Rapid synthesis of the Taxol core

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Declaration

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

Thomas Palacin

Abstract

This thesis describes the combination of prochiral/racemic electrophiles and non-stabilised nucleophiles in transition metal catalysed asymmetric transformations.

The first part of the thesis focuses on the synthetic approach towards the Taxol core, Taxadiene. The key steps involve a Cu-catalysed asymmetric conjugate addition (ACA) of alkylzirconocenes to enones and cyclisations. Three different routes towards the synthesis of Taxadiene were explored and investigations into the Cu-catalysed ACA led to the discovery of a novel domino hydrozirconation/conjugate addition/enolate trapping reaction.

The second part of this thesis builds on the Rh-catalysed asymmetric coupling of boronic acids (vinyls, benzenes and heteroaromatics) and cyclic allyl chlorides, developed in the Fletcher group. Here, the main point is to couple a similar library of boronic acids to a more challenging electrophile, a racemic tetrahydropyridine (or *N*-heterocyclic piperidene) chloride, in order to access new chiral building blocks that can be found in a variety of natural products and their derivatives. The utility of this method is demonstrated by the total and formal asymmetric synthesis of the antipsychotic drug (-)-Preclamol.

The last chapter builds on the Cu-catalysed asymmetric allylic alkylation of alkylzirconocenes to cyclic allyl chlorides, also developed in our group. The main goal of this work is once again to apply this methodology to the racemic *N*-heterocyclic piperidene chloride. Investigations led to the discovery of a kinetic resolution process which afforded novel 3-alkyl substituted tetrahydropyridines and enantioenriched 3-chloro-1,2,3,6-tetrahydropyridines in high enantioselectivities.

Acknowledgements

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Finally to my family, thank you for all the support and love you have given me during the course of this PhD. I am really grateful that you kept pushing me to finish writing up my thesis.

Abbreviations

Å	Ångstrom
AAA	Asymmetric allylic alkylation
ACA	Asymmetric conjugate addition
acac	Acetylacetonate
Ac	Acetyl
ACN	Acetonitrile
anti	*ἀντί* (Greek) opposite
aq	Aqueous
Ar	Any aryl
BDSB	Bromodiethylsulfonium bromopentachloroantimonate
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
BINOL	1,1’-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	Broadened (NMR)
Bu	Butyl
Bz	Benzoyl
c	Concentration
C	Celsius
Cl-MeO-BIPHEP	(5,5′-Dichloro-6,6′-dimethoxy-1,1′-biphenyl)-2,2′-diyl-bis(diphenyl- phosphine)
Cbz	Benzyloxycarbonyl
cod	1,5-Cyclooctadiene
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl

d	Doublet (NMR)
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIPEA	Diisopropylethylamine, Hünig's base
DKR	Dynamic kinetic resolution
DIOP	4,5-Bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolan
DMAP	4-Dimethylamino pyridine
DMAPP	Dimethylallyl pyrophosphate
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric ratio
DYKAT	Dynamic kinetic asymmetric transformation
E	Entgegen
ee	Enantiomeric excess
EI	Electron impact ionisation
e.g.	*Exempli gratia* (Latin) for example
e.r.	Enantiomeric ratio
Et	Ethyl
eq	Equivalents
ent-	Enantiomer
ESI	Electrospray ionisation
Et_2O	Diethyl ether
EtOAc	Ethyl acetate

EtOH	Ethanol
et al.	*Et alia* (Latin) and others
etc.	*Et cetera* (Latin) and other things
EWG	Electron withdrawing group
FI	Field ionisation (HRMS)
FT	Fourier transform
g	Gram
GC	Gas chromatography
Grubbs I	Grubbs' first-generation catalyst
Het	Any heteroaryl group
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMDS	Bis(trimethylsilyl)amide
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
Hz	Hertz
i	Iso
i.e.	*Id est* (Latin) that is
IPA	Isopropyl alcohol
IPP	Isopentenyl pyrophosphate
IR	Infrared
J	Coupling constant (NMR)
k	Reaction rate coefficient
L	Litre
LRMS	Low resolution mass spectrometry
m	Milli, meter or medium (IR)
m	meta
M	Molar

m/z	mass-to-charge ratio
Me	Methyl
MeOH	Methanol
Mes	Mesitylene
min(s)	Minute(s)
MOM	Methoxymethyl ether
MOP	2-diarylphosphino-1-1’-binaphthalene
Ms	Mesyl
MS	Molecular sieves
MTBE	Methyl *tert*-butyl ether
n/c	Not calculated
Naph	Naphthalene
NBS	*N*-Bromosuccinimide
NHC	*N*-heterocyclic carbene
NMO	N-methylmorpholine N-oxide
NMP	*N*-methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
N-PSS	*N-(*phenylseleno)succinimide
Nu	Nucleophile
o	Ortho
o.n.	Overnight
P	Protecting group
p	Para
Ph	Phenyl
pH	Potential of hydrogen
Piv	Pivaloyl
p*K*a	Logarithmic acid dissociation constant

ppm	Parts per million
Pr	Propyl
Pyr	Pyridine
q	Quartet (NMR)
R	Any group
R	Rectus
rac	racemic
Rf	Retention factor
RT	Room temperature
s	Singlet (NMR), or strong (IR)
S	Sinister
sat.	Saturated
Seg-PHOS	4,4′-Bi-1,3-benzodioxole-5,5′-diylbis(diphenylphosphane)
SM	Starting material
S_N2	Bimolecular nucleophilic substitution
S_N2'	Bimolecular nucleophilic substitution with allylic rearrangement
sp^2	Orbital hybridisation: 33% s and 67% p character
sp^3	Orbital hybridisation: 25% s and 75% p character
t	Triplet (NMR) or time
t	Tert
T	Temperature
TADDOL	α,α,α,α-Tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
Tc	Thiophene-2-carboxylate

TCA	Trichloroacetic acid
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyridine
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
*t*R	Retention time
Ts	Toluenesulfonyl
UV	Ultraviolet
V	Volt
Vis	Visible
w	Weak (IR)
W	Watt
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
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)
v	Wavenumber (IR)

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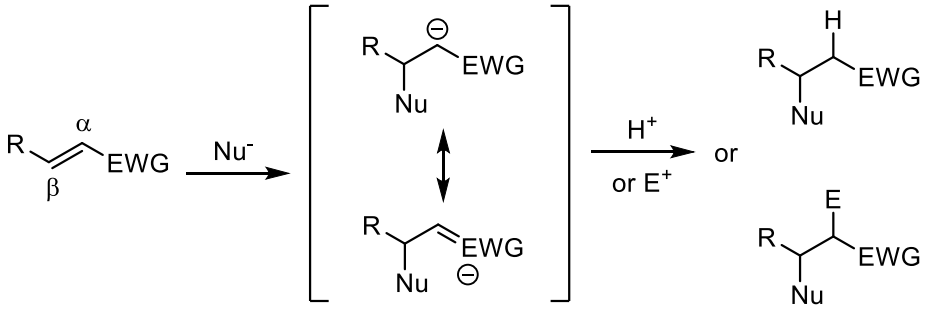
Chapter 1

1 Introduction

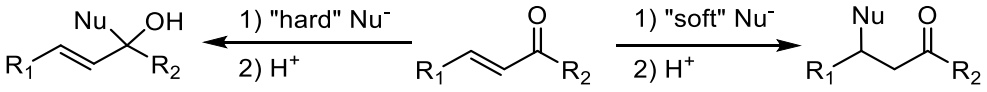
The introduction of this thesis focuses on Cu-catalysed asymmetric conjugate additions (ACAs) to cyclic systems, mainly 6-membered rings. This chapter is divided into three different parts. The two first parts describe Cu-catalysed ACAs devoted to the construction of chiral tertiary and then quaternary centres using different organometallic reagents (Grignard reagents, organozinc and alkylaluminium reagents). The last part reviews Cu-catalysed ACAs with alkylzirconium species developed within the Fletcher group.

Enantioselective 1,4-conjugate addition of carbon nucleophiles to α,β-unsaturated compounds is one of the most powerful methods in asymmetric synthesis to form a C-C bond with a new stereogenic centre.[1] The conjugate addition reaction involves the reaction of a nucleophile to an α,β-unsaturated system activated by an electron-withdrawing group (EWG). Addition of the nucleophile at the β-position of the alkene or alkyne results in the formation of a stabilised carbanion. Protonation (H^+) of the newly formed carbanion generates a single stereogenic centre, whereas addition of an electrophile (E^+) results in an α,β-disubstituted product with two new stereocentres (Scheme 1.1).[2]



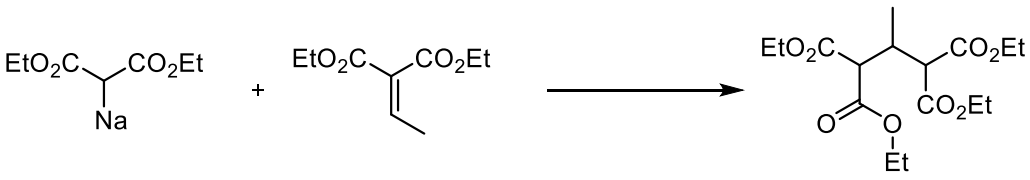
Scheme 1.1: Principle of a conjugate addition reaction

The regioselectivity of a nucleophilic addition to α,β-unsaturated carbonyl compounds is the main problem encountered in conjugate additions. Hard nucleophiles favour 1,2-addition whereas soft nucleophiles favour the β-position of the unsaturated system, resulting in the formation of a 1,4-adduct (Scheme 1.2).[2]



Scheme 1.2: Additions of hard and soft nucleophiles to α,β-unsaturated carbonyl compounds

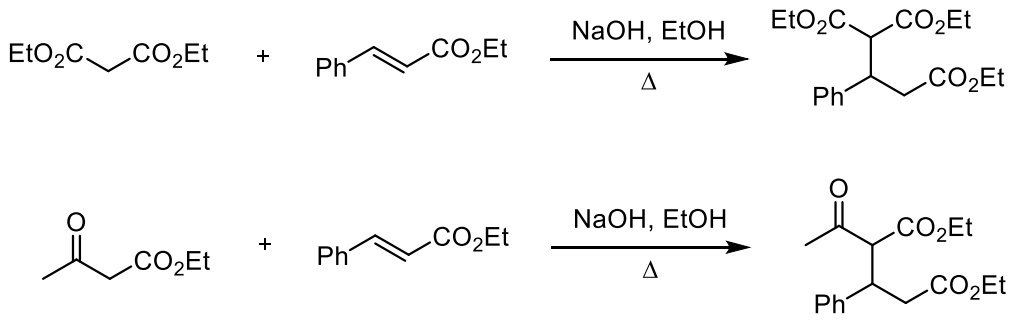
In 1883, Komnenos reported the first example of an uncatalysed conjugate addition.[3] Diethyl sodiomalonate reacted with diethyl 2-ethylidenemalonate in order to form a new 1,4-adduct (Scheme 1.3).



Scheme 1.3: First example of an uncatalysed conjugate addition by Komnenos

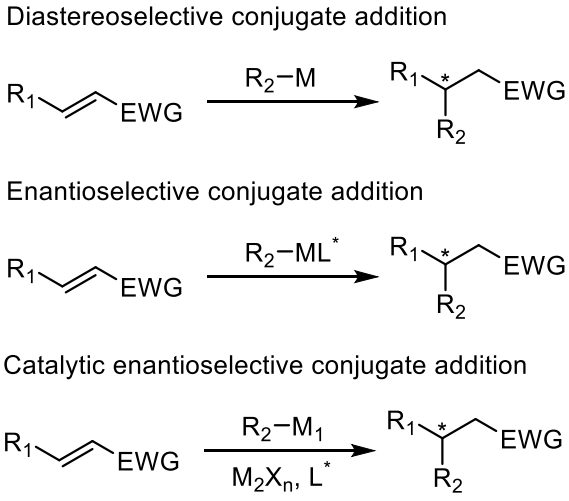
One of the most famous examples of a conjugate addition is the Michael addition where a doubly stabilised carbon nucleophile undergoes a 1,4-conjugate addition to a α,β-unsaturated carbonyl compound.[4] Indeed, Michael described in 1887 the additions of activated Michael donors, diethyl malonate and ethyl 3-oxobutanoate, to a Michael

acceptor, ethyl cinnamate (Scheme 1.4). Following his work, the conjugate addition of nucleophiles to substituted unsaturated acceptor has been usually referred to as a Michael addition.



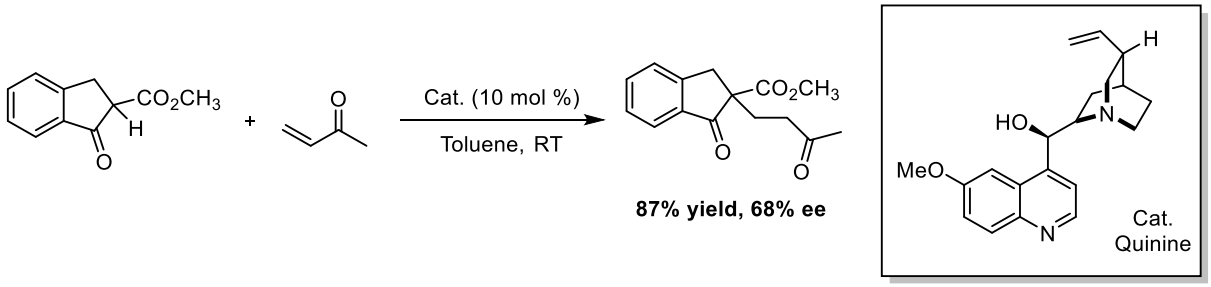
Scheme 1.4: Examples of Michael conjugate additions

Since the conjugate addition often leads to the formation of a stereogenic centre, considerable efforts have been devoted to the development of efficient stereoselective methods. Over the years, three potential strategies of ACA using organometallic reagents were investigated: diastereoselective conjugate addition, enantioselective conjugate addition and catalytic enantioselective conjugate addition (Scheme 1.5).[1]



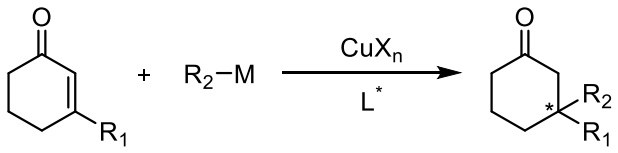
Scheme 1.5: Three different methods for ACAs

Wynberg and Helder, following the report of Langström and Bergson,[5] published the first asymmetric conjugate addition in 1975 (Scheme 1.6).[6] The addition of methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate, as a Michael donor, to methyl vinyl ketone, as a Michael acceptor, afforded the catalysed ACA product in 87% yield and 68% enantiomeric excess (ee). The reaction was catalysed by Quinine.



Scheme 1.6: First example of an ACA by Wynberg and Helder

In organometallic chemistry, copper is a metal of choice due to its high abundance and low cost. It is one of the most extensively used metals in organic synthesis.[1] We will further discuss the advancement of Cu-catalysed asymmetric conjugate additions of organometallics with cyclic Michael acceptors throughout the years (Scheme 1.7).

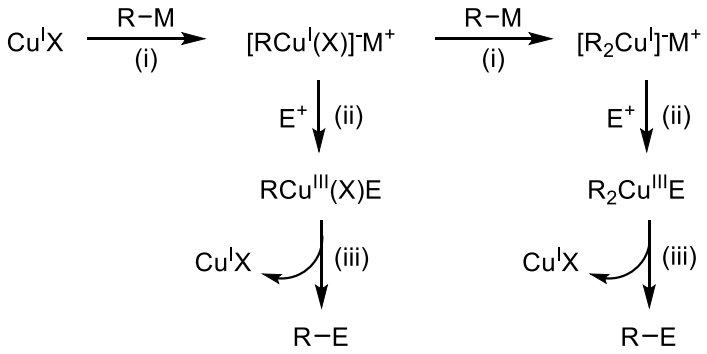


Scheme 1.7: Cu-catalysed 1,4-addition of organometallics to cyclic Michael acceptors

1.1 Cu-catalysed ACA for the construction of cyclic tertiary stereocentres

1.1.1 Generalities on Cu-catalysed ACA

Organocopper compounds often appear in the form of nucleophilic organocopper reagents, generated *in situ* from a copper(I) complex and organometallic reagents.[1] The basics of nucleophilic organocopper reaction mechanisms can be described in three elementary steps (Scheme 1.8).[7] First, (i) the transmetalation between a copper(I) salt and an organometallic reagent to give either a mono- or a diorganocuprate(I). The transmetalation between organometallic reagents (R-M) and Cu(I) complexes is favoured since copper is more electronegative than most metals (M) inducing C-Cu bonds stronger than pristine C-M bonds.[8,9] Then, (ii) the nucleophilic attack of the d-orbital of the copper(I) atom on an electrophile (E^+) to produce an organocopper(III) intermediate (oxidative addition step). The oxidation addition process is possible thanks to the polarisability and high energy of the 3d orbitals of the copper atom. A charge transfer from d^{10} electronic configuration of Cu(I) occurs upon the interaction with electrophiles (E^+) forming the Cu(III) intermediate. Finally (iii) reductive elimination of the copper(III) intermediate to give a product (R-E) and a neutral copper(I) species. Contrary to the oxidative addition, the reductive elimination step is thermodynamically favoured due to the instability of the d^8 electronic configuration of Cu(III) leading to the C-C bond formation.[7]

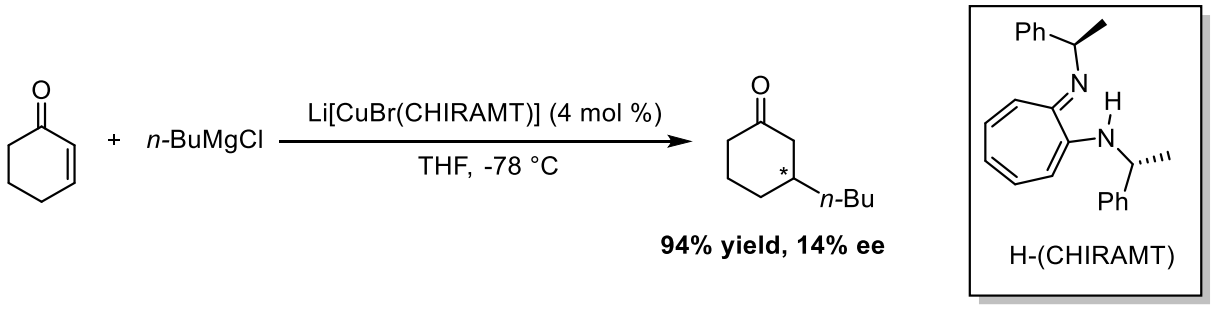


Scheme 1.8: General mechanism of nucleophilic organocopper reactions

Over the years, the Cu-catalysed ACA methodology has been developed by several research groups into one of the most robust and widely applied synthetic methods.[2,10–14] Different organometallic reagents, such as Grignard reagents,[15] organozinc reagents,[16,17] alkylaluminium reagents[18] and organoboron reagents[19] have been progressively explored in combination with copper and various ligands such as phosphoramidites,[20,21] NHC ligands,[11,22] Schiff base type ligands,[23,24] peptide-based ligands[25] and more. We will now present several examples of those developed ACAs with different organometallic reagents towards the construction of cyclic tertiary centres.

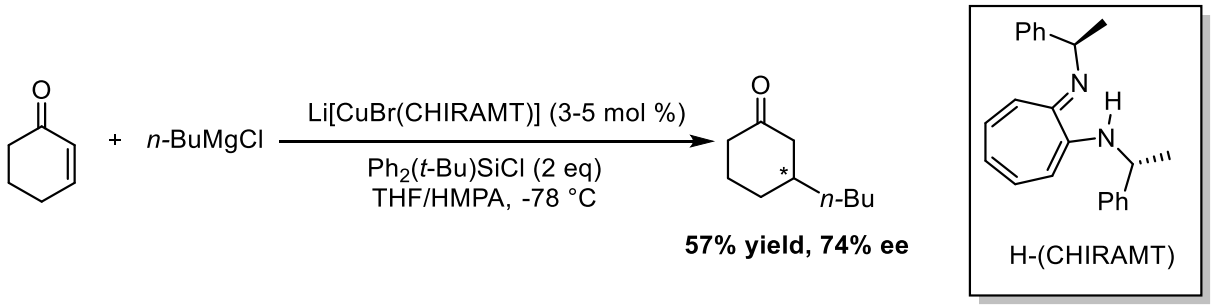
1.1.2 Cu-catalysed ACA with Grignard reagents

The first reported Cu-catalysed ACA to a cyclic Michael acceptor was performed by Lippard in 1988 with a Grignard reagent promoted by a new catalyst ligand based on *N,N*'-dialkyl-substituted aminotroponeimines.[26] The conjugate addition of *n*-BuMgCl to 2-cyclohexen-1-one with H-(CHIRAMT) as the chiral ligand afforded the 1,4-adduct in 94% yield and 14% ee (Scheme 1.9).



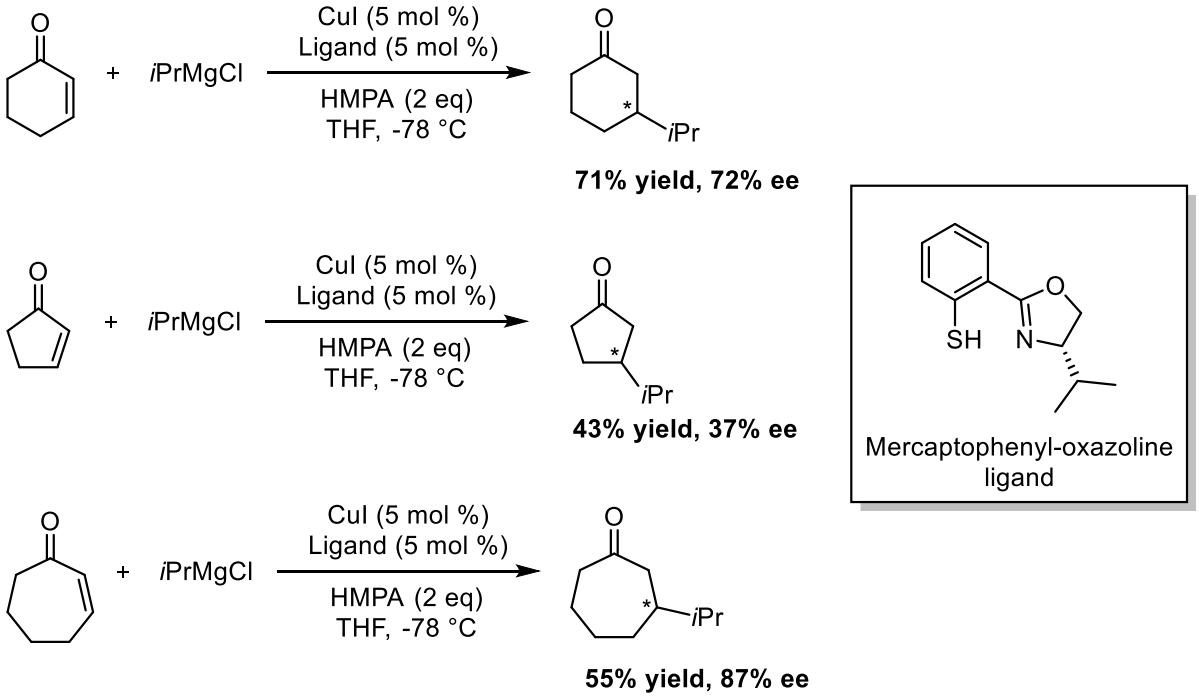
Scheme 1.9: The first reported Cu-catalysed ACA by Lippard

The low enantiomeric excess obtained, which was still a tremendous achievement at the time, was later enhanced by the addition of HMPA and a bulky silyl additive, Ph_2(*t*-Bu)SiCl, to the reaction system (Scheme 1.10).[27] The same 1,4-product was synthesised in 57% yield and 74% ee. Lippard and co-workers were also able with this newly enhanced system to broaden the scope of the enantioselective conjugate addition to include different alkyl organomagnesium compounds other than *n*-BuMgCl with the cyclic enone.[27]



Scheme 1.10: Optimisation of the Cu-catalysed ACA developed by Lippard

Pfaltz and Zhou expanded the scope of this methodology to 5- and 7-membered cyclic acceptors by using a series of synthesised chiral enantioenriched mercaptoaryl-oxazolines.[28] The addition of *i*-PrMgCl to the array of cyclic enones with CuI, the mercaptoaryl-oxazoline ligand and HMPA in THF at -78 °C afforded the 1,4-adducts in moderate yield and high enantioselectivity up to 87% ee only for the cycloheptenone 1,4-product (Scheme 1.11).



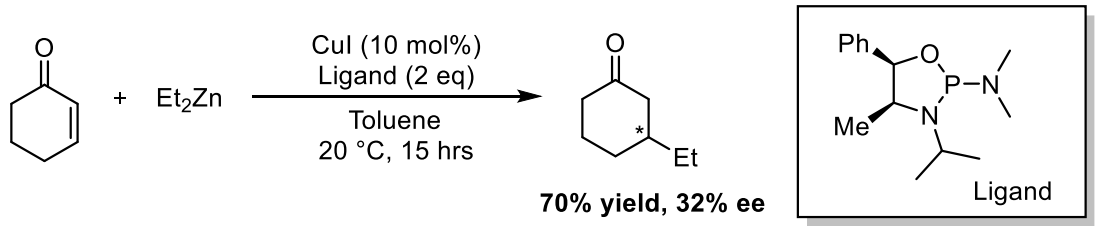
Scheme 1.11: Cu-catalysed ACAs to 5-, 6- and 7-membered cyclic acceptors

The high reactivity of Grignard reagents probably explains the moderate yield and enantioselectivity obtained, therefore most research groups went on exploring the less reactive dialkylzinc reagent in copper-catalysed asymmetric conjugate additions.

1.1.3 Cu-Catalysed ACA with dialkylzinc reagents

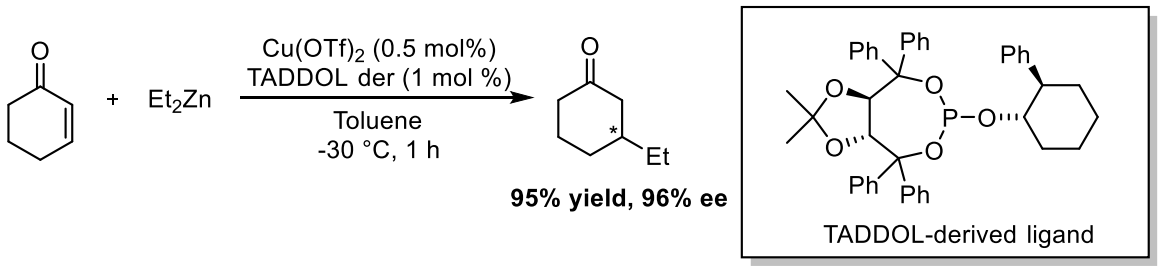
Over the last thirty years, several research groups have contributed to the investigation and improvement of the Cu-catalysed ACA with organozinc reagents to form tertiary centres. In this section, we will describe chronologically all advancements made, such as the range of cyclic acceptor used, copper source used in the reaction or the discovery of a new ligand inducing high enantioselectivity.

In 1993, Alexakis and co-workers introduced the first Cu-catalysed ACA using a dialkylzinc reagent with a cyclic acceptor.[29] Diethylzinc was added to 2-cyclohexen-1-one with CuI and a specific trivalent phosphorus ligand to afford the desired 1,4-product, 3-ethylcyclohexan-1-one in 70% yield and 32% ee (Scheme 1.12).



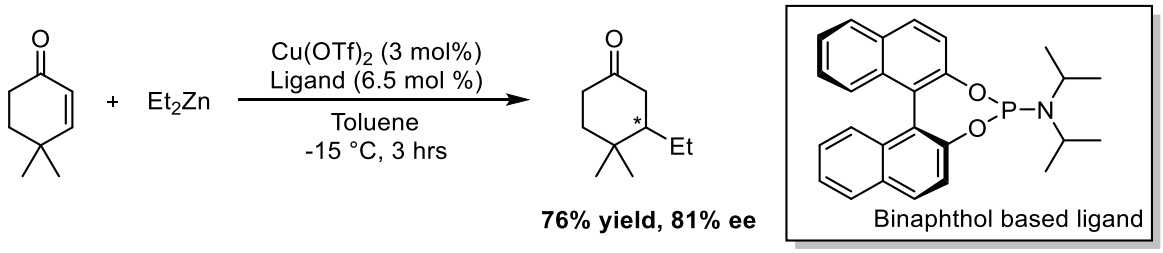
Scheme 1.12: The first reported Cu-catalysed ACA with a dialkylzinc reagent

Further investigations into this methodology revealed that the reaction time could by shortened either by replacing the copper source[30] or by switching the ligand with another trivalent phosphorus ligand.[31,32] Performing the Cu-catalysed ACA with $Cu(OTf)_2$ and a TADDOL-derived phosphorus ligand delivered in only 1 h the 1,4-adduct in 95% yield and 96% ee (Scheme 1.13).[33]



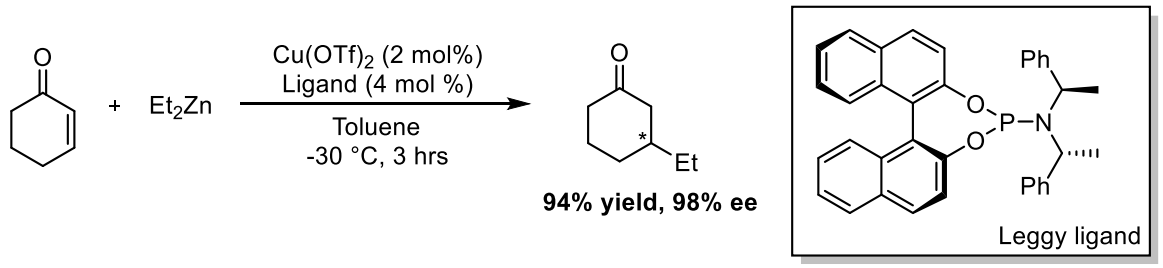
Scheme 1.13: Cu-catalysed ACA with a TADDOL-based phosphorus ligand

The Feringa group reported in 1996, a Cu-catalysed ACA to functionalised 6-membered cyclic enones using a novel BINOL-based phosphorus ligand (phosphoramidite ligand).[34] As an example, Et_2Zn was added to a substituted cyclic acceptor, 4,4-dimethylcyclohex-2-en-1-one with $Cu(OTf)_2$ to afford 3-ethyl-4,4-dimethylcyclohexan-1-one in 76% yield and 81% ee (Scheme 1.14).



Scheme 1.14: Cu-catalysed ACA using organozinc with a phosphoramidite ligand

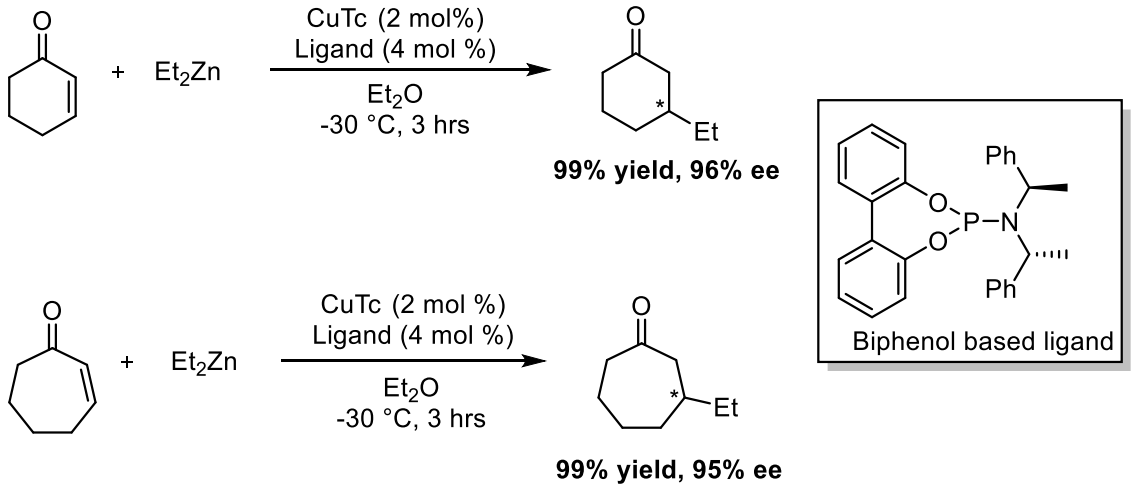
Investigation into the influence of phosphoramidite ligands in this system led to the discovery of a new phosphoramidite ligand, commonly known as Leggy's Ligand, which improved their previous results. Diethylzinc was added to 2-cyclohexen-1-one with $Cu(OTf)_2$ and Leggy's ligand to produce 3-ethylcyclohexan-1-one in 94% yield and 98% ee (Scheme 1.15).[35] Feringa and co-workers were able to obtain complete enantiocontrol for the addition of organozinc reagents to a variety of cyclic enones with this new phosphoramidite[17] and reported the first observation of a non-linear effect for the enantiomeric excess of the product compared to the enantiomeric excess of the ligand used in the Cu-catalysed asymmetric conjugate addition.[36]



Scheme 1.15: Cu-catalysed ACA using organozinc with Leggy's ligand

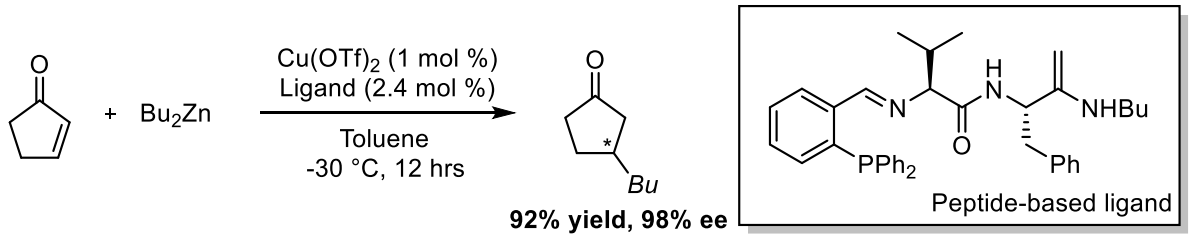
In 2002, Alexakis and co-workers improved the Cu-catalysed ACA system with the introduction of a new range of flexible biphenol ligands.[37] Investigation proved that their ACA system could tolerate a variety of different solvents such as toluene, DCM, THF, Et_2O and EtOAc which could solve problems of low solubility for some substrates. Furthermore, in this system, the commonly used copper triflate was replaced by a

cheaper source of copper carboxylates which showed that the Lewis acidity of the copper salt was not a significant factor in their reactions, in contrast to previous ACAs. The Alexakis group also showed that this newly developed system could be applied to a 7-membered cyclic enone. 3-Ethylcyclohexan-1-one and 3-ethylcycloheptan-1-one were synthesised with CuTc in respectively 99% yield and 96% ee and in 99% yield and 95% ee (Scheme 1.16).



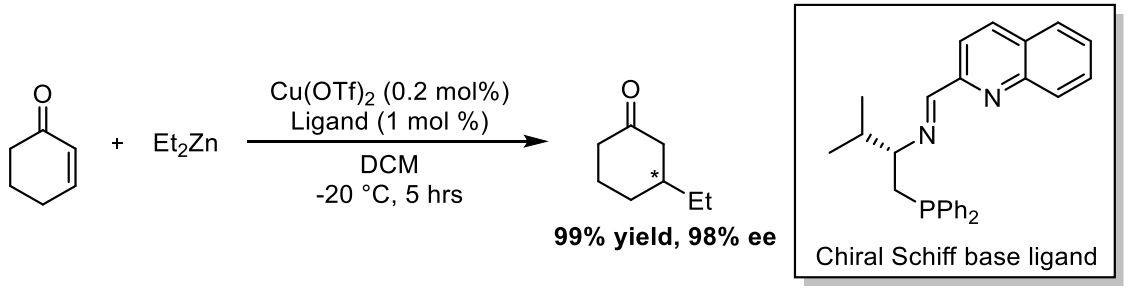
Scheme 1.16: Cu-catalysed ACAs using organozinc with a biphenol based ligand

Access to highly efficient and selective Cu-catalysed ACAs with more complex cyclic acceptors was also explored. The synthesis of a 5-membered ring 1,4-adduct was made possible by the work of Hoveyda's group.[25] Using a peptide-based chiral phosphine ligand and $Cu(OTf)_2$, 3-butyl-cyclopentan-1-one was synthesised in 92% yield and 98% ee (Scheme 1.17). The Cu-catalysed ACA to lactone was carried out by the Chan group which afforded an array of 1,4-products with an enantioselectivity up to 92% using a new complex peptide type ligand.[38]



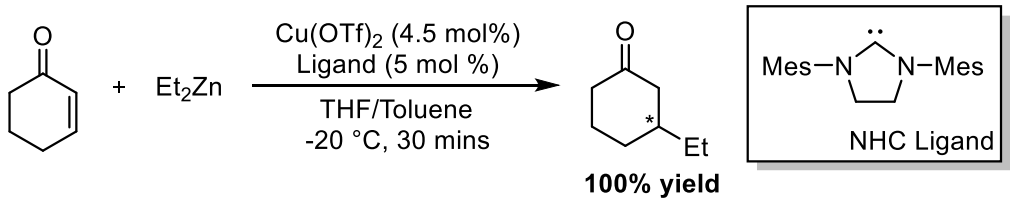
Scheme 1.17: Cu-catalysed ACA using organozinc with peptide-based ligand

Over the last decade, other research groups contributed to the Cu-catalysed ACA field by introducing new types of ligands. Hayashi and co-workers presented a chiral Schiff base type of ligand which promoted highly enantioselective 1,4-conjugate addition of dialkylzinc to cyclic enones.[23,24] For example, 3-ethylcyclohexan-1-one was synthesised with $Cu(OTf)_2$ in 99% yield and 98% ee (Scheme 1.18).



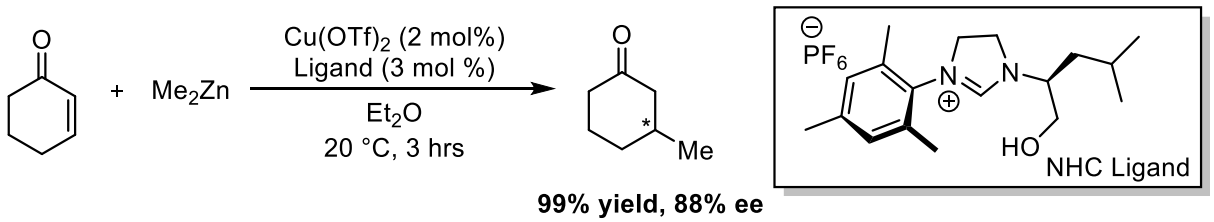
Scheme 1.18: Cu-catalysed ACA using organozinc with a chiral Schiff base based ligand

In 2001, Fraser and Woodward reported for the reaction of various enones with diethylzinc a strong ligand acceleration effect upon the addition of novel *N*-heterocyclic carbene (NHC) ligand type.[39] As an example, asymmetric addition to 3-ethylcyclohexan-1-one was accomplished in 100% yield in less than 30 mins (Scheme 1.19).



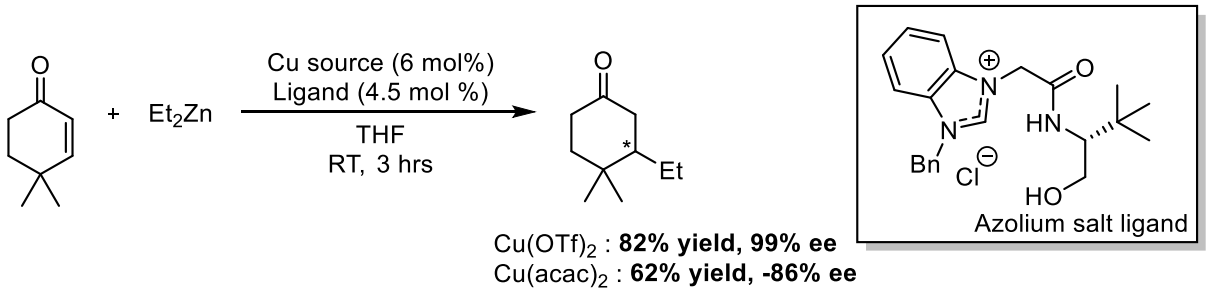
Scheme 1.19: Cu-catalysed conjugate addition using organozinc with an NHC ligand

Based on this concept, Mauduit and co-workers developed several chiral alkoxy NHC ligands which upon usage in Cu-catalysed ACAs promoted 1,4-adducts in high yield and high enantioselectivity at room temperature (Scheme 1.20).[22,40,41] NHC ligands are of significant importance in Cu-catalysed chemistry with organoaluminium.



Scheme 1.20: Cu-catalysed ACA using organozinc with NHC ligand

Finally, Sakagushi and co-workers reported a Cu-catalysed ACA with a chiral azolium salt as ligand, a ligand similar to NHC ligands.[42] The group observed a complete reversal of enantioselectivity by only changing the copper species employed. Reaction of diethylzinc to 4,4-dimethylcyclohex-2-en-1-one with $Cu(OTf)_2$ and a chiral azolium ligand afforded the corresponding optically active conjugate adduct in 82% yield and 99% ee whereas the reaction performed with $Cu(acac)_2$ instead of $Cu(OTf)_2$ led to a product with opposite configuration in 62% yield and 86% ee (Scheme 1.21).



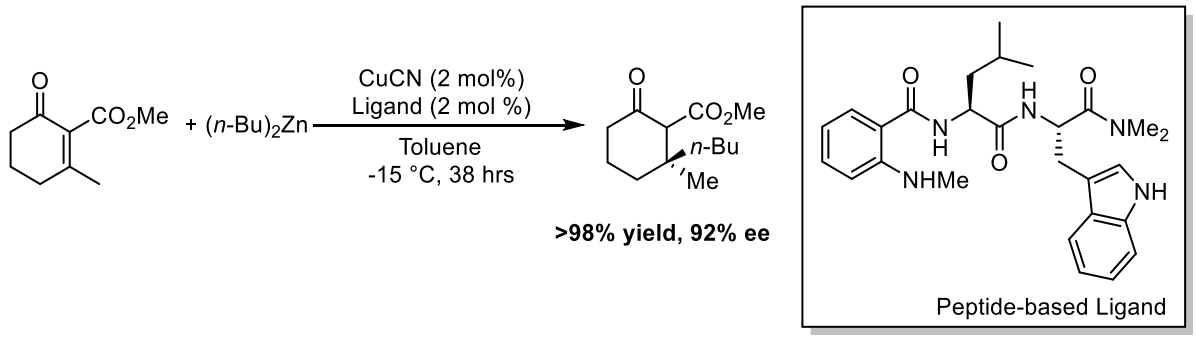
Scheme 1.21: Cu-catalysed ACA using organozinc with an azolium salt ligand

1.2 Cu-catalysed ACA for the construction of cyclic quaternary stereocentres

1.2.1 Cu-Catalysed ACA with dialkylzinc reagents

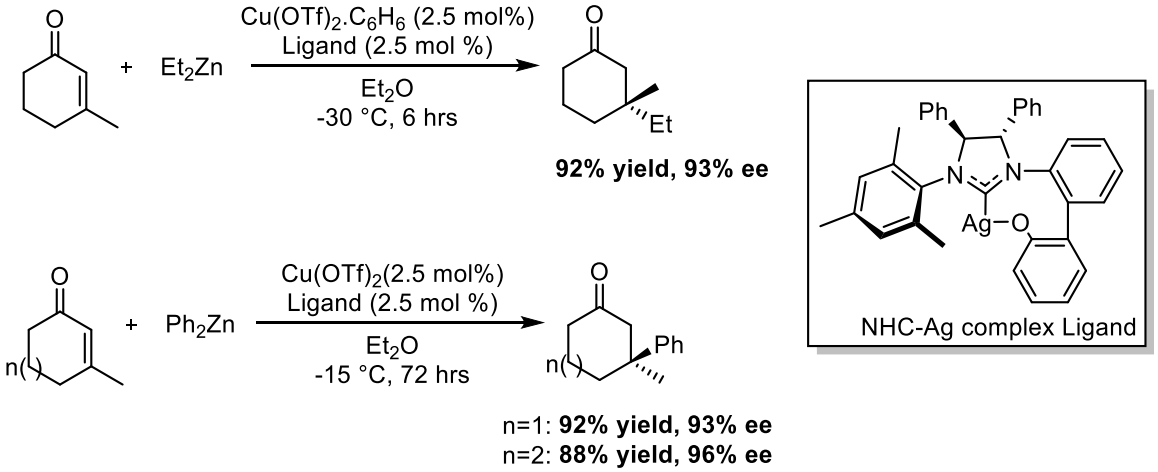
Quaternary stereocentres are found in many bioactive molecules and natural products.[43–45] Synthesising an enantioenriched all carbon quaternary centre is still considered a challenging mission in asymmetric catalysis and ACAs can be a highly effective method for forming those motifs.[46]

Dialkylzinc reagents were very popular in the copper-catalysed asymmetric conjugate addition to form tertiary stereocentres. However, their relatively low reactivity made their addition to unactivated trisubstituted cyclic enones very challenging.[47] Hoveyda and co-workers reported the first Cu-catalysed ACA with a broad variety of dialkylzincs to form cyclic quaternary stereocentres using an activated cyclic enone.[48] The increase in electrophilicity of the cyclic enone due to the presence of an ester group in the α-position of the ketone allowed the attack of dialkylzinc reagents. Addition of dibutylzinc to methyl 2-methyl-6-oxocyclohex-1-ene-1-carboxylate with CuCN and a peptide-based ligand afforded the 1,4-product in >98% yield and 92% ee (Scheme 1.22).



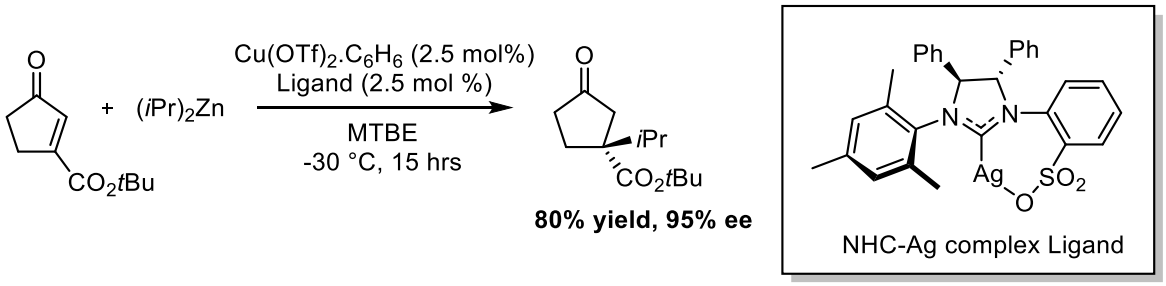
Scheme 1.22: Cu-catalysed ACA using organozinc to an activated enone

The first report of a Cu-catalysed ACA with dialkylzinc reagents on an unactivated β-substituted cyclic enone was also achieved by the Hoveyda group.[49] This achievement was allowed by the development of highly efficient NHC ligands. Dialkylzinc reagents such as diethylzinc were added to 3-methyl-cyclohex-1-one to afford product in high yield and high enantioselectivity (Scheme 1.23). Hoveyda and co-workers were also able to add diarylzinc reagents using this newly developed methodology which also worked for 7-membered ring cyclic enones (Scheme 1.23).[49]



Scheme 1.23: Cu-catalysed ACAs using organozinc to an unactivated enone

Interestingly, the Hoveyda group also investigated sterically congested but activated cyclic enones.[50] A variety of dialkylzinc reagents were added to cyclic γ-keto esters in high yield and high enantioselectivity. The Cu-catalysed ACA proceeded well with either 5- or 6-membered rings. As an example, diisopropylzinc reacted with tert-butyl 3-oxocyclopent-1-ene-1-carboxylate and delivered the desired product in 80% yield and 95% ee (Scheme 1.24).

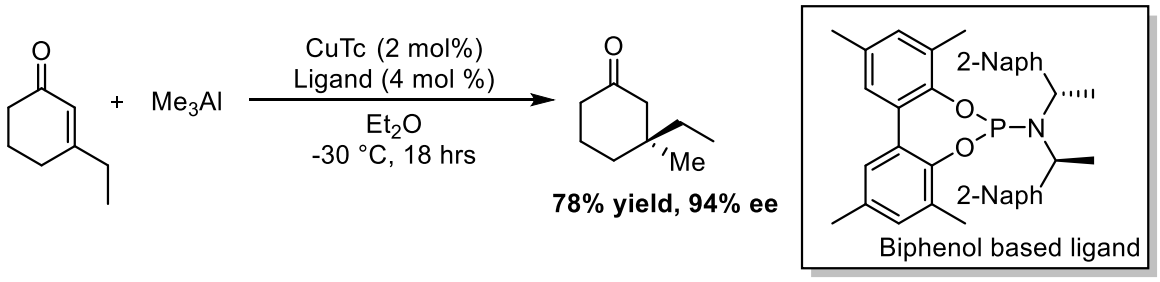


Scheme 1.24: Cu-catalysed ACA using organozinc to a cyclic γ-keto ester enone

1.2.2 Cu-Catalysed ACA with alkylaluminium reagents

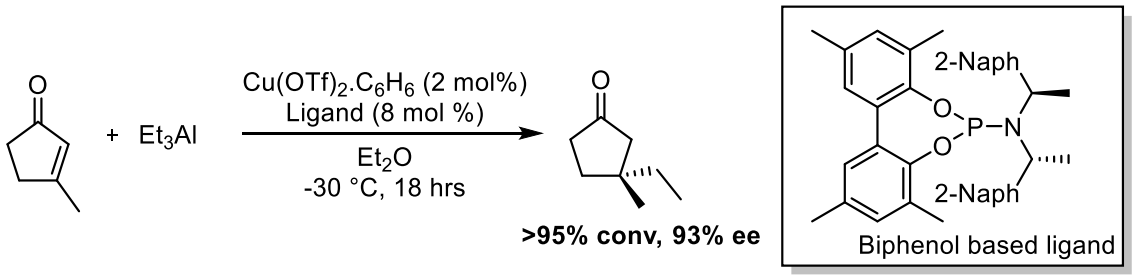
Copper-catalysed ACAs with zinc reagents to form quaternary stereocentres are difficult to perform without initial activation of the cyclic enone or using a specific highly efficient NHC ligand. Aluminium reagents are stronger Lewis-acids than zinc reagents and can coordinate to the oxygen of the enone. Performing the Cu-catalysed ACA with organoaluminium reagents, thus creating a more electrophilic coordinated cyclic enone, could allow an easier generation of stereogenic quaternary centres.

The Alexakis group reported in 2005, the first Cu-catalysed asymmetric conjugate addition to construct cyclic quaternary centres with 3-substituted cyclohexenones and trialkylaluminium reagents.[18,51] Using a biphenol type ligand and CuTc, methyl and ethyl groups could be added to a variety of cyclic hexenones in good yields and high enantioselectivity. For example, trimethylaluminium was added to 3-ethylcyclohex-2-en-1-one to afford the 1,4-adduct in 78% yield and 94% ee (Scheme 1.25).



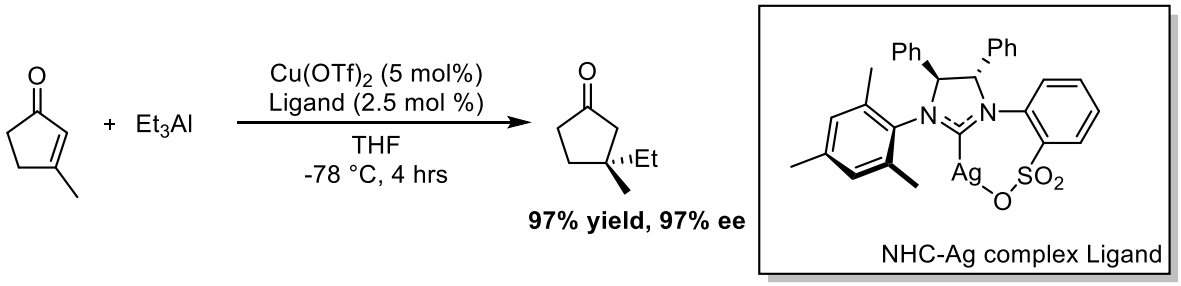
Scheme 1.25: Cu-catalysed ACA using trialkylaluminium to access quaternary stereocentres

Alexakis and Hoveyda groups both studied the Cu-catalysed ACA to five-membered rings. With the same biphenol type ligand and $Cu(OTf)_2.C_6H_6$ as the copper salt, Alexakis and co-workers were able to successfully introduce an ethyl group to 3-methyl-cyclopent-2-ene with high enantioselectivity up to 93% ee (Scheme 1.26).[52]



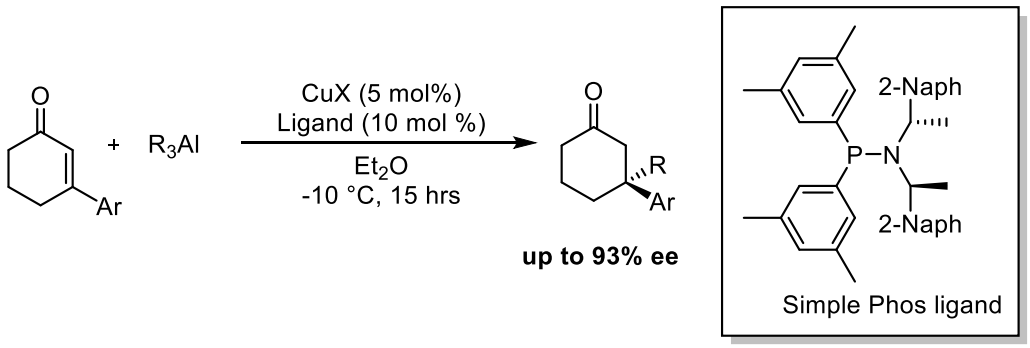
Scheme 1.26: Cu-catalysed ACA using triethylaluminium to a 5-membered ring enone

Hoveyda and co-workers obtained a similar 1,4-product with slightly higher enantiomeric excess using NHC ligands.[53] As an example, triethylaluminium was added to 3-methyl-cyclopent-2-en-1-one with $Cu(OTf)_2$ to afford (*R*)-3-ethyl-3-methylcyclopentan-1-one in 97% yield and 97% ee (Scheme 1.27). The Hoveyda group also broadened the scope of 1,4-products synthesised using this methodology. An array of 3-substituted cyclopentenones, as well as cyclohexenones and cycloheptenones were subjected to those conditions using an NHC ligand and produced 1,4-adducts in high enantioselectivity.[53]



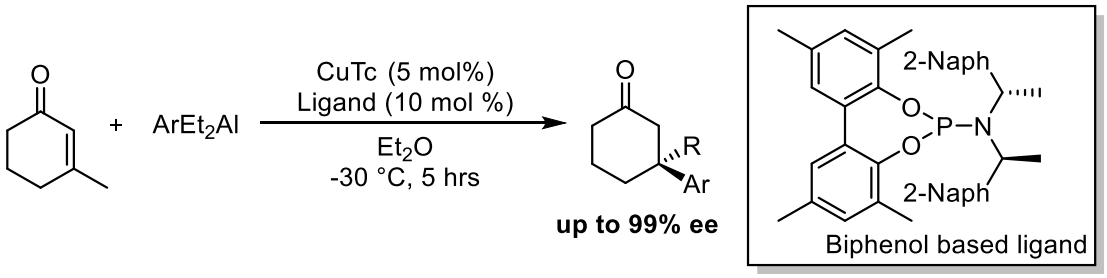
Scheme 1.27: Cu-catalysed ACA with a 5-membered ring enone using NHC ligand

Hoveyda and Alexakis then turned their attention to generating quaternary stereocentres bearing an aromatic group. Two different approaches were investigated. Either performing the Cu-catalysed ACA with cyclic enones bearing an aromatic moiety on the 3-position or introducing the aryl function using arylaluminium reagents. Alexakis and co-workers first reported, despite steric and electronic effects, the copper-catalysed ACA of trialkylaluminium to aromatic 3-cyclohex-2-en-1-ones using SimplePhos ligand with good to high enantioselectivity up to 93% ee (Scheme 1.28).[54]



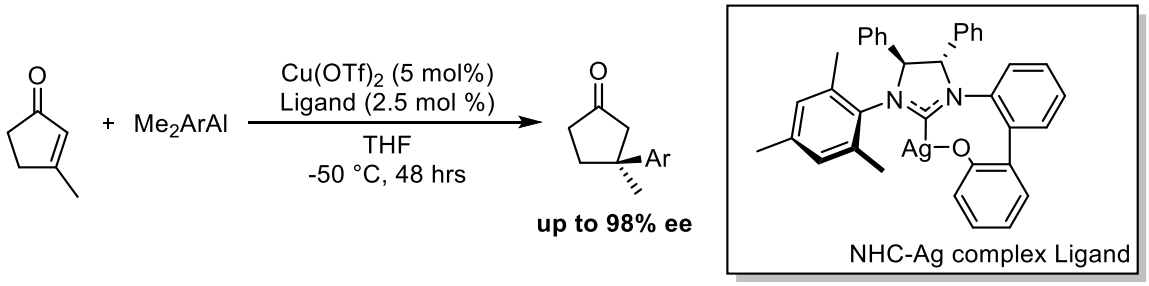
Scheme 1.28: Cu-catalysed ACA of an aromatic substituted cyclic enone

The Alexakis group then focused on the addition of monoaryldialkylaluminium reagents and were able to successfully add a variety of aryl moieties to different cyclic enones using CuTc and a biphenol based ligand with high enantioselectivity up to 99% ee (Scheme 1.29).[17,55] Reduced enantioselectivity was observed with five-membered ring enones using the newly developed system.



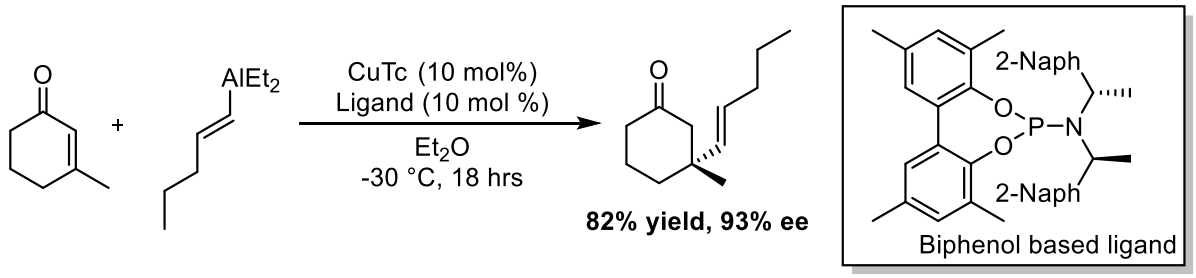
Scheme 1.29: Cu-catalysed ACA of arylaluminium reagents

Hoveyda and co-workers were able to successfully perform Cu-catalysed ACAs on 3-substituted cyclopentenones with an array of arylaluminium reagents and obtain 1,4-products in high enantioselectivity up to 98% (Scheme 1.30).[53] Once again, the combined use of an NHC ligand and a copper source gave tremendous results.



Scheme 1.30: Cu-catalysed ACA of arylaluminium reagents to 5-membered ring enone

Finally, the Alexakis group reported the Cu-catalysed ACA of alkenyl alane to a cyclic enone.[56,57] For example, (E)-diethyl(pent-1-en-1-yl)aluminium was added to 3-methylcyclohex-2-en-1-one using a combination of CuTc and a biphenol type ligand to afford the desired product in 82% yield and 93% ee (Scheme 1.31).

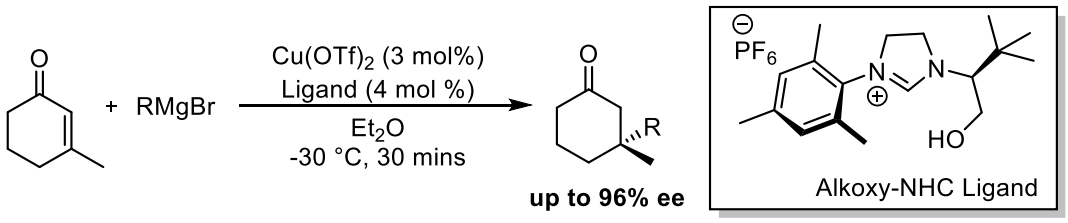


Scheme 1.31: Cu-catalysed ACA using alkenyl alane

The formation of quaternary centres bearing either an aromatic moiety or an alkene function is of particular interest as further chemistry can be performed on those particular functions, contrary to simple inert alkyl functions.

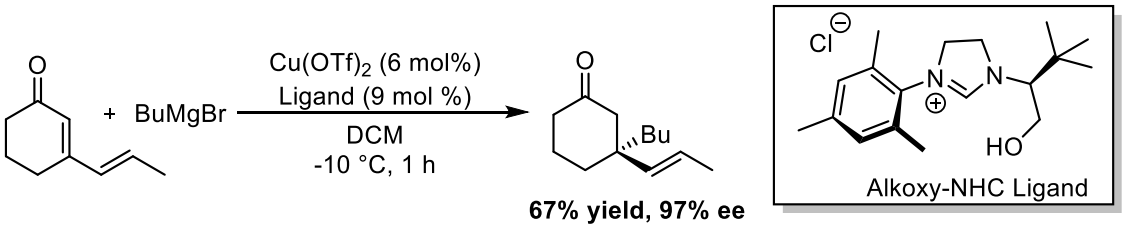
1.2.3 Cu-Catalysed ACA with Grignard reagents

Grignard reagents are easily prepared, widely commercially available and are highly reactive.[58] Alexakis and Mauduit discovered that Grignard reagents combined with NHC ligands afforded 1,4-adducts in very good yield and high enantioselectivity up to 96% ee (Scheme 1.32).[15,59] However, Cu-catalysed ACAs performed using phosphoramidites or ferrocene-based ligands were inefficient with Grignard reagents.[60]



Scheme 1.32: Cu-catalysed ACA using Grignard reagents

Interestingly, Alexakis and co-workers found that cyclic dienones subjected to the same catalytic methodology selectively afforded the 1,4-adduct and thus creating allylic quaternary centres in excellent enantioselectivity up to 97% ee (Scheme 1.33).[61]



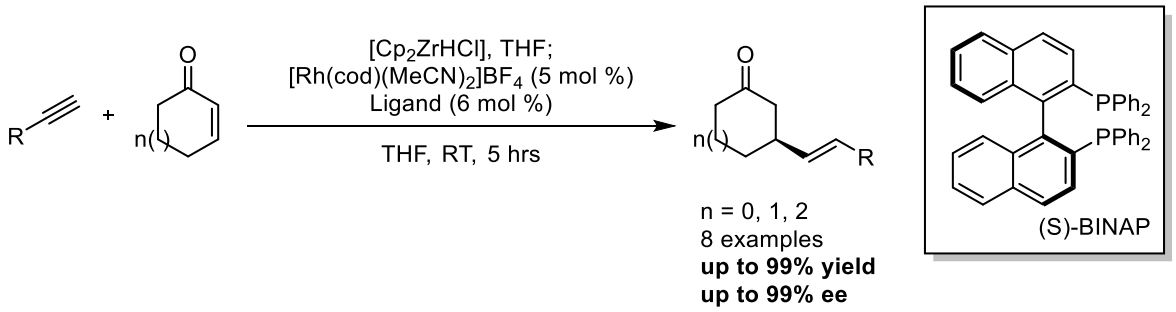
Scheme 1.33: Cu-catalysed ACA to a cyclic dienones

Tomioka and co-workers also worked on Cu-catalysed ACA with Grignard reagents.[62] Using NHC-ligands as well, they tried to broaden the scope of the system by investigating a variety of alkyl Grignard reagents and even looked at aryl Grignard reagents. Unfortunately, this methodology proved to be limited with only moderate to good enantioselectivity observed.

For the formation of quaternary stereocentres, aluminium reagents proved to be better suited in Cu-catalysed ACA, while organozinc reagents gave better results for the formation of tertiary centres.

1.3 Cu-catalysed ACA with alkylzirconium reagents

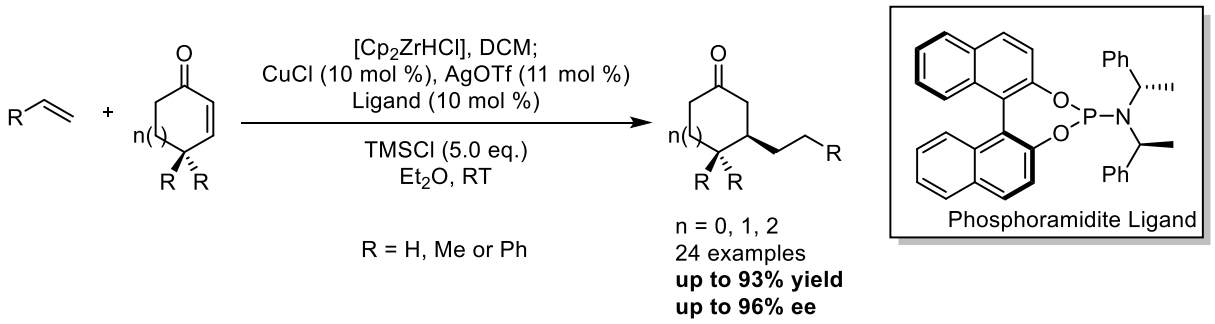
Oi and Inoue reported in 2004, a Rhodium-catalysed ACA of non-functionalised linear alkenes to cyclic enones using alkenylzirconocenes and BINAP.[63] The vinylzirconium species were generated *in situ* by hydrometalation of alkynes with Schwartz's reagent.[64] The system tolerated different sized cyclic enones and afforded 1,4-products in good to high yield and high enantioselectivity up to 99% ee (Scheme 1.34). Despite limited scope, Oi and Inoue introduced a new variety of nucleophiles for an ACA procedure. Indeed, zirconocenes reagents can easily be made from readily available olefins and tolerate a larger variety of functional groups compared to Grignard reagents, organozincs species and organoaluminium reagents.



Scheme 1.34: Rh-catalysed ACAs using organozirconium reagents

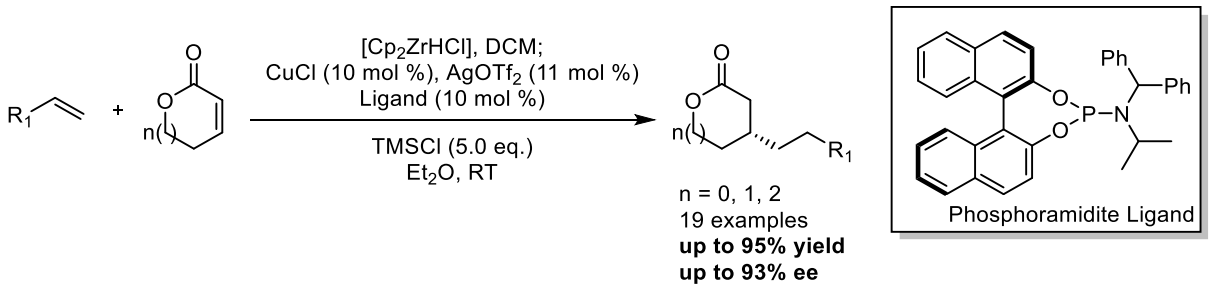
In 2012, based on the pioneering work of Wipf and co-workers,[65] the Fletcher group reported the first copper-catalysed asymmetric addition using organozirconium reagents.[66,67] An array of terminal alkenes, with different functional groups such as alkyl, aromatic rings, protected alcohol or halides, upon hydrozirconation underwent ACAs to cyclic enones with CuOTf, the phosphoramidite Leggy's ligand[20] and TMSCl. This system could be applied to 5-, 6- and 7-membered cyclic enones and delivered 24 examples of 1,4-adducts bearing tertiary generated stereocentres in good yield and high enantioselectivity up to 96% ee (Scheme 1.35).[67] The newly developed zirconium catalysed ACA was even applied to more complex molecules. Specific terminal

alkenes were then added to steroids allowing the synthesis of a natural product isolated from *Balantiopsis rosea*.[68]



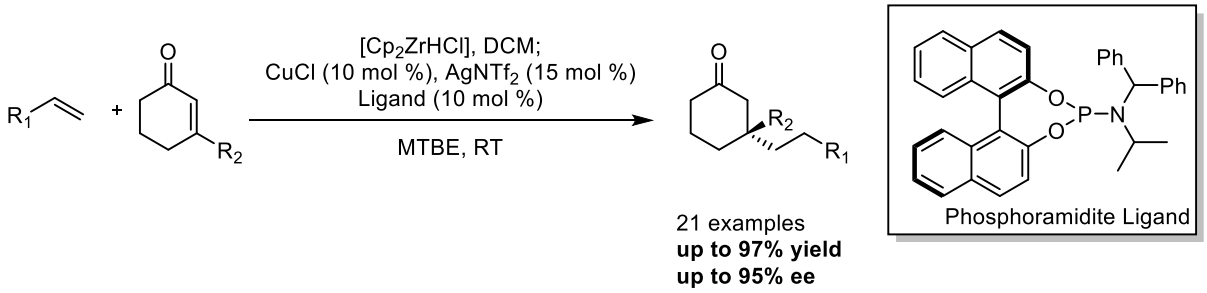
Scheme 1.35: Cu-catalysed ACAs using organozirconium reagents

In 2014, Fletcher and co-workers expended this newly developed methodology to different sized cyclic lactones.[69] 19 examples of 1,4-products bearing tertiary stereocentres were synthesised in high yield and high enantioselectivity up to 93% ee (Scheme 1.36). In this case, Leggy's ligand was replaced by another phosphoramidite commonly called Phil's ligand.



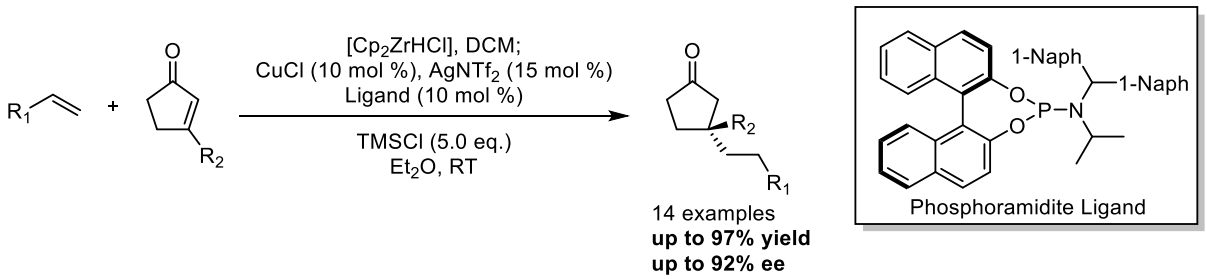
Scheme 1.36: Cu-catalysed ACA to cyclic lactones

The Fletcher group then focused on synthesising 1,4-products bearing a quaternary stereocentre using 3-substituted cyclic hexenones.[70,71] Removal of the TMSCl additive and changing CuOTf to copper triflimide ($Cu(NTf_2)$) allowed the generation of 21 successful examples in high yield and high enantioselectivity up to 95% ee (Scheme 1.37).



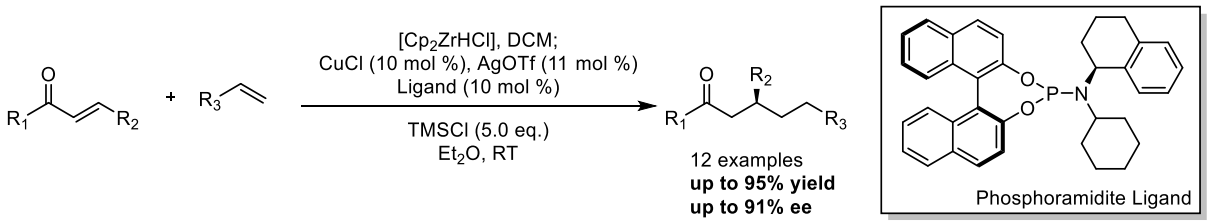
Scheme 1.37: Cu-catalysed ACA to generate quaternary stereocentres

In 2017, Fletcher and co-workers were able to overcome the difficult problem of constructing a quaternary stereocentre in five-membered cyclic enones using a more enantioselective phosphoramidite.[72] Computational analysis of ligand screening data revealed the importance of electronic and steric requirements for the reaction and led to the synthesis of specific type of phosphoramidites. 14 examples of 1,4-products were synthesised in yield up to 97% and enantioselectivity up to 92% (Scheme 1.38).



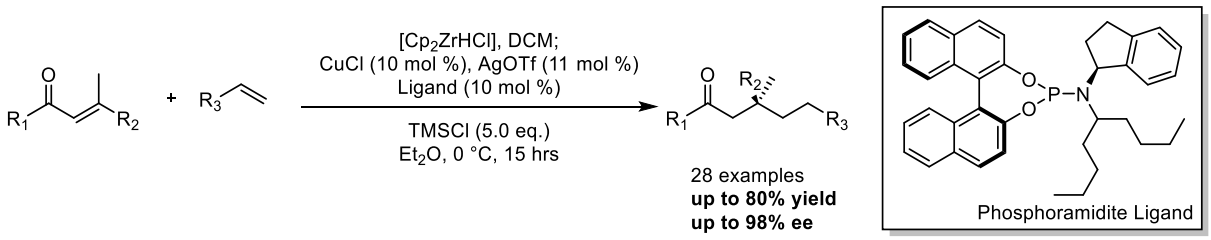
Scheme 1.38: Cu-catalysed ACA with five-membered ring enones

Fletcher and co-workers also investigated Cu-catalysed ACAs on acyclic enones.[73] A variety of functionalised nucleophiles were added to mono 3-substituted acyclic enones using CuOTf, a specific phosphoramidite and TMSCl and delivered 12 different examples of 1,4-adducts bearing a tertiary stereocentre in high yield up to 95% and high enantioselectivity up to 91% ee (Scheme 1.39).



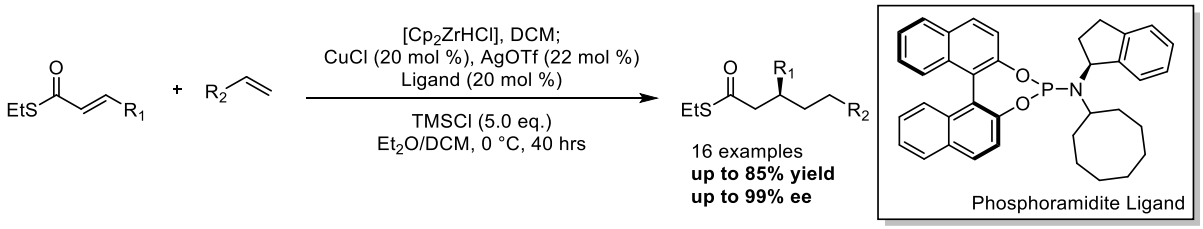
Scheme 1.39: Cu-catalysed ACA on acyclic enones

The scope of this system was then extended to acyclic 1,4-products with quaternary generated stereocentres.[74] In order to perform the reaction it was necessary to replace the ligand with another specific phosphoramidite commonly called Zhenbo's ligand and stir the reaction at 0 °C. 28 examples were synthesised in good yield and high enantioselectivity up to 98% ee (Scheme 1.40).



Scheme 1.40: Cu-catalysed ACA on substituted acyclic enones

Finally, the Fletcher group investigated the Cu-catalysed asymmetric conjugate addition of alkylzirconium reagents to α,β-unsaturated thioesters.[75] 16 examples of 1,4-adducts were delivered in high yield and high enantioselectivity up to 99% ee (Scheme 1.41).



Scheme 1.41: Cu-catalysed ACA on substituted acyclic thioesters.

The Fletcher group has been able to develop since 2012 a new copper-catalysed asymmetric conjugate addition methodology using hydrozirconated alkenes with a variety of different electrophiles to generate cyclic or acyclic 1,4-adducts bearing either a tertiary or a quaternary stereocentre.

Chapter 2

2 Enantioselective Synthesis of Taxadiene

2.1 Introduction

This introduction will describe Phil Baran's work on enantioselective total synthesis of taxanes[76–78] since it was a major source of inspiration for this first project.

2.1.1 Terpenes and the history of Taxol

Natural products and their synthetic derivatives are of immense interest in medicinal chemistry.[79] Their structural diversity is an inspiration for the investigation of synthetic paths to access new structures and they have been recognised as a major source of new drugs and new drug leads.[79] Indeed, more than half of the antitumor therapeutic agents commercially available or in late stages of clinical trials nowadays, are of natural origin.[80] At present time, cancer continues to be one of the major causes of death worldwide[81] and the discovery of drugs for its treatment is a vital part in the research and development sector.[82] Numerous drugs approved for use in cancer therapy are derived from plants,[83,84] including terpenes.

Terpenes have generated interest from the research community for a long time. Indeed, efforts into the isolation, structural elucidation and synthetic studies of terpenes have been conducted for well over a hundred years.[85] Their applications include flavours, fragrances, hormones, poisons and medicines.[85–87] Terpenes are composed of isoprene units. Classification of terpene natural products can be made by the number of building blocks present in a molecule.[85] Geraniol and Limonene are

examples of monoterpenes that are composed of two isoprene units, Farnesol belongs to sesquiterpenes whereas Taxadiene and Retinol are examples of diterpenes composed of four building blocks (Figure 2.1).

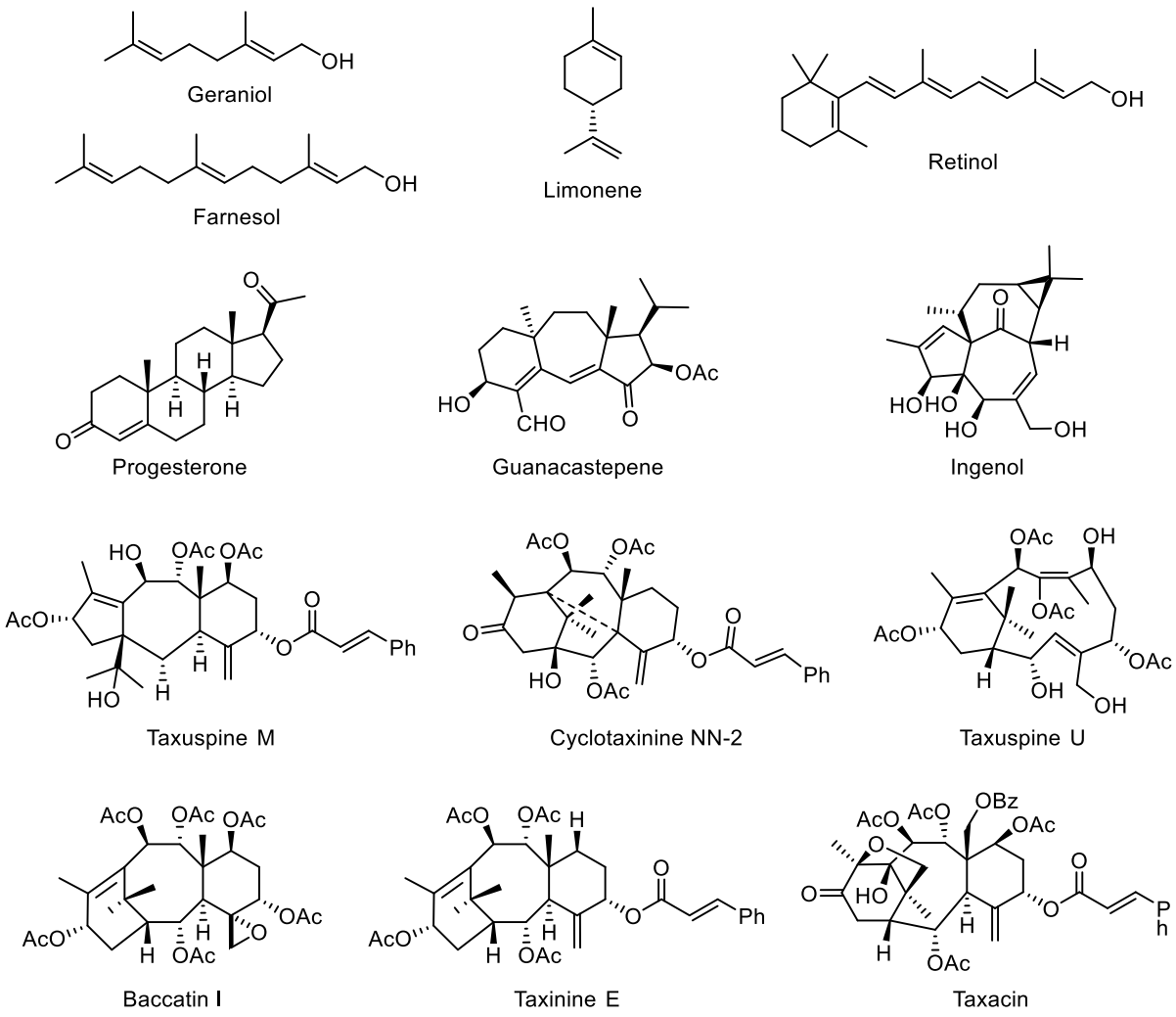
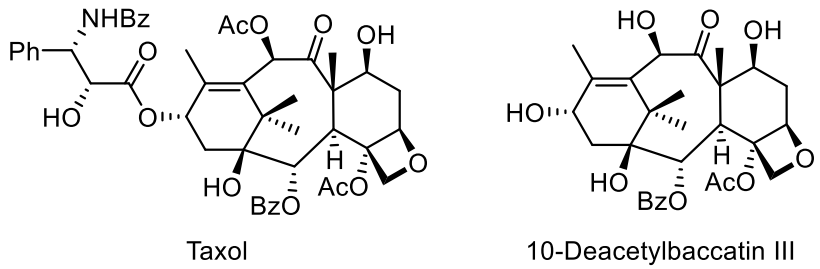


Figure 2.1: Examples of diterpenes and taxanes

Terpenes may show very different structures going from acyclic molecules to molecules bearing several rings of different sizes (Figure 2.1: Progesterone, Guanacastepene and Ingenol).[85,86] Amongst the diterpenes, taxanes are one of the most important family of over 350 natural products.[88–95] Taxanes typically feature the 6/8/6-membered ring system (Figure 2.1: Baccatin I, Taxinine E and Taxacin). Taxane derivatives differ by a change in the ring system. For example, Taxuspine M is

composed of a 5/7/6-membered ring system, Cyclotaxinine NN-2 has a 6/5/5/6-membered ring system and Taxuspine U is composed of 6/12-membered ring system (Figure 2.1). Amongst the taxane family, Taxol or Paclitaxel is probably the most famous (Figure 2.2).



Taxol 10-Deacetylbaccatin III

Figure 2.2: Taxol and its derivative 10-Deacetylbaccatin III

Taxol is a successful anticancer drug that was originally used for the treatment of ovarian and breast cancer.[96,97] Currently, Taxol is also used for the treatment of liver, lung and other types of cancer.[98,99] Its mechanism of action involves the stabilisation of microtubules.[100]

Taxol has fascinated the research community for many years. Wani and co-workers isolated Taxol from the bark of the Pacific yew tree, *Taxus brevifolia*, and described its structure for the first time in 1971.[101] However the isolation procedure is difficult, low-yielding and unsustainable.

In the late 1980s and early 1990s, research groups focused on the development of semi-synthetic pathways towards Taxol in order to prevent any over-exploitation of the yew tree and threat on the future supply of the anticancer drug. 10-Deacetylbaccatin III was easily extracted in high yield from the leaves, which can quickly regenerate, of *Taxus baccata* (Figure 2.2).[102] The large amount of 10-Deacetylbaccatin III collected was then further transformed into the desired Taxol in a few steps.[102,103]

The total synthesis of Taxol was one of the most anticipated and contested natural product syntheses in the 1990s. More than thirty research groups attempted to synthesise Taxol. Only seven groups reported the total synthesis of Taxol[104–112] while three other research groups reported its formal synthesis.[113–116] The race towards the first total synthesis ended in a tie, where the Holton group had their article first accepted for publication[105,107] but the Nicolaou group had their article published first.[106]

2.1.2 Baran's approach towards the synthesis of taxanes

Despite numerous total syntheses, the synthesis of Taxol still involved elaborate routes that require between 35 and 51 steps,[104–112] and the combined amount of man-made Taxol is less than 30 mg. Currently, the anticancer drug is manufactured using a cell-culture technology which can produce Taxol on a ton scale. Although an improvement of the chemical production of Taxol will probably never surpass current biological production, Baran proposed that a re-examination of the anticancer drug chemical synthesis could be of academic and medicinal value.

Baran chose to mimic the two-phase process for the biosynthesis of terpenes.[117] The first phase is the cyclase phase, which is composed of (i) coupling together building blocks of isopentenyl pyrophosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP) and (ii) possible cyclisations and rearrangements controlled by different enzymes. The second phase is the oxidase phase, which consists of the oxidation of alkenes and C-H bonds (Figure 2.3 top). In order to chemically mimic the two-phase process, the synthesis of taxanes would be separated in two parts.[86] First, the artificial "cyclase phase" represents the synthesis of the carbon core of any taxane molecules and, second, the artificial "oxidase phase" describes the submission of the

carbon skeleton to a series of regioselective and chemoselective oxidations (Figure 2.3, bottom).

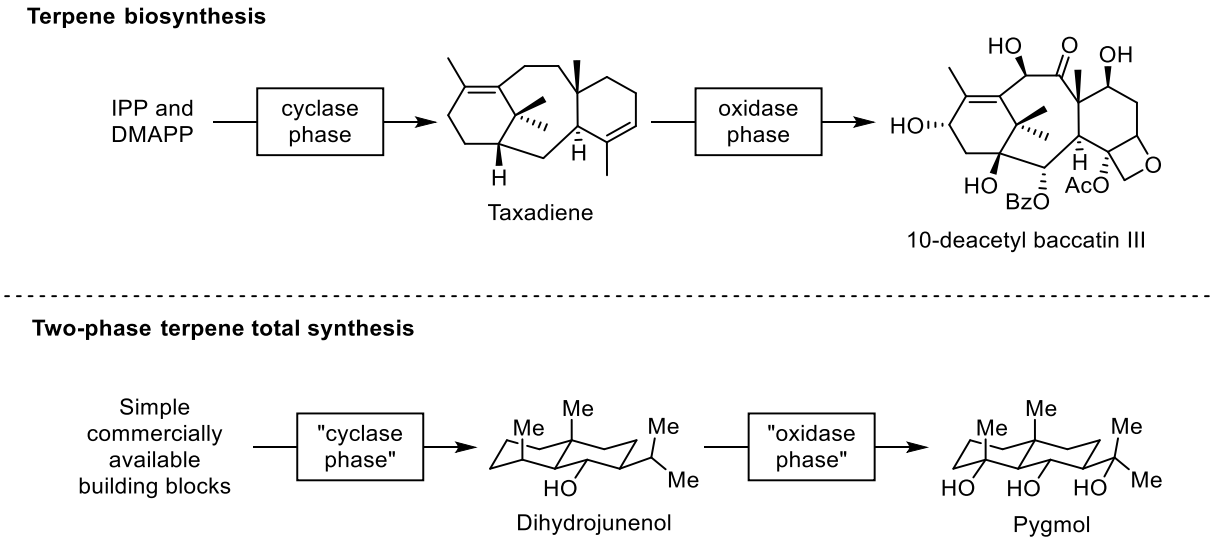


Figure 2.3: Outline of the “two-phase” approach to terpene total synthesis

The major interest of mimicking the two-phase process is to get a faster and easier access to Taxol and its analogues by divergent synthesis compared to the normal means of total synthesis. Indeed, oxidising the Taxol core at different stages will afford a variety of different compounds from the taxane pyramid (Figure 2.4).[118,119]

The biosynthesis of Taxol is thought to involve the coupling of IPPs and DMAPPs into geranylgeranyl diphosphate followed by a selective cyclisation to deliver the Taxol core, Taxadiene, nature’s cyclase phase terminal point.[120] The first access to large amounts of Taxadiene was reported by Stephanopoulos in 2010 using a bioengineering system.[121]

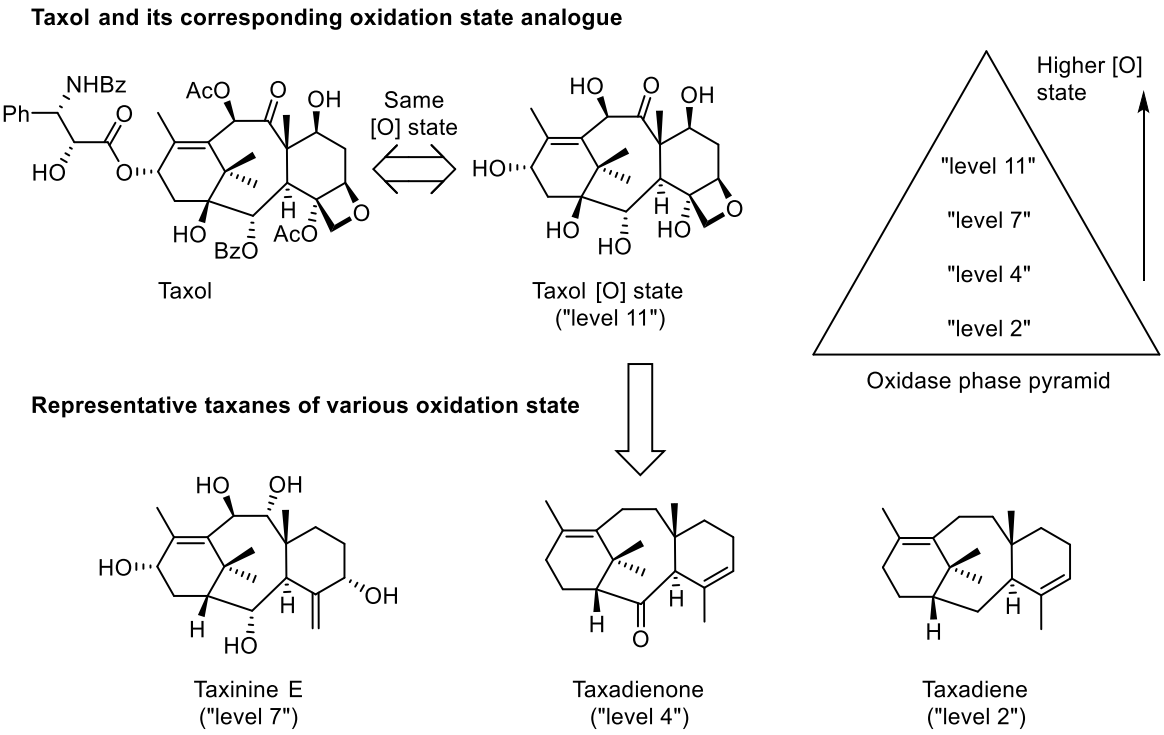


Figure 2.4: Taxol and other members of taxane family: [O] state

Baran and co-workers reported in 2012 the first scalable synthetic entry to the taxane family with rapid access to Taxadiene and minimally oxidised taxane analogues.[78] Baran thoroughly investigated the taxane framework that different research groups carried out over the years[122–128] with the aim to synthesise Taxadiene in a short, convergent and scalable route. He then designed specific disconnections of Taxadienone where its asymmetry would rely on a single enantioselective step and the formation of the AB ring system would depend on a vicinal difunctionalisation/Diels-Alder strategy (Figure 2.5).

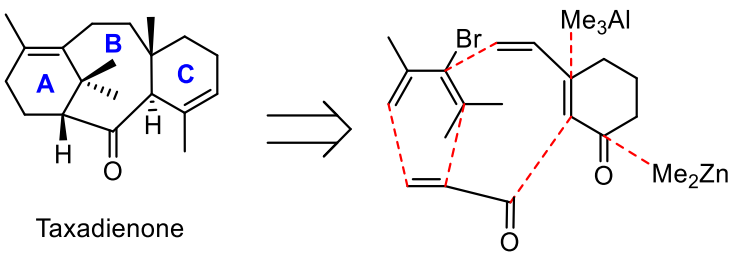
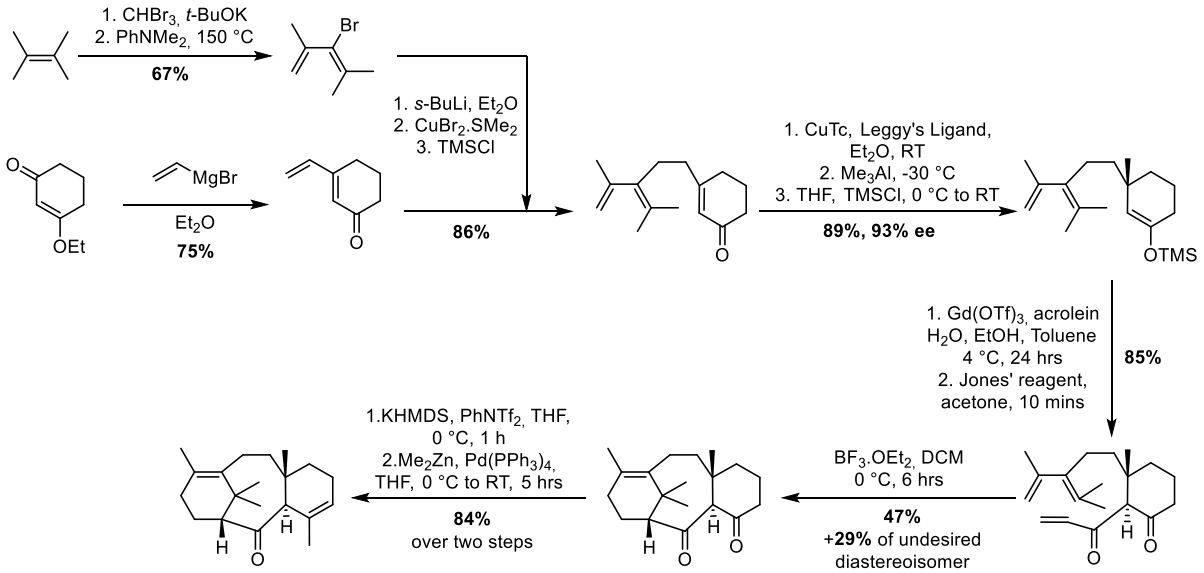


Figure 2.5: Disconnections of Taxadienone

Starting from 2,3-dimethyl-2-butene and 3-ethoxy-2-cyclohexen-1-one, Baran and co-workers were able to enantioselectively synthesise Taxadienone in seven steps on a gram-scale (Scheme 2.1).



Scheme 2.1: Baran's enantioselective synthesis of Taxadienone

Baran's synthesis can be highlighted in three key steps. The first step is the formation of the stereogenic quaternary centre using Alexakis' Cu-catalysed ACA methodology with trimethylaluminium.[18] The last steps are first a Mukaiyama aldol reaction[129] using $Gd(OTf)_3$ followed by a Diels-Alder reaction to generate the 6/8/6 tricyclic skeleton.[122–128]

Taxadienone was synthesise by the Baran research group over the course of seven days with an overall yield of 18% from the alkene starting material or 20% from the enone starting material.

From Taxadienone, three additional reactions led to the gram-scale synthesis of the Taxol core, Taxadiene with an overall yield of 53% (Scheme 2.2). The previous and only other total synthesis of Taxadiene was achieved by Williams in 1995 in 26 steps.[122]

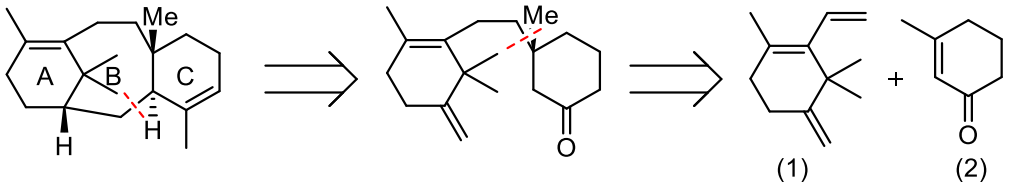
Scheme 2.2: Synthesis of Taxadiene in 3 steps from Taxadienone

With this new scalable enantioselective synthesis of simple oxidised taxanes, Baran and co-workers introduced a novel and unique way to potentially access natural products and anticancer drugs.

2.2 Project aims

Taxadiene is composed of three fused rings labelled A, B and C. One of the key steps for synthesising Taxadiene or Taxadienone is the formation of the stereocentre between rings B and C containing a methyl moiety. As previously stated, Baran showed that it was possible to access complex scaffolds using a late stage asymmetrisation strategy. He introduced the stereocentre using Alexakis' asymmetric Cu-catalysed 1,4-addition of a methyl group to ring C.[78] Our aim – since Alexakis' methodology is limited to simple alkyl units – was to perform a similar key strategy to access the Taxol core with functionalised complex nucleophiles using the ACA methodology developed in our group.[70]

A simple retrosynthesis of Taxadiene gave two starting materials: a depicted cyclic trialkene **1** and the commercially available 3-methylcyclohex-2-en-1-one **2**, respectively representing ring A and ring C (Scheme 2.3). Our projected route consisted of first coupling ring A and C by an asymmetric 1,4-addition giving the desired stereocentre and then closing ring B by oxidative cyclisation.



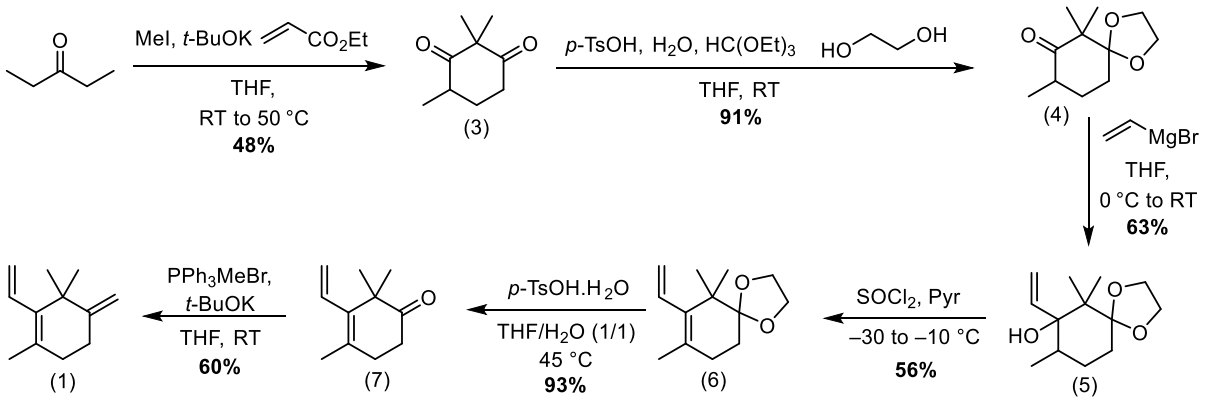
Scheme 2.3: Retrosynthesis of Taxadiene

Therefore, the main goals of this work were to: (a) synthesise the cyclic trialkene **1**, (b) develop a catalytic asymmetric 1,4 conjugate addition strategy and form ring B to access the Taxol core, (c) optimise key steps for yield/enantioselectivity and scaled up to gram-scale and (d) finally explore biocatalytic/electrochemical oxidation routes to access more complex derivatives of Taxadiene.

2.3 Results and discussion

2.3.1 Synthesis of trialkene 1

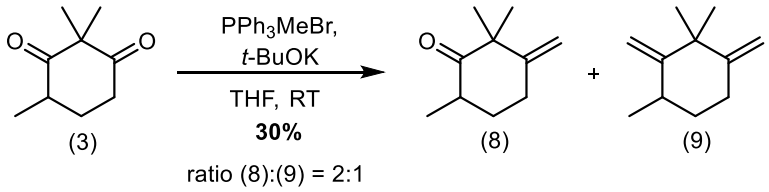
Trialkene **1** was synthesised in a six-step route with an overall yield of 9% (Scheme 2.4). Starting from pentan-3-one and ethyl acrylate, the cyclic diketone intermediate **3** was synthesised several times with an average yield of 48%, 50% being the best result obtained.[130] The less hindered ketone was then protected with uniformly high yield (89-98%). Addition of vinyl magnesium bromide on the non-protected ketone led to intermediate **5** with an average yield of 63%.[131,132] Dehydration using $SOCl_2$ provided the dialkene intermediate **6** in 56% average yield, 78% being the best result obtained.[133] Deprotection of the ketone gave **7** in 93% yield and finally the cyclic trialkene **1** was obtained with an average yield of 60% using a Wittig reaction.[134,135]



Scheme 2.4: Synthesis of trialkene **1**

The synthesis was performed several times on a large scale, and we obtained between 0.8 and 1.2 g of **1**.

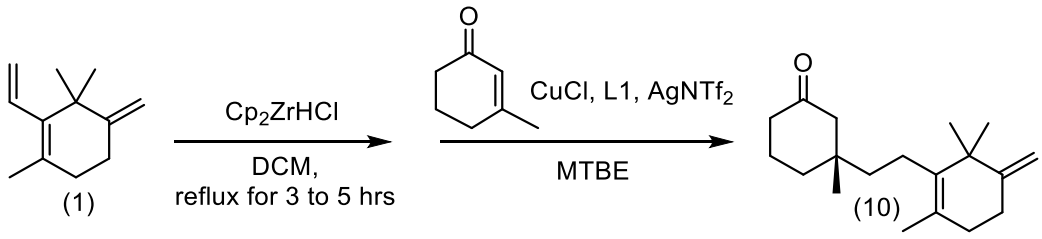
In order to access the desired cyclic trialkene **1** faster, we tried a selective Wittig reaction on diketone **3**. Unfortunately, we did not obtain the same regioselectivity observed during the protection step and obtained a mixture of both alkene **8** and dialkene **9** products. The best yield we obtained for the mono-alkene product **8** was 20% and therefore we abandoned this idea.



Scheme 2.5: Selective Wittig reaction

2.3.2 Asymmetric 1,4-conjugate additions

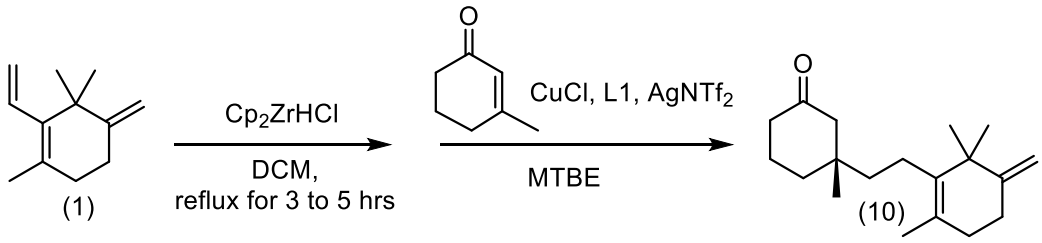
Based on previous experiences in the Fletcher group,[70] preliminary investigations were made in the asymmetric 1,4-addition of trialkene **1** to 3-methylcyclohex-2-enone **2** with $CuNTf_2$ and phosphoramidite ligand **L1** developed within the group (Scheme 2.6). This methodology can be described as a three-step process where alkenes are first activated by hydrozirconation, then mixed with the catalyst system before addition to the enone.



Scheme 2.6: Asymmetric 1,4-conjugated addition of cyclic trialkene **1**

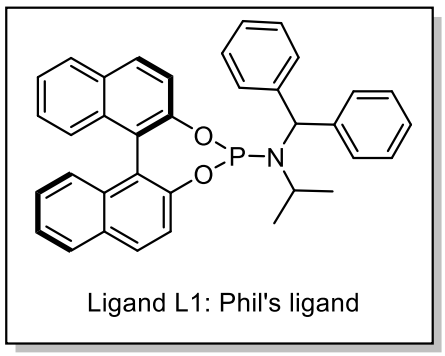
Many examples of alkenes have been tried out in the asymmetric conjugate 1,4-addition investigated in the Fletcher group,[70] but none of them are as complex as this cyclic trialkene. The starting material **1** bears two alkenes which could both undergo hydrometallation/ACA. The complexity of this fragment is probably the reason why we experienced difficulties to hydrozirconate the cyclic trialkene **1**, while simpler alkenes react easily with Schwartz reagent in less than 1 h in DCM. In order to perform the hydrometallation step, the mixture of cyclic triene and Schwartz reagent needed to be stirred for at least 4 hrs under reflux conditions. The absolute configuration of **10** was assigned by analogy with previously reported literature from the Fletcher group.[70]

The asymmetric 1,4-addition generally required a large excess of alkene.[70] As the trialkene **1** is synthesised in six steps, our first approach was to reduce the amount of alkene used in this reaction.



Entry	Eq of alkene	Eq of Cp_2ZrHCl	Yield	ee
1	1.7	1.5	none	n/c
2	1.7	1.5	none	n/c
3[a]	2.5	2.0	4%	n/c
4	2.5	2.0	31%	33%
5	2.5	2.0	35%	28%
6	2.5	2.0	22%	39%
7	1.5	1.3	2%	n/c
8	2.5	2.0	none	n/c
9	2.5	2.0	none	n/c

Conditions : cyclic enone (1.0 eq.), CuCl (0.1 eq.), ligand (0.1 eq.), $AgNTf_2$ (0.11 eq.) and ratio of solvent : DCM/MTBE : 1/5.
a : scale of the reaction 0.2 mmol instead of 0.4 mmol



Ligand L1: Phil's ligand

Table 2.1: Asymmetric 1,4-addition of trialkene **1** with different equivalents of reagents

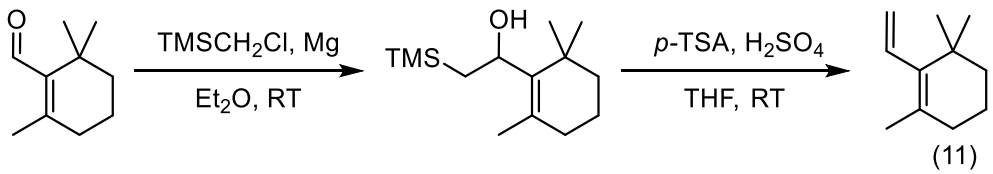
Unfortunately, at least 2.0 equivalents of Schwartz reagent and 2.5 equivalents of trialkene **1** for 0.4 mmol of 3-methylcyclohex-2-enone were required in order to obtain the product **10** in moderate (22 to 35%) yield (Entry 4, 5 and 6; Table 2.1). With less alkene (1.7 equivalents instead of 2.5) in the reaction, no product was observed (Entry 1 and 2; Table 2.1) and performing the reaction on a smaller scale (0.2 mmol) only provided 4% of product **10** (Entry 3; Table 2.1). Another attempt at reducing the amount of hydrometallated alkene delivered **10** in only 2% yield (Entry 7; Table 2.1).

The last two experiments that were tried out in this system did not work (Entry

8 and 9; Table 2.1) but revealed a problem that became recurrent with this reaction. In these examples, hydrozirconation never went fully to completion, even when mixtures were left stirring for extended times at reflux. Dissolution of the Schwartz reagent was never achieved and continuing the reaction did not deliver desired product **10**.

The highest enantiomeric excess obtained so far was 39% (Entry 6; Table 2.1), a promising result given that the reaction parameters may be further optimised. However, since synthesising the starting material **1** was a relatively arduous process, and since selective hydrometallation remained a challenge, we decided to focus our attention on optimising those conditions with a simpler starting material – cyclic dialkene **11**.

The model diene **11** is structurally related to **1** but can be synthesised in large amounts (>3g) in only two steps (Scheme 2.7). The cyclic diene **11** was prepared by reaction of commercially available β-cyclocitral with trimethylsilylmethylmagnesium chloride formed *in situ* giving the β-hydroxysilane intermediate, which upon immediate stirring with a mixture of *p*-toluene sulphonic acid and sulphuric acid gave pure diene **11** by elimination (scheme 2.7).[136] The overall yield obtained for the synthesis of the model compound **11** varied from 52 to 64%.



Scheme 2.7: Synthesis of the dialkene **11**

Before we started to work on this project, preliminary investigations were performed by one of my co-worker Dr Mireia Sidera who screened different ligands with this cyclic dialkene **11** (Table 2.2). Twenty-three different ligands were tested, mainly phosphoramidites, and the best enantioselectivity was obtained for the

asymmetric 1,4-addition using ligand **L1** with 50% ee.

Other ligands also gave similar enantioselectivity such as **L2**, **L12**, **L15**, **L21** and **L22** but furnished the product in only trace quantities. The only two other interesting ligands were **L7** and **L8**, structurally similar to **L1**, with both high yield of 90% and 75% with respective ee's of 47% ee and 44% ee. We decided to focus our optimisations on ligand **L1** because its enantioselectivity was higher, even though the test reaction only gave 54% of desired product **12**. Experience in the Fletcher group has shown that it is often easier to increase the reactivity rather than the enantioselectivity of a reaction.

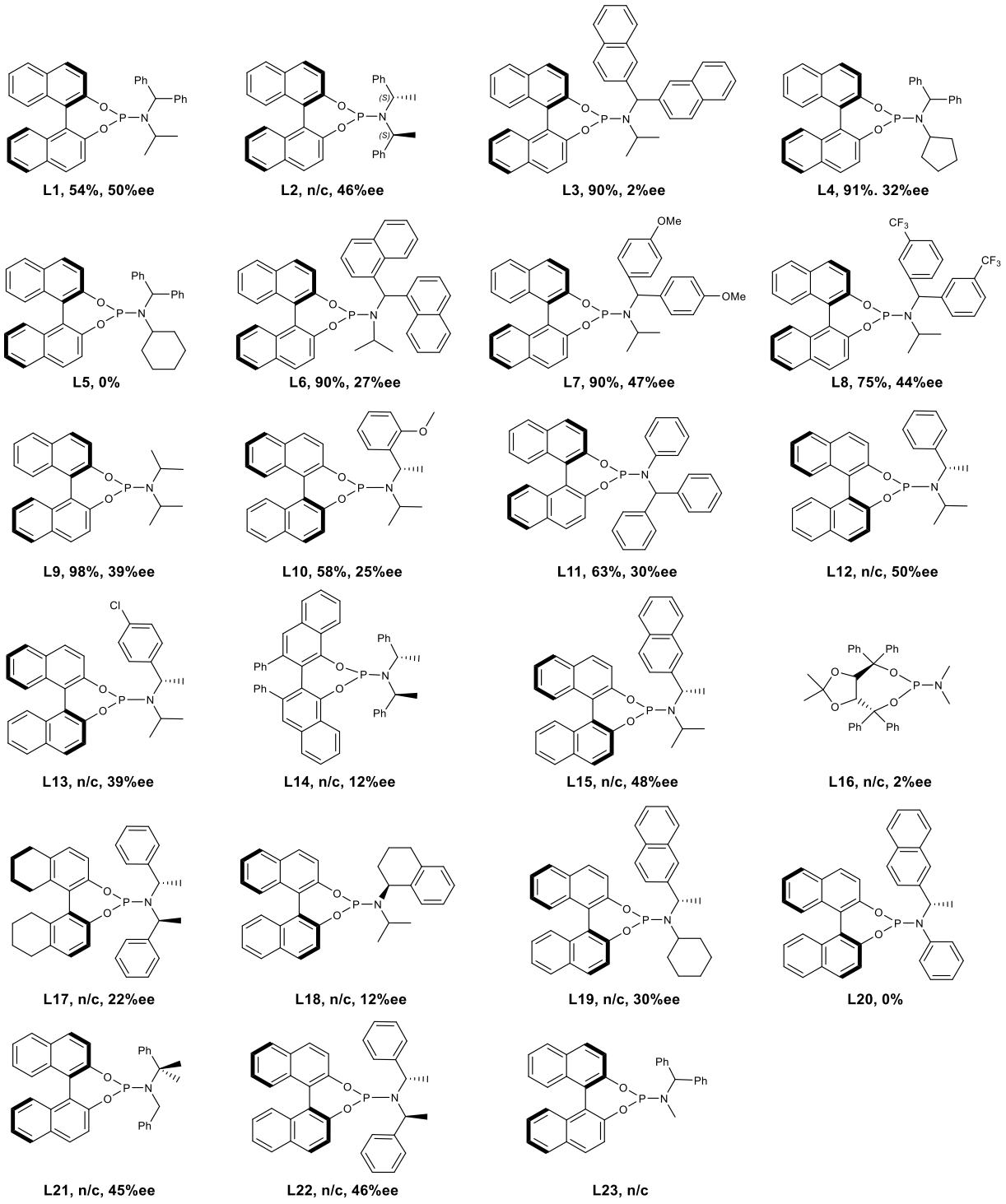


Table 2.2: Ligand screening for the ACA of **11**

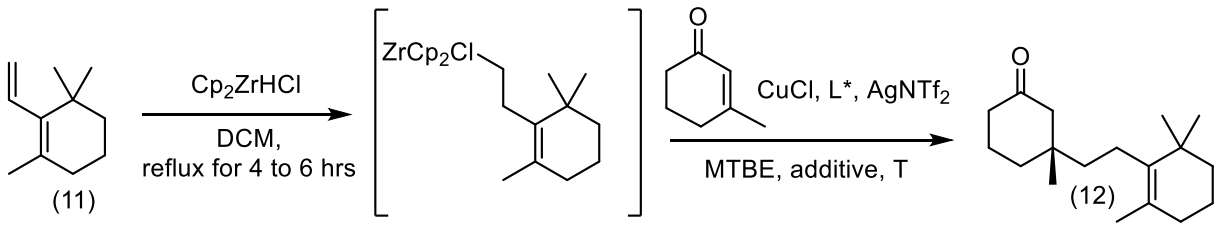
2.3.3 Optimisation of the asymmetric 1,4-addition of diene 11

First attempts at hydrometallation showed similar problems to those previously observed with cyclic triene **1**. For all test reactions, the mixture was left stirring for at least 4 hrs under reflux.

Once again, our aim for the tandem hydrometallation/asymmetric 1,4-addition was to use the model dialkene **11** in a reduced amount or as the limiting reagent. Several conditions were tested and, despite the fact that the reaction worked to some extent, yields in those experiments were limited (between 7% and 13%), as was the enantioselectivity (around 10% ee). It was expected that considerable further optimisation would be required in order to achieve comparable yields to those observed when using an excess of alkene. Thus, we continued to use 2.5 equivalents of alkene and 2.0 equivalents of Schwartz reagent for 1.0 equivalent of enone.

Unfortunately, we encountered reproducibility issues when attempting to replicate some of Dr Mireia Sidera's screening results. Indeed, yields varied between 7% and 41% and enantiomeric excess between 16% and 24% compared to the 54% yield and 50% ee previously obtained (Entry 1; Table 2.2).

Our first interesting result came with the use of an additive in the reaction. Previous work demonstrated the importance of TMSCl in 1,4-additions with unsubstituted cyclic enones.[67] Although TMSCl was determined to have no positive influence in 1,4-additions to form quaternary centres,[70] it was found to be extremely important in this particular reaction.



Entry	Ligand	T	Additive	Yield	ee
1	L1	RT	TMSCl	11%	64%
2	L1	40 °C	TMSCl	22%	76%
3	L2	RT	none	32%	48%
4	L2	RT	TMSCl	8%	66%
5	L2	40 °C	TMSCl	15%	68%
6	L7	40 °C	TMSCl	6%	42%
7	L8	40 °C	TMSCl	11%	16%
8	L2	reflux	TMSCl	18%	68%
9	L1	reflux	TMSCl	20%	66%

Conditions : alkene (2.5 eq.), Schwartz reagent (2.0 eq.), cyclic enone (1.0 eq.), CuCl (0.1 eq.), ligand (0.1 eq.), $AgNTf_2$ (0.11 eq.), additive (5.0 eq.) and ratio of solvent : DCM/MTBE : 1/5.

Table 2.3: Ligand screening for the ACA of **11** with TMSCl

Different ligands, based on the screening previously investigated (Table 2.2), were studied in the presence of TMSCl to confirm its importance in this system.

The overall yield of the reactions was not influenced by the presence of TMSCl, but the additive had a significant impact on the enantioselectivity. Indeed, in the presence of TMSCl, the enantiomeric excess increases significantly up to 64% ee (Entry 1; Table 2.3). It was not clear why in the case of the complex dialkene **11** TMSCl had a positive influence on the reaction whereas it had no effect on simpler alkenes. Heating the reaction at 40 °C increased the enantioselectivity up to 76% ee (Entry 2; Table 2.3).

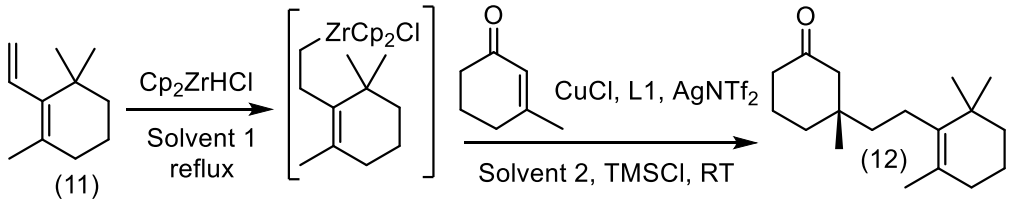
Without TMSCl, ligand **L2** gave similar results to those previously observed (Entry 3; Table 2.3). Adding TMSCl increased the enantioselectivity up to 66% ee but

diminished the yield with only 8% obtained (Entry 4; Table 2.3). However, heating up the reaction with **L2** only increased the amount of the desired product **12** formed with 15% yield, and an enantiomeric excess of 68% (Entry 5; Table 2.3).

Compared to results obtained in the previous iteration of screening, ligands **L7** and **L8** both performed poorly (Entry 6 and 7; Table 2.3). Performing the reaction under reflux, with TMSCl and ligand **L2** did not affect the yield/enantioselectivity (Entry 8; Table 2.3) whereas the enantioselectivity slightly decreased down to 66% when the reaction was performed with ligand **L1** under reflux conditions (Entry 9; Table 2.3).

TMSCl seemed to be influential only under these specific conditions and the next reactions were performed with ligand **L1** and TMSCl as additive.

The set-up of the catalytic asymmetric 1,4-additions with alkylzirconium reagents required the hydrometallation to be done in one flask, while the copper-ligand complex was prepared in another. Therefore, two different solvents were typically used. This screening part focused on the influence of those solvents on the reaction (Table 2.4). For simplification of the study, all of experiments were performed at room temperature.



Entry	Solvent 1	Solvent 2	Yield (%)	ee (%)
1	DCM	MTBE	11	64
2	Et_2O	MTBE	-	-
3	THF	MTBE	n/c	52
4	THF/DCM	MTBE	n/c	42
5	$CHCl_3$	MTBE	-	-
6	DCM	MTBE	20	72
7	DCM	DCM	n/c	48
8	DCM	Et_2O	59	80
9	DCM	Toluene	38	70
10	DCM	DCE	n/c	36
11	DCM	2-Me-THF	n/c	36

Conditions : alkene (2.5 eq.), Schwartz reagent (2.0 eq.), cyclic enone (1.0 eq.), CuCl (0.1 eq.), ligand (0.1 eq.), $AgNTf_2$ (0.11 eq.), TMSCl (5.0 eq.) and ratio of solvent : solvent 1/solvent 2 : 1/5.

Table 2.4: Solvents screening for the ACA of diene **11**

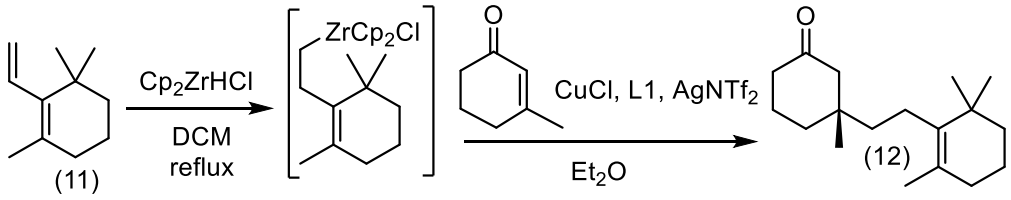
For the hydrometallation step, dialkene **11** and Schwartz reagent were dissolved in “solvent 1”. DCM, Et_2O, THF and $CHCl_3$ were all tested. The best result was found using DCM (Entry 1; Table 2.4). In Et_2O, the hydrometallation mixture did not turn clear, suggesting incomplete hydrozirconation and no product was found (Entry 2; Table 2.4). For THF and $CHCl_3$, both hydrometallation mixtures turned clear without heating. Unfortunately, the use of THF was detrimental to the enantioselectivity (Entry 3; Table 2.4) even after its replacement with DCM (Entry 4; Table 2.4). In $CHCl_3$, no product was obtained (Entry 5; Table 2.4). Despite the fact that the mixture of dialkene **11** and Schwartz reagent were dissolved in other solvents, the reaction needed to be refluxed in DCM for at least 4 hrs to complete the hydrometallation.

Formation of the copper-ligand pre-catalyst took place in a second flask. The ligand, CuCl, and $AgNTf_2$ were dissolved in “solvent 2”. Several solvents were examined, and the best results were obtained using Et_2O (Entry 8; Table 2.4). Although the enantiomeric excess only increased moderately using Et_2O up to 80%, a major raise of the yield was noticed up to 59%.

DCM, DCE and 2-Me-THF turned out to be poor choices for solvent since significant decrease of the enantioselectivity was observed (Entry 7, 10 and 11; Table 2.4). Toluene on the other hand gave interesting results with an increase in both yield and enantioselectivity (Entry 9; Table 2.4).

Finally, we decided to check how our system was performing when the reaction was submitted to a variety of different factors such as temperature (Table 2.5). When the reaction was performed at reflux with Ligand **L1**, TMSCl and DCM/Et_2O as the solvent system, a decrease in yield was observed (Entry 2 and 4; Table 2.5). Surprisingly, our previous results were not reproducible. Repeating the reaction at room temperature gave either poor results (Entry 3; Table 2.5) or a decrease in both yield and enantiomeric excess (Entry 5; Table 2.5).

Since we found that DCM was a “poor solvent 2” (Entry 7; Table 2.4), we tried to limit the amount of DCM in the reaction system. DCM was removed by rotary evaporation after hydrozirconation. The concentrated hydrozirconated solution was then added to the catalyst mixture and the experiments were carried out as before (Entry 6 and 7; Table 2.5). However, both experiments did not yield satisfactory results and significant drop in both yield and enantioselectivity were encountered.

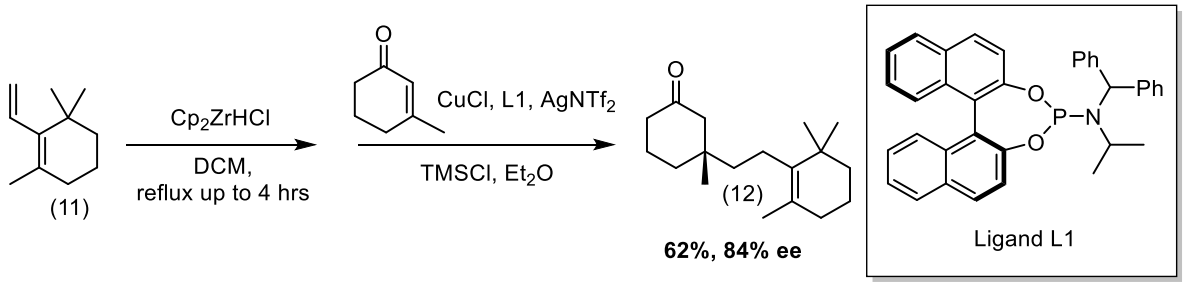


Entry	T (°C)	Other factors	Yield (%)	ee (%)
1	RT	none	59	80
2	reflux	none	44	75
3	RT	none	n/c	50
4	reflux	none	50	80
5	RT	none	39	73
6	RT	reduce DCM	15	58
7	RT	reduce DCM	n/c	45
8	RT	5 eq of alkene	62	84

Conditions : alkene (2.5 eq.), Schwartz reagent (2.0 eq.), cyclic enone (1.0 eq.), CuCl (0.1 eq.), ligand (0.1 eq.), $AgNTf_2$ (0.11 eq.), additive (5.0 eq.) and ratio of solvent : DCM/Et_2O : 1/5.

Table 2.5: temperature and other factors screening for the ACA of **11**

The best results we ever obtained with this system occurred when the equivalents of both the cyclic dialkene **11** and the Schwartz reagent were doubled, to give 62% yield and 84% ee (Scheme 2.8).



Scheme 2.8: Optimised conditions for the ACA of dialkene **11**

The absolute configuration of **12** was assigned similarly to **10** by analogy with previously reported literature from the Fletcher group.[70]

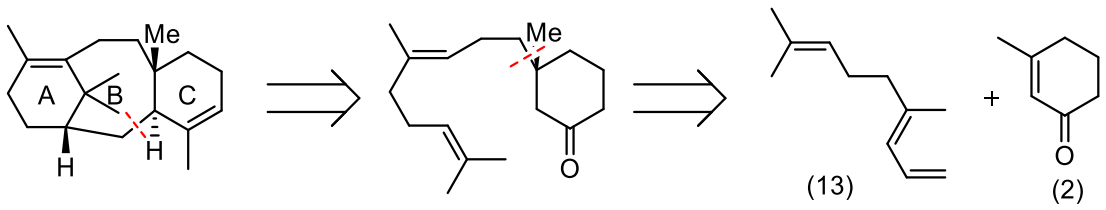
Before trying out more optimisations, we wanted to check how the cyclic trialkene **1** behaved under these new conditions.

Several experiments were set up using triene **1**. Unfortunately, the results were poorer than hoped. The desired product **10** was obtained in a yield varying between 20 and 40% and with an enantioselectivity of only 60% ee. At this point, we decided to study if the Taxol core and especially ring A could be obtained using another route.

2.3.4 Asymmetric 1,4-additions of linear trialkene 13 and 13'

Trying to access Taxadiene by coupling ring C and A together with the asymmetric 1,4 conjugate addition turned out to be more challenging than originally anticipated, especially in terms of enantioselectivity. Our new approach would be to perform the ACA earlier in the synthesis and to form ring A later on.

A revised retrosynthesis of Taxadiene gave two starting materials: a linear trialkene **13** and commercially available 3-methylcyclohex-2-enone **2** representing ring C (Scheme 2.9). Our proposed route consisted of first coupling the linear trialkene **13** and ring A by an asymmetric 1,4-conjugate addition setting the desired stereocentre, cyclising the chain into ring C and finally closing ring B by oxidative cyclisation. We hypothesised that less steric hindrance could enhance the enantioselectivity of the asymmetric 1,4 addition.



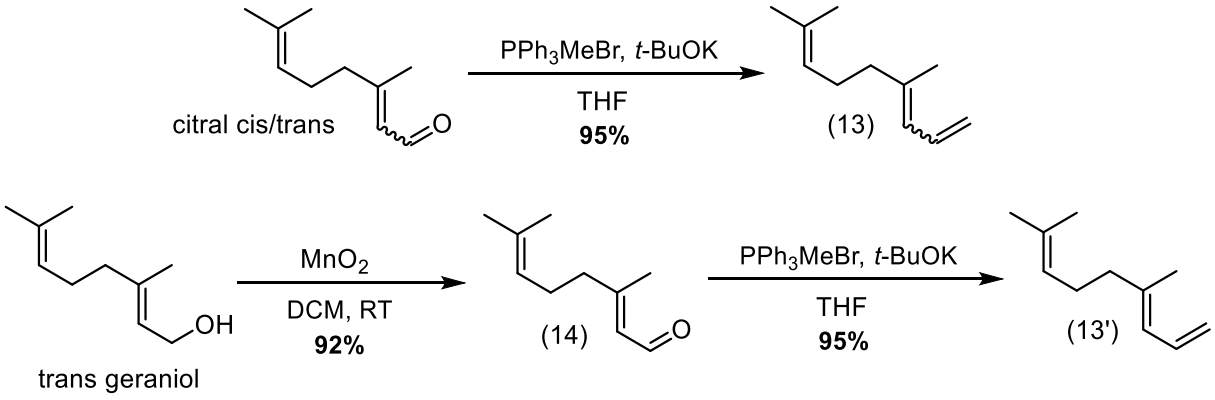
Scheme 2.9: New retrosynthesis approach

Starting material **13** was obtained from commercially available *cis/trans* citral, by a Wittig reaction. The trans linear trialkene **13'** was synthesised from *trans*-geraniol, which was first oxidised into a *trans*-citral intermediate **14** followed by the same Wittig reaction. Both routes were envisaged because we did not know what influence the

isomers would have on the asymmetric 1,4 conjugate addition.

Trans-geraniol was oxidised with manganese dioxide in DCM at room temperature and delivered trans-citral **14** in 92% yield (Scheme 2.10). *Trans*-citral **14** and citral *cis/trans* were both submitted to a mixture of *t*-BuOK and PPh_3MeBr in THF which delivered the desired linear trialkenes **13** and **13'** both in 95% yield. Contrary to the synthesis of the cyclic triene **1**, the synthesis of linear trialkenes **13** and **13'** was simple and cheap.

On larger scale, the reaction also performed well and 8 g of the desired product **13** were obtained.



Scheme 2.10 : Synthesis of linear trialkenes **13** and **13'**

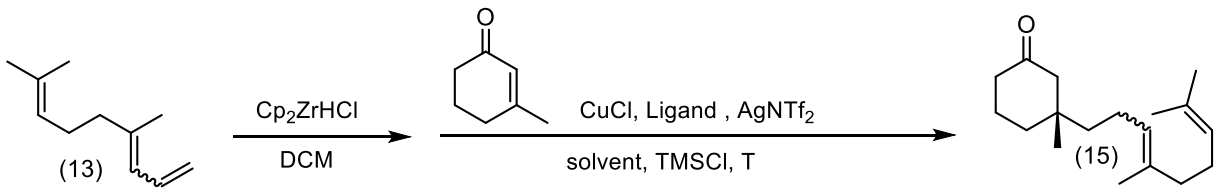
The first attempt at the asymmetric 1,4-addition was tried using the *cis/trans* mixture of linear trialkenes **13**. Our first assumption was that the linear trialkene **13** was also a more complicated structure than the ones previously studied by the Fletcher group and that the starting material **13** would behave in a similar fashion to the cyclic trialkene **1**. Therefore, we decided to apply the exact conditions we found out to be the most effective with the cyclic dialkene **11** (cf. part 1.3.3).

First of all, and to our delight, the linear trialkene **13** behaved similarly to simpler alkenes during hydrometallation. Indeed, only 1 h of stirring at room temperature was needed to complete the hydrozirconation.

Performing the asymmetric 1,4-addition with the new starting material **13** with DCM/Et_2O as solvent system, ligand **L1** at room temperature with TMSCl delivered the desired product **15** in a moderate yield up to 38% and an enantiomeric excess up to 69% (Entry 2; Table 2.6). Switching from **L1** to **L2** diminished the enantioselectivity of the reaction (Entry 3; Table 2.6).

TMSCl is normally detrimental for the ACA to form quaternary centres.[70] Removing the additive from the reaction, drastically increased the enantioselectivity of the reaction to 86% ee (Entry 4; Table 2.6).

Switching “solvent 2” in the reaction from Et_2O to MTBE, i.e. using previously reported optimal conditions to form quaternary centres with the asymmetric 1,4-conjugate additions, gave excellent results: the desired product **15** was formed in good yield up to 45% and high enantioselectivity up to 96% ee (Entry 5; Table 2.6).



Entry	Ligand	Solvent	Scale	TMSCl	T	Yield	ee
1	(*R/S*) L2	Et_2O	0.4 mmol	Yes	RT	32%	rac
2	L1	Et_2O	0.4 mmol	Yes	RT	38%	69%
3	L2	Et_2O	0.4 mmol	Yes	RT	28%	62%
4	L1	Et_2O	0.4 mmol	No	RT	20%	86%
5	L1	MTBE	0.4 mmol	No	RT	45%	96%
6	L1	MTBE	11.4 mmol	No	RT	n/c	83%
7	L1	MTBE	4 mmol	No	RT	n/c	92%
8	L1	MTBE	0.4 mmol	No	RT	20%	92%
9	L1	MTBE	0.4 mmol	No	0 °C	64%	87%
10	L1	MTBE	0.4 mmol	No	0 °C	55%	92%
11	L1	MTBE	1.33 mmol	No	0 °C	22%	91%
12[a]	L1	MTBE	1.33 mmol	No	0 °C	34%	94%
13[b]	L1	MTBE	1.33 mmol	No	0 °C	5%	n/c
14[a,e]	L1	MTBE	1.33 mmol	No	0 °C	48%	n/c
15[a,e]	L1	MTBE	2.39 mmol	No	0 °C	34%	96%
16[a,e]	L1	MTBE	5.32 mmol	No	0 °C	37%	95%
17[c,e]	L1	MTBE	1.33 mmol	No	0 °C	21%	87%
18[a,e]	L1	MTBE	1.33 mmol	No	-10 °C	43%	93%
19[a,e]	L1	MTBE	5.32 mmol	No	-10 °C	43%	96%
20[a,e]	L1	MTBE	10.64 mmol	No	-10 °C	56%	96%
21[d,e]	L1	MTBE	10.64 mmol	No	-10 °C	41%	60%
22[a,e]	L1	MTBE	10.64 mmol	No	-10 °C	45%	96%
23[d]	L1	MTBE	0.4 mmol	No	RT	n/c	60%

Conditions : alkene (2.5 eq.), Schwartz reagent (2.0 eq.), cyclic enone (1.0 eq.), CuCl (0.1 eq.), ligand (0.1 eq.), $AgNTf_2$ (0.11 eq.), additive (5.0 eq.) and ratio of solvent : DCM/solvent : 1/5. **a** : amount of MTBE divided by 2. **b** : catalyst mixture left stirring one hour at 0 °C. **c** : amount of MTBE divided by 5, ratio of solvent DCM/MTBE : 1/1. **d** : reaction perform with *trans* linear trialkene **13'. e** : reaction performed in a cooler instead of an ice bath

Table 2.6: Screening conditions for the ACA of linear trialkene **13**

When we tried to scale up the reaction with **13**, a loss in both yield and enantioselectivity was observed (Entry 6 and 7; Table 2.6).

Performing the reaction at 0 °C instead of room temperature had a tremendous impact on the yield of the reaction with the desired product **15** formed in more than 50% yield (Entry 9 and 10; Table 2.6). Unfortunately, even if we managed to keep high selectivity on a larger scale, the yield of the reaction decreased (Entry 11; Table 2.6).

We then tried out to perform the reaction with half the amount of MTBE and by adding the catalyst mixture more slowly (10 mins instead of 1 min) to the hydrozirconated alkyl solution. A slight increase in yield was observed (Entry 12; Table 2.6). Cooling down the formation of the catalyst mixture to 0 °C was detrimental for our system (Entry 13; Table 2.6).

A reaction normally performed at 0 °C is set up with a bath of ice/water which might warm up over time when the reaction is left stirring overnight. Setting up the reaction in a cooler instead of an ice/water bath prevented the reaction from warming up and an increase in yield up to 48% was obtained (Entry 14; Table 2.6).

The reaction seemed to be a delicate ecosystem since slowing down the reaction by performing it at lower temperature and concentrating the reaction both increased the reactivity. We hypothesised that (a non-observed) side reaction also took place in our system and that cooling down and concentrating the reaction tended in some way to favour the formation of the desired product **15**.

Concentrating the reaction mixture even more (1/1 ratio of DCM/MTBE) however decreased both yield and enantioselectivity (Entry 17; Table 2.6)

Scaling up the reaction even more (2.39 and 5.32 mmol), still at 0 °C, with a slow addition (10 mins) of the catalyst mixture in a ratio 1/2.5 of DCM/MTBE delivered

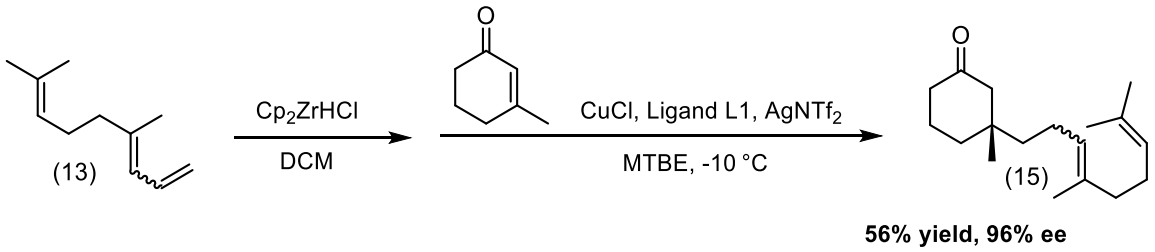
the product **15** in moderate yield (~30%) and high enantioselectivity up to 95% ee (Entry 15 and 16; Table 2.6).

Cooling down the reaction to -10 °C increased the yield of the reaction by 10% (Entry 18; Table 2.6). The reaction did not lose any reactivity when scaled up to around 5 mmol (Entry 19; Table 2.6) and an increase in yield was observed when the reaction was performed at 10.6 mmol (Entry 20 and 22; Table 2.6).

Interestingly, when we applied the same exact conditions with the linear trialkene **13'** synthesised from *trans*-geraniol, a major drop of enantioselectivity was observed (Entry 21 and 23; Table 2.6). No obvious reason was found to explain why *trans*-trialkene **13'** and *cis/trans*-trialkene **13** behaved differently, but these results were highly reproducible.

The absolute configurations of **15** and **15'** were also assigned by analogy with previously reported literature from the Fletcher group.[70]

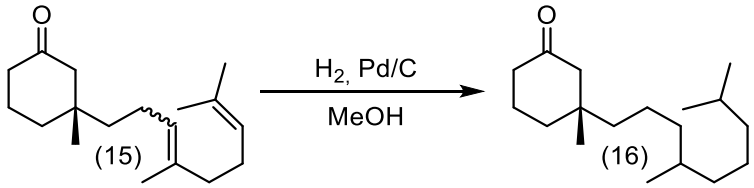
Overall, we managed to form the desired product **15** on a large (1.6 g) scale in up to 56% yield with 96% ee (Scheme 2.11).



Scheme 2.11: Optimised conditions for the ACA of linear trialkene **13**

In order to determine the enantiomeric excess of each product **15** obtained in the study described above, most of the compounds were subjected to hydrogenation (scheme 2.12). A mixture of diastereoisomers **16** was obtained and the ee was

determined by GC analysis. Removing the *cis/trans* isomers made the chromatograms easier to interpret.

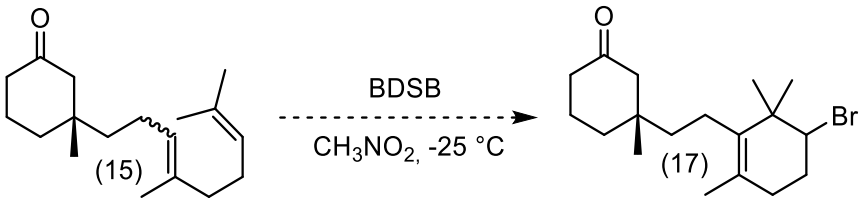


Scheme 2.12: hydrogenation of ACA product **15**

2.3.5 Closing ring A

Snyder and co-workers reported in 2009 a simple and readily handled reagent, bromodiethylsulfonium bromopentachloroantimonate (BDSB), which smoothly effects bromonium-induced cyclisations with a diverse set of compounds derived from geraniol.[137] Snyder's standard procedure for polyene cyclisation consisted of adding a solution of BDSB in CH_3NO_2 into a solution of the requisite 1,5-diene cyclisation substrate in CH_3NO_2 at various temperatures.

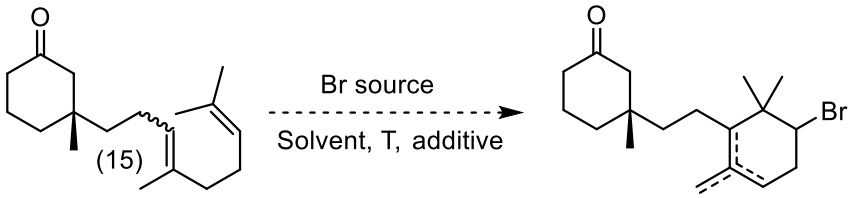
Our first attempt at performing the cyclisation at -25 °C for 1 h with this bromine source led to a mixture of three different diastereoisomers of product **17**: a disubstituted alkene, a trisubstituted alkene and the desired tetrasubstituted alkene **17** (Scheme 2.13 and Entry 2; Table 2.7).



Scheme 2.13 : Cyclisation of ACA product **15** with BDSB

A kinetic study of the reaction left stirring over two days showed us that no evolution of the ratio between the different isomers was observed over time, neither at

0 °C nor at room temperature (Entry 3 and 4; Table 2.7). Performing the reaction at room temperature overnight delivered the three isomers in 88% yield where the desired isomer **17** was the major one (Entry 4; Table 2.7).



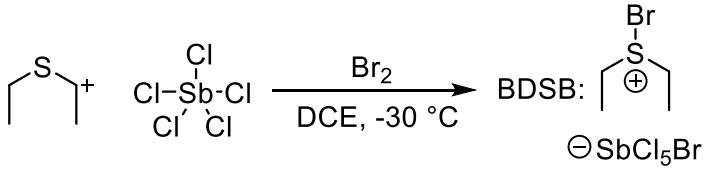
Entry	Br source	Solvent	Additive	T	Time	Nb of isomers recoverd	Major iso	Yield
1[a]	BDSB	CH_3NO_2	none	-25 °C	1 h	none	-	0%
2[a]	BDSB	CH_3NO_2	none	-25 °C	1 h	3	**17**	n/c
3[a]	BDSB	CH_3NO_2	none	0 °C	2 d	3	**17**	n/c
4[a]	BDSB	CH_3NO_2	none	RT	2 d	3	**17**	n/c
5[a]	BDSB	CH_3NO_2	none	RT	ON	3	**17**	88%
6	BDSB	CH_3NO_2	none	RT	ON	2	di	n/c
7	BDSB	CH_3NO_2	none	RT to 40 °C	ON	2	di	n/c

Conditions : dialkene (1.0 eq.), BDSB (1.0 eq). **a** : commercial BDSB

Table 2.7: First attempts at cyclising ACA product **15** with BDSB

We hypothesised that the reaction conditions could be optimised in order to obtain only the desired more stable isomer **17**.

We started to synthesise the bromine source ourselves, since BDSB was not easily obtainable, by mixing Br_2 with $SbCl_5$ and Et_2S in DCE at -30 °C, which led after recrystallisation to a pure orange, plate-like solid (Scheme 2.14).[137]



Scheme 2.14: Synthesis of BDSB

Unfortunately, even though the characterisation data of "home-made" BDSB corresponded well to that published by Snyder and co-workers,[137] it behaved differently to the commercial one.

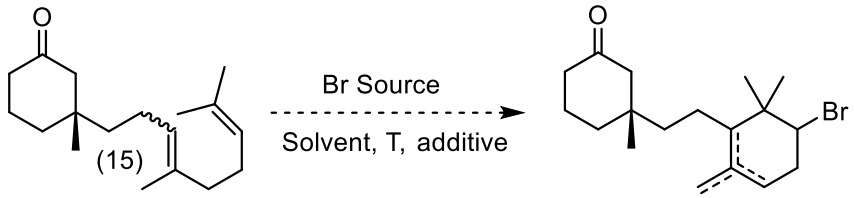
To our surprise, when the reaction was set-up with this newly formed BDSB overnight, only two isomers were formed, the disubstituted and the trisubstituted (Entry 6 and 7; Table 2.7). No traces of the tetrasubstituted product **17** were obtained and the ratio of isomers tended towards the disubstituted isomer.

Our attention shifted towards the influence of solvent in our system (Table 2.8). All the experiments were stirred for only 30 mins.

DCM and $CHCl_3$ both gave the di- and trisubstituted isomers in similar amount (Entry 1 and 2; Table 2.8). High yield was obtained with $CHCl_3$ where the mixture of products was synthesised in 77% yield (Entry 3; Table 2.8).

Similar results were observed with ACN either at room temperature or at -20 °C to the results obtained with CH_3NO_2 (Entry 5 and 6; Table 2.8). However, performing the reaction at 60 °C with ACN afforded only the disubstituted isomer (Entry 7; Table 2.8). Repeating the same reaction at room temperature gave a mixture of isomers with a poor to moderate yield (Entry 8 and 9; Table 2.8). Results with EtOAc were similar to those with CH_3NO_2 and ACN (Entry 12; Table 2.8). With DMSO the reaction did not work (Entry 10; Table 2.8) and with DMF only the undesired isomers were obtained with the trisubstituted one as the major product (Entry 11; Table 2.8).

A reaction was also set up in $CHCl_3$ with HCl in order to favour isomerisation within the reaction, but without any influence (Entry 4; Table 2.8).



Entry	Br source	Solvent	Additive	T	Time	Nb of isomers recovered	Major iso	Yield
1	BDSB	DCM	none	40 °C	30 mins	2	none	n/c
2	BDSB	$CHCl_3$	none	RT	30 mins	2	none	n/c
3	BDSB	$CHCl_3$	none	RT	30 mins	2	none	77%
4	BDSB	$CHCl_3$	HCl	RT	30 mins	2	none	n/c
5	BDSB	ACN	none	RT	30 mins	2	di	n/c
6	BDSB	ACN	none	-20 °C	30 mins	2	di	n/c
7	BDSB	ACN	none	60 °C	30 mins	none	di	n/c
8	BDSB	ACN	none	RT	30 mins	2	di	10%
9	BDSB	ACN	none	RT	30 mins	2	di	48%
10	BDSB	DMSO	none	RT	30 mins	-	-	0%
11	BDSB	DMF	none	RT	30 mins	2	tri	n/c
12	BDSB	EtOAc	none	RT	30 mins	2	di	n/c

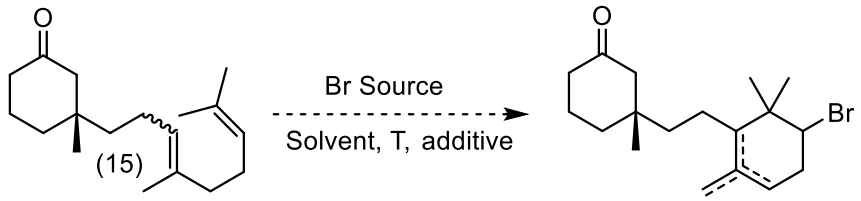
Conditions : dialkene (1.0 eq.), BDSB (1.0 eq).

Table 2.8 : Solvent screening for the cyclisation with BDSB

Since none of the solvents had a positive impact, neither on the reactivity nor on the selectivity of the reaction, we continued to use CH_3NO_2 as our solvent of choice.

Performing the reaction in CH_3NO_2 at room temperature delivered again a mixture of both undesired isomers in good yield up to 59% (Entry 1, 3 and 4; Table 2.9). With iodine in the mixture only the starting materials were recovered (Entry 2; Table 2.9). Setting up the reaction at -25 °C for 1 h gave the mixture of isomers in poor yield (Entry 5; Table 2.9) but the yield increased when the reaction was left stirring for only 5 mins suggesting that the product might have degraded (Entry 6; Table 2.9). With a large excess of BDSB, neither product nor starting materials were recovered, which

could suggest that the bromine source might be the reason for degradation (Entry 7; Table 2.9).



Entry	Br source	Solvent	Additive	T	Time	Nb of isomers recovered	Major iso	Yield
1	BDSB	CH_3NO_2	none	RT	30 mins	2	di	56%
2	BDSB	CH_3NO_2	I_2	RT	30 mins	-	-	0%
3	BDSB	CH_3NO_2	none	RT	30 mins	2	di	43%
4	BDSB	CH_3NO_2	none	RT	30 mins	2	di	59%
5	BDSB	CH_3NO_2	none	-25 °C	1 h	none	di	17%
6	BDSB	CH_3NO_2	none	-25 °C	5 mins	none	di	32%
7[a]	BDSB	CH_3NO_2	none	-25 °C	5 mins	-	-	0%
8[b]	BDSB	CH_3NO_2	none	RT	5 mins	none	di	25%
9[c]	BDSB	CH_3NO_2	none	-25 °C	30 mins	3	di	36%
10	BDSB	CH_3NO_2	Br_2	-25 °C	5 mins	3	**17**/di	n/c
11	BDSB	CH_3NO_2	none	-25 °C	5 mins	2	di	n/c

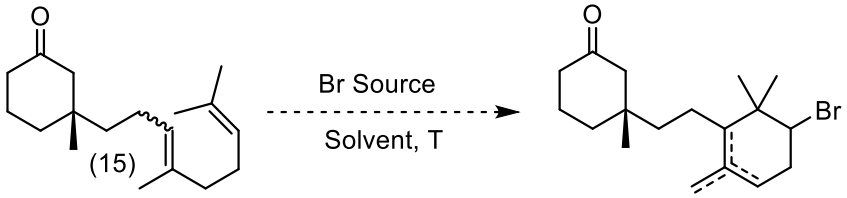
Conditions : dialkene (1.0 eq.), BDSB (1.0 eq). **a** : 1.2 eq. of BDSB instead of 1.0 eq. **b** : 1.4 mmol scale. **c** : commercial BDSB

Table 2.9: Screening of reaction times and additives with BDSB at different temperatures

Traces of the tetrasubstituted isomer were once again observed when the reaction was set up with commercially available BDSB (Entry 9; Table 2.9). To our surprise, upon addition of Br_2 to the reaction mixture the desired isomer **17** was obtained (Entry 10; Table 2.9).

Since BDSB was synthesised from bromine, we assumed that some traces of Br_2 might still be present in the commercially available BDSB and might induce the formation of the tetrasubstituted isomer **17**.

Therefore, we decided to change the bromine source of our cyclisation and used only Br_2 instead (Table 2.10).[138] To our delight, after 5 mins of stirring at -25 °C in CH_3NO_2, a mixture of only two isomers was obtained (Entry 1 and 2; Table 2.10) and the tetrasubstituted isomer **17** was the major one. Leaving the reaction stirring overnight either at -25 °C or at room temperature still gave a mixture of isomers (Entry 3 and 4; Table 2.10). Performing the reaction on a larger scale only delivered the mixture of both isomers in a moderate yield (Entry 5 and 6; Table 2.10) and increasing the amount of Br_2 made the reaction ineffective (Entry 7 and 8; Table 2.10).



Entry	Br source	Solvent	T	Time	Nb of isomers recovered	Major iso	Yield
1	Br_2	CH_3NO_2	-25 °C	5 mins	2	**17**	34%
2	Br_2	CH_3NO_2	-25 °C	5 mins	2	**17**	n/c
3	Br_2	CH_3NO_2	-25 °C	ON	2	**17**	n/c
4	Br_2	CH_3NO_2	RT	ON	2	**17**	26%
5[a]	Br_2	CH_3NO_2	-25 °C	5 mins	2	**17**	27%
6[a]	Br_2	CH_3NO_2	-25 °C	ON	2	**17**	44%
7[b]	Br_2	CH_3NO_2	-25 °C	5 mins	-	-	0%
8[c]	Br_2	CH_3NO_2	-25 °C	ON	-	-	0%

Conditions : dialkene (1.0 eq.), BDSB (1.0 eq). **a** : 0.4 mmol scale. **b :** 5.3 eq. of Br_2. **c :** 1.2 eq. of Br_2.

Table 2.10: Attempts at cyclising ACA product **15** with Br_2

None of the experiments set-up with a bromine source led to a single isomer even though the desired product **17** was obtained with bromine. We envisaged from this stage two possible options: either trying to isomerise the recovered mixture of

alkenes to obtain the desired tetrasubstituted isomer **17**, or cyclising ring A with a different method or a different electrophile than Br_2.[138]

We first tried to isomerise the mixture of the different isomers under different conditions (Figure 2.6): HCl in $CHCl_3$ at various temperature, HBr in EtOH, iodine in benzene or toluene at various temperatures, iodine in benzene with a light source, $RhCl_3 \cdot H_2O$ in EtOH at 80 °C or at reflux and $Pd(MeCN)_4$ in benzene (Figure 2.6).[139,140] Unfortunately, regardless of these conditions, it was impossible to convert the mixture of isomers into desired **17**. None of the conditions used had any impact and the same ratio of isomers was recovered in all cases.

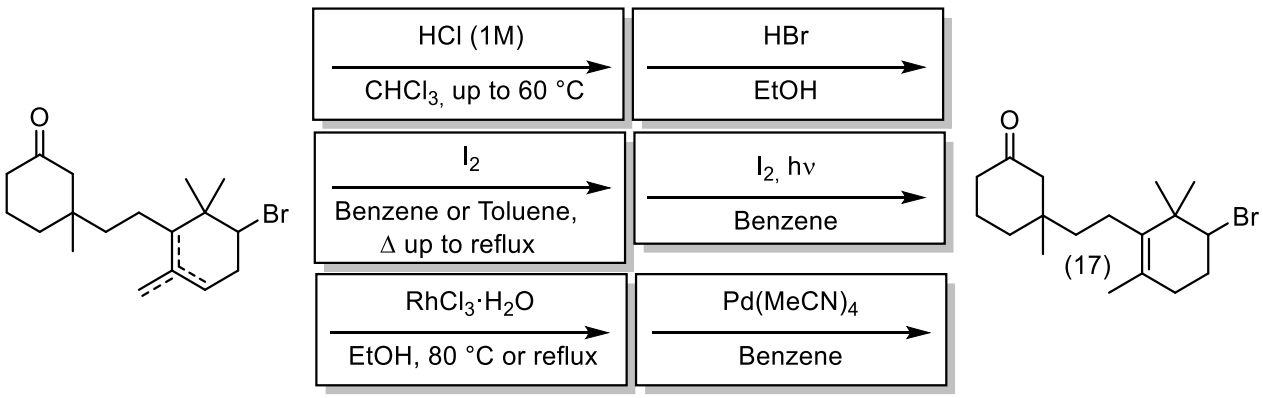
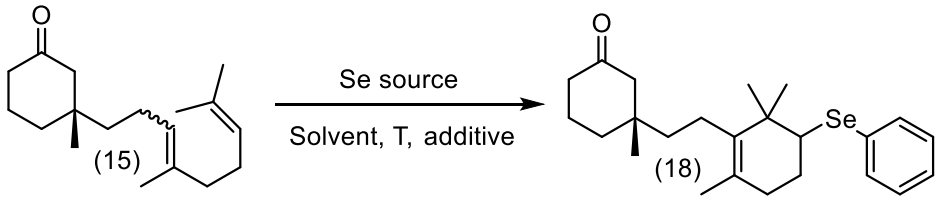


Figure 2.6: Isomerisation experiments

Organoselenium reagents such as phenylselenyl chloride (PhSeCl) and *N-(*phenylseleno)succinimide (*N*-PSS) have been employed as effective C=C bond activating agents in biomimetic cyclisation of terpenoids.[141,142]

We first tried out PhSeCl as our selenium source. Neither setting up the reaction in DCM at room temperature or under reflux, nor in $CHCl_3$ at reflux led to the cyclisation of ring A (Entry 1, 2 and 3; Table 2.11). Adding $AgSbF_6$ in the mixture at room temperature did not give the desired product **18** either (Entry 4; Table 2.11).[143]

Performing the reaction with *N*-PSS as the organoselenium reagent with TMSOTf at -78 °C delivered the desired mixture of diastereoisomers **18**, but only in 25% yield (Entry 5; Table 2.11).



Entry	Se source	Solvent	additive	T	Time	Ratio	Yield
1	PhSeCl	DCM	none	RT	n/c	1/1.5	0%
2	PhSeCl	DCM	none	40 °C	n/c	1/1.5	0%
3	PhSeCl	$CHCl_3$	none	80 °C	n/c	1/1.5	0%
4	PhSeCl	DCM	$AgSbF_6$	RT	n/c	1/1.5	0%
5	*N*-PSS	DCM	TMSOTf	-78 °C	n/c	1/1	25%
6	PhSeCl	DCM	AgOTf	0 °C	30 mins	1/1	47%
7[a]	PhSeCl	DCM	AgOTf	0 °C	90 mins	1/1	28%
8	PhSeCl	DCM	AgOTf	0 °C	45 mins	1/1	33%
9	PhSeCl	DCM	AgOTf	0 °C	5 mins	1/1	39%
10[a]	PhSeCl	DCM	AgOTf	0 °C	90 mins	1/1.5	38%
11[b]	PhSeCl	DCM	AgOTf	0 °C	90 mins	1/1	43%
12[b]	PhSeCl	DCM	AgOTf	0 °C	45 mins	1/1	53%
13	PhSeCl	DCM	AgOTf	-78 °C	30 mins	1/1	78%

Conditions : dialkene (1.0 eq.), Se source (1.0 eq) and additive (1.0 eq). **a** : 1.5 eq. of PhSeCl and AgOTf. **b :** filter the silver before adding the catalyst mixture to the dialkene solution

Table 2.11: Attempts at cyclising ACA product **15** with a Se source

Murata and co-workers described a one-step cyclisation of acyclic terpene alcohols, more specifically homogeraniol, with phenylselenyl triflate (PhSeOTf).[144]

Our starting material **15** was mixed with PhSeOTf prepared *in situ* from PhSeCl and AgOTf for 30 mins at 0 °C and a mixture of diastereoisomers **18** was obtained in 47% yield (Entry 6; Table 2.11). Leaving the reaction for 45 mins or 90 mins afforded

the diastereoisomers **18** in 28% yield and in 33% yield respectively (Entry 8 and 7; Table 2.11), suggesting a side reaction might occur. During this reaction another product was recovered, but it was not possible to elucidate its structure. Leaving the reaction stirring for only 5 mins afforded **18** in 39% yield (Entry 9; Table 2.11).

Studying the kinetics of the reaction showed that stirring the mixture for 20–30 mins was optimal. It is important to specify that AgOTf needed to be freshly made, otherwise a significant drop in both yield and enantiomeric excess was observed.

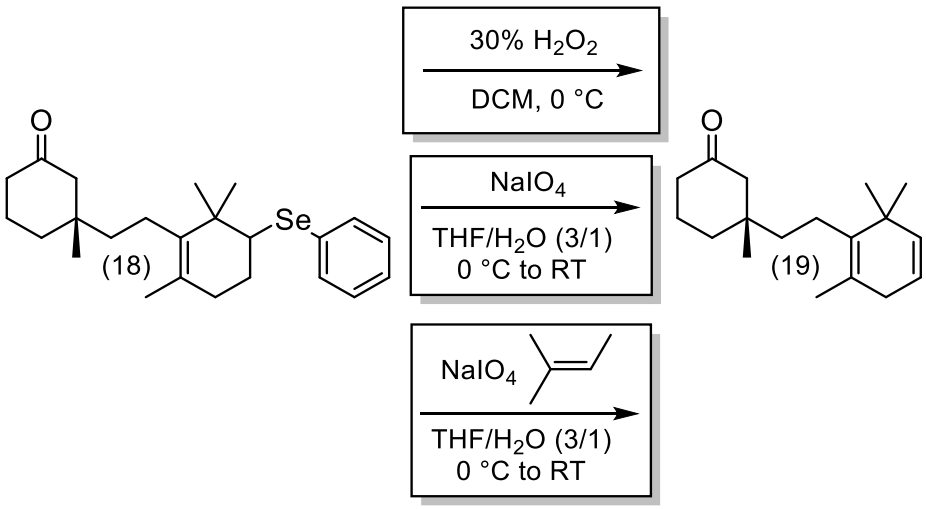
Adding an excess of PhSeOTf into the mixture (1.5 equivalents instead of 1.0) increased by 10% the yield of the reaction for the same amount of time (Entry 7 and 10; Table 2.11). Moreover, removing all traces of silver by filtering the PhSeCl and AgOTf mixture before addition into the dialkene mixture also increased the yield to 43% (Entry 11; Table 2.11).

Our best result was obtained when the reaction was set up with filtered PhSeOTf at 0 °C for 45 mins and a mixture of diastereoisomers **18** was synthesised in 53% yield (Entry 12; Table 2.11). Stirring the reaction at -78 °C produced a mixture of isomers in 78% yield (Entry 13; Table 2.11).

Further optimisation might be needed in order to obtain the optimal conditions for this reaction, but at this point we stopped our investigations to focus our attention on other potential problems.

Cyclised product **18** formed with organoselenium reagents underwent an elimination process by oxidation to form a new C=C bond (Scheme 2.15). Subjecting the selenium substrate **18** to a solution of H_2O_2 in DCM at 0 °C or to $NaIO_4$ in THF/H_2O at 0 °C afforded a mixture containing the dialkene product **19** (Scheme 2.15). Both of those conditions may lead to the formation of side products,[145,146] and so 2-methyl-2-

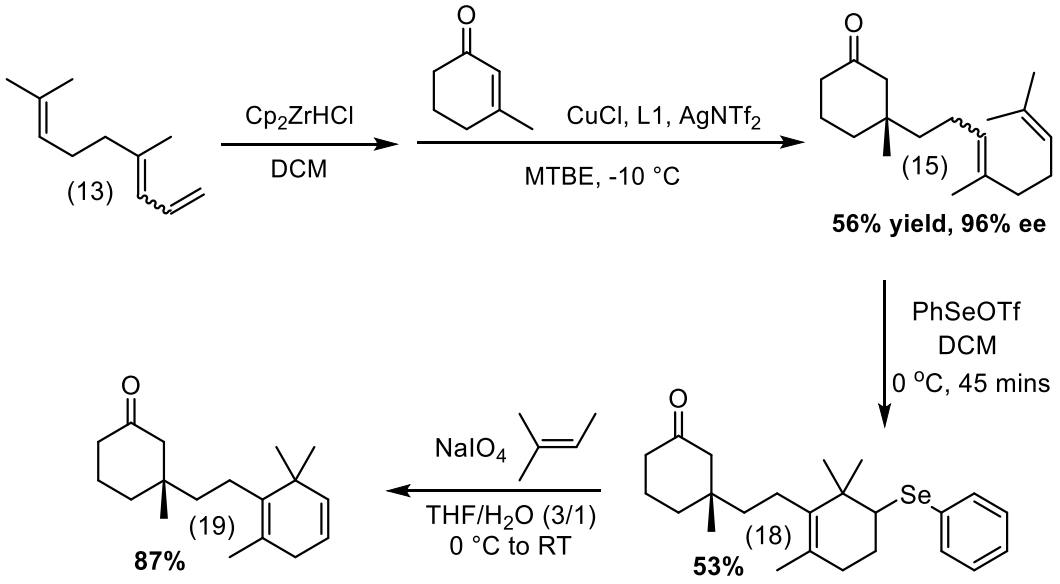
butene was added to the oxidation to react with the newly formed PhSeO which could interact with the alkenes of **19**.



Scheme 2.15: Possible oxidations of the cyclised product **18**

The desired product **19** was formed using $NaIO_4$ and 2-methyl-2-butene in THF/H_2O in 87% yield (determined by crude NMR spectroscopic analysis) contaminated with only small traces of a side product. The elimination product **19** and the side product could not be separated by column chromatography.

So far, we were able to synthesise from *cis/trans* citral (in a single step) in high yields a linear trialkene **13** that underwent the asymmetric 1,4-addition and produced intermediate **15** in 56% yield and 96% ee. Cyclisation of ring A with an organoselenium reagent afforded intermediate **18** in 54% yield and elimination of selenium moiety delivered the desired dialkene **19** in ~87% yield (Scheme 2.16). In order to access the Taxol core, it would be necessary to close ring B.



Scheme 2.16: Overall synthesis of intermediate **19**

In the initial pathway (see Scheme 2.6), **10** obtained from the cyclic trialkene **1** bore one additional carbon compared to **19**, that was supposed to link ring A and ring C to form ring B. Our route with the linear nucleophile was missing a carbon which needed to be added to close ring B and form Taxadiene.

From our latest synthesised substrate **19**, there were two possibilities:

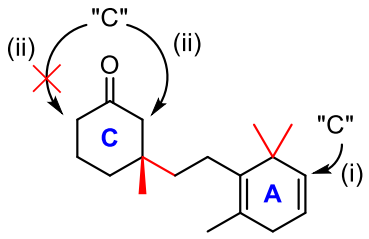


Figure 2.7: Possible addition of a carbon on **19**

- (i) Either adding the carbon on the more accessible alkene of ring A but it seemed unlikely that the following addition will be favourable, due to the steric hindrance of the geminal dimethyl group (Figure 2.7).
- (ii) Or adding the carbon at the α-position of the ketone but this addition seemed also impossible due to the steric hindrance induced by the side chain and the methyl group leading to a more favourable regioselective addition on the

unwanted side of the carbonyl (Figure 2.7).

Since closing ring B with those substrates **10** or **19** seemed unlikely, we decided to investigate a new pathway.

2.3.6 Asymmetric 1,4-conjugate addition on α-substituted cyclic enone

In order to access Taxadienone, our new approach involved incorporation of a moiety (“R”) at the α-position of the enone which could allow closure of ring B, prior to the asymmetric 1,4 addition step followed by ring closure of A using PhSeOTf (Figure 2.8).

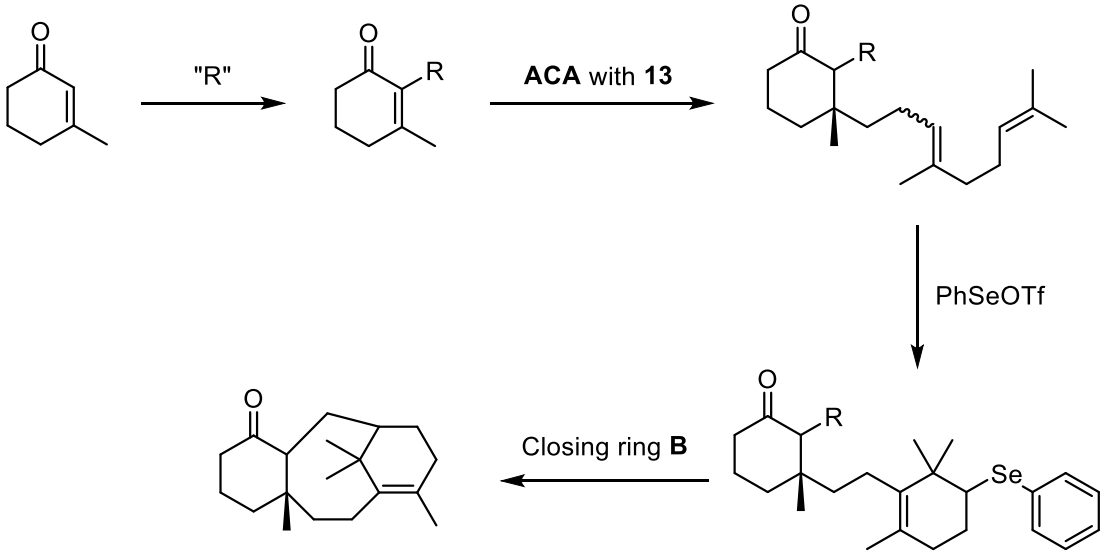


Figure 2.8: New approach towards Taxadienone

A selection of α-substituted 3-methylcyclohex-2-enone were chosen as test substrates for this new pathway. The selected moieties were a bromine, a nitrile and an ester group (Figure 2.9).

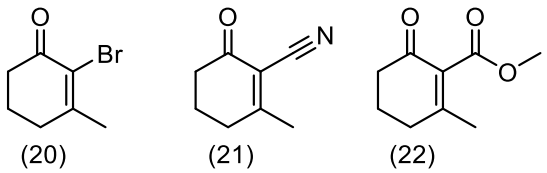
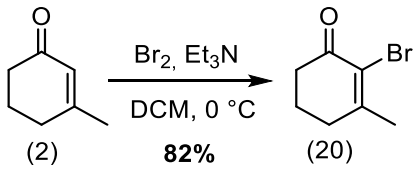


Figure 2.9: α-substituted cyclic enone targets

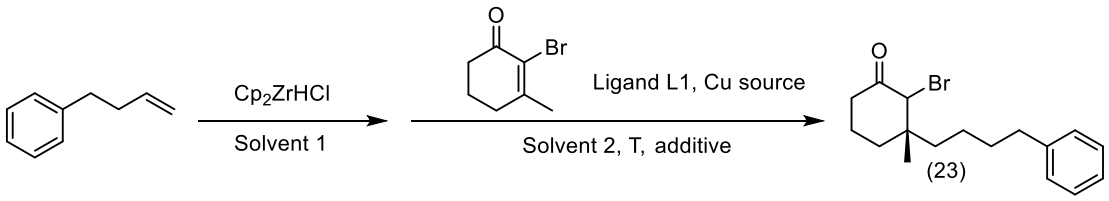
Synthesis of the α-substituted brominated **20** enone was performed by adding bromine to a solution of 3-methylcyclohex-2-enone **2** in DCM at 0 °C, followed by Et_3N in large excess to eliminate the bromine moiety in the β-position (Scheme 2.17).[147] 2-Bromo-3-methylcyclohex-2-en-1-one **20** was synthesised in 82% yield.



Scheme 2.17: Synthesis of α-substituted cyclic enone **20**

Ligand **L1** proved to be a ligand of choice for our previous system and also in other projects developed in the Fletcher group involving the synthesis of quaternary centres. We presumed that it is most likely to be similar for the asymmetric 1,4-conjugate addition with 2-bromo-3-methylcyclohex-2-en-1-one **20**. 4-Phenyl-1-butene was chosen for the investigation of this reaction instead of the linear trialkene **13**.

Our first investigation concerned the influence of the copper source in the system. Most of the different copper sources that were tried out, such as CuOTf, $CuBF_4$, CuOTs, CuOMs, $CuSbF_6$, $CuPF_6$, CuCl, CuI, CuOAc and CuTc, did not catalyse the reaction (Entry 3, and 8 to 16; Table 2.12). Traces of the desired product were observed with $CuBr{\cdot}SMe_2$ and $CuClO_4$ (Entry 2 and 7; Table 2.12).



Entry	Cu source	Additive	T	Yield	ee	Entry	Solvent 1	Solvent 2	T	Yield	ee
1	$CuNTf_2$	none	RT	13%	61%	18	DCM	DCM	RT	traces	n/c
2	$CuBr.SMe_2$	none	RT	traces	n/c	19	DCM	Et_2O	RT	9%	40%
3	CuOTf	none	RT	none	n/c	20	DCM	THF	RT	10%	20%
4	$CuNTf_2$	TMSCl	RT	6%	62%	21	DCM	Dioxane	RT	none	n/c
5	$CuNTf_2$	none	RT	9%	62%	22	DCM	2-Me-THF	RT	9%	47%
6	$CuNTf_2$	none	40 °C	9%	60%	23	DCM	Toluene	RT	7%	41%
7	$CuClO_4$	none	RT	traces	n/c	24	DCM	THF	RT	15%	10%
8	$CuBF_4$	none	RT	none	n/c	25	THF	THF	RT	traces	n/c
9	CuOTs	none	RT	none	n/c	26	DCM	THF	40 °C	traces	n/c
10	CuOMs	none	RT	none	n/c	27	DCM	THF	0 °C	none	n/c
11	$CuSbF_6$	none	RT	none	n/c						
12	$CuPF_6$	none	RT	none	n/c						
13	CuCl	none	RT	none	n/c						
14	CuI	none	RT	none	n/c						
15	CuOAc	none	RT	none	n/c						
16	CuTc	none	RT	none	n/c						
17	$CuNTf_2$	Styrene	RT	6%	36%						

Conditions : alkene (2.5 eq.), Schwartz reagent (2.0 eq.), cyclic enone (1.0 eq.), Cu source (0.1 eq.), ligand (0.1 eq.), additive (5.0 eq.) and ratio of solvent : solvent 1/solvent 2 : 1/5.

Table 2.12: Cu source and solvent screening for the ACA of **20**

As expected, the only copper source that led to synthesis of the product was $CuNTf_2$ (Entry 1; Table 2.12). A mixture of diastereoisomers **23** was afforded in 13% yield and an enantiomeric excess of 61%. No change was observed in yield or enantiomeric excess when the reaction was set-up with TMSCl (Entry 4; Table 2.12) or at 40 °C (Entry 6; Table 2.12).

Our attention then switched towards the influence of the solvents in the system (Table 2.12). All the copper sources investigations were done in a DCM/MTBE solvent

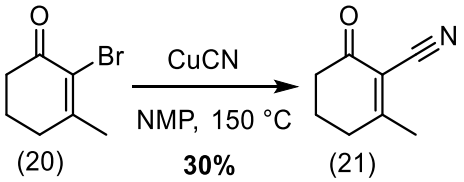
system. All the different experiments that were attempted gave worse results than the reaction performed with $CuNTf_2$ in DCM/MTBE.

Performing the reaction in DCM gave only traces of product (Entry 18; Table 2.12). Switching MTBE to either Et_2O, THF, 2-Me-THF or toluene afforded a mixture of diastereoisomers **23** with a lower enantiomeric excess (Entry 19, 20, 22 and 23; Table 2.12) and no product was observed when MTBE was replaced by dioxane (Entry 21; Table 2.12).

The experiment that delivered **23** in the higher yield was performed in a DCM/THF solvent system (Entry 24; Table 2.12). Unfortunately, neither performing the reaction in only THF (Entry 25; Table 2.12) nor stirring the reaction at various temperatures (Entry 26 and 27; Table 2.12) had any positive influence on the outcome of the reaction. The absolute configuration of **23** was assigned by analogy with previously reported literature from the Fletcher group.[70]

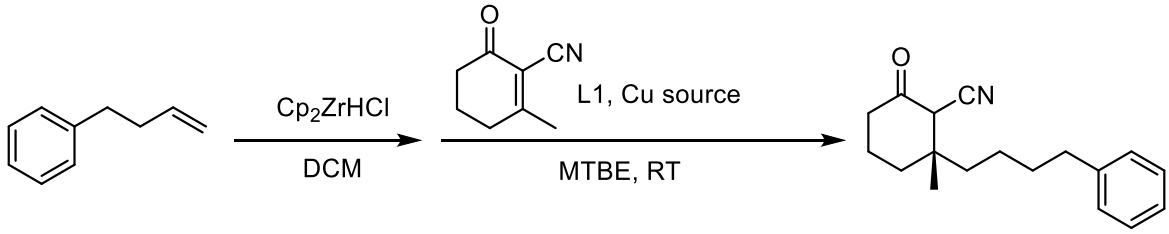
None of the variations from the conditions normally used for the asymmetric 1,4-addition to form quaternary centres had a positive influence on either yield or enantiomeric excess of the reaction. Moreover, the best results obtained were unsatisfactory and the route via 2-bromo-3-methylcyclohex-2-en-1-one **20** was then abandoned.

Preparation of 2-methyl-6-oxocyclohex-1-ene-1-carbonitrile **21** was achieved by stirring 2-bromo-3-methylcyclohex-2-en-1-one **20** and CuCN in NMP at 150 °C (Scheme 2.18).[148] The desired product was synthesised in 30% yield. No optimisation of this reaction was attempted, as enough quantity of substrate **21** was synthesised to allow a proper investigation of the asymmetric 1,4-addition.



Scheme 2.18: Synthesis of α-substituted cyclic enone **21**

Only a few copper sources were tried out with 2-methyl-6-oxocyclohex-1-ene-1-carbonitrile **21** as switching solvent seemed to only have a negative influence in the previous investigation.



Entry	Cu source	ee	Yield
1	$CuNTf_2$	n/c	none
2	$CuNTf_2$	n/c	none
3	$CuNTf_2$	n/c	none
4	CuCl	n/c	none
5	CuOAc	n/c	none
6	CuTc	n/c	none
7	CuCN	n/c	none

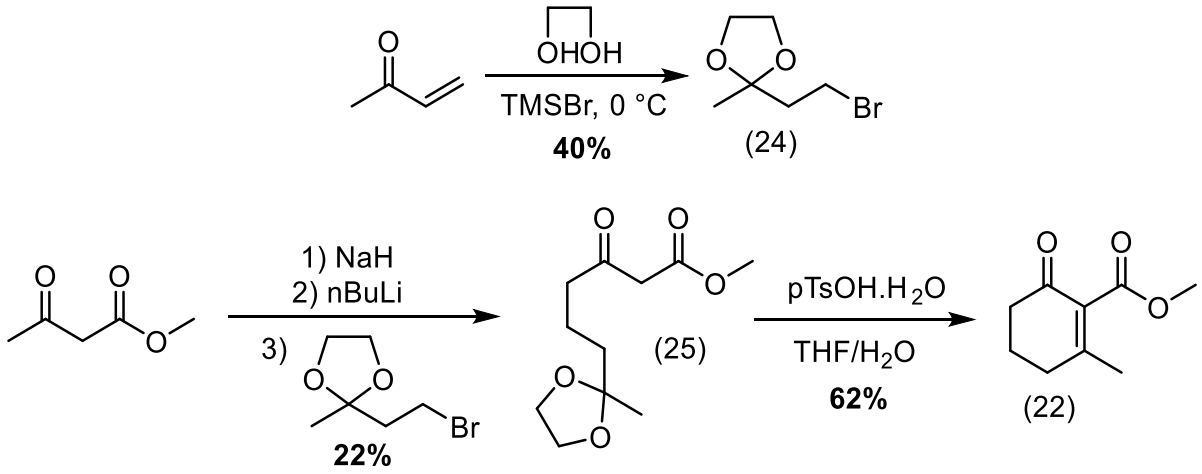
Conditions : alkene (2.5 eq.), Schwartz reagent (2.0 eq.), cyclic enone (1.0 eq.), Cu source (0.1 eq.), ligand (0.1 eq.) and ratio of solvent : DCM/ MTBE: 1/5.

Table 2.13: Cu source screening for the ACA of **21**

Neither $CuNTf_2$, CuCl, CuOAc, CuTc nor CuCN had any impact on the reaction (Entry 1 to 7; Table 2.13). No desired product was observed. Asymmetric 1,4-additions developed within the Fletcher group normally had high reactivity when $CuNTf_2$ was

involved in the process, therefore we decided to leave this substrate **21** aside and focus on the latter test substrate.

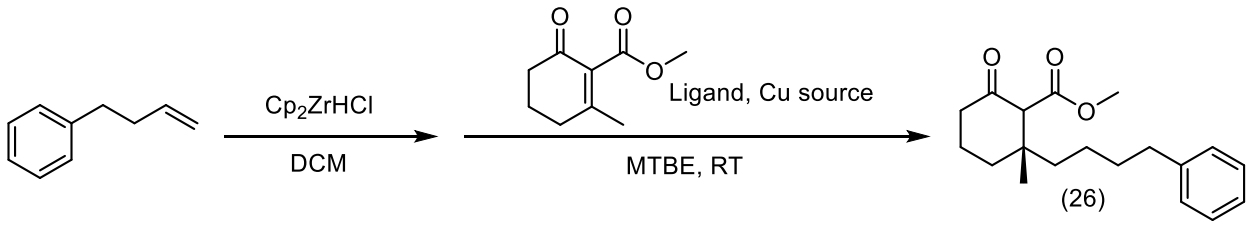
Preparation of methyl 2-methyl-6-oxocyclohex-1-ene-1-carboxylate **22** was achieved in three steps. Ethylene glycol and 3-buten-2-one were stirred together at 0 °C prior to the slow addition of TMSBr for 2 hrs which formed intermediate **24** in an average yield of 40%.[149] The intermediate was added to a solution of twice deprotonated methyl acetoacetate first by NaH and then *n*-BuLi to obtain intermediate **25**. This reaction did not perform well as **25** was obtained in only 22%.[149] Finally, the ketal intermediate **25** was left stirring overnight in acidic conditions to afford methyl 2-methyl-6-oxocyclohex-1-ene-1-carboxylate **22** in 62% yield (Scheme 2.19).[150–152]



Scheme 2.19: Synthesis of α-substituted cyclic enone **22**

Another array of different copper sources was selected with either ligand **L1** or *(S)*-BINAP for the asymmetric 1,4-addition with the new test substrate. Besides CuTc, all the different copper sources that were tried out such as $CuNTf_2$, CuOTf, CuCl, CuOAc and CuCN did not catalyse the reaction with either ligand (Entries 1–4, 6, 7, 9–12; Table 2.14). Unfortunately, the best result obtained with CuTc was only 16% yield

of a mixture of diastereoisomers **26**. We decided to stop investigating this substrate and did not check the enantiomeric excess.



Entry	Cu source	Ligand	Yield	ee
1	$CuNTf_2$	L1	none	n/c
2	CuOTf	L1	none	n/c
3	CuCl	L1	none	n/c
4	CuOAc	L1	none	n/c
5	CuTc	L1	traces	n/c
6	CuCN	L1	none	n/c
7	CuOAc	(S)-BINAP	none	n/c
8	CuTc	(S)-BINAP	traces	n/c
9	CuCN	(S)-BINAP	none	n/c
10	$CuNTf_2$	(S)-BINAP	none	n/c
11	CuOTf	(S)-BINAP	none	n/c
12	CuCl	(S)-BINAP	none	n/c
13	CuTc	L1	16%	n/c
14	CuTc	L1	n/c	n/c

Conditions : alkene (2.5 eq.), Schwartz reagent (2.0 eq.), cyclic enone (1.0 eq.), Cu source (0.1 eq.), ligand (0.1 eq.) and ratio of solvent : DCM/ MTBE: 1/5.

Table 2.14: Cu source screening for the ACA of **26**

Overall, performing the asymmetric 1,4-conjugate addition with an α-substituted 3-methylcyclohex-2-enone did not work as expected. The α-moiety probably negated the reaction due to steric hindrance. Since adding a functional group in the selected α-position of the enone seemed improbable once the chain in β-position is added and

performing the ACA once the moiety was already in place did not work, we attempted to add the moiety during the asymmetric 1,4-addition by trapping.

2.3.7 Trapping reaction

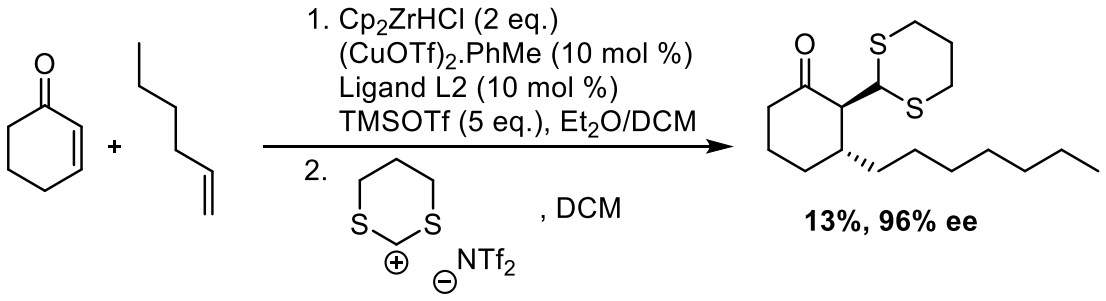
Attempts to perform the ACA followed by trapping had been tried in the Fletcher but none of them were successful. Nevertheless, we decided to investigate it further.

All the test experiments were set up at 0 °C or at room temperature with ligand **L1**, $CuNTf_2$ and DCM/MTBE as the solvent system. Either 4-phenyl-1-butene or the linear trialkene **13** were used.

A variety of different electrophiles were selected to be trapped in the reaction. We first tried out to trap Eschenmoser's salt.[153] Two experiments were envisaged: first adding the electrophile once the 1,4-addition was finished, and second adding Eschenmoser's salt at the start of the reaction. For the first reaction only the asymmetric 1,4-conjugate addition products were observed and in the second reaction the starting material was left unreacted. The same pattern was observed with either paraformaldehyde in solution, with a MOM-protected amine or with benzaldehyde.[65,153]

Our conclusion after those test reactions were that the electrophile needed to be added after the asymmetric 1,4-conjugate addition to possibly trap any substrate.

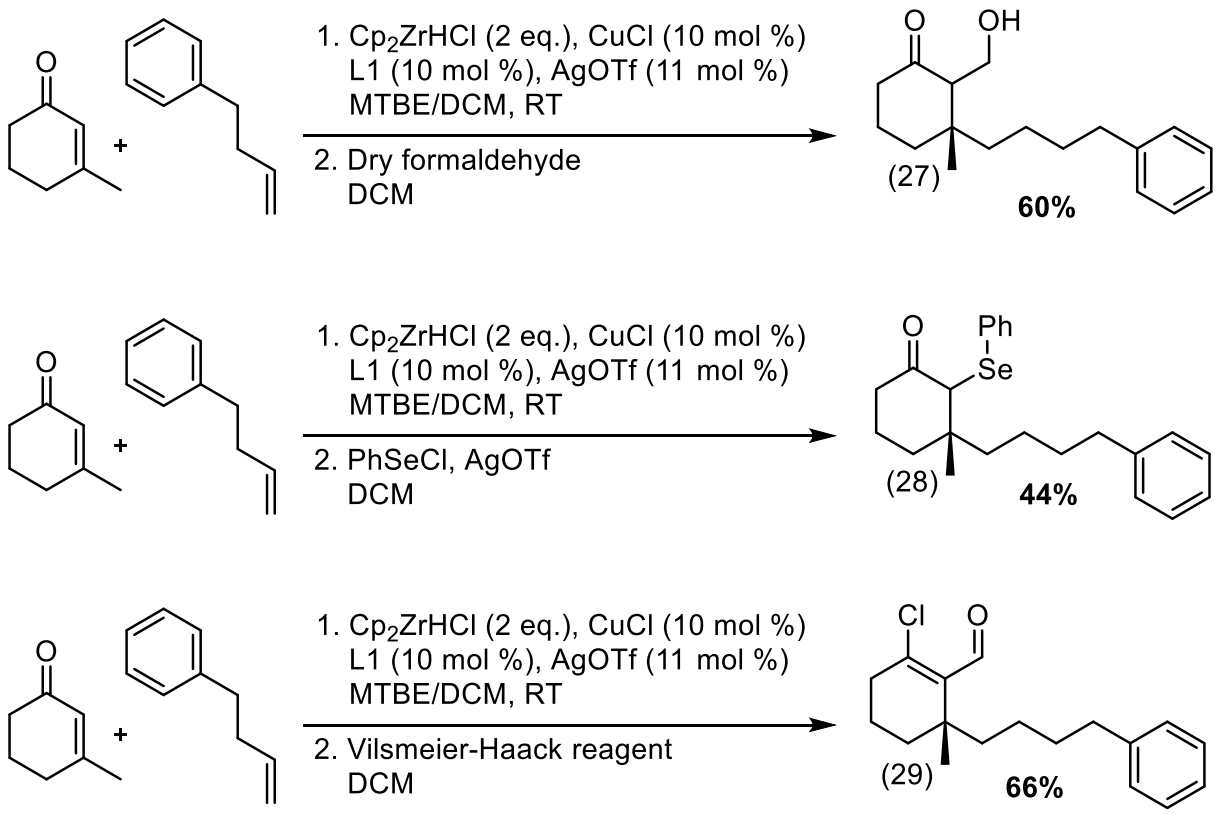
A recent publication by Sebesta and co-workers presented a domino hydrozirconation/conjugate addition/enolate trapping system using a methodology based on the ACA developed in the Fletcher group with an interesting dithiane.[154] The desired product was obtained in a low yield (13 %), which showed that it was possible to perform the enolate trapping step (Scheme 2.20). Unfortunately for us, we did not manage to reproduce the published results on our system.



Scheme 2.20: Trapping reactions with dithiane electrophile

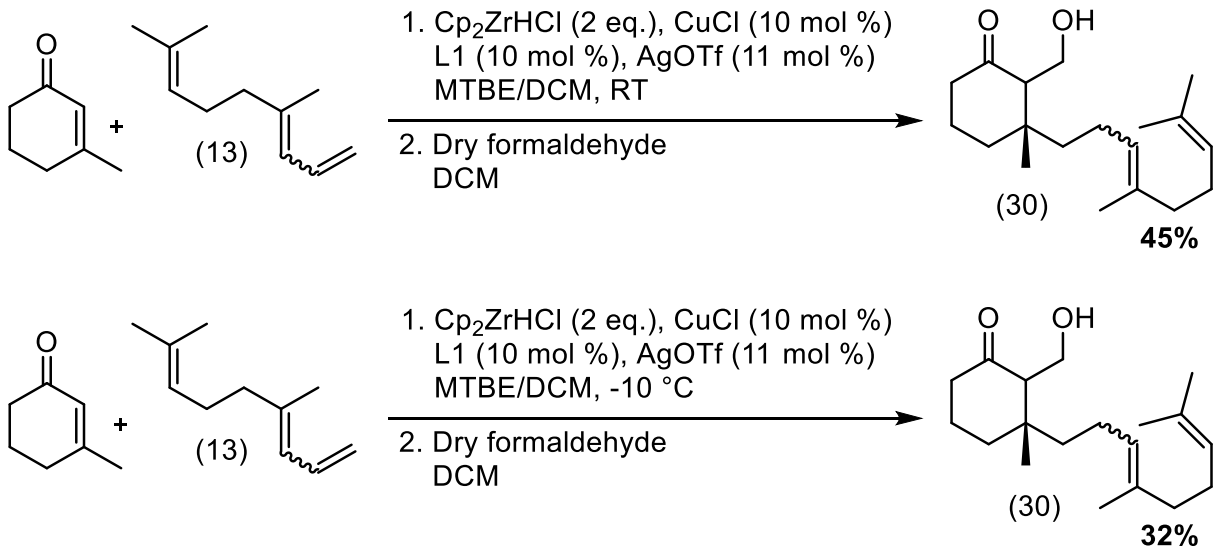
Searching deeper through literature, we discovered that Schwartz described also a domino hydrozirconation/conjugate addition/enolate trapping reaction with dry formaldehyde as the trapping agent when nickel was used instead of copper.[155]

Setting up the experiment with dry formaldehyde produced *in situ* by cracking paraformaldehyde, delivered a mixture of diastereoisomers **27** in 60% yield (Scheme 2.21). We also found that using PhSeOTf as the electrophile produced a mixture of diastereoisomers **28** in 44% yield (Scheme 2.21).[156] Furthermore, the use of Vilsmeier reagent provided an unexpected product **29** with interesting structural properties in 66% yield (Scheme 2.21).[157] The enantiomeric excess of the products were checked by my co-worker Joseph Wang by taking an aliquot of the reaction prior to the addition of the electrophiles. Enantiomeric excesses above 90% were obtained. The absolute configurations of **27**, **28** and **29** were assigned by analogy with previously reported literature from the Fletcher group.[70]



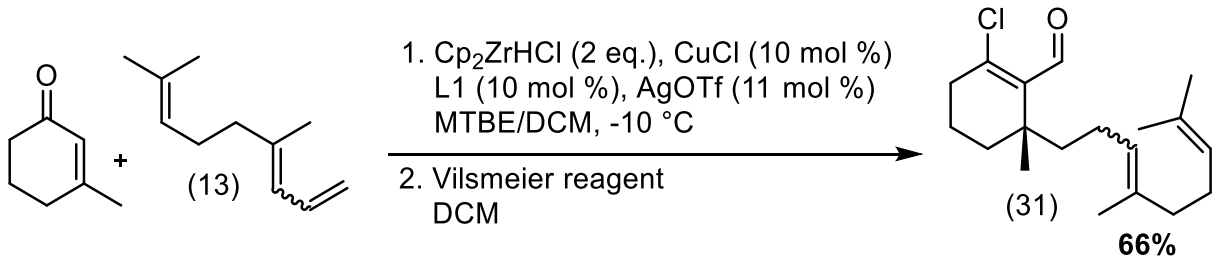
Scheme 2.21: Trapping reactions with other electrophiles

Performing the newly discovered domino reaction with linear trialkene **13** worked to some extend with dry formaldehyde as the trapping reagent. At room temperature, a mixture of diastereoisomers and isomers *Z/E* **30** was obtained in 45% yield, however when the reaction was done at -10 °C the yield went down to 32% (Scheme 2.22). No enantiomeric excess was checked for **30** as we assumed it would not be impacted by the trapping step. The absolute configuration of **30** was assigned by analogy with previously reported literature from the Fletcher group.[70]



Scheme 2.22: Trapping reactions with dry formaldehyde and linear trialkene **13**

To our delight, reaction with the Vilsmeier–Haack reagent produced a mixture of isomers *Z/E* **31** in 66% yield when the reaction was left stirring at -10 °C (Scheme 2.23). The absolute configuration of **31** was assigned by analogy with previously reported literature from the Fletcher group.[70]



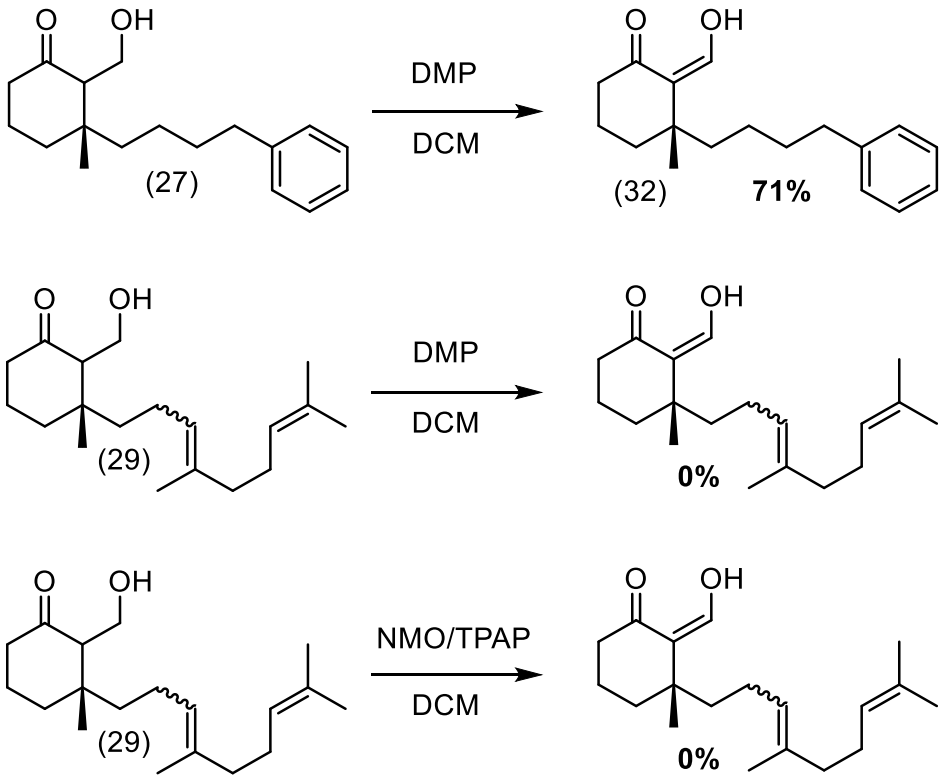
Scheme 2.23: Trapping reaction with Vilsmeier–Haack reagent and linear trialkene **13**

Hence, we discovered that the domino hydrozirconation/conjugate addition/enolate trapping was possible with three different trapping reagents and an unexpected product was observed with the Vilsmeier–Haack reagent. We then decided to focus on how we could further transform **30** or **31** in order to close ring B.

2.3.8 Further transformations

The substrates produced by the domino reaction with dry formaldehyde bear an alcohol that can be oxidised. Subjecting intermediate **27** to DMP oxidation delivered **32** in 71% yield (Scheme 2.24).[158]

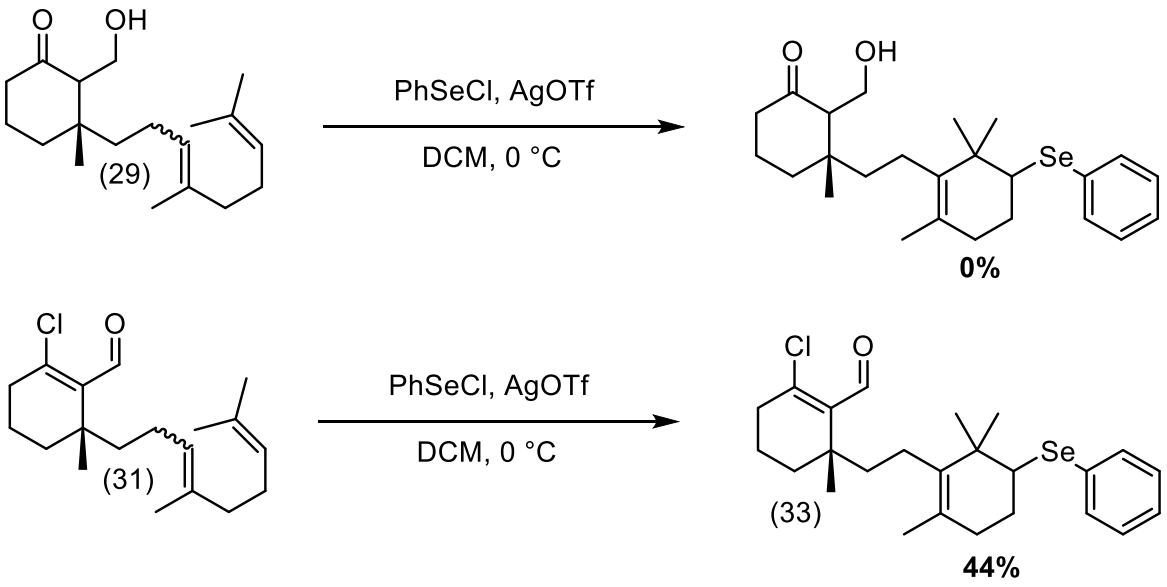
However we were not able to oxidise **29** in the desired way with either DMP or NMO/TPAP (Scheme 2.24).[159] It is possible that a side reaction occurred with the alkene of the side chain.



Scheme 2.24: Oxidations of trapped products

We also looked into the closing of ring A with PhSeOTf. No cyclised product was observed starting with **29**. The alcohol might react with PhSeOTf and prevented the cyclisation from occurring (scheme 2.25).

However, a mixture of diastereoisomers **33** was obtained from chloro-aldehyde **31** in 44% yield (scheme 2.25)

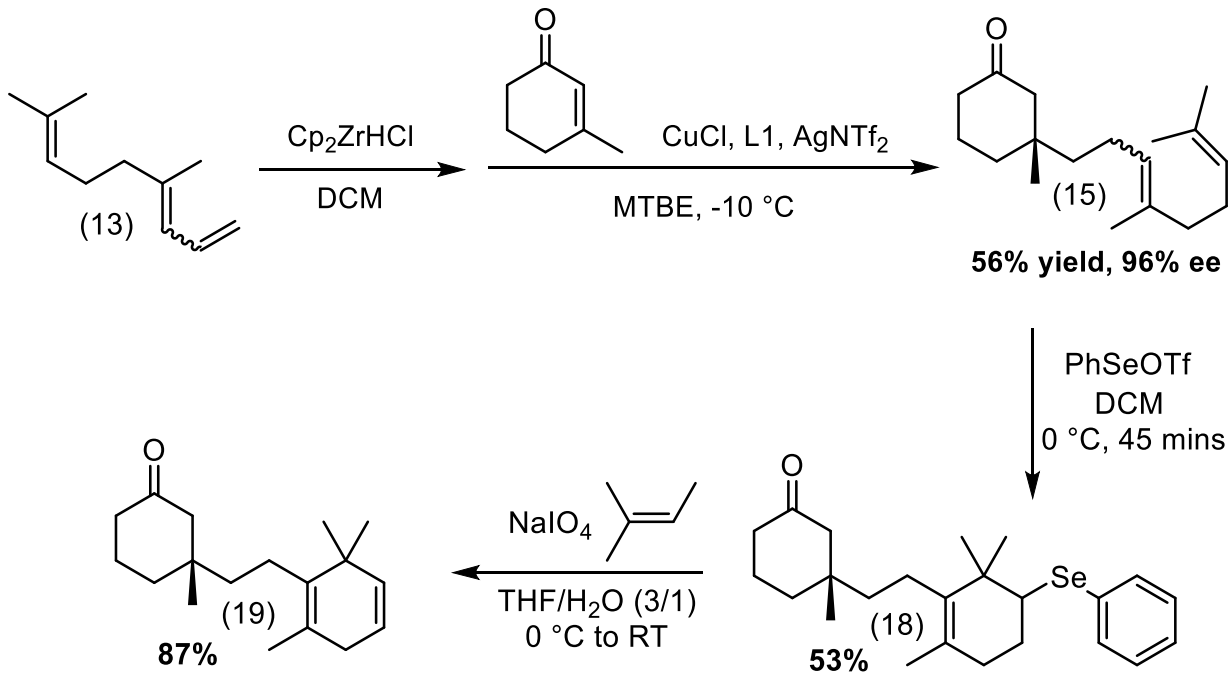


Scheme 2.25: Closing ring A of trapped products

2.4 Summary

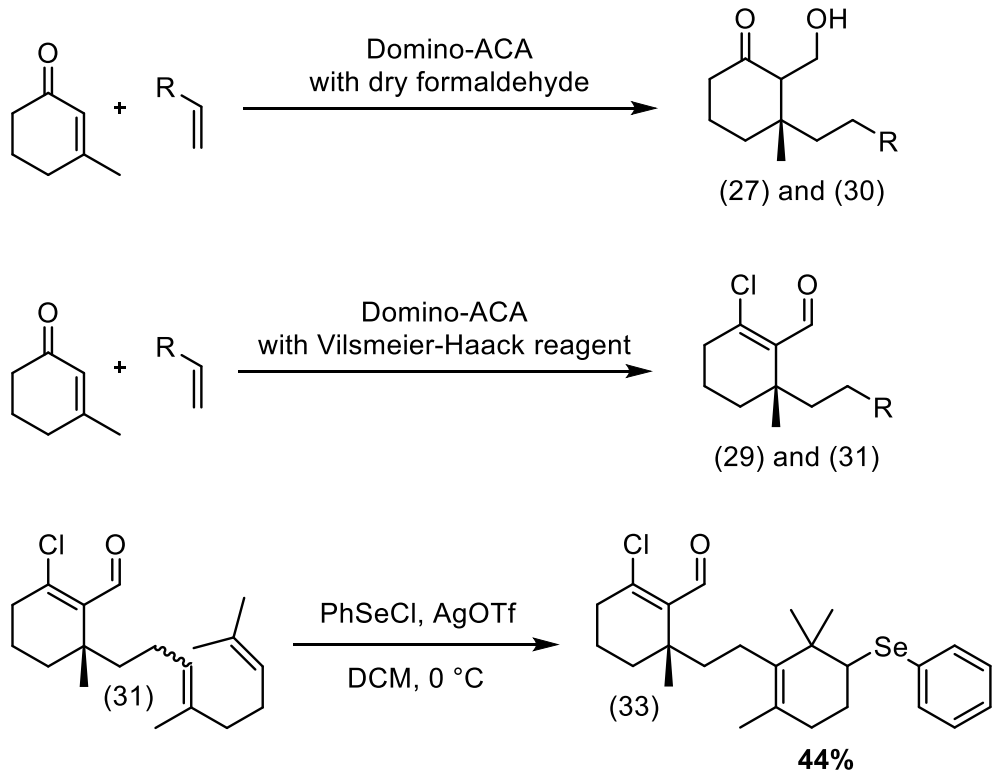
During the course of this project, we first investigated the asymmetric 1,4-conjugate addition of cyclic alkenes **1** and **11** on a cyclic enone in order to couple ring A and C of our target molecule Taxadiene. ACA products **10** and **12** were only synthesised in both low yield and low enantiomeric excess, therefore we decided to investigate linear trialkene **13** which could be later cyclised into ring A.

After optimisation, we were able to synthesise the ACA product **15** in 56% yield and 96% ee. In order to cyclise ring A, we first investigated bromine electrophiles, but a mixture of isomers was obtained. Switching to a selenium source however provided bicyclic product **18** in 54% yield**.** Further oxidation gave **19** in 87% yield. However, no cyclisation of ring B was attempted on intermediate **19,** which was missing a carbon in the α-position of the ketone (Scheme 2.16)



Scheme 2.16: Overall synthesis of intermediate **19**

Two options were then investigated in order to obtain an intermediate similar to **19**, but bearing the missing, suitably functionalised, carbon. ACAs on α-substituted cyclic enones showed only low reactivity and enantioselectivity in the best cases. However, ACAs followed by novel enolate trapping reactions provided products **27**, **29**, **30** and **31**. Closing of ring A was also possible on **31** which afford **33** in 44% yield (Scheme 2.26).



Scheme 2.26: Domino-ACA and synthesis of **33**

Unfortunately, due to lack of time we were not able to investigate the ring closure step, even though we believed it should be possible to achieve the synthesis of Taxadiene using this approach. We hypothesised that a radical process involving the selenium moiety could generate the ring closure.

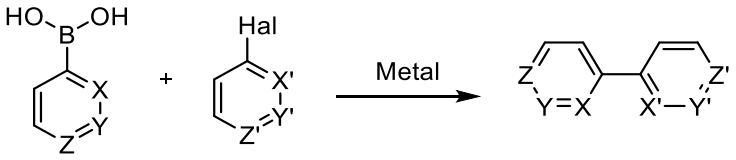
Chapter 3

3 Asymmetric Allylic Arylation of Chloro-Tetrahydropyridines

3.1 Introduction

3.1.1 The Suzuki-Miyaura cross-coupling reaction

One of the most widely used methods in order to create new C-C bonds in chemical synthesis is the metal catalysed cross-coupling reaction of two simple adducts to generate a more complex molecule.[160] The Suzuki-Miyaura reaction is one of the most famous examples of metal catalysed cross-coupling. It is a robust, convenient and widely used reaction which can be described as the cross-coupling of an sp^2-hydridised boronic acid derivative and an sp^2-hybridised halide (Scheme 3.1).[161]



Scheme 3.1: The Suzuki-Miyaura cross-coupling reaction

The Suzuki-Miyaura reaction is a key transformation to form C-C bonds and has been extensively used in drug synthesis.[162] Heteroaromatic moieties are essential units found in many drugs (Figure 3.1)[163,164] and can also be used as coupling partners in the Suzuki-Miyaura reaction.[165,166] The drug discovery industry has however been particularly interested in 3D molecules in the last few years,[162,167] while the Suzuki-

Miyaura reaction is mostly limited to the generation of "flat" compounds since it creates Csp^2-Csp^2 bonds.[168]

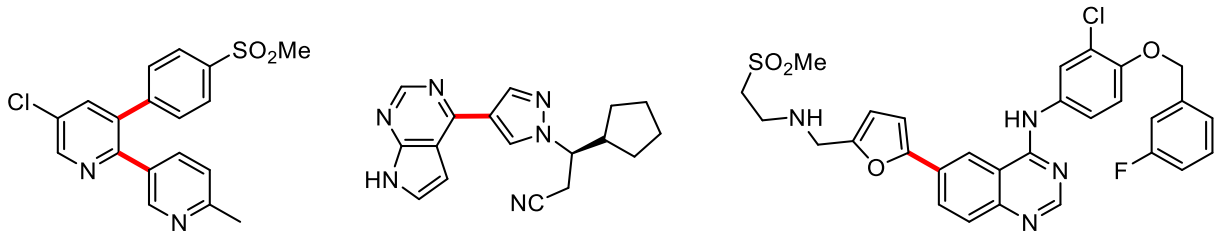


Figure 3.1: Examples of drugs where the Suzuki-Miyaura reaction is used

3.1.2 Asymmetric Suzuki-Miyaura reactions

The potential for Suzuki-Miyaura cross-coupling reactions to prepare enantioenriched molecules[169] has motivated the research community, and an array of stereospecific methodologies using enantiopure starting materials have been discovered. Research groups, like Suginome's and Hall's, reported stereospecific cross-coupling reactions starting from an enantioenriched alkylboronic acid where stereoinversion was observed at the original stereocentre (Figure 3.2).[170–172]

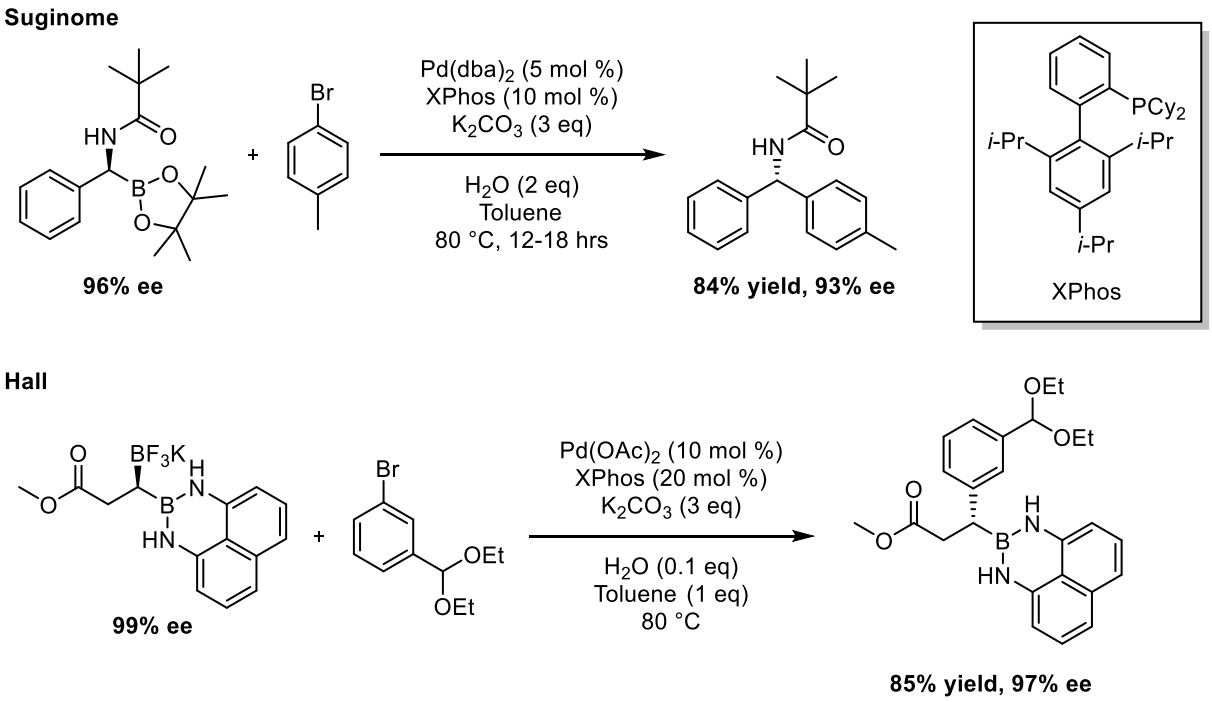


Figure 3.2: Stereospecific cross-coupling reactions with stereoinversion

Stereoretention of the stereogenic centre was also reported for the stereospecific reactions with enantiopure alkylboronic reagents developed by Molander, Crudden, Zhou and others (Figure 3.3).[173–176]

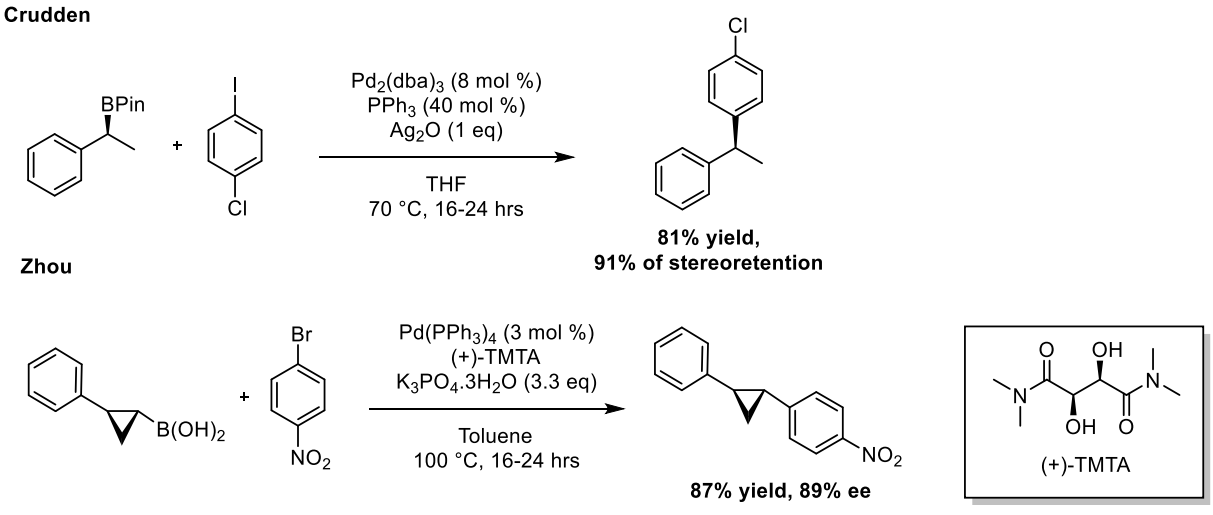
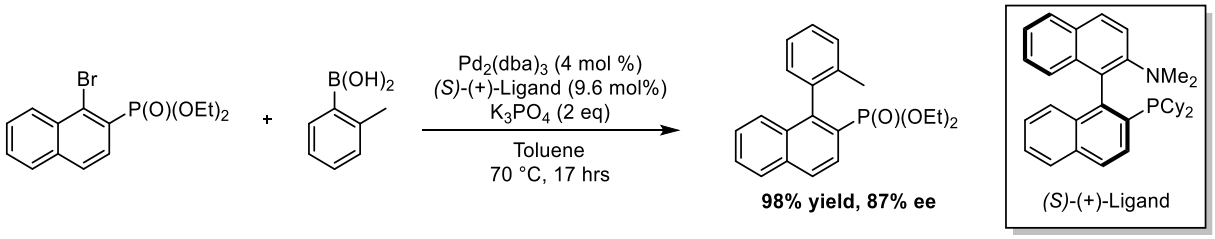


Figure 3.3: Stereospecific cross-coupling reactions with stereoretention

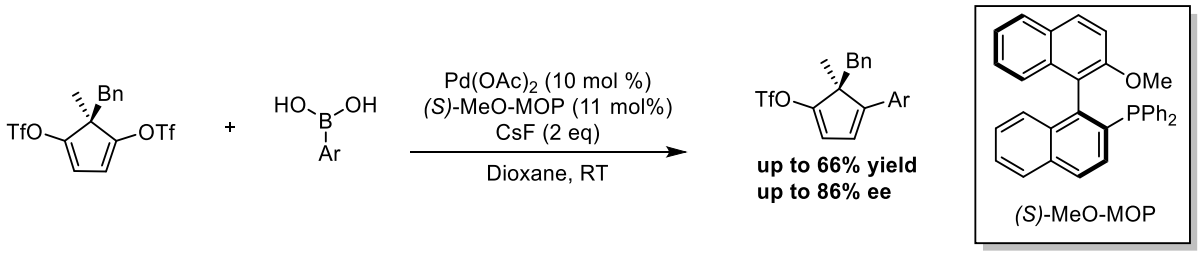
Similarly, different research groups reported stereospecific cross-coupling reactions where enantiopure halides were employed.[177–179]

The first examples of stereoselective Suzuki-Miyaura cross-coupling reactions were described in 2000 when the Cammidge and Buchwald groups both reported the synthesis of axially chiral biaryls via Pd-catalysed coupling (Scheme 3.2).[180,181]



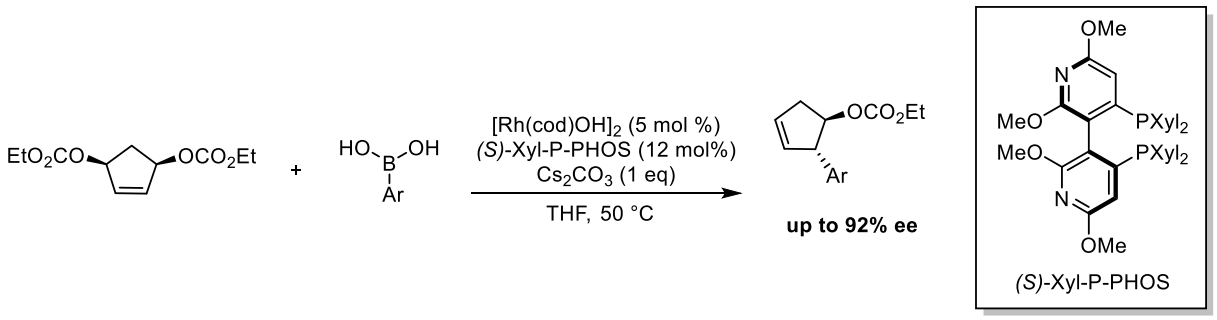
Scheme 3.2: Buchwald's synthesis of chiral biaryls

Desymmetrisation strategies using prochiral or *meso* compounds are another type of asymmetric Suzuki-Miyaura reaction.[182,183] Willis and co-workers reported the enantioselective Palladium-catalysed reaction of bis-vinyltriflates bearing a prochiral quaternary centre with arylboronic acids (Scheme 3.3).[184,185]



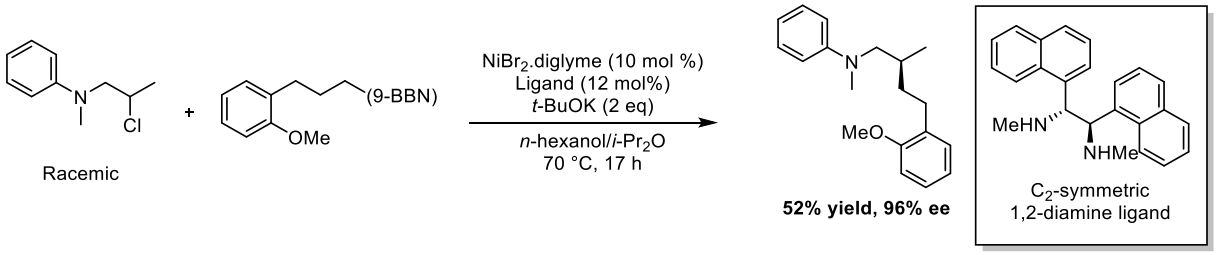
Scheme 3.3: Willis' desymmetrisation of cyclopentadienes

The Lautens' research group reported similarly the desymmetrisation of prochiral *meso* cyclopentene-1,4-diols via Rhodium-catalysed addition of aryl boronic acids (Scheme 3.4).[186,187]



Scheme 3.4: Lautens' desymmetrisation of cyclic diols derivatives

Finally, Fu and co-workers reported in 2008 a stereoconvergent amine-directed Suzuki-Miyaura reaction via Nickel-catalysed alkylations or arylations of racemic alkyl halides (Scheme 3.5).[188–191]



Scheme 3.5: Fu's α-alkylation of racemic alkyl chloride

3.1.3 Rhodium-catalysed asymmetric allylic addition of nucleophiles

The Fletcher group previously reported a catalytic asymmetric addition of sp^3-hybridised alkylzirconium compounds to racemic allyl halides (see details in chapter 4, part 4.1.5).[192–195] Attempts to extend this methodology to create Csp^2-Csp^3 bonds with sp^2-hybridised alkylzirconium reagents proved difficult, with only moderate enantioselectivity observed.[192]

Sp^2-hybridised boronic acids have been widely used in asymmetric reactions such as 1,2-additions,[196] 1,4-additions,[197,198] allylic vinylations,[199] desymmetrising allylic additions[200,201] and allylic arylations.[202] Fletcher and co-workers investigated allylic arylation reactions with racemic substrates, and reported in 2015 the Rhodium-

catalysed asymmetric allylic arylation of racemic cyclic halides with arylboronic acids.[203] This system involves [Rh(cod)(OH)$_2$] and *(S)*-Xyl-P-PHOS in the presence of Cs_2CO_3 and tolerates both electron-rich and electron-deficient arylboronic acids (Figure 3.4).

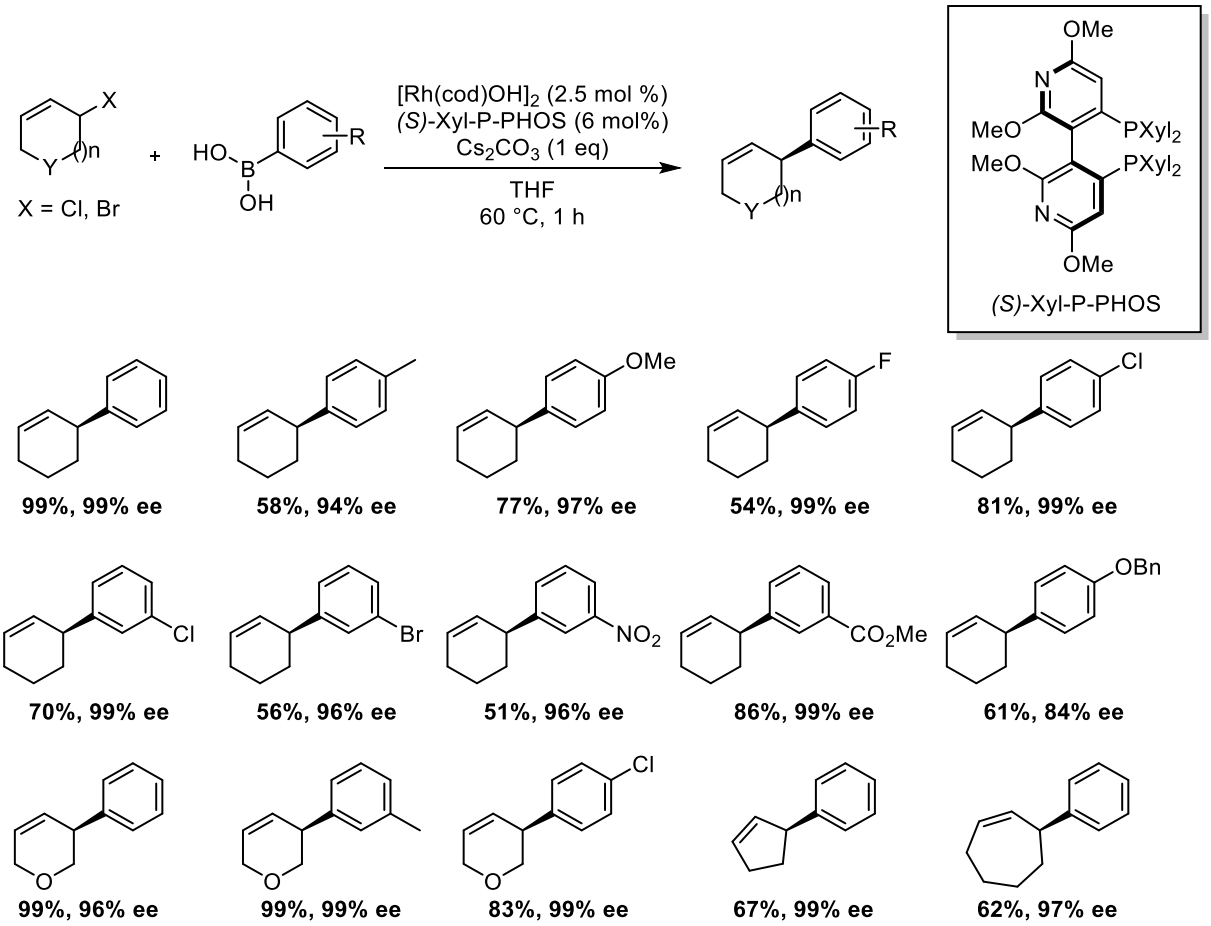


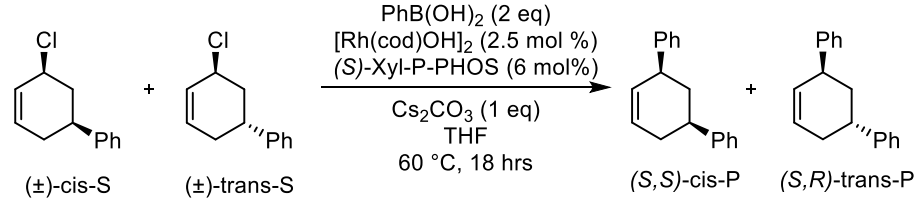
Figure 3.4: Examples of Rh-catalysed asymmetric allylic arylation

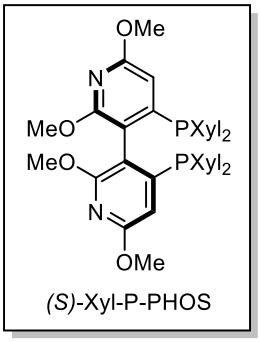
In order to obtain mechanistic insights into this system, several asymmetric allylic arylations of racemic 3-chloro-5-phenylcyclohex-1-ene with phenylboronic acids were performed. Different *cis* and *trans* ratios of racemic allyl chloride were prepared and exposed to the reaction conditions (Table 3.1).[203]

With a starting 1:25 *cis:trans* ratio of 5-phenyl substituted allyl chloride, the *cis*-product was obtained predominantly in a 25:1 *cis:trans* ratio (Entry 1; Table 3.1). The

relative stereochemistry of the starting material and product was completely inverted. Similarly, when using a *cis:trans* ratio of 1:5.3 of the allyl chloride, the *cis*-biphenyl product was again obtained predominantly in a *cis:trans* ratio of 5.3:1 with complete inversion (Entry 2; Table 3.1).

Starting the experiment with a *cis:trans* ratio in favour of the *cis*-starting material isomer (6.1:1) afforded mainly the *trans*-product with a slight loss in the *cis:trans* ratio to 1:5.3 (Entry 3; Table 3.1). Once again, relative complete inversion of configuration was observed. Finally, when the same experiment (6.1:1 ratio of *cis:trans*) was stopped after 3 hrs, the ratio of *cis:trans* only reached 1:4.5 in favour of the *trans*-biphenyl product (Entry 4; Table 3.1). The conversion of this reaction experiment was 84%, and the recovered 5-phenyl substituted allyl chloride had a *cis:trans* ratio of >50:1, which suggested that the *trans*-starting material reacted faster than its cis-isomer under these reaction conditions.





Entry	S *cis:trans*	Conversion (%)	Remaining S *cis:trans*	cis-P ee (%)	trans-P ee (%)
1	1:25	100	-	>99	98
2	1:5.3	100	-	>99	>99
3	6.1:1	100	-	98	>99
4	6.1:1	84	>50:1	97	>99

Table 3.1: Stereoselectivity of asymmetric allylic arylation

Overall, those experiments showed that a dynamic kinetic asymmetric transformation (DYKAT) process occurred with an overall inversion of configuration. Moreover, the slight erosion of diastereomeric ratio observed when the reaction started

with an excess of *cis*-allyl chloride could result from partial isomerisation from *cis* to *trans* of the starting material during the reaction.

A DYKAT is a process related to dynamic kinetic resolution (DKR). A DKR mechanism can be described as the rapid racemisation (k_{rac}) *in situ* of both enantiomers of the substrate (S) and the generation of single enantiopure product (P) in 100% theoretical yield since one enantiomer reacts faster than the other but slower than the racemisation ($k_{rac} >> k_r >> k_s$) (Figure 3.5). [204–207]

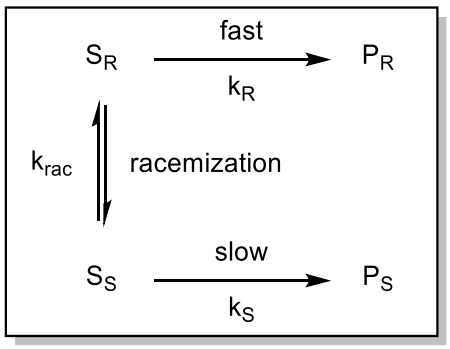
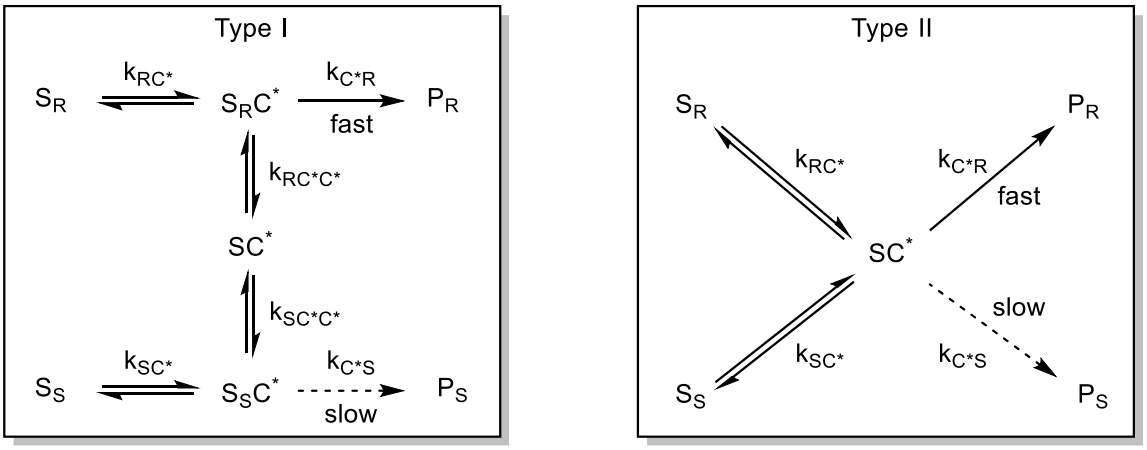


Figure 3.5: Dynamic kinetic resolution mechanism

In a DYKAT process, both enantiomers of the substrates are converted to a single enantiomer product without resolution.[204,205] The interconversion happens through the (metal-catalysed) equilibration of intermediates. Different types of DYKATs have been classified according to their mechanism (Figure 3.6).

In a type I DYKAT, the reaction of the substrates with a chiral catalyst generates a mixture of diastereomeric intermediates where one favourably gives the single enantiomer product (Figure 3.6, left).[204,205,208] In a type II DYKAT, the single enantiomer product is formed through the desymmetrisation of a single enantiomeric intermediate generated from the reaction of the substrates with the chiral catalyst (Figure 3.6, right).[204,205]



S_R, S_S = substrates enantiomers; P_R, P_S = product enantiomers
k_{RC^*}, k_{SC^*} = rate constants for formation of intermediates
k_{C^*R}, k_{C^*S} = rate constants for reaction of intermediates
$k_{RC^*C^*}$, $k_{SC^*C^*}$ = rate constants for interconversion of intermediates

Figure 3.6: Dynamic kinetic asymmetric transformations type I and II

Vinylboronic acids are difficult to use in asymmetric additions due to their relative instability. They often undergo protodeboronation[209] and polymerisation.[210,211] After investigations, Fletcher and co-workers reported the asymmetric addition of vinylboronic acids to racemic cyclic allyl chlorides using [Rh(cod)$(OH)_2$] and *(R)*-BINAP in the presence of Cs_2CO_3 in THF at 60 °C for 4 hrs (Figure 3.7).[212]

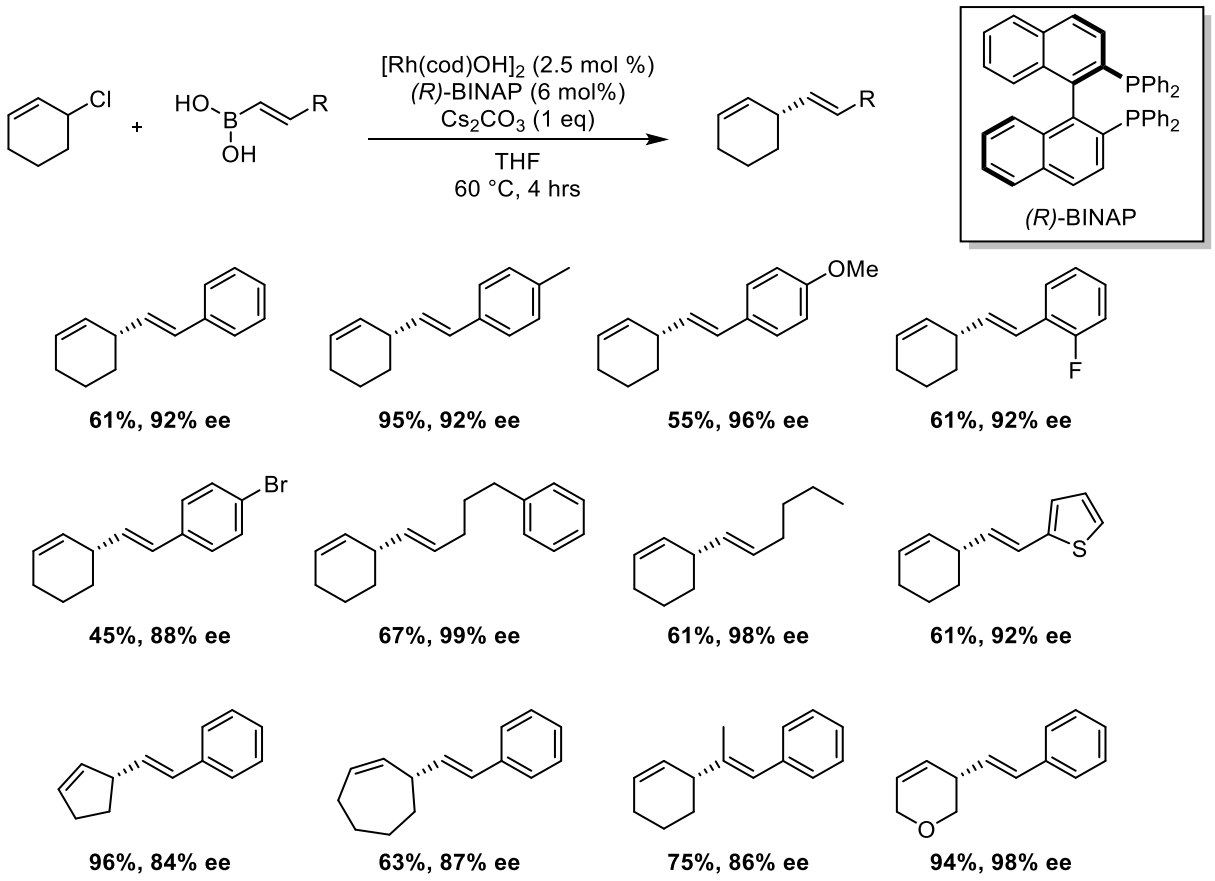


Figure 3.7: Examples of Rh-catalysed asymmetric allylic vinylation

The Fletcher group also investigated the use of heteroarylboronic acids in the Rh-catalysed asymmetric allylic arylation. Heterocycles are key components of biologically active drugs, but the methodology to form Csp^2-Csp^3 bonds with heteroaromatics is lacking despite its major importance.[213–217] Fletcher and co-workers reported in 2017 the asymmetric allylic heteroarylation of racemic cyclic allyl halides with heteroarylboronic acids using [Rh(cod)$(OH)_2$] and *(R)*-BINAP, in the presence of Cs_2CO_3 in THF at reflux for 2-3 hrs (Figure 3.8).[212]

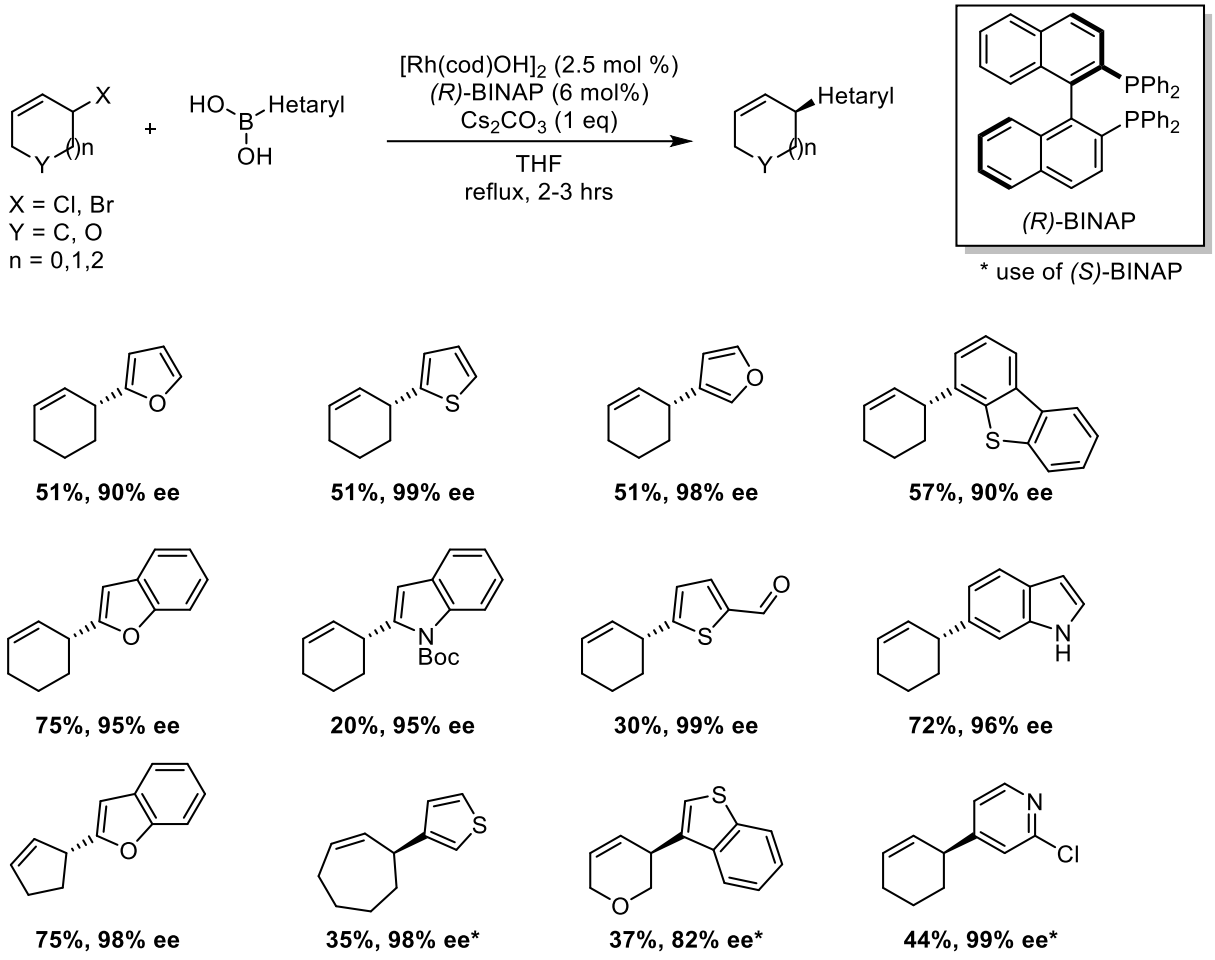


Figure 3.8: Examples of Rh-catalysed asymmetric allylic heteroarylation

The reaction system tolerated a variety of different heteroaryl moieties such as furan, thiophene, protected pyrrole, dibenzothiophene, benzofuran and protected indole as well as different electrophiles.

3.2 Project aims

The extensive study of the asymmetric allylic arylation of racemic allyl halides with arylboronic acids, heteroarylboronic acids and vinyl boronic acids performed in the Fletcher group provided promising results (Figure 3.9).[203,212]

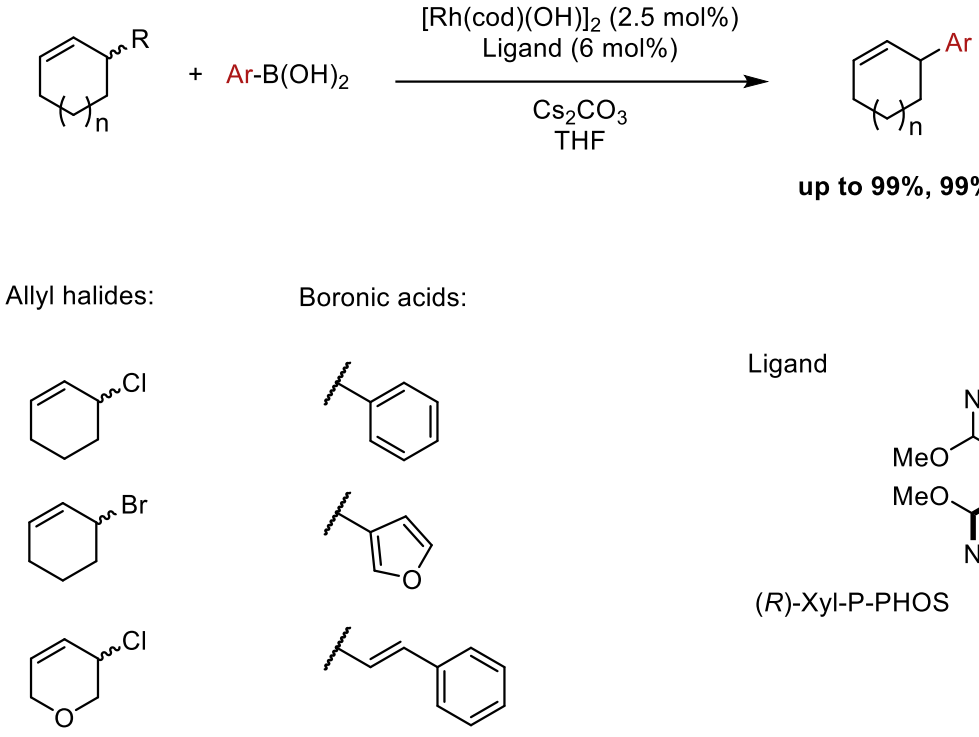
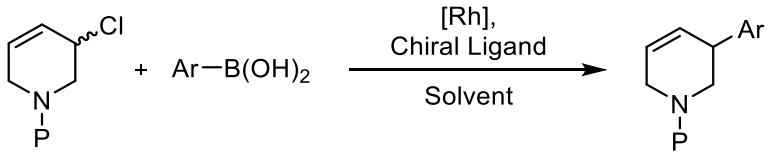


Figure 3.9: Previously reported asymmetric allylic arylation by the Fletcher group

Our interest focused on the investigation of structural motifs often found in drugs and bioactive compounds: Tetrahydropyridine (THP) and its derivatives.[218–220] The synthesis of chiral piperidine products by cross-coupling reactions is rare and relevant examples are either limited to the α-position or enantiospecific couplings.[220–222] This project consisted of applying the developed asymmetric allylic arylation to an aliphatic *N*-heterocyclic piperidene with a broad library of boronic acids. In order to avoid any possible side reaction involving the nitrogen of the tetrahydropyridine, we decided to perform our investigations on a protected coupling reagent (Scheme 3.6).



Scheme 3.6: Project aim

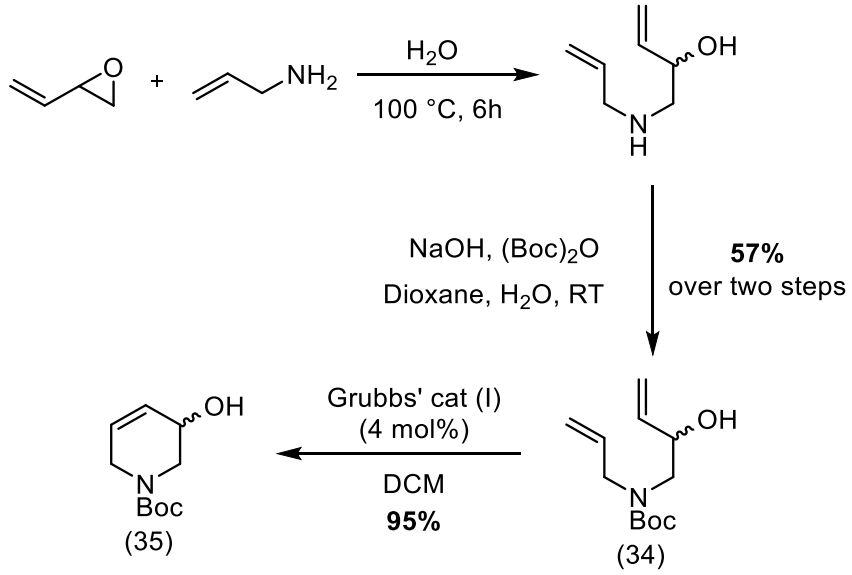
Therefore, optimisation of the previously described reaction conditions would possibly be required. Rhodium was found to be promising for the coupling reaction with allyl halides and might also be suitable with the protected *N*-heterocyclic piperidene chloride.[203]

We further aimed to demonstrate the synthetic possibilities of the coupling products by carrying out various transformation reactions and synthesising an antipsychotic drug: (-)-Preclamol[223–226]

3.3 Results and discussion

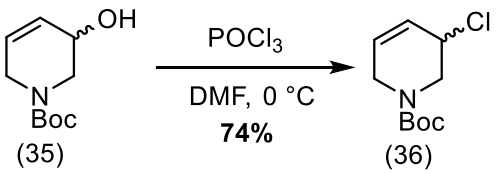
3.3.1 Preparation of the new coupling partner

Our first aim was to synthesise the new coupling partner. Based on the work of Takahata and co-workers,[227] allylamine and butadiene monoxide were mixed in order to obtain the secondary amine intermediate, which was immediately protected with a Boc group. This reaction was done several times with yields ranging from 51 to 65% and an overall yield of 57% over two steps. The next step consisted of a metathesis using Grubbs' catalyst (I). Still based on the research of Takahata and co-workers,[227] the reaction was done several times with an average yield of 95%, 99% being the best result obtained (scheme 3.6).



Scheme 3.6: Synthesis of the new coupling partner

Different chlorinating reagents were tested to transform the alcohol moiety into a chloride. PCl_3 in pyridine at 0 °C and PPh_3Cl_2 in DCM with imidazole gave the desired product **36** in respectively 29% and 17% yield. Considering the low amount of product **36** obtained, we opted for a third possibility. Using $POCl_3$ in DMF at 0 °C, we obtained the desired product **36** in 68% yield (scheme 3.7).

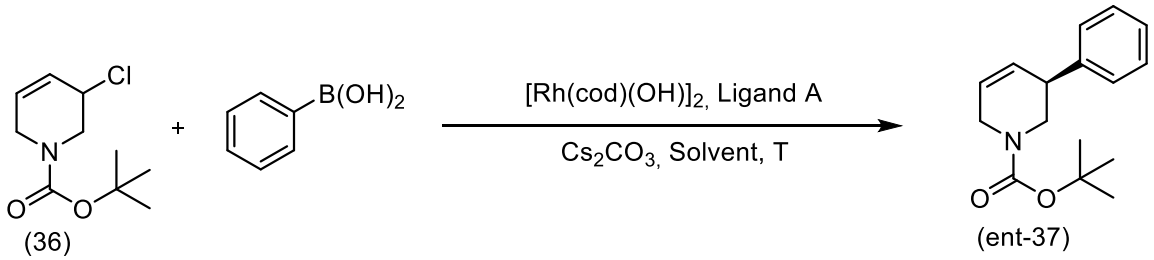


Scheme 3.7: Chlorination step using $POCl_3$

The reaction was repeated many times over the course of this project and the product **36** was obtained with an average yield of 74%, 83% being the best result obtained. The total synthesis of the starting material **36** was performed on large scale (37.5 mmol) and gave the desired product **36** in an overall yield of 40% over four steps.

3.3.2 Screening of the asymmetric allylic arylation

Our group uncovered that when racemic allyl halides were used in an asymmetric allylic arylation, arylboronic acids could be added using $[Rh(cod)OH]_2$ and *(S)*-Xyl-P-PHOS (Ligand **L24**) in THF at 60 °C with Cs_2CO_3 for 1 h.[203] Applying the same conditions to piperidene chloride **36** gave some product **ent-37** but the reaction needed to be left overnight to obtain full conversion of the starting material **36**. The desired product **ent-37** was obtained in 54% yield and an enantiomeric excess of 90% (entry 1; Table 3.2).



Entry	Solvent 1	T	Yield	ee
1	THF	60 °C	54%	90%
2	THF	80 °C	67%	89%
3	Dioxane	80 °C	71%	80%
4	Dioxane	100 °C	60%	81%

Conditions : THP chloride (1.0 eq.), Boronic acid (2.0 eq.), $[Rh(cod)(OH)]_2$ (0.025 eq.), ligand A (0.06 eq.) and Cs_2CO_3 (1.0 eq.)

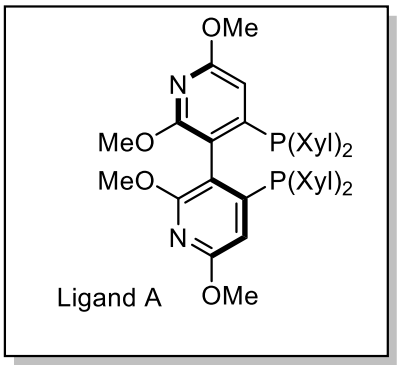


Table 3.2: Screening of solvents and temperatures

Performing the reaction at 80 °C in THF and dioxane increased the yield to around 70%, but a drop in enantioselectivity of 10% was observed with dioxane (entry 2, 3; Table 3.2). Surprisingly, the yield of the reaction obtained using dioxane decreased when the temperature increased from 80 °C to 100 °C (entry 4; Table 3.2).

Satisfied by the preliminary results obtained during the screening of the temperature and solvent, our interest shifted towards ligand screening (Figure 3.10), using the optimised conditions (80 °C in THF). P-PHOS (**L26**), Cl-MeO-BiPHEP (**L28**), Seg-PHOS (**L32**) and **L33** showed an increase in enantioselectivity while Cl-MeO-BiPHEP (**L28**) also showed an increase in reactivity (Figure 3.10). Other ligands performed either similarly to *(S)*-Xyl-P-PHOS (**L24**) (Entries D and G; Figure 3.10) or poorly (Entries F, H, K and L; Figure 3.10). We decided that the best conditions for our system was to perform the reaction using $[Rh(cod)OH]_2$ and **L28** in THF at 80 °C with Cs_2CO_3 overnight.

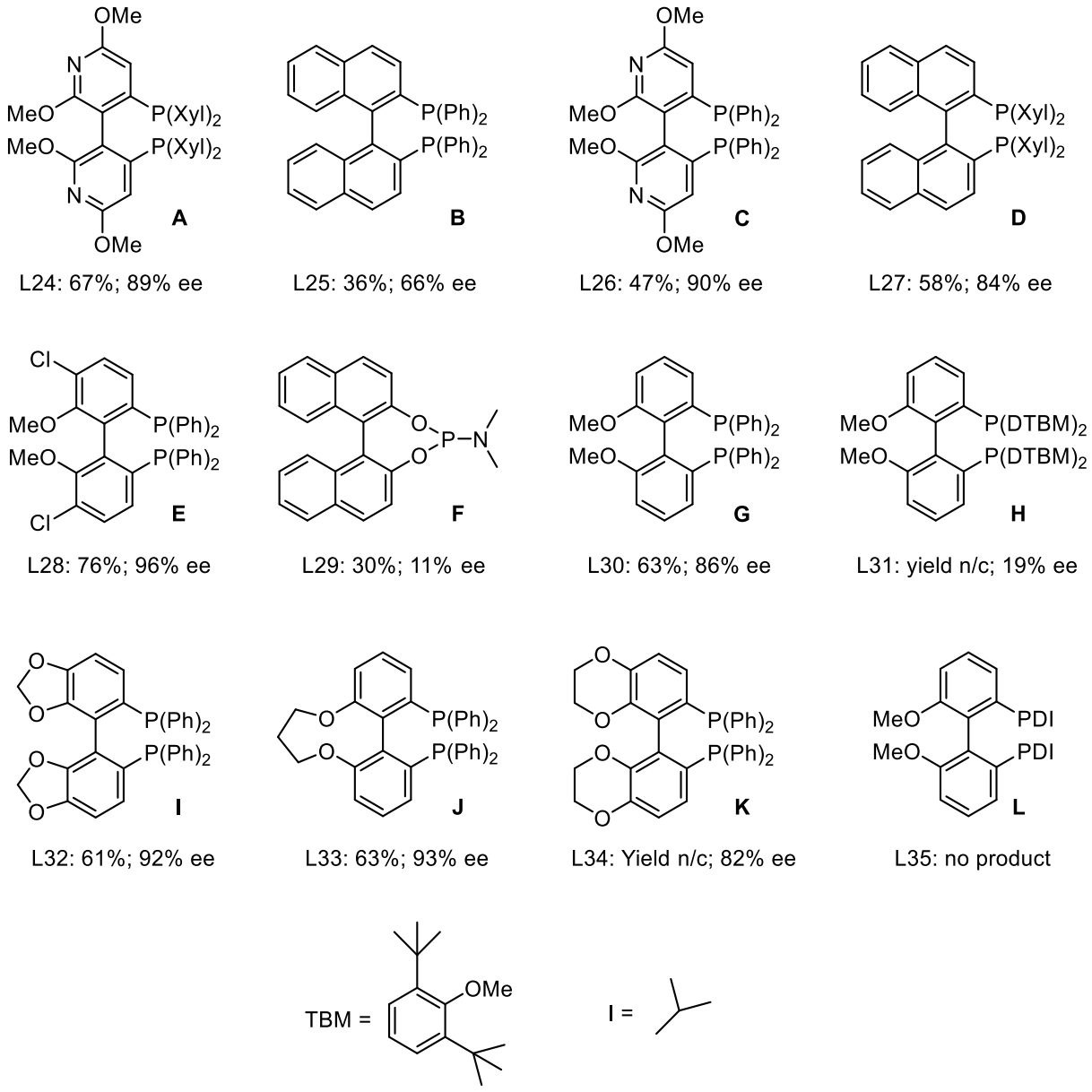
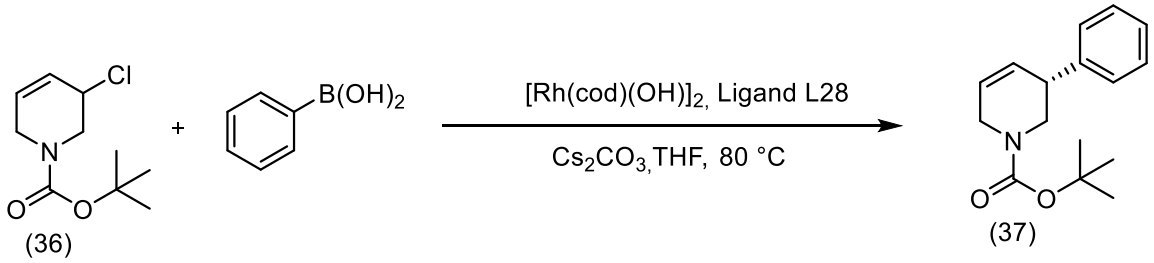


Figure 3.10: Screening of different ligands

3.3.3 Reproducibility issues

During the course of this project, we faced some reproducibility issues (Table 3.3). After synthesising a new batch of starting material **36**, a drop in both reactivity (50% yield) and enantioselectivity (80% ee) was observed (entry 1; Table 3.3). Either something was different with the piperidene chloride **36** or some part of the reaction was not functioning properly. However, neither repurifying the coupling partner **36** nor

synthesising another fresh batch was sufficient to recover results similar to those previously obtained (entry 2 and 3; Table 3.3).



Entry	H_2O	Sep flask	Yield	ee
1	None	None	50%	80%
2[a]	None	None	61%	87%
3	None	None	45%	67%
4	1eq	None	76%	92%
5	None	Yes	72%	95%
6	1 eq	Yes	72%	91%
7	None	None	82%	95%

Conditions : THP chloride (1.0 eq.), Boronic acid (2.0 eq.), $[Rh(cod)(OH)]_2$ (0.025 eq.), ligand L28 (0.06 eq.) and Cs_2CO_3 (1.0 eq.).
a : repurified THP chloride

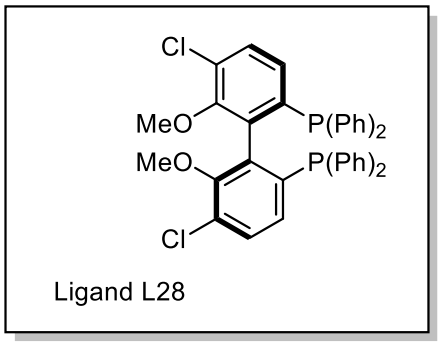
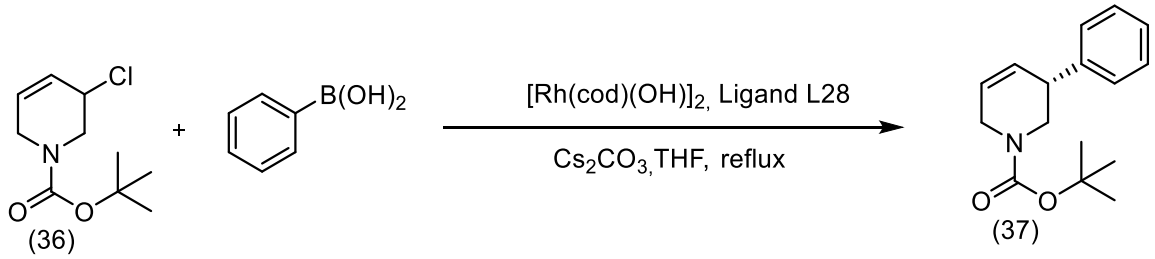


Table 3.3: Reproducibility issues

Adding an equivalent of water seemed to improve the system (entry 4; Table 3.3) but "normal" results were only obtained again by adding both starting materials to the reaction flask separately (entry 5: Table 3.3). Surprisingly, results did not improve when water was added to a system where both starting materials were added separately (entry 6; Table 3.3).

Even more disturbing, a test reaction on the normal system gave the desired results (entry 7; Table 3.3). Our hypothesis was that some kind of interaction happened when both starting materials were added simultaneously. Nevertheless, separate addition of the coupling partners became the new standard for our system.

As specified previously, the reaction was performed at 80 °C in THF without a condenser even though the boiling point of the solvent is 66 °C. The reaction was simply accomplished by heating a septum-sealed round-bottomed flask. Performing the reaction under conditions where a proper reflux was achieved using a condenser, gave lower enantioselectivity regardless of the amount of THF added (entry 1, 2 and 3; Table 3.4). The reason why using a reflux condenser gave lower reproducibility is still unclear.



Entry	THF	Reflux	Yield	ee
1	3 mL	Yes	65%	87%
2	4 mL	Yes	68%	79%
3	5 mL	Yes	60%	87%
4[a]	4 mL	None	68%	88%
5[b]	4 mL	None	63%	93%
6[c]	4 mL	None	71%	96%

Conditions : THP chloride (1.0 eq.), Boronic acid (2.0 eq.), $[Rh(cod)(OH)]_2$ (0.025 eq.), ligand L28 (0.06 eq.) and Cs_2CO_3 (1.0 eq.). **a** : reaction done in a microwave vial with a septum**. b :** reaction done in a sealed microwave vial. **c** : reaction done in a sealed microwave vial in an oil bath

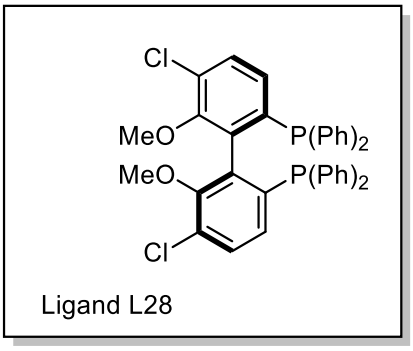
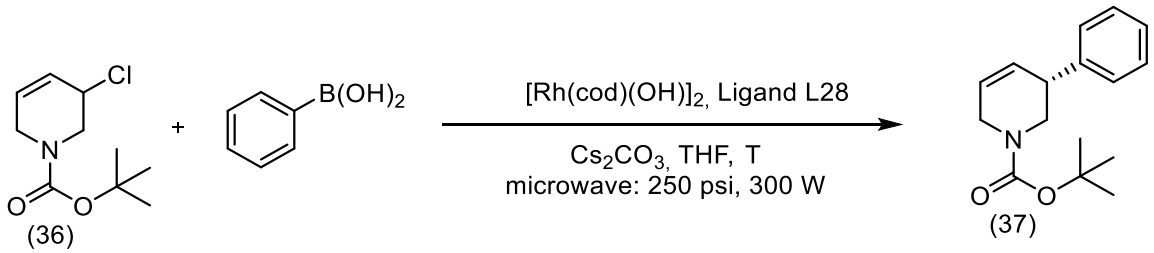


Table 3.4: Reaction performed at reflux or in a microwave vial

In order to validate our unconventional set-up, test reactions were done in microwave vials. Sealing the vial with a microwave stopper clamped with a crimper in an oil bath gave the desired results (entry 6 Table 3.4). Going further we were also

able to obtain similar results when performing the reaction under microwave conditions (Table 3.5).

Our first attempt under microwave conditions failed due to overheating the system (entry 1; Table 3.5). When performing the reaction at 80 °C good results were obtained (entry 2 and 3 Table 3.5). A simple kinetic study of the reaction performed under microwave conditions suggested that suitable conditions involved reaction at 250 psi, 300 W at 80 °C for 1 h.



Entry	T	Time	Yield	ee
1	120 °C	2 hrs	n/c	n/c
2	80 °C	2 hrs	61%	96%
3	80 °C	2 hrs	71%	95%
4[a]	80 °C	Test	n/c	94%

Conditions : THP chloride (1.0 eq.), Boronic acid (2.0 eq.), $[Rh(cod)(OH)]_2$ (0.025 eq.), ligand L28 (0.06 eq.) and Cs_2CO_3 (1.0 eq.).
a : kinetic study of the reaction

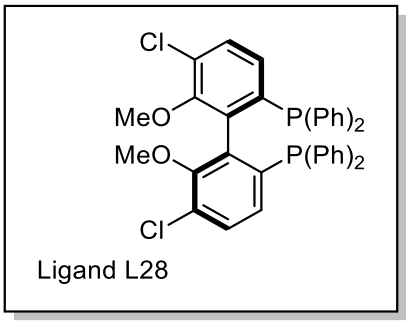


Table 3.5: Microwave performed reactions

3.3.4 Scope of the asymmetric allylic arylation

A variety of substituted arylboronic acids were coupled in the newly developed reaction conditions with uniformly high ee (92–97% ee), and good yields (>50%), except in the case of *ortho*-substituted aryl boronic acids (Figure 3.11) which, likely because of steric hindrance, gave the allylic adduct **47** in 29% yield. Indeed, naphthylboronic acids **38**, methylphenyl boronic acids **39** and **40** gave high ee and

good yields as well as methoxy **41** and **51**, phenol **50** and carboxyboronic acids **42** (Figure 3.11). Halide-substituted derivatives **43**, **44**, **45** and **46** gave high enantioselectivity as well, but lower yields were obtained. Besides the *ortho*-substitution example, no obvious correlation emerged to explain the reactivity differences between the *meta*- and *para*-substituted examples.

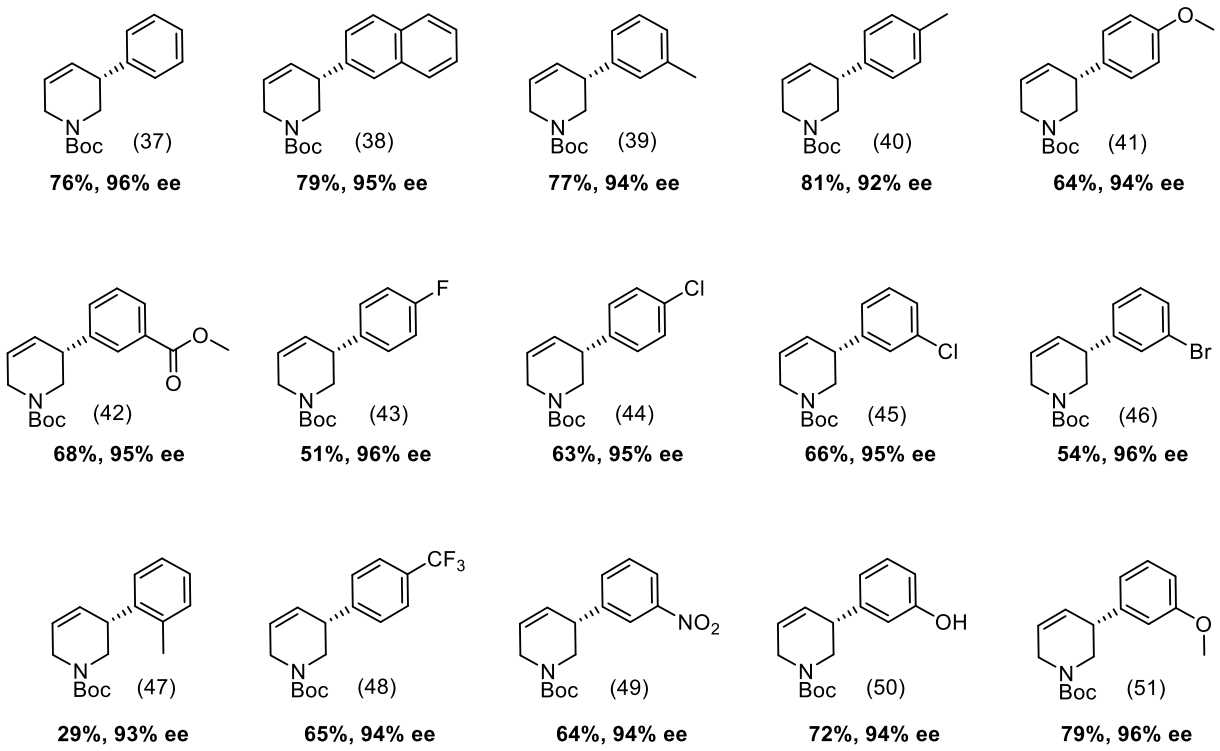


Figure 3.11: Asymmetric allylic arylation with phenyl-based aromatics

We next examined the challenging scenario where both coupling partners were heterocycles (Figure 3.12). 3-furan **53**, 2-benzofuran **57**, 3-thiophene **52** and 6-indole **56** boronic acids performed well with *N*-heterocycle **36** (Figure 3.12). Boc-protected 2-pyrrole boronic acid gave **54** in low yield, again likely due to steric effects, but excellent (95%) ee (Figure 3.12). Modified-pyridine **55** (Figure 3.12; example made by Dr Philip Schäfer) and vinylboronic acids **58**, **59** and **60** (Figure 3.12; examples made by Dr Mireia Sidera) also worked smoothly and rapidly gave complex products with very high (93–99%) ee.

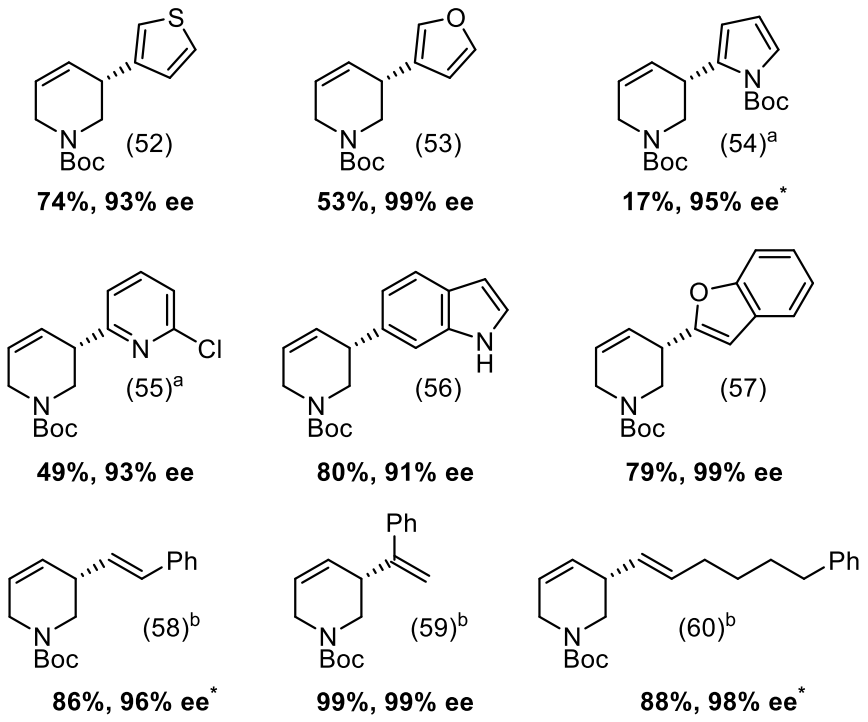


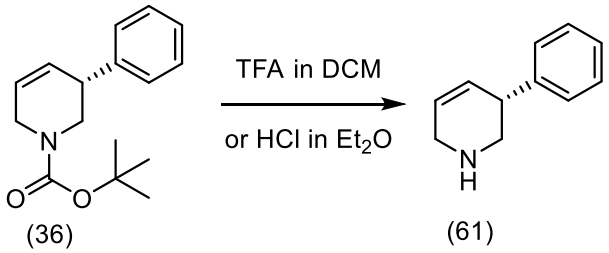
Figure 3.12: Asymmetric allylic addition of heteroaromatics and vinyls

The absolute configurations of **37**-**60** were assigned by analogy with previously reported literature from the Fletcher group.[203]

3.3.5 Further synthetic transformations and synthesis of (-)-Preclamol

After finishing the exploration of the chemical scope of the asymmetric allylic arylation reaction between the piperidene chloride **36** and a variety of arylboronic acids, we decided to explore the synthetic possibilities of the newly formed coupling products.

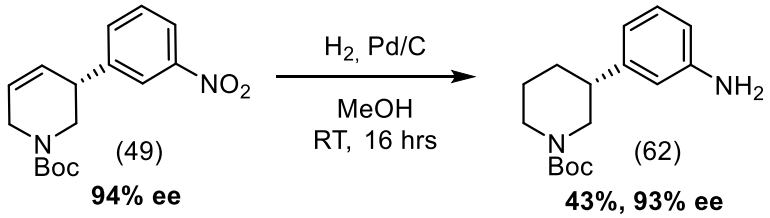
First, we attempted to remove the Boc protecting group. Hydrolysis using either TFA in DCM or HCl in Et_2O was successful (Scheme 3.8).[228]



(36) (61)

Scheme 3.8: Hydrolysis of Boc protecting group by either TFA or HCl

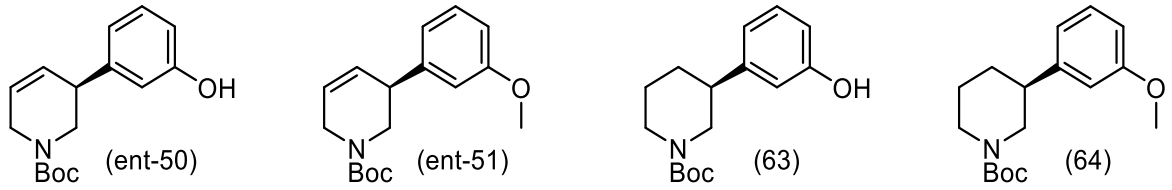
Our interest then diverted towards the possible reduction of the piperidene alkene moiety. We decided to try a double nitro- and olefin- group reduction using **49** which could broaden the potential for further transformation. To our delight, the reaction using H_2 and Pd/C gave **62** in a moderate yield but complete retention of enantiomeric ratio (scheme 3.9).



Scheme 3.9: Hydrogenation reaction

Often, enantiopure chiral drugs are prepared as racemic mixtures and resolution is accomplished via classical or chromatographic processes. Molecular construction using an asymmetric allylic arylation would be a highly attractive alternative. To demonstrate that the methodology could be used to synthesise valuable molecules, we then attempted the enantioselective total synthesis of the antipsychotic drug (-)-Preclamol.[223–226] The asymmetric synthesis of the drug had been recently reported by respectively Liao, Zhou and Bosch.[229–231]

Two asymmetric synthesis of (-)-Preclamol were accomplished. Applying the standard conditions of the asymmetric allylic arylation to 3-phenol and 3-methoxyphenyl boronic acid afforded the asymmetric coupling adducts respectively **ent-50** in 76% yield and 96%ee and **ent-51** in 70% yield and 94% ee (Figure 3.13).



62%, 95% ee **76%, 96% ee** **82%, 93% ee** **77%, 91% ee**

Figure 3.13: Asymmetric allylic arylation adducts

Following the Pd-catalysed hydrogenation, it was observed that some racemisation occurred (Figure 3.13). Therefore, in further experiments, hydrogenation was performed using Wilkinson's catalyst to avoid racemisation.[232]

The formal synthesis of (-)-Preclamol was accomplished by hydrogenation of **ent-51** followed by removal of the Boc protecting group under acidic conditions to obtain intermediate **65** previously reported by Bosch and co-workers.[229] The overall yield of the formal synthesis was 64% (Figure 3.14).

The total synthesis of the drug was achieved by hydrogenation of **ent-50**, deprotection using HCl in Et_2O followed by reductive amination of the chloride salt delivering (-)-Preclamol for an overall yield of 38% (Figure 3.14).

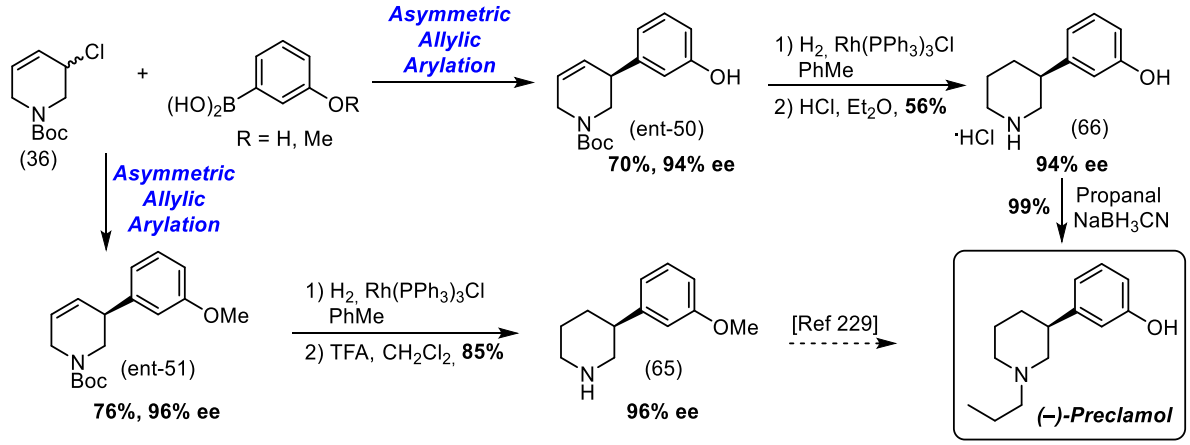
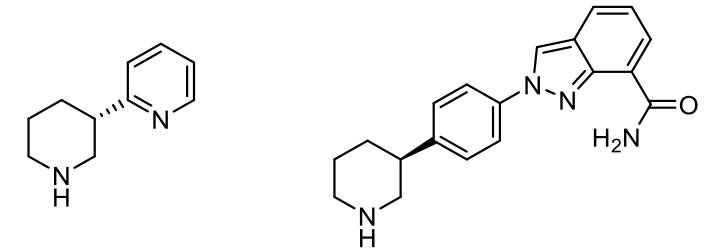


Figure 3.14: Two synthetic routes to Preclamol

Using other heteroarylboronic acids and the *N*-heterocyclic allyl chloride, Dr Philip Schäfer and Dr Mireia Sidera respectively accomplished the asymmetric syntheses of the natural product (+)-Isoanabasine and the drug Niraparib.[233–235]



(+)-Isoanabasine **Niraparib**

Figure 3.15: Niraparib and (+)-Isoanabasine

3.4 Summary

In this project we were able to synthesise a new heterocyclic building block of interest. We were able to tune previously reported conditions so that they were applicable to our new system.[203] The asymmetric allylic arylation of *N*-heterocyclic allyl chloride **36** to a variety of aryl and heteroaryl boronic acids afforded a new library of coupling partners with high enantioselectivity (> 90% ee) and for the most part good yields (>50%).

Reproducibility issues led to the discovery that the reaction could also be done in two new ways, and especially that the asymmetric coupling could also be accomplished under microwave conditions.

We also found that the coupling products could be used in further transformations and that 3-phenol and 3-methoxy asymmetric allylic alkylation products **ent-50** and **ent-51** led to the respective total and formal synthesis of (-)-Preclamol.

Gaining insight into the mechanism might provide a better understanding of the active catalytic species and the role of additives in the reaction.

The regioselectivity of the asymmetric allylic arylation should certainly be further explored with the goal of allowing highly enantioselective coupling to non-symmetrical intermediates and acyclic substrates, in order to get access to new structural motifs.

Chapter 4

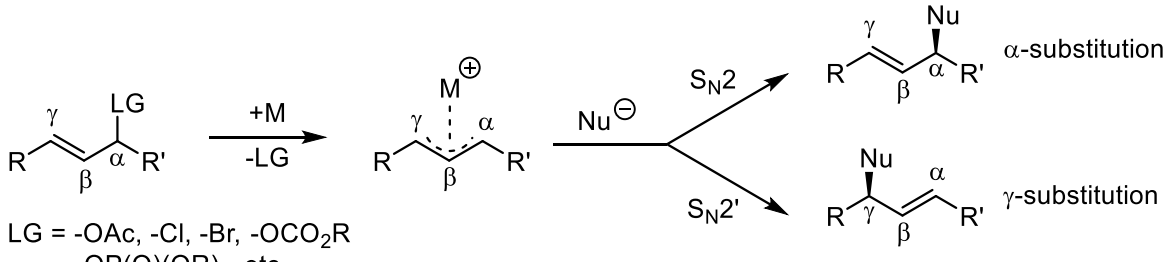
4 Asymmetric Allylic Alkylation of Chloro-Tetrahydropyridines and Kinetic Resolutions

4.1 Introduction

4.1.1 General information

Chiral, enantiomerically pure compounds are commonly generated through three main strategies: (i) resolution of racemic mixtures (most common method used in industry), (ii) chiral pool synthesis which starts from a stock of readily available enantiopure compounds such as amino acids and monosaccharides and (iii) introduction of asymmetry to a prochiral substrate.[236,237]

Generation of single enantiomers with an allylic stereogenic centre can be demonstrated either by the asymmetric allylic alkylation (AAA) (Scheme 4.1) or by the asymmetric conjugate addition (ACA) (*cf.* chapter 1).



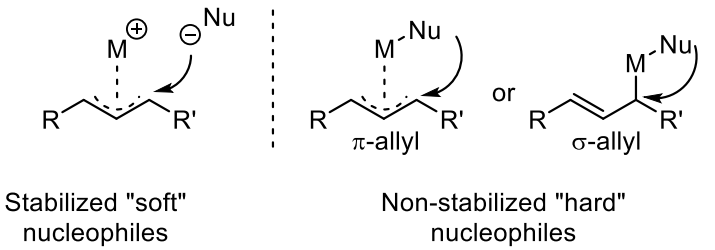
Scheme 4.1: Asymmetric allylic alkylation

One of the critical features of asymmetric allylic alkylations, being substitution reactions, is the control of the regiochemistry. Two distinct pathways are possible: (i)

either an S_N2 reaction where the nucleophile attacks at the carbon bearing the leaving group (LG) or (ii) an S_N2' reaction where the nucleophile attacks at the γ-position resulting in the allylic shift of the double bond (Scheme 4.1).[238] The regioselectivity of an AAA depends on many parameters including the allylic substrate, the leaving group, the organometallic reagent, temperature, etc.

Asymmetric allylic alkylations are one of the most general and practical metal-catalysed reactions and have been performed using a variety of transition metals such as Cu, Pd, Mo, Ni, W, Rh, Ir and more.[239] The AAA methodology can also be applied to different types of electrophiles that are chiral racemic, *meso* or achiral.[240]

Depending on the nature of the nucleophile, asymmetric allylic alkylation reactions can proceed by different mechanistic pathways. With stabilised nucleophiles, the pathway involves attack of the nucleophile directly at carbon; with non-stabilised, nucleophiles the pathway involves attack at the metal first (Scheme 4.2).

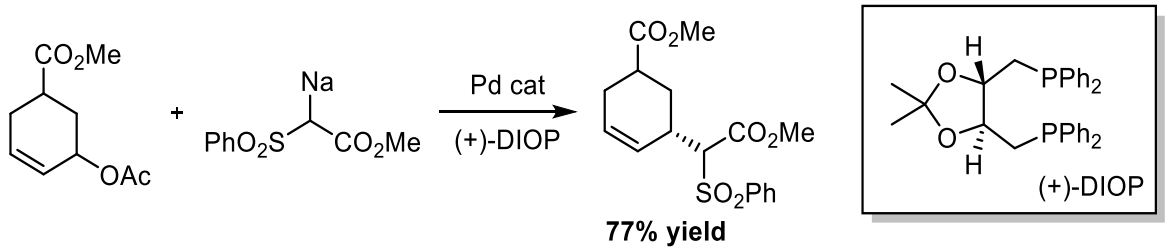


Scheme 4.2: Mechanistic pathways of stabilised and non-stabilised nucleophiles

4.1.2 AAA with stabilised nucleophiles

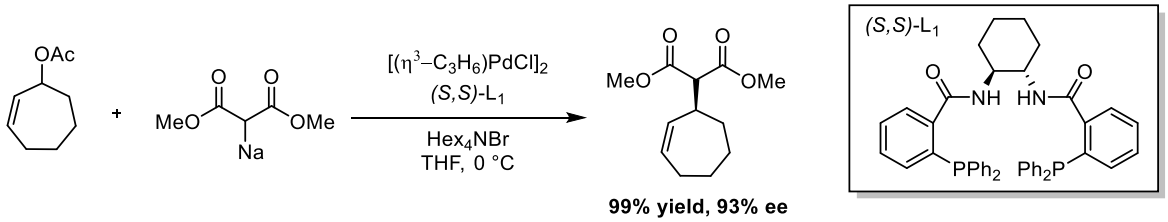
Nucleophiles with conjugate acids of pK_a <25 are generally classified as stabilised or “soft” nucleophiles. The bond breaking and bond forming events in an AAA process involving stabilised nucleophiles occur outside the coordination sphere of the metal (Scheme 4.2 left).[239] A stabilised nucleophile attacks the carbon atom of π-allyl complex to dictate the stereochemical outcome which in general leads to an overall retention of stereochemistry.

In 1977, the Trost research group reported the first AAA reaction with a stabilised nucleophile using Palladium as the transition metal catalyst (Scheme 4.3).[241]



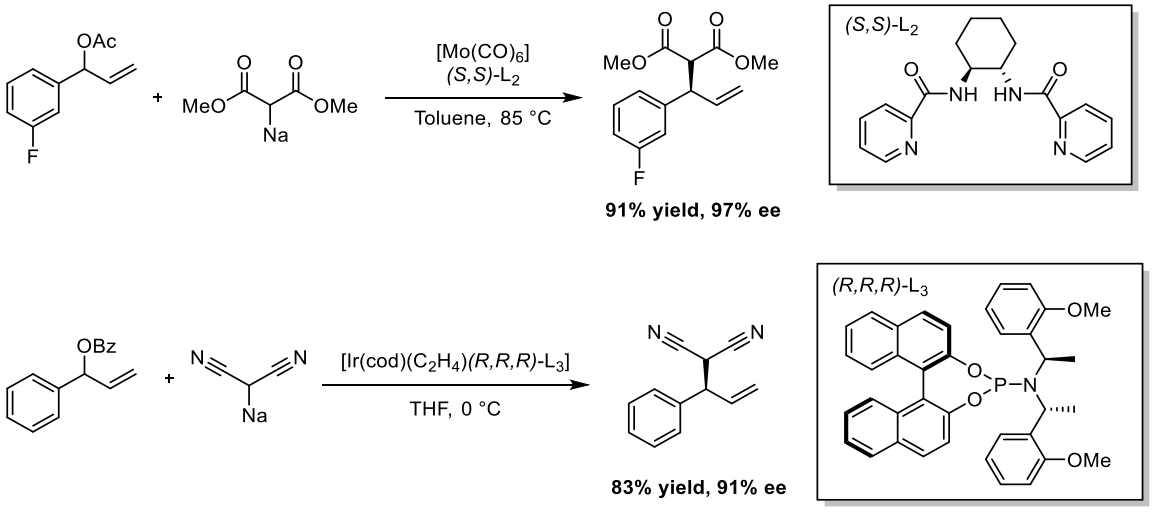
Scheme 4.3: First AAA reported by Trost

Trost and co-workers have intensively investigated Pd-catalysed AAA over the years and reported AAAs with a variety of stabilised nucleophiles such as malonates or β-ketoesters (Scheme 4.4).[239,240,242,243]



Scheme 4.4: Pd-catalysed AAA using malonate as nucleophile

The AAA reaction with "soft" nucleophiles can be achieved as well using different transition metals such as molybdenum and iridium (Scheme 4.5).[244–247]

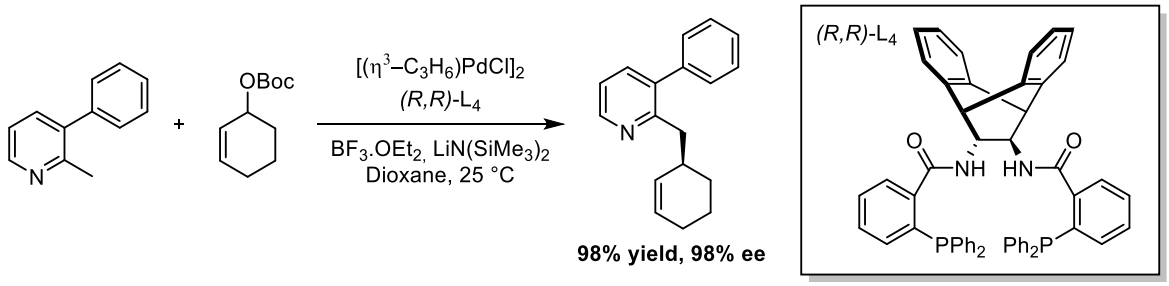


Scheme 4.5: Mo- and Ir-catalysed AAAs

4.1.3 AAA with non-stabilised nucleophiles.

Nucleophiles with conjugate acids of pK_a >25 are generally classified as non-stabilised or “hard” nucleophiles. Grignard, organozinc, and organoaluminium reagents, as well as hydride donors are examples of this class. The mechanistic pathway of non-stabilised nucleophiles in AAAs generally involves transmetalation of nucleophile with the metal catalyst followed by reductive elimination (Scheme 4.2 right).[239] As a result the stereochemistry is mainly determined by π-allyl intermediate formation.

Very few examples of transition metal-catalysed AAAs using non-stabilised nucleophiles were developed over the years, beside copper-catalysed asymmetric allylic alkylations. Amongst them, Trost and co-workers reported an enantioselective Pd-catalysed AAA using less-stabilised nucleophiles such as lithiated 2-substituted pyridines (Scheme 4.6).[248,249]

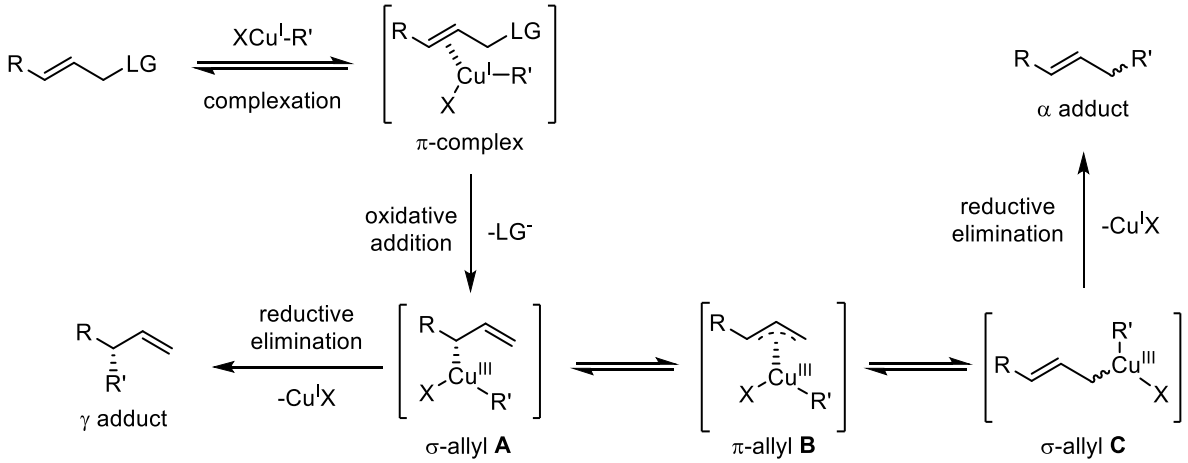


Scheme 4.6: Pd-catalysed AAA of 2-substituted pyridines

4.1.4 Cu-catalysed AAA

The general mechanism of a Cu-catalysed asymmetric allylic alkylation can be described in the following steps: (i) formation of a Cu(I) π-complex with an allyl halide substrate, (ii) the stereo-determining oxidative addition of the copper *anti* to the leaving group (LG), forming a Cu(III) σ-allyl species **A**, (iii) possible isomerisation of **A** into the Cu(III) π-allyl complex **B** followed by another isomerisation into the Cu(III) σ-complex

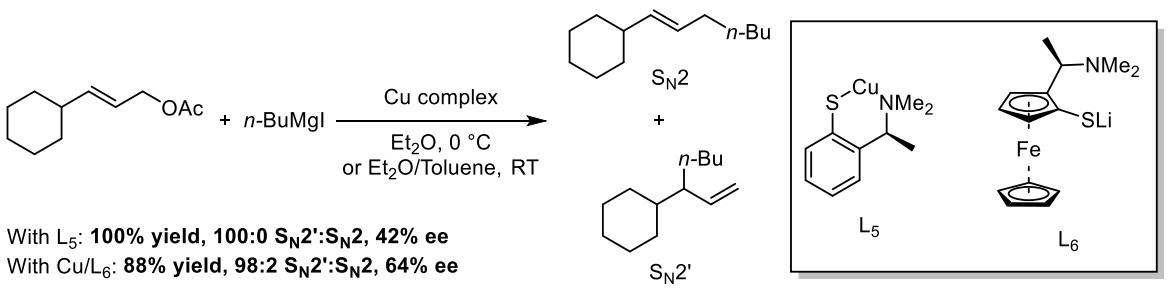
C, (iv) the reductive elimination, which determines the regioselectivity of the reaction, of either **A** or **C** into respectively the γ-adduct or the α-adduct. The reductive elimination of species **A** is determined to be kinetically more favourable than reductive elimination of **C** (Scheme 4.7).[238]



Scheme 4.7: General Cu-catalysed AAA mechanism

4.1.4.1 Cu-catalysed AAA with organomagnesium reagents

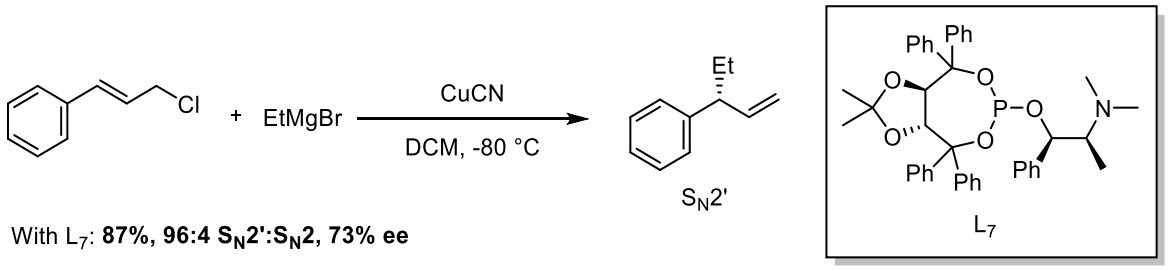
Bäckvall, van Koten and co-workers reported the first copper-catalysed asymmetric allylic alkylation using Grignard reagents in 1995.[250] An S_N2' γ-adduct was regioselectively synthesised using a chiral arenethiolatocopper(I) complex (L_5), *n*-BuMgI and an allylic acetate in 100% yield and 42% ee (Scheme 4.8).



Scheme 4.8: First Cu-catalysed AAA using an organomagnesium reagent

Investigations by the Bäckvall research group into a new ferrocene-thiolatocopper(I) complex (L_6) led to the synthesis of the γ-adduct with an improved enantiomeric excess of 64% (Scheme 4.8).[251,252]

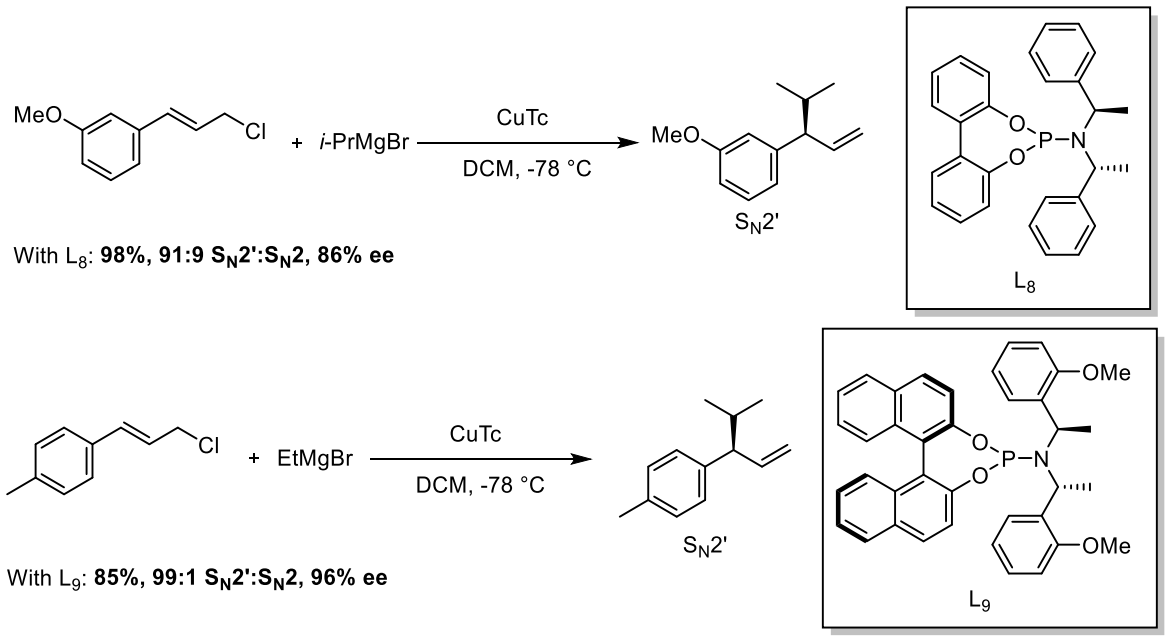
Alexakis and co-workers reported in 2001 a Cu-catalysed AAA using a TADDOL-derived ligand (L_7).[253] For example, a γ-adduct was synthesised using EtMgBr and an allylic chloride in 87% yield and 73% ee (Scheme 4.9).



With L_7: **87%, 96:4 S_N2':S_N2, 73% ee**

Scheme 4.9: Cu-catalysed AAA with a TADDOL-derived ligand (L_7)

In a second-generation system, Alexakis et al. replaced CuCN by CuTc and observed an increase in enantioselectivity when coupled with phosphoramidite ligand (L_8). This new system tolerated functionalised alkyl and aryl substituted allyl chlorides without further optimisations. For example, *i*-PrMgBr was regioselectively added to a 3-methoxy allyl chloride and afforded a γ-adduct in 98% yield and 86% ee (Scheme 4.9).[254] Replacement of ligand (L_8) by another phosphoramidite ligand (L_9) improved the enantioselectivity further. A γ-adduct was synthesised using ligand (L_9), EtMgBr and 4-methylphenyl allyl chloride in 85% yield and 96% ee (Scheme 4.10).[255,256]



Scheme 4.10: Cu-catalysed AAA with phosphoramidite ligands (L_8) and (L_9)

Okamoto and co-workers reported Cu-catalysed AAAs with organomagnesium reagents using NHC ligands.[257] However, they only managed to obtain γ-adducts with an enantioselectivity up to 70% ee. More recently, the Feringa group had another look at ferrocenyl-based ligands and reported Cu-catalysed AAAs using taniaphos-based ligands, which allowed the synthesis of γ-adducts with an enantioselectivity up to 98% ee.[258]

Alexakis, Feringa and Hall research groups respectively managed to extend their Cu-catalysed AAA methodology to include more complex electrophiles. Alexakis and co-workers applied their methodology to β-substituted acyclic and cyclic allylic chlorides (Figure 4.1a).[259] Hall et al. reported Cu-catalysed AAAs using allyl chlorides with vinylic boronate esters moieties (Figure 4.1b)[260] and Feringa and co-workers described asymmetric allylic substitutions using allyl bromides with allylic ether or vinyl ester substituents (Figure 4.1c).[261,262]

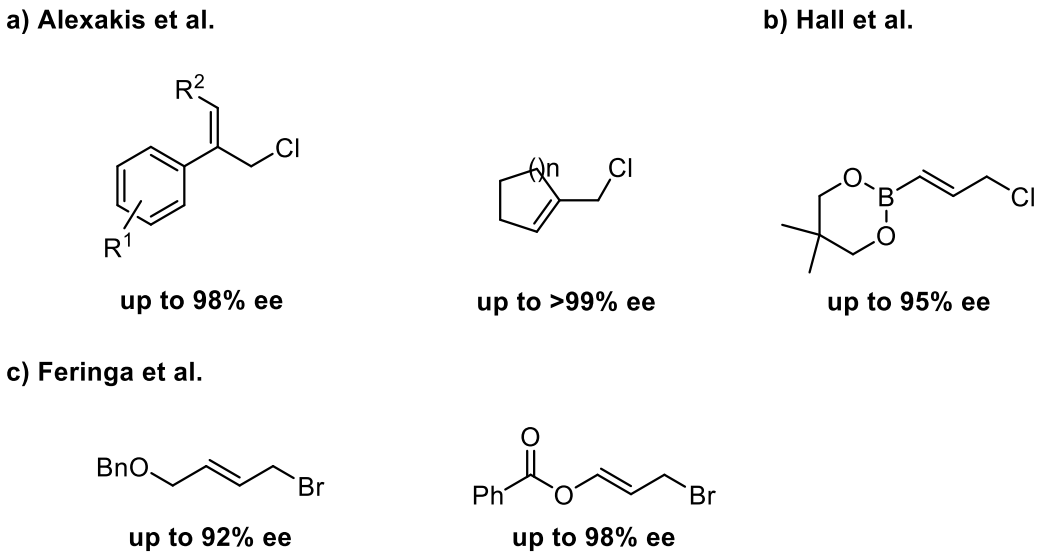
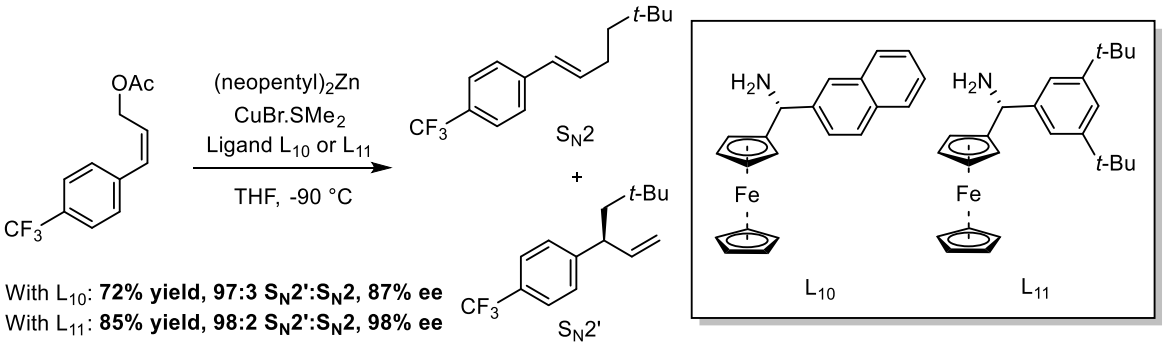


Figure 4.1: Examples of electrophiles used in Cu-catalysed AAAs

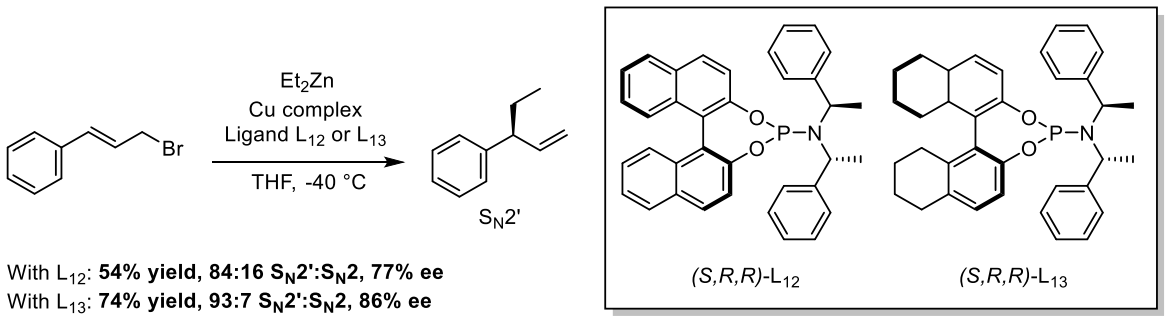
4.1.4.2 Cu-catalysed AAA with organozinc reagents

Dübner and Knochel reported in 1999 the first copper catalysed asymmetric allylic substitution using bulky organozinc reagents.[263] Initial results obtained using a ferrocenyl-based ligand (L_{10}) gave γ-adducts regioselectively with an enantiomeric excess up to 87% (Scheme 4.11). A significant drop in enantioselectivity was observed when the reaction was performed at room temperature instead of -90 °C, with the ee value decreasing from 87% to 25%. Structurally modified ligand (L_{11}) bearing a di-*tert*-butylphenyl instead of a naphthyl moiety improved the Cu-catalysed system with an increase in enantioselectivity up to 98% (Scheme 4.11).[264]



Scheme 4.11: First Cu-catalysed AAAs with organozinc reagents

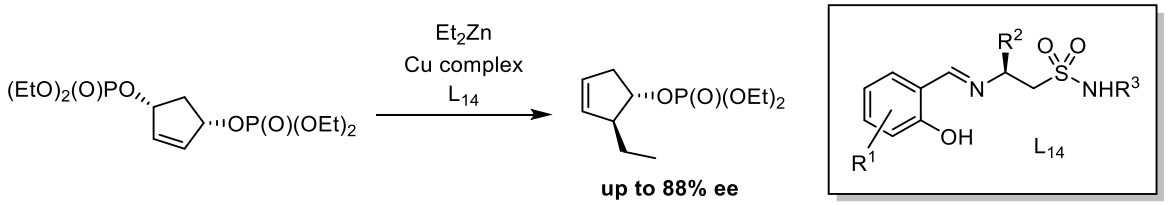
In 2001, Feringa and co-workers reported the use of linear alkylzinc reagents in Cu-catalysed AAAs.[265,266] Using phosphoramidite ligands, they were able to regioselectively and enantioselectively synthesise γ-adducts. As an example, the asymmetric allylic substitution of diethylzinc on cinnamyl bromide gave respectively the γ-adducts in 54% yield and 77% ee using (L_{12}) and in 74% yield and 86% ee with (L_{13}) (Scheme 4.12).



Scheme 4.12: Cu-catalysed AAAs with organozinc reagents using ligands (L_{12}) and (L_{13})

Further investigations by the research community led to the discovery of several Cu-catalysed AAAs involving a variety of different ligands.[267] Zhou and co-workers reported the application of spiro phosphoramidites in asymmetric allylic substitutions.[268] Hoveyda presented two different systems where either NHC ligands or peptide-based ligands were involved.[269,270] Woodward et al. introduced secondary amine-based ligands and Ohmiya and co-workers reported Cu-catalysed AAAs with bidentate phosphate ligands.[271,272]

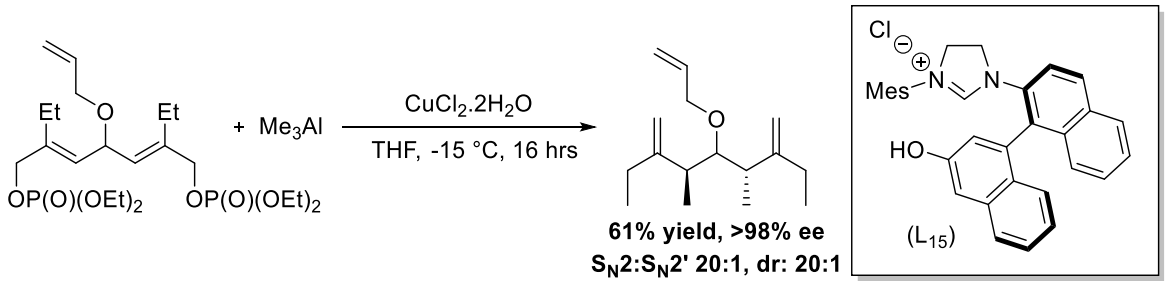
Finally, Piarulli, Gennari and co-workers reported the desymmetrisation of *meso* cyclic allylic phosphates using chiral Schiff-base ligands (Scheme 4.13).[273,274] γ-adducts were synthesised with an enantiomeric excess up to 88%.



Scheme 4.13: Desymmetrisation of *meso* compounds using Schiff-base ligands

4.1.4.3 Cu-catalysed AAA with organoaluminium reagents

Very few examples of copper catalysed asymmetric allylic alkylations using organoaluminium reagents were published. Amongst them, Hoveyda and co-workers reported the double allylic substitution of β-disubstituted olefins using an NHC ligand (L_{15}).[275] Using trimethylaluminium led to better regio- (γ:α = 20:1), diastereo- (dr 20:1) and enantiocontrol (up to 98% ee) than commonly used dialkylzinc reagents (Scheme 4.14).



Scheme 4.14: Desymmetrisation of *meso* compounds using Schiff-base ligands

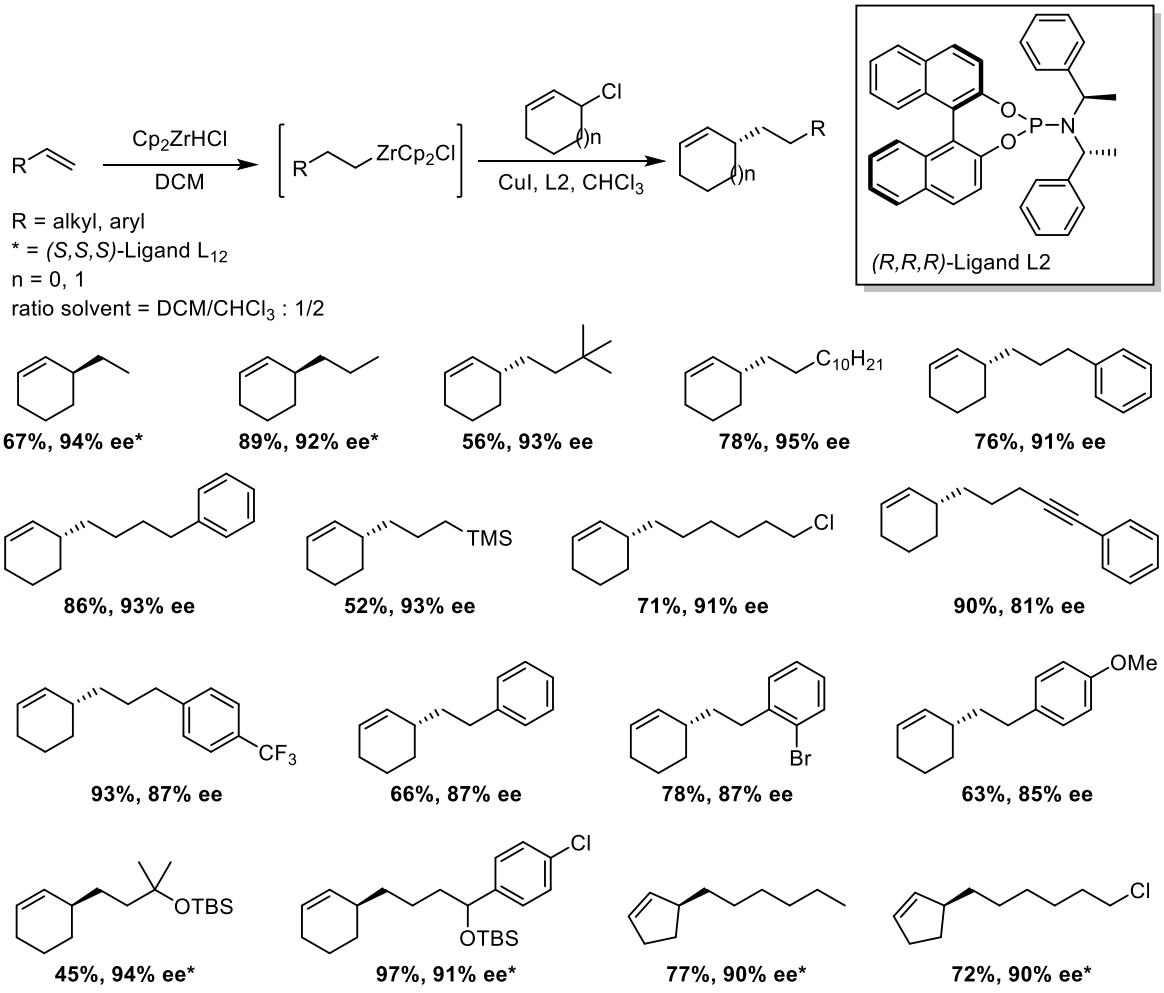
4.1.5 Cu-catalysed AAA using alkylzirconium

As previously stated (cf. chapter 1, part 1.3), the Fletcher group has reported highly enantioselective copper-catalysed asymmetric conjugate additions using alkylzirconium reagents.[66–68,71,276,277]

In 2015, Fletcher and co-workers reported the copper-catalysed AAA reaction of racemic cyclic allyl chlorides using alkylzirconium reagents with the combination of

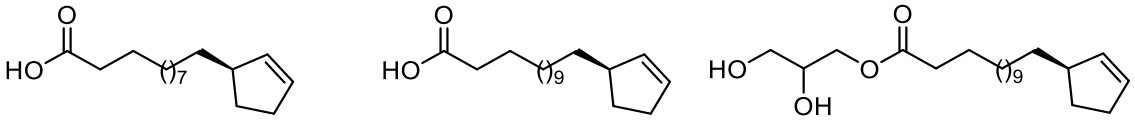
CuI and phosphoramidite ligand **L2**.[278] This reaction proceeds through a dynamic kinetic asymmetric transformation process (cf. chapter 3, part 3.1.3).

The scope of the nucleophile ranged from gaseous, short-chained alkenes to functionalised alkenes containing silanes, halides, alkynes, protected alcohols and pre-existing stereogenic centres (Scheme 4.15). The reaction worked on six- and five-membered ring allyl chlorides and afforded enantioenriched products with an enantiomeric excess up to 95%. This method was easily scaled up to grams of product.



Scheme 4.15: Cu-catalysed AAAs using alkylzirconium reagents

The synthetic utility of the methodology was demonstrated by the synthesis of three different biologically active natural products : Hydnocarpic acid, chaulmoogric acid and anthelminthicin C (Figure 4.2).[278]



Hydnocarpic acid Chaulmoogric acid Anthelminthicin C

Figure 4.2: Natural products synthesised through Cu-catalysed AAA with alkylzirconium reagents

Later a heteroatom bearing electrophile was tested in Cu-catalysed AAA with alkylzirconiums. Investigations into 3-6-dihydro-2*H*-pyranyl chloride led to the generation of products with good to high enantioselectivity (up to 93%), but with mostly poor yields (up to 33%).[194]

4.2 Project aims

As previously stated tetrahydropyridines (THPs) are crucial motifs found in numerous bioactive compounds such as alkaloids and iminosugars.[218–220] The objective of this project was to broaden the library of piperidene derivates using the asymmetric allylic alkylation (AAA) methodology developed in the Fletcher group (Scheme 4.15).[278]

Since the piperidene coupling agent was more difficult to handle than other racemic cyclic halides for the asymmetric allylic arylation reaction, optimisations of the AAA reaction conditions were required.

During investigations, and to our surprise, a very stable enantioenriched cyclic allyl chloride was recovered alongside the asymmetric allylic alkylation product. We hypothesised that the reaction might undergo a kinetic resolution process (Figure 4.3).[237,279]

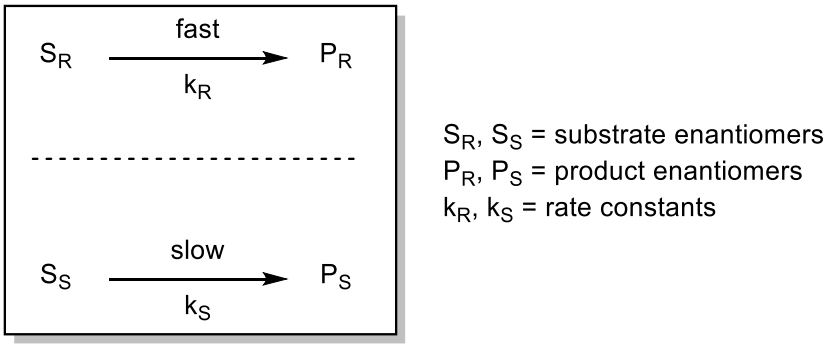


Figure 4.3: General kinetic resolution process

Therefore, the main objectives of this project were (i) to optimise the asymmetric allylic alkylation with 3-chloro-1,2,3,6-tetrahydropyridine, (ii) to apply this new methodology to a variety of alkenes and (iii) to investigate the kinetic resolution process.(Figure 4.4).

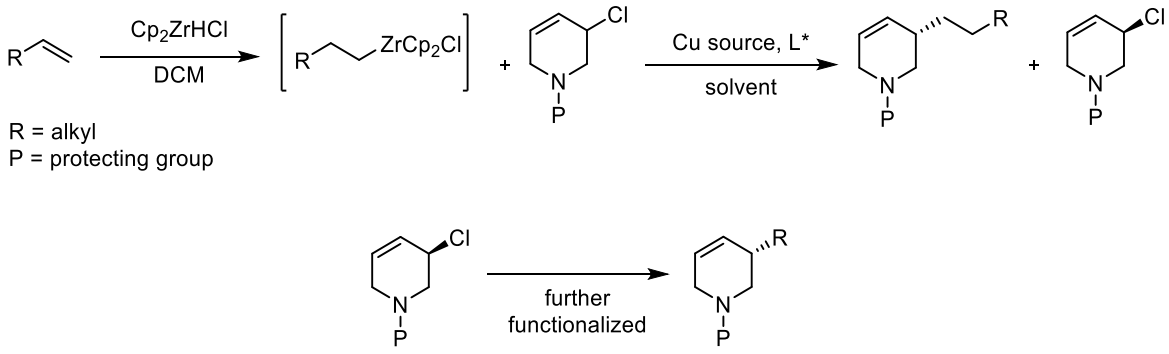


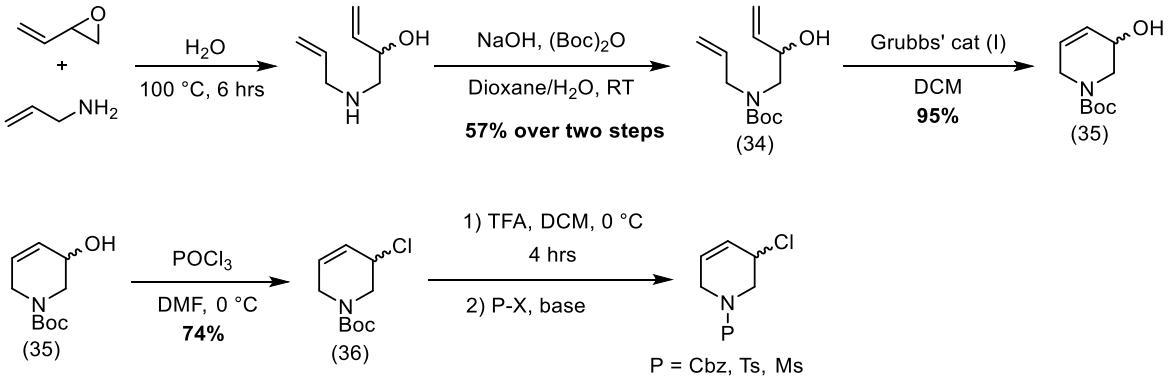
Figure 4.4: Project aims

4.3 Results and discussion

4.3.1 Preparation of the possible coupling partner

The optimal conditions for asymmetric allylic alkylation developed in the Fletcher group, use CuI and ligand **L2** in $CHCl_3$.[278] Our preliminary investigations were to observe the reactivity, and principally the enantioselectivity of the reaction with tetrahydropyridine allyl chloride under these pre-determined conditions.

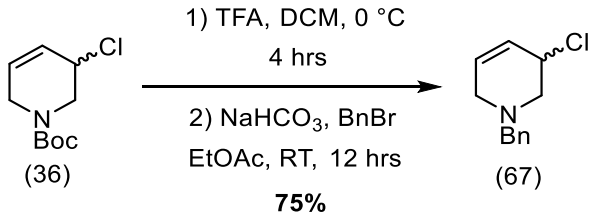
THP allyl chlorides tested, were prepared from *tert*-butyl 3-chloro-3,6-dihydropyridine-1(2*H*)-carboxylate **36** (Chapter 3, Scheme 3.6) which underwent deprotection under acidic conditions, followed by the appropriate protection protocol (Scheme 4.16).



Scheme 4.16: Preparation of THP allyl chlorides

Synthesis of benzyl protected-tetrahydropyridine allyl chloride proved to be more challenging. At first, we chose a route similar to the procedure used to synthesise the Boc-protected coupling reagent **36**. Unfortunately, protection with benzyl bromide in the epoxide opening step led to a mixture of mono- and di-benzylation products. Another attempt consisted of performing first the benzylation on the allyl amine and then coupling produced secondary amine to butadiene monoxide, which gave the dialkene intermediate in moderate yields (37% to 42%). Regrettably, it was impossible

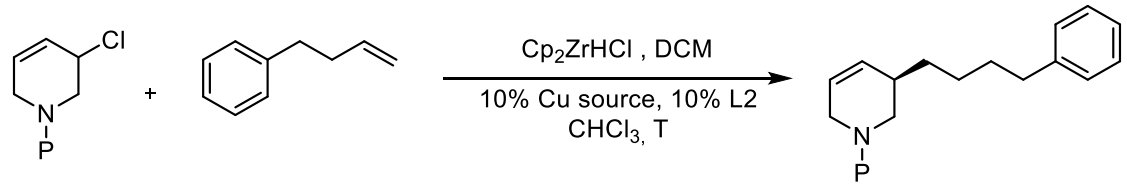
to perform the metathesis with this intermediate . Consequently, the synthesis of the benzyl-protected piperidene was achieved by carrying out the previously described synthesis of the Boc protected piperidene (Chapter 3; Scheme 3.6 and Scheme 4.16) followed by deprotection of the Boc and protection of the secondary amine by a benzyl protecting moiety (Scheme 4.17).[280,281]



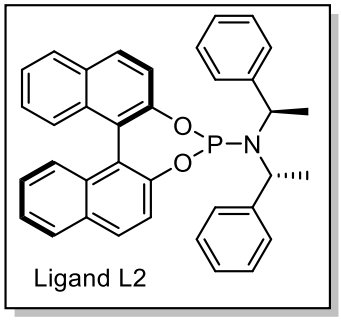
Scheme 4.17: Attempts at synthesising **67**

Early studies showed that the choice of protecting group on nitrogen has a drastic effect on reaction performance especially stereoselectivity.

Piperidene chlorides with Boc, Cbz or Ms as protecting groups gave poor enantioselectivities (lower than 10%: Entry 1, 3 and 5; Table 4.1) when subjected to the AAA. Similarly, THP with a Ts protecting group did not present any enantioselectivity (Entry 4; Table 4.1). Interestingly, a moderate yield and enantioselectivity was obtained using a benzyl-protected tetrahydropyridine (Entry 6; Table 4.1). Hence, the benzyl-protected 3-chloro-1,2,3,6-tetrahydropyridine **67** was chosen for further development. It was possible that using this protecting group could favour binding between the Nitrogen lone pair and the copper metal.[55] The aromatic moiety might undergo a π-stacking effect with the ligand which would hold the catalyst and the substrate together.



Entry	P	T	Yield	ee
1	Boc	RT	15%	9%
2	Boc	reflux	24%	0%
3	Cbz	RT	28%	5%
4	Ts	RT	27%	0%
5	Ms	RT	42%	7%
6	Bn	RT	37%	47%



Conditions : THP chloride (1.0 eq.), alkene (2.5 eq.), Schwartz reagent (2.0 eq.), Cu source (0.1 eq.), ligand L2 (0.1 eq.) and ratio of solvent : DCM/$CHCl_3$: 1/2.

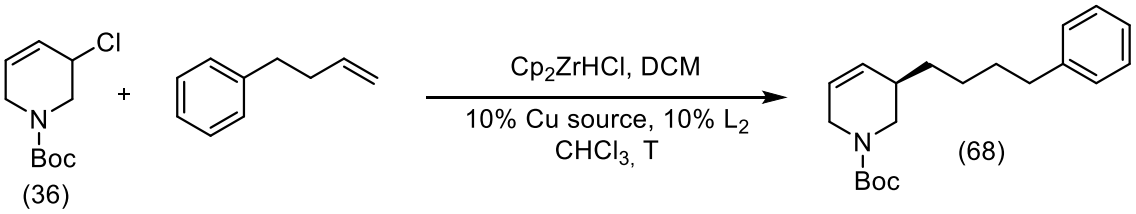
Table 4.1: Influence of the protecting group on the AAA

4.3.2 Screening of different variables

4.3.2.1 Copper source screening

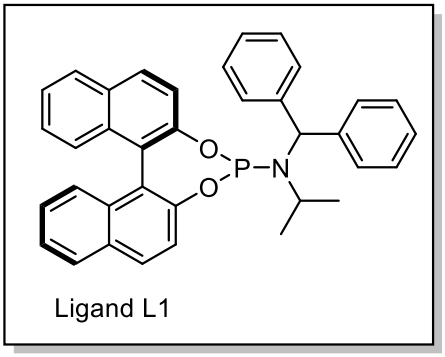
It is important to specify that during the major part of the screening investigations of the asymmetric allylic alkylation, the kinetic resolution process of the reaction was not discovered yet and, therefore, the approach towards screening aimed to obtain high yield (>50%) and high enantioselectivity simultaneously.

A short screening of different copper sources was performed with the Boc protected coupling reagent **36**. An increase in enantioselectivity up to 20% was observed when $CuClO_4$, CuOTf, or $CuPF_6(ACN)_3$ (Entry 1,2 and 4; Table 4.2) were tested compared to CuI (Entry 5; Table 4.2). Those results however confirmed the importance of the benzyl-protecting group on the enantioselectivity, since none of the other substrates produced a more enantioenriched product than 1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine **67** (Entry 12; Table 4.1 and Entry 1 to 5; Table 4.2).



Entry	Cu	T	Yield	ee
1	$CuClO_4$	RT	41%	14%
2	CuOTf	RT	50%	18%
3	CuTc	RT	70%	0%
4	$CuPF_6(ACN)_3$	RT	46%	20%
5[a]	CuI	RT	44%	9%

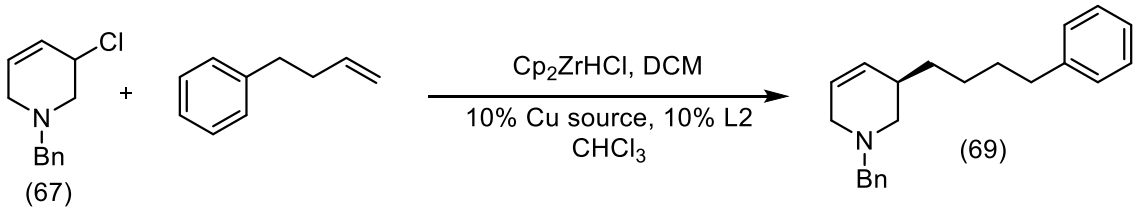
Conditions : THP chloride (1.0 eq.), alkene (2.5 eq.), Schwartz reagent (2.0 eq.), Cu source (0.1 eq.), ligand L2 (0.1 eq.) and ratio of solvent : DCM/$CHCl_3$: 1/2.
a : Ligand L2 replaced with ligand L1



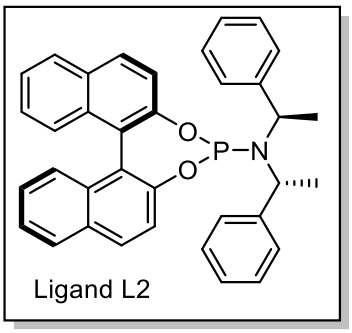
Ligand L1

Table 4.2: Copper screening with Boc-protected THP **36**

Another screening of copper source was then attempted with **67**. CuOTf, CuTc, $CuPF_6(ACN)_3$ and $CuNTf_2$ (Entry 2, 3, 4 and 5; Table 4.3) all gave lower enantioselectivity than CuI (Entry 1; Table 4.3). $CuClO_4$, CuBr and CuCl results (Entry 6, 8 and 10; Table 4.3) gave similar enantioselectivity to CuI but with lower yields obtained. As we obtained 40% yield and enantioselectivity up to 51%, we assumed that CuI was again the best copper source for this particular asymmetric allylic alkylation (Entry 9; Table 4.3).



Entry	Cu source	T	Yield	ee
1	CuI	RT	37%	47%
2	CuOTf	RT	46%	39%
3	CuTc	RT	34%	29%
4	$CuPF_6(ACN)_3$	RT	43%	38%
5	$CuNTf_2$	RT	44%	33%
6	$CuClO_4$	RT	21%	48%
7	CuCl	reflux	30%	22%
8	CuBr	RT	31%	44%
9	CuI	RT	40%	51%
10	CuCl	RT	34%	43%



Conditions : THP chloride (1.0 eq.), alkene (2.5 eq.), Schwartz reagent (2.0 eq.), Cu source (0.1 eq.), ligand L2 (0.1 eq.) and ratio of solvent : DCM/$CHCl_3$: 1/2.

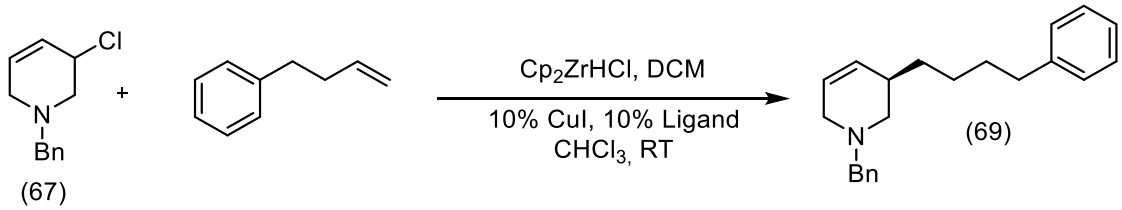
Table 4.3: Copper screening with Bn-protected THP **67**

4.3.2.2 Ligand and solvent screening

Our attention then shifted towards the influence of both ligand and solvent on the enantioselectivity of this new methodology. A selection of ligands based on results from related projects in the Fletcher group were tried and, to our delight, all of them showed moderate to high enantioselectivities (Entry 1,2, 6, 7 and 8; Table 4.4).[74,282] Ligand **L36** proved to be especially effective with an enantiomeric excess up to 88% compared to the 51% previously obtained with **L2** (Entry 9;Table 4.3).

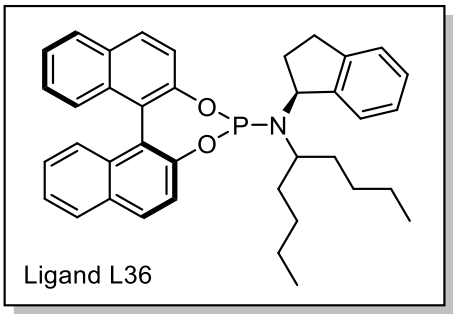
The solvent did not seem to have any real influence on the enantioselectivity. $CHCl_3$, Et_2O, MTBE and benzene gave similar results, with an enantiomeric excess around 90%. (Entry 1, 5, 10 and 11;Table 4.4). DCM and THF gave slightly lower

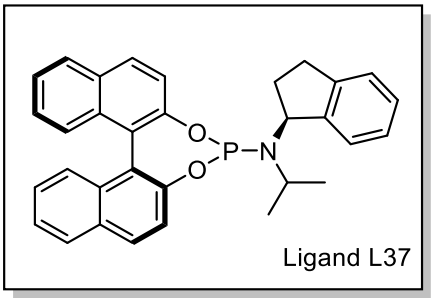
enantiomeric excess, with respectively 84% and 82% ee (Entry 4 and 9;Table 4.4). As enantioselectivity is our main focus and the variation in yield was negligible, MTBE, (up to 91% ee), and $CHCl_3$ were selected as solvents of choice for this methodology.

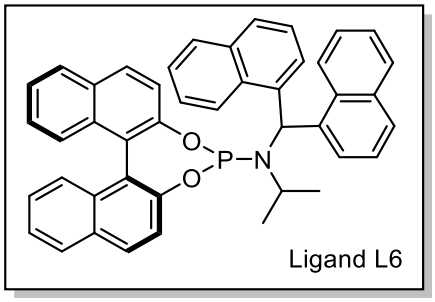


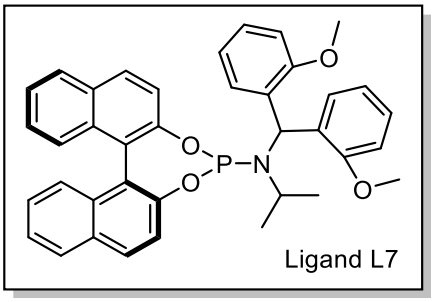
Entry	Solvent	Ligand	Yield	ee
1	$CHCl_3$	L36	27%	88%
2	$CHCl_3$	L37	30%	77%
3[a]	$CHCl_3$	L36	18%	85%
4	DCM	L36	21%	84%
5	Et_2O	L36	24%	90%
6	$CHCl_3$	L6	27%	62%
7	$CHCl_3$	L7	25%	58%
8	$CHCl_3$	L38	36%	80%
9	THF	L36	27%	82%
10	MTBE	L36	22%	91%
11	Benzene	L36	31%	89%

Conditions : THP chloride (1.0 eq.), alkene (2.5 eq.), Schwartz reagent (2.0 eq.), CuI (0.1 eq.), ligand (0.1 eq.) and ratio of solvent : DCM/$CHCl_3$: 1/2. **a** : ratio of solvent : DCM/$CHCl_3$: 1/5.









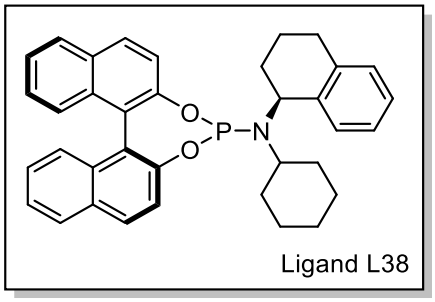


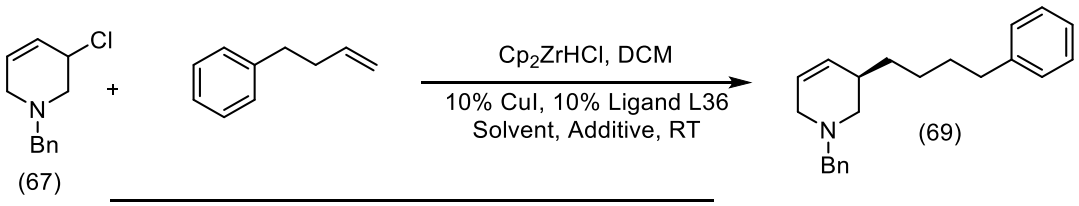
Table 4.4: Solvent and ligand screening with Bn-protected THP **67**

4.3.2.3 Additives screening

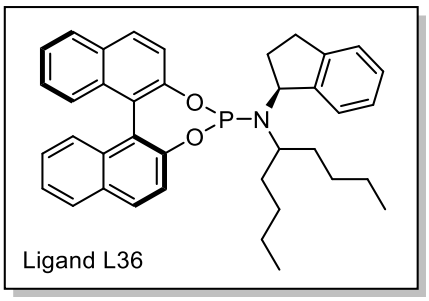
The asymmetric allylic alkylation methodology has been thoroughly investigated on different systems by the Fletcher group over the past years and it was found that additives could have a positive impact on the reaction.[67,276]

We hypothesised that the Nitrogen lone pair could either react with Lewis acids or be protonated and that this interaction might influence the enantioselectivity of the reaction.

No product nor starting material was recovered when the reaction was performed using sulfuric acid or $Zn(OTf)_2$ (Entry 3, 4 and 10; Table 4.5) and $Ti(OiPr)_4$ decreased the enantioselectivity.(Entry 9; Table 4.5). TMSCl, $B(OiPr)_3$, $B(OMe)_3$, $B(Et)_3$, $Si(OEt)_3$, $Al(OEt)_3$ and acetic anhydride (Entry 1, 2, 5, 6, 7, 8, 9 and 12; Table 4.5) gave results similar to those without any additive. The addition of more equivalents of additive still did not improve the reaction (Entry 15; Table 4.5). Unfortunately, none of the additives that were tried out had a real positive influence either on the reactivity or on the enantioselectivity for our AAA system.



Entry	Solvent	Additive	Yield	ee
1	Et_2O	TMSCl	24%	91%
2	$CHCl_3$	TMSCl	24%	87%
3	$CHCl_3$	H_2SO_4	0%	-
4	$CHCl_3$	H_2SO_4	0%	-
5	MTBE	$B(OiPr)_3$	21%	91%
6	MTBE	$B(OMe)_3$	32%	90%
7	MTBE	$B(Et)_3$	15%	91%
8	MTBE	$Si(OEt)_4$	18%	88%
9	MTBE	$Al(OEt)_3$	14%	87%
10	MTBE	$Zn(OTf)_2$	0%	-
11	MTBE	$Ti(OiPr)_4$	29%	65%
12	MTBE	$(CH_3CO)_2O$	21%	87%
13[a]	MTBE	none	31%	89%
14[b]	MTBE	none	18%	90%
15[c]	MTBE	$B(OMe)_3$	9%	89%



Conditions : THP chloride (1.0 eq.), alkene (2.5 eq.), Schwartz reagent (2.0 eq.), CuI (0.1 eq.), ligand L36 (0.1 eq.), additive (1.1 eq.) and ratio of solvent : DCM/Solvent : 1/2. **a** : addition of the alkene solution into the catalyst mixture. **b** : catalyst mixture heat up at 60 °C before addition into the alkene solution. **c** : additive (5.0 eq.)

Table 4.5: Additive screening with Bn-protected THP **67**

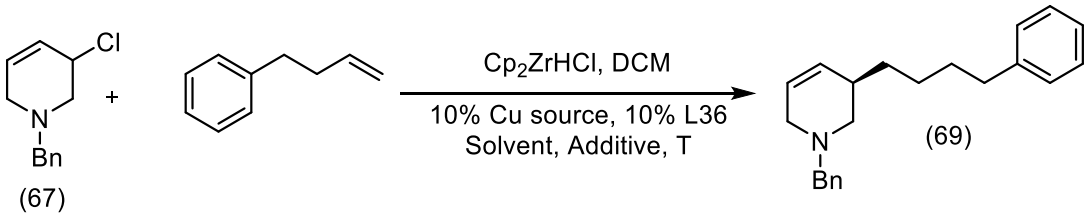
4.3.2.4 Second screening of the AAA

Changing either solvent, the proportions of materials or additives did not improve the system with ligand **L36**; hence a new screening was investigated. During our previous screening, the main issue was the poor reactivity of the asymmetric allylic alkylation, especially when the enantioselectivity was high.

Re-investigating various copper sources with ligand **L36** gave some interesting results. A significant drop of enantioselectivity was observed with CuOTf and $CuNTf_2$,

while the yield increased to approximately 50% in both test reactions (Entry 2 and 11; Table 4.6), contrary to results observed in experiments with $CuClO_4$ and $CuPF_6(ACN)_3$ (Entry 1 and 9; Table 4.6). A slight increase in yield was observed when MTBE was replaced with $CHCl_3$ (Entry 4; Table 4.6). TMSCl once again did not influence the enantioselectivity (Entry 10; Table 4.6) but to our surprise, an increase of 10% ee was observed with $B(OMe)_3$ (Entry 6; Table 4.6).

We then focused our attention on the influence of the temperature on the reaction. An increase in enantioselectivity was observed with CuOTf at 0 °C up to 72% ee (Entry 5; Table 4.6) without any major drop in yield, and up to 93% ee was obtained (Entry 8; Table 4.6) when the reaction was performed at -10 °C with a still reasonable yield of 47%. Although a higher enantioselectivity of 97% was achieved with $CuNTf_2$ only 20% yield was observed (Entry 7; Table 4.6). Diluting the reaction by increasing the amount of MTBE (ratio of DCM/MTBE changed from 1/2 to 1/5) also had a positive impact on the reaction (Entry 12; Table 4.6).



Entry	Solvent	Cu source	T	Additive	Yield	ee
1	MTBE	$CuClO_4$	RT	none	27%	94%
2	MTBE	CuOTf	RT	none	56%	63%
3	Et_2O	CuOTf	RT	none	49%	54%
4	$CHCl_3$	CuOTf	RT	none	61%	64%
5	MTBE	CuOTf	0 °C	none	64%	72%
6	MTBE	CuOTf	RT	$B(OMe)_3$	50%	77%
7	MTBE	$CuNTf_2$	0 °C	none	20%	97%
8	MTBE	CuOTf	-10 °C	none	47%	93%
9	MTBE	$CuPF_6(ACN)_3$	RT	none	29%	76%
10	MTBE	CuOTf	RT	TMSCl	61%	65%
11	MTBE	$CuNTf_2$	RT	none	48%	68%
12[a]	MTBE	CuOTf	0 °C	none	48%	88%

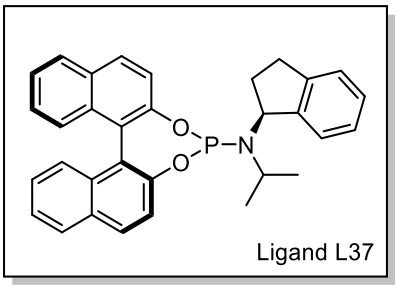
Conditions : THP chloride (1.0 eq.), alkene (2.5 eq.), Schwartz reagent (2.0 eq.), Cu source (0.1 eq.), ligand L36 (0.1 eq.), additive (1.1 eq.) and ratio of solvent : DCM/Solvent : 1/2. **a** : increase amount of MTBE, ratio of solvent : DCM/Solvent : 1/5

Table 4.6: Screening of copper source and temperature with Bn-protected THP **67**

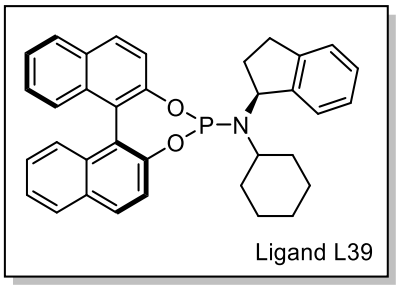
We concluded from those preliminary results that the combination of Ligand **L36** and CuOTf under temperature control was the best way to proceed with this system. A quick screening of Ligand **L37**, **L39**, **L40**, and **L41** showed decreases in enantioselectivity (Entry 1 to 4; Table 4.7).

Entry	Ligand	Yield	ee
1	L37	58%	54%
2	L39	63%	57%
3	L40	50%	55%
4	L41	61%	55%

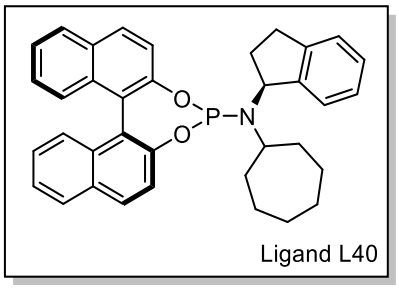
Conditions : THP chloride (1.0 eq.), alkene (2.5 eq.), Schwartz reagent (2.0 eq.), CuOTf (0.1 eq.), ligand (0.1 eq.), and ratio of solvent : DCM/MTBE : 1/2.



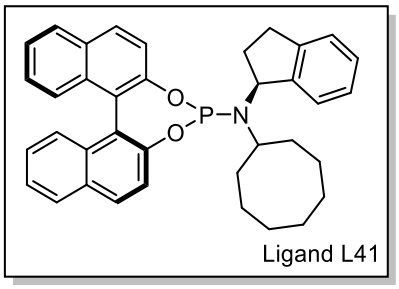
Ligand L37



Ligand L39



Ligand L40

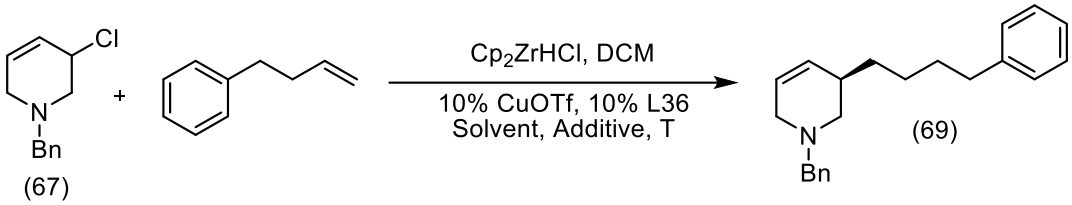


Ligand L41

Table 4.7: Ligand screening with Bn-protected THP **67** and CuOTf

Combining all the information we had gathered, we hypothesised that the best conditions for our system were to perform the reaction using CuOTf with Ligand **L36** at 0 °C with $B(OMe)_3$. Unfortunately, the results were not reproducible, especially for the enantioselectivity (Entry 2; Table 4.8). Diluting the reaction fixed the problem in terms of stereoselectivity but the results were not as good as expected. The yield of the reaction could not be improved while keeping the stereoselectivity high (Entry 3, 4

and 5; Table 4.8) and we obtained the desired product in around 50% yield and 90% enantiomeric excess.



Entry	Solvent	Ratio of solvent	T	Additive	Yield	ee
1[a]	$CHCl_3$	1/2	RT	none	25%	59%
2	MTBE	1/2	0 °C	$B(OMe)_3$	52%	66%
3	MTBE	1/5	0 °C	$B(OMe)_3$	48%	84%
4	MTBE	1/5	0 °C	$B(OMe)_3$	54%	87%
5	MTBE	1/5	0 °C	$B(OMe)_3$	54%	89%
6	MTBE	1/5	0 °C	TMSCl	48%	84%
7	$CHCl_3$	1/5	0 °C	none	40%	93%
8[b]	$CHCl_3$	1/5	0 °C	none	12%	76%
9[c]	$CHCl_3$	1/5	0 °C	none	56%	68%
10[d]	$CHCl_3$	1/5	0 °C	none	58%	85%
11[c]	$CHCl_3$	1/5	0 °C	none	40%	91%
12[d]	$CHCl_3$	1/5	0 °C	none	53%	90%
13	$CHCl_3$	1/3	RT	none	42%	54%
14	$CHCl_3$	1/5	RT	none	26%	86%
15	$CHCl_3$	1/10	RT	none	21%	90%
16	$CHCl_3$	1/20	RT	none	8%	88%
17[e]	$CHCl_3$	1/5	0 °C	$B(OMe)_3$	25%	73%
18[f]	$CHCl_3$	1/5	0 °C	$B(OMe)_3$	9%	94%

Conditions : THP chloride (1.0 eq.), alkene (2.5 eq.), Schwartz reagent (2.0 eq.), CuOTf (0.1 eq.), ligand L36 (0.1 eq.) and additive (1.1 eq.). **a** : DCM was replaced with $CHCl_3$. **b** : reaction stirred for 48h. **c** : increase equivalents of alkene (5.0 eq.) and Schwartz reagent (4.0 eq.). **d** : increase equivalents off CuOTf (0.2 eq.) and ligand L_{17} (0.2 eq.). **e** : decrease equivalent of $B(OMe)_3$ (1.0 eq). **f** : increase equivalent of $B(OMe)_3$ (2.0 eq).

Table 4.8: Experiments with initially optimised conditions.

Contrary to previously observed results (Entry 6 and 10; Table 4.6), switching $B(OMe)_3$ with TMSCl had no real impact (Entry 6; Table 4.8). Moreover, removing the additive increased the enantioselectivity up to 93% with a slight decrease in yield (Entry

7; Table 4.8). Allowing the reaction to go for 48h, increasing the amount of hydrozirconated alkene and increasing the amount of catalyst (Entry 8, 9 and 10; Table 4.8) all caused a drop in enantioselectivity. The main information those experiments revealed was that there seems to be an inverse correlation between the % yield and the enantioselectivity.

Repeating many of these reactions showed that the results were difficult to reproduce but the same overall trend was observed once again in experiments with increased amounts of either hydrozirconated alkene or catalyst. If we look closely at the results, with an excess of hydrozirconated alkene, we can observe that a higher yield of 56% induced a low enantioselectivity of 68% (Entry 9; Table 4.8) whereas lesser yield of 40% yield induced a high enantioselectivity of 91% (Entry 11; Table 4.8).

Reactions conducted with 20% catalyst loading also presented the same conclusions (Entry 10 and 12; Table 4.8). With a yield of 58%, 85% ee was obtained whereas for the repeated experiment a lower yield induced a higher enantioselectivity.

Diluting the reaction was an obvious approach to decreasing reactivity: indeed, diluting our reaction medium gave less product and higher ee (Entry 13 to 16; Table 4.8).

We observed during our investigations that when we tried to slow down the reaction either by temperature control or by dilution the enantioselectivity of the reaction increased (Entry 5, 8 and 12; Table 4.6 and Table 4.8). An increase in enantioselectivity is observed from 63% when the reaction is performed at room temperature (Entry 2, Table 4.6) to 72% at 0 °C (Entry 5, Table 4.6) and to 93% at -10 °C (Entry 12, Table 4.6). When the reaction is diluted, the enantioselectivity increased from 72% for a ratio of DCM/MTBE of 1/2 (Entry 5; Table 4.6) to 88% with a ratio of

solvent of DCM/MTBE of 1/5 (Entry 12; Table 4.6). Similarly when diluting the reaction and increasing the ratio of DCM/$CHCl_3$ from 1/3 to 1/20 the enantioselectivity increased from 54% to around 90% (Entry 13 to 16; Table 4.8).

Since we observed an inverse correlation between the % yield and enantioselectivity and that slowing down the reaction increases the ee, it seemed realistic to consider that Cu-catalysed AAA of THP allyl chlorides underwent a kinetic resolution rather than a dynamic process.

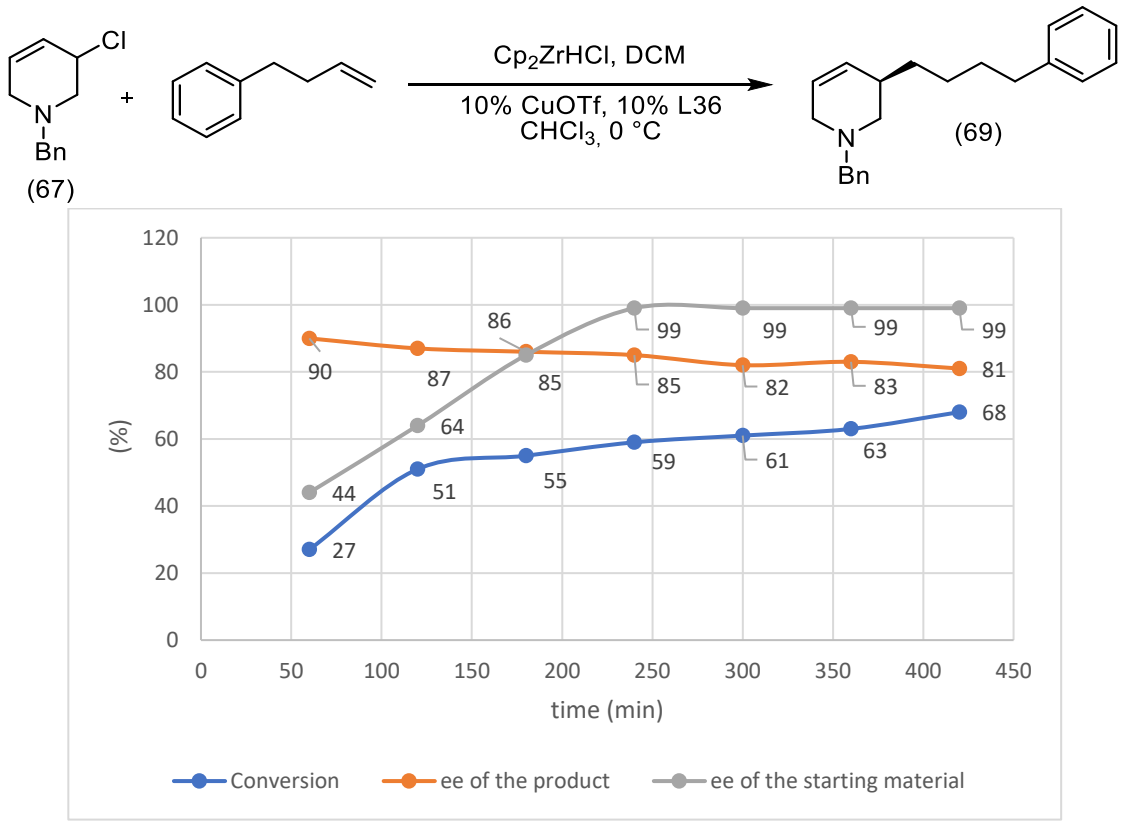
4.3.3 Kinetics studies

In order to validate the kinetic resolution hypothesis, our first step was to check the enantiomeric excess of unreacted substrate once the reaction was quenched.[237,279] To our delight, the recovered allyl chloride was enantioenriched.

According to the results of reaction condition screening, performing the reaction with CuOTf and ligand **L36** in DCM/$CHCl_3$ (1/5) at 0 °C without any additive was considered to be ideal for a kinetic study. The scale of the reaction was tripled in order to have enough material in each collected sample for proper analysis.

A sample was collected every hour for 7 hrs at 0 °C and primary results concurred with a kinetic resolution process. Indeed over time, we observed an increase in conversion (determined by ^{1}H NMR spectroscopy) from 26% at 1 h to 64% at 7 hrs (Blue line; Scheme 4.18), a decrease in enantiomeric excess of the desired product **69** from 90% at 1 h to 81% at 9 hrs (Orange line; Scheme 4.18) and an increase in enantiomeric excess of the piperidene allyl chloride from 44% at 1 h to 99% at 4 hrs (Grey line; Scheme 4.18). Interestingly the enantiomeric excess of allyl chloride stayed at 100% until the quenching of reaction. On the other hand conversion, though slowed,

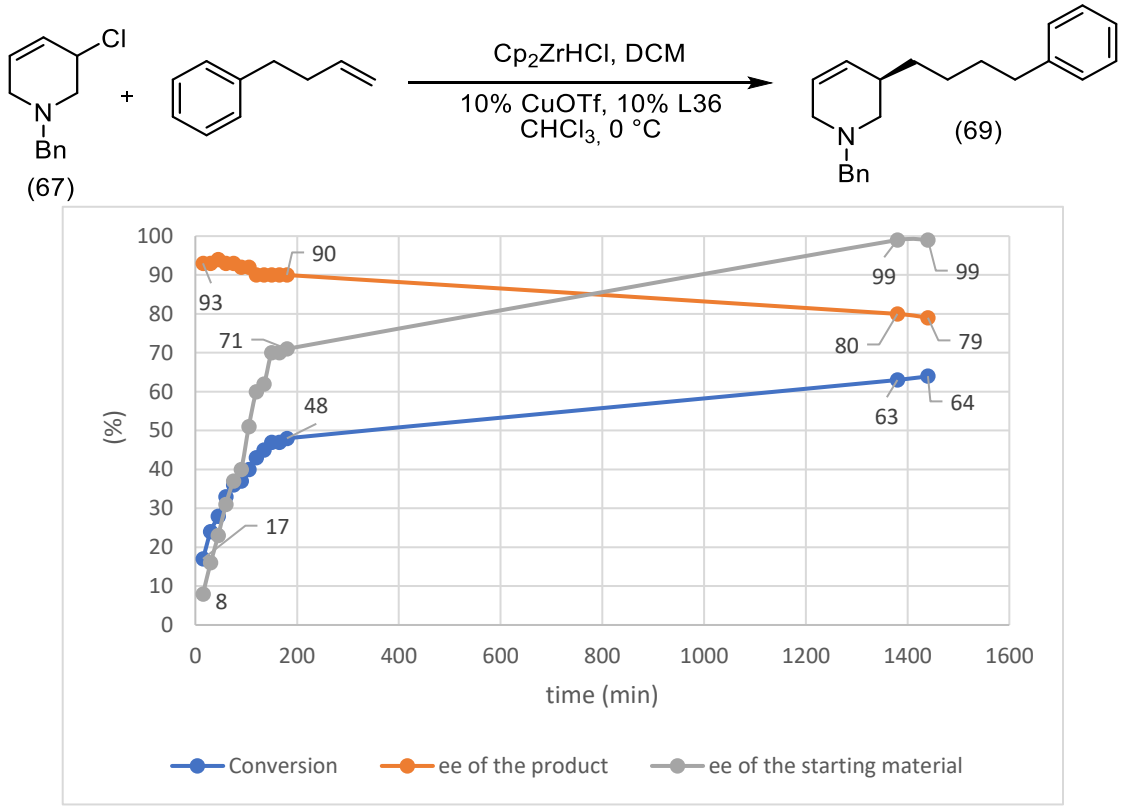
did not completely stop, showing both enantiomers of allyl chloride were reactive in AAA.



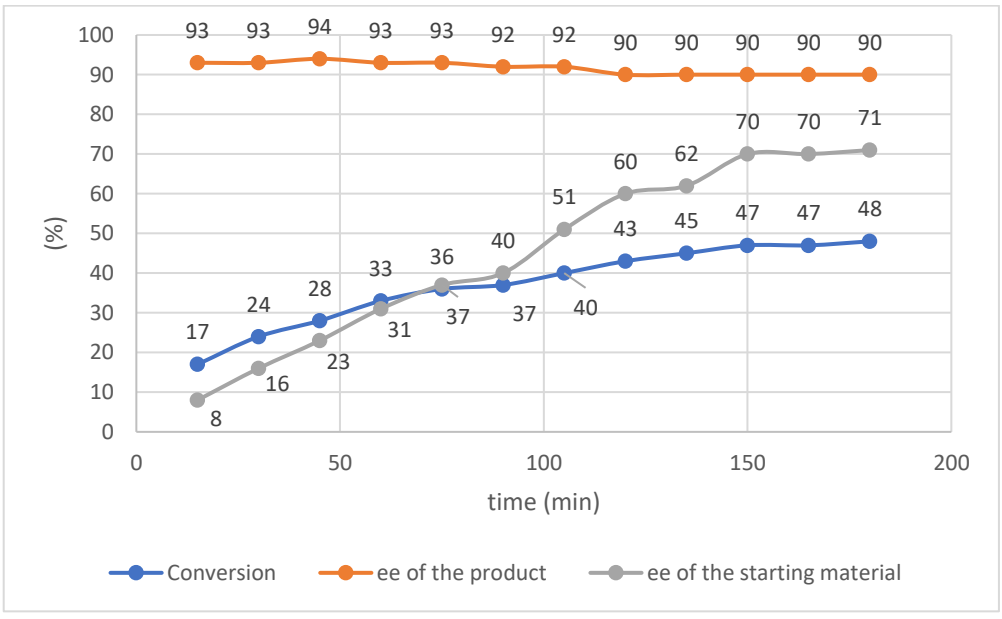
Scheme 4.18: Kinetics study of Cu-catalysed AAA at 0 °C

The conditions of a second kinetic study were unchanged, but samples were collected every 15 mins for the first 3 hrs and the reaction was left stirring for 24 hrs. The results reconfirmed a kinetic resolution. We again observed an increase in conversion over time from 17% at 15 mins to 64% at 24 hrs (Blue line; Scheme 4.19a), a slight decrease in enantiomeric excess of the product from 93% at 15 mins to 79% at 24 hrs, (Orange line; Scheme 4.19a) and finally an increase in enantiomeric excess of the starting material from 8% at 15 mins to 100% at 24 hrs (Grey line; Scheme 4.19a). It was observed that for the first few hours of the reaction, the enantiomeric excess of the product only decreased slightly from 93% at 15 mins to 90% at 3 hrs whereas the enantiomeric excess of the allyl chloride increased rapidly (Scheme

4.19b) showing one enantiomer of allyl chloride underwent AAA considerably faster than the other enantiomer.

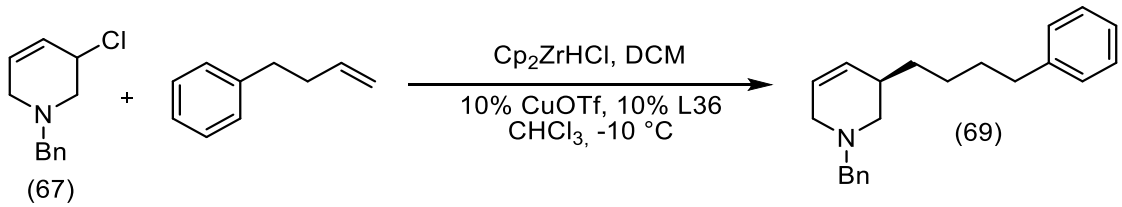


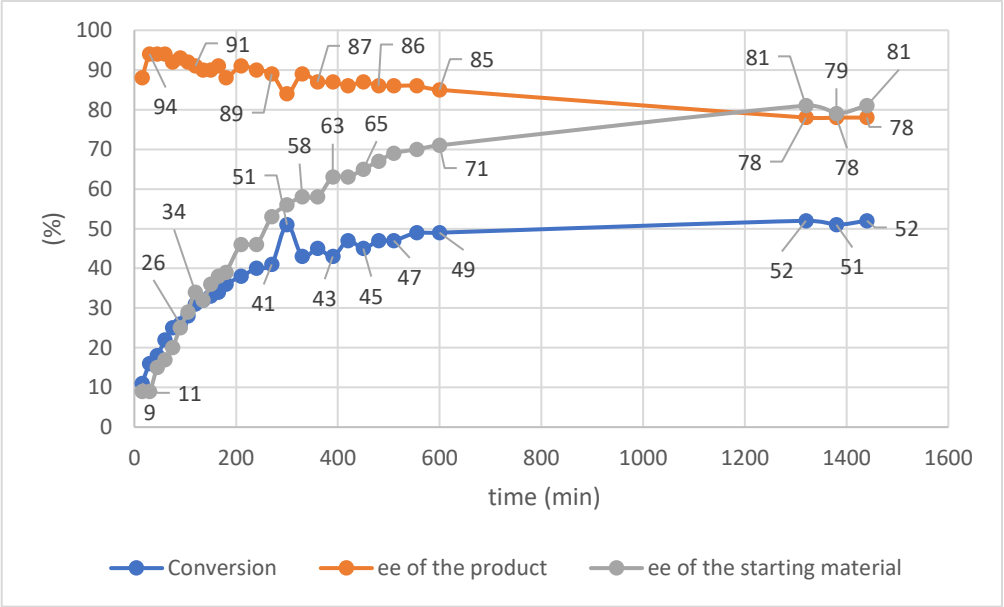
Scheme 4.19a : Kinetics study of Cu-catalysed AAA at 0 °C



Scheme 4.19b : Kinetics study of Cu-catalysed AAA at 0 °C

Finally, a last kinetic study was performed with CuOTf and ligand **L36** in DCM/$CHCl_3$ (1/5) for 24 hrs but at -10 °C. Once again, a sample was collected every 15 mins for 3 hrs, and then every 30 mins up to 10 hrs of reaction. As expected, the conversion was slightly lower than the previous two experiments and reached 52% in 24 hrs (Blue line; Scheme 4.20). The enantiomeric excess of the product decreased from 94% at 30 mins to 78% at 24 hrs (Orange line; Scheme 4.20) and the enantiomeric excess of the allyl chloride increased from 9% at 15 mins to 81% at 24 hrs (Grey line; Scheme 4.20).





Scheme 4.20 : Kinetics study of Cu-catalysed AAA at -10 °C

The main issues with kinetic resolutions are that they often produces mixtures of compounds and provide products in lower than 50% yield.[237,279] However, they become useful asymmetric reactions when two valuable chiral molecules are synthesised simultaneously.[283] Fortunately, with this methodology we had the potential to produce a library of novel 3-alkyl-subsituted tetrahydropyridines and an enantiopure rare allylic 3-chloro tetrahydropyridine, two bio/chemically significant chiral molecules for the pharmaceutical industry.[218–220]

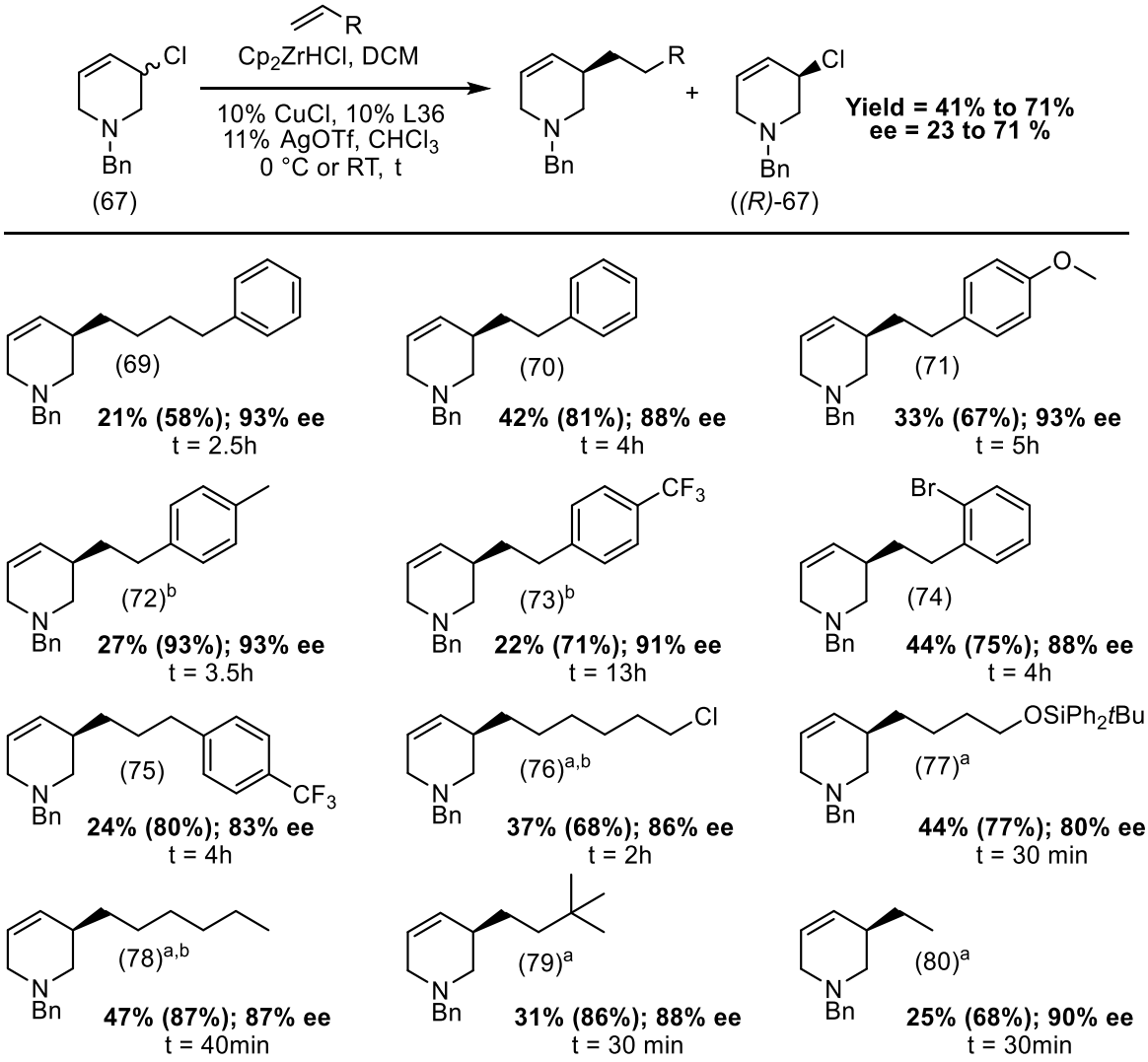
4.3.4 Scope of the AAA system

Using the information gathered during the kinetics studies with 4-phenyl-1-butene, we decided to carry out the asymmetric allylic alkylation with a variety of alkenes for 4 hrs at -10 °C. We did obtain the 3-alkyl tetrahydropyridine products, but the test reactions faced some challenges. Indeed, some reproducibility issues appeared when performing the reaction at -10 °C, which was most likely due to the possible heterogeneous nature of AAA reactions with alkyl zirconiums and the effect of low temperatures on the solubility of reactive intermediates. The reaction was also shown to be influenced by stirring speed, partly supporting this theory. We still did manage to synthesise eight different examples in low to good yields up to 55%, to characterise them and to determine the enantiomeric excess of the resolved starting material but couldn't find a way to determine the enantiomeric excess of the AAA products.

From this point, my colleague Dr Sedef Karabiyikoglu took over the project.[283] For every example described, conversion of the reaction was monitored by NMR as the AAA reaction was found to perform differently, depending on the alkyl zirconocene reagent present. The optimised time of reaction was determined when the ratio of starting material to product was 1/0.8 on NMR (Figure 4.5). The reactions were then

carried out for the appropriate time (from 30 mins to 13 hrs) and at 0 °C or room temperature to avoid those reproducibility issues. The asymmetric allylic alkylations of 3-chloro tetrahydropyridine were successful both with functionalised (**69** to **77**; Figure 4.5) and unfunctionalised alkenes (**78** to **80**; Figure 4.5). Products were formed with moderate yields and high enantioselectivities for the most part. For reasons unknown to us, a slight decrease of enantioselectivity (still above 80%) was observed with 1-allyl-4-(trifluoromethyl)benzene (**75**; Figure 4.5), 6-chlorohex-1-ene (**76**; Figure 4.5) and (but-3-en-1-yloxy)(tert-butyl)diphenylsilane (**77**; Figure 4.5).[283]

The absolute configuration of **69**-**80** were assigned by analogy with previously reported literature from the Fletcher group.[278]



Conditions : THP chloride (1.0 eq.), alkene (2.5 eq.), Schwartz reagent (2.0 eq.), CuOTf (0.1 eq.), ligand L36 (0.1 eq.) and additive (1.1 eq.). Values in parentheses represent yields calculated with respect to consumed **67**. s values and ee's of recovered allyl chloride **(*R*)-67** for each substrate are given in SI. **a** : Reactions performed at room temperature. **b** : Reactions performed by Dr Sedef Karabiyikoglu

Figure 4.5: Scope of the reaction

4.4 Summary

In this project, we applied the copper catalysed asymmetric allylic alkylation to racemic 3-chloro tetrahydropyridines in order to access a new library of functionalised piperidenes in moderate to good yields and high enantioselectivities. The 3-substituted tetrahydropyridine motif is of particular interest as it is commonly found in biologically active molecules and drugs.

In the process, we found out that the reaction underwent a kinetic resolution process rather than a DYKAT which is generally observed in the asymmetric allylic alkylations.

We performed kinetic studies of the reaction to confirm the kinetic resolution process and from those investigations we were able to synthesise a variety of 3-substituted tetrahydropyridines.

My colleague Dr Sedef Karabiyikoglu was also able to obtain complete resolution of **67** and subject **(*R*)-67** to different enantiospecific substitution reactions with thio/ethers, an ester, a malonate, a fluoride and an amine and obtained the substitution products in high enantiomeric excess and good to high yields.[283]

The reaction mechanism was studied by Density Functional Theory (DFT) by my colleague Alexandre Brethomé to gain insight in the kinetic resolution of **67**.[283]

The enantioenriched allyl chloride obtained by the kinetic resolution is of potential use in pharmaceutical industry. Indeed it was shown that it's highly stabile, easy to handle and a potential building block to access various enantiopure molecules.[283]

Chapter 5

5 Conclusions and Future Work

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

The first aim was to develop a new protocol for the synthesis of Taxadiene using an asymmetric 1,4-conjugate addition of alkylzirconocenes as the first key step. Three different approaches were investigated: ACAs of a cyclic or linear trialkene with a cyclic enone, ACAs with an α-substituted cyclic enone and ACAs followed by an enolate trapping. Taxadiene was never synthesised but valuable intermediates bearing both desired cycle A and C were obtained. The next step for this project would have been to investigate thoroughly the closure of ring B and explore biocatalytic/electrochemical oxidation applications to access derivatives of Taxadiene.

The new domino hydrozirconation/conjugate addition/enolate trapping reactions developed are of particular interest as it is possible to access complex molecules in a single step. Applying those new methodologies to a variety of different alkylzirconocenes could be of particular interest.

An asymmetric allylic arylation of a racemic chloro-tetrahydropyridine with aryl and heteroarylboronic acids was successfully developed and provided small chiral heterocyclic molecules with good yields and excellent enantioselectivities.

Using this methodology, a formal and a total synthesis of (-)-Preclamol were achieved. It would be interesting to extend this methodology to more substituted racemic chloro-tetrahydropyridine or other non-stabilised nucleophiles such as organosilanes and expand the library of chiral small molecules.

An asymmetric allylic alkylation of similar racemic chloro-tetrahydropyridines with alkylzirconocenes was also successfully developed and provided an alternative scaffold of chiral heterocyclic molecules with good yields and high enantioselectivities. Unlike the asymmetric allylic arylation methodology, it was proved that the asymmetric allylic alkylation methodology undergoes a kinetic resolution process rather than a DYKAT. Therefore an enantioenriched chloro-tetrahydropyridine was also obtained and could be subjected to a variety of different enantiospecific substitution reactions.

Chapter 6

6 Supporting Information

6.1 General information

Procedures using oxygen/moisture-sensitive materials were performed with anhydrous solvents under an atmosphere of anhydrous argon in flame-dried flasks, using standard Schlenk techniques. Analytical thin-layer chromatography was performed on pre-coated glass-backed plates (Silica Gel 60 F254; Merck), and visualised using a combination of UV light (254 nm) and aqueous basic potassium permanganate ($KMnO_4$) stain and developed upon heating. Flash column chromatography was carried out using Apollo Scientific silica gel 60 (0.040 – 0.063 nm), Merck 60 Å silica gel, VWR (40-63 μm) silica gel and Sigma Aldrich silica gel. Pressure was applied at the column head via a flow of nitrogen with the solvent system used in parentheses.

Reactions at 0 °C were performed using an ice-water bath, covered with cotton wool and aluminium foil if overnight stirring is needed. Other temperatures were obtained using a Julabo FT902 immersion cooler or the heating plate of the stirrer.

NMR spectra were recorded at room temperature on Bruker AVIII HD 400 or AVIII HD 500 spectrometers and calibrated to the solvent signal ($CDCl_3$ δ = 7.26 ppm for ^{1}H NMR, δ = 77.0 ppm for ^{13}C NMR, C_6D_6 δ = 7.16 ppm for ^{1}H NMR, δ = 128.0 ppm for ^{13}C NMR). Chemical shifts are reported in ppm from the residual solvent peak. Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or b (broadened).

Chiral HPLC separations were achieved using an Agilent 1230 Infinity series normal phase 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 Aldrich or Honeywell); 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 characterisation. 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 mins. Chiral SFC (supercritical fluid chromatography) separations were conducted on a Waters Acquity UPC2 system using Waters Empower software. Chiralpak® columns (150 × 3 mm, particle size 3 μm) were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Aldrich or Honeywell).

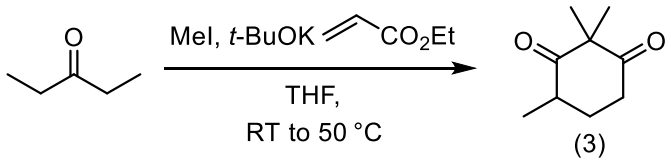
Low-resolution mass spectra were recorded using a Walters LCT premier XE. High resolution mass spectra (EI and ESI) were recorded using a Bruker MicroTOF spectrometer by the internal service at the University of Oxford. Infrared measurements (neat, thin film) were carried out using a Bruker Tensor 27 FT-IR with internal calibration in the range 600-4000 cm^{-1}. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 25 °C in a 10 cm cell in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg.cm^2 g^{-1} (concentration c given as g/100 mL).

Dry THF, $CHCl_3$, DMF, 1,4-dioxane, toluene, MTBE and DCM were collected fresh from an mBraun SPS-5 solvent purification system having been passed through anhydrous alumina columns. All other dry solvents used were dried over 3 Å or 4 Å molecular sieves and stored under argon. All other solvents were used as purchased from Sigma Aldrich, Honeywell or Fisher Scientific. Unless stated otherwise, commercially available reagents were purchased from Sigma-Aldrich, Fisher Scientific, Apollo Scientific, Acros Organics, Strem Chemicals, Alfa Aesar or TCI UK and were used without purification. Petroleum ether refers to light petroleum boiling in the range 40-60 °C. Deuterated solvents were purchased from Sigma-Aldrich.

6.2 Experimental procedures

6.2.1 Chapter 2

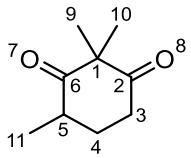
2,2,4-Trimethylcyclohexane-1,3-dione 3:



(3)

To a solution of pentan-3-one (18 mL, 0.17 mol, 1.00 eq) in THF (240 mL), was added *t*-BuOK (22.4 g, 0.20 mol, 1.18 eq) at room temperature. The mixture was then cooled down to 0 °C, stirred for 10 mins before ethyl acrylate (20 mL, 0.17 mol, 1.00 eq) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 20 mins followed by the addition of Iodomethane (30 mL, 0.49 mol, 2.87 eq). The mixture was stirred at 50 °C for 3 hrs. The reaction was quenched with water (100 mL) and extracted with EtOAc (50 mL x3). The combined organic layers were washed with brine (50 mL x2), dried over $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc (9/1)) gave 2,2,4-trimethylcyclohexane-1,3-dione **3** in 50% yield (13.1 g, 0.085 mol) as yellow oil.

TLC R_f = 0.26 (hexane/EtOAc (9/1)).



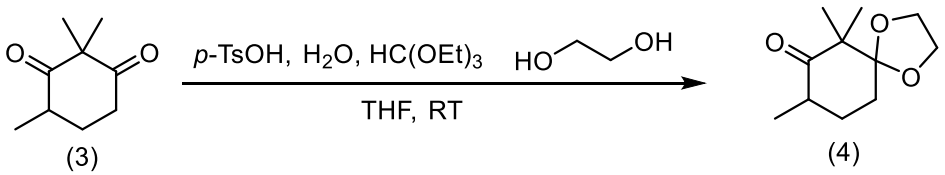
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.16 (d, *J* = 6.5 Hz, 3H, H-11), 1.24 (s, 3H, H-9 or 10), 1.36 (s, 3H, H-9 or 10), 1.48 (qd, *J* = 13.0, 5.0 Hz, 1H, H-4'), 2.11 (m, 1H, H-4''), 2.62 (ddd, *J* = 16.0, 5.0, 3.0 Hz, 1H, H-3'), 2.74 – 2.90 (m, 2H, H-3'' and H-5).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 14.8 (C-11), 19.1 (C-9 or 10), 25.9 (C-9 or 10), 26.5 (C-4), 37.2 (C-3), 40.8 (C-5), 61.1 (C-1), 210.7 (C-2), 211.4 (C-6).

HRMS (EI/FI): *m*/*z* calc. for $C_9H_{14}O_2$ $[M]^{+\cdot}$: 154.0994, found: 154.0987.

Data consistent with previously reported values.[130]

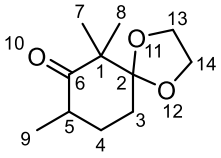
6,6,8-Trimethyl-1,4-dioxaspiro[4.5]decan-7-one 4:



(3) (4)

2,2,4-Trimethylcyclohexane-1,3-dione **3** (6.00 g, 38.9 mmol, 1.00 eq) was dissolved in THF (80 mL). Ethylene glycol (4.3 mL, 77.8 mmol, 2.00 eq), triethylorthoformate (9.7 mL, 58.4 mmol, 1.50 eq) and *p*-TsOH.H_2O (2.22 g, 11.7 mmol, 0.30 eq) were added to the solution which was stirred overnight at room temperature. The reaction was quenched by adding triethylamine (2.7 mL, 19.5 mmol, 0.50 eq). The mixture was then concentrated and purified by flash column chromatography (hexane/EtOAc (9/1)) giving 6,6,8-trimethyl-1,4-dioxaspiro[4.5]decan-7-one **4** in 98% yield (7.60 g, 38.3 mmol) as colourless oil.

TLC R_f = 0.58 (hexane/EtOAc (9/1)).



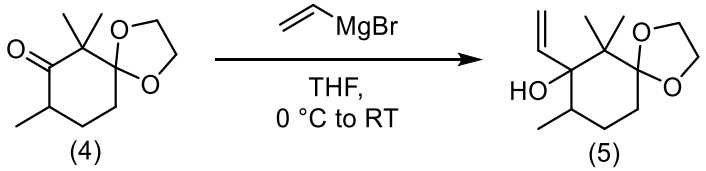
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.97 – 1.07 (m, 6H, H-7 or 8 and 9), 1.27 (s, 3H, H-7 or 8), 1.39 (qd, *J* = 13.5, 4.5 Hz, 1H, H-4'), 1.75 (ddd, *J* = 13.5, 4.5, 2.5 Hz, 1H, H-3'), 1.86 (m, 1H, H-4''), 2.13 (td, *J* = 13.5, 4.5 Hz, 1H, H-3''), 2.66 (m, 1H, H-5), 3.85 – 4.02 (m, 4H, H-13 and 14).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 14.8 (C-9), 16.6 (C-7 or 8), 24.1 (C-7 or 8), 28.3 (C-4), 30.2 (C-3), 39.2 (C-5), 54.8 (C-1), 65.4 (C-13 or 14), 65.4 (C-13 or 14), 113.7 (C-2), 213.7 (C-6).

HRMS (ESI): *m*/*z* calc. for $C_{11}H_{19}O_3$ $[M+H]^+$: 199.1329, found: 199.1326.

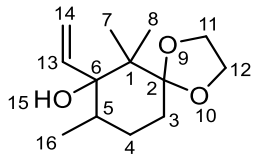
Data consistent with previously reported values.[130]

6,6,8-Trimethyl-7-vinyl-1,4-dioxaspiro[4.5]decan-7-ol 5:



In a flame-dried two-necked flask equipped with a condenser, Mg (1.34 g, 55.1 mmol, 1.50 eq) and I_2 (few crystals) were flame dried under argon. THF (15 mL) was added to the flask, which was then heated to 50 °C. A solution of vinyl bromide in THF (92 mL, 91.8 mmol, 1M, 2.50 eq) was added dropwise to the reaction mixture which was then cooled down to room temperature and stirred for 30 mins. In another flame-dried flask, 6,6,8-trimethyl-1,4-dioxaspiro[4.5]decan-7-one **4** (7.28 g, 36.7 mmol, 1.00 eq) was dissolved in THF (12 mL) and added at 0 °C to the organomagnesium solution over 30 mins using a syringe pump. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl (50 mL), extracted with EtOAc (40 mL x3), washed with brine (30 mL x2), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc (9/1)) gave 6,6,8-trimethyl-7-vinyl-1,4dioxaspiro[4.5]decan-7-ol **5** in 40% yield (3.30 g, 14.6 mmol) as a yellow oil.

TLC R_f = 0.67 (hexane/EtOAc (9/1)).



^{1}H NMR (500 MHz, Chloroform-*d*) δ ppm = 0.79 (d, *J* = 6.5 Hz, 3H, H-16), 0.86 (s, 3H, H-7 or 8), 1.07 (s, 3H, H-7 or 8), 1.44 – 1.53 (m, 2H, H-4), 1.56 (ddd, *J* = 13.5, 4.0, 3.0 Hz, 1H, H-3'), 1.73 – 1.82 (m, 1H, H-3''), 1.83 – 1.92 (m, 1H, H-5), 3.73 (d, *J* = 1.5 Hz, 1H, H-15), 3.89 – 3.94 (m, 2H, H-11 or 12), 3.99 (m, 2H, H-11 or 12), 5.18 (dd, *J* = 11.0, 2.5 Hz, 1H, H-14 cis), 5.33 (dd, *J* = 17.0, 2.5 Hz, 1H, H-14 trans), 5.64 (ddd, *J* = 17.0, 11.0, 1.5 Hz, 1H, H-13).

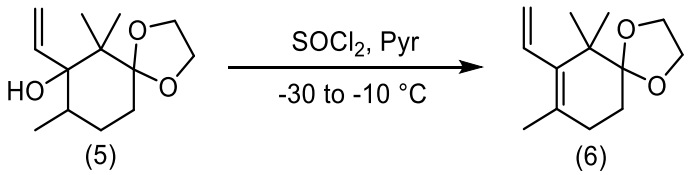
^{13}C NMR (126 MHz, Chloroform-*d*) δ ppm = 15.9 (C-16), 15.9 (C-7 or 8), 21.7 (C-7 or 8), 27.1 (C-4), 30.4 (C-3), 34.0 (C-5), 45.3 (C-1), 64.2 (C-11 or 12), 65.7 (C-11 or 12), 79.7 (C-6), 113.3 (C-2), 115.2 (C-14), 139.8 (C-13).

IR (ATR) ν_{max} /cm^{-1} = 3522 (w), 2982 (w), 2888 (w), 1450 (w), 1415 (w), 1386 (w), 1368 (w), 1346 (w), 1212 (w), 1158 (m), 1126 (s), 1075 (s), 1039 (s), 966 (s), 950 (m), 923 (s), 901 (s), 865 (w), 710 (w), 619 (w).

HRMS (ESI): *m*/*z* calc. for $C_{13}H_{22}O_3Na$ $[M+Na]^+$: 249.1461, found: 249.1457.

Data consistent with previously reported values.[132]

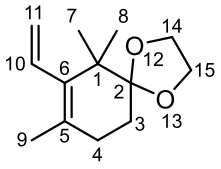
6,6,8-Trimethyl-7-vinyl-1,4-dioxaspiro[4.5]decane 6:



(5) (6)

6,6,8-Trimethyl-7-vinyl-1,4-dioxaspiro[4.5]decan-7-ol **5** (3.00 g, 13.3 mmol, 1.00 eq) was dissolved in anhydrous pyridine (33 mL, 0.4M, 13.3 mmol, 1.00 eq). The solution was cooled down to -30 °C and $SOCl_2$ (1.06 mL, 14.6 mmol, 1.10 eq) was added to the mixture dropwise. The resulting mixture was warmed to -10 °C and stirred for 4 hrs. The reaction was then diluted with hexane (50 mL), extracted with EtOAc (40 mL x2), washed with HCl (1M, 25 mL x2), saturated $NaHCO_3$ (25 mL x2) and brine (20 mL x2), dried over $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc (9/1)) gave 6,6,8-trimethyl-7-vinyl-1,4-dioxaspiro[4.5]decane **6** in 70% yield (1.93 g, 9.27 mmol) as a yellow oil.

TLC R_f = 0.83 (hexane/EtOAc (9/1)).



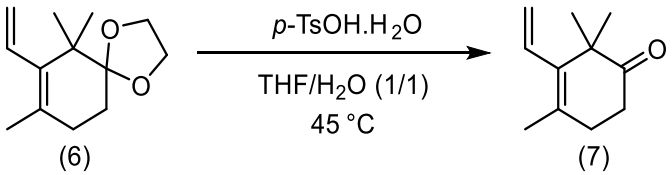
^{1}H NMR (500 MHz, Chloroform-*d*) δ ppm = 1.05 (s, 6H, H-7 and 8), 1.71 (m, 3H, H-9), 1.78 (t, *J* = 6.5 Hz, 2H, H-3), 2.18 (m, 2H, H-4), 3.90 – 4.04 (m, 4H, H-14 and 15), 4.99 (dd, *J* = 17.5, 2.5 Hz, 1H, H-11 trans), 5.27 (dd, *J* = 11.0, 2.5 Hz, 1H, H-11 cis), 6.15 (m, 1H, H-10).

^{13}C NMR (126 MHz, Chloroform-*d*) δ ppm = 21.0 (C-9), 22.9 (C-7 and 8), 26.7 (C-3), 30.7 (C-4), 42.1 (C-1), 65.0 (C-14 and 15), 112.1 (C-2), 118.9 (C-11), 127.1 (C-5), 135.0 (C-10), 137.5 (C-6).

HRMS (ESI): *m/z* calc. for $C_{13}H_{21}O_2$ $[M+H]^+$: 209.1536, found: 209.1534.

Data consistent with previously reported values.[133]

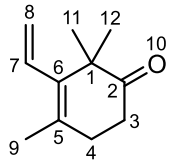
2,2,4-Trimethyl-3-vinylcyclohexanone 7:



(6) (7)

6,6,8-Trimethyl-7-vinyl-1,4-dioxaspiro[4.5]decane **6** (1.69 g, 8.10 mmol, 1.00 eq) was dissolved in THF/H_2O (60 mL, (1/1)). *p*-TsOH.H_2O (1.54 g, 8.10 mmol, 1.00 eq) was then added to the solution and the reaction was stirred at 45 °C overnight. The reaction was diluted with Et_2O (50 mL), extracted with Et_2O (30 mL x2), washed with brine (20 mL x2), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc (9/1)) gave 2,2,4-trimethyl-3-vinylcyclohexanone **7** in 94% yield (1.25 g, 7.61 mmol) as a yellow oil.

TLC R_f = 0.83 (hexane/EtOAc (9/1)).



^{1}H NMR (500 MHz, Chloroform-*d*) δ ppm = 1.19 (s, 6H, H-11 and 12), 1.82 (m, 3H, H-9), 2.43 (m, 2H, H-4), 2.58 (t, *J* = 7.0 Hz, 2H, H-3), 5.10 (dd, *J* = 17.5, 2.5 Hz, 1H, H-8 trans), 5.38 (dd, *J* = 11.0, 2.5 Hz, 1H, H-8 cis), 6.16 (m, 1H, H-7).

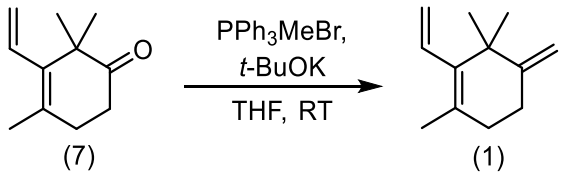
^{13}C NMR (126 MHz, Chloroform-*d*) δ ppm = 21.1 (C-9), 24.8 (C-11 and 12), 31.8 (C-4), 35.9 (C-3), 46.7 (C-1), 119.9 (C-8), 128.7 (C-5), 133.9 (C-7), 137.4 (C-6), 215.2 (C-2).

IR (ATR) ν_{max} /cm^{-1} = 2971 (w), 1714 (s), 1445 (w), 1377 (w), 1358 (w), 1239 (w), 1097 (w), 992 (w), 921 (m).

HRMS (ESI): *m/z* calc. for $C_{11}H_{17}O$ $[M+H]^+$: 165.1274, found: 165.1272.

Data consistent with previously reported values.[135]

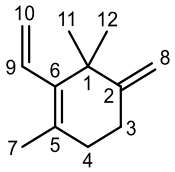
1,1,3-Trimethyl-6-methylene-2-vinylcyclohexane 1:



(7) (1)

A suspension of PPh_3.MeBr (4.18 g, 11.7 mmol, 2.00 eq) and *t*-BuOK (1.31 g, 11.7 mmol, 2.00 eq) in THF (30 mL) in a flame-dried flask was stirred for 10 mins. 2,2,4-trimethyl-3-vinylcyclohexanone **7** (0.96 g, 5.84 mmol, 1.00 eq) was then added to the mixture over 3 mins. The resulting solution was stirred at room temperature for 24 hrs. The reaction was quenched with water (30 mL), extracted with Et_2O (20 mL x2), washed with brine (10 mL x2), dried over $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash column chromatography (hexane, 100%) gave 1,1,3-trimethyl-6-methylene-2-vinylcyclohexane **1** in 79% yield (0.74 g, 4.56 mmol) as a colourless oil.

TLC R_f = 0.95 (hexane/EtOAc (9/1)).



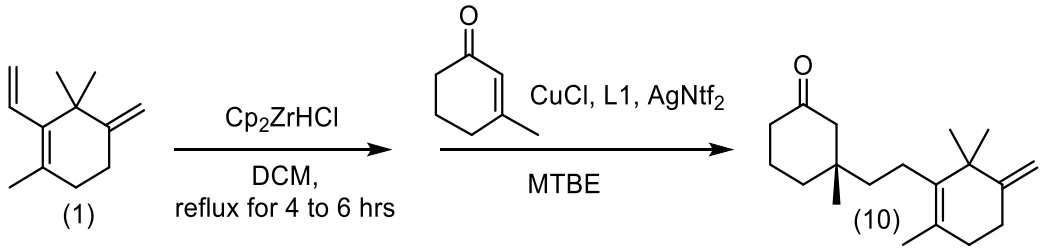
^{1}H NMR (500 MHz, Chloroform-*d*) δ ppm = 1.17 (s, 6H, H-11 and 12), 1.70 (m, 3H, H-7), 2.12 (m, 2H, H-4), 2.36 (m, 2H, H-3), 4.66 – 4.77 (m, 2H, H-8), 4.99 (dd, *J* = 17.5, 2.5 Hz, 1H, H-10 trans), 5.29 (dd, *J* = 11.0, 2.5 Hz, 1H, H-10 cis), 6.20 (m, 1H, H-9).

^{13}C NMR (126 MHz, Chloroform-*d*) δ ppm = 21.5 (C-7), 27.6 (C-11 and 12), 30.5 (C-3), 34.6 (C-4), 39.5 (C-1), 104.8 (C-8), 118.9 (C-10), 128.9 (C-5), 135.38 (C-9), 137.9 (C-6), 155.9 (C-2).

IR (ATR) ν_{max} /cm^{-1} = 3082 (w), 2971 (s), 2923 (s), 2295 (w), 2095 (w), 1640 (m), 1449 (m), 1369 (m), 1227 (w), 1174 (w), 999 (m), 920 (m), 889 (s), 768 (m), 687 (m).

HRMS (EI/FI): *m*/*z* calc. for $C_{12}H_{18}$ $[M]^{+\cdot}$: 162.1409, found: 162.1404.

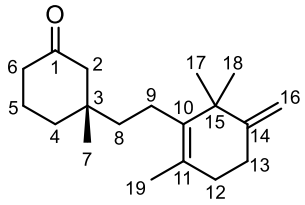
3-Methyl-3-(2-(2,2,6-trimethyl-3-methylenecyclohexyl)ethyl)cyclohexanone 10:



In a flame-dried flask equipped with a condenser, Cp_2ZrHCl (206 mg, 0.80 mmol, 2.00 eq) was added to a stirred solution of 1,1,3-trimethyl-6-methylene-2-vinylcyclohexane **1** (162 mg, 1.00 mmol, 2.50 eq) in DCM (1.2 mL). The solution was heated under reflux for 6 hrs until the solution turned clear. In a second flame-dried flask, CuCl (4.0 mg, 0.04 mmol, 0.10 eq) and *N*-benzhydryl-*N*-isopropyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (21.6 mg, 0.04 mmol, 0.10 eq) were dissolved in MTBE (2.0 mL). After stirring for 1 hr, $AgNTf_2$ (17.1 mg, 0.044 mmol, 0.11 eq) was added to the catalyst mixture, which was stirred again for 10 mins. The silver solution was then filtered through a syringe filter and added to the zirconium solution. The reaction turned black. After stirring the combined solution for 5 mins, 3-methylcyclohex-2-enone **2** (46 μL, 0.40 mmol, 1.00 eq) was added to the reaction mixture. The resulting mixture was stirred at room temperature overnight before being quenched with NH_4Cl (1M, 5 mL) and Et_2O (5 mL), extracted with Et_2O (5 mL x3), washed with saturated $NaHCO_3$ (5 mL x2), water (5 mL x2) and brine (5 mL x2), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc (9/1)) gave 3-methyl-3-(2-(2,2,6-trimethyl-3-methylenecyclohexyl)ethyl)cyclohexane **10** in 30% yield (34.0 mg, 0.12 mmol) as a colourless oil.

Enantiomeric excess (33% ee) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

TLC R_f = 0.52 (hexane/EtOAc (9/1)).

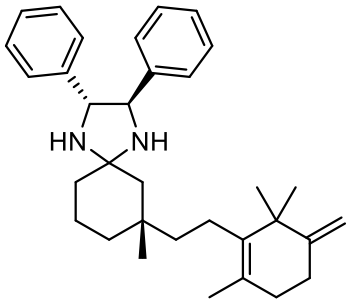


^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.92 (s, 3H, H-7), 1.08 (s, 3H, H-17 or 18), 1.08 (s, 3H, H-17 or 18), 1.24 - 1.30 (m, 2H, H-8), 1.53 (s, 3H, H-19), 1.54 - 1.65 (m, 2H, H-4), 1.78 - 1.87 (m, 2H, H-5), 1.90 - 1.99 (m, 4H, H-9 and 12), 2.05 - 2.19 (m, 2H, H-2), 2.20 - 2.26 (m, 4H, H-6 and 13), 4.62 (m, 2H, H-16).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 19.9 (C-19), 22.3 (C-5), 22.5 (C-9), 24.6 (C-7), 27.5 (C-17 and 18), 30.9 (C-13), 34.6 (C-12), 35.9 (C-4), 39.2 (C-3), 40.8 (C-15), 41.1 (C-6), 41.6 (C-8), 53.5 (C-2), 104.7 (C-16), 127.9 (C-11), 136.2 (C-10), 156.4 (C-14), 212.2 (C-1).

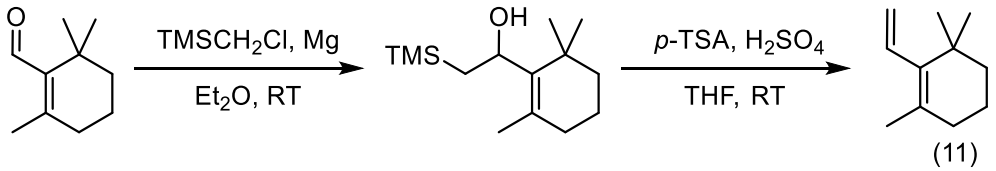
HRMS (ESI): *m/z* calc. for $C_{19}H_{31}O$ $[M+H]^+$: 275.2369, found 275.2365.

Derivatisation of cyclic ketones



Using the procedure from Alexakis and co-workers: Crude material from the 1,4-addition was transferred to a vial with $CDCl_3$ and 3 Å molecular sieves. (+)-(*R*,*R*)-1,2-diphenylethylenediamine ((+)-(*R*,*R*)-DPEN *ca.* 2 eq.) was added and the vial was shaken and allowed to stand overnight before the mixture was filtered through a glass pipette containing a small cotton plug and transferred to a NMR tube. ^{13}C NMR spectroscopy (500 MHz, 1024 scans) and comparison with racemic material was used to determine the enantiomeric excess.

1-Vinyl-2,6,6-trimethylcyclohexene 11:

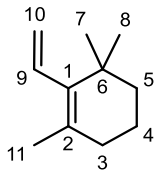


(11)

In a flame-dried flask equipped with a condenser, Mg (1.53 g, 63.0 mmol, 3.40 eq) was dissolved in Et_2O (25 mL). A crystal of iodine was added to the solution, which was stirred until the disappearance of the yellow colour. Trimethylsilylmethyl chloride (7.7 mL, 55.5 mmol, 3.00 eq) was slowly added to the mixture. The reaction was stirred vigorously for 15 mins at room temperature. A grey mixture appeared. β-cyclocitral (3.0 mL, 18.5 mmol, 1.00 eq) in Et_2O (12 mL) was added slowly to the solution, which was stirred for 1 hr at room temperature. The reaction was then poured into an ice-bath saturated in NH_4Cl (~100 mL), extracted with Et_2O (50 mL x3), washed with saturated NH_4Cl (30 mL x2) and water (20 mL x2), dried over $MgSO_4$, filtered and concentrated *in vacuo*. 3.96 g of 1-(2,6,6-trimethylcyclohex-1-en-1-yl)-2-(trimethylsilyl)ethan-1-ol crude was recovered.

In another flame-dried flask, a mixture of *p*-toluenesulfonic acid (9.39 g, 49.5 mmol, 3.00 eq) and sulfuric acid (0.88 mL, 16.5 mmol, 1.00 eq) in THF (45 mL) was prepared. The crude alcohol (3.96 g, 16.5 mmol, 1.00 eq) in THF (10 mL) was added to the solution, which was vigorously stirred for 5 mins. The reaction was then poured into an ice-bath saturated with $NaHCO_3$ (~100 mL), extracted with pentane (40 mL x3), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc (98/2)) gave 1-vinyl-2,6,6-trimethylcyclohexene **11** in 59% yield over two steps (1.64 g, 10.9 mmol) as a colourless oil.

TLC R_f = 0.29 (hexane/EtOAc (98/2)).



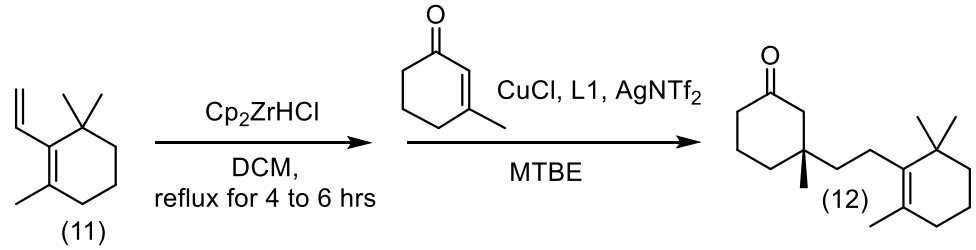
^{1}H NMR (500 MHz, Chloroform-*d*) δ ppm = 0.91 (s, 6H, H-7 and 8), 1.33 - 1.39 (m, 2H, H-5), 1.48 - 1.55 (m, 2H, H-4), 1.60 (m, 3H, H-11), 1.89 (m, 2H, H-3), 4.87 (dd, *J*=17.5, 2.5 Hz, 1H, H-10 trans), 5.14 (dd, *J*=11.0, 2.5 Hz, 1H, H-10 cis), 6.12 (m, 1H, H-9).

^{13}C NMR (126 MHz, Chloroform-*d*) δ ppm = 20.4 (C-4), 22.5 (C-11), 29.8 (C-7 and 8), 33.8 (C-3), 34.8 (C-6), 40.6 (C-5), 119.0 (C-10), 129.6 (C-2), 136.5 (C-9), 139.4 (C-1).

HRMS (EI/FI): *m*/*z* calc. for $C_{11}H_{18}$ $[M]^{+\cdot}$: 150.1409, found 150.1409.

Data consistent with previously reported values.[136]

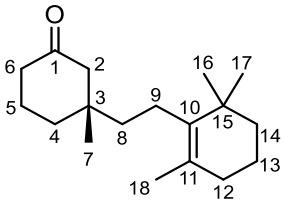
3-Methyl-3-(2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethyl)cyclohexan-1-one 12:



In a flame-dried flask equipped with a condenser, Cp_2ZrHCl (206 mg, 0.80 mmol, 2.00 eq) was added to a stirred solution of 1-vinyl-2,6,6-trimethylcyclohexene **11** (150 mg, 1.00 mmol, 2.50 eq) in DCM (1.2 mL). The solution was put under reflux for 6 hrs until the solution turned clear. In another flame-dried flask, CuCl (4.0 mg, 0.04 mmol, 0.10 eq) and *N*-benzhydryl-*N*-isopropyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (21.6 mg, 0.04 mmol, 0.10 eq) were dissolved in MTBE (2.0 mL). After stirring for 1 hr, $AgNTf_2$ (17.1 mg, 0.044 mmol, 0.11 eq) was added to the ligand mixture, which was stirred again for 10 mins. The silver solution was then filtered through a syringe filter and added to the zirconium solution. The reaction turned black. After stirring the combined solution for 5 mins, 3-methylcyclohex-2-enone **2** (46 μL, 0.4 mmol, 1.00 eq) was added to the solution. The reaction was stirred at room temperature overnight. The reaction was quenched with NH_4Cl (1M, 5 mL) and Et_2O (5 mL), extracted with Et_2O (5 mL x3), washed with saturated $NaHCO_3$ (5 mL x2), water (5 mL x2) and brine (5 mL x2), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc (9/1)) gave 3-methyl-3-(2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethyl)cyclohexan-1-one **12** in 60% yield (62.0 mg, 0.24 mmol) as colourless oil.

Enantiomeric excess of 80% was determined by GC [Macherey & Nagel, Hydrodex β-3P; 125 °C - 20 min - 2 °C per min - 160 °C - 90 min; λ = 210 nm; major enantiomer t_R = 118.0 mins; minor enantiomer t_R = 118.8 mins].

TLC R_f = 0.55 (hexane/EtOAc (9/1)).



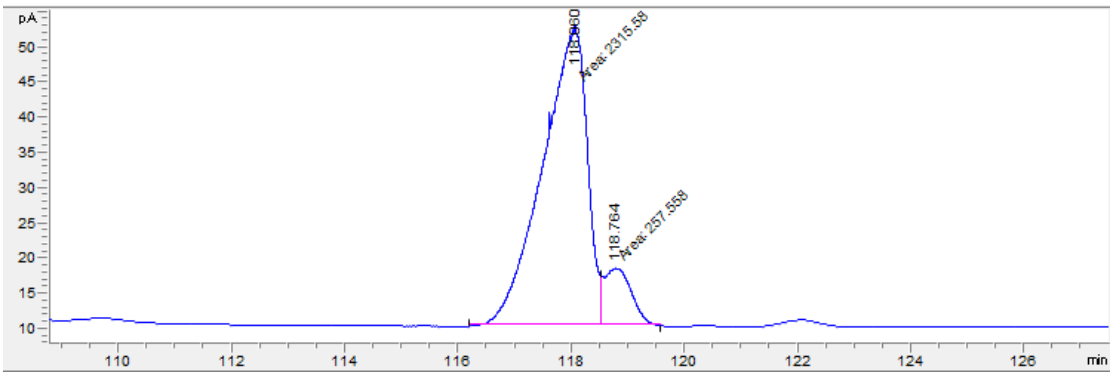
^{1}H NMR (500 MHz, Chloroform-*d*) δ ppm = 0.89 (s, 3H, H-7), 0.89 (s, 6H, H-16 and 17), 1.21 - 1.29 (m, 2H, H-8), 1.29 - 1.35 (m, 2H, H-14), 1.44 - 1.53 (m, 6H, H-4', 13 and 18), 1.54 - 1.63 (m, 1H, H-4''), 1.76 - 1.83 (m, 4H, H-5 and 12), 1.84 - 1.91 (m, 2H, H-9), 2.03 - 2.08 (m, 1H, H-2'), 2.12 - 2.17 (m, 1H, H-2'), 2.17 - 2.23 (m, 2H, H-6).

^{13}C NMR (126 MHz, Chloroform-*d*) δ ppm = 19.5 (C-13), 19.8 (C-18), 22.2 (C-9), 22.3 (C-5), 24.7 (C-7), 28.7 (C-16 and 17), 32.8 (C-12), 35.1 (C-15), 35.7 (C-4), 39.2 (C-3), 39.9 (C-14), 41.1 (C-6), 41.6 (C-8), 53.6 (C-2), 127.1 (C-11), 136.6 (C-10), 212.3 (C-1).

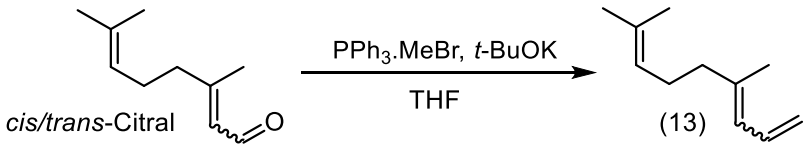
IR (ATR) ν_{max} /cm^{-1} (neat): 2926 (br), 1711 (m), 1458 (w), 1379 (w), 1284 (br), 1123 (w), 1072 (w), 910 (m), 732 (s), 647 (w).

HRMS (ESI): *m/z* calc. for $C_{18}H_{31}O$ $[M+H]^+$: 263.2369, found 263.2365.

GC traces

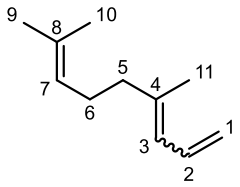


(*E,Z*)-4,8-Dimethylnona-1,3,7-triene 13:



A suspension of PPh_3.MeBr (21.4 g, 60.0 mmol, 2.00 eq) and *t*-BuOK (6.73 g, 60.0 mmol, 2.00 eq) in THF (150 mL) in a flame-dried flask was stirred for 10 mins. *Cis/trans*-Citral (5.1 mL, 30.0 mmol, 1.00 eq) was added to the reaction mixture over 5 mins. The solution was stirred at room temperature for 24 hrs. The reaction was quenched with water (80 mL), extracted with Et_2O (50 mL x3), washed with brine (50 mL x2), dried over $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash column chromatography (hexane, 100%) gave (*E,Z*)-4,8-dimethylnona-1,3,7-triene **13** in 95% yield (4.27 g, 28.4 mmol) as a colourless oil.

TLC R_f = 0.86 (hexane/EtOAc (9/1)).



***E* isomer:**

^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.63 (s, 3H, H-10), 1.69 (s, 3H, H-9), 1.77 (s, 3H, H-11), 2.02 – 2.14 (m, 4H, H-5 and 6), 4.92 – 5.02 (m, 1H, H-1 cis), 5.03 – 5.17 (m, 2H, H-1 trans and 7), 5.86 (d, *J*=11.0 Hz, 1H, H-3), 6.58 (m, 1H, H-2).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 16.7 (C-11), 17.7 (C-10), 25.7 (C-9), 26.5 (C-6), 39.9 (C-5), 114.6 (C-1), 124.0 (C-7), 125.4 (C-3), 131.7 (C-8), 133.4 (C-2), 139.6 (C-4).

***Z* isomer:**

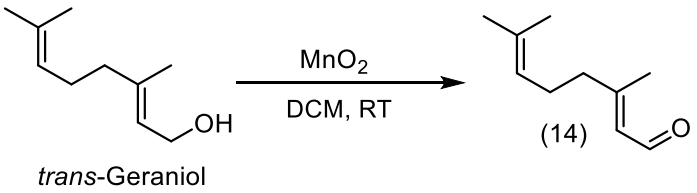
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.63 (s, 3H, H-10), 1.69 (s, 3H, H-9), 1.79 (s, 3H, H-11), 2.02 – 2.14 (m, 2H, H-6), 2.15 – 2.21 (m, 2H, H-5), 4.92 – 5.02 (m, 1H, H-1 *cis*), 5.03 – 5.17 (m, 2H, H-1 *trans* and 7), 5.86 (d, *J*=11.0 Hz, 1H, H-3), 6.58 (m, 1H, H-2).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 17.7 (C-10), 23.8 (C-11), 25.7 (C-9), 26.8 (C-6), 32.5 (C-5), 114.4 (C-1), 123.9 (C-7), 126.3 (C-3), 131.9 (C-8), 133.2 (C-2), 139.8 (C-4).

HRMS (EI/FI): *m*/*z* calc. for $C_{11}H_{18}$ $[M]^{+\cdot}$: 150.1409, found 150.1412.

Data consistent with previously reported values.[284]

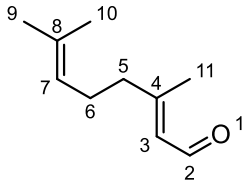
***Trans*-Citral 14:**



trans-Geraniol

In a flame-dried flask, *trans*-geraniol (10.4 mL, 60.0 mmol, 1.0 eq) was dissolved in DCM (300 mL). MnO_2 (52.2 g, 600 mmol, 10.0 eq) was then added to the solution, which was stirred at room temperature for 24 hrs. The solution was filtered through a plug of celite, washed with EtOAc (100 mL x3) and concentrated *in vacuo*. Purification by flash column chromatography (pentane/EtO_2 (9/1)) gave *trans*-citral **14** in 92% yield (8.40 g, 55.2 mmol) in a colourless oil.

TLC R_f = 0.42 (hexane/EtOAc (9/1)).



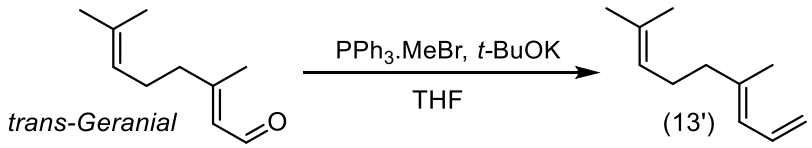
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.61 (s, 3H, H-10), 1.68 (s, 3H, H-9), 2.16 (s, 3H, H-11), 2.22 (m, 4H, H-5 and 6), 5.06 (m, 1H, H-7), 5.88 (d, *J*=8.0 Hz, 1H, H-3), 9.99 (d, *J*=8.0 Hz, 1H, H-2).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 17.6 (C-11), 17.7 (C-10), 25.7 (C-6), 25.7 (C-9), 40.6 (C-5), 122.6 (C-7), 127.4 (C-3), 133.0 (C-8), 163.9 (C-4), 191.3 (C-2).

HRMS (ESI): *m*/*z* calc. for $C_{10}H_{16}ONa$ $[M+Na]^+$: 175.1093, found 175.1094.

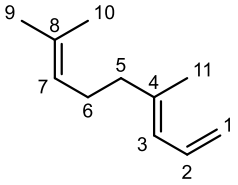
Data consistent with previously reported values.[285]

(*E*)-4,8-Dimethylnona-1,3,7-triene 13':



A suspension of PPh_3.MeBr (21.4 g, 60.0 mmol, 2.00 eq) and *t*-BuOK (6.73 g, 60.0 mmol, 2.00 eq) in THF (150 mL) in a flame-dried flask was stirred for 10 mins. *trans*-geranial (5.1 mL, 30.0 mmol, 1.00 eq) was added to the reaction mixture over 5 mins. The solution was stirred at room temperature for 24 hrs. The reaction was quenched with water (80 mL), extracted with Et_2O (50 mL x3), washed with brine (50 mL x2), dried over $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash column chromatography (hexane 100%) gave (*E*)-4,8-dimethylnona-1,3,7-triene **13** in 95% yield (4.29 g, 28.5 mmol) as colourless oil.

TLC R_f = 0.86 (hexane/EtOAc (9/1)).



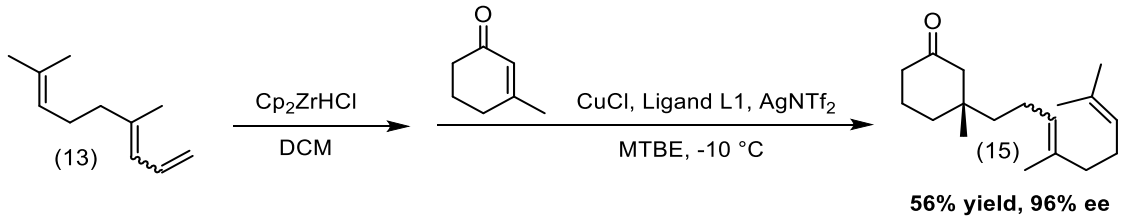
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.61 (s, 3H, H-10), 1.69 (s, 3H, H-9), 1.77 (s, 3H, H-11), 1.96 – 2.21 (m, 4H, H-5 and 6), 4.98 (dd, *J*=10.0, 2.0 Hz, 1H, H-1 cis), 5.05 – 5.16 (m, 2H, H-1 trans and 7), 5.80 – 5.91 (m, 1H, H-2), 6.58 (m, 1H, H-1).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 16.7 (C-11), 17.7 (C-10), 25.7 (C-9), 26.5 (C-6), 39.9 (C-5), 114.6 (C-1), 123.9 (C-7), 125.4 (C-3), 131.7 (C-8), 133.4 (C-2), 139.6 (C-4).

HRMS (EI/FI): *m*/*z* calc. for $C_{11}H_{18}$ $[M]^{+\cdot}$: 150.1409, found 150.1415.

Data consistent with previously reported values.[284]

(*S*)-(*E,Z*)-3-(4,8-Dimethylnona-3,7-dien-1-yl)-3-methylcyclohexan-1-one 15:

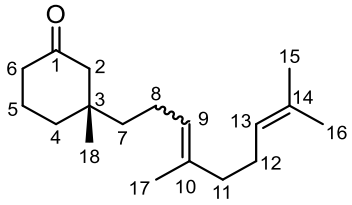


56% yield, 96% ee

In a flame-dried flask, Cp_2ZrHCl (5.47 g, 21.2 mmol, 2.00 eq) was added to a stirred solution of (*E,Z*)-4,8-dimethylnona-1,3,7-triene **13** (3.98 g, 26.5 mmol, 2.50 eq) in DCM (10.6 mL). After stirring for 1 hr, the solution turned clear. In another flame-dried flask, CuCl (105 mg, 1.06 mmol, 0.10 eq) and *N*-benzhydryl-*N*-isopropyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (574 mg, 1.06 mmol, 0.10 eq) were dissolved in MTBE (27 mL). After stirring for 1 hr, $AgNTf_2$ (454 mg, 1.17 mmol, 0.11 eq) was added to the ligand mixture, which was stirred for 10 mins. The silver solution was then filtered through a syringe filter and added to the zirconium solution. The reaction turned black. After stirring the combined solution for 5 mins, 3-methylcyclohex-2-enone **2** (1.2 mL, 10.6 mmol, 1.00 eq) was added to the solution. The reaction was stirred at room temperature overnight. The reaction was quenched with NH_4Cl (1M, 20 mL) and Et_2O (20 mL), extracted with Et_2O (20 mL x3), washed with saturated $NaHCO_3$ (20 mL x2), water (20 mL x2) and brine (20 mL x2), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc (9/1)) gave (*S*)-(*E,Z*)-3-(4,8-dimethylnona-3,7-dien-1-yl)-3-methylcyclohexan-1-one **15** in 56% yield (1.57 g, 5.98 mmol) as colourless oil.

The enantiomeric excess of **15** was determined after hydrogenation into **16**.

TLC R_f = 0.49 (hexane/EtOAc (9/1)).



***E* isomer:**

^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.96 (s, 3H, H-18), 1.26 – 1.34 (m, 2H, H-7), 1.52 – 1.67 (m, 7H, H-4', 16 and 17), 1.70 (m, 4H, H-4'' and 15), 1.88 (m, 2H, H-5), 1.97 (m, 4H, H-8 and 11), 2.06 (m, 2H, H-12), 2.10 – 2.25 (m, 2H, H-2), 2.29 (t, *J*=7.0 Hz, 2H, H-6), 5.11 (m, H-9 and 13).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 15.9 (C-17), 17.7 (C-16), 22.0 (C-8), 22.2 (C-5), 25.0 (C-18), 25.7 (C-15), 26.7 (C-12), 35.8 (C-4), 38.6 (C-3), 39.7 (C-11), 41.0 (C-6), 41.7 (C-7), 53.8 (C-2), 124.2 (C-9), 124.3 (C-13), 131.4 (C-14), 135.2 (C-10), 212.3 (C-1).

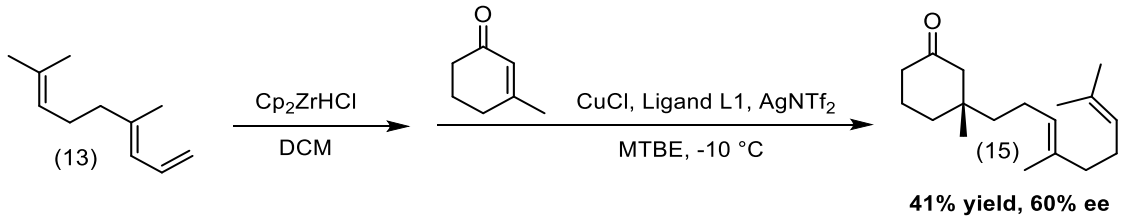
***Z* isomer:**

^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.95 (s, 3H, H-18), 1.26 – 1.34 (m, 2H, H-7), 1.52 – 1.67 (m, 4H, H-4', 16), 1.70 (m, 7H, H-4'', 15 and 17), 1.88 (m, 2H, H-5), 1.97 (m, 2H, H-11), 2.06 (m, 4H, H-8 and 12), 2.10 – 2.25 (m, 2H, H-2), 2.29 (t, *J*=7.0 Hz, 2H, H-6), 5.11 (m, 2H H-9 and 13).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 17.6 (C-16), 21.9 (C-8), 22.1 (C-5), 23.4 (C-17), 24.8 (C-18), 25.8 (C-15), 26.6 (C-12), 31.9 (C-11), 35.8 (C-4), 38.6 (C-3), 41.0 (C-6), 42.1 (C-7), 53.8 (C-2), 124.3 (C-13), 125.0 (C-9), 131.6 (C-14), 135.3 (C-10), 212.2 (C-1).

HRMS (EI/FI): *m*/*z* calc. for $C_{18}H_{30}O$ $[M]^{+\cdot}$: 262.2297, found 262.2293.

(*S*)-(*E*)-3-(4,8-Dimethylnona-3,7-dien-1-yl)-3-methylcyclohexan-1-one 15':

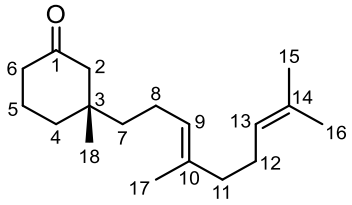


41% yield, 60% ee

In a flame-dried flask, Cp_2ZrHCl (5.47 g, 21.2 mmol, 2.00 eq) was added to a stirred solution of (*E*)-4,8-dimethylnona-1,3,7-triene **13'** (3.98 g, 26.5 mmol, 2.50 eq) in DCM (10.6 mL). After stirring for 1 hr, the solution turned clear. In another flame-dried flask, CuCl (105 mg, 1.06 mmol, 0.10 eq) and *N*-benzhydryl-*N*-isopropyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (574 mg, 1.06 mmol, 0.10 eq) were dissolved in MTBE (27 mL). After stirring for 1 hr, $AgNTf_2$ (454 mg, 1.17 mmol, 0.11 eq) was added to the ligand mixture, which was stirred again for 10 mins. The silver solution was then filtered through a syringe filter and added to the zirconium solution. The reaction turned black. After stirring the combined solution for 5 mins, 3-methylcyclohex-2-enone **2** (1.2 mL, 10.6 mmol, 1.00 eq) was added to the solution. The reaction was stirred at room temperature overnight. The reaction was quenched with NH_4Cl (1M, 20 mL) and Et_2O (20 mL), extracted with Et_2O (20 ml x3), washed with saturated $NaHCO_3$ (20 ml x2), water (20 ml x2) and brine (20 ml x2), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc (9/1)) gave (*S*)-(*E*)-3-(4,8-dimethylnona-3,7-dien-1-yl)-3-methylcyclohexan-1-one **15'** in 41% yield (1.14 g, 4.34 mmol) as colourless oil.

The enantiomeric excess of **15'** was determined after hydrogenation into **16**.

TLC R_f = 0.49 (hexane/EtOAc (9/1)).

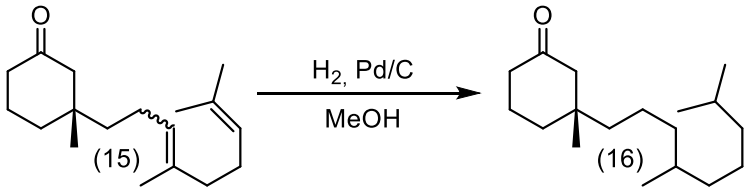


^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.96 (s, 3H, H-18), 1.27 – 1.34 (m, 2H, H-7), 1.62 (m, 7H, H-4', 16 and 17), 1.70 (m, 4H, H-4'' and 15), 1.89 (m, 2H, H-5), 1.94 – 2.03 (m, 4H, H-8 and 11), 2.07 (m, 2H, H-12), 2.12 – 2.26 (m, 2H, H-2), 2.30 (t, *J*=6.5 Hz, 2H, H-6), 5.11 (m, 2H, H-9 and 13).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 15.9 (C-17), 17.7 (C-16), 22.0 (C-8), 22.2 (C-5), 25.0 (C-18), 25.7 (C-15), 26.7 (C-12), 35.8 (C-4), 38.7 (C-3), 39.7 (C-11), 41.1 (C-6), 41.7 (C-7), 53.8 (C-2), 124.2 (C-9), 124.3 (C-13), 131.4 (C-14), 135.2 (C-10), 212.4 (C-1).

HRMS (EI/FI): *m*/*z* calc. for $C_{18}H_{30}O$ $[M]^{+\cdot}$: 262.2297, found 262.2285.

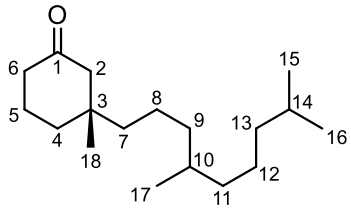
(*R*)-3-(4,8-Dimethylnonyl)-3-methylcyclohexan-1-one 16:



A solution of (*S*)-(*E,Z*)-3-(4,8-dimethylnona-3,7-dien-1-yl)-3-methylcyclohexan-1-one **15** (21.0 mg, 0.08 mmol, 1.00 eq), palladium (10% weight on carbon, 12.8 mg, 0.16 mmol, 2.00 eq) in MeOH (2.0 mL) was first purged with 30 second cycles of vacuum/argon and after purged with H_2. The mixture was then stirred for 16 hrs at room temperature under H_2 atmosphere (1 bar). The resulting mixture was then filtered over Celite®, washed with EtOAc (10 mL) and evaporated *in vacuo*. (*R*)-3-(4,8-Dimethylnonyl)-3-methylcyclohexan-1-one **16** was obtained in 91% yield without any purification (19.4 mg, 0.073 mmol) as a colourless oil.

For **15**: Enantiomeric excess of 96% was determined by GC [Macherey & Nagel, Hydrodex β-3P; 120 °C - 20 min – 0.5 °C per min - 150 °C - 60 min; λ = 210 nm; major enantiomer t_R = 109.5 mins; minor enantiomer t_R = 110.5 mins].

For **15'**: Enantiomeric excess of 60% was determined by GC [Macherey & Nagel, Hydrodex β-3P; 120 °C - 20 min – 0.5 °C per min - 150 °C - 60 min; λ = 210 nm; major enantiomer t_R = 109.6 mins; minor enantiomer t_R = 110.6 mins].

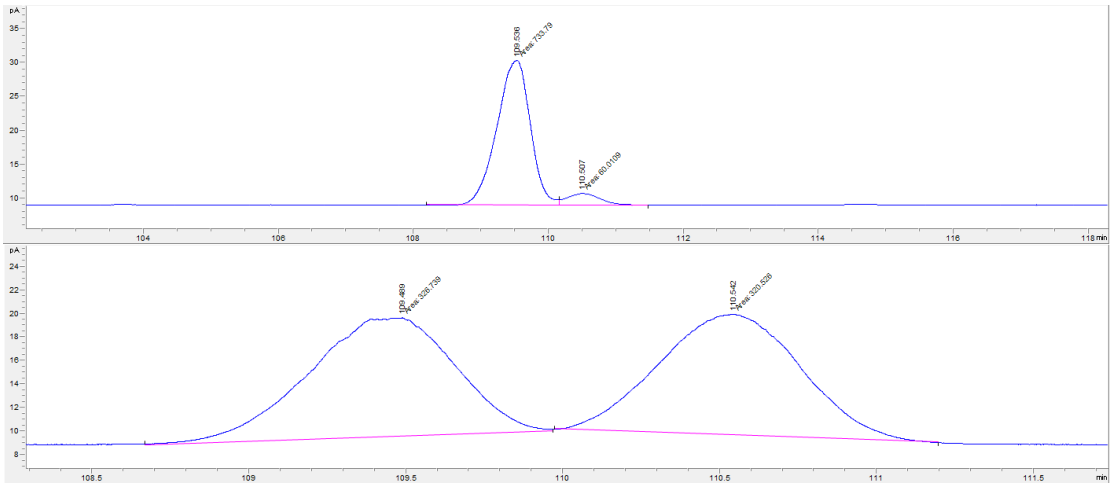


One diastereoisomer:

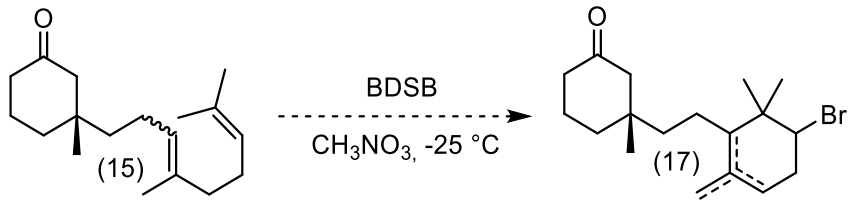
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.78 (m, 9H, H-15, 16 and 17), 0.84 (s, 3H, H-18), 0.94 – 1.02 (m, 2H, CH_2), 1.06 (m, 2H, H-13), 1.11 – 1.23 (m, 8H, $4CH_2$), 1.26 – 1.35 (m, 1H, H-10), 1.46 (m, 2H, H-4' and 14), 1.56 (m, 1H, H-4''), 1.79 (p, *J*=6.5 Hz, 2H, H-5), 1.99 – 2.15 (m, 2H, H-2), 2.20 (t, *J*=6.5 Hz, 2H, H-6). (CH_2 = H-7, 8, 9, 11 or 12).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 19.7 (C-17), 20.8 (CH_2), 22.2 (C-5), 22.6 (C-15 or 16), 22.7 (C-15 or 16), 24.8 (CH_2), 25.1 (C-18), 28.0 (C-14), 32.7 (C-10), 35.9 (C-4), 37.3 (CH_2), 37.7 (CH_2), 38.7 (C-3), 39.3 (C-13), 41.1 (C-6), 42.0 (CH_2), 53.9 (C-2), 212.4 (C-1). (CH_2 = H-7, 8, 9, 11 or 12).

GC traces of **16** for **15**



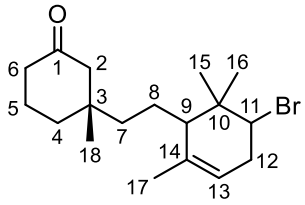
(*S*)-3-(2-(5-Bromo-2,6,6-trimethylcyclohex-1-en-1-yl)ethyl)-3-methylcyclohexan-1-one 17:



In a flame-dried flask, (*S*)-(*E,Z*)-3-(4,8-dimethylnona-3,7-dien-1-yl)-3-methylcyclohexan-1-one **15** (105 mg, 0.40 mmol, 1.00 eq) was dissolved in nitromethane (0.6 mL) and cooled to -25 °C. In another flame-dried flask, BDSB (220 mg, 0.40 mmol, 1.00 eq) was dissolved in nitromethane (0.4 mL). The BDSB solution was quickly added to the alkene solution at -25 °C. After stirring overnight at room temperature, the reaction was quenched with a solution of 5% aq $NaHCO_3$ (5 mL), 5% aq Na_2SO_3 (5 mL). The reaction was stirred for 15 mins, poured into water (5 mL), extracted with DCM (5 mL x3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/Et_2O (9/1)) gave a mixture of all isomers in 88% yield (119 mg, 0.35 mmol) as a yellow oil.

Trisubstituted isomer:

TLC R_f = 0.44 (hexane/EtOAc (9/1)).

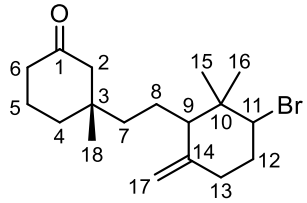


^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.97 (s, 3H, H-18), 1.31 (m, 2H, CH_2), 1.55 – 1.64 (m, 2H, CH_2), 1.66 – 1.75 (m, 5H, CH_2 and H-15 or 16), 1.78 – 1.85 (m, 3H, H-15 or 16), 1.85 – 1.94 (m, 3H, H-12' and CH_2), 1.96 – 2.08 (m, 4H, H-12'' and 17), 2.19 (m, 2H, H-2), 2.30 (t, *J*=6.5 Hz, 2H, H-6), 2.39 – 2.65 (m, 1H, H-9), 4.08 (m, 1H, H-11), 5.09 – 5.28 (m, 1H, H-13). (CH_2 = H-4, 5, 7 or 8).

HRMS (EI/FI): *m*/*z* calc. for $C_{18}H_{29}{}^{79}BrO$ $[M]^{+\cdot}$: 340.1402, found 340.1489.

Disubstituted isomer:

TLC R_f = 0.42 (hexane/EtOAc (9/1)).

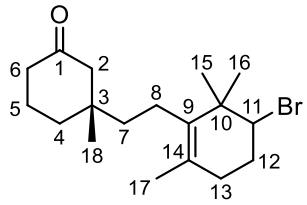


^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.85 (s, 3H, H-18), 0.92 (s, 3H, H-15 or 16), 0.98 – 1.04 (m, 3H, H-15 or 16), 1.12 – 1.31 (m, 3H, CH_2 and one H of a CH_2), 1.37 – 1.70 (m, 6H, $2CH_2$, one H of a CH_2 and H-9), 1.70 – 1.84 (m, 2H, CH_2), 2.08 (m, 2H, CH_2), 2.21 (t, *J*=7.0 Hz, 2H, H-6), 2.38 – 2.61 (m, 2H, H-2), 4.23 (m, 1H, H-11), 4.99 – 5.11 (m, 2H, H-17). (CH_2 = H-4, 5, 7 or 8).

HRMS (EI/FI): *m*/*z* calc. for $C_{18}H_{29}{}^{79}BrO$ $[M]^{+\cdot}$: 340.1402, found 340.1405.

Tetrasubstituted isomer 17:

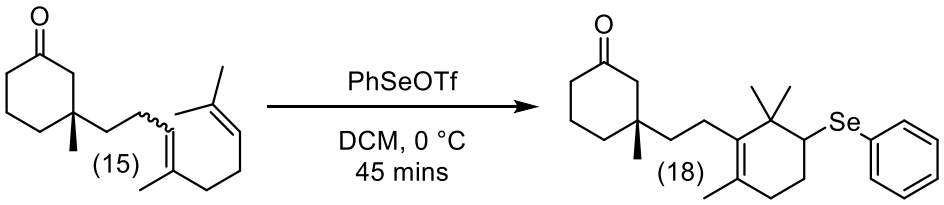
TLC R_f = 0.34 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.81 (m, 6H, H-18 and 15 or 16), 0.86 – 0.90 (m, 3H, H-15 or 16), 1.16 – 1.27 (m, 6H, $3CH_2$), 1.53 (m, 3H, H-17), 1.57 – 1.75 (m, 4H, $2CH_2$), 1.76 – 1.88 (m, 2H, CH_2), 2.06 – 2.15 (m, 2H, H-2), 2.22 (t, *J*=7.0 Hz, 2H, H-6), 3.88 – 4.14 (m, 1H, H-11). (CH_2 = H-4, 5, 7 or 8).

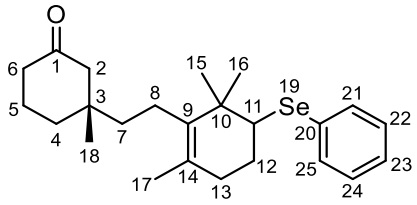
HRMS (EI/FI): *m*/*z* calc. for $C_{18}H_{29}{}^{79}BrO$ $[M]^{+}$: 340.1402, found 340.1612.

(*S*)-3-Methyl-3-(2-(2,6,6-trimethyl-5-(phenylselanyl)cyclohex-1-en-1-yl)ethyl)cyclohexan-1-one 18:



In a flame-dried flask, phenylselenium chloride (36.4 mg, 0.19 mmol, 1.00 eq) and AgOTf (48.8 mg, 0.19 mmol, 1.00 eq) was dissolved in DCM (2.5 mL) and stirred at room temperature for 10 mins. In another flame-dried flask, (*S*)-(*E,Z*)-3-(4,8-dimethylnona-3,7-dien-1-yl)-3-methylcyclohexan-1-one **15** (50.0 mg, 0.19 mmol, 1.00 eq) was dissolved in DCM (2.5 mL) and cooled to 0 °C. The newly formed phenylselenium triflate solution was then filtered through a syringe filter and transferred into the dialkene solution at 0 °C. The reaction was stirred for 45 mins before being quenched with saturated $NaHCO_3$ (5 mL). The mixture was then extracted with DCM (5 mL x3), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (pentane/Et_2O (9/1)) gave (*S*)-3-methyl-3-(2-(2,6,6-trimethyl-5-(phenylselanyl)cyclohex-1-en-1-yl)ethyl)cyclohexan-1-one **18** in 53% yield (42.8 mg, 0.10 mmol) as an orange oil.

TLC R_f = 0.39 (hexane/EtOAc (9/1)).



First diastereoisomer:

^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.97 (s, 3H, H-18), 1.12 (s, 3H, H-15 or 16), 1.28 (s, 3H, H-15 or 16), 1.36 (m, 2H, H-7), 1.56 (s, 3H, H-17), 1.59 – 1.71 (m, 2H, H-4), 1.82 – 2.09 (m, 8H, H-5, 8, 12 and 13), 2.10 – 2.26 (m, 2H, H-2), 2.26 – 2.32 (m, 2H, H-6), 3.21 – 3.30 (m, 1H, H-11), 7.24 (m, 3H, H-22, 23 and 24), 7.51 – 7.58 (m, 2H, H-21 and 25).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 19.8 (C-17), 22.3 (C-8), 22.9 (C-5), 24.7 (C-18), 25.1 (C-16), 27.8 (C-12), 28.2 (C-15), 32.7 (C-13), 35.8 (C-4), 39.2 (C-3), 39.9 (C-10), 41.1 (C-6), 41.5 (C-7), 53.5 (C-2), 57.6 (C-11), 127.0 (C-23), 127.0 (C-14), 128.9 (C-22 and 24), 131.0 (C-20), 134.2 (C-21 and 25), 135.9 (C-9), 212.1 (C-1).

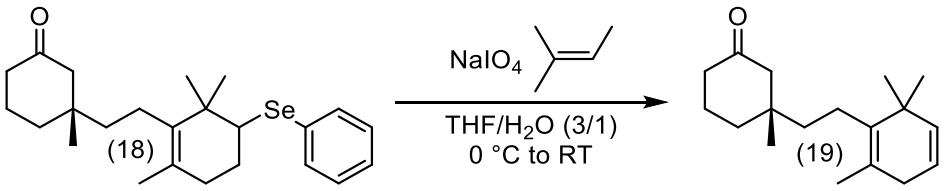
HRMS (ESI): *m*/*z* calc. for $C_{24}H_{35}O^{80}Se$ $[M+H]^{+\cdot}$: 419.1848, found 419.1847.

Second diastereoisomer:

^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.98 (s, 3H, H-18), 1.12 (s, 3H, H-15 or 16), 1.27 (s, 3H, H-15 or 16), 1.36 (m, 2H, H-7), 1.56 (s, 3H, H-17), 1.59 – 1.71 (m, 2H, H-4), 1.82 – 2.09 (m, 8H, H-5, 8, 12 and 13), 2.10 – 2.26 (m, 2H, H-2), 2.26 – 2.32 (m, 2H, H-6), 3.21 – 3.30 (m, 1H, H-11), 7.24 (m, 3H, H-22, 23 and 24), 7.51 – 7.58 (m, 2H, H-21 and 25).

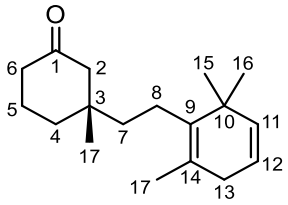
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 19.8 (C-17), 22.3 (C-8), 22.9 (C-5), 24.6 (C-18), 25.0 (C-16), 27.8 (C-12), 28.2 (C-15), 32.7 (C-13), 35.8 (C-4), 39.2 (C-3), 39.9 (C-10), 41.1 (C-6), 41.4 (C-7), 53.6 (C-2), 57.6 (C-11), 127.0 (C-23), 127.1 (C-14), 128.9 (C-22 and 24), 131.0 (C-20), 134.2 (C-21 and 25), 136.0 (C-9), 212.1 (C-1).

(S)-3-Methyl-3-(2-(2,6,6-trimethylcyclohexa-1,4-dien-1-yl)ethyl)cyclohexan-1-one 19:



In a flame-dried flask, (*S*)-3-methyl-3-(2-(2,6,6-trimethyl-5-(phenylselanyl)cyclohex-1-en-1-yl)ethyl)cyclohexan-1-one **18** (20.0 mg, 0.048 mmol, 1.00 eq) and 2-methyl-2-butene (25.4 μL, 0.24 mmol, 5.00 eq) were diluted in THF/H_2O (3/1) (1.6 mL) and the solution cooled to 0 °C. $NaIO_4$ (42.8 mg, 0.2 mmol, 4.30 eq) was then added in one portion to the reaction mixture which was then stirred for 12 hrs at room temperature. The reaction was extracted with Et_2O (5 mL x3), washed with water (5 mL x2) and brine (5 mL x2), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (Pentane/Et_2O (9/1)) gave (*S*)-3-methyl-3-(2-(2,6,6-trimethylcyclohexa-1,4-dien-1-yl)ethyl)cyclohexan-1-one **19** in 87% yield (10.9 mg, 0.042 mmol) as a yellow oil.

TLC R_f = 0.49 (hexane/EtOAc (9/1)).

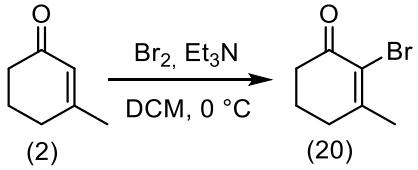


^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.92 (s, 3H, H-18), 0.98 (m, 6H, H-15 and 16), 1.27 – 1.34 (m, 2H, H-7), 1.51 – 1.66 (m, 5H, H-4 and 17), 1.73 – 1.88 (m, 2H, H-5), 1.93 – 2.04 (m, 2H, H-8), 2.05 – 2.19 (m, 2H, H-2), 2.20 – 2.26 (m, 2H, H-6), 2.47 (m, 2H, H-13), 5.35 (dt, *J*=10.0, 2.0 Hz, 1H, H-11), 5.48 (dt, *J*=10.0, 3.5 Hz, 1H, H-12).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 19.0 (C-17), 21.9 (C-8), 22.3 (C-5), 24.7 (C-18), 29.2 (C-15 and 16), 33.3 (C-13), 35.9 (C-4), 36.7 (C-3), 39.2 (C-10), 41.1 (C-6), 41.7 (C-7), 53.5 (C-2), 120.7 (C-12), 124.3 (C-14), 135.0 (C-9), 136.9 (C-11), 212.2 (C-1).

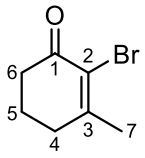
HRMS (ESI): *m*/*z* calc. for $C_{18}H_{29}O$ $[M+H]^+$: 261.22129, found 261.22143.

2-Bromo-3-methylcyclohex-2-en-1-one 20:



In a flame-dried flask, 3-methylcyclohex-2-enone **2** (2.4 mL, 20.8 mmol, 1.00 eq) was dissolved in DCM (20 mL) and the solution was cooled down to 0 °C. In another flame-dried flask, Br_2 was dissolved in DCM (20 mL). The bromine solution was then added dropwise to the enone solution which was stirred for 5 mins at 0 °C. Triethylamine (4.0 mL, 28.9 mmol, 1.40 eq) was added to the reaction mixture and stirred for an additional 5 mins at 0 °C. The reaction was quenched with HCl (1M, 15 mL), extracted with EtOAc (20 mL x3), washed with NaOH (1M, 15 mL x3), a saturated solution of $Na_2S_2O_3$ (20 mL x2), water (20 mL x2) and brine (20 mL x2), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/Et_2O (9/1)) gave 2-bromo-3-methylcyclohex-2-en-1-one **20** in 82% yield (3.24 g, 17.1 mmol) as a colourless oil.

TLC R_f = 0.24 (hexane/EtOAc (9/1)).



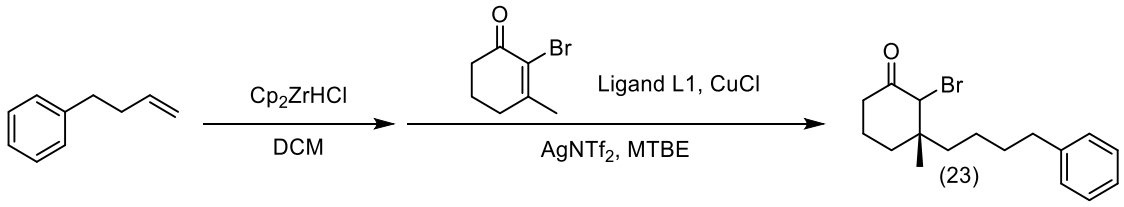
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.96 – 2.04 (m, 2H, H-5), 2.17 (s, 3H, H-7), 2.52 (t, *J*=6.0 Hz, 2H, H-4), 2.58 (t, *J*=6.0 Hz, 2H, H-6).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 21.8 (C-5), 25.9 (C-7), 34.2 (C-4), 37.7 (C-6), 122.8 (C-3), 160.3 (C-2), 191.0 (C-1).

LRMS (ES-API$^+$) *m/z* calc. for $C_7H_9{}^{79}BrONa$ $[M+Na]^+$: 210.9, found 210.9.

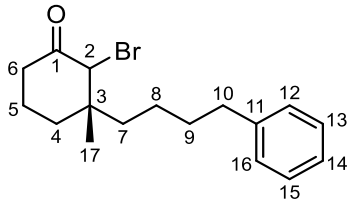
Data consistent with previously reported values.[286]

(*R*)-2-Bromo-3-methyl-3-(4-phenylbutyl)cyclohexan-1-one 23:



In a flame-dried flask, Cp_2ZrHCl (206 mg, 0.80 mmol, 2.00 eq) was added to a stirred solution of 4-phenyl-1-butene (150 μL, 1.00 mmol, 2.50 eq) in DCM (0.4 mL). After stirring for 30 mins, the solution turned clear. In another flame-dried flask, CuCl (4.0 mg, 0.04 mmol, 0.10 eq) and *N*-benzhydryl-*N*-isopropyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (21.6 mg, 0.04 mmol, 0.10 eq) were dissolved in MTBE (2.0 mL). After stirring for 1 hr, $AgNTf_2$ (17.1 mg, 0.044 mmol, 0.11 eq) was added to the ligand mixture, which was stirred again for 10 mins. The silver solution was then filtered through a syringe filter and added to the zirconium solution. The reaction turned black. After stirring the combined solution for 5 mins, 2-bromo-3-methylcyclohex-2-en-1-one **20** (75.6 mg, 0.40 mmol, 1.00 eq) was added to the solution. The reaction was stirred at room temperature overnight. The reaction was quenched with NH_4Cl (1M, 5 mL) and Et_2O (5 mL), extracted with Et_2O (5 mL x3), washed with saturated $NaHCO_3$ (5 mL x2), water (5 mL x2) and brine (5 mL x2), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/Et_2O (9/1)) gave an inseparable ~1.4:1 mixture of diastereomers at C-2 of (*R*)-2-bromo-3-methyl-3-(4-phenylbutyl)cyclohexan-1-one **23** in 13% yield (16.4 mg, 0.05 mmol) as a colourless oil.

TLC R_f = 0.44 (hexane/EtOAc (9/1)).



Major diastereomer:

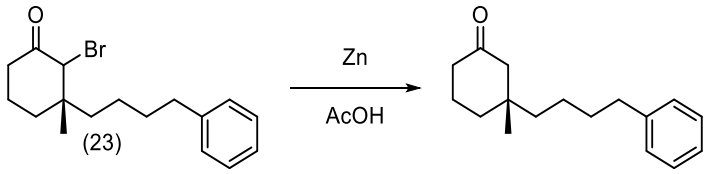
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.96 (s, 3H, H-17), 1.16 – 1.43 (m, 4H, H-7 and 8), 1.45 – 1.63 (m, 3H, H-4' and H-9), 1.75 (m, 2H, H-5), 1.88 (m, 1H, H-4''), 2.21 (m, 1H, H-6'), 2.50 – 2.62 (m, 2H, H-10), 3.00 (ddd, *J*=14.5, 10.5, 7.5 Hz, 1H, H-6''), 3.99 (m, 1H, H-2), 7.11 (m, 3H, H-12, 14 and 16), 7.17 – 7.25 (m, 2H, H-13 and 15).

Minor diastereomer:

^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.93 (s, 3H, H-17), 1.16 – 1.43 (m, 4H, H-7 and 8), 1.45 – 1.63 (m, 4H, H-4 and 9), 1.75 (m, 2H, H-5), 2.21 (m, 1H, H-6), 2.50 – 2.62 (m, 2H, H-10), 2.80 – 2.92 (m, 1H, H-6), 4.15 (m, 1H, H-2), 7.11 (m, 3H, H-12, 14 and 16), 7.17 – 7.25 (m, 2H, H-13 and 15).

HRMS (ESI): *m*/*z* calc. for $C_{17}H_{23}O^{79}BrNa$ $[M+Na]^+$: 345.0824, found 345.0826.

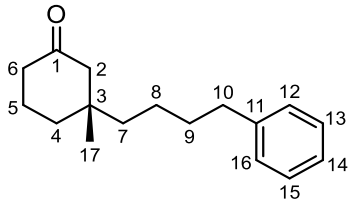
Determination of the enantiomeric excess by removal of the Br moiety:



In a flame-dried flask, (*R*)-2-bromo-3-methyl-3-(4-phenylbutyl)cyclohexan-1-one **23** (16.4 mg, 0.05 mmol, 1.00 eq) was dissolved in AcOH (1 mL) and the solution was cooled down to 0 °C. Zn (11.8 mg, 0.18 mmol, 3.50 eq) was added in small portions to the reaction mixture which was stirred for 45 mins at room temperature. The reaction was filtered, washed with AcOH (10 mL) and concentrated *in vacuo*. The recovered mixture was the diluted in deionised water (5 mL) and Et_2O (5 mL). The solution was extracted with Et_2O (5 mL x3)), dried over $MgSO_4$, filtered and concentrated *in vacuo*. (*R*)-3-methyl-3-(4-phenylbutyl)cyclohexan-1-one was obtained without any purification.

Enantiomeric excess of 60% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/i-PrOH: 98: 2; λ = 210 nm; major enantiomer t_R = 15.4 mins; minor enantiomer t_R = 16.4 mins].

TLC R_f = 0.48 (Hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.93 (s, 3H, H-17), 1.26 – 1.38 (m, 4H, H-7 and 8), 1.50 – 1.69 (m, 4H, H-4 and 9), 1.88 (m, 2H, H-5), 2.08 – 2.24 (m, 2H, H-2), 2.26 – 2.34 (t, *J*=6.5 Hz, 2H, H-6), 2.64 (t, *J*=8.0 Hz, 2H, H-10), 7.16 – 7.24 (m, 3H, H-12, 14 and 16), 7.27 – 7.35 (m, 2H, H-13 and 15).

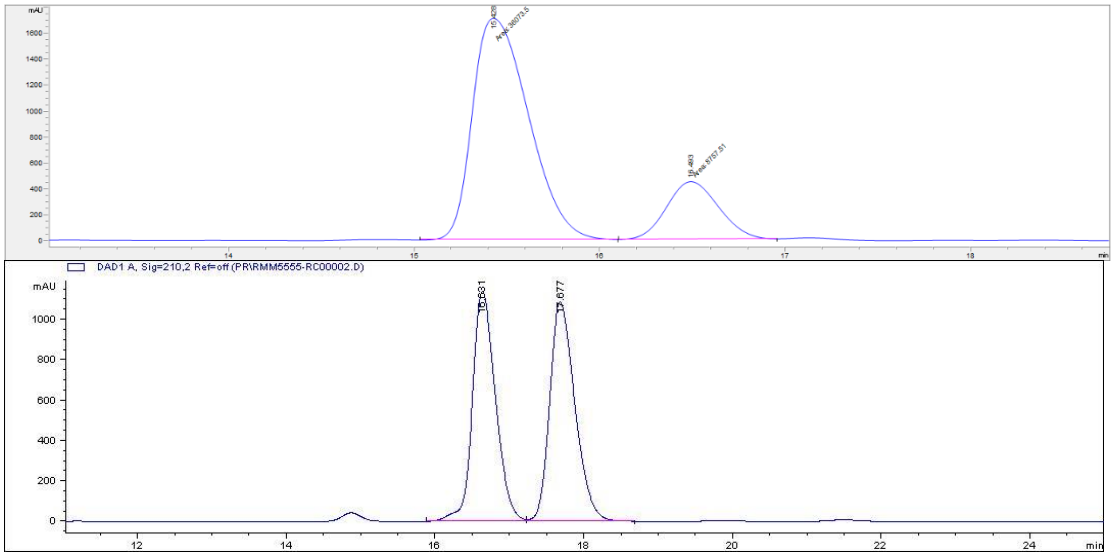
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 22.2 (C-5), 23.0 (C-8), 25.1 (C-17), 32.1 (C-9), 35.9 (C-4 and 10), 38.7 (C-3), 41.1 (C-6), 41.5 (C-7), 53.8 (C-2), 125.7 (C-14), 128.3 (C-13 and 15), 128.4 (C-12 and 16), 142.6 (C-11), 212.5 (C-1).

IR (ATR) ν_{max} /cm^{-1} = 2932 (br), 2857 (br), 1713 (s), 1252 (m), 1088 (w), 836 (w), 776 (w).

HRMS (ESI): *m*/*z* calc. for $C_{17}H_{24}ONa$ $[M+Na]^+$: 267.1719, found: 267.1715.

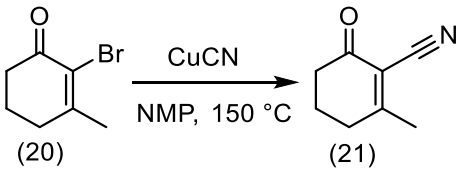
Data consistent with previously reported values.[70]

HPLC traces



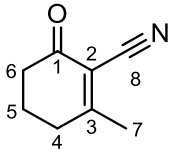
HPLC analysis of the racemic were reported by Fletcher *et al.*[70]

2-Methyl-6-oxocyclohex-1-ene-1-carbonitrile 21:



In a flame-dried flask, 2-bromo-3-methylcyclohex-2-en-1-one **20** (1.00 g, 5.30 mmol, 1.00 eq) was dissolved in NMP (13 mL). CuCN (475 mg, 5.30 mmol, 1.00 eq) was added to the reaction mixture which was stirred at 150 °C overnight. The solution was partitioned between water (30 mL) and EtOAc (30 mL). The organic phase was washed with water (10 mL x2) and brine (10 mL x2), dried over MgSO4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (DCM/MeOH (98/2)) gave 2-methyl-6-oxocyclohex-1-ene-1-carbonitrile **21** in 30% yield (214 mg, 1.58 mmol) as yellow oil.

TLC R_f = 0.46 (DCM/ MeOH (95/5)).

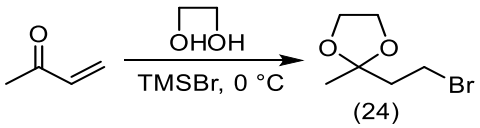


^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 2.07 (m, 2H, H-5), 2.36 (s, 3H, H-7), 2.47 – 2.55 (m, 2H, H-4), 2.55 – 2.60 (t, *J*=6.0 Hz, 2H, H-6).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 21.1 (C-5), 24.5 (C-7), 32.4 (C-4), 36.4 (C-6), 104.3 (C-2), 113.7 (C-8), 175.9 (C-3), 192.3 (C-1).

LRMS (ES-API^{+}) *m/z* calc. for C_8H_9NONa $[M+Na]^{+}$: 158.0, found 158.0.

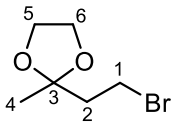
2-(2-Bromoethyl)-2-methyl-1,3-dioxolane 24:



(24)

In a flame-dried flask, 3-butene-2-one (4.2 mL, 50 mmol, 1.00 eq) and ethylene glycol (11.2 mL, 200 mmol, 4.00 eq) were mixed together and the solution cooled to 0–5 °C. TMSBr (7.9 mL, 60 mmol, 1.20 eq) was then slowly added under an inert atmosphere. The resulting mixture was stirred for 2 hrs at room temperature. The reaction mixture was then poured into a biphasic mixture of pentane (100 mL) and sodium carbonate (5% aq, 50 mL). The resulting mixture was stirred for 5 mins before washing the organic layer with 5% sodium thiosulfate (25 mL x2), water (25 mL x2) and drying over anhydrous K_2CO_3. After removal of the solvent *in vacuo*, the residue was purified by vacuum distillation (80 °C, 4 mbar vacuum) to afforded 2-(2-bromoethyl)-2-methyl-1,3-dioxolane **24** in 38% yield (3.71 g, 19 mmol) as a yellow oil.

TLC R_f = 0.53 (hexane/ EtOAc (9/1)).

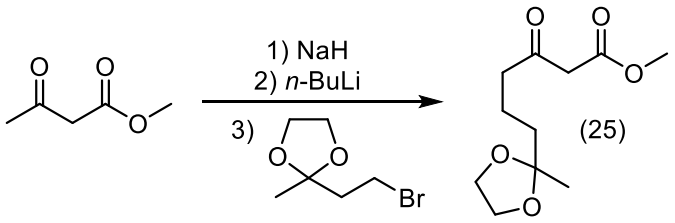


^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.33 (s, 3H, H-4), 2.22 – 2.31 (m, 2H, H-2), 3.37 – 3.45 (m, 2H, H-1), 3.88 – 4.01 (m, 4H, H-5 and 6).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 24.1 (C-4), 26.9 (C-1), 42.8 (C-2), 64.8 (C-5 and 6), 109.1 (C-3).

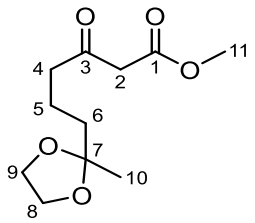
Data consistent with previously reported values.[149]

Methyl-6-(2-methyl-1,3-dioxolan-2-yl)-3-oxohexanoate 25:



In a flame-dried flask, NaH (444 mg, 11.1 mmol, 1.30 eq, 60%) was suspended in THF (20 mL) and cooled to 0 °C. Methyl acetoacetate (0.92 mL, 8.5 mmol, 1.00 eq) was added dropwise. The solution turned white and bubbles of H_2 gas were observed. After 10 mins, *n*-BuLi (3.6 mL, 8.92 mmol, 1.05 eq) was added dropwise to the reaction mixture which turned yellow. The resulting mixture was stirred for an additional 10 mins at 0 °C. A solution of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane **24** (1.83 g, 9.37 mmol, 1.10 eq) in THF (5 mL) was then rapidly added to the reaction mixture which was left to warm to room temperature. After 1 hr, the reaction was quenched with HCl (1M, 10 mL), extracted with Et_2O (10 mL x3), washed with brine (10 mL x2), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/Et_2O (7/3)) gave ethyl-6-(2-methyl-1,3-dioxolan-2-yl)-3-oxohexanoate **25** in 22% yield (435 mg, 1.89 mmol) as yellow oil.

TLC R_f = 0.30 (hexane/ EtOAc (9/1)).

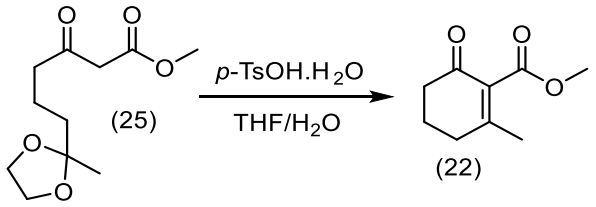


[1]H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.31 (s, 3H, H-10), 1.59 – 1.76 (m, 4H, H-5 and 6), 2.57 (t, *J*=7.0 Hz, 2H, H-4), 3.45 (s, 2H, H-2), 3.70 – 3.77 (s, 3H, H-11), 3.88 – 4.02 (m, 4H, H-8 and 9).

[13]C NMR (101 MHz, Chloroform-*d*) δ ppm = 18.5 (C-5), 26.0 (C-10), 39.1 (C-6), 42.9 (C-4), 49.9 (C-2), 52.2 (C-11), 64.7 (C-8 and 9), 109.7 (C-7), 169.6 (C-1), 205.1 (C-3).

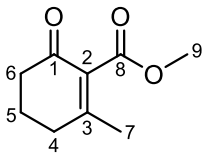
Data consistent with previously reported values.[149]

Methyl-2-methyl-6-oxocyclohex-1-ene-1-carboxylate 22:



In a flame-dried flask, ethyl-6-(2-methyl-1,3-dioxolan-2-yl)-3-oxohexanoate **25** (435 mg, 1.89 mmol, 1.00 eq) was dissolved in THF/H_2O (1/1) (14 mL). *p*-TsOH.H_2O (360 mg, 1.89 mmol, 1.00 eq) was added to the reaction mixture which was stirred at 45 °C for 16 hrs. The solution was diluted in Et_2O (20 mL), washed with brine (10 mL x2), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/Et_2O (8/2)) gave methyl-2-methyl-6-oxocyclohex-1-ene-1-carboxylate **22** in 62% yield (199 mg, 1.18 mmol) as yellow oil.

TLC R_f = 0.15 (hexane/ EtOAc (8/2)).



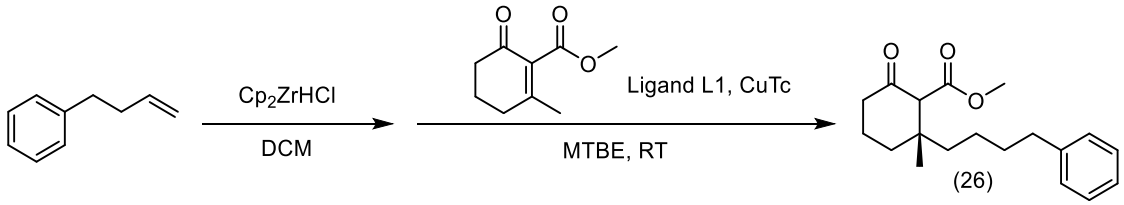
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.96 – 2.05 (m, 5H, H-5 and 7), 2.36 – 2.46 (m, 4H, H-4 and 6), 3.83 (s, 3H, H-9).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 21.7 (C-5), 22.3 (C-7), 31.7 (C-4), 36.9 (C-6), 52.2 (C-9), 133.0 (C-2), 160.6 (C-3), 167.4 (C-8), 195.0 (C-1).

LRMS (ES-API$^+$) *m/z* calc. for $C_9H_{13}O_3$ $[M+H]^+$: 169.1, found 169.1.

Data consistent with previously reported values.[151]

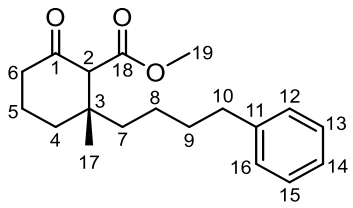
Methyl-(2*R*)-2-methyl-6-oxo-2-(4-phenylbutyl)cyclohexane-1-carboxylate 26:



In a flame-dried flask, Cp_2ZrHCl (206 mg, 0.80 mmol, 2.00 eq) was added to a stirred solution of 4-phenyl-1-butene (150.0 μL, 1.00 mmol, 2.50 eq) in DCM (0.4 mL). After stirring for 5 mins, the solution turned clear. In another flame-dried flask, CuTc (7.6 mg, 0.04 mmol, 0.10 eq) and *N*-benzhydryl-*N*-isopropyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (21.6 mg, 0.04 mmol, 0.10 eq) were dissolved in MTBE (2.0 mL). After stirring for 1 hr, $AgNTf_2$ (17.1 mg, 0.044 mmol, 0.11 eq) was added to the ligand mixture, which was stirred again for 10 mins. The silver solution was then filtered through a syringe filter and added to the zirconium solution. The reaction turned black. After stirring the combined solution for 5 mins, methyl-2-methyl-6-oxocyclohex-1-ene-1-carboxylate **22** (67.3 mg, 0.40 mmol, 1.00 eq) was added to the solution. The reaction was stirred at room temperature overnight. The reaction was quenched with NH_4Cl (1M, 5 mL) and Et_2O (5 mL), extracted with Et_2O (5 mL x3), washed with saturated $NaHCO_3$ (5 mL x3), water (5 mL x3) and brine (5 mL x3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/Et_2O (9/1)) gave an inseparable mixture of diastereomers at C-2 of methyl-(2*R*)-2-methyl-6-oxo-2-(4-phenylbutyl)cyclohexane-1-carboxylate **26** in 16% yield (19.6 mg, 0.06 mmol) as colourless oil.

The enantiomeric excess of **26** was not checked.

TLC R_f = 0.29 (hexane/EtOAc (9/1)).



Major diastereomer:

^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.93 (s, 3H, H-17), 1.23 – 1.34 (m, 3H, H-7’ and 8), 1.36 – 1.45 (m, 1H, H-4’), 1.54 – 1.60 (m, 3H, H-7’’ and 9), 1.75 – 1.97 (m, 2H, H-5), 2.07 (m, 1H, H-4’’), 2.29 – 2.34 (m, 1H, H-6’), 2.57 – 2.65 (m, 2H, H-10), 2.76 (ddd, *J*=14.0, 10.0, 7.0 Hz, 1H, H-6’’), 3.19 (s, 1H, H-2), 3.65 (s, 3H, H-19), 7.12 – 7.22 (m, 3H, H-12, 14 and 16), 7.27 (m, 2H, H-13 and 15).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 21.6 (C-5), 22.6 (C-8), 23.8 (C-17), 32.0 (C-9), 32.5 (C-4), 35.8 (C-10), 38.1 (C-7), 39.1 (C-6), 41.6 (C-3), 51.8 (C-19), 67.4 (C-2), 125.6 (C-14), 127.5 – 128.1 (C-12, 13, 15 and 16), 142.5 (C-11), 169.2 (C-18), 207.1 (C-1).

Minor diastereomer:

^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.03 (s, 3H, H-17), 1.31 (m, 3H, H-7’ and 8), 1.59 (m, 5H, H-4, 7’’ and 9), 1.72 – 1.97 (m, 2H, H-5), 2.19 – 2.37 (m, 1H, H-6’), 2.59 (t, *J*=8.0 Hz, 2H, H-10), 2.64 – 2.81 (m, 1H, H-6’’), 3.25 (s, 1H, H-2), 3.68 (s, 3H, H-19), 7.11 – 7.22 (m, 3H, H-12, 14 and 16), 7.28 (m, 2H, H-13 and 15).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 21.4 (C-5), 22.3 (C-17), 22.9 (C-8), 30.5 (C-9), 35.7 (C-10), 36.4 (C-4), 39.1 (C-6), 40.1 (C-7), 40.5 (C-3), 52.1 (C-19), 65.4 (C-2), 128.2 (C-14), 128.5 (C-12, 13, 15 and 16), 141.7 (C-11), 170.5 (C-18), 203.9 (C-1).

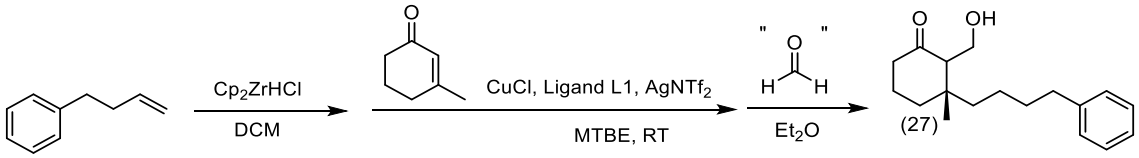
LRMS (ES-API^{+}) *m/z* calc. for $C_{19}H_{26}O_3Na$ $[M+Na]^{+}$: 325.2, found 325.2.

Cracking of *p*-formaldehyde to prepare monomeric formaldehyde solution:

The formaldehyde solution used in the trapping reaction should be prepared immediately before use and have low water content for optimal yields. This procedure for cracking the polymer is for a 2.5 mmol scale 1,4-addition reaction.

To a round bottom flask equipped with a stirrer bar was added *p*-formaldehyde (600 mg, 20.0 mmol, 20.0 eq). A Suba–Seal® and canula were then fitted and the canula was directed into another flask containing dry Et_2O (30 mL). A nitrogen balloon was then fitted to the *p*-formaldehyde containing flask and a vent needle was inserted into the Et_2O-containing flask. Care must be taken throughout these steps to prevent suck back of the solvent into the *p*-formaldehyde flask. Three cycles of vacuum and back filling with N_2 were then performed, after which the *p*-formaldehyde-containing flask was heated gently with a heat gun under a nitrogen stream (from the balloon). When the white solid in the *p*-formaldehyde flask had vanished, the system was allowed to cool for 5 mins and the formaldehyde/Et_2O solution used immediately in the subsequent trapping reaction.

(–)-(*R*)-2-(Hydroxymethyl)-3-methyl-3-(4-phenylbutyl)cyclohexan-1-one 27:

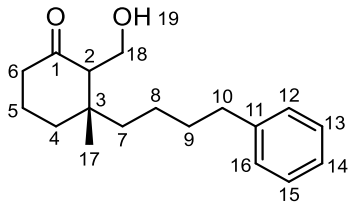


In a flame-dried flask, Cp_2ZrHCl (516 mg, 2.00 mmol, 2.00 eq) was added to a stirred solution of 4-phenyl-1-butene (375 μL, 2.50 mmol, 2.50 eq) in DCM (1.0 mL). After stirring for 10 mins, the solution turned clear. In another flame-dried flask, CuCl (9.9 mg, 0.10 mmol, 0.10 eq) and *N*-benzhydryl-*N*-isopropyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (54.0 mg, 0.10 mmol, 0.10 eq) were dissolved in MTBE (6.0 mL). After stirring for 1 hr, $AgNTf_2$ (42.7 mg, 0.11 mmol, 0.11 eq) was added to the ligand mixture, which was stirred again for 10 mins. The silver solution was then filtered through a syringe filter and added to the zirconium solution. The reaction turned black. After stirring the combined solution for 5 mins, 3-methylcyclohex-2-enone **2** (114 μL, 1.00 mmol, 1.00 eq) was added to the solution. The reaction was stirred at room temperature overnight.

Upon completion of the 1,4-addition reaction as judged by TLC, the contents of the asymmetric reaction were transferred *via* syringe into freshly prepared formaldehyde/Et_2O solution. After stirring for 5 mins, the reaction was quenched with NH_4Cl (1M, 10 mL) to form an emulsion after ~3 mins which was diluted with H_2O (10 mL) until two phases formed. The phases were partitioned, and the aqueous phase was extracted with Et_2O (15 mL x3). The combined organic extracts were washed with brine (15 mL x2), dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (hexane/EtOAc (7/3)) gave a 1.3:1 mixture of diastereomers at C-2 of (*R*)-2-(hydroxymethyl)-3-methyl-3-(4-phenylbutyl)cyclohexan-1-one **27** in 60% yield (164 mg, 0.60 mmol) as yellow oil.

Enantiomeric excess was determined by taking an aliquot of the reaction mixture prior to the trapping step and submitting it to HPLC analysis using the conditions reported by Fletcher *et al. ee* = 94%.[70]

TLC R_f = 0.15 (petroleum ether (40-60)/EtOAc (1/1)).



Major diastereomer:

^{1}H NMR (500 MHz, Chloroform-*d*) δ ppm = 0.78 (s, 3H, H-17), 1.33 – 1.42 (m, 4H, H-7 and 8), 1.46 (m, 1H, H-4'), 1.58 – 1.67 (m, 2H, H-9), 1.74 – 1.87 (m, 2H, H-4'' and 5'), 1.95 (m, 1H, H-5''), 2.23 – 2.33 (m, 1H, H-6'), 2.38 (m, 1H, H-6''), 2.49 (m, 2H, H-2 and 19), 2.58 – 2.70 (m, 2H, H-10), 3.57 (m, 1H, H-18'), 3.92 (m, 1H, H-18''), 7.16 – 7.21 (m, 3H, H-12, 14 and 16), 7.28 (m, 2H, H-13 and 15).

^{13}C NMR (126 MHz, Chloroform-*d*) δ ppm = 21.4 (C-17), 22.2 (C-5), 23.1 (C-8), 32.1 (C-9), 35.9 (C-10), 36.3 (C-4), 40.9 (C-3), 41.2 (C-7), 41.6 (C-6), 58.4 (C-18), 59.6 (C-2), 125.7 (C-14), 128.3 (C-12 and 16 or 13 and 15), 128.4 (C-12 and 16 or 13 and 15),142.4 (C-11), 215.6 (C-1).

HRMS (ESI): *m*/*z* calc. for $C_{18}H_{27}O_2$ $[M+H]^+$: 275.2006, found: 275.2005.

IR (ATR) ν_{max} /cm^{-1} = 3427 (br), 3026 (s), 2934 (s), 2858 (w), 2361 (s), 1703 (m), 1496 (m), 1454 (w) , 1034 (m).

$[\alpha]^{25}_{589}$ = -5.3 (*c* 1.1, DCM) based on the 1,4-addition product with 94% ee.

Minor diastereomer:

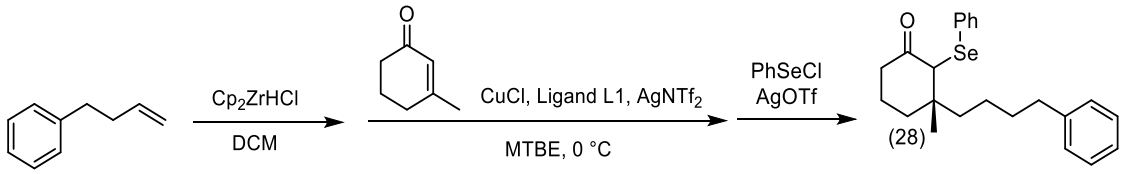
^{1}H NMR (500 MHz, Chloroform-*d*) δ ppm = 1.06 (s, 3H, H-17), 1.08 – 1.28 (m, 4H, H-7 and 8), 1.47 – 1.60 (m, 3H, H-4' and 9), 1.62 – 1.73 (m, 1H, H-5'), 1.77 (m, 1H, H-4''), 1.84 – 1.94 (m, 1H, H-5''), 2.26 – 2.33 (m, 1H, H-6'), 2.33 – 2.38 (m, 1H, H-19), 2.38 – 2.44 (m, 2H, H-2 and 6''), 2.58 (m, 2H, H-10), 3.61 (ddd, *J*=11.5, 9.5, 3.0 Hz, 1H, H-18'), 4.01 (ddd, *J*=11.5, 9.5, 4.0 Hz, 1H, H-18''), 7.12 – 7.20 (m, 3H, H-12, 14 and 16), 7.27 (m, 2H, H-13 and 15).

^{13}C NMR (126 MHz, Chloroform-*d*) δ ppm = 21.9 (C-5), 22.6 (C-8), 25.9 (C-17), 31.9 (C-9), 33.5 (C-7), 35.6 (C-4), 35.8 (C-10), 40.8 (C-3), 41.5 (C-6), 58.3 (C-18), 63.7 (C-2), 125.7 (C-14), 128.3 (C-12 and 16 or 13 and 15), 128.4 (C-12 and 16 or 13 and 15), 142.3 (C-11), 214.8 (C-1).

HRMS (ESI): *m/z* calc. for $C_{18}H_{26}O_2Na$ $[M+Na]^+$: 297.1825, found: 298.1825.

$[\alpha]^{25}_{589}$ = -3.6 (*c* 0.4, DCM) based on the 1,4-addition product with 94% ee.

(*R*)-3-Methyl-3-(4-phenylbutyl)-2-(phenylselanyl)cyclohexan-1-one 28:

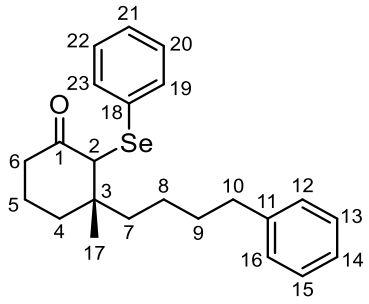


In a flame-dried flask, Cp_2ZrHCl (516 mg, 2.00 mmol, 2.00 eq) was added to a stirred solution of 4-phenyl-1-butene (375 μL, 2.50 mmol, 2.50 eq) in DCM (1.0 mL). After stirring for 10 mins, the solution turned clear. In another flame-dried flask, CuCl (9.9 mg, 0.10 mmol, 0.10 eq) and *N*-benzhydryl-*N*-isopropyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (54.0 mg, 0.10 mmol, 0.10 eq) were dissolved in MTBE (6.0 mL). After stirring for 1 hr, $AgNTf_2$ (42.7 mg, 0.11 mmol, 0.11 eq) was added to the ligand mixture, which was stirred again for 10 mins. The silver solution was then filtered through a syringe filter and added to the zirconium solution. The reaction turned black. After stirring the combined solution for 5 mins, 3-methylcyclohex-2-enone **2** (114 μL, 1.00 mmol, 1.00 eq) was added to the solution. The reaction was stirred at room temperature overnight.

In a flame dried flask, PhSeCl (383 mg, 2.00 mmol, 2.0 eq) was mixed with AgOTf (514 mg, 2.00 mmol, 2.0 eq) in DCM (5 mL). Upon completion of the 1,4-addition reaction as judged by TLC, the prepared PhSeOTf solution was filtered and added to the contents of the asymmetric reaction. After stirring for 10 mins, the reaction was quenched with NH_4Cl (1M, 10 mL). The phases were partitioned, and the aqueous phase extracted with Et_2O (15 mL x3). The combined organic extracts were washed with brine (10 mL x2), dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (petroleum ether (40-60)/EtOAc (95/5)) gave a mixture of diastereomers at C-2 of (*R*)-3-methyl-3-(4-phenylbutyl)-2-(phenylselanyl)cyclohexan-1-one **28** in 44% yield (176 mg, 0.44 mmol) as yellow oil.

No enantiomeric excess was checked for **28** as we assumed it would not be impacted by the trapping step similarly to what we observed for **27** and **29**.

TLC R_f = 0.56 (hexane/EtOAc (9/1)).



Major diastereomer:

^{1}H NMR (500 MHz, Chloroform-*d*) δ ppm = 1.16 (s, 3H, H-17), 1.21 – 1.44 (m, 4H, H-7 and 8), 1.50 – 1.62 (m, 3H, H-4' and 9), 1.65 – 1.79 (m, 2H, H-4'' and 5'), 1.84 (m, 1H, H-5''), 2.22 (m, 1H, H-6''), 2.57 (m, 2H, H-10), 3.03 – 3.14 (m, 1H, H-6''), 3.51 (m, 1H, H-2), 7.13 – 7.16 (m, 2H, H-12 and 16), 7.16 – 7.20 (m, 1H, H-14), 7.23 – 7.31 (m, 5H, H-13, 15, 20, 21 and 22), 7.50 – 7.56 (m, 2H, H-23 and 19).

^{13}C NMR (126 MHz, Chloroform-*d*) δ ppm = 21.0 (C-5), 23.2 (C-8), 25.7 (C-17), 31.9 (C-9), 32.1 (C-4), 35.8 (C-10), 35.9 (C-6), 38.3 (C-7), 40.8 (C-3), 64.2 (C-2), 125.7 (C-14), 128.1 (C-21), 128.3 (C-12 and 16 or 13 and 15), 128.3 (C-12 and 16 or 13 and 15), 129.3 (C-20 and 22), 129.3 (C-18), 134.5 (C-19 and 23), 142.4 (C-11), 208.3 (C-1).

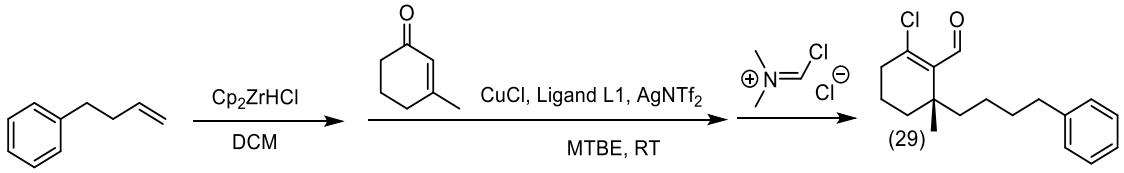
HRMS (ESI): *m/z* calc. for $C_{23}H_{29}O^{80}Se$ $[M+H]^+$: 401.1378, found: 401.1377.

Minor diastereomer:

^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.98 (s, 3H, H-17), 1.23 – 1.40 (m, 2H, H-8), 1.41 – 1.57 (m, 2H, H-4’ and 7’), 1.66 (m, 1H, H-9), 1.68 – 1.79 (m, 2H, H-4’’ and 7’’), 1.79 – 1.91 (m, 2H, H-5), 2.14 – 2.25 (m, 1H, H-6’), 2.53 – 2.66 (m, 2H, H-10), 3.13 – 3.30 (m, 1H, H-6’’), 3.41 (m, 1H, H-2), 7.18 (m, 3H, H-12, 14 and 16), 7.21 – 7.33 (m, 5H, H-13, 15, 20, 21 and 22), 7.43 – 7.48 (m, 2H, H-19 and 23).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 21.3 (C-5), 22.3 (C-8), 22.7 (C-17), 31.9 (C-9), 33.9 (C-4), 35.9 (C-6 and 10), 40.7 (C-3), 41.6 (C-7), 62.6 (C-2), 125.7 (C-14), 128.2 (C-21), 128.4 (C-12, 16, 20 and 22), 129.3 (C-13 and 15), 130.5 (C-18) 134.7 (C-19 and 23), 142.6 (C-11), 208.3 (C-1).

(+)-(*R*)-2-Chloro-6-methyl-6-(4-phenylbutyl)cyclohex-1-ene-1-carbaldehyde 29:



In a flame-dried flask, Cp_2ZrHCl (206 mg, 0.80 mmol, 2.00 eq) was added to a stirred solution of 4-phenyl-1-butene (150 μL, 1.00 mmol, 2.50 eq) in DCM (0.4 mL). After stirring for 10 mins, the solution turned clear. In another flame-dried flask, CuCl (4.0 mg, 0.04 mmol, 0.10 eq) and *N*-benzhydryl-*N*-isopropyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (21.6 mg, 0.04 mmol, 0.10 eq) were dissolved in MTBE (2.0 mL). After stirring for 1 hr, $AgNTf_2$ (17.1 mg, 0.044 mmol, 0.11 eq) was added to the ligand mixture, which was stirred again for 10 mins. The silver solution was then filtered through a syringe filter and added to the zirconium solution. The reaction turned black. After stirring the combined solution for 5 mins, 3-methylcyclohex-2-enone **2** (46 μL, 0.40 mmol, 1.00 eq) was added to the solution. The reaction was stirred at room temperature overnight.

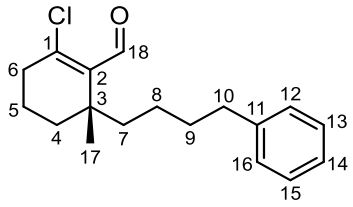
In a flame-dried flask, $POCl_3$ (820 μL, 8.80 mmol, 22.0 eq) was added in one portion to a stirred, room temperature solution of *N*,*N*-dimethylformamide (619 μL, 8.00 mmol, 20.0 eq) in DCM (5.0 mL) under a N_2 atmosphere. On large scale, the addition should be performed at 0 °C and stirring continued for 5 mins before warming to room temperature (to prevent thermal runaway). After stirring for 15 mins, the contents of the 1,4-addition reaction (judged complete by TLC) were added by syringe. After 20 mins stirring at room temperature (TLC control) the reaction flask was cooled to 0 °C and the reaction mixture diluted with DCM (5 mL). Saturated $NaHCO_3$ (~10 mL) was then added dropwise *via* syringe (on large scale use a dropping funnel) and the mixture was stirred vigorously for 15 mins. An orange sludge was obtained, which was transferred to a separatory funnel. Upon standing, two phases were formed and the upper, solid-containing, aqueous phase was extracted with DCM (20 mL x5). The combined organic extracts were washed with water (15 mL x2), dried over Na_2SO_4, filtered and concentrated *in*

vacuo. Purification by flash column chromatography (petroleum ether (40-60)/EtOAc (95/5)) (*R*)-2-chloro-6-methyl-6-(4-phenylbutyl)cyclo-hex-1-ene-1-carbaldehyde **29** in 66% yield (75.6 mg, 0.26 mmol) as yellow oil.

Enantiomeric excess was determined by taking an aliquot of the reaction mixture prior to the trapping step and submitting it to HPLC analysis using the conditions reported by Sidera *et al.* *ee* = 96%.[70]

Enantiomeric excess of 96% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/i-PrOH: 98: 2; λ = 210 nm; major enantiomer t_R = 17.1 mins; minor enantiomer t_R = 18.2 mins].

TLC R_f = 0.54 (pentane/Et_2O (7/3)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.84 (s, 3H, H-17), 1.17 – 1.32 (m, 4H, H-7 and 8), 1.36 (t, *J*=7.0 Hz, 2H, H-4), 1.50 – 1.58 (m, 2H, H-9), 2.12 – 2.39 (m, 4H, H-5 and 6), 2.51 – 2.58 (m, 2H, H-10), 7.07 – 7.15 (m, 3H, H-12, 14 and 16), 7.18 – 7.24 (m, 2H, H-13 and 14), 10.13 (s, 1H, H-18).

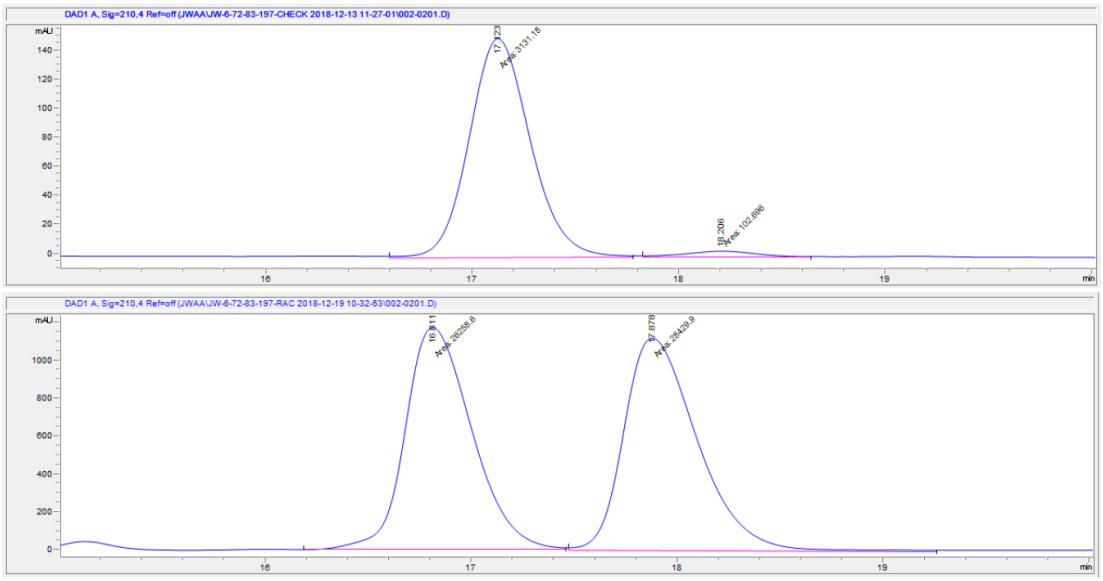
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 21.1 (C-5), 23.1 (C-8), 24.3 (C-17), 31.9 (C-4), 32.1 (C-9), 33.9 (C-3), 35.9 (C-10), 40.9 (C-7), 48.6 (C-6), 125.7 (C-14), 128.3 (C-12 and 16 or 13 and 15), 128.3 (C-12 and 16 or 13 and 15), 132.3 (C-2), 142.5 (C-11), 150.5 (C-1), 191.1 (C-18).

HRMS (ESI): *m*/*z* calc. for $C_{18}H_{24}O^{35}Cl$ $[M+H]^+$: 291.1510, found: 291.1512.

IR (ATR) ν_{max} /cm^{-1} = 2932 (br), 2857 (s), 1678 (s), 1624 (m).

$[\alpha]^{25}_{589}$ = +18 (*c* 1.0, DCM) based on the 1,4-addition product with 96% ee.

HPLC traces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mAU
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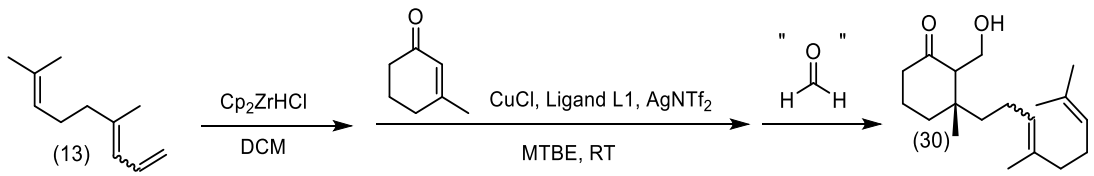
Area: 3131.16
18.206
Area: 102.696
min
DAD1 A, Sig=210,4 Ref=off (JWAA\JW-6-72-83-197-RAC 2018-12-19 10-32-53\002-0201.D)
mAU
16.911
Area: 26258.8
17.678
Area: 26429.9
min

(*S*)-3-((*E/Z*)-4,8-Dimethylnona-3,7-dien-1-yl)-2-(hydroxymethyl)-3-methylcyclohexan-1-one 30:

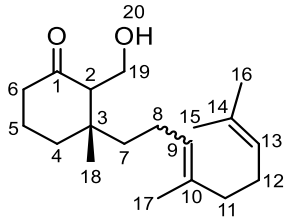


In a flame-dried flask, Cp_2ZrHCl (516 mg, 2.00 mmol, 2.00 eq) was added to a stirred solution of (*E,Z*)-4,8-dimethylnona-1,3,7-triene **13** (376 mg, 2.50 mmol, 2.50 eq) in DCM (1.0 mL). After stirring for 10 mins, the solution turned clear. In another flame-dried flask, CuCl (9.9 mg, 0.1 mmol, 0.10 eq) and *N*-benzhydryl-*N*-isopropyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (54.0 mg, 0.10 mmol, 0.10 eq) were dissolved in MTBE (6.0 mL). After stirring for 1 hr, $AgNTf_2$ (42.7 mg, 0.11 mmol, 0.11 eq) was added to the ligand mixture, which was stirred again for 10 mins. The silver solution was then filtered through a syringe filter and added to the zirconium solution. The reaction turned black. After stirring the combined solution for 5 mins, 3-methylcyclohex-2-enone **2** (114 μL, 1.00 mmol, 1.00 eq) was added to the solution. The reaction was stirred at room temperature overnight.

Upon completion of the 1,4-addition reaction as judged by TLC, the contents of the asymmetric reaction were transferred *via* syringe into freshly prepared formaldehyde/Et_2O solution. After stirring for 5 mins, the reaction was quenched with NH_4Cl (1M, 10 mL) to form an emulsion after ~3 mins which was diluted with H_2O (10 mL) until two phases formed. The phases were partitioned, and the aqueous phase was extracted with Et_2O (15 mL x3). The combined organic extracts were washed with brine (15 ml x2), dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (hexane/EtOAc (7/3)) gave 1.3:1 mixture of diastereomers at C-2 of (*S*)-3-((*E/Z*)-4,8-dimethylnona-3,7-dien-1-yl)-2-(hydroxymethyl)-3-methylcyclo-hexan-1-one **30** in 45% yield (132 mg, 0.45 mmol) as yellow oil.

No enantiomeric excess was checked for **30** as we assumed it would not be impacted by the trapping step similarly to what we observed for **27** and **29**.

TLC R_f = 0.66 (hexane/EtOAc (6/4)).



Major diastereomer (*Z* or *E*):

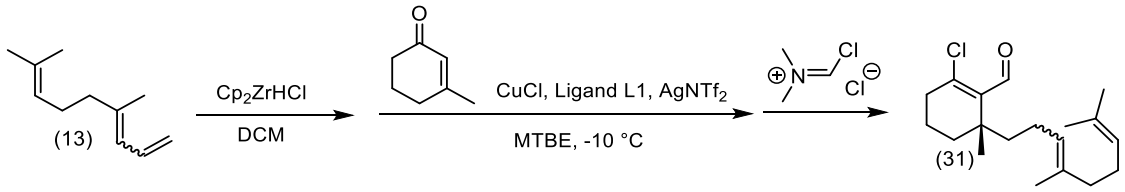
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.79 (s, 3H, H-18), 1.29 – 1.47 (m, 2H, H-7), 1.51 (m, 1H, H-4'), 1.58 – 1.63 (m, 3H, H-16), 1.68 (m, 6H, H-15 and 17), 1.77 – 1.87 (m, 2H, H-4'' and 5'), 1.92 – 2.09 (m, 7H, H-5', 8, 11 and 12), 2.29 (m, 1H, H-6'), 2.35 – 2.43 (m, 1H, H-6''), 2.45 – 2.54 (m, 2H, H-2 and 20), 3.53 – 3.67 (m, 1H, H-19'), 3.86 – 3.97 (m, 1H, H-19''), 5.05 – 5.17 (m, 2H, H-9 and 13).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 17.7 (C-16), 21.2 (C-18), 21.9 (C-8), 22.2 (C-5), 23.4 (C-17), 25.8 (C-15), 26.5 (C-12), 31.9 (C-11), 36.3 (C-4), 41.0 (C-3), 41.6 (C-7), 41.7 (C-6), 58.3 (C-19), 59.7 (C-2), 124.2 (C-13), 124.7 (C-9), 131.7 (C-14), 135.6 (C-10), 215.6 (C-1).

HRMS (ESI): *m*/*z* calc. for $C_{19}H_{32}O_2Na$ $[M+Na]^+$: 315.2294, found: 315.2295.

It was impossible to obtain other diastereomers clean enough for proper characterisation.

(*S,E/Z*)-2-Chloro-6-(4,8-dimethylnona-3,7-dien-1-yl)-6-methylcyclohex-1-ene-1-carbaldehyde 31:



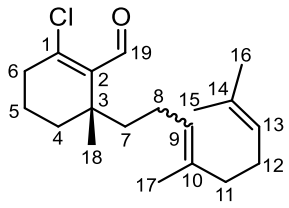
In a flame-dried flask, Cp_2ZrHCl (2.78 g, 10.8 mmol, 2.00 eq) was added to a stirred solution of (*E,Z*)-4,8-dimethylnona-1,3,7-triene **13** (2.00 g, 13.3 mmol, 2.50 eq) in DCM (0.4 mL). After stirring for 10 mins, the solution turned clear. In another flame-dried flask, CuCl (52.5 mg, 0.53 mmol, 0.10 eq) and *N*-benzhydryl-*N*-isopropyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (287.1 mg, 0.53 mmol, 0.10 eq) were dissolved in MTBE (2.0 mL). After stirring for 1 hr, $AgNTf_2$ (225 mg, 0.58 mmol, 0.11 eq) was added to the ligand mixture, which was stirred again for 10 mins. The silver solution was then filtered through a syringe filter and added to the zirconium solution. The reaction turned black. After stirring the combined solution for 5 mins, 3-methylcyclohex-2-enone **2** (600 μL, 5.30 mmol, 1.00 eq) was added to the solution. The reaction was stirred at room temperature overnight.

In a flame-dried flask, $POCl_3$ (11 mL, 117 mmol, 22.0 eq) was added in one portion to a stirred, room temperature solution of *N*,*N*-dimethylformamide (8.0 mL, 106 mmol, 20.0 eq) in DCM (50 mL) under a N_2 atmosphere at 0 °C. After stirring for 15 mins, the contents of the 1,4-addition reaction (judged complete by TLC) were added by syringe. After 20 mins stirring at 0 °C (TLC control) the reaction flask was left warmed up back to room temperature and the reaction mixture diluted with DCM (80 mL). Saturated $NaHCO_3$ (50 mL) was then added using a dropping funnel and the mixture was stirred vigorously for 15 mins. An orange sludge was obtained, which was transferred to a separatory funnel. Upon standing, two phases were formed and the upper, solid-containing, aqueous phase was extracted with DCM (50 mL x5). The combined organic extracts were washed with water (50 mL x2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether (40-

60)/EtOAc (95/5)) gave (*S,E/Z*)-2-chloro-6-(4,8-dimethylnona-3,7-dien-1-yl)-6-methylcyclohex-1-ene-1-carbaldehyde **31** in 66% yield (1.08 g, 3.50 mmol) as yellow oil.

No enantiomeric excess was checked for **31** as we assumed it would not be impacted by the trapping step similarly to what we observed for **27** and **29**.

TLC R_f = 0.66 (hexane/EtOAc (9/1)).



***E* or *Z* isomer:**

^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.94 (s, 3H, H-18) 1.21 – 1.33 (m, 2H, H-7), 1.46 (m, 2H, H-4), 1.60 (m, 6H, H-16 and 17), 1.68 (m, 3H, H-15), 1.91 – 2.01 (m, 4H, H-8 and 11), 2.02 – 2.08 (m, 2H, H-12), 2.20 – 2.35 (m, 3H, H-5 and 6'), 2.43 (m, 1H, H-6'), 5.04 – 5.13 (m, 2H, H-9 and 13), 10.19 (s, 1H, H-19).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 16.0 (C-17), 17.7 (C-16), 21.1 (C-5), 22.1 (C-8), 24.2 (C-18), 25.7 (C-15), 26.7 (C-12), 31.9 (C-4), 33.9 (C-3), 39.7 (C-11), 41.3 (C-7), 48.3 (C-6), 124.1 (C-9), 124.2 (C-13), 131.4 (C-14), 132.3 (C-2), 135.3 (C-10), 150.4 (C-1), 191.0 (C-19).

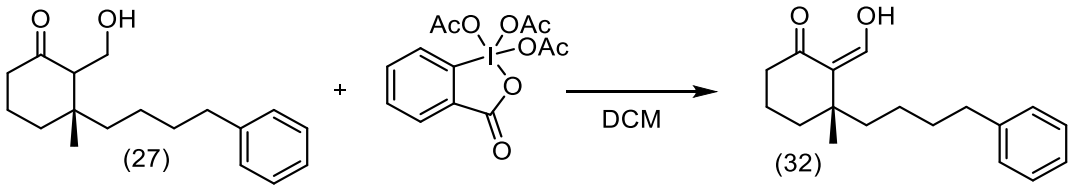
***E* or *Z* isomer:**

^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.95 (s, 3H, H-18), 1.21 – 1.33 (m, 2H, H-7), 1.46 (m, 2H, H-4), 1.60 (m, 3H, H-16), 1.68 (m, 6H, H-15 and 17), 1.91 – 2.01 (m, 2H, H-8), 2.02 – 2.08 (m, 4H, H-11 and 12), 2.20 – 2.35 (m, 3H, H-5 and 6'), 2.43 (m, 1H, H-6'), 5.04 – 5.13 (m, 2H, H-9 and 13), 10.19 (s, 1H, H-19).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 17.7 (C-16), 21.1 (C-5), 21.9 (C-8), 23.4 (C-17), 24.2 (C-18), 25.8 (C-15), 26.5 (C-12), 31.9 (C-4), 31.9 (C-11), 33.9 (C-3), 40.9 (C-7), 48.3 (C-6), 124.3 (C-13), 124.9 (C-9), 131.7 (C-14), 132.3 (C-2), 135.4 (C-10), 150.5 (C-1), 191.1 (C-19).

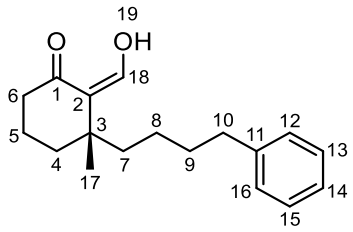
HRMS (ESI): *m*/*z* calc. for $C_{19}H_{30}O^{35}Cl$ $[M+H]^+$: 309.1980, found: 309.1981.

(*R*)-2-Hydroxy-6-methyl-6-(4-phenylbutyl)cyclohex-1-ene-1-carbaldehyde 32:



In a flame-dried flask, (*R*)-2-(hydroxymethyl)-3-methyl-3-(4-phenylbutyl)cyclohexan-1-one **27** (19.2 mg, 0.07 mmol, 1.00 eq) was dissolved in DCM (2.0 mL). DMP (46.7 mg, 0.11 mmol, 1.50 eq) was added to the reaction mixture which was then stirred at room temperature. The reaction was quenched after 3 hrs with saturated $NaHCO_3$ (5 mL), extracted with DCM (5 mL x3), washed with brine (5 mL x2), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (Pentane/Et_2O (9/1)) gave (*R*)-2-hydroxy-6-methyl-6-(4-phenylbutyl)cyclohex-1-ene-1-carbaldehyde **32** in 71% yield (14.1 mg, 0.05 mmol) as yellow oil.

TLC R_f = 0.63 (hexane/EtOAc (9/1)).

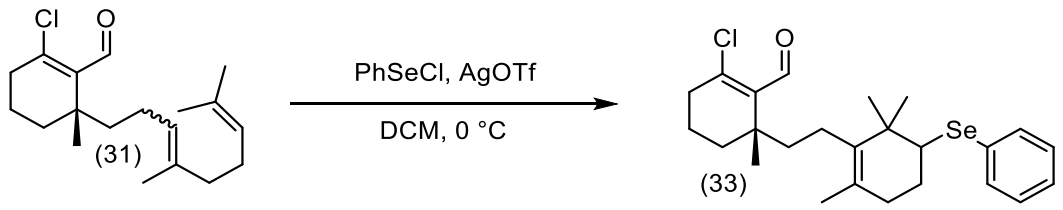


^{1}H NMR (500 MHz, Chloroform-*d*) δ ppm = 1.17 (s, 3H, H-17), 1.27 – 1.40 (m, 3H, H-4' and 7), 1.47 (m, 1H, H-8'), 1.55 – 1.65 (m, 4H, H-4'', 8'' and 9), 1.67 – 1.79 (m, 2H, H-5), 2.34 (t, *J*=6.5 Hz, 2H, H-6), 2.60 (m, 2H, H-10), 7.15 – 7.20 (m, 3H, H-12, 14 and 16), 7.23 – 7.31 (m, 2H, H-13 and 15), 8.85 (d, *J*=3.5 Hz, 1H, H-18), 15.30 (d, *J*=3.5 Hz, 1H, H-19).

^{13}C NMR (126 MHz, Chloroform-*d*) δ ppm = 17.7 (C-5), 24.0 (C-7), 28.9 (C-17), 32.0 (C-6), 32.2 (C-9), 34.3 (C-3), 34.8 (C-4), 35.9 (C-10), 42.3 (C-8), 116.9 (C-2), 125.7 (C-14), 128.3 (C-12 and 16 or 13 and 15), 128.3 (C-12 and 16 or 13 and 15), 142.5 (C-11), 186.2 (C-18), 187.5 (C-1).

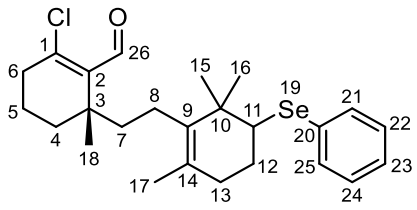
HRMS (ESI): *m*/*z* calc. for $C_{18}H_{25}O_2$ $[M+H]^+$: 273.1849, found: 273.1849.

(*S*)-2-Chloro-6-methyl-6-(2-(2,6,6-trimethyl-5-(phenylselanyl)cyclohex-1-en-1-yl)ethyl)cyclohex-1-ene-1-carbaldehyde 33:



In a flame-dried flask, phenylselenium chloride (115 mg, 0.60 mmol, 1.50 eq) and AgOTf (154 mg, 0.60 mmol, 1.50 eq) was dissolved in DCM (1.5 mL) and stirred at room temperature for 10 mins. In another flame-dried flask, (*S,E/Z*)-2-chloro-6-(4,8-dimethylnona-3,7-dien-1-yl)-6-methylcyclohex-1-ene-1-carbaldehyde **31** (116 mg, 0.40 mmol, 1.00 eq) was dissolved in DCM (2.5 mL) and cooled down to 0 °C. The newly form phenylselenium triflate solution was then filtered through a syringe filter and transferred into the dialkene solution at 0 °C. The reaction was stirred for 45 mins before being quenched with saturated $NaHCO_3$ (10 mL). The mixture was then extracted with DCM (10 mL x3), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether (40-60)/Et_2O (98/2)) gave (*S*)-2-chloro-6-methyl-6-(2-(2,6,6-trimethyl-5-(phenylselanyl)cyclohex-1-en-1-yl)ethyl)cyclohex-1-ene-1-carbaldehyde **33** in 44% yield (82.5 mg, 0.18 mmol) as an orange oil.

TLC R_f = 0.36 (hexane/EtOAc (95/5)).



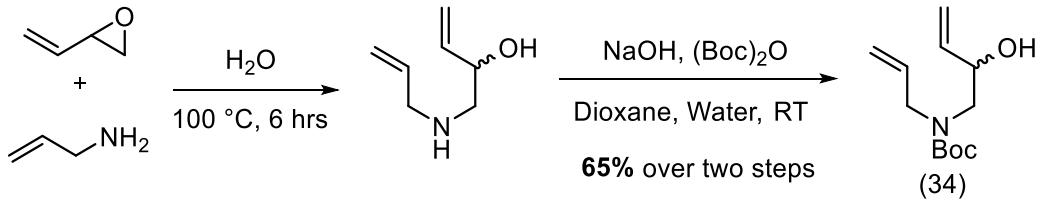
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.99 (s, 3H, H-18), 1.12 (s, 3H, H-16), 1.28 (s, 3H, H-15), 1.35 (m, 2H, H-7), 1.39 – 1.54 (m, 2H, H-4), 1.57 (s, 3H, H-17), 1.84 – 2.15 (m, 6H, H-8, 12 and 13), 2.18 – 2.52 (m, 4H, H-5 and 6), 3.17 – 3.36 (m, 1H, H-11), 7.02 – 7.37 (m, 3H, H-22, 23 and 24), 7.55 (m, 2H, H-21 and 25), 9.90 – 10.36 (m, 1H, H-26).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 19.8 (C-17), 21.1 (C-5), 22.9 (C-8), 23.8 (C-18), 25.1 (C-15), 27.7 (C-16), 28.2 (C-12), 31.9 (C-4), 32.7 (C-13), 34.3 (C-3), 39.8 (C-10), 40.8 (C-7), 47.9 (C-6), 57.5 (C-11), 127.0 (C-23), 127.1 (C-14), 129.0 (C-22 and 24), 131.0 (C-20), 132.3 (C-2), 134.2 (C-21 and 25), 135.9 (C-9), 150.3 (C-1), 191.0 (C-26).

LRMS (ES-API^{+}) *m/z* calc. for $C_{25}H_{34}O^{35}Cl^{80}Se$ $[M+H]^{+}$: 465.1, found 465.1.

6.2.2 Chapter 3

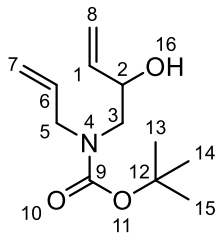
***N-tert*-Butyl allyl(2-hydroxybut-3-en-1-yl)carbamate 34:**



(34)

To a solution of allylamine (17 mL, 228 mmol, 3.00 eq) and water (1.4 mL, 75.0 mmoL, 1.00 eq) was added butadiene monoxide (6.0 mL, 75.0 mmol, 1.00 eq) at room temperature. The mixture was warmed to 100 °C and stirred for 6 hrs. The reaction mixture was then concentrated under reduced pressure. The residue was dissolved in dioxane (100 mL) and water (20 mL), then NaOH 1M (80 mL, 78.7 mmol, 1.05 eq) and $(Boc)_2O$ (17.2 g, 78.7 mmol, 1.05 eq) were added. The mixture was stirred at room temperature overnight. The residue obtained after evaporation was taken up in Et_2O (100 mL), washed with HCl (1M, 25 mL x2), water (25 mL x2) and brine (20 mL x2). The combined aqueous solutions were extracted with Et_2O (25 mL x2). The organic phases were then combined, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash column chromatography (pentane/Et_2O (3/1)) to give pure product **34** in 65% yield (11.0 g, 48.4 mmoL) as colourless oil.

TLC R_f = 0.71 (hexane/EtOAc (2/1)).



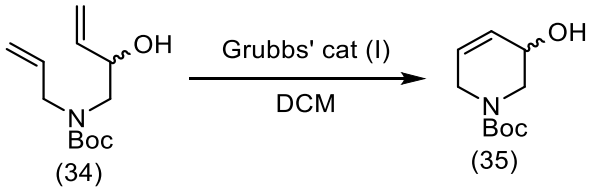
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.45 (s, 9H, H-13, 14 and 15), 3.26 (m, 2H, H-3), 3.62 (s, 1H, H-16), 3.86 (m, 2H, H-5), 4.31 (m, 1H, H-2), 5.08 – 5.19 (m, 3H, H-7 and 8'), 5.32 (d, *J* = 17.0 Hz, 1H, H-8''), 5.80 (m, 2H, H-1 and 6).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.4 (C-13, 14 and 15), 51.7 (C-5), 53.5 (C-3), 72.7 (C-2), 80.4 (C-12), 115.7 (C-8), 116.4 (C-7), 133.9 (C-6), 138.4 (C-1), 157.6 (C-9).

HRMS (ESI): *m*/*z* calc for $C_{12}H_{22}O_3NNa$ $[M+Na]^+$: 250.1414; found 250.1412.

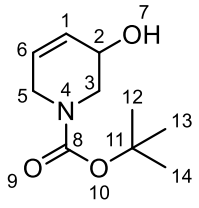
Data consistent with previously reported values.[227]

***N-tert*-Butoxycarbonyl-5-hydroxy-3-piperidene 35:**



To a solution of **34** (11.0 g, 48.4 mmol, 1.00 eq) in DCM (600 mL) under argon atmosphere was added Grubbs' catalyst, first generation (1.60 g, 1.94 mmol, 4 mol%). The solution was stirred at room temperature overnight and then concentrated under reduced pressure. The residue was purified by flash column chromatography (pentane/Et_2O (1/1)) to give **35** in 98% yield (9.40 g, 47.2 mmol) as brown oil.

TLC R_f = 0.50 (hexane/EtOAc (1/1)).



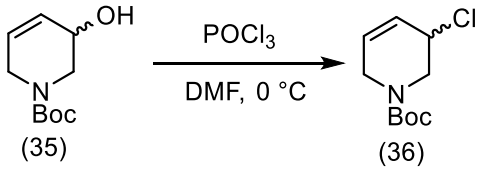
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.47 (s, 9H, H-12, 13 and 14), 1.82 (m, 1H, H-7), 3.55 (m, 2H, H-5), 3.75 – 3.85 (m, 1H, H-3'), 3.98 (m, 1H, H-3''), 4.20 (m, 1H, H-2), 5.84 (m, 1H, H-6), 5.91 (m, 1H, H-1).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.4 (C-12, 13 and 14), 43.2 (C-5), 47.4 (C-3), 63.7 (C-2), 80.1 (C-11), 127.1 (C-6), 128.2 (C-1), 155.2 (C-8).

HRMS (ESI): *m*/*z* calc for $C_{10}H_{17}O_3NNa$ $[M+Na]^+$: 222.1101; found 222.1103.

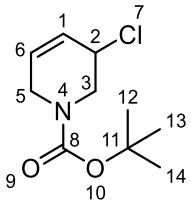
Data consistent with previously reported values.[227]

***N-tert*-Butoxycarbonyl-5-chloro-3-piperidene 36:**



$POCl_3$ (9.7 mL, 104 mmol, 2.20 eq) dropwise was added at 0 °C to a solution of **35** (9.40 g, 47.2 mmol, 1.00 eq) in DMF (97 mL) under argon atmosphere. The reaction mixture was stirred overnight at room temperature before the addition of NaOH (2M, 30 mL) at 0 °C. The aqueous phase was extracted with EtOAc (50 mL x2) and the combined organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash column chromatography. The column was eluted with pentane/Et_2O (9/1) to obtain *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** in 67% yield (6.90 g, 31.7 mmol).

TLC R_f = 0.42 (hexane/EtOAc (9/1)).



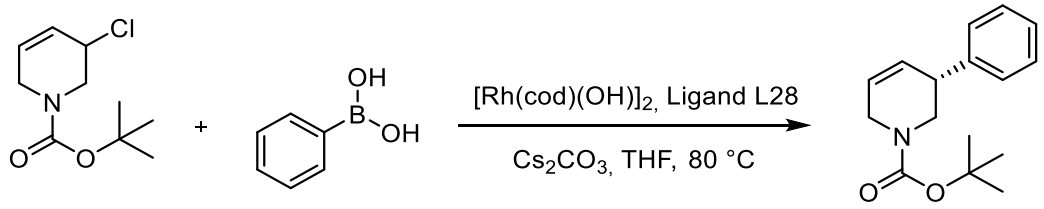
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.47 (s, 9H, H-12, 13 and 14), 3.67 and 3.83 (rotameric m, 2H, H-3), 3.89 – 3.95 and 4.06 (rotameric m, 2H, H-5), 4.50 (m, 1H, H-2), 5.76 – 5.95 (m, 2H, H-1 and 6).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.4 (C-12, 13 and 14), 42.4 and 43.1 (rotameric, C-5), 47.0 and 48.4 (rotameric, C-3), 51.7 (C-2), 80.3 (C-11), 126.7 (C-6), 128.4 (C-1), 154.5 (C-8).

IR (ATR) ν_{max} /cm^{-1} = 2977 (w), 1698 (s), 1418 (m), 1368 (m), 1336 (w), 1243 (m), 1170 (m), 1123 (m), 1061 (w), 1010 (w), 859 (w), 824 (w), 766 (w), 739 (m), 648 (w).

HRMS (CI): *m*/*z* calc. for $C_{10}H_{17}O_2N^{35}Cl$ $[M+H]^+$: 218.0942, found: 218.0942.

(+)-(*R*)-*N*-tert-Butoxycarbonyl-5-phenyl-3-piperidene 37:

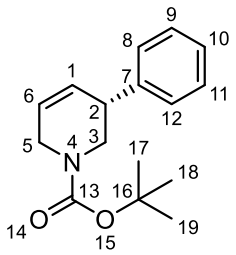


(36) (37)

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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of phenylboronic acid (97.5 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **37** in 76% yield (79.2 mg, 0.31 mmol) as a colourless oil.

Enantiomeric excess of 96% was determined by HPLC [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.4: 0.6; λ = 210 nm; minor enantiomer t_R = 7.5 mins; major enantiomer t_R = 8.1 mins].

TLC R_f = 0.42 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.19 – 1.63 (rotameric m, 9H, H-17, 18 and 19), 3.01, 3.33 – 3.46, 3.70 – 3.79 and 4.07 (rotameric m, 2H, H-3), 3.46 – 3.62 (m, 1H, H-2), 3.82 and 4.07 (rotameric m, 2H, H-5), 5.89 (m, 2H, H-1 and 6), 7.21 (d, *J* = 7.5 Hz, 2H, H-8 and 12), 7.23 – 7.27 (m, 1H, H-10), 7.31 (t, *J* = 7.5 Hz, 2H, H-9 and 11).

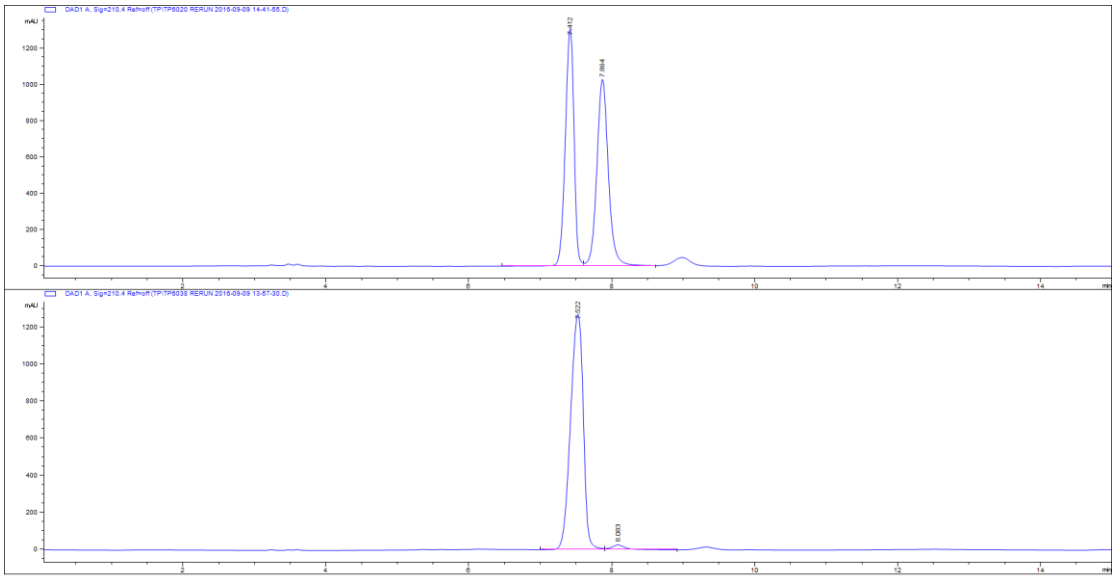
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.3 (C-17, 18 and 19), 41.5 (C-2), 43.0 and 43.6 (rotameric, C-5), 47.3 and 48.6 (rotameric, C-3), 79.5 (C-16), 125.9 (C-6), 126.7 (C-10), 127.9 (C-8 and 12), 128.2 (C-1), 128.5 (C-9 and 11), 142.2 (C-7), 154.7 (C-13).

IR (ATR) ν_{max} /cm^{-1} = 2975 (w), 1696 (s), 1452 (m), 1420 (m), 1366 (w), 1299 (m), 1237 (s), 1168 (w), 1113 (m).

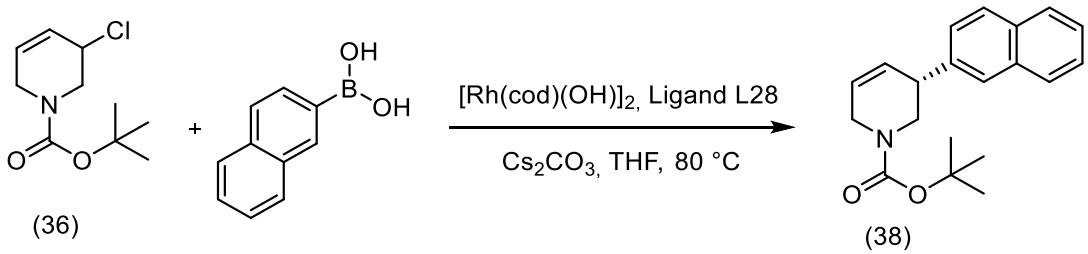
HRMS (ESI): *m*/*z* calc. for $C_{16}H_{21}O_2NNa$ $[M+Na]^+$: 282.1465, found: 282.1466.

$[\alpha]^{25}_{589}$ = +112.9 (*c* 1.00, $CHCl_3$).

HPLC traces


mAU
1200
1000
800
600
400
200
0
7.412
7.884
mAU
1200
1000
800
600
400
200
0
8.022
8.693

(+)-(*R*)-*N-tert*-Butoxycarbonyl-5-(naphthalen-2-yl)-3-piperidene 38:

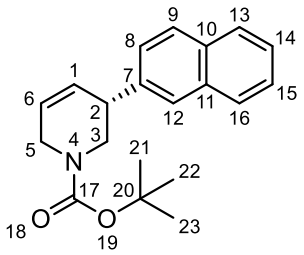


(36) (38)

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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of naphthalene-2-boronic acid (138 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **38** in 79% yield (98.0 mg, 0.32 mmol) as a colourless oil.

Enantiomeric excess of 95% was determined by HPLC [Chiralpak® IA; flow: 1.0 mL/min; hexane/i-PrOH: 85: 15; λ = 210 nm; minor enantiomer t_R = 6.6 mins; major enantiomer t_R = 13.3 mins].

TLC R_f = 0.36 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.21 – 1.57 (rotameric m, 9H, H-21, 22 and 23), 3.14, 3.44 – 3.61, 3.83 and 4.13 (rotameric m, 2H, H-3), 3.68 (m, 1H, H-2), 3.83 and 4.13 (rotameric m, 2H, H-5), 5.99 (m, 2H, H-1 and 6), 7.37 (dd, *J* = 8.5, 2.0 Hz, 1H, H-8), 7.42 – 7.50 (m, 2H, H-14 and 15), 7.66 (s, 1H, H-12), 7.79 – 7.84 (m, 3H, H-9, 13 and 16).

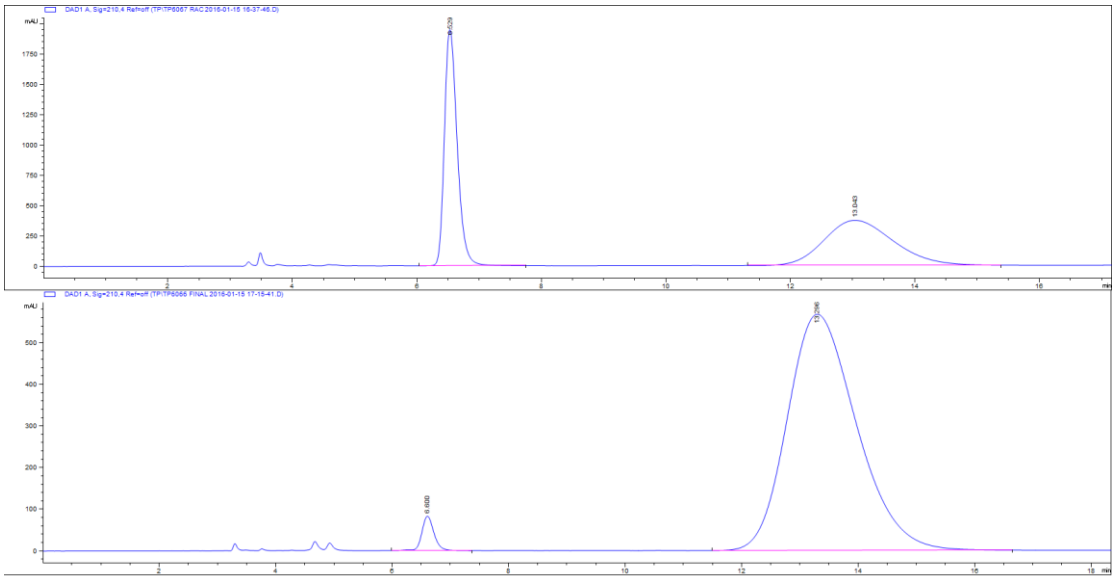
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.3 (C-21, 22 and 23), 41.7 (C-2), 43.1 and 43.7 (rotameric, C-5), 47.2 and 48.4 (rotameric, C-3), 79.5 (C-20), 125.6 (C-14 and 15), 126.0 (C-6), 126.3 (C-12), 126.4 (C-8), 127.6 (C-9), 127.7 (C-13 and 16), 128.2 (C-1), 132.5 (C-10), 133.5 (C-11), 139.6 (C-7), 154.7 (C-17).

IR (ATR) ν_{max} /cm^{-1} = 2974 (w), 2929 (w), 1695 (s), 1420 (w), 1389 (m), 1365 (w), 1331 (m), 1301 (w), 1239 (m), 1164 (m), 1110 (w), 1016 (w), 858 (w), 817 (w), 748 (m).

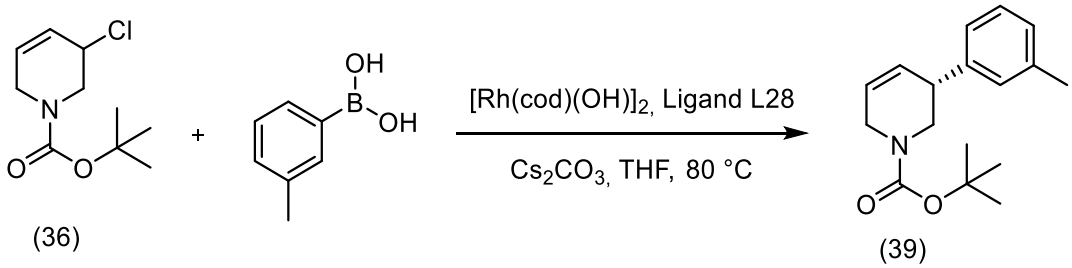
HRMS (ESI): *m*/*z* calc. for $C_{20}H_{23}O_2NNa$ $[M+Na]^+$: 332.1621, found: 332.1623.

$[\alpha]^{25}_{589}$ = +153.7 (*c* 1.00, $CHCl_3$).

HPLC traces



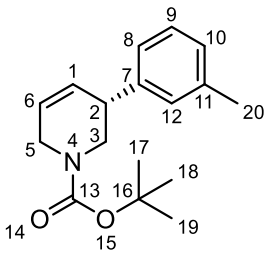
(+)-(*R*)-*N*-*tert*-Butoxycarbonyl-5-(3-methylphenyl)-3-piperidene 39:



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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 3-methylbenzeneboronic acid (109 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **39** in 77% yield (84.0 mg, 0.31 mmol) as a colourless oil.

Enantiomeric excess of 94% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; major enantiomer t_R = 4.9 mins; minor enantiomer t_R = 5.6 mins].

TLC R_f = 0.51 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.24 – 1.56 (rotameric m, 9H, H-17, 18 and 19), 2.34 (s, 3H, H-20), 2.98, 3.39, 3.70 – 3.91 and 3.93 – 4.19 (rotameric m, 2H, H-3), 3.43 – 3.59 (m, 1H, H-2), 3.70 – 3.91 and 3.93 – 4.19 (rotameric m, 2H, H-5), 5.89 (m, 2H, H-1 and 6), 7.01 (m, 2H, H-10 and 12), 7.06 (d, *J* = 7.5 Hz, 1H, H-8), 7.20 (t, *J* = 7.5 Hz, 1H, H-9).

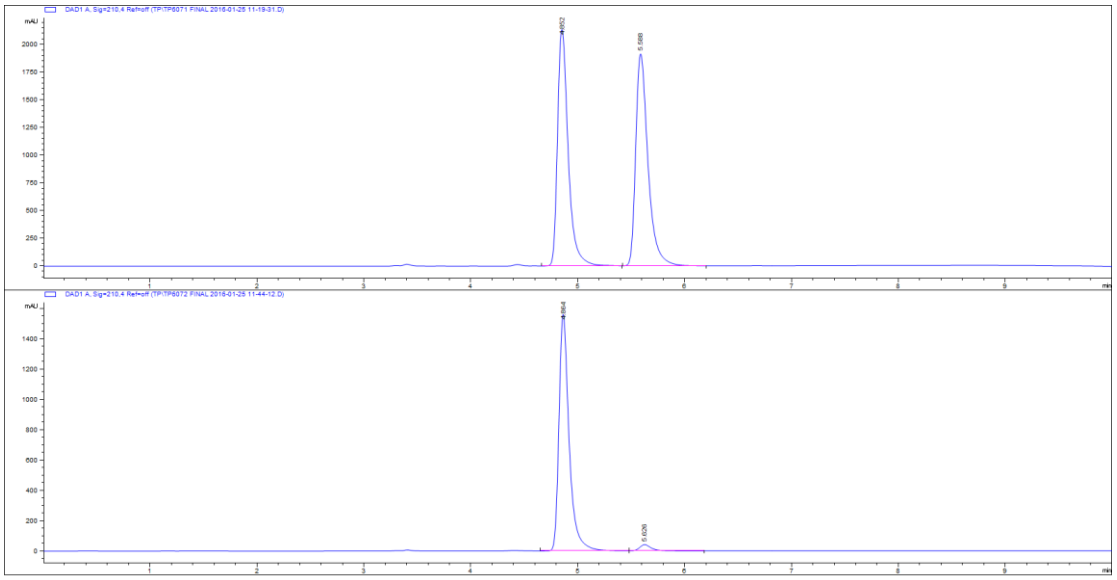
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 21.4 (C-20), 28.3 (C-17, 18 and 19), 41.51 (C-2), 43.0 and 43.6 (rotameric, C-5), 47.4 and 48.5 (rotameric, C-3), 79.4 (C-16), 124.9 (C-10), 125.7 (C-6), 127.5 (C-8), 128.4 (C-9), 128.6 (C-12), 129.4 (C-1), 138.0 (C-11), 142.2 (C-7), 154.7 (C-13).

IR (ATR) ν_{max} /cm^{-1} = 2974 (w), 2925 (w), 1696 (s), 1608 (w), 1420 (m), 1365 (m), 1295 (w), 1238 (m), 1173 (m), 1112 (m), 984 (w), 879 (w), 784 (w), 705 (w).

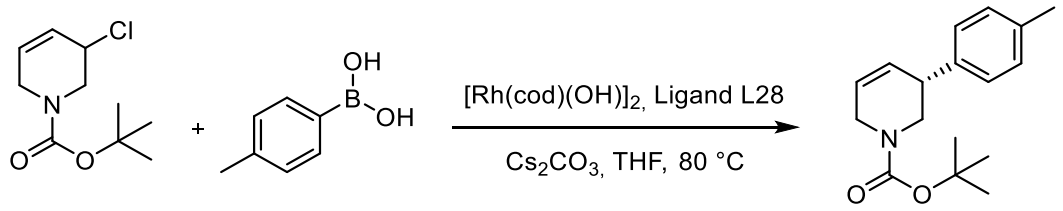
HRMS (ESI): *m*/*z* calc. for $C_{17}H_{23}O_2NNa$ $[M+Na]^+$: 296.1621, found: 296.1623.

$[\alpha]^{25}_{589}$ = +108.5 (*c* 1.00, $CHCl_3$).

HPLC traces



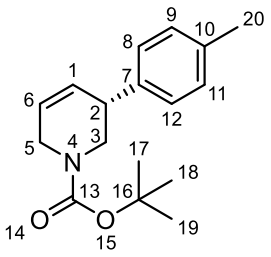
(+)-(*R*)-*N-tert*-Butoxycarbonyl-5-(4-methylphenyl)-3-piperidene 40:



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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 4-methylbenzeneboronic acid (109 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **40** in 81% yield (89.1 mg, 0.33 mmol) as a colourless oil.

Enantiomeric excess of 92% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; major enantiomer t_R = 4.9 mins; minor enantiomer t_R = 5.4 mins].

TLC R_f = 0.56 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.26 – 1.54 (rotameric m, 9H, H-17, 18 and 19), 2.33 (s, 3H, H-20), 2.97, 3.31, 3.78 and 4.06 (rotameric m, 2H, H-3), 3.49 (m, 1H, H-2), 3.78 and 4.06 (rotameric m, 2H, H-5), 5.88 (m, 2H, H-1 and 6), 7.08 – 7.15 (m, 4H, H-8, 9, 11 and 12).

^{1}H VT NMR (500 MHz, DMSO-d_6, 363K) δ ppm = 1.33 (s, 9H, H-17, 18 and 19), 2.28 (s, 3H, H-20), 3.30 (m, 1H, H-3), 3.46 (m, 1H, H-2), 3.70 (m, 1H, H-3), 3.87 – 3.96 (m, 2H, H-5), 5.81 – 5.86 (m, 1H, H-1), 5.87 – 5.92 (m, 1H, H-6), 7.09 (d, *J* = 8.0 Hz, 2H, H-8 and 12 or 9 and 11), 7.11 (d, *J* = 8.0 Hz, 2H, H-8 and 12 or 9 and 11)

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 21.0 (C-20), 28.3 (C-17, 18 and 19), 41.15 (C-2), 43.0 and 43.6 (rotameric, C-5), 47.4 and 48.7 (rotameric, C-3), 79.4 (C-16), 124.8 and 125.6 (rotameric, C-6), 127.7 (C-8 and 12), 128.6 and 129.5 (rotameric, C-1), 129.2 (C-9 and 11), 136.3 (C-10), 139.2 (C-7), 154.7 (C-13).

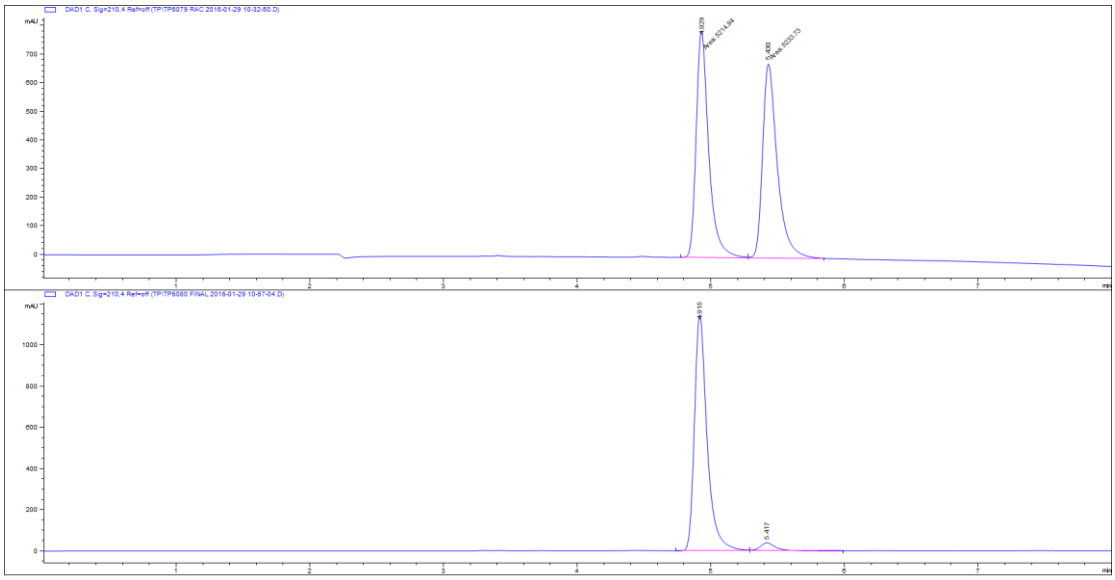
^{13}C VT NMR (126 MHz, DMSO-d_6, 363K) δ ppm = 20.9 (C-20), 28.5 (C-17, 18 and 19), 40.9 (C-2), 43.5 (C-5), 47.9 (C-3), 79.2 (C-16), 125.8 (C-6), 127.9 (C-8 and 12), 128.9 (C-1), 129.3 (C-9 and 11), 136.0 (C-10), 139.7 (C-7), 154.4 (C-13).

IR (ATR) ν_{max} /cm^{-1} = 2974 (w), 1696 (s), 1513 (w), 1419 (m), 1365 (m), 1332 (w), 1301 (w), 1237 (m), 1169 (m), 1110 (m), 1014 (w), 984 (w), 865 (w), 813 (m), 752 (w), 678 (w).

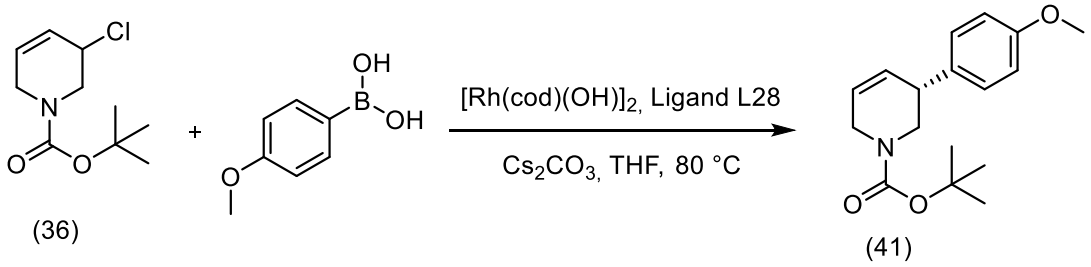
HRMS (ESI): *m*/*z* calc. for $C_{17}H_{23}O_2NNa$ $[M+Na]^+$: 296.1621, found: 296.1624.

$[\alpha]^{25}_{589}$ = +122.5 (*c* 1.00, $CHCl_3$).

HPLC traces



(+)-(*R*)-*N*-*tert*-Butoxycarbonyl-5-(4-methoxyphenyl)-3-piperidene 41:

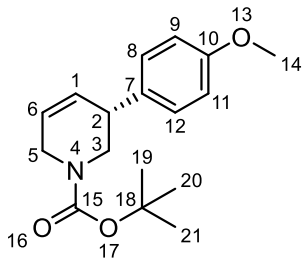


(36) (41)

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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 4-methoxybenzeneboronic acid (122 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **41** in 64% yield (74.6 mg, 0.26 mmol) as a colourless oil.

Enantiomeric excess of 94% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; major enantiomer t_R = 6.6 mins; minor enantiomer t_R = 7.9 mins].

TLC R_f = 0.35 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.38 (rotameric m, 9H, H-19, 20 and 21), 2.96, 3.34, 3.70 - 3.85 and 3.98 (rotameric m, 2H, H-3), 3.40 - 3.55 (m, 1H, H-2), 3.78 (s, 3H, H-14), 3.70 - 3.85 and 3.98 (rotameric m, 2H, H-5), 5.86 (m, 2H, H-1 and 6), 6.82 – 6.88 (m, 2H, H-9 and 11), 7.08 – 7.16 (m, 2H, H-8 and 12).

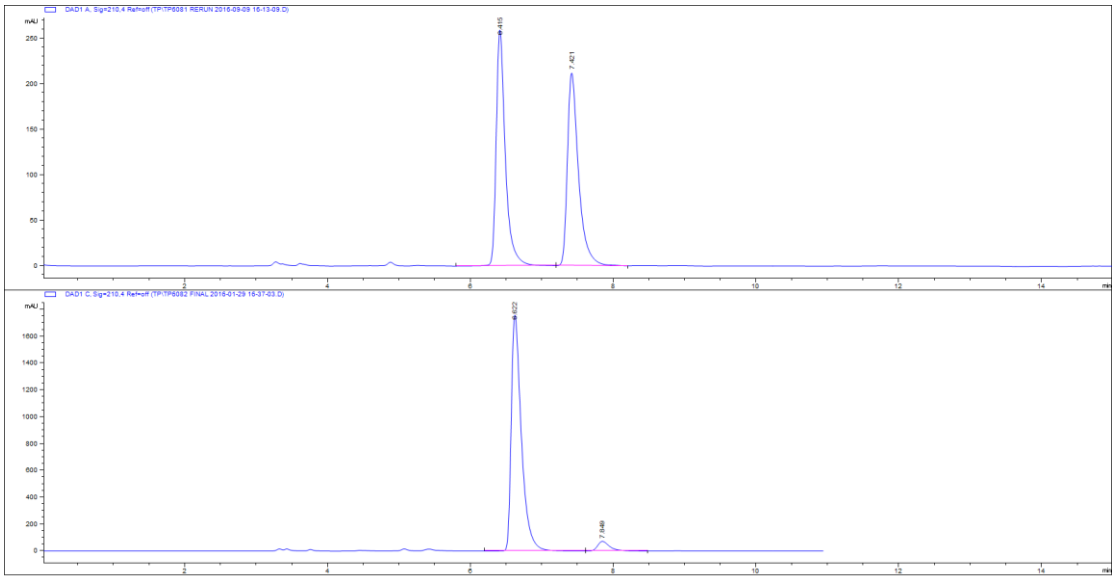
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.4 (C-19, 20 and 21), 40.8 (C-2), 43.0 and 43.7 (rotameric, C-5), 47.5 and 48.8 (rotameric, C-3), 55.4 (C-14), 79.6 (C-18), 114.0 (C-9 and 11), 124.8 and 125.7 (rotameric, C-6), 128.7 and 129.6 (rotameric, C-1), 128.9 (C-8 and 12), 134.4 (C-7), 154.8 (C-15), 158.5 (C-10).

IR (ATR) ν_{max} /cm^{-1} = 2835 (w), 1694 (s), 1612 (w), 1512 (m), 1419 (m), 1365 (m), 1331 (w), 1300 (m), 1240 (s), 1171 (s), 1113 (m), 1036 (m), 984 (w), 869 (w), 829 (m), 768 (w), 678 (w).

HRMS (ESI): *m*/*z* calc. for $C_{17}H_{23}O_3NNa$ $[M+Na]^+$: 312.1570, found: 312.1571.

$[\alpha]^{25}_{589}$ = +118.9 (*c* 1.00, $CHCl_3$).

HPLC traces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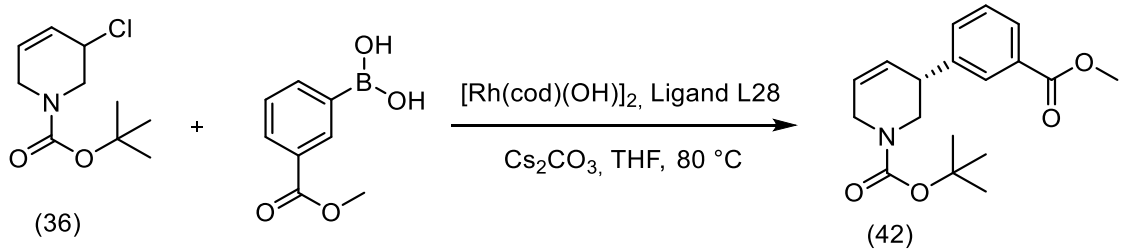
7.415
7.421
min
DAD1 C, Sig=210,4 Ref=off (TP\TP6082 FINAL 2016-01-29 16-37-03.D)
mAU
7.422
7.849
min

(+)-(*R*)-*N*-*tert*-Butoxycarbonyl-5-(3-methoxycarbonylphenyl)-3-piperidene 42:

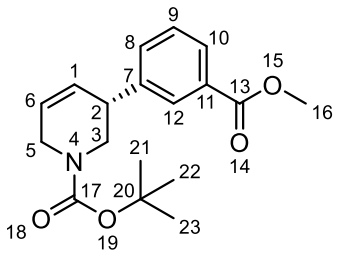


(36) (42)

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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 3-methoxycarbonylbenzeneboronic acid (144 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **42** in 68% yield (86.2 mg, 0.27 mmol) as a colourless oil.

Enantiomeric excess of 95% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 90: 10; λ = 210 nm; major enantiomer t_R = 13.0 mins; minor enantiomer t_R = 23.6 mins].

TLC R_f = 0.26 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.15 – 1.58 (rotameric m, 9H, H-21, 22 and 23), 3.08, 3.36 – 3.49, 3.71 and 3.93 – 4.17 (rotameric m, 2H, H-3), 3.56 (m, 1H, H-2), 3.89 (s, 3H, H-16), 3.93 – 4.17 (rotameric m, 2H, H-5), 5.90 (m, 2H, H-1 and 6), 7.34 – 7.38 (m, 1H, H-9), 7.38 – 7.41 (m, 1H, H-8), 7.89 (m, 2H, H-10 and 12).

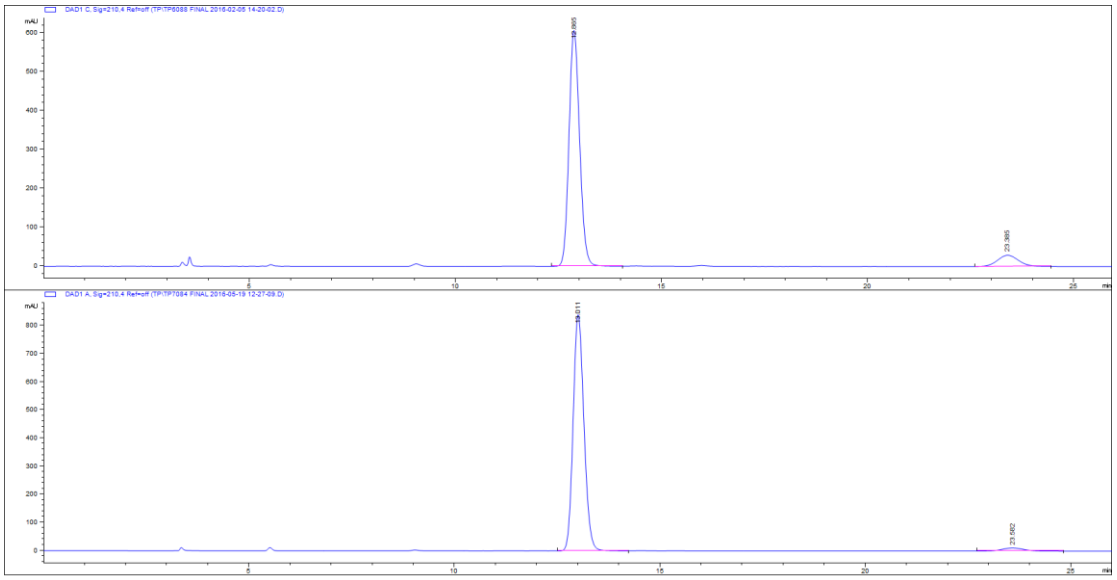
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.3 (C-21, 22 and 23), 41.3 (C-2), 43.0 and 43.6 (rotameric, C-5), 47.1 and 48.3 (rotameric, C-3), 52.1 (C-16), 79.6 (C-20), 125.6 and 126.5 (rotameric, C-6), 127.5 (C-1), 128.0 (C-10), 128.5 (C-9), 129.0 (C-12), 130.4 (C-11), 132.5 (C-8), 142.6 (C-7), 154.6 (C-17), 167.0 (C-13).

IR (ATR) ν_{max} /cm^{-1} = 2975 (w), 1723 (s), 1694 (s), 1420 (m), 1365 (m), 1286 (m), 1238 (m), 1165 (m), 1111 (m), 982 (w), 866 (w), 818 (w), 755 (m), 699 (w).

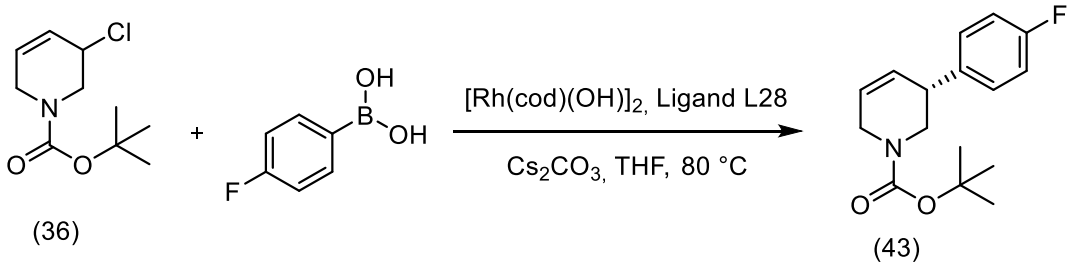
HRMS (ESI): *m*/*z* calc. for $C_{18}H_{23}O_4NNa$ $[M+Na]^+$: 340.1519, found: 340.1519.

$[\alpha]^{25}_{589}$ = +102.9 (*c* 1.00, $CHCl_3$).

HPLC traces



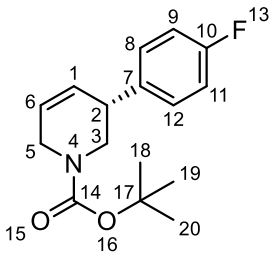
(+)-(*R*)-*N*-*tert*-Butoxycarbonyl-5-(4-fluorophenyl)-3-piperidene 43:



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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under Argon. A solution of *N*-*tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 4-fluorobenzeneboronic acid (112 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **43** in 51% yield (56.1 mg, 0.20 mmol) as a colourless oil.

Enantiomeric excess of 96% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; minor enantiomer t_R = 10.6 mins; major enantiomer t_R = 11.4 mins].

TLC R_f = 0.37 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.18 – 1.56 (rotameric m, 9H, H-18, 19 and 20), 3.03, 3.36 – 3.58, 3.66, 3.76 – 4.17 (rotameric m, 2H, H-3), 3.36 – 3.58 (m, 1H, H-2), 3.76 – 4.17 (rotameric m, 2H, H-5), 5.82 – 5.96 (m, 2H, H-1 and 6), 6.95 – 7.02 (m, 2H, H-9 and 11), 7.12 – 7.19 (m, 2H, H-8 and 12).

^{19}F NMR (376 MHz, Chloroform-*d*) δ ppm = -116.45 (1F).

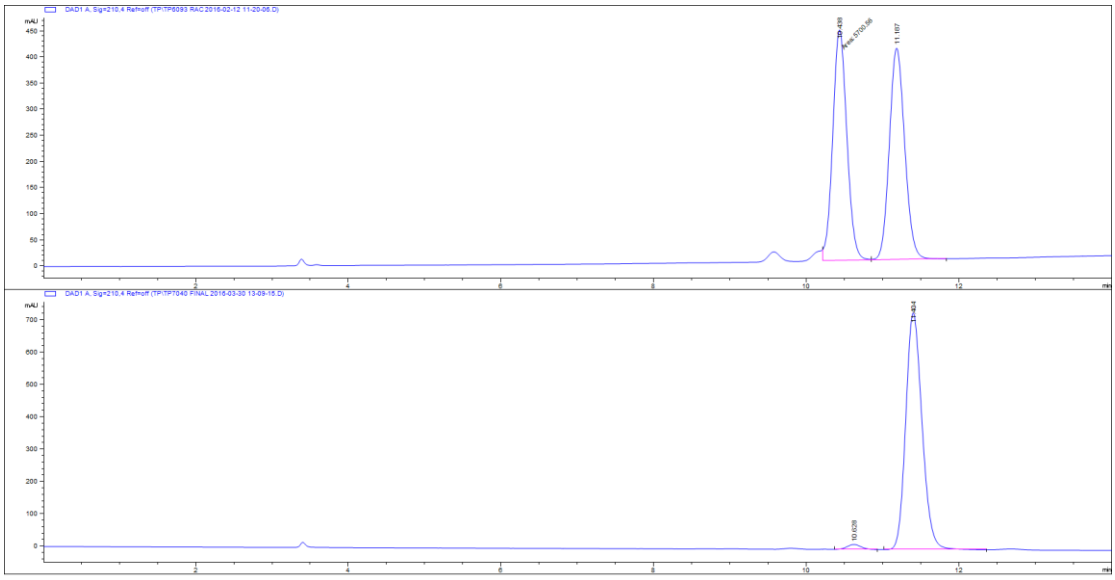
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.3 (C18, 19 and 20), 40.8 (C-2), 42.9 and 43.6 (rotameric, C-5), 47.3 and 48.5 (rotameric, C-3), 79.5 (C-17), 115.2 (d, *J* = 21.0 Hz, C-9 and 11), 125.2 and 126.2 (rotameric, C-6), 127.9 and 129.0 (rotameric, C-1), 129.3 (C-8 and 12), 137.9 (d, *J* = 3.0 Hz, C-7), 154.7 (C-14), 161.8 (d, *J* = 245.0 Hz, C-10).

IR (ATR) ν_{max} /cm^{-1} = 2975 (w), 1695 (s), 1603 (w), 1509 (m), 1420 (m), 1366 (m), 1299 (w), 1236 (m), 1170 (m), 1114 (m), 1014 (w), 865 (w), 834 (m), 767 (w), 678 (w).

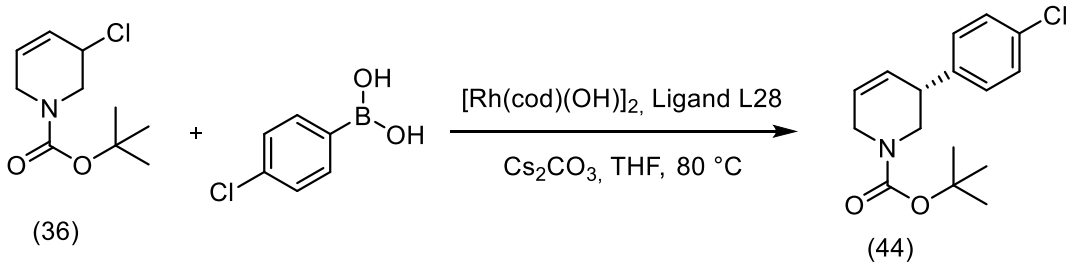
HRMS (ESI): *m*/*z* calc. for $C_{16}H_{20}O_2NFNa$ $[M+Na]^+$: 300.1370, found: 300.1370.

$[\alpha]^{25}_{589}$ = +92.2 (*c* 1.00, $CHCl_3$).

HPLC traces



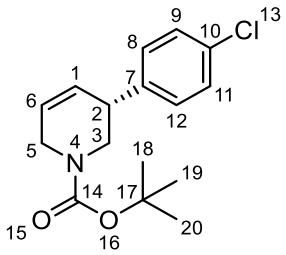
(+)-(*R*)-*N*-*tert*-Butoxycarbonyl-5-(4-chlorophenyl)-3-piperidene 44:



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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 4-chlorobenzeneboronic acid (125 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **44** in 63% yield (73.8 mg, 0.25 mmol) as a colourless oil.

Enantiomeric excess of 95% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; minor enantiomer t_R = 10.5 mins; major enantiomer t_R = 11.4 mins].

TLC R_f = 0.56 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.22 – 1.51 (rotameric m, 9H, H-18, 19 and 20), 3.05, 3.35 – 3.56, 3.65 and 3.76 – 4.18 (rotameric m, 2H, H-3), 3.35 – 3.56 (m, 1H, H-2), 3.76 – 4.18 (rotameric m, 2H, H-5), 5.80 – 5.97 (m, 2H, H-1 and 6), 7.10 – 7.15 (m, 2H, H-8 and 12), 7.24 – 7.28 (m, 2H, H-9 and 11).

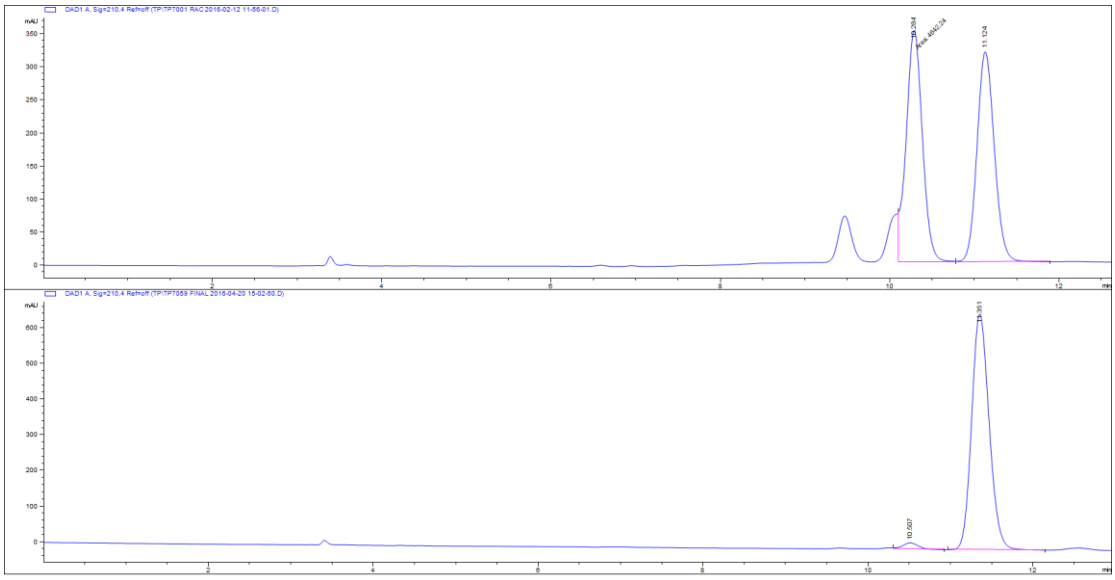
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.3 (C-18, 19 and 20), 40.9 (C-2), 42.9 and 43.6 (rotameric, C-5), 47.1 and 48.3 (rotameric, C-3), 79.7 (C-17), 125.4 and 126.4 (rotameric, C-6), 127.6 (C-1), 128.6 (C-9 and 11), 129.3 (C-8 and 12), 132.5 (C-10), 140.7 (C-7), 154.6 (C-14).

IR (ATR) ν_{max} /cm^{-1} = 2975 (w), 1695 (s), 1491 (w), 1420 (m), 1365 (m), 1333 (w), 1295 (w), 1237 (m), 1166 (m), 1116 (m), 1014 (w), 985 (w), 864 (w), 821 (w), 768 (w), 646 (w).

HRMS (ESI): *m*/*z* calc. for $C_{16}H_{20}O_2N^{35}ClNa$ $[M+Na]^+$: 316.1075, found: 316.1074.

$[\alpha]^{25}_{589}$ = +119.2 (*c* 1.00, $CHCl_3$).

HPLC traces


DAD1 A, Sig=210,4 Ref=off (TP\TP7001 RAC 2016-02-12 11-56-01.D)
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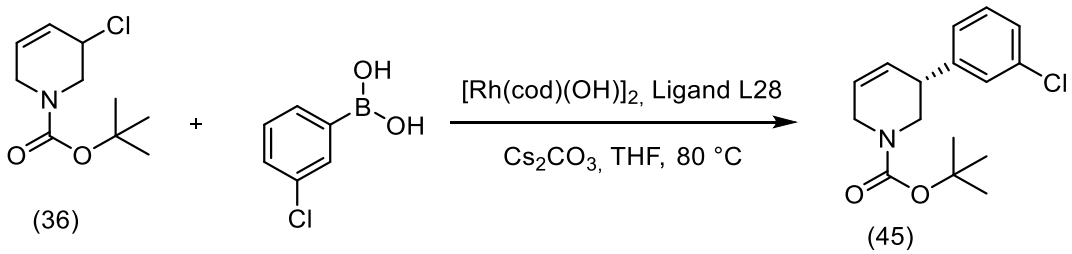
300
250
200
150
100
50
0
10.264
Area 4642.24
11.124
DAD1 A, Sig=210,4 Ref=off (TP\TP7059 FINAL 2016-04-20 15-02-50.D)
mAU
600
500
400
300
200
100
0
10.007
11.351
min

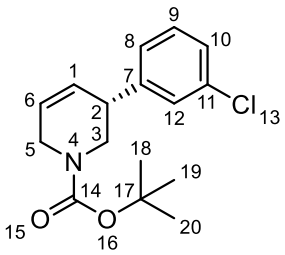
(+)-(*R*)-*N-tert*-Butoxycarbonyl-5-(3-chlorophenyl)-3-piperidene 45:



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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 3-chlorobenzeneboronic acid (125 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **45** in 66% yield (77.8 mg, 0.26 mmol) as a colourless oil.

Enantiomeric excess of 95% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; major enantiomer t_R = 5.5 mins; minor enantiomer t_R = 5.9 mins].

TLC R_f = 0.38 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.19 – 1.55 (rotameric m, 9H, H-18, 19 and 20), 3.10, 3.42 – 3.58, 3.67 and 3.79 – 4.19 (rotameric m, 2H, H-3), 3.42 – 3.58 (m, 1H, H-2), 3.79 – 4.19 (rotameric m, 2H, H-5), 5.81 – 6.00 (m, 2H, H-1 and 6), 7.09 (dt, *J* = 6.5, 2.0 Hz, 1H, H-8), 7.17 – 7.25 (m, 3H, H-9, 10 and 12).

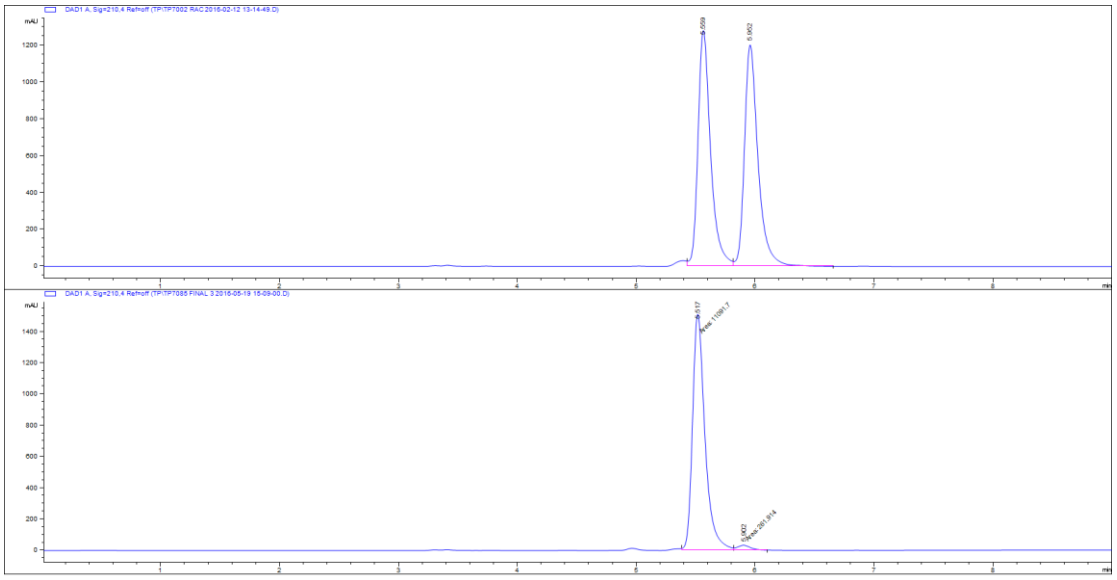
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.3 (C-18, 19 and 20), 41.2 (C-2), 43.0 and 43.6 (rotameric, C-5), 47.0 and 48.2 (rotameric, C-3), 79.7 (C-17), 126.2 (C-8), 126.6 (C-6), 126.9 (C-10), 127.3 (C-1), 128.0 (C-12), 129.7 (C-9), 134.3 (C-11), 144.3 (C-7), 154.6 (C-14).

IR (ATR) ν_{max} /cm^{-1} = 2975 (w), 1694 (s), 1596 (w), 1572 (w), 1477 (w), 1420 (m), 1365 (m), 1233 (w), 1237 (m), 1166 (m), 1115 (m), 865 (w), 785 (w), 734 (w), 697 (w).

HRMS (ESI): *m*/*z* calc. for $C_{16}H_{20}O_2N^{35}ClNa$ $[M+Na]^+$: 316.1075, found: 316.1074.

$[\alpha]^{25}_{589}$ = +121.6 (*c* 1.00, $CHCl_3$).

HPLC traces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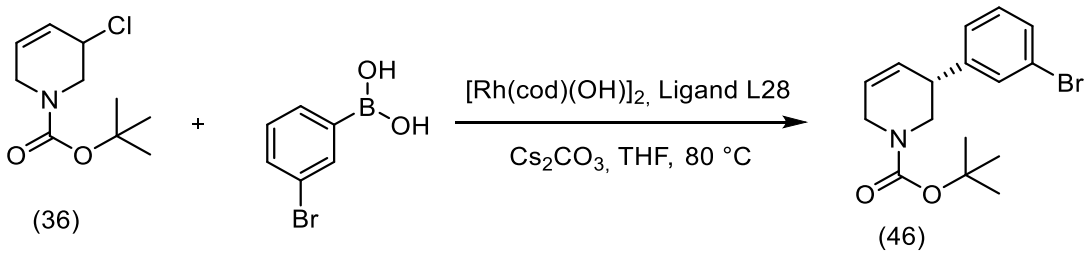
1000
800
600
400
200
0
5.559
5.902
DAD1 A, Sig=210,4 Ref=off (TP\TP7085 FINAL 3 2016-05-19 15-09-00.D)
mAU
1400
1200
1000
800
600
400
200
0
5.517
Area: 11061.7
5.902
Area: 261.814
min

(+)-(*R*)-*N-tert*-Butoxycarbonyl-5-(3-bromophenyl)-3-piperidene 46:

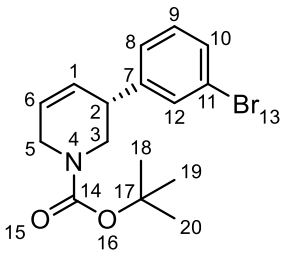


(36) (46)

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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 3-bromobenzeneboronic acid (161 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **46** in 54% yield (73.0 mg, 0.22 mmol) as a colourless oil.

Enantiomeric excess of 96% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; major enantiomer t_R = 5.8 mins; minor enantiomer t_R = 6.4 mins].

TLC R_f = 0.54 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.21 – 1.56 (rotameric m, 9H, H-18, 19 and 20), 3.09, 3.40 – 3.57, 3.66 and 3.79 – 4.18 (rotameric m, 2H, H-3), 3.40 – 3.57 (m, 1H, H-2), 3.79 – 4.18 (rotameric m, 2H, H-5), 5.81 – 5.98 (m, 2H, H-1 and 6), 7.13 (dt, *J* = 7.5, 1.5 Hz, 1H, H-8), 7.17 (t, *J* = 7.5 Hz, 1H, H-9), 7.33 – 7.38 (m, 2H, H-10 and 12).

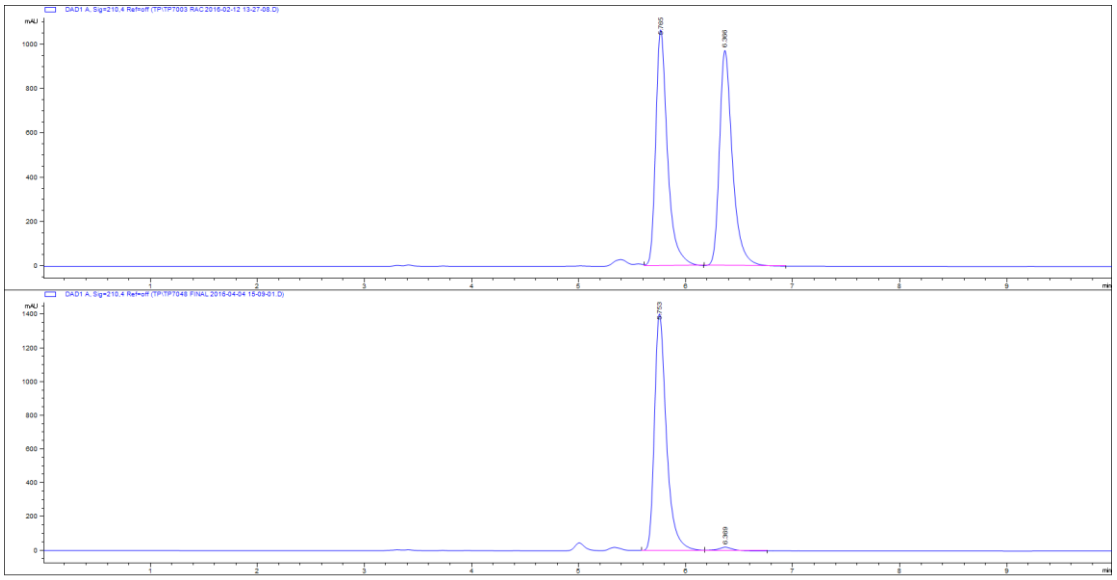
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.3 (C-18, 19 and 20), 41.2 (C-2), 42.9 and 43.6 (rotameric, C-5), 47.0 and 48.2 (rotameric, C-3), 79.7 (C-17), 122.6 (C-11), 125.6 (C-6), 126.6 (C-8), 127.3 (C-1), 129.8 (C-10), 130.0 (C-12), 130.9 (C-9), 144.6 (C-7), 154.6 (C-14).

IR (ATR) ν_{max} /cm^{-1} = 2975 (w), 1695 (s), 1593 (w), 1567 (w), 1475 (m), 1421 (m), 1365 (m), 1332 (w), 1238 (m), 1165 (w), 1116 (m), 1074 (w), 1014 (w), 864 (w), 783 (w), 697 (w), 665 (w).

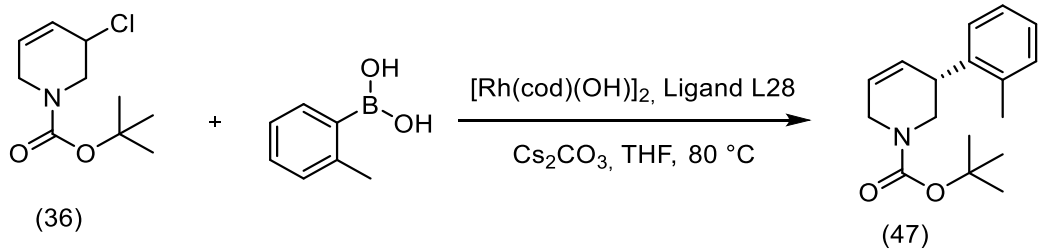
HRMS (ESI): *m*/*z* calc. for $C_{16}H_{20}O_2N^{79}BrNa$ $[M+Na]^+$: 360.0570, found: 360.0570.

$[\alpha]^{25}_{589}$ = +87.0 (*c* 1.00, $CHCl_3$).

HPLC traces


mAU
1000
800
600
400
200
0
6.765
6.369
mAU
1400
1200
1000
800
600
400
200
0
6.753
6.369

(+)-(*R*)-*N-tert*-Butoxycarbonyl-5-(2-methylphenyl)-3-piperidene 47:

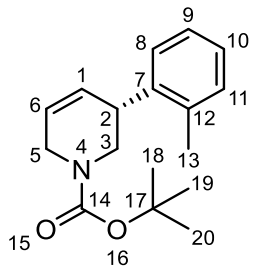


(36) (47)

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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 2-methylbenzeneboronic acid (109 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **47** in 29% yield (32.1 mg, 0.12 mmol) as a colourless oil.

Enantiomeric excess of 93% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; major enantiomer t_R = 11.1 mins; minor enantiomer t_R = 12.2 mins].

TLC R_f = 0.40 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.38 (rotameric m, 9H, H-18, 19 and 20), 2.40 (s, 3H, H-13), 3.15 – 3.33 and 3.67 – 3.91 (rotameric m, 2H, H-3), 3.67 – 3.91 (m, 1H, H-2), 3.67 – 3.91 and 3.91 – 4.21 (rotameric m, 2H, H-5), 5.84 – 5.99 (m, 2H, H-1 and 6), 7.14 (m, 4H, H-8, 9, 10 and 11).

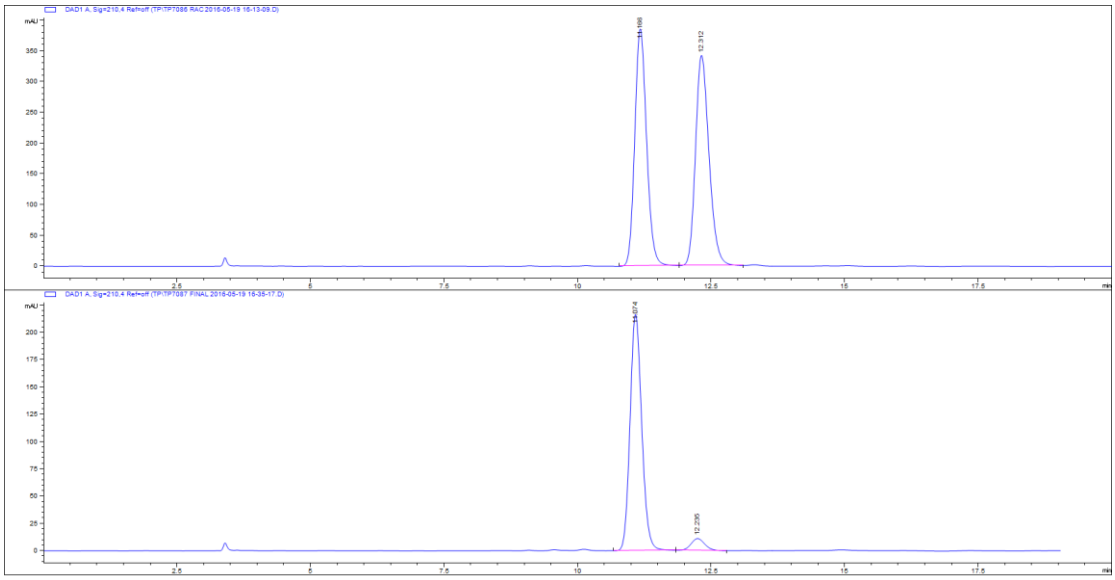
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 19.2 (C-13), 28.3 (C-18, 19 and 20), 37.7 (C-2), 43.1 (C-5), 47.2 (C-3), 79.4 (C-17), 126.1 (C-6), 126.2 (C-9), 126.6 (C-10), 127.4 (C-8), 128.9 (C-1), 130.3 (C-11), 135.7 (C-12), 139.84 (C-7), 154.6 (C-14).

IR (ATR) ν_{max} /cm^{-1} = 2974 (w), 2929 (w), 1697 (s), 1478 (w), 1458 (w), 1420 (m), 1390 (w), 1365 (m), 1330 (w), 1294 (w), 1239 (m), 1168 (m), 1119 (w), 1013 (w), 984 (w), 865 (w), 755 (w), 728 (w), 689 (w), 661 (w).

HRMS (ESI): *m*/*z* calc. for $C_{17}H_{23}O_2NNa$ $[M+Na]^+$: 296.1621, found: 296.1625.

$[\alpha]^{25}_{589}$ = +46.1 (*c* 1.00, $CHCl_3$).

HPLC traces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12.312
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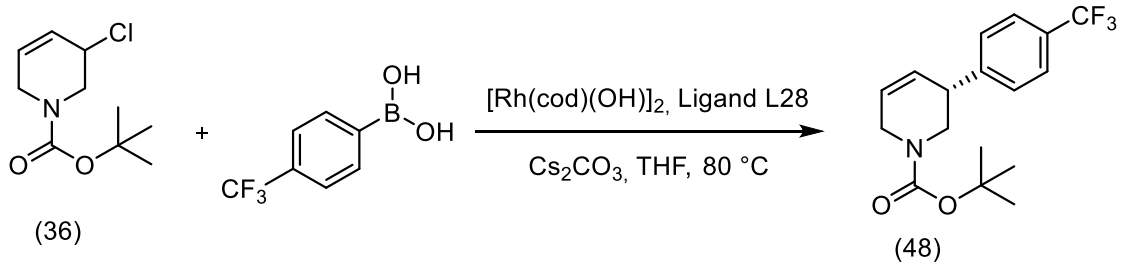
mAU
11.167
12.295
min

(+)-(*R*)-*N*-*tert*-Butoxycarbonyl-5-(4-trifluoromethylphenyl)-3-piperidene 48:

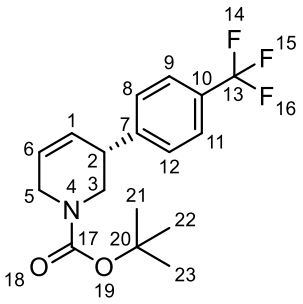


(36) (48)

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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 4-trifluoromethylbenzeneboronic acid (152 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **48** in 65% yield (85.5 mg, 0.26 mmol) as a colourless oil.

Enantiomeric excess of 94% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; minor enantiomer t_R = 7.4 mins; major enantiomer t_R = 8.5 mins].

TLC R_f = 0.30 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.12 – 1.57 (rotameric m, 9H, H-21, 22 and 23), 3.13, 3.61 and 3.79 – 4.25 (rotameric m, 2H, H-3), 3.61 (m, 1H, H-2), 3.79 – 4.25 (rotameric m, 2H, H-5), 5.82 – 6.02 (m, 2H, H-1 and 6), 7.32 (d, *J* = 8.0 Hz, 2H, H-8 and 12), 7.56 (d, *J* = 8.0 Hz, 2H, H-9 and 11).

^{19}F NMR (376 MHz, Chloroform-*d*) δ ppm = -62.44 (3F).

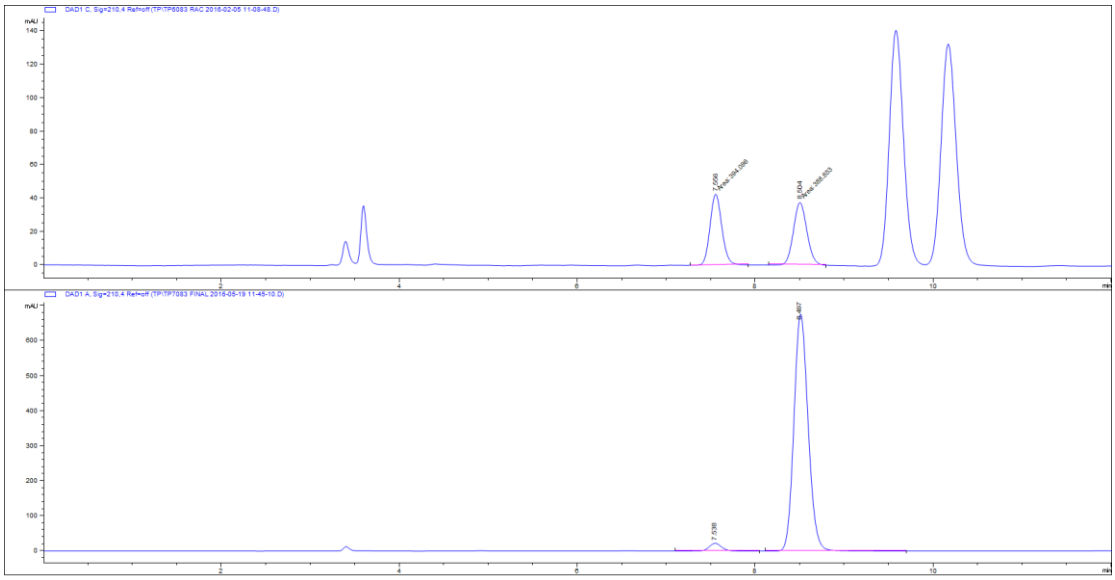
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.2 (C-21, 22 and 23), 41.4 (C-2), 43.0 and 43.7 (rotameric, C-5), 46.9 and 48.2 (rotameric, C-3), 79.7 (C-20), 124.2 (d, *J* = 272.0 Hz, C-13), 125.4 (C-9 and 11), 126.9 (C-6), 128.3 (C-8 and 12), 128.6 (C-1), 129.1 (d, *J* = 32.5 Hz, C-10), 146.3 (C-7), 154.6 (C-17).

IR (ATR) ν_{max} /cm^{-1} = 2980 (w), 1673 (m), 1617 (m), 1420 (m), 1365 (w), 1327 (s), 1238 (m), 1163 (s), 1123 (s), 1068 (m), 982 (w), 840 (w), 755 (w), 646 (w), 620 (w).

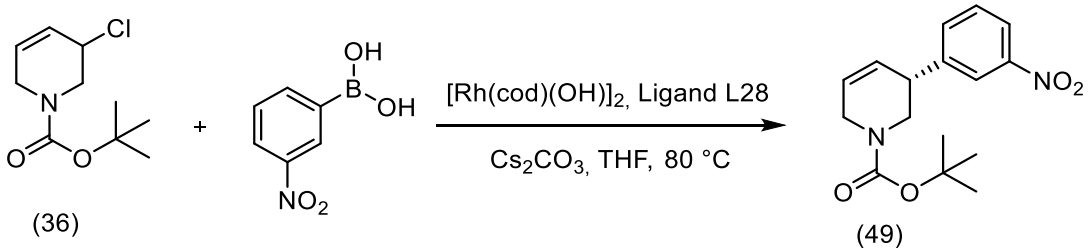
HRMS (ESI): *m*/*z* calc. for $C_{17}H_{20}O_2NF_3Na$ $[M+Na]^+$: 350.1338, found: 350.1338.

$[\alpha]^{25}_{589}$ = +111.0 (*c* 1.00, $CHCl_3$).

HPLC traces



(+)-(*R*)-*N*-*tert*-Butoxycarbonyl-5-(3-nitrophenyl)-3-piperidene 49:

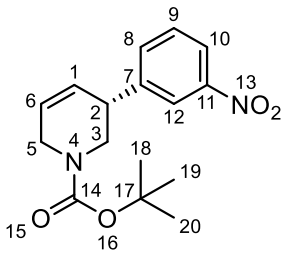


(36) (49)

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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 3-nitrobenzeneboronic acid (133 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (8/2) to obtain the pure product **49** in 64% yield (77.7 mg, 0.26 mmol) as a yellow oil.

Enantiomeric excess of 94% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 95: 5; λ = 210 nm; major enantiomer t_R = 25.4 mins; minor enantiomer t_R = 28.6 mins].

TLC R_f = 0.24 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.33 (rotameric m, 9H, H-18, 19 and 20), 3.31, 3.49 – 3.77 and 3.78 – 4.26 (rotameric m, 2H, H-3), 3.49 – 3.77 (m, 1H, H-2), 3.78 – 4.26 (rotameric m, 2H, H-5), 5.84 – 6.05 (m, 2H, H-1 and 6), 7.46 (t, *J* = 7.5 Hz, 1H, H-9), 7.55 (dt, *J* = 7.5, 1.5 Hz, 1H, H-8), 8.00 – 8.16 (m, 2H, H-10 and 12).

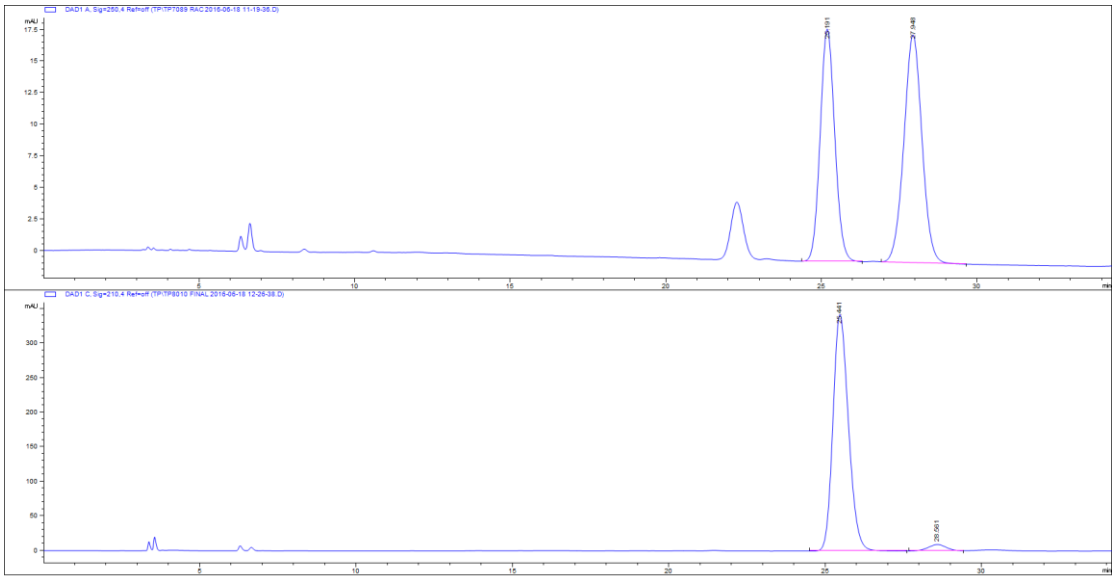
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.3 (C-18, 19 and 20), 41.1 (C-2), 43.0 and 43.7 (rotameric, C-5), 46.7 and 48.0 (rotameric, C-3), 79.9 (C-17), 121.9 (C-10), 122.7 (C-12), 126.5 (C-6), 127.3 (C-1), 129.3 (C-9), 134.2 (C-8), 144.4 (C-7), 148.4 (C-11), 154.6 (C-14).

IR (ATR) ν_{max} /cm^{-1} = 2976 (w), 2930 (w), 1695 (s), 1530 (s), 1477 (w), 1421 (m), 1390 (w), 1365 (m), 1349 (m), 1298 (w), 1239 (m), 1164 (m), 1120 (w), 1019 (w), 863 (w), 808 (w), 769 (w), 738 (w), 690 (w), 669 (w).

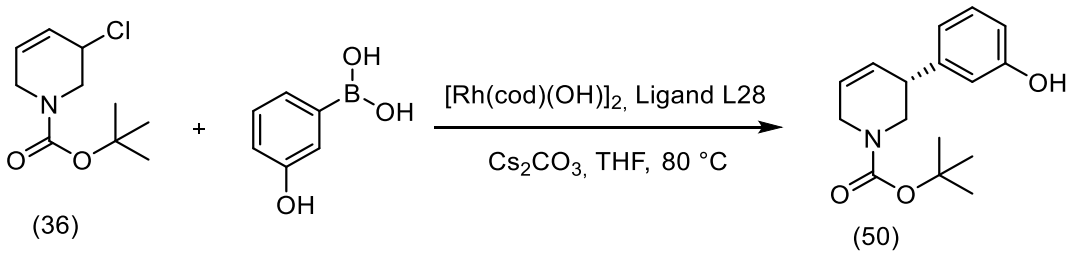
HRMS (CI): *m*/*z* calc. for $C_{16}H_{21}O_4N_2$ $[M+H]^+$: 305.1496, found: 305.1500.

$[\alpha]^{25}_{589}$ = +117.5 (*c* 1.00, $CHCl_3$).

HPLC traces



(+)-(*R*)-*N-tert*-Butoxycarbonyl-5-(3-hydroxyphenyl)-3-piperidene 50:

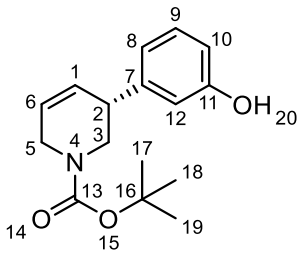


(36) (50)

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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 3-hydroxybenzeneboronic acid (110 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (7/3) to obtain the pure product **50** in 72% yield (78.9 mg, 0.29 mmol) as a colourless oil.

Enantiomeric excess of 94% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 95: 5; λ = 210 nm; major enantiomer t_R = 14.2 mins; minor enantiomer t_R = 20.3 mins].

TLC R_f = 0.29 (hexane/EtOAc (8/2)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.38 (rotameric m, 9H, H-17, 18 and 19), 3.01, 3.45, 3.67 and 3.88 – 4.20 (rotameric m, 2H, H-3), 3.45 (m, 1H, H-2), 3.80 and 3.88 – 4.20 (rotameric m, 2H, H-5), 5.87 (m, 2H, H-1 and 6), 6.65 – 6.80 (m, 3H, H-8, 10 and 12), 7.01 (s, 1H, H-20), 7.15 (t, *J* = 8.0 Hz, 1H, H-9).

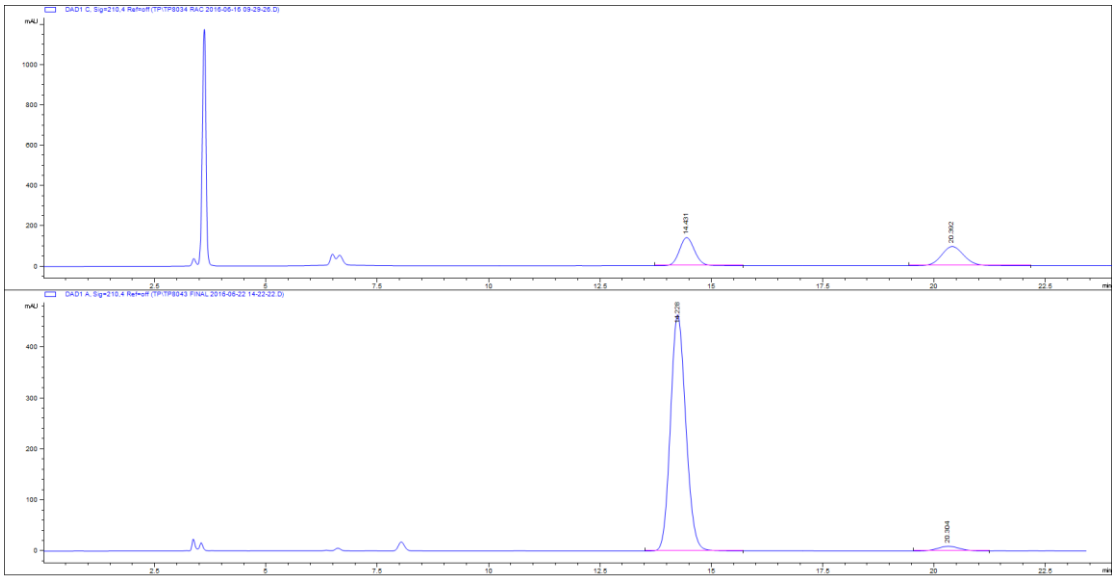
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.3 (C-17, 18 and 19), 41.4 (C-2), 43.0 and 43.7 (rotameric, C-5), 47.3 and 48.4 (rotameric, C-3), 80.0 (C-16), 113.9 (C-10), 114.9 (C-12), 119.8 (C-8), 125.6 (C-6), 128.2 (C-1), 129.6 (C-9), 143.7 (C-7), 155.2 (C-13), 156.5 (C-11).

IR (ATR) ν_{max} /cm^{-1} = 3333 (w), 2976 (w), 2929 (w), 1668 (s), 1648 (s), 1599 (m), 1588 (m), 1478 (m), 1455 (s), 1432 (s), 1391 (w), 1366 (m), 1301 (m), 1243 (s), 1157 (s), 1119 (m), 1021 (w), 953 (w), 862 (w), 813 (w), 784 (w), 754 (w), 702 (w).

HRMS (ESI): *m*/*z* calc. for $C_{16}H_{21}O_3NNa$ $[M+Na]^+$: 298.1414, found: 298.1414.

$[\alpha]^{25}_{589}$ = +126.2 (*c* 1.00, $CHCl_3$).

HPLC traces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7.5
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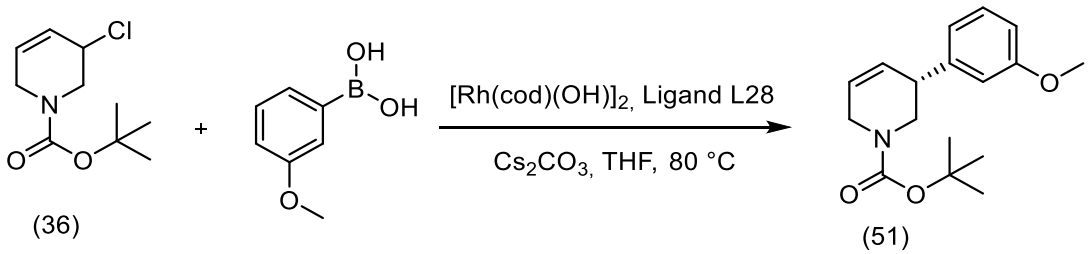
22.5
min

(+)-(*R*)-*N-tert*-Butoxycarbonyl-5-(3-methoxyphenyl)-3-piperidene 51:

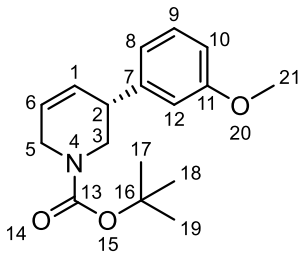


(36) (51)

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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 3-methoxybenzeneboronic acid (122 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (8/2) to obtain the pure product **51** in 79% yield (91.9 mg, 0.32 mmol) as a colourless oil.

Enantiomeric excess of 96% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 95: 5; λ = 210 nm; major enantiomer t_R = 10.8 mins; minor enantiomer t_R = 12.6 mins].

TLC R_f = 0.53 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.23 – 1.55 (rotameric m, 9H, H-17, 18 and 19), 3.01, 3.40, 3.67 – 3.89 and 4.05 (rotameric m, 2H, H-3), 3.42 – 3.58 (m, 1H, H-2), 3.78 (s, 3H, H-21), 3.67 – 3.89 and 4.05 (rotameric m, 2H, H-5), 5.88 (m, 2H, H-1 and 6), 6.73 – 6.82 (m, 3H, H-8, 10 and 12), 7.22 (t, *J* = 8.0 Hz, 1H, H-9).

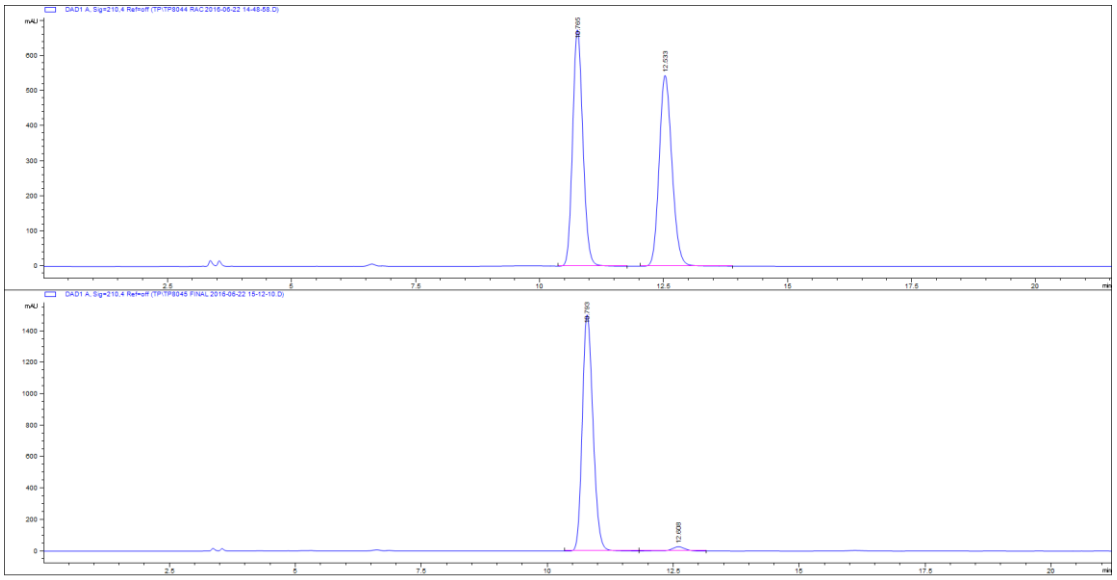
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.3 (C-17, 18 and 19), 41.5 (C-2), 42.9 and 43.6 (rotameric, C-5), 47.2 and 48.4 (rotameric, C-3), 55.2 (C-21), 79.5 (C-16), 112.1 (C-10), 113.6 (C-12), 120.3 (C-8), 125.9 (C-6), 128.2 (C-1), 129.4 (C-9), 143.9 (C-7), 154.7 (C-13), 159.7 (C-11).

IR (ATR) ν_{max} /cm^{-1} = 2975 (w), 1694 (s), 1600 (w), 1487 (w), 1454 (m), 1420 (m), 1365 (m), 1263 (m), 1238 (m), 1159 (m), 1112 (m), 1050 (w), 1018 (w), 960 (w), 866 (w), 779 (w), 750 (w), 702 (w).

HRMS (ESI): *m*/*z* calc. for $C_{17}H_{23}O_3NNa$ [M+Na]$^+$: 312.1570, found: 312.1572.

[α]$^{25}_{589}$ = +121.4 (*c* 1.00, $CHCl_3$).

HPLC traces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800
600
400
200
0
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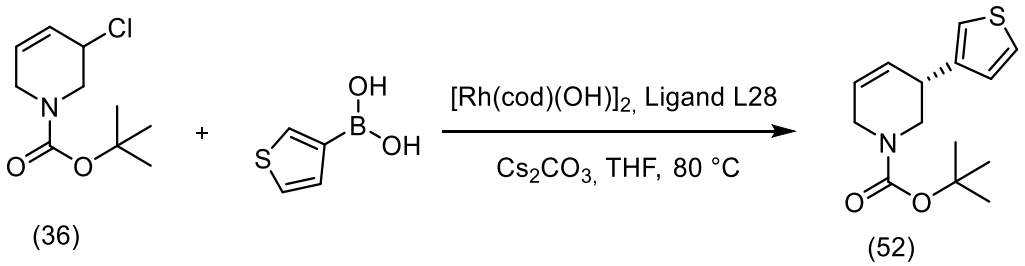
12.600
2.5
5
7.5
10
12.5
15
17.5
20
min

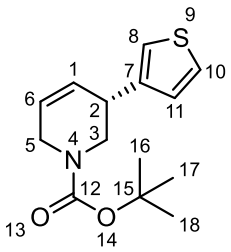
(+)-(*R*)-*N*-*tert*-Butoxycarbonyl-5-(3-thienyl)-3-piperidene 52:



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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 3-thienylboronic acid (102 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **52** in 74% yield (78.4 mg, 0.30 mmol) as a yellow oil.

Enantiomeric excess of 93% was determined by HPLC [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; major enantiomer t_R = 7.2 mins; minor enantiomer t_R = 7.8 mins].

TLC R_f = 0.43 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.20 – 1.46 (rotameric m, 9H, H-16, 17 and 18), 3.53 (rotameric m, 2H, H-3), 3.53 (m, 1H, H-2) 3.70 – 4.12 (rotameric, m, 2H, H-5), 5.66 – 5.92 (m, 2H, H-1 and 6), 6.86 – 6.99 (m, 2H, H-8 and 11), 7.17 – 7.23 (m, 1H, H-10).

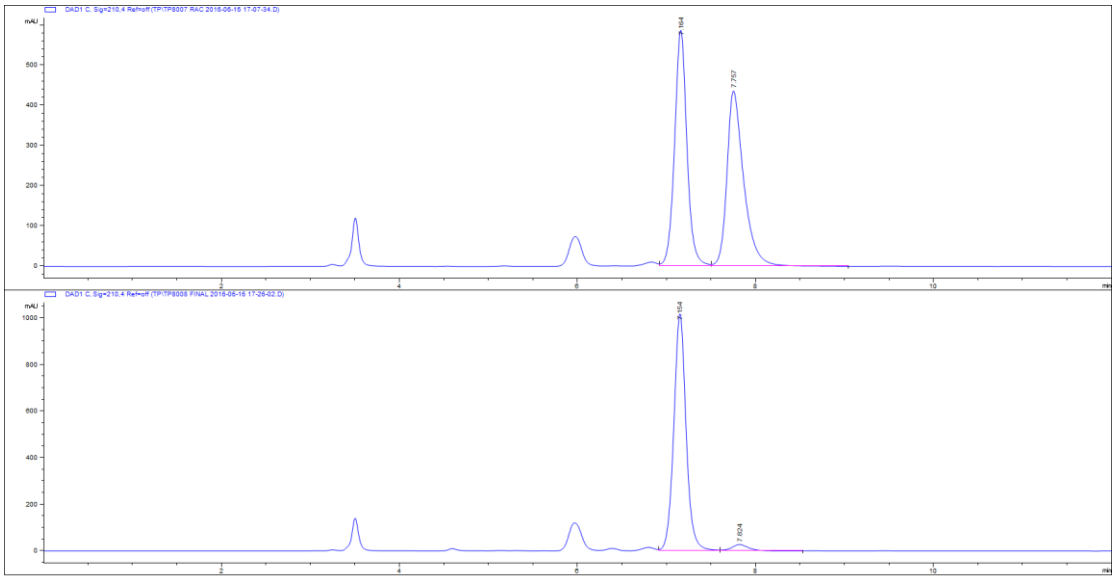
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.4 (C-17, 18 and 19), 36.9 (C-2), 42.9 (C-5), 47.5 (C-3), 79.5 (C-15), 121.1 (C-8), 125.5 (C-6), 125.6 (C-10), 127.3 (C-1), 128.1 (C-11), 142.9 (C-7), 154.7 (C-12).

IR (ATR) ν_{max} /cm^{-1} = 2976 (w), 1693 (s), 1477 (w), 1420 (m), 1365 (m), 1333 (w), 1300 (w), 1240 (m), 1172 (m), 1113 (w), 1012 (w), 959 (w), 857 (w), 781 (w), 739 (w), 648 (w).

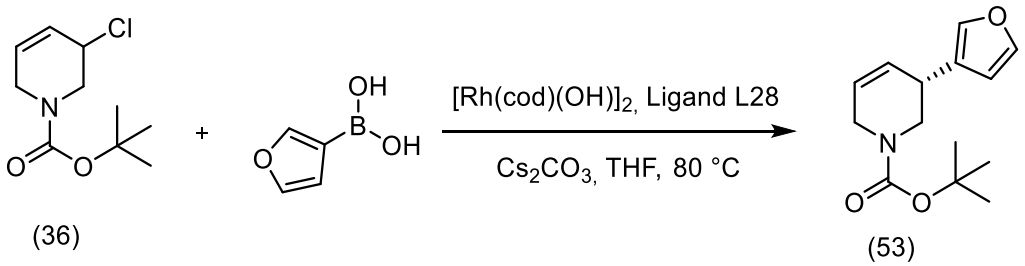
HRMS (ESI): *m*/*z* calc. for $C_{14}H_{19}O_2NSNa$ [M+Na]$^+$: 288.1029, found: 288.1028.

[α]$^{25}_{589}$ = +125.9 (*c* 1.00, $CHCl_3$).

HPLC traces



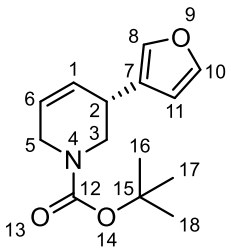
(+)-(*R*)-*N*-*tert*-Butoxycarbonyl-5-(3-furanyl)-3-piperidene 53:



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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 3-furanylboronic acid (89.5 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **53** in 53% yield (53.3 mg, 0.21 mmol) as a colourless oil.

Enantiomeric excess of 99% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; minor enantiomer t_R = 12.3 mins; major enantiomer t_R = 14.1 mins].

TLC R_f = 0.48 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.36 (rotameric m, 9H, H-16, 17 and 18), 3.15, 3.29 – 3.55, 3.61 and 3.75 – 4.14 (rotameric m, 2H, H-3), 3.29 – 3.55 (m, 1H, H-2), 3.75 – 4.14 (rotameric m, 2H, H-5), 5.70 – 5.90 (m, 2H, H-1 and 6), 6.29 (m, 1H, H-11), 7.19 – 7.25 (m, 1H, H-8), 7.36 (m, 1H, H-10).

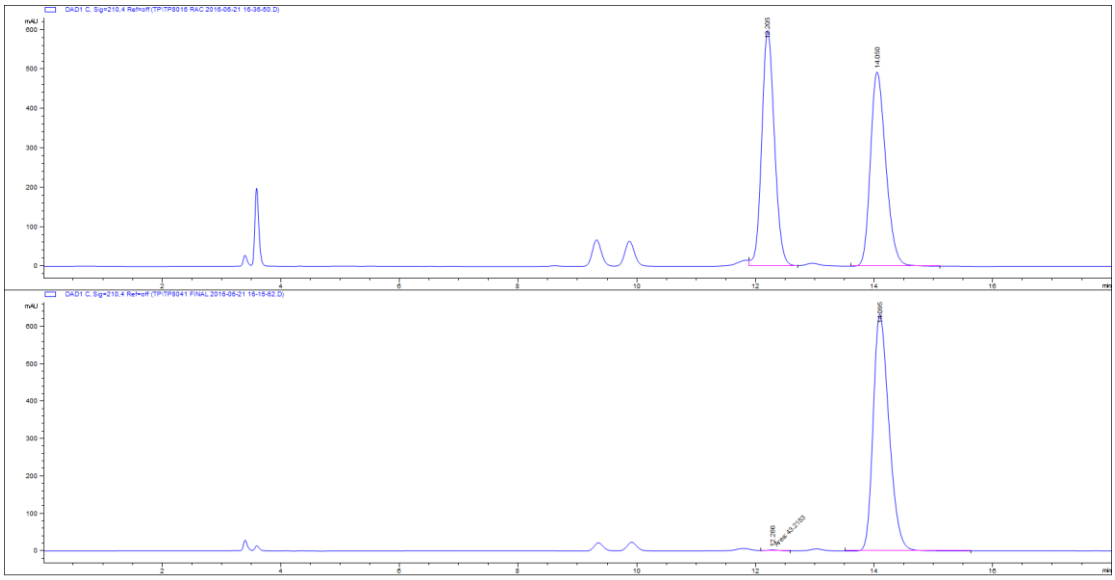
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.0 – 28.6 (m, C-16, 17 and 18), 32.5 (C-2), 42.8 and 43.6 (rotameric, C-5), 45.8 and 47.0 (rotameric, C-3), 79.6 (C-15), 110.0 (C-11), 124.6 and 125.4 (rotameric, C-6), 125.9 (C-7), 127.8 and 128.6 (rotameric, C-1), 139.4 (C-8), 143.0 (C-10), 154.8 (C-12).

IR (ATR) ν_{max} /cm^{-1} = 2976 (w), 1694 (s), 1478 (w), 1420 (m), 1391 (w), 1366 (m), 1334 (w), 1302 (w), 1238 (m), 1171 (m), 1115 (w), 1029 (w), 967 (w), 873 (w), 786 (w), 743 (w), 641 (w).

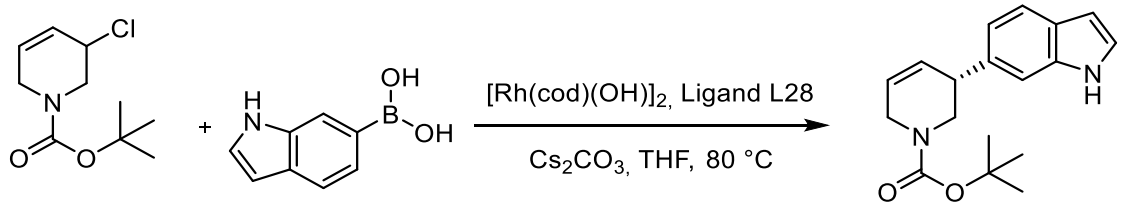
HRMS (CI): *m*/*z* calc. for $C_{14}H_{20}O_3N$ $[M+H]^+$: 250.1438, found: 250.1442.

$[\alpha]^{25}_{589}$ = +105.9 (*c* 1.00, $CHCl_3$).

HPLC traces



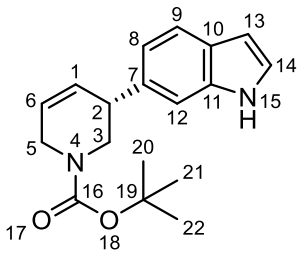
(+)-(*R*)-*N-tert*-Butoxycarbonyl-5-(6-indolyl)-3-piperidene 56:



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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 6-indolylboronic acid (129 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (1/1) to obtain the pure product **56** in 80% yield (95.4 mg, 0.32 mmol) as white crystals.

Enantiomeric excess of 91% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 95: 5; λ = 210 nm; major enantiomer t_R = 9.6 mins; minor enantiomer t_R = 14.5 mins].

TLC R_f = 0.77 (hexane/EtOAc (7/3)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.17 – 1.62 (rotameric m, 9H, H-20, 21 and 22), 3.03, 3.40 – 3.58, 3.74 – 3.96 and 3.97 – 4.34 (rotameric m, 2H, H-3), 3.65 (m, 1H, H-2), 3.74 – 3.96 and 3.97 – 4.34 (rotameric m, 2H, H-5), 5.82 – 6.03 (m, 2H, H-1 and 6), 6.53 (m, 1H, H-13), 7.01 (d, *J* = 8.0 Hz, 1H, H-8), 7.14 (m, 1H, H-14), 7.19 (m, 1H, H-12), 7.61 (d, *J* = 8.0 Hz, 1H, H-9), 8.54 (s, 1H, H-15).

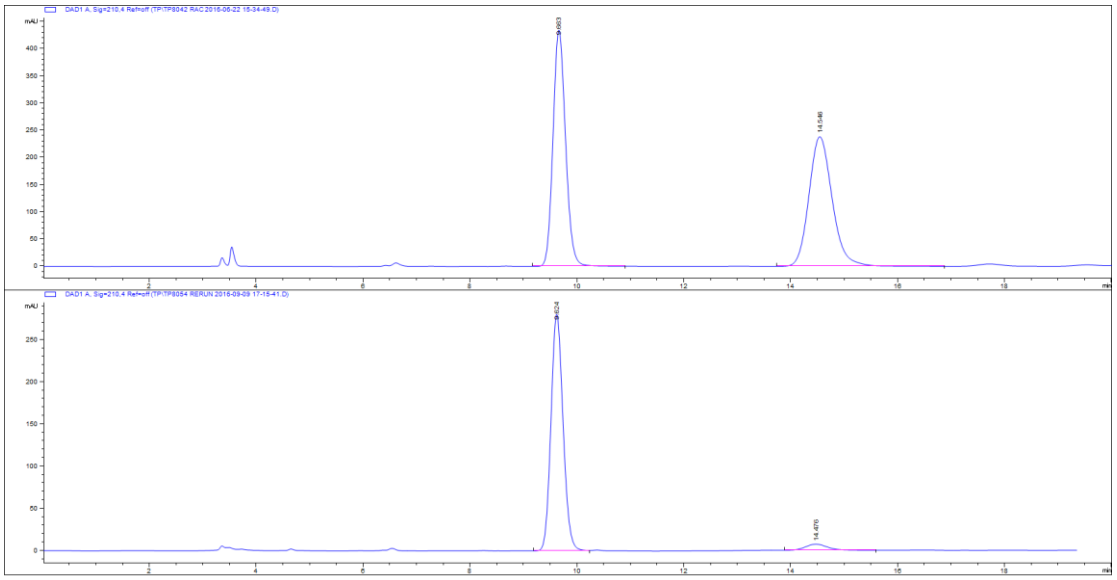
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.2 (C-20, 21 and 22), 41.8 (C-2), 43.1 and 43.7 (rotameric, C-5), 48.0 and 49.1 (rotameric, C-3), 79.5 (C-19), 102.1 (C-13), 110.3 (C-12), 120.2 (C-8), 120.6 (C-9), 124.4 (C-14), 125.4 (C-6), 126.8 (C-10), 129.2 (C-1), 135.9 (C-11), 136.2 (C-7), 155.0 (C-16).

IR (ATR) ν_{max} /cm^{-1} = 3316 (w), 2975 (w), 2924 (w), 1677 (s), 1424 (m), 1358 (w), 1299 (w), 1246 (m), 1165 (m), 1112 (w), 963 (w), 860 (w), 812 (w), 762 (w), 729 (w).

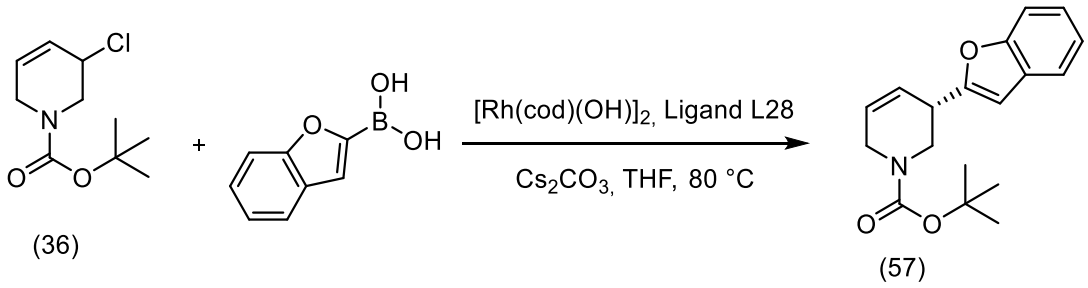
HRMS (CI): *m*/*z* calc. for $C_{18}H_{23}O_2N_2$ $[M+H]^+$: 299.1754, found: 299.1756.

$[\alpha]^{25}_{589}$ = +119.5 (*c* 1.00, $CHCl_3$).

HPLC traces



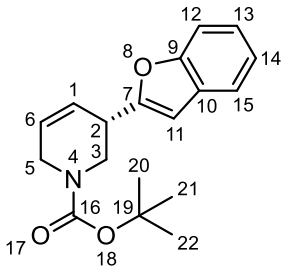
(+)-(*R*)-*N*-*tert*-Butoxycarbonyl-5-(2-benzofuranyl)-3-piperidene 57:



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 (130 mg, 0.40 mmol, 1.00 eq) were stirred in THF (2.0 mL) at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (87.1 mg, 0.40 mmol, 1.00 eq) in THF (0.75 mL) was then added *via* syringe and the flask rinsed with THF (0.25 mL) followed by a second solution of 2-benzofuranylboronic acid (130 mg, 0.80 mmol, 2.00 eq) in THF (0.75 mL), which was also added *via* syringe and the flask rinsed with THF (0.25 mL). The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with pentane/Et_2O (9/1) to obtain the pure product **57** in 79% yield (95.0 mg, 0.32 mmol) as a yellow oil.

Enantiomeric excess of 99% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; minor enantiomer t_R = 12.8 mins; major enantiomer t_R = 14.2 mins].

TLC R_f = 0.41 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.31 (rotameric m, 9H, H-20, 21 and 22), 3.52 – 3.71 and 3.89 – 4.13 (rotameric m, 2H, H-3), 3.52 – 3.71 (m, 1H, H-2), 3.72 – 3.89, 3.89 – 4.13 and 4.19 – 4.35 (rotameric m, 2H, H-5), 5.96 (m, 2H, H-1 and 6), 6.45 (m, 1H, H-11), 7.18 (td, *J* = 7.5, 1.0 Hz, 1H, H-14), 7.23 (td, *J* = 7.5, 1.5 Hz, 1H, H-13), 7.43 (m, 1H, H-12), 7.45 – 7.50 (m, 1H, H-15).

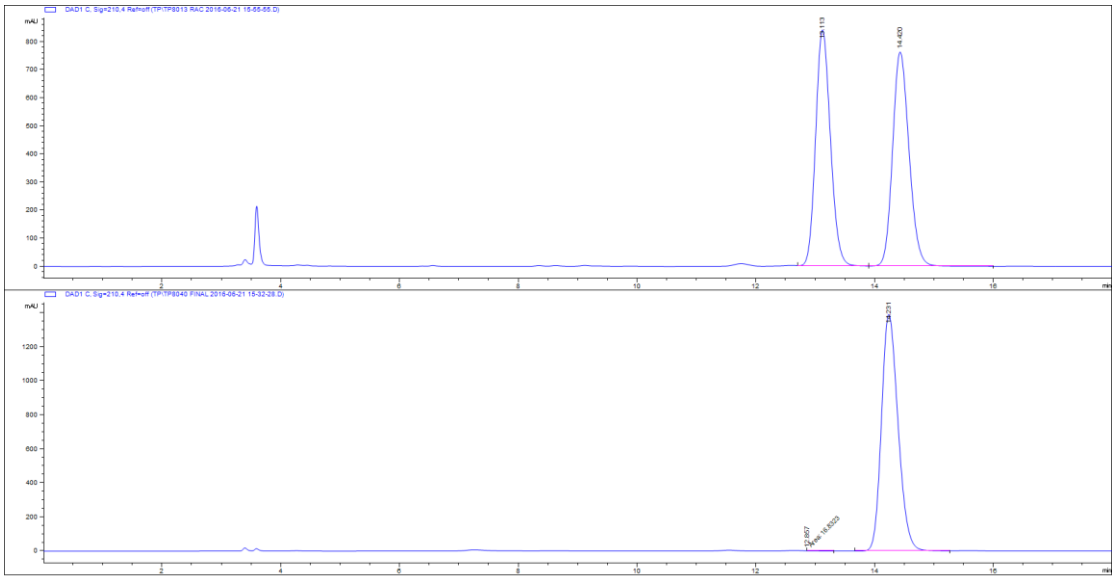
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.0 (C-20, 21 and 22), 35.6 (C-2), 42.9 and 43.6 (rotameric, C-5), 44.9 and 45.0 (rotameric, C-3), 79.5 (C-19), 103.7 (C-11), 110.9 (C-12), 120.6 (C-15), 122.6 (C-14), 123.6 (C-13), 124.6 (C-6), 127.5 (C-1), 128.6 (C-10), 154.6 (C-16), 154.9 (C-7), 158.1 (C-9).

IR (ATR) ν_{max} /cm^{-1} = 2976 (w), 1695 (s), 1585 (w), 1475 (w), 1455 (m), 1422 (m), 1391 (w), 1365 (m), 1298 (w), 1241 (m), 1169 (m), 1114 (w), 1017 (w), 929 (w), 862 (w), 803 (w), 750 (m), 647 (w).

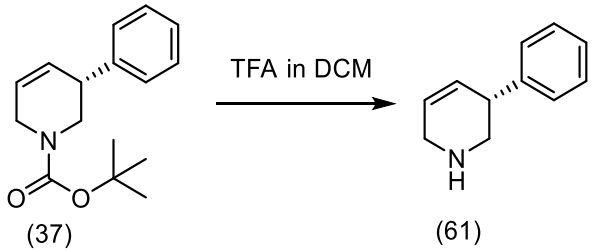
HRMS (ESI): *m*/*z* calc. for $C_{18}H_{21}O_3NNa$ $[M+Na]^+$: 322.1414, found: 322.1413.

$[\alpha]^{25}_{589}$ = +170.6 (*c* 1.00, $CHCl_3$).

HPLC traces



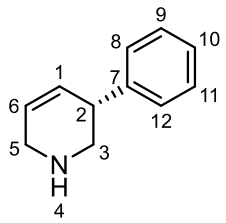
(+)-(*R*)-5-Phenyl-3-piperidene 61 :



(37) (61)

In a 10 mL round bottomed flask, (*R*)-*N*-*tert*-butoxycarbonyl-5-(phenyl)-3-piperidene **37** (25.9 mg, 0.10 mmol, 1.00 eq) was stirred in DCM (2.0 mL) under Argon. The mixture was cooled down to 0 °C. Trifluoroacetic acid (2.0 mL) was then added dropwise to the solution. The mixture was left warming up to room temperature and the reaction was stirred for 90 mins. The solution was then diluted in DCM (10 mL), previous to the addition of $NaHCO_3$ (1M, 10 mL). The organic layer was separated from the aqueous layer, which was extracted with EtOAc (10 mL x3). Combined organic layers were washed with brine (10 mL x2), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (DCM/MeOH (9/1)) led to the pure product **61** in 87% yield (13.8 mg, 0.09 mmol) as a colourless oil.

TLC R_f = 0.40 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 2.79 (m, 1H, H-3'), 3.25 – 3.34 (m, 1H, H-3''), 3.42 (m, 2H, H-5), 3.45 – 3.51 (m, 1H, H-2), 5.84 – 5.91 (m, 1H, H-1), 5.92 – 6.00 (m, 1H, H-6), 7.20 – 7.25 (m, 3H, H-8, 10 and 12), 7.29 – 7.35 (m, 2H, H-9 and 11).

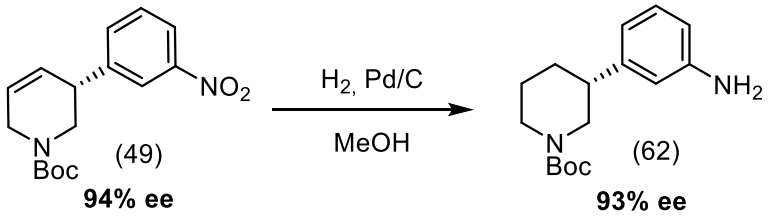
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 41.7 (C-2), 44.7 (C-5), 51.5 (C-3), 126.5 (C-10), 127.9 (C-8 and 12), 128.0 (C-6), 128.5 (C-9 and 11), 128.8 (C-1), 142.0 (C-7).

IR (ATR) ν_{max} /cm^{-1} = 3414 (w), 3027 (w), 2920 (s), 2852 (m), 2357 (w), 1659 (w), 1454 (m), 1258 (w), 1195 (w), 1120 (w), 1080 (w), 1021 (w), 902 (w), 804 (w), 757 (m), 697 (s).

HRMS (ESI): *m*/*z* calc. for $C_{11}H_{14}N$ $[M+H]^+$: 160.1121, found: 160.1121.

$[\alpha]^{25}_{589}$ = +76.6 (*c* 0.50, $CHCl_3$).

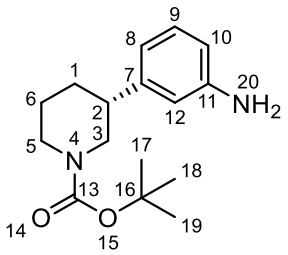
(+)-(*R*)-*N*-*tert*-Butoxycarbonyl-3-(3-aniline)-piperidine 62:



A solution of (*R*)-*N*-*tert*-butoxycarbonyl-5-(3-nitrophenyl)-3-piperidene **49** (60.9 mg, 0.20 mmol, 1.00 eq), Pd (10% on C, 21.3 mg, 0.20 mmol, 1.00 eq) in MeOH (4.0 mL) was first purged with a 30 s cycle of vacuum/argon and then purged with H_2. The mixture was stirred for 16 hrs at room temperature under H_2 atmosphere (1 bar). The resulting mixture was then filtered over Celite®, washed with EtOAc (20 mL) and evaporated *in vacuo*. Purification by chromatography (pentane/Et_2O (1/1)) gave the desired product **62** in 43% (24.9 mg, 0.09 mmol) as white crystals.

Enantiomeric excess of 93% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 80: 20; λ = 210 nm; major enantiomer t_R = 10.3 mins; minor enantiomer t_R = 14.7 mins].

TLC R_f = 0.50 (hexane/EtOAc (6/4)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.47 (s, 9H, H-17, 18 and 19), 1.51 – 1.65 (m, 2H, H-1' and 6'), 1.74 (m, 1H, H-6''), 1.96 – 2.04 (m, 1H, H-1''), 2.57 (m, 1H, H-2), 2.70 (m, 2H, H-3' and 5'), 3.54 (s, 2H, H-20), 4.15 (m, 2H, H-3'' and 5''), 6.53 – 6.58 (m, 2H, H-10 and 12), 6.63 (dt, *J* = 7.5, 1.5 Hz, 1H, H-8), 7.06 – 7.13 (m, 1H, H-9).

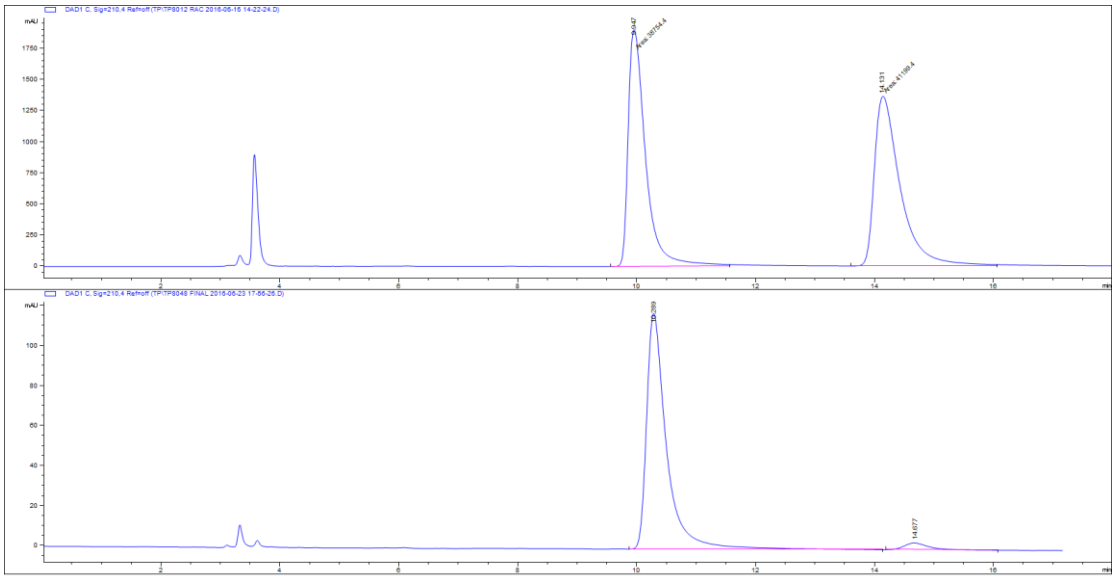
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 25.5 (C-6), 28.5 (C-17, 18 and 19), 31.7 (C-1), 42.6 (C-2), 44.0 (C-5), 50.7 (C-3), 79.4 (C-16), 113.4 (C-10), 114.0 (C-12), 117.3 (C-8), 129.4 (C-9), 144.9 (C-7), 146.5 (C-11), 154.9 (C-13).

IR (ATR) ν_{max} /cm^{-1} = 3363 (w), 2975 (w), 2933 (w), 2865 (w), 1680 (s), 1607 (m), 1422 (m), 1365 (m), 1302 (w), 1267 (m), 1166 (m), 1148 (m), 995 (w), 952 (w), 862 (w), 783 (w), 701 (w).

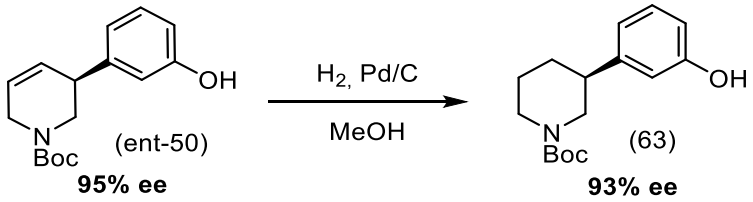
HRMS (ESI): *m*/*z* calc. for $C_{16}H_{24}O_2N_2Na$ [M+Na]$^+$: 299.1730, found: 299.1731.

[α]$^{25}_{589}$ = +95.3 (*c* 1.00, $CHCl_3$).

HPLC traces



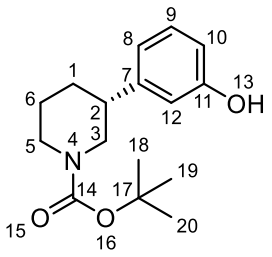
(–)-(*S*)-*N-tert*-Butoxycarbonyl-3-(3-hydroxyphenyl)-piperidine 63:



A solution of (*S*)-*N-tert*-butoxycarbonyl-5-(3-hydroxyphenyl)-3-piperidene **ent-50** (333 mg, 1.21 mmol, 1.00 eq), Pd (10% on C, 129 mg, 1.21 mmol, 1.00 eq) in MeOH (30 mL) was first purged with a 30 s cycle of vacuum/argon and then purged with H_2. The mixture was stirred for 16 hrs at room temperature under H_2 atmosphere (1 bar). The resulting mixture was then filtered over Celite®, washed with EtOAc (20 mL) and evaporated *in vacuo*. Purification by chromatography (hexane/EtOAc/Et_3N (70/29/1)) gave the desired product **63** in 82% yield (274 mg, 0.99 mmol) as a white solid.

Enantiomeric excess of 93% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 80: 20; λ = 210 nm; minor enantiomer t_R = 7.3 mins; major enantiomer t_R = 8.9 mins].

TLC R_f = 0.26 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.48 (s, 9H, H-18, 19 and 20), 1.58 (m, 2H, H-1' and 6'), 1.74 (m, 1H, H-6''), 2.00 (m, 1H, H-1''), 2.61 (m, 1H, H-2), 2.72 (m, 2H, H-3' and 5'), 3.99 – 4.30 (m, 2H, H-3'' and 5''), 6.02 (s, 1H, H-13), 6.71 (m, H-10 and 12), 6.76 (dt, *J* = 8.0, 1.0 Hz, 1H, H-8), 7.14 (t, *J* = 8.0 Hz, 1H, H-9).

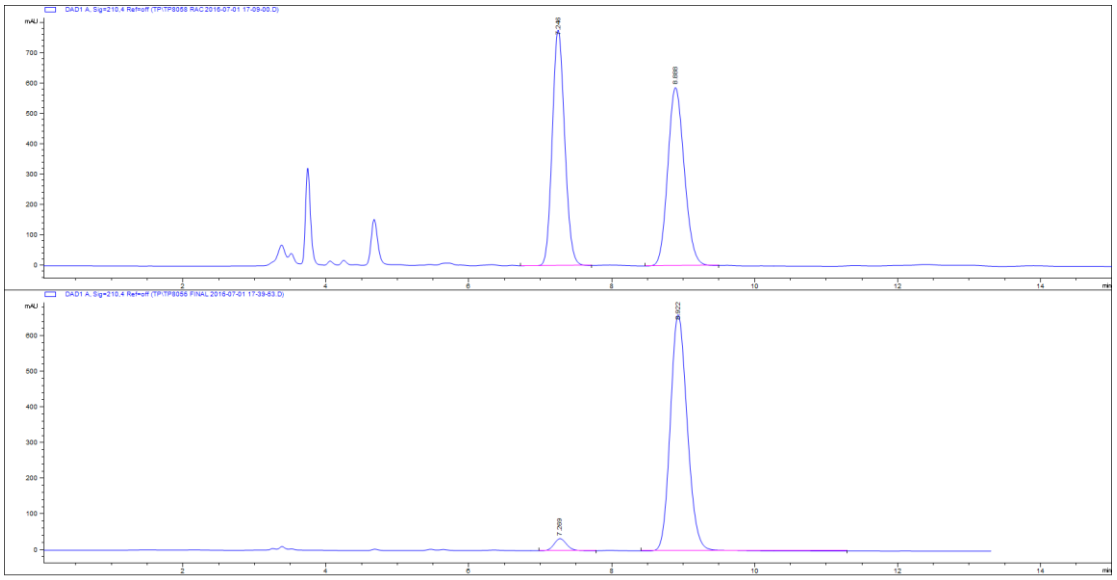
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 25.5 (C-6), 28.5 (C-18, 19 and 20), 31.6 (C-1), 42.4 (C-2), 44.7 (C-5), 50.5 (C-3), 79.9 (C-17), 113.6 (C-10), 114.3 (C-12), 119.1 (C-8), 129.6 (C-9), 145.1 (C-7), 155.1 (C-14), 156.1 (C-11).

IR (ATR) ν_{max} /cm^{-1} = 3325 (w), 2976 (w), 2934 (w), 2858 (w), 1660 (s), 1601 (m), 1588 (m), 1477 (m), 1432 (m), 1393 (w), 1367 (m), 1268 (m), 1159 (s), 1028 (w), 997 (w), 953 (w), 862 (w), 816 (w), 784 (w), 764 (w), 700 (w).

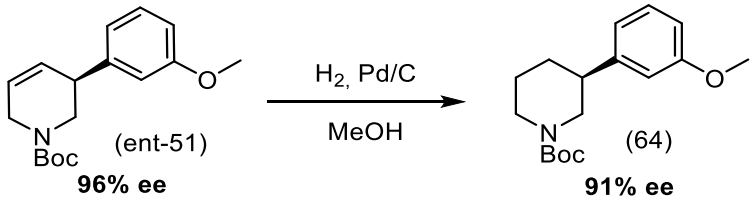
HRMS (ESI): *m*/*z* calc. for $C_{16}H_{23}O_3NNa$ $[M+Na]^+$: 300.1570, found: 300.1572.

$[\alpha]^{25}_{589}$ = –55.4 (*c* 1.00, $CHCl_3$).

HPLC traces



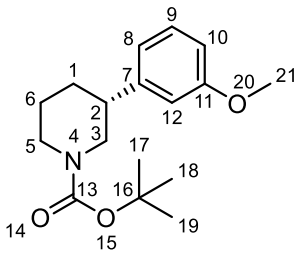
(–)-(*S*)-*N-tert*-Butoxycarbonyl-3-(3-methoxyphenyl)-piperidine 64:



A solution of (*S*)-*N-tert*-butoxycarbonyl-5-(3-methoxyphenyl)-3-piperidene **ent-51** (425 mg, 1.47 mmol, 1.00 eq), palladium (10% weight on carbon, 156 mg, 1.47 mmol, 1.00 eq) in MeOH (30 mL) was first purged with a 30s cycle of vacuum/argon and then purged with H_2. The mixture was stirred for 16 hrs at room temperature under H_2 atmosphere (1 bar). The resulting mixture was then filtered over Celite®, washed with EtOAc (20 mL) and evaporated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc/Et_3N (95/4/1)) gave the desired product **64** in 77% yield (330 mg, 1.13 mmol) as a colourless oil.

Enantiomeric excess of 91% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 95: 5; λ = 210 nm; minor enantiomer t_R = 14.5 mins; major enantiomer t_R = 17.1 mins].

TLC R_f = 0.65 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.47 (s, 9H, H-17, 18 and 19), 1.49 – 1.69 (m, 2H, H-1’ and 6’), 1.75 (m, 1H, H-6’’), 1.97 – 2.07 (m, 1H, H-1’’), 2.44 – 2.98 (m, 3H, H-2, 3’ and 5’), 3.80 (s, 3H, H-21), 4.16 (m, 2H, H-3’’ and 5’’), 6.75 – 6.79 (m, 2H, H-10 and 12), 6.83 (dt, *J* = 7.5, 1.0 Hz, 1H, H-8), 7.19 – 7.30 (m, 1H, H-9).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 25.5 (C-6), 28.5 (C-17, 18 and 19), 31.8 (C-1), 42.6 (C-2), 44.3 (C-5), 50.5 (C-3), 55.2 (C-21), 79.5 (C-16), 111.6 (C-10), 113.1 (C-12), 119.5 (C-8), 129.5 (C-9), 145.3 (C-7), 154.8 (C-13), 159.7 (C-11).

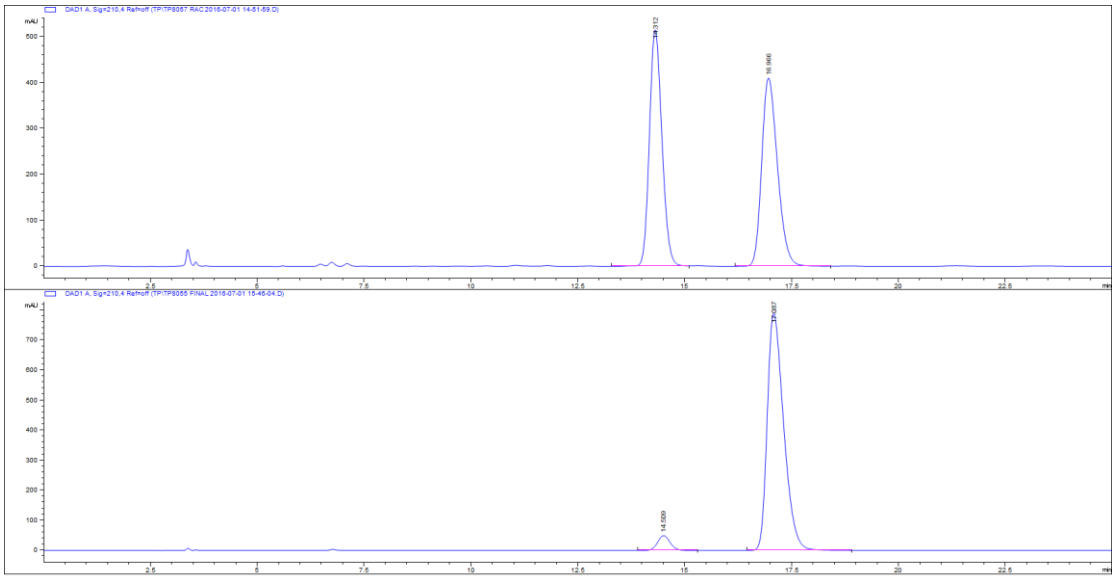
IR (ATR) ν_{max} /cm^{-1} = 2974 (w), 2934 (w), 2856 (w), 1691 (s), 1602 (w), 1584 (w), 1466 (w), 1419 (m), 1365 (w), 1285 (w), 1262 (m), 1155 (m), 1049 (w), 987 (w), 948 (w), 864 (w), 780 (w), 700 (w).

HRMS (ESI): *m*/*z* calc. for $C_{17}H_{25}O_3NNa$ $[M+Na]^+$: 314.1727, found: 314.1728.

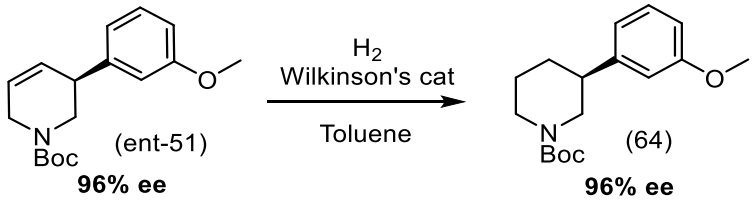
$[\alpha]^{25}_{589}$ = –46.4 (*c* 1.00, $CHCl_3$).

Data consistent with previously reported values.[229]

HPLC traces


DAD1 A, Sig=210,4 Refsoff (TP\TP8057 RAC 2016-07-01 14-51-59.D)
mAU
500
400
300
200
100
0
14.312
16.966
2.5
5
7.5
10
12.5
15
17.5
20
22.5
min
DAD1 A, Sig=210,4 Refsoff (TP\TP8055 FINAL 2016-07-01 15-46-04.D)
mAU
700
600
500
400
300
200
100
0
14.509
17.057
2.5
5
7.5
10
12.5
15
17.5
20
22.5
min

Example for the hydrogenation procedure using Wilkinson's catalyst:

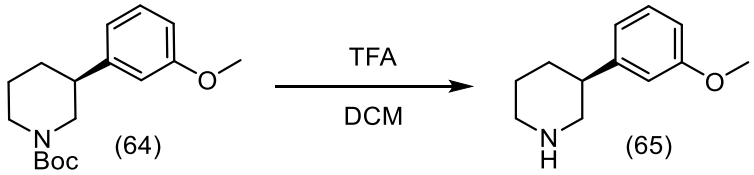


A solution of (*S*)-*N*-*tert*-butoxycarbonyl-5-(3-methoxyphenyl)-3-piperidene **ent-51** (394 mg, 1.36 mmol, 1.00 eq), Wilkinson's catalyst (231 mg, 0.25 mmol, 0.18 eq) in toluene (7.0 mL) was first purged with a 30s cycle of vacuum/argon and then purged with H_2. The mixture was stirred overnight at room temperature under H_2 atmosphere (1 bar) before the addition of SiO_2 (20 mg). The solvent was then carefully evaporated and the solid directly loaded into a chromatographic column eluting with hexane/EtOAc (9/1) to obtain the pure product **64** in 97% yield (383 mg, 1.31 mmol) as a colourless oil.

Enantiomeric excess of 96% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 95: 5; λ = 210 nm; minor enantiomer t_R = 14.5 mins; major enantiomer t_R = 17.1 mins].

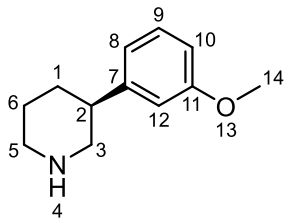
Data consistent with previously reported values.[229]

(+)-(*S*)-3-(3-Methoxyphenyl)-piperidine 65 :



In a 10 mL round bottomed flask, (*S*)-*N*-*tert*-butoxycarbonyl-3-(3-methoxyphenyl)-piperidine **64** (0.37 g, 1.26 mmol, 1.00 eq) was stirred in DCM (9.6 mL) under argon. The mixture was cooled down to 0 °C. Trifluoroacetic acid (0.96 mL, 12.6 mmol, 10.00 eq) was then added dropwise to the solution. The mixture was left warming up to room temperature and the reaction was stirred for 30 mins. The solution was then diluted in DCM (20 mL), previous to the addition of a saturated solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (20 mL x2) and the combined organic layers were washed with a saturated solution of K_2CO_3 (20 mL x2), brine (10 mL x2), dried over $MgSO_4$ and concentrated *in vacuo*. The pure product **65** was obtained in 88% yield (0.21 g, 1.11 mmol) as orange oil.

TLC R_f = 0.33 (DCM/MeOH (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.51 – 1.66 (m, 2H, H-1' and 6'), 1.78 (m, 2H, H-4 and 6''), 2.00 (m, 1H, H-1''), 2.58 – 2.70 (m, 3H, H-2, 3' and 5'), 3.06 – 3.14 (m, 1H, H-5''), 3.16 (m, 1H, H-3''), 3.80 (s, 3H, H-14), 6.72 – 6.78 (m, 2H, H-10 and 12), 6.81 (dt, *J* = 7.5, 1.0 Hz, 1H, H-8), 7.22 (t, *J* = 7.5 Hz, 1H, H-9).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 27.1 (C-6), 32.1 (C-1), 44.4 (C-2), 46.7 (C-5), 54.1 (C-3), 55.2 (C-14), 111.2 (C-10), 113.2 (C-12), 119.5 (C-8), 129.3 (C-9), 146.7 (C-7), 159.6 (C-11).

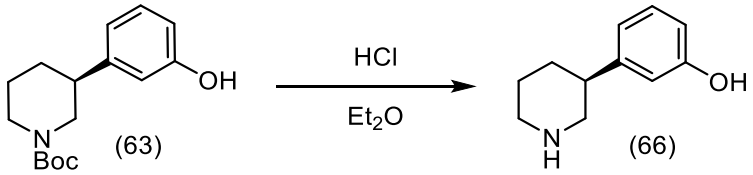
IR (ATR) ν_{max} /cm^{-1} = 3313 (br), 3000 (w), 2931 (s), 2851 (m), 1603 (s), 1585 (m), 1490 (m), 1464 (m), 1435 (m), 1267 (s), 1162 (m), 1046 (m), 931 (w), 859 (w), 783 (m), 754 (w), 699 (m).

HRMS (ESI): *m*/*z* calc. for $C_{12}H_{18}ON$ $[M+H]^+$: 192.1383, found: 192.1382.

$[\alpha]^{25}_{589}$ = +6.1 (*c* 1.00, $CHCl_3$).

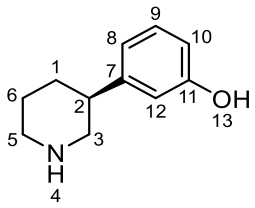
Data consistent with previously reported values.[229]

(+)-(*S*)-3-(3-Hydroxyphenyl)-piperidine 66 :



In a 10 mL round bottomed flask, (*S*)-*N*-*tert*-butoxycarbonyl-3-(3-hydroxyphenyl)-piperidine **63** (175 mg, 0.63 mmol, 1.00 eq) was stirred in HCl (6.3 mL, 1M in Et_2O, 6.30 mmol, 10.0 eq) under argon. The reaction was stirred overnight at room temperature. The formed precipitate was then filtered, washed with Et_2O (10 mL x2) and concentrated *in vacuo*. The pure product **66** was obtained in 68% yield (76.2 mg, 0.43 mmol) as a white solid.

TLC R_f = 0.42 (DCM/MeOH (8/2)).



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.65 (m, 1H, H-1'), 1.83 (m, 3H, H-1'' and 6), 2.78 – 3.02 (m, 3H, H-2, 3' and 5'), 3.24 (m, 2H, H-3'' and 5''), 6.68 (m, 3H, H-8, 10 and 12), 7.05 – 7.21 (m, 1H, H-9), 9.13 (s, 1H, H-4), 9.48 (s, 1H, H-13).

^{13}C NMR (101 MHz, DMSO-d_6) δ ppm = 22.7 (C-6), 29.9 (C-1), 39.6 (C-2), 43.3 (C-5), 48.5 (C-3), 114.3 (C-10), 114.4 (C-12), 117.9 (C-8), 130.1 (C-9), 143.7 (C-7), 158.1 (C-11).

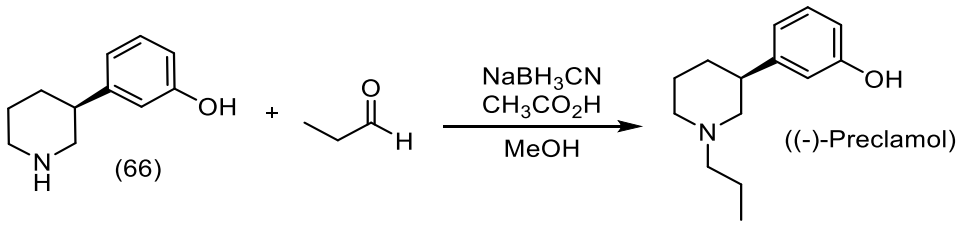
IR (ATR) ν_{max} /cm^{-1} = 3202 (w), 2951 (w), 2806 (w), 2388 (w), 2348 (w), 2180 (w), 2116 (w), 1615 (w), 1586 (m), 1492 (w), 1471 (w), 1446 (w), 1328 (w), 1283 (w), 1261 (w), 1215 (w), 1167 (w), 1066 (w), 1038 (w), 978 (w), 942 (w), 914 (w), 882 (w), 859 (w), 789 (s), 759 (w), 699 (s), 673 (w), 640 (w).

HRMS (ESI): *m*/*z* calc. for $C_{11}H_{16}ON$ $[M+H]^+$: 178.1226, found: 178.1225.

$[\alpha]^{25}_{589}$ = +6.6 (*c* 1.00, DMSO).

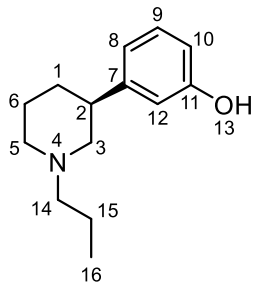
Data consistent with previously reported values.[225]

(–)-(*S*)-*N*-Propyl-3-(3-hydroxyphenyl)-piperidine ((–)-Preclamol) :



To a solution of (*S*)-3-(3-hydroxyphenyl)-piperidine **66** (40.8 mg, 0.23 mmol, 1.00 eq) in MeOH (2.0 mL) were added freshly distilled propanal (33.0 μL, 0.46 mmol, 2.00 eq) and $NaBH_3CN$ (13.1 μL, 0.25 mmol, 1.10 eq) and CH_3CO_2H (6.9 μL, 0.12 mmol, 0.50 eq). The reaction mixture was stirred overnight at room temperature, then quenched with water (10 mL) and extracted with EtOAc (10 mL x2). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (DCM/MeOH/Et_3N (90/9/1)) to give (–)-Preclamol in 99% yield (50.3mg, 0.23 mmol) as a colourless oil.

TLC R_f = 0.31 (DCM/MeOH (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.79 (t, *J* = 7.5 Hz, 3H, H-16), 1.35 – 1.57 (m, 3H, H-1' and 6), 1.63 – 1.79 (m, 2H, H-15), 1.93 (m, 3H, H-1'', 3' and 5'), 2.30 (m, 2H, H-14), 2.86 (tt, *J* = 11.5, 3.5 Hz, 1H, H-2), 3.01 (dt, *J* = 12.0, 2.5 Hz, 1H, H-5''), 3.16 (dd, *J* = 11.5, 3.5 Hz, 1H, H-3''), 6.60 – 6.67 (m, 2H, H-8 and 10), 6.71 (t, *J* = 2.0 Hz, 1H, H-12), 7.10 (t, *J* = 8.0 Hz, 1H, H-9).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 12.1 (C-16), 19.2 (C-6), 25.2 (C-15), 29.9 (C-1), 41.8 (C-2), 54.0 (C-5), 61.2 (C-14), 61.4 (C-3), 114.3 (C-10), 114.7 (C-12), 117.4 (C-8), 129.8 (C-9), 145.4 (C-7), 157.0 (C-11).

IR (ATR) ν_{max} /cm^{-1} = 3045 (w), 2934 (s), 2876 (s), 2813 (m), 2363 (w), 1737 (w), 1589 (m), 1456 (m), 1378 (w), 1283 (m), 1180 (w), 1135 (w), 1081 (w), 1031 (w), 993 (w), 959 (w), 860 (w), 784 (m), 699 (m).

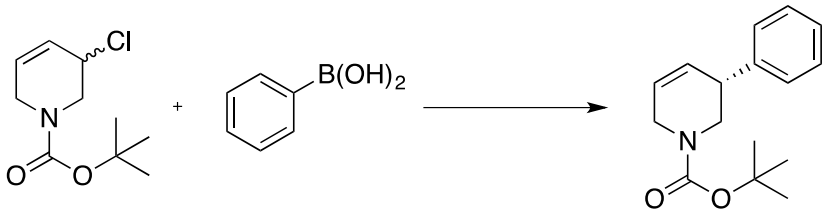
HRMS (ESI): *m*/*z* calc. for $C_{14}H_{22}ON$ $[M+H]^+$: 220.1696; found: 220.1695.

$[\alpha]^{25}_{589}$ = –11.1 (*c* 1.00, $CHCl_3$).

Data consistent with previously reported values.[229]

Procedures:

Procedure A



In a 10 mL round bottomed flask $[Rh(cod)(OH)]_2$, (+)-(R)-5,5'-dichloro-2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl and Cs_2CO_3 were stirred in THF at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene in THF was then added *via* syringe and the flask rinsed with THF, followed by a second solution of phenylboronic acid in THF, which was also added *via* syringe and the flask rinsed with THF. The resulting mixture was then stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2.

Procedure B

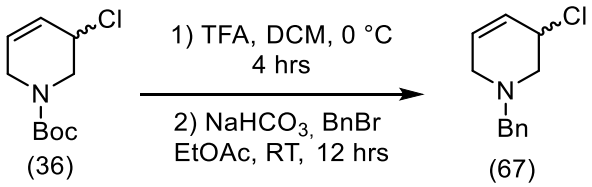
In a 10 mL microwave vial, $[Rh(cod)(OH)]_2$, (+)-(R)-5,5'-dichloro-2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl and Cs_2CO_3 were stirred in THF at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene in THF was then added *via* syringe and the flask rinsed with THF, followed by a second solution of phenylboronic acid in THF, which was also added *via* syringe and the flask rinsed with THF. The vial was then clamped, and the resulting mixture stirred for 16 hrs above reflux at 80 °C in a sealed environment before the addition of SiO_2.

Procedure C

In a 10 mL microwave vial, $[Rh(cod)(OH)]_2$, (+)-(R)-5,5'-dichloro-2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl and Cs_2CO_3 were stirred in THF at 60 °C for 30 mins under argon. A solution of *N-tert*-butoxycarbonyl-5-chloro-3-piperidene in THF was then added *via* syringe and the flask rinsed with THF followed by a second solution of phenylboronic acid in THF, which was also added *via* syringe and the flask rinsed with THF. The vial was then clamped, and the resulting mixture stirred in microwave (250 psi, 300 W) for 1 hr above reflux at 80 °C before the addition of SiO_2.

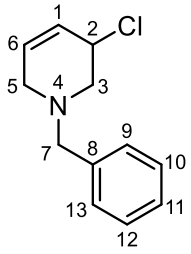
6.2.3 Chapter 4

1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine 67:



In a flame dried flask *N-tert*-butoxycarbonyl-5-chloro-3-piperidene **36** (3.50 g, 16.0 mmol, 1.00 eq) was dissolved in DCM (120 mL) and cooled to 0 °C. Trifluoroacetic acid (12 mL, 160 mmol, 10.0 eq) was added dropwise. The reaction was warmed to room temperature and monitored by TLC. Upon completion the solvent was removed *in vacuo*. In a dried flask benzyl bromide (2.1 mL, 17.6 mmol, 1.10 eq) and EtOAc (25 mL) were mixed and cooled to 0 °C. The crude material was dissolved in EtOAc (10 mL) and added to the benzyl bromide solution dropwise. $NaHCO_3$ (20.0 g, 238 mmol, 14.9 eq) was added portionwise at 0 °C. The suspension was warmed up to room temperature and stirred overnight. The reaction was diluted with EtOAc (50 mL) and first washed with H_2O (25 mL x2) then with brine (25 mL x2). Aqueous layers were back washed with EtOAc (25 mL x3). The combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash column chromatography on silica gel (hexane/EtOAc (9/1)) to give 1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine **67** in 75% yield (2.50 g, 12.0 mmol) as a colourless oil. *Note:* A decrease in yield was observed for trials in larger scale.

TLC R_f = 0.44 (hexane/EtOAc (9/1)).



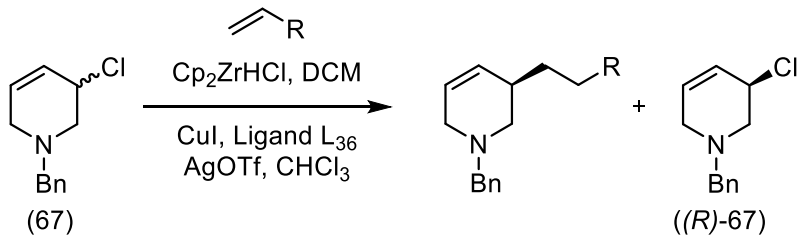
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 2.73 (dd, *J*=12.0, 6.0 Hz, 1H, H-3'), 2.96 (ddd, *J*=12.0, 4.5, 1.0 Hz, 1H, H-3''), 2.99 – 3.13 (m, 2H, H-5), 3.57 – 3.74 (m, 2H, H-7), 4.56 – 4.62 (m, 1H, H-2), 5.80 – 5.91 (m, 2H, H-1 and 6), 7.22 – 7.40 (m, 5H, H-9, 10, 11, 12 and 13).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 52.1 (C-5), 53.8 (C-2), 57.2 (C-3), 61.9 (C-7), 126.8 (C-6), 127.3 (C-11), 128.4 (C-9 and 13), 129.0 (C-10 and 12), 129.1 (C-1), 137.5 (C-8).

IR (ATR) v (cm^{-1}) neat: 3030 (br), 2802 (s), 1493 (m), 1453 (m), 1144 (w), 1071 (s), 1026 (w), 984 (m), 911 (w), 792(w), 697 (w).

HRMS (ESI): *m/z* calc. for $C_{12}H_{15}N^{35}Cl$ $[M+H]^+$ 208.0887, found 208.0888.

General Procedure 1: Cu-catalyzed asymmetric allylic alkylations:



(67) ((*R*)-67)

A round-bottom flask with a stirbar was flame dried *in vacuo* and re-filled with Ar upon cooling. The flask was charged with CuI (7.6 mg, 0.04 mmol, 0.10 eq) and ligand L36 (23.0 mg, 0.04 mmol, 0.10 eq), flushed with argon, sealed with a septum and wrapped with aluminium foil. $CHCl_3$ (2.0 mL, freshly collected from SPS) was added and the resultant colourless solution was stirred at room temperature for 1 hr. Meanwhile a separate round-bottom flask with a stirbar was flame dried *in vacuo* and re-filled with Ar upon cooling. The flask was charged with Cp_2ZrHCl (206 mg, 0.80 mmol, 2.00 eq), flushed with argon, sealed with a septum and wrapped with aluminium foil. DCM (0.4 mL) and the corresponding alkene (1.00 mmol, 2.50 eq) were added and the resultant suspension was stirred at room temperature until the mixture became completely clear (times for hydrozirconation vary with different alkene derivatives). After 1 hr fine crystalline Ag(OTf) (11.3 mg, 0.044 mmol, 0.11 eq) was quickly added to the copper catalyst solution and stirred for 15 mins until all the AgCl precipitated out. The suspension was filtered into the alkylzirconocene solution using a syringe filter and the resultant black solution was cooled to 0 °C. After 5 mins neat 1-benzyl-3 chloro-1,2,3,6-tetrahydropyridine **67** (83.1 mg, 0.40 mmol, 1.00 eq) was added with a syringe at once. The reaction was stopped at the specified time (predetermined via NMR screening experiments) by pouring into Et_2O (10 mL) in a separatory funnel. Remaining material in the flask was rinsed into the Et_2O solution with EtOAc (2 mL x2) and the resultant suspension was washed with saturated $NaHCO_3$ solution (5-7 mL x3). Aqueous phases were back washed with EtOAc (5-7 mL x2). The combined organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash column chromatography on silica gel. Yields in parenthesis were calculated with respect to consumed starting material. Enantiomeric excesses of recovered

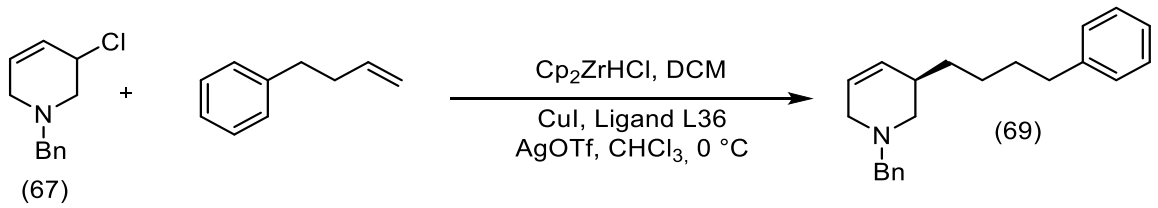
(*R*)-1-benzyl-3 chloro-1,2,3,6-tetrahydropyridine **(*R*)-67** were determined by HPLC [Chiralpak® ID; flow: 1.0 mL/min; hexane:IPA 99.3:0.7; λ = 210 nm].

Note: The heterogeneity of the solution was found to influence reaction results (rate, yield and ee). Ideally, Cu-catalyzed reactions should be conducted in a round-bottom flask with an egg-shaped stirbar, magnetically stirring at a rate of 350 rpm. Brand new septa were used to seal reaction flasks to prevent solvent evaporation.

General Procedure 2: Preparation of Racemic Products:

Racemic products were synthesised by *General Procedure 1* using racemic (3,5-dioxo-4-phosphacyclohepta[2,1-a:3,4-a']dinaphthalen-4-yl)dimethylamine (MonoPhos®). Reactions were stirred at room temperature overnight.

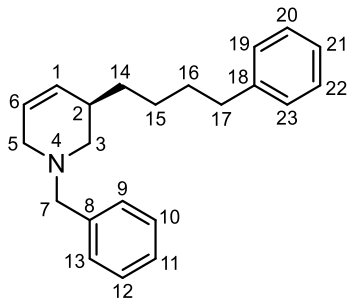
(-)-(*R*)-1-Benzyl-3-(4-phenylbutyl)-1,2,3,6-tetrahydropyridine 69:



According to *General Procedure 1;* the reaction proceeds for 2.5 hrs at 0 °C. Flash column chromatography on silica gel (hexane/EtOAc (15/1) + 0.5 % Et_3N) gave **(*R*)-67** in 64% yield (53.0 mg, 0.26 mmol, ee = 25%) and **69** in 21% (58%) yield (25.9 mg, 0.08 mmol) as a yellow oil.

Enantiomeric excess of 93% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane:IPA 99:1; λ = 210 nm; major enantiomer t_R = 11.9 mins; minor enantiomer t_R = 18.6 mins].

TLC R_f = 0.67 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.22 – 1.32 (m, 4H, H-14 and 15), 1.46 – 1.59 (m, 2H, H-16), 2.02 (dd, *J*=11.0, 7.5 Hz, 1H, H-3'), 2.21 (m, 1H, H-2), 2.45 – 2.55 (m, 2H, H-17), 2.65 (dd, *J*=11.0, 5.0 Hz, 1H, H-3''), 2.73 – 2.82 (m, 1H, H-5'), 2.96 (m, 1H, H-5''), 3.43 – 3.58 (m, 2H, H-7), 5.50 – 5.65 (m, 2H, H-1 and 6), 7.06 – 7.12 (m, 3H, H-19, 21 and 23), 7.17 – 7.21 (m, 3H, H-11, 20 and 22), 7.21 – 7.29 (m, 4H, H-9, 10, 12 and 13).

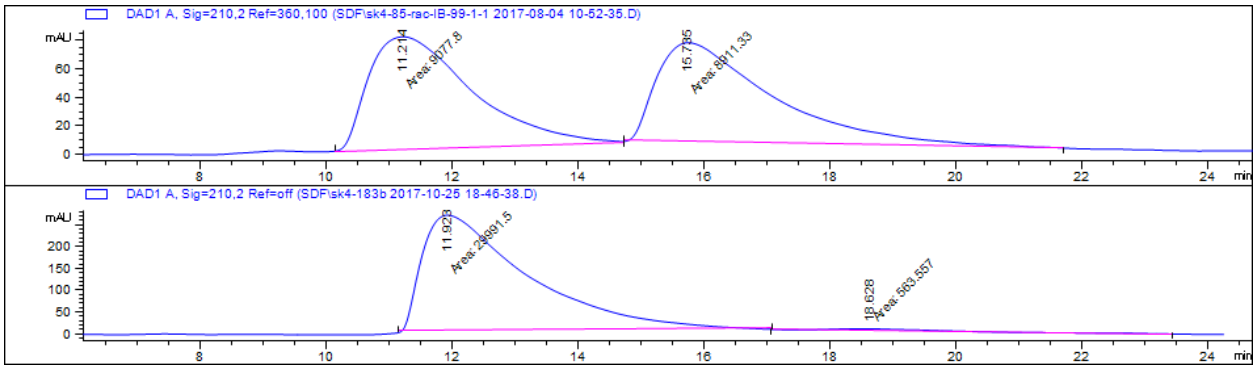
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 26.6 (C-15), 31.7 (C-16), 33.8 (C-14), 35.9 (C-17), 36.0 (C-2), 53.1 (C-5), 55.6 (C-3), 62.8 (C-7), 124.8 (C-6), 125.6 (C-21), 127.0 (C-11), 128.2 (C-20 and 22), 128.3 (C-9 and 13), 128.4 (C-19 and 23), 129.1 (C-10 and 12), 130.2 (C-1), 138.5 (C-18), 142.8 (C-8).

IR (ν_{max} /cm^{-1}): 3026 (m), 2926 (br), 2855 (w), 1494 (s) 1454 (m), 1360 (w), 1133 (s), 1026 (m), 908 (w), 729 (w), 695 (w).

HRMS (ESI): *m/z* calc. for $C_{22}H_{28}N$ $[M+H]^+$ 306.2216, found 306.2215.

$[\alpha]^{25}_{589}$ = -30.5 (*c* 0.40, $CHCl_3$) for 93% ee.

HPLC traces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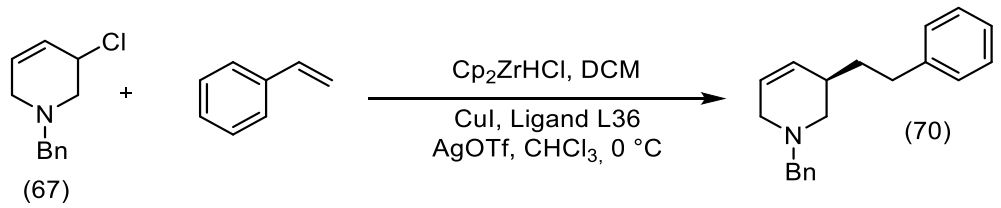
Area:8911.33
8
10
12
14
16
18
20
22
24
min
DAD1 A, Sig=210,2 Ref=off (SDF\sk4-183b 2017-10-25 18-46-38.D)
mAU
200
150
100
50
0
11.929
Area:28891.5
18.628
Area:563.557
8
10
12
14
16
18
20
22
24
min

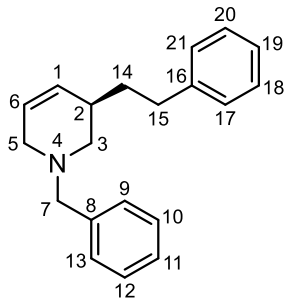
(-)-(*R*)-1-Benzyl-3-phenethyl-1,2,3,6-tetrahydropyridine 70:



According to *General Procedure 1;* the reaction proceed for 4 hrs at 0 °C. Flash column chromatography on silica gel (hexanes/EtOAc (15/1) + 0.5 % Et_3N) gave **(*R*)-67** in 48% yield (39.9 mg, 0.19 mmol, ee = 54%) and **70** in 42% (81%) yield (47.1 mg, 0.17 mmol) as a yellow oil.

Enantiomeric excess of 88% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane:IPA 97.5:2.5; λ = 210 nm; major enantiomer t_R = 10.7 mins; minor enantiomer t_R = 12.4 mins]. HPLC analysis of **70** were performed by Dr Sedef Karabiyikoglu.[283]

TLC R_f = 0.32 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.51 – 1.64 (m, 2H, H-14), 2.10 (dd, *J*=11.0, 7.0 Hz, 1H, H-3'), 2.22 (m, 1H, H-2), 2.45 – 2.56 (m, 2H, H-15), 2.65 (dd, *J*=11.0, 5.0 Hz, 1H, H-3''), 2.80 (m, 1H, H-5'), 2.95 (m, 1H, H-5''), 3.49 (m, 2H, H-7), 5.54 – 5.67 (m, 2H, H-1 and 6), 7.02 – 7.10 (m, 3H, H-17, 19 and 21), 7.17 (m, 3H, H-9, 11 and 13), 7.20 – 7.30 (m, 4H, H-10, 12, 18 and 20).

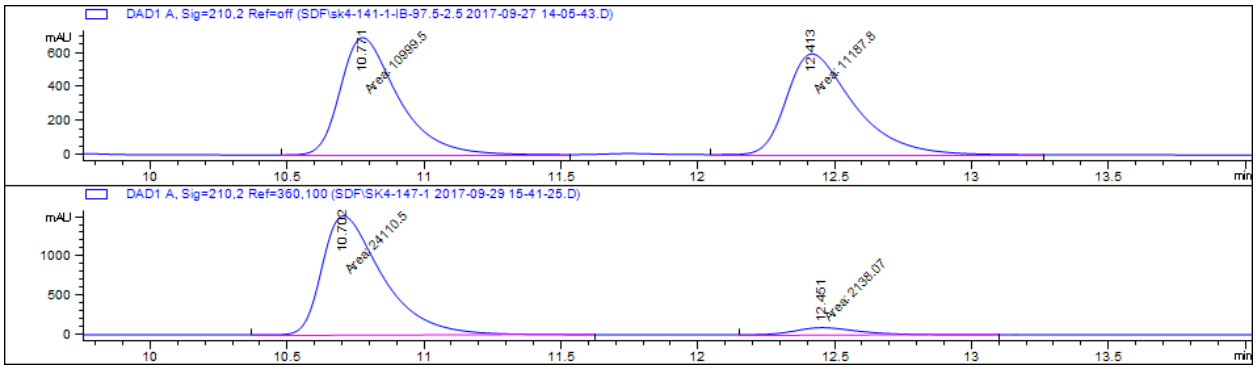
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 33.3 (C-15), 35.7 (C-2), 35.8 (C-14), 53.2 (C-5), 55.3 (C-3), 62.8 (C-7), 125.2 (C-6), 125.7 (C-19), 127.0 (C-11), 128.2 (C-9 and 13), 128.3 (C-18 and 20), 128.4 (C-17 and 21), 129.1 (C-10 and 12), 129.8 (C-1), 138.6 (C-16), 142.5 (C-8).

IR (ν_{max} /cm^{-1}): 3026 (w), 2922 (br), 2858 (w), 2793 (w), 2794 (m), 1493 (s), 1453 (m), 1140 (m), 1028 (m), 998 (s), 730 (w), 695 (w).

HRMS (ESI): *m/z* calc. for $C_{20}H_{24}N$ $[M+H]^+$ 278.1903, found 278.1902.

$[\alpha]^{25}_{589}$ = -58.8 (*c* 0.40, $CHCl_3$) for 88% ee.

HPLC traces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mAU
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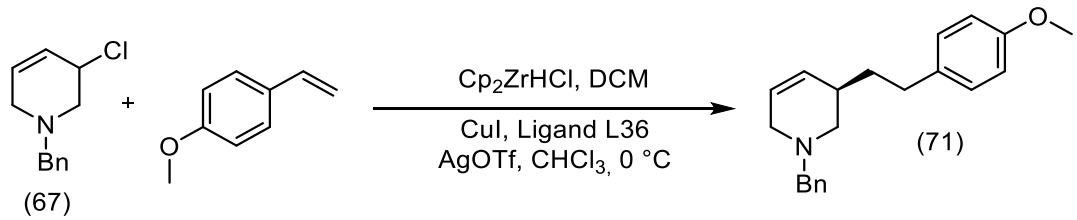
400
200
0
10.771
Area: 10999.5
12.413
Area: 11187.8
10
10.5
11
11.5
12
12.5
13
13.5
min
DAD1 A, Sig=210,2 Ref=360,100 (SDF\SK4-147-1 2017-09-29 15-41-25.D)
mAU
1000
500
0
10.702
Area: 24110.5
12.451
Area: 2138.07
10
10.5
11
11.5
12
12.5
13
13.5
min

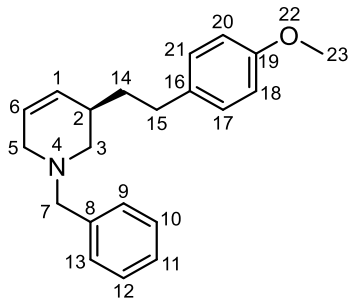
(-)-(*R*)-1-Benzyl-3-(4-methoxyphenethyl)-1,2,3,6-tetrahydropyridine 71:



According to *General Procedure 1;* the reaction proceed for 5 hrs at 0 °C. Flash column chromatography on silica gel (hexanes/EtOAc (15/1 to 9/1) + 0.5 % Et_3N) gave **(*R*)-67** in 49% yield (40.4 mg, 0.19 mmol, ee = 37%) and **71** in 33% (67%) yield (40.2 mg, 0.13 mmol) as a colourless oil.

Enantiomeric excess of 92% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane:IPA 97.5:2.5; λ = 210 nm; major enantiomer t_R = 13.4 mins; minor enantiomer t_R = 16.6 mins]. HPLC analysis of **71** were performed by Dr Sedef Karabiyikoglu.[283]

TLC R_f = 0.15 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.38 – 1.60 (m, 2H, H-14), 2.05 – 2.13 (m, 1H, H-3'), 2.20 – 2.28 (m, 1H, H-2), 2.46 (m, 2H, H-15), 2.66 (dd, *J*=11.0, 5.0 Hz, 1H, H-3''), 2.78 – 2.86 (m, 1H, H-5'), 2.92 – 3.03 (m, 1H, H-5''), 3.39 – 3.59 (m, 2H, H-7), 3.71 (s, 3H, H-23), 5.56 – 5.68 (m, 2H, H-1 and 6), 6.65 – 6.79 (m, 2H, H-18 and 20), 6.94 – 7.03 (m, 2H, H-17 and 21), 7.15 – 7.21 (m, 1H, H-11), 7.21 – 7.30 (m, 4H, H-9, 10, 12 and 13).

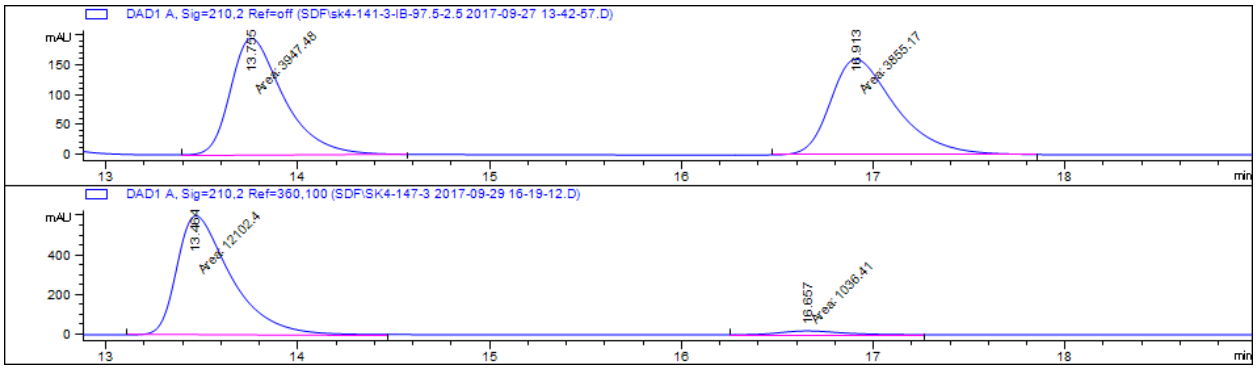
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 32.3 (C-15), 35.6 (C-2), 36.0 (C-14), 53.2 (C-5), 55.3 (C-3 or 23), 55.3 (C-3 or 23) 62.8 (C-7), 113.7 (C-18 and 20), 125.1 (C-6), 127.0 (C-11), 128.2 (C-9 and 13), 129.1 (C-10 and 12), 129.2 (C-17 and 21), 129.8 (C-1), 134.5 (C-16), 138.6 (C-8), 157.7 (C-19).

IR (ν_{max} /cm^{-1}): 3723 (m), 3027 (w), 2926 (br), 2857 (w), 2793 (m), 2750 (w), 1511 (m), 1456 (s), 1245 (w), 1141 (m), 1036 (s), 824 (w), 729 (w), 698 (w).

HRMS (ESI): *m/z* calc. for $C_{21}H_{26}ON$ $[M+H]^+$ 308.2009, found 308.2007.

$[\alpha]^{25}_{589}$ = -42.7 (*c* 0.40, $CHCl_3$) for 92% ee.

HPLC traces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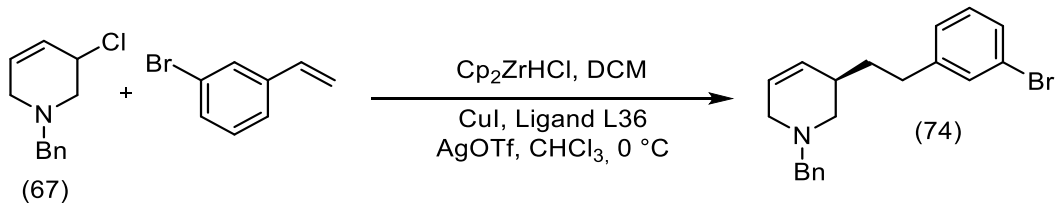
Area:3947.48
16.913
Area:3855.17
13
14
15
16
17
18
min
DAD1 A, Sig=210,2 Ref=360,100 (SDF\SK4-147-3 2017-09-29 16-19-12.D)
mAU
400
200
0
13.494
Area:12102.4
16.657
Area:1036.41
13
14
15
16
17
18
min

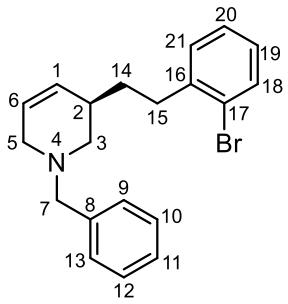
(-)-(*R*)-1-Benzyl-3-(2-bromophenethyl)-1,2,3,6-tetrahydropyridine 74:



According to *General Procedure 1;* the reaction proceed for 4 hrs at 0 °C. Flash column chromatography on silica gel (hexanes/EtOAc (15/1) + 0.5 % Et_3N) gave **(*R*)-67** in 41% yield (34.1 mg, 0.16 mmol, ee = 71%) and **74** in 44% (75%) yield (62.6 mg, 0.18 mmol) as a viscous colourless oil.

Enantiomeric excess of 88% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane:IPA 99:1; λ = 210 nm; major enantiomer t_R = 15.9 mins; minor enantiomer t_R = 18.1 mins]. HPLC analysis of **74** were performed by Dr Sedef Karabiyikoglu.[283]

TLC R_f = 0.27 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.50 – 1.60 (m, 2H, H-14), 2.14 (dd, *J*=11.0, 7.5 Hz, 1H, H-3'), 2.27 (m, 1H, H-2), 2.53 – 2.74 (m, 3H, H-3'' and 9), 2.75 – 2.84 (m, 1H, H-5'), 2.94 (m, 1H, H-5''), 3.42 – 3.56 (m, 2H, H-7), 5.41 – 5.83 (m, 2H, H-1 and 6), 6.93 (m, 1H, H-19), 7.03 – 7.14 (m, 2H, H-20 and 21), 7.14 – 7.19 (m, 1H, H-11), 7.20 – 7.30 (m, 4H, H-9, 10, 12 and 13), 7.41 (dd, *J*=8.0, 1.5 Hz, 1H, H-18).

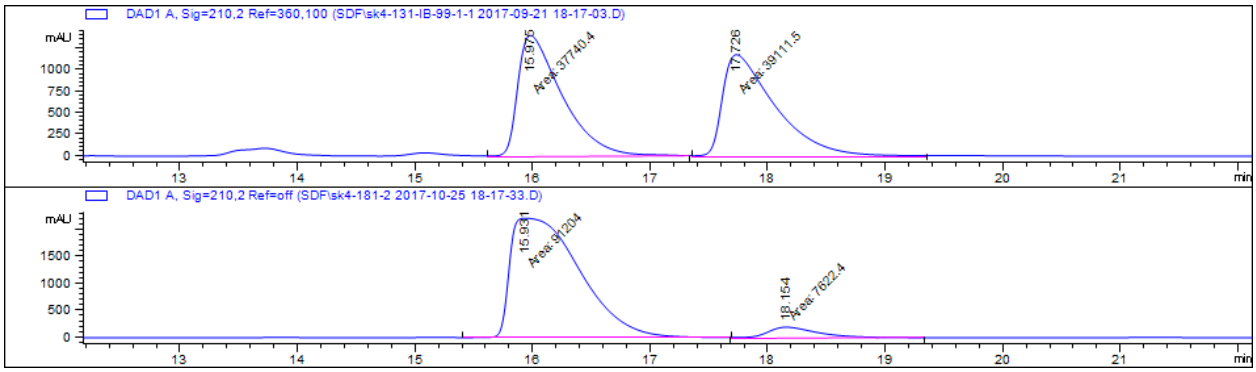
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 33.7 (C-15), 34.2 (C-14), 35.9 (C-2), 53.1 (C-5), 55.3 (C-3), 62.9 (C-7), 124.4 (C-17), 125.3 (C-6), 127.0 (C-11), 127.5 (C-20), 127.5 (C-19), 128.3 (C-9 and 13), 129.1 (C-10 and 12), 129.6 (C-1), 130.3 (C-21), 132.8 (C-18), 138.5 (C-8), 141.8 (C-16).

IR (ν_{max} /cm^{-1}): 3027 (w), 2966 (br), 2921 (s), 2861 (w), 2794 (m), 2749 (m), 1492 (s), 1202 (m), 1142 (s), 1069 (m), 748 (w), 728 (w), 696 (w).

HRMS (ESI): *m/z* calc. for $C_{20}H_{23}{}^{79}BrN$ $[M+H]^+$ 356.1008, found 356.1005.

$[\alpha]^{25}_{589}$ = -55.1 (*c* 0.70, $CHCl_3$) for 88% ee.

HPLC traces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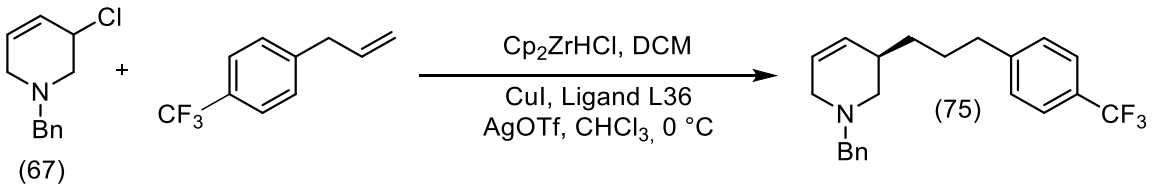
Area: 39111.5
13
14
15
16
17
18
19
20
21
min
DAD1 A, Sig=210,2 Ref=off (SDF\sk4-181-2 2017-10-25 18-17-33.D)
mAU
1500
1000
500
0
15.931
Area: 91204
18.154
Area: 7622.4
13
14
15
16
17
18
19
20
21
min

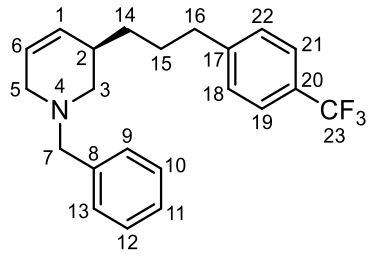
(-)-(*R*)-1-Benzyl-3-(3-(4-(trifluoromethyl)phenyl)propyl)-1,2,3,6-tetrahydropyridine 75:



According to *General Procedure 1;* the reaction proceed for 4 hrs at 0 °C. Flash column chromatography on silica gel (hexanes/EtOAc (10/1) + 0.5 % Et_3N) gave **(*R*)-67** in 70% yield (58.1 mg, 0.28 mmol, ee = 23%) and **75** in 24% (80%) yield (34.1 mg, 0.09 mmol) as a colourless oil.

Enantiomeric excess of 83% was determined by HPLC [Chiralpak® ID; flow: 1.0 mL/min; hexane:IPA 90:10; λ = 210 nm; minor enantiomer t_R = 8.9 mins; major enantiomer t_R = 9.4 mins]. HPLC analysis of **75** were performed by Dr Sedef Karabiyikoglu.[283]

TLC R_f = 0.18 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 1.29 (m, 2H, H-14), 1.41 – 1.61 (m, 2H, H-15), 1.96 – 2.05 (m, 1H, H-3'), 2.15 – 2.26 (m, 1H, H-2), 2.55 (t, *J*=8.0 Hz, 2H, H-16), 2.63 (m, 1H, H-3''), 2.74 – 2.81 (m, 1H, H-5'), 2.96 (m, 1H, H-5''), 3.42 – 3.52 (m, 2H, H-7), 5.51 – 5.64 (m, 2H, H-1 and 6), 7.14 – 7.21 (m, 3H, H-11, 18 and 22), 7.21 – 7.29 (m, 4H, H-9, 10, 12 and 13), 7.39 – 7.46 (m, 2H, H-19 and 21).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 28.6 (C-15), 33.5 (C-14), 35.9 (C-16), 36.0 (C-12), 53.1 (C-5), 55.3 (C-3), 62.8 (C-7), 125.1 (C-6), 125.2 (d, *J*=4.0 Hz, C-19 and 21), 126.2 (d, *J* = 273.5 Hz, C-23), 127.0 (C-11), 128.2 (C-9 and 13), 128.7 (C-18 and 22), 129.1 (C-10 and 12), 129.3 (d, *J*=33.0 Hz, C-20), 129.8 (C-1), 138.4 (C-8), 146.6 (C-17).

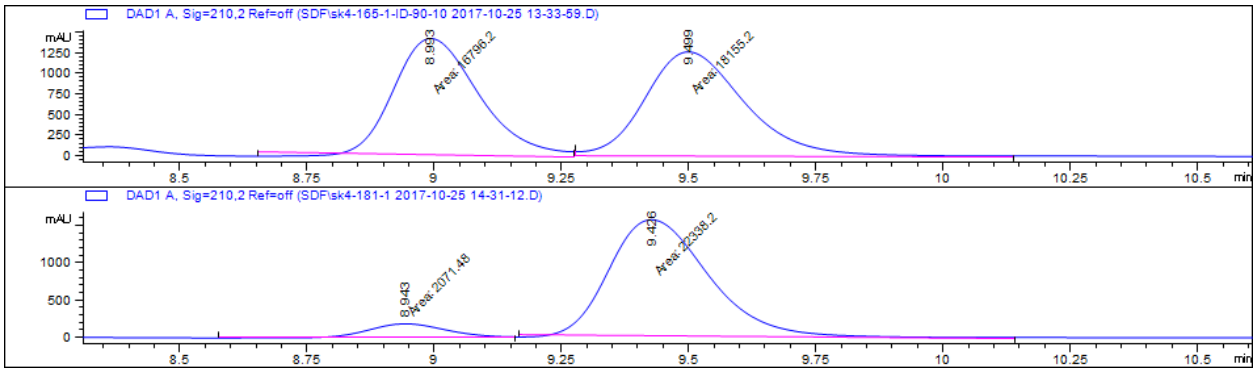
^{19}F NMR (377 MHz, Chloroform-*d*) δ ppm = -62.24 (3F).

IR (ν_{max} /cm^{-1}): 3028 (w), 2929 (br), 2859 (m), 2795 (w), 1323 (s), 1161 (s), 1116 (w), 1066 (m), 841 (w), 730 (m), 696 (w).

HRMS (ESI): *m/z* calc. for $C_{22}H_{25}NF_3$ $[M+H]^+$ 360.1934, found 360.1930.

$[\alpha]^{25}_{589}$ = -40.0 (*c* 1.08, $CHCl_3$) for 83% ee.

HPLC traces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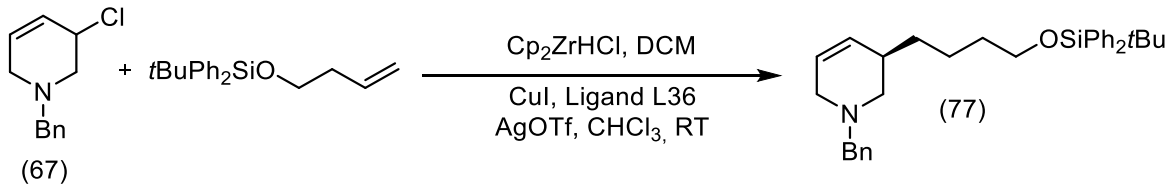
8.993
Area: 16786.2
9.499
Area: 18155.2
DAD1 A, Sig=210,2 Ref=off (SDF\sk4-181-1 2017-10-25 14-31-12.D)
8.943
Area: 2071.48
9.426
Area: 22338.2
min

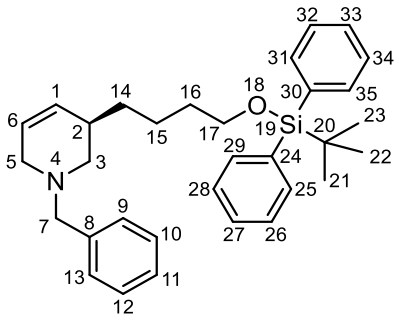
(-)-(*R*)-1-Benzyl-3-(4-((tert-butyldiphenylsilyl)oxy)butyl)-1,2,3,6-tetrahydropyridine 77:



According to *General Procedure 1;* the reaction proceeds for 30 mins at room temperature. Flash column chromatography on silica gel (hexanes/EtOAc (10/1) + 0.5 % Et_3N) gave **(*R*)-67** in 43% yield (36.1 mg, 0.17 mmol, ee = 55%) and **77** in 44% (77%) yield (85.4 mg, 0.18 mmol) as a yellow oil.

Enantiomeric excess of 80% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane:IPA 99:1; λ = 210 nm; major enantiomer t_R = 20.7 mins; minor enantiomer t_R = 21.9 mins]. HPLC analysis of **77** were performed by Dr Sedef Karabiyikoglu.[283]

TLC R_f = 0.29 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.91 – 0.99 (m, 9H, H-21, 22 and 23), 1.17 – 1.32 (m, 4H, H-14 and 15), 1.45 (m, 2H, H-16), 1.91 – 1.98 (m, 1H, H-3'), 2.17 (m, 1H, H-2), 2.64 (ddd, *J*=11.0, 5.0, 1.0 Hz, 1H, H-3''), 2.70 – 2.78 (m, 1H, H-5'), 2.90 – 2.99 (m, 1H, H-5''), 3.42 – 3.53 (m, 2H, H-7), 3.56 (t, *J*=6.5 Hz, 2H, H-17), 5.25 – 5.81 (m, 2H, H-1 and 6), 7.12 – 7.18 (m, 1H, H-11), 7.18 – 7.35 (m, 10H, H-9, 10, 12, 13, 26, 27, 28, 32, 33 and 34), 7.48 – 7.69 (m, 4H, H-25, 29, 31 and 35).

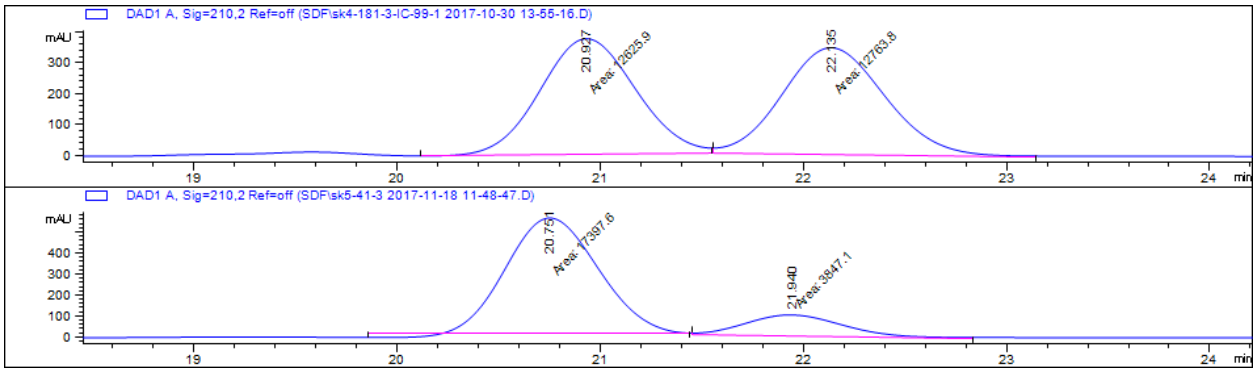
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 19.3 (C-20), 23.1 (C-15), 26.9 (C-21, 22 and 23), 32.8 (C-16), 33.7 (C-14), 36.1 (C-2), 53.1 (C-5), 55.7 (C-3), 62.9 (C-7), 63.8 (C-17), 124.8 (C-6), 127.0 (C-11), 127.6 (C-26, 28, 32 and 34), 128.2 (C-9 and 13), 129.1 (C-10 and 12), 129.5 (C-24 and 30), 129.8 (C-1), 134.1 (C-27 and 33), 135.6 (C-25, 29, 31 and 35), 138.5 (C-8).

IR (ν_{max} /cm^{-1}): 3027 (m), 2930 (br), 2796 (m), 1457 (s), 1107 (m), 822 (w), 733 (m), 699 (w).

HRMS (ESI): *m/z* calc. for $C_{32}H_{42}ONSi$ [M+H] 484.3030, found 484.3023.

$[\alpha]^{25}_{589}$ = -22.6 (*c* 0.80, $CHCl_3$) for 80% ee.

HPLC traces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200
100
0
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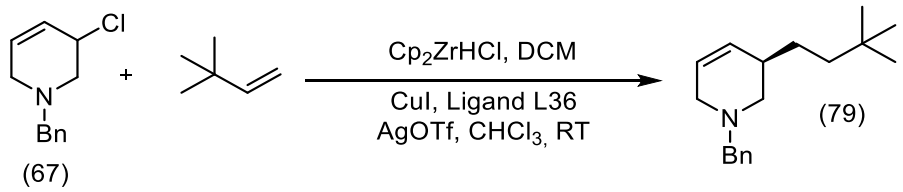
Area: 12625.9
22.135
Area: 12763.8
19
20
21
22
23
24
min
DAD1 A, Sig=210,2 Ref=off (SDF\sk5-41-3 2017-11-18 11-48-47.D)
mAU
400
300
200
100
0
20.751
Area: 17397.6
21.940
Area: 3947.1
19
20
21
22
23
24
min

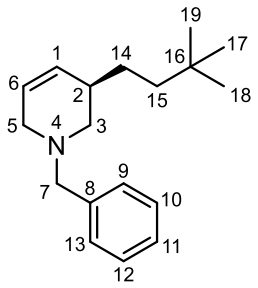
(-)-(*R*)-1-Benzyl-3-(3,3-dimethylbutyl)-1,2,3,6-tetrahydropyridine 79:



According to *General Procedure 1;* the reaction proceeds for 30 mins at room temperature. Flash column chromatography on silica gel ($CHCl_3$ to hexanes/EtOAc (9/1) + 0.5 % Et_3N) gave **(*R*)-67** in 64% yield (52.8 mg, 0.25 mmol, ee = 30%) and **79** in 31% (86%) yield (31.9 mg, 0.12 mmol) as a colourless oil.

Enantiomeric excess of 88% was determined by HPLC [Chiralpak® ID; flow: 1.0 mL/min; hexane:IPA 90:10; λ = 210 nm; minor enantiomer t_R = 6.5 mins major enantiomer t_R = 7.5 mins]. HPLC analysis of **79** were performed by Dr Sedef Karabiyikoglu.[283]

TLC R_f = 0.39 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.79 – 0.87 (m, 9H, H-17, 18 and 19), 1.20 – 1.26 (m, 2H, H-15), 1.44 – 1.60 (m, 2H, H-14), 2.10 (dd, *J*=10.5, 7.5 Hz, 1H, H-3'), 2.17 (m, 1H, H-2), 2.69 – 2.77 (m, 1H, H-3''), 2.82 – 2.90 (m, 1H, H-5'), 3.04 (m, 1H, H-5''), 3.48 – 3.64 (m, 2H, H-7), 5.59 – 5.73 (m, 2H, H-1 and 6), 7.20 – 7.30 (m, 1H, H-11), 7.29 – 7.38 (m, 4H, H-9, 10, 12 and 13).

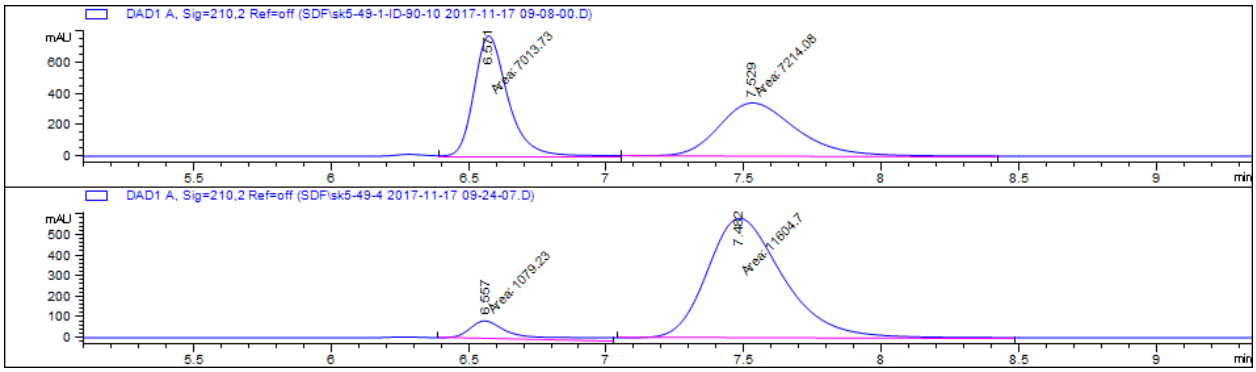
^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 29.3 (C-14), 29.4 (C-17, 18 and 19), 30.2 (C-16), 36.8 (C-2), 41.3 (C-15), 53.2 (C-5), 55.6 (C-3), 62.9 (C-7), 124.6 (C-6), 126.9 (C-11), 128.2 (C-9 and 13), 129.1 (C-10 and 12), 130.4 (C-1), 138.6 (C-8).

IR (ν_{max} /cm^{-1}): 2952 (br), 2863 (m), 1456 (s), 1393 (m), 1137 (m), 995 (s), 726 (w), 694 (w).

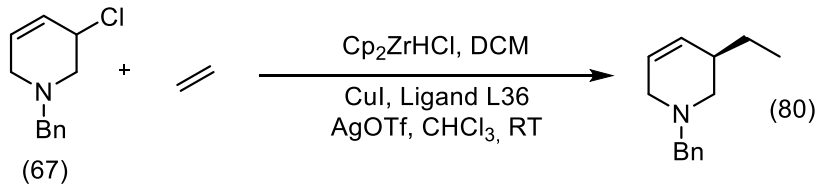
HRMS (ESI): *m/z* calc. for $C_{18}H_{28}N$ [M+H] 258.2216, found 258.2218.

$[\alpha]^{25}_{589}$ = -50.7 (*c* 0.80, $CHCl_3$) for 88% ee.

HPLC traces


DAD1 A, Sig=210,2 Ref=off (SDF\sk5-49-1-ID-90-10 2017-11-17 09-08-00.D)
mAU
600
400
200
0
6.571
Area: 7013.73
7.529
Area: 7214.08
5.5
6
6.5
7
7.5
8
8.5
9
min
DAD1 A, Sig=210,2 Ref=off (SDF\sk5-49-4 2017-11-17 09-24-07.D)
mAU
500
400
300
200
100
0
6.557
Area: 1079.23
7.482
Area: 11604.7
5.5
6
6.5
7
7.5
8
8.5
9
min

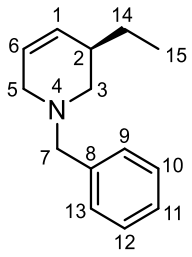
(-)-(*R*)-1-Benzyl-3-ethyl-1,2,3,6-tetrahydropyridine 80:



According to *General Procedure 1;* the reaction proceeds for 30 mins at room temperature, under 1 atm of ethylene gas. Flash column chromatography on silica gel ($CHCl_3$ to hexanes/EtOAc (9/1) + 0.5 % Et_3N) gave **(*R*)-67** in 63% yield (52.4 mg, 0.25 mmol, ee = 34%) and **80** in 25% (68%) yield (20.4 mg, 0.10 mmol) as a colourless oil.

Enantiomeric excess of 90% was determined by HPLC [Chiralpak® IC; flow: 1.0 mL/min; hexane:IPA 97:3; λ = 210 nm; major enantiomer t_R = 16.0 mins; minor enantiomer t_R = 16.9 mins]. HPLC analysis of **80** were performed by Dr Sedef Karabiyikoglu.[283]

TLC R_f = 0.30 (hexane/EtOAc (9/1)).



^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm = 0.81 (t, *J*=7.5 Hz, 3H, H-15), 1.21 – 1.35 (m, 2H, H-14), 1.94 – 2.05 (m, 1H, H-3'), 2.07 – 2.18 (m, 1H, H-2), 2.68 (ddd, *J*=11.0, 5.0, 1.0 Hz, 1H, H-3''), 2.72 – 2.79 (m, 1H, H-5'), 2.94 – 3.02 (m, 1H, H-5''), 3.44 – 3.55 (m, 2H, H-7), 5.54 – 5.65 (m, 2H, H-1 and 6), 7.14 – 7.20 (m, 1H, H-11), 7.21 – 7.31 (m, 4H, H-9, 10, 12 and 13).

^{13}C NMR (101 MHz, Chloroform-*d*) δ ppm = 11.4 (C-15), 26.7 (C-14), 37.7 (C-2), 53.1 (C-5), 55.4 (C-3), 62.9 (C-7), 124.8 (C-6), 126.9 (C-11), 128.2 (C-9 and 13), 129.1 (C-10 and 12), 130.0 (C-1), 138.6 (C-8).

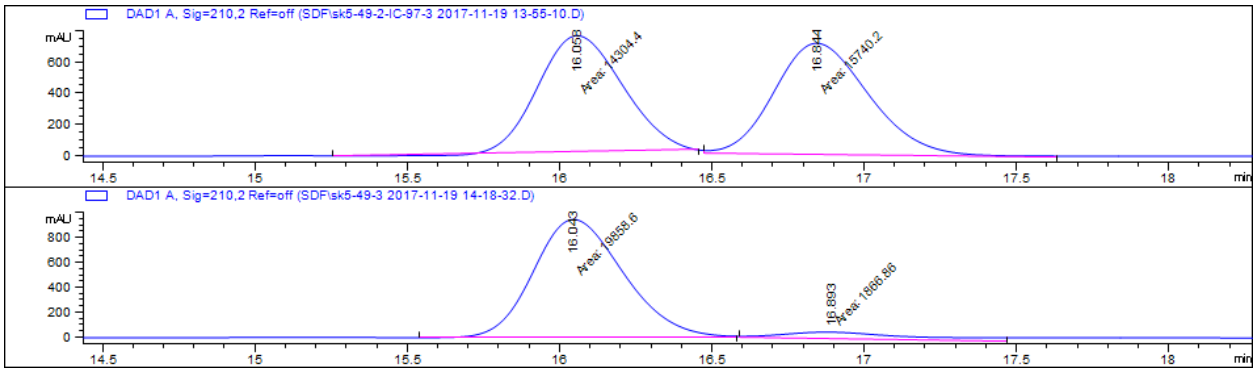
IR (ν_{max} /cm^{-1}): 3027 (w), 2960 (m), 2923 (br), 2793 (m), 2748 (w), 1492 (s), 1151 (s), 978 (m), 750 (w), 727 (w), 697 (w).

HRMS (ESI): *m/z* calc. for $C_{14}H_{20}N$ $[M+H]^+$ 202.1590, found 202.1589.

For corresponding Cbz carbamate; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ ppm = 0.92-0.94 (rotameric m, 3H), 1.25-1.43 (m, 2H), 2.10 and 2.16 (rotameric bs, 1H), 3.04-3.24 (m, 1H), 3.66-4.04 (m, 3H), 5.11-5.19 (rotameric m, 2H), 5.60 and 5.66 (rotameric bd, *J*=10.0 Hz, 1H), 5.76 (bdd, *J*=10.0, 1.8 Hz, 1H), 7.07-7.50 (m, 5H).

$[\alpha]^{25}_{589}$ = -39.2 (*c* 0.75, $CHCl_3$) for 90% ee for Cbz carbamate.

HPLC traces


DAD1 A, Sig=210,2 Ref=off (SDF\sk5-49-2-IC-97-3 2017-11-19 13-55-10.D)
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200
0
16.058
Area: 14304.4
16.844
Area: 15740.2
14.5
15
15.5
16
16.5
17
17.5
18
min
DAD1 A, Sig=210,2 Ref=off (SDF\sk5-49-3 2017-11-19 14-18-32.D)
mAU
800
600
400
200
0
16.043
Area: 19858.6
16.893
Area: 1866.86
14.5
15
15.5
16
16.5
17
17.5
18
min

Kinetic resolution of 67 in Cu-catalysed asymmetric addition:

First kinetic study of Cu-catalysed AAA at 0 °C :

Time (mins)	Conversion (%)	ee of **69** (%)	ee of ***R*-67** (%)
60	27	90	44
120	51	87	64
180	55	86	85
240	59	85	99
300	61	82	99
360	63	83	99
420	68	81	99
4320	100	62	99

Second kinetic study of Cu-catalysed AAA at 0 °C :

Time (mins)	Conversion (%)	ee of **69** (%)	ee of ***R*-67** (%)
15	17	93	8
30	24	93	16
45	28	94	23
60	33	93	31
75	36	93	37
90	37	92	40
105	40	92	51
120	43	90	60
135	45	90	62
150	47	90	70
165	47	90	70
180	48	90	71
1380	63	80	99
1440	64	79	99

First kinetic study of Cu-catalysed AAA at -10 °C :

Time (mins)	Conversion (%)	ee of **69** (%)	ee of ***R*-67** (%)
15	11	88	9
30	16	94	9
45	18	94	15
60	22	94	17
75	25	92	20
90	26	93	25
105	28	92	29
120	31	91	34
135	32	90	32
150	33	90	36
165	34	91	38
180	36	88	39
210	38	91	46
240	40	90	46
270	41	89	53
300	51	84	56
330	43	89	58
360	45	87	58
390	43	87	63
420	47	86	63
450	45	87	65
480	47	86	67
510	47	86	69
555	49	86	70
600	49	85	71
1320	52	78	81
1380	51	78	79
1440	52	78	81

Chapter 7

7 References

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