105.9 (C-3'), 111.6 (C-4'), 121.3 (C-7'), 123.2, 125.1, 126.8 (3C, ArCH), 127.3 (ArC), 128.6, 129.6 (2C, ArCH), 137.4 (C-1), 153.7, 155.1 (2C, ArC), 173.7 (C=O); **$[\alpha]^{20}_{589}$** = –25.6° (*c* 0.6, $CHCl_3$); **LRMS** (ESI): *m*/*z* calc. for $C_{19}H_{19}N_2O_2^+$ $[M+H]^+$: 307.1, found: 307.1.

Non-regioselective Enamine Formation

1-(4,4-Dimethyl-3-(2-(4-methoxyphenyl)ethyl)cyclohex-1-en-1-yl)pyrrolidine[234,235]



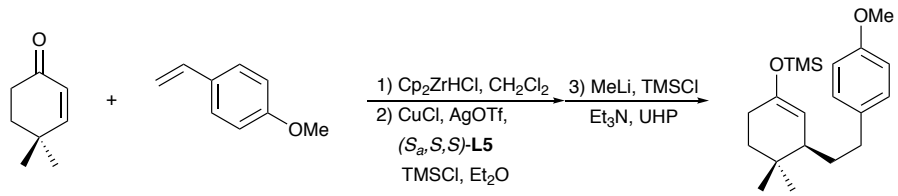
A modified procedure of Carlson *et al.* was used for the non-regioselective enamine synthesis with pyrrolidine.[234] To a solution of pyrrolidine (0.14 mL, 2.0 mmol, 10.0 eq) and 4,4-dimethyl-3-(2-(3-methoxy-phenyl)ethyl)cyclohe-xanone (52 mg, 0.2 mmol, 1.00 eq) in toluene (0.8 mL) was added

at 0 °C $TiCl_4$ (1 M solution in toluene, 0.2 mL, 0.2 mmol, 1.00 eq). After stirring for 1 h at 0 °C the ice bath was removed and the reaction mixture was allowed to stir for 1 h at room temperature. The resulting mixture was filtered through a pad of Celite®, washed with diethyl ether (20 mL) and evaporated *in vacuo* to give a mixture of products as a yellow oil (50 mg). Due to its instability no further purification was performed.

IR (ATR) ν_{max} /cm^{-1} = 2954br, 1714l, 1512l, 1464s, 1367s, 1300s, 1245l, 1177s, 1037s, 822s; **HRMS** (ESI): *m*/*z* calc. for $C_{21}H_{32}NO^+$ $[M+H]^+$: 314.2478, found: 314.2472.

The ^{1}H-NMR spectrum shows signals at 4.19 and 4.25 ppm for the highlighted proton which is due to the formation of the other regioisomer 1-(4,4-dimethyl-5-(2-(4-methoxyphenyl)ethyl)cyclohex-1-en-1-yl)pyrrolidine (1:1 ratio). In addition, the ^{1}H-NMR spectrum shows remaining starting material.

TMS enolate trapping with MeLi and TMSCl, (*R*)-((3-(4-methoxyphenethyl)-4,4-dimethylcyclohex-1-en-1-yl)oxy)trimethylsilane 17[93]



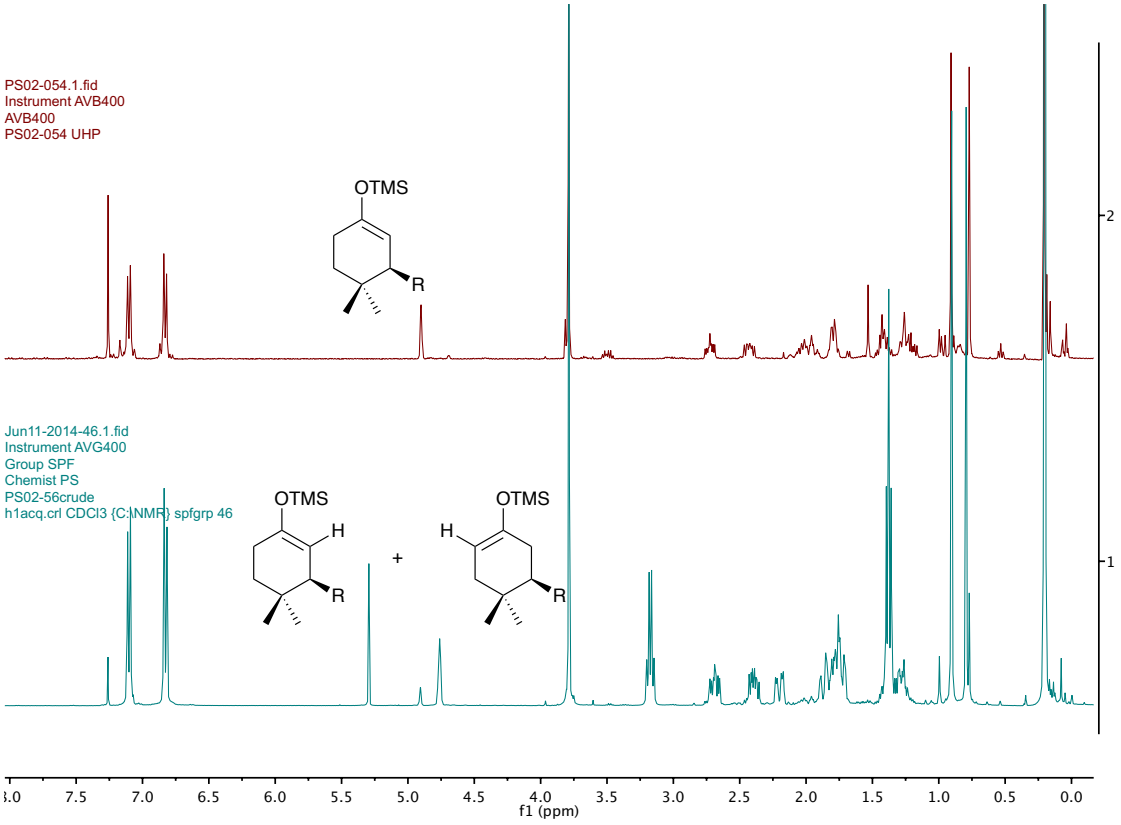
4-Vinylanisole **3** (0.14 mL, 1.0 mmol, 2.50 eq) was added at room temperature to a solution of Cp_2ZrHCl (206 mg, 0.80 mmol, 2.00 eq) in dichloromethane (0.4 mL) and was allowed to stir for about 20 min (I). In a second flask, a solution of CuCl (4.0 mg, 40 µmol, 0.10 eq) and (*Sa,S,S*)-**L5** (21.6 mg, 40 µmol, 0.10 eq) in diethyl ether (2.0 mL) was prepared at room temperature. After 1 h AgOTf (11.3 mg, 44 µmol, 0.11 eq) was added and the resulting mixture was allowed to stir for additional 15 min before it was added at 0 °C dropwise via syringe and filter to solution I. After 15 min 4,4-dimethyl-2-cyclohexen-1-one **4** (53 µL, 0.40 mmol, 1.00 eq) and trimethylsilyl chloride (0.25 mL, 2.0 mmol, 5.00 eq) were added and the solution was allowed to stir for 16 h at 0 °C.

The reaction mixture was then cooled to –78 °C, followed by addition of MeLi (1.6 M in Et_2O, 0.65 mL, 1.04 mmol, 2.60 eq). After 1 h, TMSCl (0.18 mL, 1.44 mmol. 3.60 eq) was added, and stirring was continued for 1 h at –78 °C. Triethylamine (0.67 mL, 4.8 mmol, 12 eq) and urea hydrogen peroxide (376 mg, 4.00 mmol, 10 eq) were added successively, the cooling bath was removed, and stirring was continued for additional 24 h at room temperature. The reaction mixture was diluted with diethyl ether (ca. 3 mL). After stirring was continued for 20 min the mixture was filtered over Celite® evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica (petrol/CH_2Cl_2 4:1, 1% NEt_3) to afford (*R*)-((3-(4-methoxyphenethyl)-4,4-dimethylcyclohex-1-en-1-yl)oxy)trimethylsilane as a colourless oil in 8% yield (11 mg, 0.03 mmol).

The compound was stable enough to be measure the proton and carbon spectra. Further analysis failed due to the poor stability of the compounds.

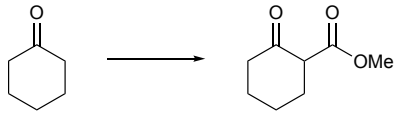
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.21 (s, 9 H), 0.77 (s, 3 H), 0.91 (s, 3 H), 1.16 – 1.30 (m, 2 H), 1.34 – 1.49 (m, 2H), 1.71 – 1.85 (m, 2 H), 1.88 – 2.09 (m, 2 H), 2.43 (ddd, *J* = 13.9, 10.4, 6.6 Hz, 1 H), 2.72 (ddd, *J* = 14.5, 10.4, 5.1 Hz, 1H), 3.79 (s, 3 H), 4.90 (s, 1 H), 6.78 – 6.89 (m, 2 H), 7.06 – 7.14 (m, 2 H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 0.6, 21.8, 27.6, 28.5, 31.8, 33.5, 36.5, 44.3, 55.4, 107.4, 113.9, 129.4, 135.1, 149.7, 157.8.

^{1}H-NMR spectra compared with non-regioselective TMS-enolate formation, generated with TMSOTf and NEt_3 in CH_2Cl_2.



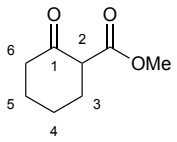
6.3.3 Approaches with Modified Starting Materials

2-(Methoxycarbonyl)cyclohexanone[236]



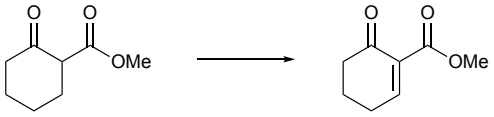
A mixture of NaH (60% dispersion in mineral oil, 1.5 g, 38 mmol, 1.25 eq) and dimethyl carbonate (2.53 mL, 30 mmol, 2.50 eq) in tetrahydrofuran (7.5 mL) was heated up to reflux. A solution of cyclohexanone (1.23 mL, 12 mmol, 1.00 eq) in tetrahydrofuran (3 mL) was added dropwise over 10 min and stirred for further 1 h under reflux. A spatula tip of KH was added 2 min after the addition of cyclohexanone began to initiate the reaction. The reaction mixture was cooled down with an ice-water bath, hydrolyzed by the addition of acetic acid (3 M, aq. 11 mL) and transferred into brine (15 mL). The aqueous phase was washed with dichloromethane (4 × 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The resulting

residue was purified by vacuum distillation (bp 47 °C at 0.3–0.4 mmHg) to give 2-(methoxycarbonyl)cyclohexanone as a colourless liquid in 48% yield (902 mg, 5.8 mmol).



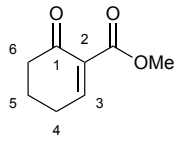
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.58 – 1.96 (m, 4 H, H-4, H-5), 2.12 – 2.34 (m, 4 H, H-3, H-6), 3.78 (s, 3 H, CO_2CH_3), 12.19 (s, 1 H, OH); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 21.9, 22.4, 22.4, 29.1 (C-3, C-4, C-5, C-6), 51.4 (CH_3), 97.7 (C-2), 172.2, 173.1 (C-1, CO_2CH_3); **LRMS** (ESI): *m*/*z* calc. for $C_8H_{12}NaO_3^+$ $[M+Na]^+$: 179.1, found: 179.1.

2-(Methoxycarbonyl)cyclohex-2-en-1-one 24[237]



2-(Methoxycarbonyl)cyclohexanone (0.613 g, 4.0 mmol, 1.00 eq) was added dropwise at 0 °C to a solution of phenylselenyl chloride (0.843 g, 4.4 mmol, 1.10 eq) and pyridine (0.48 mL, 6 mmol, 1.50 eq) in dichloromethane (24 mL). After the reaction mixture was stirred for 90 min at 0 °C, HCl (1 M, 5 mL) was added at room temperature. The organic phase was washed with $NaHCO_3$ (sat. aq., 20 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*.

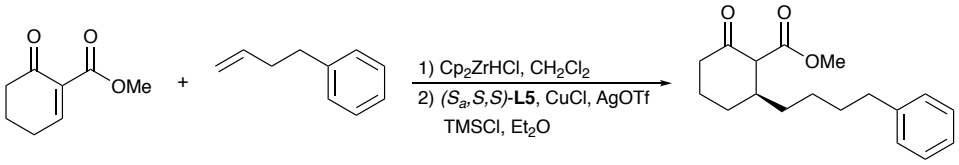
To a solution of the crude product in dichloromethane (75 mL) was added H_2O_2 (35% aq., 1.2 mL, 12.0 mmol. 3.00 eq) at 0 °C over 30 min. The reaction mixture was stirred for further 2 h at 0 °C. The organic phase was washed with H_2O (30 mL) and $NaHCO_3$ (sat. aq., 30 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The resulting residue was used without further purification and to give 2-(methoxycarbonyl)cyclohex-2-en-1-one as a yellow liquid in 91% yield (560 mg, 3.6 mmol).



^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.09 (tt, J = 6.4 Hz, 2 H, H-5), 2.47 – 2.68 (m, 4 H, H-4, H-6), 3.84 (s, 3 H, CO_2CH_3), 7.74 (t, J = 4.2 Hz, 1 H, H-3); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 22.2 (C-5), 26.2, 38.8 (C-4, C-6), 52.2 (CH_3), 133.0 (C-2),

156.6 (C-3), 165.3 (CO_2CH_3), 194.5 (C-1); **LRMS** (ESI): *m/z* calc. for $C_8H_{10}NaO_3^+$ $[M+Na]^+$: 177.1, found: 177.1.

2-Carboxymethyl-3-(4-phenylbutyl)cyclohexan-1-one 25

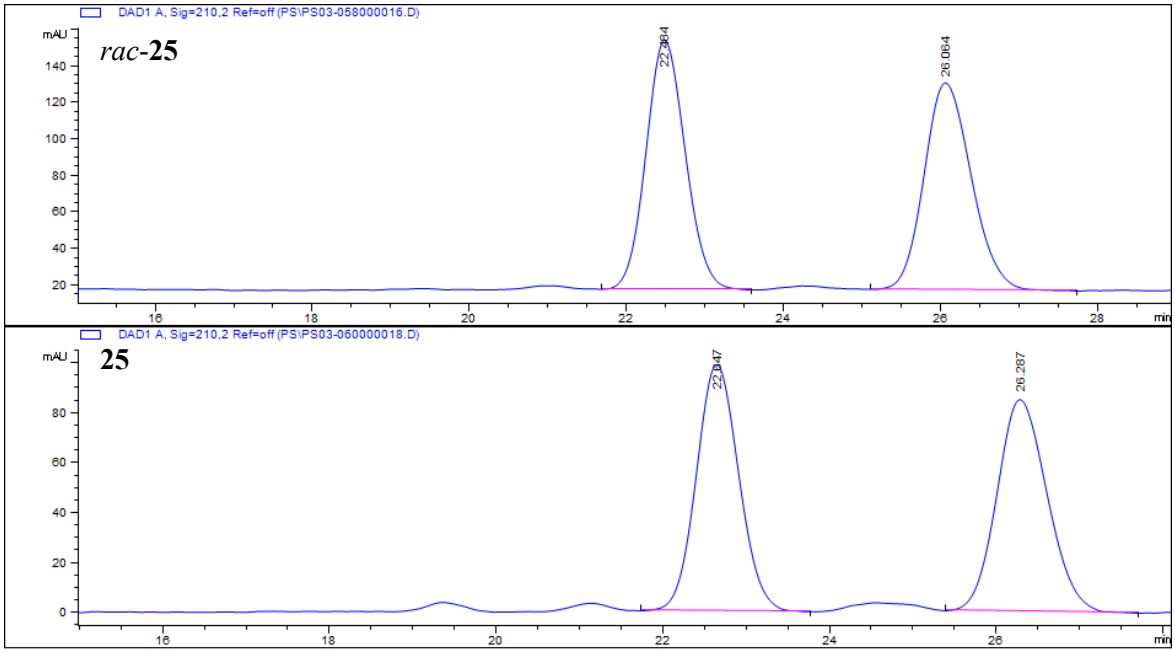


4-Phenyl-1-butene (0.15 mL, 1.0 mmol, 2.50 eq) was added at room temperature to a solution of Cp_2ZrHCl (206 mg, 0.80 mmol, 2.00 eq) in dichloromethane (0.4 mL) and was allowed to stir for about 20 min (I). In a second flask, a solution of CuCl (4.0 mg, 40 µmol, 0.10 eq) and **L5** (21.6 mg, 40 µmol, 0.10 eq) in diethyl ether (2.0 mL) was prepared at room temperature. After 1 h AgOTf (11.3 mg, 44 µmol, 0.11 eq) was added and the resulting mixture was allowed to stir for additional 15 min before it was added at 0 °C dropwise via syringe and filter to solution I. After 15 min 2-(methoxycarbonyl)cyclohex-2-en-1-one **24** (62 µL, 0.40 mmol, 1.00 eq.) and trimethylsilyl chloride (0.25 mL, 2.0 mmol, 5.00 eq) were added and the solution was allowed to stir for 16 h at 0 °C. The reaction mixture was diluted with diethyl ether (ca. 3 mL) and quenched with NH_4Cl (1 M aq., ca. 1.5 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with $NaHCO_3$ (sat. aq., 15 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica (toluene/EtOAc 98:2) to give impure 2-carboxymethyl-3-(4-phenylbutyl)cyclohexan-1-one as a yellow oil (27 mg).

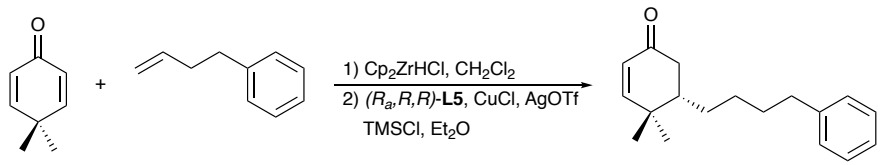
HPLC analysis indicated an enantiomeric excess of 0% [Chiralpak® IC; flow: 1.5 mL/min; hexane/*i*-PrOH 9:1; λ = 210 nm; t_R = 22.7 min and t_R = 26.3 min].

Due to purification problems and a number of by-products with similar polarity a pure sample could not be isolated for full analysis. **HRMS** (EI): *m/z* calc. for $C_{16}H_{22}NaO$ $[M+Na]^+$: 253.1563, not found.

HPLC traces for 25:



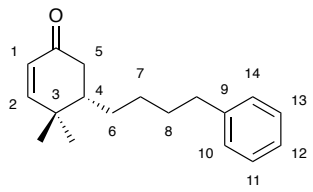
(+)-(*S*)-4,4-Dimethyl-5-(4-phenylbutyl)cyclohex-2-en-1-one 27



4-Phenyl-1-butene (0.15 mL, 1.0 mmol, 2.50 eq) was added at room temperature to a solution of Cp_2ZrHCl (206 mg, 0.80 mmol, 2.00 eq) in dichloromethane (0.4 mL) and was allowed to stir for about 20 min (I). In a second flask, a solution of CuCl (4.0 mg, 40 µmol, 0.10 eq) and *(Ra,R,R)*-**L5** (21.6 mg, 40 µmol, 0.10 eq) in diethyl ether (2.0 mL) was prepared at room temperature. After 1 h AgOTf (11.3 mg, 44 µmol, 0.11 eq) was added and the resulting mixture was allowed to stir for additional 15 min before it was added at 0 °C dropwise via syringe and filter to solution I. After 15 min 4,4-dimethylcyclohex-2,5-dien-1-one[238] (49 mg, 0.40 mmol, 1.00 eq.) and trimethylsilyl chloride (0.25 mL, 2.0 mmol, 5.00 eq) were added and the solution was allowed to stir for 16 h at 0 °C. The reaction mixture was diluted with diethyl ether (ca. 3 mL) and quenched with NH_4Cl (1 M aq., ca. 1.5 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with $NaHCO_3$ (sat. aq., 15 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica

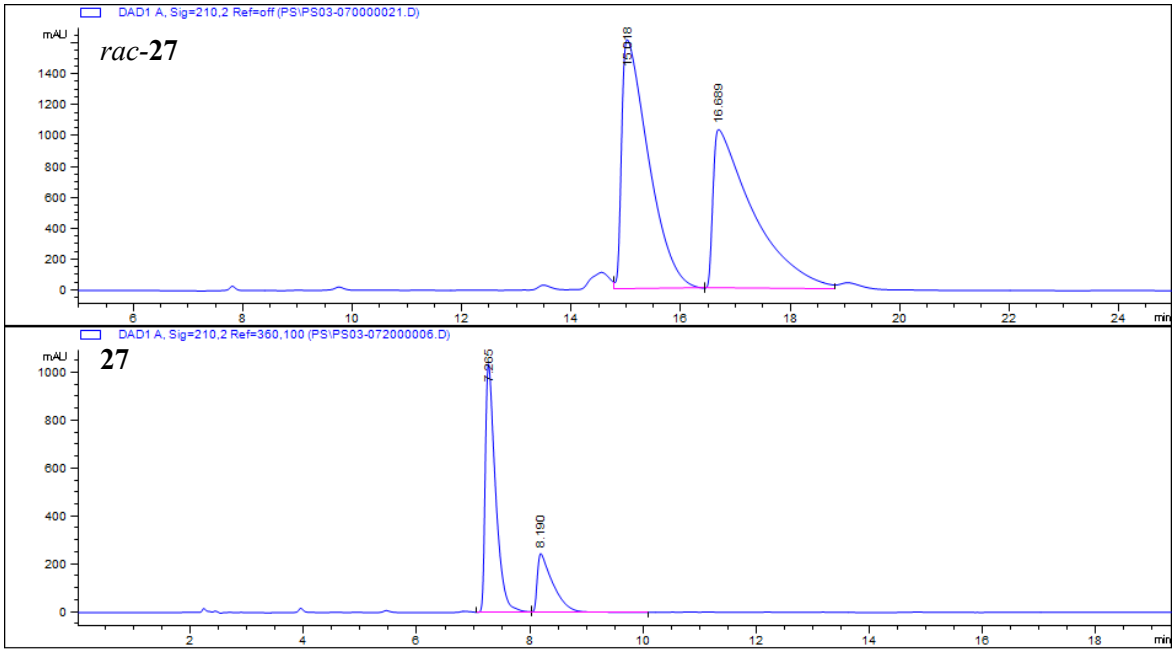
(petrol/Et_2O 9:1) to give (+)-(*S*)-4,4-dimethyl-5-(4-phenylbutyl)cyclohex-2-en-1-one as a yellow oil in 36% yield (37 mg, 0.11 mmol).

HPLC analysis indicated an enantiomeric excess of 48% [Chiralpak® IB; flow: 1.5 mL/min; hexane/*i*-PrOH 99:1; λ = 210 nm; major enantiomer t_R = 7.3 min, minor enantiomer t_R = 8.2 min]. The reproducibility of the HPLC traces for both racemic and asymmetric samples was very poor.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3 H, CH_3), 0.99 – 1.21 (m, 5 H, CH3, C-6_a, C-7_a), 1.34 – 1.63 (m, 4 H, C-6_b, C-7_b, C-8_a, C-8_b), 1.66 – 1.76 (m, 1 H, C-4), 2.05 (dd, *J* = 16.9, 13.1 Hz, 1 H, C-5_a), 2.42 (ddd, *J* = 16.9, 4.1, 1.0 Hz, 1 H, C-5_b), 2.47 – 2.61 (m, 2 H, $PhCH_2$), 5.77 (dd, *J* = 10.1, 0.9 Hz, 1 H, C-1), 6.56 (d, *J* = 10.1 Hz, 1 H, C-2), 7.04 – 7.15 (m, 3 H, C-10, C-12, C-14), 7.16 – 7.27 (m, 2 H, C-11, C-13); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 20.4 (CH_3), 27.1 (C-6 or C-7), 27.8 (CH_3), 29.9 (C-6 or C-7), 31.7 (C-8), 36.0 (Ph*C*H_2), 36.3 (C-3), 39.4 (C-5), 43.5 (C-4), 125.8, 126.5, 128.4, 128.5 (6C, C-1, C-10, C-11, C12, C-13, C-14), 142.5 (C-9), 161.3 (C-2), 200.3 (C=O); $[\alpha]^{25}_{589}$ = +7.5° (*c* 1.0, $CHCl_3$); **IR** ν_{max} /cm^{-1} = 2932s, 2859s, 1677l, 1495s, 1465s, 1378s, 1270s, 1124s, 789s, 747s, 699m; **HRMS** (ESI): *m*/*z* calc. for $C_{18}H_{25}O^+$ $[M]^+$: 257.1900, found: 257.1903.

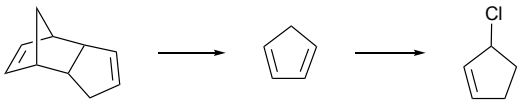
HPLC traces for 27:



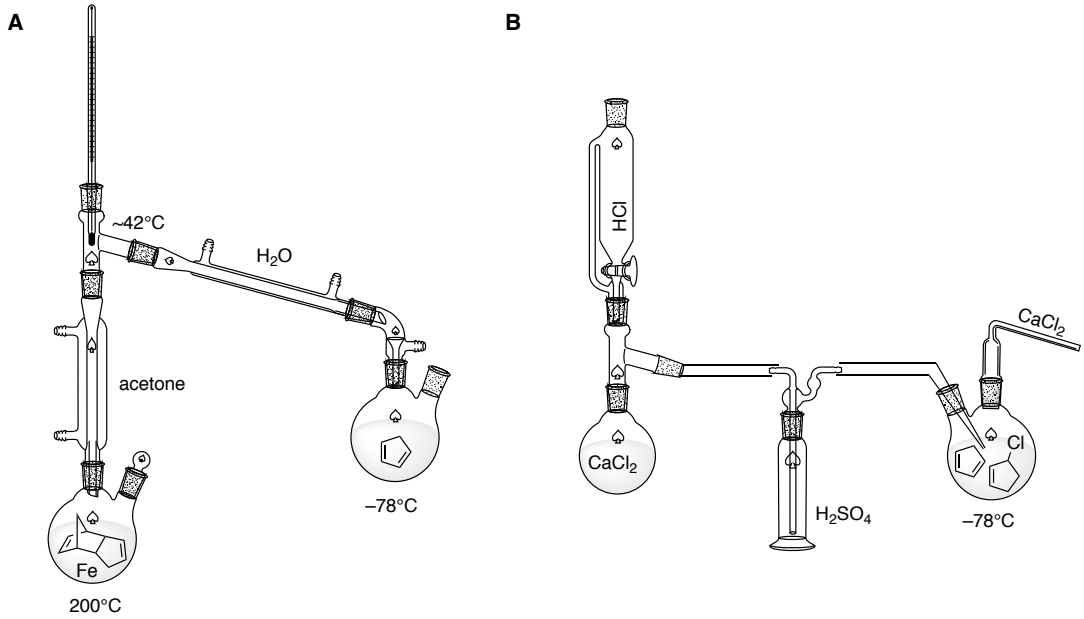
6.4 Experimental Procedures for Chapter 3

6.4.1 Starting Materials

3-Chlorocyclopent-1-ene[239]



In a flame-dried distillation system (**A**) dicyclopentadiene (ca. 200 mL) and iron shavings were added to a 500 mL two-neck flask, attached to a Liebig condenser filled with acetone. The retro-Diels-Alder reaction was initiated by heating up the dimer to up to 200 °C under vigorous stirring. Cyclopentadiene was collected in a two-neck flask at –78 °C. After two-thirds of the dicyclopentadiene had been pyrolyzed (ca. 4 h), the residue was discarded according to the literature procedure.

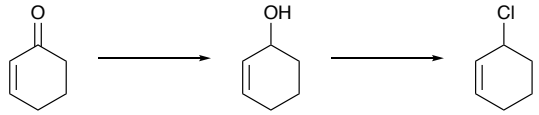


For the subsequent hydrochlorination hydrogen chloride was bubbled rather quickly into a two-neck flask filled with cyclopentadiene (48 g, 0.72 mol) at –78 °C (**B**). For producing hydrogen chloride concentrated hydrochloric acid was added dropwise (1 drop/sec) to $CaCl_2$, leading through a washing bottle filled with concentrated sulphuric acid as bubbler and additional drying agent (ca. 250 mL HCl and 370 g $CaCl_2$ was used, separated into several batches). Towards the end of this procedure the flask was weighed quickly until a weight conversion of 90% was observed (95% via

NMR). The crude was purified by kugelrohr destillation (r.t, 40 mbar, 15 min) to remove impurities. Further distillation (r.t., <5 mbar, 30 min) gave 3-chlorocyclopent-1-ene as a colourless liquid (98% purity). The crude or pure product should be stored in a –78 °C freezer.

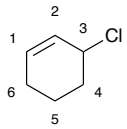
^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.17 – 2.29 (m, 1 H), 2.34 – 2.46 (m, 2 H), 2.56 – 2.76 (m, 1 H), 5.00 – 5.15 (m, 1 H), 5.87 – 6.01 (m, 1 H), 6.03 – 6.18 (m, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 31.22, 34.66, 65.81, 132.29, 136.30.

3-Chlorocyclohex-1-ene[39]



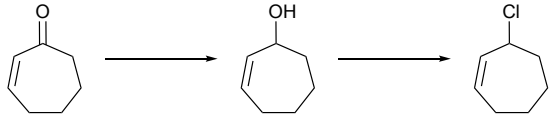
A solution of cyclohexen-1-one (10 mL, 104.8 mmol, 1.00 eq) and cerium(III) chloride heptahydrate (39.03 g, 104.8 mmol, 1.00 eq) in methanol (50 mL) was cooled to 0 °C and sodium borohydride (4.16 g, 110 mmol, 1.05 mmol) was added in portions. The ice-bath was removed and the reaction was allowed to stir for 2 h at room temperature. After cooling to 0 °C the reaction mixture was quenched with water (100 mL) and extracted with diethyl ether (3 × 80 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give crude cyclohex-2-enol (8.54 g), which was used without further purification.

A mixture of cyclohex-2-enol (8.54 g, 87.0 mmol, 1.00 eq.) and pyridine (0.70 mL, 8.70 mmol, 0.10 eq) was cooled to 0 °C and phosphorous trichloride (2.51 mL, 28.71 mmol, 0.33 eq) was added dropwise. The reaction mixture was allowed to warm up to room temperature and stirring was continued for 1 h. Under vigorous stirring pentane (50 mL) was added, the organic layer was evaporated *in vacuo* (30 °C, 400 mbar). Then the organic (top) layer was then removed by pipette and purified by Kugelrohr distillation (200 mmbar, 85 °C) for 15 min to remove pyridine. Further distillation (60 mmbar, 110 °C) for 1 h gave pure 3-chlorocyclohex-1-ene in 62% yield (6.10 g, 5.23 mmol, 50% over two steps).



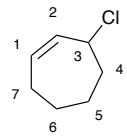
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.59-1.71 (m, 1 H, H-5_a or H-6_a), 1.84 – 1.95 (m, 1 H, H-5_a or H-6_a), 1.96 – 2.17 (m, 4 H, H-4_a, H-4_b, H-5_b, H-6_b), 4.60 – 4.62 (m, 1 H, H-3), 5.80 – 5.86 (m, 1 H, H-2), 5.84 – 5.90 (m, 1 H, H-1); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 18.4 (C-5), 24.7 (C-4), 32.4 (C-6), 55.6 (C-1), 128.1 (C-3), 131.3 (C-2);

3-Chlorocyclohept-1-ene



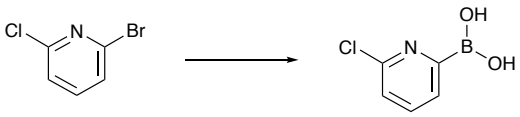
A solution of cyclohepten-1-one (2.0 mL, 18.4 mmol, 1.00 eq) and cerium(III) chloride heptahydrate (6.88 g, 18.5 mmol, 1.01 eq) in methanol (20 mL) was cooled to 0 °C and sodium borohydride (0.70 g, 18.5 mmol, 1.01 eq) was added in portions. The ice-bath was removed and the reaction was allowed to stir for 2 h at room temperature. After cooling to 0 ºC the reaction mixture was quenched with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give crude cyclohept-2-en-1-ol (1.70 g), which was used without further purification.

A mixture of cyclohex-2-en-1-ol (1.69 g, 15.1 mmol, 1.00 eq) and pyridine (122 µL, 1.51 mmol, 0.10 eq) was cooled to 0 °C and phosphorous trichloride (0.44 mL, 5.0 mmol, 0.33 eq) was added dropwise. The reaction mixture was allowed to warm up to room temperature and stirring was continued for 1 h. The top layer of the resulting mixture was purified via Kugelrohr destillation (200 mbar at 85 °C for 15 min, then 200 mbar at 130 °C for 15 min) to give 3-chlorocyclohept-1-ene as a colourless liquid in 67% yield (1.32 g, 10.0 mmol 54% over two steps, contains ~15% 1,3-cycloheptadiene).

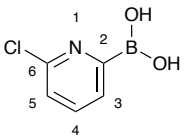


^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.51 – 1.61 (m, 1 H, H-6_a), 1.62 – 1.76 (m, 2 H, H-5_a, H-6_b), 1.96 – 2.09 (m, 3 H, H-4_a, H-4_b, H-5_b), 2.09 – 2.20 (m, 1 H, H-7_a), 2.21 – 2.30 (m, 1 H, H-7_b), 4.64 – 4.79 (m, 1 H, H-3), 5.82 – 5.89 (m, 2 H, H-1, H-2); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 26.35 (C-5), 26.81 (C-6), 28.35 (C-7), 36.55 (C-4), 60.45 (C-3), 133.23, 134.17 (C-1, C-2).

6-Chloropyridin-2-ylboronic acid[240,241]

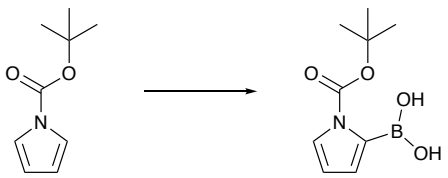


To a solution of *n*-butyllithium (19.5 mL, 31 mmol, 1.6 M in hexanes, 1.2 eq) in tetrahydrofuran (50 mL) was slowly added a solution of 2-bromo-6-chloropyridine (4.98 g, 25.9 mmol, 1.00 eq) in tetrahydrofuran (10 mL) at –78 °C. The mixture was stirred for 45 min, then triisopropyl borate (7.2 mL, 31 mmol, 1.2 eq) was added and the resulting mixture was stirred for additional 2 h at –78 °C. The reaction mixture was allowed to warm up to room temperature over 3 h and quenched by slow addition of NaOH (200 mL, aq. 3%). The top organic layer was removed and the resulting aqueous layer was acidified with HCl (*ca.* 80 mL, 2 N) to pH ~5, keeping the internal temperature below 5 °C. The resulting suspension was extracted with ethyl acetate (2 × 150 mL), all organic layers were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a pale brown solid. The crude product was recrystallized in diethyl ether/EtOAc (100:1, 80 mL) to provide 6-chloropyridin-2-ylboronic acid as a white off solid in 61% yield (2.48 mg, 15.8 mmol).



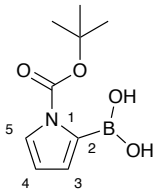
^{1}H-NMR (400 MHz, DMSO): δ 7.49 (d, J = 7.5 Hz, 1 H), 7.69 – 7.88 (m, 2 H), 8.44 (br, 2 H, OH); **LRMS** (ESI): m/z calc. for $C_5H_6BClNO_2^+$ $[M+H]^+$: 158.0, found: 158.0.

N-(*tert*-Butoxycarbonyl)-pyrrole-2-boronic acid[242]



To a solution of diisopropylamine (1.54 mL, 11.0 mmol, 1.10 eq) in tetrahydrofuran (20 mL) was slowly added *n*-butyllithium (4.4 mL, 11.0 mmol, 2.5 M in hexane, 1.10 eq) at –78 °C. The mixture was allowed to warm up to 0 °C and was stirred for 20 min. Afterwards the mixture was cooled down to –78 °C again and a solution of *N*-Boc-pyrrole (1.67 mL, 10.0 mmol, 1.00 eq) in tetrahydrofuran (3.5 mL) was slowly added and stirred for additional 2.5 h at –78 °C. Then a

solution of trimethyl borate (3.35 mL, 30.0 mmol, 3.00 eq) in tetrahydrofuran (1 mL) was added dropwise and the mixture was allowed to warm up to room temperature over night. The reaction mixture was carefully quenched with HCl (27 mL, aq. 0.33 N), stirred for additional 20 min and extracted with diethyl ether (3 × 20 mL). The combined organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure until a solid began to precipitate. The solid was collected, washed with diethyl ether (0 °C) and dried *in vacuo* to give *N*-(*tert*-butoxycarbonyl)-pyrrole-2-boronic acid as a white off solid in 51% yield (1.08 g, 5.12 mmol).



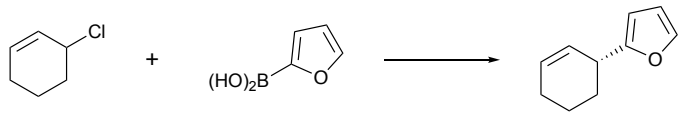
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.62 (s, 9 H, $C(CH_3)_3$), 6.26 (dd, *J* = 3.2, 3.2 Hz, 1 H, H-3), 7.07 – 7.15 (m, 3 H, H-4, OH), 7.45 (dd, *J* = 3.2, 1.6 Hz, 1 H, H-5); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 27.95 ($C(CH_3)_3$), 85.54 ($C(CH_3)_3$), 112.00 (C-3), 127.04 (C-5), 128.67 (C-4), 152.22 (C=O); **LRMS** (ESI): *m*/*z* calc. for $C_9H_{15}BNO_4^+$ $[M+H]^+$: 212.1, found: 212.1.

6.4.2 Application to O-, S- and N-Heteraromatics

General procedure for the synthesis of racemic products

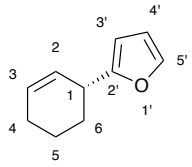
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (±)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-bromocyclohexene (46 µL, 0.4 mmol, 1.00 eq) and heteroarylboronic acid (1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for ca. 2 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with the corresponding solvent to obtain the racemic product.

(+)-(*R*)-2-(Cyclohex-2-en-1-yl)furan 34



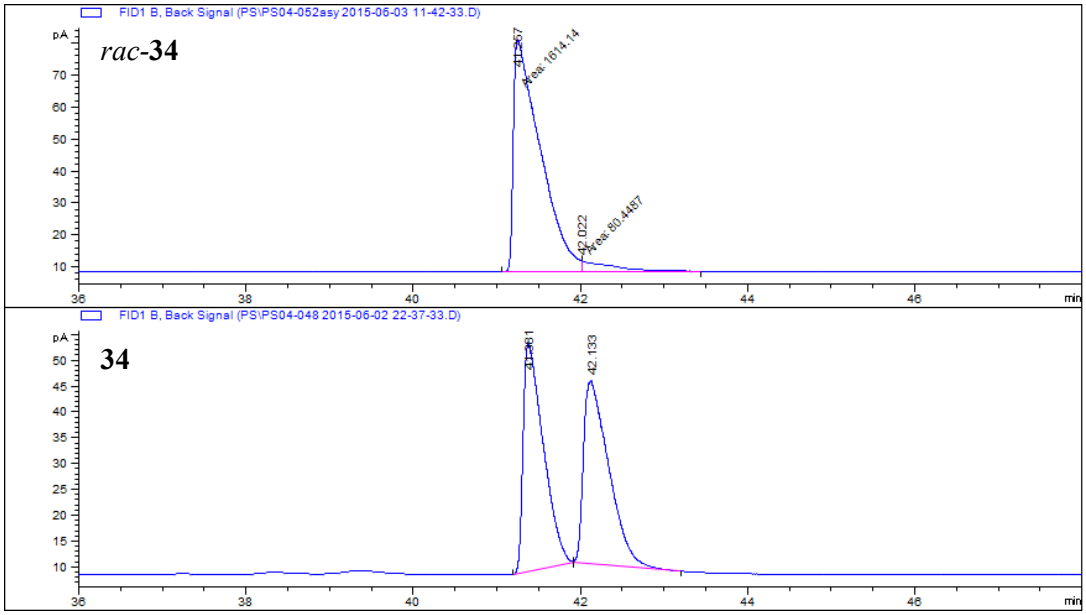
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*R*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and 2-furanylboronic acid (134.3 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 2 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with pentane to obtain (+)-(*R*)-2-(cyclohex-2-en-1-yl)furan in 51% yield (30.4 mg, 0.20 mmol).

GC analysis indicated an enantiomeric excess of 90% [Hydrodex® *β*-3 P; flow: 3.6 mL/min; 10 min at 60 °C, then 1 °C/min to 85 °C, hold it for 15 min; major enantiomer t_R = 41.3 min; minor enantiomer t_R = 42.1 min].

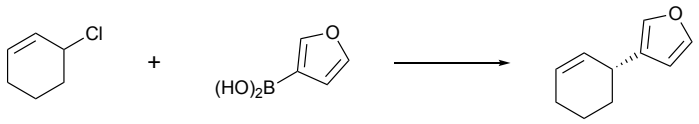


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.55 – 1.81 (m, 3 H, H-5_a, H-5_b, H-6_a), 1.92 – 2.13 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.37 – 3.57 (m, 1 H, H-1), 5.72 – 5.81 (m, 1 H, H-2), 5.81 – 5.91 (m, 1 H, H-3), 5.99 (d, *J* = 3.1 Hz, 1 H, H-3'), 6.28 (dd, *J* = 3.2, 1.9 Hz, 1 H, H-4'), 7.32 (d, *J* = 1.8 Hz, 1 H, H-5'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 20.6 (C-5), 25.1 (C-4), 28.4 (C-6), 35.2 (C-1), 104.6 (C-3'), 110.1 (C-4'), 127.3 (C-2), 128.9 (C-3), 141.1 (C-5'), 159.1 (C-2'); **IR** (ATR) ν_{max} /cm^{-1} = 2937l, 2868s, 1646m, 1347m, 1156s, 1072m, 1008l, 884s, 742l; **$[\alpha]^{25}_{589}$** = +167.9° (*c* 1.00, $CHCl_3$); **HRMS** (EI/FI): *m*/*z* calc. for $C_{10}H_{12}O^+$ $[M]^+$: 148.0888, found: 148.0890.

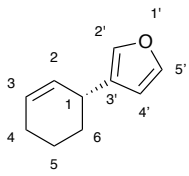
GC traces for 34:



(+)-(*R*)-3-(Cyclohex-2-en-1-yl)furan 35



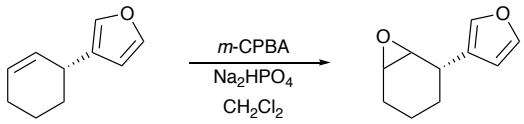
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*R*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and 3-furanylboronic acid (134.3 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 2 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with pentane to obtain (+)-(*R*)-3-(cyclohex-2-en-1-yl)furan in 51% yield (30.4 mg, 0.20 mmol).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.53 – 1.66 (m, 2 H, H-5_a, H-6_a), 1.67 – 1.78 (m, 1 H, H-5_b), 1.91 – 2.00 (m, 1 H, H-6_b), 2.01 – 2.08 (m, 2 H, H-4_a, H-4_b), 3.18 – 3.38 (m, 1 H, H-1), 5.64 – 5.75 (m, 1 H, H-2), 5.75 – 5.83 (m, 1 H, H-3), 6.30 (d, J = 1.8 Hz, 1 H, H-4'), 7.20 (s, 1 H, H-2'), 7.36 (d, J = 1.7 Hz, 1 H, H-5');

^{13}C-NMR (101 MHz, $CDCl_3$) δ 20.8 (C-5), 25.2 (C-4), 30.6 (C-6), 32.3 (C-1), 110.2 (C-4'), 128.0 (C-3), 129.7 (C-2), 129.9 (C-3'), 138.9 (C-2'), 142.9 (C-5'); **IR** (ATR) ν_{max} /cm^{-1} = 2930m, 1158m, 1068m, 1024m, 872l, 785l, 760l, 724m, 660m; **$[\alpha]^{25}_{589}$** = +136.4° (*c* 1.00, $CHCl_3$); **HRMS** (EI/FI): *m*/*z* calc. for $C_{10}H_{12}O^+$ $[M]^+$: 148.0888, found: 148.0889.

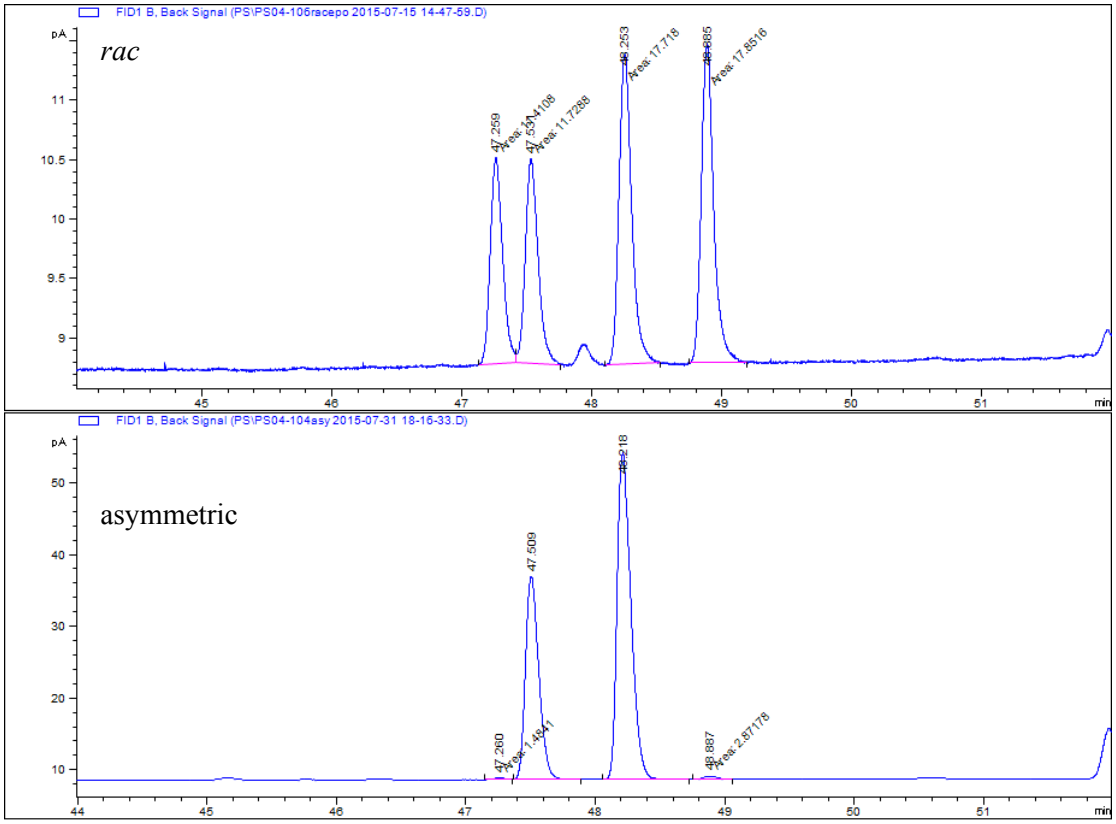
For ee-determination



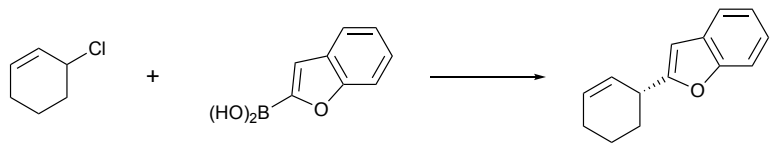
35 (1.00 eq) was dissolved in CH_2Cl_2 (2 mL, for 0.15 mmol scale reaction) under an argon atmosphere. *m*-CPBA (2.00 eq) and Na_2HPO_4 (3.00 eq) were added at room temperature and the reaction mixture was stirred for 2 h. The reaction mixture was diluted with Et_2O (4 mL) and quenched with an aqueous solution of saturated $Na_2S_2O_3$ (4 mL). The organic layer was washed with NaOH (1 M aq., 3 × 5 mL), dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The crude mixture of diastereoisomeric epoxides was directly analyzed by GC chromatography using a chiral non-racemic stationary phase.

GC analysis indicated an enantiomeric excess of 98% [Hydrodex *β*-3 P; flow: 3.6 mL/min; 10 min at 60 °C, then 2 °C/min to 150 °C; major diasteriomers, t_R = 47.5 min/48.3 min; minor diasteriomers, t_R = 47.3 min/48.8 min].

GC traces for epoxidised 35:

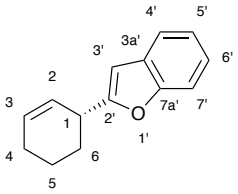


(+)-(*R*)-2-(Cyclohex-2-en-1-yl)benzofuran 36



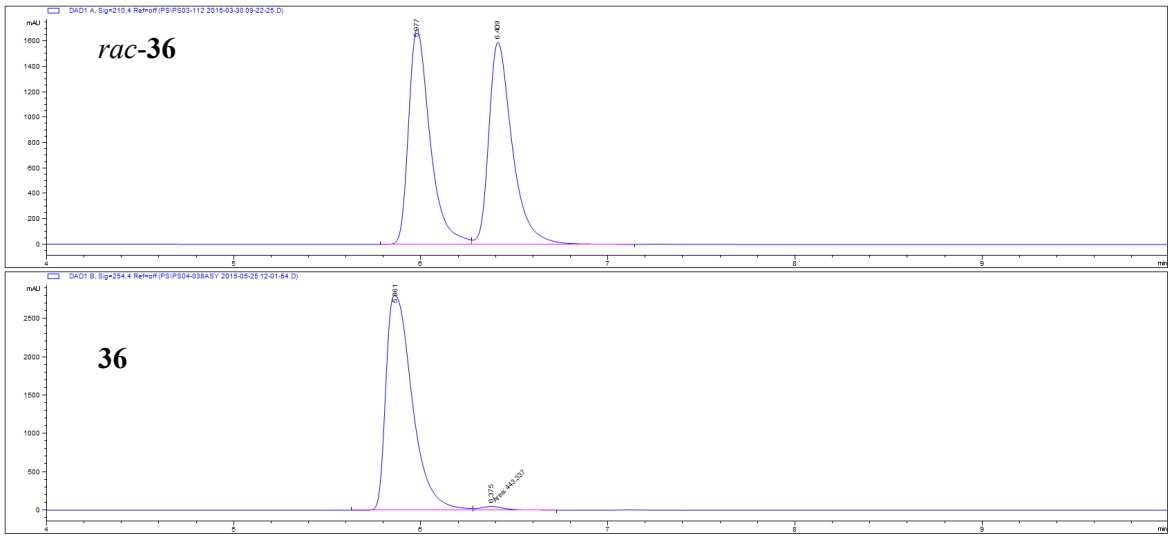
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*R*)-Xyl-P-Phos (18.2 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and 2-benzofuranylboronic acid (129.6 mg, 0.8 mmol, 2.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 1.5 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with pentane to obtain (+)-(*R*)-2-(cyclohex-2-en-1-yl)benzofuran in 75% yield (57.0 mg, 0.30 mmol).

HPLC analysis indicated an enantiomeric excess of 95% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH 99.9:0.1; λ = 210 nm; major enantiomer t_R = 5.9 min; minor enantiomer t_R = 6.4 min].

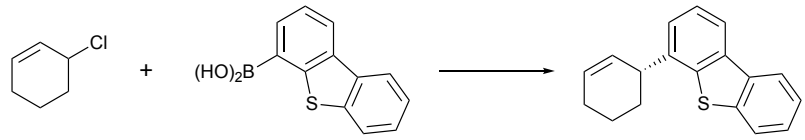


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.59 – 1.71 (m, 1 H, H-5_a), 1.72 – 1.83 (m, 1 H, H-5_b), 1.90 (dddd, J = 12.8, 9.6, 7.0, 2.9 Hz, 1 H, H-6_a), 2.02 – 2.15 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.55 – 3.68 (m, 1 H, H-1), 5.81 – 5.90 (m, 1 H, H-2), 5.90 – 5.99 (m, 1 H, H-3), 6.40 (s, 1 H, H-3'), 7.20 (m, 2 H, H-5', H-6'), 7.43 (d, J = 7.8 Hz, 1 H, H-4'), 7.47 – 7.53 (m, 1H, H-7'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 20.3 (C-5), 25.0 (C-4), 27.9 (C-6), 35.4 (C-1), 101.7 (C-3'), 110.8 (C-4'), 120.3 (C-7'), 122.4, 123.2 (C-5', C-6'), 126.4 (C-2), 128.84 (C-3a' or C-7a'), 129.5 (C-3), 154.7 (C-3a' or C-7a'), 162.1 (C-2'); **IR** (ATR) ν_{max} /cm^{-1} = 2933s, 1584s, 1454l, 1254l, 1164m, 949s, 873s, 795m, 748l, 725s; **$[\alpha]^{25}_{589}$** = +167.5° (*c* 1.00, $CHCl_3$); **HRMS** (EI): *m*/*z* calc. for $C_{14}H_{14}O^+$ [M]$^+$: 198.1045, found: 198.1047.

HPLC traces for 36:

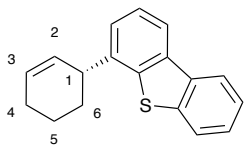


(–)-(*R*)-4-(Cyclohex-2-en-1-yl)dibenzo[*b,d*]thiophene 38



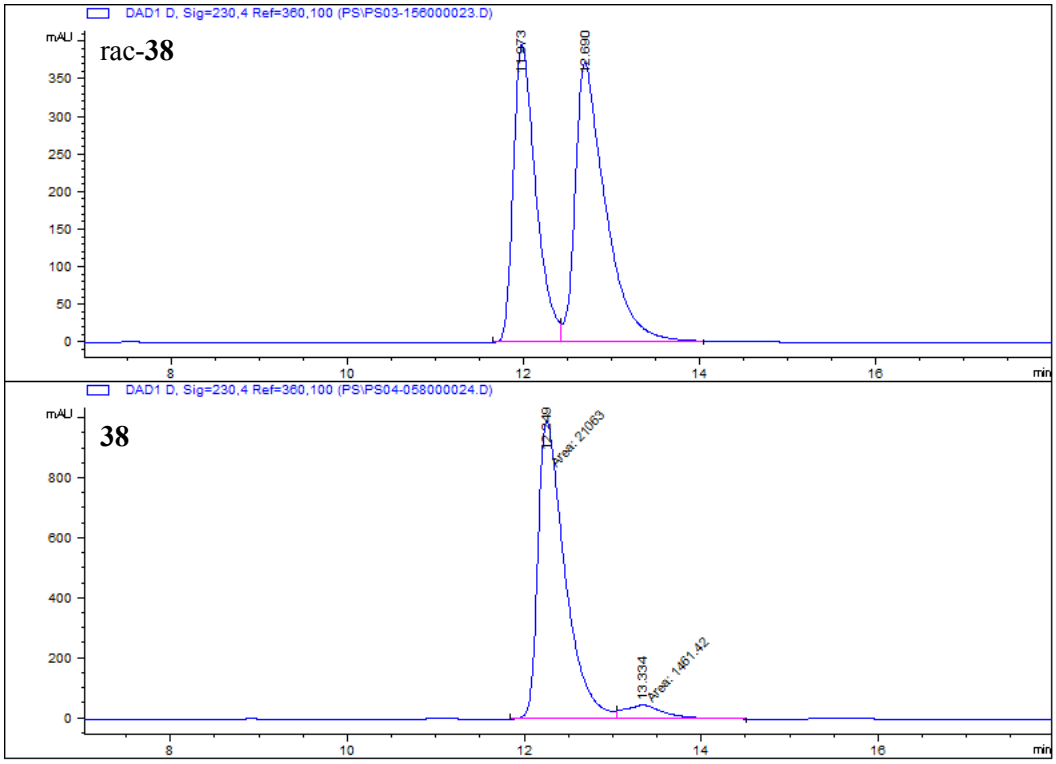
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*R*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. 4-Dibenzothienylboronic acid (274 mg, 1.20 mmol, 3.00 eq) and a solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 2.5 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with pentane to obtain (–)-(*R*)-4-(cyclohex-2-en-1-yl)dibenzo[*b,d*]thiophene in 57% yield (58.5 mg, 0.23 mmol).

HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH 99.7:0.3; $\lambda = 230$ nm; major enantiomer $t_R = 12.3$ min; minor enantiomer $t_R = 13.3$ min].

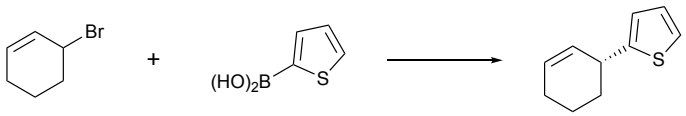


^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.65 – 1.89 (m, 3 H, H-5_a, H-5_b, H-6_a), 2.11 – 2.26 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.78 (dddd, $J = 8.2, 5.6, 2.7, 2.7$ Hz, 1 H, H-1), 5.79 – 5.88 (m, 1 H, H-2), 6.04 (dddd, $J = 9.8, 3.7, 3.6, 2.3$ Hz, 1 H, H-3), 7.34 (dd, $J = 7.4, 1.1$ Hz, 1 H, H_{Ar}), 7.41 – 7.50 (m, 3 H, H_{Ar}), 7.83 – 7.90 (m, 1 H, H_{Ar}), 8.04 (dd, $J = 7.8, 1.2$ Hz, 1 H, H_{Ar}), 8.12 – 8.20 (m, 1 H, H_{Ar}); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 21.3 (C-5), 25.2 (C-4), 29.5 (C-6), 41.4 (C-1), 119.6 (CH_{Ar}), 121.8 (CH_{Ar}), 122.9 (CH_{Ar}), 124.4 (CH_{Ar}), 124.9 (CH_{Ar}), 125.6 (CH_{Ar}), 126.7 (CH_{Ar}), 129.0 (C-2), 129.6 (C-3), 136.0 (C_q), 136.3 (C_q), 138.7 (C_q), 139.3 (C_q), 140.7 (C_q); **IR** (ATR) ν_{max} /cm^{-1} = 3059s, 3021s, 2928m, 2859s, 1443m, 1399s, 1048s, 797s, 749l, 718s; **$[\alpha]^{25}_{589}$** = –1.0° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{18}H_{17}S^+$ $[M+H]^+$: 265.1040, found: 265.1045.

HPLC traces for 38:

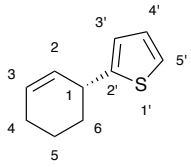


(+)-(*R*)-2-(Cyclohex-2-en-1-yl)thiophene 39



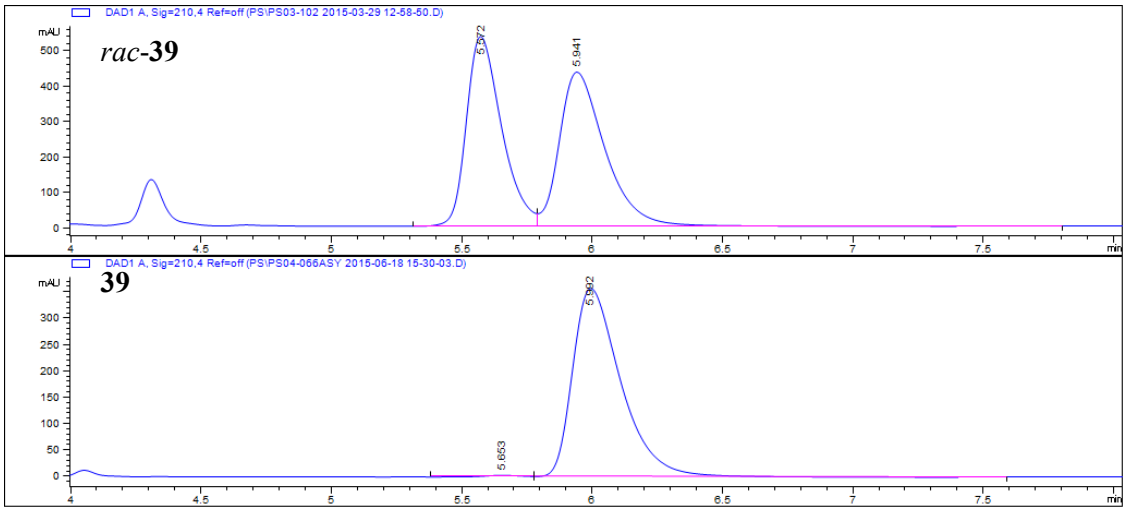
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*R*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-bromocyclohexene (46 µL, 0.4 mmol, 1.00 eq) and 2-thienylboronic acid (153.6 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 1.5 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with pentane to obtain (+)-(*R*)-2-(cyclohex-2-en-1-yl)thiophene in 51% yield (33 mg, 0.20 mmol).

HPLC analysis indicated an enantiomeric excess of 99% [Chiralpak® ID; flow: 1.0 mL/min; hexane/*i*-PrOH 99.9:0.1; λ = 210 nm; minor enantiomer t_R = 5.6 min; major enantiomer t_R = 5.9 min].

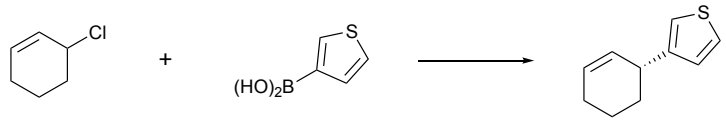


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.57 – 1.69 (m, 1 H, H-6_a), 1.69 – 1.83 (m, 2 H, H-5_a, H-5_b), 1.98 – 2.16 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.64 – 3.75 (m, 1 H, H-1), 5.74 – 5.82 (m, 1 H, H-2), 5.83 – 5.93 (m, 1 H, H-3), 6.83 (d, J = 3.4 Hz, 1 H, H-5'), 6.94 (dd, J = 5.1, 3.4 Hz, 1 H, H-4'), 7.14 (d, J = 5.1 Hz, 1 H, H-5'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 20.7 (C-5), 24.9 (C-4), 32.5 (C-6), 36.7 (C-1), 122.9 (C-5'), 123.3 (C-3'), 126.5 (C-4'), 128.3 (C-3), 129.7 (C-2), 150.5 (C-2'); **IR** (ATR) ν_{max} /cm^{-1} = 3021s, 2931m, 2858s, 2835s, 1455s, 850s, 821s, 758s, 723s, 692l, 652m; **$[\alpha]^{25}_{589}$** = +77.4° (*c* 0.50, $CHCl_3$); **HRMS** (EI/FI): *m*/*z* calc. for $C_{10}H_{12}S^+$ $[M]^+$: 164.0660, found: 164.0661.

HPLC traces for 39:

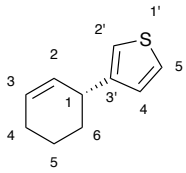


(+)-(*R*)-3-(Cyclohex-2-en-1-yl)thiophene 40



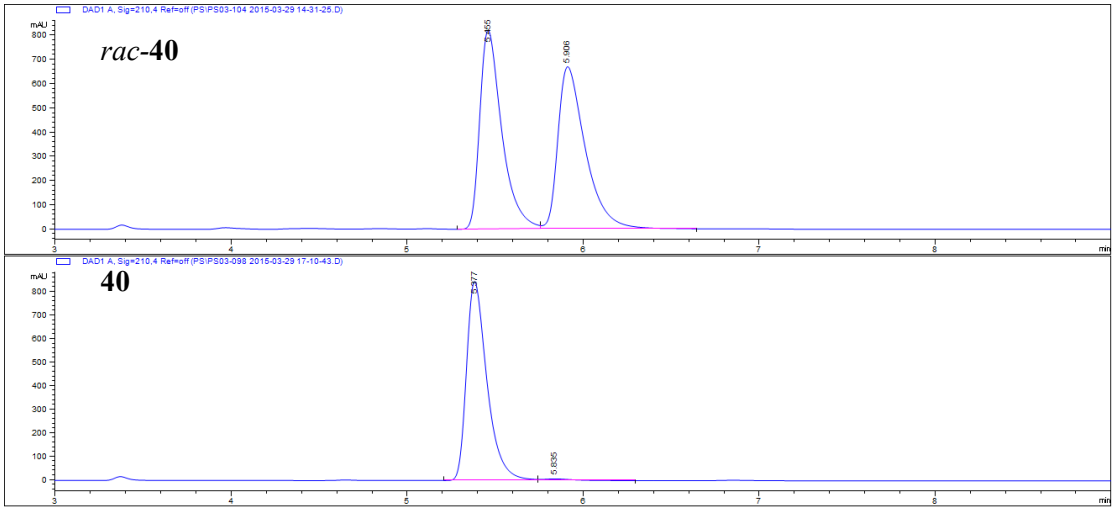
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*R*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and 3-thienylboronic acid (153.6 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 1.5 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with pentane to obtain (+)-(*R*)-3-(cyclohex-2-en-1-yl)thiophene in 56% yield (37.0 mg, 0.22 mmol).

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® ID; flow: 1.0 mL/min; hexane/*i*-PrOH 99.9:0.1; $\lambda = 210$ nm; major enantiomer $t_R = 5.4$ min; minor enantiomer $t_R = 5.8$ min].

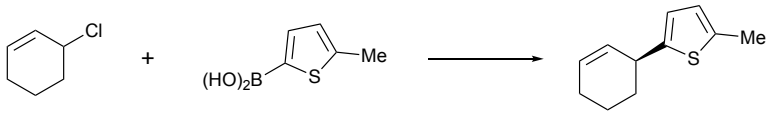


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.59 – 1.70 (m, 2 H, H-5_a, H-6_a), 1.71 – 1.81 (m, 1 H, H-5_b), 1.99 – 2.06 (m, 1 H, H-6_b), 2.07 – 2.16 (m, 2 H, H-4_a, H-4_b), 3.46 – 3.61 (m, 1 H, H-1), 5.76 – 5.84 (m, 1 H, H-2), 5.84 – 5.93 (m, 1 H, H-3), 7.00 (d, $J = 2.9$ Hz, 1 H, H-2'), 7.02 (d, $J = 5.0$ Hz, 1 H, H-4'), 7.29 (dd, $J = 5.0, 2.9$ Hz, 1 H, H-5'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 21.0 (C-5), 25.2 (C-4), 31.3 (C-6), 37.1 (C-1), 120.0 (C-2'), 125.3 (C-5'), 127.6 (C-4'), 128.0 (C-3), 130.1 (C-2), 147.3 (C-3'); **IR** (ATR) ν_{max} /cm^{-1} = 2931m, 2858s, 2835s, 854s, 839s, 777l, 745s, 736s, 651m, 637s; **$[\alpha]^{25}_{589}$** = +46.5° (*c* 1.00, $CHCl_3$); **HRMS** (EI/FI): *m*/*z* calc. for $C_{10}H_{12}S^+$ $[M]^+$: 164.0660, found: 164.0653.

HPLC traces for 40:

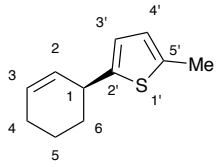


(–)-(*S*)-2-(Cyclohex-2-en-1-yl)-5-methylthiophene 41



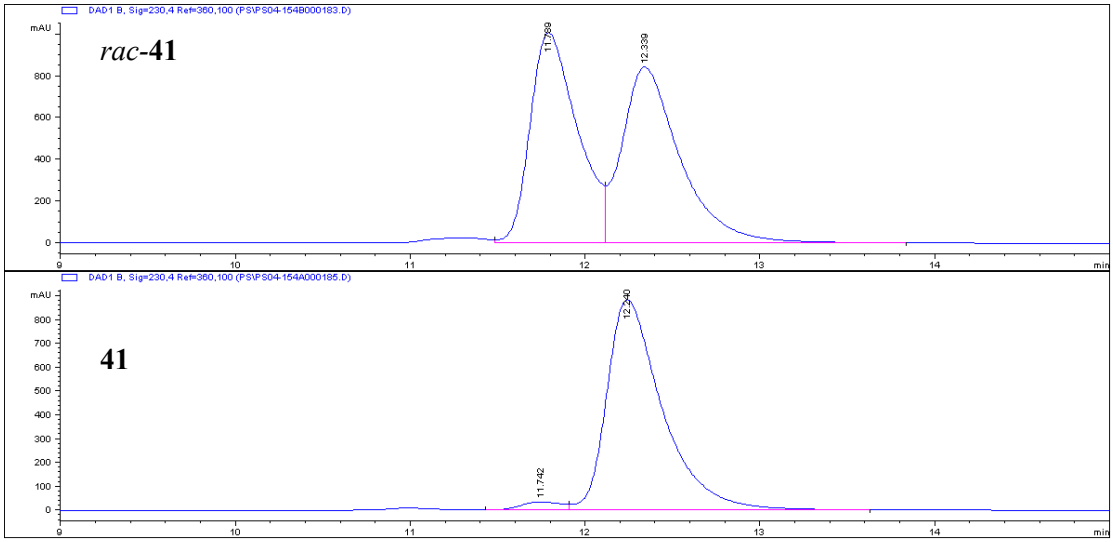
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and 5-methyl-2-thienylboronic acid (170.4 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added at room temperature *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was stirred for 12 h at room temperature. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with pentane to obtain (–)-(*R*)-2-(cyclohex-2-en-1-yl)-5-methylthiophene in 45% yield (32.5 mg, 0.13 mmol).

HPLC analysis indicated an enantiomeric excess of 95% [Chiralpak® AY-H; flow: 0.4 mL/min; hexane; λ = 210 nm; minor enantiomer t_R = 11.7 min; major enantiomer t_R = 12.2 min].

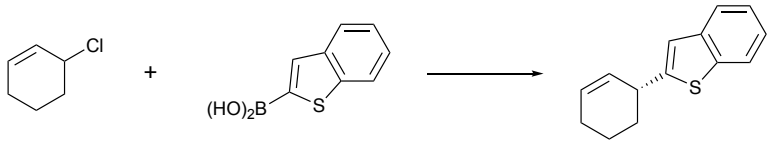


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.56 – 1.82 (m, 3 H, H-5_a, H-5_b, H-6_a), 2.00 – 2.09 (m, 3 H, H-4_a, H-4_b, H-6_b), 2.44 (s, 3 H, CH_3), 3.52 – 3.66 (m, 1 H, H-1), 5.74 – 5.79 (m, 1 H, H-2), 5.80 – 5.85 (m, 1 H, H-3), 6.57 (d, *J* = 3.5 Hz, 1 H, H-4'), 6.59 (d, *J* = 3.5 Hz, 1 H, H-3'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 15.5 (CH_3), 20.8 (C-5), 25.1 (C-4), 32.5 (C-6), 37.0 (C-1), 123.2 (C-3'), 124.7 (C-4'), 128.3 (C-3), 130.0 (C-2), 137.4 (C-5'), 148.3 (C-2'); **IR** (ATR) ν_{max} /cm^{-1} = 3021s, 2931m, 2859s, 1445s, 1232s, 1045s, 876s, 796l, 760s, 723s; **$[\alpha]^{25}_{589}$** = –68.4° (*c* 0.50, $CHCl_3$); **HRMS** (EI/FI): *m/z* calc. for $C_{11}H_{14}S^+$ $[M]^+$: 178.0816, found: 178.0821.

HPLC traces for 41:



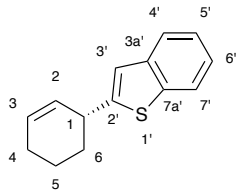
(+)-(*R*)-2-(Cyclohex-2-en-1-yl)benzo[*b*]thiophene 42



In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*R*)-Xyl-P-Phos (18.2 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and benzo[*b*]thien-2-ylboronic acid (142.4 mg, 0.8 mmol, 2.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for

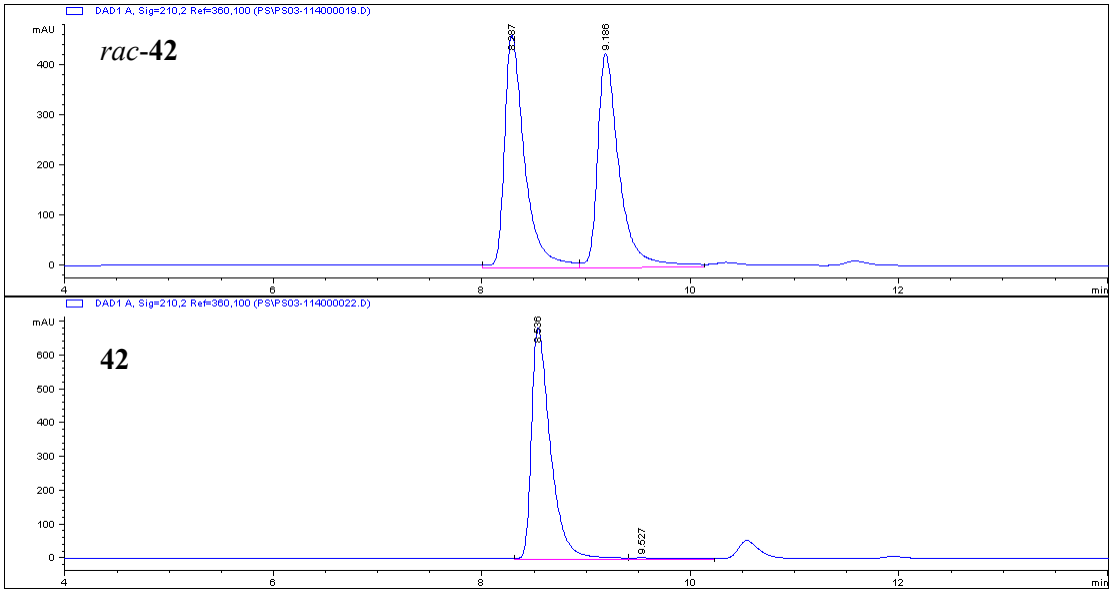
2 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with pentane to obtain (+)-(*R*)-2-(cyclohex-2-en-1-yl)benzo[*b*]thiophene in 23% yield (18.8 mg, 0.09 mmol).

HPLC analysis indicated an enantiomeric excess of 99% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH 99.9:0.1; $\lambda = 210$ nm; major enantiomer $t_R = 8.5$ min; minor enantiomer $t_R = 9.5$ min].

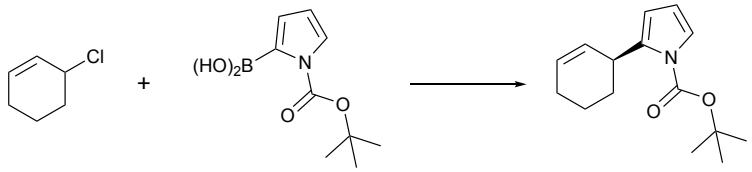


^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.58 – 1.73 (m, 1 H, H-5_a), 1.74 – 1.88 (m, 2 H, H-5_b, H-6_a), 1.99 – 2.17 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.69 – 3.81 (m, 1 H, H-1), 5.83 – 5.89 (m, 1 H, H-2), 5.91 (ddd, $J = 10.0$, 5.8, 3.5 Hz, 1 H, H-3), 7.05 (s, 1 H, H-3'), 7.25 (dd, $J = 8.2$, 7.1 Hz, 1 H, H-5'), 7.30 (dd, $J = 8.2$, 7.2 Hz, 1 H, H-6'), 7.67 (d, $J = 7.6$ Hz, 1 H, H-7'), 7.77 (d, $J = 8.2$ Hz, 1 H, H-4'); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 20.7 (C-5), 25.1 (C-4), 32.1 (C-6), 37.5 (C-1), 120.2 (C-3'), 122.4 (C-4'), 123.0 (C-7'), 123.6 (C-5'), 124.2 (C-6'), 129.0 (C-2), 129.1 (C-3), 139.4, 140.2 (C-3a', C-7a'), 151.4 (C-2'); **IR** (ATR) ν_{max} /cm^{-1} = 2931m, 2858s, 2835l, 1457s, 1435m, 1068s, 856s, 825s, 745l, 726l; **$[\alpha]^{25}_{589}$** = –159.0° (*c* 1.00, $CHCl_3$); **HRMS** (EI): *m*/*z* calc. for $C_{14}H_{14}S^+$ $[M+H]^+$: 214.0816, found: 214.0819.

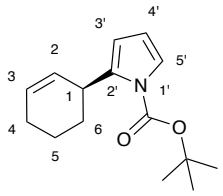
HPLC traces for 42:



(*S*)-*N*-(*tert*-Butoxycarbonyl)-2-(cyclohex-2-en-1-yl)-1*H*-pyrrole

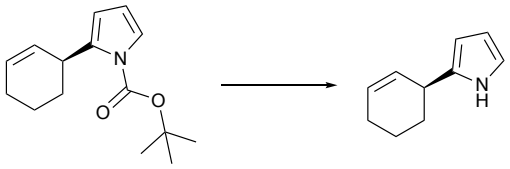


In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and *N*-(*tert*-butoxycarbonyl)-pyrrole-2-boronic acid (253.2 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 12 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (97:3). The product could not be separated in this step from impurities.



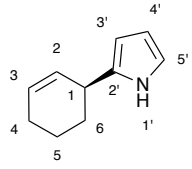
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.55 –1.67 (m, 3 H, H-5_a, H-5_b, H-6_a), 1.59 (s, 9 H, $C(CH_3)_3$), 1.93 – 2.08 (m, 3 H, H-4_a, H-4_b, H-6_b), 4.06 (ddd, J = 5.6, 2.8, 2.8 Hz, 1 H, H-1), 5.68 – 5.76 (m, 1 H, H-2), 5.79 – 5.85 (m, 1 H, H-3), 5.98 (ddd, J = 3.3, 1.9, 0.9 Hz, 1 H, H-3'), 6.08 (dd, J = 3.3, 3.3 Hz, 1 H, H-4'), 7.23 (dd, J = 3.4, 1.9 Hz, 1 H, H-5'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 20.1 (C-5), 25.3 (C-4), 28.2 ($C(CH_3)_3$), 29.6 (C-6), 34.1 (C-1), 83.5 ($C(CH_3)_3$), 109.9 (C-4'), 111.9 (C-3'), 121.4 (C-5'), 128.1 (C-3), 129.3 (C-2), 139.5 (C-2'), 149.6 (C=O); **IR** (ATR) ν_{max} /cm^{-1} = 2930s, 1740s, 1401s, 1369s, 1324l, 1163m, 1119m, 1062s, 722s; **HRMS** (ESI): m/z calc. for $C_{15}H_{22}NO_2^+$ $[M+H]^+$: 248.1645, found: 248.1646.

(–)-(*S*)-2-(Cyclohex-2-en-1-yl)-1*H*-pyrrole 44



A solution of (*S*)-*N*-(*tert*-Butoxycarbonyl)-2-(cyclohex-2-en-1-yl)-1*H*-pyrrole (42.0 mg, 0.17 mmol) and K_2CO_3 (117 mg, 0.85 mmol) in methanol (1.7 mL) was stirred for 3 h at 60 °C. The reaction was diluted with EtOAc. Al_2O_3 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a flash chromatography column and eluted with petrol ether and ethyl acetate (97:3) to obtain (–)-(*S*)-2-(cyclohex-2-en-1-yl)-1*H*-pyrrole in 58% yield over 2 steps (17 mg, 0.12 mmol).

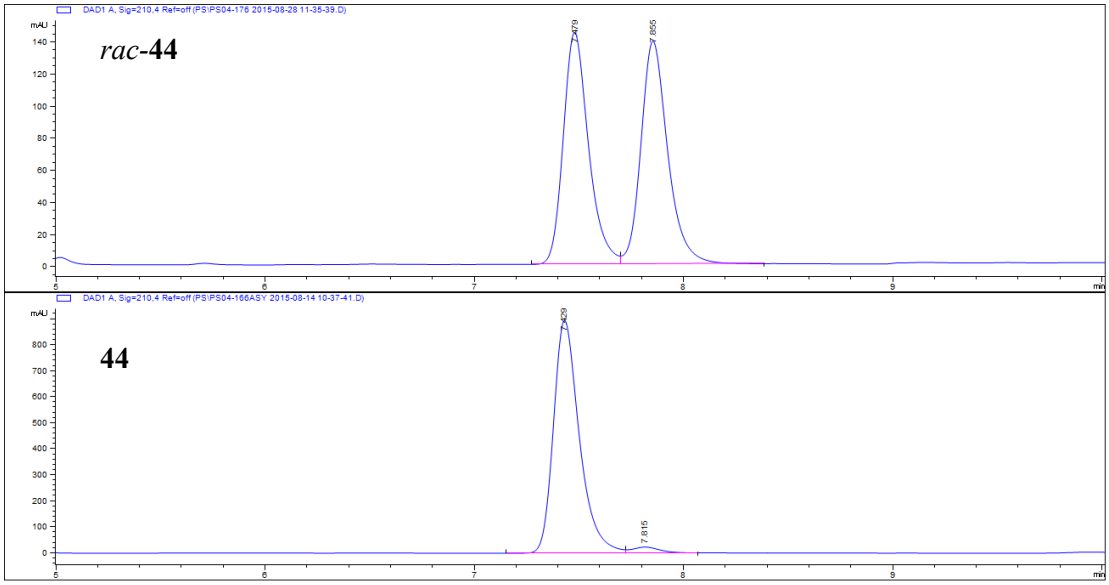
HPLC analysis indicated an enantiomeric excess of 95% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH 99:1; λ = 210 nm; major enantiomer t_R = 7.4 min; minor enantiomer t_R = 7.8 min].



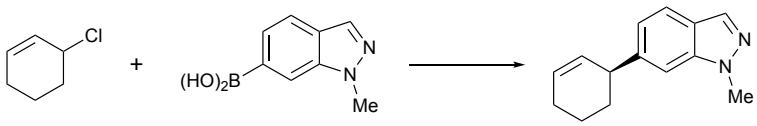
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.56 – 1.77 (m, 3 H, H-5_a, H-5_b, H-6_a), 1.94 – 2.04 (m, 1 H, H-6_b), 2.04 – 2.15 (m, 2 H, H-4_a, H-4_b), 3.50 (m, 1 H), 5.73 – 5.83 (m, 1 H, H-2), 5.89 (dddd, J = 9.6, 3.2, 3.2, 2.9 Hz, 1 H, H-3), 5.93 – 6.00 (m, 1 H, H-3'), 6.12 – 6.23 (m, 1 H, H-4'), 6.63 – 6.78 (m, 1 H, H-5'), 8.00 (br, 1 H, NH); **^{13}C-NMR**

(101 MHz, $CDCl_3$) δ 20.65 (C-5), 25.00 (C-4), 30.87 (C-6), 34.5 (C-1), 104.5 (C-3'), 108.3 (C-4'), 116.1 (C-5'), 128.4 (C-2), 128.9 (C-3), 136.1 (C-2'); **IR** (ATR) ν_{max} /cm^{-1} = 3384m, 2930m, 2858s, 2836s, 1431s, 1094s, 1026s, 791s, 765s, 714l; **$[\alpha]^{25}_{589}$** = –128.9° (*c* 0.70, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{10}H_{14}N^+$ $[M+H]^+$: 148.1121, found: 148.1121.

HPLC traces for 44:



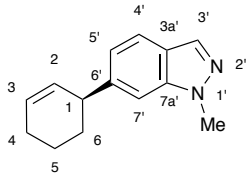
(–)-(*S*)-6-(Cyclohex-2-en-1-yl)-1-methyl-1*H*-indazole 46



In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and 1-methyl-1*H*-indazole-6-boronic acid (211.2 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added to the flask *via* syringe and rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 2 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and

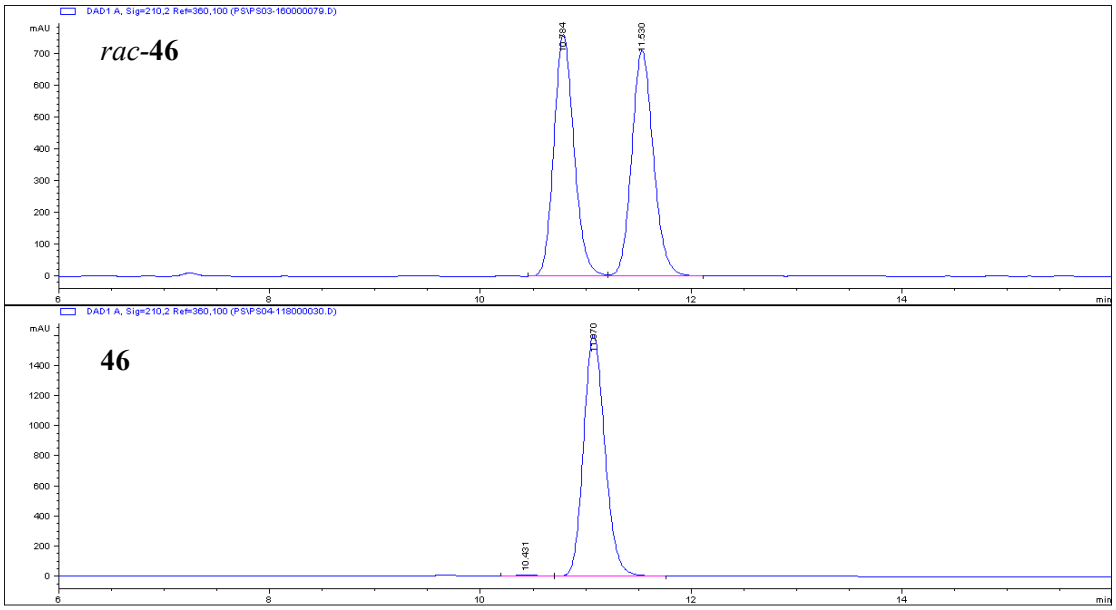
ethyl acetate (6:1) to obtain (–)-(*S*)-6-(cyclohex-2-en-1-yl)-1-methyl-1*H*-indazole in 67% yield (57.0 mg, 0.27 mmol) as an off white solid.

HPLC analysis indicated an enantiomeric excess of 99% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH 95:5; $\lambda = 210$ nm; minor enantiomer $t_R = 10.8$ min; major enantiomer $t_R = 11.6$ min].

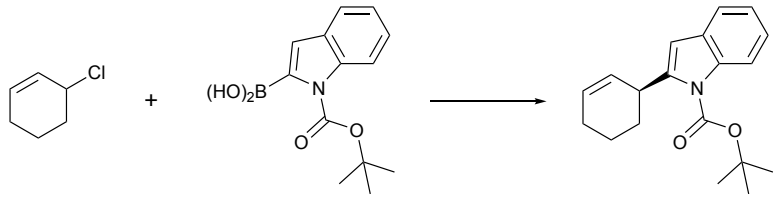


***T*mp** = 82 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 1.49 – 1.64 (m, 2 H, H-5$_a$, H-6$_a$), 1.69 (m, 1 H, H-5$_b$), 1.94 – 2.11 (m, 3 H, H-4$_a$, H-4$_b$, H-6$_b$), 3.49 (m, 1 H, H-1), 3.98 (s, 3 H, NCH_3), 5.71 (dd, $J = 10.2$, 2.4 Hz, 1 H, H-2), 5.82 – 5.95 (m, 1 H, H-3), 6.96 (dd, $J = 8.4$, 1.3 Hz, 1 H, H-5'), 7.12 (d, $J = 1.5$ Hz, 1 H, H-7'), 7.56 (d, $J = 8.3$ Hz, 1 H, H-4'), 7.84 (s, 1 H, H-3'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 21.2 (C-5), 25.1 (C-4), 32.8 (C-6), 35.4 (NCH_3), 42.2 (C-1), 107.2 (C-7'), 120.7 (C-4'), 121.5 (C-5'), 122.6 (C-3a'), 128.8 (C-3), 130.0 (C-2), 132.4 (C-3'), 140.4 (C-7a'), 145.4 (C-6'); **IR** (ATR) ν_{max} /cm^{-1} = 2930l, 2859s, 1622m, 1473m, 1440s, 1373s, 1223m, 947s, 839m, 769s; **$[\alpha]^{25}_{589}$** = –166.7° (*c* 1.00, $CHCl_3$); **HRMS** (EI/FI): *m*/*z* calc. for $C_{14}H_{16}N_2^+$ $[M]^+$: 212.1313, found: 212.1310.

HPLC traces for 46:

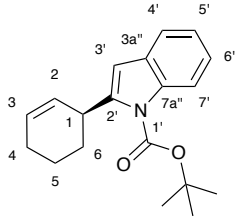


(–)-(*S*)-*N*-(*tert*-Butoxycarbonyl)-2-(cyclohex-2-en-1-yl)-1*H*-indole 47



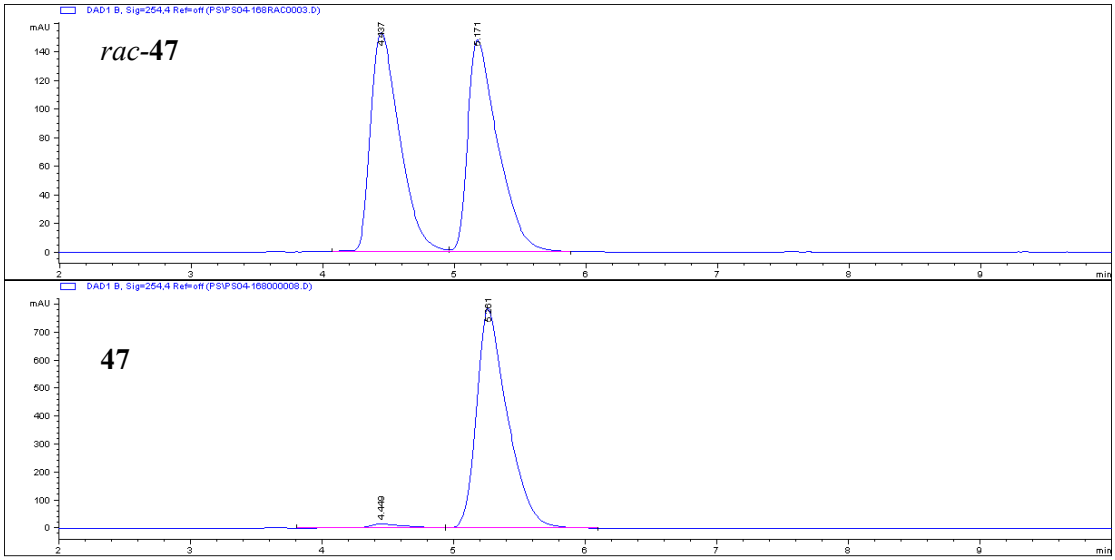
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and *N*-(*tert*-butoxycarbonyl)-indole-2-boronic acid (313.3 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 20 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (97:3) to obtain (–)-(*S*)-*N*-(*tert*-butoxycarbonyl)-2-(cyclohex-2-en-1-yl)-1*H*-indole in 20% yield (24.0 mg, 0.08 mmol).

HPLC analysis indicated an enantiomeric excess of 95% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH 99:1; λ = 210 nm; minor enantiomer t_R = 4.5 min; major enantiomer t_R = 5.3 min].

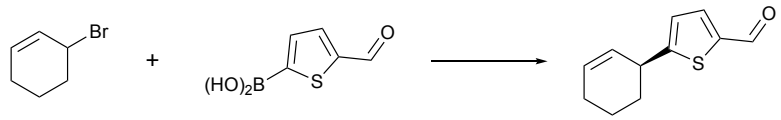


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.56 – 1.78 (m, 3 H, H-5$_a$, H-5$_b$, H-6$_a$), 1.69, (s, 9 H, C(CH_3)$_3$), 2.01 – 2.14 (m, 3 H, H-4$_a$, H-4$_b$, H-6$_b$), 4.17 – 4.29 (m, 1 H, H-1), 5.78 – 5.87 (m, 1 H, H-2), 5.87 – 5.94 (m, 1 H, H-3), 6.39 (s, 1 H, H-3'), 7.18 (ddd, *J* = 7.4, 7.3, 1.3 Hz, 1 H, H-5'), 7.21 – 7.26 (m, 1 H, H-6'), 7.45 (d, *J* = 7.3 Hz, 1 H, H-4'), 8.12 (d, *J* = 8.3 Hz, 1 H, H-7'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 19.9 (C-5), 25.4 (C-4), 28.4 (C(*C*H_3)$_3$), 29.6 (C-6), 34.8 (C-1), 83.9 (*C*(CH$_3$)$_3$), 108.3 (C-3'), 115.9 (C-7'), 120.0 (C-4'), 122.7 (C-5'), 123.5 (C-6'), 128.6 (C-3), 128.9 (C-2), 129.3, 137.1 (C-3a', C-7a'), 145.4 (C-2'), 150.7 (C=O); **IR** (ATR) ν_{max} /cm^{-1} = 2930s, 1731l, 1454s, 1370m, 1329l, 1162m, 1116s, 1086s, 745s; **$[\alpha]^{25}_{589}$** = –33.6° (*c* 0.50, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{19}H_{23}NO_2Na^+$ $[M+Na]^+$: 320.1621, found: 320.1621.

HPLC traces for 47:

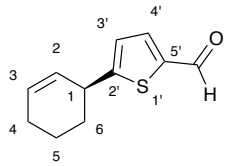


(–)-(*S*)-5-(Cyclohex-2-en-1-yl)thiophene-2-carbaldehyde 48



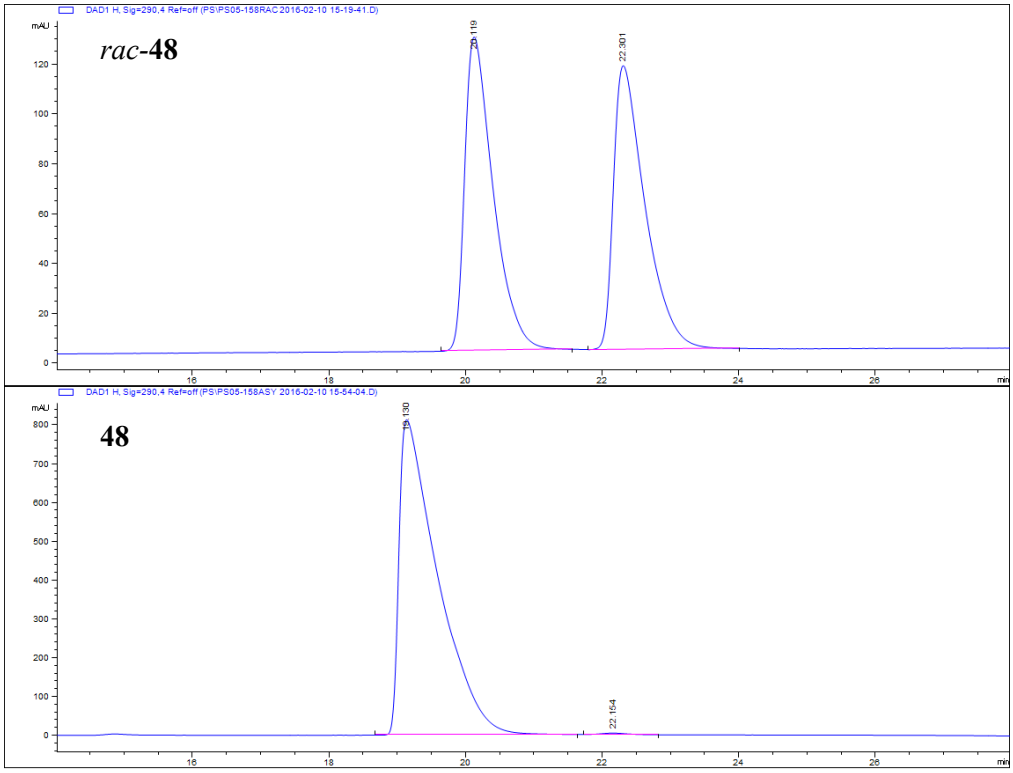
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-bromocyclohexene (46 µL, 0.4 mmol, 1.00 eq) and 5-formyl-2-thienylboronic acid (187.2 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 2 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (95:5) to obtain (–)-(*S*)-5-(cyclohex-2-en-1-yl)thiophene-2-carbaldehyde in 30% yield (23.1 mg, 0.12 mmol).

HPLC analysis indicated an enantiomeric excess of greater than 99% [Chiralpak® IB; flow: 1.4 mL/min; hexane/*i*-PrOH 99.5:0.5; $\lambda = 210$ nm; major enantiomer $t_R = 19.1$ min; minor enantiomer $t_R = 22.2$ min].

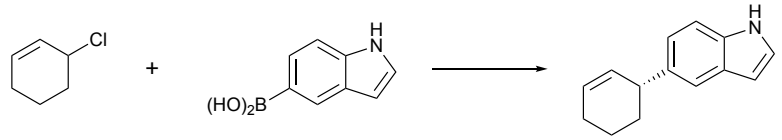


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.58 – 1.80 (m, 3 H, H-5_a, H-5_b, H-6_a), 2.02 – 2.15 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.67 – 3.76 (m, 1 H, H-1), 5.69 – 5.82 (m, 1 H, H-2), 5.85 – 5.97 (m, 1 H, H-3), 6.95 (d, J = 3.8 Hz, 1 H, H-4'), 7.62 (d, J = 3.8 Hz, 1 H, H-3'), 9.82 (s, 1 H, CHO); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 20.5 (C-5), 24.9 (C-4), 32.2 (C-6), 37.6 (C-1), 125.3 (C-4'), 128.2 (C-2), 129.8 (C-3), 136.9 (C-3'), 141.7 (C-2'), 162.4 (C-5'), 182.8 (CHO); **IR** (ATR) ν_{max} /cm^{-1} = 2932s, 2858s, 1665l, 1445m, 1227s, 1050s, 811s, 773l, 724s, 669s; **$[\alpha]^{25}_{589}$** = –209.5° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{11}H_{13}OS^+$ $[M+H]^+$: 193.0682, found: 193.0683.

HPLC traces for 48:

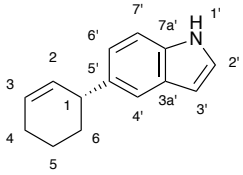


(–)-(*R*)-5-(Cyclohex-2-en-1-yl)-1*H*-indole 49c



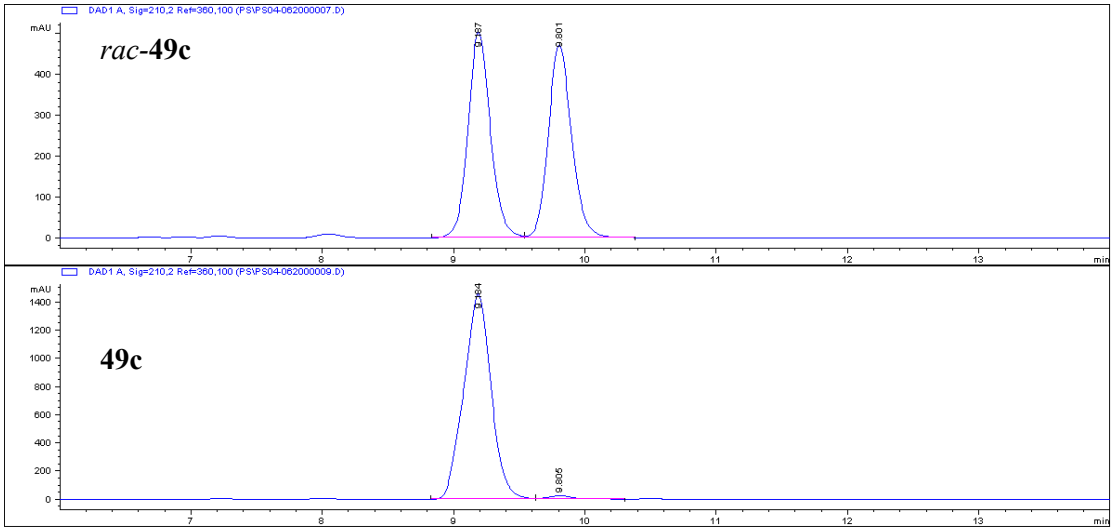
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*R*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and 5-indolylboronic acid (193.2 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 1.5 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (9:1, 1% Et_3N) to obtain (–)-(*R*)-5-(cyclohex-2-en-1-yl)-1*H*-indole in 41% yield (33 mg, 0.16 mmol).

HPLC analysis indicated an enantiomeric excess of 96% [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH 97:3; λ = 210 nm; major enantiomer t_R = 9.1 min; minor enantiomer t_R = 9.8 min]

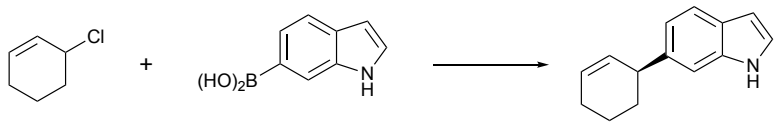


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.59 – 1.73 (m, 2 H, H-5_a, H-6_a), 1.74 – 1.86 (m, 1 H, H-5_b), 2.02 – 2.19 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.53 (m, 1 H, H-1), 5.76 – 5.87 (m, 1 H, H-2), 5.87 – 5.96 (m, 1 H, H-3), 6.53 (dd, *J* = 2.5, 2.5 Hz, 1 H, H-2'), 7.10 (dd, *J* = 8.4, 1.6 Hz, 1 H, H-6'), 7.18 (d, *J* = 2.8 Hz, 1 H, H-3'), 7.33 (d, *J* = 8.3 Hz, 1 H, H-7'), 7.51 (d, *J* = 1.6 Hz, 1 H, H-4'), 8.03 (br, 1 H, NH); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 21.5 (C-5), 25.3 (C-4), 33.4 (C-6), 42.1 (C-1), 102.6 (C-2'), 110.9 (C-7'), 119.4 (C-4'), 122.6 (C-6'), 124.4 (C-3'), 127.9 (C-3), 128.1 (C-7a'), 131.4 (C-2), 134.6 (C-3a'), 138.3 (C-5'); **IR** (ATR) ν_{max} /cm^{-1} = 3410m, 2926m, 1474s, 1453s, 1415s, 1336s, 895s, 806s, 764m, 722l; **$[\alpha]^{25}_{589}$** = –161.4° (*c* 1.00, $CHCl_3$); **HRMS** (EI/FI): *m*/*z* calc. for $C_{14}H_{15}N^+$ $[M]^+$: 197.1204, found: 197.1212.

HPLC traces for 49c:

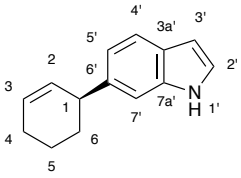


(–)-(*S*)-6-(Cyclohex-2-en-1-yl)-1*H*-indole 49d



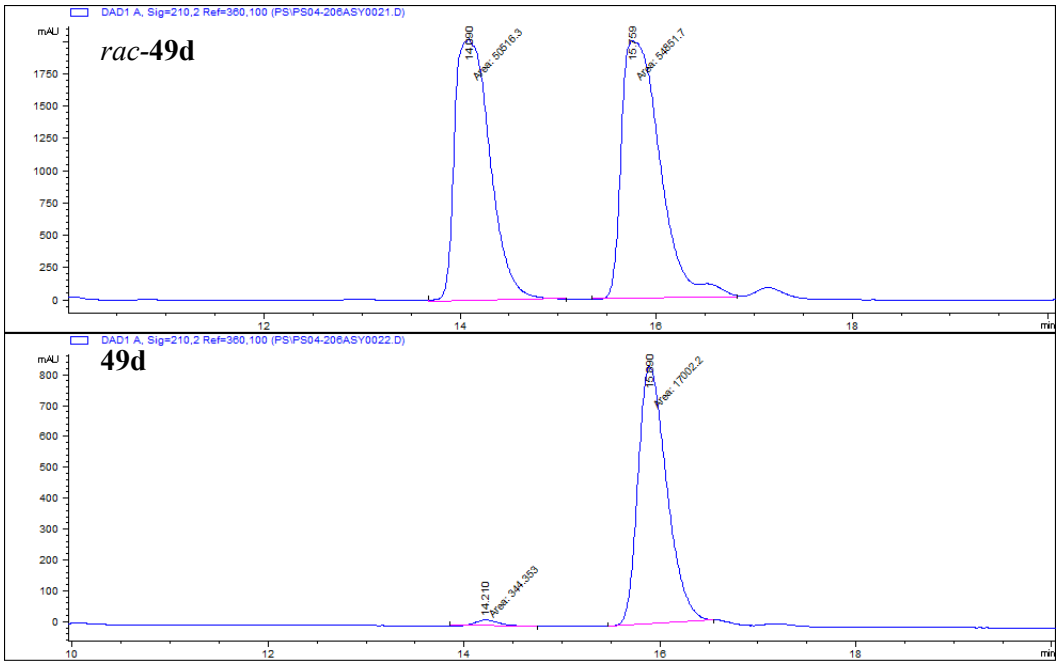
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and 6-indolylboronic acid (193.2 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added to the flask *via* syringe and rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 1.5 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (9:1) to obtain (–)-(*S*)-6-(cyclohex-2-en-1-yl)-1*H*-indole in 72% yield (57.0 mg, 0.29 mmol).

HPLC analysis indicated an enantiomeric excess of 96% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH 98:2; $\lambda = 210$ nm; minor enantiomer $t_R = 14.2$ min; major enantiomer $t_R = 15.9$ min].

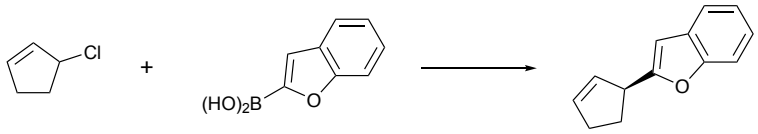


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.62 – 1.72 (m, 2 H, H-5_a, H-6_a), 1.75 – 1.83 (m, 1 H, H-5_b), 2.05 – 2.16 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.54 (dddd, J = 8.3, 5.6, 2.8, 2.8 Hz, 1 H, H-1), 5.77 – 5.87 (m, 1 H, H-2), 5.93 (dddd, J = 9.8, 3.6, 3.5, 2.3 Hz, 1 H, H-3), 6.53 (ddd, J = 3.1, 2.1, 1.0 Hz, 1 H, H-3'), 7.04 (dd, J = 8.1, 1.5 Hz, 1 H, H-5'), 7.16 (dd, J = 3.2, 2.4 Hz, 1 H, H-2'), 7.23 – 7.28 (m, 1 H, H-7'), 7.59 (d, J = 8.2 Hz, 1 H, H-4'), 8.02 (br, 1 H, NH); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 21.4 (C-5), 25.3 (C-4), 33.2 (C-6), 42.2 (C-1), 102.5 (C-3'), 109.9 (C-7'), 120.5 , 120.6 (C-4', C-5'), 123.90(C-2'), 126.3 (C-3a'), 128.2 (C-3), 131.1 (C-2), 136.2 (C-7a'), 141.0 (C-6'); **IR** (ATR) ν_{max} /cm^{-1} = 3412l, 3019s, 2926m, 2851s, 1450m, 1341m, 1090s, 813m, 766s, 724m; **$[\alpha]^{25}_{589}$** = –119.2° (*c* 1.00, $CHCl_3$); **HRMS** (Ammonia CI): *m*/*z* calc. for $C_{14}H_{16}N^+$ $[M+H]^+$: 198.1277, found: 198.1282.

HPLC traces for 49d:

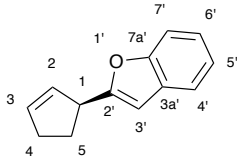


(–)-(*S*)-2-(Cyclopent-2-en-1-yl)benzofuran 50



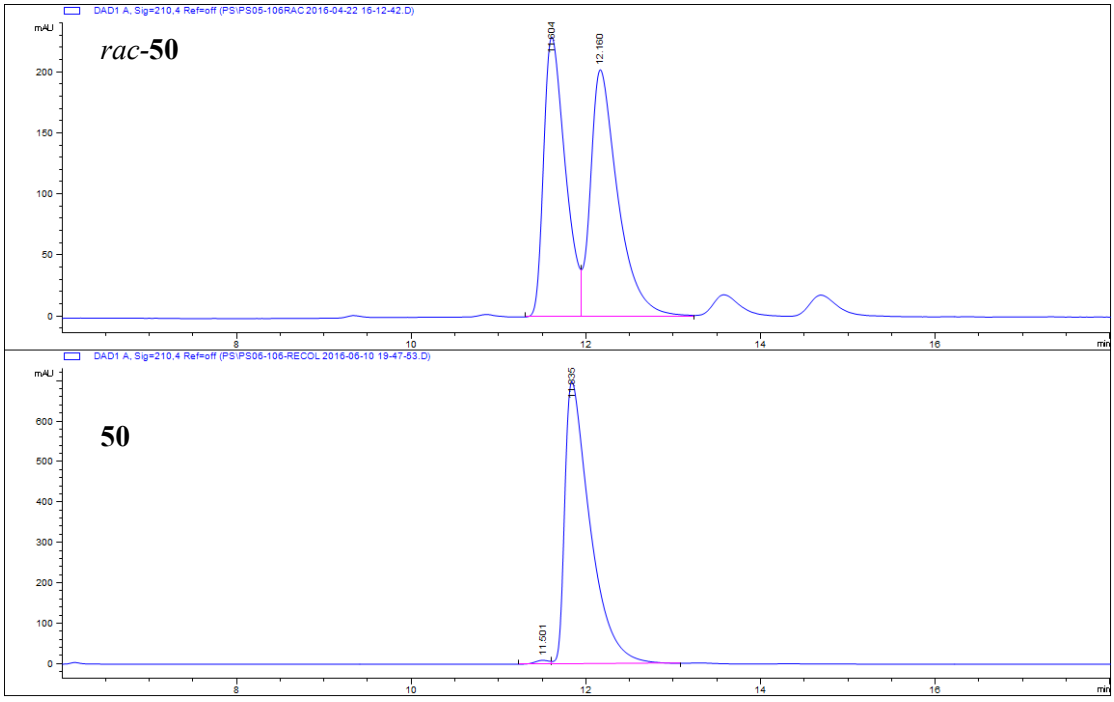
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (9.2 mg, 0.02 mmol, 0.05 eq), (*S*)-SINAP (29.8 mg, 0.048 mmol, 0.12 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclopentene (1 M in THF, 0.4 mL, 0.4 mmol, 1.00 eq) and 2-benzofuranylboronic acid (259.2 mg, 1.6 mmol, 4.00 eq) in THF (1.1 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 4 h protected from light. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with pentane to obtain (–)-(*R*)-2-(cyclohept-2-en-1-yl)benzofuran in 75% yield (55.3 mg, 0.30 mmol).

HPLC analysis indicated an enantiomeric excess of 99% [Chiralpak® IE; flow: 0.7 mL/min; hexane; λ = 210 nm; minor enantiomer t_R = 11.5 min; major enantiomer t_R = 11.8 min].

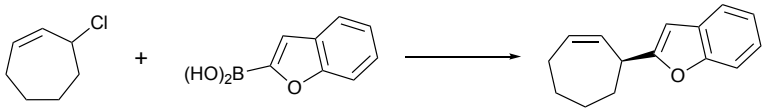


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.96 – 2.11 (m, 1 H, H-5$_a$), 2.32 – 2.50 (m, 2 H, H-4$_a$, H-5$_b$), 2.50 – 2.61 (m, 1 H, H-4$_b$), 4.04 – 4.12 (m, 1 H, H-1), 5.82 – 5.89 (m, 1 H, H-2 or H-3), 5.95 – 6.03 (m, 1 H, H-2 or H-3), 6.38 (s, 1 H, H-3'), 7.13 – 7.24 (m, 2 H, H-5', H-6'), 7.43 (ddd, *J* = 7.2, 1.7, 0.8 Hz, 1 H, H-7'), 7.45 – 7.50 (m, 1 H, H-4'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 29.9 (C-5), 32.3 (C-4), 44.9 (C-1), 100.9 (C-3'), 111.0 (C-7'), 120.5 (C-4'), 122.5 (C-5'), 123.3 (C-6'), 129.0 (C-3a' or C-7a'), 130.8, 133.4 (C-2, C-3), 154.9 (C-3a' or C-7a'), 162.1 (C-2'); **IR** (ATR) ν_{max} /cm^{-1} = 2944s, 2851s, 1585s, 1454m, 1253m, 1165s, 1010s, 951s, 798s, 742l; **$[\alpha]^{25}_{589}$** = –223.7° (*c* 1.00, $CHCl_3$). **HRMS** (ESI): *m*/*z* calc. for $C_{13}H_{13}O^+$ $[M+H]^+$: 193.0682, found: 193.0683.

HPLC traces for 50:



(–)-(*S*)-2-(Cyclohept-2-en-1-yl)benzofuran 51

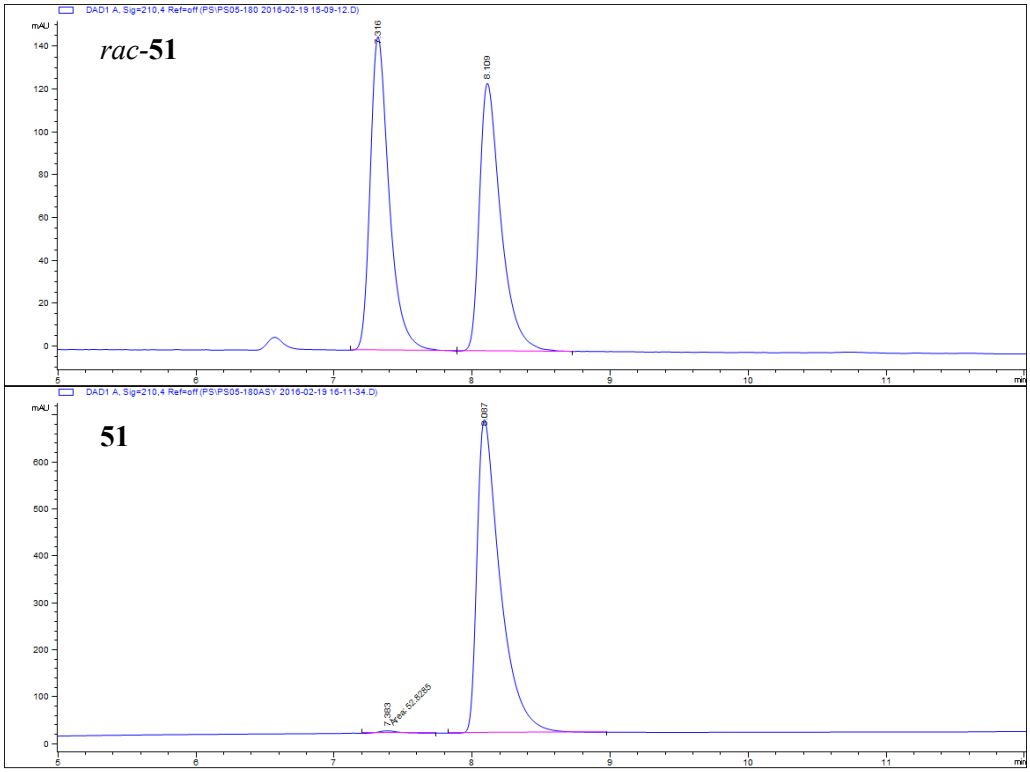


In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocycloheptene (52 µL, 0.4 mmol, 1.00 eq) and 2-benzofuranylboronic acid (194.3 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 2 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with pentane to obtain (–)-(*S*)-2-(cyclohept-2-en-1-yl)benzofuran in 24% yield (20.4 mg, 0.10 mmol).

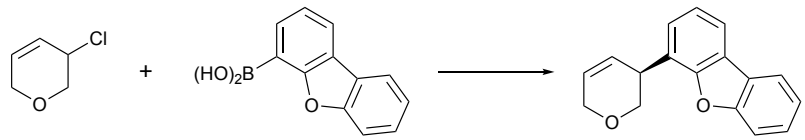
HPLC analysis indicated an enantiomeric excess of 99% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH 99.9:0.1; $\lambda = 210$ nm; minor enantiomer $t_R = 7.4$ min; major enantiomer $t_R = 8.1$ min].

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.43 – 1.56 (m, 1 H), 1.65 – 1.80 (m, 2 H), 1.82 – 2.00 (m, 2 H), 2.01 – 2.12 (m, 1 H), 2.18 – 2.30 (m, 2 H), 3.70 – 3.86 (m, 1 H), 5.89 – 6.02 (m, 2 H), 6.44 (s, 1 H), 7.13 – 7.25 (m, 2 H), 7.40 – 7.46 (m, 1 H), 7.47 – 7.54 (m, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 27.0, 28.8, 29.9, 32.5, 40.5, 101.4, 111.0, 120.5, 122.5, 123.3, 129.0, 132.7, 133.3, 154.8, 162.4; **IR** (ATR) ν_{max} /cm^{-1} = 2924l, 2853s, 1584s, 1454l, 1254l, 1167s, 799s, 746l, 688s; **$[\alpha]^{25}_{589}$** = –70.4° (*c* 1.00, $CHCl_3$); **HRMS** (EI): *m*/*z* calc. for $C_{15}H_{16}O^+$ $[M]^+$: 212.1201, found: 212.1194.

HPLC traces for 51:



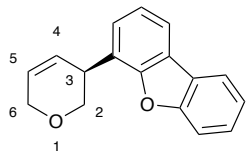
(–)-(*S*)-4-(3,6-Dihydro-2*H*-pyran-3-yl)dibenzofuran 52



In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chloro-3,6-dihydro-2*H*-pyran (45 µL, 0.4 mmol,

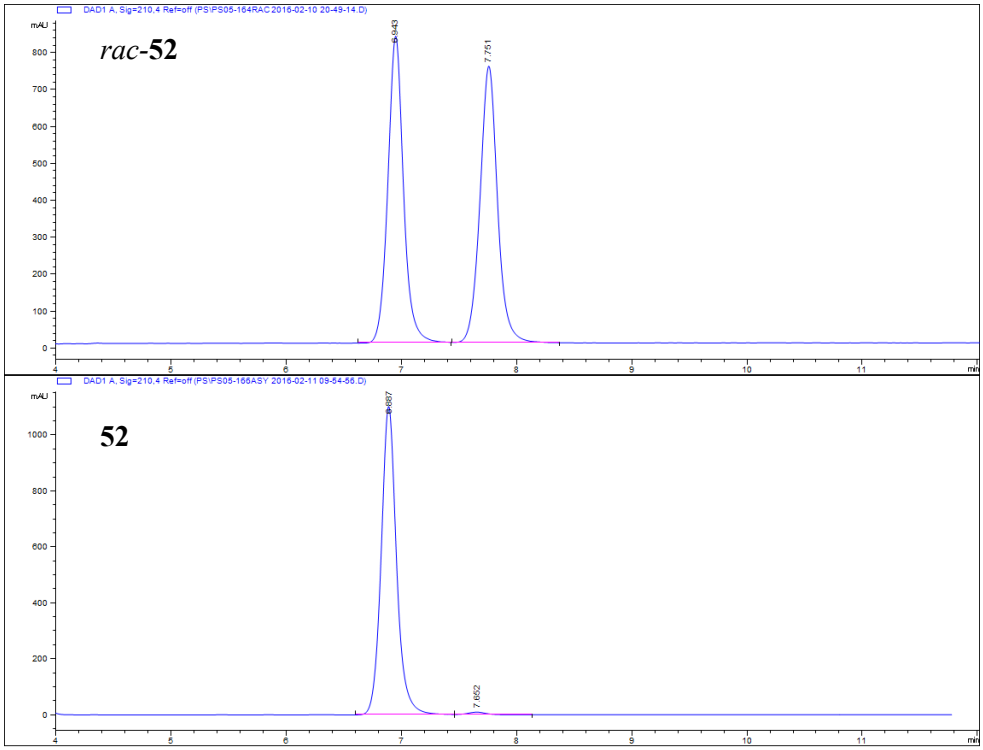
1.00 eq) and 4-(dibenzofuranyl)boronic acid (254.4 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The resulting mixture was then stirred for 2 h at reflux before the addition of NaOH (2 M, aq. 0.2 mL). The aqueous phase was extracted with Et_2O (2 × 0.5 mL). The combined organic extracts were washed with water (0.5 mL), dried with $MgSO_4$ and filtered. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (6:1) to obtain (–)-(*S*)-4-(3,6-dihydro-2*H*-pyran-3-yl)dibenzofuran in 60% yield (59.3 mg, 0.24 mmol).

HPLC analysis indicated an enantiomeric excess of 98% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH 95:5; λ = 210 nm; major enantiomer t_R =6.9 min; minor enantiomer t_R = 7.7 min].

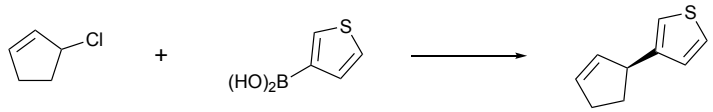


^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85 (dd, *J* = 10.5, 5.4 Hz, 1 H, H-2_a), 4.21 – 4.34 (m, 4 H, H-2_b, H-3, H-6_a, H-6_b), 6.02 – 6.10 (m, 2 H, H-4, H-5), 7.35 (m, 2 H, H_{Ar}), 7.41 (dd, *J* = 7.6, 1.4 Hz, 1 H, H_{Ar}), 7.47 (ddd, *J* = 8.3, 7.8, 1.4 Hz, 1 H, H_{Ar}), 7.60 (d, *J* = 8.2 Hz, 1 H, H_{Ar}), 7.85 (dd, *J* = 7.6, 1.4 Hz, 1 H, H_{Ar}), 7.96 (d, *J* = 7.7 Hz, 1 H, H_{Ar}); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 35.1 (C-3), 65.6 (C-6), 69.6 (C-2), 111.8 (CH_{Ar}), 119.1 (CH_{Ar}), 120.8 (CH_{Ar}), 122.8 (CH_{Ar}), 123.1 (CH_{Ar}), 124.0 (C_q), 124.6 (C_q), 126.0 (C_q), 126.4 (CH_{Ar}), 126.9 (C-4 or C-5), 127.2 (CH_{Ar}), 127.8 (C-4 or C-5), 154.4 (C_q), 156.1 (C_q); **IR** (ATR) ν_{max} /cm^{-1} = 2924l, 2853s, 1584s, 1454l, 1254l, 1167s, 799s, 746l, 688s; **$[\alpha]^{25}_{589}$** = –70.4° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{17}H_{15}O_2^+$ $[M+H]^+$: 251.1068, found: 251.1067.

HPLC traces for 52:

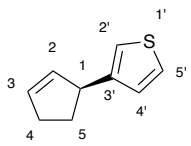


(–)-(*S*)-3-(Cyclopent-2-en-1-yl)thiophene 53



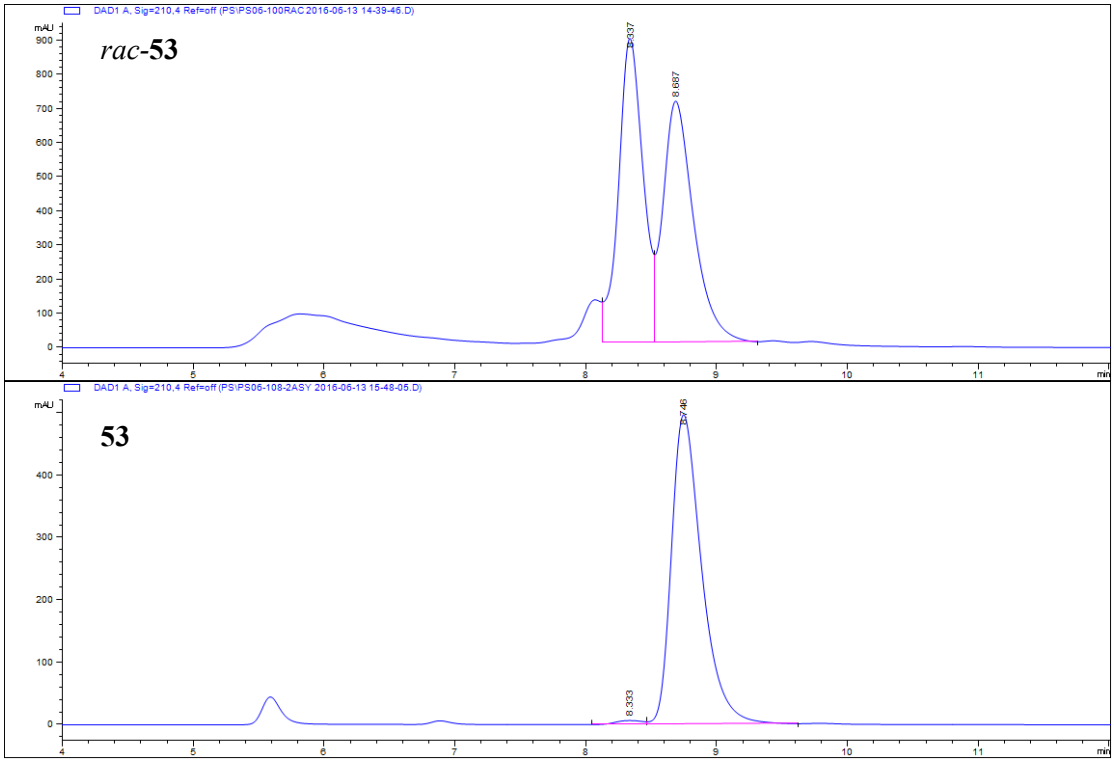
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (9.2 mg, 0.02 mmol, 0.05 eq), (*S*)-BINAP (29.8 mg, 0.048 mmol, 0.12 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclopentene (1 M in THF, 0.4 mL, 0.4 mmol, 1.00 eq) and 3-thienylboronic acid (153.6 mg, 1.20 mmol, 3.00 eq) in THF (1.1 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 4 h protected from light. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with pentane to obtain (–)-(*S*)-3-(cyclopent-2-en-1-yl)thiophene in 70% yield (44.0 mg, 0.28 mmol).

HPLC analysis indicated an enantiomeric excess of 98% [Chiralpak® AY-H; flow: 0.6 mL/min; hexane/*i*-PrOH 99.9:0.1; $\lambda = 210$ nm; minor enantiomer $t_R = 8.3$ min; major enantiomer $t_R = 8.8$ min].

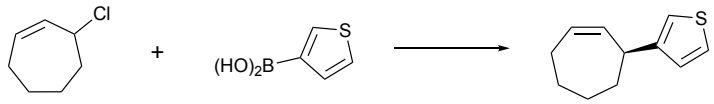


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.64 – 1.76 (m, 1 H, H-5_a), 2.22 – 2.36 (m, 2 H, H-4_a, H-5_b), 2.36 – 2.46 (m, 1 H, H-4_b), 3.86 – 3.96 (m, 1 H, H-1), 5.67 – 5.78 (m, 1 H, H-2 or H-3), 5.78 – 5.86 (m, 1 H, H-2 or H-3), 6.81 – 6.92 (m, 2 H, H-2', H-4' or H-5'), 7.18 (dd, $J = 4.7$, 3.2 Hz, 1 H, H-4' or H-5'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 32.2 (C-4), 32.6 (C-5), 46.3 (C-1), 119.1, 125.5, 127.3 (C-2', C-4', C-5'), 131.6, 133.9 (C-2, C-3), 147.1 (C-3'); **IR** (ATR) ν_{max} /cm^{-1} = 2943s, 1583s, 1564s, 1451l, 1387s, 1137s, 1105m, 1023s, 830s, 742s, 698; **$[\alpha]^{25}_{589}$** = –153.9° (*c* 1.00, $CHCl_3$); **HRMS** (EI): *m*/*z* calc. for $C_9H_{10}S^+$ $[M]^+$: 150.0503, found: 150.0494.

HPLC traces for 53:

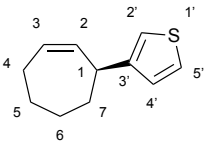


(–)-(*S*)-3-(Cyclohept-2-en-1-yl)thiophene 54



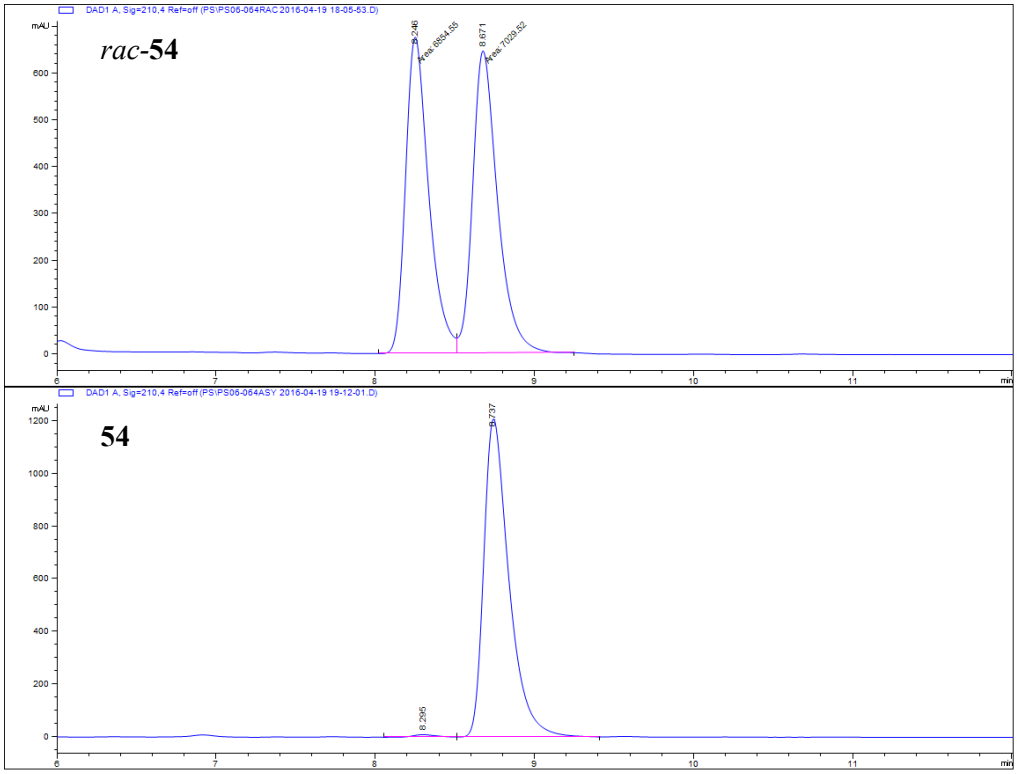
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocycloheptene (52 µL, 0.4 mmol, 1.00 eq) and 3-thienylboronic acid (153.6 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 2.5 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with pentane to obtain (–)-(*S*)-3-(cyclohept-2-en-1-yl)thiophene in 35% yield (17.0 mg, 0.14 mmol).

HPLC analysis indicated an enantiomeric excess of 98% [Chiralpak® IB; flow: 0.6 mL/min; hexane/*i*-PrOH 99.9:0.1; λ = 210 nm; minor enantiomer t_R = 8.2 min; major enantiomer t_R = 8.7 min].

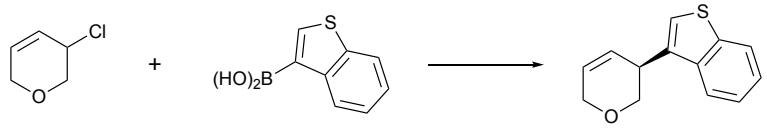


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.39 – 1.52 (m, 1 H, H-5$_a$), 1.61 – 1.83 (m, 3 H, H-5$_b$, H-6$_a$, H-7$_a$), 1.85 – 1.98 (m, 2 H, H-6$_b$, H-7$_b$), 2.13 – 2.29 (m, 2 H, H-4$_a$, H-4$_b$), 3.63 – 3.74 (m, 1 H, H-1), 5.74 – 5.92 (m, 2 H, H-2, H-3), 6.95 – 7.02 (m, 2 H, H-2', H-4'), 7.23 – 7.29 (m, 1 H, H-5'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 27.0 (C-5), 28.8 (C-4), 29.9 (C-7), 35.1 (C-6), 41.9 (C-1), 119.2 (C-2' or C-4'), 125.4 (C-5'), 127.3 (C-2' or C-4'), 131.6, 136.5 (C-2, C-3), 147.8 (C-3'); **IR** (ATR) ν_{max} /cm^{-1} = 3017s, 2920l, 2851s, 1443s, 857s, 842s, 771l, 687s, 648s; **$[\alpha]^{25}_{589}$** = –63.4° (*c* 1.00, $CHCl_3$); **HRMS** (EI): *m*/*z* calc. for $C_{11}H_{14}S^+$ $[M]^+$: 178.0816, found: 178.0813.

HPLC traces for 54:

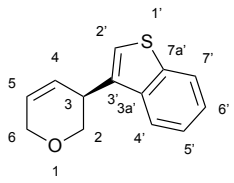


(–)-(*S*)-3-(Benzo[*b*]thiophen-3-yl)-3,6-dihydro-2*H*-pyran 55



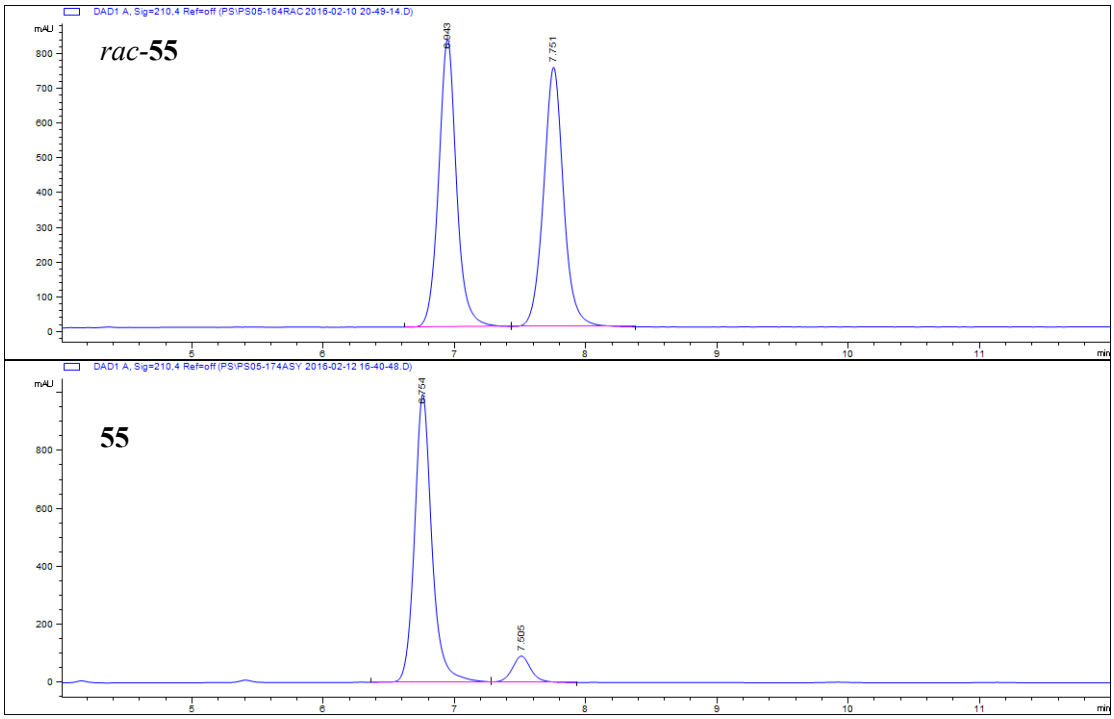
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chloro-3,6-dihydro-2*H*-pyran (45 µL, 0.4 mmol, 1.00 eq) and benzo[*b*]thien-3-ylboronic acid (214 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was added *via* syringe and the flask rinsed with additional THF (0.5 mL). The resulting mixture was then stirred for 2 h at reflux before the addition of NaOH (2 M, aq. 0.2 mL). The aqueous phase was extracted with Et_2O (2 × 0.5 mL). The combined organic extracts were washed with water (0.5 mL), dried with $MgSO_4$ and filtered. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with pentane and diethyl ether (95:5) to obtain (–)-(*S*)-3-(benzo[*b*]thiophen-3-yl)-3,6-dihydro-2*H*-pyran in 37% yield (32.0 mg, 0.15 mmol).

HPLC analysis indicated an enantiomeric excess of 82% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH 99:1; λ = 210 nm; major enantiomer t_R = 6.8 min; minor enantiomer t_R = 7.5 min].



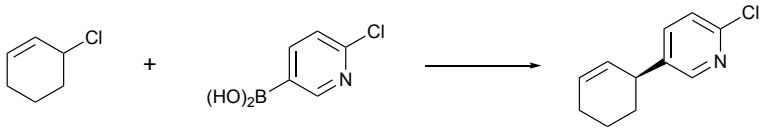
^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.76 (dd, *J* = 11.0, 6.4 Hz, 1 H, H-2$_a$), 3.93 – 4.01 (m, 1 H, H-3), 4.16 (dd, *J* = 10.9, 4.8 Hz, 1 H, H-2$_b$), 4.24 – 4.30 (m, 2 H, H-6$_a$, H-6$_b$), 5.98 (dddd, *J* = 10.3, 2.4, 2.3, 2.3 Hz, 1 H, H-5), 6.05 (dddd, *J* = 10.2, 2.3, 2.3, 2.2 Hz, 1 H, H-4), 7.22 (s, 1 H, H-2'), 7.32 – 7.43 (m, 2 H, H-5', H-6'), 7.77 – 7.84 (m, 1 H, H-4'), 7.84 – 7.92 (m, 1 H, H-7'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 35.3 (C-3), 65.7 (C-6), 69.4 (C-2), 121.6 (C-4'), 123.1 (C-2'), 123.2 (C-7'), 124.1, 124.4 (C-5', C-6'), 127.2 (C-4), 127.4 (C-5), 136.5 (C-3'), 138.3 (C-3a'), 140.9 (C-7a'); **IR** (ATR) ν_{max} /cm^{-1} = 2924s, 2846l, 1457l, 1429m, 1187s, 1102m, 1081m, 765l, 729s, 703s; **$[\alpha]^{25}_{589}$** = –4.6° (*c* 0.50, $CHCl_3$); **HRMS** (Ammonia CI): *m*/*z* calc. for $C_{13}H_{13}OS^+$ $[M+H]^+$: 217.0682, found: 217.0684.

HPLC traces for 55:



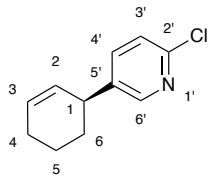
6.4.3 Pyridinylboronic acids

(–)-(*S*)-2-Chloro-5-(cyclohex-2-en-1-yl)-pyridine 56a



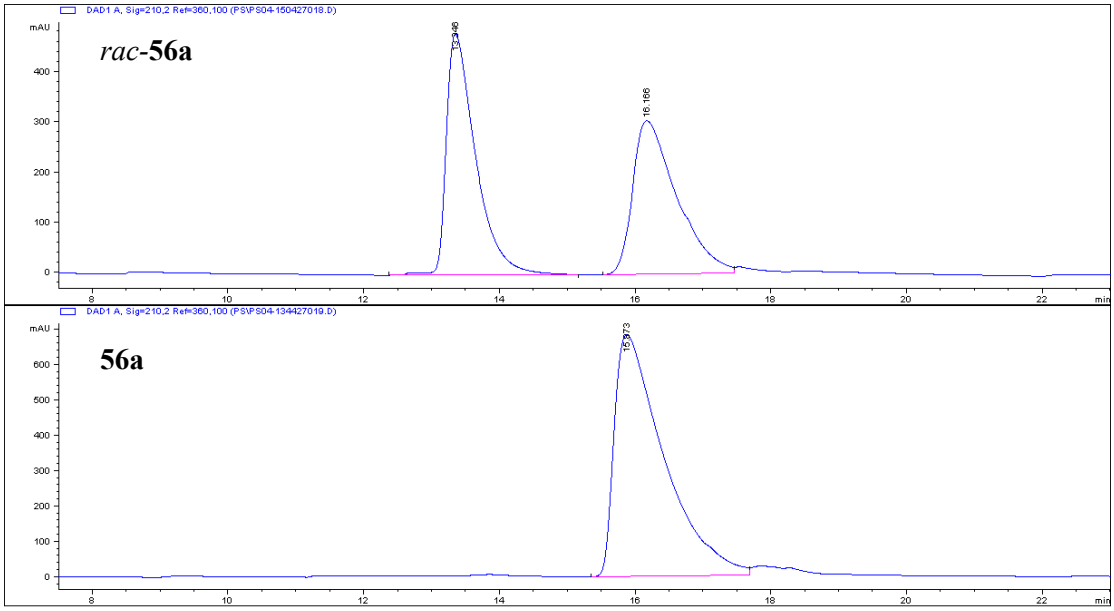
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (390.9 mg, 1.20 mmol, 3.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and 6-chloro-3-pyridinylboronic acid (188.8 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 2 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (97:3) to obtain (–)-(*S*)-2-chloro-5-(cyclohex-2-en-1-yl)-pyridine in 57% yield (44.4 mg, 0.23 mmol).

HPLC analysis indicated an enantiomeric excess of greater than 99% [Chiralpak® AY-H; flow: 1.5 mL/min; hexane/*i*-PrOH 99.4:0.6; $\lambda = 210$ nm; minor enantiomer $t_R = 13.4$ min; major enantiomer, $t_R = 16.2$ min].

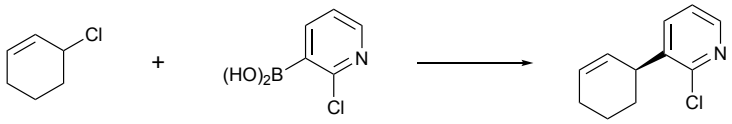


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.49 (dddd, $J = 13.1, 10.2, 8.1, 3.1$ Hz, 1 H, H-6_a), 1.56 – 1.76 (m, 2 H, H-5_a, H-5_b), 1.95 – 2.06 (m, 1 H, H-6_b), 2.06 – 2.14 (m, 2 H, H-4_a, H-4_b), 3.42 (dddd, $J = 8.3, 5.6, 2.9, 2.9$ Hz, 1 H, H-1), 5.58 – 5.67 (m, 1 H, H-2), 5.91 – 6.00 (m, 1 H, H-3), 7.24 (d, $J = 8.2$ Hz, 1 H, H-3'), 7.49 (dd, $J = 8.2, 2.6$ Hz, 1 H, H-4'), 8.23 (d, $J = 2.6$ Hz, 1 H, H-6'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 20.8 (C-5), 24.9 (C-4), 32.4 (C-6), 38.7 (C-1), 124.0 (C-3'), 128.3 (C-2'), 130.0 (C-3'), 138.2 (C-4'), 140.8 (C-5'), 149.2 (C-2'), 149.4 (C-6'); **IR** (ATR) ν_{max} /cm^{-1} = 2930m, 2861s, 1564s, 1455l, 1379s, 1137s, 1105l, 833s, 629s; **$[\alpha]^{25}_{589}$** = –116.2° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{11}H_{13}ClN^+$ $[M+H]^+$: 194.0731, found: 194.0733.

HPLC traces for 56a:

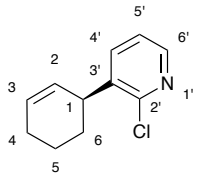


(–)-(*S*)-2-Chloro-3-(cyclohex-2-en-1-yl)-pyridine 56b



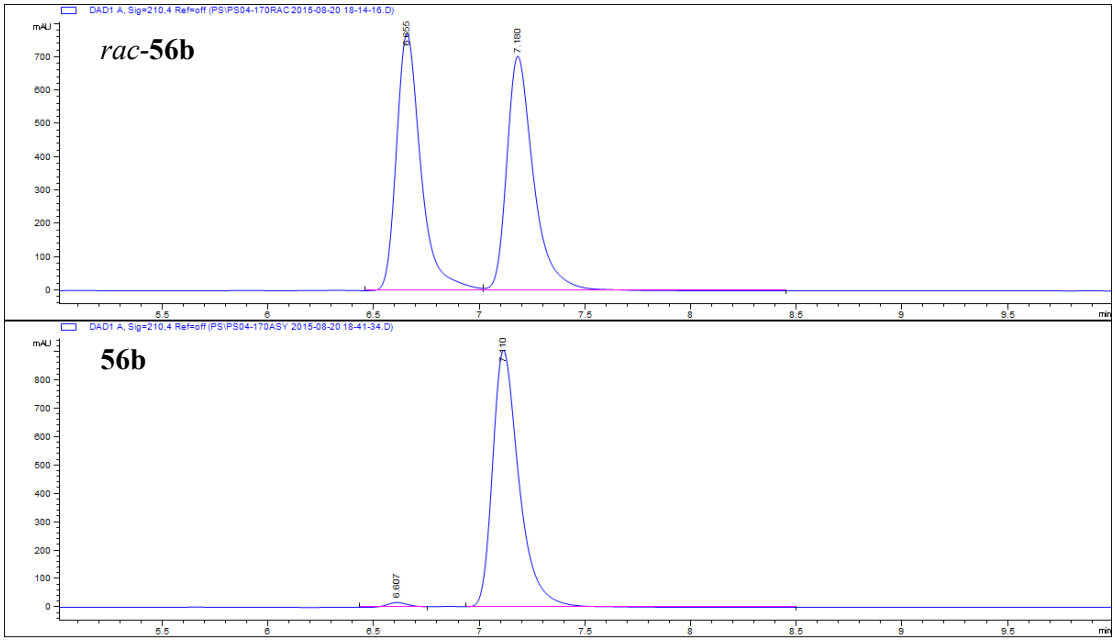
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and 2-chloro-3-pyridinylboronic acid (188.8 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 12 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (97:3) to obtain (–)-(*S*)-2-chloro-3-(cyclohex-2-en-1-yl)-pyridine in 26% yield (20.1 mg, 0.10 mmol).

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH 99.4:0.6; $\lambda = 210$ nm; minor enantiomer $t_R = 6.7$ min; major enantiomer $t_R = 7.2$ min].

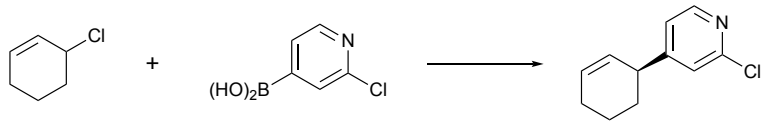


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.44 – 1.55 (m, 1 H, H-6_a), 1.60 – 1.68 (m, 2 H, H-5_a, H-5_b), 2.04 – 2.19 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.82 (dddd, J = 8.3, 5.5, 2.7, 2.7 Hz, 1 H, H-1), 5.60 (dddd, J = 10.1, 2.5, 2.4, 2.4 Hz, 1 H, H-2), 6.00 (dddd, J = 9.9, 3.7, 3.7, 2.2 Hz, 1 H, H-3), 7.19 (dd, J = 7.6, 4.7 Hz, 1 H, H-5'), 7.59 (dd, J = 7.6, 2.0 Hz, 1 H, H-4'), 8.23 (dd, J = 4.7, 1.9 Hz, 1 H, H-6'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 20.5 (C-5), 25.0 (C-4), 29.6 (C-6), 37.9 (C-1), 122.7 (C-5'), 128.0 (C-2), 130.4 (C-3), 138.0 (C-4'), 140.0 (C-3'), 147.2 (C-6'), 151.2 (C-2'); **IR** (ATR) ν_{max} /cm^{-1} = 2929s, 1561m, 1405l, 1071m, 1060m, 806s, 789m, 723m, 652m; **$[\alpha]^{25}_{589}$** = –17.2° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{11}H_{13}ClN^+$ $[M+H]^+$: 194.0731, found: 194.0733.

HPLC traces for 56b:

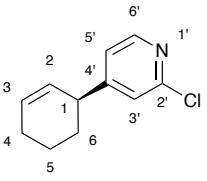


(–)-(*S*)-2-Chloro-4-(cyclohex-2-en-1-yl)-pyridine 56c



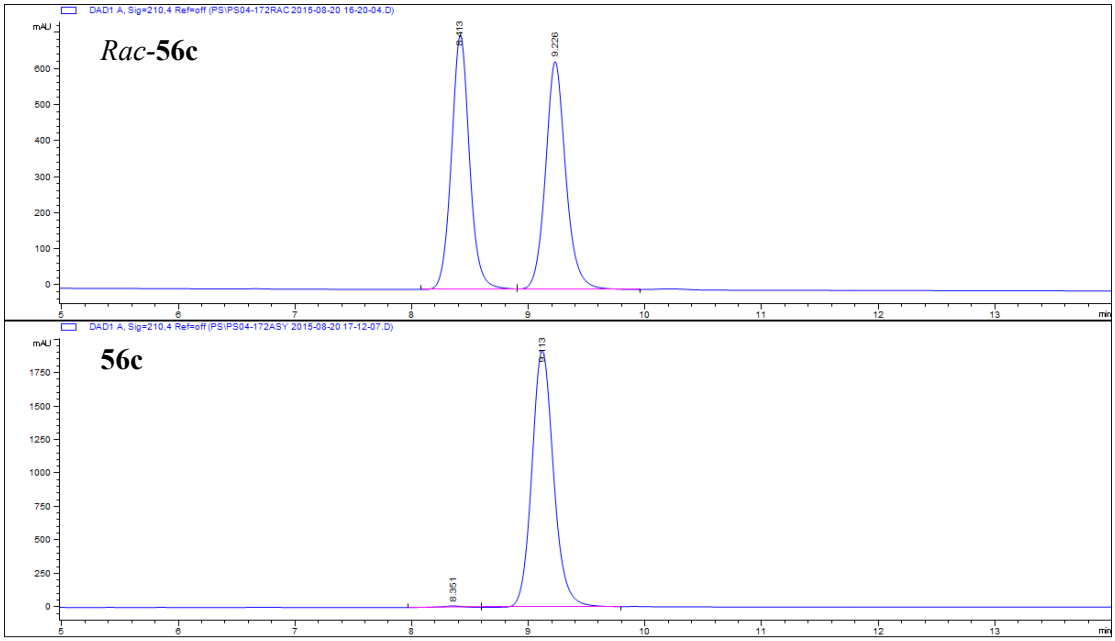
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and 2-chloro-4-pyridinylboronic acid (188.8 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 12 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (97:3) to obtain (–)-(*S*)-2-chloro-4-(cyclohex-2-en-1-yl)-pyridine in 44% yield (34.3 mg, 0.18 mmol).

HPLC analysis indicated an enantiomeric excess of 99% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH 99.4:0.6; $\lambda = 210$ nm; minor enantiomer $t_R = 8.4$ min; major enantiomer $t_R = 9.2$ min].

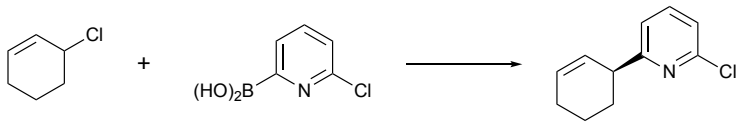


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.44 – 1.80 (m, 3 H, H-5_a, H-5_b, H-6_a), 1.93 – 2.05 (m, 1 H, H-6_b), 2.05 – 2.14 (m, 2 H, H-4_a, H-4_b), 3.29 – 3.44 (m, 1 H, H-1), 5.62 (ddd, $J = 10.1, 2.5, 2.5$ Hz, 1 H, H-2), 5.90 – 6.02 (m, 1 H, H-3), 7.06 (dd, $J = 5.2, 1.6$ Hz, 1 H, H-5'), 7.17 (d, $J = 1.6$ Hz, 1 H, H-3'), 8.26 (d, $J = 5.1$ Hz, 1 H, H-6'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 20.8 (C-5), 24.9 (C-4), 31.7 (C-6), 41.0 (C-1), 122.1 (C-5'), 123.6 (C-3'), 127.4 (C-2), 130.4 (C-3), 149.6 (C-6'), 151.7 (C-2'), 159.0 (C-4'); **IR** (ATR) ν_{max} / cm^{-1} = 2931s, 1590l, 1544m, 1380m, 1121s, 1184m, 911s, 733m, 722m, 679s; **$[\alpha]^{25}_{589}$** = –117.3° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{11}H_{13}ClN^+$ $[M+H]^+$: 194.0731, found: 194.0732.

HPLC traces for 56c:

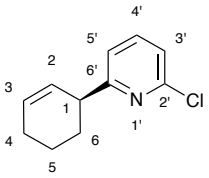


(–)-(*S*)-2-Chloro-6-(cyclohex-2-en-1-yl)-pyridine 56d



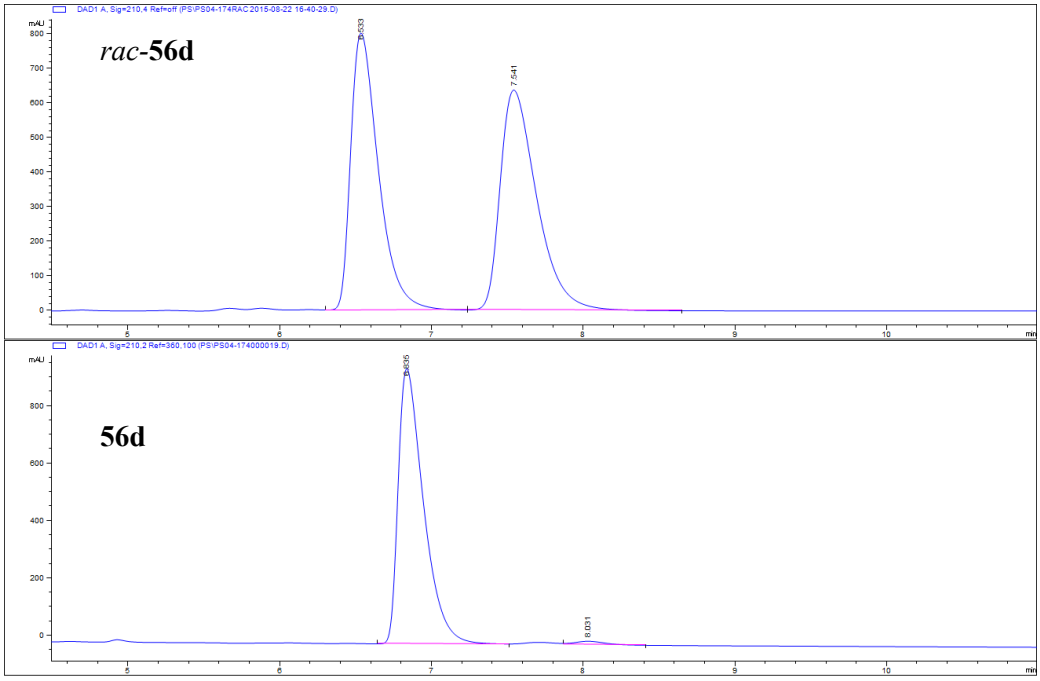
In a 25 mL round bottomed flask $[Rh(cod)(OH)]_2$ (11.5 mg, 0.025 mmol, 0.0125 eq), (*S*)-BINAP (37.3 mg, 0.06 mmol, 0.03 eq) and Cs_2CO_3 (1.95 g, 6.0 mmol, 3.00 eq) were stirred in THF (5.0 mL) at reflux for 30 min. 3-Chlorocyclohexene (225 µL, 2.0 mmol, 1.00 eq) was added to a sonicated solution of 6-chloro-2-pyridinylboronic acid (944 mg, 6.0 mmol, 3.00 eq) and water (108 µL, 6.0 mmol, 3.00 eq) in THF (8 mL). The resulting mixture was added *via* syringe and the flask rinsed with additional THF (2 mL). The reaction mixture was refluxed for 12 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (97:3) to obtain (–)-(*S*)-2-chloro-6-(cyclohex-2-en-1-yl)-pyridine in 63% yield (245 mg, 1.27 mmol).

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® ID; flow: 1.0 mL/min; hexane/*i*-PrOH 99.7:0.3; λ = 210 nm; major enantiomer t_R = 6.8 min; minor enantiomer t_R = 8.0 min].

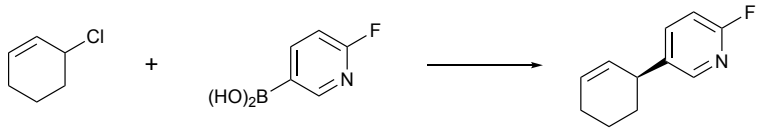


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.59 – 1.75 (m, 3 H, H-5_a, H-5_b, H-6_a), 2.03 – 2.13 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.56 (dddd, J = 7.9, 5.4, 2.8, 2.8 Hz, 1 H, H-1), 5.71 – 5.79 (m, 1 H, H-2), 5.93 (dddd, J = 9.8, 3.6, 3.6, 2.3 Hz, 1 H, H-3), 7.11 (dd, J = 7.6, 0.9 Hz, 1 H, H-5'), 7.14 (dd, J = 7.9, 0.9 Hz, 1 H, H-3'), 7.56 (dd, J = 7.9, 7.6 Hz, 1 H, H-4'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 20.9 (C-5), 25.1 (C-4), 30.5 (C-6), 43.7 (C-1), 120.2 (C-5'), 121.7 (C-3'), 128.0 (C-2), 129.7 (C-3), 139.0 (C-4'), 150.8 (C-2'), 166.7 (C-5'); **IR** (ATR) ν_{max} /cm^{-1} = 2931s, 1581m, 1557m, 1435l, 1156s, 1133m, 791m, 727m, 663s; **[α]$^{25}_{589}$** = –72.0° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): *m/z* calc. for $C_{11}H_{13}ClN^+$ [M+H]$^+$: 194.0731, found: 194.0733.

HPLC traces for 56d:

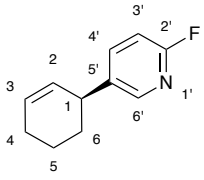


(–)-(*S*)-2-Fluoro-5-(cyclohex-2-en-1-yl)-pyridine 57



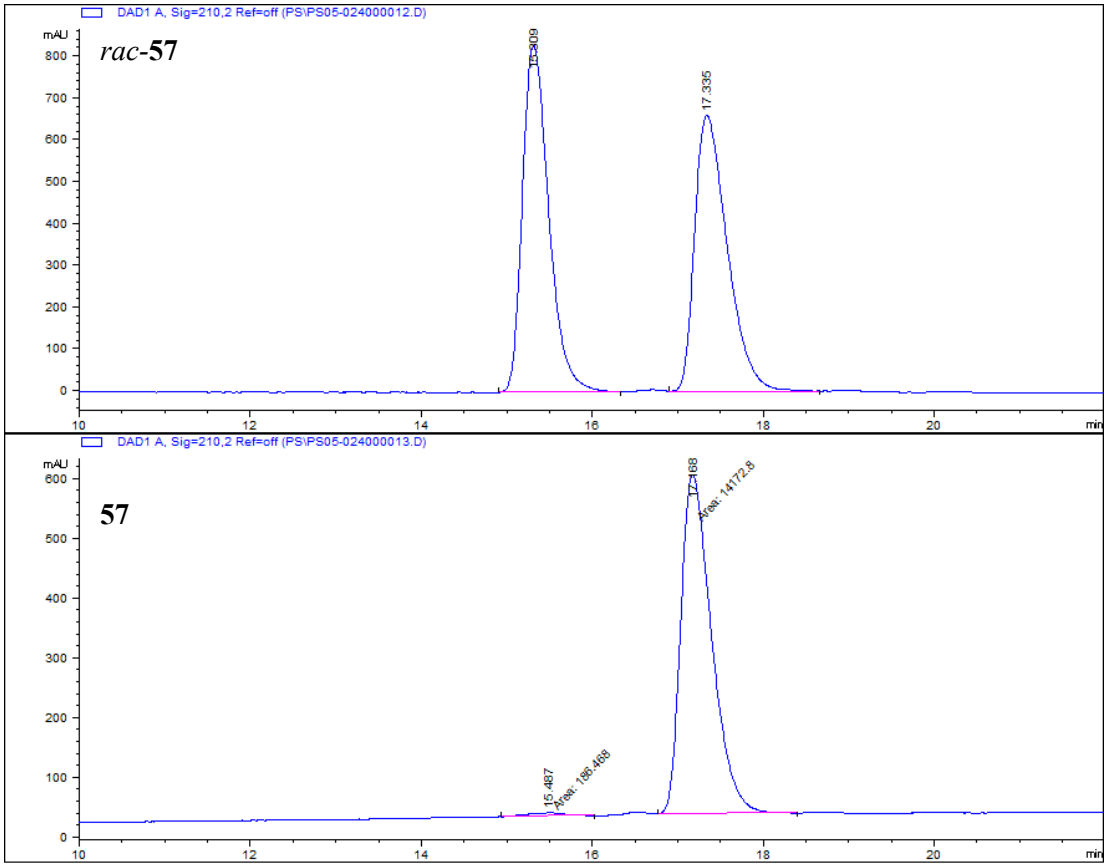
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (130.3 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at reflux for 30 min. A solution of 3-chlorocyclohexene (45 µL, 0.4 mmol, 1.00 eq) and 6-fluoro-3-pyridinylboronic acid (134.3 mg, 1.20 mmol, 3.00 eq) in THF (1.5 mL) was then added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 2 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (97:3) to afford in 52% yield (30.4 mg, 0.21 mmol).

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® ID; flow: 1.0 mL/min; hexane/*i*-PrOH 99.7:0.3; $\lambda = 210$ nm; minor enantiomer $t_R = 15.5$ min; major enantiomer $t_R = 17.2$ min].

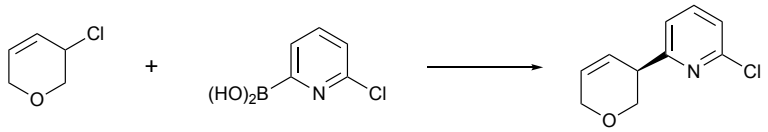


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.44 (dddd, $J = 13.1, 10.2, 8.1, 3.1$ Hz, 1 H, H-6_a), 1.49 – 1.62 (m, 1 H, H-5_a), 1.58 – 1.72 (m, 1 H, H-5_b), 1.89 – 2.01 (m, 1 H, H-6_b), 1.98 – 2.08 (m, 2 H, H-4_a, H-4_b), 3.37 (dddd, $J = 8.3, 5.6, 2.8, 2.8$ Hz, 1 H, H-1), 5.50 – 5.65 (m, 1 H, H-2), 5.88 (dddd, $J = 9.9, 3.7, 3.7, 2.3$ Hz, 1 H), 6.79 (dd, $J =$ 8.4 Hz, $^3J_{H\text{-}F} = 3.0$ Hz, 1 H, H-3), 7.55 (ddd, $J = 8.1, 8.1, 2.6$ Hz, 1 H, H-5), 7.98 (d, $J = 2.5$ Hz, 1 H, H-6); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 20.7 (C-5), 24.8 (C-4), 32.4 (C-6), 38.5 (C-1), 109.0 (d, $^2J_{C\text{-}F} = 37.3$ Hz, C-3'), 140.4 (d, $^4J_{C\text{-}F} = 7.7$ Hz, C-5'), 146.7 (d, $^3J_{C\text{-}H} = 14.3$ Hz, C-6'), 162.4 (d, $^1J_{C\text{-}F} = 236.9$ Hz, C-2'); **^{19}F-NMR** (376 MHz, $CDCl_3$) δ –72.18 (d, $J = 8.1$ Hz); **IR** (ATR) ν_{max} /cm^{-1} = 2931s, 1670s, 1593m, 1483l, 1385s, 1250s, 829s, 656s; **$[\alpha]^{25}_{589}$** = –66.4° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{11}H_{13}FN^+$ $[M+H]^+$: 178.1027, found: 178.1027.

HPLC traces for 57:

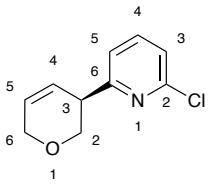


(–)-(*S*)-2-Chloro-6-(3,6-dihydro-2H-pyran-3-yl)pyridine 58



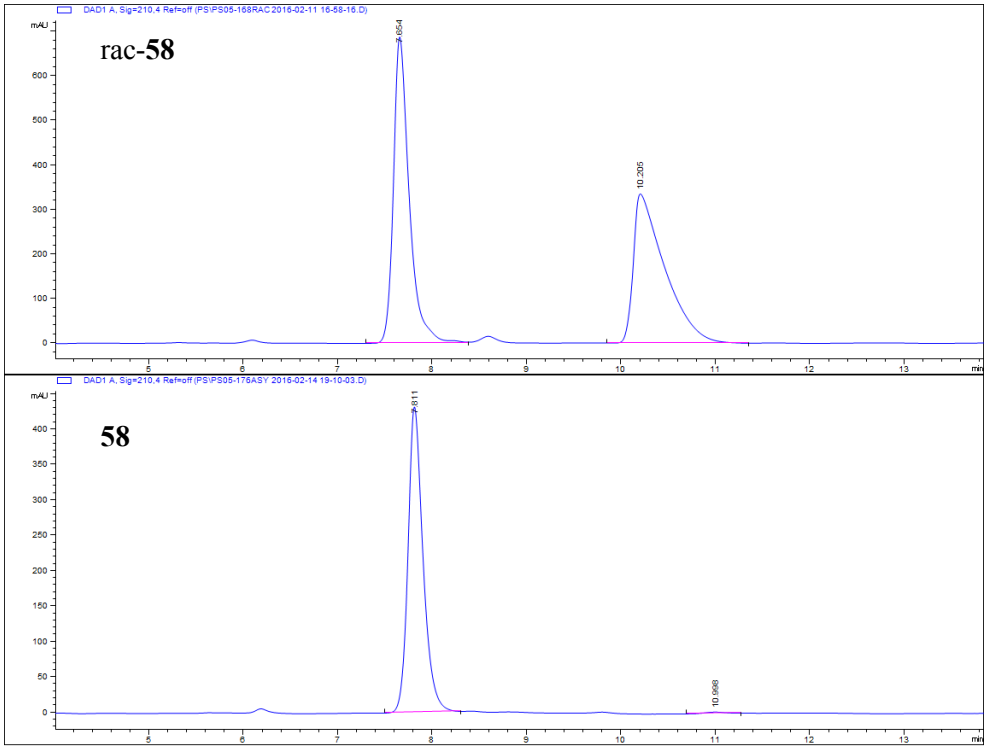
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*S*)-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (390.9 mg, 1.20 mmol, 3.00 eq) were stirred in THF (2 mL) at reflux for 30 min. 3-Chloro-3,6-dihydro-2*H*-pyran (45 µL, 0.4 mmol, 1.00 eq) was added to a sonicated solution of 6-chloro-2-pyridinylboronic acid (189 mg, 1.20 mmol, 3.00 eq) and water (22 µL, 1.20 mmol, 3.00 eq) in THF (1.5 mL). The resulting mixture was added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 2 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (9:1) to obtain (–)-(*S*)-2-chloro-6-(3,6-dihydro-2*H*-pyran-3-yl)pyridine in 74% yield (58.1 mg, 0.30 mmol).

HPLC analysis indicated an enantiomeric excess of 99% [Chiralpak® IA; flow: 1.2 mL/min; hexane/*i*-PrOH 99.2:0.8; λ = 210 nm; major enantiomer t_R = 7.8 min; minor enantiomer t_R = 11.0 min].

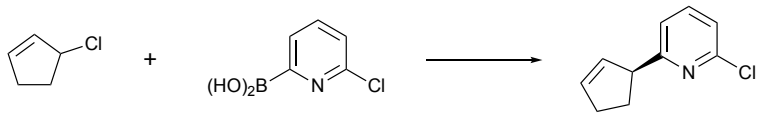


^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.56 – 3.65 (m, 1 H, H-3), 3.88 (dd, *J* = 11.2, 4.7 Hz, 1 H, H-2$_a$), 4.04 (dd, *J* = 11.2, 4.7 Hz, 1 H, H-2$_b$), 4.19 – 4.23 (m, 2 H, H-6$_a$, H-6$_b$), 5.92 – 6.03 (m, 2 H, H-4, H-5), 7.18 (dd, *J* = 7.9, 0.9 Hz, 1 H, H-5'), 7.23 (dd, *J* = 7.6, 0.9 Hz, 1 H, H-3'), 7.59 (dd, *J* = 7.7, 7.7 Hz, 1 H, H-4'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 43.1 (C-3), 65.6 (C-6), 69.3 (C-2), 121.0 (C-3'), 122.3 (C-5'), 125.59, 128.3 (C-4, C-5), 139.2 (C-4'), 150.9 (C-2'), 162.9 (C-6'); **IR** (ATR) ν_{max} /cm^{-1} = 1582l, 1559l, 1436l, 1411m, 1157m, 1135l, 1114m, 1088l, 795ls, 744m; **[α]$^{25}_{589}$** = –97.4° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{10}H_{11}ClNO^+$ $[M+H]^+$: 196.0524, found: 196.0524.

HPLC traces for 58:

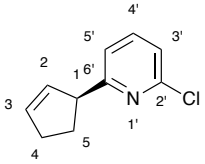


(–)-(*S*)-2-Chloro-6-(cyclopent-2-en-1-yl)-pyridine 59



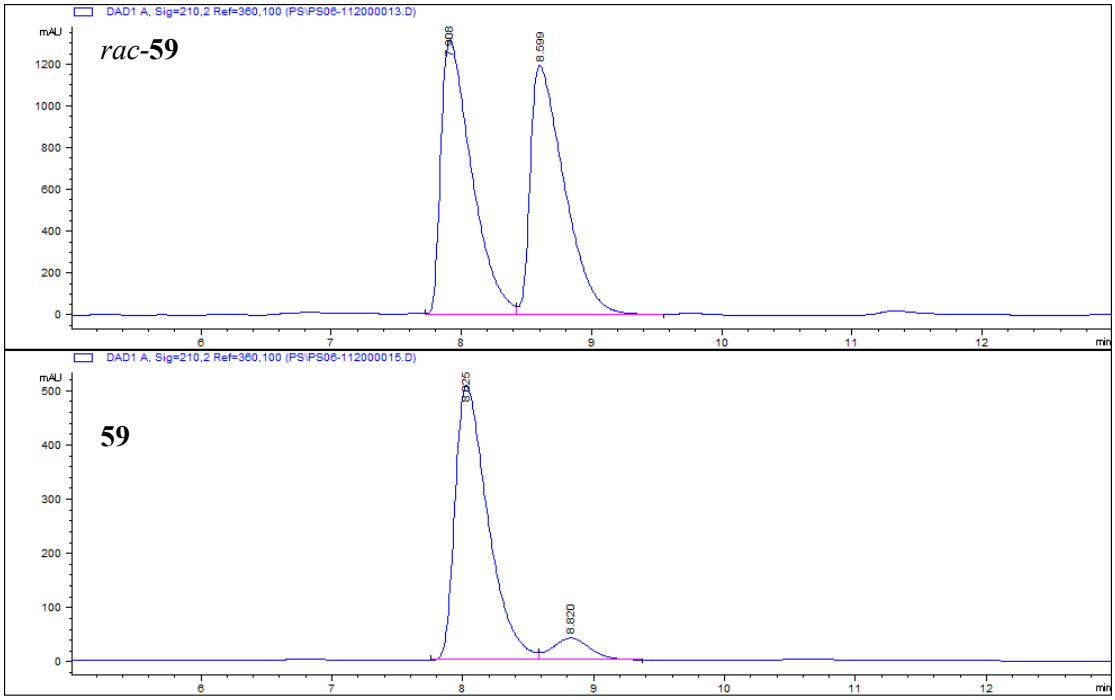
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (9.2 mg, 0.02 mmol, 0.05 eq), (*S*)-BINAP (29.8 mg, 0.048 mmol, 0.12 eq) and Cs_2CO_3 (390.9 mg, 1.20 mmol, 3.00 eq) were stirred in THF (2 mL) at 60 °C for 30 min. 3-Chloropentene (1 M in THF, 0.4 mL, 0.4 mmol, 1.00 eq) was added to a sonicated solution of 6-chloro-2-pyridinylboronic acid (189 mg, 1.20 mmol, 3.00 eq) and water (22 µL, 1.20 mmol, 3.00 eq) in THF (1.5 mL). The resulting mixture was added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 2 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (97:3) to obtain (–)-(*S*)-2-chloro-6-(cyclopent-2-en-1-yl)-pyridine in 28% yield (20.1 mg, 0.11 mmol).

HPLC analysis indicated an enantiomeric excess of 83% [Chiralpak® ID; flow: 1.0 mL/min; hexane/*i*-PrOH 99.7:0.3; $\lambda = 210$ nm; major enantiomer $t_R = 8.0$ min; minor enantiomer $t_R = 8.8$ min].

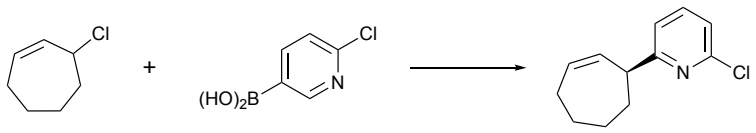


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.79 – 1.96 (m, 1 H, H-5_a), 2.31 – 2.60 (m, 3 H, H-4_a, H-4_b, H-5_b), 3.96 – 4.14 (m, 1 H, H-1), 5.75 – 5.86 (m, 1 H, H-2 or H-3), 5.92 – 6.04 (m, 1 H, H-2 or H-3), 7.06 (d, $J = 7.6$ Hz, 1 H, H-3' or H-5'), 7.14 (dd, $J = 7.8$, 1.0 Hz, 1 H, H-3' or H-5'), 7.55 (dd, $J = 7.7$, 7.7 Hz, 1 H, H-4'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 32.0 (C-5), 32.6 (C-4), 53.5 (C-1), 119.7, 121.7 (C-3', C-5'), 132.4, 133.6 (C-2, C-3), 139.2 (C-4'), 150.7 (C-2'), 166.9 (C-6'); **IR** (ATR) ν_{max} /cm^{-1} = 2941s, 1582l, 1558l, 1437l, 1409m, 1159s, 1133m, 795m, 745m, 729m; **$[\alpha]^{25}_{589}$** = –117.5° (*c* 1.00, $CHCl_3$). **HRMS** (EI/FI): *m*/*z* calc. for $C_{10}H_{10}ClN^+$ $[M]^+$: 179.0502, found: 179.0489

HPLC traces for 59:

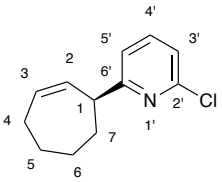


(+)-(*S*)-2-Chloro-6-(cyclohept-2-en-1-yl)-pyridine 60



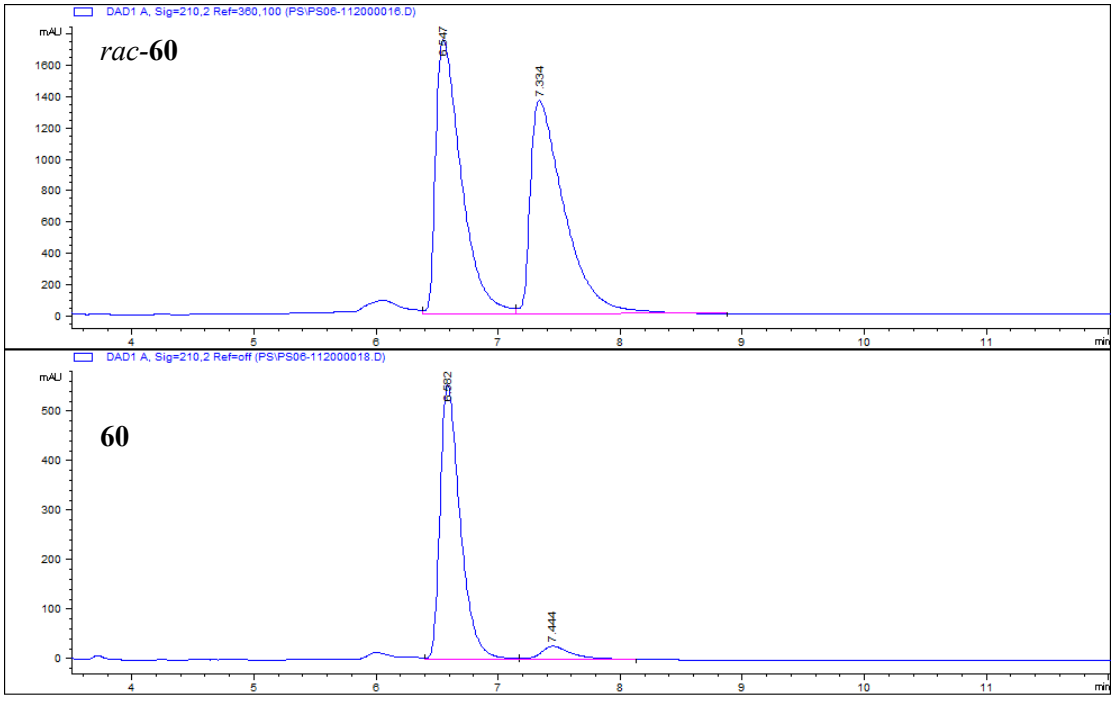
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (9.2 mg, 0.02 mmol, 0.05 eq), (*S*)-BINAP (29.8 mg, 0.048 mmol, 0.12 eq) and Cs_2CO_3 (390.9 mg, 1.20 mmol, 3.00 eq) were stirred in THF (2 mL) at reflux for 30 min. 3-Chlorocycloheptene (52 µL, 0.4 mmol, 1.00 eq) was added to a sonicated solution of 6-chloro-2-pyridinylboronic acid (189 mg, 1.20 mmol, 3.00 eq) and water (22 µL, 1.20 mmol, 3.00 eq) in THF (1.5 mL). The resulting mixture was added *via* syringe and the flask rinsed with additional THF (0.5 mL). The reaction mixture was refluxed for 2 h. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol ether and ethyl acetate (97:3) to obtain (+)-(*S*)-2-chloro-6-(cyclohept-2-en-1-yl)-pyridine in 22% yield (18.3 mg, 0.09 mmol).

HPLC analysis indicated an enantiomeric excess of 85% [Chiralpak® ID; flow: 1.0 mL/min; hexane/*i*-PrOH 99.7:0.3; λ = 210 nm; major enantiomer t_R = 6.6 min; minor enantiomer t_R = 7.4 min].

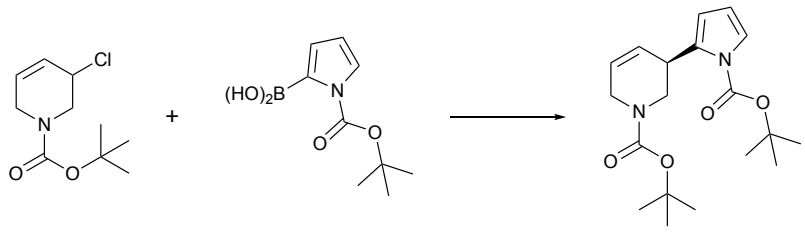


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.37 – 1.50 (m, 1 H, H-5_a,), 1.63 – 1.88 (m, 4 H, H-5_b, H-6_a, H-7_a, H-7_b), 1.89 – 1.99 (m, 1 H, H-6_b,), 2.16 – 2.28 (m, 2 H, H-4_a, H-4_b), 3.66 – 3.76 (m, 1 H, H-1), 5.75 – 5.84 (m, 1 H, H-2), 5.91 (dddd, *J* = 11.8, 6.5, 5.3, 2.3 Hz, 1 H, H-3), 7.10 – 7.17 (m, 2 H, H-3', H-5'), 7.57 (dd, *J* = 7.7, 7.7 Hz, 1 H, H-4'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 26.9 (C-5), 28.9 (C-4), 30.4 (C-6), 34.8 (C-7), 48.9 (C-1), 120.0, 121.7 (C-3', C-5'), 132.9 (C-3), 134.4 (C-2), 139.2 (C-4'), 150.7 (C-2'), 167.5 (C-6'); **IR** (ATR) ν_{max} /cm^{-1} = 2923l, 2851s 1583l, 1559l, 1439l, 1416m, 1157m, 1134m, 795m, 721s; **$[\alpha]^{25}_{589}$** = +1.9° (*c* 1.00, $CHCl_3$); **HRMS** (CI): *m/z* calc. for $C_{12}H_{15}ClN^+$ $[M+H]^+$: 208.0888, found: 208.0890.

HPLC traces for 60:



(–)-(R)-*N*-*tert*-Butoxycarbonyl-2-(*N*-(*tert*-butoxycarbonyl)-1*H*-pyrrole)-3-piperidene 69

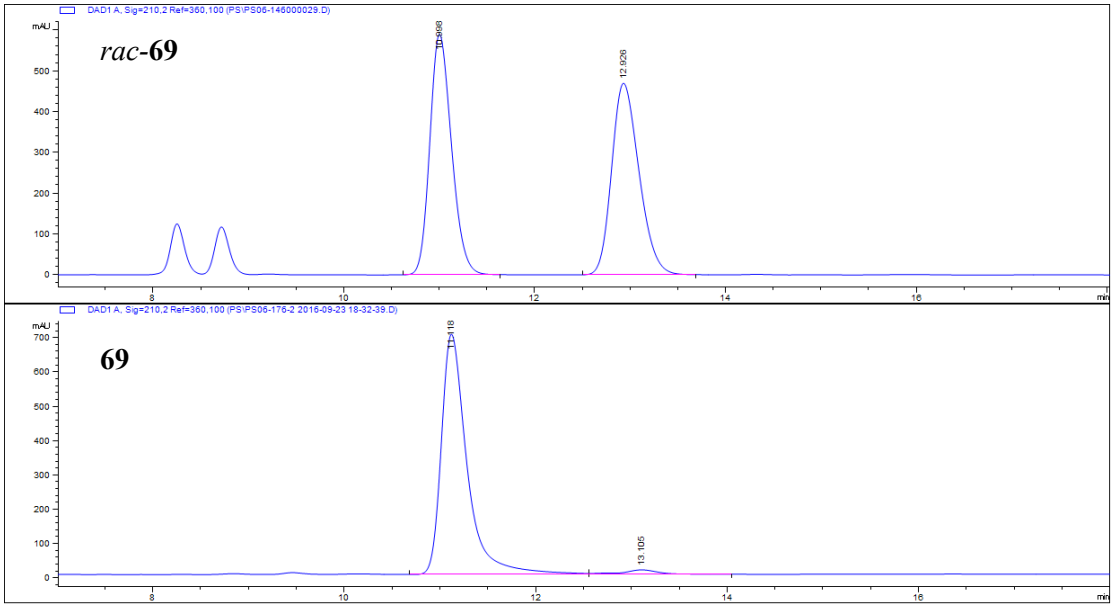


In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), *(S)*-BINAP (14.9 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (360.3 mg, 1.20 mmol, 3.00 eq) were stirred in THF (2 mL) at 80 °C for 30 min. A solution of *N*-*tert*-butoxycarbonyl-5-chloro-3-piperidene (86.8 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) and a solution of *N*-(*tert*-butoxycarbonyl)pyrrole-2-boronic acid (253 mg, 1.20 mmol, 3.00 eq) in THF (0.75 mL) were sequentially added *via* syringe and both flasks were rinsed with THF (0.25 mL each). The resulting mixture was then stirred for 16 h at 80 °C in a sealed flask. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with petrol/EtOAc (9:1) to afford (–)-(*R*)-*N*-*tert*-butoxycarbonyl-5-(*N*-(*tert*-butoxycarbonyl)-1*H*-pyrrole)-3-piperidene in 17% yield (23.9 mg, 0.07 mmol).

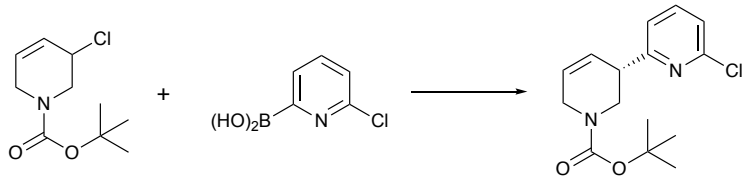
HPLC analysis indicated an enantiomeric excess of 95% [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH 98:2; $\lambda = 210$ nm; major enantiomer $t_R = 11.1$ min; minor enantiomer $t_R = 13.1$ min].

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.13 – 1.50 (rotameric m, 9 H, CH_3), 1.60 (s, 9 H, CH_3), 3.33 – 3.37, 3.64 – 3.79 (rotameric m, 2 H), 3.80 – 4.13 (rotameric m, 2 H), 4.13 – 4.41 (rotameric m, 1 H), 5.67 – 5.99 (rotameric m, 3 H), 6.04 (dd, $J = 3.3, 3.3$ Hz, 1 H), 7.19 – 7.30 (m, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 28.2 (3C), 28.2 (3C), 34.8, 43.2, 46.4, 79.1, 83.6, 110.3, 113.8, 121.9, 126.4, 127.2, 135.2, 149.6, 154.9; **IR** (ATR) ν_{max} /cm^{-1} = 2977s, 1739l, 1694l, 1480s, 1424m, 1368m, 1325l, 1239m, 1165l, 1118l, 1064s; **$[\alpha]^{25}_{589}$** = –3.6° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{19}H_{28}N_2O_4Na^+$ $[M+Na]^+$: 371.1941, found: 371.1939.

HPLC traces for 69:

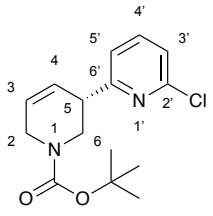


(+)-(*S*)-*N*-*tert*-Butoxycarbonyl-5-(2-chloro-6-pyridinyl)-3-piperidene 70



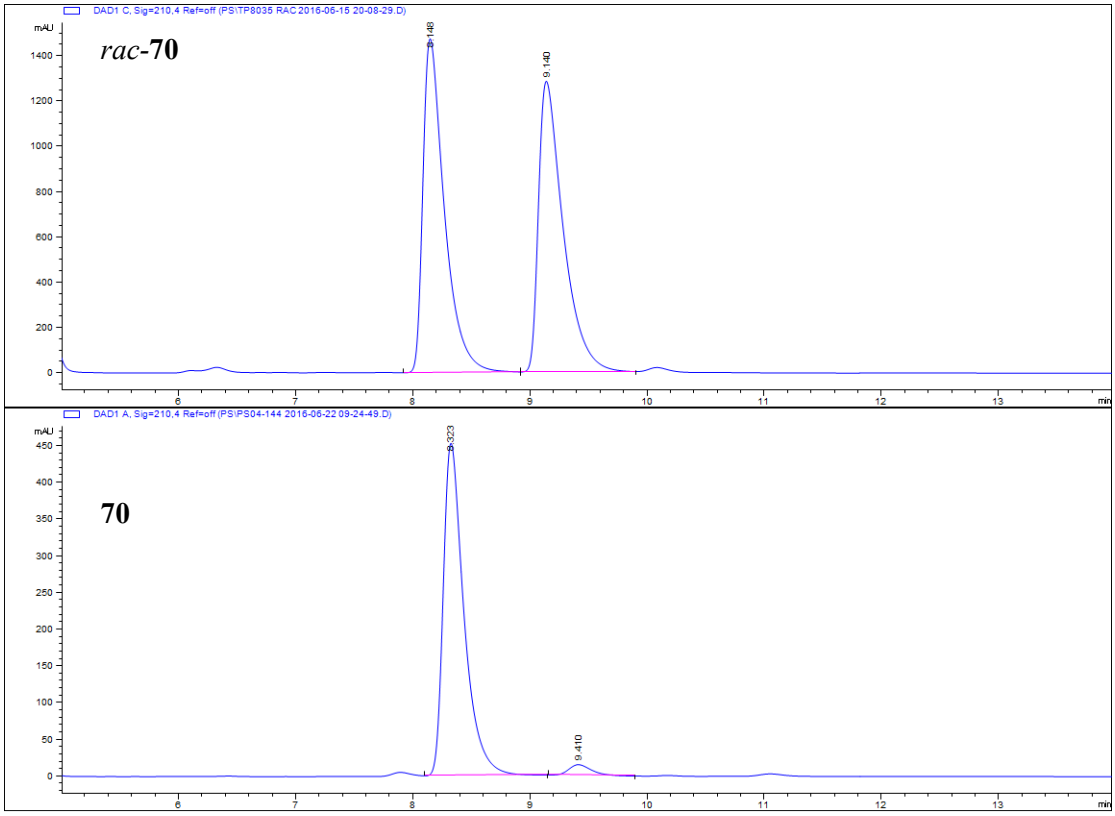
In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$ (4.6 mg, 0.01 mmol, 0.025 eq), (*R*)-(+)-5,5′-dichloro-2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl (15.6 mg, 0.024 mmol, 0.06 eq) and Cs_2CO_3 (390.9 mg, 1.20 mmol, 3.00 eq) were stirred in THF (2 mL) at 80 °C for 30 min. A solution of *N*-*tert*-butoxycarbonyl-5-chloro-3-piperidene (86.8 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) and a sonicated solution of 6-chloro-2-pyridinylboronic acid (189 mg, 1.20 mmol, 3.00 eq) and water (22 µL, 1.20 mmol, 3.00 eq) in THF (0.75 mL) were sequentially added *via* syringe and both flasks were rinsed with THF (0.25 mL each). The resulting mixture was then stirred for 16 h at 80 °C in a sealed flask. SiO_2 (20 mg) was added and the solvent was then carefully evaporated. The resulting solid was directly loaded onto a chromatographic column and eluted with a petrol/ethyl acetate (gradient from 15 to 20%) to afford (+)-(*S*)-*N*-*tert*-butoxycarbonyl-5-(2-chloro-6-pyridinyl)-3-piperidene in 40% yield (47.2 mg, 0.16 mmol).

HPLC for analysis indicated an enantiomeric excess of 95% [Chiralpak® IB; flow: 1.2 mL/min; hexane/*i*-PrOH 99.2:0.8; $\lambda = 210$ nm; major enantiomer $t_R = 8.3$ min; minor enantiomer $t_R = 9.4$ min].



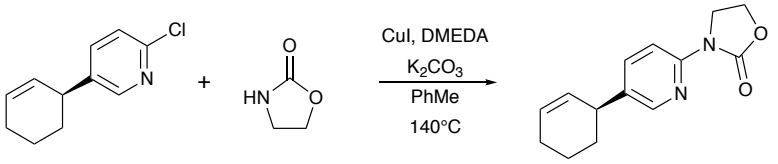
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.23 – 1.43 (rotameric m, 9 H, $C(CH_3)_3$), 3.45 – 4.33 (rotameric m, 5 H, H-2_a, H-2_b, H-5, H-6_a, H-6_b), 5.96 (m, 2 H, H-3, H-4), 7.10 (d, $J = 7.6$ Hz, 1 H, H-3'), 7.20 (d, $J = 7.9$ Hz, 1 H, H-5'), 7.56 (dd, $J = 7.8$, 7.8 Hz, 1 H, H-4'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 28.4 ($C(CH_3)_3$), 43.2, 43.6 (C-2, C-5), 46.8 (C-6), 79.7 ($C(CH_3)_3$), 120.7 (C-3'), 122.3 (C-5'), 125.9, 127.7 (C-3, C-4), 139.1 (C-4'), 151.1 (C-6'), 154.7 (C=O), 162.8 (C-2'); **IR** (ATR) ν_{max} /cm^{-1} = 1697l, 1583s, 1561s, 1415l, 1367m, 1131s, 1302m, 1239s, 1162l, 797s; **$[\alpha]^{27}_{589}$** = +45.9° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{15}H_{19}N_2O_2ClNa^+$ $[M+Na]^+$: 317.1038, found: 317.1028.

HPLC traces for 70:

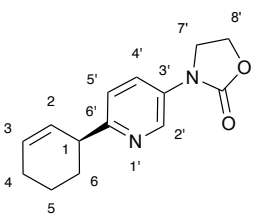


6.4.4 Further Synthetic Transformations and Synthesis of a Natural Product

(–)-(*S*)-3-(5-(Cyclohex-2-en-1-yl)pyridin-2-yl)oxazolidin-2-one 71

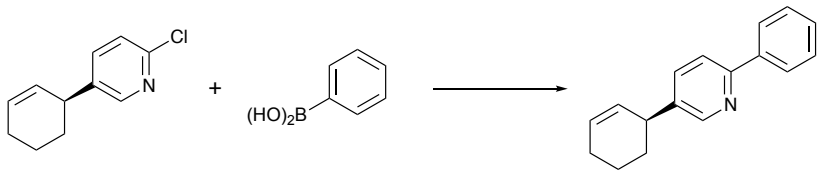


In a 5 mL round bottomed flask purged with argon were added (–)-(*S*)-2-chloro-5-(cyclohex-2-en-1-yl)-pyridine **56a** (35 mg, 0.18 mmol, 1.00 eq), 2-oxazolidinone (24 mg, 0.27 mmol, 1.50 eq), copper(I) iodide (34 mg, 0.18 mmol, 1.00 eq), *N,N′*-dimethylethylenediamine (0.2 mL, 0.27 mmol, 1.50 eq) and K_2CO_3 (50 mg, 0.36 mmol, 2.00 eq) and suspended in toluene (1.0 mL). The flask was sealed and the mixture was then stirred for 60 h at 140 °C. The reaction was quenched at room temperature by the addition of NH_4Cl (sat. aq., 2 mL). The mixture was extracted with ethyl acetate (2 × 3 mL) and the combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The resulting residue was purified by SiO_2 flash column chromatography and eluted with petrol ether:EtOAc (1:1) to produce (–)-(*S*)-3-(5-(cyclohex-2-en-1-yl)pyridin-2-yl)oxazolidin-2-one in 53% yield (67% brsm, 23.1 mg, 0.09 mmol).



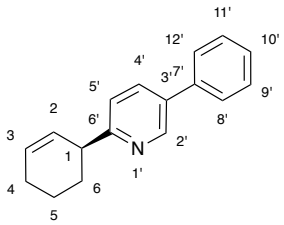
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.52 (dddd, J = 13.0, 10.1, 8.0, 2.9 Hz, 1 H, H-6$_a$), 1.57 – 1.67 (m, 1 H, H-5$_a$), 1.67 – 1.77 (m, 1 H, H-5$_b$), 1.95 – 2.04 (m, 1 H, H-6$_b$), 2.05 – 2.13 (m, 2 H, H-4$_a$, H-4$_b$), 3.32 – 3.47 (m, 1 H, H-1), 4.21 – 4.33 (m, 2 H, H-7$_a$', H-7$_b$'), 4.44 – 4.53 (m, 2 H, H-8$_a$', H-8$_b$'), 5.60 – 5.70 (m, 1 H, H-2), 5.93 (dddd, J = 9.9, 3.7, 3.7, 2.3 Hz, 1 H, H-3), 7.55 (dd, J = 8.7, 2.4 Hz, 1 H, H-4'), 8.12 (d, J = 8.6 Hz, 1 H, H-3'), 8.17 (d, J = 2.4 Hz, 1 H, H-6'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 20.8 (C-5), 24.9 (C-4), 32.4 (C-6), 38.7 (C-1), 44.1 (C-7'), 62.0 (C-8'), 112.6 (C-3'), 128.8 (C-2), 129.3 (C-3), 137.1 (C-5'), 137.3 (C-4'), 146.7 (C-6'), 149.2, 155.1 (C-2', C=O); **IR** (ATR) ν_{max} /cm^{-1} = 2929s, 1745l, 1602s, 1482m, 1407l, 1225m, 1227m, 1045s, 1010s, 835s, 753s; **$[\alpha]^{25}_{589}$** = –119.3° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{14}H_{17}N_2O_2^+$ $[M+H]^+$: 245.1285, found: 245.1286.

(–)-(*S*)-2-(Cyclohex-2-en-1-yl)-6-phenylpyridine 72



In a 5 mL round bottomed flask were added **56a** (38.7 mg, 0.20 mmol, 1.00 eq), benzeneboronic acid (36.3 mg, 0.30 mmol, 1.50 eq), palladium(II) acetate (2.3 mg, 0.01 mmol, 0.05 eq), SPhos (8.2 mg, 0.02 mmol, 0.10 eq) and K_2CO_3 (83 mg, 0.60 mmol, 3.00 eq). MeCN (0.75 mL) and H_2O (0.5 mL, degassed by sonication *in vacuo* for 2 min prior to the addition) were added and the flask was sealed under Ar. The resulting mixture was stirred for 1 h at 100 °C. The reaction mixture was then extracted with ethyl acetate (2 × 3 mL), dried over $MgSO_4$, filtered over a plug of Celite® and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica and eluted with petrol ether:EtOAc (97:3) to afford (–)-(*S*)-2-(cyclohex-2-en-1-yl)-6-phenylpyridine in 58% yield (27.3 mg, 0.12 mmol).

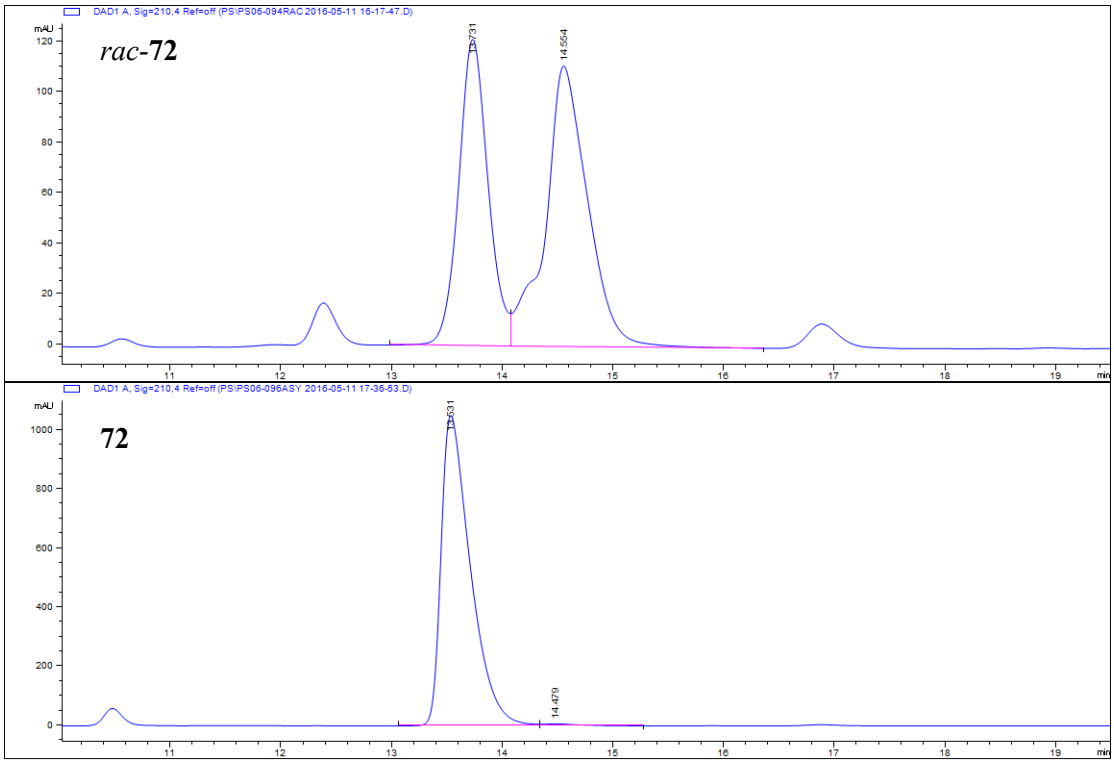
HPLC analysis indicated an enantiomeric excess of 98% [Chiralpak® IE; flow: 1.0 mL/min; hexane/*i*-PrOH 98:2; $\lambda = 210$ nm; major enantiomer $t_R = 13.5$ min; minor enantiomer $t_R = 14.5$ min].



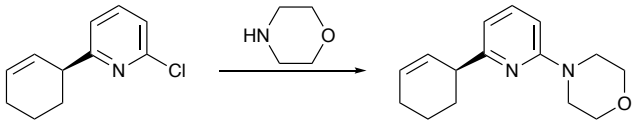
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.52 – 1.72 (m, 2 H, H-5_a, H-6_a), 1.72 – 1.82 (m, 1 H, H-5_b), 1.99 – 2.17 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.47 – 3.49 (m, 1 H, H-1), 5.67 – 5.77 (m, 1 H, H-2), 5.97 (dddd, $J = 9.9$, 3.7, 2.3, 2.3 Hz, 1 H, H-3), 7.36 – 7.43 (m, 1 H, H-10'), 7.43 – 7.52 (m, 2 H, H-9', H-11'), 7.60 (dd, $J = 8.1$, 2.3 Hz, 1 H, H-4'), 7.67 (dd, $J = 8.2$, 0.9 Hz, 1 H, H-3'), 7.93 – 8.05 (m, 2 H, H-8', H-12'), 8.56 (d, $J = 2.3$ Hz, 1 H, H-6'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 20.9 (C-5), 24.9 (C-4), 32.3 (C-6), 39.0 (C-1), 120.2 (C-3'), 126.8 (C-8', C-12'), 128.6, 128.7, 128.8 (C-2, C-9', C-10', C-11'), 129.4 (C-3), 136.0 (C-4'), 139.4 (C-7'), 140.2 (C-5'), 149.4 (C-6'), 155.3 (C-2'); **IR** (ATR) ν_{max} /cm^{-1} = 3021s, 2929m, 2857s, 1473l, 1446s,

1021s, 843s, 784s, 742l, 724s, 694m; **[α]$^{25}_{589}$** = –126.8° (*c* 1.00, $CHCl_3$); **HRMS** (EI/FI): *m*/*z* calc. for $C_{17}H_{17}N^+$ $[M]^+$: 235.1361, found: 235.1349.

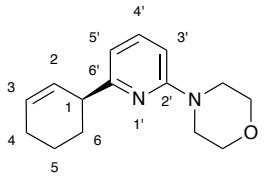
HPLC traces for 72:



(–)-(*S*)-4-(6-(Cyclohex-2-en-1-yl)pyridin-2-yl)morpholine 73

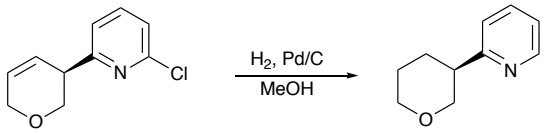


(–)-(*S*)-2-Chloro-6-(cyclohex-2-en-1-yl)-pyridine **56d** (36 mg, 0.16 mmol) in morpholine (0.5 mL) was stirred for 16 h at 130 °C in a sealed vial under argon. Water (1 mL) and ethyl acetate (2 mL) were then added and the aqueous layer extracted with ethyl acetate (2 mL). The combined organic layers were washed with brine (1 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude was purified by column chromatography over silica and eluted with petrol/EtOAc (9:1) to give (–)-(*S*)-4-(6-(cyclohex-2-en-1-yl)pyridin-2-yl)morpholine in 38% yield (50% brsm, 15.1 mg, 0.06 mmol).



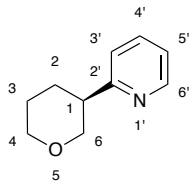
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.59 – 1.69 (m, 1 H, H-5_a), 1.75 (dddd, J = 12.4, 10.6, 8.3, 2.8Hz, 2 H, H-5_b, H-6_a), 1.97 – 2.10 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.42 (m, 1 H, H-1), 3.46 – 3.55 (m, 4 H, $N(CH_2)_2$), 3.76 – 3.86 (m, 4 H, $O(CH_2)_2$), 5.79 – 5.85 (m, 2 H, H-2, H-3), 6.45 (d, J = 8.4 Hz, 1 H, H-3'), 6.58 (d, J = 7.4 Hz, 1 H, H-5'), 7.43 (dd, J = 8.3, 7.3 Hz, 1 H, H-4'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 21.3 (C-5), 25.3 (C-4), 30.0 (C-6), 44.0 (C-1), 45.9 ($N(CH_2)_2$), 67.0 ($O(CH_2)_2$), 104.1 (C-3'), 111.6 (C-5'), 128.2, 129.6 (C-2, C-3), 137.9 (C-4'), 159.3 (C-2'), 163.8 (C-6'); **IR** (ATR) ν_{max} /cm^{-1} = 2925s, 2848s, 2581l, 1452l, 1371s, 1248m, 1120m, 976s, 791s, 736s; **$[\alpha]^{25}_{589}$** = –10.6° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): *m*/*z* calc. for $C_{15}H_{20}N_2O^+$ $[M+H]^+$: 245.1648, found: 245.1648.

(+)-(*S*)-2-(Tetrahydro-2*H*-pyran-3-yl)pyridine 74



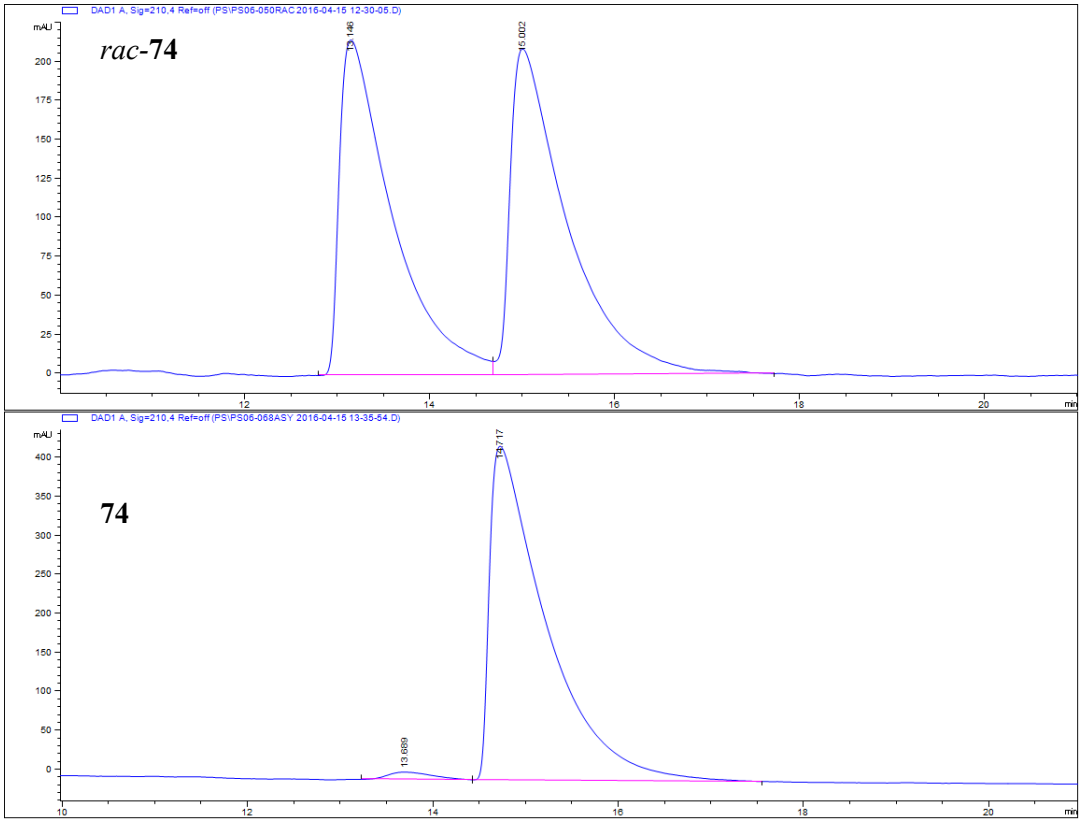
A 5 mL round bottomed flask was charged with (–)-(*S*)-2-chloro-6-(3,6-dihydro-2*H*-pyran-3-yl)pyridine **58** (51 mg, 0.26 mmol, 1.00 eq), Pd/C (10% on carbon, 3.4 mg, 3.2 μmol, 0.015 eq) and $NaHCO_3$ (21.8 mg, 0.26 mmol, 1.00 eq). MeOH (5 mL) was added and the reaction mixture was stirred overnight at room temperature under H_2 atmosphere (using a balloon). The resulting mixture was then filtered over Celite® and evaporated *in vacuo* to afford the chloride salt. The crude was then diluted in EtOAc (2 mL), washed with K_2CO_3 (sat. aq. 2 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to obtain (+)-(*S*)-2-(tetrahydro-2*H*-pyran-3-yl)pyridine in 79% yield (33.5 mg, 0.21 mmol).

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH 99:1; λ = 210 nm; minor enantiomer t_R = 13.7 min; major enantiomer t_R = 14.7 min].

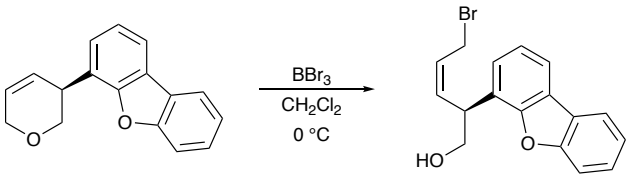


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.65 – 1.98 (m, 3 H, H-4_a, H-5_a, H-5_b), 2.02 – 2.12 (m, 1 H, H-4_b), 3.02 (dddd, *J* = 10.8, 10.8, 4.0, 4.0 Hz, 1 H, H-3), 3.49 (ddd, *J* = 11.3, 11.2, 2.9 Hz, 1 H, H-6_a), 3.60 (dd, *J* = 10.8, 10.8 Hz, 1 H, H-2_a), 3.98 (m, 1 H, H-6_b), 4.08 (ddd, *J* = 11.2, 4.2, 2.0 Hz, 1 H, H-2_b), 7.12 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1 H, H-5'), 7.16 – 7.21 (m, 1 H, H-3'), 7.61 (ddd, *J* = 7.7, 7.7, 1.9 Hz, 1 H, H-4'), 8.54 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1 H, H-6'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 26.0 (C-5), 29.5 (C-4), 44.8 (C-3), 68.3 (C-6), 72.5 (C-2), 121.7 (C-5'), 122.3 (C-3'), 136.6 (C-4'), 149.5 (C-6'), 162.2 (C-2'); **IR** (ATR) ν_{max} /cm^{-1} = 2936m, 2847m, 1590m, 1472m, 1435m, 1088l, 1031s, 856s, 777s, 750s; **$[\alpha]^{25}_{589}$** = +5.2° (*c* 1.00, $CHCl_3$); **HRMS** (CI): *m*/*z* calc. for $C_{10}H_{14}NO^+$ $[M+H]^+$: 164.1070, found: 164.1072.

HPLC traces for 74:



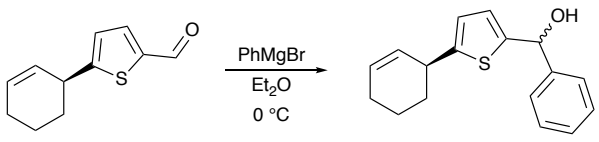
(+)-(*S,Z*)-5-Bromo-2-(dibenzofuran-4-yl)pent-3-en-1-ol 75



Boron tribromide (1 M in CH_2Cl_2, 0.17 mL, 0.17 mmol) was added over 5 min to a solution of (–)-(*S*)-4-(3,6-dihydro-2*H*-pyran-3-yl)dibenzofuran **52** (42.7 mg, 0.17 mmol) in CH_2Cl_2 (0.6 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C before the addition of water (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by column chromatography over silica and eluted with petrol ether:EtOAc (4:1) to obtain (+)-(*S,Z*)-5-bromo-2-(dibenzofuran-4-yl)pent-3-en-1-ol in 75% yield (42.3 mg, 0.13 mmol).

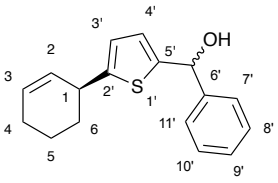
^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.02 (dd, *J* = 10.7, 7.5 Hz, 1 H), 4.05 – 4.14 (m, 2 H), 4.18 – 4.26 (m, 1 H), 4.53 (ddd, *J* = 9.7, 6.9, 6.9 Hz, 1 H), 5.95 – 6.03 (m, 1 H), 6.07 (dd, *J* = 10.7, 9.8 Hz, 1 H), 7.29 – 7.39 (m, 3 H), 7.48 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 1 H), 7.61 (d, *J* = 8.3 Hz, 1 H), 7.86 (dd, *J* = 6.0, 2.9 Hz, 1 H), 7.95 (d, *J* = 7.7 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 26.9, 41.8, 65.4, 111.9, 119.6, 120.9, 123.0, 123.4, 124.4 (2C), 124.7, 126.0, 127.4, 128.6, 133.5, 154.2, 156.1; **IR** (ATR) ν_{max} /cm^{-1} = 3381s, 2937s, 1474s, 1450m, 1423m, 1328s, 1205m, 1185l, 1052ms, 843s, 753l; **$[\alpha]^{25}_{589}$** = +128.7° (*c* 1.00, $CHCl_3$); **HRMS** (EI): *m*/*z* calc. for $C_{17}H_{15}BrO_2^+$ $[M]^+$: 330.0255, found: 330.0252.

(–)-((*S*)-5-(Cyclohex-2-en-1-yl)thiophen-2-yl)phenylmethanol 76



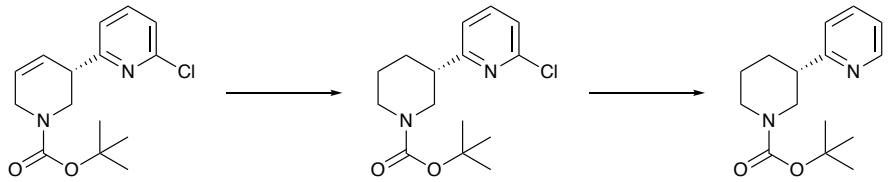
Phenylmagnesium bromide (3.0 M in Et_2O, 75 µL, 0.25 mmol, 2.30 eq) was added dropwise to a solution of (–)-(*S*)-5-(cyclohex-2-en-1-yl)thiophene-2-carbaldehyde **48** (21.0 mg, 0.11 mmol, 1.00 eq) in Et_2O (0.5 mL) at 0 °C. After 5 min the reaction mixture was allowed to reach room

temperature and was stirred 45 min. NH_4Cl (sat. aq., 2 mL) was then added and the resulting mixture was extracted with Et_2O (2 × 3 mL). The combined extracts were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica and eluted with petrol ether and EtOAc (95:5) to obtain (–)-((*S*)-5-(cyclohex-2-en-1-yl)thiophen-2-yl)phenylmethanol in 81% yield (24.1 mg, 0.09 mmol, 1:1 d.r., verified by ^{13}C-NMR).



^{1}H-NMR (500 MHz, DMSO-d_6) δ 1.50 – 1.60 (m, 2 H, H-5$_a$, H-6$_a$), 1.61 – 1.72 (m, 1 H, H-5$_{b,}$), 1.92 – 2.03 (m, 3 H, H-4$_a$, H-4$_b$, H-6$_{b,}$), 3.56 – 3.63 (m, 1 H, H-1), 5.65 – 5.71 (m, 1 H, H-2), 5.76 – 5.82 (m, 1 H, H-3), 5.84 (d, *J* = 4.3 Hz, 1 H, C*H*OH), 6.11 (m, 1 H, OH-1, OH-2), 6.64 (ddd, *J* = 3.5, 3.5, 0.9 Hz, 1 H, H-4'), 6.68 (ddd, *J* = 3.5, 1.9, 0.9 Hz, 1 H, H-3'), 7.22 – 7.27 (m, 1 H, H-9'), 7.30 – 7.36 (m, 2 H, H-7', H-11'), 7.38 – 7.43 (m, 2 H, H-8', H-10'); **^{13}C-NMR** (126 MHz, DMSO-d_6) δ 20.6 and 20.7 (1C, rotameric, C-5), 24.8 (C-4), 32.4 and 32.4 (1C, rotameric, C-6), 36.6 and 36.6 (1C, rotameric, C-1), 71.8 (COH), 123.1 and 123.2 (1C, rotameric, C-4'), 123.8 and 123.8 (1C, rotameric, C-3'), 126.5 (C-8', C-10'), 127.5 (C-9'), 128.3 and 128.4 (1C, rotameric, C-3), 128.5 (2C, rotameric, C-7', C-11'), 130.1 and 130.1 (1C, rotameric, C-2), 145.4, 148.2 and 148.2 (1C, rotameric), 149.1 and 149.2 (1C, rotameric, C-2', C-5', C-6'); **$[\alpha]^{25}_{589}$** = –79.7° (*c* 1.00, $CHCl_3$); **IR** (ATR) ν_{max} /cm^{-1} = 2932m, 1116l, 1089m, 1067l, 1047sh, 1028sh, 991l, 950m, 700s. **HRMS**: not obtained.

(+)-(*S*)-*N*-*tert*-Butoxycarbonyl-3-(pyridin-2-yl)-piperidine

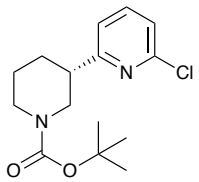


(+)-(*S*)-*N*-*tert*-Butoxycarbonyl-5-(2-chloro-6-pyridinyl)-3-piperidene **70** (44.3 mg, 0.15 mmol, 1.00 eq) was dissolved in toluene (2 mL) and $(PPh_3)_3RhCl$ (25 mg, 0.03 mmol, 0.18 eq) was added. The reaction mixture was stirred overnight at room temperature under H_2 atmosphere (using a

balloon). The catalyst was then filtered off using a silica plug and washed with EtOAc (5 mL). The solvent was evaporated *in vacuo* to afford (+)-(*S*)-*N*-*tert*-butoxycarbonyl-3-(2-chloro-6-pyridinyl)-piperidine (quant.) which was used in the next step without further purification. For an analytical purposes an aliquot of the crude was purified by column chromatography over silica and eluted with petrol/EtOAc (8:2).

The crude was diluted in MeOH (4 mL) and $NaHCO_3$ (12.6 mg, 0.15 mmol, 1.00 eq) and Pd/C (10% on carbon, 3.2 mg, 3.0 µmol, 0.02 eq) were added. The resulting mixture was stirred overnight at room temperature under H_2 (using a balloon). The solids were removed by filtration through Celite®. The solvent was then evaporated to afford crude (+)-(*S*)-*N*-*tert*-butoxycarbonyl-3-(pyridin-2-yl)-piperidine. For an analytical purposes an aliquot of the crude was purified by column chromatography over silica and eluted with petrol ether:EtOAc (8:2).

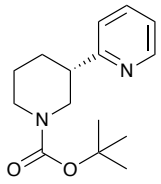
Analytical data for (+)-(*S*)-*N*-*tert*-Butoxycarbonyl-3-(2-chloro-6-pyridinyl)-piperidine



^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 1.50 – 1.62 (m, 1 H), 1.64 – 1.88 (m, 2 H), 1.94 – 2.06 (m, 1 H), 2.72 – 2.87 (m, 2 H), 2.88 – 3.16 (m, 1 H), 3.91 – 4.33 (m, 2 H), 7.08 (d, J = 7.6 Hz, 1 H), 7.15 (d, J = 7.9 Hz, 1 H), 7.56 (dd, J = 7.8, 7.8 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 25.1, 28.6 (3C), 30.7, 44.0 (2C), 48.8, 79.6, 120.5, 122.3, 139.1, 151.1, 154.9, 163.9; **IR** (ATR) ν_{max} /cm^{-1} = 2934s, 1689l, 1583s, 1558s, 1415l, 1365sm, 1260m, 1160l, 1145l, 795s; **$[\alpha]^{25}_{589}$** = +73.6° (*c* 1.00, $CHCl_3$) measured for 89% ee; **HRMS** (ESI): *m*/*z* calc. for $C_{15}H_{22}ClN_2O_2^+$ $[M+H]^+$: 297.1364, found: 297.1362.

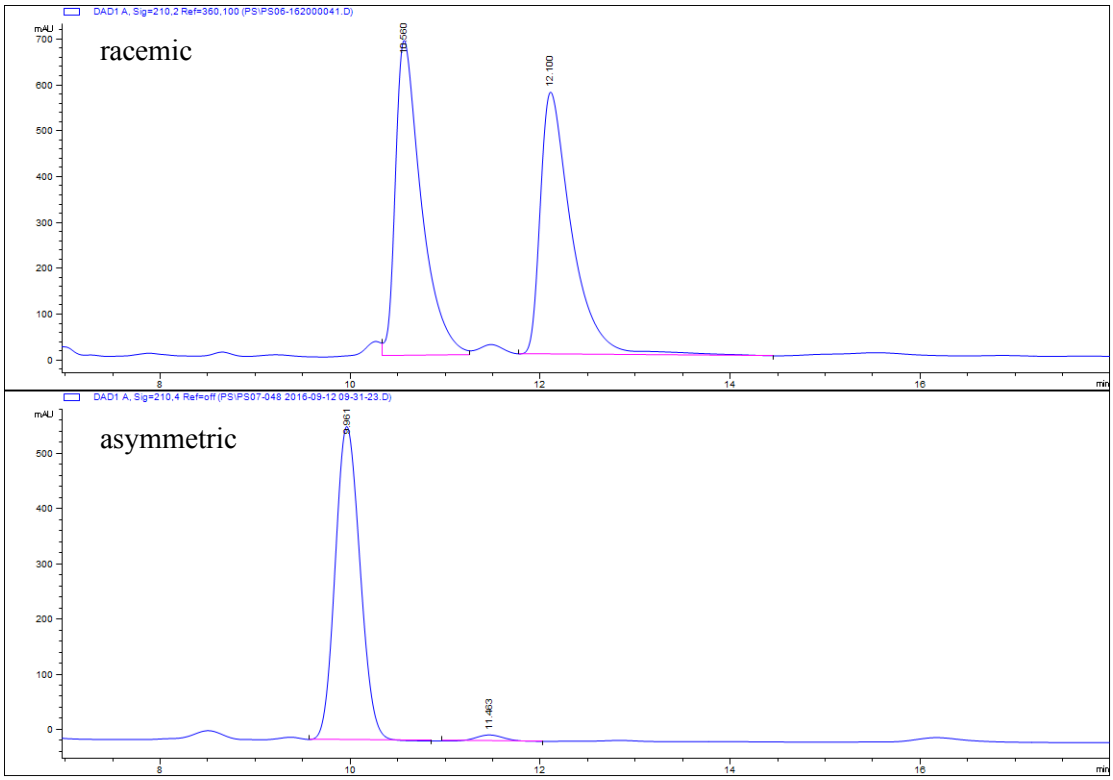
Analytical data for (+)-(*S*)-*N*-*tert*-butoxycarbonyl-3-(2-pyridinyl)-piperidine

HPLC analysis indicated an enantiomeric excess of 95% [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH 80:20; λ = 210 nm; major enantiomer t_R = 10.0 min; minor enantiomer t_R = 11.5 min].

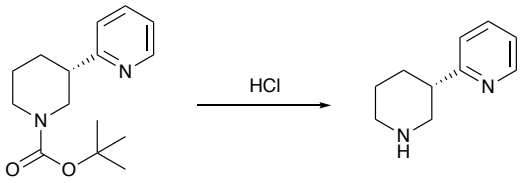


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 1.51 – 1.67 (m, 1 H), 1.68 – 1.86 (m, 2 H), 1.98 – 2.10 (m, 1 H), 2.66 – 2.88 (m, 2 H, H-3), 2.89 – 3.16 (m, 1 H), 3.86 – 4.48 (m, 2 H), 7.12 (ddd, J = 7.5, 4.9, 1.2 Hz, 1 H), 7.16 (ddd, J = 7.8, 1.1, 1.1 Hz, 1 H), 7.60 (ddd, J = 7.7, 7.7, 1.9 Hz, 1 H), 8.53 (ddd, J = 4.9, 1.9, 0.9 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 25.3, 28.6 (3C), 30.9 (C-6), 44.2, 44.4, 49.2, 79.5, 121.7, 122.2, 136.6, 149.4, 155.0, 162.8; **IR** (ATR) ν_{max} /cm^{-1} = 2933s, 1688l, 1590s, 1472s, 1418m, 1365s, 1259m, 1172m, 1144m, 768s; **$[\alpha]^{25}_{589}$** = +58.4° (*c* 1.00, $CHCl_3$) measured for 89% ee; **HRMS** (ESI): *m*/*z* calc. for $C_{15}H_{23}N_2O_2^+$ $[M+H]^+$: 263.1754, found: 263.1754.

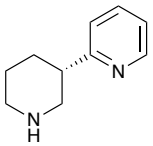
HPLC traces for (+)-(*S*)-*N*-*tert*-butoxycarbonyl-3-(2-pyridinyl)-piperidine:



(+)-(*S*)-3-(Pyridin-2-yl)-piperidine, (+)-(*S*)-isoanabasine 78



HCl (4 N in dioxane, 0.4 mL, 1.6 mmol, 10.0 eq) was added dropwise to a solution of crude (+)-(*S*)-*N*-*tert*-butoxycarbonyl-3-(pyridin-2-yl)-piperidene (0.15 mmol, 1.00 eq) in dioxane (2 mL). The reaction mixture was stirred for 20 h at room temperature. The solvent was then evaporated and the crude was dissolved in NaOH (1 M, aq., 5 mL). The mixture was extracted with CH_2Cl_2 (3 × 3 mL), washed with brine (2 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica and eluted with CH_2Cl_2:MeOH:Et_3N (90:9:1) to afford (+)-(*S*)-isoanabasine in 38% yield (over 3 steps, 9.2 mg, 0.06 mmol). The spectroscopic data matches the reported values in the literature.[176]

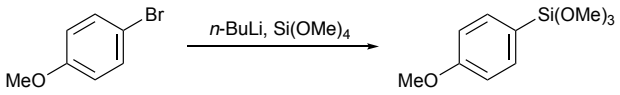


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.50 – 1.66 (m, 1 H), 1.66 – 1.83 (m, 2 H), 1.97 – 2.06 (m, 1 H), 2.66 (ddd, *J* = 12.3, 12.0, 2.4 Hz, 1 H), 2.75 – 2.91 (m, 2 H), 3.07 (ddd, *J* = 12.6, 3.1, 3.1 Hz, 1 H), 3.15 – 3.30 (m, 1 H), 7.08 (dd, *J* = 7.4, 5.0 Hz, 1 H), 7.12 (d, *J* = 7.9 Hz, 1 H), 7.57 (dd, *J* = 7.7, 7.7 Hz, 1 H), 8.50 (d, *J* = 4.9 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 26.6, 30.9, 45.8, 46.5, 52.2, 121.5, 121.8, 136.5, 149.2, 163.8; **$[\alpha]^{25}_{589}$** = +11.1° (*c* 1.00, $CHCl_3$, 95% ee), (Lit: $[\alpha]^{20}_{589}$ +15.2° (*c* 1.0, EtOH)); **LRMS** (ESI): *m*/*z* calc. for $C_{10}H_{15}N_2^+$ $[M+H]^+$: 163.1, found: 163.1.

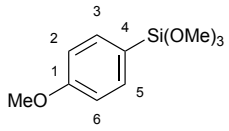
6.5 Experimental procedures for Chapter 4

6.5.1 Starting Materials

4-(Trimethoxysilyl)anisole 79

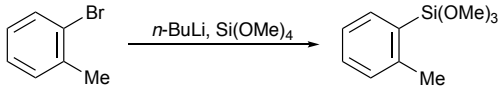


An adapted procedure from the literature was followed.[207] A solution of *n*-BuLi (1.4 M in THF, 3.6 mL, 5.0 mmol, 1.00 eq) was added to a solution of *p*-bromoanisole (626 µL, 5.0 mmol, 1.00 eq) in THF (30 mL) over 3 min at –78 °C. After 1 h, the resulting solution was added via cannula to a solution of tetramethyl orthosilicate (2.2 mL, 15.0 mmol, 3.00 eq) in THF (40 mL) at –78 °C over 10 min. After 2 h, the reaction was quenched with a THF:water mixture (9:1, 1 mL) and allowed to slowly warm up to room temperature. Diethyl ether (50 mL) and water (10 mL) were added, the phases were separated and the aqueous layer was extracted with diethyl ether (50 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica and eluted with petrol ether:EtOAc (95:5) to obtain 4-(trimethoxysilyl)anisole in 53% yield (607 mg, 2.65 mmol).

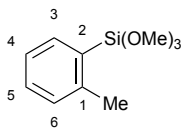


^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.54 (s, 9 H, $SiOCH_3$), 3.75 (s, 3 H, $PhOCH_3$), 6.87 (d, J = 8.7 Hz, 2 H, H-2, H-6), 7.52 (d, J = 8.7 Hz, 2 H, H-3, H-5); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 50.9 ($SiOCH_3$), 55.2 ($PhOCH_3$), 113.9 (2C, C-2, C-6), 120.4 (C-4), 136.6 (2C, C-3, C-5), 161.7 (C-1); **HRMS** (EI) *m*/*z* calc. for $C_{10}H_{16}O_4Si^+$ $[M]^+$: 228.0812, found: 228.0809.

2-Tolyltrimethoxysilane 80a[207]

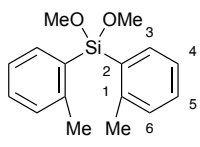


A solution of *n*-BuLi (1.4 M in THF, 3.6 mL, 5.0 mmol, 1.00 eq.) was added to a solution of 2-bromotoluene (0.6 µL, 5.0 mmol, 1.00 eq.) in THF (15 mL) over 3 min at –78 °C. After 1 h, the resulting solution was added via cannula to a solution of tetramethyl orthosilicate (4.4 mL, 30.0 mmol, 3.00 eq) in THF (20 mL) at –78 °C over 10 min. After 2 h, the reaction was quenched with a THF:water mixture (9:1, 1 mL) and allowed to slowly warm up to room temperature. Diethyl ether (50 mL) and water (10 mL) were added, the phases were separated and the aqueous layer was extracted with diethyl ether (50 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica and eluted with petrol ether:EtOAc (95:5) to obtain 2-tolyltrimethoxysilane in 24% yield (251 mg, 1.18 mmol).



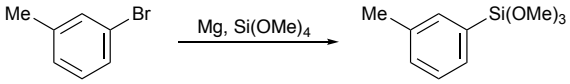
^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3 H, CCH_3), 3.62 (s, 9 H, OCH_3), 7.14 – 7.23 (m, 2 H, H-4, H-6), 7.34 (td, *J* = 7.7, 7.5, 1.6 Hz, 1 H, H-5), 7.64 – 7.70 (m, 1 H, H-3); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 22.5 (CCH_3), 50.7 (OCH_3), 124.9 (C-4), 128.6 (C-1), 130.0 (C-6), 130.9 (C-5), 136.5 (C-3), 144.7 (C-2); **HRMS** (EI) *m*/*z* calc. for $C_{10}H_{16}O_3Si^+$ $[M]^+$: 212.087, found: 212.084;

Bis-(2-tolyl)dimethoxysilane **80b** was obtained in 24% yield (159.1 mg, 0.58 mmol).

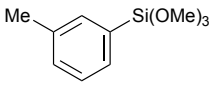


^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 6 H, CCH_3), 3.56 (s, 6 H, OCH_3), 7.10 – 7.16 (m, 2 H, H-6), 7.22 (tt, *J* = 7.3, 1.2, 0.6 Hz, 2 H, H-4), 7.33 (td, *J* = 7.5, 1.6 Hz, 2 H, H-5), 7.81 (dd, *J* = 7.4, 1.6 Hz, 2 H, H-3); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 22.3 (CCH_3), 50.5 (OCH_3), 125.0 (C-4), 129.9 (C-6), 130.5 (C-5), 131.9 (C-1), 136.5 (C-3), 144.3 (C-2); **IR** (ATR) ν_{max} /cm^{-1} = 2937s, 2836s, 1449s, 1189s, 1134s, 1081l, 805m, 742m, 692s; **HRMS** (EI) *m*/*z* calc. for $C_{16}H_{20}O_2Si^+$ $[M]^+$: 272.1227, found: 272.1226.

3-Tolyltrimethoxysilane 81

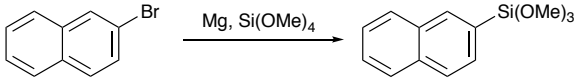


An adapted procedure from the literature was followed.[243] In a flame-dried 25 mL round bottomed flask equipped with a reflux condenser and charged magnesium turnings (267 mg, 11.0 mmol, 1.10 eq). Diethyl ether (4.0 mL) was added to the magnesium turnings. The reaction was initiated by the addition of 1 mL of a solution of 3-bromotoluene (1.09 mL, 10.0 mmol, 1.00 eq) in diethyl ether (9 mL) and gentle heating. The rest of the solution was then added at such a rate that the diethyl ether maintained a moderate reflux. The 3-tolylmagnesium bromide solution was then added via syringe over 10 min to a second flame-dried 50 mL round bottomed flask containing tetramethyl orthosilicate (4.4 mL, 30.0 mmol, 3.00 eq) in diethyl ether (20 mL) at –40 °C. The resulting mixture was allowed to warm up to room temperature and poured into pentane (80 mL). The mixture was washed with H_2O (3 × 20 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by column chromatography over silica and eluted with petrol ether:EtOAc (97:3) to obtain 3-tolyltrimethoxysilane in 38% yield (811 mg, 3.82 mmol).



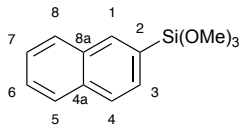
^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3 H, CCH_3), 3.66 (s, 9 H, OCH_3), 7.26 – 7.35 (m, 2 H, H_{Ar}), 7.44 – 7.53 (m, 2 H, H_{Ar}); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 21.6 (C*C*H_3), 51.0 (OCH_3), 128.1 (C_{Ar}), 129.3 (C_q), 131.6 (C_{Ar}), 131.9 (C_{Ar}), 135.5 (C_{Ar}), 137.6 (C_q); **IR** (ATR) ν_{max} /cm^{-1} = 2943s, 2841s, 1190s, 1074l, 867s, 809m, 778m, 722m, 700s, 658s; **HRMS** (EI) *m*/*z* calc. for $C_{10}H_{16}O_3Si^+$ $[M]^+$: 212.0863, found: 212.0861.

Trimethoxy(naphthalen-2-yl)silane 82



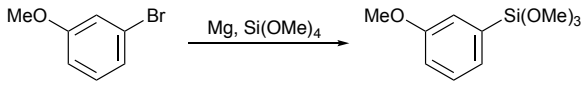
An adapted procedure from the literature was followed.[243] In a flame-dried 25 mL round bottomed flask equipped with a reflux condenser and charged magnesium turnings (266 mg, 11.0 mmol, 1.00 eq). Diethyl ether (4.0 mL) and two iodine crystals were added to the magnesium turnings. The reaction was initiated by the addition of 1 mL of a solution of 2-bromonaphthalene (2.08 g,

10.0 mmol, 1.00 eq) in diethyl ether (9 mL) and gentle heating. The rest of the solution was then added at such a rate that the diethyl ether maintained a moderate reflux. The naphthylmagnesiumbromide solution was then added via syringe over 10 min to a second flame-dried 50 mL round bottomed flask containing tetramethyl orthosilicate (4.4 mL, 30.0 mmol, 3.00 eq) in diethyl ether (13 mL) at –30 °C. The resulting mixture was then warmed to room temperature and stirred overnight. The reaction mixture was diluted with H_2O (20 mL) and extracted with pentane (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The resulting crude was purified via Kugelrohr distillation (1 mbar, 150 °C) to remove by-products. Further distillation (1 mbar, 210 °C) gave the pure product in 51% yield (1.27 g, 5.12 mmol).



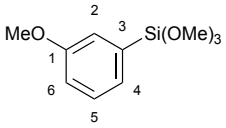
^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 9 H, CH_3), 7.46 – 7.57 (m, 2 H, H-6, H-7), 7.69 (d, J = 8.0 Hz, 1 H, H-3), 7.81 – 7.92 (m, 3 H, H-4, H-5, H-8), 8.21 (s, 1 H, H-1); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 51.1 (CH_3), 126.2, 126.9, 127.1 (C-6, C-7, C_q), 127.5, 127.9, 128.6 (C-4, C-5, C-8), 130.3 (C-3), 132.9 (C_q), 134.6 (C_q), 136.5 (C-1). **IR** (ATR) ν_{max} /cm^{-1} = 2943s, 2841s, 2361s, 1191s, 1081l, 859s, 811m, 744s, 713ms; **HRMS** (EI) *m*/*z* calc. for $C_{14}H_{16}O_3Si^+$ $[M]^+$: 248.0863, found: 248.0864

3-(Trimethoxysilyl)anisole 83



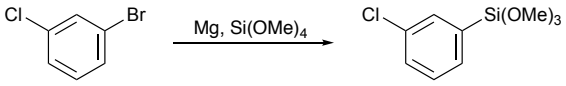
An adapted procedure from the literature was followed.[240] In a flame-dried 25 mL round bottomed flask equipped with a reflux condenser and charged magnesium turnings (267 mg, 11.0 mmol, 1.10 eq). Diethyl ether (4.0 mL) was added to the magnesium turnings. The reaction was initiated by the addition of 1 mL of a solution of 3-bromoanisole (1.26 mL, 10.0 mmol, 1.00 eq) in diethyl ether (9 mL) and gentle heating. The rest of the solution was then added at such a rate that the diethyl ether maintained a moderate reflux. The 3-anisolemagnesium bromide solution was then added via syringe over 10 min to a second flame-dried 50 mL round bottomed flask containing tetramethyl orthosilicate (4.4 mL, 30.0 mmol, 3.00 eq) in diethyl ether (13 mL) at –30 °C. The

resulting mixture was allowed to warm up to room temperature. H_2O (20 mL) was added and the aqueous phase was extracted with pentane (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude was purified via Kugelrohr distillation (1 mbar, 150 °C) to remove byproducts. Further distillation (1 mbar, 175 °C) gave the pure product in 22% yield (511 g, 2.23 mmol).

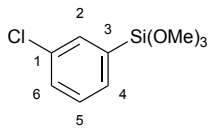


^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 9 H, $SiOCH_3$), 3.83 (s, 3 H, $PhOCH_3$), 6.99 (ddd, J = 8.2, 2.8, 1.1 Hz, 1 H, H-6), 7.16 – 7.20 (m, 1 H, H-2), 7.23 (dt, J = 7.2, 1.0 Hz, 1 H, H-4), 7.33 (ddd, J = 8.2, 7.2, 0.5 Hz, 1 H, H-5); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 51.0 ($Si-OCH_3$), 55.3 ($Ph-OCH_3$), 116.7 (C-6), 119.7 (C-2), 127.1 (C-4), 129.4 (C-5), 130.9 (C-3), 159.3 (C-1); **IR** (ATR) ν_{max} /cm^{-1} = 2943s, 2841s, 1190s, 1074l, 867s, 809m, 778m, 722m, 700s, 658s; **LRMS** (ESI) *m*/*z* calc. for $C_{10}H_{16}NaO_4Si^+$ $[M+Na]^+$: 251.1, found: 251.0.

(3-Chlorophenyl)trimethoxysilane 84

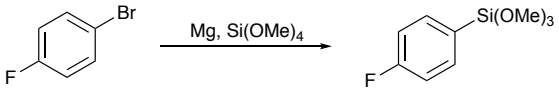


An adapted procedure from the literature was followed.[243] In a flame-dried 25 mL round bottomed flask equipped with a reflux condenser and charged magnesium turnings (334 mg, 13.7 mmol, 1.37 eq). Diethyl ether (4.0 mL) was added to the magnesium turnings. The reaction was initiated by the addition of 1 mL of a solution of 1-bromo-3-chlorobenzene (1.09 mL, 10.0 mmol, 1.00 eq) in diethyl ether (9 mL) and gentle heating. The rest of the solution was then added at such a rate that the diethyl ether maintained a moderate reflux. The 3-chlorophenylmagnesium bromide solution was then added via syringe over 10 min to a second flame-dried 50 mL round bottomed flask containing tetramethyl orthosilicate (4.4 mL, 30.0 mmol, 3.00 eq) in diethyl ether (13 mL) at –30 °C. The resulting mixture was then warmed to room temperature and stirred overnight. The reaction mixture was diluted with H_2O (20 mL) and extracted with pentane (2 × 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The pure product was obtained via Kugelrohr distillation (1 mbar, 170 °C) in 63% yield (1.46 g, 6.27 mmol).

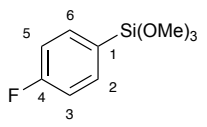


^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 9 H, CH_3), 7.33 (ddd, J = 7.9, 7.2, 0.6 Hz, 1 H, H-5), 7.42 (ddd, J = 8.0, 2.2, 1.2 Hz, 1 H, H-4), 7.51 (dt, J = 7.2, 1.1, 1.1 Hz, 1 H, H-6), 7.61 (ddd, J = 2.2, 1.0, 0.5 Hz, 1 H, H-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 51.1 (CH_3), 129.7 (C-5), 130.9 (C-4), 132.3 (C-1), 132.8 (C-6), 134.6 (C-3), 134.7 (C-2); **IR** (ATR) ν_{max} /cm^{-1} = 2944s, 2843s, 1467s, 1391s, 1190m, 1137m, 1074l, 784l, 693l; **HRMS** (EI) not found.

(4-Fluorophenyl)trimethoxysilane 85a[243]

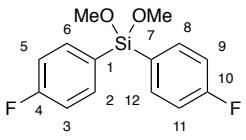


In a flame-dried 25 mL round bottomed flask equipped with a reflux condenser and charged magnesium turnings (334 mg, 13.7 mmol, 1.37 eq). Diethyl ether (4.0 mL) was added to the magnesium turnings. The reaction was initiated by the addition of 1 mL of a solution of 1-bromo-4-fluorobenzene (1.09 mL, 10.0 mmol, 1.00 eq) in diethyl ether (9 mL) and gentle heating. The rest of the solution was then added at such a rate that the diethyl ether maintained a moderate reflux. The 4-fluorophenylmagnesiumbromide solution was then added via syringe over 10 min to a second flame-dried 50 mL round bottomed flask containing tetramethyl orthosilicate (4.4 mL, 30.0 mmol, 3.00 eq) in diethyl ether (13 mL) at –30 °C. The resulting mixture was then warmed to room temperature and stirred overnight. The reaction mixture was diluted with H_2O (20 mL) and extracted with pentane (2 × 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The pure product was obtained via Kugelrohr distillation (1 mbar, 100 °C) in 53% yield (1.14 g, 5.26 mmol).



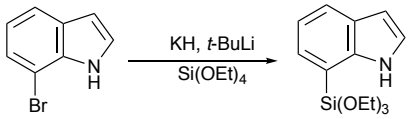
^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 9 H, CH_3), 7.05 – 7.13 (m, 2 H, H-3, H-5), 7.60 – 7.68 (m, 2 H, H-2, H-6); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 51.0 (CH_3), 115.4 (d, J_{CF} = 19.9 Hz, C-3, C-5), 125.3 (C-1), 137.1 (d, J_{CF} = 7.8 Hz, C-2, C-6), 164.8 (d, J_{CF} = 250.3 Hz, C-4); **^{19}F-NMR** (376 MHz, $CDCl_3$) δ –109.16; **HRMS** (EI) *m*/*z* calc. for $C_9H_{12}O_3Si^+$ $[M–H]^+$: 215.0534, found: 215.0536.

Attempting to generate the siloxane via a lithiation procedure[207] resulted in the bis-(4-fluorophenyl)dimethoxysilane **85b** as a major product in 5% yield

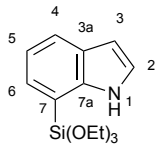


^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 6 H, CH_3), 7.04 – 7.13 (m, 4 H, H-3, H-5, H-9, H-11), 7.59 – 7.67 (m, 4 H, H-2, H-6, H-8, H-12); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 51.0 (CH_3), 115.4 (d, J_{CF} = 19.9 Hz, C-3, C-5, C-9, C-11), 127.8 (d, J = 3.5 Hz, C-1, C-7), 137.1 (d, J_{CF} = 7.5 Hz, C-2, C-6, C-8, C-12), 164.7 (d, J_{CF} = 250.3 Hz, C-4, C-10); **^{19}F-NMR** (376 MHz, $CDCl_3$) δ –109.37; **LRMS** (ESI) *m*/*z* calc. for $C_{14}H_{15}F_2O_2Si^+$ $[M+H]^+$: 281.1, found: 281.1.

7-Indolyltriethoxysilane 99

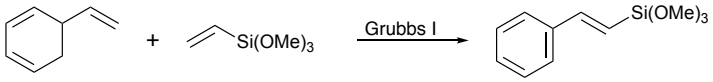


An adapted procedure was used from the literature.[165] KH (450 mg, 11.3 mmol, 1.13 eq.) was suspended in THF (2.5 mL) at 0 °C. A solution of 7-bromoindole (1.96 g, 10.0 mmol, 1.00 eq.) in THF (15 mL) was added and the mixture was stirred for 15 min. After cooling to –78 °C, a solution of *t*-BuLi (1.7 M in pentane, 11.8 mL, 20.0 mmol, 2.00 eq.) was added over 5 min. The mixture was allowed to warm up to room temperature, stirred for 5 min and re-cooled to –78 °C. The resulting solution was then added via cannula to a solution of tetraethyl orthosilicate (6.6 mL, 30.0 mmol, 3.00 eq) in THF (20 mL) at –78 °C over 10 min. The reaction mixture was allowed to warm up to room temperature over night. Ethyl acetate (70 mL) and water (20 mL) were added, the phases were separated and the organic phase was washed with brine (10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The resulting residue was purified by column chromatography over silica and eluted with petrol ether:EtOAc (95:5) to obtain 7-indolyltriethoxysilane in 31% yield (867 mg, 3.14 mmol, purity 89%).

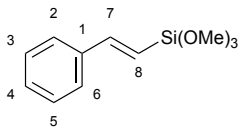


^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.0, 7.0 Hz, 9 H, CH_3), 3.92 (q, *J* = 7.1, 7.0, 7.0 Hz, 6 H, CH_2), 6.55 (dd, *J* = 3.2, 2.2 Hz, 1 H, H-3), 7.14 (dd, *J* = 7.9, 7.0 Hz, 1 H, H-5), 7.24 – 7.27 (m, 1 H, H-2), 7.43 (dd, *J* = 7.0, 1.2 Hz, 1 H, H-6), 7.75 (dt, *J* = 7.9, 1.1, 1.1 Hz, 1 H, H-4), 9.31 (s, 1 H, NH); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 18.40 (CH_3), 58.99 (CH_2), 102.12 (C-3), 111.25 (C_q), 119.46 (C-5), 123.46 (C-4), 124.28 (C-2), 126.81 (C-6), 128.85 (C_q), 140.68 (C_q).

(*E*)-*β*-(Trimethoxysilyl)styrene 103[244]



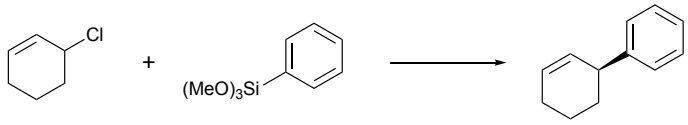
A 10 mL round bottomed flask was charged with bis(tricyclohexylphosphine)-benzylidine ruthenium(IV) dichloride (82 mg, 0.1 mmol, 0.02 eq.). Dichloromethane (3 mL), vinyltrimethoxysilane (766 µL, 5.00 mmol, 1.00 eq.) and styrene (575 µL, 5.00 mmol, 1.00 eq.) were added subsequentially and the resulting mixture was stirred at reflux conditions for 16 h. Volatiles were evaporated *in vacuo* and the pure product was obtained via Kugelrohr distillation (1 mbar, 190 °C) in 55% yield (622 mg, 2.77 mmol).



^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.63 (s, 9 H, CH_3), 6.14 (d, *J* = 19.4 Hz, 1 H, H-7), 7.23 (d, *J* = 19.4 Hz, 1 H, H-7), 7.29 – 7.38 (m, 3 H, H-2, H-4, H-6), 7.46 – 7.51 (m, 2 H, H-3, H-5); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 50.82 (CH_3), 115.93 (C-8), 126.95, 128.72, 129.06, 137.53, 149.95 (C-7); **HRMS** (EI): *m*/*z* calc. for $C_{11}H_{16}O_3Si^+$ $[M–H]^+$: 223.087, found: 223.080.

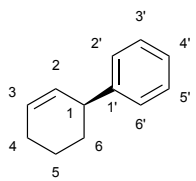
6.5.2 Application to Other Aryltrimethoxysilanes

(–)-(*S*)-Cyclohex-2-enylbenzene 88



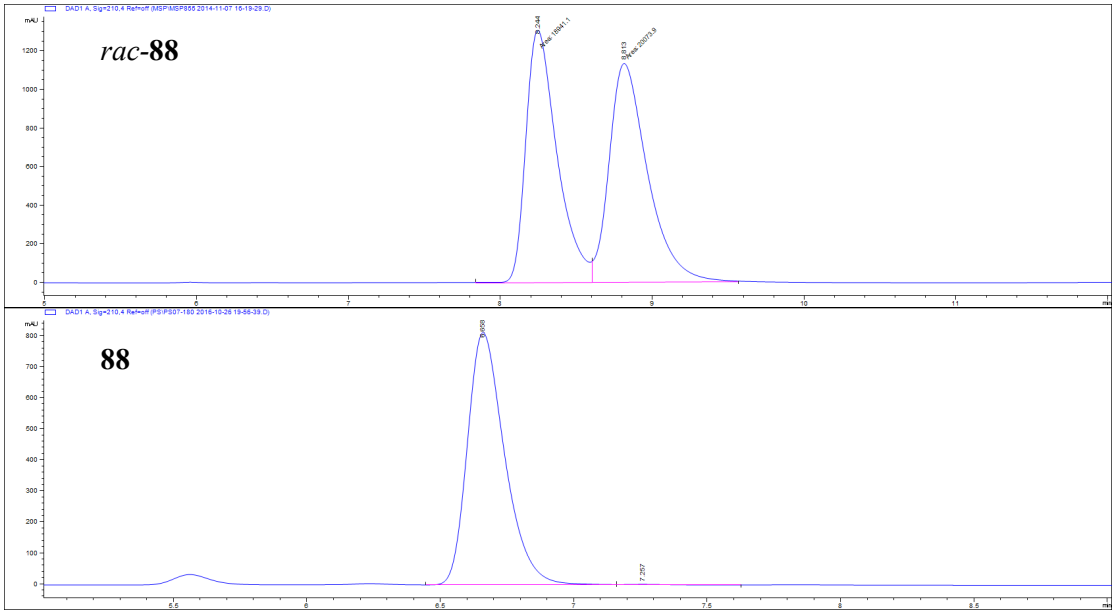
In a 10 mL round bottomed flask $[Rh(cod)(MeCN)_2]BF_4$ (7.6 mg, 0.02 mmol, 0.05 eq) and (*S*)-BINAP (18.7 mg, 0.03 mmol, 0.075 eq) were stirred in THF (0.7 mL) at reflux for 30 min. A solution of phenyltrimethoxysilane (173.0 mg, 0.80 mmol, 2.00 eq), tetrabutylammonium fluoride (1 M in THF, 0.8 mL, 0.8 mmol, 2.00 eq) and 3-chlorocyclohex-1-ene (45 µL, 0.40 mmol, 1.00 eq) in THF (0.3 mL) was then added *via* syringe and the flask rinsed with THF (0.2 mL). The resulting mixture was then refluxed for 3 h. The solvent was then carefully evaporated and the resulting mixture was directly loaded onto a chromatographic column and eluted with pentane to obtain (–)-(*S*)-cyclohex-2-enylbenzene in 65% yield (39.5 mg, 0.26 mmol).

HPLC analysis indicated an enantiomeric excess of 99% [Chiralpak® ID; flow: 0.6 mL/min; hexane/*i*-PrOH 99.9:0.1; $\lambda = 210$ nm; major enantiomer $t_R = 6.7$ min; minor enantiomer $t_R = 7.3$ min].

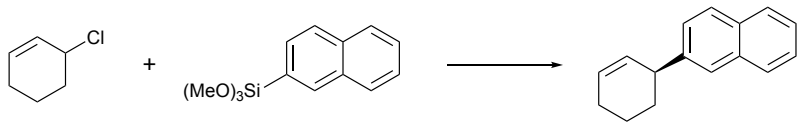


^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.43 – 1.61 (m, 2 H, H-5$_a$, H-6$_a$), 1.62 – 1.73 (m, 1 H, H-5$_b$), 1.89 – 1.98 (m, 1 H, H-6$_b$), 2.01 (m, 2 H, H-4$_a$, H-4$_b$), 3.33 (m, 1 H, H-1), 5.60 – 5.74 (m, 1 H, H-2), 5.81 (ddd, $J = 9.9$, 6.1, 3.4 Hz, 1 H, H-3), 7.08 – 7.18 (m, 3 H, H-2', H-4', H-6'), 7.22 (m, 2 H, H-3', H-5'); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 21.4 (C-5), 25.2 (C-4), 32.8 (C-6), 42.0 (C-1), 126.1 (C-4), 127.9 (C-2', C-6'), 128.4 (C-3', C-5'), 128.5 (C-3), 130.3 (C-2), 146.8 (C-1'); $\mathbf{[\alpha]^{25}_{589}} = -74.6°$ (*c* 1.0, $CHCl_3$), [Lit: $[\alpha]^{20}_{589} = -134.6°$ (*c* 0.55 $CHCl_3$) for 99% ee)][156]; **HRMS** (EI/FI): *m*/*z* calc. for $C_{12}H_{14}^+$ $[M]^+$: 158.1094, found: 158.1096.

HPLC traces for 88:

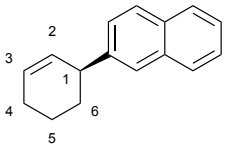


(–)-(*S*)-2-(Cyclohex-2-en-1-yl)naphthalene 89



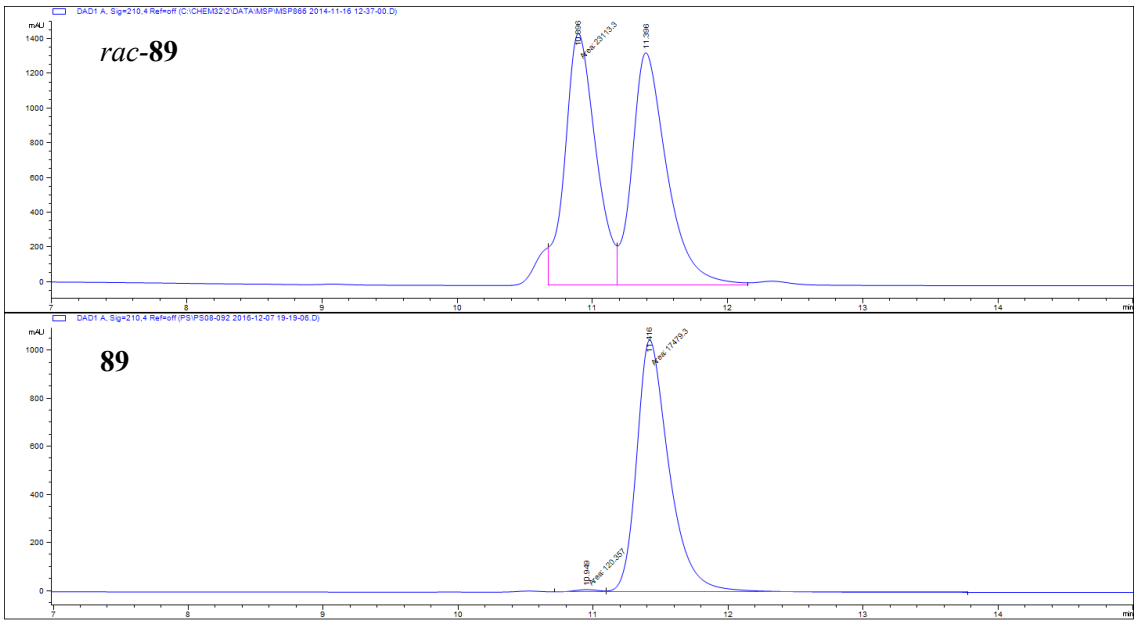
In a 10 mL round bottomed flask $[Rh(cod)(MeCN)_2]BF_4$ (7.6 mg, 0.02 mmol, 0.05 eq) and (*S*)-BINAP (18.7 mg, 0.03 mmol, 0.075 eq) were stirred in THF (0.7 mL) at reflux for 30 min. A solution of trimethoxy(naphthalen-2-yl)silane (198.7 mg, 0.80 mmol, 2.00 eq), tetrabutyl-ammonium fluoride (1 M in THF, 0.8 mL, 0.8 mmol, 2.00 eq) and 3-chlorocyclohex-1-ene (45 µL, 0.40 mmol, 1.00 eq) in THF (0.3 mL) was then added *via* syringe and the flask rinsed with THF (0.2 mL). The resulting mixture was then refluxed for 3 h. The solvent was then carefully evaporated and the resulting mixture was directly loaded onto a chromatographic column and eluted with pentane to obtain (–)-(*S*)-2-(cyclohex-2-en-1-yl)naphthalene in 52% yield (43.4 mg, 0.21 mmol).

Enantiomeric excess of 99% was determined by HPLC [Chiralpak® IA; flow: 0.6 mL/min; hexane; λ = 210 nm; minor enantiomer t_R = 11.0 min; major enantiomer t_R = 11.4 min].

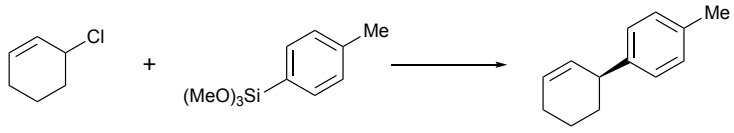


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.60 – 1.72 (m, 2 H, H-5_a, H-6_a), 1.73 – 1.83 (m, 1 H, H-5_b), 2.04 – 2.17 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.51 – 3.63 (m, 1 H, H-1), 5.77 – 5.85 (m, 1 H, H-2), 5.92 – 6.00 (m, 1 H, H-3), 7.37 (dd, J = 8.5, 1.8 Hz, 1 H, H-3'), 7.40 – 7.48 (m, 2 H, C-6', C-7'), 7.62 – 7.68 (m, 1 H, H-1'), 7.80 (m, 3 H, H-4', H-5', H-8'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 21.3 (C-5), 25.3 (C-4), 32.6 (C-6), 42.1 (C-1), 125.3, 125.9, 126.0 (C-1', C-6', C-7'), 126.9 (C-3'), 127.7, 127.7, 128.0 (C-4', C-5', C-8'), 128.8 (C-3), 130.2 (C-2), 132.3, 133.7, 144.2 ($3C_q$); **$[\alpha]^{25}_{589}$** = –74.5° (c 0.4, $CHCl_3$), [Lit: $[\alpha]^{20}_{589}$ = –221.1° (c 0.91 $CHCl_3$) for 89% ee)][156]; **HRMS** (EI) m/z calc. for $C_{16}H_{16}^{+}$ $[M]^{+}$: 208.1247, found: 184.1239.

HPLC traces for 89:



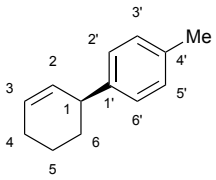
(–)-(*S*)-3-(4-Methylphenyl)cyclohexene 90



In a 10 mL round bottomed flask $[Rh(cod)(MeCN)_2]BF_4$ (7.6 mg, 0.02 mmol, 0.05 eq) and (*S*)-BINAP (18.7 mg, 0.03 mmol, 0.075 eq) were stirred in THF (0.7 mL) at reflux for 30 min. A solution of *p*-tolyltrimethoxysilane (164 µL, 0.80 mmol, 2.00 eq), tetrabutylammonium fluoride

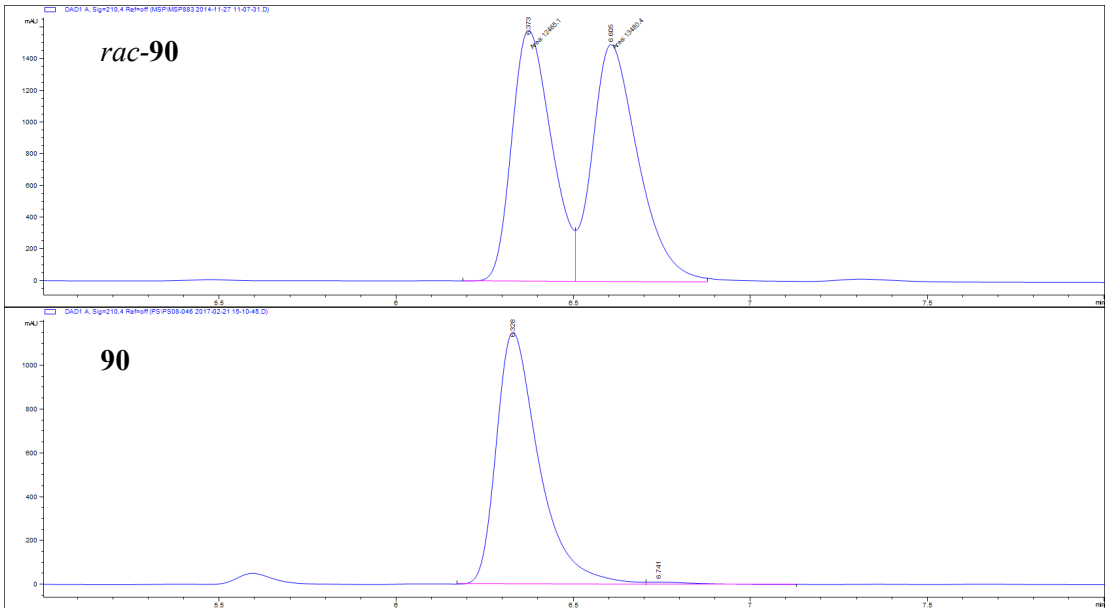
(1 M in THF, 0.8 mL, 0.8 mmol, 2.00 eq) and 3-chlorocyclohex-1-ene (45 µL, 0.40 mmol, 1.00 eq) in THF (0.3 mL) was then added *via* syringe and the flask rinsed with THF (0.2 mL). The resulting mixture was then refluxed for 3 h. The solvent was then carefully evaporated and the resulting mixture was directly loaded onto a chromatographic column and eluted with pentane to obtain (–)-(*S*)-3-(4-methylphenyl)cyclohexene in 53% yield (36.8 mg, 0.21 mmol).

Enantiomeric excess of 98% was determined by HPLC [Chiralpak® IC; flow: 0.7 mL/min; hexane; λ = 210 nm; major enantiomer t_R = 6.3 min; minor enantiomer t_R =6.7 min].

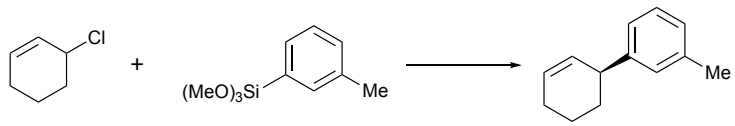


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.51 – 1.70 (m, 2 H, H-5$_a$, H-6$_a$), 1.72 – 1.83 (m, 1 H, H-5$_b$), 1.99 – 2.07 (m, 1 H, 6$_b$), 2.08 – 2.14 (m, 2 H, H-4$_a$, H-4$_b$), 2.35 (s, 3 H, CH_3), 3.35 – 3.45 (m, 1 H, H-1), 5.70 – 5.77 (m, 1 H, H-2), 5.86 – 5.94 (m, 1 H, H-3), 7.14 (s, 4 H, H-2', H-3', H-5', H-6'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 21.2 (CH_3), 21.4 (C-5), 25.2 (C-4), 32.8 (C-6), 41.6 (C-1), 127.8 (2C$_{Ar}$), 128.3 (C-3), 129.1 (2C$_{Ar}$), 130.6 (C-2), 135.6 (C-4'), 143.8 (C-1'); **$[\alpha]^{25}_{589}$** = –143.9° (*c* 1.0, $CHCl_3$), [Lit: $[\alpha]^{20}_{589}$ = –128.0° (*c* 0.47 $CHCl_3$) for >94% ee)][156]; **HRMS** (EI) *m*/*z* calc. for $C_{14}H_{16}^+$ $[M]^+$: 172.1247, found: 172.1248.

HPLC traces for 90:

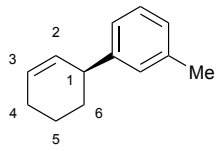


(–)-(*S*)-3-(3-Methylphenyl)cyclohexene 91



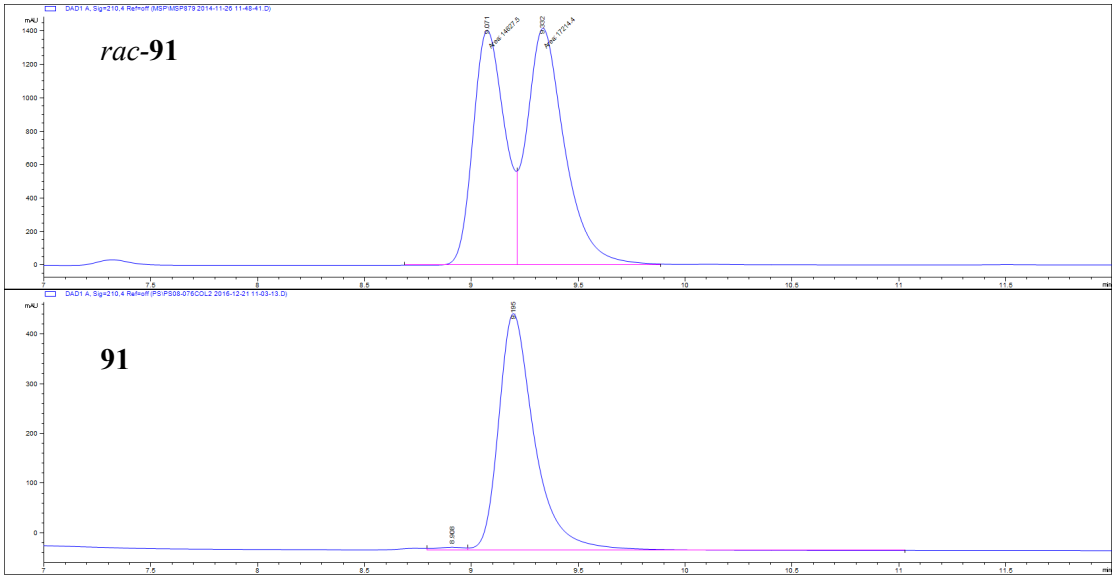
In a 10 mL round bottomed flask $[Rh(cod)(MeCN)_2]BF_4$ (7.6 mg, 0.02 mmol, 0.05 eq) and (*S*)-BINAP (18.7 mg, 0.03 mmol, 0.075 eq) were stirred in THF (0.7 mL) at reflux for 30 min. A solution of 3-tolyltrimethoxysilane (170 mg, 0.80 mmol, 2.00 eq), tetrabutylammonium fluoride (1 M in THF, 0.8 mL, 0.8 mmol, 2.00 eq) and 3-chlorocyclohex-1-ene (45 µL, 0.40 mmol, 1.00 eq) in THF (0.3 mL) was then added *via* syringe and the flask rinsed with THF (0.2 mL). The resulting mixture was then refluxed for 3 h. The solvent was then carefully evaporated and the resulting mixture was directly loaded onto a chromatographic column and eluted with pentane to obtain (–)-(*S*)-3-(3-methylphenyl)cyclohexene in 48% yield (32.9 mg, 0.19 mmol).

Enantiomeric excess of 98% was determined by HPLC [Chiralpak® IB; flow: 0.5 mL/min; hexane; λ = 210 nm; minor enantiomer t_R = 8.9 min; major enantiomer t_R = 9.2 min].

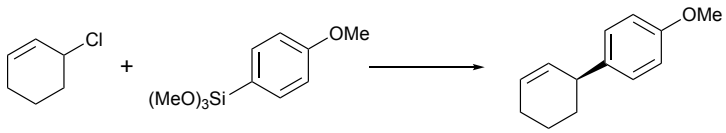


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.56 – 1.74 (m, 2 H, H-5_a, H-6_a), 1.78 – 1.87 (m, 1 H, H-5_b), 2.02 – 2.11 (m, 1 H, H-6_b), 2.11 – 2.20 (m, 2 H, H-4_a, H-4_b), 2.41 (s, 3 H, CH_3), 3.36 – 3.50 (m, 1 H, H-1), 5.75 – 5.84 (m, 1 H, H-2), 5.90 – 6.00 (m, 1 H, H-3), 7.05 – 7.14 (m, 3 H, H_{Ar}), 7.21 – 7.28 (m, 1 H, H_{Ar}); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 21.4 (C-5), 21.6 (CH_3), 25.2 (C-4), 32.8 (C-6), 42.0 (C-1), 124.9, 126.9, 128.3, 128.3, 128.6 ($4C_{Ar}$, C-2), 130.48 (C-3), 137.9 (C_q), 146.8 (C_q); **$[\alpha]^{25}_{589}$** = –73.5° (*c* 1.0, $CHCl_3$), [Lit: $[\alpha]^{20}_{589}$ = –117.0° (*c* 0.96 $CHCl_3$) for 97% ee)][156]; **HRMS** (EI) *m*/*z* calc. for $C_{14}H_{16}^+$ $[M]^+$: 172.1247, found: 172.1250.

HPLC traces for 91:

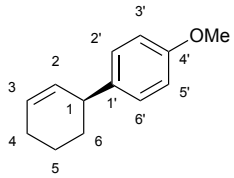


(–)-(*S*)-3-(4-Methoxyphenyl)cyclohexene 93



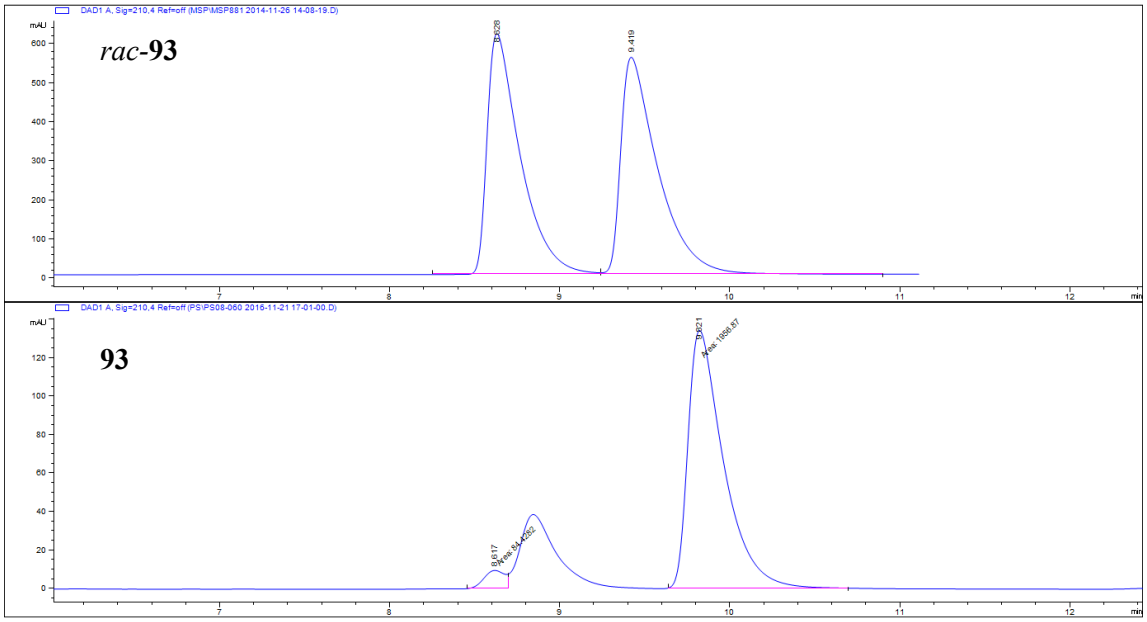
In a 10 mL round bottomed flask $[Rh(cod)(MeCN)_2]BF_4$ (7.6 mg, 0.02 mmol, 0.05 eq) and (*S*)-BINAP (18.7 mg, 0.03 mmol, 0.075 eq) were stirred in THF (0.7 mL) at reflux for 30 min. A solution of 4-(trimethoxysilyl)anisole (183.0 mg, 0.80 mmol, 2.00 eq), tetrabutylammonium fluoride (1 M in THF, 0.8 mL, 0.8 mmol, 2.00 eq) and 3-chlorocyclohex-1-ene (45 µL, 0.40 mmol, 1.00 eq) in THF (0.3 mL) was then added *via* syringe and the flask rinsed with THF (0.2 mL). The resulting mixture was then refluxed for 3 h. The solvent was then carefully evaporated and the resulting mixture was directly loaded onto a chromatographic column and eluted with pentane/diethyl ether (95:5) to afford the product in 32% yield (35.6 mg, 0.20 mmol, impure, contains ~25% anisole).

Enantiomeric excess of 92% was determined by HPLC [Chiralpak® IB; flow: 0.6 mL/min; hexane; λ = 210 nm; minor enantiomer t_R = 8.6 min; major enantiomer t_R = 9.8 min].

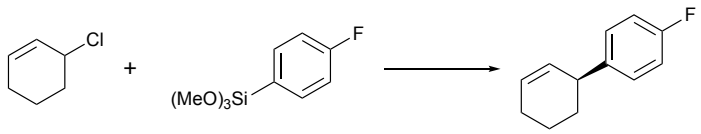


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.47 – 1.80 (m, 3 H, H-5_a, H-5_b, H-6_a), 1.94 – 2.04 (m, 1 H, H-6_b), 2.04 – 2.13 (m, 2 H, H-4_a, H-4_b), 3.32 – 3.42 (m, 1 H, H-1), 3.80 (s, 3 H, OCH_3), 5.67 – 5.74 (m, 1 H, H-2), 5.84 – 5.92 (m, 1 H, H-3), 6.81 – 6.88 (m, 2 H, H-3', H-5'), 7.11 – 7.18 (m, 2 H, H-2', H-6'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 21.3 (C-5), 25.2 (C-4), 32.9 (C-6), 41.1 (C-1), 55.4 (OCH_3), 113.8 (2C, C-3', C-5'), 128.28 (C-3), 128.75 (2C, C-2', C-6'), 130.64 (C-2), 138.93 (C-1'), 157.98 (C-4'); **HRMS** (EI) *m/z* calc. for $C_{13}H_{16}O^+$ $[M]^+$: 188.1196, found: 188.1194; **$[\alpha]^{20}_{589}$** n.d.‡‡.

HPLC traces for 93:



(–)-(*S*)-3-(4-Fluorophenyl)cyclohexene 94

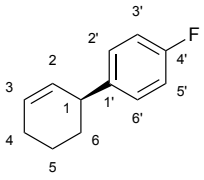


In a 10 mL round bottomed flask $[Rh(cod)(MeCN)_2]BF_4$ (7.6 mg, 0.02 mmol, 0.05 eq) and (*S*)-BINAP (18.7 mg, 0.03 mmol, 0.075 eq) were stirred in THF (0.7 mL) at reflux for 30 min. A solution of (4-fluorophenyl)trimethoxysilane (173.0 mg, 0.80 mmol, 2.00 eq), tetrabutylammonium fluoride (1 M in THF, 0.8 mL, 0.8 mmol, 2.00 eq) and 3-chlorocyclohex-1-ene (45 µL, 0.40 mmol,

‡‡ Not determined due to large amounts of impurities.

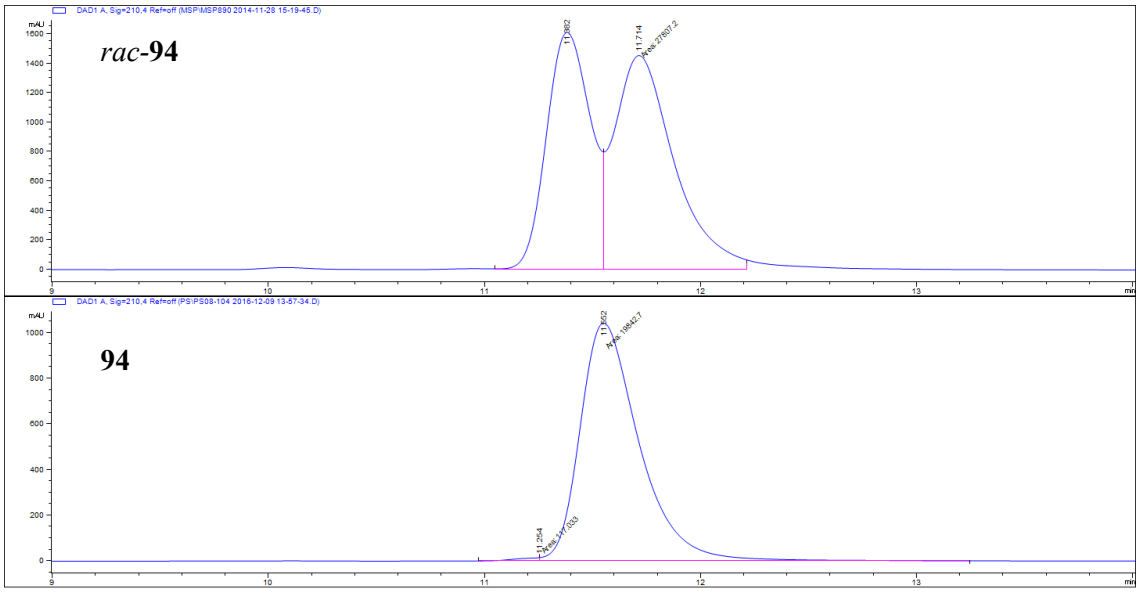
1.00 eq) in THF (0.3 mL) was then added *via* syringe and the flask rinsed with THF (0.2 mL). The resulting mixture was then refluxed for 3 h. The solvent was then carefully evaporated and the resulting mixture was directly loaded onto a chromatographic column and eluted with pentane to obtain (–)-(*S*)-3-(4-fluorophenyl)cyclohexene in 51% yield (35.6 mg, 0.20 mmol).

Enantiomeric excess of 99% was determined by HPLC [Chiralpak® ID; flow: 0.4 mL/min; hexane; λ = 210 nm; minor enantiomer t_R = 11.3 min; major enantiomer t_R = 11.6 min].

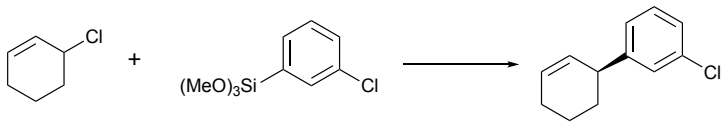


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.47 – 1.57 (m, 1 H, H-6_a), 1.62 (ddddd, J = 12.5, 9.8, 7.3, 6.2, 2.4 Hz, 1 H, H-5_a), 1.73 (dddd, J = 14.7, 6.8, 5.1, 2.7 Hz, 1 H, H-5_b), 1.96 – 2.05 (m, 1 H, H-6_b), 2.06 – 2.15 (m, 2 H, H-4_a, H-4_b), 3.35 – 3.44 (m, 1 H, H-1), 5.64 – 5.72 (m, 1 H, H-2), 5.84 – 5.95 (m, 1 H, H-3), 6.91 – 7.05 (m, 2 H, H-3', H-5'), 7.12 – 7.23 (m, 2 H, H-2', H-6'); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 21.2 (C-5), 25.1 (C-4), 32.9 (C-6), 41.2 (C-1), 115.1 (d, J = 21.3 Hz, C-2', C-6'), 128.7 (C-3), 129.2 (d, J = 7.9 Hz, C-3', C-5'), 130.1 (C-2), 142.4 (d, J = 3.2 Hz, C-1'), 161.5 (d, J = 243.4 Hz, C-4'); **^{19}F-NMR** (376 MHz, $CDCl_3$) δ –117.66; **$[\alpha]^{20}_{589}$** = –108.2° (*c* 1.0, $CHCl_3$), [Lit: $[\alpha]^{20}_{589}$ = –112.4° (*c* 1.09 $CHCl_3$) for 99% ee)][156]; **HRMS** (EI) *m*/*z* calc. for $C_{12}H_{13}F^+$ $[M]^+$: 176.0996, found: 176.1001.

HPLC traces for 94:

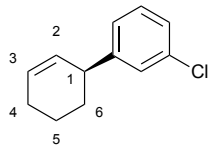


(–)-(*S*)-3-(3-Chlorophenyl)cyclohexene 95



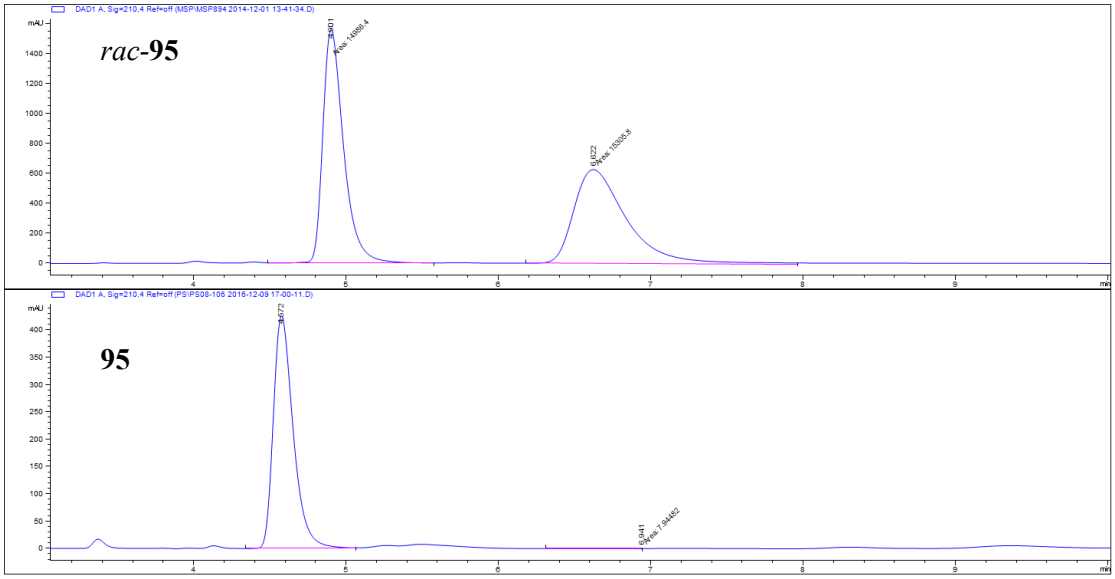
In a 10 mL round bottomed flask $[Rh(cod)(MeCN)_2]BF_4$ (7.6 mg, 0.02 mmol, 0.05 eq) and (*S*)-BINAP (18.7 mg, 0.03 mmol, 0.075 eq) were stirred in THF (0.7 mL) at reflux for 30 min. A solution of (3-chlorophenyl)trimethoxysilane (186.2 mg, 0.80 mmol, 2.00 eq), tetrabutylammonium fluoride (1 M in THF, 0.8 mL, 0.8 mmol, 2.00 eq) and 3-chlorocyclohex-1-ene (45 µL, 0.40 mmol, 1.00 eq) in THF (0.3 mL) was then added *via* syringe and the flask rinsed with THF (0.2 mL). The resulting mixture was then refluxed for 3 h. The solvent was then carefully evaporated and the resulting mixture was directly loaded onto a chromatographic column and eluted with pentane to obtain (–)-(*S*)-3-(3-chlorophenyl)cyclohexene in 54% yield (41.8 mg, 0.22 mmol).

Enantiomeric excess of 99% was determined by HPLC [Chiralpak® ID; flow: 1.0 mL/min; hexane; λ = 210 nm; major enantiomer t_R = 4.6 min; major enantiomer t_R = 6.9 min].

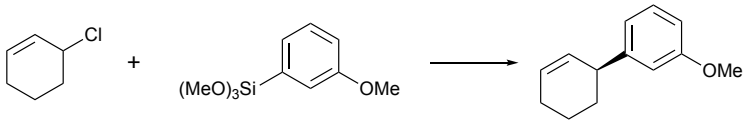


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.49 – 1.59 (m, 1 H, H-6_a), 1.59 – 1.68 (m, 1 H, H-5_a), 1.69 – 1.79 (m, 1 H, H-5_b), 1.97 – 2.06 (m, 1 H, H-6_b), 2.06 – 2.14 (m, 2 H, H-4_a, H-4_b), 3.32 – 3.45 (m, 1 H, H-1), 5.64 – 5.73 (m, 1 H, H-2), 5.88 – 5.98 (m, 1 H, H-3), 7.11 (dt, *J* = 7.6, 1.5, 1.5 Hz, 1 H, H_{Ar}), 7.15 – 7.27 (m, 3 H, H_{Ar}); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 21.1 (C-5), 25.1 (C-4), 32.6 (C-6), 41.7 (C-1), 126.1 (C_{Ar}), 126.3 (C_{Ar}), 128.0 (C_{Ar}), 129.1 (C-3), 129.4 (C-2), 129.6 (C_{Ar}), 134.2 (C_q), 148.9 (C_q); **$[\alpha]^{20}_{589}$** = –131.1° (*c* 1.00, $CHCl_3$), [Lit: $[\alpha]^{20}_{589}$ = –132.2° (*c* 1.18 $CHCl_3$) for 99% ee][156]; **HRMS** (EI/FI) m/z calc. for $C_{12}H_{13}Cl^+$ $[M]^+$: 192.0706, found: 192.0708;

HPLC traces for 95:

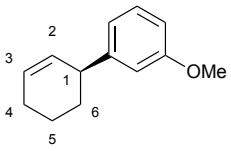


(–)-(*S*)-3-(3-Methoxyphenyl)cyclohexene 96



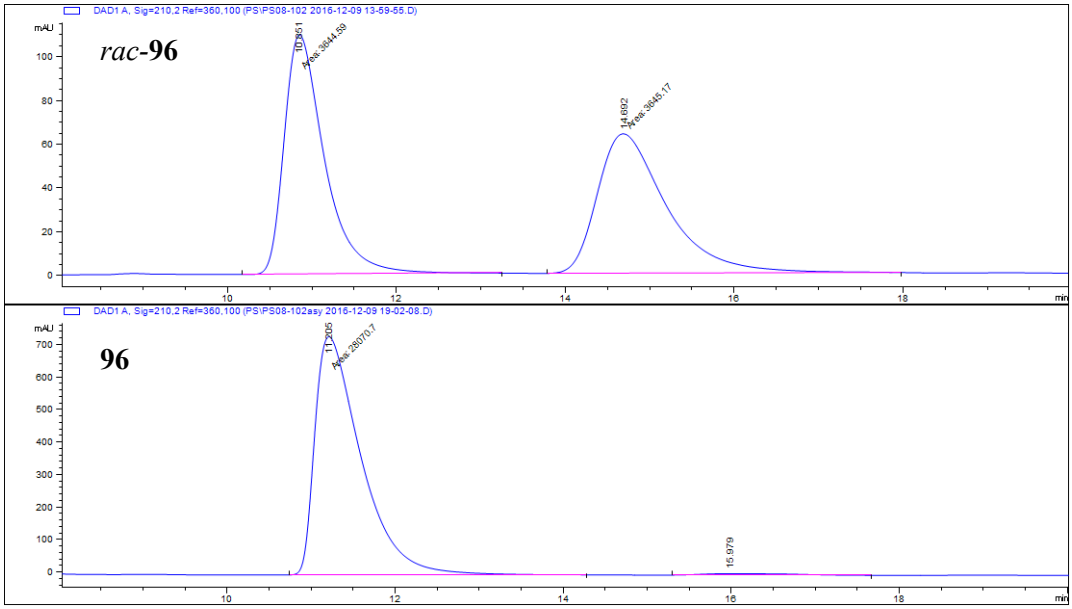
In a 10 mL round bottomed flask $[Rh(cod)(MeCN)_2]BF_4$ (7.6 mg, 0.02 mmol, 0.05 eq) and (*S*)-BINAP (18.7 mg, 0.03 mmol, 0.075 eq) were stirred in THF (0.7 mL) at reflux for 30 min. A solution of 3-(trimethoxysilyl)anisole (183 mg, 0.80 mmol, 2.00 eq), tetrabutylammonium fluoride (1 M in THF, 0.8 mL, 0.8 mmol, 2.00 eq) and 3-chlorocyclohex-1-ene (45 µL, 0.40 mmol, 1.00 eq) in THF (0.3 mL) was then added *via* syringe and the flask rinsed with THF (0.2 mL). The resulting mixture was then refluxed for 3 h. The solvent was then carefully evaporated and the resulting mixture was directly loaded onto a chromatographic column and eluted with pentane to obtain (–)-(*S*)-3-(3-methoxyphenyl)cyclohexene in 51% yield (38.5 mg, 0.20 mmol, impure). The racemic product was generated via similar synthesis with (±)-BINAP instead of (*S*)-BINAP.

Enantiomeric excess of 96% was determined by HPLC [Chiralpak® ID; flow: 1.0 mL/min; hexane; λ = 210 nm; major enantiomer t_R = 11.2 min; minor enantiomer t_R = 16.0 min].

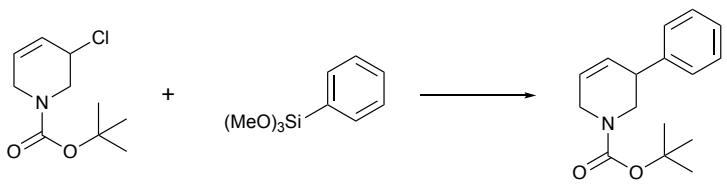


^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.52 – 1.81 (m, 3 H, H-5_a, H-5_b, H-6_a), 1.96 – 2.13 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.34 – 3.44 (m, 1 H, H-1), 3.81 (d, J = 3.9 Hz, 3 H, OCH_3), 5.67 – 5.76 (m, 1 H, H-2), 5.86 – 5.94 (m, 1 H, H-3), 6.72 – 6.85 (m, 3 H, H_{Ar}), 7.23 (t, J = 7.8 Hz, 1 H, H_{Ar}); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 21.34 (C-5), 25.2 (C-4), 32.6 (C-6), 42.0 (C-1), 55.3 (OCH_3), 111.3 (C_{Ar}), 113.7 (C_{Ar}), 120.4 (C_{Ar}), 128.6 (C-3), 129.3 (C_{Ar}), 130.2 (C-2), 148.5 (C_q), 159.7 (C_q); **$[\alpha]^{20}_{589}$** = n.d.[§§]; **HRMS** (EI) *m*/*z* calc. for $C_{13}H_{16}^{+}$ $[M]^{+}$: 188.120, found: 188.117; The spectral data matches the reported data in the literature for the racemic compound.[245]

HPLC traces for 96:



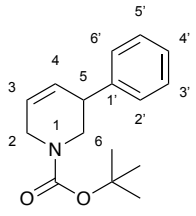
(±)-*N-tert*-Butoxycarbonyl-5-phenyl-3-piperidene 106



In a 10 mL round bottomed flask $[Rh(cod)(MeCN)_2]BF_4$ (7.6 mg, 0.02 mmol, 0.05 eq) and (±)-BINAP (18.7 mg, 0.03 mmol, 0.075 eq) were stirred in THF (0.7 mL) at reflux for 30 min. A

[§§] Not determined due to large amounts of impurities.

solution of phenyltrimethoxysilane (173.0 mg, 0.80 mmol, 2.00 eq), tetrabutylammonium fluoride (1 M in THF, 0.8 mL, 0.8 mmol, 2.00 eq) and *N-tert*-butoxycarbonyl-5-chloro-3-piperidene (86.8 mg, 0.40 mmol, 1.00 eq) in THF (0.3 mL) was then added *via* syringe and the flask rinsed with THF (0.2 mL). The resulting mixture was then refluxed over night. The solvent was then carefully evaporated and the resulting mixture was directly loaded onto a chromatographic column and eluted with petrol/EtOAc (95:5) to afford the product in 46% yield (29 mg, 0.19 mmol).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.19 – 1.63 (m, 9 H), 3.01, 3.33 – 3.46, 3.70 – 3.79 and 4.07 (rotameric m, 2H), 3.46 – 3.62 (m, 1H), 3.82 and 4.07 (rotameric m, 2H), 5.89 (br s, 2H), 7.19 – 7.27 (m, 3H), 7.31 (m, 2H); **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 28.3 (3C), 41.5, 42.9 and 43.6 (rotameric, 1C), 47.3 and 48.5 (rotameric, 1C), 79.5, 125.9, 126.7, 127.9 (2C), 128.2, 128.5 (2C), 142.2, 154.7; **HRMS** (ESI): *m*/*z* calc. for $C_{16}H_{21}O_2NNa^+$ $[M+Na]^+$: 282.1465, found: 282.1466.

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