ASYMMETRIC TRANSITION METAL-CATALYSED ALKYL ADDITION TO IMINES WITH CHIRAL PHOSPHINE LIGANDS

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Thesis submitted to the University of Nottingham

for the degree of Doctor of Philosophy

July 2009

Declaration

I declare that this thesis is the result of my own work and has not, whether in the same or a different form, been presented to this or any other university in support of an application for any degree other than that for which I am now a candidate.

Samir El Hajjaji

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Acknowledgements

Special thanks must go to my supervisor Prof. Simon Woodward for providing me with an interesting research project and excellent academic support. I would also like to thank Dr Martin Fox for industrial supervision and encouragement and ideas, as well as staff from Chirotech (Colin Dewar, Dr Graham Meek, Dr Paul Moran, Dr Chris Cobley and others) who were very friendly and helpful during my placement. I am grateful to the EPSRC and Chirotech for funding.

I would like to thank all members of C29 I enjoyed to work and spend time with: Xiaoping Tang, Matthias Welker, Daniel Glynn, Dr Kallol Biswas (…ghurabaaa!), Dr David Bernier, Dr Antonella de Roma, Dr Ferrucio Bertolini, Dr Ross Fryatt, Dr Andy Novak, Dr Maurizio Solinas, Dr Daniella Giunta, Dr Rebecca Meadows, Giulia Fiorani, Rosie Crampton and Phil Andrews.

Extended thanks to my family including my mum, brothers (Khalid, Abdelilah, Said, Jamal), sisters (Nawel, Fatima) as well as Hafida, Meriem, Abdou, Yassin, Ilyas, Iman, Adam, khali Larsen, khali Mhammad, khalti Vadela, khalti Radia and khalti Khadija. Many thanks go to my exceptional housemates & friends I will never forget (Atith, Ahmad Zia, Shuaib al yemeni, Ismael al londoni, Ahmed al misri, Ossama al dimashqi, Ussam al baghdadi, Talal al dimashqi, Abdelsalam al djazairi and Shaz Aslam). I should not omit to thank the person who first welcomed me to Nottingham and with whom I have shared very interesting and thoughtful discussions, Mrs Dorrit Tyack.

ABSTRACT

The research project presented in this thesis deals with the development of the alkylation of protected aldimines using organoaluminium and organozinc compounds as alkylating agents. To this end, efforts have been focused into the methylation reaction using trimethylaluminium and dimethylzinc. It was hoped to establish promising conditions using the methylate group and then to extend the catalytic system to other interesting nucleophiles. In the case of organoaluminium alkylation the reaction was extended to other nucleophiles, namely to the allyl and propargyl groups. The identificaton of suitable metal catalysts as well as diphosphine ligands was carried out by means of extensive high throughput screening. On the one hand $[IrCl(COD)]_2$ proved to be very efficient when associated to $AlMe_3$ or DABAL-Me_3 in the non-enantioselective 1,2-addition reactions to aldimines (100% conversion in 3 h). On the other hand, $[RhCl(COD)]BF_4$ was found to be able to efficiently catalyse the enantioselective 1,2-addition of Me_2Zn to aldimine substrates (100% conversion in 3 h - up to 99% e.e.).

A preliminary screening of a range of aldimines bearing different protecting groups aimed at selecting the most interesting substrate in terms of reactivity and ease of cleavage of the protecting group. Once this substrate had been identified, a range of derivatives was synthesised in order to appraise the scope of the newly developed reaction. The diphenylphosphinoyl (dpp) protecting group turned out to be the best activating group for aldimines tested within the framework of this study. In addition to being easy to introduce, the dpp group can also be removed easily under mild conditions.

What is more, the presence of a phosphorus atom on this protecting group is a feature which was used to determine the enantiomeric excess by ^{31}P NMR spectroscopy, thus providing a novel and efficient screening tool at disposal.

In the course of this investigation, various issues were faced and tackled. One of them was the unexpected non-reproducibility taking place in the Rh-catalysed Me_2Zn addition reaction; however, a deeper thinking of the reaction mechanism enabled us to solve this problem to eventually get a more robust catalytic system. Another one was the formation of a reduction product as a by-product of the Rh-catalysed Me_2Zn addition reaction.

Finally, several interesting attempts (Et_2Zn addition, aliphatic imine synthesis), findings (effect of ligand bite angle) and hypotheses (testing of the BPM ligand) made during this study deserve to be studied further for improvement and optimisation.

Abbreviations

acac	acetylacetonate
anisyl	methoxybenzyl
benzyl	phenylmethyl
Boc	*tert*-butoxycarbonyl
Bod	bicyclo[2.2.2]octa-2,5-diene
Chy	cyclohexyl
COD	1,5-cyclooctadiene
COE	cyclooctene
CuTC	copper (I) thiophene-2-carboxylate
DABAL	1,4-diazabicyclo-[2.2.2]-octane *bis*(trimethylaluminium)
DABCO	1,4-diazabicyclo-[2.2.2]-octane
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4,4-dimethylamino pyridine
e.e.	enantiomeric excess
EI	electron impact
eq	equivalent
ESI	electrospray ionisation
FG	functional group
GC	gas chromatography
HOBt	hydroxybenzotriazole
HMPA	hexamethylphosphoramide

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
LAC	ligand-accelerated catalysis
LDC	ligand-decelerated catalysis
MS	mass spectrometry
NBD	2,5-norbornadiene
NMP	*N*-methylpyrrolidinone
Ns	*p*-nitrobenzenesulfonyl
PG	protecting group
PT	proton transfer
SFC	supercritical fluid chromatography
TC	thiophene-2-carboxylate
Tf	trifluoromethanesulfonate
Temp.	temperature
TLC	thin layer chromatography
tosyl	*p*-toluenesulfonyl

Chapter I

Introduction

1.1 Metal-catalysed asymmetric synthesis

1.1.1 Introduction

Asymmetric syntheses of organic molecules are important in the pharmaceutical, agrochemical,[1] fragrance and flavour[2] industries. For example, chirality-control in pharmaceuticals can be significant in terms of safety; often only one of the enantiomers of a pharmaceutical has desirable biological activity, while the other enantiomer is often inactive or even, in the worst case, has adverse effects.[3] Thus, it is highly desirable to produce medicinal compounds in enantiomerically pure forms. Examples of property differenciation within enantiomer pairs are numerous and often dramatic. Examples such as Ethambutol[4] (**1**, **2**) and Thalidomide (**3**, **4**) emphasise the reasons for commercial interest and the incentive for producing enantiomerically pure materials (Figure 1).

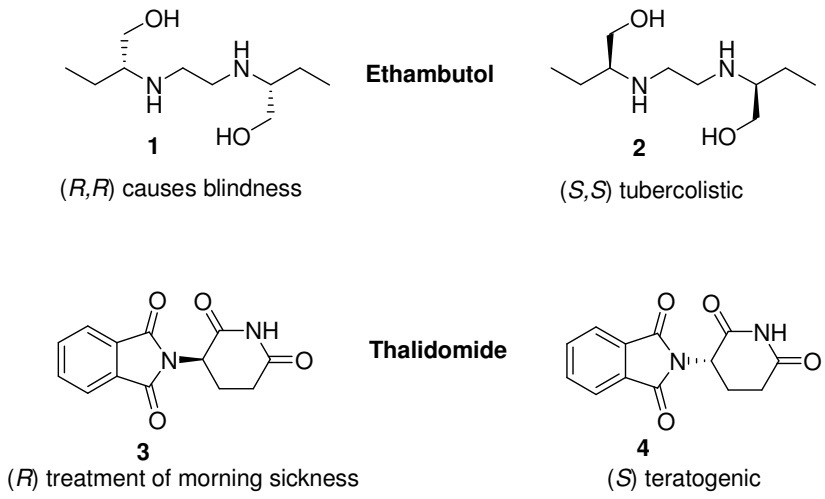


Figure 1: Differences in the properties of enantiomers.

The production of optically pure materials has generally presented significant challenges. Several methods for obtaining optically active compounds can be utilised:[5]

- use of naturally occuring chiral pool materials: amino acids, hydroxyl acids, carbohydrates, terpenes, alkaloids.
- separation of racemates: classical resolution, resolution by direct crystallisation, kinetic resolution.
- creation from prochiral compounds: asymmetric synthesis (enzymic methods and non-enzymic methods).

Of the many possible approaches to synthesise enantiomerically pure compounds, enantioselective catalysis is arguably the most elegant method. Asymmetric catalysis is an ideal method for synthesising optically active compounds in large quantity. Tremendous effort has been devoted to developing new asymmetric catalysis reactions and to improving the enantioselectivity and reaction efficiency of existing asymmetric catalysis reactions.[6] To realise maximum chiral multiplication, such catalysts should efficiently differentiate enantiotopic groups or faces of prochiral molecules. For that purpose, homogeneous metal complexes have come to be one of the most powerful and general tools available. Indeed, metal-mediated asymmetric catalysis has been intensively studied in the four decades since the first report of homogeneous Cu-catalysed asymmetric cyclopropanation.[7] Although at first only modest enantioselectivities were realised, notable advances have been achieved during the last three decades. Rh-phosphine complex catalysed asymmetric hydrogenation of dehydro amino alcohols[8,9]

and Ti-tartrate complex catalysed asymmetric epoxidation of allylic alcohols[10] were early milestones in metal-catalysed asymmetric catalysis, realising high enantioselectivity and broad substrate scope. These reactions demonstrated the high practicality of asymmetric catalysis and this was notably recognised in the award of a Nobel Prize to Profs. Knowles, Noyori and Sharpless for their seminal work on chirally catalysed hydrogenation and oxidation reactions.[11]

1.1.2 Design of asymmetric catalysis

In metal-catalysed asymmetric catalysis, high selectivity and reactivity can be realised by selecting the proper catalyst, substrate, and reaction conditions. Catalytic function is typically determined by the central metal used, while reactivity and enantioselectivity are more finely tuned by chiral organic ligands coordinated to the central metal. A delicate balance of electronic and steric factors determines the efficiency of a chiral metal catalyst. The proper choice of chiral ligands is crucial to realising efficient intermolecular chirality transfer from catalyst to substrate. Ligands with central chirality, axial chirality and/or planar chirality have proven to be effective. The diverse catalytic activities of metallic species combined with the virtually infinite availability of chiral organic ligands have so far made possible a broad spectrum of asymmetric reactions. Given the countless possible combinations of metal and chiral ligands, future prospects in this area seem bright.

On the basis of the tremendous accumulated knowledge of organometallic compounds brought to us through mechanistic study, rational design and optimisation of catalyst is sometimes possible. For well-precedented

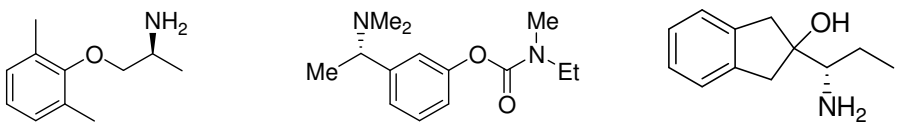
reactions, rational design can be considered appropriate. On the other hand, for unprecedented asymmetric reactions, the screening of suitable metals, chiral ligands and reaction conditions is still required during early development.

Currently, both screening and rational optimisation through mechanistic studies are often required to achieve highly enantioselective metal-catalysed asymmetric methods. Either random screening or rational design alone rarely lead to superior chiral catalysts.

1.2 Asymmetric synthesis of α-methyl amines

1.2.1 Importance of chiral amines

Asymmetric preparations of α-substituted chiral amines are a very important process due to the predominant role that α-chiral amines play in several drugs and natural products. Moreover, such chiral amines often possess pronounced biological activity in their own right, and hence are of increasing commercial value in the fine chemical and pharmaceutical areas in view of their application as resolving agents, chiral auxiliaries/chiral bases and catalysts for asymmetric synthesis. Examples of these amines (Figure 2) are Mexitil **5** (antiarrhythmic agent), Rivastigmine **6** (anti-Alzehimer) and Indanorex **7** (amphetamine).

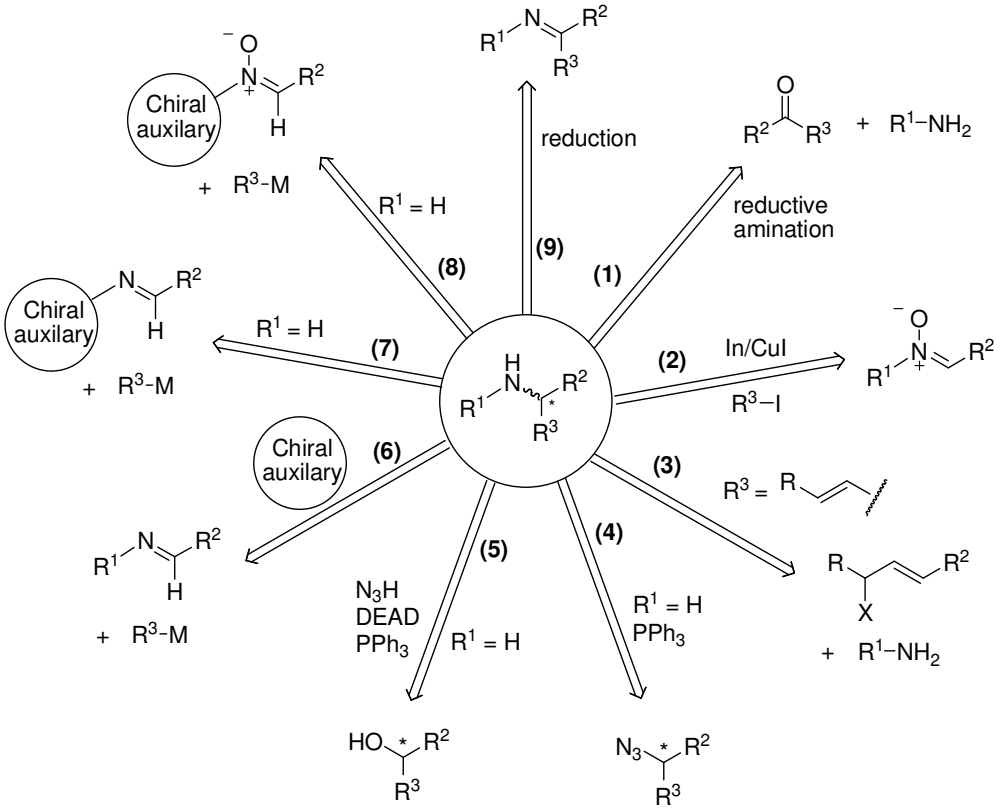


5 **Mexitil** **6** **Rivastigmine** **7** **Indanorex**

Figure 2: Examples of chiral amines used as pharmaceuticals.

1.2.2 Overview of the synthesis of *α*-substituted chiral amines

The preparation of *α*-substituted chiral amines can be carried out via several synthetic methods. The non exhaustive overview presented in Scheme 1 highlights some of the most important asymmetric and non asymmetric reactions available to date.



Scheme 1: Overview of the synthesis of *α*-substituted chiral amines.

If the starting material utilised in the transformation is an imine, two approaches may be considered depending on its nature: reduction (Equ. 9) or the 1,2-addition of a nucleophile (Equ. 3-8). The reduction of ketimines which is a powerful method including a range of reactions such as

hydrogenation, transfer hydrogenation, hydrosilylation and borohydride reduction is developed later in this chapter (*cf.* 1.3.1 - Table 1). These reduction reactions can also be applied to oximes (Equ. 1, R^1 = OH).[12]

Another attractive approach is the direct reductive amination (Equ. 1) which corresponds to the direct reduction of an imine resulting from the reaction of the corresponding ketone and amine. This reaction has been carried out in an asymmetric fashion with metal catalysts[13] and organocatalysts.[14]

Another popular synthetic route starting from aldimine substrates is the alkylation. Indeed, the literature is abundant with procedures enabling the introduction of a variety of nucleophiles onto aldimines. Resulting products of these alkylation reactions include propargyl amines[15] and allylamines (*cf.* 5.1.2.1.1 - Table 1) among many other examples. As with the reduction of ketimines, this transformation can be carried out in an asymmetric fashion. The chirality can be induced here by adding an external chiral auxiliary. For example, the addition of organolithium reagents work successfully on *N*-(4-methoxyphenyl) protected imine in the presence of stoichiometric amounts of the specific chiral amine[16] or *bis*-isoxazoline[17] used as an auxilary.

The chirality can also be induced by using an internal chiral auxiliary on the substrate itself (Equ. 7-8). This strategy was used in the addition of allylic metal compounds[18] and organocuprate reagents[19] to aldimines derived from 1-(*R*)-phenylethylamine. Similarly, several allylic metal reagents based on Al/Ti,[20] Zn[21] and Mg/Cu[21] above have been added with excellent diastereoselectivity to imines derived from (*S*)-valine. Turning away from imines, SAMP-hydrazones (SAMP: (*S*)-1-amino-2-methoxymethyl

pyrrolidine) are also very useful for highly asymmetric additions of organolithium,[22] and organocerium reagents[23] to yield optically active hydrazines that can be subsequently converted to the amine (reduction with Raney-Ni) without loss of optical purity. α-substituted chiral amines can also be prepared by alkylation of nitrone substrates which affords the hydroxylamine that can be subsequently converted to the amine. This can be done either asymmetrically (Equ. 8)[24] or racemically (Equ. 2).[25] Finally, α-substituted chiral amines can be prepared from azide substrates via a Staudinger reaction (Equ. 4);[26] the azide substrate can be prepared enantioselectively via a Mitsunobu reaction (Equ. 5).[27]

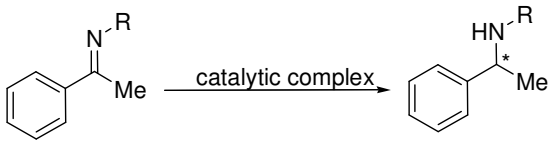
1.3 Asymmetric synthesis of amines from imines

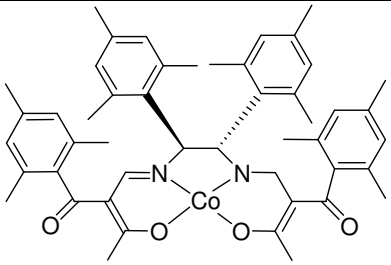
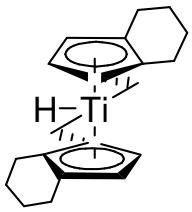
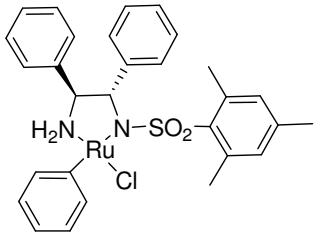
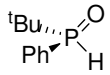
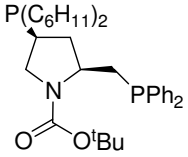
Preparation of chiral amines can be attained from imines substrates via two main different approaches: asymmetric reduction of ketimines and asymmetric 1,2-addition to aldimines; and it is the latter method which has been studied in this thesis.

1.3.1 Asymmetric reduction of ketimines

Reduction of prochiral ketimines is the most commonly used route to obtain optically active amines and this covers a broad field of reactions using metal catalysed processes. Some of the most interesting results reported in the literature are those that utilise acetophenone-based imines as substrates, and are listed below (Table 1).

Table 1: Enantioselective reduction of acetophenone-based imines.

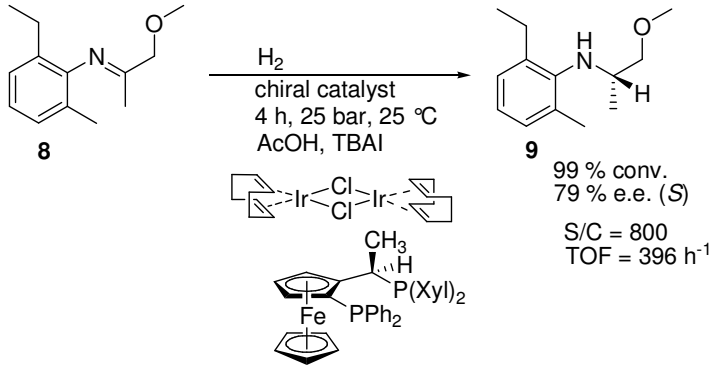


Entry	R	Conditions	Catalytic complex	Results
1[28]	O ‖ PPh_2	$NaBH_2(OEt)$ $(O\text{-}CH_2\text{-}THF)$ 0 °C, 4 h		90% yield, 97% e.e.
2[29]	Me	$PhSiH_3$, pyrrolidine, MeOH, RT, 12 h		95% yield, 99% e.e.
3[30]	Ph	HCOOH, Et_3N, CH_2Cl_2, 28 °C, 36 h		72% yield, 77% e.e.
4[31]	O ‖ PPh_2	H_2, 25 bar, pyridine, toluene, RT, 120 h	$[Ir(COD)Cl]_2$ / 	100% conv, 70% e.e.
5[31]	Ph			100% conv, 0% e.e.
6[31]	CH_2- Ph			100% conv[(a)], 76% e.e.
7[32]	CH_2- Ph	H_2, 100 bar, phthalimide toluene, 5 °C, 24 h	$[Ir(COD)Cl]_2$ / 	95% conv., 85-93% e.e.

(a) Time = 168 h.

The examples of Table 1 reflect the most developed enantioselective processes for reductions of ketimines known so far: borohydride reduction (Entry 1), hydrosilylation (Entry 2), transfer hydrogenation (Entry 3), and hydrogenation (Entries 4-7).

Another important example in the field of enantioselective hydrogenation is the one developed by Bläser and Spindler[33,34] during the course of the synthesis of a precursor of (*S*)-metolachlor, a popular herbicide sold all over the world. This molecule which is from the chloroacetanilide family is a *N*-chloracetylated, *N*-alkoxy alkylated ortho disubstituted aniline (Scheme 2).



Scheme 2: Preparation of (*S*)-metolachlor by enantioselective hydrogenation.

It is obtained by hydrogenation of the corresponding imine in presence of a catalyst generated *in situ* from $[Ir(COD)Cl]_2$ and (*R*,*S*)-PPF–$P(3,5\text{-}Xyl)_2$ (xyliphos). This catalyst shows a high catalytic activity (396 h^{-1}) and a moderate, but industrially acceptable, enantioselectivity (79% e.e.).

At production scales, this transformation is carried out on a 10 m^3 reactor, at 80 bars and 50 °C. At the time when this transformation was reported, these results set a new standard concerning catalyst activity and productivity for a homogeneous enantioselective hydrogenation.

As can be seen in Table 1, the range of catalysts used in these processes involves various metals such as cobalt(II), titanium(III), ruthenium(II), and iridium(I), with *e.e.* values reaching 99% (Entry 2).

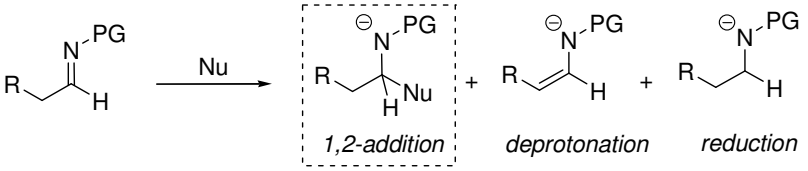
Many advantages can be found to these reactions. For example, transfer hydrogenation (Entry 3) using stable organic hydrogen donors (HCO_2H) is an attractive route in view of the low hazardous properties of such reducing agents and operational simplicity. However, these reactions require either expensive catalysts, harsh conditions (Entries 4-7) or offer insufficient reaction rates (Entries 2-7). These drawbacks have directed the study presented in this thesis to a second focus for the synthesis of chiral amines: the asymmetric 1,2-addition of carbanions to aldimines.

1.3.2 Asymmetric 1,2-addition of carbanions to aldimines

1.3.2.1 Nucleophilic attack reaction on protected aldimines

Although imines are versatile intermediates for the synthesis of chiral α-branched amines, primarily due to the ready availability of a wide range of aldehyde and ketone starting materials, their use is not without problems. For the vast majority of aldehyde and ketone precursors, *N*-substitution is required to prevent oligomerization or other decomposition pathways. In addition to play a stabilising role, *N*-substitution can also be used to activate the imine. Many imines are hydrolytically unstable, depending both upon the steric and electronic properties of the aldehyde or ketone precursor, and upon the nitrogen substituent. In addition, imines are poor electrophiles and, upon

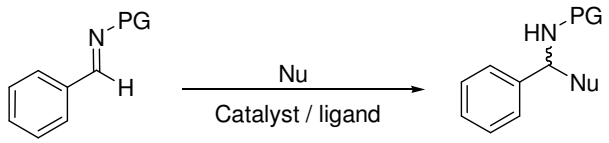
treatment with basic carbanion nucleophiles, are prone to competitive α-deprotonation, resulting in aza-enolate formation (Scheme 3).



PG: protecting group
Nu: nucleophile

Scheme 3: Problems encountered in the 1,2-addition to aldimines.

To avoid these potential issues, studies in this thesis have been restricted to 1,2-additions of carbanions to benzaldimines *N*-substituted with groups that make them more resistant to hydrolysis (Scheme 4).



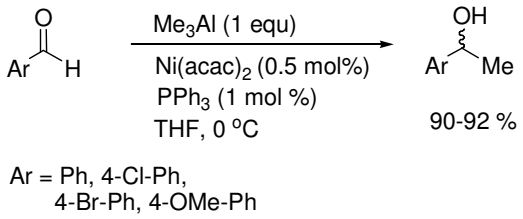
O
PG = $\overset{\|}{P}Ph_2$, tosyl, benzyl, anisyl

Scheme 4: Nucleophilic attack on protected imines.

1.3.2.2 Catalytic systems for the methylation

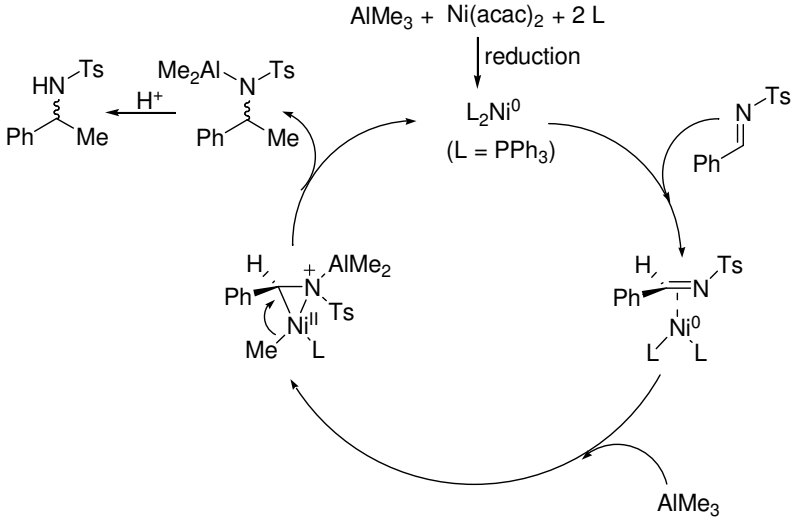
1.3.2.2.1 Nickel catalysed asymmetric methylation

Nickel-catalysed methylation of aldehydes using trimethylaluminium as an alkylation reagent was reported by Fujisawa *et al.*[35] in 1998. It was found that the addition of a phosphine ligand, such as triphenylphosphine, improved the reactivity of the catalyst and considerably increased the product yield. The reaction was carried out in THF at 0 ºC and affords the methylated alcohol with a range of yields exceeding 83% (Scheme 5).



Scheme 5: **Nickel catalysed methylation of aryl aldehydes.**

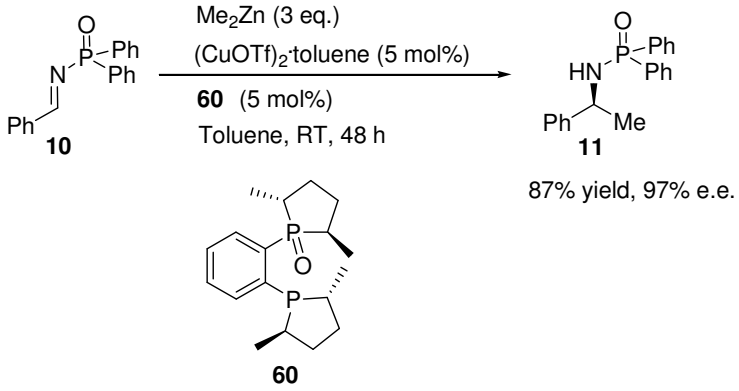
It can be suggested that this methylation of imines proceeds as follows (Scheme 6): the reaction of nickel acetylacetonate and triphenylphosphine in presence of trimethylaluminium gives rise to a Ni^0 catalytic species that will coordinate with the C=N bond. An excess of trimethylaluminium activates the imine by coordination to the nitrogen which enables a methyl transfer process from nickel. Finally, the Ni^0 catalytic species is released and the subsequent addition of acid affords the *N*-tosyl protected methylated amine.



Scheme 6: Proposed catalytic cycle for the 1,2-addition of $AlMe_3$ to *N*-tosyl protected benzaldimine.

1.3.2.2.2 Copper catalysed asymmetric methylation

The copper-catalysed addition of dialkylzinc reagents to electrophiles, which proceeds *via* an organocopper intermediate, is a well established process which has been used in many asymmetric processes such as conjugate addition[36,37] and nucleophilic addition reaction.[38] Charette *et al.*[39,40,41] have reported the copper-catalysed addition of diorganozinc reagents to *N*-phosphinoylarylimines. This reaction proceeds with high yields and enantioselectivities in the presence of a catalytic amount of (*R*,*R*)-Me-DuPHOS monoxide (BozPHOS) chiral ligand (Scheme 7).



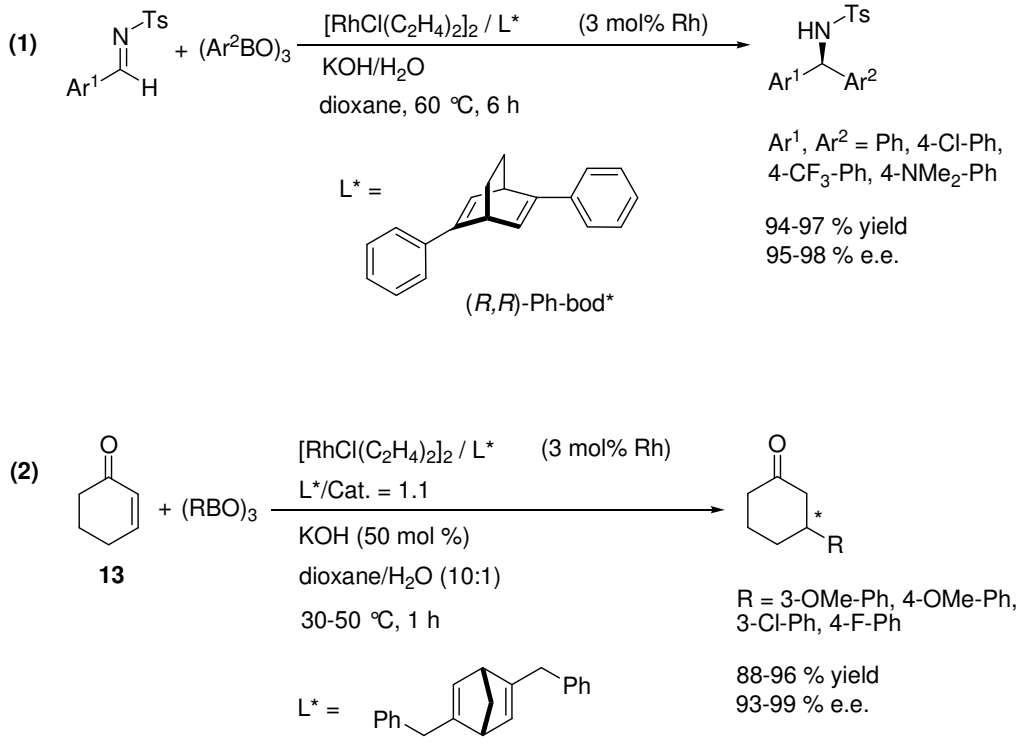
Scheme 7: Copper-catalysed methylation of *N*-phosphinoylbenzaldimine.

Although this transformation is highly efficient, it should be noted that it has two drawbacks that cannot be neglected: the high sensitivity of the Cu^{I} catalyst (which requires handling in a glove box) and a long reaction time (48 h).

1.3.2.2.3 Rhodium catalysed asymmetric methylation

The observation that rhodium complexes coordinated with chiral diene ligands are highly active and enantioselective catalysts for the asymmetric

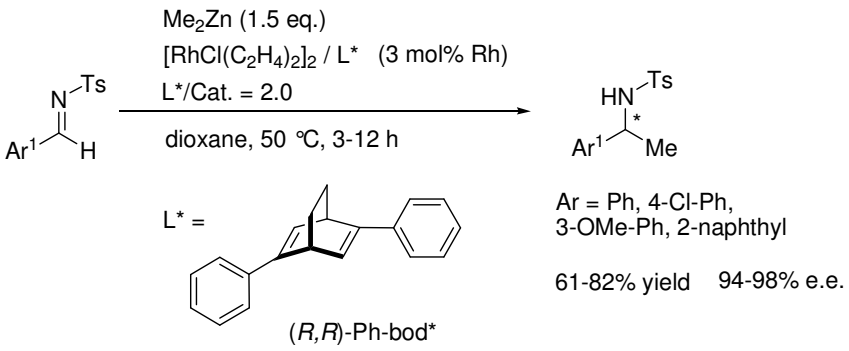
addition of arylboron reagents to imines[42,43] as well as to α,β-unsaturated carbonyl compounds[44] (Scheme 8), led Hayashi's group to conduct the first example of a rhodium-catalysed methyl-transfer reaction.



Scheme 8: Use of rhodium with chiral diene ligands in the asymmetric addition of aryl boroxines reported by Hayashi.

Indeed, as shown on Scheme 8, a range of arylboroxines (and/or boronic acids) can be successfully added to electrophiles such as *N*-tosyl protected aldmines (Equ. 1) and α,β-unsaturated enones (Equ. 2) in an enantioselective fashion. These transformations are catalysed by a chiral Rh(I) catalytic species formed by reaction of [RhCl*bis*(ethylene)] dimer with the appropriate chiral diene ligand. The reported conditions were then used by Hayashi to perform the addition of another type of nucleophile: dimethylzinc. It was found that under these conditions dimethylzinc was a better methylating

reagent than methylboronic acid. Therefore, in 2006, Hayashi *et al.*[45] reported the asymmetric addition of dimethylzinc to *N*-tosylarylamines catalysed by a chiral rhodium-diene complex, with high yield and enantioselectivity (Scheme 9).

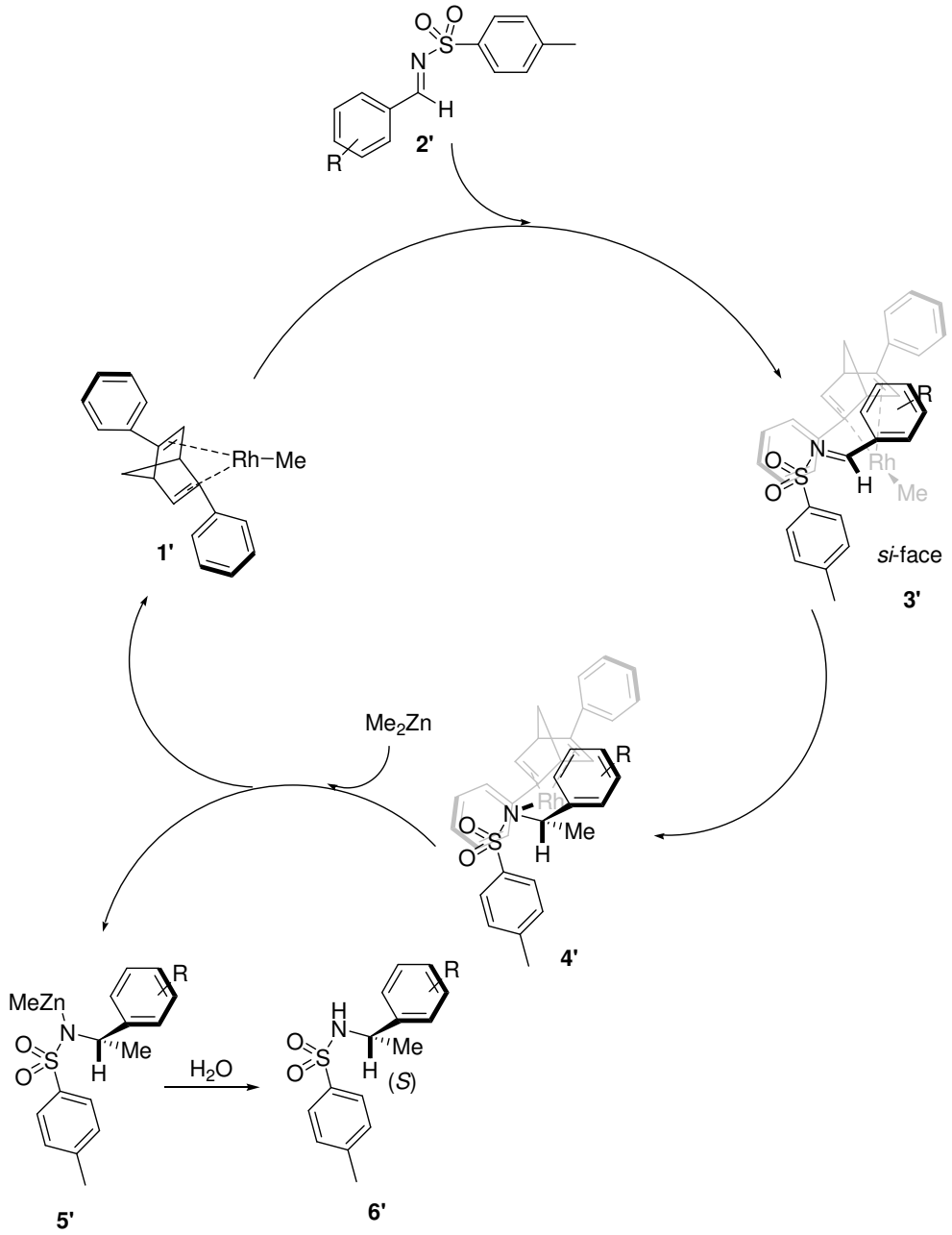


Scheme 9: Rhodium catalysed asymmetric methylation of aryl aldimines.

The methylation of several *N*-tosylarylimines having different substituents on the aromatic nuclei was perfomed; electron-withdrawing substituents such as chloro, fluoro, and trifluoromethyl groups, smoothly give the corresponding amines in high yields (83-84%) with high *e.e.* values (94-98% e.e.). On the other hand, in the reaction of imines with electron-donating substituents, a longer reaction time (6 h) is required to complete the reaction. The methylation of imines with an ortho substituent and 2-naphthylimine is sluggish, and the increase of the catalyst loading is needed to acquire the corresponding products sufficiently.

Regarding the reaction mechanism (Scheme 10), this rhodium-catalyzed methylation may proceed via a methylrhodium species which is formed by the reaction of [RhCl(diene)] with dimethylzinc. Methyl rhodium complexes such as $[RhMe(COD)]_2$ and [RhMe(COD)L] are known,[46,47] the former of

which is thermally unstable. Addition of the methylrhodium **1'** to the C=N bond of imine **2'** forms the aminorhodium species **4'**, which undergoes the σ-bond metathesis with Me_2Zn to regenerate the methylrhodium species **1'** and to produce the methylated product **5'** as a zinc amide.



Scheme 10: Mechanism of the Rh-catalysed Me_2Zn addition to *N*-tosyl protected aryl imines, suggested by Hayashi.

The existence of **4'** is supported by the evidence provided by Hartwig *et al.* [48] who reported the insertion of imines into an aryl-rhodium bond to form the resulting amido complex. The *S* configuration of the product **6'** obtained with (*R*,*R*)-Ph-Bod* is rationalized by the coordination of imine **2'** to a rhodium on its *si*-face, the coordination with the other face being much less favourable due to the steric repulsions caused by both of two phenyl groups on the diene ligand. This phenomenon is also observed in the arylation of imine catalysed by a very similar catalytic system.[49]

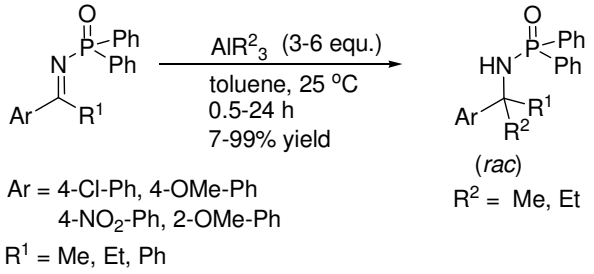
In spite of the high efficiency of this reaction, one should note that the choice of the tosyl fragment as a protecting group can be problematic. Indeed, the fact that it requires harsh conditions to be removed may cause significant side reactions. For example, within the framework of the investigation mentioned above, the reductive deprotections of phenyl(4-chlorophenyl)methylamine tosylamide were attempted with Li/NH_3 and SmI_2/HMPA. These reductions resulted in the formation of a significant amount of diphenylmethylamine, thus making the efficient access to the free amine difficult.

1.3.2.2.4 Other recent systems in literature

A) Addition of trialkyl aluminium reagents to *N*-phosphinoylketimine

A noteworthy example of synthesis of α-trisubstituted amines from ketimines and using trialkyl aluminium reagents was reported by Bräse in 2008.[50] In contrast to the well established 1,2-addition of organozinc reagents to aromatic ketones,[51] the application of ketimines as alkyl or aryl group acceptors under similar conditions has proved much more challenging. For

that reason, the conditions developed by Bräse (Scheme 11) are of great interest.

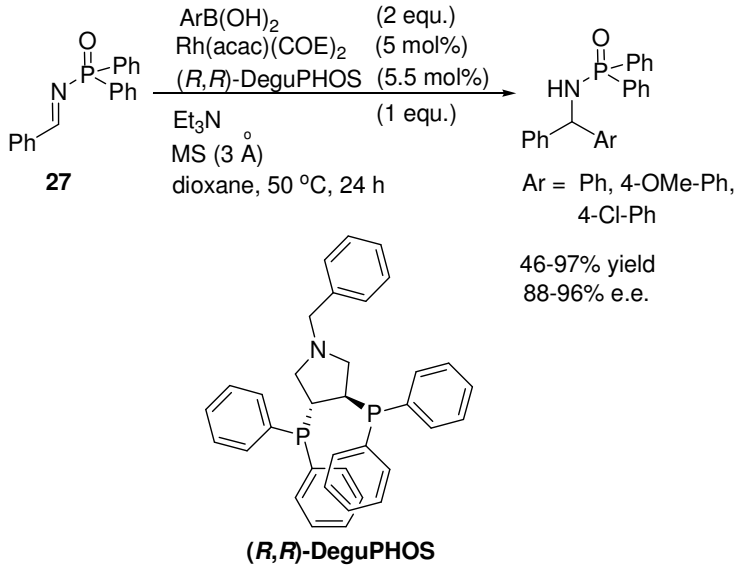


Scheme 11: Synthesis of *α*-trisubstituted by 1,2-addition to ketimines.

This reaction proceeds at room temperature without the use of any additional reagents and enables the preparation of the desired protected amine in excellent yields up to 99%. Furthermore, this procedure is adapted to a range of acetophenone- and benzophenone-derived ketimines as shown by the electron withdrawing and electron releasing group aryl substituents tolerated.

B) Addition of aryl groups to *N*-phosphinoylimines

Although arylboronic acids are poor nucleophiles, rhodium(I) phosphine complexes can efficiently catalyse their addition to *N*-arene sulfonyl imines.[52,53] Ellman *et al.*[54] reported a highly enantioselective addition of arylboronic acids to *N*-diphenylphosphinoyl imine (Scheme 12). While the deprotection of the *p*-toluenesulfonyl protecting group can be problematic and costly (e.g. use of SmI_2), the cleavage conditions of the diphenylphosphinoyl group are much easier[39,55] thus making it more desirable.

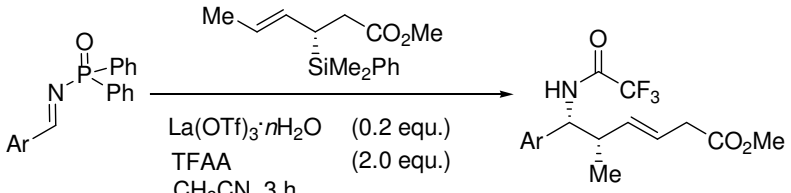


Scheme 12: Addition of aryl boronic acids to *N*-phosphinoylimines.

When the reaction is performed in presence of activated powdered MS 3Å and one equivalent of Et_3N (to prevent imine hydrolysis) the amine product could be obtained in good yield and good enantioselectivity. Furthermore, these reaction conditions with slight modifications could be applied successfully to alkylimines[56] which are known for being challenging substrates.

C) Direct allylation of *N*-phosphinoylimines

Methodologies used to carry out allylation of imines include the use of allyl boronates,[57] allyl stananes[58] and chiral silanes.[59] An interesting nucleophilic addition of allyl groups to *N*-phosphinylimines has been reported by Porco *et al*. (Scheme 13).[60]



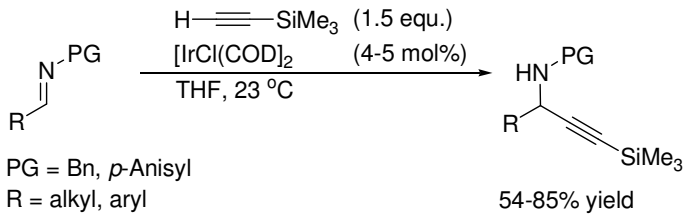
Ar	Yield (%)	dr	er
4-OMe-Ph	87	15:1	89:11
2-naphthyl	99	15:1	96:4

Scheme 13: Allylation of *N*-phosphinoylimines with organosilanes.

This reaction corresponds to the addition of a chiral organosilane by rare earth metal trilfate/trifluoroacetic anhydride activation and affords the trifluoroacetamide product. It should be noted that the resulting product of this reaction which is formed via an *in situ* derivatisation step was unexpected by the authors. A screening of different rare-earth metal triflates was carried out and led to the identification of $La(OTf)_3 \cdot nH_20$ as an efficient catalyst. Furthermore this reaction affords moderate to good yields and is tolerant towards a range of aryl substituents.

D) Direct addition of TMS-acetylene to aldimines

Carbanion addition to *N*-alkyl aldimines typically prescribes the use of Lewis acid additives (*i.e.* $BF_3 \cdot Et_2O$) as a means of activating the aldimine substrate. Moreover imine addition reactions typically require the use of stoichiometric quantities of alkali, alkaline earth, or transition metal carbanions, or alternatively organoboranes, -silanes, or -stannanes. In 2001, Carreira *et al.*[15] reported a novel process which was considerably simplified over previously documented C=N addition reactions, proceeding at room temperature and requiring only *N*-alkyl or *N*-aryl aldimines, trimethylsilylacetylene and catalytic amounts (4-5 mol%) of $[IrCl(COD)]_2$ (Scheme 14).



Scheme 14: Addition of TMS-acetylene to aldimines.

The main advantages of this process are the fact that the Ir(I) catalyst which is used is commercially available and that the reaction can be carried out in the absence of solvent thus providing for a highly atom-economical process.

E) Separation of racemates

Most of the chiral synthetic methods presented in this thesis focus on asymmetric synthesis; however, it should be noted that other chiral methods of synthesis can be utilised, notably the separation of racemates. The separation of racemates include a range of methods: classic resolution, resolution by direct recrystallisation and kinetic resolution.

Despite its "low technology" image, classical resolution via diastereoisomer crystallisation is widely used industrially and in particular furnishes a large proportion of optically active drugs which are not derived from natural products. In 1992, the examination of a representative group of optically active drugs[61] showed that 65% owed their optical activity to classical resolution. Classical resolution can be very useful provided there is suitable functionality in the molecule through which to form a diastereoisomer, and usually, access to both enantiomers. There are clearly many instances where resolution is both economically viable and the method of choice.[62,63]

Kinetic resolution was first discovered by Marckwald and McKenzie in 1899[64] in the esterification reaction of racemic mandelic acid. This process is

based on the difference of reaction rates of two enantiomers in a chemical reaction, thereby creating an excess of the less reactive enantiomer.

Finally, resolution by direct crystallisation is also an attractive method since auxiliairies and reagents other than solvent are not required. In simple terms, the principle of this method[65] depends on the occurence of some substances as crystalline conglomerates (racemic mixtures) rather than racemic compounds. Although in bulk a conglomerate is optically neutral, individual crystals contain only one enantiomer, whereas in a racemic compound individual crystals contain equal amounts of both enantiomers.

1.4 Methylating reagents

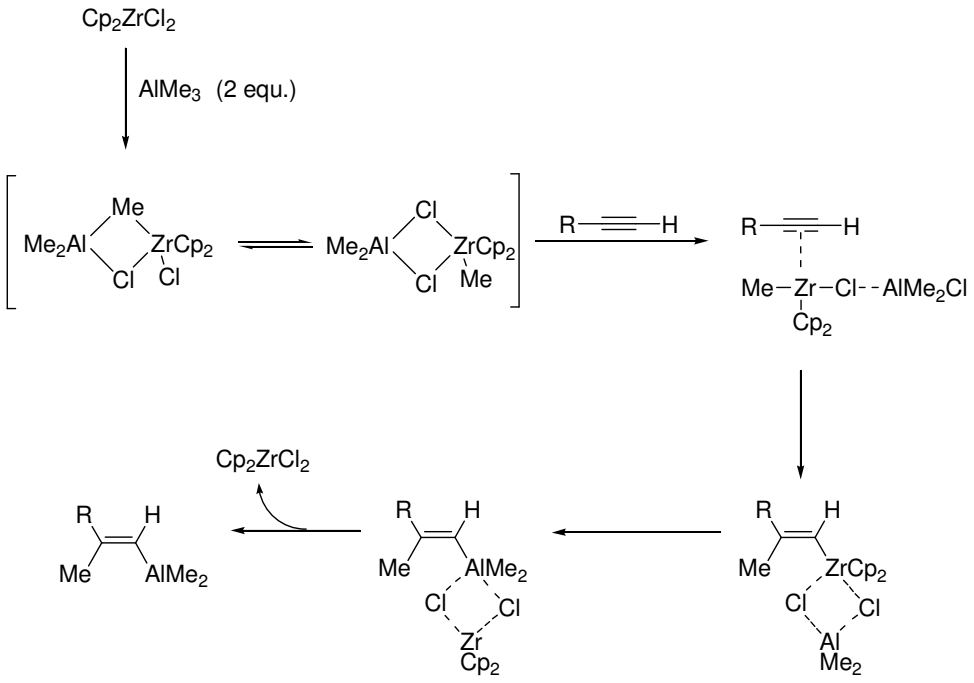
1.4.1 Organoaluminium compounds

Although known as a highly reactive species for more than a century, it is only since the 1950s that organoaluminium compounds have attained widespread use, triggered by the pioneering work of Karl Ziegler (Nobel prize laureate in 1963). Compared with the organometallic compounds of groups 1 and 2, aluminium organyls excel in the ease of their addition to alkenes and alkynes. The regio- and stereoselectivity of these carbaluminations, as well as of the related hydroaluminations with R_2AlH, are an additional asset. Organoaluminium compounds, which are derivatives of the cheapest of the active metals, may gradually substitute organolithium and organomagnesium compounds as more-economical reducing and alkylating agents.

1.4.1.1 $AlMe_3$ as a methylating reagent

1.4.1.1.1 Use and applications of $AlMe_3$

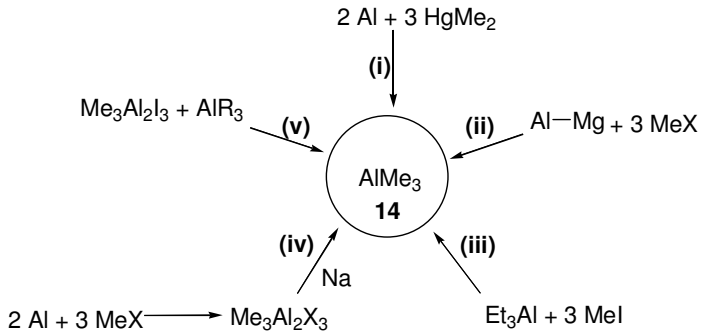
Trimethylaluminium (TMA) is a pyrophoric colourless liquid that is perhaps the most industrially important organoaluminium compound. It is mainly used for the production of methylaluminoxane, an activator for Ziegler-Natta catalysts for olefin polymerisation.[66,67] TMA is also employed as a methylation agent. Tebbe's reagent, which is used for the methylenation of esters and ketones, is prepared from TMA. TMA also forms a complex with the tertiary amine DABCO, which is safer to handle than TMA itself.[68] In combination with Cp_2ZrCl_2 (zirconocene dichloride), TMA participates in carboalumination reactions of alkynes to give vinyl aluminium species which are useful in organic synthesis in a reaction known as carbozirconation[69,70] (Scheme 15).



Scheme 15: Negishi zirconium-mediated carboalumination reaction.

1.4.1.1.2 Preparation

Alkylaluminium compounds were originally prepared on a laboratory scale by transmetallation of mercury compounds (Figure 3 - route i). Later on, many other methods were developed by different groups, some of which are reported in Figure 3.



Entry	Route	Conditions	Yield (%)
1[71]	(i)	/[a]	/[a]
2[72]	(ii)	30-170 °C, 30 h	70-80
3[73]	(iii)	92 °C, 18 h	95
4[74]	(iv)	X = Cl, autoclave, reflux, 25 h	63
5[75]	(v)	R = Et, 100 °C, 6.5 h	90
6[76]		R = Et : ultrasonic, RT, 2.5 h	86

(a) Not reported.

Figure 3: Preparations of trimethylaluminium reported for a laboratory scale.

As it can be seen, trimethylaluminium (and other trialkylaluminium reagents) can be prepared from either aluminium metal (routes i, iv) or other aluminium derivatives (routes ii, iii, v). Often, the ease of the reaction depends on the nature of the solvents and the method of the activation of the aluminium metal; the latter can be done by grinding aluminium with Et_3Al (to remove surface oxides) and/or by other means such as ultrasonic irradiation (route v) or addition of iodine. On an industrial scale, trimethylaluminium is prepared by the reaction of aluminium metal with chloromethane to give $Al_2Cl_2Me_4$, in a reaction commonly known as the Ziegler direct process. This intermediate

is then reduced with sodium and the product Al_2Me_6 is removed by fractional distillation (Scheme 16).

$$2\ Al + 6\ MeCl + 6\ Na \longrightarrow \underset{\mathbf{14}}{Al_2Me_6} + 6\ NaCl$$

Scheme 16: Industrial preparation of trimethylaluminium.

Triethylaluminium and higher alkyl compounds can be prepared from the metal, an appropriate alkene and hydrogen gas at elevated temperatures and pressures (Scheme 17). This route is relatively cost-effective and, as a result, these alkylaluminium compounds have found many commercial applications.

$$2\ Al + 3\ H_2 + 6\ CH_2{=}CH_2 \xrightarrow[10\text{-}20\ MPa]{60\text{-}110\ ^\circ C} \underset{\mathbf{15}}{Al_2(CH_2CH_3)_6}$$

Scheme 17: Preparation of higher alkyl aluminium compounds.

1.4.1.1.3 Structure and bonding

Steric factors have a powerful effect on the structures of alkylaluminiums. Where dimers are formed the long weak bridging bonds are easily broken. This tendency increases with the bulkiness of the ligand. The species $AlMe_3$ which features an aluminium atom bonded to three methyl groups can only be observed in the gas phase in an equilibrium with Al_2Me_6. As for the solid and solution states, the dimeric form is exclusive.

Alkylaluminium dimers are similar in structure to the analogous dimeric halides but the bonding is different. In the halides, the bridging Al-Cl-Al bonds are 2*c*,2*e* bonds (2-center-2-electron bonds); that is each Al-Cl bond

involves an electron pair. In the alkyl aluminium dimers the Al-C-Al bonds are longer than the terminal Al-C bonds (214 and 197 pm, respectively for $AlMe_3$[77]), which suggests that they are 3*c*,2*e* bonds, with one bonding pair shared across the Al-C-Al unit, somewhat analogous to the bonding in diborane, B_2H_6 (Figure 4).

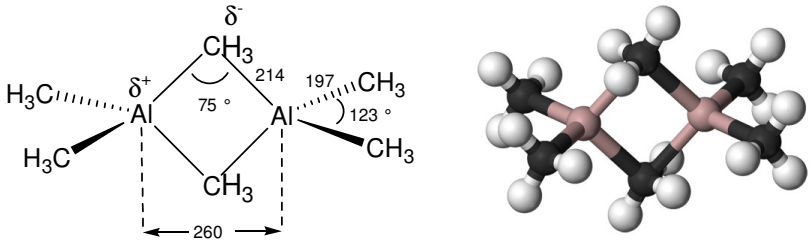


Figure 4: Structure of trimethylaluminium (distances in pm).

The Al-Al distance in Al_2Me_6 (260 pm) which has a 2*e*3*c* Al-C-Al bridge is significantly shorter than in Al_2Cl_6 (340 pm) which has a 2*e*2*c* Al-X-Al bridge. The short distance in Al_2Me_6 is indicative of a direct Al-Al interaction as this length only marginally surpasses the sum of the covalent radii of two Al atoms (2 × 126 ppm). In an extreme representation that involves an Al-Al σ bond, Al(sp^2) hybridization rather than Al(sp^3) is assumed[78] (Figure 5).

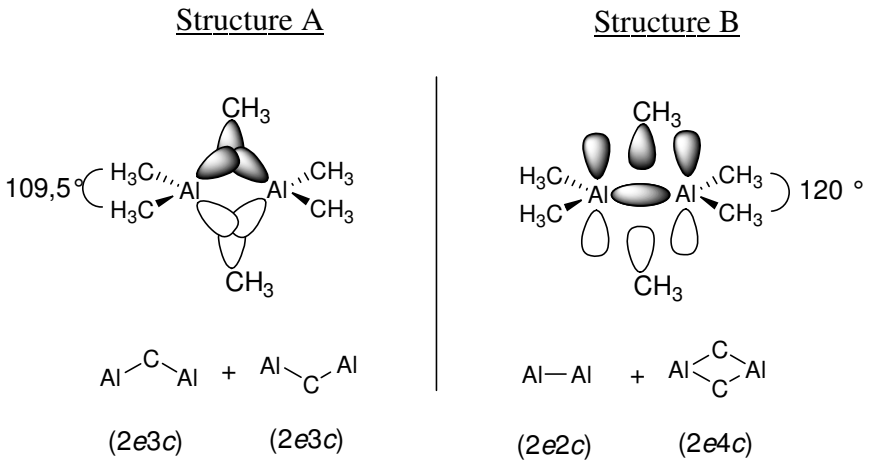


Figure 5: Extreme formulations of the dimeric structure of trimethylaluminium.

The case of structure A is in agreement with the considerable increase in the $C_{terminal}$-Al-$C_{terminal}$ angle beyond 109.5 °. The smaller bond angle Al-C_{bonded}-Al reflects a compromise between optimal orbital overlap and tolerable $Al^{\delta+}/Al^{\delta-}$ repulsion. The actual situation probably lies between the alternatives of structures A and B.

1.4.1.1.4 DABAL-trimethyl

Attempts to realise stabilised reagents derived from trimethylaluminium through the formation of Lewis acid/base pairs have been reported first by Schumann, Blum and co-workers.[79] Recently, it has been reported by Woodward[68] that a remarkably air-stable $AlMe_3$ adduct $(AlMe_3)_2$•DABCO, called DABAL-Me_3 (Figure 6), could be applied to the asymmetric methylation of aldehydes.

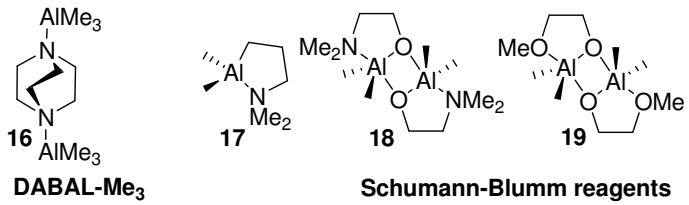


Figure 6: Intramolecularly stabilised alkylaluminium reagents.

DABAL-Me_3, which is now commercially available, can be readily prepared in one step from DABCO and neat $AlMe_3$. Although somewhat moisture sensitive it can be easily handled without the need for an inert atmosphere (unlike $AlMe_3$ which is pyrophoric). In comparison to the Schumann-Blumm reagents (**17**[80], **18**[81], **19**[82]) DABAL-Me_3 **16** is prepared directly from inexpensive, commercially available materials and is an extremely convenient source of carbanions.

1.4.2 Organozinc compounds

1.4.2.1 General features

Organozincs have been known since the preparation of diethylzinc by Frankland[83] in 1849 at Marburg (Germany). These organometallic reagents were often used to form new carbon-carbon bonds until in 1900 Grignard[84] discovered a convenient preparation of the equivalent organomagnesium compounds. These reagents were found to be more reactive species toward a broad range of electrophiles and afforded generally higher yields compared to organozincs. However, some reactions were still performed with zinc organometallics such as the Reformatsky reaction[85] and Simmons-Smith cyclopropanation.[86] The intermediate "organometallics" (a zinc enolate and a zinc carbenoid) were easier to handle and more selective than the corresponding magnesium organometallics. The functional-group tolerance of organozinc reagents[87] remained largely ignored by synthetic chemists and it only became clear in the 1980s that organozinc compounds are able to undergo a large range of transmetallations with transition metals due to the presence of empty low-lying *d*-orbitals leading to highly reactive intermediates. Thus, unreactive zinc reagents can produce highly reactive organometallic intermediates capable of reacting with many electrophiles that are otherwise unreactive toward organozincs. This behaviour can be explained by the presence of d-orbitals at the transition-metal center that makes a number of new reaction pathways available that were not accessible to the zinc precursors since the empty *d*-orbitals of zinc are too high in energy to participate to most organic reactions. It is the combination of the high tolerance of functionalities

of organozinc derivatives with a facile transmetallation to many transition metal complexes, which makes organozincs such valuable reagents.

1.4.2.2 Reactivity of organozinc reagents

There are three important classes of organozinc reagents: (i) organozinc halides of the general formula RZnX (ii) diorganozincs of the general formula R^1ZnR^2 in which R^1 and R^2 are two organic groups and (iii) zincates of the general formula $R^1(R^2)(R^3)$ZnMet in which the metal (Met) is usually Li or MgX. The reactivity of these zinc reagents increases with the excess of negative charge of the zinc center (Figure 9).

alkynyl < alkyl < alkenyl ≤ aryl < benzyl < allyl

$RZnX < R_2Zn < R_3ZnMgX < R_3ZnLi$

Figure 9: Reactivity order of zinc organometallics.

The high covalent degree of the carbon-zinc bond together with its low polarity leads to a moderate reactivity for these organometallics towards many electrophiles. Only reactive electrophiles react in the absence of a catalyst. In general, a direct reaction of organozincs with carbon electrophiles is not efficient and low yields are obtained. The addition of a catalyst is usually needed. The presence of empty *p*-orbitals at the zinc center facilitates transmetallations and a number of transition metal organometallics can be prepared in this way. These reagents can be highly reactive towards organic electrophiles since the low-lying *d*-orbitals are able to coordinate and activate many electrophilic reagents.

Because this thesis focuses mainly on diorganozincs only these will be considered in detail in the following introduction.

1.4.2.3 Dimethylzinc

Dimethyl- and diethylzinc were the first main group organometallic compounds to be synthesised and characterised; the events and deliberations leading up to their preparation by Frankland more than 150 years ago have recently (2001) been reviewed by Seyferth.[83] Dimethylzinc or "zincmethylium" as first named by Frankland, $Zn(CH_3)_2$ is a colourless liquid originally prepared by the action of methyl iodide on zinc (or zinc sodium alloy) at elevated temperature (Figure 7 - entry 1). Since the discovery of this process (1884), most of the literature procedures reporting in the synthesis of Me_2Zn rely mainly either on the same approach with slightly modified conditions (Entry 2) or on reacting zinc bromide (or chloride) with methyl organometallics (Entries 3-4). Both approaches work efficiently and afford the product often in very good yields.

$$Zn + MeX \xrightarrow{(i)} \underset{\mathbf{20}}{ZnMe_2} \xleftarrow{(ii)} ZnX_2 + MeY$$

Entry	Route	Conditions	Yield (%)
1[83,83]	(i)	X = I, 150-160 °C	/[a]
2[88]		X = halogens, DMF, 50-60 °C	90
3[89]	(ii)	X = Br, Y = halogens, Li, ultrasonic, toluene/THF, 0 °C, 10-20 min	100
4[90]		X = Cl, Y = Li, THF, RT, 5 min	100

(a) Not reported.

Figure 7: Selected preparations of dimethylzinc from the literature.

Regarding the structural data (Figure 8), [83,91,92] several studies of the vibrational spectrum of Me_2Zn have made it clear that the valence angle C-Zn-C is 180° and that the barrier to internal rotation is negligeable.[93] Additionaly, computational population analyses[94] indicate that the *3d* electrons of Zn must be regarded as non-bonding and the Zn-C bond as a pure σ-bond.

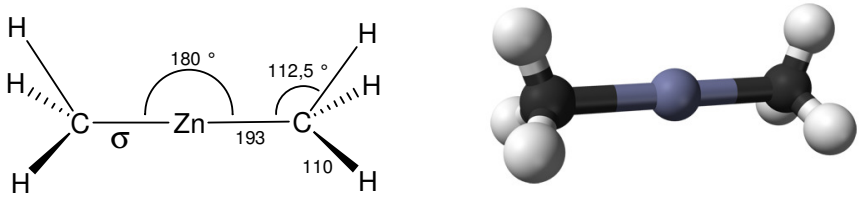


Figure 8: Structure of dimethylzinc (distances in pm).

Binary organozinc compounds such as Me_2Zn are monomeric. The molecules are linear and have low melting and boiling points. Whereas self-association through Zn-R-Zn 2*e*3*c* bridges is apparently disfavoured, Zn-H-Zn 2*e*3*c* bridges are formed readily. Dimethylzinc has been used for a long time to introduce methyl groups into organic molecules or to synthesise organometalic compounds where a very mild methylation source is required. The Grignard reagents MeMgX, which are easier to handle and less inflammable have, however, replaced dimethyl zinc in most of the laboratory synthesis.

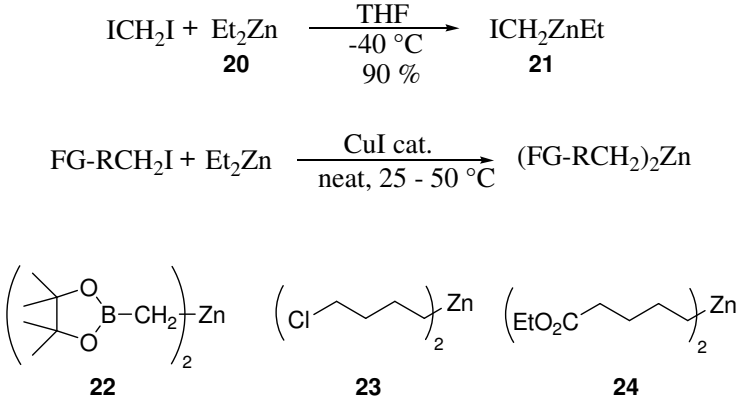
1.4.2.4 Preparation of diorganozincs

1.4.2.4.1 I/Zn exchange

Diorganozincs ZnR_2 are usually more reactive toward electrophiles than organozinc halides RZnX. However, a wide range of methods is available for the preparation of the latter, the oldest being the direct insertion of zinc to an alkyl halide (usually an alkyl iodide) leading to an alkylzinc intermediate that,

on distillation, provides the liquid diorganozinc (R_2Zn).[83,95] This method is applicable only to non-functionalized diorganozincs bearing lower alkyl chains (up to hexyl) due to the thermic instability of higher homologues.

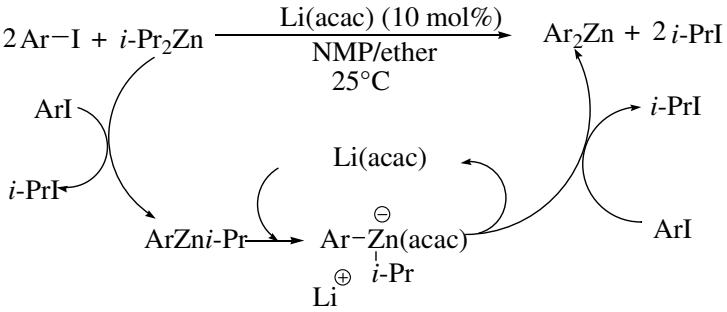
The I/Zn exchange reaction using Et_2Zn allows the preparation of a broad range of diorganozincs. The ease of the exchange reaction depends on the stability of the newly produced diorganozincs. Thus, diiodomethane smoothly reacts with Et_2Zn in THF at -40 °C providing the corresponding mixed ethyl(iodomethyl)zinc reagent with quantitative yield. The I/Zn exchange is catalysed by the addition of CuI (0.3 mol%). After the evaporation under vacuum of excess Et_2Zn and ethyl iodide formed during the reaction, the resulting diorganozincs are obtained in excellent yields (Scheme 18).[96]



Scheme 18: Diorganozincs obtained by I/Zn exchange.

A more reactive exchange reagent (*i*-Pr_2-Zn) can be used instead of Et_2Zn. This organometallic has to be free of salts if optically active diorganozincs need to be prepared. However, the presence of magnesium salts has a beneficial effect on the rate of exchange and a range of mixed zinc reagents of the type RZn(*i*-Pr) can be prepared under mild conditions.[97]

Since the isopropyl group is also transferred in the reaction with an electrophile at a comparable rate as the second R group, an excess of electrophile has to be added and tedious subsequent separations may be required. A more straightforward approach is possible for diarylzincs. In this case, the I/Zn exchange is catalysed by lithium salts and can be performed under very mild conditions (Scheme 19).[98]



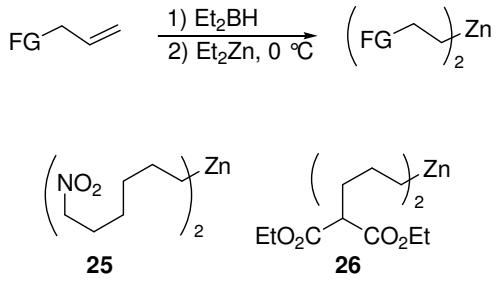
Scheme 19: Li(acac) catalysed synthesis of diarylzincs.

The intermediate formation of a zincate enhances the nucleophilic reactivity of the substituents attached to the central zinc atom and makes it more prone to undergo an iodine-zinc exchange reaction. Thus, the addition of catalytic amounts of Li(acac) to an aryl iodide and *i*-Pr_2Zn allows the transfer of the two *i*-Pr groups with the formation of Ar_2Zn and *i*-PrI (2 eq.). This method allows the preparation of highly functionalised diarylzinc reagents that undergo typical reactions of diorganozincs.

1.4.2.4.2 B/Zn exchange

Various organoboranes react with Et_2Zn or *i*-Pr_2Zn providing the corresponding diorganozinc. Pioneered by Zakharin and Okhlobystin[99] and Thiele and co-workers,[100] the method provides a general entry to a broad range of diorganozincs. Remarkably, functionalised alkenes bearing a nitro group or

an alkylidenemalonate function are readily hydroborated with Et_2BH prepared *in situ* and converted to diorganozinc reagents (Scheme 20).

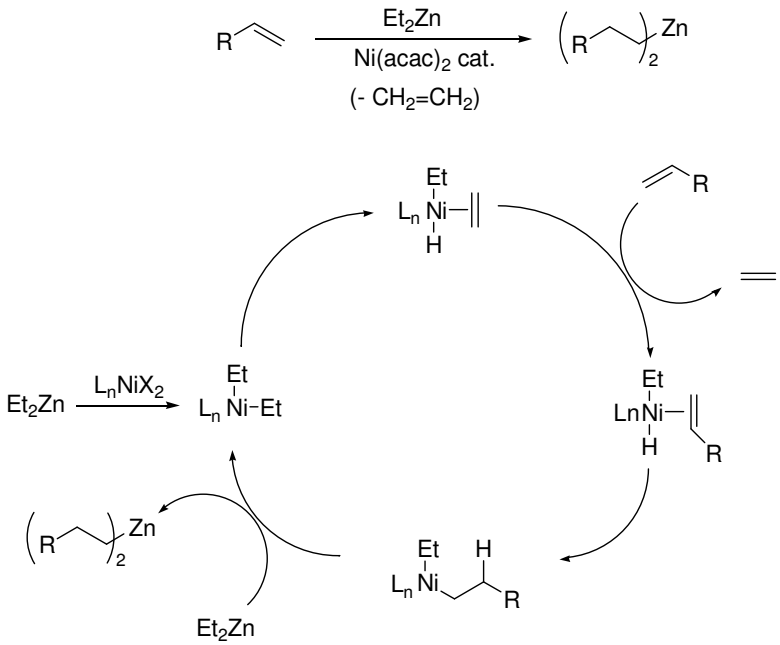


Scheme 20: Preparation of functionalized diorganozincs using B/Zn exchange.

The exchange reaction proceeds usually under mild conditions and tolerates a wide range of functional groups. It is applicable to the preparation of allylic and benzylic diorganozincs as well as secondary and primary dialkylzincs[101] and dialkenylzincs.[102]

1.4.2.4.3 Hydrozincation of alkenes

Diorganozincs can also be prepared by a nickel-catalysed hydrozincation. The reaction of Et_2Zn with $Ni(acac)_2$ may produce a nickel hydride that adds to an alkene leading after transmetallation with Et_2Zn, to a dialkylzinc. This reaction proceeds in the absence of solvent and at temperatures between 50-60 °C. A number of functionalised olefins, like allylic alcohols or amines can be directly used. They afford the expected products in 60-75% yield (Scheme 21).[103]



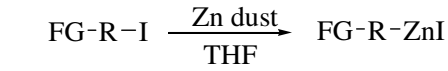
Scheme 21: Ni-catalysed hydrozincation of alkenes.

This method is especially well suited for the preparation of functionalised diorganozincs for the asymmetric addition to aldehydes.

1.4.2.5 Preparation of organozinc halides

The reactivity of organozinc halides strongly depends on the electronegativity of the carbon attached to zinc and on the aggregation of the zinc reagent. A stabilisation of the negative carbanionic charge by inductive or mesomeric effect leads to a more ionic carbon-zinc bond and to a higher reactivity.

The oxidative addition of zinc dust to functionalised organic halides allows the preparation of a broad range of polyfunctional organozinc iodides (Scheme 22).



FG = CO_2R, CN, halide, $(RCO)_2N$, $(TMS)_2N$, RNH, NH_2, RCONH, $(RO)_3Si$, $(RO)_2PO$, RS, RSO, RSO_2, PhCOS

Scheme 22: Functionalised organozinc compounds prepared by oxidative addition.

As a general rule, both the nature of the zinc and its activation are important. Finely cut zinc foil or zinc dust can be used. Zinc slowly oxidises in air and is covered by an oxide layer. Its activation which is of great importance is done by removing the oxide layer via chemical methods.[104]

1.5 Aims and objectives

The aim of the research project presented herein is to develop a new enantioselective catalytic system for the 1,2-addition of alkyl nucleophiles to aldimines. The methyl group was chosen as the first nucleophile to be tested, therefore trimethylaluminium and dimethylzinc were used as primary alkylating agents. Even though a few processes have already been reported in the literature in this field, they present some shortcomings, thus allowing room for better systems to be developed. Unlike Charette's[39,40,41] and Hayashi's[44] metal-catalysed Me_2Zn addition reactions, we aimed to identify a novel reaction that would ideally fulfill the following criteria: relatively short reaction time, commercial availability of all reagents including ligand and catalyst, easy handling of the ligand and catalyst under air.

Since no antecedent of this type of imine chemisty existed within the laboratory, we embarked on this totally new project based exclusively on

literature reports. Consequently, modern high throughput screening was an essential tool that we aimed to take advantage of to identify leads.

The ultimate goal of the development of this methodology is to expand the newly discovered methylation system in hand by further elaboration to useful targets such as biologically active molecules or their precursors.

Chapter II

Synthesis of substrates

2.1 Synthesis of the substrates

At the project's inception five benzaldimines with different steric and electronic properties were synthesised in order to observe the effect of the nature of the protecting group on potential imine alkylation reactions. Thus, various protecting groups such as the diphenylphosphinoyl, the tosyl and the *tert*-butyl carbamate as electron withdrawing groups, the benzyl as an aliphatic group, and finally the anisyl as a coordinating group, have been used in imine methylation reactions (Figure 10).

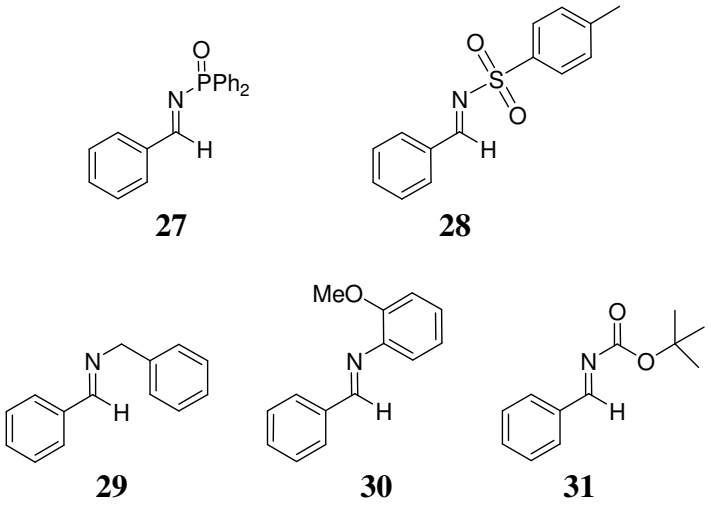


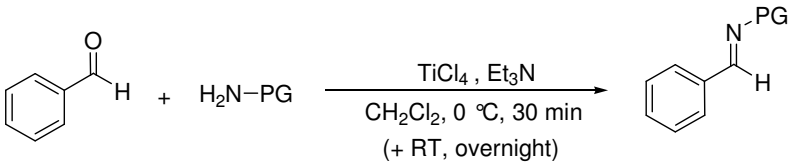
Figure 10: Synthesised imines used as substrates.

The synthesis of benzylidene *N*-tosylimine **28** was achieved by condensation of benzaldehyde and the corresponding amine, in presence of trifluoroacetic anhydride in refluxing CH_2Cl_2[105] or by using a Dean-Stark trap with refluxing toluene.[106] On the other hand, a third method involving the use of the Lewis acid $TiCl_4$ in a basic solution of triethylamine in CH_2Cl_2 at room temperature

afforded the *N*-tosylimine with a good yield (71%) in a single step. Likewise, imines **27**, **29** and **30** were synthesised using the same method.

Dropwise addition of $TiCl_4$ to a solution of triethylamine, benzaldehyde and the corresponding amine in CH_2Cl_2 at 0 ºC, provided imines **27-30** in 71-89% yield (Table 2). All the amines used in the synthesis were commercially available.

Table 2: Synthesis of benzaldimines.



Entry	Imine	PG (protecting group)	Yield (%)[a]
1	**27**[169]	$POPh_2$	71
2	**28**[107]	SO_2-Tol	71[b]
3	**29**[162]	CH_2-C_6H_5[c]	89[d]
4	**30**[107]	2-OMe-C_6H_4	85[d]

(a) Isolated yield. Purified by flash chromatography on silica gel.
(b) Yield valid when purification is carried out on a 3 mmol scale.
(c) Synthesis of this imine under simpler conditions (CH_2Cl_2, molecular sieves, RT, overnight) afforded the product with the same yield.
(d) No purification required.

The mechanism of formation of these imines is quite simple (Figure 11). After activation of the aldehyde by titanium (IV) chloride (Lewis acid), attack of the amine at the carbonyl occurs. Proton transfer generates an oxonium ion that can eliminate to give the iminium cation which can be quenched to lead to the desired imine.

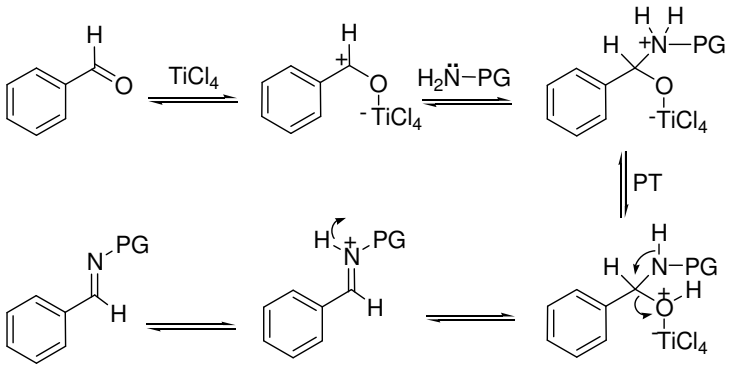
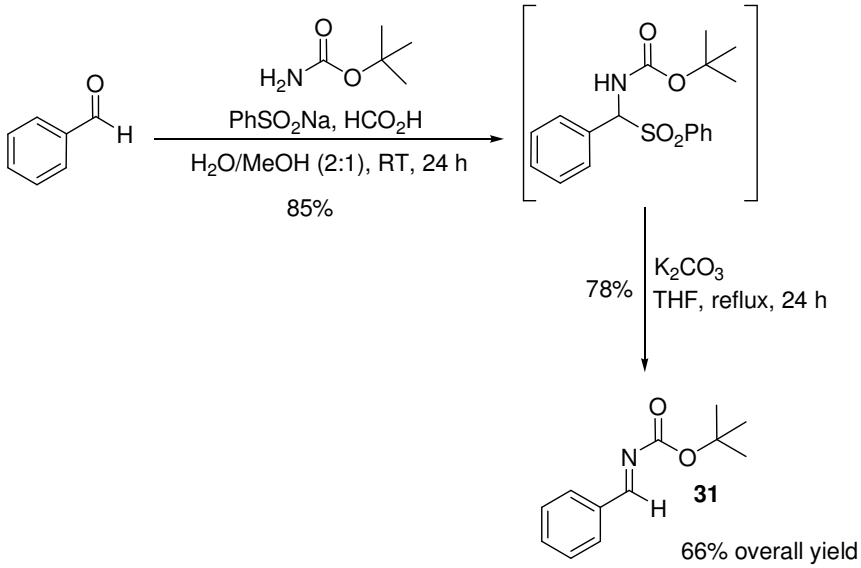


Figure 11: Mechanism for the formation of benzaldimines promoted by $TiCl_4$.

As illustrated in the mechanism, the presence of titanium chloride is crucial for the success of the reaction since it compensates the lack of nucleophilicity of the amide. However, since the benzylidene *N*-benzylamine (Entry 3) is rather nucleophilic, it was possible to synthesise **29** with a more convenient route involving only the use of dichloromethane and molecular sieves at room temperature, with an identical yield (89%). Finally, *tert*-butyl benzylidenecarbamate **31** was synthesised in a completely different way.[108] Synthesis of **31** (Scheme 23) was achieved in two steps *via* a sulfone intermediate. In the first step, benzaldehyde, *tert*-butylcarbamate and sodium benzenesulfinate react together with formic acid to generate the corresponding sulfone. Treatment of the crude sulfone with the weak base K_2CO_3 in refluxing THF afforded the pure imine with a 66% overall yield.

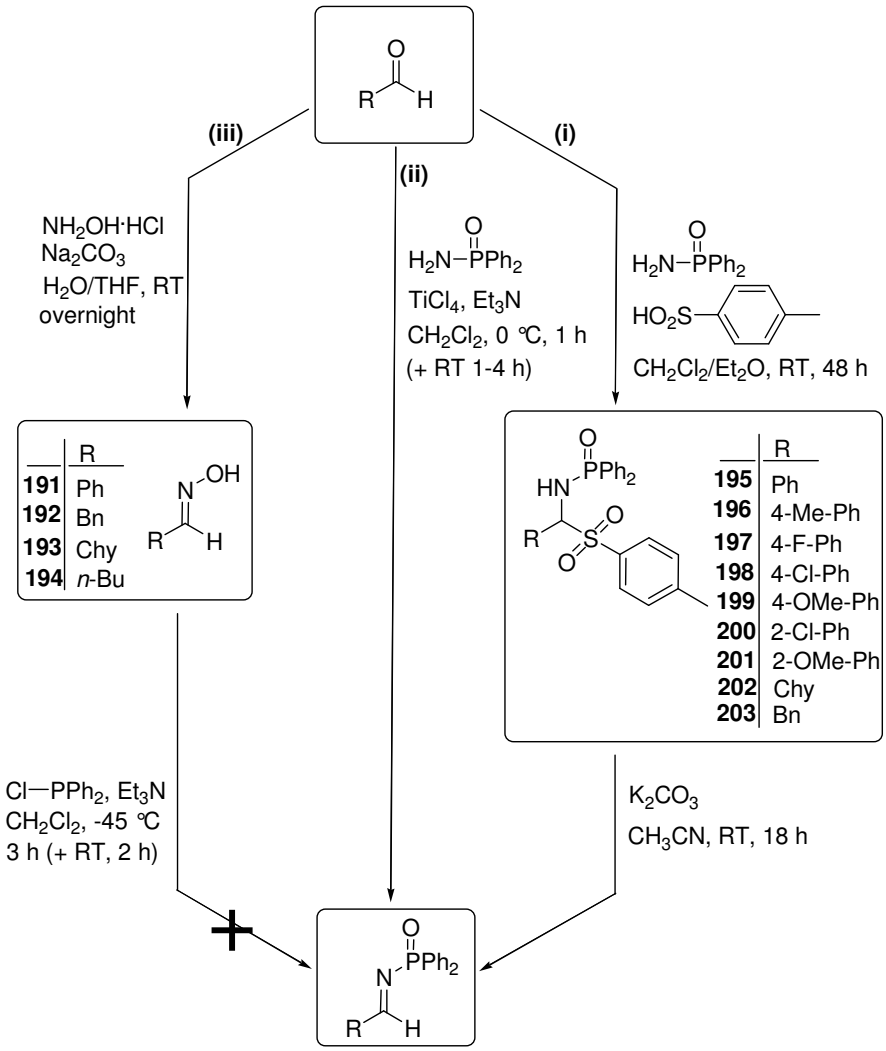


Scheme 23: Synthesis of *tert*-butyl benzylidenecarbamate.

The need to use a sulfone as an intermediate can probably be explained by the instability of product **31** in the presence of acids and strong Lewis acids. Precipitation of the insoluble SO_2Ph adduct provides an alternative driving force.

2.2 Synthetic routes of access to diphenylphosphinoyl protected imines

During the course of our investigation, the most useful protecting group turned out to be the diphenylphosphinoyl group (*cf* 4.2). Therefore, we investigated other ways of preparing diphenylphosphinoyl protected aldimines, in the most efficient and convenient way possible. An overview of the literature enabled us to distinguish three main synthetic routes (Scheme 24), including one we already used, all using an aldehyde as a starting material.



Scheme 24: Synthetic routes for the preparation of diphenylphosphinoyl protected aldimines.

The first route (Equ. i)[109,39] consisted in forming a sulfonyl adduct of the amine, by reacting the aldehyde with toluenesulfinic acid and diphenylphosphinic amide at room temperature. The resulting adduct can then be deprotected with a base such as potassium carbonate to afford the desired imine. Although this method may seem attractive, it should be noted that long reaction times are required (3 days in total to achieve the crude imine). Furthermore, in our hands the isolation of the sulfonyl adduct intermediate turned out to be problematic and this method was deemed not viable for future

syntheses. The second route (Equ. ii),[169] the titanium (IV) chloride promoted condensation between the aldehyde and diphenylphosphinic amide, in the presence of triethylamine (traps the free HCl in the reaction mixture) afforded the desired imine in 21-88% yield. Finally, a third method (Equ. iii)[110] which consists in making an oxime intermediate (in quantitative yield) that subsequently undergoes a reaction with chlorodiphenylphosphine at a low temperature (-45 °C) in CH_2Cl_2, reportedly affords the desired imine. However, the second step involving the introduction of the phosphorus containing group turned out to be impossible to achieve in our hands. The reasons for this are not clear since other groups have used this route. It should be noted that the primary literature suggests the involvement of a radical mechanism in that step and also reports occasional unexplained failures of the reaction, thus demonstrating the high sensitivity of the reaction conditions. A low temperature ^{31}P NMR investigation in deuterated dichloromethane was carried out in an attempt to get a better understanding of the reaction but this did not prove helpful. Indeed, it was found that the reaction between the oxime and chlorodiphenylphosphine occurred instantly to generate a substantial range of peaks in the ^{31}P NMR spectrum and in a wide range of chemical shifts. No evolution could be observed at all in the ^{31}P NMR spectrum even after several hours of reaction. The particular asset of that method is that it could potentially give access to aliphatic imines, which are challenging substrates since they are enolisable compounds.

We eventually opted for the initial $TiCl_4$ promoted condensation (Equ. ii) because of the simple conditions required: single step synthesis, short reaction time and simple purification (filtration through Celite + flash chromatography). One major advantage of this synthesis is the fact that both of the starting materials are commercially available. However, as the price of diphenylphosphinic amide is quite high (5 g for £100 from Sigma Aldrich) we thought it was necessary to prepare this compound in the laboratory. It can be synthesised by reacting diphenylphosphinic chloride (5 g for £8 from Sigma Aldrich) with liquid ammonia[169] in CH_2Cl_2 (-78 °C to RT, overnight) to give rise to the precipitation of a white crystalline solid (92% yield) that was used without further purification for the synthesis of **27**. Interestingly, no report in the literature was found for a version of this reaction using the safer standard aqueous ammonia solution instead of liquid ammonia which requires cautious handling because of the hazard known for this chemical (corrosive and extremely irritating). Consequently, we ran the reaction using aqueous ammonia at room temperature for two hours and were very pleased to see that it was as efficient as liquid ammonia at -78 °C to afford diphenylphosphinic amide with an identical yield.

While using the $TiCl_4$ promoted condensation method, we were also pleased to find that a simple scale-up of the reaction could increase the chemical yield (Figure 12). For instance, in the synthesis of **27** the initial 71% yield (Table 2 – entry 1) could be increased to 88% (Figure 12) by scaling up the reaction by a factor of two.

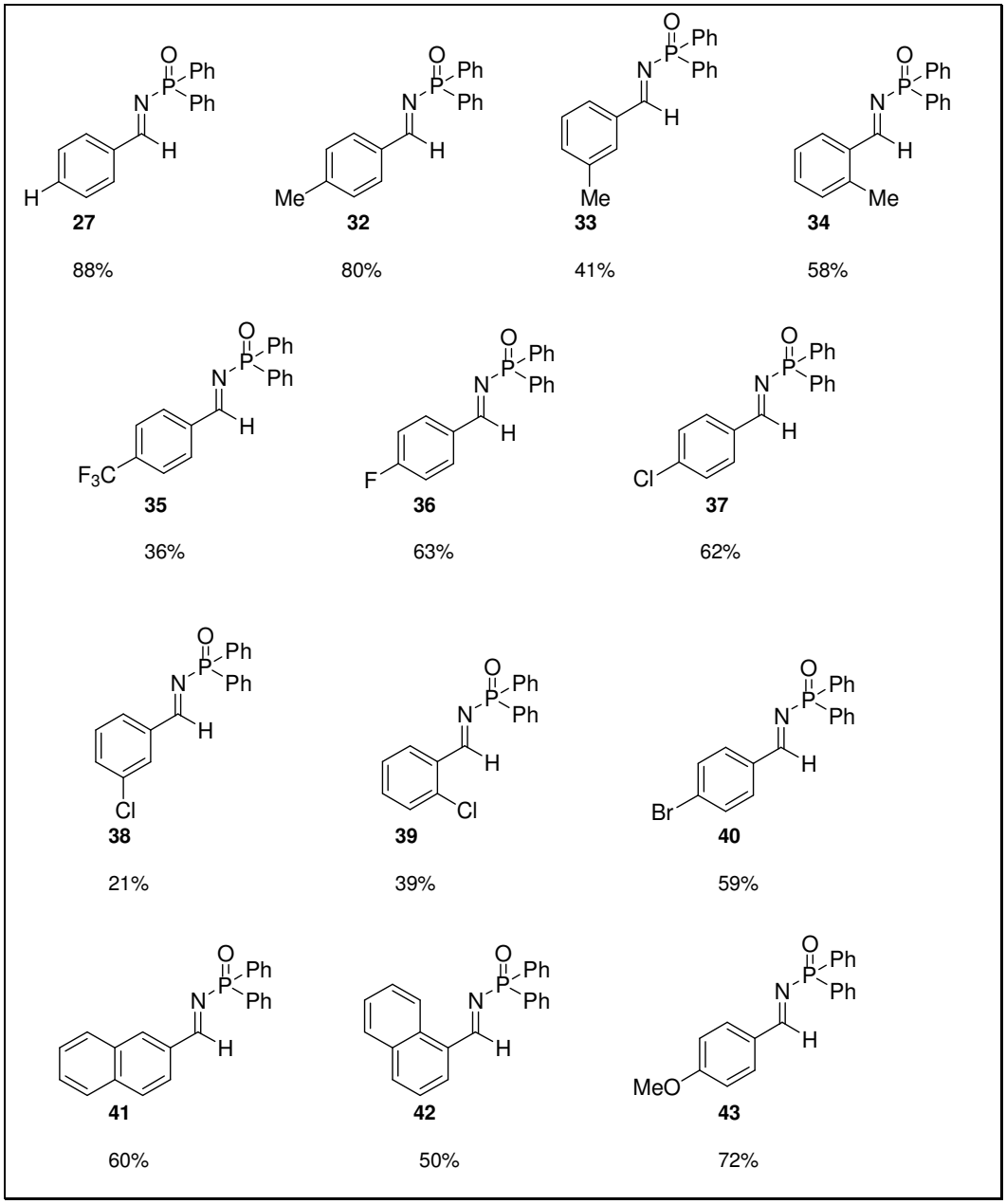


Figure 12: Range of diphenylphosphinoyl protected aryl imines prepared in 21-88% isolated yield.

A wide range of substrates with aryl substituents was prepared. The chemical yield of their synthesis is quite variable (21-88%) depending on the hydrolytic stability of the imine which is obtained. Therefore, one of the least stable imine turned out to be imine **38** bearing the *m*-chlorophenyl substituent while one of the most stable was imine **27**. From a practical point of view, each of these

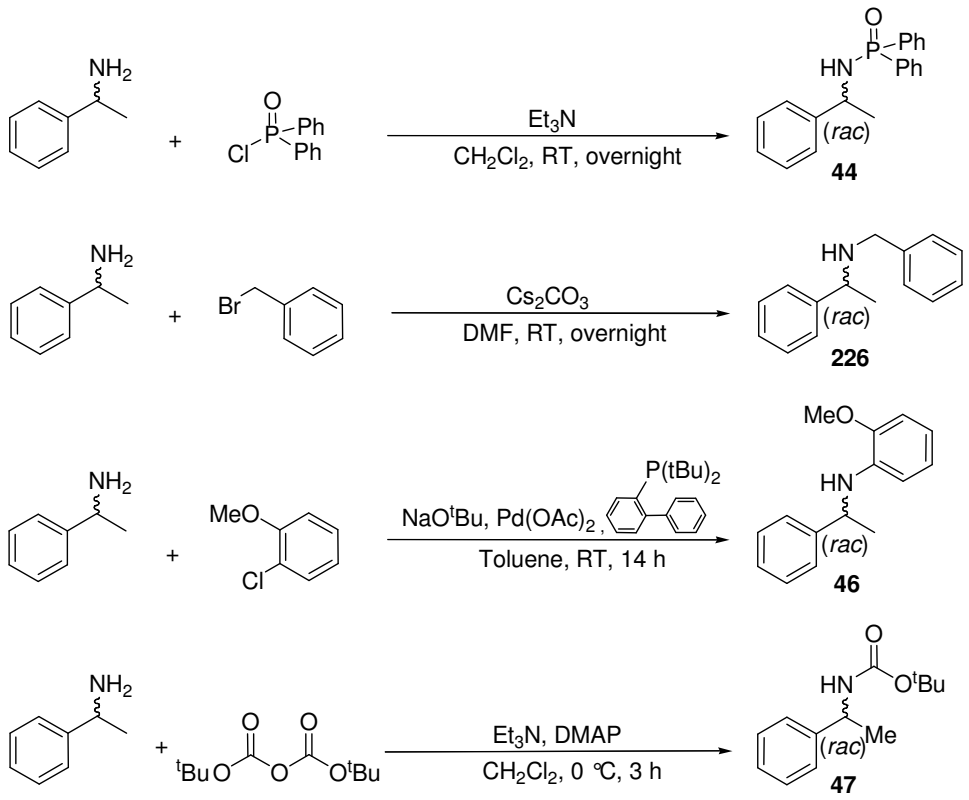
imines could be stored for several weeks under an inert atmosphere, at room temperature and in the absence of light, without any significant hydrolysis.

Chapter III

Measurement of the enantiomeric excess

3.1 Synthesis of the racemates

In order to gather the data of the imine methyl addition compounds (for future *e.e.* assays), it was required first of all to synthesise the racemates. These can be prepared in two different ways. The first method consists in reacting (±)-α-methylbenzylamine with a suitable electrophile introducing the protecting group on the nitrogen (Scheme 25).

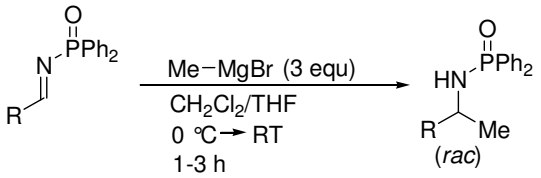


Scheme 25: Synthesis of the racemates.

In the case of amines **44** and **45**, simple basic conditions were required. In the case of **46** in which the halide is an aryl halide, use of the chemistry of Buchwald[111] was necessary to afford the amine. Finally, **47** was prepared by simply using Boc anhydride (di-*tert*-butyl dicarbonate) in a basic solution of a mixture Et_3N/DMAP in dichloromethane.

The second method of preparation of these racemates consisted in reacting the imine with MeMgBr thus reducing the aldimine into an α-methylated amine (Table 3).

Table 3: Synthesis of racemates using methyl Grignard reagent.



Entry	R	Product	Yield (%)
1	Ph	**44**	92
2	4-Me-Ph	**48**	83
3	3-Me-Ph	**49**	98
4	2-Me-Ph	**50**	93
5	4-Cl-Ph	**51**	96
6	4-Ph-CF_3	**52**	89
7	4-F-Ph	**53**	93
8	4-Cl-Ph	**54**	96
9	4-CF_3-Ph	**55**	91
10	3-Cl-Ph	**56**	94
11	2-Cl-Ph	**57**	91
12	4-Br-Ph	**58**	87
13	4-OMe-Ph	**59**	94
14	2-naphthyl	**60**	92
15	1-naphthyl	**61**	90

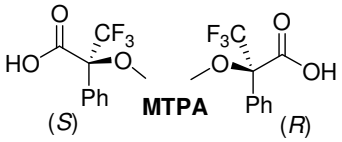
Unlike the first method, this second method can be generalised and used with any aromatic aldimine. The reaction is run in THF and a minimum amount of dichloromethane to solubilise the imine. In addition to being an inexpensive nucleophile, the high reactivity of methyl Grignard reduces substantially the reaction time. Therefore the reaction conditions make this method very attractive for its simplicity and cost-effectiveness.

3.2 Measurement of the enantiomeric excess

3.2.1 Phosphorus NMR assay

The most time consuming aspect of (L*)M promoted asymmetric catalysis is often the identification of an optimal ligand. High throughput screening where the *e.e.* value of a large number of reactions can be determined quickly is highly desirable. Various methods are available to determine the *e.e.* values of chiral molecules, including chiroptical, spectroscopic and chromatographic techniques, each finding preference in certain circumstances. It was quickly realised that measurement of the *e.e.* of **44** using HPLC was quite time consuming, partly because of the non-availability of an autosampler in our HPLC unit. An alternative to HPLC could be the use of G.C. (which was available locally with an autosampler) but the high molecular weight of the diphenylphosphinoyl group could not make GC viable.

It was decided that the use of chiral shift reagents in NMR spectroscopy could be a solution to these difficulties. Indeed, although enantiomers cannot be distinguished in NMR spectroscopy in an achiral medium, since the resonances of enantiotopic nuclei are isochronous, chiral shift reagents may be able to form complexes that can be distinguished because their resonances are anisochronous. Of the several types of NMR experiment available to assay enantiopurity, chiral derivatisation relies upon conversion of substrate enantiomers to diastereomers upon interaction with a chiral probe compound. For example, Mosher's acid[112] - MTPA (α-methoxytrifluorophenylacetic acid) is one of the most commonly used (Scheme 26).



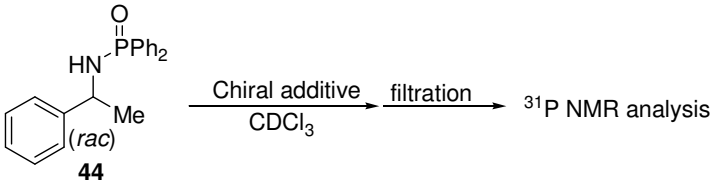
Scheme 26: α-methoxytrifluorophenylacetic acid commonly known as Mosher's acid.

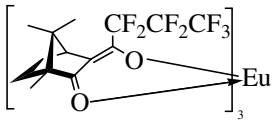
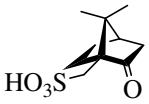
However, any derivatisation for NMR assay would entail a deprotection step of the diphenylphosphinoyl group to get the free amine. Such lengthy procedures would then favour the use of GC instead of NMR (GC often gives a better resolution than NMR). Consequently the use of NMR could be advantageous if, and only if, a direct determination of the *e.e.* value carried out in a single step could be done. Chiral lanthanide NMR probes[113,114] such as Yb(III) and Eu(III) *β*-diketonate complexes are well known organic chiral chelates that have the ability to form diasteromeric complexes that induce variations of the chemical shifts of different enantiomers. These reagents function by acting as Lewis acids, forming a complex with the substance under analysis, which acts as a nucleophile. Induced shifts with this type of complexes are attributed to a pseudo-contact or dipolar interaction between the reagent and the nucleophile.

We undertook a study in which different chiral additives were tested with the hope of finding one that could enable us to determine the *e.e.* by NMR spectroscopy. The fact that imine **27** could be detected by ^{31}P NMR spectroscopy, pushed us into making use of this feature to our advantage. ^{31}P NMR offered a larger range of resonance than ^{1}H and greater sensitivity than ^{13}C making the probability of finding an observable and measurable difference of chemical shifts between the *R* and the *S* enantiomers higher. Four chiral additives were tested in $CDCl_3$ (Table 4): *L*-(+)-tartaric acid, *D*-(-)-tartaric acid,

Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] and (1*S*)-10-camphorsulfonic acid.

Table 4: Testing of various chiral additives in ^{31}P NMR spectroscopy.



Entry	Chiral additive	Observation in ^{31}P NMR
1	L-(+)-tartaric acid	none
2	D-(-)-tartaric acid	none
3	Europium chelate complex 	none
4	(1*S*)-10-camphorsulfonic acid 	**split**

We found that neither tartaric acid (which has a very poor solubility in $CDCl_3$) nor the Eu chiral complex, had an effect on the amide ^{31}P NMR signals of **44**. However, we were pleased to see that camphorsulfonic acid (Figure 13) which has better solubility, was able to split the amide ^{31}P NMR signal, thus allowing direct determination of the *e.e.* of **44**. Indeed, in the ^{31}P NMR spectrum, under normal circumstances, both the *R* and the *S* enantiomers have the same chemical shift and appear as a singlet. By addition of a sufficient amount of (1*S*)-10-camphorsulfonic acid to the amine (beforehand dissolved in $CDCl_3$) followed by a filtration, analysis of the sample by ^{31}P NMR showed the amide under the form of two signals corresponding to the two enantiomers (Figure 13).

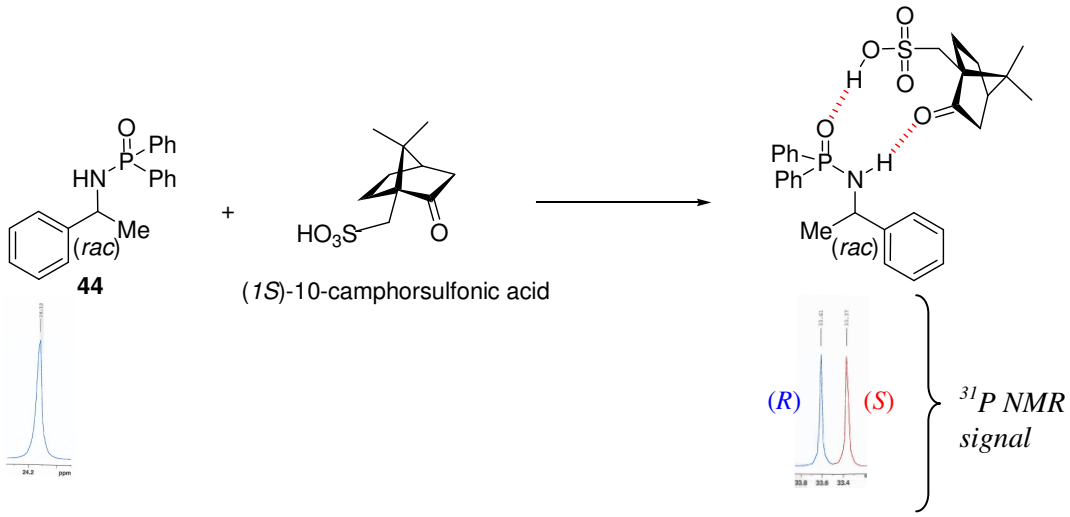


Figure 13: (1*S*)-10-camphorsulfonic acid used as a chiral shift reagent in ^{31}P NMR spectroscopy.

Although the cause of the split of the NMR signal has not been entirely delineated, we suggest that the complexation of the amide with the acid is due to a hydrogen bonding interaction ($P{=}O_{amide}$---HO_3S_{acid} and NH_{amide}---$O{=}C_{acid}$). An optimisation of the quantity of acid required was carried out on a racemic sample (Figure 14).

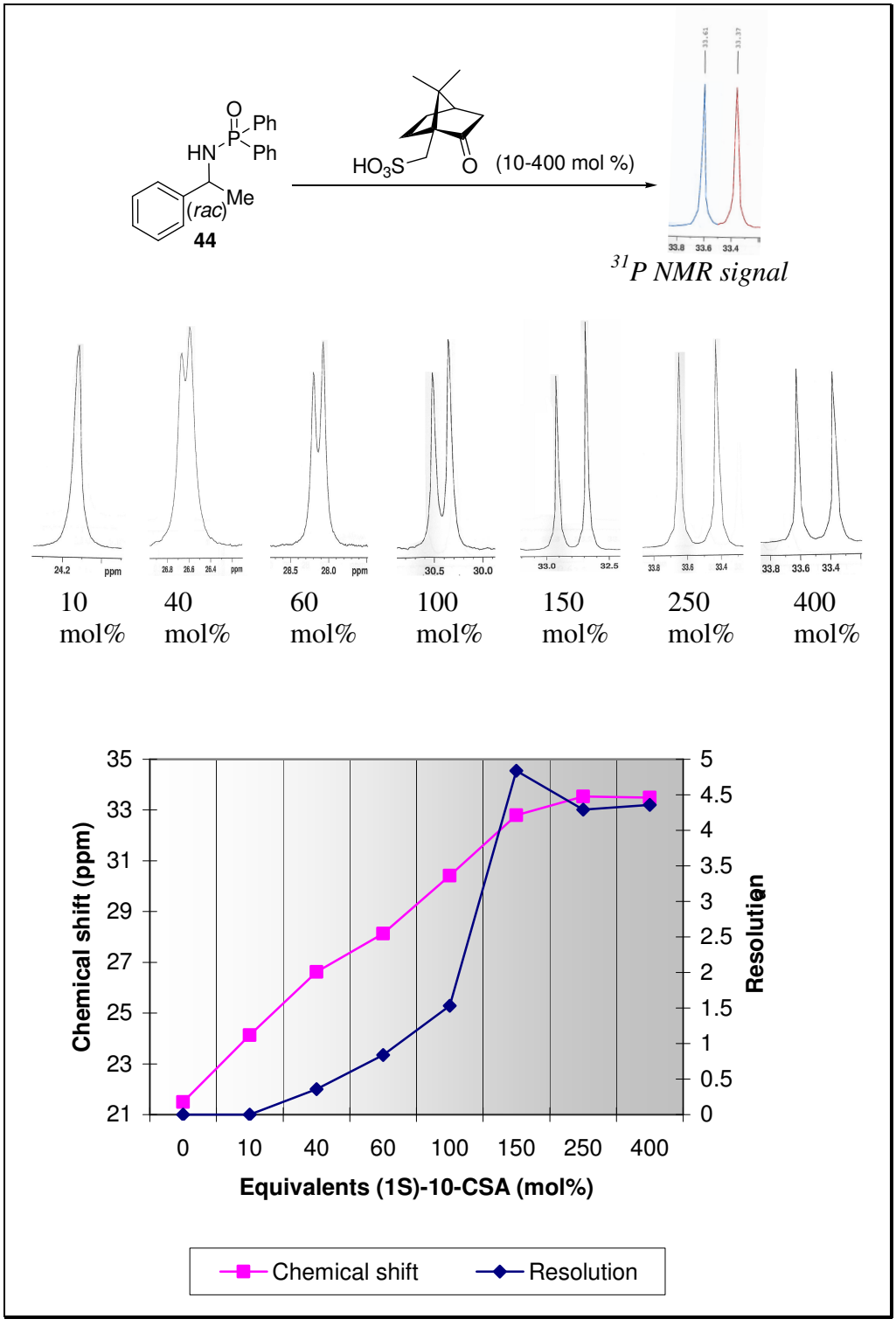
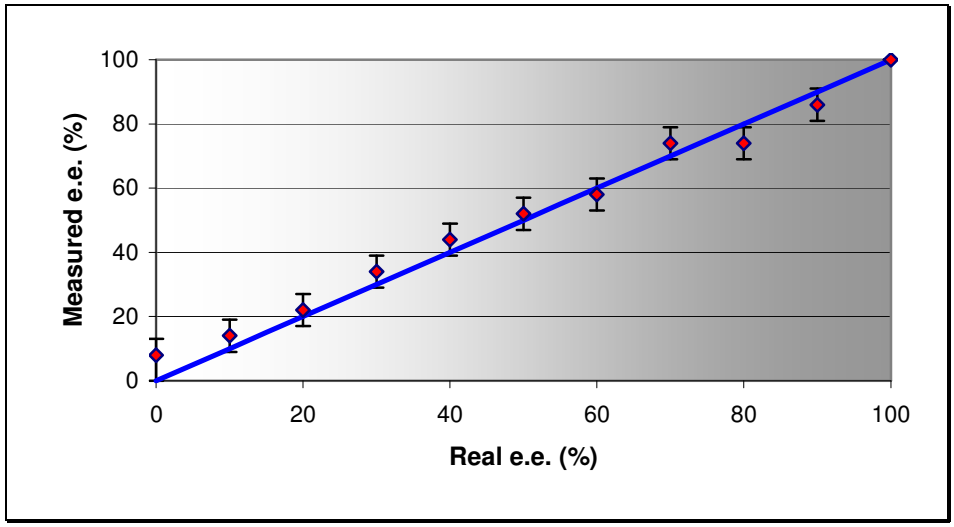


Figure 14: Effect of (1*S*)-10-CSA on the amide ^{31}P NMR signal.

(a) Resolution in ppm calculated according to the formula $R = (2x\Delta Z) / (W_A+W_B)$ where ΔZ is the separation between peaks A and B, W_A and W_B the widths at the base of peaks A and B respectively.

When increasing the amount of (1*S*)-10-CSA, a clear change of both the chemical shift (deshielding of the phosphorus nucleus) and the resolution could be observed. It turned out that the best resolution was attained with 1.5 equivalents of acid. Above that limit, the lack of solubility of (1*S*)-10-CSA in $CDCl_3$, confirmed by a plateau of the chemical shift, resulted in a reduction of the resolution. In order to measure how accurate this method was and also to make sure that the split generated was genuinely due to the two enantiomers, the *e.e.* values of standard solutions made of the two enantiopure synthesised amides were measured (Graph1).



Graph1: Reliability of the method.

From Graph 1, we can deem this unusual and innovative method as being fairly reliable (± 4%), albeit not being as accurate as HPLC. This method was used during screenings as a preliminary means to select the samples deserving to be analysed by HPLC, thus saving a considerable amount of time.

3.2.2 GC assay

During the course of the investigation, while the ^{31}P NMR technique was used to identify samples reaching a reasonable enantioselectivity, more accurate assay methods had to be utilised for samples having good *e.e.* values. To this end, three methods were used: chiral HPLC, chiral SFC and chiral GC.

Although HPLC assays are highly accurate, SFC was temporarily preferred later on as it turned out that highly UV absorbant impurities could co-elute with the enantiomer of the injected sample and thus making the analysis irreproducible and erroneous. The nature and the source of these impurities have not been identified yet; however perplexing cases of irreproducible analytics in HPLC is a known phenomenon which can have multiple sources such as the solvent grade, the mobile phase or the temperature and lengthy investigations are usually required to solve them when they occur. A remarkable recent finding in this field was reported by Hintermann[115] who found that adventitious trace amounts of water in the eluant affected dramatically the analysis in a normal-phase chiral HPLC system. Furthermore, he found that if this amount of water was controlled and added deliberately, it could improve substantially the peak resolution. Advantages of SFC over HPLC are numerous: lower fluid viscosity, higher efficiencies per unit time, ease of control of the solvent power (via pressure and temperature), etc.

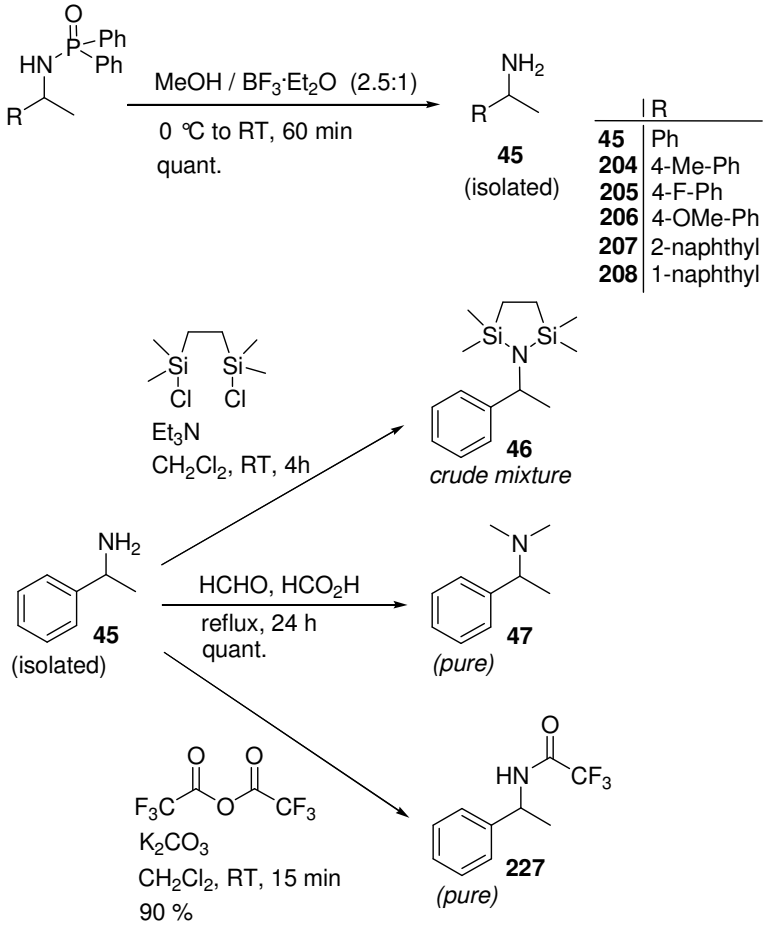
Finally, a method of choice for the *e.e.* assay was identified and focuses on GC analysis. While the protected diphenylphosphinoyl amide could be injected directly into the HPLC or SFC system, a removal or change of the heavy $P(O)Ph_2$ protecting group (MW = 201 g mol^{-1}) was necessary for a GC assay. It

should be noted that one the great advantage of the diphenylphosphinoyl group over other protecting groups is its facile removal under mild conditions. This is due to the lack of interaction of the nitrogen lone pair with phosphorus as shown by a X-ray data[116] that indicates nitrogen in the diphenylphosphinamide group to be tetrahedral, as opposed to the trigonal nitrogen often observed in the sulfonamide unit.

Our first approach consisted in getting the free amine by carrying out a dephosphinylation in a Lewis acid-promulgated methanolysis (Scheme 27).[117] The phosphinamide protecting group was treated with excess boron trifluoride etherate in methanol. Different MeOH/BF_3·Et_2O ratios were investigated (10:1, 5:1 and 2.5:1) and ratio 2.5:1 where the amount of methanol is minimised gave a slightly better isolation of the free amine. Acid washing with 2M HCl of the reaction product allows removal of the phosphinate by-product by a simple extraction and furnishes the amine in aqueous solution as the hydrochloride salt. Finally, the free amine was obtained by basification with 6M NaOH. Other similar literature procedures were employed but were either less efficient[118] or required a lengthier protocol[119] than the BF_3 promoted methanolysis deprotection.

As expected, a test injection of the free amine **45** in GC (without special modification to the column) proved to be unsatisfactory owing to the adsorption of the solute, resulting in peak tailing. Therefore it was necessary to convert this free amine into a suitable derivative prior to analysis. Derivatisation of amines is employed not only to reduce the polarity but also to improve the volatility, selectivity, sensitivity, and separation of the amine

signals. A wide range of derivatisation reactions are available.[120] Silylation, permethylation and acylation were tried as representative examples.



Scheme 27: Deprotection and derivatisation reactions of the methylated products.

The amino group is not very reactive to silylating reagents, and its conversion into a silyl derivative is normally difficult. However, by using literature conditions,[121,122] silyl derivative **46** could be prepared by reaction of **45** with Stabase chloride (1,2-*bis*(chlorodimethylsilyl)ethane) in the presence of triethylamine, in dichloromethane. Unfortunately, the Stabase adduct **46** was obtained as a crude mixture that required an inconvenient purification step (distillation) that rendered this method unattractive as we were aiming for an ideal quick derivatisation procedure.

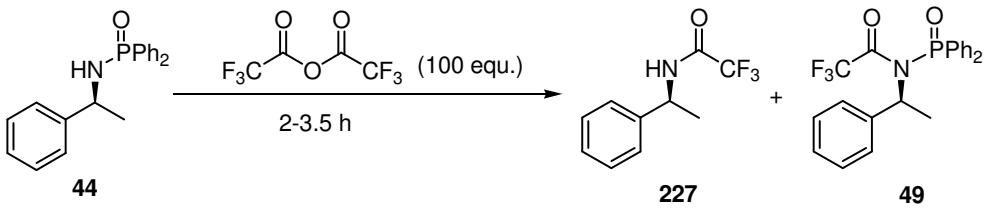
Permethylation, carried out with the Eschweiler-Clark reaction[123,124] was performed on free amine **45** to prepare tertiary amine **47**. Although the reaction time is fairly long, it has the advantage of being straightforward, easy to perform and clean since it gives the pure desired amine without any purification. Unfortunately, this reaction failed to afford the product when carried out *in situ*, even after removal of the methanol used to provide **45**.

Finally, acylation which is one of the most popular derivatisation reactions for primary and secondary amines was carried out. Reaction of trifluoroacetic anhydride with primary amine **45** in presence of potassium carbonate, in dichloromethane at room temperature were found to be the optimal conditions to obtain trifluoroacetamide derivative **227**. Use of a base such as triethylamine in this reaction was attempted and proved unsuccessful; on account of the nucleophilic feature of triethylamine, the reaction affords in this case the trifluorocetamide as a minor product and $Et_3N{\cdot}TFA$ and $Et_3N{\cdot}HCl$ (HCl workup) as major products that could not be isolated. As with the Eschweiler-Clark reaction product **47**, the reaction did not work when carried out *in situ*.

The fact that the preparation of a derivative systematically failed when the free amine used as a starting material was not properly isolated in the presence of excess BF_3 and traces of methanol pushed us into considering another strategy: a straight permutation of the protecting groups from **44** to **227** or in other words a trans-acylation. A single example of such a transformation in the literature[125] consists in reacting *N*-diphenylphosphinoyl protected compound with trifluoroacetic acid at room temperature for 2 hours to afford a crude product which needs to be purified by distillation. Such a protocol could obviously not be suitable for our derivatisation since it requires a distillation, a

time-consuming step. Consequently, the latter was modified and it was found that treatment of **44** with a large excess of TFAA and no other reagents could give the desired trifluoroacetamide **227**. Interestingly, monitoring of the reaction by ^{1}H NMR spectroscopy suggested that two amides are formed in this reaction: the monoamide and the diamide, the diamide being converted progressively to the monoamide in time. Different reaction conditions were tried and it was found that the amount of monoamide was increased if the reaction was carried out at room temperature instead of reflux (Table 5).

Table 5: Effect of the temperature on the derivatisation reaction.



44 **227** **49**

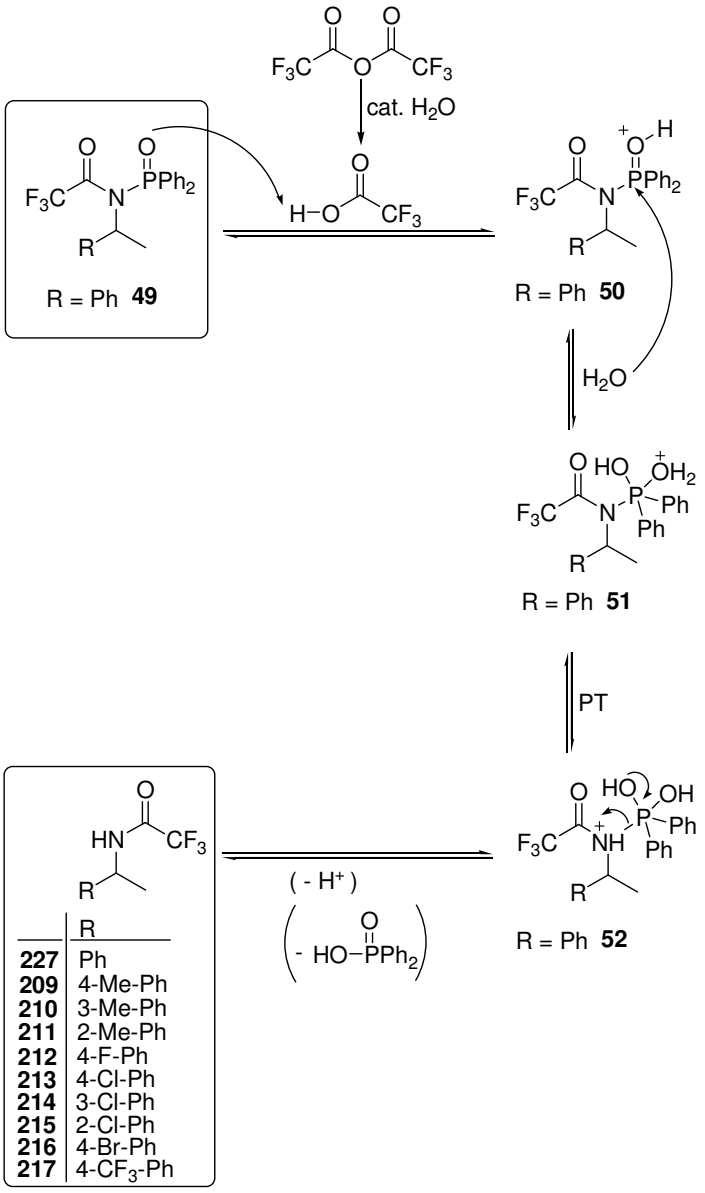
Entry	Temp.	Ratio 227:49 [a]
1	reflux	63 : 37
2	RT	82 : 18

(a) Determined by ^{1}H NMR spectroscopy.

A mass spectrometry monitoring of that derivatisation reaction was carried out in order to confirm formation of products **227** and **49**. The detection of compound **44 (**which amount decreases in time) and detection of by-product diphenylphosphinic acid $P(O)Ph_2OH$ (which amount increases in time) did confirm the progressive deprotection of the starting material and possibly of diamide **49**.

TFAA was present in a large excess since it was used both as a reagent and a solvent. It should be noted that this reaction was performed under "wet" conditions since it was carried out in an open vessel. The fact that compound

49 could be converted into **227** made us think that a third reagent was involved and we supposed that it was water coming from atmospheric moisture. The hypothesis seemed very sound since it could explain why the amount of **49** was decreasing in time. To verify it, we decided to observe the effect of the addition of a small amount of water in the reaction mixture. It turned out that not only this (exothermic) addition was beneficial to the reaction because it could dissolve entirely the reaction mixture, but it has also a catalytic effect in the conversion **49**→**227** thus confirming the hypothesis. The reaction taking place with water seems to be a simple acid-catalysed mono-hydrolysis of the diamide (Scheme 28).



	R
227	Ph
209	4-Me-Ph
210	3-Me-Ph
211	2-Me-Ph
212	4-F-Ph
213	4-Cl-Ph
214	3-Cl-Ph
215	2-Cl-Ph
216	4-Br-Ph
217	4-CF_3-Ph

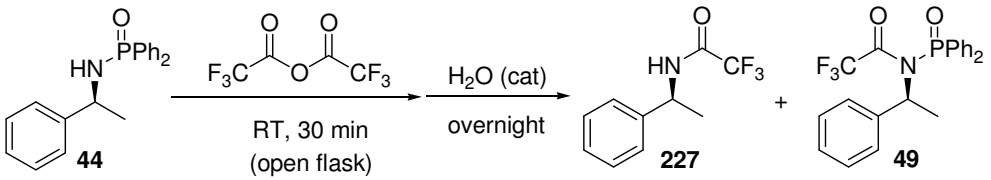
Scheme 28: Reaction mechanism of the mono-hydrolysis of diamide 49.

The mechanism proceeds via protonation of one of the carbonyl of diamide **49** to give activated species **50** that undergoes a nucleophilic attack by water. The result of that attack gives intermediate **51**. Finally, a proton transfer is followed by the departure of the monoamide moiety to give compound **227** and diphenylphosphinic amide. These new conditions using TFAA at room temperature followed by a catalytic amount of water afforded successfully the desired trifluoroacetamide albeit with a low yield (*c.a.* 50%). This procedure is

attractive in many ways since it is carried at room temperature, is solvent free, is carried out in an open vessel and requires a simple purification (filtration through Pasteur pipette of silica to remove $Ph_2P(O)OH$).

The influence of other parameters was evaluated (Table 6): the reaction time, the amount of TFAA and the amount of solvent. It was found that the conditions in which no diamide is formed were the ones found precedently, that is to say 100 equivalents of TFAA and no solvent (Entry 1). The addition of dichloromethane was tested because the reaction mixture is heterogeneous in TFAA; we found that the presence of dichloromethane, regardless of its amount (Entries 2-3 and 4-5), was not favourable for the removal of **49**. Finally, the decrease of the amount of TFFA from 100 equivalents to 10 equivalents was attempted and gave almost an equal ratio between **49** and **227** (Entries 4-5).

Table 6: Optimisation of the derivatisation reaction.



Entry	Eq. of TFAA	V CH_2Cl_2 (mL)	Results	
			Ratio 227:49 [a]	Observation [b]
1	100	0	100 : 0	no impurities
2	100	1.0	>90 : 10	minor impurities
3	100	4.0	>90 : 10	minor impurities
4	10	1.0	53 : 46	major impurity
5	10	4.0	54 : 47	major impurity

(a) Determined by ^{1}H and ^{31}P NMR spectroscopy.
(b) Qualitative analysis of the ^{31}P NMR spectrum.

It should be noted that this trans-acylation reaction does not racemise or alter the enantiopurity of the starting material which makes the derivatisation process safe. To check this, an enantiopure sample was derivatised and GC analysis confirmed complete retention of enantiopurity.

Chapter IV

Catalyst discovery

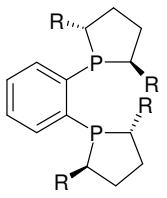
Within this thesis, a series of ligands and catalysts were screened in order to identify novel asymmetric catalytic systems for the synthesis of chiral amines. To this end, a commercially available ligand supplied by an industrial collaborator, (*R,R*)-Me-DuPHOS, has played a major role in this investigation.

4.1 Ligands

4.1.1 DuPHOS ligand

4.1.1.1 Methyl-DuPHOS

Asymmetric phosphine ligands play a dominant role in novel transition metal-catalysed enantioselective syntheses; for that reason, they have been subject to continuous development. The design of the DuPHOS ligand was initiated by Burk[126] in 1993. Burk and co-workers prepared a homochiral series of C_2-symmetric 1,2-*bis*(phospholano)-benzene ligands (Figure 15) that afforded efficient catalysts for the highly enantioselective hydrogenation and hydrosilylation of various unsaturated substrates. More particularly, use of DuPHOS in the rhodium-catalysed hydrogenation of α-(*N*-acylamino) acrylates showed enantioselectivities approaching 100% e.e.

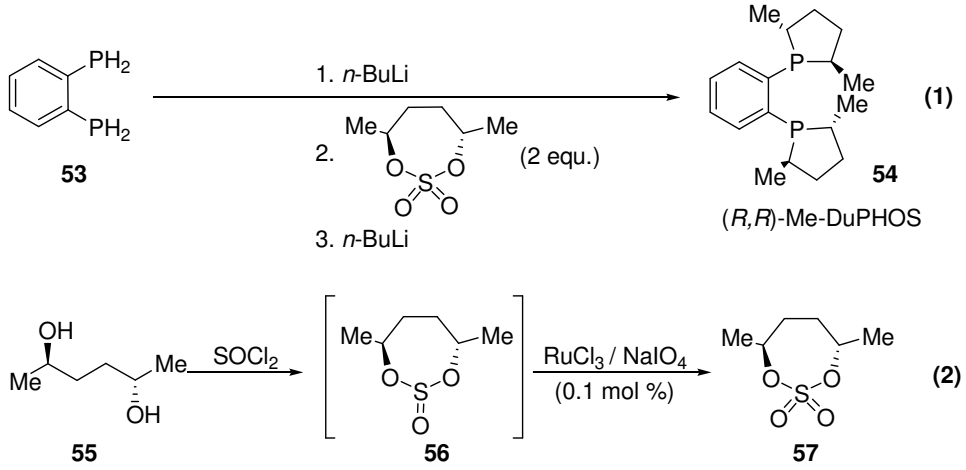


R = Me, Et, *n*-Pr, *i*-Pr

Figure 15: (*R,R*)-DuPHOS ligand series developed by Burk.

Preparation of the Me-DuPHOS ligand (Scheme 29) is carried out in three steps from the 1,2-phenyl*bis*phosphine **53**. An initial basic treatment of the

*bis*phosphine with *n*-BuLi generates the dilithium species and subsequent reaction with the cyclic sulphate **57** leads to nucleophilic opening of one cyclic sulphate by each phosphide. Finally, the second *n*-BuLi addition allows deprotonation of each remaining P-H and induces smooth closure to the five-membered phospholane rings. In line with the S_N2 character of the reaction, complete inversion of stereochemistry occurs at the stereogenic carbon centers of the cyclic sulphate to provide phosphines of opposite absolute configuration.



Scheme 29: Synthesis of the (*R,R*)-Me-DuPHOS ligand.

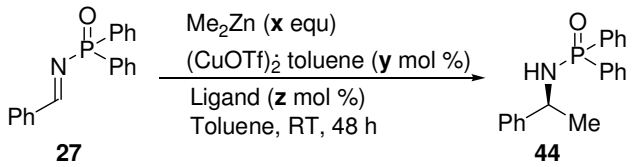
Synthesis of sulfate **57** is performed in two steps from the chiral 1,4-diol **55**. The crystalline diol **55** is readily converted to the corresponding 1,4-diol cyclic sulphate **57** by reaction with thionyl chloride, followed by ruthenium-catalysed oxidation ($RuCl_3/NaIO_4$) of the intermediate cyclic sulfite **56** which is not isolated.

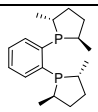
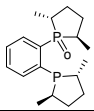
4.1.1.2 Me-DuPHOS monoxide (BozPHOS)

A recent use of the Me-DuPHOS ligand in the metal-catalysed enantioselective synthesis was reported by Charette[40] in the addition of dialkylzinc to imines. In

his investigation, Charette reported the enantioselective addition of diethylzinc to *N*-diphenylphosphinoylimines. In order to identify the optimal ligand in terms of both conversions and enantiomeric ratios, numerous mono- and bidentate phosphines were screened and the investigation disclosed that the (*R,R*)-Me-DuPHOS **54** was the best ligand (96% conversion, 93% e.e.) using these conditions [$Cu(OTf)_2$, Et_2Zn, toluene, 0 °C, 18 h]. In a later investigation with Me_2Zn,[41] Charette demonstrated that the use of a modified version of the Me-DuPHOS ligand, in which only one of the two phosphorus atoms is oxidised (Me-DuPHOS monoxide or BozPHOS), gave better results than the non-oxidised version of the ligand (Table 7).

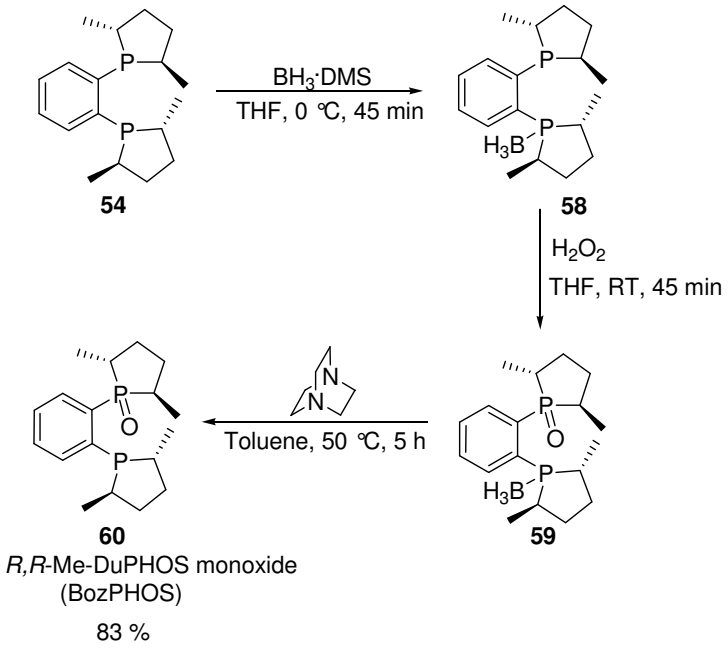
Table 7: Comparative results of (*R,R*)-Me-DuPHOS and (*R,R*)-Me-DuPHOS monoxide.



Ligand		Loadings x	y	z	Results yield (%)	e.e. (%)
(*R,R*)-Me-DuPHOS **54**		10	9.5	10	51	90
(*R,R*)-Me-DuPHOS monoxide **60**		3	5	5	87	97

Even with the best loadings which were found with (*R,R*)-Me-DuPHOS, the BozPHOS ligand gives better results with lower loadings. Nevertheless, in both cases the reaction is very slow. The BozPHOS ligand is synthesised in three steps from (*R,R*)-Me-DuPHOS with a 83% yield (Scheme 30). The mono-

oxidation which is carried out is possible due to the protection of one of the two phosphorus atoms with a borane in the first step. Then, the remaining phosphine is oxidised by use of hydrogen peroxide, and finally deprotection occurs with the addition of DABCO in the third and last step.



Scheme 30: Synthesis of the (*R,R*)-Me-DuPHOS monoxide ligand (BozPHOS).

It has been noted that for $ZnMe_2$/Cu(I) additions to imines, BozPHOS is a better ligand than Me-DuPHOS. Moreover, it has the advantage of being less air sensitive.

4.1.2 Feringa's ligand

Feringa and co-workers have described the synthesis of a variety of phosphoramidites and their application as ligands in the copper catalysed conjugate addition of dialkylzinc reagents to assess the effect of ligand variation in the asymmetric catalysis. Their study led to the design of a new

effective group of phosphoramidite ligands (Figure 16) that was tested in conjugate addition reactions.

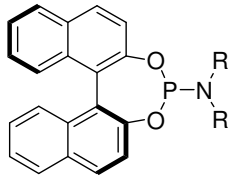
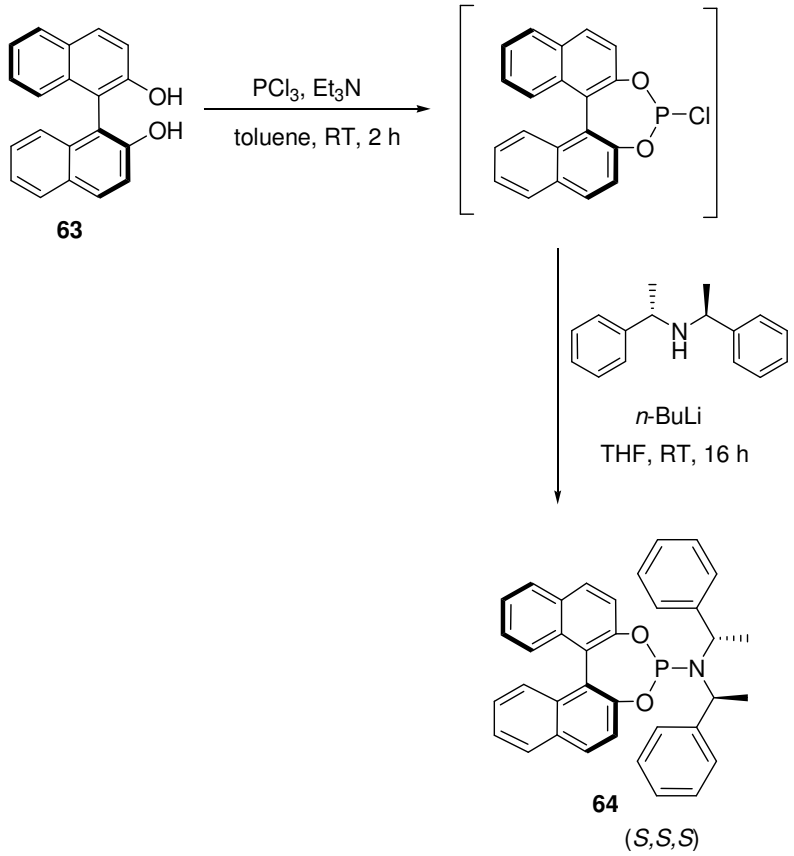


Figure 16: Monodentate phosphoramidite ligand developed by Feringa.

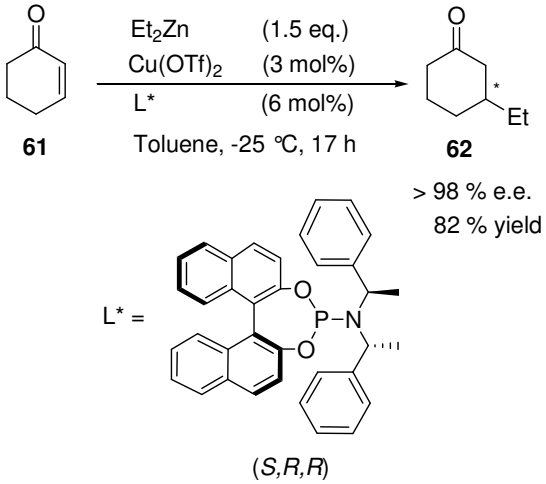
This phosphoramidite is made of two parts, one chiral binaphthol core of *S* configuration and an exocyclic chiral secondary amine.

It is prepared in a two step sequence (Scheme 31). This one pot procedure consists in mixing together a warm solution of phosphorus trichloride PCl_3 and chiral binaphthol in a Et_3N solution in toluene to generate the phosphoryl chloride. Then, treatment of the mixture with the chiral secondary amine in presence of *n*-BuLi in THF leads to the formation of the phosphoramidite.



Scheme 31: Synthesis of (*S,S,S*)-Feringa's ligand.

Numerous NR_2 groups have been tested in the enantioselective copper-catalysed diethylzinc addition to the model substrate cyclohexenone. There is no straightforward relation between the molecular architecture of the phosphoramidite ligand, for instance steric requirements, and the enantioselectivities observed. It was also observed a major influence of the nature of the amine part of the ligand whereas the effects of variation in the binaphthol unit are less prominent. However, a delicate balance seems to exist between the increase of steric hindrance and the chirality of the amine moiety. The best ligand has proved to be a phenylethyl group (Scheme 32).[127]



Scheme 32: Efficiency of the (*S,R,R*) Feringa's ligand in the 1,4-addition of diethylzinc to cyclohexenone.

It is interesting to note that the mismatched ligand with the absolute configuration (*S*,*S*,*S*) gives a lower 75% e.e.

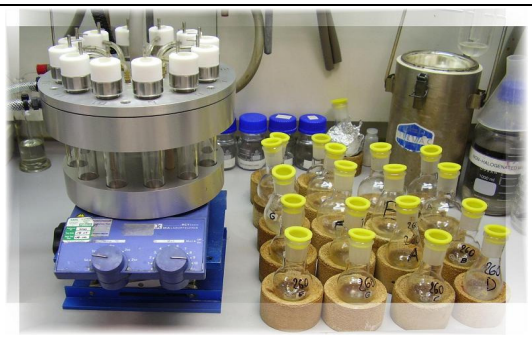
It is suggested that the mechanism of the reaction proceeds from a transmetallation of the Cu(I)-complex and diethylzinc via an ethyl group transfer to the copper. The enone coordinates to the ethyl copper species by π-complexation of the olefinic bond. The Lewis acidic Zn(II) centre probably activates the enone through complexation to the carbonyl oxygen (zinc is a slightly more electronegative than copper). This substrate binding and activation is likely to involve a bimetallic complex. Finally, the remaining sites in the tetrahedral coordination sphere of the copper ion are occupied by two phosphoramidite ligands providing a favourable pathway for π-face selective ethyl transfer.

4.2 Screening of reaction conditions

4.2.1 High throughput screening

Once the chiral ligands previously mentioned (*R,R*-Me-DuPHOS **54**, *R,R*-BozPHOS **60** and *S,S,S*-Feringa **64**) were prepared, we undertook an initial screening in which several conditions using different nucleophiles, catalysts and ligands were tested. A high throughput screening approach using a carousel multireactor unit allowing the simultaneous run of up to twelve reactions under inert atmosphere was employed (Figure 17a). The enantioselectivity reached in these reactions was determined and analysed with a range of powerful analytical methods at our disposal: ^{31}P NMR spectroscopy, HPLC, SFC and GC (Figure 17b); each one being respectively used at the most appropriate time depending on how advanced the study was.

(a)



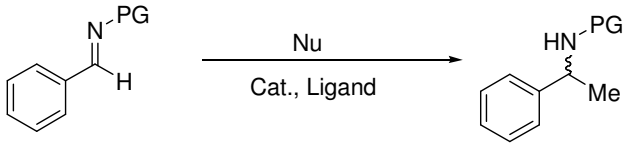
(b)

Figure 17: High throughput screening tools.
(a) A heated carousel multireactor running 12 reactions simultaneously under inert atmosphere.
(b) Modern computer-controlled chiral GC machines equipped with autosamplers.

4.2.2 Exploration of Fujisawa's and Charette's conditions

Conditions described in the literature for methylation of imines were trialled (Table 8). On the one hand, we were pleased to see that the Fujisawa's conditions (Conditions A) using nickel(II) as a catalyst were reproducible and gave an excellent result not only for **28** but also for **27**. On the other hand, we were surprised to see the poor results obtained in the reproduction of Charette's conditions (Conditions B) and more especially in the case of substrate **27** (26% conversion) that was expected to give an 87% yield according to Charrette's report (Table 7).

Table 8: Results obtained for the methylation reactions using Charettte's and Fujisawa's conditions.[35,41]



	PG
27	$P(O)Ph_2$
28	Ts
29	Bn
30	2-OMe-Ph

Cond.	Nu	Catalyst	Ligand	Solvent, Temp., Time	Conversion (%)[a] 27	28	29	30
A[b]	$AlMe_3$	$Ni(acac)_2$	PPh_3	THF 0 °C overnight	**97**	**100**	nd	nd
B[c]	Me_2Zn	$(CuOTf)_2$	BozPHOS	Toluene RT 48 h	26	14	nd	4

(a) Estimated by ^1H NMR spectroscopy.
(b) Fujisawa's conditions.[35]
(c) Charrette's conditions.[41]

However, the only difference that can be reported between conditions B and the original Charette's conditions is the form of Me_2Zn used in the reaction. In

Charette's original report, neat Me_2Zn was used, but because of its unavailability in our lab we opted for the use of a 2 M Me_2Zn solution in toluene as an alternative. Initial attempts at measurement of the conversion were problematic as the measured values were erroneous due to decomposition of the unreacted starting imine into benzaldehyde and the corresponding amide. Obviously, this decomposition was the result of the acidic workup which highlights the sensitivity of aldimines. Thereby, to remedy this problem, several different quenching reagents were tried and slightly alkaline NH_4Cl turned out to be better than MeOH, TMSCl or a saturated aqueous solution of $NaHCO_3$.

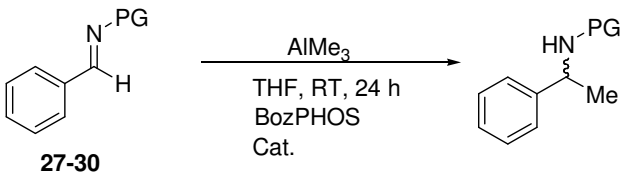
4.2.3 Screening of copper and iridium catalysts

Screening of several catalysts associated either with BozPHOS or Feringa's ligand were carried out in order to find some first reaction conditions that could be optimised later on. All initial reactions were carried out for 24 h for convenience. Monitoring the reaction by TLC was quite inefficient because of the poor separation between the imine and the corresponding methylated amine.

4.2.3.1 Screening of copper catalysts

Screening of different Cu(I) catalysts-based with BozPHOS was carried out and their effects on imines **27-30** noted (Table 9). They were all carried out in THF, at room temperature, for one day.

Table 9: $AlMe_3$ addition catalysed by copper.



27-30

Cond.	Catalyst	Conversion (%) [a]			
		27	**28**	**29**	**30**
C	$(CuOTf)_2$	26	nd	2	2
D	CuTC	17	9	nd	nd
E	$[Cu(MeCN)_4]BF_4$	**65**	5	nd	nd

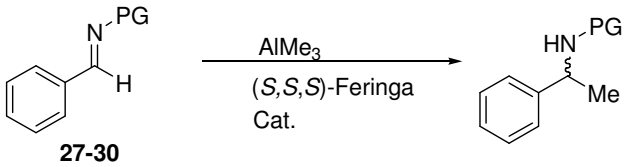
(a) Estimated by ^1H NMR spectroscopy.

Apart from the change of nucleophile (Me_2Zn vs $AlMe_3$), conditions **C** and **B** differ only in the solvent (toluene vs THF) and afford essentially the same results which shows that the solvent is not playing a key role here. Then, in conditions **D** and **E**, more stable copper(I) catalysts were tested. The main drawback of copper(I) triflate is its high air sensitivity (it requires handling in a glove box) and we found it useful to test sources such as copper(I) thiophene-2-carboxylate (**D**) and *tetrakis* acetonitrile copper(I) tetrafluoroborate (**E**) not only because they are less sensitive to air but also to observe the effects of their ligands. Conversions obtained in these conditions are quite poor on the whole and the only substrate that stands out is **27** within conditions **E** (65% conversion).

4.2.3.2 Screening of iridium catalysts

Three sources of iridium catalysts, associated with the (*S*,*S*,*S*)-Feringa ligand were tested in this screening: one source of Ir(III), [$Ir(acac)_3$], and two sources of Ir(I) [$[Ir(Cl)COD]_2$, $[Ir_2(Cl)(OMe)(COD)_2]$]. Similarly to the screening of copper catalysts, reactions were all carried out in THF, for one day (Table 10).

Table 10: $AlMe_3$ addition catalysed by iridium.



27-30

Cond.	Cat.	Solvent, Temp., Time	Conversion (%)[a] 27	28	29	30
F	$Ir(acac)_3$	THF RT, 24 h	13	nd	nd	nd
G	$Ir(acac)_3$	THF 50 °C, 24 h	11	2	1	nd
H	$[Ir(Cl)COD)]_2$	THF 50 °C, 24 h	**96**	1	2	nd
I	$[Ir_2(Cl)(OMe)(COD)_2]$	THF 50 °C, 24 h	**> 99**	2	2	nd

(a) Estimated by ^1H NMR spectroscopy.

Under conditions **F** and **G**, $Ir(acac)_3$ gave quite poor results, and an increase in temperature from room temperature (**F**) to 50 °C (**G**) barely changed the conversion for **27**. In conditions **H**, use of dichloro-*bis*(1,5-cyclooctadiene)-diiridium(I) gave an excellent conversion that reached 96% for **27**. Finally, in conditions **I**, use of chloromethoxy-*bis*(1,5-cyclooctadiene)-diiridium(I) gave

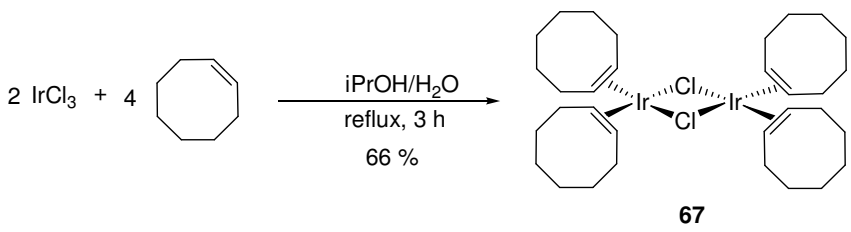
results even better than with **H** as conversion reached with **27** exceeds 99%. With regard to the enantiomeric excess, only amines resulting from reactions in which conversion was higher than 25% (conditions **C**, **E**, **H**, **I**) were analysed by chiral HPLC. Unfortunately, *e.e.* values were all lower than 10% which means that there was no enantoselectivity in these reactions and that the development of an appropriate ligand was required.

4.2.4 Development of the new iridium(I) catalysed $AlMe_3$ addition reaction

Once we identified a suitable nucleophile and catalyst to carry out the methyl addition to the diphenylphosphinoyl imine, namely trimethylaluminium and chloro*bis*(cyclooctadiene) iridium(I) dimer, we studied the scope of these two elements to check if the reaction conditions could be improved.

4.2.4.1 Synthesis of di-μ-chlorotetrakis (cyclooctene) diiridium(I)

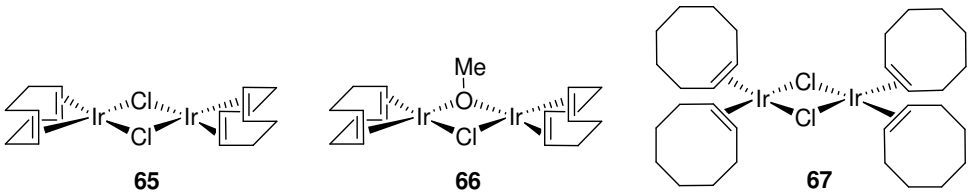
The effect of other sources of iridium(I) were screened to check whether the presence of the cyclooctadiene in the iridium catalyst is crucial to the success of the reaction. Thus, di-μ-chlorotetrakis (cyclooctene) diiridium(I) was prepared (Scheme 33) in a reasonable yield (66%).



67

Scheme 33: Synthesis of di-μ-chlorotetrakis (cyclooctene) diiridium(I).

Reaction of iridium (III) chloride with cyclooctene refluxed within a degassed mixture water/isopropanol afforded the bright yellow complex. Although being light sensitive and requiring storage at a low temperature (cold room), this complex is much easier to prepare than its cyclooctadiene analogues. We observed that the activity of this iridium catalyst, in terms of conversion, is identical to the ones we previously observed with other iridium(I) based catalyst, namely $[Ir(Cl)COD]_2$ and $Ir_2(Cl)(OMe)(COD)_2$ (Figure 17). Indeed using any one of these three catalysts affords the methylated amine with a complete conversion after reflux in THF for 3 hours.

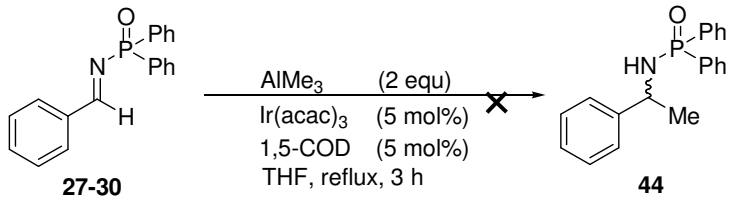


65 66 67

Figure 17: Iridium(I) based catalysts tested in the methyl addition reaction with $AlMe_3$.

4.2.4.2 Importance of the cyclooctadiene group

The fact that the efficiency of the reaction does not depend only on iridium precursors **65** and **66** indicates that the presence of the COD coligand is not crucial to the success of the reaction. This argument is supported by one observation made in an earlier experiment in which $Ir(acac)_3$ and 1,5-COD were used together as a catalyst (Scheme 34).



Scheme 34: Use of 1,5-COD and Ir(acac)$_3$ as a catalyst in the methyl addition.

Failure of this experiment made clear that the cyclooctadiene group does not strongly promote the reaction.

4.3 Screening of ligands and preformed catalysts

4.3.1 Screening of ligands

Once the best reaction conditions had been identified (imine **27**, $AlMe_3$, $[IrCl(COE)]_2$ and a suitable method for the measurement of the enantiomeric excess attained, the next goal was to increase the enantioselectivity of the reaction. To this end, a wide range of ligands having different skeletons, functionalities, and electronic and steric properties was screened.

The first set of ligands tested in the different screenings (Figure 18), which comprises 10 ligands, mostly chiral diphosphines, includes 6 families: DuPHOS, BPE, Trost, PhanePHOS, Chiraphite and Kelliphite. Chiral diphosphines play a pivotal role as ligands in metal-catalyzed asymmetric hydrogenation. In particular C_2-symmetric 1,2-*bis*phospholanes form highly enantioselective catalysts for the hydrogenation of a range of different prochiral olefins. Due to their excellent and versatile catalytic performance in asymmetric hydrogenation,[128] we were very keen to test some of them in 1,2-addition reactions of imines to see if related performance could be observed.

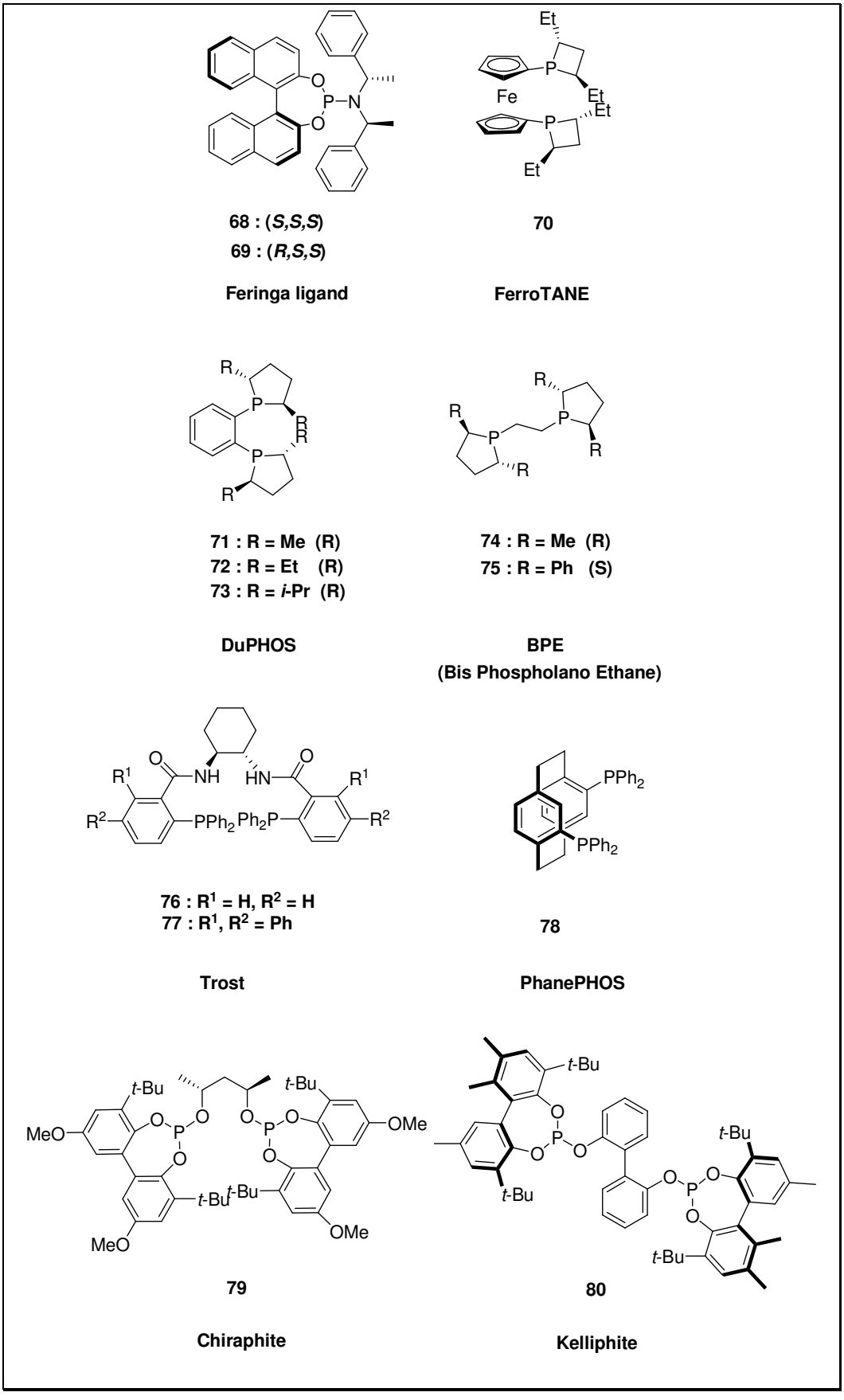
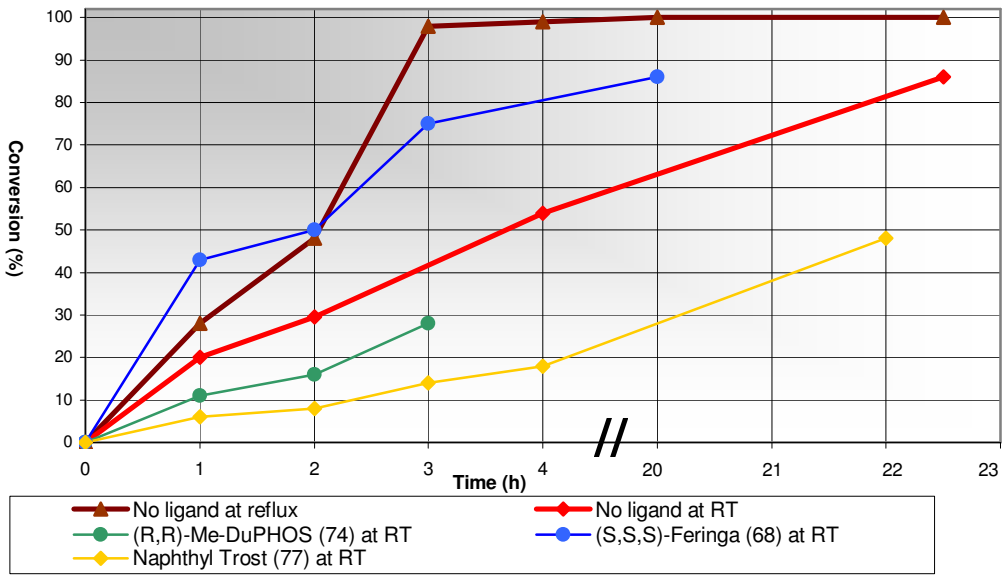


Figure 18: First set of ligands tested in the series of screening.

However, before proceeding to the screening in itself, we thought it was necessary to carry out a very basic kinetic study of the reaction. Consequently the conversion of the reaction was monitored using benzaldimine **27**, trimethylaluminium, $[Ir(Cl)(COD)]_2$ and THF. The kinetic influence of three ligands (**68**, **74** and **77**) was observed at room temperature (Graph 2).



Graph 2: Monitoring of the conversion in the methyl addition reaction. Reactions carried out at room temperature.

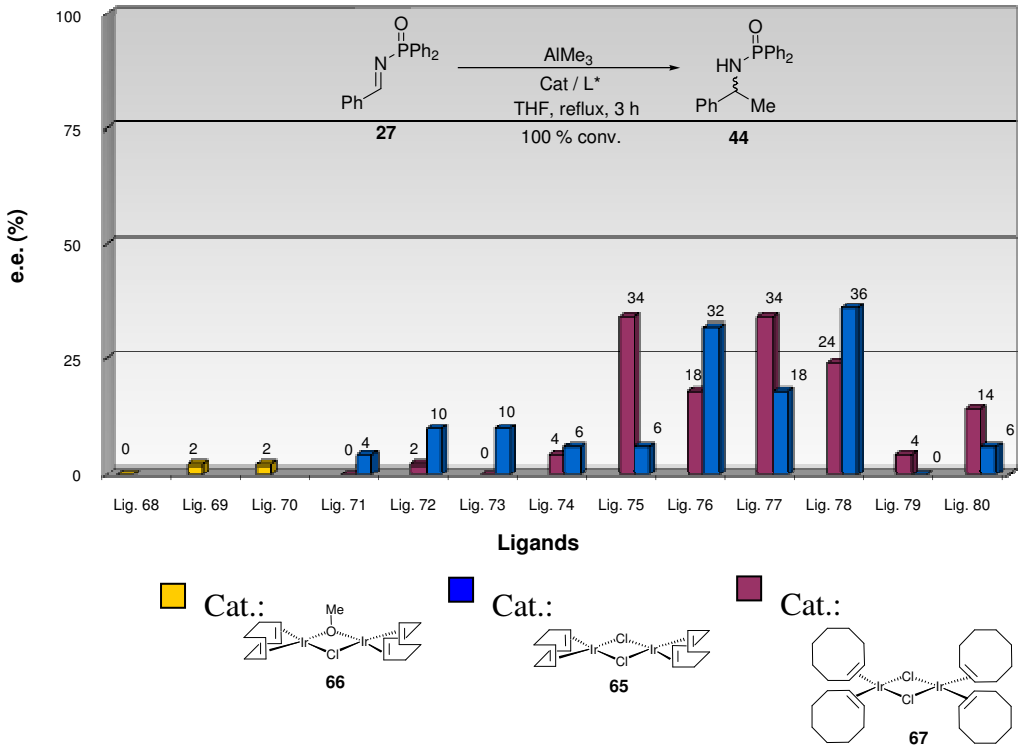
Surprisingly, it was observed that the three ligands tested responded quite differently in terms of kinetics. We could observe two phenomena resulting from the nature of the ligand bound to the metal center: a ligand-accelerated catalysis (LAC) and a ligand-decelerated catalysis (LDC); phenomena that affect the rate (Graph 2) and selectivity (Graph 3) of the transformation. When the ligand is bound, the rate of product formation can either be slowed down ($\upsilon_{ML} < \upsilon_M$ where υ_{ML} is the overall rate of product formation in presence of the

ligand, and υ_M is the rate of the reference reaction in the absence of the ligand in question), remain the same ($\upsilon_{ML} = \upsilon_M$), or be increased ($\upsilon_{ML} > \upsilon_M$).

Therefore we found that in the case of *S,S,S*-Feringa **68** a LAC was exhibited, while in the case of **74** and **77** a LDC was observed. According to Sharpless,[129] the likely explanation of a LDC phenomenon is the creation of an effective chiral environment that often results in extra steric crowding around the binding/catalytic site, which eventually leads to a rate deceleration (case of **74** and **77**).

Using this kinetic study, initial reaction temperature of 50 °C and a reaction time of 24 h could be optimised so that completion could be reached in only 3 hours at reflux temperature (67 °C in THF).

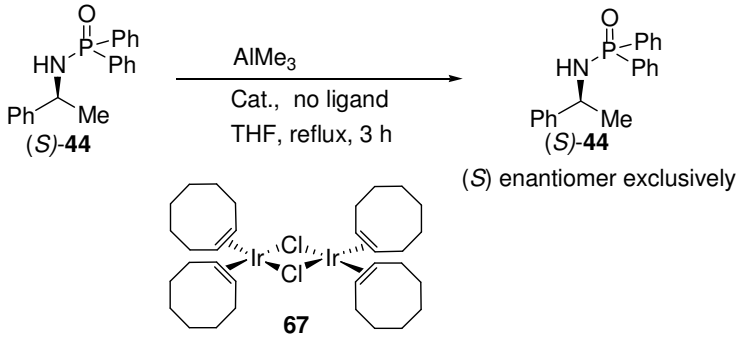
Ligands (**71**-**80**) were screened under the conditions identified (Graph 3). While ligands **71** to **73** were screened with $Ir_2Cl(OMe)(COD)_2$, ligands **74** to **80** were screened with both $[IrCl(COD)]_2$ and $[IrCl(COE)_2]_2$ in order to observe possible differences of activities between the two catalysts. Results of the screening revealed that the two iridium catalysts can show a substantial difference in terms of enantioselectivity depending on the chiral ligand which is used. Indeed, one good example which exemplify this behaviour is ligand **75**; with **75**, $[IrCl(COD)]_2$ gave only 6% e.e. while $[IrCl(COE)_2]_2$ gave 34% e.e.



Graph 3: Screening of ligands in the $AlMe_3$ addition reaction using Ir (I) based catalyst.

Th *e.e.* values obtained with ligands **68**-**80** are quite low as a whole (0-36% e.e.) which shows a poor enantioselectivity is engendered with this range of ligands. However, among them, four ligands stand out as their *e.e.* values exceed 30%: **75**, **76**, **77** and **78**. The highest *e.e.* value in this screening (36%) was reached with ligand **78** while using $[IrCl(COD)]_2$. Since quite poor enantioselectivity was observed we speculated a racemisation process was occurring in the reaction, as if it was the case that would explain the very low *e.e.* values reached. To check this hypothesis the enantiopure product prepared from the corresponding commercially available amine was exposed to the reaction conditions (Scheme 35). Two possibilities were considered:

- presence of a racemisation in the catalytic process which would give an equal mixture of the two enantiomers of the amine as a product
- absence of a racemisation in the catalytic process which would give the starting material with the same absolute configuration



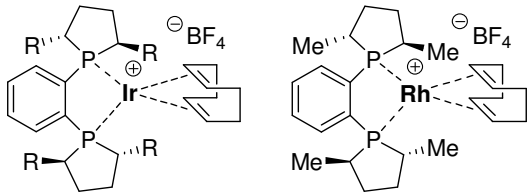
Scheme 35: Absence of racemisation in the catalytic process.

It was apparent there was a complete absence of racemisation in the reaction as no change was noticed in the absolute configuration of the amine. Therefore, the hypothesis of product racemisation was eliminated.

4.3.2 Screening of preformed catalysts

Once the ligands had been tested in the chemistry of Graph 3, other possibilities were considered as only poor enantioselectivity had been realised. One drawback in not using preformed catalysts is the possibility of a racemic reaction promoted by unligated iridium species. With preformed catalysts, which are preferred in asymmetric hydrogenation, ligand free background reactions are minimised.

Both iridium and rhodium preformed catalysts were tested with $AlMe_3$ (Figure 19). These preformed catalysts are both BF_4 salts of Ir or Rh(COD) DuPHOS.



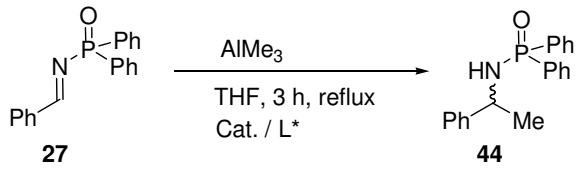
81: R=Me (R)
82: R=Et (R)

83

Figure 19: Iridium and rhodium DuPHOS preformed catalysts tested.

In respect of the enantioselectivity the highest *e.e.* value was reached with **83** which gave only 32% e.e. (Table 11).

Table 11: Screening of preformed catalysts with trimethylaluminium.



27 **44**

Entry	Ligand	Conversion[a] (%)	e.e.[b] (%)
1	**81**	65	12
2	**82**	100	6
3	**83**	100	32

(a) Determined by ^{1}H NMR spectroscopy.
(b) Determined by Supercritical Fluid Chromatography.

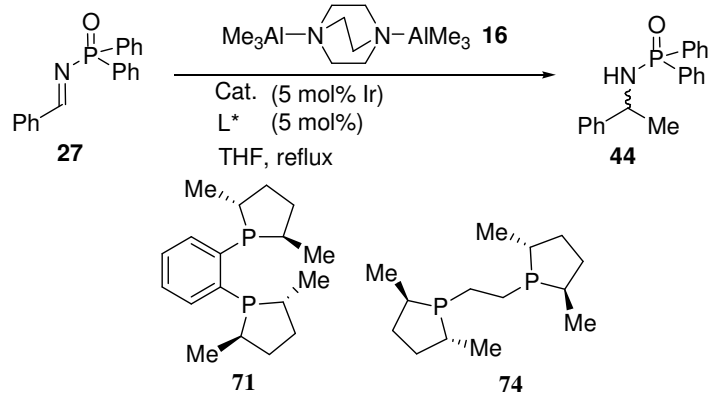
The fact that the best results (albeit poor) were obtained with a rhodium preformed catalyst drew our attention to this metal. For this reason, our next studies focused on the screening of many other rhodium preformed catalysts for imine methylation.

4.4 Optimisation and scope of the iridium(I)-catalysed $AlMe_3$ addition reaction

4.4.1 Use of DABAL-Me_3 as a methylating agent

The air stable trimethylaluminium DABAL-Me_3 was also tested in the methyl addition reaction (Table 12). As expected we found that as with $AlMe_3$, presence of the iridium catalyst was crucial to the success of the reaction (Entries 1-2). Two different ligands (**71**, **74**) were tested, and although they showed a slightly higher enantioselectivity compared with $AlMe_3$, they gave very low *e.e.* values (Entries 3-4).

Table 12: Results obtained with DABAL-Me_3 as a methylating agent.



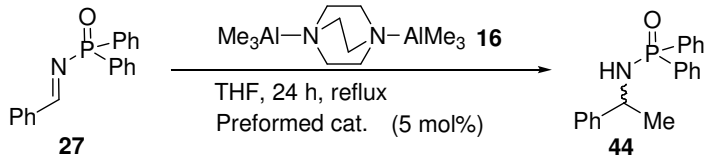
Entry	Catalyst	L*	Time	Conversion[a] (%)	e.e.[b] (%)
1	none	/	3 h	1	/
2	**67**	/	3 h	98	/
3	**67**	**71**	overnight	100	14
4	**67**	**74**	overnight	100	10

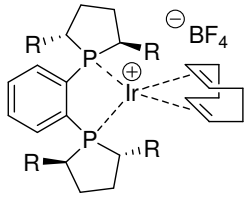
(a) Determined by ^{1}H NMR spectroscopy.
(b) Determined by ^{31}P NMR spectroscopy.

Iridium and rhodium preformed catalysts previously tested with $AlMe_3$ (*cf.* 4.4.1.2) were also tested with DABAL-Me_3 to see if any difference of reactivity would be observed between the two analogues. Interestingly, although in the absence of ligand both $AlMe_3$ and DABAL-Me_3 performed

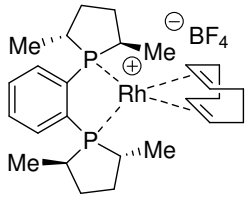
with the same efficiency, in this new system, DABAL-Me_3 was found to be a much less active nucleophile (Table 13). Indeed, the maximum conversion reached with DABAL-Me_3 was only 4%, and it is known for sure that this loss of activity cannot be entirely due to the preformed catalyst given that $AlMe_3$ gave with the same preformed catalysts moderate to very good conversions (65-100% conversion).

Table 13: Screening of preformed catalysts with DABAL-Me_3.





81: R=Me (R)
82: R=Et (R)



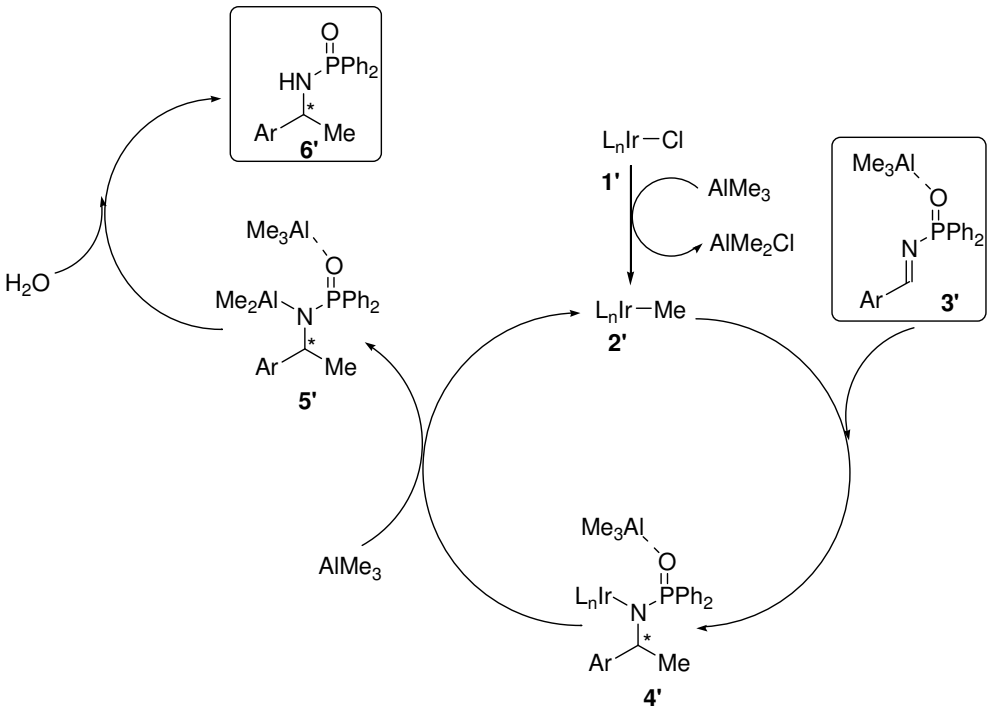
83

Entry	Preformed cat.	Conversion [a] (%)	e.e. [b] (%)
1	**81**	4	/
2	**82**	0	/
3	**83**	4	/

(a) Determined by ^1H NMR spectroscopy.
(b) Determined by Supercritical Fluid Chromatography.

The proposed methylation mechanism with $AlMe_3$ and DABAL-Me_3 is identical (Scheme 36). In the first step, the Ir catalyst **1'** reacts with the organoaluminium reagent to generate the active catalytic species L_nIr-Me **2'**. Then, the imine substrate **3'** which is activated by Lewis acidic $AlMe_3$, undergoes a methyl transfer from the newly formed catalytic species **2'**. This results in the formation of a methylated protected amine **4'** which bears a chiral

centre α to the Me group. Finally, another equivalent of $AlMe_3$ intervenes and introduces a N-Al bond that replaces the former N-Ir bond, to give **5'**.



Scheme 36: Suggested mechanism of the Ir(I)-catalysed methylation reaction.

Finally, in the last step compound **5'** is quenched by water to afford the desired methylated protected amine **6'**.

4.4.2 Addition of other nucleophiles

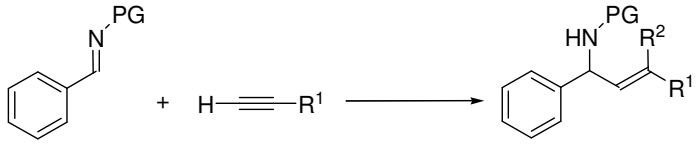
Having seen the results obtained in the addition of the methyl group to imines, we were keen to try new types of nucleophiles other than the alkyl. Thus, we tried successively the addition of an alkenyl group and the addition of an alkynyl group.

4.4.2.1 Ir (I)-catalysed addition of alkenylaluminium

4.4.2.1.1 Allylamine synthesis

Allylamines are fundamental building blocks in organic chemistry and their synthesis is an important industrial and synthetic goal. The allylamine fragment can be encountered in natural products, but often it is transformed to a range of products by functionalization, reduction, or oxidation of the double bond. Thus allylamines have been used as starting materials for the synthesis of numerous compounds such as amino acids, different alkaloids and carbohydrate derivatives. Several ways to synthesize allylamines[130] have been developed and aldimines are one potential starting material. Methods described in the literature for this way of synthesis of allylamines use exclusively hydrozirconation of alkynes to generate the nucleophile that reacts with the imine. Some of the results reported in the literature that have drawn our interest are reported below (Table 14).

Table 14: Syntheses of allylamines from benzaldimines reported in the literature.



PG: protecting group

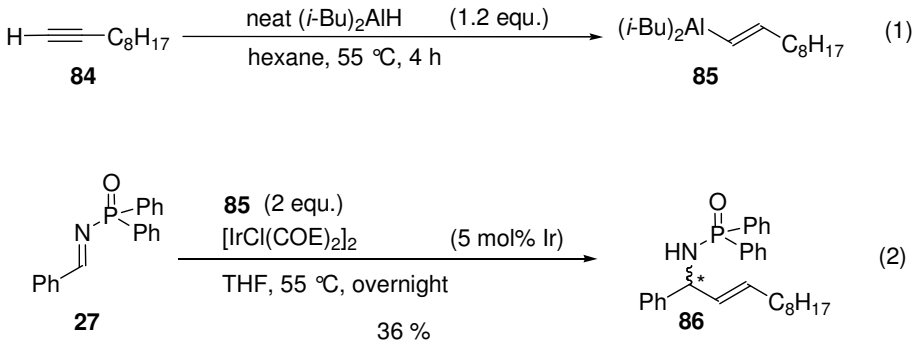
Entry	Conditions		R^1	R^2	PG	Yield (%)
1[131]	1) Cp_2ZrHCl		t-but	H	Ts	99
2[131]	2) $[RhCl(COD)]_2$ (2 mol%) dioxane, RT, 1 h		t-but	H	$PO(OEt)_2$	63
3[132]	1) Cp_2ZrHCl	(1.5 eq.)	n-but	H	$POPh_2$	76
	2) Me_2Zn toluene, RT, 2 h	(1.5 eq.)				
4[132]	1) $AlMe_3$	(2 eq.)	n-hex	Me	SO(p-Tol)	80
	Cp_2ZrHCl	(0.03 eq.)				
	H_2O	(1 eq.)				
	CH_2Cl_2, 0 °C, 40 min					
	2) -15 °C, 20 h (*addition of imine*)					

In these three examples, in the first step, alkenylzirconocene complexes were readily generated by use of the Schwartz reagent Cp_2ZrHCl. Then, additives such as $[RhCl(COD)]_2$ (Entries 1-2), Me_2Zn (Entry 3) or – more surprising – water (Entry 4) act as catalysts and enable to afford the addition product with respectable yields when the amine is activated by an electron withdrawing group.

4.4.2.1.2 Addition of alkenylaluminium

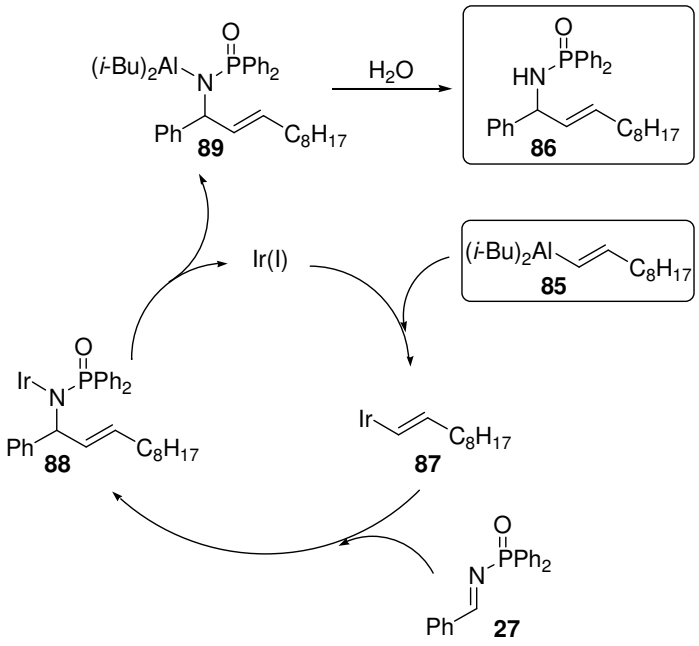
A similar approach in which an alkenylaluminium nucleophile is generated was used (Scheme 37). Hydroalumination of dec-1-yne by using neat DIBAL-H (Equ. 1) generates the aluminium reagent which is directly used to react as a nucleophile with the imine (Equ. 2). The allylamine which is formed is

obtained with a quite poor yield (36%) but it should be noted that this reaction has not been optimized yet.



Scheme 37: Alkenylaluminium addition to diphenylphosphinoyl benzaldimine.

By analogy to the mechanism proposed by Taguchi[133] in the addition of alkenylzirconocene chlorides to aldimine derivatives, it can be suggested that our reaction involves the transfer of an alkenyl group from aluminium to iridium metal (transmetalation) giving an alkenyliridium species **87** and the following insertion of the carbon-nitrogen double bond of the benzaldimine into the Ir-carbon bond to afford **88** (Scheme 38).



Scheme 38: Suggested catalytic cycle for the formation of the allylic amine.

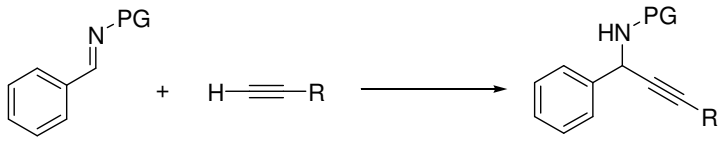
4.4.2.2 Ir (I)-catalysed addition of alkynylaluminium

4.4.2.2.1 Propargylamine synthesis

Similarly to allylamines, propargylamines can serve as important building blocks for organic synthesis; they have broad applications and are often used as intermediates in preparation of complex natural products and pharmaceuticals. While the addition of acetylenes to carbonyl compounds has been the subject of a large number of publications, the use of imines and related C=N electrophiles as substrates has been much less developed, mostly as a result of the reduced reactivity of these compounds compared to aldehydes and ketones.[134]

Table 1**5** reports some interesting results found in recent publications. These selected results incude only non-enantioselective reactions.

Table 15: Syntheses of propargylamines from benzaldimines reported in the literature.

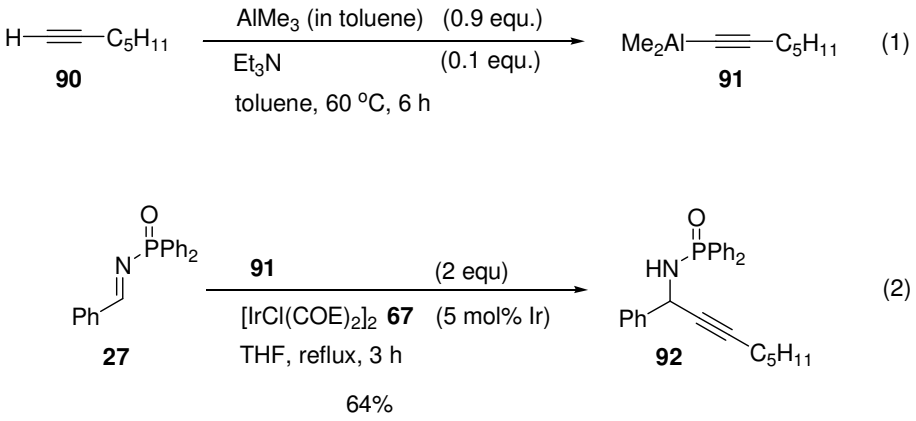


PG: protecting group

Entry	Conditions	R	PG	Yield (%)
1[135]	Me_2Zn (1.5 eq.) toluene, 50 °C, 24 h	Ph	Ts	80
2[132]		Ph	$P(O)Ph_2$	69
3[132]		*n*-hexyl	Ts	67
4[136]	$[IrCl(COD)]_2$ (5 mol%) THF, RT, 24 h	TMS	C_6H_5-*p*-(OMe)	85

4.4.2.2.2 Addition of alkynylaluminium

An alkenyl addition to benzaldimine **27** was carried out, again using an organoaluminium nucleophile (Scheme 39). This nucleophile was generated by a nucleophilic substitution of the acetylinic proton of heptyne by $AlMe_3$ (Equ. 1). Then, in a second step, the alkenyl aluminium complex (crude mixture) was used in our catalytic system to finally obtain the propargylic amine (Equ. 2).



Scheme 39: Alkenylaluminium addition to diphenylphosphinoyl benzaldimine.

Unfortunately, when this reaction was carried out without the presence of catalyst, the chemical yield was found to be essentially quantitative. However, this method could be utilised in an enantioselective reaction providing that the high background reaction could be successfully minimised.

Chapter V

Catalyst enhancement and reaction optimisations

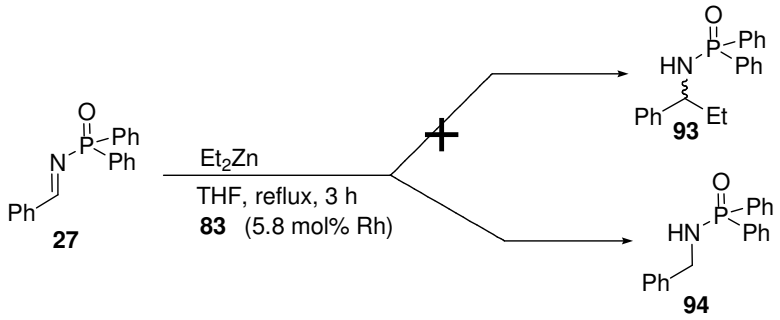
5.1 Optimisation of the rhodium catalytic system

5.1.1 Addition of Et_2Zn

Although this project has been essentially focused on the methyl addition, it should be noted that this rhodium catalysed dimethylzinc addition reaction offers a potential great scope of nucleophiles. It can theoretically be extended to various other alkyls (diorganozincs, or alternatively organozinc halides), aryls[137] or functionalised groups.

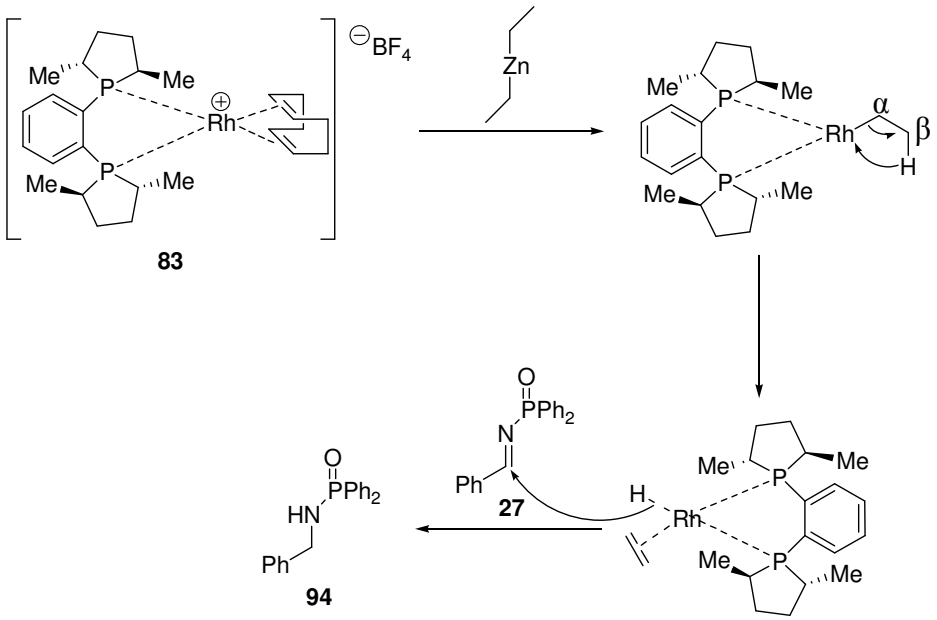
As the addition of the methyl group to imine **27** was efficient under conditions we had developed, it was of interest to check if the addition of another alkyl group such as the ethyl group would be effective. An important feature of Et_2Zn when compared to its homologue Me_2Zn is its lower C-Zn bond dissociation enthalpy; values of these enthalpies are 374 and 312 kJ.mol^{-1} for Me_2Zn and Et_2Zn respectively,[138] which corresponds to a difference of 62 kJ mol^{-1}.

Addition of diethyl zinc was then carried out (Scheme 40), but disappointingly it wasn't the chiral ethyl addition product which was obtained, but the reduction product resulting from a β-hydride elimination reaction.



Scheme 40: Rhodium catalysed Et_2Zn addition to diphenylphosphinoyl imine 27.

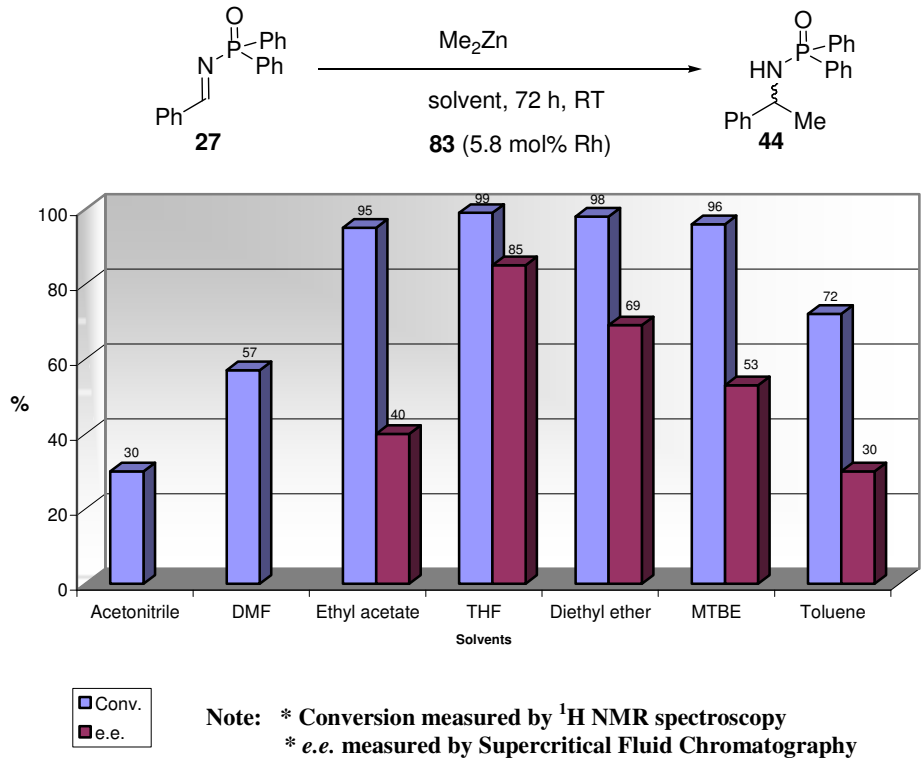
In an undesirable β-hydride elimination, the ethyl group which is bonded to the rhodium metal centre is converted into the corresponding metal-bonded hydride and ethylene. This could not occur without the presence of hydrogens on the beta carbon to rhodium and the presence of a vacant site *cis* to the ethyl group. The mechanism shown (Scheme 41) indicates a four-center transition state in which the hydride is transferred to the metal.



Scheme 41: Beta-hydride elimination occurring with diethylzinc and 83.

5.1.2 Screening of solvents

Before going further in the new rhodium preformed catalyst screening, an optimisation of the reaction conditions was required. Thereby a range of organic solvents was screened in the addition of Me_2Zn to imine **27**. The results of this screening (Graph 4) suggest that there is a correlation between the polarity of the solvent and the effectiveness of the reaction.



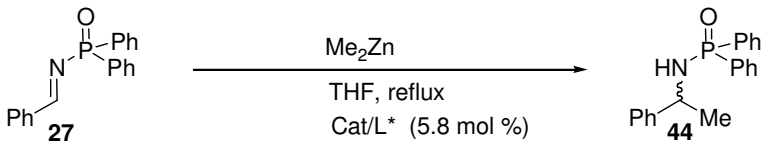
Graph 4: Screening of solvents in the Rh catalysed Me_2Zn addition reaction.

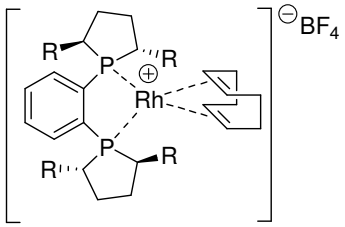
In Graph 4, in which solvents are sorted from the most to the least polar from left to right (based on dipole moment), two general trends can be observed. On the one hand, from acetonitrile to THF, conversion and *e.e.* increase; on the other hand, from THF to toluene, conversion and *e.e.* decrease. These two trends point towards THF which gives at the same time the highest conversion (99%) as well as the highest *e.e.* (85%). Consequently, THF was the solvent used as an optimal solvent from then on. It should be noted that no correlation between catalyst solubility in the solvent and outcome could be established.

5.1.3 Further screening of preformed catalysts

A wide range of preformed rhodium and iridium catalysts bearing different types of chiral *bis*phosphines were tested in the Me_2Zn imine addition reaction.

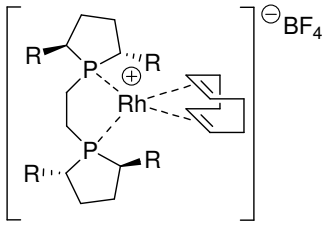
Families of ligands tested include DuPHOS, BPE, FerroTANE and 5-Ferrocenyl (Figure 19).





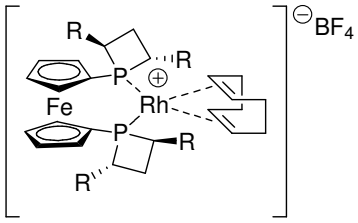
83: R = Me (*R*)
95: R = Et (*R*)
96: R = *i*-Pr (*S*)

Rh - DuPHOS



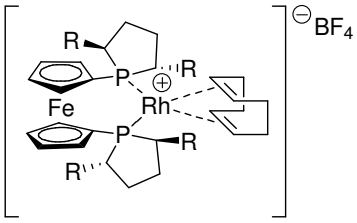
97: R = Me (*R*)
98: R = Et (*S*)
99: R = *i*-Pr (*S*)
100: R = Ph (*S*)

Rh - BPE



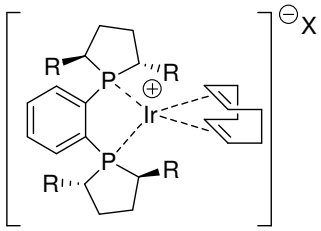
101: R = Me (*R*)
102: R = Et (*S*)
103: R = *i*-Pr (*S*)
104: R = *t*-Bu (S)

Rh - FerroTANE



105: R = Me (*R*)
106: R = Et (*S*)
107: R = *i*-Pr (*S*)

Rh - 5-Ferrocenyl



81: R = Me (*R*) , X = BF_4
108: R = Et (*S*) , X = PF_6

Ir – DuPHOS

Figure 19: Preformed catalysts tested in the ligand screening with dimethylzinc.

The results of this screening (Table 16) identified two main families of ligands giving good enantioselectivities: Rh-DuPHOS and Rh-BPE. The highest enantioselectivity (Entry 2) was reached with **83** which gave 94% e.e. In the presence of 7% dichloromethane in the reaction solvent (Entries 3-4), solubility of **83** is complete but the *e.e.* and conversion go down slightly. With **95**, **97** and **98**, *e.e.* slightly decreases but remains moderately good (75-82%). Interestingly, when the substituent in the *bis*phosphine is an isopropyl group (**96** and **99**) no reaction occurs at all. This clearly shows that steric hindrance is a key factor to the success of the reaction. When rhodium-BPE is substituted with a phenyl group (**100**), a dramatic drop of the enantioselectivity is observed (36% e.e.); this observation leads to the conclusion that the reaction is favoured by a ligand moiety in which the substituent is a small alkyl group.

Table 16: Results obtained in the ligand screening with dimethylzinc.

Entry	Ligand	Time	Conv.[a] (%)	e.e.[b] (%)
1	**83**	2 h	74	**92**
2		overnight	100	**94**
3	**83**[(c)]	2 h	49	**89**
4		overnight	98	**84**
5	**95**	2 h	61	**82**
6		overnight	99	**80**
7	**96**	2 h	nd	nd
8		overnight	nd	nd
9	**97**	1 h	37	**76**
10		3 h	93	**75**
11	**98**	1 h	49	**80**
12		3 h	84	**80**
13	**99**	1 h	nd	nd
14		3 h	nd	nd
15	**100**	1 h	35	36
16		3 h	95	31
17	**101**	3 h	42	38
18	**102**	3 h	15	0
19	**103**	3 h	18	0
20	**104**	3 h	69	0
21	**105**	3 h	26	32
22	**106**	3 h	nd	nd
23	**107**	3 h	15	7
24	**81**	3 h	nd[d]	nd
25	**108**	3 h	nd	nd

(a) Determined by ^{1}H NMR spectroscopy.
(b) Determined by Supercritical Fluid Chromatography.
(c) Solvent: THF/dichloromethane (93/7).
(d) Formation of an unidentified compound.

In the case of the rhodium-BPE catalyst **97**, Burk[139] who first reported the synthesis and application of this family of catalyst, highlighted the large dihedral angle (24° for the SbF_6^- version of **97**) between the P-Rh-P plane and the plane defined by the COD olefin midpoints and Rh (C_M-Rh-C_M). Strong steric interactions between the asymmetric phosphine ligand and COD are responsible for this distortion from the expected square-planar geometry. Similar distortions are seen in ligands of this family bearing different

substituents as well as in a related Rh-complex bearing the chiral ligand BINAP[140] and indicate a highly asymmetric environment that should strongly influence π-facial selectivity during binding of prochiral unsaturated substrates. In fact, an extensive crystallographic study of five-membered Rh-*bis*phosphine–diolefin complexes of the type $[Rh(PP)(diolefin)]^+$ carried out by Heller *et al.*[141] demonstrated that most crystal structures of this type of catalyst show a deviation from the ideal square-planar arrangement. A more detailed consideration of the structures shows that there are also other deviations from the square-planar structure occurring than the tetrahedral distortion. If one defines the ideal square-planar arrangement according to Figure 20 as the x/y plane with rhodium in the point of origin, the tetragonal distortion corresponds to the rotation of the diolefin around the y-axis. The similarly possible rotation around the x-axis results in a square-pyramidal arrangement with the rhodium atom at the top of the pyramid.[142]

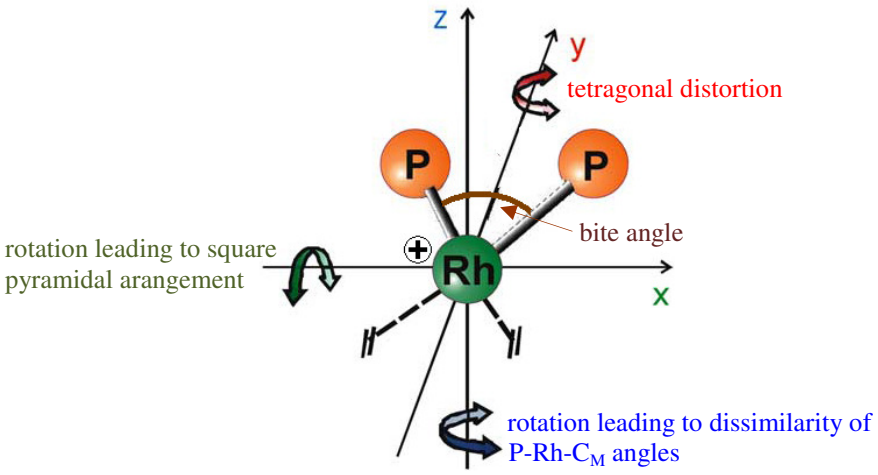


Figure 20: Square-planar $[Rh(PP)(diolefin)]^+$ complex in the x/y-plane, with rhodium in the point of origin.

The tetrahedral distortion, a "twist" of the diolefin, is generally explained by steric demands of the diphosphine ligand. Comparison of the dihedral angles (P-Rh-P/C_M-Rh-C_M) for cataysts [(*S,S*)-Me-DuPHOS Rh(COD)]BF_4 (*S*,*S*-**83**) and [(*R,R*)-Et-DuPHOS Rh(COD)]BF_4 (*S*,*S*-**95**), 16.4° and 21.1° respectively, confirms this assumption. Finally, a rotation of the diolefin around the z-axis is also imaginable, it leads to a situation in which the two P–Rh–C_M angles become dissimilar. All three disturbances influence and depend on each other.

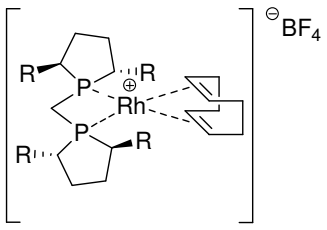
To conclude, the steric demand fixed by the alkyl substituents on the ligand moiety generates geometrical distortions on the cationic rhodium complex which result in an increase or decrease of the enantioselectivity as proven by our experimental evidence. Therefore, a small group such as the methyl is preferred to the ethyl which is preferred to the phenyl or isopropyl group.

There is a clear correlation between the chelation bite angle[143] (P-Rh-P) that is determined crystallograhically for the diphosphine ligand backbone and the outcome of the addition reaction in terms of enantioselectivity. For example, the Rh-BPE family (**97**, **98**) gives a good enantioselectivity; but not as good as the Rh-DuPHOS (**83**, **95**); this difference could be explained by the fact that the degree of ring strain is more important with the Rh-DuPHOS family since it has a smaller bite angle due to the phenyl group of the DuPHOS moiety. As a comparison, [(*S,S*)-Me-DuPHOS Rh(COD)]SbF_6 and [(*R,R*)-Me-BPE Rh(COD)]SBF_6 have bite angles of 84.8° and 85.1° respectively;[143] analogous complexes tested, e.g. (*R,R*)-Me-DuPHOS Rh(COD)]BF_4 **83** (Table 15, entry

2, 93% e.e.) and [(*R,R*)-Me-BPE Rh(COD)]BF_4 **97** (Table 5, entry 10, 75% e.e.) support our theory.

Similarly, total or partial collapse of the enantioselectivity in the Rh-FerroTANE and Rh-5-Ferrocenyl (**101**-**107**) catalysed reactions can be explained by the wide bite angle existing in these ligands (98.3° for analogous [Rh(NBD)(Et-FerroTANE)]BF_4 complex[144]). Indeed, X-ray structures of FerroTANE complexes highlight some peculiar structural features that may affect on their catalytic behaviour: the large bite angle and the high tilting of the phosphetane moieties relative to each other, which is enforced by the bulky ferrocene backbone.[144,145] However the possible implications of these peculiar geometric features have not been fully rationalised yet.

An interesting Rh-preformed catalyst to try would be Rh-BPM **109**[146,147] (Figure 21) because of its smaller bite angle (74.10° for (*R*,*R*)-Ph-BPM Rh(acac) complex[148]). If the theory is true, enantioselectivity which could be reached with this preformed catalyst could exceed that achieved with **83**.



109

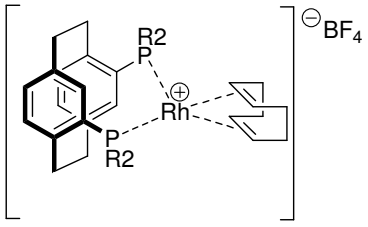
Figure 21: [BMP Rh(COD)]BF_4 preformed catalyst.

Obviously this is only a general trend since not all the preformed catalysts tested follow the rule and it should be borne in mind that this theory can only

give a partial explanation since other factors such as the steric and electronic properties of the preformed catalysts also intervene.

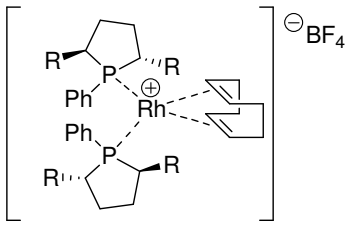
Finally, screening of two Ir-DuPHOS ligands (Entries 24-25) was unsuccessful as no addition product was formed. In the case of **81** a certain amount of unidentified compound was detected by thin layer chromatography; isolation and characterisation of this compound was carried out but did not enable clear identification of this compound.

A second set of other rhodium preformed catalysts was tested (Figure 22). This new set comprises two families: PhanePHOS and PhePHOS.



R = *i*-Pr (*R*) 110
R = Ph (*S*) 111
R = 4-F-Ph 112

Rh – PhanePHOS



R = Me (*R*) 114
R = Et (*R*) 115

Rh - PhePHOS

Figure 22: Second set of preformed catalysts tested in the ligand screening with dimethylzinc.

Results obtained with these preformed catalysts (Table 17) show that the PhanePHOS and PhePHOS family do not seem to be very enantioselective (0-36% e.e.).

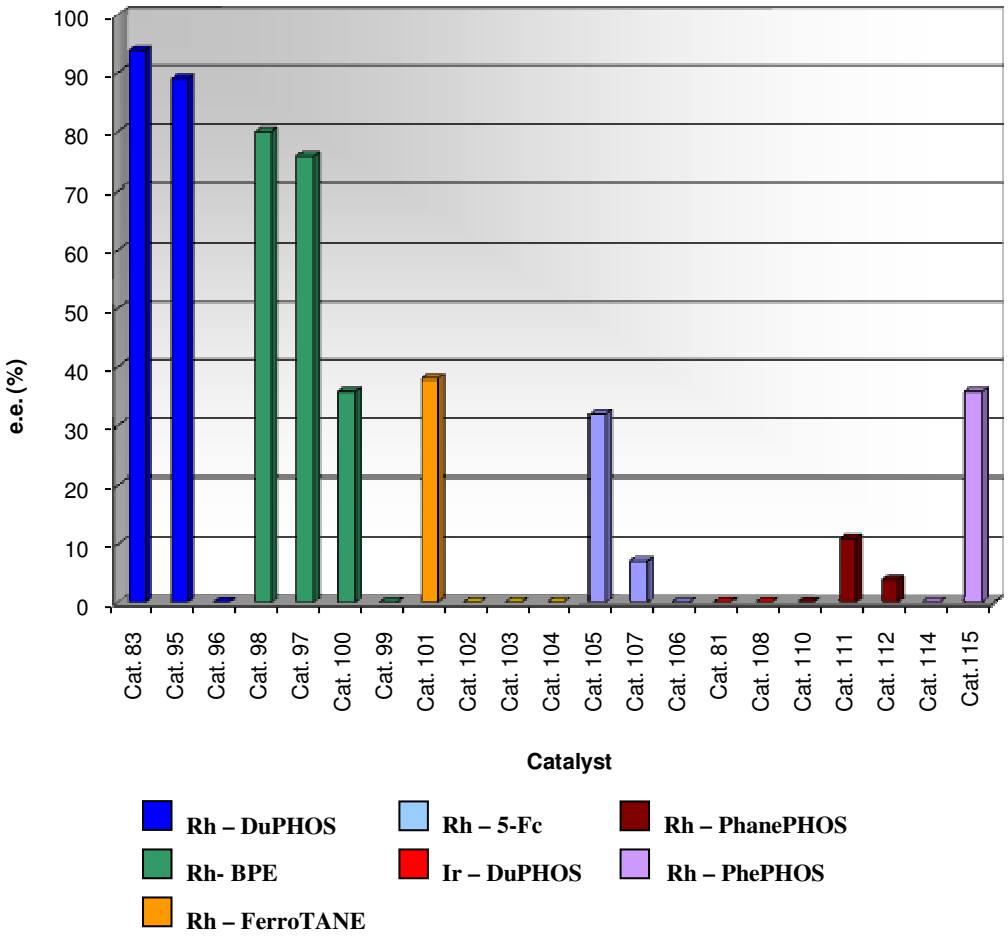
Table 17: Results obtained with the second set of preformed catalysts in the ligand screening with dimethylzinc.

Entry	Ligand	e.e.[a] (%)
1	**110**	0
2	**111**	11
3	**112**	4
4	**114**	0
5	**115**	36

(a) Determined by Supercritical Fluid Chromatography.

Indeed, neither the the PhanePHOS ligands (Entries 1-3, 0-11% e.e.) nor the PhePHOS ligands (Entries 4-5, 0-36% e.e.) gave high *e.e.* values.

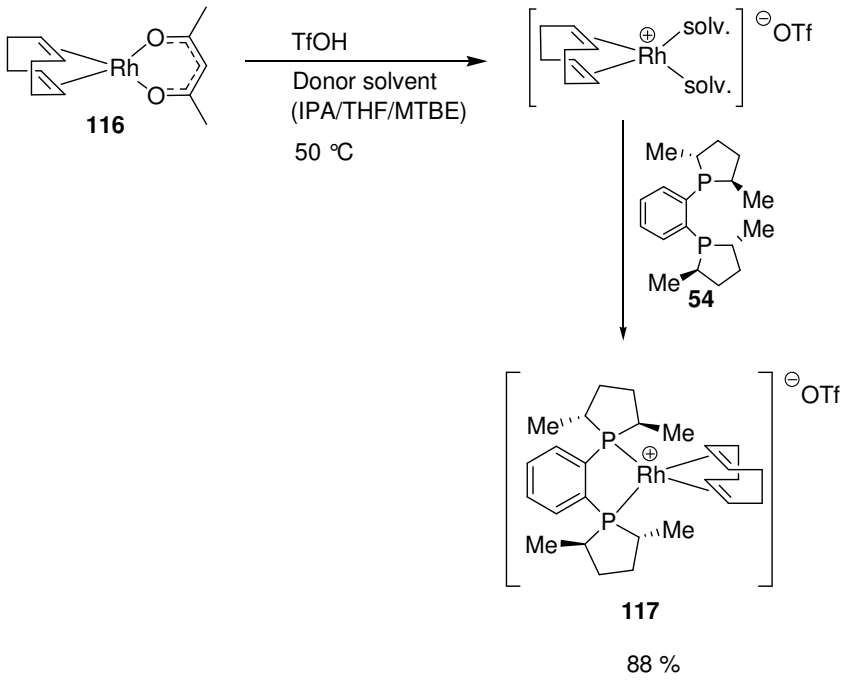
Graph 5 summarises the enantioselectivities obtained with the preformed catalysts screening thus giving a good visual comparison. As it can be seen, the most efficient preformed catalyst discovered was [(*R*,*R*)-Me-DuPHOS) Rh(COD)][BF_4] **83**.



Graph 5: Comparison of the different catalysts tested in the screening with Me_2Zn.

It was considered that a tuning of this catalyst by different alterations could lead to an enhancement of its efficiency either in terms of activity or more importantly in enantioselectivity. Therefore, two minor alterations were carried out on **83**: a change of the counteranion and a change of the leaving group. As mentioned earlier, an attempt to make this preformed catalyst more soluble in THF wasn't entirely successful (Table 15 – entries 3-4) as although it was managed to make it totally soluble in the presence of dichloromethane a drop in the enantioslectivity was observed.

Another solution to achieve this goal was to modify a part of the preformed catalyst so that it becomes more soluble in THF while keeping the same activity at the same time. Consequently, it was decided to prepare and test a homologue of **83** having the tetrafluoroborate counteranion replaced by a triflate counteranion, **117**. Preparation of the preformed catalyst **117** is a straightforward two step synthesis from commercially available [Rh(COD)(acac)] (Scheme 42). Addition of trific acid into a warm solution of [Rh(COD)(acac)] in a mixture of donor solvent causes the displacement of the acetylacetonate group in order to form a solvato species.



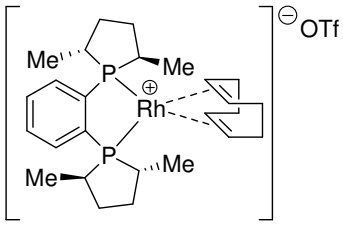
Scheme 42: Synthesis of [(*R,R*)-Me-DuPHOS) Rh(COD)]OTf.

Then, neat addition of (*R,R*)-Me-DuPHOS to the solvato species causes precipitation of the desired preformed catalyst in a good yield (88%). The hypothesis that the triflate salt of the preformed catalyst would be more soluble was verified experimentally; furthermore it was found that equal levels of

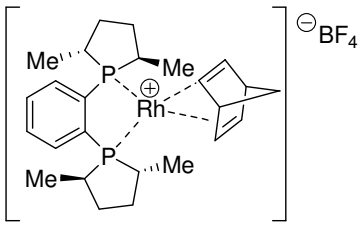
acitivity and enantioselectivity were reached with the two salts ({Table 16, entry 2} vs {Table 18, entry 1}).

Given that the change of the counteranion was not successful in increasing the efficiency of **83**, another alteration was carried out: replacement of the COD leaving group by a NBD group with **119** (Table 18, entry 2).

Table 18: Results obtained with catalysts 118 and 119 in the ligand screening with dimethylzinc.



118



119

Entry	Ligand	*e.e.*[a] (%)
1	**118**	93
2	**119**	93

(a) Determined by Supercritical Fluid Chromatography.

Although COD and NBD may seem to be very similar, they cause slight structural differences in Rh-*bis*phosphine-diolefin complexes such as a shorter C_M-Rh bond length and a smaller C_M-Rh-C_M with NBD.[149]

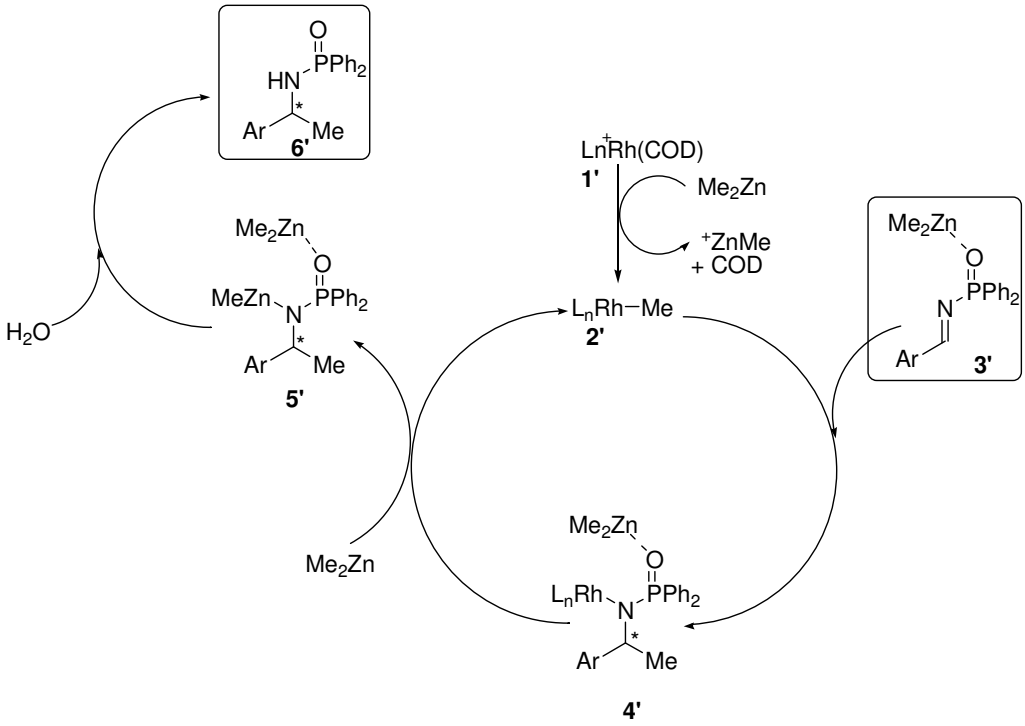
One attractive advantage of NBD precatalysts over COD complexes is its lower cost which in turn can make costs of ligands and catalysts significantly reduced. One other element that pushed us into trying the NBD group (**119**) is the fact that in a reported study carried out in the field of hydrogenation,[150] the time required for conversion of half of one same substrate ((*Z*)-*N*-benzoylaminocinnamate) with the COD complex is six times as long as with the NBD complex.

This type of NBD precatalyst can be easily prepared following the procedure of Schrock and Osborn[151] by the reaction of Rh(NBD)acac with the chiral ligand and subsequent addition of HBF_4. Another quite general methodology developed by Heller[152] consists in the treatment of the relevant COD complexes with an excess of NBD (Scheme 43).

$$[Rh(COD)(P\text{-}P^*)]BF_4 \underset{}{\overset{NBD}{\rightleftharpoons}} [Rh(NBD)(P\text{-}P^*)]BF_4$$

Scheme 43: Synthesis of Rh complexes with a NBD counter ligand developed by Heller.

The mechanism of the Me_2Zn addition reaction (Scheme 40) is similar to the mechanism proposed for the Ir(I)-catalysed $AlMe_3$ addtion reaction presented earlier (Scheme 44).



Scheme 44: Suggested mechanism for the Rh(I) catalysed Me_2Zn addition reaction.

In the first step, reaction between Rh catalyst **1'** and diorganozinc reagent generates the active catalytic species L_nRh-Me **2'**. Then, this species carries out a methyl transfer to the imine substrate **3**' which is activated by Lewis acidic Me_2Zn. This results in the formation of compound **4**' which bears a chiral center α to the Me group. Finally, intervention of another equivalent of Me_2Zn replaces the former N-Rh bond by a N-Zn bond to give **5**'. In the last step compound **5**' is quenched by water to afford the desired methylated protected amine **6'**.

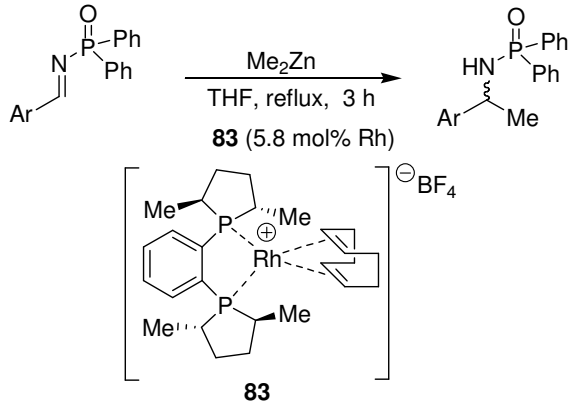
5.2 Problem of reproducibility

The different screenings led to the conclusion that the best preformed catalyst for our catalytic system using solely benzaldimine **27** as substrate was **83**; the next move was then to evaluate and compare the tolerance of the newly found system towards different aryl substituents. Therefore nine substrates bearing different substituents at different positions were tested (Table 19).

Substituents such as the *p*-methoxy phenyl group (Entry 7) seemed to perform poorly both in terms of activity and enantioselectivity, thus showing a limited tolerance towards electron donating groups. This observation that an electron donating substituent on the aromatic ring decreases the rate of the reaction was equally observed in Cu(II)-catalysed Me_2Zn addition developed by Charette *et al.*[40]

In the case of the 1-naphthyl group (Entry 8), the reaction does not proceed at all while it runs smoothly with the 2-naphthyl group (Entry 9), highlighting here a non-tolerance of excessively sterically hindered substrates. All other substrates gave a reasonable enantioselectivity (Entries 1-6).

Table 19: Substrate tolerance of the Me_2Zn addition reaction.



83

Entry	Ar		*e.e.*[a] (%)
1	Ph	**27**	74-94
2	4-F-Ph	**36**	80
3	4-Cl-Ph	**37**	84
4	4-Br-Ph	**40**	62
5	4-CF_3-Ph	**35**	76
6	4-Me-Ph	**32**	70
7	4-OMe-Ph	**43**	50 [b]
8	1-naphthyl	**42**	/ [c]
9	2-naphthyl	**41**	74

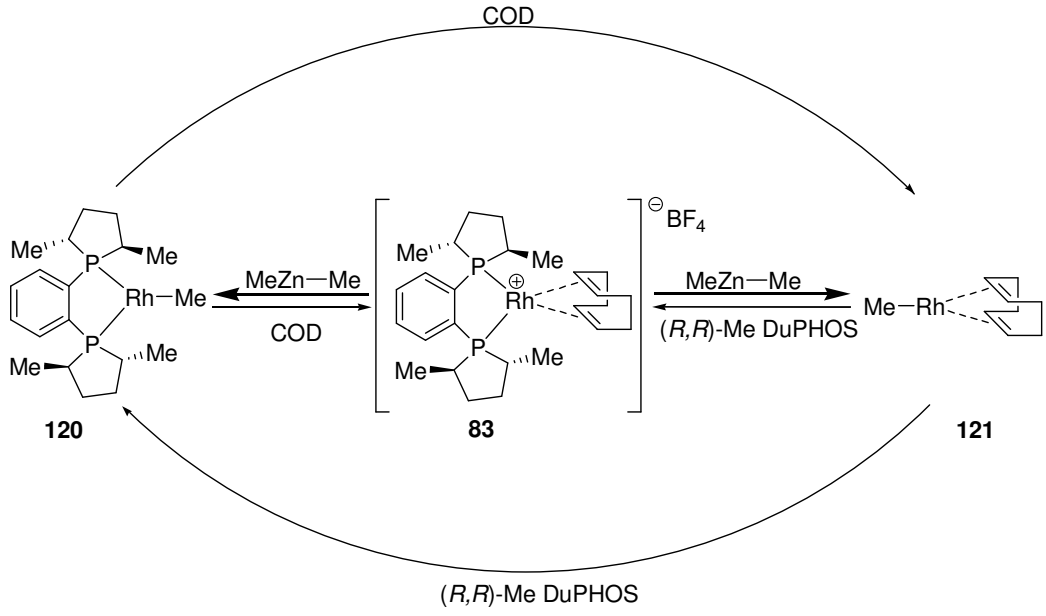
(a) Measured by HPLC (OD-H column, 95:5 hexane/IPA,1.0 ml/min).
(b) Low conversion.
(c) No reaction occurred.

Surprisingly, while it was previously found that use of benzaldimine **27** as a substrate could reach an enantioselectivity of up to 94% e.e. (*cf*. Table 15), we were disappointed to realise that this enantioselectivity could be significantly variable (Entry 1), going in the worst cases down to 75% e.e. This gap was obviously not acceptable and an investigation was undertaken to identify the source of the problem and to make the system more robust.

5.2.1 Effect of the ligand/metal ratio

This problem of reproducibility was thought to be related to the formation of an undesired achiral catalytic species, generated in random amounts, each time the reaction was run. This achiral species has to compete with the active chiral species which we aim to generate between the Rh precursor and Me_2Zn.

If one considers the reaction between Me_2Zn and the Rh catalyst **83**, the transfer of the nucleophilic methyl group from Me_2Zn can occur through two different approaches that may compete with another. The first one is an attack of the Rh centre of **83** by the methyl group that leads to the displacement of the COD coligand, in which case species **120** is formed (Scheme 45). The second one is the same nucleophilic attack that results this time in the displacement of the DuPHOS ligand, in which case species **121** is formed.



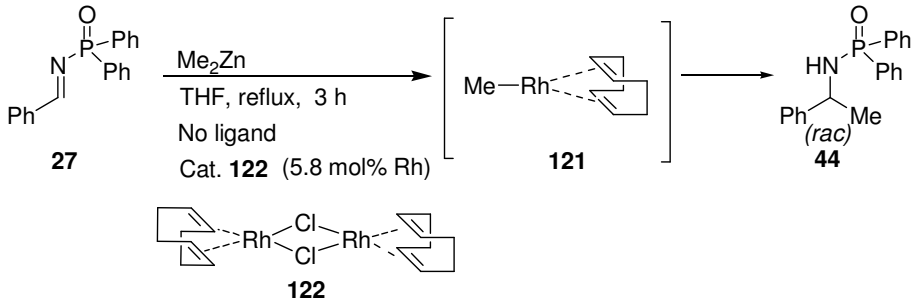
Scheme 45: Chiral and achiral species competing as a nucleophile.

In other words, two different catalytic species are formed according to a pathway differing only in the nature of the leaving group. The rhodium-

ethylene bond dissociation energy being estimated to only ca. 130 kJ mol^{-1},[153] the ratio **121/120** should be fairly small. Nevertheless, species **121** being catalytically more active than **120**, even a small amount can be very detrimental to the enantioselectivity. The Rh-Me bond energy being fairly low (52.0 kJ mol^{-1},[154] so lower than Rh-ethylene) one can say that formation of compounds **120** and **121** from **83** may be reversible.

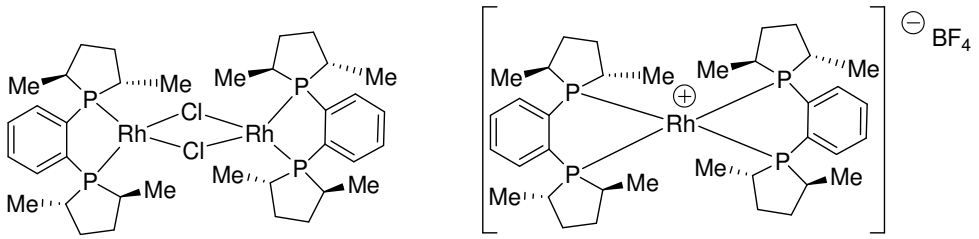
In the context of [4+2] cycloaddtion chemistry, Hayashi evaluated the relationship between the catalyst activity and the nature of the ligand on the transition metal. He demonstrated that a rhodium-diene complex is much more active than its rhodium-*bis*phosphine counterpart as a catalyst.[155] His quantitative evaluation of several ligands in a rhodium catalysed intramolecular [4+2] cycloaddition reaction was carried out in a kinetic study and it was found that the reaction catalysed by the Rh-COD complex proceeded very fast while rhodium-dppe and rhodium-dppb catalysts counterparts (dppe = 1,2-*bis*(diphenylphosphanyl)ethane; dppb = 1,2-*bis*(diphenylphosphanyl)butane) were at least twenty times slower.

To verify that achiral species **121** gives indeed the racemic product, the same Me_2Zn addition reaction was run using this time $[Rh(Cl)COD]_2$ as a catalyst, in the absence of any ligand (Scheme 46).



Scheme 46: Effect of racemisation caused by achiral catalytic species Rh(Me)(COD).

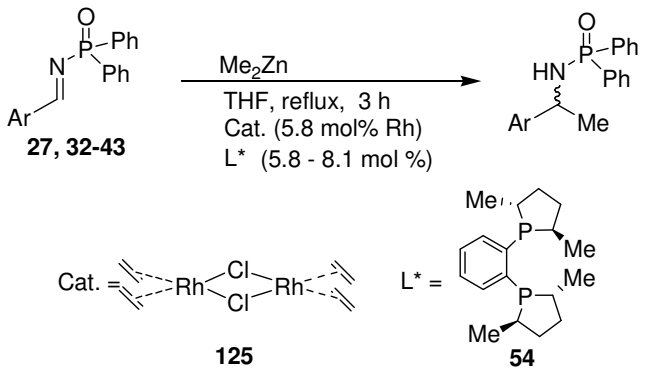
As expected, the reaction afforded the racemic product which confirmed our hypothesis regarding the consequences of the generation of **121**, namely a racemisation process. The ratio ligand/metal being fixed to 1:1 in **83**, we thought that a trivial solution to solve the problem would be to modify this ratio by increasing the amount of ligand. This way, the presence of deliberately added free excess (*R,R*)-MeDuPHOS would convert any achiral species **121** directly into **120**. Also, to diminish the formation of **121**, it was decided to replace the COD coligand with a *bis*(ethylene) analogue since the latter is known for being a better leaving group. Unlike COD (or COE) which is a high boiling point liquid (b.p. = 150 °C), ethylene has the advantage of being a gas; therefore, when ethylene is displaced by the methyl group (or maybe the solvent, THF), the process is not reversible as ethylene gas cannot be coordinated back to rhodium. In the case of the COD group (**83**), the same process is reversible to some extent (slower exchange metal-coligand) which makes it less labile and eventually allows generation of a certain amount of highly active achiral species **121**. By using the highly labile *bis*(ethylene) coligand, it is inferred that the possible rhodium catalytic species reacting with Me_2Zn (to obtain **120**) is [(*R,R*)-Me DuPHOS Rh(Cl)]$_2$ **123** (Figure 23). The formation of another species, **124**, could also be envisaged; this latter being a Rh atom substituted with four phospholanes would be catalytically inactive as all sites on Rh are occupied.



123 **124**

Figure 23: Possible rhodium species generated in the catalytic process.

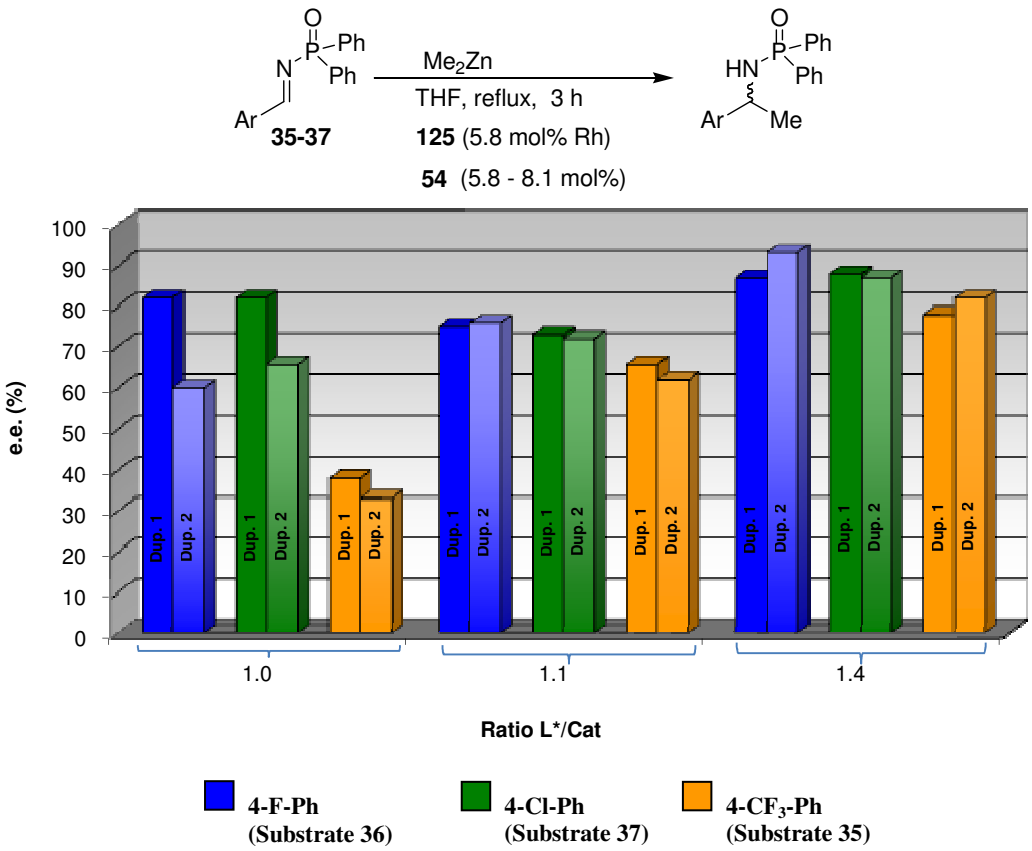
To verify the outcome of the above-mentioned hypothesis, the catalytic system was therefore altered by using chloro*bis*(ethylene)rhodium(I) dimer as a catalyst and an excess of (*R,R*)-Me DuPHOS ligand (Scheme 47).



Scheme 47: Me_2Zn addition reaction carried out with $[Rh(Cl)(C_2H_4)_2]_2$ as a catalyst.

The reproducibility of the transformation was checked by running the reaction twice in the very same conditions, and with different ratios ligand/metal in order to compare results obtained with the duplicates (Graph 6). As it can be clearly seen, on the one hand when the ligand and the metal are used in equimolar proportions (L*/Rh = 1.0), a significant gap is visible between the enantioselectivity reached between duplicates of the same reaction. A remarkable example is the case of the *p*-fluoro benzaldimine **36** in which the enantioselectivities obtained in the two duplicates show a gap of 22% whilst a

slight increase of 0.1 mol% of ligand (i.e. L*/Rh = 1.1) reduces this gap down to 1%, thus making a valuable difference.



Graph 6: Effect of the L*/Rh ratio on the reproducibility of the Me_2Zn addition reaction. Comparison of duplicates.

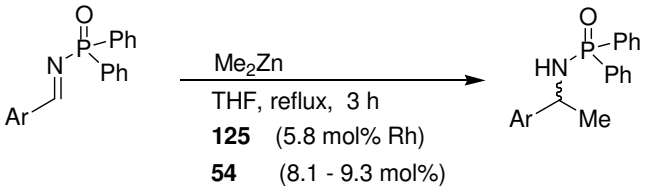
A noteworthy trend is the fact that increasing the amount of ligand does increase the enantioselectivity. In the case of the *p*-trifluorobenzaldimine **35**, the *e.e.* evolves progressively from 33% to 62% and 82% with respective L*/Rh ratios of 1.0, 1.1 and 1.4. The fact that our rhodium catalysed system exhibits ligand retarded catalysis, this increase has its limits since an excessive amount of ligand reduces the activity. These results supported strongly and confirmed our hypothesis expounded earlier. Consequently, we decided to keep

the new catalytic system which has an excess of ligand, for further optimisation.

5.2.2 Effect of the reaction scale

The influence of another parameter of the reaction, the scale on which it was performed, was tested. The reaction was scaled up by a factor 2 from 0.30 mmol (usual scale) to 0.60 mmol. Four substrates were tested and the variation of the enantioselectivity in two different ligand/catalyst ratios measured (Table 20).

Table 20: Effect of the reaction scale on the reproducibility of the enantioselectivity.



Entry	Ar		*e.e.* (%)[a]			
			[0.30 mmol scale]		[0.60 mmol scale]	
			L*/cat. = 1.4	L*/cat. = 1.6	L*/cat. = 1.4	L*/cat. = 1.6
1	Ph	**27**	97	81	93	93
2	4-CH_3-Ph	**32**	89	81	93	93
3	4-CF_3-Ph	**35**	75	75	86	86
4	4-F-Ph	**36**	86	88	89	90

(a) Determined by GC after derivatisation.

Results show that on a 0.30 mmol scale, the variability of the enantioselectivity can still be significant in some cases (Entries 1-2) or minor in others (Entries 3-4). On the other hand, on a 0.60 mmol scale, not only the steadiness of the reproducibility is increased (highest variation is 1% e.e – entry 4), but the

enantioselecivity as a whole is also increased from 2% (Entry 4) to 15% (Entries 1-2-3).

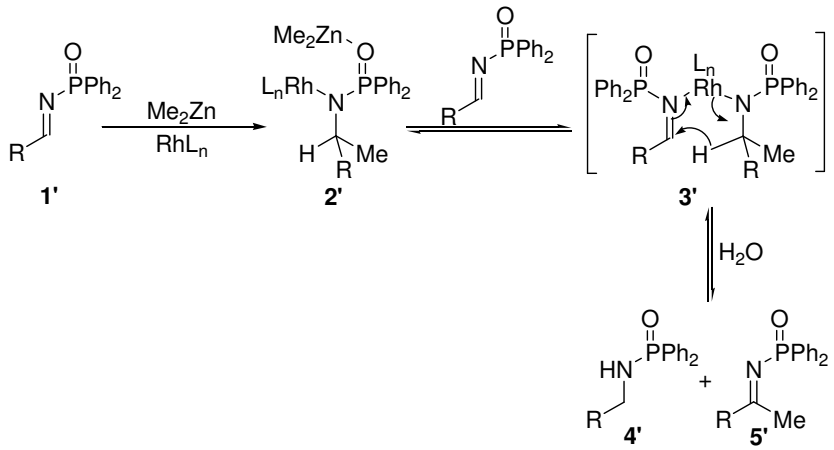
It is assumed that the explanation of this finding is merely due to the fact that the instrumental level of accuracy of the amounts of chemicals weighed out on the balance, is higher when the reaction is scaled-up. Indeed, the amount of catalyst and ligand goes up from 3.4 mg and 9.6 mg to 6.8 mg and 19.2 mg when shifting from a 0.30 to a 0.60 mmol scale respectively.

5.3 Formation of the reduction product

5.3.1 Meerwein-Ponndorf-Verley rearrangement

The formation of an unusual byproduct which could be detected by ^{1}H NMR spectroscopy drew our attention during the optimisation stage of the Me_2Zn reaction. The identification of this byproduct was carried out by means of spectroscopic data and it turned out to be the product resulting from the reduction of the substrate. This identification was confirmed by synthesing the reduction product and by comparing the spectroscopic data which perfectly matched.

Initially, the formation of the reduction product puzzled us since unlike Et_2Zn, no β hydride elimination can take place with Me_2Zn. This option being ruled out, the other most likely reaction that could generate a reduction product was a Meerwein-Ponndorf-Verley (MPV) rearrangement. In this reaction (Scheme 48) the rhodium-catalyzed hydride shift from the α carbon of amine **2'** to the C=N bond of the imine proceeds via a six-membered transition state. This transition state gives rise to two compounds, the MPV reduction product **2'** and the Oppenauer oxidation product ketimine **5'**.



Scheme 48: Meerwein-Ponndorf-Verley reduction occurring as a side reaction in the Me_2Zn addition reaction.

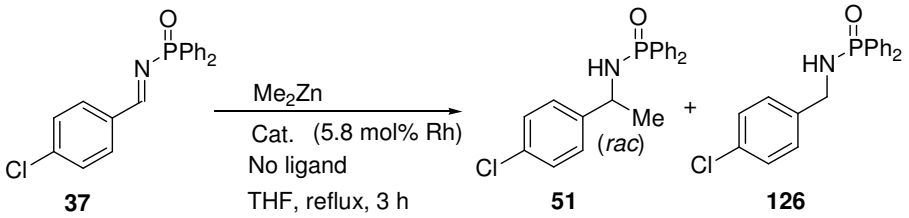
The metal promoting the formation of the six-membered transition state could possibly not be rhodium as it is suggested in the above-mentioned scheme. A basic experimental attempt to determine the nature of the coordinating metal in **3'** was undertaken. It was found that the absence of either the Rh catalyst or Me_2Zn resulted in the total recovery of the starting material; a result which could not contribute to the mechanistic understanding of the process taking place.

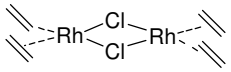
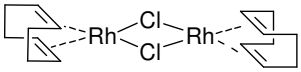
Unfortunately, the hypothesis that the MPV reduction reaction is taking place has not been proven yet. In fact, generation of the Oppenauer oxidation product **5'** was not experimentally observed; none of its possible decomposition products due to its hydrolytic unstability were observed either by NMR spectroscopy which may suggest that **5'** undergoes another unidentified reaction.

In order to minimise or inhibit the formation of the MPV product it was necessary to gain insight into which parameters could affect the formation of

this byproduct. Two parameters were identified in our study: the catalyst coligand (Table 22) and the ligand/metal ratio (*cf.* 5.2.5, table 22). Indeed, it was found that the nature of the catalyst coligand which may seem to be a non significant factor could favour substantially the formation of the MPV product **126**.

Table 22: Influence of the catalyst coligand on the formation of the MPV reduction product 126.



Entry	Catalyst		51:126 ratio [a]
1		**125**	10 : 90
2		**122**	54 : 46

(a) Determined by ^{1}H NMR spectroscopy.

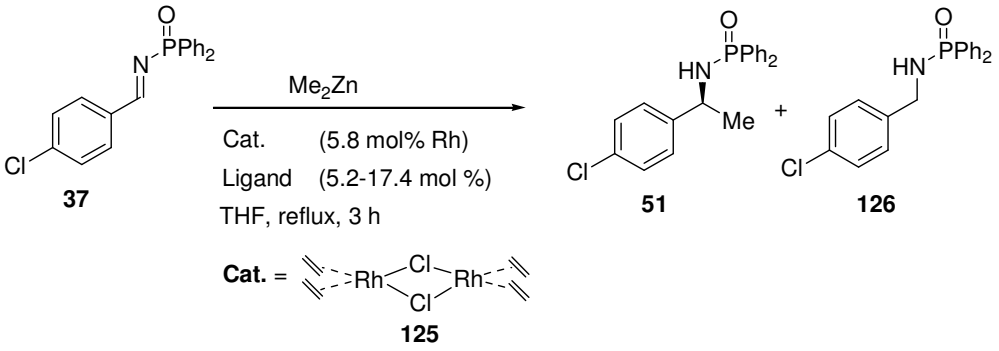
This was realised when catalysts **125** and **122** were employed under the same conditions in the Me_2Zn addition reaction. Surprisingly, although both catalysts have the same acitivity, **125** which has an ethylene coligand and **122** which has a COD coligand afforded a 10:90 (Entry 1) and 54:46 (Entry 2) methyl addition product:MPV product ratio respectively.

5.3.2 Effect of BozPHOS

As presented in the introduction (*cf.* 1.3.2.2.2, Scheme 7), in the Cu(I)-catalysed Me_2Zn addition reaction developed by Charette *et al.*,[39,40,41] it was found that the Me-DuPHOS monoxide ligand (or BozPHOS) was performing

better than the Me-DuPHOS ligand. Charette and coworkers also found that the genuine catalyst participating in the reaction is actually not Cu-DuPHOS, but Cu-BozPHOS which is formed by an *in situ* oxidation.[156] Consequently, this interesting fact encouraged us to evaluate the effect of BozPHOS both as a ligand and as an additive on the Me_2Zn addition reaction to *p*-Cl-benzaldimine **37** (Table 23).

Table 23: Effect of BozPHOS as ligand and additive on the Me_2Zn addition reaction.



Entry	L*/Rh ratio	Ligand	Additive	Results		
				Conv.[a] (%)	Ratio[a] 51:126	*e.e.*[b] (%)
1	0	none	none	100	10 : 90	0
2	0.9	(*R,R*)-Me-DuPHOS	none	100	67 : 33	86-91
3			BozPHOS[c]	100	91 : 9	90
4		BozPHOS	none	100	84 : 16	85
5	1.8	(*R,R*)-Me-DuPHOS	none	100	95 : 5	86-90
6			BozPHOS[d]	100	96 : 4	87
7			1,5-COD[e]	100	95 : 5	88
8		BozPHOS	none	100	92 : 8	91
9	1.4	(*R,R*)-Me-DuPHOS	none	100	92 : 8	82
10	2.2			86	94 : 6	80
11	3.0			11	72 : 28	78

(a) Determined by ^{1}H NMR spectroscopy.
(b) Determined by GC after derivatisation.
(c) Loading = 5 mol%.
(d) Loading = 2 mol%.
(e) Loading = 10 mol%.

Three elements were measured: conversion, enantioselectivity and methyl addition product/reduction product ratio. In the absence of ligand, the reaction affords the racemic product (as expected) and mainly the MPV product (Entry 1). When the reaction is run with a 0.9 L*/cat. ratio, addition of BozPHOS as an additive with DuPHOS seems to be effective to reduce the formation of the MPV product (Entries 2-3). However under this ratio, when BozPHOS is used as the main ligand (Entry 4) a greater amount of MPV product is generated while the enantioselectivity does not vary substantially (85-91% e.e, entries 2-4). Nevertheless, no solid finding can be drawn from such results since it is known that a problem of reproducibility does exist when the ligand/metal ratio is low. When the reaction is run with a 1.8 L*/cat. ratio, the amount of MPV product is very small (relative amount : 4-5%, entries 5-7). Under this ratio, the absence or presence of BozPHOS as an additive (Entries 5-6) is not detrimental since identical values of conversion, *e.e.* and methyl addtion product/reduction product ratio are measured. However when BozPHOS is the main ligand (Entry 8) a slight increase in enantioselectivity (91% e.e.) can be measured. The effect of the addition of free 1,5-COD was also tested (Entry 7); interestingly, the presence of 10 mol% of free 1,5-COD does not affect the outcome of the reaction since the results obtained in the presence or absence of this additive are almost identical. Based on Scheme 41, the addition of 1,5-COD should favour the formation of active achiral Rh catalyst bearing the COD group as a coligand. Unfortunately, this hypothesis could not be verified by this single test reaction. Finally, the reaction was run with a 1.4, 2.2 and 3.0 L*/Rh ratios (Entries 9-11) in order to observe the trend obtained with the increase of amount of ligand. As anticipated, a drop of the activity and of the selectivity

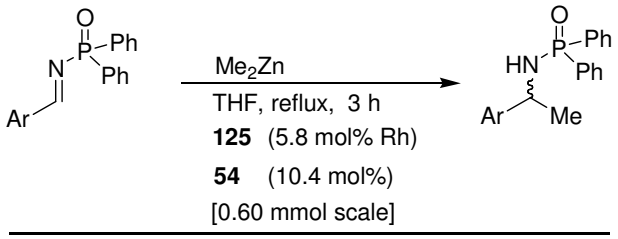
was observed when the amount of ligand was excessively high (Entries 10-11) since the present transformation corresponds to a ligand-retarded catalysis.

5.4 Effect of various optimisation parameters

5.4.1 Effect of substrate scope

Once the parameters related to the non-reproducibility, namely the ligand/metal ratio and the reaction scale, were identified and successfully solved, the reaction reached a good level of optimisation and it was therefore decided to test the newly developed conditions on seven substrates (Table 21).

Table 21: Me_2Zn addition reaction carried out on optimised conditions.



Entry	Ar		*e.e.* [a] (%)
1	Ph	**27**	97 (*R*)
2	4-Cl-Ph	**37**	90
3	4-Br-Ph	**40**	90
4	4-CF_3-Ph	**35**	89
5	3-Me-Ph	**33**	92
6	2-Me-Ph	**34**	91
7	2-Cl-Ph	**39**	> 99

(a) Determined by GC after derivatisation.

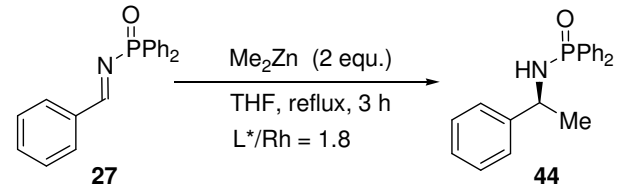
The level of enantioselectivity reached with the new conditions where the ligand/metal ratio is 1.8 and the reaction scale 0.60 mmol, was outstanding. Indeed, the range of substrates which was tested afforded enantioselectivites in the range 90-99% e.e. The *e.e.* value reached with **27** increased from 93% to

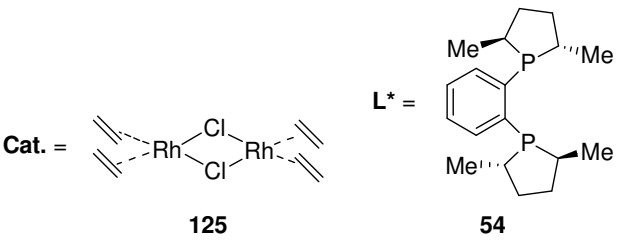
97% (Entry 1), from 84% to 90% (Entry 2) with **37**, and from 62% to 90% (Entry 3) with **40**.

5.4.2 Effect of catalyst loading

The catalyst loading of the Me_2Zn addition reaction which was set to 5.8 mol% for all reactions carried out in the study presented in this thesis. Obviously this loading is viable on a laboratory scale but very problematic on the industrial scale because of the price of rhodium which is fairly expensive. Consequently it was decided to test the reaction with a loading of Rh catalyst of 3.0 mol%, almost half of the usual loading (Table 24).

Table 24: Influence of the catalyst loading on performance of the reaction.





Entry	Cat. loading (mol% of Rh)	Conv. [a] (%)	*e.e.* [b] (%)
1	5.8	98	97
2	3.0	95	97

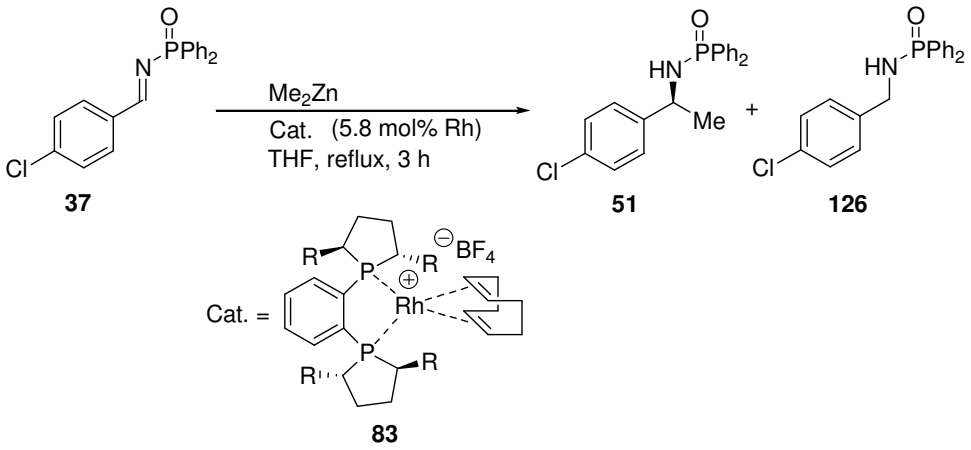
(a) Determined by ^{1}H NMR spectroscopy.
(b) Determined by GC after derivatisation.

Under this lower catalyst loading both activity and selectivity remained constant which shows that catalyst **125** is not used up to its highest limit and that a smaller amount could be successfully run.

5.4.3 Effect of free DuPHOS

As mentioned earlier, during the course of this study on the Me_2Zn addition reaction, it was found that the ligand/metal ratio was essential to get a good reproducibility and a good selectivity (*cf.* 5.2.2.1 **-** Graph 6). This discovery led us to use the couple (*R*,*R*)-Me-DuPHOS/$[RhCl(C_2H_4)_2]_2$ with a ratio of 1.8 instead of (*R*,*R*)-Me-DuPHOS Rh(COD)]BF_4 **83**. The positive effect of the excess of ligand being successfully demonstrated, an attempt to prove that this same excess could also be beneficial to the couple (*R*,*R*)-Me-DuPHOS/**83** was carried out. Therefore the Me_2Zn addition reaction was run with substrate **37**, catalyst **83**, and a sufficient amount of free DuPHOS ligand so that the overall ligand/metal ratio was equal to 1.8 (Table 25).

Table 25: Effect of free DuPHOS when combined with catalyst 83.



Entry	Additive	Ratio L*/cat.	Results		
			Conv. [a] (%)	51:126 ratio [a]	*e.e.* [b] (%)
1	none	1.0	100	90 : 10	82
2	(*R,R*)-Me-DuPHOS[c]	1.8	21	88 : 12	64

(a) Determined by ^{1}H NMR spectroscopy.
(b) Determined by GC after derivatisation.
(c) Loading = 4.6 mol%.

When catalyst **83** is used in the absence of free DuPHOS ligand which means that the ligand/metal ratio is equal to 1.0, a complete conversion and reasonable selectivity is obtained (Entry 1). But surprisingly, in the presence of 4.6 mol% of excess free DuPHOS ligand (ligand/metal = 1.8), a dramatic drop in the activity and in enantioselectivity is observed (Entry 2). Finally, no significant change in the amount of reduced byproduct **126** was observed. A possible explanation for the unexpected poor performance caused by the addition of free DuPHOS ligand in the present system could be that the Rh catalyst gets converted into an inactive species such as **124,** in which the Rh atom is tetrasubstituted with phospholanes, thus having all sites blocked.

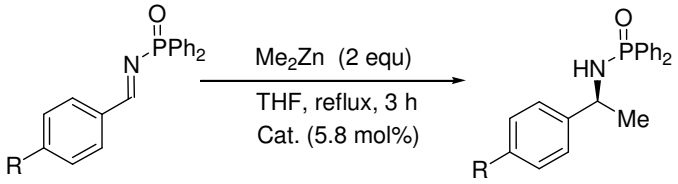
5.4.4 Effect of time and temperature

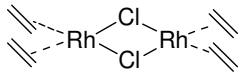
When the problem of reproducibility first arose, different parameters were studied; among them two were related to the formation of the catalytic complex: the reaction time and the temperature. To this end two different reaction conditions were tested:

- Conditions A: reaction run on a 0.60 mmol scale, ligand and catalyst stirred at room temperature for 90 min.
- Conditions B: reaction run on a 0.60 mmol scale, ligand and catalyst stirred at 60 ^{o}C for 110 min.

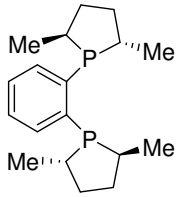
The influence on the enantioselectivity was then measured for both conditions and for two different ligand/Rh ratios (Table 26).

Table 26: Influence of time and temperature on the enantioselectivity.



Cat. = 

125

L* = 

54

Entry	R		*e.e.* (%) [a]			
			Conditions A[b]		Conditions B[c]	
			L*/Rh = 1.4	L*/Rh = 1.6	L*/Rh = 1.4	L*/Rh = 1.6
1	H	**27**	81	67	90	89
2	CF_3	**35**	84	82	85	85
3	F	**36**	72	72	62	88

(a) Determined by GC after derivatisation.
(b) Reaction run on a 0.60 mmol scale, ligand and catalyst stirred at room temperature for 90 min.
(c) Reaction run on a 0.60 mmol scale, ligand and catalyst stirred at 60°C for 110 min.

For a ligand/metal ratio of 1.6, the enantioselectivity is higher when the reaction is run under conditions B; for instance, in the case of substrate **27** (Entry 1), conditions A afford a 67% e.e. while conditions B afford a 89% e.e. Also, under conditions A the *e.e.* tends to decrease when switching from ratio 1.4 to ratio 1.6 while this decrease is not observed under conditions B.

Chapter VI

Conclusion

Conclusion

In conclusion, the goals and objectives of this research project have been successfully reached though further studies would be beneficial to bring more potential to the methodology which we have developed.

On the one hand, an effective iridium(I) catalytic system in the $AlMe_3$ (or DABAL-Me_3) addition reaction was identified. We showed that, in this system, addition of other organoaluminium nucleophiles such as the alkenyl group or the alkynyl group was suitable with the reaction conditions. Screening of different ligands to make the reaction enantioselective showed little success as the best result of this screening was obtained with **78** with only 36% e.e. The different screenings which were carried out led us to develop a new method for the measurement of the enantiomeric excess taking advantage of the presence of ^{31}P atom on the substrate. This ^{31}P NMR based technique was found to not be as accurate as chromatographic separation techniques such as HPLC or GC; nonetheless it is much more time saving in the identification of leads in high throughput screening.

On the other hand, the second goal achieved in this investigation was to identify another catalytic system enabling the effective and enantioselective addition of Me_2Zn to diphenylphosphinoyl protected imines. This new system catalysed by a rhodium(I) preformed catalyst, [(*R*,*R*)-Me-DuPHOS Rh(COD)]BF_4 **83** proved to be effective as it affords the methylated amine with very high conversion (~ 100%) and high *e.e.* (up to > 99%). A comprehensive screening of other rhodium and iridium preformed catalysts found that **83** was

the most enantioselective. A single attempt to carry out a Et_2Zn addition reaction in the conditions found with **83** proved unsuccessful, thus suggesting that a β hydride elimination is taking place with such alkyl groups and that the present rhodium-catalysed system requires further elaboration to increase the scope of nucleophiles. The Rh-catalysed methylation reaction was then improved by replacing catalyst **83** with $[RhCl(C_2H_4)]_2$ and (*R*,*R*)-Me-DuPHOS ligand, to get good reproducibility.

It should be noted that the two catalytic systems developed in this investigation both use commercially available catalysts and organometallic reagents, which is quite a substantial advantage compared to other similar transformations reported by other groups. Regarding the future work, some findings such as the effect of the ligand bite angle which have not been investigated thoroughly because of lack of time need further attention in order to find a highly performant catalyst. If the testing of BPM ligand **109,** which has been suggested earlier because of its small bite angle, is positive, the design and the synthesis of an entire family of derived ligands could be envisaged. Last but not least, the fact that the diphenylphosphinoyl protected amine product can be recrystallised smoothly (in CH_2Cl_2/hexanes) is a great advantage since it enables access to virtually enantiopure chiral amines.

Finally, once all the methodology is fully developed and optimised, a number of biologically active compounds featuring a chiral amine moiety could be easily synthesised, thus illustrating the usefulness of our novel reactions.

Chapter VII

Experimental procedures

Experimental procedures

7.1 Synthesised compounds

7.2 General methods

7.3 General procedures

7.4 Synthesis of aldimine susbstrates

7.5 Synthesis of racemates

7.6 Synthesis of trifluoroacetamides and acetamides

7.7 Deprotection and isolation of amines

7.8 Synthesis of ligands and catalysts

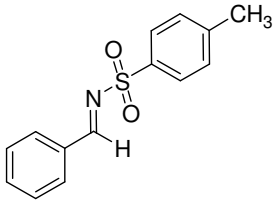
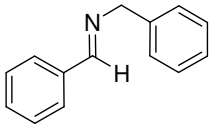
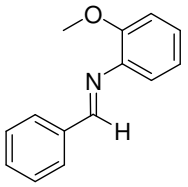
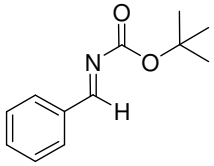
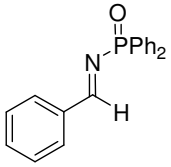
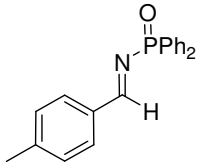
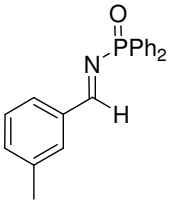
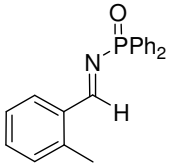
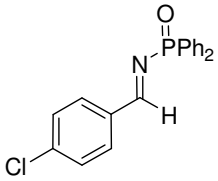
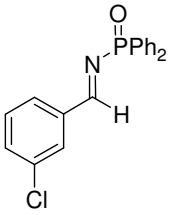
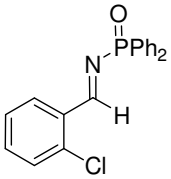
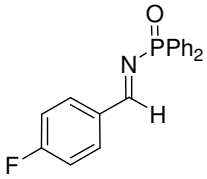
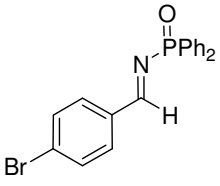
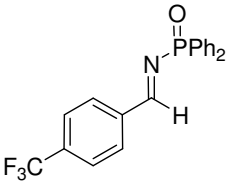
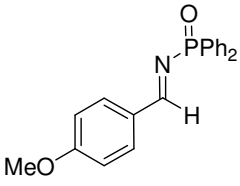
7.9 Synthesis of oximes

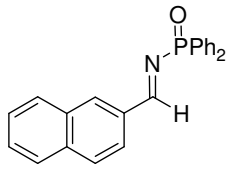
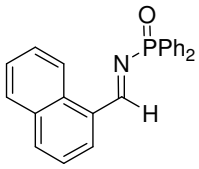
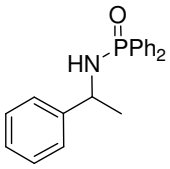
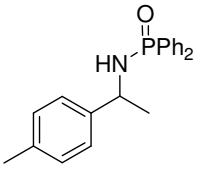
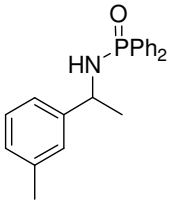
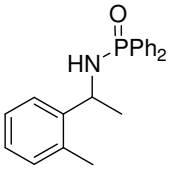
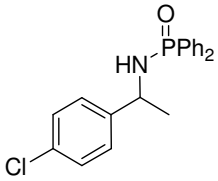
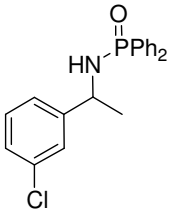
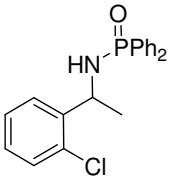
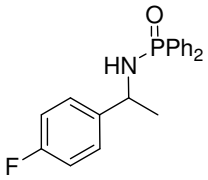
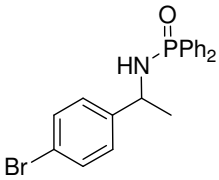
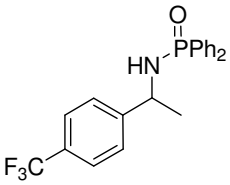
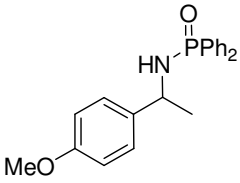
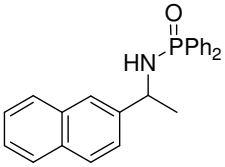
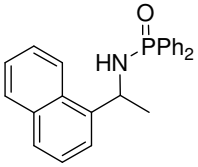
7.10 Synthesis of sulfonyl adducts

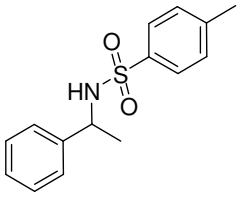
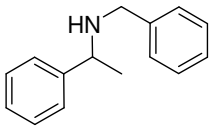
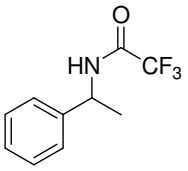
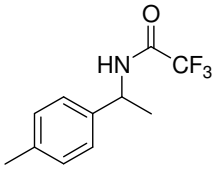
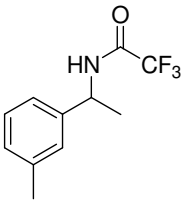
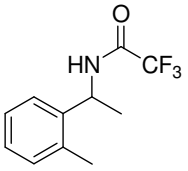
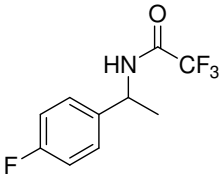
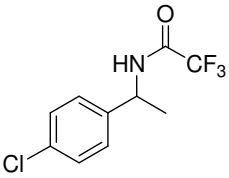
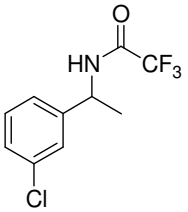
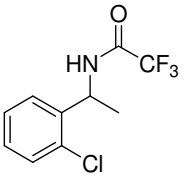
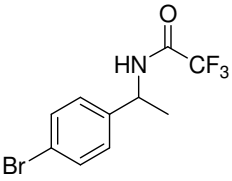
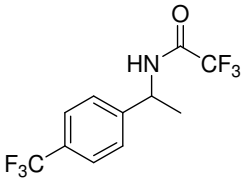
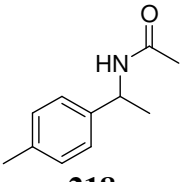
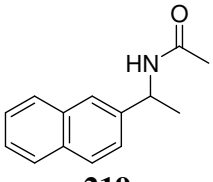
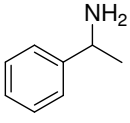
7.11 Synthesis of the allyl and propargyl addition products

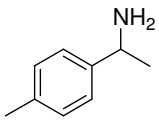
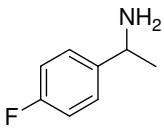
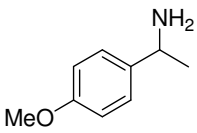
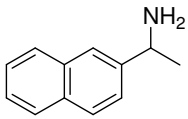
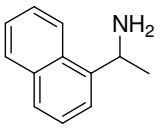
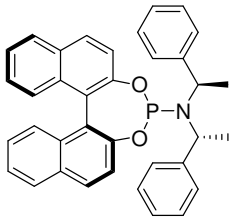
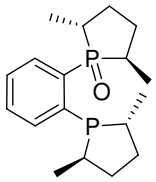
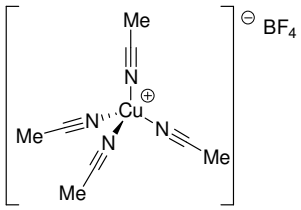
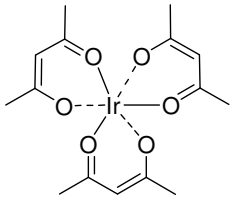
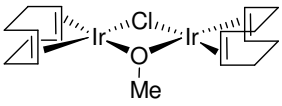
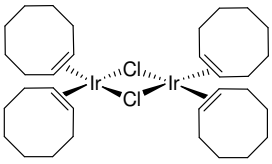
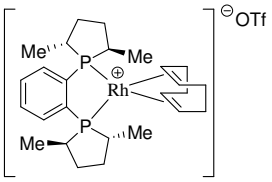
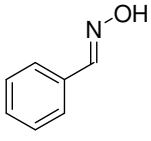
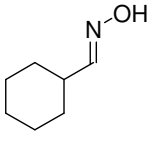
7.12 Miscellaneous

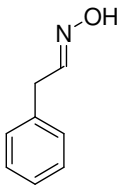
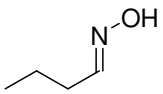
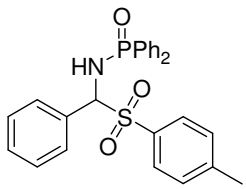
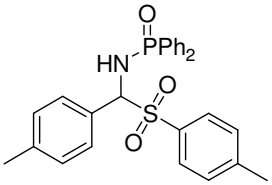
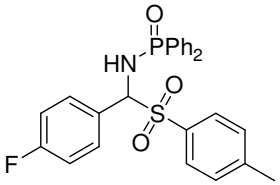
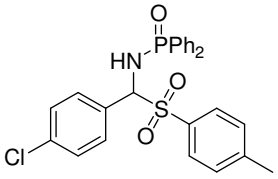
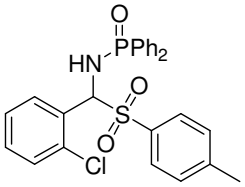
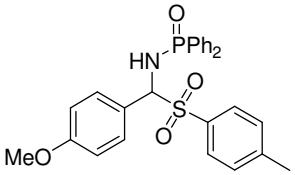
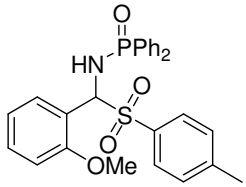
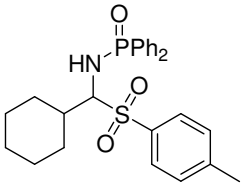
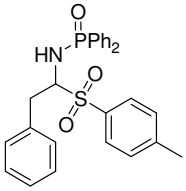
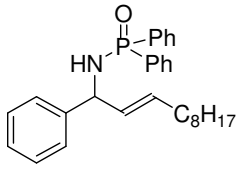
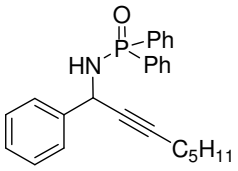
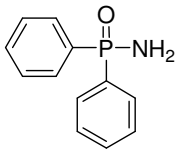
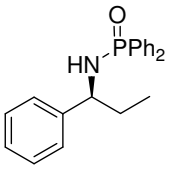
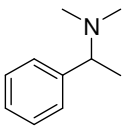
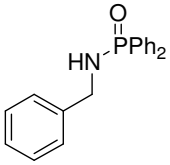
7.1 Synthesised compounds

 **28** *pp 41*	 **29** *pp 41*	 **30** *pp 41*
 **31** *pp 43*	 **27** *pp 41*	 **32** *pp 47*
 **33** *pp 47*	 **34** *pp 47*	 **37** *pp 47*
 **38** *pp 47*	 **39** *pp 47*	 **36** *pp 47*
 **40** *pp 47*	 **35** *pp 47*	 **43** *pp 47*

 **41** ***pp 47***	 **42** ***pp 47***	 **44** ***pp 50***
 **48** ***pp 115***	 **49** ***pp 115***	 **50** ***pp 115***
 **54** ***pp 115***	 **56** ***pp 115***	 **57** ***pp 115***
 **53** ***pp 115***	 **58** ***pp 115***	 **55** ***pp 115***
 **59** ***pp 115***	 **60** ***pp 115***	 **61** ***pp 115***

 **220** ***pp 76***	 **226** ***pp 50***	 **227** ***pp 64***
 **209** ***pp 64***	 **210** ***pp 64***	 **211** ***pp 64***
 **212** ***pp 64***	 **213** ***pp 64***	 **214** ***pp 64***
 **215** ***pp 64***	 **216** ***pp 64***	 **217** ***pp 64***
 **218**	 **219**	 **45** ***pp 60***

 **204** ***pp 60***	 **205** ***pp 60***	 **206** ***pp 60***
 **207** ***pp 60***	 **208** ***pp 60***	 **64** ***pp 73***
 **60** ***pp 71***	 **221** ***pp 78***	 **222** ***pp 79***
 **65** ***pp 81***	 **66** ***pp 81***	 **68** ***pp 81***
 **83** ***pp 111***	 **191** ***pp 44***	 **193** ***pp 44***

 **192** ***pp 44***	 **194** ***pp 44***	 **195** ***pp 44***
 **196** ***pp 44***	 **197** ***pp 44***	 **198** ***pp 44***
 **200** ***pp 44***	 **199** ***pp 44***	 **201** ***pp 44***
 **202** ***pp 44***	 **203** ***pp 44***	 **86** ***pp 94***
 **92** ***pp 96***	 **223** ***pp 44***	 **224** ***pp 99***
 **225** ***pp 60***	 **94** ***pp 99***	

7.2 General methods

All reactions were run under an argon atmosphere with rigid exclusion of moisture from the glassware using standard Schlenk techniques on a dual manifold. Reaction solvents were dried and freshly distilled from suitable drying agents prior to use. THF was distilled from sodium-benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Thin layer chromatography (TLC) was performed on Merck silica gel 60 $F_{254+366}$ pre-coated plates (0.25 mm) silica. The plates were visualised by the use of a combination of ultraviolet light (254 and 366 nm) and/or aqueous potassium permanganate with heating.

Liquid chromatography was by forced flow (flash chromatography) with the solvent systems indicated using silica gel 60 (220-240 mesh) supplied by Fluka. Nuclear magnetic resonance spectra (^{1}H, ^{13}C, ^{31}P, ^{19}F) were recorded either on a JEOL EX270, Bruker DPX400, Bruker AV400 and Bruker AV(III)400 spectrometers, using Me_4Si as an internal reference. For all samples δ values were referenced to residual $CHCl_3$. Data are reported as follows: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sept = septet, m = multiplet and br = broad), coupling constant in Hz, integration, and assignment. Infrared absorption spectra were recorded on a Nicolet Avatar 320 FT-IR, a Perkin Elmer 1600 Series FTIR and a Bruker Tensor 27 machine. Mass spectra (MS) were recorded at high resolution (HRMS) on a Bruker ApexIV FT-ICR mass spectrometer using

Electrospray (ES) or electron impact (EI) techniques. Optical rotations were measured using a Bellingham Stanley ADP440 digital polarimeter at ambient temperature in units of 10^{-1} ^{o} cm^2 g^{-1} (c in g/100 cm^3). Enantioselectivities were determined by ^{31}P NMR spectroscopy, chiral GC or chiral HPLC. GC analyses were performed on a Varian 3380 gas chromatograph using a Chiracil-dex CB, lipodex A and 2,6-γ columns under the conditions given. Chiral HPLC used Daicel Chiracel OD-H (250 mm) and Chiracel AD-H (250 mm) stationary phase columns on rigorously purified samples.

The dimethylzinc samples used were commercial products from the following sources: $ZnMe_2$ (2.0 M toluene solution; Fluka or Aldrich). (*R,R*)-Me-DUPHOS used in the synthesis of BozPHOS was provided by Chirotech Ltd (Dow Pharma) and was used as received. The ligands **70**-**80** and preformed catalysts **81**-**83**, **95**-**108**, **110**-**115** were generously offered by Chirotech Ltd (Dr Reddy's), and were used as received.

7.3 General procedures

7.3.1 Methylation of imines with $AlMe_3$ in the screening of copper and iridium catalysts (Table 9, conditions C,D,E; Table 10, conditions F,G,H)

In a 20 mL flame dried Schlenk tube purged under argon and equipped with a magnetic stirrer bar, was successively charged the ligand (0.025 mmol, 5 mol%), the catalyst (0.025 mmol, 5 mol%) and 4.5 mL of dry solvent. The solution was stirred for about 30 min before introducing the imine substrate

(0.50 mmol, 1 eq.) and stirring for another 15 min. Next, dropwise addition of a 2M $AlMe_3$ solution in hexanes (0.50 mL, 2 eq.) was carried out and the solution was left under stirring and under argon at the appropriate temperature for 24 h, upon which time the solution was quenched by cautious addition of MeOH. The mixture was filtered through a small pad of Celite and the solvent evaporated off. Conversion was measured by ^{1}H NMR spectroscopy analysis using deuterated chloroform deactivated by passage through basic alumina (to remove HCl and water). Enantiomeric excess was measured by chiral HPLC using an AD-H column.

7.3.2 Methylation of imines using $AlMe_3$ and $Ni(acac)_2$ (Fujisawa's conditions – Table 8, conditions A)

In a 20 mL flame dried Schlenk tube purged under argon and equipped with a magnetic stirrer bar, was dissolved $Ni(acac)_2$ (0.025 mmol, 5 mol%) and 2 mL of dry THF at 0 °C. In the meantime, in a 10 mL flame dried round-bottom flask under argon, were dissolved the triphenylphosphine (0.050 mmol, 10 mol%) and the imine substrate (0.50 mmol, 1 eq.) in 3 mL of dry THF. Next, the two solutions were mixed in the Schlenk tube, at 0 °C, for 10 min. Then, after the dropwise addition of a 2M $AlMe_3$ solution in hexanes (0.50 mL, 2 eq.), the mixture was stirred overnight at 0 °C. Acidic workup with MeOH, filtration on Celite and evaporation of the solvent afforded a product which was analysed by ^{1}H NMR spectroscopy.

7.3.3 Methylation of imines using Me_2Zn and $(CuOTf)_2$ (Charette's conditions - Table 9, conditions C)

In the same flask, BozPHOS ligand (8.1 mg, 0.025 mmol, 5 mol%) and $(CuOTf)_2$•toluene (12.6 mg, 0.025 mmol, 5 mol%) were dissolved in toluene (1.5 mL). The resulting heterogeneous solution was stirred for 1 h at room temperature.

A 2M dimethylzinc solution (0.75 mL, 1.5 mmol, 3 eq.) was added at room temperature and the resulting yellow/green suspension was stirred for an additional 30 min before the imine (0.50 mmol, 1 eq.) in toluene (3 mL and 1.5 mL) was transferred (with a cannula or a syringe) to the catalyst solution. After stirring for 48 h at room temperature, the reaction was quenched with saturated NH_4Cl and the aqueous layer was extracted rapidly with CH_2Cl_2 (3 times). The combined organic layers were dried over Na_2SO_4. Conversion was measured by ^1H NMR spectroscopy.

7.3.4 Ligand screening of the iridium catalysed $AlMe_3$ addition to benzaldimine 27

In a 20 mL flame dried Schlenk tube purged under argon and equipped with a magnetic stirrer bar, was successively charged the ligand (0.015 mmol, 5 mol%), the catalyst (0.015 mmol, 5 mol%) and 4.0 mL of dry solvent. The solution was stirred for about 5-10 min before introducing the imine substrate (0.30 mmol, 1 eq.), 1.0 mL of dry solvent and being left to stir for another 10 min. Next, dropwise addition of a 2M $AlMe_3$ solution in hexanes (0.60 mmol, 2 eq.) was carried out and the solution was left under stirring and under argon at the appropriate temperature and time. The reaction mixture was finally

quenched by cautious addition of NH_4Cl. The mixture was extracted 3 times with CH_2Cl_2 and the organic layer was dried over Na_2SO_4, filtered through cotton wool and the solvent was evaporated. Conversion was measured by ^1H NMR spectroscopy analysis using deuterated chloroform deactivated by passage through basic alumina (to remove HCl and water). Enantiomeric excess was measured by chiral HPLC and/or by ^{31}P NMR spectroscopy using 5 equivalents of (1*S*)-10-camphorsulfonic acid.

7.3.5 Preformed catalysts screening in the Me_2Zn addition to benzaldimine 27

In a 20 mL flame dried Schlenk tube purged under argon and equipped with a magnetic stirrer bar, was charged the preformed catalyst (5.8 mol%) and 4.0 mL of dry THF. The solution was stirred for about 1 min upon which time was introduced the imine substrate (0.30 mmol, 1 eq.) and 1.0 mL of dry THF. The mixture was left under stirring for 10 min at room temperature. Next, dropwise addition of a 2M Me_2Zn solution in toluene (0.30 mL, 0.60 mmol, 2 eq.) was carried out and the solution was left under stirring and under argon at the appropriate temperature and time. The reaction mixture was finally quenched by cautious addition of NH_4Cl. The mixture was extracted 3 times with CH_2Cl_2 and the organic layer was dried over Na_2SO_4, filtered through cotton wool and the solvent was evaporated. Conversion was measured by ^1H NMR spectroscopy analysis using deuterated chloroform deactivated by passage through basic alumina. Finally, the product was isolated by preparative TLC (EtOAc/CH_2Cl_2 1:1) and analysed by chiral SFC or chiral HPLC for *e.e.* determination.

7.3.6 Optimised conditions for the $[RhCl(C_2H_4)_2]_2$ catalysed Me_2Zn addition reactions

In a 20 mL flame dried Schlenk tube purged under argon and equipped with a magnetic stirrer bar, was successively charged the [RhCl*bis*(ethylene)] dimer (7.8 mg, 17.4 μmol, 5.8 mol% Rh), (*R*,*R*)-Me-DuPHOS (19.2 mg, 62.6 μmol, 10.4 mol%) and 4.0 mL of dry THF. The solution was stirred for about 30 min at room temperature upon which time was introduced the imine substrate (0.60 mmol, 1 eq.) and 1.0 mL of dry solvent. The mixture was left under stirring for 10 min. Next, dropwise addition of a 2M Me_2Zn solution in toluene (0.60 mL, 1.20 mmol, 2 eq.) was carried out and the solution was left under stirring and under argon at reflux temperature for 3 hours. The reaction mixture was finally quenched by cautious addition of NH_4Cl. The mixture was extracted three times with CH_2Cl_2 and the organic layer was dried over Na_2SO_4, filtered through cotton wool and the solvent was evaporated. Conversion was measured by ^1H NMR spectroscopy analysis using deuterated chloroform deactivated by passage through basic alumina. Finally, the product was isolated by flash chromatography (EtOAc/CH_2Cl_2 1:1) and derivatised for chiral GC assay.

7.3.7 Protecting group exchange – conversion of methylated products into trifluoroacyl or acyl derivatives

A 10 mL vial equipped with a magnetic stirrer was charged with the pure protected secondary amine (c.a. 30 mg) and trifluoroacetic anhydride (50 eq.) or acetyl chloride (50 eq.) with DMAP (7 mol%). The suspension was stirred for 30 min before the slow and cautious addition of 2 drops of distilled water,

(**EXOTHERMIC!**). The resulting solution was stirred overnight and the reaction mixture was transferred in a larger container before quenching it cautiously with $NaHCO_3$ (30 mL, **EXOTHERMIC!**). The mixture was extracted with CH_2Cl_2 (3 x 20 mL), dried over Na_2SO_4, filtered and evaporated to dryness. Finally, the crude mixture was purified by filtration over a pad of silica or by flash chromatography with elution with CH_2Cl_2. Samples were assessed pure by ^1H NMR spectroscopy and were used directly for *e.e.* determination by chiral GC.

7.3.8 Enantiomeric excess determination by ^{31}P NMR spectroscopy

A sample of crude methylated protected amine was dissolved in $CDCl_3$ and placed in a vial. Solid (1*S*)-10-camphorsulfonic acid (4.0 eq.) was added and the suspension was shaken and filtered. The filtrate was then collected in 5 mm NMR tube which was capped for NMR analysis. The ^{31}P NMR were acquired under standard conditions and the relative enantiomeric composition determined by integration of the two main signals corresponding to the enantiomers. This technique was found to be of sufficient accuracy (± 6%) to allow preliminary screening by ^{31}P NMR spectroscopy to be carried out.

7.3.9 Synthesis of diphenylphosphinoyl protected benzaldimines

The approach of Scheidt[157] proving to be the most reliable it was employed with the following modifications. A mixture of $Ph_2P(O)(NH_2)$ (5.43 g, 25.0 mmol), aldehyde (2.95 mL, 25.0 mmol) and NEt_3 (12.3 mL, 87.5 mmol) in CH_2Cl_2 (250 mL) was cooled to 0 ^oC and $TiCl_4$ (12.5 mmol) in dichloromethane (12.5 mL) added over 5 mins. The reaction was stirred for 1 h

at 0 °C and 1-4 h at room temperature (depending on the substrate as recommended by Jennings). The reaction mixture was promptly filtered through Celite with a dichloromethane wash (3 x 5 mL) and evaporated to a white solid. The crude product (which is not fully soluble in the initial chromatographic eluent) was transferred as a suspension to the top of a 4 cm diameter x 9 cm high silica column using 7:3 EtOAc:light petroleum (b.p. 40-60 °C). Elution with the same solvent system (300-400 mL) gave residual aldehyde. Continued elution with 1:1 EtOAc:CH_2Cl_2 (300 mL) gave the imine product as a white solid. Yields obtained were within the range 40-70%. Lower yields were associated with slower elution of the products and occasional batches of over activated silica.

7.3.10 Racemic methylation of imines with MeMgBr

A flame dried Schlenk tube was charged with the desired imine substrate (3.13 mmol) in dried Et_2O (20 mL). The suspension was cooled down to 0 °C, addition of a minimum amount of dichloromethane was carried out (c.a. 10 mL) to solubilise the compound. Finally, MeMgBr (3.1 mL of 3.0 M Et_2O solution, 9.39 mmol) was slowly added to the solution. The reaction mixture was stirred first at 0 °C for 30 min and next at room temperature for 1 h after which time it was quenched at 0°C with water (20 mL). The product was extracted into dichloromethane (3 x 20 mL), the combined organic extracts were washed successively with water (50 mL) and brine (50 mL), dried over Na_2SO_4 and the solvent removed *in vacuo* to afford the crude amine. Purification by flash chromatography (silica; EtOAc:CH_2Cl_2 1:1) gave the pure protected secondary amine (80-90%).

7.3.11 Preparation of diphenylphosphinoyl protected imines

In a 250 mL flame-dried three-neck round-bottomed flask purged with argon, *P*,*P*-diphenylphosphinic amide (5.00 g, 23.0 mmol, 1.0 eq.), aldehyde (72.0 mmol, 3.1 eq.), triethylamine (19.2 mL, 138 mmol, 7.0 eq.), dichloromethane (90 mL) and molecular sieves were added and the flask was cooled to 0 °C. Then, titanium tetrachloride (1.50 mL, 13.8 mmol, 0.6 eq.) was introduced dropwise into the solution. The reaction mixture was stirred for another 30 min at 0 °C, warmed to room temperature, stirred overnight, poured into anhydrous ether (200 mL) and filtered through a pad of a 1:1 mixture of Florisil and Celite. The filtrate was evaporated under reduced pressure to give a yellow powder which was directly purified by flash chromatography [CH_2Cl_2/EtOAc] to yield a solid compound which was immediately dried and kept under inert atmosphere.

7.3.12 Deprotection of diphenyphosphinoyl protected methylation products[158]

To a solution of diphenyphosphinoyl protected amine in CH_2Cl_2 (3 mL) under argon at 0 °C, was added MeOH (5 mL) and BF_3•Et_2O (excess). The solution was then stirred overnight after which time H_2O (2 mL) was added and the solution was extracted with CH_2Cl_2 (3 x 5 mL), basified with $NaHCO_3$ and then extracted with further portions of CH_2Cl_2 (3 x 5 mL). The organic layers were combined, washed with brine (5 mL), dried (Na_2SO_4), filtered, and the solvent removed *in vacuo* to yield the free amine.

7.3.13 Synthesis of oximes[159]

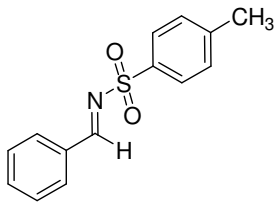
In a 100 mL round-bottomed flask was prepared a solution of aldehyde (17.7 mmol) in THF (30 mL). Hydroxylamine hydrochloride (1.39 g, 20.0 mmol, 1.2 eq.) was dissolved in H_2O (10.0 mL) and added to the stirring solution of aldehyde. Sodium carbonate (1.00 g, 10.0 mmol, 0.6 eq.) was dissolved in H_2O (10.0 mL) and added to the reaction mixture. The reaction was completed in 1 hour as monitored with thin-layer chromatography. The organic and aqueous layers were separated; then, the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with water and brine and dried over $MgSO_4$. After filtering, the solvent was concentrated to give a yellow sticky oil. The reaction mixture was purified by flash silica chromatography; however, the *cis*- and *trans*-isomers could not be separated.

7.3.14 Synthesis of sulfinic acid adducts[160]

A 250 mL three-necked round-bottomed flask equipped with a magnetic stirring bar was charged with diphenylphosphinic amide (1.91 g, 8.79 mmol). Dichloromethane (15 mL) and diethylether (73 mL) were added successively into the flask. The resulting suspension was stirred for 5 min and the aldehyde (13.19 mmol, 1.5 eq.) was added dropwise. *p*-Toluenesulfinic acid (2.06 g, 13.19 mmol, 1.5 eq.) was then added in one portion at room temperature. The reaction mixture was capped and allowed to stir for 48 hours during which time a white precipitate was slowly formed. The reaction mixture was filtered through a sintered glass funnel and the white solid was washed with diethylether (20 mL) and dried under vacuum to afford the sulfonyl adduct.

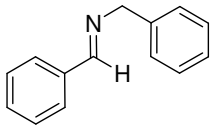
7.4 Synthesis of aldimine substrates

_N_-Benzylidene-4-methylbenzenesulfonamide (28)[161]



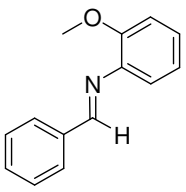
In a 250 mL flame-dried three-neck round-bottom flask purged with argon, *p*-toluenesulfonamide (3.08 g, 18 mmol, 1.0 eq.), benzaldehyde (1.8 mL, 18 mmol, 1.0 eq.), triethylamine (15.0 mL, 108 mmol, 7.0 eq.), dichloromethane (85 mL) were added and the flask was cooled to 0 °C. Then, titanium tetrachloride (1.20 mL, 10.8 mmol, 0.6 eq.) was introduced dropwise into the solution. The reaction mixture was stirred for another 30 min at 0 °C, warmed to room temperature, stirred overnight, poured into anhydrous ether (160 mL) and filtered through a pad of a 1:1 mixture of Florisil and Celite. The filtrate was evaporated under reduced pressure to give a yellow powder which was directly purified by flash chromatography on silica gel (Petrol/EtOAc 8:2) to afford 3.32 g (71%) of a shiny white solid; **m.p.** 111-112 °C; Lit.[161] 108-114 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 9.05 (s, 1H, HC=N), 7.90 (d, 2H, *J* = 8.4 Hz, *Ar*), 7.62 (t, 1H, *J* = 7.6 Hz, *Ar*), 7.94 (d, 2H, *J* = 8.4 Hz, *Ar*), 7.50 (t, 2H, *J* = 7.6 Hz, *Ar*), 7.37 (d, 2H, *J* = 8.0 Hz, *Ar*), 2.45 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 170.2, 144.6, 135.2, 135.0, 132.4, 131.4, 129.9, 129.2, 128.2, 21.7; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 1596, 1450, 1318, 1223, 1156, 1088, 867, 782, 754; $\mathbf{R}_f$ 0.30 Petrol/EtOAc 8:2).

***N*-Benzylidene(phenyl)methanamine (29)**[162]



In a 250 mL flame-dried three-neck round-bottom flask purged with argon, benzylamine (1.1 mL, 10 mmol, 1.0 eq.), benzaldehyde (1.0 mL, 10 mmol, 1.0 eq.), triethylamine (8.4 mL, 60 mmol, 7.0 eq.), dichloromethane (50 mL) were added and the flask was cooled to 0 °C. Then, titanium tetrachloride (0.66 mL, 6 mmol, 0.6 eq.) was introduced dropwise into the solution. The reaction mixture was stirred for another 30 min at 0 °C, warmed to room temperature, stirred overnight, poured into anhydrous ether (90 mL) and filtered through a pad of a 1:1 mixture of Florisil and Celite. The filtrate was evaporated under reduced pressure to give 1.74g (89%) of an yellow oil which did not need further purification; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.27 (s, 1H, HC=N), 7.69-7.73 (m, 2H, *Ar*), 7.10- 7.40 (m, 8H, *Ar*), 4.73 (s, 2H, $CH_{2\ benzyl}$); **^{13}C NMR** ($CDCl_3$, 100 MHz); δ_C 162.1, 139.5, 137.3, 130.9, 128.8, 128.7, 128.4, 128.2, 127.2, 65.2; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2847, 1957, 1889, 1816, 1702, 1644, 1580, 1496, 1343, 1027, 858.

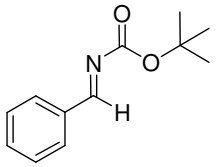
***N*-Benzylidene-*o*-anisidine (30)**[163]



In a 100 mL flame-dried three-neck round-bottom flask purged with argon, *o*-anisidine (1.7 mL, 15 mmol, 1.0 eq.), benzaldehyde (1.5 mL, 15 mmol, 1.0 eq.), triethylamine (12.6 mL, 90 mmol, 7.0 eq.), dichloromethane (60 mL)

were added and the flask was cooled to 0 °C. Then, titanium tetrachloride (1.0 mL, 9 mmol, 0.6 eq.) was introduced dropwise into the solution. The reaction mixture was stirred for another 30 min at 0 °C, warmed to room temperature, stirred overnight, poured into anhydrous ether (130 mL) and filtered through a pad of a 1:1 mixture of Florisil and Celite. The filtrate was evaporated under reduced pressure to give 2.68 g (85%) of a thick dark orange oil which did not need further purification; **^{1}H NMR** ($CDCl_3$, 400 MHz) 8.49 (s, 1H, HC=N), 7.96 (m, 2H, *Ar*), 7.30-7.85 (m, 7H, *Ar*), 3.89 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 161.4, 152.3, 141.9, 137.4, 131.4, 129.8, 129.1, 129.0, 128.8, 128.7, 126.8, 55.9; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2838, 1702, 1629, 1579, 1496, 1177, 1116, 1027, 975, 880.

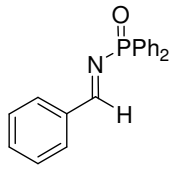
***tert*-Butyl benzylidenecarbamate (31)**[164]



In a 100 mL flame dried round-bottom flask under argon, sodium benzenesulfinate (4.10 g, 25 mmol, 2.5 eq.) and *tert*-butyl carbamate (1.17 g, 10 mmol, 1.0 eq.) were dissolved in a mixture of water (20 mL) and methanol (10 mL). Then, benzaldehyde (2.0 mL, 20 mmol, 2.0 eq.) was introduced to the mixture before to acidify it with concentrated formic acid to pH 2-3, and the mixture was stirred for 24 hours. After cooling at 0 °C, the resulting solid was separated by filtration, rinsed with water and petroleum ether, solubilised in CH_2Cl_2 (30 mL) and the organic layer was dried over Na_2SO_4. After concentration *in vacuo*, 2.95 g (85%) of crude *tert*-butyl phenyl (phenylsulfonyl)methylcarbamate was obtained. Finally, this intermediate

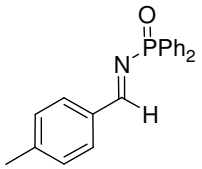
sulfone (764 mg, 2.20 mmol, 1.0 eq.) was treated with anhydrous potassium carbonate (1.80 g, 13 mmol, 5.9 eq.) in refluxing THF (40 mL) for 24 hours. Filtration through Celite and concentration *in vacuo* afforded 351 mg (78%) of pure imine; **m.p.** 165-166 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.85 (s, 1H, HC=N), 7.91-7.87 (m, 2H, *Ar*), 7.56-7.50 (m, 1H, *Ar*), 7.46-7.42 (m, 2H, *Ar*), 1.57 (s, 9H, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 169.9, 162.9, 134.3, 133.8, 130.4, 129.0, 82.5, 28.2; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3428, 2904, 1964, 1732, 1644, 1498, 1365, 1185, 1002, 848.

***N*-Benzylidene-*P,P*-diphenylphosphinic amide (27)**[169]



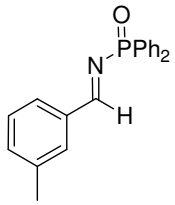
Preparation according to general procedure 7.3.9 performed on a 25 mmol scale gave title compound as a white solid (6.69 g, 88%). **m.p.** 136-137 °C; Lit.[163] 134-141 °C; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ_H 9.33 (d, 1H, J_{PH} = 32.0 Hz, HC=N), 7.90-8.10 (m, 6H, *Ar*), 7.45-7.66 (m, 9H, *Ar*); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 174.1 (d, *J* = 8 Hz), 136.1 (d, *J* = 25 Hz), 134.0, 133.2 (d, *J* = 127 Hz), 132.1 (d, *J* = 3 Hz), 131.9 (d, *J* = 10 Hz), 130.5, 129.3, 128.8 (d, *J* = 12 Hz); **^{31}P NMR** ($CDCl_3$, 162MHz) δ_P 25.7; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2990, 1625, 1578, 1443, 1198, 1127, 846, 832, 736; **HRMS** [found (ESI) MH^+ 307.1038 $C_{19}H_{16}NOP$ requires *M* 307.1042]; $\mathbf{R}_f$ 0.30 (EtOAc/Pet. Ether 40-60 °C 7:3).

***N*-(4-Methylbenzylidene)-*P,P*-diphenylphosphinic amide (32)**[165]



Preparation according to general procedure 7.3.9 performed on a 25 mmol scale gave title compound as a white solid (6.42 g, 80%). **m.p.** 153-155 °C; Lit.[165] 154 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.29 (d, J_{PH} = 32.0 Hz, 1H, HC=N), 7.88-7.99 (m, 6H, *Ar*), 7.40-7.54 (m, 6H, *Ar*), 7.32 (s, 1H, *Ar*), 7.30 (s, 1H, *Ar*), 2.44 (s, 3H, *Ar*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 173.9 (d, *J* = 8 Hz), 145.0, 133.9 (d, *J* = 49 Hz), 133.3 (d, *J* = 125 Hz), 132.0 (d, *J* = 3 Hz), 131.9 (d, *J* = 9 Hz), 130.6, 130.0, 128.7 (d, *J* = 12 Hz), 22.2; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 24.8; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2989, 1618, 1605, 1571, 1439, 1185, 1126, 1107, 861, 838 cm^{-1}; **HRMS** [found (ESI) MH^+ 320.1188 $C_{20}H_{18}NOP$ requires *M* 320.1199]; $\mathbf{R}_f$ 0.32 (CH_2Cl_2/EtOAc 1:1).

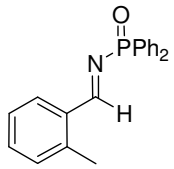
***N*-(3-Methylbenzylidene)-*P,P*-diphenylphosphinic amide (33)**[166]



Preparation according to general procedure 7.3.9 performed on a 17 mmol scale gave title compound a white solid (2.25 g, 41%). **m.p**. 114-118 ^{o}C; Lit.[166] 116-118 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.30 (d, J_{PH} = 32.0 Hz, 1H, HC=N), 7.99.-7.97 (m, 1H, *Ar*), 7.970-7.954 (m, 1H, *Ar*), 7.954-7.940 (m, 1H, *Ar*), 7.94-7.92 (m, 1H, *Ar*), 7.84 (s, 1H, Ar), 7.83-7.77 (m, 1H, *Ar*), 7.59-7.37 (m, 6H, *Ar*), 7.41 (s, 1H, *Ar*), 7.39 (s, 1H, *Ar*), 2.45 (s, 3H, CH_3); **^{13}C NMR**

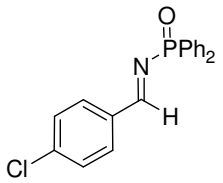
(100 MHz, $CDCl_3$) δ_C 174.5, 139.1, 136.3, 134.9, 133.4 (d, *J* = 125 Hz), 132.1 (d, *J* = 3 Hz), 131.9 (d, *J* = 9 Hz), 130.6, 129.2, 128.8 (d, *J* = 13 Hz), 128.2, 21.6; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 24.9; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2989, 1623, 1601, 1585, 1438, 1187, 1126, 1108, 842; **HRMS** [found (ESI) MH^+ 320.1195 $C_{20}H_{18}NOP$ requires *M* 320.1199]; $\mathbf{R}_f$ 0.22 (EtOAc/CH_2Cl_2 8:2).

_N_-(2-Methylbenzylidene)-_P,P_-diphenylphosphinic amide (34)[167]



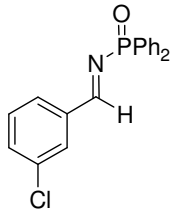
Preparation according to general procedure 7.3.9 performed on a 23 mmol scale gave title compound as a white solid (4.23 g, 58%); **m.p.**[168] 102 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.65 (d, J_{PH} = 32.0 Hz, 1H, HC=N), 8.18 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, *Ar*), 8.030-8.005 (m, 1H, Ar), 8.005-7.990 (m, 1H , Ar), 7.990-7.975 (m, 1H, *Ar*), 7.975 (m, 1H, *Ar*), 7.55-7.43 (m, 7H, *Ar*), 7.35 (t, *J* = 7.6 Hz, 1H, *Ar*), 7.29 (s, 1H, *Ar*), 2.70 (s, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.8 (d, *J* = 8.0 Hz), 141.4, 134.1 (d, *J* = 2.0 Hz), 133.9, 133.5 (d, *J* = 123 Hz), 133.5, 132.0 (d, *J* = 3.0 Hz), 131.9 (d, *J* = 9.0 Hz), 130.1, 128.8 (d, *J* = 13.0 Hz), 126.7, 20.0; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 24.8; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2989, 1617, 1597, 1571, 1439, 1186, 1125, 1107, 849; **HRMS** [found (ESI) MH^+ 320.1195 $C_{20}H_{18}NOP$ requires *M* 320.1199]; $\mathbf{R}_f$ 0.25 (EtOAc/CH_2Cl_2 8:2).

***N*-(4-Chlorobenzylidene)-*P,P*-diphenylphosphinic amide (37)**[169]



Preparation according to general procedure 7.3.9 performed on a 8.76 mmol scale gave title compound as a white solid (1.86 g, 62%); **m.p.** 127-128 °C; Lit.[163] 122-130 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.28 (d, J_{PH} = 31.6 Hz, 1H, HC=N), 7.98-7.88 (m, 6H, *Ar*), 7.50 (m, 8H, *Ar*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.6 (d, J = 8 Hz), 140.3, 134.5 (d, J = 25 Hz), 133.7 (d, J = 129 Hz), 133.6, 132.3, 132.2 (d, J = 2 Hz), 132.2, 131.8 (d, J = 10 Hz), 131.6, 129.6, 128.8 (d, J = 12 Hz);**^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 25.0; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2991, 1621, 1595, 1569, 1489, 1439, 1191, 1126, 1092, 833; **HRMS** [found (ESI) MH^+ 340.0657 $C_{19}H_{15}ClNOP$ requires M 340.0653]; $\mathbf{R}_f$ 0.25 (EtOAc/CH_2Cl_2 8:2).

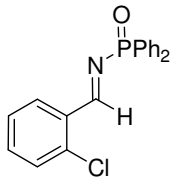
***N*-(3-Chlorobenzylidene)-*P,P*-diphenylphosphinic amide (38)**[169,170]



Preparation according to general procedure 7.3.9 performed on a 13.2 mmol scale gave title compound as a sticky off-white solid (941 mg, 21%). **m.p.**[168] 116 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.28 (d, J_{PH} = 32.0 Hz, 1H, HC=N), 8.06 (br s, 1H, *Ar*), 7.97 (br s, 1H, *Ar*), 7.95 (d, J = 1.6 Hz, 1H, *Ar*), 7.94 (br s, 1H, *Ar*), 7.92 (d, J = 1.2 Hz, 1H, *Ar*), 7.82 (d, J = 7.8 Hz, 1H, *Ar*), 7.58-7.42 (m, 8H, *Ar*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.4 (d, J = 7 Hz), 137.6 (d, J =

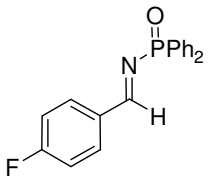
25 Hz), 135.5, 133.7, 132.8 (d, *J* = 127 Hz), 132.2 (d, *J* = 3 Hz), 131.8 (d, *J* = 9 Hz), 130.5, 129.3, 129.1, 128.8 (d, *J* = 12 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 25.1; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3631, 2993, 2945, 2839, 1625, 1438; **HRMS** [found (ESI) MH+ 340.0640 $C_{19}H_{15}ClNOP$ requires *M* 340.0653; $\mathbf{R}_f$ 0.32 (EtOAc/CH_2Cl_2 8:2).

_N_-(2-Chlorobenzylidene)-_P,P_-diphenylphosphinic amide (39) [41]



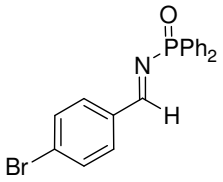
Preparation according to general procedure 7.3.9 performed on a 23 mmol scale gave title compound as a white solid (3.07 g, 39%). **m.p.** 109-110 °C; Lit.[41] 109-111; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.76 (d, J_{PH} = 31.0 Hz, 1H, HC=N), 8.31 (d, *J* = 7.6 Hz, 1H, *Ar*), 8.000-7.975 (s, 1H, *Ar*), 7.975-7.959 (s, 1H, *Ar*), 7.959-7.943 (s, 1H, *Ar*), 7.943-7.910 (s, 1H, *Ar*), 7.56-7.43 (m, 8H, *Ar*), 7.43-7.36 (t, *J* = 7.2 Hz, 1H, *Ar*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 170.7 (d, *J* = 7 Hz), 138.6, 134.7, 133.2 (d, *J* = 128 Hz), 132.4, 132.3 (d, *J* = 3 Hz), 132.0 (d, *J* = 9 Hz), 130.8, 129.7, 128.9 (d, *J* = 12 Hz), 127.4; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 25.1; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2992, 1614, 1592, 1439, 1273, 1192, 1125, 1107, 835; **HRMS** [found (ESI) MH^+ 340.0654 $C_{19}H_{15}ClNOP$ requires *M* 340.0653]; $\mathbf{R}_f$ 0.23 (EtOAc/CH_2Cl_2 9:1).

***N*-(4-Fluorobenzylidene)-*P,P*-diphenylphosphinic amide (36)**[171]



Preparation according to general procedure 7.3.9 performed on a 43.1 mmol scale gave title compound as a white solid (8.81 g, 63%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H 9.93 (d, J_{PH} = 31.8 Hz, 1H, HC=N), 8.09-7.87 (m, 6H, *Ar*), 7.55-7.36 (m, 6H, *Ar*), 7.18 (t, *J* = 8.7 Hz, 2H, *Ar*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 173.9 (d, *J* = 8 Hz), 134.9 (d, *J* = 213 Hz), 133.3 (d, *J* = 127 Hz), 132.1 (d, *J* = 3 Hz), 131.9 (d, *J* = 9 Hz), 131.0 (d, *J* = 24 Hz), 129.2 (d, *J* = 50 Hz), 128.9 (d, *J* = 12 Hz), 126.9, 125.5, 124.4; **^{31}P NMR** (121 MHz, $CDCl_3$) δ_P 26.1; **^{19}F NMR** (282 MHz, $CDCl_3$) δ_F -104.3; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2990, 1621, 1595, 1569, 1439, 1190, 1126, 1091, 833; **HRMS** [found (ESI) MH^+ 324.0955 $C_{19}H_{15}FNOP$ requires *M* 324.0948]; $\mathbf{R}_f$ 0.30 (EtOAc/CH_2Cl_2 1:1).

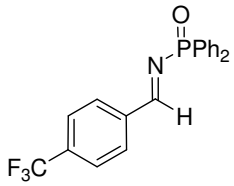
***N*-(4-Bromobenzylidene)-*P,P*-diphenylphosphinic amide (40)**[172,173]



Preparation according to general procedure 7.3.9 performed on a 25 mmol scale gave title compound as a white solid (6.98 g, 59%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.29 (d, J_{PH} = 32.0 Hz, 1H, HC=N), 7.980-7.955 (m, 2H, *Ar*), 7.955-7.938 (m, 2H, *Ar*), 7.938-7.925 (m, 1H, *Ar*), 7.925-7.900 (m, 1H, *Ar*), 7.55-7.42 (m, 8H, *Ar*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.6 (d, *J* = 7 Hz), 140.3, 134.6 (d, *J* = 25 Hz), 133.0 (d, J = 127 Hz), 132.2 (d, *J* = 2 Hz), 131.9

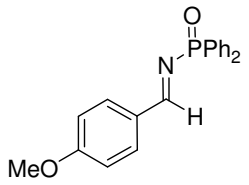
(d, J = 9 Hz), 131.6, 129.7, 128.9 (d, J = 13 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 25.0; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2991, 1621, 1589, 1567, 1439, 1190, 1125, 1069, 831; **HRMS** [found (ESI) MH^+ 384.0146 $C_{19}H_{15}BrNOP$ requires M 384.0147]; $\mathbf{R}_f$ 0.30 (EtOAc/CH_2Cl_2 1:1).

N-(4-(Trifluoromethyl)benzylidene)-*P,P*-diphenyl-phosphinic amide (35)[169,172]



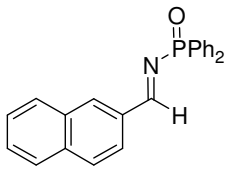
Preparation according to general procedure 7.3.9 performed on a 8.8 mmol scale gave title compound as a white solid (861 mg, 36%). **m.p.** 127-128 °C; Lit.[169] 124-126 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H 9.39 (d, J_{PH} = 31.6 Hz, 1H, HC=N), 8.13 (s, 1H, *Ar*), 8.11 (s, 1H, *Ar*), 7.97 (m, 1H, *Ar*), 7.96 (m, 1H, *Ar*), 7.94 (m, 1H, *Ar*), 7.92 (m, 1H, *Ar*), 7.77 (s, 1H, *Ar*), 7.75 (s, 1H, *Ar*), 7.56-7.40 (m, 6H, *Ar*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.5 (d, J = 7 Hz), 138.8 (d, J = 25 Hz), 135.0 (d, J = 33 Hz), 133.2, 132.4 (d, J = 2 Hz), 131.7 (d, J = 131 Hz), 131.9 (d, J = 10 Hz), 128.9 (d, J = 13 Hz), 126.2 (q, J = 4 Hz), 125.2, 122.5, 53.7; **^{19}F NMR** (282 MHz, $CDCl_3$) δ_F -63.1; **^{31}P NMR** (121 MHz, $CDCl_3$) δ_P 26.5; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2992, 1627, 1582, 1484, 1324, 1175, 1128, 1066, 830; **HRMS** [found (ESI) MH^+ 374.0917 $C_{20}H_{15}F_3NOP$ requires M 374.0916]; $\mathbf{R}_f$ 0.26 (EtOAc/CH_2Cl_2 7:3).

***N*-(4-Methoxybenzylidene)-*P,P*-diphenylphosphinic amide (43)**[169]



Preparation according to general procedure 7.3.9 performed on a 8.8 mmol scale gave title compound as a white solid (2.23 g, 72%). **m.p.** 145-146 °C; Lit.[169] 147-149 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.23 (d, J_{PH} = 32.0 Hz, 1H, HC=N), 8.00-7.97 (m, 1H, *Ar*), 7.97-7.95 (m, 1H, *Ar*), 7.95-7.94 (m, 1H, *Ar*), 7.94-7.92 (m, 1H, *Ar*), 7.92-7.90 (m, 1H, *Ar*), 7.51-7.40 (m, 6H, *Ar*), 7.00 (s, 1H, *Ar*), 6.98 (s, 1H, *Ar*), 3.87 (s, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.9 (d, *J* = 7 Hz), 132.7, 132.5 (d, *J* = 126 Hz), 132.0, 131.9 (d, *J* = 3 Hz), 131.8 (d, *J* = 9 Hz), 128.8, 128.7, 114.7, 55.9; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 24.8; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2987, 1619, 1572, 1513, 1259; **HRMS** [found (ESI) MH^+ 336.1140 $C_{20}H_{18}NO_2P$ requires *M* 336.1148]; $\mathbf{R}_f$ 0.25 (EtOAc/ Pet. ether 40-60 °C 7:3).

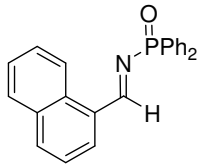
***N*-(Naphthalen-2-ylmethylene)-*P,P*-diphenylphosphinic amide (41)** [169]



Preparation according to general procedure 7.3.9 performed on a 24.3 mmol scale gave title compound as a white solid (5.16 g, 60%). **m.p.** 172-173 °C; Lit.[169] 172-174 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.48 (d, J_{PH} = 32.0 Hz, 1H, HC=N), 8.35 (s, 1H, *Ar*), 8.23 (dd, *J* = 8.8 Hz, *J* = 1.6 Hz, *Ar*), 8.04-7.96 (m, 5H, *Ar*), 7.94 (d, *J* = 8.8 Hz, 1H, *Ar*), 7.90 (d, *J* = 8.0 Hz, 1H, *Ar*), 7.62 (td, *J* =

7.0 Hz, *J* = 1.4 Hz, 1H, *Ar*), 7.58 (td, *J* = 7.0 Hz, *J* = 1.4 Hz, 1H, *Ar*), 7.55-7.43 (m, 6H, *Ar*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 173.6 (d, *J* = 8 Hz), 145.9, 134.8, 133.5, 132.8 (d, *J* = 125 Hz), 132.2, 132.0 (d, *J* = 9 Hz), 129.8, 129.2, 129.1, 128.8 (d, *J* = 20 Hz), 128.3, 127.3, 125.4, 124.1; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 25.0; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2990, 1615, 1439, 1188, 1126, 1107, 843; **HRMS** [found (ESI) MH^+ 365.1188 $C_{23}H_{18}NOP$ requires *M* 365.1199]; $\mathbf{R}_f$ 0.29 (EtOAc/CH_2Cl_2 1:1).

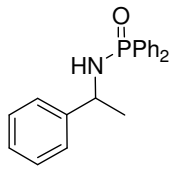
_N_-(Naphthalen-1-ylmethylene)-_P,P_-diphenylphosphinic amide (42)[169]



Preparation according to general procedure 7.3.9 performed on a 8.8 mmol scale gave title compound as a white solid (1.52 g, 49%). **m.p.** 121-122 °C; Lit.[169] 118-120 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.94 (d, J_{PH} = 33.2 Hz, 1H, HC=N), 9.28 (d, *J* = 8.4 Hz, 1H, *Ar*), 8.22 (dd, *J* = 7.2 Hz, *J* = 0.8 Hz, 1H, *Ar*), 8.09-7.99 (m, 5H, *Ar*), 7.92 (d, *J* = 8.0 Hz, 1H, *Ar*), 7.73-7.66 (ddd, *J* = 7.2 Hz, *J* = 1.4 Hz, *Ar*), 7.63-7.55 (m, 2H, *Ar*), 7.55-7.43 (m, 6H, *Ar*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 173.9 (d, *J* = 8 Hz), 134.9, 134.1 (d, *J* = 15 Hz), 133.8, 133.4 (d, *J* = 130 Hz), 132.7, 132.1 (d, *J* = 3 Hz), 131.8 (d, *J* = 9 Hz), 131.0 (d, *J* = 24 Hz), 129.2, 128.9 (d, *J* = 20 Hz), 128.7, 126.9, 125.5, 124.4; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 25.1; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3673, 3063, 2990, 1674, 1607, 1587, 1462; **HRMS** [found (ESI) MH^+ 365.1190 $C_{23}H_{18}NOP$ requires *M* 365.1199]; $\mathbf{R}_f$ 0.30 (EtOAc/Pet.Ether 7:3).

7.5 Synthesis of racemates

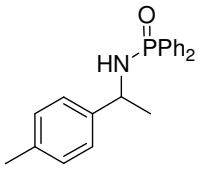
(±)-*P,P*-Diphenyl-*N*-(1-phenylethyl)phosphinic amide (44)[41]



In a 200 mL flame dried round-bottom flask under argon, was prepared a solution of methylbenzylamine (2.0 mL, 15.7 mmol, 1.0 eq.) and triethylamine (4.4 mL, 31.4 mmol, 2.0 eq.) in CH_2Cl_2 (75 mL). This solution was cooled at 0 °C before the dropwise addition of diphenylphosphinic chloride. The resulting mixture was stirred at room temperature overnight, poured into an equal volume of saturated aqueous ammonium chloride and extracted with CH_2Cl_2 (3×40 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give 4.54 g (90%) of a white solid; **m.p.** 150-152 °C; Lit.[41] 147-149 °C; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ_H 7.95-7.60 (m, 4H, *Ar*), 7.60-7.10 (m, 11H, *Ar*), 4.40 (q, 1H, *J* = 7.7 Hz, CH), 3.22 (m, 1H, NH), 1.58 (d, 3H, *J* = 7.7 Hz, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 145.0 (d, *J* = 6.7 Hz), 133.2 (d, *J* = 128 Hz), 132.4 (d, *J* = 9.4 Hz), 132.1 (d, *J* = 129 Hz), 131.9 (d, *J* = 9.5 Hz), 131.8 (d, *J* = 3.6 Hz), 131.7 (d, *J* = 2.6 Hz), 128.5, 128.5 (d, *J* = 12.4 Hz), 128.3 (d, *J* = 12.5 Hz), 127.1, 125.9, 51.0, 25.9 (d, *J* = 3.1 Hz); **^{31}P NMR** ($CDCl_3$, 162MHz) δ_P 21.9; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3150, 1436, 1179, 1125, 1036; **HRMS** [found (ESI) MH^+ 322.1342 $C_{20}H_{20}NOP$ requires *M* 322.1355]; $\mathbf{R}_f$ 0.17 (EtOAc/Pet. Ether 8:2).

The HPLC assay: Chiralcel AD-H, isocratic (*n*-Hexane:*i*-PrOH 85:15, 1.0 mL/min), λ = 280 nm, t_1 = 13.4 min (*R*), t_2 = 15.8 min (*S*).

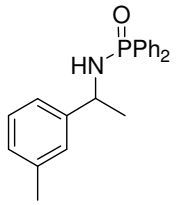
(±)-*P,P*-Diphenyl-*N*-(1-*p*-tolylethyl)phosphinic amide (48)[174]



Preparation according to general procedure 7.3.10 performed on a 1.8 mmol scale gave title compound as a white solid (520 mg, 86%). **m.p.**[168] 121 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.87-7.92 (m, 2H, *Ar*), 7.80-7.87 (m, 2H, *Ar*), 7.40-7.50 (m, 4H, *Ar*), 7.33-7.40 (m, 2H, *Ar*), 7.17 (d, 2H, *J* = 8.0 Hz, *Ar*), 7.11 (d, 2H, *J* = 8.0 Hz, *Ar*), 4.35 (m, 1H, CH_α), 3.21 (dd, 1H, *J* = 7.0 Hz, *J* = 3.6 Hz, NH), 2.96 (s, 3H, CH_{3Ar}), 1.55 (d, 3H, *J* = 7.8 Hz, $CH_{3\beta}$) **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 142.1 (d, *J* = 7.0 Hz), 136.7, 132.4 (d, *J* = 9.4 Hz), 131.9 (d, *J* = 9.4 Hz), 131.8 (d, *J* = 2.7 Hz), 131.7 (d, *J* = 2.7 Hz), 129.2, 128.4 (d, *J* = 12.6 Hz), 128.3 (d, *J* = 12.4 Hz), 125.8, 50.8, 25.9 (d, *J* = 3.0 Hz), 21.0; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 22.4; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3380, 2982, 1515, 1439, 1185; **HRMS** [found (ESI) MH^+ 337.1498 $C_{21}H_{22}NOP$ requires M 337.1512]; $\mathbf{R}_f$ 0.29 (EtOAc/Pet. ether 7:3).

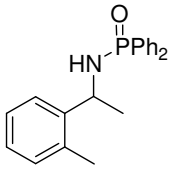
The HPLC assay: Chiralcel OD-H column, isocratic (*n*-Hexane/*i*-PrOH 95:5, 1.0 mL/min), λ = 240 nm, t_1 = 14.0 min, t_2 = 18.9 min.

(±)-*P,P*-Diphenyl-*N*-(1-*m*-tolylethyl)phosphinic amide (49)[41]



Preparation according to general procedure 7.3.10 performed on a 3.1 mmol scale gave title compound as a white solid (840 mg, 80%). **m.p.**[168] 130-131 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.96-7.88 (dd, *J* = 7.0 Hz, *J* = 11.8 Hz, 2H, *Ar*), 7.88-7.79 (dd, *J* = 7.0 Hz, *J* = 11.8 Hz, 2H, *Ar*), 7.54-7.41 (m, 4H, *Ar*), 7.41-7.35 (m, 2H, *Ar*), 7.25-7.18 (m, 1H, *Ar*), 7.13-7.08 (m, 1H, *Ar*), 7.08-7.03 (m, 2H, *Ar*), 4.37 (dd, *J* = 7.8 Hz, *J* = 2.8 Hz, 1H, CH_α), 3.16 (dd, *J* = 7.4 Hz, *J* = 2.8 Hz, 1H, NH), 2.33 (s, 3H, CH_{3Ar}), 1.57 (d, *J* = 7.8 Hz, 3H, $CH_{3\alpha}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 145.0 (d, *J* = 6.1 Hz), 138.2, 133.3 (d, *J* = 128 Hz), 132.6 (d, *J* = 9.1 Hz), 132.2 (d, *J* = 130 Hz), 132.0 (d, *J* = 9.1 Hz), 131.9, 131.8, 128.6 (d, *J* = 12.2 Hz), 128.6, 128.4, 128.0, 126.8, 123.0, 51.2, 26.1 (d, *J* = 3.0 Hz), 21.6; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 22.4; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3381, 2982, 1592, 1439, 1185, 1124; **HRMS** [found (ESI) MH^+ 337.1505 $C_{21}H_{22}NOP$ requires *M* 337.1512]; $\mathbf{R}_f$ 0.29 (EtOAc/Pet. ether 7:3).

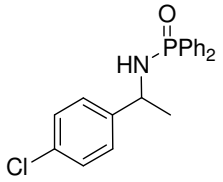
(±)-*P,P*-Diphenyl-*N*-(1-*m*-tolylethyl)phosphinic amide (50)



Preparation according to general procedure 7.3.10 performed on a 3.0 mmol scale gave title compound as a white solid (932 mg, 93%). **m.p.** 139-142 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.98-7.92 (m, 1H, *Ar*), 7.92-7.87 (m, 1H, *Ar*), 7.81-7.76 (m, 1H, *Ar*), 7.76-7.71 (m, 1H, *Ar*), 7.55-7.49 (m, 1H, *Ar*), 7.49-7.40 (m, 4H, *Ar*), 7.37-7.30 (2H, m, *Ar*), 7.30-7.23 (m, 1H, *Ar*), 7.16 (dt, *J* = 7.6Hz, *J* = 1.2 Hz, 1H, *Ar*), 7.09-7.03 (m, 1H, *Ar*), 4.62 (dq, *J* = 7.8 Hz, *J* = 3.2 Hz, 1H, CH_α), 3.30 (dd, 1H, *J* = 5.6 Hz, *J* = 3.2 Hz, NH), 2.02 (s, 3H, CH_3), 1.51

(d, *J* = 6.4 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.7 (d, *J* = 7.0 Hz), 133.3 (d, *J* = 150 Hz), 132.4 (d, *J* = 9.7 Hz), 131.8 (d, *J* = 9.4 Hz), 131.8 (d, *J* = 2.4 Hz), 131.7 (d, *J* = 2.7 Hz), 130.3, 128.4 (d, *J* = 12.5 Hz), 128.2 (d, *J* = 12.7 Hz), 126.8, 126.5, 124.7, 47.1, 26.0 (d, *J* = 3.0 Hz), 18.8; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 22.6; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2981, 1439, 1184, 1125, 1086, 958, 852; **HRMS** [found (ESI) MH^+ 337.1509 $C_{21}H_{22}NOP$ requires *M* 337.1512]; $\mathbf{R}_f$ 0.35 (EtOAc/Pet. ether 7:3).

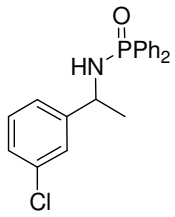
(±)-*N*-(1-(4-Chlorophenyl)ethyl)-*P,P*-diphenylphosphinic amide (54)[174]



Preparation according to general procedure 7.3.10 performed on a 3.1 mmol scale gave title compound as a white solid (149 mg, 91%). **m.p.**[168] 176-177 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.86-7.96 (m, 2H, *Ar*), 7.76-7.85 (m, 2H, *Ar*), 7.42-7.55 (m, 4H, *Ar*), 7.34-7.42 (m, 2H, *Ar*), 7.25-7.31 (m, 2H, *Ar*), 7.20-7.25 (m, 2H, *Ar*), 4.38 (dq, *J* = 7.4 Hz, *J* = 3.2 Hz, 1H, CH), 3.20 (dd, *J* = 5.6 Hz, *J* = 4.0 Hz, 1H, NH), 1.56 (d, *J* = 7.8 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.5 (d, *J* = 6.1 Hz), 132.8 (d, *J* = 127 Hz), 132.7, 132.3 (d, *J* = 9.6 Hz), 132.0 (d, *J* = 129 Hz), 131.9, 131.9 (d, *J* = 9.5 Hz), 131.8, 128.6, 128.5 (t, *J* = 11.9 Hz), 127.4, 50.4, 25.8 (d, *J* = 3.9 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 22.5; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3378, 2983, 1493, 1439, 1261, 1096; **HRMS** [found (ESI) MH^+ 357.0966 $C_{20}H_{19}ClNOP$ requires *M* 357.0963]; $\mathbf{R}_f$ 0.25 (100% EtOAc).

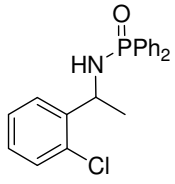
The HPLC assay: Chiralcel OD-H column, isocratic (*n*-Hexane/ *i*-PrOH 95:5, 1.0 mL/min), λ = 240 nm, t_1 = 16.2 min, t_2 = 19.0 min.

(±)-*N*-(1-(3-Chlorophenyl)ethyl)-*P,P*-diphenylphosphinic amide (56)



Preparation according to general procedure 7.3.10 performed on a 1.0 mmol scale gave title compound as a white solid (300 mg, 84%). **m.p.** 182-184 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.99-7.87 (m, 2H, *Ar*), 7.87-74 (m, 2H, *Ar*), 7.57-7.42 (m, 4H, *Ar*), 7.42-7.32 (m, 2H, *Ar*), 7.30-7.13 (m, 4H, *Ar*), 4.45-4.30 (m, 1H, CH_α), 3.32 (dd, *J* = 5.6 Hz, *J* = 9.6 Hz, 1H, NH), 1.57 (d, *J* = 6.8 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 147.1, 134.3, 132.3 (d, *J* = 9.6 Hz), 132.0, 131.8 (d, *J* = 9.5 Hz), 131.9 (d, *J* = 2.8 Hz), 129.8, 128.5 (t, *J* = 12.9 Hz), 127.2, 126.1, 124.3, 50.6, 25.8 (d, *J* = 3.5 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 22.7; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3692, 2984, 2361, 1600, 1452, 1119, 1124; **HRMS** [found (ESI) MH^+ 357.0977 $C_{20}H_{19}ClNOP$ requires *M* 357.0966]; $\mathbf{R}_f$ 0.25 (100% EtOAc).

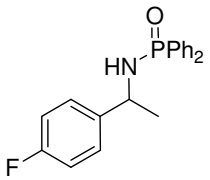
(±)-*N*-(1-(2-Chlorophenyl)ethyl)-*P,P*-diphenylphosphinic amide (57)



Preparation according to general procedure 7.3.10 performed on a 2.8 mmol scale gave title compound as a free flowing white powder (986 mg, 99%). **m.p.**

189-190 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.950-7.915 (d, *J* = 1.2 Hz, 1H, *Ar*), 7.915-7.898 (d, *J* = 1.6 Hz, 1H, *Ar*), 7.898-7.884 (d, *J* = 0.8 Hz, 1H, *Ar*), 7.884-7.850 (d, *J* = 1.2 Hz, 1H, *Ar*), 7.82-7.79 (s, 1H, *Ar*), 7.790-7.773 (d, *J* = 1.2 Hz, 1H, *Ar*), 7.768 (s, 1H, *Ar*), 7.759-7.730 (d, 1H, *J* = 1.6 Hz, *Ar*), 7.55-7.48 (m, 1H, *Ar*), 7.48-7.41 (m, 3H, *Ar*), 7.41-7.38 (m, 1H, *Ar*), 7.38-7.31 (m, 2H, *Ar*), 7.31-7.24 (m, 2H, *Ar*), 7.24-7.15 (m, 1H, *Ar*), 4.75 (m, *J* = 7.8 Hz, 1H, CH_α), 3.49 (dd, *J* = 5.6 Hz, *J* = 9.6 Hz, 1H, NH), 1.57 (d, *J* = 7.8 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 142.3 (d, *J* = 5.6 Hz), 132.9 (d, *J* = 127 Hz), 132.3 (d, *J* = 9.6 Hz), 131.9, 131.8 (d, *J* = 9.4 Hz), 131.7 (d, *J* = 2.8 Hz), 131.1, 129.8, 128.4 (d, *J* = 12.4 Hz), 128.2 (d, *J* = 12.5 Hz), 128.1, 127.4, 127.1, 49.1, 25.0 (d, *J* = 3.7 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 22.8; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3694, 2983, 1602, 1439, 1187, 1108, 958; **HRMS** [found (ESI) MH^+ 357.0969 $C_{20}H_{19}ClNOP$ requires *M* 357.0966]; $\mathbf{R}_f$ 0.28 (EtOAc/Pet. ether 7:3).

(±)-*N*-(1-(4-Fluorophenyl)ethyl)-*P,P*-diphenylphosphinic amide (53)[174]

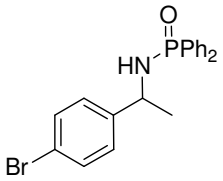


Preparation according to general procedure 7.3.10 performed on a 3.1 mmol scale gave title compound as a white solid (953 mg, 90%). **m.p.** 158-160 °C; Lit.[175] 157-159 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.83-7.98 (m, 2H, *Ar*), 7.75-7.83 (m, 2H, *Ar*), 7.42-7.58 (m, 4H, *Ar*), 7.35-7.42 (m, 2H, *Ar*), 7.30-7.35 (m, 4H, *Ar*), 4.38 (dq, *J* = 7.8 Hz, CH_{benzyl}), 3.34 (m, 1H, NH), 1.57 (d, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 161.8 (d, *J* = 244 Hz), 140.8 (d, *J* = 3.0 Hz), 132.3 (d, *J* = 9.4 Hz), 131.9 (d, *J* = 9.1 Hz), 131.8 (d, *J* = 1.9 Hz), 128.4 (t,

J = 12.1 Hz), 127.6 (d, *J* = 8.0 Hz), 115.2 (d, *J* = 21.3 Hz), 50.3, 25.9 (d, *J* = 2.5 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 22.5; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3377, 2894, 1493, 1439, 1187; **HRMS** [found (ESI) MH^+ 340.1261 $C_{20}H_{19}FNOP$ requires *M* 340.1257]; $\mathbf{R}_f$ 0.25 (100% EtOAc).

The HPLC assay: Chiralcel OD-H column, isocratic (*n*-Hexane/*i*-PrOH 95:5, 1.0 mL/min), λ = 240 nm, t_1 = 15.0 min, t_2 = 18.5 min.

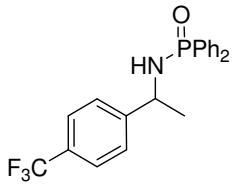
(±)-*N*-(1-(4-Bromophenyl)ethyl)-*P*,*P*-diphenylphosphinic amide (58)[176]



Preparation according to general procedure 7.3.10 performed on a 2.6 mmol scale gave title compound as a white solid (920 mg, 88%). **m.p.**[168] 172 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.95-7.90 (m, 1H, *Ar*), 7.90-7.86 (m, 1H, *Ar*), 7.84-7.80 (m, 1H, *Ar*), 7.80-7.76 (m, 1H, *Ar*), 7.55-7.44 (m, 4H, *Ar*), 7.44-7.42 (m, 1H, *Ar*), 7.42-7.40 (m, 1H, *Ar*), 7.40-7.34 (m, 2H, *Ar*), 7.20-7.17 (m, 1H, *Ar*), 7.17-7.14 (m, 1H, *Ar*), 4.36 (dq, *J* = 7.8 Hz, *J* = 3.2 Hz, 1H, CH_α), 3.15 (dd, *J* = 5.4 Hz, *J* = 4.0 Hz, 1H, NH), 1.55 (d, *J* = 7.8 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 144.0 (d, *J* = 6.0 Hz), 132.8 (d, *J* = 127 Hz), 132.3 (d, *J* = 9.7 Hz), 132.0 (d, *J* =129 Hz), 131.9 (d, *J* = 9.4 Hz), 131.8, 128.5 Hz (d, *J* = 11.9 Hz), 128.4 (d, *J* = 12.5 Hz), 127.8, 120.9, 50.4, 25.8 (d, *J* = 3.8 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 22.6; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2984, 1412, 1195, 1124, 647; **HRMS** [found (ESI) MH^+ 400.0465 $C_{20}H_{19}BrNOP$ requires *M* 400.0460]; $\mathbf{R}_f$ 0.25 (100% EtOAc).

The HPLC assay: Chiralcel OD-H column, isocratic (*n*-Hexane/*i*-PrOH 95:5, 1.0 mL/min), λ = 240 nm, t_1 = 16.7 min, t_2 = 19.6 min.

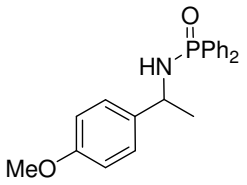
(±)-*P,P*-Diphenyl-*N*-(1-(4-(trifluoromethyl)phenyl)ethyl)phosphinic amide (55)[177]



Preparation according to general procedure 7.3.10 performed on a 5.4 mmol scale gave title compound as a white solid (1.90 g, 91%). **m.p.**[168] 185 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.85-7.98 (m, 2H, *Ar*), 7.72-7.83 (m, 2H, *Ar*), 7.49-7.61 (m, 3H, *Ar*), 7.42-7.49 (m, 3H, *Ar*), 7.30-7.42 (m, 4H, *Ar*), 4.46 (dq, *J* = 7.8 Hz, *J* = 2.8 Hz, 1H, CH), 3.25 (dd, *J* = 5.6 Hz, *J* = 3.6 Hz, 1H, NH), 1.58 (d, *J* = 7.8 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 148.9 (d, *J* = 5.6 Hz), 132.7 (d, *J* = 127 Hz), 132.3 (d, *J* = 9.6 Hz), 132.0 (d, *J* = 2.8 Hz), 131.9 (d, *J* = 9.3 Hz), 131.9 (d, *J* = 2.9 Hz), 131.8 (d, *J* = 129 Hz), 129.5, 129.2, 128.6 (d, *J* = 12.6 Hz), 128.4 (d, *J* = 12.6 Hz), 126.4, 125.5 (q, *J* = 3.8 Hz), 50.6, 25.8 (d, *J* = 4.1 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 22.69; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3339, 2984, 1621, 1439, 1327, 1126; **HRMS** [found (ESI) MNa^+ 412.1049 $C_{21}H_{19}F_3NOP$ requires *M* 412.1048]; $\mathbf{R}_f$ 0.25 (100% EtOAc).

The HPLC assay: Chiralcel OD-H column, isocratic (*n*-Hexane/*i*-PrOH 95:5, 1.0 mL/min), λ = 240 nm, t_1 = 14.7 min, t_2 = 17.2 min.

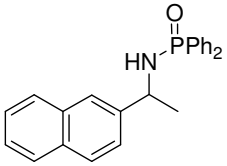
(±)-*N*-(1-(4-Methoxyphenyl)ethyl)-*P,P*-diphenylphosphinic amide (59)[174]



Preparation according to general procedure 7.3.10 performed on a 0.16 mmol scale gave title compound as a white solid (50.1 mg, 91%). **m.p.**[168] 139-141 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H 8.02-7.77 (m, 4H, *Ar*), 7.56-7.29 (m, 6H, *Ar*), 7.23 (d, *J* = 8.7 Hz, 2H, *Ar*), 6.87 (d, *J* = 8.7 Hz, 2H, *Ar*), 4.47-4.27 (m, 1H, CH_α), 3.12 (dd, *J* = 5.7 Hz, *J* = 9.3 Hz, 1H, NH), 1.57 (d, *J* = 6.9 Hz, 3H, CH_3), **^{31}P NMR** (121 MHz, $CDCl_3$) δ_P 23.6. This data was in accordance with literature reports.

The HPLC assay: Chiralcel OD-H column, isocratic (*n*-Hexane/*i*-PrOH 95:5, 1.0 mL/min), λ = 240 nm, t_1 = 20.1 min, t_2 = 23.2 min.

(±)-*N*-(1-(Naphthalen-2-yl)ethyl)-*P,P*-diphenylphosphinic amide (60)[178]

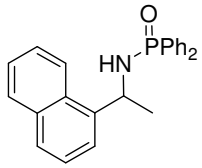


Preparation according to general procedure 7.3.10 performed on a 3.1 mmol scale gave title compound as a white solid (1.12 g, 97%). Found C 76.49, H 5.90; N 3.64%. Calc. For $C_{24}H_{22}NOP$ C 77.61; H 5.90; N 3.64%; **m.p.**[168] 100-102 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.89-7.98 (m, 2H, *Ar*), 7.73-7.88 (m, 5H, *Ar*), 7.66 (s, 1H, *Ar*), 7.39-7.55 (m, 7H, *Ar*), 7.29-7.38 (m, 2H, *Ar*), 4.57 (m, *J* = 7.8 Hz, 1H, CH_α), 3.31 (dd, *J* = 5.6 Hz, *J* = 9.2 Hz, 1H, NH), 1.67 (d, *J* = 7.8 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 142.3 (d, *J* = 6.7 Hz), 133.2, 133.1 (d, *J* = 127 Hz), 132.4 (d, *J* = 9.6 Hz), 132.6, 132.0 (d, *J* = 130

Hz), 131.9 (d, *J* = 9.4 Hz), 131.8, 131.7 (d, *J* = 2.4 Hz), 131.4, 128.4 (t, *J* = 12.2 Hz), 127.8, 127.6, 126.1, 125.8, 124.5, 124.3, 51.1, 25.9 (d, *J* = 3.1 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 22.6; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3380, 2982, 1439, 1185, 1125; **HRMS** [found (ESI) MH^+ 372.1506 $C_{24}H_{22}NOP$ requires *M* 372.1512]; $\mathbf{R}_f$ 0.25 (100% EtOAc).

The HPLC assay: Chiralcel OD-H column, isocratic (*n*-Hexane/*i*-PrOH 95:5, 1.0 mL/min), λ = 240 nm, t_1 = 16.3 min, t_2 = 19.2 min.

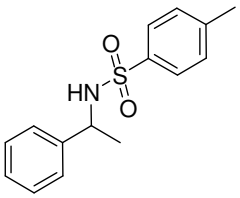
(±)-*N* -(1-(Naphthalen-1-yl)ethyl)-*P,P*-diphenylphosphinic amide (61)[179]



Preparation according to general procedure 7.3.10 performed on a 0.15 mmol scale gave title compound as a white solid (30.5 mg, 55%). **m.p.** 160-161 °C; Lit.[180] 163-164 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.84-8.03 (m, 4H, *Ar*), 7.73-7.84 (m, 3H, *Ar*), 7.61-7.69 (m, 1H, *Ar*), 7.35-7.58 (m, 7H, *Ar*), 5.26 (m, 1H, CH_α), 3.37 (m, 1H, NH), 1.72 (d, *J* = 7.6 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 142.6 (d, *J* = 6.7 Hz), 133.2, 133.0 (d, *J* = 125 Hz), 132.6 (d, *J* = 9.6 Hz), 132.5, 132.1 (d, *J* = 128 Hz), 131.9 (d, *J* = 9.4 Hz), 131.6, 131.5 (d, *J* = 2.4 Hz), 131.4, 128.4 (t, *J* = 12.2 Hz), 127.8, 127.6, 126.1, 125.8, 124.5, 123.9, 51.3, 26.0 (d, *J* = 3 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 23.4; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3690, 3606, 2982, 2338, 1602, 1439, 1239, 1124; **HRMS** [found (ESI) MH^+ 372.1512 $C_{24}H_{22}NOP$ requires 372.1512; $\mathbf{R}_f$ 0.25 (100% EtOAc).

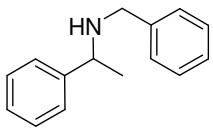
The HPLC assay: Chiralcel OD-H column, isocratic (*n*-Hexane/*i*-PrOH 95:5, 1.0 mL/min), λ = 240 nm, t_1 = 18.9 min, t_2 = 27.1 min.

(±)-4-Methyl-*N*-(1-phenylethyl)benzenesulfonamide (220)[181,182]



Preparation according to Fujisawa's procedure described in 7.2.2. The product was obtained as a colourless oil which solidified upon standing (0.35 mmol scale, 92 mg, 97% yield); **m.p.** 77-80 °C; Lit.[181,182] 79-82 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.75-7.05 (m, 9H, *Ar*), 4.94 (d, 1H, *J* = 7.8 Hz, NH), 4.46 (dq, 1H, *J* = 7.8 Hz, *J* = 7.8 Hz, CH), 2.39 (s, 3H, CH_{3tosyl}), 1.42 (d, 3H, *J* = 7.8 Hz, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 142.9, 142.2, 137.7, 129.7, 128.6, 127.5, 127.2, 127.1, 53.4, 23.5, 21.4; **HRMS** [found (ESI) MH^+ 298.0877 $C_{15}H_{17}NO_2S$ requires 298.0872]; $\mathbf{R}_f$ 0.33 (EtOAc/Pet. ether 2:8).

(±)-*N*-Benzyl-1-phenylethanamine (226)[183]

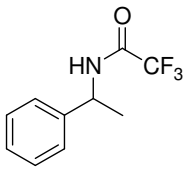


In a 250 mL flame-dried two-neck round-bottom flask purged with argon, (±)-*α*-methylbenzylamine (1.90 mL, 15 mmol, 1.0 eq.) is diluted in DMF (75 mL). Next, cesium carbonate (4.90 g, 15 mmol, 1.0 eq.) was introduced forming a white suspension which was stirred for 30 min at room temperature. Finally, benzyl bromide (2.15 mL, 18 mmol, 1.0 eq.) was added dropwise and the reaction mixture was stirred overnight, quenched with 2M NaOH and extracted with ethyl acetate. Purification by flash chromatography on silica gel (Petrol/EtOAc 8:2) afforded 2.24 g (70%) of a light yellow liquid; **^{1}H NMR**

($CDCl_3$, 400 MHz) δ_H 7.50-7.10 (m, 10H, *Ar*), 3.87 (q, 1H, *J* = 7.6 Hz, CH), 3.68 (d, 2H, *J* = 8.0 Hz, CH_2), 1.78 (s, 1H, NH), 1.42 (d, 3H, *J* = 7.6 Hz, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 145.8, 140.9, 128.8, 128.7, 128.4, 127.2, 127.1, 127.0, 57.8, 51.9, 24.8; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3330, 2846, 2797, 1952, 1813, 1602, 1495, 1370, 1111, 1071, 1028, 827; $\mathbf{R}_f$ 0.23 (Petrol/EtOAc 8:2).

7.6 Synthesis of trifluoroacetamides and acetamides

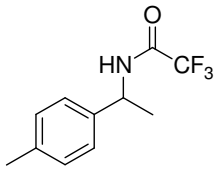
(±)-2,2,2-Trifluoro-*N*-(1-phenylethyl)acetamide (227)[184]



White solid. **m.p.** 65-66 °C; Lit.[184] 65-66 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44-7.37 (m, 2H, *Ar*), 7.37-7.30 (m, 3H, *Ar*), 7.55 (s, 1H, NH), 5.16 (dq, 1H, *J* = 7.1 Hz, *J* = 7.6 Hz, CH_α), 1.60 (d, 3H, *J* = 7.1 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 156.6 (d, *J* = 36 Hz), 141.2, 129.4, 128.5, 126.5, 116.1 (d, *J* = 36 Hz), 50.1, 21.4; **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F -75.9; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3429, 2984, 1724, 1530, 1171; **HRMS** [found (ESI) MNa^+ 240.0600 $C_{10}H_{10}F_3NO$ requires *M* 240.0607]; $\mathbf{R}_f$ 0.38 (EtOAc/Pet.Ether 7:3). (*R*) enantiomer: $[\alpha]_D^{25}$ = 65.4 (*c* 1.24, CH_2Cl_2); Lit.[185] $[\alpha]_D^{20}$ = 115.3 (*c* 1.24, CH_2Cl_2).

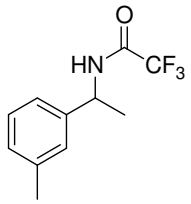
The GC assay: 25 m CP-Chiracil-Dex CB column, 100 °C (isothermal), He carrier gas, 12 psi, (R) 27.5 min, (S) 27.3 min.

(±)-2,2,2-Trifluoro-*N*-(1-*p*-tolylethyl)acetamide (209)[186]



White solid. **^{1}H NMR** (270 MHz, $CDCl_3$) δ_H 7.35-7.10 (m, 4H, *Ar*), 6.40 (br s, 1H, NH), 5.15 (q, *J* = 7.0 Hz, 1H, CH_α), 2.36 (s, 3H, CH_{3Ar}), 1.62 (d, *J* = 7.0 Hz, 3H, $CH_{3\alpha}$); **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F -75.9; $\mathbf{R}_f$ 0.36 (CH_2Cl_2/Pet. Ether 6:4). This compound was synthesised solely for GC assay purposes and its data was sufficient to compare with literature.

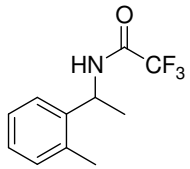
(±)-2,2,2-Trifluoro-*N*-(1-*m*-tolylethyl)acetamide (210)



White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25-7.32 (m, 1H, *Ar*), 7.10-7.18 (m, 1H, *Ar*), 7.55 (s, 1H, NH), 5.12 (dq, *J* = 7.4 Hz, 1H, CH_α), 2.38 (s, 3H, CH_{3Ar}), 1.59 (d, *J* = 7.8 Hz, $CH_{3\alpha}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 156.2 (q, *J* = 37 Hz), 140.8, 138.8, 128.9, 128.9, 127.0, 123.1, 115.8 (q, *J* = 287 Hz), 49.9, 21.4, 21.1; **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F -75.9; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3422, 2983, 1722, 1529, 1171; **HRMS** [found (ESI) MNH_4^+ 249.1199 $C_{11}H_{12}F_3NO$ requires *M* 249.1209]; $\mathbf{R}_f$ 0.35 (CH_2Cl_2/Pet. Ether 6:4). This compound was synthesised solely for GC assay purposes and its data was sufficient to compare with literature.

The GC assay: 25 m 2,6-γ-cyclodextrin column, 70 °C (isothermal), He carrier gas, 12 psi, t_1 = 115.0 min, t_2 = 115.1 min.

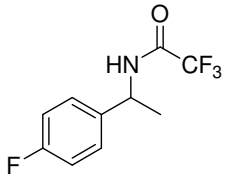
(±)-2,2,2-Trifluoro-*N*-(1-*o*-tolylethyl)acetamide (211)



White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31-7.19 (m, 4H), 6.37 (br s, 1H), 5.34 (quintet, J = 7.2 Hz, 1H), 2.37 (s, 3H), 1.58 (d, J = 7.2 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 156.1 (q, J = 36.8 Hz), 138.8, 136.0, 131.1, 128.1, 126.6, 124.6, 115.8 (q, J = 286.3 Hz), 46.3, 20.5, 19.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F -75.8; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3428, 3012, 1723, 1528, 1171; **R_f** 0.37 (CH_2Cl_2/Pet. ether 6:4); **HRMS** [found (ESI) MH^+ 232.0943 $C_{11}H_9F_6NO$ requires M 232.0944]. This compound was synthesised solely for GC assay purposes and its data was sufficient to compare with literature.

The GC assay: 25 m CP-Chiracil-Dex CB column, 100 °C (isothermal), He carrier gas, 12 psi, t_1 = 31.7 min, t_2 = 32.5 min.

(±)-*N*-(1-(4-Fluorophenyl)ethyl)-2,2,2-trifluoroacetamide (212)

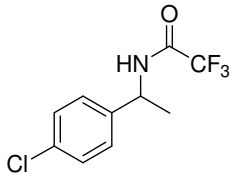


White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.40-7.20 (m, 2H, *Ar*), 7.20-7.00 (m, 2H, *Ar*), 6.45 (br s, 1H, NH), 5.15 (q, J = 7.0 Hz, 1H, CH_α), 1.59 (d, J = 7.0 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 162.4 (d, J = 245.5 Hz), 156.3 (d, J = 37.1 Hz), 136.7 (d, J = 10.6 Hz), 127.9 (d, J = 8.2 Hz), 115.9 (d, J = 21.5 Hz), 115.7 (d, J = 286.2 Hz), 49.1, 21.1; **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F -

75.9, -113.8; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3450, 3100, 2254, 1724, 1400, 1200; **HRMS** [found (ESI) MNa^+ 258.0520 $C_{10}H_9F_4NO$ requires M 258.0512]; $\mathbf{R}_f$ 0.35 (CH_2Cl_2/Pet. Ether 6:4). This compound was synthesised solely for GC assay purposes.

The GC assay: 25 m CP-Chiracil-Dex CB column, 100 °C (isothermal), He carrier gas, 12 psi, t_1 = 32.4 min, t_2 = 35.2 min.

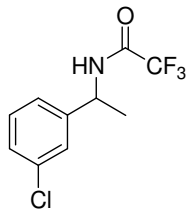
(±)-*N*-(1-(4-Chlorophenyl)ethyl)-2,2,2-trifluoroacetamide (213)



White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38-7.33 (m, 2H, *Ar*), 7.29-7.25 (m, 2H, *Ar*), 7.49 (s, 1H, NH), 5.12 (dq, 1H, *J* = 7.0 Hz, CH_α), 1.58 (d, 3H, *J* = 7.0 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 156.4 (q, *J* = 37.1 Hz), 139.5, 134.1, 129.2, 127.7, 114.4, 49.3, 21.1; **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F -75.9; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3429, 3011, 1726, 1529, 1495, 1169; **HRMS** [found (ESI) MNa^+ 274.0217 $C_{10}H_9ClF_3NO$ requires M 274.0217]; $\mathbf{R}_f$ 0.35 (CH_2Cl_2/Pet. Ether 6:4). This compound was synthesised solely for GC assay purposes and its data was sufficient to compare with literature.

The GC assay: 25 m CP-Chiracil-Dex CB column, 120 °C (isothermal), He carrier gas, 12 psi, t_1 = 35.9 min, t_2 = 37.0 min.

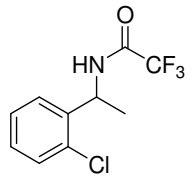
(±)-*N*-(1-(3-Chlorophenyl)ethyl)-2,2,2-trifluoroacetamide (214)



White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.550-7.515 (m, 1H, *Ar*), 7.515-7.490 (m, 1H, *Ar*), 7.230-7.207 (m, 1H, *Ar*), 7.207-7.180 (m, 1H, *Ar*), 7.42 (br s, 1H, NH), 5.11 (dq, J = 7.8 Hz, J = 7.4 Hz, 1H, CH_α), 1.58 (d, J = 7.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 156.5 (q, J = 37.1 Hz), 143.0, 134.9, 130.4, 128.4, 126.4, 124.5, 115.8 (q, J = 286.0 Hz), 49.4, 21.1; **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F -75.9; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3429, 3050, 2254, 1726, 1210, 1170, ; **HRMS** [found (ESI) MNa^+ 274.0213 $C_{10}H_9ClF_3NO$ requires M 274.0217]; $\mathbf{R}_f$ 0.35 (CH_2Cl_2/Pet. Ether 6:4). This compound was synthesised solely for GC assay purposes and its data was sufficient to compare with literature.

The GC assay: 25 m CP-Chiracil-Dex CB column, 115 °C (isothermal), He carrier gas, 12 psi, t_1 = 82.5 min, t_2 = 84.7 min.

(±)-*N*-(1-(2-Chlorophenyl)ethyl)-2,2,2-trifluoroacetamide (215)

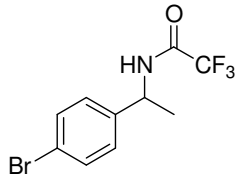


White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.46-7.38 (m, 1H, *Ar*), 7.37-7.30 (m, 1H, *Ar*), 7.30-7.23 (m, 2H, *Ar*), 7.78 (br s, 1H, NH), 5.44 (dq, J = 7.8 Hz, J = 7.2 Hz, CH_α), 1.61 (d, J = 7.8 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 156.1 (q, J = 37.1 Hz), 138.0, 133.0, 130.5, 129.3, 127.4, 127.4, 115.8 (q, J

= 286.2 Hz), 48.2, 20.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F -75.9; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3691, 3432, 2950, 2360, 1728, 1602, 1529, 1170, 660; **HRMS** [found (ESI) MNa^+ 274.0202 $C_{10}H_9ClF_3NO$ required *M* 274.0217]; $\mathbf{R}_f$ 0.35 (CH_2Cl_2/Pet. Ether 6:4). This compound was synthesised solely for GC assay purposes and its data was sufficient to compare with literature.

The GC assay: 25 m CP-Chiracil-Dex CB column, 120 °C (isothermal), He carrier gas, 12 psi, t_1 = 18.2 min, t_2 = 20.0 min.

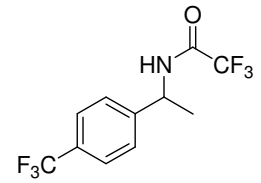
(±)-*N*-(1-(4-Bromophenyl)ethyl)-2,2,2-trifluoroacetamide (216)[187]



White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.52-7.55 (m, 1H, *Ar*), 7.48-7.55 (m, 1H, *Ar*), 7.21-7.24 (m, 1H, *Ar*), 7.17-7.21 (m, 1H, *Ar*), 7.40 (s, 1H, NH), 5.11 (m, 1H, CH_{benzyl}), 1.58 (d, *J* = 7.2 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 156.4 (q, *J* = 37.1 Hz), 140.0, 132.2, 128.0, 122.2, 117.2, 114.4, 111.5, 49.3, 21.1; **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F -75.9; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3429, 3011, 1726, 1530, 1492, 1170; **HRMS** [found (ESI) MNa^+ 317.9701 $C_{10}H_9BrF_3NO$ requires *M* 317.9712]; $\mathbf{R}_f$ 0.35 (CH_2Cl_2/Pet. Ether 6:4). This compound was synthesised solely for GC assay purposes and its data was sufficient to compare with literature.

The GC assay: 25 m CP-Chiracil-Dex CB column, 115 to 125 °C at 0.2 °C/min + 15 min at 125 °C (ramp), He carrier gas, 12 psi, t_1 = 57.0 min, t_2 = 58.0 min.

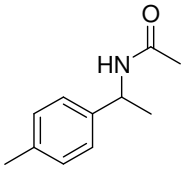
(±)-2,2,2-Trifluoro-*N*-(1-(4-(trifluoromethyl)phenyl)ethyl)acetamide (217)[187]



White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.65 (s, 1H, *Ar*), 7.63(s, 1H, *Ar*), 7.45 (s, 1H, *Ar*), 7.43 (s, 1H, *Ar*), 7.61(s, 1H, NH), 5.19 (dq, *J* = 7.2 Hz, 1H, CH_α), 1.61 (d, *J* = 7.2 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 156.7, 156.3, 145.0, 130.6, 130.3, 126.5, 126.1, 126.1, 126.0, 126.0, 122.6, 117.2, 114.3, 111.5, 49.5, 21.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F -62.5, -75.8; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3430, 3011, 1728, 1622, 1531, 1327, 1171; **HRMS** [found (ESI) MNH_4^+ 303.0928 $C_{11}H_9F_6NO$ requires *M* 303.0927]; $\mathbf{R}_f$ 0.35 (CH_2Cl_2/Pet. Ether 6:4). This compound was synthesised solely for GC assay purposes and its data was sufficient to compare with literature.

The GC assay: 25 m CP-Chiracil-Dex CB column, 100 °C (isothermal), He carrier gas, 12 psi, t_1 = 45.4 min, t_2 = 47.6 min.

(±)-*N*-(1-*p*-Tolylethyl)acetamide (218)[188]

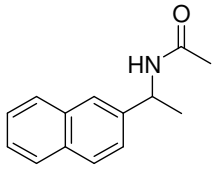


Pale yellow solid. **^{1}H NMR** (270 MHz, $CDCl_3$) δ_H 7.30-7.00 (m, 4H, *Ar*), 6.15 (br s, 1H, NH), 5.07 (q, *J* = 7.1 Hz, 1H, CH_α), 2.33 (s, 3H, CH_{3Ar}), 1.95 (s, 3H, $COCH_3$), 1.47 (d, *J* = 7.1 Hz, 3H, CH_3); **^{13}C NMR** (68 MHz, $CDCl_3$) δ_C 169.4, 140.6, 137.2, 129.5, 126.4, 48.7, 23.6, 22.0, 21.3; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3441,

3050, 2987, 2400, 2253, 1663, 1509, 1373; **HRMS** [found (ESI) MNa^+ 200.1041 $C_{11}H_{15}NO$ requires *M* 200.1046]; $\mathbf{R}_f$ 0.30 (100% EtOAc). This compound was synthesised solely for GC assay purposes.

The GC assay: 25 m CP-Chiracil-Dex CB column, 165 °C (isothermal), He carrier gas, 12 psi, t_1 = 9.0 min, t_2 = 9.3 min.

(±)-*N*-(1-(Naphthalen-2-yl)ethyl)acetamide (219)[189]

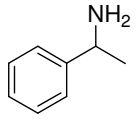


White solid. **^{1}H NMR** (270 MHz, $CDCl_3$) δ_H 7.90-7.70 (m, 4H, *Ar*), 7.60-7.35 (m, 3H, *Ar*), 5.87 (br s, 1H, NH), 5.32 (q, *J* = 7.0 Hz, 1H, CH_α), 2.02 (s, 3H, $COCH_3$), 1.59 (d, *J* = 7.0 Hz, 3H, $CH_{3\alpha}$); **^{13}C NMR** (68 MHz, $CDCl_3$) δ_C 169.1, 140.5, 133.3, 132.7, 128.6, 127.8, 127.6, 126.2, 125.9, 124.7, 124.5, 48.8, 23.5, 21.6; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3645, 3441, 3000, 2253, 1665, 1382; **HRMS** [found (ESI) MNa^+ 236.1040 $C_{14}H_{15}NO$ requires M 236.1046]; $\mathbf{R}_f$ 0.30 (100% EtOAc). This compound was synthesised solely for GC assay purposes and its data was sufficient to compare with literature.

The GC assay: 25 m CP-Chiracil-Dex CB column, 160 °C (isothermal), He carrier gas, 12 psi, t_1 = 21.9 min, t_2 = 22.9 min.

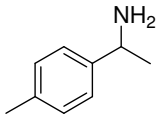
7.7 Deprotection and isolation of amines

(±)-1-Phenylethanamine (45)[190]



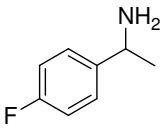
Preparation according to general procedure 7.3.12 gave title compound as a colourless liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.62-7.32 (m, 4H, *Ar*), 7.31-7.20 (m, 1H, *Ar*), 4.13 (q, *J* = 6.8 Hz, 1H, CH_α), 1.51 (br s, 2H, NH_2), 1.41 (d, *J* = 6.8 Hz, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 148.0, 128.7, 127.0, 125.9, 51.5, 29.8; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3376, 2965, 2493, 1584, 1493, 1452, 1373; **HRMS** [found (ESI) MNa^+ 144.0767 $C_8H_{11}N$ requires *M* 144.0784].

(±)-1-*p*-Tolylethanamine (204)[191,192]



Preparation according to general procedure 7.3.12 gave title compound as a colourless liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.28 (d, *J* = 8.0 Hz, 2H, *Ar*), 7.20 (d, *J* = 8.0 Hz, 1H, *Ar*), 4.12 (q, *J* = 6.8 Hz, 1H, CH_α), 2.39 (s, 3H, CH_{3Ar}), 1.96 (br s, 2H, NH_2), 1.43 (d, *J* = 6.8 Hz, 3H, $CH_{3\alpha}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 144.8, 136.4, 129.5, 122.8, 51.1, 25.7, 21.1; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3667, 3374, 2965, 2337, 1677, 1607, 1514, 1451, 1372; **HRMS** [found (ESI) MH^+ 136.1105 $C_9H_{13}N$ requires *M* 136.1121].

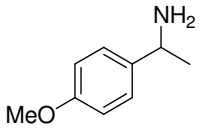
(±)-1-(4-Fluorophenyl)ethanamine (205)[193]



Preparation according to general procedure 7.3.12 gave title compound as a colourless liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.30 (m, 2H, *Ar*), 7.00 (m,

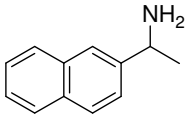
2H, *Ar*), 4.10 (q, *J* = 6.4 Hz, 1H, CH_α), 1.93 (br s, 2H, NH_2), 1.35 (d, *J* = 6.4 Hz, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 161.8 (d, *J* = 232 Hz), 143.5, 127.4, 115.4, 50.8, 25.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F -116.3; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3667, 3376, 2966, 2337, 1888, 1603, 1510, 1373, 1240, 1157; **HRMS** [found (ESI) MH^+ 140.0854 $C_8H_{10}FN$ requires *M* 140.0870].

(±)-1-(4-Methoxyphenyl)ethanamine (206)[191]



Preparation according to general procedure 7.3.12 gave title compound as a colourless liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.23 (d, *J* = 8.6 Hz, 1H, *Ar*), 6.83 (d, *J* = 8.6 Hz, 1H, *Ar*), 4.02 (q, *J* = 6.6 Hz, 1H, CH_α), 3.73 (s, 3H, CH_{3Ar}), 1.60 (br s, 2H, NH_2), 1.33 (d, *J* = 6.6 Hz, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 158.3, 139.9, 126.7, 113.7, 55.0, 50.5, 25.6; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3666, 3374, 2962, 2492, 2056, 1883, 1611, 1513, 1464, 1373; **HRMS** [found (ESI) MH^+ 152.1061 $C_9H_{13}NO$ requires *M* 152.1070].

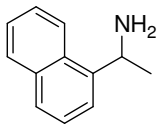
(±)-1-(Naphthalen-2-yl)ethanamine (207)[194]



Preparation according to general procedure 7.3.12 gave title compound as a white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.84 (d, *J* = 3.6 Hz, 3H, *Ar*), 7.79 (s, 1H, *Ar*), 7.53-7.42 (m, 3H, *Ar*), 4.30 (q, 6.6 Hz, 1H, CH_α), 1.61 (s, 2H, NH_2), 1.49 (d, *J* = 6.6 Hz, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 145.5, 133.8, 132.9, 128.5, 128.1, 127.9, 126.3, 125.8, 124.9, 124.0, 51.7, 26.0; **IR**

υ_{max} ($CHCl_3$)/ cm^{-1} 3661, 3061, 2965, 1601, 1508, 1376, 1127; **HRMS** [found (ESI) MH^+ 172.1109 $C_{12}H_{13}N$ requires *M* 172.1121].

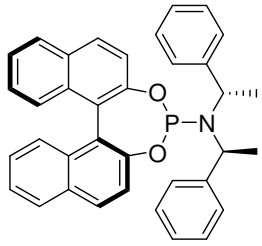
(±)-1-(Naphthalen-2-yl)ethanamine (208)[195]



Preparation according to general procedure 7.3.12 gave title compound as a colourless liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.16 (d, *J* = 8.4 Hz, 1H, *Ar*), 7.90 (d, *J* = 7.6, *J* = 1.6 Hz, 1H, *Ar*), 7.77 (d, *J* = 8.0 Hz, 1H, *Ar*), 7.68 (d, *J* = 6.8 Hz, 1H, *Ar*), 7.59-7.54 (m, 1H, *Ar*), 7.54-7.47 (m, 2H, *Ar*), 4.97 (q, *J* = 6.8 Hz, 1H, CH_α), 1.72 (br s, 1H, NH), 1.58 (d, *J* = 6.8 Hz, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 143.6, 134.2, 131.0, 129.2, 127.5, 126.2, 125.9, 125.7, 123.2, 121.6, 46.8, 25.1; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3666, 3377, 2996, 1597, 1511, 1449, 1396; **HRMS** [found (ESI) MH^+ 172.1112 $C_{12}H_{13}N$ requires *M* 172.1121].

7.8 Synthesis of ligands and catalysts

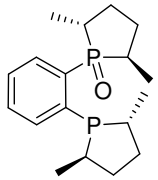
***O-O'*-(*S*)-(1,1'-Dinaphthyl-2-2'-diyl)-*N,N'*-di-(*S,S*)-1-phenylethyl phosphoramidite (64)**[196]



In a 50 mL round-bottomed flask the amine hydrochlorate salt was dissolved in a minimum amount of CH_2Cl_2 and basified with an even amount of a 2M NaOH solution. The solution was stirred for approximately 1 h before isolating the free amine (colourless liquid) by extraction with CH_2Cl_2 followed by a drying over Na_2SO_4 and concentration in *vacuuo*. In a 250 mL two neck round-bottomed flask under argon equipped with a magnetic stirrer and fitted with an inert atmosphere filtration tube was introduced PCl_3 (8.6 mmol, 0.75 mL), Et_3N (17.2 mmol, 2.40 mL) and toluene (10 mL). The mixture was cooled down to -60 °C. Next was added a warm solution (60 °C) of (*S*)-2,2'-binaphthol (1 eq., 8.6 mmol, 2.46 g) in toluene (40 mL) by means of a cannula, over 10 min. The resulting mixture was stirred for 2 h, warmed to room temperature, filtered under argon atmosphere and the filtrate was treated with Et_3N (8.32 mmol, 1.18 mL) and the freshly isolated free secondary amine (7.32 mmol, 1.65 g) at -40 °C. After 16 h at room temperature the reaction mixture was filtered to give the crude product as a yellow oil which was immediately purified by flash chromatography on silica gel (Pet. ether/CH_2Cl_2 3:1) and recrystallisation in Et_2O/CH_2Cl_2. Finally, 1.58 g (40%) of a white foam was obtained. $\mathbf{[\alpha]_D}^{20}$ = +46.0, (*c* = 0.79, $CHCl_3$); Lit.[197] +11[198] (c = 0.79, $CHCl_3$); **m.p.** 86-87 °C; Lit[196] 87-89; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.09 (d, 1H, *J* = 8.8 Hz, *Ar*), 8.01 (d, 1H, *J* = 8.0 Hz, *Ar*), 7.91 (d, 1H, *J* = 9.2 Hz, *Ar*), 7.66 (d, 1H, 8.8 Hz), 7.40-7.55 (m, 5H, *Ar*), 7.15-7.40 (m, 13H, *Ar*), 4.50 (q, *J* = 7.2 Hz, 2H, CH), 1.78 (d, *J* = 7.2 Hz, 6H, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 150.9, 150.8, 150.1, 143.4, 133.2, 133.1, 131.7, 130.8, 130.7, 129.9, 128.6, 128.4, 128.3, 128.1, 127.6, 127.5, 127.0, 127.4, 127.2, 125.1, 124.7, 122.9, 122.7, 54.9, 54.8, 23.4, 23.3; **^{31}P** ($CDCl_3$, 162 MHz) δ_P 151.3; **IR** υ_{max}

($CHCl_3$)/ cm^{-1} 3568, 3050, 2361, 1592, 1507,1437, 1328, 1070, 949; **HRMS** [found (ESI) MH^+ 540.2058 $C_{36}H_{30}NO_2P$ requires *M* 540.2087]; $\mathbf{R}_f$ 0.30 (Pet. ether/CH_2Cl_2 3:1).

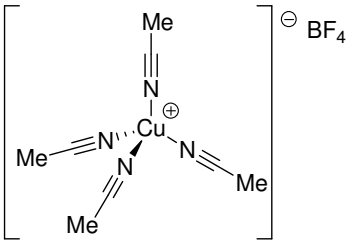
(2*R*,5*R*)-1-{2[(2*R*,5*R*)2,5-Dimethylphospholan-1-yl]phenyl}-2,5 dimethylphospholane 1-oxide (BozPHOS) (60)[41]



To a solution of (*R,R*)-Me-DUPHOS (500 mg, 1.63 mmol, 1.0 equiv) in THF (16 mL, 0.1 M) was added BH_3•DMS (10 M, 180 mL, 1.80 mmol, 1.1 equiv) at 0 °C. The mixture was stirred 45 min at this temperature and treated with H_2O_2 (30% (v/v) 2.0 mL, 19.60 mmol, 12.0 eq.). After 45 min of additional stirring at room temperature, the reaction was quenched with saturated Na_2SO_3 (until basic pH) at 0 °C. Aqueous layers were extracted with EtOAc (3x20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was immediately dissolved in toluene (16 mL, 0.1 M) and treated with DABCO (275 mg, 2.45 mmol, 1.5 eq.) at 50 °C. The reaction mixture was further stirred for 5 h at 50 °C, evaporated under reduced pressure and directly purified on silica gel [EtOAc/MeOH 95:5] to afford 431 mg (83%) of a white air-stable solid; $\mathbf{[\alpha]_D}^{20}$ = -134.3, (*c* = 0.67, benzene); Lit.[41] -250.5 (*c* = 0.65, benzene); **m.p.** 124-125 °C; Lit.[41] 123-125 °C; **^{1}H NMR** (C_6D_6, 400 MHz) δ_H 7.59 (m, 1H, *Ar*), 7.43 (m, 1H, *Ar*), 7.21-7.13 (m, 2H, *Ar*), 2.94-2.68 (m, 2H, CH-*PO*, 2.63-2.52 (m, 1H, CH-*P*), 2.20-1.93 (m, 5H, CH_2 and CH_3-*CHPO*), 1.92-1.70 (m, 2H, CH_2), 1.50-1.26 (m, 4H, CH and CH_3), 1.20-1.03 (m, 7H,

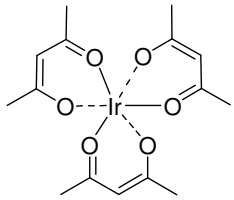
CH, CH_3-*CHP* and CH_3-*CHPO*), 0.95 (dd, 3H, J_{PH} = 17.6 Hz, J = 7.6 Hz, CH_3-*CHP*); **^{13}C NMR** (C_6D_6, 100 MHz) δ_C 144.0, 139.1, 134.2, 130.5, 128.3, 37.9, 37.6, 37.1, 34.8, 34.6, 31.9, 31.7, 31.5, 20.1, 18.3, 17.4, 12.8; **^{31}P NMR** (C_6D_6, 162MHz) δ_P 63.4, 9.7; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2918, 2858, 1447, 1160, 757, 736, 677; **HRMS** [found (ESI) MH^+ 323.1691 $C_{18}H_{28}OP_2$ requires *M* 323.1688]; **R_f** 0.20 (100% EtOAc).

Tetrakis acetonitrile copper(I) tetrafluoroborate (221)[199]



In a 100 mL Erlenmeyer flask fitted with a magnetic stirrer, copper(I) oxide (1.00 g, 13.56 mmol, 1.0 eq.) was dissolved in acetonitrile (25 mL). Next, 48% HBF_4 (5.0 mL, 38.3 mmol, 2.8 eq.) was slowly added to the resulting suspension and the mixture was heated up to 75 °C until complete dissolution had occured. Then the solution was hot filtered and the filtrate was collected into a hot Erlenmeyer flask before to be left to cool to room temperature, time during which few crystals of the complex appear. Finally, recrystallisation at 0 °C was carried out for one hour until a large crop of crystals had formed. Quick filtration and washings with dry ether afforded 3.13 g (73%) of colourless crystals; (Found C 27.48; H 3.42; N 17.50%. Calc. For $C_8H_{12}BCuF_4N_4$[200] C 30.55; H 3.85; N 17.81%); **m.p.** 155-160 °C; Lit.[199] 159-161 °C; **^{1}H NMR** (C_2D_6O, 400 MHz) δ_H 2.07 (s, 12H, CH_3); **^{13}C NMR** (C_2D_6O, 100 MHz) δ_C 117.9, 1.0; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2945, 2303, 2274, 1417, 1366, 1284.

Tris(acetylacetonate) iridium(III) (222)[201]



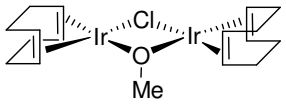
In a 10 mL Schlenck tube equipped with a magnetic stirrer bar, iridium (III) chloride trihydrate (0.142 mmol, 50.0 mg) was dissolved in distilled water (3.0 mL). The solution was warmed up to 70 °C to reach complete solubilisation. Next, acetylacetonate (0.568 mmol, 58 μL) was introduced and the solution was stirred for 15 min after which time a small amount of a saturated solution of $NaHCO_3$ (1 mL) was added to get a neutral pH. Then, the reaction vessel was fitted with a condenser and the mixture was heated at 70 °C for 48 h during which time the colour of the reaction solution lightened considerably. An orange-yellow solid was collected by vacuum filtration and recristallised from boiling methanol. The purified product was obtained as a bright yellow powder (25.7 mg, 37%). **m.p.** 268-269 °C; Lit.[202] 269-271 °C; **^{1}H NMR** (C_2D_6SO, 400 MHz) δ_H 5.50 (s, 1H, CH_{enol}), 1.88 (s, 6H, CH_3); **^{13}C NMR** (C_2D_6SO, 100 MHz) δ_C 185.3, 101.8, 27.0; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3566, 3004, 1556, 1524, 1392.

Di-*μ*-chloro-*bis*(1,5-cyclooctadiene)-diiridium(I) (65)[203]

In a 100 mL Schlenk flask equipped with a magnetic stirrer and purged with argon, iridium trichloride trihydrate (1.0 g, 2.84 mmol, 1.0 eq.) was dissolved in 15 mL of degassed distilled water, to which a mixture of degassed

isopropanol (30 mL) and 1,5-cyclooctadiene (3.0 mL, 24.45 mmol, 8.6 eq.) was added portion wise and stirred at reflux temperature for about 18 hours. This resulted in a colour change from brown toward red. The resulting solution was concentrated to about 50% of its original volume by distillation of the solvent under argon. Upon slow cooling to room temperature, dark brown crystals precipitated, which were filtered, washed with cold methanol and dried under vacuum to afford 518 mg (27%) of the complex; **m.p.** 202-205 °C (dec.); Lit.[204,205] > 200 °C (dec.); **^{1}H NMR** (C_2D_6SO, 270 MHz) δ_H 4.19 (d, J = 2.0 Hz, 8H, CH), 2.36-2.12 (m, 8H, CH_2), 1.92-1.70 (m, 8H, CH_2); **^{13}C NMR** (C_2D_6SO, 100 MHz) δ_C 74.0, 30.7; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2977, 2965, 2934, 2934, 2830, 2337, 1506, 1472, 1448, 1323, 1010, 979, 904.

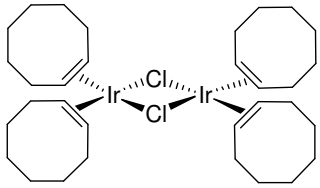
Di-μ-methoxy-*bis*(1,5-cyclooctadiene)-diiridium(I) (66)



A 100mL round-bottom flask equipped with a magnetic stirrer and purged with argon was charged with a solution of potassium hydroxide (25 mg, 0.445 mmol, 2.0 eq.) in degassed methanol (5 mL). Addition of a suspension of $[IrCl(1,5\text{-}COD)]_2$ (149 mmol, 0.222 mmol, 1.0 eq.) in methanol turns the colour of the initially orange-black suspension to dark yellow. After being stirred for 30 minutes at room temperature, 40 mL of degassed distilled water were added, changing the colour of the solution to bright yellow. Finally, the yellow-green precipitate was collected by filtration, using a fine sintered-glass filter, washed with water (6×5 mL), and vacuum dried over phosphorus(V) oxide to give 108 mg (73%) of the black/orange complex; (Found: C, 30.69; H,

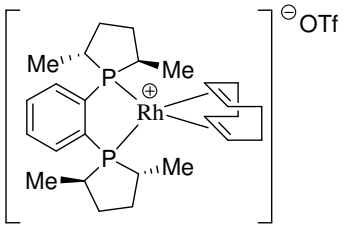
4.15%. Calc. For $C_{17}H_{27}ClIr_2O$ C, 30.60; H, 4.08%); **m.p.** 192-193 °C (dec.); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.62-3.45 (m, 8H, CH), 3.25 (s, 3H, CH_3), 2.40-2.10 (m, 8H, CH_2), 1.50-1.20 (m, 8H, CH_2); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 57.4, 54.2, 31.4; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2878, 2344, 1562, 1446, 1321, 1054, 1002, 969.

Di-*μ*-chlorotetrakis(cyclooctene)diiridium(I) (68)[204]



In a 10 mL flame dried Schlenk tube equipped with a magnetic stirrer and purged with argon, iridium trichloride trihydrate (1.00 g, 2.84 mmol, 1.0 eq.) was dissolved in 11 mL of degassed isopropanol (HPLC grade) and 4 mL of degassed distilled water before adding cyclooctene (2.0 mL, 5.4 eq.). The reaction mixture was stirred at room temperature for 5 minutes and then refluxed for 3 hours under a low stream of argon passing through the system. During this reflux, the initially dark green solution turned yellow-orange. Finally, the reaction mixture was cooled down to room temperature, filtered through a glass sinter, and then dried with high vacuum overnight to remove residual cyclooctene. 843 mg (66%) of the complex were obtained as a yellow-orange solid; (Found: C, 41.90; H, 7.21%. Calc. For $C_{32}H_{56}Cl_2Ir_2$ C, 42.89; H, 7.30%); **m.p.** 160-162 °C (dec.); Lit.[206] 160-165 °C (dec.); **^{1}H NMR** ($CDCl_3$, 270 MHz) δ_H 2.30-2.60 (m, 6H, 3x CH_2), 1.2-1.9 (m, 8H, 3x CH_2, 2x CH); **^{13}C NMR** (C_6D_6, 100 MHz) δ_C 64.3, 31.1, 30.8, 27.2, 2.0; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2925, 2853, 1588, 1466.

1,2-*bis*((2*R*,5*R*)-2,5-Dimethylphospholano) benzene) (1,5-cyclooctadiene)rhodium(I) triflate (118)



A 50 mL flame dried Schlenck tube fitted with a stirring bar was purged under argon and then charged with (1,5-cycloocatadiene)(acetylacetonato)rhodium(I) (7.00 g, 19.34 mmol), degassed THF (4.6 mL) and MTBE (23 mL). This mixture was stirred at -50 °C until all material was dissolved. Another 50 mL flame dried Schlenck tube purged under argon was charged with degassed isopropanol (9.3 mL – HPLC grade) and triflic acid (2.10 mL, 23.73 mmol) was slowly added whilst maintaining a temperature of -78 °C.

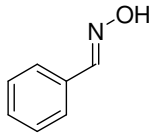
In a third 50 mL flame dried Schlenck tube purged under argon (*R*,*R*)-Me-DuPHOS (5.93 g, 19.35 mmol) was introduced and dissolved in degassed THF (12 mL). The triflic acid solution in isopropanol was added continuously over 25 minutes whilst maintaining a gentle reflux by means of a dosing pump to give a transparent yellow/brown homogeneous solution. The mixture was stirred at reflux temperature for approximately 20 minutes. The (*R*,*R*)-Me-DuPHOS solution in THF was once again added continuously over 25 minutes whilst maintaining a gentle reflux by means of the dosing pump. This addition caused almost immediate precipitation of the crystalline product. Finally, the reaction mixture was cooled down to room temperature and filtered under argon. The filter and the Schlenck tube were rinsed twice with degassed isopropanol and the residual solvent removed under vacuum. The filter cake

was finally rinsed three times with a degassed 3:2 THF/MTBE solution and vacuum dried to constant to afford 11.38 g (88%) of a red shiny solid; **$[\alpha]_D$** = -46.39, (*c* = 0.53, $CHCl_3$); **m.p.** 147-151 °C (dec.); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.70 (m, 4H, , $CH_{aryl\ DuPHOS}$), 5.62 (s, 2H, $=CH_{COD}$), 5.05 (s, 2H, $=CH_{COD}$), 2.58-2.80 (m, 4H, $CH_{2\ DuPHOS}$), 2.30-2.56 (m, 8H, $CH_{2\ COD}$), 1.82-2.00 (m, 2H, CH_{DuPHOS}), 1.50-1.62 (m, 2H, CH_{DuPHOS}), 1.40-1.50 (m, 6H, $CH_{3\ DuPHOS}$), 0.98-1.10 (m, 6H, $CH_{3\ DuPHOS}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 133.1, 133.0, 132.6, 107.9, 93.6, 93.5, 60.2, 45.5, 41.2, 38.9, 37.9, 37.3, 37.1, 34.7, 32.6, 31.0, 28.7, 28.3, 17.7, 14.3; **^{31}P NMR** ($CDCl_3$, 162 MHz) 77.5, 75.6; **^{19}F NMR** ($CDCl_3$, 377 MHz) -153.0; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3696, 3605, 2947, 1602, 1455, 1288, 1088, 1031, 996.

7.9 Synthesis of oximes

Oximes were synthesised according to general procedure 7.3.13.

Benzaldehyde oxime (191)[207]

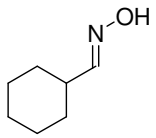


Purification by flash chromatography afforded one fraction of 1:1 *cis*/*trans* isomers and another fraction containing exclusively the *cis* isomer. Both fractions were clear yellowish oils.

***Cis* isomer**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 9.40 (s, 1H, OH), 8.23 (s, 1H, HC=N), 7.63 (m, 2H, *Ar*), 7.42 (m, 3H, *Ar*). ***Cis/trans* mixture of isomers**:

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.51 (s, 2H, OH), 8.23 (s, 2H, HC=N), 7.63 (m, 4H, *Ar*), 7.42 (m, 6H, *Ar*); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 150.8, 132.1, 130.6, 130.2, 129.1, 127.1; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3579, 3315, 2909, 1955, 1895, 1493, 1451, 1304, 1263, 949; **HRMS** [found (ESI) MNa^+ 144.0422 C_7H_7NO requires *M* 144.0420]; $\mathbf{R}_f$ *cis* 0.62, $\mathbf{R}_f$ *trans* 0.72 ($CHCl_3$/EtOAc 1:1).

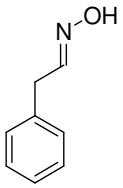
Cyclohexanecarbaldehyde oxime (193)[208]



Purification by flash chromatography afforded a colourless oil that was an inseparable mixture of *cis*-oxime/*trans*-oxime/hydroxylamine in a 50:21:29 ratio. **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 157.7, 157.2, 38.8, 37.3, 34.1, 30.5, 29.7, 27.2, 25.7, 25.5; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3669, 3587, 3312, 3011, 2935, 2856, 1653, 1450, 1309, 964; **HRMS** [found (EI) M^+ 127.1129 $C_7H_{13}NO$ requires *M* 127.0992]; $\mathbf{R}_f$ 0.72 ($CHCl_3$/EtOAc 1:1).

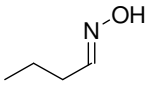
***Cis*-oxime isomer: ^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 9.28 (s, 1H, OH), 7.31 (d, 1H, *J* = 7.0 Hz, HC=N), 2.20 (m, 1H, CH_α), 1.05-1.82 (m, 10H, CH_2). ***Trans*-oxime isomer: ^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 9.28 (s, 1H, OH), 7.52 (d, 1H, *J* = 7.6 Hz, HC=N), 2.20 (m, 1H, CH_α), 1.05-1.82 (m, 10H, CH_2); **Hydroxylamine isomer: ^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 9.28 (s, 2H, NH+OH), 2.96 (m, 1H, C=CH), 1.05-1.82 (m, 10H, CH_2)

2-Phenylacetaldehyde oxime (192)[208]



Purification by flash chromatography afforded two fractions of *cis*/*trans* isomers in 98:2 ratio (crystalline needles) and 94:6 ratio (waxy bright brown solid) respectively. **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3751, 3587, 3328, 3011, 1558, 1454, 1420, 1357, 1310, 895; **HRMS** [found (ESI) MH^+ 137.0747. C_8H_9NO requires *M* 137.0757]; $\mathbf{R}_f$ 0.11 (Hexane/EtOAc 90:10). ***Cis*-isomer: m.p.** 97-98 °C, Lit.[209] 99 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.95 (s, 1H, OH), 7.33-7.40 (m, 2H, *Ar*), 7.26-7.33 (m, 3H, *Ar*), 7.96 (t, 1H, *J* = 5.6 Hz, HC=N), 3.80 (d, 2H, *J* = 5.6 Hz, CH_2); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 151.2, 137.0, 129.2, 129.10, 127.0, 32.0. ***Trans*-isomer: ^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.80-10.60 (s, 1H, OH), 7.26-7.40 (m, 5H, *Ar*), 7.60(t, 1H, *J* = 7.4 Hz, HC=N), 3.60 (d, 2H, *J* = 7.4 Hz, CH_2); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 151.0, 137.3, 129.11, 129.06, 127.3, 127.2, 37.2.

Butyraldehyde oxime (194)[210]



Was afforded as an inseparable 1:1 mixture of *cis*/*trans* isomers. Colourless oil. **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3668, 3588, 3289, 3011, 2968, 2876, 1720, 1656, 1462; **HRMS** [found (EI) MNa^+ 87.1077 C_4H_9NO requires *M* 87.0679]; $\mathbf{R}_f$ 0.81 ($CHCl_3$/EtOAc 1:1).

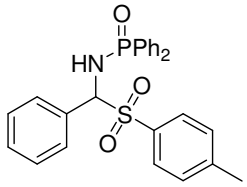
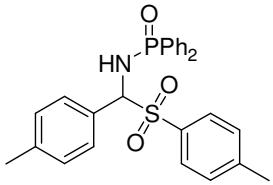
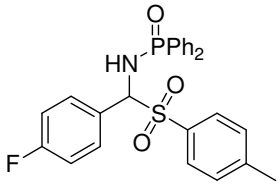
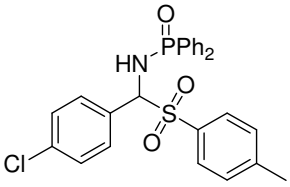
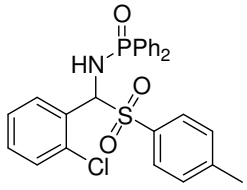
***Cis* isomer**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 9.78 (s, 1H, OH), 7.41 (t, 1H, *J* = 7.4 Hz, HC=N), 2.35 (tq, 2H, *J* = 7.2 Hz, *J* = 7.6 Hz, $CH_2\beta$), 1.50 (tq, 2H, *J* =

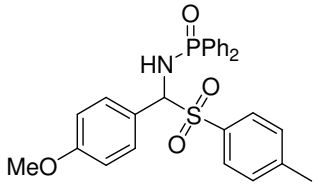
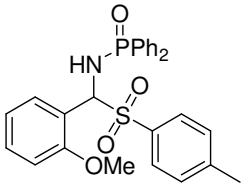
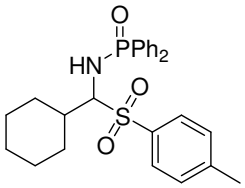
7.4 Hz, *J* = 7.6 Hz, $CH_{2\alpha}$), 0.96 (t, 3H, *J* = 7.2 Hz, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 153.0, 31.7, 20.2, 14.1. ***Trans* isomer**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 9.42 (s, 1H, OH), 7.41 (t, 1H, *J* = 5.4 Hz, HC=N), 2.35 (dt, 2H, *J* = 7.2 Hz, *J* = 7.4 Hz, $CH_2\beta$), 1.50 (tq, 2H, *J* = 7.4 Hz, *J* = 5.4 Hz, $CH_{2\alpha}$), 0.94 (t, 3H, *J* = 7.2 Hz, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 152.4, 27.2, 19.7, 13.9.

7.10 Synthesis of sulfonyl adducts

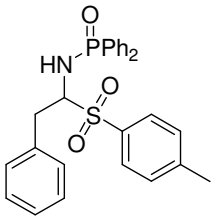
Sulfonyl adducts were prepared according to general procedure 7.2.14. Most of them were obtained as crude mixtures which could not be succesfully purified by recrystallisation. Therefore, with the exception of **203**, only the IR data is reported in Table 26 for these compounds.

Table 26: Comparison of IR data of synthetised crude sulfonyl adduct compounds.

Entry	Compound	IR υ_{max} ($CHCl_3$)/ cm^{-1}
1	***P*, *P*-Diphenyl-*N*-(phenyl (tosyl)methyl)-phosphinic amide**  **195**	3692, 3009, 1624, 1600, 1454, 1191, 1129
2	***P*,*P*-Diphenyl-*N*-(p-tolyl (tosyl)methyl)-phosphinic amide**  **196**	3688, 3008, 1604, 1439, 1181, 1131
3	***P*,*P*-Diphenyl-*N*-((4-fluorophenyl) (tosyl)methyl)-phosphinic amide**  **197**	3689, 2998, 1601, 1510, 1439, 1192, 1131, 950
4	***P*,*P*-Diphenyl-*N*-((4-chlorophenyl) (tosyl)methyl)-phosphinic amide**  **198**	3691, 2989, 2948, 1711, 1600, 1439, 1182, 1132, 950
5	***P*,*P*-Diphenyl-*N*-((2-chlorophenyl) (tosyl)methyl)-phosphinic amide**  **200**	3688, 3009, 1602, 1439, 1191, 1132, 951

6	***P,P*-Diphenyl-*N*-((4-methoxyphenyl) (tosyl)methyl)-phosphinic amide**  **199**	3693, 3000, 1600, 1572, 1439, 1180, 1132, 950
7	***P,P*-Diphenyl-*N*-((2-methoxyphenyl) (tosyl)methyl)-phosphinic amide**  **201**	3690, 3009, 1602, 1439, 1177, 1132, 950
8	***P,P*-Diphenyl-*N*-(cyclohexyl (tosyl)methyl)-phosphinic amide**  **202**	3691, 3061, 2937, 2859, 1707, 1599, 1439, 1176, 1132, 950

***P,P*-Diphenyl-*N*-(2-phenyl-1-tosylethyl)phosphinic amide (203)**

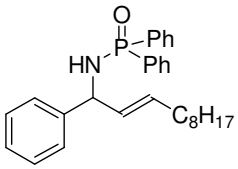


Purification by washing with water (2x20 mL) and recrystallisation in $CHCl_3/Et_2O$ afforded the title compound as a white solid with 94% purity by ^{1}H NMR spectroscopy. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.88-7.91 (d, 2H, *J* = 12.4 Hz, *Ar*), 7.32-7.60 (m, 3H, *Ar*), 7.20-7.32 (m, 14H, *Ar*), 4.74 (m, 1H, CH_α), 3.86 (t, 1H, *J* = 10.4 Hz, CH_β), 3.60 (dd, 1H, *J* = 2.6 Hz, *J* = 14.2 Hz, CH_β), 3.13 (dd, 1H, *J* = 9.2 Hz, *J* = 14.4 Hz, NH); **^{13}C NMR** ($CDCl_3$, 100

MHz) δ_C 145.4, 144.6, 135.3, 132.4, 132.3, 132.20, 132.16, 132.10, 132.06, 130.6, 130.1, 130.04, 129.97, 129.4, 129.0, 128.9, 128.8, 128.6, 128.5, 127.7, 125.3, 73.9, 37.8, 22.1, 21.8; **^{31}P NMR** ($CDCl_3$, 162 MHz) δ_P 23.9; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3610, 3050, 2338, 1596, 1456, 1302, 1124; **HRMS** [found (ESI) MH^+ 477.1457 $C_{27}H_{26}NO_3PS$ requires *M* 477.1444].

7.11 Synthesis of the allyl and propargyl addition products

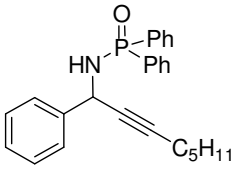
(±)-*P,P*-Diphenyl-*N*-(1-phenylundec-2-enyl)phosphinic amide (86)



In a 50 mL flame dried round-bottom flask equipped with a magnetic stirrer and purged with argon, was introduced 1-decyne (0.54 mL, 3.00 mmol) and anhydrous hexane (3.0 mL). Next, after cooling down the solution to 0 °C, neat diisobutylaluminium hydride (0.51 mL, 3.60 mmol) was added while stirring. Finally, the reaction mixture was warmed up to 55 °C and stirred at this temperature for 4 hours to form dibutyl(dec-1-enyl)aluminium ($(^iBu)_2Al(CH)_2C_8H_{17}$. In another 10 mL flame dried Schlenck tube under argon, di-μ-chlorotetrakis(cyclooctene)diiridium(I) (5.2 mg, 5.75 μmol) was dissolved in THF (2.0 mL) and diphenylphosphinoyl benzaldimine (37.0 mg, 0.115 mmol) was added after complete dissolution. Then, previously synthesised dibutyl(dec-1-enyl)aluminium (64.5 mg, 0.230 mmol) was added slowly into the solution at room temperature. The reaction mixture was then allowed to be stirred overnight, at 55 °C. Purification by flash chromatography on silica gel

(Petroleum ether/EtOAc 8:2) afforded 18.4 mg (36%) of a colourless liquid; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ_H 7.80-8.00 (m, 4H, *Ar*), 7.60-7.20 (m, 11H, *Ar*), 5.58-5.72 (dd, *J* = 6 Hz, *J* = 15 Hz, 1H, CH_{vinyl}), 5.43-5.58 (m, 1H, CH_{vinyl}), 4.73-4.88 (m, 1H, CH_{benzyl}), 3.21-3.34 (m, 1H, NH), 1.90-2.05 (m, 1H, CH_{2allyl}), 1.10-1.40 (s, 12H, CH_{2octyl}), 0.88 (m, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 132.9, 132.7, 132.6, 132.4, 129.0, 128.8, 128.6, 128.0, 127.5, 127.3, 57.3, 32.5, 32.2, 29.7, 29.6, 29.5, 29.3 (d, *J* = 3 Hz), 23.0, 14.4; **^{31}P NMR** ($CDCl_3$, 162 MHz) δ_P 23.5; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3366, 2993, 1439, 1184; **HRMS** [found (ESI) MNa^+ 468.2422. $C_{29}H_{36}NOP$ requires *M* 468.2447]; **Rf** 0.30 (Petroleum ether/EtOAc 8:2).

(±)-*P,P*-Diphenyl-*N*-(1-phenyloct-2-ynyl)phosphinic amide (92)

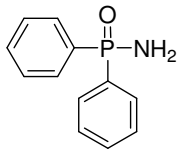


A 20 mL flame dried Schlenck tube under argon was charged with a 2M solution of $AlMe_3$ in toluene (1.5 mL, 3.0 mmol). Then, triethylamine (42 μL, 0.3 mmol) was added and the mixture was stirred at room temperature for 10 minutes. Finally, 1-heptyne (435 μL, 3.3 mmol) was added and the mixture was heated up to 60 °C for 6 hours. The product (hept-1-ynyldimethylaluminum) was stored overnight under argon, and kept away from light. The next day, in 20 mL flame dried Schlenck tube under argon, di-*μ*-chlorotetrakis(cyclooctene)diiridium(I) (13.4 mg, 15 μmol) was dissolved in THF (4.0 mL) and diphenylphosphinoyl benzaldimine (91.6 mg, 0.30 mmol) was added with another portion of THF (1.0 mL) after complete dissolution. Then, previously synthesised hept-1-ynyldimethylaluminum (0.30 mL, 0.6

mmol) was added slowly into the solution at room temperature, causing a change of colour from orange to dark. The reaction mixture was then heated to reflux temperature for 3 hours. Purification by flash chromatography on silica gel (Petrol. ether/EtOAc 4:6) afforded 77.0 mg (64%) of a colourless liquid; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ_H 8.20-8.00 (m, 2H, *Ar*), 7.90-7.75 (m, 2H, *Ar*), 7.70-7.55 (m, 2H, *Ar*), 7.55-7.00 (m, 9H, *Ar*), 5.14 (m, 1H, CH), 3.53 (m, 1H, NH), 2.30-2.10 (m, 2H, $CH_{2propargyl}$), 1.50-1.10 (m, 6H, CH_3), 1.00-0.60 (m, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 141.3 (d, *J* = 5 Hz), 133.0 (d, *J* = 126 Hz), 132.2 (d, *J* = 7 Hz), 132.2 (d, *J* = 9 Hz), 128.8 (d, J = 2 Hz), 128.6, 128.0, 127.6, 86.6, 80.0 (d, *J* = 9 Hz), 47.1, 31.4, 28.6, 22.5, 19.1, 14.3; **^{31}P NMR** ($CDCl_3$, 162 MHz) 23.2; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3388, 3046, 1602, 1439, 1186, 1125; **HRMS** [found (ESI) MH^+ 402.1980. $C_{26}H_{28}NOP$ requires *M* 402.1981]; **Rf** 0.32 (Petrol. ether/EtOAc 4:6).

7.12 Miscellaneous

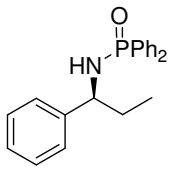
P,P-Diphenylphosphinic amide (223)[169]



In a 1 L two-neck round-bottom flask equipped with a magnetic stirring bar, to a solution of diphenylphosphinic chloride (5.0 mL, 27.2 mmol) in THF (70 mL) was slowly added 35% aqueous solution of ammonia (3.6 mL, 65.5 mmol). The resulting white cloudy mixture was allowed to be stirred for 2

hours, upon which time the suspension was filtered through a glass sinter, dried over Na_2SO_4, filtered again and evaporated to dryness under reduced pressure to give a white solid (98%) which could be recrystallised in hot toluene to give 4.32 g (76%) of the product. **m.p.** 160-161 °C; Lit.[16] 160-161 °C; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ_H 7.87-7.82 (m, 4H, *Ar*), 7.36-7.40 (m, 6H, *Ar*), 3.51 (s, 2H, NH_2); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 133.8 (d, J = 130 Hz), 132.1 (d, J = 14 Hz), 132.0 (d, J = 5 Hz), 128.7 (d, J = 19 Hz); **^{31}P NMR** ($CDCl_3$, 162 MHz) δ_P 23.2; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 1560, 1438, 1172, 1125, 1108, 894, 757, 737, 720; **HRMS** [found (TOF) M-H 217.0585 $C_{12}H_{12}NOP$ requires M 217.0584]; **R_f** 0.38 (EtOAc:MeOH 94:6).

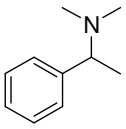
(*S*)-*P,P*-Diphenyl-*N*-(1-phenylpropyl)phosphinic amide (224)[41]



In a 200 mL round-bottomed flask under argon was prepared a solution of (*S*)-1-phenylpropylamine (2.0 mL, 13.76 mmol) and Et_3N (3.8 mL, 27.24 mmol, 2 eq.) in dichloromethane (75 mL). This solution was cooled down to 0 °C before the dropwise addition of diphenylphosphinic chloride (2.6 mL, 13.62 mmol, 1 eq.). The resulting mixture was stirred at room temperature overnight, poured into an equal volume of saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give 4.54 g (99%) of a white solid. **m.p.** 118-120 °C; Lit.[41] 118-119 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.92 (m, 1H, *Ar*), 7.90 (m, 1H, *Ar*), 7.89 (m, 1H, *Ar*), 7.87 (m, 1H, *Ar*), 7.82-7.78 (m, 1H, *Ar*), 7.78-7.74 (m, 1H, *Ar*), 7.54-7.48 (m, 1H, *Ar*), 7.48-7.41 (m, 3H, *Ar*), 7.38-7.31 (m,

3H, *Ar*), 7.31-7.29 (m, 1H, *Ar*), 7.29-7.22 (m, 1H, *Ar*), 7.22-7.18 (m, 1H, *Ar*), 7.18-7.15 (m, 1H, *Ar*), 4.19-4.06 (m, 1H, CH_α), 3.28 (dd, *J* = 6.4 Hz, *J* = 9.6 Hz, NH), 2.10-1.97 (m, 1H, CH_β), 1.94-1.80 (m, 1H, CH_β), 0.80 (t, *J* = 7.5 Hz, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 139.8 (d, *J* = 8 Hz), 132.5 (d, *J* = 129 Hz), 132.3 (d, *J* = 9 Hz), 132.0 (d, *J* = 2 Hz), 128.7 (d, *J* = 3 Hz), 128.6, 127.9, 127.5, 44.8; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 22.5; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3383, 2976, 1454, 1409, 1186, 1124, 1109; **HRMS** [found (ESI) MH^+ 336.1503 $C_{21}H_{22}NOP$ requires *M* 336.1512]; **$[\alpha]_D^{20}$** = -45.94, (*c* = 2.54, MeOH); Lit.[41] -53.1 (*c* = 2.54, MeOH); **Rf** 0.45 (100% EtOAc).

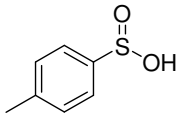
***N,N*-Dimethyl-1-phenylethanamine (47)**[123]



In a 50 mL non-flame dried round-bottomed flask fitted with a magnetic stirrer was introduced (±)-α-methylbenzylamine (1.9 mL, 15.1 mmol). Then, a dropwise addition of aqueous formaldehyde solution (37% - 5.2 mL) was followed by a dropwise addition of aqueous formic acid solution (90% - 6 mL). The resulting mixture was heated for 24 h, cooled down to room temperature, basified with NaOH pellets and extracted with Et_2O (3x20 mL). The combined Et_2O layers were dried ($MgSO_4$), filtered and then concentrated under reduced pressure to give a light yellow oil. This oil was distilled *in vacuo* to give 1.96 g of a colourless oil (87%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.21-7.37 (m, 5H, *Ar*), 3.26 (q, *J* = 7.8 Hz, 1H, CH_α), 2.21 (s, 6H, N-CH_3), 1.39 (d, *J* = 7.8 Hz, 3H, $CH_{3\alpha}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 144.2, 128.5, 128.4, 127.7, 67.2, 43.4, 20.5; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 2981, 2865, 2823, 2780, 1680, 1452; **HRMS**

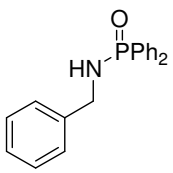
[found (ESI) MH^+ 150.1269 $C_{10}H_{15}N$ requires 1503.1277; $\mathbf{R}_f$ 0.22 (EtOAc/CH_2Cl_2 7:3).

_p_-Toluenesulfinic acid (225)[39]



A 200 mL Erlenmeyer flask containing a 10% vol/vol HCl solution was heated to 65 °C. Meanwhile a 100 mL Erlenmeyer flask containing the sodium p-toluenesulfinate salt (7.98 g, 44.9 mmol) was kept under stirring and heated at the same temperature. Then, addition of hot HCl into the salt was carried out slowly until the resulting pH became lower than 3 and the salt was completely dissolved. Finally the solution was allowed to recrystallise at 4 °C and the precipitate was filtered and dried under vacuum to afford 4.31 g of white crystals (61%); **m.p.** 84-85 °C; Lit.[211] 85 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.58 (d, 2H, *J* = 8.4 Hz, *Ar*), 7.31 (d, 2H, *J* = 8.4 Hz, *Ar*), 7.49 (s, 1H, OH), 2.41 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 143.6, 143.0, 130.0, 125.4, 21.8; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3671, 3242, 3043, 2989, 2926, 1596, 1327, 1144; **HRMS** [found (ESI) MNa^+ 179.0127. $C_7H_8O_2S$ requires *M* 179.0137]; $\mathbf{R}_f$ 0.18 (EtOAC/MeOH 80:20).

_N_-Benzyl-_P_,_P_-diphenylphosphinic amide (94)



White yellowish solid. **m.p.** 111-113 °C; Lit.[212] 110-112 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.00-7.87 (m, 4H, *Ar*), 7.52-7.34 (m, 8H, *Ar*), 7.34-7.26 (m, 2H, *Ar*), 7.26-7.20 (m, 1H, *Ar*), 4.10 (t, J = 7.6 Hz, 2H, CH_2), 3.54 (m, 1H, NH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 139.9 (d, J = 8 Hz), 132.5 (d, J = 129 Hz), 132.3 (d, J = 9 Hz), 132.0 (d, J = 2 Hz), 128.7 (d, J = 3 Hz), 128.6, 127.9, 127.5, 44.8; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 23.7; **IR** υ_{max} ($CHCl_3$)/ cm^{-1} 3372, 2986, 1439, 1183, 1125; **HRMS** [found (ESI) MH^+ 308.1209. $C_{19}H1_8NOP$ requires M 308.1199]; $\mathbf{R}_f$ 0.35 (EtOAc/CH_2Cl_2 1:1).

References

[1] a) G. M. Ramos Tombo, D. Bellus, *Angew. Chem.*, **1991**, *103*, 1219-1241. b) H. P. Fischer, H. P. Buser, P. Chemla, P. Huxley, W. Lutz, S. Mirza, G. M. Ramos Tombo, G. Van Lommen, V. Sipido, *Bull. Soc. Chim. Belg.*, **1994**, *103*, 565-581.

[2] R. Noyori, *Chemtech*, **1992**, *22*, 366.

[3] A well known and sad example is the thalidomide tragedy. A drug mainly prescribed to pregnant women and that turned out to be both a sedative-hypnotic medication and a potent teratogen. This drug was marketed as a racemate and only one of the 2 enantiomers had the desired activity.

[4] a) R. G. Wilkinson, R. G. Shepherd, J. P. Thomas, C. Baughn, *J. Am. Chem. Soc.*, **1961**, *83*, 2212-2213. b) R. G. Wilkinson, R. G. Shepherd, J. P. Thomas, C. Baughn, *Am. Rev. Respir. Dis.*, **1961**, *83*, 891-893.

[5] J. Crosby, *Tetrahedron*, **1991**, *47*, 4789-4846.

[6] I. Ojima (Ed.) Catalytic asymmetric synthesis, 2nd edn., Wiley, New York, **2000**.

[7] H. Nozaki, S. Moriuti, H. Takaya, R. Noyori, *Tetrahedron Lett.*, **1966**, *7*, 5239-5244.

[8] S. Knowles, M. J. Sabacky, *Chem. Comm.*, **1968**, 1445-1446.

[9] T. P. Dang, H.B. Kagan, *Chemm. Commun.*, **1971**, 481.

[10] T. Katsuki, K.B. Sharpless, *J. Am. Chem. Soc.*, **1980**, *102*, 5974-5976.

[11] Nobel lectures can be read on http://nobelprize.org/nobel_prizes/chemistry/laureates/2001.

[12] H. Brunner, R. Becker, S. Gauder, *Organomet.*, **1986**, *5*, 739-746.

[13] a) H. U. Bläser, H. P. Buser, H. P. Jalett, B. Pugin, F. Spindler, *Synlett,* **1999**, 867-868. b) R. Kadyrov, T. H. Riermeier, *Angew. Chem. Int. Ed.,* **2003**, *42*, 5472-5474. c) Y. X. Chi, Y. G. Zhou, X. M. Zhang, *J. Org. Chem.,* **2003**, *68*, 4120-4122. d) R. Kadyrov, T. H. Riermeier, U. Dingerdissen, V. Tararov, A. Börner, *J. Org. Chem.,* **2003**, *68*, 4067-4070.

[14] R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2006**, *128*, 84-86.

[15] C. Fischer, E. M. Carreira, *Org. Lett.*, **2001**, *3*, 4319-4321.

[16] K. Tomioka, I. Inoue, M. Shindo, K. Koga, *Tet. Lett.*, **1990**, *31*, 6681-6684.

[17] S. E. Denmark, N. Nakajima, O. J. C. Nicaise, *J. Am. Chem. Soc.*, **1994**, *116*, 8797-8798.

[18] a) Y. Yamamoto, T. Komatsu, K. Murayama, *J. Am. Chem. Soc.*, **1984**, *106*, 5031-5033. b) Y. Yamamoto, T. Komatsu, K. Murayama, W. Ito, *J. Am. Chem. Soc.*, **1986**, *108*, 7778-7786.

[19] C. Boga, D. Savoia, A. Umani-Ronchi, *Tet. Asymm.*, **1990**, *1*, 291-294.

[20] H. Tanaka, K. Inoue, U. Pokorski, M. Taniguchi, S. Torii, *Tet. Lett.*, **1990**, *31*, 3023-3026.

[21] A. Bocoum, D. Savoia, A. Umani-Ronchi, *Chem. Comm.*, **1993**, 1542-1544.

[22] D. Enders, H. Schubert and C. Niibling, *Angew. Chem., Int. Ed. Engl.,* **1986**, *25*, 1109-1110.

[23] a) S. Denmark, T. Weber, D.W. Piotrowski, *J. Am. Chem. Soc.*, **1987**, *109*, 2224-2225. b) D. Enders, J. Schankat, K. Klatt, *Synlett,* **1994**, 795-797.

[24] Z. Y. Chang, R. M. Coates, *J. Org. Chem.*, **1990**, *55*, 3475-3483.

[25] Y. S. Yang, Z. L. Shen, T. P. Loh, *Org. Lett.*, **2009**, *11*, 1209-1212.

[26] H. Staudinger, J. Meyer, *Helv. Chim. Acta.*, **2004**, *2*, 635-646.

[27] O. Mitsunobu, Y. Yamada, *Bull. Chem. Soc. Jap.*, **1967**, *40*, 2380-2382.

[28] Mukaiyama T., Yamada T., Nagata T., Sugi K.D., *Chem. Lett.*, **1997**, *26*, 493-494.

[29] S. L. Buchwald, X. Verdaguer, U. E. W. Lange, M. T. Reding, *J. Am. Chem. Soc.*, **1996**, *118*, 6784- 6785.

[30] U. Noyori, A. Fujii, Hashigushi S., T. Ikariya, *J. Am. Chem. Soc.*, **1996**, *118*, 4916-4917.

[31] X. B. Jiang, A. J. Minnaard, B. Hessen, B. L. Feringa, A. L. L. Duchateau, J. G. O. Andrien, J. A. F. Boogers, J. G. Vries, *Org. Lett.*, **2003**, *5*, 1503-1506.

[32] T. Morimoto, K. Achiwa, *Tet. Asymm.*, **1995**, *6*, 2661-2664.

[33] H. U. Bläser, F. Spindler, *The chiral switch of metolachlor*, In: E.N. Jacobsen *et al., Comprehensive Asymmetric Catalysis*, Springer: Berlin, **1999**, pp 1427–1437.

[34] H. U. Bläser, H. P. Buser , R. Hausel, H. P. Jalett, F. Spindler, *J. Organomet. Chem.*, **2001**, *621*, 34–38.

[35] T. Fujisawa, T. Ichiyanagi, S. Kuniyama, M. Shimizu, *Chem. Lett.*, **1998**, 1033-1034.

[36] a) A. Alexakis, S. Mutti, J. F. Normant, *J. Am. Chem. Soc.,* **1991**, *113*, 6332-6334. b) A. Alexakis, J. Burton, J. Vastra, P. Mangeney, *Tet. Asymm.,* **1997**, *8*, 3987-3990.

[37] a) A. H. M. de Vries, A. Meetsma, B. L. Feringa, *Angew. Chem., Int. Ed. Engl.,* **1996**, *35*, 2374-2376. b) B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. de Vries, *Angew. Chem. Int. Ed.,* **1997**, *36*, 2620-2623.

[38] H. Fujihara, K. Nagai, K. Tomioka, *J. Am. Chem. Soc.,* **2000**, *122*, 12055-12056.

[39] A. B. Charette, A. A. Boezio, A. Côté, *Proc. Nat. Acad. Sci.*, **2004**, *101*, 5405-5410.

[40] A. B. Charette, A. A. Boezio, A. Côté, *J. Am. Chem. Soc.,* **2003**, *125*, 1692-1693.

[41] A. B. Charette, A. A. Boezio, A. Côté, J. Pytkowicz, *J. Am. Chem. Soc.,* **2003**, *125*, 14260-14261.

[42] a) N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani, T. Hayashi, *J. Am. Chem. Soc,*. **2004**, *126*, 13584-13585. b) Y. Otomaru, N. Tokunaga, R. Shintani, T. Hayashi, *Org. Lett.,* **2005**, *7*, 307-310.

[43] Other reports on the catalytic enantioselective arylation of arylimines: a) T. Hayashi, M. Ishigedani, *J. Am. Chem. Soc*., **2000**, *122*, 976-977. b) N. Hermanns, S. Dahmen, C. Bolm, S. Brase, *Angew. Chem. Int. Ed.,* **2002**, *41*, 3692-3694. c) M. Kuriyama, T. Soeta, X. Hao, Q. Chen, K. Tomioka, *J. Am. Chem. Soc*., **2004**, *126*, 8128-8129. d) T. Hayashi, M. Kawai, N. Tokunaga, *Angew. Chem. Int. Ed*., **2004**, *43*, 6125-6128. e) D. J. Weix, Y. Shi, J. A. Ellman, *J. Am. Chem. Soc.* **2005**, *127*, 1092-1093.

[44] a) T. Hayashi, K. Ueyama, N. Tokunaga, K. Yoshida, *J. Am. Chem. Soc*., **2003**, *125*, 11508-11509. b) R. Shintani, K. Ueyama, I. Yamada, T. Hayashi, *Org. Lett*., **2004**, *6*, 3425-3427. c) Y. Otomaru, A. Kina, R. Shintani, T. Hayashi, *Tet. Asymm.,* **2005**, *16*, 1673-1679. d) Y. Otomaru, K. Okamoto, R. Shintani, T. Hayashi, *J. Org. Chem.,* **2005**, *70*, 2503-2508. e) R. Shintani, T. Kimura, T. Hayashi, *Chem. Comm.*, **2005**, 3213-3214. f) R. Shintani, K.Okamoto, T. Hayashi, *Org. Lett*., **2005**, *7*, 4757-4759. g) C. Defieber, J. -F. Paquin, S. Serna, E. M. Carreira, *Org. Lett.,* **2004**, *6*, 3873-3876. h) J. -F. Paquin, C. Defieber, C. R. J. Stephenson, E. M. Carreira, *J. Am. Chem. Soc.,*

2005, *127*, 10850-10851. i) J. -F. Paquin, C. R. J. Stephenson, C. Defieber, E. M. Carreira, *Org. Lett.,* **2005**, *7*, 3821-3824.

[45] T. Hayashi, Y. Yasuhara, T. Nishimura, *Org. Lett.*, **2006**, *8*, 979-981.

[46] G. F Schmidt, E. L. Muetterties, M. A. Beno, J. M. Williams, *Proc. Nat. Acad. Sci.,* **1981**, *78*, 1318-1320.

[47] M. A. Kulzick, R. T. Price, R. A. Andersen, E. L. Muetterties, *J. Organomet. Chem.,* **1987**, *333*, 105-118.

[48] C. Krug, J. F. Hartwig, *J. Am. Chem. Soc*., **2004**, *126*, 2694-2695.

[49] N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.*, **2004**, 126, 13584-13585.

[50] R. Reingruber, S. Bräse, *Chem. Comm.*, **2008**, 105-107.

[51] a) P. I. Dosa, G. C. Fu, *J. Am. Chem. Soc.,* **1998**, *120*, 445-446. b) C. Garcia, L. K. La Rochelle, P. J. Walsh, *J. Am. Chem. Soc.*, **2002**, *124*, 10970-10971.

[52] a) M. Ueda, A. Saito, N. Miyaura, *Synlett*, **2000**, 1637-1639. b) M. Kuriyama, T. Soeta, X. Hao, Q. Chen, K. Tomioka, *J. Am. Chem. Soc.*, **2004**, *126*, 8128-8129.

[53] a) T. Hayashi, K. Yamasaki, *Chem. Rev.*, **2003**, *103*, 2829-2844. b) K. Fagnou, M. Lautens, *Chem. Rev.*, **2003**, *103*, 169-196.

[54] D. J. Weix, Y. Shi, J. A. Ellman, *J. Am. Chem. Soc.,* **2005**, *127*, 1092-1093.

[55] a) R. Ramage, D. Hopton, M. Parrott, G. W. Kenner, G. A. Moore, *J. Chem. Soc. Perkin Trans. 1*, **1984**, 1357–1370. b) H. M. I. Osborn, J. B. Sweeney, *Synlett*, **1994**, 145-147. c) P. J. Andersson, D. Guijarro, D. Tanner, *J. Org. Chem.*, **1997**, *62*, 7364-7375.

[56] M. Trincado, J. A. Ellman, *Ang. Chemie. Int. Ed.,* **2008**, *47*, 5623-5626.

[57] a) R. T. Wu, M. J. Chong, *J. Am. Chem. Soc.*, **2006**, *128*, 9646-9647. b) M. Sugiura, H. Keiichi, S. Kobayashi, N. -W. Tseng, M. Lautens, *Org. Synth.*, **2006**, *83*, 170-176.

[58] a) H. Nakamura, H. Iwama, Y. Yamamoto, *Chem. Comm.*, **1996**, 1459-1460. b) N. Solin, J. Kjellgren, K. J. Szabo, *J. Am. Chem. Soc.*, **2004**, *126*, 7026-7033.

[59] a) R. Berger, K. Duff, J. L. Leighton, *J. Am. Chem. Soc.*, **2004**, *126*, 5686-5687. b) D. Lipomi, J. S. Panck, *Org. Lett.*, **2005**, *7*, 4701-4704.

[60] W. W. Ong, A. B. Beeler, S. Kesavan, J. S. Panek, J. A. Porco Jr, *Angew. Chem. Int. Ed.*, **2007**, *46*, 7470-7472.

[61] H. J. Roth, A. Kleeman, T. Beisswneger, *Pharmaceutical Chemistry*, C. Ellis Horwood, John Wiley & Sons: New York, **1988**, *1*.

[62] P. J. Reider, P. Davis, L. D. Hughes, E. J. S. Grabowski, *J. Org. Chem.*, **1987**, *52*, 955-957.

[63] T. Sawayama, M. Tsukamoto, T. Sasagawa, S. Naruto, J. Matsumoto, H. Uno, *Chem. Pharm. Bull.*, **1989**, *37*, 1382.

[64] W. Marckwald, A. McKenzie, *Ber.*, **1899**, *32*, 2130.

[65] J. Jacques, A. Collet, S. H. Willen, *Enantiomers, Racemates and Resolutions*, Wiley-Interscience, New York, **1981**.

[66] a) K. Ziegler, E. Holzkamp, H. Breil, H. Martin, *Angew. Chem.,* **1955**, *67*, 541. b) K. Ziegler, *Adv. Org. Chem.*, **1968**, *6*, 1-17.

[67] a) G. Natta, *Angew. Chem.,* **1957**, *69*, 686. b) G. Natta, *Angew. Chem.*, **1964**, *76*, 964.

[68] K. Biswas, O. Prieto, P. J. Goldsmith, S. Woodward, *Angew. Chem. Int. Ed.,* **2005**, *44*, 2272–2274.

[69] a) E. Negishi, D. E. Van Horn, *J. Am. Chem. Soc.*, **1978**, *100*, 2252-2254. b) E. Negishi, H. Matsushita, *Org. Synth.*, **1990**, *7*, 245-249.

[70] S. Danishefsky, D. F. Harvey, *J. Am. Chem. Soc.*, **1985**, *107*, 6647-6652.

[71] a) G. B. Buckton, W. Odling, *Justus Liebigs Ann. Chem. (Suppl.)*, **1865**, *4*, 1865-1866. b) G. B. Buckton, W. Odling, *Proc. R. Soc.*, **1865**, *14*, 19-21.

[72] K. Ziegler, K. Nagel, *U.S. Pat. 2*, **1956**, *744*, 127

[73] a) S. P. Diefenbach, *U.S. Pat. 4*, **1982**, *364*, 872. b) S. P. Diefenbach, *U.S. Pat. 4*, **1982**, *364*, 873. c) S. P. Diefenbach, *U.S. Pat. 4*, **1982**, *364*, 874.

[74] A. Grosse, J. Mavity, *J. Org. Chem.*, **1940**, *5*, 106-121.

[75] S. H. Eidt, S. C. Watson, G. C. Heilig, *U. S. Pat. 4*, **1978**, *118*, 409.

[76] P. H. Yang, K. F. Liou, Y. T. Lin, *J. Organomet. Chem.*, **1986**, *307*, 238-273.

[77] A. F. Holleman, E. Wiberg, *Inorganic Chemistry*, Academic Press: San Diego, **2001**.

[78] C. Elschenbroich, *Organometallics* (3rd edition), Wiley-VCH: Weinheim, Germany, **2005**, 114.

[79] a) W. Baidossi, A. Rosenfeld, B. C. Wassermann, S. Schutte, H. Schumann, J. Blum, *Synthesis*, **1996**, 1127-1130. b) H. Schumann, B.C. Wasserman, S. Schutte, B. Heymer, S. Nickel, T. D. Seub, S. Wernik, J. Demtshuk, F. Girgsdies, R. Wiemann, *Z. Anorg. Allg. Chem.*, **2000**, *626*, 2081-2095.

[80] a) H. Schumann, B.C. Wasserman, S. Schutte, B. Heymer, S. Nickel, T. D. Seub, S. Wernik, J. Demtshuk, F. Girgsdies, R. Wiemann, *Z. Anorg. Allg. Chem.*, **2000**, *626*, 2081-2095. b) W. Baidossi, A. Rosenfeld, B. C. Wassermann, S. Schutte, H. Schumann, J. Blum, *Synthesis,* **1996**, 1127-1130.

[81] D. Gelman, H. Schumann, J. Blum, *Tet. Lett*., **2000**, *41*, 7555-7558.

[82] J. Blum, O. Berlin, D. Milstein, Y. Ben-David, B. C. Wassermann, S. Schutte, H. Schumann, *Synthesis,* **2000**, *4*, 571-575.

[83] E. Frankland, *Ann. Chem. Pharm.,* **1849**, *71,* 213–216.

[84] V. Grignard, *Compt. Rend. Acad. Sci. Paris*, **1900**, 130, 1322.

[85] a) S. Reformatsky, *Chem. Ber.,* **1887**, 20, 1210-1211. b) S. Reformatsky, *Chem. Ber.,* **1895**, *28*, 2842. c) A. Fürstner, *Synthesis*, **1989**, 571-590. d) A. Fürstner, *Angew. Chem. Int. Ed.*, **1993**, *32*, 164-189.

[86] a) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.,* **1958**, *80*, 5323-5324. b) H. E. Simmons, T. L. Cairns, A. Vladuchick, C. M. Hoiness, *Org. React.,* **1972**, *20*, 1. c) J. Furukawa, N. Kawabata, J. Nishimma, *Tet. Lett.*, **1966**, *7*, 3353-33544. d) M. Nakamura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.,* **2003**, *125*, 2341-2350. e) E. Nakamura, K. Sekiya, I. Kuwajima, *Tet. Lett.*, **1987**, *28*, 337-340.

[87] E. Erdik, *Organozinc reagents in organic synthesis*, CRC Press: London, **1996**.

[88] R. Bucourt, R. Joly, *Compt. Rend.*, **1962**, *254*, 1655-1656.

[89] C. Petrier, J. L. Luche, C. Dupuy, *Tet. Lett.*, **1984**, *25*, 3463-3466.

[90] a) C. Petrier, J. De Souza Barbosa, C. Dupuy, J. L. Luche, *J. Org. Chem.*, **1985**, *50*, 5761-5765. b) M. Nanjo, T. Oda, K. Moshida, *J. Organomet. Chem.*, **2003**, *672*, 100-108.

[91] G. M. Bancroft, D. K. Creber, M. A. Ratner, J. W. Moskowitz, S. Topiol, *Chem. Phys. Lett.*, **1977**, *50*, 233-238.

[92] a) K. S. Rao, B. P. Stoicheff and R. Turner, *Can. J. Phys.*, **1960**, *38*, 1516-1525.

[93] a) D. R. J. Boyd, H. W. Thompson, R. L. Williams, *Discuss. Faraday Soc.*, **1950**, *9*, 154-160. b) I. S. Butler, M. L. Newbury, *Spectrochim. Acta A*, **1977**, *33*, 699-703.

[94] A. Almenningen, T. U. Helgaker, A. Haaland, S. Samdal, *Acta Chem. Scand. A*, **1982**, *36*, 159-166.

[95] E. Frankland, *Ann. Chem. Pharm.,* **1849**, *71*, 171.

[96] M. J. Rozema, A. Sidduri, P. Knochel, *J. Org. Chem.,* **1992**, *57*, 1956-1958.

[97] L. Micouin, P. Knochel, *Synlett*, **1997**, 327-328.

[98] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.,* **2004**, *43*, 1017-1021.

[99] L. I . Zakharin, O. Y. Okhlobystin, *Z. Obshch. Chim. (Russian Journal of General Chemistry)*, **1960**, *30*, 1234. b) L. I . Zakharin, O. Y. Okhlobystin, *Engl. Trans.*, 2109, *Chem. Abstr.*, **1961**, *55*, 9319.

[100] a) K. H. Thiele, P. Zdunneck, *J. Organomet. Chem.*, **1965**, *4*, 10-17. b) K. H. Thiele, G. Engelhardt, J. Köhler, M. Arnstedt, *J. Organomet. Chem.,* **1967**, *9*, 385-393.

[101] a) F. Langer, J. Waas, P. Knochel, *Tet. Lett.,* **1993**, *34*, 5621-5622. b) F. Langer, L. Schwink, A. Devasagayaraj, P. Y. Chavant, P. Knochel, *J. Org. Chem.,* **1996**, *61*, 8229-8243.

[102] a) M. Shrebnik, *Tet. Lett.*, **1991**, *32*, 2449-2452. b) W. Oppolzer, R. N. Radinov, *Helv. Chim. Acta.,* **1992**, *75*, 170-173. c) W. Oppolzer, R. N. Radinov, *J. Am. Chem. Soc.,* **1993**, *115*, 1593-1594.

[103] a) S. Vettel, A. Vaupel, P. Knochel, *Tet. Lett.*, **1995**, *36*, 1023-1026. b) S. Vettel, A. Vaupel, P. Knochel, *J. Org. Chem.*, **1996**, *61*, 7473-7481.

[104] a) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.*, **1988**, *53*, 2390-2392. b) M. Gaudemar, *Bull. Soc. Chim. Fr.,* **1962**, 974-987. c) E. Erdik, *Tetrahedron*, **1987**, *43*, 2203-2209. d) J. K. Gawronsky, *Tet. Lett.,* **1984**, *25*, 2605-2608. e) G. Picotin, G. Miginiac, *Tet. Lett.*, **1987**, *28*, 4551-4552.

[105] K. Y. Lee, C. J. Lee, J. N. Kim, *Tet. Lett.*, **2003**, *44*, 1231-1234.

[106] J. H. Wynne, S. E. Price, J. R. Rorer, W. M. Stalick*, Synth. Comm.*, **2003**, *33*, 341-352.

[107] a) B. Krzyzanowska, W. J. Stec, *Synthesis*, **1982**, 270-273. b) W. B. Jennings, C. J. Lovely, *Tet. Lett.*, **1988**, *29*, 3725-3728. c) K. A. Scheidt, D. L. Gray, R. C. Miller, D. M. Ballweg, *Org. Lett.,* **2005***, 7,* 1403-1406.

[108] a) P. Gizecki, R. Ait Youcef, C. Poulard, R. Dhal, G. Dujardin, *Tet. Lett.*, **2004**, *45*, 9589-9592. b) A. E. Greene, J. N. Denis, A. M. Kanazawa, *J. Org. Chem.*, **1994**, *59*, 1238-1240. c) J. B. F. N. Engberts, J. Strating, *Recueil des Travaux Chimiques des Pays-Bas*, **1965**, *84*, 942-950.

[109] J. N. Desrosiers, A. Côté A. Boezio, A. B. Charrette, *Org. Synth.*, **2006**, *83*, 5-13.

[110] a) J. Lin, J. R. Cashman, *J. Pharm. Exp. Ther.*, **1997**, *282*, 1269-1279. b) D. R. Boyd, J. F. Malone, M. R. McGuckin, W. B. Jennings, M. Rutherford, B. M. Saket**,** *J. Chem. Soc. Perkin Trans. II*, **1988**, 1145-1148.

[111] S. L. Buchwald., J. P. Wolfe, H. Tomori, J. P. Sadighi , J. Yin, *J. Org. Chem.*, **2000**, *65*, 1158-1174.

[112] J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.*, **1969**, *34*, 2543–2549.

[113] K. A. Kime, R. E. Sievers, *Aldrichimica Acta*, **1977**, *10*, 54-62.

[114] D. Parker, *Chem. Rev.*, **1991**, *91*, 1441-1457.

[115] L. Hintermann, *J. Org. Chem.*, **2007**, *72*, 9790-9793.

[116] M. Hague, C. N. Caughlan, *Chem. Comm.,* **1966**, 921-922.

[117] A. A. Cantrill, H. M. I. Osborn, J. Sweeney, *Tetrahedron*, **1998**, *54*, 2181-2208.

[118] Procedure: 20% aqu. HCl at reflux for 2 h. M. Shi, Z. Y. Lei, Q. Xu, *Adv. Synth. Cat.*, **2006**, *348*, 2237-2242.

[119] J. -N. Desrosiers, A. Côté, A. A. Boezio, A. B. Charette, *Org. Synth.*, **2006**, *83*, 5-17.

[120] H. Kataoka , *J. Chromatogr. A*, ,**1996**, *733*, 19-34.

[121] S. Djuric, J. Venit, P. Magnus, *Tet. Lett.*, **1981**, *22*, 1787-1790.

[122] I. Ojirna, I. I-Iabus, *Tet. Lett.,* **1990**, *31*, 4289-4292.

[123] P. Wipf, S. Ribe, *J. Org. Chem.*, **1998**, *63*, 6454-6455.

[124] a) W. Eschweiler, *Ber.*, **1905**, *38*, 880-882. b) H. T. Clarke, H. B. Gillespie, S. Z. Weisshaus, *J. Am. Chem. Soc.*, **1933**, *55*, 4571-4587.

[125] C. G. Shin, Y. Yonezawa, K. Watanabe, J. Yoshimura, *Bull. Chem. Soc. Jpn.,* **1981**, *54*, 3811-3814.

[126] M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.*, **1993,** *115*, 10125-10138.

[127] B. L. Feringa, L. A. Arnold, R. Imbos, A. Mandoli, A. H. M. Vries, R. Naasz, *Tetrahedron*, **2000**, *56*, 2865-2878.

[128] For some recent reviews see: a) J. M. Brown, In *Comprehensive Asymmetric Catalysis*, Springer: Berlin, **2004**. b) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, In *Comprehensive Asymmetric Catalysis*, Springer: Berlin, **1999**, 121–182. c) U. Nagel, J. Albrecht, In *Topics in Catalysis*, Springer: US, **1998**, *5*, 3–23. d) M. J. Burk, F. Bienewald, In *Transition Metals for Organic Synthesis*, Wiley–VCH: Weinheim, **1998**. e) M. Beller, C. Bolm, In *Transition Metals for Organic Synthesis*, Wiley–VCH: Weinheim, **1998**, *2*, 13–25.

[129] D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem. Int. Ed.*, **1995**, *34*, 1059-1070.

[130] M. Johannsen , K. A. Jörgensen, *Chem. Rev.*, **1998,** *98,* 1689-1708.

[131] T. Taguchi, Hanzawa Y., Kakuuchi A., *Tet.Lett.*, **2003**, *44*, 923-926.

[132] P. Wipf, R. L. Nunes, S. Ribe, *Helv. Chim. Acta*, **2002**, *85*, 3478-4388.

[133] T. Taguchi, Hanzawa Y., Kakuuchi A., *Tet.Lett.*, **2003**, *44*, 923-926.

[134] a) D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.*, **2000**, 33, 373-381. b) L. Pu, *Tetrahedron*, **2003**, *59*, 9873-9886. c) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.*, **2004**, 4095-4105.

[135] P. G. Cozzi, S. Alesi, L. Zani, C. Bolm, *J. Org. Chem.*, **2006**, *71*, 1558-1562.

[136] E. M. Carreira, C. Fischer, *Org. Lett.*, **2001**, *3*, 4319-4321.

[137] D. J. Weix, Y. Shi, J. A. Ellman, *J. Am. Chem. Soc,* **2005**, *127*, 1092-1093.

[138] D. W. Smith, *J. Organomet. Chem.* **1999,** *585,* 150-153.

[139] M. J. Burk, J. E. Feaster, R. L. Harlow, *Organometallics*, **1990**, *9*, 2653–2655.

[140] K. Toriumi, T. Ito, H. Takaya, T. Souchi, R. Noyori, *Acta Crystallogr.*, **1982**, *38*, 807-812.

[141] H. J. Drexler, S. Zhang, A. Sun, A. Spannenberg, A. Arrieta, A. Preetz, D. Heller, *Tet. Asymm.*, **2004**, *15*, 2139–2150.

[142] a) C. Laporte, C. Böhler, H. Schönberg, H. Grützmacher, *J. Organomet. Chem.*, **2002**, *641*, 227–234. b) H. Berger, R. Nesper, P. S. Pregosin, H. Rüeger, M. Wörle, *Helv. Chim. Acta*, **1993**, *76*, 1520–1538.

[143] a) P. W. N. M. vanLeeuwen, P. C. J. Camer, J. N. H. Reek, P. Dierkes, *Chem. Rev.*, **2000**, *100*, 2741–2769. b) P. Dierkes, P. W. N. M. vanLeeuwen, *J. Chem. Soc. Dalton Trans.*, **1999**, 1519–1529.

[144] J. You, H. -J. Drexler, S. Zhang, C. Fischer, D. Heller, *Angew. Chem. Int. Ed.*, **2003**, *42*, 913-916.

[145] A. Marinetti, F. Labrue, B. Pons, S. Jus, L. Ricard, J. -P. Genêt, *Eur. J. Inorg. Chem.*, **2003**, 2583-2590.

[146] F. Guillen, M. Rivard, M. Toffano, J. Y. Legros, J. C. Daran, J. C. Fillaud, *Tetrahedron*, **2002**, *58*, 5895-5904.

[147] M. Jackson, I. C. Lennon, *Tet. Lett.*, **2007**, *48*, 1831–1834.

[148] A. T. Axtell, J. Klosin, G. T. Whiteker, *Organometallics*, **2009**, *28*, 2993-2999.

[149] K. Toriumi, T. Ito, H. Takaya, T. Souchi, R. Noyori, *Acta Crystallogr.*, **1982**, *38*, 807-812.

[150] a) A. Borner, D. Heller, *Tet. Lett.*, **2001**, *42,* 223-225. b) C. J. Cobley, I. C. Lennon, R. McCague, J. A. Ramsden, A. Zanotti-Gerosa, *Tet. Lett.*, **2001**, *42,* 7481–7483.

[151] R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc*. **1971**, *93*, 2397–2407.

[152] D. Heller, S. Borns, W. Baumann, R. Selke, *Chem. Ber*., **1996**, *129*, 85–89.

[153] a) D. Carmona, J. Ferrer, E. Lalaguna, M. Lorenzo, F. J. Lahoz, S. Elipe, L. A. Oro, *Eur. J. Inorg. Chem.*, **2002**, 259-263. b) R. C. Mehrotra, A. Singh, *Organometallic Chemistry: A Unified Approach*, *Wiley, New York*, **1992**. c) J. A. M. Simões, J. L. Beauchamp, *Chem. Rev.,* **1990**, *90*, 629-688.

[154] P. E. M. Siegbahn, *J. Phys. Chem.,* **1995**, *99*, 12723-12729.

[155] R. Shintani, Y. Sannohe, T. Tsuji, T. Hayashi, *Angew. Chem. Int. Ed.,* **2007**, *46*, 7277-7280.

[156] A. B. Charette, A. A. Boezio, A. Côté, *Angew. Chem.*, **2004**, *43*, 6525-6528.

[157] D. M. Ballweg, R. C. Miller, D. L. Gray, K. A. Scheidt, *Org. Lett.*, **2005**, *7*, 1403-1406.

[158] A. A. Cantrill, H. M. I. Osborn, J. Sweeney, *Tetrahedron*, **1998**, *54*, 2181-2208.

[159] J. Lin, J. R. Cashman, *J. Pharm. Exp. Ther.*, **1997**, *282*, 1269-1279.

[160] A. Côté, J. -N. Desrosiers, A. A. Boezio, A. B. Charette, *Org. Synth.*, **2006**, *83*, 5-17.

[161] a) T. Jin., G. Feng, M. Yang, T. Li, *Synth. Comm.*, **2004**, *34*, 1277-1283. b) G. I. Georg, G. C. B. Harriman, S. A. Peterson, *J. Org. Chem.*, **1995**, *60*, 7366–7368.

[162] W. B. Jennings, C. J. Lovely, *Tetrahedron*, **1991**, *29*, 5561-5568.

[163] W. B. Jennings, C. J. Lovely, *Tet. Lett.*, **1988**, *29*, 3725-3728.

[164] a) P. Gizecki, R. Ait Youcef, C. Poulard, R. Dhal, G. Dujardin, *Tet. Lett.*, **2004**, *45*, 9589-9592. b) A. E. Greene, J. N. Denis, A. M. Kanazawa, *J. Org. Chem.*, **1994**, *59*, 1238-1240. c) J. B. F. N., Engberts, J. Strating, *Recl. Trav.Chim*, **1965**, *84*, 942-950.

[165] I. Sato, K. Hosoi, R. Kodaka, K. Soai, *Eur. J. Org. Chem.*, **2002**, *18*, 3115-3118.

[166] X. -M. Zhang, H. -L. Zhang, W. -Q. Lin, L. -Z. Gong, A. -Q. Mi, X. Cui, Y. -Z. Jiang, K. -B. Yu, *J. Org. Chem.*, **2003**, *68*, 4322-4329.

[167] J. B. Sweeney, A. A. Cantrill, M. G. B. Drew, A. B. McLaren, S. Thobhani, *Tetrahedron*, **2006**, *62*, 3694-3703.

[168] Melting point not reported in the literature.

[169] P. S. Iyer, J. M. Janjic, B. W. Day, *J. Comb. Chem.*, **2005**, *7*, 322-330.

[170] J. Chen, D. Li, H. Maa, L. Cun, J. Zhu, J. Deng, J. Liao, *Tet. Lett.*, **2008**, *49*, 6921-6923.

[171] M. Shi, G. -L. Zhao, *Tet. Lett.*, **2002**, *43*, 4499-4502.

[172] D. R. Boyd, J. F. Malone, M. R. Mc Guckin, W. B. Jennings, M. Rutherford, B. M. Saket, *J. Chem. Soc. Perkin Trans. 2*, **1988**, 1145-1150.

[173] P. Pinho, P. G. Andersson**,** *Tetrahedron*, **2001**, *57*, 1615-1618.

[174] Y. -Q. Wang, S. -M. Lu, Y. -G. Zhou, *J. Org. Chem.*, **2007**, *72*, 3729-3734.

[175] L. Maier, P. J. Diel, *Phosphorus, Sulfur, Silicon and the related elements*, **1996**, *115*, 273-300.

[176] B. -M. Park, S. Mun. J. Yun, *Adv. Synth. Cat.,* **2006**, *348*, 1029-1032.

[177] K. A. Nolin, R. W. Ahn, F. D. Toste, *J. Am. Chem. Soc.*, **2005**, *127*, 12462-12463.

[178] C. R. Graves, K. A. Scheidt, S. T. Nguyen, *Org. Lett.*, **2006**, *8*, 1229-1232.

[179] B. Kryzanowska, W. J. Stec, *Synthesis*, **1982**, *4*, 270-273.

[180] K. D. Berlin, D. H. Burpo, *Proc. Okla. Acad. Sci.*, **1968**, *48*, 121-127.

[181] D. H. R. Barton, M. R. Britten-Kelly, D. Ferreira, *J. Chem. Soc. Perkin Trans. 1*, **1978**, 1090-1100.

[182] R. D. Guthrie, D. A. Jaeger, W. Meiter, D. J. Cram, *J. Am. Chem. Soc.*, **1971**, *93*, 5137-5153.

[183] B. C. Ranu, A. Majee, A. Sarkar, *J. Org. Chem.*, **1998**, *63*, 370-373.

[184] a) M. J. Saxby, *Org. Mass Spec.*, **1969**, *2*, 835-842. b) S. Weinstein, L. Leiserowitz, *Acta Cryst. Sec. B*, **1980**, *36*, 1406-1418. c) R. Corbi, *Anal. Chem.*, **1970**, *42*, 974-979.

[185] S. Pache, C. Botuha, R. Franz, E. P. Kuendig, *Helv. Chim. Acta*, **2000**, *83*, 2436–2451.

[186] M. Jakubcova, A. Meddour, J. -M. Péchiné, Ahmed Baklouti, J. Courtieu, *J. Fluo. Chem.*, **1997**, *86*, 149-153.

[187] S. P. Allwein, J. C. McWilliams, E. A. Secord, D. R. Mowrey, T. D. Nelson, M. H. Kress, *Tet. Lett.*, **2006**, *47*, 6409-6412.

[188] René T. Stemmler, C. Bolm, *Tet. Lett.*, **2007**, *48*, 6189-6191.

[189] R. Sanz, A. Martinez, V. Guilarte, J. M. Alvarez-Guitierrez, F. Rodriguez, *Eur. J. Org. Chem.*, **2007**, 4642-4645.

[190] J. C. Metcalfe, J. F. Stoddart, G. Jones, T. H. Crawshaw, E. Gavuzzo, D. J. Williams, *Chem. Comm.*, **1981**, 432-434.

[191] A. Roocker, P. Radtzitky, *Bull. Soc. Chim. Belg.*, **1963**, *72*, 202-207.

[192] Kindler, Peschke, Brandt, *Chem. Ber.*, **1935**, *68*, 2241-2243.

[193] P. L. Pickard, S. H. Jenkins Jr., *J. Am. Chem. Soc.*, **1953**, *75*, 5899-5901.

[194] A. W. Ingersoll, J. H. Brown, C. K. Kim, W. D. Beauchamp, G. Jennings, *J. Am. Chem. Soc.*, **1936**, *58*, 1808-1810.

[195] F. F. Blicke, C. E. Maxwell, *J. Am. Chem. Soc.*, **1939**, *61*, 1780-1782.

[196] A. Rimkus, N. Sewald, *Org. Lett.*, **2003**, *5*, 79-80.

[197] A. Alexakis, M. V. Augustin, *Chem. Eur. J.*, **2007**, *13*, 9647-9662.

[198] The reported $[\alpha]_D^{20}$ in this publication (the only one reported in the literature) is thought to be erroneous.

[199] B. J. Hathaway, D. G. Holah, J. D. Postlethwaite, *J. Chem. Soc.*, **1961**, 3215-3218.

[200] Decomposition of this catalyst occurs under prolonged drying under high vacuum. Therefore the sample analysed in elementary analysis was "wet".

[201] a) W. Richard, F. Renate, *European Patent EP1088812*, **2004**. b) J. E. Collins, M. P. Castellani, A. L. Rheingold, E. J. Miller, William E. Geiger, A. L. Rieger, P. H. Rieger, *Organomet.*, **1995**, *14*, 1232-1238. c) T. Sagae, J. Taniuchi, *US Patent 6,* **2004**, *753*, 43.

[202] F. P. Dwyer, A. M. Sargeson, *J. Am. Chem. Soc.*, **1953**, *75*, 984-985.

[203] a) C. Joyanta, P. Susmita, R. Sujit, *J. Am. Chem. Soc.*, **2005**, *127*, 6162-6163. b) R. Walter, S. Kirchner, R. Franz, *U.S. Patent* 6, 399, 804, **2002**.

[204] J. L. Herde, J. C. Lambert, C.V. Senoff, *Inorg. Synth.*, **1974**, *15*, 18-20.

[205] D. Markovic, J. F. Hartwig, *J. Am. Chem. Soc.,* **2007***, 129*, 11680–11681.

[206] Sigma Aldrich reference: *RegBook* **1** (2), 3075:F / *Structure Index* **1**, 487:B:8.

[207] M. S. Raasch, *J. Org. Chem.*, **1970**, *35*, 3470-3483.

[208] Wuyts, *Bull. Soc. Chim. Belg.*, **1930**, *39*, 58-63.

[209] J. Lin, J. R. Cashman, *J. Pharm. Exp. Ther.*, **1997**, *282*, 1269-1279.

[210] P. S. Bailey, T. P. Carter, L. M. Southwick, *J. Org. Chem.*, **1972**, *37*, 2997-3004.

[211] L. B. Krassnova, A. K. Yudin, *J. Org. Chem.*, **2004**, *69*, 2584-2587.

[212] T. A. Modro, M. A. Lawry, E. Murphy, *J. Org. Chem.*, **1978**, *43*, 5000-5006.