Phosphoramidite ligand design for the enantioselective conjugate addition of alkylzirconium reagents to enones

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Declaration

This thesis describes work carried out in the Chemistry Research Laboratory, Oxford, between October 2010 and March 2014 under the supervision of Dr Stephen Fletcher. The thesis is a result of my own work, except when stated otherwise, and has not been submitted for any other degree at this or any other university.

Philippe M. C. Roth.

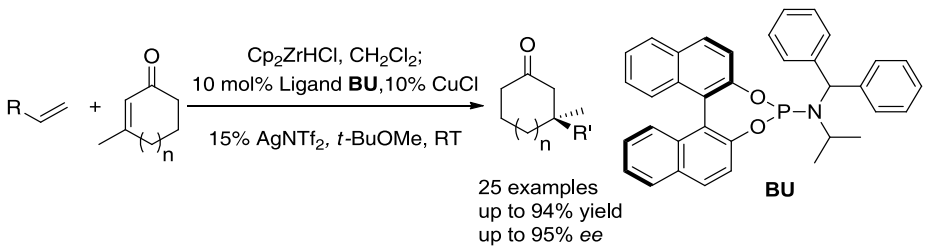
Abstract: Phosphoramidite ligand design for the enantioselective conjugate addition of alkylzirconium reagents to enones

Philippe M. C. Roth, Saint Anne's College, Trinity 2014

The development of new methods to make carbon-carbon bonds asymmetrically remains a challenge in organic chemistry. Indeed, the development of highly selective methods often proceeds on a trial and error basis. The way chiral information is transferred to the substrate is unclear in many reactions, limiting further development. We focus here on developing an asymmetric conjugate addition of alkylzirconium nucleophiles to Michael acceptors. The development of new phosphoramidite ligands, supported by a computer based model, allowed further development of the reaction.

First, existing methods to introduce enantioselectively chirality are described. Then we discuss ligands, and modern ways to parameterise experimental data using computational methods. In chapter two, after discussing the use of alkenes as reagents, especially processes initiated by hydrometallation, we describe a new conjugate addition reaction using cyclic enones that achieves both high yields and levels of enantioselectivity.

In chapter three, various applications of phosphoramidite ligands are discussed and we describe the synthesis of a variety of different phosphoramidites and identification of important structural features of these ligands. New, efficient ligands are obtained and a computer model is developed to account for the selectivity of the reaction discussed in chapter two. Chapter four describes the development of an enantioselective synthesis of quaternary centres with novel ligands used to optimise the new system. Lastly, chapter five describes the extension of the method to some linear enones, using different ligands.



Scheme i: Chapter 4, results using a new phosphoramidite ligand

Overall, we have developed a variety of ligands which were used to expand the enone scope of a conjugate addition and an understanding of what factors make these ligands effective.

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Je dédie cette thèse à mon père qui m'a tout appris.

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Abbreviations

Å	Ångstrom(s)
Ac	acetyl
ACA	asymmetric conjugate addition
aq.	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br.	broad (spectral)
brsm	based on recovered starting material
i-Bu	isobutyl
n-Bu	normal (primary) butyl
t-Bu	tertiary butyl
Bz	benzoyl
°C	degrees Celsius
cat.	catalytic
Cbz	benzyloxycarbonyl
cm^{-1}	wavenumber
Cp	cyclopentadienyl
δ	chemical shift
d	doublet (spectral)
DCM	dichloromethane
DCE	1,2-dichloroethane
dd	doublet of doublets (spectral)
ddd	doublet of doublet of doublets (spectral)
ddt	doublet of doublet of triplets (spectral)
DFT	density functional theory
DMAP	4-dimethylaminopyridine
dq	doublet of quartets (spectral)
dt	doublet of triplets (spectral)

dtd	doublet of triplet of doublets (spectral)
ee	enantiomeric excess
EI	electron ionisation
eq	equivalents
ESI	electrospray ionisation
Et	ethyl
g	gram(s)
gCOSY	gradient Correlation Spectroscopy
gHSQC	gradient Heteronuclear Single Quantum Coherence
^{1}H	proton
h	hour(s)
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	hertz
IR	infra-red
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
L	litre(s)
LFER	linear free energy relationship
µm	micrometer(s)
M	molar (moles per litre)
m	multiplet (spectral)
mbar	millibar(s)
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
M.p.	melting point
m/z	mass to charge ratio

nm	nanometre(s)
NMR	nuclear magnetic resonance
NHC	*N*-Heterocyclic Carbene
Nu	nucleophile
PG	protecting group
Ph	phenyl
ppm	parts per million
i-Pr	isopropyl
PTFE	polytetrafluoroethylene
q	quartet (spectral)
quant	quantitative
quin	quintet (spectral)
QSSR	quantitative structure selectivity relationship
R	generic organic group
RT	room temperature
s	singlet (spectral)
sat.	saturated
sxt	sextet (spectral)
t	triplet (spectral)
t-BuOMe	*tert*-Butyl methyl ether
td	triplet of doublets (spectral)
tdd	triplet of doublet of doublets (spectral)
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
TS	transition state
THF	tetrahydrofuran
UV	ultraviolet

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Chapter 1: General introduction

The ability to synthesise new molecules is at the core of organic chemistry. Interesting synthetic targets are often natural products or other bioactive molecules, a large number which are chiral, posing a challenge for both academic and industrial chemists. Developing catalytic enantioselective methods is a promising solution to this problem.[1]

In the field of drug discovery, a recent trend in marketed drugs has been towards those incorporating flat structures.[2] These molecules are indeed synthesised by established, robust and convenient methods used in the chemical industry.[3] Many major industrial processes synthesise structure which are generally not considered drug-like.[4] Indeed, drug candidates incorporating many aromatic rings and are more likely to fail.[4] Moreover, a significant number of industrial syntheses utilise sp^2-sp^2 (or sp^2-sp) couplings for the preparation of C–C bonds, as exemplified by the Suzuki and Sonogashira couplings, resulting in the incorporation of a large number of aryl ring moieties,[5] and are therefore, more likely to fail.[6]

Surprisingly, 87% of the chiral centres contained in drug intermediates are incorporated from commercial building blocks.[5] This is due to the fact that industrial methods establishing new chiral centres are scarce.[7] Optimisation of enantioselective processes requires time and intensive research. However, the molecules are more likely to be more efficient in term of medical drugs.[3] Indeed, these molecules are more rigid, a property which ensures the body readily targets them. Comparatively, molecules bearing biaryl groups possess a higher number of conformations (due to higher degree of rotation in the sp^2-sp^2 bond). This latest property may make these molecules less efficient as only one of these conformation maight be biologically active. Therefore, there is a real need for new methods to tackle these issues and develop useful reactions.

Chirality

According to Lord Kelvin's definition, chirality is a geometrical property of molecules which are not superimposable upon their mirror image (Figure 1.1).[8] The mathematical definition of chirality states that a chiral object lacks symmetry operations of the second kind. These improper symmetry operations include reflection (occurring through a plane), inversion (through a point), and a combination of both rotation and reflection.

Whilst a molecule and its non-superimposable mirror image (its enantiomer) are chemically indistinguishable, they interact differently with other chiral species, and thus exhibit different biological properties as living systems are themselves chiral and can discriminate between enantiomers.

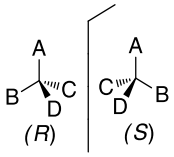


Figure 1.1: Two enantiomers.

Therefore, the ability to selectively synthesise one enantiomer, called asymmetric synthesis, is an important tool for chemists to develop.[9] As organic molecules mostly contain carbon-carbon bonds, the ability to synthesise C-C bonds enantioselectively is a key challenge.[10]

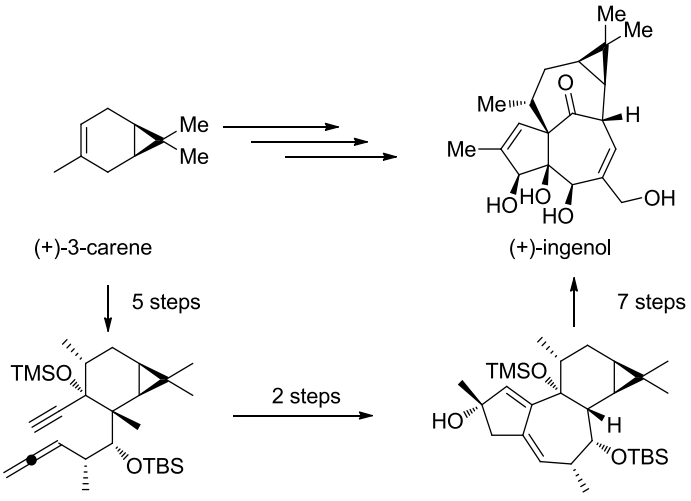
A molecule containing several stereocentres can have multiple configurations beyond a pair of enantiomers. These additional configurations are called diastereomers. The more stereogenic centres present in a molecule, the more possible diastereomers exist. The total number of stereoisomers in a molecule containing *n* chiral centres is up to 2^n, including all different enantiomers and diastereomers. Due to this large number of possible configurations, the ability to synthesise these chiral centres selectively is critical. Indeed, chiral centres contained in natural products are usually set and stable. Each step introducing a chiral centre will have to be stereoselective in order to avoid the synthesis of undesired diastereomers. Therefore,

stereoselective variants are required for almost every single reaction which makes a new chiral centre. The development of such methods is the core of asymmetric synthesis.

Ways to introduce chirality asymmetrically

Chiral pool and diastereomers

A common method to prepare an enantiomerically enriched product is to use a starting material which is already enantiomerically enriched. These building blocks are usually derived from natural products, known as the chiral pool strategy.[11] This strategy is generally attractive as stereochemical considerations are reduced, as the desired chiral centres are already present and can often to be kept intact throughout the synthetic sequence, as exemplified by Baran's synthesis of (+)-ingenol from (+)-3-carene (Scheme 1.1). In this example, the ultimate stereochemistry of most of the stereogenic centres in the product originate from the stereochemistry of the starting material.[12] The main drawback of this method is that it relies on the availability of appropriate starting materials in sufficient quantity and purity. Such starting materials may be in limited supply, restricting this strategy to small scales and increasing its expense. Another major limitation is that only one enantiomer of some natural products may be available. In this case, this method may not allow the synthesis of all desired isomers of a given product, especially if the target molecule contains several centres.

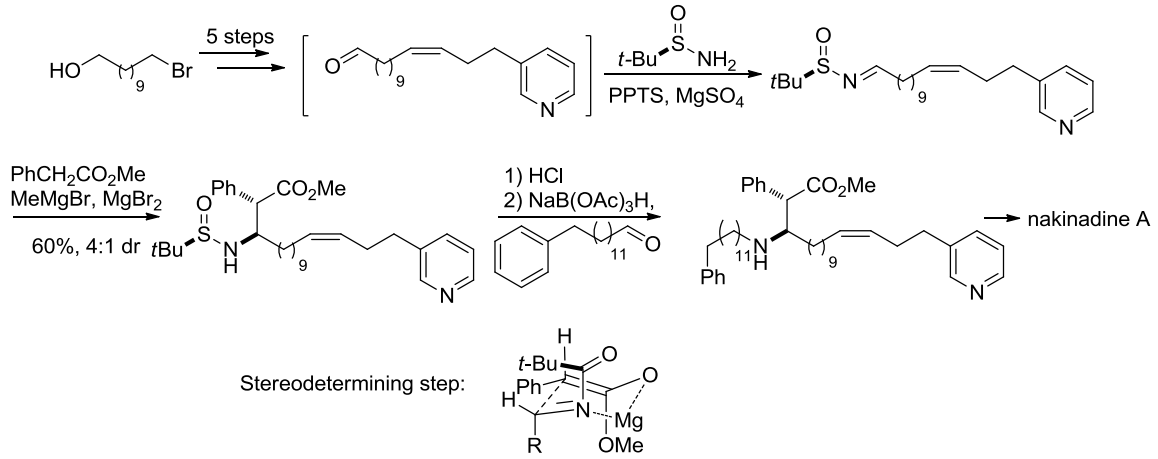


Scheme 1.1: Baran's synthesis of (+)-ingenol.

Chiral auxiliaries as directing groups

Another common strategy to control asymmetry in a molecule is to temporarily introduce a chiral directing group.[13] This directing group allows the selective synthesis of the new stereocentre. A chiral auxiliary can influence the steric course of the reaction, for example by blocking nucleophilic attack at one face of a prochiral electrophile. Many different chiral auxiliaries[14] and synthetic methods using them[15] have been reported. This strategy may provide higher levels of stereoselectivity as the methodologies are usually more established. A significant advantage of this method is the chiral auxiliary changes the physical characteristics of the molecule, potentially making it more crystalline (compared to a relatively greasy hydrocarbon core). This specific property might be useful in order to increase the enantiomeric excess of the product by recrystalisation.The main drawback of this approach is that chiral auxiliaries need to be added and removed, thereby adding steps into the synthetic sequence and reducing atom economy.

Scheme 1.2 illustrates the use a chiral sulfoxide as an auxiliary in the synthesis of nakinadine A by Davies.[16] In this example, the chiral group is removed by the action of HCl in a sequence that further functionalises the molecule, thereby mitigating the usual inefficiency inherent in this strategy.

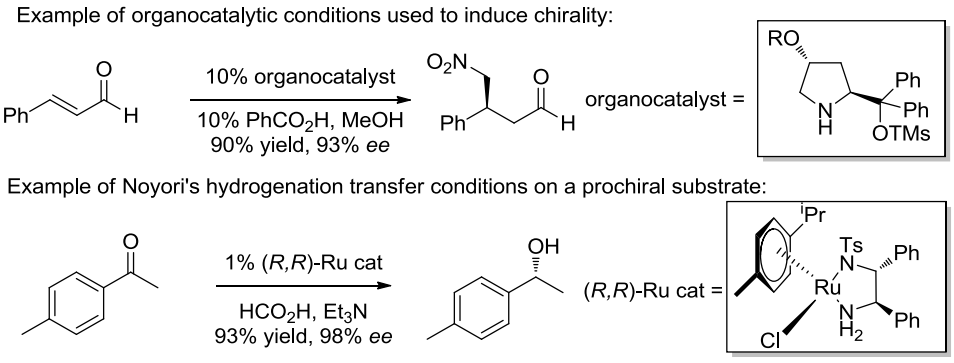


Scheme 1.2: Davies' synthesis of (−)-(2*S*, 3*R*, *Z*)-nakinadine A using a chiral auxiliary.

Enantioselective reactions

Another, more recent approach to asymmetric synthesis uses prochiral substrates in combination with a stereoselective reagent or catalyst. In such reactions, a non-racemic reagent or catalyst introduces chirality in the molecule while a chemical bond is affected.

Discrimination between stereoisomers can be achieved in various ways. For example a stoichiometric reagent or solvent can induce asymmetry during the course of the reaction, and such processes were extensively explored in the 1980s and 90s. A more modern approach is to use organocatalysts to control the asymmetry of a newly-formed chiral centre (Scheme 1.3).[17] Another common approach, which will be expanded below, is through the use of organometallic species as catalysts. Typically in these cases, the chirality derives from the ligand. An example of an enantioselective reaction using Noyori's catalyst is given below.[18]



Scheme 1.3: Example of enantioselective reactions.

Importance of asymmetric catalytic reactions

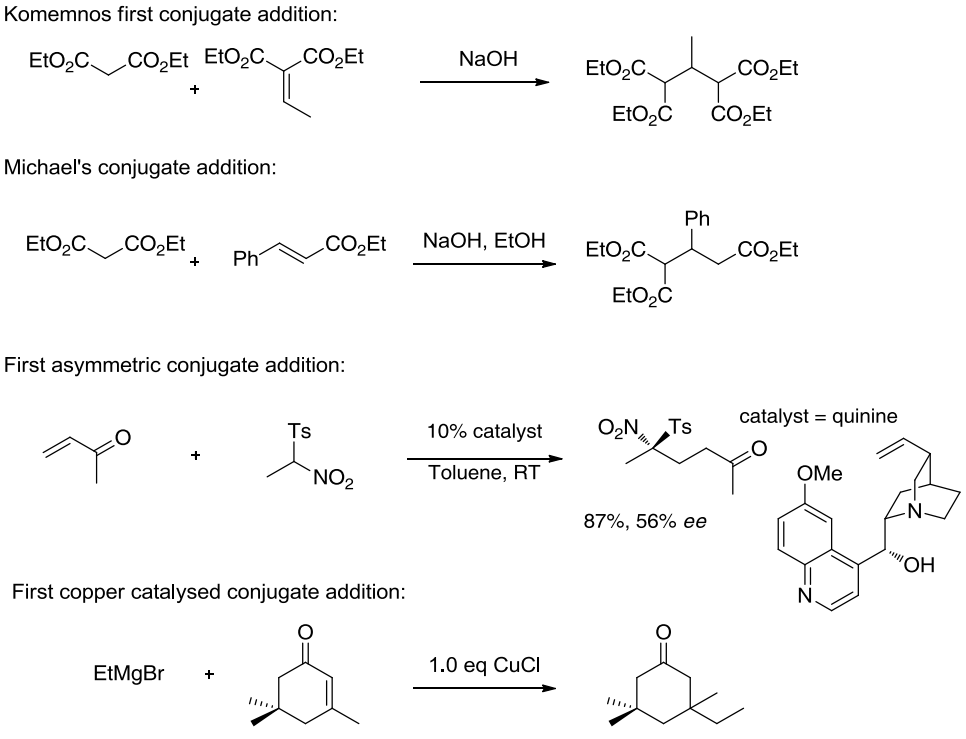
Asymmetric catalysis has completely changed the approach to synthesis and revolutionised the way chemists build molecules.[19] The use of transition metals in asymmetric catalysis has helped tremendously in the selective synthesis of biologically-relevant molecules.[20]

The discovery and application of some powerful catalytic asymmetric methods was awarded the Nobel Prize in Chemistry in 2001. Noyori[21] and Knowles[22] received the award for "their work on chirally catalysed hydrogenation reactions" (for illustration, see example above, Scheme 1.3) and Sharpless[23] "for his work on chirally catalysed oxidation reactions". Since this

pioneering work, tremendous advances have been made, with many novel metal catalysed methods being developed. However, despite these accomplishments and significant ongoing work, there are still major challenges remaining in asymmetric catalysis. Importantly, there is a need to design new reactions using non-toxic metals which catalyse reactions under mild conditions. Furthermore, the transfer of chiral information from the ligand to the product throughout most reactions remains poorly understood. Such mechanistic understanding is highly desirable and would undoubtedly help to achieve higher levels of selectivity in these reactions. However, at present the key factors that control asymmetric catalysis typically remain elusive.

Conjugate addition

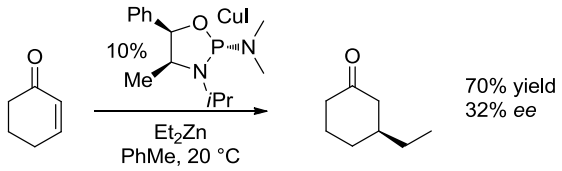
Conjugate addition has emerged as a powerful tool to develop new carbon-carbon bonds.[24] The first conjugate addition was reported by Komemnos[25] and Michael[26] in the 1880s (Scheme 1.4). Only in 1975 was the first asymmetric conjugate addition reported by Wynberg, using quinine as an organocatalyst to facilitate addition to an enone.[27]



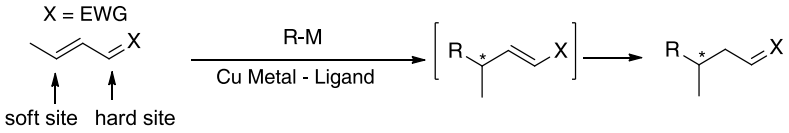
Scheme 1.4: Different examples of conjugate addition.

Although some early examples of catalysts for conjugate addition reactions have been reported using cobalt,[28] nickel,[29] palladium[30] and rhodium,[31-33] copper has since been explored widely and is now established as one of the common metals to facilitate this reaction. Used in organic chemistry as early as 1936 by Gilman,[34] the first reports of copper's stoichiometric[35] and catalytic[36] activity in conjugate addition reactions are more recent. In 1988, Lippard described the first copper-catalysed enantioselective conjugate addition of Grignard reagents to cyclohexenone.[37]

In 1993, Alexakis reported using dialkyl zinc in a similar asymmetric process (Scheme 1.5).[38] Since then, copper-catalysed asymmetric 1,4-addition reactions have developed tremendously.



Scheme 1.5: Alexakis's first use of dialkyl zinc as a nucleophile.[38]



Scheme 1.6: Generic copper catalysed conjugate addition.

Generally, the implementation of such conjugate addition reactions follows a common pattern: a primary organometallic transmetallates with copper to provide a copper nucleophile which then catalyses the conjugate addition to a Michael acceptor (Scheme 1.6). In this molecule, the α-position relative to the electron-withdrawing group is electrophilic. Indeed, the induction from the adjacent electron withdrawing group removes some electron density in this particular position. The localised high charge density makes this carbon a hard electrophile. By conjugation, the γ-position is also electrophilic. However, due to the conjugation, the charge density is lower and more spread out. This makes the γ-carbon a soft electrophile. Therefore each electrophilic site

has a different type of reactivity. The copper contains large *d* orbitals which allow the delocalisation of the charge attached to it. This property makes the copper a soft metal.

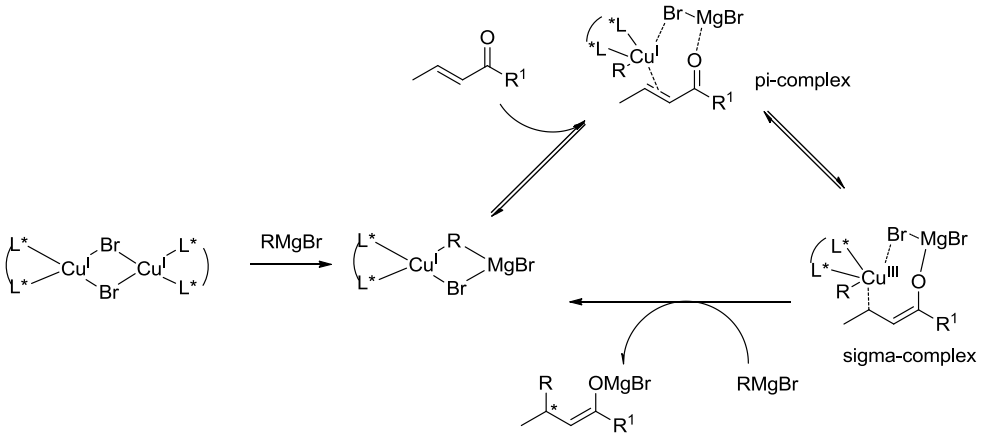
The first organometallic source is normally very hard, meaning it would typically undergo 1,2-addition to the Michael acceptor. Once transmetallated, the copper species predominates and is much more reactive than any background conjugate addition reaction. As the copper is a soft nucleophile due to its *d* orbitals, it can chelate to the enone and eventually undergo a 1,4-addition.

The primary organometallic reagents typically used are Grignard reagents, organoaluminiums and organozinc reagents. These are very reactive and require cryogenic temperatures to perform the reaction effectively. The high reactivity of these reagents is often incompatible with many common functional groups. In term of reactivity, dialkyl zinc organometallics are less reactive than Grignard reagents. Organoaluminium reagents are even more reactive and proved useful recently while organolithium species are the most reactive in many cases and have been used traditionally (forming Gilman reagents) to perform conjugate addition.[39] However, general methods to use organolithium species are scarce in asymmetric catalytic in general due to their extremely high pattern of reactivity.

Despite extensive work for many years the mechanisms of these reactions are still not completely clear (Scheme 1.7).[39] However, the broad strokes of mechanism are generally understood as a whole and are briefly described here using the case of a Grignard reagent being added to an enone as an example. The copper and ligands tend to form different species which are in equilibrium in solution. An active species is formed when the Grignard reagent reacts with a copper species.[39-41] This active species then reacts with the Michael acceptor, forming a π-complex. A hard Lewis acid, here $MgBr_2$, coordinates to the carbonyl oxygen atom while the copper interacts with the olefin. This tandem reactivity seems to be a key part of the reaction mechanism. Then, a transient copper(III) σ-complex is formed leading to fast reductive elimination. The resulting enolate is converted to the corresponding product upon work up. The copper cation is released in

solution where it can reform an active catalyst for a new reaction cycle. In some cases, other mechanistic routes such as carbo-cupration seem to be favoured.[39]

There are some differences depending on the nature of the organometallic species.[39] In the case of dialkyl zinc, there is transmetallation of one alkyl group to the copper before both metals (copper and zinc) interact with the enone in a similar way to the one described above. The case of lithiated species is a bit different as well as the metals forms clusters in solution. These break when interacting with nucleophiles. But this is essentially the same mechanism occurring each time.



Scheme 1.7: Generic mechanism of copper catalysed conjugate addition of a Grignard reagent to an enone.[42]

A number of reviews[42,43] have been published recently on the topic, including extensive contributions from Feringa[44,45] and Alexakis.[46,47] These reactions can be used to trigger further functionalisation processes by domino reactions[48] and have been used to synthesise many natural products,[49] and have been the subject of investigations on their mechanism.[50] Despite wide use in academia, copper catalysed reactions based on the conjugate addition of dialkylzinc have not been used on large scale due to safety issues.[51] Indeed, a specific issue with species such as Et_2Zn comes from the quenching of the reaction. Indeed any spare molecule of this particular organometallics left will produce some highly flammable gas (*e.g*. ethane). The large amount of gas would require a large space (or it would dramatically increase the pressure of the reactor). This specific issue prevents the use of this type of method. In addition, the dialkyl zinc reagents are

expensive (10 times more expensive than their Grignard equivalents), thereby limiting the interest of such method. New reactions have to be developed in order to achieve asymmetric conjugate addition under milder conditions that can be safely applied on larger scale. This work is the main focus of this thesis.

Ligands

A significant factor contributing to the success of asymmetric organometallic methods is the design and use of chiral ligands to control reactivity and selectivity.[52] These molecules, usually containing an organic core, are linked to the metal through covalent, non-covalent or electrostatic interactions.[53] Some self-assembling ligands which produce catalytically active clusters in solution have also been developed.[54] Ligand symmetry, e.g. C_2-symmetry, is often important in their reactivity.[55] Usually the symmetry is used to minimise the potential numbers of ways of association of reagent and catalyst.

In case of a reaction with a prochiral substrate, ligands either block or favour, one intermediate diastereomeric transition state over the other, thus selectively forming the product. In contrast to chiral directing groups which require a stoichiometric amount of chiral material, chiral ligand can normally be used catalytically as the source of asymmetry.

Ideally, a ligand should be easily synthesised and handled, and highly modular in order to tune the structure for high selectivity. In some cases, they derive from natural products such as sparteine (Figure 1.2).[56]

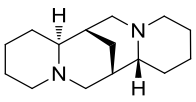


Figure 1.2: (−)-Sparteine

Privileged ligands

Some families of ligands are efficient in many different reactions that are seemingly unrelated. The term "privileged" was coined by Jacobsen to describe these families of ligands.[52] There are roughly a dozen families of privileged ligands (Figure 1.3). Their versatility makes them

extensively used. They have diffent factors introducing chirality (such as Brintzinger's ligand dispaying an axial chirality).

When a new asymmetric reaction is being developed, chemists often test these different ligand families to see which, if any, can induce asymmetry into the reaction. Once an efficient ligand has been identified, different variants within the same class can be screened in order to discover the optimal ligand for the reaction. Hundreds of ligands exist within each class, and this variety allows chemists to fine-tune the selectivity of the reaction.

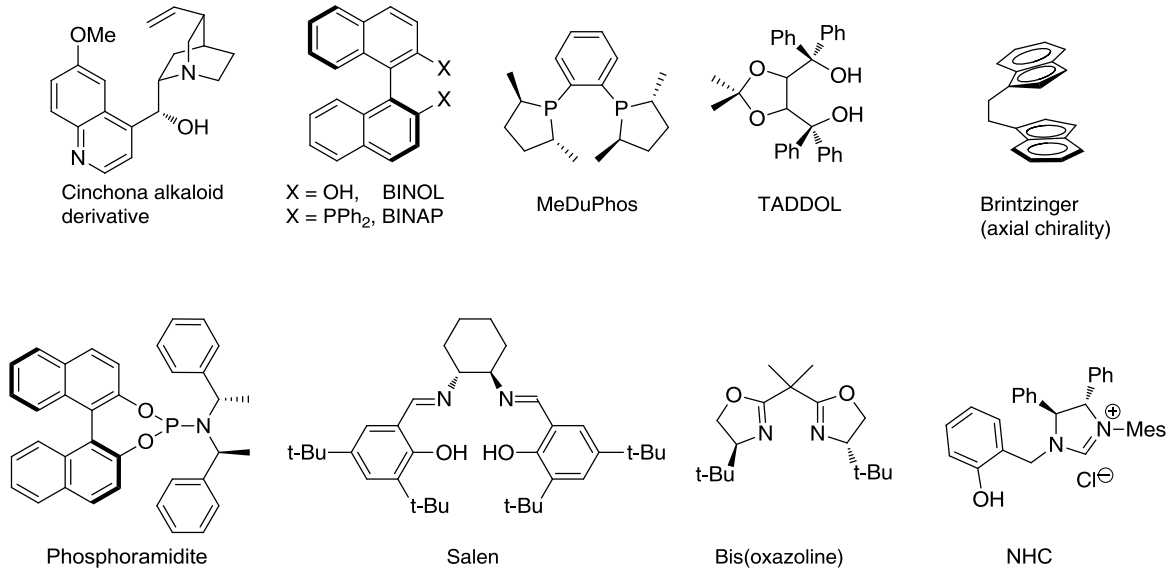


Figure 1.3: Families of privileged ligands

Since Jacobsen's list was published, many more ligands have been reported within each family, [43,57] and several new privileged classes have been identified. Amongst them, NHC (*N*-heterocyclic carbenes) ligands have become important in the field (both as ligands and as organocatalysts).[58] Similarly, phosphoramidite ligands have been incorporated in this list.[59,60] There is still constant work to improve the current structures for new reactions.

Common methods to design new ligands

From achiral ligands

One way to design new chiral ligands is to base them on existing, efficient non-chiral ligands. To achieve this, generally, an efficient ligand is first selected and then modified to render it chiral, and

then obtained in a non-racemic form either through asymmetric synthesis or resolution. Addition of non-racemic chiral substituents to the existing scaffold is a common approach. The new ligand is now chiral and may impart enantioselectivity during the reaction. This approach was used by Cramer to develop simple chiral phosphine ligands from achiral ones (Figure 1.4).[61]

There are a number of potential problems with this approach which limit its general applicability. For example, addition of an extra bulky substituent can modify the chemistry of the ligand if the metal-coordinating site is obstructed. Additionally, the chiral substituents might be far from the reaction centre and have little or no influence on the stereoselectivity of the reaction.

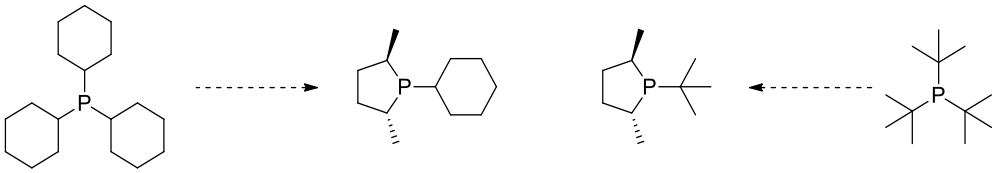


Figure 1.4: Design of chiral phosphine ligands from achiral phosphine ligands.[61]

Design based on mechanistic considerations

The rational design of ligands based upon knowledge of a reaction mechanism is an important strategy. A recent example, also reported by Cramer, involves a new chiral ligand for C-H bond functionalisation (Figure 1.5). Addition of substituents around a cyclopentadienyl core was envisaged as a way to block access to some faces of the metal.[62]

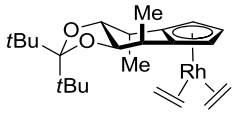


Figure 1.5: Cramer's cyclopentadienyl ligand

Improvement from known ligands

Many chemists attempt to improve the selectivity of ligands by altering the symmetry or the skeleton of a known ligand. The overall approach generally involves altering the steric properties of the ligand to make the new ligand more selective. For example, Mazet[63] and Aponick[64] have both modified well known *P*,*N*-containing ligands (Figure 1.6). In a similar way, other parameters such as electron density have been modified and found to affect the nature and

selectivity of the ligand. The development of fluorinated phosphine ligands or incorporation of carbohydrate-based scaffolds are such examples.[43,65]

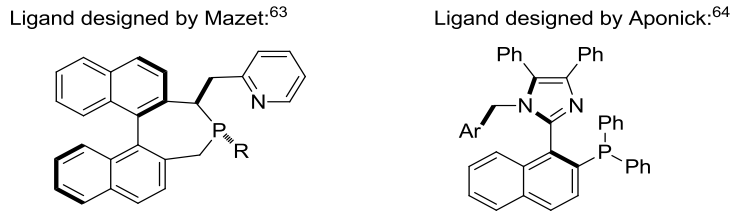


Figure 1.6: Different *P*,*N* ligand engineered by Mazet and Aponick

Phosphoramidite ligands

Following the introduction of phosphoramidite ligands by Feringa in 1996, they have been employed widely as effective ligands and have been recently classified as being a privileged family of ligands.[59,60] They are monodentate species which are easily synthesisable and modular in their structure, and often induce exceptionally high levels of stereocontrol (Figure 1.7). Variations with different 'backbones' namely, the bidentate non-amino portion, such as binaphthol (shown) or taddol, are known.[66,67] The way they interact with metals to induce asymmetry during reactions is not entirely understood.

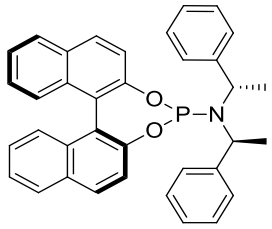


Figure 1.7: Phosphoramidite ligand (Feringa's ligand **A**).

Understanding and predicting the reactivity patterns of catalytic systems: Quantitative structure selectivity relationship (QSSR)

LFER in asymmetric reactions

The study of the relationship between the structure and reactivity of organic molecules is extremely important in understanding reaction mechanisms.[68] Quantitative structure activity relationships (QSAR) are mathematical models which attempt to explain the reactivity of chemical

systems. In these models, the activity or efficiency of a reaction is linked with the structure of the catalyst or substrate. Analogous correlations, between structure and biological activity have long been used in medicinal chemistry[69] but the use of this approach in catalyst design, more precisely called quantitative structure selectivity relationships (QSSR), is virtually unexplored.[70]

In the field of asymmetric catalysis, most research uses empirical methods and catalytic systems are generally sensitive to any alteration of reaction parameters. The energy difference between diastereomeric transition states (TS) leading to enantiomeric products is low (~10 kJ mol^{-1} at room temperature) making it difficult to study and quantify all the important interactions by classical methods.[71] These energy differences are similar to the energy for the rotation around a single carbon-carbon bond.

A linear free-energy relationship (LFER) is a mathematical correlation which relates the logarithm of a reaction rate ($\Delta\Delta G^{\ddagger}$) or equilibrium constant ($\Delta\Delta G^{\circ}$) for one series of reactions with a physical parameter of the reactions.[72] The ability to establish a LFER for a reaction can provide deeper understanding of the influential parameters. It can be predictive if the model is sufficiently robust.

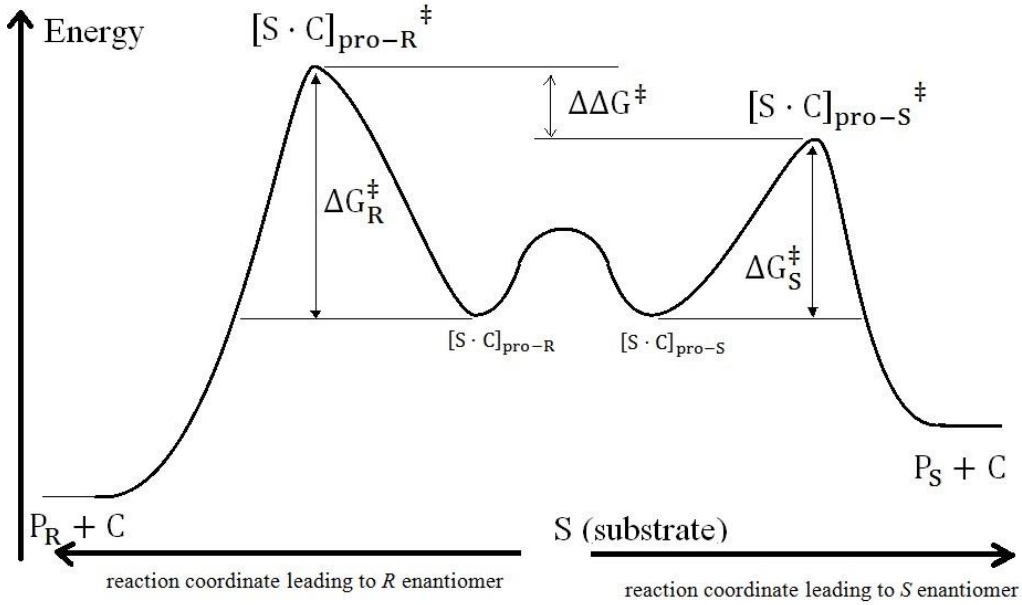


Figure 1.8: Reaction coordinate diagram for the application of the Curtin-Hammett principle to an asymmetric catalytic reaction. S = substrate, $[S{\cdot}C]_{pro\text{-}R/S}$ = diastereomeric substrate (R/S) + catalyst

(C) complex. $[S \cdot C]_{pro\text{-}S}$ = diastereomeric substrate (S) + catalyst (C) complex. $[S \cdot C]^{\ddagger}_{pro\text{-}R/S}$ = diasteremoeric substrate transition state. P_R, P_S = enantiomer *R*/*S* of the product.

To develop LFERs, two conditions are required:

- The evaluated variable can be modified systematically when all other variables are kept constant.
- The evaluated variable must have a proportional and meaningful effect on the reaction under study, relative to a reference reaction.

In the case of asymmetric reactions, a LFER relates to the asymmetric induction of chirality using the Curtin-Hammett principle (Figure 1.8).

The Curtin-Hammett principle links the kinetic profile of a reaction to its product distribution.[73] It states that, for a reaction which contains a pair of rapidly-interconverting reactive intermediates or reactants, each leading to a different product, the product ratio will depend both on the difference in energy between the two conformers and the free energy of the transition state going to each product. As a result, the product distribution will not necessarily reflect the equilibrium distribution of the two intermediates.

As asymmetric catalytic systems often involve the rapid equilibrium between diastereomeric substrate-catalyst complexes, the Curtin-Hammett principle can be applied. It indicates in this case that the reaction will proceed via the pathway with the lowest activation energy ($\Delta G^{\ddagger}$).[74]

By using a Gibbs free energy relationship (Equation 1.1), a representation of the relative rates of the formation of enantiomers ($\Delta\Delta G^{\ddagger}$) can be correlated to the enantiomeric ratio of the product (Equation 1.6).

$\Delta G = -RT \ln K_r$ **(Equation 1.1)**

$\Delta\Delta G^{\ddagger} = \Delta G_R^{\ddagger} - \Delta G_S^{\ddagger} = -RT \ (\ln K_S - \ln K_R)$ **(Equation 1.2)**

$\Delta\Delta G^{\ddagger} = -RT \ (\ln K_S - \ln K_R)$ **(Equation 1.3)**

$$\Delta\Delta G^{\ddagger} = -RT \ln\left(\frac{K_S}{K_R}\right) \quad \textbf{(Equation 1.4)}$$

$$\Delta\Delta G^{\ddagger} = -RT \ln 10 \times \log\left(\frac{K_S}{K_R}\right) \quad \textbf{(Equation 1.5)}$$

$$\Delta\Delta G^{\ddagger} = -RT \ln 10 \times \log(er) \quad \textbf{(Equation 1.6)}$$

K_r is the rate constant of the reaction, K_R is the rate constant of the reaction for the synthesis of enantiomer (*R*), K_S is the equilibrium constant of the reaction for the synthesis of enantiomer (*S*). (er) is the enantiomeric ratio of the product.

LFERs can explain and predict the influence of a substituent on a ligand. Similarly, LFER application can be used to study substrates of a catalytic system (Figure 1.9). LFER have been used in asymmetric catalytic systems to explore the relationships between electronic properties, acidity, steric bulk, and quadrupole moment to enantiomeric ratio.[72] Some important examples are detailed below.

Methodology of modelling

An accurate LFER requires the systematic perturbation of the studied system with ligands or substrates, and the ability to quantify the outcome.[48] To establish a correlation, the data under study have to be relevant to the reaction. The first task consists of identifying which critical part of the molecule needs to be perturbed and modelled.

To do so, chemists generally think in term of mechanism and transition state.[52] The stereoselectivity in the product is induced by the ligands and presumably, specific parts of the ligands are largely responsible for the selectivity of the ligand. Therefore, these 'key regions' are identified to allow their parameterisation. To investigate these key parameters, different methods exist:

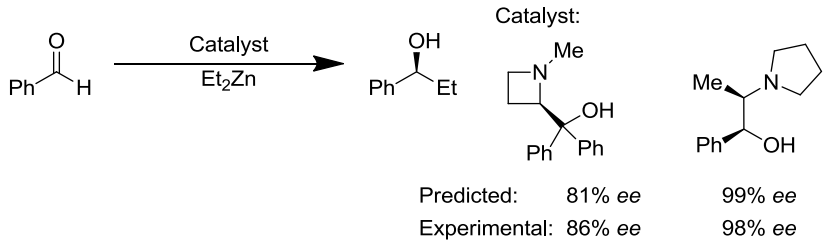
- Considering a plausible mechanism of the reaction, guessing how chirality is transferred in the transition state (TS) and therefore estimating which physical part of the ligand most strongly affects the energies of competing transition states. A drawback is that the real and

proposed mechanisms may differ significantly from what is envisioned (*e.g*. the reaction may occur through aggregation of different species present in solution). Therefore, the viability of this approach depends on having an accurate understanding of the reaction. More specifically, the necessity to grasp the details of the mechanism is crucial (*e.g*. for an aldol reaction, the assumption of a Zimmerman-Traxler transition state will show the 1,3-diaxal interactions are to be taken into account to explain the selectivity of the reaction).

- Using DFT (density functional theory) calculations to locate and analyse TSs on the potential energy surface (PES). By analysing the calculated intermediates, key regions of the ligand can be identified. However, this method may require many iterations to identify a plausible mechanism.

- If the mechanism is unknown, an empirical approach can be used, in which the ligand, catalyst and substrate are systematically varied until a major effect is noticed. This process may reveal key parameters, allowing for more detailed study. This approach relies heavily upon serendipity and may require extensive experimentation. Importantly, the reaction mechanism has to remain constant across a broad range of variations examined.

One of the pioneers in this area was Kozlowski, who established a semi-empirical model for asymmetric reactions. She first analysed boron aldol and allylation reactions and studied factors leading to enantioselectivity. She then established a model which determined which key parameters are affected by which type of ligand.[75] Afterwards, she designed a predictive model (using DFT calculation) for the enantioselective alkylation of aldehydes by dialkyl zinc, successfully predicting new chiral ligands for asymmetric induction (up to 98% *ee*) (Scheme 1.8).[76] She used the same method to predict the best ligand derived from sparteine in an asymmetric lithiation/ addition reaction.[77]



Scheme 1.8: Kozlowski's design of new ligands for asymmetric reaction.[76]

Modelling parameters and establishing correlations

Once key components of the ligand that influence enantioselectivity are identified, they must be parameterised. The usual way of computer correlation requires first modelling and then some experimental probe to check the accuracy of the attempted correlation.

As discussed below, choosing a means of parameterisation is another critical step. Indeed, each structural modification of the ligand requires parameterisation in order to later establish a correlation.

Modern computer-assisted methods can be used to model steric and/or electronic parameters.[72,78] Parameterisation methods record properties (polarisability, size, etc…) from the 'key factors' of the ligands or substrate. Different computational methods will weight these factors differently, and hence not all physical properties will affect the system to the same extent. Choosing appropriate parameters is both important and not trivial.

Once useful parameters are established, a correlation between experimental and modelled data can be attempted by linear regression. Typically, several parameters are implemented to achieve an efficient fitting of the data. More accurate models are expected to give a stronger correlation. While a higher correlation coefficient can be obtained by introducing extra cross-terms, ideally, the correlation obtained should be interpretable in a meaningful way.

Once the correlation is established, a 'test' series of ligands can be used to check the comprehensive nature of the model. If the model is effective, it could even be predictive.

Below, we describe some widely used methods of parameterising the structural features of ligands and substrates.

a) Hammett/Taft σ-parameters

One of the first ways of quantifying structural variation was developed by Hammett. This traditional method to establish a QSSR model has been implemented using Hammett parameters and derivatives thereof.[79] These parameters were established by systematically changing the substituents at the *meta*- and *para*- positions of benzoic acid from electron rich to electron poor, and comparing the pK_a of the acid. These correlations were obtained though studying the rate of hydrolysis of benzoate esters (Scheme 1.9). Taft modified the Hammett equation to take into consideration the steric influence of substituents; the more sterically hindered the ester, the slower the rate of hydrolysis.

Jacobsen used Hammett σ-electronic parameters to establish a LFER on his asymmetric epoxidation reaction.[80] He determined parameters to be modelled using a plausible mechanism supported by DFT calculations. A successful combination of Hammett and infrared based parameters (as a proxy for electronic effects) was used by Sigman when examining a C-H amination reaction.[81]

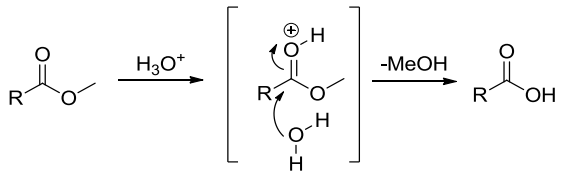
b) Taft/ Charton parameters

Charton parameters, derived from the Taft equation, are also widely used,[82] whereby the van der Waals radius of the substituent can be related to the rate of reaction. An often occurring limitation of the use of Charton parameters is that they are only valid in conformationally rigid systems, *i.e*. these parameters are not valid if the mechanism changes due to, for example, rotation of the substituents about a bond at a significant rate when compared to the rate of the reaction under study.[71]

Charton parameters were used by Sigman and co-workers to correlate the selectivity of a reaction to ligand structure. Working on the Nozaki−Hiyama−Kishi (NHK) allylation, they decided to model the effect of the alteration of one substituent on the ligand as they noticed this specific part of the ligand strongly affected the stereoselectivity.[83]

Through parameterising this substituent, they could model the system and predict key ligand features. Using the same approach, Sigman was able to model Denmark's cyclopropanation,

Pfaltz's allylic allylation, and Komatsu's alkene aziridination methods (after these methods were published and established).



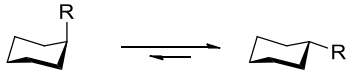
Scheme 1.9: The rate of this hydrolysis reaction depends on the size of R; this is the basis for how Taft/Charton parameters were defined.

Charton parameters have been used recently by Mazet *et al* to explain the isomerisation behaviour of allylic alcohols;[84] they probed the effect of different substrates using previously gained mechanistic insight as a supporting basis. In the copper-catalysed cyclopropanation of alkenes,[85] Carbo used Charton parameters, supported by DFT calculations, to correlate the predicted and experimentally determined enantioselectivity of several ligands.

Wiskur established a LFER with Charton parameters to support her mechanistic studies of a silylation-based kinetic resolution.[86] Bugault and Constantieux used Charton parameters to explain the selectivity of an organocatalysed conjugate addition on nitro-olefins.[87] Similarly, Alexakis has used Charton parameters to model an organocatalysed 1,2-sulfone rearrangement after empirical observations that the steric bulk of the substrate affected the result.[88]

c) A values

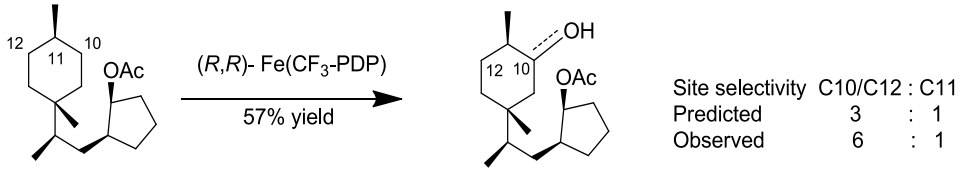
'A values' or 'Winstein−Holness values'[89] can be used to quantify steric factors. The A value of a group is related to the ratio of axial to equatorial conformers of the corresponding group on a cyclohexane ring (Scheme 1.10).



Scheme 1.10: Definition of the A value parameters (Winstein-Holness).

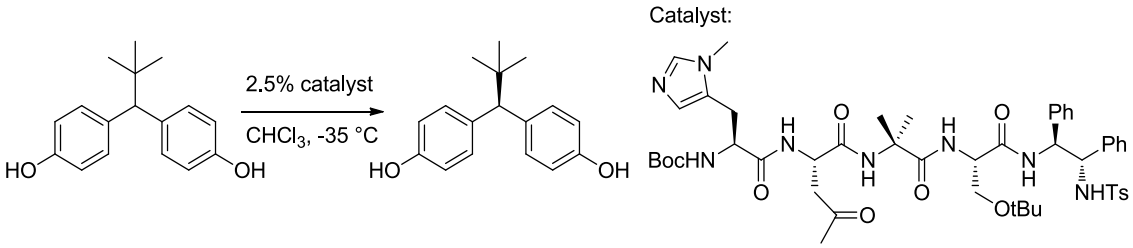
The expected 1,3-diaxal steric repulsion favours the equatorial conformer to a greater extent for larger substituents. This A value is therefore purely steric.

Using ‘A values’, White developed a predictive model in a C-H oxidation reaction (Scheme 1.11). White also added an extra term to include electronic properties,[90] this model was used to predict the regioselectivity of such oxidation reactions. Her initial modelling hypothesis was that the steric bulk of ligand on the metal would lead to some selectivity. The importance of the electronic factor was later revealed by DFT calculations on the catalyst precursor.



Scheme 1.11: White's prediction of selective C-H oxidation on a (+)-nectaryl derivative.

Miller and Sigman, in a desymmetrisation reaction of a diarylmethane-bis(phenol) (Scheme 1.12),[91] compared ‘A values’ and Charton parameters. Here, ‘A values’ explained the observed reactivity more accurately than Charton parameters. The bulky *t*-butyl group was taken as reference as it seemed important in the postulated mechanism.



Scheme 1.12: Miller's desymmetrisation reaction

d) Sterimol

Sterimol parameters take into account the dimensions of substituents, one length (L) and two orthogonal width parameters (B_1 and B_5) (Figure 1.9).[92] The width parameters are calculated for each substituent when viewed along the axis of the primary bond. B_1 refers to the minimal width of the substituent and is therefore dependent upon branching of the substituent. B_5 refers to the maximum size of the substituent. The use of these parameters takes, at least partially, into account the anisotropy of substituents.

The Sigman group developed a model for the Nozaki−Hiyama−Kishi (NHK) ketone propargylation which highlights the advantages of sterimol parameters. They decided to model two ligand substituents, whose alteration affected the enantioselectivity. Based on this approach, an initial model based on modified Charton parameters was established, which was predictive of novel and selective ligands.[93] However, the Charton parameters did not identify clearly the most important characteristics of the reaction. A further study using sterimol parameters led to a better model with greater predictability.[71]

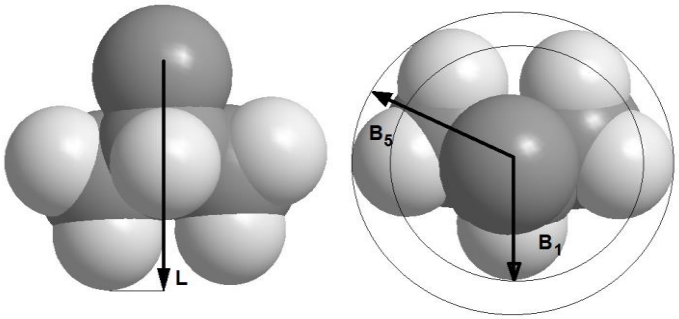
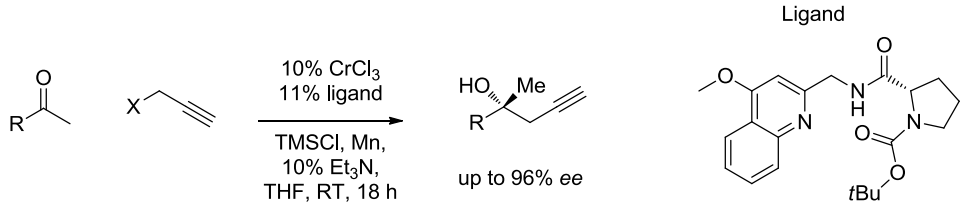


Figure 1.9: Parameterisation of an isopropyl group using Verloop's sterimol parameters.

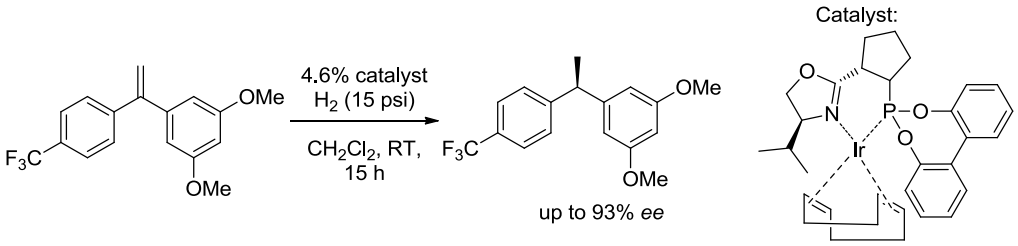
Using sterimol parameters, the model could be extended to ketones (Scheme 1.13). A substituent on the ligand and the structure of the ketone were determined to be key factors affecting enantioselectivity. This model was predictive and allowed optimisation of both ligand and substrate.[94]



Scheme 1.13: Sigman's study of the Nozaki-Hiyama-Kishi (NHK) ketone propargylation.

Using sterimol parameters, Song and co-workers established a QSSR for the catalytic asymmetric ethylation of ketones.[95] The discovery of key ligand substituents was empirical and based on easily derivatised and available precursors. A model, using both Charton and sterimol parameters, was established which allowed the design of efficient ligands and optimisation of the substrate scope.[96]

However, the inability of sterimol parameters to take into consideration non-steric interactions limits their use in some systems. Sigman recently observed that sterimol parameters were unable to fully explain the enantioselectivity trend of an iridium-catalysed reduction (Scheme 1.14).[97] He therefore extended this model by taking into consideration other descriptors, such as infrared vibrations. When combining infrared observations with a sterimol parameter model, Sigman established a comprehensive and predictive model to design an optimal substrate.[97] The combination of sterimol parameters and infrared spectroscopy was used to reassess models for different reaction systems and predict optimal substrates for certain catalysts under well-defined conditions.



Scheme 1.14: Sigman's study of iridium catalysed reduction.

Polarisability and H-bond length

The inclusion of IR data in Sigman's model highlights that the physical properties of molecules can be modelled to explain their reactivity. In their enantioselective thiourea-catalysed cationic polycyclisations, Jacobsen and Knowles quantitatively correlated the polarisability of substrates to induced enantioselectivity,[98] which helped to explain the observed selectivity in the process. The strength and direction of H-bonds was also used by Jacobsen to help understand enantioselectivity in study of an asymmetric Strecker reaction.[99]

The importance of DFT in supporting a QSSR derived mechanism

In addition to work based on QSSR relationships, theoretical studies (based on methods such as DFT) can provide insight into reactivity. Denmark recorded the effect that different alkyl groups present in the catalyst could have on enantioselectivity (QSSR) and used DFT studies to help develop a more meaningful and accurate model of supporting mechanism. [100]

Conclusion

Physical organic methods for correlating enantioselectivity to ligand structure are extremely promising and relatively unexplored tools for explaining reactivity in catalytic asymmetric reactions. Their use allows a better understanding of catalytic asymmetric reactions, and can even provide predictive power. Many parameters have been defined and exploited during the mid-20th century, and modern studies indicate that these can be used to explain reactivity in catalytic asymmetric reactions. However, no easily applicable parameters have been shown to be generally useful enough to serve as an obvious first choice in attempting to explain enantioselectivity patterns.

This field is still relatively new and many organic reactions have not been studied. In fact, most of the well-known "privileged ligands" have not even been studied, despite their obvious importance. These approaches have great potential in the prediction of new structures for highly stereoselective ligands, which could streamline asymmetric reaction development and organic synthesis, increasing the pace of research and optimising laboratory time.

As far as the methods have been developed, computational studies heavily rely on experimental insight (to engineer the method and to check the accuracy of the model). Therefore, the research is essentially performed by experimental research.

Chapter 2: Copper catalysed conjugate addition of alklyzirconocenes to cyclic enones

General Introduction

Alkenes are among the most readily available and inexpensive starting materials as they are derived from natural petroleum (by various processes such as cracking).[101] As well as being easily obtained, alkenes are generally stable, easy to handle, and can be used in many different classes of reactions to provide highly functionalised products. In addition, alkenes have been widely used in asymmetric methodology as they are often prochiral, making them suitable for the generation of new stereogenic centres.

Modern synthetic methods to produce olefins as substrates

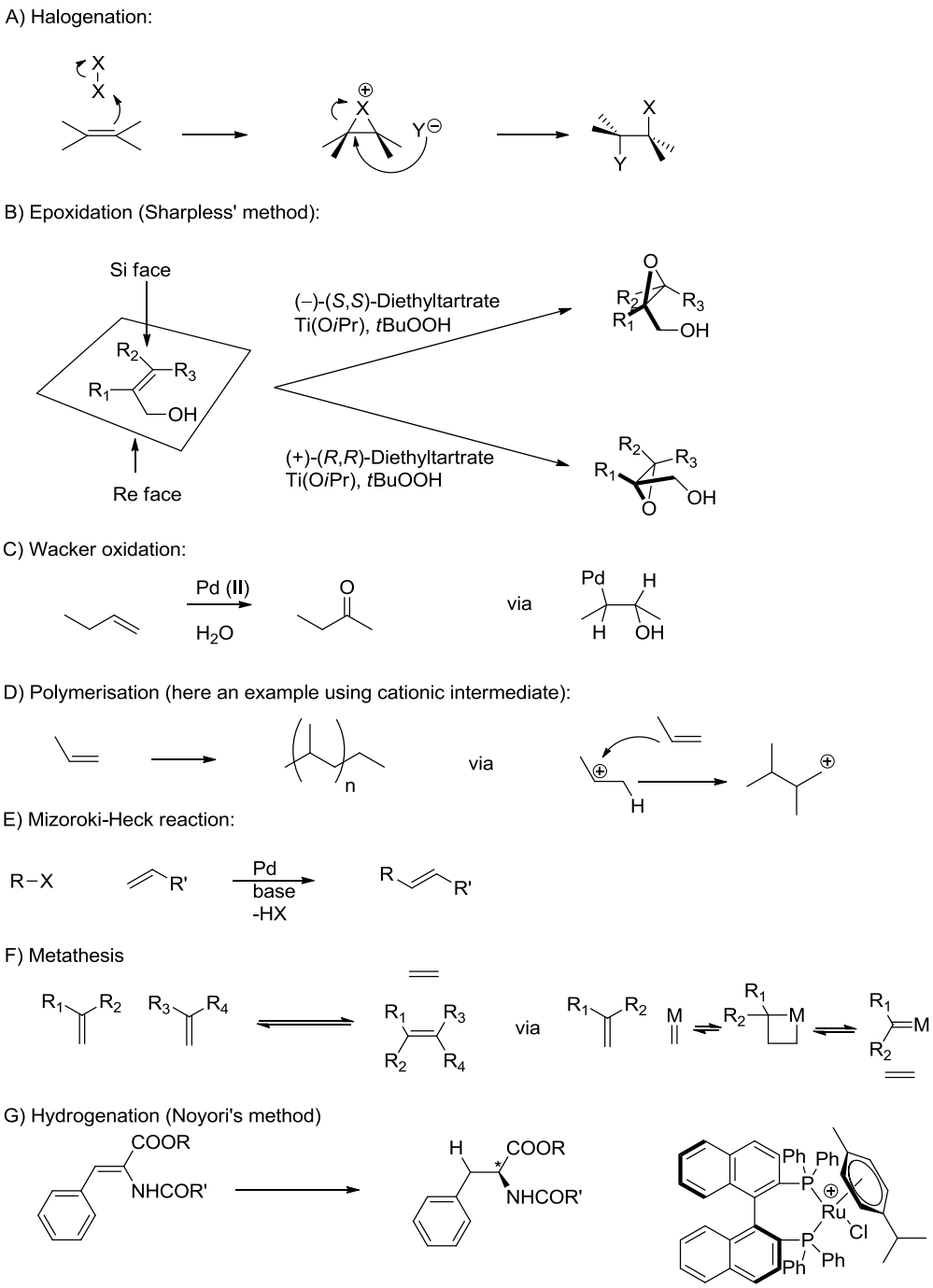
Below, we briefly survey methods that use olefins as starting materials. This is followed by a discussion of procedures for the hydrometallation of olefins, methodology central to this thesis, before moving on to original experimental work that uses this methodology.

Halogenations and Oxidations: The electron rich nature of olefins allows them to undergo a variety of important reactions. In particular, halogenation is a powerful means of functionalising molecules.[102] In this case (Scheme 2.1, A), the nucleophilic alkene reacts with strongly electrophilic halogens, forming an ionic intermediate which is trapped by a nucleophile to provide a halogenated molecule. As for most of these important reactions, an asymmetric variant exists.[103]

Similarly, epoxidation (Scheme 2.1, B), allows the formation of a new reactive functional group. The latter can occur enantioselectively via different methods including Sharpless' epoxidation, a powerful method recognised by the Nobel prize in 2001.[23]

The Wacker reaction[104] is a robust, industrially used,[105] process wherein the alkene is selectively converted to a methyl ketone (Scheme 2.1, C). Palladium (II) and copper (I) are used

catalytically with stoichiometric oxygen as the oxidant. The palladium (II) binds to the alkene, then a molecule of water attacks the complex and is incorporated into the molecule.



Scheme 2.1: Generic reactions using alkenes as starting material.

Carbon-carbon bond formation: The properties of alkenes have been used to design reactions establishing new carbon-carbon bonds. Several important methods allow the synthesis of polymers

(Scheme 2.1, D).[106] Ziegler-Natta polymerisation uses hafnium, titanium or zirconium catalysts in the polymerisation of alpha-olefins. This process can proceed under homogeneous or heterogeneous conditions.[107]

The Mizoroki-Heck reaction is another common method to form carbon-carbon bonds using olefins as substrate (Scheme 2.1, E). A palladium catalyst couples an unsaturated halide (or triflate) with an alkene in the presence of a base to form a substituted alkene.[108] These methods are compatible with a wide range of substrates and can be carried out on large scales.[105] A Nobel prize in 2010 was partially awarded for this reaction, further underscoring the importance of alkene-based chemistry.[109]

Olefin metathesis has become a very widely-used organic reaction (Scheme 2.1, F).[105] This reaction is an overall exchange of substituents between different olefins. Chauvin, Grubbs, and Schrock were awarded the 2005 Nobel prize in Chemistry for their contributions to the development of metathesis.[110] In these reactions, a transition metal atom (*e.g.* ruthenium/ molybdenum) binds to an alkene and catalyses a [2+2] cycloaddition to give a metallacyclobutane intermediate, which later undergoes a retro [2+2] cycloaddition to give a metal-carbene intermediate. Further cycloaddition / retro-cycloaddition reactions eventually give the metathesis products. A number of different catalysts can now be used to achieve the efficient synthesis of new alkenes, tolerating many functional groups.[111]

Reduction: Methods using hydrogen or hydrogenation transfer are used widely to reduce alkenes; Knowles and Noyori received a part of the 2001 Nobel prize in Chemistry for their work in developing asymmetric versions of this reaction (Scheme 2.1, g).[21, 22] Hydrogenation has been developed extensively and is applicable with a wide range of metals and substrates, under both homogeneous and heterogeneous conditions.

Hydrometallation

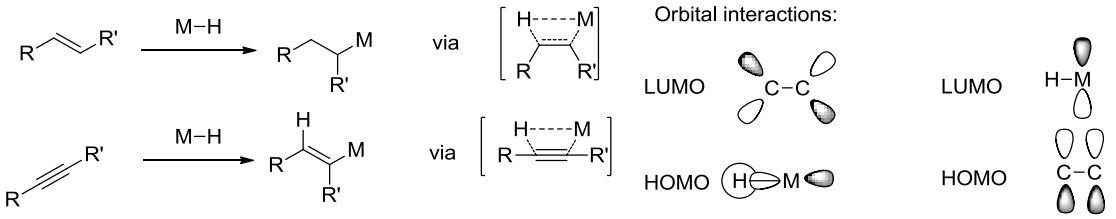
Hydrometallation is a process in which a metal-hydride bond adds to an unsaturated system such as olefins.[112] Overall, the new σ-bonds are more stable than the combination of the original π-

system and hydrometallating agent, making this reaction thermodynamically favourable. Orbital overlap between both species (Scheme 2.2) allows an efficient interaction. The reaction occurs via initial complexation of both species, to form a π-complex, followed by stereospecific *syn*-addition of the metal and the hydrogen to the unsaturated carbon atoms. The hydrometallation involves two different interactions:

- The first one involves the LUMO from the carbon carbon π- bond with the HOMO of the hydrometallating agent. This interaction occurs because of the favourable orbital overlap in space and energy matching. Such interaction breaks both the carbon carbon π-bond (by filling the antibonding orbital) and the metal hydride bond (as the atomic orbitals previously forming the σ-bond interact with the carbon carbon LUMO).

- The second interaction similarly involves the geometrically and energetically compatible orbitals LUMO from the hydrometallating agent and the HOMO from the carbon double bond. Here as well both orbitals are orthogonal to the broken bonds (carbon carbon π-bond and metal hydride σ-bond), therefore allowing a favourable interaction.

The combination of the previously mentioned interactions breaks two existing bonds (carbon carbon π-bond and metal hydride σ-bond) and forms two new stable chemicals bonds (metal carbon σ-bond and carbon hydrogen bond σ-bond).



Scheme 2.2: Hydrometallation reaction of alkene/alkyne with the orbital interaction.

This process occurs very efficiently for alkynes due to their electron rich *sp* character. Comparatively, alkenes may suffer from β-hydride eliminations, making the process potentially

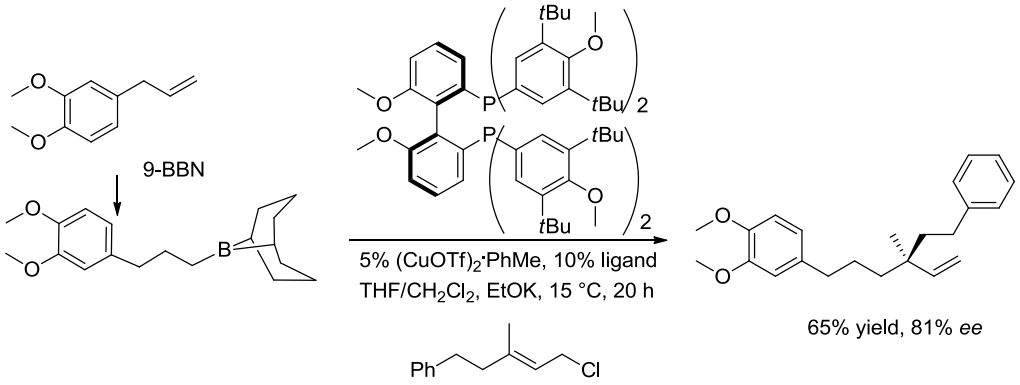
reversible. In the case of kinetically viable reversibility, the final product is ultimately that which is most thermodynamically stable. Factors such as steric interactions can allow hydrometallation processes to occur regioselectively.

Once hydrometallated, the new organometallic species can be further functionalised by taking advantage of the intrinsic new reactivity of the carbon-metal bond. However, organometallics are often less stable than alkenes and can degrade (*e.g*. they can hydrolyse or undergo other unwanted reactions). In practice, to overcome this sensitivity of organometallic reagents, they should be used shortly after hydrometallation.

Common hydrometallation reactions include hydroborations,[113] hydrosilation[114] and (as discussed in detail below) hydrozirconation with Schwartz-type reagents.[115] Among these regioselective processes, hydroboration and hydrozirconation are the most used methods due to the mild conditions of the reaction. Brown discovered that boron-based reagents could be used to generate organoborane species and exploited their reactivity.[113]

An important use for hydrometallated species is their use as a nucleophilic reagent. Indeed, the hydrometallation strategy readily forms an organometallic species. This latter can be activated in order to use the hydrocarbon chain for a further reaction. The main advantage of this strategy is the late formation of an organometallics which can be used readily. Hydroborated alkenes can undergo transmetallation to produce organozinc reagents.[116] This method, when combined with copper catalysis, allowed Feringa to perform asymmetric conjugate addition reactions.[67,117] Recently, Sawamura reported hydroborations of alkenes and direct use of these species as nucleophiles in copper catalysed conjugated addition[118] and allylic alkylation reactions[20] (Scheme 2.3). The method allowed the formation of quaternary carbon centres, which are typically challenging targets for such methods.[119] In this case, the reaction occurs by copper insertion and there is the present of a transient allyl species. The selectivity of the following reductive elimination creating either a S_N2 or a S_N2' adduct is influenced by the ligand. An electron rich ligand will stabilisted the allyl intermediate (and slow down the reductive elimination) therefore

favouring the S_N2 product (more stable as there is a the alkene is substituted). On the contrary, an electron withdrawing ligand will destabilise the intermediate and increase the pace of the reductive elimination, favouring the S_N2' product.



Scheme 2.3: Sawamura's allylic alkylation reaction.

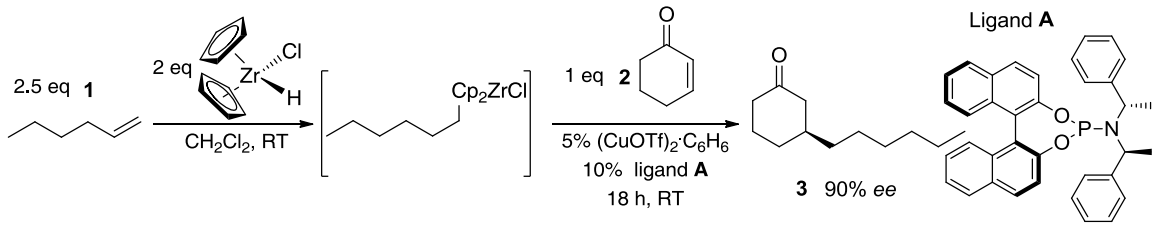
Conjugate addition

Asymmetric conjugate additions are a useful type of reactions. Methods have been published using a wide range of organo-[120] and organometallic-catalysts (including noble-metal catalysts *e.g.* rhodium),[33] with copper emerging as the metal catalyst of choice for adding primary organometallic reagents.[47,121] Processes using primary organometallic reagents are believed to undergo transmetallation to copper, and then addition to a Michael acceptor, which is often an enone.[33, 47] The primary organometallic is typically an organoaluminium or organozinc species, both of which are pyrophoric, or a more easily handled Grignard reagent. These reagents, however, generally have low compatibility with other functional groups.[47]

At the start of this work in 2010, the literature had no example of organometallic enantioselective conjugate addition method using copper catalysts, starting directly from alkenes using hydrometallation *in situ*. The aim of this research was to develop a method to allow the use of alkenes as the equivalents of primary organometallic nucleophiles in enantioselective conjugate addition. This new methodology would hopefully offer advantages over methods already known in the literature.

Progress in the development of the new methodology

At the start of this DPhil, work had been performed on this project by Dr Rebecca Maksymowicz, in the early stages of her own doctoral studies. She had developed a methodology to perform conjugate additions to cyclohexenone enantioselectively, achieving up to 90% *ee* (Scheme 2.4). This work was built upon research done by Wipf in the 1990's which allowed alkylzirconocenes to add to enones non-enantioselectively.[122] The new enantioselective method used alkylzirconocene reagents, prepared by addition of the Schwartz reagent to a terminal alkene in CH_2Cl_2 at room temperature. Upon completion of the hydrozirconation of hex-1-ene (**1**) (observable by formation of a clear yellow solution), the mixture was added to a premixed solution containing copper(I) triflate-benzene complex and a phosphoramidite ligand **A**. After mixing the species for five minutes, 2-cyclohexen-1-one (**2**) was added and the reaction left to stir overnight to afford adduct **3**. The reaction mechanism was unknown but assumed to be similar to that reported in Wipf's work or in other copper-catalysed conjugate addition reactions.[39,47] The reaction concentration, ratio of alkene to Schwartz reagent, catalyst loading are kept identical during all further studies described (Chapter 2-5) unless stated otherwise.



Scheme 2.4: Method developed by Dr Rebecca Maksymowicz in September 2010.

Although the reaction was reproducible, the desired ketone (**3**) could be isolated only in about 20% yield. All yield in this thesis are isolated yield. Additionally, the copper triflate complex ($(CuOTf)_2 \cdot C_6H_6$) was very air sensitive; finally, the method used to determine the enantioselectivity took several days as it required some derivatisation.

Without a sufficiently effective chromophore, UV detection could not be utilised to determine the enantiomeric ratio of products. Without access to GC apparatus at the time, the analysis to determine the enantiomeric excess had to be performed by derivatisation with (*R*,*R*)-(+)-DPEN (**4**)

using a procedure reported by Alexakis (Figure 2.1).[122,123] Integration of the ratio of resulting diastereomers (**5**) by ^{13}C NMR spectroscopy was used to determine the enantiomeric excess. This particular method was shown relatively accurate to determine *ee*s (± 5% *ee*) and required more than 1000 scans on 50 mg samples using a 500 MHz NMR setup. This method was effective but in practice was time-consuming.

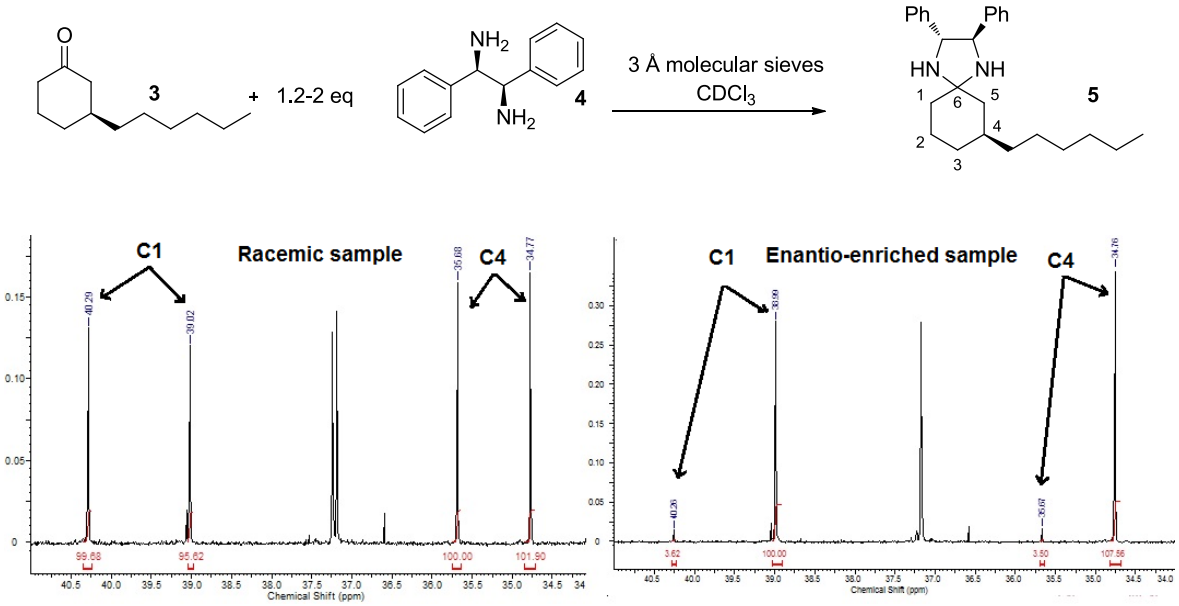
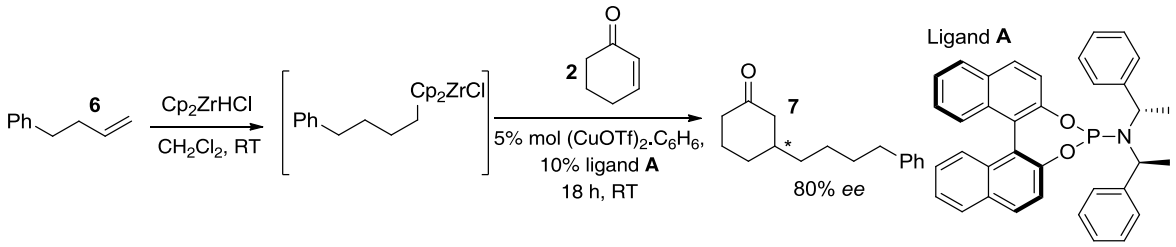


Figure 2.1: Method used to derivatise cyclic ketones and ^{13}C NMR integration of the corresponding diastereomers (left racemic product, right enantio-enriched product).

We decided to change the substrate so that a UV active product would be obtained. This product would allow us to use an HPLC with UV detector to determine the *ee* of the product. Wipf reported that styrene has a tendency to hydrozirconate at both the α- and β-positions of the alkene (due to electronic factors) so 4-phenyl-but-1-ene (**6**), a substrate bearing an aromatic ring, was used. Using previously developed conditions, the new product (**7**) was produced with 80% *ee*. Hypothetically, the reason for this decrease of enantioselectivity was the potential steric interaction of the phenyl ring with part of the catalyst. While lower enantioselectivity was observed using this alkene, it was much easier to determine the enantiomeric excess of the product (**7**) (Scheme 2.5). We therefore continued to use this alkene in subsequent optimisations of the reactions.



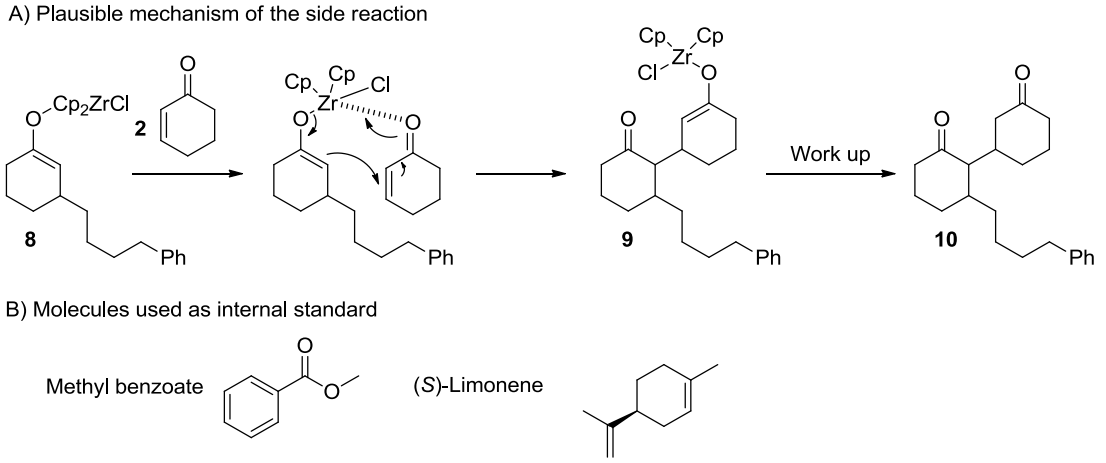
Scheme 2.5: New screening reaction using HPLC to analyse the enaniomeric excess.

Improving the yield

The yield of the reaction was low (around 20%) despite complete consumption of the starting material. Therefore it was assumed that either the starting material underwent a side reaction or the product was not stable under the reaction or purification conditions. To investigate the cause of the low yield, the reaction was carried out under racemic conditions on a larger scale (2 mmol instead of 0.4 mmol). Again, only 20% yield of the desired ketone (**7**) was obtained, but we were able to isolate a by-product (23% yield) which was then characterised and determined to be the ketone (**10**) (Scheme 2.6, A). It was assumed that during the course of the reaction, the enolate (**8**) initially formed during 1,4-addition underwent further reactions with another molecule of the enone starting material **2**. This side reaction therefore lowers the yield dramatically as one molecule of by-product (**9**) formed (turning into (**10**) upon work-up) consumes two molecules of starting material (**2**). The relative stereochemistry was not looked into but the two substituents are assumed to be anti to limit steric interactions. It was assumed the same process explained the low yield observed in the asymmetric reactions as well. It is likely that the new intermediate (**9**) can keep reacting and form polymer (never isolated).

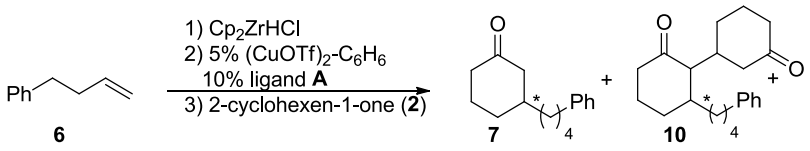
Attempts to calculate the conversion by ^{1}H NMR spectroscopy using an internal standard (Scheme 2.6 B) (methyl benzoate) failed because the ^{1}H NMR peaks from the desired product (**7**) and the by-product (**10**) were completely superimposed. Possibly this molecule could affect the reaction by chelating to the catalyst. As the NMR spectra were not clear due to complete proton overlap, (*S*)-limonene was used as an internal standard in ^{13}C NMR spectroscopy. Integration of the resulting spectra showed disappearance of the starting material and large amount of both product (**7**) and by-product (**10**). Better results arised from the used of GC methods. Monitoring reactions by GC-MS

also showed the presence of by-product (**10**) and this side reaction was always found to occur under the reaction conditions. In some cases, by-product (**9**) presumably kept reacting to form oligomers or polymers which were never explicitly observed.



Scheme 2.6: A) Plausible mechanism of the side reaction, B) Molecules used as internal standard.

In an attempt to minimise this undesired reaction, we screened other solvents and reagents stoichiometries (Table 2.1).



Entry	Solvent	Isolated yield of (**7**)	*ee*	Isolated yield of by-product (**10**)
1	CH_2Cl_2	21%	81%	23%
2	Et_2O	37%	79%	20%
3	THF	30%	75%	26%
4	Toluene	33%	70%	17%
5	Et_2O / 3 eq Schwartz 4 eq. alkene **6**	31%	80%	24%
6	Et_2O / 4 eq Schwartz	26%	74%	22%

	5 eq. Alkene **6**			

Table 2.1: Screening solvent and nucleophile stoichiometries.
Conditions: alkene (**6**) (2.5 eq), Cp_2ZrHCl (2.0 eq), $(CuOTf)_2 \cdot C_6H_6$ (0.05 eq), ligand **A** (0.1 eq), enone (**2**) (1.0 eq), RT, *ee*s determined by HPLC.

Changing solvents (entries 1-4) gave very similar results in term of yield (always less than 40%) and a similar amount of by-product was isolated in all cases. Therefore an excess of nucleophile (Schwartz reagent/alkene combination, entries 5-6) was used to attempt to limit the number of side reactions. This did not result in higher yields and this gave the indication that the side reaction was fast under our reaction conditions.

Other groups have also observed undesired side reactions through enolate trapping,[124] including Brønsted acids catalysed double 1,4-addition reactions.[125] It was assumed that the zirconium enolate (**8**) was the origin of the side reactions and that the desired reaction (copper catalysed conjugate addition) and further 1,4-addition (of the zirconium enolate) occur at comparable rate.[126,127] Interestingly, Hoveyda reported the trapping of lactone enolates *in situ* with an aldehyde (benzaldehyde) could avoid related polymerisation reactions to create the corresponding aldol adduct. Hoveyda could then obtain the desired 1,4-addition products by using a retro-aldol reaction.[128] To do so, he used a base which shifted the equilibrium of the reaction towards ketone and aldehydes.

Zirconium enolates formed from esters have also been shown to promote polymerisation.[129] A literature survey of the behaviour of zirconium enolates reveals some apparently contradictory results on their stability (Figure 2.2). Indeed, they seem to be stable under low temperature conditions (−78 °C)[129] but some groups report reactivity of these reagents at this specific temperature.[130]

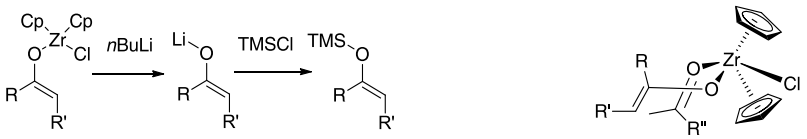
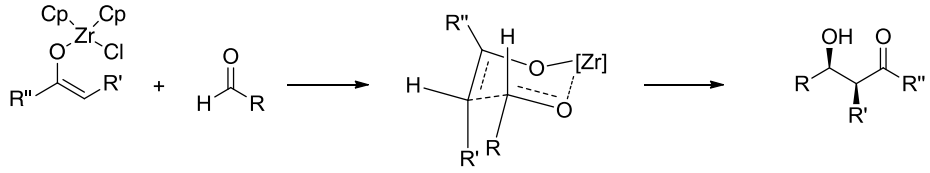


Figure 2.2: Evans' zirconium enolate trapping (left) and zirconium enolate structure (right).

Evans reported trapping zirconium enolates as silyl enol ethers in a two-step procedure. First by transmetallation from zirconium to lithium (*n*-BuLi at −78 °C) and then by addition of TMSCl.[130] These reaction conditions were required as zirconium is highly oxophilic, resulting in a strong zirconium-oxygen bond.

Some zirconium enolates have been isolated[127] at low temperature (–78 °C) and characterised by X-ray crystallography.[131] Based on a reported x-ray structure we hypothesised that the zirconium enolate structure may hold additional ketone starting material in close vicinity (as shown in Figure 2.2), facilitating the undesired oligomerisation reaction. Related structures have been invoked by other chemists performing aldol chemistry using zirconium enolates,[132] for example Yamamoto and Evans, who showed that zirconium enolates perform aldol reactions to give products with a preferred "*erythroi*" configuration (Scheme 2.7).[126, 130, 133]



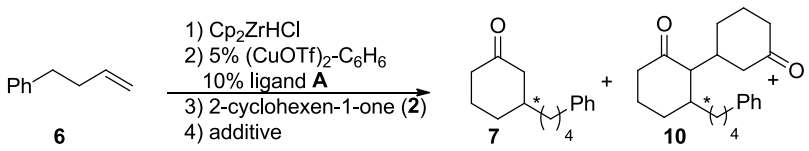
Scheme 2.7: Zirconium enolates facilitating aldol reaction.

Based on these insights, different strategies were envisioned: 1) Use of an unreactive sacrificial ketone which could be used to occupy an empty coordination site on the zirconium enolate. If this ketone would bind competitively to the enolate relative to cyclohexenone then it would inhibit the side reaction; 2) Use of a reagent to trap the enolate. Therefore the second undesired conjugate addition would not occur.

Based on these strategies, a series of reactions were performed where we either added a potential trapping reagent or added a sacrificial ketone (keeping all other parameters constant). Roughly a third of this work was performed by Dr Rebecca Maksymowicz.

A control reaction was run and no product was formed when no metal (CuOTf) was used (only reduced allylic alcohol was recovered). Adding one equivalent of TMSCl (Table 2.2, entry 1)

improved the yield of the reaction in CH_2Cl_2 to 37% and the enantioselectivity to 85% *ee*, but this was poorly reproducible. 5 equivalents of TMSCl (entries 2-4) increased the yield of ketone (**7**) to 40% and the enantioselectivity to 87% *ee* but the reaction was again poorly reproducible in CH_2Cl_2 (entry 3 versus 4). Change of solvent and temperature (entries 5-7) did not improve the yield. Using more reactive silicon sources (entries 8-12) to attempt to promote the change of enolate from zirconium to silicon was detrimental to enantioselectivity. Other silicon sources did not improve the results either (entries 13-17). The interesting and unexpected result here was the case of the increase in enantioselectivity when TMSCl was added. When TMSCl was used, the reaction time was also reduced from about 12 hours to ~3 hours with most substrates examined, presumably because of the substrate activation. The effect of TMSCl on copper catalysis had been studied[134] and it has been shown that silicon-based reagents can sometimes improve results.[135] It is possible that the silyl reagent activates the carbonyl while the copper interacts with the carbon-carbon double bond.

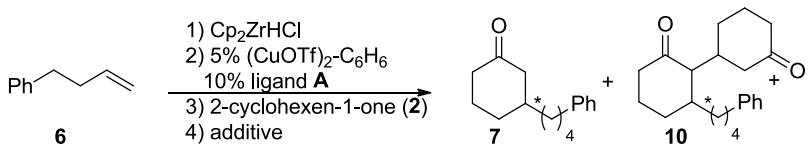


Entry	Reagent	Solvent	Equivalents of additive	Isolated yield of (**7**)	*ee*	Isolated yield of by-product (**10**)
1	TMSCl	CH_2Cl_2	1	20%	85%	Not isolated
2	TMSCl	Et_2O	5	37%	89%	27%
3	TMSCl	CH_2Cl_2	5	35%	85%	Not isolated
4	TMSCl	CH_2Cl_2	5	21%	77%	30%
5	TMSCl	CH_2Cl_2 / 0°C	5	31%	82%	Not isolated
6	TMSCl	*t*-BuOMe	5	16%	80%	Not isolated
7	TMSCl	Me-THF	5	33%	80%	Not isolated
8	TMSOTf	Et_2O	1	Not isolated	48%	Not isolated
9	TMSOTf	Et_2O	5	40%	63%	27%

10	TMSBr	Et_2O	3	traces	0%	Not isolated
11	TMSI	Et_2O	3	traces	0%	Not isolated
12	TMSI	Et_2O	2	traces	60%	Not isolated
13	IPrDMS-Cl	Et_2O	5	30%	74%	16%
14	TES-Cl	Et_2O	5	34%	78%	Not isolated
15	TBDMS-Cl	Et_2O	5	27%	75%	Not isolated
16	TBS-OTf	Et_2O	5	25%	25%	Not isolated
17	TIPS-Cl	Et_2O	5	29%	77%	Not isolated

Table 2.2: Screening of silyl based additives.
Conditions: alkene **6** (2.5 eq), Cp_2ZrHCl (2.0 eq), $(CuOTf)_2 \cdot C_6H_6$ (0.05 eq), ligand **A** (0.1 eq), enone **2** (1.0 eq), additive, RT. *ee*s determined by HPLC.

As the boron-oxygen bond is also strong, we supposed that boron based reagents as additives may be effective for enolate trapping. A set of boron based reagents was examined (Table 2.3 entries 1-6) but no improvements were observed. A large number of equivalenst of additives was used as TMSCl was most efficient in this ratio. No addition of ethyl nucleophile in entries 3-5 was noticed presumably because the boron reagent was not activated into an 'ate' complex. Other oxophilic reagents based on titanium and aluminium (entries 7-9) also did not improve results. The absence of copper (entry 10) or the use of other additives such as additional ligand (entry 12), LiCl (entry 11), and bases (entries 13-15) also did not improve the results.



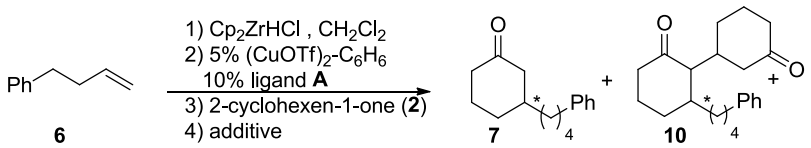
Entry	Reagent	Other /Solvent	Equivalents of additive	Isolated yield of (**7**)	*ee*	Isolated yield of **(10)**
1	$B(OMe)_3$	Et_2O	5	11%	81%	20%
2	$B(OiPr)_3$	Et_2O	5	7%	77%	Not isolated
3	Et_3B 1M hexane	Et_2O	5	26%	79%	25%

4	Et_3B 1M hexane	CH_2Cl_2	5	25%	75%	Not isolated
5	Et_3B 1M hexane	0°C	5	31%	82%	Not isolated
6	$BF_3 \cdot OEt_2$	Et_2O	1	0%		Not isolated
7	$Ti(OiPr)_4$	Et_2O	2.5	0%		Not isolated
8	$TiCl_4$ (1M hexane)	Et_2O	2.5	0%		Not isolated
9	$Al(OEt)_3$	Et_2O	2	14%	69%	Not isolated
10	TMSCl	Et_2O / No Copper added	5	traces		0%
11	LiCl	Et_2O	5	25%	46%	Not isolated
12	Ligand **B**	Et_2O / 5 eq TMSCl	0.1	37%	90%	Not isolated
13	TMEDA	Et_2O / 5 eq TMSCl	0.5	0%		Not isolated
14	Hunig's base	Et_2O / 5 eq TMSCl	0.5	33%	59%	Not isolated
15	K_2CO_3	Et_2O / 5 eq TMSCl	0.5	30%	83%	Not isolated

Table 2.3: Screening of other additives.
Conditions: alkene (**6**) (2.5 eq), Cp_2ZrHCl (2.0 eq), $(CuOTf)_2 \cdot C_6H_6$ (0.05 eq), ligand **A** (0.1 eq), enone (**2**) (1.0 eq), additive, RT. *ee*s determined by HPLC.

To obtain a better yield, the strategy of adding a chemical to occupy zirconium empty orbital (as described above) to inhibit the side reaction was investigated (Table 2.4). Addition of alcohols (entries 1,2 and 5) mostly led to quenching of the reaction, likely due to the presence of an acidic proton. Use of alcoholate was detrimental as well as it quenched the reaction (entries 3 and 4). Other Lewis basic additives were added to attempt to occupy the empty orbital of the zirconium enolate. Nitrogen-containing additives (entries 6-11) essentially stopped the reaction, while ketones (entries 12-14) did not affect the outcome of the reaction much at all. Mixing ketones or nitrogen additives

with TMSCl (entries 15-19) also did not lead to an increase in selectivity. Other Lewis bases were tried (entries 20-24) but they did not improve the yield of the reaction either. Use of deuterated acetone was done to try to compare result with regular acetone in case of trapping. Although this approach was unsuccessful, it is worth noting that even in the presence of reactive chemicals such as acetic anhydride the reaction proceeded (entry 20), suggesting that the method was robust. No by product or side reaction was observed.



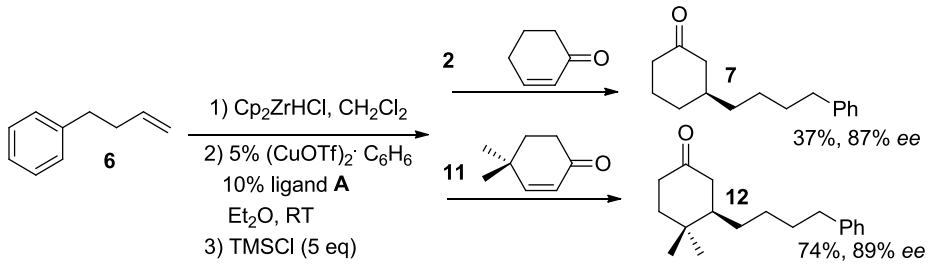
Entry	Additive	Solvent	Equivalent	Isolated yield of (**7**)	*ee*	Isolated yield of (**10**)
1	*t*-BuOH	Et_2O	5	10% (brsm)	72%	Not isolated
2	*t*-BuOH	Et_2O	2.5	traces	50%	Not isolated
3	*t*-BuONa	Et_2O	2.5	4%	79%	Not isolated
4	*t*-BuOK	Et_2O	2.5	traces	81%	Not isolated
5	Propanol	Et_2O	2.5	traces	50%	Not isolated
6	Dimethylpyrimidinone	Et_2O /Added before copper	2.5	49% (brsm)	0%	5%
7	Dimethylpyrimidinone	Et_2O / Added after copper	2.5	0%		Not isolated
8	1-Methyl-2-pyrrolidinone	Et_2O	2.5	traces	50%	Not isolated
9	Pyridine	Et_2O	2.5	0%		Not isolated
10	Pyridine	Et_2O	2	0%		Not isolated
11	1-Methylimidazole	Et_2O	2	0%		Not isolated
12	Benzophenone	Et_2O	2	25%	74%	Not isolated
13	Benzophenone	Et_2O	1.1	31%	76%	Not isolated
14	Cyclohexanone	Et_2O	2	24%	67%	Not isolated
15	1,5-di-*t*-Butyl, 3-methylpyridine	Et_2O / 5 eq TMSCl	1.5	22%	76%	22%

16	1,5-di-*t*-Butyl, 3-methylpyridine	Et_2O / 5 eq TMSC	0.5	40%	86%	22%
17	Diethyl methylphosophonate	Et_2O / 5 eq TMSC	1.5		23%	Not isolated
18	3-Pentanone	Et_2O / 5 eq TMSC	1.5	30%	87%	Not isolated
19	Cyclododecanone	Et_2O / 5 eq TMSC	1.5	~ 25%	63%	Not isolated
20	Acetic anhydride	Et_2O	5	~ 20%	66%	Not isolated
21	Diethylcarbonate	Et_2O	2	18%	77%	Not isolated
22	Deuterated acetone	Et_2O	2	14%	72%	Not isolated
23	DMSO	Et_2O	2	0%		Not isolated
24	PPh_3	Et_2O	2.5	Not isolated	43%	Not isolated

Table 2.4: Screening of additives possessing an electronic lone pair.
Conditions: alkene (**6**) (2.5 eq), Cp_2ZrHCl (2.0 eq), $(CuOTf)_2 \cdot C_6H_6$ (0.05 eq), ligand **A** (0.1 eq), enone (**2**) (1.0 eq), additive, RT. *ee*s determined by HPLC.

A different substrate

As these above efforts to minimise the side reaction were unsuccessful, it was decided to change the substrate used in the reaction. We set out to find a substrate that would not suffer from the same competitive side reactions and it was hoped that if the rate of 1,4-addition and oligomerisation were substantially different, then the yield of the reaction would be higher. Acyclic ketones did not give acceptable levels of enantioselectivity at this stage and will be discussed in chapter 5.

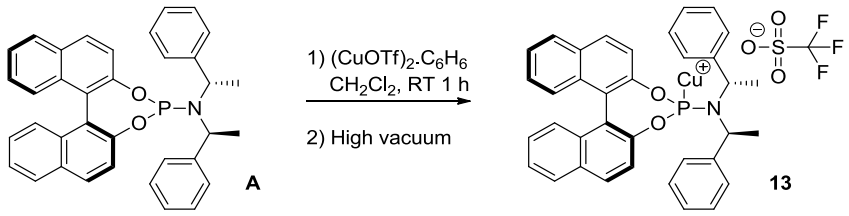


Scheme 2.8: Screening of different enones.

Other cyclic ketones were tested by Dr Rebecca Maksymowicz (Scheme 2.8). Hindered dimethyl enone (**11**) gave ketone (**12**) with high yields (74%) and *ee* (89%). This suggested that 1,4-

addition and by-product formation are not highly competitive with this ketone, presumably for steric reasons. From that point, (**11**) was used as a standard substrate.

The optimal conditions were found to involve using Et_2O as solvent with TMSCl. From this point, air stable precatalyst complex (**13**), prepared by Dr Rebecca Maksymowicz (Scheme 2.9), was used and the results became highly reproducible. The complex (**13**) was preformed by mixing a 0.5:1 ratio of $(CuOTf)_2 \cdot C_6H_6$ and Feringa's ligand **A** (*i.e.* 1:1 ratio of copper to ligand). After stirring one hour, the solvent was filtered, removed under high vacuum and the complex, obtained as a grey powder, was stored under argon. The filtration ensures there is no free copper species in solution. This complex is now commercially available (Sigma Aldrich catalogue number: L512532) and was used for all subsequent screenings in this chapter.



Scheme 2.9: Synthesis of complex (**13**).

Substrate scope

Alkene screening

We tested the scope of alkenes compatible with these reaction conditions (Table 2.5). Dr Rebecca Maksymowicz performed approximately half of these experiments. As before, the enantiomeric excess of the compounds was determined by derivatisation of the molecules with (+)-(*R*,*R*)-DPEN (**4**) followed by ^{13}C NMR spectroscopy using Alexakis's method[123] or by HPLC using a non-racemic chiral solid phase. High levels of enantiomeric excess (89% *ee*) and yields (67-74%) were observed with alkenes bearing aromatic substituents as well as with terminal linear alkenes (entries 1-4). Sterically hindered *tert*-butyl (**19**) and cyclohexyl-substituted olefins (**21**) and

(**23**) respectively (Entries 5-7) performed well, giving 65% yield and 84% *ee* and up to 74% yield and 93% *ee* (entry 6).

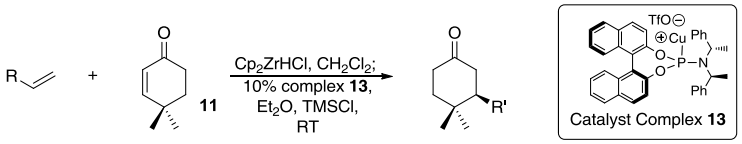
The method tolerated the incorporation of terminal alkene (**25**) to produce (**26**) with 71% yield and 78% *ee*. Here, the reaction was performed by using 10 equivalents of the alkene (**25)** to statistically favour mono hydrozirconation. The incorporation of an internal alkyne (**27**) (entry 9) was interesting as the alkyne was not hydrozirconated and the reaction still proceeded swiftly, suggesting an electron rich triple bond could be incorporated without too much decrease in selectivity (62% yield, 72% *ee*).

Application of the method to styrenyl substrate (**29**), which are activated relative to olefins, was also successful (entries 10 and 11). The naphthyl group (**31**) could be introduced in good yield and enantiomeric excess (entry 11). This functional group frequently appears in material science and ligand design because of its steric bulk and ability to induce π-stacking interactions. This method therefore allows the engineering of molecule bearing this key functional group.

Substrates with different heteroatoms were tested under these conditions. Product (**34**) (entry 12), obtained with low yield and selectivity (19% yield, 71% *ee*) is interesting as the intermediate nucleophilic species would be present in solution with a strong electrophile (allylic chloride (**33**)). However, there was no detection of any other product which could explain the low yield due to a side reaction. Incorporation of alkenes bearing terminal bromides (entries 13-14) resulted in ketones (**36**) (58% yield) and (**38**) (66% yield) with high level of enantioselectivity (76% *ee*). Interestingly, no trapping of the bromide was observed here compred to the side reactions observed previously. It was assumed the reason was the electrophilic bromide was not activeated here while the zirconium adduct increased the nucleophilicity of the enolate at the optimisation stage (through interaction with a second ketone).

This result was interesting as similar methods do not tolerate generally the incorporation of alkylhalides in the nucleophilic adduct. Internal alkenes (not shown) were tested but gave disappointing yields. These products may potentially be further functionalised in order to make more complex molecules. Protected alcohols (entries 15 & 16) could be obtained with high levels of stereocontrol and acceptable yields (54% yield and 80% *ee* for (**40**) and 49% yield, 94% *ee* for (**42**)).

The incorporation of a silyl group (**43**) (entry 17) was achieved using allyl silane as nucleophile (53% yield, 96% *ee*) although the reaction had to be performed at 0 °C to obtain high yield.



Entry	Substrate	Product	Yield[a]	*ee*[b]	Entry	Substrate	Product	Yield[a]	*ee*[b]
1	**6**	**12**	74%	(*R*)-89%[c,d]	10	**29**	**30**	56%	(*R*)-82%[c]
2	**14**	**15**	65%	(*R*)-89%[c]	11	**31**	**32**	52%	(*R*)-71%[c]
3	**1**	**16**	67%	(*R*)-89%[d]	12	**33**	**34**	19%	(*R*)-71%[d]
4	**17**	**18**	70%	(*R*)-89%[d]	13	**35**	**36**	66%	(*R*)-76%[c,d]
5[e]	**19**	**20**	65%	(*R*)-84%[d]	14	**37**	**38**	58%	(*R*)-76%[c,d]
6	**21**	**22**	74%	(*R*)-93%[d]	15	**39**	**40**	54%	(*R*)-80%[c]
7	**23**	**24**	60%	(*R*)-87%[d]	16	**41**	**42**	49%	(*R*)-94%[d]
8[g]	**25**	**26**	71%	(*R*)-78%[d]	17[h]	**43**	**44**	53%	(*R*)-96%[d]
9[e]	**27**	**28**	62%	(*R*)-72%[c]	18 19	**45**	**46**	62%[f] 93%[f]	(*R*)-85%[d,i] (*R*)-70%[i,j]

[a]Isolated yield. [b]Absolute configurations known, determined or assigned by analogy. [c]Ee determined by HPLC. [d]Ee determined by derivatization and ^{13}C NMR spectroscopy.[e]Reaction heated at hydrometallation stage. [f]Isolated as a 1:1 mixture of diastereomers. [g]Ten equivalents of the alkene was used. [h]Reaction performed at 0 ºC. [i]Ee determined by removal of the silyl group and HPLC. [j]Conditions: alkene **45** (2.0 eq.), Cp_2ZrHCl (1.7 eq.), **13** (0.05 eq.), 1.90 grams of product isolated.

Table 2.5: Scope of alkenes.
Conditions: alkene (2.5 eq.), Cp_2ZrHCl (2 eq.), enone (**11**) (1 eq.), complex (**13**) **(**0.1 eq.), TMSCl (5 eq), RT).

A more complex molecule bearing a halogen atom, a protected alcohol and an aromatic ring (**45**) (entry 18) was used to give product (**46**) with 62% yield and 85% *ee*. As the starting alcohol was

racemic, product (**46**) was obtained a 1:1 mixture of diastereomers. This product shows that the present method can be used to greatly increase the complexity of molecules. The same reaction on a much larger scale (*i.e*. 4.8 mmol instead of 0.4 mmol) was performed while reducing the catalyst loading to 5%, the equivalents of alkene (**45**) to 2.0 and the excess of Schwartz reagent to 1.7 equivalents. In this case (**46**) was obtained in 90% yield (1.90 g of product) with 70% *ee*, showing that the method was scalable but that 10% catalyst loading was required to obtain high levels of enantioselectivity (see next section).

The current method allows the incorporation of many functional groups, some of which were previously unreported to be compatible with copper catalysed asymmetric 1,4-addition reactions (entries 12, 13 and 14), with high enantioselectivity. In some cases (unreactive starting alkene (**19**), entries 5 and highly reactive (**43**), entry 17), the temperature was modified to optimise the reaction. Unfortunately, despite average yields, no by-product could be detected except a trace of reduce enone (into allylic alcohol) in some cases.

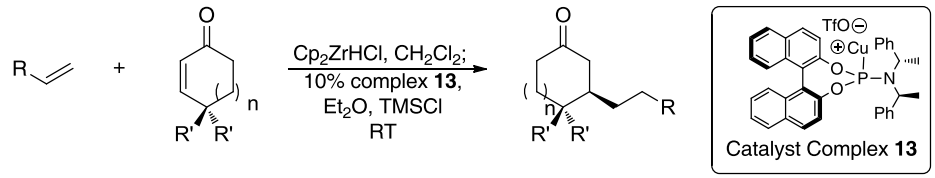
Enone scope

After testing alkenes, a short survey of enones was performed and tested using the current method (Table 2.6). Entries 1, 5, 6 were performed by Dr Rebecca Maksymowicz.

Cyclopentenone (**47**) (entry 1) gave 23% yield and 75% *ee* at room temperature (entry 1a) while performing the reaction at 0 °C (entry 1b) gave slightly higher yield (29%) and enantiomeric excess (85% *ee*). Although these results were relatively poor, cyclopentenone (**47**) has been shown by Alexakis to be a challenging substrate for asymmetric conjugate addition reactions.[47] It is believed that the molecule is very "flat" and therefore obtaining high *ee* requires a specialised catalyst system.[47]

Use of 2-cyclohexen-1-one (**2**) (entries 2 & 3a) gave ketones (**3**) & (**7**) with acceptable yield (59%) and excellent enantiocontrol (90% *ee* for (**3**) 93% *ee* for (**7**)). More specifically, the results on entry 2 were better than during the screening of reagents. The reason was attributed to more practise of the same reaction and the higher scale (0.40 mmol instead of 0.20 mmol). The tested reaction using alkene (**6**) and enone (**2**) (entry 3b) was scaled up. The reaction was performed 1.7 equivalents

of alkene, 1.5 equivalents of Schwartz and 10% complex (**13**) on 35 mmol scale. The reaction yielded ketone (**7**) with 60% yield (4.83 g) and 89% *ee*. This showed the reaction tolerates large scale.



Entry	Enone	Product	Yield[a]	*ee*[b]	Entry	Enone	Product	Yield[a]	*ee*[b]
1a 1b[d]	**47**	**48**	23% 29%	(*S*)-75%[c] (*S*)-85%[c]	4	**49**	**50**	75%	(*R*)-90%[c]
2	**2**	**3**	59%	(*R*)-93%[e]	5	**51**	**52**	73%	(*S*)-91%[c]
3a 3b[f]	**2**	**7**	59% 60%	(*S*)-90%[c] (*S*)-89%[c]	6	**53** *E*/*Z* = 9.1/1	**54**	50%	60%[c,g]

[a]Isolated yield. [b]Absolute configurations known, determined or assigned by analogy. [c]Ee determined by HPLC. [d]Reaction performed at 0 ºC. [e]Ee determined by derivatization and ^{13}C NMR spectroscopy. [f]Conditions: Schwartz reagent (1.5 eq), alkene (1.7 eq). [g]Absolute configuration not determined.

Table 2.6: Scope of enones.
Conditions: alkene (2.5 eq.), Cp_2ZrHCl (2 eq.), enone (1 eq.), complex (**13**) (0.1 eq.), TMSCl, (5 eq), RT).

The method was then tested on the more hindered substrate (**49**) (entry 4) with excellent results (75% yield, 90% *ee*). These results indicate that a high steric bulk one further carbon from the reacting centre does not affect the outcome of the reaction. On 2-cyclohepten-1-one (**51**) (entry 5), the corresponding ketone (**52**) was obtained with 73% yield and 91% *ee*. This result indicates that the method is not only selective with 6-membered rings.

A larger ring enone (**53**) (*E*/*Z* ratio of 9.1:1) was then tested (entry 6) and the relatively low selectivity (50% yield and 60% *ee*) observed showed that this method is not as effective with such large ring sizes. Indeed, large ring tends to behave similarly to acyclic molecules and the current method is not effective with linear enones (see chapter 5 for discussion about linear enones). Enone bearing a Methyl substituent in α-position could react (not shown) but gave low yield (less than 30%

and only a 1:1 *dr*). To conclude, the current method tolerates different cyclohexenones, but the use of most different ring sizes would require further optimisation.

Determination of absolute configuration of the cyclic ketones

The light is the sum between two components (polarised lights), each turning into a different direction orthogonal to the direction of propagation of the light. Normally these two components cancel each other. However, they have the ability to interact differently with chiral molecules. Circular dichroism is the method using this property to study chiral molecules. The absolute stereochemistry of the molecule is directly related to the sign of the CD spectrum (circular dichroism). The difference of frequency of each polarised component of the light after going through a chiral molecule is called the Cotton effect whose sign can be linked with bosute configuration (Figure 2.3).[136] A large amount of research has been performed to accurately link the CD signal to the absolute configuration of a cyclic ketone using the octant rule.[136] The octants are areas of space separated by symmetry planes of the C=O group in the molecule. When one of these octants is occupied by a substituent on a carbon of the cyclohexanone, the symmetry of the molecule is lowered (Figure 2.2). Therefore, this method was used to attribute the absolute configuration of the ketone.

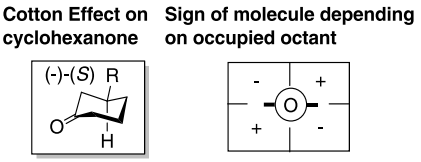
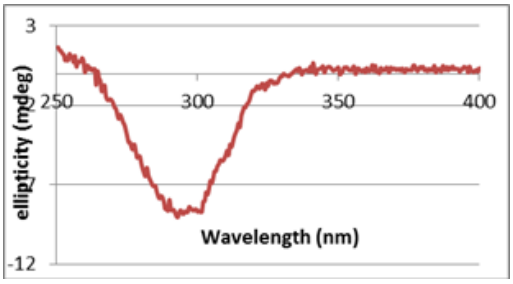


Figure 2.2: Octant projection on a substituted cyclohexanone.

Optical rotations allowed us to assign the absolute configuration to the remainder of the products by analogy.[137] Overall we could conclude that the (*S*, *S*, *S*)-ligand **A** catalyses the formation of ketone (**3**) with an (*S*)-centre.



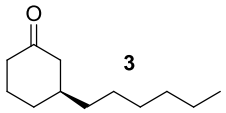


Figure 2.3: CD spectrum of ketone (**3)**.

Conclusions and future work

A new reaction using alkenes as primary organometallic nucleophile equivalents was developed. Using an air stable catalyst, alkenes can be hydrozirconated *in situ* and these add enantioselectively to a set of cyclic enones. In terms of the alkene, the substrate scope is wide and many functional groups which are not compatible in similar reactions with other organometallic agents can be used. In principle this new reaction could be used to synthesise complex molecules in a facile, rapid fashion under mild conditions. The method is compatible with several cyclic enones, although this aspect is quite limited and further extensions will require additional work.

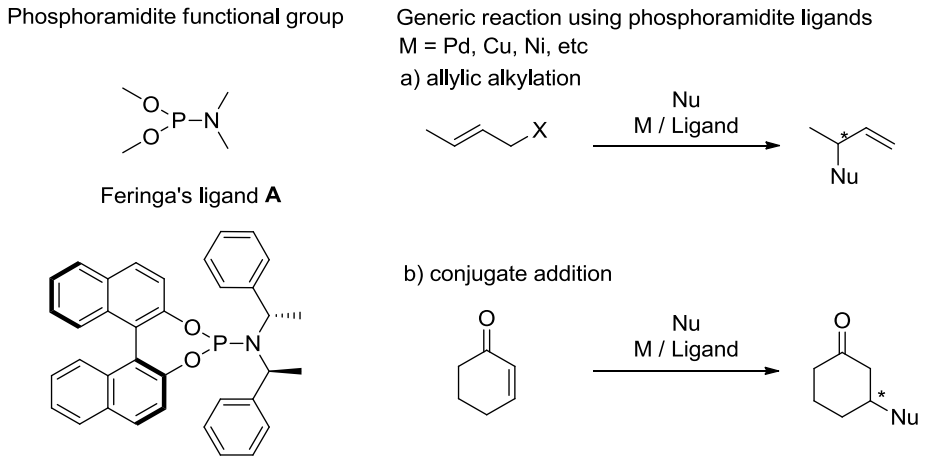
Chapter 3: Design of new phosphoramidite ligands

Introduction

The development of modular chiral ligands has led to the discovery of several chemical reactions using transition metal: ligand complexes that catalyse various reactions with impressive levels of enantioselectivity.[9, 52]

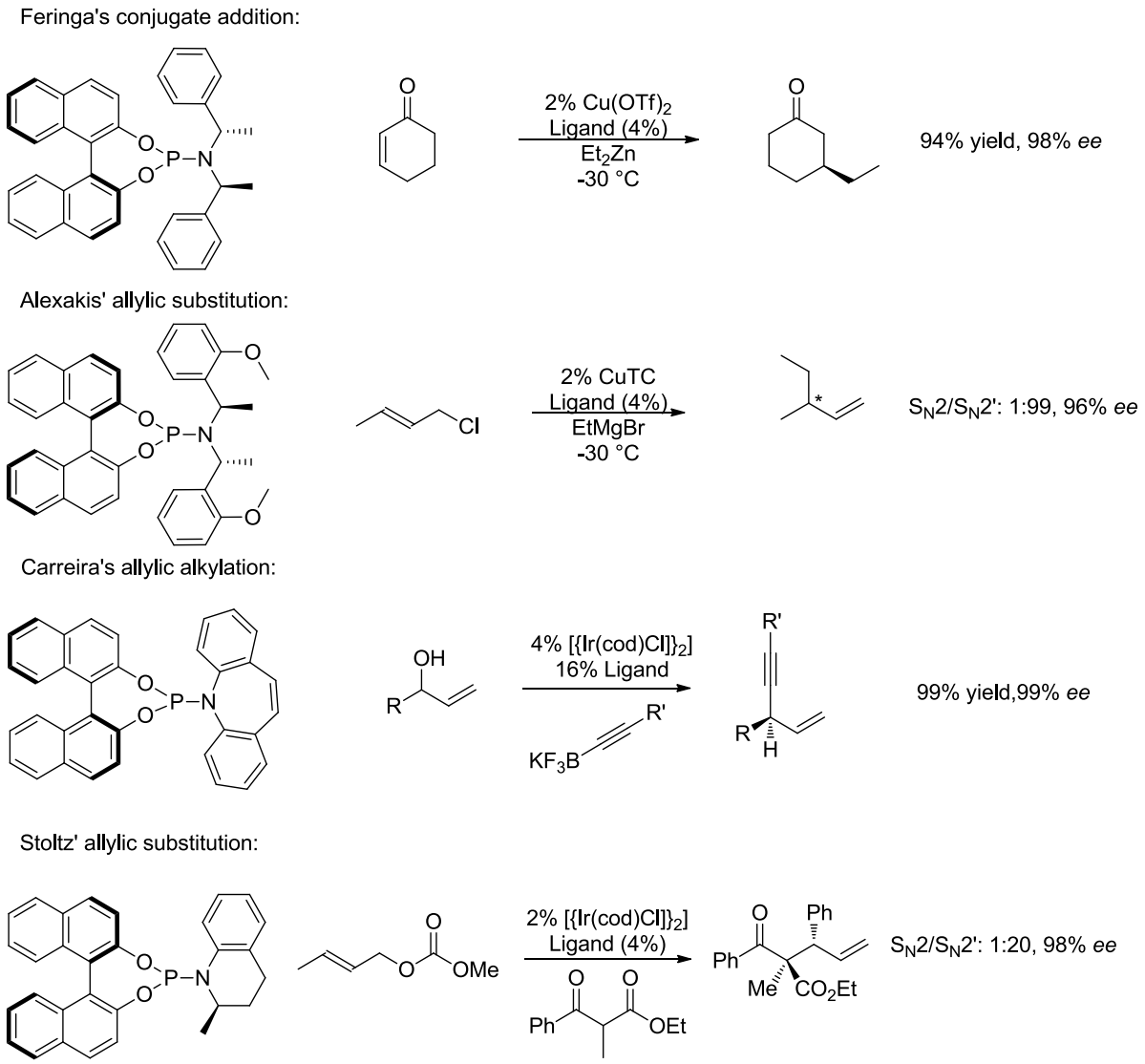
In the family of privileged ligands, phosphoramidites stand out as a particularly widely used class. Indeed, one of their assets is their versatility in controlling selectivity in many types of unrelated reactions.[66]

Phosphoramidite ligands were introduced to the field of asymmetric catalysis by Feringa and co-workers in their studies of the copper-catalysed conjugate addition of alkyl zinc reagents to enones.[67] Alexakis used taddol based phosphoramidite ligands a few years later.[138] The combination of copper and phosphoramidite ligands has been extensively used for conjugate additions to a wide range of Michael acceptors,[47, 117, 139] including the synthesis of all-carbon quaternary centres[140, 141] (and subsequent tandem reactions),[142] and the desymmetrisation of substituted cyclopentenediones.[143] Copper-phosphoramidite complexes also catalyse cross coupling reactions[144] and allylic alkylation reactions as demonstrated by Alexakis[145] and Feringa.[146]



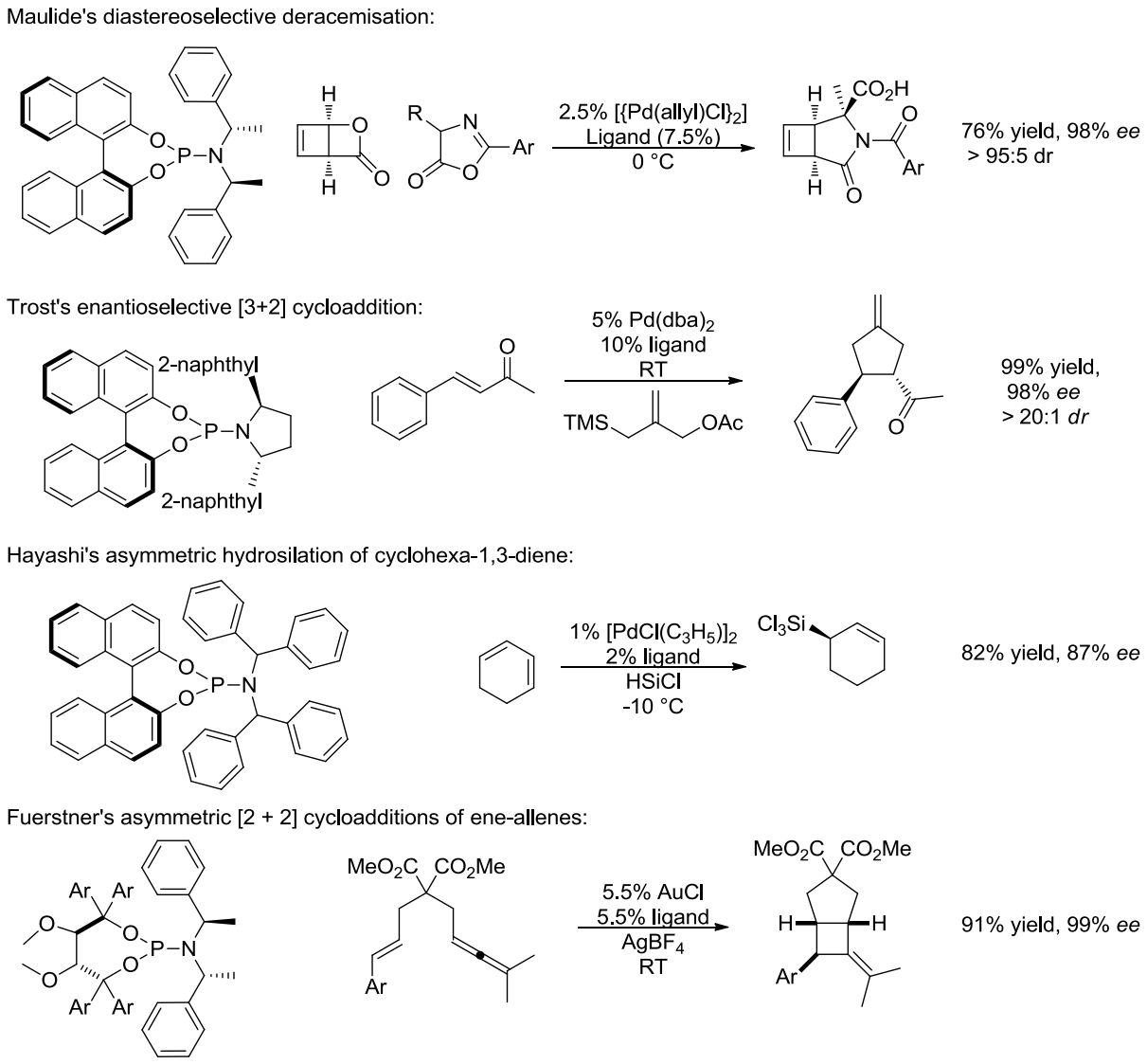
Scheme 3.1: Phosphoramidite ligands and common reactions performed by this type of ligands.

Another metal that has proven highly useful in combination with phosphoramidite ligands is iridium. Alexakis introduced a ligand (Scheme 3.2) which gave high levels of stereocontrol for allylic alkylation reactions.[147] Hartwig[148-150], Carreira[151], Stoltz,[152] You[153] and Feringa[154] have all thoroughly studied similar allylic alkylations. During these studies it became apparent that phosphoramidites can sometimes be limited by a crucial factor: that the ligands themselves can react with some of the more reactive organometallic reagents, such as aluminium compounds.[155] In order to compensate for this limitation of phosphoramidite ligands, some analogous phosphine ligands have been developed to survive harsh reaction conditions.[156]



Scheme 3.2: selected asymmetric copper and iridium methods that use phosphoramidite ligands.

In combination with palladium, phosphoramidite ligands have been used in cross coupling reactions with alkenes[157], the hydrosilation of cyclohexa-1,3-diene,[158] and hydrogenolysis,[159] deracemisation[160], de-epimerisation (deracemisation of epimers)[161] and desymmetrisation reactions as described by Maulide and Hayashi.[162] Asymmetric cycloadditions catalysed by palladium and phosphoramidite ligands have been extensively explored by Mascarenas,[163] Trost[164, 165], Tambar,[166] and Hayashi.[167]

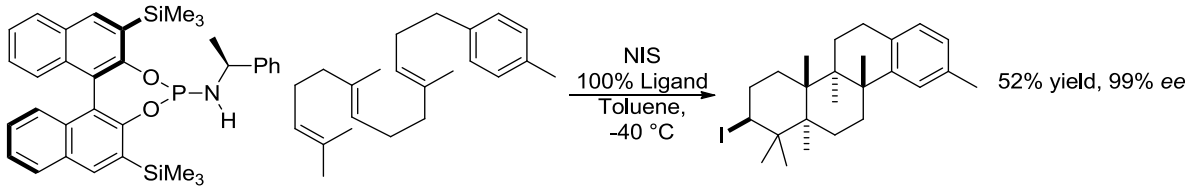


Scheme 3.3: Selected reactions using palladium/gold and phosphoramidite ligands.

Rhodium has also proven to be a highly valuable transition metal which works efficiently with phosphoramidite ligands for conjugate addition[32] and hydrogenation reactions.[168,169] Other

reactions such as Dong's hydroacylation[170] and Yu's allylic C-H activation also rely on this combination.[171] It can also catalyse asymmetric cycloadditions as shown by Hayashi,[172] and Gong has developed this combination in a novel method for performing enantioselective allylic alkylations.[173]

Phosphoramidite ligands have also proven effective in achieving high levels of asymmetric induction when used in combination with Ni, Au and Ag. Using nickel complexes, Doyle described the arylation of pyridinium salts,[174] and Fuerstner[175], Toste[176] and Zhao[177] have developed cycloadditions catalysed by gold.



Scheme 3.4: Ishihara's enantioselective halocyclisation of polyprenoids.

These methods demonstrate the versatility of phosphoramidite ligands. Further, phosphoramidites are able to catalyse some reactions in the absence of metals, such as the halocyclisation of polyprenoids demonstrated by Ishihara (Scheme 3.4).[178]

Mechanistic studies

As they are so widely used, some groups have attempted to gain insight into the mechanism of asymmetric induction in these reactions by studying the structure and behaviour of phosphoramidite ligands. Overall it seems that metal-phosphoramidite complexes are relatively labile in solution and have a tendency to form aggregates. Gschwind studied[179] the solution aggregation of complexes of phosphoramidite ligands and palladium. She has also performed similar studies on copper-based systems,[180] including the analysis of a transmetallation from alkyl zinc to copper.[41] A variety of techniques, including DOSY NMR spectroscopy, were used to characterise the formation of large aggregates.[50, 181] Gschwind's work, in combination with the extensive previous literature,[39] led to the identification of the most stable solution species, which may reflect the structure of the active catalyst.

Mechanistic studies on reactions involving phosphoramidite ligands have tended to provide experimental data in support of mechanistic hypotheses. However, the predictive power of these studies remains, to the best of our knowledge, quite limited. Curiously, in most models of copper catalysed asymmetric addition reactions, the structure of the phosphoramidite ligand is not actually taken into account. Some copper-phosphoramidite catalysed reactions have been studied by DFT, including Woodward's asymmetric conjugate addition,[182] and Alexakis's allylic alkylation.[183]

Even though DFT applied to a chemical system can provide insight into the overall reactivity of a system, it usually does not take into account interactions between metal and ligand. An exception to this general trend is a study by Rovis of Rh/Co phosphoramidite ligand complexes, which is based on x-ray structures and also takes into account metal-ligand interactions.[184]

Using DFT, mechanistic studies of allylic alkylations were carried out by You,[153] Gong[173] and Hartwig[148,149,185] Helmchen studied the effect of the ligand on the reactivity of iridium in allylic alkylations.[186] Like Hartwig,[149] his mechanism involves the selective insertion of iridium into a C-H bond of the ligand. The newly-formed species is essential to explaining the observed selectivity. Using x-ray structures and NMR analysis, Gade[187] studied the structure of metal-ligand complexes of gold, rhodium and palladium in solution. He analysed the process of coordination from the metal to the ligand and the interaction of the metal-ligand complex with the substrate. Through this approach, key steric interactions responsible for the selectivity of the reaction could be identified. Leitner studied the origin of selectivity in the nickel catalysed hydrovinylation of styrene by a coherent model based on DFT calculations.[188] He found that one phenyl ring of the phosphoramidite ligand significantly affected coordination to the metal and proposed that this effect was likely important in the selective synthesis of the different enantiomers.

Background and scope of this study

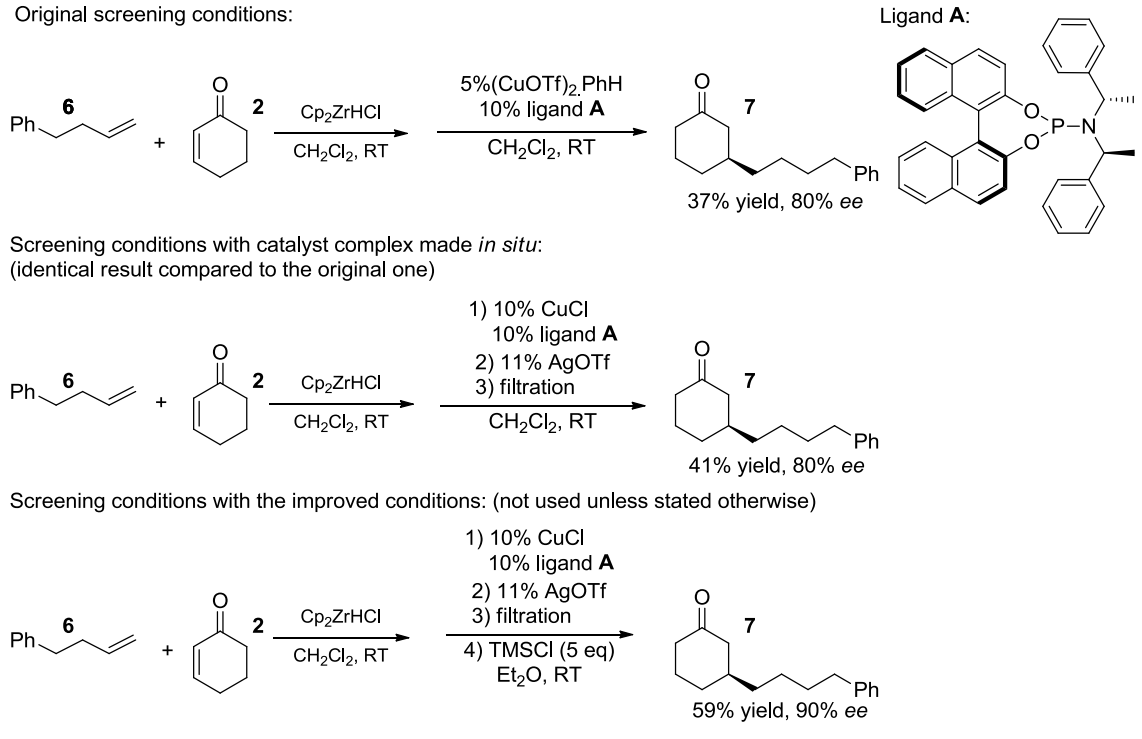
As described in chapter 2, we developed a new method that induced high enantioselectivity during the synthesis of cyclic ketones bearing a tertiary carbon centre.[189,190] These reactions involve the conjugate addition of alkenes (as alkylmetal nucleophile equivalents) to enones at room

temperature, without the need for premade organometallic species. Many different terminal alkenes can be used as nucleophiles and there is significantly improved functional group compatibility compared to related methods.

During our previous investigations, we discovered that Feringa's ligand **A** was a highly effective ligand and we therefore decided to examine related phosphoramidite ligands. Close structural analogues were much less selective. This chapter concerns the correlation of ligand structure with the *ee* of the final products. Using these data in combination with computational methods and NMR studies provides insight into the structure-reactivity relationship of phosphoramidite ligands in this asymmetric conjugate addition.

Screening conditions

As previously described, the best enantioselectivity was obtained when the reaction was performed by first hydrozirconating a terminal alkene (such as (**6**)) in CH_2Cl_2 at room temperature.



Scheme 3.5: Screening conditions used in this chapter.
Conditions: alkene (**6**) (2.5 eq), Cp_2ZrHCl (2.0 eq), enone (**2**) (1.0 eq), copper source (0.1 eq), ligand **A** (0.1 eq), enone (**7**) (1.0 eq) , RT, *ee*s determined by chiral HPLC).

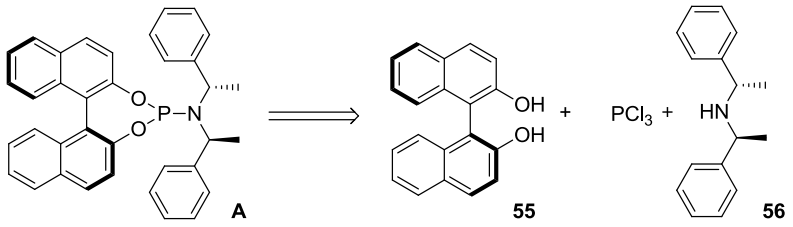
Upon completion, the mixture was added to a stirred solution of the catalyst (premixed copper and ligand) and stirred until the reaction was finished. In the following studies we, perform the reaction exactly the same way, but vary the choice of ligand.

In our 'optimised' conditions where the model product (**7**) is synthesised with 90% *ee*, the solvent was Et_2O and an additive (TMSCl, 5 equivalents) was used. For the purpose of this work, the solvent was CH_2Cl_2 and no additive was used. This set of conditions was used at the start of the DPhil and was therefore kept identical for coherence and comparison between data. These simpler conditions are called 'normal' or 'screening conditions', and were always used unless stated otherwise. This set of conditions led to an observed enantioselectivity of 80% *ee*. The catalyst used in all cases is copper triflate, either made by mixing CuCl and AgOTf (followed by filtration) or directly from $(CuOTf)_2 \cdot PhH$. Copper from both origins displayed the same enantioselectivity with <2% *ee* difference. The latter copper source was more oxygen sensitive and was used less frequently, especially in later studies, for this reason. Each value given in this chapter refers to the enantioselective addition of 4-phenyl-butene (**6**) to cyclohexenone (**2**), keeping ratio of reagents the same for all reactions.

Synthesis of ligands

There are a number of known methods to make phosphoramidite ligands.[191] The general strategy is to couple a non-racemic binaphthol backbone to a secondary amine. The following explanatory schemes use ligand **A** as a model but these procedures were followed for all ligands.

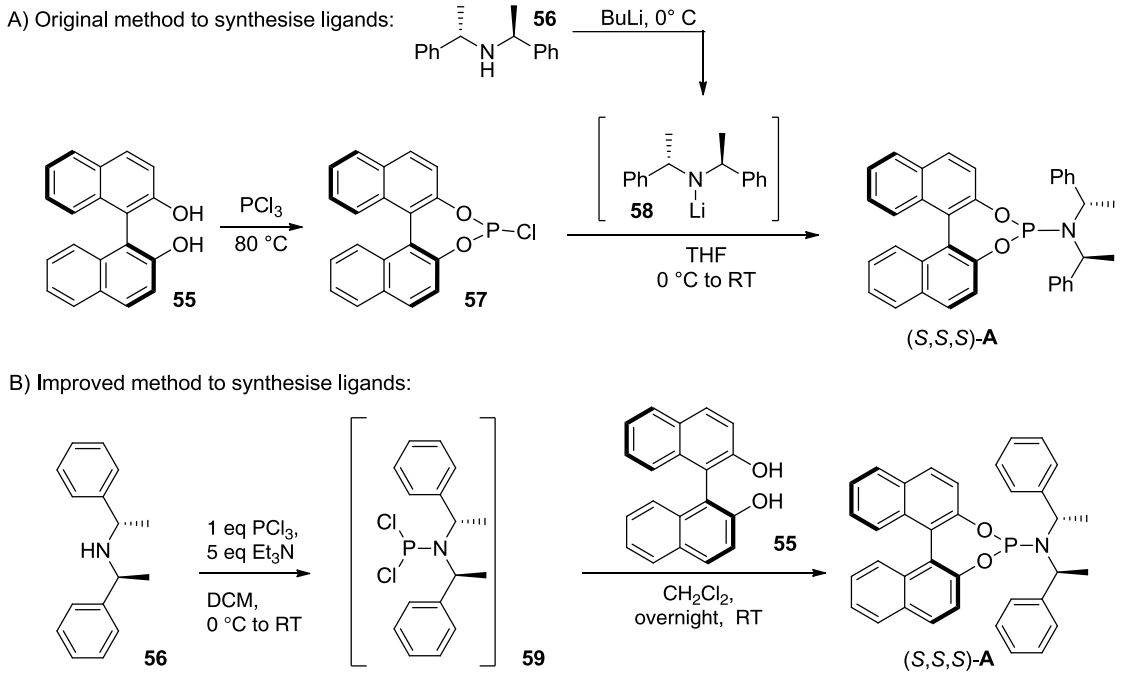
Coupling reactions



Scheme 3.6: General retrosynthesis of phosphoramidite ligands.

The following ligands were provided by the chemical company DSM: **D**, **E**, **L**, **M**, **S**, **V**. Other ligands made by collaborators were synthesised using the standard literature procedure[191]

Initially, we synthesised phosphoramidite ligands according to the method of Feringa (Scheme 3.7 A).[192, 193] In this procedure, a large excess of PCl_3 (8 equivalents) and the corresponding binaphthol (**55**) are mixed to synthesise a bench stable phosphorichloridite **(57**). The appropriate amine (**56**) is deprotonated with BuLi (stirred for 1 hour at 0 ºC) to give intermediate (**58**) which is added to a solution containing the phosphorochloridite (**57**), and stirred at room temperature overnight. In our hands this method was not reliable for any substrate, typically giving yields below 25% (literature values up to 80%).[59] The literature mentions use of base and azeotropic distillation (with toluene) can increase but none of these methods gave good results.

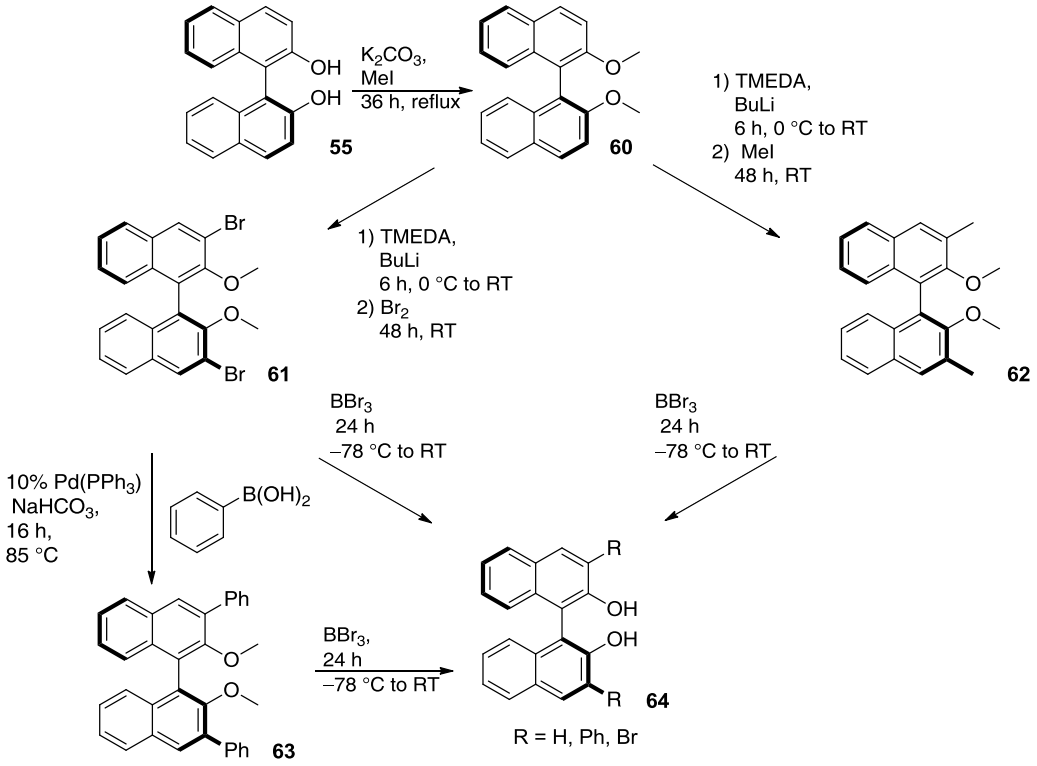


Scheme 3.7: Original (A) and improved (B) method to synthesise phosphoramidite ligands.

Therefore, the method reported by Trost[164] was used to synthesise most of the ligands as we found it was much more effective (Scheme 3.8). This method gave the ligand in one step by premixing Et_3N, PCl_3, the corresponding amine (**56**), and the binaphthol (**55**), and stirring them together overnight. This method was readily scalable (from 50 mg to 12 g) and produced the corresponding ligand in acceptable (50%) to quantitative (99%) yields.

Synthesis of phosphoramidites containing different backbones

In order to screen different types of ligands, some modified binaphthol backbones were required. This work was largely performed by Dr Rebecca Maksymowicz. Using Wipf's method,[194] binaphthol (**55)** was protected by methoxy groups. From there, several options were available. **60** was *ortho*-lithiated twice using BuLi and then trapped with an electrophile (MeI or Br_2). This step allowed the further elaboration of backbone group functionality. During the synthesis of ligand **J**, phenyl (**62**) was produced by Suzuki coupling.[192] After the binaphtol backbone was either kept with bromine, (**61**), possessed Methyl substituents (62), modified with Phenyl groups (**63**), the methoxy group could be selectively removed. BBr_3 was used to deprotect the methoxy binaphthol into the corresponding bis-phenol groups (**64**).



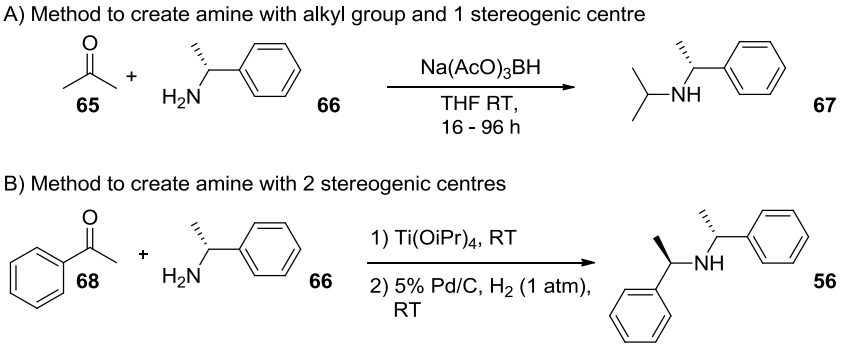
Scheme 3.8: Method used to modify the binaphthol backbone of the ligands.

Synthesis of amines

Most of the amines required to make these ligands were synthesised using a direct Schiff condensation. Primary amine **(66**) and ketone (**65**) were mixed and the imine formed was reduced

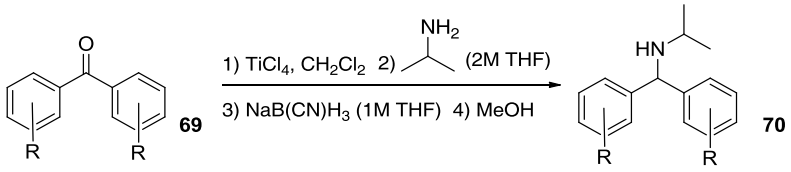
in situ[191, 195] with $NaB(OAc)_3H$ to give (**67**). This method was robust as no overalkylated product was detected (Scheme 3.9, method A).[196]

Amines bearing two chiral centres, for example (**56**), (Scheme 3.9, method B) were synthesised by Schiff condensation,[197] reduction and recrystallisation. In this case, a strong Lewis acid was required for the condensation of (**66**) and (**68**), and catalytic palladium and hydrogen were required for the reduction



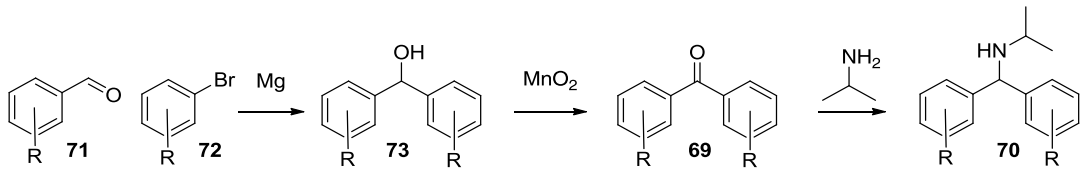
Scheme 3.9: Original methods employed to synthesise secondary amines.

.While these strategies were generally efficient, no product was observed with less reactive (aromatic) ketones (such as (**66**) or benzophenone and substituted benzophenone). These are hindered and stabilised by conjugation. When extra $Ti(OiPr)_4$ or $TiCl_4$ was added to the mixture of ketone and amines it only led to the synthesis of trace amounts of the desired product. The use of a more reactive reducing agent ($NaBH_4$) gave only reduced starting material. Eventually, a method reported by Gilbert turned out to be efficient.[198] This method consists of sequential addition of reagents: ketone (**69**) and $TiCl_4$ were first mixed CH_2Cl_2, before the amine in THF was added, followed finally by a solution of $NaB(CN)H_3$ in THF and some MeOH. The mechanism involves the activation of the ketone, then imine formation, followed by a slow hydride reduction *in situ*. The desired amines were produced in acceptable yields (*ca* 50%). For more hindered substrates, the reaction was performed at reflux in a sealed tube using CH_2Cl_2 or 1,2-dichloroethane as solvent.



Scheme 3.10: Method to synthesise secondary amines (**70**) from aromatic ketones (**69**).

In cases where the ketone precursor (**69**) was not commercially available, it was synthesised using a strategy inspired by Dong[199] consisting of iterative steps. A secondary benzylic alcohol (**73**) was made by addition of a Grignard reagent (made from (**72**)) to an aldehyde (**71**). The alcohol (**73**) was oxidised to produce the corresponding ketone (**69**) under mild conditions (MnO_2). The corresponding secondary amine (**70**) could then be synthesised as described previously.



Scheme 3.11: Generic route to synthesise secondary aromatic amines (**70**) from non-commercial ketones (**69**). R= MeO, H, CF_3, Me.

Identification of a suitable part of the ligand to vary

Absolute configuration and screening of the BINOL backbone

We tried to identify which ligand moieties had a strong influence on selectivity. Ligands **D**, **E** were provided DSM while **C**, **D**, **J** and **K** were synthesised dy collaborators using a literature procedure.[191] While screening reaction conditions (Figure 3.1) with (*S*,*S*,*S*) Feringa's ligand **A**, we obtained the *S* ketone (**7**), and as expected (*R*,*R*,*R*) ligand *ent*-**A** gave *R*-(**7**).

The absolute configuration of the product was found to be determined by the backbone, so that (*R, S, S*)-**B** gave the *R*-, and (*S, R, R*)-**B** gave the *S*-, product. This happened for all BINOL derivatives as well. When using a binaphthol backbone, the general effect of the amido moiety was to control the level of enantioselectivity but it had no effect on the preferred enantiomer. To further study these and related effects, we made a series of ligands with different backbones **C**-**K** and examined them using our screening conditions (Figure 3.1).

As described above, firstly, a diastereomer of Feringa's ligand **A**, ligand **B** was tried. This gave 74% *ee* (versus 80% *ee* for Feringa's ligand **A**), showing this diastereomer induces less selectivity. Ligands with simplified diol backbones (catechol, biphenol) gave poor enantioselectivity (17-25% *ee*). The spirocyclic ligand **E** gave intermediate selectivity (64% *ee*).

The ligand **F** was not better than the original and therefore its diastereomer was not tested. None of the other backbones tested here gave better selectivity than the original binaphthol backbone. Ligands derived from binaphthol modified at the 3,3' or 7,7' positions with various groups (Br, Me, Ph) were less selective (28-67% *ee*). Consequently, the original binaphthol motif was retained in all subsequent ligands.

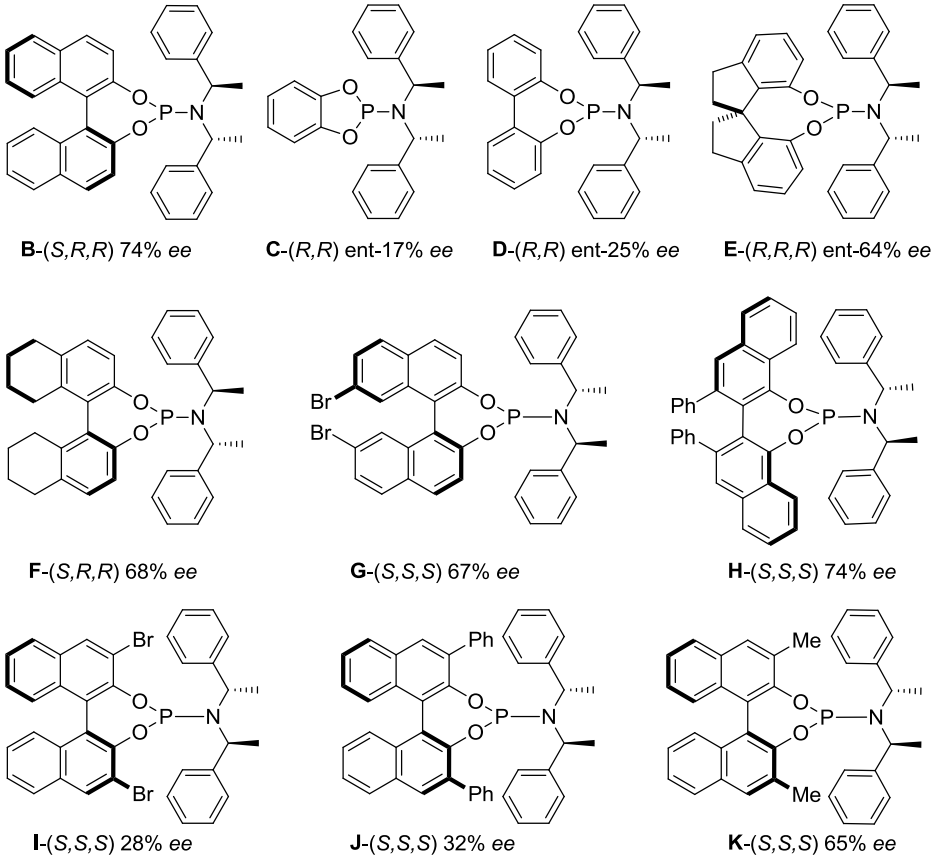


Figure 3.1: Screening of the BINOL backbone of the phosphoramidite ligands. Unless stated otherwise ('ent'), the absolute configuration of the ketone (**7**) is *S*.

Screening the amido moiety: simple variations

Structural variations of the amido group were examined using ligands derived from simple amines (Figure 3.2). The goal here was to identify the key parameters responsible for higher enantioselectivity. Ligands **L**, **M** and **S** were provided by DSM while ligands ligand **Q** was synthesised by collaborator using literature procedure.[191]

Ligands with small alkyl groups (**L** & **M**) gave poor enantioselectivity (7-17% *ee*) while ligands with slightly more bulky groups (**N** and **O**) gave somewhat better enantioselectivity (37-

56% *ee*). However, the adamantyl-substituted ligand **P** only induced 17% *ee*. There was a clear influence of steric bulk about the amine on the observed *ee*, but it was not obvious how to interpret these results. It seemed that moderately bulky amido groups are optimal.

We also examined several simple modifications to Feringa's ligand **A** by making ligands with modified amido substituents. Known Alexakis' ligand **Q** (43% *ee*), a naphthyl variant **R** (76% *ee*), and simple demethylated derivatives (**S** & **T**) were tested. While these results did not lead to any particular insight, a naphthyl substituted ligand **U** with an isopropyl group on the amine gave a respectable level of enantioselectivity (68% *ee*). Interestingly, the conversion was identical with all tested ligands. The fact that a small isopropyl *N*-substituent could be a part of an efficient ligand was found to be intriguing.

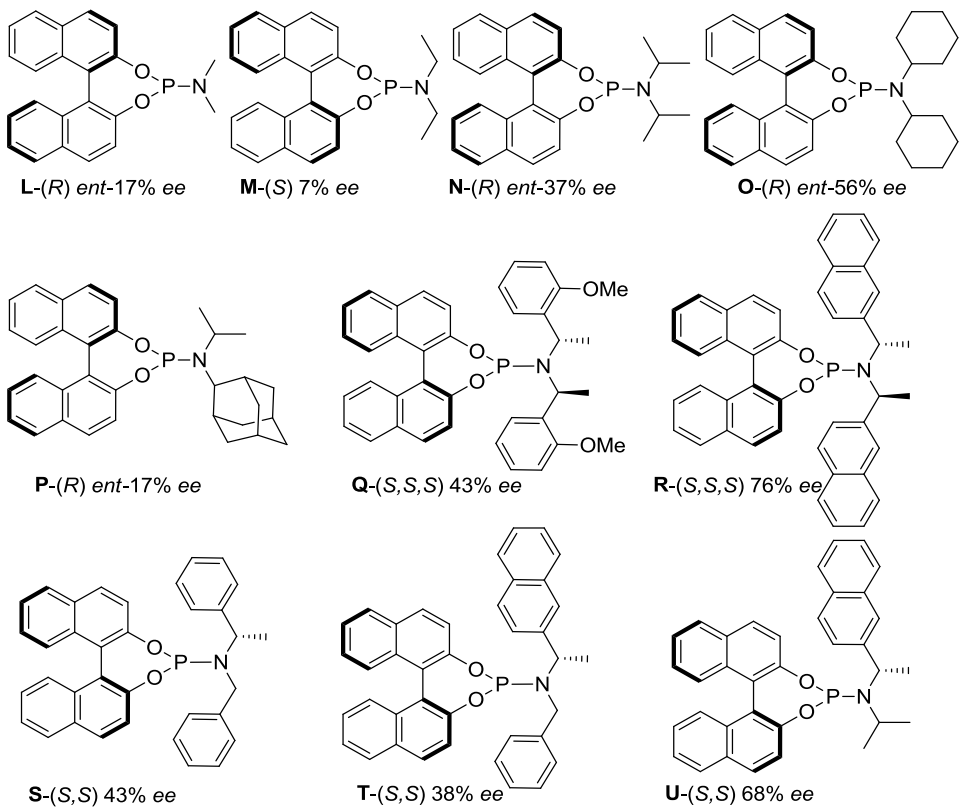


Figure 3.2: Screening of phosphoramidite ligands **L** to **U**. Unless stated otherwise (ent), the absolute configuration of the produced ketone (**7**) is *S*.

Screening the amido unit: 2-Naphthyl-CHMe probe

While keeping the 2-naphthyl-CHMe moiety the same, the other group on the amine was modified (Figure 3.3). Ligand **V** was provided by DSM. Across the series from **V** to **X** the enantioselectivity progressively increased with substituent size (methyl, ethyl, cyclohexyl) from 15-72% *ee*. Similar cyclic alkyl substituents gave comparable levels of enantioselectivity.

Ligands bearing a secondary alkyl *N*-substituent (**W**-**AA**) gave good levels of selectivity. However the selectivity is not simply related to the presence of steric bulk (**X** vs **AA**). Use of '1-naphtyl-CH-Me' motif (**AC** & **AD**) or sp_2 hybridised (**AB**) *N*-substituents were detrimental to enantioselectivity. These results suggest that a secondary alkyl *N*-substituent imparts some selectivity and, further ligands bearing *N*-isopropyl substituents were tested.

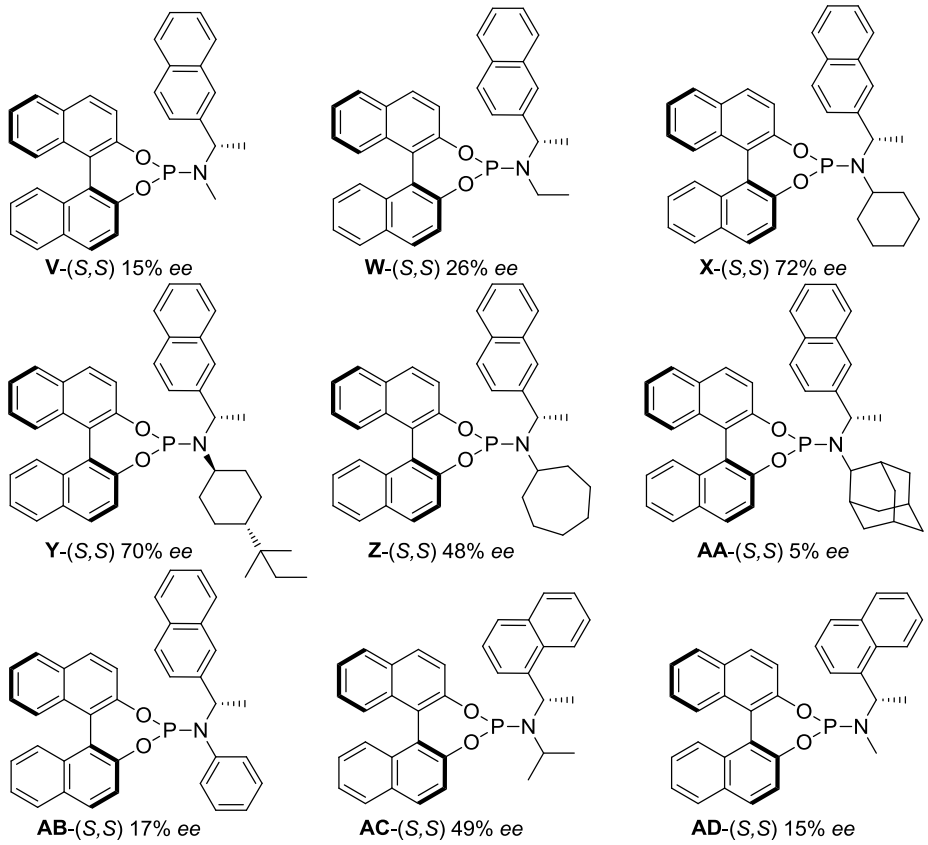


Figure 3.3: Screening of '2-Naphthyl-CHMe' unit on phosphoramidite ligands. Ketone (**7**) was produced with absolute configuration *S*.

Investigating the effect of the 2-naphtyl-CH-Me unit

We were curious to find out why the naphthyl unit gave high enantioselectivity when used in combination with a branched secondary amine group. To investigate the relative contributions of steric and electronic factors to this effect, this naphthyl unit was varied (Figure 3.4) while maintaining a *N*-isopropyl group on the amine. α-methyl-aryl amido groups with different aromatic substituents were tested. As this specific motif is common in commercially available building blocks, a variety of substituted benzene rings could be used to probe steric and electronic effects. While the ligand bearing a simple phenyl group **AE** gave 51% *ee*, mono-substituted phenyl rings gave *ee*s that were about 10-20% higher. Ligand **AE** was synthesised by collaborators using literature procedure.[191]

Ligands bearing electron-donating benzene rings overall induced similar enantioselectivity to their electron withdrawing analogues. Although there were differences observed, they were deemed to be subtle and hard to interpret.

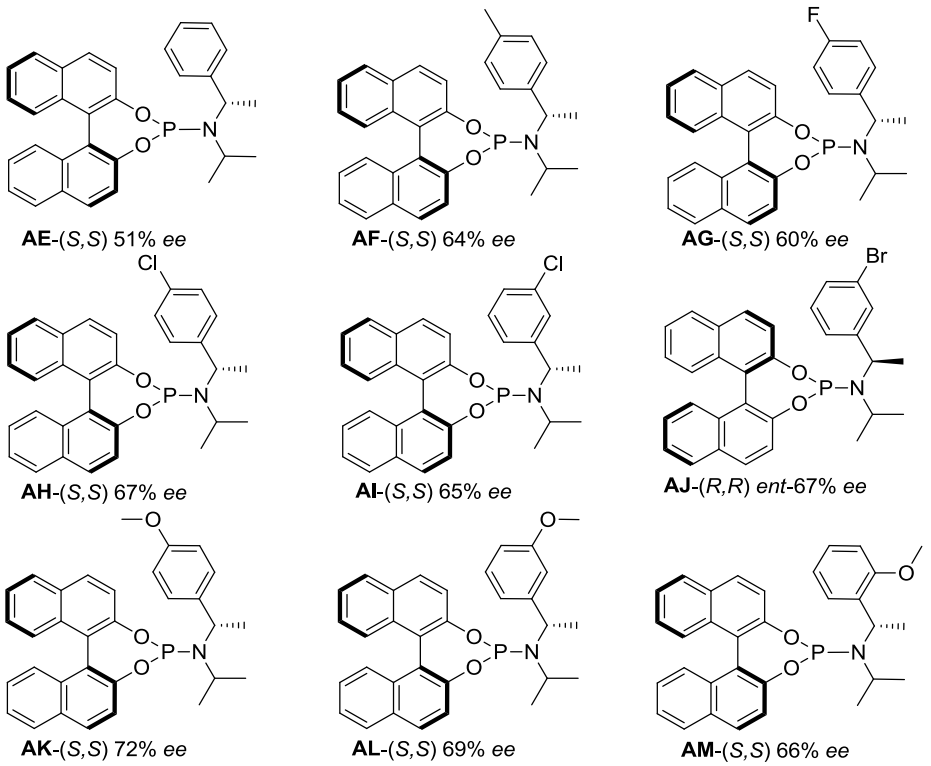


Figure 3.4: Screening of substituted phenyl rings on phosphoramidite ligands. Unless stated otherwise ('ent'), the absolute configuration of the ketone (**7**) was *S*.

More dramatic variations of the naphthyl group were investigated (Figure 3.5). Ligands bearing two or three fused rings were examined (**AN**-**AR**). Some of these (**AN**, **AO**, **AP**) turned out to induce enantioselectivities similar (72-75% *ee*) to Feringa's ligand **A**. Some *N*-substituents (**AR**-**AW**) tested were achiral, which makes the amines and ligands easier to synthesise. Amongst these ligands, **AS** is an isomer of Feringa's ligand **A** and was found to induce almost identical levels of *ee* (78% *ee* and 80% *ee* for **A**). To investigate if this resulted from the simple incorporation of the appropriate groups, the isomer **AW** was synthesised and tested. As it gave only 55% *ee*, it showed that the connectivity of the groups is important.

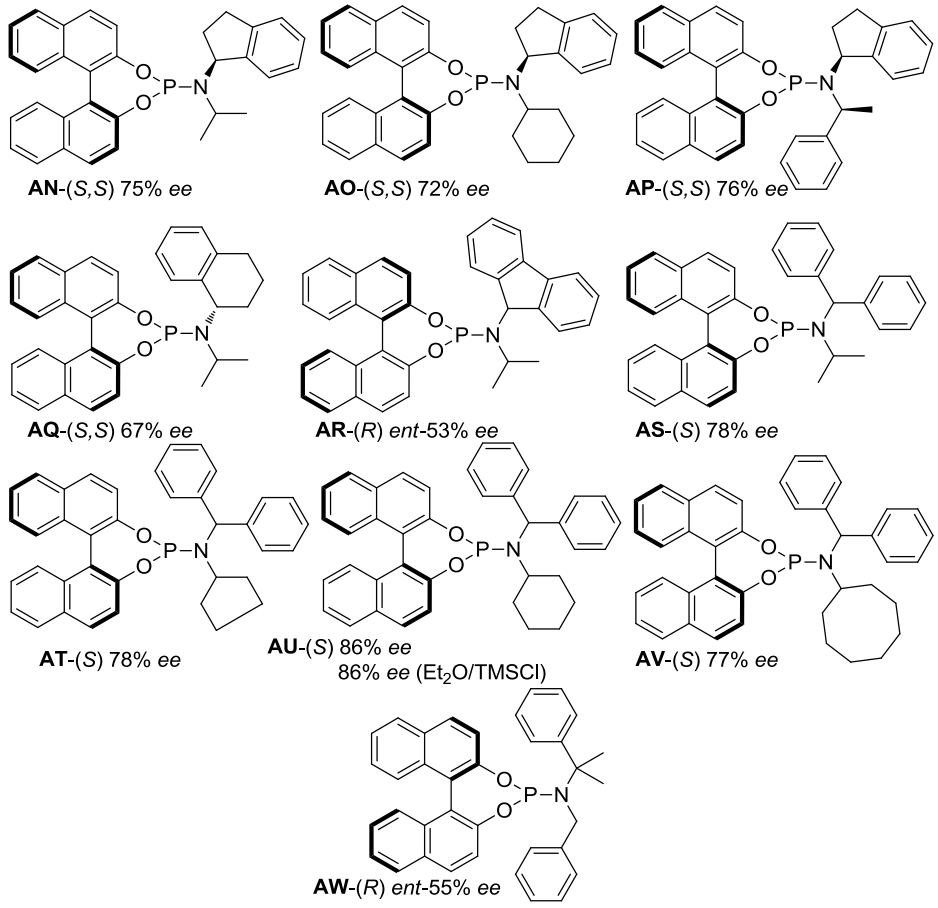


Figure 3.5: Screening of phosphoramidite ligands with multiple rings/ two aromatics units. Unless stated otherwise ('ent'), the absolute configuration of ketone (**7**) was *S*.

Replacing the isopropyl group with cycloalkyls was next investigated, so ligands **AT**-**AV** were synthesised. These produced only slightly modified *ee*s, and **AU** gave the best results (86% *ee*) when tested under both screening and optimised conditions.

One surprise was the high selectivity induced by ligands bearing non-chiral amines. A clear advantage is that achiral amines are easier, faster and cheaper to make. Additionally, no unwanted diastereomer that may be inadvertently formed during synthesis needs to be removed. Another advantage is the absence of diastereomers of the ligands themselves, in contrast to Feringa's ligand **A**. Therefore for these ligands, a complete set of stereoisomeric ligands consists of only of the two enantiomers.

Correlation of enantioselectivity with steric parameters

To probe the importance of steric factors upon stereoinduction, a correlation between structural and electronic descriptors of the ligand with experimental enantioselectivity was sought. Indeed, the overall trend was difficult to rationalise without further analysis. As a wide range of modifications were investigated, it seemed necessary to use computed parameters since empirical steric and electronic parameters such as Hammett constants were not readily available for all substituents tested. Establishing a correlation between calculated parameters and experimental enantioselectivity would highlight key interactions in a quantitative way. Computational analysis of the data and correlation were performed by Dr Robert Paton at the University of Oxford.

To derive a model relating phosphoramidite structure to selectivity, we analysed fourteen of the synthesised ligands (seen in Figure 3.6 (Black circles), ligands from figures 3.2, 3.3, .4 and 3.5), which induced between 37-78% *ee* (training set). The selected ligands had the same general structure, namely the presence of an *N*- isopropyl substituent, while the other amido substituent had two variable groups for which we computed steric parameters. By focussing only on the variation of R_1 and R_2 (Figure 3.6), each of the ligands was assumed to retain structural similarity. This resemblance ensures that its role in the selectivity-determining TS would not change. Therefore the same steric and electronic parameters would be applicable across this group of ligands. The steric properties of a given substituent can be defined experimentally by several different parameters.

We chose to use sterimol parameters, as used by Sigman,[71] because they take into account spatial information along three dimensions for a given substituent and thus account to some degree

for the anisotropy of substituents. For the unreported substituents, the sterimol parameters were calculated using homemade software from DFT optimised structures.

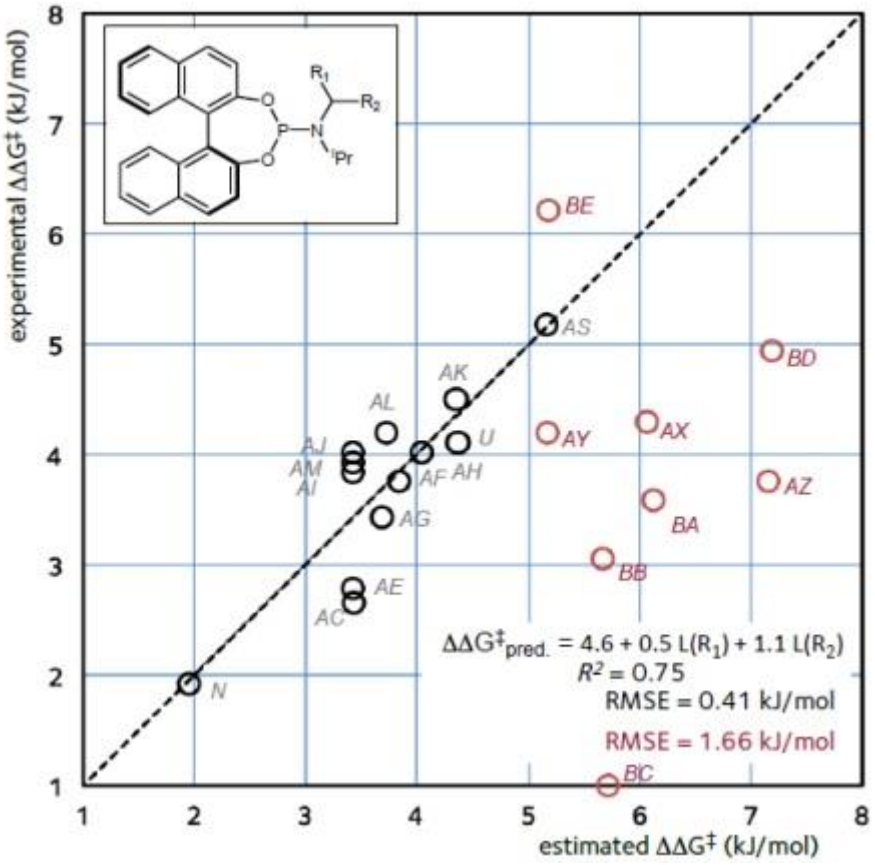


Figure 3.6: Correlation between experimental and steric model values. (black: training set, red: test set).

The construction of a LFER between experimental selectivity (expressed logarithmically in terms of $\Delta\Delta G^{\ddagger}$) and the normalised sterimol parameters computed for each of the variable substituents was then performed (Figure 3.6). To enable the comparison of different structures the two substituents were arranged so that R_1 was the larger of the two. The performance of the resulting mathematical model was assessed in terms of the linear correlation coefficient, R_2, where a value of 1.0 indicates a perfect linear fit.

The following model equation was derived from the data:

$\Delta\Delta G^{\ddagger}_{predicted} = 4.6 + 0.5L_1 + 1.1\ L_{2.}$ (**Equation 3.1**)

The variance in selectivity could be largely described using only the two sterimol L (i.e. length) parameters of the two variable positions (R_1 and R_2) in a simple additive expression with good correlation (R^2 = 0.66). While a stronger correlation could be obtained by introducing extra cross-terms and their associated fitting parameters, the simplicity of this model was favoured. Indeed by using only the two L parameters, the possibility of overfitting is minimised. Also, the physical interpretation of the cross-terms would be unclear. The resulting expression illustrates the importance of both the substituents' length (quantified by the L parameter): increasing length is predicted to enhance enantioselectivity by this model.

The correlation established between enantioselectivity and the two length parameters indicated that desirable amine moieties would possess two long substituents (such as aryl rather than methyl groups). The weights of each L term (0.5 and 1.1) suggest they are roughly equally important. Or at least, it means their importance is in the same order of magnitude. We therefore opted to investigate the selectivity of ligands containing two identical aromatic amine substituents. It is interesting to note that in this steric only model for selectivity, similarly-sized ligands (e.g. **AC**, **AE**, **AI**, **AM**, **AJ**) are predicted to be equally selective, and yet do give rise to experimentally different enantioselectivities. This suggests a role for the electronic nature of each of the substituents in determining enantioselectivity, as was observed to a degree in our earlier experimental studies.

Design of 3rd generation ligands

As discussed in detail below, a new set of ligands (**AX**-**BH**, Figure 3.7) was synthesised in order to test this model. Architecturally inspired by equation 3.1 (Figure 3.6), the new ligands possessed the same core structure with long aromatic substituents and varied electron-donating ability of substituents on the aryl rings (R_1 and R_2).

The predicted and experimental $\Delta\Delta G^{\ddagger}$ values of these ligands are plotted in red on figure 3.6. The current model poorly predicted the selectivity for this generation of ligands. For instance, ligands with similarly-sized amine substituents (*e.g.* **BA** & **AX** or **AY** & **BE**) were expected from equation 3.1 to give similar enantioselectivities. However, they produced a wide range of

enantioselectivities. If, as the model predicts, only steric factors were important, then these ligands should have induced enantioselectivity according to the model and all results should have been on the diagonal. The failure of this predicted correlation suggests that a model based solely on steric factors is inadequate, and that electronic contributions must be considered.

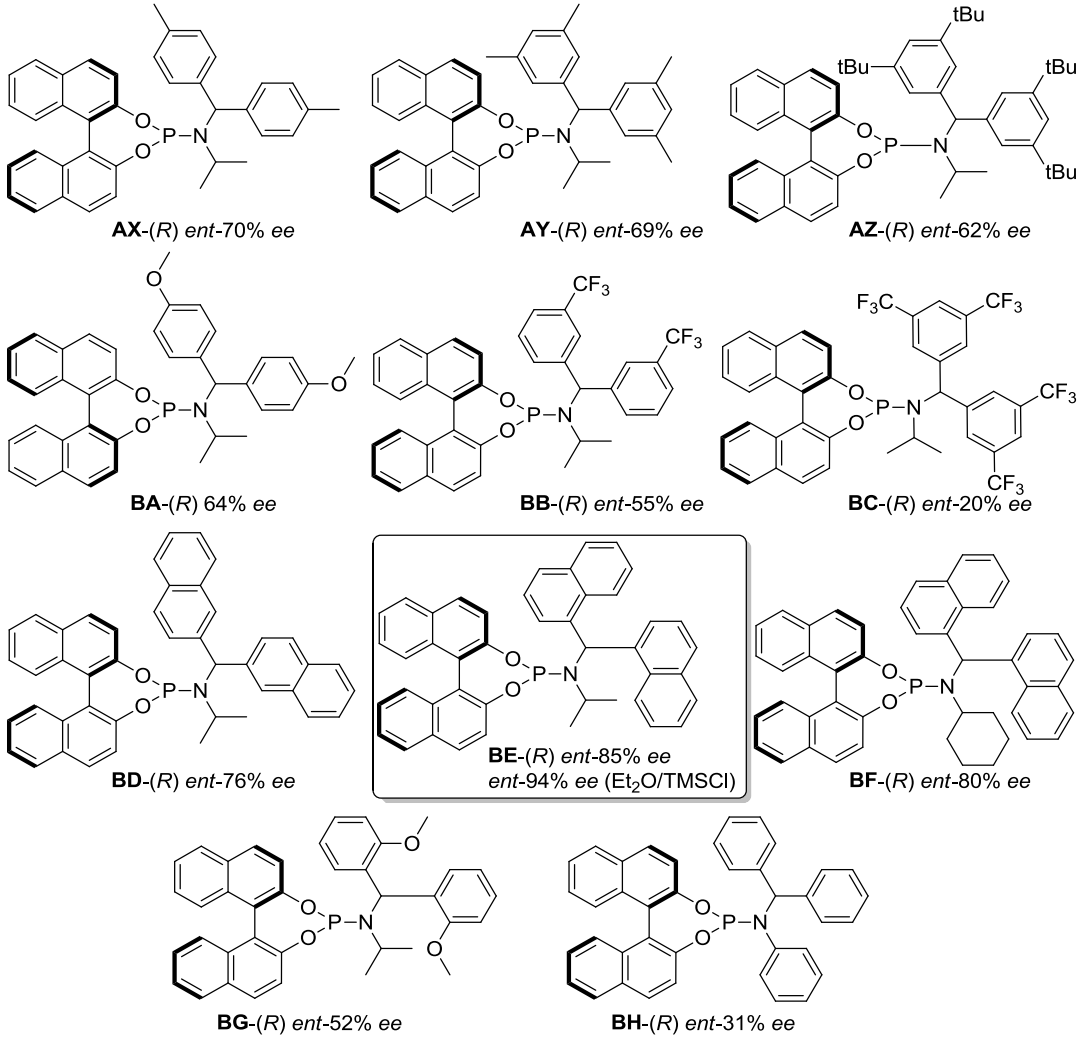


Figure 3.7: Ligands synthesised to test the correlation model. The absolute configuration of the produced ketone (**7**) was *R* in the results from this table.

The presence of electron rich substituents such as methyl (**AX**, **AY**), *t*-butyl (**AZ**) or methoxy (**BA**, **BG**) groups reduced the enantioselectivity (52-69% *ee*). The position of substitution was important in the case of methoxy substituent (*c.f.* **BA** 64% *ee* and **BG** 52% *ee*). Similarly, ligands with electron withdrawing groups (**BB** & **BC**) showed a sharp decrease in

enantioselectivity (20-55% *ee*). This effect is unlikely to simply be a steric effect, as significant variation was seen between sterically similar substituents: see methyl (**AY** and **AZ**) vs. CF_3 (**BB** and **BC**). The replacement of phenyl rings with naphthyl rings (**BD**, **BE** and **BF**) gave results similar Feringa's ligand **A** (76%-85% *ee*). Surprisingly, ligand **BF** with naphthyl groups gave lower selectivity than its phenyl counter part **AU** (Figure 3.5). Interestingly, ligand **BE** gave even higher enantioselectivity using 'optimised' conditions (94% *ee*, Chapter 2). This ligand was tested using the 'optimised' conditions as it induced the highest enantioselectivity under the 'standard' test conditions examined here.

Conformational studies by NOE/NOESY analysis

We next opted to study the copper-ligand complexes in solution. The aim was to identify the major conformer in solution and determine how this varies between different ligands. We wanted to understand why ligands **A** and **AS** gave similar results (80% and 78% *ee*) while the apparently similar ligand **BC** was much less selective (20% *ee*). We also anticipated that the structural similarities, but selectivity differences, between unsubstituted **AS** and tetratrifluoromethyl analogue **BC** (20% ee) may result from differences in the catalyst's three-dimensional structure. To probe interactions of this kind, NOE/NOESY experiments were performed on three copper-ligand complexes (Cu:**A 13**; Cu:**AS**, **74**; Cu:**BC 74** , Schemes 3.8-3.10).

Samples were prepared by premixing the ligand and CuCl for one hour before adding AgOTf and filtering the mixture after an additional 15 minutes of stirring. Upon removal of the solvent under high vacuum, deuterated CH_2Cl_2 was added for NMR spectroscopy. We found that if deuterated solvents were used in the initial steps, the complex usually decomposed. Presumably, this is a result of impurities in commercial deuterated solvents. More precisely, CH_2Cl_2 could either contain oxygen or this solvent can release some protons upon interaction with light. Any of these problems can be very detrimental to the studied system. Using this protocol, each sample was analysed and compared.

Copper complex 13 with Feringa's ligand A

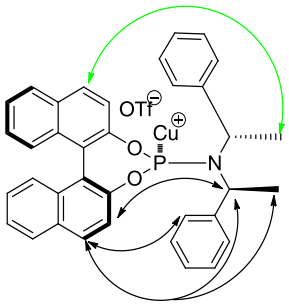


Figure 3.8: NOE results using complex (**13**) (CuOTf:**A).**

In complex (**13**) (containing Feringa's ligand **A**), the binaphthol backbone strongly interacts with one of the amido substituents (Figure 3.8). The methyl of the other amido substituent slightly interacts with the other naphthyl group of the backbone. Interactions between the binaphthol backbone and the amido part are assumed to have some effect on the enantioselectivity of the reaction. The importance of related interactions was pointed out by Alexakis in his investigation of phosphanamine ligands.[156]

Copper complex 74 with ligand AS

Study of complex (**74**), derived from ligand **AS**, revealed close interactions between the isopropyl group, the benzylic proton and one side of the binaphthol backbone (Figure 3.9). There was also evidence of a weak interaction between the isopropyl group and the other half of the binaphthol backbone.

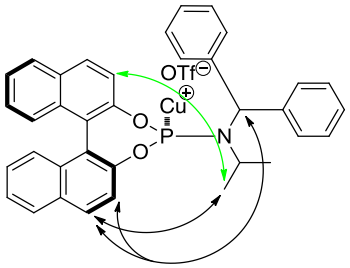


Figure 3.9: NOE results using complex (**74).**

Copper complex with ligand BC

Study of complex (**75**), containing ligand **BC**, revealed only weak interactions by NOE analysis (Figure 3.10). Due to overlap between ^{1}H NMR signals, some possible interactions were obscured. However, a weak interaction between the backbone and the isopropyl group could be detected.

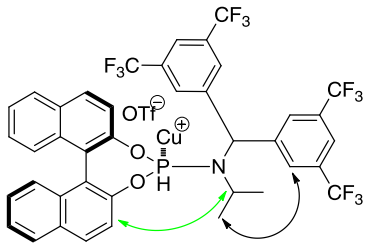


Figure 3.10: NOE results using complex (**75**).

Comparison between copper-ligand complexes

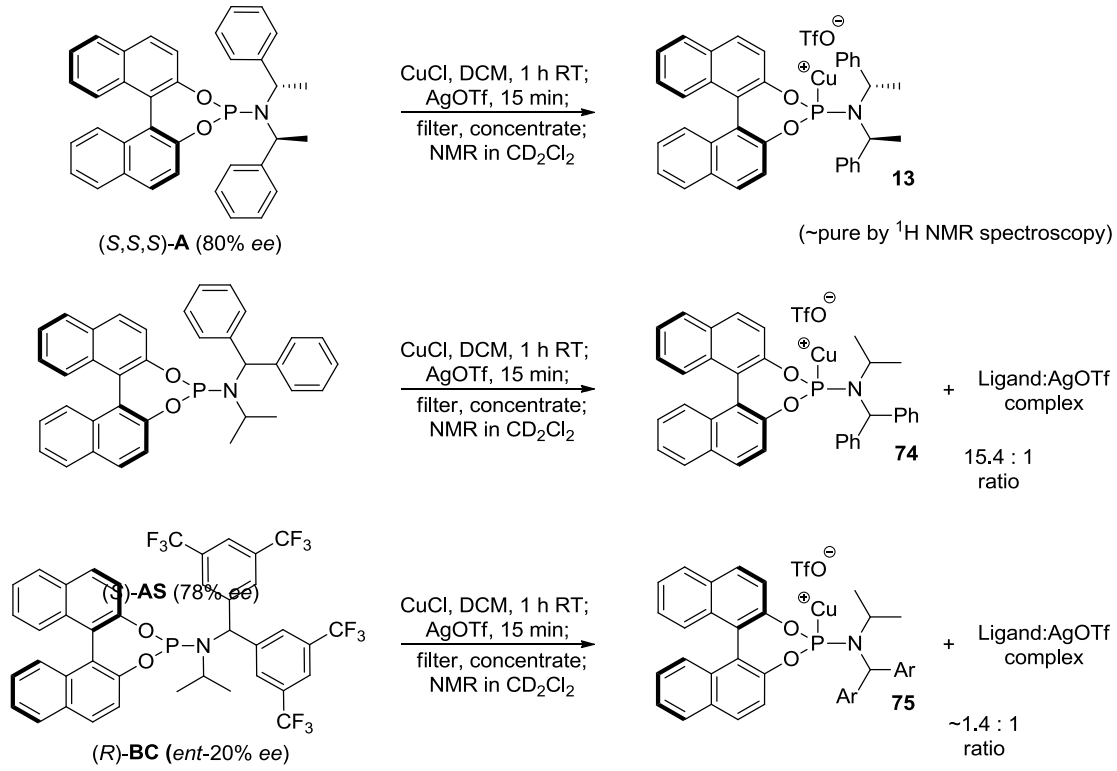
NOE and NOESY NMR spectroscopy experiments with CuOTf:L complexes indicated that **AS** and **BC** exhibit a similar conformational preference in solution. The least efficient ligand **BC** shows only weak interactions between the binaphthol backbone and the amido substituents, suggesting a different conformational preference.

Importance of the AgOTf salts

While studying the conformation of copper-ligand complexes by NMR, we identified extra species: AgOTf:ligand complexes. The assignement of the spectrum signals was performed by comparison with authentic samples.

These species were formed at least partially because of the method used to prepare the complexes; the copper complexes were made by premixing the ligand with one equivalent of CuCl before adding a slight excess (1.1 eq) of AgOTf to prepare the desired complexes. The ratio of the AgOTf: ligand to CuOTf: ligand complexes formed were found to depend on the particular ligand involved. The reation are calculated by ^{1}H NMR spectrum analysis.

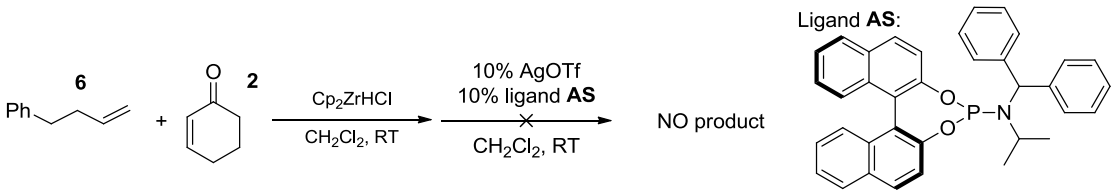
More precisely, the higher the efficiency of the ligand, the more CuOTf: ligand was present in solution (Scheme 3.12). Indeed, complex (**13**) (80% *ee*) did not detectibly form a AgOTf:**A** species. Conversely complex (**74**), (78% *ee*) has a ratio of 15.4 CuOTf:**AS** to 1 AgOTf:**AS** whereas complex (**75**) (20% *ee*) gave a ratio of 1.4 CuOTf:**BC** to 1.0 AgOTf:**BC** by NMR spectroscopy.



Scheme 3.12: NMR spectroscopic studies of ligand: CuOTf complexes in solution.

Additionally, copper complexes (**13**) and (**74**) (with ligands **A** and **AS** respectively) were easily synthesised. On the other hand, complex (**75**) was actually relatively hard to prepare using ligand **BE** for NMR analysis as degradation often occurred during the reaction conditions. EXSY (exchange spectroscopy) demonstrated that AgOTf:**BC** and CuOTf:**BC** undergo rapid metal/ligand exchange on the NMR timescale at room temperature.

A control experiment, using AgOTf:ligand complexes, did not form any product in the conjugate addition (Scheme 3.13). This excluded the possibility of silver catalysing a competing reaction. Further analysis of the different catalysts was performed via computer based methods.



Scheme 3.13: Attempt to perform the reaction using silver triflate – ligand complexes.

DFT studies of copper-ligand complexes

To gain insight into the structure of the complexes in solution we used computational methods. The aim was to determine the lowest energy conformation of the different ligands and compare these results with the NOE experiments. This work was performed by Dr Robert Paton who modelled complexes (**13)**, (**74)**, (**75)** (containing respectively ligands **A**, **AS** and **BC)** using the chloride counter ion instead of triflate in order to simplify the number of possible conformations produced.

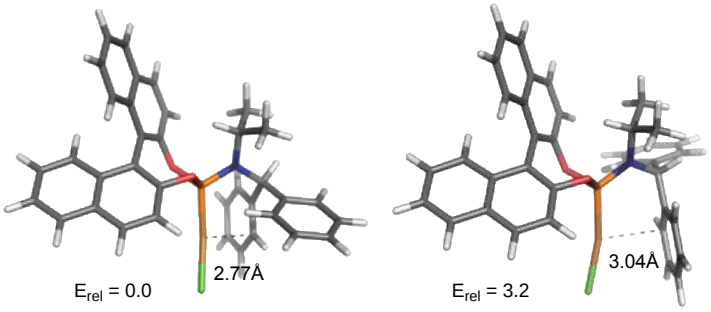


Figure 3.11: B97D/6-31G(d) lowest energy conformers of **AS**:CuCl (relative energies in kJ/mol).

For complex (**74**) (Figure 3.11), DFT calculations showed that there were two low energy conformers with a slight energy difference (3.2 kJ/mol). In agreement with NOE experiments, the calculated structures showed that the *N*-isopropyl group interacts with the binaphthol backbone. Additionally, one aromatic group interacts with copper (the metal-aryl distance is 2.77 Å, less than the sum of their respective Van der Waals radii).

The DFT calculations on the complex (**75**) (Figure 3.12) showed two different conformations with limited interactions between the amido group and the BINOL backbone,

consistent with NOE experiments. A comparatively lower copper – π interaction (distance 3.07 Å) was calculated.

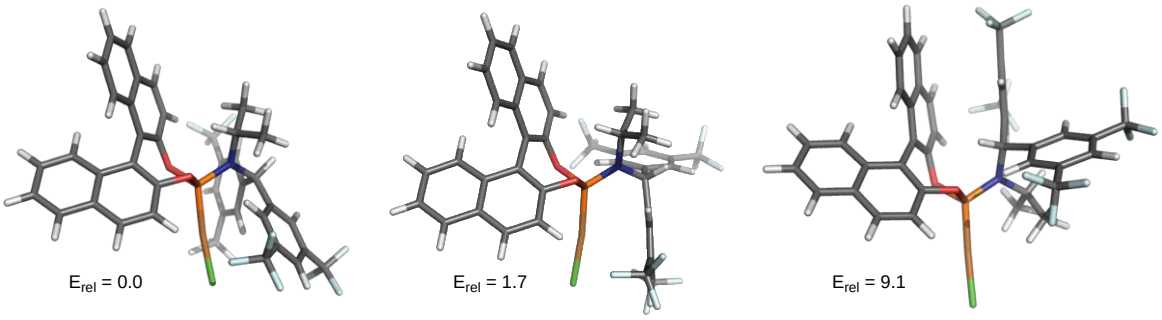


Figure 3.12: B97D/6-31G(d) lowest energy conformers of **BC**:CuCl (relative energies in kJ/mol).

Similar DFT analyses on the complex (**13**) (Figure 3.13) were in agreement agree with NOE experiments (Figure 3.13). As shown in figure 3.13 (right hand side) the lowest energy conformers of (**13**) and (**74**) are remarkably similar.

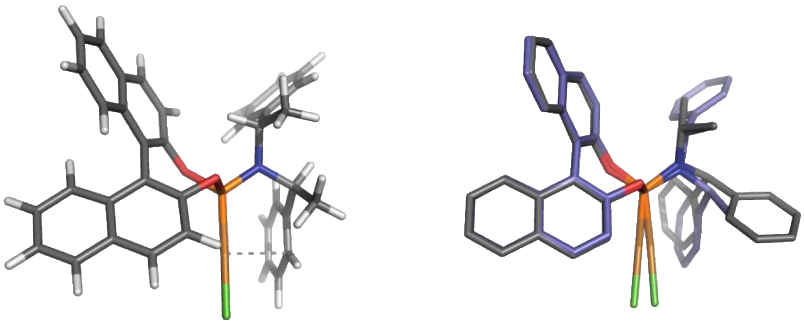


Figure 3.13. B97D/6-31G(d) lowest energy conformer of **A**:CuCl and superimposition of complex (**13**) and complex (**74**) (right).

Further interpretation

As mentioned above, NOE and NOESY NMR spectroscopy experiments tend to indicate the similarity in conformation between both complexes (**13**) and (**74**). DFT calculations performed on CuCl:L complexes also suggest the presence of similarity between the lowest energy conformations of both catalysts.

These results are consistent with enantioselectivity being dependent on the ability of the phosphoramidite to readily form a stable CuOTf complex. It seems that the addition of electron withdrawing groups (4 x CF_3 in **BE**) removes electron density from the coordinating P-atom making the complex less stable than in the case of **A** and **AS**. Presumably, copper not bound to the chiral ligand (*e.g*. CuOTf) is able to catalyse the racemic background reaction,[122] leading to an erosion of observed enantioselectivity. Indeed Wipf developed a similar methodology to create racemically similar adducts using $CuBr{\cdot}SMe_2$. In addition, this phenomenon means there is less active catalyst present in solution to catalyse the reaction, likely leading to an erosion of enantioselectivity (see chapter 2). Interestingly our reaction time (~2 hours) is similar to Wipf (4 hours), showing a slow increase of pace by the ligand. It could be interested to study in details the kinetics of the reaction with different ligands although it does not seem to be extremely important effects qualitatively. This hypothesis may explain a trend observed in the correlation of selectivity with ligand parameters (Figure 3.6, black circles): there is a correlation between selectivity and steric parameters, but there are clusters of several ligands of very similar size but with differing $\Delta\Delta G^{\ddagger}$ values. These ligands differ by the identity of aromatic substituents and their substitution pattern. Here electronic effects may affect the ability of the ligand to form an effective catalyst complex as observed by NMR spectroscopy.

Correlation of enantioselectivity with steric and electronic parameters

The results of our correlation studies, NOE analysis, and DFT calculations suggest that electronic factors are a crucial factor to obtaining high enantioselectivity in this reaction. Therefore another correlation between experimental enantioselectivity and calculated parameters was sought by Dr Robert Paton (using the same 22 ligands (Figures 3.2, 3.4 and 3.5) from the previous correlation, shown in black, Figure 3.14). Using the HOMO energy of the amido substituents as means to quantify the electronic nature of each substituent, and presumably also phosphoramidite electron donating ability, the new model displayed an effective correlation. The new correlation is described by the equation 3.2:

$\Delta\Delta G^{\ddagger}_{predicted} = 3.8 + 1.2\ HOMO \times (1+1.5\ L_2) - L_1 \times L_2$. (**Equation 3.2**)

Equation 3.2 contains four fitting parameters. Here, electronic and steric parameters are both taken into account. In term of physical meaning, the model pointed out that the length of both R_1 and R_2 substituents are critical as are the electronics of both the overall ligand and one of the R-groups. It is believed that electronics plays a role in both formation of a stable phosphorus-copper bond and in establishing a secondary interaction between the metal centre and one of the amido substituents (*vida infra*).

This agreed with our prior conclusion that these R groups interact with the metal centre and heavily influence the selectivity. The correlation obtained here was good ($R^2 = 0.79$) and shows a root mean square error of 0.50 kJ/mol.

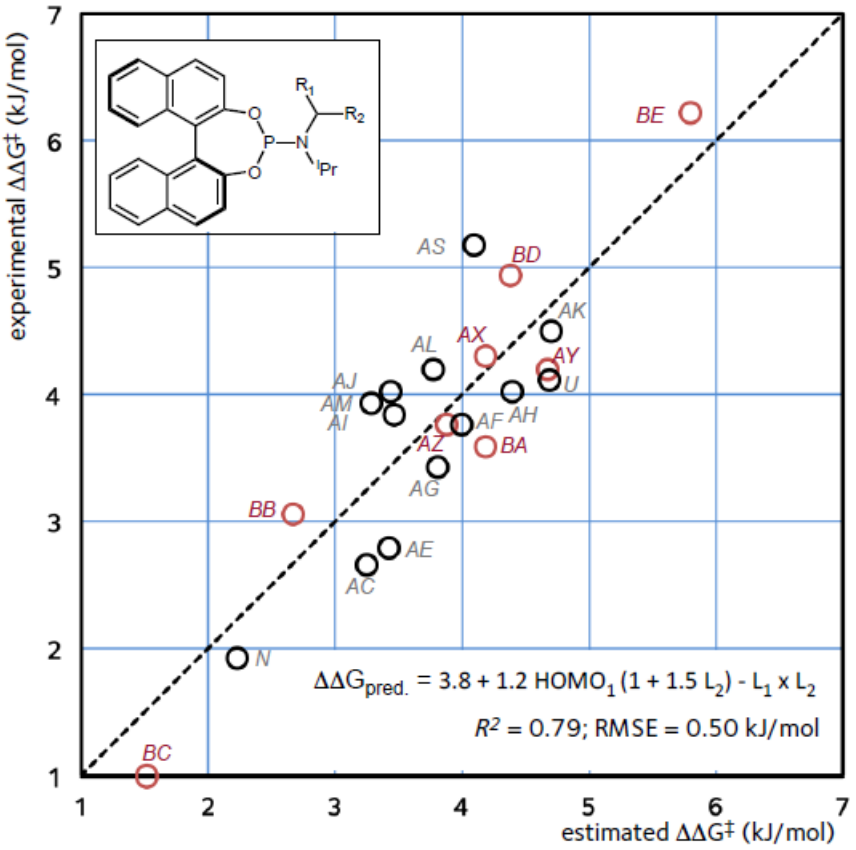
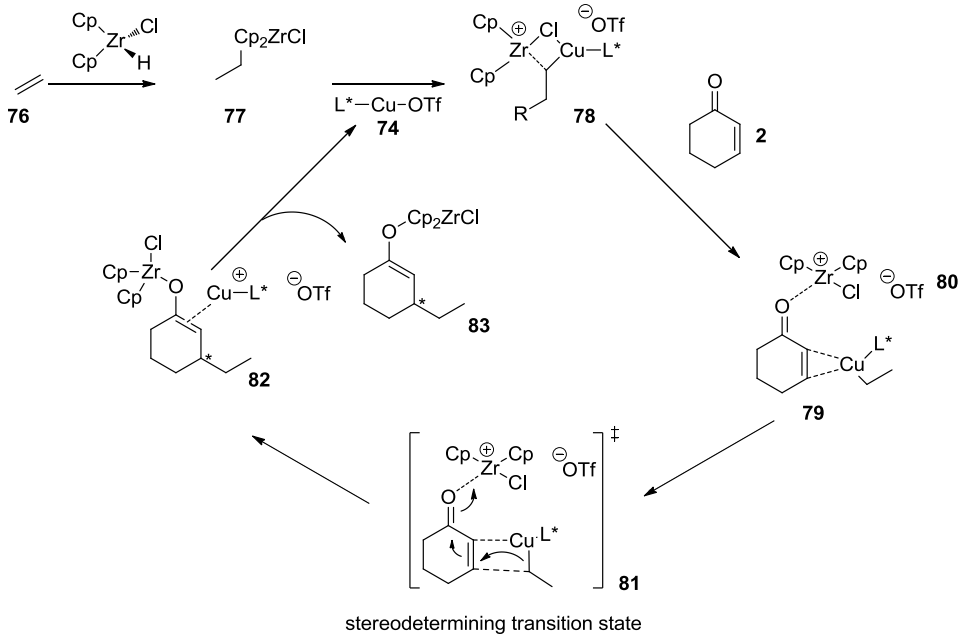


Figure 3.14: Correlation between experimental data and calculated sterics and electronic effects.

DFT calculations:

To further clarify the role of the phosphoramidite ligand in the reaction, the mechanism of a conjugate addition catalysed by Cu:**AS** complex was examined Dr Robert Paton, using DFT calculations (Scheme 3.14). Unfortuntely, no NMR studies have been performed yet on this reaction. Using ethylene (**76**) as the olefin, the interactions between the complex and the hydrozirconated alkene (**77**) were calculated. The result indicated that complex (**78**) forms spontaneously. Species (**78**) was stable and was located as a minimum on the potential energy surface (PES). Subsequent energy calculations were calculated relative to (**78**) (Figure 3.15).

After transmetallation, the zirconocene coordinated to enone (**2**) to form complex (**79**), more stable than (**78**) by over 25 kcal/mol. The zirconocene (**80**) coordinated to the oxygen of the enone while the alkyl-copper binds to the olefin. Then addition of the alkyl group to the enone occurs. As the ligand **AS** is chiral, coordination of (**79**) to either enone π-enantioface leads to non-equivalent diastereomeric intermediates of (**81**). Calculations allowed localisation and comparison of the energy between the different competing transition states of the conjugate addition to the different enantiofaces of the enone.



Scheme 3.14: Calculated catalytic cycle. (L* = **AS**)

In this case, calculations indicate alkyl addition by carbocupration (**81**) from both potential transition states (Figure 3.16). The calculations did not show the presence of the transient presence of a formal copper (III) species (although there are no experimental evidence investigated). After the addition occurred, a zirconium enolate is formed (the strong zirconium-oxygen bond is the driving force of the reaction) while the copper species was stabilised by forming π-complex, resulting in the relatively stable species (**82**).

By contrast, lithiocuprates are believed to operate via a Cu(I)/Cu(III) catalytic cycle while Grignard additions are generally thought to react via an equivalent oxidative addition/reductive elimination pathway.[200]

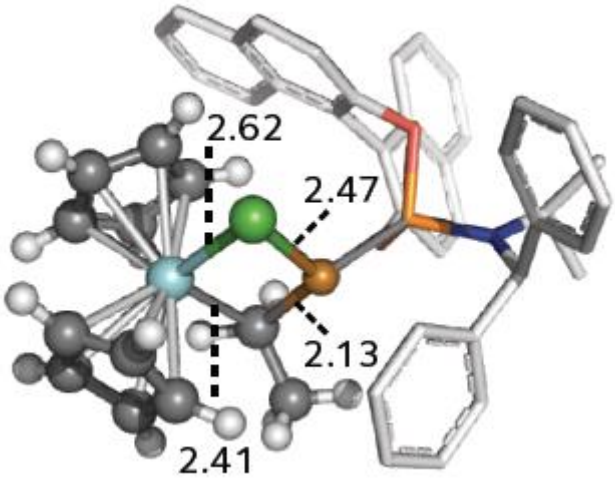


Figure 3.15: DFT model of the transmetallated complex (**78**).

The activation barriers for the diastereomeric transition states were calculated to be 8.4 and 13.0 kcal/mol respectively. These values suggest that this mechanism is plausible.

As the conjugate addition is irreversible, the carbocupration step determines the enantioselectivity. Calculations found that addition to enone (**2**) on the *Si*-face, corresponding to the experimentally observed product, is energetically favoured (Figure 3.16). This energetic difference arises from interactions between the two aryl groups of the ligand and the Lewis acid-coordinated substrate: in particular the close proximity between one of the phenyl groups and the $ZrCp_2Cl$ group in the disfavoured *re* transition state (Figure 3.16, right) is emphasized.

si-face:	-35.6	-27.2	-64.3
re-face:	-26.9	-22.6	-60.9

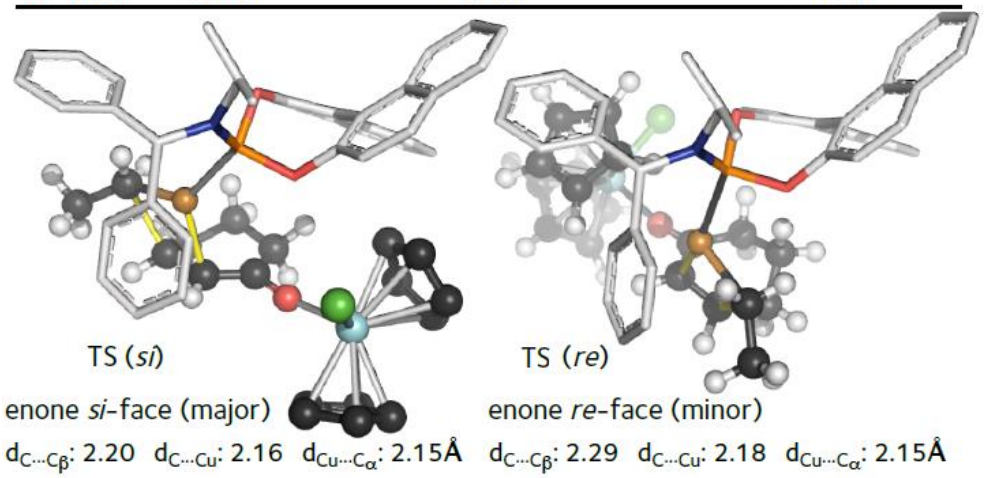


Figure 3.16: Comparison of DFT calculated transition states resulting from the nucleophilic addition of zirconocene on both *Si* and *Re* faces of enone (**2**).

This interaction generates a steric clash and triggers a movement of the ligand. This movement reduces the extent of coordination to copper by the other phenyl group. In the TS-*Si*, the distance between the copper and the closest (ipso) C atom is 2.76 Å while in the TS-*Re* it is 3.03 Å. The unfavourable steric interaction involving the aryl groups in TS-*Re* is maximised by elongation of this substituent. This supports the model derived from our linear correlation of selectivity with steric parameters.

The importance of the electronic nature of these rings, as emphasized by our NMR and DFT studies is also apparent in the computed TSs, since proximity of one of the rings to the metal centre provides a more favourable contribution to the relative energy of the major **TS**-*si*.

Conclusion

Using the asymmetric conjugate addition reaction developed in the group, we investigated the stereochemical role of the phosphoramidite ligand in the asymmetric conjugate addition on cyclohexenone. After systematic modification of the ligand scaffold, a correlation with sterimol parameters was performed to predict the characteristics of optimal ligands. Using this model, new phosphoramidite ligands bearing non-chiral amido substituents were synthesised. This prediction led to the discovery of an efficient ligand (up to 94% *ee*).

DFT calculations and NMR spectroscopy were used to analyse catalyst complexes in solution. Strong interactions between the binaphthol backbone and the amido substituents and a strong metal-ligand interaction were correlated with enantioselective ligands. Using this insight, a more descriptive correlation taking into account sterics and electronics of the ligand was established.

A plausible mechanism was calculated by DFT. This mechanism was coherent with the hypothesis made during our study in regard to ligand-metal interaction.

The method used in this study could potentially be applied to different systems. In addition, the large library of ligands could be tested on different reactions requiring phosphoramidite ligand.

Chapter 4: Copper catalysed conjugate addition of alklyzirconocene to cyclic enones to give quaternary centres

General introduction

All-carbon quaternary stereogenic centres are widely recognised as one of the most challenging synthetic targets.[164,201] Importantly, a significant number of natural products[202] with interesting biological activity contain quaternary centres.[203,204] Amongst them, Taxol[205] is a medicinally important molecule with anticancer properties while Standishinal[206] possess promising anticarcinogenic properties (Figure 4.1). The importance of molecules such as these, and the current lack of generally useful methods for the stereoselective synthesis of quaternary centres,[204,207] highlight the need for new methods to be developed in this area.

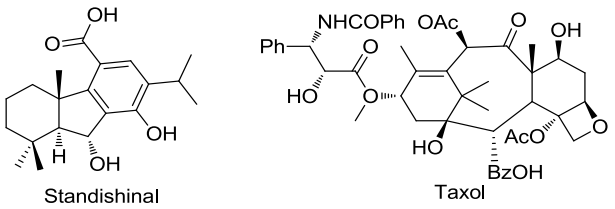


Figure 4.1: Selected natural products containing all-carbon stereogenic centres.

One approach to stereogenic quaternary centres is through the addition of a nucleophilic reagent to a tertiary Michael acceptor using an organometallic catalyst. In this case, a pre-made organometallic is transmetallated to the metal catalyst which then gives the desired product. Although methods using different metal catalysts[208] such as rhodium[209,210] and palladium[204,211] exist, the use of copper to catalyse such asymmetric conjugate additions is one of the most widely used methods.[45,47,121,140,212] Copper is cheap and often provides high selectivity. Tertiary enones are relatively unreactive as substrates due to steric blocking by the substituent and to decreased electrophilicity resulting from an inductive effect (in the case of common alkyl substituents). To

counteract this problem, the usual strategies, reviewed in detail in the next section, to form quaternary centre are:

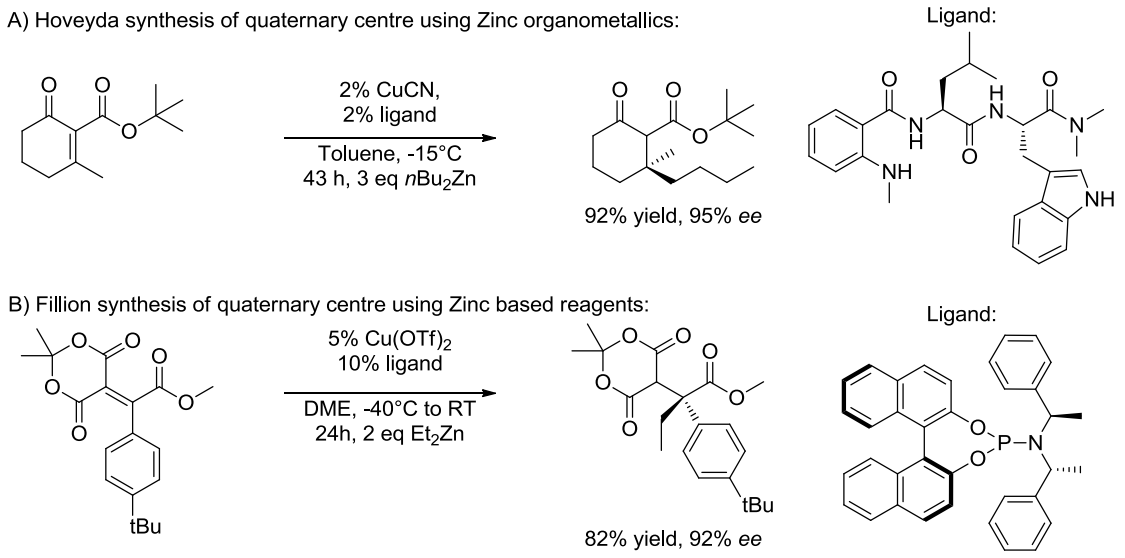
- To use a more reactive electrophile.
- To use a more active catalyst.
- To use a more reactive nucleophile.

The use of copper catalysts in quaternary centre forming conjugate addition reactions was pioneered by Alexakis and Hoveyda. The original methods, as describe below, tended to use an amino acid or phosphorus-based ligand. More recently, the development of NHC ligands has increased the scope and efficiency of these reactions.

Methods using primary organometallics

Zinc reagents

Using premade and relatively unreactive dialkylzinc reagents, Hoveyda synthesised quaternary centres from activated Michael acceptors such as enones bearing an extra withdrawing group[213] and nitro-olefins[214] using a peptide-based catalyst (Figure 4.1, A).

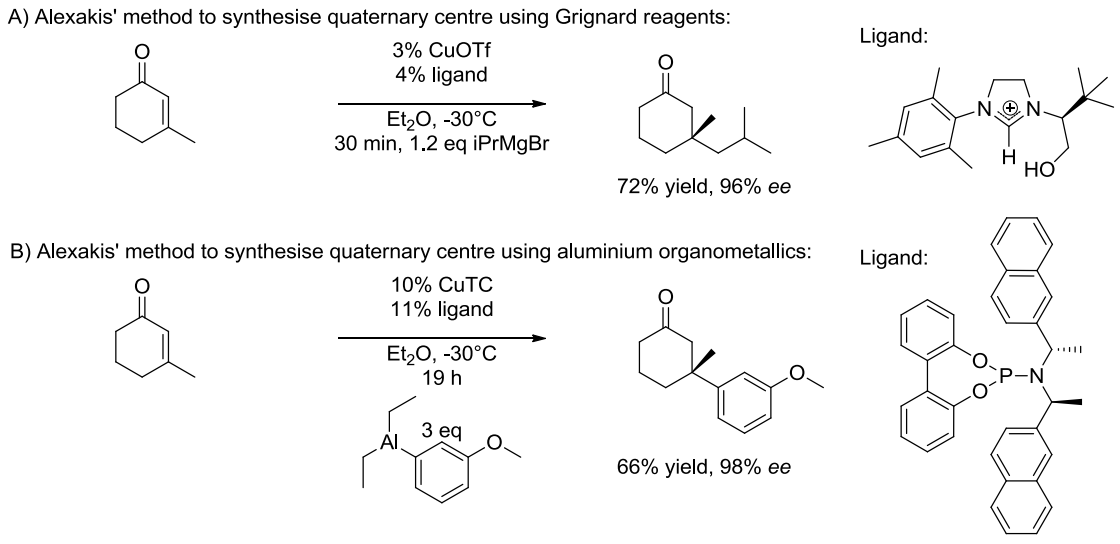


Scheme 4.1: Hoveyda's and Fillion's method to synthesise quaternary centres.

Hoveyda then developed a method using NHC ligands to synthesise all carbon quaternary centres from unactivated enones.[215] In this case, the higher reactivity of the ligand-metal combination allows for aryl zinc reagents to react. Using a phosphoramidite ligand, Fillion developed a method to react diethyl zinc with Meldrum's acid derivatives with high levels of enantiomeric excess (Figure 4.1, B).[139,141,216].

Grignard reagents

As trisubstituted enones are relatively unreactive, Alexakis used Grignard reagents in combination with an NHC-based copper catalyst to synthesise quaternary centres with high yield and enantioselectivity (Scheme 4.2, A).[217] The method has since been extended significantly. In some cases, with polyunsaturated systems, the method could be used to favour 1,4-addition over 1,6-conjugate addition to synthesise quaternary centres with high enantioselectivity.[218] Similarly, Tomioka used C_2 symmetric NHC ligands[219] while Williams used the combination of a Grignard reagent and a copper catalyst to synthesise (−)-neovibsanin G and related natural products.[220]



Scheme 4.2: Alexakis' syntheses of quaternary centres with Grignard (A) & aluminium reagents (B).

Aluminium reagents

Alexakis has also used premade aluminium salts to synthesise quaternary centres enantioselectively (Scheme 4.2, B).[221] The higher reactivity of the organoaluminium reagents allows the formation of quaternary centres with high yields and excellent enantioselectivity. Indeed, the aluminium reacts not only as a nucleophile to perform a conjugate addition, but also as a Lewis acid (due to empty orbital on the metal) which serves to enhance the reactivity of the electrophile. The method is versatile and was used to synthesise natural products, such as taxadiene by Baran[205] and (+)−9‑Oxoeuryopsin by Maldonado.[222]

Because of the high reactivity of alkyl aluminium reagents, the reaction works with simple unactivated enones. Some of the ligands used in these methods are phosphoramidites.[60] However, these ligands tend to react with the aluminium salts[155] so phosphines which are structurally similar to the phosphoramidites have been developed[156, 223, 224] where the absence of phosphorus-oxygen bond prevents side reactions. The recent use of NHC ligands has improved the reliability of these methods. Using NHC ligands, Hoveyda and Alexakis each reported a procedure using both alkyl and aryl aluminium reagents that was remarkably efficient with the difficult 4-methyl-cyclopentenone substrate.[225] Interestingly as well, in Scheme 4.2, B), the aryl group is activated and transferred over alkyl group, allowing a specific transfer. Recently, the scope of these reaction has been extended to acyclic substrates.[226] The scope of the aluminium reagents has also been extended to alkenyl nucleophiles.[210, 227-230] These methods typically involve hydrometallation of an alkyne by an aluminium-based reagent, although Hoveyda recently reported the use of a multistep procedure, making organometallics *in situ* through a zirconium-based intermediate.[231]

These methods are all based on premade organometallics, except for those generated from alkynes and aluminium.[231] The high reactivity of these species allows them to react effectively with enones but raises safety issues. Some pyrophoric reagents (dialkyl zinc and alkylaluminum) require extra safe storage and handling. In addition, it has to be noted that these chemicals possess a limited functional group tolerance, due to the reactive nature of the organometallic. As a

consequence, only simply substituted nucleophiles can be synthesised with these methods, although they have been shown to effectively react with some substrates bearing functional groups. These issues prevent further use and scale up of these methods.[51] Although the alkenyl substrates allow the incorporation of some functional groups,[228, 231] the addition of alkyl equivalents remains very limited in term of functional group compatibility. In figure 4.2, all alkyl nucleophiles previously used in such copper catalysed conjugate additions have been summarised, and are classified according to the nature of the primary organometallics. It can be seen that the functional group tolerance is essentially non-existent except for one example of an acetate that has been used with a specific activated electrophile[213] and alkenes. This lack of functional group tolerance is detrimental to a wider application of this reaction. Indeed, some important targets cannot be synthesised using these methods because functionality necessary for their synthesis could not be incorporated easily.[232]

Another issue is the poor atom economy of these methods. The copper catalyst is only able to transfer one group from dialkyl zinc and aluminium reagents, producing a large amount of waste in the process even if the reaction conversion is high. However, it has to be noticed that the method developed during this studies does not fix this issue as a large excess of alkene (2.5 eq) and Schwartz reagent (2 eq) are used in the standard system. Although reduction of the excess of reagent is possible, the methods developed here still need further optimisation to reduce waste.

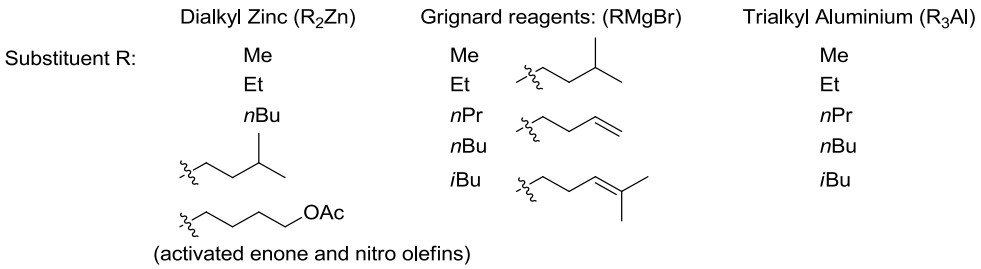


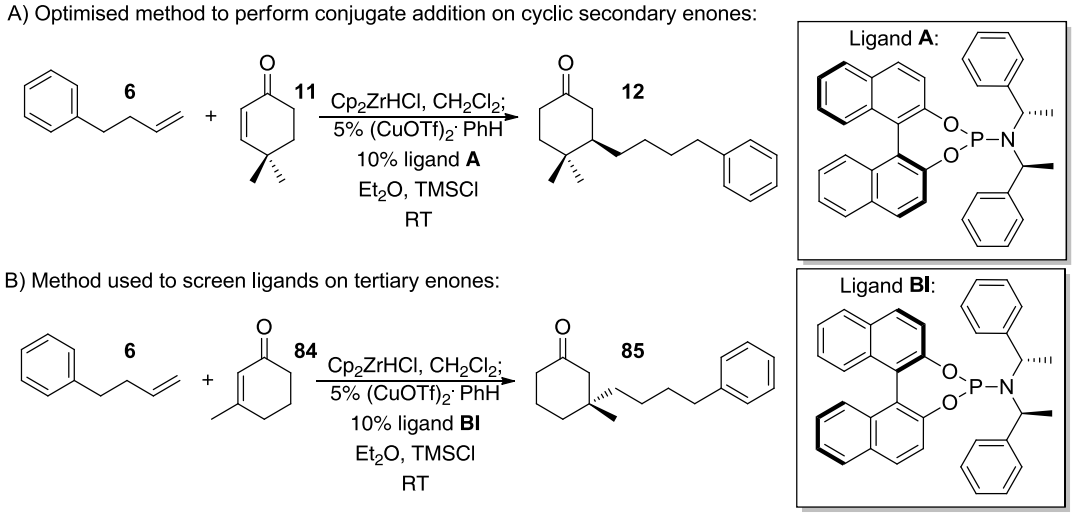
Figure 4.2: List of *n*-alkyl nucleophiles previously used in ACA to form quaternary centres.

In chapter 2, the development of an enantioselective conjugate addition reaction is described, using alkenes as nucleophile to generate tertiary centres. The organozirconium

nucleophiles were generated *in situ*, thus bypassing the need for highly reactive premade organometallics and tolerated several functional groups. We decided to investigate the application of our methodology to the synthesis of quaternary centres and this work is described below.

Engineering the new methodology

Our initial studies required a model substrate. By analogy to our previous study, we decided to use a substrate similar in shape to cyclohex-2-enone (**2**) and therefore used 3-methylcyclohex-2-enone (**84**) for the current optimisation to form **(85**) (Scheme 4.3).



Scheme 4.3: (A) Method to synthesise cyclic tertiary centres and (B) method used to screen ligands to synthesise quaternary centres.
Conditions: alkene (**6**) (2.5 eq), Cp_2ZrHCl (2.0 eq), $CuOTf)_2{\cdot}C_6H_6$ (0.1 eq), ligand (0.1 eq), enone (1.0 eq), TMSCl (5.0 eq), RT, *ee*s determined by chiral HPLC**).**

The first step consisted in screening ligands from the homemade library described in Chapter 3. A large part of the initial screening (36 examples) was performed by Dr Rebecca Maksymowicz. She synthesised ligands **BI** and **BJ**.[191] To start screening, the same set of conditions from chapter 2 was used. It has to be noticed that screening has a relatively low conversion (~50%) and yields were always low (~25%), the main by-product being the enone reduced into the corresponding alcohol.

Alkene (**6**) was hydrometallated using Schwartz reagent in CH_2Cl_2 at room temperature and then added to a stirred solution of the ligand and the copper source (copper triflate) in Et_2O. The enone and TMSCl were added sequentially and the reaction was stirred overnight. This method gave the desired ketone (**85**) bearing a quaternary centre after the 1,4-conjugate addition. All cited *ee*s in screening correspond to this reaction, (reagents ratios and conditions kept constant (Scheme 4.3).

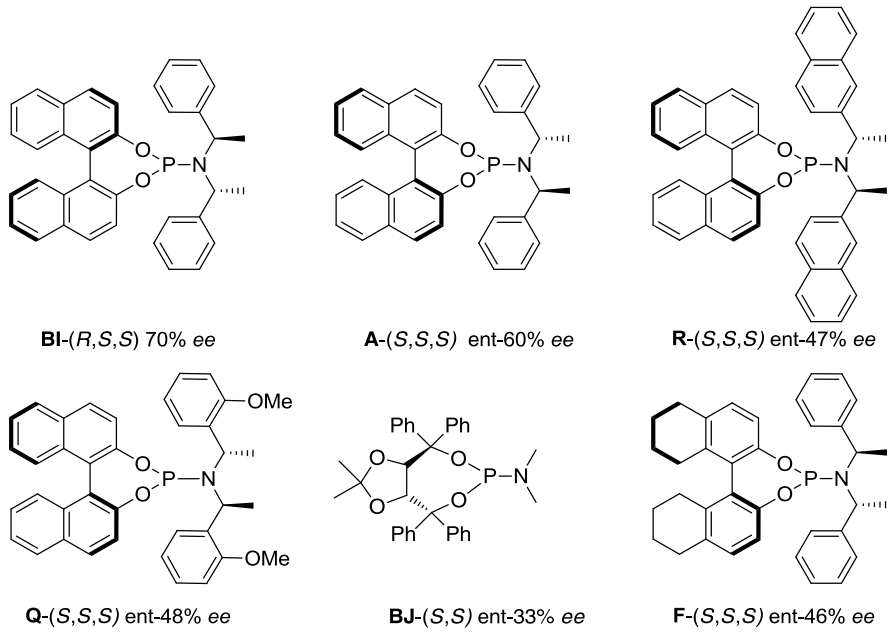


Figure 4.3: Screening known ligands. Unless stated otherwise ('ent'), ketone **85** was produced with absolute configuration *R*.

Using Feringa's ligand **A**, which was optimal for the synthesis of tertiary centres, the quaternary ketone was obtained with 60% *ee* while the (*R, S, S*)-diastereoisomer **BI** gave the product with 70% *ee* (Figure 4.3). As previously (Chapter 3), the stereochemistry of the ketone (**85**) was dictated by the stereochemistry of the binaphthol backbone, where a (*R*)-binaphthol backbone induces the (*R*) enantiomer of (**85**). Common related ligands (Figure 4.3) were also examined and these were all detrimental to selectivity; for example Alexakis' ligand **Q** gave 48% *ee* while taddol based ligand **BJ** gave 33% *ee*.

The VANOL based ligand **H** (Figure 4.4) gave 34% *ee* while a ligand bearing bromides at the binaphthol 7,7'-position **G** gave a surprising 54% *ee*. Any modification on the BINOL-3,3'

position (**I**, **K**, **BK**, **J**) led to a loss of enantioselectivity. A variation bearing a simplified biphenol backbone **D**, and spirocyclic **E** did not provide higher selectivity. Ligand **BK** and **BL** were synthesised according to the literature.[191]

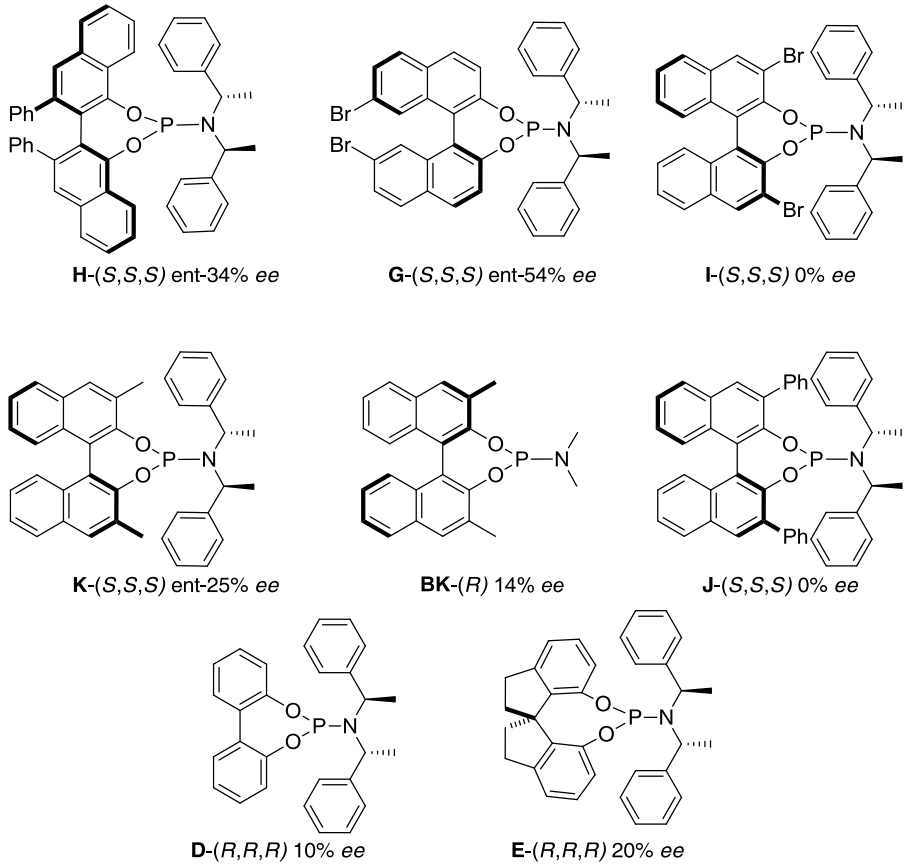


Figure 4.4: Screening of ligand with BINOL backbone modification. Unless stated otherwise ('ent'), the absolute configuration of the produced ketone (**85**) is *R*.

As none of these ligands seemed any better than ligand **BI**, we decided to modify the amine substituents more systematically while retaining the binaphthol backbone. A variety of ligands with different alkyl bulk (Figure 4.5) were screened but they gave consistently low results (15-47% *ee*). Surprisingly, methyl **L** and adamantyl **P** substituted ligands gave the very close *ee* values (33% *ee* and 32% *ee*). A ligand bearing two nitrogen atoms **BL** was tested but only delivered 15% *ee* in the reaction. As no obvious trend could be interpreted from these results, it was decided to test again ligands from derivatives of Feringa's ligand **BI**.

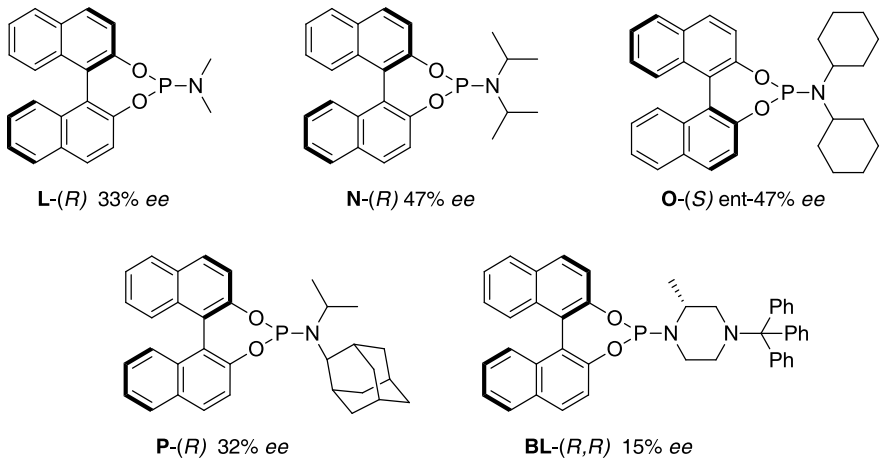


Figure 4.5: Screening of various ligands bearing different *N*-substituents. Unless stated otherwise ('ent'), the absolute configuration of the produced ketone **(85)** is *R*.

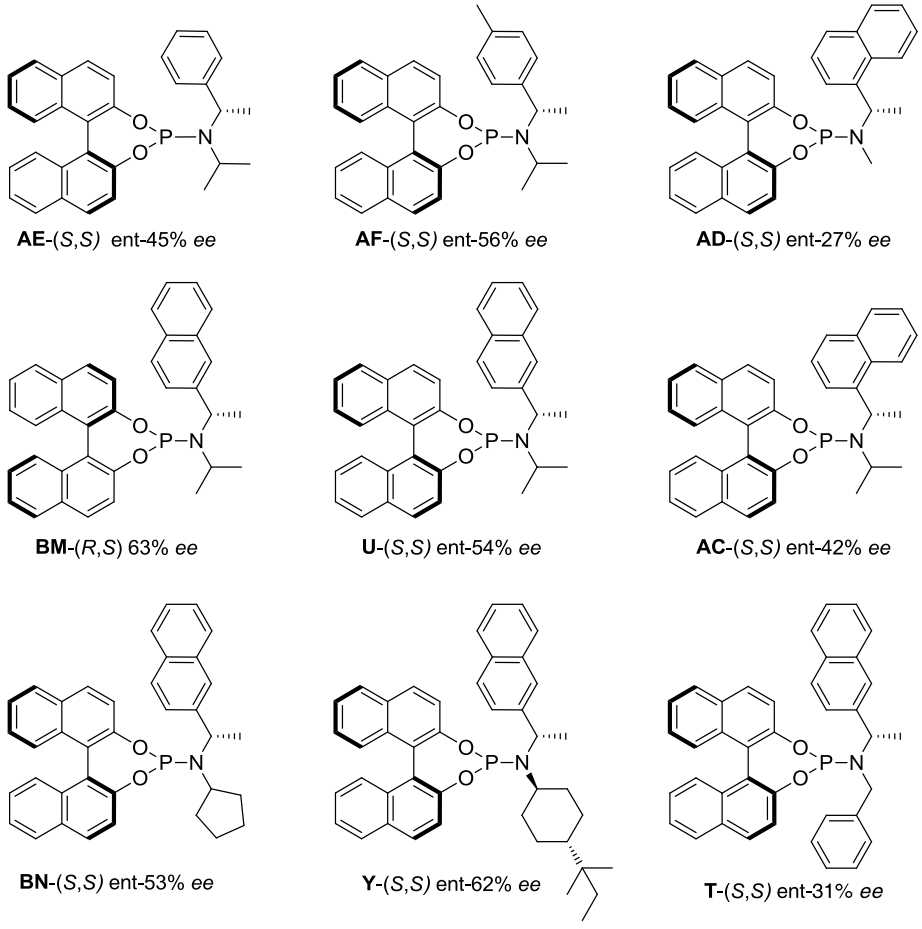


Figure 4.6: Screening of ligand bearing '1-benzyl' and 'Naphthyl-CH-Me' *N*-substituents. Unless stated otherwise ('ent'), the produced ketone **(85)** had absolute configuration *R*.

The 'isopropyl' type ligands discussed in Chapter 3 were tested next. Ligands with simple α-methyl-benzyl *N*-substituents (**AE** & **AF,** Figure 4.6) or 1-Naphtyl-methyl *N*-substituents (**AD** & **AC**) did not increase the observed *ee* (27-56% *ee*). Ligand **BM** and **BN** were synthesised according to the literature procedure.[191]

1-Naphtyl-methyl *N*-substituents **BM** induced a similar enantioselectivity to **BI** (63% *ee*) while its diastereomer **U** gave a lower *ee* (54% *ee*). This selectivity amongst diastereomers is consistent with the one observed for Feringa's ligand **A** & **BI**. Changing the 'isopropyl' unit to cyclic (**BN**, **Y**) or benzylic (**T**) groups did not increase the observed *ee* (31-62% *ee*).

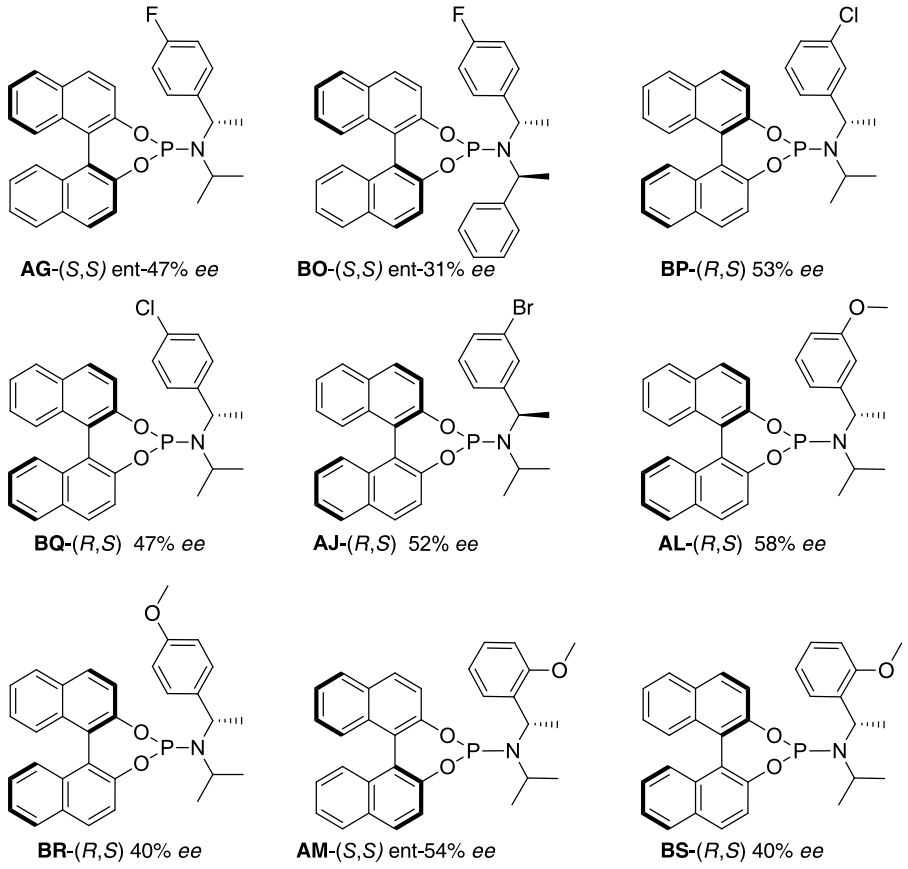


Figure 4.7: Screening of ligands with different α-methyl-benzyl *N*-substituents. Unless stated otherwise ('ent'), the produced ketone (**85**) had the absolute configuration *R*.

Similarly to the screening performed in chapter 3, ligands bearing modification on the α-methyl-benzyl *N*-substituent were tested (Figure 4.7). Ligands **BO**, **BP**, **BQ**, **BR** and **BS** were synthesised by collaborators using literature procedure.[191] Halogen and methoxy substituents at

different aromatic positions gave consistently mediocre results (31-58% *ee*). Interestingly, the methoxy (*R*,*S*)-**AM** gave 40% *ee* while its diastereomer (*S*,*S*)-**BS** gave 54% *ee*. This result was surprising as it displays an unusual diastereomeric substitution effect. No obvious trend could be seen in these results.

As the isopropyl *N*-substitution did not decrease the enantioselectivity, additional analogous ligands were tested (Figure 4.8). Ligands (*S*,*S*)-**AN** and its diastereomer (*R*,*S*)-**BT** gave similar results (65 & 64% *ee* respectively. This higher enantioselectivity was encouraging. Substitution of the α-methyl-benzyl 'unit' with bicyclic *N*-substituents (**AO**, **AQ**, **AR**, and **BU**) led to similar *ee*s, **AQ** standing out with 67% *ee*. Other modified ligands (**BH**, **AP**, **S**) were tested and only **AP** induced asymmetry to a similar level (64% *ee*) to Feringa's diastereomer **BI**.

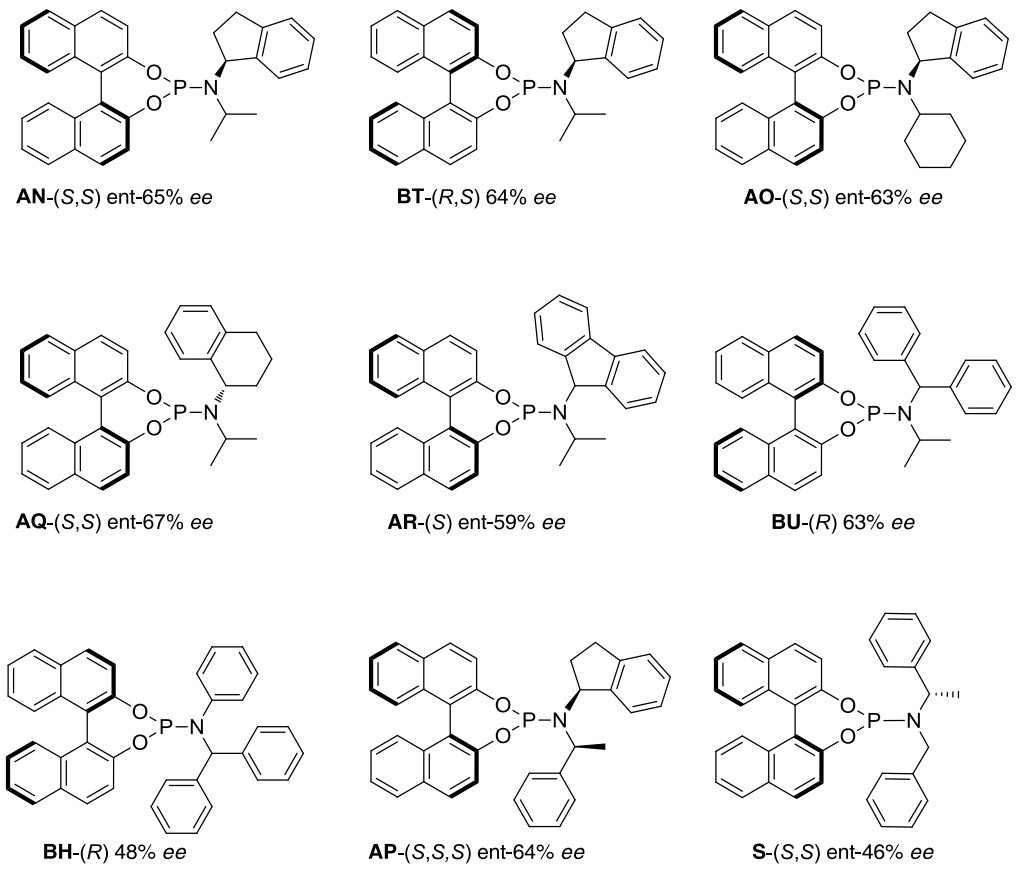


Figure 4.8: screening of ligands modified from Feringa's ligand **A**. Unless stated otherwise, the absolute configuration of the produced ketone (**85**) was *R*.

At this point, only minor enantioselectivity increase had been reached (67% *ee* for **AQ**) compared to Feringa's diastereomer **BI** (67% *ee*). No clear trend suggested which characteristics of the ligand were ideal. Also, the results indicated the system was not optimised. Indeed, reactions did not go to completion and the enone **(84**) was often reduced to the corresponding allylic alcohol under the reaction conditions. This happens because the hydrozirconation is an equilibrium. Therefore there is always a trace of Schwartz reagent in solution. As it is a fairly good reducing agent, it can reduce the enone. We decided to vary other reaction parameters, using the best ligand screened so far, **BI**. Other ligands, especially **BU**, (the (*R*)-enantiomer of ligand **AS**, see Chapter 3) would also be screened as they looked promising in these studies. Ligands **BI**, **BJ**, **BT** and **BU** were synthesised by collaborators according to literature procedure.[191]

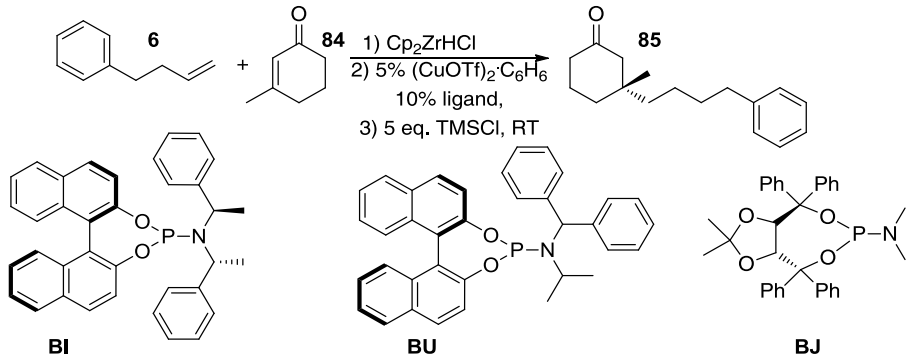
Investigations into making a predictive model were unsuccessful as the range of enantioselectivities obtained by the ligand did not cover a range as wide as it is required

Screening copper sources and solvent

The reaction conditions did not lead to conversion, which was attributed to the use of unoptimised conditions for the less reactive electrophile (**84**). We decided to alter the copper source and solvent to optimise the current system. A significant part of this work was performed by Dr Mireia Sidera (52 screening conditions).

Using the copper triflate-benzene complex and ligands **BI** and **BU**, solvents were screened (Table 4.1) at room temperature, which did not lead to any improvement. Using ligand **BU** and **BJ** (entries 1-13), common solvents were screened and the results were not better. Dimethoxypyridine (entries 10 & 14) poisoned and stopped the reaction to proceed. Varying the amount of TMSCl (entry 6 versus entry 5) decreased the selectivity to 30% *ee*. Ethereal solvents (entries 2-5, 9, 11, 13) gave a wide variation in results, but none was better than Et_2O (entry 5) with 63% *ee*. Comparatively, chlorinated solvents were not as good (entries 1, 12) with a maximum of 50% *ee* for CH_2Cl_2. Any attempt at removing the solvent after hydrozirconation led to poor results as the reactions does not proceeds and stops at an early stage.

Using ligand **BI**, solvents were screened (entries 14- 24). Here, Et_2O (entry 16) was best with 70% *ee*, while other ethers performed poorly (entries 15, 19-20, 24). Chlorinated solvents gave lower *ee*s with this ligand (entries 17, 18, 23) with maximum of 14% *ee* in DCE. Et_2O was the best solvent (entry 16, 70% *ee*), but the new level of stereocontrol was still low and therefore further modifications to these conditions were explored.

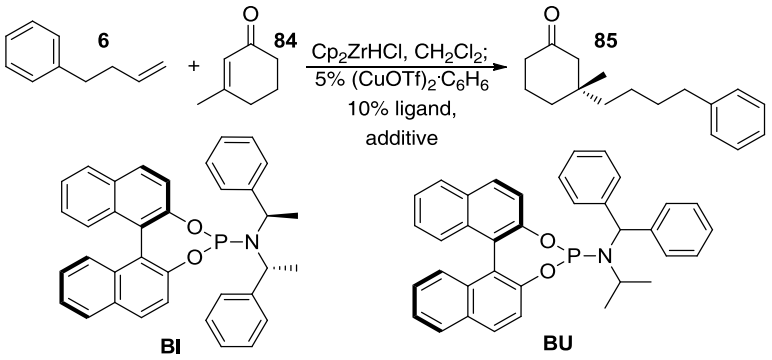


Entry	Ligand	Solvent	Enantiomeric excess (*ee*)
1	**BU**	CH_2Cl_2	50%
2	**BU**	THF	26%
3	**BU**	2-Me-THF	5%
4	**BU**	*t*-BuOMe	50%
5	**BU**	Et_2O	63%
6	**BU**	Et_2O	30%
7	**BJ**	Et_2O	20%
8	**BU**	Toluene	34%
9	**BU**	DME	20%
10	**BU**	DMP	No reaction
11	**BU**	*i*Pr_2O	22%
12	**BU**	DCE	18%
13	**BU**	Anisole	46%
14	**BI**	Dimethoxy-pyridine	No reaction
15	**BI**	1,4-dioxane	40%
16	**BI**	Et_2O	70%
17	**BI**	DCE	14%
18	**BI**	$CHCl_3$	11%
19	**BI**	2-Me-THF	52%
20	**BI**	*t*-BuOMe	10%
21	**BI**	EtOAc	44%
22	**BI**	Hexane	40%
23	**BI**	CH_2Cl_2	6%

24	**BI**	THF	38%

Table 4.1: Screening of solvents using $(CuOTf)_2 \cdot PhH$.
Conditions: alkene (**6**) (2.5 eq), Cp_2ZrHCl (2.0 eq), $(CuOTf)_2 \cdot C_6H_6$ (0.05 eq), ligand (0.1 eq), enone (**84**) (1.0 eq), TMSCl (5.0 eq), RT. *ee*s determined by chiral HPLC**.**

Using ligands **BI** and **BU**, Et_2O and 1,2-dichloroethane (as it has a higher boiling point) were screened at different temperature (Table 4.2, entries 1-8). Using ligand **BU** in Et_2O (entries 1-4), room temperature was optimum (entry 3). Similar results were found with ligand **BI** (entries 5 & 6) using 1,2-dichloroethane as solvent (entry 7 & 8). This phenomenon is unusul in asymmetric catalysis but is observed consistently with this chemistry. Presumably, the alklylzirconocene is badly affected by a change of temperature. A different Lewis acid (boronic ester, entries 9-10) was detrimental and TMSCl seems better to activate the enone. As none of the screening led so far to an increase of enantioselectivity, we decided to change the copper source. None the reactions screened thus far proceeded to completion but a significant amount of reduced starting material was isolated.



Entry	Ligand	Solvent	Temperature	Additive (equivalents)	Enantiomeric excess (*ee*)
1	**BU**	Et_2O	0°C	TMSCl (5)	19%
2	**BU**	Et_2O	10°C	TMSCl (5)	40%
3	**BU**	Et_2O	RT	TMSCl (5)	63%
4	**BU**	Et_2O	40°C	TMSCl (5)	60%
5	**BI**	Et_2O	10°C	TMSCl (5)	68%
6	**BI**	Et_2O	RT	TMSCl (5)	70%
7	**BU**	DCE	40°C	TMSCl (5)	2%
8	**BU**	DCE	60°C	TMSCl (5)	20%
9	**BI**	Et_2O	RT	$B(OMe)_3$ (5)	36%

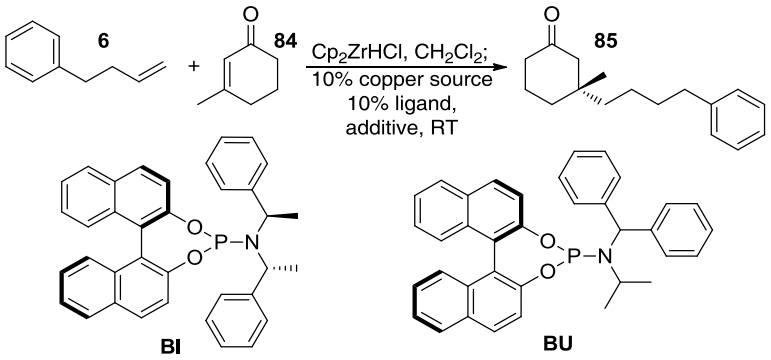
10	**BI**	Et_2O	RT	$B(OMe)_3$ (2.5)	42%

Table 4.2: Screening of temperatures using $(CuOTf)_2 \cdot PhH$.
Conditions: alkene **6** (2.5 eq), Cp_2ZrHCl (2.0 eq), $(CuOTf)_2 \cdot C_6H_6$ (0.05 eq), ligand (0.1 eq), enone **84** (1.0 eq), additives, RT. *ee*s determined by chiral HPLC**.**

Still using both ligands **BI** and **BU**, copper sources were screened in both Et_2O and CH_2Cl_2 (Table 4.3). Using ligand **BI**, halogenated copper sources (CuCl, CuBr) led to racemic (or nearly racemic) products (entries 1-4). Various copper triflates (entries 5, 6, 9, 10) gave lower selectivity, while other sources (CuOAc and CuTC) gave almost no selectivity (entries 7 & 8). Ligand **BU** did not show any increase in enantioselectivity (entries 11-17) when used with the same copper sources. We therefore decided to try non-commercial copper sources. To make these, CuCl and the corresponding ligand were mixed for one hour before a silver salt of the desired counter ion was added. After another 15 minutes of stirring, the reaction mixture was filtered to remove silver salts and give the desired copper species in solution.

The new copper sources were tested (entries 18-30). It was found that a triflimidate counter ion led to an increase of enantioselectivity to 80% *ee* (entry 19) in Et_2O and a similar 78% *ee* in CH_2Cl_2 (entry 20). Triflimidate counter ions are used widely in asymmetric synthesis.[233] They are normally more active counter-ions because of their more dissociate character. Indeed they possess high electro-withdrawing properties, a large volume, and therefore a lower charge density, making the corresponding metal more cationic and more reactive. [233] As the enones are poorly reactive, we reasoned that it was this enhancement of the reactivity at the metal that was increasing the observed reactivity.

This copper source was so reactive that an external Lewis acid was no longer necessary and therefore was not included in further screening (entries 21-30). As it seemed that a more dissociated counter ion than triflate was required, other copper sources were examined in screening (entries 23-30). Copper perchlorate (entries 23 – 26) reached 69% *ee* (entry 23) while the $CuSbF_6$ counter ion (entry 27-30) led to a maximum of 73% *ee* (entry 29). This series of more dissociated counter ions proved to be much better in general. We then decided to try optimising these conditions to reach higher levels of selectivity by screening temperature and solvents.



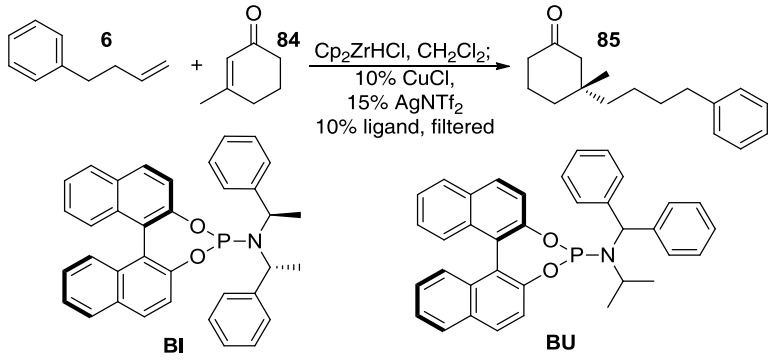
Entry	Copper source	Ligand	Solvent	Additive (equivalent)	Enantiomeric excess (*ee*)
1	CuCl	**BI**	CH_2Cl_2	TMSCl (5)	6%
2	CuBr	**BI**	CH_2Cl_2	TMSCl (5)	2%
3	CuCN	**BI**	CH_2Cl_2	TMSCl (5)	0%
4	$CuBr.SMe_2$	**BI**	CH_2Cl_2	TMSCl (5)	0%
5	$Cu(MeCN)_4.OTf$	**BI**	Et_2O	TMSCl (5)	28%
6	$Cu(MeCN)_4.BF_4$	**BI**	Et_2O	TMSCl (5)	23%
7	CuTC	**BI**	Et_2O	TMSCl (5)	2%
8	$Cu(OAc)_2$	**BI**	Et_2O	TMSCl (5)	1%
9	$Cu(MeCN)_2.OTf$	**BU**	CH_2Cl_2	TMSCl (5)	49%
10	$Cu(t\text{-}BuCN)_2.OTf$	**BU**	CH_2Cl_2	TMSCl (5)	45%
11	CuCl	**BU**	Et_2O	TMSCl (5)	6%
12	CuBr	**BU**	Et_2O	TMSCl (5)	3%
13	CuCN	**BU**	Et_2O	TMSCl (5)	3%
14	CuTC	**BU**	CH_2Cl_2	TMSCl (5)	9%
15	CuOAc	**BU**	CH_2Cl_2	TMSCl (5)	2%
16	$CuBr.SMe_2$	**BU**	CH_2Cl_2	TMSCl (5)	2%
17	CuI	**BU**	CH_2Cl_2	TMSCl (5)	8%
18	$CuCl + AgPF_6$	**BU**	Et_2O	TMSCl (5)	0%
19	$CuCl + AgNTf_2$	**BI**	Et_2O	TMSCl (5)	82%
20	$CuCl + AgNTf_2$	**BI**	CH_2Cl_2	TMSCl (5)	78%
21	$CuCl + AgNTf_2$	**BI**	CH_2Cl_2		86%
22	$CuCl + AgNTf_2$	**BU**	CH_2Cl_2		49%
23	$CuCl + AgClO_4$	**BI**	CH_2Cl_2		69%
24	$CuCl + AgClO_4$	**BU**	CH_2Cl_2		61%
25	$CuCl + AgClO_4$	**BI**	Et_2O		27%

26	CuCl + $AgClO_4$	**BU**	Et_2O		78%
27	CuCl + $AgSbF_6$	**BI**	Et_2O		0%
28	CuCl + $AgSbF_6$	**BU**	Et_2O		2%
29	CuCl + $AgSbF_6$	**BI**	CH_2Cl_2		73%
30	CuCl + $AgSbF_6$	**BU**	CH_2Cl_2		41%

Table 4.3: Screening of copper source and solvent.
Conditions: alkene (**6**) (2.5 eq), Cp_2ZrHCl (2.0 eq), copper source (0.1 eq), ligand (0.1 eq), enone (**84**) (1.0 eq), additive, RT. *ee*s determined by chiral HPLC**.**

Optimisation of results

Using the best new copper source ($CuNTf_2$ made *in situ*), solvents were screened with both ligands **BI** (Table 4.4, entries 1-10) and **BU** (entries 11-16). It was checked that silver and ligand tgether did not catalyse any background reaction, ensuring any spare silver metal is not detrimental to the observed enantioselectivity.



Entry	Ligand	Solvent	Temperature	Enantiomeric excess (*ee*)
1	**BI**	CH_2Cl_2	0 °C	74%
2	**BI**	CH_2Cl_2	10 °C	76%
3	**BI**	CH_2Cl_2	RT	86%
4	**BI**	CH_2Cl_2	40 °C	80%
5	**BI**	THF	RT	77%
6	**BI**	2-Me-THF	RT	80%
7	**BI**	$CHCl_3$	RT	79%
8	**BI**	Anisole	RT	88%
9	**BI**	*t*-BuOMe	RT	86%

10	**BI**	Toluene	RT	90%
11	**BU**	Et_2O	RT	67%
12	**BU**	2-Me-THF	RT	88%
13	**BU**	THF	RT	56%
14	**BU**	Toluene	RT	80%
15	**BU**	$CHCl_3$	RT	87%
16	**BU**	Anisole	RT	87%

Table 4.4: Screening of solvent using $CuNTf_2$ made *in situ*.
Conditions: alkene (**6**) (2.5 eq), Cp_2ZrHCl (2.0 eq), CuCl (0.1 eq), $AgNTf_2$ (0.15 eq), ligand (0.1 eq), enone (**84**) (1.0 eq), RT. *ee*s determined by chiral HPLC**.**

When using ligand **BI** in CH_2Cl_2, varying the temperature between 0 ºC and 40 ºC led to no increase in selectivity although the results were all above 70% *ee* (entries 1-4), similarly to Table 4.2. A solvent screen showed that ethereal solvents (entries 5, 6, 9, 20) gave similar results between 76% *ee* (THF, entry 5) and 86% *ee* (*t*-BuOMe, entry 9). Surprisingly, as in our hands it was never previously observed to be good for selectivity, toluene increased the enantioselectivity to 90% *ee* (entry 10).

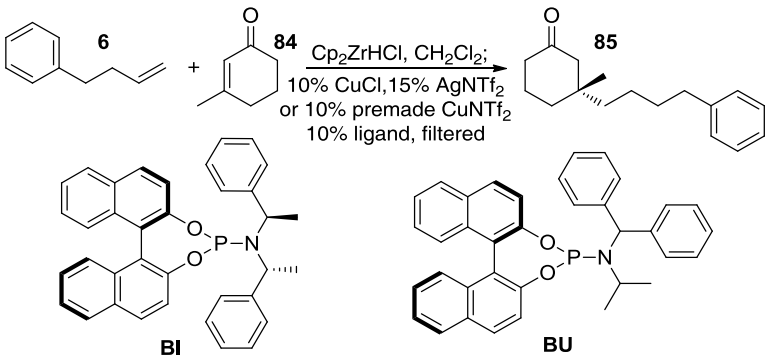
As ligand **BU** behaved similarly, it was decided to use it to screen solvents as well (entries 11-16). Here, THF and Et_2O gave disappointing enantioselectivities (56% *ee* and 67% *ee* respectively in entries 13 & 11). Although toluene gave a lower *ee* (80%, entry 14), the other ethereal and chlorinated solvents gave all similar and encouraging results (87-88% *ee* entries 12, 15, 16). With these results reaching excellent levels of selectivity, it was then decided to keep screening solvents on a larger scale (0.40 mmol instead of 0.2 mmol) and to register yields. Indeed, the new catalyst system here allowed the reaction to finish much faster (between 4-12 h) and with full conversion.

Defining an optimal set of conditions

In the following screening conditions, yields were recorded to ensure the reactivity was optimal (Table 4.5). Both ligands **BI** and **BU** were used. Using ligand **BI** in toluene and in Et_2O gave the product with acceptable yields ~62% yield and excellent ~90% *ee* (entries 2 & 4). Comparatively, 2-Me-THF (entry 5) led to excellent yield (90%) albeit with slightly lower *ee* (84%). With 71% yield and 78% *ee*, DCE still seemed to be suboptimal (entry 6). Interestingly, *t*-

BuOMe (entry 3) gave good results (83% yield and 86% *ee*). Overall, these results display either excellent yield or enantioselectivity. Using ligand **BU**, excellent levels of enantioselectivity were recorded in the tested solvents (90% *ee* or more in entries 7-10). While toluene (entry 10) gave an excellent result (92% yield, 90% *ee*), it was decided that *t*-BuOMe (entry 9) would be kept as a solvent as it gave the highest enantioselectivity (94% *ee*) despite only acceptable yield (66%). Other ethers and chlorinated solvents also displayed excellent results (entries 8 & 9). The overall conclusion here was that ligand **BU** is more efficient than ligand **BI**, and we therefore kept using ligand **BU** in further studies.

Any attempt to perform the hydrozirconation in different solvent did not lead to high reactivity and were not pursued further.



Entry	Copper source	Ligand	Solvent	Yield	Enantiomeric excess (*ee*)
1	CuCl + $AgNTf_2$	**BI**	CH_2Cl_2	66%	78%
2	CuCl + $AgNTf_2$	**BI**	Et_2O	64%	88%
3	CuCl + $AgNTf_2$	**BI**	*t*-BuOMe	83%	86%
4	CuCl + $AgNTf_2$	**BI**	Toluene	62%	91%
5	CuCl + $AgNTf_2$	**BI**	2-Me-THF	90%	84%
6	CuCl + $AgNTf_2$	**BI**	DCE	71%	78%
7	CuCl + $AgNTf_2$	**BU**	$CHCl_3$	74%	92%
8	CuCl + $AgNTf_2$	**BU**	Anisole	70%	90%
9	CuCl + $AgNTf_2$	**BU**	*t*-BuOMe	66%	94%
10	CuCl + $AgNTf_2$	**BU**	Toluene	92%	90%
11	Premade $CuNTf_2$	**BI**	Et_2O	83%	78%

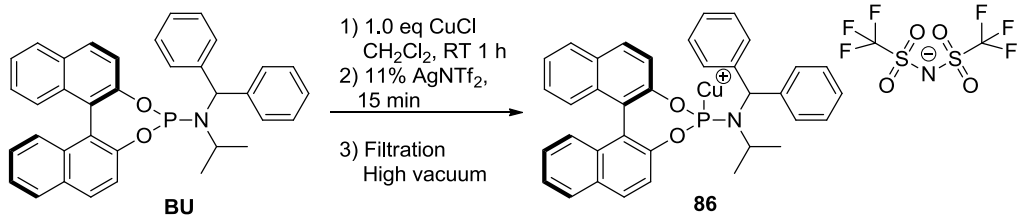
12	Premade $CuNTf_2$	**BI**	2-Me-THF	62%	90%
13	Premade $CuNTf_2$	**BU**	THF	65%	89%
14	Premade $CuNTf_2$	**BU**	Toluene	72%	90%

Table 4.5: Screening of solvents recording the yields.
Conditions: alkene (**6**) (2.5 eq), Cp_2ZrHCl (2.0 eq), CuCl (0.1 eq), $AgNTf_2$ (0.15 eq), ligand (0.1 eq), enone (**84**) (0.4 mmol, 1.0 eq), RT. *ee*s determined by chiral HPLC**.**

Overall, a wide range of solvents was found to be compatible with this new method to synthesise all-carbon quaternary centres. This result was particularly interesting as many related methods only achieve high selectivity under a more narrow range of conditions.

Premade catalyst:

Some premade catalyst complex (**86**) was synthesised in order to facilitate the reaction protocol (Scheme 4.4). To do this, CuCl and the ligand **BU** were mixed together for 1 hour before $AgNTf_2$ was added. The solution/mixture was stirred for an additional 15 minutes before filtration and concentration under high vacuum. Using this premade catalyst complex, results similar to the conditions made *in situ* (entries 11-14) were achieved, albeit with slightly lower values of yield and/or *ee*. We tentatively attribute this loss of selectivity/yield to the presence of residual silver salts due to incomplete removal during filtration (Chapter 3). It is assumed the silver present in the complex is transformed (reaction with light or oxidation) in a new species which is detrimental for the selectivity. When it was analysed by 1H NMR studies, this complex was essentially pure (~2% traces of impurity on the spectrum). For this reason we continued to generate the complex *in situ* for further studies.



Scheme 4.4: Synthesis of the premade complex (**86**).

Final ligand screening

As the observed results were excellent, it was decided to test some of the new ligands (Figure 4.9), developed previously (Chapter 3). This seemed to be a good opportunity to test the family of phosphoramidite ligands bearing an achiral amine moiety. Using the optimised conditions (Table 4.5, entry 9, giving 94% *ee*), some ligands were tested.

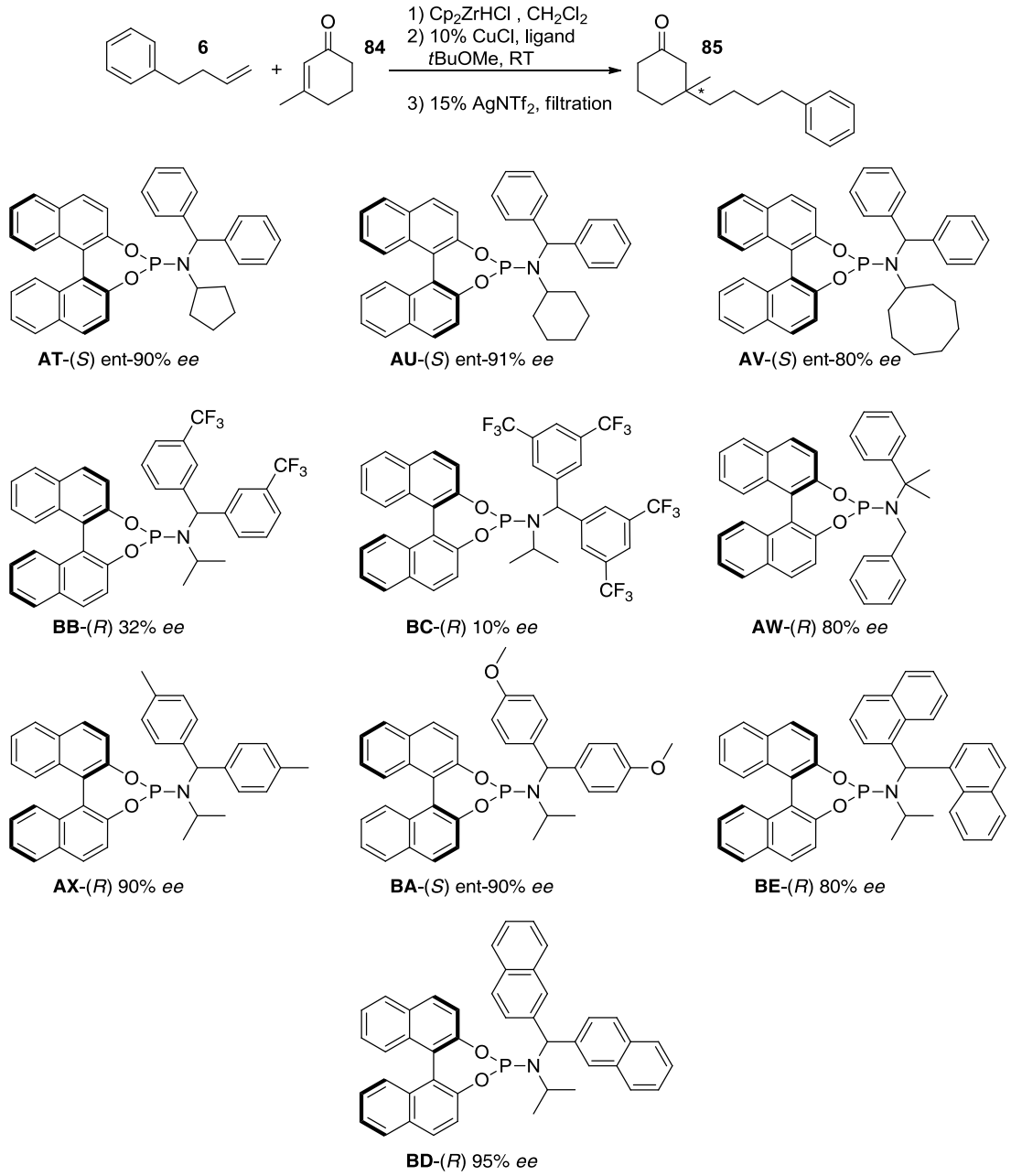


Figure 4.9: Final screening of ligands using the optimised conditions. Unless stated otherwise ('ent'), the absolute configuration of the synthesised ketone (**85**) is *R*.

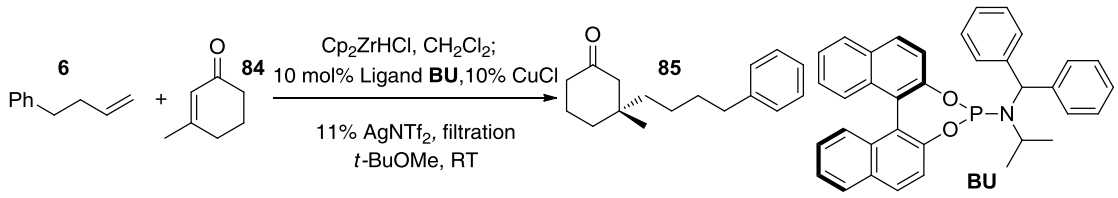
Alteration of the *N*-isopropyl to cyclic equivalents (**AT**, **AU**, **AV**) led to similarly high *ee*s for **AT** and **AU** (~90% *ee*) while **AV** was slightly lower (80% *ee*). Ligand (**BB** & **BC**) bearing electron withdrawing groups on the phenyl led to a sharp decrease in *ee*s. Ligands with comparatively more electron rich substituents (**AX** and **BA**) maintained similar levels of enantioselectivity (90% *ee*). Ligand **AW**, isomer of **BU**, gave slightly lower results (80% *ee*). Using ligands with benzylic naphthyls substituent **BE** and **BD** gave high selectivity. Ligand **BD**, with 2-naphthyl-substitution, gave an excellent enantioselectivity (95% *ee*), slightly better than **BU**.

Five of the tested ligands give 90% *ee* or more. These results suggest this reaction will prove useful on a broad range of substrates, as the enantioselectivity could be tuned for a given substrate by simply screening ligands. After designing a wide set of optimal conditions, the substrate scope was investigated, simply using **BU** to show the efficiency of the simple ligand.

Scaling up and substrate scope

Large scale

We decided to scale up our method to see if the excellent yields and selectivities achieved on the millimolar scale are maintained (Table 4.6).



Entry	Scale of the reaction (mmol)	Product (gram)	Yield	*ee*
1	0.4	0.065	65%	(*R*)-94%
2	2.5	0.578	95%	(*R*)-93%
3	6.3	1.46	94%	(*R*)-92%

Table 4.6: Reaction performed at large scale.

One of the following examples was performed by Dr Mireia Sidera. We carried out the addition of (**6**) to (**84**) to produce (**85**) on 2.5 mmol and 6.4 mmol scales. While the reaction scale

on the standard 0.4 mmol scale produced an acceptable yield (entry 1) of 66% with excellent enantioselectivity (94%), at 2.5 mmol the yield increased to 95% while maintaining excellent enantioselectivity. At the 6.3 mmol scale (entry 3), excellent yield and selectivity were maintained even when reducing the alkene excess from 2.5 equivalents to 2 and the Schwartz reagent from 2 to 1.7.

This set of results showed that the method still performs well on a large scale without safety hazards. Although the hydrometallation step is slightly exothermic, no problems were observed with the produced reagent on these scales.

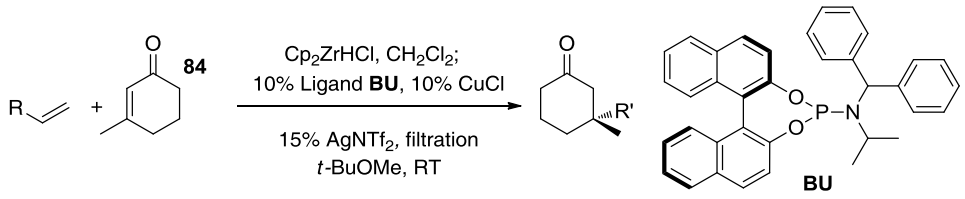
Alkene scope

After obtaining optimal conditions, the substrate scope was investigated, starting with the simple alkene. This work was done in collaboration with Dr Mireia Sidera and Dr Rebecca Maksymowicz, who did roughly half of this work (10 of 19 alkenes tested).

Simple alkenes

First, some simple nucleophiles, similar to those previously published,[229] were used (Table 4.7) using the standard reaction conditions.

Simple gaseous alkenes (1 atmosphere) such as ethylene (**76**), prop-1-ene (**88**) and isobutene (**90**) (entries 1-3) performed well, giving the corresponding ketones in excellent yields and *ee*s. The use of longer terminal alkenes (entries 4-6) also gave consistently good yield and selectivity, although use of a sterically-hindered alkene (**19**) lowered both yield and *ee* somewhat (entry 5). These results showed that the new method is efficient for simple hydrocarbon alkenes. Product (**87**) was given to Professor Alexakis who used GC-MS to determine its absolute configuration (by comparing our sample with another one he made before). The absolute configuration of all the other molecules in this chapter is attributed by analogy to the sign of optical rotation as determined by polarimetry.



Entry	Substrate	Product	Yield[a] (%)	*ee*[b,c] (%)	Entry	Substrate	Product	Yield[a] (%)	*ee*[b,c] (%)
1	**76**	**87**	81	(*R*)-91	4	**1**	**92**	97	(*R*)-95
2	**88**	**89**	79	(*R*)-93	5[d]	**19**	**93**	62	(*S*)-86
3	**90**	**91**	76	(*S*)-94	6	**17**	**94**	67	(*R*)-94

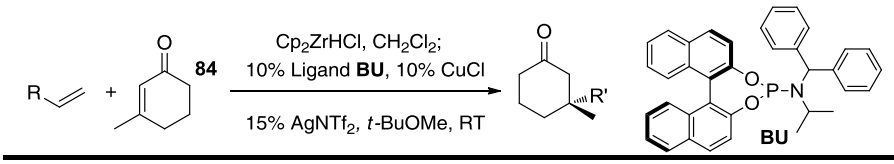
[a]Isolated yield. [b]Absolute configurations known, determined or assigned by analogy. [c]Ee determined by derivatization and ^{13}C NMR spectroscopy. [d]Reaction heated at hydrometallation stage.

Table 4.7: Simple alkene scope.
Conditions: alkene (2.5 eq), Cp_2ZrHCl (2.0 eq), CuCl (0.1 eq), ligand (0.1 eq), $AgNTf_2$ (0.15 eq), enone (**84**) (1.0 eq), RT.

Functionalised alkene scope

After this series of simple examples, alkenes containing functional groups were tested (Table 4.8). Aromatic substituents were well-tolerated (entries 1, 7, 9, 12), although styrene derivatives (**29**) and (**97**) somewhat less so (entries 2 & 3a). Increasing the excess of alkene and Schwartz reagent was enough to overcome the lower reactivity observed when using a reactive benzylic chloride group (entry 3b).

Simple terminal bis-alkene (**25**) (entry 4), using 10 equivalents of alkene to favour statistically mono hydrozirconation, was introduced. Internal alkene (**23**) (entry 5) was used to make **100** using normal conditions. The addition of a terminal bromine (**35**) (entry 6) proceeded with high selectivity (79% *ee*) and acceptable yield (53%). This type of substrate can be used for further functionalisation. Here as well, no internal trapping could be observed, presumably because the leaving group is not activated. Protected secondary and tertiary alcohols are compatible with the method (entries 7-10, 12), tolerating different protecting group (silyl, benzyl).



Entry	Substrate	Product	Yield[a]	*ee*[b]
1	**14**	**95**	65%	(*R*)-90%[c]
2	**29**	**96**	70%	(*S*)-75%[c]
3a	**97**	**98**	24%	(*S*)-41%[c]
3b[d]			66%	(*S*)-70%[c]
4[e]	**25**	**99**	75%	(*R*)-78%[f]
5	**23**	**100**	48%	(*S*)-86%[f]
6	**35**	**101**	53%	(*R*)-79%[f]
7	**39**	**102**	53%	(*R*)-89%[c]
8	**41**	**103**	75%	(*R*)-92%[f]
9	**104**	**105**	61%	(*R*)-90%[c]
10	**106**	**107**	84%	(*R*)-89%[c]
11	**43**	**108**	82%	(*S*)-95%[c]
12	**45**	**109**	82%	(*R*)-89%[c,g,h]

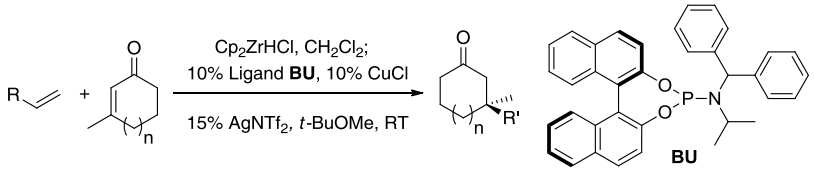
[a]Isolated yield. [b]Absolute configurations known, determined or assigned by analogy. [c]Ee determined by HPLC. [d]Conditions: alkene (3.5 eq.), Cp_2ZrHCl (3 eq.). [e]Conditions: alkene (10 eq.). [f]Ee determined by derivatization an ^{13}C NMR spectroscopy. [f]Conditions: TMSCl (5 eq.). [e]Ee determined by derivatization [f]Ee determined by derivatization and ^{13}C NMR spectroscopy. [g]Isolated as a 1:1 mixture of diastereomers. [h]Ee determined by removal of the silyl group and HPLC.

Table 4.8: Functionalised alkene scope.
Conditions: alkene (2.5 eq), Cp_2ZrHCl (2.0 eq), CuCl (0.1 eq), ligand (0.1 eq), $AgNTf_2$ (0.15 eq), enone (**84**) (1.0 eq), RT.

Interestingly, an allylic TMS alkene (**43)** provides high selectivity (entry 11) in this reaction which alters the normal reactivity patterns of allylsilanes. Finally, heavily functionalised nucleophile (**45**) (entry 12) delivered the corresponding product (**109**) with 82% yield and 89% *ee* as a 1:1 mixture of diastereomers as the starting alcohol is racemic.

Enone screening

After exploring the alkene scope, the enone scope of the reaction was investigated (Table 4.9). Dr Rebecca Maksymowicz performed entry 4.



Entry	Substrate	Product	Yield[a]	*ee*[b]
1a	**110**	**111**	4%	(*R*)-66%[c]
1b[d]			56%	(*R*)-65%[c]
2a	**112**	**113**	11%	(*R*)-76%[c]
2b[e]			7%	(*R*)-80%[c]
2c[f]			34%	(*R*)-73%[c]
3	**114**	**115**	58%	(*R*)-92%[c]
4	**116**	**117**	23%	(*S*)-10%[c]
5a	**118**	**119**	50%	(*R*)-80%[c]
5b[g]			51%	(*R*)-82%[c]
6	**118**	**120**	70%	(*R*)-90%[h]

[a]Isolated yield. [b]Absolute configurations known, determined or assigned by analogy (see the experimental section). [c]Ee determined by HPLC. [d]Conditions: alkene (5 eq.), Cp_2ZrHCl (3 eq.), reaction performed at 0°C. [e]Conditions: ligand **BU**, toluene used as solvent. [f]Conditions: TMSCl (5 eq.). [g]CH_2Cl_2 used as solvent [h]Ee determined by derivatisation (see supporting information).

Table 4.9: Enone scope.
Conditions: alkene (2.5 eq), Cp_2ZrHCl (2.0 eq), CuCl (0.1 eq), ligand (0.1 eq), $AgNTf_2$ (0.15 eq), enone (1.0 eq), RT.

Use of a 5-member ring enone (**110)** (entry 1) was not optimal but it gave (**111)** with acceptable results when modifying the method slightly (entry 1b). (56% yield and 65% *ee*). Similarly, isophorone (**112)** could be used to produce (**113**) selectively by adding some TMSCl (entry 2c, 34% yield and 73% *ee*). Both 5-member rings and isophorone has proved to be difficult substrate on many occasions.[229]

An Et-substituted enone produced ketone (**115)** selectively (entry 3). Enone (**116**) with phenyl conjugated was utterly detrimental to the selectivity (entry 4). Possibly, the use of different ligands could improve the enantioselectivty as this system is different. This was attributed to the bulk of the substrate. A 7-member ring (**118**) enone provided high to excellent enantioselectivity (entries 5 & 6). In case of low yield, reduction of the enone into the allylic alcohol was observed.

Overall, the method was very efficient in adding simple alkyl chains to enone (**84**) (most results above 90% *ee*), even for relatively bulky alkenes (**19**). Consistently high yield and enantioselectivity are achieved in the presence of a broad range of functional groups such as protected alcohols, halogens, silyl groups, and alkenes. These features are a significant improvement over previously reported methods for this transformation and suggest that this method may find use in total synthesis of complex molecules. The use of functionalised nucleophiles is now achievable and the method can be tuned by varying conditions.

The scope of the method is more limited with respect to the enone. Indeed, challenging substrates such as 5-membered enones (**110**) and isophorone (**112**) are fairly unreactive, preferentially undergoing reduction of the starting enone. This process presumably occurs because there is a small amount of Schwartz reagent released in solution (as the hydrometallation reaction is an equilibrium). The Schwartz reagent then reduces the enone into the corresponding allylic alcohol (as the molecule possesses an hydride). 6-Membered rings are tolerated, although hindrance at the 4-position can render them unreactive (Table 4.7, entry 4) and 7-membered ring (**118)** is also well tolerated.

Therefore this method, although powerful, is limited to a narrow scope of Michael acceptors. This is an area where the method could be improved so it becomes more general and more robust. This drawback is potentially mitigated by the possibility of tuning the method for a particular substrate by varying the stoichiometry, ligand, solvent, and temperature to achieve high selectivity in a given case.

Conclusion and future work

The method presented here enables the synthesis of ketones containing all-carbon quaternary centres at the β-position with high selectivity. This method, although limited to a small set of cyclic enones, is effective in a wide range of conditions which can be tuned to provide selectivity for difficult substrates. In particular, this method allows the addition of simple and (previously unreported) functionalised nucleophiles, up to multigram scales effectively. However, the method suffers from a narrow enone scope, a weakness which could potentially be fixed in the future by further exploring the unusually broad set of conditions which give high selectivity.

Chapter 5: Copper catalysed conjugate addition of alklyzirconocenes to linear enones

Introduction

As previously discussed, the asymmetric conjugate addition of organometallic species is one of the most powerful ways to synthesise new C-C bonds enantioselectively. While a large number of methods have been developed to work with a variety of Michael acceptors[234] some challenges remain in term of reactivity and selectivity. Amongst the key remaining challenges, asymmetric additions to acyclic enones still remain difficult despite intensive investigation for a number of years. The difficulty in obtaining high levels of asymmetry in additions to these substrates is often ascribed to the fact that they undergo s-cis/s-trans conformational interconversion at a high rate on the reaction timescale.[47] Therefore the catalyst must either be able to differentiate between these conformers, or to react efficiently (to give the same single enantiomer product) with both of these isomers in order to deliver the corresponding ketone with high enantioselectivity.

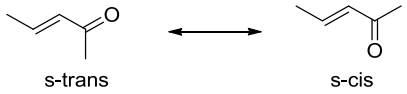


Figure 5.1: Interconversion between *s-cis* and *s-trans* conformers.

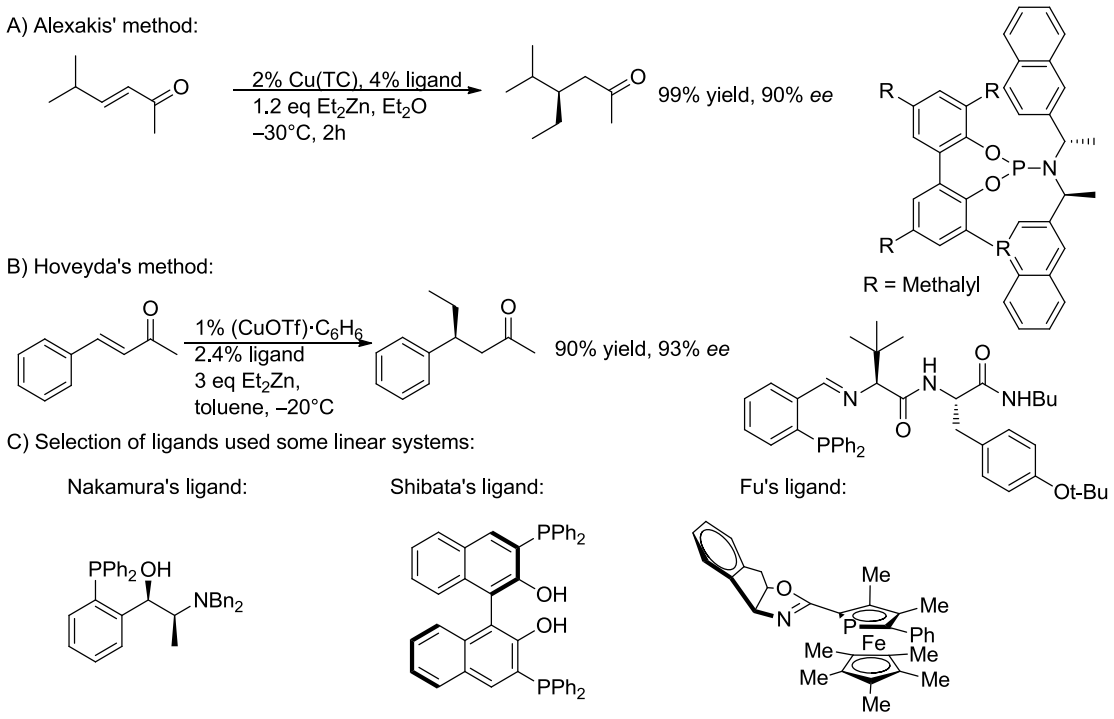
These linear substrates are of interest for several reasons, including the fact that many natural products and drug-like molecules feature methyl substituents at tertiary stereogenic centres.[235] This moiety is challenging to synthesise, but could in principle be readily accessible via asymmetric conjugate addition on an appropriately methylated enone.

Previous work

Zinc reagents

Enantiomerically enriched linear ketones can be obtained using a combination of dialkyl zinc reagents and copper catalysts bearing a chiral ligand. This method has been explored by many

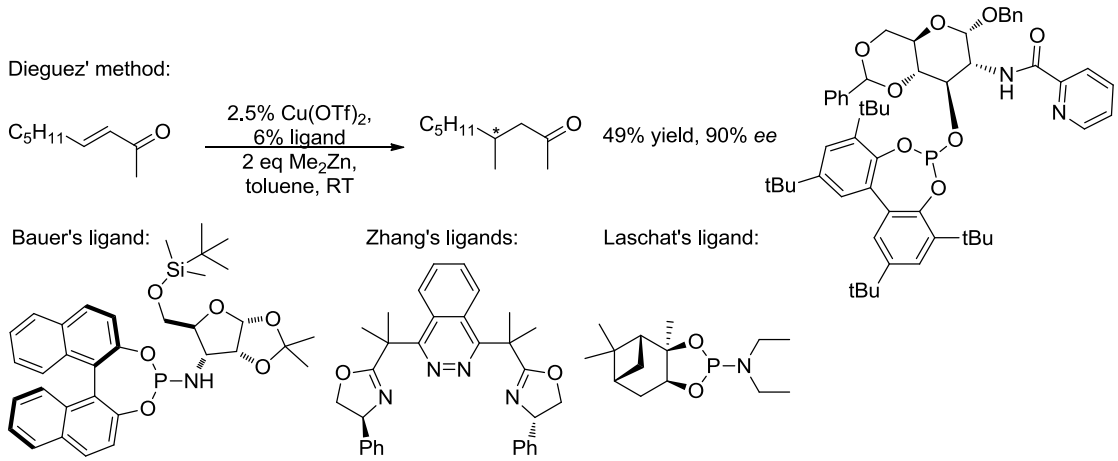
influential chemists including Woodward and Alexakis using phosphoramidite ligands[236-238] (up to 96% *ee*) (Scheme 5.1, A). Zhang reached 90% *ee* using a *P*,*N*-ligand.[239] Hoveyda[240] (Scheme 5.1,B) and Nakamura[241] (Scheme 5.1, C) used, respectively, aminohydroxyphosphine and peptidic phosphine ligands while Shibata performed a similar reaction using a catalyst based on binaphthol backbones.[242] Fu reported the use of ferrocene based ligand to achieve high enantioselectivity.[243]



Scheme 5.1: Methods used by Hoveyda (A), Alexakis (B) and selection of ligands (C)

Other methods that allow efficient ACA to linear substrates have been also been developed. Bauer reported a sugar-based phosphoramidite ligand to add Et_2Zn to chalcones with modest enantioselectivity (77% *ee*) but good yield (81%).[244] Zhang has recently reported a system was based on bridged bisoxazoline ligands.[245] Dieguez has developed a different system using a range of alkyl zinc reagents using a novel sugar-based phosphite/pyridine ligand, achieving good results (49% yield, 90% *ee*) (Scheme 5.2).[246] Laschat and co-workers reported a similar addition with P-stereogenic pinene-derived phosphoramidite ligands but achieved only low enantioselectivities (50% *ee*),[247] while Sagakushi used NHC ligands to achieve 96% *ee*.[248] Alexakis

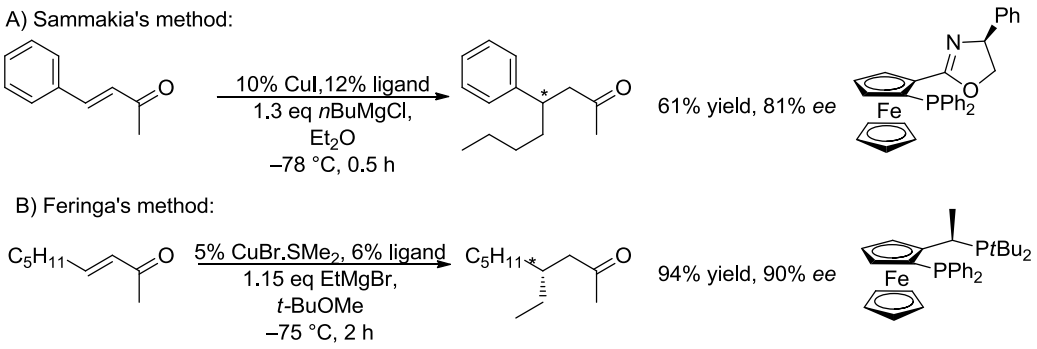
reported conditions which allowed highly selective 1,4 and 1,6 additions of dialkyl zinc to linear substrates (98% *ee* and 97% *ee* respectively).[249]



Scheme 5.2: Various other methods to add dialkyl zinc to linear enones.

Magnesium based reagents

Grignards have been widely used as organometallic reagents in many different reactions. In the case of ACA to linear substrates, there are only limited reports, the first was by Sammakia in 1997 (Scheme 5.3, A).[250] In 2004, Feringa[251] reported using Grignards with a ferrocene based ligand with which he obtains high enantioselectivity (90% *ee*) (Scheme 5.3, B). Overall, only the addition of MeMgBr occurs smoothly with low catalyst loading.[121, 251] In the case of other Grignard reagents, Feringa demonstrated that the reaction conditions generally need to be altered when the substrate was bulky in order to obtain high levels of selectivity. [20]



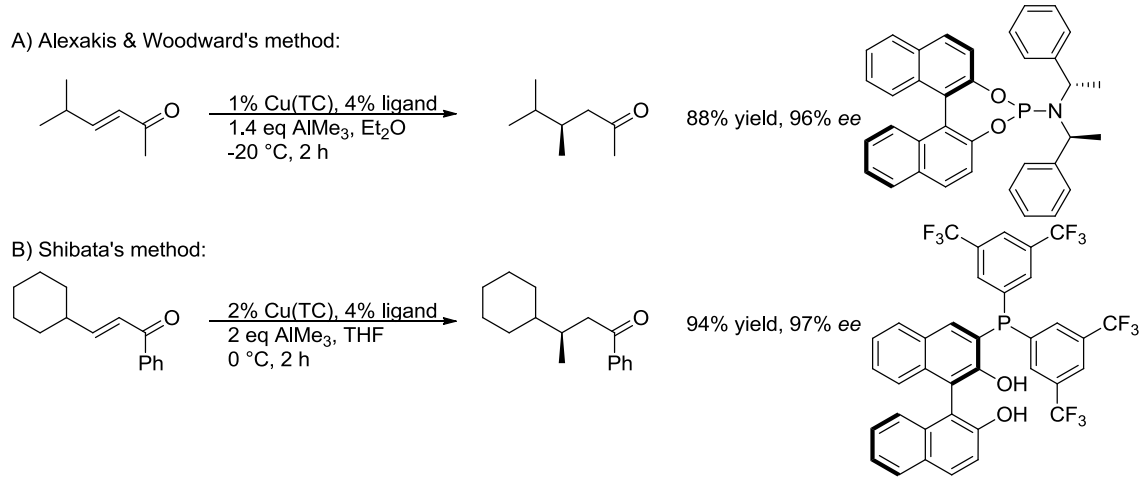
Scheme 5.3: Sammakia and Feringa's methods.

A more recent method worked with phosphoramidite ligands and was less sensitive to substrate hindrance although it did not reach a selectivity higher than 80% *ee*.[193]

Lately, a method using Tol-BINAP as ligand allowed the synthesis of linear ketones with high enantioselectivity (96% *ee* and above) and the intermediates could be trapped to form cyclopropanes.[252] Despite these encouraging results, this class of substrate still remains challenging.[253]

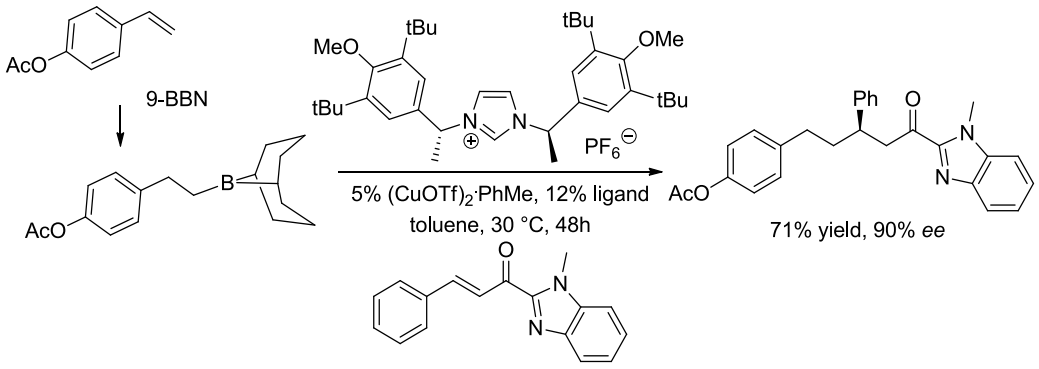
Aluminium based reagents

Another strategy involves using an organoaluminium reagent. A copper-phosphoramidite ligand catalyst developed by Alexakis and Woodward (Scheme 5.4, A),[236, 254] enabled the addition of alkyl and alkenyl aluminiums to linear enones. Shibata reported the addition of trimethyl aluminium to linear enones, using binaphthol-based ligands, to give tertiary and quaternary linear products[226] with excellent results (97% yield, 98% *ee*) (Scheme 5.4, B).[226, 230] Recently, Hoveyda has reported the synthesis of linear quaternary ketones by adding aryl, alkyl,[228] alkenyl[231] groups with high enantioselectivity when using NHC-based copper catalysts. Zhang has recently reported a method based on phosphoramidite ligand, reaching 92% *ee* and 82% yield using a $Cu(OAc)_2 \bullet H_2O$ source[255]



Scheme 5.4: Alexakis and Woodward's method and Shibata's method.

Boron based reagents



Scheme 5.5: Sawamura's method.

Sawamura *et al.* recently reported an alternative method to add to linear imidazol-2-yl-α,β-unsaturated ketones (Scheme 5.5). Alkylboron reagents, obtained through the hydroboration of alkenes, were used to perform conjugate additions with excellent results (up to 93% *ee*) using a copper-NHC ligand catalyst.[118]

Summary of current methods and discussion of the new system

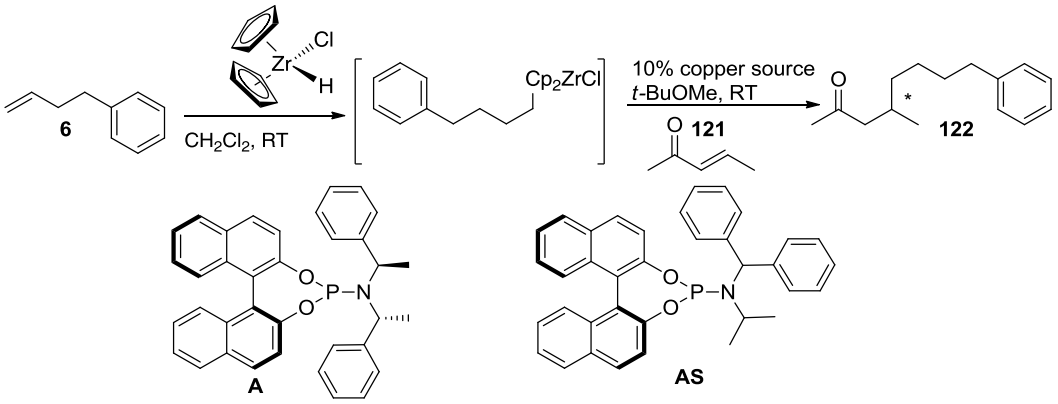
The methods discussed above allow asymmetric 1,4-addition to a wide range of linear enones with excellent selectivity. However, for the most part, they all suffer from the drawback of using premade organometallics species which are potentially hazardous to handle due to their extremely high reactivity. Most of these reactions also require cryogenic temperatures, due to the reactivity of the organometallics. However, Lipshutz developed a useful method to obtain similar products by using CuH-species in asymmetric reduction procedures.[256]

In chapters 2 and 4, we recently reported the copper catalysed formation of tertiary ketones[189, 190, 257] while chapter 4 mentioned the synthesis of quaternary cyclic ketones[258] by asymmetric conjugate addition of alkylzirconium reagents. These methods work at room temperature and provided a wide range of different ketones. They start by the hydrometallation of a terminal alkene by the Schwartz reagent[259], followed by reaction with the catalytic species to give these new ketones with high enantiomeric excess. However, none of these methods allowed the efficient synthesis of highly enantioenriched β-substituted linear ketones. Additionally, our previous

methods do not allow the addition of a methyl group to enones, except in the case of the synthesis quaternary centre (Chapter 4). This is because the method requires the hydrozirconation of an alkene, which necessarily contains at least two carbon atoms (ethylene being the smallest alkene). Therefore to address both issues, we chose a linear enone with one methyl at the 3-position, (*E*)-3-penten-2-one (**121)** (Table 5.1), which would yield a linear ketone containing a methyl group at a stereogenic centre.

Initial screening

As linear enones are typically challenging substrates for asymmetric conjugate addition, we first started by using the conditions developed for the formation of cyclic quaternary centres (Table 5.1). This model system used a catalyst composed of $CuNTf_2$ made *in situ* and a phosphoramidite ligand in *t*-BuOMe (entry 1). Although the reaction was complete within 1 hour under these conditions, the obtained ketone (**122**) had a relatively low *ee* (33% *ee*).

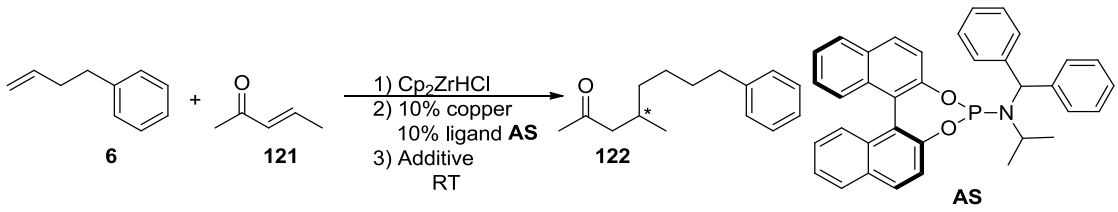


Entry	Copper source	Ligand	Enantiomeric excess (*ee*)
1	$CuNTf_2$	**A**	33%
2	$CuNTf_2$	**AS**	44%
3	$CuBF_4$	**AS**	7%
4	$CuPF_6$	**AS**	8%
5	$CuClO_4$	**AS**	50%
6	$CuSbF_6$	**AS**	40%
7	CuOTf	**AS**	55%

8*	CuOTf	**AS**	60%

Table 5.1: Screening of copper source (*addition of 5 equivalent of TMSCl). Conditions: alkene (**6**) (2.5 eq), Cp_2ZrHCl (2.0 eq), copper (0.1 eq), ligand (0.1 eq), enone (**121**) (1.0 eq), *t*-BuOMe, RT. *ee*s determined by chiral HPLC.

We began optimisation of the reaction by screening copper sources. The non-commercially available copper salts were prepared by mixing CuCl, a ligand and a silver salt and then filtering off the precipitate. It was quickly determined that the diphenyl isopropyl ligand **AS** (entry 2) gave better results (44% *ee*) than Feringa's ligand **A** (33% *ee*). Using ligand **AS**, copper sources were screened. Copper sources with BF_4 and PF_6 (entries 3 & 4) gave poor enantioselectivities (7% & 8% *ee* respectively). In contrast, improved selectivity could be obtained using perchlorate (entry 5, 50% *ee*), antimony fluoride (entry 6, 40% *ee*) and triflate counter ions (entry 7, 55% *ee*). The use of triflate in combination with TMSCl gave slightly improved enantioselectivity (entry 8, 60% *ee*); these conditions were therefore used in conjunction with ligand **AS** to examine different solvents.



Entry	Copper source	Solvent	Additive	Enantiomeric excess (*ee*)
1	CuOTf	Et_2O		50%
2	CuOTf	Et_2O	TMSCl	65%
3	CuOTf ligand complex **74**	Et_2O	TMSCl	65%
4	CuOTf	THF		46%
5	CuOTf	THF	TMSCl	38%
6	CuOTf	$CHCl_3$		46%
7	CuOTf	CH_2Cl_2		50%
8	CuOTf	Toluene		40%
9	CuOTf	1,4-dioxane		50%
10	CuOTf	1,4-dioxane	TMSCl	64%
11	CuOTf	DCE		40%

12	CuOTf	DCE	TMSCl	27%
13	$CuNTf_2$	Et_2O		45%
14	$CuNTf_2$	Et_2O	TMSCl	40%
15	$CuClO_4$	1,4-dioxane		60%
16	$CuClO_4$	1,4-dioxane	TMSCl	16%

Table 5.2: Screening of solvent.
Conditions: alkene (**6**) (2.5 eq), Cp_2ZrHCl (2.0 eq), copper (0.1 eq), ligand **AS** (0.1 eq), enone (**121**) (1.0 eq), RT. *ee*s determined by chiral HPLC.

When different solvents were tested under these reaction conditions (Table 5.2), Et_2O was found to give relatively good results (entries 1-3), especially in the presence of TMSCl (entry 2, 65% *ee*). The results were the same if the premade ligand-complex was used for the reaction (entry 3, 65% *ee*). Other chlorinated solvents did not perform as well. THF (entry 4) gave lower enantioselectivity and the addition of TMSCl (entry 5) made it worse. 1,4-dioxane on the other hand gave similar results, including with TMSCl (entries 9 and 10). These promising results showed a Lewis acid and ether solvents seem to make the process more selective. Chlorinated solvents led to poorer results (entries 6, 7, 11 & 12) and the addition of TMSCl was detrimental to enantioselectivity in these solvents (entries 11 & 12).However, no attemps at removing the solvent after the hydrozirconation step was performed. Some of the best copper source from previous screening were tested on this substrate but did not produce any higher results (entries 13-16). From these results we decided to examine ligands using CuOTf/Et_2O/TMSCl (5 equivalents).

Ligand screening

The use of electron rich analogues of ligands (Figure 5.2), bearing methoxy groups gave similar *ee* values, with *para*-methoxy substituted ligand **BA** giving 64% *ee* and the *ortho*-isomer **BG** giving slightly lower enantioselectivity (52% *ee*). A derivative of ligand **AS**, with a cyclohexyl group linked to the amine unit **BF**, gave the same enantioselectivity (66% *ee*). Extra bulky *tetra*-*t*-butyl substituted **AZ** was detrimental to selectivity (10% *ee*), whereas 3,3'-modified **J** and **K** also gave significantly lower enantioselectivity (5% *ee* and 30% *ee*, respectively). A change of amido substituent from phenyl to naphthyl rings **BD** improved the selectivity to 71% *ee*. Interestingly, neither changing the isomer from 2-naphthyl to 1-naphthyl (**BE**), nor independently altering the

alkyl group on the amine (**AU**), affected the selectivity significantly. As these three ligands, **BD**, **BE** and **BF**, gave very similar enantioselectivity, we decided to further explore similar structures and conditions.

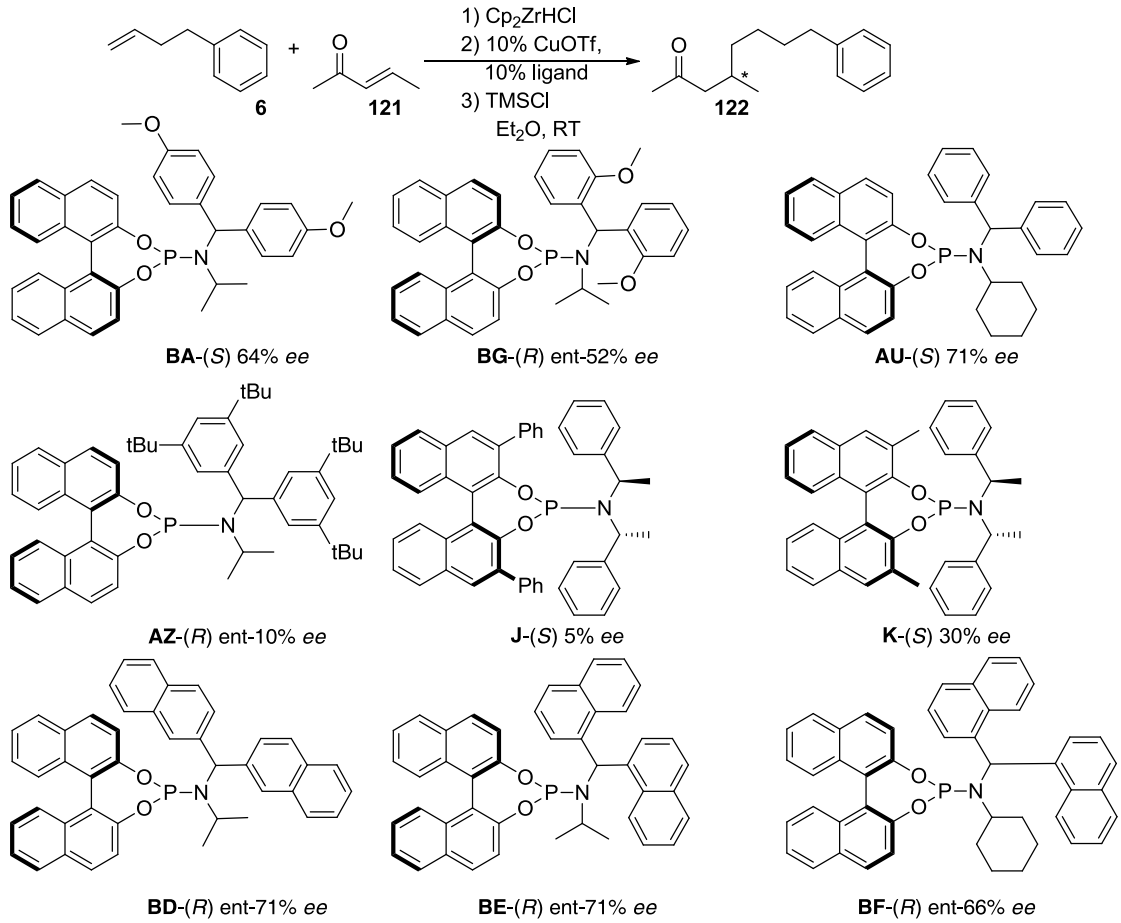
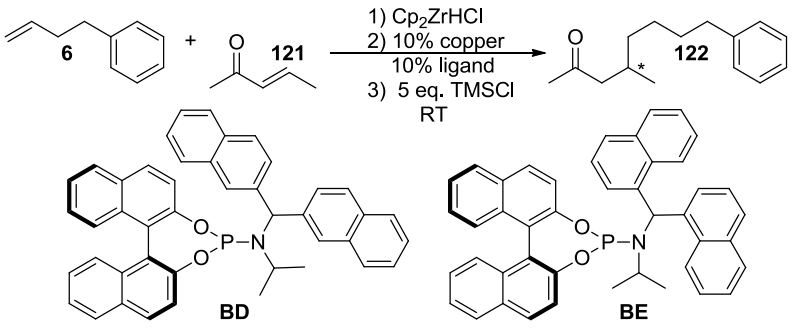


Figure 5.2: Screening of ligands.

Unless stated otherwise ('ent'), absolute configuration of ketone (**122**) was *S*.



Entry	Copper source	Ligand	Solvent	Temperature	Enantiomeric excess (*ee*)

1	CuOTf	**BD**	Et_2O	RT	71%
2	CuOTf	**BD**	1,4-dioxane	RT	64%
3	$CuClO_4$	**BD**	Et_2O	RT	3%
4	CuOTf	**BE**	Et_2O	RT	71%
5	CuOTf	**BE**	Et_2O	0 °C	2%
6	$CuClO_4$	**BE**	1,4-dioxane	RT	67%

Table 5.3: Screening conditions using ligands **BD** and **BE**.
Conditions: alkene **6** (2.5 eq), Cp_2ZrHCl (2.0 eq), copper (0.1 eq), ligand (0.1 eq), enone **121** (1.0 eq), RT. *ee*s determined by chiral HPLC.

Using ligands **BD** and **BE**, any change in the temperature, copper source or solvent decreased the observed enantioselectivity (Table 5.3, entries 1-6). Therefore we screened further ligands, as this system seemed to be very sensitive to small changes in the conditions, despite giving promising levels of enantioselectivity.

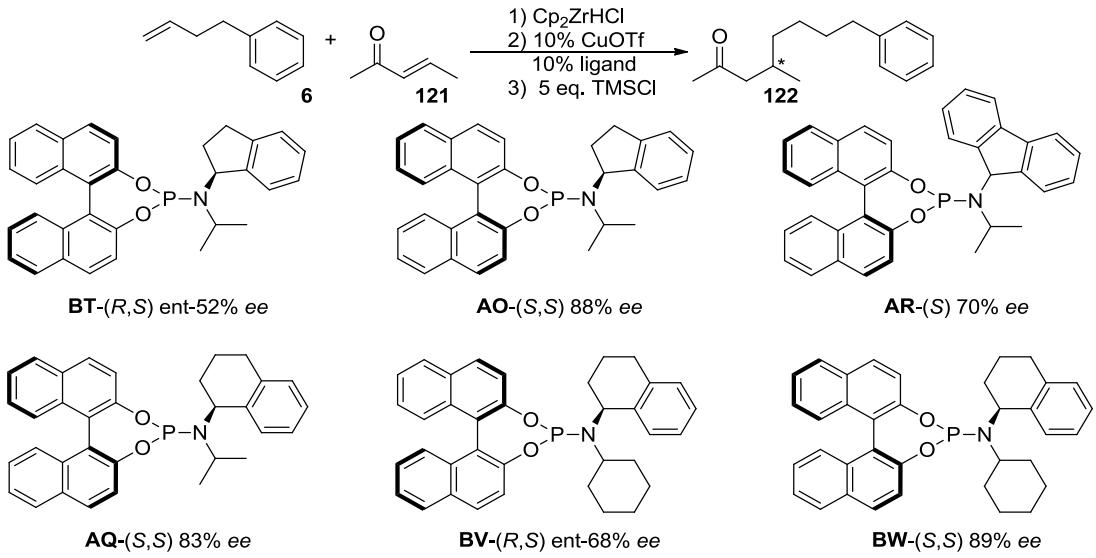


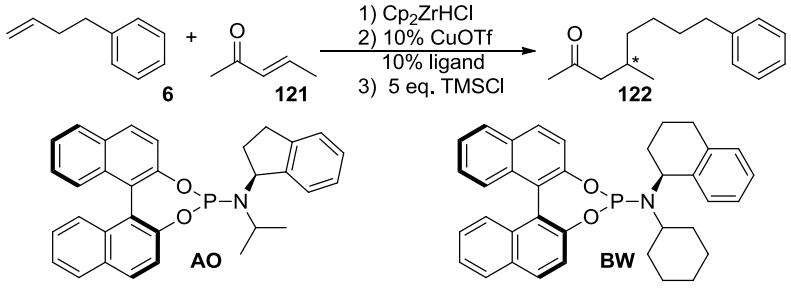
Figure 5.3: Screen of different ligands. Unless stated otherwise ('ent'), the absolute configuration of the ketone (**122**) was *S*.

New ligands were screened (Figure 5.3). It was decided to use ligands with groups roughly similar to a naphthyl unit as it was a good motif in the previous screening. Ligands **BT**, **BU**, **BV**, **BW** were synthesised according to the literature procedure.[191] Some of these ligands eventually gave much higher enantioselectivity. Ligand **BT** of absolute configuration (*R, S*) gave 52% enantioselectivity while its diastereomer (*S, S*) **AO** produced the desired ketone with 88% *ee*.

Ligands **AQ**, bearing a tetrahydronaphthalene unit instead of an aminoindan unit, provided the product with slightly lower enantioselectivity (83% *ee*). The similar ligand **AR** with a fluorenyl group gave 70% *ee*. Different analogues of ligand **AO**, bearing a cyclohexyl ring, were tested. While **BV** (*R*, *S*) was less selective, ligand **BW** gave 89% enantioselectively. We decided that this result was acceptable, and to screen other conditions in order to further optimise the reaction.

Optimisation of the conditions

First, using ligand **AO** (Table 5.4, entries 1) in Et_2O at 0 ºC did not bring any improvement (88% *ee*) whereas when using *t*-BuOMe (entry 2) as a solvent it slightly reduced the enantioselectivity (85% *ee*). In parallel, we decided to screen other conditions using ligand **BW**.



Entry	Copper source	Ligand	Solvent	Temperature	Additive (0.25 equivalent)	Enantiomeric excess (*ee*)
1	CuOTf	**AO**	Et_2O	0 ºC		88%
2	CuOTf	**AO**	*t*-BuOMe	RT		85%
3	CuOTf	**BW**	*t*-BuOMe	RT		89%
4	CuOTf	**BW**	*t*-BuOMe	0 ºC		83%
5	CuOTf	**BW**	THF	RT		80%
6	CuOTf	**BW**	1,4-dioxane	RT		85%
7	$CuClO_4$	**BW**	*t*-BuOMe	RT		0%
8	$CuNTf_2$	**BW**	Et_2O	RT		5%
9	CuOTf	**BW**	Et_2O	0 ºC		91%

10	Premade CuOTf-ligand complex **123**	**BW**	Et_2O	0 ºC		91%
11	CuOTf	**BW**	Et_2O	0 ºC	BF_3	9%
12	CuOTf	**BW**	Et_2O	0 ºC	Ti(*O*iPr)$_4$	5%
13	CuOTf	**BW**	Et_2O	0 ºC	*i*POH	55%
14	CuOTf	**BW**	Et_2O	0 ºC	*t*-BuONa	22%
15	CuOTf	**BW**	Et_2O	0 ºC	Benzophenone	62%
16	CuOTf	**BW**	Et_2O	0 ºC	AgOTf	71%
17	CuOTf	**BW**	Et_2O	0 ºC	H_2O	70%
18	CuOTf	**BW**	Et_2O	0 ºC	Ac_2O	48%

Table 5.4: Screening conditions using ligands **AO** and **BW**.
Conditions: alkene (**6**) (2.5 eq), Cp_2ZrHCl (2.0 eq), copper (0.1 eq), ligand (0.1 eq), enone (**121**) (1.0 eq). *ee*s determined by chiral HPLC.

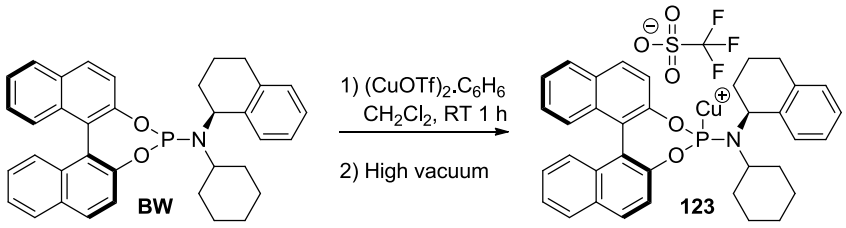
A brief solvent screen (entries 3-6) led to no increase of selectivity for THF (80% *ee*), *t*-BuOMe (89% *ee*) and 1,4-dioxane (85% *ee*), and a loss of enantioselectivity was noticed at 0 ºC (entry 4, 83% *ee*). Some other copper sources were not more successful (entries 7 & 8). The reaction was performed at 0 ºC using Et_2O as solvent (entries 9 & 10), giving a modest increase in enantioselectivity (91% *ee*). The results were reproducible when using a premade solid catalyst complex (entry 10).

We tested the effect of various additives on the reaction (entries 11-17). The aim was trying to perturb the system in the hope that the outcome would be favourable in terms of obtaining higher enantioselectivity. Adding Lewis acids (BF_3 & Ti(O*i*Pr)$_4$), entries 11 & 12) led to almost racemic reaction products (9% *ee* & 5% *ee* respectively). Use of *i*-PrOH, *t*-BuONa, Ac_2O, benzophenone and H_2O all led to a significant loss of enantioselectivity (entries 13 -18). Intriguingly, addition of AgOTf (entry 16) was mildly detrimental to the enantioselectivity (85% *ee*). This result is significant because throughout this work, CuOTf was made by adding AgOTf to

CuCl in the reaction flask. While the remaining AgOTf was filtered off, it is likely that some residual AgOTf would remain in any such reaction, potentially lowering the enantioselectivity. A control reaction using AgOTf and no copper did not proceed, ruling out any AgOTf as an active catalyst. However, it is possible there could be less active catalyst (copper and ligand bound) if silver competitively binds to the ligand. This could lead to lower results.

Premade copper ligand complex

From this screen we decided that extra additives were not required beyond TMSCl, and to use the best set of conditions (entry 9) to test the substrate scope of the reaction. To facilitate the protocol, it was decided to produce a premade copper-ligand complex (**123**) containing ligand **BW** and the appropriate copper salt (Scheme 5.6). As this solid is easy to handle, it makes the reaction faster to set up and makes the results much more reproducible. The complex was prepared by mixing a 0.5:1 ratio of $(CuOTf)_2 \cdot C_6H_6$ and the corresponding amount of ligand. After stirring for one hour, the solvent was removed under high vacuum and the complex, obtained as a grey powder, was stored under argon.



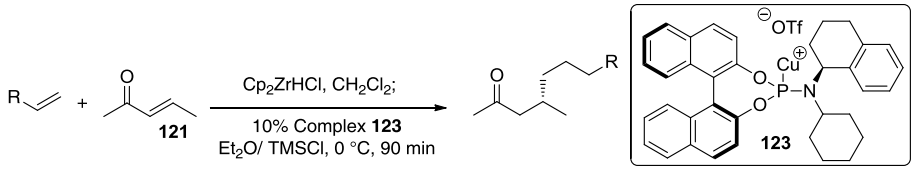
Scheme 5.6: Synthesis of complex (**123**).

Using this complex with 4-phenylbutene (**6**) as the pre-nucleophile produced the corresponding linear ketone (**122**) with both high yield (93%) and enantioselectivity (91% *ee*).

Substrate scope

Alkene scope

With this method in hand, it was decided to explore the range of alkenes and enones compatible with the reaction (Table 5.5). Firstly, simple alkenes were tested using this method. Phenyl containing alkenes (entries 1 & 2) produced the corresponding ketones (**124**) and (**126**) with a good yield (73% or more) and excellent enantioselectivity (91% *ee*).



Entry	Starting Alkene	Product	Yield[a]	*ee*[b]
1	**14**	**124**	73%	(*S*)-91%[c]
2	**125**	**126**	76%	(*S*)-91%[c]
3	**1**	**127**	90%	(*S*)-91%[d]
4	**128**	**129**	58%	(*S*)-~89%[d,e]
5	**104**	**130**	49%,	(*S*)-91%[c]
6	**45**	**131**	95%	(*S*)-91%[c,f,g]
7	**29**	**132**	58%	(*R*) No separation[h]
8	**133**	**134**	No reaction	No reaction

[a]Isolated yield. [b]Absolute configurations known, determined or assigned by analogy. [c]Ee determined by HPLC. [d]Ee determined by GC. [e] (+/-) 5% ee. [f]Isolated as a 1:1 mixture of diastereomers. [g]Ee determined by removal of the silyl group and HPLC. [h]Separation attempted on HPLC and GC.

Table 5.5: Screening the alkene scope.
Conditions: alkene (2.5 eq), Cp_2ZrHCl (2.0 eq), complex (**123**) (0.1 eq), enone (**121**) (1.0 eq), TMSCl (5.0 eq), 0 ºC.

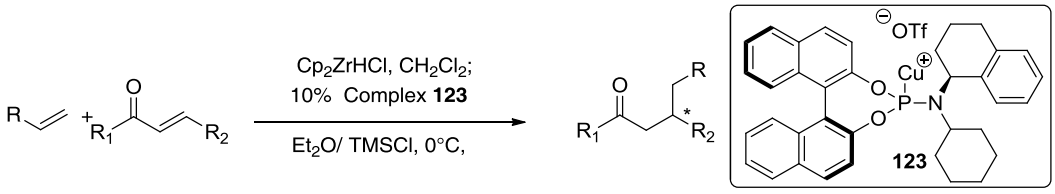
A test with 1-hexene **1** (entry 3) produced the corresponding linear substrate (**127**) with excellent yield (90%) and enantioselectivity (91% *ee*). Although this substrate was simple, it showed that a phenyl ring is not required to produce the ketone with high enantioselectivity. This molecule was used to determine the absolute configuration of the molecules based on comparison to the published literature (by comparison of the sign of optical rotation).[236] As the other molecules are similar, the mechanism is assumed to be identical and therefore the absolute configurations are attributed by analogy.

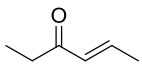
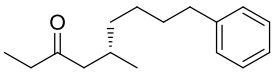
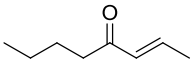
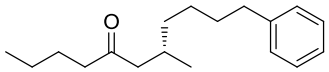
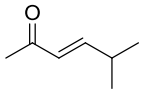
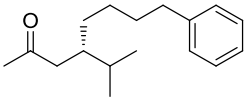
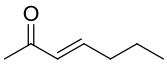
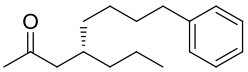
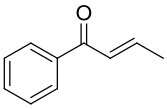
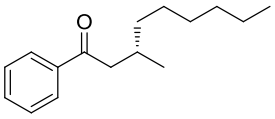
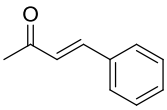
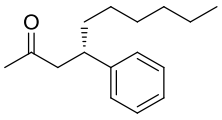
After these first examples, some more challenging substrates were tried. Interestingly, reactions were usually quite chemoselective. The chloride functional group (**126**) is not generally tolerated with Grignard reagents for instance. Alkenes possessing chloride (entries 4 & 6) and protected alcohol moieties (entries 5 & 6) could be used efficiently as nucleophiles. The yields are usually average to excellent. Noteworthy, a highly functionalised molecule (**45**) (entry 6) bearing a chlorine, a protected alcohol and an aromatic group produced the corresponding linear substrate with excellent results (95% yield, 91% *ee* as determined on the corresponding alcohol after deprotection) in a 1:1 *dr* ratio.

However, some substrates were difficult to deal with. When a styrene derivative (**29**) (entry 7) was used the product could not be separated by HPLC. Unfortunately, no readily method was available to derivatise it as Alexakis'method is not reliable for linear ketone.[123] An inseparable mixture of products (~1:8 by ^{1}H NMR) was obtained, in which it is believed that the minor product arises from hydrozirconation at the benzylic position of the styrene. A similar problem was detected by Wipf when hydrozirconating styrene.[122] Lastly, an alkene bearing a sulphur atom **(133)** did not react at all (entry 8). The reaction mixture stayed yellow (instead of turning green as normally occurs) and no detectable amount of product was formed. It is thought the soft sulphur atom chelated the copper and completely poisoned the catalyst, inhibiting the reaction. However, these results globally show this methodology is robust in term of alkene modifications.

Enone scope

The range of compatible enones was assessed (Table 5.6). Increasing the size of the alkyl substituent on enones (**135**) and (**137**) (entries 1 & 2) produced the corresponding ketones (**136**) and (**138**) respectively with good to excellent yield (94% and 75% respectively) and excellent enantioselectivity (91% *ee*).



Entry		Starting enone	Product		Yield[a]	*ee*[b]
1	**135**			**136**	94%	(*S*)-91%[c]
2	**137**			**138**	75%	(*S*)-91%[c]
3	**139**			**140**	59%	(*S*)-~66%[c,d]
4	**141**			**142**	77%	(*S*) No separation[e]
5	**143**			**144**	66%,	(*S*)-~80%[c,d]
6	**145**			**146**	59%	(*S*)-33%[c]

[a]Isolated yield. [b]Absolute configurations known, determined or assigned by analogy. [c]Ee determined by HPLC. [d] +/- 5% ee.[e]Separation attempted on HPLC and GC.

Table 5.6: Screening the enone scope of the reaction.
Conditions: alkene (2.5 eq), Cp_2ZrHCl (2.0 eq), complex (**123**) (0.1 eq), enone (1.0 eq), TMSCl (5.0 eq), 0 ºC.

A substituted enone with an isopropyl group (**139**) (entry 3) produced the corresponding linear ketone with an acceptable yield (59%) and reduced enantioselectivity (~66% *ee*). Although the separation is not perfect for this particular molecule this is the best available after

screening 8 different HPLC solid chiral phase. This substrate is known to be relatively challenging and often requires optimisation of the reaction conditions to achieve good selectivity.[238, 260]

Unfortunately, no condition was found to separate the enantiomers of the ketone (**142**) due to its highly apolar nature. Therefore, no further similar enone substrates (bearing longer alkyl chairs) were investigated due to the difficulty of working with such apolar molecules. No easy method to derivatise it was found obvious. Enones bearing a phenyl group (**143**) (entry 5) and (**145**) (entry 6) were then examined. In the case of (**143**) (entry 5), the desired product (**144**) was obtained with acceptable yield (66%) and slightly lower enantioselectivity (80% ee). While this result could likely be improved through tuning the conditions, even this unoptimised result shows that such enones can still react selectively. However, the phenyl ring on (**145**), presumably reducing the reactivity of the substrate through both steric and electronic effects (entry 6), gave ketone (**146**) with acceptable yield (59%) but low enantioselectivity (33% *ee*).

It has to be noted that using the enones substituted with phenyl groups resulted in a significant increase in the reaction time needed to reach completion (from 90 minutes up to 3 hours). For the last substrates, some ligand screening is likely to increase the observed enantioselectivity.

The absolute configuration of these molecules was assigned by analogy to ketones **(144)**[261] and (**146**),[262] known in literature. As the absolute sense of chemistry was the same for (**144**) and (**146**), the other enones were assumed to have the same absolute sense of stereochemistry, as we assume a similar mechanism in each case.

Overall, this screen of substrates showed that excellent results were obtained for the model substrate (93% yield, 91% *ee*) and that enantioselectivity is maintained when the alkene substrate is altered (except (**129**), table 5.5, entry 4). The reactions were always observed to go to completion within 3 hours. All isolated yields are excellent for the simple alkyl substituted substrates and still acceptable for more complicated alkenes. In this regard, the methodology seems robust. In terms of enone scope, the method is not as robust. Although the method tolerates simple changes next to the carbonyl (Table 5.6, entries 1 & 2), the presence of aromatic substituents in (**143**) and (**145**) is

detrimental to enantioselectivity (entry 5). Substitution at the alkene is not well tolerated and leads to a drop in enantioselectivity (entries 3 & 6).

Compared to other methods using premade organometallics,[240, 254] this method produces similar results for simple alkenes. However, this method proceeds under mild conditions and tolerates the use of alkenes that were previously unreported in asymmetric conjugate additions. The only method with a comparably wide range of nucleophiles was reported by Sawamura and co-workers, but their enone scope is limited to the use of imidazol-2-yl α,β-unsaturated ketone which is quite specific and unusual.[118] Our method is complementary to that of Sawamura, and could be used when the addition of a more functionalised alkene is required. In terms of enone scope, this method is more limited. As previously mentioned in the introduction, the main challenge of asymmetric conjugate addition to linear enones remains the lack of a generally useful method for a wide range of substrates.[121] The current method is relatively robust, but there is still room for improvement. For instance, some ligands, only tested on the model substrate, could produce higher selectivity on different enones.

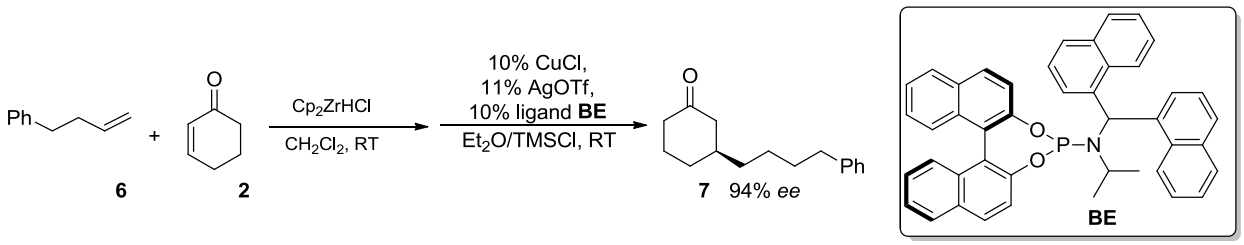
Conclusion

An efficient method was developed for the asymmetric conjugate addition of alkenes to linear enones. By generating organometallic species *in situ*, simple alkenes can be added enantioselectively to linear enones, widely recognised as challenging substrates for asymmetric conjugate addition reactions. This method can use a convenient premade catalyst complex which is stable for months when stored under argon. Further, the method tolerates a wide range of alkenes, albeit with a somewhat limited enone scope. The high enantioselectivity is achieved through the use of new phosphoramidite ligands which are easily synthesised on a multigram scale. Lastly, this method proceeds under mild conditions (0 ºC) and avoids the hazards and inconveniences associated with traditional premade organometallic reagents. Further work in this area by additional optimisation could lead to a more general method applicable to a wider range of enones.

Chapter 6: Conclusion

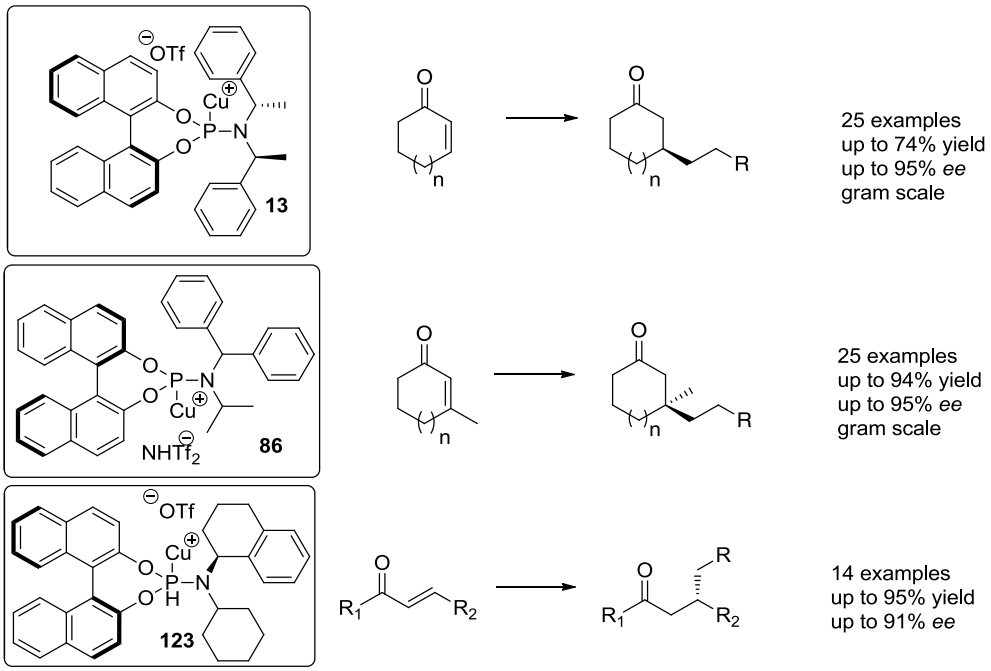
Conclusion

In the course of this DPhil, a series of new phosphoramidite ligands were synthesised. They were used to develop a copper catalysed asymmetric conjugate addition reaction using alkyl zirconium species (Scheme 6.1).



Scheme 6.1: Optimal conditions for the reaction using cyclohexenone (**2**) as electrophile.

A computational model correlating ligands properties with experimental results was established. This efficient model takes into account both the steric and electronic properties of ligands.



Scheme 6.2: Summary of complexes and enone scope of the reaction.

This work led to the synthesis of new, efficient, and easily synthesised ligands. These ligands were then used to improve the conjugate addition reaction.

The scope of this reaction is now broad in term of the enones that can be used (tertiary cyclic and linear ketones, synthesis of cyclic quaternary centres) (Scheme 6.2). Many functionalised alkenes bearing previously unreported functional groups could be used in all the systems mentioned above.

In addition, these reactions tolerate larger scale use where the results tend to improve dramatically, contrarily to similar previously reported copper catalysed asymmetric addition reactions. During the course of this DPhil, a series of bench stable copper triflate-ligands complex were synthesised, (**13**) being now commercially available from Sigma-Aldrich. This provides a stable source of copper triflate, which is well known to be unstable to air and moisture and difficult to work with.

Future work

Future work in this area would include extension of the substrate scope of the conjugate addition to other Michael acceptors (*e.g.* nitro olefin). For instance, the method is not general for all acyclic substrates, and it is likely that alternative methods could be found. Importantly, such studies could allow the formation of linear quaternary products, which is currently not possible. There is possibility to expand the scope of the reaction through using internal alkenes. Indeed Schwartz reagent is known to migrate from an internal to a terminal position. Therefore, internal olefins could act as potential hidden terminal nucleophiles in molecules. The use of the described methods in natural product synthesis is also possible. Indeed, the methods tolerate large scale and allow the synthesis of highly functionalised molecules.

There is a large potential of expanding this chemistry by looking into the trapping of enolate present here. Indeed, some evidence of their reactivity was found but was not exploited here.

It seems unlikely, though, that intermolecular process could happen as the Schwartz reagent is likely to reduce the electron withdrawing group present.

The ability to engineer the reaction in a one pot process by doing hydrozirconation and then adding solid copper and ligand can be investigated as well.

Another aspect of this chemistry can be investigated. Indeed, no real insight of the mechanism has been experimentally performed in this thesis. There is a potential to increase the results this way and get a better understanding.

Importantly, the new family of phosphoramidite ligands could be used to study other (unrelated to copper-catalysed zirconium chemistry) organometallic reactions. Indeed, there are many metals and unrelated reactions that currently use these privileged ligands (*cf* introduction chapter 3). There may be potential to use these ligands to develop new asymmetric processes or to improve existing reactions where phosphoramidites ligands are involved. The use of this series of phosphoramidite ligands to develop structure-reactivity relationships likely has tremendous potential to lead to advanced mechanistic understanding as well as the prediction of new ligands for use in these reactions. Therefore, further use of the approach described in chapter 3 could widely benefit the field of asymmetric catalysis as it would facilitate catalyst development and allow research to proceed at a faster pace.

Chapter 7: Experimental Sections

General Information

Procedures using oxygen- and/or 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 precoated glass-backed plates (Silica Gel 60 F_{254}; Merck), and visualised using a combination of UV light (254 nm) and aqueous ceric ammonium molybdate (CAM), aqueous basic potassium permanganate stains or vanillin solution. 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, Sigma Aldrich silica gel. Pressure was applied at the column head via hand bellows or a flow of nitrogen with the solvent system used in parentheses.

Cooling of reaction mixtures to 0 °C was achieved using an ice-water bath. Other low temperatures were obtained using a Julabo FT902 immersion cooler.

Unless stated otherwise, solution NMR spectra were recorded at room temperature; ^{1}H and ^{13}C nuclear magnetic resonance experiments were carried out using Bruker DPX-200 (200/50 MHz), AVN-400 (400/100 MHz), DQX-400 (400/100 MHz) or AVC-500 (500/125 MHz) spectrometers. 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) and m (multiplet). Coupling constant and resonance patterns are described as they appear in spectra. Labels H and H' refer to diastereotopic protons attached to the same carbon and impart no stereochemical information. Assignments were made with the assistance of gCOSY, DEPT-135, gHSQC and gHMBC or gHMQC NMR spectra.

Numbering and names of structures accompanying reported data is non-IUPAC, and solely for reference.

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.

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 Rathburn); all eluent systems were isocratic.

Chiral GC measurements were conducted on a HP6890 (H_2 as vector gas) or HP6850 (H_2 as vector gas) GC 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 (RT) are given in min.

Infrared measurements (neat, thin film) were carried out using a Bruker Tensor 27 FT-IR with internal calibration in the range 4000-600 cm^{-1}.Optical rotations were recorded using a Perkin-Elmer 241 Polarimeter. CD spectra were recorded using an Applied Photophysics ChiraScan CD/Fluorometer.

In those cases where silver salts were used the resulting solutions were filtered using syringe filters PTFE (0.2 µm, 13 mm diameter) from Camlab.

Chemicals

Dry THF, CH_2Cl_2, Et_2O, PhMe, benzene, hexane, pentane, DME, acetonitrile were collected fresh from an mBraun SPS-800 solvent purification system having been passed through anhydrous alumina columns. Dry tert-butyl methyl ether and 2-Me-THF were purchased from Acros with an AcroSeal®. All other dry solvents used were dried over 3 Å molecular sieves and stored under argon. All other solvents were used as purchased from Sigma Aldrich, Rathburn or Fisher Scientific. 1,2-dichloroethane was distilled before use.

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. TMSCl, styrene, allyl chloride and 4,4-dimethylcyclohex-2-enone **11** were distilled before use and stored in Schlenk flasks under an argon atmosphere. (*E*)-pent-3-en-2-one **121** and (*E*)-5-methylhex-3-en-2-one **139** were distilled and stored at –20 °C Deuterated solvents were purchased from Sigma-Aldrich (CD_2Cl_2, $CDCl_3$, CD_3CN). Toluene was bubbled with a flow or N_2 for 30 minutes before use.

Schwartz reagent was prepared according to the literature procedure[263] from Cp_2ZrCl_2 provided by Strem Chemicals. $(CuOTf)_2 \cdot C_6H_6$ was synthesised using a modified literature procedure[264] and carefully maintained under an inert atmosphere. $(CuOTf)_2 \cdot C_6H_6$ should be a white or off-white powder, not green or brown. The following ligands were provided by DSM: **D**, **E**, **L**, **M, S, V**

Methods to synthesise ketones

Synthesis of racemic product:

Using a modified procedure of Wipf *et al*.,[265] Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (2.0 mL) under an argon atmosphere. After stirring for about 40 min, $CuBr \cdot Me_2S$ (82 mg, 0.40 mmol 1.0 eq), was added to the reaction mixture and the resulting black mixture was allowed to stir for an additional 10 min before enone (0.40 mmol, 1.0 eq) was added via syringe over about 1 min. Stirring at room temperature was continued arbitrarily for 15 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography of the residue (EtOAc/petrol; SiO_2) gave the desired cyclic ketone.

General procedure 1: Screening conditions

The copper reagent (0.02 mmol, 0.1 eq) and the phosphoramidite ligand (0.02 mmol, 0.1 eq) were dissolved in the reaction solvent (0.20 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (103.0 mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene (**6**) (0.08 mL, 0.5 mmol, 2.5 eq) in CH_2Cl_2 (1.0 mL) under an argon atmosphere. After stirring for about 20 min, the resulting clear yellow solution was transferred via syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before the enone (0.20 mmol, 1.0 eq) was added dropwise via syringe. The reaction was stirred until complete (TLC control (EtOAc/Petrol 9:1)). The reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography of the residue (EtOAc/petrol; SiO_2) gave the desired ketone.

General procedure 2: Screening conditions using copper triflate benzene complex

$(CuOTf)_2 \cdot (C_6H_6)$ (5.0 mg, 0.01 mmol, 0.05 eq) and the phosphoramidite ligand (10.7 mg, 0.02 mmol, 0.1 eq) were dissolved in the reaction solvent (1.0 mL) under an argon atmosphere and

allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (103.0 mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (0.5 mmol, 2.5 eq) in CH_2Cl_2 (0.20 mL) under an argon atmosphere. After stirring for about 40 min, the resulting clear yellow solution was transferred via syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before the enone (0.20 mmol, 1.0 eq) was added dropwise via syringe. The reaction was stirred until complete (TLC control (EtOAc/Petrol 9:1)). The reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography of the residue (EtOAc/petrol; SiO_2) gave the desired ketone.

General procedure 3: Screening conditions with copper source made *in situ*

CuCl (1.8 mg, 0.02 mmol, 0.10 eq) and the phosphoramidite ligand (0.020 mmol, 0.10 eq) were dissolved in the reaction solvent (1.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. Then the appropriate silver salt (0.022 mmol, 0.11 eq) was added and the suspension was stirred for another 15 minutes. In another flask, Cp_2ZrHCl (103.0 mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene **6** (75 µL, 0.5 mmol, 2.5 eq) in CH_2Cl_2 (0.20 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the hydrozirconation solution. The resulting dark/brown mixture was allowed to stir for an additional 10 minutes before the enone (0.20 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 15 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography (EtOAc/petrol; SiO_2) of the residue gave the desired ketone.

General procedure 4: Optimal conditions to synthesise tertiary centres in Et_2O/TMSCl with copper-ligand complex made in situ from silver salt

CuCl (1.8 mg, 0.02 mmol, 0.10 eq) and the phosphoramidite ligand (0.020 mmol, 0.10 eq) were dissolved in Et_2O (1.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. Then AgOTf (5.7 mg, 0.022 mmol, 0.11 eq) was added and the suspension was stirred

for another 15 minutes. In another flask, Cp_2ZrHCl (103.0 mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (0.5 mmol, 2.5 eq) in CH_2Cl_2 (0.20 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the hydrozirconation solution. The resulting dark/brown mixture was allowed to stir for an additional 10 minutes before the enone (0.20 mmol, 1.0 eq) and TMSCl (0.13 mL, 1.0 mmol, 5.0 eq) were added dropwise *via* syringe. Stirring continued 15 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography (EtOAc/petrol; SiO_2) of the residue gave the desired ketone.

General procedure 5: Optimal conditions to synthesise tertiary centres in Et_2O/TMSCl with copper-ligand complex made from copper triflate benzene complex

$(CuOTf)_2{\cdot}(C_6H_6)$ (10.1 mg, 0.02 mmol, 0.05 eq) and the phosphoramidite ligand (21.2 mg, 0.04 mmol, 0.1 eq) were dissolved in Et_2O (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 40 min, the resulting clear yellow solution was transferred via syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before the enone (0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. The reaction was stirred until complete (TLC control (EtOAc/Petrol 9:1)). The reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography of the residue (EtOAc/petrol; SiO_2) gave the desired ketone.

General procedure 6: Optimal catalytic asymmetric conjugate addition with premade copper-ligand complex: synthesis of tertiary ketones.

(Note: This is the preferred procedure and was used in most cases in chapter 2).

Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for about 40 min, the resulting clear yellow solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex (0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before enone (0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. The reaction was stirred until complete (TLC control (EtOAc/Petrol 1:9)). The reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M. aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography of the residue (EtOAc/petrol; SiO_2) gave the desired ketone.

General procedure 7: Conditions for catalytic asymmetric conjugate addition synthesising quaternary centres using premade copper complex

Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for about 40 min, the resulting clear yellow solution was transferred via syringe over about 1 min to a clear colourless stirred solution of $CuNTf_2$-ligand complex (**86**) (35.3 mg, 0.040 mmol, 0.10 eq) in solvent (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before cyclic tertiary enone (0.40 mmol, 1.0 eq) was added dropwise via syringe. The reaction was stirred for 12 h. The reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M. aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography of the residue (EtOAc/petrol; SiO_2) gave the desired cyclic ketone.

General procedure 8: Conditions for catalytic asymmetric conjugate addition synthesising quaternary centres using catalyst made in situ

CuCl (1.8 mg, 0.02 mmol, 0.10 eq) and the phosphoramidite ligand (0.020 mmol, 0.10 eq) were dissolved in Et_2O (1.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. Then $AgNTf_2$ (0.022 mmol, 0.11 eq) was added and the suspension was stirred for another 15 minutes. In another flask, Cp_2ZrHCl (103.0 mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (0.5 mmol, 2.5 eq) in CH_2Cl_2 (0.20 mL) under an

argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the hydrozirconation solution. The resulting dark/brown mixture was allowed to stir for an additional 10 minutes before the enone (0.20 mmol, 1.0 eq) and TMSCl (0.13 mL, 1.0 mmol, 5.0 eq) were added dropwise *via* syringe. Stirring continued 15 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography (EtOAc/petrol; SiO_2) of the residue gave the desired ketone.

Methods for derivatisation and deprotection

General method 9: Derivatisation of cyclic tertiary ketones

Using the procedure from Alexakis and coworkers:[123] 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 (**4**) ((+)-(*R*,*R*)-DPEN *ca.* 1.2-2 eq.) was added and the vial was shaken and allowed to stand for at least 1 h 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.

General method 10: Derivatisation of cyclic quaternary ketones

Using the procedure from Alexakis and co-workers[123]: 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 (**4**) *ca.* 2-2.5 eq.) was added and the vial was shaken and allowed to stand between 24 and 72 hours 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.

General method 11: Deprotection of alcohols

The protected alcohol (24.5 mg, 0.06 mmol, 1.0 eq) was dissolved in THF (1.0 mL) at room temperature and TBAF·$3H_2O$ (1M, solution in THF, 0.12 mL, 0.12 mmol, 2.0 e) was added. The reaction mixture was stirred till starting material disappearance (TLC control 9:1, Petrol/EtOAc). Et_2O (2 mL) and saturated brine (1 mL) were then added. The mixture was partitioned between the

aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 2 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The obtained alcohol was analysed by HPLC.

Method to synthesise copper complexes

General method 12: synthesis of copper complexes from copper triflate benzene complex

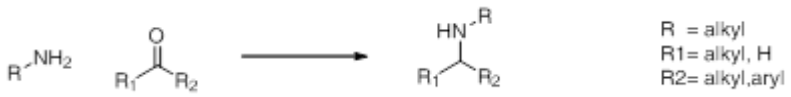
To a flame dried Schlenk flask containing $(CuOTf)_2 \cdot (C_6H_6)$ (0.5 eq) at room temperature under an argon atmosphere was added the phosphoramidite ligand (1.0 eq) and then CH_2Cl_2 (10 mL). This mixture was stirred for 1 h before the resulting clear colourless solution was cannula filtrated into another Schlenk flask. The solvent was then gently removed by use of an oil-pump vacuum (with liquid nitrogen trapping). The resulting off-white solid was dried for at least one extra hour under oil-pump vacuum before storing the catalyst complex under argon.

General method 13: synthesis of copper complexes from copper chloride

To a flame dried Schlenk flask, at room temperature under an argon atmosphere was added CuCl (46 mg, 0.47 mmol, 1 eq.) and the phosphoramidite ligand (0.47 mmol, 1.0 eq.) followed by CH_2Cl_2 (10 mL). This mixture was stirred for 1 h before silver salt (0.52 mmol, 1.1 eq) was added to the clear solution and stirred for a further 20 min. On the addition of the silver salt, the solution turns grey and a precipitate is formed (AgCl). The resulting solution was cannula filtrated into another Schlenk flask. The solvent was then gently removed by use of an oil-pump vacuum (with liquid nitrogen trapping). The resulting off-white solid was dried for at least one extra hour under oil-pump vacuum before storing the catalyst complex under argon.

Method to synthesise amines

General procedure 14: synthesis of alkyl amines



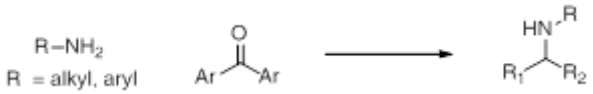
According to a modified procedure from Davies and coworkers,[266] the corresponding ketone (2.0 eq.) was added to a stirring solution of primary amine (1.0 eq) in THF (*ca* 0.2 M) at room temperature. After 5 min, $NaB(OAc)_3H$ (1.5 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 18-48 h. Et_2O (15 mL) and $NaHCO_3$ (aq. sat., ca 10 mL) were added to the suspension and stirring was continued for 30 min. The mixture

was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title amine.

NB: in case of recrystallization, the crude residue was then suspended in Et_2O, HCl (37% aq. solution) was added (2-5 drops or 2-5 mL on gram scale synthesis) until a white solid precipitated. The precipitate was isolated by filtration and washed with EtOAc and then recrystallized to give the HCl salt of the desired secondary amine. The crystals were added to a stirring biphasic mixture containing CH_2Cl_2 and a saturated NaOH solution. After stirring for 15 minutes the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), dried (Na_2SO_4), filtered and concentred *in vacuo* to afford the desired secondary amine. The amine was used without further purification or recrystallization.

NB: In some cases, this reaction can be followed straight away by the synthesis of the corresponding ligand.

General procedure 15: synthesis of aryl amines



According to a modified procedure from Gilbert, [198] $TiCl_4$ (1.1 eq, 1 M solution in CH_2Cl_2) was added slowly to a solution cooled at 0 °C of aryl-ketone (1.0 eq) in CH_2Cl_2 (0.2 M solution). The solution was stirred for 10 minutes at room temperature and then a solution of amine (2.2 eq) in THF (2 M solution) was added dropwise to the reaction mixture. The reaction mixture was stirred for 3 hours. A solution of $NaB(CN)H_3$ (1.2 eq) in THF (1 M solution) was added slowly to the reaction mixture. MeOH (1/3 volume of CH_2Cl_2 of first solution) was added slowly to the reaction mixture. The reaction mixture was stirred at room temperature for 18 hours. NaOH (2 M aq solution) was added slowly and the reaction mixture was stirred for 30 min. The reaction mixture was filtered on celite and washed with EtOAc. $NaHCO_3$ (aq. sat.) were added to the suspension. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with EtOAc (3 times). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Purification by flash column chromatography (SiO_2) gave the desired amine.

Method to synthesise ligands

General procedure 16: Phosphoramidite ligand synthesis from secondary amines

According to a modified procedure from Feringa[192, 193] or Rajanbabu,[191] secondary amine (0.90 mmol, 1.0 eq) was dissolved in THF (4.0 mL) and the solution was cooled to 0 °C. BuLi (1.6 M solution in hexane, 0.7 mL, 1.12 mmol, 1.2 eq) was added dropwise to the solution over about 3 minutes and the reaction mixture was stirred for 1 hour at 0 °C. A solution of phosphorochloridite (0.90 mmol, 1.0 eq) in THF (4.0 mL) was added and the resulting mixture stirred for 10 minutes at 0 °C. The reaction was allowed to warm to room temperature and stirred for 18 hours. Et_2O (*ca* 10 mL) was added and the reaction mixture was stirred for an additional 20 minutes before the reaction mixture was filtered through a layer of celite that was sitting on top of a very thin layer of silica gel and washed with Et_2O (*ca* 5 mL). The filtrate was concentrated *in vacuo*. Et_2O (*ca* 2 mL) was added to precipitate impurities, and the impurities were removed by filtration through celite and a very thin layer of silica. The solid was washed with Et_2O (*ca* 5 mL) and the combined filtrate was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford desired phosphoramidite ligand as an off white foam. Purification by flash column chromatography gave the desired phosphoramidite.

General procedure 17: Phosphoramidite ligand synthesis from primary amines

According to a modified procedure of RajanBabu[191] and Davies,[191, 195] $NaB(OAc)_3H$ (8.78 mmol, 3.0 eq) and ketone (2.93 mmol, 1.0 eq) were added to a stirred solution of primary amine (2.93 mmol, 1.0 eq) in THF (15 mL) at room temperature. The reaction mixture was stirred for 24 h before a saturated aqueous solution of $NaHCO_3$ (3 mL) was added and stirring continued for 15 additional minutes before EtOAc (10 mL) was added and the aqueous phase was separated and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was then suspended in EtOAc, HCl (37% aq. solution) was added (5-15 drops) until a white solid precipitated. The precipitate was collected by filtration, washed with EtOAc and then recrystallized to give the HCl salt of the desired secondary amine. The crystals were added to a stirring biphasic mixture containing CH_2Cl_2 and a saturated NaOH solution and stirred for an additional 15 min before the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), filtered and concentred *in vacuo* to give the desired secondary amine. The secondary amine was dissolved in THF (8.0 mL) and the solution was cooled to 0 °C. BuLi (1.6 M solution in hexane, 2.2 mL, 3.50 mmol, 1.2 eq) was added dropwise over about 5 minutes to the stirred and cooled solution. A solution of phosphorochloridite (2.93 mmol, 1.0 eq) in THF (4.0 mL) was added and the resulting mixture stirred for 10 minutes at 0 °C. The reaction was allowed to warm to room temperature and stirred for 18 hours. Et_2O (*ca* 20 mL) was added and the reaction mixture was

stirred for another 20 minutes. The reaction mixture was filtered through a layer of celite sitting on a very thin layer of silica and washed with Et_2O (10 mL). The filtrate was concentrated *in vacuo*. Et_2O (10 mL) was added to precipitate impurities, and the impurities were removed by filtration through celite and a very thin layer of silica. The solid was washed with Et_2O (10 mL) and the combined filtrate was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford desired phosphoramidite as a off white foam. Purification by flash column chromatography gave the desired phosphoramidite.

General procedure 18: Improved method for the synthesis of phosphoramidite ligands (used in most cases).

According to a modified procedure from Trost and coworkers,[164] triethylamine (5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (1.0 eq.) in CH_2Cl_2 (7 mL / mmol amine). The ice bath was removed and the solution left to warm to room temperature before amine (1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring before binaphthol (1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 20 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography, the ligand was obtained as a crystalline solid.

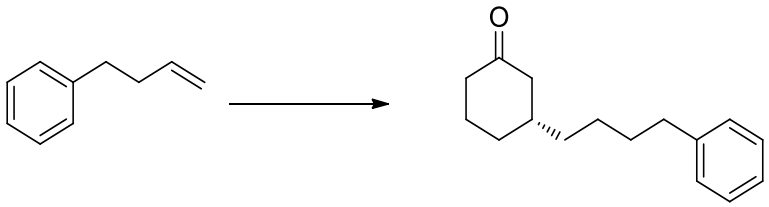
General procedure 19: Synthesis of phosphochloridite intermediate.

According to a modified procedure from Feringa and coworkers, [192, 193] BINOL (1.0 eq.) was added to a flask containing PCl_3 (5.0-8.0 eq). The mixture was warmed at 80 °C for 3 hours and let cooled down to room temperature before toluene was added (5 times the volume of PCl_3). The mixture was azeotropically distilled until the mixture left was a thick oil. Then the addition of toluene and distillation was repeated three times until the solid was put under high vacuum. The obtained solid was then kept under an argon atmosphere at -20 °C.

Characterisation of enones:

Catalytic asymmetric 1,4-addition of alkenes to synthesise cyclic tertiary ketones

(+)-(*R*)-3-(4-phenylbutyl)cyclohexanone (ent-7)



CuCl (1.8 mg, 0.02 mmol, 0.10 eq) and the phosphoramidite ligand **BE** (0.020 mmol, 0.10 eq) were dissolved in Et_2O (1.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. Then AgOTf (5.7 mg, 0.022 mmol, 0.11 eq) was added and the suspension was stirred for another 15 minutes. In another flask, Cp_2ZrHCl (103.0 mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene **6** (75 µL, 0.5 mmol, 2.5 eq) in CH_2Cl_2 (0.20 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the hydrozirconation solution. The resulting dark/brown mixture was allowed to stir for an additional 10 minutes before cyclohexenone **2** (45 µL, 0.40 mmol, 1.0 eq) and TMSCl (0.13 mL, 1.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring continued 15 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to give an oil. Flash column chromatography (EtOAc/petrol; 19:1; SiO_2) of the residue gave the desired 3-(4-phenylbutyl)cyclohexanone ent-**7** (27 mg, 0.12 mmol, 60%).

The data is consistent with literature.[189]

HPLC analysis indicated an enantiomeric excess of 94% *ee* [Chiralpak® IC; flow: 1.5 mL/min; hexane/i-PrOH: 99: 1; λ = 210 nm; major enantiomer (+)-(*R*)-3-(4-phenylbutyl)cyclohexanone, t_R = 19.30 min; minor enantiomer (–)-(*S*)-3-(4-phenylbutyl)cyclohexanone, t_R = 21.20 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.25 - 7.33 (m, 2 H), 7.13 - 7.23 (m, 3 H), 2.61 (t, *J* = 7.6 Hz, 2 H), 2.39 - 2.47 (m, 1 H), 2.32 - 2.39 (m, 1 H), 2.21 - 2.31 (m, 1 H), 1.95 - 2.09 (m, 2 H), 1.84 - 1.94 (m, 1 H), 1.71 - 1.83 (m, 1 H), 1.55 - 1.70 (m, 3 H), 1.26 - 1.45 (m, 5 H).

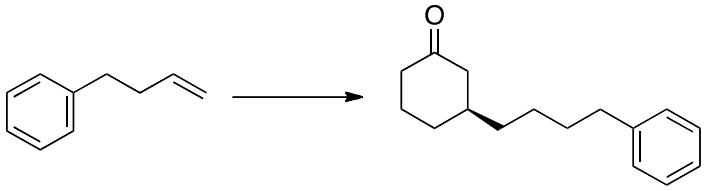
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 25.3, 26.3, 31.3, 31.4, 35.8, 36.4, 39.0, 41.5, 48.2, 125.6, 128.1 (2 C), 128.3 (2 C), 142.5, 212.0.

HRMS (EI) m/z calcd for $C_{20}H_{24}O$ $[M]^+$: 230.1671, found: 230.1675.

$[\alpha]^{24}_{589}$ = +5.92 (*c* 1.30, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 700, 749, 1453, 1711, 2856, 2929.

(–)-(*S*)-3-(4-phenylbutyl)cyclohexanone (7)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of but-3-en-1-ylbenzene **6** (0.15 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **13** (30.0 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before cyclohexenone **2** (39 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at room temperature was continued for 150 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:19 EtOAc/petrol; SiO_2) gave (–)-(*S*)-3-(4-phenylbutyl)cyclohexanone **7** (54.3 mg, 0.24 mmol, 59%) as a colourless oil.

HPLC analysis indicated an enantiomeric excess of 90% *ee* [Chiralpak® IC; flow: 1.5 mL/min; hexane/i-PrOH: 95: 5; λ = 210 nm; minor enantiomer (+)-(*R*)-3-(4-phenylbutyl)cyclohexanone, t_R = 8.50 min; major enantiomer (–)-(*S*)-3-(4-phenylbutyl)cyclohexanone, t_R = 9.0 min].

Absolute configuration assigned by analysis of optical rotation and circular dichroism spectra.[267 136]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.25 - 7.33 (m, 2 H), 7.13 - 7.23 (m, 3 H), 2.61 (t, *J* = 7.6 Hz, 2 H), 2.39 - 2.47 (m, 1 H), 2.32 - 2.39 (m, 1 H), 2.21 - 2.31 (m, 1 H), 1.95 - 2.09 (m, 2 H), 1.84 - 1.94 (m, 1 H), 1.71 - 1.83 (m, 1 H), 1.55 - 1.70 (m, 3 H), 1.26 - 1.45 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.0, 142.5, 128.3 (2 C), 127.9 (2 C), 125.6, 48.2, 41.5, 39.0, 36.4, 35.8, 31.5, 31.3, 26.3, 25.3.

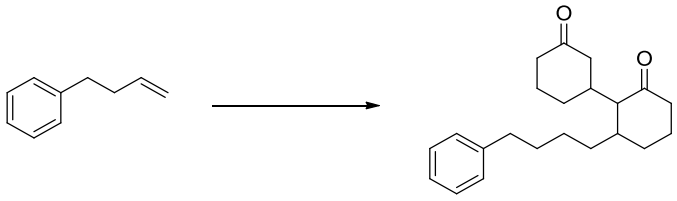
HRMS (EI) m/z calcd for $C_{20}H_{24}O$ $[M]^+$: 230.1671, found: 230.1675.

$[\alpha]^{24}_{589}$ = –11.96 (*c* 1.52, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2929, 2856, 1711, 1453, 749, 700.

CD: Θ (γ) = –7.94 (293.0 nm), (c = 0.41 mg/ml in CH_3CN).

6-(4-phenylbutyl)-[1,1'-bi(cyclohexane)]-2,3'-dione (10)



Cp_2ZrHCl (1.05 g, 4.16 mmol, 2.0 eq) was added to a stirred, room temperature, solution of but-3-en-1-ylbenzene **6** (0.68mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (4 mL) under an argon atmosphere. After stirring for 15 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of $CuBr{\cdot}SMe_2$ (428 mg, 2,08 mmol, 1.0 eq) in CH_2Cl_2 (4 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before cyclohexenone **2** (0.201, 2.08 mmol, 1.0 eq) were added dropwise via syringe. Stirring at room temperature was continued for 150 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) gave 6-(4-phenylbutyl)-[1,1'-bi(cyclohexane)]-2,3'-dione **10** (119 mg, 0.24 mmol, 23%) as a colourless oil.

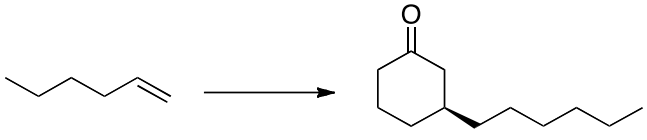
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.23 - 7.34 (m, 3 H), 7.18 (s, 2 H), 2.53 - 2.66 (m, 2 H), 2.41 - 2.51 (m, 1 H), 2.20 - 2.40 (m, 4 H), 1.93 - 2.19 (m, 4 H), 1.72 - 1.90 (m, 2 H), 1.41 - 1.70 (m, 7 H), 1.10 - 1.39 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 213.4, 210.7, 142.3, 128.3 (2 C), 128.2 (2 C), 125.6, 61.0, 46.0 (s, 1 C), 44.8, 41.3, 41.2, 40.6, 40.2, 38.7, 38.0, 35.7, 31.9, 31.3, 29.5, 25.0.

HRMS (EI) m/z calcd for $C_{22}H_{30}O_2$ $[M]^+$: 326.2246, found: 326.2249.

IR (ν_{max} /cm^{-1}): 2952, 1705, 1717, 1451, 751, 698.

(–)-(*S*)-3-Hexylcyclohexanone (3)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 1-hexene **1** (0.13 mL, 1.00 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After

stirring for 20 min, the resulting clear yellow solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **13** (30.0 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before cyclohexenone **2** (39 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at room temperature was continued for 2.5 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:19 EtOAc/petrol; SiO_2) gave (–)-(*S*)-3-hexylcyclohexanone **3** (44 mg, 0.24 mmol, 59%) as a colourless oil. Enantiomeric excess (93% *ee*) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

Characterisation data were consistent with those reported in the literature for the corresponding racemic compound: ^{1}H, ^{13}C, IR, MS.[265]

Absolute configuration assigned by analysis of the optical rotation and circular dichroism spectra.[267 136]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 2.43 (ddt, *J* = 13.7, 4.0, 1.9, Hz, 1 H), 2.32 - 2.39 (m, 1 H), 2.21 - 2.31 (m, 1 H), 1.96 - 2.11 (m, 2 H), 1.85 - 1.94 (m, 1 H), 1.72 - 1.83 (m, 1 H), 1.56 - 1.71 (m, 1 H), 1.27 (br. s., 11 H), 0.89 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.2, 48.2, 41.5, 39.1, 36.6, 31.8, 31.3, 29.3, 26.6, 25.3, 22.6, 14.1.

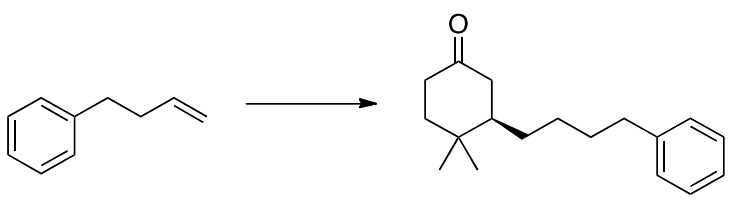
HRMS (EI) *m/z* calcd for $C_{12}H_{22}O$ $[M]^+$: 182.1671, found: 182.1663.

$[\alpha]^{24}_{589}$ = –10.0 (*c* 1.00, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2925, 1717, 1422.

CD: Θ (γ) = –9.04 (293 nm), (c = 0.70 mg/ml in CH_3CN).

(–)-(*R*)-4,4-dimethyl-3-(4-phenylbutyl)cyclohexanone (12)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene **6** (0.15 mL, 4.0 mmol, 10 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 30 min at room temperature, CH_2Cl_2 (0.40 mL) was added. The resulting clear yellow solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **13** (30.0 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for 10 min before 4,4-dimethylcyclohex-2-enone **11** (53 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at room temperature was continued for 3 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:19 EtOAc/petrol; SiO_2) gave (–)-(*R*)-4,4-dimethyl-3-(4-phenylbutyl)cyclohexanone **12** (76.7 mg, 0.30 mmol, 74%) as colourless crystals.

HPLC analysis indicated an enantiomeric excess of 91% *ee* [Chiralpak® IB; flow: 1.0 mL/min; hexane/i-PrOH: 99.4:0.6; λ = 210 nm; minor enantiomer (+)-(*S*)-4,4-dimethyl-3-(4-phenylbutyl)cyclohexanone, t_R = 10.14 min; major enantiomer (–)-(*R*)-4,4-dimethyl-3-(4-phenylbutyl)cyclohexanone, t_R = 10.63 min].

Absolute configuration assigned by analysis of optical rotation and circular dichroism spectra.[267 136]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.24 - 7.34 (m, 2 H), 7.14 - 7.22 (m, 3 H), 2.56 - 2.65 (m, 2 H), 2.35 - 2.48 (m, 2 H), 2.21 - 2.33 (m, 1 H), 1.97 - 2.11 (m, 1 H), 1.68 - 1.77 (m, 1 H), 1.52 - 1.66 (m, 4 H), 1.36 - 1.52 (m, 2 H), 1.12 - 1.25 (m, 1 H), 1.04 - 1.11 (m, 1 H), 1.03 (s, 3 H), 1.00 (s, 3 H),

^{13}C NMR (100 MHz, $CDCl_3$) δ_H /ppm 212.30, 142.5, 128.4 (s, 2 C), 128.3 (s, 2 C), 125.7, 46.7, 42.88, 40.5, 38.3, 35.9, 32.8, 31.5, 30.4, 28.7, 27.1, 19.5

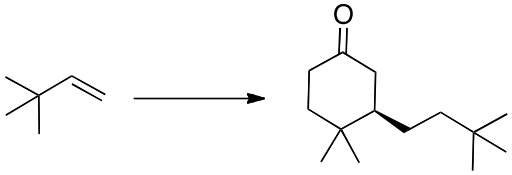
HRMS (EI) m/z calcd for $C_{18}H_{26}O$: 258.1984, found: 258.1979.

$[\alpha]^{24}_{589}$ = –17.79 (*c* 0.73, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2932, 2858, 1711, 698.

CD : Θ (γ) = –2.23 (295.5 nm), (c = 0.57 mg/ml in CH_3CN).

(–)-(*R*)-3-(3,3-dimethylbutyl)-4,4-dimethylcyclohexanone (20)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 3,3-dimethylbut-1-ene **19** (0.13 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 60 min at room temperature, CH_2Cl_2 (0.20 mL) was added and the reaction mixture was heated to 30 °C for 40 min and then allowed to cool to room temperature. The resulting clear yellow solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **13** (30.0 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before 4,4-dimethylcyclohex-2-enone **11** (53 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at room temperature was continued for 18 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (3:97 EtOAc/petrol; SiO_2) gave (–)-(*R*)-3-(3,3-dimethylbutyl)-4,4-dimethylcyclohexanone **20** (54 mg, 0.26 mmol, 65%) as a colourless oil. Enantiomeric excess (84% *ee*) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 2.33 - 2.46 (m, 2 H), 2.21 - 2.29 (m, 1 H), 1.98 - 2.07 (m, 1 H), 1.65 - 1.74 (m, 1 H), 1.48 - 1.62 (m, 2 H), 1.32 - 1.42 (m, 1 H), 1.20 - 1.30 (m, 1 H), 1.02 (s, 3 H), 0.99 (s, 3 H), 0.89 - 0.97 (m, 2 H), 0.85 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.2, 47.8, 43.0, 42.2, 40.4, 38.3, 33.0, 30.3, 29.2 (3 C), 28.7, 25.3, 19.5.

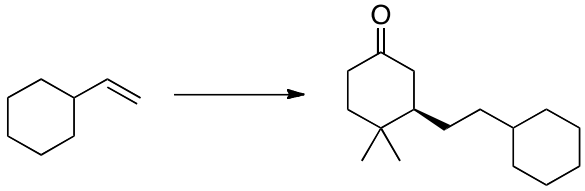
HRMS (EI) m/z calcd for $C_{14}H_{26}O$ $[M]^+$: 210.1984, found: 210.1986.

$[\alpha]^{24}_{589}$ = –23.0 (*c* 0.52, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2954, 2866, 1715, 1469, 1390.

Absolute configuration assigned by optical rotation.[267 136]

(–)-(*R*)-3-(2-cyclohexylethyl)-4,4-dimethylcyclohexanone (22)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of vinylcyclohexane **21** (0.14 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the resulting clear yellow solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand **13** complex (30.0 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 20 min before 4,4-dimethylcyclohex-2-enone **11** (53 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at room temperature was continued arbitrarily for 18 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (1 M aq., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (3:97 EtOAc/petrol; SiO_2) gave (–)-(*R*)-3-(2-cyclohexylethyl)-4,4-dimethylcyclohexanone **22** (72.0 mg, 0.30 mmol, 75%) as a colourless oil. Enantiomeric excess (93% *ee*) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

Absolute configuration assigned by optical rotation.[267 136]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 2.33 - 2.47 (m, 2 H), 2.20 - 2.31 (m, 1 H), 1.96 - 2.06 (m, 1 H), 1.60 - 1.74 (m, 7 H), 1.50 - 1.59 (m, 2 H), 1.36 - 1.46 (m, 1 H), 102 - 1.27 (m, 8 H), 1.01 (s, 3 H), 0.97 (s, 3 H).

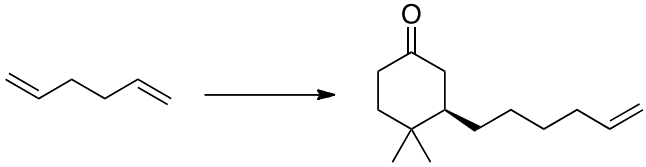
^{13}C NMR (100 MHz, $CDCl_3$) δ_H /ppm 212.3, 47.1, 42.9, 40.4, 38.3, 37.8, 37.7, 35.3, 33.7, 32.9, 28.7, 27.7, 26.6, 26.3, 26.3, 19.5.

HRMS (EI) m/z calcd for $C_{16}H_{28}O$ $[M]^+$: 236.2140, found: 236.2149.

$[\alpha]^{24}_{589}$ = –17.2 (*c* 0.47, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2926, 1714, 1458

(–)-(*R*)-3-(Hex-5-en-1-yl)-4,4-dimethylcyclohexanone (26)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 1,5-hexadiene **25** (0.48 mL, 4.0 mmol, 10.0 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 120 min at room temperature, CH_2Cl_2 (0.40 mL) was added. After stirring for an additional 100 min, the resulting clear yellow solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **13** (30.0 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 20 min before 4,4-dimethylcyclohex-2-enone **11** (53 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at room temperature was continued arbitrarily for 20 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (3:97 EtOAc/petrol; SiO_2) gave (–)-(*R*)-3-(hex-5-en-1-yl)-4,4-dimethylcyclohexanone **26** (60 mg, 0.29 mmol, 71%) as a colourless oil. Enantiomeric excess (78% *ee*) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

Absolute configuration assigned by optical rotation.[267 136]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /5.79 (ddt, *J* = 17.0, 10.3, 6.7, 6.7 Hz, 1 H), 4.89 - 5.07 (m, 2 H), 2.34 - 2.49 (m, 2 H), 2.21 - 2.32 (m, 1 H), 1.97 - 2.10 (m, 3 H), 1.67 - 1.77 (m, 1 H), 1.52 - 1.66 (m, 2 H), 1.44 - 1.52 (m, 1 H), 1.30 - 1.43 (m, 3 H), 1.06 - 1.26 (m, 2 H), 1.03 (s, 3 H), 0.99 (s, 3 H).

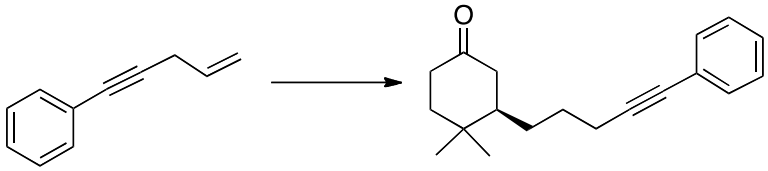
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.3, 138.8, 114.4, 46.8, 42.9, 40.5, 38.3, 33.7, 32.8, 30.4, 28.9, 28.7, 26.9, 19.5.

HRMS (EI) m/z calcd for $C_{14}H_{24}O$: 208.1827, found: 208.1832.

$[\alpha]^{24}_{589}$ = –23.17 (*c* 0.72, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2929, 2858, 1714, 1464, 908.

(–)-(*R*)-4,4-Dimethyl-3-(5-phenylpent-4-yn-1-yl)cyclohexanone (28)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of pent-4-en-1-yn-1-ylbenzene **27** (0.15 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.45 mL) under an argon atmosphere The reaction flask was placed in a preheated bath at 40 ºC and after stirring at this temperature for 25 min the flask was removed and the reaction mixture allowed to cool to room temperature. The resulting clear orange solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **13** (30.0 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for 10 min before 4,4-dimethylcyclohex-2-enone **11** (53 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at room temperature was continued for 4 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:33 EtOAc/petrol; SiO_2) gave (–)-(*R*)-4,4-dimethyl-3-(5-phenylpent-4-yn-1-yl)cyclohexanone **28** (67 mg, 0.25 mmol, 62%) as a colourless oil. Absolute configuration assigned by optical rotation.[267 136]

HPLC analysis indicated an enantiomeric excess of 82% *ee* [Chiralpak® AY-H; flow: 1.2 mL/min; hexane/i-PrOH: 96:4; λ = 210 nm; minor enantiomer (+)-(*S*)-4,4-dimethyl-3-(5-phenylpent-4-yn-1-yl)cyclohexanone, t_R = 8.1 min; major enantiomer (–)-(*R*)-4,4-dimethyl-3-(5-phenylpent-4-yn-1-yl)cyclohexanone, t_R = 9.99 min].

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.36 - 7.42 (m, 2 H), 7.27 - 7.31 (m, 3 H), 2.44 - 2.48 (m, 1 H), 2.41 (dt, *J* = 6.9, 3.7 Hz, 3 H), 2.25 - 2.33 (m, 1 H), 2.10 (ddd, *J* = 14.8, 12.1, 0.8 Hz, 1 H), 1.76 - 1.83 (m, 1 H), 1.66 - 1.76 (m, 2 H), 1.63 (dd, *J* = 12.9, 4.7 Hz, 1 H), 1.51 - 1.59 (m, 1 H), 1.46 (ddq, *J* = 12.9, 9.9, 6.5, 6.5, 6.5 Hz, 1 H), 1.13 - 1.28 (m, 1 H), 1.07 (s, 3 H), 1.03 (s, 3 H).

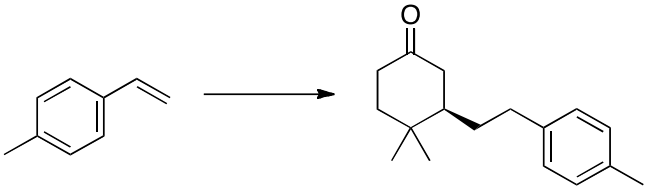
^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 212.0, 131.5 (2 C), 128.2 (2 C), 127.5, 123.9, 89.7, 81.0, 46.4, 42.9, 40.4, 38.3, 32.9, 29.8, 28.7, 26.6, 19.5, 19.4.

HRMS (ESI) *m/z* calcd for $C_{19}H_{24}NaO$ $[M+Na]^+$: 291.1719, found: 291.1721.

$[\alpha]^{20}_{589}$ = –25.17 (*c* 1.00, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2955, 1713, 1490, 1367, 757, 692.

(–)-(*R*)-4,4-Dimethyl-3-(4-methylphenethyl)cyclohexanone (30)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 1-methyl-4-vinylbenzene **29** (0.14 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. The resulting clear orange solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **13** (30.0 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for 10 min before 4,4-dimethylcyclohex-2-enone **11** (53 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at room temperature was continued for 18 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:19 EtOAc/petrol; SiO_2) gave (–)-(*R*)-4,4-dimethyl-3-(4-methylphenethyl)cyclohexanone **30** (55 mg, 0.23 mmol, 56%) as a colourless oil.

HPLC analysis indicated an enantiomeric excess of 82% *ee* [Chiralpak® IB; flow: 1.0 mL/min; hexane/i-PrOH: 99.4:0.6; λ = 210 nm; minor enantiomer (+)-(*S*)-4,4-dimethyl-3-(4-methylphenethyl)cyclohexanone, t_R = 11.10 min; major enantiomer (–)-(*R*)-4,4-dimethyl-3-(4-methylphenethyl)cyclohexanone, t_R = 12.10 min].

Absolute configuration assigned by optical rotation.[267 136]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.09 - 7.13 (m, 2 H), 7.04 - 7.08 (m, 2 H), 2.66 - 2.73 (m, 1 H), 2.54 (ddd, *J* = 15.0, 4.0, 2.4 Hz, 1 H), 2.35 - 2.47 (m, 2 H), 2.32 (s, 3 H), 2.24 - 2.31 (m, 1 H), 2.14 (dd, *J* = 14.0, 12.0 Hz, 1 H), 1.88 (dddd, *J* = 13.2, 10.6, 6.9, 2.4 Hz, 1 H), 1.68 - 1.74 (m, 1 H), 1.52 - 1.64 (m, 2 H), 1.29 - 1.37 (m, 1 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

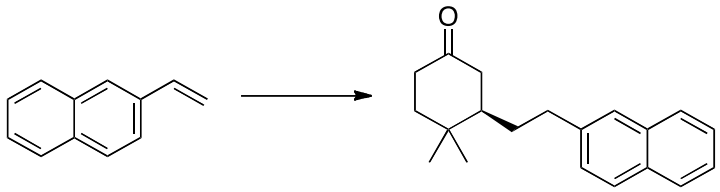
^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 212.0, 139.0, 135.3, 129.1 (2 C), 128.2 (2 C), 46.2, 42.8, 40.3, 38.3, 33.3, 32.9, 32.8, 28.6, 21.0, 19.5.

HRMS (ESI) *m/z* calcd for $C_{17}H_{24}NaO$ $[M+Na]^+$: 267.1722, found: 267.1719.

$[\alpha]^{20}_{589}$ = –15.12 (*c* 0.85, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2924, 1717, 1040, 808.

(–)-(*R*)-4,4-Dimethyl-3-(2-(naphthalen-2-yl)ethyl)cyclohexanone (32)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 2-vinylnaphthalene **31** (160.2 mg, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 30 min, the resulting dark red clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **13** (30.0 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before 4,4-dimethylcyclohex-2-enone **11** (53 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at room temperature was arbitrarily continued for 15 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (3:97 EtOAc/petrol; SiO_2) gave (–)-(*R*)-4,4-dimethyl-3-(2-(naphthalen-2-yl)ethyl)cyclohexanone **32** (59 mg, 0.21 mmol, 52%) as a colourless oil.

HPLC analysis indicated an enantiomeric excess of 71% [Chiralpak® IC; flow: 1.0 mL/min; hexane/i-PrOH: 90:10; λ = 210 nm; minor enantiomer (+)-(*S*)-4,4-dimethyl-3-(2-(naphthalen-2-yl)ethyl)cyclohexanone, t_R = 12.50 min; major enantiomer (–)-(*R*)-4,4-dimethyl-3-(2-(naphthalen-2-yl)ethyl)cyclohexanone, t_R = 13.30 min].

Absolute configuration assigned by optical rotation.[267 136]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.76 - 7.87 (m, 3 H), 7.62 (s, 1 H), 7.41 - 7.51 (m, 2 H), 7.33 (dd, *J* = 8.5, 1.6 Hz, 1 H), 2.87 - 2.94 (m, 1 H), 2.55 - 2.67 (m, 2 H), 2.38 - 2.49 (m, 1 H), 2.25 - 2.35 (m, 1 H), 2.13 - 2.24 (m, 1 H), 1.94 - 2.05 (m, 1 H), 1.67 - 1.76 (m, 1 H), 1.54 - 1.64 (m, 2 H), 1.38 - 1.50 (m, 1 H), 1.02 (s, 6 H).

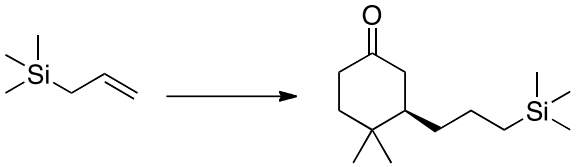
^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 211.9, 139.5, 133.6, 132.0, 128.0, 127.6, 127.4, 127.1, 126.3, 125.9, 125.2, 46.1, 42.8, 40.2, 38.2, 33.8, 32.8, 32.5, 28.6, 19.6.

HRMS (EI) m/z calcd for $C_{20}H_{24}O$ $[M]^+$: 280.1827, found: 280.1827.

$[\alpha]^{24}_{589}$ = –1.23 (*c* 0.32, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2958, 2863, 1714, 913, 747.

(–)-(*R*)-4,4-Dimethyl-3-(2-(trimethylsilyl)ethyl)cyclohexanone (44)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of allyltrimethylsilane **42** (0.13 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 10 min, the resulting clear orange solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **13** (30.0 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) at 0 °C under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before 4,4-dimethylcyclohex-2-enone **11** (53 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 4 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (3:97 EtOAc/petrol; SiO_2) gave (–)-(*R*)-4,4-dimethyl-3-(2-(trimethylsilyl)ethyl)cyclohexanone **44** (50.6 mg, 0.21 mmol, 53%) as a yellow oil. Enantiomeric excess (96% *ee*) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

Absolute configuration assigned by optical rotation.[267 136]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 2.35 - 2.47 (m, 2 H), 2.22 - 2.32 (m, 1 H), 2.05 (dd, *J* = 14.7, 12.3 Hz, 1 H), 1.67 - 1.76 (m, 1 H), 1.57 - 1.66 (m, 1 H), 1.46 - 1.57 (m, 2 H), 1.33 - 1.45 (m, 1 H), 1.04 - 1.17 (m, 2 H), 1.02 (s, 3 H), 0.99 (s, 3 H), 0.46 - 0.57 (m, 1 H), 0.34 - 0.44 (m, 1 H), -0.03 (s, 9 H).

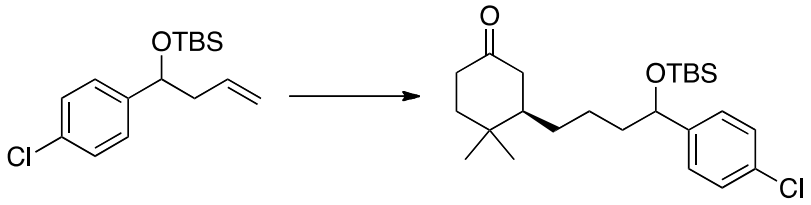
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.5, 46.6, 42.9, 40.5, 38.3, 34.6, 32.8, 28.7, 21.9, 19.5, 16.8, -1.7 (3 C).

HRMS (EI) m/z calcd for $C_{14}H_{28}OSi$ $[M]^+$: 240.1909, found: 240.1914.

$[\alpha]^{20}_{589}$ = –25.51 (*c* 1.07, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2954, 2860, 2360, 2341, 1715, 835.

(–)-(3-*R*)-3-(4-((tert-butyldimethylsilyl)oxy)-4-(4-chlorophenyl)butyl)-4,4-dimethylcyclohexanone (46)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of tert-butyl((1-(4-chlorophenyl)but-3-en-1-yl)oxy)dimethylsilane **45** (0.23 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.45 mL) under an argon atmosphere. The resulting clear yellow solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **13** (30.0 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for 10 min before 4,4-dimethylcyclohex-2-enone **11** (53 μL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at room temperature was continued for 5 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:33 EtOAc/petrol; SiO_2) gave (–)-(*3R*)-3-(4-((tert-butyldimethylsilyl)oxy)-4-(4-chlorophenyl)butyl)-4,4-dimethylcyclohexanone **46** (107 mg, 0.25 mmol, 63%) as a colourless oil.

Enantiomeric excess (85% *ee*) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

The enantiomeric excess was also determined by HLPC on a chiral non-racemic stationary phase of the corresponding deprotected alcohol. The dr and *ee* ratios are assumed to be the same for the silyl and deprotected alcohol. The silyl protecting group was removed by addition of TBAF· $3H_2O$ (1 M in THF, 2 eq) to a solution of the silyl ether in THF (0.8 M solution) and stirring overnight at room temperature. Filtration of the crude mixture over silica gel afforded the deprotected alcohol quantitatively. HPLC analysis indicated a 1:1 diastereomeric ratio and an enantiomeric excess of 85% [Chiralpak® AY-H; flow: 1.2 mL/min; hexane/i-PrOH: 92:8; λ = 210 nm; minor enantiomer (+)-(3*S*)-(4-(4-chlorophenyl)-4-hydroxybutyl)-4,4-dimethylcyclohexanone, t_R = 19.38 min & 34.00

min; major enantiomer (–)-(3*R*)-(4-(4-chlorophenyl)-4-hydroxybutyl)-4,4-dimethylcyclohexanone, t_R = 16.56 min & 25.21 min].

Absolute configuration assigned by optical rotation.[267 136]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.25 - 7.30 (m, 2 H), 7.18 - 7.24 (m, 2 H), 4.59 (q, *J* = 6.1 Hz, 1 H), 2.33 - 2.46 (m, 2 H), 2.21 - 2.30 (m, 1 H), 2.01 (br. t, *J* = 13.4, 13.4 Hz, 1 H), 1.63 - 1.74 (m, 2 H), 1.56 - 1.63 (m, 2 H), 1.40 - 1.55 (m, 3 H), 1.25 - 1.40 (m, 1 H), 1.08 - 1.24 (m, 1 H), 1.00 (d, *J* = 2.8 Hz, 3 H), 0.97 (s, 3 H), 0.88 (s, 9 H), 0.02 (s, 3 H), -0.15 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.2, 144.2, 132.4, 128.2 (2 C), 127.1 (2 C), 74.2, 46.7, 42.8, 41.0, 40.4, 38.2, 32.8, 30., 28.7, 25.8 (3 C), 23.3, 19.4, 18.1, -4.7, -5.0.

HRMS (ESI) *m/z* calcd for $C_{24}H_{39}ClO_2SiNa$ $[M+Na]^+$: 445.2300, found: 445.2301.

$[\alpha]^{20}_{589}$ = –13.17 (*c* 1.02, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2954, 1715, 1089, 859.

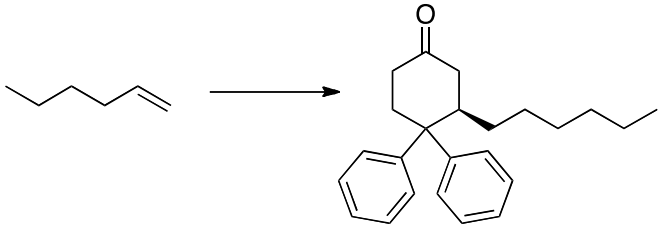
Large scale:

Cp_2ZrHCl (2.12 g, 9.21 mmol, 1.7 eq) was added to a stirred, room temperature, solution of tert-butyl((1-(4-chlorophenyl)but-3-en-1-yl)oxy)dimethylsilane **45** (2.84 mL, 9.66 mmol, 2.0 eq) in CH_2Cl_2 (4.2 mL) under an argon atmosphere. The resulting clear yellow solution was transferred via syringe over about 5 min to a clear colourless stirred solution of CuOTf-ligand complex **13** (181.7 mg, 0.242 mmol, 0.05 eq) in Et_2O (24.1 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for 10 min before 4,4-dimethylcyclohex-2-enone **11** (0.64 mL, 4.83 mmol, 1.0 eq) and then TMSCl (3.1 mL, 24.16 mmol, 5.0 eq) were added dropwise via syringe. Stirring at room temperature was continued overnight before the reaction was quenched by pouring the solution onto an iced mixture of NH_4Cl (1 M aq., *ca* 100 mL) and Et_2O (*ca* 50 mL) and the resulting mixture was partitioned between water and Et_2O and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 200 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:33 EtOAc/petrol; SiO_2) gave (–)-(3*R*)-3-(4-((tert-butyldimethylsilyl)oxy)-4-(4-chlorophenyl)butyl)-4,4-dimethylcyclohexanone **46** (1.90 g, 4.49 mmol, 93%) as a colourless oil.

The enantiomeric excess was determined by HLPC on a chiral non-racemic stationary phase of the corresponding deprotected alcohol. The dr and *ee* ratios are assumed to be the same for the silyl and deprotected alcohol. The silyl protecting group was removed by addition of TBAF·$3H_2O$ (1 M in THF, 2 eq) to a solution of the silyl ether in THF (0.8 M solution) and stirring overnight at room temperature. Filtration of the crude mixture over silica gel afforded the

deprotected alcohol quantitatively. HPLC analysis indicated a 1:1 diastereomeric ratio and an enantiomeric excess of 70% [Chiralpak® AY-H; flow: 1.2 mL/min; hexane/i-PrOH: 92:8; λ = 210 nm; minor enantiomer (+)-(3*S*)-(4-(4-chlorophenyl)-4-hydroxybutyl)-4,4-dimethylcyclohexanone, t_R = 19.55 min & 34.19 min; major enantiomer (–)-(3*R*)-(4-(4-chlorophenyl)-4-hydroxybutyl)-4,4-dimethylcyclohexanone, t_R = 16.98 min & 25.75 min].

(–)-(*R*)-3-Hexyl-4,4-diphenylcyclohexanone (50)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 1-hexene **1** (0.13 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.45 mL) under an argon atmosphere. The resulting clear yellow solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **13** (30.0 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for 10 min before 4,4-diphenylcyclohex-2-enone **49** (100 mg, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at room temperature was continued arbitrarily for 18 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:49 EtOAc/petrol; SiO_2) gave (–)-(*R*)-3-hexyl-4,4-diphenylcyclohexanone **50** (101 mg, 0.30 mmol, 75%) as a colourless solid.

HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® IB; flow: 1.0 mL/min; hexane/i-PrOH:. 95:5; λ = 210 nm; minor enantiomer (+)-(*S*)-3-hexyl-4,4-diphenylcyclohexanone, t_R = 5.77 min; major enantiomer (–)-(*R*)-3-hexyl-4,4-diphenylcyclohexanone, t_R = 6.34 min].

Absolute configuration assigned by optical rotation.[267 136]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.53 (d, *J* = 7.6 Hz, 2 H), 7.36 (t, *J* = 7.9 Hz, 2 H), 7.24 - 7.31 (m, 4 H), 7.17 - 7.23 (m, 1 H), 7.09 - 7.16 (m, 1 H), 3.04 (br. s., 1 H), 2.93 - 3.00 (m, 1 H), 2.81 (dd, *J* = 14.8, 5.0 Hz, 1 H), 2.62 (td, *J* = 13.6, 4.4 Hz, 1 H), 2.49 (dt, *J* = 14.7, 2.8 Hz, 1 H), 2.36 - 2.43 (m, 1 H), 2.27 - 2.35 (m, 1 H), 1.36 - 1.48 (m, 1 H), 1.17 - 1.26 (m, 2 H), 1.02 - 1.16 (m, 7 H), 0.83 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 211.6, 146.6, 145.0, 128.9 (2 C), 128.3 (2 C), 126.6 (2 C), 126.4 (2 C), 126.1, 125.7, 48.7, 43.0, 42.2, 38.3, 31.5, 30.0, 29.5, 29.0, 28.0, 22.5, 14.0.

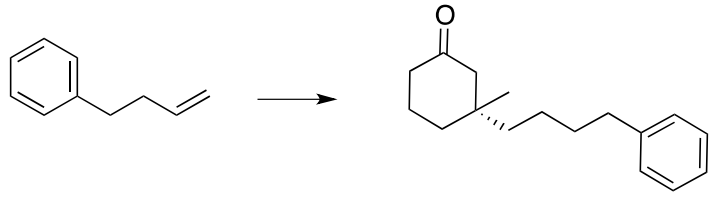
HRMS (ESI) *m/z* calcd for $C_{24}H_{30}NaO$ $[M+Na]^+$: 357.2189, found: 357.2186.

$[\alpha]^{20}_{589}$ = –194.11 (*c* 1.02, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2927, 2388, 1713, 1460, 701.

Catalytic asymmetric 1,4-addition of alkenes to synthesise cyclic quaternary ketones

(–)-(*R*)-3-Methyl-3-(4-phenylbutyl)cyclohexanone (85)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite **BU** (21.6 mg, 0.040 mmol, 0.10 eq) were dissolved in *t*-BuOMe (2.0 mL) under an argon atmosphere and the resulting mixture allowed to stir at room temperature. After 1 hour, $AgNTf_2$ (23.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 min. In another flask, Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene **6** (0.15 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the clear yellow solution containing the alkene/zirconium mixture. The resulting black mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone **84** (45 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring was continued for about 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) gave (–)-(*R*)-3-methyl-3-(4-phenylbutyl)cyclohexanone **85** (65 mg, 0.27 mmol, 66%) as a colourless oil. Absolute configuration assigned by analogy to compound **87**.

HPLC analysis indicated an enantiomeric excess of 94% [Chiralpak® IC; flow: 1 mL/min; hexane/i-PrOH: 98:2; λ = 210 nm; major enantiomer (–)-(*R*)-3-methyl-3-(4-phenylbutyl)cyclohexanone, t_R = 16.8 min; major enantiomer (+)-(*S*)-3-methyl-3-(4-phenylbutyl)cyclohexanone, t_R = 17.9 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.16 - 7.23 (m, 2 H), 7.04 - 7.12 (m, 3 H), 2.53 (br. t, *J* = 6.8, 6.8 Hz, 2 H), 2.19 (t, *J* = 6.8 Hz, 2 H), 2.06 - 2.13 (m, 1 H), 1.97 - 2.05 (m, 1 H), 1.76 (quin, *J* = 6.8 Hz, 2 H), 1.39 - 1.61 (m, 4 H), 1.21 (d, *J* = 2.4 Hz, 4 H), 0.82 (s, 3 H).

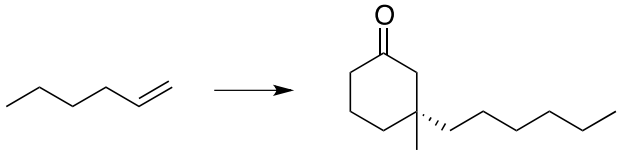
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.4, 142.5, 128.3 (2 C), 128.2 (2 C), 125.6, 53.7, 41.4, 41.0, 38.5, 35.8, 35.7, 32.0, 25.0, 22.9, 22.1.

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

$[\alpha]^{20}_{589}$ = −2.8 (*c* 0.92, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2932, 2857, 1713, 1252, 1088, 836, 776.

(+)-(*R*)-3-Hexyl-3-methylcyclohexanone (92)



CuCl (2.7 mg, 0.03 mmol, 0.10 eq) and the ligand **BU** (15.4 mg, 0.03 mmol, 0.10 eq) were dissolved in *t*-BuOMe (1.5 mL) and stirred at room temperature for 1 h. In another flask Cp_2ZrHCl (154 mg, 0.60 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 1-hexene **1** (94 μL, 0.75 mmol, 2.50 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After 1 h the solution became clear and yellow. $AgNTf_2$ (12.8 mg, 0.033 mmol, 0.11 eq) was then added to the Cu-ligand mixture and it was stirred for 10 min and filtered via syringe over 1 min to the hydrozirconation reaction flask. The resulting dark mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone **84** (33 μL, 0.30 mmol, 1.0 eq) was added dropwise via syringe. Stirring at room temperature was continued for 12 h before the reaction was quenched by the addition of Et_2O (*ca* 4 mL) and then NH_4Cl (1 M aq., *ca* 2 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 12 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 12 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Flash column chromatography of the yellow residue (1:9, EtOAc/petrol; SiO_2) gave (+)-(*R*)-3-hexyl-3-methylcyclohexanone **92** (38 mg, 0.29 mmol, 95%) as a colourless oil. Enantiomeric excess (96% *ee*) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 2.25 (t, *J* = 6.8 Hz, 2 H), 2.16 (d, *J* = 13.4 Hz, 1 H), 2.08 (d, *J* = 13.4 Hz, 1 H), 1.90 – 1.76 (m, 2 H), 1.61 (dt, *J* = 13.1, 6.4 Hz, 1 H), 1.56 – 1.46 (m, 1 H), 1.34 – 1.15 (m, 10 H), 0.87 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.6, 54.0, 41.7, 41.2, 38.7, 35.9, 31.9, 30.1, 25.2, 23.4, 22.8, 22.3, 14.2.

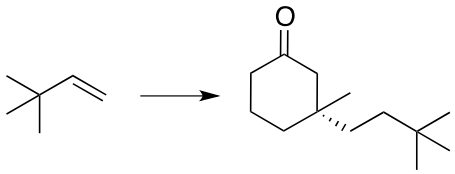
HRMS (ESI) *m*/*z* calcd for $C_{13}H_{24}NaO$ $[M+Na]^+$: 219.1719, found: 219.1715.

IR (ATR) ν (cm^{-1}): 1459, 1712, 2856, 2928.

[α]$^{20}_{589}$ = -2.42 (*c* 0.66, $CHCl_3$). Lit. [α]$^{20}_{589}$ = -1.63 (*c* 1.00, $CHCl_3$) for 50% *ee*]

Absolute configuration assignment by comparison with literature.[224]

(–)-(*S*)-3-(3,3-Dimethylbutyl)-3-methylcyclohexanone (93)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite **BU** (21.6 mg, 0.040 mmol, 0.10 eq) were dissolved in *t*-BuOMe (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. $AgNTf_2$ (23.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 min. In another flask, Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 3,3-dimethyl-1-butene **19** (0.13 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.80 mL) under an argon atmosphere and heated at 40°C for 1 h before being cooled to room temperature once the hydrozirconation was complete (clear yellow solution). The stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the clear yellow solution. The resulting black mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone **84** (45 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) afforded (–)-(*S*)-3-(3,3-dimethylbutyl)-3-methylcyclohexanone **93** (38.9 mg, 0.20 mmol, 50%) as a colourless oil.

Enantiomeric excess (86% *ee*) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

Absolute configuration assigned by analogy to compound **87**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 2.28 (t, *J* = 6.8 Hz, 2 H), 2.06 - 2.22 (m, 2 H), 1.85 (dt, *J* = 13.0, 6.5 Hz, 2 H), 1.59 - 1.67 (m, 1 H), 1.48 - 1.57 (m, 1 H), 1.19 (d, *J* = 3.7 Hz, 2 H), 1.06 - 1.16 (m, 2 H), 0.90 (s, 3 H), 0.86 (s, 9 H).

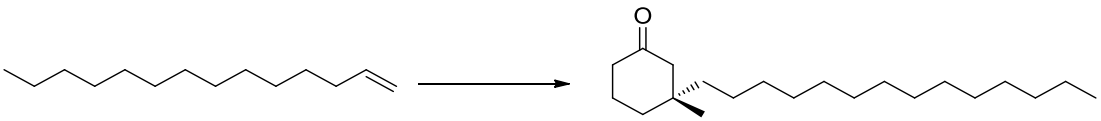
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.5, 54.0, 41.1, 38.3, 37.0, 35.7, 35.6, 30.0, 29.3 (3 C), 25.0, 22.1.

HRMS (ESI) *m*/*z* calcd for $C_{13}H_{24}NaO$ $[M+Na]^+$: 219.1719, found: 219.1713.

[α]$^{20}_{589}$ = −3.43 (*c* 0.81, $CHCl_3$).

IR (ATR) ν (cm^{-1}): 1364, 1467, 1713, 2952.

(–)-(*R*)-3-Methyl-3-tetradecylcyclohexanone (94)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand **BU** (21.6 mg, 0.040 mmol, 0.10 eq) were dissolved in *t*-BuOMe (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. $AgNTf_2$ (17.2 mg, 0.060 mmol, 0.11 eq) was added and the suspension was stirred for another 15 min. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 1-tetradecene **17** (0.25 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the clear yellow solution. The resulting black mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone **84** (45 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:19 EtOAc/petrol; SiO_2) gave (–)-(*R*)-3-methyl-3-tetradecylcyclohexanone **94** (83 mg, 0.27 mmol, 67%) as a colourless oil.

Enantiomeric excess (94% *ee*) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

Absolute configuration assigned by analogy to compound **87**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 2.26 (t, *J* = 6.6 Hz, 2 H), 2.18 (d, *J* = 13.5 Hz, 1 H), 2.09 (d, *J* = 13.5 Hz, 1 H), 1.85 (quin, *J* = 6.6 Hz, 2 H), 1.62 (dt, *J* = 13.5, 6.6 Hz, 1 H), 1.52 (dt, *J* = 13.5, 6.6 Hz, 1 H), 1.19 - 1.31 (m, 26 H), 0.90 (s, 3 H), 0.87 (t, *J* = 6.6 Hz, 3 H).

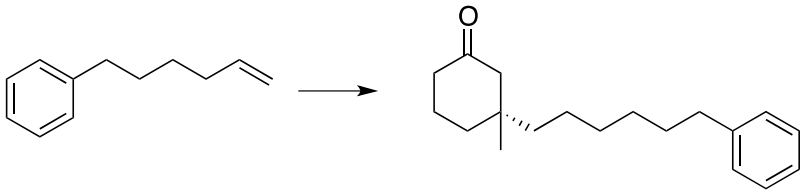
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.4, 53.8, 41.6, 41.0, 38.6, 35.8, 31.9, 30.3, 29.48 - 29.79 (br. m, 7 C), 29.3, 25.1, 23.3, 22.7, 22.1, 14.1.

HRMS (ESI) *m*/*z* calcd for $C_{21}H_{40}NaO$ $[M+Na]^+$: 331.2971, found: 331.2974.

$[\alpha]^{20}_{589}$ = −0.74 (*c* 1.00, $CHCl_3$).

IR (ATR) ν (cm^{-1}): 776, 1217, 1228, 1367, 1456, 1739, 2852, 2923.

(–)-(*R*)-3-Methyl-3-(4-phenylhexyl)cyclohexanone (95)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand **BU** (21.6 mg, 0.040 mmol, 0.10 eq) were dissolved in *t*-BuOMe (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. $AgNTf_2$ (23.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 min. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 6-phenyl-1-hexene **14** (0.18 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the clear yellow solution. The resulting black mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone **84** (45 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) gave (–)-(*R*)-3-methyl-3-(4-phenylhexyl)cyclohexanone **95** (70.9 mg, 0.26 mmol, 65%) as a colourless oil.

HPLC analysis indicated an enantiomeric excess of 90% *ee* [Chiralpak® IC; flow: 1 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; major enantiomer (–)-(*R*)-3-methyl-3-(4-phenylhexyl)cyclohexanone t_R = 19.3 min; minor enantiomer (+)-(*S*)-3-methyl-3-(4-phenylhexyl)cyclohexanone, t_R = 20.4 min].

Absolute configuration assigned by analogy to compound **87**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.16 - 7.26 (m, 2 H), 7.03 - 7.14 (m, 3 H), 2.52 (t, *J* = 7.6 Hz, 2 H), 2.19 (t, *J* = 6.5 Hz, 2 H), 2.06 - 2.13 (m, 1 H), 1.98 - 2.04 (m, 1 H), 1.78 (quin, *J* = 6.5 Hz, 2 H), 1.48 - 1.63 (m, 3 H), 1.38 - 1.47 (m, 1 H), 1.09 - 1.32 (m, 8 H), 0.83 (s, 3 H).

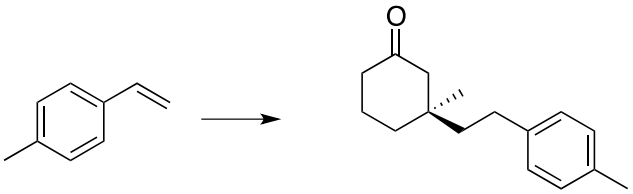
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.5, 142.8, 128.4 (2 C), 128.2 (2 C), 125.6, 53.8, 41.6, 41.0, 38.6, 35.9, 35.8, 31.5, 30.2, 29.2, 25.1, 23.2, 22.1.

HRMS (ESI) *m*/*z* calcd for $C_{19}H_{28}NaO$ $[M+Na]^+$: 295.2032, found: 295.2020.

$[\alpha]^{20}_{589}$ = −11.10 (*c* 0.91, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2929, 2855, 1711, 1495, 1454, 699.

(–)-(*R*)-3-Methyl-3-(4-methylphenylethyl)cyclohexanone (96)



CuCl (1.8 mg, 0.02 mmol, 0.10 eq) and the ligand **BU** (10.8 mg, 0.02 mmol, 0.10 eq) were dissolved in *t*-BuOMe (1.0 mL) and stirred at room temperature for 1 h. In another flask Cp_2ZrHCl (103 mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 1-methyl-4-vinylbenzene **1g** (66 μL, 0.50 mmol, 2.5 eq) in CH_2Cl_2 (0.20 mL) under an argon atmosphere. After 40 min the solution became clear and yellow. $AgNTf_2$ (8.5 mg, 0.022 mmol, 0.11 eq) was then added to the Cu-ligand mixture and it was stirred for 10 min and filtered via syringe over 1 min to the hydrozirconation reaction flask. The resulting dark mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone **84** (23 μL, 0.20 mmol, 1.0 eq) was added dropwise via syringe. Stirring at room temperature was continued for 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) gave (–)-(*R*)-3-methyl-3-(4-methylphenylethyl)cyclohexanone **96** (32 mg, 0.14 mmol, 70%) as a colourless oil. HPLC analysis indicated an enantiomeric excess of 75% *ee* [Chiralpak® IC; flow: 1.0 mL/min; hexane/i-PrOH: 95:5; λ = 210 nm; major enantiomer (–)-(*R*)-3-methyl-3-(4-methylphenylethyl)cyclohexanone, t_R = 12.13 min; minor enantiomer (+)-(*S*)-3-methyl-3-(4-methylphenylethyl)cyclohexanone, t_R = 13.31 min].

Absolute configuration assigned by analogy to compound **87**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.07 (q, *J* = 8.1 Hz, 3 H), 2.60 – 2.48 (m, 1 H), 2.35 – 2.30 (m, 4 H), 2.30 – 2.11 (m, 3 H), 1.99 – 1.81 (m, 2 H), 1.70 (ddd, *J* = 13.1, 8.1, 5.6 Hz, 1 H), 1.63 (tdd, *J* = 6.9, 4.8, 1.4 Hz, 1 H), 1.60 – 1.50 (m, 3 H), 1.01 (s, 3 H).

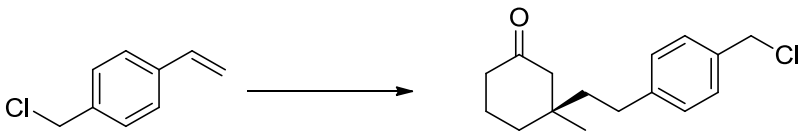
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.2, 139.5, 135.4, 129.2, 128.3, 99.7, 53.8, 44.3, 41.2, 38.9, 36.1, 29.7, 25.1, 22.3, 21.1.

HRMS (ESI) *m*/*z* calcd for $C_{16}H_{22}NaO$ $[M+Na]^+$: 253.1563, found: 253.1557.

IR (ATR) ν (cm^{-1}): 1457, 1515, 1710, 2935.

[α]$^{20}_{589}$ = −7.70 (*c* 0.45, $CHCl_3$).

(–)-(*R*)-3-(4-(Chloromethyl)phenethyl)-3-methylcyclohexanone (98)



CuCl (1.8 mg, 0.02 mmol, 0.10 eq) and the ligand **BI** (10.8 mg, 0.02 mmol, 0.10 eq) were dissolved in *t*-BuOMe (1.0 mL) and stirred at room temperature for 1 h. In another flask Cp_2ZrHCl (155 mg, 0.60 mmol, 3.0 eq) was added to a stirred, room temperature, solution of 1-(chloromethyl)-4-vinylbenzene **97** (99 μL, 0.70 mmol, 3.5 eq) in CH_2Cl_2 (0.20 mL) under an argon atmosphere. After 40 min the solution became clear and yellow. $AgNTf_2$ (8.5 mg, 0.022 mmol, 0.11 eq) was then added to the Cu-ligand mixture and it was stirred for 10 min and filtered via syringe over 1 min to the hydrozirconation reaction flask. The resulting dark mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone **84** (23 μL, 0.20 mmol, 1.0 eq) was added dropwise via syringe. Stirring at room temperature was continued for 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) gave (–)-(*R*)-3-(4-(chloromethyl)phenethyl)-3-methylcyclohexanone **98** (32 mg, 0.14 mmol, 70%) as a colourless oil. HPLC analysis indicated an enantiomeric excess of 70% *ee* [Chiralpak® IC; flow: 1.0 mL/min; hexane/i-PrOH: 90:10; λ = 210 nm; major enantiomer (–)-(*R*)-3-(4-(chloromethyl)phenethyl)-3-methylcyclohexanone, t_R = 19.71 min; minor enantiomer (+)-(*S*)-3-(4-(chloromethyl)phenethyl)-3-methylcyclohexanone, t_R = 20.85 min].

Absolute configuration assigned by analogy to compound **87**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.31 (d, *J* = 8.1 Hz, 2 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 4.58 (s, 2 H), 2.54 - 2.63 (m, 2 H), 2.25 - 2.36 (m, 3 H), 2.15 - 2.23 (m, 1 H), 1.92 (t, *J* = 6.6 Hz, 2 H), 1.68 - 1.77 (m, 1 H), 1.61 - 1.67 (m, 1 H), 1.53 - 1.60 (m, 2 H), 1.03 (s, 3 H).

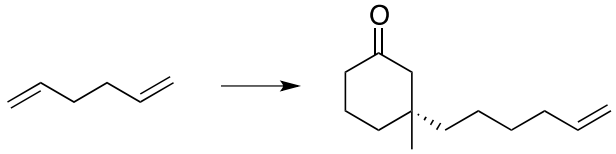
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.6, 142.5, 128.3 (2 C), 128.2 (2 C), 125.6, 51.8, 41.1, 36.4, 35.8, 33.3, 32.1, 29.4, 22.5, 21.7.

HRMS (ESI) *m*/*z* calcd for $C_{16}H_{21}NaO$ $[M+Na]^+$: 287.1173, found: 287.1173.

IR (ν_{max} /cm^{-1}): 838, 1180, 1456, 1597, 2982.

$[\alpha]^{20}_{589}$ = −3.48 (*c* 0.89, $CHCl_3$).

(–)-(*R*)-3-(Hex-5-en-1-yl)-3-methylcyclohexanone (99)



CuCl (1.8 mg, 0.02 mmol, 0.10 eq) and ligand **BU** (10.8 mg, 0.02 mmol, 0.10 eq) were dissolved in *t*-BuOMe (1.0 mL) and stirred at room temperature for 1 h. In another flask Cp_2ZrHCl (103 mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 1,5-hexadiene **25** (238 μL, 2.00 mmol, 10 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After 40 min the solution became clear and yellow. $AgNTf_2$ (8.5 mg, 0.022 mmol, 0.11 eq) was then added to the Cu-ligand mixture and it was stirred for 10 min and filtered via syringe over 1 min to the hydrozirconation reaction flask. The resulting dark mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone **84** (23 μL, 0.20 mmol, 1.0 eq) was added dropwise via syringe. Stirring at room temperature was continued for 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) gave (–)-(*R*)-3-(hex-5-en-1-yl)-3-methylcyclohexanone **99** (29 mg, 0.15 mmol, 75%) as a colourless oil. Enantiomeric excess (78% *ee*) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

Absolute configuration assigned by analogy to compound **87**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 5.79 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1 H), 5.05 – 4.88 (m, 2 H), 2.27 (t, *J* = 7.0 Hz, 2 H), 2.31 – 2.05 (m, 2 H), 2.08 – 1.98 (m, 2 H), 1.85 (qd, *J* = 7.1, 5.4 Hz, 2H), 1.69 – 1.48 (m, 2H), 1.41 – 1.31 (m, 2 H), 1.29 – 1.22 (m, 4 H), 0.91 (s, 3 H).

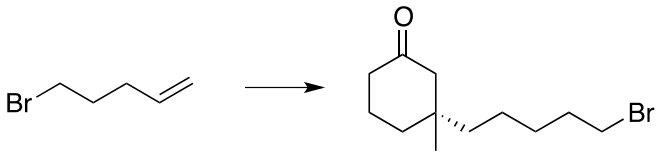
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.6, 139.0, 114.6, 53.9, 41.6, 41.2, 38.8, 35.9, 33.8, 29.6, 25.3, 22.9, 22.3.

HRMS (ESI) *m*/*z* calcd for $C_{13}H_{22}NaO$ $[M+Na]^+$: 217.1563, found: 321.1558.

IR (ATR) ν (cm^{-1}): 1461, 1714, 2855, 2931.

[α]$^{20}_{589}$ = −3.43 (*c* 0.13, $CHCl_3$).

(–)-(*R*)-3-(5-Bromopentyl)-3-methylcyclohexanone (101)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite **BU** (21.6 mg, 0.040 mmol, 0.10 eq) were dissolved in *t*-BuOMe (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. $AgNTf_2$ (23.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 mins. In another flask, Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 5-bromo-1-pentene **35** (0.12 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the clear yellow solution. The resulting black mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone **84** (45 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) (–)-(*R*)-3-(5-bromopentyl)-3-methylcyclohexanone **101** (55.0 mg, 0.21 mmol, 53%) as a colourless oil.

Enantiomeric excess (79% *ee*) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

Absolute configuration assigned by analogy to compound **87**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 3.40 (t, *J* = 6.7 Hz, 2 H), 2.28 (t, *J* = 6.7 Hz, 2 H), 2.14 - 2.21 (m, 1 H), 2.06 - 2.13 (m, 1 H), 1.80 - 1.92 (m, 4 H), 1.58 - 1.69 (m, 1 H), 1.49 - 1.58 (m, 1 H), 1.41 (br. s., 2 H), 1.19 - 1.32 (m, 4 H), 0.92 (s, 3 H).

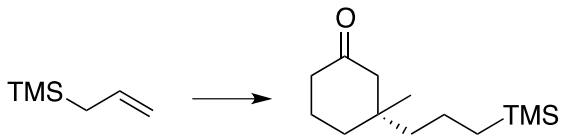
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.3, 53.7, 41.3, 41.0, 38.6, 35.8, 33.8, 32.7, 28.8, 25.0, 22.6, 22.1.

HRMS (ESI) *m*/*z* calcd for $C_{12}H_{21}BrNaO$ $[M+Na]^+$: 283.0668, found: 283.0665.

[α]$^{20}_{589}$ = −2.06 (*c* 0.65, $CHCl_3$).

IR (ATR) ν (cm^{-1}): 2934, 1709, 1461, 1227, 729.

(+)-(*S*)-3-Methyl-3-(3-(trimethylsilyl)propyl)cyclohexanone (103)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and ligand **BU** (21.6 mg, 0.04 mmol, 0.10 eq) were dissolved in *t*-BuOMe (2.0 mL) and stirred at room temperature for 1 h. In another flask Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 1-trimethylsilyl-1-propene **41** (80 μL, 0.50 mmol, 2.50 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After 40 min the solution became clear and yellow. $AgNTf_2$ (17.0 mg, 0.044 mmol, 0.11 eq) was then added to the Cu-ligand mixture and it was stirred for 10 min and filtered via syringe over 1 min to the hydrozirconation reaction flask. The resulting dark mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone **84** (45 μL, 0.40 mmol, 1.0 eq) was added dropwise via syringe. Stirring at room temperature was continued for 12 h before the reaction was quenched by the addition of Et_2O (*ca* 6 mL) and then NH_4Cl (1 M aq., *ca* 3 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 15 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 15 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) gave (+)-(*S*)-3-methyl-3-(3-(trimethylsilyl)propyl)cyclohexanone **103** (37 mg, 0.33 mmol, 82%) as a colourless oil. Enantiomeric excess (97% *ee*) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

Absolute configuration assigned by analogy to compound **87**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 2.27 (t, *J* = 6.9 Hz, 2 H), 2.18 (d, *J* = 13.4 Hz, 1 H), 2.09 (d, *J* = 13.5 Hz, 1H), 1.91 – 1.79 (m, 2 H), 1.68 – 1.58 (m, 1 H), 1.58 – 1.47 (m, 1 H), 1.34 – 1.18 (m, 4 H), 0.90 (s, 3H), 0.50 – 0.39 (m, 2 H), -0.03 (s, 9 H).

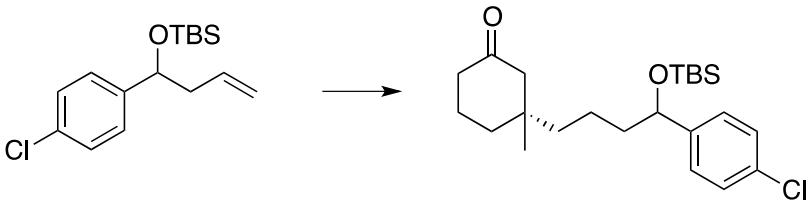
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.6, 54.0, 46.2, 41.2, 39.0, 36.0, 25.1, 22.3, 17.8, 17.5, -1.4 (3C).

HRMS (ESI) *m*/*z* calcd for $C_{13}H_{26}NaOSi$ $[M+Na]^+$: 249.1645, found: 249.1645.

IR (ATR) ν (cm^{-1}): 1247, 1458, 1714, 2926, 2928.

[α]$^{20}_{589}$ = +0.21 (*c* 1.43, $CHCl_3$).

(+)-(3*R*)-3-(4-((*tert*-Butyldimethylsilyl)oxy)-4-(4-chlorophenyl)butyl)-3-methylcyclohexanone (109)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand **BU** (21.6 mg, 0.040 mmol, 0.10 eq) were dissolved in *t*-BuOMe (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. $AgNTf_2$ (23.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 min. In another flask, Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of *tert*-butyl((1-(4-chlorophenyl)but-3-en-1-yl)oxy)dimethylsilane **45** (0.30 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. The stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the clear yellow hydrozirconation solution. The resulting black mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone **84** (45 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) gave (+)-(3*R*)-3-(4-((*tert*-butyldimethylsilyl)oxy)-4-(4-chlorophenyl)butyl)-3-methylcyclohexanone **109** (133.9 mg, 0.32 mmol, 82%) as a colourless oil. Absolute configuration assigned by analogy to compound **87**. HPLC analysis of the alcohol derivative indicated a ~ 1:1 diasteromeric ratio and an enantiomeric excess of 89% *ee* [Chiralpak® IC; flow: 1.0 mL/min;

hexane/i-PrOH: 88:12; λ = 210 nm; major enantiomer (+)-(3*R*)-3-(4-((*tert*-butyldimethylsilyl)oxy)-4-(4-chlorophenyl)butyl)-3-methylcyclohexanone, t_R = 16.7 min & 20.9 min; minor enantiomer (—)-(3*S*)-3-(4-((*tert*-btyldimethylsilyl)oxy)-4-(4-chlorophenyl)-butyl)-3-methylcyclohexanone, t_R = 19.5 min & 22.5 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.22 - 7.27 (m, 2 H), 7.15 - 7.21 (m, 2 H), 4.58 (ddd, *J* = 7.4, 4.6, 2.7 Hz, 1 H), 2.20 - 2.28 (m, 2 H), 2.03 - 2.16 (m, 2 H), 1.75 - 1.88 (m, 2 H), 1.44 - 1.67 (m, 4 H), 1.12 - 1.37 (m, 4 H), 0.86 (s, 3 H), 0.86 (s, 9 H), 0.00 (s, 3 H), -0.17 (d, *J* = 1.2 Hz, 3 H).

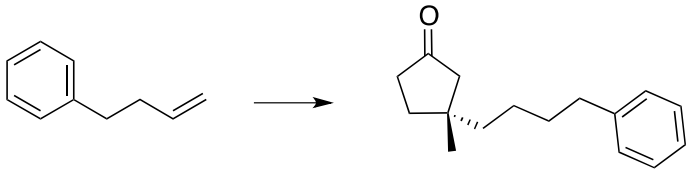
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.2, 144.2, 132.3, 128.2 (2 C), 127.1 (2 C), 74.2, 53.7, 41.7, 41.4, 41.0, 38.6, 35.8, 25.8 (3 C), 24.8, 22.1, 19.4, 18.1, -4.6, -5.0.

HRMS (ESI) *m*/*z* calcd for $C_{23}H_{37}ClNaO_2Si$ $[M+Na]^+$: 431.2144, found: 431.2144.

[α]$^{20}_{589}$ = +0.51 (*c* 1.22, $CHCl_3$).

IR (ATR) ν (cm^{-1}): 776, 836, 1088, 1252, 1713, 2857, 2932.

(–)-(*R*)-3-Methyl-3-(4-phenylbutyl)cyclopentanone (111)



CuCl (1.8 mg, 0.02 mmol, 0.10 eq) and phosphoramidite ligand **BU** (18.8 mg, 0.020 mmol, 0.10 eq) were dissolved in t-BuOMe (1.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. $AgNTf_2$ (8.5 mg, 0.022 mmol, 0.11 eq) was added and the suspension was stirred for another 15 min. In another flask, Cp_2ZrHCl (309.0 mg, 1.60 mmol, 3.0 eq) was added to a stirred, room temperature, solution of hex-4-en-1-ylbenzene **6** (0.3 mL, 2.0 mmol, 5.0 eq) in CH_2Cl_2 (0.80 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the clear yellow solution. The resulting black mixture was cooled with an ice bath allowed to stir for an additional 20 min before 3-methyl-2-cyclopentanone **110** (20 µL, 0.20 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h leaving the ice melts so the reaction mixture slowly warmed up . The reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) gave (–)-(*R*)-3-methyl-3-(4-

phenylbutyl)cyclopentanone **111** (25.8 mg, 0.11 mmol, 56%) as a colourless oil. Absolute configuration assigned by analogy to compound **87**.

HPLC analysis indicated an enantiomeric excess of 65% *ee* [Chiralpak® AY-H; flow: 1 mL/min; hexane/i-PrOH: 95:5; λ = 210 nm; major enantiomer (+)-(*R*)-3-methyl-3-(4-phenylhexyl)cyclopentanone, t_R = 9.50 min; minor enantiomer (–)-(*S*)-3-methyl-3-(4-phenylhexyl)cyclopentanone, t_R = 8.60 min].

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.25 - 7.33 (m, 2 H), 7.13 - 7.22 (m, 3 H), 2.64 (t, *J* = 7.6 Hz, 2 H), 2.26 - 2.32 (m, 2 H), 2.05 - 2.12 (m, 1 H), 1.98 - 2.05 (m, 1 H), 1.73 - 1.85 (m, 2 H), 1.64 (dt, *J* = 15.1, 7.4 Hz, 2 H), 1.26 - 1.47 (m, 4 H), 1.05 (s, 3 H).

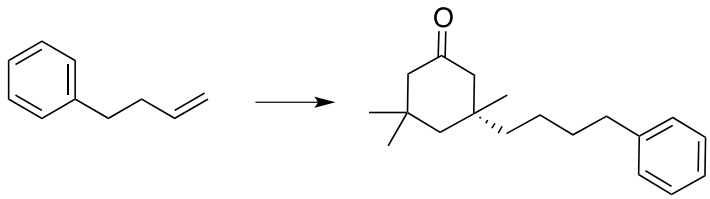
^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 220.2, 142.5, 128.3 (2 C), 128.3 (2 C), 125.7, 52.2, 41.6, 39.5, 36.8, 35.8, 35.2, 32.1, 25.0, 24.4.

HRMS (ESI) *m*/*z* calcd for $C_{16}H_{22}NaO$ $[M+Na]^+$: 253.1563, found: 253.1562.

[α]$^{20}_{589}$ = +22.64 (*c* 0.53, $CHCl_3$).

IR (ATR) ν (cm^{-1}): 2930, 1711, 1496, 1454, 699.

(+)-(*R*)-3,3,5-Trimethyl-5-(4-phenylbutyl)cyclohexanone (113)



CuCl (3.1 mg, 0.030 mmol, 0.10 eq) and the phosphoramidite **BU** (17.3 mg, 0.030 mmol, 0.10 eq) were dissolved in *t*-BuOMe (1.5 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. $AgNTf_2$ (13.4 mg, 0.035 mmol, 0.11 eq) was added and the suspension was stirred for another 15 min. In another flask, Cp_2ZrHCl (161.9 mg, 0.63 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene **6** (0.12 mL, 0.78 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 1 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the clear yellow solution. The resulting black mixture was allowed to stir for an additional 10 min before isophorone **112** (47 µL, 0.31 mmol, 1.0 eq) and TMSCl (0.19 mL, 1.5 mmol) was added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column

chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) gave (+)-(*R*)-3,3,5-trimethyl-5-(4-phenylbutyl)cyclohexanone **112** (29 mg, 0.11 mmol, 34%) as a yellow oil.

HPLC analysis indicated an enantiomeric excess of 73% *ee* [Chiralpak® AY-H; flow: 1 mL/min; hexane/i-PrOH: 95:5; λ = 210 nm; major enantiomer (+)-(*R*)-3,3,5-trimethyl-5-(4-phenylbutyl)cyclohexanone, t_R = 6.8 min; minor enantiomer (–)-(*S*)-3,3,5-trimethyl-5-(4-phenylbutyl)cyclohexanone, t_R = 8.0 min].

Absolute configuration assigned by analogy to compound **87**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.17 - 7.26 (m, 2 H), 7.06 - 7.14 (m, 3 H), 2.54 (t, *J* = 7.6 Hz, 2 H), 2.07 - 2.16 (m, 3 H), 2.05 (m, *J* = 0.7 Hz, 1 H), 1.39 - 1.59 (m, 4 H), 1.14 - 1.35 (m, 4 H), 0.96 (s, 6 H), 0.92 (s, 3 H).

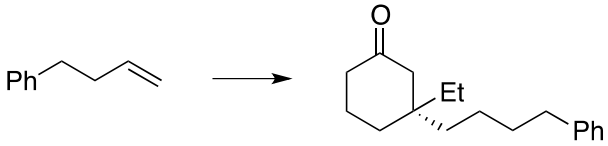
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.6, 142.5, 128.3 (2 C), 128.3 (2 C), 125.7, 54.3, 53.1, 49.0, 44.6, 38.8, 36.1, 35.9, 32.2, 32.1, 30.6, 27.4, 23.0.

HRMS (ESI) *m*/*z* calcd for $C_{19}H_{28}NaO$ $[M+Na]^+$: 295.2032, found: 295.2025.

[α]$^{20}_{589}$ = +4.30 (*c* 1.15, $CHCl_3$).

IR (ATR) ν (cm^{-1}): 2951, 1712, 1667, 1496, 1279, 903, 747, 699,

(+)-(*R*)-3-Ethyl-3-(4-phenylbutyl)cyclohexanone (115)



CuCl (1.8 mg, 0.02 mmol, 0.10 eq) and ligand **BU** (10.8 mg, 0.02 mmol, 0.10 eq) were dissolved in *t*-BuOMe (1mL) and stirred at room temperature for 1 h. In another flask Cp_2ZrHCl (103 mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene **6** (75 μL, 0.50 mmol, 2.50 eq) in CH_2Cl_2 (0.20 mL) under an argon atmosphere. After 40 min the solution became clear and yellow. $AgNTf_2$ (8.5 mg, 0.022 mmol, 0.11 eq) was then added to the Cu-ligand mixture and it was stirred for 10 min and filtered via syringe over 1 min to the hydrozirconation reaction flask. The resulting dark mixture was allowed to stir for an additional 10 min before 3-ethyl-2-cyclohexenone **84** (22 μL, 0.17 mmol, 0.85 eq) was added dropwise via syringe. Stirring at room temperature was continued for 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo.

Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) gave (+)-(*R*)-3-ethyl-3-(4-phenylbutyl)cyclohexanone **115** (25 mg, 0.09 mmol, 58%) as a colourless oil.

HPLC indicated an enantiomeric excess of 92% *ee* [Chiralpak® ID; flow: 1 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; major enantiomer (+)-(*R*)-3-ethyl-3-(4-phenylbutyl)cyclohexanone, t_R = 9.72 min; minor enantiomer (–)-(*S*)-3-ethyl-3-(4-phenylbutyl)cyclohexanone, t_R = 9.44 min].

Absolute configuration assigned by analogy to compound **87**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.24 - 7.35 (m, 2 H), 7.12 - 7.23 (m, 3 H), 2.62 (t, *J* = 7.8 Hz, 2 H), 2.28 (t, *J* = 6.7 Hz, 2 H), 2.13 - 2.21 (m, 2 H), 1.78 - 1.89 (m, 1 H), 1.49 - 1.67 (m, 4 H), 1.16 - 1.37 (m, 6 H), 0.76 (t, *J* = 7.6 Hz, 3 H).

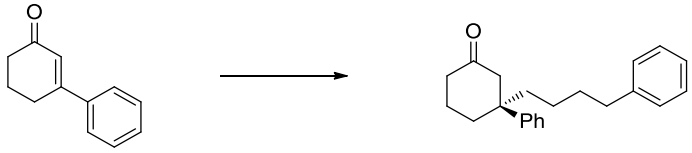
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 212.9, 142.8, 128.6 (3 C), 125.9 (2 C), 52.1, 41.3, 41.1, 36.6, 36.1, 33.6, 32.3, 29.7, 22.7, 21.9, 7.6.

HRMS (ESI) *m*/*z* calcd for $C_{18}H_{26}NaO$ $[M+Na]^+$: 281.1876, found : 281.1875.

[α]$^{20}_{589}$ = +2.40 (*c* 0.50, $CHCl_3$).

IR (ATR) ν (cm^{-1}): 1496, 1604, 1713, 2925, 3025.

(+)-(*S*)-3-phenyl-3-(4-phenylbutyl)cyclohexanone (117)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and ligand **BU** (21.6 mg, 0.04 mmol, 0.10 eq) were dissolved in *t*-BuOMe (2.0mL) and stirred at room temperature for 1 h. In another flask Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene **6** (0.15 mL, 0.50 mmol, 2.50 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After 40 min the solution became clear and yellow. $AgNTf_2$ (17.0 mg, 0.044 mmol, 0.11 eq) was then added to the Cu-ligand mixture and it was stirred for 10 min and filtered via syringe over 1 min to the hydrozirconation reaction flask. The resulting dark mixture was allowed to stir for an additional 10 min before 3-phenyl-2-cyclohexenone **116** (69 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Stirring at room temperature was continued for 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and

concentrated in vacuo. Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) gave (+)-(*S*)-3-phenyl-3-(4-phenylbutyl)cyclohexanone **117** (28 mg, 0.09 mmol, 23%) as a colourless oil.

HPLC indicated an enantiomeric excess of 10% *ee* [Chiralpak® AY-H; flow: 1 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; major enantiomer (+)-(*S*)-3-phenyl-3-(4-phenylbutyl)cyclohexanone, t_R = 7.91 min; minor enantiomer (–)-(*R*)-3-phenyl-3-(4-phenylbutyl)cyclohexanone, t_R = 10.01 min].

Absolute configuration assigned by analogy to compound **87**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.21 - 7.31 (m, 2 H), 7.12 - 7.20 (m, 5 H), 7.04 - 7.10 (m, 1 H), 6.93 - 7.02 (m, 2 H), 2.83 (d, *J* = 14.1 Hz, 1 H), 2.31 - 2.47 (m, 3 H), 2.16 - 2.26 (m, 2 H), 2.03 - 2.15 (m, 1 H), 1.90 (ddd, *J* = 14.1, 10.1, 3.4 Hz, 1 H), 1.69 - 1.80 (m, 1 H), 1.65 (dd, *J* = 12.3, 4.5 Hz, 1 H), 1.54 - 1.60 (m, 1 H), 1.46 - 1.54 (m, 1 H), 1.33 - 1.45 (m, 2 H), 0.99 - 1.13 (m, 1 H), 0.77 - 0.94 (m, 1 H).

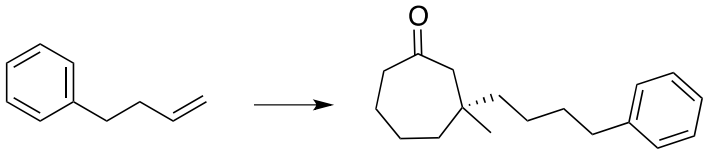
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 211.4, 145.1, 142.4, 128.4 (2 C), 128.2 (2 C), 128.2 (2 C), 126.4 (2 C), 126.1, 125.6, 51.1, 46.1, 43.0, 41.0, 36.5, 35.6, 31.8, 23.1, 21.5.

HRMS (ESI) *m*/*z* calcd for $C_{22}H_{26}NaO$ $[M+Na]^+$: 329.1876, found : 329.1867.

$[\alpha]^{20}_{589}$ = +0.07 (*c* 0.17, $CHCl_3$).

IR (ATR) ν (cm^{-1}): 1496, 1604, 1713, 2925, 3025.

(+)-(*R*)-3-Methyl-3-(4-phenylbutyl)cycloheptanone (119)



CuCl (3.1 mg, 0.030 mmol, 0.10 eq) and the phosphoramidite ligand **BU** (17.3 mg, 0.030 mmol, 0.10 eq) were dissolved in CH_2Cl_2 (1.5 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. $AgNTf_2$ (13.4 mg, 0.035 mmol, 0.11 eq) was added and the suspension was stirred for another 15 min. In another flask, Cp_2ZrHCl (161.9 mg, 0.63 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene **6** (0.12 mL, 0.78 mmol, 2.5 eq) in CH_2Cl_2 (0.31 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the clear yellow solution. The resulting black mixture was allowed to stir for an additional 10 min before 3-methyl-2-cycloheptenone **118** (41 µL, 0.31 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring

continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:9 EtOAc/petrol; SiO_2) gave (+)-(*R*)-3-methyl-3-(4-phenylbutyl)cycloheptanone **119** (41 mg, 0.16 mmol, 51%) as a colourless oil.

HPLC indicated an enantiomeric excess of 82% *ee* [Chiralpak® IC; flow: 1 mL/min; hexane/i-PrOH: 95:5; λ = 210 nm; major enantiomer (+)-(*R*)-3-methyl-3-(4-phenylbutyl)cycloheptanone, t_R = 10.7 min; minor enantiomer (–)-(*S*)-3-methyl-3-(4-phenylbutyl)cycloheptanone, t_R = 11.7 min].

Absolute configuration assigned by analogy to compound **87**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.16 - 7.26 (m, 2 H), 7.04 - 7.13 (m, 3 H), 2.54 (t, *J* = 7.6 Hz, 2 H), 2.45 (d, *J* = 12.0 Hz, 1 H), 2.25 - 2.36 (m, 3 H), 1.64 - 1.75 (m, 2 H), 1.37 - 1.63 (m, 6 H), 1.10 - 1.34 (m, 4 H), 0.81 (s, 3 H).

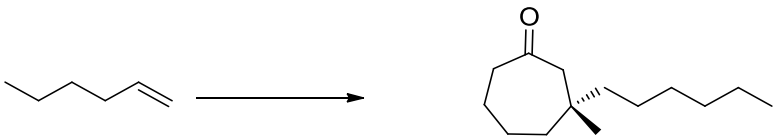
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 214.2, 142.6, 128.3 (2 C), 128.2 (2 C), 125.6, 54.7, 43.9, 42.6, 42.4, 35.9, 35.2, 32.1, 25.9, 24.6, 24.1, 23.1.

HRMS (ESI) *m*/*z* calcd for $C_{18}H_{26}NaO$ $[M+Na]^+$: 281.1876, found: 281.1876.

[α]$^{20}_{589}$ = +4.83 (*c* 0.63, $CHCl_3$).

IR (ATR) ν (cm^{-1}): 699, 1454, 1713, 2360, 3026.

(–)-(*R*)-3-Hexyl-3-methylcycloheptanone (120)



CuCl (3.1 mg, 0.030 mmol, 0.10 eq) and the phosphoramidite **BU** 17.3 mg, 0.030 mmol, 0.10 eq) were dissolved *t*-BuOMe (1.5 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. $AgNTf_2$ (13.4 mg, 0.035 mmol, 0.11 eq) was added and the suspension was stirred for another 15 min. In another flask, Cp_2ZrHCl (161.9 mg, 0.63 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 1-Hexene **1** (0.10 mL, 0.78 mmol, 2.5 eq) in CH_2Cl_2 (0.31 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the clear yellow solution. The resulting black mixture was allowed to stir for an additional 10 min before 3-methyl-2-cycloheptenone **118** (41 µL, 0.31 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The

mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:19 EtOAc/petrol; SiO_2) gave (–)-(*R*)-3-hexyl-3-methylcycloheptanone **120** (45 mg, 0.21 mmol, 70%) as a colourless oil. Absolute configuration assigned by analogy to compound **87**.

Enantiomeric excess (90% *ee*) was determined by HPLC analysis of the corresponding enone. The enone was obtained using a modified procedure from Stahl and coworkers.[12] A flask containing $Pd(TFA)_2$ (18.9mg, 0.057 mmol, 1 eq) and the ketone (12 mg, 0.057 mmol, 1 eq) was flashed with oxygen (balloon, 1 atm). DMSO (8 µL, 0.11 mmol, 2 eq) and toluene (0.5 mL) were added and the suspension was warmed at 80°C for 12 hours. After cooling down, the mixture was concentrated in *vacuo* and purified by flash column chromatography (1:19 EtOAc/petrol; SiO_2) to give the desired enone that was directly analysed by HPLC.

HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® IC; flow: 1 mL/min; hexane/i-PrOH: 95:5; λ = 225 nm; major enantiomer (–)-(*R*)-3-methyl-3-(4-phenylhexyl)cyclohexanone t_R = 20.2 min; minor enantiomer (+)-(*S*)-3-methyl-3-(4-phenylhexyl)cyclohexanone, t_R = 21.4 min]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 2.45 (d, *J* = 12.0 Hz, 1 H), 2.26 - 2.38 (m, 3 H), 1.64 - 1.77 (m, 2 H), 1.49 - 1.63 (m, 3 H), 1.37 - 1.47 (m, 1 H), 1.08 - 1.29 (m, 10 H), 0.78 - 0.86 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 214.3, 54.8, 43.9, 42.5 (2 C), 35.2, 31.8, 30.0, 26.0, 24.7, 24.2, 23.4, 22.6, 14.1.

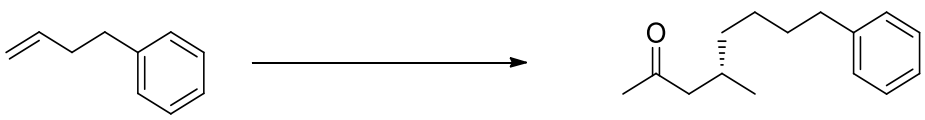
HRMS (ESI) *m/z* calcd for $C_{14}H_{26}NaO$ $[M+Na]^+$: 233.1876, found: 233.1876.

[α]$^{20}_{589}$ = -0.60 (*c* 0.95, $CHCl_3$).

IR (ATR) ν (cm^{-1}): 699, 1229, 1368, 1455, 1730, 2929.

Catalytic asymmetric 1,4-addition of alkenes to synthesise acyclic tertiary ketones

(–)-(*S*)-4-methyl-8-phenyloctan-2-one (122)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of pent-4-en-1-ylbenzene **6** (0.15 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-pent-3-en-2-one **121** (39 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 60 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:33 EtOAc/petrol; SiO_2) gave (−)-(*S*)-4-methyl-8-phenyloctan-2-one **122** (82.0 mg, 0.37 mmol, 94%) as a colourless oil.

HPLC analysis indicated an enantiomeric excess of 91% *ee* [Chiralpak® AY-H; 0.6 mL/min; hexane/i-PrOH: 99.4: 0.6; λ = 210 nm; minor enantiomer (+)-(*R*)-4-methyl-8-phenyloctan-2-one, t_R = 18.6 min; major enantiomer (−)-(*S*)-4-methyl-8-phenyloctan-2-one, t_R = 22.8 min].

Absolute configuration was attributed by analogy with (−)-(*S*)-4-methyldecan-2-one **127**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.17 - 7.33 (m, 2 H), 6.98 - 7.14 (m, 3 H), 2.47 - 2.63 (m, 2 H), 2.22 - 2.39 (m, 1 H), 2.08 - 2.20 (m, 1 H), 2.04 (s, 3 H), 1.91 (dd, *J* = 12.8, 6.6 Hz, 1 H), 1.46 - 1.58 (m, 2 H), 1.17 - 1.37 (m, 3 H), 1.05 - 1.16 (m, 1 H), 0.81 (d, *J* = 6.6 Hz, 3 H).

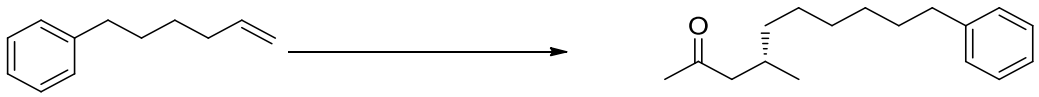
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 209.1, 142.7, 128.4 (2 C), 128.2 (2 C), 125.6, 51.2, 36.7, 35.9, 31.5, 30.5, 29.2, 26.6, 19.8.

HRMS (EI) m/z calcd for $C_{15}H_{22}NaO$ $[M+Na]^+$: 241.1563, found: 241.1565.

$[\alpha]_{20}^{589}$ = –5.77 (c 0.26, $CHCl_3$).

IR (νmax /cm-1): 2930, 1716, 1496, 747, 699.

(−)-(*S*)-4-methyl-10-phenyldecan-2-one (124)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of hex-5-en-1-ylbenzene **14** (0.18 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere.

After stirring for 25 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-pent-3-en-2-one **121** (39 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 90 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:34 EtOAc/petrol; SiO_2) gave (−)-(S)-4-methyl-10-phenyldecan-2-one **124** (72.5 mg, 0.29 mmol, 73% yield) as a colourless oil.

HPLC analysis indicated an enantiomeric excess of 91% *ee* [Chiralpak® AY-H; 1.0 mL/min; hexane/*i*-PrOH: 98: 2 ; λ = 210 nm; minor enantiomer (+)-(*R*)-4-methyl-10-phenyldecan-2-one, t_R = 6.4 min; major enantiomer (−)-(*S*)-4-methyl-10-phenyldecan-2-one, t_R = 7.2 min].

Absolute configuration was attributed by analogy with (−)-(*S*)-4-methyldecan-2-one **127**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.15 - 7.27 (m, 2 H), 7.02 - 7.13 (m, 3 H), 2.44 - 2.66 (m, 2 H), 2.26 - 2.38 (m, 1 H), 2.08 - 2.18 (m, 1 H), 1.98 - 2.06 (m, 3 H), 1.80 - 1.95 (m, 1 H), 1.53 (quin, *J* = 7.5 Hz, 2 H), 1.12 - 1.32 (m, 7 H), 1.00 - 1.11 (m, 1 H), 0.80 (d, *J* = 6.6 Hz, 3 H).

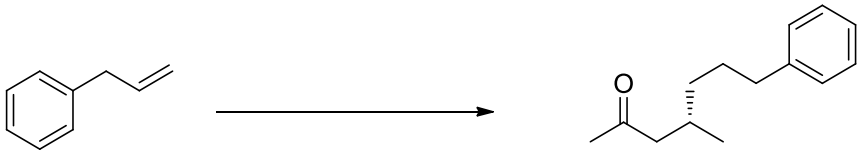
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 209.1, 142.8, 128.3 (2 C), 128.2 (2 C), 125.5, 51.2, 36.8, 35.9, 31.4, 30.4, 29.6, 29.24, 29.19, 26.8, 19.8.

HRMS (EI) m/z calcd for $C_{17}H_{27}O$ $[M+H]^+$: 247.20564, found: 247.20584.

$[\alpha]_{20}^{589}$ = –3.9 (c 2.10, $CHCl_3$).

IR (νmax /cm-1): 2931, 1716, 1459, 749, 699.

(−)-(*S*)-4-methyl-7-phenylheptan-2-one (126)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of allylbenzene **125** (0.13 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 35 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-pent-3-en-2-one **121** (39 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 90 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:34 EtOAc/petrol; SiO_2) gave (−)-(S)-4-methyl-7-phenylheptan-2-one **126** (63.4 mg, 0.31 mmol, 76% yield) as a colourless oil.

HPLC analysis indicated an enantiomeric excess of 91% *ee* [Chiralpak® IC; 1.3 mL/min; hexane/i-PrOH: 99.3: 0.7 ; λ = 210 nm; major enantiomer (−)-(*S*)-4-methyl-7-phenylheptan-2-one, t_R = 11.8 min; minor enantiomer (+)-(*R*)-4-methyl-7-phenylheptan-2-one, t_R = 12.5 min].

Absolute configuration was attributed by analogy with (−)-(*S*)-4-methyldecan-2-one **127**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.17 - 7.26 (m, 2 H), 7.04 - 7.14 (m, 3 H), 2.43 - 2.59 (m, 2 H), 2.27 - 2.42 (m, 1 H), 2.09 - 2.21 (m, 1 H), 2.00 - 2.08 (m, 3 H), 1.87 - 2.00 (m, 1 H), 1.46 - 1.63 (m, 2 H), 1.21 - 1.35 (m, 1 H), 1.06 - 1.19 (m, 1 H), 0.82 (d, *J* = 6.6 Hz, 3 H).

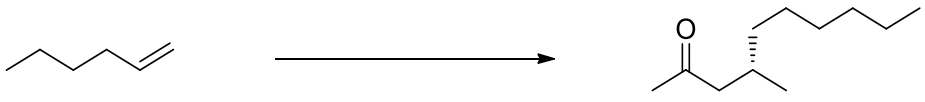
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 205.7, 142.5, 128.3 (2 C), 128.3 (2 C), 125.2, 51.2, 36.5, 36.0, 30.4, 29.1, 28.9, 19.7.

HRMS (EI) m/z calcd for $C_{14}H_{20}NaO$ $[M+Na]^+$: 227.1406, found: 227.1401.

$[\alpha]_{20}^{589}$ = –21.24 (c 1.52, $CHCl_3$).

IR (νmax /cm-1): 2930, 1716, 1454, 749, 699.

(−)-(*S*)-4-methyldecan-2-one (127)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of hex-1-ene **1** (0.12 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 45 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-pent-3-en-2-one **121** (39 μL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 90 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:49 EtOAc/petrol; SiO_2) gave (−)-(*S*)-4-methyldecan-2-one **127** (62.5 mg, 0.36 mmol, 90%) as a colourless oil.

GC analysis indicated an enantiomeric excess of 91% [Macherey & Nagel, Hydrodex® β-3P; 60-0-2-110-1-140; λ = 210 nm; major enantiomer (−)-(*S*)-4-methyldecan-2-one, t_R = 32.9 min; minor enantiomer (+)-(*R*)-4-methyldecan-2-one, t_R = 33.5 min].

Absolute configuration was attributed by analogy with published literature of (−)-(*S*)-4-methyldecan-2-one **127**. The analytical data are in agreement with the literature.[236]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 2.40 (dd, *J* = 16.0, 5.6 Hz, 1 H), 2.21 (dd, *J* = 16.0, 8.6 Hz, 1 H), 2.12 (s, 3 H), 1.90 - 2.04 (m, 1 H), 1.20 - 1.37 (m, 9 H), 1.05 - 1.20 (m, 1 H), 0.84 - 0.91 (m, 6 H).

^{13}C NMR (100 MHz, $_{CDCl3}$) δ_C /ppm 209.2, 51.3, 36.9, 31.8, 30.4, 29.4, 29.3, 26.9, 22.6, 19.8, 14.1.

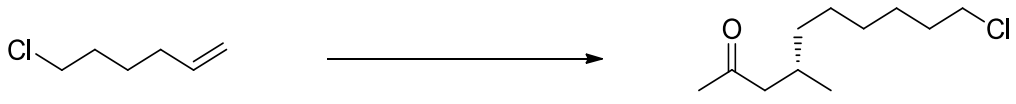
HRMS (EI) m/z calcd for $C_{11}H_{20}NaO$ $[M+Na]^+$: 227.1406, found: 227.1401.

$[\alpha]_{20}^{589}$ = –20.96 (c 1.52, $CHCl_3$).

IR (νmax /cm-1): 2930, 1716, 1454, 1336, 1217, 749, 699

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(−)-(*S*)-10-chloro-4-methyldecan-2-one (129)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 6-chlorohex-1-ene **128** (0.13 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 30 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-pent-3-en-2-one **121** (39 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 90 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:33 EtOAc/petrol; SiO_2) gave (−)-(S)-10-chloro-4-methyldecan-2-one **129** (48.1 mg, 0.23 mmol, 58%) as a colourless oil.

GC analysis indicated an enantiomeric excess of roughly 89% *ee* [Macherey & Nagel, Hydrodex® β-3P; 65-0-1-150-5-3-170; λ = 210 nm; major enantiomer (−)-(*S*)-10-chloro-4-methyldecan-2-one, t_R = 106.3 min; minor enantiomer (+)-(*R*)-10-chloro-4-methyldecan-2-one, t_R = 106.6 min].

Absolute configuration was attributed by analogy with (−)-(*S*)-4-methyldecan-2-one **127**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 3.52 (t, *J* = 6.7 Hz, 2 H), 2.35 - 2.50 (m, 1 H), 2.18 - 2.27 (m, 1 H), 2.12 (s, 3 H), 1.97 (dd, *J* = 12.2, 6.3 Hz, 1 H), 1.70 - 1.81 (m, 2 H), 1.36 - 1.49 (m, 2 H), 1.21 - 1.35 (m, 5 H), 1.15 (dd, *J* = 7.0, 2.4 Hz, 1 H), 0.88 (d, *J* = 6.7 Hz, 3 H).

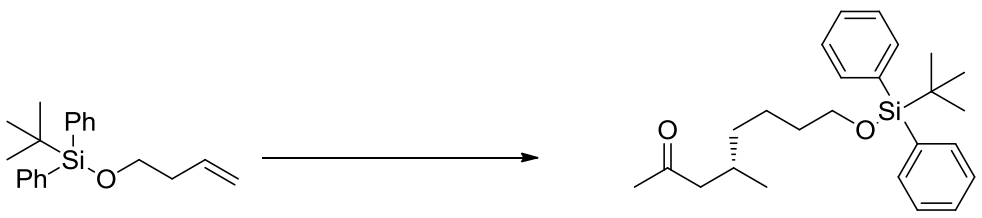
^{13}C NMR (100 MHz, $_{CDCl3}$) δ_C /ppm 209.1, 51.2, 45.1, 36.7, 32.5, 30.4, 29.1, 28.9, 26.8, 26.7, 19.7.

HRMS (EI) m/z calcd for $C_{11}H_{22}OCl$ $[M+H]^+$: 205.13537, found: 205.13516.

$[\alpha]_{20}^{589}$ = –3.43 (c 1.40, $CHCl_3$).

IR (νmax /cm-1): 2929, 1716, 1449, 1217, 750, 699

(−)-(*S*)-8-((tert-butyldiphenylsilyl)oxy)-4-methyloctan-2-one (130)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of (but-3-en-1-yloxy)(tert-butyl)diphenylsilane **104** (314 mg, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 45 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-pent-3-en-2-one **121** (39 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 90 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:49 EtOAc/petrol; SiO_2) gave (−)-(*S*)-8-((*tert*-butyldiphenylsilyl)oxy)-4-methyloctan-2-one **130** (77.5 mg, 0.19 mmol, 49% yield) as a colourless oil.

HPLC analysis indicated an enantiomeric excess of 91% *ee* [Chiralpak® IB; 1.0 mL/min; hexane/i-PrOH: 99.4: 0.6 ; λ = 210 nm; minor enantiomer (+)-(*R*)-8-((*tert*-butyldiphenylsilyl)oxy)-4-methyloctan-2-one t_R = 5.8 min; major enantiomer (−)-(*S*)-8-((*tert*-butyldiphenylsilyl)oxy)-4-methyloctan-2-one, t_R = 6.4 min].

Absolute configuration was attributed by analogy with (−)-(*S*)-4-methyldecan-2-one **127**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.69 (d, *J* = 1.7 Hz, 2 H), 7.66 - 7.68 (m, 2 H), 7.35 - 7.48 (m, 6 H), 3.67 (t, *J* = 6.6 Hz, 2 H), 2.37 - 2.49 (m, 1 H), 2.16 - 2.27 (m, 1 H), 2.13 (s, 3 H), 1.93 - 2.05 (m, 1 H), 1.50 - 1.63 (m, 2 H), 1.11 - 1.48 (m, 4 H), 1.04 - 1.10 (m, 9 H), 0.90 (d, *J* = 6.6 Hz, 3 H).

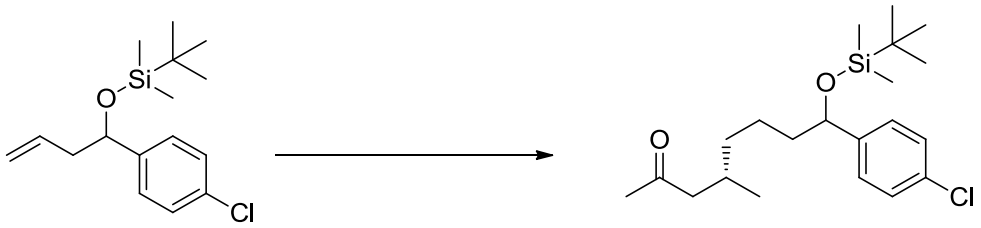
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 209.1, 135.5 (5 C), 134.1, 129.5 (2 C), 127.6 (4 C), 63.8, 51.2, 36.6, 32.6, 30.4, 29.2, 26.8 (3 C), 23.1, 19.7, 19.2.

HRMS (EI) m/z calcd for $C_{25}H_{36}O_2Na$ $[M+Na]^+$: 419.23768, found: 419.23724.

$[\alpha]_{20}^{589}$ = –4.19 (c 2.10, $CHCl_3$).

IR (νmax /cm-1): 2958, 1717, 1459, 751, 702.

(+)-(4-*S*)-8-((*tert*-butyldimethylsilyl)oxy)-8-(4-chlorophenyl)-4-methyloctan-2-one (131)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of *tert*-butyl((1-(4-chlorophenyl)but-3-en-1-yl)oxy)dimethylsilane **45** (0.30 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 45 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-pent-3-en-2-one **121** (39 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 90 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:33 EtOAc/petrol; SiO_2) gave (+)-(4-*S*)-8-((*tert*-butyldimethylsilyl)oxy)-8-(4-chlorophenyl)-4-methyloctan-2-one **131** (148.7 mg, 0.38 mmol, 95% yield) as a colourless oil. Absolute configuration was attributed by analogy with (−)-(*S*)-4-methyldecan-2-one **127** and the positive value of the polarimetry was assumed to be due to the diastereomeric mixture.

HPLC analysis of the alcohol derivative indicated an enantiomeric excess of 89% *ee* [Chiralpak® IC; 1.0 mL/min; hexane/i-PrOH: 98: 2 ; λ = 210 nm; major enantiomer (+)-(4-*S*)-8-((*tert*-butyldimethylsilyl)oxy)-8-(4-chlorophenyl)-4-methyloctan-2-one t_R = 6.1 min; minor enantiomer (−)-(4-*R*)-8-((*tert*-butyldimethylsilyl)oxy)-8-(4-chlorophenyl)-4-methyloctan-2-one, t_R = 6.5 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.41 - 7.44 (m, 1 H), 7.39 - 7.41 (m, 1 H), 7.36 (br. s., 1 H), 7.33 - 7.36 (m, 1 H), 4.75 (ddd, *J* = 7.2, 5.1, 2.0 Hz, 1 H), 2.47 - 2.56 (m, 1 H), 2.29 - 2.39 (m, 1 H), 2.26 (br. s., 3 H), 2.05 - 2.16 (m, 1 H), 1.61 - 1.84 (m, 2 H), 1.22 - 1.59 (m, 4 H), 1.02 (s, 9 H), 0.97 - 1.01 (m, 3 H), 0.17 (d, *J* = 1.2 Hz, 3 H), 0.00 (d, *J* = 2.0 Hz, 3 H).

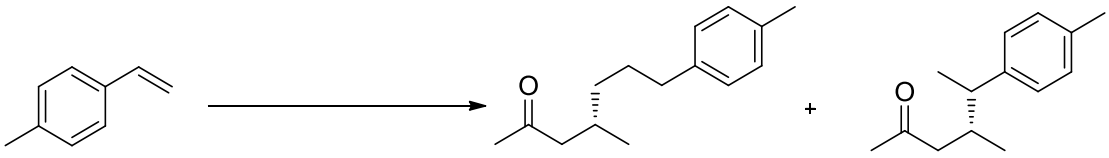
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 208.9, 144.3, 132.3, 128.2 (2 C), 127.2 (2 C), 74.3, 51.2, 40.9, 36.6, 30.4, 29.1, 25.6 (3 C), 22.8, 19.7, 18.2, -4.6, -4.9.

HRMS (EI) m/z calcd for $C_{21}H_{35}O_2ClNaSi$ $[M+Na]^+$: 405.19871, found: 405.19878.

$[\alpha]_{20}^{589}$ = +2.33 (c 2.15, $CHCl_3$).

IR (νmax /cm-1): 2958, 1716, 1459, 1335, 749, 699.

(−)-(*R*)-4-methyl-7-(*p*-tolyl)heptan-2-one (132)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 1-methyl-4-vinylbenzene **29** (0.13 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 60 min, the resulting red clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-pent-3-en-2-one **121** (39 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 90 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:33 EtOAc/petrol; SiO_2) gave a mixture of products containing mainly of (−)-(*R*)-4-methyl-7-(*p*-tolyl)heptan-2-one **132** (48 mg, 0.23 mmol, 58% yield) as a colourless oil. The other product (15% by ^{1}H NMR integration) was mainly assumed to be (4 *R*,5 *R*)-4-methyl-5-(*p*-tolyl)hexan-2-one as hydrozirconation in benzilic position has been reported.

HPLC analysis did not provide any separation but just showed a mixture of inseparable molecules.

Absolute configuration was attributed by analogy to (−)-(*S*)-4-methyldecan-2-one **127**.

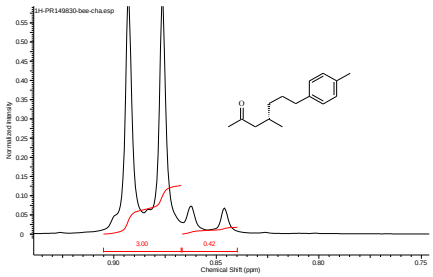
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 6.92 - 7.07 (m, 4 H), 2.32 - 2.62 (m, 3 H), 2.23 - 2.29 (m, 4 H), 2.13 - 2.23 (m, 1 H), 2.01 - 2.06 (m, 3 H), 1.89 - 2.01 (m, 1 H), 1.47 - 1.58 (m, 1 H), 1.31 - 1.44 (m, 1 H), 1.15 (d, *J* = 7.1 Hz, 1 H), 0.87 - 0.93 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 208.9, 139.3, 135.2, 129.0 (2 C), 128.2 (2 C), 51.2, 38.9, 35.6, 32.9, 30.4, 29.0, 21.0, 19.7.

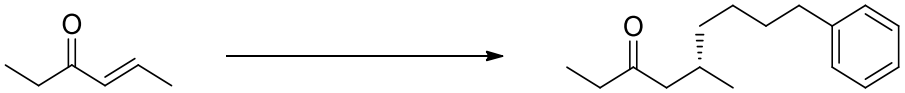
HRMS (EI) m/z calcd for $C_{14}H_{21}O$ $[M+H]^+$: 205.15869, found: 205.15845.

$[\alpha]_{20}^{589}$ = –27.13 (c 1.15, $CHCl_3$).

IR (νmax /cm-1): 2958, 1719, 1455, 753, 702.



(+)-(*S*)-5-methyl-9-phenylnonan-3-one (136)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of pent-4-en-1-ylbenzene **6** (0.15 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-hex-4-en-3-one **135** (45 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 90 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:33 EtOAc/petrol; SiO_2) gave (+)-(*S*)-5-methyl-9-phenylnonan-3-one **136** (87.6 mg, 0.37 mmol, 94% yield) as a colourless oil. Absolute configuration was attributed by analogy with ketones **144** & **146**.

HPLC analysis indicated an enantiomeric excess of 91% *ee* [Chiralpak® IC; 1.0 mL/min; hexane/i-PrOH: 99.1: 0.9 ; λ = 210 nm; major enantiomer (+)-(*S*)-5-methyl-9-phenylnonan-3-one t_R = 8.0 min; minor enantiomer (−)-(*R*)-5-methyl-9-phenylnonan-3-one, t_R = 8.5 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.16 - 7.27 (m, 2 H), 7.01 - 7.13 (m, 3 H), 2.52 (t, *J* = 7.7 Hz, 2 H), 2.24 - 2.39 (m, 3 H), 2.06 - 2.19 (m, 1 H), 1.92 (dq, *J* = 13.0, 6.6 Hz, 1 H), 1.45 - 1.59 (m, 2 H), 1.17 - 1.35 (m, 3 H), 1.03 - 1.16 (m, 1 H), 0.96 (t, *J* = 7.7 Hz, 3 H), 0.80 (d, *J* = 6.7 Hz, 3 H).

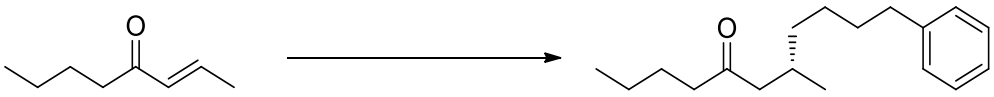
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 211.6, 142.6, 128.3 (2 C), 128.2 (2 C), 125.5, 49.8, 36.7, 36.4, 35.8, 31.5, 29.2, 26.6, 19.8, 7.7.

HRMS (EI) m/z calcd for $C_{16}H_{25}O$ $[M+H]^+$: 233.18999, found: 233.19008.

$[\alpha]_{20}^{589}$ = +1.33 (c 2.31, $CHCl_3$).

IR (νmax /cm-1): 2959, 1716, 1459, 750, 699.

(+)-(*S*)-7-methyl-11-phenylundecan-5-one (138)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of pent-4-en-1-ylbenzene **6** (0.15 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-oct-2-en-4-one **137**(60 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 120 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:49 EtOAc/petrol; SiO_2) gave (+)-(*S*)-7-methyl-11-phenylundecan-5-one **138** (79.0 mg, 0.30 mmol, 75% yield) as a colourless oil.

HPLC analysis indicated an enantiomeric excess of 91% *ee* [Chiralpak® IE; 1.0 mL/min; hexane/i-PrOH: 99.4: 0.6 ; λ = 210 nm; major enantiomer (+)-(*S*)-7-methyl-11-phenylundecan-5-one t_R = 7.0 min; minor enantiomer (−)-(*R*)-7-methyl-11-phenylundecan-5-one, t_R = 7.4 min].

Absolute configuration was attributed by analogy with ketones **144** & **146**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.16 - 7.25 (m, 2 H), 7.04 - 7.14 (m, 3 H), 2.53 (t, *J* = 7.7 Hz, 2 H), 2.23 - 2.32 (m, 3 H), 2.08 - 2.16 (m, 1 H), 1.92 (dd, *J* = 12.8, 6.2 Hz, 1 H), 1.41 - 1.60 (m, 4 H), 1.17 - 1.32 (m, 5 H), 1.05 - 1.15 (m, 1 H), 0.83 (t, *J* = 7.3 Hz, 3 H), 0.80 (d, *J* = 6.8 Hz, 3 H).

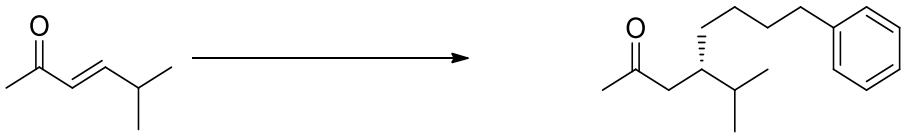
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 211.4, 142.7, 128.4 (2 C), 128.2 (2 C), 125.6, 50.3, 43.1, 36.7, 35.9, 31.5, 29.1, 26.6, 25.9, 22.3, 19.9, 13.9.

HRMS (EI) m/z calcd for $C_{18}H_{29}O$ $[M+H]^+$: 261.22129, found: 261.22089.

$[\alpha]_{20}^{589}$ = +1.03 (c 2.63, $CHCl_3$).

IR (νmax /cm-1): 2955, 1717, 1459, 1243 749, 700.

(+)-(*S*)-4-isopropyl-8-phenyloctan-2-one (140)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of pent-4-en-1-ylbenzene **6** (0.15 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 25 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-5-methylhex-3-en-2-one **139** (53 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 120 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:49 EtOAc/petrol; SiO_2) gave (+)-(*S*)-4-isopropyl-8-phenyloctan-2-one **140** (59.0 mg, 0.24 mmol, 59% yield) as a colourless oil.

HPLC analysis indicated an enantiomeric excess of roughly 66% *ee* [Chiralpak® IB; 1.0 mL/min; hexane/i-PrOH: 99.2: 0.8 ; λ = 210 nm; major enantiomer (+)-(*S*)-4-isopropyl-8-phenyloctan-2-one t_R = 5.5 min; minor enantiomer (−)-(*R*)-4-isopropyl-8-phenyloctan-2-one, t_R = 5.7 min].

Absolute configuration was attributed by analogy with ketones **144** & **146**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.15 - 7.30 (m, 2 H), 7.03 - 7.13 (m, 3 H), 2.52 (t, *J* = 7.5 Hz, 2 H), 2.25 - 2.35 (m, 1 H), 2.10 - 2.18 (m, 1 H), 2.05 (s, 3 H), 1.72 - 1.82 (m, 1 H), 1.61 (td, *J* = 6.8, 4.2 Hz, 1 H), 1.47 - 1.57 (m, 2 H), 1.16 - 1.32 (m, 3 H), 1.05 - 1.14 (m, 1 H), 0.77 (d, *J* = 6.8 Hz, 3 H), 0.74 (d, *J* = 6.8 Hz, 3 H).

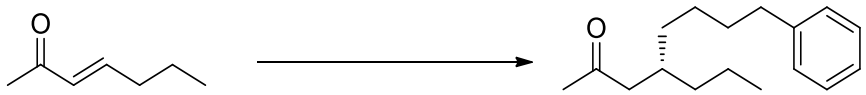
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 209.6, 142.7, 128.4 (2 C), 128.2 (2 C), 125.6, 45.4, 39.3, 35.8, 31.7, 31.1, 30.3, 29.6, 27.0, 19.5, 18.4.

HRMS (EI) m/z calcd for $C_{17}H_{26}NaO$ $[M+Na]^+$: 269.1876, found: 269.1885.

$[\alpha]_{20}^{589}$ = +7.62 (c 2.60, $CHCl_3$).

IR (νmax /cm-1): 2958, 1716, 1459, 749, 699.

(−)-(*S*)-8-phenyl-4-propyloctan-2-one (142)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of pent-4-en-1-ylbenzene **6** (0.15 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 60 min, the resulting red clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-hept-3-en-2-one **141** (56 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 90 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:39 EtOAc/petrol; SiO_2) gave a mixture of products containing mainly of (−)-(*S*)-8-phenyl-4-propyloctan-2-one **142** (76.5 mg, 0.31 mmol, 77% yield) as a colourless oil.

HPLC analysis did not provide any separation of enantiomers.

Absolute configuration was attributed by analogy to ketones **144** and **146**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 2.46 - 2.57 (m, 2 H), 2.24 (d, *J* = 6.6 Hz, 2 H), 2.03 (s, 3 H), 1.79 - 1.90 (m, 1 H), 1.45 - 1.58 (m, 2 H), 1.04 - 1.30 (m, 8 H), 0.80 (t, *J* = 7.1 Hz, 3 H).

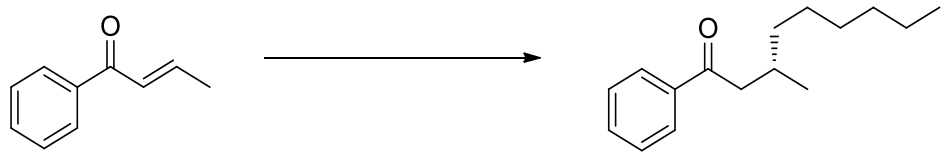
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 209.3, 142.6, 128.3 (2 C), 128.2 (2 C), 125.6, 48.7, 36.3, 35.8, 33.7, 33.6, 31.6, 30.4, 26.2, 19.7, 14.3.

HRMS (EI) m/z calcd for $C_{14}H_{21}O$ $[M+H]^+$: 205.15869, found: 205.15845.

$[\alpha]_{20}^{589}$ = +3.53 (c 1.36, $CHCl_3$).

IR (νmax /cm-1): 2952, 1716, 1455, 1292, 748, 699.

(+)-(*S*)-3-methyl-1-phenylnonan-1-one (144)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of hex-1-ene **1** (0.12 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 25 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-1-phenylbut-2-en-1-one **142** (58 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 120 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:50 EtOAc/petrol; SiO_2) gave (+)-(*S*)-3-methyl-1-phenylnonan-1-one **144** (62.0 mg, 0.27 mmol, 66% yield) as a colourless oil.

HPLC analysis indicated an enantiomeric excess of roughly 80% *ee* [Chiralpak® IA; 1.2 mL/min; hexane/i-PrOH: 99.5: 0.5 ; λ = 210 nm; minor enantiomer (−)-(*R*)-3-methyl-1-phenylnonan-1-one t_R = 19.5 min; major enantiomer (+)-(*S*)-3-methyl-1-phenylnonan-1-one, t_R = 20.7 min].

Absolute configuration was attributed by comparison with literature.[261] Characterisation was consistent with literature.[261]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.90 - 8.03 (m, 2 H), 7.51 - 7.64 (m, 1 H), 7.37 - 7.50 (m, 2 H), 2.95 (dd, *J* = 15.8, 5.6 Hz, 1 H), 2.75 (dd, *J* = 15.8, 8.0 Hz, 1 H), 2.09 - 2.24 (m, 1 H), 1.17 - 1.43 (m, 10 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.88 (t, *J* = 6.5 Hz, 3 H).

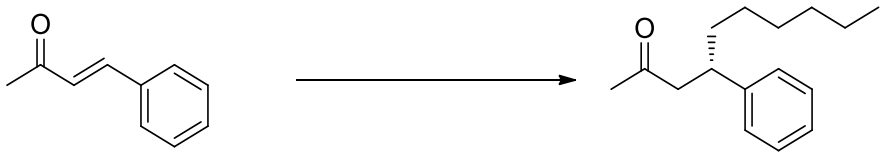
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 200.5, 137.4, 132.8, 128.5 (2 C), 128.1 (2 C), 46.0, 37.1, 31.8, 29.8, 29.4, 27.0, 22.6, 20.0, 14.1.

HRMS (EI) m/z calcd for $C_{16}H_{25}O$ $[M+H]^+$: 233.18999, found: 233.18956.

$[\alpha]_{20}^{589}$ = +5.85 (c 2.95, $CHCl_3$).

IR (νmax /cm-1): 2956, 1686, 1449, 1285, 751, 691.

(−)-(*S*)-4-phenyldecan-2-one (146)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of hex-1-ene **1** (0.12 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 25 min, the resulting yellow clear solution was transferred via syringe over about 1 min to a clear colourless stirred solution of CuOTf-ligand complex **123** (30.5 mg, 0.040 mmol, 0.10 eq) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 5 min and then cooled with an ice bath and stirred for a further 5 minutes before (*E*)-4-phenylbut-3-en-2-one **145** (59 mg, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued for 120 min before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography of the yellow residue (1:33 EtOAc/petrol; SiO_2) gave (−)-(*S*)-4-phenyldecan-2-one **146** (59.0 mg, 0.24 mmol, 59% yield) as a colourless oil.

HPLC analysis indicated an enantiomeric excess of 33% *ee* [Chiralpak® IB; 1.9 mL/min; hexane/i-PrOH: 99: 1 ; λ = 210 nm; major enantiomer (−)-(*S*)-4-phenyldecan-2-one, t_R = 4.3 min; minor enantiomer (+)-(*R*)-4-phenyldecan-2-one, t_R = 4.7 min].

Absolute configuration was attributed by analogy with the literature value for the same compound.[262] Characterisation data was consistent with literature.[268]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.18 - 7.28 (m, 3 H), 7.07 - 7.16 (m, 3 H), 2.95 - 3.14 (m, 1 H), 2.65 (dd, *J* = 7.2, 1.8 Hz, 2 H), 1.95 (s, 3 H), 1.43 - 1.61 (m, 2 H), 1.04 - 1.21 (m, 7 H), 0.78 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 208.0, 144.6, 128.4 (2 C), 127.4 (2 C), 126.3, 50.9, 41.3, 36.4, 31.7, 30.6, 29.2, 27.3, 22.6, 14.0.

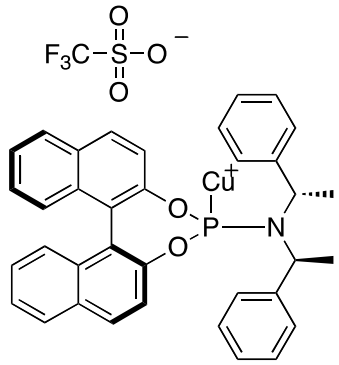
HRMS (EI) m/z calcd for $C_{16}H_{25}O$ $[M+H]^+$: 233.18999, found: 233.18956.

$[\alpha]_{20}^{589}$ = −1.78 (c 2.25, $CHCl_3$).

IR (νmax /cm-1): 2958, 1689, 1449, 1285, 749, 699.

Characterisation of complexes:

Copper triflate- Feringa ligand A: complex (13)



To a flame dried Schlenk flask containing $(CuOTf)_2 \cdot (C_6H_6)$ (239 mg, 0.48 mmol, 0.5 eq) at room temperature under an argon atmosphere was added the phosphoramidite ligand **A** (513 mg, 0.95 mmol, 1.0 eq) and then CH_2Cl_2 (10 mL). This mixture was stirred for 1 h before the resulting clear colourless solution was cannula filtrated into another Schlenk flask. The solvent was then gently removed by use of an oil-pump vacuum (with liquid nitrogen trapping). The resulting off-white solid was dried for at least one extra hour under oil-pump vacuum before storing the catalyst complex **13** under argon.

^{1}H NMR (500 MHz, CD_2Cl_2) δ_H /ppm 8.14 (d, *J* = 8.8 Hz, 1 H), 7.94 - 8.07 (m, 3 H), 7.69 (d, *J* = 8.8 Hz, 2 H), 7.45 - 7.61 (m, 10 H), 7.19 - 7.44 (m, 6 H), 4.59 - 4.71 (m, 2 H), 1.89 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (125 MHz, CD_2Cl_2) δ_C /ppm 149.4 (d, *J* = 14.2 Hz), 148.2 (d, *J* = 3.9 Hz), 141,41, 141, 37, 133.0, 132.80, 132.5, 131.5, 131.2, 129.6 (4 C), 129.0, 128.7, 128.5 (2 C), 127.8 (4 C), 127.7, 127.2, 127.1, 126.9, 125.97, 125.90, 123.64, 123.60, 122.1, 121.2, 121.1, 53.8 (2 C under solvent peak), 22.0 (2 C).

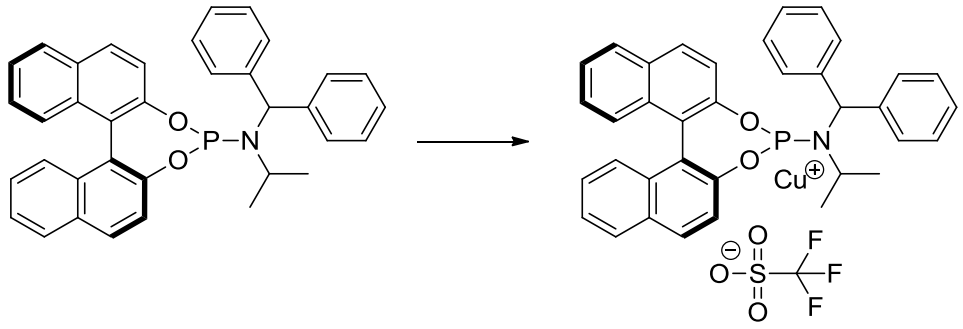
^{31}P NMR (200 MHz, CD_2Cl_2) δ_P /ppm 124.1 (br, s).

^{19}F NMR (500 MHz, CD_2Cl_2) δ_F /ppm –78.2 (s).

HRMS (EI) *m*/*z* calcd for $C_{36}H_{30}CuNO_2P$ $[M - CF_3O_3S]^+$: 602.1310, found: 602.1319. Also found: CuL_2 cald for $C_{72}H_{60}CuN_2O_4P_2$ $[M]^+$: 1141.3324, found: 1141.3325.

IR (ν_{max} /cm^{-1}):, 1223, 1025, 949, 827, 748, 670, 633.

Copper triflate-ligand AS: complex (74) (preparation with copper triflate benzene complex)



To a flame dried Schlenk flask containing $(CuOTf)_2 \cdot (C_6H_6)$ (239 mg, 0.48 mmol, 0.5 eq.) at room temperature under an argon atmosphere was added the phosphoramidite ligand **AS** (513 mg, 0.95 mmol, 1.0 eq.) and then CH_2Cl_2 (10 mL). This mixture was stirred for 1 h before the resulting clear colourless solution was filtrated through a syringe filter into another Schlenk flask. The solvent was then gently removed by use of an oil-pump vacuum (with liquid nitrogen trapping). The resulting off-white solid was dried for at least one extra hour under oil-pump vacuum before storing the catalyst complex **74** under argon.

^{1}H NMR (500 MHz, CD_2Cl_2) δ_H /ppm 8.08 (d, *J* = 9.1 Hz, 1 H), 8.05 (d, *J* = 8.8 Hz, 1 H), 7.92 (t, *J* = 8.8 Hz, 2 H), 7.48 - 7.58 (m, 9 H), 7.41 - 7.48 (m, 1 H), 7.32 - 7.41 (m, 5 H), 7.30 - 7.32 (m, 1 H), 7.26 (d, *J* = 3.8 Hz, 2 H), 5.82 (d, *J* = 22.0 Hz, 1 H), 3.49 - 3.51 (m, 1 H), 1.06 (apparent t, *J* = 6.1 Hz, 6 H).

^{13}C NMR (125 MHz, CD_2Cl_2) δ_C /ppm 149.0 (d, *J* = 7 Hz), 148.2 (d, *J* = 7 Hz), 142.0, 133.2, 132.6, 131.7, 131.3, 130.5 (2 C), 130.3 (2 C), 129.2 (2 C), 129.0 (2 C), 128.8 (2 C), 128.1 (2 C), 127.6 (2 C), 127.3 (2 C), 127.2, 127.2, 126.2, 126.1, 123.8, 121.8, 121.5, 121.0, 61.4(d, *J* = 22 Hz), 61.2, 22.8, 22.5. (CF_3O_3S not seen).

^{31}P NMR (200 MHz, CD_2Cl_2) δ_P /ppm 123.2 (br. s., 1 P).

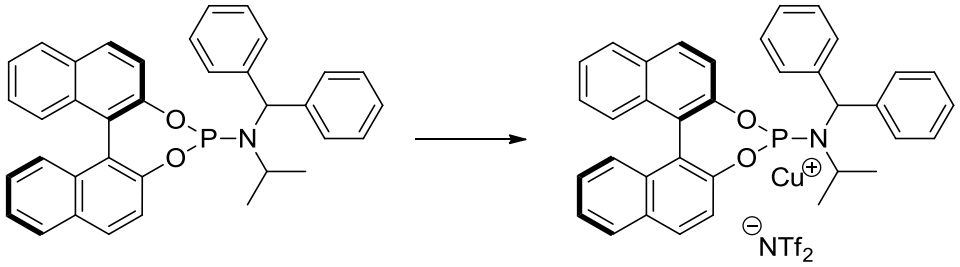
^{19}F NMR (380 MHz, CD_2Cl_2) δ_F /ppm -76.3 (s, 1 F).

HRMS (EI) *m*/*z* calcd for $C_{36}H_{30}CuNO_2P$ $[M - CF_3O_3S]^+$: 602.1310, found: 602.1319.

IR (ν_{max}/cm^{-1}): 2970, 1739, 1367, 1228, 1217

$[\alpha]^{20}_{589}$ = +101.29 (*c* 1.42, $CHCl_3$).

Copper triflimidate-ligand BU: complex (86)



To a flame dried Schlenk flask, at room temperature under an argon atmosphere was added CuCl (46 mg, 0.47 mmol, 1 eq.) and the phosphoramidite ligand **BU** (253 mg, 0.47 mmol, 1.0 eq.) followed by CH_2Cl_2 (10 mL). This mixture was stirred for 1 h before $AgNTf_2$ (200 mg, 0.52 mmol, 1.1 eq) was added to the clear solution and stirred for a further 20 min. On the addition of the $AgNTf_2$ the solution turns grey and a precipitate is formed (AgCl). The resulting solution was cannula filtrated into another Schlenk flask. The solvent was then gently removed by use of an oil-pump vacuum (with liquid nitrogen trapping). The resulting off-white solid was dried for at least one extra hour under oil-pump vacuum before storing the catalyst complex **86** under argon.

^{1}H NMR (400 MHz, C_6D_6) δ_H /ppm 7.86 (d, *J* = 8.8 Hz, 1 H), 7.71 (d, *J* = 8.8 Hz, 1 H), 7.52 - 7.65 (m, 3 H), 7.28 - 7.45 (m, 9 H), 7.24 (d, *J* = 8.8 Hz, 2 H), 7.17 - 7.22 (m, 2 H), 7.02 - 7.12 (m, 2 H), 6.85 (dt, *J* = 23.0, 8.0 Hz, 2 H), 5.38 - 5.54 (m, 1 H), 3.38 - 3.53 (m, 1 H), 0.74 (d, *J* = 6.6 Hz, 3 H), 0.60 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, C_6D_6) δ_C /ppm 148.6 (d, *J* = 12.4 Hz), 147.9 (d, *J* = 4.8 Hz), 141.7 (d, *J* = 6.7 Hz), 141.2 (d, *J* = 8.6 Hz), 132.9, 132.7, 132.6, 132.6, 131.5, 130.6, 130.5, 130.3, 129.2, 129.1, 129.0, 127.3, 127.3 (2C), 127.1, 127.0, 127.0, 126.9, 126.0, 125.9, 123.2, 123.1, 122.1, 122.1, 121.5, 121.4, 120.8 (2C), 120.0 (q, *J* = 323 Hz, 2C), 61.0 (d, *J* = 23.0 Hz), 48.8 (d, *J* = 4.8 Hz), 22.1, 22.0.

^{19}F NMR (470 MHz, C_6D_6) δ_F /ppm -76.0 (s, 6F).

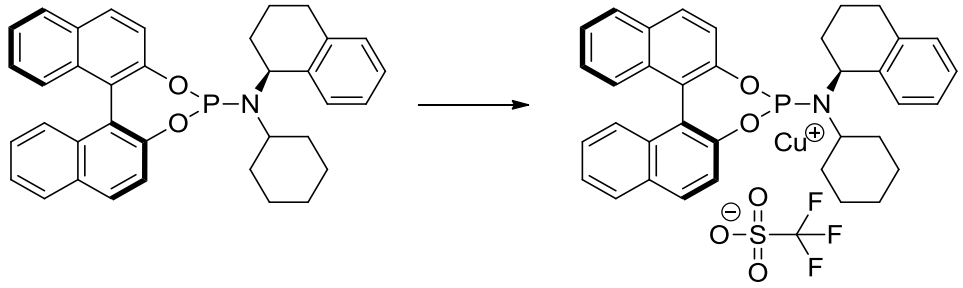
^{31}P NMR (200 MHz, C_6D_6) δ_P /ppm 121.59 (br. s, 1P).

HRMS (EI) *m/z* calcd for $C_{38}H_{30}CuF_6N_2O_6PS_2$ $[M]^+$: 882.0483, found: 882.0455.

$[\alpha]^{24}_{589}$ = –98.79 (*c* 1.00, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 1325, 1197, 1133, 1060, 950, 834.

Preparation of Copper–Ligand Complex (123)



To a flame dried Schlenk flask containing $(CuOTf)_2 \cdot (C_6H_6)$ (531.5 mg, 1.05 mmol, 0.5 eq) at room temperature under an argon atmosphere was added the phosphoramidite ligand **BW** (1148 mg, 2.10 mmol, 1.0 eq) and then CH_2Cl_2 (10 mL). This mixture was stirred for 70 minutes before the resulting clear colourless solution was filtrated into another Schlenk flask. The solvent was then gently removed by use of an oil-pump vacuum (with liquid nitrogen trapping). The resulting off-white solid was dried for at least one extra hour under oil-pump vacuum before storing the catalyst complex **123** under argon.

^{1}H NMR (500 MHz, CD_2Cl_2) δ_H /ppm 7.91 - 8.25 (m, 4 H), 7.75 (d, *J* = 6.9 Hz, 1 H), 7.43 - 7.66 (m, 4 H), 7.05 - 7.43 (m, 7 H), 4.41 - 4.74 (m, 1 H), 2.90 - 3.40 (m, 2 H), 2.55 - 2.83 (m, 1 H), 2.44 (br. s., 1 H), 2.28 (br. s., 1 H), 2.13 (br. s., 2 H), 1.83 (br. s., 4 H), 1.59 (br. s., 1 H), 1.44 (br. s., 2 H), 0.98 (d, *J* = 6.9 Hz, 2 H), 0.69 (br. s., 1 H).

^{13}C NMR (125 MHz, CD_2Cl_2) δ_C /ppm 149.3, 149.2, 148.3, 148.2, 139.5, 133.0, 132.6, 132.4, 131.7, 131.2 (2 C), 129.2, 128.9, 128.9 (2 C), 128.3, 127.7, 127.4, 127.3 (2 C), 127.1, 126.2, 126.1, 123.7, 121.9, 121.5, 120.9, 57.3, 55 (1C under solvent peak) 29.8 (2 C), 26.7, 26.1, 25.5 (2 C), 22.8 (2 C).

^{31}P NMR (200 MHz, CD_2Cl_2) δ_P /ppm 124.4 (br. s)

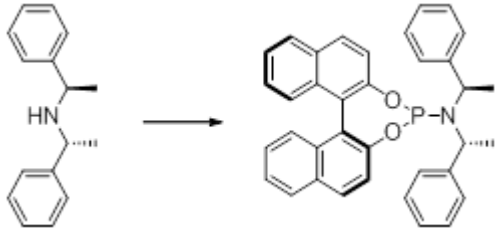
HRMS (EI) m/z calcd for $C_{36}H_{34}CuNO_2P$ $[M - CF_3O_3S]^+$: 606.1618, found: 606.1619.

$[\alpha]_{20}^{589}$ = +121.20 (c 1.15, $CHCl_3$).

IR (νmax /cm-1): 2933, 2857, 1653, 1226, 1030, 982, 831, 637.

Characterisation of ligands:

(*S*,*R*,*R*)-*N*,*N*-bis((*R*)-1-phenylethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine B



According to a modified procedure from Trost,[164] triethylamine (0.77 mL, 5.5 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.1 mL, 1.1 mmol, 1.0 eq.) in CH_2Cl_2 (3.5 mL). The ice bath was removed and the solution left to warm to room temperature before (*R*)-bis((R)-1-phenylethyl)amine (0.25 mL, 1.1 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (318 mg, 1.1 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h. The solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2), the ligand **B** was obtained as a crystalline white solid (369 mg, 0.68 mmol, 61%).

Data were consistent with literature.[192]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.96 (d, *J* = 8.5 Hz, 2 H), 7.91 (dd, *J* = 7.7, 5.8 Hz, 2 H), 7.61 (d, *J* = 8.8 Hz, 1 H), 7.45 (d, *J* = 8.5 Hz, 1 H), 7.36 - 7.43 (m, 3 H), 7.20 - 7.33 (m, 4 H), 7.06 - 7.17 (m, 9 H), 4.44 - 4.65 (m, 2 H), 1.74 (d, *J* = 7.3 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.1 (d, *J* = 6.5 Hz), 149.6, 132.8 (d, *J* = 7.4 Hz), 131.4, 130.5, 130.2 (2 C), 129.4 (2 C), 128.3 (2 C), 128.1 (2 C), 127.9 (2 C), 127.7 (4 C), 127.1 (d, *J* = 6.5 Hz, 2 C), 126.6 (2 C), 125.9 (d, *J* = 3.7 Hz, 2 C), 124.7 (2 C), 124.4 (2 C), 124.0 (d, *J* = 5.5 Hz, 1 C), 122.4 (2 C), 122.4, 121.7 (d, *J* = 1.8 Hz), 52.3 (d, *J* = 12.0 Hz, 2 C).

^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 146.57 (s, 1P).

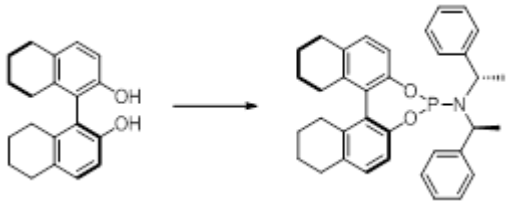
HRMS (EI) *m/z* calcd for $C_{35}H_{30}NO_2P$ $[M]^+$: 527.2014, found: 527.2018.

$[\alpha]^{20}_{589}$= +108.75 (*c* 0.84, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2974, 1590, 1232, 928, 798, 751.

MP: 88-90 °C.

(*R*,*S*,*S*)-(11b*S*)-*N*,*N*-bis((*S*)-1-phenylethyl)-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine F



According to a modified procedure from Trost,[164] triethylamine (0.71 mL, 5.1 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.09 mL, 1.0 mmol, 1.0 eq.) in CH_2Cl_2 (4 mL). The ice bath was removed and the solution left to warm to room temperature before (−)-bis[(*S*)-1-phenylethyl]amine (0.23 mL, 1.0 mmol, 1.0 eq.) was added to the stirring solution. After 5 h (*S*)-(−)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′−bi-2-naphthol (300 mg, 1.0 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h. The solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (84:15:1; Petrol: CH_2Cl_2: Et_3N; SiO_2), ligand **F** was obtained as a crystalline white solid (335 mg, 0.61 mmol, 60%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.13 - 7.23 (m, 10 H), 7.10 (q, *J* = 8.3 Hz, 2 H), 6.83 (dd, *J* = 33.4, 8.3 Hz, 2 H), 4.33 - 4.44 (m, 2 H), 2.58 - 2.92 (m, 6 H), 2.27 (ddt, *J* = 43.3, 16.6, 6.5, 6.5 Hz, 2 H), 1.73 - 1.87 (m, 6 H), 1.66 (s, 6 H), 1.47 - 1.61 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 149.6, 149.2 (d, *J* = 8.3 Hz), 143.9 (2 C), 138.5, 137.8, 134.5, 132.7, 129.9, 129.3, 128.5 (2 C), 128.5 (2 C), 128.1 (3 C), 127.5, 126.9 (2 C), 119.5, 119.5, 119.2 (2 C), 54.9, 54.8, 29.7, 29.5, 28.4, 28.1, 23.4, 23.3, 23.2 (2 C), 23.2, 23.0.

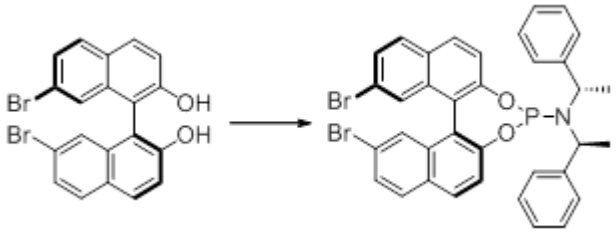
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 146.99 (s, 1 P).

HRMS (EI) *m/z* calcd for $C_{36}H_{37}NO_2P$ $[M - H]^+$: 546.2562, found: 546.2587.

$[\alpha]^{20}_{589}$= −95.16 (*c* 1.24 , $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2933, 2340, 1494, 1201, 940, 763, 698.

(*S*,*S*,*S*)-10,13-dibromo-*N*,*N*-bis((*S*)-1-phenylethyl)dinaphtho[(*S*)-2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine G



According to a modified procedure from Trost,[164] triethylamine (0.20 mL, 1.4 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.02 mL, 0.3 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-bis((*S*)-1-phenylethyl)amine (0.07 mL, 0.28 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-7,7'-dibromo-[1,1'-binaphthalene]-2,2'-diol (124 mg, 0.28 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 10 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2), the ligand **G** was obtained as a crystalline white solid (110 mg, 0.15 mmol, 56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.08 - 8.18 (m, 1 H), 7.96 - 8.02 (m, 1 H), 7.93 (d, *J* = 8.8 Hz, 1 H), 7.66 (d, *J* = 8.8 Hz, 1 H), 7.61 (d, *J* = 8.8 Hz, 1 H), 7.29 - 7.39 (m, 2 H), 7.14 - 7.26 (m, 10 H), 6.83 - 7.13 (m, 4 H), 4.37 - 4.48 (m, 1 H), 1.70 (d, *J* = 6.9 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.8 (d, *J* = 10.2 Hz), 150.1, 142.8, 132.5, 131.5, 131.2, 131.1, 130.3, 130.0, 129.7, 129.5, 129.4, 128.8, 128.64, 128.61, 127.9 (2 C), 127.9, 127.8 (4 C), 127.5 (d, *J* = 3.7 Hz), 126.8 (2 C), 126.4 (d, *J* = 6.5 Hz), 123.9 (d, *J* = 5.5 Hz), 123.7, 123.6 (d, *J* = 1.8 Hz), 120.9 (d, *J* = 2.8 Hz), 118.9, 118.4, 54.6 (d, *J* = 10.2 Hz, 2 C), 23.0 (d, *J* = 12.0 Hz, 2 C).

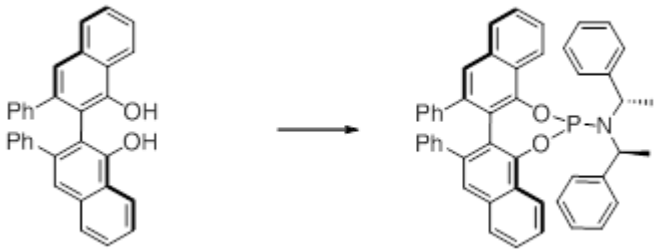
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 152.83 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{36}H_{27}Br_2NO_2P$ $[M-1]^+$: 694.0146, found: 694.0154.

$[\alpha]^{20}_{589}$ = −27.69 (*c* 2.00, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2968, 1584, 1492, 1326, 1233, 946, 818, 755, 696.

(*S*,*S*,*S*)-9,10-diphenyl-*N*,*N*-bis((*S*)-1-phenylethyl)dinaphtho[(*S*)1,2-d:2',1'-f][1,3,2]dioxaphosphepin-2-amine H



According to a modified procedure from Trost,[164] triethylamine (0.20 mL, 1.4 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.02 mL, 0.3 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-bis((*S*)-1-phenylethyl)amine (0.07 mL, 0.28 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-3,3'-diphenyl-[2,2'-binaphthalene]-1,1'-diol (125 mg, 0.28 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 10 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2), the ligand **H** was obtained as a crystalline white solid (143 mg, 0.21 mmol, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.42 (dd, *J* = 8.2, 3.8 Hz, 1 H), 7.86 (d, *J* = 8.2 Hz, 1 H), 7.80 (d, *J* = 7.9 Hz, 1 H), 7.66 - 7.73 (m, 1 H), 7.57 - 7.63 (m, 1 H), 7.49 - 7.55 (m, 1 H), 7.43 (d, *J* = 3.2 Hz, 1 H), 7.31 - 7.37 (m, 2 H), 7.15 - 7.24 (m, 3 H), 7.03 - 7.14 (m, 6 H), 6.92 - 6.98 (m, 2 H), 6.85 - 6.91 (m, 2 H), 6.69 (d, *J* = 5.4 Hz, 4 H), 6.56 - 6.63 (m, 2 H), 6.38 - 6.46 (m, 2 H), 4.51 - 4.72 (m, 2 H), 1.76 - 1.99 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 147.7, 147.4 (d, *J* = 7.4 Hz), 142.6, 140.7, 140.5, 140.5, 134.2 (2 C), 133.9 (2 C), 129.2 (2 C), 129.1 (2 C), 128.4 (3 C), 128.0 (1 C), 127.9 (5 C), 127.5 (3 C), 127., 127.1, 126.8 (s, 5 C), 126.8, 126.4, 126.2, 126.1, 125.8, 125.8, 125.1 (d, *J* = 4.6 Hz), 124.2, 124.0, 122.6, 122.1, 54.3 (d, *J* = 11.1 Hz, 2 C), 22.9 (2 C).

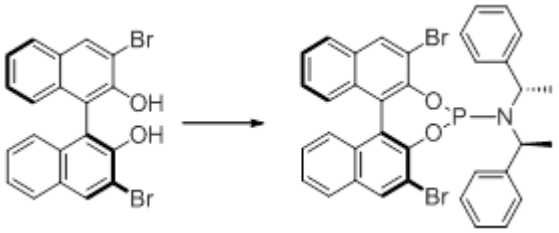
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 154.58 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{36}H_{27}Br_2NO_2P$ $[M]^+$: 694.0146, found: 694.0154.

$[\alpha]^{20}_{589}$ = −15.20 (*c* 1.00, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 3060, 2966, 2338, 1768, 1241, 1075, 959, 896, 761.

2,6-dibromo-*N*,*N*-bis((*S*)-1-phenylethyl)dinaphtho[(*S*)-2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine I



According to a modified procedure from Trost,[164] triethylamine (0.68 mL, 4.8 mmol, 5.0 eq.) was added dropwise to a stirred a solution cooled at 0 °C of PCl_3 (0.09 mL, 0.97 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-bis((*S*)-1-phenylethyl)amine (0.22 mL, 0.97 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-3,3'-dibromo-[1,1'-binaphthalene]-2,2'-diol (433 mg, 0.97 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h.before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2), the ligand **I** was obtained as a crystalline white solid (465 mg, 0.67 mmol, 68%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.31 (s, 1 H), 8.21 (s, 1 H), 7.84 (d, *J* = 8.2 Hz, 1 H), 7.79 (d, *J* = 8.2 Hz, 1 H), 7.35 - 7.47 (m, 2 H), 7.16 - 7.31 (m, 13 H), 7.07 (d, *J* = 8.5 Hz, 1 H), 4.40 - 4.57 (m, 2 H), 1.58 - 1.76 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 147.8 (d, *J* = 10.2 Hz), 146.9, 143.3, 133.4, 133.1, 132.5, 132.3, 132.2, 131.0, 128.6 (apparent d, *J* = 1.8 Hz, 3 C), 128.4 (6 C), 127.9, 127.63, 127.61, 127.4, 127.3 (2 C), 126.9, 126.8, 126.3, 126.0 (d, *J* = 5.5 Hz), 125.8, 122.7, 117.4, 117.1 (d, *J* = 1.8 Hz), 56.8 (d, *J* = 12.9 Hz, 2 C), 23.5 - 23.8 (m, 2 C).

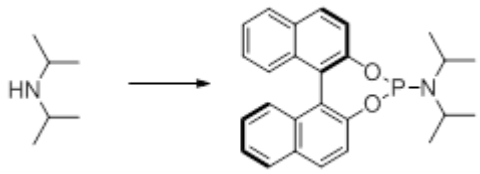
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 151.71 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{36}H_{29}Br_2NO_2P$ $[M+H]^+$: 696.0303, found: 696.0160.

$[\alpha]^{20}_{589}$= +110.28 (*c* 1.00, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2970, 1739, 1579, 924, 817, 750.

N,*N*-diisopropyl-(*S*)-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine N



According to a modified procedure from Trost,[164] triethylamine (0.9 mL, 6.4 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.11 mL, 1.3 mmol, 1.0 eq.) in CH_2Cl_2 (9 mL). The ice bath was removed and the solution left to warm to room temperature before the diispropylamine (0.18, 1.3 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (368 mg, 1.3 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2), the ligand **N** was obtained as a crystalline white solid (334 mg, 0.80 mmol, 63%).

Date were consistent with literature.[164]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.97 (d, *J* = 8.8 Hz, 1 H), 7.91 (dd, *J* = 8.5, 3.5 Hz, 3 H), 7.52 (d, *J* = 8.8 Hz, 1 H), 7.45 (d, *J* = 8.8 Hz, 1 H), 7.38 - 7.43 (m, 3 H), 7.30 - 7.34 (m, 1 H), 7.25 - 7.29 (m, 1 H), 7.20 - 7.25 (m, 1 H), 3.30 - 3.47 (m, 2 H), 1.24 (d, *J* = 6.9 Hz, 6 H), 1.15 - 1.21 (d, *J* = 6.9 Hz , 6 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.4 (d, *J* = 6.5 Hz), 150.2, 132.8 (d, *J* = 1.8 Hz), 132.7, 131.3, 130.5, 130.1, 129.3, 128.22, 128.19, 127.12, 127.10, 125.9, 125.8, 124.6, 124.2, 124.0 (d, *J* = 5.5 Hz), 122.5, 122.4 (d, *J* = 1.8 Hz), 121.9 (d, *J* = 1.8 Hz), 44.8, 44.7, 24.5 (2 C), 24.5 (2 C).

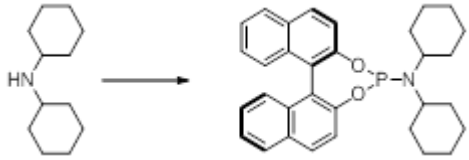
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 152.33 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{26}H_{26}NO_2P$ $[M]^+$: 415.1701, found: 415.1706.

$[\alpha]^{20}_{589}$= −447.07 (*c* 0.67, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2970, 1233, 951, 749.

(*R*)-*N*,*N*-dicyclohexyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine O



According to a modified procedure from Trost,[164] triethylamine (0.77 mL, 5.5 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.1 mL, 1.1 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL). The ice bath was removed and the solution left to warm to room temperature before dicyclohexylamine (0.22 mL, 1.1 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (316 mg, 1.1 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2), ligand **O** was obtained as a crystalline white solid (233 mg, 0.47 mmol, 43%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.96 (d, *J* = 8.8 Hz, 1 H), 7.87 - 7.93 (m, 3 H), 7.51 (d, *J* = 8.8 Hz, 1 H), 7.38 - 7.46 (m, 4 H), 7.32 (d, *J* = 8.8 Hz, 1 H), 7.20 - 7.29 (m, 2 H), 2.71 - 2.88 (m, 2 H), 1.88 (d, *J* = 11.7 Hz, 2 H), 1.67 - 1.80 (m, 4 H), 1.50 - 1.66 (m, 6 H), 1.47 (d, *J* = 11.0 Hz, 2 H), 0.80 - 1.09 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.4 (d, *J* = 6.7 Hz), 150.2, 132.8, 132.7, 131.2, 130.4, 130.1, 129.3, 128.2, 128.1, 127.0, 127.0, 125.9, 125.8, 124.5, 124.2, 124.0 (d, *J* = 5.7 Hz), 122.4 (d, *J* = 1.9 Hz), 122.1, 121.8 (d, *J* = 2.9 Hz), 54.1 (d, *J* = 10.5 Hz, 2 C), 35.1 (2 C), 26.4 (2 C), 26.3 (2 C), 25.4 (4 C).

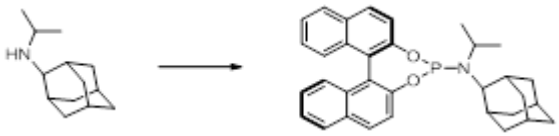
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 153.16 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{32}H_{34}NO_2P$ $[M]^+$: 495.2327, found: 495.2327.

$[\alpha]^{20}_{589}$ = −296.80 (*c* 1.09, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2931, 2854, 2360, 1588, 1231, 1061, 950, 766.

(*R*)-*N*-((1r,3r,5r,7r)-adamantan-2-yl)-*N*-isopropyldinaphtho[(*R*)-2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine P



According to a modified procedure from Trost,[164] triethylamine (0.70 mL, 5.0 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.09 mL, 1.0 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL). The ice bath was removed and the solution left to warm to room temperature before (1r,3r,5r,7r)-*N*-isopropyladamantan-2-amine (195 mg, 1.0 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (289 mg, 1.0 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 79:20:1 SiO_2), ligand **P** was obtained as a crystalline white solid (353 mg, 0.69 mmol, 69%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.97 (d, *J* = 8.8 Hz, 1 H), 7.91 (dd, *J* = 8.8, 5.7 Hz, 3 H), 7.54 (d, *J* = 8.8 Hz, 1 H), 7.37 - 7.49 (m, 4 H), 7.32 (d, *J* = 8.8 Hz, 1 H), 7.17 - 7.29 (m, 2 H), 3.62 (td, *J* = 6.6, 3.2 Hz, 1 H), 3.32 - 3.44 (m, 1 H), 2.65 (t, *J* = 15.0 Hz, 2 H), 2.14 - 2.24 (m, 1 H), 2.05 (br. s., 1 H), 1.91 (d, *J* = 8.8 Hz, 6 H), 1.77 (br. s., 2 H), 1.61 - 1.72 (m, 2 H), 1.00 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.9 (d, *J* = 6.5 Hz, 1 C), 150.2, 132.9, 132.9, 131.3, 130.4, 130.2, 129.4, 128.3, 128.2, 127.21, 127.23, 125.9, 125.8, 124.6, 124.3 (d, *J* = 5.5 Hz), 124.2, 122.61, 122.57, 121.5, 59.5 (d, *J* = 16.6 Hz), 46.2 (d, *J* = 3.7 Hz), 39.7, 39.5, 38.6 (d, *J* = 4.6 Hz), 35.6 (d, *J* = 2.8 Hz), 35.0 (d, *J* = 7.4 Hz), 31.9 (d, *J* = 20.6 Hz), 31.6 (d, *J* = 17.6 Hz), 27.8, 27.7, 23.1, 21.8.

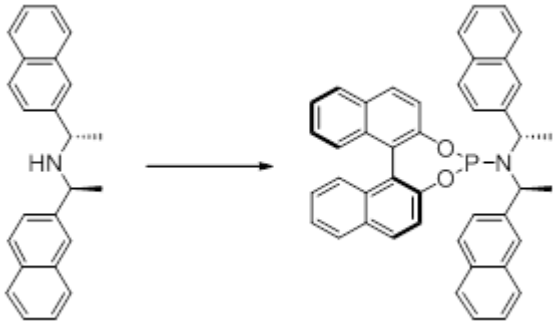
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 147.52 (br. s., 1 P).

HRMS (EI) *m/z* calcd for $C_{33}H_{34}NO_2P$ $[M]^+$: 507.2327, found: 507.2328.

$[\alpha]^{20}_{589}$= −293.39 (*c* 1.05, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2905, 2851, 1591, 1507, 1232, 941, 821, 751.

(*S*,*S*,*S*)-*N*,*N*-bis(1-(naphthalen-2-yl)ethyl)dinaphtho[2,1-d:1',2'-f] [1,3,2] dioxaphosphepin-4-amine R



According to a modified procedure from Trost,[164] triethylamine (794 µL, 5.7 mmol, 5.0 eq.) was added dropwise to a solution cooled at 0 °C of PCl_3 (99 µL, 1.1 mmol, 1.0 eq.) in CH_2Cl_2 (7 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-bis-((*S*)-1-(naphthalen-1-yl)ethyl)amine (371 mg, 1.1 mmol, 1.0 eq.) was added to the stirring solution. (*S*)-binaphthol (326 mg, 1.1 mmol, 1.0 eq.) was added to the suspension after 5 h and the subsequent mixture was left stirring for an additional 12 h before the solution was then filtered on a small pad of silica and celite® and washed with CH_2Cl_2. The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (SiO_2, 78:17:1 Petrol: CH_2Cl_2: Et_3N), the title ligand **R** was obtained as a crystalline white solid (35 g, 0.05 mmol, 5%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.98 (d, *J* = 8.8 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 7.9 Hz, 2H), 7.65 (d, *J* = 8.8 Hz), 7.52 (d, *J* = 8.6 Hz, 4H), 7.45-7.32 (m, 10H), 7.31-7.20 (m, 5H), 4.76-4.65 (m, 2H), 1.88 (s, 3H), 1.87 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.0 (d, *J* = 7.6 Hz), 149.5, 140.2 (2 C), 132.8, 132.8, 132.7, 132.3, 131.4, 130.5, 130.3, 129.5, 128.3 (2 C), 128.1, 127.9 (2 C), 127.3 (4 C), 127.2, 127.1, 126.0 (2 C), 125.9, 125.6 (2 C), 125.6 (2 C), 124.7, 124.5, 124.1, 124.0 (2 C), 122.4, 122.4, 122.4, 121.8, 121.8, 52.4 (d, *J* = 12.2 Hz), 22.0.

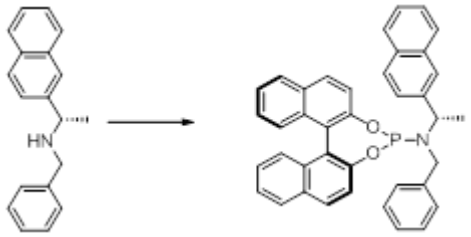
^{31}P NMR (200 MHz, CD_2Cl_2) δ_P /ppm 146.3 (s, 1P).

HRMS (EI/FI) *m/z* calcd for $C_{44}H_{34}NO_2P$ $[M]^+$: 639.2327, found: 639.2197.

$[\alpha]^{20}_{589}$ = −518.29 (*c* 0.59, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 3487, 2970, 2160, 1739, 1366, 1229, 1217, 1114, 1069, 944, 819, 747.

(*S*,*S*)-*N*-benzyl-*N*-(1-(naphthalen-2-yl)ethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine T



According to a modified procedure from Trost,[164] triethylamine (1.0 mL, 7.7 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.11 mL, 1.3 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-*N*-benzyl-1-(naphthalen-2-yl)ethanamine (381 mg, 1.3 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (366 mg, 1.3 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 79:20:1 SiO_2), ligand **T** was obtained as a crystalline white solid (215 mg, 0.37 mmol, 29%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.95 (dd, *J* = 8.8, 2.4 Hz, 2 H), 7.80 - 7.90 (m, 3 H), 7.66 - 7.77 (m, 3 H), 7.60 (dd, *J* = 8.8, 6.5 Hz, 2 H), 7.43 - 7.51 (m, 2 H), 7.35 (t, *J* = 7.2 Hz, 1 H), 7.21 - 7.30 (m, 3 H), 7.07 - 7.20 (m, 7 H), 7.04 (d, *J* = 8.8 Hz, 1 H), 4.17 (dq, *J* = 14.2, 7.2 Hz, 1 H), 3.97 (d, *J* = 14.8 Hz, 1 H), 2.97 (d, *J* = 15.0 Hz, 1 H), 1.70 (dd, *J* = 7.2, 4.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.2 (d, *J* = 4.8 Hz, 1 C), 149.6, 141.2, 138.6, 133.4, 132.9, 132.8 (d, *J* = 1.9 Hz,), 132.5, 131.4, 130.5, 130.3, 130.2, 128.6, 128.5 (s2 C), 128.3, 128.2 (2 C), 128.2, 127.9, 127.8, 127.1, 127.0, 126.9, 126.3, 126.1, 126.05, 126.01, 125.9, 125.3 (d, *J* = 1.9 Hz), 124.8, 124.5, 124.1, 122.4 (d, *J* = 1.9 Hz), 122.3, 121.6, 57.7 (d, *J* = 23.0 Hz), 48.4 (d, *J* = 2.9 Hz), 23.5 (d, *J* = 33.0 Hz).

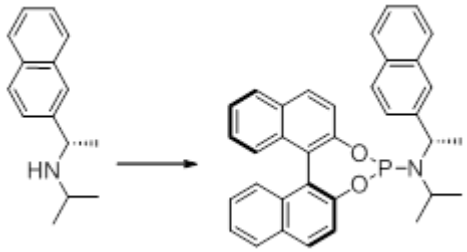
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 142.49 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{39}H_{30}NO_2P$ $[M]^+$: 575.2014, found: 575.2022.

$[\alpha]^{20}_{589}$= +31.26 (*c* 1.00, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2971, 1739, 1463, 1366, 1230, 1217, 917, 749.

(*S*,*S*)-(+)-Isopropyl- 1-(naphthalen-2-yl)ethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine U



According to a modified procedure from Feringa[192, 193] or Rajanbabu,[191] (*S*)-*N*-(1-(naphthalen-2-yl)ethyl)propan-2-amine (1.38 g, 5.5 mol, 1.0 eq) was dissolved in THF (8.0 mL) and the solution was cooled to 0 °C. BuLi (2.5 M solution in hexane, 2.6 mL, 6.6 mmol, 1.2 eq) was added dropwise to the solution over about 3 minutes. A solution of (*S*)-phosphorochloridite (2.1 g, 5.5 mmol, 1.0 eq) in THF (8.0 mL) was added and the resulting mixture stirred for 10 minutes at 0 °C. The reaction was allowed to warm to room temperature and stirred for 18 hours. Et_2O (*ca* 20 mL) was added and the reaction mixture was stirred for an additional 20 minutes before the reaction mixture was filtered through a layer of celite that was sitting on top of a very thin layer of silica gel and washed with Et_2O (*ca* 25 mL). The filtrate was concentrated *in vacuo*. Et_2O (*ca* 25 mL) was added to precipitate impurities, and the impurities were removed by filtration through celite and a very thin layer of silica. The solid was washed with Et_2O (*ca* 25 mL) and the combined filtrate was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford desired phosphoramidite as an off white foam. Purification by flash column chromatography (1: 39 EtOAc/petrol; SiO_2) gave the desired phosphoramidite ligand **U** (1.87 g, 3.3 mmol, 60%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.0 - 8.0 (m, 2 H), 7.9 (m, *J* = 8.2, 1.9 Hz, 1 H), 7.9 (ddd, *J* = 7.3, 5.4, 2.0 Hz, 2 H), 7.8 - 7.9 (m, 2 H), 7.8 (d, *J* = 8.8 Hz, 1 H), 7.6 (dd, *J* = 8.8, 0.6 Hz, 1 H), 7.5 - 7.6 (m, 2 H), 7.4 - 7.4 (m, 2 H), 7.4 - 7.4 (m, 2 H), 7.3 (d, *J* = 8.5 Hz, 1 H), 7.2 - 7.3 (m, 3 H), 4.7 (dq, *J* = 13.8, 6.8 Hz, 1 H), 3.4 (dq, *J* = 13.8, 6.6 Hz, 1 H), 1.8 (d, *J* = 6.6 Hz, 3 H), 1.2 (d, *J* = 6.6 Hz, 3 H), 1.0 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.4 (d, *J* = 7.6 Hz), 150.0, 133.4, 132.8, 132.7, 132.4, 131.3, 130.4, 130.3, 129.5, 128.3, 128.2, 128.0, 127.9, 127.6, 127.1, 127.1, 126.0, 126.0, 125.9, 125.8, 125.7, 125.3, 125.3, 124.7, 124.3, 124.1, 124.0, 122.4, 122.2, 53.3, 46.6, 24.4 (d, *J* = 19.1 Hz,), 24.0 (d, *J* = 4.8 Hz), 23.3 (d, *J* = 4.8 Hz).

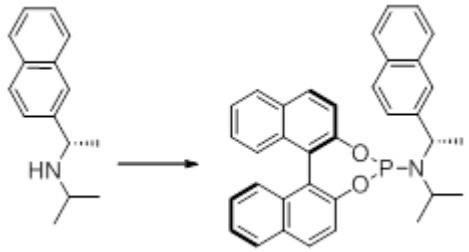
^{31}P NMR (200 MHz $CDCl_3$) δ_P /ppm 151.89 (s, 1 P).

HRMS (EI) *m/z* calcd for $C_{35}H_{30}NO_2P$ $[M]^+$: 527.2014, found: 527.2014.

$[\alpha]^{24}_{589}$ = +3.52 (*c* 0.99, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2972, 2384, 1463, 1233, 938, 822, 750.

(*R*,*S*)-*N*-isopropyl-*N*-((*S*)-1-(naphthalen-2-yl)ethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine



According to a modified procedure from Trost,[164] triethylamine (0.66 mL, 4.8 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.08 mL, 1.0 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-*N*-isopropyl-2,3-dihydro-1H-inden-1-amine (204 mg, 1.0 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (274 mg, 0.8 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 79:20:1 SiO_2), the ligand was obtained as a crystalline white solid (199 mg, 0.38 mmol, 39%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.01 (d, *J* = 8.8 Hz, 1 H), 7.95 (t, *J* = 8.8 Hz, 2 H), 7.92 (d, *J* = 8.8 Hz, 1 H), 7.78 - 7.85 (m, 4 H), 7.73 - 7.77 (m, 1 H), 7.62 (d, *J* = 8.8 Hz, 1 H), 7.58 (d, *J* = 8.8 Hz, 1 H), 7.44 - 7.50 (m, 2 H), 7.38 - 7.44 (m, 3 H), 7.30 - 7.34 (m, 1 H), 7.23 - 7.26 (m, 2 H), 4.72 (quin, *J* = 7.3 Hz, 1 H), 3.35 (tt, *J* = 13.2, 6.7 Hz, 1 H), 1.71 (d, *J* = 6.7 Hz, 3 H), 1.41 (d, *J* = 6.7 Hz, 3 H), 0.99 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.2 (d, *J* = 6.5 Hz), 149.9, 133.1, 132.9 (d, *J* = 1.8 Hz), 132.8, 132.4, 131.4, 130.5, 130.4, 129.5, 128.4, 128.2, 128.0, 127.7 , 127.5, 127.2, 127.2, 127.1, 126.04, 126.01, 125.9, 125.7, 125.5 (d, *J* = 1.8 Hz), 124.8, 124.4, 124.1 (d, *J* = 5.5 Hz), 122.5, 122.53, 122.47, 121.9 (d, *J* = 2.8 Hz), 51.7 (d, *J* = 7.4 Hz), 46.2, 46.0, 24.6, 24.5.

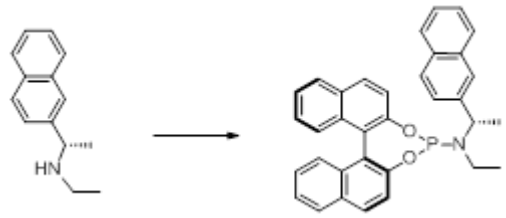
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 148.83 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{35}H_{30}NO_2P$ $[M]^+$: 527.2014, found: 527.2018.

$[\alpha]^{20}_{589}$= −404.84 (*c* 1.05 , $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2971, 1591, 1232, 945, 822, 750.

(*S*,*S*)-*N*-ethyl-*N*-(1-(naphthalen-2-yl)ethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine W



According to a modified procedure from Feringa[192, 193] or Rajanbabu,[191] (*S*)-*N*-ethyl-1-(naphthalen-2-yl)ethanamine (191 mg, 0.96 mol, 1.0 eq) was dissolved in THF (3.0 mL) and the solution was cooled to 0 °C. BuLi (2.5 M solution in hexane, 0.46 mL, 1.15 mmol, 1.2 eq) was added dropwise to the solution over about 3 minutes. A solution of (*S*)-phosphorochloridite (222 mg, 0.59 mmol, 1.0 eq) in THF (2.0 mL) was added and the resulting mixture stirred for 10 minutes at 0 °C. The reaction was allowed to warm to room temperature and stirred for 15 hours. Et_2O (*ca* 20 mL) was added and the reaction mixture was stirred for an additional 20 minutes before the reaction mixture was filtered through a layer of celite that was sitting on top of a very thin layer of silica gel and washed with Et_2O (*ca* 25 mL). The filtrate was concentrated *in vacuo*. Et_2O (*ca* 25 mL) was added to precipitate impurities, and the impurities were removed by filtration through celite and a very thin layer of silica. The solid was washed with Et_2O (*ca* 25 mL) and the combined filtrate was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford desired phosphoramidite as an off white foam. Purification by flash column chromatography (1: 33 EtOAc/petrol; SiO_2) gave the desired phosphoramidite **W** (91 mg, 0.18 mmol, 19%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.01 (d, *J* = 8.5 Hz, 1 H), 7.96 (d, *J* = 8.5 Hz, 1 H), 7.94 (d, *J* = 7.9 Hz, 1 H), 7.89 - 7.92 (m, 2 H), 7.87 (s, 1 H), 7.83 (s, 1 H), 7.76 - 7.80 (m, 1 H), 7.74 (d, *J* = 8.5 Hz, 1 H), 7.61 (d, *J* = 8.5 Hz, 1 H), 7.50 - 7.56 (m, 2 H), 7.42 (d, *J* = 8.5 Hz, 2 H), 7.36 - 7.41 (m, 2 H), 7.35 (d, *J* = 8.5 Hz, 1 H), 7.25 (d, *J* = 1.6 Hz, 1 H), 7.22 (d, *J* = 8.8 Hz, 1 H), 4.63 - 4.88 (m, 1 H), 2.76 (dqd, *J* = 14.3, 7.1, 7.1, 7.1, 4.4 Hz, 1 H), 2.38 (dqd, *J* = 14.1, 6.9, 6.9, 6.9, 3.5 Hz, 1 H), 1.88 (dd, *J* = 7.1, 2.7 Hz, 3 H), 0.75 (t, *J* = 7.1 Hz, 3 H)

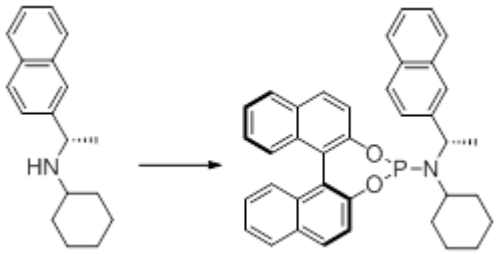
^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.5 (d, *J* = 5.7 Hz), 149.7, 141.3 (d, *J* = 3.8 Hz, 1 C), 133.3, 132.8, 132.8 (s, 1 C), 132.5, 131.3, 130.5, 130.2, 129.8, 128.3, 128.23, 128.18, 127.9, 127.7, 127.1, 127.0, 126.2, 126.0, 125.9, 125.8, 125.7, 125.6, 124.7, 124.3, 124.1, 122.3 (d, *J* = 1.9 Hz), 122.0, 121.9, 55.6, 38.5, 22.2, 15.5.

^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 148.14 (s, 1 P).

$[\alpha]^{20}_{589}$= +79.27 (*c* 0.55, $CHCl_3$).

HRMS (EI) *m/z* calcd for $C_{34}H_{28}NO_2P$ $[M]^+$: 513.1858, found: 513.1859.

(*S*,*S*)-11b)-*N*-cyclohexyl-*N*-(1-(naphthalen-2-yl)ethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine X



According to a modified procedure from Trost,[164] triethylamine (1.05 mL, 7.5 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (131 µL, 1.5 mmol, 1.0 eq.) in CH_2Cl_2 (9 mL). The ice bath was removed and the solution left to warm to room temperature before previously synthesised (*S*)-*N*-(1-(naphthalen-2-yl)ethyl)cyclohexanamine (354 mg, 1.4 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (429 mg, 1.5 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (SiO_2, 78:17:1 Petrol: CH_2Cl_2:Et_3N), the title ligand **X** was obtained as a crystalline white solid (322 mg, 0.57 mmol, 41%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.81 - 8.13 (m, 8 H), 7.77 (d, *J* = 7.3 Hz, 1 H), 7.34 - 7.66 (m, 8 H), 7.28 (d, *J* = 5.7 Hz, 2 H), 4.75 (br. s., 1 H), 2.84 (br. s., 1 H), 1.94 (br. s., 1 H), 1.83 (br. s., 3 H), 1.31 - 1.72 (m, 6 H), 0.77 - 1.01 (m, 2 H), 0.56 (d, *J* = 10.7 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 151.0 (d, *J* = 7.4 Hz), 150.5, 143.5, 133.9, 133.4, 133.2, 132.9, 131.8, 130.9, 130.8, 130.0, 128.8, 128.6, 128.5, 128.3, 128.1, 127.6, 127.6, 126.5 (2 C), 126.5, 126.4, 126.2, 125.8, 125.2, 124.8, 124.6 (d, *J* = 5.5 Hz), 122.9, 122.5, 122.1, 56.1 (d, *J* = 5.5 Hz), 54.4 (d, *J* = 16.6 Hz), 35.4, 34.6 (d, *J* = 5.5 Hz), 26.7 (2 C), 25.9, 24.8 (d, *J* = 17.6 Hz).

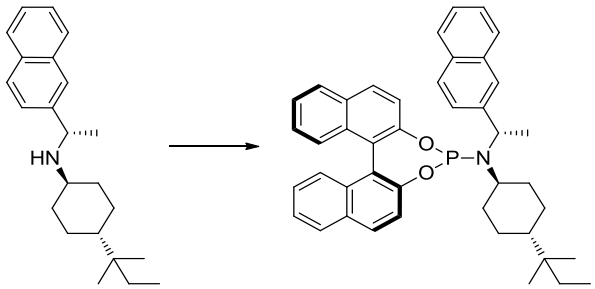
^{31}P NMR (200 MHz, CD_2Cl_2) δ_P /ppm 152.43 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{38}H_{34}NO_2P$ $[M]^+$: 567.2327, found: 567.2317.

$[\alpha]^{20}_{589}$ = −6.11 (*c* 1.03 , $CHCl_3$).

IR (ν_{max}/cm^{-1}): 3302, 2928, 2160, 1590, 1328, 1229, 946, 819, 789, 746, 624.

(*S*,*S*)-*N*-((*S*)-1-(naphthalen-2-yl)ethyl)-*N*-(4-(tert-pentyl)cyclohexyl)dinaphtho[2,1-d:1',2'-f][(S)-1,3,2]dioxaphosphepin-4-amine Y



According to a modified procedure from Trost,[164] triethylamine (0.72 mL, 5.6 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.1 mL, 1.1 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL). The ice bath was removed and the solution left to warm to room temperature before ((*S*)-*N*-(1-(naphthalen-2-yl)ethyl)-4-(*tert*-pentyl)cyclohexanamine (363 mg, 1.1 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (321 mg, 1.1 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2), the ligand **Y** was obtained as a crystalline white solid (278 mg, 0.44 mmol, 40%).

^{1}H NMR (500 MHz, CD_3CN) δ_H /ppm 7.89 (d, *J* = 8.5 Hz, 1 H), 7.67 - 7.84 (m, 6 H), 7.59 - 7.64 (m, 2 H), 7.35 - 7.39 (m, 1 H), 7.29 - 7.35 (m, 2 H), 7.21 - 7.28 (m, 2 H), 7.20 (d, *J* = 2.5 Hz, 1 H), 7.04 - 7.09 (m, 3 H), 6.97 - 7.02 (m, 1 H), 4.48 - 4.64 (m, 1 H), 2.84 - 2.97 (m, 1 H), 1.74 (dt, *J* = 5.0, 2.5 Hz, 8 H), 1.50 (d, *J* = 6.9 Hz, 2 H), 1.30 - 1.41 (m, 1 H), 1.17 - 1.30 (m, 2 H), 1.01 - 1.14 (m, 2 H), 0.39 - 0.49 (m, 6 H), 0.34 (t, *J* = 7.4 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 151.0 - 151.7, 150.4, 133.8, 133.4, 133.2, 132.9, 131.7, 130.8, 130.0, 128.7, 128.5, 128.5 (2 C), 128.1, 128.1, 128.0, 127.6 (d, *J* = 2.8 Hz), 126.7, 126.5 (2 C), 126.4, 126.3, 126.0, 125.1, 124.7, 122.9, 122.7, 122.5, 122.3, 121.6, 54.6 (d, *J* = 8.3 Hz), 51.5 (d, *J* = 9.2 Hz), 44.4, 35.5 (2 C), 34.7, 32.6, 26.6, 24.2 (2 C), 23.1 (d, *J* = 8.3 Hz), 22.6 (d, *J* = 5.5 Hz).

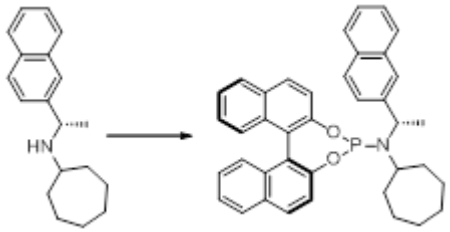
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 152.23 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{43}H_{44}NO_2P$ $[M]^+$: 637.3110, found: 637.3119.

$[\alpha]^{20}_{589}$ = −6.24 (*c* 0.49, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 3056. 2961, 2358, 1619, 1507, 1231, 894 , 749.

(*S*,*S*)-*N*-cycloheptyl-*N*-((*S*)-1-(naphthalen-2-yl)ethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine Z



According to a modified procedure from Feringa[192, 193] or Rajanbabu,[191] (*S*)-*N*-(1-(naphthalen-2-yl)ethyl)cycloheptanamine (178 mg, 0.59 mol, 1.0 eq) was dissolved in THF (5.0 mL) and the solution was cooled to 0 °C. BuLi (2.5 M solution in hexane, 0.28 mL, 0.70 mmol, 1.2 eq) was added dropwise to the solution over about 3 minutes. A solution of (*S*)-phosphorochloridite (222 mg, 0.59 mmol, 1.0 eq) in THF (4.0 mL) was added and the resulting mixture stirred for 10 minutes at 0 °C. The reaction was allowed to warm to room temperature and stirred for 18 hours. Et_2O (*ca* 20 mL) was added and the reaction mixture was stirred for an additional 20 minutes before the reaction mixture was filtered through a layer of celite that was sitting on top of a very thin layer of silica gel and washed with Et_2O (*ca* 25 mL). The filtrate was concentrated *in vacuo*. Et_2O (*ca* 25 mL) was added to precipitate impurities, and the impurities were removed by filtration through celite and a very thin layer of silica. The solid was washed with Et_2O (*ca* 25 mL) and the combined filtrate was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford desired phosphoramidite as an off white foam. Purification by flash column chromatography (1: 49 EtOAc/petrol; SiO_2) gave the desired phosphoramidite **Z** (19 mg, 0.03 mmol, 6%).

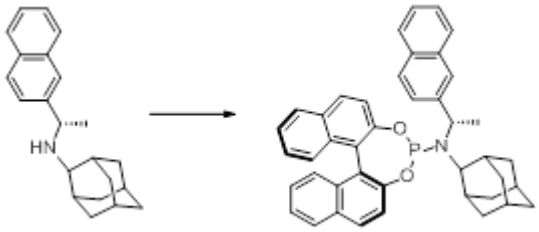
^{1}H NMR (500 MHz, CD_2Cl_2) δ_H /ppm 8.02 (d, *J* = 8.8 Hz, 1 H), 7.94 - 7.99 (m, 2 H), 7.87 - 7.94 (m, 3 H), 7.72 - 7.87 (m, 3 H), 7.57 (d, *J* = 9.5 Hz, 1 H), 7.47 - 7.54 (m, 2 H), 7.43 (s, 1 H), 7.31 - 7.40 (m, 3 H), 7.19 - 7.30 (m, 3 H), 4.60 - 4.74 (m, 1 H), 2.90 - 3.04 (m, 1 H), 1.93 - 2.04 (m, 1 H), 1.82 (s, 1 H), 1.77 (d, *J* = 7.3 Hz, 3 H), 1.54 - 1.66 (m, 2 H), 1.45 - 1.52 (m, 1 H), 1.29 - 1.38 (m, 2 H), 1.18 - 1.26 (m, 1 H), 1.04 (br. s., 2 H), 0.81 - 0.98 (m, 1 H), 0.58 - 0.71 (m, 1 H).

^{13}C NMR (125 MHz, CD_2Cl_2) δ_C /ppm 150.9 (d, *J* = 7.6 Hz, 1 C), 150.6, 134.0, 133.4, 133.2, 133.0, 131.9, 131.1, 130.8, 130.3, 128.9, 128.7, 128.5, 128.3, 128.1, 127.4, 127.3, 126.6, 126.5, 126.2, 126.0, 125.9, 125.3, 124.9, 124.6, 124.5, 122.9, 122.8, 122.5, 122.1, 58.1, 55.2, 30.6, 30.3, 27.8, 27.4, 26.1, 25.7, 25.5.

^{31}P NMR (200 MHz, CD_2Cl_2) δ_P /ppm 151.85 (s, 1 P).

HRMS (EI) *m/z* calcd for $C_{39}H_{36}NO_2P$ $[M]^+$: 581.2484, found: 581.2493.

(*R*,*S*)-*N*-((1*S*,3*S*,5*S*,7*S*)-adamantan-2-yl)-*N*-((*S*)-1-(naphthalen-2-yl)ethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AA



According to a modified procedure from Feringa[192, 193] or Rajanbabu,[191] (1*S*,3*S*,5*S*,7*S*)-*N*-((*S*)-1-(naphthalen-2-yl)ethyl)adamantan-2-amine (225 mg, 0.74 mol, 1.0 eq) was dissolved in THF (3.0 mL) and the solution was cooled to 0 °C. BuLi (2.5 M solution in hexane, 0.35 mL, 0.88 mmol, 1.2 eq) was added dropwise to the solution over about 3 minutes. A solution of (*S*)-phosphorochloridite (222 mg, 0.59 mmol, 1.0 eq) in THF (2.0 mL) was added and the resulting mixture stirred for 10 minutes at 0 °C. The reaction was allowed to warm to room temperature and stirred for 15 hours. Et_2O (*ca* 20 mL) was added and the reaction mixture was stirred for an additional 20 minutes before the reaction mixture was filtered through a layer of celite that was sitting on top of a very thin layer of silica gel and washed with Et_2O (*ca* 25 mL). The filtrate was concentrated *in vacuo*. Et_2O (*ca* 25 mL) was added to precipitate impurities, and the impurities were removed by filtration through celite and a very thin layer of silica. The solid was washed with Et_2O (*ca* 25 mL) and the combined filtrate was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford desired phosphoramidite as an off white foam. Purification by flash column chromatography (1: 33 EtOAc/petrol; SiO_2) gave the desired phosphoramidite **AA** (79 mg, 0.13 mmol, 17%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.01 (d, *J* = 8.8 Hz, 1 H), 7.88 - 7.96 (m, 3 H), 7.83 - 7.87 (m, 1 H), 7.73 - 7.79 (m, 2 H), 7.57 (dd, *J* = 8.5, 6.7 Hz, 2 H), 7.48 - 7.54 (m, 2 H), 7.38 - 7.46 (m, 2 H), 7.33 - 7.38 (m, 2 H), 7.28 - 7.33 (m, 2 H), 7.18 - 7.25 (m, 2 H), 4.92 (br. d, *J* = 5.0 Hz, 1 H), 3.09 - 3.27 (m, 1 H), 2.69 (br. d, *J* = 12.3 Hz, 1 H), 2.63 (d, *J* = 12.3 Hz, 1 H), 2.14 (br. s., 1 H), 1.94 - 2.05 (m, 2 H), 1.71 - 1.83 (m, 2 H), 1.61 - 1.71 (m, 4 H), 1.59 (d, *J* = 6.7 Hz, 3 H), 1.52 (br. s., 2 H), 1.26 - 1.33 (m, 1 H).

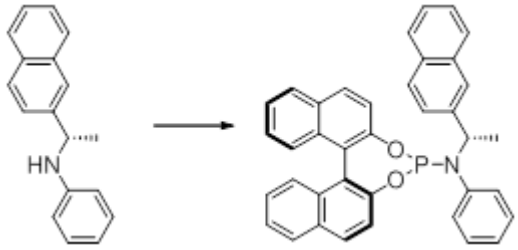
^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 151.3, 149.8, 140.1, 133.2, 133.0, 132.8, 132.4, 131.3, 130.4, 130.1, 129.6, 128.3, 128.04, 127.97, 127.5, 127.3 (2 C), 127.2, 126.8, 126.0, 125.9, 125.7 (2 C), 125.7, 124.7, 124.1, 122.6 (d, *J* = 1.9 Hz), 122.2, 62.9, 54.0, 53.4, 39.7, 38.9, 38.4 (d, *J* = 4.8 Hz), 35.4 (d, *J* = 2.9 Hz), 34.3 (d, *J* = 5.7 Hz), 32.4, 32.2, 31.6, 31.5, 27.5 (2 C).

^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 136.82 (s, 1 P).

HRMS (EI) *m/z* calcd for $C_{42}H_{38}NO_2P$ $[M]^+$: 619.2640, found: 619.2623.

$[\alpha]^{20}_{589}$= −28.43 (*c* 0.61, $CHCl_3$).

(*S*,*S*)-*N*-((*S*)-1-(naphthalen-2-yl)ethyl)-*N*-phenyldinaphtho[(*S*)-2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AB



According to a modified procedure from Trost,[164] triethylamine (0.60 mL, 4.32 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.08 mL, 0.87 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-*N*-(1-(naphthalen-2-yl)ethyl)aniline (214 mg, 0.87 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (248 mg, 0.87 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2), the ligand **AB** was obtained as a crystalline white solid (133 mg, 0.23 mmol, 27%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.01 (d, *J* = 8.8 Hz, 1 H), 7.93 (d, *J* = 8.5 Hz, 1 H), 7.81 - 7.87 (m, 2 H), 7.77 (d, *J* = 8.8 Hz, 1 H), 7.70 - 7.73 (m, 1 H), 7.66 (d, *J* = 8.8 Hz, 1 H), 7.62 (d, *J* = 8.8 Hz, 1 H), 7.45 - 7.51 (m, 2 H), 7.37 - 7.44 (m, 4 H), 7.34 (d, *J* = 8.5 Hz, 1 H), 7.20 - 7.30 (m, 3 H), 7.17 (d, *J* = 8.8 Hz, 1 H), 6.96 - 7.05 (m, 3 H), 6.89 - 6.95 (m, 2 H), 5.20 (quin, *J* = 6.9 Hz, 1 H), 1.70 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 149.8 (d, *J* = 8.6 Hz), 149.1, 139.8 (d, *J* = 10.5 Hz), 139.6 (d, *J* = 1.9 Hz), 133.0, 132.9 (d, *J* = 1.9 Hz), 132.6, 132.5, 131.4, 131.2, 131.1, 130.4, 130.3, 129.3, 128.3, 128.1 (3 C), 128.0 (2 C), 127.5, 127.4, 127.1, 127.1, 126.7, 126.5, 126.2, 126.0, 125.9, 125.8 (2 C), 124.8, 124.4, 122.3, 122.2 (d, *J* = 1.9 Hz), 121.5 (d, *J* = 2.9 Hz), 57.1 (d, *J* = 18.1 Hz), 21.1 (d, *J* = 4.8 Hz).

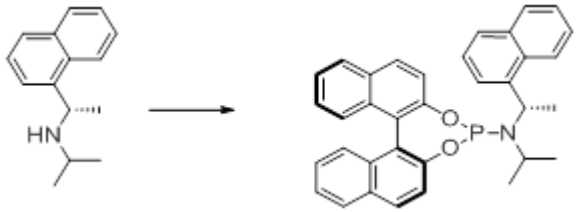
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 142.33 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{38}H_{28}NO_2P$ $[M-1]^+$: 561.1850, found: 561.1858.

$[\alpha]^{20}_{589}$= +80.53 (*c* 0. 95, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 3056, 2361, 1591, 1506, 1221, 946, 820, 749.

(*S*,*S*)-*N*-isopropyl-*N*-((*S*)-1-(naphthalen-1-yl)ethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AC



According to a modified procedure from Trost,[164] triethylamine (1.00 mL, 7.4 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.13 mL, 1.5 mmol, 1.0 eq.) in CH_2Cl_2 (10.9 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-*N*-(1-(naphthalen-1-yl)ethyl)propan-2-amine (317 mg, 1.5 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (426 mg, 1.5 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 79:10:1 → 69:20:1, SiO_2), the ligand **AC** was obtained as a crystalline white solid (413 mg, 0.78 mmol, 52%).

Data consistent with literature.[191]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.30 (d, *J* = 6.9 Hz, 1 H), 8.09 (d, *J* = 8.2 Hz, 1 H), 8.02 (d, *J* = 8.8 Hz, 1 H), 7.91 - 7.97 (m, 2 H), 7.84 (dd, *J* = 8.2, 5.4 Hz, 2 H), 7.75 (d, *J* = 8.8 Hz, 1 H), 7.67 (t, *J* = 7.4 Hz, 1 H), 7.61 (d, *J* = 8.8 Hz, 1 H), 7.48 - 7.58 (m, 2 H), 7.42 - 7.47 (m, 2 H), 7.35 - 7.42 (m, 3 H), 7.23 - 7.31 (m, 2 H), 5.41 (dq, *J* = 14.4, 7.3 Hz, 1 H), 3.48 (dtt, *J* = 9.9, 6.6, 6.6, 3.5, 3.5 Hz, 1 H), 1.90 (dd, *J* = 7.4, 2.7 Hz, 3 H), 1.10 (d, *J* = 6.6 Hz, 3 H), 0.57 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.4 (d, *J* = 6.5 Hz), 150.0, 143.3, 133.9, 132.9, 132.6, 131.4, 130.5, 130.2, 129.9, 129.4, 129.1, 128.3, 128.2, 127.2, 127.1, 127.1, 126.1, 126.0, 125.8, 125.7, 125.4, 124.7, 124.3, 124.1 (d, *J* = 6.5 Hz), 123.6 (d, *J* = 5.5 Hz), 122.4, 122.3, 122.0, 121.8 (d, *J* = 1.2 Hz), 49.6 (d, *J* = 25.0 Hz), 46.9 (d, *J* = 1.8 Hz), 25.4 (d, *J* = 26.0 Hz), 22.5, 22.0.

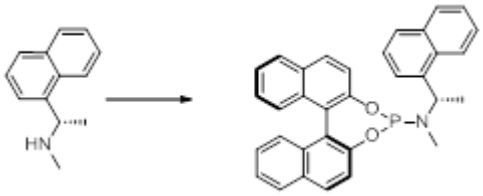
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 151.81 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{35}H_{30}NO_2P$ $[M]^+$: 527.2014, found: 527.2014.

$[\alpha]^{20}_{589}$ = −221.69 (*c* 0.86 , $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2972, 2384, 1463, 1233, 938, 822, 750.

(*S*,*S*)-*N*-methyl-*N*-((*S*)-1-(naphthalen-1-yl)ethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AD



According to a modified procedure from Trost,[164] triethylamine (1.0 mL, 7.1 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.12 mL, 1.4 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL). The ice bath was removed and the solution left to warm to room temperature before (S)-*N*-methyl-1-(naphthalen-1-yl)ethanamine (261 mg, 1.4 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (403 mg, 1.4 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2), the ligand **AD** was obtained as a crystalline white solid (86.9 mg, 0.17 mmol, 12%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.41 (dd, *J* = 8.2, 1.6 Hz, 1 H), 8.06 (d, *J* = 8.5 Hz, 1 H), 8.01 (d, *J* = 8.2 Hz, 1 H), 7.94 - 7.98 (m, 2 H), 7.89 (d, *J* = 8.2 Hz, 1 H), 7.74 (t, *J* = 7.4 Hz, 1 H), 7.70 (d, *J* = 7.3 Hz, 1 H), 7.62 (dd, *J* = 8.2, 5.0 Hz, 1 H), 7.52 - 7.59 (m, 3 H), 7.42 - 7.51 (m, 5 H), 7.36 - 7.41 (m, 1 H), 7.28 - 7.36 (m, 3 H), 5.71 (dd, *J* = 10.4, 6.9 Hz, 1 H), 1.94 - 2.11 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.4 (d, *J* = 5.5 Hz), 149.6, 136.6 (d, *J* = 11.1 Hz), 134.2, 132.9, 132.7, 131.7, 131.5, 130.7, 130.3 (2 C), 130.1, 129.0, 128.4, 128.3, 127.1 (2 C), 127.0, 126.3, 126.1, 125.7, 124.9, 124.6 (2 C), 124.0 (d, *J* = 4.6 Hz), 123.8, 123.7, 122.7 (d, *J* = 1.8 Hz), 122.2, 121.9, 52.3, 27.4 (d, *J* = 3.7 Hz), 19.9 (d, *J* = 8.3 Hz).

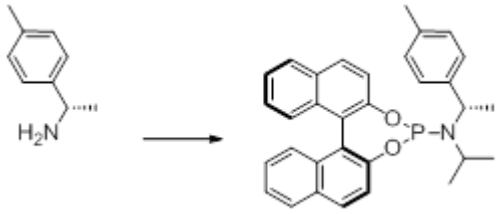
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 142.49 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{33}H_{26}NO_2P$ $[M]^+$: 499.1701, found: 499.1697.

$[\alpha]^{20}_{589}$= +143.60 (*c* 1.02, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 3010. 2977, 2342, 1732, 1705, 967, 839, 698.

(*S*,*S*)-*N*-isopropyl-*N*-((*S*)-1-(*p*-tolyl)ethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AF



According to a modified procedure from Davies[266] and Trost,[164] acetone (0.28 mL, 3.78 mmol, 2.0 eq.) was added to a stirring solution of (*S*)-1-(*p*-tolyl)ethanamine (0.28 mL, 1.89 mmol, 1.0 eq.) in THF (10 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (821 mg, 2.81 mmol, 1.5 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (15 mL) and $NaHCO_3$ (aq. sat., *ca* 15 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired amine as a yellow oil (193mg).

In the meantime, triethylamine (0.76 mL, 5.4 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.1 mL, 1.1 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL). The ice bath was removed and the solution left to warm to room temperature before previously synthesized (*S*)-*N*-(1-(*p*-tolyl)ethyl)propan-2-amine (193 mg, 1.1 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (311 mg, 1.1 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2), the ligand **AF** was obtained as a crystalline white solid (339 mg, 0.69 mmol, 63%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.98 (d, *J* = 8.8 Hz, 1 H), 7.92 (d, *J* = 8.2 Hz, 1 H), 7.87 (d, *J* = 8.2 Hz, 1 H), 7.80 (d, *J* = 8.8 Hz, 1 H), 7.54 (d, *J* = 8.8 Hz, 1 H), 7.50 (d, *J* = 7.9 Hz, 2 H), 7.37 - 7.43 (m, 3 H), 7.35 (d, *J* = 8.8 Hz, 1 H), 7.31 (d, *J* = 8.2 Hz, 1 H), 7.20 - 7.27 (m, 4 H), 4.49 (dq, *J* = 14.3, 7.2 Hz, 1 H), 3.34 (dq, *J* = 13.4, 6.9 Hz, 1 H), 2.39 (s, 3 H), 1.71 (d, *J* = 6.9 Hz, 3 H), 1.14 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.9 (d, *J* = 7.4 Hz), 150.5, 143.1, 136.6, 133.3, 133.1, 131.7, 130.9, 130.7, 129.9, 129.4 (2 C), 128.7, 128.6, 127.61, 127.63, 127.4 4, 127.40, 126.4,

126.2, 125.1, 124.7, 124.5 (d, *J* = 5.5 Hz), 122.9, 122.7, 122.1 (d, *J* = 1.8 Hz), 53.1 (d, *J* = 19.4 Hz), 46.9 (d, *J* = 3.7 Hz), 25.1, 24.3 (d, *J* = 3.7 Hz), 23.6 (d, *J* = 4.6 Hz), 21.5.

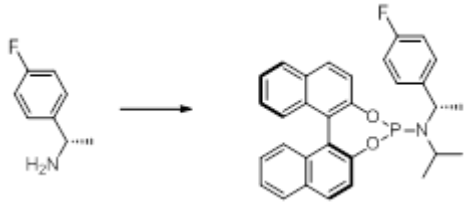
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 152.11 (s, 1 P)

HRMS (EI) *m/z* calcd for $C_{32}H_{30}NO_2P$ $[M]^+$: 491.2014, found: 491.2007.

$[\alpha]^{20}_{589}$= +130.92 (*c* 0.67, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2972, 1726, 1591, 1463, 1232, 1206, 947, 820, 751.

(*R*,*S*)-(11b*S*)-*N*-((*S*)-1-(4-fluorophenyl)ethyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AG



$NaB(OAc)_3H$ (0.83 g, 4.3 mmol, 2.0 eq.) and acetone (0.25 mL, 4.3 mmol, 2.0 eq.) were added to a stirred solution (*S*)-1-(4-fluorophenyl)ethanamine (0.23 mL, 1.7 mmol, 1.0 eq.) at room temperature. The reaction mixture was stirred for 24 h before a saturated aqueous solution of $NaHCO_3$ (10 mL) was added and stirring continuously for 15 min. Et_2O (*ca* 20 mL) was added and the aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*.

Triethylamine (0.77 mL, 5.5 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.10 mL, 1.1 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-*N*-(1-(4-fluorophenyl)ethyl)propan-2-amine (200 mg, 1.1 mmol, 1.0 eq.) was added to the stirring solution. After 5 h (*S*)-binaphthol (315 mg, 1.1 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (84:15:1; Petrol: CH_2Cl_2: Et_3N; SiO_2), ligand **AG** was obtained as a crystalline white solid (226 mg, 0.46 mmol, 41%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.04 (d, *J* = 8.8 Hz, 1 H), 7.98 (d, *J* = 8.5 Hz, 1 H), 7.93 (d, *J* = 8.5 Hz, 1 H), 7.86 (dd, *J* = 8.5, 0.2 Hz, 1 H), 7.56 - 7.66 (m, 3 H), 7.42 - 7.51 (m, 3 H), 7.34 - 7.40 (m, 2 H), 7.27 - 7.34 (m, 2 H), 7.11 - 7.20 (m, 2 H), 4.50 - 4.61 (m, 1 H), 3.34 - 3.45 (m, 1 H), 1.76 (dd, *J* = 7.2, 0.3 Hz, 3 H), 1.20 (d, *J* = 6.9 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.8, 150.3, 141.8, 133.3, 133.1, 131.8, 130.9, 130.7, 129.9, 129.5, 129.1, 129.0, 128.7, 128.6, 127.6, 127.5, 126.4, 126.3, 125.2, 124.8, 124.5 (d, *J* = 5.5 Hz), 122.8, 122.5, 122.1, 115.5, 115.4, 52.8, 47.0, 25.1, 24.3, 23.6.

^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 151.77 (s, 1 P).

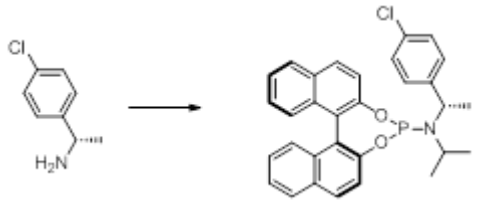
^{19}F NMR (400 MHz, $CDCl_3$) δ_F /ppm –116.65 (s, 1 F).

HRMS (EI) *m/z* calcd for $C_{31}H_{27}FNO_2P$ $[M]^+$: 495.1764, found: 495.1882.

$[\alpha]^{20}_{589}$= +196.44 (*c* 1.24 , $CHCl_3$).

IR (ν_{max}/cm^{-1}): 750, 822, 947, 1231, 1591, 2360, 2973.

(*S*,*S*)-(11b*S*)-*N*-((*S*)-1-(4-chlorophenyl)ethyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AH



$NaB(OAc)_3H$ (0.64 g, 3.0 mmol, 1.5 eq.) and acetone (0.29 mL, 4.0 mmol, 2.0 eq.) were added to a stirred solution (*S*)-4-chloro-α-methylbenzylamine (0.28 mL, 2.0 mmol, 1.0 eq.) in THF (10 mL) at room temperature. The reaction mixture was stirred for 24 h before a saturated aqueous solution of $NaHCO_3$ (10 mL) was added and stirring continued for 15 min. Et_2O (*ca* 10 mL) was added and the aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Triethylamine (0.71 mL, 5.1 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.09 mL, 1.0 mmol, 1.0 eq.) in CH_2Cl_2 (4 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-*N*-(1-(4-chlorophenyl)ethyl)propan-2-amine (200 mg, 1.0 mmol, 1.0 eq.) was added to the stirring solution. After 5 h (*S*)-binaphthol (289 mg, 1.0 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (84:15:1; Petrol: CH_2Cl_2: Et_3N; SiO_2), ligand **AH** was obtained as a crystalline white solid (220 mg, 0.43 mmol, 43%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.04 (d, *J* = 8.8 Hz, 1 H), 7.98 (d, *J* = 8.5 Hz, 1 H), 7.93 (d, *J* = 8.5 Hz, 1 H), 7.86 (d, *J* = 8.8 Hz, 1 H), 7.59 (m, *J* = 8.5 Hz, 3 H), 7.41 - 7.50 (m, 5 H), 7.34 - 7.39 (m, 2 H), 7.27 - 7.34 (m, 2 H), 4.54 (dq, *J* = 14.0, 7.2 Hz, 1 H), 3.33 - 3.44 (m, 1 H), 1.75 (d, *J* = 7.2 Hz, 3 H), 1.20 (d, *J* = 6.6 Hz, 3 H), 1.00 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.5, 150.1, 144.5, 133.1, 132.9, 132.6, 131.6, 130.7, 130.5, 129.7, 128.7, 128.7, 128.6, 128.5, 128.4, 127.4, 127.3, 126.2, 126.1, 125.0, 124.6, 124.2, 122.5, 122.3, 121.9, 52.8, 46.8, 24.8, 24.1, 23.4.

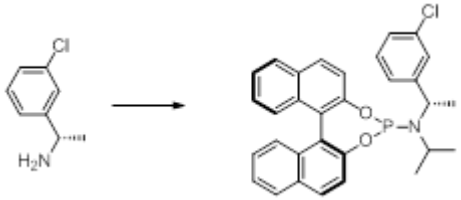
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 151.50 (s, 1 P).

HRMS (EI) *m/z* calcd for $C_{31}H_{27}ClNO_2P$ $[M]^+$: 511.1468, found: 511.1542.

$[\alpha]^{20}_{589}$= +104.67 (*c* 1.20 , $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2972, 2360, 1619, 1328, 949, 821, 749.

(*S*,*S*)-(11b*S*)-*N*-((*S*)-1-(3-chlorophenyl)ethyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AI



$NaB(OAc)_3H$ (0.64 g, 3.0 mmol, 1.5 eq.) and acetone (0.29 mL, 4.0 mmol, 2.0 eq.) were added to a stirred solution (*S*)-3-chloro-α-methylbenzylamine (0.28 mL, 2.0 mmol, 1.0 eq.) in THF (10 mL) at room temperature. The reaction mixture was stirred for 24 h before a saturated aqueous solution of $NaHCO_3$ (10 mL) was added and stirring continued for 15 min. Et_2O (*ca* 10 mL) was added and the aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*.

Triethylamine (0.71 mL, 5.1 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.09 mL, 1.0 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-*N*-(1-(3-chlorophenyl)ethyl)propan-2-amine (200 mg, 1.0 mmol, 1.0 eq.) was added to the stirring solution. After 5 h (*S*)-binaphthol (289 mg, 1.0 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (84:15:1; Petrol: CH_2Cl_2: Et_3N; SiO_2), ligand **AI** was obtained as a crystalline white solid (266 mg, 0.52 mmol, 52%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.99 (d, *J* = 8.8 Hz, 1 H), 7.93 (d, *J* = 8.2 Hz, 1 H), 7.89 (d, *J* = 7.7 Hz, 1 H), 7.83 (d, *J* = 8.8 Hz, 1 H), 7.62 (m, *J* = 2.1, 2.1 Hz, 1 H), 7.55 (d, *J* = 8.8 Hz, 1 H), 7.50 (d, *J* = 7.7 Hz, 1 H), 7.39 - 7.45 (m, 3 H), 7.22 - 7.39 (m, 6 H), 4.49 (dq, *J* = 14.0, 7.1 Hz, 1 H), 3.36 (dq, *J* = 13.5, 7.1 Hz, 1 H), 1.72 (d, *J* = 7.1 Hz, 3 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 0.96 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.7 (d, *J* = 7.4 Hz), 150.3, 148.4, 134.7, 133.3, 133.1, 131.8, 131.0, 130.8, 130.0, 130.0, 128.7, 128.7, 127.8, 127.6, 127.6, 127.2, 126.5, 126.3, 125.6, 125.2, 124.8, 124.5, 122.7, 122.5, 122.1, 53.1 (d, *J* = 19.4 Hz), 47.1 (d, *J* = 5.5 Hz), 24.8 (d, *J* = 19.4 Hz), 24.3 (d, *J* = 4.6 Hz), 23.6 (d, *J* = 5.5 Hz).

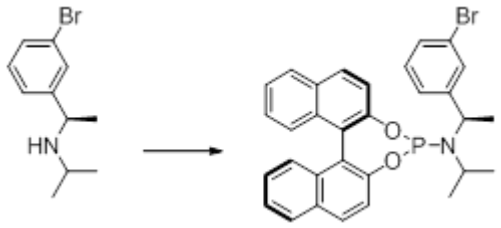
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 151.46 (s, 1 P).

HRMS (EI) *m/z* calcd for $C_{31}H_{27}ClNO_2P$ $[M]^+$: 511.1468, found: 511.1548.

$[\alpha]^{20}_{589}$= +153.52 (*c* 0.88 , $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2974, 2340, 1505, 1232, 821, 749.

(*R*,*R*)-*N*-((*R*)-1-(3-bromophenyl)ethyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AJ



According to a modified procedure from Trost,[164] triethylamine (0.62 mL, 4.4 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.08 mL, 0.9 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL). The ice bath was removed and the solution left to warm to room temperature before (*R*)-*N*-(1-(3-bromophenyl)ethyl)propan-2-amine (214 mg, 0.8 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (253.4 mg, 0.8 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol:CH_2Cl_2:Et_3N; 82:17:1 SiO_2), the ligand **AJ** was obtained as a crystalline white solid (337 mg, 0.60 mmol, 68%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.99 (d, *J* = 8.8 Hz, 1 H), 7.92 (d, *J* = 8.2 Hz, 1 H), 7.86 - 7.89 (m, 1 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.78 (s, 1 H), 7.51 - 7.58 (m, 2 H), 7.38 - 7.47 (m, 3 H), 7.36 (d, *J* = 8.8 Hz, 1 H), 7.20 - 7.32 (m, 5 H), 4.48 (dq, *J* = 14.0, 7.0 Hz, 1 H), 3.34 (dq, *J* = 13.4, 7.0 Hz, 1 H), 1.70 (d, *J* = 7.0 Hz, 3 H), 1.15 (d, *J* = 7.0 Hz, 3 H), 0.95 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.7 (d, *J* = 7.4 Hz), 150.3, 148.7, 133.3, 133.1, 131.8, 130.9, 130.7, 130.3, 130.2, 130.0, 128.73, 128.69, 127.6, 127.5, 126.5, 126.3, 126.1, 126.0, 125.2, 124.8, 124.4 (d, *J* = 5.5 Hz), 122.9, 122.7 (d, *J* = 1.8 Hz), 122.5, 122.1 (d, *J* = 2.8 Hz), 53.1 (d, *J* = 19.4 Hz), 47.1 (d, *J* = 4.6 Hz), 25.3, 24.3, 23.6 (d, *J* = 5.5 Hz).

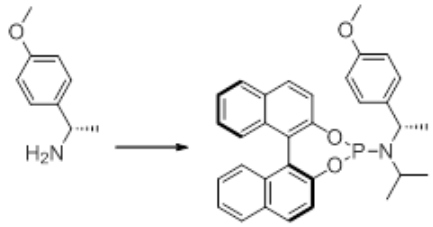
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 151.47 (s, 1 P).

HRMS (EI) *m/z* calcd for $C_{31}H_{27}BrNO_2P$ $[M]^+$: 555.0957, found: 555.0963.

$[\alpha]^{20}_{589}$ = −107.12 (*c* 0.63, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2973, 1591, 1429, 1233, 822, 751.

(*S*,*S*)-*N*-isopropyl-*N*-((*S*)-1-(4-methoxyphenyl)ethyl)dinaphtho[S-2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AK



According to a modified procedure from Davies[266] and Trost,[164] acetone (0.25 mL, 3.4 mmol, 1.1 eq.) was added to a stirring solution of (*S*)-1-(4-methoxyphenyl)ethanamine (0.45 mL, 3.1 mmol, 1.0 eq.) in THF (9 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (487 mg, 3.1 mmol, 1.2 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 72 h. Et_2O (15 mL) and $NaHCO_3$ (aq. sat., *ca* 15 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired amine as a yellow oil (150 mg, 0.77 mmol.

In the meantime, triethylamine (0.54 mL, 3.9 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.07 mL, 0.8 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL). The ice bath was removed and the solution left to warm to room temperature before the freshly prepared (*S*)-*N*-(1-(2-methoxyphenyl)ethyl)propan-2-amine (150 mg, 0.8 mmol, 1.0 eq., half of the crude) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (222 mg, 0.8 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2:Et_3N; 82:17:1 SiO_2), the ligand **AK** was obtained as a crystalline white solid (23 mg, 0.04 mmol, 5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.98 (d, *J* = 8.8 Hz, 1 H), 7.92 (d, *J* = 8.2 Hz, 1 H), 7.76 - 7.89 (m, 2 H), 7.50 (s, 3 H), 7.41 (s, 4 H), 7.22 - 7.30 (m, 3 H), 6.93 (s, 2 H), 4.48 (dd, *J* = 14.2, 7.1 Hz, 1 H), 3.85 (s, 3 H), 3.32 (s, 1 H), 1.69 (d, *J* = 7.1 Hz, 3 H), 1.14 (d, *J* = 7.1 Hz, 3 H), 0.92 - 1.04 (d, *J* = 6.6 Hz, 3 H).

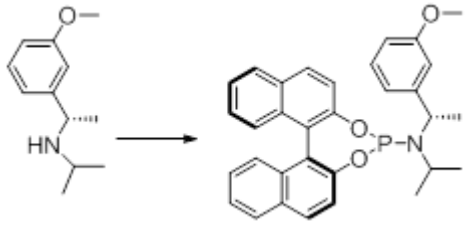
^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 155.3, 150.5, 150.1, 137.2, 134.1, 134.1, 133.1, 131.0, 130.3, 129.1, 128.5, 128.0, 127.7, 127.4 (d, *J* = 7.1 Hz), 127.3, 126.2, 125.1, 124.4, 124.1, 124.1 (d, *J* = 4.6 Hz), 122.1, 122.0, 121.9, 120.4, 110.1, 55.0, 46.9, 46.7 (d, *J* = 3.7 Hz), 24.8 (d, *J* = 28.0 Hz), 22.5, 21.0.

^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 149.74 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{32}H_{30}NO_3P$ $[M]^+$: 507.1963, found: 507.1959.

IR (ν_{max}/cm^{-1}): 2952, 1595, 1463, 950, 822, 751.

(*S*,*S*)-*N*-isopropyl-*N*-((*S*)-1-(3-methoxyphenyl)ethyl)dinaphtho[S-2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AL



According to a modified procedure from Trost and coworkers,[164] triethylamine (0.63 mL, 3.6 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.08 mL, 0.9 mmol, 1.0 eq.) in CH_2Cl_2 (4 mL). The ice bath was removed and the solution left to warm to room temperature before the freshly prepared (*S*)-*N*-(1-(3-methoxyphenyl)ethyl)propan-2-amine (176 mg, 0.9 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (261 mg, 0.9 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol:CH_2Cl_2:Et_3N; 82:17:1 SiO_2), the ligand **AL** was obtained as a crystalline white solid (365 mg, 0.67 mmol, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 8.00 (d, *J* = 8.8 Hz, 1 H), 7.94 (d, *J* = 8.4 Hz, 1 H), 7.85 (dd, *J* = 17.2, 8.4 Hz, 2 H), 7.57 (dd, *J* = 8.8, 0.7 Hz, 1 H), 7.29 - 7.48 (m, 6 H), 7.15 - 7.28 (m, 4

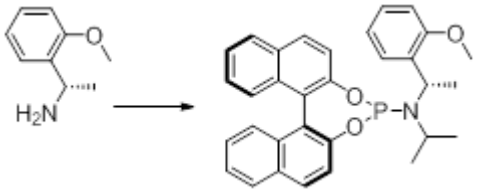
H), 6.84 (s, 1 H), 4.51 (dd, *J* = 14.6, 7.1 Hz, 1 H), 3.90 (s, 3 H), 3.37 (s, 1 H), 1.74 (dd, *J* = 7.2, 1.2 Hz, 3 H), 1.14 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 155.3, 150.5, 150.2, 135.9, 132.9, 132.6, 131.3, 130.5, 130.1, 129.3, 128.4, 128.1, 127.5, 127.4 (d, *J* = 6.5 Hz), 127.2 (2 C), 125.9, 125.7, 124.6, 124.5, 124.4 (d, *J* = 4.6 Hz), 122.4, 122.5, 121.9, 120.6, 110.2, 55.2, 46.8, 46.6, 24.8, 22.3, 21.5.

^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 149.21 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{32}H_{30}NO_3P$ $[M]^+$: 507.1963, found: 507.1964.

(*S*,*S*)-*N*-isopropyl-*N*-((*S*)-1-(2-methoxyphenyl)ethyl)dinaphtho[2,1-d:1',2'-f][S-1,3,2]dioxaphosphepin-4-amine AM



According to a modified procedure from Davies[266] and Trost,[164] acetone (0.11 mL, 1.5 mmol, 1.1 eq.) was added to a stirring solution of (*S*)-1-(2-methoxyphenyl)ethanamine (0.16 mL, 1.4 mmol, 1.0 eq.) in THF (9 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (590 mg, 2.9 mmol, 2 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 72 h. Et_2O (15 mL) and $NaHCO_3$ (aq. sat., *ca* 15 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired amine as a yellow oil (265 mg, 1.37 mmol, 88%).

In the meantime, triethylamine (0.48 mL, 3.4 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.06 mL, 0.7 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL). The ice bath was removed and the solution left to warm to room temperature before the freshly prepared (*S*)-*N*-(1-(2-methoxyphenyl)ethyl)propan-2-amine (132 mg, 0.7 mmol, 1.0 eq., half of the crude) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (197 mg, 0.7 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2), the ligand **AM** was obtained as a crystalline white solid (195 mg, 0.38 mmol, 56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.02 (d, *J* = 7.3 Hz, 1 H), 7.99 (d, *J* = 8.8 Hz, 1 H), 7.93 (d, *J* = 8.2 Hz, 1 H), 7.88 (d, *J* = 8.2 Hz, 1 H), 7.79 (d, *J* = 8.8 Hz, 1 H), 7.58 (d, *J* = 8.5 Hz, 1 H), 7.38 - 7.47 (m, 3 H), 7.35 (d, *J* = 8.5 Hz, 1 H), 7.24 - 7.31 (m, 4 H), 7.13 (t, *J* = 7.4 Hz, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 4.88 - 5.06 (m, 1 H), 3.87 (s, 3 H), 3.32 - 3.45 (m, 1 H), 1.71 (dd, *J* = 7.4, 2.4 Hz, 3 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.65 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 155.3, 150.5 (d, *J* = 6.5 Hz), 150.1, 135.9, 132.9, 132.6, 131.3, 130.5, 130.1, 129.3, 128.3, 128.2, 127.5, 127.4 (d, *J* = 6.5 Hz), 127.1 (2 C), 125.9, 125.7, 124.6, 124.2, 124.1 (d, *J* = 4.6 Hz), 122.4, 122.2, 121.9, 120.6, 110.2, 55.2, 46.8 (d, *J* = 23.0 Hz), 46.6 (d, *J* = 3.7 Hz), 24.8 (d, *J* = 28.0 Hz), 22.3, 21.5.

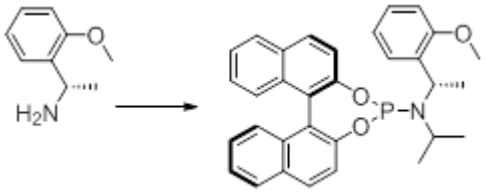
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 151.97 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{32}H_{30}NO_3P$ $[M]^+$: 507.1963, found: 507.1951.

$[\alpha]^{20}_{589}$= +188.30 (*c* 0.98, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2973, 1590, 1233, 950, 822, 750.

(*R*,*S*)-*N*-isopropyl-*N*-((*S*)-1-(2-methoxyphenyl)ethyl)dinaphtho[2,1-d:1',2'-f][R-1,3,2]dioxaphosphepin-4-amine



According to a modified procedure from Davies[266] and Trost,[164] acetone (0.11 mL, 1.5 mmol, 1.1 eq.) was added to a stirring solution of (*S*)-1-(2-methoxyphenyl)ethanamine (0.16 mL, 1.4 mmol, 1.0 eq.) in THF (9 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (590 mg, 2.9 mmol, 2 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 72 h. Et_2O (15 mL) and $NaHCO_3$ (aq. sat., *ca* 15 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired amine as a yellow oil (265 mg, 1.37 mmol, 88%).

In the meantime, triethylamine (0.48 mL, 3.4 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.06 mL, 0.7 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL). The ice bath was removed and the solution left to warm to room temperature before the freshly prepared (*S*)-*N*-(1-(2-methoxyphenyl)ethyl)propan-2-amine (132 mg, 0.7 mmol, 1.0 eq., half of the crude) was added to

the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (197 mg, 0.7 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol:CH_2Cl_2:Et_3N; 82:17:1 SiO_2), the ligand was obtained as a crystalline white solid (155 mg, 0.30 mmol, 44%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.00 (d, *J* = 8.8 Hz, 1 H), 7.88 - 7.96 (m, 3 H), 7.76 (d, *J* = 6.9 Hz, 1 H), 7.59 (d, *J* = 8.8 Hz, 1 H), 7.51 (d, *J* = 8.8 Hz, 1 H), 7.37 - 7.46 (m, 3 H), 7.34 (d, *J* = 8.8 Hz, 1 H), 7.18 - 7.30 (m, 3 H), 7.06 (t, *J* = 7.1 Hz, 1 H), 6.85 (d, *J* = 7.9 Hz, 1 H), 5.00 (dq, *J* = 14.7, 7.1 Hz, 1 H), 3.82 (s, 3 H), 3.53 (quint, *J* = 6.6, 4.1 Hz, 1 H), 1.74 (dd, *J* = 7.4, 1.7 Hz, 3 H), 1.15 (d, *J* = 6.6 Hz, 3 H), 0.63 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 155.9, 151.2, 151.1, 150.6, 135.8, 133.3, 133.2, 131.8, 130.9, 130.7, 129.8, 128.7, 128.6, 128.0, 127.8, 127.6, 127.6, 126.4, 126.2, 125.1, 124.7, 124.5, 122.9 (d, *J* = 2.8 Hz), 122.0, 121.0, 110.7, 55.7, 46.7, 46.6 (d, *J* = 6.5 Hz), 25.4, 23.3, 22.8.

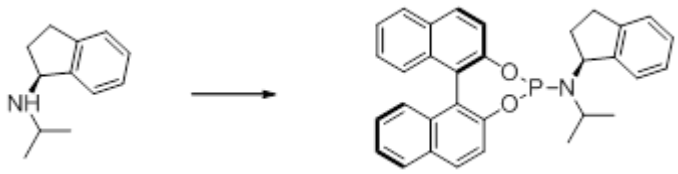
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 150.48 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{32}H_{30}NO_3P$ $[M]^+$: 507.1963, found: 506.1951.

$[\alpha]^{20}_{589}$= +253.00 (*c* 0.86, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2971, 2350, 1739, 1204, 865, 750.

(*R*,*S*)-*N*-((*S*)-2,3-dihydro-1H-inden-1-yl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine



According to a modified procedure from Trost,[164] triethylamine (0.72 mL, 5.16 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.09 mL, 0.8 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-*N*-isopropyl-2,3-dihydro-1H-inden-1-amine (181 mg, 0.8 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (296 mg, 0.8 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After

flash column chromatography (Petrol:CH_2Cl_2:Et_3N; 82:17:1 SiO_2), the ligand was obtained as a crystalline white solid (92 mg, 0.19 mmol, 18%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.96 (dd, *J* = 8.8, 4.7 Hz, 2 H), 7.92 (s, 0 H), 7.88 - 7.91 (m, 1 H), 7.54 (d, *J* = 8.8 Hz, 1 H), 7.50 (d, *J* = 8.8 Hz, 1 H), 7.37 - 7.44 (m, 3 H), 7.30 - 7.34 (m, 1 H), 7.19 - 7.27 (m, 3 H), 7.10 - 7.18 (m, 2 H), 4.74 (q, *J* = 8.8 Hz, 0 H), 3.22 (tt, *J* = 12.5, 6.1 Hz, 1 H), 2.90 - 2.98 (m, 1 H), 2.62 (dt, *J* = 16.0, 8.2 Hz, 1 H), 2.10 - 2.21 (m, 1 H), 1.38 (d, *J* = 6.6 Hz, 3 H), 1.23 (d, *J* = 6.6 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 150.0, 149.9 (d, *J* = 5.5 Hz), 143.0, 132.7 (d, *J* = 9.2 Hz), 131.3, 130.5, 130.1, 129.3, 128.3, 128.1, 127.3, 127.1, 127.0, 126.4, 126.1, 125.94, 125.86, 125.0, 124.6, 124.4, 124.4, 123.92, 123.88, 122.5, 122.4, 122.1, 59.2, 46.2, 46.1, 30.3 (2 C), 30.2.

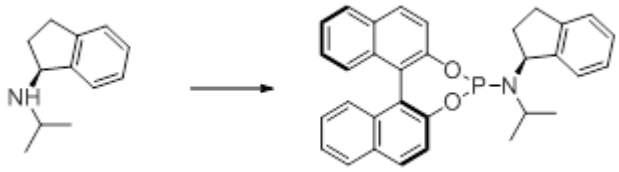
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 150.68 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{32}H_{28}NO_2P$ $[M]^+$: 489.1858, found: 489.1865.

$[\alpha]^{20}_{589}$= −217.51 (*c* 0.65 , $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2968, 1724, 1462, 1233, 947, 822, 751.

(*S*,*S*)-*N*-((*S*)-2,3-dihydro-1H-inden-1-yl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][S-1,3,2]dioxaphosphepin-4-amine AN



According to a modified procedure from Trost,[164] triethylamine (0.72 mL, 4.00 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.09 mL, 0.8 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL). The ice bath was removed and the solution left to warm to room temperature before (S)-*N*-isopropyl-2,3-dihydro-1H-inden-1-amine (180 mg, 0.8 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (296 mg, 0.8 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 74:25:1 SiO_2), the ligand **AN** was obtained as a crystalline white solid (86 mg, 0.18 mmol, 17%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.95 (d, *J* = 8.5 Hz, 1 H), 7.89 (q, *J* = 6.3 Hz, 2 H), 7.63 (d, *J* = 7.3 Hz, 1 H), 7.58 (d, *J* = 8.5 Hz, 1 H), 7.50 (d, *J* = 8.5 Hz, 1 H), 7.41 (d, *J* = 7.9 Hz, 3 H), 7.31 (d, *J* = 8.5 Hz, 2 H), 7.17 - 7.26 (m, 4 H), 7.14 (br. d, *J* = 3.5 Hz, 1 H), 4.76 (s, 1 H), 3.35 (dd, *J* = 12.5, 5.8 Hz, 1 H), 2.97 (dd, *J* = 14.5, 9.1 Hz, 1 H), 2.72 (dt, *J* = 15.9, 8.5 Hz, 1 H), 2.42 - 2.53 (m, 1 H), 2.11 - 2.20 (m, 1 H), 1.31 (d, *J* = 6.3 Hz, 3 H), 1.21 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.3, 150.2, 150.0, 144.5, 143.1, 132.8, 132.7, 131.3, 130.5, 130.2, 129.5, 128.2, 128.2, 127.3, 127.13, 127.08, 126.4, 125.9, 125.8, 124.8, 124.6, 124.6, 124.3, 124.0 (d, *J* = 5.5 Hz), 122.3, 121.6, 59.4 (d, *J* = 17.6 Hz), 45.9 (d, *J* = 7.4 Hz), 36.6, 30.1, 25.0, 23.9.

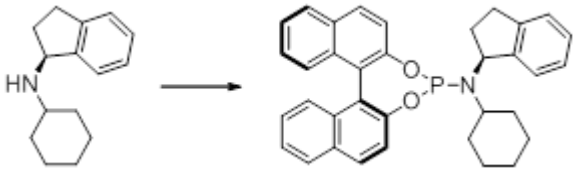
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 152.66 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{32}H_{28}NO_2P$ $[M]^+$: 489.1858, found: 489.1865.

$[\alpha]^{20}_{589}$= +145.52 (*c* 0.75 , $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2969, 1590, 1232, 947, 790, 751.

(*S*,*S*)-*N*-cyclohexyl-*N*-((*S*)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AO



According to a modified procedure from Trost,[164] triethylamine (0.53 mL, 3.8 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.07 mL, 0.8 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-*N*-cyclohexyl-2,3-dihydro-1H-inden-1-amine (193 mg, 0.8 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (219 mg, 0.8 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 84:15:1 SiO_2), the ligand **AO** was obtained as a crystalline white solid (125 mg, 0.23 mmol, 31%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.95 (d, *J* = 8.8 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 1 H), 7.86 (d, *J* = 8.2 Hz, 1 H), 7.83 (d, *J* = 8.8 Hz, 1 H), 7.61 (d, *J* = 7.6 Hz, 1 H), 7.55 (d, *J* = 8.8 Hz, 1 H),

7.49 - 7.52 (m, 1 H), 7.36 - 7.43 (m, 3 H), 7.29 - 7.34 (m, 2 H), 7.15 - 7.26 (m, 4 H), 4.76 (dt, *J* = 12.3, 8.2 Hz, 1 H), 2.91 (dd, *J* = 15.3, 8.8 Hz, 1 H), 2.59 - 2.79 (m, 2 H), 2.34 - 2.45 (m, 1 H), 2.00 - 2.13 (m, 2 H), 1.91 (d, *J* = 11.7 Hz, 1 H), 1.67 - 1.80 (m, 2 H), 1.50 - 1.66 (m, 2 H), 1.35 - 1.49 (m, 1 H), 1.02 (q, *J* = 12.9 Hz, 1 H), 0.77 - 0.96 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.8 (d, *J* = 8.3 Hz), 150.5, 144.8, 143.6, 133.3 (d, *J* = 1.8 Hz), 133.1, 131.7, 130.9, 130.6, 129.9, 128.7, 128.6, 127.6, 127.5 (2 C), 126.8, 126.4, 126.2, 125.2, 125.1, 125.0, 124.7, 124.5 (d, *J* = 5.5 Hz), 122.8 (d, *J* = 1.8 Hz), 122.6, 122.0 (d, *J* = 2.8 Hz), 60.8 (d, *J* = 15.7 Hz), 55.1, 55.0, 36.7, 35.3, 30.4, 26.8, 26.7, 25.9.

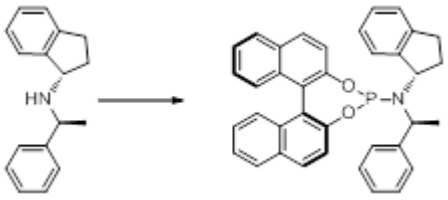
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 152.74 (s, 1 P).

HRMS (EI) *m/z* calcd for $C_{35}H_{32}NO_2P$ $[M]^+$: 529.2171, found: 529.2175.

$[\alpha]^{20}_{589}$= +130.83 (*c* 0.88, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2931, 1590, 1463, 1232, 1328, 948, 751.

(*S*,*S*,*S*)-*N*-((*S*)-2,3-dihydro-1H-inden-1-yl)-*N*-((*S*)-1-phenylethyl)dinaphtho[2,1-d:1',2'-f][(*S*)-1,3,2]dioxaphosphepin-4-amine AP



According to a modified procedure from Trost,[164] triethylamine (0.54 mL, 3.8 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.07 mL, 0.8 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-*N*-((*S*)-1-phenylethyl)-2,3-dihydro-1H-inden-1-amine (210 mg, 0.8 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (220 mg, 0.8 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2),ligand **AP** was obtained as a crystalline white solid (171 mg, 0.31 mmol, 40%).

^{1}H NMR (500 MHz, CD_3CN) δ_H /ppm 8.01 (d, *J* = 8.8 Hz, 1 H), 7.95 (d, *J* = 8.2 Hz, 1 H), 7.85 (d, *J* = 7.9 Hz, 1 H), 7.74 (d, *J* = 8.8 Hz, 1 H), 7.57 (dd, *J* = 8.2, 3.3 Hz, 3 H), 7.49 (d, *J* = 8.8 Hz, 1

H), 7.38 - 7.47 (m, 5 H), 7.31 - 7.37 (m, 3 H), 7.25 - 7.31 (m, 2 H), 7.16 - 7.23 (m, 3 H), 4.64 - 4.77 (m, 1 H), 4.52 (quin, *J* = 7.3 Hz, 1 H), 3.06 (ddd, *J* = 15.8, 9.1, 3.2 Hz, 1 H), 2.71 - 2.82 (m, 1 H), 2.52 - 2.62 (m, 1 H), 2.19 - 2.33 (m, 1 H), 1.72 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.3 (d, *J* = 9.2 Hz), 149.9, 144.1, 143.4, 143.3, 132.9, 132.7, 131.4, 130.5, 130.3, 129.6, 128.3, 128.21, 128.17 (2 C), 127.5, 127.4, 127.4, 127.23, 127.17, 126.8, 126.2, 126.0, 125.9, 125.5 (d, *J* = 1.8 Hz), 124.8, 124.7, 124.4, 124.2 (d, *J* = 5.5 Hz), 122.42, 122.36, 121.3, 61.1 (d, *J* = 18.5 Hz), 54.1 (d, *J* = 7.4 Hz), 36.7, 30.4, 23.4.

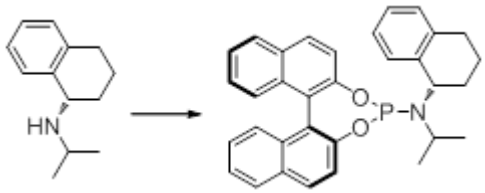
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 151.48 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{37}H_{29}NO_2P$ $[M-H]^+$: 550.1936, found: 550.1942.

$[\alpha]^{20}_{589}$= −13.76 (*c* 0.89, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 3063, 2970, 1735, 1270, 951, 749.

(*S*,*S*)-(11b*S*)-*N*-isopropyl-*N*-((*S*)-1,2,3,4-tetrahydronaphthalen-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AQ



According to a modified procedure from Trost,[164] triethylamine (1.29 mL, 9.2 mmol, l.5 eq.) was added dropwise to a solution cooled at 0 °C of PCl_3 (0.16 mL, 1.8 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-*N*-isopropyl-1,2,3,4-tetrahydronaphthalen-1-amine (0.35 mg, 1.8 mmol, 1.0 eq.) was added to the stirring solution. (*S*)-binaphthol (0.53 mg, 1.8 mmol, 1.0 eq.) was added to the suspension after 5 h and the subsequent mixture was left stirring 12 h. The solution was then filtered on a small pad of silica and celite® and washed with CH_2Cl_2. The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (SiO_2, 88:17:1 Petrol: CH_2Cl_2: Et_3N), the title ligand **AQ** was obtained as a crystalline white solid (540 mg, 1.1 mmol, 60%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.96 (d, *J* = 8.8 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 1 H), 7.84 - 7.89 (m, 2 H), 7.80 (d, *J* = 8.8 Hz, 1 H), 7.51 (d, *J* = 8.8 Hz, 2 H), 7.36 - 7.43 (m, 3 H), 7.28 - 7.35 (m, 2 H), 7.20 - 7.27 (m, 2 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 7.06 (d, *J* = 7.6 Hz, 1 H), 4.41 (td, *J*

= 11.2, 5.4 Hz, 1 H), 3.23 - 3.37 (m, 1 H), 2.77 - 2.89 (m, 1 H), 2.61 - 2.73 (m, 1 H), 2.13 - 2.24 (m, 1 H), 1.93 - 2.05 (m, 1 H), 1.91 (ddd, *J* = 10.7, 5.4, 2.7 Hz, 1 H), 1.53 (d, *J* = 9.8 Hz, 1 H), 1.34 (d, *J* = 6.6 Hz, 3 H), 1.27 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 151.1 (d, *J* = 9.3 Hz), 150.4, 138.9, 133.3, 133.1, 131.7, 130.8, 130.7, 129.9, 129.4, 129.1, 128.7, 128.6, 127.7, 127.6, 127.0, 126.4, 126.2, 126.1, 125.1, 124.7, 124.6, 124.5, 122.9, 122.6, 121.7, 47.3, 47.2, 34.0, 30.2, 26.5, 23.9, 22.8.

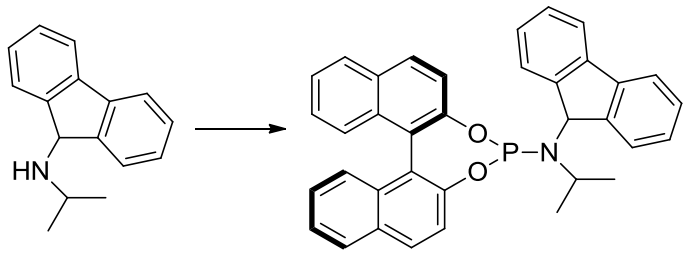
^{31}P NMR (200 MHz, CD_2Cl_2) δ_P /ppm 153.69 (s, 1P).

HRMS (EI/FI) *m/z* calcd for $C_{33}H_{30}NO_2P$ $[M]^+$: 503.2014, found: 503.2017.

$[\alpha]^{20}_{589}$= +175.1 (*c* 1.8, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 3486, 2970, 1739, 1366, 1229, 1217, 1152, 1072, 815, 790, 748, 693, 627.

(*R*)-*N*-(9H-fluoren-9-yl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AR



According to a modified procedure from Trost,[164] triethylamine (0.84 mL, 6.0 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.11 mL, 1.2 mmol, 1.0 eq.) in CH_2Cl_2 (8 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-isopropyl-9H-fluoren-9-amine (267 mg, 1.2 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (219 mg, 1.2 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2), ligand **AR** was obtained as a crystalline white solid (364 mg, 0.67 mmol, 56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.07 (d, *J* = 8.5 Hz, 1 H), 7.91 - 8.00 (m, 2 H), 7.86 (d, *J* = 7.3 Hz, 1 H), 7.81 (d, *J* = 8.5 Hz, 1 H), 7.77 (d, *J* = 8.5 Hz, 1 H), 7.72 (d, *J* = 8.5 Hz, 2 H), 7.66 (d, *J* = 6.9 Hz, 1 H), 7.60 (d, *J* = 7.6 Hz, 1 H), 7.43 (quin, *J* = 7.6 Hz, 3 H), 7.23 - 7.38 (m, 6 H),

7.15 - 7.22 (m, 1 H), 5.27 (s, 1 H), 2.38 - 2.54 (m, 1 H), 1.30 (d, *J* = 6.9 Hz, 3 H), 1.09 - 1.19 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.3 (d, *J* = 9.2 Hz), 150.1, 145.4, 144.5, 141.7, 140.7, 133.3, 133.1, 131.9, 130.9, 130.2, 128.8, 128.7, 128.6, 128.5, 127.6, 127.6 (2 C), 127.4, 127.2, 126.5, 126.4 (2 C), 126.0, 125.3, 124.9 (2 C), 124.6, 122.8 (d, *J* = 6.5 Hz), 122.0, 120.3, 119.9, 62.5, 48.5, 26.9 (d, *J* = 13.9 Hz), 26.7 (d, *J* = 13.9 Hz).

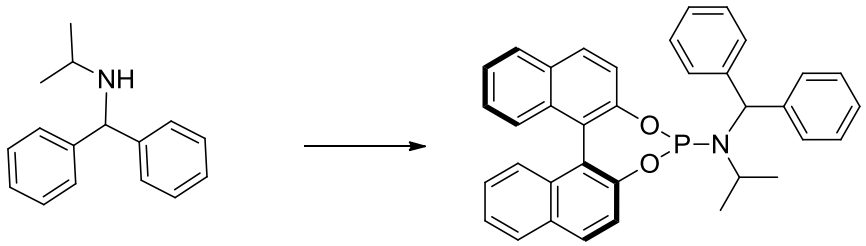
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 149.07 (s, 1 P).

HRMS (EI) *m/z* calcd for $C_{36}H_{28}NO_2P$ $[M]^+$: 537.1858, found: 537.1854.

$[\alpha]^{20}_{589}$= −87.32 (*c* 0.99, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 3064, 2966, 1771, 1231, 1072, 947, 821, 747.

(*S*)-*N*-Benzhydryl-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AS



According to a modified procedure from Trost,[9] triethylamine (12.4 mL, 88.8 mmol, 5.00 eq) was added dropwise over about 8 min to a stirred, cooled (water / ice bath) solution of PCl_3 (1.55 mL, 17.75 mmol, 1.00 eq) in CH_2Cl_2 (100 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-benzhydrylpropan-2-amine (4.00 g, 17.75 mmol, 1.00 eq) was added to the stirring solution. (*S*)-Binaphthol (5.08 g, 17.75 mmol, 1.00 eq) was added to the suspension after 5 hours and the subsequent mixture was left stirring overnight. The solution was then filtered over a small silica (3 mm) and celite (1.5 mm) pad and then washed with CH_2Cl_2. After removing the solvent *in vacuo*, flash column chromatography of the yellow residue (82:17:1; Petrol/CH_2Cl_2/ Et_3N; SiO_2) gave phosphoramidite **AS** (8.10 g, 15.42 mmol, 86%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.98 (d, *J* = 8.8 Hz, 1 H), 7.92 (d, *J* = 7.6 Hz, 2 H), 7.87 (d, *J* = 8.8 Hz, 1 H), 7.58 (d, *J* = 7.6 Hz, 2 H), 7.50 (q, *J* = 7.6 Hz, 4 H), 7.28 - 7.45 (m, 11 H), 7.23 - 7.28 (m, 1 H), 5.81 (d, *J* = 17.0 Hz, 1 H), 3.68 (dq, *J* = 11.8, 6.3 Hz, 1 H), 1.18 (d, *J* = 6.3 Hz, 3 H), 1.06 (d, *J* = 6.3 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.4 (d, *J* = 7.4 Hz), 149.8, 143.5 (d, *J* = 5.5 Hz), 143.3, 132.7, 131.3, 130.4, 130.1, 129.3, 129.0 (2 C), 128.7 (2 C), 128.3 (2 C), 128.2, 128.2 (2 C), 128.1 (2 C), 127.2, 127.0 (2 C), 127.0, 125.9, 125.8, 124.6, 124.3, 124.0, 122.4, 122.1, 121.6, 60.6, 46.8, 23.2, 23.0.

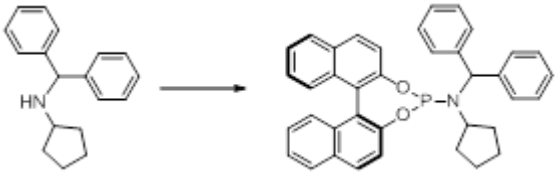
^{31}P NMR (200 MHz $CDCl_3$) δ_P /ppm 150.67.

HMRS (EI) *m/z* calcd for $C_{36}H_{30}NO_2P$ $[M]^+$: 539.2014, found: 539.2016.

$[\alpha]^{20}_{589}$ = +192.27 (*c* 1.23, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 3060, 1590, 1250, 982, 747.

(*S*)-*N*-benzhydryl-*N*-cyclopentyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AT



According to a modified procedure from Trost,[164] triethylamine (2.50 mL, 17.9 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.31 mL, 3.58 mmol, 1.0 eq.) in CH_2Cl_2 (26 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-benzhydrylcyclopentanamine (0.90 g, 3.58 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (1.02 g, 3.58 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 30 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 80:19:1 SiO_2), ligand **AT** was obtained as a crystalline white solid (1.02 g, 1.77 mmol, 49%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.96 (d, *J* = 8.8 Hz, 1 H), 7.91 (d, *J* = 8.2 Hz, 1 H), 7.84 (d, *J* = 7.9 Hz, 1 H), 7.62 (d, *J* = 8.8 Hz, 1 H), 7.49 (d, *J* = 8.8 Hz, 1 H), 7.34 - 7.45 (m, 8 H), 7.20 - 7.33 (m, 8 H), 7.05 (d, *J* = 8.5 Hz, 1 H), 5.70 (d, *J* = 12.3 Hz, 1 H), 3.60 (sxt, *J* = 8.8 Hz, 1 H), 1.90 (d, *J* = 8.5 Hz, 1 H), 1.81 (br. s., 1 H), 1.46 - 1.64 (m, 2 H), 1.29 - 1.45 (m, 2 H), 1.11 - 1.27 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.0 (d, *J* = 8.3 Hz), 149.7, 143.0 (d, *J* = 3.7 Hz), 142.7, 132.8, 132.5, 131.3, 130.4, 130.2, 129.5, 129.0, 128.6 (d, *J* = 1.8 Hz, 2 C), 128.2, 128.2 (3 C),

128.1, 128.0 (3 C), 127.14, 127.11, 126.9, 125.9, 125.7, 124.7, 124.3, 124.1 (d, *J* = 5.5 Hz), 122.4 (d, *J* = 1.8 Hz), 122.2, 121.6 (d, *J* = 1.8 Hz), 61.4 (d, *J* = 15.7 Hz), 57.7 (d, *J* = 8.3 Hz), 53.4, 32.8, 32.2 (d, *J* = 8.3 Hz), 23.6 (d, *J* = 11.1 Hz).

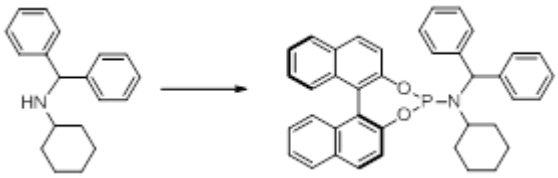
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 149.78 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{38}H_{32}NO_2P$ $[M]^+$: 565.2171, found: 565.2167.

$[\alpha]^{20}_{589}$= +207.75 (*c* 1.08, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2958, 2360, 1739, 1590, 1463, 1230, 947, 750.

(*S*)-*N*-benzhydryl-*N*-cyclohexyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AU



According to a modified procedure from Trost,[164] triethylamine (1.57 mL, 11.30 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.19 mL, 2.26 mmol, 1.0 eq.) in CH_2Cl_2 (17 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-benzhydrylcyclohexanamine (0.60 g, 2.26 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (0.65 g, 2.26 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 30 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 80:19:1 SiO_2), ligand **AU** was obtained as a crystalline yellow solid (0.72 g, 1.21 mmol, 54%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.86 - 8.00 (m, 3 H), 7.78 (d, *J* = 8.5 Hz, 1 H), 7.48 - 7.56 (m, 2 H), 7.19 - 7.47 (m, 16 H), 5.77 (d, *J* = 16.7 Hz, 1 H), 3.02 (br. d, *J* = 2.5 Hz, 1 H), 1.80 (d, *J* = 10.1 Hz, 1 H), 1.42 - 1.68 (m, 4 H), 1.28 - 1.41 (m, 2 H), 0.91 (q, *J* = 13.1 Hz, 1 H), 0.56 - 0.73 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.3 (d, *J* = 6.5 Hz), 149.8, 143.5 (d, *J* = 6.5 Hz), 143.4, 132.8, 132.6, 131.3, 130.4, 130.1, 129.3, 129.1 (d, *J* = 2.8 Hz), 128.7 (2 C), 128.2 (4 C), 128.1, 128.0 (2 C), 127.0 (2 C), 126.9 (2 C), 125.9, 125.8, 124.6, 124.3, 124.0 (d, *J* = 5.5 Hz), 122.3, 121.9, 121.7 (d, *J* = 2.8 Hz), 60.7, 55.8, 33.8, 33.6, 26.1, 26.0, 25.3.

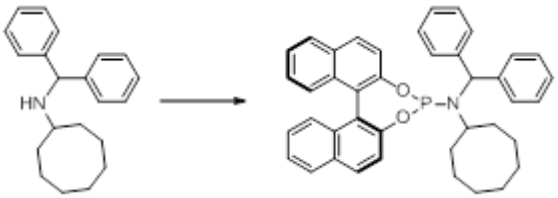
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 151.28 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{39}H_{34}NO_2P$ $[M]^+$: 579.2327, found: 529.2327.

$[\alpha]^{20}_{589}$= +219.32 (*c* 1.45, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2937, 2854, 1739, 1449, 1231, 948, 751.

(*S*)-*N*-benzhydryl-*N*-cyclooctyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AV



According to a modified procedure from Trost,[164] triethylamine (1.16 mL, 8.34 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.15 mL, 1.67 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-benzhydrylcyclooctanamine (490 mg, 1.67 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (478 mg, 1.67 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 20 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 80:19:1 SiO_2), ligand **AV** was obtained as a crystalline orange solid (350 mg, 0.61 mmol, 36%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.93 (d, *J* = 8.8 Hz, 1 H), 7.89 (d, *J* = 8.2 Hz, 1 H), 7.85 (d, *J* = 8.2 Hz, 1 H), 7.66 - 7.77 (m, 1 H), 7.17 - 7.53 (m, 18 H), 5.70 (d, *J* = 15.1 Hz, 1 H), 3.38 (br. dd, *J* = 7.3, 3.2 Hz, 1 H), 1.58 - 1.94 (m, 4 H), 1.54 (s, 1 H), 1.30 - 1.44 (m, 1 H), 0.99 - 1.26 (m, 5 H), 0.81 - 0.98 (m, 2 H), 0.65 (br. s., 1 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.6 (d, *J* = 6.5 Hz), 150.3, 133.2, 131.7, 131.0, 130.6, 130.0 (2 C), 129.1, 129.0, 128.7 (6 C), 128.55 (3 C), 128.51, 127.5, 127.4 (2 C), 127.3, 126.3 (d, *J* = 8.3 Hz), 125.0, 124.8, 124.4 (d, *J* = 4.6 Hz), 122.8, 122.5, 122.2, 62.9, 62.7, 56.3, 26.5 (2 C), 26.1 (2 C), 25.6 (2 C).

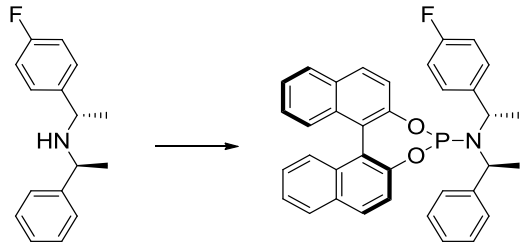
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 150.05 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{41}H_{37}NO_2P$ $[M-1]^+$: 606.2562, found: 606.2562.

$[\alpha]^{20}_{589}$= +178.27 (*c* 0.99, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2921, 1591, 1464, 1328, 1237, 1054, 948, 821, 750.

N-((*S*)-1-(4-fluorophenyl)ethyl)-*N*-((*S*)-1-phenylethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine



According to a modified procedure from Trost,[164] triethylamine (0.54 mL, 3.8 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.07 mL, 0.8 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-1-(4-fluorophenyl)-*N*-((*S*)-1-phenylethyl)ethanamine (188 mg, 0.8 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (221 mg, 0.8 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (~ 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 82:17:1 SiO_2), the ligand was obtained as a crystalline white solid (203 mg, 0.36 mmol, 47%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.02 (d, *J* = 8.8 Hz, 1 H), 7.93 (d, *J* = 8.2 Hz, 1 H), 7.79 - 7.87 (m, 2 H), 7.75 (d, *J* = 8.8 Hz, 1 H), 7.58 (d, *J* = 8.8 Hz, 1 H), 7.40 - 7.45 (m, 2 H), 7.35 - 7.40 (m, 2 H), 7.31 - 7.35 (m, 1 H), 7.18 - 7.30 (m, 5 H), 7.06 - 7.13 (m, 3 H), 6.78 - 6.91 (m, 2 H), 4.40 (dt, *J* = 10.7, 7.3 Hz, 2 H), 1.68 (t, *J* = 7.4 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 162.6, 160.6, 150.4 (d, *J* = 10.2 Hz), 149.6, 143.0, 138.9, 132.9, 132.8, 131.4, 130.5, 130.3, 129.6, 129.5 (d, *J* = 3.7 Hz), 129.5 (d, *J* = 2.8 Hz), 128.3, 128.1, 127.9 (d, *J* = 2.8 Hz), 127.8 (2 C), 127.2, 127.1, 126.8, 126.1, 125.9, 124.8, 124.4, 123.8, 122.4, 122.3, 121.1, 114.5, 114.3, 54.5 (d, *J* = 10.2 Hz), 53.8 (d, *J* = 11.1 Hz), 23.1 (d, *J* = 12.0 Hz), 22.8.

^{19}F NMR (470 MHz, $CDCl_3$ δ_F /ppm -116.19 (s, 1 F)

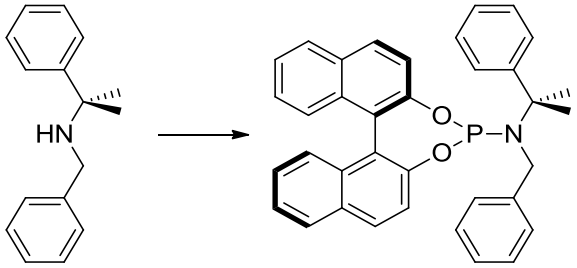
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 151.27 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{36}H_{28}NO_2FP$ $[M]^+$: 556.1842, found: 556.1847.

$[\alpha]^{20}_{589}$= +60.36 (*c* 0.55, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2975, 1238, 950, 749.

(*R*)-*N*-benzyl-*N*-(2-phenylpropan-2-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AW



According to a modified procedure from Trost,[164] triethylamine (2.17 mL, 15.5 mmol, 5.0 eq.) was added dropwise to a stirred solution of PCl_3 (0.27 mL, 3.11 mmol, 1.0 eq.) cooled at 0 °C in CH_2Cl_2 (23 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-benzyl-2-phenylpropan-2-amine (0.70 g, 3.11 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (890 mg, 3.11 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 30 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 80:19:1 SiO_2), ligand **AW** was obtained as a crystalline white solid (1.10 g, 2.04 mmol, 66%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.99 (d, *J* = 8.8 Hz, 1 H), 7.92 (d, *J* = 8.8 Hz, 1 H), 7.84 (d, *J* = 8.8 Hz, 2 H), 7.60 - 7.67 (m, 3 H), 7.39 - 7.46 (m, 3 H), 7.28 - 7.38 (m, 5 H), 7.23 - 7.26 (m, 1 H), 7.13 - 7.22 (m, 5 H), 7.08 (td, *J* = 6.1, 2.4 Hz, 1 H), 4.13 (dd, *J* = 16.4, 1.9 Hz, 1 H), 3.41 (dd, *J* = 16.4, 0.9 Hz, 1 H), 1.78 (d, *J* = 4.1 Hz, 3 H), 1.62 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 151.1 (d, *J* = 5.5 Hz), 150.1, 147.3 (d, *J* = 2.8 Hz), 142.2, 133.3, 133.1, 131.9, 130.9, 130.6, 130.5, 128.7, 128.6 (3 C), 128.5 (2 C), 128.2 (4 C), 128.2 (2 C), 127.6, 127.5, 127.4, 127.2 (d, *J* = 2.8 Hz), 126.6, 126.4 (d, *J* = 3.7 Hz, 2 C), 122.8 (d, *J* = 1.8 Hz), 122.4 (d, *J* = 1.8 Hz), 122.1, 61.9, 47.7 (d, *J* = 4.6 Hz), 33.1, 30.8 (d, *J* = 10.2 Hz).

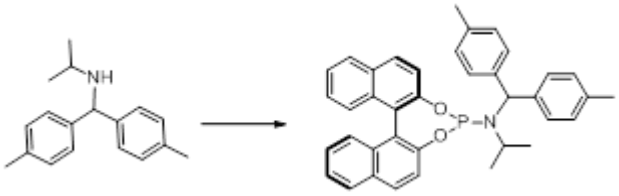
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 146.91 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{36}H_{30}NO_2P$ $[M-1]^+$: 539.2014, found: 539.2007.

[α]$^{20}_{589}$ = −194.66 (*c* 1.09, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 3016, 2970, 1435, 1367, 1216.

(*R*)-*N*-(di-*p*-Tolylmethyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AX



According to a modified procedure from Trost,[164] triethylamine (1.60 mL, 11.61 mmol, 5.0 eq.) was added dropwise to a stirred solution of PCl_3 (0.20 mL, 2.32 mmol, 1.0 eq.) cooled at 0 °C in CH_2Cl_2 (17 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-(di-p-tolylmethyl)propan-2-amine (589 mg, 2.32 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (665 mg, 2.32 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 30 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 80:19:1 SiO_2), ligand **AX** was obtained as a crystalline white solid (574 mg, 1.04 mmol, 43%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.92 (d, *J* = 8.8 Hz, 1 H), 7.87 - 7.91 (m, 2 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.33 - 7.46 (m, 7 H), 7.25 - 7.31 (m, 2 H), 7.22 (d, *J* = 7.3 Hz, 5 H), 7.15 - 7.19 (m, 2 H), 5.65 (d, *J* = 17.7 Hz, 1 H), 3.58 (dq, *J* = 11.0, 6.6 Hz, 1 H), 2.40 (s, 3 H), 2.38 (s, 3 H), 1.08 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.5 (d, *J* = 6.5 Hz), 149.9, 140.7 (d, *J* = 6.5 Hz), 140.6 (d, *J* = 4.6 Hz), 136.55, 136.51, 132.73, 132.69, 131.3, 130.5, 130.1, 129.3, 129.0 (2 C), 128.9 (2 C), 128.8, 128.7, 128.7, 128.7, 128.2, 128.2, 127.1, 127.0, 125.9, 125.8, 124.6, 124.3, 124.0 (d, *J* = 4.6 Hz), 122.4, 122.2, 121.7, 60.3, 46.7, 23.1, 22.9, 21.13, 21.10.

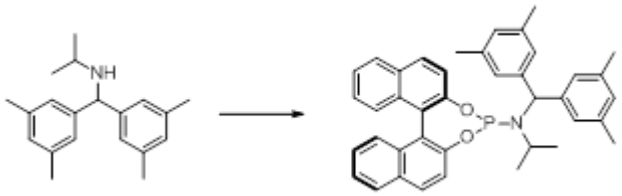
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 150.84 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{38}H_{34}NO_2P$ $[M]^+$: 567.2327, found: 567.2348.

[α]$^{20}_{589}$ = −157.46 (*c* 1.00, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2974, 1510, 1232, 947, 820, 721.

(*R*)-*N*-(bis(3,5-dimethylphenyl)methyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AY



According to a modified procedure from Trost,[164] triethylamine (2.50 mL, 17.79 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.31 mL, 3.55 mmol, 1.0 eq.) in CH_2Cl_2 (26 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-(bis(3,5-dimethylphenyl)methyl)propan-2-amine (1.0 g, 3.55 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (1.02 g, 3.55 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 30 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 79:20:1: SiO_2), ligand **AY** was obtained as a crystalline white solid (1.53 g, 2.57 mmol, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.98 (d, *J* = 8.8 Hz, 1 H), 7.95 (t, *J* = 7.4 Hz, 2 H), 7.89 (d, *J* = 8.8 Hz, 1 H), 7.39 - 7.50 (m, 5 H), 7.30 - 7.37 (m, 2 H), 7.24 - 7.30 (m, 1 H), 7.16 (s, 2 H), 7.01 (s, 3 H), 6.98 (s, 1 H), 5.62 (d, *J* = 18.3 Hz, 1 H), 3.64 (br. d, *J* = 5.0 Hz, 1 H), 2.43 (s, 6 H), 2.41 (s, 6 H), 1.11 (d, *J* = 6.3 Hz, 3 H), 1.03 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.6 (d, *J* = 7.4 Hz), 150.0, 143.7, 143.7, 143.7, 137.6, 137.5, 132.8 (d, *J* = 9.2 Hz), 131.3, 130.5, 130.2, 129.4, 128.6 (3 C), 128.3, 128.2, 127.2, 127.1, 126.8, 126.8 (3 C), 126.8, 125.9, 125.8, 124.7, 124.3, 124.1 (d, *J* = 4.6 Hz), 122.5, 122.2, 121.8, 60.6 (d, *J* = 26.0 Hz), 46.7, 23.1, 22.9, 21.6 (4 C).

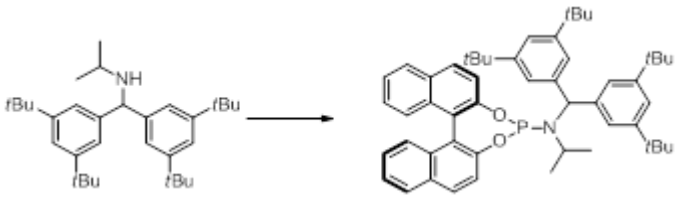
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 151.05 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{40}H_{38}NO_2P$ $[M]^+$: 595.2640, found: 595.2632.

$[\alpha]^{20}_{589}$ = −122.04 (*c* 1.55, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2960, 2100, 11789, 1380, 1229, 1213.

(*R*)-*N*-(bis(3,5-di-*tert*-Butylphenyl)methyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine AZ



According to a modified procedure from Trost,[164] triethylamine (1.00 mL, 7.33 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.12 mL, 1.23 mmol, 1.0 eq.) in CH_2Cl_2 (9 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-(bis(3,5-di-*tert*-butylphenyl)methyl)propan-2-amine (553 mg, 1.23 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (458 mg, 1.23 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 20 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash columns chromatography (Petrol: CH_2Cl_2: Et_3N; 79.5:20:0.5: SiO_2) and (Petrol: CH_2Cl_2: Et_3N; 85:15:0.03: SiO_2), ligand **AZ** was obtained as a crystalline white solid (472 mg, 0.61 mmol, 50%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.86 - 7.95 (m, 3 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.33 - 7.45 (m, 8 H), 7.25 - 7.33 (m, 3 H), 7.19 - 7.24 (m, 1 H), 7.14 (d, *J* = 0.9 Hz, 2 H), 5.64 (d, *J* = 18.9 Hz, 1 H), 3.54 (dq, *J* = 9.8, 6.5 Hz, 1 H), 1.37 (s, 18 H), 1.31 - 1.35 (m, 18 H), 1.00 - 1.08 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.8 (d, *J* = 6.5 Hz), 150.5 (2 C), 150.2 (2 C), 150.1, 143.4, 142.7 , 132.8 (2 C), 132.7 (2 C), 131.3, 130.4, 130.1, 129.3, 128.2, 128.2, 127.13, 127.11, 125.9, 125.8, 124.6, 124.2, 124.0 (d, *J* = 5.5 Hz), 123.3 (d, *J* = 4.6 Hz), 123.2, 122.3, 122.3, 121.7, 120.2, 120.1, 61.5 (d, *J* = 27.0 Hz), 46.8, 35.0 (2 C), 34.9 (2 C), 31.6 (6 C), 31.5 (6 C), 22.9, 22.9.

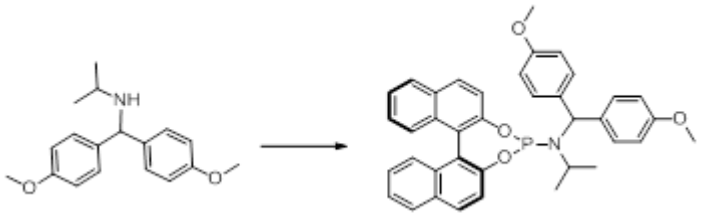
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 152.00 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{47}H_{38}NO_2P$ $[M\text{-}i\text{Pr}]^+$: 720.3970, found: 720.4001.

$[\alpha]^{20}_{589}$= −80.83 (*c* 1.09, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2964, 1739, 1593, 1463, 1367, 1231, 750.

(*S*)-*N*-(bis(4-methoxyphenyl)methyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine BA



According to a modified procedure from Trost,[164] triethylamine (1.15 mL, 8.28 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.14 mL, 1.66 mmol, 1.0 eq.) in CH_2Cl_2 (12 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-(bis(4-methoxyphenyl)methyl)propan-2-amine (472 mg, 1.66 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (474 mg, 1.66 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 30 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 80:19:1 SiO_2), ligand **BA** was obtained as a crystalline white solid (438 mg, 0.73 mmol, 44%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.92 (d, *J* = 8.5 Hz, 1 H), 7.89 (dd, *J* = 7.9, 4.1 Hz, 2 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.33 - 7.46 (m, 6 H), 7.25 - 7.31 (m, 3 H), 7.19 - 7.24 (m, 5 H), 7.14 - 7.19 (m, 2 H), 5.65 (d, *J* = 17.3 Hz, 1 H), 3.58 (td, *J* = 6.6, 4.1 Hz, 1 H), 2.40 (s, 3 H), 2.38 (s, 3 H), 1.08 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.9 (d, *J* = 6.5 Hz, 1 C), 150.4, 141.2 (d, *J* = 5.5 Hz), 141.1 (d, *J* = 3.7 Hz), 137.0, 136.9, 133.2, 133.1, 131.7, 130.9, 130.6, 129.8, 129.4 (2 C), 129.3 (2 C), 129.2 29.2, 129.2, 129.1, 128.7, 128.6, 127.6, 127.5, 126.3, 126.2, 125.1, 124.7, 124.4 (d, *J* = 5.5 Hz), 122.9, 122.7, 122.1 (d, *J* = 2.8 Hz), 60.5, 47.1, 23.6, 23.3, 21.6 (2 C).

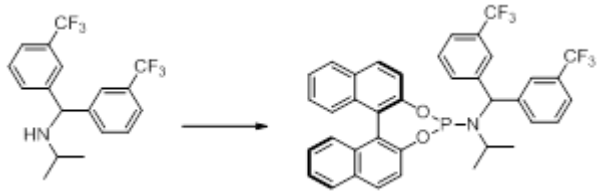
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 150.85 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{38}H_{34}NO_2P$ $[M-1]^+$: 598.2147, found: 598.2151.

$[\alpha]^{20}_{589}$= +144.24 (*c* 0.99, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 3016, 2970, 1730, 1436, 1369, 1229, 899, 732.

(*R*)-*N*-(bis(3-(Trifluoromethyl)phenyl)methyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine BB



According to a modified procedure from Trost,[164] triethylamine (1.00 mL, 7.72 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.13 mL, 3.11 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-(bis(3-(trifluoromethyl)phenyl)methyl)propan-2-amine (521 mg, 1.44 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (413 mg, 1.44 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 30 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 80:19:1 SiO_2), ligand **BB** was obtained as a crystalline white solid (652 mg, 0.96 mmol, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.95 (d, *J* = 8.8 Hz, 1 H), 7.89 (t, *J* = 7.6 Hz, 2 H), 7.82 (s, 1 H), 7.79 (d, *J* = 8.8 Hz, 1 H), 7.73 (s, 1 H), 7.61 - 7.66 (m, 1 H), 7.58 (d, *J* = 7.6 Hz, 1 H), 7.50 - 7.56 (m, 2 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.38 - 7.44 (m, 4 H), 7.36 (d, *J* = 7.6 Hz, 1 H), 7.19 - 7.30 (m, 4 H), 5.80 (d, *J* = 16.4 Hz, 1 H), 3.59 (sxt, *J* = 6.2 Hz, 1 H), 1.14 (d, *J* = 6.6 Hz, 3 H), 0.97 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 149.8 (d, *J* = 7.4 Hz), 149.4, 143.7, 132.7 (d, *J* = 9.2 Hz), 132.2, 131.9, 131.4, 131.1, 131.0, 130.8, 130.54, 130.1, 129.5, 129.0, 128.8, 128.3 (d, *J* = 8.3 Hz), 127.1, 127.0, 126.1, 126.0, 125.7 (t, *J* = 4.2 Hz), 125.5 (t, *J* = 3.2 Hz), 125.2 (d, *J* = 2.8 Hz), 124.8, 124.5, 124.3 (dd, *J* = 7.4, 3.7 Hz, 2 C), 123.8 (d, *J* = 5.5 Hz), 123.0 (d, *J* = 2.8 Hz), 122.0, 121.73, 121.69, 60.0 (d, *J* = 23.0 Hz), 47.1, 23.2, 23.0 (d, *J* = 4.6 Hz).

^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 149.00 (s, 1P).

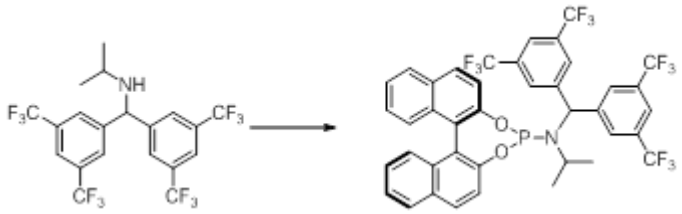
^{19}F NMR (380 MHz, $CDCl_3$) δ_F /ppm -62.5 (s, 3 F), -62.6 (s, 3 F).

HRMS (EI) *m/z* calcd for $C_{38}H_{28}F_6NO_2P$ $[M-1]^+$: 675.1762, found: 675.1758.

$[\alpha]^{20}_{589}$ = −159.00 (*c* 1.01, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2975, 1591, 1329, 1231, 1165, 1125, 948, 828, 803, 751.

(*R*)-*N*-(bis(3,5-bis(trifluoromethyl)phenyl)methyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine BC



According to a modified procedure from Trost and coworkers,[164] triethylamine (1.23 mL, 8.81 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.14 mL, 1.61 mmol, 1.1 eq.) in CH_2Cl_2 (11 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-(bis(3,5-bis(trifluoromethyl)phenyl)methyl)propan-2-amine (730 mg, 1.47 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (546 mg, 1.90 mmol, 1.3 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 20 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_2O; 4.3:0.3:0.3: SiO_2) and then (Petrol: CH_2Cl_2: Toluene; 4.2:0.6:0.6: SiO_2), ligand **BC** was obtained as a crystalline white solid (452 mg, 0.56 mmol, 38%).

^{1}H NMR (500 MHz, CD_2Cl_2) δ_H /ppm 8.00 (d, *J* = 8.8 Hz, 1 H), 7.96 (d, *J* = 12.0 Hz, 1 H), 7.86 - 7.94 (m, 4 H), 7.74 - 7.84 (m, 3 H), 7.39 - 7.51 (m, 3 H), 7.32 - 7.38 (m, 1 H), 7.11 - 7.30 (m, 5 H), 5.94 (d, *J* = 15.8 Hz, 1 H), 3.58 (dq, *J* = 12.0, 6.4 Hz, 1 H), 1.19 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, CD_2Cl_2) δ_C /ppm 149.9 (d, *J* = 7.4 Hz), 149.7, 145.2 (d, *J* = 4.6 Hz), 145.2, 133.2, 132.8, 132.7, 132.5, 132.4, 132.3, 132.2, 131.4, 131.3, 130.4, 129.7 (2 C), 129.5 (2 C), 129.0, 128.9, 128.7, 127.5, 127.3, 126.8, 126.8, 125.7, 125.4, 125.0 (d, *J* = 4.6 Hz), 124.2 (d, *J* = 5.5 Hz), 122.7, 122.6, 121.8, 60.1 (d, *J* = 23.0 Hz), 48.0, 23.4 (2 C).

^{31}P NMR (200 MHz, CD_2Cl_2) δ_P /ppm 147.96 (s, 1P).

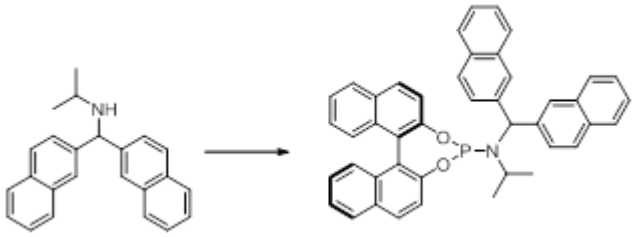
^{19}F NMR (380 MHz, $CDCl_3$) δ_F /ppm -62.8 (s, 6 F), -62.9 (s, 6 F).

HRMS (EI) *m/z* calcd for $C_{40}H_{26}F_{12}NO_2P$ $[M\text{-}i\text{Pr}]^+$: 811.1510, found: 811.1501.

$[\alpha]^{20}_{589}$ = −130.93 (*c* 1.08, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 1372, 1279, 1174, 1136, 949, 822.

(*R*)-*N*-(di(Naphthalen-2-yl)methyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine BD



According to a modified procedure from Trost,[164] triethylamine (1.87 mL, 13.4 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.23 mL, 2.68 mmol, 1.0 eq.) in CH_2Cl_2 (17 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-(di(naphthalen-2-yl)methyl)propan-2-amine (782 mg, 2.68 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (767 mg, 2.68 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 30 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 89:10:1 → 80:20:1, SiO_2), ligand **BD** was obtained as a crystalline white solid (1230 mg, 1.92 mmol, 72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.03 (s, 1 H), 7.85 - 7.96 (m, 7 H), 7.71 - 7.79 (m, 2 H), 7.66 (br. dd, *J* = 8.5, 1.6 Hz, 2 H), 7.59 (s, 1 H), 7.52 - 7.57 (m, 2 H), 7.34 - 7.51 (m, 7 H), 7.26 - 7.33 (m, 3 H), 7.19 - 7.24 (m, 1 H), 6.02 (d, *J* = 17.7 Hz, 1 H), 3.63 - 3.77 (m, 1 H), 1.15 (d, *J* = 6.6 Hz, 3 H), 1.08 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.8 (d, *J* = 7.4 Hz), 150.2, 141.3, 141.2, 133.8, 133.6, 133.2, 133.1, 133.0, 131.8, 130.9, 130.7, 129.9, 128.7, 128.7 (2 C), 128.6 (3 C), 128.4, 128.14, 128.09 (d, *J* = 3.7 Hz), 128.0, 127.7 (d, *J* = 3.7 Hz), 127.6, 127.6, 127.5, 126.6, 126.5, 126.4 (3 C), 126.4, 126.3, 125.1, 124.8, 124.4 (d, *J* = 5.5 Hz), 122.8, 122.6, 122.2, 61.6, 47.5, 23.7, 23.6.

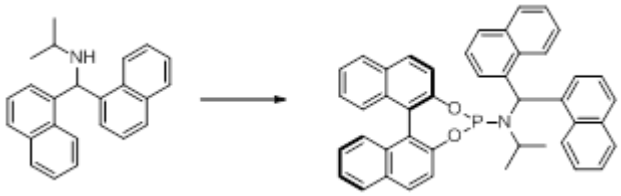
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 150.18 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{44}H_{34}NO_2P$ $[M]^+$: 639.2327, found: 639.2354.

$[\alpha]^{20}_{589}$= −67.66 (*c* 0.99, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2970, 1739, 1367, 1229, 1216, 946, 820, 751.

(*R*)-*N*-(di(naphthalen-1-yl)methyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine BE



According to a modified procedure from Trost,[164] triethylamine (0.78 mL, 5.68 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.10 mL, 1.12 mmol, 1.0 eq.) in CH_2Cl_2 (8 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-(di(naphthalen-1-yl)methyl)propan-2-amine (365 mg, 1.12 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (321 mg, 1.12 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 30 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 77:12:1: SiO_2), the ligand was obtained as a crystalline white solid (283 mg, 0.44 mmol, 39%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.39 (br. s., 1 H), 7.61 - 7.98 (m, 9 H), 7.31 - 7.59 (m, 10 H), 6.97 - 7.31 (m, 7 H), 3.81 (d, *J* = 5.7 Hz, 1 H), 1.10 - 1.37 (m, 3 H), 0.94 (br. s., 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.7, 150.1, 138.9, 138.0, 134.6, 134.4, 133.2, 133.0, 131.7, 131.4, 130.7, 130.6, 129.6, 129.4, 129.2, 129.1, 128.9, 128.8, 128.6, 128.6, 127.5, 127.4, 126.7, 126.6, 126.3, 126.13, 126.09, 126.0, 125.5 (4 C), 125.1, 124.6, 124.5 (d, *J* = 5.5 Hz), 124.0, 123.8, 122.7, 122.6, 121.9, 55.1 (d, *J* = 26.0 Hz), 48.5, 24.6, 23.6.

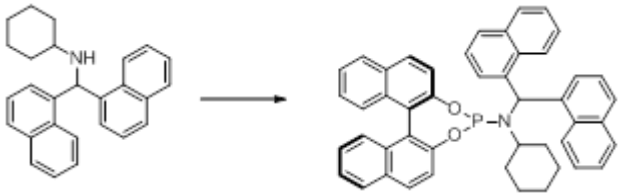
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 148.61 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{44}H_{34}NO_2P$ $[M]^+$: 639.2327, found: 639.2354.

$[\alpha]^{20}_{589}$ = −79.63 (*c* 1.05, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2970, 1739, 1368, 1229, 1216.

(*R*)-*N*-Cyclohexyl-*N*-(di(naphthalen-1-yl)methyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine BF



According to a modified procedure from Trost,[164] triethylamine (1.96 mL, 14.10 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.25 mL, 2.80 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-(di(naphthalen-1-yl)methyl)cyclohexanamine (1.03 g, 2.80 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*R*)-binaphthol (806 mg, 2.80 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 35 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol: CH_2Cl_2: Et_3N; 79:20:1: SiO_2), ligand **BF** was obtained as a crystalline white solid (415 mg, 0.61 mmol, 22%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 8.41 (br. s., 1 H), 7.90 - 8.02 (m, 2 H), 7.72 - 7.89 (m, 7 H), 7.31 - 7.61 (m, 11 H), 7.11 - 7.29 (m, 7 H), 3.23 (br. s., 1 H), 1.99 (br. s., 1 H), 1.10 - 1.77 (m, 6 H), 0.74 (d, *J* = 11.0 Hz, 1 H), 0.38 - 0.63 (m, 2 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 150.6, 150.1, 134.6, 134.4, 133.2, 132.9, 131.7, 131.4, 130.6, 130.5, 129.6, 129.4 (2 C), 129.2, 128.9 (2 C), 128.7 (2 C), 128.6, 128.5 (2 C), 127.4 (2 C), 127.3, 126.6 (2 C), 126.3 (2 C), 126.2, 126.04, 126.01 (2 C), 125.4, 125.4, 125.0, 124.7, 124.1, 123.8, 122.7, 122.4, 57.5, 55.8, 26.8 (3 C), 25.6 (2 C).

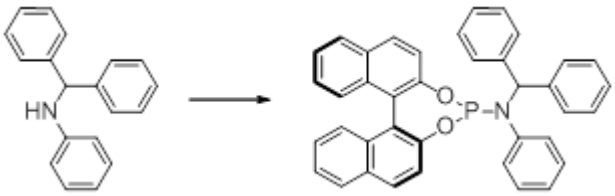
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 148.95 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{47}H_{38}NO_2P$ $[M]^+$: 679.2640, found: 679.2650.

$[\alpha]^{20}_{589}$= −79.63 (*c* 1.05, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2930, 1730, 1420, 1350, 1213, 750.

(*S*)-*N*-benzhydryl-*N*-phenyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine



According to a modified procedure from Trost,[164] triethylamine (0.86 mL, 6.2 mmol, 5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of PCl_3 (0.11 mL, 1.2 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL). The ice bath was removed and the solution left to warm to room temperature before *N*-

benzhydrylaniline (279 mg, 1.2 mmol, 1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (*S*)-binaphthol (356 mg, 1.2 mmol, 1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 15 h before the solution was then filtered on a small pad of silica and celite® and rinsed with CH_2Cl_2 (*ca* 15 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (Petrol:CH_2Cl_2:Et_3N; 82:17:1 SiO_2), the ligand was obtained as a crystalline white solid (284 mg, 0.52 mmol, 42%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.96 (d, *J* = 8.8 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 1 H), 7.78 (d, *J* = 8.2 Hz, 1 H), 7.47 (d, *J* = 8.2 Hz, 1 H), 7.44 (d, *J* = 8.8 Hz, 1 H), 7.38 - 7.42 (m, 1 H), 7.31 - 7.38 (m, 6 H), 7.28 - 7.30 (m, 2 H), 7.24 - 7.27 (m, 4 H), 7.18 - 7.23 (m, 3 H), 7.00 - 7.05 (m, 2 H), 6.87 - 6.96 (m, 3 H), 6.77 (d, *J* = 8.8 Hz, 1 H), 6.12 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 149.8 (d, *J* = 8.6 Hz), 148.9, 143.3, 141.6 (d, *J* = 3.8 Hz), 140.7 (d, *J* = 2.9 Hz), 132.8, 132.3, 131.4, 130.3, 130.2, 129.6 (d, *J* = 1.9 Hz, 2 C), 129.5 (d, *J* = 1.9 Hz, 2 C), 129.1, 128.7, 128.7, 128.7, 128.3, 128.2, 128.1 (2 C), 128.0, 127.9, 127.3, 127.13, 127.10, 126.9, 126.0, 125.6, 125.4, 124.8 (s, 1 C), 124.3 (s, 1 C), 124.2 (s, 1 C), 122.1 (d, *J* = 1.9 Hz, 1 C), 122.0, 121.2 (d, *J* = 1.9 Hz), 113.5, 68.0 (d, *J* = 18.1 Hz).

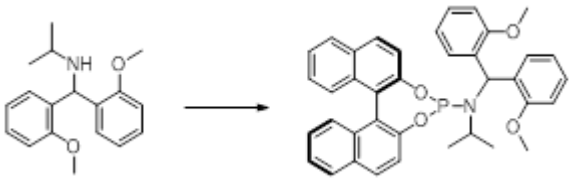
^{31}P NMR (200 MHz, $CDCl_3$) δ_P /ppm 141.81 (s, 1P).

HRMS (EI) *m/z* calcd for $C_{31}H_{28}NO_2P$ $[M]^+$: 538.1934, found: 538.1936.

$[\alpha]^{20}_{589}$= +236.06 (*c* 0.99, $CHCl_3$).

IR (ν_{max}/cm^{-1}): 2978, 1628, 1453, 1319, 821, 749.

(*R*)-*N*-(bis(2-methoxyphenyl)methyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine BG



According to a modified procedure from Trost,[9] triethylamine (5.1 mL, 36.7 mmol, 5.00 eq) was added dropwise over about 8 min to a stirred, cooled (water / ice bath) solution of PCl_3 (0.64 mL, 7.4 mmol, 1.00 eq) in CH_2Cl_2 (50 mL). The ice bath was removed and the solution left to warm to

room temperature before *N*-(bis(3-methoxyphenyl)methyl)propan-2-amine (2.1 g, 7.4 mmol, 1.00 eq) was added to the stirring solution. (*R*)-Binaphthol (2.1 g, 7.4 mmol, 1.00 eq) was added to the suspension after 5 hours and the subsequent mixture was left stirring overnight. The solution was then filtered over a small silica (3 mm) and celite (1.5 mm) pad and then washed with CH_2Cl_2. After removing the solvent *in vacuo*, flash column chromatography of the yellow residue (80:19:1; Petrol/CH_2Cl_2/ Et_3N; SiO_2) gave phosphoramidite (*R*)-*N*-(bis(3-methoxyphenyl)methyl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (4.2 g, 7.0 mmol, 95%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.85 - 7.97 (m, 4 H), 7.54 (d, *J* = 7.6 Hz, 1 H), 7.51 (d, *J* = 8.9 Hz, 1 H), 7.36 - 7.47 (m, 5 H), 7.28 - 7.34 (m, 4 H), 7.19 - 7.26 (m, 1 H), 6.97 - 7.06 (m, 2 H), 6.96 (dd, *J* = 8.2, 1.8 Hz, 2 H), 6.45 (d, *J* = 16.3 Hz, 1 H), 3.96 (s, 3 H), 3.88 (s, 3 H), 3.58 (dtd, *J* = 13.3, 6.6, 6.6, 1.8 Hz, 1 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 156.7, 156.5, 150.8, 150.2, 132.7, 131.6, 131.4, 131.2, 130.7, 130.5, 130.5, 130.4, 130.0, 129.2, 128.3 (2 C), 128.1 (2 C), 127.1, 127.0, 125.8, 125.7, 124.5, 124.1, 122.6, 122.5, 121.7, 119.9 (2 C), 110.6 (2 C), 55.4 (2 C), 49.1, 48.8, 47.1, 23.0, 21.9.

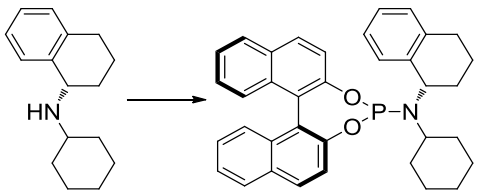
^{31}P NMR (160 MHz $CDCl_3$) δ_P /ppm 148.8 (d, *J* = 15.6 Hz, 1 P)

HMRS (EI) *m*/*z* calcd for $C_{36}H_{30}NO_2P$ $[M]^+$: 599.2225, found: 599.2231.

$[\alpha]^{20}_{589}$ = −89.70 (*c* 2.00, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2972, 1589, 1463, 1232, 1053, 948, 751, 695.

(*S*,*S*)-(11b*S*)-*N*-cyclohexyl-*N*-((*S*)-1,2,3,4-tetrahydronaphthalen-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine BW



According to a modified procedure from Trost,[164] triethylamine (14.1 mL, 101.1 mmol, 5 eq.) was added dropwise to a solution cooled at 0 °C of PCl_3 (1.77 mL, 20.2 mmol, 1.0 eq.) in CH_2Cl_2 (150 mL). The ice bath was removed and the solution left to warm to room temperature before (*S*)-*N*-cyclohexyl-1,2,3,4-tetrahydronaphthalen-1-amine (4.65 g, 20.2 mmol, 1.0 eq.) was added to the stirring solution. (*S*)-binaphthol (5.81 g, 20.2 mmol, 1.0 eq.) was added to the suspension after 5 h

and the subsequent mixture was left stirring 15 h. The solution was then filtered on a small pad of silica and celite® and washed with CH_2Cl_2. The resulting solution was concentrated under reduced pressure to afford a yellow residue. After flash column chromatography (SiO_2, 78:17:1 Petrol: CH_2Cl_2: Et_3N), the title ligand was obtained as a crystalline white solid (10.9 g, 20.2 mmol, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.96 (d, *J* = 8.5 Hz, 1H), 7.90 (dd, *J* = 8.5, 5.3 Hz, 2H,), 7.85 (d, *J* = 7.9 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.50 (dd, *J* = 9.7, 8.8 Hz, 2H), 7.43-7.36 (m, 3H), 7.35-7.29 (m, 2H), 7.28-7.15 (m, 3H), 7.06 (d, *J* = 7.9 Hz, 1H), 4.41 (td, *J* = 10.9, 5.4 Hz, 1H), 2.87-2.61 (m, 3H), 2.21-2.13 (m, 1H), 2.09 (d, *J* = 12.3 Hz, 1H), 2.03 (d, *J* = 11.7 Hz), 1.98-1.85 (m, 2H), 1.84-1.75 (m, 1H), 1.71 (dd, *J* = 12.9, 1.9 Hz, 1H), 1.64 (d, *J* = 12.3 Hz, 1H), 1.59-1.43 (m, 3H), 1.40-1.25 (m, 1H), 1.10-0.99 (m, 1H), 0.98-0.91 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 151.2 (d, *J* = 9.3 Hz), 150.4, 139.1, 138.8, 133.3, 133.3, 133.1, 131.7, 130.8, 130.7, 130.0, 129.4, 129.0, 128.7, 128.5, 127.6, 126.9, 126.4, 126.2, 126.0, 125.1, 124.7, 124.6, 122.9, 122.5, 121.7, 55.8 (d, *J* = 11.1 Hz) 55.3 (d, *J* = 10.9 Hz), 37.6, 34.5, 34.1, 30.2, 26.9, 26.8, 25.9, 22.8.

^{31}P NMR (200 MHz, CD_2Cl_2) δ_P /ppm 153.9 (s, 1P).

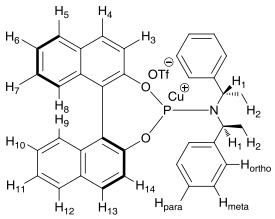
HRMS (EI/FI) *m/z* calcd for $C_{36}H_{34}NO_2P$ $[M]^+$: 543.2327, found: 543.2212;

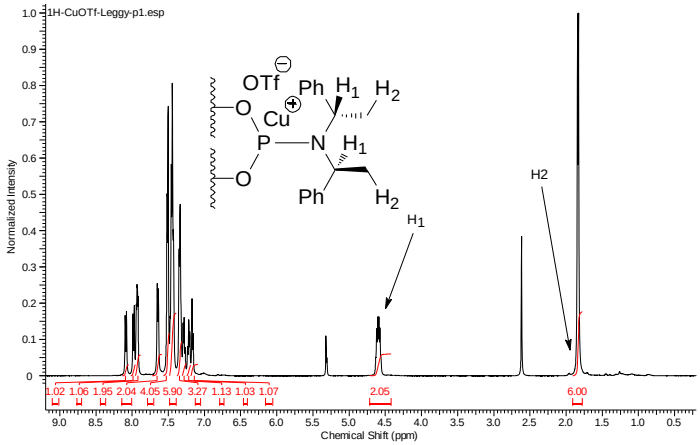
$[\alpha]^{20}_{589}$= +141.2 (*c* 0.99, $CHCl_3$);

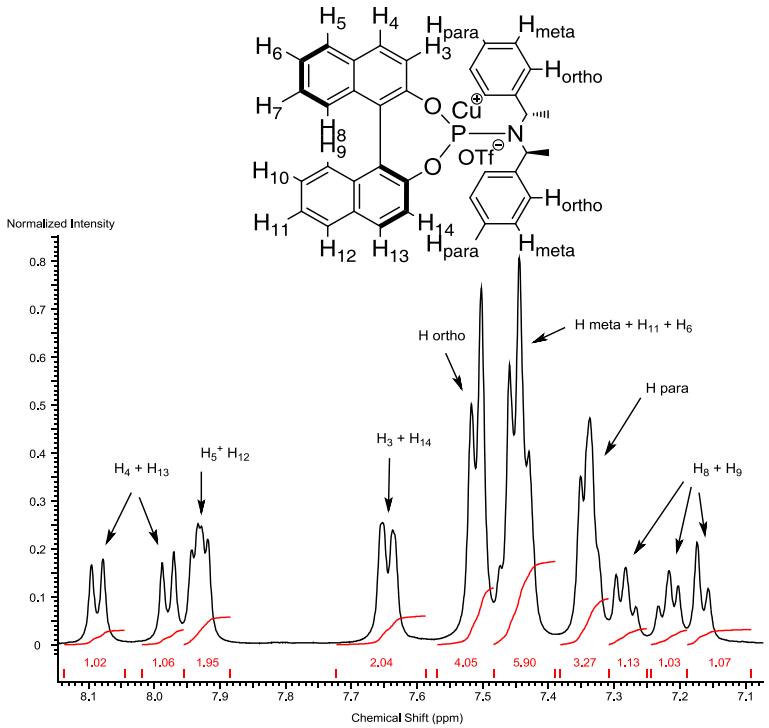
IR (ν_{max}/cm^{-1}) 3474, 2928, 2160, 2022, 2001, 1590, 1328, 1229, 946, 819, 789, 746, 694, 679, 625.

Analysis of the copper triflate-Feringa ligand A Complex 13

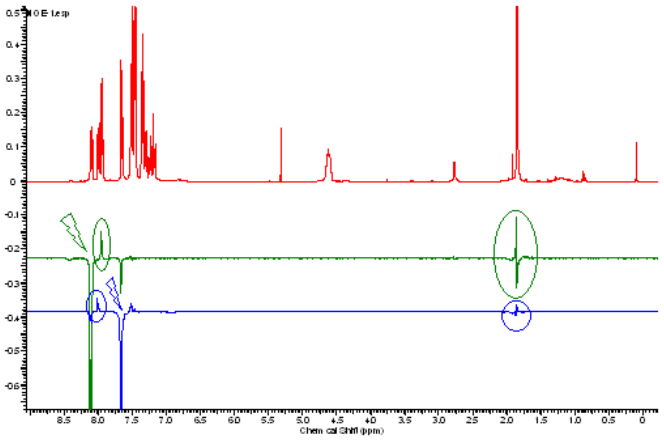
^{1}H NMR assignments

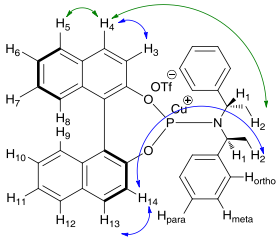


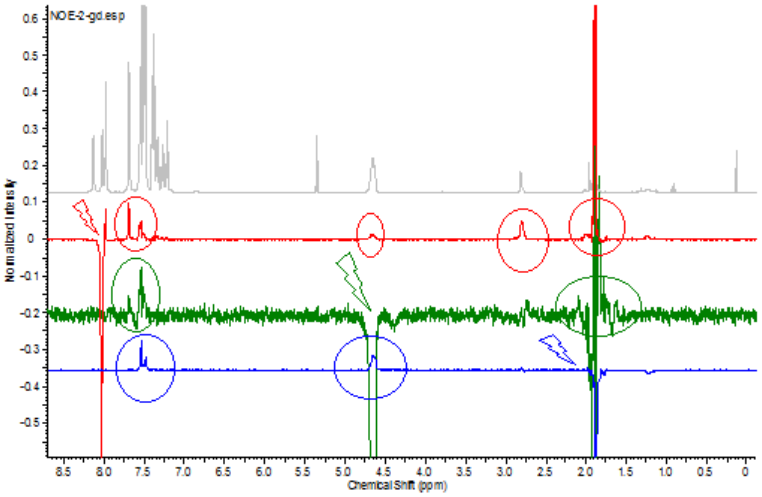


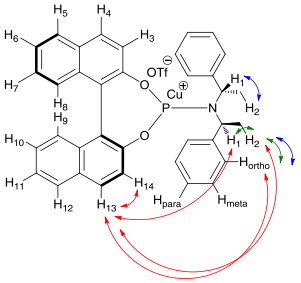


NOE/NOESY NMR Spectroscopy

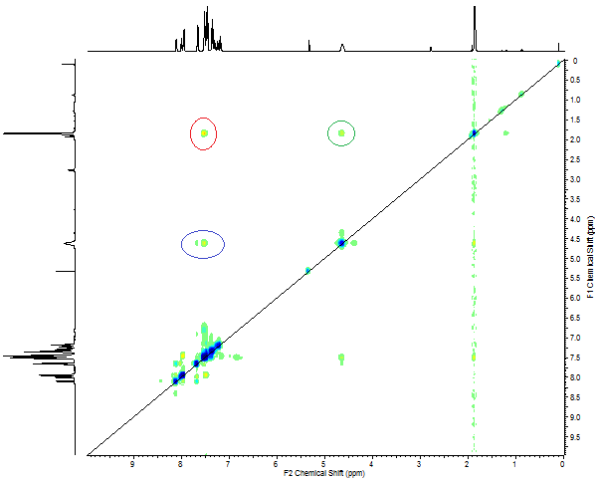


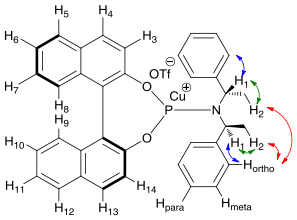






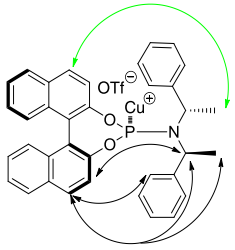
2D NOESY





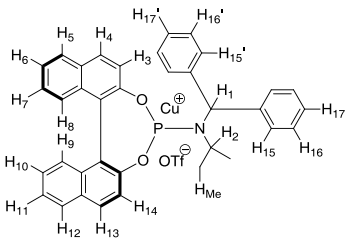
Conclusion

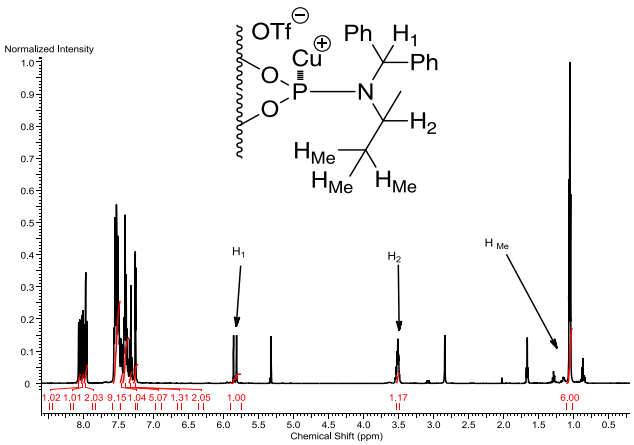
Important interactions in black. A weak interaction is shown in green.

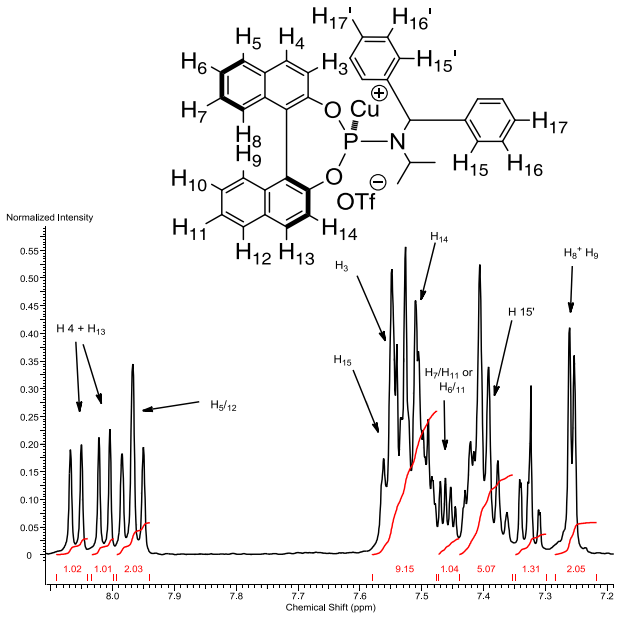


CuOTf-Ligand AS Complex 74

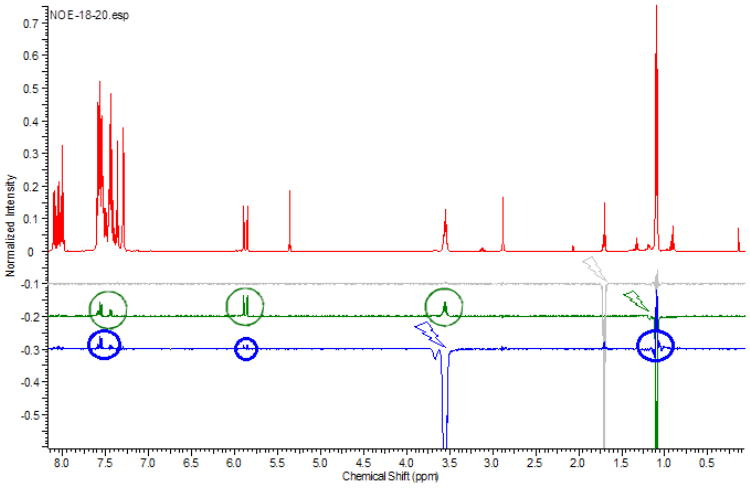
^{1}H NMR assignments

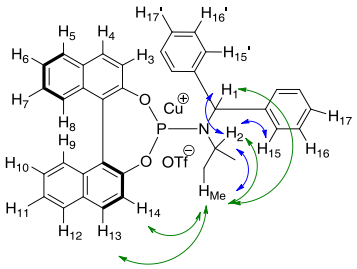


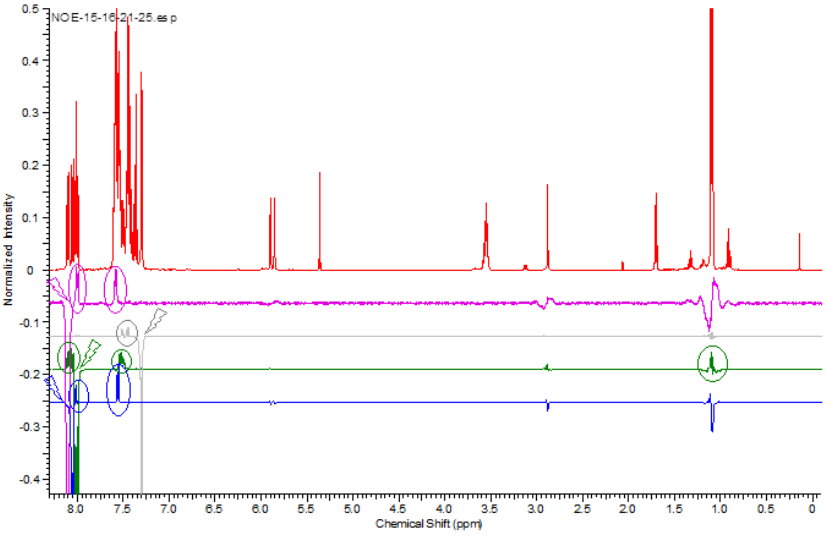


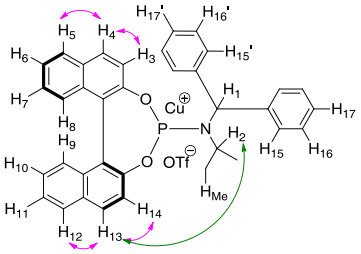


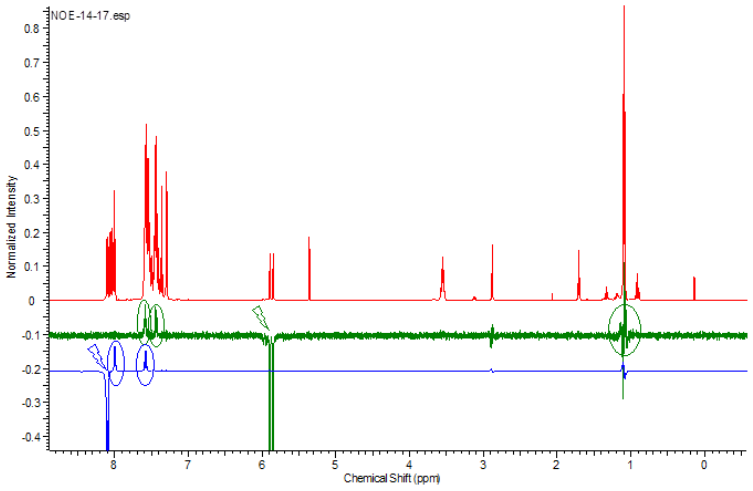
NOE experiments

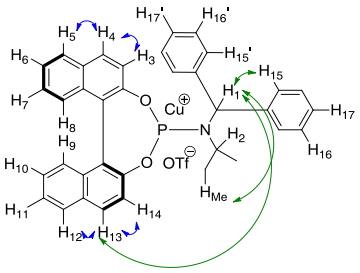






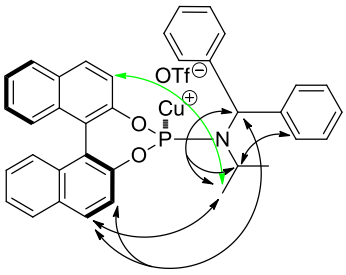






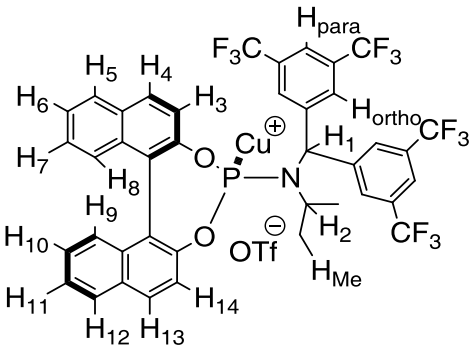
Conclusion

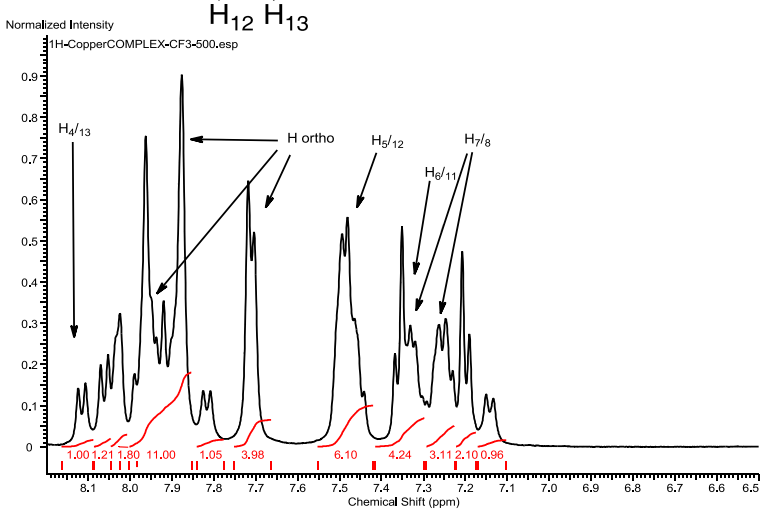
Important interactions in black. A weak interaction is shown in green.

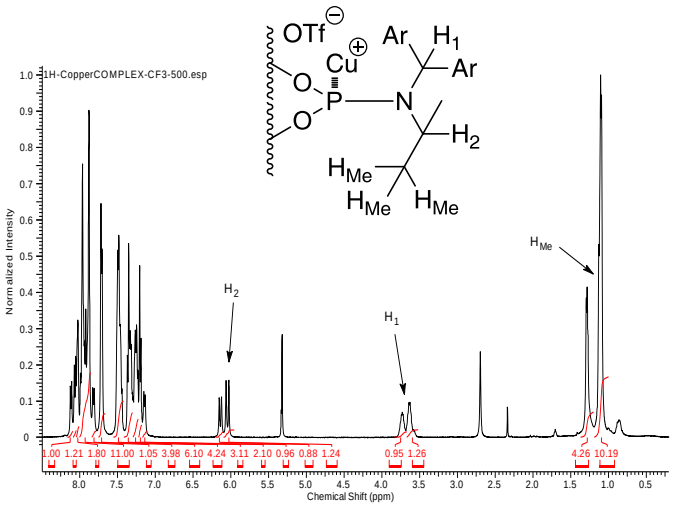


CuOTf- ligand BC complex in CH_2Cl_2 75

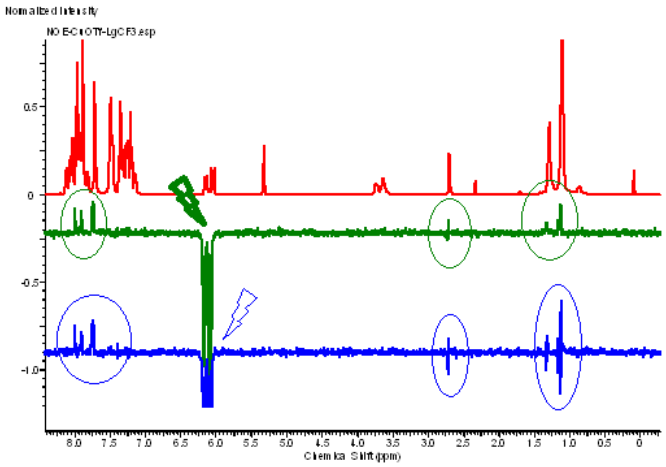
^{1}H NMR assignments

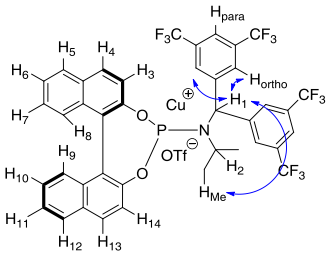




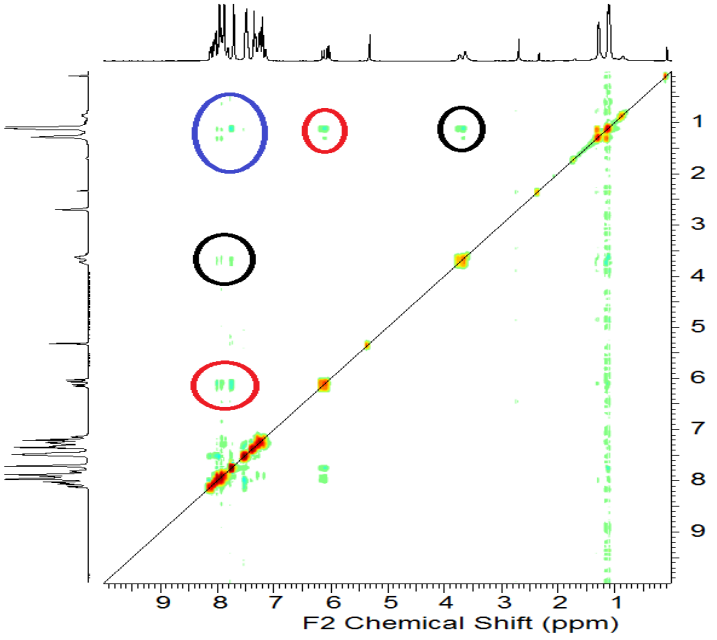


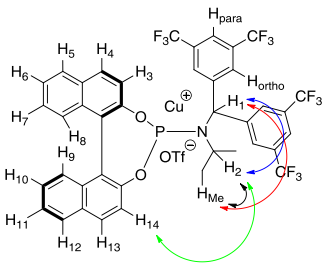
NOE experiments





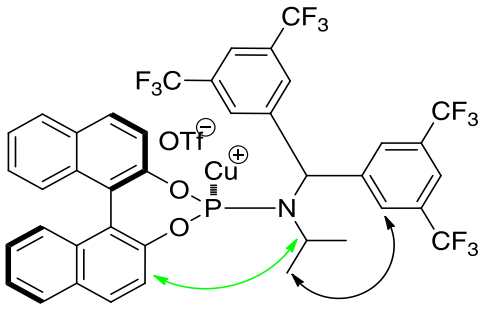
NOESY experiment





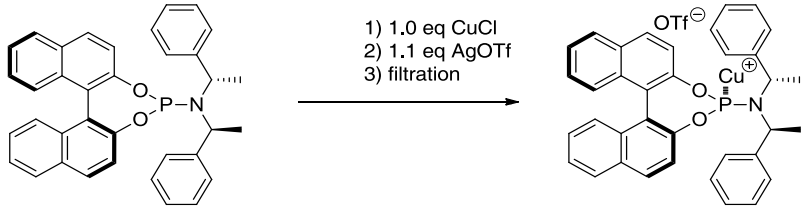
Conclusion

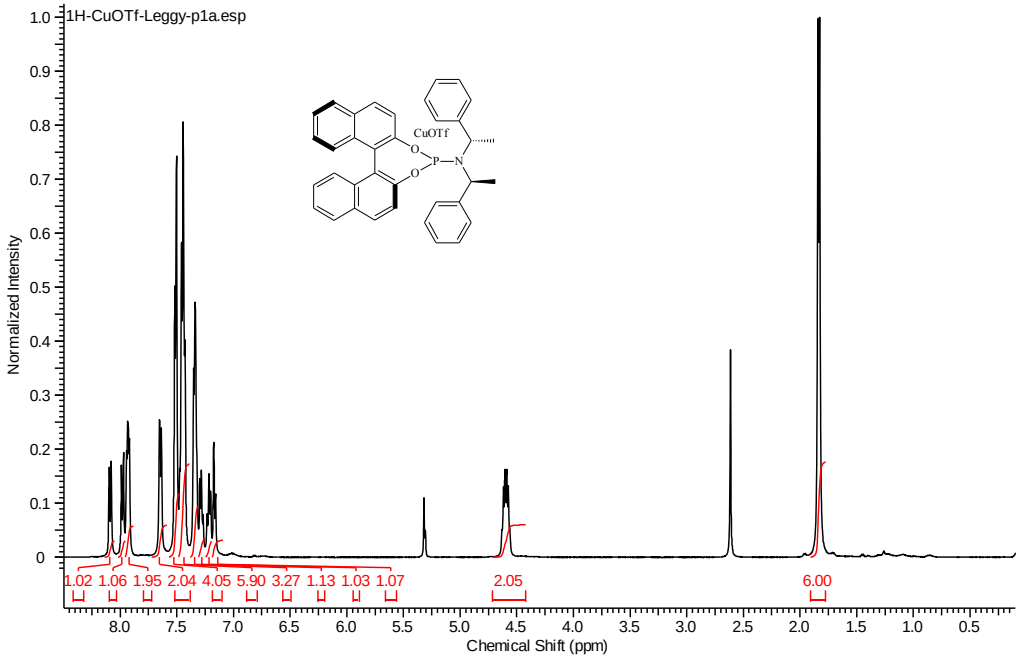
Important interactions in black. A weak interaction is shown in green



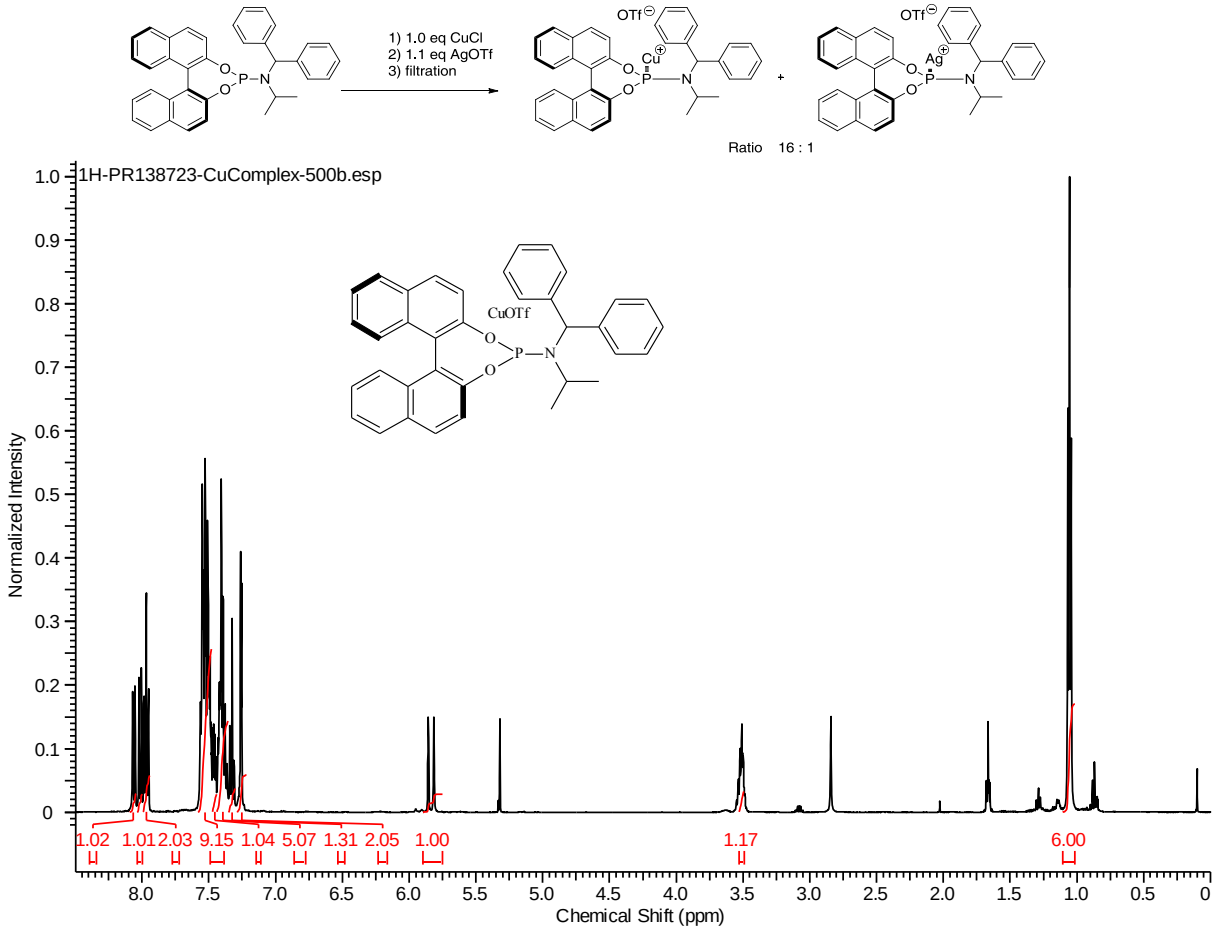
NMR analysis of catalyst complexes in solution:

Copper triflate Feringa ligand A complex 13.

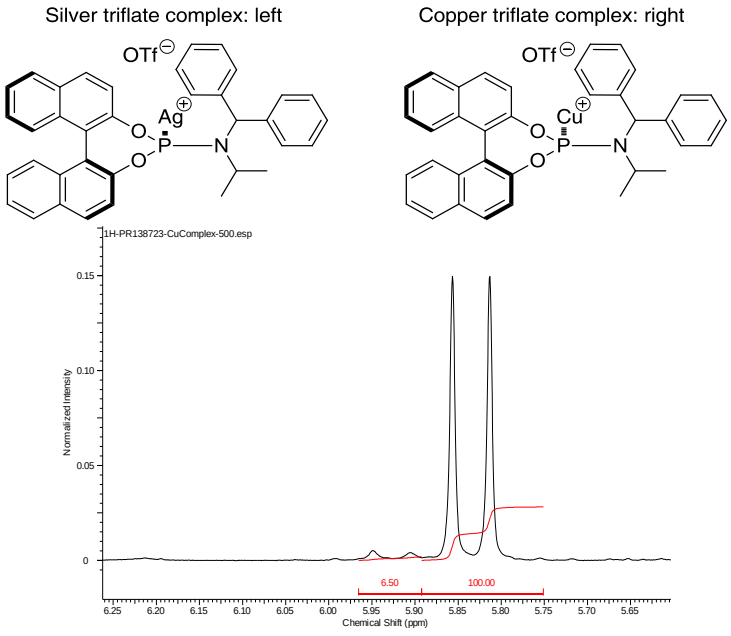




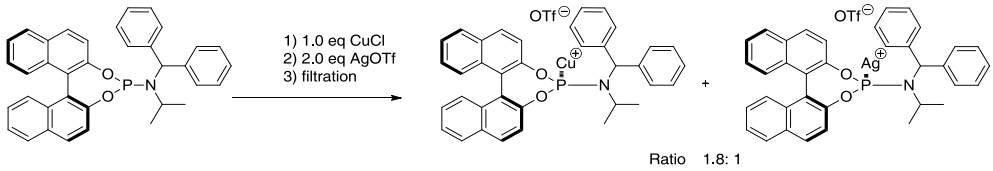
Copper triflate complex with ligand AS: 74

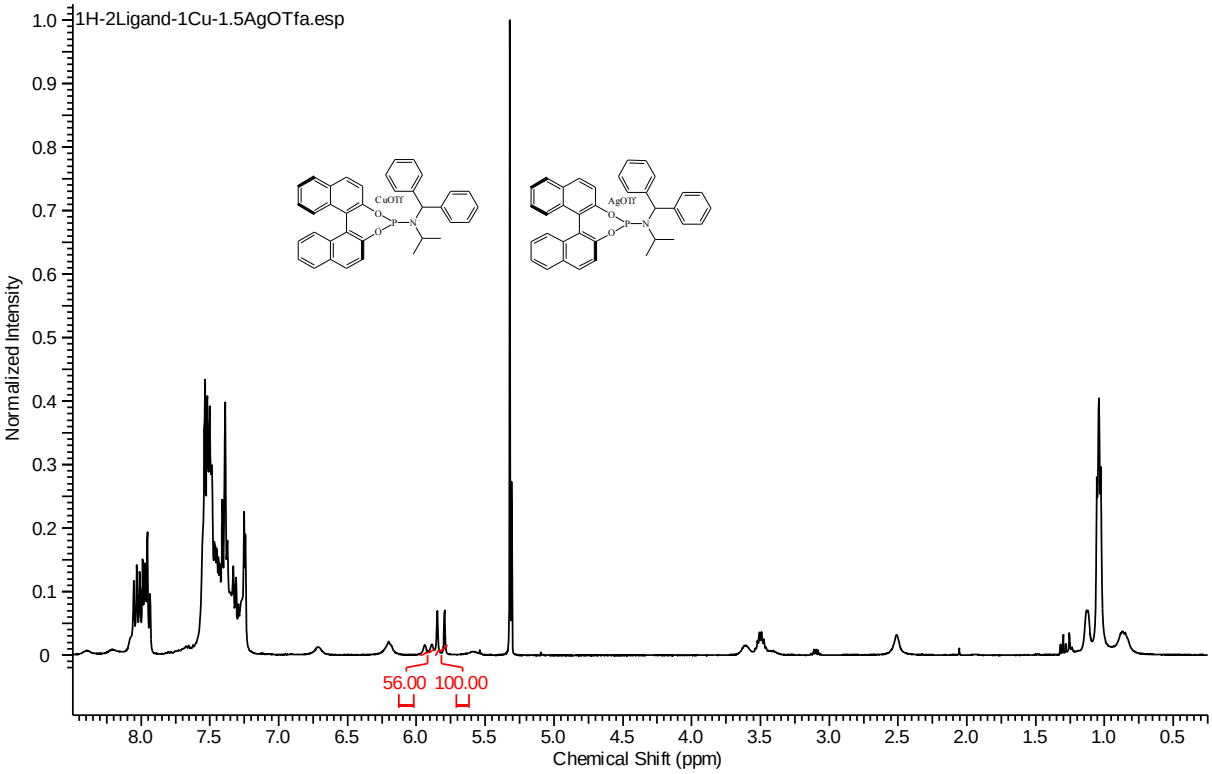


Zoom of1H NMR signal on characteristic peaks of both species

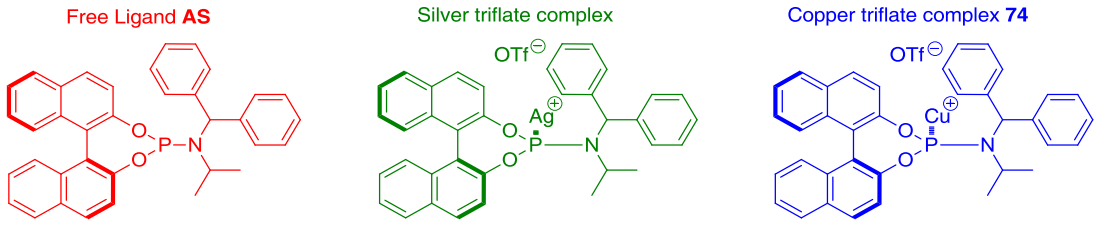


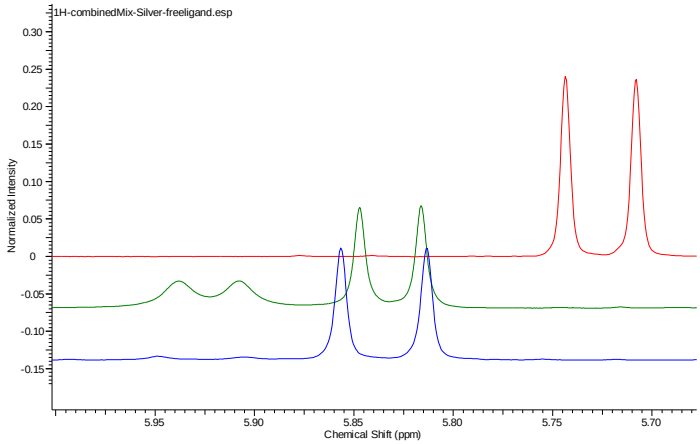
Synthesis of complex by using an excess of silver triflate:



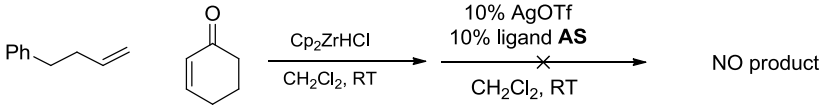


Comparison of NMR signals: free ligand (red), reaction condition mixture (blue), mixture obtained with an excess of silver triflate (green).



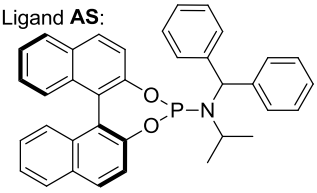


Attempt to perform the reaction using silver triflate only:

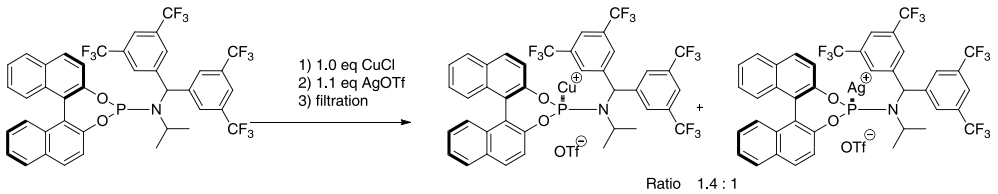


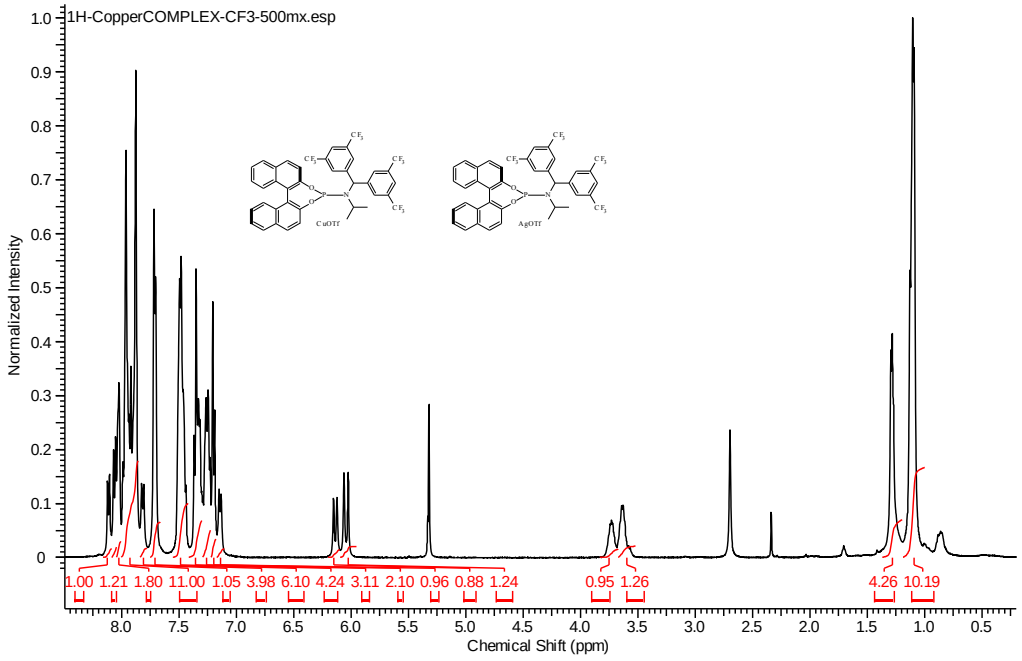
NO product

Ligand **AS**:

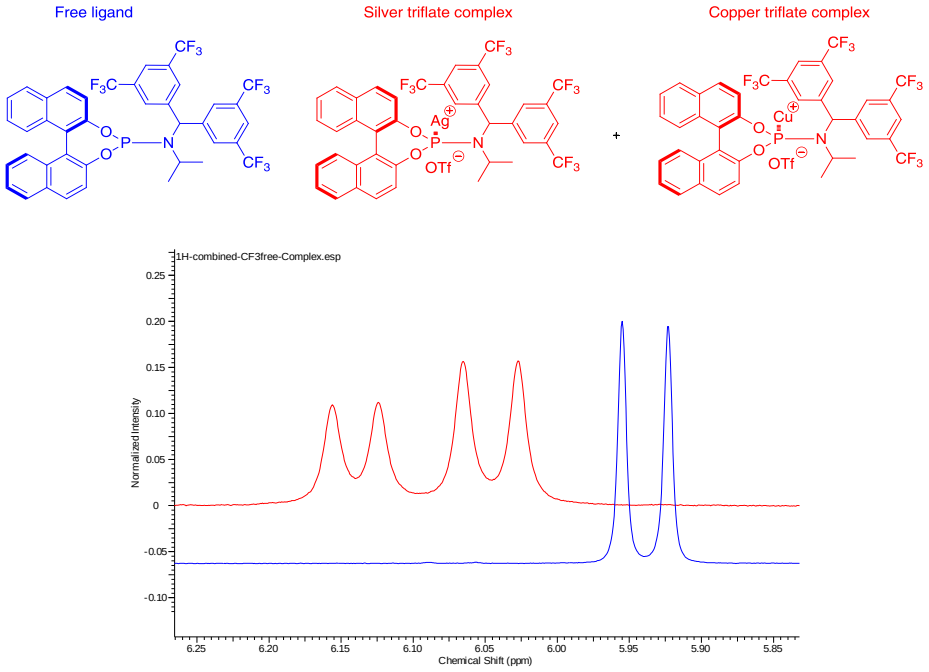


Copper triflate complex with isopropyl ligand BC:

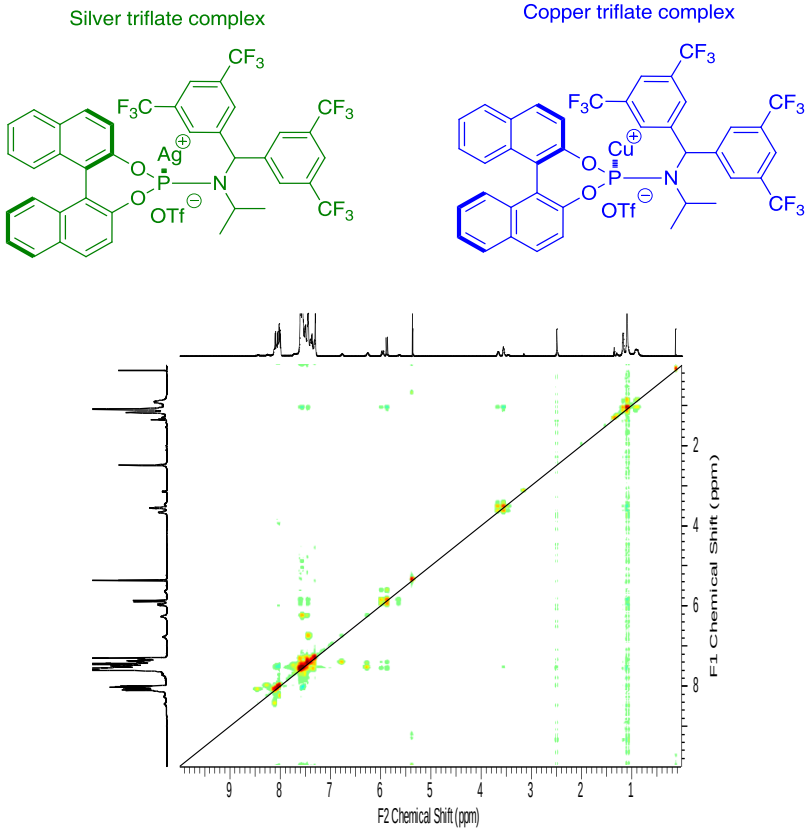




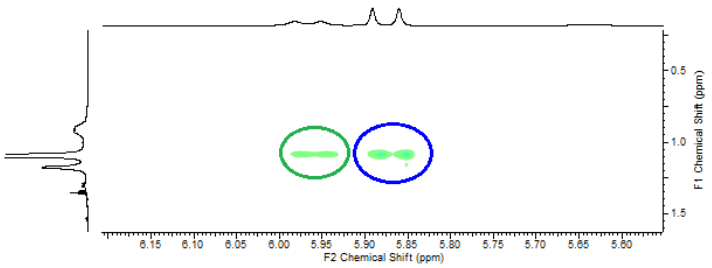
<u>Comparison of ^{1}H NMR signal of free ligand BC (blue) with the copper-ligand complex obtained in the reaction conditions (red):</u>

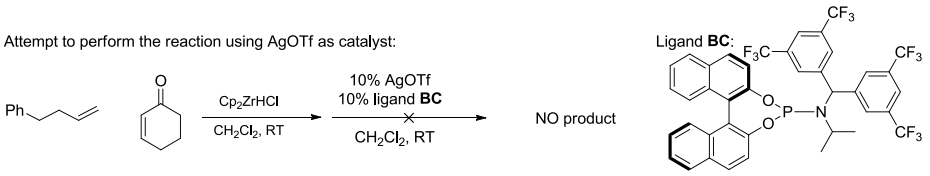


EXSY experiment on the complexes obtained in the reaction conditions:



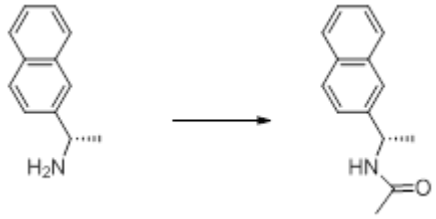
Zoom in the region around 5.90 ppm. The spot show interconversion between the species:





Characterisation of amines and ligand precursors:

(*S*)-*N*-(1-(naphthalen-2-yl)ethyl)acetamide



According to a modified procedure from Canet and coworkers,[269] acetyl chloride (0.11 mL, 1.53 mmol, 1.0 eq.) was added to a stirring solution at 0 °C of (*S*)-1-(naphthalen-2-yl)ethanamine (262 mg, 1.53 mmol, 1.0 eq) and triethylamine (0.26 mL, 1.83 mmol, 1.2 eq) in Et_2O (12 mL) at room temperature. After 10 min, the reaction mixture was filtered through celite and washed with Et_2O (10 mL). The mixture was concentrated *in vacuo* to afford the free amine. The amine was used without further purification. Flash column chromatography of the residue (Petrol: EtOAc; 4:1 → 1:4 SiO_2) gave the desired (*S*)-*N*-(1-(naphthalen-2-yl)ethyl)acetamide) (301 mg, 1.46 mmol, 92%).

Data was consistent with previous published literature.[270]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.75 - 7.83 (m, 3 H), 7.73 (br. s, 1 H), 7.44 - 7.48 (m, 2 H), 7.41 (dd, *J* = 8.6, 1.8 Hz, 1 H), 6.81 (d, *J* = 7.8 Hz, 1 H), 5.24 (quin, *J* = 7.2 Hz, 1 H), 1.94 (s, 3 H), 1.50 (d, *J* = 6.8 Hz, 3 H).

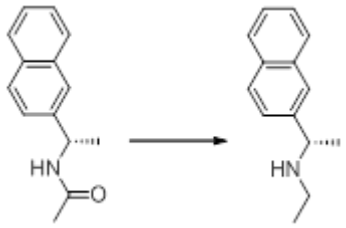
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 169.4, 140.7, 133.1, 132.4, 128.1, 127.6, 127.4, 126.0, 125.6, 124.6, 124.3, 48.6, 23.0, 21.5.

HRMS (ESI) *m/z* calcd for $C_{22}H_{28}N$ $[M+H]^+$: 236.1043, found: 236.1046.

$[\alpha]^{20}_{589}$= +186.46 (*c* 0.48, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 3276, 2931, 1738, 1645, 1602, 1441, 1216.

(*S*)-*N*-(1-(naphthalen-2-yl)ethyl)acetamide



According to a modified procedure from Brown and coworkers,[271] $LiAlH_4$ (0.70 mL, 2.81 mmol, 2.0 eq) was added dropwsie to a stirring solution at 0 °C of (*S*)-*N*-(1-(naphthalen-2-yl)ethyl)acetamide (301 mg, 1.41 mmol, 1.0 eq.) in Et_2O (20 mL). The reaction mixture was heated under reflux for 15 hours. EtOAc (5 mL) and water (10 mL) were added to the reaction mixture which was stirred for an additional 10 minutes before NaOH (15 mL, 3 M aq solution) was added to the reaction mixture. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with $NaHCO_3$ (aq. sat., *ca* 15 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title amine as a yellow oil (191 mg, 0.95 mmol, 68%). The amine was used without further purification.

Data was consistent with previous published literature.[272]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 7.80 - 7.87 (m, 3 H), 7.75 (s, 1 H), 7.39 - 7.53 (m, 3 H), 3.97 (q, *J* = 6.6 Hz, 1 H), 2.56 - 2.64 (m, 1 H), 2.45 - 2.56 (m, 1 H), 1.51 - 1.83 (m, 1 H), 1.46 (d, *J* = 6.6 Hz, 3 H), 1.11 (t, *J* = 7.3 Hz, 3 H).

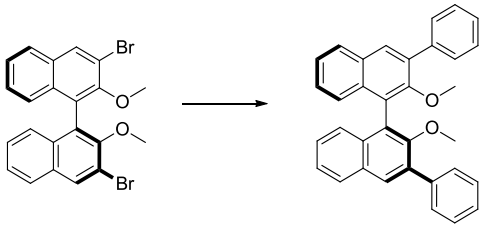
^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 133.4, 132.8, 128.2, 127.7, 127.6, 125.9, 125.4, 125.2, 124.8 (2 C), 58.4, 42.1, 24.2, 15.4.

HRMS (ESI) *m/z* calcd for $C_{22}H_{28}N$ $[M+H]^+$: 236.1043, found: 236.1046.

$[\alpha]^{20}_{589}$= +186.46 (*c* 0.48, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 3276, 2931, 1738, 1645, 1602, 1441, 1216.

(*S*)-2,2'-dimethoxy-3,3'-diphenyl-1,1'-binaphthalene



According to a modified procedure from Feringa,[192] (*S*)-bromo-methoxybinaphthol (700 mg, 1.48 mmol, 1.0 eq), $PhB(OH)_2$ (398 mg, 3.26 mmol, 2.2 eq) and an aqueous solution of $NaHCO_3$ (748 mg in 9 mL of H_2O, 8.89 mmol, 6.0 eq) were added sequentially to a solution of $Pd(PPh_3)_4$ (171.3 mg, 0.14 mmol, 0.1 eq) in DME (10 mL). The reaction mixture was then heated to reflux (100 °C) for 36 hours (TLC control in 9:1 Petrol: EtOAc for completion of the reaction). Upon cooling, CH_2Cl_2 (10 mL) and H_2O (5 mL) were added to the reaction mixture. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Flash column chromatography of the yellow residue (1:1 Toluene/petrol; SiO_2) gave (*S*)-2,2'-dimethoxy-3,3'-diphenyl-1,1'-binaphthalene (492.5 mg, 1.09 mmol, 74%) as a yellow oil.

Data consistent with literature.[192]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 8.00 (s, 2 H), 7.93 (d, *J* = 8.3 Hz, 2 H), 7.79 (d, *J* = 8.3 Hz, 4 H), 7.48 (t, *J* = 7.6 Hz, 4 H), 7.37 - 7.45 (m, 4 H), 7.24 - 7.32 (m, 4 H), 3.20 (s, 6 H).

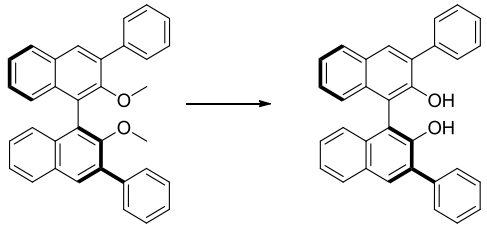
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 154.0 (2 C), 138.9, 135.0, 133.6 (2 C), 130.8, 130.5 (2 C), 129.3 (2 C), 128.3 (2 C), 128.0, 127.3 (2 C), 126.3 (2 C), 125.9, 125.8, 125.0 (2 C), 60.5 (2 C).

HRMS (EI) *m*/*z* calcd for $C_{34}H_{26}O_2[M]^+$: 466.1933, found: 466.1942

$[\alpha]^{20}_{589}$ = −5.71 (*c* 1.40, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2939, 1738, 1351, 1204, 750.

(*S*)-3,3'-diphenyl-[1,1'-binaphthalene]-2,2'-diol



According to a modified procedure from Wipf,[194] BBr_3 (4.2 mL, 4.2 mmol, 4.0 eq, 1 M solution in CH_2Cl_2) was added slowly to a stirring solution at –78 °C of (*S*)-2,2'-dimethoxy-3,3'-diphenyl-1,1'-binaphthalene (492 mg, 1.05 mmol, 1.0 eq) in CH_2Cl_2 (20 mL). The reaction mixture was warmed to 0 °C and stirred arbitrarily for 24 hours before H_2O (5 mL) was added to the reaction mixture. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Flash column chromatography of the yellow residue (1:1 Toluene/petrol; SiO_2) gave (*S*)-3,3'-diphenyl-[1,1'-binaphthalene]-2,2'-diol (425 mg, 0.97 mmol, 91%).

Data consistent with literature.[194]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 8.08 (s, 2 H), 7.97 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 7.1 Hz, 4 H), 7.54 (t, *J* = 7.6 Hz, 4 H), 7.45 (q, *J* = 7.6 Hz, 4 H), 7.37 (t, *J* = 7.6 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 5.42 (br. s., 2 H).

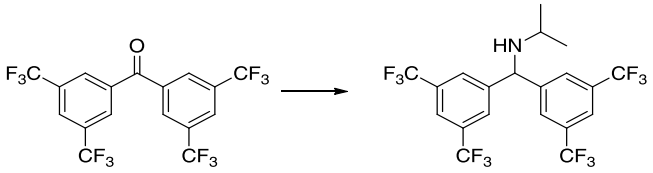
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 150.1 (2 C), 137.4 (2 C), 132.9 (2 C), 131.4 (2 C), 130.6 (2 C), 129.6 (4 C), 129.4 (2 C), 128.4 (4 C), 128.4 (2 C), 127.7 (2 C), 127.3 (2 C), 124.3 (2 C), 124.2 (2 C), 112.4 (2 C).

HRMS (EI) *m*/*z* calcd for $C_{34}H_{26}O_2[M]^+$: 438.1620, found: 438.1627

$[\alpha]^{20}_{589}$= +58.40 (*c* 0.83, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2971, 1730, 1426, 1229.

N-(bis(3,5-bis(trifluoromethyl)phenyl)methyl)propan-2-amine



According to a modified procedure from Gilbert, [198] $TiCl_4$ (6.1 mL, 6.1 mmol, 1.1 eq, 1 M solution in CH_2Cl_2) was added slowly to a solution cooled at 0 °C of bis(3,5-bis(trifluoromethyl)phenyl)methanone (2.5 g, 5.5 mmol, 1.0 eq) in CH_2Cl_2 (30 mL). The solution was stirred for 5 minutes at room temperature and a solution of isopropylamine (1.0 mL, 12.1 mmol, 2.2 eq) in THF (6 ml, 2 M solution) was added dropwise to the reaction mixture. The reaction flask was stirred for 3 hours. A solution of $NaB(CN)H_3$ (0.415 g, 6.61 mmol, 1.2 eq) in THF (7 mL, 1 M solution) was added slowly to the reaction mixture. MeOH (10 mL) was added slowly to the reaction mixture. The reaction mixture was stirred at room temperature for 18 hours. NaOH (~20 mL, 2 M aq solution) was added slowly and the reaction mixture was stirred for 30 min. The reaction mixture was filtered on celite and washed with EtOAc (~30 mL). The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. Flash column chromatography of the residue (Petrol: CH_2Cl_2: Et_2O; 89: 10: 1; SiO_2) gave the desired *N*-(bis(3,5-bis(trifluoromethyl)phenyl)methyl)propan-2-amine (0.73 g, 1.46 mmol, 27%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H /ppm 7.88 (s, 4 H), 7.80 (s, 2 H), 5.21 (s, 1 H), 2.70 (spt, J = 6.2 Hz, 1 H), 1.27 (br. s., 1 H), 1.14 (d, J = 6.2 Hz, 6 H).

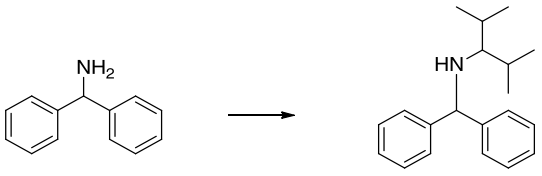
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 145.5 (2 C), 131.0 - 133.2 (m, 2 C), 127.3 - 127.4 (m, 2 C), 127.3 (2 C), 124.5 (2 C), 121.8 (s, 2 C), 63.4, 46.6, 23.1 (2 C).

^{19}F NMR (380 MHz, $CDCl_3$) δ_F /ppm -62.85 (s, 12 F).

HRMS (ESI) *m*/*z* calcd for $C_{20}H_{16}F_{12}N$ $[M+H]^+$: 498.1085, found: 498.1086.

IR (ν_{max} /cm^{-1}): 1371, 1276, 1168, 1126, 898, 712.

N-benzhydryl-2,4-dimethylpentan-3-amine



According to a modified procedure from Gilbert,[198] $TiCl_4$ (5.8 mL, 5.8 mmol, 1.1 eq, 1 M solution in CH_2Cl_2) was added slowly to a solution cooled at 0 °C of 2,4-dimethylpentan-3-one (0.74 mL, 5.2 mmol, 1.0 eq) in CH_2Cl_2 (15 mL). The solution was stirred for 5 minutes at room temperature before diphenylmethanamine (0.9 mL, 5.2 mmol, 1.0 eq) was added dropwise to the reaction

mixture. The reaction mixture was stirred for an additional 3 hours before a solution of $NaB(CN)H_3$ (0.495 g, 7.9 mmol, 1.5 eq) was added. The reaction mixture was stirred at room temperature for 18 hours before NaBH4 (61 mg, 0.19 mmol, 0.05 eq) and MeOH (5 mL) were added and the reaction mixture was stirred for another 20 hours. NaOH (~20 mL, 2 M *aq* solution) was then added slowly and the reaction mixture was stirred for 30 min. The reaction mixture was filtered on celite and washed with EtOAc (~30 mL). The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic phase was concentrated *in vacuo*. Et_2O (~10 mL) was added to the oil. HCl (aq 2.0 M, ~2 mL) was added dropwise for about 1 min. The mixture was partitioned between the aqueous and Et_2O layers and the organic phase extracted with HCl (aq 2.0 M, 15 mL). Then CH_2Cl_2 (10 mL) was added to the combined aqueous phases and NaOH (aq saturated with brine solution, 25%) was added till the mixture became basic (pH paper, pH~14). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the desired *N*-benzhydryl-2,4-dimethylpentan-3-amine (0.50 g, 1.77 mmol, 34%). The amine was used without further purification.

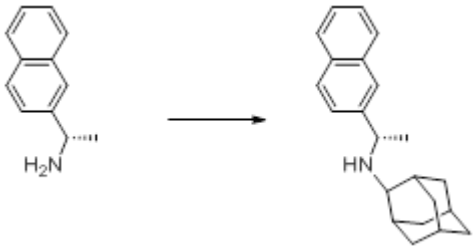
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.42 - 7.50 (m, 4 H), 7.31 (t, *J* = 7.5 Hz, 4 H), 7.22 (tt, *J* = 7.5, 1.3 Hz, 2 H), 4.99 (s, 1 H), 2.13 - 2.23 (m, 1 H), 1.87 (dtd, *J* = 13.7, 6.8, 4.5 Hz, 2 H), 1.35 (br. s., 1 H), 0.91 (apparent t, *J* = 6.8 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 145.1 (2 C), 128.2 (4 C), 127.7 (4 C), 126.7 (2 C), 65.6, 63.9 (, 29.9 (2 C), 20.9 (2 C), 18.8 (2 C).

HRMS (ESI) *m*/*z* calcd for $C_{20}H_{28}N$ $[M+H]^+$: 282.2212, found: 282.2216.

IR (ν_{max} /cm^{-1}): 2956, 1739, 1492, 1452, 1217, 1067, 742, 699.

(*S*)-*N*-(1-(naphthalen-2-yl)ethyl)adamantan-2-amine



According to a modified procedure from Davies and coworkers,[266] (1r,3r,5r,7r)-adamantan-2-one (220 mg, 1.46 mmol, 1.0 eq.) was added to a stirring solution of (*S*)-1-(naphthalen-2-yl)ethanamine (257 mg, 1.46 mmol, 1.0 eq) in THF (12 mL) at room temperature. After 5 min,

$NaB(OAc)_3H$ (621mg, 2.93 mmol, 2.0 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (15 mL) and $NaHCO_3$ (aq. sat., *ca* 10 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title amine as a yellow oil (224 mg, 0.73 mmol, 50%). The combined organic phase was concentrated *in vacuo.* EtOAc (*ca* 5 mL) was added to the oil. HCl (aq 2.0 M, *ca* 2 mL) was added dropwise for about 1 min. The mixture was partitioned between the aqueous and Et_2O layers and the organic phase extracted with HCl (aq 2.0 M, 15 mL). . The crystals were recrystallized in EtOAc/EtOH. Then CH_2Cl_2 (10 mL) was added to the combined aqueous phases and NaOH (*aq*. saturated with brine solution, 25%) was added till the mixture became basic (pH paper, pH>14). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the free amine. The amine was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 10.07 (br. s., 1 H), 9.40 (br. s., 1 H), 8.00 - 8.17 (m, 2 H), 7.95 (d, *J* = 8.5 Hz, 1 H), 7.89 - 7.93 (m, 1 H), 7.85 - 7.89 (m, 1 H), 7.50 - 7.57 (m, 2 H), 4.59 (t, *J* = 6.6 Hz, 1 H), 3.72 (br. d, *J* = 6.6 Hz, 1 H), 3.00 (d, *J* = 9.1 Hz, 1 H), 2.92 (d, *J* = 13.2 Hz, 1 H), 2.61 (d, *J* = 12.9 Hz, 1 H), 2.44 (br. s., 1 H), 2.26 (br. s., 1 H), 2.24 (d, *J* = 6.9 Hz, 3 H), 2.00 (br. s., 1 H), 1.78 (d, *J* = 10.1 Hz, 1 H), 1.72 (d, *J* = 13.2 Hz, 2 H), 1.68 (br. s., 2 H), 1.52 (d, *J* = 12.3 Hz, 1 H), 1.46 (d, *J* = 12.3 Hz, 1 H), 1.29 (d, *J* = 12.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 151.4, 149. 9, 139.8, 133.22, 132.9, 132.8, 132.4, 131.3, 130.4, 130.1, 129.6, 128.3, 128.05, 128.00, 127.5, 127.3 (2 C), 127.2, 126.8, 126.0, 125.9, 125.7 (2 C), 125.7, 124.7, 124.1, 122.5, 122.2, 61.70, 54.00, 53.40, 39.7, 38.9, 38.4, 35.4, 34.3, 32.4, 32.2, 31.63, 31.51, 27.51 (2 C).

HRMS (ESI) *m/z* calcd for $C_{22}H_{28}N$ $[M+H]^+$: 306.2219, found: 306.2215.

$[\alpha]^{20}_{589}$= +10.16 (*c* 1.22, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 2915, 2853, 1587, 1478, 749.

(*S*)-*N*-isopropyl-2,3-dihydro-1H-inden-1-amine



According to a modified procedure from Davies and coworkers,[266] acetone (0.32, 4.3 mmol, 2.0 eq.) was added to a stirring solution of (*S*)-2,3-dihydro-1H-inden-1-amine (0.28 mL, 2.15 mmol, 1.0 eq) in THF (10 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (912 mg, 5.16 mmol, 2.4 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (15 mL) and $NaHCO_3$ (aq. sat., *ca* 10 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title amine as a yellow oil (0.36 g, 1.50 mmol, 65%). The amine was used without further purification.

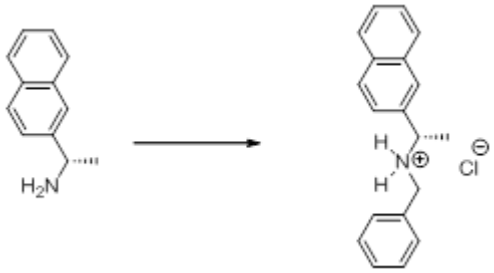
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.35 - 7.48 (m, 1 H), 7.23 (dt, *J* = 9.5, 4.8 Hz, 3 H), 4.36 (t, *J* = 6.7 Hz, 1 H), 3.10 - 3.21 (m, 1 H), 3.04 (ddd, *J* = 15.7, 8.6, 4.8 Hz, 1 H), 2.82 (dt, *J* = 15.7, 7.6 Hz, 2 H), 2.45 (dtd, *J* = 12.5, 7.6, 7.6, 4.8 Hz, 1 H), 1.81 - 1.93 (m, 1 H), 1.12 - 1.27 (apparent t, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 144.8, 143.1, 127.0, 125.9, 124.3, 123.8, 60.0, 46.2, 33.8, 29.9, 23.0, 22.2.

HRMS (ESI) *m/z* calcd for $C_{12}H_{18}N$ $[M+H]^+$: 176.1428, found: 176.1434.

IR (ν_{max}/cm^{-1}) 2946, 1378, 851, 753.

(*S*)-*N*-benzyl-1-(naphthalen-2-yl)ethanamine



According to a modified procedure from Davies and coworkers,[266] benzaldehyde (0.21, 2.07 mmol, 1.0 eq.) was added to a stirring solution of (*S*)-1-(naphthalen-2-yl)ethanamine (355 mg, 2.07 mmol, 1.0 eq.) in THF (20 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (615 mg, 2.9 mmol, 1.4 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (20 mL) and $NaHCO_3$ (aq. sat., *ca* 20 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title amine as a yellow oil (0.38 g, 1.28 mmol, 61%). The amine was dissolved in Et_2O (*ca*

5 mL) and HCl (5 drops conc.) was added. The amine was then recrystallized in EtOAc/MeOH. The combined organic phase was concentrated *in vacuo*. Et_2O (*ca* 10 mL) was added to the oil. HCl (aq 2.0 M, *ca* 2 mL) was added dropwise for about 1 min. The mixture was partitioned between the aqueous and Et_2O layers and the organic phase extracted with HCl (aq 2.0 M, 15 mL). Then CH_2Cl_2 (10 mL) was added to the combined aqueous phases and NaOH (aq saturated with brine solution, 25%) was added till the mixture became basic (pH paper, pH>14). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the free amine. The amine was used without further purification.

Data consistent with literature.[273]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 10.61 (br. s., 1 H), 10.40 (br. s., 1 H), 7.97 (d, *J* = 8.5 Hz, 1 H), 7.92 (s, 1 H), 7.87 - 7.91 (m, 2 H), 7.84 (dd, *J* = 8.5, 1.6 Hz, 1 H), 7.52 - 7.56 (m, 2 H), 7.45 - 7.49 (m, 2 H), 7.28 - 7.40 (m, 3 H), 4.23 (t, *J* = 7.0 Hz, 1 H), 3.86 - 3.96 (m, 1 H), 3.63 (quin, *J* = 7.0 Hz, 1 H), 1.88 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 133.4, 133.3, 133.1, 130.8 (2 C), 130.0, 129.6, 129.2, 128.8 (2 C), 128.2, 127.9, 127.8, 126.9, 126.7, 124.7, 57.5, 48.5, 20.7.

MS (ESI) *m*/*z* $[M+H]^+$: 262.2 (100).

IR (ν_{max}/cm^{-1}) 2978, 1453, 932, 749.

N-isopropyladamantan-2-amine



According to a modified procedure from Davies and coworkers,[266] 2-adamantanone (400 mg, 2.66 mmol, 1.0 eq.) was added to a stirring solution of isopropylamine (0.23 mL, 2.66 mmol, 1.0 eq.) in THF (15 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (846 mg, 4.0 mmol, 1.5 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (20 mL) and $NaHCO_3$ (aq. sat., *ca* 20 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title amine as a yellow oil (0.51 g, 2.63 mmol, 99%). The amine was used without further purification.

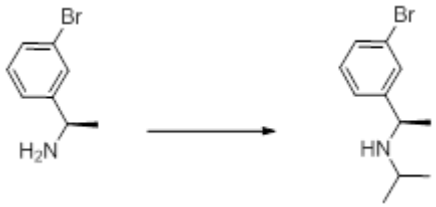
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 2.8 (dt, *J* = 12.4, 6.1 Hz, 1 H), 2.7 (br. s., 1 H), 1.8 (br. s., 1 H), 1.7 - 1.8 (m, 6 H), 1.7 (br. s., 1 H), 1.6 (br. s., 4 H), 1.5 (br. s., 1 H), 1.4 (br. d, *J* = 1.0 Hz, 1 H), 1.0 (d, *J* = 6.1 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 58.2 (s, 1 C), 44.6 (s, 1 C), 37.9 (s, 1 C), 37.8 (s, 3 C), 32.1 (s, 1 C), 31.3 (s, 3 C), 27.8 (s, 1 C), 27.5 (s, 1 C), 23.3 (s, 1 C).

HRMS (ESI) *m/z* calcd for $C_{13}H_{24}N$ $[M+H]^+$: 194.1903, found: 194.1901.

IR (ν_{max}/cm^{-1}) 2965, 1452, 1171, 1032, 747.

(*R*)-*N*-(1-(3-bromophenyl)ethyl)propan-2-amine



According to a modified procedure from Davies and coworkers,[266] acetone (0.28 mL, 3.78 mmol, 2.0 eq.) was added to a stirring solution of (*R*)-1-(3-bromophenyl)ethanamine (0.28 mL, 1.90 mmol, 1.0 eq.) in THF (10 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (1.00 g, 5.16 mmol, 2 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (15 mL) and $NaHCO_3$ (aq. sat., *ca* 15 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title amine as a yellow oil (0.43 g, 1.77 mmol, 94%). The amine was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.45 (t, *J* = 1.7 Hz, 1 H), 7.35 (dt, *J* = 7.5, 1.7 Hz, 1 H), 7.13 - 7.26 (m, 2 H), 3.85 (q, *J* = 6.1 Hz, 1 H), 2.61 (dt, *J* = 12.5, 6.1 Hz, 1 H), 1.31 (d, *J* = 6.1 Hz, 3 H), 1.02 (d, *J* = 6.1 Hz, 3 H), 0.99 (d, *J* = 6.1 Hz, 3 H).

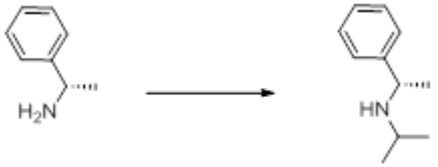
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 148.1, 130.0, 129.9, 129.6, 125.1, 122.5, 54.7, 45.7 , 24.5, 23.7, 21.8.

HRMS (ESI) *m/z* calcd for $C_{11}H_{17}BrN$ $[M+H]^+$: 242.0541, found: 242.0539.

$[\alpha]^{20}_{589}$= +51.94 (*c* 1.06, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 2961, 1569, 1467, 1171, 1068, 783, 696.

(*S*)-*N*-(1-phenylethyl)propan-2-amine



According to a modified procedure from Davies and coworkers,[266] acetone (0.38 mL, 5.16 mmol, 2.0 eq.) was added to a stirring solution of (*S*)-1-phenylethanamine (0.35 mL, 2.50 mmol, 1.0 eq.) in THF (10 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (1.00 g, 5.16 mmol, 2 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (15 mL) and $NaHCO_3$ (aq. sat., *ca* 15 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title amine as a yellow oil (0.39 g, 2.38 mmol, 46%). The amine was used without further purification.

Data in accordance with published literature.[274]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.20 - 7.33 (m, 4 H), 7.11 - 7.18 (m, 1 H), 3.87 (d, *J* = 6.5 Hz, 1 H), 2.58 (spt, *J* = 6.5 Hz, 1 H), 1.32 (d, *J* = 6.5 Hz, 3 H), 0.97 (t, *J* = 5.9 Hz, 6 H).

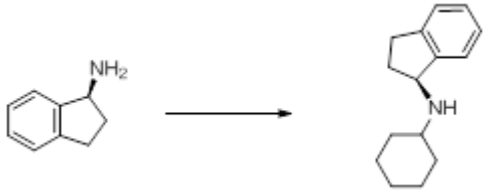
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 146.2, 143.3, 127.0, 126.1, 124.5, 123.8, 60.0, 54.7, 34.8, 34.5, 33.6, 30.2, 26.1, 25.1, 25.0.

HRMS (ESI) *m/z* calcd for $C_{11}H_{18}N$ $[M+H]^+$: 164.1434, found: 164.1434.

$[\alpha]^{20}_{589}$= –46.53 (*c* 0.90, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 2925, 2851, 1449, 1370, 1127, 888, 746.

(*S*)-*N*-cyclohexyl-2,3-dihydro-1H-inden-1-amine



According to a modified procedure from Davies and coworkers,[266] cyclohexanone (0.20 mL, 1.94 mmol, 1.0 eq.) was added to a stirring solution of (*S*)-2,3-dihydro-1H-inden-1-amine (0.25 mL, 1.94 mmol, 1.0 eq.) in THF (10 mL) at room temperature. After 5 min, $NaB(OAc)_3H$

(0.62 g, 2.9 mmol, 1.5 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (15 mL) and $NaHCO_3$ (aq. sat., *ca* 15 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title amine as a yellow oil (0.38 g, 1.79 mmol, 92%). The amine was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.36 - 7.46 (m, 1 H), 7.14 - 7.33 (m, 3 H), 4.41 (t, *J* = 6.7 Hz, 1 H), 2.98 - 3.12 (m, 1 H), 2.85 (dt, *J* = 15.7, 7.8 Hz, 1 H), 2.69 - 2.79 (m, 1 H), 2.42 - 2.56 (m, 1 H), 1.92 - 2.09 (m, 2 H), 1.76 - 1.90 (m, 3 H), 1.71 (dd, *J* = 10.8, 1.5 Hz, 1 H), 1.13 - 1.47 (m, 6 H).

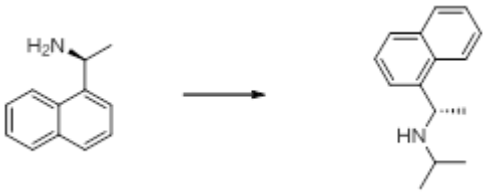
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 146.2, 143.3, 127.0, 126.1, 124.5, 123.8, 60.0, 54.7, 34.8, 34.5, 33.6, 30.2, 26.1, 25.1, 25.0.

HRMS (ESI) *m/z* calcd for $C_{15}H_{22}N$ $[M+H]^+$: 216.1747, found: 216.1753.

$[\alpha]^{20}_{589}$= –27.81 (*c* 0.97, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 2925, 2851, 1449, 1370, 1127, 888, 746.

(*S*)-*N*-(1-(naphthalen-1-yl)ethyl)propan-2-amine



According to a modified procedure from Davies and coworkers,[266] acetone (0.63 mL, 8.6 mmol, 2.0 eq.) was added to a stirring solution of (*S*)-1-(naphthalen-1-yl)ethanamine (0.69 mL, 4.3 mmol, 1.0 eq.) in THF (15 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (1.82 g, 8.6 mmol, 2.0 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (30 mL) and $NaHCO_3$ (aq. sat., *ca* 30 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title amine as a yellow oil (0.634 g, 2.97 mmol, 69%). The amine was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 8.25 (d, *J* = 8.3 Hz, 1 H), 7.88 - 7.99 (m, 1 H), 7.79 (d, *J* = 8.1 Hz, 1 H), 7.72 (d, *J* = 7.1 Hz, 1 H), 7.44 - 7.63 (m, 3 H), 4.89 (q, *J* = 6.4 Hz, 1 H), 3.42 (br. s., 1 H), 2.85 (spt, *J* = 6.4 Hz, 1 H), 1.56 (d, *J* = 6.6 Hz, 3 H), 1.15 (d, *J* = 6.4 Hz, 3 H), 1.12 (d, *J* = 6.4 Hz, 3 H).

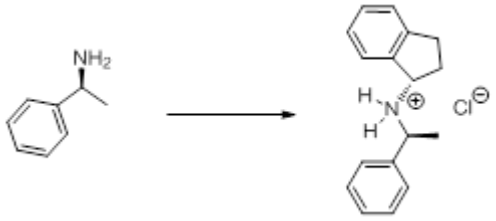
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 140.8, 133.9, 131.1, 128.9, 127.1, 125.8, 125.6, 125.2, 122.7, 122.6, 50.0 , 45.9 , 24.0 , 23.5, 22.1.

HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO$ $[M+H]^+$: 214.1590, found: 214.1590.

$[\alpha]^{20}_{589}$= –49.28 (*c* 0.95, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 2961, 2360, 1510, 1379, 1171, 799.

(*S*)-*N*-((*S*)-1-phenylethyl)-2,3-dihydro-1H-inden-1-amine



According to a modified procedure from Alexakis and coworkers,[197] Ti(O*i*Pr)$_4$ (6.1 mL, 20.63 mmol, 2.5 eq) was added to a mixture of (*S*)-1-phenylethanamine (1.1 mL, 8.25 mmol, 1 eq) and 1-indanone (1.0 mL, 8.25 mmol, 1.0 eq). After 6 hours, Pd/C (0.4 g 0.82 mmol, 0.1 eq) was added and the flask was flashed 3 times with H_2 and put under 1 atmosphere of H_2 for 96 hours. Then EtOAc (30 mL) and $NaHCO_3$ (aq. sat., *ca* 30 mL) was added. The solution was stirred for 30 minutes and filtered over celite. The mixture was partitioned between the aqueous and EtOAc layers and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated to about 5 mL. HCl (37%, *ca*2 mL) was added and the amine was recrystallized in Petrol/EtOAc/MeOH (*ca* 1:9: a few drops) to give the desired amine salt (0.42 g 1.54 mmol, 18%). The crystals were added to a stirring biphasic mixture containing CH_2Cl_2 and a saturated NaOH solution for 15 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), filtered and concentred *in vacuo* to afford the desired secondary amine as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 10.31 (br. s., 1 H), 9.95 (br. s., 1 H), 7.82 (d, *J* = 7.5 Hz, 2 H), 7.48 (t, *J* = 7.5 Hz, 2 H), 7.41 (br. t, *J* = 8.3, 8.3 Hz, 2 H), 7.29 (d, *J* = 4.2 Hz, 2 H), 7.18 (dt,

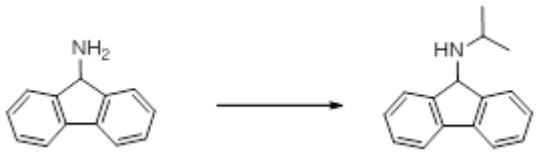
J = 8.3, 4.0 Hz, 1 H), 4.26 - 4.48 (m, 2 H), 3.75 (dt, *J* = 16.4, 8.4 Hz, 1 H), 2.64 - 2.84 (m, 2 H), 2.20 (sxt, *J* = 7.5 Hz, 1 H), 1.87 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 146.4, 137.0, 136.1, 129.9, 129.5 (2 C), 128.9, 127.9 (2 C), 126.5, 126.3, 125.6, 60.7, 57.3, 30.8, 30.1, 21.8.

HRMS (ESI) *m/z* calcd for $C_{17}H_{20}N$ $[M]^+$: 238.1590, found: 238.1588.

IR (ν_{max}/cm^{-1}) 2965, 1731, 1167 , 751.

N-isopropyl-9H-fluoren-9-amine



According to a modified procedure from Davies and coworkers,[266] acetone (1.50 mL, 5.5 mmol, 2.0 eq.) was added to a stirring solution of 9H-fluoren-9-amine (500 mg, 2.76 mmol, 1.0 eq.) in THF (10 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (0.87 g, 2.84 mmol, 1.5 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (20 mL) and NaHCO3 (aq. sat., *ca* 20 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title product as a colourless oil (0.535 g, 2.39 mmol, 87%). The amine was used without further purification.

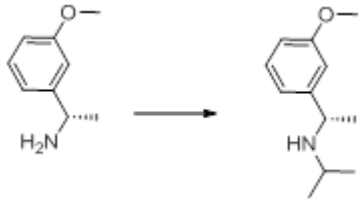
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.67 - 7.81 (m, 4 H), 7.33 - 7.49 (m, 4 H), 4.96 (s, 1 H), 3.30 (dt, *J* = 12.2, 6.4 Hz, 1 H), 2.07 (br. s., 1 H), 1.18 (d, *J* = 6.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 159.6, 147.5, 129.2, 118.7, 112.0, 111.8, 55.0, 54.9, 45.4, 24.6, 23.8, 21.9.

HRMS (ESI) *m/z* calcd for $C_{16}H_{18}N$ $[M]^+$: 224.1434, found: 224.1443.

IR (ν_{max}/cm^{-1}) 2961, 1600, 1256, 1047, 749.

(*S*)-1-(3-methoxyphenyl)ethanamine



According to a modified procedure from Davies and coworkers,[266] acetone (0.28 mL, 3.78 mmol, 2.0 eq.) was added to a stirring solution of (*S*)-1-(3-methoxyphenyl)ethanamine (0.28 mL, 1.89 mmol, 1.0 eq.) in THF (15 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (0.60g, 2.84 mmol, 1.5 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (30 mL) and $NaHCO_3$ (aq. sat., *ca* 30 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title product as a yellow oil (0.35 g, 1.82 mmol, 96%). The amine was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.23 (t, *J* = 8.1 Hz, 1 H), 6.84 - 6.95 (m, 2 H), 6.77 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1 H), 3.88 (q, *J* = 6.6 Hz, 1 H), 3.80 (s, 3 H), 2.65 (spt, *J* = 6.2 Hz, 1 H), 2.04 (br. s, 1 H), 1.34 (d, *J* = 6.6 Hz, 3 H), 1.03 (d, *J* = 6.2 Hz, 3 H), 1.01 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 159.6, 147.5, 129.2, 118.7, 112.0, 111.8, 55.0, 54.9, 45.4, 24.6, 23.8, 21.9.

HRMS (ESI) *m/z* calcd for $C_{12}H_{20}NO$ $[M]^+$: 194.1539, found: 194.1538.

$[\alpha]^{20}_{589}$= –57.03 (*c* 0.87, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 2961, 2866, 2361, 1600, 1466, 1256, 1047, 743.

(*S*)-*N*-Methyl-1-(naphthalen-2-yl)ethanamine



According to a modified procedure from Pallavicini and coworkers,[275] ethyl chloroformate (0.18 mL, 1.93 mmol, 1.1 eq) was added to a stirring solution of (*S*)-(–)-1-(2-naphthyl)ethylamine (300 mg, 1.91 mmol, 1.0 eq) and Et_3N (0.28 mL, 2.0 mmol, 1.15 mmol) at 0 °C in CH_2Cl_2 (10 mL). The

solution was stirred for 2 hours at room temperature before addition of H_2O (*ca* 3 mL) and HCl (3 mL, 2 M). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL), dried (Na_2SO_4), filtered and concentred *in vacuo.* The oil was then dissolved in THF (15 mL) and stirred at 0 °C for 5 minutes. $LiAlH_4$ (0.87 mL, 3.5 mmol, 4 M solution in Et_2O) was added slowly and the reaction mixture was stirred for 1 hour at reflux before cooling down at room temperature. H_2O (*ca* 3 mL) and HCl (3 mL, 2 M) were added and the reaction mixture was filtered through celite. Et_2O (10 ml) was added. The phases were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL), dried ($MgSO_4$), filtered and concentred *in vacuo* to afford the desired secondary amine 261.1 mg (1.40 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.87 (br. d, *J* = 8.8 Hz, 3 H), 7.78 (s, 1 H), 7.44 - 7.59 (m, 3 H), 3.84 (q, *J* = 6.6 Hz, 1 H), 2.38 (s, 3 H), 1.54 (br. s., 1 H), 1.47 (d, *J* = 6.6 Hz, 3 H).

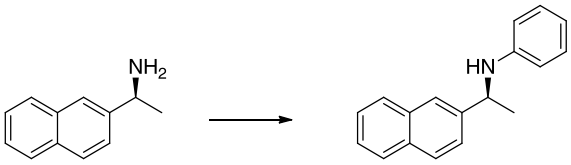
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 142.7, 133.3, 132.7, 128.1, 127.6, 127.5, 125.8, 125.3, 125.1, 124.7, 60.2, 34.5, 23.8.

HRMS (ESI) *m/z* calcd for $C_{13}H_{16}N$ $[M]^+$: 182.1277 found: 182.1277.

$[\alpha]^{20}_{589}$= –61.3 (*c* 0.98, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 3053, 2966, 2790, 1601, 1451, 1136, 853, 747.

(*S*)-*N*-isopropyl-1,2,3,4-tetrahydronaphthalen-1-amine



According to a modified procedure from Alexakis and coworkers,[276] Pd_2DBA_3 (43.7 mg, 0.09 mmol, 0.05 eq), (*R*)-BINAP (59.5 mg, 0.19 mmol, 0.10 eq), (*S*)-(–)-1-(2-naphthyl)ethylamine (327 mg, 1.91 mmol, 1.0 eq) and *t*-BuONa (0.25 g, 1.91 mmol, 1 eq) were added successively in a solution of toluene at room temperature. The mixture was stirred for 5 minutes at room temperature. Then bromobenzene (0.22 mL, 1.91 mmol, 1.0 eq) was added and the reaction mixture was stirred for 18 hours at 90 °C. The mixture was allowed to cool down to room temperature before a filtration on a short pad of silica and wash with EtOAc. $NaHCO_3$ (aq. sat., *ca* 5 mL) was added. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic phase was concentrated by rotaryevaporator. The crude residue was then suspended in Et_2O, HCl (37% aq. solution) was

added (2-5 drops) until a white solid precipitated. The crystals were added to a stirring biphasic mixture containing CH_2Cl_2 and a saturated NaOH solution for 15 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), filtered and concentred *in vacuo* to afford the desired secondary amine 427.9 mg (1.73 mmol, 90%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.84 - 7.93 (m, 4 H), 7.56 - 7.60 (m, 1 H), 7.49 - 7.56 (m, 2 H), 7.13 - 7.24 (m, 2 H), 6.70 - 6.80 (m, 1 H), 6.57 - 6.68 (m, 2 H), 4.72 (q, *J* = 6.6 Hz, 1 H), 4.01 - 4.37 (m, 1 H), 1.66 (d, *J* = 6.6 Hz, 3 H).

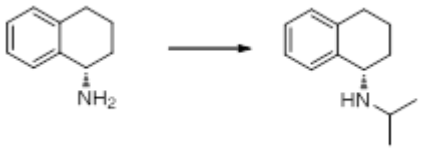
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 147.3, 142.7, 133.5, 132.7, 129.1 (2 C), 128.4, 127.8, 127.6, 126.0, 125.4, 124.4, 124.2, 117.3, 113.3 (2 C), 53.6, 25.0.

HRMS (EI) *m/z* calcd for $C_{18}H_{17}N$ $[M]^+$: 247.1361 found: 247.1368.

$[\alpha]^{20}_{589}$= –7.58 (*c* 0.27, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 3410, 3052, 1602, 1505, 1319, 748.

(*S*)-*N*-isopropyl-1,2,3,4-tetrahydronaphthalen-1-amine



According to a modified procedure from Davies and coworkers,[266] acetone (2.6 mL, 35 mmol, 5.0 eq.) was added to a stirring solution of (*S*)-1-(naphthalen-2-yl)ethan-1-amine (2.5 mL, 17.6 mmol, 1.0 eq.) in THF (15 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (5.6 g, 26.4 mmol, 1.5 eq.) was tipped into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (200 mL) and NaHCO3 (aq. sat., *ca* 200 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 50 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title product as a yellow oil (2.64 g, 13.9 mmol, 79%). The amine was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.34 - 7.43 (m, 2 H), 7.12 - 7.22 (m, 2 H), 7.05 - 7.11 (m, 1 H), 3.83 (t, *J* = 4.5 Hz, 1 H), 3.07 (spt, *J* = 6.2 Hz, 1 H), 2.79 - 2.88 (m, 1 H), 2.69 - 2.78 (m, 1 H), 1.90 - 2.02 (m, 1 H), 1.83 - 1.90 (m, 1 H), 1.71 - 1.82 (m, 1 H), 1.23 (d, *J* = 7.1 Hz, 1 H), 1.15 (d, *J* = 6.2 Hz, 3 H), 1.13 (d, *J* = 6.2 Hz, 3 H)

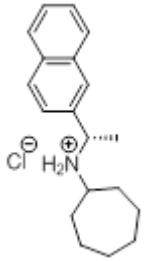
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 140.2, 137.2, 129.0, 128.9, 126.5, 125.8, 52.4, 45.9, 29.4, 29.0, 24.2, 22.9, 18.9.

HRMS (ESI) *m/z* calcd for $C_{13}H_{20}N$ $[M]^+$: 190.1590, found: 190.1590.

$[\alpha]^{20}_{589}$= +1.37 (*c* 1.08, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 3486, 2999, 2970, 1738, 1442, 1367, 1216, 738.

(*S*)-*N*-(1-(Naphthalen-2-yl)ethyl)cycloheptanamine



According to a modified procedure of RajanBabu[191] and Davies,[191, 195] $NaB(OAc)_3H$ (0.57 g, 2.67 mmol, 2.0 eq) and cycloheptanone (0.16 mL, 1.30 mmol, 1.0 eq) were added to a stirred solution of (*S*)-(–)-1-(2-naphthyl)ethylamine (0.23 g, 1.30 mmol, 1.0 eq) at room temperature. The reaction mixture was stirred for 24 h before a saturated aqueous solution of $NaHCO_3$ (3 mL) was added and stirring continuously for 15 minutes. EtOAc (10 mL) was added and the aqueous phase was separated and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was then suspended in EtOAc, HCl (37% aq. solution) was added (2-5 drops) until a white solid precipitated. The precipitate was recrystallized with EtOH to give the HCl salt of the desired secondary amine (178 mg, 0.58 mmol, 44%). The crystals were added to a stirring biphasic mixture containing CH_2Cl_2 and a saturated NaOH solution for 15 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), filtered and concentred *in vacuo* to afford the desired secondary amine as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 10.11 (br. s., 1 H), 9.64 (br. s., 1 H), 8.05 (s, 1 H), 7.93 - 8.01 (m, 2 H), 7.87 - 7.93 (m, 1 H), 7.85 (br. dd, *J* = 6.1, 3.8 Hz, 1 H), 7.39 - 7.63 (m, 2 H), 4.54 (br. t, *J* = 6.7, 6.7 Hz, 1 H), 2.64 - 2.91 (m, 1 H), 2.26 - 2.48 (m, 1 H), 2.06 - 2.17 (m, 2 H), 2.04 (d, *J* = 6.7 Hz, 3 H), 1.85 - 1.99 (m, 1 H), 1.65 - 1.83 (m, 2 H), 1.48 (br. td, *J* = 9.6, 9.6, 3.8 Hz, 2 H), 1.29 - 1.44 (m, 4 H), 1.09 - 1.27 (m, 2 H).

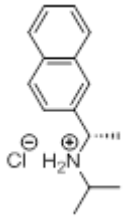
^{13}C NMR (101 MHz, $CDCl_3$) δ_C /ppm 133.9, 133.3, 133.1, 129.5, 128.1, 127.6, 127.3, 126.6, 126.5, 124.6, 57.5, 56.5, 32.1, 29.3, 27.6, 27.4, 24.1, 23.5, 21.2.

HRMS (ESI) *m*/*z* calcd for $C_{19}H_{26}N$ $[M+H]^+$: 268.2060, found: 268.2061.

$[\alpha]^{24}_{589}$ = +6.52 (*c* 0.34, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2932, 2490. 1458, 772

(*S*)-*N*-(1-(Naphthalen-2-yl)ethyl)propan-2-amine



According to a modified procedure of RajanBabu[191] and Davies,[191, 195] $NaB(OAc)_3H$ (1.86 g, 8.80 mmol, 3.9 eq) and acetone (0.22 mL, 2.93 mmol, 1.3 eq) were added to a stirred solution (*S*)-(–)-1-(2-naphthyl)ethylamine (0.35 g 2.0 mmol, 1.0 eq) at room temperature. The reaction mixture was stirred for 24 h before a saturated aqueous solution of $NaHCO_3$ (3.0 mL) was added and stirring continuously for 15 minutes. EtOAc (*ca* 10 mL) was added and the aqueous phase was separated and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was then suspended in EtOAc, HCl (37% aq. solution) was added (2-5 drops) until a white solid precipitated. The precipitate was recrystallized with EtOH to give the HCl salt of the desired secondary amine. The crystals were added to a stirring biphasic mixture containing CH_2Cl_2 and a saturated NaOH solution for 15 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), filtered and concentred *in vacuo* to afford the desired secondary amine (0.42 g, 1.97 mmol, 96%) as yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 10.14 (br. s., 1 H), 9.85 (br. s., 1 H), 8.06 (s, 1 H), 7.97 (s, 2 H), 7.92 (dd, *J* = 6.0, 3.5 Hz, 1 H), 7.85 - 7.90 (m, 1 H), 7.50 - 7.58 (m, 2 H), 4.47 - 4.59 (m, 1 H), 2.92 - 3.05 (m, 1 H), 2.03 (d, *J* = 6.6 Hz, 3 H), 1.56 (d, *J* = 6.6 Hz, 3 H), 1.42 (d, *J* = 6.3 Hz, 3 H).

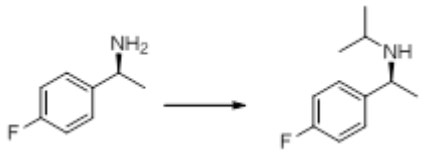
^{13}C NMR (125 MHz, $CDCl_3$) δ_C /ppm 133.8, 133.4, 133.2, 129.8, 128.1, 127.8, 127.4, 126.8, 126.7, 124.5, 56.6, 48.4, 21.3, 20.5, 17.9.

HRMS (ESI) *m*/*z* calcd for $C_{15}H_{20}N$ $[M+H]^+$: 214.1590, found: 214.1595.

[α]$^{24}_{589}$ = +40.2 (*c* 0.52, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 2802, 2978, 2696, 2485, 752.

(*S*)-*N*-(1-(4-fluorophenyl)ethyl)propan-2-amine



According to a modified procedure from Davies and coworkers,[266] acetone (0.25 mL, 4.3 mmol, 2.0 eq.) was added to a stirring solution of (*S*)-1-(4-fluorophenyl)ethanamine (0.23 mL, 1.70 mmol, 1.0 eq.) in THF (15 mL) at room temperature. After 5 min, $NaB(OAc)_3H$ (0.83 g, 4.3 mmol, 2.0 eq.) was added into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (30 mL) and $NaHCO_3$ (aq. sat., *ca* 30 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title amine as a yellow oil (0.24 g, 1.37 mmol, 79%). The amine was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.28 - 7.42 (m, 2 H), 6.91 - 7.08 (m, 2 H), 4.34 - 4.58 (m, 1 H), 3.95 (q, *J* = 6.6 Hz, 1 H), 2.65 (dt, *J* = 12.5, 6.6 Hz, 1 H), 1.38 (d, *J* = 6.6 Hz, 3 H), 1.06 (t, *J* = 6.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 163.1, 160.7, 128.3, 128.2, 115.4, 114.8, 52.6, 45.9, 23.9, 23.2, 21.3.

^{19}F NMR (380 MHz, CDCl3) δ_F /ppm -116.32 (s, 1 F).

HRMS (ESI) *m/z* calcd for $C_{11}H_{17}FNO$ $[M+H]^+$: 182.1340, found: 182.1339.

[α]$^{20}_{589}$= –52.39 (*c* 0.98, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 2965, 1510, 1402, 1227, 839.

N-benzhydrylcyclohexanamine



According to a modified procedure from Davies,[195] cyclohexanone (0.63 mL, 6.11 mmol, 1.1 eq) was added to a stirred solution of diphenylmethanamine (1.20 mL, 6.42 mmol, 1.0 eq) in THF (20 mL) at room temperature. After 5 minutes, $NaB(OAc)_3H$ (1.94 g, 9.21 mmol, 1.5 eq) was added in one portion. The resulting suspension was stirred for about 48 hours, before Et_2O (10 mL) and $NaHCO_3$ (aq. sat., *ca* 10 mL) were added to the suspension and stirring was continued for 15 additional minutes before the mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was concentrated *in vacuo* (*ca* 5 mL). Then HCl (aq 2.0 M, 1 mL) was added dropwise. The mixture was partitioned between the aqueous and Et_2O layers and the organic phase extracted with HCl (aq 2.0 M, 3 × 10 mL). Then CH_2Cl_2 (20 mL) was added to the combined aqueous phases and NaOH (saturated with brine aq solution, 25%) was added till the mixture became basic (pH paper, pH>14). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the desired *N*-benzhydrylcyclopentanamine (1.01 g, 3.76 mmol, 61%). The amine was used without further purification.

Data in accordance with published literature.[277]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.39 (d, *J* = 7.1 Hz, 4 H), 7.25 - 7.33 (m, 4 H), 7.15 - 7.23 (m, 2 H), 5.05 (s, 1 H), 2.35 - 2.52 (m, 1 H), 1.96 (br. d, *J* = 11.6 Hz, 2 H), 1.65 - 1.78 (m, 2 H), 1.57 (br. s., 1 H), 1.35 (br. s, 1 H), 1.03 - 1.26 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 144.8 (2 C), 128.3 (4 C), 127.3 (4 C), 126.7 (2 C), 63.6, 53.9, 33.9 (2 C), 26.2, 24.3 - 25.6 (2 C).

MS (ESI) *m*/*z* $[M+H]^+$: 266.2 (100).

IR (ν_{max} /cm^{-1}): 3025, 2925, 2890, 1739, 1492, 1368, 1229, 700.

N-benzhydrylcyclopentanamine



According to a modified procedure from Davies,[195] cyclopentanone (0.63 mL, 7.13 mmol, 1.1 eq) was added to a stirred solution of diphenylmethanamine (1.20 mL, 6.42 mmol, 1.0 eq) in THF (20 mL) at room temperature. After 5 minutes, $NaB(OAc)_3H$ (2.13 g, 10.7 mmol, 1.5 eq) was added in

one portion. The resulting suspension was stirred for about 48 hours, before Et_2O (10 mL) and $NaHCO_3$ (aq. sat., *ca* 10 mL) were added to the suspension and stirring was continued for 15 additional minutes before the mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was concentrated *in vacuo* (*ca* 5 mL). Then HCl (aq 2.0 M, 1 mL) was added dropwise. The mixture was partitioned between the aqueous and Et_2O layers and the organic phase extracted with HCl (aq 2.0 M, 3 × 10 mL). Then CH_2Cl_2 (20 mL) was added to the combined aqueous phases and NaOH (saturated with brine aq solution, 25%) was added till the mixture became basic (pH paper, pH>14). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the desired *N*-benzhydrylcyclopentanamine (1.30 g, 5.17 mmol, 76%). The amine was used without further purification.

Data in accordance with published literature.[278]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.41 - 7.51 (m, 4 H), 7.35 (apparent td, J = 7.6, 1.7 Hz, 4 H), 7.21 - 7.30 (m, 2 H), 2.96 - 3.15 (m, 1 H), 1.83 - 2.00 (m, 2 H), 1.72 (br. s., 2 H), 1.48 - 1.63 (m, 3 H), 1.35 - 1.46 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 144.5 (2 C), 128.4 (4 C), 127.2 - 127.6 (m, 4 C), 126.5 - 127.0 (m, 2 C), 65.6, 57.6, 33.2 (2 C), 23.8 (2 C).

MS (ESI) *m*/*z* $[M+H]^+$: 252.2 (100).

IR (ν_{max} /cm^{-1}): 2970, 1739, 1449, 1367, 1229, 700.

N-Benzhydrylcyclooctanamine



According to a modified procedure from Davies,[195] cyclooctanone (0.7363 mL, 5.54 mmol, 1.1 eq) was added to a stirred solution of diphenylmethanamine (0.86 mL, 4.9 mmol, 1.0 eq) in THF (20 mL) at room temperature. After 5 minutes, $NaB(OAc)_3H$ (1.764 g, 8.3 mmol, 1.5 eq) was added in one portion. The resulting suspension was stirred for about 48 hours, before Et_2O (10 mL) and $NaHCO_3$ (aq. sat., *ca* 10 mL) were added to the suspension and stirring was continued for 15 additional minutes before the mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was concentrated *in vacuo* (*ca* 5 mL). Then HCl (aq 2.0 M, 1 mL) was added dropwise. The mixture was partitioned

between the aqueous and Et_2O layers and the organic phase extracted with HCl (aq 2.0 M, 3 × 10 mL). Then CH_2Cl_2 (20 mL) was added to the combined aqueous phases and NaOH (saturated with brine aq solution, 25%) was added till the mixture became basic (pH paper, pH *ca* 14). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the desired *N*-benzhydrylcyclooctanamine (0.98 g, 3.34 mmol, 60%). The amine was used without further purification.

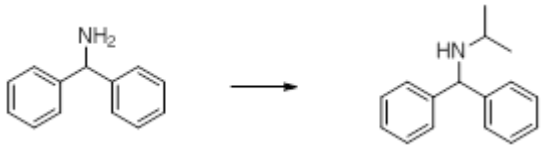
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.57 - 7.78 (m, 4 H), 7.45 - 7.55 (m, 4 H), 7.33 - 7.44 (m, 2 H), 5.21 (s, 1 H), 2.89 (br. s., 1 H), 2.04 (s, 2 H), 1.93 (br. s., 2 H), 1.51 - 1.85 (m, 11 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 144.5 (2 C), 128.1 (4 C), 127.2 (4 C), 126.6 (2 C), 63.8, 54.2, 31.8 (2 C), 27.4 (2 C), 25.4, 23.1.

HRMS (ESI) *m/z* calcd for $C_{21}H_{28}N$ $[M]^+$: 294.2209, found: 294.2216.

IR (ν_{max} /cm^{-1}):, 1738, 1492, 1368, 751.

N-Benzhydrylpropan-2-amine



According to a modified procedure from Davies,[7] acetone (1.9 mL, 2.58 mmol, 2.0 eq) was added to a stirred solution of diphenylmethanamine (2.26 mL, 12.9 mmol, 1.0 eq) in THF (100 mL) at room temperature. After 5 minutes, $NaB(OAc)_3H$ (4.10 g, 19.4 mmol, 1.5 eq) was added in one portion. The resulting suspension was stirred for about 48 hours, before Et_2O (50 mL) and $NaHCO_3$ (aq. sat., *ca* 50 mL) were added to the suspension and stirring was continued for 15 additional minutes before the mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 30 mL). The combined organic phase was concentrated *in vacuo* to one third of its volume (*ca* 20 mL). Then HCl (aq 2.0 M, 25 mL) was added dropwise over about 5 min. The mixture was partitioned between the aqueous and Et_2O layers and the organic phase extracted with HCl (aq 2.0 M, 25 mL). Then CH_2Cl_2 (20 mL) was added to the combined aqueous phases and NaOH (aq, 25%) was added till the mixture became basic (pH paper, pH>14). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was dried ($MgSO_4$), filtered and

concentrated *in vacuo* to afford the desired *N*-benzhydrylpropan-2-amine (1.91 g, 8.45 mmol, 65%). The amine was used without further purification.

Data in accordance with published literature.[8]

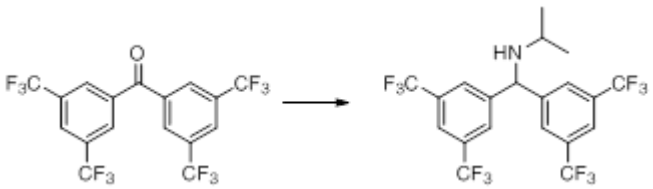
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.41 (br. d, *J* = 7.3 Hz, 4 H), 7.32 (br. t, *J* = 7.6, 7.6 Hz, 4 H), 7.22 (br. tt, *J* = 7.3, 7.3, 1.2, 1.2 Hz, 2 H), 5.00 (s, 1 H), 2.77 (spt, *J* = 6.3 Hz, 1 H), 1.37 - 1.67 (m, 1 H), 1.11 (d, *J* = 6.4 Hz, 6 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 144.5 (2 C), 128.4 (4 C), 127.3 (4 C), 126.8 (2 C), 64.2, 46.1, 23.1 (2 C).

MS (ESI) *m*/*z* $[M+H]^+$: 226.2 (100).

IR (ν_{max} /cm^{-1}): 2960, 1493, 1167, 1028, 700.

N-(bis(3,5-bis(trifluoromethyl)phenyl)methyl)propan-2-amine



According to a modified procedure from Gilbert,[198] $TiCl_4$ (6.1 mL, 6.1 mmol, 1.1 eq, 1 M solution in CH_2Cl_2) was added slowly to a cooled solution of bis(3,5-bis(trifluoromethyl)phenyl)methanone (2.5 g, 5.5 mmol, 1.0 eq) in CH_2Cl_2 (30 mL) cooled at 0 °C. The solution was stirred for 5 minutes at room temperature and a solution of isopropylamine (1.0 mL, 12.1 mmol, 2.2 eq) in THF (6 ml, 2 M solution) was added dropwise to the reaction mixture. The reaction flask was stirred for an additional 3 hours before a solution of $NaB(CN)H_3$ (0.415 g, 6.61 mmol, 1.2 eq) in THF (7 mL, 1 M solution) was added slowly to the reaction mixture. MeOH (10 mL) was then added slowly to the reaction mixture and the reaction mixture was stirred at room temperature for an additional 18 hours before NaOH (*ca* 20 mL, 2 M aq solution) was added slowly and the reaction mixture was stirred for 30 min. The reaction mixture was filtered on celite and washed with EtOAc (*ca* 30 mL). The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. Flash column chromatography of the residue (Petrol: CH_2Cl_2: Et_2O; 89: 10: 1; SiO_2) gave the desired *N*-(bis(3,5-bis(trifluoromethyl)phenyl)methyl)propan-2-amine (0.73 g, 1.46 mmol, 27%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H /ppm 7.88 (s, 4 H), 7.80 (s, 2 H), 5.21 (s, 1 H), 2.70 (spt, *J* = 6.2 Hz, 1 H), 1.27 (br. s., 1 H), 1.14 (d, *J* = 6.2 Hz, 6 H).

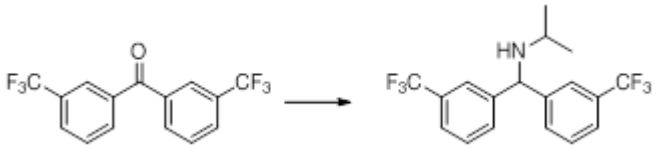
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 145.5 (2 C), 131.0 - 133.2 (m, 2 C), 127.3 - 127.4 (m, 2 C), 127.3 (2 C), 124.5 (2 C), 121.8 (s, 2 C), 63.4, 46.6, 23.1 (2 C).

^{19}F NMR (380 MHz, $CDCl_3$) δ_F /ppm −62.85 (s, 12 F).

HRMS (ESI) *m*/*z* calcd for $C_{20}H_{16}F_{12}N$ $[M+H]^+$: 498.1085, found: 498.1086.

IR (ν_{max} /cm^{-1}): 1371, 1276, 1168, 1126, 898, 712.

N-(bis(3-(Trifluoromethyl)phenyl)methyl)propan-2-amine



According to a modified procedure from Gilbert,[198] $TiCl_4$ (3.5 mL, 3.50 mmol, 1.1 eq, 1 M solution in CH_2Cl_2) was added slowly to a solution at 0 °C of bis(3-(trifluoromethyl)phenyl)methanone (1.0 g, 4.00 mmol, 1.0 eq) in CH_2Cl_2 (17 mL). The solution was stirred for 15 minutes at room temperature before a solution of isopropylamine (0.59 mL, 6.90 mmol, 2.2 eq) in THF (3 ml, *ca* 1.5 M solution) was added dropwise to the reaction mixture. The reaction flask was stirred for 3 additional hours before a solution of $NaB(CN)H_3$ (0.237 g, 3.77 mmol, 1.2 eq) in THF (4 mL, 1 M solution) was added slowly to the reaction mixture. MeOH (5.7 mL) was then added slowly to the reaction mixture and the reaction mixture was stirred at room temperature for an additional 18 hours before NaOH (*ca* 10 mL, 2 M *aq* solution) was added slowly and the reaction mixture was stirred for 30 min. The reaction mixture was filtered on celite and washed with EtOAc (*ca* 10 mL). $NaHCO_3$ (aq. sat., *ca* 10 mL) were added to the suspension. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic phase was concentrated *in vacuo.* Et_2O (*ca* 10 mL) was added to the oil. HCl (aq 2.0 M, *ca* 2 mL) was added dropwise for about 1 min. HBr (1 mL, *a.q*, 55% solution) was added dropwise and the mixture was left for 1 hour. The mixture was partitioned between the aqueous and Et_2O layers and the organic phase extracted with HCl (aq 2.0 M, 15 mL). Then CH_2Cl_2 (10 mL) was added to the combined aqueous phases and NaOH (*aq* saturated with brine solution, 25%) was added till the mixture became basic (pH paper, pH>14). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The

combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the desired *N*-(bis(3-(trifluoromethyl)phenyl)methyl)propan-2-amine (0.545 g, 1.5 mmol, 48%). The amine was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.69 (s, 2 H), 7.58 (d, *J* = 7.6 Hz, 2 H), 7.48 - 7.53 (m, 2 H), 7.40 - 7.47 (m, 2 H), 5.09 (s, 1 H), 2.72 (spt, *J* = 6.3 Hz, 1 H), 1.27 (br. s., 1 H), 1.11 (d, *J* = 6.3 Hz, 6 H).

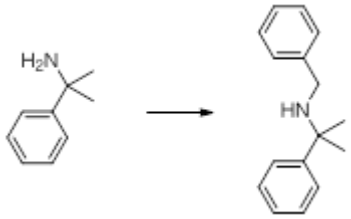
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 144.8 (br. s., 2 C), 131.1 (2 C), 130.7 (2 C), 129.1 (4 C), 124.2 (q, *J* = 4.0 Hz, 1 C), 124.0 (q, *J* = 4.0 Hz, 1 C), 63.8, 46.3, 23.1 (2 C).

^{19}F NMR (380 MHz, $CDCl_3$) δ_F /ppm –62.51 (s, 6 F).

HRMS (ESI) *m*/*z* calcd for $C_{16}H_{10}F_{10}N$ $[M+H]^+$: 406.0648, found: 406.0639.

IR (ν_{max} /cm^{-1}): 2966, 1449, 1325, 1163, 1120, 707.

N-benzyl-2-phenylpropan-2-amine



According to a modified procedure from Zhong, [279] a solution containing benzaldehyde (0.76 mL, 7.53 mmol, 1.0 eq) and cumylamine (1.1 mL, 44 mmol, 1.0 eq) in toluene (20 mL) was refluxed for 18 hours with a Dien-Stark apparatus. Upon cooling to room temperature, MeOH (17.5 mL) and $NaBH_4$ (317 mg, 9.8 mmol, 1.3 eq) was added in 3 portions. The reaction mixture was stirred for an additional 3 hours before H_2O (20 mL) was added to the reaction mixture. After 10 minutes, $CHCl_3$ (15 mL) was added to the reaction mixture. the mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with $CHCl_3$ (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the desired *N*-benzyl-2-phenylpropan-2-amine (1.4 g, 6.21 mmol, 82%). The amine was used without further purification.

Data consistent with published literature.[279]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.57 (dd, *J* = 8.3, 1.0 Hz, 3 H), 7.40 (t, *J* = 7.7 Hz, 2 H), 7.33 - 7.36 (m, 3 H), 7.25 - 7.31 (m, 2 H), 3.52 (s, 2 H), 1.57 (s, 6 H), 1.56 (br. s., 1 H),.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 147.8, 141.3, 128.3 (2 C), 128.2 (2 C), 128.2 (2 C), 126.7, 126.3 (, 125.9 (2 C), 56.1, 47.6, 29.7 (2 C).

HRMS (ESI) *m*/*z* calcd for $C_{16}H_{10}F_{10}N$ $[M+H]^+$: 226.1587, found: 226.1590.

IR (ν_{max} /cm^{-1}): 2966, 1494, 1451, 1184, 754, 696.

N-(di-*p*-Tolylmethyl)propan-2-amine



According to a modified procedure from Gilbert, [198] $TiCl_4$ (4.4 mL, 4.4 mmol, 1.1 eq, 1 M solution in CH_2Cl_2) was added slowly to a solution at 0 °C of di-*p*-tolylmethanone (0.850 g, 4.0 mmol, 1.0 eq) in CH_2Cl_2 (22 mL). The solution was stirred for 5 minutes at room temperature and a solution of isopropylamine (0.76 mL, 8.90 mmol, 2.2 eq) in THF (5 ml, *ca* 1.5 M solution) was added dropwise to the reaction mixture. The reaction flask was stirred for an additional 3 hours before a solution of $NaB(CN)H_3$ (0.305 g, 4.85 mmol, 1.2 eq) in THF (5 mL, 1 M solution) was added slowly to the reaction mixture. MeOH (7.5 mL) was then added slowly to the reaction mixture and the reaction mixture was stirred at room temperature for an additional 18 hours before NaOH (*ca* 10 mL, 2 M aq solution) was added slowly and the reaction mixture was stirred for 30 min. The reaction mixture was filtered on celite and washed with EtOAc (*ca* 10 mL). $NaHCO_3$ (aq. sat., *ca* 10 mL) were added to the suspension. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic phase was concentrated *in vacuo.* Et_2O (*ca* 10 mL) was added to the oil. Then HCl (aq 2.0 M, *ca* 2 mL) was added dropwise for about 1 min. The mixture was partitioned between the aqueous and Et_2O layers and the organic phase extracted with HCl (aq 2.0 M, 15 mL). Then CH_2Cl_2 (20 mL) was added to the combined aqueous phases and NaOH (aq saturated with brine solution, 25%) was added till the mixture became basic (pH paper, pH >14). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the desired *N*-(di-*p*-tolylmethyl)propan-2-amine (0.622 g, 2.45 mmol, 61%). The amine was used without further purification.

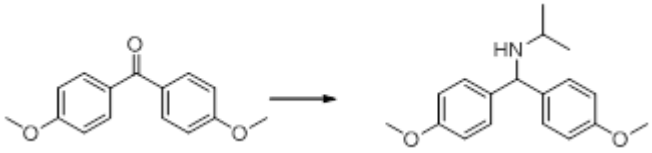
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.24 - 7.30 (m, 4 H), 7.11 (d, *J* = 8.1 Hz, 4 H), 4.92 (s, 1 H), 2.75 (spt, *J* = 6.3 Hz, 1 H), 2.32 (s, 6 H), 1.38 (br. s., 1 H), 1.09 (d, *J* = 6.3 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 141.8 (2 C), 136.2 (2 C), 129.1 (4 C), 127.2 (4 C), 63.6, 46.0, 23.2 (2 C), 21.0 (2 C).

HRMS (ESI) *m*/*z* calcd for $C_{18}H_{24}N$ $[M+H]^+$: 254.1903, found: 254.1902.

IR (ν_{max} /cm^{-1}): 2960, 1510, 1460, 1167, 807, 768.

N-(bis(4-methoxyphenyl)methyl)propan-2-amine



According to a modified procedure from Gilbert,[198] $TiCl_4$ (7.7 mL, 7.7 mmol, 1.1 eq, 1 M solution in CH_2Cl_2) was added slowly to a solution at 0 °C of bis(4-methoxyphenyl)methanone (1.7 g, 7.0 mmol, 1.0 eq) in CH_2Cl_2 (38 mL). The solution was stirred for 10 minutes at room temperature and a solution of isopropylamine (1.33 mL, 15.4 mmol, 2.2 eq) in THF (15 ml, 1 M solution) was added dropwise to the reaction mixture. The reaction flask was stirred for an additional 3 hours before a solution of $NaB(CN)H_3$ (0.53 g, 8.4 mmol, 1.2 eq) in THF (8 mL, 1 M solution) was added slowly to the reaction mixture. MeOH (12 mL) was then added slowly to the reaction mixture and the reaction mixture was stirred at room temperature for an additional 18 hours before NaOH (*ca* 15 mL, 2 M *aq* solution) was added slowly and the reaction mixture was stirred for 30 min. The reaction mixture was filtered on celite and washed with EtOAc (*ca* 15 mL). $NaHCO_3$ (aq. sat., *ca* 15 mL) were added to the suspension. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with EtOAc (3 × 15 mL). The combined organic phase was concentrated *in vacuo*. Et_2O was added to the oil (*ca* 8 mL). Then HCl (aq 2.0 M, *ca* 3 mL) was added dropwise for about 5 min. The mixture was partitioned between the aqueous and Et_2O layers and the organic phase extracted with HCl (aq 2.0 M, 25 mL). Then CH_2Cl_2 (20 mL) was added to the combined aqueous phases and NaOH (aq saturated with brine solution, 25%) was added till the mixture became basic (pH paper, pH>14). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the desired *N*-(bis(4-methoxyphenyl)methyl)propan-2-amine (0.94 g, 3.3 mmol, 47%). The amine was used without further purification.

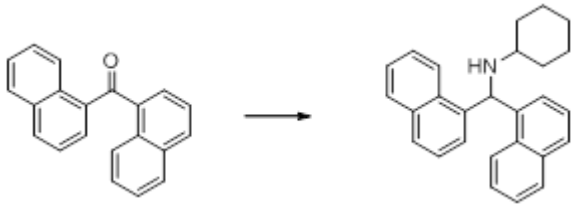
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.24 - 7.33 (m, 4 H), 7.12 (d, *J* = 7.8 Hz, 4 H), 4.94 (s, 1 H), 2.77 (spt, *J* = 6.2 Hz, 1 H), 2.33 (s, 6 H), 1.30 (br. s., 1 H), 1.10 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 141.8 (2 C), 136.2 (2 C), 128.7 - 129.5 (m, 4 C), 127.2 (4 C), 63.6, 46.0, 23.2 (2 C), 21.0 (2 C).

HRMS (EI) *m*/*z* calcd for $C_{18}H_{23}NO_2$ $[M+H]^+$: 285.1729, found: 285.1729.

IR (ν_{max} /cm^{-1}): 2960, 1510, 1468, 1379, 1365, 1167, 1021, 807, 768.

N-(di(Naphthalen-1-yl)methyl)cyclohexanamine



According to a modified procedure from Gilbert, [198] $TiCl_4$ (5.8 mL, 5.8 mmol, 1.1 eq, 1 M solution in CH_2Cl_2) was added slowly to an a solution at 0 °C of di(naphthalen-1-yl)methanone (1.5 g, 5.3 mmol, 1.0 eq) in DCE (20 mL) in a sealed tube. The solution was stirred for an additional 10 minutes at room temperature before a solution of cyclohexylamine (1.7 mL, 11.7 mmol, 2.2 eq) in DCE (6 mL) was added dropwise to the reaction mixture. The reaction flask was sealed and heated under reflux (80 °C) for another 3 hours. Once cooled to room temperature, $NaB(CN)H_3$ (0.67 g, 10.6 mmol, 2.0 eq) and a solution of isopropylamine (1.3 mL, 15.6 mmol, 2.2 eq) in DCE (10 mL) were added dropwise sequentially to the reaction mixture. The reaction flask was sealed and heated under reflux (90°C) for 15 hours. The reaction mixture was allowed to cool down to room temperature and then cooled with an ice bath. NaOH (*ca* 20 mL, 2 M *aq* solution) was added slowly and the reaction mixture was stirred for 1 hour. The reaction mixture was filtered on celite and washed with CH_2Cl_2 (*ca* 20 mL). $NaHCO_3$ (aq. sat., *ca* 15 mL) were added to the suspension. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Purification by two flash column chromatography (Toluene; SiO_2) and then (95:5 ; Petrol/EtOAc; SiO_2) of the residue gave the desired amine (1.03 g, 2.81 mmol, 53%).

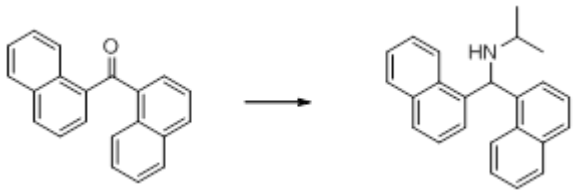
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 8.08 - 8.32 (m, 2 H), 7.87 - 7.96 (m, 2 H), 7.79 (d, *J* = 8.1 Hz, 2 H), 7.55 (d, *J* = 6.8 Hz, 2 H), 7.46 - 7.52 (m, 4 H), 7.43 (t, *J* = 8.1 Hz, 2 H), 6.66 (s, 1 H), 2.65 - 2.83 (m, 1 H), 2.03 - 2.28 (m, 2 H), 1.69 - 1.85 (m, 2 H), 1.50 - 1.66 (m, 3 H), 1.05 - 1.37 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 139.2 (1 C), 134.1 (2 C), 131.4 (2 C), 128.9 (3 C), 127.6 (2 C), 126.2 (2 C), 125.6 - 125.8 (2 C), 125.5 (2 C), 125.4 (2 C), 123.1 (2 C), 55.4 (1 C), 55.0 (1 C), 34.1 (2 C), 26.1 (1 C), 25.2 (2 C).

HRMS (ESI) *m*/*z* calcd for $C_{27}H_{28}N$ $[M+H]^+$: 366.2216, found: 366.2205.

IR (ν_{max} /cm^{-1}): 3457, 3016, 2970, 1738, 1375, 1228, 776.

N-(di(Naphthalen-1-yl)methyl)propan-2-amine



According to a modified procedure from Gilbert, [198] $TiCl_4$ (7.8 mL, 7.8 mmol, 1.0 eq, 1 M solution in CH_2Cl_2) was added slowly to a solution at 0 °C of di(naphthalen-1-yl)methanone (2.0 g, 7.1 mmol, 1.0 eq) in DCE (20 mL) in a sealed tube. The solution was stirred for 10 minutes at room temperature and then a solution of isopropylamine (1.3 mL, 15.6 mmol, 2.2 eq) in DCE (1.3 mL) was added dropwise to the reaction mixture. The reaction flask was sealed and heated under reflux (80 °C) for an addtionnal 4 hours. Once cooled to room temperature, $NaB(CN)H_3$ (0.53 g, 8.5 mmol, 1.2 eq) and a solution of isopropylamine (1.3 mL, 15.6 mmol, 2.2 eq) in DCE (1.3 mL) were added dropwise sequentially to the reaction mixture. The reaction flask was sealed and heated under reflux (90°C) for an additional 18 hours before the reaction mixture was allowed to cool down to room temperature and then cooled with an ice bath before NaOH (*ca* 40 mL, 2 M *aq* solution) was added slowly and the reaction mixture was stirred for 1 hour. The reaction mixture was filtered on celite and washed with EtOAc (*ca* 50 mL). $NaHCO_3$ (aq. sat., *ca* 35 mL) were added to the suspension. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with EtOAc (3 × 30 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Purification by two flash column chromatography (Toluene; SiO_2) and then (95:5 ; Petrol/EtOAc; SiO_2) of the residue gave the desired amine (0.364 g, 1.12 mmol, 16%) as a yellow solid.

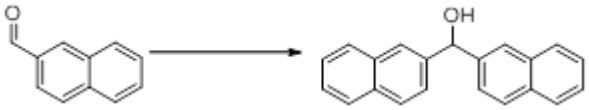
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.94 - 8.00 (m, 2 H), 7.85 (d, *J* = 8.1 Hz, 2 H), 7.63 (d, *J* = 7.2 Hz, 2 H), 7.52 - 7.58 (m, 4 H), 7.46 - 7.52 (m, 2 H), 6.68 (s, 1 H), 3.22 (spt, *J* = 6.3 Hz, 1 H), 1.65 (s, 1 H), 1.31 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 139.0 (1 C), 134.1 (1 C), 131.4 (1 C), 128.9 (2 C), 127.6 (2 C), 126.3 (2 C), 125.5 (2 C), 125.4 (2 C), 55.6 (1 C), 47.4 (1 C), 23.3 (2 C).

HRMS (ESI) *m*/*z* calcd for $C_{24}H_{24}N$ $[M+H]^+$: 326.1888, found: 326.1903

IR (ν_{max} /cm^{-1}):3457, 3016, 2970, 1738, 1375, 1228, 776.

Di(naphthalen-2-yl)methanol



According to a modified procedure from Dong *et al*., [199] THF (*ca* 30 mL) was added to immerse magnesium turnings (1.01 g, 41.6 mmol, 1.3 eq). The reaction was heated at 40 °C and I_2 (1 crystal) was added to the stirring mixture. After 10 minute, 2-bromonaphtalene (2.17 mL, 15.65 mmol, 1.05 eq) and THF (20 mL) was added slowly to the reaction mixture. The reaction mixture was refluxed for 3 hours. Upon cooling at room temperature, 2-naphthaldehyde (5.1 g, 32.0 mmol, 1.0 eq) was added dropwise (1 drop/second) to the reaction mixture and stirred for 18 hours. H_2O (*ca* 30 mL), HCl (*ca* 20 mL, 2 M) and Et_2O (*ca* 40 mL) were added successfully to the reaction mixture which was stirred at room temperature for an additional 20 minutes before the mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with Et_2O (3 × 50 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give di(naphthalen-2-yl)methanol (9.0 g, 31.6 mmol, 99%) as a colourless solid. The molecule was used without further purification.

Data was consistent with literature.[199]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.95 (s, 2 H), 7.81 - 7.90 (m, 5 H), 7.80 (s, 1 H), 7.48 - 7.55 (m, 5 H), 7.47 (d, *J* = 1.7 Hz, 1 H), 6.15 (s, 1 H), 2.59 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 140.9 (2 C), 133.2 (2 C), 132.9 (2 C), 128.4 (2 C), 128.1 (2 C), 127.7 (2 C), 126.2 (2 C), 126.0 (2 C), 125.2 (2 C), 124.9 (2 C), 76.4.

HRMS (ESI) *m*/*z* calcd for $C_{21}H_{16}NaO$ $[M+Na]^+$: 307.1093, found: 307.1091

IR (ν_{max} /cm^{-1}): 3450, 2970, 1739, 1436, 1217, 897, 757.

Di(naphthalen-2-yl)methanone



According to a modified procedure from Tsubaki *et al*., [280] MnO_2 (8.4 g, 96.7 mmol, 10 eq) was added to a stirring solution of di(naphthalen-2-yl)methanol (2.75 g, 9.68 mmol, 1.0 eq) in CH_2Cl_2 (20 mL) at room temperature. The solution was stirred for 24 hours. The reaction mixture was then filtered over celite and concentrated *in vacuo* to give the desired di(naphthalen-2-yl)methanone (2.70g, 9.56 mmol, 99%) as colourless solid. The molecule was used without further purification.

Data were consistent with published literature.[199]

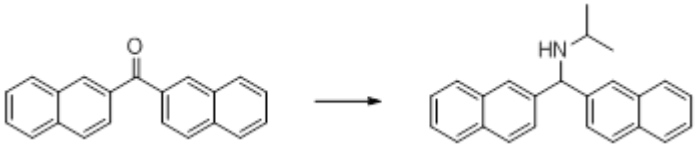
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 8.34 (s, 2 H), 8.00 - 8.03 (m, 4 H), 7.95 (apparent t, *J* = 7.2 Hz, 4 H), 7.65 (apparent td, *J* = 7.6, 1.2 Hz, 2 H), 7.58 (apparent td, *J* = 7.6, 1.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 196.8 (1 C), 135.3 (2 C), 135.2 (2 C), 132.3 (2 C), 131.8 (2 C), 127.8 (4 C), 126.8 (4 C), 125.9 (4 C).

MS (ESI) $[M+Na]^+$: 305.1 (100)

IR (ν_{max} /cm^{-1}): 2915, 1653, 1379, 1334, 1194, 763.

N-(di(naphthalen-2-yl)methyl)propan-2-amine



According to a modified procedure from Gilbert, [198] $TiCl_4$ (10.3 mL, 10.3 mmol, 1.1 eq, 1 M solution in CH_2Cl_2) was added slowly to asolution at 0 °C of di(naphthalen-2-yl)methanone (2.65 g, 9.38 mmol, 1.0 eq) in CH_2Cl_2 (50 mL). The solution was stirred for 10 minutes at room temperature and then a solution of isopropylamine (1.8 mL, 20.6 mmol, 2.2 eq) in THF (10 ml, 2 M solution) was added dropwise to the reaction mixture. The reaction flask was stirred for an additional 3 hours. A solution of $NaB(CN)H_3$ (0.71 g, 11.2 mmol, 1.2 eq) in THF (12 mL, 1 M solution) was added slowly to the reaction mixture. MeOH (17 mL) was then added slowly to the reaction mixture and the reaction mixture was stirred at room temperature for an additional 18 hours before NaOH (*ca* 25 mL, 2 M *aq* solution) was added slowly and the reaction mixture was

stirred for 30 min. The reaction mixture was filtered on celite and washed with EtOAc (*ca* 20 mL). $NaHCO_3$ (aq. sat., *ca* 15 mL) were added to the suspension. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Purification by flash column chromatography (93:7; Petrol/EtOAc; SiO_2) gave *N*-(di(naphthalen-2-yl)methyl)propan-2-amine (2.24 g, 6.9 mmol, 74%) as a colourless solid.

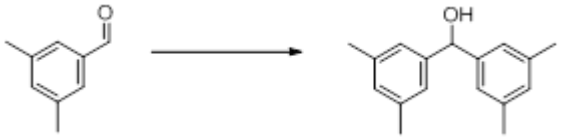
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 8.15 (s, 2 H), 8.03 (d, *J* = 8.4 Hz, 2 H), 7.95 (d, *J* = 8.4 Hz, 4 H), 7.74 (dd, *J* = 8.4, 1.5 Hz, 2 H), 7.56 - 7.67 (m, 4 H), 5.51 (s, 1 H), 3.06 (spt, *J* = 6.2 Hz, 1 H), 1.72 (br. s., 1 H), 1.36 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 141.8 (2 C), 133.4 (2 C), 132.6 (2 C), 128.2 (2 C), 127.9 (2 C), 127.6 (2 C), 126.0 (2 C), 125.9 (2 C), 125.7 (2 C), 125.6 (2 C), 64.3 (1 C), 46.2 (1 C), 23.3 (2 C).

HRMS (ESI) *m*/*z* calcd for $C_{32}H_{52}N$ $[M+H]^+$: 326.1888, found: 326.1903

IR (ν_{max} /cm^{-1}): 3055, 2960, 1600, 1362, 907, 757, 734.

Bis(3,5-dimethylphenyl)methanol



According to a modified procedure from Deng *et al*., [199] THF (*ca* 10 mL) was added to immerse magnesium turnings (471 mg, 11.94 mmol, 1.3 eq). The reaction was heated at 40°C before I_2 (1 crystal) was added to the solution. After 10 minute, 1-bromo-3,5-dimethylbenzene (2.17 mL, 15.65 mmol, 1.05 eq) and THF (5 mL) was added slowly to the reaction mixture. The reaction mixture was refluxed for an additional 4 hours. Upon cooling at room temperature, 3,5-dimethylbenzaldehyde (2.0 g, 14.91 mmol, 1.0 eq) was added dropwise (1 drop /second) to the reaction mixture and stirred for an additional 18 hours before H_2O (*ca* 10 mL), HCl (*ca* 5 mL, 2 M) and Et_2O (*ca* 10 mL) were added successfully to the reaction mixture which was stirred at room temperature for 20 minutes. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with Et_2O (3 × 15 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give bis(3,5-dimethylphenyl)methanol (3.7g, 15.35 mmol, 98%) as a colourless solid. The molecule was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.01 (s, 4 H), 6.91 (s, 2 H), 5.71 (s, 1 H), 2.31 (s, 12 H), 1.59 (br. s., 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 143.9 (2 C), 137.9 (2 C), 129.1 (2 C), 124.2 (2 C), 76.3 (1 C), 21.3 (2 C).

HRMS (ESI) *m*/*z* calcd for $C_{17}H_{20}NaO$ $[M+Na]^+$: 263.1406, found: 263.1408.

IR (ν_{max} /cm^{-1}): 2970, 1750, 1373, 1215, 1056, 896, 750, 702.

bis(3,5-dimethylphenyl)methanone



According to a modified procedure from Tsubaki *et al.*, [280] MnO_2 (8.0 g, 92.3 mmol, 6 eq) was added to a stirring solution of bis(3,5-dimethylphenyl)methanol (3.7 g, 15.3 mmol, 1.0 eq) in CH_2Cl_2 (30 mL) at room temperature. The solution was stirred for an additional 18 hours before additional MnO_2 (8.0 g, 92.3 mmol, 6 eq) was added to the reaction mixture and the reaction mixture was stirred for another 24 hours. The reaction mixture was then filtered over celite and concentrated *in vacuo* to give the desired bis(3,5-dimethylphenyl)methanone (3.5 g, 14.7 mmol, 96%) as colourless solid. The molecule was used without further purification

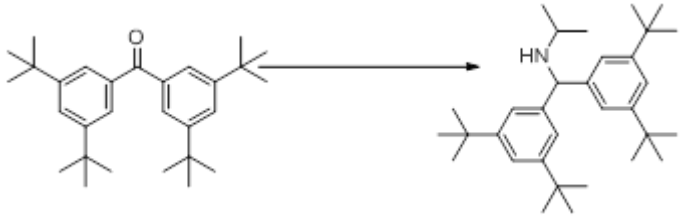
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.39 (s, 4 H), 7.22 (s, 2 H), 2.38 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 197.6 (1 C), 138.0 (2 C), 137.8 (4 C), 133.9 (2 C), 127.7 (4 C), 21.2 (4 C).

HRMS (ESI) *m*/*z* calcd for $C_{17}H_{18}NaO$ $[M+Na]^+$: 261.1250, found: 261.1244.

IR (ν_{max} /cm^{-1}): 2915, 1649, 1599, 1379, 1320, 1192, 763.

N-(bis(3,5-di-tert-butylphenyl)methyl)propan-2-amine



According to a modified procedure from Gilbert, [198] $TiCl_4$ (6.9 mL, 6.90 mmol, 1.1 eq, 1 M solution in CH_2Cl_2) was added slowly to a solution at 0 °C of bis(3,5-di-tert-butylphenyl)methanone (2.55 g, 6.27 mmol, 1.0 eq) in CH_2Cl_2 (35 mL). The solution was stirred for 10 minutes at room temperature before a solution of isopropylamine (1.2 mL, 13.8 mmol, 2.2 eq) in THF (7 ml, 2 M solution) was added dropwise to the reaction mixture. The reaction flask was stirred for 3 hours. A solution of $NaB(CN)H_3$ (0.47 g, 7.5 mmol, 1.2 eq) in THF (7.5 mL, 1 M solution) was added slowly to the reaction mixture. MeOH (11.4 mL) was then added slowly to the reaction mixture and the reaction mixture was stirred at room temperature for an additional 18 hours before NaOH (*ca* 20 mL, 2 M *aq* solution) was added slowly and the reaction mixture was stirred for 30 min. The reaction mixture was filtered on celite and washed with CH_2Cl_2 (*ca* 20 mL). $NaHCO_3$ (aq. sat., *ca* 15 mL) were added to the suspension. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Petrol (*ca* 25 mL) and Et_2O (*ca* 15 mL) were added to the crude mixture. Concentrated HCl (*ca* 5 mL, 37% w/v solution) was added. The mixture was left and crystals formed after 1 hour. The reaction flask was then stored at -20°C overnight. The reaction mixture was filtered and washed with cold petrol. The crystals were collected and dried under high vacuum to give the desired *N*-(bis(3,5-di-tert-butylphenyl)methyl)propan-2-amine (0.51 g, 1.11 mmol, 18%).

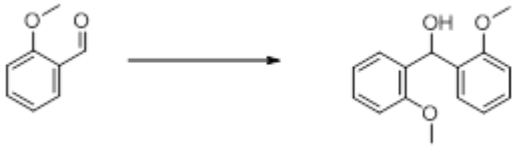
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.31 (br. s., 4 H), 7.29 (br. s., 2 H), 4.98 (br. s., 1 H), 2.68 - 2.86 (m, 1 H), 1.37 - 1.40 (m, 1 H), 1.35 (br. s, 36 H), 1.14 (d, *J* = 6.2 Hz, 6 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 150.3 (4 C), 143.9 (2 C), 121.7 (4 C), 120.5 (2 C), 65.7 (1 C), 46.2 (1 C), 34.8 (2 C), 31.5 (12 C), 23.3 (2 C).

HRMS (ESI) *m*/*z* calcd for $C_{32}H_{52}N$ $[M+H]^+$: 450.4092, found: 450.4094

IR (ν_{max} /cm^{-1}): 2960, 2867, 1598, 1477, 1393, 1248, 876, 728.

Bis(2-methoxyphenyl)methanol



According to a modified procedure from Diederich *et al.*[281], THF (~30 mL) was added to immerse magnesium turnings (1.1 g, 38.5 mmol, 1.05 eq). The reaction was heated at 40°C before I_2 (1 crystal) was added to the solution. After 10 minute, 1-bromo-2-methoxybenzene (4.8 mL, 47.7

mmol, 1.3 eq) and THF (15 mL) was added slowly to the reaction mixture. The reaction mixture was refluxed for 4 hours. Upon cooling at room temperature, 2-methoxybenzaldehyde (4.4 mL, 36.7 mmol, 1.0 eq) was added dropwise (1 drop/second) to the reaction mixture and stirred for 18 hours. H_20 (~40 mL), HCl (~25 mL, 2 M) and Et_2O (~40 mL) were added successfully to the reaction mixture which was stirred at room temperature for 20 minutes. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with Et_2O (3 × 50 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give bis(2-methoxyphenyl)methanol (8.5 g , 34.7 mmol, 94%) as a colourless solid. The molecule was used without further purification.

Data was consistent with published literature.[281]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.27 - 7.31 (m, 2 H), 7.23 - 7.27 (m, 2 H), 6.95 (td, *J* = 8.3, 0.9 Hz, 2 H), 6.91 (d, *J* = 8.3 Hz, 2 H), 6.37 (d, *J* = 5.4 Hz, 1 H), 3.84 (s, 6 H), 3.57 (dd, *J* = 5.4, 0.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 156.8 (2 C), 130.9 (2 C), 128.4 (2 C), 127.8 (2 C), 120.5 (2 C), 110.4 (2 C), 67.4, 55.4 (2 C).

HRMS (ESI) *m*/*z* calcd for $C_{15}H_{16}NaO_3$ $[M+Na]^+$: 267.0992, found: 267.0999.

IR (ν_{max} /cm^{-1}): 2970, 1759, 1342, 1204.

Bis(2-methoxyphenyl)methanone



According to a modified procedure from Diederich *et al*.[281] MnO_2 (7.6 g, 88.0 mmol, 5 eq) was added to a stirring solution of bis(2-methoxyphenyl)methanol (4.2 g, 17.4 mmol, 1.0 eq) in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for an additional 18 hours before additional MnO_2 (7.6 g, 88.0 mmol, 5 eq) was added to the reaction mixture and the reaction mixture was stirred for another 24 hours. The reaction mixture was then filtered over celite and concentrated *in vacuo* to give the desired bis(2-methoxyphenyl)methanone (3.3 g, 13.7 mmol, 79%) as colourless solid. The molecule was used without further purification

Data was consistent with published literature.[281]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.52 (dd, *J* = 7.6, 2.0 Hz, 2 H), 7.44 (ddd, *J* = 8.3, 7.4, 2.0 Hz, 2 H), 6.99 (td, *J* = 8.3, 0.7 Hz, 2 H), 6.92 (d, *J* = 8.3 Hz, 2 H), 3.67 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 195.3, 158.2 (2 C), 132.5 (2 C), 130.3 (2 C), 130.2 (2 C), 120.3 (2 C), 111.4 (2 C), 55.6 (2 C).

HRMS (ESI) *m/z* calcd for $C_{15}H_{14}NaO$ $[M+Na]^+$: 265.0835, found: 265.0836.

IR (ν_{max} /cm^{-1}): 2970, 1730, 1597, 1369, 1250, 1023, 751.

N-(bis(2-methoxyphenyl)methyl)propan-2-amine



According to a modified procedure from Gilbert,[198] $TiCl_4$ (15.2 mL, 15.1 mmol, 1.1 eq, 1 M solution in CH_2Cl_2) was added slowly to a solution at 0 °C of bis(2-methoxyphenyl)methanone (3.33 g, 13.8 mmol, 1.0 eq) in CH_2Cl_2 (40 mL). The solution was stirred for 10 minutes at room temperature and then a solution of isopropylamine (3.5 mL, 41.2 mmol, 3.0 eq) in THF (20 ml, 2 M solution) was added dropwise to the reaction mixture. The reaction flask was stirred for an additional 6 hours before a solution of $NaB(CN)H_3$ (4.32 g, 68.7 mmol, 5.0 eq) in THF (68 mL, 1 M solution) was added slowly to the reaction mixture. MeOH (24 mL) was then added slowly to the reaction mixture and the reaction mixture was stirred at room temperature for an additional 18 hours before NaOH (*ca* 50 mL, 2 M *aq* solution) was added slowly and the reaction mixture was stirred for 30 min. The reaction mixture was filtered on celite and washed with Et_2O (~70 mL). $NaHCO_3$ (aq. sat., *ca* 50 mL) were added to the suspension. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with Et_2O (3 × 50 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Et_2O (~50 mL) were added to the crude mixture. Concentrated HCl (~5 mL, 37% w/v solution) was added. The mixture was left and crystals formed after 5 min.

The mixture was partitioned between the aqueous and Et_2O layers and the organic phase extracted with HCl (aq 2.0 M, 3 × 30 mL). Then CH_2Cl_2 (20 mL) was added to the combined aqueous phases and NaOH (aq saturated with brine solution, 25%) was added till the mixture became basic (pH paper, pH~14). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was dried

($MgSO_4$), filtered and concentrated *in vacuo* to afford the desired *N*-(bis(2-methoxyphenyl)methyl)propan-2-amine (2.14 g, 7.4 mmol, 54%). The amine was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.37 (d, *J* = 7.3 Hz, 2 H), 7.20 (td, *J* = 7.7, 1.5 Hz, 2 H), 6.93 (t, *J* = 7.3 Hz, 2 H), 6.85 (d, *J* = 8.3 Hz, 2 H), 5.63 (s, 1 H), 3.80 (s, 6 H), 2.76 (spt, *J* = 6.2 Hz, 1 H), 1.86 - 2.25 (m, 1 H), 1.12 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 157.2 (2 C), 131.8 (2 C), 128.5 (2 C), 127.4 (2 C), 120.3 (2 C), 110.7 (2 C), 55.4 (2 C), 52.5, 46.2, 23.1 (2 C).

HRMS (ESI) *m/z* calcd for $C_{18}H_{24}NO_2[M+H]^+$: 286.1802, found: 286.1804

IR (ν_{max} /cm^{-1}): 2950, 1771, 1709, 1598, 1380, 1351, 1229.

N-(bis(3,5-dimethylphenyl)methyl)propan-2-amine



According to a modified procedure from Gilbert, [198] $TiCl_4$ (16.2 mL, 16.2 mmol, 1.1 eq, 1 M solution in CH_2Cl_2) was added slowly to a solution cooled at 0 °C of bis(3,5-dimethylphenyl)methanone (3.5 g, 14.7 mmol, 1.0 eq) in CH_2Cl_2 (80 mL). The solution was stirred for 10 minutes at room temperature and then a solution of isopropylamine (2.8 mL, 32.3 mmol, 2.2 eq) in THF (17 ml, 2 M solution) was added dropwise to the reaction mixture. The reaction flask was stirred for an additional 3 hours before a solution of $NaB(CN)H_3$ (1.1 g, 17.6 mmol, 1.2 eq) in THF (18 mL, 1 M solution) was added slowly to the reaction mixture. MeOH (26 mL) was then added slowly to the reaction mixture and the reaction mixture was stirred at room temperature for an additional 18 hours before NaOH (*ca* 30 mL, 2 M *aq* solution) was added slowly and the reaction mixture was stirred for 30 min. The reaction mixture was filtered on celite and washed with EtOAc (*ca* 20 mL). $NaHCO_3$ (aq. sat., *ca* 15 mL) were added to the suspension. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated

in vacuo to give an oil. Purification by flash column chromatography (19:1; Petrol/EtOAc; SiO_2) gave the desired amine (2.44 g, 8.6 mmol, 59%) as a white solid.

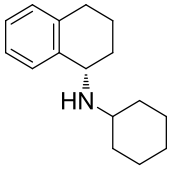
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.00 (s, 4 H), 6.85 (s, 2 H), 4.83 (s, 1 H), 2.75 (dt, J = 12.5, 6.3 Hz, 1 H), 2.30 (s, 12 H), 1.24 - 1.39 (m, 1 H), 1.10 (d, J = 6.3 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 144.6 (2 C), 137.8 (4 C), 128.4 (2 C), 125.0 (4 C), 64.2 (1 C), 46.1 (1 C), 23.2 (2 C), 21.4 (4 C).

HRMS (ESI) *m/z* calcd for $C_{20}H_{28}N$ $[M+H]^+$: 282.2225, found: 282.2216.

IR (ν_{max} /cm^{-1}): 2956, 1598, 1469, 1375, 1166, 861, 740.

(*S*)-*N*-cyclohexyl-1,2,3,4-tetrahydronaphthalen-1-amine



According to a modified procedure,[266] cyclohexanone (2.5 mL, 23.9 mmol, 1.0 eq.) was added to a stirring solution of (*S*)-1,2,3,4-tetrahydronaphthalen-1-amine (3.5 mL, 23.9 mmol, 1.0 eq.) in THF (50 mL) at room temperature. After 10 min, $NaB(OAc)_3H$ (6.59 g, 31.1 mmol, 1.3 eq.) was tipped into the reaction mixture at room temperature and the resulting suspension was stirred for 48 h. Et_2O (30 mL) and $NaHCO_3$ (aq. sat., *ca* 30 mL) were added to the suspension and stirring was continued for 30 min. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (3 × 40 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired title product as an orange oil (4.65 g, 20.3 mmol, 85%). The amine was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 7.26 (d, J = 7.7 Hz, 1 H), 7.10-7.01 (m, 2 H), 6.97 (d, J = 7.7 Hz, 1 H), 3.78 (app. t, J = 4.7 Hz, 1 H), 2.77-2.68 (m, 1 H), 2.67-2.52 (m, 2 H), 1.99-1.50 (m, 9 H), 1.29-1.00 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 139.9, 136.9, 128.6, 128.5, 126.0, 125.4, 53.8, 51.5, 34.5, 33.1, 29.0, 28.7, 25.9, 24.9, 24.6, 18.5.

HRMS (ESI) *m/z* calcd for $C_{16}H_{24}N$ $[M]^+$: 230.1903, found: 230.1903;

$[\alpha]^{20}_{589}$ = +1.37 (*c* 1.08, $CHCl_3$).

IR (ν_{max}/cm^{-1}) 3302, 2924, 1448, 1109, 888, 766, 739, 694.

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