Palladium and Copper-Catalysed (C-C)-Bond Formation

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Basel, den 06. July 2004

Prof. Dr. Marcel Tanner
Dekan

To Aneta

Nothing great in the world has been accomplished without passion

Georg Wilhelm Friederich Hegel

Remerciements

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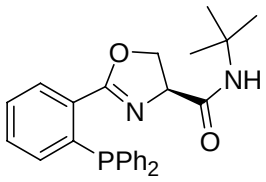
Copper-Catalysed Conjugate Additions

Conjugate 1,4-additions of carbon nucleophiles to α,β-unsaturated ketones are valuable C-C bond forming reactions that furthermore allow introduction of stereogenic centers.(1) Copper-catalysed reactions have been successfully employed in a variety of syntheses, for example for (-)-solavetivone(2) or prostaglandins.(3) Improvement of enantioselectivity through design of more effective ligands is thus highly desirable.

The ligands depicted below were synthesised and tested, with excellent enantioselectivities on selected substrates.



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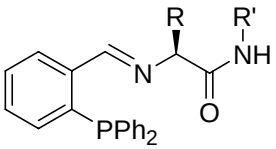

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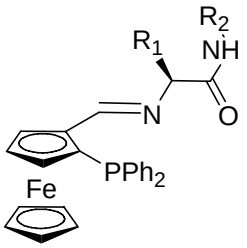
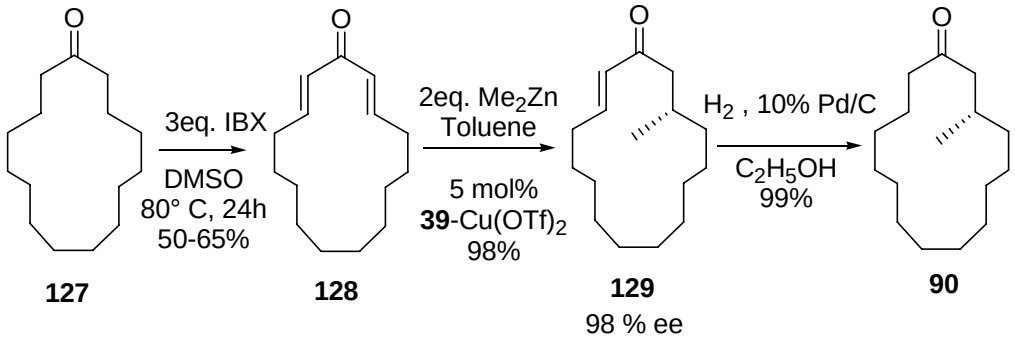


(S_{Fc})-**61**

Muscone Synthesis

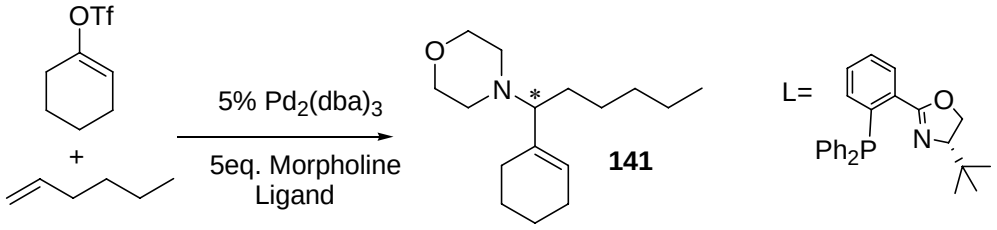
Musk odorants are a family of molecules possessing a very nice smell, of central importance for the fragrance industry. Application of the methodology developed for the copper-catalysed conjugate addition to the synthesis of (*S*)-muscone allowed the obtaining of product **90** in high yield and excellent enantiomeric purity.



Multicomponent Heck-Allylic substitution Reaction

Synthetic methodology which allows for a rapid increase in molecular complexity is extremely valuable in organic chemistry, particularly if it generates more than one new carbon-carbon bond at a time, accommodates considerable functionality and is broad in scope.

Design of a reaction sequence involving a Heck reaction followed by an allylic substitution allowed the obtaining of compound **141** depicted below.



1. Introduction

The concept of chirality is known in chemistry for more than a century. Louis Pasteur resolved in 1850 a mixture of tartric acid salts by picking out crystal types on the basis of their differing appearance. Pasteur observed that optically active isomers polarised the light and that this must be due to an asymmetric grouping of atoms. The 'asymmetry' concept was further developed by Van't Hoff and Le Bel and the term 'chirality' coined by lord Kelvin in 1904 in his Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light in which he stated: 'I call any geometrical figure chiral if its image in a plane mirror cannot be brought to coincide with itself'. The term Chiral is derived from the Greek name 'kheir' meaning 'hand'. Indeed, left and right hands are an example of chirality (Figure 1).

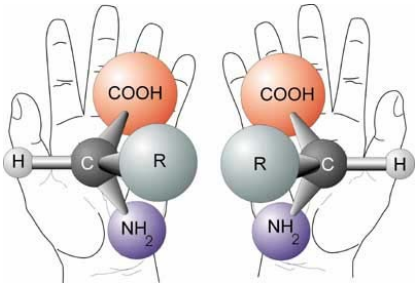
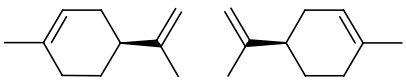


Figure 1. Chirality

Chirality plays an important role in biology. Many compounds in living systems are chiral. In consequence, the result of interactions between chiral molecules depends on the isomer forms of the involved molecules. A well known example, (+)-limonene smells of orange whereas (-)-limonene has a lemon fragrance (Figure 2).



(-)-limonene (+)-limonene

Figure 2. Limonene enantiomers

The possible different interactions of enantiomers with biological systems are especially important for the pharmaceutical industry. For example, (*S*)-ibuprofen reaches therapeutic concentrations in blood in 12 minutes versus 30 minutes for the racemic mixture. As well, (*S*)-Ketoprofen is an analgesic whereas (*R*)-ketoprofen is prescribed for prevention of periodontal disease. More dramatic, (*R*)-thalidomide is a sedative whereas (*S*)-thalidomide is teratogenic and led to feotal malformations when taken by pregnant women. Therefore, stereoselective syntheses affording enantiopure molecules are of fundamental importance. In the year 2000, pure enantiomeric drugs sold worldwide represented 123 Mrd. US$ and their part is constantly increasing, expected to reach 170 Mrd. US$ in 2005.

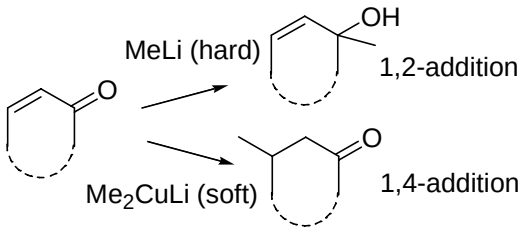
Possible methods to obtain enantiopure compounds are classical racemate resolution, even though only 50 % yield can be reached, or biocatalysis using enzymes, restricted to specific substrates and natural occurring reactions. An efficient alternative to these limited methods is the catalytic enantioselective synthesis, using chiral catalysts to achieve enantioselective transformations. A catalytic reaction is one in which a catalyst is used to accelerate the reaction. Using a chiral catalyst, it is possible to selectively accelerate the reaction giving one enantiomere. Research in this field was recently awarded with the Nobel price (W.S. Knowles, R. Noyori, K.B. Sharpless, 2001) and is the subject of this dissertation.

2. Copper-Catalysed Conjugate Additions

2.1 Introduction

Conjugate 1,4-additions of carbon nucleophiles to α,β-unsaturated ketones are valuable C-C bond forming reactions that furthermore allow introduction of stereogenic centers.[1] Copper-catalysed reactions have been successfully employed in a variety of syntheses, for example for (-)-solavetivone[2] or prostaglandins.[3]

The most interesting feature of the copper-catalysed conjugate addition to α-β unsaturated ketone is the high selectivity for the 1,4-addition. Selectivity for 1,4 or 1,2-additions is related to Hard and Soft Acids and Bases theory (HSAB-principle) and Frontier Molecular Orbital Theory (FMO).[4] Hard nucleophiles as (MeLi or Grignard reagents) usually are highly polarised, with small ion radii (high charge density) and have low lying HOMO. Soft nucleophiles are generally not polarised, with low charge density and high lying HOMO with large molecular orbital coefficients at the reactive center. Hard nucleophiles are selective for the 1,2-addition on enones whereas soft nucleophiles as cuprates give the 1,4-addition product (Scheme 1).



Scheme 1. 1,4 and 1,2-additions

The Klopman-Salem[5] equation for interaction of a nucleophile N and an electrophile E combines the HSAB and FMO principles (Equation 1).

$$\Delta E = \underbrace{-\frac{Q_N Q_E}{\varepsilon R_{NE}}}_{\text{Coulomb term}} + \underbrace{\frac{2(c_N c_E \beta)^2}{E_{HOMO}(N) - E_{LUMO}(E)}}_{\text{Frontier Orbital term}}$$

Q: charge density
ε : dielectric constant
R : distance (N-E)
c : coefficient of MO
β : resonance integral
E : energy of MO

Equation 1. Klopman-Salem equation

Indeed, for a soft nucleophile implying a soft-soft interaction with the enone, the dominant interaction is the frontier orbital term because of small $\Delta E(HOMO_N / LUMO_E)$ and small charge densities reducing the Coulomb term (Equation 1). Examination of the LUMO-coefficients of the enones shows the largest coefficient located at the β-position to the carbonyl group, thus implying nucleophilic attack at that position according to the FMO theory (Figure 3).

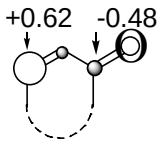


Figure 3. 1,4-addition, LUMO coefficients

With hard nucleophiles, the frontier orbital term is small because of large $\Delta E(HOMO_N / LUMO_E)$ (Equation 1). The dominant interaction is thus described by the Coulomb term, i.e. electrostatic interactions. Examination of the charge density on the enone indicates that the higher charge density is located at the carbon of the carbonyl group thus explaining the preferred attack of hard nucleophiles at that position (Figure 4).

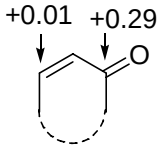
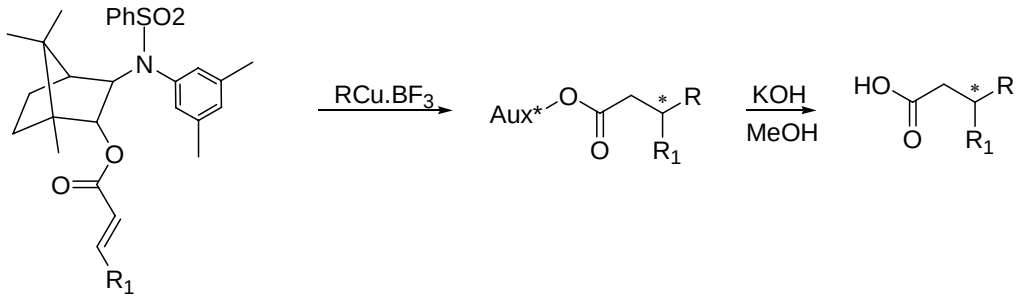


Figure 4. 1,2-addition, charge densities

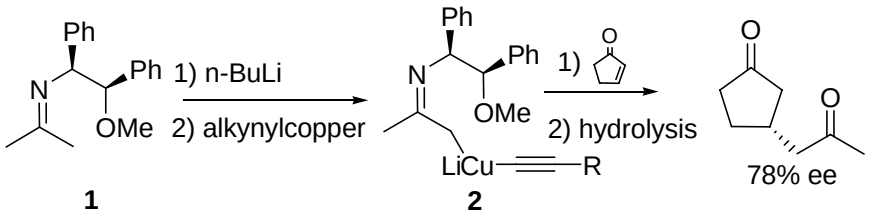
2.1.1 Grignard and Organolithium Reagents

The asymmetric version of the 1,4-addition of cuprates to enones is of fundamental importance since it allows the formation of stereogenic centers. Early attempts employed chiral auxiliaries covalently linked either to the enone substrate or to the organocopper reagent. After a diastereoselective 1,4-addition, removal of the chiral auxiliary resulted in an overall enantioselective reaction. For example, Helmchen reported the use of a chiral hydroxysulfonamide auxiliary for 1,4-additions on α,β-unsaturated esters (Scheme 2).[6] Diastereoselectivities of 99/1 could be obtained using lithium or Grignard based cuprates.



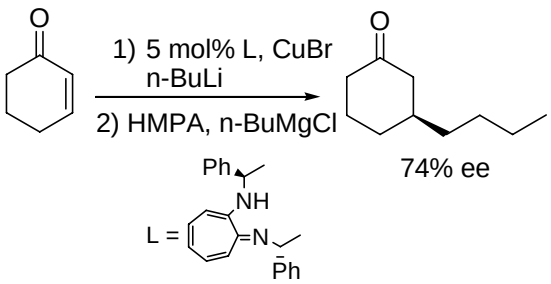
Scheme 2. Diastereoselective conjugate addition

Chiral copper reagents with covalently linked transferable chiral auxiliary were also explored, as for example the chiral cuprate **2** formed by reaction of copper with the chiral imine **1** (Scheme 3).



Scheme 3. Transferable chiral auxiliary

The main disadvantage of chiral auxiliaries is the stoichiometric amounts of expensive chiral material that have to be employed for the reaction. Therefore, a version with catalytic amounts of a metal and a chiral ligand had to be developed. The pioneering work of Lippard with tropone based ligands demonstrated that an enantioselective catalytic 1,4-addition reaction was possible, even though with low enantioslectivity.[7] Additives such as HMPA and $Ph_2(t\text{-Bu})SiCl$ improved the enantioslectivity to 74% ee for addition of Grignard reagents to cyclohexenone (Scheme 4) thus motivating further research in this field.



Scheme 4. Conjugate addition on cyclohexenone

Several ligands have been optimized for Grignard additions, with 2-cyclohexenone becoming the standard test substrate (Figure 5).

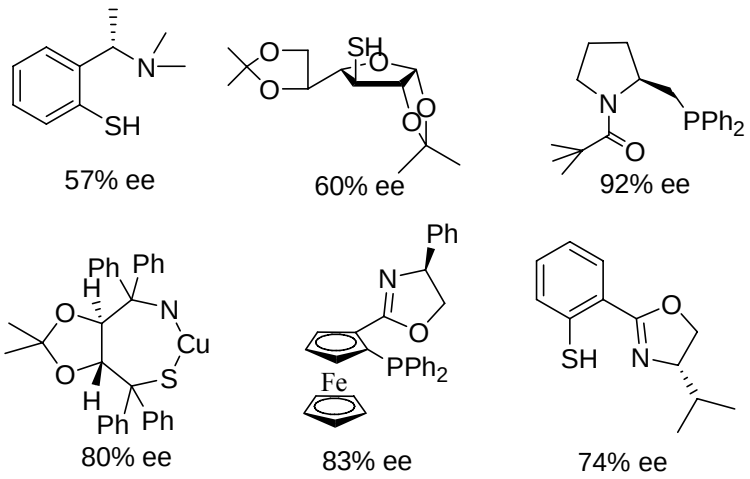
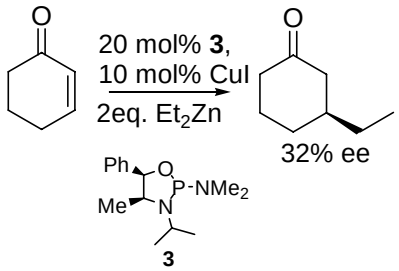


Figure 5. Ligands for copper-catalysed conjugate addition on cyclohexenone

2.1.2 Organozinc Reagents

In the late eighties, an important development was initiated with the use of organozinc reagents reported by Luche and later by Soai using a nickel ephedrine-based catalyst.[8] Indeed, use of organozinc reagents is advantageous over Grignard or lithium reagents that can react with the carbonyl group before transmetallation with copper occurs. Organozinc reagents are less basic and are tolerant to a wide variety of functional groups. The first example of a copper-catalysed 1,4-addition of an organozinc reagent to enones was reported by Alexakis, using ephedrine-based ligand **3** (Scheme 5).[9]



Scheme 5. Conjugate addition using organozinc reagent

Since then, a variety of ligands for copper-catalysed 1,4-addition of organozinc to enones have been developed. Detailed studies by Bolm[10] revealed that the reaction is highly sensitive to a large

number of factors that govern catalyst activity and enantioselectivity, such as solvent, temperature and concentrations. Generally the ligand must be adjusted to each class of substrates. Generally, cyclopentenone was found to be a much more demanding substrate than cyclohexenone. Also, ligands for acyclic enones or cyclic enones are different. Most of the reported ligands are based on phosphorus due to the high affinity of this soft lewis base for copper. Distinction can be made between phosphines, phosphonites, phosphite and phosphoramidites ligands.

a) Phosphoramidites:

Phosphoramidites monodentate ligands based on (S)-2,2'-binaphtol (BINOL) **4** (Figure 6) or α,α,α',α'-tetraphenyl-2,2'-dimethyl-1,3-dioxolane-4,5-dimethanol (TADDOL) **7** were reported by Feringa to have electron donor-acceptor properties between those of arylphosphine and arylphosphites.[11] BINOL-based ligands revealed excellent enantioselectivities for both cyclic and acyclic substrates. Increased enantioselectivity was observed when sterically demanding substituents were introduced at nitrogen. Thus, 98% ee could be achieved for diethylzinc addition on cyclohexenone with ligand **5**. Nevertheless, conjugate addition on cyclopentenone was found to give only moderate enantioselectivities, in contrasts to reactions using C_2-symmetric bidentate phosphoramidite ligand **6**.

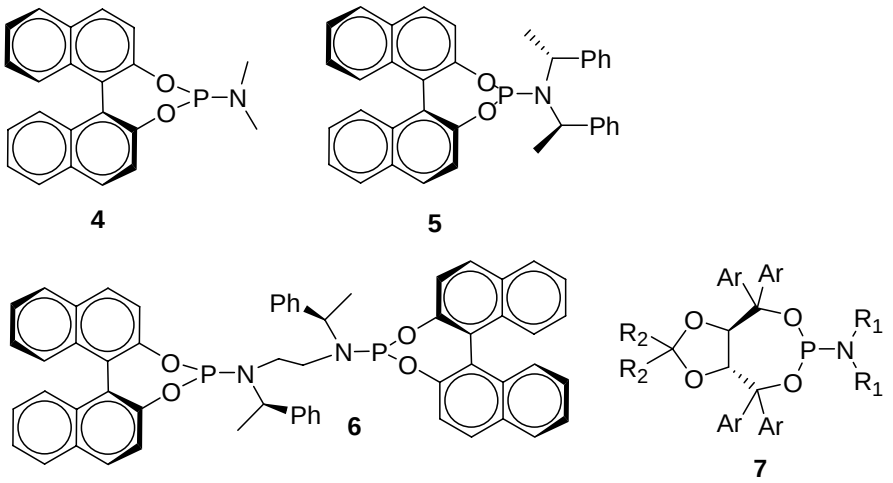


Figure 6. Phosphoramidite ligands

TADDOL-based ligands **7** were also found to be very effective for conjugate addition of organozinc reagents on cyclopentenone. Compared to BINOL-based ligands where increased steric hindrance on nitrogen enhanced the enantioselectivity, the opposite effect was reported for TADDOL-based ligands.[12]

b) Phosphites:

The first successful chiral phosphite ligands were reported by our group.[13] Using phosphinooxazoline **8** (Figure 7), high enantioselectivities were obtained on cyclohexenone, cyclopentenone and acyclic substrates. Introducing bulky substituents at the 3,3' positions of the BINOL backbone further improved the enantioselection for cyclopentenone, reaching 94% ee.[14]

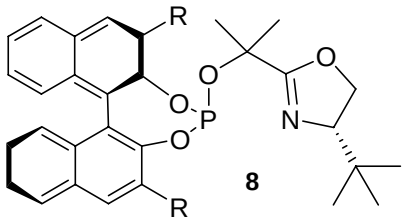


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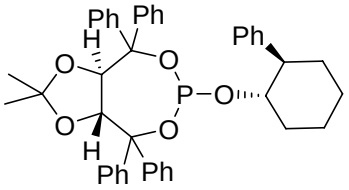
Figure 7.

Monodentate phosphites based on TADDOL and BINOL were reported by Alexakis.[15] The TADDOL based ligands **9** (Figure 8) were the most successful giving 96% ee for diethylzinc addition on cyclohexenone. BINOL based bisphosphite **10** was reported by Chan. It was successfully used for the conjugate addition of organozinc to novel substrates, α,β-unsaturated lactones.[16]



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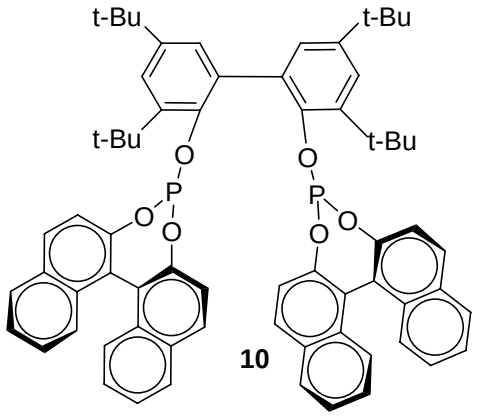

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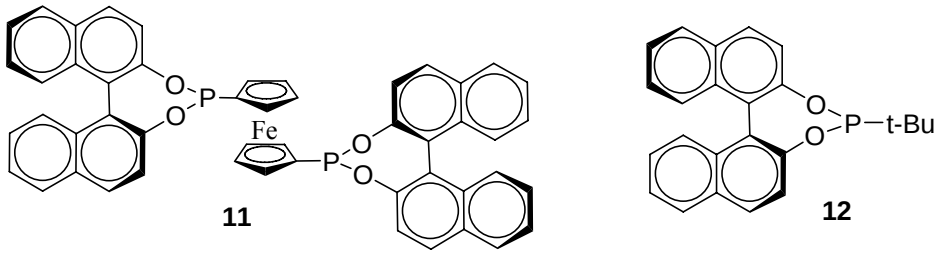
Figure 8.

c) Phosphonite:

Most phosphonites reported so far displayed only moderate enantioselectivity on test substrates. A TADDOL based ligand reported by Alexakis gave only 54% ee for diethylzinc addition on cyclohexenone.[17] The BINOL based phosphonite **12** similarly gave 41% ee (Figure 9).[18]



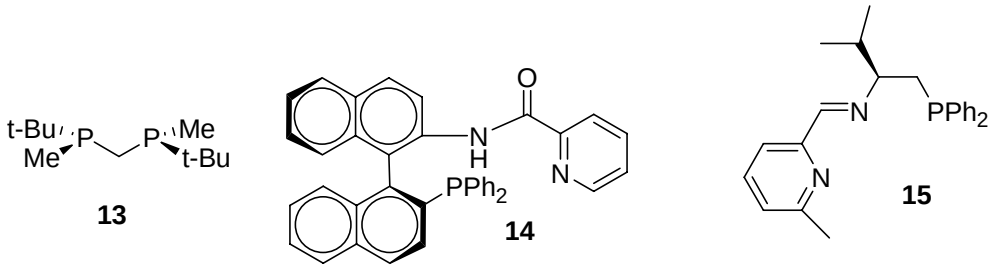
11 **12**

Figure 9.

Reetz *et al.* tested the ferrocene based phosphonite **11,** initially developed for rhodium catalysed hydrogenation,[19] for copper-catalysed conjugate addition. Impressive enantiomeric excess of 96-98% were obtained for diethylzinc addition to cyclohexenone and lactones.

d) Phosphines:

The first successful application of phosphines was reported by Imamoto[20] using the chiral phosphorus ligand **13** (Figure 10). An ee of 83% ee was obtained for the diethylzinc addition to cyclohexenone. Improvement for both cyclic and acyclic enones was achieved by Zhang with ligand **14**, giving 92% ee for diethylzinc addition on cyclohexenone and for the first time 98% ee for chalcones.[21] Also interesting is ligand **15**, with 91% ee on cyclohexenone.[22]



13 **14** **15**

Figure 10.

Recently, Hoveyda reported the use of modular peptide-based phosphines **16** (Figure 11). A combinatorial approach to ligand optimisation led to specific combinations of amino-acids for each class of substrates.

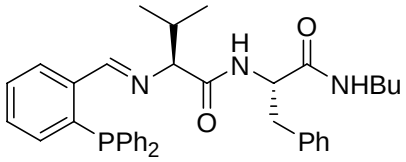


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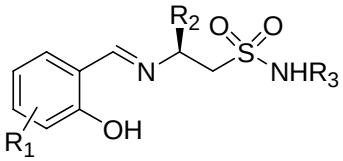
Figure 11.

e) Non-phosphorus ligands:

After the report by Noyori of copper-catalysed conjugate additions with achiral copper-sulfonamide complexes, Sewald developed chiral sulfonamides which induced moderate enantioselectivities.[23] Successful examples of chiral sulfonamide ligands **17** (Figure 12) were found by Genari using high-throughput screening.[24] An ee of 90% ee could be reached for diethylzinc addition to cyclohexenone. Acyclic substrates on the other hand gave much lower enantioselectivities.



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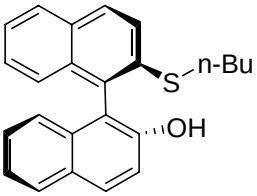

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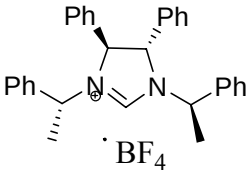

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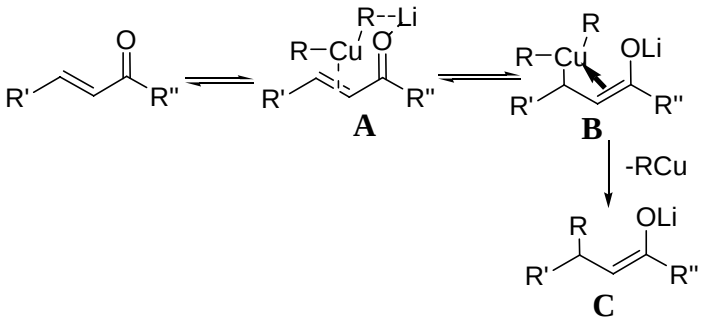
Figure 12.

Because of the high affinity of sulfur for copper, Woodward studied BINOL-derived thiols **18** which gave 77% ee with acyclic enones.[25]. Alexakis reported moderate enantioselectivities for the diaminocarben ligand **19.**[26]

2.1.3 Mechanism

The mechanism of copper-catalysed conjugate addition is remaining a subject of investigation. After that early proposal of single electron transfer has been rejected[27], more plausible mechanisms have been proposed over the last decade. Still, no direct evidence supporting the postulated catalyst structure has been reported so far. Nevertheless, kinetic studies, NMR spectroscopy and theoretical calculations have led to a commonly accepted general mechanism. In the reaction of cuprates with enones, the first step is the reversible coordination of copper on the

enone, forming the π-complex **A** (Scheme 6). NMR-spectroscopic studies have demonstrated that complex **A** is a reactive intermediate of the reaction.[28] Kinetic studies have shown that the reaction rate depends directly on the concentration of **A**. Next occurs the oxidative addition to form a σ-bound Cu(III) species to form **B**, even though the formation of the supposed Cu(III) could not be demonstrated so far. The accelerating effect of strong σ-donating ligands as sulfur or phosphines could be correlated to stabilization of this Cu(III) intermediate[29]After reductive elimination the enolate **C** is formed. The kinetic isotope effects in conjugate addition to cyclohexenone were determined by Singleton *et al.* with the conclusion that the rate-limiting step is the C-C bond formation to form the enolate **C**.[30]



Scheme 6. Mechanism for the 1,4-addition of cuprates to enones

The precise nature of the cuprate formed with organolithium is important. In 1952 Gilman reported the formation of a reactive cuprate $Li(R_2Cu)$ by addition of one equivalent of organolithium to an unreactive and unstable monoorganocopper RCu reagent (Equation 2) [31].

$$CuX + LiR \xrightarrow{-LiX} CuR \xrightarrow{LiR} Li(CuR_2)$$

Equation 2. Cuprates

Nevertheless, organocuprates display remarkable structural diversity. Depending on the ligands, solvents, counter ions or additives, a wide variety of structures has been observed, ranging from monomeric to complex aggregates as the neutral dimeric structure **20**[32] or the ionic cuprate **21** reported for *t*-$Bu_2CuLi_2CN(THF)(pmdeta)_2$ (pmdeta= pentamethyldiethylentriamine, Figure 13).[33]

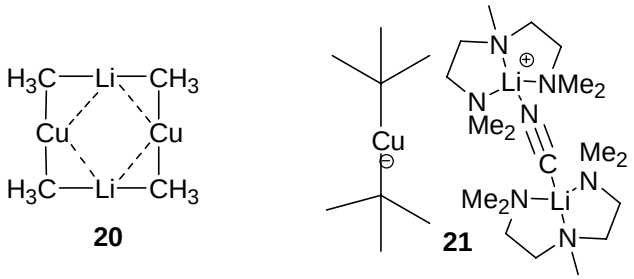


Figure 13.

The reactivity of cuprates was reported to be correlated to the C-Cu-C angle.[34] Using B3LYP/631A method for geometry optimization, the energy of the frontier molecular orbitals of $(CH_3)_2Cu^-$ was examined for various C-Cu-C angles (Figure 14). Whereas a near to linear geometry was found to be suited for SN_2 substitution reactions, a bent geometry was ideal for the formation of a π-complex with the enone (structure **A** in Scheme 6).

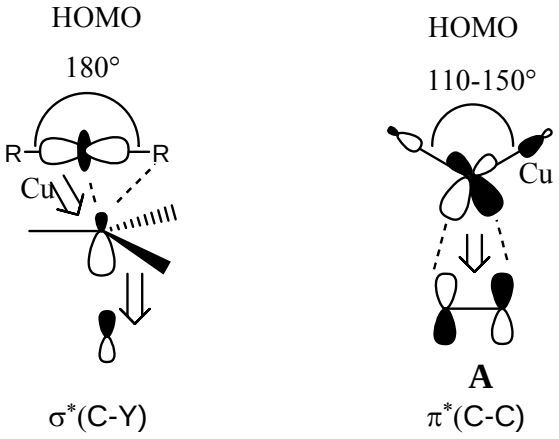
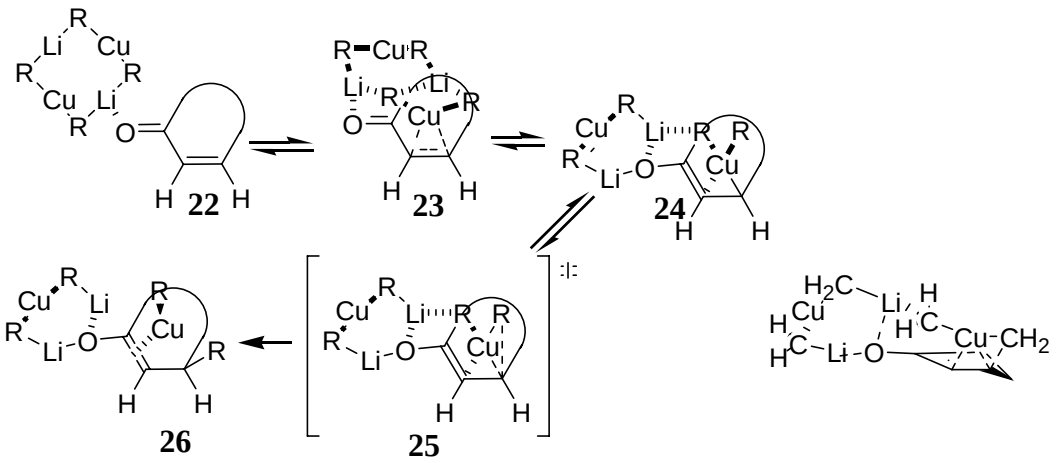


Figure 14. Angle-reactivity correlation

2.1.4 Enantioselectivity

Taking the dimeric cuprate model, recent theoretical calculations have brought some insight in to the origin of enantioselectivity observed with chiral catalysts.[35] In this model, copper/olefin (soft/soft) and lithium/carbonyl (hard/hard) interactions are the main factors. Stable copper-enone π-complexes have been observed using NMR techniques by several research groups.[36] The rate determining step was found to be the C-C bond formation to form **26** (Scheme 7) by reductive elimination of Cu(III) to Cu(I) from **24**. The proposed mechanism is in accordance with kinetic data obtained previously by Krauss and Smith who showed that the 1,4-addition of cuprates is first-order in both cuprate dimer and enone.[37]



Scheme 7. Cu(III) intermediate

In distinction to previous assumptions that the enantioselective step may occur by enone face discrimination during the coordination of the cuprate on the enone to form **23**, as for example in model **27** (Figure 15) reported by Tomioka *et al.,* [38] Nakamura proposed that the enantioselection occurs during the reductive elimination from Cu(III) to Cu(I), the role of the chiral ligand being to selectively accelerate this reductive elimination on one of the diastereoisomeric copper-enolate **24** intermediates (Scheme 8).

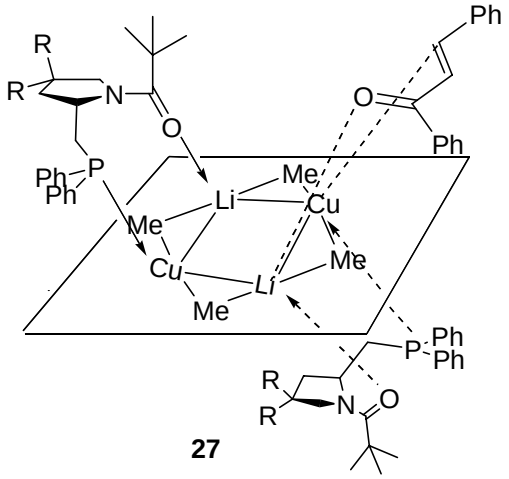
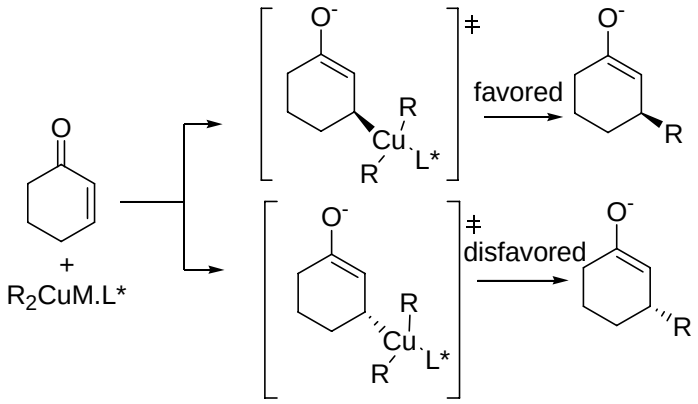


Figure 15. Face discrimination

Nevertheless, this mechanism is proposed for cuprates, *i.e.* with organolithium reactants, and it is not clear whether or not these results can be transposed to the conjugate addition with organozinc reagents.



Scheme 8. Enantioselection

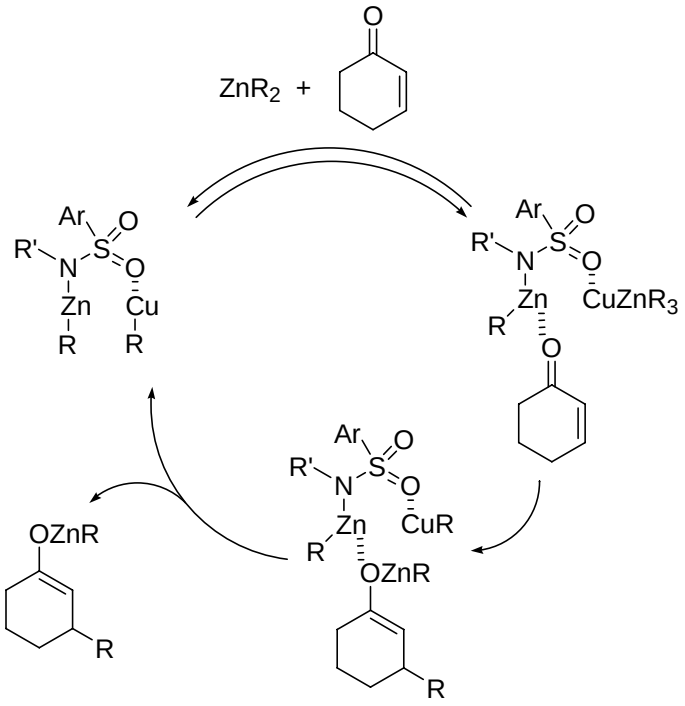
The only extensive mechanistic studies were published by Noyori dealing with chiral sulfonamide ligands, following the reaction by measuring the intensity of the C-O stretching band of the zinc enolate in the IR-spectrum.[39] The reaction turned out to proceed with first-order kinetics in both Et_2Zn and enone as well as in CuCN and sulfonamide. The bidentate catalyst coordinates here both the copper and the organozinc reagent, itself coordinated to the carbonyl of the enone (Scheme 9). Because Zn is much more electropositive than Cu, all hard anions are bound to Zn. Noteworthy, protic ligand reacts with ZnR_2 to form $RZnNR'SO_2Ar$ by elimination of hydrocarbon RH (Equation 3).[40] Because the reaction proceeds with first-order kinetics in both Et_2Zn and enone, the turnover rate is limited by the alkyl-transfer step and not by the product releasing step.

$$R'NHSO_2Ar + ZnR_2 \longrightarrow RZnNR'SO_2Ar + RH$$

$$CuX + ZnR_2 \longrightarrow CuR + RZnX$$

$$RZnNR'SO_2Ar + CuR \longrightarrow (RZnNR'SO_2Ar)(CuR)$$

Equation 3. Reaction of protic ligands with diethylzinc



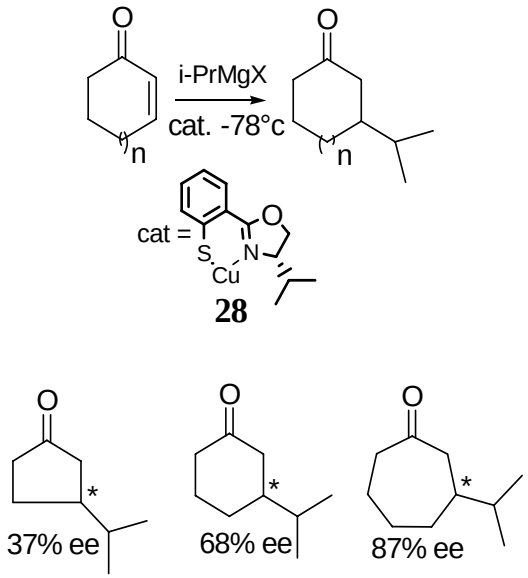
Scheme 9. Catalytic cycle

Similarly to Gilmans cuprate, they assumed a mixed-metal cluster $CuZnR_3$. When Et_2Zn and CuX are mixed in solution, a metathetic anion exchange takes place under the control of the metal redox potentials, giving EtZnX and CuEt. The CuEt is reported to interact with Et_2Zn to form an active mixed-metal cluster compound $CuZnEt_3$.

2.2 Synthesis and Applications of New Ligands

2.2.1 Aim of the Work

Various oxazoline-containing ligands have been applied to copper-catalysed conjugate addititon to enones. In contrast to its success in allylic alkylations,[41] BOX ligands (bisoxazoline) were not effective in copper-catalysed conjugate additions. Following Van Kotens results with thiol ligands,[42] Pfaltz *et al.* reported a thio-oxazoline ligand **28** that showed promising results with grignard reagents (Scheme 10).[43]



Scheme 10. Conjugate addition with thiol-oxazoline ligand **28**.

When using organozinc reagents, the majority of the reported ligands rely on phosphorus coordination. BINOL-based phopshoramidites ligands **4** (Figure 6) reported by Feringa showed very interesting enantioselectivities.(44) Thus, a BINOL-oxazoline P,N ligand **29** (Figure 16) was developed in the group and revealed interesting enantioselectivities upon variation of the R substituents at the BINOL moiety.(13)

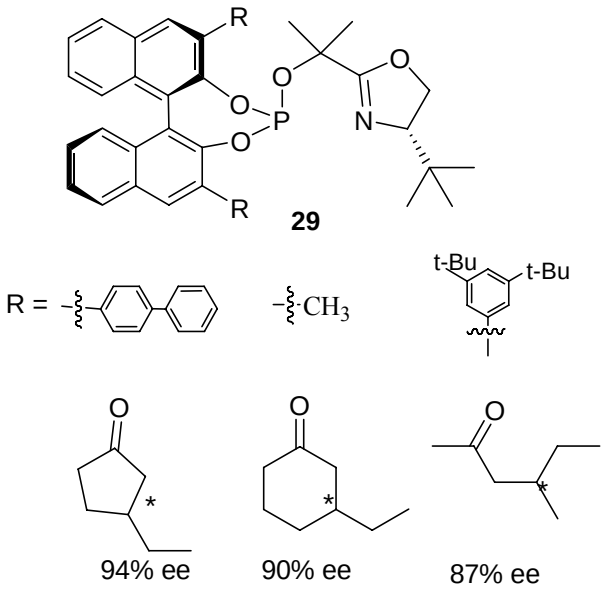
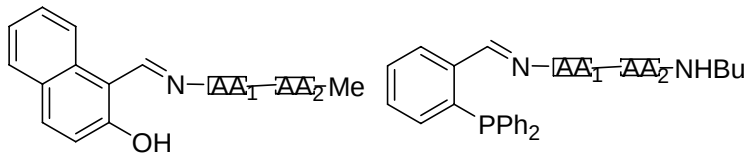


Figure 16. Conjugate additions with ligand **29**.

2.2.1.1 Schiff-Base Ligands

Amino acid-based Schiff base ligands **30** (Figure 17) were introduced by Inoue for catalysed 1,2-conjugate additions on aldehydes.[46] Using a combinatorial approach, Hoveyda recently reported a modular peptide-based ligand **31** that showed high enantioselectivities on both cyclic and acyclic enones.[47]



30 **31**

Figure 17. Schiff base ligands

Upon variation of the peptidic chain, adaptation of the ligand to each substrate class could be achieved (Figure 18).

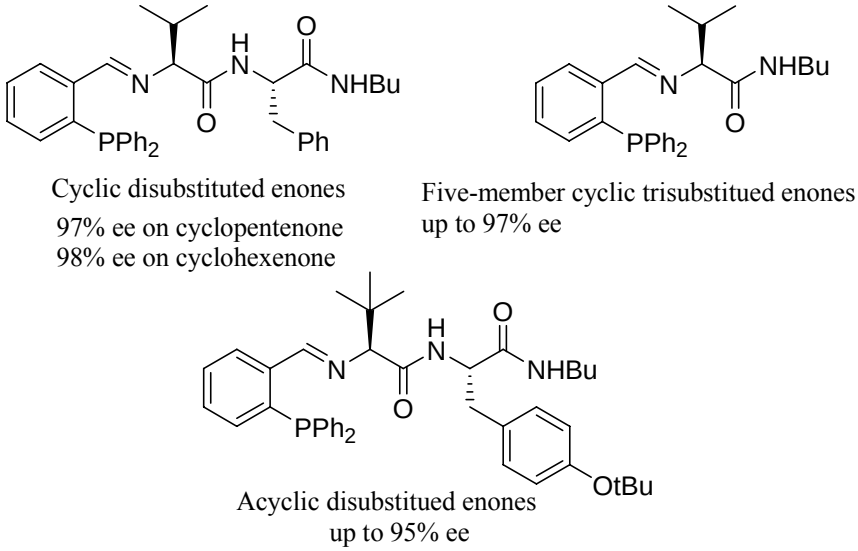


Figure 18. Ligand specificity

In comparison to PHOX ligands that are moderately effective, the very high enantioselectivities obtained with ligands **31** called for further investigations since coordination sites of both ligand types shows similarities (Figure 19).

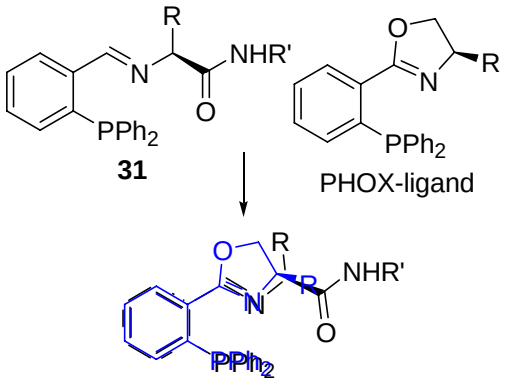


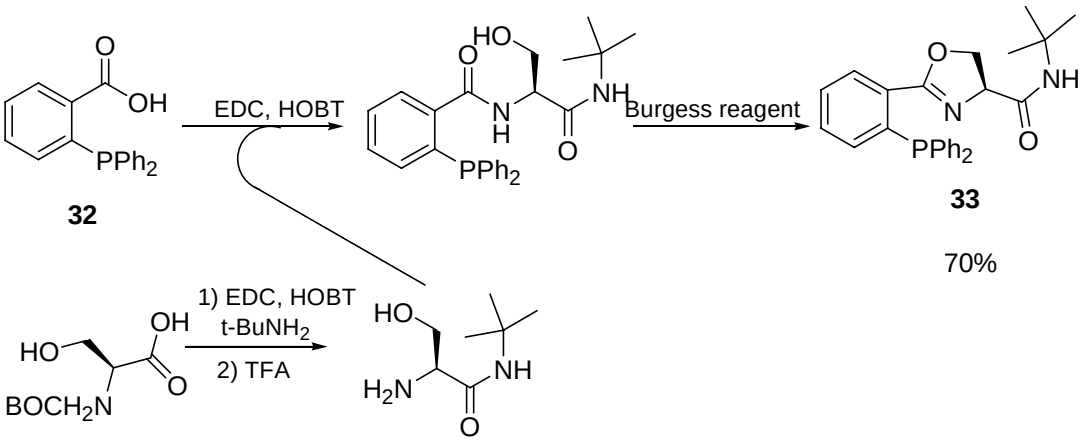
Figure 19. Ligands superposition

The aim of the present work was thus to investigate the important functionalities of ligand **31** by systematic variations of the substituents R and R'. Also, suspecting the amide functionality to play a crucial role by presenting a third coordinating group, synthesis of phopshine-oxazolines with an amide side-chain was necessary. Finally, modification of the phosphinoaryl part led to synthesis of ferrocene ligands.

2.2.2 Imine ligands

2.2.2.1 Phosphine-oxazoline amides

The synthesis of phopshine-oxazoline-amide **33** was obtained by coupling diphenylphosphino-benzoic acid **32** (Scheme 11) with a functionalised amino acid (serine).



Scheme 11. Ligand synthesis

The copper(II)-complex was formed using a 1/1 Cu(II)/ligand ratio in dichloromethane. The copper(II) source was the commercially available Cu(II)trifluoromethansulfonate. Precipitation with pentane led to analytically pure copper complex. Test reactions with the obtained complex on cyclohexenone were conducted at room temperature using 5 mol% of catalyst and 1.5 equivalent of diethylzinc for 24 hours. The complex was found to be insoluble in toluene, the usual solvent for copper-catalysed conjugate additions, thus adjunction of small amounts of polar cosolvents was necessary. Enantioselectivities were found to vary depending on the nature and ratio of used cosolvent (Table 1).

Table 1. Solvent influence on Cu-catalysed diethylzinc addition to cyclohexenone[a]

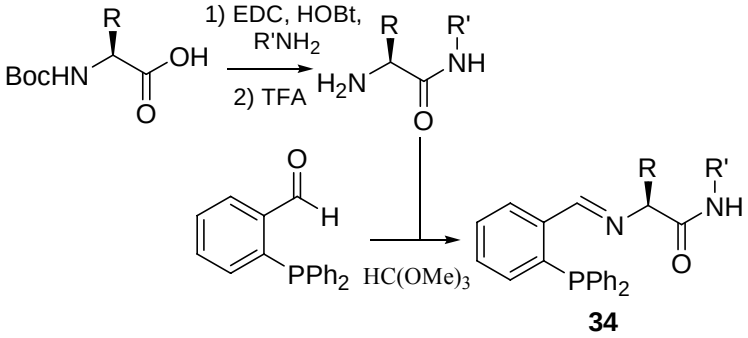
Entry	Temp. (°C)	Solvents (ratio)	Yield (%)[b]	*ee* (%)[b]
1	+25	Tol/CH_2Cl_2 (8/2)	30	20 (*S*)
2	+25	Tol/THF (9.5/0.5)	77	35 (*S*)
3	+25	Tol/THF(8/2)	50	50 (*S*)
4	+25	THF	33	22 (*S*)

[a] All reactions were carried out under argon using 5 mol% of **33**-$Cu(OTf)_2$ for 12 hours.
[b] Determined by GC.

Dichloromethane (Entry 1, Table 1) was detrimental both for yields and enantioselectivity, whereas THF lowers the yields but increased the *ee* when a 8/2 toluene/THF mixture was used (Entry 3/2, 3/4, Table 1). Nevertheless, enantioselectivities obtained were moderate, thus calling for optimisation of ligand structure through systematic variations of phosphine-imine ligands **34** (Scheme 12) to determine the most important functionalities.

2.2.2.2 Schiff-base ligands

Schiff base ligands **34** were obtained by coupling suitably functionalized amino acids with diphenylphosphinobenzaldehyde in trimethylorthoformate. The substitution on BOC-protected amino acids was introduced by amide formation with EDC/HOBT followed by removal of the Boc group in acidic solution.



Scheme 12. Schiff base ligand synthesis

The obtained imino-phosphine ligands **34** are not air-stable, whereas the copper complex generated from these ligands could be handled without special care. Thus, the copper-complexes were formed immediately by using a 1/1 Cu(II)OTf_2/ligand ratio in dichloromethane. Precipitation with pentane led to analytically pure copper complexes. The following ligands were synthesized and tested:

a) Pheylalanine-derived ligands:

BOC-protected phenylalanine amino acids were functionalised according to Scheme 12 and coupled with diphenylphosphinobenzaldehyde to give ligand **35** and **36** (Figure 20). Their copper complexes were formed and used for diethylzinc addition to cyclohexenone, cyclopentenone and non-3-en-2-one.

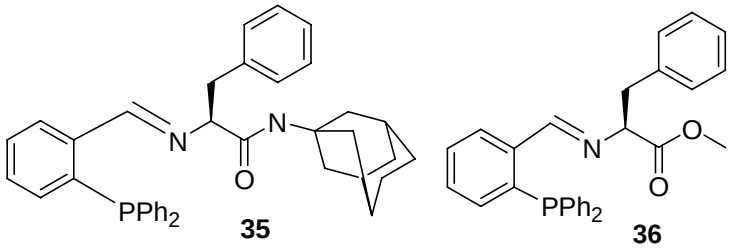


Figure 20.

Table 2. Ligands enantioselectivity for Cu-catalysed diethylzinc addition[a]

Entry	Ligand	Temp. (°C)	Cyclopent. % *ee* (% conv)[b]	Cyclohex. % *ee* (% conv)[b]	Nonenone % *ee* (% conv)[b]
1	**35**	+25	93.5 *R* (90)	93.4 *R* (95)	65 (+) (90)
2	**35**	-30	87 *R* (72)	90 *R* (90)	60 (+) (90)
3	**36**	-30	5 *R* (50)	57 *R* (90)	5 (+) (90)

[a] All reactions were carried out under argon using 5 mol% of **L**-Cu$(OTf)_2$ in toluene for 12 hours. [b] Determined by GC.

The catalyst formed with ligand **35** shows acceptable enantioselectivities with each class of substrate, giving generally better results at room temperature than at low temperature (Entries 1,2, Table 2). In contrast, ligand **36** bearing an ester instead of a bulky amide group showed poor or no enantioselection (Entry 3, Table 2)

b) Valine-derived ligands:

The synthesis of the valine-derived ligands is identical to the synthesis of phenylalanine-derived ligands described above.

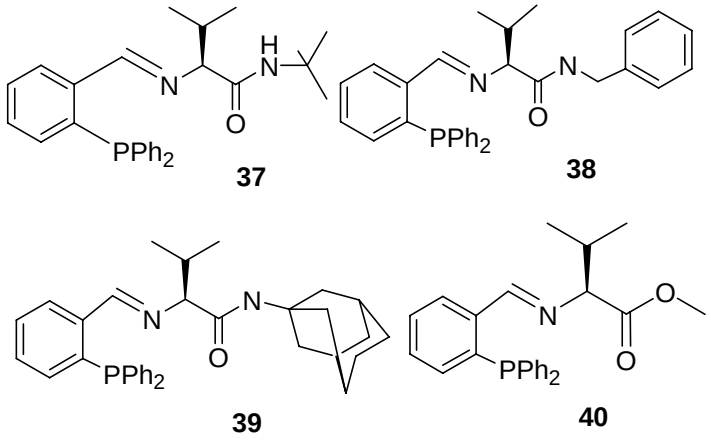


Figure 21.

Valine-derived copper complexes were formed and tested for diethylzinc conjugate addition to cyclohexenone, cyclopentenone and non-3-en-2-one.

Table 3. Ligands enantioselectivity for Cu-catalysed diethylzinc addition[a]

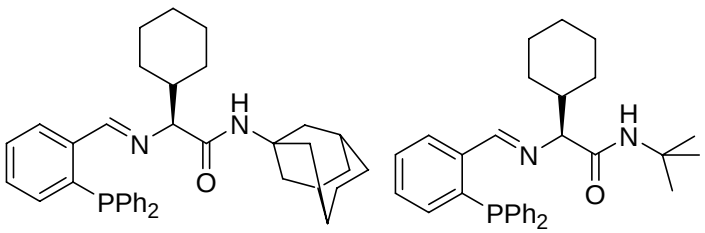
Entry	Ligand	Temp. (°C)	Cyclopent. % *ee* (% conv.)[b]	Cyclohex. % *ee* (% conv.)[b]	Nonenone % *ee* (% conv.)[b]
1	**37**	+25	**95** *R* **(89)**	94.5 *R* (98)	68 (+) (90)
2	**37**	-30	90 *R* (86)	92 *R* (98)	75 (+) (79)
3	**38**	+25	73 *R* (82)	36 *R* (98)	63 (+) (85)
4	**38**	-30	85.5 *R* (80)	85.2 *R* (98)	76.6(+)(84)
5	**39**	+25	93 *R* (85)	**97.8** *R* **(98)**	68(+)(90)
6	**39**	-30	80 *R* (84)	92.3 *R* (98)	72 (+)(92)
7	**40**	+25	11 *R* (50)	40.5 *R* (80)	7 (+) (80)
8	**40**	-30	15 *R* (80)	64 *R* (80)	10 (+) (80)

[a] All reactions were carried out under argon using 5 mol% of **L**-Cu(OTf)$_2$ in toluene for 12 hours. [b] Determined by GC.

All catalysts displayed high reactivity and enantioslectivity, apart from the ester ligand **40** (Entries 7,8, Table 3). The highest enantioselectivities were obtained with ligands **37** and **39,** having a bulky amide substituent. Surprisingly, the ees were higher at RT than at -30 °C. An impressive 97.8% ee could be achieved on cyclohexenone with ligand **39**, rivaling the peptidic ligands reported by Hoveyda.[47]

c) Cyclohexylglycine-derived ligands:

The synthesis of the cyclohexylglycine-derived ligands is identical to the synthesis of phenylalanine-derived ligands described above. Noteworthy, cyclohexylglycine is a non-natural amino acid.



41 **42**

Figure 22.

The corresponding cyclohexylglycine-derived copper complexes were formed and tested for conjugate addition of diethylzinc to cyclohexenone, cyclopentenone and non-3-en-2-one in toluene.

Table 4. Ligands enantioselectivity for Cu-catalysed diethylzinc addition[a]

Entry	Ligand	Temp. (°C)	Cyclopent. % *ee* (% conv.)[b]	Cyclohex. % *ee* (%conv.)[b]	Nonenone % *ee* (% conv.)[b]
1	**41**	+25	94*R* (87)	96.4 *R* (98)	80(+)(80)
2	**41**	-30	89*R* (86)	90 *R* (98)	82(+) (79)
3	**42**	+25	93*R* (82)	96.6 *R* (98)	82(+) (85)
4	**42**	-30	90*R* (80)	93 *R* (98)	83(+) (84)

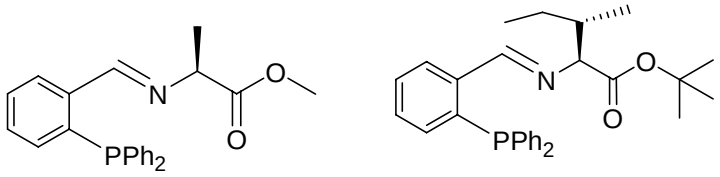
[a] All reactions were carried out under argon using 5 mol% of **L**-Cu(OTf)$_2$ in toluene for 12 hours. [b] Determined by GC.

Ligands **41** and **42** displayed almost identical enantioselectivities. Ligand **42** was slightly superior to the valine-derived N-*tert*butyl amide ligand **37**, thus indicating that steric bulk on the amino acid moiety is needed. In case of ligand **41**, the large cyclohexyl substituent in conjunction with N-

adamantyl amide substitution is deleterious compared to the valine-derived N-adamantyl amide ligand **39**. Thus, fine-tuning of the steric balance between the amino acid substituent and the amide functionality is required.

d) Valine and isoleucine derive ester ligands:

The synthesis of valine- and isoleucine-derived ester ligands is identical to the synthesis of phenylalanine-derived ligands described above.



43 **44**

Figure 23.

Their copper complexes were formed and tested for diethyl-zinc conjugate addition on cyclohexenone, cyclopentenone and non-3-en-2-one in toluene.

Table 5. Ligands enantioselectivity for Cu-catalysed diethylzinc addition[a]

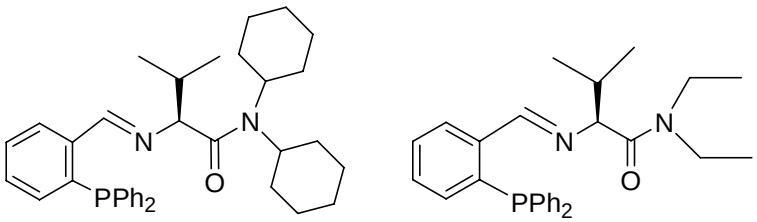
Entry	Ligand	Temp. (°C)	Cyclopent. % *ee* (% conv.)[b]	Cyclohex. % *ee* (% conv.)[b]	Nonenone % *ee* (% conv.)[b]
1	**43**	+25	7 *R* (32)	13 *R* (60)	30 (+) (27)
2	**43**	-30	5 *R* (30)	25 *R* (42)	36 (+)(24)
3	**44**	+25	3 *R* (35)	54 *R* (50)	8 (+)(20)

[a] All reactions were carried out under argon using 5 mol% of **L**-Cu(OTf)$_2$ in toluene for 12 hours. [b] Determined by GC.

These ligands were found to form relatively unreactive catalysts and displayed very poor enantioselectivities. This might be due to the nature of the amino acid employed and, on the other side, to the ester functionality which also gave poor results with others ligands. It appeared that the amide is needed, presenting a third coordinating site.

e) Valine-derived ligands with tertiary amide functionality:

To determine if a secondary amine is necessary, analogous ligands with a tertiary amide group were synthesised. The synthesis of these valine-derived ester ligands is identical to the synthesis of phenylalanine-derived ligands described above.



45 **46**

Figure 24.

Their copper complexes were formed and tested for diethyl-zinc conjugate addition on cyclohexenone, cyclopentenone.

Table 6. Ligands enantioselectivity for Cu-catalysed diethylzinc addition[a]

Entry	Ligand	Temp. (°C)	Cyclopent. % *ee* (% conv.)[b]	Cyclohex. % *ee* (% conv.)[b]
1	**45**	+25	40 *R* (75)	24 *R* (90)
2	**46**	+25	58 *R* (70)	62 *R* (90)

[a] All reactions were carried out under argon using 5 mol% of **L**-Cu(OTf)$_2$ in toluene for 12 hours. [b] Determined by GC.

Both ligands showed low enantioselectivities, confirming that a secondary amide is essential for achieving high enantioslectivities. An secondary amide might be necessary to coordinate the organozinc reagent after deprotonation as reported for amide ligands with organozinc reagents (Figure 25, Equation 3).[(48)]

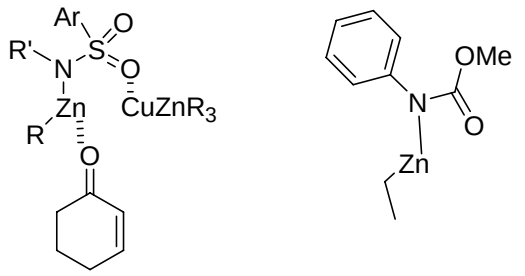


Figure 25.

2.2.2.3 Optimisation of the Experimental Conditions

Using the valine-derived ligand **37**, solvents, temperature and the amount of Et_2Zn were varied to determine the optimal conditions. Indeed, copper-catalysed reactions are generally highly sensitive to reaction conditions such as solvent, temperature, reagents nature and equivalencies. Concerning the temperature, the optimum was found around room temperature, in distinction to most conjugate additions reported which were conducted at low temperatures.

Various solvents were tested on cyclohexenone using two equivalents of diethylzinc and 5 mol% catalyst formed from valine-derived ligand **37**. Polar or coordinating solvents such as THF were found deleterious for enantioselectivity (Figure 26).

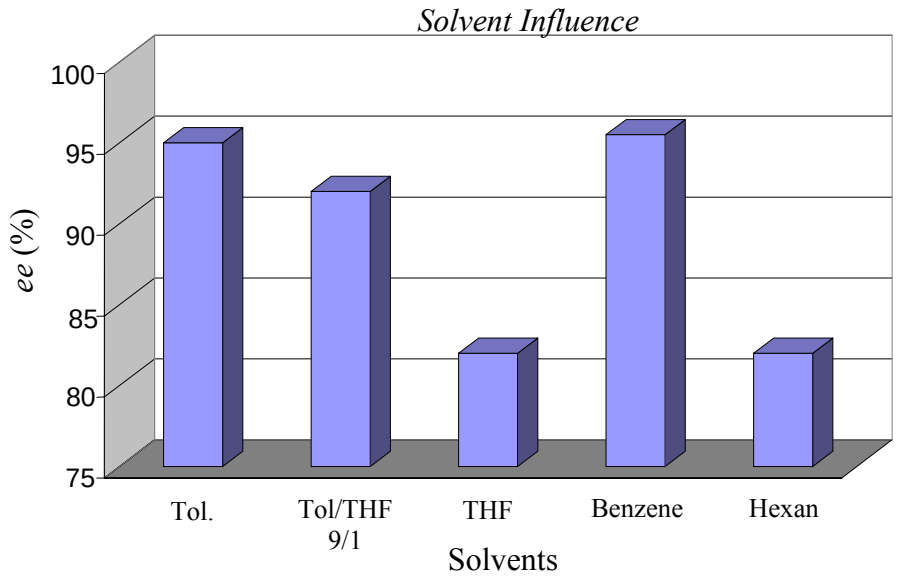


Figure 26. Solvent influence

Benzene was slightly superior to toluene. Using toluene as solvent, the amount of diethylzinc was varied, as depicted in the Figure 27. Only subtle changes in enantioselectivity were observed when the amount was increased from 1.0 to 3.0 molar equivalents with respect to the enone.

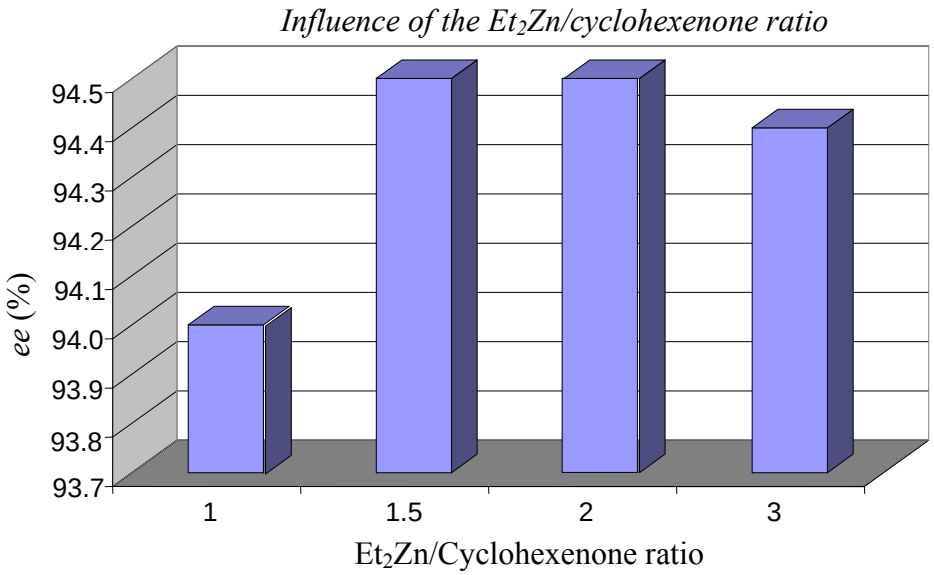
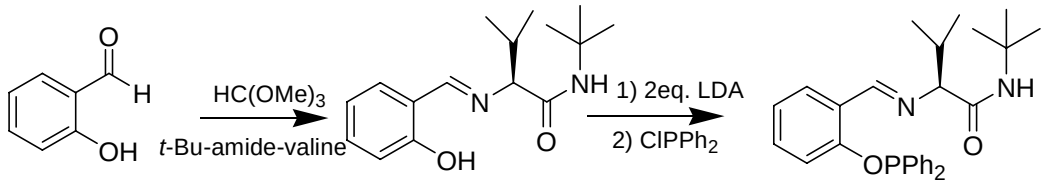


Figure 27. Influence of the Et_2Zn/Cyclohexenone ratio

2.2.2.4 Phosphite ligands

For further ligand optimisation, variation of the diphenylphosphine moiety was investigated. The synthesis of hydroxy ligand **48** and diphenylphospshite ligand **49** was obtained by coupling the functionalised amino acid with salicylaldehyde **47** to form the imine, followed by formation of the phopshite with chlorodiphenylphosphine under basic conditions (Scheme 12). Strong organolithium bases are incompatible with the imine functionality, thus LDA was the most appropriate base. Two equivalents had to be employed since the *tert*-butyl-amide is also acidic.



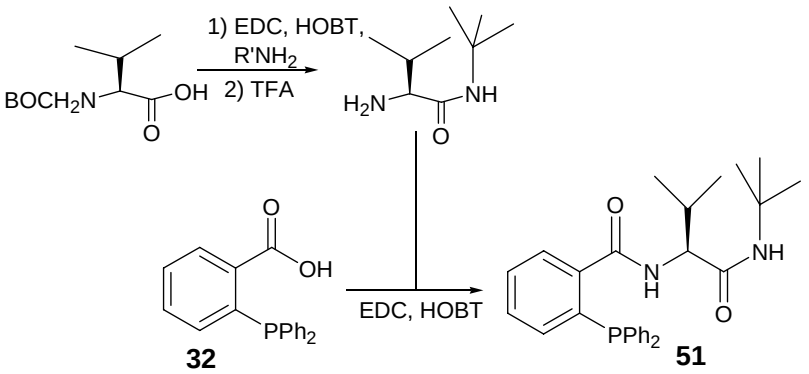
47 **48** **49**

Scheme 12.

The reaction was also carried out with chlorodicyclohexylphosphine (ligand **50**). However, the results in the copper-catalysed diethylzinc conjugate addition indicated that copper complexes with the phosphite ligand **49** and **50** were unreactive. This might be due to the different electronic properties of the phosphite moiety or the larger chelate ring. Using the catalyst derived from the phenol ligand **48**, no enantioselection could be detected in the 1,4-addition to cyclohexenone or cyclopentenone.

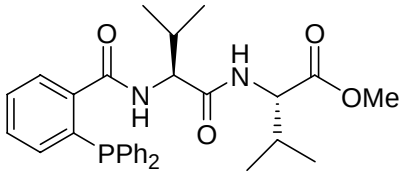
2.2.2.5 Amides ligands

The major problem encountered with Schiff base ligands is the high sensitivity of the imine functionality to nucleophiles and acids. As a result, chromatographic purification on silica-gel is often problematic due to the acidity of the silica. Expecting an higher stability, the amide ligand **51** was obtained from commercially available diphenylphosphinobenzoic acid **32** and tertbutyl-amide valine (Scheme 13).



Scheme 13.

Copper complexes were formed with copper(II)$(OTf)_2$ as described above. The reaction of cyclohexenone with two equivalents of diethylzinc in toluene for 12 hours at room temperature gave moderate enantioselectivity (68% ee, 95% conv.) so that further investigations with that ligand type were abandoned. In the mean time, an interesting publication dealing with this type of ligand has been published by Breit *et al.*[49] High enantioselectivities were achieved upon varying the copper source (97% ee for diethylzinc addition to cyclohexenone with CuBr with dipeptide ligand **52**, Figure 28)



52

Figure 28.

2.2.3 Ferrocene Ligands

The discovery of ferrocene[50] and its structural elucidation by two separate research groups marked the birth of contemporary organometallic chemistry. This revolutionary advance in organometallic chemistry was recognised by a Nobel prize in chemistry in 1973.[51] Several of these ferrocene complexes form the basis for important industrial processes, as for example the 10 000 tons production of herbicides produced per year using a P,P bidentate ferrocene ligand.[51]

2.2.3.1 Ferrocenes and chirality

One of the most interesting features of ferrocene-based ligands is the chirality induced by substitutions at the cyclopentadienyl rings (Figure 29). The planar chirality is obtained by 1,2 substitution of one Cp ring as in **53**. If the ferrocene is substituted with a chiral side chain, planar and central chirality can be combined as in **54**. When the ferrocene is 1,1' substituted, a conformation with an axial chirality could be obtained, as in **55**.

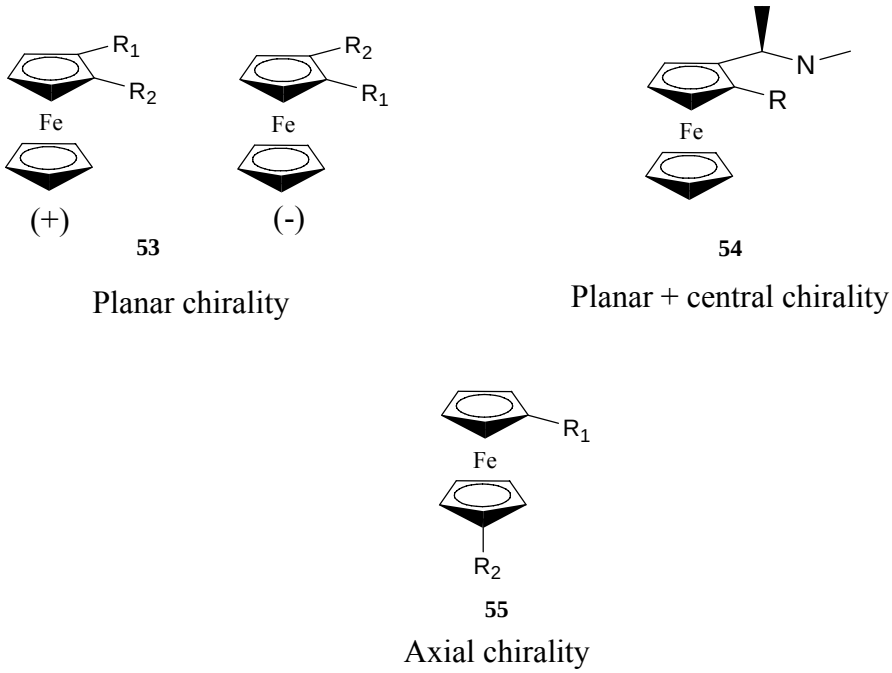


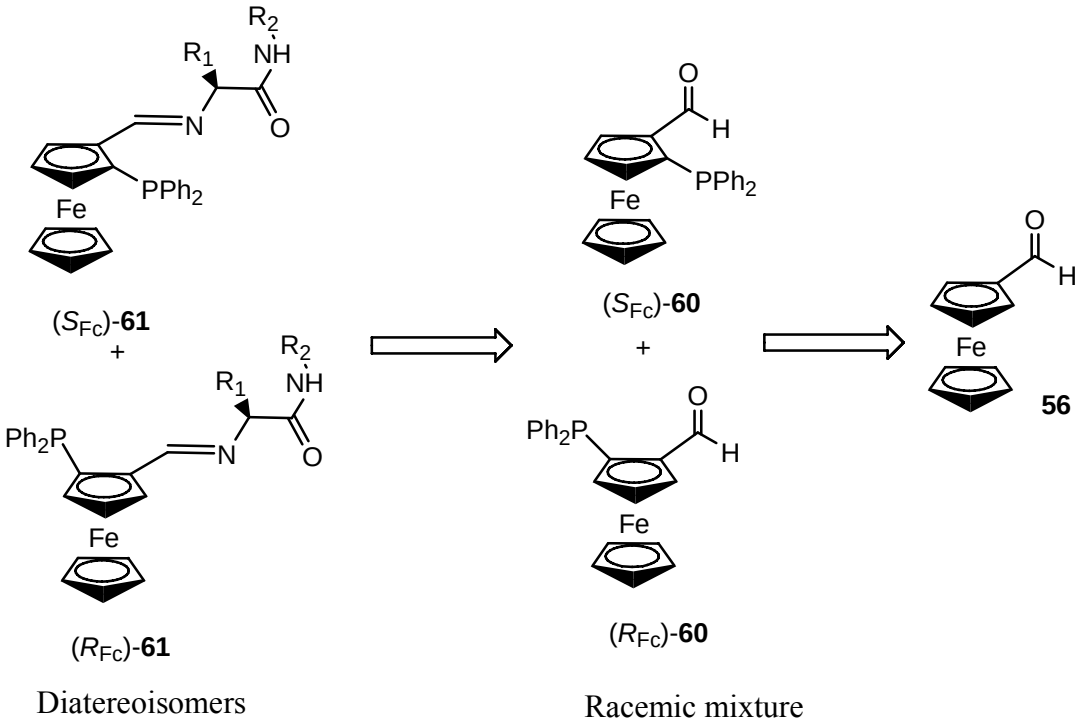
Figure 29. Ferrocenes and chirality

Moreover, the ferrocene possesses the following interesting characteristics:

- Adequate rigidity: The backbone of a chiral ligand should not be too flexible so as to provide an appropriate chiral environment.

- Easy derivatisation: The cyclopentadienyl ring in ferrocene carries a partial negative charge and is susceptible to electrophilic substitution reactions. Ferrocene reacts $3x10^6$ times faster than benzene.
- Chirality.
- Steric properties: the ferrocene moiety could act as a major sterically hindering substituent on the catalyst.
- Electronic properties: The partial negative charge of the Cp ring gives the ferrocene a donor quality. For example, ferrocene amine is a stronger base than aniline, and ferrocene carboxylic acid is a weaker acid than benzoic acid.
- Stability: Ferrocene is thermally stable and tolerant to oxygen and moisture.
- Inexpensive and readily available.

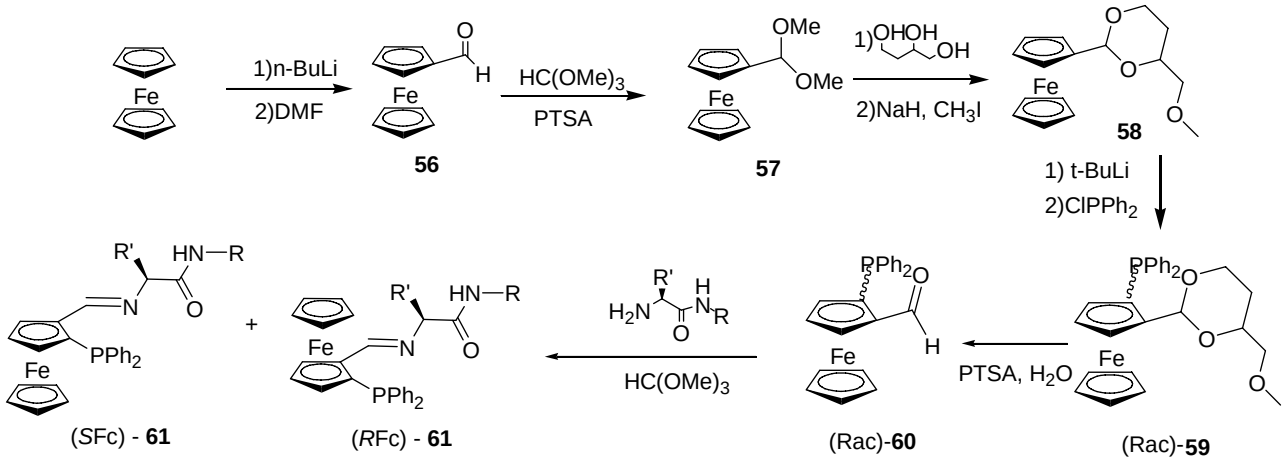
Thus, ligands presenting the central chirality on the amino acid side chain together with the planar chirality on the ferrocene were obtained following the retrosynthetical Scheme depicted below (Scheme 14).



Scheme 14.

Coupling the phosphino ferrocenyl-aldehyde **60** prepared from ferrocenyl-aldehyde **56**, with functionalized amino acids afforded the ligand **61** (Scheme 14). Noteworthy, introduction of the diphenylphosphino group on the ferrocene aldehyde **56** was done in a non-stereoselective manner, thus forming a racemic mixture of phosphino-aldehyde **60**. Coupling with natural L-amino acids thus afforded diastereoisomeric pairs **61** that could be separated by simple silica-gel

chromatography. Having two stereogenic centers in the molecule, both diastereoisomers must be synthesised and tested since a match/mismatch relation could be observed between the two stereocenters if they both influence the stereoselectivity. The synthesis of the racemic phosphino-ferrocenyl-aldehyde **60** followed Kagans procedure for aldehyde ortholithiation.[52] Starting from commercial ferrocene, monolithiation with n-butyllithium followed by quenching with dimethylformamide afforded the ferrocene aldehyde **56** in 90% yield (Scheme 15).[53] The obtained ferrocenecarboxaldehyde was quantitatively converted to the dimethyl acetal **57** by heating in neat trimethyl orthoformate in presence of acid catalyst. Transacetalization of the crude acetal **57** with commercially available racemic 1,2,4-butanetriol afforded the acetal **58** and a minor amount of dioxolane at room temperature.



Scheme 15.

Protection of the free hydroxyl group as its methyl ether was then performed using sodium hydride and iodomethane in quantitative yield. Ortholithiation with *t*-BuLi in diethyl ether followed by quenching with chlorodiphenylphosphine afforded the racemic phosphino-acetal **59**. The auxiliary group was removed under acidic condition to afford the ortho-substituted aldehyde **60**. The phosphino-aldehyde **60** was air stable. Coupling with the functionalised amino acid gave a diastereoisomeric pair **61** that could be separated by silica-gel chromatography. No oxidation occurred during this purification process, nevertheless prolonged stay on silica-gel results in partial imine bond cleavage. It was possible to crystallize the (*S, R*$_{Fc}$) *tert*-butyl-amide valine ligand **62**, thus confirming its absolute stereochemistry.

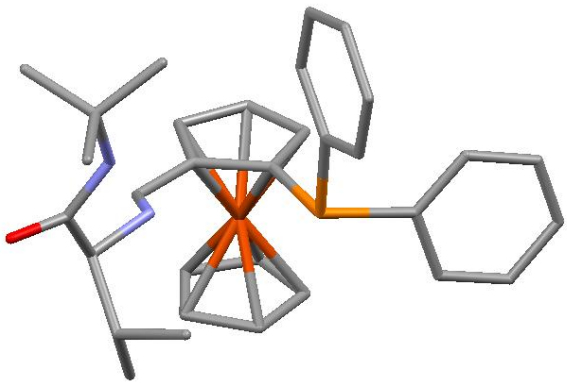


Figure 30. X-ray structure of (S, R_{Fc})-**62**

The *tert*-butyl-amide valine ligands **62** (Figure 31) were tested for copper-catalysed conjugate addition of diethylzinc to cyclohexenone with various copper salts and copper/ligand ratios (Table 7).

Table 7. Ligands enantioselectivity for Cu-catalysed diethylzinc addition on cyclohexenone[a]

Entry	Ligand	Temp. (°C)	Copper salt	Copper/ligand ratio	Conv.(%)[b]	*ee* (%)[b]
1	(*S*, R_{Fc})	0	Cu(II)OTf_2	1/1	95	10 (*S*)
2	(*S*, S_{Fc})	0	Cu(II)OTf_2	1/1	95	70 (*R*)
3	(*S*, R_{Fc})	+25	Cu(II)OTf_2	1/1	95	11 (*S*)
4	(*S*, S_{Fc})	+25	Cu(II)OTf_2	1/1	95	75 (*R*)
5	(*S*, R_{Fc})	0	Cu(I)OTf	1/1	50	3 (S)
6	(*S*, S_{Fc})	0	Cu(I)OTf	1/1	95	84 (R)
7	(*S*, R_{Fc})	+25	Cu(I)OTf	1/1	96	12 (*S*)
8	(*S*, S_{Fc})	+25	Cu(I)OTf	1/1	95	86.5(R)
9	(*S*, R_{Fc})	0	Cu(I)OTf	1/2	94	11 (*S*)
10	(*S*, S_{Fc})	0	Cu(I)OTf	1/2	85	93 (R)
11	(*S*, R_{Fc})	+25	Cu(I)OTf	1/2	95	12 (*S*)
12	(*S*, S_{Fc})	+25	Cu(I)OTf	1/2	95	95 (R)
13	(*S*, S_{Fc})	0	Cu(I)PF_6	1/2	25	85 (R)

[a] All reactions were carried out under argon using 3 mol% of catalyst **62** in toluene for 12 hours. [b] Determined by GC.

Reactions at room temperatures gave always better yields and enantioselectivities than at 0 °C. Preformed catalysts with Cu(II) salt (Entries 1-4, Table 7) gave lower enantioselectivities than when formed in situ with Cu(I) salt (Entries 5-8, Table 7). Using Cu(I), a metal/ligand ratio of 1/2 was clearly giving superior catalysts than with a 1/1 ratio (Entries 9-12/5-8). Most interesting, each

diastereoisomeric ligand pair showed pronounced difference in enantioselectivity, thus indicating that the ferrocenyl moiety plays an important role in the reaction. A clear match/mismatch situation is observed (Entries 11/12, Table 7).

Several ferrocene-based imine ligands were synthesized by coupling suitably functionalised amino acids with racemic phosphino ferrocenylaldehyde **60** (Figure 31).

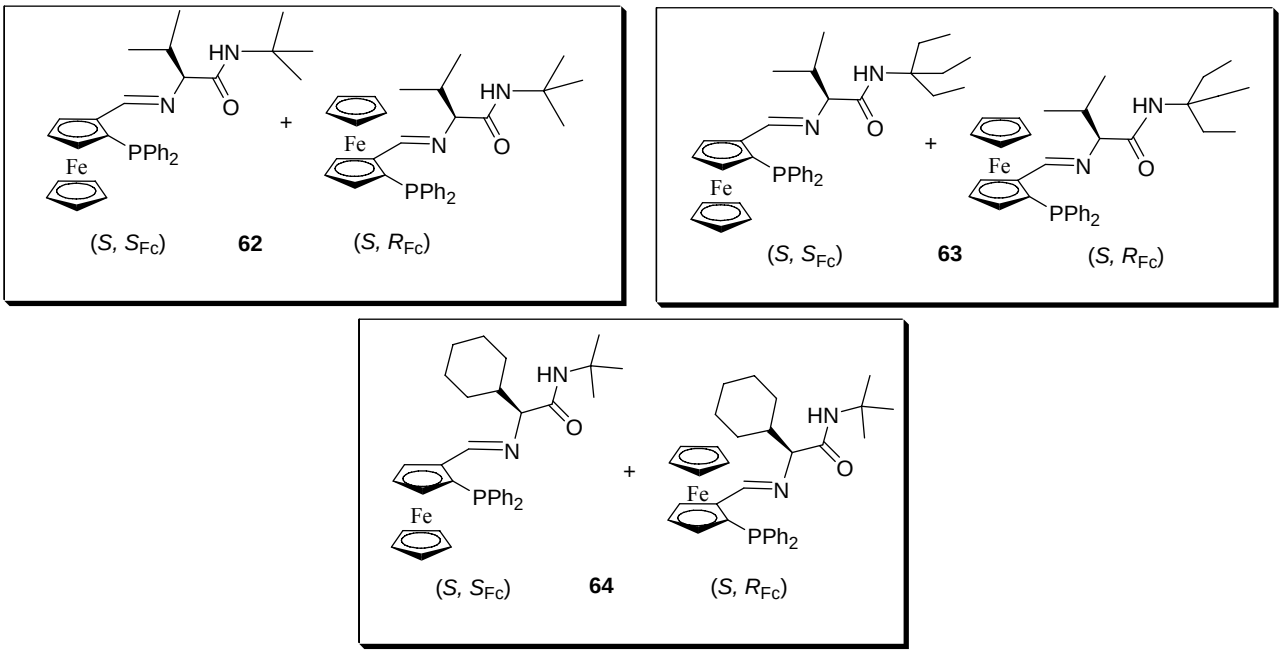
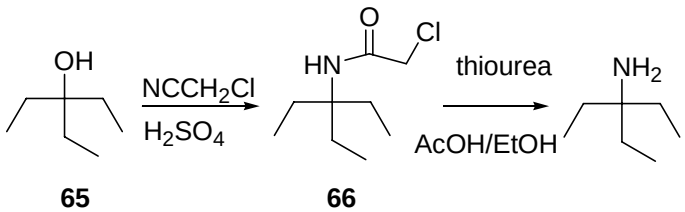


Figure 31.

The diethylpropylamine necessary for the formation of **63** was obtained in three steps following a literature procedure starting from commercially available triethylacarbinol **65** via a Ritter reaction with chloroacetonitrile. Acidic work-up afforded the chloroacetamide **66** that was converted to the amine by cleavage of the chloroacetamide group with thiourea, thus avoiding use of HCN (scheme 16).[54]



Scheme 16.

The copper complexes were formed *in situ* and tested for diethylzinc conjugate addition to cyclohexenone and cyclopentenone in toluene. The mismatched (*S, R*$_{Fc}$) ligands (Table 7) were not investigated in most case.

Table 8. Ligands enantioselectivity for Cu-catalysed diethylzinc addition[a]

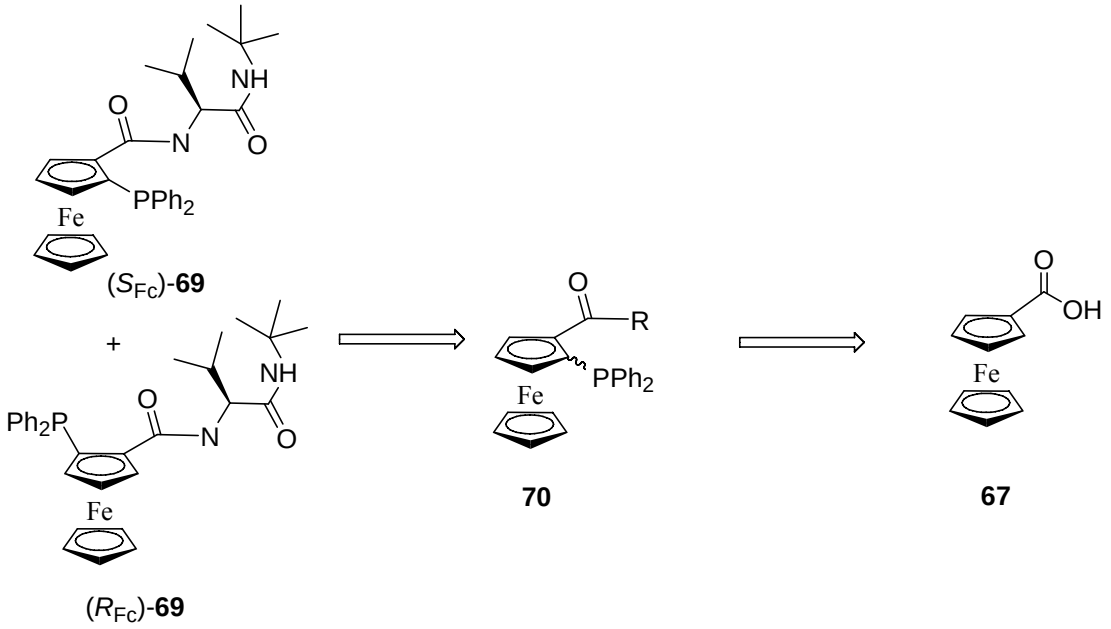
Entry	Ligand	Temp. (°C)	Cyclopent. % *ee* (% conv.)[b]	Cyclohex. % *ee* (%conv.)[b]
1	(*S, S*$_{Fc}$)-**62**	+25	94 *R* (32)	95.5 *R* (95)
2	(*S, S*$_{Fc}$)-**63**	+25	93 *R* (30)	96.5 *R* (90)
3	(*S, S*$_{Fc}$)-**64**	+25	88 *R* (35)	97 *R* (95)

[a] All reactions were carried out under argon using 3 mol% of **L**-Cu(OTf) in toluene for 12 hours. [b] Determined by GC.

All ligands showed slighltly increased enantioselectivity compared to their non-ferrocene analogues. However, if compared with the large influence of the ferrocenyl moiety in case of the mismatched ligand, the limited influence of the ferrocenyl moiety is surprising. This might be due to small amounts of uncomplexed copper(I) or presence of trace amount of diatereoisomeric complex because of difficulty to totaly separate the diastereoisomeric pairs by silica-gel chromatography.

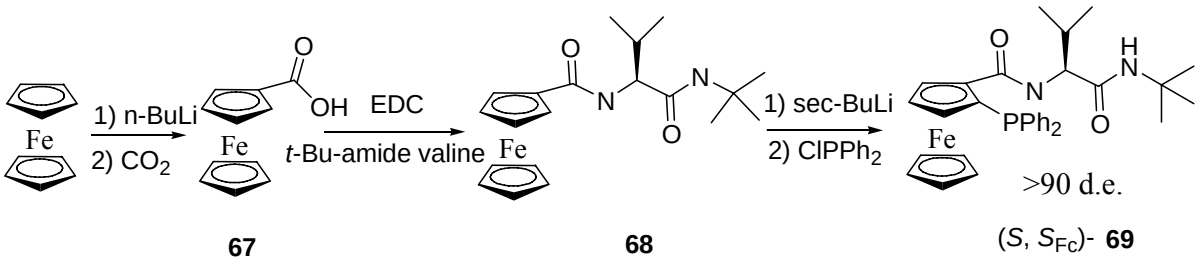
2.2.3.2 Ferrocene-amide ligands

Although the imine group on Schiff-base ferrocene ligands **61** is more stable than on the simple amino acids ligands **34**, substitution by an amide group would simplify the purification processes and the overall stability in solution. Moreover, the amide function can act as a directing group for orthometalation, avoiding long reaction sequences to introduce substituents. Thus, a synthesis following the retrosynthetic scheme 17 was considered using tertbutyl-amide valine.



Scheme 17.

Starting from commercially available ferrocene, monolithiation with n-BuLi[53] followed by reaction with carbon dioxyde afforded the ferrocene carboxylic acid **67** in 65% yield (Scheme 18). The ferrocene amide **68** was obtained by coupling with N-*tert*-butylvalinamide with EDC. Ortholithiation with various organolithium reagents showed *sec*-BuLi in THF at -78°C to be the most effective base. Quenching with chlorodiphenylphosphine gave the (*S, S*$_{Fc}$)-phosphinoferrocene **69** with more than 90% diastereoisomeric excess.



Scheme 18.

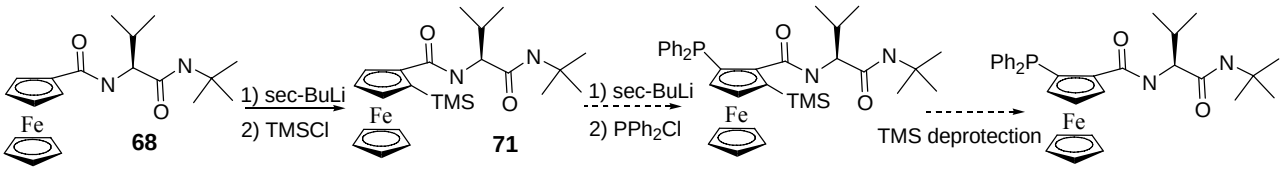
The high d.e. obtained was not ideal since only one diatereoisomere could thus be formed and tested.

Table 9. Ligands enantioselectivity for Cu-catalysed diethylzinc addition on cyclohexenone[a]

Entry	Ligand	Temp. (°C)	Copper salt	Copper/ligand ratio	Conv. (%)[b]	*ee* (%)[b]
1	(*S, S*$_{Fc}$)-**69**	0	Cu(I)OTf	1/2	65	0
2	(*S, S*$_{Fc}$)-**69**	+25	Cu(I)OTf	1/2	90	7 (*S)*

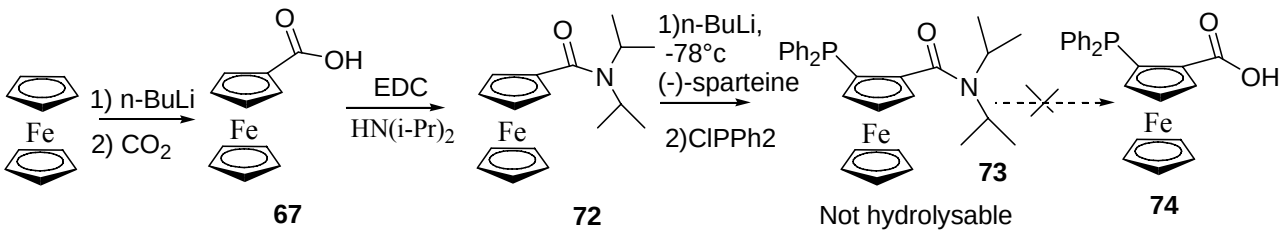
[a] All reactions were carried out under argon using 3 mol% of catalyst in toluene for 12 hours. [b] Determined by GC.

Test for diethylzinc addition to cyclohexenone gave very low enantioselectivity **(**Entries 1,2 Table 9), confirming the mismatched configuration. A possible solution to obtain the other diatereoisomer was the two-step ortholithiation with introduction of an easily cleavable blocking substituent during the first step such as TMS, that forces a second ortholitiation to occur on the opposite face (Scheme 19).



Scheme 19.

Unfortunately, introduction of TMS to form **71** (Scheme 19) was low yielding, probably because of the steric bulk of the TMSCl reagent hindering the approach to the ferrocene.
An enantioselective pathway was thus necessary to obtain the other diastereoisomere (Scheme 20).



Scheme 20.

The ferrocene carboxylic acid **67** was formed as described above. EDC coupling with diisopropylamine afforded the ferrocene amide **72**. The diisopropylamide moiety acts in the next step as ortholithiating group, reported by Snieckus *et al.* to be enantioselective in the presence of

enantiomerically pure sparteine. Reaction with n-BuLi and (-)-sparteine followed by quenching with chlordiphenylphosphine afforded the ferrocene **73** in 90% yield and 97% ee.[55]
Surprisingly, the hydrolysis of the amide did not occur under a variety of strongly basic or acidic conditions, and no procedure has been described by Snieckus.

2.2.3.3 Axially chiral ligands

An interesting variation is the formation of axially chiral ferrocenes. To achieve an axial chirality on a ferrocene, one must block the possible rotation of the two cyclopentadienyl moieties (Figure 32).

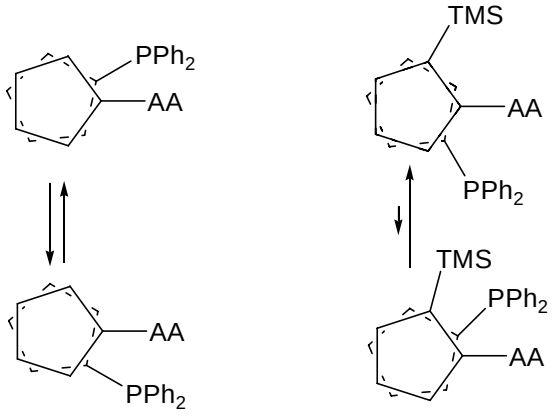
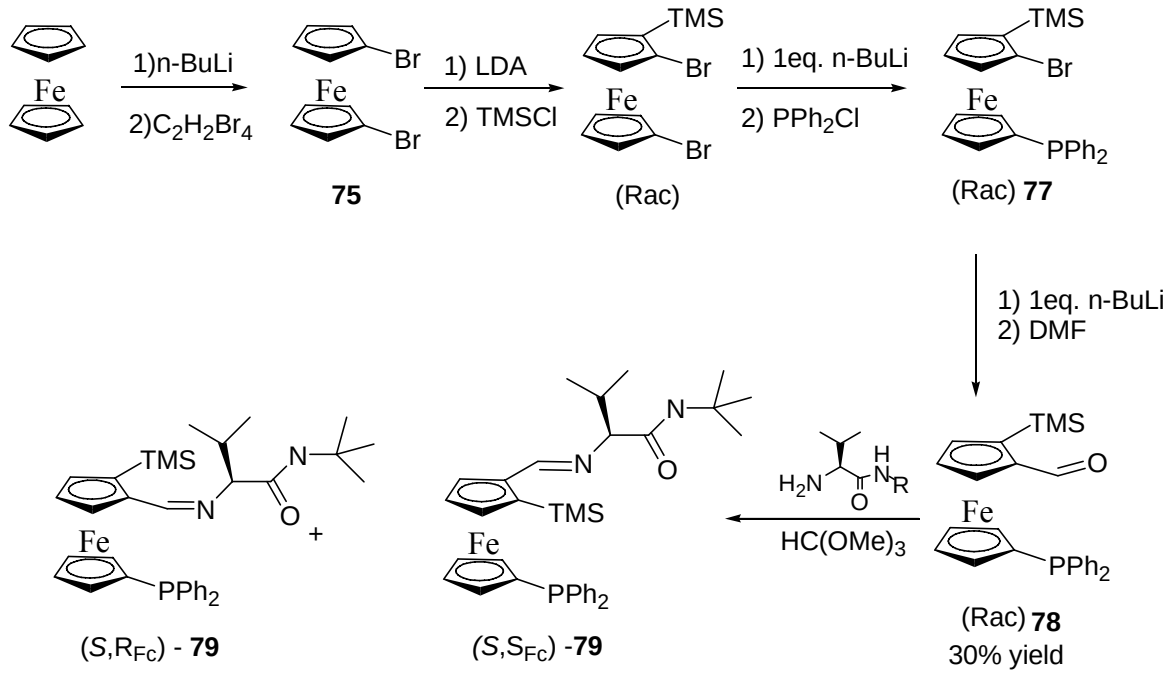


Figure 32.

A bulky substituent such as TMS is thus required to induce steric repulsions upon rotation. The formed ferrocene would thus act as a bridge inducing distortions in the coordination sphere of the copper complex. Here again, because of presence of an additional stereogenic unit on the amino acid side-chain, a diatereoisomeric match/mismatch pair situation could appear and therefore the synthesis of both diatereoisomers is needed. A convenient approach to simultaneous synthesis of the diastereoisomeric pair is depicted below (Scheme 21).



Scheme 21.

Starting from commercially available ferrocene, a bis-lithiation[56] with two equivalents of n-BuLi afforded the 1,1'-dilithioferrocene intermediate that is brominated in the presence of tetrabromoethane to give **75**. The bromo substituent acted as an ortholithiating group upon reaction with one equivalent of LDA at -78 °C in THF.[57] Quenching with TMSCl afforded the racemic TMS substituted dibromo ferrocene **76**. Reaction with one equivalent of n-BuLi at -78 °C followed by quenching with chlordiphenylphosphine allows the substitution of the bromo for the diphenylphosphine moiety exclusively at the less hindered cyclopentadienyl ring to give **77**. A second lithiation with n-BuLi followed by quenching with DMF finally gave the desired aldehyde **78** in 30% overall yield. Enantiomeres were separated on chiral preparative HPLC because the formed diastereoisomeric ligand pairs upon coupling with the functionalised amino acids **79**, could not be separated by silica-gel chromatography.

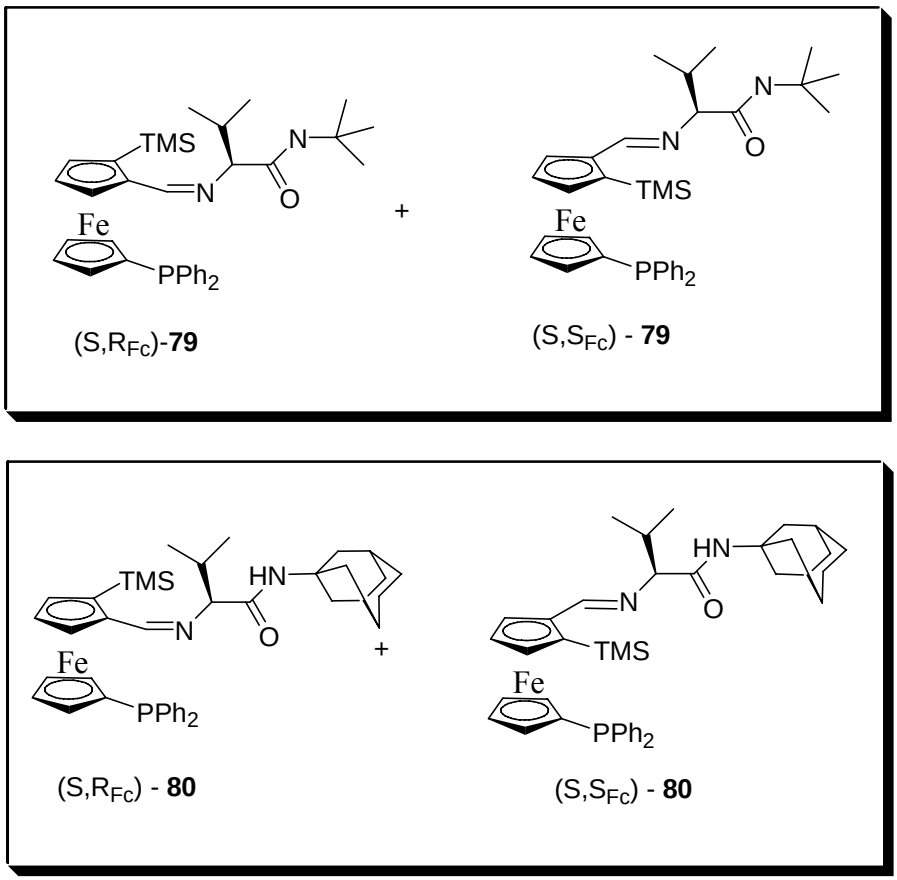


Figure 33.

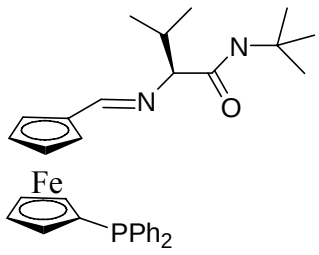
The valine derived ligands **79** and **80** (Figure 33) were synthesised and the catalyst formed in situ with a 2/1 ligand /metal ratio. Catalysts were tested for diethylzinc conjugate addition to cyclohexenone in toluene for 12 hours.

Table 10. Ligands enantioselectivity for Cu-catalysed diethylzinc addition to cyclohexenone[a]

Entry	Ligand	Temp. (°C)	Copper salt	Conv. (%)[b]	*ee* (%)[b]
1	(S,S_{Fc})-**79**	-30	Cu(I)OTf	95	80(R)
2	(S,R_{Fc})-**79**	-30	Cu(I)OTf	89	10(R)
3	(S,S_{Fc})-**79**	+25	Cu(I)OTf	94	78(R)
4	(S,R_{Fc})-**79**	+25	Cu(I)OTf	80	5 (R)
5	(S,S_{Fc})-**80**	-30	Cu(I)OTf	80	81(R)
6	(S,R_{Fc})-**80**	-30	Cu(I)OTf	95	15(R)
7	(S,S_{Fc})-**80**	+25	Cu(I)OTf	95	80 (R)
8	(S,R_{Fc})-**80**	+25	Cu(I)OTf	90	23(R)
9	**81**	+25	Cu(I)OTf	92	58 (R)

[a] All reactions were carried out under argon using 3 mol% of catalyst in toluene for 12 hours. [b] Determined by GC.

As previously, a match/mismatch relation was observed between diastereoisomeric pairs (Entries 1/2 and 5/6 Table 10). The obtained enantioselectivities were generally lower than those with planar chiral ligands **61**. Noteworthy, the enantioselectivity at low temperatures (-30 °C) is better than that at room temperature. This might be due to a temperature dependent conformational change by rotation of the cyclopentadienyl rings, thus loosing the ligands rigidity. The ligand **81** without TMS on the ferrocene has also been synthesized by skipping the TMS introduction step (Figure 34). Catalysis with **81** has demonstrated the expected effect of TMS since its enantioselectivity is situated between that of the two diastereoisomers having the TMS group (Entry 9, Table 10).



81

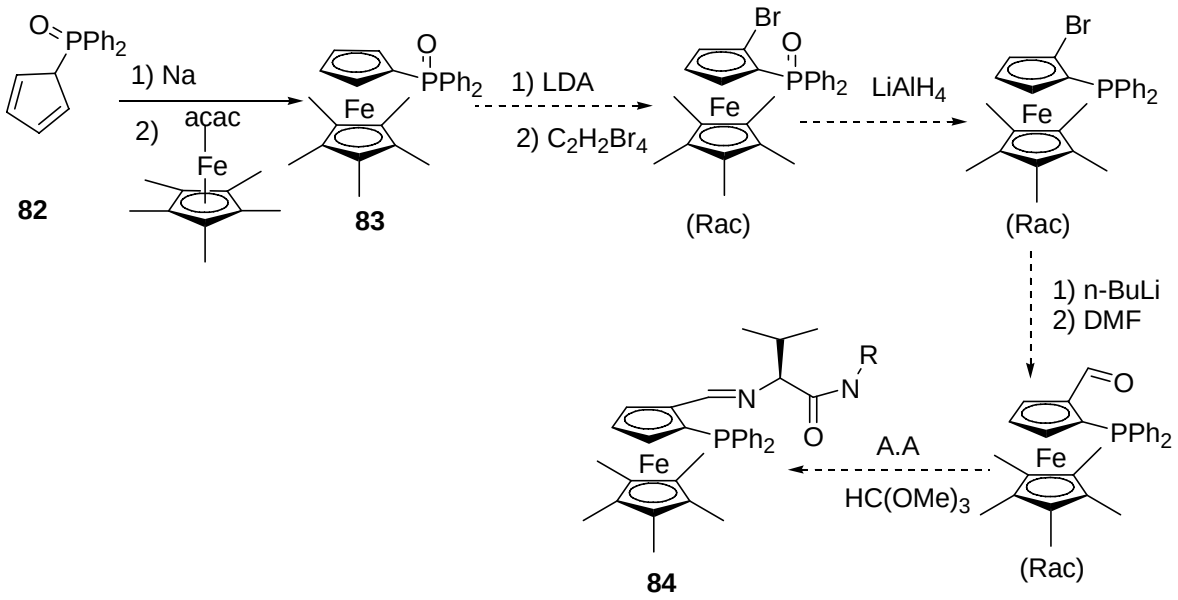
Figure 34.

2.3 Discussion

Among the ferrocenyl derived ligands, the planar chiral ligands **61** showed the best enantioselectivities. An important match/mismatch effect could be observed, indicating as expected that the chirality on the ferrocene has a strong influence on the overall enantioselectivity. It is therefore expected that this type of ligands could find applications in numerous catalysed reactions, and present an interesting starting point for further investigations.

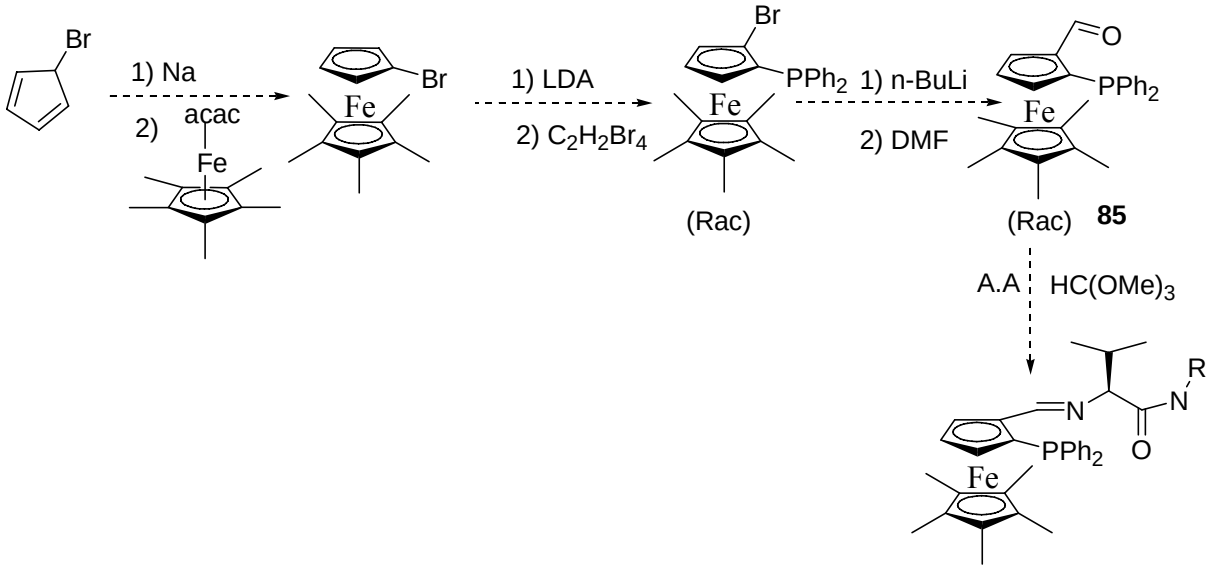
Exchange of the lower cyclopentadienyl ring for a pentamethylcyclopentadiene would be of interest since Cp* has different electronic and steric properties. Unfortunately, substitutions at the upper cyclopentadiene ring of CpFeCp* derivatives such as **83** are more difficult than on Cp_2Fe ferrocenes. Thus, a similar pathway to that depicted in Scheme 14 for ferrocene is impossible. An ortholithiating group that favors further substitutions is thus necessary.[58] This can be obtained by functionnalisation of a free cyclopentadiene with the desired ortholithiating group followed by formation of the ferrocene with Cp*. Diphenylphosphine oxide has been reported to act as ortholithiation directing group[58] and was thus chosen for the synthesis. Formation of the cyclopentadienyl-diphenylphosphite **82** was achieved by reaction of sodium cyclopentadienyl with chlorodiphenylphosphine oxide. Further reaction with sodium forms the functionalised

cyclopentadienyl anion that was reacted with Cp*Fe(acac) to form the desired ferrocene **83**. The introduced phosphine oxide could then be exploited as ortholithiating group. Unfortunately, bromination with tertrabromoethane was unsuccessful, as well as with other brominating agents (Scheme 22).



Scheme 22.

A different synthesis starting with bromocyclopentadienyl could be an alternative (Scheme 23). The bromine, that was indeed reported as a possible ortholithiating group and used as such for the synthesis of axial chiral ferrocenes **79**, could be used for introduction of a diphenylphosphino group. Subsequent lithiation and quenching with DMF would produce the desired phosphinoaldehyde **85.**



Scheme 23.

3. Muscone Synthesis

3.1 Introduction

Fragrances have an ancient history in most civilizations. Employed for spiritual or therapeutic purposes, they were extracted from plants or animals for ages. Chemistry in the second half of the 19th century opened the way to synthetically synthesised fragrances such as vanillin **86** or coumarin **87** (Figure 35).

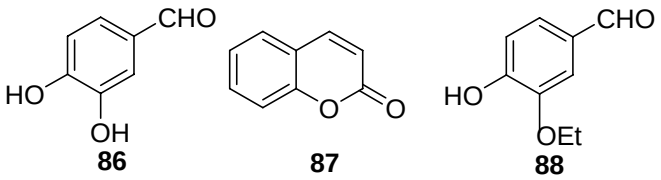


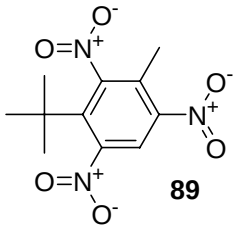
Figure 35. Fragrances

Synthesis of fragrances gained in interest with the development of the fragrance industry and demand for molecules with new odor characteristics obtained initially by modifications of existing molecules, as for example ethyl-vanillin **88** that has better olfactive characteristics than its natural counterpart **86** (Figure 35). Also, avoiding fastidious isolation from plants allowed drastic reduction in cost and improvement in quality. For example, to obtain 1kg of jasmine fragrance, extraction of eight million jasmine flowers is necessary. As well, 100g strawberry flavor would be extracted from 1000kg strawberries.(62) Musk odorants were extracted since antiquity from the male musk deer *Moschus moschiferus*, today an endangered specie on the WWF list of protected animals.

Figure 36. *Moschus Moschiferus*

Musk odorants are a family of molecules possessing a 'very nice, warm, sweet, animal and powerful'(63) smell, of central importance for perfume constitution thus forming its bottom note being long-lasting, tenacious and substantive. The musks synthesis story began at the end of the

nineteenth century with the serendipitous discovery of 2-tert-butyl-4-methyl-1,3,5-trinitrobenzene **89** (Figure 37) by Albert Bauer whilst he was experimenting with the synthesis of TNT-derived explosives by Friedel-Crafts reaction of *tert*-butyl-halides on trinitrotoluene.[64]



89

Figure 37.

The formed product **89** posses a characteristic musky odor, and was a commercial success under the name of 'Bauer Musk'. Soon after, Ruzicka identified the macrocyclic ketone (*R*)-(-)-muscone (3-methylcyclopentadecan-1-one) **90** as the natural main odorous principle of musk pod.[65] Nevertheless, synthetic difficulties and comparatively high price did not allow him to supersede the nitro-musks **91** (Figure 38), even though their photochemical reactivity caused discoloration and skin sensitisation. These problems led to the developpement of new molecules, polycyclic compounds (**92**, **93**, **94**, Figure 38), that are still today the most used musk odorants.

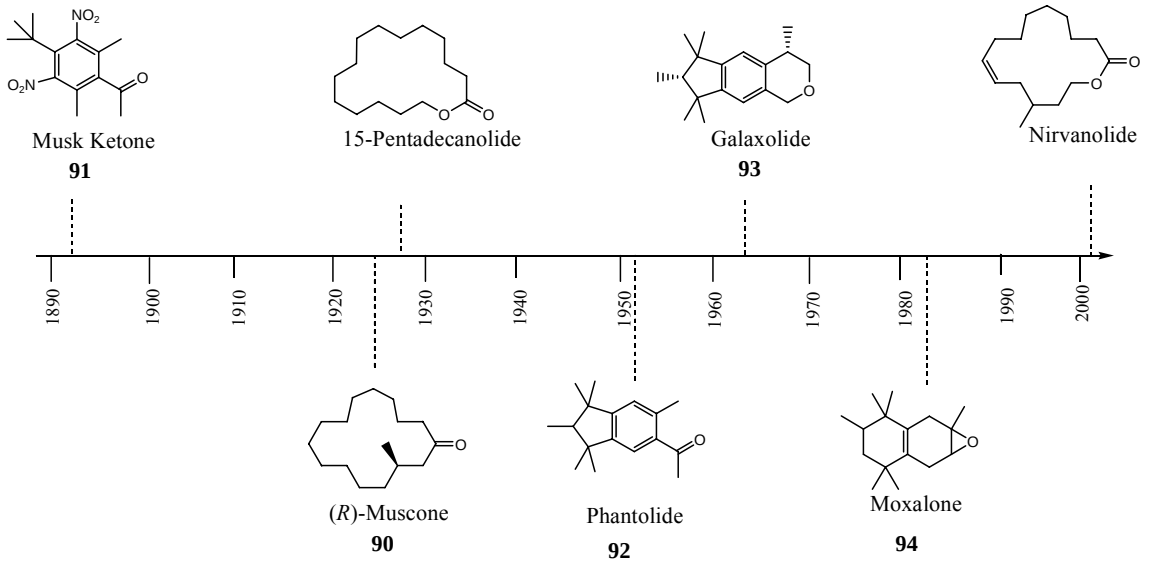


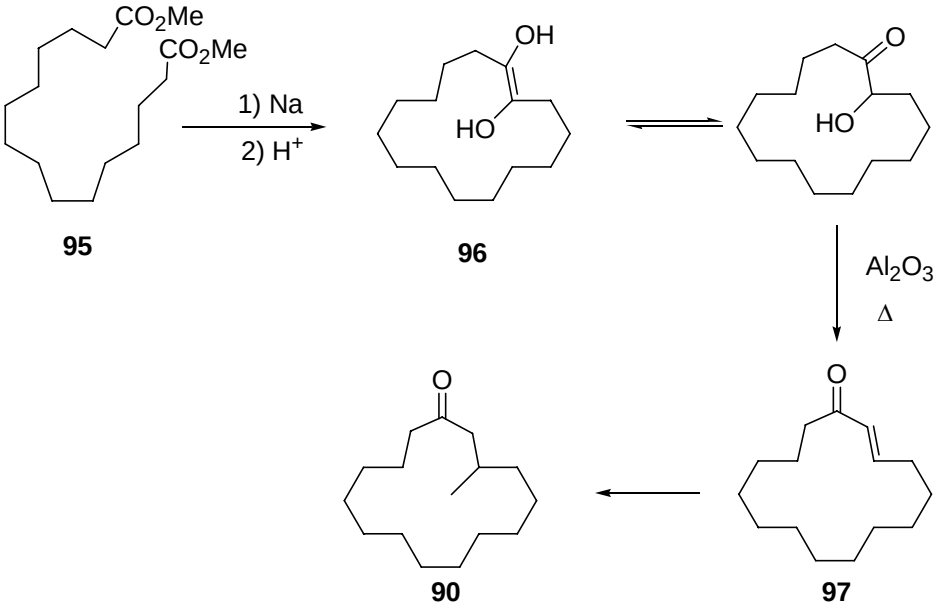
Figure 38. Development of musk fragrances.

However, use of nitro or polycyclic musks began recently to decline due to their toxicity and low biodegradability.[66] Today the importance of macrocyclic musks is increasing again because of their interesting biodegradability properties.[67] Their main handicap remains the relatively high price compared to nitro or polycyclic musks, due to the complexity of synthesis of the macrocyclic

large ring (14-17 membered rings). Indeed, high dilution (<1nM) is generally required to avoid dimerization or polymerization. Recent macrocyclisation strategies initially developed for the synthesis of antibiotic macrolides[68] have been exploited in the last 20 years to overcome these difficulties. Focusing on the synthesis of racemic muscone, some pioneering syntheses deserve particular attention. Key steps are generally macrocyclisation or ring expansion.

3.1.1 macrocyclisation

As mentioned above, the main problem generally occurring when attempting a macrocyclisation reaction is the competitive dimerisation or polymerisation. High dilutions are a possible solution but are not practical on industrial scale. Alternative solutions that circumvent that problem were brought by surface reaction on metal as the acyloin condensation reaction of α,ω-diesters on sodium metal (Scheme 24). Concentration of around 1M could be employed.[69]

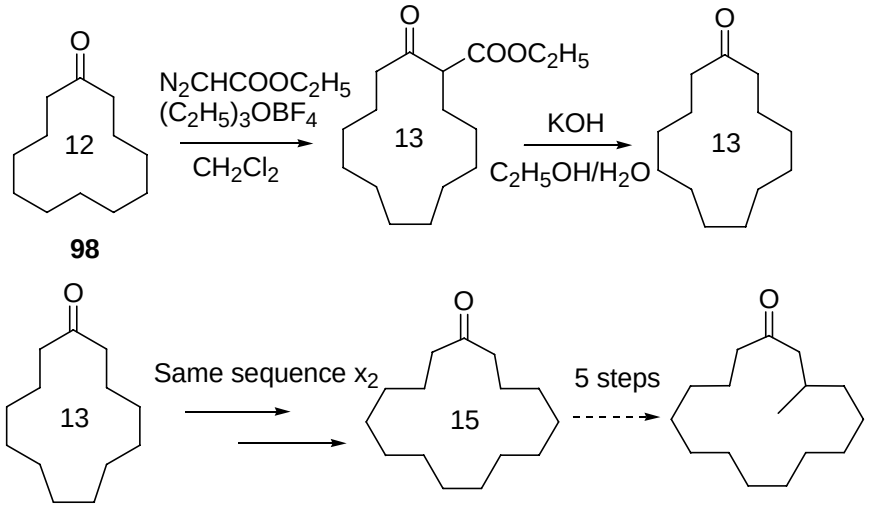


Scheme 24. Acyloin condensation

The intramolecular reaction of 1,15 pentadecadionate **95** provided **96** which was dehydrated over alumina to the α,β-unsaturated ketone **97**. The enone **97** could be then converted to racemic muscone **90**.

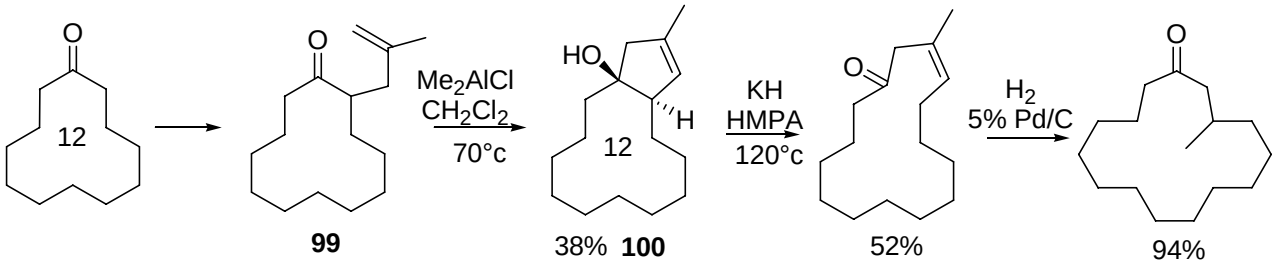
3.1.2 Ring enlargement

Ring enlargement became an interesting option for muscone synthesis when cyclododecanone **98** came to the market as one of the downstream products of the butadiene oligomerisation. Interesting but low yielding sequential ring expansions chemistry[70] followed by five step dehydratation sequence[71] has first been applied (Scheme 25) but more interesting and practical was the Firmenich ring expansion process (Scheme 26).



Scheme 25. Sequential ring expansion

The synthesis involves two key steps: a Lewis-acid mediated intramolecular ene reaction (**99)** and the β-cleavage of the potassium alkoxide derived from **100** to the macrocyclic muscone.[72]



Scheme 26.

Nevertheless, synthesis of enantiomerically pure (*R)*-muscone remained challenging. The reason why enantioselective synthesis is necessary is that enantiomers have generally different biological

properties due to interactions with peptide-built biological receptors made of chiral (L)-amino acids (Figure 39).

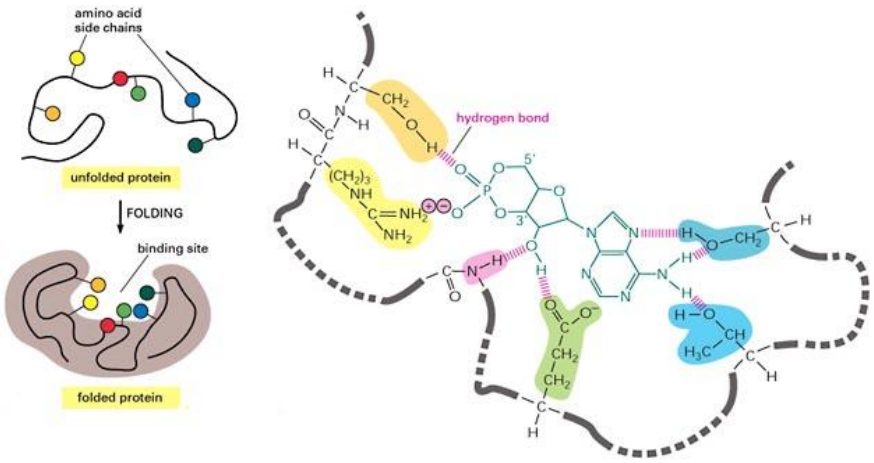
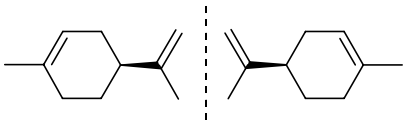


Figure 39. Interaction with receptor

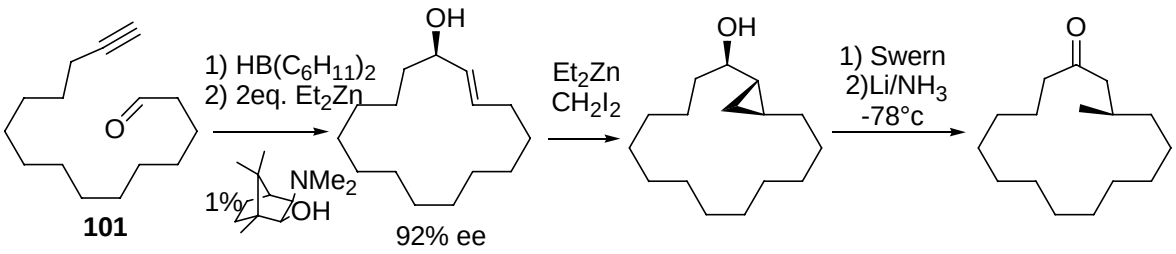
A well known example, (+)-limonene smells of orange whereas (-)-limonene has a lemon fragrance (Figure 40).



(-)-limonene (+)-limonene

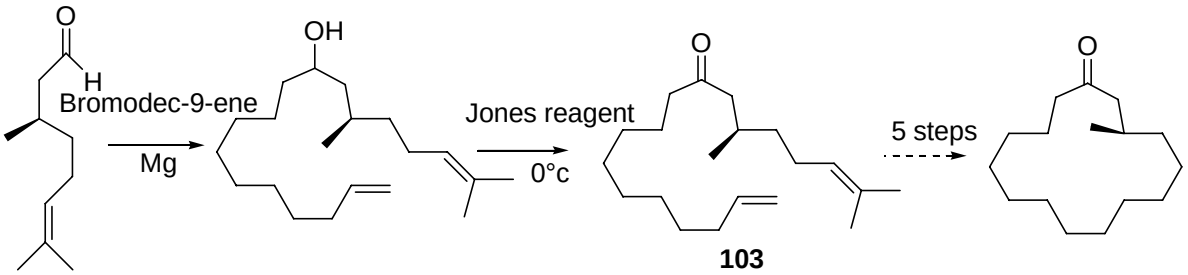
Figure 40.

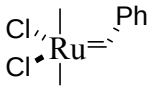
In the case of muscone, the (-)-(*R*)-muscone was described as 'very nice, rich and powerful' with an odor threshold of 61 ppb whereas the musk note of its (+)-(*S*)-enantiomer was found to be 'poor, and less strong' with an odor threshold of 233 ppb.[73] Despite these characteristics, only very few enantioselective syntheses have been achieved, and generally suffer from excessive length, low chemical and optical yield or scarcity of starting material. Nevertheless, some interesting syntheses have been achieved, such as Oppolzer's synthesis (Scheme 27).[74]



Scheme 27.

Starting with 14-pentadecynal **101**, hydroboration followed by transmetallation with diethyl zinc in presence of 1% (+)-DAIB (3-exo-(dimethylamino)-isoborneol) allowed the ring closing with good substrate concentration (0.05M). The synthesis is then completed by a stereoselective Simmons-Smith cyclopropanation followed by an oxidation and reduction step. Also remarkable, the ring closing olefin metathesis using Grubbs catalyst **102**,[75] inspired from the strategy employed by Fürstner in the synthesis of (+)-12-methyl-13-tridecanolide.[76] The source of chirality was found in (+)-citronellal (Scheme 28)

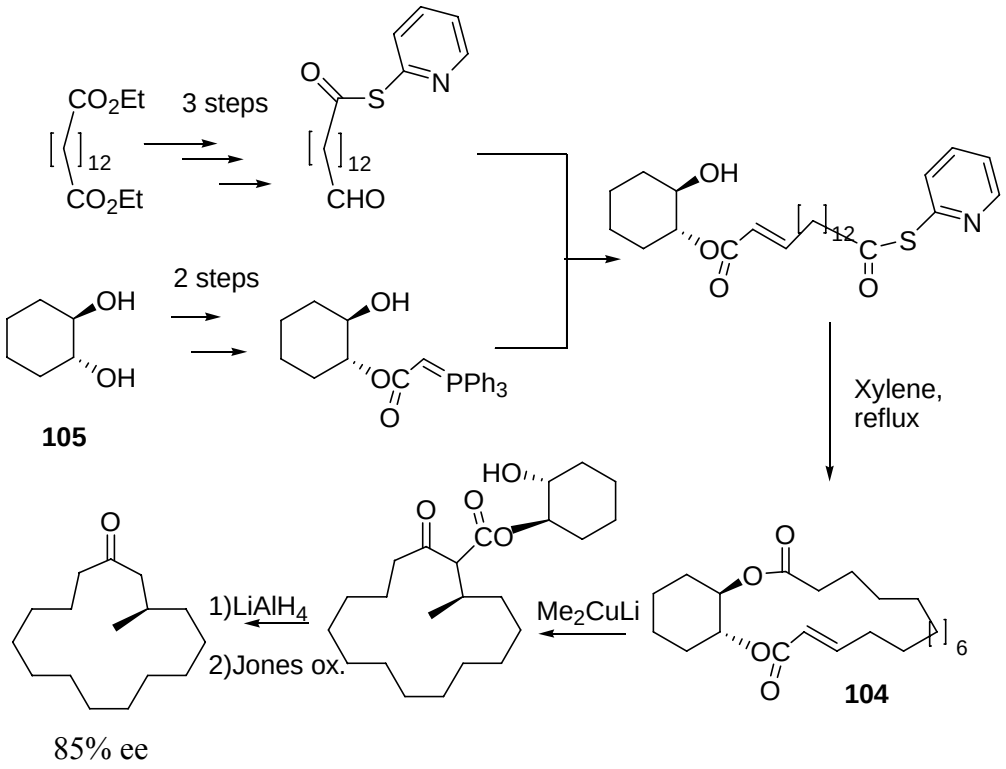




102

Scheme 28.

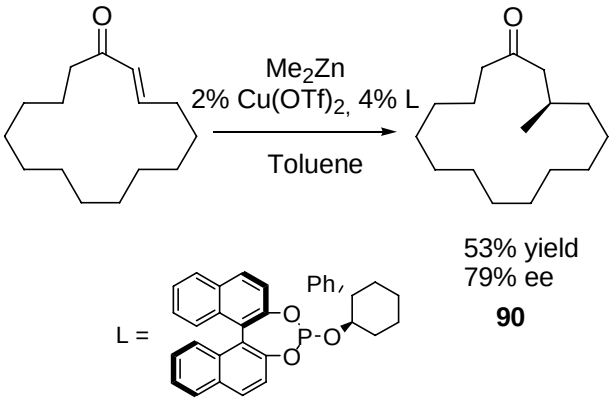
Unfortunately, the direct cyclisation of **103** with 5 mol% catalyst failed due to the inertness of ruthenium alkylidene **102** toward RCM of terminally substituted olefins,[77] implying five further steps to remove the olefinic gem-dimethyl substitution with diene **103**. Also notable, Sakai's stereocontrolled synthesis via diastereoselective conjugate addition to a cyclic α,β-unsaturated ester of (*R,R*)-cyclohexane-1,2-diol **104** accompanied by spontaneous Dieckmann condensation (Scheme 29).[78]



Scheme 29.

The high diastereoselectivity in dimethyl cuprate conjugate addititon to diester **104** was found to be due to face selectivity. The two ester groups, which are positioned close to each other, subsequently undergo Dieckmann cyclisation. Nevertheless, the intramolecular transesterification[79] had to be carried under high dilution conditions to give **104** in modest yield (57%).

(*R)*-Muscone of high optical purity could be obtained by non-catalytic conjugate addition of dimethyl cuprates with chiral ligands derived from camphor.[80] More desired catalytic synthesis through copper-catalysed 1,4-additions were found to be only moderately enantioselective (Scheme 30).[81] Nevertheless, the reaction attracted our attention due to its potential to lead to (*R*)-muscone in an atom economical manner.

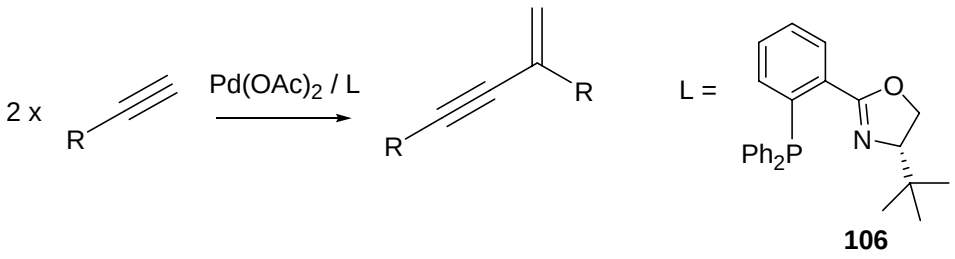


Scheme 30. Copper-catalysed muscone synthesis

3.2 Synthesis

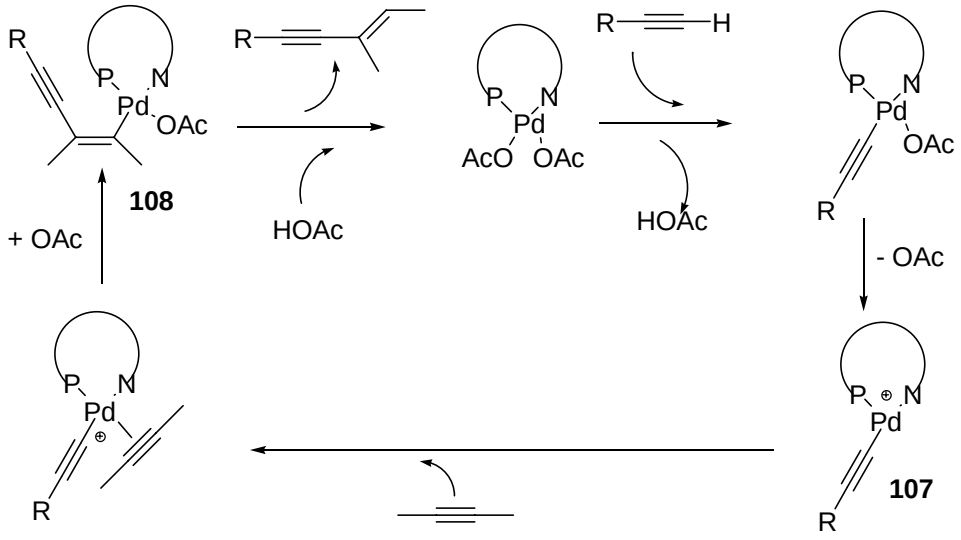
3.2.1 Palladium-Catalysed Macrocyclisation.

Palladium-catalysed macrocyclisation was recently reported from our laboratory.[82] Phosphine-oxazoline ligands **106** were found to be very effective for palladium-catalysed homo and cross-coupling of alkynes (Scheme 31), affording excellent yields, high turnover numbers and high regiocontrol. The obtained enynes are valuable precursors to a variety of functionalised compounds, and in particular the muscone macrocycle.



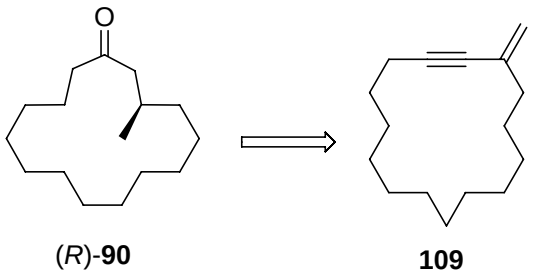
Scheme 31. Palladium-catalysed coupling of alkynes

The presumed mechanism[83] involves the formation of an palladium(II)-alkynyl complex **107** followed by coordination of a second alkyne and carbometalation leading to **108** (Scheme 32). The high regioselectivity for the internal insertion on the coordinated alkyne is related to steric and electronic effects in formation of the most stable Pd-C bond.



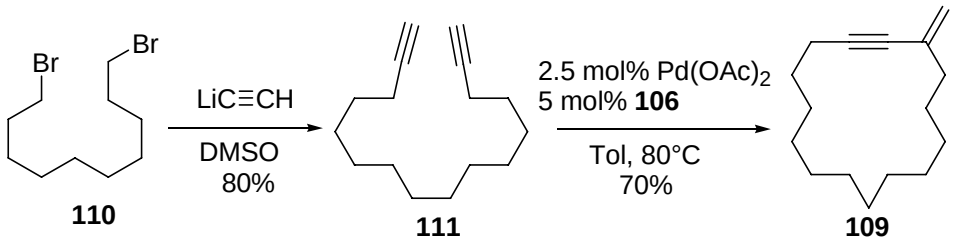
Scheme 32. Mechanism

In particular, 3-methylen-cyclopentadec-1-yne **109** was considered for the synthesis of (*R*)-muscone **90** (Scheme 33).



Scheme 33.

Using a dilute solution of 5 mol% of ligand **106** and 2.5 mol% of $Pd(OAc)_2$ (0.25mM), a solution of hexadeca-1,15-diyne **111** (0.11M) was slowly added via a syringe pump over 24h in order to favor the cyclisation over the competing intermolecular reaction (Scheme 34).



Scheme 34.

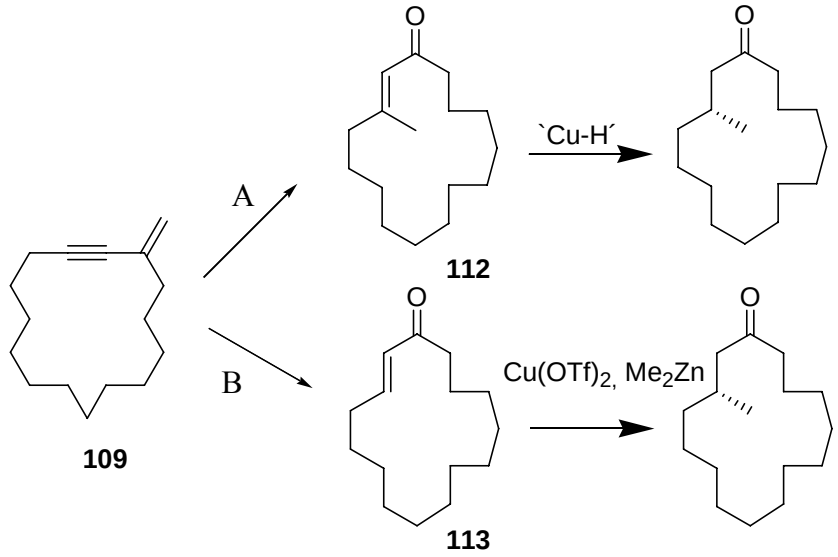
The enyne product **109** was obtained in 70% yield.[(84)] The possibility to reach higher yields by testing solvents of different viscosity was explored. The viscosity could have a direct influence on the ratio between intra- and intermolecular reaction through reduced molecular agitation thus hindering an approach of neighboring molecules.

Table 11. Solvents influence

Solvent	Viscosity (mPa.s)	Dielectric constant (ε)	Yield %[a] (Time h)
Hexane	0.31	1.88	70 % (48 h)
Toluene	0.59	2.38	70 % (96 h)
Cyclohexane	1.0	2.24	85% (12 h)
1,4-dioxane	1.2	2.25	0% (12 h)

[a] Determined by GC.

The reaction was tested in hexane, dioxane and cyclohexane, a solvent with similar solvating properties to toluene but higher viscosity constant (Table 11). The reaction was performed using 4 mol% of $Pd(OAc)_2$ and 2 equivalents of ligand **106** in 2l of solvent (0.2mM). The hexadeca-1,15-diyne in solution in 25ml of solvent (0.36M) was added together with 5% of tridecane as internal standard by syringe pump over 8 hours. The reaction was followed by taking samples every hour and monitoring conversion by G.C. Results indicated that whereas the reaction was slow in toluene, cyclohexane as solvent increased the conversion and reaction speed, reaching 85% conversion in 12 hours. Having the macrocycle **109** in hands, several strategies to obtain the muscone macrocycle were possible (Scheme 35).

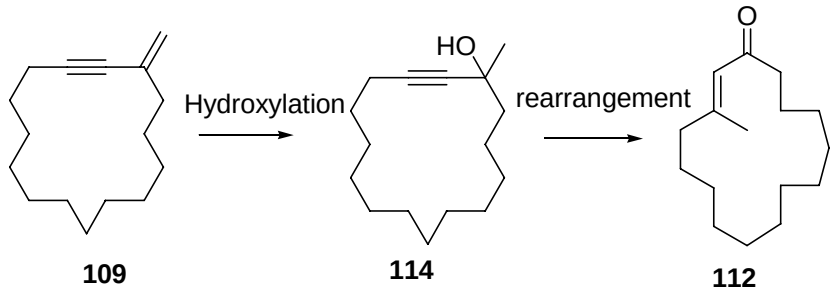


Scheme 35. Possible pathways

Two different pathways were considered for converting **109** to muscone. Pathway A (Scheme 35) takes the 3-methylcyclopentadecenone **112** as intermediate for a copper-hydride catalytic enantioslective 1,4-addition. Pathway B goes through cyclopentadecenone **113** for an copper-catalysed 1,4-addition of dimethylzinc.

3.2.2 Copper-Hydride Conjugate Addition

A straightforward possible route to 3-methylcyclo-pentadecenone **112** involves hydroxylation of enyne **109** to give intermediate **114** that could undergo rearrangement to enone **112** (Scheme 36)



Scheme 36.

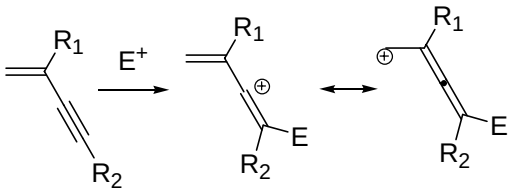
Hydroxylation by electrophilic adition of acids to obtain **114** was explored. The reaction was expected to ocur chemo- and regioselectively on the double bond in a Markovnikov manner. Indeed, alkenes are more reactive than alkynes toward electrophilic addition. This can be explained by the different stabilities of the cations being formed in the rate-determining step of addition, *i.e.*. substituted carbonium ions *vs.* substituted vinyl cations.[85] Surprisingly, the olefinic moiety of the enyne **109** did not react with the employed acids (Table 12).

Table 12. Reactivity of enyne **109** toward electrophilic addition of acids

Entry	Solvent	Acid	Temp. (°C)	Time (h)	Conv. (%)[b]
1	Hexane	4eq. HOTf	-78	12	0
2	Hexane	4eq. HOTf	0	12	0
3	CH_2Cl_2	4eq. HOTf	23	12	0
4	*i*-propanol	4 eq. HOTf	Reflux	12	0
5	CH_2Cl_2	4eq. TFA	23	12	0
6	Hexane	5eq. H_2SO_4	23	24	0
7	CH_2Cl_2	5eq. H_2SO_4	23	24	0
8	CH_2Cl_2	6 eq. AcOH	23	24	0
9	*i*-propanol	4 eq. AcOH	Reflux	12	0

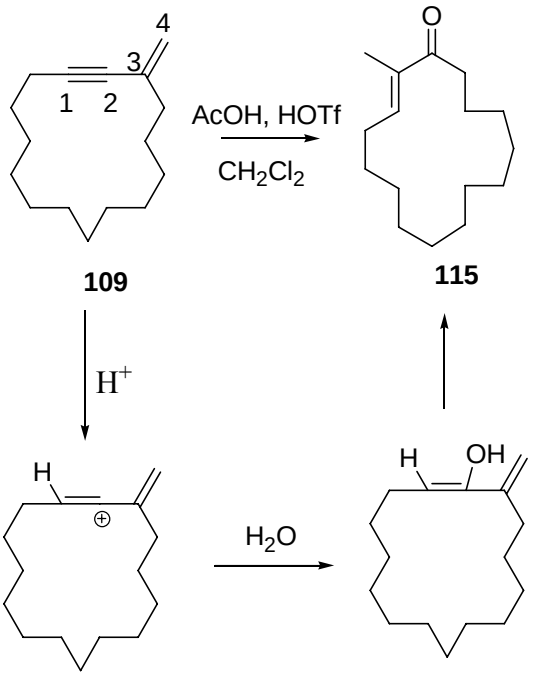
[b] Determined by GC.

Indeed, enynes were found to react differently from isolated olefins. Because of the polarization of the conjugated enyne system, the attack of electrophiles is hindered and takes place regioselectively at C-1 of the carbon-carbon triple bond thus forming a vinyl cation near the C-C double bond so as to be stabilised by the rest of the system (Scheme 37).[86]



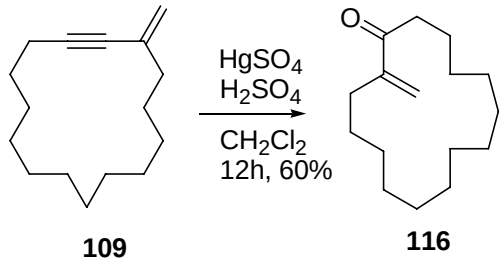
Scheme 37. Reactivity of enyne systems toward electrophiles

Only the reaction conducted in presence of acetic acid and trifluoromethanesulfonic acid in dichloromethane gave the enone **115** in high yields (70-80% yield, Scheme 38). The reaction, referred to as the Rupe rearrangement,[87] is an acid-catalysed reaction occurring by electrophilic addition on C-1 of the alkyne **109** to form stabilized vinylcation. Nucleophilic attack of water on the vinyl-cation forms the enol (tautomeric form of the ketone **115**) with concomitant isomerisation of the exocyclic double-bond to the more stable endocyclic double-bond.[88]



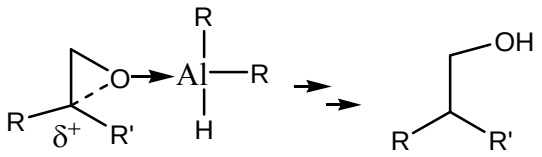
Scheme 38. Reaction with acetic acid and trifluoromethanesulfonic acid

Catalysed hydroxylation with $HgSO_4$ gave the 2-methylenecyclopentadecanone **116** (Scheme 39) that is not suited for muscone synthesis. Oxymercuration of enynes is chemoselective for the acetylenic moiety and regioselective favoring hydration next to the double bond, here also presumably because of stabilization of the intermediate vinyl cation.



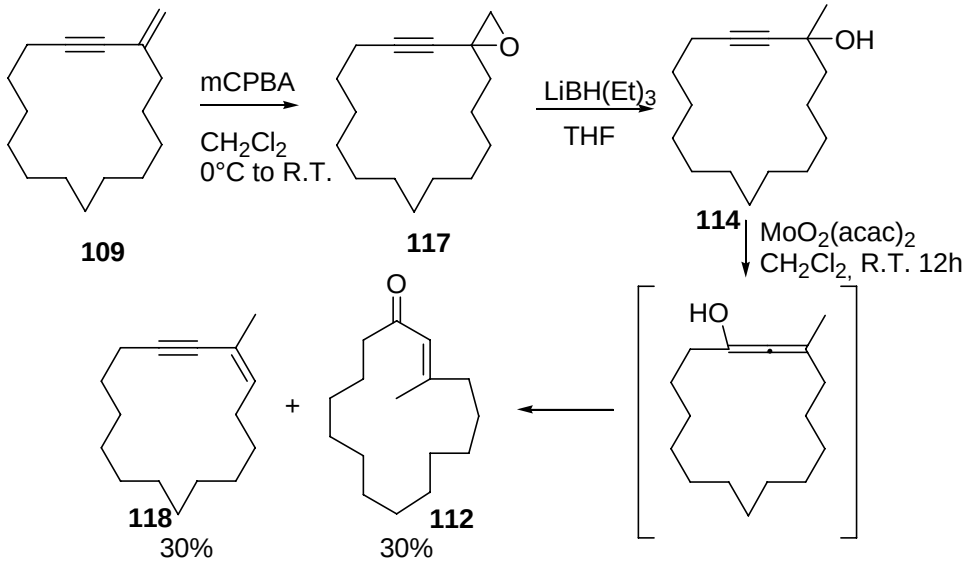
Scheme 39. Reaction with mercuric salts

Epoxydation of conjugate enynes was reported to be chemoselective for the alkene.[89] mCPBA was reacted with the enyne **109** to give the **117** in 70% yield (Scheme 41). The epoxyde was subsequently opened regioselectivly on the less hindered side by $LiBEt_3H$ ('super hydride'), giving the desired carbinol **114**. Interestingly, $LiBEt_3H$ exhibited the opposite regioselectivity to DIBAL or $LiBH_4$, that were reported to form the less substituted alcohol, presumably because of aluminium coordination on the epoxide favoring an S_N1-type pathway (Scheme 40).[90]



Scheme 40. Aluminium coordination on epoxide

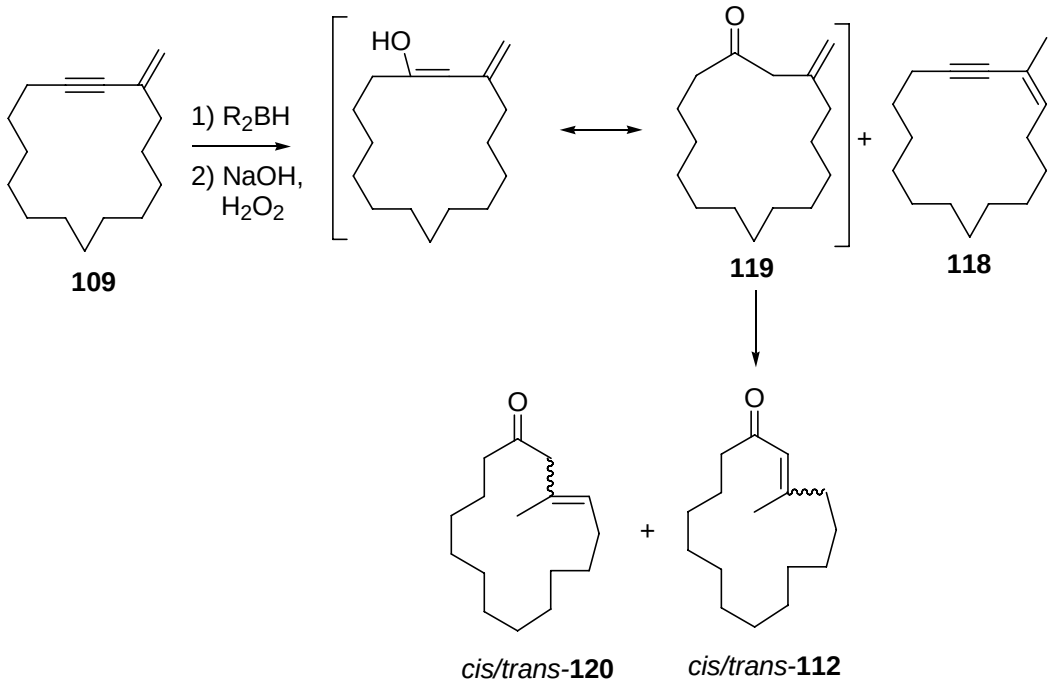
The alcohol rearrangement occurred with 20% $MoO_2(acac)_2$ in dichlormethane at room temperature for 12 hours (Scheme 41).[91]



Scheme 41.

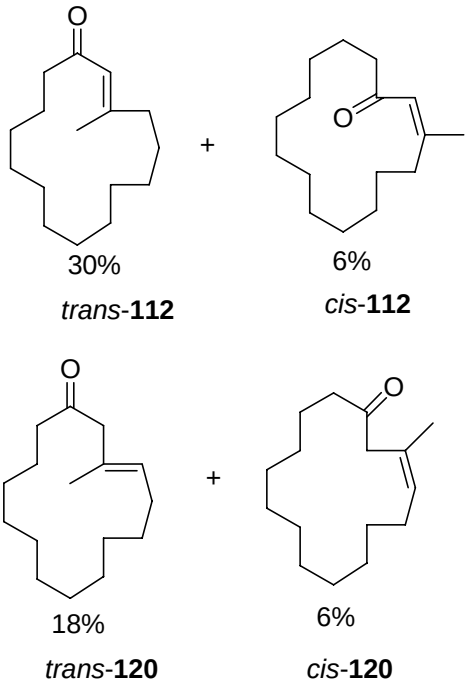
The expected 3-methylcyclopentadecenone **112** was obtained in 30% yield, accompanied by enyne **118**, probably resulting from dehydration of the carbinol **114** to the internal alkene. Noteworthy, a Meyer-Schuster rearrangement could also be possible for the isomerisation of carbinols to enone.[92]

Because of the low yield observed for the formation of 3-methylcyclopentadecenone **112**, synthesis through a more direct pathway, a chemoselective oxidative hydroboration was studied (Scheme 42).



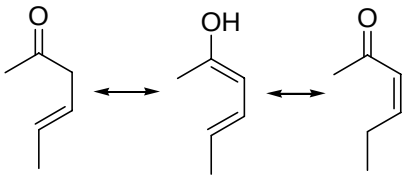
Scheme 42.

Different borane reagents were reported to exhibit very different selectivities toward double and triple bonds.[93] Thus is it possible to achieve preferential hydroboration of the triple bond selectively in presence of the double bond. Disiamyl borane or 9-BBN were reported to be unselective whereas dibromoborane is highly selective for the acetylenic bond and generally regioselective in an anti-Markovnikov manner. Applied to the enyne **109**, the ketone **119** was obtained in 60 % total yield. Macrocyclic enones were previously reported to be flexible enough to form isomers.[94] Here also an isomeric mixture of *cis/trans* α,β-unsaturated and β,γ-unsaturated ketones was obtained, with the *trans* isomer being predominant for α,β-unsaturated ketones **112** and **120** (Scheme 42 and 43). Isomerisation presumably occurs while quenching with NaOH(aq.). Separation of the **112** isomeres from the mixture was possible by silica-gel chromatography using hexane/Et_2O 100/1 eluant. Separation of the *trans*-**112** from the *cis*-**112** isomere could be realised, but 8-10% of contaminant *cis*-isomere was observed.



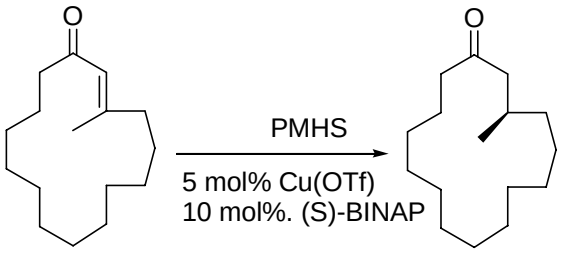
Scheme 43. Cis/trans ratios

Photochemical[95] or acid-catalysed isomerisation of β,γ to α,β-unsaturated ketones has been abundantly documented and showed to proceed through an enol intermediate (Scheme 44).[96]



Scheme 44. Isomerisation

The *trans*-3-methylcyclopentadecenone **112** was isolated by silica-gel chromatography and subjected to copper-catalysed hydride conjugates addition with (*S*)-BINAP as ligand and polymethylhydrosiloxane (PMHS) as a safe and inexpensive hydride source (Scheme 45).[97]



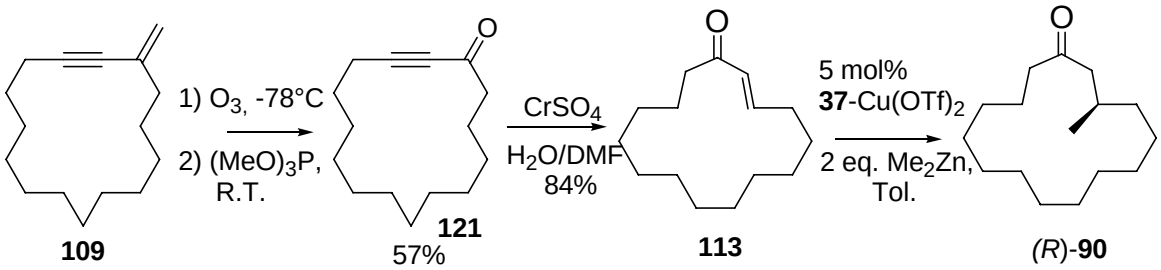
60% ee, 55 % yield

Scheme 45.

The obtained enantioselectivity was low with 60% ee. In addition, the reaction was sluggish giving only 55% yield of (*R*)-muscone **90**. An alternative synthesis was thus needed and, therefore, the path b in Scheme 35 was investigated.

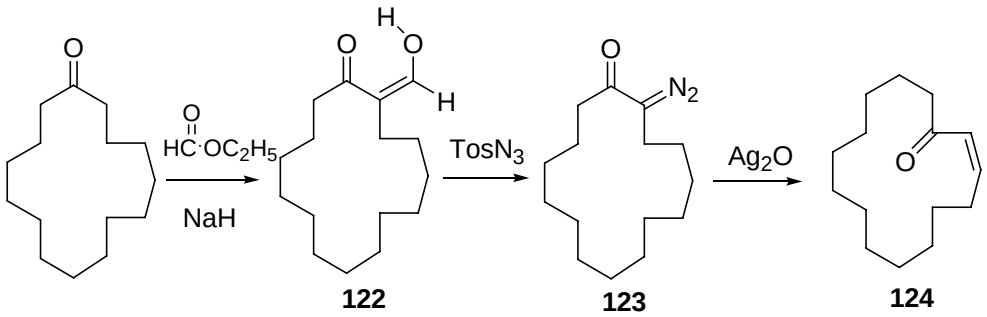
3.2.3 Copper-Catalysed Dimethylzinc Addition

Pathway b illustrate the use of cyclopentadecenone **113** as substrate for a copper-catalysed 1,4-addition of dimethylzinc (Scheme 46).



Scheme 46.

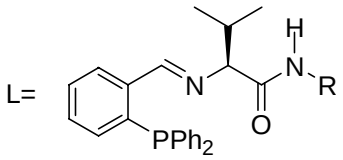
The above described pathway between intermediates **109** and **113** has been investigated by Lücking.[82] The selective oxydation of the enyne double bond in **109** was achieved in 57 % yield by ozonolysis.[99] The treatment of the obtained ynone **121** with aqueous solution of chrome(II)-sulfate in DMF[100] gave the desired *trans*-enone **113** in 84% yield. The *trans* conformation was confirmed by ^{1}H-NMR analysis. The chemical shift in $CDCl_3$ of the β-ethylenic hydrogen is at 6.78 ppm for the *trans* conformation and 6.20 ppm for the *cis*. The *cis*-cyclopentadecenone **124** (Scheme 47) was synthesised following Regitz's procedure[101] in order to examine its reactivity also.



Scheme 47. Synthesis of the *cis*-isomere

Claisen condensation with formic acid ethyl ester gives the α-methylene ketone **122**. The formyl group is acting as α-hydrogen activating group for the reaction with *p*-toluensulfonazide to form the α-diazo ketone **123**. The silver-oxyde catalysed N_2-cleavage gives the *cis*-cyclopentadecenone **124** with high selectivity by a hydride migration on an intermediate carbenoide cyclopentadecanone.

The last and crucial step of the synthesis of **90** in Scheme 46 involved an enantioselective copper-catylsed 1,4-addition of dimethylzinc. Oxazoline-phosphite ligands[13] **29** (Figure 16) were reported to give moderate enantioselectivities (67% ee, 34% yield).[84] Also, a new generation of ligands developed for copper-catalysed 1,4-additions were tested (Figure 41). The major problem encountered was the low reactivity of the substrate, requiring high reaction temperatures. This in turn lowered the yields due to 1,4-addition of the formed zinc-enolate to the starting enone. Maximal temperature to avoid this side reaction was generally observed to be around 20 °C. At lower temperatures, complexes containing the valine-based P-N ligands **37** and **39** were found to be the most reactive and enantioslective (Table 13).



37 R = *t*-Bu
39 R = 1-Adamantyl

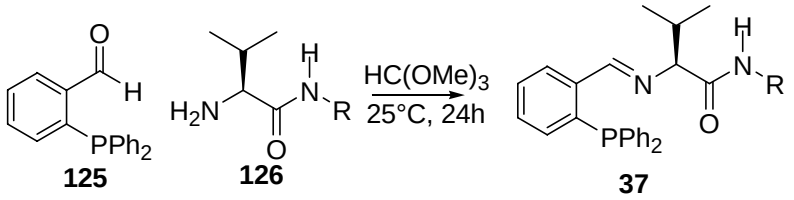
Figure 41.

Table 13. Temperature influence on Cu-catalysed dimethylzinc addition to **113** and **124**[a]

Entry	Substrate	Temp.(°C)	Conv.(%)[b]	Yield (%)[b]	ee (%)[c]
1	**113**	-30	10	10	40 (*R*)
2	**113**	+25	60	55	58 (*R*)
3	**113**	+50	100	20	50 (*R*)
4	**124**	0	60	60	58 (*S*)
5	**124**	+25	70	65	50 (*S*)

[a] All reactions were carried out under argon using 5 mol% of **37**-$Cu(OTf)_2$ in toluene for 24 hours.[b] Determined by GC using tridecane as internal standard. [c] Determined by GC (M.N. Hydrodex β-3P)

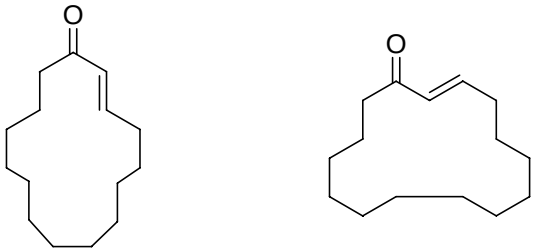
Complexes were formed using a 1/1 Cu(II)/ligand ratio in dichloromethane. Precipitation with pentane led to analytically pure copper complexes. The ligand **37** was synthesised in one step by coupling diphenylphosphine-benzaldehyde **125** with suitably functionalised amino acid **126** in trimethyl orthoformate and used without further purification (Scheme 48).



Scheme 48.

Employing 5 mol% catalyst and 1.5 equivalent of dimethylzinc at -30 °C, the yield obtained was of 10% after 24 hours (Entry 1, Table 13). No trace of dimer could be detected by gas chromatographic analysis. As the reaction temperature was elevated to 25 °C, the yield increased to 55% (Entry 2, Table 13) whereas at 50 °C the yield dropped to 30% due to oligomerisation (Entry 3, Table 13). The optimal temperature with respect to enantioselectivity appeared to be approximatively 25 °C (58% ee, Entry 2, Table 13). The *cis*-cyclopentadecenone **124** appeared to be more reactive than the *trans.* The enantioselectivity slightly increased to 58% ee of the opposite enantiomer (Entry 4, Table 13).

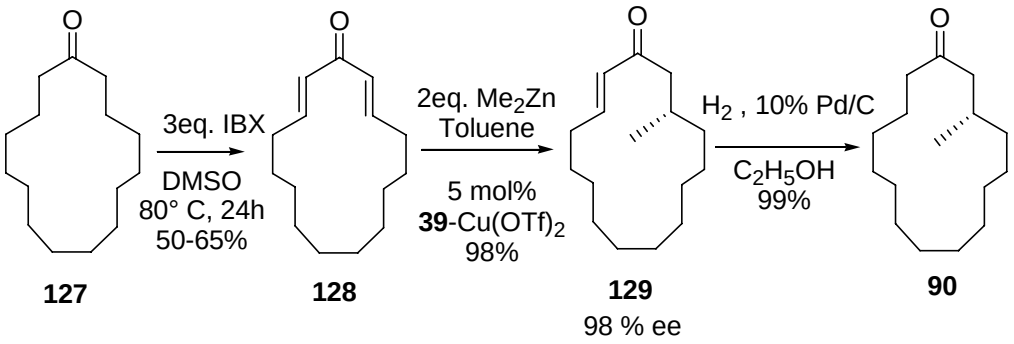
A novel approach was necessary to shorten the synthesis and overcome the lack of reactivity and enantioselectivity. Theoretical calculations supported the hypothesis that the *s-cis* and *s-trans* conformations of the macrocycle (Figure 42) coexists in solution and could be responsible for the moderate enantioselection observed.



s-trans **113** *s-cis* **113**

Figure 42.

The use of cyclopentadeca-2,14-dienone **128** (Scheme 49) provided an elegant solution to the problem. An increase in reactivity and enantioselectivity was observed by lowering the LUMO and creating a more rigid macrocycle. DFT-calculations conducted on possible conformations of **128** favors the *s-trans* conformation. Starting with commercially available cyclopentadecanone **127**, α,β-dehydrogenation with IBX (1-hydroxy-1,2-benziodoxol-3(1H)-1-oxide) following a procedure recently reported by Nicolaou[104] yielded the cyclopentadeca-2,14-dienone **128** in 50% to 65% yield.



Scheme 49.

While the starting ketone **127** was fully consumed, **113** was obtained as a side product, which could be separated by silica-gel chromatography and reused. Yields were found to be dependant on the reaction temperature, substrate concentration and solvents. It is noteworthy that IBX can be regenerated with Oxone®.[105] The dienone **128** was subjected to enantioselective catalytic copper-catalysed conjugate addition of dimethylzinc.

Table 14. Temperature influence on Cu-catalysed dimethylzinc addition to **128**[a]

Entry	Ligand	Temp. (°C)	Conv.(%)[b]	Yield[b]	*ee* (%)[c]
1	**37**	+25	99	85	70 (S)
2	**37**	-30	98	97	95 (S)
3	**39**	-30	98	98	98 (S)

[a] All reactions were carried out under argon using 5 mol% of **37**/**39**-Cu(OTf)$_2$ in toluene for 48 hours. [b]Determined by GC using tridecane as internal standard [c] Determined by GC (M.N. Hydrodex β-3P) and HPLC of **129** on Daicel AS.

The reaction occurred with 5 mol% catalyst and 2 equivalents of dimethylzinc. No trace of 3,14-dimethyl-cyclopentadecanone (resulting from a second dimethylzinc addition) could be detected by gas chromatography. Indeed, the first conjugate addition led to a stable zinc(3-methyl-cyclopentadeca-1,14-dienolate) that did not react further with nucleophiles such as dimethylzinc. Nevertheless, it can react at 25 °C with initial dienone (Entry 1, Table 14). A temperature of -30 °C was found optimal for both yield and enantioselectivity with 98% yield and 98% ee (*S*) (Entry 3, Table 14). The enantiomeric excess was found to be constant over the whole reaction time (Figure 43).

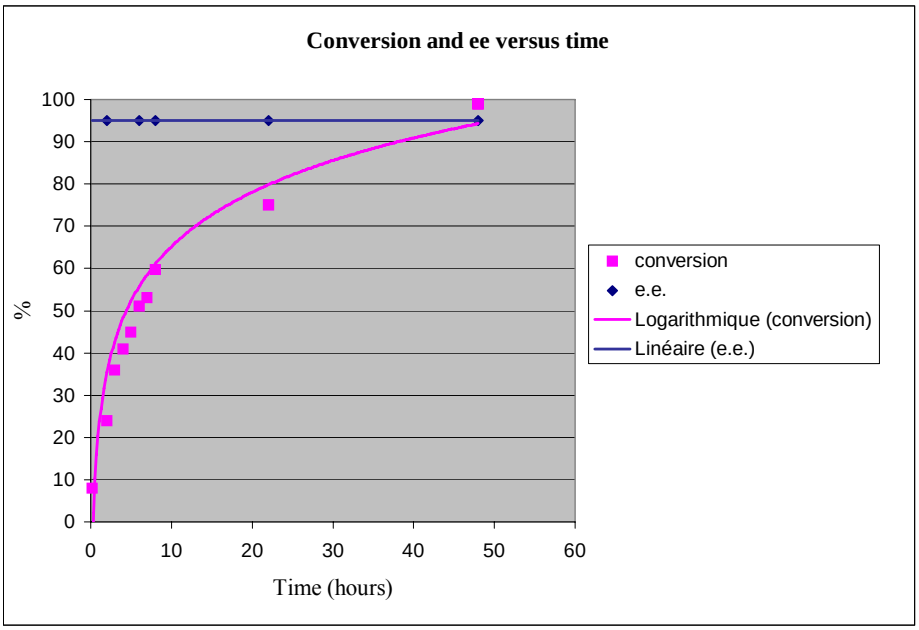


Figure 43. Conversion and ee *vs* time

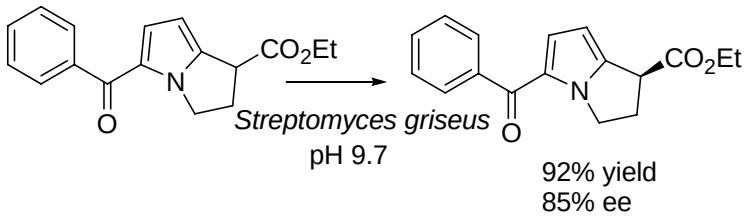
Interestingly, the product had the same (*S)* configuration than that obtained with *cis*-cyclopentadecenone **124** and opposite to that obtained from *trans*-cyclopentadecenone **113**. (*S*)-Muscone was obtained quantitatively after hydrogenation over Pd/C.

3.3 Discussion

A very efficient route to obtain 98% ee muscone has been established. To the best of our knowledge, this is the first example of nearly enantiopure muscone synthesis obtained by a copper-catalysed reaction. Moreover, these results demonstrate that simple amino acid-based ligands are highly efficient for conjugate additions on cyclic disubstituted enones. It can be postulated that the low enantioselection reported in synthesis of muscone by copper-catalysed conjugate additions on enones **113** or **124** could to be due to their facile *s-cis/s-trans* transconformation due to a more flexible conformation compared to the dienone.

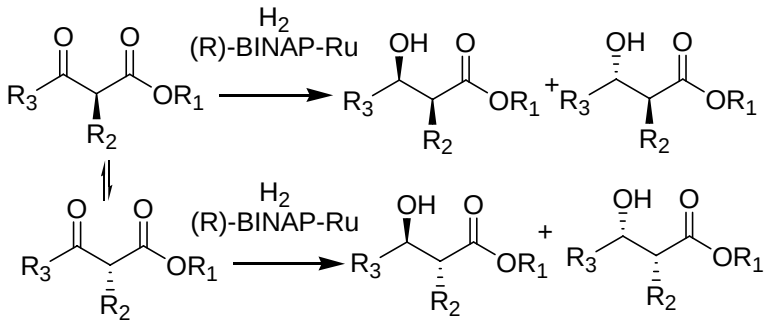
3.4 Kinetic Resolution of Enones

The resolution of racemic mixtures is an important process due to the ease of preparing racemic products and the number of transformations that can be exploited to react one enantiomer in preference to the other.[60] The major limitation of this technique is that the maximum theoretical yield of obtained enantiopure compound cannot be higher than 50%. In some cases, the unreacted enantiomer can be racemised and resubmitted to resolution in order to increase the yield (*dynamic* kinetic resolution). If that is possible, theoretically 100% of the racemic mixture can be converted to one enantiomer. This can be obtained by enzymatic reaction or in tandem with a chemical racemisation to provide enantiopure products. For example, Sih has reported the dynamic kinetic resolution of ethyl ester with the protease *Streptomyces griseus* in alkaline solution with 92% yield and 85% ee (Scheme 50).[60]



Scheme 50.

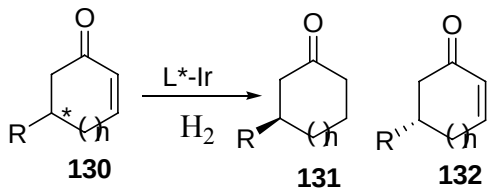
The first reported example of dynamic kinetic resolution by purely chemical means was reported by Noyori in 1989 with a Ru-BINAP hydrogenation catalyst on β-ketoester which readily isomerises via an enol intermediate.[60] The reduction with Ru-BINAP catalyst gave one of the four diastereomers in high de and ee (Scheme 51).



Scheme 51.

Despite the numerous kinetic resolutions or dynamic kinetic resolutions reported, no example of such a reaction on enone substrates by hydrogenation of the C-C double bond has been reported.

In connection with the synthesis of muscone, a possible kinetic resolution of intermediate **129** (Scheme 49) was investigated to increase the enantiomerical purity of the remaining enone. Thus, iridium-catalysed hydrogenation of racemic enone **130** was expected to produce a mixture of optically active ketone **131** and untouched non-racemic enone **132** (Scheme 52).



Scheme 52.

The following substrates were synthesized:

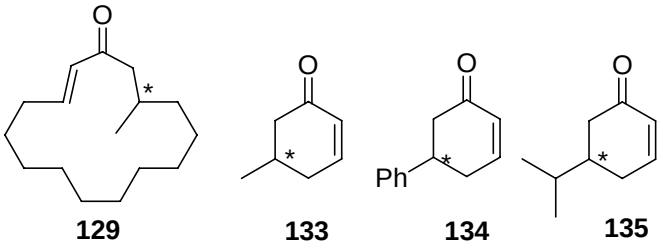
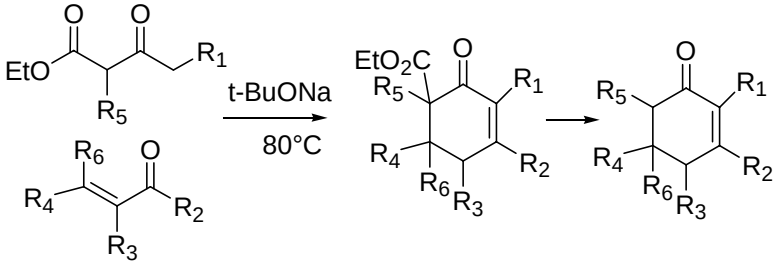


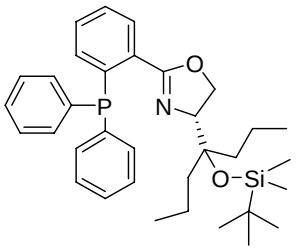
Figure 44.

The substrates **133-135** were obtained by a tandem Michael addition-aldol condensation of β-keto esters to conjugate enones followed by saponification and decarboxylation following the procedure reported by Koo *et al.* (Scheme 53).[60]

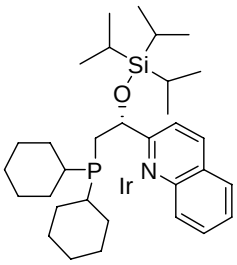


Scheme 53.

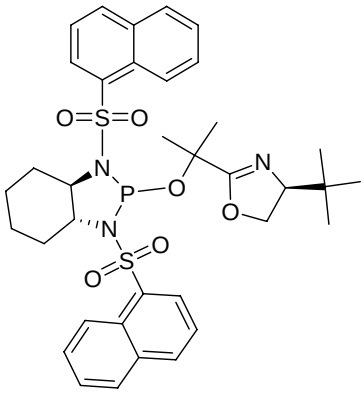
The following ligands synthesised previously in our laboratory and described in the dissertations of I. Escher, J. Blankenstein,K. Zhang, N. Zimmerman and R. Hilgraf were tested for the kinetic resolution of **133** at room temperature in dichloromethane under one bar of hydrogen. The observed selectivity factors S are listed under the employed ligand formulas in Figure 45.



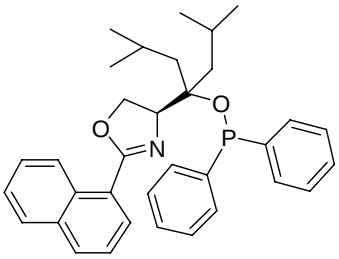
BKS107: S=1.1



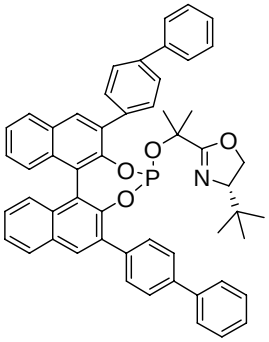
ZMN707: S=1.6



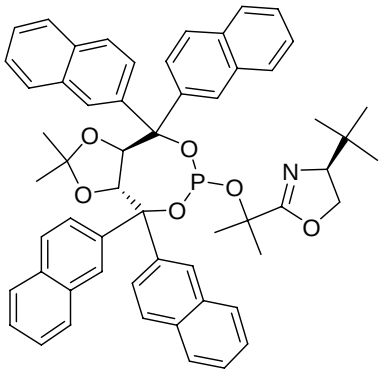
HLR665: S=1.4



BKS054: S=1.2



EHIEC289: S= 1.23



HLR572: S= 1.3

Figure 45. Selectivities (S) on substrate **133**

The reaction conditions were optimized for 5-methylcyclohexenone **133** with the iridium complex formed from ligand ZMN707 under 25 bars of hydrogen. Solvents were found to have an important influence on the selectivities, with aprotic apolar solvents giving the best results (Figure 46).

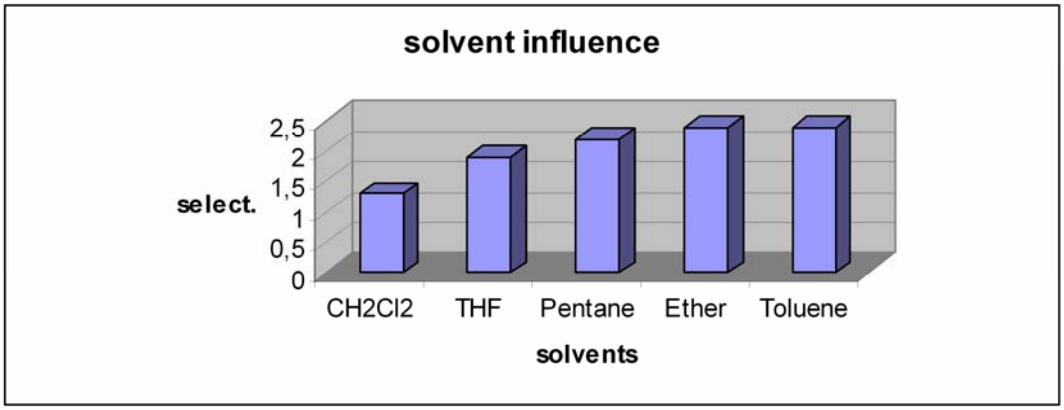
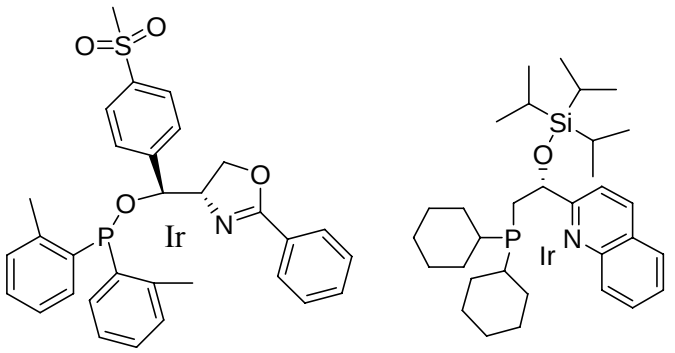


Figure 46. Solvent influence

Using toluene as solvent, the most effective ligands on six-membered cyclic enones were found to be the ligands described by N. Zimmermann (zmn707) and K. Zhang (X68) (Figure 47).



X_{68} **ZMN707**

Figure 47.

The selectivities were found to be correlated with the steric bulk present on the cyclohexenones (Table 15).

Table 15. Ligands selectivity (S) for Ir-catalysed hydrogenation[a]

Entry	Ligand	Enone **133** (S)	Enone **134** (S)	Enone **135** (S)
1	**X68**	2.9	3.3	**4.5**
2	**ZMN707**	2.4	1.7	2.3

[a] All reactions were carried out under argon using 3 mol% of **L**-Ir in toluene for 1 hours under 25 bars hydrogen pressure at room temperature.

Ligand **X68** gave the best results, showing a remarkable selectivity factor of 4.5 for enone **135**.

4. Multicomponent Heck-Allylic Substitution Reaction

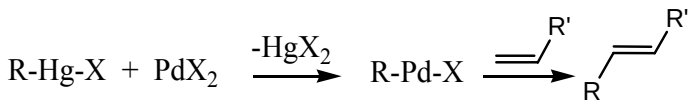
4.1 Introduction

Synthetic methodology which allows for a rapid increase in molecular complexity is extremely valuable in organic chemistry, particularly if it generates more than one new carbon-carbon bond at a time, accommodates considerable functionality and is broad in scope.

Multicomponent reactions (MCRs) are one pot reactions involving three or more reactants that react in a domino-cascade fashion to produce a single product. The obvious challenge with the optimization of such reactions lies in the control of the numerous possible side-reactions leading to unwanted products. Since the discovery of the multicomponent Ugi and Passerini reactions, MCRs have attracted much attention due to their synthetic efficiency. Indeed, high structural complexity can be achieved in a one pot reaction, without demanding purifications. Thus, the process has been extensively studied for synthesis of libraries of high value for drug development.

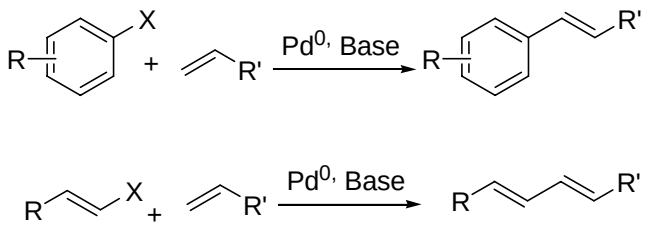
4.1.1 Heck Reaction

The palladium-catalysed alkenylation or arylation of alkenes, known as the Heck reaction, was discovered in the late sixties by Heck and Mizoroki[106] It is a nice reaction tolerating a wide variety of functional groups such as cyano, ether, ester or carboxyl groups. Additionally, it is insensitive to water, some reactions being performed efficiently in aqueous solutions.[107] Although this new method proved to be very efficient for C-C bond formation, it did not receive initially the broad attention that its potential would call for. The major drawback was the use of stoichiometric amounts of palladium salts and toxic organomercurials (Scheme 53).[108]



Scheme 53. Transmetalation with organomercurials

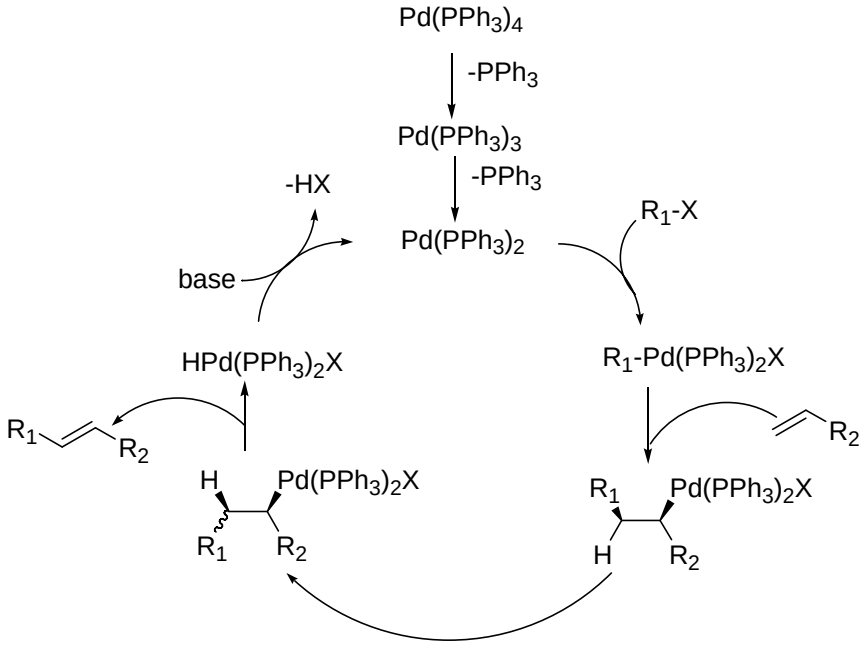
It was subsequently observed that a catalytic amount of palladium could be used in presence of stoichiometric amount of copper(II) salts or thallium salts.[109] The solution to avoid toxic organometallics turned out to be the use of aryl or vinyl halides or triflates (Scheme 54).[110]



X = I, Br, OTf, N_2^+, COCl

Scheme 54. Heck reaction with halides and triflates

Although details of the Heck reaction are still under investigation, the commonly accepted mechanism follows a four-step catalytic cycle (Scheme 55).[111]



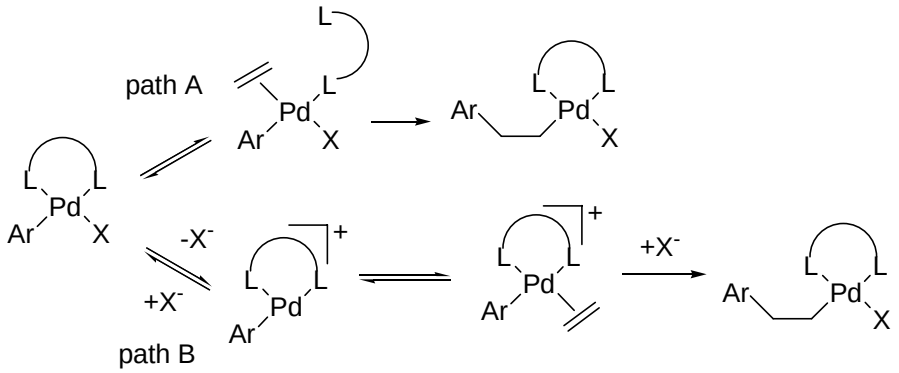
Scheme 55. Catalytic cycle

The catalytically active complex is assumed to be a 14-electron palladium(0) specie generated in situ. The first step is assumed to be a oxydative addition, generating a σ-organopalladium(II) complex. In the next step, after elimination of one ligand (when halides are used), the complex coordinates the alkene molecule, which *syn*-inserts into the σ-organopalladium bond via a four-center transition state.[112] After internal rotation, a β or β'-hydride *syn*-elimination occurs, and finally, regeneration of the active complex is achieved after reductive elimination. Kinetic

investigations[113] indicated that the oxidative addition may be the rate determining step. However, recent kinetic studies conducted with *p*-bromobenzaldehyde and butyl acrylate show *a contrario* that the resting state of the catalyst within the catalytic cycle is the intermediate derived from oxydative additions.[113].

4.1.1.1 Neutral versus cationic pathways

Next to the original aryl or vinyl halides used for the Heck reaction, Cacchi and Stille[114] introduced aryl and vinyl triflates. Whereas the oxydative addition with halides gives a strong Pd-X bond, the Pd-OTf bond with triflates is very labile. Thus, with aryl or vinyl halides as substrates, the dissociation of one ligand is necessary so that the coordination of the olefin can take place (Scheme 56).

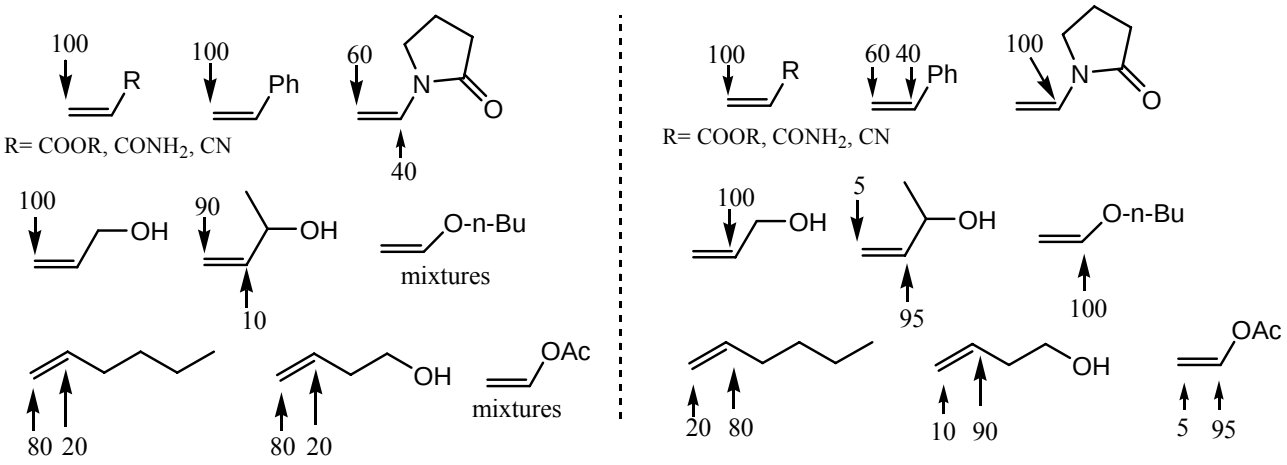


Scheme 56. Neutral and cationic pathways

Although pentacoordinated intermediates were also postulated, calculations conducted by Thorn and Hoffmann[115] showed that the energy barrier for the generation of the reactive intermediate in a pentacoordinated complex is higher than that of a tetracoordinated. With aryl or vinyl triflates, the situation is much different because of the free vacant coordination site resulting from the ion-pair structure of the Pd-OTf complex. The vacant coordination site generated with triflates allowed the use of bidentate chelating ligands, improving the enantioselection (cationic pathway). Indeed, the low enantioselectivity generally observed with halides is presumably due to the decomplexation of one ligand end (neutral pathway).[116] However, in some case dissociation of monophosphine ligand in preference to triflate was also reported,[147a] as well as dissociation of halides with 1,10-phenanthroline ligands.[117]

4.1.1.2 Regioselectivity

With strongly coordinating anions, the regioselectivity correlates with the steric hindrance, since the C-C bond is usually formed at the less substituted terminus of the olefin (path B, Scheme 56). With labile anions (path A, Scheme 56), electronic factors predominate and the (C-C)-bond is generally formed on the olefin terminus having the less partial charge (Figure 48).[118]

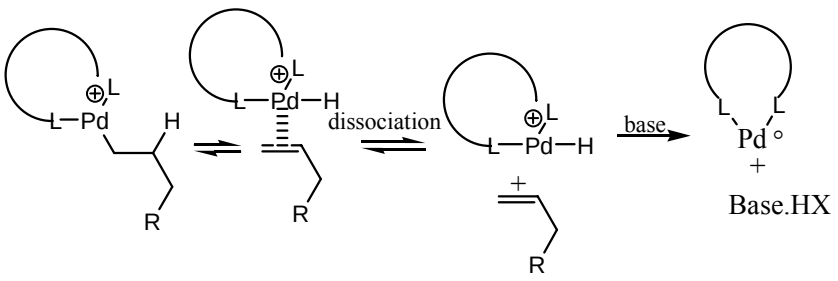


with halides with triflates

Figure 48. Regioselectivity

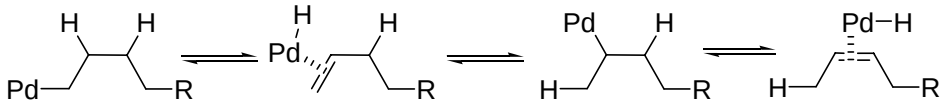
4.1.2 Palladium-Hydride Complexes

The β-hydride elimination occurs in a *syn* manner. Dissociation from the olefin gives a palladium(II)-hydride complex, that is subsequently reduced to Palladium(0) by reductive elimination of HX, presumably by deprotonation of the palladium-hydride complex by the stoichiometric amount of base necessary for the reaction (Scheme 57).



Scheme 57. β-Hydride elimination

In some cases when palladium-hydride stays coordinated to the olefin, migration of the newly formed alkene double bond is observed.[119] It is postulated that migration proceeds through a series of β-hydride elimination-readdition steps (Scheme 58)



Scheme 58. Palladium-hydride migration

Suppression of isomerisation was observed under specific conditions, e.g. by addition of Ag(I) or Tl(I) salts[118] or use of triflates. Silver and thallium salts being postulated to sequester halides anions from the complex, these observations indicate that the cationic pathway could be related with the suppression of isomerisation. It can be postulated that two factors govern the isomerisation ability of a complex: The stability of the olefin-palladium(II) complex and the stability against reductive elimination of the palladium(II)-hydride resulting from the β-hydride elimination. Indeed, it was proposed that the isomerisation efficiency is related to the dissociation-association ability of the olefin from the palladium(II)-hydride complex,[118] slow dissociation from the olefin promoting isomerisation. In this context, distinction must be made between electron rich complexes resulting from a neutral pathway and electron poor complexes resulting from cationic pathway (Scheme 56). Electron rich palladium, as bromopalladium(II)-hydride, coordinates best with electron deficient olefins, due to better overlap of the metal d orbital with the π* orbital of the olefin (π-backdonation).[118] The amount of π-backbonding depends strongly on how electron-rich the metal center is and whether or not there are electron-withdrawing groups on the akene to make it a better acceptor ligand. Thus, electron deficient palladium complexes, as cationic palladium-hydride with triflate counteranion, show less π-backdonation on alkenes, thus forming unstable palladium-alkene complexes.[118,120] Moreover, the nature of the ligand has a predominant influence on the outcome of the dissociation-insertion equilibrium.

4.1.2.1 Stability of palladium hydride

Even after dissociation of the olefin from the palladium hydride complex, recoordination can occur, allowing palladium-hydride migration if there is no reductive elimination in the meantime. Thus, relative stabilities of neutral versus cationic palladium-hydride complexes must be examined. A theoretical study on reductive eliminations on group 10 metals[121] concluded that the higher the

electron density on the metal, the slower the reductive elimination rates. Unfortunately, experimental data[122] describing the reductive elimination of HX from halo(hydrido)palladium complexes is scarce, presumably due to the unstability of such complexes. Indeed, palladium-hydrides are known to be hydride as well as proton donors, and were reported to be unstable toward acids or bases (Equation 4.).[123]

$$L_2PdHCl + HCl \longrightarrow L_2PdCl_2 + H_2$$

$$L_2PdHCl + Et_3N \longrightarrow L_2Pd + EtN_3H^+ + Cl^-$$

Equation 4.

Moreover, dismutations were also reported (equation 5).[123]

$$2HPd(dppe)^+ \longrightarrow Pd(dppe)^{2+} + Pd(dppe) + H_2$$

Equation 5.

Comparative studies in the group 10 transition metals showed that palladium is more hydridic than platinium and nickel. Also, the palladium-hydride acidity is stronger compared to platinium-hydride but equal to nickel-hydride.[123] For the 18 electron cationic complex $HPd(PNP)_2^+$, the pKa was found to be between 18 and 22.[123] Nevertheless, the detailed mechanism of the reductive elimination remains obscure. According to the principle of microscopic reversibility, oxydative addition and reductive elimination must follow the same route but in different directions, so that reductive elimination could be deduced from the opposite reaction, the oxydative addition. Oxydative additions were intensively studied, and three main mechanisms were postulated.[124,125]

- synchronous oxidative addition:

$$[L_nM] + HCl \longrightarrow [L_nM(H)(Cl)]$$

- Electrophilic oxidative addition:

$$[L_nM] \xrightarrow{H^+} [LnMH]^+ \xrightarrow{Cl^-} [L_nM(H)(Cl)]$$

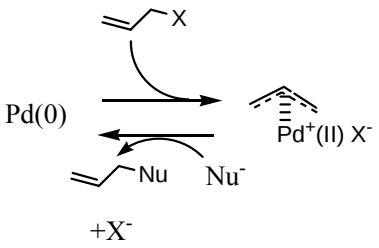
- Nucleophilic addition:

$$[L_nM] \xrightarrow{Cl^-} [LnMCl]^- \xrightarrow{H^+} [L_nM(H)(Cl)]$$

Even though there is no experimental data concluding on the mechanism for the reductive elimination, if the reductive elimination would be an inverse electrophilic oxidative addition, the direct formation of cationic palladium-hydrides with triflates would favor the reductive elimination of the hydride from the complex.

4.1.3 Allylic Substitution Reaction

Since the first description of stoichiometric palladium-catalysed allylic substitution by Tsuji in 1965 (Scheme 59),[126] the reaction has become one of the most versatile C-C bond-forming reaction. Extensive investigations have defined substrate and nucleophile tolerance, regioselectivity and stereoselectivity.[127]



Scheme 59. Allylic substitution

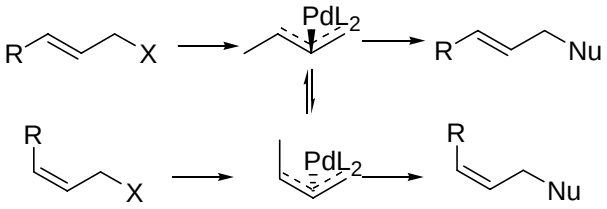
The most commonly used leaving group is the acetate, but halides, sulfones, ethers, epoxides, carbonates, carbamates, phosphates could be also employed. Depending on the nature of the leaving group, the reaction can proceed through a neutral complex if the leaving group acts as strongly coordinating anion on palladium or a more reactive cationic complex with labile conteranions. A wide variety of nucleophiles were described such as stabilised carbanions, amines, hydrides and organometallic reagents. Various nitrogen-containing compounds such as primary and secondary amines, sodium azide, protected hydroxylamines, phtalimides, 2-pyridone, sulfonamides and di-*tert*–butyl iminodicarboxylate have been employed as nucleophiles.

Enantioselective allylic alkylation has been investigated using chiral ligands.[128] Hayashi *et al.* reported interesting examples of allylic alkylation with allylic acetates and diketonate anions, using ferrocene-based diphosphines. It is commonly accepted that Pd° species involved in the catalytic cycle are stabilised by phosphines, thus numerous diphosphine ligands were reported at that time. Bisoxazoline ligands introduced by Pfaltz *et al.* inspired new generations of N-N and P-N based ligands that proved to give very high enantioselectivities.[150]

The generally accepted mechanism of palladium-catalysed reaction is composed of two steps.[129] First Pd^0 reacts with the allylic substrate to provide an (η^3-allyl)palladium(II) complex. This

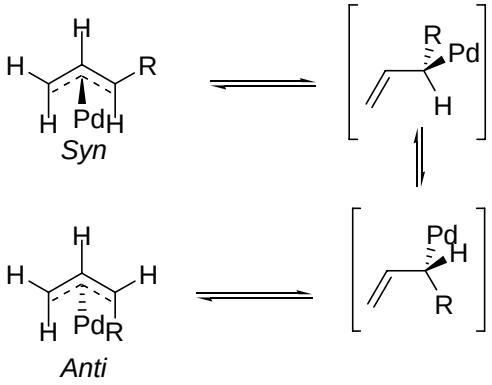
complex can isomerise in various ways and this can have important consequences on the course of the reaction.[130] The second step involves nucleophilic attack on the allylic complex termini and regenerates Pd^0. With 'hard' nucleophiles the second step occurs through coordination of the nucleophile to the palladium-allyl complex followed by reductive elimination. With 'soft' nucleophiles (stabilised carbanions or amines) the reaction occurs through nucleophilic attack at one of the two allylic termini of the complex. In general, with amine nucleophiles, the allyl system is attacked at the less substituted carbon.[131] Nevertheless, it depends on the polarisation of the π-allyl system. With π-acceptors ligands that induce a higher positive charge on the π-allyl-metal complex that might be located on the more substituted allylic terminus where a stabilisation by hyperconjugation is possible, thus rendering this terminus more reactive toward nucleophilic attack.[132]

Even though the reaction rate with amine nucleophiles is lower than the rates observed with stabilized carbon nucleophiles, very good yields can be obtained after prolonged reaction times. Usually, the double bond stereochemistry is lost during the reaction (Scheme 60).



Scheme 60. Isomerisation

This is due to the π-σ-π palladium isomerisation resulting in a *syn-anti* interconversion favoring the less hindered *syn* isomer (Scheme 61).

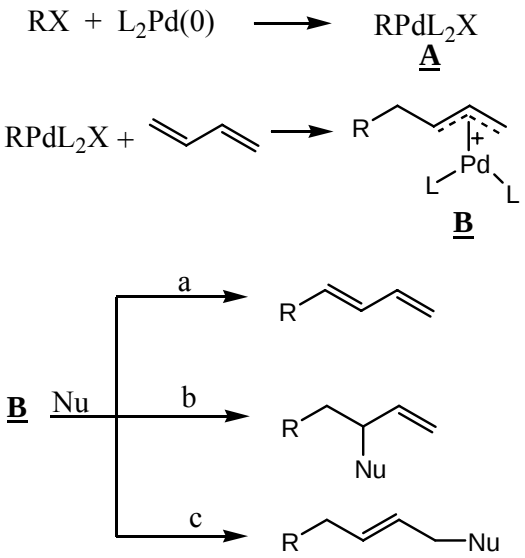


Scheme 61. *Syn-anti* interconversion

The arylpalladium complexes involved in these substitution reactions have been thoroughly investigated. They are often relatively easy to crystallize and since palladium(II) is diamagnetic, the complexes can be analysed by NMR techniques[131]

4.1.4 Multicomponent Reaction

The palladium-catalysed reaction of vinyl halides with conjugate dienes in presence of amine nucleophiles was first reported by Heck and Larock.[135] The reaction involves the initial formation of a σ-palladium complex **A** (Scheme 62) by oxydative addition of an aryl or vinyl halide to a Pd(0) specie. Reaction of the formed σ-palladium complex with conjugated dienes in a Heck-reaction manner is believed to form a π-allylic palladium intermediate **B** (Scheme 62).[135] The π-allylic palladium complex could then undergo β-hydride elimination to substituted diene (path a) or reaction of nucleophiles to form allylated products (path b and c, Scheme 62).

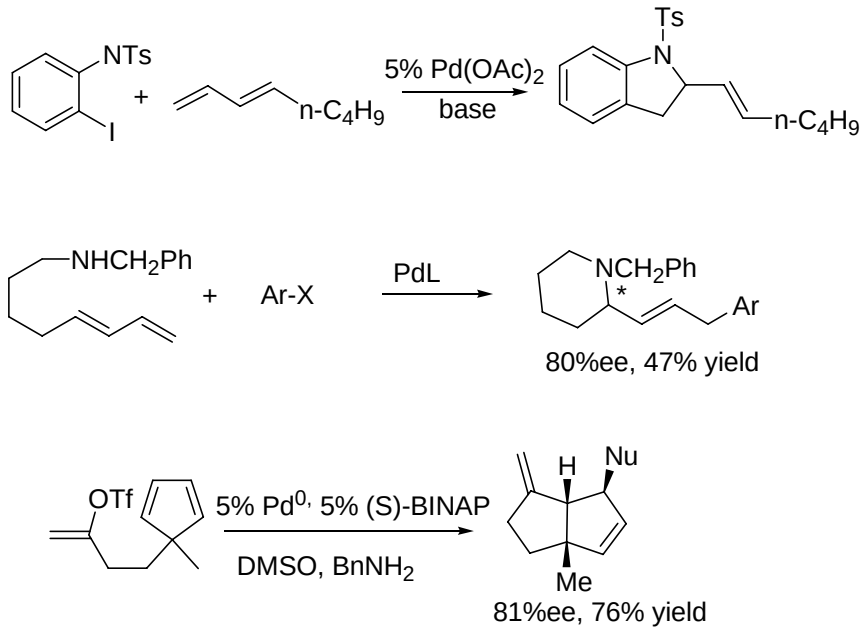


Scheme 62.

Phosphines as ligands were reported to be beneficial or detrimental to the yields depending on the nature of the nucleophile or the olefin, but no general prediction could be made.[135, 136] Secondary amine nucleophiles as morpholine or piperidine gave good results, with a predominant substitution at the less substituted end of the π-allylic palladium complexes (path c, Scheme 62). It was generally observed that nitrogen nucleophiles are very sensitive to the steric hindrance present on the π-allylic palladium intermediate.[137] Also, primary amines showed enhanced tendencies to attack the internal π-allylic terminus (path b, Scheme 62).[138] Strongly basic amines as

diethylamine gave mainly elimination to diene (path a, Scheme 62). In general, path a is in competition with the desired allyic substitution (b and c). Also, the formation of regioisomers due to the possible addition of vinyl palladium on both ends of the alkenes (Figure 48), or E/Z mixtures due to nucleophilic substitution on *syn-anti* π-allyl palladium complexe (Scheme 61) cannot be totally suppressed.

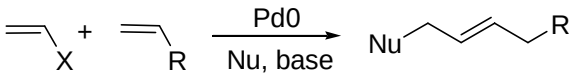
Intramolecular versions were reported[139] giving access to heterocycles or polycyclic compounds (Scheme 63). Noteworthy, if the ligand L is chiral, it is possible to create a stereogenic center if the reaction follows path b in Scheme 62.



Scheme 63.

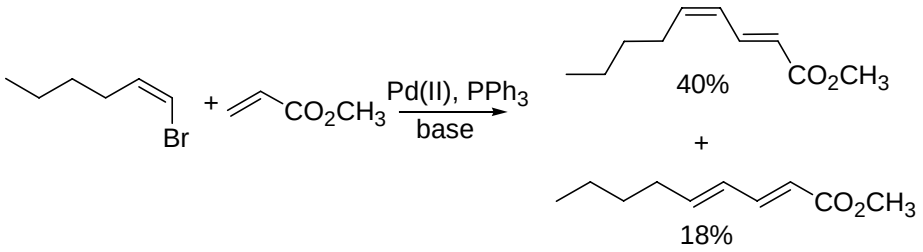
The reaction conditions are generally critical to the success or failure of the reaction. Polar solvents and temperatures of 80-120 °C are required, especially with electron rich substrates such as anilines. Other factors critical to the success of the process are the nature and stoichiometry of the base employed and the presence of a chloride source. Of these, the nature of the base is often the most important. Acetate, carbonate and bicarbonate have proven to be the most successful. The nature of the base has a strong influence on the reaction rate and selectivity. Sodium and potassium salts have proven to be the most generally useful bases. The addition of LiCl or Bu_4NCl to the reaction often has a profound effect on the yield and rate of reaction. Usually one equivalent of the chloride reagent per aryl or vinylic halide or triflate is employed, although catalytic amounts are sometimes effective. The addition of more chloride reagent usually slow down the reaction substantially and usually affords little improvement in yields. The effect of n-Bu_4NCl seems to have little to do with solubility or phase transfer effects, since LiCl is in general equally effective and gives often more reproducible results.

Indirect observations indicated that the reaction could be feasible not only with 1,3-dienes as substrates (Scheme 63) but also with simple olefins (Scheme 64).



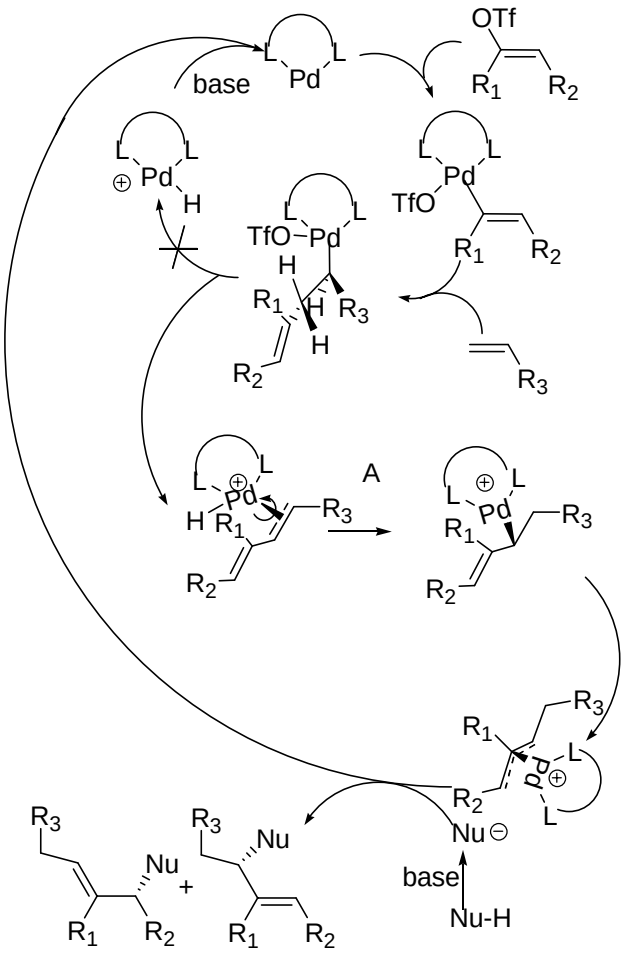
Scheme 64. Reaction with olefins

Indeed, loss of conformation in the Heck reaction was reported[140] and proposed to be due to the formation of a π-allylic palladium complexe by palladium-hydride isomerisation which readily converts *anti* complexes to the more stable *syn* isomer before elimination of the hydridopalladium to produce a diene (Scheme 65).



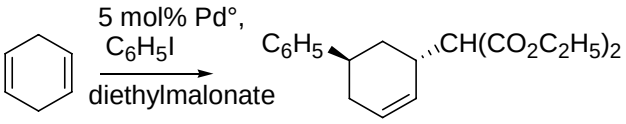
Scheme 65. Observed loss of stereochemistry during Heck reaction

Moreover, Larock reported the formation and isolation of π-allyl palladium complexes by reaction of vinylic mercurials with olefins in presence of Pd(II) salts.[141] The mechanism commonly accepted involves isomerisation via a palladium-hydride complex in the key step (step A, Scheme 66).



Scheme 66. Mechanism

The isomerisation via a palladium-hydride complex does not proceed by complete separation of the palladium-hydride complex from the alkene, as jugged from the exclusive formation of the *trans* product from 1,4-cyclohexadiene (Scheme 67).[141,142]



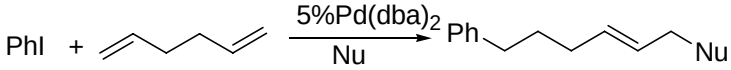
Scheme 67. Reaction with 1,4-cyclohexadiene.

The other steps of the cycle are similar to the already described steps consisting of an allylic substitution and a Heck reaction. As for reaction with diene substrates, the reaction conditions play a predominant role and are fairly similar to these described above, with special emphasis on the need to use only mild bases.[143,144] Strong bases such as KOtBu, NaH, NaOH, BuLi, NEt_3, n-$BuNH_2$ give consistently lower yields. Also, secondary amines were found to give better results than primary.[143]

Allylic substitutions with amine nucleophiles were generally found to be highly sensitive to steric hindrance. The amine generally attacks at the least substituted or least hindered end of the π-allyl palladium complex.[137,140,143] Also, unhindered monosubstituted terminal alkenes react well.

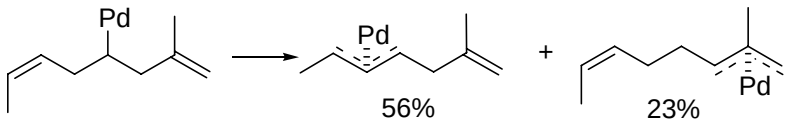
As precedently, phosphines as ligands were reported to be beneficial or detrimental to the yield depending on the nature of the nucleophile or the olefin, with no possible prediction.

Addition of Cholride under the form of Bu_4NCl or LiCl was reported to be beneficial[145] in particular when not only simple olefins are used as substrates but also non conjugated dienes (Scheme 68).



Scheme 68. Reaction with non-conjugate dienes

With these substrates, formation of a π-allyl palladium complex is obtained after migration of the palladium-hydride by successive addition-elimination steps. Larock reported that palladium can reversibly migrate up and down on even very long carbon chains,[142] as for example on tetradeca-1,13-diene with 10 carbons between the double bonds. With vinyl halides as substrates, the migration has a tendency to occur toward the less substituted end of the molecule (Scheme 69).[145,146]



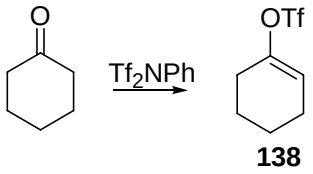
Scheme 69. Migration toward the less substituted end

Noteworthy, vinyl or phenyl triflates were reported to be fairly unreactive.[142,147] Thus, most of reported similar reactions were obtained with halides.[136] That could explain the lack of reported enantioselective tandem-reactions, since halides favor the unselective 'neutral pathway' (Scheme 56).

4.2 Synthesis of Allylic Amines

4.2.1 Optimisation

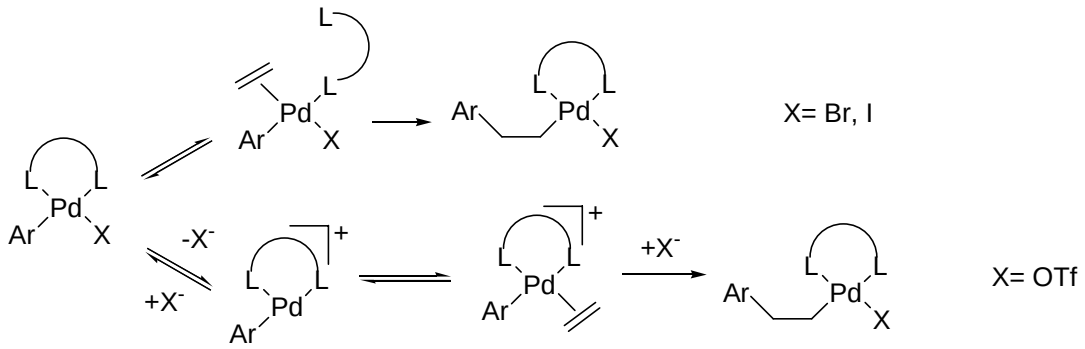
Cyclohex-1-en-1-yl triflate[149] **138** (Scheme 70) prepared form cyclohexanone with pehyl-methanesulfonamide triflate, and 1-hexene were chosen as reactants.



138

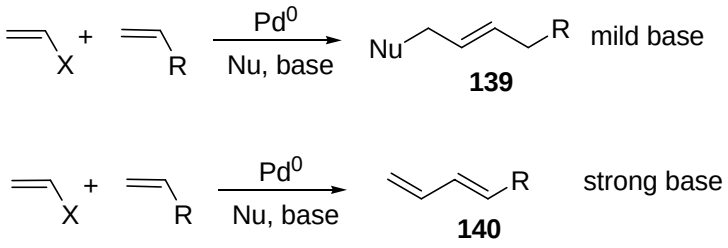
Scheme 70.

Triflates rather than halides were chosen because of the high enantioselectivities generally reported in enantioselective Heck reactions.[149] The alkenyl triflate **138** is expected to lead to a cationic palladium complex with retention of the chelate coordination of the chiral bidentate ligand allowing efficient transfer of the chiral information from the catalyst to the substrate (Scheme 71).



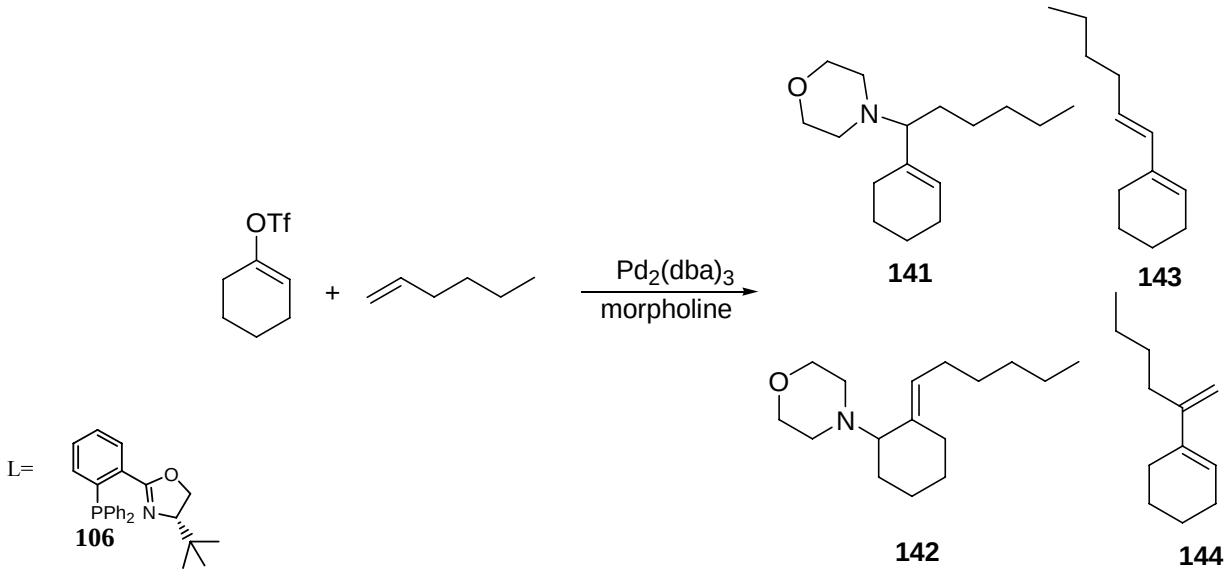
Scheme 71.

The chosen ligand was the *tert*-butyl-substituted (phosphinoaryl)-oxazoline **106** because of the excellent reactivity and enantioselectivities reported in the allylic substitution reactions as well as enantioselective Heck reactions.[150] We have chosen morpholine as nucleophile and base because of its relatively low basicity. Strong bases were reported to favor the Heck reaction product **140** over the domino product **139** (Scheme 72).[151]



Scheme 72.

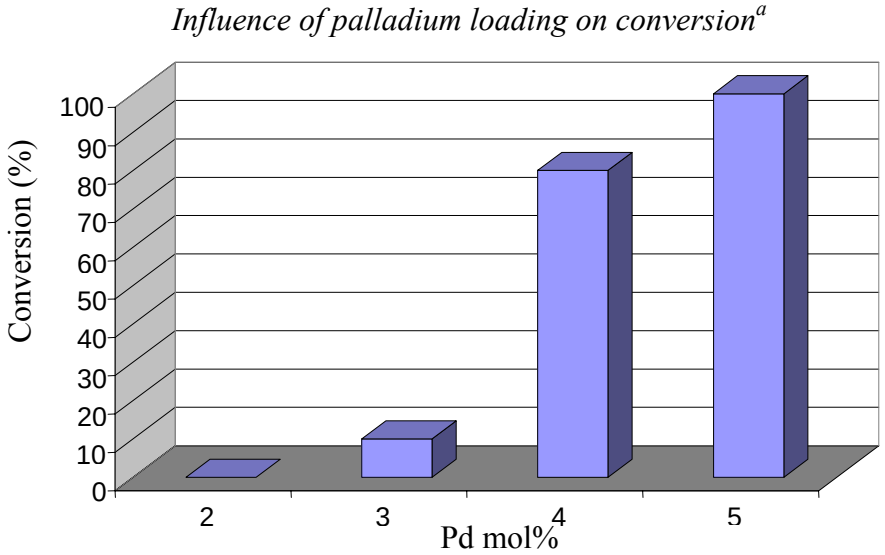
Commercially available and air stable $Pd_2(dba)_3$ was used as source of Palladium(0) for the reaction. The catalyst was preformed by stirring the $Pd_2(dba)_3$ with two equivalents of ligand **106** in degassed DMA, then substrates were added and the reaction mixture kept at 80°c for 72 hours. Adjustment of reaction conditions (catalyst loading, solvents, temperature) were found to be necessary to achieve high conversions (Scheme 73)



Scheme 73. Multicomponent reaction

Under such conditions, a mixture of products was obtained. On one side, the desired products resulting from the tandem reaction (**141** and **142** in a 2.5/1 ratio) and on the other side the competing Heck reaction products (**143** and **144** in a 1/2 ratio). The tandem products derived only from the non-branched Heck reaction product intermediates, presumably because of lower steric hindrance.

4.2.1.1.Influence of palladium loading on conversion

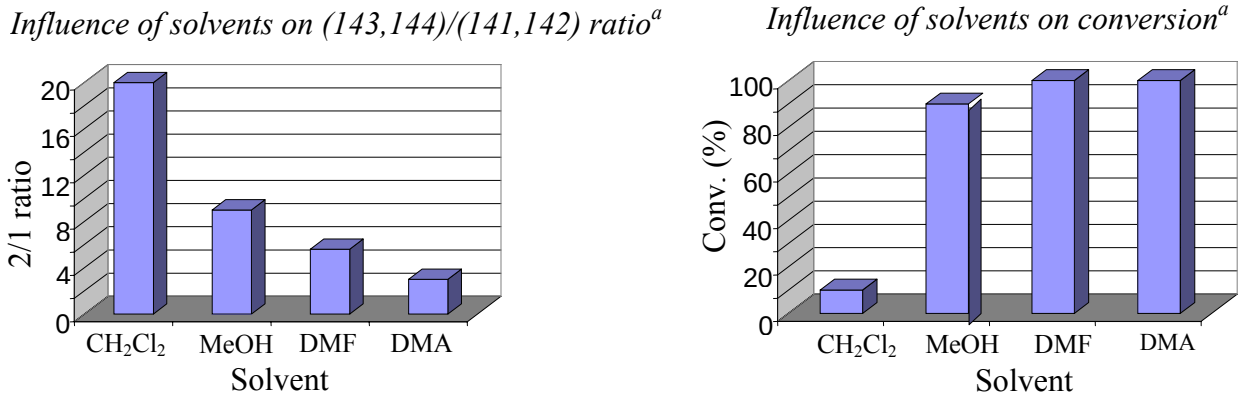


[a] Pd mol% reported to the alkenyl triflate substrate, 5eq. of morpholine, 5 eq. of 1-hexene, 80°c, 72h, DMF

Figure 49. Influence of palladium loading on conversion

Palladium loading of at least 5 mol% was found to be necessary (Figure 49). The listed conversions correspond to the formation of products **141, 142** plus **143, 144**. Noteworthy, the non-catalytic reaction conducted with a stoichiometric amount of catalyst, without base, followed by one pot addition of nucleophile after 24 hours gave only the Heck reaction products **143** and **144**.

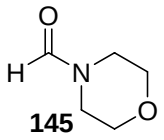
4.2.1.2 Influence of solvents on conversion and (143,144)/(141,142) ratio



[a] 5 mol% Pd reported to alkenyl triflate substrate,2eq. L, 5eq. of morpholine, 5 eq. of 1-hexene, 80°c, 72h

Figure 50.

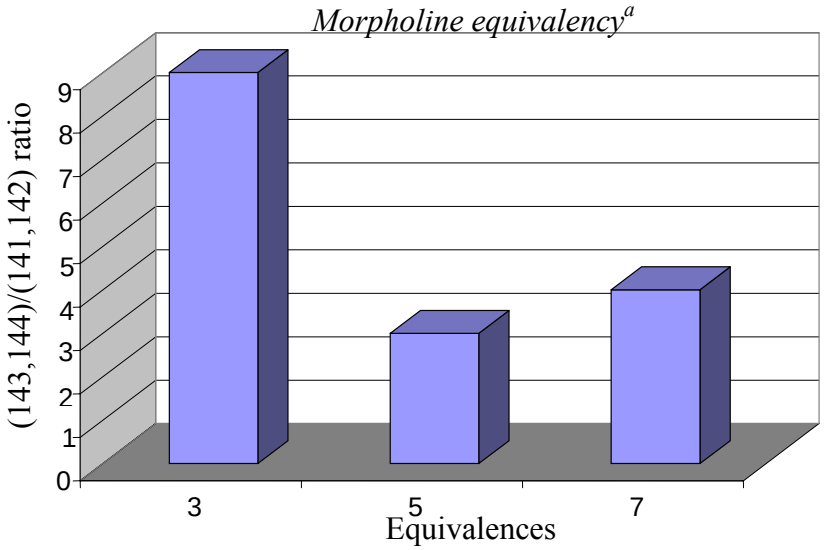
The conversion and **(143,144)**/**(141,142)** ratio are dramatically affected by the solvent (Figure 50). Polar aprotic solvents are best suited, presumably because they solvate the best the intermediate cationic complex. Use of DMA proved to be superior to DMF, due to competing formation of **145** from transamidation of DMF with morpholine (Figure 51).



145

Figure 51. Product from reaction between morpholine and DMF

Furthermore, the amount of morpholine was varied in DMA as solvent (Figure 52).

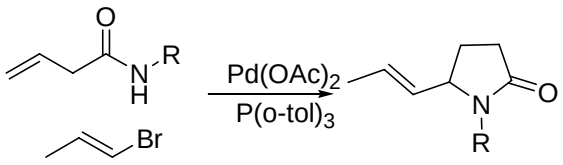


[a] 5 mol% Pd reported to alkenyl triflate substrate,2eq. Ligand, 5 eq. of 1-hexene, 80°c, 72h, DMA

Figure 52.

Surprisingly high morpholine amounts were necessary, with 5 equivalents being optimal. This high amount of morpholine could explain the low yields generally observed since presence of base favors the Heck reaction products **143, 144** by competitive hydride elimination from the palladium-hydride complex before isomerisation. Improvement in yields could go through lowering the amount of nucleophile. The concentration of morpholine was lowered by sequential additions over the whole reaction time or continuous addition by means of a syringe pump. In both case yields were not improved but the conversion was complete, giving mainly the diene product resulting from the Heck reaction. From these experiments, it appears that equilibrium in nucleophile concentration must be reached. High morpholine concentration increases the solution basicity thus directing the reaction toward the Heck reaction, whereas a too low nucleophile concentration lowers the probability of reaction of the formed π-allyl intermediate with the nucleophile. A

reaction involving intramolecular nucleophilic substitution proved to be more effective for that kind of reaction (Scheme 74).[152]



Scheme 74. Intramolecular tandem reaction

Nucleophiles more basic than morpholine depicted below (Figure 53) were also tested, but the yields detected by GC-MS were extremely low.

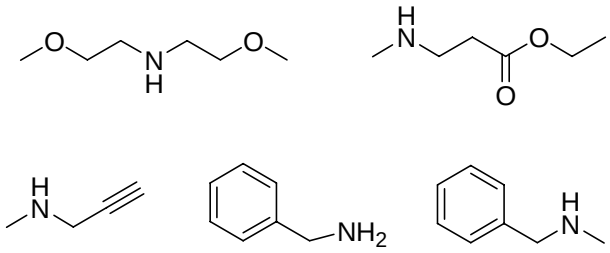


Figure 53.

The palladium source was also varied in order to determine its influence. In every case conversions were complete but $Pd(PPh_3)_4$ was found to give the same range of (**143,144)**/(**141,142)** ratios as $Pd_2(dba)_3$ whereas palladium(II) as $Pd(OAc)_2$ gave somewhat lower ratios. $Pd_2(dba)_3$ is thus best suited for the reaction. Complexes of $Pd_2(dba)_3$ with various ligands were examined. Phopshine ligands (Entries 1-3, Table 15) such as BINAP or P(*n*-Bu)$_3$ gave similar results as ligand **106**, with equivalent conversions and slightly better (**143,144)**/(**141,142)** ratios. Noteworthy, BINAP complexes are more reactive in toluene and give better (**143,144)**/(**141,142)** ratios. Amine ligands (Entries 4,5, Table 15) gave unreactive complexes and low selectivity for the desired products **141,142**.

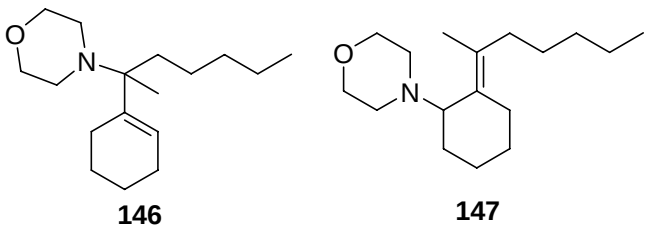
Table 15. Ligands and solvents influence on the multicomponent reaction[a]

Entry	Solvent	Ligand	**(143,144)/(141,142)** ratio[b]	Conv. (%)[b]
1	DMF	3eq. BINAP	1.86	50
2	Toluene	3eq. BINAP	1.50	100
3	DMF	3eq. P(*n*-Bu)$_3$	2.33	100
4	THF	2eq.diaminonaphtalene	9	5
5	Toluene	2eq.diaminonaphtalene	9	5
6	DMF	3eq. P(OMe)$_3$	1	20
7	Toluene	3eq. P(OMe)$_3$	4	10
8	DMF	3eq. P(OPh)$_3$	1	15
9	Toluene	3eq. P(OPh)$_3$	1	10

[a] All reactions were carried out under argon. [b]Determined by GC

Most interesting, phosphite ligands (Entries 6-9, Table 15) are the most selective in favor of the desired tandem products **141** and **142** but form less reactive complexes.

The low yield generally obtained is possibly related to the high proportion of unreactive branched Heck reaction product **144**. Indeed, no tandem reaction product **146** or **147** (Figure 54) resulting from the branched intermediate was observed.



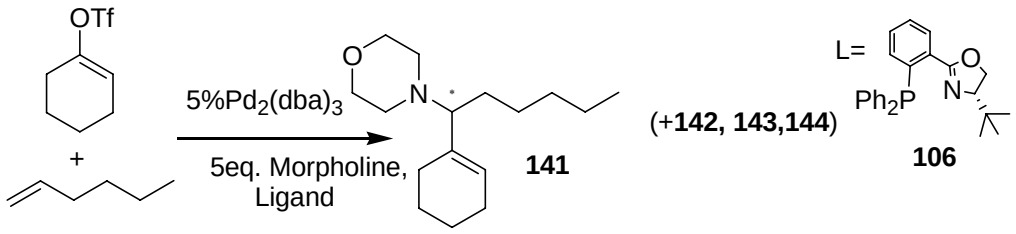
146 **147**

Figure 54.

4.2.1.3 Enantioselective version

Although the yield remained moderate using the optimised conditions for the reaction, use of chiral *tert*-butyl substituted (phosphinoaryl)-oxazoline **106** was expected to give chiral allyl-amine products. Indeed, we obtained 86% ee in DMF (Entry1, Table 16) whereas use of DMA as solvent lowered the ee to 72% ee but improved slightly the yield (Entry 2, Table 16). Use of additives such

as LiCl or Bu_4NCl acting as chloride source were detrimental for enantioselection (Entry 3 and 4, Table 16).



Scheme 75.

Table 16. Solvent and additives influence [a]

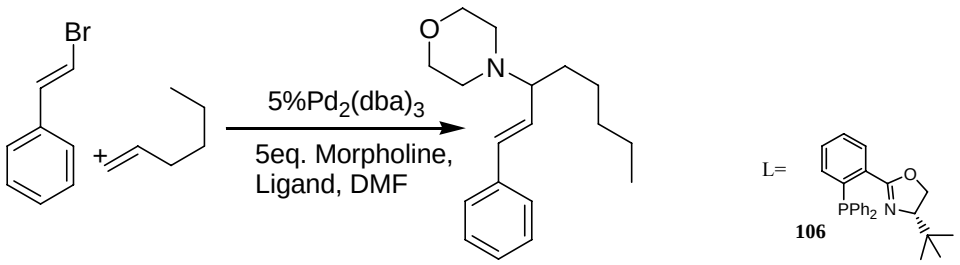
Entry	Solvent	Additive	Pd mol%	Eq. hexene	Eq. morpholine	T (°C)	Time (d)	Yield (%)[b]	*ee* **141** (%)[b]
1	DMF	-	5	5	5	80	5	15	86
2	DMA	-	5	5	5	100	4	25	72
3	DMF	2eq. LiCl	5	5	5	100	4	12	72
4	DMF	2eq.TBAC	5	5	5	100	3	10	66

[a] All reactions were carried out under argon using 5 mol% of **106**-$Pd_2(dba)_3$. [b]Determined by GC

4.2.2 Substrates

4.2.2.1 Halides

The reaction has been tested on other substrates. Halides were examined for the possible different reactivity due to the stronger coordination ability of halides compared to triflates (Scheme 76).



Scheme 76.

Use of vinyl halides gives better yields but no enantioselectivity (Table 17). This might be due, as previously, to partial dissociation of the bidentate ligand caused by strongly coordinating counter-

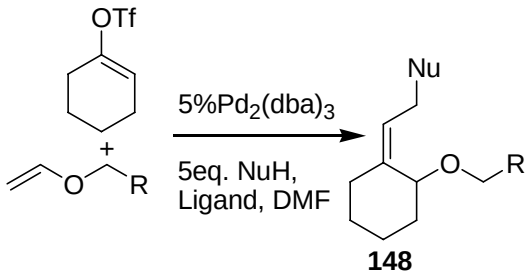
ions such as bromide (neutral pathway). This restricts the use of vinyl halides to monodentates ligands in order to achieve enantioselection.

Table 17. Reaction with β-bromostyrene[a]

Entry	Solvent	Additive	Pd mol%	Eq. hexene	Eq. morpholine	T (°C)	Time (d)	Yield (%)[b]	*ee* **155** (%)[b]
1	DMF		5	5	5	110	5	25	4
2[c]	DMF		5	5	5	110	4	4	-
3	DMF	3eq.Ag_3PO_4	5	5	5	110	4	30	3
4	DMF	7eq.Ag_3PO_4	5	5	5	110	4	29	4
5	DMF	10eq.TBAC	5	5	5	100	4	15	8

[a] All reactions were carried out under argon using 5 mol% of **106**-$Pd_2(dba)_3$. [b]Determined by GC. [c] no ligand added

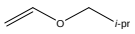
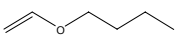
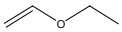
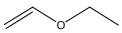
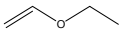
4.2.2.2 Vinyl ethers



Scheme 77

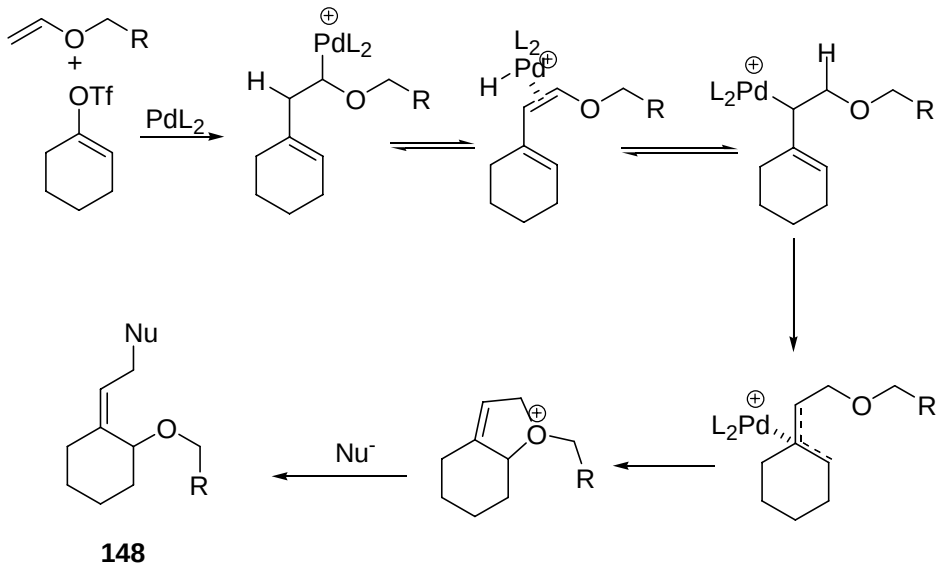
The electronic properties of the substrate proved to have a direct influence on the reaction. Indeed, electron poor substrates such as styrene were unreactive. The reaction was thus tested with electron rich substrates as enolethers (Scheme 77). Electron deficient palladium complexes such as cationic palladium-hydride with triflate as counteranion coordinate more strongly with electron rich alkenes. Indeed, obtained results were in most case superior to previous reactions with 1-hexene or styrene using 5% palladium complex in DMA or DMF and five equivalents of morpholine as nucleophile at 80 °C for two days. Yields in the range of 40-50% were obtained with enolethers (Table 18), with little influence of the steric hindrance of the substrate. Enantioselectivity were high with 93% ee (Entry 2, Table 18) in the case of butylvinyl ether and generally in the range of 80-90% ee.

Table 18. Reaction with vinyl ethers[a]

Entry	Solvent	Pd mol%	Substrate	Eq. Nucleoph.	T (°C)	Time (d)	Yield (%)[b]	*ee* **148** (%)[b]
1	DMF	5		5. morpholine	95	2	45	90
2	DMF	5		5. morpholine	80	2	40	93
3	DMF	5		5. morpholine	80	2	50	84
4	DMA	5		3. morpholine	80	2	50	88
5	DMA	5		5.bis(methoxy)-ethylamine	80	2	50	-

[a] All reactions were carried out under argon using 5 mol% of **106**-$Pd_2(dba)_3$. [b]Determined by GC.

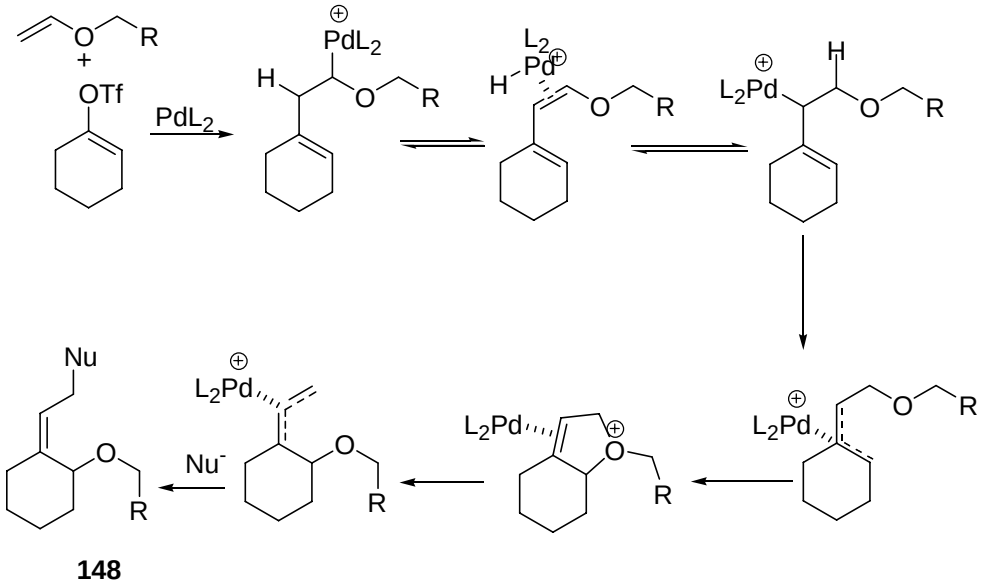
The obtained product **148** was unexpected. Presumably, it resulted from an intramolecular rearrangement depicted in Scheme 78. After *syn*-insertion of palladium on the vinylether, β-hydride elimination and subsequent isomerisation via palladium-hydride complex, the π-allyl complex was formed and underwent an intramolecular nucleophilic attack at the allylic terminus of the complex by the neighbouring ethers oxygen. This led to an oxonium intermediate that was suited for a nucleophilic attack by nucleophiles to form the product.



148

Scheme 78.

Another possible pathway involving rearrangement of the π-allyl intermediate through a cyclic oxonium is depicted in Scheme 79 below:

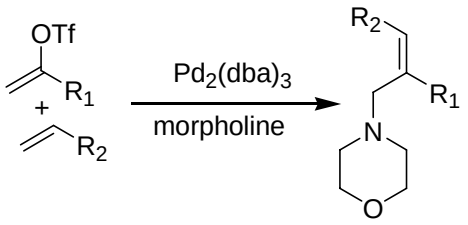


148

Scheme 79.

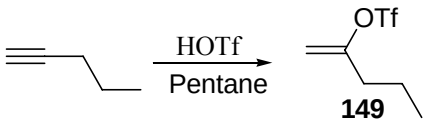
4.2.2.3 Acyclic triflates

Use of acyclic alkenyl triflates was experimented in order to expand the reaction's scope (Scheme 80). This type of substrate could additionally offer the advantage of low steric hindrance, thus enhancing the reaction yields that are often sensitive to steric hindrance.



Scheme 80.

Substrates were obtained by addition of triflic acid on alkynes (Scheme 81).[153]



Scheme 81.

The reaction above works well with simple alkynes but gives low yields (<10% yield) with the substrates depicted in Figure 55.

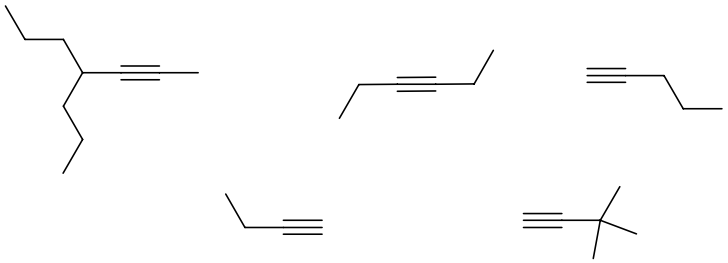
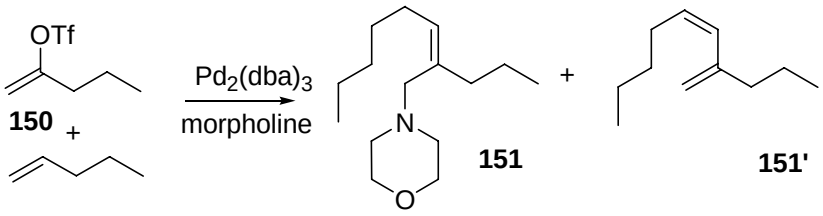


Figure 55.

The catalyst was optimised using 1-hexene and pentenyl triflate **150**. The nucleophilic attack generally occurred at the less hindered end of the π-allyl complex, thus forming achiral compound **151** (Scheme 82).



Scheme 82.

Phosphite ligands appeared to give very good **151'**/**151** ratios and conversions (Entries 7-9, Table 19). THF as solvent was found to be best suited for **151'**/**151** ratio with phosphite ligand (Entry 9, Table 19). TADDOL-based ligands (Entries 10-12, Table 19) were reactive but the **151'**/**151** ratios were lower than with phosphites. Phosphine or amine ligands such as phosphino-oxazolines (entry 1, Table 4.5), bisoxazolines (Entry 2, Table 19), 1,10-phenantroline (entry 3, Table 19) or diphenylphosphine-propane (Entry 4, Table 19) did not gave satisfactory **151'**/**151** ratios. Noteworthy, dppf gave significantly better **151'**/**151** selectivity than other diposphines (Entry 5, Table 19).

Table 19. Ligand and solvent influence on reaction with acyclic triflates[a]

Entry	Solvent	Ligand	**151'/151** ratio	Conv. (%)[b]
1	DMF	PHOX **106**	1	100
2	THF	BISOX **106**	2	50
3	THF	**153**	1.5	100
4	THF	dppp	1.50	100
5	THF	dppf	0.67	100
6	THF	**154**	0	0
7	DMF	$P(OMe)_3$	0.07	90
8	Toluene	$P(OMe)_3$	0.11	90
9	THF	$P(OMe)_3$	0.10	95
10	THF	HR477	0.25	90
11	THF	HR678	0.66	90
12	THF	HR461	1	90
13	THF	**152**	0.3	85

[a] All reactions were carried out under argon. [b]Determined by GC

Steric hindrance on the ligand seems also to play an important role since the small trimethyl phosphite ligands (Entries 7-9, Table 19) gives better selectivities than more bulky phosphite ligands (Entries 10-13, Table 19).

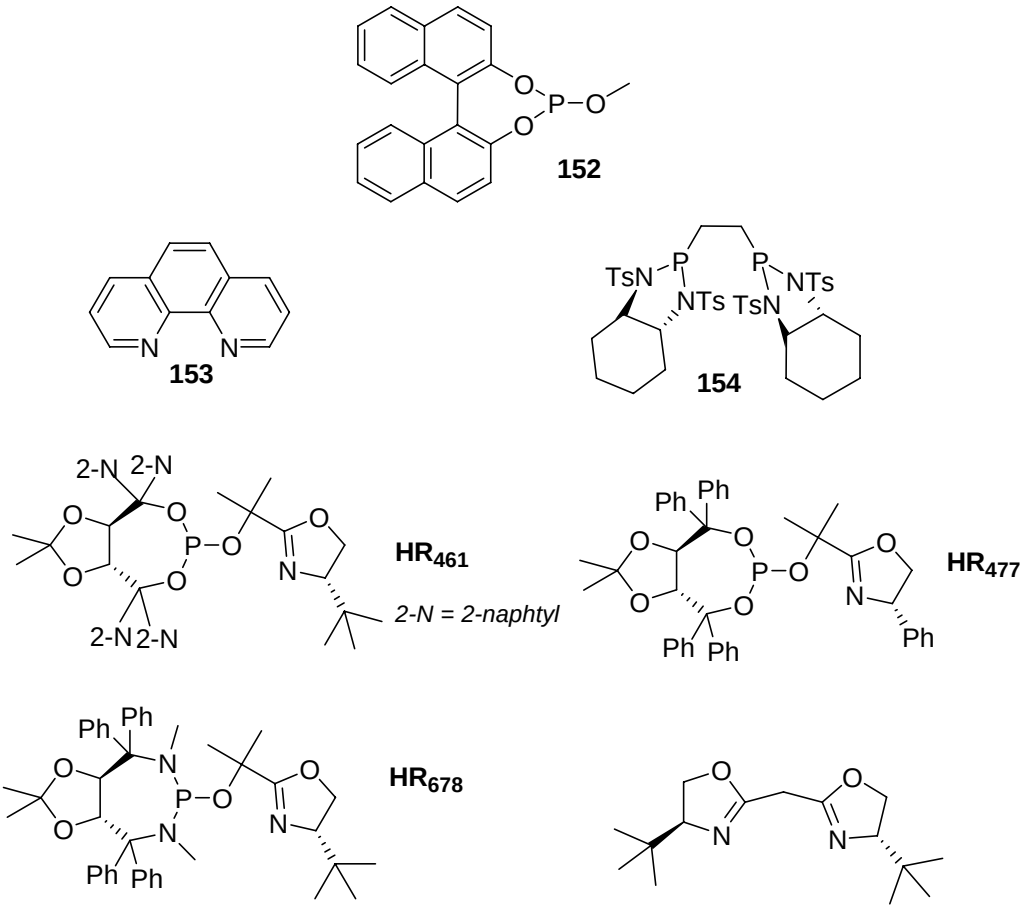


Figure 56.

The success of the palladium-hydride isomerisation can be correlated to its coordination on the alkene. The amount of 1-hexene was lowered from 5 equivalents to one equivalent. Slight decrease in selectivity was observed, indicating that excess alkene is required.

4.3 Discussion

Study of the reaction has highlighted its limitations but shows promise that enantioselective synthesis is feasible by multicomponent reactions. Observations indicate several reasons for the low yields obtained with cyclohexenyl triflates, the main being presumably their high regioselectivity toward the internal olefin terminus during the Heck reaction step with tested substrates. Use of acrylates could therefore improve the yields. Also, the reaction seems to be highly sensitive to steric hindrance, probably due to difficulty of nucleophilic attack on sterically hindered π-allyl intermediates, a feature also found in allylic substitutions. This problem could be overcome by intramolecular nucleophilic substitution where the nucleophile stays in proximity of the reactants. Electron rich substrates as enolethers show better reactivity, thus indicating that

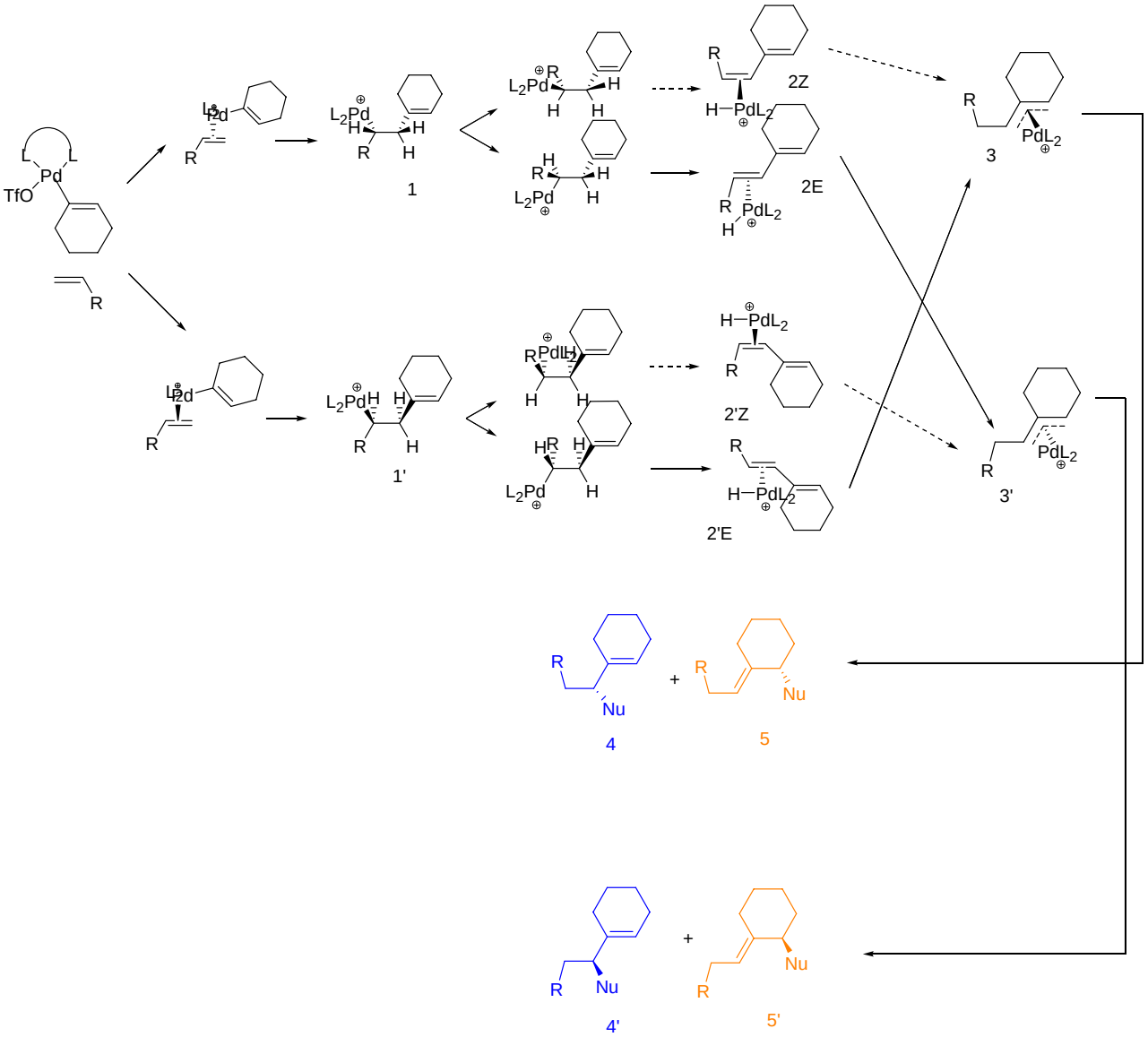
electronic factors play a predominant role. This is also supported by the huge reactivity difference in relation to the electronic properties of the ligand. Reactions conducted with vinyl halides are generally higher yielding than with vinyl triflates. This could have several reasons:

- Relative unstability of the cationic palladium-hydride intermediate with triflates compared to the neutral complex (with strongly coordinating halides).
- Faster dissociation of the alkene from a cationic palladium-hydride because of low π-backbonding from metal to the alkene.
- Regioselectivity of the addition on olefins directed toward the external terminus.

Surprisingly, electron poor ligands such as phosphites (strong metal to ligand π-backbonding, poor σ-donor) are superior to more electron rich phopshine ligands (weaker π-backbonding, stronger σ-donation) or amines (no π-backbonding, good σ-donor).[152] This might be due to formation of more reactive π-allyl palladium complexes through increasing the electrophilicity of the complex. Noteworthy, attack of the nucleophile on the more hindered allylic terminus could be facilitated because of induced positive charge located at the more substituted allylic terminus.

4.3.1 Enantioselectivity

The enantiomeric excesses obtained by reacting cyclohexenyl triflate with 1-hexene demonstrated that formation of stereogenic centers is possible by a multicomponant Heck-allylic substitution reaction. Enantioselection could result from the Heck-reaction step, the allylic substitution step or a combination of both. When integrating a enantioselective Heck-reaction step in the tandem Heck-allylic substitution, the mechanism leading to enantioselectivity is examined in the case of insertion on the 'less hindered end' of the alkene (Scheme 83). The olefin insertion step can occur on both sides of the alkene thus forming intermediates 1 and 1'. The β-elimination step can then lead to E and/or Z alkene (2E, 2Z and 2'E, 2'Z), generally in favor of the E isomer (plain arrows). Each of these isomers can form *syn* π-allyl complexes by isomerisation via a palladium-hydride complex (3,3') that subsequently can undergo nucleophilic substitution.



Scheme 83.

Depending on the selectivity of the nucleophilic attack at one allylic terminus, one isomer or an isomer mixture (4/5) can be obtained. Most important, enantiomeric excess of the obtained products (4 and 5) is clearly not only depending on the face discrimination during the alkene coordination step giving 1 or 1'(the 'Heck-reaction' step). Indeed, even though the face coordination would occur selectively giving only 1, an unselective β-elimination step that would not only produce the E alkene (2E) but also the Z (2Z) would lead to formation diastereoisomeric π-allyl complexes 3 and 3', and subsequently to a racemic mixture of products 4/4' and/or 5/5'.

5. Experimental section

5.1 General Experimental Points

^{1}H-NMR: spectra were recorded on a Varian Gemini 300 (300 MHz) spectrometer as well as on Bruker Avance 400, 500, and 600 MHz NMR spectrometers equipped with BBO broadband (500 MHz) and BBI inverse (600 MHz) probe heads. When necessary, the signals were assigned by APT, DEPT, COSY, HMQC, HMBC, and NOESY measurements. References:

^{1}H NMR: TMS $\delta = 0$ ppm or $CHC1_3 = 7.26$ ppm

^{13}C NMR: TMS $\delta = 0$ ppm or $CHC1_3 = 77.0$ ppm

^{31}P NMR: $(PhO)_3P{=}O$ (58% solution in $CDC1_3$) = -18.0 ppm

IR: spectra were recorded on a Perkin Elmer 1600 séries FTIR spectrometer. Spectra of liquids were measured neat as thin films between two sodium chloride plates, those of solids as t KBr disks.

El and FAB: mass spectra were carried out at the Department of Chemistry at the University of Basel on mass spectrometers VG70-250 (EI) and Finnigan MAT 1312 (FAB). The ions were generated by electron ionization (El, 70 eV) or bombardment with fast xenon atoms (FAB), using of 3-nitrobenzyl alcohol (3-NBA) as matrix and sometimes potassium chloride as additive in the latter case. The data are given in mass units per charge (m/z).

ESI: mass spectra were measured with a Finnigan MAT LCQ octapole mass spectrometer.

Elemental analyses: Department of chemistry at the University of Basel, Leco CHN-900 (C-, H-, N-detection) and Leco RO-478 analysers. The data are indicated in mass percents.

G.C.: Carlo Erba HRGC Mega2 Series MFC 800 chromatographs. Achiral separations were mostly performed on the column Restek rtx-1701, 0.25 μm, 30 m, 60 kPa He or H2, chiral separations on several β- or γ-CD modified capillary columns.

HPLC: Shimadzu Systems with a SCL-10A System Controller, CTO-10AC column oven, LC10-AD pump System, DGU-14A degasser, and a SPD-M10A Diode Array Detector or a UV-vis detector (220 nm and 254 nm). Chiral columns Chiracel OD-I I, OB-H, OJ and Chiralpak AD and AS from Daicel Chemical Industries Ltd. were used (250mm x 4.6 mm) at a flow of 0.5 $ml.min^{-1}$ hexan/isopropanol mixtures at temperatures between 20 °C and 40 °C.

Optical rotations were measured in a Perkin Elmer Polarimeter 341, sodium lamp, 1 dm cuvette lengths, c in g/100 ml.

TLC: Macherey-Nagel Polygram plates SIL GAJV254, 0.2 mm silica with fluorescence indicator.

Column chromatographic separations were performed on silica 60 (particle size 40-63 μm, 230-400 mesh) purchased al Merck, or Uetikon Chemie, accelerated by pressurised air or nitrogen (flash chromatography).

High-pressure hydrogenations (up to 50 bars) were carried out in 60 ml autoclaves of Premex AG, Lengnau, Switzerland. Hydrogen gas used in all experiments was purchased at Carbagas Switzerland at quality 45 (99.995%).

Reactions with air- or moisture-sensitive compounds were performed under an argon atmosphere using standard Schlenk techniques, or in a nitrogen atmosphere in a M. Braun glove box (H_20 <1 ppm, O2 <2 ppm). Glassware was oven-dried and then flame-dried under vacuum prior to use.

5.2 Purification of Chemicals

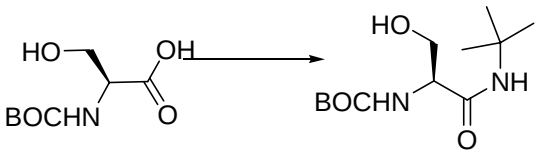
Diethyl ether, tetrahydrofuran, and toluene were dried over sodium/benzophenone, pentane over sodium-potassium alloy/benzophenone, dichloromethane over CaH_2 and freshly distilled under a stream of nitrogen prior to use. Other solvents were purchased dry at Fluka or Aldrich in septum sealed bottles and kept in an inert atmosphere over molecular sieves. When needed, solvents were degassed prior to use by three freeze-pump-thaw cycles. Diethylamine, diisopropylamine, and triethylamine were dried over CaF_2 and distilled under argon. Phosphorus trichloride was refluxed overnight under argon to remove hydrogen chloride and subsequently distilled under argon.

5.3 Abbreviations

arom.	aromatic
BINAP	2,2´-bis(diphenylphosphino)-1,1´-binaphthyl
BOC	*tert*-butoxacarbonyl
B.p.	boiling point
calc.	calculated
cat.	catalyst
CD	circular dichroisms
CI-MS	chemical ionisation
DABCO	1,4-diazabicyclo[2,2,2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI-MS	electron impact
eq	equivalent
FAB-MS	fast atom bombardment
GC	gas chromatoraphy
HPLC	high pressure liquid chromatography
IR	infrared spectrum
L	ligand
M	metal
M.p.	melting point
MS	mass spectrometry
Nu	nucleophile
R	organic substituent
R_f	retention factor
rt	room temperature
S	solvent
TBME	*tert*-butyl methyl ether
Tf	trifluoromethanesulfonyl
Tf_2NPh	1,1,1- trifluoro-N-phenyl-N-[(trifluoromethyl)sulfonyl]-methanesuldonimide
THF	tetrahydrofuran
TLC	tin layer chromatography
TMEDA	N,N,N´,N´-tetramethylethanediamine
TON	turnover number
t_R	retention time
triflate	trifluoromethanesulfonate

5.4 Synthesis of Phosphino-Oxazoline ligands

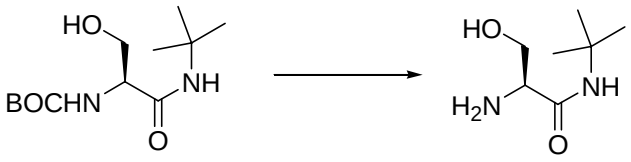
5.4.1 Synthesis of *tert*-butyl (S)-1-(*tert*-butylcarbamoyl)-2-hydroxyethylcarbamate



General Procedure. Tert-butylamine (1 ml, 9.7 mmol) and Boc-Ser-OH (2 g, 9.7 mmol) were suspended in dichloromethane (100ml) and cooled to O °C. Triethylamine (10.7 mmol, 1.48 ml) was added and the reaction mixture stirred for 15 minutes. EDC.HCl (3.7 g, 19.4 mmol) was added and the mixture stirred for a further 10 min. HOBt (1.3 g, 9.7mmol) was added and the reaction was stirred overnight, warming to room temperature. Water (70 ml) was added and the layers were separated. The organic layer was washed with 1M aq.HCl (50ml), saturated aq. $NaHCO_3$ (50ml) and dried (Na_2SO_4). After filtration and removal of the solvent under reduced pressure, NMR analysis showed the amide with >93 % purity which was used in the next step without further purification.

$C_{12}H_{24}N_2O_4$	(260.33)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.37 (s, 9H), 1.42 (s, 9H), 4.0 (m, 1H), 4.3 (m,1H), 4.5 (m, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 26 (CH_3), 28 (CH_3), 54 (C), 59 (CH_2), 61 (CH), 80 (C), 157 (C), 167 (C)

5.4.2 Synthesis of (S)-*N*-*tert*-butyl-2-amino-3-hydroxypropanamide

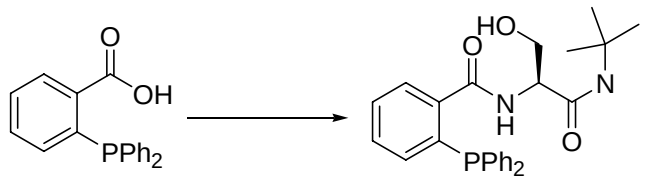


General Procedure. The crude amide (0.87 g, 3.3 mmol) was dissolved in anhydrous dichloromethane (80 ml) and trifluoroacetic acid (1.5 ml, 20 mmol) was added slowly over 5 minutes. The mixture was stirred for 8 hours at room temperature and then cooled to 0 °C. Saturated Na_2CO_3 (aq.) was added slowly (caution- gas evolved) until pH>10. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 30 ml). The combined

organic layers were dried (Na_2SO_4) and the solvent removed under vacuum. The product was be purified by column chromatography (SiO_2). Yield 90 %.

$C_7H_{16}N_2O_2$	(160.21)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 1.39 (s, 9H), 3.63 (m, 1H), 4.1 (m, 1H), 4.4 (m,1H), 6.35 (s, 1H), 7.51 (s, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 29 (CH_3), 52 (CH), 55 (C), 63 (CH_2), 168 (C)
Rf	0.3 (EtOac/Hexane 5/5)

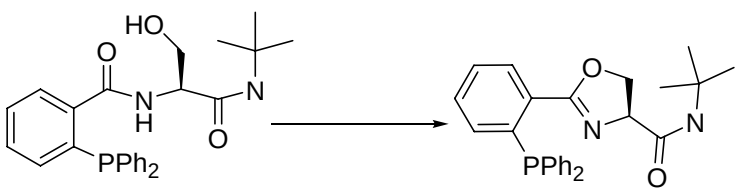
5.4.3 Synthesis of N-((S)-1-(*tert*-butylcarbamoyl)-2-hydroxyethyl)-2-(diphenylphosphino)-benzamide



Coupling following the general procedure (5.4.1) with (diphenylphosphino)benzoic acid (1.9 g, 6.2 mmol) and *tert*-butylserine-amide (1 g, 6.2 mmol) in 70 ml of degassed dichloromethane for 8 hours. Solvents for extraction were also degassed. Yield 93 %.

$C_{26}H_{29}N_2O_3P$	(448.49)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.31 (s, 9H), 4.38 (dd, 1H), 4.43 (dd, 1H), 4.55 (m, 1H), 6.22 (s, 1H), 7.0-7.99 (m, 14H)
^{31}P-NMR (162 MHz, $CDCl_3$)	δ -7.4

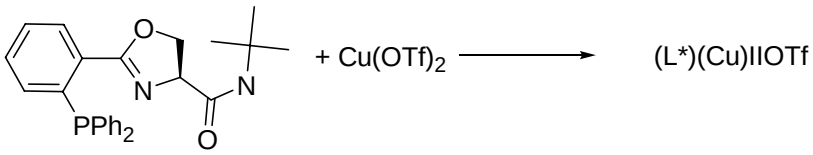
5.4.4 Synthesis of (S)-*N*-*tert*-butyl-4,5-dihydro-2-(2-(diphenylphosphino)-phenyl)oxazole-4-carboxamide **33**



The amidoalcohol (1.5 g, 3.3 mmol) and the *Burgess-Reagent* (0.86 g, 3.6 mmol) were placed under argon in an ampoule equipped with a magnetic stirring bar and a *Young*® valve, dissolved with 10 ml of degassed tetrahydrofuran. The ampoule was sealed under argon and the mixture stirred at 70 °C for 3h. The crude reaction mixture was directly purified by chromatography on silica-gel (SiO_2) using degassed solvents (EtOAc/Hexane 5/5). 70 % yield.

$C_{26}H_{27}N_2O_2P$	(430.48)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.36 (s, 9H), 4.49 (m, 2H), 4.68 (t, 1H, *J* = 8Hz), 7.0 (m, 1H), 7.2-7.35 (m, 12H), 7.9 (m, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 29 (CH_3), 51.2 (C), 70.5 (CH_2), 70.6 (CH), 128-139 (CH), 164.5 (C), 171 (C)
^{31}P-NMR (162 MHz, $CDCl_3$)	δ -12.5
Ir (KBr)	3303, 3052, 2966, 1675, 1521, 1476, 1433, 1363, 1226, 1092, 1050, 962, 849, 743, 695, 509
Rf	0.4 (hexan/ethyl acetate 6/4)
$(\alpha)_D^{20}$	-4.9 (c = 4.1, $CHCl_3$)

5.4.5 Copper-complex formation



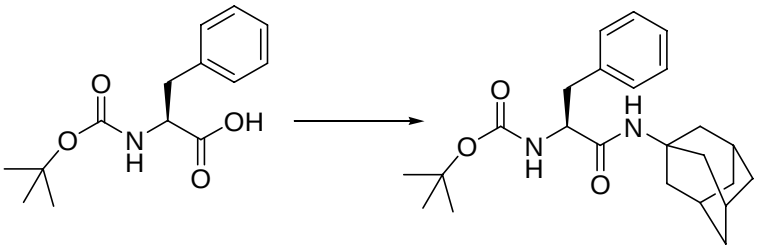
Synthesis following the general procedure (5.5.1.4) with oxazoline ligand **33** (0.5 g, 1.16 mmol) and copper (II)trifluormethanesulfonate (0.42 g, 1.16 mmol)

$C_{27}H_{27}CuF_3N_2O_5PS$	(643,09)
ESI-MS	493.1 (L+Cu, 100), 494.2 (31), 495.1 (49), 496.2 (10)

5.5 Synthesis of Imine ligands

5.5.1 *N*-adamantylphenylalanine-amide ligand

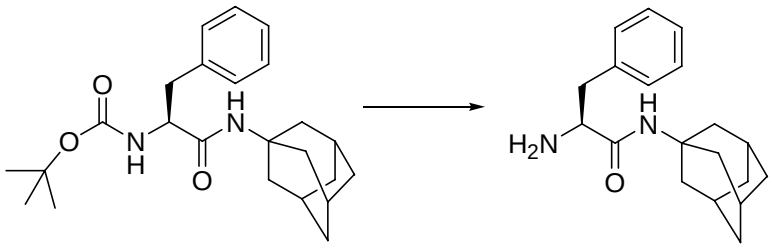
5.5.1.1 *tert*-butyl (S)-1-(adamantylcarbamoyl)-2-phenylethylcarbamate



Synthesis following the general procedure (5.4.1) with Boc-Phenylalanine (1 g, 3.7 mmol) and 1-Aminoadamantyl (0.7 g, 2.7 mmol) in 70 ml of dichloromethane for 12 hours. Yield 95 %

$C_{24}H_{34}N_2O_3$	(398.54)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 1.43 (s, 9H), 1.63 (m, 6H), 1.81 (m, 6H), 2.0 (m, 3H), 2.9 (m, 1H), 3.1 (m, 1H), 4.1 (m, 1H), 5.1 (m, 1H), 5.48 (m, 1H), 7.2-7.33 (m, 5H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 28.7 (CH), 29.7 (CH_3), 36.6, 39.6, 41.7, 52.3 (C), 52.5(C), 80.3 , 127-129 (CH),137.5 (C), 155.7 (C), 170.0 (C)

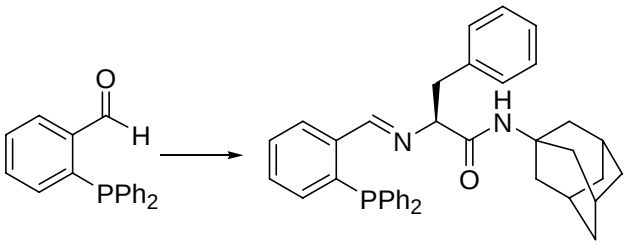
5.5.1.2 Synthesis of (S)-2-amino-N-adamantyl-3-phenylpropanamide



Synthesis following the general procedure (5.4.2) with Boc-*N*-adamantylphenylalanine-amide (1 g, 2.5 mmol) in 50 ml of dichloromethane for 10 hours. Yield 94 %.

$C_{19}H_{26}N_2O$	(298.42)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 1.63 (m, 6H), 1.95 (m, 6H), 2.1 (m, 3H), 2.7 (dd, 1H, *J* = 8.2, 4.1Hz, CH_2), 3.2 (dd, 1H, *J* = 0.42), 3.45 (q, 1H, *J* = 4.3Hz, CH_2), 7.2-7.33 (m, 5H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 29.8, 36.8, 41.5, 41.9, 51.5, 57.3(CH), 127-129 (CH),137.5 (C), 173.5 (C)

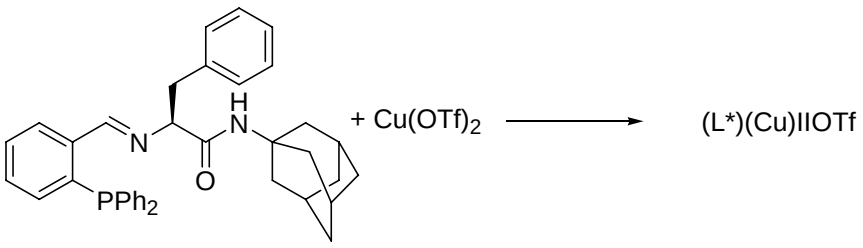
5.5.1.3 Synthesis of (S)-2-(2-(diphenylphosphino)benzylideneamino)-N-adamantyl-3-phenylpropanamide **35**



General procedure. N-adamantylphenylalanine-amide (1 g, 3.3 mmol) and diphenylphosphino benzaldehyde (0.95 g, 3.3 mmol) were dissolved in degassed trimethylorthoformate (15 ml) and stirred overnight. If HCl salt of the amine is used, 1.1 eq. of triethylamine is added. After 12 to 14 hours, the color turns from yellow to colourless. The solution was stripped to dryness under vaccum to give a white powder. NMR analysis showed the amine with >98 % purity wich was used in the next step without further purification (decomposition over silica-gel chromatography). Yield 95 %

$C_{38}H_{39}N_2OP$	(570.7)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.55 (m, 6H), 2.08 (m, 3H), 2.15 (m, 6H), 2.3 (dd, 1H), 3.25 (dd, 1H), 3.7 (dt, 1H), 6.55-7.4 (m, 19H), 7.72 (d, 1H, *J* = 3.3Hz)
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -13.3

5.5.1.4 Copper-complex formation



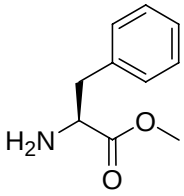
General procedure. The phosphino-imine ligand **35** (1g, 1.75 mmol) was placed together with one equivalent of copper (II)-trifluormethanesulfonate (0.63 g, 1.75 mmol) under argon atmosphere in a 50 ml flask equipped with a stirring bar. Degassed dichloromethane (10 ml) was added and the reaction mixture stirred at room temperature for 2h. A dark green solution was obtained. This green

solution was stripped to dryness and redissolved in dichloromethane, filtered and the complex precipitated with hexane to generate a green solid. The solid was characterized using ESI-MS

$C_{39}H_{39}CuF_3N_2O_4PS$	783.32
ESI-MS	1203.3 (45, 2L+Cu), 782.3 (50, L+Cu+Otf), 633.1 (100, L+Cu)

5.5.2 Methylphenylalanine-ester ligand

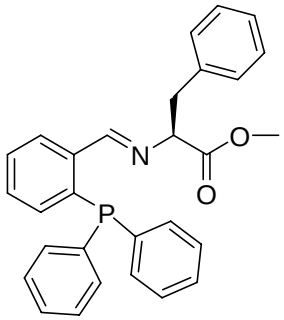
5.5.2.1 Synthesis of (S)-methyl 2-amino-3-phenylpropanoate



Synthesis following the general procedure (5.4.1, 5.4.2) with Boc-Phenylalanine (1g, 3.6 mmol) in methanol. Yield 89%.

$C_{10}H_{13}NO_2$	(179.22)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 2.99 (m, 1H), 3.26 (m, 1H), 3.61 (s, 3H), 3.9 (t, 1H), 7.0-8.1 (m, 5H)

5.5.2.2 Synthesis of (S)-methyl 2-(2-(diphenylphosphino)benzylideneamino)-3-phenylpropanoate **36**

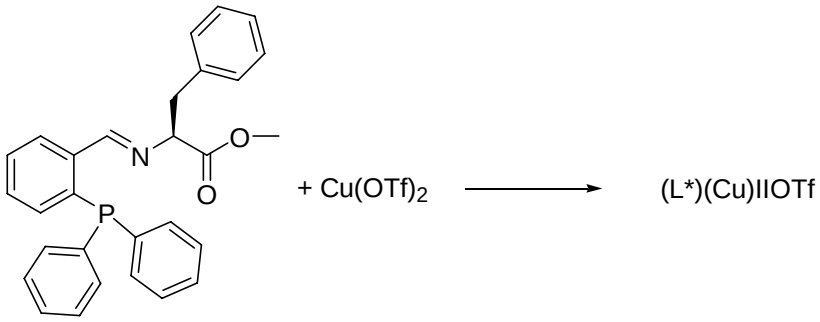


Synthesis following the general procedure (5.5.1.3) with methylphenylalanine-ester (1 g, 5.5 mmol) and diphenylphosphino benzaldehyde (1.6 g, 5.5 mmol). 98 % yield.

$C_{29}H_{26}NO_2P$	(451.5)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.9 (m, 1H), 3.25 (m, 1H), 3.6 (s, 3H), 4.1 (t, 1H, *J* = 7.3 Hz), 6.8-8.0 (m, 14H), 8.7 (d, 1H)

5.5.2.3 Copper-complex formation



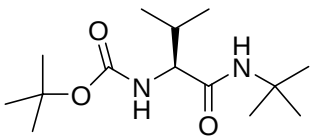
Synthesis following the general procedure (5.5.1.4) with phosphino-imine ligand (0.5 g, 1.1 mmol) and copper (II)-trifluormethanesulfonate (0.4 g, 1.1 mmol)

$C_{30}H_{26}CuF_3NO_5PS$ (664.11)

ESI-MS 965.1 (43, 2L+Cu), 663.2 (50, L+Cu+OTf), 514.3 (100, L+Cu)

5.5.3 *tert*-butylvaline-amide ligand

5.5.3.1 *tert*-butyl (*S*)-1-(*tert*-butylcarbamoyl)-2-methylpropylcarbamate

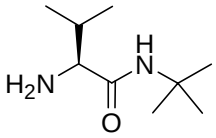


Synthesis following the general procedure (5.4.1) with Boc-Valine (2.1 g, 9.7 mmol) and *tert*-butylamine (1 ml, 9.7 mmol) in dichloromethane for 12 hours. Yield 94 %.

$C_{14}H_{28}N_2O_3$ (272.38)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.9 (dd, 6H), 1.32 (s, 9H), 1.41 (s, 9H), 2.05 (m, 1H), 3.7 (m, 1H)

5.5.3.2 (S)-*N*-*tert*-butyl-2-amino-3-methylbutanamide



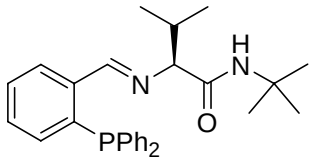
Synthesis following the general procedure (5.4.2) with Boc-*tert*-butylvaline-amide (1g, 3.6 mmol) in 50 ml of dichloromethane for 10 hours. Yield 96 %

$C_9H_{20}N_2O$ (172.27)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.8-0.95 (dd, 6H, *J* = 7.5, 61.0 Hz), 1.34 (s, 9H), 2.25 (m, 1H), 3.0 (d, 1H, 4.2 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 17, 20, 29, 31, 51 (C), 61, 174 (C)

5.5.3.3 Synthesis of (S)-2-(2-(diphenylphosphino)benzylideneamino)-*N*-*tert*-butyl-3-methylbutanamide **37**



Synthesis following the general procedure (5.5.1.3) with *tert*-butylvaline amide (1 g, 5.8 mmol) and diphenylphosphino benzaldehyde (1.68 g, 5.8 mmol). Yield 98 %.

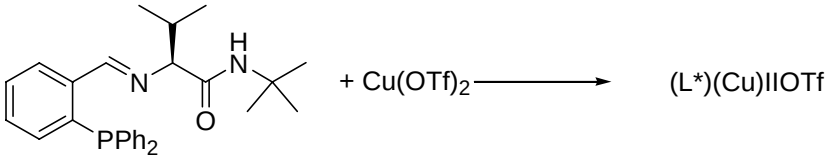
$C_{28}H_{33}N_2OP$ (444.55)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.38-0.59 (dd, 6H, *J* = 6.8, 83.6), 1.39 (s, 9H), 2.10 (m, 1H), 3.44 (d, 1H, *J* = 1.5 Hz), 6.90-7.77 (m, 14H), 8.43 (d, 1H, *J* = 3.6 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 16.9, 19.7, 29.4, 32.8, 51.5 (C), 81.7, 128.7-135.1, 161.8 (C)

^{31}P-NMR (162 MHz, $CDCl_3$) δ = -12

5.5.3.4 Copper-complex formation



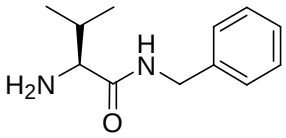
Synthesis following the general procedure (5.5.1.4) with phosphino-imine ligand (0.5 g, 1.12 mmol) and copper (II)-trifluormethanesulfonate (0.4 g, 1.12 mmol)

$C_{29}H_{33}CuF_3N_2O_4PS$ (657.16)

ESI-MS (MeOH) 950.9 (45, 2L+Cu), 656.1 (55, L+Cu+OTf), 507.3 (100, L+Cu)

5.5.4 Aniline-valine-amide

5.5.4.1 Synthesis of (S)-2-amino-N-benzyl-3-methylbutanamide

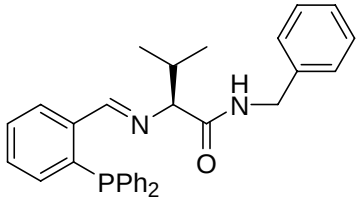


Synthesis following the general procedure (5.4.1, 5.4.2) with Boc-valine (1 g, 4.6 mmol) and benzylamine (0.5 ml, 4.6 mmol). Yield 89%.

$C_{12}H_{18}N_2O$ (206.28)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.9 (d, 3H, *J* = 11.2Hz), 1.0 (d, 3H, *J* = 11.2 Hz), 2.1(m, 1H), 3.52 (d, 1H, *J* = 4.2Hz), 4.5 (m, 2H), 6.7-7.2 (m, 19H)

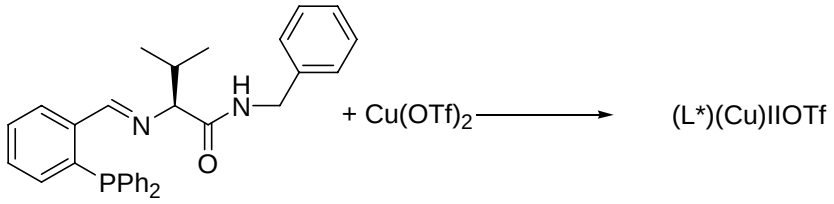
5.5.4.2 Synthesis of (S)-2-(2-(diphenylphosphino)benzylideneamino)-*N*-benzyl-3-methylbutanamide **38**



Synthesis following the general procedure (5.5.1.3) with benzylaminevaline-amide (1 g, 4.8 mmol) and diphenylphosphino benzaldehyde (1.4 g, 4.8 mmol). 98% yield.

$C_{31}H_{31}N_2OP$	(478.56)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.5 (d, 3H, *J* = 13.1Hz), 0.7 (d, 3H, *J* = 13.1 Hz), 2.3 (m, 1H), 3.62 (d, 1H, *J* = 4.3Hz), 4.3 (dd, 1H), 4.5 (dd, 1H), 6.65-7.4 (m, 19H), 8.4 (d, 1H, *J* = 4.2 Hz)

5.5.4.3 Copper-complex formation

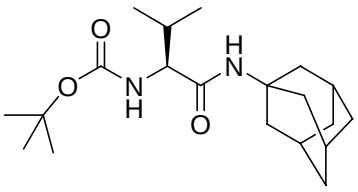


Synthesis following the general procedure (5.5.1.4) with phosphino-imine ligand (0.5 g, 1.0 mmol) and copper (II)-trifluormethanesulfonate (0.37 g, 1.0 mmol)

$C_{32}H_{31}CuF_3N_2O_4PS$	(691.18)
ESI-MS	1019.4 (30, 2L+Cu), 690.3 (55, L+Cu+OTf), 541.3 (100, L+Cu)

5.5.5 *N*-adamantylvaline ligand

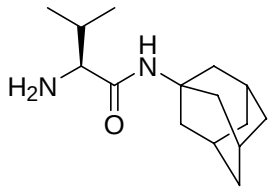
5.5.5.1 Synthesis of tert-butyl (S)-1-(adamantylcarbamoyl)-2-methylpropylcarbamate



Synthesis following the general procedure (5.4.1) with Boc-Valine (1 g, 4.6 mmol) and 1-aminoadamantyl (0.86 g, 4.6 mmol) in dichloromethane for 10 hours. Yield 93 %.

$C_{20}H_{34}N_2O_3$	(350.5)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.92 (dd, 6H, *J* = 7.7, 15.4 Hz), 1.43 (s, 9H), 1.66 (m, 6H), 1.97 (m, 6H), 2.06 (m, 3H), 3.68 (t, 1H, *J* = 0.86 Hz), 5.05 (m, 1H), 5.48 (m, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 19.6, 28.7, 29.8, 31.5 (C), 36.7 (CH), 41.9 (CH), 52.5(C), 60.9, 156.2 (C), 170.7 (C)

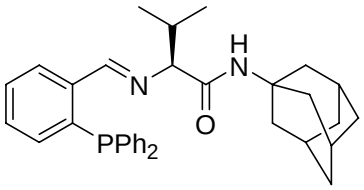
5.5.5.2 Synthesis of (S)-2-amino-N-adamantyl-3-methylbutanamide



Synthesis following the general procedure (5.4.2) with Boc-*N*- adamantylvaline-amide (1g, 2.8 mmol) in 50 ml of dichloromethane for 12 hours. Yield 94 %

$C_{15}H_{26}N_2O$	(250.38)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.53-0.69 (dd, 6H, *J* = 7.1,53.5 Hz), 1.4 (m, 6H), 1.72 (m, 6H), 1.78 (m, 3H), 1.91 (m, 1H), 2.79 (d, 1H, *J* = 7.1 Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 16.4 (CH_3), 20.1 (CH_3), 29.8 (CH), 31.3 (CH), 36.8 , 42.0, 51.5 (C), 60.9 (CH), 173.7 (C)

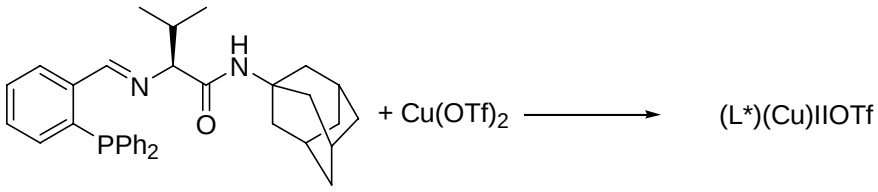
5.5.5.3 Synthesis of (S)-2-(2-(diphenylphosphino)benzylideneamino)-N-adamantyl-3-methylbutanamide **39**



Synthesis following the general procedure (5.5.1.3) with *N*-adamantylvaline-amide (1 g, 3.9 mmol) and diphenylphosphino benzaldehyde (1.16 g, 3.9 mmol). 98 % yield

$C_{34}H_{39}N_2OP$	(522.66)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.39 (d, 3H, *J* = 9.2Hz), 0.6 (d, 3H, *J* = 9.2Hz), 1.65 (m, 6H), 2.05 (m, 10H), 3.45 (d, 1H), 6.9-7.8 (m, 10H), 8.44 (d, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 16.7 (CH_3), 19.6 (CH_3), 29.9 (CH), 36.8, 42.2, 51.7 (C), 80.5 (CH), 128.0-136.1, 161.5 (C)
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -14.06

5.5.5.4 Copper-complex formation

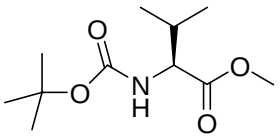


Synthesis following the general procedure (5.5.1.4) with phosphino-imine ligand (0.5 g, 0.95 mmol) and copper (II)-trifluormethanesulfonate (0.35 g, 0.95 mmol)

$C_{35}H_{39}CuF_3N_2O_4PS$	(735.28)
ESI-MS	1107.3 (43, 2L+Cu), 734.2 (51, L+Cu+OTf), 585.3 (L+Cu)

5.5.6 Methylvaline-ester ligand

5.5.6.1 *tert*-butyl (S)-1-(methoxycarbonyl)-2-methylpropylcarbamate

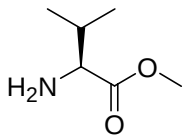


Synthesis following the general procedure (5.4.1) with Boc-Valine (1g, 4.6 mmol) in methanol for 10 hours. Yield 89 %

$C_{11}H_{21}NO_4$ (231.29)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (d, 3H , *J* = 6.8 Hz), 0.93 (d, 3H , *J* = 6.8 Hz), 1.41 (s, 9H), 2.1 (m, 1H), 3.7 (s, 3H), 5.0 (d, 1H, *J* = 8.3 Hz)

5.5.6.2 Synthesis of (S)-methyl 2-amino-3-methylbutanoate

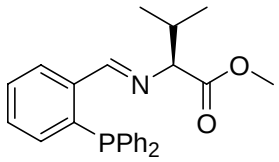


Synthesis following the general procedure (5.4.2) with Boc-methylvaline-amide (1g, 4.3 mmol) in 50 ml of dichloromethane for 12 hours. Yield 94 %

$C_6H_{13}NO_2$ (131.17)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.9 (d, 3H , *J* = 7.0 Hz), 1.1 (d, 3H , *J* = 7.0 Hz), 2.3 (m, 1H), 3.55 (s, 3H), 4.2 (d, 1H, *J* = 8.0 Hz)

5.5.6.3 Synthesis of (S)-methyl 2-(2-(diphenylphosphino)benzylideneamino)-3-methylbutanoate **40**

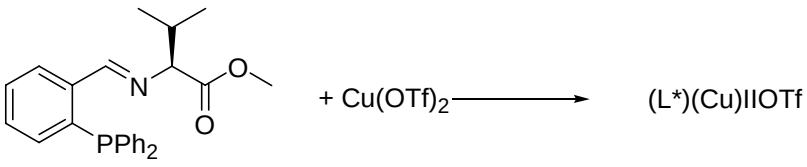


Synthesis following the general procedure (5.5.1.3) with methylvaline-ester (1 g, 7.6 mmol) and diphenylphosphino benzaldehyde (1.16 g, 3.9 mmol). 98 % yield

$C_{25}H_{26}NO_2P$ (403.45)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.86 (d, 3H , *J* = 7.1 Hz), 1.12 (d, 3H , *J* = 7.1 Hz), 2.5 (m, 1H), 3.7 (s, 3H), 4.6 (d, 1H, *J* = 8.0 Hz), 8.1 (s, 1H), 7.04-7.6 (m, 14H)

5.5.6.4 Copper-complex formation

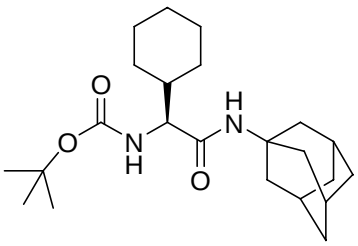


Synthesis following the general procedure (5.5.1.4) with phosphino-imine ligand (0.5 g, 1.24 mmol) and copper (II)-trifluormethanesulfonate (0.45 g, 1.24 mmol)

$C_{26}H_{26}CuF_3NO_5PS$	(616.07)
ESI-MS	869.4 (37, 2L+Cu), 615.3 (48, L+Cu+OTf), 466.3 (100, L+Cu)

5.5.7 *N*-adamantlycyclohexylglycine-amide ligand

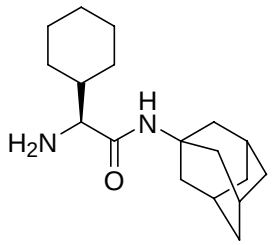
5.5.7.1 Synthesis of *tert*-butyl (S)-(adamantylcarbamoyl)(cyclohexyl)methylcarbamate



Synthesis following the general procedure (5.4.1) with Boc-cyclohexylglycine (1g, 3.88 mmol) and 1-aminoadamantyl (0.73 g, 3.9 mmol). 92 % yield

$C_{23}H_{38}N_2O_3$	(390.56)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.9-1.2 (m, 6H), 1.43 (s, 9H), 1,66 (m, 6H), 1,71 (m, 4H), 1.9 (m, 6H), 2.07 (m, 3H), 3.67 (t, 1H, *J* = 8.2Hz), 5.06 (d, 1H, *J* = 8.3Hz), 5.44 (s, 1H)

5.5.7.2 Synthesis of (S)-2-amino-2-cyclohexyl-N-adamantylacetamide

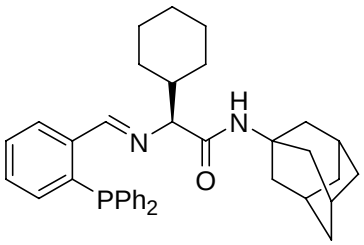


Synthesis following the general procedure (5.4.2) with Boc-*N*-adamantylcyclohexylglycine-amide (1g, 2.5 mmol) in 50 ml of dichloromethane for 11 hours. Yield 93 %

$C_{18}H_{30}N_2O$ (290.44)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.95-1.27 (m, 6H), 1,67 (m, 10H), 2.0 (m, 6H), 2.07 (m, 4H), 3.82 (d, 1H, J = 3.5Hz)

5.5.7.3 Synthesis of (S)-2-(2-(diphenylphosphino)benzylideneamino)-2-cyclohexyl-*N*-adamantylacetamide **41**

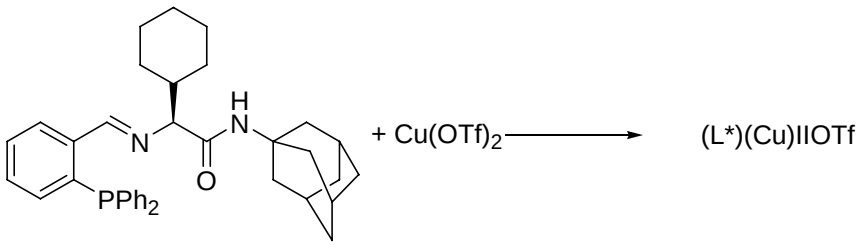


Synthesis following the general procedure (5.5.1.3) with *N*- adamantylcyclohexylglycine-amide (1 g, 7.6 mmol) and diphenylphosphino benzaldehyde (1.16 g, 3.9 mmol). 98 % yield

$C_{37}H_{43}N_2OP$ (562.72)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.90-1.35 (m, 6H), 1,7 (m, 10H), 2.1 (m, 10H), 3.42 (d, 1H), 6.8-7.8 (m, 14H), 8.3 (s, 1H)

5.5.7.4 Copper-complexe formation

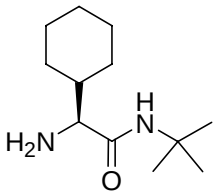


Synthesis following the general procedure (5.5.1.4) with phosphino-imine ligand (0.5 g, 0.88 mmol) and copper (II)trifluormethanesulfonate (0.32 g, 0.88 mmol)

$C_{38}H_{43}CuF_3N_2O_4PS$	(775.34)
ESI-MS	1187.3 (43, 2L+Cu), 774.3 (52, L+Cu+OTf), 625.4 (100, L+Cu)

5.5.8 *tert*-butlycyclohexylglycine-amide ligand

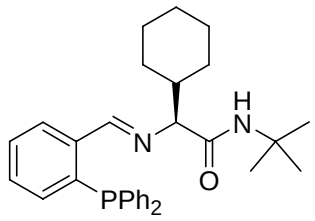
5.5.8.1 Synthesis of (S)-*N*-*tert*-butyl-2-amino-2-cyclohexylacetamide



Synthesis following the general procedure (5.4.1, 5.4.2) with Boc-cyclohexylglycine (1g, 3.2 mmol) and *tert*-butylamine (0.33 ml , 3.9 mmol) Yield 89%.

$C_{12}H_{24}N_2O$	(212.33)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.95-1.32 (m, 5H), 1.35 (s, 9H), 1.50-1.92 (m, 5H), 3.06 (d, 1H, *J* = 4.2 Hz), 5.05 (s, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 27, 27.2, 29 (CH_3), 31, 41.5 (CH), 51 (C), 61 (CH), 173.5 (C)

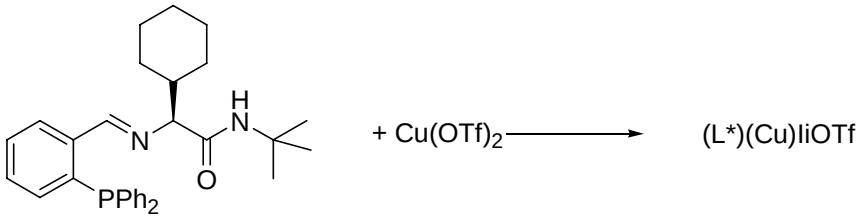
5.5.8.2 Synthesis of (S)-2-(2-(diphenylphosphino)benzylideneamino)-*N*-*tert*-butyl-2-cyclohexylacetamide **42**



Synthesis following the general procedure (5.5.1.3) with *tert*-butylcyclohexylglycine-amide (1 g, 4.7 mmol) and diphenylphosphino benzaldehyde (1.36 g, 4.7 mmol).97 % yield

$C_{31}H_{37}N_2OP$	(484.61)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 1.1-1.4 (m, 5H), 1.4 (s, 9H), 1.45-1.85 (m, 5H), 3.87 (d, 1H, *J* = 4.2 Hz), 8.05 (s, 1H), 7.1-7.6 (m, 14H)

5.5.8.3 Copper-complex formation

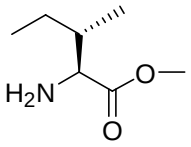


Synthesis following the general procedure (5.5.1.4) with phosphino-imine ligand (0.5 g, 1.0 mmol) and copper (II)-trifluormethanesulfonate (0.37 g, 1.0 mmol)

$C_{32}H_{37}CuF_3N_2O_4PS$	(697.23)
ESI-MS	1031.2 (45, 2L+Cu), 696.3 (55, L+Cu+OTf), 547.3 (100, L+Cu)

5.5.9 Methylisoleucine-ester

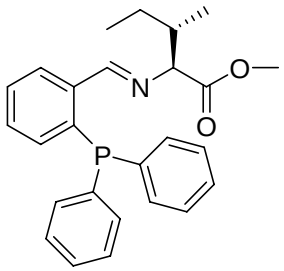
5.5.9.1 Synthesis of (2S,3S)-methyl 2-amino-3-methylpentanoate



Synthesis following the general procedure (5.4.1, 5.4.2) with Boc-isoleucine (1g, 4.3 mmol) Yield 90%.

$C_7H_{15}NO_2$	(145.2)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.95 (t, 3H, *J* = 6.9Hz), 1.1 (d, 3H, *J* = 7.0Hz), 1.41 (m, 1H), 1.51 (m, 1H), 2.19 (m, 1H), 3.8 (s, 3H), 4.1 (m, 1H)

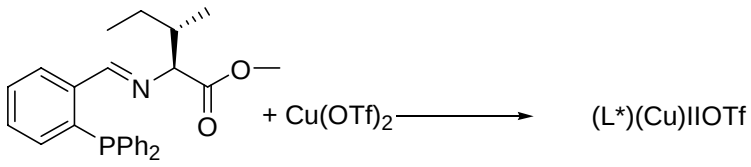
5.5.9.2 Synthesis of (2S,3S)-methyl 2-(2-(diphenylphosphino)benzylideneamino)-3-methylpentanoate **44**



Synthesis following the general procedure (5.5.1.3) with methylisoleucine-ester (1 g, 6.8 mmol) and diphenylphosphino benzaldehyde (2.0 g, 6.8 mmol). 97 % yield

$C_{26}H_{28}NO_2P$	(417.48)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.72 (t, 3H, *J* = 7.1Hz), 0.8 (d, 3H, *J* = 7.0Hz), 1.2-1.4 (m, 2H), 1.97 (m, 1H), 3.65 (s, 3H), 3.67 (d, 1H), 6.8-8.1 (m, 14H), 8.9 (d, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 11.3 (CH_3), 16.0 (CH_3), 22.7, 25.2, 34.5, 38.3 (CH) 52.1 (CH_3), 79.6 (CH), 128-140 (CH), 162.2 (CH), 172.6 (C)

5.5.9.3 Copper-complex synthesis



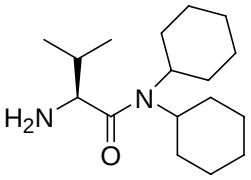
Synthesis following the general procedure (5.5.1.4) with phosphino-imine ligand (0.5 g, 1.2 mmol) and copper (II)trifluormethanesulfonate (0.43 g, 1.2 mmol)

$C_{27}H_{28}CuF_3NO_5PS$ (630.09)

ESI-MS 897.2 (40, 2L+Cu), 629.2 (56, L+Cu+OTf), 480.1 (100, L+Cu)

5.5.10 Dicyclohexylvaline-amide

5.5.10.1 Synthesis of (S)-2-amino-N,N-dicyclohexyl-3-methylbutanamide



Synthesis following the general procedure (5.4.1, 5.4.2) with Boc-valine (1g, 4.6 mmol) and dicyclohexylamine (0.83g, 4.6 mmol). Yield 92%.

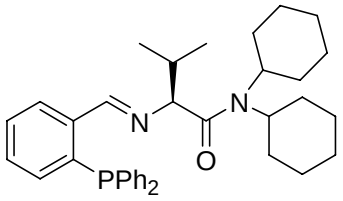
$C_{17}H_{32}N_2O$ (280.45)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.75 (d,3H), 0.85 (d, 3H), 1.0-1.8 (m, H), 2.5 (m, 1H), 3.6 (m, 1H), 3.68 (dt, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_3), 25.5, 26.0, 27.2, 31.3, 32.0 (CH), 53.2 (CH), 56.0 (CH), 175.3 (C)

EI-MS 280 (1), 237 (2), 209 (7), 180 (3.5), 166 (3) ,138 (4), 128 (3), 98 (4), 72 (100), 55 (24), 41 (10)

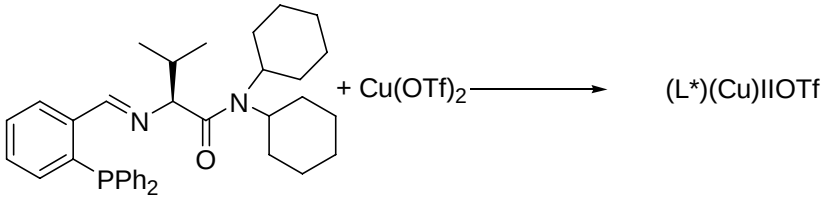
5.5.10.2 Synthesis of (S)-2-(2-(diphenylphosphino)benzylideneamino)-N,N-dicyclohexyl-3-methylbutanamide **45**



Synthesis following the general procedure (5.5.1.3) with dicyclohexylvaline-amide (1 g, 3.5 mmol) and diphenylphosphino benzaldehyde (1.0 g, 3.5 mmol). 98 % yield.

$C_{36}H_{45}N_2OP$	(552.73)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.6 (d,3H), 0.75 (d, 3H), 0.9-1.6 (m, H), 2.1 (m, 1H), 4.0 (m, 1H), 3.68 (dt, 2H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 21.2 (CH_3), 25.9, 26.3, 27.3, 31.5, 32.0 (CH), 53.2 (CH), 79.0 (CH), 125-135 (CH), 162 (CH), 173.3(C)
^{31}P-NMR (162 MHz, $CDCl_3$)	δ -16.7

5.5.10.3 Copper-complex synthesis

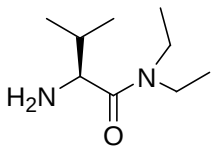


Synthesis following the general procedure (5.5.1.4) with phosphino-imine ligand (0.5 g, 0.9 mmol) and copper (II)-trifluormethanesulfonate (0.32 g, 0.9 mmol)

$C_{37}H_{45}CuF_3N_2O_4PS$	(765.34)
ESI-MS	1167.5 (45, 2L+Cu), 764.2 (55, L+Cu+OTf), 615.3 (100, L+Cu)

5.5.11 Diethylvaline-amide ligand

5.5.11.1 Synthesis of (S)-2-amino-N,N-diethyl-3-methylbutanamide



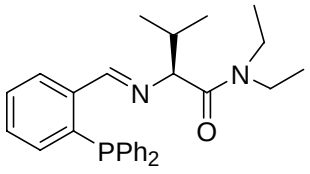
Synthesis following the general procedure (5.4.1, 5.4.2) with Boc-valanine (1g, 4.9 mmol) and diethylamine (0.52 ml, 4.9 mmol). Yield 89%.

$C_9H_{20}N_2O$ (172.27)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.86 (dd, 6H, *J* = 3.6 Hz), 1.03 (t, 3H, *J* = 7.2Hz), 1,12 (t, 3H, *J* = 7.2Hz), 1.75 (m, 1H), 3.12 (m, 2H), 3.24 (d, 1H, *J* = 6.6Hz), 3.31 (m, 1H), 3.51 (m, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 12 (CH_3), 14 (CH_3), 17 (CH_3), 21 (CH_3), 33 (CH) , 41 (CH_2), 42 (CH_2), 57 (CH), 174 (C)

5.5.11.2 Synthesis of (S)-2-(2-(diphenylphosphino)benzylideneamino)-N,N-diethyl-3-methylbutanamide **46**



Synthesis following the general procedure (5.5.1.3) with diethylvaline-amide (1 g, 5.8 mmol) and diphenylphosphino benzaldehyde (1.68 g, 5.8 mmol). 98 % yield.

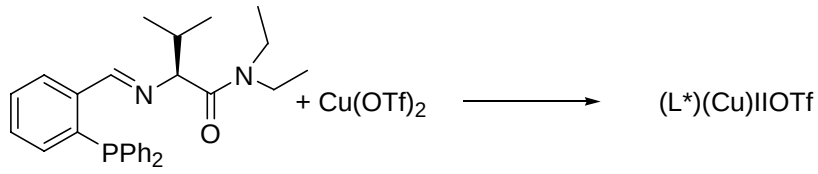
$C_{28}H_{33}N_2OP$ (444.55)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.63 (d, 3H, *J* = 7.6Hz), 0.87 (d, 3H, *J* = 7.6Hz), 0.98 (t, 3H, *J* = 6.3 Hz), 1.03 (t, 3H, *J* = 6.3 Hz), 2.3 (m, 1H), 2.9-3.3 (m, 4H), 3.7 (d, 1H, *J* = 10Hz), 6.8-8.1 (m, 14H), 8.92 (d, 1H, *J* = 7.5Hz)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 13 (CH_3), 15 (CH_3), 20 (CH_3), 21 (CH_3), 32 (CH), 40 (CH_2), 41 (CH_2), 80 (CH), 126-134 (CH), 161 (CH), 172 (C)

^{31}P-NMR (162 MHz, $CDCl_3$) δ -17.0

5.5.11.3 Copper complex synthesis



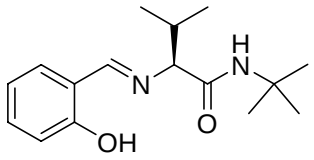
Synthesis following the general procedure (5.5.1.4) with phosphino-imine ligand (0.5 g, 1.1 mmol) and copper (II)-trifluormethanesulfonate (0.40 g, 1.1 mmol)

$C_{29}H_{33}CuF_3N_2O_4PS$ (657.16)

ESI-MS 951.4 (44, 2L+Cu), 656.2 (57, L+Cu+OTf), 507.2 (100, L+Cu)

5.5.12 *tert*-butylvaline-amide

5.5.12.1 Synthesis of (S)-2-(2-hydroxybenzylideneamino)-*N*-*tert*-butyl-3-methylbutanamide **48**



Synthesis following the general procedure (5.5.1.3) with *tert*-butylvaline-amide (1 g, 5.8 mmol) and salicylaldehyde (0.72 g, 5.8 mmol). 97 % yield.

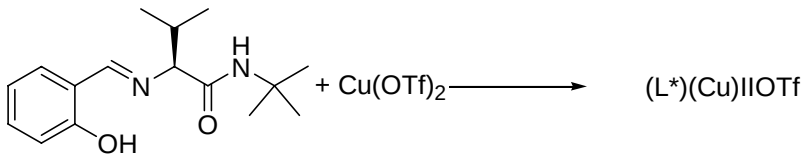
$C_{16}H_{24}N_2O_2$ (276.37)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.88 (d, 3H, *J* = 0.72Hz), 0.96 (d, 3H, *J* = 7.2Hz), 1.33 (s, 9H), 2.42 (m, 1H), 3.57 (d, 1H, *J* = 6.0Hz), 6.7-7.3 (m, 4H, Ar), 8.19 (s, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 18 (CH_3), 20 (CH_3), 29 (CH_3), 32 (CH), 52 (C), 80 (CH), 117-135 (CH, Ar), 161 (C), 168 (CH), 171 (C)

EI-MS	276 (47), 261 (1.5), 234 (1), 219 (4), 193 (1.5), 176 (100), 162 (47), 142 (29), 121 (10), 107 (23), 77 (22), 58 (24), 41 (23)
IR (KBr)	3329, 3212, 3053, 2931, 2872, 2790, 2364, 1673, 1535, 1570, 1523, 1391, 1360, 1224, 1153, 1046, 929, 762, 734, 569

5.5.12.2 Copper-complexe synthesis

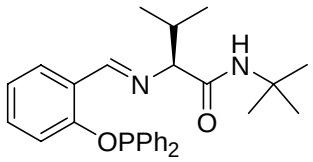


Synthesis following the general procedure (5.5.1.4) with benzylacohol ligand (0.5 g, 1.8 mmol) and copper (II)-trifluormethanesulfonate (0.65 g, 1.8 mmol)

$C_{17}H_{24}CuF_3N_2O_5S$	(488.99)
ESI-MS	338.1 (100, L+Cu)

5.6 Phosphite ligands

5.6.1 Synthesis of (S)-2-(2-diphenylphosphinitbenzylideneamino)-*N*-*tert*-butyl-3-methylbutanamide **49**

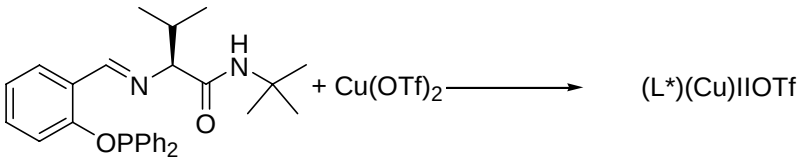


General Procedure. Under argon, the benzylacohol **48** (0.5 g, 1.8 mmol) was dissolved in 30 ml of dry tetrahydrofuran and cooled to -78 °C before slow addition of lithium diisopropylamine (2.7 mmol) over 5 min. The reaction mixture was further stirred for 25 min at -78 °C (color turns from pale yellow to coulorless). Chlorodiphenylphosphine (0.43 ml, 2.35 mmol) was added dropwise over 3 min and the reaction mixture was allowed to warm to room temperature over 30 min. The reaction mixture was stripped to dryness and redissolved in degassed diethyl ether, filtered and immediately purified by silica-gel chromatography under inert atmosphere. (Diethyl ether/hexane 9/1) to afford the diphenylphosphinite ligand **49** as a white solid. 75 % Yield.

$C_{28}H_{33}N_2O_2P$ (460.55)

^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.9 (d, 3H, *J* = 7.0Hz), 0.96 (d, 3H, *J* = 7.0Hz), 1.34 (s, 9H), 2.43 (m, 1H), 3.57 (d, 1H, *J* = 5.5Hz), 6.7-7.8 (m, 14H, Ar), 8.25 (s, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 18 (CH_3), 19 (CH_3), 29 (CH_3), 33 (CH), 51 (C), 81 (CH), 117-138 (CH, Ar), 161 (C), 168 (CH), 171 (C)
^{31}P-NMR (162 MHz, $CDCl_3$)	δ 112.2
Rf (diethyl ether/hexane 9/1)	0.25

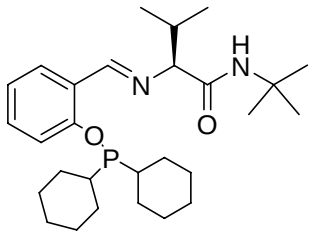
5.6.2 Copper-complex synthesis



Synthesis following the general procedure (5.5.1.4) with phosphinite-imine ligand (0.3 g, 0.65 mmol) and copper (II)-trifluormethanesulfonate (0.24 g, 0.65 mmol)

$C_{29}H_{33}CuF_3N_2O_5PS$	(673.16)
ESI-MS	983.4 (36, 2L+Cu), 672.1 (48, L+Cu+OTf), 523.2 (100, L+Cu)

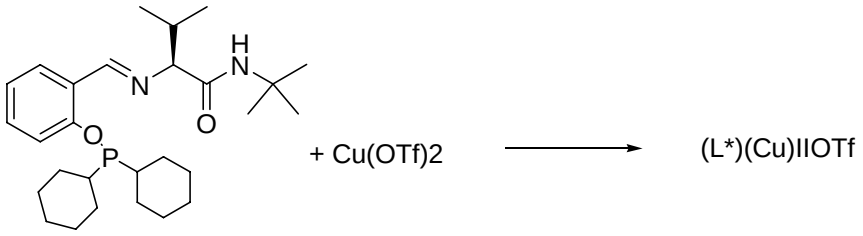
5.6.3 Synthesis of (S)-2-(2-dicyclohexylphosphinitbenzylideneamino)-*N*-*tert*-butyl-3-methylbutanamide



Synthesis following the general procedure (5.6.1) with benzylacohol (0.5 g, 1.08 mmol) and chlorodicyclohexylphosphine (1.4 mmol). 55 % Yield.

$C_{28}H_{45}N_2O_2P$	(472.64)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.8 (d, 3H), 1.05 (d, 3H), 1.1-2.0 (m, 22H), 1.35 (s, 9H), 2.61 (m, 1H), 3.5 (m, 1H), 6.65 (s, 1H), 8.55 (s, 1H)

5.6.4 Copper-complex synthesis



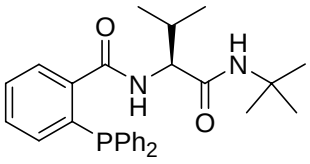
Synthesis following the general procedure (5.5.1.4) with phosphinite-imine ligand (0.3 g, 0.63 mmol) and copper (II)-trifluormethanesulfonate (0.23 g, 0.63 mmol)

$C_{29}H_{45}CuF_3N_2O_5PS$ (685.26)

ESI-MS 1007.6 (44, 2L+Cu), 684.2 (49, L+Cu+OTf), 535.3 (100, L+Cu)

5.7 Synthesis of Amide Ligands

5.7.1 Synthesis of *N*-((*S*)-1-(*tert*-butylcarbamoyl)-2-methylpropyl)-2-(diphenylphosphino)benzamide **51**



Coupling following the general procedure (5.4.1) with (diphenylphosphino)benzoic acid (1.9 g, 6.2 mmol) and *tert*-butylvaline-amide (1.07 g, 6.2 mmol) in 70 ml of degassed dichloromethane for 8 hours. Solvents for extraction were also degassed. Yield 93 %.

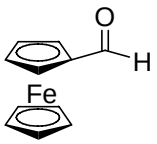
$C_{28}H_{33}N_2O_2P$ (460.55)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.45-0.60 (dd, 6H, J = 7.0, 74.0), 1.42 (s, 9H), 2.8 (m, 1H), 4.6 (m, 1H), 6.98-7.9 (m, 14H)

ESI-MS 525.3 (52, L+Cu), 524.4 (34), 523.5 (100)

5.8 Synthesis of Ferrocene-imine ligands

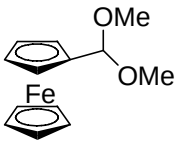
5.8.1 Synthesis of ferrocenecarbaldehyde **56**



In an argon-flushed flask was introduced ferrocene (10 g, 53.75 mmol) and dried under high vacuum for 12 h. Dry Potassium *tert*-butoxide (0.75 g, 6.7 mmol) was added under argon and the mixture was dissolved in 300 ml of dry tetrahydrofuran and cooled at -78°C in a dry ice/acetone bath. Over a period of 15 min, *t*-BuLi (0.1 mol) was added dropwise and the mixture stirred at -78 °C for 2h before dropwise addition of DMF (0.12 mol, 9.7 ml). The cooling bath was removed and the solution allowed to warm to -30 °C. At this point the solution was hydrolysed with water (20 ml), which turned the mixture deep red. Solvents were removed under vacuum and the aldehyde extracted with dichloromethane (3 x 100 ml). Extracts were combined and the solvent removed under vacuum. Products were separated by flash chromatography on silica-gel using first hexane (first fraction: unreacted ferrocene) then dichloromethane (second fraction: ferrocene monoaldehyde). Yield 90 %.

$C_{11}H_{10}FeO$	(214.04)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 4.20 (s, 5H), 4.6 (s, 2H), 4.8 (s, 2H), 9.95 (s, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 70.0, 72.3
Rf (CH_2Cl_2)	0.6

5.8.2 Synthesis of (dimethoxymethyl)ferrocene **57**



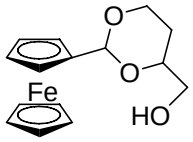
Ferrocenecarbaldehyde **56** (5 g, 23.3 mmol) was dissolved in 50 ml of trimethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid monohydrate (0.2 g, 1.0 mmol) was added. The dark red solution was refluxed for 12h. The solution was filtered on Celite and further eluted with diethyl ether until the filtrate was colorless. After removal of the solvents and drying under vacuum overnight, crude acetal **57** was quantitatively isolated.

$C_{13}H_{16}FeO_2$ (260.11)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.29 (s, 6H), 4.13 (m, 2H), 4.15 (s, 5H), 4.3 (m, 2H), 5.41 (s, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 52.5 (CH_3), 67.5 (CH_3), 68.2 (CH_3), 69.2 (CH_3), 85.5 (C), 102.9 (CH)

5.8.3 Synthesis of (2-ferrocenyl-1,3-dioxan-4-yl)methanol

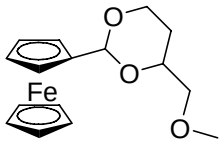


Butane-1,2,4-triol (2.5 g, 23.4 mmol) was introduced under argon in a 100 ml flask and dried by mixing with dry diethyl ether and removing the solvent under vacuum overnight. The triol was dissolved in 30 ml of dry dichloromethane, 15 g of activated 4A molecular sieves and a catalytic amount of camphorsulfonic acid (0.26 g, 1.1 mmol) were introduced. The crude ferrocene-acetal **57** was dissolved in 10 ml of dry dichloromethane, added to the flask and stirred overnight at room temperature. The crude reaction mixture was directly filtered on Celite, eluted with dry dichloromethane and the solvent removed under vacuum. The obtained yellow triol acetal was placed in freezer for 3 days. The yellow crystals formed were washed with a minimum amount of cold toluene and filtered. Yield 75 %.

$C_{15}H_{18}FeO_3$ (302.15)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.39 (m, 1H), 1.8 (m, 1H), 3.65 (m, 2H), 3.95 (m, 2H), 4.12 (m, 2H), 4.20 (s, 5H), 4.22 (m, 1H), 4.4 (m, 2H), 5.41 (s, 1H)

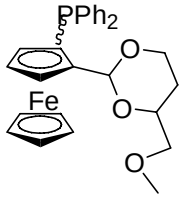
5.8.4 Synthesis of 2-ferrocenyl-4-(methoxymethyl)-1,3-dioxane **58**



Sodium hydride (20.0 mmol) was placed in a flask under inert atmosphere and 10 ml of dry tetrahydrofuran was added. The mixture was cooled at 0 °C and the triol-acetal (4 g, 13.2 mmol) in 40 ml of dry tetrahydrofuran was added dropwise over one hour (*caution*. Hydrogen evolved). Iodomethane (1.3 ml, 20.0 mmol) was then added dropwise and the reaction mixture allowed to warm to room temperature overnight. The reaction mixture was cooled to 0 °C and methanol slowly added until bubbling ceased. Solvents were removed under vacuum and the crude brown oil was purified by flash chromatography on silica-gel (Hexane/diethyl ether 6/4) followed by crystalisation in freezer. Yellow crystals, 92 % yield.

$C_{16}H_{20}FeO_3$	(316.17)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.47 (m, 1H), 1.8 (m, 2H), 3.45 (s, 3H), 3.55 (m, 2H), 3.9 (m, 1H), 4.0 (m, 1H), 4.1-4.35 (m, 10H), 5.40 (s, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 27.9 (CH_2), 59.3, 66.5, 66.6, 67.7, 67.8, 68.7, 69.5, 75.5, 75.9, 85.9, 100.0
Rf (Hexane / diethyl ether 6/4)	0.5

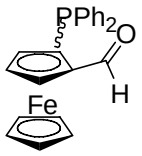
5.8.5 Synthesis of (2-(4-(methoxymethyl)-1,3-dioxan-2-yl)ferrocenyl)diphenylphosphine **59**



The triol-acetal **58** (2 g, 6.3 mmol) was placed under argon in a flask and dissolved in dry diethyl ether (30 ml). The solution was cooled to -78 °C and *t*-BuLi (1.1 equivalent) was added dropwise, giving a yellow precipitate. The cooling bath was removed and the reaction mixture stirred at room temperature for one hour, the solution turning to orange. The reaction mixture was cooled again at –30 °C and chlorodiphenylphosphine (1.2 eq., 1.4 ml) was added dropwise. The solution was allowed to warm to room temperature and further stirred for 3 hours before quenching with degassed water (1 ml), and the solvents were removed under vacuum. The crude reaction mixture was purified by flash chromatography on silica-gel (Hexane / diethyl ether 8/2). Yield 63 %

$C_{28}H_{30}FeO_3P$	(501.35)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.35 (m, 1H), 1.75 (m, 1H), 2.91 (d, 2H), 3.1 (s, 3H), 3.5 (m, 1H), 3.9 (m, 1H), 4.05 (s, 5H), 4.25 (m, 2H), 5.62 (d, 1H), 7.1-7.6 (m, 10H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 23 (CH_2), 59.8, 66.2, 66.4, 67.3, 68.7, 71.3, 76.5, 77.3, 100.7, 128-137
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -24.1
Rf (Hexane / diethyl ether 8/2)	0.3

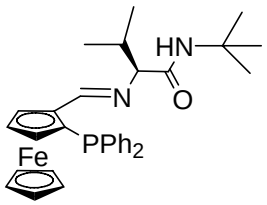
5.8.6 Synthesis of 2-(diphenylphosphino)ferrocenecarbaldehyde **60**



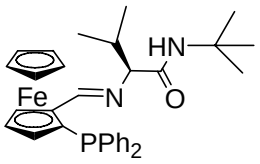
The phosphino acetal **59** (1 g, 2.0 mmol) was dissolved under argon in dry dichloromethane (25 ml) and 7 ml of degassed water were added followed by *p*-toluenesulfonic acid monohydrate (0.6 g, 3.0 mmol). The solution was stirred at room temperature for 12 h and extracted with diethyl ether. Solvents were removed under vacuum and the reaction product purified by flash chromatography on silica-gel (Hexane / diethyl ether 5/5). Yield 90 %.

$C_{23}H_{20}FeOP$	(399.22)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 4.07 (m, 1H), 4.21 (s, 5H), 4.69 (m, 1H), 5.1 (m, 1H), 7.1-8.0 (m, 10H), 10.21 (d, 1H, J = 3.0Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 71.1, 74.2, 76.2, 80.3, 83.4, 128.3, 130.0, 132.2, 135.5, 136.3, 193.3
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -26.0

5.8.7 Synthesis of (*S,* S_{Fc}) and (*S,* R_{Fc})-2-((2-(diphenylphosphino)-ferrocenyl)methyleneamino)-*N*-*tert*-butyl-3-methylbutanamide **62**



(S, S_{Fc})



(S, R_{Fc})

Synthesis following the general procedure (5.5.1.3) with *tert*-butylvaline-amide (0.43 g, 2.5 mmol) and racemic diphenylphosphino-ferrocenecarbaldehyde **60** (1 g, 2.5 mmol). A minimal amount of degassed dichloromethane was added to solubilise the diphenylphosphino-ferrocenaldehyde. The reaction mixture was left to stirr at room temperature for 24 hours. The solution was stripped to dryness under vaccum to give an orange-red powder. The crude reaction mixture was directly purified by chromatography on silica-gel (SiO_2) using degassed solvents (Hexane/Et_2O 8/2). Single crystals of the (S, R_{Fc})-diastereoisomer suitable for X-ray crystallography were obtained by recrystallisation from Et_2O. Yield: 80 %

Analytical Data of (S, S_{Fc})

$C_{32}H_{37}FeN_2OP$	(552.47)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.23 (d, 3H, J = 0.7Hz), 0.54 (d, 3H, „J = 0.7Hz), 1.52 (s, 9H), 1.95 (m, 1H), 3.35 (m, 1H), 3.74 (m, 1H), 4.16 (s, 5H), 4.4 (m, 1H), 4.76 (m, 1H), 7.05-7.6 (m, 10H), 8.05 (s, 1H)
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -21.3
IR (KBr)	3311, 3069, 2960, 2869, 1669, 1513, 1452, 1433, 1360,1278, 1224, 1106, 1025, 1001, 820, 742, 696, 619, 489, 457
ESI-MS	613.4 (7), 614.5 (3), 615.3 (M+Cu, 100), 616.3 (37), 617.3 (49), 618.3 (16), 619.3 (3)
$(\alpha)_D^{20}$	-42.0 (c = 0.4, $CHCl_3$)
Rf	0.31 (hexane/Et_2O 8/2)

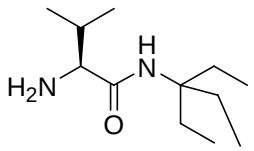
Analytical Data of (S, R_{Fc})

$C_{32}H_{37}FeN_2OP$	(552.47)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.80 (d, 3H, J = 0.7Hz), 0.90 (d, 3H, „J = 0.7Hz), 1.19 (s, 9H), 2.1 (m, 1H), 3.34 (d, 1H, J = 0.51Hz), 3.87 (m, 1H), 4.11 (s, 5H), 4.48 (m, 1H), 4.94 (m, 1H), 7.1-7.55 (m, 10H), 8.18 (s, 1H)

^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -24.4
IR (KBr)	3361, 3080, 2959, 2924, 2845, 1667, 1636, 1516, 1453, 1433, 1364, 1318, 1280, 1280, 1224, 1106, 1002, 829, 746, 698, 604, 589, 496, 483, 443
$(\alpha)_D^{20}$	-84.8 (c = 0.65, $CHCl_3$)
Rf	0.40 (hexane/Et_2O 8/2)

5.9 Synthesis of Diethylpropylvaline-amide Ferrocenyl Ligand

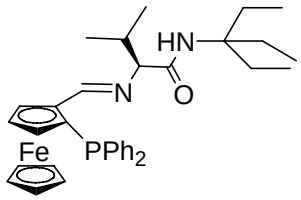
5.9.1 Synthesis of (*S*)-2-amino-*N*-(3-ethylpentan-3-yl)-3-methylbutanamide



Synthesis following the general procedure (5.4.1, 5.4.2) with Boc-valine (1 g, 4.6 mmol) and 1,1-diethyl-propylamine (4.6 mmol). Yield 89%.

$C_{12}H_{26}N_2O$	(214.35)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.70 (t, 9H, *J* = 0.76Hz), 0.75 (d, 3H, *J* = 0.68 Hz), 0.91 (d, 3H, *J* = 0.68 Hz), 1.63 (m, 6H), 2.23 (m, 1H), 3.05 (d, 1H, *J* = 0.40 Hz), 6.87 (s, 1H)

5.9.2 Synthesis of (*S, S*$_{Fc}$)-2-((2-(diphenylphosphino)-ferrocenyl)methyleneamino)-*N*-(3-ethylpentan-3-yl)-3-methylbutanamide **63**

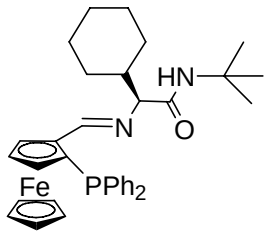


Synthesis following the general procedure (5.8.7) with diethylpropylvaline-amide (0.54 g, 2.5 mmol) and racemic diphenylphosphino-ferrocenecarbaldehyde (1 g, 2.5 mmol). A minimal amount of degassed dichloromethane was added to solubilise the diphenylphosphino-ferrocenaldehyde.

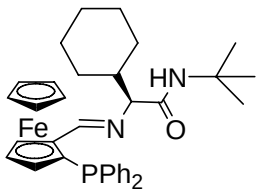
The reaction mixture was left to stirr at room temperature for 24 hours. The solution was stripped to dryness under vaccum to give an orange-red powder. The crude reaction mixture was directly purified by chromatography on silica-gel (SiO_2) using degassed solvents (Hexane/Et_2O 7/3). Yield 30%

$C_{35}H_{43}FeN_2OP$	(594.55)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.2 (d, 3H, *J* = 0.68Hz), 0.55 (d, 3H, *J* = 0.68Hz), 0.86 (t, 9H, d, 3H, *J* = 0.76Hz), 1.87 (m, 6H), 2.0 (m, 1H), 3.35 (m, 1H), 3.7 (s, 1H), 4.15 (s, 5H), 4.41 (m, 1H), 4.76 (m, 1H), 6.94-7.5 (m, 10H), 8.03 (s, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 8.7, 18.5, 21.1, 28.7, 33.5, 61.0, 71.8, 72.0, 72.5, 75.0, 75.9, 128-137, 185
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -22.3
$(\alpha)_D^{20}$	-39.0 (c = 0.5, $CHCl_3$)
Rf	0.5 (hexane /Et_2O 7/3)

5.10 Synthesis of Synthesis of (S,S_{Fc}) and (S,R_{Fc})-2-((2-(diphenylphosphino)-ferrocenyl)methyleneamino)-*N*-*tert*-butyl-2-cyclohexylacetamide **64**



(S, S_{Fc})



(S, R_{Fc})

Synthesis following the general procedure (5.8.7) with *tert*-butylcyclohexylglycine-amide (0.53 g, 2.5 mmol) and racemic diphenylphosphino-ferrocenecarbaldehyde (1 g, 2.5 mmol). Yield 60%

Analytical Data for (S, S_{Fc})

$C_{35}H_{41}FeN_2OP$	(592.53)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.5-1.80 (m, 6H), 1.53 (s, 9H), 3.35 (m, 1H), 3.7 (m, 1H), 4.16 (s, 5H), 4.39 (t, 1H, *J* = 0.33Hz), 4.73 (m, 1H), 7.1-7.5 (m, 10H), 8.0 (s, 1H)
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -21.4

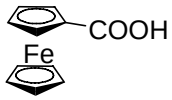
$(\alpha)_D^{20}$	-45.0 (c = 0.5, $CHCl_3$)
Rf	0.33 (hexane/Et_2O 8/2)

Analytical Data for (*S, R_{Fc}*)

$C_{35}H_{41}FeN_2OP$	(592.53)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.0-1.55 (m, 5H), 1.21 (s, 9H), 1.85 (m, 1H), 3.35 (d, 1H, *J* = 0.43Hz), 3.85 (m, 1H), 4.11 (s, 5H), 4.48 (t, 1H, *J* = 0.3Hz), 4.93 (m, 1H), 6.28 (s, 1H), 7.1-7.55 (m, 10H), 8.15 (d, 1H, *J* = 0.2Hz)
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -24.5
$(\alpha)_D^{20}$	-90.0 (c = 0.6, $CHCl_3$)
Rf	0.41 (hexane/Et_2O 8/2)

5.11 Synthesis of Ferroceme-amide Ligands

5.11.1 Synthesis of ferrocenecarboxylic acid **67**

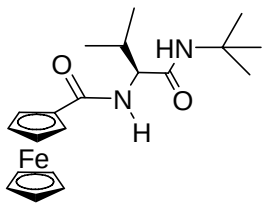


In an argon-flushed two-neck flask was introduced ferrocene (10 g, 53.75 mmol) and dried under high vacuum for 12 h. Dry Potassium *tert*-butoxide (0.75 g, 6.7 mmol) was added under argon and the mixture was dissolved in 300 ml of dry tetrahydrofuran and cooled at -78°C in a dry ice/acetone bath. Over a period of 15 min, *t*-BuLi (0.1 mol) was added dropwise and the mixture stirred at that temperature for 2h. 5g of dry-ice were introduced in a flask and CO_2 transferred to the reaction mixture by canula (*caution:* pressure must be released).The cooling bath was removed and the solution allowed to warm to -30 °C while CO_2 was kept bubling. The colour turned deep red. At this point the solution was hydrolysed with water (20 ml) and the acid extracted with dichloromethane (3 x 100 ml). Extracts were combined and the solvent removed under vacuum. Products were separated by flash chromatography on silica-gel using first hexane (first fraction: unreacted ferrocene) then hexane/ethyl acetate (second fraction: ferrocenecarboxylic acid). Yield 65 %.

$C_{11}H_{10}FeO_2$ (230.04)

^{1}H-NMR (400 MHz, $CDCl_3$)	δ 4.26 (s, 5H), 4.48 (s, 2H), 4.88 (s, 2H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 63.5, 70.5, 71, 72.3, 112
Rf	0.45 (hexane/EtOAc 7/3)

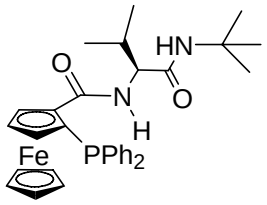
5.11.2 Synthesis of *N*-((*S*)-1-(*tert*-butylcarbamoyl)-2-methylpropyl)ferrocenecarboxamide **68**



Synthesis following the general procedure (5.4.1) with ferrocenecarboxylic acid **67** (2 g, 8.7 mmol) and *tert*-butylvaline-amide (1.5g, 8.7 mmol) in dichloromethane for 12 hours. The crude reaction mixture was filtered over celite eluting with dichloromethane. Solvents were removed under vacuum and the filtrate purified by silica-gel chromatography eluting with EtOAc/Hexane 7/3. Yield 94 %.

$C_{20}H_{28}FeN_2O_2$	(384.29)
^{1}H-NMR (400 MHz, $CDCl_3$) :	δ 1.0 (t, 6H, *J* = 0.43Hz), 1.37 (s, 9H), 2.1 (m, 1H), 4.2 (s, 6H), 4.38 (s, 2H), 4.72 (s, 2H), 5.89 (s, 1H), 6.45 (s, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 19.1, 20.1, 29.2, 32.2, 63.2, 69.2, 70.5, 71.2, 169, 172
IR (KBr)	3309, 3086, 2966, 2873, 1629, 1540, 1457, 1389, 1363, 1308, 1267, 1226, 1106, 1022, 1002, 920, 817, 771, 702, 638, 569, 484

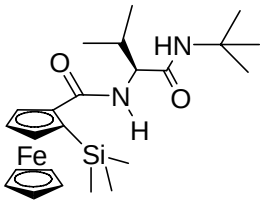
5.11.3 Synthesis of *N*-((*S*,S_{Fc})-1-(*tert*-butylcarbamoyl)-2-methylpropyl)-2-(diphenylphosphino)ferrocenecarboxamide **69**



To a suspension of ferrocenecarboxamide **68** (0.5 g, 1.3 mmol) in 50 ml of dry tertrahydrofuran at -78 °C was added dropwise under argon three equivalents of a 1.3M solution of *sec*-BuLi. The reaction mixture was left to stirr at -78 °C for two hours, the colour turning to deep red before addition of chlorodiphenylphosphine (0.83 ml, 4.5 mmol). The reaction mixture became yellow and was allowed to warm to room temperature over one hour. Solvents were evaporated and the residu stripped to dryness under high vacuum, redissolved in 5ml of dry diethyl ether, filtered and immediately purified by column chromatography on silica-gel eluting with hexane/EtOAc (5/5). Yield 70%

$C_{32}H_{37}FeN_2O_2P$	(568.47)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.65 (d, 3H, *J* = 0.75Hz), 0.77 (d, 3H, *J* = 0.75Hz), 1.4 (s, 9H), 2.05 (m, 1H), 3.76 (m, 1H), 4.14 (m, 1H), 4.17 (s, 5H), 4.45(t, 1H, *J* = 0.25Hz), 5.15 (m, 1H), 5.9 (m, 1H), 7.1-7.7 (m, 10H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 19.0, 20.0, 23.3, 29.2, 31.2, 52.3, 60.2,63.3, 70.9, 71.2, 75.0, 129-139, 170, 172
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -23.69
ESI-MS (MeOH)	629.4 (2), 631.3 (M+Cu, 100), 632.3 (27), 633.3 (44), 634.2 (14), 635.2 (2), 1197.3 (5), 1198.1 (2), 1199.1 (2M+Cu, 44), 1200.1 (34), 1201.1 (32), 1202.1 (17), 1203.1 (4)
Rf	0.5 (hexane/EtOAc 5/5)

5.11.4 Synthesis of *N*-((*S*,S_{Fc})-1-(*tert*-butylcarbamoyl)-2-methylpropyl)-2-(trimethylsilyl)ferrocenecarboxamide **71**

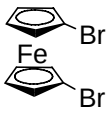


Synthesis following the procedure described in 5.11.3 with ferrocenecarboxamide **68** (0.5g, 1.3 mmol) and chlorotrimethylsilane (4.5 mmol). Yield 10%.

$C_{23}H_{36}FeN_2O_2Si$	(456.47)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.31 (s, 9H), 1.04 (m, 6H) 1.34 (s, 9H), 2.15 (m, 1H), 4.14 (m, 1H), 4.22 (s, 5H), 4.32 (m, 1H), 4.45(m, 1H), 4.74 (m, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	0.5 (CH_3), 19, 20, 29.3, 30.4, 53, 54, 70.5, 170
ESI-MS (MeOH)	456.3 (12), 457.4 (100), 458.3 (32), 459.2 (10)

5.12 Axially Chiral Ligands

5.12.1 Synthesis of 1-1'-dibromoferrocene **75**



In a argon-flushed flask was introduced ferrocene (10 g, 53.75 mmol) and dried under high vacuum for 12 h. The mixture was dissolved in 300 ml of dry tetrahydrofuran and cooled at -78 °C in a dry ice/acetone bath. Over a period of 15 min, *n*-BuLi (0.1 mol) was added dropwise and the mixture stirred at that temperature for 2h before dropwise addition over 12h of a solution of tetrabromoethane (0.12 mol) in 10 ml of dry terahydrofuran. The cooling bath was removed and the solution allowed warming to -30 °C. At this point the solution was hydrolysed with water (20 ml), which turned the mixture deep red. Solvents were removed under vacuum and the aldehyde extracted with dichloromethane (3 x 100 ml). Extracts were combined and the solvent removed under vacuum. Products were separated by flash chromatography on silica-gel using first hexane (first fraction: unreacted ferrocene) then dichloromethane (second fraction: dibromoferrocene). Yield 90 %.

$C_{10}H_8Br_2Fe$	(343.82)

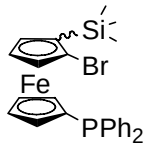
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 4.17 (s, 4H), 4.42 (s, 4H)
MS	344 (100), 263 (3.5), 199 (2), 182 (2), 157 (2), 128 (91), 102 (13.5), 78 (4.5), 56 (22)

5.12.2 Synthesis of 2(bromo(1'-bromo)ferrocenyl)trimethylsilane **76**

To a suspension of dibromoferrocene **75** (3g, 8.7 mmol) in 70 ml of dry tertrahydrofuran at -78° C was added dropwise under argon a solution of LDA prepared by addition of 5.6ml of a 2M solution of *n*-BuLi on a solution of 1.6 ml (11.3 mmol) of diisopropylamine in 10 ml of THF at -78 °C. The reaction mixture was left to stirr at -78 °C for two hours, the colour turning to deep red before addition of chlorotrimethylsilane (8.7 mmol). The reaction mixture became yellow and was allowed to warm to room temperature over one hour. The reaction was quenched with 10 ml of water, extracted with diethyl ether (3x 80 ml), the solvents evaporated and the residu purified by column chromatography on silica-gel eluting with hexane. Yield 70%

$C_{13}H_{16}Br_2FeSi$	(416.0)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.34 (s, 9H), 4.02 (d, 1H, *J* = 0.1Hz), 4.07 (m, 1H), 4.16 (m, 1H), 4.3 (t, 1H, *J* = 0.23Hz), 4.41 (m, 1H), 4.47 (m, 1H), 4.57 (m, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 0.2, 70.7, 70.8, 71.7, 72.9, 73.4, 74.1, 76.2, 78.8, 84.7
Rf	0.6 (hexane)

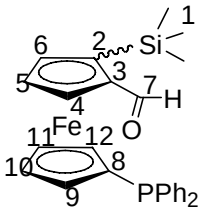
5.12.3 2-(bromo(1'-diphenylphosphine)ferrocenyl)trimethylsilane **77**



To a solution of **76** (1.5g, 3.6 mmol) in 150 ml of dry tetrahydrofuran under argon at -78° C was added dropwise 2.25 ml (3.65 mmol) of a 1.6M solution of n-BuLi in hexane. After 20 min, 0.69 ml of chlorodiphenylphosphine (3.7 mmol) were slowly added at -78° C over a period of 30 min. The resulting mixture was stirred for an additional 3h at -78°C, then slowly allowed to warm up to room temperature and stirred overnight under argon. The orange suspension was quenched with 10 ml of water, extracted with diethyl ether (3x 100 ml) and the solvents evaporated before purification by column chromatography on silica-gel using hexane/EtOac as eluent. Yield 80%

$C_{25}H_{26}BrFePSi$	(521.28)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.28 (s, 9H), 3.94 (m, 1H), 4.14 (m, 1H), 4.18 (m, 1H), 4.3 (m, 1H), 4.39 (m, 1H), 4.42 (m, 1H), 4.44 (m, 1H), 7.3-7.45 (m, 10H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 0.1, 73.4, 75.1, 75.5, 75.6, 77.1, 128-134
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -19.4
Rf	0.4 (hexane/EtOAc 7/3)

5.12.4 Synthesis of 2-(carbaldehyde(1'-diphenylphosphine)ferrocenyl)trimethylsilane **78**

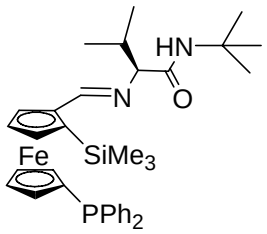


To a solution of **77** (1.0g, 1.9 mmol) in 70 ml of dry tetrahydrofuran under argon at -20° C was added dropwise 1.25 ml (2.0 mmol) of a 1.6M solution of n-BuLi in hexane. After one hour, 0.63 ml of DMF (7.7 mmol) were slowly added at -20° C and the resulting mixture was stirred for an additional hour at -20°C, then slowly allowed to warm up to room temperature. The orange suspension was quenched with 5 ml of water, extracted with diethyl ether (3x 80 ml) and the solvents evaporated before purification by column chromatography on silica-gel using hexane/EtOAc as eluent. Yield 70%. The enantiomers were separated by semipreparative HPLC.

After separation, single crystals suitable for X-ray crystallography were obtained by recrystallisation from hexane/isopropanol.

$C_{26}H_{27}FeOPSi$	(470.4)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.25 (s, 9H, H1), 4.21 (s, 1H, 12), 4.23 (s, 1H, H9), 4.43 (s, 1H, H6), 4.48 (s, 1H, H10), 4.52 (s, 1H, H11), 4.56 (s, 1H, H5), 4.82 (s, 1H, H4), 7.3-7.4 (m, 10H, Ar), 9.8 (s, 1H, H7)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 0.3 (C1), 72.4 (C11), 72.7 (C10), 73.8 (C12), 74.7 (C9), 75.3 (C2), 75.5 (C6), 76.4 (C5), 77.3 (C8), 81.2 (C4), 83.9 (C3), 129-132 (C Ar), 194.3 (C7)
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -20.47
ESI-MS (MeOH)	531.3 (7), 533.3 (100, M+Cu), 534.3 (35.2), 535.3 (55.3), 536.3 (17.5), 493.4 (81.6, M+Na), 494.4 (27.7)
Rf	0.4 (Hexane/EtOAc 9/1)
HPLC	*Daicel,* Chiracel OD-H (250 mm x 4.6 mm), hexan/isopropanol 99/1, 0.9 mL/min; T = 20° C, *R*t (S_{Fc}) = 15.2 min , (R_{Fc}) = 16.3 min
$(\alpha)_D^{20}$	S_{Fc} : +72.0 (c = 0.36, $CHCl_3$)

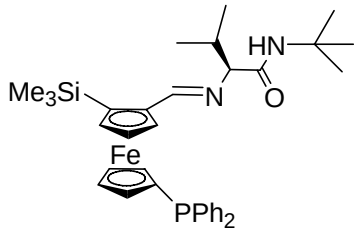
5.12.5 Synthesis of (S,S_{Fc})-*N*-*tert*-butyl-3-methyl-2-((2-trimethylsilanyl-(1'-diphenylphosphine)ferrocenylmethyleme)-amino)-butyramide **79**



Synthesis following the general procedure (5.8.7) with *tert*-butylvaline-amide (36 mg, 0.21 mmol) and (S_{Fc})-2-(carbaldehyde(1'-diphenylphosphine)ferrocenyl)trimethylsilane **78** (0.1 g, 0.21 mmol). The reaction mixture was left to stirr at room temperature for 24 hours. The solution was stripped to dryness under vaccum to give an orange-red powder. The crude reaction mixture was directly purified by chromatography on silica-gel (SiO_2) using degassed solvents (Hexane/Et_2O 8/2). Yield 90%

$C_{35}H_{45}FeN_2OPSi$	(624.65)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.26 (s, 9H), 1.05 (m, 6H), 1.39 (s, 9H), 2.5 (m, 1H), 3.85 (m, 1H), 4.21 (s, 1H), 4.39 (s,1H), 4.42 (s, 1H), 4.45 (s, 1H), 4.77 (m, 2H), 4.98 (s, 1H), 6.18 (s, 1H), 7.2-7.7 (m, 10H), 8.59 (d, 1H, *J* = 1.46Hz)
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -22.7
ESI-MS (MeOH)	685.4 (7), 686.5 (3), 687.5 (100), 688.4 (52), 689.4 (24)

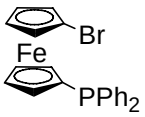
5.12.6 Synthesis of (S,R_{Fc})-*N*-*tert*-butyl-3-methyl-2-((2-trimethylsilanyl-(1'-diphenylphosphine)ferrocenylmethyleme)-amino)-butyramide **79**



Synthesis following the procedure described in 5.12.5, with *tert*-butylvaline-amide (36 mg, 0.21 mmol) and (R_{Fc})-2-(carbaldehyde(1'-diphenylphosphine)ferrocenyl)trimethylsilane **78** (0.1 g, 0.21 mmol). Yield 90%

$C_{35}H_{45}FeN_2OPSi$	(624.65)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.25 (s, 9H), 0.88 (m, 6H), 1.40 (s, 9H), 2.6 (m, 1H), 3.6 (m, 1H), 4.20 (s, 1H), 4.4 (s,1H), 4.41 (s, 1H), 4.47 (s, 1H), 4.78 (m, 2H), 5.1 (s, 1H), 6.41 (s, 1H), 7.2-7.7 (m, 10H), 8.4 (d, 1H, *J* = 1.38Hz)
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -22.0

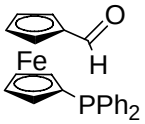
5.12.7 Synthesis of bromo(1'-diphenylphosphino)ferrocene



Synthesis following the procedure decribed in 5.12.3 (1.0g, 2.9 mmol). The orange suspension was quenched with 10 ml of water, extracted with diethyl ether (3x 100 ml) and stored at -30 °Cduring 24h for crystallisation. Yield 70%

$C_{22}H_{18}BrFeP$	(449.1)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 4.03 (m, 1H), 4.1 (s, 1H), 4.19 (m, 3H), 4.33 (m, 1H), 4.4 (m, 2H), 7.4-7.55 (m, 10H)
^{13}C-NMR (100 MHz, $CDCl_3$)	68, 69, 70, 72, 75, 78, 79, 128-135
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -19.1
MS	448 (100), 369 (94), 365 (2), 313 (20), 291 (8), 263 (4), 233 (7), 183 (27), 141 (5), 115 (11), 77 (4), 56 (14)

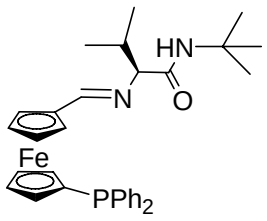
5.12.8 Synthesis of carbaldehyde(1'-diphenylphosphino)ferrocene



Synthesis following the procedure decribed in 5.12.4 (0.5g, 1.1 mmol).
The orange suspension was quenched with 5 ml of water, extracted with diethyl ether (3x 80 ml) and the solvents evaporated before purification by column chromatography on silica-gel using hexane/EtOAc (8/2) as eluent. Yield 80% .

$C_{23}H_{19}BrFeOP$	(398.22)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 4.20 (s, 2H), 4.49 (s, 4H), 4.68 (s, 2H), 7.3-7.45 (m, 10H), 9.66 (s, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	70.9, 72.8, 74.8, 128-134, 193.8
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -20.9

5.12.9 Synthesis of (*S*)-*N*-tert-butyl-2-((1'-diphenylphosphine)ferrocenylmethylene-amino)-3-methyl-butyramide **81**

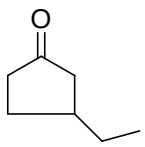


Synthesis following the procedure described in 5.12.5, with *tert*-butylvaline-amide (0.22 g, 1.25 mmol) and carbaldehyde(1'-diphenylphosphino)ferrocene (0.5 g, 1.25 mmol).

$C_{32}H_{37}FeN_2OP$	(552.47)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.77 (d, 6H, *J* = 0.55Hz), 1.26 (s, 9H), 2.05 (m, 1H), 3.15 (d, 1H, *J* = 0.55Hz), 4.06 (d, 2H, *J* = 0.88Hz), 4.27 (t, 2H, *J* = 0.2Hz), 4.44 (m, 2H),4.54 (m, 1H), 4.63 (m, 1H), 6.7 (s, 1H), 7.3-7.45 (m, 10H), 7.77 (s, 1H)
^{31}P-NMR (162 MHz, $CDCl_3$)	δ = -22.4
ESI-MS (MeOH)	614.3 (14), 615.4 (100), 616.3 (58), 617.4 (10)

5.13. Copper-catalysed 1,4-Addition of Diethylzinc to Enones

5.13.1 1,4 addition to cyclopentenone, Synthesis of 3-ethyl-cyclopentanone



General procedure 5.13.1.1 for catalysis with Non-ferrocene ligands.

The adamantylvaline-amide ligand **39** copper-complex described in paragraph 5.5.5.4 (15 mg, 0.02 mmol, 5 mol%) was placed under argon in an ampoule equipped with a magnetic stirring bar and a *Young*® valve, dissolved with 3 ml of degassed toluene. The ampoule was sealed under argon and the mixture stirred at room temperature for 30 min. To this green solution were added dropwise under argon stream two equivalents of 1.0M diethyl zinc solution (0.8 mmol, 0.8 ml), turning the colour to yellow, followed by one equivalent of cyclopentenone (0.4 mmol). The reaction mixture was stirred at room temperature for 12 h before quenching with 0.5 ml of saturated NH_4Cl solution

and extraction with 5 ml of diethyl ether. The organic layer was filtrated and submitted to G.C. and G.C-M.S analysis. The solvents were evaporated and the reaction mixture purified by column chromatography on silica-gel (pentan/diethyl ether 8/2)

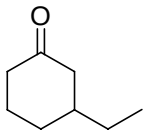
General procedure 5.13.1.2 for catalysis with Ferrocene ligands

The ferrocenyl ligand (*S*, R_{Fc})-**62** (10 mg, 0.018 mmol, 5 mol%) was introduced under argon (glove box) in an ampoule equipped with a magnetic stirring bar and a *Young*® valve together with 3.8 mg (0.018 mmol) of $Cu^{I}(OTf)$, and dissolved with 3ml of degassed toluene. The reaction mixture was stirred at room temperature for 30 min. and two equivalents of diethyl zinc (0.72 mmol, 0.72 ml, 1M solution) were added dropwise, turning the colour to yellow. One equivalent of cyclopentenone (0.36 mmol) was added, and the reaction mixture stirred at room temperature for 12 hours. Treatement and analysis following the procedure 5.13.1.1.

Analytical Data of : $C_7H_{12}O$ (112.17)

^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.91 (t, 3H, *J* = 7.2 Hz), 1.4-3.45 (m, 9H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 12.0, 28.3, 29.0, 38.0, 38.6 (CH), 44.5, 219.5 (C)
MS	112 (43), 97 (3), 94 (0.5), 83 (100), 79 (3), 70 (16), 55 (67), 51 (3), 41 (31)
GC	t_R = 10.1 min (*Restek Rtx1701,* 30 m x 0.25 mm x 0.25 µm, 60 kPa He or H_2, Temp: 60 °C, 1°/min, 80 °C, 30°/min, 250 °C) t_R = 11.7 min (+, *R*), 12.1 min (-, *S*), (*Ivadex 7,* 60 kPa He, Temp : 60 °C, 3°/min, 120 °C, 10°/min, 160 °C)

5.13.2 1,4-addition to cyclohexenone, Synthesis of 3-ethyl-cyclohexanone



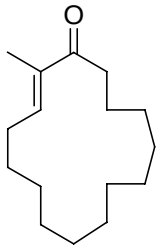
Catalysis following the procedure described in 5.13.1.1 or 5.13.1.2.

Analytical Data of : $C_8H_{14}O$	(126.20)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.92 (t, 3H, *J* = 7.4 Hz), 1.0-2.45 (m, 11H)
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 11.0, 25.5, 29.4, 31.0, 40.6 (CH), 41.5, 48.0, 212.0 (C)

MS	126 (25), 111 (3), 108 (1), 97 (53), 83 (78), 70 (27), 55 (100), 41 (93)
GC	t_R = 18.1 min (*Restek Rtx1701,* 30 m x 0.25 mm x 0.25 µm, 60 kPa He or H_2, Temp: 60 °C, 1°/min, 80 °C, 30 °C /min, 250 °C)
	t_R = 10.5 min (*R*), 10.8 min (*S*), (*Lipodex A,* 60 kPa He, Temp : 60 °C, 0.8°C/min, 70 °C, 30°C/min, 180 °C)

5.14 Muscone Synthesis

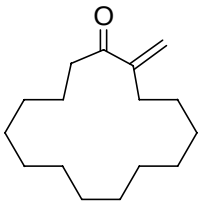
5.14.1 Synthesis of (E)-2-Methyl-cyclopentadec-2-enone **115**



To a solution of enyne **109** (0.4 g, 1.83 mmol) in 10 ml of dichloromethane at room temperature was added 475 µl of acetic acid (8 mmol). The reaction was left to stirr for 45 min. and 0.78 ml of trifluoromethane sulfonic acid (9 mmol) were added dropwise. The reaction was left at room temperature for 12h and neutralised by dropwise addition at 0° C of 15 ml of saturated Na_2CO_3. The reaction mixture was extracted with dichloromethane (2x 50 ml) and the solvents evaporated before purification by column chromatography on silica-gel using hexane/EtOAc (9.5/0.5) as eluent. Yield 75%.

$C_{16}H_{28}O$	(236.39)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.1-1.5 (m, 20H), 1.78 (s, 3H), 2.21 (m, 2H), 2.61 (t, 2H, *J* = 0.88 Hz), 6.61 (td, 1H, *J* = 0.7, 0.14 Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 11.7 (CH_3), 23.0, 25.5, 28.7, 29.4, 29.5, 29.8, 31.9, 32.1, 37.6 (12x CH_2), 137.5 (C), 142.8 (CH), 202.8 (C)

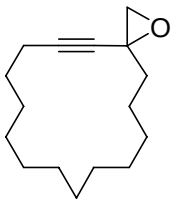
5.14.2 Synthesis of 2-Methylenecyclopentadecanone **116**



To a solution of enyne **109** (0.4 g, 1.83 mmol) in 10 ml of dichloromethane at room temperature were added 80 µl of nitric acid (8 mmol), folowed by 50 mg of HgSO4 and 3 ml of water. The reaction was stirred at 40° C for 3 hours, at room temperature for 12 hours and neutralised by dropwise addition at 0° C of 15 ml of saturated Na_2CO_3. The reaction mixture was extracted with diethyl ether (2x 50 ml) and the solvents evaporated before purification by column chromatography on silica-gel using hexane/EtOAc (9.5/0.5) as eluent. Yield 60%.

$C_{16}H_{28}O$	(236.39)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.2-1.31 (m, 16H), 1.5-1.7 (m, 4H), 2.6 (t, 2H), 5.15 (d, 2H, J = 8 Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 22.8, 25.2, 28.9, 29.0, 29.3, 29.8, 31.3, 39.8, 124.6 (CH_2), 145.0 (C), 202.6 (C)

5.14.3 Synthesis of 1-Oxa-spiro[2.14]heptadec-4-yne **117**

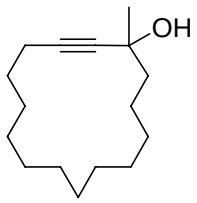


To a solution of enyne **109** (0.15 g, 0.69 mmol) in 15 ml of dichloromethane at 0 °C were added 200 mg of mCPBA (1.16 mmol) and 500 mg of $NaHCO_3$ (5.9 mmol).The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was extracted with diethyl ether (2x 50 ml) and the solvents evaporated before purification by column chromatography on silica-gel using hexane/EtOAc (9.5/0.5) as eluent. Yield 70%

$C_{16}H_{26}O$	(234.38)

^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.2-1.6 (m, H), 2.16 (t, 2H, *J* = 0.64Hz), 2.68 (d, 1H, *J* = 0.53Hz), 2.90 (d, 1H, *J* = 0.53Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 22.9, 24.5, 25.9, 28.8, 29.0, 29.3, 31.6, 31.9, 32.1, 37.1, 45.9, 51.5 (C), 55.1 (CH_2), 78.9 (C), 84.3 (C)

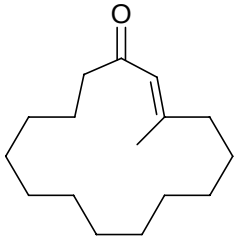
5.14.4 Synthesis of 1-Methyl-cyclopentadec-2-ynol **114**



The 1-Oxa-spiro[2.14]heptadec-4-yne **117** (0.2 g, 0.85 mmol) was dissolved in 10 ml of dry THF and the reaction mixture cooled to 0° C before addition of $LiBH(Et)_3$ (100 µl, 0.85 mmol). The reaction was further stirred 15 min. at 0°c before quenching with 5 ml of water and extraction with diethyl ether. Solvents were removed under vacuum and the residu purified by column chromatography on silica-gel using hexane/EtOAc as eluent.Yield 70%

$C_{16}H_{28}O$	(236.39)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.2-1.4 (m, 18H), 1.42 (s, 3H), 1.43-1.62 (m, 4H), 2.0 (1H, OH), 2.16 (t, 2H, *J* = 0.71 Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 22.9, 25.1, 28.8, 29.0, 29.8, 30.5 (CH_3) , 31.7, 32.1, 38.4, 44.4, 68.7 (C), 84.0 (C), 85.8 (C)
Rf	0.6 (hexane/EtOAc 8/2)

5.14.5 Synthesis of (*E*)-3-Methyl-cyclopentadec-2-enone **112**



5.14.5.1 Synthesis by isomerisation

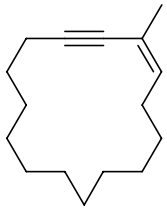
To a solution of carbinol **114** (35 mg, 0.15 mmol) in 15 ml of dichloromethane at room temperature were added 9 mg of $MoO_2(acac)_2$ (0.027 mmol).The reaction mixture was further stirred for 6 hours then refluxed for 12 hours. 5 ml of water were added and the reaction mixture extracted with diethyl ether (2x 50 ml). The solvent was evaporated before purification by column chromatography on silica-gel using hexane/EtOAc (8/2) as eluent. Yield 30%.

5.14.5.2 Synthesis by oxidative-hydroboration

The enyne **109** (0.5 g, 2.3 mmol) was dissolved in 40 ml of dry dichloromethane and 3.45 ml of a 1M solution of $Br_2BH.SMe_2$ (3.45 mmol) was added dropwise. The reaction mixture was strirred at room temperature for 12 hours before addition of 2 ml of a 30% H_2O_2 solution and 15 ml of a 1 M solution of NaOH. The reaction mixture was refluxed for one hour before filtration on celite and extraction with diethyl ether (3x 50 ml). The solvent was evaporated before purification by column chromatography on silica-gel using hexane/Et_2O (100/1) as eluent. Yield 30%.

$C_{16}H_{28}O$	(236.39)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 1.1-1.4 (m, 18H), 2.11 (s, 3H), 2.31 (m, 2H), 2.62 (t, 2H, *J* = 0.75 Hz), 6.2 (s, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 19.1 (CH_3), 25.8, 26.0, 26.9, 27.1, 27.2, 27.5, 40.4, 44.8 (12x CH_2), 124.1 (CH), 158.9 (C), 202.7 (C)
Rf	0.8 (hexane/EtOAc 8/2)

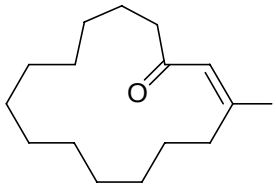
5.14.6 Synthesis of 2-Methyl-cyclopentadec-1-en-3-yne **118**



The enyne product was obtained as a side product under the reaction conditions described in 5.14.5. Yield 30%

$C_{16}H_{26}$	(218.38)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 1.15-1.70 (m, 20H), 1.8 (s, 3H), 2.15 (m, 2H), 2.36 (t, *J* = 5.3, 2H), 5.55 (t, *J* = 0.55 Hz, 1H)
^{13}C-NMR (MHz, $CDCl_3$)	δ = 19.25, 24,5 (CH_3), 26.8, 26.9, 27.1, 27.3, 27.4, 27.8, 30.5, 80.58 (C), 93.8 (C), 118.7 (C), 136.9 (CH)
Rf	0.9 (hexane/EtOAc 8/2)

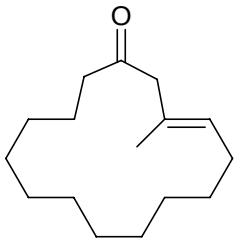
5.14.7 Synthesis of (*Z*)-3-Methyl-cyclopentadec-2-enone **112**



The enone product **112** was obtained as a side product under the reaction conditions described in 5.14.5.2 (yield 6%).

$C_{16}H_{28}O$	(236.39)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 1.1-1.4 (m, 18H), 1.86 (s, 3H), 2.33 (m, 2H), 2.75 (t, 2H, *J* = 0.73 Hz), 6.13 (s, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 25.5 (CH_3), 25.9, 26.8, 26.9, 27.0, 27.1, 27.2,32.1, 44.0 (12x CH_2), 125.4 (CH), 159.3 (C), 198.3 (C)
Rf	0.65 (hexane/EtOAc 95/5)

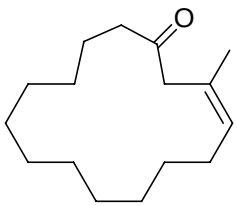
5.14.8 Synthesis of (*E*)-3-Methyl-cyclopentadec-3-enone **120**



The product **120** was obtained as a side product under the reaction conditions described in 5.14.5.2 (yield 18%)

$C_{16}H_{28}O$	(236.39)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 1.1-1.4 (m, 18H), 1.6 (s, 3H), 2.06 (m, 2H), 2.38 (t, 2H, *J* = 0.77), 2.97 (s, 2H), 5.3 (t, 1H, *J* = 0.7 Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 16.9 (CH_3), 22.8, 23.0, 25.7, 26.9, 27.0, 27.1, 27.2, 29.1, 31.9, 40.6, 55.4, 129.8 (C), 130.7 (CH), 210.9 (C)
Rf	0.58 (hexane/EtOAc 95/5)

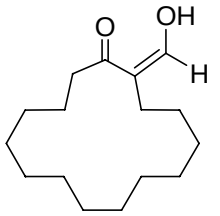
5.14.9 Synthesis of (*Z*)-3-Methyl-cyclopentadec-3-enone **120**



The product **120** was obtained as a side product under the reaction conditions described in 5.14.5.2 (6%).

$C_{16}H_{28}O$	(236.39)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 1.1-1.4 (m, 18H), 1.65 (s, 3H), 2.05 (m, 2H), 2.37 (m, 2H), 3.11 (s, 2H), 5.39 (t, 1H, *J* = 0.7 Hz)
Rf	0.58 (hexane/EtOAc 95/5)

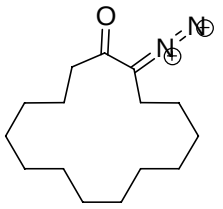
5.14.10 Synthesis of 2-hydroxymethylene-cyclopentadecanone **122**



To a suspension of sodium ethanolate (2.27 g, 33.4 mmol) and formic acid ethyl ester (2.68 ml, 33,5 mmol) in 50 ml of diethyl ether at 0 °C was added dropwise a solution of cyclopentacanone (5 g, 22.3 mmol) dissolved in 5 ml of diethyl ether. The reaction mixture was stirred two hours at room temperature and quenched with 20 ml of ice-cold water. After acidification with acetic acid, the product was extracted with diethyl ether (2x 50 ml). The solvent was evaporated before crystalisation in Et_2O (5 ml). Yield 60%

$C_{16}H_{28}O_2$	(252.39)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.2-1.5 (m, 20H), 1.69 (m, 2H), 2.15 (t, 2H, *J* = 0.83Hz), 2.4 (t, 2H, *J* = 0.70Hz), 8.05 (d, 1H, *J* = 0.64Hz), 15.1 (d, 1H, *J* = 0.63Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 24-28.5 (11x CH_2), 30.5 (CH_2), 37 (CH_2), 113 (C), 180 (CH), 197 (C)

5.14.11 Synthesis of 2-diazo-cyclopentadecanone **123**

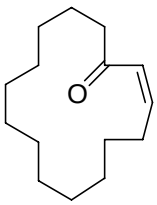


To a solution of **122** (2g, 7.9 mmol) and triethylamine (15.8 mmol) in dichloromethane (50 ml) at -10 °C was added dropwise a solution of p-toluenesulfonyl azide (1.55 g, 7.9 mmol) keeping the temperature below 5 °C. After stirring for two hours at -10 °C, the reaction mixture was quenched with 10 ml of sat. aq. NaOH solution, and extracted with diethyl ether (2 x 50 ml). The solvent was evaporated before crystalisation in Et_2O (5 ml). Yield 70%

$C_{15}H_{26}N_2O$	(250.38)

^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.15-1.4 (m, 20H), 1.52 (m, 2H), 1.70 (m, 2H), 2.4 (t, 2H, *J* = 0.6Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 24-28.5 (11x CH_2), 38 (CH_2), 135 (C), 148(C)
Rf	0.45 (hexane/EtOAc 8/2)

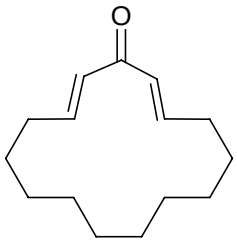
5.14.12 Synthesis of (*Z*)-cyclopentadec-2-enone **124**



The diazo compound **123** (1g, 4 mmol) was dissolved in THF (20 ml) and treated with Ag_2O (458 mg, 2 mmol) dissolved in 5 ml water at room temperature for 36 hours (*Caution*, nitrogen degagement). After filtration of the silver oxyde, the reaction mixture was quenched with 10 ml of sat. aq. Potassium carbonate, and extracted with diethyl ether (2 x 70 ml). The solvent was evaporated before crystalisation in toluene (5 ml). Yield 30%

$C_{15}H_{26}O$	(222.37)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 1.2-1.31 (m, 16H), 1.48 (m, 2H), 1.65 (m, 2H), 2.43 (m, 2H), 2.68 (m, 2H), 5.97-6.05 (dt, 1H, *J* = 7.3, 11.5 Hz), 6.21 (dt, 1H, *J* = 1.1, 11.5 Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 24, 26-28.5 (10x H_2C), 44 , 128, 150, 203
MS	222 (14), 207 (1), 193 (3.5), 179 (5), 165 (5), 137 (5), 123 (6), 111 (13), 98 (36.5), 81 (34), 55 (81), 41 (100)
Rf	0.65 (hexane/Et_2O 9/1)

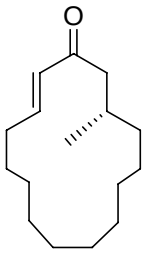
5.14.13 Synthesis of cyclopentadeca-2,14-dienone **128**



Cyclopentadecanone (1.8 g, 8.0 mmol) was dissolved in 30 ml of DMSO and 10 ml of fluorobenzene. IBX (6.7 g, 24.0 mmol) was added and the reaction mixture stirred at 80 °C for 24 hours, forming a white precipitate. The reaction was quenched by slow addition of $NaHCO_3$ at 0 °C followed by filtration over celite® eluting with dichloromethane. The filtrate was extracted with dichloromethane (2 x 150 ml), Et_2O (150 ml), the solvent was removed under vacuum and the residu purified by column chromatography over silica-gel, eluting with hexane/EtOAc 9/1 to give the product as a colorless oil (1.1 g, 4.8 mmol, 60% yield).

$C_{15}H_{24}O$	(220.35)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.18-1.35 (m, 12H), 1.51 (m, 4H), 2.23 (m, 4H), 6.20 (dt, 2H, *J* = 1.6, 15.6 Hz), 6.63 (dt, 2H, *J* = 8.0, 15.6 Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 26.7, 27.3, 27.6, 27.8, 32.2, 130.2 , 148.7, 193.4
MS	220 (7.5), 205 (1), 191 (2), 179 (11), 163 (7), 149 (13), 135 (14), 109 (19), 95 (55), 81 (67), 67 (54), 55 (81), 41 (100)
Rf	0.45 (hexane/EtOAc 9/1)

5.14.14 Synthesis of (*S*)-(*E*)-14-Methyl-cyclopentadec-2-enone **129**

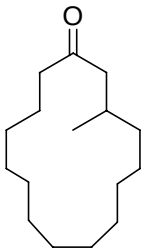


The adamantylvaline-amide ligand **39** copper-complex (17.6 mg, 0.02 mmol, 5 mol%) was placed under argon in an ampoule equipped with a magnetic stirring bar and a Young® valve, dissolved with 3 ml of degassed toluene. The ampoule was sealed under argon and the mixture

stirred for 30 min at -30 °C. To this green solution were added dropwise under argon stream two equivalents of 1.0 M dimethyl zinc solution in heptane (0.8 mmol, 0.8 ml), turning the colour to yellow, followed by cyclopentadeca-2,14-dienone (88 mg, 0.4 mmol). The reaction mixture was stirred at -30 °C for 48 h before quenching with 3 ml of saturated NH_4Cl solution, addition of 5 µl of n-tridecane as internal standard and extraction with 5 ml of diethyl ether. The organic layer was filtered and submitted to GC and GC-MS analysis. The solvents were evaporated and the reaction mixture purified by column chromatography on silica gel eluting with hexane/EtOAc 9/1 to give the product as a colorless oil (93.7 mg, 0.39 mmol, 98%).

$C_{16}H_{28}O$	(236.39)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.89 (d, *J* = 6.8, 3H), 1.10-1.30 (m, 18H), 2.0-2.15 (m, 1H), 2.2-2.35 (m, 2H), 2.35 (d, 2H, *J* = 10.0 Hz), 6.11 (dt, 1H, 1.6, 15.6 Hz), 6.74 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$)	δ 20.5, 24.5, 26.9, 27.0, 27.1, 27.2, 27.3, 27.5, 30.6, 31.7, 34.3, 49.2, 131.4, 148.2, 201.3.
MS (EI, m/z, %)	236 (M^+, 22), 221 (6.5), 178 (6), 151 (4), 135 (8), 123 (14), 109 (29), 81 (57), 67 (41), 55 (100), 41 (98).
HPLC	(250 mm x 4.6 mm Daicel, Chiracel AS , 223 nm, hexan/isopropanol 98.5/1.5, 0.5 mL/min, 293K): 21.1 min (*R*), 24.1 min (*S)*.
Rf	0.55 (hexane/EtOAc 9/1);).

5.14.15 Synthesis of 3-Methyl-cyclopentadecanone **90**



5.14.15.1 Synthesis by copper-hydride conjugate addition

The (*S*)-BINAP ligand (31 mg, 0.05 mmol) together with 10 mg of $Cu^I(OTf)$ (0.047 mmol, 5 mol%) and 5 mg of *t*BuONa (0.05 mmol) were introduced under argon (glove box) in an ampoule

equipped with a magnetic stirring bar and a *Young*® valve and dissolved in 2 ml of degassed toluene. The reaction mixture was cooled to 0° C and stirred for 30 min. before addition of 1 ml of PMHS (50%, dimethysilyl copolymere) and 0.23 g of the (*E*)-3-Methyl-cyclopentadec-2-enone **112** (1.0 mmol). The reaction mixture was stirred at 0° C for 24 hours. Treatement and analysis following the procedure 8.1.1. Yield 55%

5.14.15.2 Synthesis by copper-catalysed dimethyl zinc conjugate addition

Catalysis following the procedure described in 5.13.1.1, with enone **113** or **124** (0.5 mmol, 111 mg) and dimethyl zinc (1.0 mmol, 0.5 ml) at room temperature for 24 hours.

5.14.15.3 Synthesis by hydrogenation of the enone **129**

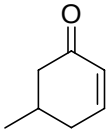
The enone **129** (0.1 g, 0.42 mmol) was dissolved in 5 ml of ethanol together with 5 mg of Pd/C. The reaction mixture was stirred for one hour at room temperature with slow bubbling of hydrogen gas (ambient pressure) trough the solution, introduced through a stainless-steel needle. The reaction mixture was quenched with 0.5 ml of water, filtrated an extracted with diethyl ether (10 ml). The purification was obtained by column chromatography on silica-gel (hexan / Diethylether 9/1). Yield 97%

$C_{16}H_{30}O$	(238.41)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ = 0.94 (d, *J* = 6.7, 3H), 1.10-1.49 (m, 20H), 1.50-1.58 (m, 2H), 1.95-2.12 (m, 1H), 2.18 (dd, *J* = 15.0, 5.1, 1H), 2.35-2.50 (m, 3H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ = 21.1 (), 23.1, 25.1, 26.2, 26.3, 26.5, 26.6, 26.7, 26.8, 27.2, 27.6 (10x *C*H_2), 29.0 (), 35.6, 42.1, 50.8 (3x *C*H_2), 212.0 (C)
MS	238 (16), 223 (7), 209 (12), 180 (5), 163 (3), 149 (4.5), 135 (5), 125 (18), 97 (25), 85 (47), 69 (45), 41 (100)
Rf	0.59 (hexan / Diethylether 9/1)
GC	t_R = 10.5 min (*Restek Rtx1701,* 30 m x 0.25 mm x 0.25 µm, 60 kPa He or H_2, Temp: 60° C, 1° C /min, 80°C, 30°C/min, 250 °C)

t_{R} = 11.7 min (+, *R*), 12.1 min (-, *S*), (*M.N. Hydrodex β-3P,* 75 kPa He, Temp : 60°C, 15° C/min, 120° C, 0.7° C/min, 150° C, 15° C/min, 180°C

5.15. Kinetic resolution of Enones

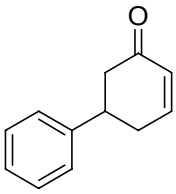
5.15.1 Synthesis of 5-methyl-cyclohex-2-enone **133**



General Procedure. To a solution of ethylester butyric acid (0.038 mol, 4.4 g) and butenal (0.038 mol, 2.6 g) in *t*-BuOH (50 ml) was added 9.12 g of *t*-BuONa (0.095 mol, 2.5 eq.) at 0 °C. The reaction mixture was stirred at 80° C for 12 hours. Upon cooling to room temperature, the mixture was quenched with an 1M HCl solution (15 ml), diluted with a 1/1 mixture of ether and benzene (70 ml) and washed with 1M NaOH solution (25 ml x 2). The collected organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The purification was obtained by column chromatography on silica-gel. (2/8 EtOAc/hexane).

Analytical Data of : $C_7H_{10}O$	(110.15)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.05 (d, 3H, *J* = 0.65Hz), 2.03 (m, 1H), 2.1 (m, 1H), 2.2 (m, 1H), 2.4 (m, 1H), 2.5 (m, 1H), 6.0 (m, 1H), 7.0 (m, 1H)
MS	110 (23), 95 (3), 81 (0.3), 79 (0.3), 68 (100), 65 (2), 55 (4), 51 (2), 41 (6)
GC	(*Ivadex 7,* 60 kPa H_2, Temp : 60°C for 45min, 15° C /min, 180) t_{R} = 34.06 min and 40.29 min. For the reduced enone **131** : t_{R} = 23.3 min and 26.2 min

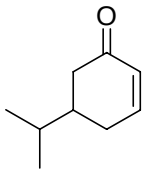
5.15.2 Synthesis of 5-Phenyl-cyclohex-2-enone **134**



Synthesis following the general procedure 5.15.1 with ethylester butyric acid (0.038 mol) and 3-Phenyl-propenal (0.038 mol). The product was purified first by Kugelrohr destillation (150 °C, 26 mbar) followed by column chromatography on silica-gel (2/8 EtOAc/hexane).

Analytical Data of : $C_{12}H_{12}O$	(172.22)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 2.5-2.75 (m, 4H), 3.35 (m, 1H), 6.14 (dd, 1H, *J* = 0.25, 0.73Hz), 7.05 (m, 1H), 7.23-7.36 (m, 5H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 34.1, 41.4, 45.3, 127-130, 143.6, 149.9, 199.6
GC	(*Ivadex 7,* 70 kPa H_2, Temp : 65° C, 4° C /min, 170°C) t_R = 25.76 min and 26.14 min. For the reduced enone **131** : t_R = 24.43 min and 24.53 min

5.15.3 Synthesis of 5-Isopropyl-cyclohex-2-enone **135**



Synthesis following the general procedure 5.15.1 with ethylester butyric acid (0.038 mol) and 4-Methyl-pent-2-enal (0.038 mol).

Analytical Data of : $C_9H_{14}O$	(138.21)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.9 (d, 6H), 1.5-1.95 (m, 5H), 2.6 (m, 1H), 6.09 (m, 1H), 6.8 (dd, 1H, *J* = 1.1, 1.7Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 20, 30.5, 32, 42.2, 42.5, 130.2, 151.5, 201.1
MS	138 (10), 123 (1), 110 (0.5), 95 (13), 91 (1), 81 (2.5), 68 (100), 67 (24), 55 (7), 41 (18)

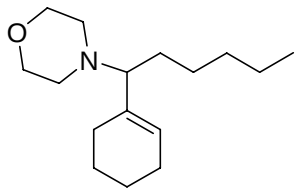
GC (*Lipodex A,* 60 kPa H_2, Temp : 80°C, 1°C/min, 120°C, 15°C /min, 170°C) t_R = 28.00 min and 28.97 min. For the reduced enone **131** : t_R = 18.67 min and 20.27 min.

5.15.4 Kinetic resolution : hydrogenation of enones

General Procedure : A solution of 5-Isopropyl-cyclohexenone **135** (0.05 g, 0.36 mmol) and 17.5 mg of iridium catalyst **X68** (0.011 mmol, 3 mol%) in 1 ml of dry toluene was stirred in a 2 ml screw-cap vial placed in a high-pressure autoclave under 25 bar H_2 for one hour at room temperature. The reaction was set up in glove-box under inert atmosphere. The reaction was quenched with 0.5 ml of water, the organic phase extracted. After filtration through a syringe filter, the solution was directly used for GC and GC-MS analysis. For retention times, see 5.14.15.3 and 5.15.1-5.15.3.

5.16. Multicomponent Reaction

5.16.1 Synthesis of 4-(1-Cyclohex-1-enyl-hexyl)-morpholine **141**

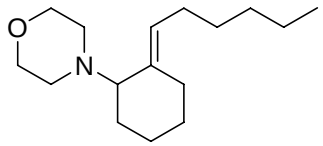


General Procedure: The PHOX ligand **106** (8.4 mg, 0.021 mmol) and 5 mg of $Pd_2(dba)_3$ (0.0054 mmol, 5 mol%) were introduced under argon in an ampoule equipped with a magnetic stirring bar and a *Young*® valve and dissolved in 4 ml of degassed DMA. The mixture was stirred for 30 min. before addition of 38 µl of cyclohexenyltriflate **138** (0.21 mmol), 87 µl of morpholine (1.0 mmol) and 133 µl of 1-hexene (1.0 mmol). The reaction mixture was heated to 80° C and stirred for 72 hours, the colour turning to yellow. The reaction was quenched with 1 ml of water and extracted with diethyl ether (2 x 10 ml). After filtration through a syringe filter, the solution was directly used for GC and GC-MS analysis. Purification was realized by column chromatography on silica-gel (hexane/EtOAc 9/1).

Analytical Data of : $C_{16}H_{29}NO$ (251.41)

^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.89 (t, *J* = 0.75 Hz, 3H, CH_3), 1.2-1.35 (m, 8H), 1.5-1.65 (m, 4H), 1.89 (m, 2H), 2.02 (m, 2H), 2.3-2.5 (m, 4H), 3.68 (t, 4H, J = 0.43 Hz), 5.5 (m, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 15.1 (CH_3), 23.6 (CH_2), 23.9 (CH_2), 25.3 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 27.3 (CH_2), 29.9 (CH_2), 33.1 (CH_2), 52.7 (CH_2), 68.0, 73.5, 126.6 (CH), 140.6 (C)
MS	251 (1.5), 180 (100), 170 (9), 152 (1.5), 121 (1), 107 (1.5), 95 (5), 67 (7), 55 (7), 41 (11)
GC	(*SE 54,* 60 kPa H_2, Temp : 130°C, 30 min, 1°C/min, 160°C, 15°C /min, 175°C) t_R = 26.00 min and 27.2 min.
Rf	0.15 (hexane/EtOAc 9/1)

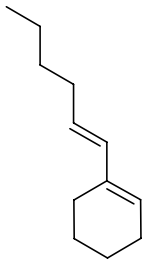
5.16.2 4-(2-Hexylidene-cyclohexyl)-morpholine **142**



Synthesis following the general procedure 5.16.1.

Analytical Data of : $C_{16}H_{29}NO$	(251.41)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.89 (t, *J* = 0.8 Hz, 3H, CH_3), 1.19-1.42 (m, 11H), 1.68-1.80 (m, 1H), 1.9-2.1 (m, 4H), 2.2-2.5 (m, 4H), 3.68 (t, 4H, *J* = 0.47 Hz), 4.2-4.4 (m, 1H), 5.2 (t, 1H, *J* = 0.56 Hz)
MS	251 (4), 208 (3.5), 194 (2), 180 (100), 164 (10), 152 (2), 126 (9), 109 (5), 95 (15), 67 (12), 55 (9), 41 (9)
Rf	0.45 (hexane/EtOAc 9/1)

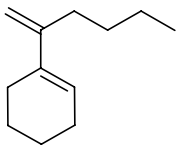
5.16.3 1-Hex-1-enyl-cyclohexene **143**



Synthesis following the general procedure 5.16.1.

Analytical Data of : $C_{12}H_{20}$	(164.29)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.9 (t, 3H), 1.32 (m, 4H), 1.55-1.70 (m, 4H), 2.1 (m, 6H), 5.55 (m, 1H), 5.63 (m, 1H), 6.0 (d, 1H, *J* = 1.56 Hz)
MS	165 (4), 164 (33), 149 (2), 135 (23), 121 (25), 117 (2.5), 107 (30), 93 (47), 79 (100), 67 (45), 55 (19), 53 (13), 41 (40)
Rf	0.93 (hexane/EtOAc 9/1)

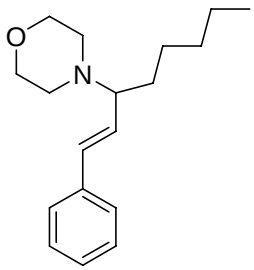
5.16.4 1-(1-Methylene-pentyl)-cyclohexene **144**



Synthesis following the general procedure 5.16.1.

Analytical Data of : $C_{12}H_{20}$	(164.29)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.9 (t, 3H), 1.32 (m, 4H), 1.55-1.70 (m, 4H), 2.1 (m, 6H), 4.8 (s, 1H), 4.9 (s, 1H), 5.9 (t, 1H, *J* = 0.4 Hz)
MS	164 (13), 149 (5), 135 (3), 122 (77), 109 (2), 107 (81), 93 (48), 79 (100), 67 (21), 53 (21.5), 41 (43)
Rf	0.93 (hexane/EtOAc 9/1)

5.16.5 Synthesis of 4-[1-(2-Cyclohex-1-enyl-vinyl)-hexyl]-morpholine **155**



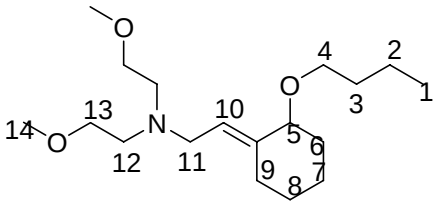
Synthesis following the general procedure 5.16.1 with β-bromostyrene (0.21 mmol, 27 µl).

Analytical Data of : $C_{18}H_{27}NO$ (273.41)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.86 (m, 3H), 1.28 (m, 8H), 2.45-2.68 (m, 4H), 2.82 (m, 1H), 3.7 (t, 4H, *J* = 0.44 Hz), 6.1 (qd, 1H, *J* = 1.0, 1.9 Hz), 6.43 (d, 1H, *J* = 1.9 Hz), 7.1-7.5 (m, 5H)

GC (*SE 54,* 60 kPa H_2, Temp : 130°C, 30 min, 1°C /min, 160°C, 15°C /min, 175°C) t_R = 26.50 min and 27.40 min.

5.16.6 Synthesis of [2-(2-Butoxy-cyclohexylidene)-ethyl]-bis-(2-methoxy-ethyl)-amine **148**



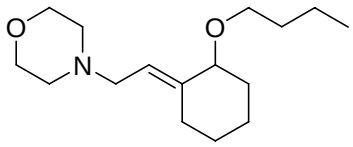
Synthesis following the general procedure 5.16.1 with butylvinyl ether (1.0 mmol, 100 µl) and Bis-(2-methoxy-ethyl)-amine (1.0 mmol, 110 µl). Yield 50%

Analytical Data of : $C_{18}H_{35}NO_3$ (313.48)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J* = 0.7, C1), 1.25-1.85 (m, 10H, 1.35 C8, 1.36 C2, 1.47 C7, 1.53 C3, 1.62 C8, 1.63 C6, 1.80 C6C7), 2.16 (m, 2H, C9), 2.71 (t, 4H, *J* = 0.6 Hz, C12), 3.24 (m, 3H, C4C11), 3.34 (m, 7H, C4C14), 3.47 (t, 4H, *J* = 0.6 Hz, C13), 3.63 (t, 1H, *J* = 0.35 Hz, C5), 5.41 (t, 1H, *J* = 0.69Hz, C10)

^{13}C-NMR (100 MHz, $CDCl_3$)	δ 14.0 (C1), 19.5 (C2), 22.0 (C7), 25.5 (C9), 27.4 (C8), 32.1 (C3), 34.2 (C6), 51.5 (C11), 53.6 (C12), 58.8 (C14), 67.6 (C4), 71.1 (C13), 81.0 (C5), 120.2 (C10), 142.1 (C); NOE C10-C5
Rf	0.19 (hexane/EtOAc 8/2)

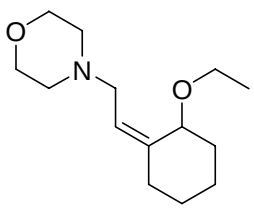
5.16.7 Synthesis of (*E*)-4-[2-(2-Butoxy-cyclohexylidene)-ethyl]-morpholine



Synthesis following the general procedure 5.16.1 with butylvinyl ether (1.0 mmol, 100 µl) and morpholine (1.0 mmol, 87 µl).

Analytical Data of : $C_{16}H_{29}NO_2$	(267.41)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.9 (t, 3H), 1.25-1.55 (m, 6H), 1.55-1.65 (m, 2H), 1.72-1.81 (m, 2H), 2.17 (t, 2H), 2.43 (m, 4H), 3.03 (d, 2H), 3.20-3.35 (m, 2H), 3.67 (m, 1H), 3.72 (t, 4H), 5.35 (t, 1H)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 14.3 (CH_3), 19.9, 22.5, 26.1, 27.7, 32.5, 33.1, 34.6, 54.0, 55.7, 67.4, 68.1, 81.3, 119.0, 140.4
ESI-MS	268.2 (M+H, 100), 269.2 (22), 270.5 (5)
Rf	0.20 (hexane/EtOAc 8/2)
GC	(*SE 54,* 60 kPa H_2, Temp : 120°C, 0.5°C /min, 150°C, 1°C /min, 160, 15°C) t_R = 28.50 min and 29.30min.

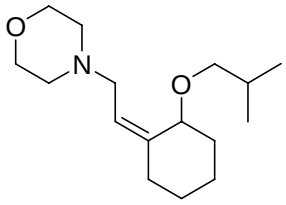
5.16.8 Synthesis of 4-[2-(2-Ethoxy-cyclohexylidene)-ethyl]-morpholine



Synthesis following the general procedure 5.16.1 with ethylvinyl ether (1.0 mmol, 80 µl) and morpholine (1.0 mmol, 87 µl).

Analytical Data of : $C_{14}H_{25}NO_2$	(239.35)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 1.18 (t, 3H, *J* = 0.8 Hz), 1.25-1.60 (m, 2H), 1.70-1.82 (m, 2H), 1.92-2.00 (m, 2H), 2.43 (m, 4H), 3.03 (d, 2H, *J* = 0.70 Hz), 3.25-3.4 (m, 2H), 3.68 (m, 2H), 3.72 (t, 4H, *J* = 0.52 Hz), 4.31 (t, 1H, *J* = 0.17 Hz), 5.41 (t, 1H, *J* = 0.70 Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 15.9 (CH_3), 21.25 , 28.8, 33.1, 33.2, 54.0, 55.6, 62.9, 67.4, 72.4 (CH), 122.1, 143.3
ESI-MS	240.2 (100, M+H), 241.2 (14), 242.2 (3)
GC	(*SE 54,* 60 kPa H_2, Temp : 130°C, 30 min, 1°C /min, 160°C, 15°C /min, 175°C) t_R = 28.10 min and 28.87 min

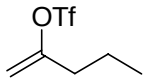
5.16.9 Synthesis of 4-[2-(2-Isobutoxy-cyclohexylidene)-ethyl]-morpholine



Synthesis following the general procedure 5.16.1 with 2-Methyl-1-vinyloxy-propane (1.0 mmol, 105 µl) and morpholine (1.0 mmol, 87 µl).

Analytical Data of : $C_{16}H_{29}NO_2$	(267.41)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.9 (dt, 6H), 1.25-1.68 (m, 2H), 1.70-1.86 (m, 2H), 1.92-2.05 (m, 2H), 2.45 (m, 4H), 3.03 (d, 2H), 3.20-3.35 (m, 2H), 3.68 (m, 2H), 3.72 (t, 4H), 4.25 (t, 1H), 5.41 (t, 1H, *J* = 0.70 Hz)
GC	(*SE 54,* 60 kPa H_2, Temp : 130°C, 30 min, 1°C /min, 160°C, 15°C /min, 175°C) t_R = 27.30 min and 28.15 min

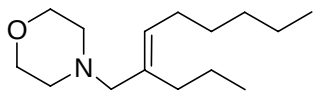
5.16.10 Synthesis of Trifluoromethanesulfonic acid 1-methylene-butyl ester **149**



To a solution of 1-pentyne (5 g, 0.073 mol) in 10 ml of pentane at -30 °C was added dropwise 11 g of Trifluoromethanesulfonic acid (0.073 mol) over 15 min. turning the colour to deep red. The reaction mixture was left to warm to room temperature over 45 min. and quenched with dropwise addition of $NaHCO_3$ (10 ml). After extraction with diethyl ether (2 x 50 ml) and evaporation of the solvents, the product was purified by distillation. Yield 60%

Analytical Data of : $C_6H_9F_3O_3S$	(218.19)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.95 (t, 3H), 1.58 (m, 2H), 2.31 (t, 2H), 4.92 (dt, 1H, *J* = 0.37, 0.1 Hz), 5.08 (d, 1H, *J* = 0.37 Hz)
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 13.5 (CH_3), 19.7 (CH_2), 36.1 (CH_2), 104.5 (CH_2), 120.5 (CF_3), 157.2 (C)
MS	218 (0.5), 190 (23), 139 (1.5), 126 (35.5), 87 (13), 73 (8), 69 (100), 53 (16)

5.16.10 Synthesis of 4-(2-Propyl-oct-2-enyl)-morpholine **151**

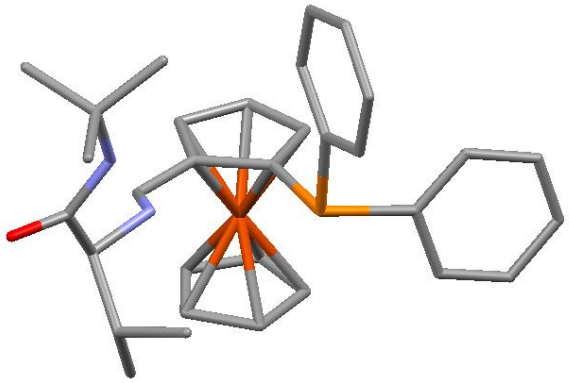


Synthesis following the general procedure 5.16.1 with vinyltriflate (0.2 mmol, 35 µl) and morpholine (1.0 mmol, 87 µl).

Analytical Data of : $C_{15}H_{29}NO$	(239.4)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.89 (m, 6H), 1.2-1.4 (m, 8H), 1.96-2.1 (m, 4H), 2.35 (m, 4H), 2.81 (s, 2H), 3.7 (m, 4H), 5.32 (t, 1H)
^{13}C-NMR (75 MHz, $CDCl_3$)	δ 14.4, 14.5, 21.9, 22.9, 28.0, 29.9, 31.3, 32.0, 53.9, 66.0, 67.5, 129.0 (CH), 141.3 (C)

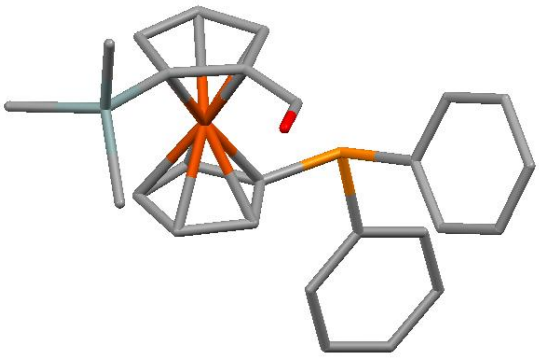
6. X-Ray structures

6.1 Structure of (S,R_{Fc})-2-((2-(diphenylphosphino)-ferrocenyl)methyleneamino)-*N*-*tert*-butyl-3-methylbutanamide **62**



Summenformel	C32H37FeN2OP	Volumen [Å^3]	2882.32
Molmasse	552.47	Z	4
Strahlung	MoK$_\alpha$ (λ= 071023)	Temp. [K]	173
Raumgruppe	P 2$_1$ 2$_1$ 2$_1$	D$_{calc}$ [g/cm^3]	1.273
Kristallklasse	Orthorombic	R-Wert [%]	0.041
a [Å]	10.2689 (2)	Farbe	Orange
b [Å]	10.2829 (3)		
c [Å]	27.2962 (4)		
α [°]	90		
β [°]	90		
γ [°]	90		

6.2 Structure of (S_{Fc})-2-(carbaldehyde(1'-diphenylphosphino)ferrocenyl)trimethylsilane **78**



Summenformel	$C_{26}H_{27}FeOPSi$	Volumen [Å^3]	1175.79
Molmasse	470.40	Z	2
Strahlung	MoK_α (λ= 071023)	Temp. [K]	173
Raumgruppe	P-1	D_{calc} [g/cm^3]	1.329
Kristallklasse	Triclinic	R-Wert [%]	0.0567
a [Å]	8.3914 (2)	Farbe	Orange
b [Å]	11.4523		
c [Å]	12.5228 (4)		
α [°]	87.6705 (14)		
β [°]	83.0527 (15)		
γ [°]	79.8767 (17)		

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Eidesstattliche Erklärung

Ich erkläre, dass ich die Dissertation “Palladium and Copper-Catalysed (C-C)-Bond Formation“ nur mit der darin angegebenen Hilfe verfasst und bei keiner anderen Universität und keiner anderen Fakultät der Universität Basel eingereicht habe.

Basel, den 26.07.2004