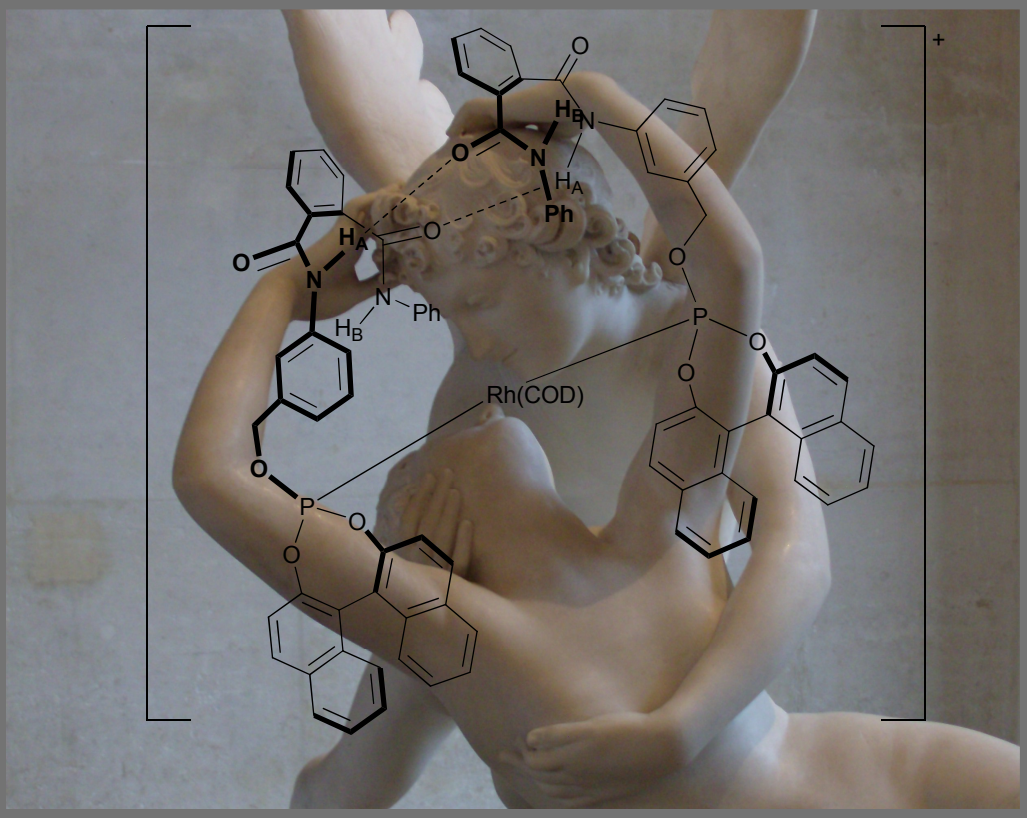
"Combinatorial and Supramolecular Approaches to Monodentate Phosphorus-Ligands for Transition Metal Catalyzed Asymmetric Reactions"



UNIVERSITÁ DEGLI STUDI DELL'INSUBRIA
DIPARTIMENTO DI SCIENZE CHIMICHE E AMBIENTALI

DOTTORATO DI RICERCA IN SCIENZE CHIMICHE XXIII CICLO

PhD Thesis
Settore Disciplinare: CHIM/06

TUTOR: Prof. Umberto PIARULLI
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Dottorando:

STEFANO CARBONI

Anno Accademico 2009/2010

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Chapter 1

Introduction and literature review

Abstract
In this chapter the evolution of monodentate P-ligands in asymmetric catalysis is shortly traced from its beginning to the advent of combinatorial and supramolecular approaches used in homogeneous transition metal catalysis.

1.1 GENERAL INTRODUCTION

Since van't Hoff and Le Bel introduced 135 years ago the tetrahedral model of the carbon atom to explain the optical activity of organic molecules and provide a structural basis for molecular stereochemistry, scientists have been fascinated by the challenge to achieve absolute stereocontrol in chemical transformations starting from achiral compounds. Chirality has been denoted as "signature of life", and it is not unexpected that questions on the origin, control and amplification of homochirality are intimately associated with chemical evolution and the origin of life.

In spite of the incredible importance, asymmetric catalysis has not been considered as a fundamental research area until 1968. In fact, besides enzymatic processes, only few examples of enantioselective catalytic reactions were known at that time, and in view of the generally low enantiomeric excesses, many chemists doubted that synthetic chiral catalysts would ever play an important role in asymmetric synthesis. Shortly after, the situation changed dramatically as spectacular progress was made in the rhodium-catalyzed hydrogenation of olefins (Knowles, Noyori, Horner, Kagan), culminating in the famous Monsanto process for L-DOPA, and in the selective epoxidation and dihydroxilation of olefins (Sharpless). Since then, asymmetric catalysis based on chiral catalysts which are metal complexes containing chiral organic ligands has undergone explosive growth.

Without any doubts, transition metal-mediated asymmetric hydrogenation is one of the most important process and a well-established and efficient methodology for the catalytic reduction of many prochiral substrates such as alkenes, imines and ketones. There have been several significant breakthroughs in the field and now a myriad of chiral Ru-, Rh- and Ir-coordination compounds (mostly phosphorus-containing derivatives) capable of mediating this transformation with very high enantioselectivities are known. The development of commercial processes has rendered this transformation highly desiderasble to both academia and industry.

During these decades, research efforts have been directed towards the development of chiral ligands with attractive industrial profiles, which means that they should induce high stereoselectivities, be easily prepared and not be covered by current patents. Combinatorial and high-throughput synthetic strategies have led to the development of a number of highly efficient monodentate and bidentate phosphorus and nitrogen-containing ligands for many different asymmetric reactions (e.g. hydrogenation, hydroformylation, allylic alkylation and conjugate addition) that utilise either standard covalent chemistry or supramolecular interactions.

The formation of bidentate ligands by non-covalent interactions, so called *supramolecular*, is now a cutting-edge strategy for the combinatorial search of new selective catalysts and the object of the scientific interest of several important research groups worldwide.[1]

Our research group has a long-standing interest in the search for combinatorial/high-throughput approaches to enantioselective catalysis,[2] and for this reason it has followed the recent evolution in *P*-ligand design with high interest, providing significant contributions in this field.[3] In

particular supramolecular bidentate ligands have been recently the object of our attention because they merge the advantages of monodentate ligands (*i.e*. easy and fast preparation, possibility of a combinatorial screening of ligand combinations) with those of their bidentate counterparts (*i.e*. rigidity and preorganisation). In particular, our goal is to achieve the self-assembly exploiting non-covalent interactions such as coordinative interactions and hydrogen bondings.

Moreover, the present work of thesis accounts for our early efforts in a new and virtually unexplored direction: pursuing the selective assembly of two *different* ligands around a metal centre exploiting the intrinsic thermodynamic preference of the system in favour of the heterocomplex. Significant results in this sense were obtained combining ligands having complementary electronic properties in the presence of a metal source, as it will be discussed below. The resulting complexes were exploited for the catalysis of reactions promoted by rhodium and palladium, where the role played by the heteroleptic complex emerged clearly.

Before describing the guidelines and the results of these projects, it can be helpful showing briefly the role of monodentate P-ligands in different transition-metal catalyzed reactions (Chapter 1). Particular interest was made to asymmetric 1,4 conjugate addition, allylic substitution and homogeneous asymmetric hydrogenation of olefins.[4] as powerful transformations for industrial applications. The latter transformation is arguably one of the most intensely studied topic in organometallic chemistry and it exemplifies well the evolution of phosphorus ligand design that has led to self-assembled bidentate ligands.

In Chapter 2 a new approach to the selective formation of heterocomplexes combining π-acceptor phosphite ligands with σ-donor phosphinamines is presented. ^{31}P NMR studies are described which show preferential formation phosphite /C_1-symmetric aminophosphine heterocomplex (70 – 100% selectivity). The results of the screening of ligand combinations in several kinds of different reactions are discussed.

In Chapter 3 the synthesis of supramolecular monodentate P-ligands through coordinative bonding was investigated taking advantages of a cobalt(III)-salen complex as template. The screening of these P-ligands was studied in several enantioselective catalytic applications, showing good activity and moderate enantioselectivity in several palladium-catalyzed asymmetric reactions.

In Chapter 4 the synthesis of a library of novel chiral supramolecular ligands containing a phthalamide moiety capable of hydrogen bonding interactions was reported. The new ligands, named *PhthalaPhos*, are easy to prepare from inexpensive starting materials, and displayed an excellent level of enantioselectivity in the hydrogenation of benchmark olefins (methyl 2-acetamidoacrylate and acetamidostyrene) as well as of more challenging, industrially relevant substrates. In two reported cases, namely the cyclic enamide *N*-(3,4-dihydronaphthalen-1-yl)acetamide and β^2-dehydro aminoester (*E*)-methyl 2-(acetamidomethyl)-3-phenylacrylate, our ligands rival or even outperform the best results obtained with known ligands. The pre-catalytic Rh complex of one of these ligands was

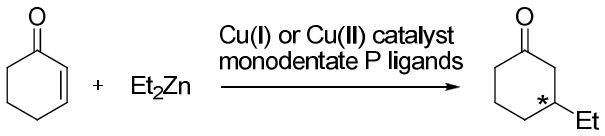
fully characterized by NMR, IR and MS spectroscopy. These studies show that a supramolecular bidentate ligand is formed in the Rh complex by ligand self-association through a pair of interligand hydrogen bonds.

1.2 MONODENTATE P-LIGANDS IN ENANTIOSELECTIVE CATALYSIS

In this chapter a brief overview of the most important asymmetric applications of monodentate *P*-ligands was discussed. Particular interest was made to asymmetric 1,4 conjugate addition, allylic substitution and hydrogenation as powerful transformation for industrial applications.

1.2.1 Asymmetric 1,4 conjugate addition

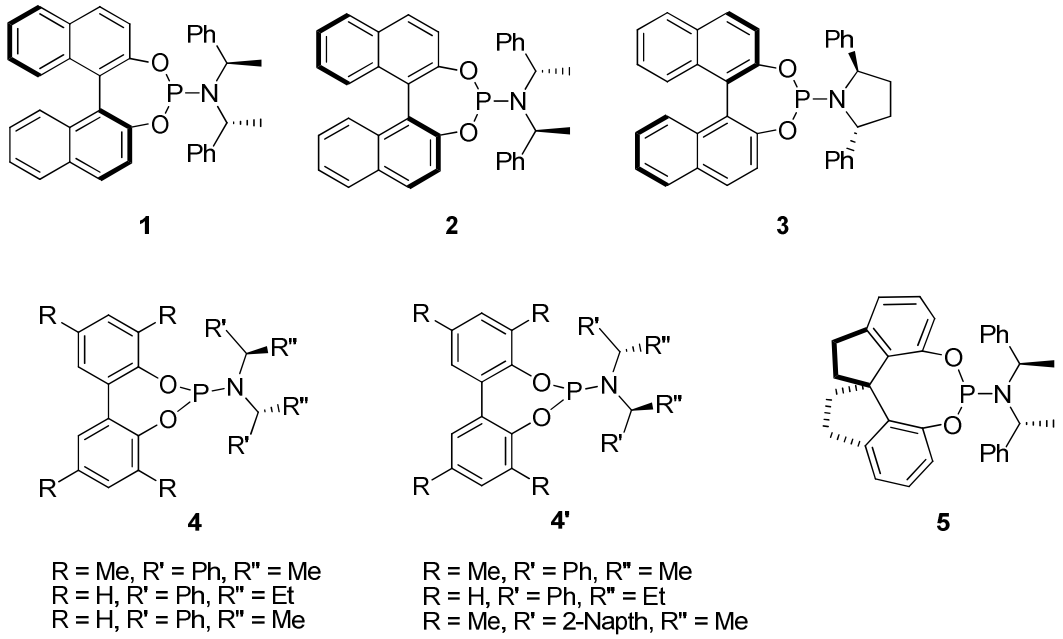
The copper catalyzed conjugate addition of diethylzinc to cyclohexenone (Scheme 1.1), as a benchmark reaction for monodentate phosphorus ligands was first reported by Alexakis in 1993 making use of phosphoramidite ligands (Scheme 1.2).[5]



Scheme 1.1 1,4-Conjugate addition of diethylzinc to cyclohexenone

Subsequently, the activity of $Cu(OTf)_2$ in the presence of chiral monophosphites and phosphoramidites derived from TADDOL was reported by Alexakis. [6] Altough biphenylphosphite ligands bearing a stereoidal third phosphorus substituent showed some catalytic activity but moderate enantioselectivity,[7] the best efficiencies were obtained with phosphoramidites derived from BINOL either with an achiral amino group[8] or a chiral one as in **1**-**3**.[9] Different phosphoramidite ligands **4** prepared from biphenol and optically active amine were also shown to be very efficient for the enantioselective conjugate addition of dialkylzinc derivatives to cyclic and acyclic enones.[10] Sterically demanding phosphoramidites derived from partially hydrogenated atropoisomeric H_8-BINOL provide an efficient enantioselective conjugate addition of diethylzinc to cyclohexenone.[11] Phosphoramidites built on spiranic diol have also shown excellent efficiencies in the conjugate addition of diethyl zinc to cyclohexenone leading to over 98% ee (ligands **5**).[12] A P-H phosphonite ligand based on biphenyl-2,2'-bisfenchol as diol showed good enantioselectivity in the enantioselective copper-catalyzed reaction.[13] Not only zinc derivatives but also trialkylalumnium derivatives lead to very good levels of

enantioslectivity upon addition to conjugate enones[14] and nitroalkenes[15] in the presence of biphenol phosphoramidite ligands associated to a copper precursor.



Scheme 1.2 Examples of performing monodentate P-ligands in the asymmetric conjugate additions

Besides enones, other Michael acceptors such as nitroolefins have been alkylated with Et_2Zn under copper catalysis conditions in the presence of phosphites, phosphonites and phosphoramidites derived from TADDOL and BINOL,[16] and biphenol.[17]

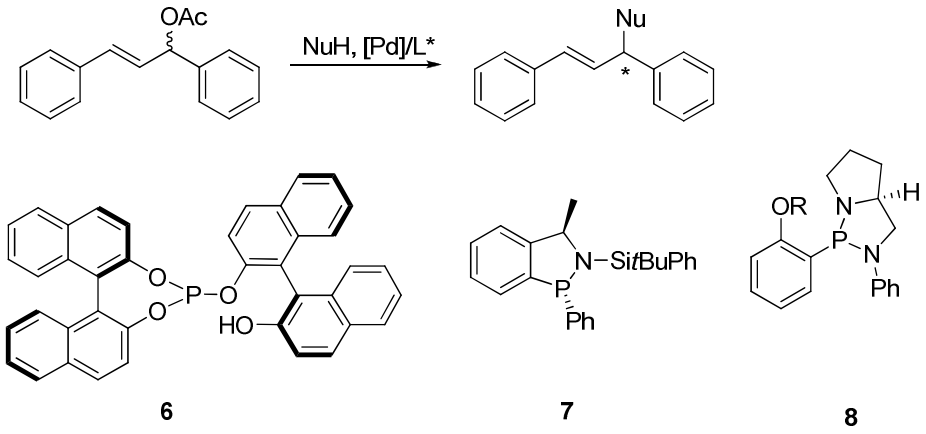
α-β Unsaturated imines have also been used to prepare enamine derivatives with excellent enantioslectivities upon addition of Et_2Zn in the presence of a copper salt and phosphoramidite ligands.[18] Conjugate addition of alkyl-zinc or –aluminium reagents to alkylidene malonate derivatives has been carried out with phosphonites and phosphoramidites with satisfactory to excellent enantiometric excesses.[19]

The addition of aryl and vinyl groups to cyclohexenone, which is not always possible from zinc reagents, has been efficiently performed with aryl and vinyl boron derivaties by using rhodium catalysts associated to phosphoramidite ligands. Thus, >98% ee was obtained from $PhB(OH)_2$ or $PhBF_3K$ in the presence of selected phosphoramidite ligands.[20]

1.2.2 Asymmetric Allylic Substitution

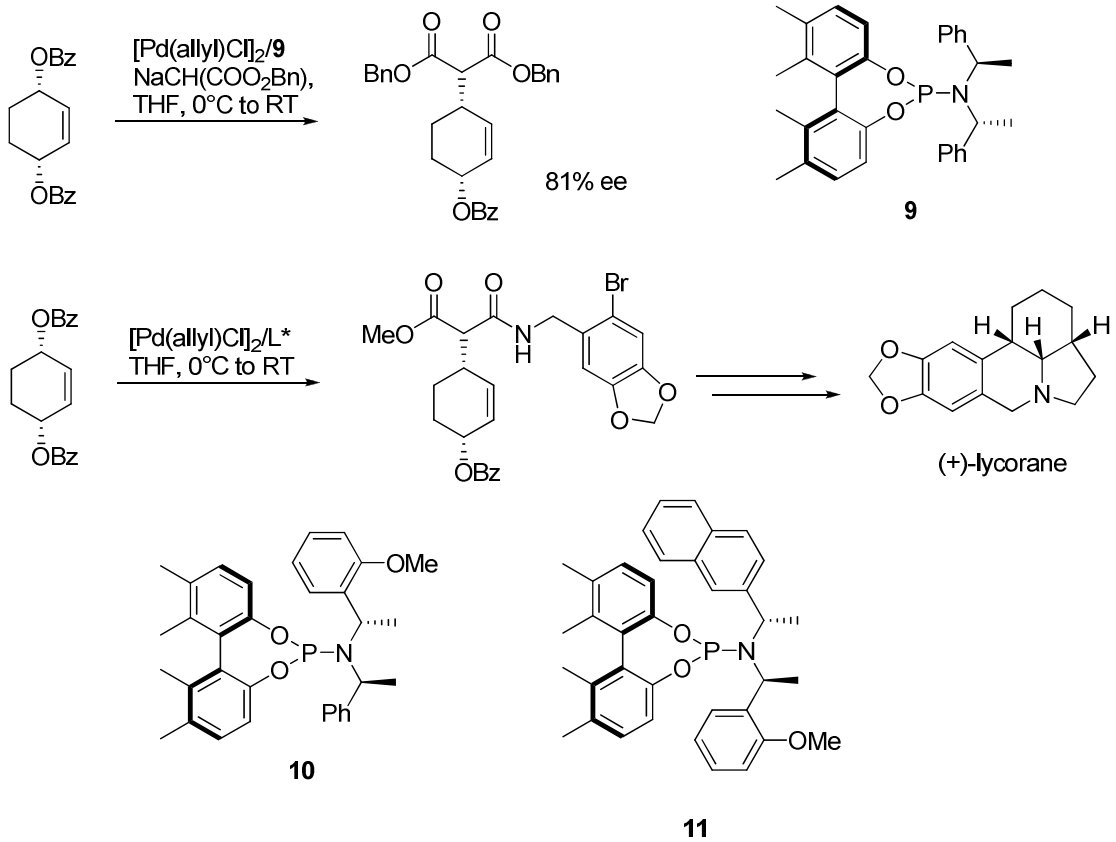
Metal-catalyzed asymmetric allylic substitution has been extensively investigated. Among all chiral ligands designed and reported for the benchmark allylic alkylation with 1,3 diphenyl propenyl acetate, some chiral monodentate phosphites, phosphoramidites, monoaminophosphonites and

diaminophosphonites have been used. Thus, malonate has been successfully allylated in 95% ee with ligand **6** (Scheme 1.3),[21] and in 70% ee with **1**.[22]



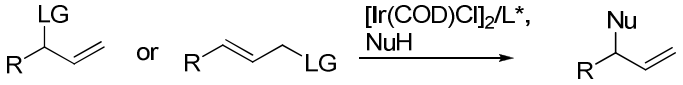
Scheme 1.3 Pd-catalyzed asymmetric alkylation

Amines have also been used as nuclephile in high ee with ligand **8** (87-95% ee) and with **6**.[23] The reaction of *cis*-1,4-dibenzoyloxy-2-cyclohexene with a malonate using chiral monodentate phosphoramidite ligand **9** or with α-methoxycarbonylacetamide derivative using ligand **10** or **11** yielded the desymmetrized cyclohexene with high enantioselectivity. The former reaction opened a highly efficient short total synthesis of (+)-γ-lycorane (Scheme 1.4).[24]



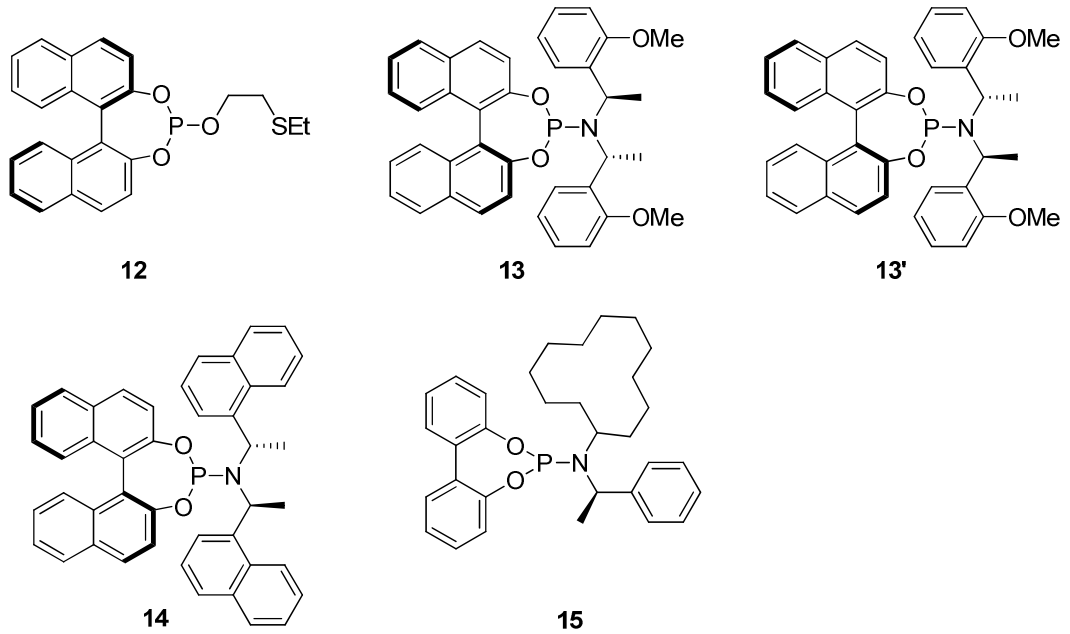
Scheme 1.4 Total Synthesis of (+)-γ-lycorane.

Reactions with non-symmetric allylic carbamates, acetates or phosphates with a wide range of nucleophiles (malonates, alkyl or aryl-amines, aliphatic alcohols or phenol derivatives), in the presence of iridium complexes bearing chiral phosphite, or phosphoramidite ligands, afforded the branched isomers with high region- and enantioselectivities (Scheme 1.5).



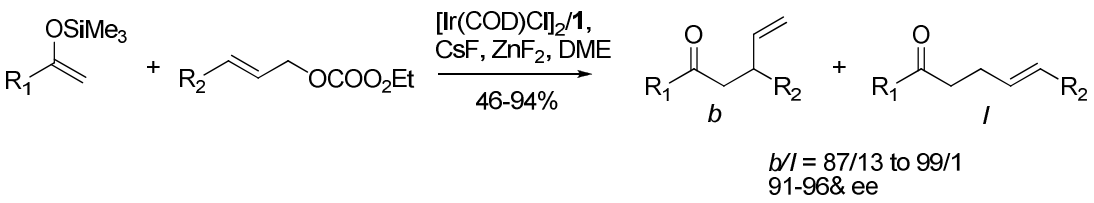
Scheme 1.5 Asymmetric Ir-catalyzed alkylation

Phosphite **12** allowed the addition of malonate[25] or glycinate[26] in high yields, good regioselectivities and high level of enantioselectivities. Phosphoramidites have been used more frequently and have led to high region- and enantioselectivities for the allylation of malonates (with ligand **1**[27] and **13**[28]), nitroethane or ethyl α-nitroacetate (with ligand **13**[29]), amines (with ligands **1**,[30] **13'**,[31] **14**,[32] **15**[33]), alcohols (with **1** and **14**[34]) and potassium silanoate (with **1**[35]) (Scheme 1.6).



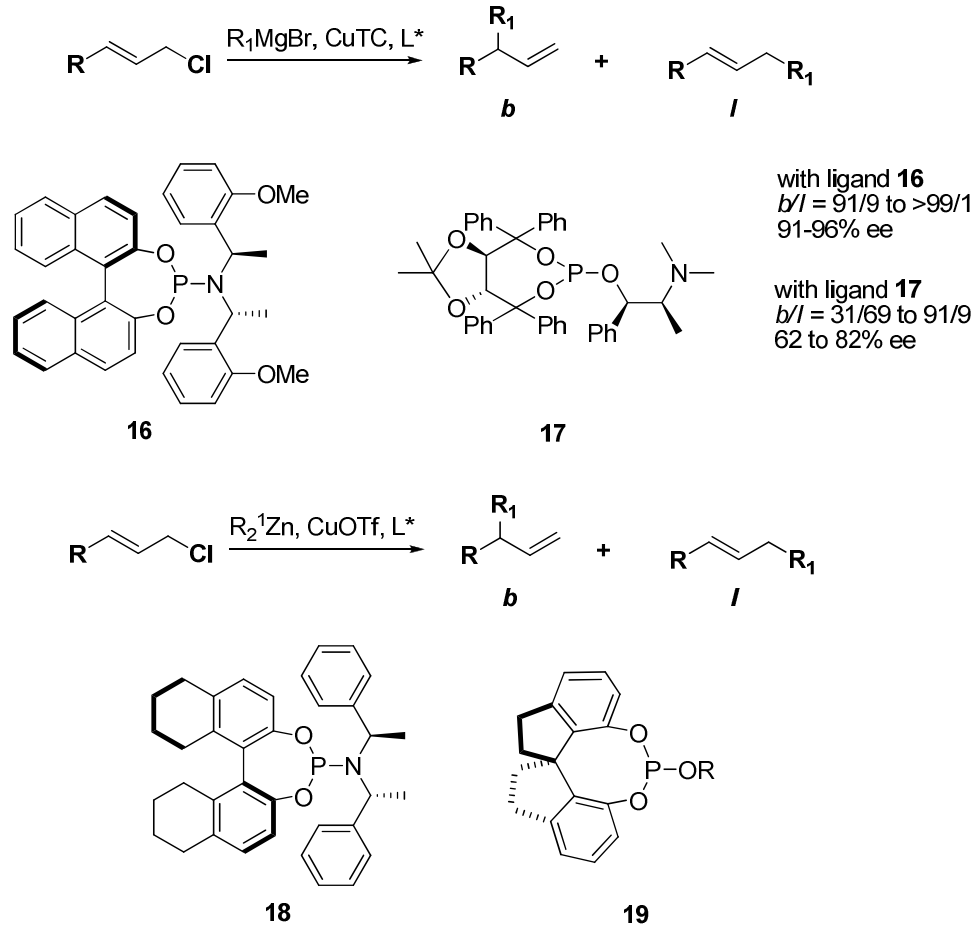
Scheme 1.6 Ligands used for asymmetric Ir-catalyzed alkylation

Branched enones can be produced by reaction of trimethylsilylenol ethers with allylic carbonates in the presence of a catalytic amount of $[Ir(COD)Cl]_2$ and the phosphoramidite ligand **1** in high enantiomeric excesses (91-96%) and regioselectivities (87/13-99/1) (Scheme 1.7).[36]



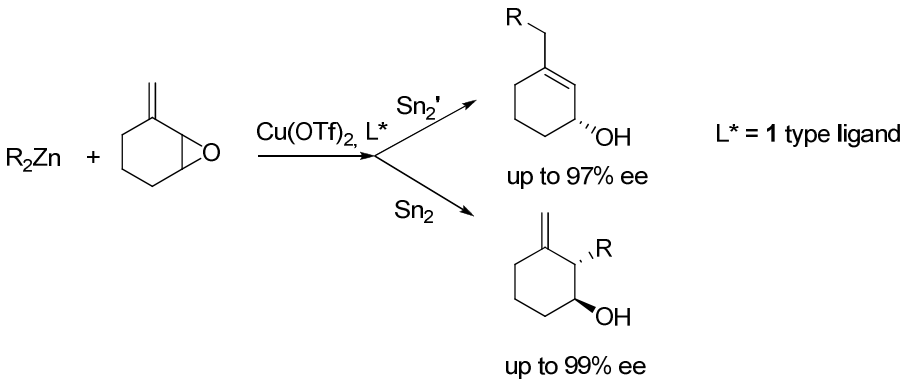
Scheme 1.7 Ir-catalyzed reaction of trimethylsilylenol ethers with allylic carbonates

Copper-catalyzed coupling reaction of substituted allylic substrates with Grignard or dialkylzinc reagents in the presence of chiral phosphoramidite **16** or **18**,[37] or phosphite **17** or **19**,[38] afforded the related terminal olefins with good regioselectivities and enantioselectivities (Scheme 1.8).



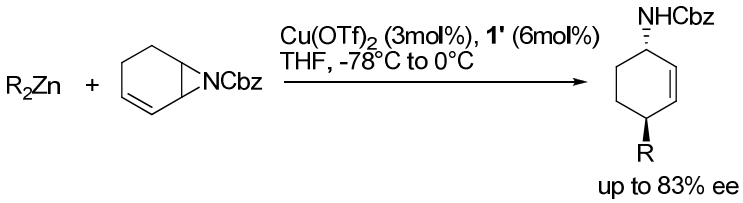
Scheme 1.8 Copper-catalyzed coupling reaction of substituted allylic substrates with Grignard or dialkylzinc reagents (TC = tiophene-2-carboxylate).

Kinetic resolution of allylic epoxides with dialkylzinc species in the presence of chiral copper-phosphoramidite catalysts was reported by Pineschi et al. (Scheme 1.9).[39] Allylic and homoallylic alcohols were isolated with good to excellent enantioselectivities. The regioselectivity of the reaction depends on the absolute configuration of the chiral catalyst.



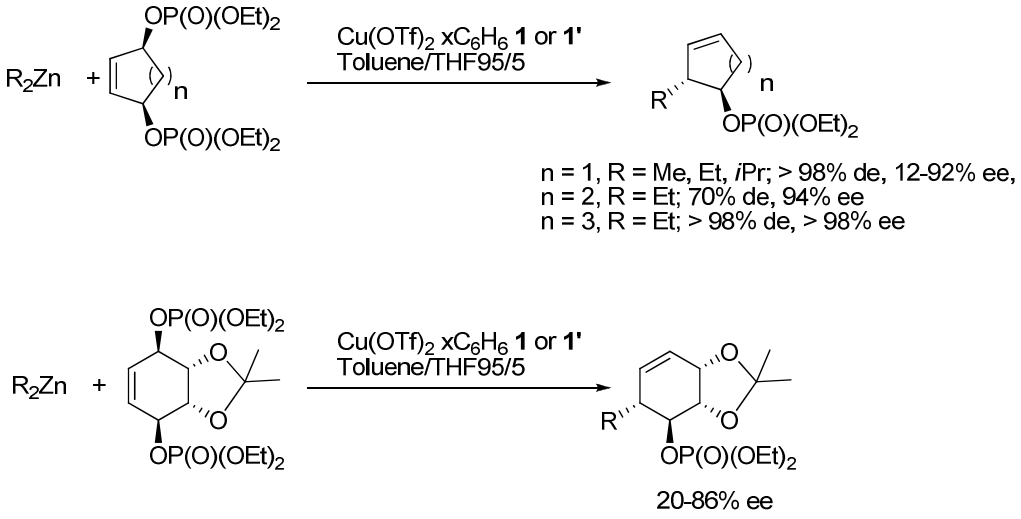
Scheme 1.9 Products of kinetic resolution with dialkyl zinc in dependence on the reaction mechanism

Extension of this reaction to 2-alkenyl aziridines was also examined (Schiral 1.10).[40] Chiral copper-phosphoramidite complexes were shown to be very efficent for the ring-opening reaction. The dialkylzinc addition was *anti*-stereoselective and allylic amines were isolated with good enantioselectivities (up to 83% ee).



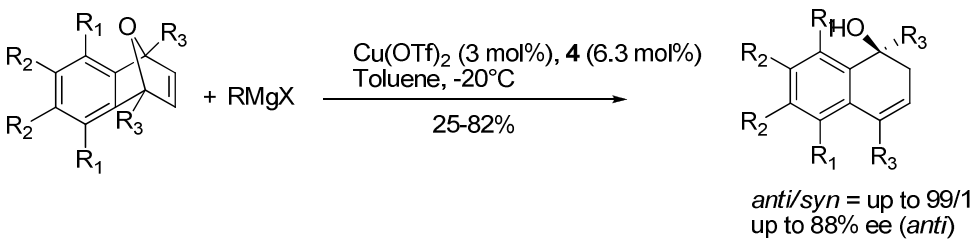
Scheme 1.10 Cu-catalyzed opening of 2-alkenyl aziridines with dialkyl zinc

Highly region-, diastereo and enantioslective desymmetrization of five-, six-, and seven-membered meso cyclic allylic diethyl-phosphates with organozinc compounds was described by Piarulli and Gennari.[41] Good to excellent enantioselectivities were observed with phosphoramidites **1** or **2**. Selectivities (de and ee) were highly dependent on the size of the ring (Scheme 1.11).



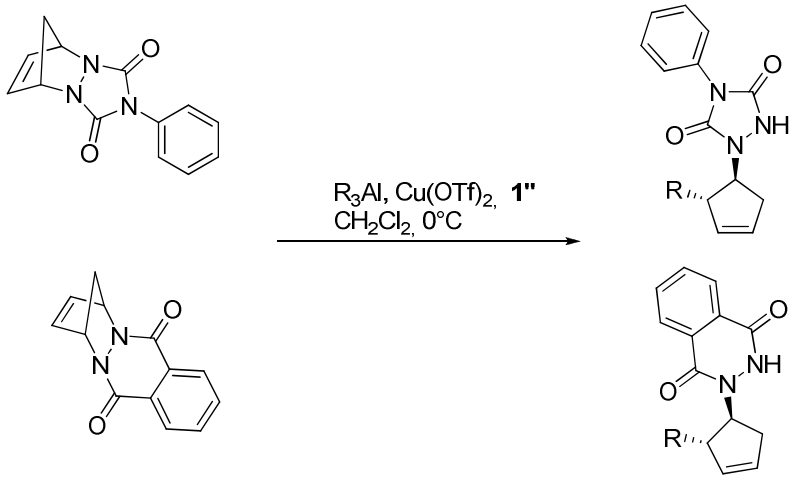
Scheme 1.11 Desymmetrization of cyclic meso allylic diethyl-phosphates with organozinc compounds

Enantioselective ring opening of oxabicyclic alkenes with Grignard reagents in the presence of copper and spirophosphoramidite was disclosed by Zhou et al. (Scheme 1.12).[42] The corresponding alcohols were obtained in excellent diastereoselectivities and in moderate to good enantiomeric excesses.



Scheme 1.12 Enantioselective ring opening of oxabicyclic alkenes with Grignard reagents

Regio- and enatioselective asymmetric ring opening of 1,3-cyclopentadiene-heterodienophile cycloadducts with trialkylaluminium species and copper-phosphoramidite **1"** was reported by Pineschi et al. (Scheme 1.13).[43] 1,2-disubstituted cyclopentenes were prepared in up to 86% ee. Alexakis et al.[44] have pointed out that extreme care was required in this reaction as BINOL- or biphenol based phosphoramidites could react with trimethylaluminium in non-coordinating solvents (toluene, dichloromethane) to give dimethylaminophosphines. These phosphines can act as ligands in the nucleophilic ring opening of bicyclic hydrazines and then modify the selectivities.

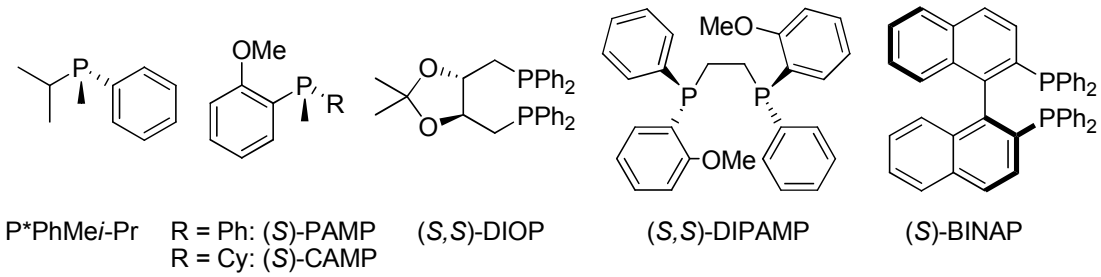


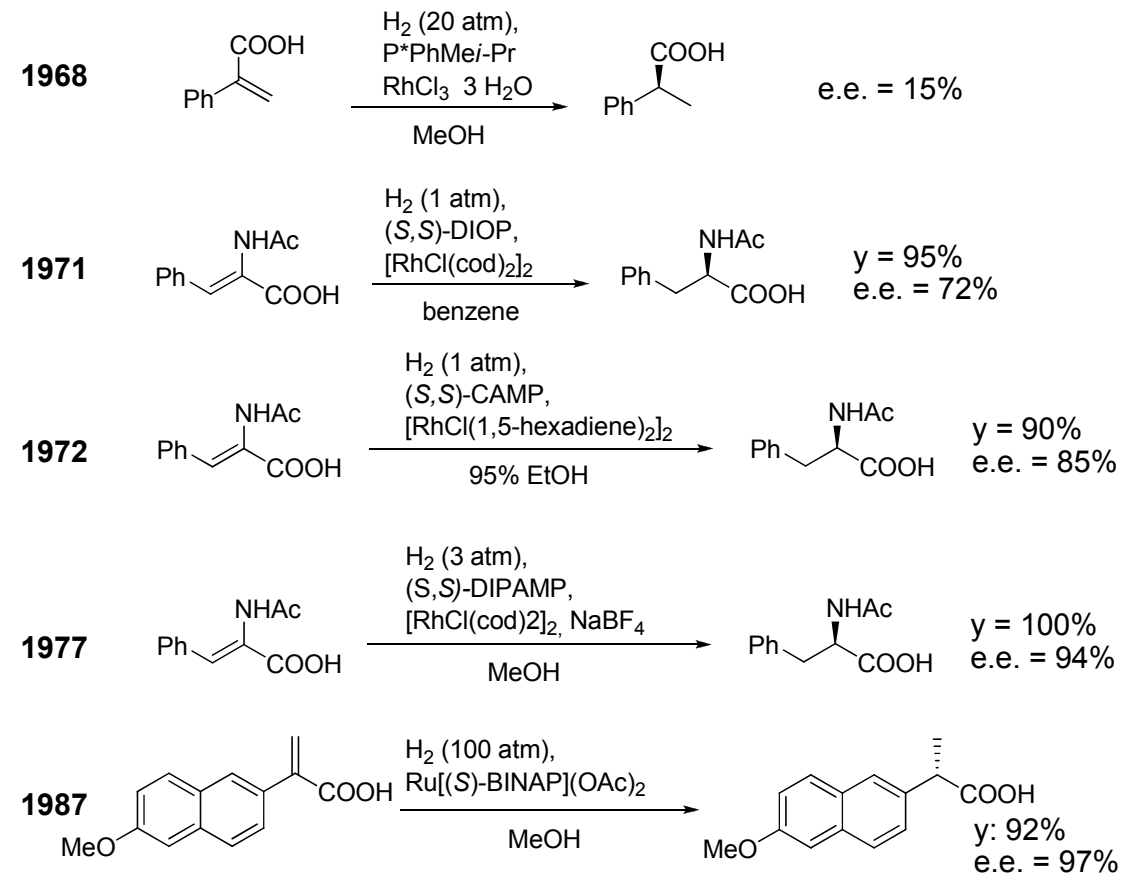
Scheme 1.13 Regio- and enantioselective asymmetric ring opening of 1,3-cyclopentadiene-heterodienophile cycloadducts with trialkylaluminium

1.2.3 Rhodium catalyzed asymmetric hydrogenation[45]

The first asymmetric olefin hydrogenation was achieved, with up to 15% e.e., by Knowles[46a] and Horner[46b] in 1968 using a rhodium complex bearing two chiral monodentate phosphines. Although Knowles could later obtain significantly higher levels of enantioselectivity in the hydrogenation of α-dehydroaminoacids using PAMP and CAMP ligands (Scheme 1.14),[47] an even more impressive breakthrough was made in the same period by Kagan.[48] He reported the first bis-phosphine ligand, DIOP, for Rh-catalyzed asymmetric hydrogenation. The successful application of DIOP resulted in several significant directions for ligand design in asymmetric hydrogenation. Chelating bis-phosphines could lead to superior enantioselectivity compared to monodentate phosphines. Additionally, C_2 symmetry was an important structural feature for developing new efficient chiral ligands. Kagan's seminal work immediately led to the rapid development of chiral bis-phosphorus ligands. Knowles later reported a C_2-symmetric chelating bis-phosphine ligand, DIPAMP,[49] which, due to its high catalytic efficiency in Rh-catalyzed asymmetric hydrogenation of dehydroaminoacids, was quickly employed in the industrial production of L-DOPA,[50a] [(*S*)-3,4-dihydroxyphenylalanine, wich had proved useful in the treatment of Parkinson's disease]. The success of practical synthesis of L-DOPA *via* asymmetric hydrogenation represented a milestone work, for which Knowles was awarded the Nobel Prize in 2001.[50b]

Following the significant contributions by Knowles and Kagan came the development of thousands of chiral phosphorus ligands for asymmetric hydrogenation over the 1980s and 1990s, the overwhelming majority of which were C_2 or C_1-symmetric bidentate *P,P*-ligands. Among these, Noyori's BINAP must be mentioned (Scheme 1.14),[51] whose ruthenium complexes efficiently catalyze the enantioselective reduction of olefins and ketones. For having developed this very important catalytic system, Noyori received the Nobel Prize in 2001.[51f]

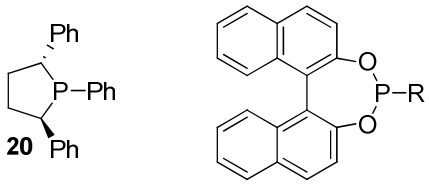




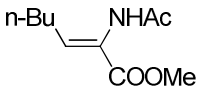
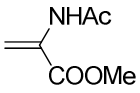
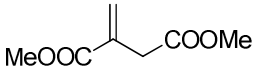
Scheme 1.14 The first most important asymmetric olefin hydrogenation reactions using phosphorus ligands

In the context of such "explosion" of the interest in *P,P*-bidentate ligands for asymmetric hydrogenation, despite having been the first enantioselective systems, monodentate *P*-ligands were somehow "neglected", as far as asymmetric hydrogenation is concerned: for some thirty years the rigidity typical of bidentate systems was deemed a possible indispensable requirement for the stereochemical information of the ligand to be efficiently transferred to the hydrogenation product.

The widely accepted dominance of the bidentate diphosphorus ligands was questioned for the first time in 1999, when Guillen and Fiaud reported a rhodium complex of 1,2,5-triphenylphospholane **20** (Scheme 1.15), a monodentate species of the DuPHOS-type. The Rh-complex of **20** could reduce methyl 3-phenyl-2-acetamidopropenoate with 82% e.e..[52] Orpen, Pringle, and co-workers attained the hydrogenation of methyl 2-acetamidoacrylate in 92% e.e. with the asymmetric monophosphonite **21** and thus demonstrated that a higher enantioselectivity with respect to comparable C_2-symmetric diphosphonite analogues was possible (Scheme 1.15).[53] Reetz and Sell showed in response that through the exchange of the *t*-butyl group for an ethyl group (**22**) the enantioselectivity can be further increased.[54] Dimethyl itaconate was also hydrogenated with the same catalyst with a respectable 90% e.e.. However, in spite of this, a related diphosphonite ligand delivered >99% e.e.. The old rule considering chelating diphosphorus ligands as superior still appeared to hold. A comparison between the performances of the monodentate ligands just described is set in Scheme 1.15.



21: R = *t*-Bu
22: R = Et
23: R = (*R*)-OCH(Me)Ph
24: R = NMe_2

Substrate	Ligand	e.e. (%)
	**20**	82
	24	98
	**21**	92
	22	94
	24	> 99
	**22**	90
	23	> 99
	5	94

Scheme 1.15 Rh-catalyzed hydrogenation of pro-chiral olefins

A clear tie in regard to performance, with enantioselectivities that could not be topped, was achieved with the use of monodentate binaphthol phosphites and phosphoramidites. In 2000 Reetz and Mehler prepared the monophosphite **23**.[55] The corresponding catalyst induces >99% e.e. in the hydrogenation of dimethyl itaconate. Particularly noteworthy is the high substrate: rhodium ratio of up to 5000:1, which still guarantees complete conversion in 20 h under atmospheric pressure. Surprisingly, the configuration of the stereogenic carbon atom of the benzyl ether does not play any kind of role, and the enantioselectivity of this type of ligand is dominated by the chiral binaphthyl unit.

Phosphoramidites, a ligand class that had only recently been introduced into asymmetric hydrogenation in the form of hybrid chelate ligands,[56] showed able to induce excellent

enantioselectivity as monodentate ligands. De Vries, Feringa, and co-workers could reduce standard substrates in > 94% e.e. with a rhodium complex based upon the binaphthol phosphoramidite **24** (MonoPhos), once the reaction conditions had been optimized.[57]

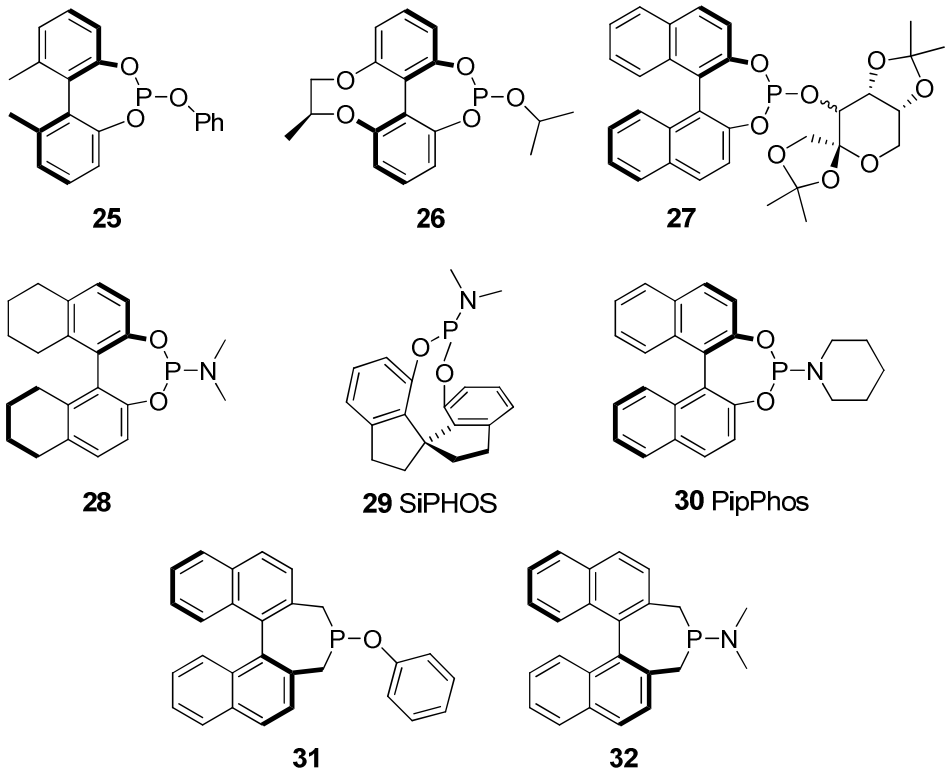
It should be noted that all of these early examples of highly enantioselective monodentate ligands were phosphorus derivatives of binaphthol. Based on the crystal structure of a Pt(II) complex with monophosphonite ligands, Orpen and Pringle proposed a plausible explanation that later was to be helpful in the development of other selective mono-phosphorus ligands.[58] Through the *cis* coordination both the sterically demanding monophosphonite ligands take up an exceptionally stable configuration around the metal centre, and the rotation about the P-O bond is reduced. In this conformation the two biaryl fragments point out of the plane of the projection in what is described as edge-on arrangement. In a virtual coordination system two diagonally opposing squares are occupied (Scheme 1.16 A). The squares at the top left and bottom right are not effectively occupied, because of the planar arrangement of the two phenyl groups in the plane of the projection (face-on). From investigations with chelating diphosphorus ligand complexes it was known that such an alternating edge/face arrangement[59] can support the diastereo-differentiating coordination of a pro-chiral substrate through the minimization of repulsive interactions.[60] In contrast, by the *cis* coordination of the diphosphonite ligands the stabilized rotamer is that in which the biaryl units are in the face-on orientation; none of the squares is favoured (Scheme 1.16 B). Thus the chances of diastereomeric recognition of the pro-chiral substrate are greatly reduced.

Scheme 1.16 Quadrant diagrams for (a) monophosphonite and (b) diphosphonite ligands

On the basis of this general model and supported by first semi-empirical calculations from de Vries and Feringa[61] it became clear that, for the mechanism of chiral transfer in asymmetric hydrogenation, mono- and diphosphorus ligands do not necessarily fundamentally differ. By year 2000 it was understood that the requirement originally laid down by Kagan, that the catalyst must be conformationally rigid, is clearly also achievable with two appropriate monodentate monophosphorus ligands.[62]

Not surprisingly, however, no single ligand proved "universal", because there cannot be such a thing as a general catalyst. When encountering cases in which enantioselectivity is insufficient, a "traditional" combinatorial approach would suggest to prepare and screen further, structurally modified derivatives. This is what was done exploiting the high modularity of the simple ligands discussed above: in the case of BINOL phosphites, for example, the substitution of naphthyl rings and the alkoxy moiety were modified in turn, which led to the preparation of a large number of catalysts.[63]

In a similar way, a large number of monodentate phosphoramidites, [64,65b] were prepared and tested as ligands for the Rh- and Ir-catalyzed reactions such as, respectively: (i) the asymmetric hydrogenation of α- and β-dehydroaminoacid derivatives and dimethyl itaconate;[65a] (ii) the asymmetric hydrogenation of ketoimines,[64s,z] and hydrogenation of quinoaxilines.[64t] Several monodentate phosphinites,[66a-b,e] and aminophosphinites,[66c] phosphines[66d] and phospholane[66f] were reported as well. Some of the best-performing ligands are shown in Scheme 1.17.



Scheme 1.17 Example of some of the best-performing ligands

The concept itself of utilizing libraries of modular ligands for asymmetric transition-metal catalysis was not new, having also been developed by Burgess,[67] Gilbertson,[68] Kobayashi,[69] Waldmann,[70] Berkessel,[71] Schmalz,[72] Ding,[73] and others.[74]

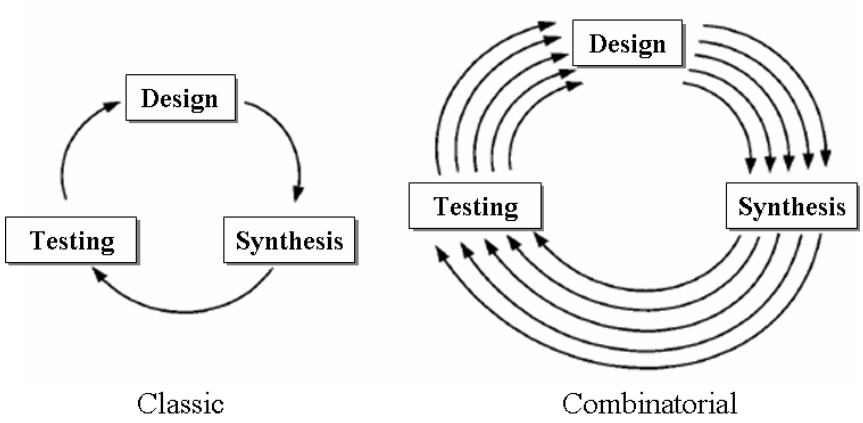
1.3 Combinatorial homogeneous transition-metal catalysis using mixtures of ligands

1.3.1 Combinatorial catalysis "General Concept"

The development of new catalysts is a challenging task. In many cases the correlation between their features (structural, electronic) and their performance (activity, selectivity, lifetime) is not easily

established. Therefore an iterative process of design, synthesis and testing is usually followed to improve catalyst performance. Combinatorial chemistry and "high-speed screening" technology can accelerate this process considerably, allowing for the simultaneous evaluation of a large number of candidates (Scheme 1.18).

In most general terms, the key-idea of combinatorial methods is to synthesize and screen large libraries of chemical entities as fast as possible using special techniques, rather than performing the task sequentially in a traditional and thus time-consuming manner.



Scheme 1.18 Comparison between classic and combinatorial methods

When performing a synthetic combinatorial chemistry experiment, two basically different strategies may be followed to create a library of compounds: *split-and-mix* (also termed split and pool) method developed by Furka[75b] and *parallel synthesis* employing appropriate laboratory equipment.
Solution or solid phase parallel methods are not new, and nowadays this approach is used routinely.[75] The important issue of automated solution-phase synthesis in an integrated system has been reviewed.[75d] Parallel screening of catalysts and biocatalysts is also practiced widely,[76] made possible by modern automation and robotics. Miniaturized equipment such as microreactors[77] or micro-fluidic chips (lab-on-a-chip)[78] may in the future allow for small-scale reactions and analyses within a single device in a high-throughput manner.

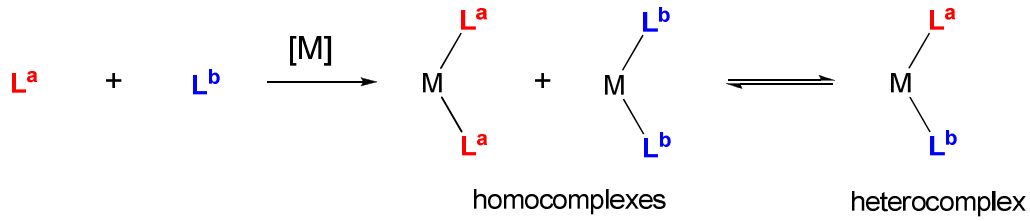
The term "combinatorial homogeneous catalysis" is not well defined. Most often, it simply means parallel synthesis and rapid evaluation of a large number of soluble catalysts. This includes not only the synthesis and testing of structurally different ligands/catalysts, but also the study of the influence of temperature, pressure, solvent, and additives. Multiple substrate screening as introduced by Kagan and Satyanarayana[79b] and ourselves[79a] is another practical facet of combinatorial homogeneous catalysis.

1.3.2 Combinatorial transition metal catalysis using ligand mixtures – "The concept"

The synthetic and mechanistic work described above inspired Reetz and co-workers to propose a new method in combinatorial homogeneous transition-metal catalysis: the use of mixtures of monodentate ligands.

The idea of mixtures may sound counterintuitive because chemists traditionally aim for single well-defined homogeneous catalysts. However, as first demonstrated in 2002/2003,[80,81] the concept is viable if applied properly.

The methodology is relevant whenever at least two monodentate ligands L are coordinated to the metal M of the active catalyst [ML_n] in the transition state of a reaction.[80,81] Thus its applicability goes beyond the field of asymmetric hydrogenation, as it will be discussed below. The simplest case involves a mixture of two such ligands L^a and L^b, in which three different catalysts exist in equilibrium with one another, namely the two homocomplexes [ML^aL^a] and [ML^bL^b] and the corresponding heterocomplex [ML^aL^b] (Scheme 1.19). If the ratio of components M, L^a, and L^b is chosen to be 1:1:1, then the ratio of [ML^aL^a]/[ML^bL^b]/[ML^aL^b] is not necessarily statistical (1:1:2). Rather, under thermodynamic conditions very different ratios are likely to result. The ideal case would constitute an equilibrium completely in favour of the heterocomplex [ML^aL^b], because then only a single well-defined catalyst would exist in the reaction flask. If ligand exchange is fast and reversible (which is the general case), the position of the equilibrium can be influenced by adjusting the amounts of the ligands L^a and L^b relative to each other and relative to the metal. Even if a mixture of catalysts exists the concept is valid, provided the heterocombination is more reactive and more selective than either of the two homocombinations.



Scheme 1.19 The concept of using mixtures of chiral monodentate ligands

This applies to every kind of selectivity, including enantio-, diastereo-, and regioselectivity. If such selectivities are not relevant in a given reaction, this approach may still be of interest, namely when attempting to increase the rate of a reaction. The concept featured in Scheme 1.19 is related but certainly not identical to the idea of dynamic combinatorial chemistry as developed by Sanders *et al.*[82a] and Lehn.[82b]

Since the catalytic profiles of homocomplexes [ML^aL^a] and [ML^bL^b] are already difficult to predict by theory, anticipating the catalytic properties of the respective heterocomplex [ML^aL^b] is even more challenging. Therefore, in order to identify the optimal heterocombination from a library of ligands, an empirical combinatorial protocol is necessary.[80] As time goes on and more experience accumulates, trends and hopefully theoretical models will emerge, which will aid the practicing chemist in new situations.

As the size of a library of *n* monodentate ligands increases, so does catalyst diversity as a consequence of mixing (Table 1.1). For example, once 20 different ligands have been prepared, not only are 20 different catalyst systems accessible according to traditional thinking, but also 190 additional catalysts in the form of the respective heterocombinations. Upon expanding the size of a library of monodentate ligands to 50, 100, or 200, the calculated number of heterocombinations increases drastically to 1225, 4950, and 19900, respectively. Thus, an explosion of catalyst diversity is possible without the need to synthesize any new ligands. Not all of the theoretically possible combinations may be meaningful in a given case, and these can be eliminated from further consideration on chemical grounds, thereby reducing the screening effort.

Table 1.1 Mixtures of monodentate ligands generate high catalyst diversity without the need to prepare new ligands

Number of ligands (*n*)	**Number of binary heterocombinations** $= \frac{n \times (n-1)}{2}$
20	190
50	1225
100	4950
150	11175
200	19900
500	124750

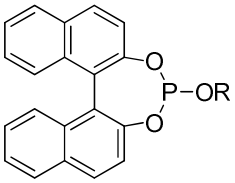
Thus far only monodentate *P*-ligands have been tested in mixtures, although in principle monodentate *C*, *N*, *O*, or *S*-ligands can also be considered. Rapid ligand exchange is necessary, which may not always be the case. It should be noted how the mechanistic dividing line between the concept just described and the traditional use of additives or activators may not be sharp in some cases.[83]

In the studies reported so far, only very small ligand libraries were constructed, which means that the full potential of the mixture concept has not been exploited. Nevertheless, significant results have accumulated.

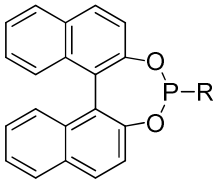
1.3.3 Combinatorial transition metal catalysis using mixtures of chiral ligands

The seminal study by Reetz *et al.*[80] is shortly outlined below, because it effectively shows the potentialities of this methodology.

Rh-catalyzed olefin hydrogenation was performed using a relatively small library of eight BINOL-derived phosphites **33a–h**, five phosphonites **34a–e**, and the chloride **35** as the monodentate ligands (Scheme 1.20).[80] The pro-chiral olefins which were considered for asymmetric hydrogenation were *N*-acetamido acrylates, *N*-acyl enamines and dimethyl itaconate. $Rh(cod)_2BF_4$ was treated with two equivalents of monodentate ligands (2.0 eq of one ligand or, alternatively, 1 eq of two different ligands) with formation of the precatalysts $Rh(cod)L_2BF_4$. The library of 14 ligands under consideration allows for 91 heterocombinations, but only 31 were actually tested.



33 **a**: R = CH_3
b: R = C_2H_5
c: R = *c*-C_6H_{11}
d: R = $C(CH_3)_3$
e: R = C_6H_5
f: R = 2,6-$(CH_3)_2C_6H_3$
g: R = $CH(CH_3)_2$
h: R = 9-fluorenyl

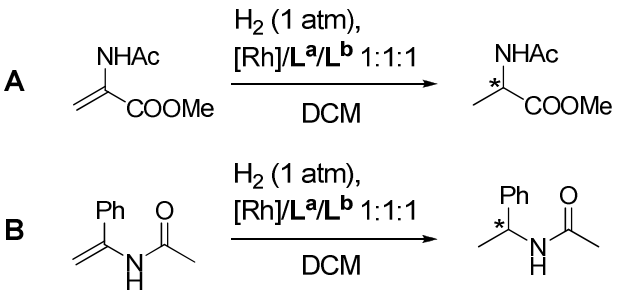


34 **a**: R = CH_3
b: R = C_2H_5
c: R = *c*-C_6H_{11}
d: R = $C(CH_3)_3$
e: R = C_6H_5

35: R = Cl

Scheme 1.20 Monodentate phosphorus ligands for Rh-catalyzed assymetric hydrogenation of pro-chiral olefins

This means that a mere 30% of chemical space was explored. In the hydrogenation of methyl 2-acetamidoacrylate (Scheme 1.21 A) several hits were identified, revealing moderately positive effects in several cases. An effect is defined as positive if the heterocombination results in an enantioselectivity which is higher than that of the best respective homocombination.



Scheme 1.21 Rh-catalyzed hydrogenation of (a) methyl 2-acetamidoacrylate and (b) *N*-(1-phenylvinyl)acetamide

One of the notable hits is the combination (*R*)-**33a**/(*R*)-**33f**, leading to 84.6% (*S*) ee, compared to the respective homocombinations (*R*)-**33a** and (*R*)-**33f**, which result in e.e. values of only 76.6% (*S*) and 32.4% (*S*), respectively. The best catalyst in the whole library of homo-and heterocombinations is the heterocombination comprising (*R*)-**34a**/(*R*)-**34c**, which leads to 97.9% (*S*) ee. The respective homocombinations result in markedly lower e.e. values of 91.8% (*S*) and 92.0% (*S*), respectively. This initial set of experiments indicates that the combination of a sterically small ligand and a bulky ligand constitutes the mixture of choice. This observation was made in numerous subsequent cases as well, although exceptions exist.

In the Rh-catalyzed asymmetric hydrogenation of *N*-acyl enamines (Scheme 1.21 B), the combinatorial search was confined to the use of the mini-library **34a–e** and **35**. The positive effect of mixing ligands proved to be much more dramatic than in the case of the other substrates. Upon performing a total of only 30 hydrogenation experiments, several highly selective combinations were discovered. For example, the best catalyst for the hydrogenation of α-acetamido styrene is again the "small/large" heterocombination (*R*)-**34a**/(*R*)-**34d** (96.1% e.e. for enantiomer *S*). This positive effect needs to be compared to the performance of the respective homocombinations: (*R*)-**34a**/(*R*)-**34a** (75.6% e.e. for enantiomer *S*) and (*R*)-**34d**/(*R*)-**34d** (13.2% e.e. for enantiomer *S*).

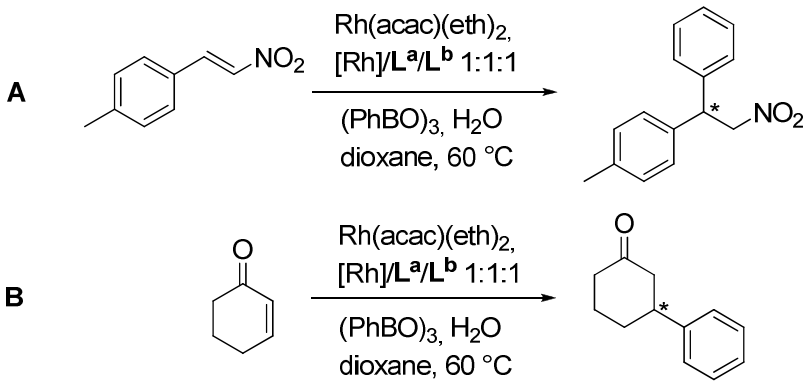
All of these experiments were performed using a Rh/L^a/L^b ratio of 1:1:1. To explore the possible effect of varying the ratio of the two phosphonites **34a**/**34d** while maintaining the original ratio of metal to total amount of ligand (Rh/L = 1:2), additional hydrogenations were carried out employing *N*-(1-phenylvinyl)acetamide (Scheme 1.21 B). Upon raising the relative amount of the bulky *t*-butyl phosphonite (**34a**/**34d** = 1:3), the enantiomeric excess increased to 97.4% (*S*). When doing the opposite (**34a**/**34d** = 3:1), the e.e. value decreased to 85.0% (*S*). Thus, this early study demonstrated that a variation of the ligand ratio in a heterocombination constitutes a further tool for catalyst optimization. Furthermore, it should be noted that in this particular case the bulkier of the two ligands dominates when attempting to increase enantioselectivity beyond the e.e. value obtained with the "usual" 1:1 ratio of ligands L^a and L^b.

These and other results of this early study demonstrated that the enhancement of enantioselectivity and reaction rate as a result of mixing two chiral monodentate ligands was not just a fortuitous event observed in a single case, but that a new principle in combinatorial asymmetric catalysis had emerged.

Immediately following the initial report from Reetz *et al*.,[80a] a note by de Vries, Feringa, *et al.* appeared,[84] describing the benefits of mixing certain BINOL-derived phosphoramidites in the Rh-catalyzed hydrogenation of β-(acylamino)acrylates with formation of the β-amino acid derivatives. Later on, again Reetz reported that the stereoselectivity of the same reaction could be improved using appropriate mixtures of phosphites and phosphonites.[85]

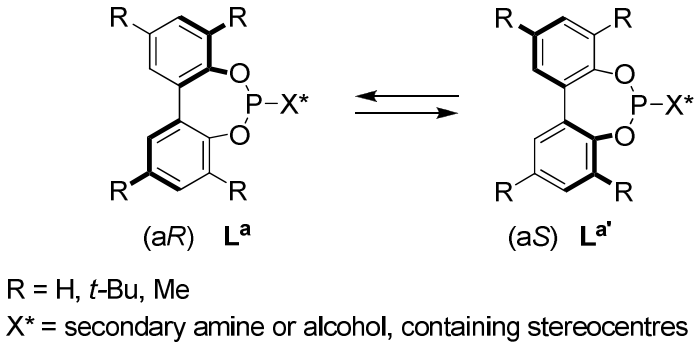
As stated above, the principle of mixing monodentate ligands in transition metal-catalyzed reactions is not restricted to asymmetric hydrogenation. It was also applied by Feringa and co-workers

to the asymmetric Rh-catalyzed conjugate addition of aryl boronic acids (Scheme 1.22),[86] a synthetically useful reaction type originally developed by Miyaura, Hayashi *et al.*[87] and applied by others.[88] Only three monodentate *P*-ligands were tested in this study, and the effect of mixing was remarkable, although the results had little practical utility (up to 47% e.e. in reaction A, up to 77% e.e. in reaction B, Scheme 1.22). Interestingly, in several cases the heterocombination of two ligands having opposite stereochemical preferences proved more enantioselective than the corresponding homocombinations.



Scheme 1.22 Rh-catalyzed conjugate addition of aryl boronic acids

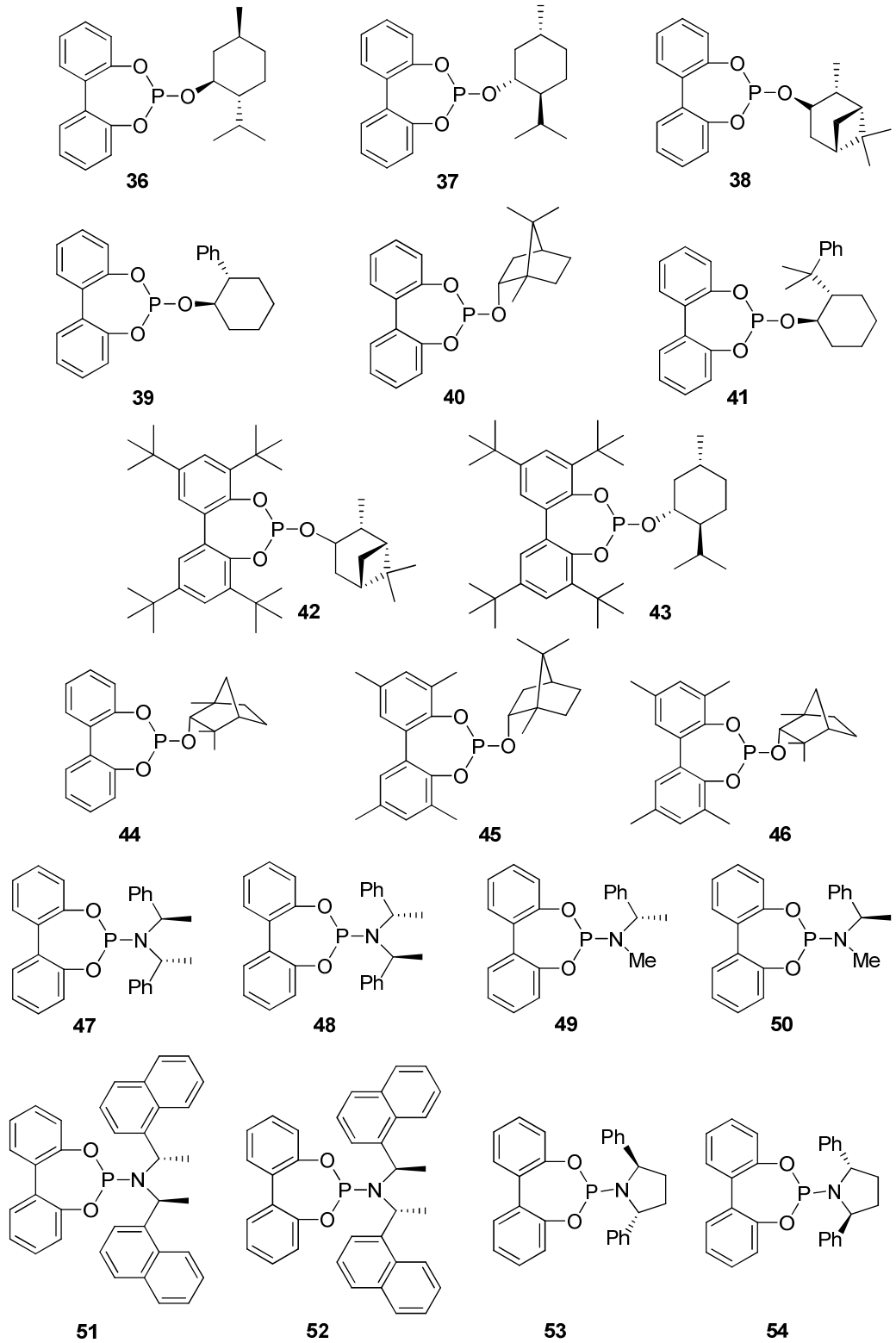
Also our research group provided a significant contribution in this field of organometallic catalysis: extending the concept of mixing monodentate compounds, Gennari and Piarulli *et al.* exploited the dynamic behaviour of ligands composed of fluxional "axially chiral" *tropos* moieties (i.e. having a stereogenic axis free to rotate) and a covalently attached configurationally stable entity in Rh-catalyzed olefin hydrogenation (Scheme 1.23).[89] If two different ligands of this kind are used in a mixture, an intriguing situation arises.



Scheme 1.23 Chiral phosphorus ligands based on a chiral *P*-bound alcohol or secondary amine and a flexible (tropos) *P*-bound biphenol unit

When employing a "single" ligand, two diastereomeric homocomplexes [ML^aL^a] and [$ML^{a'}L^{a'}$] as well as the heterocomplexes [$ML^aL^{a'}$] are possible. Consequently, three diastereomers are actually involved in the mixture, that are likely to have different catalytic profiles in terms of activity and

enantioselectivity. Moreover, the ratio of the three species is not expected to be statistical (1:1:2). In the case of two different ligands L^a and L^b of this kind, up to 10 different species may be formed: $[ML^aL^a]$, $[ML^aL^{a'}]$, $[ML^{a'}L^{a'}]$, $[ML^bL^b]$, $[ML^bL^{b'}]$, $[ML^{b'}L^{b'}]$, $[ML^aL^b]$, $[ML^aL^{b'}]$, $[ML^{a'}L^b]$ and $[ML^{a'}L^{b'}]$.[81] Intriguing observations

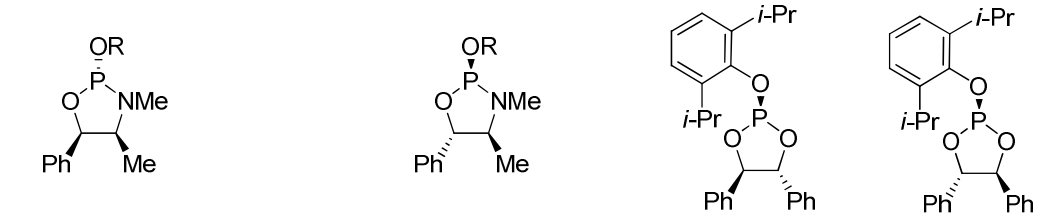


Scheme 1.24 Libraryof 20 ligands, 11 phosphites [$P(O)_2O$ **36**–**46**] and 8 phosphoramidites [$P(O)_2N$ **47**–**54**]

were made in a study employing such compounds as **36**-**54** as ligands in the Rh-catalyzed hydrogenation of methyl 2-acetamidoacrylate. A total of 85 reactions were performed, which means that only a portion of the total chemical space was actually explored. No homocombination of the ligands **36**-**54** performs well (e.e.'s range from 0 to 55%). When ligand heterocombinations were used, certain phosphite/phosphoramidite combinations proved to be optimal. The best hit is **39**/**48**, which leads to an e.e. value of 87% compared to 53% e.e. and 52% e.e. for the respective homocombinations. It is also clear that **39**/**48** constitutes the matched system, because **39**/**47** provides an e.e. value of only 35%. Similar results were observed when hydrogenating other substrates such as enamides and dimethyl itaconate. From a practical point of view the asymmetric hydrogenation of methyl 2-acetamidoacrylate is best performed classically by using a single ligand; for example, the best phosphite ligand for hydrogenation of methyl 2-acetamidoacrylate is picked as a result of testing a library of derivatives differing in the nature of the RO- group at phosphorus. This is true in this particular example, but it may not be so in all cases. The importance of the present study lies in the proof of principle and in the mechanistic lessons learned therein. Extensive kinetic investigations were included, which led to a useful mathematical model. The same library was utilized in Rh-catalyzed Miyaura–Hayashi reactions,[87] for example the one shown in Scheme 1.22 B.[90] Enantioselectivities of up to 95% e.e. were observed when using the heterocombination **41**/**54**, compared to only 70% e.e. and 36% e.e. for the respective homocombinations.

In another study by Reetz *et al.* it was shown that structurally very different types of chiral monodentate *P*-ligands can also be used successfully in mixtures.[91] These include ephedrine and pseudo-ephedrine-derived oxazaphospholidines such as **55** and **56** (Scheme 1.25), known types of compounds that had previously been used by Alexakis *et al.* as single ligands in Cu-mediated conjugate additions and other reactions.[92] In the study regarding mixtures, the small library of six ligands shown in Scheme 1.25 was extended to include the C_2-symmetric phosphites **57** and **58** (*R*,*R* and *S*,*S* configuration, respectively).[91] The performance of these ligands as homocombinations in the Rh-catalyzed hydrogenation of such substrates as dimethyl itaconate proved to be poor (0–56% e.e.).[91] Some improvements were observed through pair wise mixing. However, the best hit constitutes a mixture in which one of the components is a BINOL-derived monophosphonite, as in (*R*)-**34d**/**56b**, which gives rise to an e.e. value of 89% (*R*). These results are all the more remarkable because one of the respective homocombinations induces the opposite sense of enantioselectivity. The diastereomeric heterocombination (*S*)-**34d**/**56b** results in considerably lower enantioselectivity (52% e.e. for the *S* enantiomer), which means that this is the mismatched case.

Chemical modification of BINOL leads to added structural diversity in the respective *P*-ligands, although this is accomplished at the cost of additional synthetic efforts. If only one naphthyl moiety in BINOL is modified, C_2 symmetry no longer holds, which means that the P atoms in the respective phosphites, phosphonites, or phosphoramidites turn into stereogenic centres (P_R or P_S). This gives rise to two diastereoisomers.



55 **a**: R = 2-naphthyl
b: R = *t*-butyl
c: R = 2,6-diisopropylphenyl

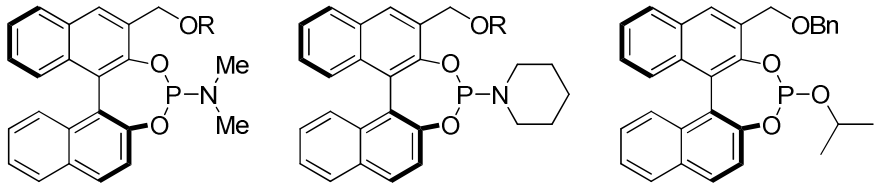
56 **a**: R = methyl
b: R = *t*-butyl
c: R = 2,6-diisopropylphenyl

57

58

Scheme 1.25 Ephedrine and pseudo-ephedrine-derived oxazaphospholidines **55**-**56** and the C_2-symmetric phosphite ligands **57**-**58**

Reetz and co-workers prepared such compounds (Scheme 1.26), for example **59**–**61**, in the hope that the stereogenic units positioned closer to the Rh centre would exert special effects.[93]



59 **a**: R = Bz
b: R = Me
c: R = Bn

60 **a**: R = Bz
b: R = Me
c: R = Bn

61

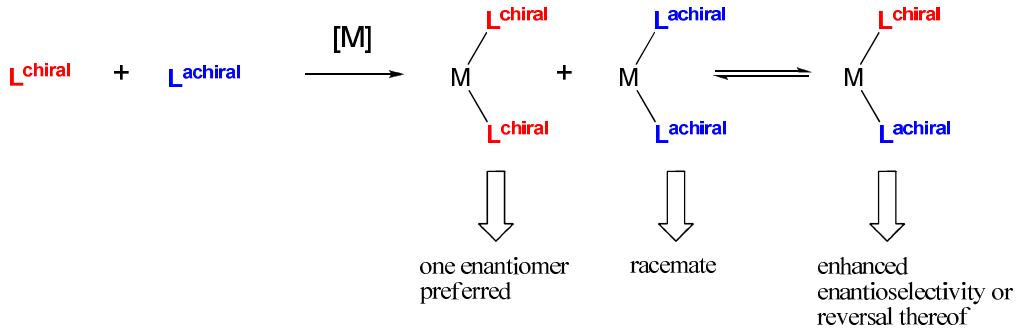
Scheme 1.26 Diastereomeric phosphoramidite **59**-**60** and phosphite **61** ligands with stereogenic phosphorus centers

The single ligands as homocombinations proved to be quite effective in olefin hydrogenation reactions, as in the reduction of methyl 2-acetamidoacrylate with e.e. values in the range 97% to greater than 99%. In some cases an unusual effect was observed, namely that a mixture of two diastereomers differing only in the absolute configuration at phosphorus is more effective than either of the two respective homocombinations. The interesting area of ligands having stereogenic centres at phosphorus[94] has not been explored systematically in the present context.

1.3.4 Combinatorial transition metal catalysis using mixtures comprising a chiral and an achiral P-ligand

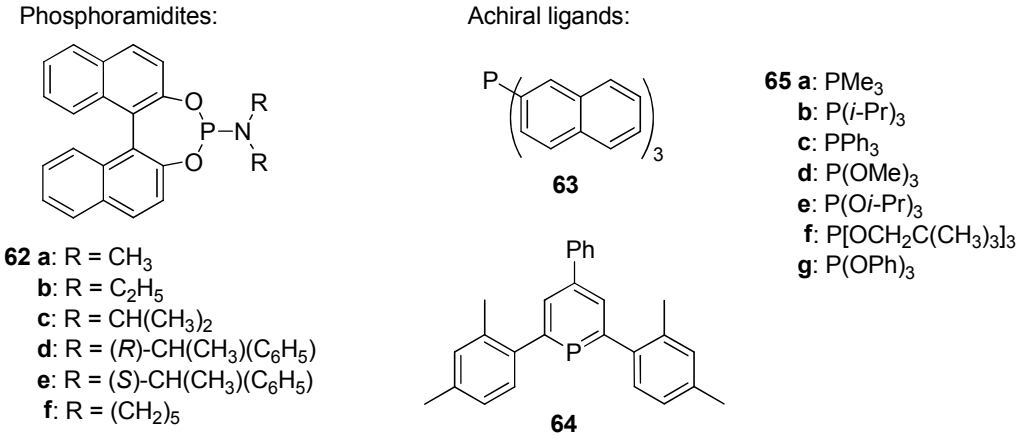
Early on, Reetz *et al.* also contemplated the use of mixtures of chiral and achiral ligands in Rh-catalyzed hydrogenation (Scheme 1.27).[80b-d] This proposal seems counterintuitive, because one of the homocombinations in the mixture is achiral, necessarily leading to a racemic product. However, as before, the heterocombination may define the outcome of the reaction if it is more reactive and more

enantioselective than the homocombinations. Since vast numbers of achiral *P*-ligands are available at low cost, high structural diversity regarding the heterocombination is readily accessible.



Scheme 1.27 The concept of using mixtures of monodentate chiral and achiral ligands in transition-metal-catalyzed asymmetric reactions

Initially representatives of the three BINOL-derived types of *P*-ligands such as phosphites **33**, phosphonites **34** (Scheme 1.20) and phosphoramidites **62** (Scheme 1.28) were each tested in mixtures with different achiral monodentate *P*-ligands such as **63** or **64** (Scheme 1.28) and one fluxional (*tropos*) phosphite **66** (Scheme 1.29), in hydrogenation of methyl 2-acetamidoacrylate serving as the model reaction.[80d]

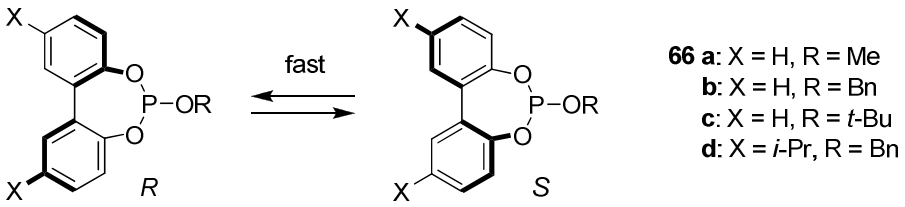


Scheme 1.28 Phosphoramidite **62**, achiral phosphine **63**-**65** ligands

In most cases enantioselectivity decreased, which may not be surprising. However, in several instances the sense of enantioselectivity was reversed upon using an achiral ligand as one of the components, especially when employing mixtures of **33** and tris(2-naphthyl)phosphine (**63**) or the phosphinine **64**, respectively. For example, the homocombination (*R*)-**34a**/(*R*)-**34a** is a respectable ligand system in the hydrogenation of methyl 2-acetamidoacrylate (92% e.e. for enantiomer *S*), whereas the heterocombination (*R*)-**34a**/**64** induces reversal of the enantioselectivity (58% e.e. for enantiomer

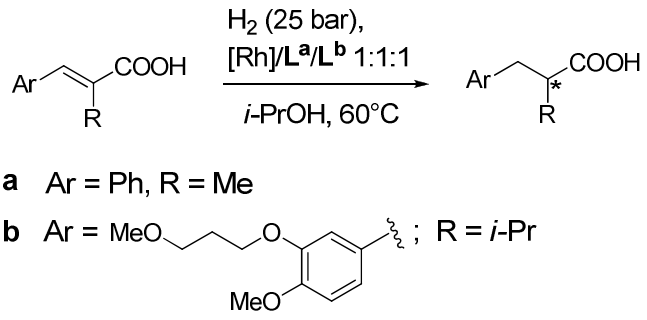
R).[80d] Energetically, such a switch is dramatic ($\Delta\Delta G^{\ddagger}$ = 2.6 kcal mol^{-1}), which means that the mixing effect is pronounced. Of course, to get a product with opposite absolute configuration, it is best to use the enantiomeric form of the BINOL-derived ligands (*S*)-**33** or (*S*)-**34**, which provide much higher e.e. values. Nevertheless, the results are of theoretical interest, and they also set the stage for further research using other mixtures of chiral and achiral monodentate ligands.[80 b,c]

Upon applying the mixture concept to chiral and achiral monodentate *P*-ligands more systematically, remarkable observations were made.[80b,c] In this study β-*N*-acylamino acrylates were used as model substrates, with phosphite **33a** and phosphonite **34d** serving as the chiral *P*-ligands. In addition to the achiral *P*-ligands **65**, fluxional diphenol-derived (*tropos*) phosphites **66** (Scheme 1.29) were also employed. A relatively short combinatorial search was made in the study of the Rh-catalyzed asymmetric hydrogenation of *Z*-3-acetamido-2-butenoate.[80c] It can be seen that pronounced effects result when using the *t*-butyl phosphonite **34d** as the chiral ligand in combination with achiral ligands. The homocombination **34d** leads to an e.e. value of only 45%. Upon employing a 1:1 mixture of **34d** and trimethyl phosphite (**65d**) or triphenyl phosphite (**65g**), the e.e. value climbs to 84 and 88%, respectively. When using the configurationally fluxional phosphites **66** in combination with **34d**, even higher enantioselectivities are observed. Accordingly, **34d**/**66a**, **34d**/**66b**, and **34d**/**66d** lead to e.e. values of 98, 98, and 94%, respectively. In contrast, the sterically demanding fluxional phosphite **66c** in combination with the bulky phosphonite **34d** results in an almost racemic product. This result is reminiscent of the behaviour of two bulky chiral *P*-ligands, whose combination generally leads to low levels of enantioselectivity. Similar effects were observed when hydrogenating other β-acylamino acrylates and dimethyl itaconate. For example, when hydrogenating dimethyl itaconate ligand **34d** alone results in an e.e. value of 77%, whereas the use of **34d**/**65g** or **34d**/**66a** boosts enantioselectivity to 94% e.e. in both cases.[80c]



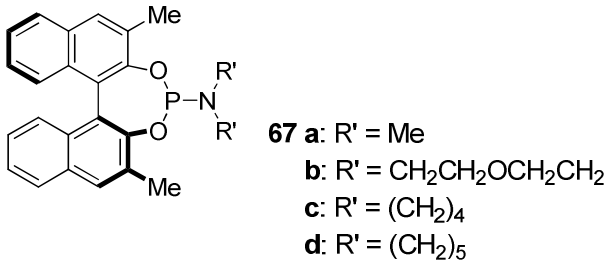
Scheme 1.29 Fluxional diphenolderived (tropos) phosphites

Subsequent to these studies, Feringa, de Vries, *et al.* applied the idea of using a mixture of a chiral and an achiral monodentate *P*-ligand in the hydrogenation of α,β-unsaturated acids of the type shown in Scheme 1.30, leading to the corresponding chiral dihydrocinnamic acid derivatives.[95]



Scheme 1.30 The Rh-catalyzed hydrogenation of α,β-unsaturated acids

These are key intermediates in the synthesis of a number of bioactive compounds such as renin inhibitors, γ-secretase inhibitors, enkephalinase inhibitors, endothelin receptor antagonists, and opioid antagonists. A variety of different BINOL-derived phosphoramidites **62** with various achiral and chiral R groups in the amino group were first tested in respective mixtures with triphenylphosphine (**65c**) using substrate **a** (Scheme 1.30). Unfortunately, improvements in enantioselectivity were meagre. In contrast, *ortho*-dimethyl derivatives **67** led to notable positive effects when used in mixtures with triphenylphosphine (**65c**). For example, ligand **67d** failed completely when used alone, and this homocombination resulted in racemic product in a slow reaction. In contrast, upon using the heterocombination **65c**/**67d**, a fast and quantitative reaction was found to occur with 85% e.e. Upon tuning the achiral phosphine, further improvements proved to be possible, as in the heterocombination comprising tris(xylyl)phosphine and **67d**, leading to 92% e.e.

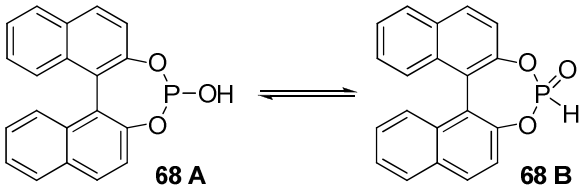


Scheme 1.31 3,3'-dimethyl substituted BINOL-derived phosphormidite ligands

In other cases involving industrially relevant substrates such as **b** (Scheme 1.30), even higher e.e. values were achieved. Similar developments were subsequently reported for other types of substrates such as *N*-formyl dehydroaminoacid esters[96a] and 2-(acetylaminomethyl)-3-aryl acrylic acid esters.[96]

In a more recent study Reetz *et al.* reported once more the remarkable effect that the process of mixing chiral and achiral monodentate *P*-ligands can induce, specifically in the Ir-catalyzed asymmetric hydrogenation of pro-chiral ketimines.[97] In this attempt the cheap phosphorous acid diester **68** was utilized as the chiral component together with various achiral monodentate *P*-ligands. Phosphorous acid diesters are known to exist in an equilibrium P^{V}-P^{III}, the penta-valent form P^{V} being

favoured as in **68B** (Scheme 1.32). However, it is well known that transition metals bind to the P atom in the three-valent form, as shown by crystal structures and spectroscopic data.[98] Several ketimines were subjected to Ir-catalyzed hydrogenation with formation of the corresponding chiral amines. The results show that the chiral ligand **68** alone is a poor ligand (7–36% e.e.), whereas the heterocombination with achiral triphenylphosphine **65c**/**68** leads to e.e. values of 88–92%.

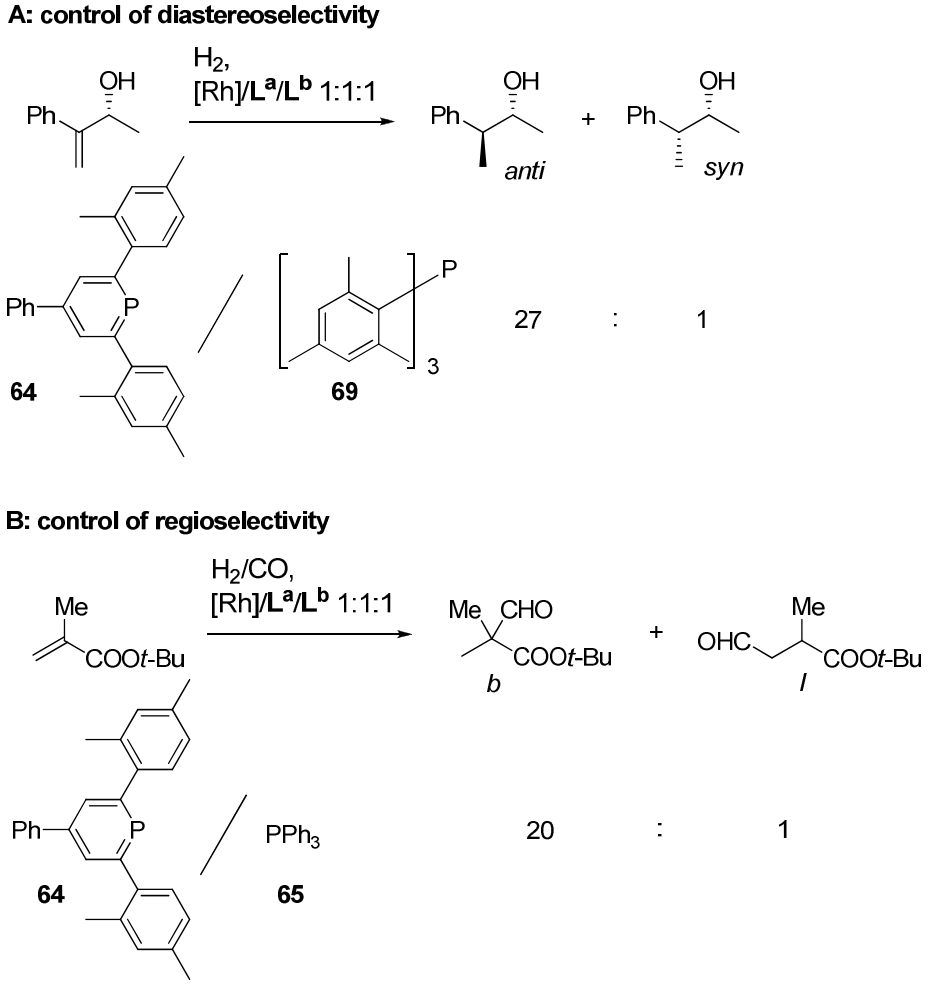


L^a / L^b / [Rh]	L^a	L^b	Conv. (%)	e.e. (%)
2 : 0 : 1	**68**	-	20-30	7-36
1 : 1: 1	**68**	PPh_3	90-100	88-92

Scheme 1.32 Iridium-catalyzed hydrogenation of ketimines

1.3.5 Controlling the diastereo- and regioselectivity

The combinatorial concept of applying mixtures of monodentate *P*-ligands was also extended to include the control of diastereoselectivity.[99] Diastereoselective reactions where the stereochemical information existing on the substrate influences the creation of new stereogenic unit(s) ("1,*n*-asymmetric induction")[100] were studied using a library of 21 mostly achiral monodentate *P*-ligands. For example, in the case of the hydrogenation of chiral allylic alcohols (Scheme 1.33 A) 150 reactions were performed (although a total of 210 different heterocombinations are possible), which led to the identification of 15–20 positive hits. These are the heterocombinations which display a higher diastereoselectivity than either of the two respective homocombinations alone. Some of the hits resulted in extremely high diastereoselectivities (*anti*/*syn* ratio up to 27:1, using combination of the phosphines **64**/**69**).



Scheme 1.33 (a) hydrogenation of chiral allylic alcohols; (b) hydroformylation of olefins.

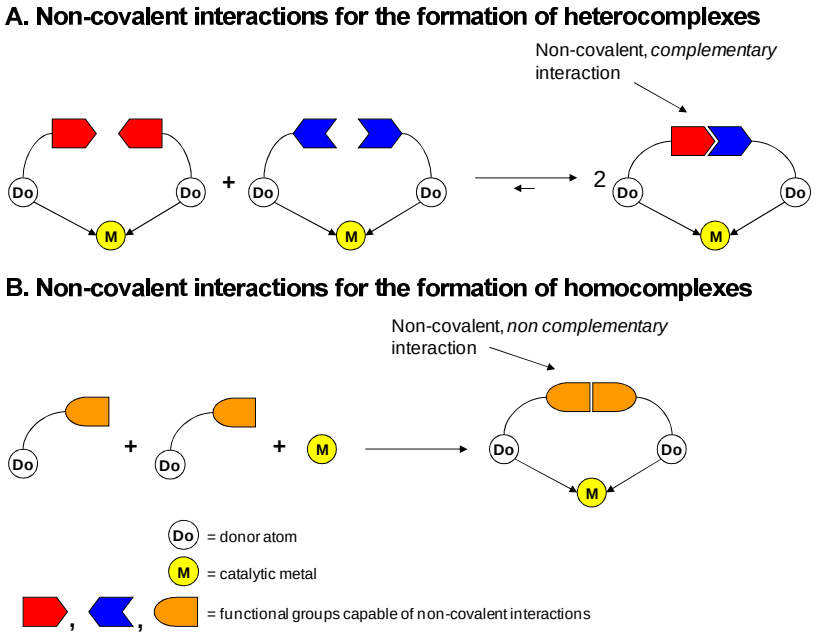
In principle, any parameter of a catalytic profile can be influenced by using mixtures of monodentate ligands. It was thus attempted to influence the regioselectivity of transition-metal-catalyzed reactions by applying this type of combinatorial catalysis. The Rh-catalyzed hydroformylation of olefins was chosen as a first target.[101,102] Many different achiral monodentate *P*-ligands are potential candidates for such an endeavour, but the combinatorial search was confined to a small library of 14 simple phosphine and phosphite ligands. *t*-butyl metacrylate (Scheme 1.33 B) was chosen as the model olefin with formation of the branched product with a quaternary C atom and the linear regioisomer. As expected, the most common *P*-ligands favour the linear product. Thus, it was a challenge to find a catalyst system which leads to a strong preference for the branched aldehyde. It was found that 12 heterocombinations induce the preferential formation of the branched product, despite the fact that the respective homocombinations all display opposite regioselectivity favouring the linear isomer. The best catalyst system, obtained by combination of the phosphinine **64** and triphenylphosphine **65c**, led to a 8.4:1 *b*/*l* ratio, while the corresponding homocombinations induce ratios of 0.76:1 and 0.72:1, respectively. This system was then optimized by tuning the reaction conditions (80 bar CO/H_2 = 1:1; 40 °C, 30 h, substrate/Rh= 50:1, L^a/L^b=1:1; Rh/total ligands = 1:2.4; toluene as solvent). As a result,

the regioselectivity climbed to 20:1, which means 95% regioselectivity in favour of the branched product.

1.4 SUPRA MOLECULAR BIDENTATE *P,P* –LIGANDS

1.4.1 Basic principle

As reported in section 1.3.2, when two ligands L^a and L^b are added to a metal source, the two homocomplexes $[ML^aL^a]$ and $[ML^bL^b]$ compete with the heterocomplex $[ML^aL^b]$ for acting as the catalyst. As a consequence, when the heterocomplex is the most selective species, the homocomplexes lower the overall selectivity of the process, unless the catalytic activity of the heterocomplex is exceedingly higher. The relative amounts of hetero- and homocomplexes were studied by NMR spectroscopy and it was found that, under thermodynamic control (fast and reversible ligand exchange), the heterocomplex/homocomplexes ratios often exceed the statistical value (2:1:1).[80,103] It was also reported that the amount of heterocomplex can be enhanced by carefully tuning the L^a/L^b ratio, with consequent optimisation of the overall selectivity of the catalytic transformation.[104] Nevertheless, non-covalent interactions soon appeared as a clever way to achieve the exclusive formation of the heteroleptic complexes from mixtures of monodentate ligands. To this end, supramolecular ligands capable of *complementary interactions* (Scheme 1.34 A) are required, so that attractive interactions take place only between different ligands.[105]



Scheme 1.33 Schematic representation of supramolecular bidentate ligands formed by complementary (A) and non-complementary interactions (B)..

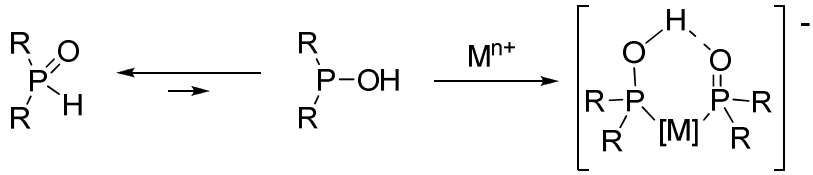
The heterocomplexes formed in this way are expected to have reduced degrees of freedom[106] compared to the complexes of normal monodentate ligands, and thus supramolecular ligands somehow resemble traditional bidentate ligands. According to this analogy, they are often referred to as *supramolecular bidentate ligands* or *self-assembled ligands*, thanks to their ability to spontaneously form bidentate systems in solution. These terms also apply to those supramolecular ligands that are only capable of *non-complementary* interactions (Scheme 1.34 B):[105] indeed these systems are still capable of forming rigid and conformationally restricted complexes, although they cannot selectively form heterocomplexes when used in a mixture, which quite reduces their "combinatorial appeal". Using non-covalent interactions, ligands can be linked to other molecules for different purposes than forming supramolecular bidentate ligands,[107] and these applications are not discussed in the present review.

In this section, supramolecular bidentate ligands are classified on the basis of the non-covalent interactions they rely on, hydrogen bonding and coordinative bonding being by far the most widely exploited.

1.4.2 Self-assembly through hydrogen-bonding interactions

1.4.2.1 Secondary phosphine oxides

Secondary phosphine oxides (SPOs) form an unusual class of ligands,[108a] that are stable and inert to water. This is due to the tautomerization equilibrium that is in favour of the stable oxide, but in 1968 it was found that the equilibrium can be shifted by the addition of a metal precursor (Scheme 1.35)[108b] and in 1975 the formation of platinum complexes based on SPOs were reported.[109]



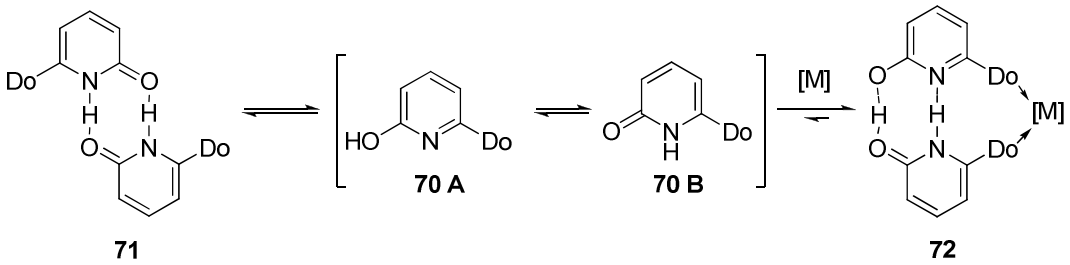
Scheme 1.35 Tautomeric forms of SPOs: SPOs exist in equilibrium between pentavalent (phosphine oxide form) and trivalent (phosphinite form) tautomeric structures. Although at room temperature the phosphine oxide form is the more stable one, it is the phosphonite form that coordinates to the transition metal

Although they were not specifically designed as supramolecular ligands, this class of compounds represent the first example of ligands that form a bidentate ligand via a hydrogen bond. In this particular case between the phosphine oxide and the alcohol, as was later confirmed by X-ray analysis.[110] In 1986 it was reported that these platinum complexes are active in the hydroformylation and hydrogenation reaction and that the ligands were operating as bidentate ligands.[111] Much later it was found that the class of ligands can be used for a variety of reactions such palladium-catalyzed

cross coupling reactions,[112] platinum catalyzed nitrile hydrolysis and iridium catalyzed hydrogenation. In most examples, however, the ligands were employed as monodentate ligands rather than supramolecular bidentate ligands. In some of the reactions the ligands might rearrange into the supramolecular bidentate, but in many reports where the ligands were added *in situ* and the ligation was not investigated in detail. Various chiral SPOs have been prepared by the groups of Feringa and de Vries, which provide fascinating new opportunities to this field.[113]

1.4.2.2 Systems relying on hydrogen bonding between polar heterocycles

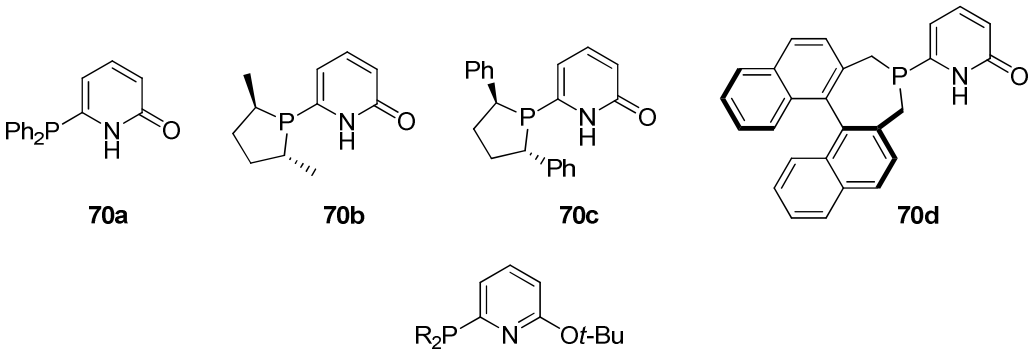
The first example of self-assembled bidentate ligand was reported by Breit and Seiche in 2003.[114] As a platform for hydrogen bonding, the tautomer system 2-pyridone (**70B**)/2-hydroxypyridine (**70A**), firstly prepared and employed in different context by Nakamura *et al.*,[115] was employed. The parent system (Do = H) is known to dimerize in aprotic solvents to form predominantly the symmetrical pyridone dimer **71** (Scheme 1.36).[116] However, if Do is a donor atom capable of binding to a metal centre (e.g. PPh_2), the equilibrium can be shifted towards the mixed hydroxypyridine/pyridone dimer **72**. This intermediate may be stabilized by the chelation effect exhibited through coordinative binding to the metal centre (Scheme 1.36). In fact reaction of 2 equiv of 6-diphenylphosphanyl-2-pyridone (**70a**, Do = PPh_2, Scheme 1.37) with $Pt(cod)Cl_2$ furnished quantitatively *cis*-$PtCl_2$(**70a**)$_2$, which showed the expected hydrogen-bonding network both in solution and in the solid state.



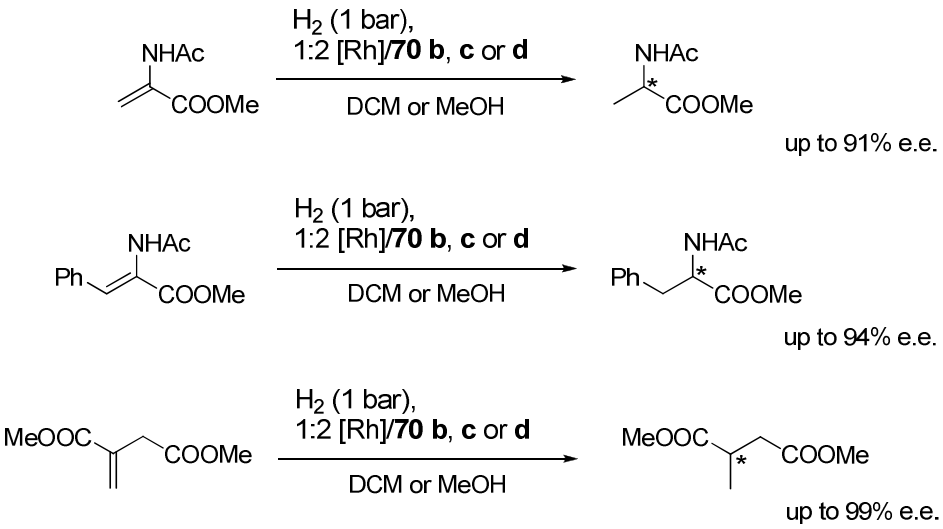
Scheme 1.36 The Breit system for the self-assembly of a monodentate P-ligand[114a]

A rhodium catalyst derived from ligand **70a** displayed the typical behaviour of a bidentate ligand in the hydroformylation of terminal alkenes.[114] Thus, excellent regioselectivity in favour of the linear aldehyde was noted for hydroformylation of a range of functionalized terminal alkenes (Scheme 1.38). Among them, even those with functional groups capable of hydrogen bonding were tolerated. However, the hydrogen-bonding network in the ligands and thus the chelating binding mode can be disrupted by employing either temperatures above 110 °C or protic solvents such as methanol and acetic acid; low regioselectivity results were obtained in this case.

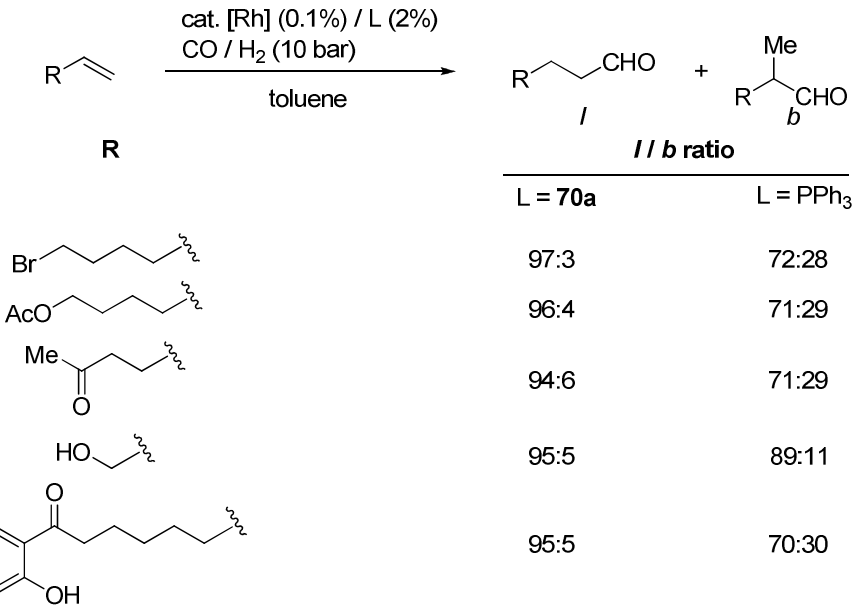
Recently, Börner, Breit *et al.* reported the synthesis of several derivatives **70** bearing a chiral phosphine group (Scheme 1.37).[117]



71 a-d: non self-assembling analogues



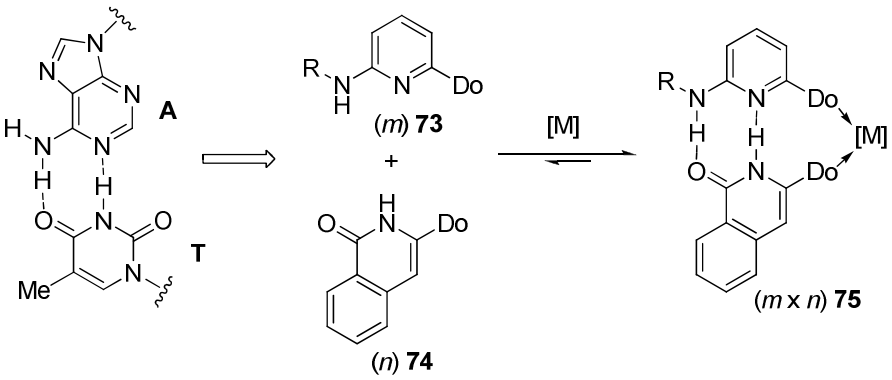
Scheme 1.37 The enantioselective Rh-catalyzed hydrogenation of pro-chiral olefins with self-assembled rhodium complexes



Scheme 1.38 Rh-catalyzed hydroformylation of functionalized terminal alkenes

The new ligands were shown by ^{31}P-NMR to be able to self assemble in the presence of a rhodium source in a similar way to **70a**. The corresponding self-assembled rhodium complexes were employed for catalyzing the enantioselective hydrogenation of pro-chiral olefins such as methyl 2-acetamidoacrylate (up to 91% e.e.), methyl *Z*-2-acetamidocinnamate (up to 94% e.e.) and dimethyl itaconate (up to 99% e.e.). Remarkably, all the self-assembling ligands **70** performed better than the corresponding *O*-*t*-Bu-protected hydroxypyridine-derivatives **71** (unable to self-assemble), thus demonstrating once again the efficiency of this strategy. It should be noted that, although ligands **70** behave undoubtedly as a supramolecular bidentate ligands, the systems **70** / [Rh] are actually homocomplexes, since the two tautomers –the hydroxypyridine **70A** and the pyridone **70B**– equilibrate rapidly, the complementarity of their interaction cannot be exploited to achieve a selective formation of the heterocomplex. Mixing two pyridone ligands with different donor sites would result in mixtures of heterodimeric and homodimeric catalysts. Thus this first example of supramolecular bidentate catalyst is not suitable for achieving a selective formation of the heterocomplex.

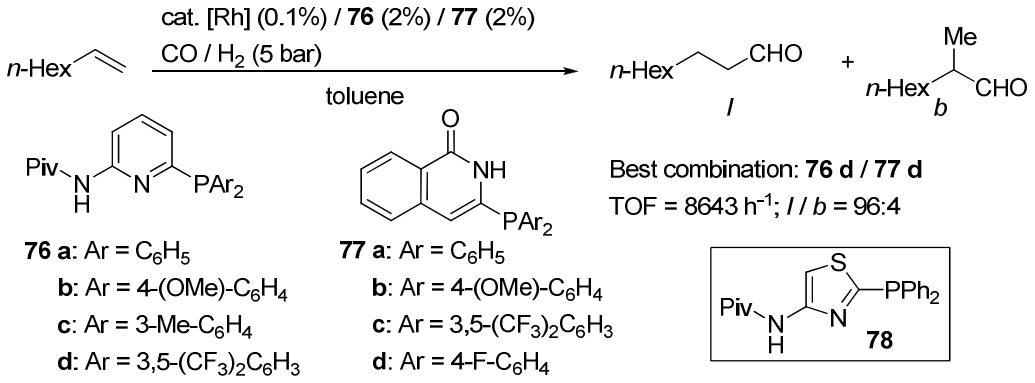
The heterodimeric structure would require the self-assembly of two (non-interconverting) complementary species through hydrogen bonding –a principle employed by nature in DNA base pairing. Thus an A-T base-pair model relying on the aminopyridine **73**/isoquinolone **74** platform was selected to serve for specific heterodimeric ligand assembly (Scheme 1.39).[118a]



Scheme 1.39 Self-assembly through hydrogen bonding of the adenine/thymine systems

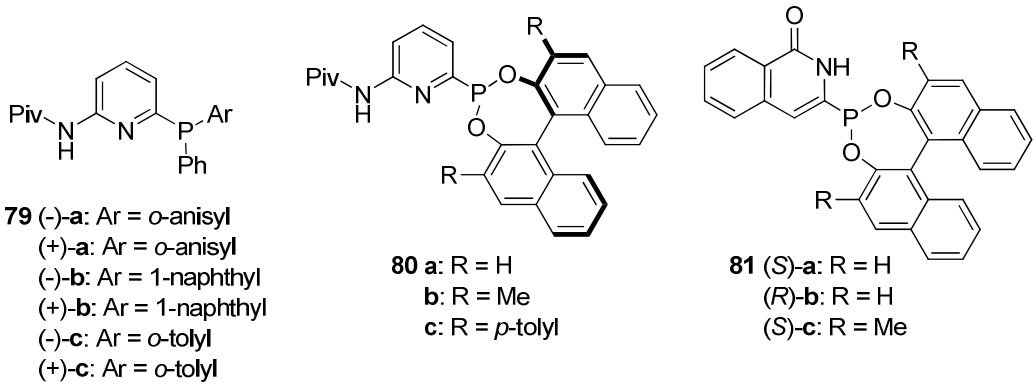
When phosphine ligands based on this platform were mixed in the presence of a Pt(II) salt, the heterodimeric complex (**75**) formed exclusively. An X-ray structure of **75** (Do^x = Do^y = PPh_2) shows the expected hydrogen bonding network reminiscent of the Watson–Crick base pairing of A and T in DNA. NMR studies provided support that a similar structural situation occurs also in solution. The first 4 × 4 self-assembled ligand library based on hydrogen bonding was generated and explored for regioselective hydroformylation of terminal alkenes (Scheme 1.40). In this study a catalyst was identified ([Rh][**76d**][**77d**]) that operated with outstanding activity (TOF = 8643 h^{-1}) and regioselectivity (*n* / *i* = 96:4).[118a] Also other heterocyclic platforms analogous to the A-T base pair

were subsequently screened,[118b] and it was found that thiazole **78** could interact with isoquinolone **77** so strongly that their interaction was unaffected even by protic solvents such as methanol.



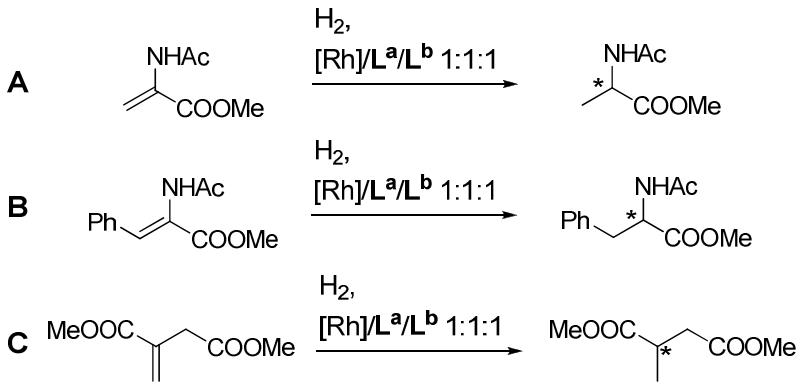
Scheme 1.40 Regioselective hydroformylation of 1-octene using 4 × 4 self-assembled ligand library based on hydrogen bonding

Subsequently, the same concept was applied in the enantioselective Rh-catalyzed olefin hydrogenation.[119] In this case the two substituents at the P atom bound to the heterocycles are either two different aryl groups (so that P is stereogenic) or the BINOL moieties, leading to the respective phosphonites **80** and **81** (Scheme 1.41), which dimerize spontaneously.



Scheme 1.41 Self-assembled chiral phosphine and phosphonite ligand library for Rh-catalyzed olefin hydrogenation

The respective Rh-complexes obtained by their heterocombinations lead to high enantioselectivity (>90% e.e.) in the hydrogenation of dehydroamino acid esters (methyl 2-acetamidoacrylate and methyl α-acetylamino cinnamate) and dimethyl itaconate (Scheme 1.42).

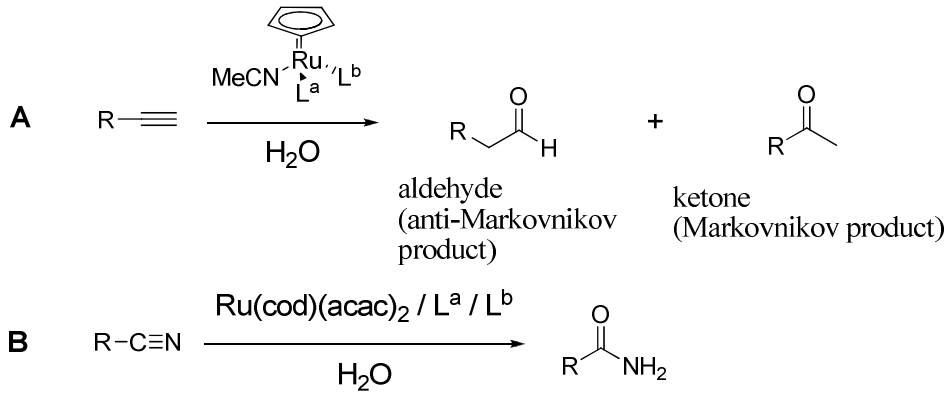


Scheme 1.42 Rh-catalyzed hydrogenation of (a) methyl 2-acetamidoacrylate, (b) α-acetylamino cinnamate and (c) dimethyl itaconate

It was also shown that one of the partners can harbour a diphenylphosphanyl moiety. This corresponds to the use of a mixture of an achiral and chiral monodentate *P*-ligands mentioned in Paragraph 1.3.4.

Recently, Breit and co-workers took advantages of the geometric properties (bite angles close to 105°) and electronic features (electron poor) of these supramolecular catalysts displaying excellent reactivity and selectivity also in the nickel-catalyzed hydrocyanation of akenes.[120]

Heterocombinations of achiral ligands of the **76** / **77** type were subsequently screened in the Ru-catalyzed hydration of alkynes,[121] with the aim of maximizing the amount of anti-Markovnikov aldehyde product (Scheme 1.43 A).[122]



Scheme 1.43 The Ru-catalyzed hydration of alkynes and nitriles

With the best heterocombination, up to > 99:1 selectivities were obtained in favour of the anti-Markovnikov product.

Another application found by the Breit group for their achiral ligands **76** / **77** is the Ru-catalyzed hydration of nitriles (Scheme 1.43 B).[123,124]

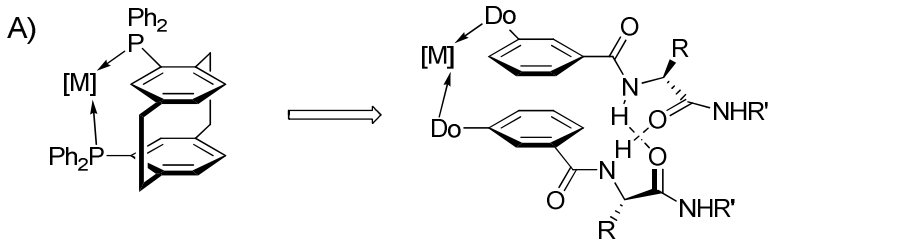
On the base of hydrogen bonding between polar heterocycles such as 2,6-diaminopyridine and barbituric acid-derived phosphines, Jun *et al.* developed recyclable catalysts for Rh-catalyzed

hydroacylation of olefins,[125] which however do not form supramolecular bidentate ligands and thus will not be discussed here.

1.4.2.3 Self-assembly through hydrogen bonding between peptides

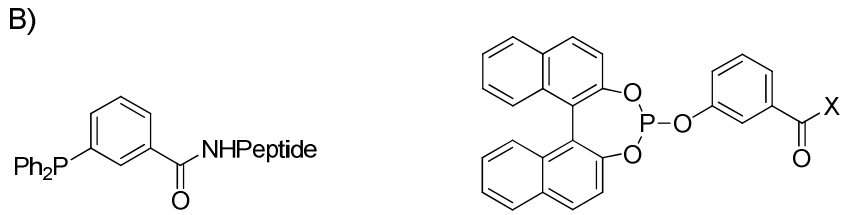
Very recently the group of Prof. Breit developed also another family of supramolecular bidentate ligands[126] that mimic the well known PhanePhos ligand.[127] After an inspection of molecular models, *meta*-carboxypeptidyl-substituted triarylphosphines **82** (Do = PPh_2 in Scheme 1.44) or phosphites **83** (Do = $OP(OAr)_2$) turned out to be suitable candidates to provide a PhanePhos-like structure. An inter-ligand helical hydrogen-bonding network, as indicated in Scheme 1.45, could be expected. This in turn might induce a planar chiral π-stacking arrangement of the two meta-substituted arene rings which resembles the planar stereogenic element found in PhanePhos.

The coordination properties of ligands **82** and **83** were investigated in the presence of *cis*-$Pt(cod)Cl_2$ or $Rh(cod)_2BF_4$. All of the homocombinations except **83**, formed the corresponding self-assembled ligand complex. The complexes were studied by X-ray analysis. The *cis*-coordinated phosphine ligands are linked by pairs of interligand N–H···O=C hydrogen bonds of the peptidyl side chain, which adopt a helical conformation.



PhanePhos: chiral ligand with stereogenic plane

"SupraPhanePhos": the stereochemical information of the peptide residues is transferred to the aryl groups



82 a: Peptide = ValValOMe
b: Peptide = ValAlaOMe
c: Peptide = *t*-LeuValOMe

83 (*S*)-**a**: X = NHValValOMe
(*R*)-**b**: X = NHValAlaOMe
(*R*)-**c**: X = OMe

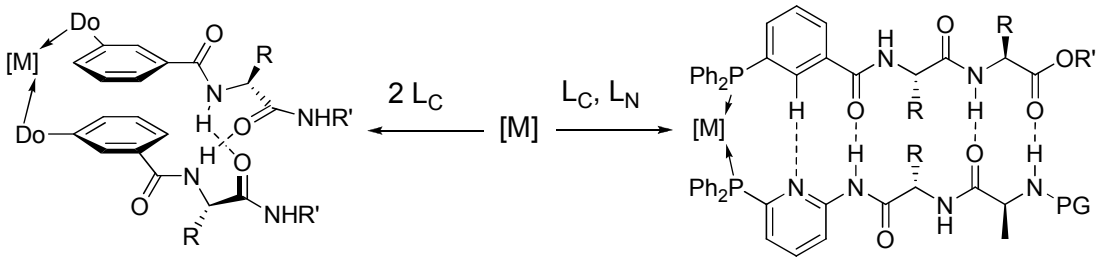
Scheme 1.44 (a) Schematic representation of "SupraPhanePhos"; (b) peptidyl phosphines **82** and peptidyl phosphites **83**

Interestingly, the *meta*-substituted arene rings of the two neighbouring phosphine ligands **82** adopt a PhanePhos-type conformation. This π–π interaction (~ 3.30 Å) is also expected to additionally contribute to the stabilization of the supramolecular metal-induced ligand assembly.[128] Additionally, a hydrogen-bonding intermolecular network is formed between the homodimeric complexes in the crystalline state. NMR studies indicated that a similar geometry is prevalent in solution in aprotic solvents such as $CDCl_3$ as well. The homocombinations of ligands **82** and **83**, in the presence of $Rh(cod)_2BF_4$, were tested in the hydrogenation reactions shown in Scheme 1.44: the best combinations (involving ligands **83**) gave enantioselectivity levels comparable with those of PhanePhos ligands (up to 99% e.e.).

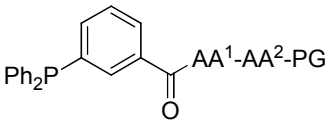
It should be noted how this new approach does not allow, in its first version, to selectively prepare heterocombinations of ligands, because the hydrogen-bond interaction utilized lacks the complementarity required for this task: combining different ligands in the presence of a metal source would result in a mixture of homo- and heterocomplexes.

Shortly after the first communication, however, Breit *et al.* addressed the issue of exploiting self-assembly based on peptidic structures as a new platform to generate heterodimeric complexes selectively,[129] which enabled a new combinatorial approach to novel chelation-emulating ligand libraries for metal complex catalysis.

Thus, as a peptidyl ligand complementary to the *C*-linked peptide-based *P*-ligand L_C, a *N*-linked peptidic system such as L_N was chosen (Scheme 1.45, right-hand side). Molecular modelling suggested that complementary hydrogen bonding between the amide functions of both systems might occur and induce the formation of an antiparallel β-sheet structure. Indeed, mixing of C-linked phosphane-functionalized peptidyl ligands (L_C) with the complementary N-linked phosphane-functionalized peptidyl counterparts (L_N) in the presence of platinum(II) and rhodium(I) transition-metal salts led to the selective formation of heterobidentate complexes $[MX_2\text{-}(L_C \cdot L_N)]$. Detailed conformational analysis in solution, theoretical investigations, and X-ray studies showed the formation of a two-stranded, antiparallel, β-sheet structure. The factors that influence the equilibria between heterodimeric complexes and homodimeric complexes were studied in detail, which provided insights into the importance of individual non-covalent interactions. Furthermore, the antiparallel, β-sheet, self-assembly template system has served as basis for the generation of a heterobidentate ligand library, which has been explored in *linear*-selective asymmetric hydroformylation of styrene (Scheme 1.46). From these experiments it became evident that the β-sheet self-assembly template does not only cause the selective formation of heterobidentate ligand arrangements, but although in a remote position relative to the catalytically active centre can induce a moderate enantioselectivity (up to 38%) in the course of a catalytic reaction.[129]

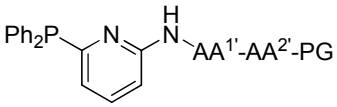


C-linked peptides: L_C



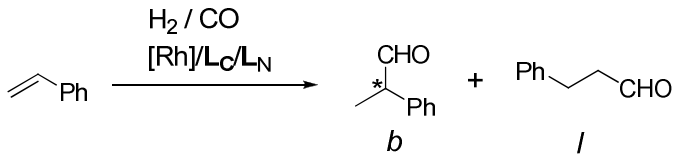
84	**a**	Gly	-	OEt
	b	Val	-	OMe
	c	Val	-	NH*n*Bu
	d	Val	Val	OMe
	e	Val	Ala	OMe
	f	Ala	Val	OMe
	g	*t*Leu	Val	OMe
	h	DVal	DVal	OMe
	i	-	-	OMe
	j	-	-	NHBz

N-linked peptides: L_N



85	**a**	Val	Val	Boc
	b	Ala	Val	Boc
	c	Val	-	Fmoc
	d	Ala	-	Fmoc
	e	Val	-	Moc
	f	Ala	-	Moc
	g	-	-	Piv
	h	-	-	COBz

Scheme 1.45 Expanding the concept of self-assembly of monodentate ligands through formation of secondary structures: two complementary metal binding sites with two otherwise flexible appended peptide chains are directed to form a conformationally stable folded β-sheet upon coordination of a metal ion

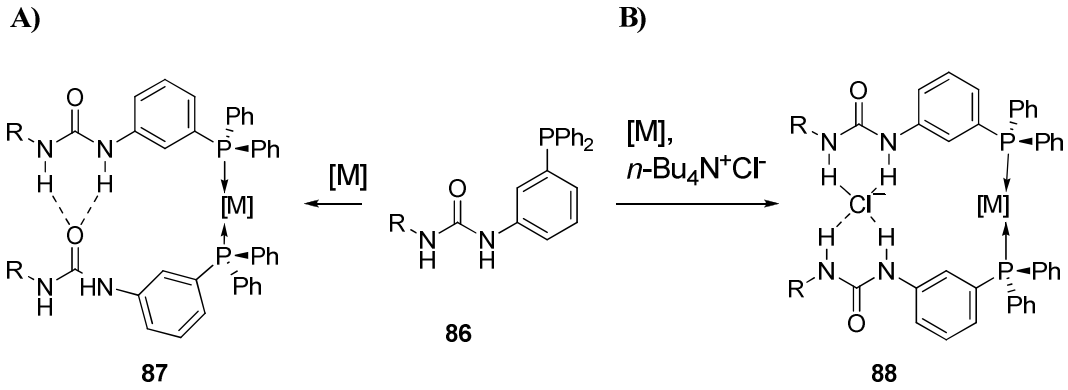


Scheme 1.46 Rh-catalyzed assymetric hydroformylation of styrene

1.4.2.4 Systems exploiting the hydrogen bonding properties of urea derivatives

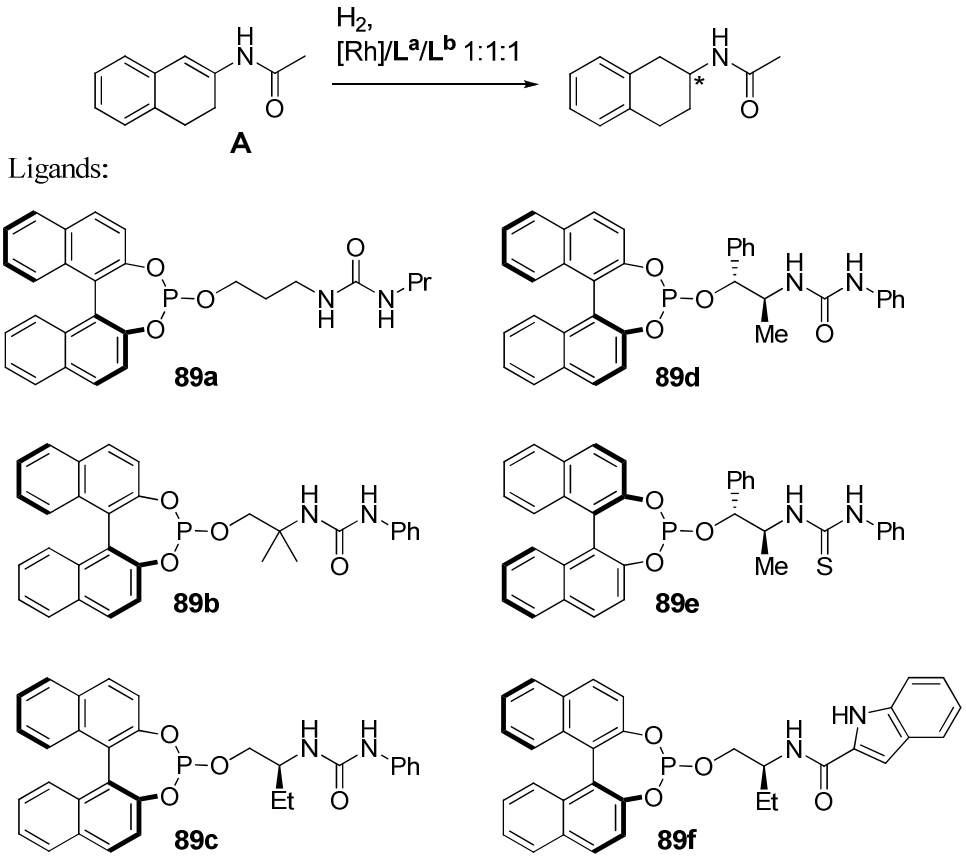
Love and co-workers described the formation of transition metal complexes (namely with palladium and rhodium) containing the urea–phosphine ligand (**86**)(R = Ph, Scheme 1.47). When $PdCl_2(CH_3CN)_2$ was used as a palladium source, a 1:3 mixture of cis/trans complexes (measured by NMR) was obtained, which was assumed to have a polymeric nature with intermolecular hydrogen bonding due to its insolubility in commonly used solvents. [130] Alternatively, when Pd(cod)(CH_3)Cl was reacted with **86** (R = CH_2CO_2Et), as reported independently by Reek and co-workers, [131] only the

formation of the *trans* complex **87** was observed (Scheme 1.47 A). In this case, the formation of the intramolecularly hydrogen bonded species was assumed on the basis of its solubility and spectroscopic properties. Interestingly, on addition of nBu_4NCl (Scheme 1.47 B), the formation of an anionic complex **88** incorporating the chloride anion intramolecularly bonded between the two urea units, was observed in both works.[130,]



Scheme 1.47 The urea-based phosphine ligand complexes formation via (a) self-association or (b) anion-templation

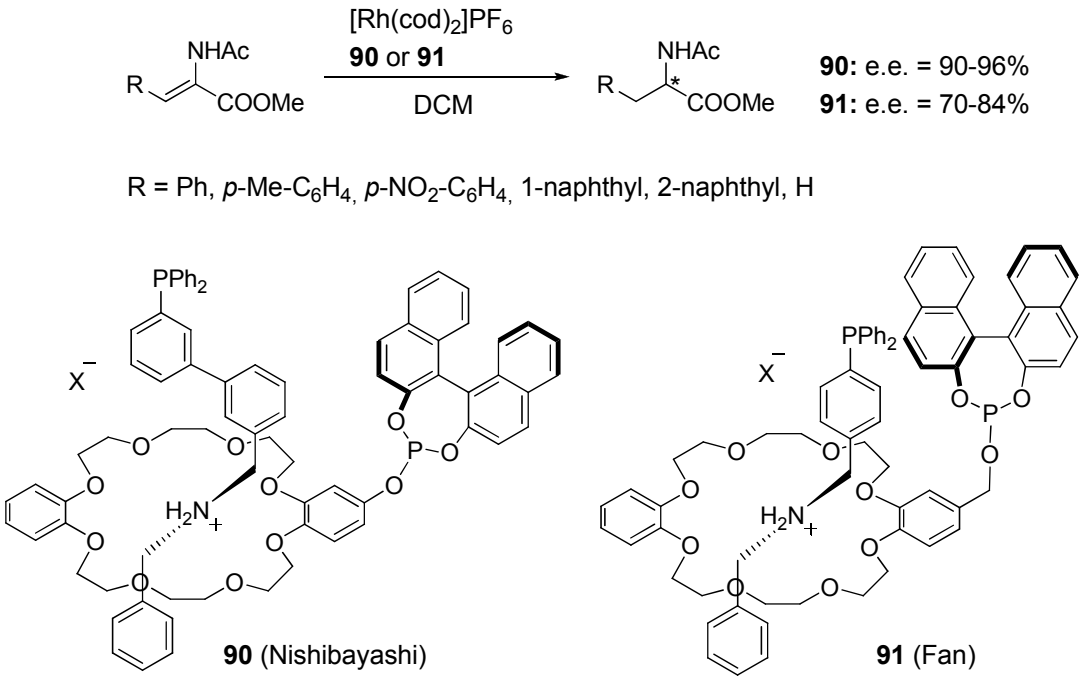
Later on, Reek and co-workers developed a new class of chiral urea-functionalised phosphite (**89**), called *UREAphos* (Scheme 1.48), which are capable of self-assembling in the presence of a rhodium source to give the supramolecular homocomplexes, as suggested by NMR studies. Rhodium complexes of *UREAphos* ligands were screened in the enantioselective hydrogenation of both benchmark substrates (up to 96% e.e. with dimethyl itaconate and up to 94% e.e. with methyl 2-acetamido acrylate) and challenging, industrially relevant olefins such as enamide **A** (up to 76%, scheme 1.48).[131b]



Scheme 1.48 Rh-catalyzed asymmetric hydrogenation of *N*-(3,4-dihydro-2-naphthalenyl)-acetamide

1.4.2.5 Pseudo-rotaxanes held together by the interaction between a secondary ammonium salt and a crown ether

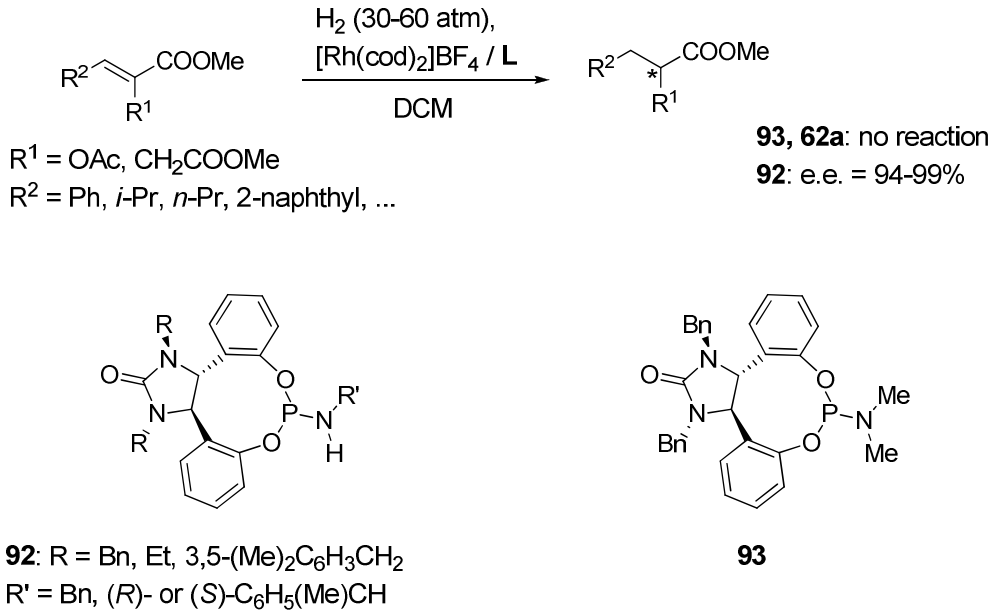
Nishibayashi *et al.*[132] and Fan *et al.*[133] independently reported new self-assembled ligands formed by reaction between a secondary ammonium salt and a crown ether of the proper size each bearing a phosphorus donor atom (a phosphine and a BINOL-phosphite, respectively). These supramolecular bidentate ligands possess a stereogenic plane and thus exist as mixtures of diastereoisomers (only one diastereomer for ligand is displayed in Scheme 1.49), but when a rhodium source is added a single species (whose stereochemistry has not been clarified yet) is apparently formed. Several ammonium salts and crown ether macrocycles were prepared and screened as ligands for rhodium in hydrogenation reactions of α-dehydroaminoacids. With the best axle-macrocycle heterocombinations (**90** for Nishibayashi and **91** for Fan, Scheme 1.49) fair to good levels of stereoselectivity were obtained: 90 to 96% e.e. with Nishibayashi's system and 70-84% e.e. with Fan's system.



Scheme 1.49 Rh-catalyzed asymmetric hydrogenation of pro-chiral olefins with supramolecular chiral phosphorous ligands based on a pseudorotaxane complex

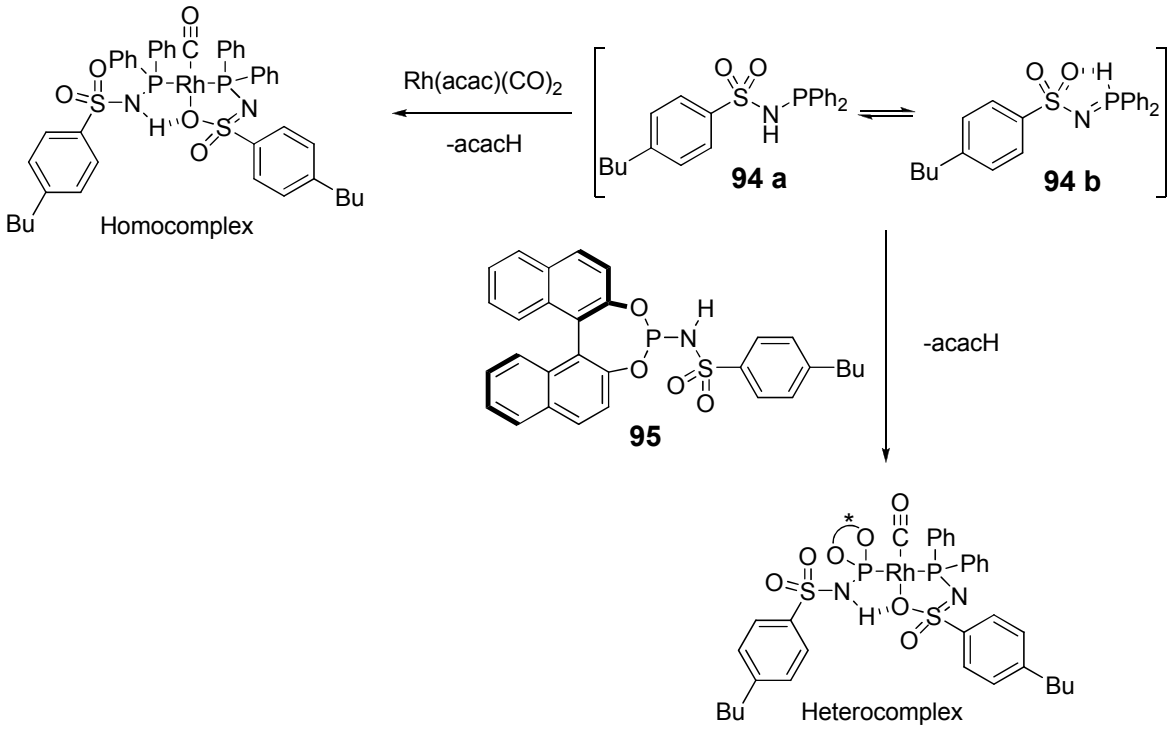
1.4.2.6 Other systems

In 2006 Ding and co-workers reported that phosphoramidites **92** (Scheme 1.50), derived from primary amines (*i.e.* having a N-H able to act as a hydrogen bond donor), in the presence of a rhodium source in solution, form the corresponding hydrogen-bonded mono-complexes, as it was demonstrated with NMR experiments and DFT calculations.[134] The new ligands were screened in the hydrogenation of (*Z*)-methyl α-(acetoxy)acrylates and (*E*)-β-(aryl)itaconates, where the **92** complexes resulted highly stereoselective. On the contrary the complex **93**, unable to form hydrogen bonds, turned out to be catalytically not active. Thus the rigidity conferred to the complex by the presence of the hydrogen bonds here has a dramatic effect on the outcome of the reaction. It should be remarked that this self-assembled system is not suitable for the selective formation of heterocomplexes, because it exploits an interaction which is not complementary: mixing different ligands would certainly result in a mixture of hetero- and homocomplexes.



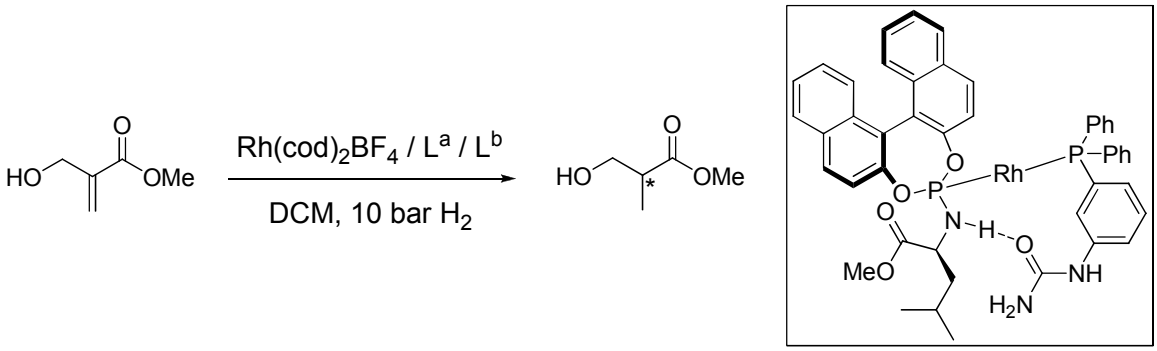
Scheme 1.50 Rh(I)-catalyzed asymmetric hydrogenation of (*Z*)-methyl α-(acetoxy)acrylates and (*E*)-β-aryl itaconate derivatives with DpenPhos ligands

Reek *et al.* have recently reported that ligands of the families **94** and **95** are able to self-assemble forming the corresponding heterocomplexes as shown in Scheme 1.51:[135] compound **94** exists in solution at room temperature as a mixture of tautomers **a** and **b**. On addition of $Rh(acac)(CO)_2$, compound **94** forms the corresponding "homocomplex". In this complex, the *P*-ligands feature a *trans* disposition and are held together by the hydrogen bond between the sulfonamidic proton of **a** and one of the oxygens of **b**. In the presence of a similar ligand existing as a single tautomer (**95**, probably because of the different basicity of the phosphorus atom), however, **94** forms the hydrogen-bonded heterocomplex with complete selectivity. The homo- and heterocomplexes of ligands **94** and **95** proved able to catalyze the hydrogenation reactions only after protonation with HBF_4•OMe_2, which facilitates the dissociation of the sulfonamidic oxygens necessary for the catalytic cycle to take place. In the hydrogenation of methyl 2-acetamidoacrylate the heterocomplex **94** / **95** proved slightly less stereoselective than the homocomplex of **95** (91% vs. 96% e.e.), and this means that in this case the presence an achiral ligand has a negative effect on the level of stereocontrol.[135] Even if there is no improvement of the catalyst performance when the heterocomplex is used, the way for a new type of self assembly through hydrogen bonding is open, and further results will probably come.

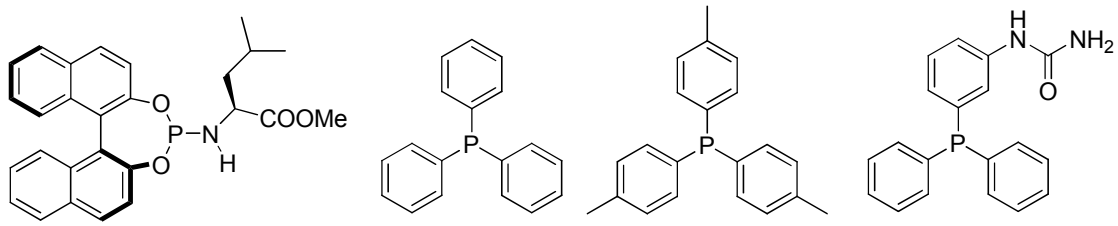


Scheme 1.51 Selective formation of heterocomplex and a control experiment

Very recently Reek *et al.* proposed a new class of supramolecular bidentate ligands held together by hydrogen bonding between a primary amine-derived chiral phosphoramidite (**96**) and an achiral phosphine bearing an urea group (**96**).[136] The level of selectivity in the formation of the supramolecular heteroleptic complex was determined by ^{31}P-NMR spectroscopy. It is important to note that hydrogen bonding is not the only responsible for the selective formation of the heteroleptic complex: the phosphoramidite-phosphine rhodium heterocomplexes themselves are shown to be thermodynamically favoured due to the complementary electronic properties of the two classes of ligands (σ-donor phosphines and π-acceptor phosphoramidites). The heterocomplexes are formed with a high level of selectivity (70-97%) even in the absence of functional groups capable of hydrogen bonding, which plays the role of improving the selectivity up to > 99%., and turned out to promote the asymmetric hydrogenation of several derivatives of methyl 2-hydroxymethylacrylate with very good enantioselectivity (up to > 99% e.e).



L^a	L^b	% heterocomplex	e.e. (%)	Abs. conf.
96	-	-	31	*S*
96	**65 c**	91	94	*R*
96	**97**	97	94	*R*
96	**98**	> 99	> 99	*R*



96 **65 c** **97** **98**

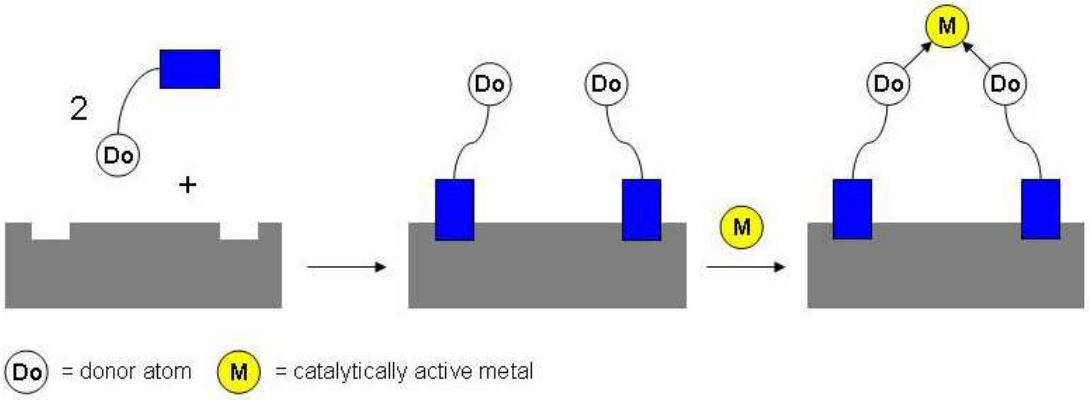
Scheme 1.52 Chiral phosphoramidite LEUPhos and achiral aromatic phosphine ligands used the asymmetric hydrogenation of methyl 2-hydroxymethylacrylate

Remarkably, as in other cases when a chiral and an achiral ligand are mixed, the streochemical preference of the heterocomplex is opposite to that of the chiral ligand homocomplex.

1.4.3 Self-assembly through coordinative bonding

1.4.3.1 Three-component systems based on the use of a template

In 2003 Reek, van Leeuwen and co-workers reported the first example of supramolecular bidentate ligand based on coordinative bonding.[137a] In general terms, this new strategy involves a metal-containing template which binds and thus positions two monodentate ligands having an additional donor site (Do in Scheme 1.53). Subsequent chelation to a catalytically active transition metal M generates the catalyst or precatalyst (Scheme 1.53).

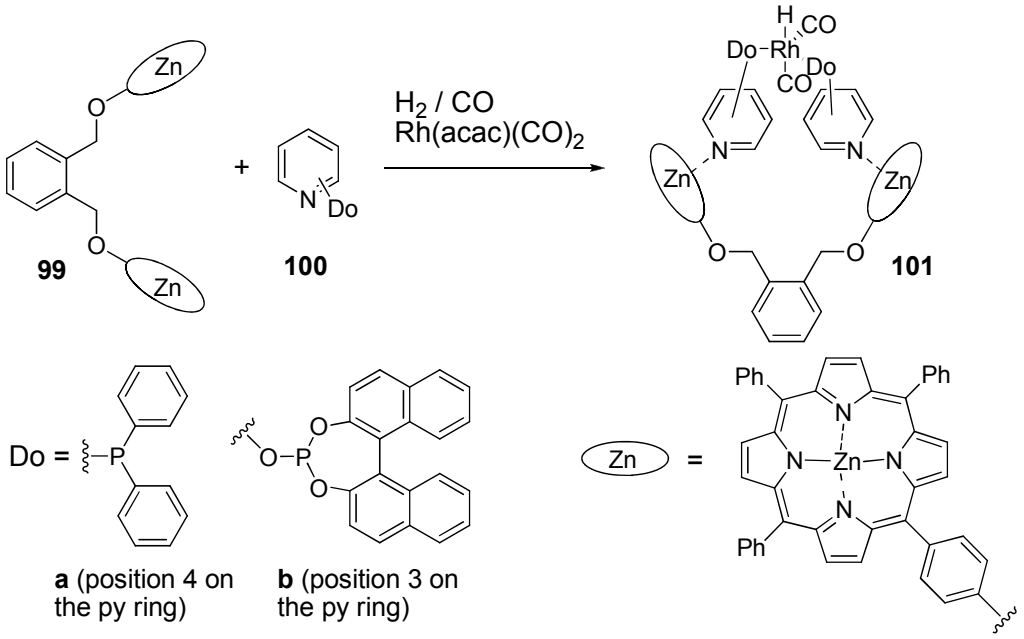


Scheme 1.53 Schematic representation of a self-assembled chelating ligand

The template is often a bis{Zn(porphyrin)} complex such as **99** (Scheme 1.54), which binds the additional donor site (usually a pyridine moiety) bearing the *P*-ligand.

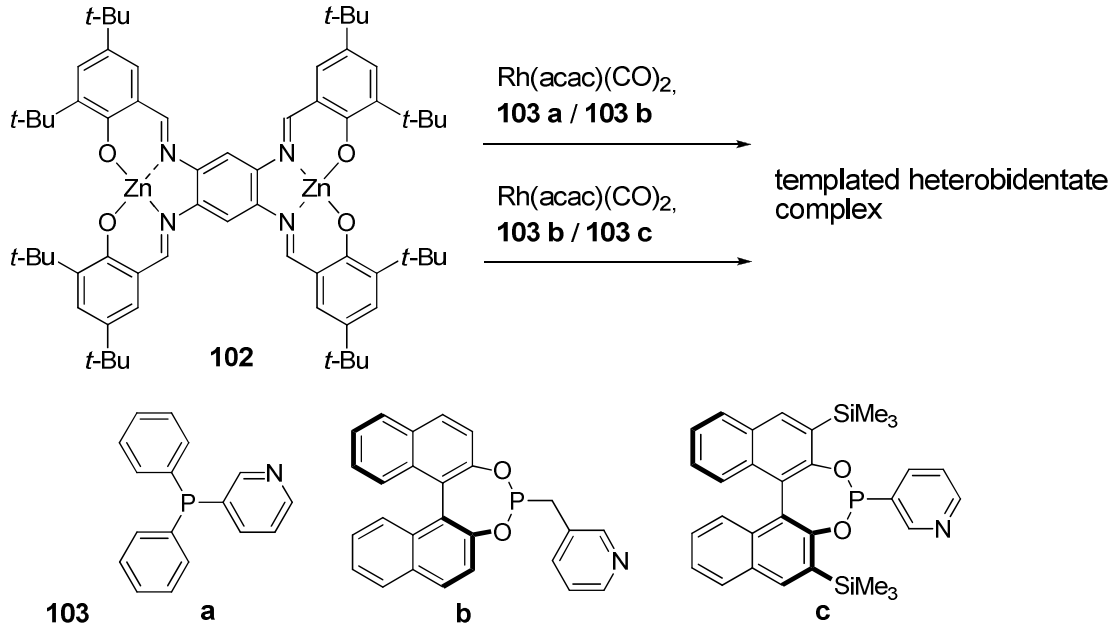
The latter can be either chiral or achiral depending on the application of the supramolecular ligand. In the first report on this strategy for self-assembly,[137a] the application of both chiral and achiral systems as ligands for Rh-catalyzed hydroformylation was described: compared to the corresponding monodentate ligands **100a** and **100b**, the supramolecular ligands **101** behave much more similarly to "classic" covalent bidentate ligands, giving higher *l* / *b* ratios (up to 94:6) in the hydroformylation of 1-octene and better e.e.'s (up to 33%) in the hydroformylation of styrene. Although the modular nature of ligands **101** allows in principle the combinatorial screening of different templates and ditopic *P*,*N*-ligands **100**, an obvious limitation of this strategy seemed to be that the latter have to be identical, as the binding sites of the template are identical: treating **99** with a mixture of different *P*,*N*-ligands should result in a mixture of three supramolecular species.

Quite surprisingly, however, this does not happen in several cases when the template **102** is used (Scheme 1.55): some combinations of *P*,*N*-ditopic ligands were reported to form the corresponding heterobidentate complexes with high selectivity, as demonstrated by ^{31}P-NMR studies.[137 b-c] The authors tentatively ascribe this unexpected selectivity for the heterocomplexes to steric factors.[137 b] In the hydroformylation of styrene the heterocomplexes showed a level of stereoselectivity much higher (up to 72% e.e.) than those observed both with the corresponding ligands in the absence of a template and with the above-discussed homocomplex **101**



Scheme 1.54 Transition metal catalyst [HRh(**101**)(**100**)$_2$)(CO)$_2$] formed by selfassembly of pyridyldiphenylphosphine **100** on dimeric zinc(II) porphyrin **99** and in the presence of a rhodium precursor

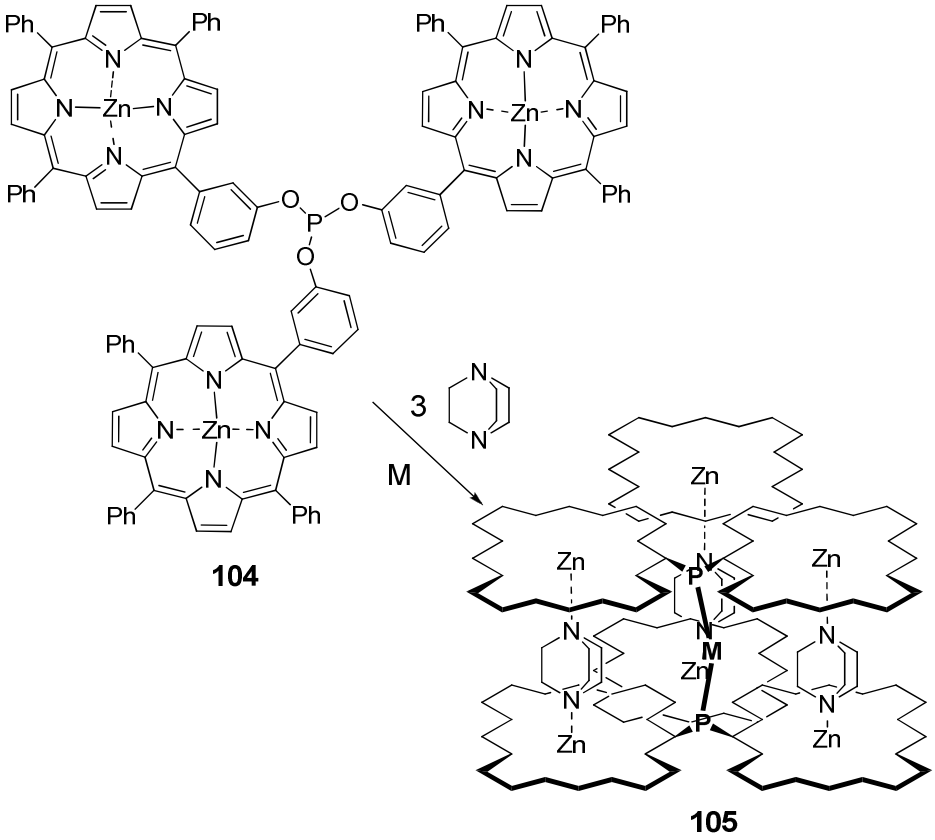
Homoleptic Rh-complexes obtained using template **102** gave poor results in the asymmetric hydrogenation of benchmark substrates.[137c] In the previous examples bis-porphyrins were used as templates to form bidentate ligands.



Scheme 1.55 Formation of the templeted heterobidentate complex

Alternatively, ditopic nitrogen ligands such as DABCO (diaza-[2.2.2]-bicyclooctane) can be used as templates to form 2: 1 assemblies with zinc(II) porphyrins. If these porphyrins are functionalised with

ligands, i.e. phosphines or phosphites, this self-assembly process can also lead to chelating bidentate ligands. Reek *et al.* realized this kind of self-assembly utilizing a phosphite bearing three zinc-porphyrin moieties (**104**), in order to increase the rigidity of the complex (Scheme 1.56).[138]



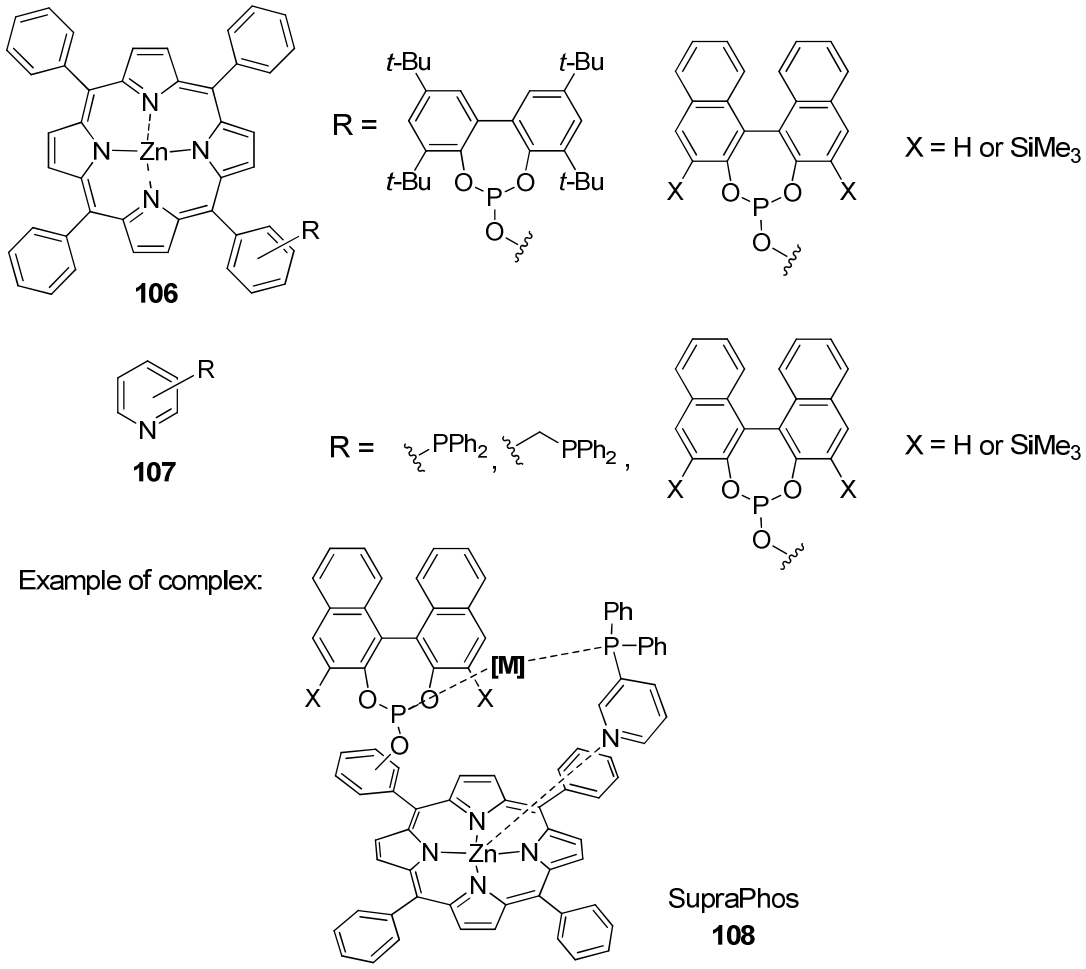
Scheme 1.56 Representation of the formation of a multicomponent assembly from ligand **83**, template (dabco), and a transition-metal catalyst M. P = monodentate phosphorus ligand

The rhodium-complex **105** was used as a catalyst in the hydroformylation of 1-octene giving a *l* / *b* ratio ten times higher than that obtained with ligand **104** in the absence of template.

1.4.3.2 Two-component systems of ligands with complementary coordinating properties

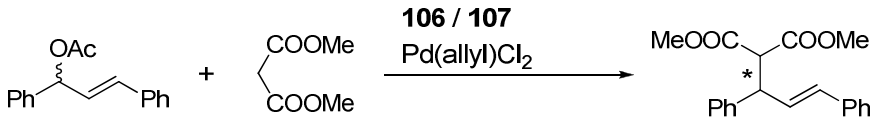
In this section examples of bidentate ligands assembled *via* direct interactions between monomeric ligand building blocks rather than *via* a template are discussed.

In 2004 Reek, van Leeuwen and co-workers reported a supramolecular strategy to make bidentate ligands based on metal–ligand interactions that involves simply mixing monomeric ligand building blocks.[139] They prepared phosphite functionalised porphyrins that would combine with nitrogen-containing phosphorus ligands for the self-assembly of bidentate ligands. Importantly, this approach leads to the formation of bidentate ligands with two different donor atoms (Scheme 1.57).



Scheme 1.57 The formation of a bidentate ligand and its transition-metal complex by selfassembly

The coordination behaviour of the supramolecular ligands was investigated performing UV–Vis titrations and NMR experiments: it turned out that the pyridyl moiety selectively coordinates to the zinc(II) porphyrin **106**, with a binding constant in the expected range (K = 3.8 × 10^3 M^{-1}). The formation of a bidentate chelating system occurs with a chelate energy of 7 kJ mol^{-1}. 48 supramolecular systems of the **108** type were prepared from small **106** and **107** libraries (14 members overall) and screened in Pd-catalyzed Tsuji-Trost allylic alkylations (Scheme 1.58).[140]



Scheme 1.58 Pd-catalyzed Tsuji-Trost allylic alkylations

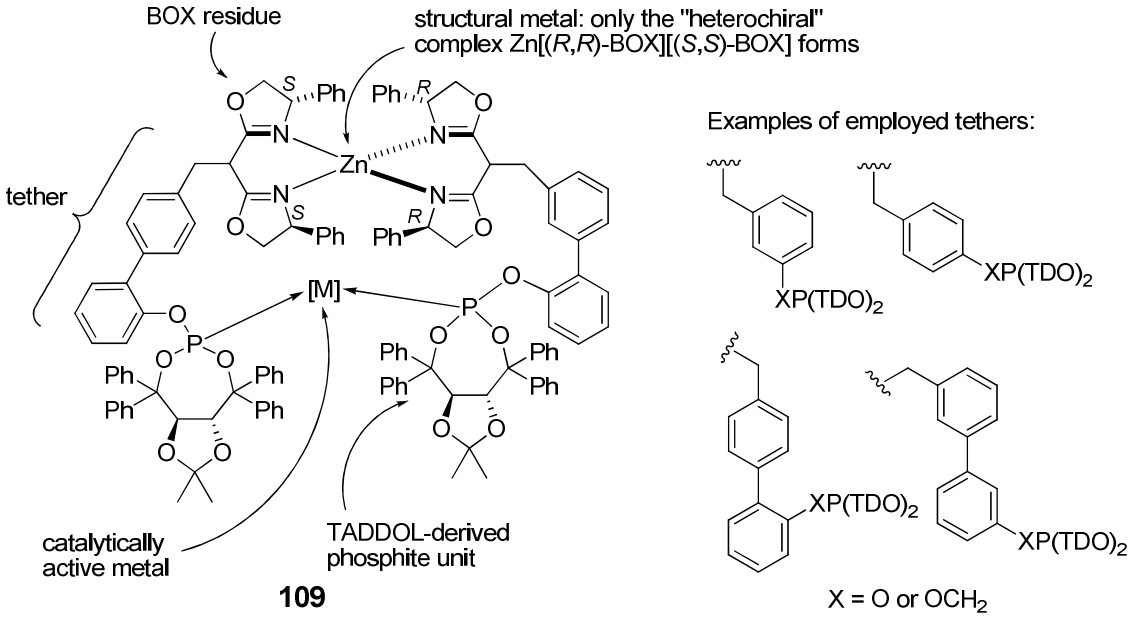
The self-assembled systems proved significantly more active than the corresponding monodentate ligands, yet their enantioselectivity (up to 70% e.e.) was in some cases slightly inferior (a ligand of the series **106** gave 97% e.e. alone).[139a,b,d,f]The systems **108** were screened also in the Rh-catalyzed hydroformylation of styrene [139b,d] and in the Rh-catalyzed hydrogenation of the challenging substrate

N-(3,4-dihydro-2-naphthalenyl)acetamide (Scheme 1.33, up to 94% e.e.)[139c] and of benchmark substrates.[139d]

Recently Reek and co-workers developed also an analogous self-assembled ligand based on tin(IV) rather than zinc(II) porphyrines,[139e] which did not show better catalytic properties (for the hydroformylation reaction) compared to the parent system based on zinc.

1.4.3.3 Two-component systems of ligands with complementary stereochemistry

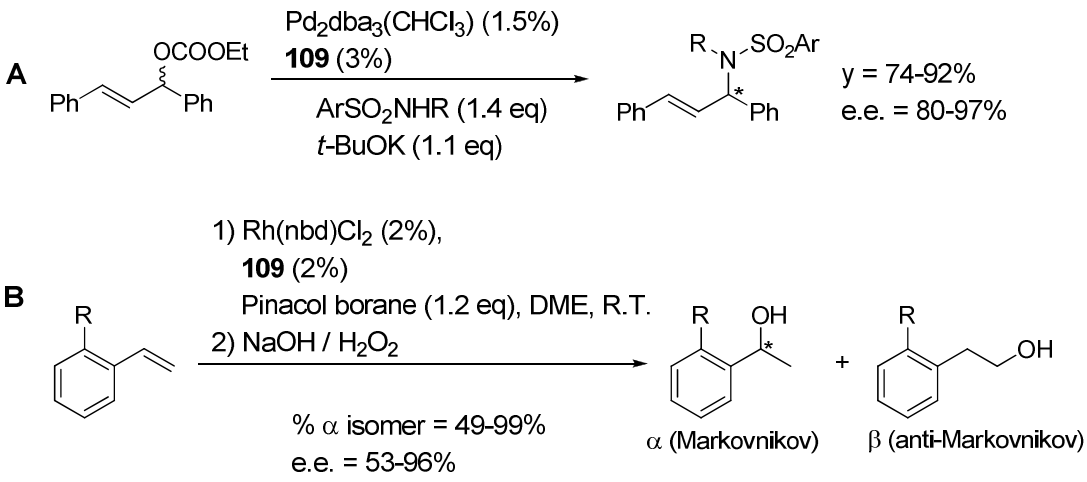
In 2004 Takacs *et al.*[141] reported a different strategy to prepare chiral bidentate bis-phosphite ligands which is probably the most elegant among the self-assembly methods based on coordinative bond appeared so far: a modular assembly around a structural metal is used to selectively form a heteroleptic complex (an example is shown in Scheme 1.59).



Scheme 1.59 Preparation of $(box)_2Zn$ complex and its transition-metal complex **106**

The selectivity of this strategy relies on the fact that the bis-oxazoline (BOX) moieties contained in their subunits are able to form stable tetrahedral zinc(II) complexes only if they have opposite configurations.[142] The bifunctional subunits have a second set of ligating groups (TADDOL-based phosphites) that are suitably disposed for binding a second metal that acts as the catalytically active centre. Two series of subunits having BOX residues with opposite configuration were synthesized, from which a ligand library of 50 self-assembled ligands (mostly differing in the tether portion) was constructed. In a first catalytic screening on the palladium-catalyzed asymmetric allylic amination (Scheme 1.60 A), enantioselectivities between 20% and 97% were reported, compared to 48% e.e. for the bis-monodentate TADDOL phenylphosphine analogues. Nine ligand combinations

gave products with e.e.'s above 90%, indicating that the bidentate ligands clearly outperformed the monodentates.



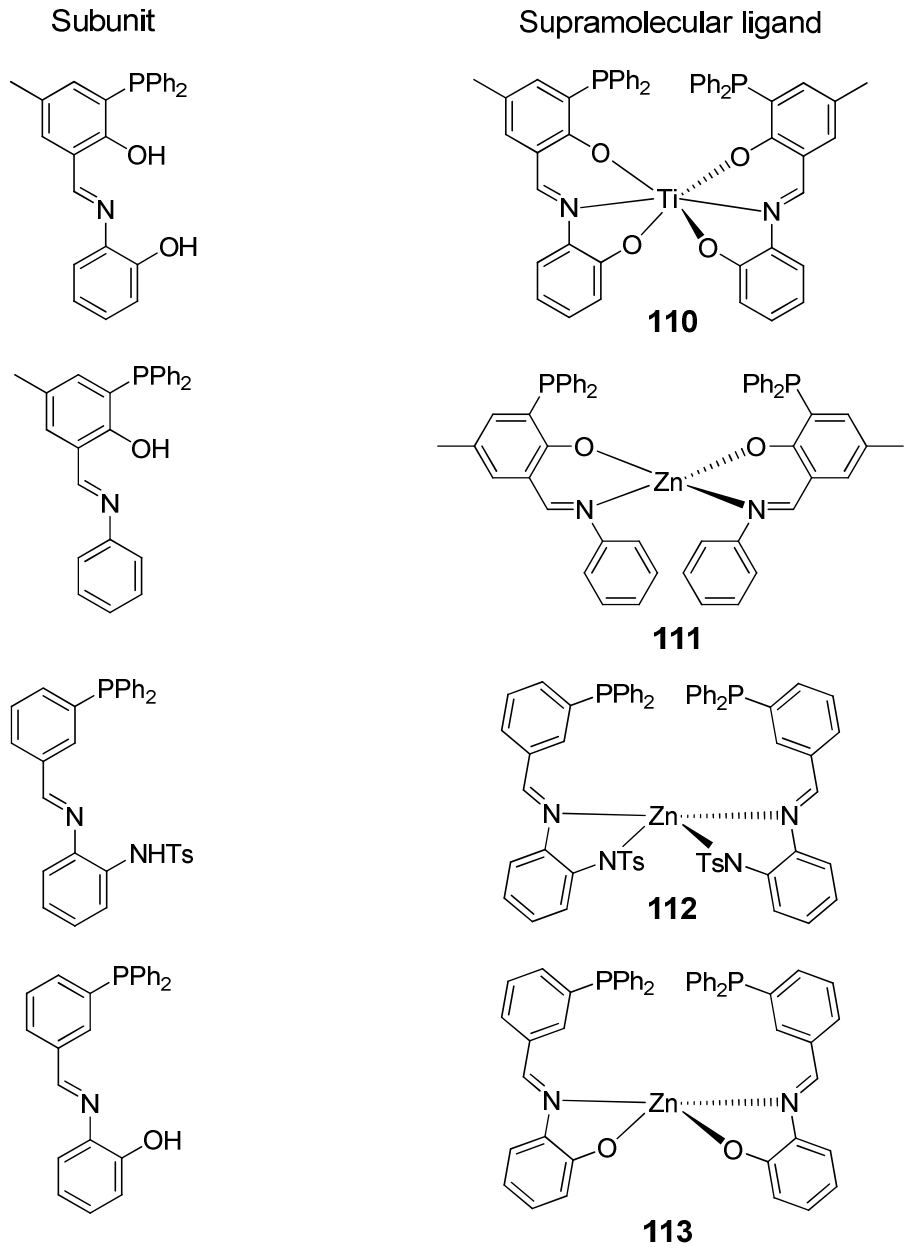
Scheme 1.60 (a) The palladium-catalyzed asymmetric allylic amination and (b) Rh-catalyzed asymmetric hydroboration of olefins

The same library was later screened in the Rh-catalyzed asymmetric hydroboration of olefins (Scheme 1.60 B):[141c,143] good levels of regioselectivity for the chiral Markovnikov product were generally achieved. Also the level of enantioselectivity was outstanding for several heterocombinations. A library of similar supramolecular ligands having chiral biphenyl (BIPHEP)-derived instead of TADDOL-derived phosphite residues was screened in the hydrogenation of methyl 2-acetamidoacrylate, giving up to 82% e.e.'s.[141b]

1.4.3.4 Two-component homoleptic systems

In 2007 van Leeuwen and co-workers reported a new family of homoleptic achiral supramolecular ligands formed by self-assembly of identical subunits.[144] Each subunit contains both a phosphorus atom, necessary for coordinating the catalytic transition metal, and two hard donor atoms able to complex a second metal such as titanium(IV) or zinc(II). Some of these supramolecular systems are shown in Scheme 1.61.

The new self-assembled ligands were screened in the Rh-catalyzed hydroformylation of 1-octene, giving in several cases better levels of regioselectivity (yet not outstanding in general terms) compared to the corresponding subunits: in particular, with ligands **112** and **110** *l* / *b* ratios of 13 and 21 respectively were obtained. X-ray diffraction studies were performed on the best performing ligand **113**, for which a natural bite angle of 110° was also calculated by molecular mechanics.



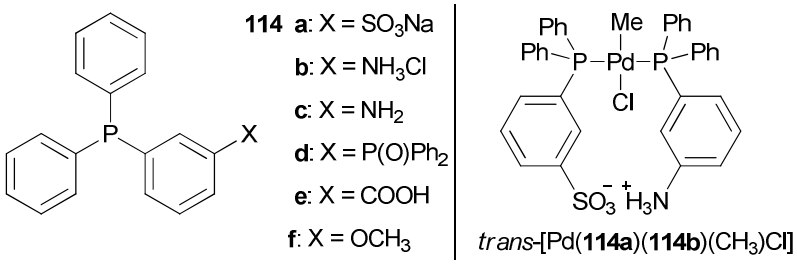
Scheme 1.61 The new supramolecular diphosphine ligands

1.4.4 Self-assembly through ionic and van der Waals interactions

In recent years, some research groups have been trying to exploit also other kinds of non-covalent interactions for achieving the self-assembly of supramolecular bidentate ligands.

To this end, *ionic interactions* appeared particularly promising thanks to their intrinsic complementarity: given two sets of ligands bearing negative and positive charges respectively, the Coulombic charge attraction should obviously favour only the interaction between cations and anions, while the compounds having the same charge should repulse each other. For this reason, in principle this self-assembly strategy should allow the highly selective formation of supramolecular

heterocomplexes. In 2007, van Leeuwen and co-workers published the results of the first attempt to put this principle in practice.[145] A library of meta-substituted phosphanes (Scheme 1.62) was synthesized, some of which possess functional groups able, in principle, to form ion pairs either by ion exchange or by direct acid-base reaction. Binary mixtures of ligands were combined in the presence of Pt-sources, and the formation of the complexes was monitored by ^{31}P-NMR.

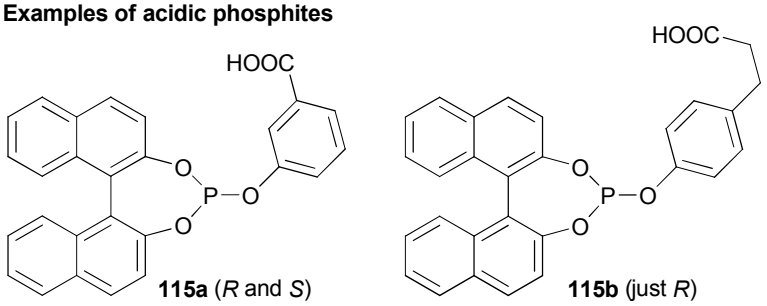


Scheme 1.62 Ionic interactions for the formation of heterocomplexes.

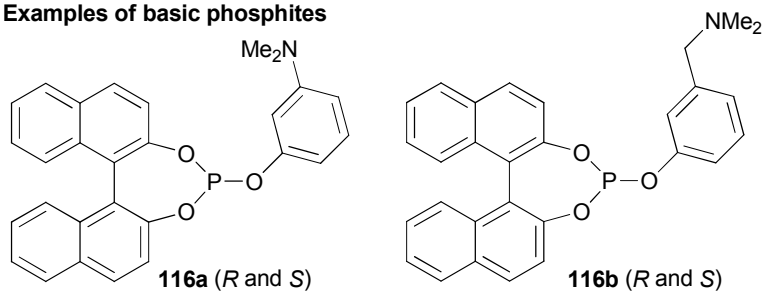
Only the combination **114a / 114b** gave preferential formation of the heteroleptic square-planar Pt-complex (upon removal of the by-product NaCl by precipitation), the ratio between hetero- and homocomplexes varying from 77:23 to 97:3 depending on the experimental conditions. The other ligand combinations led to statistical mixtures of complexes. Both NMR and X-ray diffraction data clearly showed that in the heterocomplex the ligands have a trans arrangement: the crucial role played by the ionic interaction in the heterocomplex can be seen form X-ray structure of complex trans-[Pd(**114a**)(**114b**)(CH_3)Cl], whose charged functional groups are in close proximity. No catalytic application of the heteroleptic complex was reported so far by the authors.

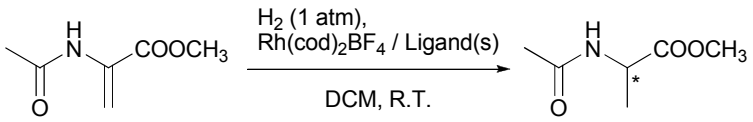
Also our research group recently developed a self-assembly strategy relying on ionic interactions, according to which the ion-pairs were expected to form by direct interaction between ligands bearing an acidic and a basic functional group, respectively. [146] A small library of chiral BINOL-derived monodentate phosphites containing either a carboxylic acid (-COOH) or a tertiary amine (-NMe2) was synthesized. The ligand combinations were screened in the enantioselective rhodium-catalyzed hydrogenation of methyl 2-acetamidoacrylate. Some heterocombinations of basic and an acidic phosphite displayed a higher activity and a slightly better enantioselectivity compared to the corresponding homocombinations [up to 90% e.e. using (*R*)-**115a**/(*R*)-**116b**, shown in Scheme 1.63].

Examples of acidic phosphites



Examples of basic phosphites

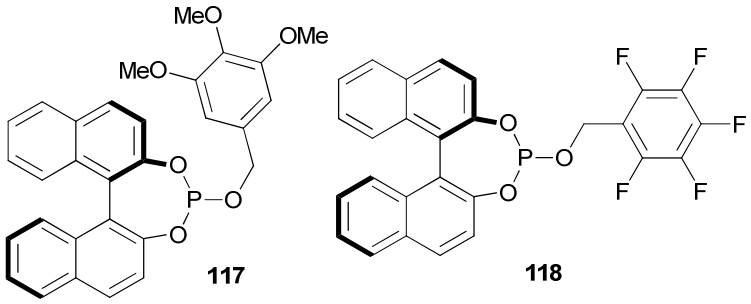




L^a	L^b	Conv. (%)	e.e. (%)	Abs. conf.
(*R*)-**115a**	-	100	80	*S*
-	(*R*)-**116b**	30	86	*S*
(*R*)-**115a**	(*R*)-**116b**	100	90	*S*

Scheme 1.63 Acidic and basic phosphite ligands and their application in Rh-catalyzed asymmetric hydrogenation.

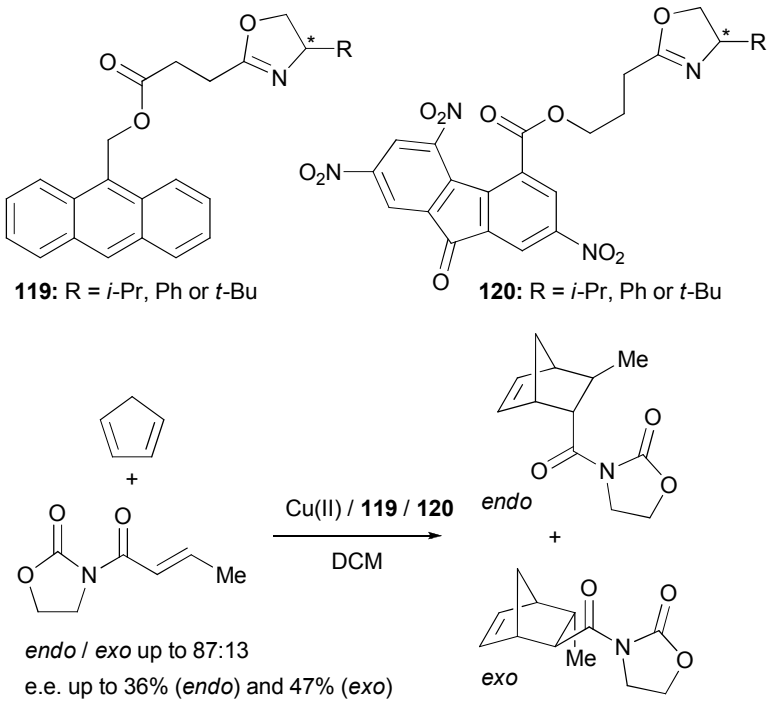
The nature and extent of the interaction between the acidic and basic ligands in the rhodium complexes were studied by spectroscopic methods. The formation of an intramolecular salt between the carboxylic acid and the tertiary amine could be observed from the IR spectra of acid/base mixtures in the presence of a rhodium source. However, only moderate heterocomplex/homocomplexes ratios (up to 70:30) could be determined by ^{31}P NMR. Despite this low level of selectivity in the heterocomplex formation, this remains so far the only example of ionic interaction-based self-assembly strategy of some catalytic utility. The attractive interactions between aromatic rings with opposite electronic distribution can be viewed as a possible candidate for promoting the self-assembly of supramolecular bidentate ligands. Our research group recently tried to develop a novel self-assembly strategy relying on the π-π interaction between an electron-poor and electron-rich arene. [147] With this goal, a library of chiral ligands was prepared, whose members are BINOL-derived phosphites each containing an electronrich or an electronpoor aromatic ring (Scheme 1.64).



Scheme 1.64 Library of chiral phosphites endowed with electron-rich and electron-poor arene rings: two representatives.

Unfortunately, ^{31}P NMR studies carried out on electon-rich/electron-poor phosphite mixtures in the presence of a rhodium source showed no selectivity, statistic heterocomplex/homocomplexes mixtures (2:1:1) being detected in all cases. We thus concluded that, in solution, arene-arene interactions are too weak for driving the selective formation of heterocomplexes.

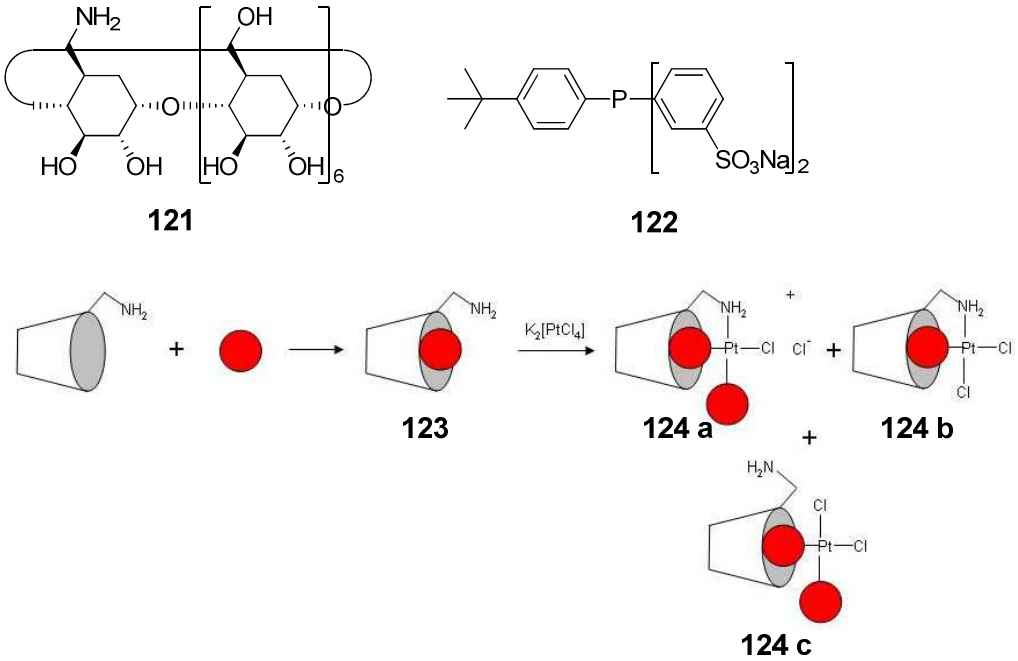
Schulz and co-workers also made an attempt to take advantage of electon-rich/electron poor arene-arene interactions for forming supramolecular ligands: [148] chiral oxazolines functionalised with anthracene (**119**) and trinitrofluorenone groups (**120**) were prepared and combined in the presence of a copper(II) source. The obtained complexes were screened in the Diels-Alder reaction between cyclopentadiene and an oxazolidinone-derivative, but no improvement in catalytic activity and stereoselectivity derived from using ligand mixtures rather than homocombinations (Scheme 1.65).



Scheme 1.65 Chiral oxazolines functionalised with electron-rich (**119**) and electron-poor (**120**) aromatic stsyems, and their application in Cu(II)-catalyzed Diels-Alder reaction.

Although it is very difficult to investigate what happens in solution [paramagnetic copper(II) complex cannot be analysed by NMR], on the base of the catalytic results the authors concluded that also in this case the arene-arene interactions are unable to promote the selective formation of the heterocomplex, a mixture of complexes being present.

The formation of an inclusion compound was exploited by Monflier et al. to form a water-soluble, supramolecular bidentate P,N-ligand whose Pt-complex was studied by NMR spectroscopy. [149] A cyclodextrine functionalized with an amino group was used as the host and the phosphine as the guest (Scheme 1.66).



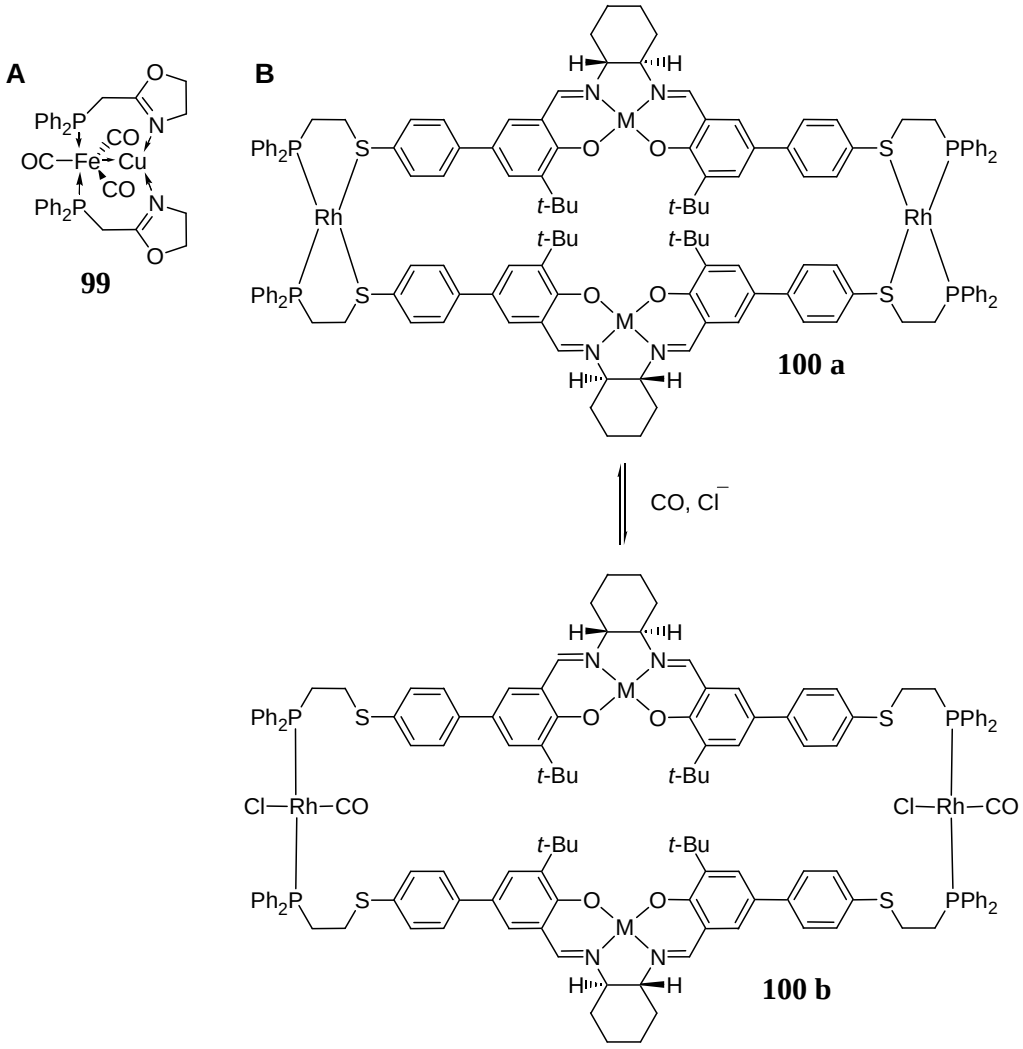
Scheme 1.60 Formation of the supramolecular bidentate ligand (**123**) from 6'-amino-6'-deoxycyclomaltoheptaose (**121**) and disodium bis(3-sulfonatophenyl)(4-tert-butylphenyl)phosphane (**122**)

1.4.5 Other self-assembled ligands

P-ligands are probably the class of ligand on which the concept of self-assembly has been most intensely studied in recent years. There are at least three reasons for this fact:

1) they coordinate very well transition metals such as Pd, Rh, Ir, Ru, Ni, that play a central role in some of the most important organometallic reactions;
2) their coordination properties can be easily studied by ^{31}P-NMR spectroscopy;
3) historically they have been the testing ground on which the groups involved in the development of new self-assembled systems have been competing.

Nevertheless, the concept of self-assembly has been applied also to other ligands than those in which the phosphorus atoms are employed for complexing the catalytic metal. For example, the role of the phosphorus atoms can be to coordinate the soft "structural" metal, while a harder metal will be the catalytic species (Scheme 1.67 A).[150a,b] In another example two rhodium *P,S*-complexes have been used as switchable linkers between two subunits each bearing a complex of the catalytic metal (Scheme 1.67 B).[151] Finally, there are obviously also examples of self-assembled system completely devoid of phosphorus atoms.[150c-e]

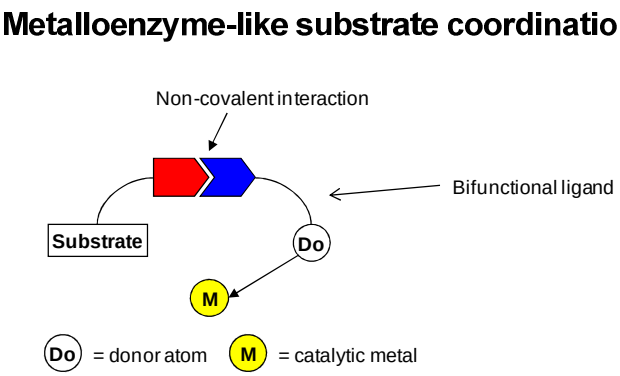


Scheme 1.67 Synthesis of (a) phosphinooxazoline ligands and (b) the allosteric tweezer complexes[150, 151]

These ligands, however, go far outside the scope of this short summary, and therefore they are not discussed here.

1.4.6 Transition-state stabilization by a secondary substrate-ligand interaction

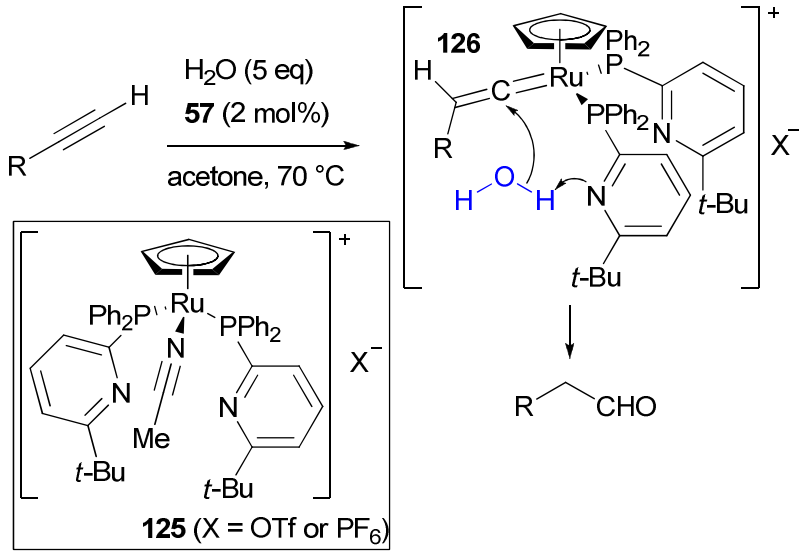
The effectiveness of enzymes, still unrivalled by any artificial catalytic system, is due to their ability of stabilising the transition state of a specific transformation by multiple interactions.[152] The action of several well-placed functional groups allows to achieve catalysis with very high substrate selectivity, reaction selectivity and stereoselectivity. On the contrary, man-made catalysts rarely exploit this approach, predominantly utilising just one centre for interacting with one or more reactants. However, in the 1970s chemists started to take inspiration from Nature's catalysts, and terms such as "*artificial enzymes*" and "*biomimetic chemistry*" appeared in the literature. A number of supramolecular catalytic systems were reported, which were capable of non-covalently binding the reaction substrate and precisely positioning it relative to the catalytic site, thus allowing a high level of activity and/or selectivity.[153] These include both transition metal and metal-free catalysts, but only the former (Scheme 1.68) will be discussed in the present review.



Scheme 1.68 Schematic representation of a supramolecular catalyst coordinating the reaction substrate.

Most of the examples of metalloenzyme mimics appeared so far in the literature have been developed for reactions, such as hydrolysis of esters and phosphates and redox reactions, of limited interest from the synthetic point of view. Surprisingly, for a long time the world of biomimetic catalysis and the vast area of traditional transition metal catalysis (*i.e.* involving metals such as Pd, Ni, Pt, Rh or Ru and important organic transformations such as hydrogenation, hydroformylation, carbonylation, hydrocyanation or arylation) have lived sort of 'parallel lives', and only seldom met.[154] For several research groups active in the latter area, the recent rediscovery of monodentate ligands and the subsequent effort to build supramolecular bidentate ligands by means of non-covalent interactions have been the occasion to approach concepts belonging to supramolecular and biomimetic catalysis. As a consequence, bifunctional ligands have started being employed also for creating metalloenzyme-like, substrate-coordinating catalysts for synthetically relevant reactions, some of which are reviewed below.

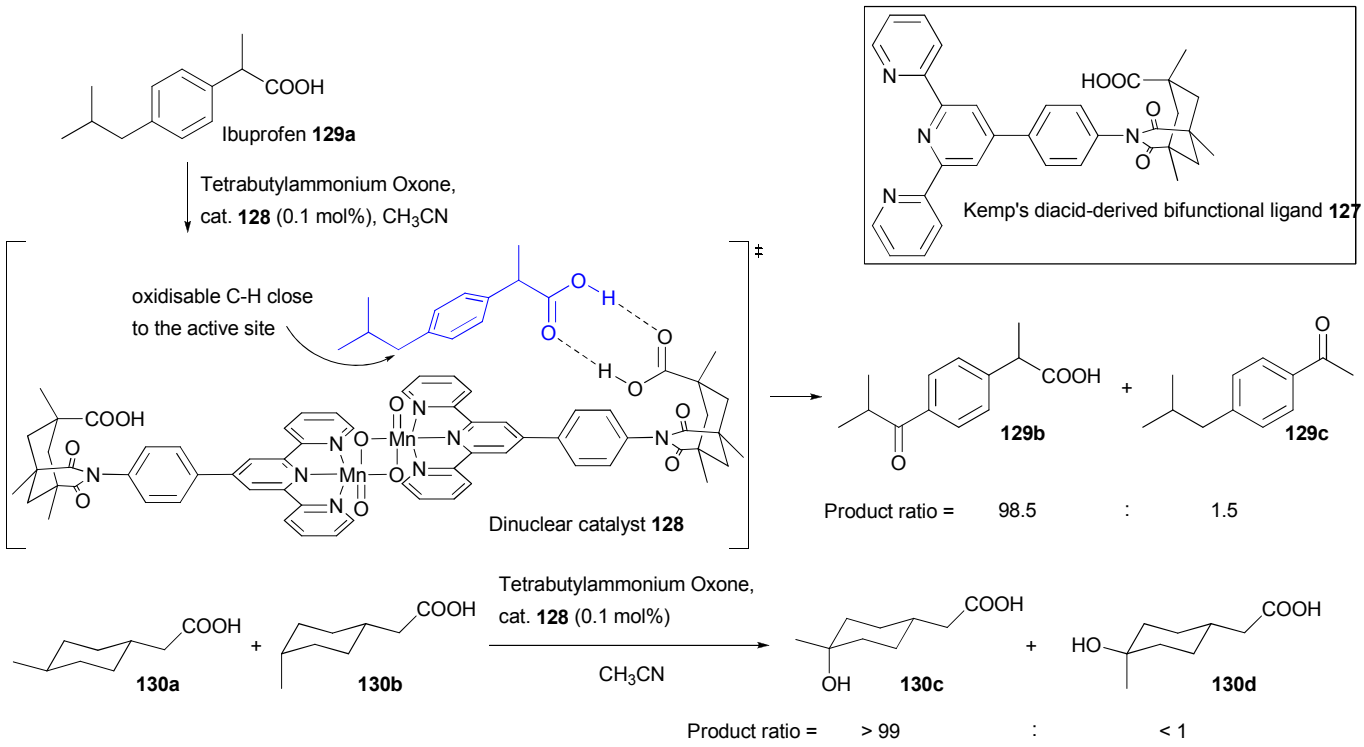
In the 2001-2005 period, three papers by Grotjahn and co-workers appeared reporting the development of a highly efficient bifunctional ruthenium catalyst (**125**) for the anti-Markovnikov hydration of alkynes (Scheme 1.69).[155]



Scheme 1.69 A highly efficient bifunctional organometallic catalyst for the anti-Markovnikov hydration of alkynes.

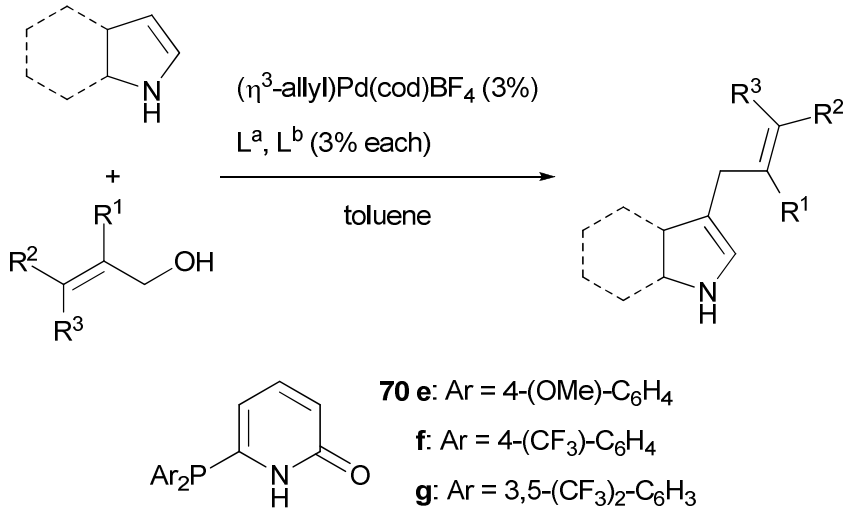
Although the reaction mechanism has not been fully clarified yet,[156] the vinylidene-ruthenium intermediate **126** is likely to be involved in the catalytic cycle. The basic nitrogen atoms present in the pyridine rings were demonstrated to be indispensable for a high catalytic activity: catalysts lacking these atoms are much less active than **125**. These atoms may help catalysis in two key steps: (i) the formation of the vinylidene complex **126** from a terminal alkyne; (ii) the subsequent addition of water to C1 of the vinylidene (Scheme 1.69).

In 2006 Crabtree, Brudvig and co-workers reported the bifunctional ligand **127**, whose dinuclear manganese complex **128** catalyzes the regioselective oxidation of C-H groups of suitable carboxylic acids.[157] The carboxylic acid recognition unit present in the catalyst is able to bind the COOH group of the substrate, which is positioned in such a way that one of its oxidisable C-H groups reacts selectively. The **128**-catalyzed oxidation of Ibuprofen **129a** (Scheme 1.70) occurred with high selectivity in favour of compound **129b** (**129b**/**129c** = 98.5/1.5), while no selectivity between the two products (**129b** and **129c**) could be realised with a related catalyst lacking the COOH groups. In the oxidation of a mixture of *trans*- and *cis*-(4-methylcyclohexyl) acetic acid (**130a** and **130b**), just the former substrate (**130a**) reacted, yielding product **130c** as a single diastereomer. Indeed, only in the **130a**-catalyst adduct an oxidisable CH is present at the right distance and with the right orientation relative to the catalytic centre.



Scheme 1.70 Two examples of regioselective oxidation promoted by supramolecular catalyst **125**.

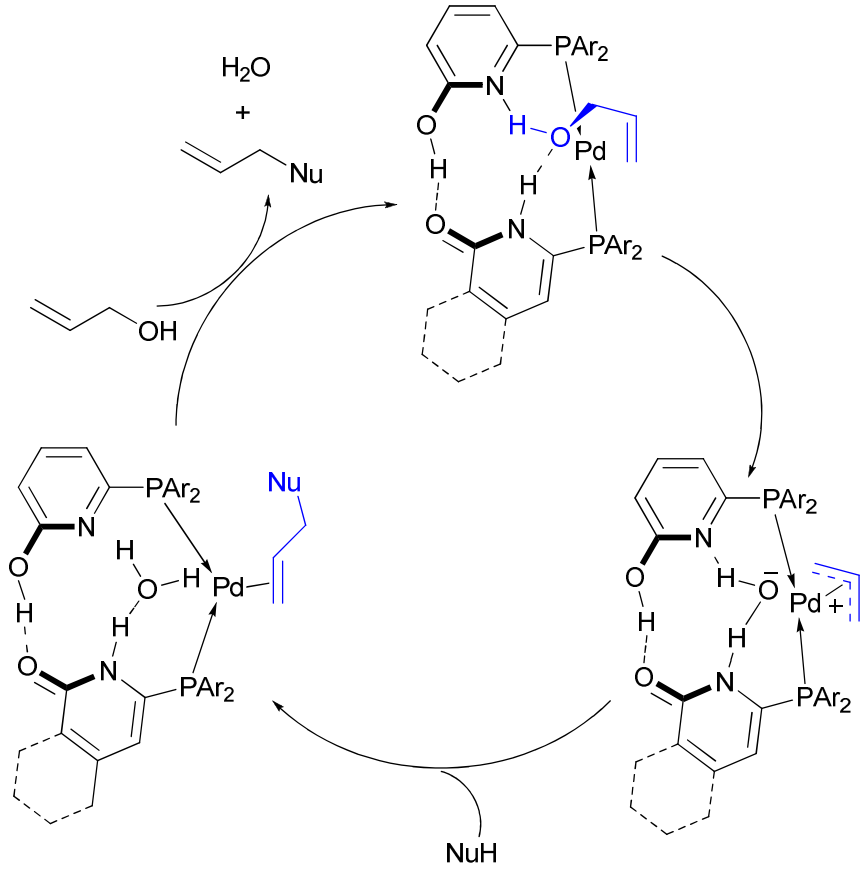
Breit and co-workers recently developed several interesting examples of bifunctional transition metal catalysts capable of non-covalently binding and activating the reaction substrate. In 2008, homo- and heterocombinations of achiral ligands **70a** (Scheme 1.38), **70e-g** (Scheme 1.71), **70b**, **70c** and **70c** (Scheme 1.37) were employed for developing a novel Pd-catalyzed allylation of indoles and pyrroles with allylic alcohols (Scheme 1.71).



Scheme 1.71 Pd-catalyzed allylation of indoles and pyrroles with allylic alcohols promoted by homo- and heterocombinations of ligands **70a-g.**

Apparently, here the hydrogen bonding network goes beyond its structural role (*i.e.*, holding the two ligands together) and assists the hydroxy group to become a better leaving group during the

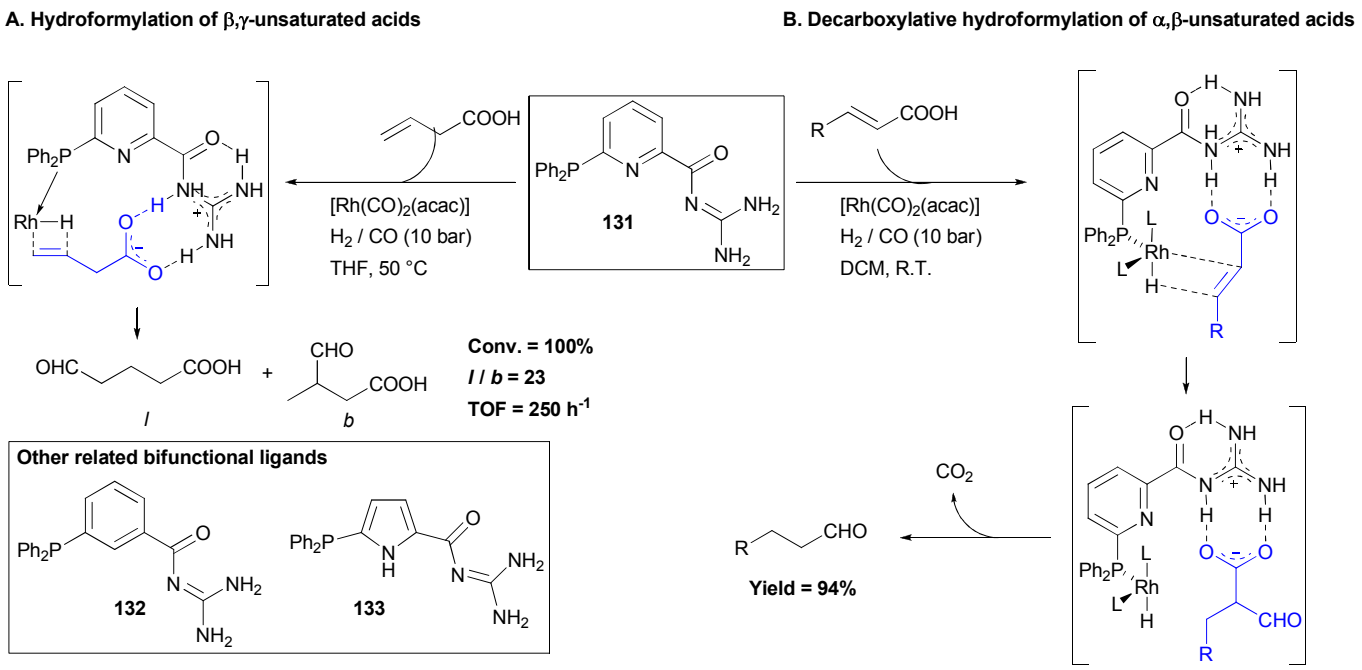
allylic substitution process. This effect was rationalised by the authors with a tentative catalytic cycle which is shown in Scheme 1.72. In this novel reaction, the self-complementary, electron-poor ligands **70g** provided the most active catalysts and were thus used for exploring the reaction scope, which includes a large number of allylic alcohols besides several indole and pyrrole derivatives. This piece of work clearly shows how bifunctional, metalloenzyme-like catalytic systems not only improve the catalytic performance (activity and selectivity), but can also disclose new kinds of reactivity, not accessible with traditional monofunctional catalysts.



Scheme 1.72 Proposed catalytic cycle for the Pd-catalyzed allylation of indoles and pyrroles with allylic alcohols promoted by homo- and heterocombinations of ligands **70a-g.**

In the same year, Breit and co-workers reported the new phosphine ligand **131** (Scheme 1.73), endowed with an acylguanidine recognition unit capable of a two-point interaction with hydrogen bond-acceptor groups.[158] In particular, the acylguanidine group can strongly bind the COOH group, and this directing effect was exploited for achieving the regioselective hydroformylation of unsaturated carboxylic acids (Scheme 1.73). The Rh complex of ligand **131** catalyzed the γ-selective hydroformylation of α,β-unsaturated acids (Scheme 1.74 A) with high selectivity and improved activity (*l*/*b* ratio = 23, TOF = 250 h^{-1}) compared to simple monodentate ligands such as PPh_3 (*l*/*b* ratio = 1.3, TOF = 30 h^{-1}).[158a] In a subsequent contribution,[158d] the same authors showed how activity and selectivity could be further improved by a fine-tuning of the

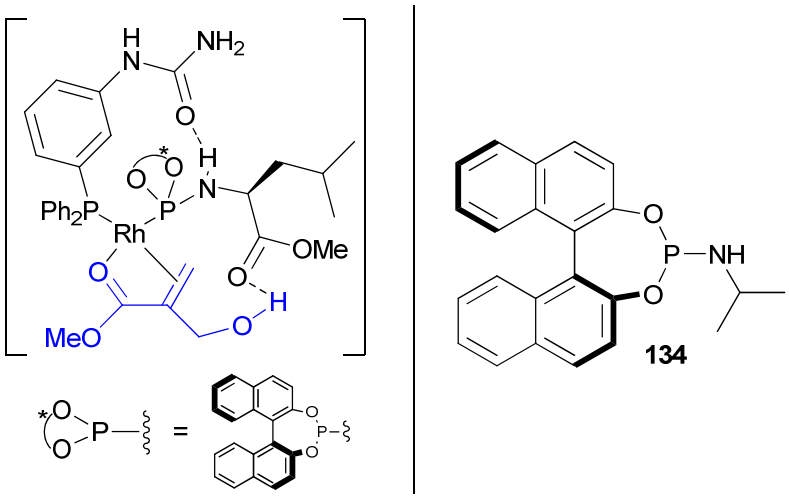
electronic properties of the ligand. Moreover, the substrate scope was further investigated, and a deeper understanding of mechanistic details of the reaction could be gained by a series of control experiments. In another paper published in 2008, Breit and co-workers reported the use of the Rh complex of ligand **131** as a catalyst for the decarboxylative hydroformylation of α,β-unsaturated acids (Scheme 1.73 B):[158b] in the presence of this kind of substrate, the acylguanidine group directs the reaction at the α-carbon of the acid. The formed α-carboxyaldehyde, which cannot be isolated, readily undergoes decarboxylation, thus forming a saturated aldehyde where the formyl group has replaced the carboxylic group. This kind of mechanism, outlined in Scheme 1.73 B, is supported by the observation that the reaction of [1-^{13}C]-oct-2-enoic acid gives rise to the exclusive formation of unlabeled 1-octanal. The substrate scope of this reaction was investigated with a number of α,β-unsaturated acid substrates. In 2009 the same authors reported the use of other, related phosphine ligands (**132** and **133**) in the Rh-catalyzed chemoselective reduction of aldehydes and in the tandem hydroformylation-hydrogenation of olefins.[158c]



Scheme 1.73 Use of bifunctional ligand **131** in the γ-selective hydroformylation of β,γ-unsaturated acids (A) and in the α-selective decarboxylative hydroformylation of α,β-unsaturated acids (B). Other related bifunctional ligands are shown in the box.

The last substrate-orientation effect that is discussed in tihis section was observed by Reek and co-workers in the enantioselective hydrogenation of 2-hydroxymethylacrylate promoted by the supramolecular Rh complex discussed in Section 1.4.2.6 (see Scheme 1.52).[136a] On the base of DFT calculations, the authors proposed an intermediate where substrate **29a** is hydrogen-bonded to the ester group of ligand (Scheme 1.74). This substrate-orientation effect is suggested also by the drop of enantioselectivity observed (i) when using ligand **133** (still capable of forming the supramolecular bidentate ligand, but devoid of any hydrogen bond-acceptor group) or (ii) when

the OH group of the substrate is protected.



Scheme 1.74 DFT-calculated structure of an intermediate of the hydrogenation of substrate catalyzed by the supramolecular complex.

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Chapter 2

Combination of a Binaphthol-derived Phosphite and a C_1-Symmetric Phosphinamine Generates Heteroleptic Catalysts in Rh- and Pd-mediated Reactions

Abstract

In this Chapter the synthesis of several enantiomerically pure phosphites and phosphinamines is described. DFT calculations showed that the phophite-phosphinamine rhodium heterocomplex is more stable than two homocomplexes by 11.29 kcal/mol. ^{31}P NMR complexation studies, using $Rh(acac)(C_2H_4)$ as the rhodium source, showed the preferential formation of phosphite/C_1-symmetric aminophosphine heterocomplex with selectivities ranging from moderate (70%) to excellent (100%). The homo- and heterocombinations of phosphites and of the C_1-symmetric phosphinamines were then screened in the Rh- and Ir-catalyzed hydrogenation of olefins and in the Pd-catalyzed asymmetric allylic substitution of rac-1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate. Remarkably, the 1:1 combination of a binol-derived phosphite and a phosphinamine induced reversal of the enantioselectivity and, in the case of the palladium-catalyzed asymmetric allylic substitution, also a modest increase of the enantioselectivity.[1]

2.1 GENERAL INTRODUCTION

In recent years, monodentate phosphorus ligands (e.g. phosphites, phosphonites, phosphoramidites and phosphinamines) have held the stage in asymmetric catalysis. In addition to their outstanding activity and selectivity, comparable or even superior to those of bidentate ligands, the convenient, fast and practical preparation from commercially available materials underlines their potential for industrial applications. Furthermore, the modular nature of all these ligands allows the synthesis of a wide variety of representatives, thereby making a combinatorial approach possible.

In 2002–3, an important breakthrough in this area was made independently by the groups of Reetz and Feringa, who used a binary mixture of chiral monodentate P-ligands in several asymmetric rhodium catalyzed reactions. By mixing two ligands (L^a and L^b) in the presence of Rh, three species can be formed: RhL^aL^a, RhL^bL^b (homocomplexes), and RhL^aL^b (heterocomplex) (see paragraph 1.1.2.2). The heterocombination is often more reactive and more (regio-, diastereo- and enantio-) selective than either of the two homocombinations. Moreover, under thermodynamic control (fast and reversible ligand exchange) the heterocomplex : homocomplexes ratios usually exceed the statistical value (2 : 1 : 1). In these cases the preferential formation of heteroleptic catalysts from two monodentate ligands is probably favoured by weak interactions, such as van der Waals, π-stacking or dipole–dipole interactions. The ideal case would constitute an equilibrium completely in favour of the heterocomplex $[RhL^aL^b]$ because then only a single well-defined catalyst would exist in the reaction, and the undesired competition of the less selective homocomplexes would be avoided.

We were intrigued by the remarkable selectivities reported for the mixtures of chiral ligands (binol-derived phosphites, phosphonites and phosphoramidites) with achiral phosphines. In particular, the 1 : 1 mixture of a chiral phosphite with an achiral phosphine was reported to induce reversal of the enantioselectivity in the Rh-catalyzed hydrogenation of *N*-acetamido acrylate (compared to the chiral phosphite alone). The only possible explanation for this peculiar behaviour is the selective formation of the phosphite–phosphine Rh-heterocomplex, favoured by electronically matching one σ-donor ligand (phosphine) and one π-acceptor ligand (phosphite).

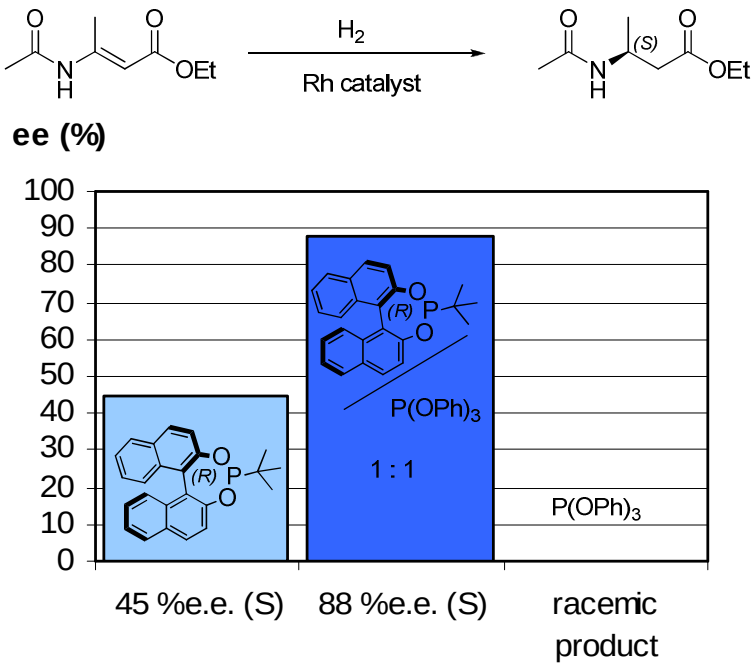
2.2 RESULTS AND DISCUSSION

2.2.1 Thermodynamic approach to the selective formation of heteroleptic complexes

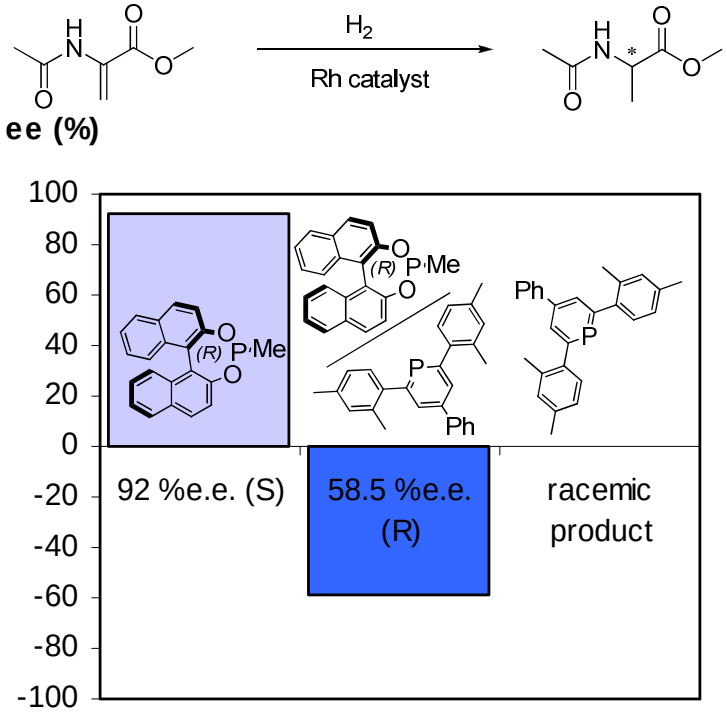
In the frame of our studies directed to the selective formation of heterocomplexes resulting from the combination of different ligands, we considered the exploitation of the intrinsic thermodynamic preference of heterocomplexes *Vs* homocomplexes. In other words, we wondered if ligands having complementary electronic properties could favourably interact through a metal centre with the effect of increasing the thermodynamic stability of the heterocomplex over the homocomplexes. The obvious advantage of such an approach consists in using simple monodentate ligands instead of the sophisticated bifunctional ligands necessary for supramolecular interactions to take place.

The fact that mixtures of monodentate ligands L^a and L^b, in the presence of a metal source M, can lead to distributions of complexes L^aML^b : L^aML^a : L^bML^b significantly different from the statistical (2 : 1 : 1) had been previously reported in the literature and generally attributed to steric effects: the heterocomplex L^aML^b were found the more favoured the more L^a and L^b differ in terms of steric bulk. For example, Feringa and Minnaard reported that up to 91% of the heterocomplex is formed by mixing $Rh(acac)(C_2H_4)_2$ with two different monodentate phosphoramidites.[2] Alternatively, the observed preference for the heterocomplex can be due by weak interactions, such as van der Waals, π-stacking or dipole–dipole interactions. Moreover, the peculiar catalytic results often observed when a chiral (BINOL-derived phosphites, phosphonites and phosphoramidites) and an achiral monodentate ligand (phosphine) are combined clearly demonstrate that in these cases the heterocomplex L^aML^b plays a central role in determining the stereochemical outcome of the reaction. In most cases a decrease of enantioselectivity was observed, which may not be surprising. However, in several instances the enantioselectivity increased or even reversed upon using an achiral ligand as one of the components.[3,4] In a first example (shown in Scheme 2.1) the e.e. value climbs to 88 % when the *tert*-butylphosphonite used as the chiral ligand in combination with achiral triphenylphosphite (1:1 mixture), while the homocombination of the phosphonite leads to an e.e. of only 45 %.[3]

A second example shown in Scheme 2.2, where it can be seen that the heterocombination of 1:1 mixture of a methylphosphonite with an achiral phosphine induced reversal of the enantioselectivity in Rh(I)-catalyzed hydrogenation of methyl 2-acetamido acrylate.[4]



Scheme 2.1 Rh(I)-catalyzed hydrogenation of β-*N*-acylamino acrylate using 1:1 mixture of a chiral and an achiral ligand: increase of enentioselectivity[3]



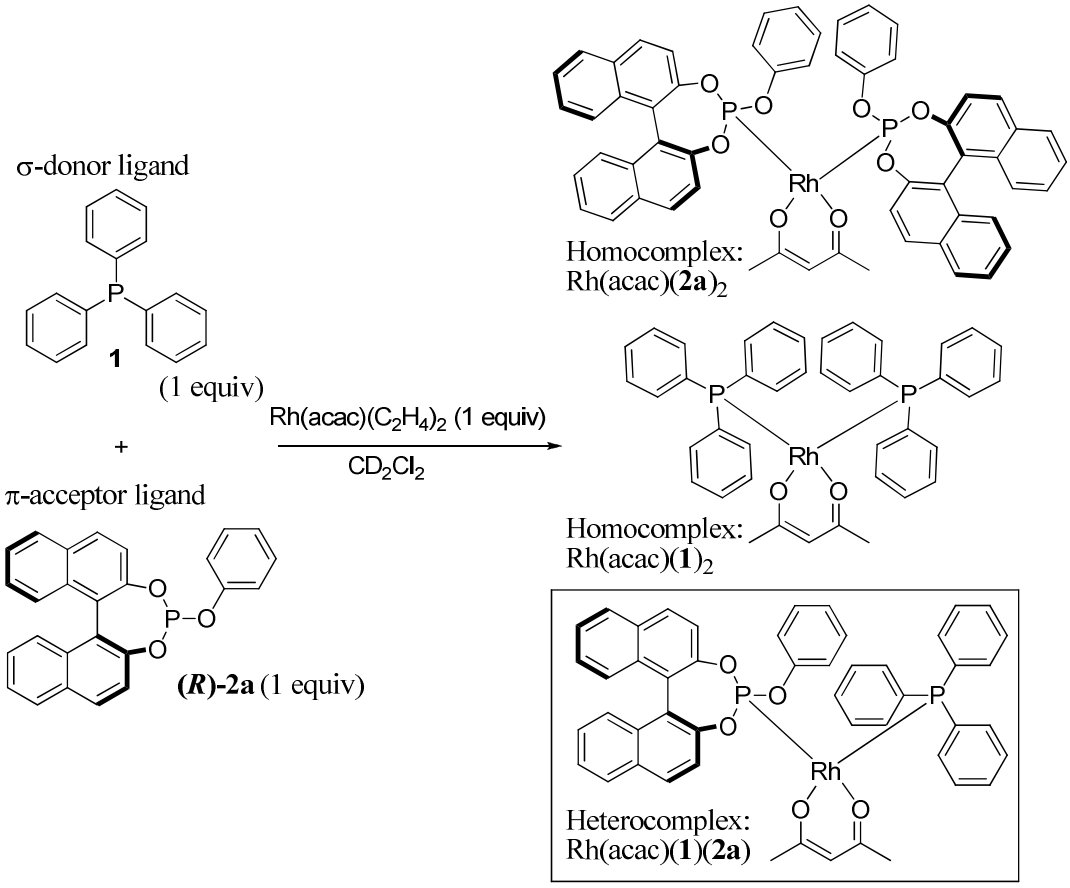
Scheme 2.2 Rh(I)-catalyzed hydrogenation of methyl 2-acetamidoacrylate using 1:1 mixture of a chiral and an achiral ligand: inverse sense of enantioselectivity[4]

To the best of our knowledge, basically no attempt has been reported to verify whether the key-role played by the heterocomplex is due to its selective formation (i.e.: no or very little L^aML^a and L^bML^b to compete with) or to its higher activity compared to the corresponding homocomplexes.

Intrigued by these results, obtained combining a strongly σ-donor ligand (an achiral phosphine) with a π-acceptor one (a BINOL-derived phosphite, phosphonite or phosphoramidite), we set to verify if the selective formation of the heterocomplexes could be obtained by combination of electronically complementary ligands.

2.2.1.1 Selective formation of phosphite/phosphine heterocomplex

It was initially decided to verify the ability of triphenylphosphine **1** to selectively form a heteroleptic complex when combined with the known chiral phosphite (*S*)-**2a** in the presence of a source of rhodium(I) [Scheme 2.3].

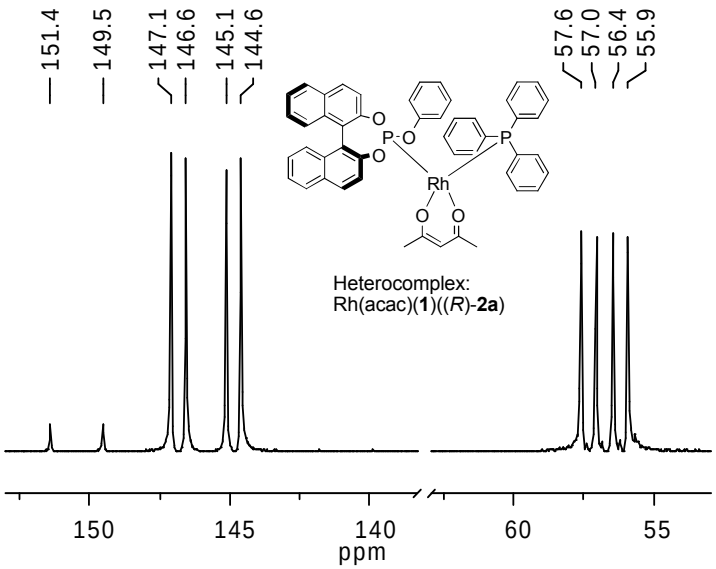


Scheme 2.3 Possible complexes of 1:1 mixture of triphenylphosphine **1** with phenyl phosphite (*R*)-**2a**

According to our expectations, when the single phosphite ligands (homocombinations) were treated with $Rh(acac)(C_2H_4)_2$, one or two doublet signals were visible depending on Rh / L ratio: the upfield signal corresponds to the mono-complex, while the downfield one is due to the homocomplex. As typically observed with phosphite ligands, the value of the $^1J_{P,Rh}$ coupling constant was typically about 303 Hz for both the mono- and homocomplex.

Triphenylphosphine **1** showed a more complex behaviour, with either a broad signal or sharp doublets at 49.2 and 31.9 ppm ($^1J_{P,Rh}$ = 175 Hz and 134 Hz, respectively) being visible depending on the stoichiometry.

When the mixture of **1** and (*R*)-**2a** (1 equiv each) and Rh(acac)(C_2H_4)$_2$ was dissolved in CD_2Cl_2, a quite clean heterocomplex was formed with *cis* disposition of the two *P*-ligands and heterocomplex / homocomplexes ratio = 94 : 6 (Scheme 2.4, $^2J_{P,P}$ = 85 Hz; $^1J_{Rh,phosphite}$ = 318 Hz; $^1J_{Rh,phosphine}$ = 182 Hz).



Scheme 2.4 ^{31}P NMR spectra of 1 : 1 mixture of triphenylphosphine **1** and phenyl phosphite (*R*)-**2a** with Rh(acac)(eth)$_2$ as Rh source.

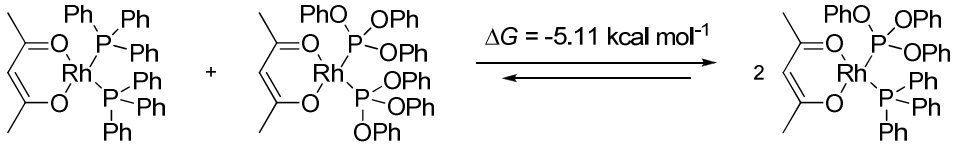
The high observed amount of heterocomplex is in agreement with our initial hypothesis about a possible favourable interaction between the σ-donor phosphine and the π-acceptor phosphite through the metal. We thus felt encouraged to further develop this new approach to the selective formation of heterocomplexes, as described below.

2.2.1.2 DFT calculations on a phosphite-phosphine and phosphite- phosphinamine Rh heterocomplex

Thanks to collaboration with the research group of prof. Tvaroška of the Slovak Academy of Sciences, DFT calculations at the B3LYP/SDD level of theory[5] were performed in order to confirm that the phosphite-phosphine heterocomplexes are thermodynamically favoured over the corresponding homocomplexes. The calculation carried out on the isodesmic reaction shown in Scheme 2.5 shows that the heterocomplex is more stable than the two homocomplexes by 5.11 kcal mol^{-1}.

This result confirmed the validity of our approach, and we decided to prepare two ligand libraries with complementary electronic properties to combine in new NMR and catalytic experiments. However, while chiral BINOL-derived phosphites are a well-known and easy-to-prepare class of ligands, enantiomerically pure chiral phosphines are generally difficult to synthesize. A long and time-consuming synthetic procedure would have been in contrast with our general goal of dealing with

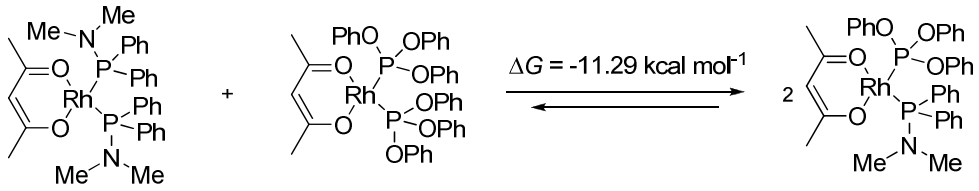
cheap and easy-to-prepare monodentate ligands, and thus only achiral phosphine would have been to be considered. As a consequence, the explorable combinatorial space would have been seriously limited, together with the probability of discovering efficient catalytic systems.



Scheme 2.5 DFT calculations at the B3LYP/SDD level of theory on the isodesmic reaction of phosphite-phosphine heterocomplex

In view of these considerations, we wondered if the phosphine ligand could be substituted by another σ-donor phosphorus ligand, still retaining the thermodynamic preference for the formation of the Rh-heterocomplex. We turned our attention to chiral phosphinamines,[6] which are easy to prepare enantiomerically pure, and have ^{31}P-NMR spectral properties fairly similar to those of phosphines, thus reflecting a similar electronic situation.

Preliminary DFT calculations, carried out on a phosphite/phosphinamine combination (Scheme 2.6) at the B3LYP/SDD level of theory,[5] showed that the phosphite-phosphinamine rhodium heterocomplex is more stable than the two homocomplexes by as much as 11.29 kcal mol^{-1}.

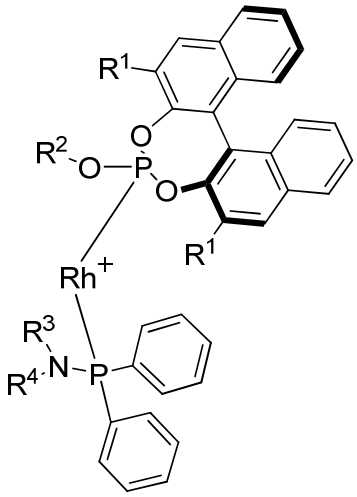


Scheme 2.6 DFT calculations at the B3LYP/SDD level of theory on the isodesmic reaction of phosphite-phosphinamine heterocomplex

We thus set to prepare a library of phosphite and one of phosphinamines as described in the following Paragraph, section 2.2.2.

2.2.2 Synthesis of the ligand libraries

We opted for chiral ligands based on BINOL derived phophites, and on C_2- or C_1-symmetric phosphinamines because these modular structures allow an easy tuning of the catalytic properties of ligands. The proposed ligand structures are shown in Scheme 2.7.

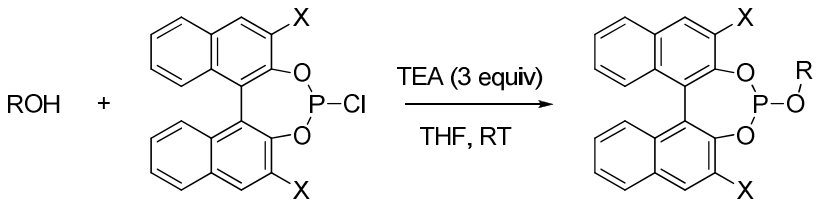


Scheme 2.7 Attractive σ-donor – π-acceptor interactions between ligands with complementary electronic properties

2.2.2.1 Synthesis of the chiral phosphite library

A library of BINOL-derived phosphites was prepared reproducing, with little modifications, synthetic protocols reported in the literature. Commercially available (*R*)- and (*S*)-1,1'-bi-(2-naphthol) (BINOL) were the starting material for the synthesis.

The phosphite ligands were easily prepared by condensation of appropriate phosphorochloridites with alcohols or phenols in the presence of an excess of triethylamine (Scheme 2.8): **2a**,[7] **2b**[8] and **2c**[9], **2e**,[10] **2f**[11] are known products.

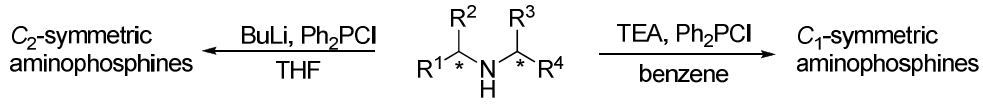


Scheme 2.8 Synthesis of BINOL-derived phosphites

The phosphite ligands proved stable when kept at low temperature under nitrogen, but they slowly degraded when stored at room temperature.

2.2.2.2 Synthesis of the chiral phosphinamine library

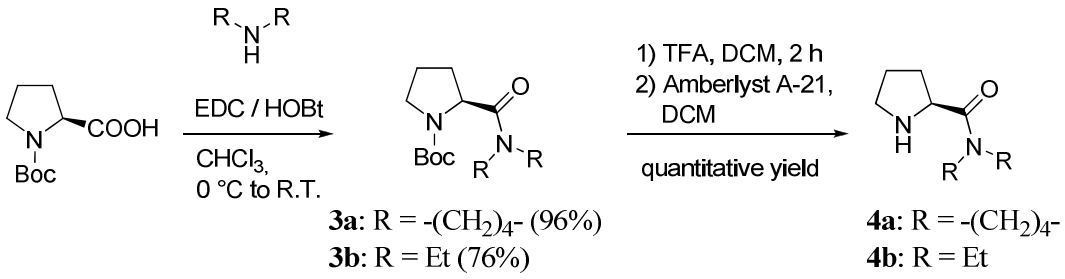
The phosphinamine ligands were prepared by condensation of dihenylphosphinic chloride (Ph_2PCl) with various amines, most of which commercially available, in the presence of triethylamine for C_1 symmetric or BuLi for C_2-symmetric phosphinamines (Scheme 2.9).



Scheme 2.9 Synthesis of chiral phosphinamine library

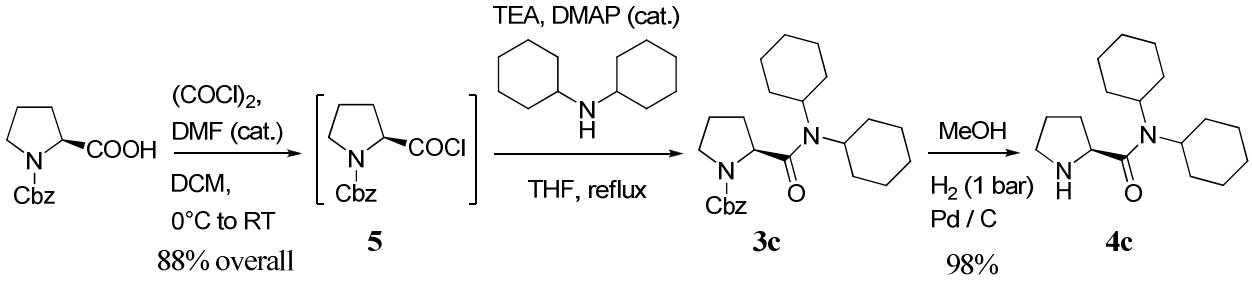
2.2.2.2.1 Preparation of non commercially available chiral amines

Prolinamides **4a** and **4b** were prepared from *N*-Boc-L-proline according to the simple two-step sequence shown in Scheme 2.10.



Scheme 2.10 Synthesis of prolinamides **4a** and **4b**

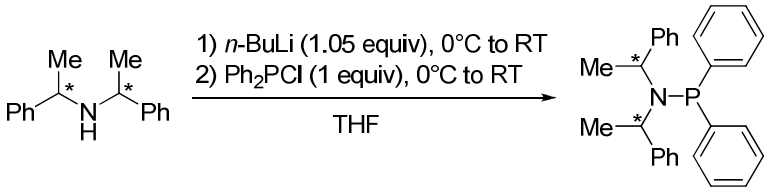
As shown in Scheme 2.11, for preparing amine **4c** it was necessary to react dicyclohexylamine with the *N*-Cbz-L-proline acyl chloride **5** (prepared as described in the literature[12]), because this sterically encumbered amine had proven unreactive to the condensing reagents utilised for preparing **3a** and **3b**.



Scheme 211 Synthesis of prolinamide **4c**

2.2.2.2.2 Synthesis of the C_2-symmetric phosphinamines (SimplePhos ligands)

The SimplePhos ligand **6a**, developed by Alexakis *et al.*, was prepared (in both the enantiomeric forms) following the original procedure[6] with some variations, as shown in Scheme 2.12. In particular, we found unnecessary to protect the ligand as BH_3-complex (as described in the original paper), and we were able to isolate it –yet in moderate yield– directly from the reaction crude. The obtained yield is hovewer somehow lower than the overall yield obtained with the original condensation-protection-deprotection sequence (31 % vs. 55%).



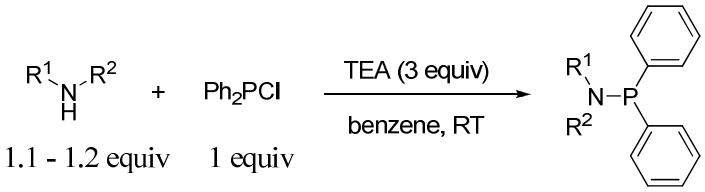
31% (*R*,*R*)- and (*S*,*S*)-**6a**

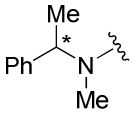
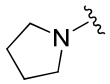
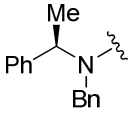
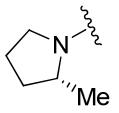
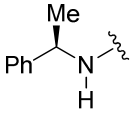
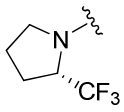
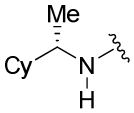
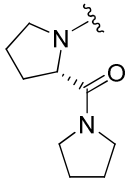
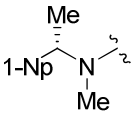
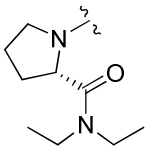
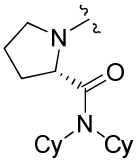
Scheme 2.12 Preparation of the C_2-symmetric phosphinamines (*R*,*R*)- and (*S*,*S*)-**6a**

Remarkably, (*R*,*R*)- and (*S*,*S*)-**6a** could not be prepared under the experimental conditions described below for C_1-symmetric phosphinamines, because sterically encumbered bis(1-phenylethyl)amine did not react in the presence of a weak base such as TEA.

2.2.2.2.3 Synthesis of the C_1-symmetric phosphinamines

All of the C_1-symmetric phosphinamines were prepared by reacting the corresponding amines with commercially available diphenylphosphinic chloride (Ph_2PCl) in the presence of an excess of TEA, according to a modification of a known procedure[13] (Scheme 2.13). The latter experimental protocol, indeed, proved more simple and practical than the one reported by Alexakis *et al.* for the synthesis of SimplePhos ligands.



Compound	R^1 N R^2	Yield (%)	Compound	R^1 N R^2	Yield (%)
(*R*)- and (*S*)-**6b**		84	**6g**		85
(*R*)-**6c**		52	(*R*)-**6h**		77
(*R*)-**6d**		87	(*S*)-**6i**		86
(*R*) and (*S*)-**6e**		75	(*S*)-**6j**		36
(*S*)-**6f**		81			
			(*S*)-**6k**		38
			(*S*)-**6l**		42

Scheme 2.13 Synthesis of C_1-symmetric phosphinamines **6b-6l**

All of the C_1-symmetric phosphinamines **6b-6l** (Scheme 2.13) turned out to be very sensitive to acids: they undergo rapid degradation on silica and could be chromatographed only on alumina using an eluent containing TEA (~ 5%, see the Experimental Section). In solution the ligands proved also moderately prone to undergo oxidation by atmospheric oxygen, while they are fairly stable in the solid state. The instability of these ligands to both hydrolysis and oxidation is inversely proportional to the steric bulk of the amine moiety, **6a** being the most stable of all the prepared phosphinamines.

The phosphinamine ligands are stable in the solid state if kept at low temperature under a nitrogen atmosphere.

2.2.3 NMR studies on the phosphite/phosphinamine metal complexes

Several phosphite/phosphinamine combinations were treated with a metal source, and the obtained complexes were studied by ^{1}H- and ^{31}P-NMR spectroscopy, in order to confirm if the corresponding heteroleptic complex would be selectively formed as predicted by the DFT calculations presented above.

2.2.3.1 Complexation experiments with rhodium (I)

A number of homo- and heterocombinations of phosphites **2a**-**2d** and phosphinamines **6b**-**6e** were screened in complexation experiments in the presence of $Rh(acac)(C_2H_4)_2$.
The phosphite mono- and homocomplexes gave the expected doublet signals. Similarly, also the phosphinamine homocombinations gave one or two doublet signals depending on Rh / L ratio, where the upfield signal corresponds to the mono-complex and the downfield one is due to the homocomplex. Chemical shifts and coupling constants of several mono- and homocomplexes are listed in Table 2.1.

Table 2.1 Chemical shifts and coupling constants

Entry	Ligand	Monocomplex		Homocomplex	
		δ (ppm)	**$^{1}J_{P,Rh}$ (Hz)**	**δ (ppm)**	**$^{1}J_{P,Rh}$ (Hz)**
1	(*S*)- **2a**	141.4	303.0	150.4	303.1
2	(*R*)- or (*S*)- **2b**	147.1	292.3	157.6	295.1
3	(*R*)- **2c**	146.6	293.4	158.9	295.8
4	(*R*)- **2d**	141.2	293.8	151.8	299.8
5	(*R*)- or (*S*)-**6b**	101.3	193.0	104.8	203.6
6	(*R*)-**6c**	105.5	193.0	107.2	205.4
7	(*R*)-**6d**	79.2	187.6	83.6	199.1
8	(*S*)-**6e**	77.9	187.2	81.9	198.7

The possible combinations between phosphites **2a**-**2d** and phosphinamines **6b**-**6e** form a 4 × 4 matrix which would require 32 experiments to be covered, considering that two diastereoisomeric combinations are to be examined for each couple of ligands. In order to limit the number of complexation experiments, we opted for a positional scanning covering one line and one column of the matrix (14 experiments in total): all the possible diastereoisomeric combinations of the phosphinamine ligands with phosphites (*R*)- and (*S*)- **2b** were analyzed first, then the aminophosphine giving the highest hetero/homocomplexes ratio (**6b**) was combined with all of the phosphites. The results of these experiments are listed in Table 2.2 in terms of percent of heterocomplex formed calculated from the ^{31}P-NMR integrals of all the observed complexes (i.e. heterocomplex + homocomplexes and mono-complexes, when detected). All of the ^{31}P-NMR spectra of these complexation experiments are printed

in the Experimental Section. It can be noted that the heterocomplexes were formed with selectivity ranging from moderate (70%) to excellent (> 99%).

Table 2.2 Preference for the formation of heterocomplex between phosphites and phosphinamines

Phosphites	**Phosphinamines**				
	(*R*)-**6b**	(*S*)-**6b**	(*S*)-**6c**	(*R*)-**6d**	(*S*)-**6e**
(*S*)- **2a**	**83%**	**> 99%**			
(*R*)- **2b**	**99%**	**96%**	**81%**	**74%**	**70%**
(*S*)- **2b**			**81%**	**81%**	**84%**
(*R*)- **2c**	**94%**	**81%**			
(*R*)- **2d**	**96%**	**> 90%**			

From the values of the observed coupling constants of the heterocomplexes, listed in Table 2.3, it can be also deduced that in all of them the ligands are in a *cis* arrangement:[14] this means that the labile ethylene ligands of the rhodium source have been displaced by the phosphite and the phosphinamine as expected, while the chelating acetylacetonate (acac) ligand remained in place.

Table 2.3 Posphosrus coupling constants of the Rh(I) heterocomplexes of phosphite and phosphinamine

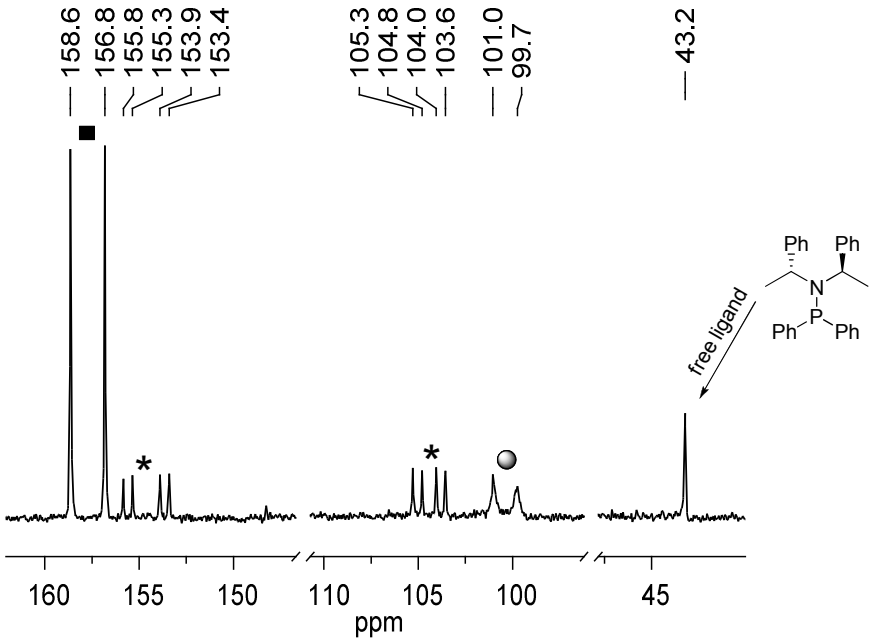
Entry	**Heterocomplex**	**Phosphite**		**Phosphinamine**		$^{2}J_{P,P}$ **(Hz)**
		δ (ppm)	$^{1}J_{P,Rh}$ **(Hz)**	**δ (ppm)**	$^{1}J_{P,Rh}$ **(Hz)**	
1	(*R*)-**2b**/(*R*)-**6b**	157.1	309.8	103.8	193.2	83.5
2	(*R*)-**2b**/(*S*)-**6b**	155.4	310.1	103.9	192.5	84.7
3	(*R*)-**2b**/(*R*)-**6c**	156.4	310.0	107.5	199.1	80.4
4	(*S*)-**2b**/(*R*)-**6c**	156.1	310.8	104.2	194.6	84.3
5	(*R*)-**2b**/(*R*)-**6d**	157.1	314.6	77.7	183.1	87.3
6	(*S*)-**2b**/(*R*)-**6d**	156.9	314.7	78.4	182.9	87.6
7	(*R*)-**2b**/(*S*)-**6e**	156.9	316.0	76.1	183.0	87.0
8	(*S*)-**2b**/(*S*)-**6e**	157.1	316.1	76.0	182.4	87.1
9	(*S*)-**2a**/(*R*)-**6b**	147.0	324.8	102.8	187.6	86.3
10	(*S*)-**2a**/(*S*)-**6b**	147.4	324.6	103.3	189.6	85.3
11	(*R*)-**2c**/(*R*)-**6b**	157.1	310.2	103.9	193.5	83.6
12	(*R*)-**2c**/(*S*)-**6b**	155.5	309.8	104.1	193.0	85.1
13	(*R*)-**2d**/(*R*)-**6b**	154.7	310.2	106.8	196.8	82.9
14	(*R*)-**2d**/(*S*)-**6b**	152.0	311.4	105.8	195.9	83.6

From a more careful look on Table 2.2 the following general observations can be drawn:

- phosphinamine **6b** generally leads to the highest level of selectivity for the heterocomplex (from 81% up to 99%, depending on which phosphite it is combined with), while phosphinamines **6c-e**, combined with phosphite **2b**, all give similar levels of selectivity (from 70 up to 84%);

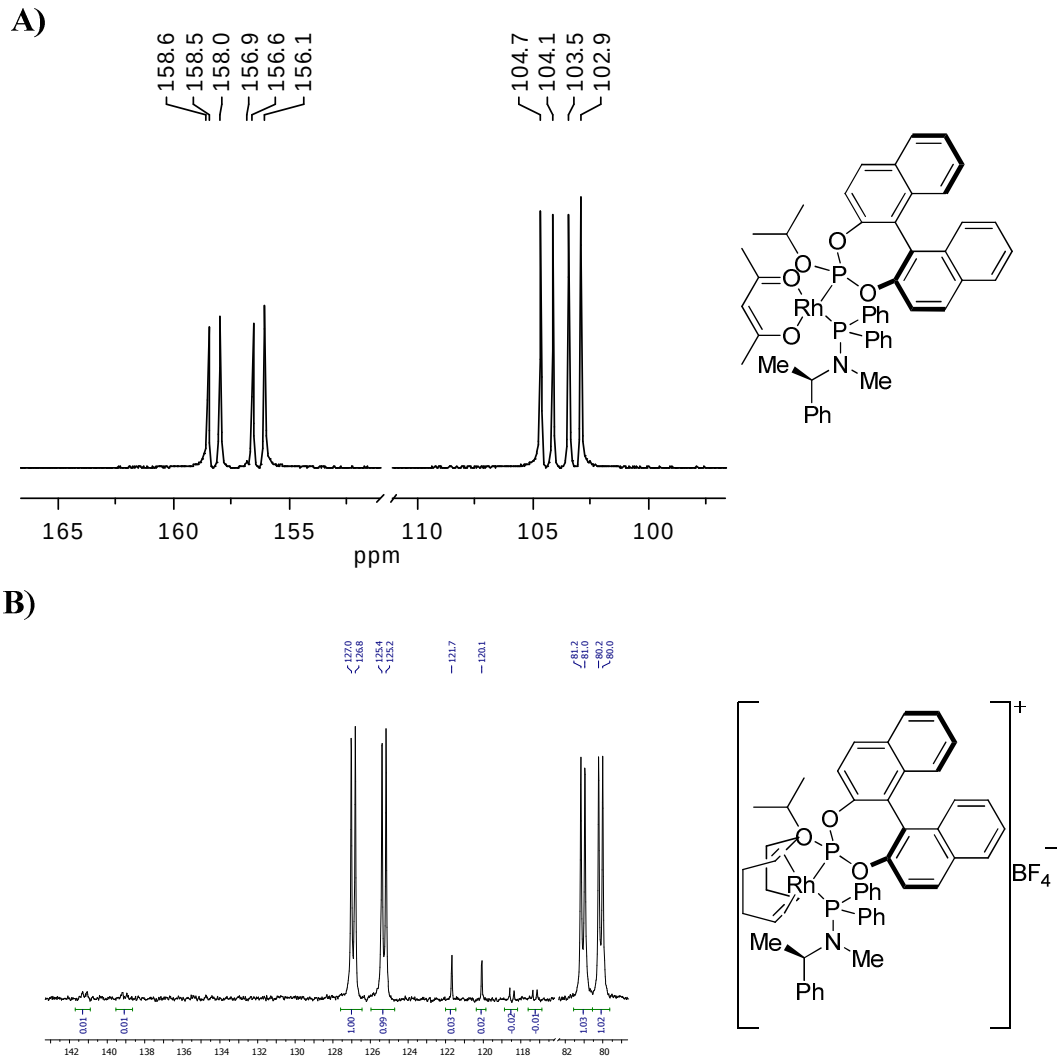
- A comparison between the selectivities observed with diastereoisomeric ligand combinations [for example (*S*)-**2a**/(*R*)-**6b** and (*S*)-**2a**/(*S*)-**6b**] denotes the presence of a moderate yet definite matched/mismatched effect, except for the combinations involving phosphite **6c**;
- The level of selectivity observed in all experiments is high enough to support the hypothesis of a thermodynamic bias in favour of the phosphite/phosphinamine heterocomplex.

When the C_2-symmetric SimplePhos ligand **6a** was combined with phosphite ligands, no selective formation of the heterocomplex was observed. On the contrary, an under-statistical quantity of heterocomplex (about 2 : 8 heterocomplex/homocomplexes) formed, using the hetrocombination (*R*,*R*)-**6a**/(*R*)-**2b** (Scheme 2.14). Taken together with the observation that **6a**, in the presence of $Rh(acac)(C_2H_4)_2$, forms exclusively its mono-complex, the lack of selectivity observed in this case can be ascribed to steric factors: bulky **6a** does not allow (or hardly does) other ligands to occupy the adjacent *cis* position around the rhodium atom.



Scheme 2.14 ^{31}P-NMR spectra of the rhodium complexes resulting from the combination of $Rh(acac)(C_2H_4)_2$ with ligands (*R*,*R*)-**6a** and (*R*)-**2b**, where (■) = $[Rh(acac)\mathbf{2b}_2]^+$ homocomplex; (●) = $[Rh(acac)(C_2H_4)\ \mathbf{6a}]^+$ homocomplex; (*) = $[Rh(acac)(\mathbf{2b})(\mathbf{6a})]^+$ heterocomplex

The complexation experiment on the combination (*R*)-**2b**/(*R*)-**6b** (Scheme 2.15 A), which had given the highest level of selectivity for the heterocomplex, was repeated using a different rhodium source (Scheme 2.15 B): $Rh(cod)_2BF_4$ was chosen in order to reproduce more precisely the actual conditions of catalytic hydrogenations, where this complex is widely used.



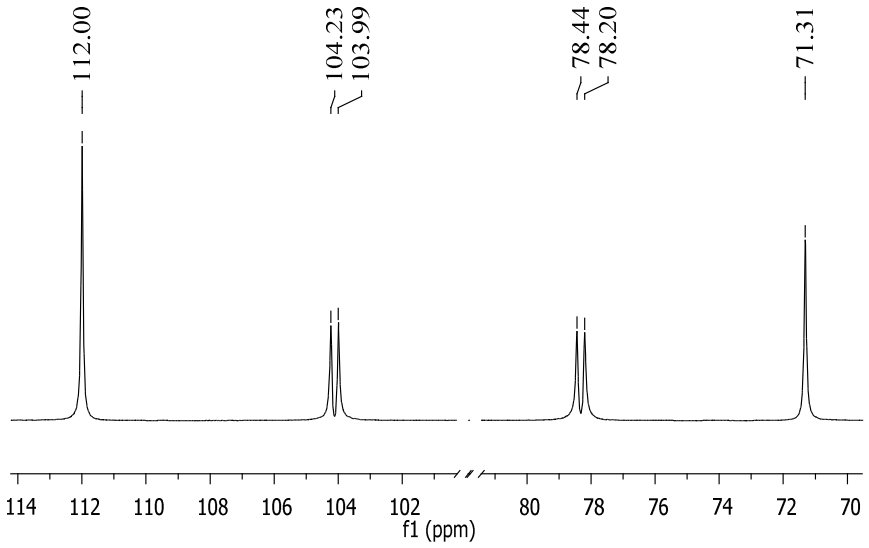
Scheme 2.15 ^{31}P-NMR spectra of the rhodium complexes resulting from the combination of ligands (*R*)-**2b**/(*R*)-**6b** with: A) Rh(acac)(C_2H_4)$_2$ and B) Rh(cod)$_2$$BF_4$

As it can be seen from Scheme 2.15 B, also in the presence of Rh(cod)$_2$$BF_4$ the heteroleptic complex forms almost quantitatively. The following coupling constants are observed: $^1J_{\text{Rh-phosphite}}$ = 264.6 Hz; $^1J_{\text{Rh-phosphinamine}}$ = 153.0 Hz; $^2J_{\text{P-P}}$ = 34.7 Hz. Such values, yet smaller than those observed in the presence of Rh(acac)(C_2H_4)$_2$, are still consistent with a *cis* disposition of the ligands, one of the two cod ligand having been displaced. This experiment demonstrates that the new thermodynamic approach is compatible with the conditions required for the catalysis of asymmetric hydrogenations and we were stimulated to start a catalytic screening (see Paragraph 2.2.4).

2.2.3.2 Complexation experiments with palladium (II)

Since the new strategy for self-assembly we are presenting relies on favourable electronic interactions between the ligands *through the metal*, the nature of the metal does obviously play a primary role in making it successful. As a consequence, a general extension of the method based on phosphite/phosphinamine combinations to any transition metal is not possible, and every metal has to be studied separately. On the other hand, it is perfectly possible that other 'complementary' classes of ligands give good results with metals where phosphites and phosphinamines fail.

We made a preliminary attempt to extend the use of phosphite/phosphinamine combinations to palladium (II), a metal having important applications in many catalytic reactions. Thus we treated $Pd(CH_3CN)_2Cl_2$ with the ligand combination (*R*)-**2b**/(*R*)-**6b** and studied, as above, the formed complexes by ^{31}P-NMR. The obtained spectrum is shown in Scheme 2.16.



Scheme 2.16 ^{31}P NMR spectrum of ligand combination (*R*)-**2b** and (*R*)-**6b** with $Pd(CH_3CN)_2Cl$

Since phosphorus and palladium nuclei do not couple, only the phosphorus-phosphorus coupling through palladium is visible, provided that the phosphorus atoms are diastereotopic. Thus, the mono- and homocomplexes give rise to singlet signals (the chemical shifts of the homocomplexes are: 112.0 ppm for the phosphite; 71.3 ppm for the phosphinamine), and the heterocomplex gives two doublets from which the coupling constant $^2J_{P\text{-}P}$ can be calculated.

As it can be seen in Scheme 2.16, a basically statistical distribution of hetero- and homocomplexes was obtained, with heterocomplex / homocomplexes ratio = 56 : 44 and $^2J_{P\text{-}P}$ = 36.9 Hz. The chemical shifts of the two doublets are 104.1 and 78.3 ppm.

If confirmed by a screening of several heterocombinations, this preliminary result seems to indicate that there is no thermodynamic preference for the phosphite/phosphinamine palladium heterocomplexes, unlike what happens with rhodium.

2.2.4 Catalytic screening of the phosphite/phosphinamine complexes

With a new method for selectively generation heteroleptic rhodium complexes in hands, we have begun to study their catalytic properties starting from the reaction on which we are most experienced, i.e. the enantioselective hydrogenation of pro-chiral olefins. The ligands that performed best in hydrogenations were subsequently screened also in palladium-catalyzed allylic alkylation reactions.

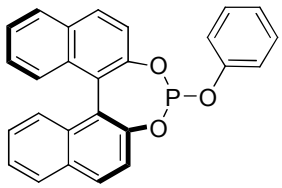
2.2.4.1 Rhodium(I)-catalyzed enantioselective hydrogenation of olefins

So far our libraries have been screened on several substrates: methyl 2-acetamidoacrylate **7**, *N*-(1-phenylvinyl)acetamide **8**, methyl 2-acetamidocinnamate **9**, methyl (*Z*)-3-acetamidocrotonate **10**, methyl 3-*N*-acetylamino-2-phenyl-2-propenoate **11**. This work of screening has been also carried out in collaboration with prof. De Vries (DSM-The Netherlands) and the results, which are not concluded yet, are summarised below.

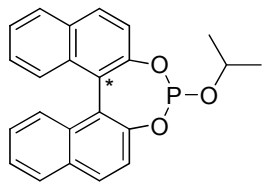
*2.2.4.1.1 Enantioselective hydrogenation of methyl 2-acetamidoacrylate **7***

The asymmetric hydrogenation of methyl 2-acetamidoacrylate **7** to give the methyl *N*-acetyl alanine methyl ester **12** was initially carried out in DCM at room temperature under atmospheric pressure. $Rh(cod)_2BF_4$ was used as the rhodium source with a 1 mol% loading. The pure ligands ("homocombinations") were used in a 2.2 mol% amount, while for the heterocombinations 1.1 mol% of each ligand was employed. The results of this screening are reported in Table 2.4.
All of the ligands employed in the catalytic screening described below are shown in Scheme 2.17.

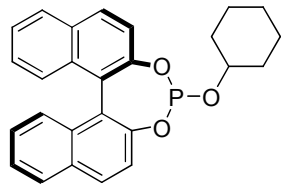
Phosphite library



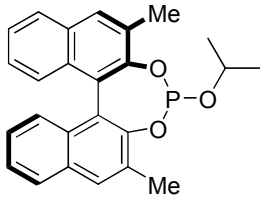
(*S*)-**2a**



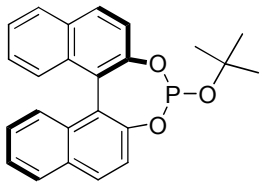
(*R*)- and (*S*)-**2b**



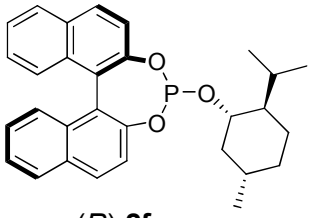
(*R*)-**2c**



(*R*)-**2d**

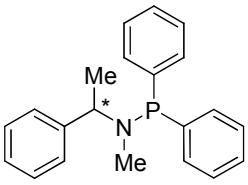


(*R*)-**2e**

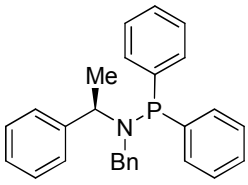


(*R*)-**2f**

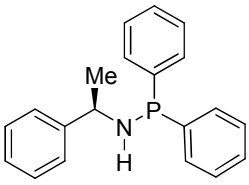
Phosphinamine library



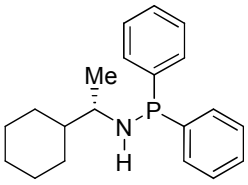
(*R*)- and (*S*)-**6b**



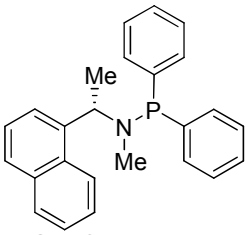
(*R*)-**6c**



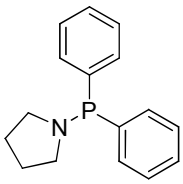
(*R*)-**6d**



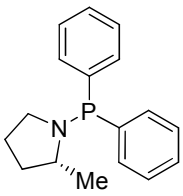
(*S*)-**6e**



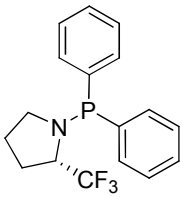
(*S*)-**6f**



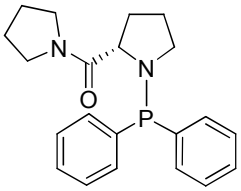
6g



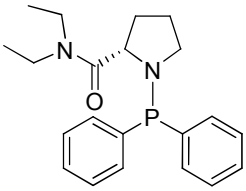
(*R*)-**6h**



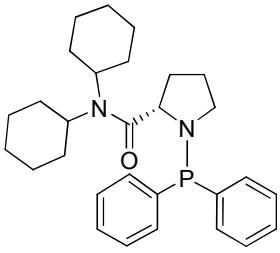
(*S*)-**6i**



(*S*)-**6j**

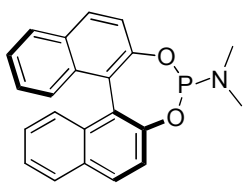


(*S*)-**6k**

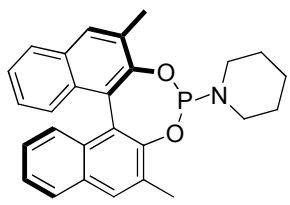


(*S*)-**6l**

Phosphoramidite library



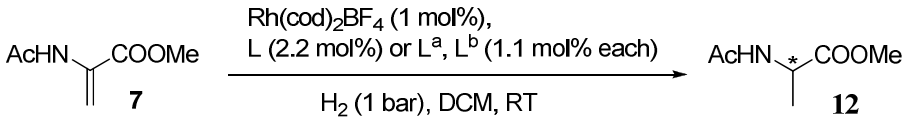
L1



L2

Scheme 2.17 Ligands employed in the Rh (I) catalyzed hydrogenation of pro-chiral olefins

Table 2.4 Rh(I)-catalyzed hydrogenations of methyl 2-acetamidoacrylte

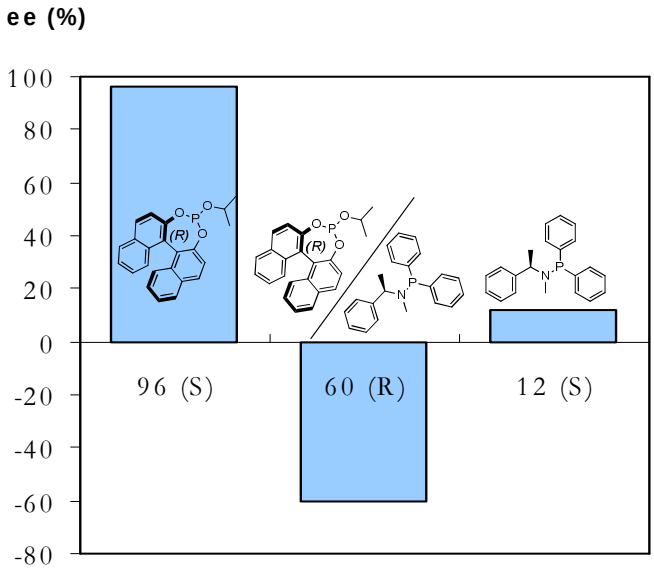


Entry	Ligands	After 16 h (1 bar H_2)	
		Conv. [%]	**e.e. [%] (abs. conf.)**
	Homocombinations		
1	(*S*)-**2a**	100	80 (*R*)
2	(*R*)-**2b**	100	96 (*S*)
3	(*S*)-**2b**	100	96 (*R*)
4	(*R*)-**2c**	100	97 (*S*)
5	(*R*)-**2d**	100	42 (*S*)
6	(*R*)-**2e**	100	95 (*S*)
7	(*R*)-**2f**	100	74 (*S*)
8	(*R*,*R*)-**6a**	0	-
9	(*R*)-**6b**	52	12 (*S*)
10	(*S*)-**6b**	57	12 (*R*)
11	(*R*)-**6c**	3	10 (*R*)
12	(*R*)-**6d**	100	6 (*R*)
13	(*S*)-**6e**	100	6 (*R*)
14	(*S*)-**6f**	0	-
15	**6g**	100	rac.
16	(*R*)-**6h**	74	6 (*R*)
17	(*S*)-**6i**	100	55 (*R*)
18	(*S*)-**6j**	15	28 (*S*)
19	(*S*)-**6l**	100	11 (*S*)
	Heterocombinations		
20	(*R*,*R*)-**6a**/(*R*)-**2b**	78	91 (*S*)
21	(*R*,*R*)-**6a**/(*R*)-**2c**	100	95 (*S*)
22	(*S*,*S*)-**6a**/(*R*)-**2c**	96	92 (*S*)
23	(*R*)-**6b**/(*S*)-**2a**	9	4 (*R*)
24	(*R*)-**6b**/(*R*)-**2b**	**87**	**60 (*R*)**
25	(*R*)-**6b**/(*R*)-**2c**	**85**	**46 (*R*)**
26	(*R*)-**6b**/(*R*)-**2d**	**34**	**13 (*R*)**
27	(*R*)-**6b**/(*R*)-**2e**	**70**	**20 (*R*)**
28	(*R*)-**6b**/(*R*)-**2f**	**45**	**32 (*R*)**
29	(*S*)-**6b**/(*S*)-**2a**	**13**	**6 (*S*)**
30	(*S*)-**6b**/(*R*)-**2b**	48	40 (*R*)
31	(*S*)-**6b**/(*R*)-**2c**	42	56 (*R*)
32	(*S*)-**6b**/(*R*)-**2d**	13	16 (*R*)
33	(*S*)-**6b**/(*R*)-**2e**	**67**	**12 (*R*)**
34	(*S*)-**6b**/(*R*)-**2f**	**44**	**20 (*R*)**
35	(*R*)-**6c**/(*S*)-**2a**	5	14 (*R*)
36	(*R*)-**6c**/(*R*)-**2b**	11	55 (*S*)
37	(*R*)-**6c**/(*S*)-**2b**	25	57 (*R*)
38	(*R*)-**6c**/(*R*)-**2c**	73	78 (*S*)
39	(*R*)-**6c**/(*R*)-**2d**	9	12 (*S*)

40	(*R*)-**6c**/(*R*)-**2e**	55	58 (*S*)
41	(*R*)-**6c**/(*S*)-**2e**	83	80 (*R*)
42	(*R*)-**6c**/(*R*)-**2f**	14	37 (*S*)
43	(*R*)-**6d**/(*S*)-**2a**	100	44 (*R*)
44	(*R*)-**6d**/(*R*)-**2b**	100	rac.
45	(*R*)-**6d**/(*S*)-**2b**	100	6 (*R*)
46	(*R*)-**6d**/(*R*)-**2c**	100	9 (*S*)
47	(*R*)-**6d**/(*R*)-**2d**	100	23 (*R*)
48	(*R*)-**6d**/(*R*)-**2e**	100	20 (*S*)
49	(*R*)-**6d**/(*S*)-**2e**	100	42 (*R*)
50	(*R*)-**6d**/(*R*)-**2f**	100	13 (*R*)
51	(*S*)-**6e**/(*S*)-**2a**	100	22 (*R*)
52	(*S*)-**6e**/(*R*)-**2b**	100	6 (*R*)
53	(*S*)-**6e**/(*S*)-**2b**	**100**	**40 (*S*)**
54	(*S*)-**6e**/(*R*)-**2c**	**100**	**9 (*S*)**
55	(*S*)-**6e**/(*R*)-**2d**	100	20 (*R*)
56	(*S*)-**6e**/(*R*)-**2e**	100	25 (*S*)
57	(*S*)-**6e**/(*S*)-**2e**	**100**	**19 (*S*)**
58	(*S*)-**6e**/(*R*)-**2f**	100	3 (*R*)
59	(*S*)-**6f**/(*S*)-**2a**	5	12 (*R*)
60	(*S*)-**6f**/(*R*)-**2b**	8	60 (*S*)
61	(*S*)-**6f**/(*S*)-**2b**	100	93 (*R*)
62	(*S*)-**6f**/(*R*)-**2c**	100	93 (*S*)
63	(*S*)-**6f**/(*R*)-**2d**	6	12 (*S*)
64	(*S*)-**6f**/(*R*)-**2e**	92	65 (*S*)
65	(*S*)-**6f**/(*S*)-**2e**	85	77 (*R*)
66	(*S*)-**6f**/(*R*)-**2f**	4	n.d.
67	**6g**(*R*)-**2e**	**100**	**14 (*R*)**
68	**6g**/(*R*)-**2c**	100	10 (*S*)
69	(*R*)-**6h**/(*R*)-**2b**	100	12 (*R*)
70	(*R*)-**6h**/(*S*)-**2b**	**100**	**50 (*S*)**
71	(*R*)-**6h**/(*R*)-**2c**	100	8 (*S*)
72	(*R*)-**6h**/(*R*)-**2e**	100	10 (*R*)
73	(*R*)-**6h**/(*R*)-**2f**	96	15 (*S*)
74	(*S*)-**6i**/(*R*)-**2b**	100	32 (*R*)
75	(*S*)-**6i**/(*S*)-**2b**	**100**	**78 (*S*)**
76	(*S*)-**6i**/(*R*)-**2c**	100	54 (*R*)
77	(*S*)-**6i**/(*R*)-**2e**	100	28(*R*)
78	(*S*)-**6i**/(*R*)-**2f**	100	16 (*S*)
79	(*S*)-**6j**/(*R*)-**2b**	97	77 (*S*)
80	(*S*)-**6j**/(*R*)-**2c**	94	79 (*S*)
81	(*S*)-**6j**/(*R*)-**2d**	96	31 (*S*)
82	(*S*)-**6j**/(*R*)-**2e**	100	84 (*S*)
83	(*S*)-**6j**/(*R*)-**2f**	100	60 (*S*)
84	(*S*)-**6k**/(*S*)-**2b**	100	82 (*R*)
85	(*S*)-**6l**/(*R*)-**2b**	100	91 (*S*)
86	(*S*)-**6l**/(*S*)-**2b**	80	70 (*R*)
87	(*S*)-**6l**/(*R*)-**2c**	10	11(*S*)
88	(*S*)-**6l**/(*R*)-**2e**	71	50 (*S*)
89	(*S*)-**6l**/(*R*)-**2f**	**7**	**8 (*R*)**

Unlike the phosphites, well known for their good catalytic properties in the hydrogenation processes,[10b,15] the phosphinamines behaved quite poorly in this reaction, providing *N*-acetyl alanine methyl ester with moderate to good conversions and with low enantiomeric excesses (see entries 8-20). SimplePhos ligand **6a**, possibly due to its considerable steric bulk, showed no activity at all. Its combinations with phosphites **2b** and **2c** showed a slightly decreased level of stereoselectivity compared to phosphite homocombinations, thus indicating that in this case the phosphite homocomplex is the basically only species capable of catalytic activity. This result is consistent with the observations made on the heterocombinations involving **6a** during the NMR studies (see Paragraph 2.2.3).

Much more interesting results could be obtained when C_1-symmetric phosphinamines were combined with phosphites: in several cases (entries 24-29, 33-34, 53-54, 70, 75 and 89, data in bold font) the 1:1 combination of BINOL-derived phosphite **2** and phosphinamine **6** induced reversal of the enantioselectivity in the hydrogenation of metyl 2-acetamidoacrylate, compared to both the phosphite and the phosphinamine alone. The typical example is shown in Scheme 2.18, where the combination (*R*)-**6b**/(*R*)-**2b** gave 60% e.e. for the enantiomer *R* of product **14** (Table 2.4, entry 24), while the homocomplexes of both ligand (*R*)-**6b** and (*R*)-**2b** are *S*-selective (Table 2.4, entry 9 and entry 2, respectively). This is clearly the sign that a heteroleptic catalyst is active in the hydrogenation reaction.



Scheme 2.18 Rh(I) catalyzed hydrogenation of methyl 2-acetamidoacrylate with ligands (*R*)-**6b** and (*R*)-**2b**: heteroleptic catalyst is active in the hydrogenation reaction

Similarly, the reversal of enantioselectivity observed when mixing chiral phosphite (*R*)-**2e** with achiral phosphinamine **6g** (Table 2.4, entry 67) can be determined by nothing but the heteroleptic complex which is formed around the rhodium centre.

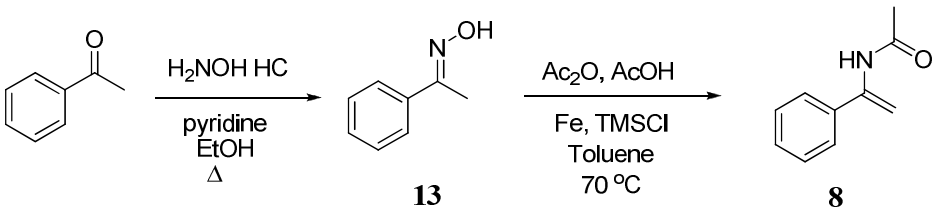
In several other cases the heterocombinations showed opposite stereochemical preference compared to one of the ligands: this kind of result can be considered indicative of a catalytic role played by

heterocomplex when the stereochemical preference of the more active ligand is reversed (entries 31, 32, 47, 50, 52, 55, 58, 69, 72, 74, 76, 77), which excludes that a mere competition between the two homocomplexes is taking place. For example, the combination (*S*)-**6b**/(*R*)-**2c** gave 56% e.e. for enantiomer *R* (Table 2.4, entry 31), thus reversing the stereochemical preference of the more active and selective ligand (*R*)-**2c** (which gave 97% e.e. for enantiomer *S*, 100% conversion, entry 4) and retaining that of phosphinamine (*S*)-**6b** (12% e.e. for enantiomer *R*, 57% conversion, entry 10): the fact that the stereochemical preference of the 'slower' ligand [(*S*)-**6b**] is retained indicates that a heteroleptic complex is determining the stereochemistry of the product in this case.

It should be noted that the above-discussed tendency to give this phenomenon of 'inversion' of the stereochemical preference is not the same for all phosphinamine ligands: it appears to be strong for ligands **6b** and **6e**, less marked for **6h**, **6i** and **6d**, absent in the heterocombinations involving **6f** and **6j**. This does not mean necessarily that the latter ligands do not form the heteroleptic complexes with phosphites. It might simply indicate that their heterocomplexes have the same stereochemical preference of the homocomplexes or are poorly active.

*2.2.4.1.2 Enantioselective hydrogenation of N-(1-phenylvinyl)acetamide **8***

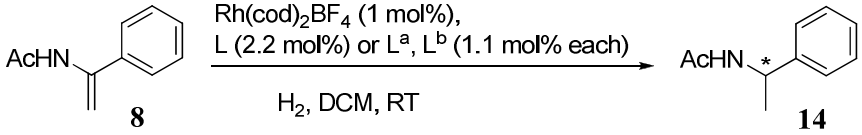
Asymmetric hydrogenation of enamides gives access to enantioenriched acylated amines that can be hydrolyzed to the free chiral amines.[16] We thus synthesized *N*-(1-phenylvinyl)acetamide from the acetophenone oxime **13**, which was acylated and then converted into the amide by a radical reaction in the presence of iron.[17] A small amount of trimethylsilyl chloride was added for activating the iron powder (Scheme 2.19).



Scheme 2.19 Synthesis of enamides from the corresponding ketone via the oxime

The ligand screening in the enantioselective hydrogenation of *N*-(1-phenylvinyl)acetamide **8** was carried out in DCM under 5 bar of hydrogen pressure. $Rh(cod)_2BF_4$ was used as the rhodium source with a 1 mol% loading. The pure ligands ("homocombinations") were used in a 2.2 mol% amount, while for the heterocombinations 1.1 mol% of each ligand was employed. The results of the screening are summarised above in Table 2.5. The ligands are shown in Scheme 2.17.

Table 2.5 Rh(I)-catalyzed hydrogenations of *N*-(1-phenylvinyl)acetamide



Entry	Ligands	After 16 h (5 bar H_2)	
		Conv. [%]	**e.e. [%] (abs. conf.)**
	Homocombinations		
1	(*S*)-**2a**	100	86 (*R*)
2	(*R*)-**2b**	100	92 (*S*)
3	(*S*)-**2b**	100	92 (*R*)
4	(*R*)-**2c**	100	90 (*S*)
5	(*R*)-**2d**	100	6 (*S*)
6	(*R*)-**2e**	100	79 (*S*)
7	(*R*)-**2f**	100	77 (*S*)
8	(*R*,*R*)-**6a**	30	29 (*R*)
9	(*R*)-**6b**	83	7 (*R*)
10	(*S*)-**6b**	74	7 (*S*)
11	(*R*)-**6c**	53	4 (*S*)
12	(*R*)-**6d**	100	12 (*R*)
13	(*S*)-**6e**	100	4 (*R*)
14	(*S*)-**6f**	38	10 (*S*)
15	**6g**	100	rac.
16	(*R*)-**6h**	100	26 (*S*)
17	(*S*)-**6i**	100	70 (*S*)
18	(*S*)-**6j**	30	12 (*S*)
19	(*S*)-**6k**	30	12 (*S*)
20	(*S*)-**6l**	40	rac.
	Heterocombinations		
21	(*R*,*R*)-**6a**/(*R*)-**2e**	99	89 (*S*)
22	(*R*)-**6b**/(*S*)-**2a**	15	rac.
23	(*R*)-**6b**/(*R*)-**2b**	99	57 (*R*)
24	(*R*)-**6b**/(*R*)-**2c**	80	56 (*R*)
25	(*R*)-**6b**/(*R*)-**2d**	95	29 (*R*)
26	(*R*)-**6b**/(*R*)-**2e**	99	61 (*S*)
27	(*R*)-**6b**/(*R*)-**2f**	100	51 (*R*)
28	(*S*)-**6b**/(*S*)-**2a**	49	17 (*S*)
29	(*S*)-**6b**/(*R*)-**2b**	**96**	**38 (*R*)**
30	(*S*)-**6b**/(*R*)-**2c**	**92**	**31 (*R*)**
31	(*S*)-**6b**/(*S*)-**2b**	98	40 (*S*)
32	(*R*)-**6c**/(*S*)-**2a**	**78**	**9 (*S*)**
33	(*R*)-**6c**/(*R*)-**2b**	60	6 (*S*)
34	(*R*)-**6c**/(*R*)-**2c**	**70**	**12 (*R*)**
35	(*R*)-**6c**/(*R*)-**2e**	77	12 (*S*)
36	(*R*)-**6c**/(*R*)-**2f**	44	20 (*S*)
37	(*R*)-**6c**/(*S*)-**2b**	99	44 (*R*)
38	(*R*)-**6d**/(*S*)-**2a**	60	8 (*R*)

39	(*R*)-**6d**/(*R*)-**2b**	100	60 (*S*)
40	(*R*)-**6d**/(*R*)-**2c**	100	rac.
41	(*R*)-**6d**/(*R*)-**2e**	100	22 (*S*)
42	(*R*)-**6d**/(*R*)-**2f**	100	rac.
43	(*R*)-**6d**/(*S*)-**2b**	100	4 (*R*)
44	(*S*)-**6e**/(*S*)-**2a**	**100**	**36 (*S*)**
45	(*S*)-**6e**/(*R*)-**2b**	100	6 (*S*)
46	(*S*)-**6e**/(*R*)-**2c**	100	rac.
47	(*S*)-**6e**/(*R*)-**2e**	100	18 (*S*)
48	(*S*)-**6e**/(*R*)-**2f**	100	17 (*R*)
49	(*S*)-**6e**/(*S*)-**2b**	**100**	**43 (*S*)**
50	(*S*)-**6e**/(*S*)-**2e**	100	27 (*R*)
51	(*S*)-**6f**/(*S*)-**2a**	30	rac.
52	(*S*)-**6f**/(*R*)-**2b**	35	16 (*S*)
53	(*S*)-**6f**/(*R*)-**2c**	**39**	**11 (*R*)**
54	(*S*)-**6f**/(*R*)-**2e**	79	22 (*S*)
55	(*S*)-**6f**/(*R*)-**2f**	30	rac.
56	(*S*)-**6f**/(*S*)-**2b**	75	9 (*S*)
57	(*S*)-**6f**/(*S*)-**2c**	n.a.	n.a.
58	(*R*)-**6h**/(*R*)-**2b**	**100**	**58 (*R*)**
59	(*R*)-**6h**/(*R*)-**2c**	**100**	**60 (*R*)**
60	(*R*)-**6h**/(*R*)-**2e**	100	10 (*S*)
61	(*R*)-**6h**/(*R*)-**2f**	**100**	**40 (*R*)**
62	(*R*)-**6h**/(*S*)-**2b**	100	72 (*S*)
63	(*S*)-**6i**/(*S*)-**2b**	100	60 (*S*)
64	(*S*)-**6i**/(*R*)-**2c**	**100**	**54 (*R*)**
65	(*S*)-**6i**/(*R*)-**2d**	**100**	**24 (*R*)**
66	(*S*)-**6i**/(*R*)-**2e**	100	20 (*S*)
67	(*S*)-**6i**/(*R*)-**2f**	**100**	**44 (*R*)**
68	(*S*)-**6i**/(*R*)-**2b**	**100**	**53 (*R*)**
69	(*S*)-**6j**/(*R*)-**2b**	100	84 (*S*)
70	(*S*)-**6j**/(*R*)-**2c**	100	83 (*S*)
71	(*S*)-**6j**/(*R*)-**2d**	100	6 (*S*)
72	(*S*)-**6j**/(*R*)-**2e**	100	73 (*S*)
73	(*S*)-**6j**/(*R*)-**2f**	n.a.	n.a.
74	(*S*)-**6k**/(*R*)-**2b**	100	82 (*S*)
75	(*S*)-**6k**/(*R*)-**2c**	100	80 (*S*)
76	(*S*)-**6k**/(*R*)-**2e**	98	70 (*S*)
77	(*S*)-**6k**/(*R*)-**2f**	100	56 (*S*)
78	(*S*)-**6k**/(*S*)-**2b**	100	84 (*R*)
79	(*S*)-**6l**/(*R*)-**2b**	99	64 (*S*)
80	(*S*)-**6l**/(*S*)-**2b**	100	86 (*R*)

Similarly to what observed for methyl 2-acetamidoacrylate **7**, phosphinamines appear to be quite poor ligands for the hydrogenation of *N*-(1-phenylvinyl)acetamide **8**, especially in terms of enantioselectivity (e.e. from 4 to 70%, entries 8-20), whereas the phosphite ligands allow to obtain good levels of conversion and stereoselectivity (entries 1-4) with the exception of 3,3'-methyl substituted BINOL-derived phosphite (*R*)-**2d** (entry 5).

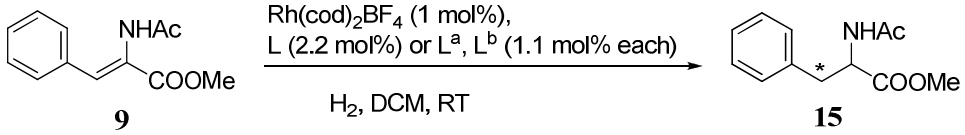
Also with substrate **8** we could observe in many cases (entries 29, 30, 32, 34, 44, 49, 53, 58, 59, 61, 64, 65, 67-69, data in bold font) that the phosphite/phosphinamine heterocombination have stereochemical preference opposite to that of both ligands, which indicates that the heterocomplex plays a major role in determining the reaction outcome. As in the hydrogenation of methyl 2-acetamidoacrylate, also here some phosphinamines (**6b**, **6e**, **6h**, **6i**, **6j**) showed a more marked tendency than others (**6f**, **6k**, **6l**) to give the inversion of the stereochemical preference. Unfortunately, the maximum level of enantioselectivity that could be obtained with these combinations is only moderate [60% e.e. for enantiomer *R* obtained with the combination (*R*)-**6h**/(*R*)-**2c**], Table 2.7, entry 59], significantly lower than that of the phosphite homocombination [(*R*)-**2c** gave 90% e.e. for enantiomer *S*].

Several other heterocombinations gave stereochemical preference opposite to that of one of the ligands (entries 21, 25, 26, 31, 37, 39, 41, 45, 47, 48, 62, 63, 78), which can be attributed to the heterocomplex, when it is the preference of the more active ligand to be reversed.

*2.2.4.1.3 Enantioselective hydrogenation of methyl 2-acetamidocinnamate **9***

The asymmetric hydrogenation of methyl 2-acetamidocinnamate **9** to give the *N*-acetylphenylalanine methyl ester **15** was investigated also. The library screening including phosphites, phosphinamines and phosphoramidites (Scheme 2.17) was performed with a Premex A-96 multireactor or with the Argonaut Endeavor multireactor autoclave. Hydrogenation reactions were performed in parallel at room temperature in dichloromethane with 25 bar hydrogen pressure. $Rh(cod)_2BF_4$ was used as the rhodium source with a 1 mol% loading. The pure ligands ("homocombinations") were used in a 2.2 mol% amount, while for the heterocombinations 1.1 mol% of each ligand was employed. The selected screening results are shown in Table 2.6.

Table 2.6 Rh(I)-catalyzed hydrogenations of methyl 2-acetamidocinnamate with selected ligands



9 **15**

Entry	Ligands	After 16 h (25 bar H_2)	
		Conv. [%]	**e.e. [%]**[a]
	Homocombinations		
1	(*R*)-**2a**	n.a.	n.a.
2	(*S*)-**2b**	100	89
3	(*R*)-**2b**	100	-89
4	(*R*)-**L2**	100	-92

5	(*R*)-**6b**	4[b]	-3
6	(*R*)-**6e**	100	-24
7	(*R*)-**6h**	100	4
8	(*S*)-**6i**	100	-14
9	(*S*)-**6j**	73	-27
	Heterocombinations		
10	(*R*)-**6b**/(*S*)-**2b**	93	-23
11	**(*R*)-6b/(*R*)-2b**	**7**	**43**
12	(*R*)-**6e**/(*S*)-**L2**	100	-89
13	**(*R*)-6h/(*S*)-2b**	**100**	**-55**
14	(*R*)-**6h**/(*R*)-**2b**	100	17
15	(*S*)-**6i**/(*S*)-**2b**	100	-81
16	**(*S*)-6i/(*R*)-2b**	**100**	**36**
17	(*S*)-**6i**/(*S*)-**L2**	100	-79
18	(*S*)-**6j**/(*S*)-**2b**	100	86

[a] Absolute configurations were not determined; [b] e.e. value could not be determined accurately due to low conversion.

A similar trend was observed in the Rh(I)-catalyzed asymmetric hydrogenation of methyl 2-acetamidocinnamate **9** with selected ligands (Table 2.6). Phosphinamines appear to be quite poor ligands for the hydrogenation of **9**, especially in terms of enantioselectivity (e.e. from 3 to 27%, Table 5.7, entries 4-8), whereas the phosphite and phosphoramidite ligands allow to obtain good levels of conversion and stereoselectivity (entries 1-3).

Also in the case of methyl 2-acetamidocinnamate we could observe that the phosphite/phosphinamine heterocombinations gave inversion of stereochemical preference to that of both ligands (Table 2.6, entries 11, 13, and 16, data in bold font), which indicates that the heterocomplex plays a major role in determining the reaction outcome.

In few cases the heterocombination showed opposite stereochemical preference compared to the more active ligand, which excludes that a mere competition between the two homocomplexes is taking place (Table 2.6, entries 10 and 15). For example, the combination (*S*)-**6i**/(*S*)-**2b** gave -81% e.e. (Table 2.6, entry 15), thus reversing the stereochemical preference of the more active and selective ligand (*S*)-**2b** (which gave 89 % e.e. entry 2) and retaining that of phosphinamine (*S*)-**6i** (-14% e.e., entry 8): the fact that the stereochemical preference of the 'slower' ligand [(*S*)-**6i**] is retained indicates that a heteroleptic complex is determining the stereochemistry of the product in this case.

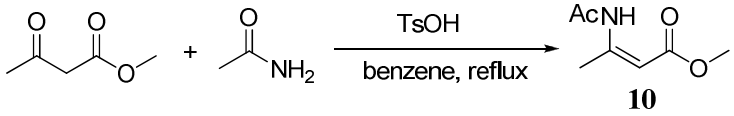
The combinations of the phosphinamines with phosphoramidite ligands give a slightly decreased level of stereoselectivity compared to its homocombination without any inversion of stereocontrol.

*2.2.4.1.4 Enantioselective hydrogenation of methyl (Z)-3-acetamidocrotonate **10***

Another important class of compounds used in the development of drugs is β-amino acids. These can be made by hydrogenation of the corresponding dehydro β-amino acids. There is a large

difference in behaviour of *E*- and *Z*-enamides in the hydrogenation.[18] The Z-isomer is generally more difficult to hydrogenate than *E*-izomer and usually gives the product with lower enantioselectivity. This could be explained by an intramolecular hydrogen bond between the NH of the amide and carbonyl of the ester, which makes the coordination of the substrate to the rhodium more difficult leading to lower reaction rates and enantioselectivities.

The enantioselective hydrogenation of β-acylamino acrylates[19] gives access to chiral β-amino acid derivatives which are important pharmaceutical building blocks.[20] For this reason, the selected ligand library was screened in the hydrogenation of methyl (*Z*)-3-acetamidocrotonate **10** to give methyl-3-acetamidobutanoate **16**. The substrate was prepared in excellent yield in a one-step condensation and dehydration reaction of methyl 3-oxobutanoate with acetamide (Scheme 2.20).[21]

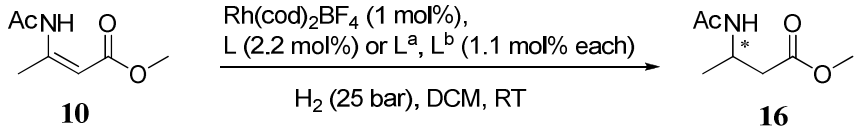


10

Scheme 2.20 Synthesis of methyl (*Z*)-3-acetamidocrotonate

The hydrogenation of methyl (*Z*)-3-acetamidocrotonate **10** with selective ligands was performed by using Premex A-96 multireactor. Hydrogenation reactions were performed in parallel at room temperature in dichloromethane with 25 bar hydrogen pressure. $Rh(cod)_2BF_4$ was used as the rhodium source with a 1 mol% loading. The pure ligands ("homocombinations") were used in a 2.2 mol% amount, while for the heterocombinations 1.1 mol% of each ligand was employed. The results are reported in Table 2.7.

Table 2.7 Rh(I)-catalyzed hydrogenations of (*Z*)-3-acetamidocrotonate with selected ligands



10 **16**

Entry	Ligands	After 16 h (25 bar H_2)	
		Conv. [%]	**e.e. [%][a]**
	Homocombinations		
1	(*R*)-**6b**	0	-
2	(*R*)-**6e**	90	19
3	(*R*)-**6h**	8	rac.
4	(*S*)-**6i**	39	31
5	(*S*)-**6j**	0	-
	Heterocombinations		
6	(*R*)-**6b**/(*R*)-**2a**	0	-
7	(*R*)-**6b**/(*S*)-**2b**	0	-
8	(*R*)-**6b**/(*S*)-**L1**	3	20

9	(*R*)-**6b**/(*S*)-**L2**	0	-
10	(*R*)-**6e**/(*R*)-**2a**	83	-18
11	(*R*)-**6e**/(*S*)-**2b**	97	22
12	(*R*)-**6e**/(*S*)-**L1**	96	26
13	(*R*)-**6e**/(*S*)-**L2**	74	5
14	(*R*)-**6h**/(*R*)-**2a**	76	2
15	(*R*)-**6h**/(*S*)-**2b**	97	32
15	(*R*)-**6h**/(*S*)-**L1**	59	22
17	(*R*)-**6h**/(*S*)-**L2**	9	10
18	(*S*)-**6i**/(*R*)-**2a**	82	38
19	(*S*)-**6i**/(*S*)-**2b**	98	17
20	(*S*)-**6i**/(*S*)-**L1**	58	28
21	(*S*)-**6i**/(*S*)-**L2**	44	36
22	(*S*)-**6j**/(*R*)-**2a**	2[b]	-10
23	(*S*)-**6j**/(*S*)-**2b**	7	24
24	(*S*)-**6j**/(*S*)-**L1**	1[b]	6
25	(*S*)-**6j**/(*S*)-**L2**	2[b]	11

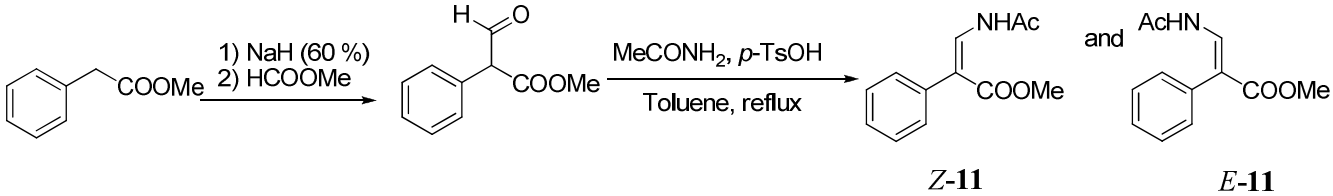
[a] Absolute configurations were not determined; [b] e.e. value could not be determined accurately due to low conversion.

Unfortunately, as it can be seen from the results (Table 2.7), all tested phosphinamine combinations either with phosphite (**2a** or **2b**) or with phosphoramidite (**L1** or **L2**) behaved very poorly showing low activity and selectivity. We did not try to use more polar or protic solvents in order to break intramolecular hydrogen bond in the substrate or to use another isomer (*E*)-3-acetamidocrotonate.

*2.2.4.1.5 Enantioselective hydrogenation of methyl 3-*N*-acetylamino-2-phenyl-2-propenoate **11***

The hydrogenation of α-substituted β-amidoacrylates gives β^2-amino acid derivatives, which have a potential for two stereogenic centres at C2 in their backbone. These compounds are building blocks for the synthesis of β-peptides and thus are the object of a wide interest.

An isomeric mixture of the substrates *Z*-**11** and *E*-**11** was readily prepared from commercially available methyl phenylacetate by formylation and condensation of the resulting formyl esters X with acetamide (Scheme 2.21).[22]



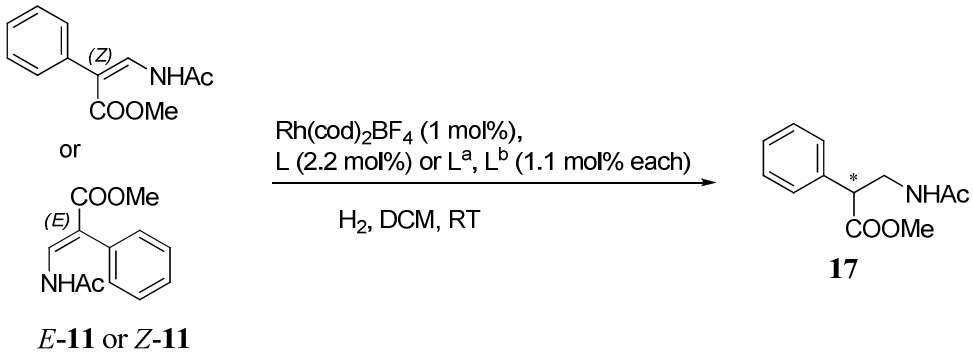
Z-**11** *E*-**11**

Scheme 2.21 Synthesis of methyl 3-*N*-acetylamino-2-phenyl-2-propenoate

Intramolecular hydrogen bonding between the β-amide hydrogen and ester carbonyl group in the (*Z*)-isomer was evident in the ^{1}H NMR spectra, where a significant downfield shift of the β-amide proton

(δ 10–11) was observed. The (*E*)- and (*Z*)-isomers could be readily separated by conventional column chromatography.

The hydrogenation of methyl 3-*N*-acetylamino-2-phenyl-2-propenoate **11** with selective ligands was performed by using Premex A-96 multireactor. Hydrogenation reactions were performed in parallel at room temperature in dichloromethane with 25 bar hydrogen pressure. $Rh(cod)_2BF_4$was used as the rhodium source with a 1 mol% loading. The pure ligands ("homocombinations") were used in a 2.2 mol% amount, while for the heterocombinations 1.1 mol% of each ligand was employed (Scheme 2.22).



E-**11** or *Z*-**11**

Scheme 2.22 Rh(I)-catalyzed hydrogenation of methyl 3-*N*-acetylamino-2-phenyl-2-propenoate

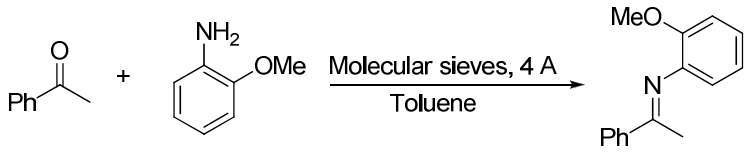
Unfortunately, hydrogenation reactions employing combinations of phosphinamines ((*R*)-**6b**, (*R*)-**6e**, (*R*)-**6h**, (*S*)-**6i**, (*S*)-**6j**) with phosphites [(*R*)-**2a** and (*S*)-**2b**] or phosphoramidites (**L1** or **L2**) in DCM led to product with only poor conversions (up to 18% for *E*-**10** and up to 5% for *Z*-**10**). Therefore, enantiomeric accesses were determined.

2.2.4.2 Iridium-catalyzed enantioselective hydrogenation of imines

Literature precedents have shown that iridium is the metal of choice in the hydrogenation of imines.[23] We were interested in investigating whether iridium complexes of our chiral monodentate phosphinamines with phosphites or phosphoramidites could also act as efficient enantioselective hydrogenation catalysts. Our initial studies were aimed at the preparation of cationic iridium complexes containing a phosphinamine ligand L^a, and either the same phosphinamine, a phosphite, or phosphoramidite as the secondary ligand L^b. Two equivalents of ligand (in case of homocombinations) or one equivalent of each ligand were treated with $[Ir(cod)Cl]_2$ to the corresponding pre-catalysts (presumably of formula $[Ir(cod)L_2]^+$ and $[Ir(cod)L^aL^b]^+$ respectively). We briefly investigated the scope of the catalyst with two imine substrates.

2.2.4.2.1 Enantioselective hydrogenation of N*-(2-Methoxy-phenyl)-(1-phenyl-ethylidene)-amine*

Asymmetric hydrogenation of *N*-(2-Methoxy-phenyl)-(1-phenyl-ethylidene)-amine **18** was chosen as a model reaction. The substrate synthesis is very simple and product was obtained in quantitative yield in one step from acetophenone and *o*-anisidine (Scheme 2.23).

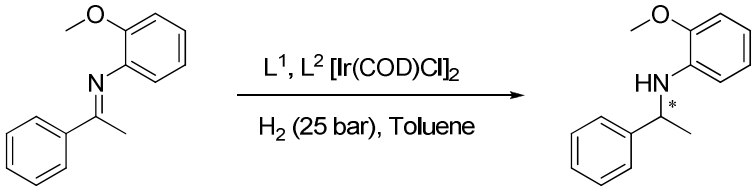


18

Scheme 2.23 Synthesis of *N*-(2-Methoxy-phenyl)-(1-phenyl-ethylidene)-amine **18**

The hydrogenation reactions employing phosphinamine combinations [(*R*)-**6b**, (*R*)-**6e**, (*R*)-**6h**, (*S*)-**6i**, (*S*)-**6j**] with phosphites [(*R*)-**2a** and (*S*)-**2b**] or phosphoramidites (**L1** or **L2**) were performed by using Premex A-96 multireactor. Hydrogenation experiments were performed in parallel at room temperature in dichloromethane with 25 bar hydrogen pressure. $[Ir(cod)Cl]_2$ was used as the iridium source with a 1 mol% loading. The pure ligands ("homocombinations") were used in a 2.2 mol% amount, while for the heterocombinations 1.1 mol% of each ligand was employed. The results are reported in Table 2.8.

Table 2.8 Ir-catalyzed hydrogenation of *N*-(2-Methoxy-phenyl)-(1-phenyl-ethylidene)-amine



18 **19**

Entry	Ligands	After 16 h (25 bar H_2)	
		Conv. [%]	**e.e. [%]**[a]
	Homocombinations		
1	(*R*)-**6b**	1	n.a.
2	(*R*)-**6e**	32	n.a.
3	(*R*)-**6h**	2	n.a.
4	(*S*)-**6i**	0	n.a.
	Heterocombinations		
6	(*R*)-**6b**/(*R*)-**2a**	94	0
7	(*R*)-**6b**/(*S*)-**2b**	100	0
8	(*R*)-**6b**/(*S*)-**L1**	9	n.a.
9	(*R*)-**6b**/(*S*)-**L2**	12	n.a.
10	(*R*)-**6e**/(*R*)-**2a**	20	9
11	(*R*)-**6e**/(*S*)-**2b**	31	30
12	(*R*)-**6e**/(*S*)-**L1**	7	n.a.

13	(*R*)-**6e**/(*S*)-**L2**	4	n.a.
14	(*R*)-**6h**/(*R*)-**2a**	65	-1
15	(*R*)-**6h**/(*S*)-**2b**	88	0
15	(*R*)-**6h**/(*S*)-**L1**	8	n.a.
17	(*R*)-**6h**/(*S*)-**L2**	15	n.a.
18	(*S*)-**6i**/(*R*)-**2a**	100	-5
19	(*S*)-**6i**/(*S*)-**2b**	100	-6
20	(*S*)-**6i**/(*S*)-**L1**	14	n.a.
21	(*S*)-**6i**/(*S*)-**L2**	14	n.a.

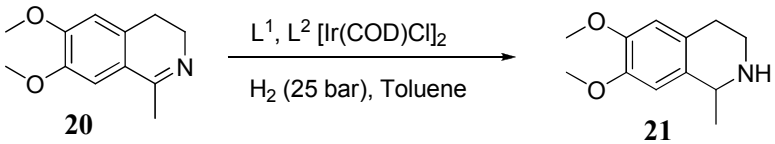
[a] Absolute configurations were not determined; n.a. – not analyzed.

As it can be seen in Table 2.8, phosphinamines are poorly active ligands also in the Ir-catalyzed hydrogenation. The highest conversion (32 %) was observed with ligand (*R*)-**6e** (entry 2). However, the ligand heterocombinations led to notably high activities. In particular, in the case of combinations (*R*)-**6b**/(*S*)-**2b**, (*S*)-**6i**/(*R*)-**2a**, and (*S*)-**6i**/(*S*)-**2b** (Table 2.8, entries 7, 18 and 19), full conversions were obtained. Unfortunately, we observed low levels of enantioselectivity (up to 30 % e.e.; samples with conversion lower than 20 % were not analyzed by chiral HPLC).

*2.2.4.2.2 Enantioselective hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroxyisoquinoline **20***

We next studied the hydrogenation of isoquinoline **20**, which led to the formation of 1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-isoquinoline **21**. For the initial screening phosphinamines [(*R*)-**6b**, (*R*)-**6e**, (*R*)-**6h**, (*S*)-**6i**, (*S*)-**6j**)], phosphites [(*R*)-**2a** and (*S*)-**2b**)] or phosphoramidites (**L1** or **L2**) were employed. The reactions were performed in a Premex A-96 multireactor. Hydrogenation reactions were performed in parallel at room temperature in dichloromethane under 25 bar hydrogen pressure. $[Ir(cod)Cl]_2$ was used as the iridium source with a 1 mol% loading. The pure ligands ("homocombinations") were used in a 2.2 mol% amount, while for the heterocombinations 1.1 mol% of each ligand was employed. The results are reported in Table 2.10.

Table 2.9 Ir-catalyzed hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroxyisoquinoline in a Premex A-96 multireactor



20 **21**

Entry	Ligands	After 16 h (25 bar H_2)	
		Conv. [%]	**e.e. [%]**[a]
	Homocombinations		
1	(*R*)-**6b**	1	n.a.
2	(*R*)-**6e**	24	n.a.
3	(*R*)-**6h**	0	-
4	(*S*)-**6i**	0	-

Heterocombinations			
6	(*R*)-**6b**/(*R*)-**2a**	29	n.a.
7	(*R*)-**6b**/(*S*)-**2b**	41	43
8	(*R*)-**6b**/(*S*)-**L1**	37	-3
9	(*R*)-**6b**/(*S*)-**L2**	56	-58
10	(*R*)-**6e**/(*R*)-**2a**	89	17
11	**(*R*)-6e/(*S*)-2b**	**91**	**63**
12	(*R*)-**6e**/(*S*)-**L1**	39	4
13	(*R*)-**6e**/(*S*)-**L2**	68	4
14	(*R*)-**6h**/(*R*)-**2a**	52	1
15	(*R*)-**6h**/(*S*)-**2b**	32	44
15	(*R*)-**6h**/(*S*)-**L1**	62	11
17	(*R*)-**6h**/(*S*)-**L2**	57	-49
18	(*S*)-**6i**/(*R*)-**2a**	76	13
19	(*S*)-**6i**/(*S*)-**2b**	44	47
20	(*S*)-**6i**/(*S*)-**L1**	8	n.a.
21	(*S*)-**6i**/(*S*)-**L2**	42	n.a.

[a] Absolute configurations were not determined; n.a. – not analyzed.

Similarly to what observed for *N*-(2-Methoxy-phenyl)-(1-phenyl-ethylidene)-amine **18**, phosphinamines appear to be quite poor ligands for the hydrogenation of **20**, and gave almost no reaction. Again, the highest conversion (up to 24%) was observed with ligand (*R*)-**6e** (Table 2.9, entry 2), while other phosphinamines showed no activity. Also in this case the enantiomeric access was not analysed.

Also with substrate **20**, we could observe in many cases that the phosphinamine/phosphite or phosphinamine/phosphoramidite heterocombination lead to increased conversions. The combination (*R*)-**6e**/(*S*)-**2b** gave the most interesting result, furnishing product **21** with 63% e.e. and almost complete conversion. Thus, we decided to investigate these results more in detail: we took four ligands our library [(*R*)-**6b**, (*R*)-**6e**, (*S*)-**2b** and **L2**] and compared the results of the Premex A-96 (96 high-pressure reactors) screening with those obtained with the Endeavor multireactor (8 autoclaves) (Table 2.10).

Table 2.10 Ir-catalyzed hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroxyisoquinoline in the Endeavor multireactor

Entry	**Ligands**	**After 16 h (25 bar H_2)**	
		Conv.[%][a]	**e.e. [%]**[b]
homocombinations			
1	(*R*)-**6b**	n.d.	13
2	(*R*)-**6e**	39	13
3	(*S*)-**2b**	55	55
4	(*R*)-**L2**	39	-46
heterocombinations			

5	(*R*)-**6b**/(*R*)-**L2**	40	-40
6	(*R*)-**6e**/(*S*)-**2b**	89	52

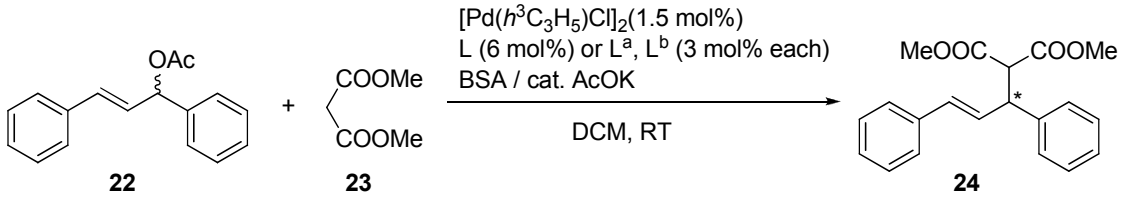
[a] conversions were estimated from the chiral HPLC % areas using the calibration straight line obtained, in the Premex-96 experiment, by plotting the conversions determined by achiral GC against the chiral HPLC % areas;
[a] Absolute configurations were not determined; n.d. = not determined.

Unfortunately, every further attempt to reproduce the best result obtained with combination (*R*)-**6e**/(*S*)-**2b** failed, although the effect of every single parameter on the reaction outcome was investigated. It was thus decided to end up the experiments on iridium catalyzed hydrogenations.

2.2.4.3 Palladium-catalyzed enantioselective allylic alkylation

In the attempt to extend the use of phosphite/phosphinamine combinations to palladium(II), we also performed a screening of our phosphite and phosphinamine libraries (Scheme 2.11) in the enantioselective allylic alkylation of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **22** with dimethyl malonate **23**. The reactions were carried out in DCM in the presence of $[Pd(\eta^3C_3H_5)Cl]_2$ (1.5 mol%) and *N*,*O*-bis(trimethylsilyl)-acetamide (BSA). The pure ligands ("homocombinations") were used in a 6 mol% amount, while for the heterocombinations 3 mol% of each ligand was employed. The results obtained so far are shown in Table 2.11.

Table 2.11 Palladium-catalyzed asymmetric allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate



Entry	Ligands	After 1 h, RT	
		Conv. [%]	**e.e. [%] (abs. conf.)**
	Homocombinations		
1	(*S*)-**2a**	41	25 (*S*)
2	(*R*)-**2b**	100	58 (*S*)
3	(*R*)-**2c**	100	40 (*S*)
4	(*R*)-**2d**	60	73 (*R*)
5	(*R*)-**2e**	100	45 (*S*)
6	(*R*,*R*)-**6a**	96	72 (*R*)
7	(*R*)-**6b**	100	68 (*R*)
8	(*S*)-**6b**	100	68 (*S*)
9	(*R*)-**6c**	100	rac.
10	(*R*)-**6d**	94	7 (*S*)
11	(*S*)-**6e**	100	15 (*R*)

12	(*S*)-**6f**	100	64 (*S*)
13	(*S*)-**6j**	100	rac.
14	(*S*)-**6l**	86	35 (*S*)
	Heterocombinations		
15	(*R*,*R*)-**6a**/(*R*)-**2b**	100	74 (*R*)
16	(*R*)-**6b**/(*S*)-**2a**	100	20 (*S*)
17	(*R*)-**6b**/(*R*)-**2b**	100	69 (*S*)
18	(*R*)-**6b**/(*R*)-**2c**	100	16 (*S*)
19	(*R*)-**6b**/(*R*)-**2d**	100	56 (*R*)
20	(*R*)-**6b**/(*R*)-**2e**	100	36 (*S*)
21	(*S*)-**6b**/(*S*)-**2a**	100	60 (*S*)
22	(*S*)-**6b**/(*R*)-**2b**	100	69 (*S*)
23	(*S*)-**6b**/(*R*)-**2c**	100	39 (*S*)
24	(*S*)-**6b**/(*R*)-**2d**	100	31 (*R*)
25	(*S*)-**6b**/(*R*)-**2e**	100	46 (*S*)
26	(*R*)-**6c**/(*R*)-**2b**	76	44 (*S*)
27	(*R*)-**6c**/(*S*)-**2b**	100	31 (*R*)
28	(*R*)-**6d**/(*R*)-**2b**	100	14 (*S*)
29	(*R*)-**6d**/(*S*)-**2b**	100	18 (*R*)
30	(*S*)-**6e**/(*R*)-**2b**	100	rac.
31	(*S*)-**6e**/(*S*)-**2b**	100	6 (*R*)
32	(*S*)-**6f**/(*R*)-**2b**	100	47 (*S*)
33	(*S*)-**6f**/(*S*)-**2b**	100	20 (*R*)
34	(*S*)-**6j**/(*R*)-**2b**	83	65 (*S*)
35	(*S*)-**6l**/(*R*)-**2b**	90	44 (*S*)

From the data shown above it can be seen that in this reaction the effect of mixing ligands on the stereoselectivity is less evident than in Rh-catalyzed hydrogenations, which is in agreement with the lack of selectivity in the Pd heterocomplex formation that was observed in the first NMR studies. There are no heterocombinations showing stereochemical preference opposite to that of both the ligands, although the selectivity of one of the ligands is reversed in several cases (entries 15-18, 20, 24, 29, 33).

However, a peculiar stereochemical outcome was observed for the diastereoisomeric combinations (*R*)-**6b**/(*R*)-**2b** and (*S*)-**6b**/(*R*)-**2b** (entry 17 and 22, respectively), which both led to the *S* enantiomer of product **24** with the same enantiomeric excess (69%). Therefore, surprisingly both combinations retain the stereochemical preference of phosphite (*R*)-**2b** (58% e.e., *S*, entry 2) with an improved selectivity, whatever is the configuration of phosphinamine **6b** (whose enantiomer *R* gives the with 68% e.e. with preference for *R*, entry 7). Whereas the result obtained with combination (*S*)-**6b**/(*R*)-**2b** can be attributed to (*S*)-**6b** homocomplex, the *S*-selectivity of combination (*R*)-**6b**/(*R*)-**2b**, higher than that of (*R*)-**2b** homocomplex, must be due to the presence of a heteroleptic complex with higher activity than the homocomplexes.

In conclusion, although the palladium heterocomplexes are not formed in a selective fashion, their presence influences the stereochemical outcome, just as observed for several other literature examples of ligand mixtures.

2.3 CONCLUSIONS

In this Chapter the development of a novel strategy for the selective formation of heteroleptic transition metal complexes has been started, whose main advantage consists in involving simple and easy-to-prepare monodentate ligands without need of supramolecular interactions.

DFT calculations have shown that combinations of phosphites and phosphinamines should be able to selectively form the heteroleptic rhodium complexes thanks to their complementary electronic properties. For this reason, two small libraries of chiral phosphites and phosphinamines have been synthesized. Complexation experiments monitored by ^{31}P-NMR spectroscopy have shown that indeed combinations of monodentate phosphite and phosphinamine ligands form the corresponding heteroleptic rhodium(I) complexes with a selectivity ranging from moderate to very high. An extension of the use of phosphite/phosphinamine combinations to palladium(II) complexes has been attempted, but in this case a statistical heterocomplex / homocomplexes ratio has been detected.

Phosphite/phosphinamine combinations have been screened in Rh- and Ir-catalyzed hydrogenations and Pd-catalyzed allylic alkylations. Especially in the Rh-catalyzed hydrogenation case, typical phenomena due to the presence of heteroleptic complexes (e.g. reversed sense of stereoselection of the combinations compared to the ligands alone) have been observed. Unfortunately, the heterocombinations screened so far never reached a level of enantioselectivity high enough to justify a synthetic interest.

2.4 EXPERIMENTAL SECTION

2.4.1 General remarks

All reactions were carried out in flame-dried glassware with magnetic stirring under nitrogen atmosphere, unless otherwise stated. All commercially available reagents were used as received. The solvents were dried by distillation over the following drying agents and were transferred under nitrogen: CH_2Cl_2 (CaH_2), MeOH (CaH_2), THF (Na), benzene (Na), toluene (Na), hexane (Na), Et_3N (CaH_2). Dry Et_2O and $CHCl_3$ (over molecular sieves in bottles with crown cap) were purchased from Fluka and stored under nitrogen. The reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) or aluminum oxide 60 Å F_{254} on glass plates (0.25 mm thickness). Visualization was accomplished by

irradiation with a UV lamp and/or staining with potassium permanganate, ninhydrin or anisaldehyde solution. Flash column chromatography was performed using either neutral alumina (50-200 μm) or silica gel (60 Å, particle size 40-64 μm), following the procedure by Still and co-workers. Proton NMR spectra were recorded on a spectrometer operating at 400.13 MHz. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (Me_4Si) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm; CD_2Cl_2 = 5.32 ppm; d_6-DMSO = 2.50 ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, dd = doublet-doublet, dq = doublet-quartet. ^{13}C-NMR spectra were recorded on a 400 MHz spectrometer operating at 100.56 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.23 ppm; CD_2Cl_2 = 54.00 ppm; d_6-DMSO = 39.51 ppm). ^{31}P NMR spectra were recorded on a 400 MHz spectrometer operating at 162 MHz, with complete proton decoupling. ^{31}P NMR chemical shifts are reported in ppm (δ) relative to external 85% H_3PO_4 at 0 ppm (positive values downfield). The coupling constant values are given in Hz. Infrared spectra were recorded on a standard FT/IR; peaks are reported in cm^{-1}. Optical rotation values were measured on an automatic polarimeter with a 1 dm cell at the sodium D line. Gas chromatography was performed on a GC instrument equipped with a flame ionization detector, using a chiral capillary column. Mass spectra (MS) were performed on a hybrid quadrupole time of flight mass spectrometer equipped with an ESI ion source. High resolution mass spectra (HRMS) were performed on a Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics) – 4.7 T Magnet (Magnex) equipped with ESI source.

2.4.2 Materials

The commercially available reagents were used as received. While (*R*)- and (*S*)-1,1'-bi-(2-naphthol) (BINOL) is commercially available, 3,3'- methyl substituted BINOL derivative (3,3'-Me BINOL) and the corresponding phosphorochloridites (BINOL-PCl and 3,3'-Me BINOL-PCl) could be prepared from BINOL according to literature procedures which have been already described in Experimental Section of Chapter 4.

Amines (+)-bis[(*R*)-1-phenylethyl]amine, (-)-bis[(*S*)-1-phenylethyl]amine, (*R*) or (*S*)-*N*-methyl-1-phenylethanamine, (*R*)-*N*-benzyl-1-phenylethanamine, (*R*)-1-phenylethanamine, (*S*)-1-cyclohexylethanamine, (*S*)-*N*-methyl-1-(naphthalen-1-yl)ethanamine, pyrrolidine, (*R*)-2-methylpyrrolidine, (*R*)-2-methylpyrrolidine, (*S*)-2-(pyrrolidinecarbonyl)pyrrolidine are commercially available.

2.4.3 Hydrogenation experiments

Note! $Rh(cod)_2BF_4$ is a very hygroscopic solid that in contact with the moisture of the air tends to become deliquescent and insoluble in organic solvents (and thus unsuitable for experiments of catalysis). For this reason it should be stored under nitrogen in a Schlenk tube (possibly at low temperature) and handled with care for limiting the contact with moisture as much as possible.

General procedure for the hydrogenations at atmosphere pressure

The reactions were performed using standard Schlenk techniques. Seven oven-dried glass test tubes with stirring bars were employed: in each one the ligand (0.022 equiv, 0.00922 mmol) or the mixture of ligands (0.011 equiv, 0.00461 mmol each) was weighted, and then the test tubes were placed in a Schlenk and subjected to three vacuum/nitrogen cycles. A 1.048 mM CH_2Cl_2 stock solution of $[Rh(cod)_2BF_4]$ (4 mL, 0.01 equiv, 0.00419 mmol) was added and the mixtures were stirred for 30 min under nitrogen. A solution of the substrate (0.419 mmol) in CH_2Cl_2 (4 mL) was finally added. The reaction mixtures were subjected to three vacuum/hydrogen cycles and then left stirring overnight at room temperature under ambient H_2 pressure. Samples were taken for chiral GC analysis.

General procedure for hydrogenations at 25 bar hydrogen pressure in Parr multireactor with a computer-controlled FKV^{TM} machine

A Parr multireactor with a computer-controlled FKV^{TM} machine allows six reactions in parallel under hydrogen pressure. L^a (0.011 equiv, 0.00407 mmol) and L^b (0.011 equiv, 0.00407 mmol) [or, alternatively, 0.022 mmol, 0.00814 mmol of a single ligand] were weighted in special glass vessels. The vessels were purged with nitrogen and a 0.462 mM CH_2Cl_2 stock solution of $[Rh(cod)_2BF_4]$ (8 mL, 0.01 equiv, 0.00370 mmol) was added in each one. After 30 min substrate (60 mg, 0.370 mmol, 1 equiv) was added and the vessels were placed in the respective autoclaves and purged one time with argon and three times with H_2 (5 bar). The reactions were stirred overnight under pressure of hydrogen and then analysed by chiral GC for conversion and e.e. determination.

General procedure for the hydrogenations at 25 bar hydrogen pressure in the Premex A-96 multireactor.

Stock solutions of the ligands (0.05 M) were prepared in dry dichloromethane, and stored in a glovebox. A solution of $[Rh(cod)_2OTf]$ or $[Ir(COD)Cl]_2$ in dry dichloromethane was prepared prior to use (0.025 M); the substrate was dissolved in the appropriate solvent (0.052 M). In a glovebox, 0.1 mL (5×10^{-3} mmol) of each of the stock solutions of ligands L^a and L^b were dispensed (using a Zinnser Lizzy robot) in the reaction vessels (96 vessels, in a 12×8 plate). After shaking for some 5 min, 0.09 mL (2.25×10^{-3} mmol) of the stock solution of rhodium or iridium source were added. After shaking

for some 5 min, the solution of the substrate 2.3 mL (0.12 mmol) was added. The reactions were capped and hydrogenated overnight at the hydrogen pressure required. After completion, the reactors were opened and samples were analysed by chiral GC for conversion and e.e. determination.

General procedure for the hydrogenations in the Argonaut Endeavor multireactor autoclave.

The autoclave allowed eight hydrogenation reactions in parallel in glass vessels. L^a (0.011 mmol) and L^b (0.011 mmol) [or alternatively, 0.022 mmol of a single ligand], $[Rh(cod)_2OTf]$ (0.01 mmol, 4.06 mg) or $[Ir(COD)Cl]_2$ (5.1×10^{-3} mmol, 3.4 mg) were weighed in the reaction vessels. DCM (0.1 mL) was added and the resulting mixture is manually shaken until a solution is obtained (about 5-15 sec). The substrate stock solution in the appropriate solvent (5 mL, 0.4 mmol) was finally added. The vessels were placed in the reactor and the appropriate solvent was added (5 mL). The reaction vessels were then semi-automatically purged repeatedly with N_2 and H_2, before applying a hydrogen pressure and stirring. After completion of the reaction, the reactors were opened and samples were analysed by chiral GC for conversion and e.e. determination.

Enantioselective hydrogenation of methyl 2-acetamidoacrylate 7

The hydrogenation experiments were performed using standard Schlenk techniques at atmosphere pressure. GC conditions: capillary column: MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin, 0.25 μm; diameter = 0.25 mm; length = 25 m; carrier: hydrogen; flow: 1 mL/min; oven temperature: 140 °C for 6 min, then a 8 °C/min gradient is applied): $t_{substrate}$ = 3.7 min; t_R = 4.6 min; t_S = 5.2 min.

The retention times of the products (t_R and t_S) were matched to the corresponding enantiomers (*R* and *S)* on the basis of the results obtained with ligand (*S*)-**2b**, which has been reported to be highly *R*-selective in the Rh-catalyzed hydrogenation of methyl 2-acetamidoacrylate.[24]

Enantioselective hydrogenation of N-(1-phenylvinyl)acetamide 8

The hydrogenation experiments were run in hydrogenations in Parr multireactor with a computer-controlled FKV™ machine at 25 bar hydrogen pressure. GC conditions: capillary column: MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin, 0.25 μm; diameter = 0.25 mm; length = 25 m; carrier: hydrogen; flow: 1.3 mL/min; oven temperature: 160 °C for 8 min, then a 8 °C/min gradient is applied; t_R = 6.7 min; t_S = 6.9 min; $t_{substrate}$ = 8.6 min.

The retention times of the products (t_R and t_S) were matched to the corresponding enantiomers (*R* and *S)* on the basis of the stereochemical preference of ligand (*S*)-**2b**, which has been reported to be highly *R*-selective in the Rh-catalyzed hydrogenation of *N*-(1-phenylvinyl)acetamide.[25]

Enantioselective hydrogenation of methyl 2-acetamidocinnamate 9

The hydrogenation experiments were run in hydrogenations in the 96-Multireactor or in the Argonaut Endeavor multireactor autoclave at 25 bar hydrogen pressure. GC conditions: capillary column: CP-Chirasil-l-Val, 0.25 μm; diameter = 0.25 mm; length = 25 m; carrier: hydrogen; flow: 1.3 mL/min; oven temperature: 160 °C for 8 min, then a 8 °C/min gradient is applied; t_{E1} = 7.82 min; t_{E2} = 8.27 min; $t_{substrate}$ = 12.91 min.

Enantioselective hydrogenation of methyl (Z)-3-acetamidocrotonate 10

The hydrogenation experiments were run in hydrogenations in the 96-Multireactor at 25 bar hydrogen pressure. GC conditions: capillary column: CP-Chirasil-Dex-CB, 0.25 μm; diameter = 0.25 mm; length = 25 m; carrier: N_2; flow: 1.0 mL/min; oven temperature: 160 °C isothermal; t_{E1} = 11.08 min; t_{E2} = 11.27 min.

Enantioselective hydrogenation of methyl 3-N-acetylamino-2-phenyl-2-propenoate 11

The hydrogenation experiments were run in hydrogenations in the 96-Multireactor at 25 bar hydrogen pressure. Enantiomeric access was not analysed due to low conversions.

Enantioselective hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroxyisoquinoline 20

The hydrogenation experiments were run in hydrogenations in the 96-Multireactor at 25 bar hydrogen pressure. The enantiomers were analyzed by HPLC using a chiral column: CHIRALCEL OD-H, 250 mm × 4.6 mm, ID 5 μm; eluent: *n*-heptane/2-propanol/DEA, 95:5:0.05; flow 1.5 mL/min; temperature 45 ^{o}C; V_{inj} = 5 μL, λ = 254 nm; Run time 20 min; $t_{substrate}$ = 6.3 min; t_{E1} = 8.78 min; t_{E2} = 10.45 min.

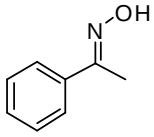
2.4.4 Palladium-catalyzed allylic alkylation

$[Pd(\eta^3C_3H_5)Cl]_2$ (2.81 mg, 0.0077 mmol) and the ligand (0.0311 mmol) or mixture of ligands (0.0155 mmol each) were dissolved under nitrogen in degassed CH_2Cl_2 (1.0 mL). The resulting clear solution was stirred for 20 min at RT, then a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (129 mg, 0.51 mmol) in degassed CH_2Cl_2 (1.0 mL), dimethyl malonate (170 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (BSA, 370 μL, 1.5 mmol), and a pinch of AcOK were added. The reaction mixture was stirred at room temperature. After 1h the solution was diluted with Et_2O (5 mL) and saturated aqueous NH_4Cl (25 mL) was added. The phases were separated and the aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. An aliquot of the crude was passed through a pad of silica using 5:1 hexane/EtOAc as the eluent. The solvents were removed under vacuum and the residue was directly analyzed by HPLC for the

determination of the enantiomeric excess. HPLC conditions: column: CHIRALCEL OD-H; eluent: 99:1 hexane/isopropanol; flow: 0.3 mL/min; λ = 250 nm; t_R = 24 min, t_S = 26 min.

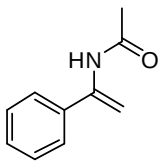
2.4.5 Synthesis of hydrogenating substrates

Acetophenone oxime



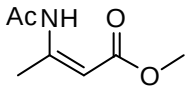
A mixture of acetophenone (11.7 mL, 100 mmol), hydroxylamine hydrochloride (14.8 g, 213 mmol), and pyridine (15 mL) in ethanol (abs. 150 mL) was refluxed for 3 h and subsequently the ethanol was removed under vacuum. While stirring vigorously in an ice-bath, ice water (150 mL) was added upon which the oxime crystallized from the solution. These crystals were filtrated, washed with ice water (50 mL) and dried. The product was quantitatively isolated as a white solid, and was used in the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) ppm δ 9.84 (s, 1H), 7.69 (dd, *J* = 6.6 Hz, *J* = 3.0 Hz, 2H), 7.44 (dd, *J* = 5.0 Hz, *J* = 1.8 Hz, 3H), 2.38 (s, 3H). **^{13}C NMR** (100 MHz, APT, $CDCl_3$) ppm δ 156.8 (C_q), 137.2 (C_q), 130.0 (CH), 129.3 (2×CH), 126.8 (2×CH), 13.2 (CH_3).

N-(1-Phenylvinyl)acetamide (8)



To toluene (45 mL) was added acetophenone oxime (**21**, 4.06 g, 30 mmol), acetic anhydride (8.5 mL, 90 mmol), acetic acid (5.1 mL, 90 mmol) and iron powder -325 mesh (3.36 g, 60 mmol). This mixture was stirred at 70 °C for 4 hours, then allowed to cool down to room temperature and filtered over Celite and subsequently washed with toluene (2 × 30 mL). The filtrate was washed with 2N NaOH (2 × 45 mL), dried over $MgSO_4$ and evaporated in vacuo. The product was purified by column chromatography on silica using EtOAc:hexane 2:1 as the eluent. The product was obtained as a slightly yellow solid (3.1 g, 64 %). **^{1}H NMR** (400 MHz, CD_3CN) ppm δ 7.89 (bs, 1H), 7.54 – 7.47 (m, 2H), 7.46 – 7.36 (m, 3H), 5.68 (s, 1H), 5.05 (s, 1H), 2.05 (s, 3H). **^{13}C NMR** (101 MHz, APT, CD_3CN) ppm δ 170.1 (C_q), 142.5 (C_q), 138.9 (C_q), 129.1 (2×CH), 126.89 (CH), 118.01 (C_q), 102.33 (C_q), 23.93 (CH_3).

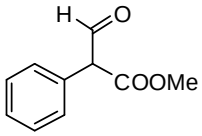
Methyl (*Z*)-3-acetamidocrotonate (10)



To a solution of methylacetoacetate (5.6 mL, 51.67 mmol) in dry benzene (52 mL) were added acetamide (6.1 g, 103.34 mmol) and *para*-toluensulfonic acid (30.5 mg, 0.16 mmol), and the mixture was refluxed using Dean Stark condenser for 36 h. The raction mixture was then filtered, concentrated in vacuo, diluted with water (150 mL) and extrected into ether (3×150 mL). After extraction solvent was evaporated and the crude mixture was purified by column chromatography on silica using EtOAc:hexane 4:1 as the eluent. The product was obtained as a whith

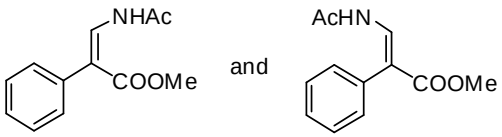
solid (3.72 g, 46 %). **^{1}H NMR** (400 MHz, $CDCl_3$) ppm δ 11.11 (bs, 1H), 4.92 (d, *J* = 0.9 Hz, 1H), 3.71 (s, 3H), 2.39 (d, *J* = 0.9 Hz, 3H), 2.16 (s, 3H). **MS** (ESI +): calcd. for $C_7H_{11}NO_3$: 157.07, found: 158.38 $[M+H]^+$.

Methyl 3-oxo-2-phenylpropanoate



A NaH 60% suspention (2 mol) was added over a period of 45 min at RT with stirring and under a dry N_2 stream to a solution of the methylphenylacetate (7.2 mL, 0.5 mol) in methyl formate (80 mL, 9.9 mol). The reaction mixture was stirred at RT for 4 hours and then added to 0.1 M HCl (310 mL) solution. After extraction with Et_2O (2 × 150 mL), the organic layer was anhydrified with Na_2SO_4, and then the solvent was removed under reduced pressure. The crude product was purificated by distillation (2-3 mbar pressure, 135 ^oC) and quantitatively obtained as yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$) showed a 1:5 mixture of aldol–enol tautomers. Aldo tautomer: ppm δ 9.81 (d, *J* = 2.8 Hz, 1H), 7.45 – 7.28 (m, 5H), 4.53 (d, *J* = 2.8 Hz, 1H), 3.82 (s, 3H); Enol tautomer: ppm δ 12.05 (d, *J* = 12.7 Hz, 1H), 7.38 – 7.27 (m, 6H), 3.82 (s, 3H).

Methyl 3-*N*-acetylamino-2-phenyl-2-propenoate [*Z*-11 and *E*-11)



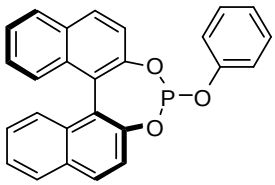
A mixture of formyl ester reported above (9.15 g, 51.4 mmol), acetamide (6.08 g, 102.8 mmol) and a catalytic amount of *para*-toluenesulfonic acid in toluene (100 mL) was heated at reflux with a Dean–Stark apparatus under a nitrogen atmosphere for 3.5 h. At the end of the reaction period, the reaction mixture was allowed to cool to room temperature and the excess acetamide filtered and thoroughly washed with toluene. The filtrate was evaporated under reduced pressure to give an isomeric mixture of the enamide **11**. Purification by flash chromatography on silica using EtOAc : hexane 1:4 as the eluent 1) first gave the (*Z*)-enamide ***Z*-11** a as a white solid (2.32 g, 19%). **^{1}H NMR** (400 MHz, $CDCl_3$) ppm δ 10.72 (br d, *J* = 9.6 Hz, 1H), 7.64 (d, *J* = 11.4 Hz, 1H), 7.4 – 7.28 (m, 5H), 3.80 (s, 3H), 2.23 (s, 3H). **^{13}C NMR** (101 MHz, APT, $CDCl_3$) ppm δ 169.6 (C_q), 168.8 (C_q), 138.2 (CH), 136.4 (C_q), 129.9 (2×CH), 128.5 (2×CH), 127.7 (CH), 111.4 (C_q), 52.2 (CH_3), 24.2 (CH_3). The (*E*)-isomer ***E*-11** was then eluted and isolated as a white solid (4 g, 31%). **^{1}H NMR** (400 MHz, $CDCl_3$) ppm δ 8.29 (d, *J* = 12.2 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 3H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.31-726 (m, 2H), 3.78 (s, 3H), 2.04 (s, 3H). **MS** (ESI +): calcd. for $C_{12}H_{13}NO_3$: 219.09, found: 220.28 $[M+H]^+$.

2.4.6 General procedure for the preparation of BINOL-derived phosphite ligands

Phenol and menthol were used as received. The other alcohols (liquid at RT) were anhydrified over 3 Å molecular sieve beads.

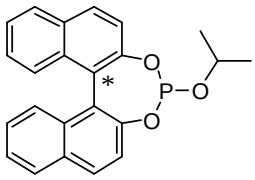
To a solution of the corresponding alcohols or phenol (1.1 equiv) and triethylamine (3 equiv) in THF (8 mL/mmol of BINOL-PCl or 3,3'-Me BINOL-PCl) BINOL-PCl or 3,3'-Me BINOL-PCl (1 equiv) was added as a solid at RT. The reaction was stirred overnight and then filtered through a pad of celite. The solvent was evaporated under reduced pressure to afford a white foam. The crude was purified by column chromatography on silica gel (typical eluent: neat DCM). The phosphites are less polar than the impurities, thus were eluted as the first fraction.

(*R*)- and (*S*)-4-phenoxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine [(*R*)-2a and (*S*)-2a]



The product was prepared according to the General Procedure using (*S*)-BINOL-PCl (400 mg, 1.14 mmol), phenol (118 mg, 1.25 mmol), and triethylamine (0.47 mL, 3.42 mmol). It was purified by column chromatography on silica gel (eluent: DCM) to afford a white solid. Yield = 91%. **^{1}H-NMR** (400 MHz, $CDCl_3$) ppm δ 8.03 (d, *J* = 8.8 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H,), 7.59 (d, *J* = 8.7 Hz, 1H,), 7.48- 7.38 (m, 6H), 7.31- 7.23 (m, 4H), 7.17 (d, *J* = 7.53 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) ppm δ 150.4, 149.0, 139.3, 133.2, 132.4, 131.8, 131.1, 130.7, 129.8, 128.8, 128.5, 127.3, 126.6, 125.3, 122.7, 121.9. **^{31}P-NMR** (162 MHz, $CDCl_3$) ppm δ 185.0. **$[\alpha]^{24}_{D}$** = for *S* enantiomer: +221.6 (CH_2Cl_2, *c* = 1). **FT-IR** (film): ν = 3054, 1587, 1228, 948, 819, 743 cm^{-1}. **MS** (ESI +): calcd. for $C_{26}H_{17}O_3P$: 408.09, found: 409.23 $[M+H]^+$. **MP** = 164-166°C.

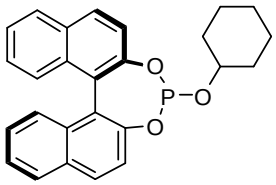
(*R*)- and (*S*)-4-isopropoxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine [(*R*)-2b and (*S*)-2b]



The product was prepared according to the General Procedure using (*R*)- or (*S*)-BINOL-PCl (400 mg, 1.14 mmol), *iso*-propanol (95 μL, 1.25 mmol), and triethylamine (0.47 mL, 3.42 mmol). It was purified by column chromatography on silica gel (eluent: DCM) to afford a white solid. Yield = 91%. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 7.97-7.89 (m, 4H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.44-7.34 (m, 5H), 7.24 (t, *J* = 7.6 Hz, 2H), 4.58-4.47 (m, 1H), 1.31 (dd, *J* = 6.2 Hz, 12.8 Hz, 6H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 148.72, 148.10, 133.19, 131.69, 130.42, 128.72, 127.45, 126.56, 125.31, 122.26, 69.96, 25.01. **^{31}P-NMR** (162 MHz, CD_2Cl_2) ppm δ 147.3. **$[\alpha]^{25}_{D}$** = for *R* enantiomer: -254.7 (CH_2Cl_2 *c*

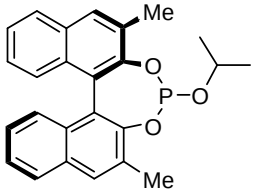
= 0.1). **FT-IR** (film): ν = 3054, 2967, 1588, 1212, 938, 746 cm^{-1}. **HRMS**: calcd for $C_{23}H_{19}O_3P$: 374.1145, found: 375.1179 $[M+H]^+$. **MP** = 80-82°C.

(*R*)-4-(cyclohexyloxy)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine [(*R*)-2c]



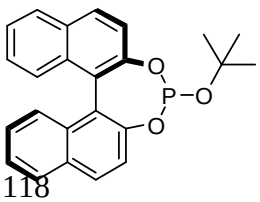
The product was prepared according to the General Procedure using (*R*)-BINOL-PCl (400 mg, 1.14 mmol), cyclohexanol (130 μL, 1.25 mmol), and triethylamine (0.47 mL, 3.42 mmol). It was purified by column chromatography on silica gel (eluent: DCM) to afford a white solid. Yield = 90%. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 8.04 (d, *J* = 8.9 Hz, 1H,), 8.01-7.98 (m, 3H,), 7.56 (d, *J* = 8.8 Hz, 1H), 7.50-7.44 (m, 3H), 7.40-7.36 (m, 2H), 7.33-7.29 (m, 2H), 4.28 (m, 1H), 2.05-1.94 (m, 2H), 1.82-1.73 (m, 2H), 1.64-1.50 (m, 3H), 1.38-1.20 (m, 3H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 149.0, 148.3, 132.2, 131.7, 131.0, 130.4, 129.0, 128.9, 127.4, 127.3, 126.9, 126.8, 125.7, 125.5, 123.4, 122.7, 122.5, 122.4, 75.4 (d, $J_{C,P}$ = 13 Hz), 35.3, 35.0, 25.8, 24.5. **^{31}P-NMR** (162 MHz, $CDCl_3$) ppm δ 149.4. **$[\alpha]^{25}_D$** = -303 (CH_2Cl_2, *c* = 1). **FT-IR** (film): ν = 3057.6, 2934.2, 2858.0, 1618.9, 1508.1, 1462.7, 1231.3, 944.9, 866.8 cm^{-1}. **MS** (ESI +): calcd. for $C_{26}H_{23}O_3P$: 414.15, found: 415.31 $[M+H]^+$. **MP** = 78-80°C.

(*R*)-4-isopropoxy-2,6-dimethyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine [(*R*)-2d]



The product was prepared according to the General Procedure using (*R*)-3,3'-Me BINOL-PCl (240 mg, 0.63 mmol), *iso*-propanol (55 μL, 0.70 mmol), and triethylamine (0.26 mL, 1.88 mmol). It was purified by column chromatography on silica gel (eluent: DCM) to afford a white solid. Yield = 83%. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 7.92-7.89 (m, 3H), 7.87 (s, 1 H), 7.44 (m, 2 H), 7.29-7.20 (m, 4 H), 4.59 (m, 1 H), 2.66 (d, *J* = 0.6 Hz, 3 H), 2.62 (d, *J* = 0.6 Hz, 3 H), 1.38 (d, *J* = 6.1 Hz, 3 H), 1.33 (d, *J* = 6.2 Hz, 3 H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 148.8, 147.7, 132.3, 132.1, 131.7, 131.0, 130.4, 130.1, 128.3, 128.2, 127.4, 127.3, 125.9, 125.8, 125.6, 125.5, 124.9, 124.9, 123.4, 79.9 (d, $J_{C,P}$ = 14.4 Hz), 25.2, 25.0, 18.3, 17.8. **^{31}P-NMR** (162 MHz, CD_2Cl_2) ppm δ 148.2. **$[\alpha]^{22}_D$** = -547.6 ($CHCl_3$, *c* = 1). **FT-IR** (KBr): ν = 3057.6, 3025.8, 2967.0, 2924.5, 1492.6, 1454.1, 1433.8, 1091.5, 1071.3, 1026.0, 914.1, 883.2 cm^{-1}. **HRMS** (ESI +): calcd. for $C_{25}H_{23}O_3P$: 402.12770, found: 425.12718 $[M + Na]^+$. **MP** = 65°C. (dec).

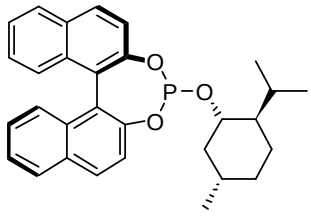
(*R*)-4-*tert*-butoxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine [(*R*)-2e]



The product was prepared according to the General Procedure using (*S*)-BINOL-PCl (400 mg, 1.14 mmol), *tert*-butanol (120 μL, 1.25 mmol), and

triethylamine (0.47 mL, 3.42 mmol). It was purified by column chromatography on silica gel (eluent: DCM) to afford a white solid. Yield = 83%. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 8.03 (d, *J* = 8.7 Hz, 1H), 8.01-7.98 (m, 3H), 7.55 (d, *J* = 8.9 Hz, 1H), 7.50-7.45 (m, 2H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.40-7.36 (m, 2H), 7.33-7.28 (m, 2H), 1.57 (br s, 9H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 148.7, 148.1, 133.5, 133.3, 132.2, 131.8, 130.9, 130.3, 129.1, 129.0, 127.5, 127.4, 126.9, 126.8, 125.7, 125.5, 125.0 (d, $J_{C,P}$ = 5.3 Hz), 123.8 (d, $J_{C,P}$ = 3.7 Hz), 123.1, 122.6, 79.5 (d, $J_{C,P}$ = 10.0 Hz), 31.7 (d, $J_{C,P}$ = 8.3 Hz). **^{31}P-NMR** (162 MHz, CD_2Cl_2) ppm δ 154.8. **$[\alpha]^{22}_{D}$** = -332 (CH_2Cl_2, *c* = 1). FT-IR (film): ν = 3050.3, 2975.6, 1589.1, 1463.7, 1369.2, 1202.0, 1172.5, 932.4, 826.3 cm^{-1}. **HRMS** (ESI +): calcd. for $C_{24}H_{21}O_3P$: 488.11205, found: 411.11248 $[M+Na]^+$. **MP** = 125-126°C.

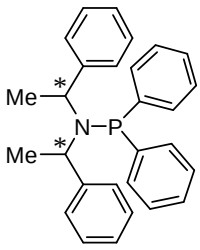
(*R*)-4-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)dinaphtho[2,1-*d*:1',2'*f*][1,3,2] dioxaphosphepine [(*R*)-2f]



The product was prepared according to the General Procedure using (*R*)-BINOL-PCl (400 mg, 1.14 mmol), (+)-menthol (178 mg, 1.25 mmol), and triethylamine (0.47 mL, 3.42 mmol). It was purified by column chromatography on silica gel (eluent: DCM) to afford a white solid. Yield = 92%. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 8.05 (d, *J* = 8.8 Hz), 8.03-7.99 (3H, m), 7.68 (1H, d, *J* = 8.8 Hz), 7.58 (1H, d, *J* = 8.8 Hz, 1H) -7.51-7.47 (m, 2H), 7.45 (d, *J* = 8.8 Hz, 1H,), 7.39 (m, 2H), 7.33-7.29 (m, 2H), 4.19 (ddt, *J* = 4.8 Hz, *J* = 8.7 Hz, *J* = 10.7 Hz, 1H), 2.40 (m, 1H), 2.17 (m, 1H), 1.77-1.69 (m, 2H), 1.54-1.39 (m, 2H), 1.24 (m, 1H), 1.10 (dt, *J* = 3.3 Hz, *J* =12.5 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.90 (m, 1H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 148.9, 148.4, 133.5, 133.2, 130.9, 130.3, 129.1, 129.0, 127.4, 126.9, 126.8, 125.7, 125.6, 123.5, 122.7, 122.5, 77.7 (d, $J_{C,P}$ = 16.2 Hz), 49.3, 44.8, 34.7, 32.4, 26.1, 23.5, 22.4, 21.5, 16.2. **^{31}P-NMR** (162 MHz, $CDCl_3$) ppm δ 154.1. **$[\alpha]^{25}_{D}$** = -347 (CH_2Cl_2, *c* = 1). FT-IR (film): ν = 3056.6, 2955.4, 2923.6, 2868.6, 1618.9, 1590.0, 1508.1, 1462.7, 1201.4, 945.9, 824.4 cm^{-1}. **HRMS** (ESI +): calcd. for $C_{30}H_{31}O_3P$: 470.20836, found: 471.20855 $[M+H]^+$. **MP** = from 188°C with dec.

2.4.7 Synthesis of phosphinamine ligands

1,1-diphenyl-*N*,*N*-bis((*R*)-1-phenylethyl)phosphinamine and 1,1-diphenyl-*N*,*N*-bis((*S*)-1-phenylethyl)phosphinamine [(*R*,*R*)-6a or (*S*,*S*)-6a]

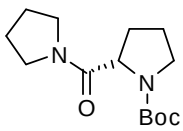


To a stirred solution of (+)-bis[(*R*)-1-phenylethyl]amine or (-)-bis[(*S*)-1-phenylethyl]amine (0.220 mL, 0.96 mmol, 1 equiv) in THF (5 mL) at -78°C, a 1.6 M solution of *n*-BuLi in hexanes (0.60 mL, 0,96 mmol, 1 equiv) was added. The reaction mixture was stirred at -78°C for 10 min, then allowed to warm to RT. After stirring for 2 h, the mixture was cooled back to -78°C and a solution of

chlorodiphenylphosphine (0.170 mL, 0,96 mmol) in THF (3 mL) was slowly added dropwise. The reaction mixture was allowed to warm to RT and it was stirred overnight. After reaction the solvent was evaporated and the crude product was purified by column chromatography on silica gel to afford a white solid in 31% yield (eluent: 9:1 hexane / DCM). CAS for (*R*,*R*) 1176789-48-2, for (*S*,*S*) 959680-39-8. ^{1}H-NMR (400 MHz, C_6D_6) ppm δ 7.88-7.84 (m, 2H), 7.38-7.34 (m, 2H), 7.29-7.23 (m, 3H), 7.17-7.08 (m, 13H), 4.63 (sext, *J* = 7.0 Hz, 2H), 1.51 (d, *J* = 6.8 Hz, 6H). **^{13}C-NMR** (100 MHz, C_6D_6) ppm δ 144.8, 140.5, 140.4, 140, 134.3, 134.1, 132.7, 132.6, 129.1, 128.7, 128.6, 128.57, 128.55, 128.3, 128.2, 128.1, 127.9, 127, 56.8, 56.7, 21.9, 21.8. **^{31}P-NMR** (162 MHz, C_6D_6) ppm δ 42.4. **$[\alpha]^{25}_{D}$** = for the *S*,*S* enantiomer: -233 ($CHCl_3$, *c* = 1). **FT-IR** (film): ν = 3057.2, 2967.5, 2928.5, 1585, 1494, 1435.1, 1275.7, 1200.6, 1118.3, 1089.3, 742.9, 697.2 cm^{-1}. HRMS (ESI +): calcd = 410.2037, found = 410.2028. **MP** = 56-57°C.

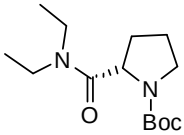
2.4.7.1 Synthesis of non-commercial chiral amines

(*S*)-*N*-boc-2-(pyrrolidinecarbonyl)pyrrolidine (3a)



To a stirred solution of *N*-Boc-L-proline (500 mg, 2.32 mmol, 1 equiv) in $CHCl_3$ (20 mL) at 0°C, EDC (490 mg, 2.55 mmol, 1.1 equiv) and HOBT·H_2O (400 mg, 2.55 mmol, 1.1 equiv) were added in the order. After 5 min pyrrolidine (0.214 mL, 2.55 mmol, 1.1 equiv) was added and the mixture was stirred for 10 min at 0°C and then overnight at RT. The solution was washed with 1 M HCl aqueous solution (2 × 20 mL) and then with $NaHCO_3$ saturated aqueous solution (2 × 20 mL). The organic layer was anhydrified with Na_2SO_4, and then the solvent was removed under reduced pressure to afford pale yellow oil. The product was used in the next step without further purification. Yield = 96%. **^{1}H-NMR** (400 MHz, $CDCl_3$): mix of rotamers, ppm δ 4.5 (dd, *J* = 2.3 Hz, *J* = 7.3 Hz, 0.5H), 4.37 (dd, *J* = 5.2 Hz, *J* = 7.7 Hz, 0.5H), 3.75 (m, 0.5 H), 3.66-3.41 (m, 5.5H), 2.27-1.73 (m, 8H), 1.48 (s, 4.5H), 1.42 (s, 4.5H).

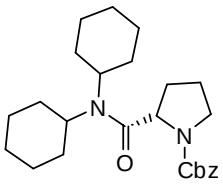
(*S*)-*N*-boc-2-(diethylaminocarbonyl)pyrrolidine (3b)



To a stirred solution of *N*-Boc-L-proline (500 mg, 2.32 mmol, 1 equiv) in $CHCl_3$ (20 mL) at 0°C EDC (490 mg, 2.55 mmol, 1.1 equiv) and HOBT·H_2O (400 mg, 2.55 mmol, 1.1 equiv) were added in the order. After 5 min diethylamine (0.266 mL, 2.55 mmol, 1.1 equiv) was added dropwise and the mixture was stirred at 0°C for 10 min and then overnight at RT. The solution was washed with 1 M HCl aqueous solution (2 × 20 mL) and then with $NaHCO_3$ saturated aqueous solution (2 × 20 mL). The organic layer was anhydrified with Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford a colourless solid which was

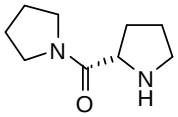
used in the next step without further purification. Yield = 76%. **^{1}H-NMR** (400 MHz, $CDCl_3$): mixture of rotamers, ppm δ 4.61 (br d, *J* = 5.6 Hz, 0.4H), 4.47 (dd, *J* = 3.2 Hz, *J* = 8.0, 0.6H), 3.67-3.41 (m, 6H), 2.23-2.02 (m, 2H), 1.91-1.81 (m, 2H), 1.47 (s, 4.5H), 1.43 (s, 4.5H), 1.25 (m, 3H), 1.13 (m, 3H).

(*S*)-*N*-Cbz-2-(diciclohexylaminocarbonyl)pyrrolidine (3c)



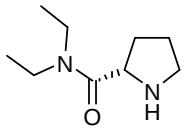
To a solution of *N*-Cbz-L-prolinyl chloride **5** (470 mg, 1.76 mmol, 1 equiv) and DMAP (a crystal) in THF (10 mL) a solution of dicyclohexylamine (0.37 mL, 1.86 mmol, 1.05 equiv) and TEA (1 mL, 7.08 mmol, 4 equiv) in THF (10 mL) was added. The resulting mixture was refluxed overnight. THF was removed and the residue was redissolved in DCM, and then washed with water and anhydrified before removing the solvent. The crude was purified by flash chromatography (eluent DCM/AcOEt from 95:5 to 70:30) to afford the desired product as a white solid. Yield = 88%. **^{1}H-NMR** (300 MHz, $CDCl_3$): mix of rotamers, ppm δ 7.3 (m, 5H), 5.1 (m, 2H), 4.7 (m, 0.5H), 4.5 (m, 0.5H,), 3.7-3.4 (m, 4H), 2.2-0.9 (m, 24H).

(*S*)-2-(pyrrolidinecarbonyl)pyrrolidine (4a)



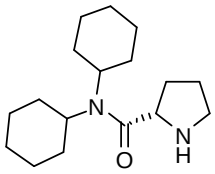
At 0°C, TFA (3mL, 39 mmol, 18 equiv) was added to a solution of *N*-boc-prolinamide (*S*)-*N*-boc-2-(pyrrolidinecarbonyl)pyrrolidine **3a** (590 mg, 2.2 mmol, 1 equiv) in DCM (5 mL). The mixture was stirred for 3 h at RT, then the volatiles were removed to afford a yellow oil. The crude was dissolved in DCM (5 mL), Amberlyst A21 resin was added and the mixture was stirred overnight, then filtered. The solvent was evaporated to afford brown-yellow oil in quantitative yield. CAS 41721-00-0. **^{1}H-NMR** (400 MHz, $CDCl_3$) ppm δ 7.11 (br s, 1H), 4.77 (m, 1H), 3.65-3.36 (m, 6H), 2.54 (m, 1H), 2.17 (m,1H), 2.11-1.95 (m, 6H).

(*S*)-2-(diethylaminocarbonyl)pyrrolidine (4b)



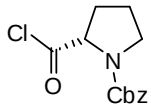
TFA (3mL, 39 mmol, 22 equiv) was added to a solution of *N*-boc-diethyl-prolinamide **3b** (480 mg, 1.8 mmol, 1 equiv) in DCM (5 mL) kept at 0°C. The mixture was stirred for 3 h at RT, and then the volatiles were removed to afford a yellow oil. The crude oil was dissolved in DCM (5 mL), Amberlyst A21 resin was added and the mixture was stirred overnight, then filtered and the solvent was evaporated to afford a pale-yellow oil in quantitative yield. CAS 41721-01-1. **^{1}H-NMR** (300 MHz, $CDCl_3$) ppm δ 4.81 (m, 1H), 3.69-3.31 (m, 6H), 2.52 (m, 1H), 2.28-1.90 (m, 3H), 2.11-1.95 (m, 6H).

(*S*)-2-(diciclohexylaminocarbonyl)pyrrolidine (4c)



5% Pd/C (320 mg, 0.15 mmol) was added to a solution of (*S*)-*N*-Cbz-2-(dicyclohexylaminocarbonyl)pyrrolidine **3c** (620 mg, 1.50 mmol) in MeOH (15 mL). The resulting suspension was subjected to three vacuum/hydrogen cycles and then reacted overnight under 1 bar of hydrogen pressure. The catalyst was filtered off through a celite pad and the solvent was evaporated to afford a clean oil in quanitative yield, which was used in the next step without purification. **^{1}H-NMR** (300 MHz, $CDCl_3$): mixture of rotamers, ppm δ 4.2 (m, 0.5H), 4.1 (m, 0.5H), 3.7-3.4 (m, 4H), 2.2-0.9 (m, 24H).

N-Cbz-L-prolinyl chloride (5)



Oxalyl chloride (0.265 mL, 3.03 mmol, 1.71 equiv) was slowly added dropwise to a stirred solution of *N*-Cbz-L-proline (446 mg, 1.77 mmol, 1 equiv) and DMF (2 drops) in DCM (6 mL), kept at 0°C. The mixture was allowed to reach RT and stirred for 5 h, and then the volatiles were removed at rotavapor and under high vacuum to afford *N*-Cbz-L-prolinyl chloride **5**. CAS 61350-60-5. The product was used in the next step without purification.

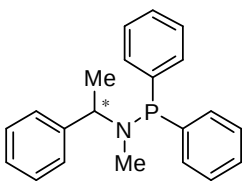
2.4.7.2 Preparation of C_1-symmetric dipheylphosphinamines

General procedure

Chlorodiphenylphosphine (0.7 mL, 830 mg, 3.76 mmol, 1 equiv) was added dropwise to a stirred solution of the selected primary or secondary amine (4.70 mmol, 1.25 equiv) and Et_3N (0.68 mL, 4.89 mmol, 1.3 equiv) in benzene (10 mL). The mixture was stirred overnight and then dry hexane (10 mL) was added for favouring the precipitation of the ammonium salt. The obtained suspension was filtered under nitrogen through a short pad of celite. The filtrate was concentrated at rotavapor to give the crude product, which was purified by column chromatography using short pads of neutral alumina as the stationary phase. Eluent mixtures containing 2-5% Et_3N had to be used in order to prevent product degradation in the column. Similarly, for preventing product degradation on the alumina plates (and thus unreliability of the TLC analysis), they had to be pre-eluted with eluent mixtures containing Et_3N (1-2%).

The phosphinamine ligands showed a moderate tendency to undergo oxidation by atmospheric oxygen when in solution. They proved fairly stable in the solid state.

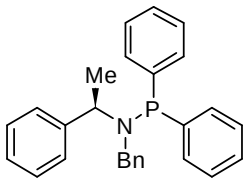
(*R*)-and (*S*)-*N*-methyl-1,1-diphenyl-*N*-(1-phenylethyl)phosphinamine [(*R*)-6b and (*S*)-6b]



The product was prepared according to the General Procedure using (*R*) or (*S*)-*N*-methyl-1-phenylethanamine (700 μL, 4.70 mmol), chlorodiphenylphosphine (0.7 mL, 3.76 mmol) and triethylamine (0.68 mL, 4.89 mmol). It was purified

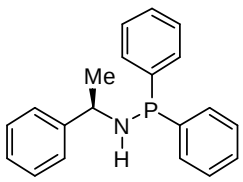
by column chromatography on neutral alumina (eluent: hexane / CH_2Cl_2 / TEA 9:1:0.3) to afford a white solid. CAS for enantiomer *S* 52364-43-9, for enantiomer *R* 76152-62-0. Yield = 84%. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 7.46-7.26 (m, 15H), 4.67 (qd, $J_{H,P}$ = 10.7 Hz, $J_{H,H}$ = 7.0 Hz, 1H), 2.27 (d, $J_{H,P}$ = 2.9 Hz, 3H), 1.63 (d, $J_{H,H}$ = 7.0Hz, 3H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 144.6 (d, $J_{C,P}$ = 6.0 Hz), 140.4, 140.3, 133.1, 132.9, 132.5, 132.3, 129.0, 128.7, 128.1, 127.4, 64.2 (d, $J_{C,P}$ = 38.7 Hz), 32.3 (d, $J_{C,P}$ = 9.7 Hz), 19.6 (d, $J_{C,P}$ = 9.8 Hz). **^{31}P-NMR** (162 MHz, CD_2Cl_2) ppm δ 61.0. **$[\alpha]^{25}_D$** = for the *S* enantiomer: +88.0 (CH_2Cl_2, *c* = 1). **FT-IR** (film): ν = 3067.2, 2969.8, 2872.5, 1952.6, 1585.2, 1432.8, 1200.4, 1155.2, 919.8 cm^{-1}. **MS** (ESI +): calcd. for $C_{21}H_{22}NP$: 319.17, found: 320.38 $[M+H]^+$. **MP** = 42-43 °C.

(*R*)-*N*-benzyl-1,1-diphenyl-*N*-(1-phenylethyl)phosphinamine [(*R*)-6c]



The product was prepared according to the General Procedure using (*R*)-*N*-benzyl-1-phenylethanamine (980 μl, 4.70 mmol), chlorodiphenylphosphine (0.7 mL, 3.76 mmol) and triethylamine (0.68 mL, 4.89 mmol). It was purified by column chromatography on neutral alumina (eluent: hexane / CH_2Cl_2 / TEA 9:1:0.3) to afford a colourless oil which crystallized on standing givinig a white solid. Yield = 52%. CAS 1176789-49-3. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 7.58 (m, 2 H), 7.42-7.22 (m, 14 H), 7.12 (m, 2 H), 6.97 (dd, *J* = 2.1 Hz, *J* = 7.7 Hz, 2 H,), 4.20 (d, J_{AB} = 15.1 Hz, 1 H), 4.15 (dq, $J_{H,H}$ = 7.1 Hz, $J_{H,P}$ = 18.0 Hz, 1H), 4.06 (d, J_{AB} = 15.1 Hz, 1 H), 1.71 (d, *J* = 7.1 Hz, 3 H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 141.3, 141.1, 140.3, 133.8, 133.5, 132.7, 132.5, 129.3, 129.0, 128.9, 128.8, 128.7, 128.5, 128.5, 128.3, 128.3, 127.7, 127.5, 58.0 (d, $J_{C,P}$ = 25.4 Hz), 54.1 (d, $J_{C,P}$ = 9.2 Hz), 21.7 (d, $J_{C,P}$ = 18.4 Hz). **^{31}P-NMR** (162 MHz, CDCl3) ppm δ 44.8 . **$[\alpha]^{22}_D$** = +88.6 (CH_2Cl_2, *c* = 1). **FT-IR** (film): ν = 3051.8, 2974.7, 2925.5, 1240.0, 973.9, 879.4 cm^{-1}. **HRMS** (ESI +): calcd. for $C_{27}H_{26}NP$ 395.18756, found: 396.18804 $[M+H]^+$. **MP** = 62-63°C.

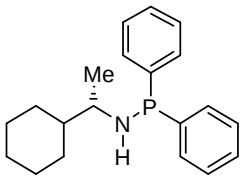
(*R*)-1,1-diphenyl-*N*-(1-phenylethyl)phosphinamine [(*R*)-6d]



The product was prepared according to the General Procedure using (*R*)-1-phenylethanamine (600 μL, 4.70 mmol), chlorodiphenylphosphine (0.7 mL, 3.76 mmol) and triethylamine (0.68 mL, 4.89 mmol). It was purified by column chromatography on neutral alumina (eluent: hexane / CH_2Cl_2 / TEA 9:1:0.3) to afford a clean oil. Yield = 87%. CAS 66067-96-7. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 7.85-7.19 (m, 15H), 4.40 (m, 1H), 2.45 (br s, 1H), 1.56 (d, $J_{H,H}$ = 6.9 Hz, 3H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 147.6 (d, $J_{C,P}$ = 4.6 Hz), 143.4 (d, $J_{C,P}$ = 14.4 Hz), 143.2 (d, $J_{C,P}$ = 12.0 Hz), 131.83, 131.78, 131.64, 131.60, 129.09, 129.02, 128.96, 128.90, 128.84, 127.4, 127.0, 57.3 (d, $J_{C,P}$ = 23.5 Hz), 26.5 (d, $J_{C,P}$ = 7.3 Hz). **^{31}P-NMR** (162 MHz, CD_2Cl_2) ppm δ 36.0. **$[\alpha]^{25}_D$** = +6.5 (CH_2Cl_2, *c* = 0.8). **FT-IR** (film): ν =

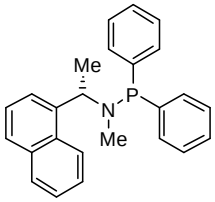
3362.3, 3289.0, 3065.3, 2966.9, 2866.7, 1952.6, 1585.2, 1433.8, 1369.2, 1203.6, 1026.9, 943.9, 828.3.740.5 cm^{-1}. **MS** (ESI +): calcd. for $C_{20}H_{20}NP$: 305.14, found: 306.18 $[M+H]^+$.

(*S*)-*N*-(1-cyclohexylethyl)-1,1-diphenylphosphinamine [(*S*)-6e]



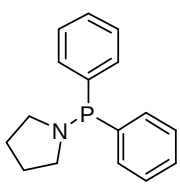
The product was prepared according to the General Procedure using (*S*)-1-cyclohexylethanamine (720 μ, 4.70 mmol), chlorodiphenylphosphine (0.7 mL, 3.76 mmol) and triethylamine (0.68 mL, 4.89 mmol). It was purified by column chromatography on neutral alumina (eluent: hexane / CH_2Cl_2 / TEA 9:1:0.3) to afford a clean oil. Yield = 75%. CAS 1176789-50-6. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 7.45-7.31 (m, 10H), 3.05 (m, 1H), 1.92-0.97 (m, 15H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 144.8 (d, $J_{C,P}$ = 12.8 Hz), 144.2 (d, $J_{C,P}$ = 11.1 Hz), 131.6, 131.5, 131.4, 131.3, 128.85, 128.81, 128.79, 128.75, 59.0 (d, $J_{C,P}$ = 24.9 Hz), 46.3 (d, $J_{C,P}$ = 6.3 Hz), 30.1, 29.4, 27.4, 27.2, 27.1, 21.3 (d, $J_{C,P}$ = 5.9 Hz). **^{31}P-NMR** (162 MHz, CD_2Cl_2) ppm δ 37.5. **$[\alpha]^{25}_D$** = +18.0 (CH_2Cl_2, *c* = 1). **FT-IR** (film): ν = 3369.0, 3290.9, 3067.3, 2923.6, 2850.7, 1585.2, 1432.9, 1153.2, 1094.9, 960.0, 739.6, 699.1 cm^{-1}. **MS** (ESI +): calcd. for $C_{20}H_{26}NP$: 311.19, found: 312.41 $[M+H]^+$.

(*S*)-*N*-methyl-*N*-(1-(naphthalen-1-yl)ethyl)-1,1-diphenylphosphinamine [(S)-6e]



The product was prepared according to the General Procedure using (*S*)-*N*-methyl-1-(naphthalen-1-yl)ethanamine (840 μL, 4.70 mmol), chlorodiphenylphosphine (0.7 mL, 3.76 mmol) and triethylamine (0.68 mL, 4.89 mmol). It was purified by column chromatography on neutral alumina (eluent: hexane / CH_2Cl_2 / TEA 9:1:0.3) to afford a white solid. Yield = 81%. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 8.42 (m, 1H), 7.94 (m, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.57-7.50 (m, 6H), 7.44-7.42 (m, 3H), 7.27-7.21 (m, 5H), 5.51 (dq, $J_{H,H}$ = 6.9 Hz, $J_{H,P}$ = 9.8 Hz, 1H), 2.27 (d, $J_{H,P}$ = 2.9 Hz, 3H), 1.73 ($J_{H,H}$ = 6.9 Hz, 1H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 140.3 (d, $J_{C,P}$ = 8.0 Hz), 140.2, 139.4 (d, $J_{C,P}$ = 9.6 Hz), 140.4, 140.3, 140.1, 139.5, 139.4, 134.9, 133.9, 133.8, 132.7, 132.2, 132.0, 130.2, 129.4, 129.2, 128.8, 128.7, 128.6, 128.5, 128.4, 126.5, 126.2, 125.7, 125.5, 125.4, 124.9, 59.9 (d, $J_{C,P}$ = 40.0 Hz), 31.4 (d, $J_{C,P}$ = 10.4 Hz), 18.8 (d, $J_{C,P}$ = 6.0 Hz). **^{31}P-NMR** (162 MHz, CD_2Cl_2) ppm δ 61.9. **$[\alpha]^{22}_D$** = +321.1 (CH_2Cl_2, *c* = 1). FT-IR (film): ν = 3047.9, 2970.8, 2932.2, 2865.7, 1589.0, 1430.9, 1308.5, 1151.3, 979.7, 908.3, 837.9 cm^{-1}. **HRMS** (ESI +): calcd. for $C_{30}H_{31}O_3P$: 392.15386, found: 369.15341 $[M+Na]^+$. **MP** = 114-115°C.

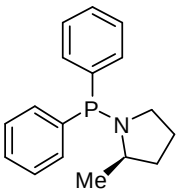
1-(diphenylphosphino)pyrrolidine (6g)



The product was prepared according to the General Procedure using pyrrolidine (1.5 mL, 18 mmol), chlorodiphenylphosphine (0.7 mL, 3.76 mmol). It was purified by column chromatography on neutral alumina (eluent: hexane / CH_2Cl_2 / TEA 9:1:0.3)

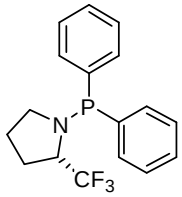
to afford a white solid. Yield = 85%. CAS 22859-55-8. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 7.48-7.36 (m, 10H), 3.10 (dt, *J* = 3.8 Hz, *J* = 6.5 Hz, 4H), 1.82 (m, 4H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 140.1 (d, $J_{C,P}$ = 13.2 Hz), 132.8, 132.6, 128.9, 128.8, 128.7, 50.3 (d, $J_{C,P}$ = 12.9 Hz), 27.1 (d, $J_{C,P}$ = 5.2 Hz). **^{31}P-NMR** (162 MHz, CD_2Cl_2) ppm δ 48.2. **MS** (ESI +): calcd. for $C_{16}H_{18}NP$: 255.11, found: 278.15 $[M+Na]^+$.

(*R*)-1-(diphenylphosphino)-2-methylpyrrolidine [(*R*)-6h]



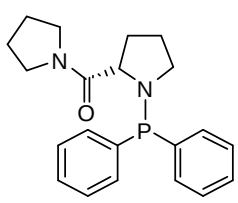
The product was prepared according to the General Procedure using (*R*)-2-methylpyrrolidine (0.490 mL, 4.70 mmol), chlorodiphenylphosphine (0.7 mL, 3.76 mmol) and triethylamine (0.68 mL, 4.89 mmol). It was purified by column chromatography on neutral alumina (eluent: hexane / CH_2Cl_2 / TEA 9:1:0.3) to afford a clean oil. Yield = 77%. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 7.51-7.35 (m, 10H), 3.67 (m, 1H), 3.03 (m, 1H), 2.76 (m, 1H,), 2.04 (dq, *J* = 7.2 Hz, *J* =12.0 Hz, 1H), 1.87 (m, 1H), 1.70 (m, 1H), 1.56 (m, 1H), 1.33 (d, *J* = 6.0 Hz, 3H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 140.8 (d, $J_{C,P}$ = 8.5 Hz), 139.9 (d, $J_{C,P}$ = 17.1 Hz), 133.3, 133.1, 132.3, 132.1, 129.0, 128.7, 128.7, 128.5, 59.1 (d, $J_{C,P}$ = 30.5 Hz) , 47.4 (d, $J_{C,P}$ = 9.3 Hz) , 35.1 (d, $J_{C,P}$ = 6.1 HZ), 25.8, 23.3 (d, $J_{C,P}$ = 8.0 Hz). **^{31}P-NMR** (162 MHz, CD_2Cl_2) ppm δ 42.6. **$[\alpha]^{25}_{D}$** = -29.0 (CH_2Cl_2, *c* = 1). **FT-IR** (film): ν = 3066.3, 2959.2, 2864.7, 1585.2, 1478.2, 1432.9, 1370.8, 1063.5, 743.4, 698.1 cm^{-1}. **MS** (ESI +): calcd. for $C_{17}H_{20}NP$: 269.12, found: 292.33 $[M+Na]^+$.

(*S*)-1-(diphenylphosphino)-2-(trifluoromethyl)pyrrolidine [(*R*)-6i]



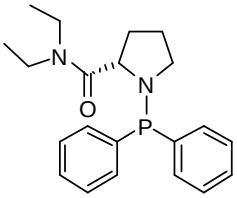
The product was prepared according to the General Procedure using (*R*)-2-methylpyrrolidine (650 mg, 4.70 mmol), chlorodiphenylphosphine (0.7 mL, 3.76 mmol) and triethylamine (0.68 mL, 4.89 mmol). It was purified by column chromatography on neutral alumina (eluent: hexane / CH_2Cl_2 / TEA 9:1:0.3) to afford a white solid. Yield = 86%. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 7.50-7.37 (m, 10H), 4.16 (m, 1H), 3.11 (m, 1H), 2.79 (m, 1H), 2.14-1.79 (m, 3H), 1.65 (m, 1H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 139.4 (d, $J_{C,P}$ = 7.3 Hz), 138.5 (d, $J_{C,P}$ = 16.2 Hz), 133.7, 133.5, 131.8, 131.6, 129.8, 128.9, 128.8, 128.7, 65.8 (dq, $J_{C,P}$ = 34.6 Hz, $J_{C,F}$ = 28.8 Hz) , 47.9 (d, $J_{C,P}$ = 9.7 Hz), 27.6 (d, $J_{C,P}$ = 3.6 Hz), 26.0. **^{31}P-NMR** (162 MHz, CD_2Cl_2) ppm δ 57.4 (1P, q, $J_{P,F}$ = 16.5 Hz). **$[\alpha]^{25}_{D}$** =:+16.7 (CH_2Cl_2, *c* = 1). FT-IR (film): ν = 3069.2, 2982.4, 2916.8, 1959.3, 1887.0, 1586.2, 1480.0, 1433.3,1285.3, 745.4 cm^{-1}. **MS** (ESI +): calcd. for $C_{17}H_{17}F_3NP$: 323.11, found: 324.75 $[M+H]^+$. **MP** = 79-81°C.

(*S*)-1-(diphenylphosphino)-2-(pyrrolidine-1-carbonyl)pyrrolidine [(*S*)-6j]



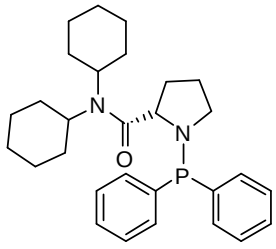
The product was prepared according to the General Procedure using (*S*)-2-(pyrrolidinecarbonyl)pyrrolidine **4a** (395 mg, 2.35 mmol), chlorodiphenylphosphine (0.35 mL, 1.88 mmol) and triethylamine (0.34 mL, 2.44 mmol). It was purified by column chromatography on neutral alumina (eluent: hexane / CH_2Cl_2 / TEA 9:1:0.3) to afford a white solid. Yield = 36%. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 7.58-7.54 (m, 2H), 7.44-7.32 (m, 8H), 4.36 (m, 1H), 3.65 (m, 1H), 3.48-3.39 (m, 3H), 3.17 (m, 1H), 2.90 (m, 1H), 2.10 (m, 1H), 2.00-1.71 (m, 7H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 172.7, 139.2 (d, $J_{C,P}$ = 7.6 Hz), 138.1 (d, $J_{C,P}$ = 9.2 Hz), 132.4, 132.3, 132.1, 131.9, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 63.8 (dq, $J_{C,P}$ = 38.3 Hz), 47.6 (d, $J_{C,P}$ = 4.7 Hz), 46.2, 46.0, 31.0 (d, $J_{C,P}$ = 6.3 Hz), 26.3, 25.9, 24.1. ^{31}P-NMR (162 MHz, CD_2Cl_2) ppm δ 48.7. **MS** (ESI +): calcd. for $C_{21}H_{25}N_2OP$: 352.16, found: 375.43 $[M+Na]^+$.

(*S*)-1-(diphenylphosphino)-2-(*N*,*N*-diethylaminocarbonyl)pyrrolidine [(*S*)-6k]



The product was prepared according to the General Procedure using (*S*)-2-(diethylaminocarbonyl)pyrrolidine **4b** (400 mg, 2.35 mmol), chlorodiphenylphosphine (0.35 mL, 1.88 mmol) and triethylamine (0.34 mL, 2.44 mmol). It was purified by column chromatography on neutral alumina (eluent: hexane / CH_2Cl_2 / TEA 9:1:0.3) to afford a white solid. Yield = 38%. **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 7.57-7.53 (m, 2H), 7.44-7.32 (m, 8H), 4.46 (m, 1H), 3.68-3.30 (m, 4H), 3.18 (m, 1H), 2.92 (m, 1H), 2.10-1.86 (m, 3H), 1.72 (m, 1H), 1.25-1.10 (m, 6H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 173.1, 139.2 (d, $J_{C,P}$ = 7.0 Hz), 138.7 (d, $J_{C,P}$ = 14.1 Hz), 132.4, 132.2, 132.0, 128.2, 128.0, 127.8, 127.7, 63.9 (d, $J_{C,P}$ = 32.2 Hz) , 48.1 (d, $J_{C,P}$ = 3.6 Hz), 30.1 (d, $J_{C,P}$ = 11.6 Hz), 26.7, 26.1, 25.7, 25.6, 25.3. **^{31}P-NMR** (162 MHz, CD_2Cl_2) ppm δ 48.7. **MS** (ESI +): calcd. for $C_{21}H_{27}N_2OP$: 377.18, found: 377.03 $[M+Na]^+$.

(*S*)-*N*,*N*-dicyclohexyl-1-(diphenylphosphino)pyrrolidine-2-carboxamide [(*S*)-6l]



The product was prepared according to the General Procedure using (*S*)-2-(dicyclohexylaminocarbonyl)pyrrolidine **4c** (165 mg, 0.59 mmol), chlorodiphenylphosphine (90 μL, 0.48 mmol) and triethylamine (0.90 mL, 0.62 mmol). It was purified by column chromatography on neutral alumina (eluent: hexane / CH_2Cl_2 / TEA 9:1:0.3) to afford a white solid. Yield = 42%. $[\alpha]^{25}_D$ =: -35.5 (CH_2Cl_2, *c* = 1). **^{1}H-NMR** (400 MHz, CD_2Cl_2) ppm δ 7.58-7.55 (m, 2H), 7.44-7.34 (m, 8H), 4.42 (m, 1H), 3.17 (m, 1H), 2.98 (m, 1H), 2.05 (m, 1H), 2.08-1.10 (m, 25H). **^{13}C-NMR** (100 MHz, CD_2Cl_2) ppm δ 173.2, 140.0 (d, $J_{C,P}$ = 14.0 Hz), 139.4 (d, $J_{C,P}$ = 10.9 Hz), 132.5, 132.2, 132.0,

128.4, 128.0, 127.9, 127.8, 61.9 (d, $J_{C,P}$ = 31.9 Hz) , 47.7, 41.7, 40.5, 31.8, 25.9, 14.7, 12.8. **^{31}P-NMR** (162 MHz, CD_2Cl_2) ppm δ 50.0. FT-IR (film): ν = 3050.8, 2929.3, 2853.7, 1646.9, 1433.8, 1363.4, 1156.1, 893.8 cm^{-1}. **MS** (ESI +): calcd. for $C_{29}H_{39}N_2OP$: 462.27, found: 485.40 $[M+Na]^+$. **MP** = 120-121°C.

2.4.8 Complexation experiments

General procedure

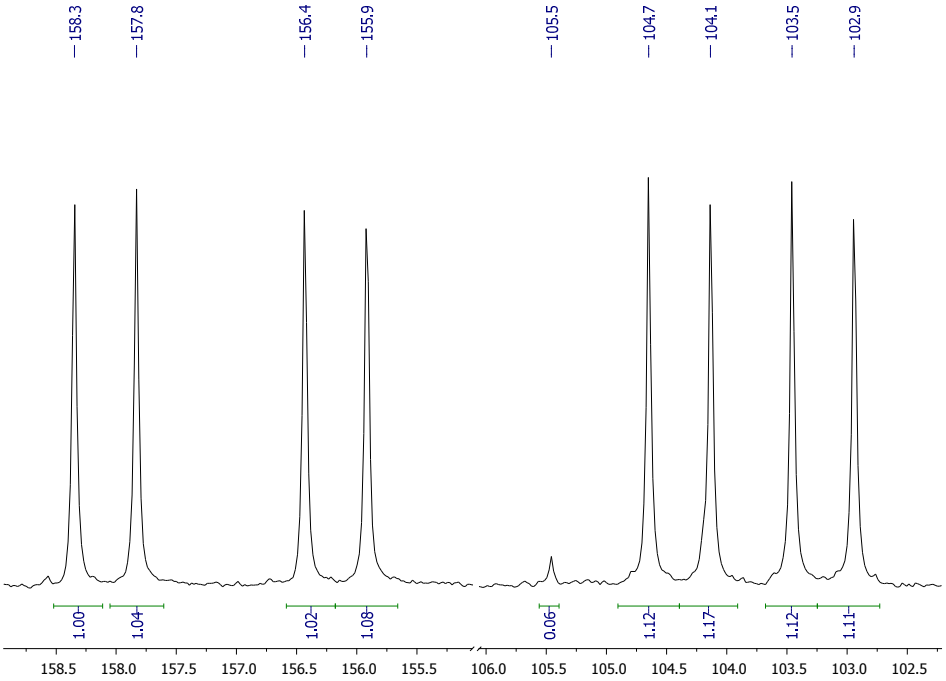
Note! Most of the phosphite ligands use to degrade in $CDCl_3$ even after solvent filtration trough alumina.

The complexation experiments were run in NMR tubes under nitrogen atmosphere and monitored by ^{1}H and ^{31}P NMR spectroscopy. The typical scale of the experiments was 0.0134 mmol of metal source in 0.75 mL of deuterated solvent (0.018 M concentration) and up to 0.0268 mmol of ligand or ligands (0.0134 mmol each). In all of the experiments CD_2Cl_2 was used as the solvent.

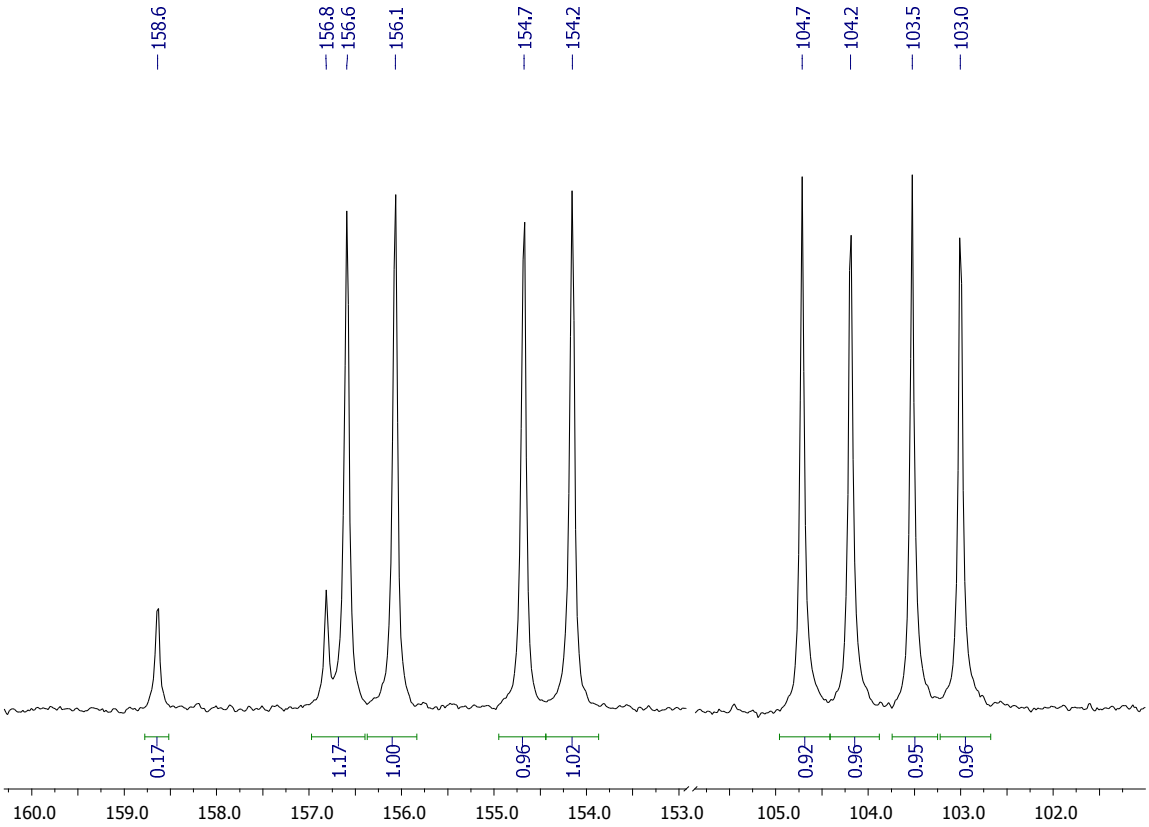
Experiments with one ligand: CD_2Cl_2 was added to a 1:1 mixture of the selected metal source and the ligand, then ^{1}H and ^{31}P-NMR spectra were recorded. The mono-ligated species was usually dominant at this stage; more ligand was added (always monitoring the experiment by NMR) until the doublet signal of the homocomplex appeared.

Ligand combinations: CD_2Cl_2 was added to a 1:1:1 mixture of ligand A, ligand B and the selected metal source then ^{1}H and ^{31}P NMR spectra were recorded. It is important to remark that the formation of the heterocomplexes proved kinetically quite slow, and an equilibration time of the order of 1-2 h was necessary for observing the hetero/homocomplexes ratios reported into Table 5.2.

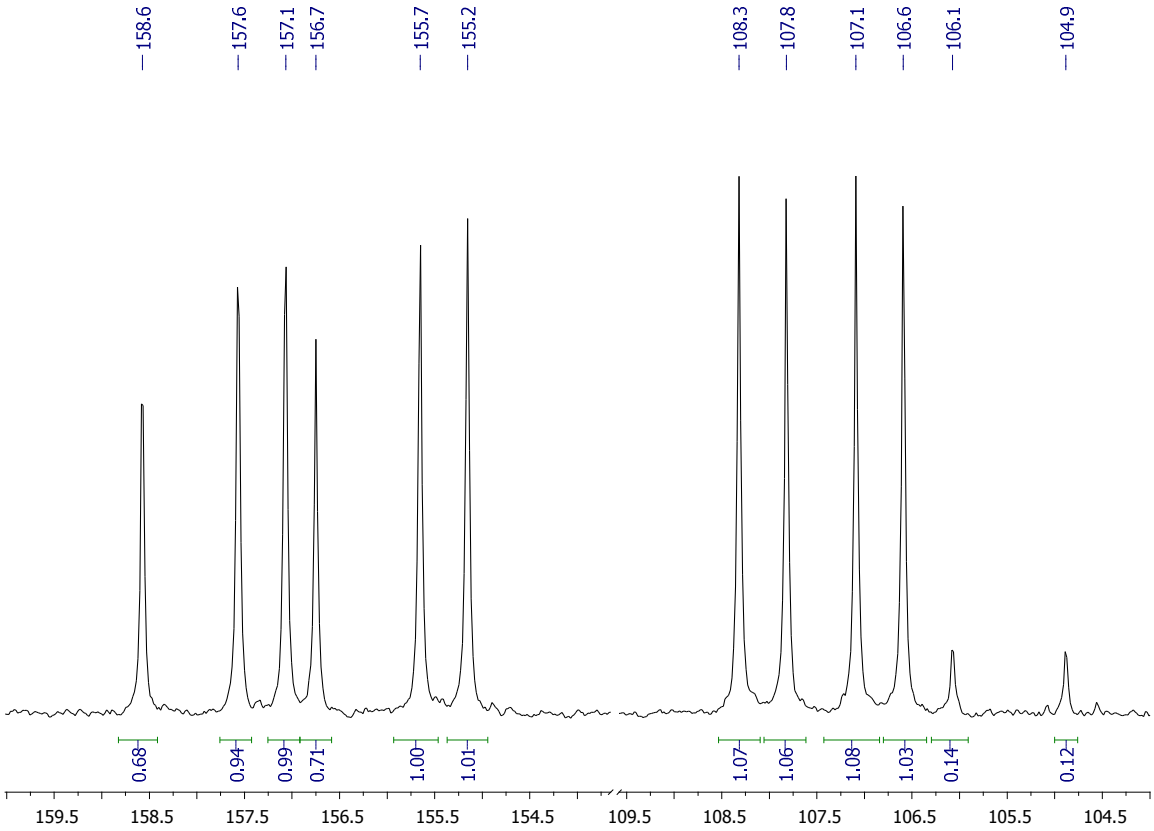
(*R*)-**2b**/(*R*)-**6b**: Heterocomplex/**6b** Homocomplex = 99 : 1



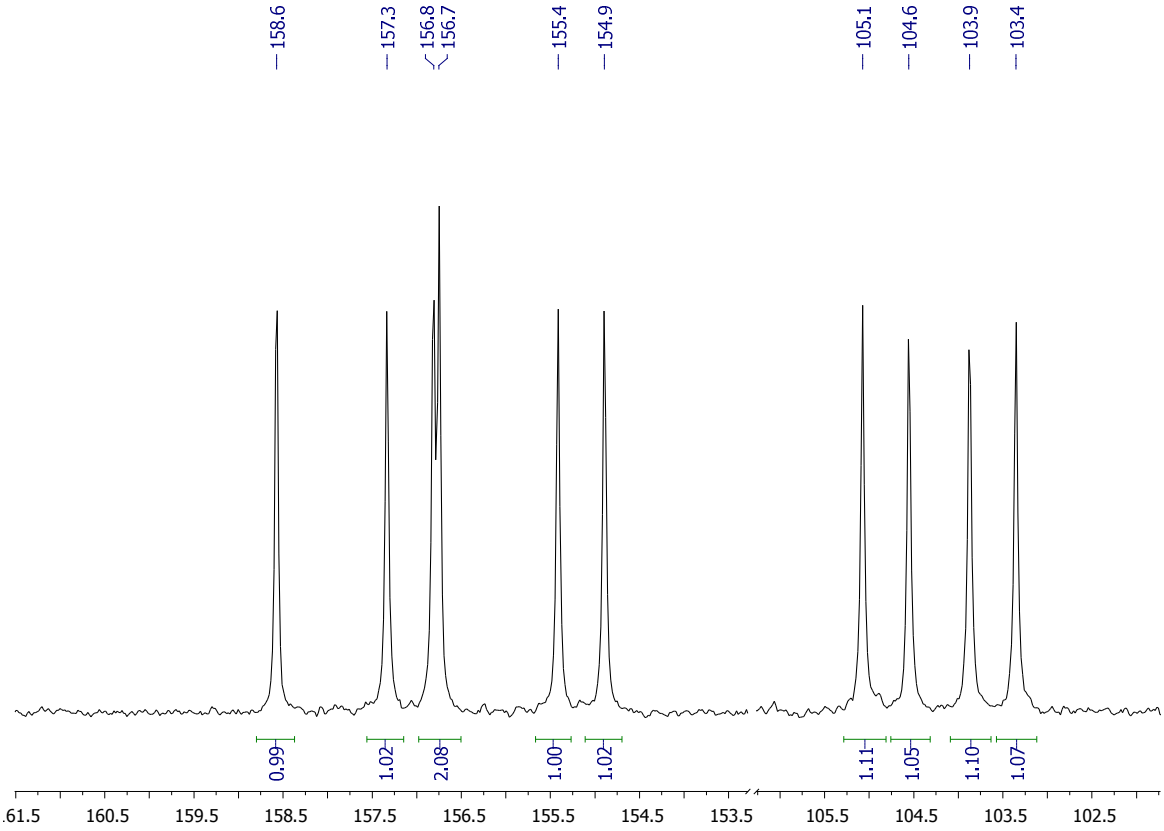
(*R*)-**2b**/(*S*)-**6b**: Heterocomplex/**6b** Homocomplex = 96 : 4



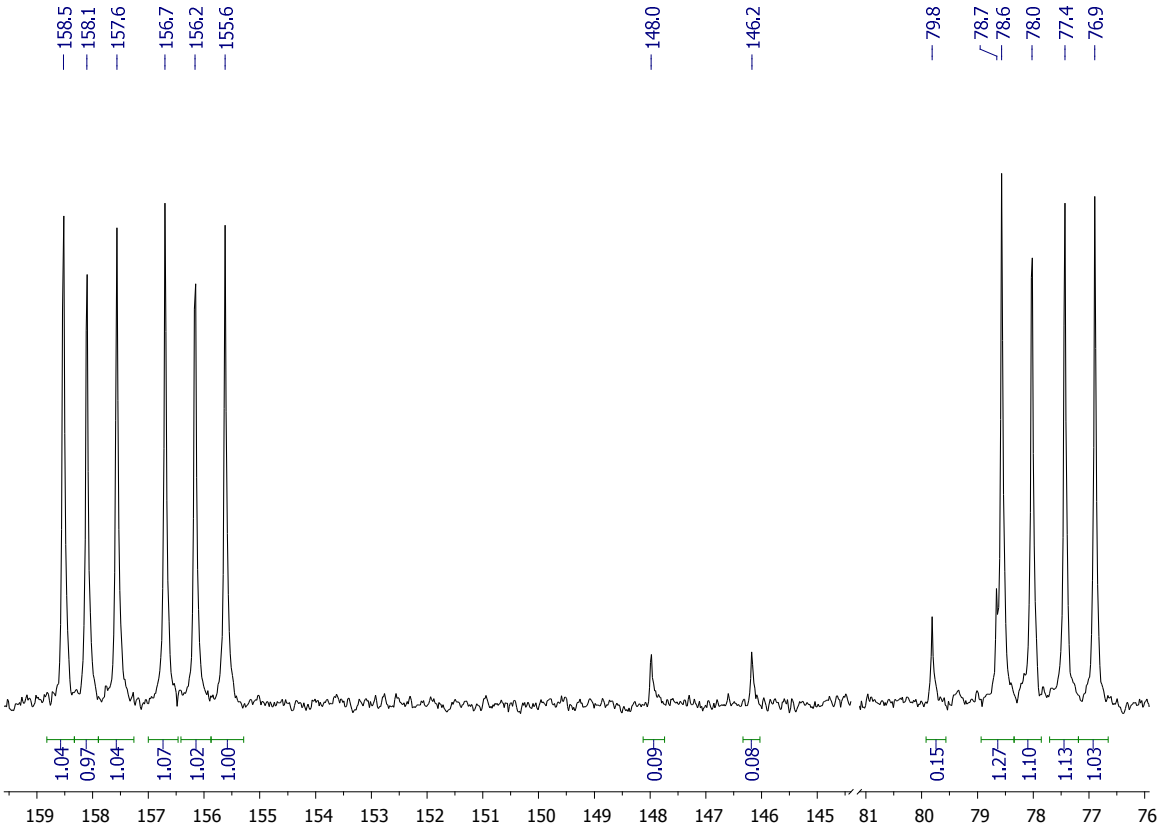
(*R*)-**2b**/(*R*)-**6c**: Heterocomplex/**2b** Homocomplex /**6c** Monocomplex = 81 : 14 : 5



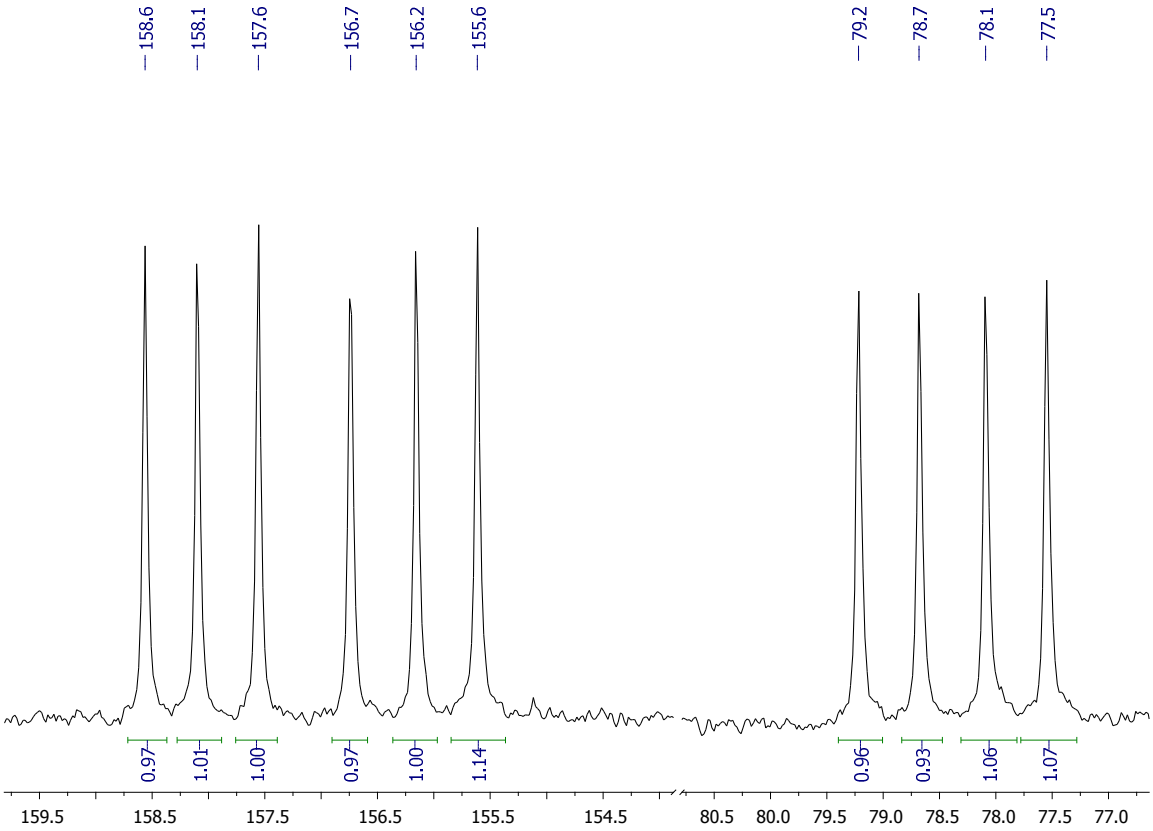
<u>*S*)-**2b**/(*R*)-**6c**: Heterocomplex/**6b** Homocomplex / = 81 : 19</u>



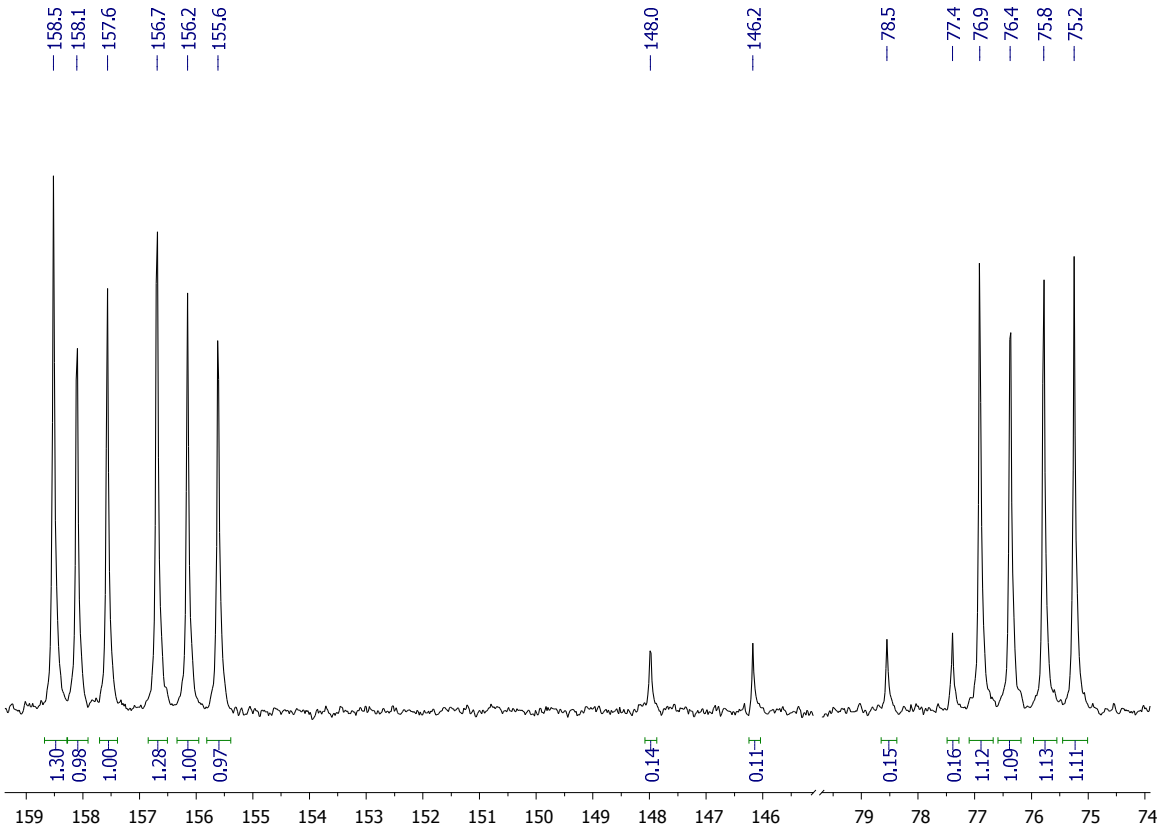
(*R*)-**2b**/(*R*)-**6d**: Heterocomplex/**2b** Homocomplex /**2b** Monocomplex /**6d** Monocomplex = 74 : 18 : 3 :5



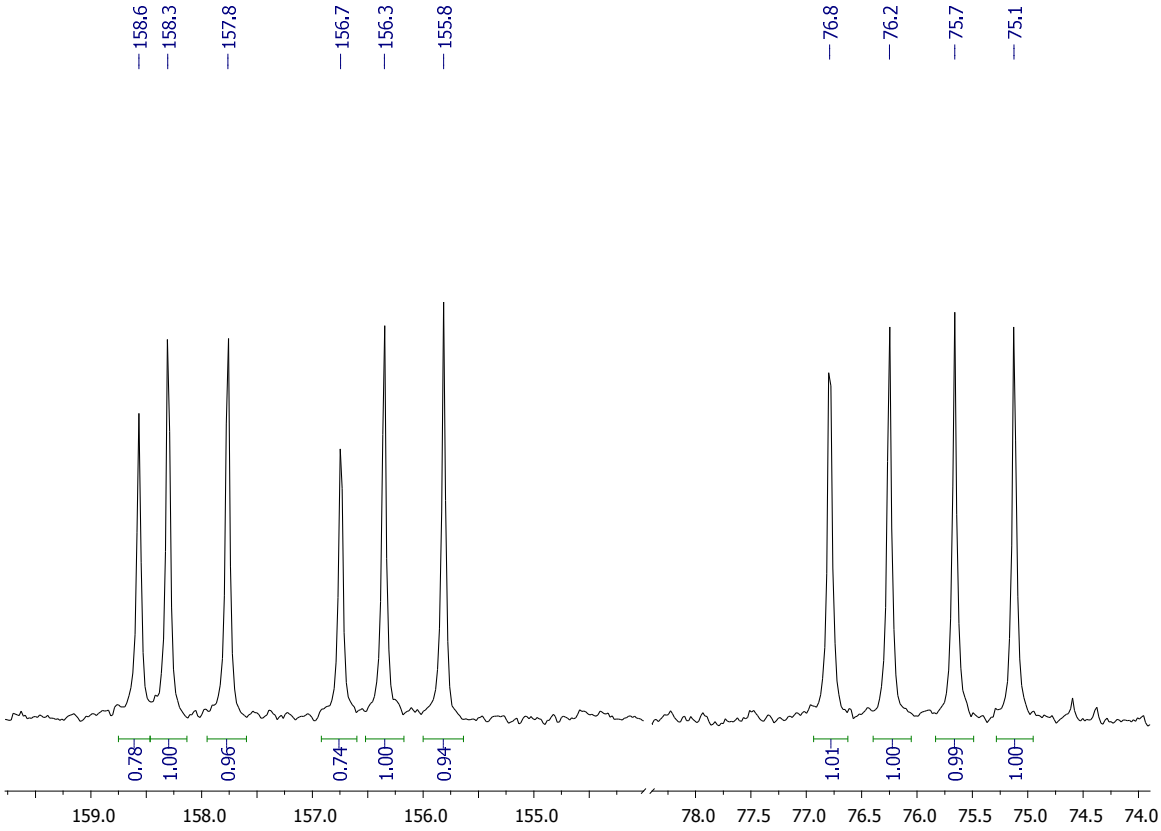
(*S*)-**2b**/(*R*)-**6d**: Heterocomplex/**6d** Homocomplex = 81 : 19



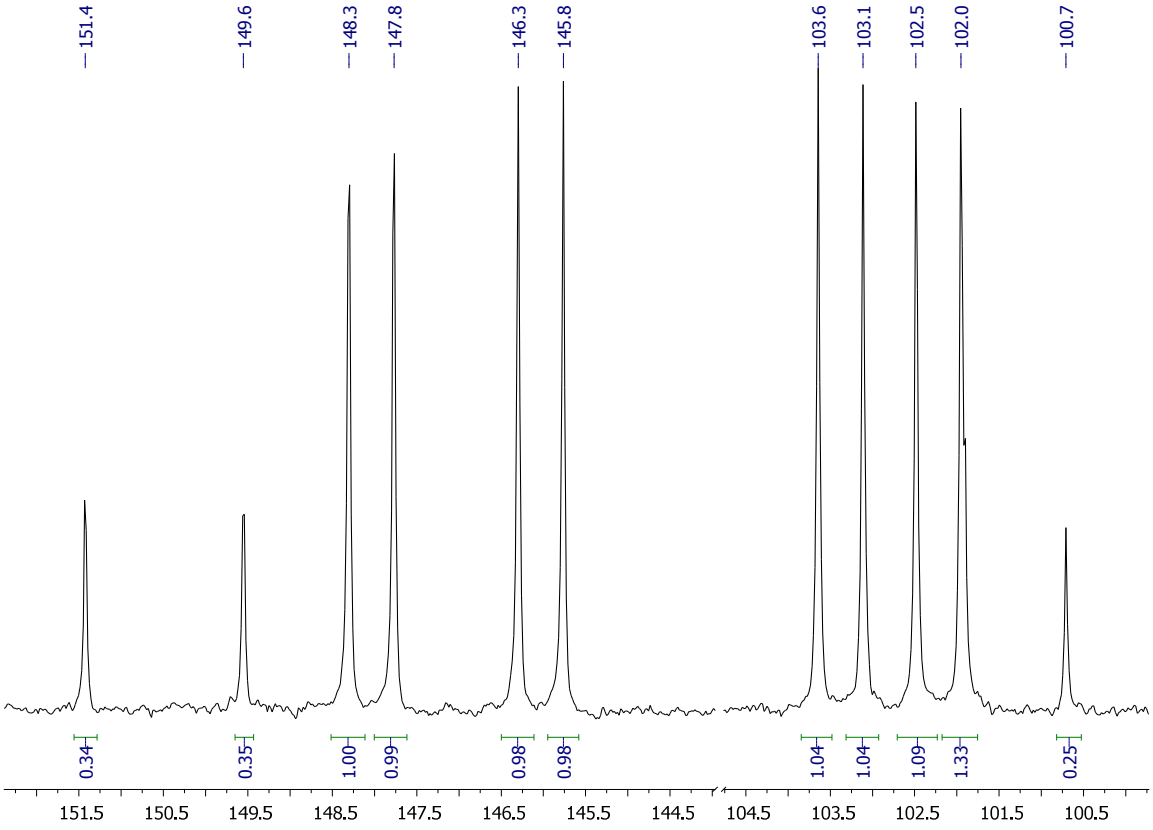
(*R*)-**2b**/(*S*)-**6e**: Heterocomplex /**2b** Homocomplex /**2b** Monocomplex /**6e** Monocomplex = 70 : 21 : 4 :5



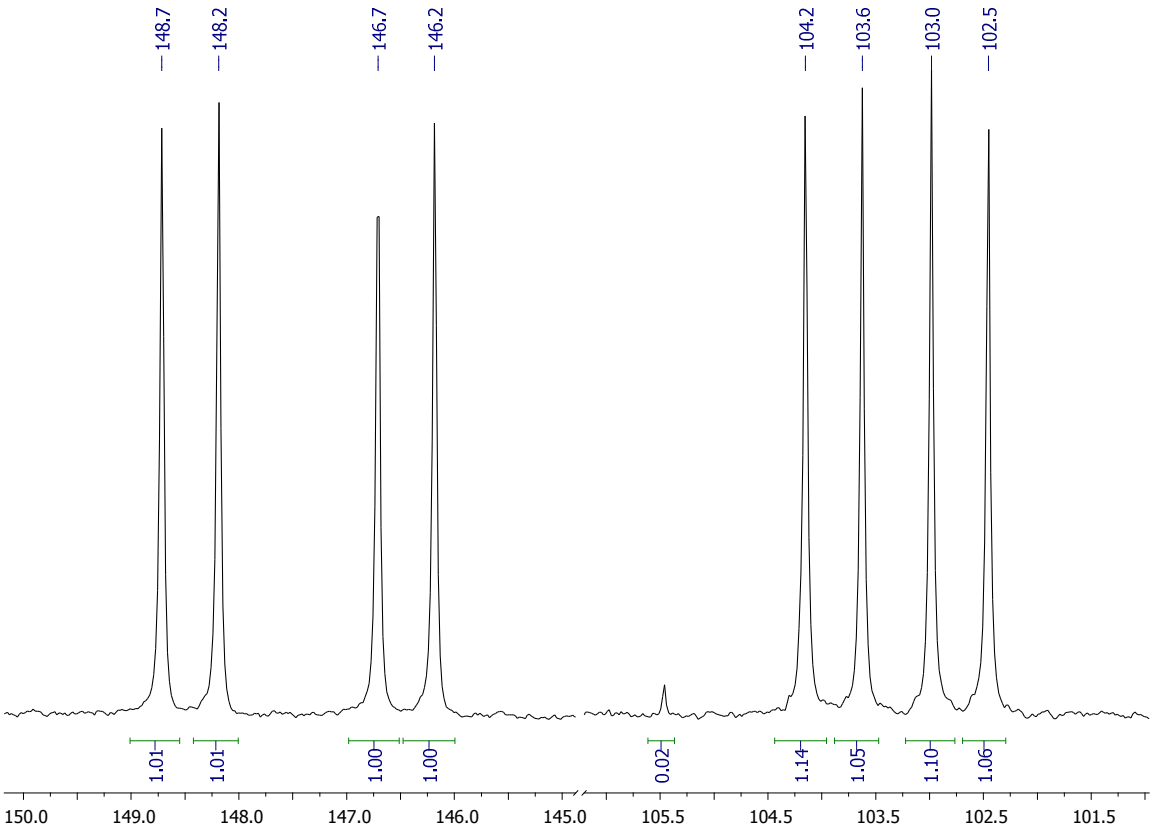
(*S*)-**2b**/(*S*)-**6e**: Heterocomplex/**2b** Homocomplex = 84 : 16



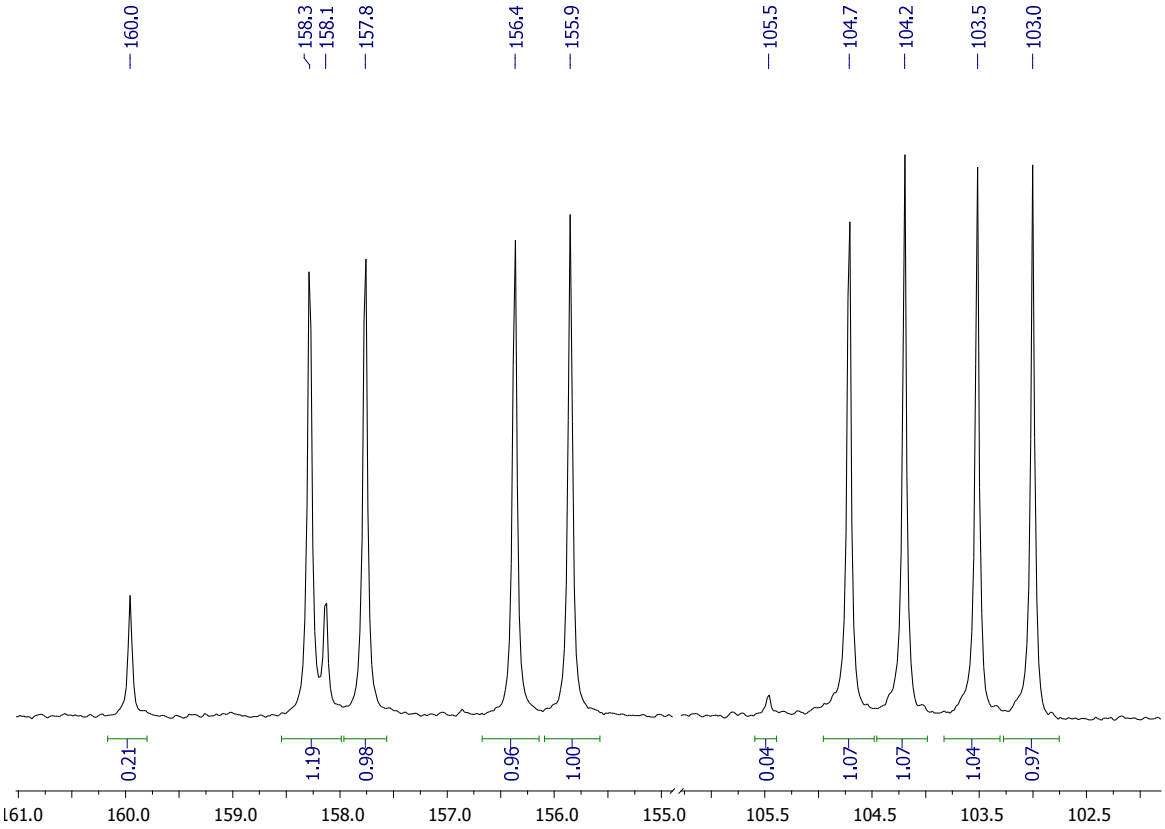
(*S*)-**2a**/(*R*)-**6b**: Heterocomplex/**2a** Homocomplex /**6b** Monocomplex = 83 : 7 : 10



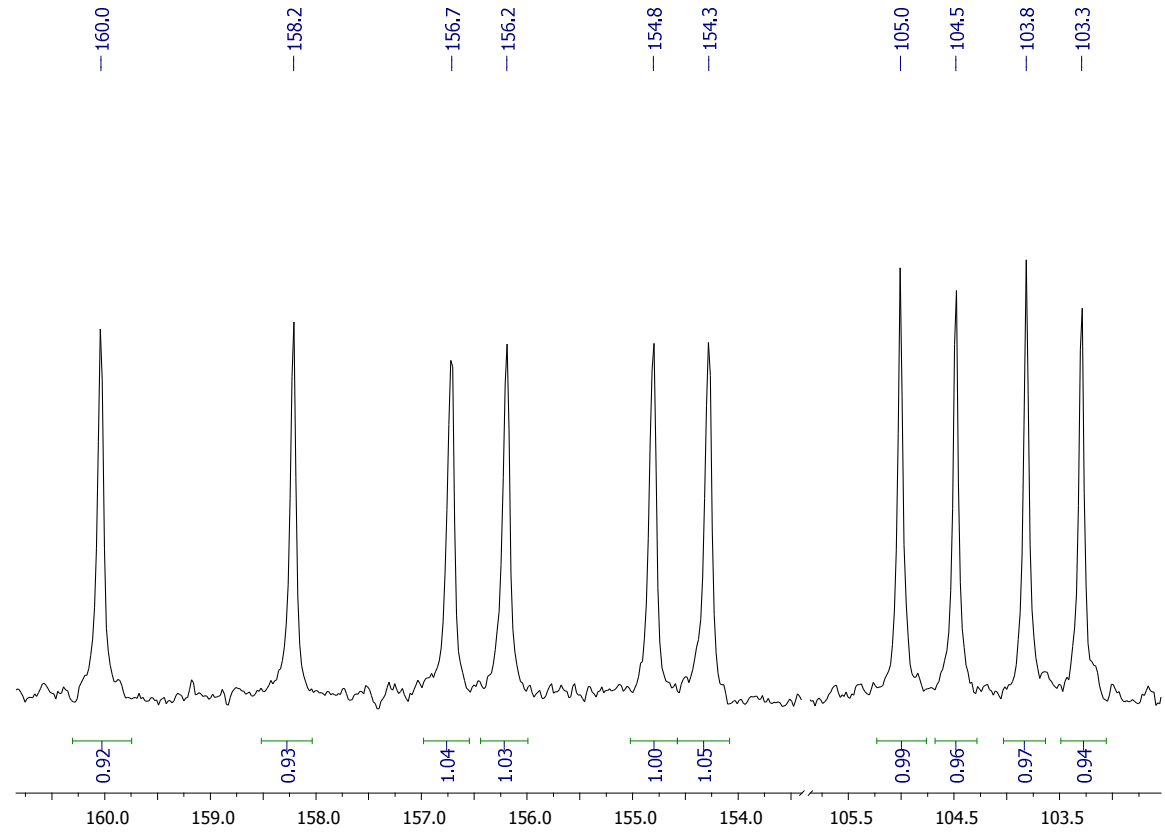
(*S*)-**102a**/(*S*)-**112b**: Heterocomplex/**112b** Homocomplex > 99 : 1



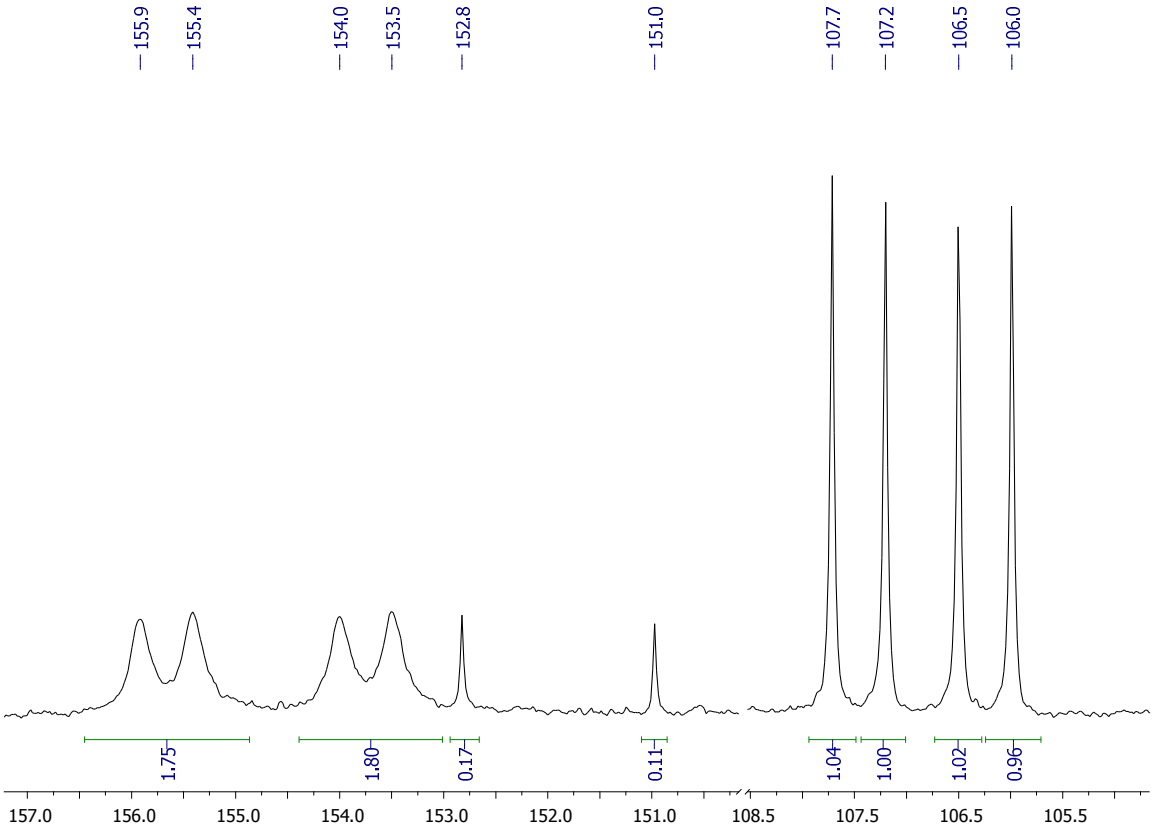
(*R*)-**2c**/(*R*)-**6b**: Heterocomplex/**2c** Homocomplex /**6b** Homocomplex = 94 : 5 :1



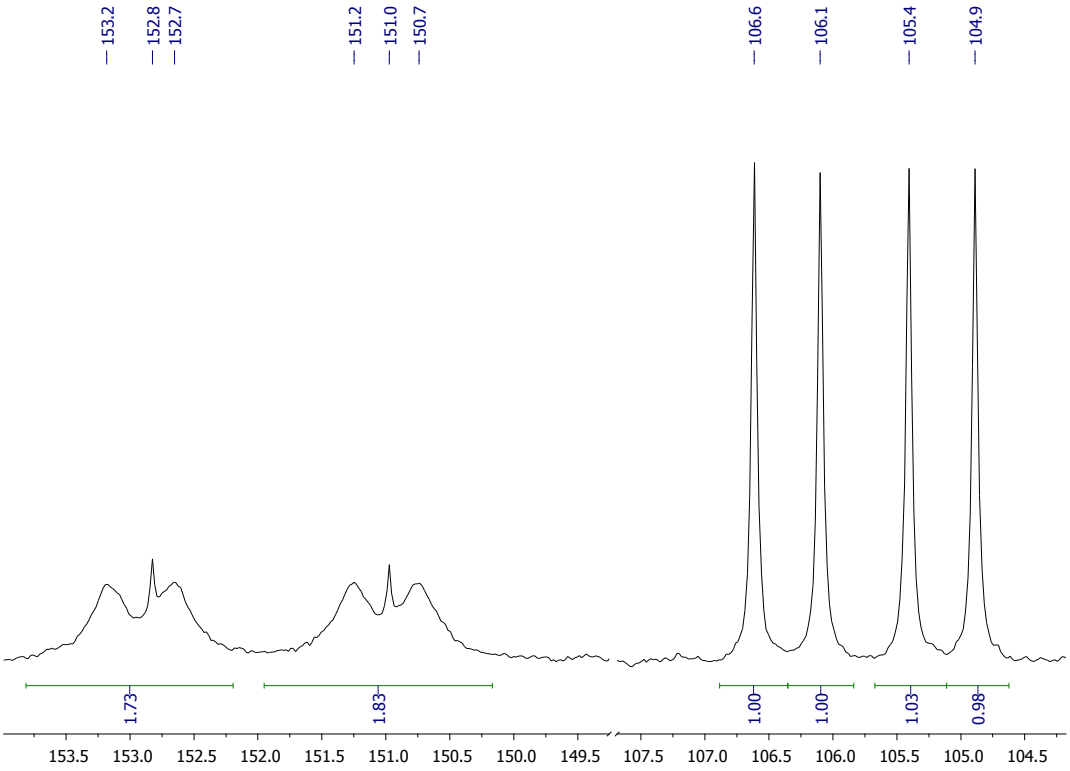
(*R*)-**2c**/(*S*)-**6b**: Heterocomplex/**2c** Homocomplex = 81 : 19



(*R*)-**2d**/(*R*)-**6b**: Heterocomplex/**2d** Homocomplex = 96 : 4



(*R*)-**2d**/(*S*)-**6b**: Heterocomplex/**2d** Homocomplex > 9 :1 (an exact assessment was not possible in this case)



2.4.9 Computational calculations

Methods

The structures of the ligands were pre-optimised using the semi-empirical PM6 Hamiltonian,[26] within the Mopac2009 programme.[27] Rhodium was considered as a +1 cation in square planar geometry, bearing the anionic acac ligand, $(CH_3COCHCOCH_3)^-$, and bound in a bidentate fashion through the oxygen atoms. The whole complex is a closed-shell neutral molecule. After pre-optimisation using PM6,[27] calculations were performed at the B3LYP/SDD level of theory[28] in the Gaussian03 programme suite.[29] The employed basis set consists of SDD effective core potential[30] for rhodium and Dunning-Hay valence double-ζ basis D95V set for the remaining atoms. All degrees of freedom were free to optimise with default convergence criteria. The nature of the obtained stationary points was confirmed by frequency calculation within the same level of theory. Free energies of isodesmic reactions were calculated in order to minimise the error resulting from inadequate treatment of electron correlation.

Results

In the Scheme 2.5 (see section 2.2.1.2), the hypothetical reaction could be described as ligand exchange between two homocomplexes, $[Rh(P[OPh]_3)_2(acac)]$ and $[Rh(PPh_3)_2(acac)]$, forming the heterocomplex $[Rh(PPh_3)(P[OPh]_3)(acac)]$. Calculated energies in kcal/mol, at temperature T = 298 K, are shown in Table 2.13. From the results it can be concluded that the heterocomplex formation is favoured. The calculated quantities are as following: E = electronic energy, G = Gibbs free energy, H = enthalpy, TS = temperature (298 K) times entropy.

Table 2.12 Calculated energies for phosphite-phosphine heterocomplex at T = 298 K temperature

	E	**G**	**H**	**TS**
phosphite	-1869661.80	-1869289.38	-1869196.66	92.67
phosphine	-1586441.70	-1586074.30	-1585994.36	79.90
heterocomplex	-1728055.28	-1727684.39	-1727599.01	85.34
reaction	-7.06	-5.11	-7.00	-1.89

In the Scheme 2.6 (see section 2.2.1.2), the hypothetical reaction could be described as ligand exchange between two homocomplexes, $[Rh(P[OPh]_3)_2(acac)]$ and $[Rh(PPh_2NMe_2)_2(acac)]$, forming the heterocomplex $[Rh(PPh_2NMe_2)(P[OPh]_3)(acac)]$). Calculated energies in kcal/mol, at temperature T = 298 K, are shown in Table 2.14. Again, the heterocomplex formation is significantly favoured.

Table 2.13 Calculated energies for phosphite-phosphinamine heterocomplex at T = 298 K temperature

	E	**G**	**H**	**TS**
phosphite	-1869661.80	-1869289.38	-1869196.66	92.67

phosphinamine	-1464618.28	-1464258.05	-1464181.99	76.02
heterocomplex	-1667143.61	-1666779.35	-1666692.96	86.35
reaction	-7.15	-11.29	-7.27	4.02

Optimized geometries as XYZ coordinates for all 5 structures (two phosphite complexes are identical), distances in Ångstroms:

Rh(P[OPh]$_3$)$_2$(acac)]

```
  89
scf: -2979.497982
Rh    -0.275792    -1.234429     0.098781
 H    -3.287161    -5.167736    -1.419462
 C    -3.251852    -4.076613    -1.352398
 C    -1.930415    -3.586031    -0.797230
 H    -4.072873    -3.720629    -0.719070
 H    -3.413584    -3.652023    -2.351877
 O    -1.863385    -2.287251    -0.617288
 C    -0.887744    -4.497791    -0.523886
 C     0.391057    -4.162024    -0.019281
 H    -1.081734    -5.545582    -0.720786
 C     1.424062    -5.242992     0.225777
 O     0.792563    -2.951846     0.274500
 H     1.670685    -5.278076     1.294943
 H     1.070644    -6.228127    -0.091784
 H     2.347785    -4.994602    -0.310568
 O     3.116909    -0.921044     0.716179
 P     1.587478    -0.101742     0.746580
 O     1.908411     1.298481    -0.179944
 O     1.833479     0.543219     2.331051
 O    -2.035624     1.293014    -1.577465
 P    -1.594314     0.609197    -0.031340
 O    -3.206026     0.580127     0.591228
 O    -1.067080     1.962001     0.861707
 C     1.207603     0.030862     3.496484
 C     1.838551    -0.999326     4.213931
 C     0.015724     0.624161     3.944815
 C     1.258276    -1.442690     5.416985
 H     2.759647    -1.429850     3.831958
 C    -0.552012     0.172067     5.150631
 H    -0.442221     1.412728     3.355461
 C     0.065004    -0.858594     5.888262
 H     1.737362    -2.237826     5.983321
 H    -1.473013     0.624266     5.510483
 H    -0.378402    -1.202313     6.819603
 C     3.022616     2.172082    -0.193603
 C     3.208502     2.874808    -1.397950
 C     3.867316     2.372247     0.913247
 C     4.265855     3.796429    -1.496789
 H     2.531535     2.689405    -2.226694
 C     4.924461     3.294341     0.793413
 H     3.695258     1.829566     1.835245
 C     5.129490     4.008491    -0.403058
 H     4.415447     4.342223    -2.425359
 H     5.584982     3.454355     1.642292
```

```
H     5.948608     4.718663    -0.482739
C     3.647872    -1.659489    -0.359887
C     4.628547    -2.608905    -0.022592
C     3.274396    -1.444503    -1.699905
C     5.242223    -3.357584    -1.041836
H     4.894447    -2.741268     1.021635
C     3.892070    -2.207015    -2.708865
H     2.525464    -0.701187    -1.956401
C     4.874727    -3.163595    -2.389551
H     6.005940    -4.087731    -0.783977
H     3.606086    -2.044612    -3.745444
H     5.351338    -3.742977    -3.176136
C    -1.499334     3.311595     0.782029
C    -2.831570     3.674466     1.047356
C    -0.510945     4.271253     0.505282
C    -3.174552     5.039671     1.024499
H    -3.566169     2.905372     1.258459
C    -0.868848     5.632133     0.495170
H     0.506626     3.944989     0.314689
C    -2.199851     6.019957     0.750963
H    -4.201847     5.334357     1.225146
H    -0.110300     6.383514     0.289737
H    -2.472665     7.072300     0.741104
C    -1.228089     1.252506    -2.738801
C    -0.782376     2.476148    -3.266985
C    -0.954239     0.031535    -3.381560
C    -0.050822     2.476041    -4.469089
H    -1.016831     3.397755    -2.742373
C    -0.215342     0.045639    -4.579361
H    -1.315367    -0.898154    -2.952797
C     0.237046     1.262608    -5.127023
H     0.289361     3.419293    -4.889980
H     0.000748    -0.893061    -5.084182
H     0.802571     1.266495    -6.055494
C    -4.299621    -0.210189     0.169056
C    -4.834807    -1.119936     1.096889
C    -4.890990    -0.012667    -1.091897
C    -5.988916    -1.847799     0.754217
H    -4.350646    -1.239561     2.061643
C    -6.039709    -0.754625    -1.424806
H    -4.455642     0.703581    -1.780754
C    -6.593230    -1.670449    -0.507455
H    -6.414972    -2.546631     1.470279
H    -6.505888    -0.608301    -2.396405
H    -7.486856    -2.232100    -0.768437
```

[Rh(PPh$_3$)$_2$(acac)]

```
  83
scf: -2528.15767805
C    -1.211722    -2.967171     0.825890
C    -1.605488    -2.121621    -0.234652
C    -1.826766    -2.684850    -1.508237
C    -1.681759    -4.069808    -1.712532
C    -1.307495    -4.909573    -0.647310
C    -1.068470    -4.351240     0.623283
P    -1.777973    -0.262661     0.047480
```

Rh	0.039795	1.254192	0.055591
O	1.448004	2.743843	0.018458
C	1.230785	4.030910	-0.036338
C	-0.042321	4.651988	-0.044223
C	-1.285882	3.982940	0.010443
C	-2.578800	4.779524	0.000319
C	-3.015954	0.211357	-1.301484
C	-4.373969	-0.165150	-1.259318
C	-5.245190	0.193938	-2.305119
C	-4.765198	0.930685	-3.405871
C	-3.410652	1.312708	-3.449468
C	-2.542384	0.958744	-2.399708
C	-2.807361	-0.214161	1.635868
C	-2.656101	0.894351	2.496616
C	-3.413355	0.986349	3.679607
C	-4.329107	-0.028344	4.017923
C	-4.482353	-1.138222	3.164422
C	-3.727727	-1.229196	1.979872
O	-1.443163	2.684787	0.071720
P	1.814032	-0.281003	0.001417
C	3.531859	0.482140	-0.228918
C	4.303043	0.298166	-1.392287
C	5.575867	0.894227	-1.506630
C	6.087727	1.679518	-0.458357
C	5.315667	1.870518	0.705946
C	4.045213	1.281363	0.816414
C	1.751178	-1.526343	-1.412343
C	1.391792	-1.014919	-2.680359
C	1.363551	-1.853223	-3.808427
C	1.678627	-3.220732	-3.679146
C	2.010468	-3.739564	-2.414268
C	2.048504	-2.896478	-1.286277
C	2.135886	-1.272027	1.576015
C	3.283018	-2.080851	1.735251
C	3.511915	-2.760600	2.945419
C	2.603009	-2.627947	4.014933
C	1.471478	-1.803425	3.869420
C	1.241481	-1.128245	2.655176
C	2.484609	4.885868	-0.102870
H	-3.032633	1.890801	-4.289812
H	-1.502398	1.275179	-2.413180
H	-5.439201	1.207901	-4.213496
H	-6.291811	-0.098470	-2.258269
H	-4.764788	-0.725133	-0.415271
H	-2.121165	-2.052923	-2.340843
H	-1.031113	-2.557640	1.815049
H	-1.952992	1.678081	2.233361
H	-3.843968	-2.102935	1.344329
H	-1.858474	-4.485912	-2.701561
H	-0.772980	-4.986613	1.455006
H	-3.285472	1.846300	4.333251
H	-5.183688	-1.930041	3.417911
H	-1.202091	-5.980729	-0.804472
H	-4.911852	0.041935	4.933744
H	0.776624	-1.676559	4.696455
H	0.385544	-0.466461	2.547615

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 H     2.784397    -3.148423     4.952717
 H     4.399051    -3.379842     3.057094
 H     4.013080    -2.156513     0.933413
 H     1.127124     0.036191    -2.774813
 H     2.290182    -3.319859    -0.316982
 H     3.931235    -0.312377    -2.209342
 H     3.451398     1.448228     1.710824
 H     1.091565    -1.443286    -4.778437
 H     2.234301    -4.797672    -2.299565
 H     6.161421     0.738590    -2.410065
 H     5.700061     2.478264     1.522140
 H     1.654769    -3.872674    -4.549542
 H     7.071514     2.135687    -0.544693
 H    -0.063853     5.734989    -0.094201
 H    -3.154136     4.565082     0.910390
 H    -2.397788     5.856791    -0.062939
 H    -3.196425     4.466010    -0.850939
 H     3.132986     4.659946     0.752735
 H     3.052569     4.636481    -1.008473
 H     2.252862     5.955269    -0.107668
```

[Rh(PPh$_3$)(P[OPh]$_3$)(acac)]

```
   86
scf: -2753.833454
Rh    -0.317372    -1.246075     0.027370
 H     2.021742    -5.823282     0.839647
 C     2.219137    -4.751075     0.748928
 C     0.946022    -3.954077     0.540279
 H     2.901382    -4.575076    -0.091737
 H     2.731253    -4.402955     1.655505
 O     1.125813    -2.666187     0.388584
 C    -0.309610    -4.603635     0.527108
 C    -1.562009    -3.972467     0.345120
 H    -0.313468    -5.677654     0.673766
 C    -2.833967    -4.799921     0.362708
 O    -1.748651    -2.691622     0.146685
 H    -3.301670    -4.776425    -0.630542
 H    -2.642806    -5.840891     0.639338
 H    -3.550156    -4.358705     1.065850
 P    -2.063043     0.334376    -0.241731
 O     2.635436     0.467320     0.915708
 P     1.377292     0.195313    -0.279724
 O     2.503963    -0.142564    -1.564440
 O     1.001779     1.790916    -0.776769
 C     1.857675     2.907498    -0.935558
 C     2.916450     2.901889    -1.862216
 C     1.546507     4.053832    -0.183352
 C     3.678893     4.073926    -2.025556
 H     3.131257     1.999896    -2.423616
 C     2.313515     5.219638    -0.363509
 H     0.713860     4.020979     0.512477
 C     3.382988     5.233562    -1.281673
 H     4.501590     4.078764    -2.736800
 H     2.075209     6.112106     0.210529
 H     3.974866     6.135436    -1.417445
 C     2.440619     0.507189     2.312134
```

C	2.797264	1.691452	2.982094
C	1.982980	-0.622323	3.016909
C	2.696197	1.744301	4.384392
H	3.150296	2.540083	2.403469
C	1.876135	-0.551154	4.418725
H	1.727488	-1.525962	2.472953
C	2.231500	0.626142	5.107232
H	2.980461	2.653860	4.908573
H	1.521400	-1.418617	4.970694
H	2.154698	0.669417	6.190928
C	3.369774	-1.253598	-1.662543
C	3.086823	-2.231544	-2.632060
C	4.532638	-1.321056	-0.873247
C	3.988287	-3.296018	-2.816638
H	2.178903	-2.147479	-3.222289
C	5.423636	-2.393136	-1.064335
H	4.715908	-0.551085	-0.131285
C	5.157910	-3.381593	-2.034027
H	3.778280	-4.052607	-3.569199
H	6.325753	-2.452168	-0.459744
H	5.854638	-4.203198	-2.181974
C	-1.901582	1.860589	0.848462
C	-2.390724	3.127859	0.475080
C	-1.273382	1.703192	2.102799
C	-2.262483	4.223500	1.350537
H	-2.850250	3.275301	-0.497160
C	-1.147984	2.796664	2.979550
H	-0.869752	0.733650	2.385593
C	-1.645840	4.060498	2.606681
H	-2.639253	5.198208	1.049351
H	-0.654308	2.660116	3.938268
H	-1.548242	4.907637	3.281831
C	-2.415055	0.990347	-1.970708
C	-3.670285	1.545770	-2.305933
C	-1.405865	0.926832	-2.952537
C	-3.909042	2.034044	-3.603560
H	-4.467617	1.578892	-1.568196
C	-1.643997	1.417571	-4.249896
H	-0.440313	0.497270	-2.707969
C	-2.894307	1.974062	-4.579119
H	-4.880597	2.455955	-3.850054
H	-0.855337	1.364347	-4.996348
H	-3.078382	2.351413	-5.582438
C	-3.746928	-0.347251	0.261293
C	-4.391861	-1.270434	-0.590441
C	-4.354408	0.000397	1.483773
C	-5.634933	-1.819804	-0.233517
H	-3.923225	-1.564355	-1.525450
C	-5.597520	-0.556082	1.845560
H	-3.875086	0.707420	2.154295
C	-6.243443	-1.464866	0.987582
H	-6.123983	-2.524129	-0.902661
H	-6.056103	-0.274876	2.790752
H	-7.205508	-1.890481	1.264015

[Rh(PPh$_2$NMe$_2$)$_2$(acac)]

```
   79
scf: -2334.019559
Rh    -0.141441    -1.117071     0.094583
 H     2.476463    -4.368992     2.218472
 C     2.013393    -4.753826     1.300240
 C     0.835000    -3.877041     0.913408
 H     1.716098    -5.794250     1.461968
 H     2.776792    -4.714121     0.513092
 O     1.140078    -2.630913     0.655840
 C    -0.466054    -4.425275     0.862366
 C    -1.641010    -3.719891     0.509418
 H    -0.574168    -5.473627     1.117061
 C    -2.978874    -4.440192     0.509934
 O    -1.694937    -2.461082     0.162370
 H    -3.389019    -4.465934    -0.508344
 H    -2.892587    -5.465414     0.882448
 H    -3.694367    -3.887253     1.130777
 P    -1.692795     0.557982    -0.442597
 N    -1.504067     1.359845    -2.030333
 C    -2.545174     2.292280    -2.504573
 C    -0.935523     0.542924    -3.119659
 H    -2.921577     2.908538    -1.683228
 H    -2.109726     2.961838    -3.259908
 H    -3.404058     1.769251    -2.961245
 H    -0.430931     1.196058    -3.847482
 H    -0.209247    -0.166899    -2.709323
 H    -1.708043    -0.031504    -3.663924
 H     2.312911    -1.694597     2.872047
 C     3.043057    -0.915702     2.596631
 H     3.763683    -1.354437     1.903078
 H     3.580348    -0.599835     3.502527
 N     2.401233     0.276825     2.000928
 P     1.827932     0.179386     0.286393
 C     1.391388     0.857139     2.920077
 H     1.887226     1.122747     3.863745
 H     0.952422     1.765500     2.496371
 H     0.570145     0.152459     3.136639
 C    -3.524338     0.061133    -0.508719
 C    -4.560468     0.825942     0.066041
 C    -3.861992    -1.066289    -1.291860
 C    -5.909049     0.464911    -0.124165
 H    -4.329528     1.706208     0.658338
 C    -5.208114    -1.420725    -1.491792
 H    -3.073400    -1.675615    -1.720182
 C    -6.237947    -0.658564    -0.905058
 H    -6.695170     1.064297     0.329721
 H    -5.451616    -2.291325    -2.096930
 H    -7.279134    -0.935532    -1.055341
 C    -1.695135     2.004187     0.756421
 C    -1.186939     3.270149     0.407246
 C    -2.137768     1.778465     2.079532
 C    -1.141969     4.305635     1.361291
 H    -0.810278     3.438475    -0.595999
 C    -2.095717     2.812176     3.031222
 H    -2.502403     0.795731     2.370402
 C    -1.600417     4.083139     2.673117
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 H    -2.442444     2.625840     4.045066
 H    -1.565531     4.883412     3.408891
 C     2.101214     1.984934    -0.214576
 C     1.709769     2.406083    -1.501094
 C     2.774512     2.889047     0.631047
 C     1.983439     3.716062    -1.935908
 H     1.193668     1.722909    -2.165123
 C     3.036398     4.204163     0.202918
 H     3.104089     2.550361     1.608548
 C     2.643147     4.622654    -1.082957
 H     1.685067     4.024970    -2.935337
 H     3.553789     4.893496     0.866702
 H     2.854162     5.635851    -1.418431
 C     3.323587    -0.573983    -0.579810
 C     4.622003    -0.070592    -0.350113
 C     3.133836    -1.604787    -1.520028
 C     5.721467    -0.603768    -1.046399
 H     4.774216     0.730192     0.368860
 C     4.233358    -2.130455    -2.226213
 H     2.134230    -1.995876    -1.685830
 C     5.529086    -1.633795    -1.990023
 H     6.719522    -0.213148    -0.860992
 H     4.077080    -2.924624    -2.952947
 H     6.378696    -2.040747    -2.534117
```

[Rh(PPh$_2$NMe$_2$)(P[OPh]$_3$)(acac)]

```
   84
scf: -2656.766044
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 H    -3.625475    -4.322460    -1.346402
 C    -3.289632    -4.477116    -0.312421
 C    -1.972514    -3.757260    -0.092962
 H    -3.208319    -5.551373    -0.123453
 H    -4.057111    -4.048042     0.343147
 O    -2.042709    -2.452703    -0.201555
 C    -0.802646    -4.492523     0.196296
 C     0.481504    -3.943391     0.426966
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 C     1.652972    -4.856866     0.732653
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 H     1.360283    -5.910746     0.741906
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 N    -2.591860     0.579177    -2.298907
 P    -2.145342     0.496839    -0.555857
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 P     1.272480     0.246602     0.035171
```

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O	1.831291	1.094406	1.439357
C	3.162303	-1.394177	-1.281342
C	4.277658	-2.210265	-1.017771
C	2.466946	-1.489589	-2.501658
C	4.702086	-3.133324	-1.989465
H	4.790510	-2.105592	-0.066298
C	2.897420	-2.424147	-3.461866
H	1.611530	-0.850689	-2.699352
C	4.012705	-3.247613	-3.214587
H	5.569011	-3.759359	-1.790763
H	2.361411	-2.502352	-4.404952
H	4.342792	-3.961994	-3.964445
C	2.148694	2.718707	-1.050090
C	1.561814	3.955791	-1.365378
C	3.538537	2.589370	-0.873266
C	2.385129	5.086080	-1.517946
H	0.484158	4.018321	-1.477377
C	4.347051	3.731635	-1.022098
H	3.969140	1.628019	-0.617711
C	3.779837	4.979561	-1.347317
H	1.935966	6.045478	-1.763760
H	5.422160	3.641404	-0.885504
H	4.413901	5.854913	-1.464145
C	2.183026	0.550488	2.688479
C	2.533229	1.491288	3.674377
C	2.195337	-0.831072	2.960953
C	2.899577	1.042633	4.955191
H	2.519156	2.546982	3.420943
C	2.561974	-1.261879	4.250228
H	1.932763	-1.552442	2.193114
C	2.914528	-0.335874	5.250509
H	3.173311	1.767762	5.718075
H	2.571837	-2.327331	4.469041
H	3.197746	-0.680742	6.241685
C	-1.968008	2.323901	-0.142642
C	-1.272318	2.692699	1.024798
C	-2.600623	3.314223	-0.921456
C	-1.208044	4.043730	1.412741
H	-0.778398	1.939436	1.632421
C	-2.527135	4.666088	-0.538279
H	-3.144539	3.024503	-1.816187
C	-1.833905	5.034257	0.632220
H	-0.665537	4.318166	2.313696
H	-3.014874	5.425550	-1.145238
H	-1.780986	6.078825	0.930532
C	-3.814015	0.156390	0.244734
C	-4.998630	0.702828	-0.290996
C	-3.862142	-0.572874	1.448245
C	-6.226151	0.507762	0.367511
H	-4.960271	1.269151	-1.217859
C	-5.089232	-0.756055	2.113462
H	-2.949977	-0.999172	1.855798
C	-6.273913	-0.219309	1.573985
H	-7.137112	0.927383	-0.053123
H	-5.118294	-1.316019	3.045335

```
H     -7.222191     -0.363369      2.087067
```

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Chapter 3

Chiral (salen)Co(III)(*N*-benzyl-L-serine)-derived phosphites: monodentate P-ligands for enantioselective catalytic applications

Abstract

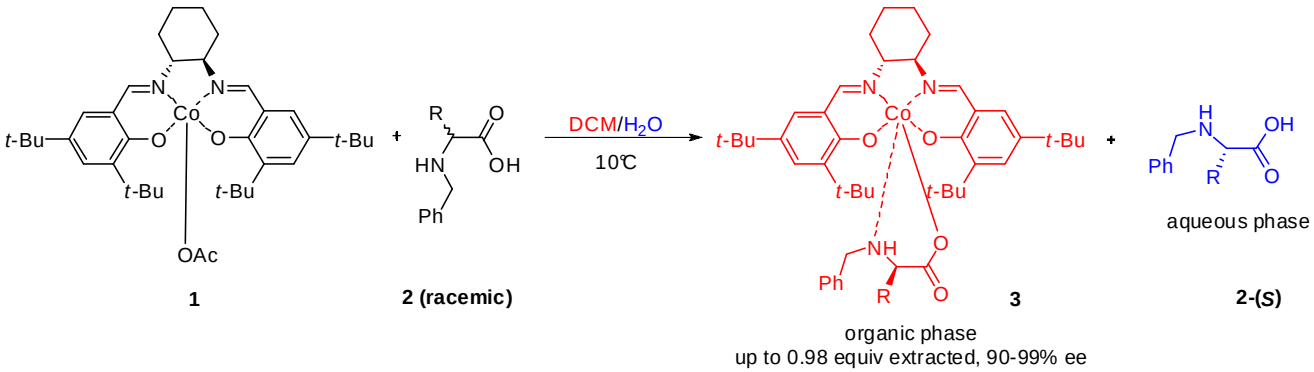
In this Chapter the screening of a series of salen-bearing monodentate P-ligands was studied in several enantioselective catalytic applications, showing good activity and moderate enantioselectivity in several palladium-catalyzed asymmetric reactions.

A small library of ligands was synthesized reacting the (S,S)-salen-cobalt(III)-N-benzyl-L-serine complex with four diol-derived chlorophosphites affording phosphites 7a–7d in moderate yields (37–72%). Structural studies of these monodentate phosphite ligands and of their Rh-complexes were performed in solution by ^{1}H and ^{31}P NMR spectroscopy.[1]

3.1 GENERAL INTRODUCTION

We widely discussed, in the chapter 1, supramolecular interactions and , more specifically, coordinative bonds have been used to induce higher stereoselectivity in catalytically active complexes. Both chiral and achiral scaffolds, such as porphyrins or bisoxazolines binding chiral Schiff-bases functionalities constituted a privileged class of ligands for enantioselective transition-metal catalytic applications. Among these chiral (salen)cobalt(III) and cobalt (II) complexes were successfully employed in several asymmetric transformations.

Recently, our group has reported a novel approach to the resolution of racemic *N*-benzyl α-amino acids (*N*-Bn-AA) by liquid-liquid extraction, using the lipophilic chiral (salen)cobalt(III) complex (*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclo-hexanediaminocobalt(III) acetate, in excellent yield and enantioselectivity.[2a] As a result of the thermodynamic-controlled resolution by extraction, one enantiomer of the *N*-benzyl amino acid predominates in the aqueous phase, while the other enantiomer is driven into the organic phase by complexation to the cobalt center (Scheme 3.1).



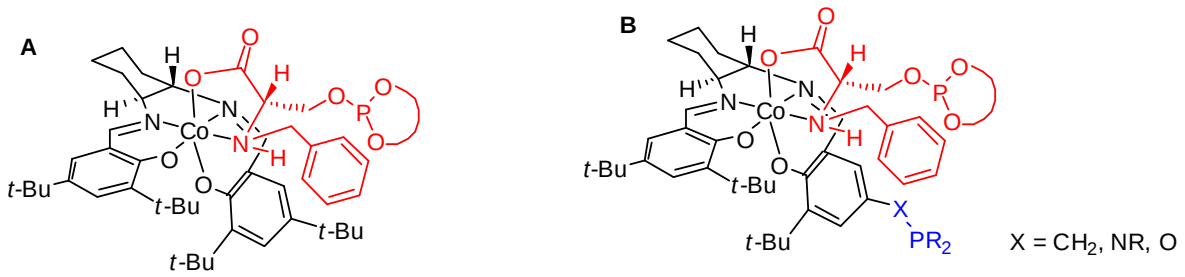
Scheme 3.1 Resolution of a racemic mixture of *N*-benzyl amino acids by liquid-liquid extraction using (salen)cobalt(III) complexes.

This methodology has shown the optimal results when temperature is controlled at 10°C and the salen-complex is reacted in presence of an excess of racemic amino acids mixture in a typical ratio 1 : 2. The complexed amino acid can be then released by a reductive (Co^{III} /Co^{II}) counter-extraction into an aqueous phase in presence of $Na_2S_2O_4$ or ascorbic acid as reductive agents. The original chiral Co^{III} complex can be regenerated and reused with essentially no loss of selectivity.

Spectroscopic and molecular modelling investigations revealed a *cis*-β-folded arrangement around the octahedral cobalt ion of the (*R,R*)-salen ligand in the (*N*-Bn-AA)Co(salen) complex, with the remaining two *cis* coordination sites being occupied by the *N*-benzylamino acid. [2c] The amino acid coordination takes place in such a way that a meridional arrangement of the three oxygen and three nitrogen atoms is obtained (meridional N_3O_3 structure). Using the (*R,R*)-salen ligand, the favored diastereomeric complex contains the (*R*)-enantiomer of the *N*-benzylamino acid, while the absolute configuration of the additional stereogenic elements (the octahedral cobalt and the tetrasubstituted

nitrogen of the *N*-benzylamino acid) was assigned as *D* and (*S*), respectively. As a consequence, the *N*-benzylamino acid is nicely accommodated in the binding pocket of the chiral cobalt complex.

The keen interest towards the design and the synthesis of new *P*-ligand architectures, together with the renaissance of monodentate *P*–ligands since 2000 (see chapter 1, paragraph 1.1), [3] prompted us to take advantage of well-defined salen[4]-cobalt(III)-*N*-Bn-AA coordination geometry and to develop a salen-cobalt(III)-*N*-benzyl-serine complex as a chiral platform for the preparation of new families of both monodentate and supramolecular bidentate *P*-ligands (Scheme 3.2). L-serine was initially chosen because of its free hydroxylic group which can be functionalized to afford phosphites. Working with natural amino acids, (*S*,*S*)-N,N'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclo-hexanediaminocobalt(II) complex was used as starting material.

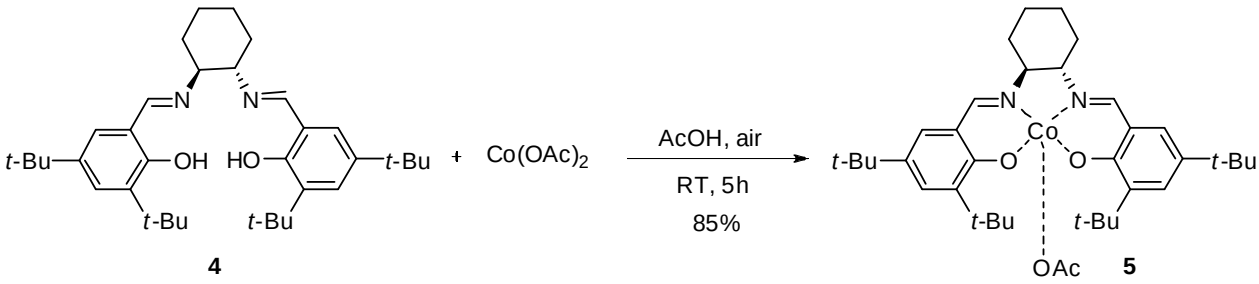


Scheme 3.2 (A) Monodentate (salen)cobalt(III)(*N*-Bn-Ser) phosphites, (B) Bidentate hybrid *P*-ligands suitable for the formation of transition metal-catalysts by the supramolecular approach.

3.2 RESULTS AND DISCUSSION

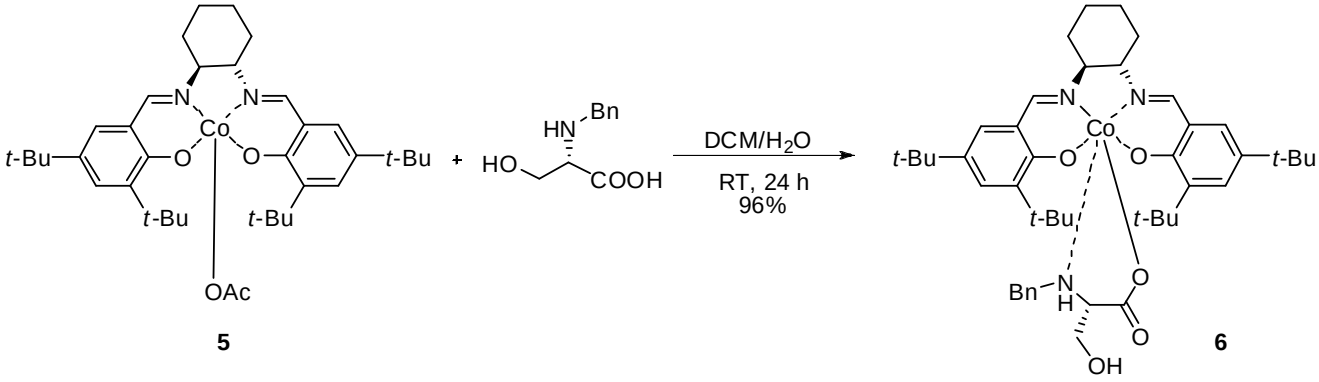
3.2.1 Synthesis of salen-based monodentate *P*-ligands

The chiral (salen)cobalt(III) acetate complex **5** was prepared following well estabilished-oxidative procedures in presence of air/AcOH,[5] starting from commercially available (*S*,*S*)-salen ligand **4** and cobalt(II)acetate (Scheme 3.3).



Scheme 3.3 Synthesis of chiral(salen)cobalt(III) acetate **5**.[5]

(*S*,*S*)-salen-cobalt(III)-acetate **5** was reacted with an excess (2.0 equiv.) L-serine in a DCM/H_2O 1:1 mixture at RT for 24 h. As this process is not a resolution, the control of temperature is not a determining variable (Scheme 3.4). This reaction was also performed on a multigram scale and complex **6** was obtained in excellent yield (96%) after chromatographic purification over silica gel, thus confirming the excellent stability of these complexes.



Scheme 3.4 Synthesis of the (*S*,*S*)-salen-cobalt(III)-*N*-benzyl-L-serine complex **6**.

The amino acid complexation procedure could be realized by three different methods:

A) biphasic water/dichloromethane extraction;

B) biphasic water/dichloromethane treatment and recovery of the uncomplexed amino acid by filtration;

C) stirring a suspension of the racemic *N*-Bn amino acid with dichloromethane solution of [Co(III)(OAc)] complex and recovery of the uncomplexed amino acid by filtration.[2a,b]

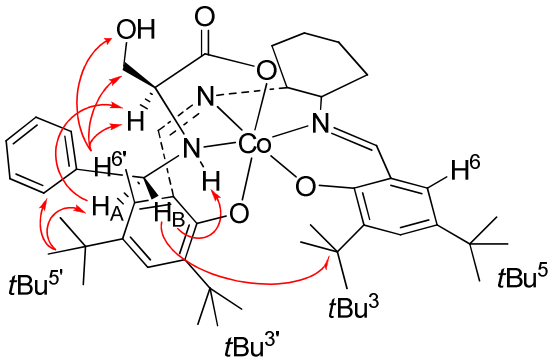
All these methods could be independently used without no substantially loss of conversions and stereoselectivities even if method A is preferred to method C for more hydrophilic amino acid (such as serine and threonine). This is probably due to the limited solubility of these amino acids in dichloromethane and the complexation becomes extremely slow.

Another important point is the nitrogen substitution. Tipically, during the resolution of a racemic mixture of amino acids, *N*-unsubstituted and *N*-monosubstituted amino acids with a small substituent (*e.g.* methyl), reacted with the chiral selector to form the complex, hovewer, the small substituent does not provide sufficient steric interactions for a chiral discrimination. On the contrary, *N*,*N*-disubstituted amino acids are too bulky and this prevents the formation of the complex. Apparently, benzyl is the most suitable *N*-substituent to be accommodated in the chiral environment of the metal complex. [2a,b] In our case, even if the enantiodiscrimination is not a fundamental step, *N*-benzyl amino acids were used as well and no attempts aimed at the use of *N*-unsubstituted amino acids was investigated.

^{1}H NOESY studies were then performed on complex **6** to demonstrate a similar configuration of the octahedral cobalt ion and arrangement of the substituents with respect to the well-known "matched" complex (*R*,*R*)salen-cobalt(III)-*N*-Bn-D-alanine.[2c] The NOESY spectrum of (*S*,*S*)salen-cobalt(III)-*N*-

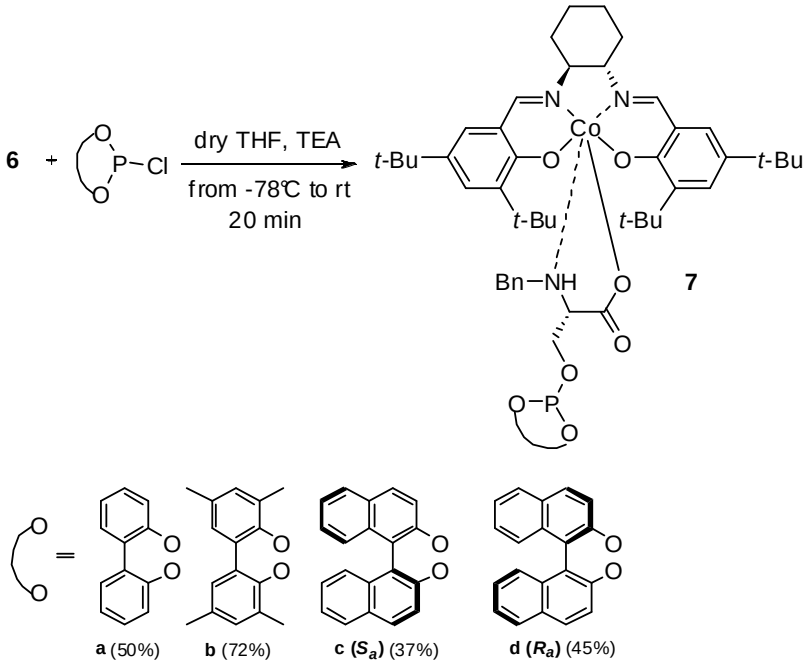
Bn-L-serine revealed that the two benzylic protons H_A and H_B strongly interact through space with the *tert*-butyl groups of the ligand. In particular, proton H_A gives a cross-peak with *t*-Bu$^{5'}$, and proton H_B with *t*-Bu^{3}. A NOE contact is also clearly visible between the protons in the *ortho* positions of the *N*-Bn moiety and the *t*-Bu$^{5'}$. Additional NOE contacts are observed between the NH of *N*-Bn-(*S*)-serine and the ligand backbone. On the other hand, the C-H stereocenter of the *N*-Bn-serine is in NOE contact with H_A and the proton H$^{6'}$ but not with the N-H. This suggest that the N-H pointed out in the opposite direction with respect to the C-H stereocenter of serine. Therefore, being the nitrogen atom locked in the coordination to cobalt, its absolute configuration can be determined as *R*. The NOESY spectrum also revealed that the –OH proton of serine does not give any significant NOE contact because it probably points out with respect to the plane of the complex. (Scheme 3.5 and experimental section).

This spectroscopic study suggests that the amino acid is well-accommodated in the "binding pocket" of the chiral cobalt complex and the hydroxyl group can be easily functionalized notwithstanding the hindrance architecture of the whole complex.



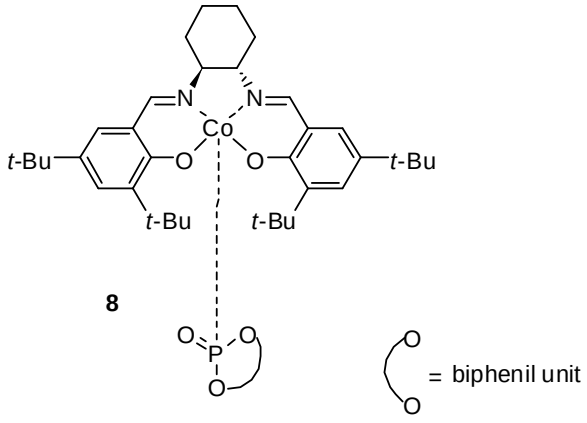
Scheme 3.5 NOE contacts in "matched" complex (*S*,*S*)salen-cobalt(III)-*N*-Bn-L-serine.

The corresponding phosphite ligands **7a-7d** were then synthesized by reaction of complex **6** with four (*tropos* and *atropos*) diol derived clorophosphites.[6] The chlorophosphites were added at low temperature and the reaction mixtures were then warmed to room temperature and stirred for 20 min. After purification by flash chromatography, phosphites **7a-7d** were obtained in moderate yields (37-72%, Scheme 3.6).



Scheme 3.6 Synthesis of the (*S*,*S*)-salen-cobalt(III)-*N*-benzyl-L-serine derived phosphites **7a-7d**.

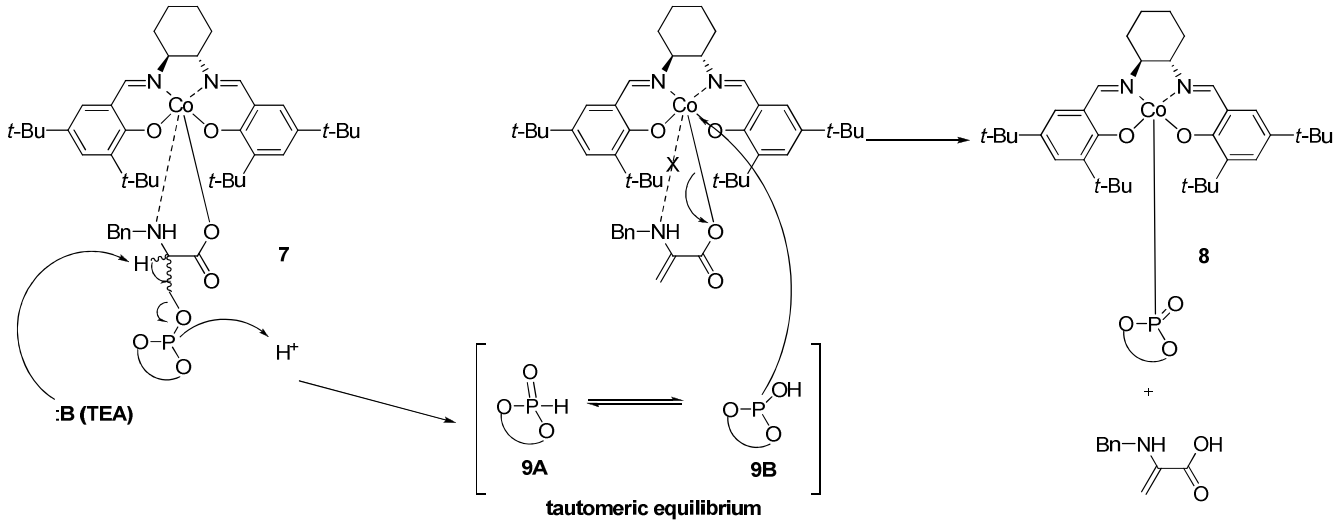
Most importantly, the reaction time was optimized to preserve the integrity of the complexes. We found that longer reaction times were not beneficial to the yields and causing decomposition of the product. In the synthesis of **7a**, a decomposition product **8** was isolated and tentatively characterized as a cobalt(III) complex containing the chiral salen moiety, a biphenyl phosphorous acid diester ligand, and no trace of the *N*-benzylamino acid (Scheme 3.7).



Scheme 3.7 by-product obtained from a hypothetic Arbuzov's type rearrangement.

The structure of this specific was supported by the ^{31}P NMR spectrum where a singlet at δ 37.5 ppm was detected. Chiral phosphorous diesters, which exist in a tautomeric equilibrium between a $(RO)_2$P-OH and a $(RO)_2$P=O form, have been recently reported by Reetz to perform as active and enantioselective ligands in the Ir-catalised hydrogenation of imines. [7] From a mechanistic point of view, it can be assumed that, once formed, phosphite **7** activates the OH group of serine towards an

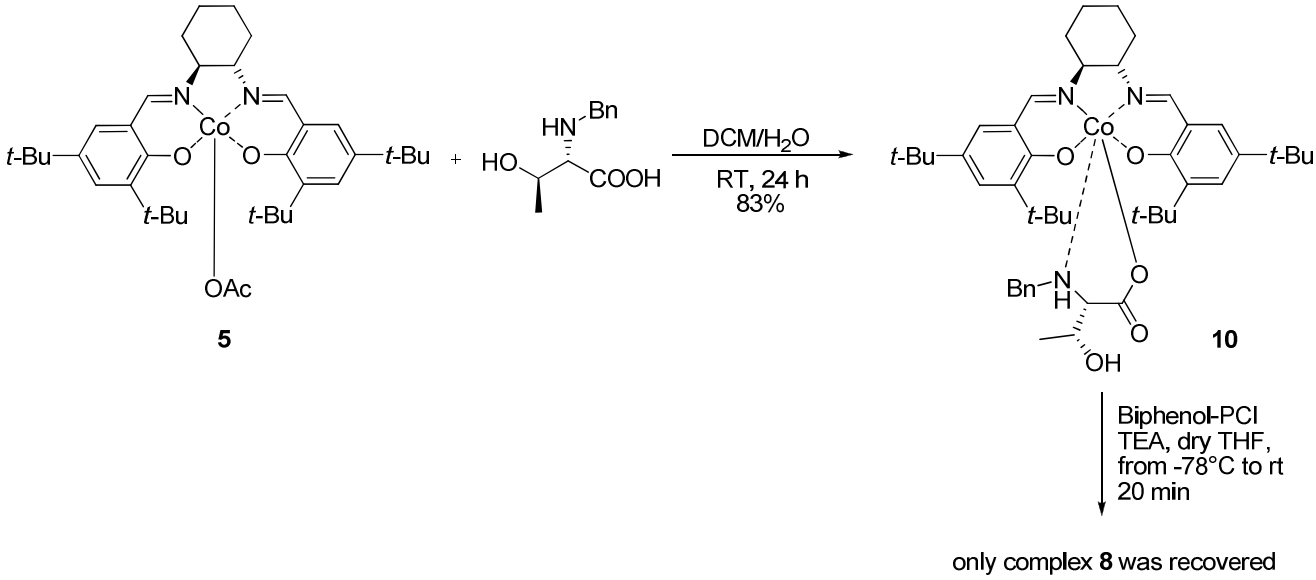
elimination reaction (Arbuzov's type rearrangement),[8] which is promoted by the base (TEA) present in the reaction medium. The biphenyl phosphorous acid diester **9** which is thus formed, exists in a tautomeric equilibrium between **9A** and **9B**. Although such equilibrium generally favors **9A**,[7] some X-ray crystallography evidences showed that **9B**-like derivatives are able to coordinate a transition metal center affording very stable complexes.[9] For this reason, it is plausible that phosphorous acid diester **9B** is able to coordinate the cobalt center displacing the amino acid derivative (Scheme 3.8). Even if we have not X-ray crystallographic evidences, we can hypothesize that the cobalt(III) center forms a square pyramidal phosphonate complex where the Co(III) is directly linket to P and the salen moiety binds in an equatorial fashion while the P is axial.[10]



Scheme 3.8 Hypothetic mechanism pathway of decomposition of (*S*,*S*)-salen-cobalt(III)-*N*-benzyl-L-serine/threonine derived phosphites in basic conditions.

An indirect proof of the existence of **8** was related to the absence of the formation of a P-Rh bond when ^{31}P NMR complexation studies were performed in the presence of a Rh source. Indeed, the recorded ^{31}P spectra showed the characteristic singlet of **8** at δ 37.5 ppm when both **8** was added in ratio 1 : 1 and in ratio 2 : 1 to the Rh source.

An analogous synthetic pathway was attempted using *N*-benzyl-L-threonine instead of serine to study the effect of an additional stereogenic center closed to the P-atom. The chiral (*S*,*S*)-salen-cobalt(III)-*N*-benzyl-L-threonine complex was prepared and isolated, after flash chromatography, in good yield (83%). Unfortunately, all attempts to proceed further with the formation of the phosphite met with no success and only the decomposition complex described above was isolated (Scheme 3.9).



Scheme 3.9 Synthesis of the (*S*,*S*)-salen-cobalt(III)-*N*-benzyl-L-threonine complex **10**.

3.2.2 Structural and complexation studies of salen-based monodentate *P*-ligands

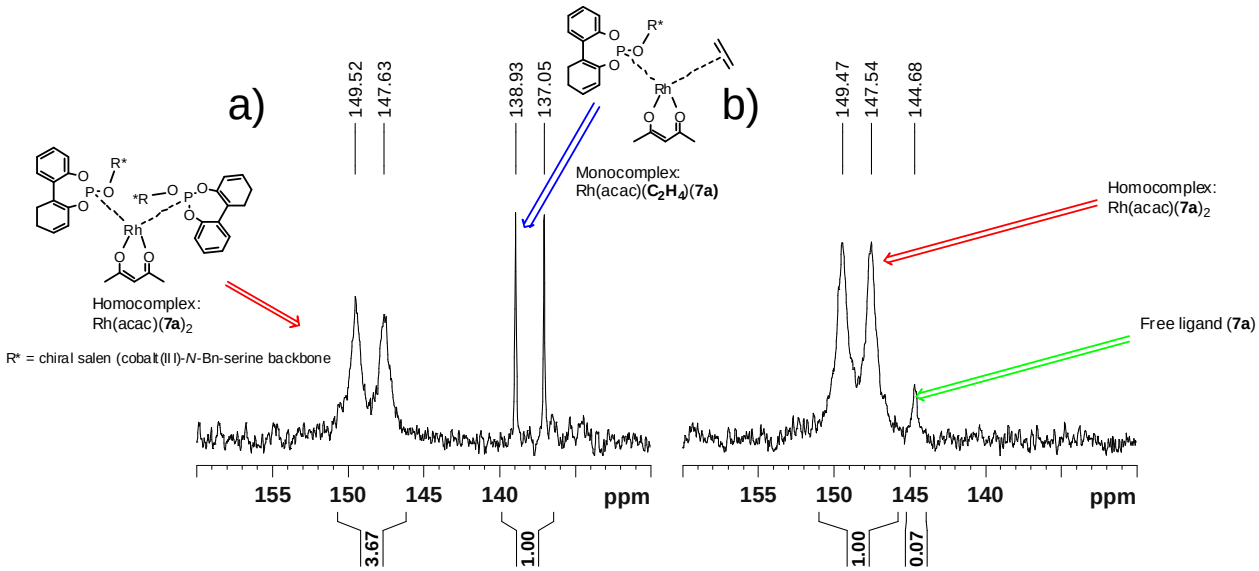
NMR investigations of the ligands were then undertaken. The experiments were conducted in $CDCl_3$, which was degassed and passed over a short pad of neutral alumina. ^{31}P NMR spectra of the phosphites displayed in all cases a singlet at similar chemical shifts as reported in Table 3.1.

Table 3.1 Chemical shifts of ligands **7a-d.**

Entry	Ligand	δ (ppm)
1	**7a**	144.6
2	**7b**	147.1
3	**7c**	146.6
4	**7d**	141.2

The complexation of ligand **7a**, which was chosen as representative of the ligand library, with $[Rh(acac)(C_2H_4)_2]$ was then studied (Scheme 3.10). A doublet at δ 148.6 ppm ($J_{P\text{-}Rh}$ = 312.2 Hz) and a doublet at δ 138.0 ppm ($J_{P\text{-}Rh}$ = 302.2 Hz) were observed in ratio 3:1 upon addition of 1.0 equiv. of **7a** with respect to the rhodium source. In this case, the downfield doublet (138 ppm) was attributed to the complex in which only one ethylene molecule has been substituted by P ligand (monocomplex Rh(acac)(**7a**)(ethylene)), while the upfield doublet was assigned to the complex containing two ligands units coordinated to the rhodium center (homocomplex: Rh(acac)(**7a**)$_2$). When the ratio **7a**/Rh was increased to 2.1:1, the spectrum displayed only a doublet at δ 148.6 ppm plus a small singlet at δ

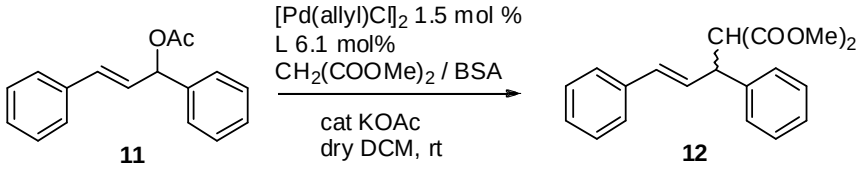
144.6 ppm ($J_{P\text{-}Rh}$ = 312.2 Hz) corresponding to excess ligand. Interestingly, two ligands can be accommodated around the rhodium atom notwithstanding their steric hindrance.



Scheme 3.10 ^{31}P NMR spectra of the rhodium complexes resulting from the combination of ligand **7a** with $Rh(acac)(C_2H_4)_2$ in **a)** 1 : 1 ratio and **b)** 2.1 : 1 ratio.

3.2.3 Catalytic screening of salen-derived monodentate P-ligands

The ligands were then screened for several enantioselective catalytic applications. Unfortunately, in the rhodium catalyzed enantioselective hydrogenation of functionalized olefins and in the rhodium catalyzed asymmetric conjugate addition of arylboronic acids to enones, reduction of cobalt(III) to cobalt(II) was observed, as a rapid change in colour of the reactions mixtures from green to brown (typical for salen-Co(II) derivative), with consequent loss of the (salen)Co(*N*-Bn-Ser) phosphite ligand integrity. The brown species was isolated and characterization by NMR spectroscopy was tried but all attempts to record the NMR-spectra failed probably due to the paramagnetic character of Co(II) metal center. On the contrary, when the Pd-catalyzed allylic substitution of rac-1,3-diphenyl-3-acetoxyprop-1-ene **11** (Scheme 3.11)[11] with dimethyl malonate was tested, the ligands proved perfectly stable and gave excellent conversions, albeit with low enantiomeric excess (up to 35% e.e. using ligand **7a**).



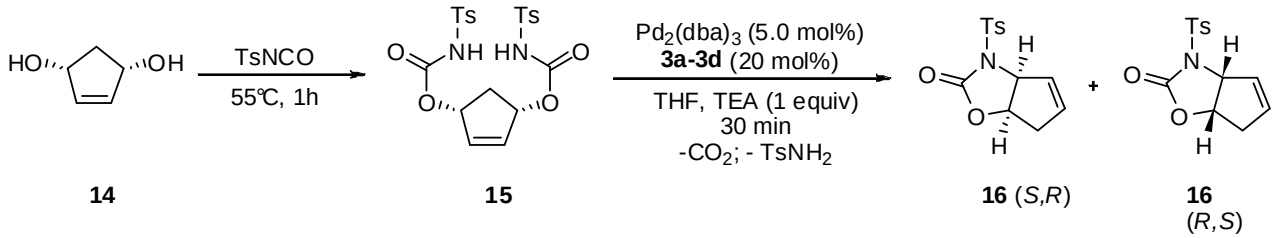
Scheme 3.11 Pd-catalyzed enantioselective allylic substitution of rac-1,3-diphenyl-3-acetoxyprop-1-ene.

Quite surprisingly, the use of bulkier 3,3',5,5'-tetramethyl-2,2'-biphenol derivative **7b** gave the opposite enantiomer, while the use of axially chiral BINOL derivatives **7c** and **7d** led to racemic products (Table 3.2) . As a proof of the positive effect of our ligands on this kind of transformation, the reaction was run only in presence of the Pd source leading to poor conversion after 24 h (entry 1, Table 3.2). An attempt to improve enantioselectivity was done reducing the reaction temperature from RT to -10°C. Unfortunately, a drastic decrease in conversion was obtained (entry 4, Table 3.2).

Table 3.2 Screening of ligands **7a-7d** in the Pd-catalyzed allylic alkylation of rac-1,3-diphenyl-3-acetoxyprop-1-ene.

Entry	Ligand	Reaction Time (h)	Temperature (°C)	Conv. (%)	ee (%)
1	**none**	24	25	11	-
2	**7a**	5	25	100	12
3	**7b**	5	25	100	-35
4	**7b**	5	-10	<5%	-
5	**7c**	5	25	100	3
6	**7d**	5	25	100	8

Ligands **7a-7d** were then screened in the Pd-catalyzed desymmetrization of *meso*-cyclopenten-2-ene-1,4-diol biscarbamate **13** (Scheme 3.12).[12] This intramolecular allylic substitution reaction was developed by Trost and co- workers and has proven a very powerful method in several synthetic approaches to biologically relevant targets. [13] The ligands used in the original examples are chiral bidentate phosphines and give the product with excellent enantioselectivity (ee up to 99 %)[14] while, to our knowledge, no monodentate phosphite ligands have ever been reported for this reaction.



14 **15** **16** (*S*,*R*) **16** (*R*,*S*)

Scheme 3.12 Pd-catalyzed enantioselective desymmetrization of *meso*- cyclopenten-2-ene-1,4-diol biscarbamate **13**.

The reaction was performed using 10 mol% of palladium (5% of the dimer Pd_2dba_3) and 20 mol% of ligands **7a-7d**. In several cases, a stoichiometric amount of triethylamine (TEA), which has been reported to increase the enantioselectivity of the reaction,[14] was added to the mixture. The results are summarized in Table 3.3.

Table 3.3 Screening of ligands **7a-7d** in the Pd-catalyzed desymmetrization of *meso*- cyclopenten-2-ene-1,4-diol biscarbamate **13**.

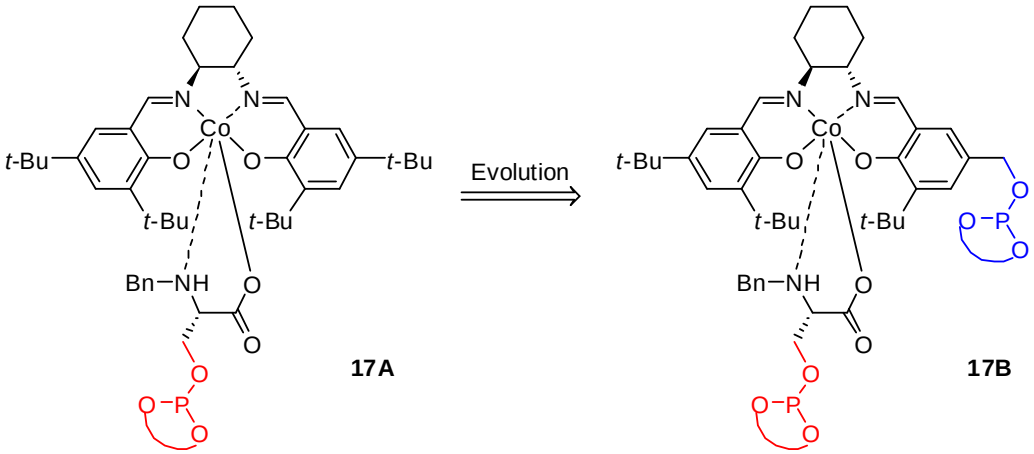
Entry	Ligand	Temperature (°C)	TEA	Conv. (%)	16 (S,R):(R,S)
1	**None**	25	No	-	-
2	**7a**	25	No	96	50:50
3	**7a**	25	Yes	100	15:85
4	**7a**	0	Yes	85	18:82
5	**7b**	25	Yes	90	48:52
6	**7b**	0	Yes	90	28:72
7	**7c**	25	No	100	90:10
8	**7c**	25	Yes	99	80:20
9	**7d**	25	No	100	35:65
10	**7d**	25	Yes	93	32:68

Reaction conversions were always good, in many cases quantitative, with all four ligands (**7a-7d**). Addition of TEA to the reaction with ligand **7a** was fundamental to achieve higher levels of enantioselectivity[14] while, in the case of ligand **7c**, TEA had a negative effect. (At the moment, we are not able to give a plausible explanation to this behavior.) Remarkably, the use of complex **7a**, containing a *tropos* biphenol moiety (entries 3, 4), afforded enantiomeric ratios comparable (yet opposite) to **7c**, containing an *atropos* (S_a)-1,1'-binaphthyl moiety (entries 7, 8). All these observations confirm that the chiral and well organized structure of the salen-cobalt(III)-*N*-benzyl-L-serine complex is relevant in determining the stereochemical outcome of the reaction.

3.2.4 Synthesis of salen-based supramolecular bidentate *P*-ligands

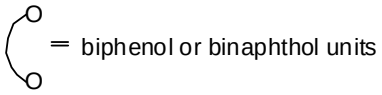
Coordination complexes have been recently used for the preparation of supramolecular bidentate P-ligands.[15] In this approach, two monodentate P-ligands self-assemble around a transition metal (Rh, Pd) by virtue of an additional coordinative bonding of nitrogen to a transition metal such as zinc. Key-players in this research field are Reek, [16] Takacs[17].The advantage of these supramolecular approaches is the expectation that degrees of freedom in the respective transition metal coordination complex are reduced, resulting in the simulation of a preorganised bidentate system with predictable geometric properties, as in conventional bidentate ligands.

Having in hand the stable salen-cobalt(III)-*N*-Bn-L-serine-monodentate phosphites, we were intrigued by the possibility to introduce a secondary additional phosphorous functionality in the salen moiety to realize a new class of supramolecular bidentate P-ligands (Scheme 3.13).



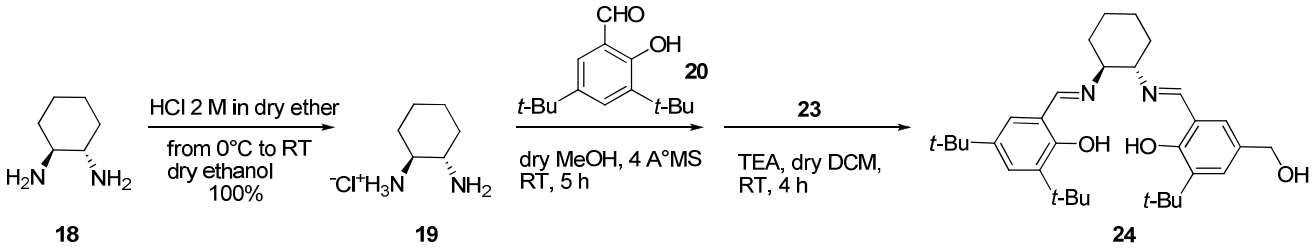
Generic structures of (*S,S*)-salen-cobalt(III)-*N*-Bn-L-serine **monodentate** phosphites

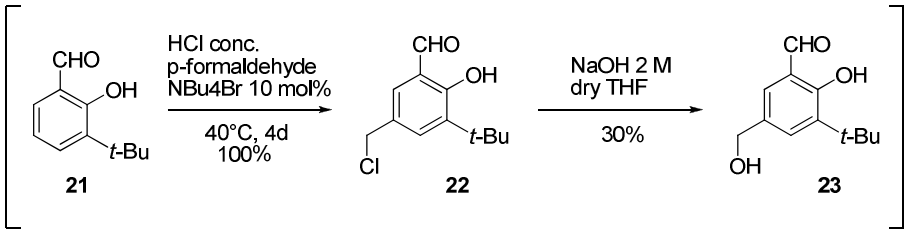
Generic structures of **supramolecular** (*S,S*)-salen-cobalt(III)-*N*-Bn-L-serine **bidentate** phosphites



Scheme 3.13 Generic.structures of (*S,S*)-salen-cobalt(III)-*N*-Bn-L-serine monodentate P-ligands (**17A**) and supramolecular bidentate ligands (**17B**).

The synthesis of the supramolecular bidentate P-ligands **17B** required the preparation of unsymmetrical salen[18] containing a $–CH_2OH$ group (blue pointed out in Scheme 3.4) by sequential condensation of (*S,S*)-1,2 diaminocyclohexane with 3,5-di-*tert*-butylsalicylaldehyde and 3-*tert*-butyl-5-hydroxymethylsalicylaldehyde **23**,[19] following the one-pot protocol by Weck and co-workers (Scheme 3.14).[20]



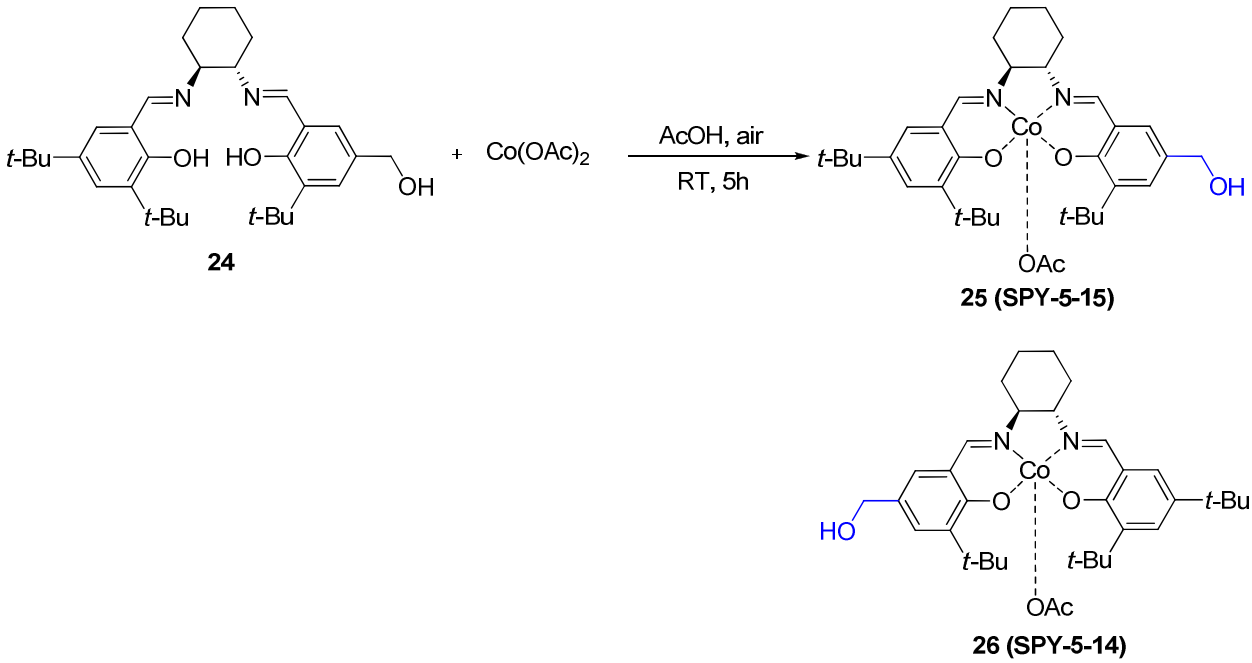


Scheme 3.14 Synthesis of unsymmetrical (*S,S*)-salen backbone **24**.

This methodology has the advantage of avoiding the isolation step of the monoamine intermediate that is prone to the undesired disproponation reaction.[21]

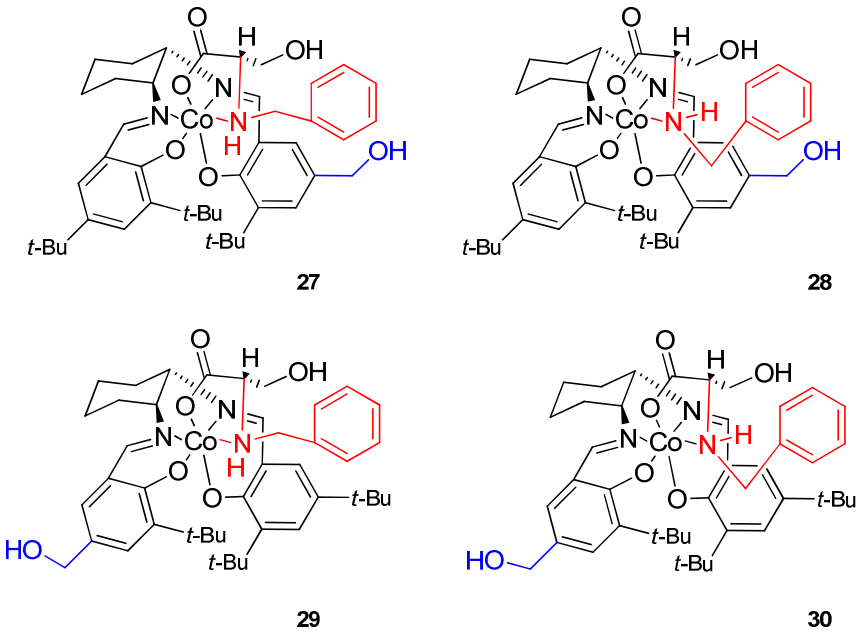
The preparation of nonracemic unsymmetrical salen ligand **24** started with monoprotection of one amine moiety of (*S,S*)-1,2 diaminocyclohexane **18** as monoammonium chloridrate salt by reaction with

2.0 M hydrogen chloride in ether. The first condensation between the monoammonium salt **19** and 3,5-di-*tert*-butylsalicylaldehyde was carried out in a1:1 (v/v) mixture of anhydrous methanol at room temperature. The presence of activated molecular sieves has a crucial role to remove the water that is formed during the reaction thus reducing the reaction time. After the first condensation was complete, a solution of the 3-*tert*-butyl-5-hydroxymethylsalicylaldehyde **23** in dichloromethane was added to the reaction system, followed by the slow addition of an excess of anhydrous triethylamine as a deprotective base. The target unsymmetrical salen ligand **24** was isolated in good yield (75%).
The salen-cobalt(III)-acetate complex was then synthesized in good yield (75%) (as a 1:1 mixture of two inseparable diastereoisomers (**25** and **26**)) by an oxidative reaction in presence of air/AcOH (Scheme 3.15).[5]



Scheme 3.15 Synthesis of unsymmetrical (*S*,*S*)-salen-cobalt(III)(OAc) complex.

Addition of (*N*)-Bn-L-Ser to the mixture of **25** and **26** (1:1), following the well-known liquid-liquid extraction procedure,[2] led to the formation of the different diastereomeric complexes for which a perfect isolation and a complete characterization was not possible. In principle, several stereoisomers can be obtained, due to the presence of different stereogenic elements and namely: (a) the stereocenters at the amino acid (*S*) and the diamine (*S*,*S*), the stereocenter at N; (b) the helicity of the octahedral Co complex (Λ), (c) the disposition of the three oxygen and the three nitrogen of the salen and amino acid ligand (*mer*) and finally (d) the position of the $–CH_2OH$ bound to the salicylaldehyde unit. To the best of our knowledge the *mer* arrangement is apparently typical for this kind of complexes and the helicity is fixed by the configuration of the diamine.[2c] Starting from an inseparable mixture of **25** and **26**, a mixture of four diastereomers differing from the position of the $-CH_2OH$ and the stereochemistry of the N-amino acid atom can be obtained (Scheme 3.16).



Scheme 3.16 Possible diastereomers can be formed by liquid-liquid extraction of mixture of **25** and **26** (1:1) with *N*-Bn-L-serine.

As explorative test, the mixture of diastereomers (**27-30**) was reacted with biphenol-PCl but only the decomposition of the cobalt architecture was detected.

Further studies are being aimed at the development of a procedure to obtain the unsymmetrical (*S,S*)-salen-ligand and the corresponding unsymmetrical (*S,S*)-salen-cobalt(III)-*N*-Bn-L-serine bidentate P-ligand in a pure diastereoisomeric fashion.

3.3 CONCLUSIONS

In this Chapter, we have investigated the use of an octahedral (*S,S*)-(salen)cobalt(III)-*N*-benzyl-L-serine complex for the formation of monodentate phosphites, to be used as chiral ligands in enantioselective catalytic applications. The ligands were obtained in moderate yields by reaction of (*S,S*)-(salen)cobalt(III)-*N*-benzyl-L-serine with diol-derived chlorophosphites. These phosphites showed a remarkable air and moisture stability.

^{31}P-NMR complexation studies of ligand **7a**, chosen as representative of the ligand library, were performed in presence of [Rh(acac)(C_2H_4)$_2$] as Rh(I) source. Upon addition of 2.1 equiv. of salen-based P-ligand with respect to the Rh source, a stable Rh-homocomplex with two ligand units coordinated to the metal center was detected. Interestingly the formation of this complex has been took place in spite of the steric hindrance of the salen backbone.

The small ligand library was then screened for several asymmetric catalytic applications, showing good activity and moderate enantioselectivity in the palladium catalyzed desymmetrization of meso-cyclopenten-2-ene-1,4-diol biscarbamate.

Further studies were aimed at the desymmetrization of the salen unit to introduce a secondary additional phosphorous functionality in the salen moiety to realize a new class of supramolecular bidentate P-ligands. these preliminary attempts led to the formation of inseparable mixtures of diastereomers and the reaction with biphenol-PCl led to the decomposition of the whole complex structure. Next aims are being focused on synthetic pathways able to afford the unsymmetrical (*S*,*S*)-salen-ligand and the corresponding unsymmetrical (*S*,*S*)-salen-cobalt(III)-*N*-Bn-L-serine bidentate P-ligand in a pure diastereoisomeric fashion.

3.4 EXPERIMENTAL SECTION

3.4.1 General remarks

All reactions were carried out in flame-dried glassware with magnetic stirring under nitrogen atmosphere, unless otherwise stated. Commercially available dry solvents (over molecular sieves in bottles with crown cap) were stored under nitrogen and used without further distillation. TEA was distilled over CaH_2 under nitrogen. Reactions were monitorated by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} precoated glass plates (0,25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a permanganate alkaline solution. Flash chromatography was performed using silica gel 60Å, particle size 40-64μm, following the procedure by Still and co-workers.[22] ^{1}H NMR spectra were recorded on a spectrometer operating at 400.13 MHz. Proton chemical shift are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ 7.28 ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, dd = doublet of doublet.^{1}H COSY and ^{1}H NOESY spectra of **6** were recorded using a 20 mM solution of complex in $CDCl_3$. ^{13}C NMR spectra were recorded on a 400 MHz spectrometer operating at 100.56 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as internal standard ($CDCl_3$, 77.0 ppm). ^{31}P-NMR spectra were recorded on a 400 MHz spectrometer operating at 162 MHz, with complete proton decoupling. ^{31}P-NMR chemical shifts are reported in ppm (δ) relative to external 85% H_3PO_4 at 0 ppm (positive value downfield). Infrared spectra were recorded on a standard FT/IR spectrometer; bands are reported in cm^{-1}. Optical rotation values were measured on a automatic polarimeter with a 1 dm cell at the sodium D line (λ = 589 nm). HPLC analyses were performed with a chiral stationary phase column CHIRALCEL OD-H (eluent hexane/isopropanol 90:10, flow 0,6 mL/min, tr = 35 min (first enantiomer) 44 min (second enantiomer), λ = 254 nm. High resolution mass spectra (HRMS) were performed on Fourier Transform Ion Ciclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics) - 4.7 T Magnet (Magnex).

Commercially available reagents were used as received. (*S,S*)-N,N'-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclo-hexanediaminocobalt(III) acetate **5**,[5] *N*-benzyl-L-serine,[23] and diol derived monochlorophosphites were synthesized as reported in the literature.[24]

3.4.2 General procedure for the Pd-catalyzed allylic alkylation of rac-1,3-diphenyl-3-acetoxyprop-1-ene.[11]

$[Pd(\eta^3C_3H_5)Cl]_2$ (2.81 mg, 0.0077 mmol) and the ligand (0.0311 mmol) were dissolved under nitrogen in degassed CH_2Cl_2 (1.0 mL). The resulting clear solution was stirred for 20 min at RT, then a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (129 mg, 0.51 mmol) in degassed CH_2Cl_2 (1.0 mL), dimethyl malonate (170 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (BSA, 370 μL, 1.5 mmol), and a pinch of AcOK were added. The reaction mixture was stirred at room temperature. After 1h the solution was diluted with Et_2O (5 mL) and saturated aqueous NH_4Cl (25 mL) was added. The phases were separated and the aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Conversion was determined by ^1H NMR analysis of the crude reaction mixture. An aliquot of the crude was passed through a pad of silica using 5:1 hexane/EtOAc as the eluent. The solvents were removed under vacuum and the residue was directly analyzed by HPLC for the determination of the enantiomeric excess. HPLC conditions: column: CHIRALCEL OD-H; eluent: 99:1 hexane/isopropanol; flow: 0.3 mL/min; λ = 250 nm; t_R = 24 min, t_S = 26 min.

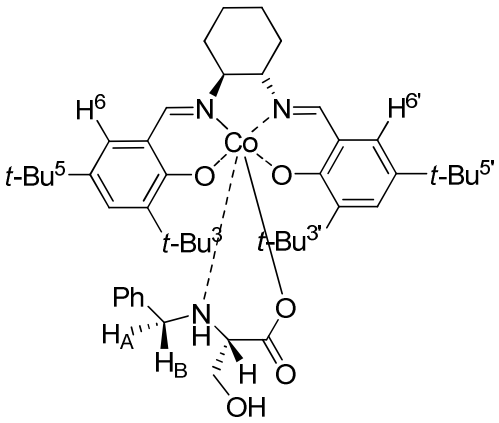
3.4.3 General procedure for the Pd-catalised desymmetrization of meso-cyclopenten-2-ene1,4 diol biscarbamate.[14]

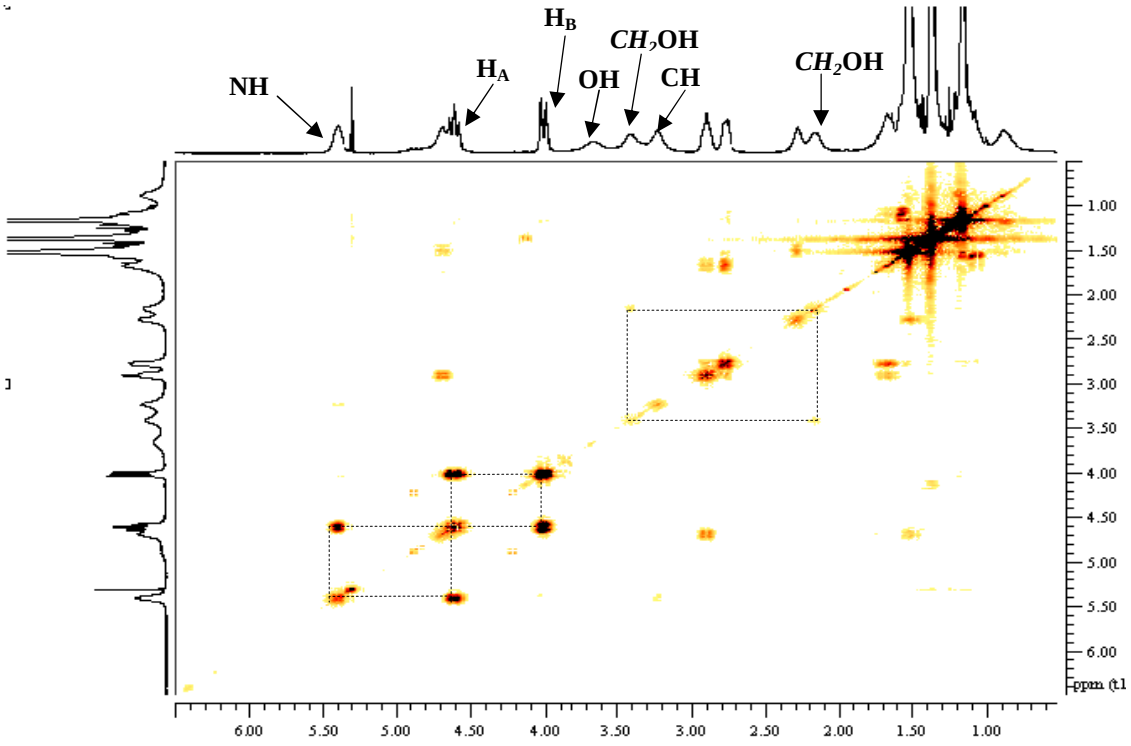
To a solution of the meso-cyclopenten-2-ene-1,4-diol (10 mg, 0.099 mmol) in 0.5 mL of THF, tosyl isocyanate (35 μL, 0.232 mmol, 2.35 equiv) was added. The mixture was stirred at rt for 15 min to give a colorless solution then heated to 55 °C for 1 h. The reaction was cooled back to rt, and triethylamine (14.0 μL, 0.099 mmol, 1.0 equiv) was added as additive in specific cases. The resulting white slurry was brought to the chosen temperature conditions and a solution of tris(dibenzylidine acetone)dipalladium(0) chloroform complex (5.1 mg, 4.94 μmol) and ligand (20.25 μmol) in 0.5 mL of THF was added (the solution of the Pd-source and the ligand was prepared under nitrogen and stirred for 40 min at rt, 10 min at 55°C and finally cooled back to rt). The reaction solution was stirred for 30 min. The solvent was removed in vacuo and purified by flash chromatography on a short pad of silica gel (10 cm, hexane/AcOEt 80:20) gave the desired products as a slightly brown solid. Conversions were determined by NMR analysis of the crude reaction mixture. Enantiomeric excesses

were determined by chiral HPLC (column Chiralcel OD-H, n-hexane/2-propanol 90:10, flow 0,6 ml/min).

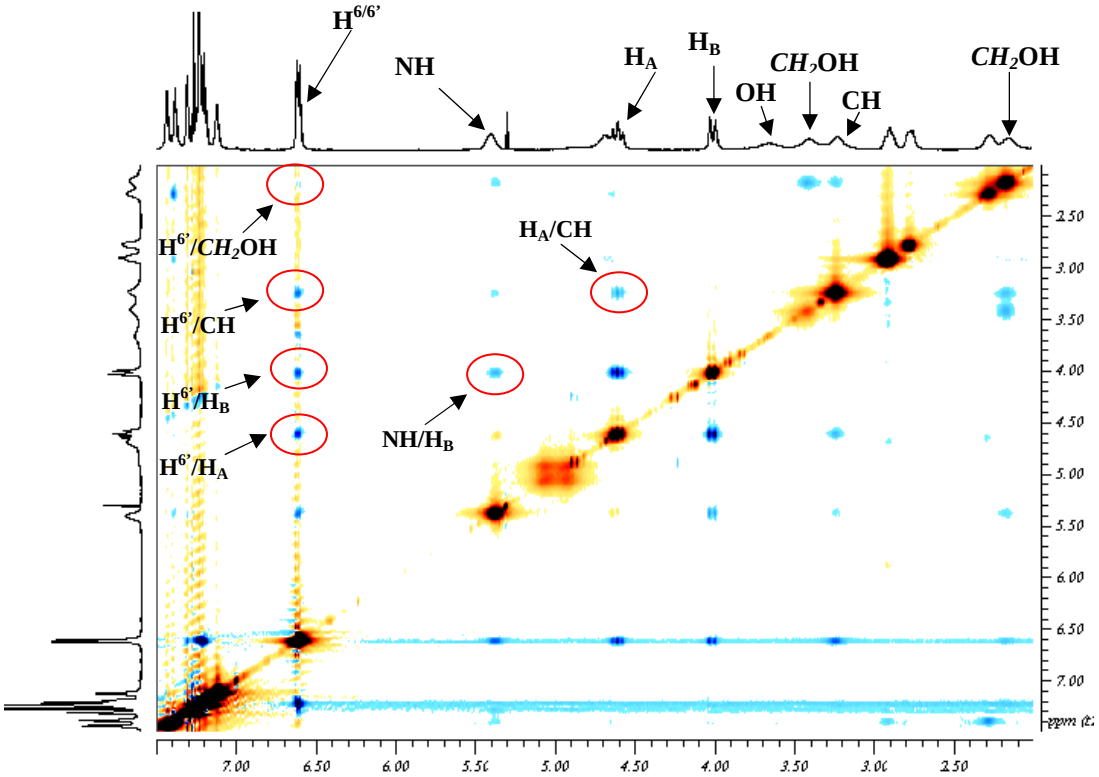
3.4.4 Synthesis of (*S,S*) salen-cobalt(III)-*N*-Bn-L-serine complex 6.

To a solution of the cobalt complex (*S,S*)-(salen)Co(III)(OAc) (**5**) (1.65 g, 2.38 mmol) in dichloromethane (300 mL) at rt in a 1 L round-bottom flask, a solution of *N*-Bn-L-serine (464 mg, 1.0 equiv, 2.38 mmol) in H_2O (100 mL) was added. The biphasic mixture was stirred vigorously overnight at RT, then transferred to a separating funnel. The organic phase was removed and the aqueous phase washed twice with dicholoromethane (40 mL). The combined organic phases were washed once with H_2O (40 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude was purified by flash chromatography (dicholoromethane/methanol 95:5) to afford the product as a green powder (1.82 g, yield 96%). Mp decomposition at 160 °C. $[\alpha]_{22}^{D}$= 1671.1 (c = 0.027, $CHCl_3$); IR (nujol) ν_{max} 3346, 3215, 2730, 1638, 1644, 1615, 1524, 1377, 1256, 1168, 1015, 930, 781 cm^{-1}. ^1H NMR (CDCl3) δ 7.92 (s, 1H), 7.44 (d, 1H, J=2.4 Hz), 7.39 (s, 1H), 7.30 (d, 1H, J=2.4 Hz), 7.26-7.19 (m, 4H),7.13 (d, 1H, J=2.3), 6.62 (d, 2H, J=7.0 Hz), 5.35 (m, 1H) 4.63(m, 2H), 4.02 (d, 1H, J=13.6 Hz), 3.43-3.25 (m, 3H), 2.94 (m, 1H), 2.80 (m, 1H), 2.29 (m, 1H), 2.18 (m, 1H), 1.73-1.61 (m, 3H), 1.54 (s, 9H), 1.38 (s, 19 H), 1.18 (s, 9H), 1.0-0.94 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ 163.7, 163.3, 162.6, 160.1, 144.3, 141.1, 137.3, 136.9, 134.4, 129.8, 129.2, 128.9, 128.2, 125.7, 122.6, 117.4, 75.2, 70.8, 62.7, 55.4, 35.8, 34.0, 33.8, 31.5, 31.4, 31.0, 29.7, 29.6, 25.1, 22.6 ppm. HRMS (ESI+) m/z calcd for $[C_{46}H_{64}CoNaN_3O_5]^+$: 820.40702 $[M^+Na]^+$; found: 820.40507.

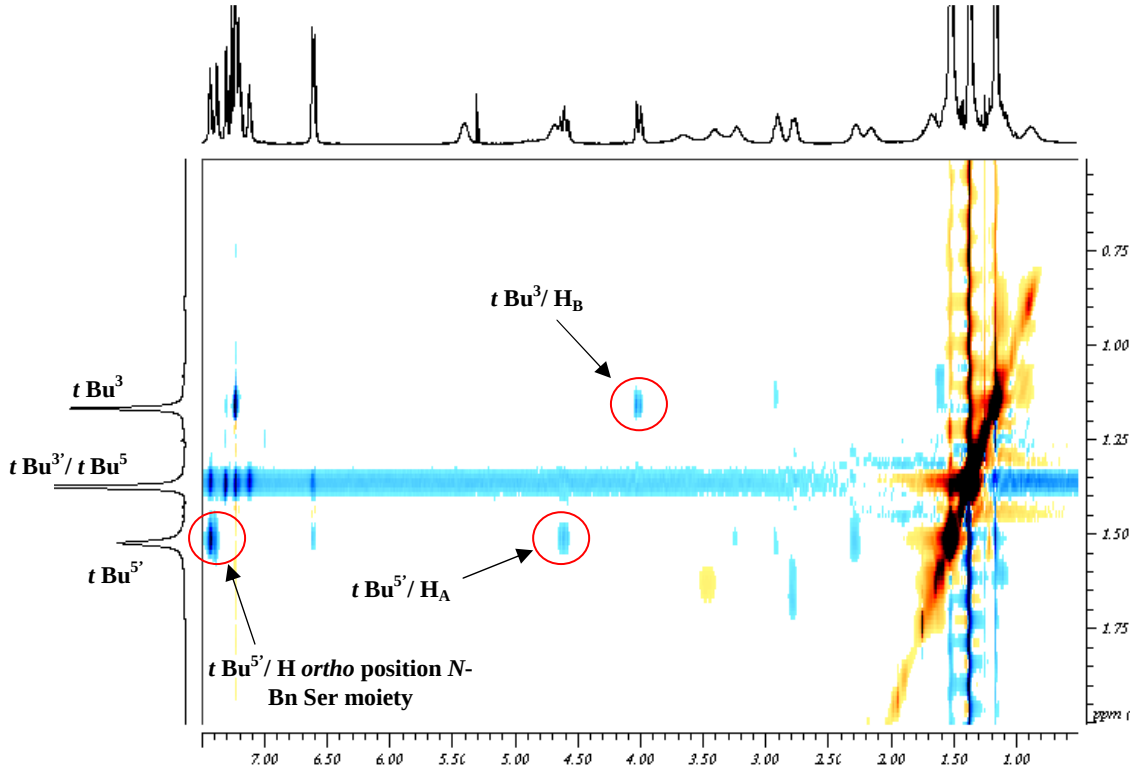




Section of ^{1}H-COSY spectrum of (*S*,*S*)salen-cobalt(III)-*N*-Bn-L-serine with cross-peaks corresponding to the interactions of the hydrogen atoms of the L-*N*-Bn-Ser portion.

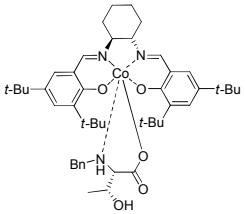


Section of ^{1}H-NOESY spectrum of (*S*,*S*)-salen-cobalt(III)-*N*-Bn-L-serine showing spatial interactions between protons of the L-serine backbone and the chiral salen ligand.



Section of ^{1}H-NOESY spectrum of (*S*,*S*)-salen-cobalt(III)-*N*-Bn-L-serine showing spatial interactions between protons H_A and H_B of the benzyl group of (*S*)-*N*-Bn-Ser and *t*-butyl groups of the chiral salen ligand.

3.4.5 Synthesis of (*S*,*S*) salen-cobalt(III)-*N*-Bn-L-threonine complex 10.



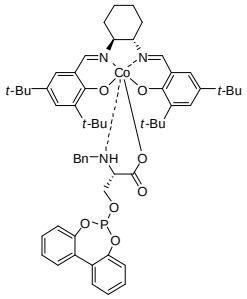
(*S*,*S*) salen-cobalt(III)-*N*-Bn-L threonine complex **10** was synthesized following the same procedure reported above for compound **6** (Yield: 83%).

IR (nujol): υ_{max} 3367, 2918, 2723, 1655, 1631, 1574, 1544, 1526, 1406, 1270, 1256, 1208, 1168, 1128, 1098, 1056, 1024, 987, 932, 915 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (s, 1H), 7.53 (s, 1H), 7.46 (s, 1H), 7.32-7.16 (m, 5H), 7.14 (s, 1H), 6.60 (s, 1H), 6.58 (s, 1H), 4.81-4.60 (m, 2H), 4.33-4.18 (m, 2H), 3.40-3.34 (m, 2H), 3.15-3.03 (m, 2H), 2.86 (d, J = 8.4 Hz, 1H), 2.45-2.35 (m, 1H), 2.00-1.81 (m, 3H), 1.60-1.52 (m, 3H), 1.55 (s, 9H), 1.42 (s, 9H), 1.37 (s, 9H), 1.19 (s, 9H), 0.72 ppm (d, J = 4.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.7, 165.4, 163.7, 163.6, 161.0, 145.4, 141.7, 138.5, 137.3, 135.6, 130.9, 130.4, 130.2, 129.8, 129.2, 126.1, 122.9, 118.0, 76.0, 71.3, 68.8, 67.8, 57.1, 36.5, 36.4, 32.1, 31.5, 30.5, 30.3, 29.8, 25.3, 24.5, 20.0 ppm. HRMS (ESI+) m/z calcd for $[C_{47}H_{66}N_3O_5CoNa]^+$: 834.4227 $[M+Na]^+$; found: 834.4259. Elemental analysis calcd (%) for $C_{47}H_{66}N_3O_5Co$ (MW = 811.99): C 69.52, H 8.19, N 5.17; found: C 69.21, H 8.21, N 4.87.

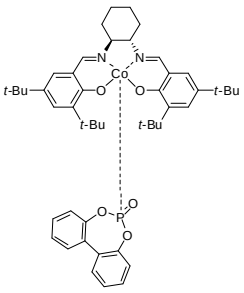
3.4.6 General procedure for the synthesis of the .(*S*,*S*)-salen-Co(III)-*N*-Bn-L-serine complex phosphites 7a-7d.

The (*S*,*S*)-Salen-Co(III)-*N*-Bn-L-Serine complex **6** (120 mg, 0.15 mmol) was dissolved in THF (1.0 mL) in a schlenk under nitrogen atmosphere. Freshly distilled TEA (42 μL, 0.3 mmol, 2 equiv) was added to the green solution at RT and the whole mixture was cooled to -78 °C. A solution of the diol derived monochlorophosphite (0.18 mmol, 1.2 equiv) in THF (1.0 mL) was added dropwise and the reaction mixture was allowed to warm to rt. After 20 min the solvent was removed under reduced pressure and the crude was quickly purified by flash chromatography to afford the product as a green fine powder.

(*S*,*S*)-salen-Co(III)-*N*-Bn-L-serine-biphenyl phosphite 7a.

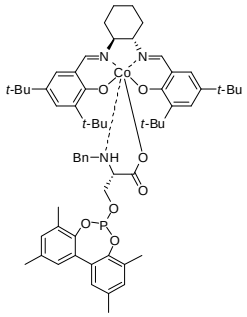


(hexane/AcOEt 3:2 R_f = 0.50) (76 mg, yield 50%). $[\alpha]_{23}^{D}$= -681.8 (c = 0.094, $CHCl_3$). IR (nujol) ν_{max} 3231, 2705, 1672, 1643, 1615, 1529, 1377, 1321, 1250, 1207, 1168, 1096, 1015, 897, 739 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.84 (s, 1H), 7.44-7.43 (m, 4H), 7.36-7.12 (m, 12H), 6.65 (d, 2H, J=7.3 Hz), 5.16 (m, 1H), 4.66(dd, 1H, J = 13.6 Hz, J = 3.8 Hz), 4.12 (dd, 1H, J = 5.9 Hz, J = 3.8 Hz), 4.02 (m, 2H), 3.46 (m, 1H), 2.98 (m, 1H), 2.82 (m, 1H), 2.71 (m, 1H), 1.96-1.55 (m, 4H), 1.55 (s, 10H), 1.42 (s, 9H), 1.36 (s, 10H), 1.17 (s, 10H) ppm. ^{13}C-NMR ($CDCl_3$) δ 179.8, 164.9, 163.5, 163.4, 160.7, 150.1, 149.3, 144.9, 141.2, 137.7, 137.0, 135.2, 131.8, 130.4, 130.3, 130.1, 129.8, 129.7, 129.6, 129.4, 129.1, 128.8, 126.0, 125.7, 125.6, 122.8, 122.5, 122.4, 120.9, 118.1, 117.9, 75.9, 70.6, 65.5, 65.3, 64.89, 64.8, 55.9, 36.2, 34.5, 34.2, 32.0, 31.9, 31.1, 30.3, 29.9, 29.3, 25.0, 24.3 ppm. ^{31}P-NMR ($CDCl_3$) δ 164.6 ppm. HRMS (ESI+) m/z calcd for $[C_{58}H_{71}CoNaN_3O_7P]^+$: 1034.42538 $[M+Na]^+$; found: 1034.42271.



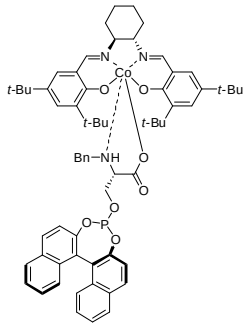
Decomposition by-product 8: ^{1}H-NMR ($CDCl_3$) δ 8.30 (bs, 1H), 8.01 (bs, 1H), 7.51 (d, 1H, J=2.4 Hz), 7.44 (d, 1H, J=2.4 Hz), 7.32 (dd, 1H, J = 7.4 Hz, J = 1.3 Hz), 7.26 (d, 1H, J = 7.2 Hz), 7.21 (d, 1H, J=2.4 Hz), 7.17 (d, 1H, J=2.4 Hz), 7.13-7.04 (m, 2H), 6.99-6.95 (m, 1H), 6.68-6.64 (m, 1H), 6.14 (d, 1H, J=7.7 Hz), 5.47 (d, 1H, J=8.2 Hz), 4.25-4.18 (m, 1H), 3.73-3-67 (m, 1H), 2.91 (d, 1H, J=10.5 Hz), 2.78 (d, 1H, J=9.7 Hz), 2.09-2.05 (m, 2H), 1.96-1.87 (m, 1H), 1.78-1.68 (m, 1H), 1.63-1.49 (m, 2H), 1.48 (s, 9H), 1.43 (s, 9H), 1.40 (s, 9H), 1.22 (s, 9H) ppm. ^{31}P-NMR ($CDCl_3$) δ 37.5 ppm.

(*S*,*S*)-salen-Co(III)-*N*-Bn-L-serine-3,3',5,5'biphenyl phosphite 7b.



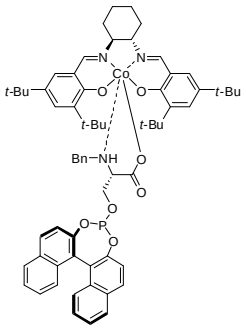
(hexane/AcOEt 3:1 R_f = 0.40) (115 mg, yield 72%). $[\alpha]_{23}^{D}$= -1050.8 (c = 0.077, $CHCl_3$); IR (nujol) ν_{max} 3251, 3232, 2726, 1680, 1645, 1618, 1535, 1380, 1320, 1257, 1212, 1168, 1093, 1015, 860, 739 cm^{-1}. ^{1}H-NMR (CDCl3) δ 7.81 (s, 1H), 7.42 (d, 1H, J = 2.5 Hz), 7.38-7.28 (m, 4H), 7.27 (d, 1H, J = 2.4 Hz), 7.18 (s, 1H), 7.12-7.11 (m, 2H), 7.06 (s, 1H), 7.00 (d, 1H, J = 2.3 Hz), 6.75 (m, 2H), 6.51 (s, 1H), 5.04 (m, 1H), 4.68 (m, 1H), 4.34 (m, 1H), 4.15 (dd, 1H, J = 14.3 Hz, J = 7.13 Hz), 4.01-3.92 (m, 2H), 3.52 (m, 1H), 2.89-2.78 (m, 2H), 2.62-2.58 (m, 1H), 2.46 (s, 3H), 2.37 (s, 6H), 2.30 (s, 3H), 1.83-1.70 (m, 3H), 1.57 (s, 9H), 1.50 (s, 9H), 1.36 (s, 10H), 1.23-1.17 (m, 11H) ppm. ^{13}C-NMR (CDCl3) δ 179.3, 164.8, 163.5, 147.4, 145.0, 144.8, 141.2, 137.6, 135.6, 135.1, 134.8, 133.9, 132.1, 131.9, 131.3, 131.2, 130.7, 130.4, 130.2, 129.6, 129.5, 129.0, 128.4, 127.7, 126.0, 122.8, 118.2, 75.9, 71.0, 66.3, 66.1, 65.9, 60.8, 55.9, 36.1, 34.6, 34.1, 32.2, 31.9, 31.3, 30.3, 29.9, 29.5, 25.0, 23.9, 21.3, 17.4, 16.9, 14.6 ppm. ^{31}P-NMR ($CDCl_3$) δ 150.7 ppm. HRMS (ESI+) m/z calcd for $[C_{62}H_{79}CoNaN_3O_7P]^+$: 1090.48798 $[M+Na]^+$; found: 1090.48576.

(*S*,*S*)-salen-Co(III)-*N*-Bn-L-serine-(*S*$_a$)-binaphthyl-phosphite phosphite 7c.



(hexane/AcOEt 2:1 R_f = 0.40) (62 mg, yield 37%). $[\alpha]_{22}^{D}$= -775.2 (c = 0.078, $CHCl_3$); IR (nujol) ν_{max} 3159, 2722, 1660, 1634, 1615, 1526, 1365, 1321, 1255, 1230, 1168, 945, 828, 730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.06 (d, 1H, J = 8.8 Hz), 7.97 (d, 1H, J = 8.3 Hz), 7.87 (d, 1H, J = 8.5 Hz), 7.82 (d, 1H, J = 8.8 Hz), 7.77 (m, 1H), 7.62 (d, 1H, J = 8.7 Hz), 7.50-7.33 (m, 9H), 7.31-7.26 (m, 3H), 7.13 (d, 1H, J = 8.7 Hz), 7.08-7.06 (m, 2H), 6.73 (m, 2H), 5.32 (m, 1H), 4.67 (m, 1H), 4.16-4.04 (m, 3H), 3.59 (m, 1H), 3.46 (m, 1H), 2.80 (m, 1H), 2.73-2.68 (m, 2H), 1.77-1.63 (m, 3H), 1.54 (s, 9H), 1.42 (s, 9H), 1.41-1.35 (m, 2H), 1.33 (s, 9H), 1.19-1.12 (m, 10H) ppm. ^{13}C-NMR ($CDCl_3$) δ 179.2, 164.4, 163.1, 162.9, 160.7, 152.0, 147.7, 146.8, 144.5, 140.8, 137.3, 136.9, 134.8, 132.9, 132.1, 131.7, 131.0, 130.7, 130.5, 130.4, 130.2, 129.9, 129.8, 129.3, 128.6, 128.5, 128.4, 127.2, 127.0, 126.6, 126.5, 126.2, 125.7, 125.4, 124.9, 122.1, 122.0, 121.6, 119.3, 118.0, 117.7, 75.5, 69.7, 64.6, 64.5, 63.6, 63.5, 55.4, 35.8, 34.1, 33.7, 31.6, 31.4, 30.4, 30.1, 29.8, 29.5, 29.1, 28.5, 24.4, 23.6 ppm. ^{31}P-NMR ($CDCl_3$) δ 146.6 ppm. HRMS (ESI+) m/z calcd for $[C_{66}H_{75}CoNaN_3O_7P]^+$: 1134.45668 $[M+Na]^+$; found: 1134.45474.

(*S*,*S*)-salen-Co(III)-*N*-Bn-L-serine-(R_a)-binaphthyl-phosphite phosphite 7d.



(hexane/AcOEt 2:1 R_f = 0.40) (75 mg, yield 45%). $[\alpha]_{23}^{D}$= -1227.3 (c = 0.055, $CHCl_3$); IR (nujol) ν_{max} 3221, 2725, 1670, 1652, 1634, 1521, 1377, 1314, 1256, 1168, 1095, 1023, 945; 823, 744 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.06-7.59 (m, 3H), 7.80 (s, 1H), 7.59 (d, 1H, J=8.7 Hz), 7.51-7.45 (m, 2H), 7.42-7.27 (m, 7H), 7.20 (d, 1H, J=2.4 Hz), 7.09-6.96 (m, 5H), 6.59-6.57 (m, 3H), 4.85 (m, 1H), 4.59 (m, 1H), 4.17-4.09 (m, 2H), 3.91 (m, 1H), 3.42 (m, 1H), 2.88-2.75 (m, 2H), 2.61 (m, 1H), 1.99-1.85 (m, 3H), 1.56-1.41 (m, 19H), 1.36-1.34 (m, 10H), 1.28-1.25 (m, 1H), 1.22-1.12 (m, 11H) ppm. ^{13}C-NMR ($CDCl_3$) δ 179.2, 164.4, 162.9, 161.2, 159.6, 148.3, 147.0, 144.4, 140.8, 137.1, 136.4, 134.8, 132.7, 132.3, 131.6, 130.8, 130.6, 129.9, 129.8, 129.3, 129.1, 129.0, 128.8, 128.4, 128.3, 126.9, 126.8, 126.4, 126.3, 126.0, 125.6, 125.2, 125.1, 124.5, 123.9, 123.5, 122.6, 75.5, 70.4, 66.3, 66.1, 65.1, 55.5, 35.7, 34.1, 33.7, 31.7, 31.4, 30.6, 29.8, 29.4, 29.0, 24.5, 23.7 ppm. ^{31}P-NMR ($CDCl_3$) δ 144.2 ppm. HRMS (ESI+) m/z calcd for $[C_{66}H_{75}CoNaN_3O_7P]^+$: 1134.45668 $[M+Na]^+$; found: 1134.45423.

3.4.7 Complexation Experiments

General procedure

All experiments were conducted using $CDCl_3$ pre-emptively passed over a short plug of neutral alumina.

The complexation experiments were run in NMR tubes under nitrogen atmosphere and monitored by ^{1}H and ^{31}P NMR spectroscopy. The typical scale of the experiments was 6.51 μmol of metal source ($[Rh(acac)(C_2H_4)_2]$) in 500 μL of deuterated solvent (0.013 M concentration). The clear yellow solution was titrated by addition of defined aliquots (150 μL each) of ligand **7a**, chosen as representative of the ligand library, in such a way the ratio Rh : L was 1 : 1. At this stage two specie was obtained namely homocomplex (Rh(acac)(**7a**)$_2$) and monocomplex (Rh(acac)(**7a**)(ethylene)) in a 3 : 1 ratio. Upon addition of a second aliquot of ligand, the exclusive formation of the homocomplex appeared, showing the good coordinative features of our P-ligands notwithstanding their steric hindrance.

^{31}P NMR spectra have been reported on paragraph 3.1.2.

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Chapter 4

PhthalaPhos: Chiral Supramolecular Ligands for Enantioselective Rhodium-Catalyzed Hydrogenation Reactions

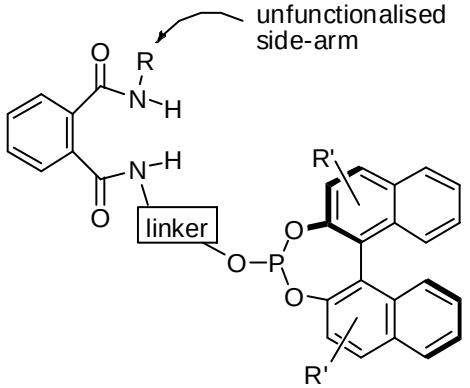
Abstract

In this chapter the synthesis of a library of novel chiral supramolecular ligands containing a phthalamide moiety capable of hydrogen bonding interactions is reported. The new ligands, named PhthalaPhos, are easy to prepare from inexpensive starting materials, and displayed an excellent level of enantioselectivity in the hydrogenation of benchmark olefins (methyl 2-acetamidoacrylate and acetamidostyrene) as well as of more challenging, industrially relevant substrates. In two reported cases, namely the cyclic enamide N-(3,4-dihydronaphthalen-1-yl)acetamide and β²-dehydro aminoester (E)-methyl 2-(acetamidomethyl)-3-phenylacrylate, our ligands rival or even outperform the best results obtained with known ligands. The pre-catalytic Rh complex of one of these ligands was fully characterized by NMR, IR and MS spectroscopy. These studies show that a supramolecular bidentate ligand is formed in the Rh complex by ligand self-association through a pair of interligand hydrogen bonds.[1]

4.1 GENERAL INTRODUCTION

Chemists have largely taken inspiration from Nature in the development of new approaches to synthetic challenges. Combinatorial chemistry stems from the concept of evolution, where random mutation of a chemical structure gives rise to libraries of compounds, from which an optimal lead can be found with high probability. On the other hand, Nature makes wide use of noncovalent interactions to build its complex supramolecular architectures and to achieve efficient and selective transformations. In recent years, combinatorial and supramolecular approaches to the development of new ligands for asymmetric catalysis gained momentum.[2,6b] The term 'supramolecular ligand' encompasses all the ligands possessing, besides the atom(s) coordinating the catalytic metal, an additional functionality capable of non-covalent interactions (mainly hydrogen[3] or coordinative bonds[4], as widely reported in chapter 1) which can play the following role: (i) self-assemble two monodentate ligands to form a so-called 'supramolecular bidentate ligand';[5] (ii) bind the substrate(s) in proximity to the catalytic metal center[6] in analogy to metalloenzymes.[7] Among the different kinds of non-covalent interactions that have been used so far for developing supramolecular ligands,[5] hydrogen bonds are arguably the most practical and efficient[3,6] for several reasons: (i) functional groups capable of hydrogen bonding (*e.g.* amides, ureas, guanidines) are stable and relatively easy-to-introduce; (ii) H-bonds are created dynamically and reversibly in the reaction medium (where catalysis is to take place), being able to self-repair when broken, and often coexist with other interactions in a 'noninvasive' manner.

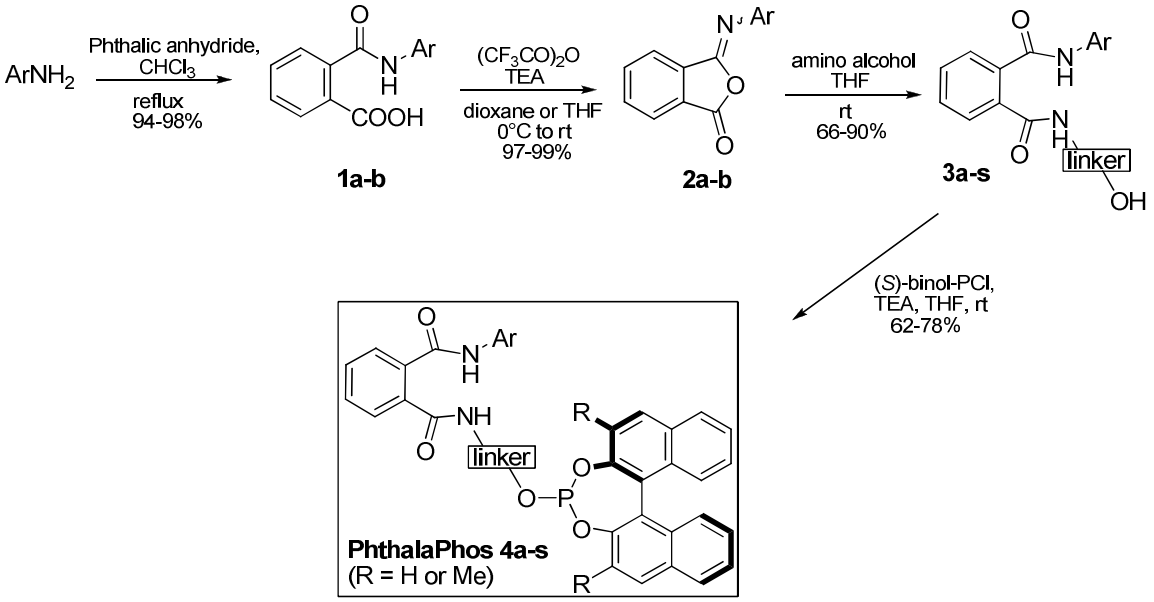
In this chapter, as a result of our continued interest in developing supramolecular ligands,[8] we report the design and synthesis of a novel class of chiral monodentate phosphite ligands, named PhthalaPhos, which contain a phthalic acid primary diamide moiety (Scheme 4.1). Such phthalamidic group displays both donor and acceptor hydrogen bonding properties that, in principle, can give rise to supramolecular interactions both between the ligands and with the reaction substrate. The modular nature of the PhthalaPhos ligands allows to tune their properties by simply varying structural elements such as the linker, the BINOL moiety and the ancillary amide group (*i.e.* the amide not connected to the phosphite group), thus allowing a parallel-combinatorial ligand optimization.[2a,c]



Scheme 4.1 General structure of Phthalaphos ligands

4.2 SYNTHESIS OF PHTHALAPHOS LIBRARY

The Phthalaphos ligands were easily prepared in four steps as reported in Scheme 4.2. Phthalic anhydride was treated with a primary amine to give in good yield the corresponding phthalic acid monoamides **1**.[9] Dehydration of the latter in presence of trifluoroacetic anhydride gave phthalisoimides **2** in high yields, whose reaction with a chosen amino alcohol led to phthalic acid diamides **3**.[10] To give PhthalaPhos ligands **4**.



Scheme 4.2 PhthalaPhos synthetic protocol

This protocol allows the synthesis of PhthalaPhos ligands starting from cheap and available materials and in relatively short time (2-3 days). Indeed, as reported in Experimental Section, monoacids **1** and isoimides **2** can be obtained by a simple precipitation and only diamide mono-alcohols and final ligands necessitate a chromatographic purification. All PhthalaPhos ligands are solids and have also been demonstrated good stability and an easy-handiness.

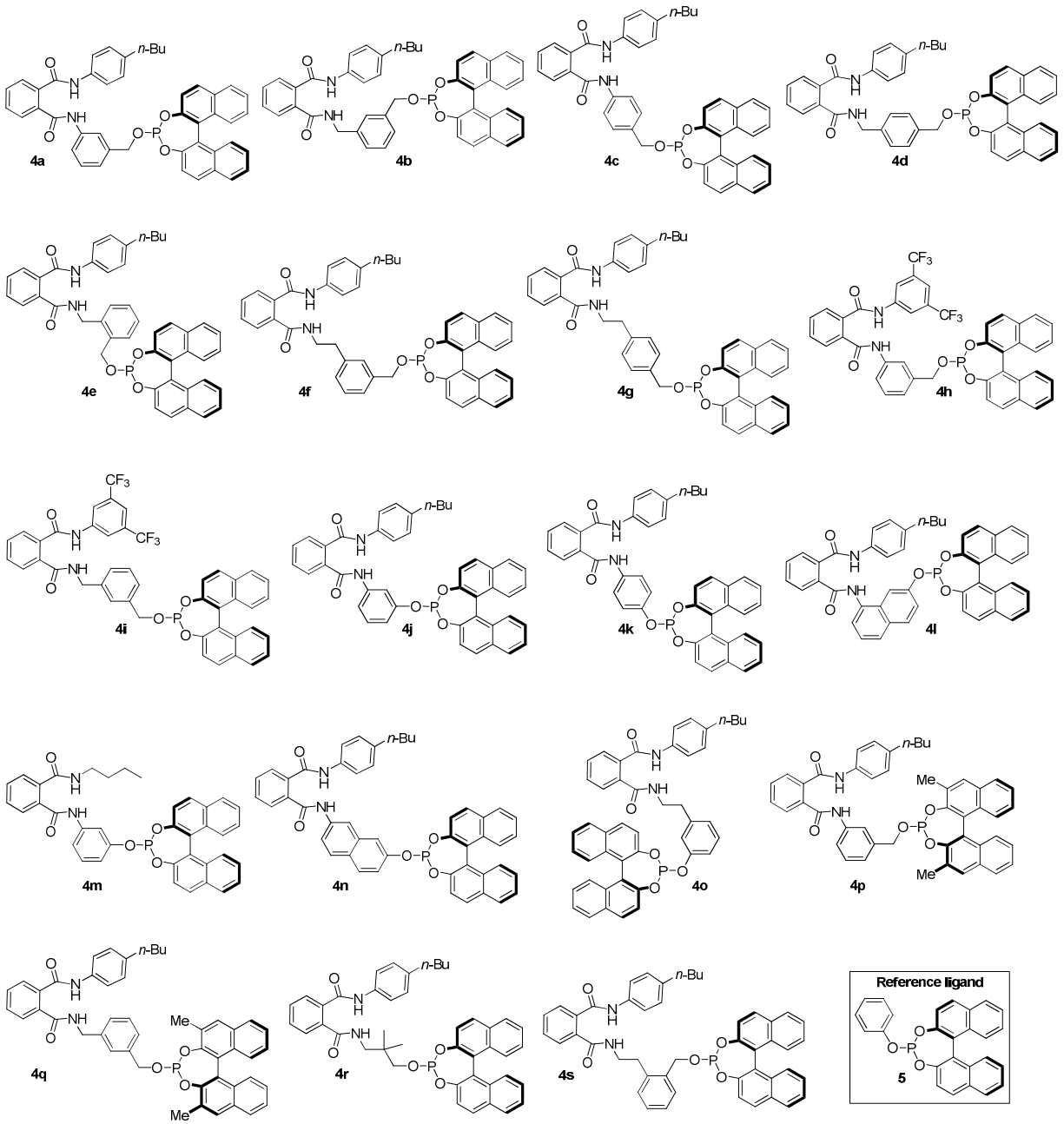
Our library was composed of 19 members on the whole (Scheme 4.3). Terms of variation of the PhthalaPhos backbone were substantially three:

(i) the ancillary amine (all ligands were synthesized from 4-*n*Bu-aniline except for ligands **4h** and **4i** for which 3,5-bis-trifluoromethyl aniline was used as starting material and for ligand **4m** which was obtained from *n*Bu-amine. This exceptions were dictated to investigate whether the different acidities of NH- amide groups had a positive effect on the self-assembly *via* hydrogen-bonding)

the linker (various amino alcohols were used to investigate the role of geometry properties on the self-assembly and on the stereoselective processes: ligands **4a-k**, **4m**, **4o-4q** and **4s** were obtained starting from aromatic amino alcohols varying the position of the substituents on the ring and the length of

amino alcohol side-chains. Whenever the amino aclcohol linkers were not commercially available, their synthesis could be obtained through a limited number of synthetic steps following previously published procedures (see Experimental Section). Moreover, a more constrained ligand **4r** was synthesized starting from the 2,2-dimethyl-3-amino propan-1-ol (Thorpe-Ingold effect). Finally, ligands **4l** and **4n** were built from a naphthalene unit as linker.

(ii)

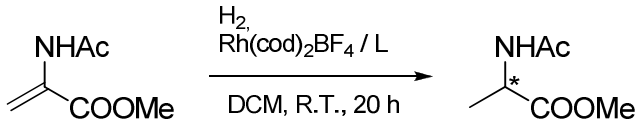


Scheme 4.3 PhthalaPhos library and reference phosphite **5**.

(iii) the binaphthol unit (all ligands were obtained from (*S*)-binaphthol except for ligands **4p-q** for which two methyl groups were introduced on the binaphthol backbone in 3-3' position).

4.3 CATALYTIC APPLICATIONS: RHODIUM-CATALYZED ASYMMETRIC HYDROGENATIONS

We assessed the catalytic properties of the new ligands in the hydrogenation of classical benchmark substrates, namely, methyl 2-acetoamidoacrylate (**S1**) (Table 4.1) and *N*-(1-phenyl-vinyl)acetamide (**S2**) (Table 4.2), taking the known phosphite **5** as touchstone.[11,12]



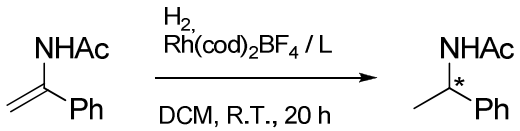
S1 **P1**

Entry	Ligand	$P_{hydrogen}$ = 1 bar, **S1**/L/Rh = 100/2.2/1, reaction time = 20 h	
		Conv. (%)	*ee* (%), abs. conf.
1	**4a**	100	**94, *R***
2	**4b**	100	**98, *R***
3	**4c**	100	**92, *R***
4	**4d**	99	**94, *R***
5	**4e**	100	**99, *R***
6	**4f**	100	**98, *R***
7	**4g**	98	**95, *R***
8	**4h**	100	89, *R*
9	**4i**	100	**98, *R***
10	**4j**	100	86, *R*
11	**4k**	100	77, *R*
12	**4l**	100	**94, *R***
13	**4m**	100	83, *R*
14	**4n**	100	78, *R*
15	**4o**	100	**94, *R***
16	**4p**	-	-
17	**4q**	-	-
18	**4r**	100	**98, *R***
19	**4s**	100	**> 99, *R***
20	**5**	100	84, *R*

Table 4.1. Screening of the Phthalaphos ligands in the hydrogenation of methyl 2-acetamidoacrylate **S1**.

The results of this preliminary screening turned out to be very encouraging: four ligands gave ee values higher than 97% with substrate **S1** (Table 4.1, entries 2, 5, 6 and 9), and six reached the same level of performance with **S2** (Table 4.2, entries 1-2, 5-8). Remarkably, the reference ligand **5**, featuring the same binol phosphite moiety as **4a–i**, gave only 84%ee with **S1** and 90% ee with **S2** (Table 4.1 and Table 4.2, entries 20), which suggests that the phthalamide residue significantly influences the catalytic properties of these ligands. Further support to this conclusion came from the effect on the enantioselectivity displayed by the linker, particularly evident in the case of ligands **4h**

and **4i**, for which a subtle variation of the linker length resulted in remarkably different ee values (**S1**, **4h**: 89%ee, **4i**: 98%ee; **S2**, **4h**: 97% ee, **4i**: 83% ee). Indeed, if the phthalamide residue were a simple bystander and **4a–i** behaved as "normal" monodentate phosphites, only negligible differences in enantioselectivity should be expected for the ligands. Another interesting observation is that not always the best ee values with **S1** and **S2** were obtained with the same ligands, which underlines the advantage of the combinatorial approach followed in the ligand design.



S2 **P2**

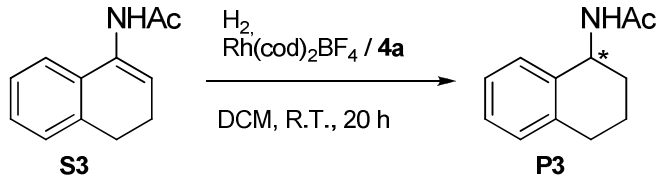
Entry	Ligand	$P_{hydrogen}$ = 5 bar, **S2**/L/Rh = 100/2.2/1, reaction time = 20 h	
		Conv. (%)	*ee* (%), abs. conf.
1	**4a**	100	**98, *R***
2	**4b**	100	**98, *R***
3	**4c**	100	**93, *R***
4	**4d**	100	**96, *R***
5	**4e**	100	**97, *R***
6	**4f**	100	**98, *R***
7	**4g**	100	**99, *R***
8	**4h**	100	**97, *R***
9	**4i**	100	83, *R*
10	**4j**	100	86, *R*
11	**4k**	100	79, *R*
12	**4l**	100	72, *R*
13	**4m**	100	77, *R*
14	**4n**	100	89, *R*
15	**4o**	100	**92, *R***
16	**4p**	99	10, *R*
17	**4q**	100	37, *S*
18	**4r**	100	**96, *R***
19	**4s**	100	**96, *R***
20	**5**	100	90, *R*

Table 4.2. Screening of the Phthalaphos ligands in the hydrogenation of *N*-(1-phenylvinyl)acetamide **S2**.

To explore the scope of the PhthalaPhos ligands, we decided to investigate the Rh-catalyzed hydrogenation of more challenging substrates such as cyclic enamide **S3** [*N*- (3,4-dihydronaphthalen-1-yl)acetamide] and β^2-dehydro amino ester **S4** [(*E*)-methyl 2-(acetamidomethyl)-3-phenylacrylate], both of which are industrially relevant compounds.[3p]

Initially studies of **S3** were carried out to optimize the hydrogenation pressure using ligand **4a** as representatives of the whole library. As reported in Table 4.3, the best conversion and enantioselectivity were reached under 20 bar of hydrogen pressure (entry 4) but a only slightly lower result, in terms of conversion, was obtained with a lower pressure of 12 bar, which was therefore

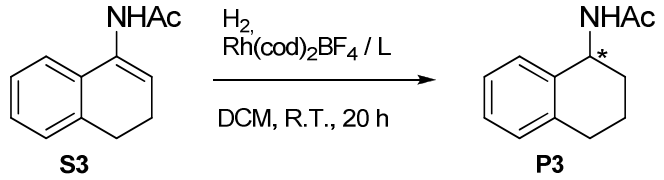
chosen to screen the library. A short series of tests (Table 4.3, entries 5-7) showed as the ratio Rh/L has to be fixed to 1:2 to obtain the highest conversions and stereoselectivities.



Entry	Rh/**4a**	**S3**/Rh = 100/1, reaction time = 20 h		
		$P_{hydrogen}$ (bar)	Conv. (%)	*ee* (%), abs. conf.
1	1:2.2	1	77	91, *R*
2	1:2.2	5	83	86, *R*
3	1:2:2	12	98	**96, *R***
4	1:2.2	20	99	**96, *R***
5	1:1	12	77	90, *R*
6	1:3.3	12	99	**96, *R***
7	2:1	12	86	74, *R*

Table 4.3. Study of the effect of hydrogen pressure and Rh/L ratio in the hydrogenation of *N*-(3,4-dihydronaphthalen-1-yl)acetamide **S3** carried out with ligand **4a**.

Having in hand the optimized conditions we hydrogenated **S3** and all results are reported in Table 4.4.[13] The results of this screening were quite variegated both in terms of activity and enantioselectivity, and excellent conversion and ee value were attained with ligand **4a** (Table 4.4, entry 1). The conversions followed more or less the same trend as the ee values, the most stereoselective ligands being also the most active. Poor results were obtained with reference ligand **5** (Table 4.4, entry 20).

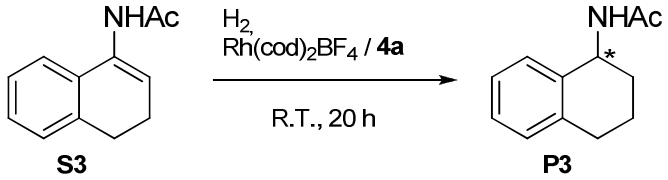


Entry	Ligand	$P_{hydrogen}$ = 12 bar, **S3**/L/Rh = 100/2.2/1, reaction time = 20 h	
		Conv. (%)	*ee* (%), abs. conf.
1	**4a**	99	**96, *R***
2	**4b**	90	**93, *R***
3	**4c**	9	60, *R*
4	**4d**	98	**92, *R***
5	**4e**	6	24, *R*
6	**4f**	46	**86, *R***
7	**4g**	5	48, *R*

8	**4h**	22	73, *R*
9	**4i**	9	28, *R*
10	**4j**	29	11, *R*
11	**4k**	15	0
12	**4l**	12	12, *R*
13	**4m**	10	2, *R*
14	**4n**	18	3, *R*
15	**4o**	7	21, *R*
16	**4p**	2	-
17	**4q**	4	-
18	**4r**	3	-
19	**4s**	45	23, *R*
20	**5**	30	53, *R*

Table 4.4. Screening of the Phthalaphos ligands in the hydrogenation of *N*-(3,4-dihydronaphthalen-1-yl)acetamide **S3**.

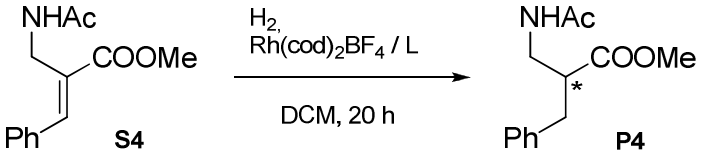
Additionally, the fact that the enantioselectivity strongly decreased increasing the polarity of the solvent (Table 4.5, entry 2) and dropped dramatically in the presence of isopropanol which can act as a H-bond donor (Table 4.5, entry 3) confirms that hydrogen-bonding interactions between the phthalamide groups play a crucial role in the activity and selectivity of the catalyst. To the best of our knowledge, the 96% ee obtained with ligand **4a** is the highest ever obtained for this substrate with phosphite ligands, and rivals the best literature precedents, obtained with a monodentate phosphoramidite (84% ee at rt, 98% ee at -20°C)[14] and a bisphosphine (98% ee at rt).[15]



Entry	Reaction solvent	$P_{hydrogen}$ = 12 bar, **S3**/L/Rh = 100/2.2/1, reaction time = 20 h	
		Conv. (%)	*ee* (%), abs. conf.
1	DCM	99	**96, *R***
2	THF / DCM 7:1	70	57, *R*
3	*i*-PrOH / DCM 7:1	77	21, *R*
4	toluene / DCM 7:1	82	**87, *R***
5	AcOEt / DCM 7:1	94	67, *R*

Table 4.5. Solvent screening in the hydrogenation of *N*-(3,4-dihydronaphthalen-1-yl)acetamide **S3** carried out with ligand **4a**.[a] The pre-catalytic complex was prepared in DCM (0.9 mL) see General Procedure (Experimental Section). To the complex solution the selected solvent (7.1 mL) was added, followed by substrate **S3** as a solid. The obtained mixture was then hydrogenated as described in the General Procedure.

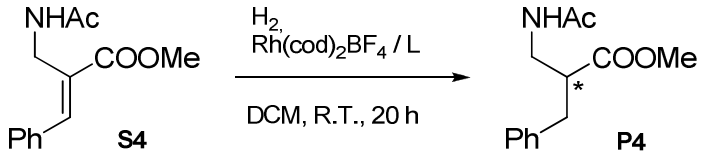
The screening of the ligand library on **S4** required a hydrogen pressure of 50 bar (as reported in table 4.6) due to the lower reactivity of this substrate (Table 4.7). Also in this screening the enantioselectivity varied quite widely and appeared to be linked to the catalytic activity.



Entry	Ligand	$P_{hydrogen}$ (bar)	T (°C)	**S4**/L/Rh = 100/2.2/1, reaction time = 20 h	
				Conv. (%)	*ee*, $[\alpha]_D$ sign
1	**4a**	1	20	13	30, (+)
2	**4a**	5	20	40	64, (+)
3	**4a**	5	40	79	50, (+)
4	**4a**	12	20	83	**68, (+)**
5	**4a**	25	20	82	**64, (+)**
6	**4a**	50	20	96	**64, (+)**
7	**4b**	1	20	9	28, (+)
8	**4b**	5	20	36	42, (+)
9	**4b**	5	40	59	30, (+)
10	**4b**	12	20	77	**64, (+)**
11	**4b**	25	20	89	**52, (+)**
12	**4b**	50	20	98	**62, (+)**

Table 4.6. Study of the effect of hydrogen pressure and temperature in the hydrogenation of (*E*)-methyl 2-(acetamidomethyl)-3-phenylacrylate **S4** carried out with ligand **4a** and ligand **4b**.

Ligands **4c** and **4i** (Table 4.7, entries 3 and 9) gave very high ee values and good conversions, while the other ligands displayed moderate to fair enantioselectivity. Again, the reference phosphite **5** gave only very low conversion and ee with this substrate (Table 4.7, entry 19).



Entry	Ligand	$P_{hydrogen}$ = 50 bar, T = 20 °C, **S4**/L/Rh = 100/2.2/1, reaction time = 20 h	
		Conv. (%)	*ee*, $[\alpha]_D$ sign
1	**4a**	96	**64, (+)**
2	**4b**	98	**62, (+)**
3	**4c**	75	**91, (+)**
4	**4d**	96	54, (+)
5	**4e**	8	31, (+)
6	**4f**	27	**67, (+)**
7	**4g**	73	**74, (+)**
8	**4h**	23	43, (+)
9	**4i**	87	**98, (+)**
10	**4j**	27	4, (+)

11	**4k**	57	28, (–)
12	**4l**	79	14, (–)
13	**4n**	35	0
14	**4o**	41	0
15	**4p**	27	6, (+)
16	**4q**	11	12, (–)
17	**4r**	30	0
18	**4s**	50	14, (–)
19	**5**	6	32, (+)

Table 4.7. Screening of the Phthalaphos ligands in the hydrogenation of (*E*)-methyl 2-(acetamidomethyl)-3-phenylacrylate **S4**.

Most importantly, 98% is the highest ee ever obtained with substrate **S4**, and only one highly stereoselective ligand having been reported so far.[3p]

4.4 SPECTROSCOPIC STUDIES

Encouraged by these results, we decided to investigate the role of hydrogen bonding in the catalytic properties of the PhthalaPhos ligands. The precatalyst obtained by treating a representative ligand (**4a**, 2 equiv) with $[Rh(cod)_2]BF_4$ (cod=1,5-cyclooctadiene, 1 equiv) in CH_2Cl_2 or CD_2Cl_2 was studied by spectroscopic methods.

4.4.1 NMR-, HRMS- and IR- studies

Initially, we studied the complexation properties of ligand **4a** by titration of a standard solution of $Rh(cod)_2BF_4$ chosen as Rh(I) source. When the ratio Rh/L was 1:2 the ^{31}P NMR spectrum of the Rh complex displayed a clean doublet at 122.0 ppm with $J_{Rh,P}$ = 257.7 Hz (Figure 4.1) which matched with the ^{1}H NMR spectrum (see Experimental Section) and the result of HRMS analysis (m/z 1643.49193, Figure 4.2) and indicated the formation of the cationic species $[Rh(\mathbf{4a})_2(cod)]^+$, where the phosphite groups occupy two adjacent *cis* positions.

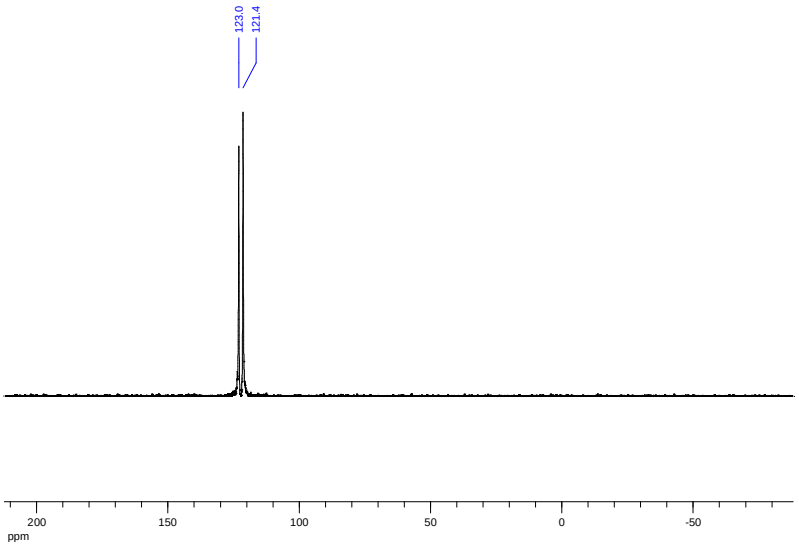


Figure 4.1. Complex [Rh(cod)(**4a**)$_2$BF$_4$] (10 mM solution in CD_2Cl_2): ^{31}P NMR spectrum (162 MHz).

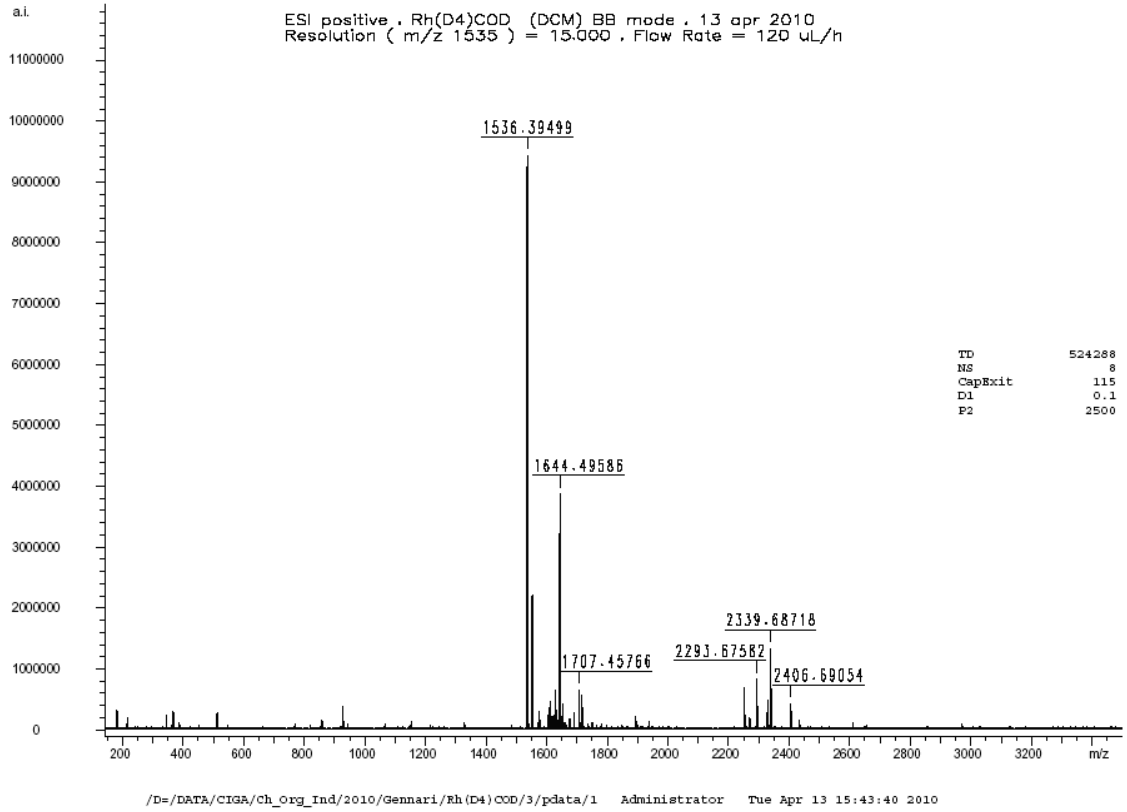
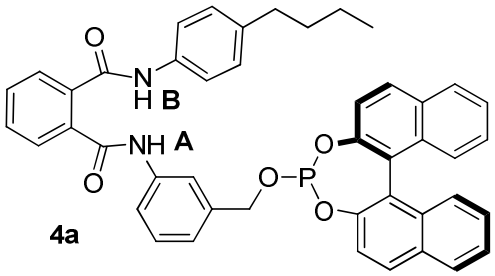


Figure 4.2. HRMS spectrum of complex [Rh(**4a**)$_2$(cod)BF$_4$] in DCM solution.

Only one set of signals could be detected in the NMR spectra of the Rh complex, and the two coordinated molecules of 4a could not be distinguished.

The hydrogen bonding state of the NH protons (NH_A and NH_B, Scheme 4.4) for both the free ligand and the Rh complex was then investigated by ^{1}H NMR spectroscopy, and in particular the following data were collected: 1) temperature coefficient ($\Delta\delta/DT$) of each NH proton; 2) kinetics of H/D exchange of the amide protons upon addition of excess CD_3OD; 3) downfield shift of the NH protons in the presence of excess CD_3OD. These experiments, which are commonly used to differentiate

between random-coil peptides and peptides in hydrogen-bonded conformations,[16,17] were conducted in dilute (1.2 mM) solutions in CD_2Cl_2. This concentration was chosen since aggregation, at least of the Rh complex, is not significant at 1.2 mM, as determined by studying the dependence of the NH chemical shifts on the concentration in the 20.0–0.3 mM range.



Scheme 4.4. Ligand **4a** used as representatives of the ligand library for spectroscopic studies

From the experimental results, which are outlined in Table 4.8 and reported in detail in the Experimental Section, the following conclusions can be drawn: on the one hand, no evidence of intramolecular hydrogen bonding could be found for the free ligand **4a**, which, moreover, shows a strong tendency to intermolecular aggregation even at high dilution. On the other hand, proton NH_A in the Rh complex is definitely involved in an intramolecular hydrogen bond, as confirmed by its downfield chemical shift (δ=9.6 ppm), its reduced rate of exchange with CD_3OD ($t_{1/2}$=47 min), and limited shift when CD_3OD is added (Δδ=0.27 ppm). Proton NH_B, conversely, appears to be in a non-bonded state.

	Free ligand **4a**		[Rh(**4a**)$_2$(cod)]BF_4	
	NH_A[b]	NH_B[b]	NH_A[b]	NH_B[b]
δ (ppm)	8.692	8.342	9.604	8.506
Δδ/ΔT (ppb $^{K-1}$)	n.d[c]	n.d[c]	-12.94	1.73
H/D exchange: $t_{1/2}$ (min)	12.2	14.9	47.1	28.5
Δδ in presence of excess CD_3OD	0.654	0.742	0.274	0.558

Table 4.8: Results of ^{1}H NMR studies on NH protons of ligand **4a** and its Rh complex.[a]
[a] c=1.2 mm in CD_2Cl_2. [b] Assignment of H_A and H_B was based on the NOESY and COSY spectra. [c] Not determined: no linear dependence observed.

Consistent with these observations, two distinct NH stretching bands (ν=3409.5 and 3268.8 cm^{-1}) were detected in the IR spectrum of the Rh complex (1.2 mM solution in CH_2Cl_2), while only one band could be found for the free ligand (ν = 3408.6 cm^{-1})as reported in Figure 4.3.

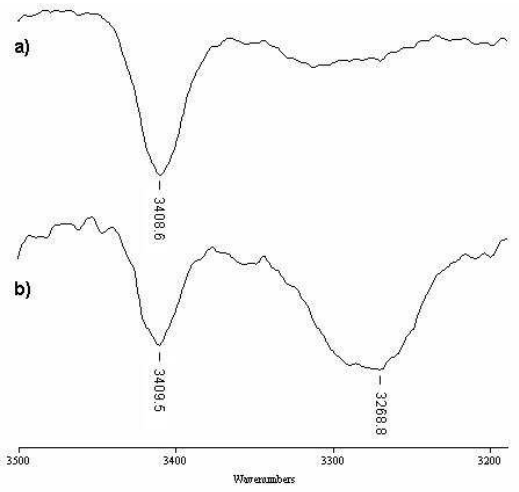


Figure 4.3. N-H stretching IR bands of (a) free ligand **4a** and (b) complex [Rh(**4a**)$_2$(cod)BF$_4$] (1.2 mM DCM solutions).

Also, detection of the C=O stretching band of the Rh complex at a lower wavenumber than that of the free ligand (ν =1661.4 vs. 1676.8 cm^{-1}) confirmed the presence of an intramolecular hydrogen bond (Figure 4.4).

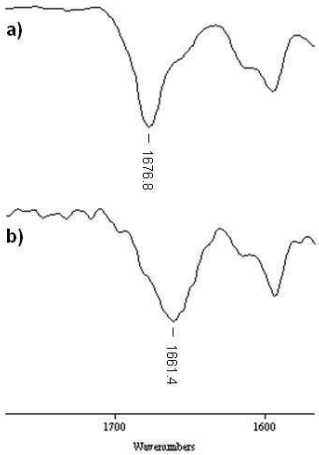


Figure 4.4. C=O stretching IR bands of (a) free ligand **4a** and (b) complex [Rh(**4a**)$_2$(cod)BF$_4$] (1.2 mM DCM solutions).

4.4.2 DFT CALCULATIONS

We ran a Monte Carlo conformational search[18,19,] of the precatalyst [Rh(**4a**)$_2$(cod)]+ using AMBER* force field[20] for the phthalamide region and a frozen core for the Rh(cod) phosphite complex, which was previously optimized with DFT calculations at the B3LYP/LACVP level of theory.[21] A number of low-energy conformers were identified which, in agreement with the spectroscopic data, are characterized by interligand hydrogen bonding involving proton NHA. These low-energy conformers were used as starting geometries for DFT optimization[21] of the entire precatalyst [Rh(**4a**)$_2$(cod)]$^+$, which showed that the double hydrogen-bond array displayed in Figure 4.5 is highly favored over

other arrangements involving a single hydrogen-bonding interaction (see the Experimental Section for details). In the DFT calculated structure shown in Figure 4.5, the ligands are held together by two hydrogen bonds between proton NH_A of each ligand and the carbonyl group of the ancillary amide, bearing NH_B, of the other ligand. Therefore, the two molecules of **4a** behave as a supramolecular bidentate ligand with a reduced degree of conformational freedom compared to two simple monodentate phosphites coordinated to a rhodium center.[22] This may explain the superior stereoselectivity displayed by PhthalaPhos ligands compared to simple monodentate phosphites, although substrate orientation in the catalytic cycle through hydrogen bonding with the ligand could also play a crucial role.[3o]

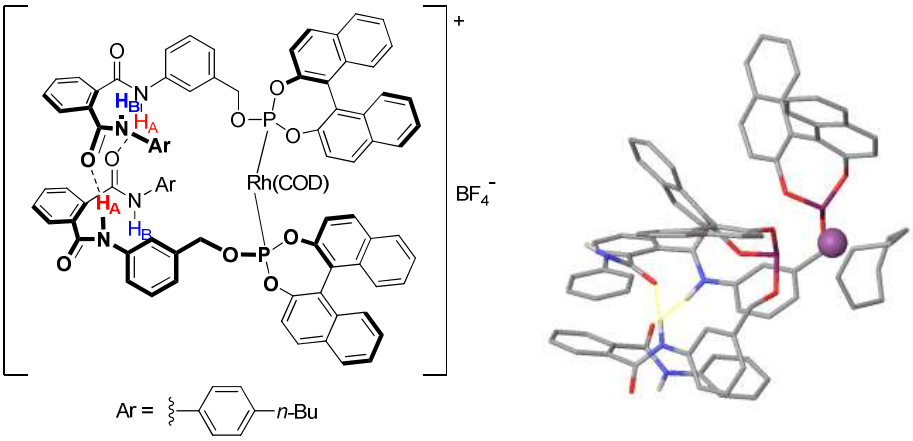


Figure 4.5. Supramolecular bidentate precatalyst [Rh(**4a**)$_2$(cod)]$^+$ and DFT calculated structure. Heteroatoms (N, O, P, Rh) are shown in black, carbon atoms in gray, and amide hydrogen atoms in light gray. For clarity, all hydrogen atoms bound to carbon are omitted.

4.5 CONCLUSIONS

In conclusion, a library of novel chiral supramolecular ligands containing a phthalamide moiety capable of hydrogen- bonding interactions has been prepared. The new ligands, named PhthalaPhos, are easily prepared from inexpensive starting materials and show excellent enantioselectivity in the hydrogenation of both benchmark olefins and challenging substrates of potential industrial interest. The precatalytic Rh complex of one of these ligands was fully characterized and studied by NMR, IR, and mass spectroscopy, which confirmed the presence of hydrogen bonds between the coordinated ligands, and thus formation of a supramolecular bidentate ligand. Further work is underway to expand the scope of PhthalaPhos ligands to other substrates and different transition metal catalyzed processes.

4.6 EXPERIMENTAL SECTION

4.6.1 General Remarks

All reactions were carried out in flame-dried glassware with magnetic stirring under nitrogen atmosphere, unless otherwise stated. The solvents for reactions were distilled over the following drying agents and transferred under nitrogen: CH_2Cl_2 (CaH_2), MeOH (CaH_2), THF (Na), dioxane (Na), Et_3N (CaH_2). Dry Et_2O and $CHCl_3$ (over molecular sieves in bottles with crown cap) were purchased from Fluka and stored under nitrogen. The reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a potassium permanganate alkaline solution. Flash column chromatography was performed using silica gel (60 Å, particle size 40-64 μm) as stationary phase, following the procedure by Still and co-workers.[23] Proton NMR spectra were recorded on a spectrometer operating at 400.13 MHz. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm; CD_2Cl_2, δ = 5.32 ppm; $[D]_6$DMSO, δ = 2.50 ppm; CD_3OD, δ = 3.33 ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, dd = doublet-doublet, td = triplet-doublet. ^{13}C-NMR spectra were recorded on a 400 MHz spectrometer operating at 100.56 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.23 ppm; CD_2Cl_2, δ = 54.00 ppm; $[D]_6$DMSO, δ = 39.51 ppm; CD_3OD, δ = 49.05 ppm). ^{31}P NMR spectra were recorded on a 400 MHz spectrometer operating at 162 MHz, with complete proton decoupling. ^{31}P NMR chemical shifts are reported in ppm (δ) relative to external 85% H_3PO_4 at 0 ppm (positive values downfield). ^{19}F NMR were recorded on a 300 MHz spectrometer operating at 282 MHz. ^{19}F NMR chemical shifts are reported in ppm (δ) relative to external $CFCl_3$ at 0 ppm (positive values downfield). The coupling constant values are given in Hz. Infrared spectra were recorded on a standard FT/IR spectrometer. Optical rotation values were measured on an automatic polarimeter with a 1 dm cell at the sodium D line (λ = 589 nm). Gas chromatography was performed on a GC instrument equipped with a flame ionization detector, using a chiral capillary column. High resolution mass spectra (HRMS) were performed on a Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics) – 4.7 T Magnet (Magnex) equipped with ESI source, available at CIGA (Centro Interdipartimentale Grandi Apparecchiature) c/o Università degli Studi di Milano. Low resolution mass spectra (MS) were acquired either on a Thermo-Finnigan LCQ Advantage mass spectrometer (ESI ion source) or on a VG Autospec M246 spectrometer (FAB ion source). Elemental analyses were performed on a Perkin Elmer Series II CHNS/O Analyzer 2000.

4.6.2 Materials

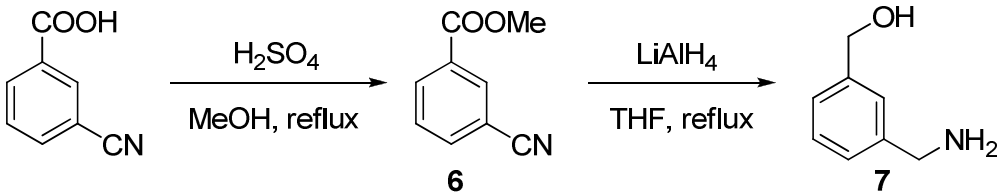
Phthalic anhydride sometimes contains large amounts of phthalic acid. In such cases, the mixture could be easily re-converted into the pure anhydride by melting it into an open flask and strongly heating for 10 minutes. On cooling down to R.T., pure phthalic anhydride crystallized as a white solid. Phthalic anhydride was stored in a desiccator. The other commercially available starting materials [(3-aminophenyl)methanol, (4-aminophenyl)methanol, 3-cyanobenzoic acid, methyl 4-cyanobenzoate, 2-cyanobenzaldehyde, methyl 3-(bromomethyl)benzoate, methyl 4-(bromomethyl)benzoate and (*S*)-2,2'-dihydroxy-1,1'-binaphthalene (BINOL)] were used as received. Chlorophosphite BINOL-PCl was prepared from (*S*)-2,2'-dihydroxy-1,1'-binaphthalene on gram scale according to a literature procedure.[24] Non-commercially available substrates for catalysis experiments [*N*-(1-phenylvinyl)acetamide, *N*-(3,4-dihydronaphthalen-1-yl)acetamide and (*E*)-methyl 2-(acetamidomethyl)-3-phenylacrylate] were prepared according to literature procedures.[25] Ligand **5** has been previously described:[26] its physical and spectroscopic data are superimposable with those reported in the literature.

4.6.3 Synthesis of PhthalaPhos ligands

Experimental procedures and full characterization of ligands **4a-i** are reported below. The whole PhthalaPhos library is displayed in Figure 4.3 (see page 186).

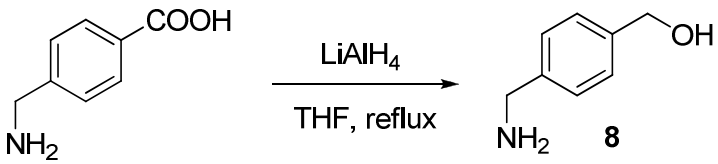
4.6.3.1 Preparation of non-commercially available starting aminoalcohols.

Non-commercially available aminoalcohols were prepared by slight modification of known procedures. The spectroscopic properties of compounds **6**-**15** comply with those reported in the literature. Compounds **10** and **13**, which we prepared as described below, are also commercially available.

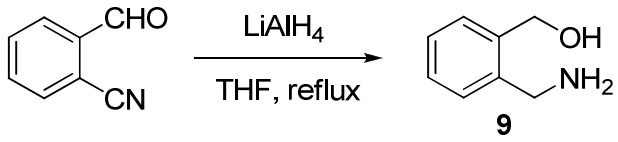


(3-(Aminomethyl)phenyl)methanol 7. A solution 3-cyanobenzoic acid (2 g, 13.59 mmol, 1 eq) and 96% H_2SO_4 (0.68 mL, 12.23 mmol, 0.9 eq) in dry MeOH (27 mL) was refluxed for 3h. MeOH was partially evaporated and the residue was poured in water (20 mL) and extracted with AcOEt (4 × 30 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (3 × 20 mL) and dried on Na_2SO_4. Evaporation of the organic solvent gave pure methyl 3-cyanobenzoate **6** as a colorless oil which slowly crystallized in the cold (2.124 g, 13.18 mmol, 97% yield).[27] Compound **6** (2.113 g, 13.11

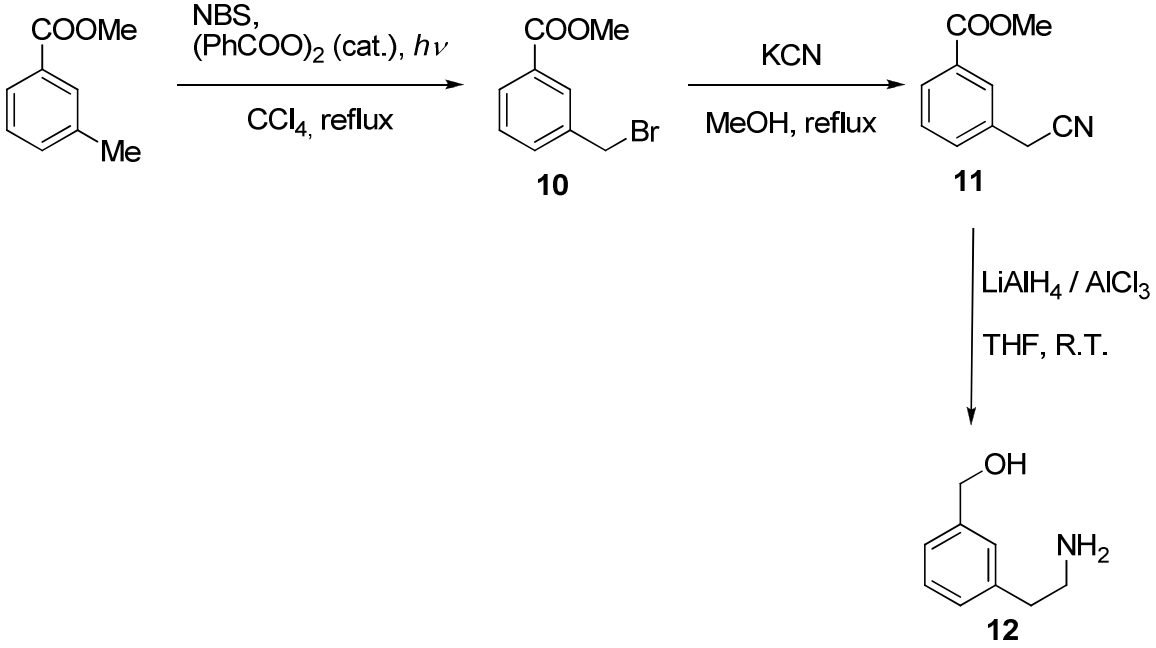
mmol, 1 eq) was dissolved in THF (10 mL) and added dropwise to a stirred suspension of $LiAlH_4$ (1.49 g, 39.33 mmol, 3 eq) in THF (70 mL) kept at 0 °C. The mixture was heated to reflux and stirred overnight. The reaction was cooled to 0 °C and slowly quenched with H_2O (1.5 mL) / 15% NaOH (1.5 mL) / H_2O (4.5 mL). After stirring for 15 min at R.T., the obtained suspension was filtered on a pad of celite (washing with AcOEt). The filtrate was evaporated giving (3-(aminomethyl)phenyl)methanol **7**[S28] as a white solid (1.74 g, 97% yield), which was pure enough for being used in the next step.



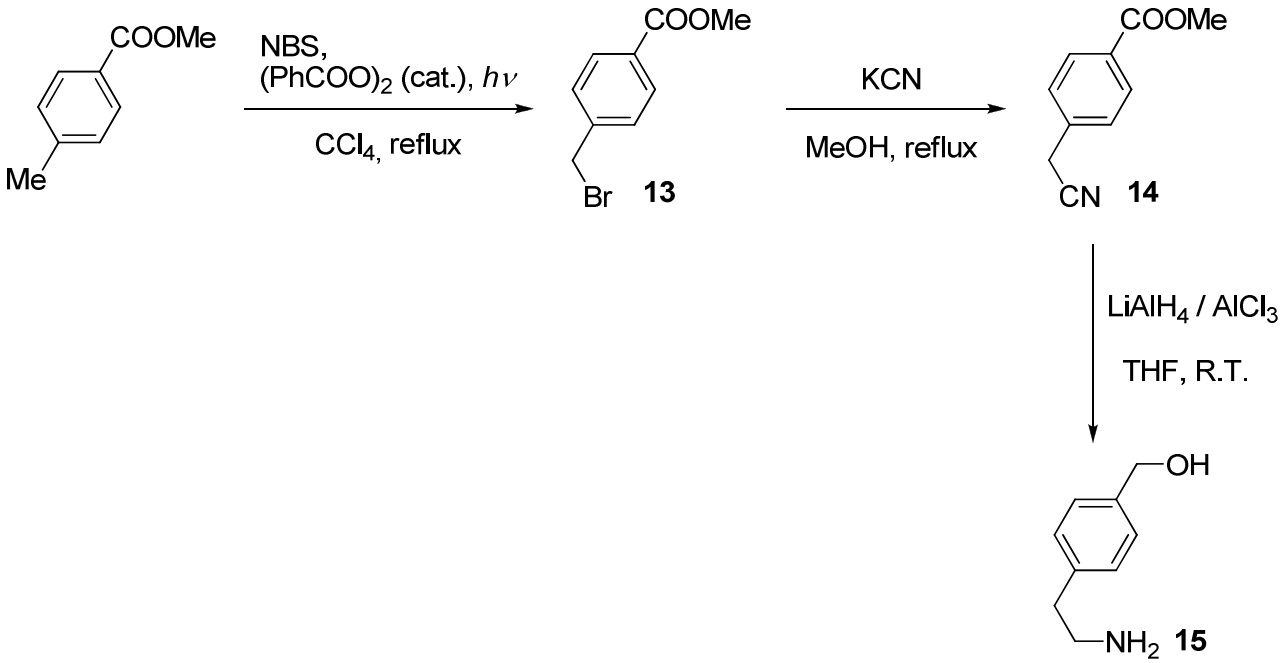
(4-(Aminomethyl)phenyl)methanol 8. $LiAlH_4$ (2.01 g, 52.92 mmol, 4 eq) was added in three portions to a stirred suspension of commercially available 4-(aminomethyl)benzoic acid (2 g, 13.23 mmol, 1 eq) in THF (20 mL) kept at 0 °C. The mixture was heated to reflux and stirred overnight before cooling down again to 0 °C and quenching with H_2O (2 mL) / 15% NaOH (2 mL) / H_2O (6 mL). After stirring for 10 min at R.T. the mixture was filtered on a pad of celite (washing with AcOEt). Evaporation of the filtrate gave (4-(aminomethyl)phenyl)methanol **8**[S29] as a white solid (1.179 g, 65% yield), which was used without purification.



(2-(Aminomethyl)phenyl)methanol 9. A solution of commercially available 2-cyanobenzaldehyde (0.5 g, 3.81 mmol, 1 eq) in THF (6 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.434 g, 11.439 mmol, 3 eq) in THF (15 mL) kept at 0 °C. The resulting dark mixture was stirred at R.T. for 5 h before quenching at 0 °C with H_2O (0.43 mL) / 15% NaOH (0.43 mL) / H_2O (1.29 mL). After stirring for 10 min at R.T. the mixture was filtered on celite (washing with AcOEt). Evaporation of the filtrate gave product **9**[S30] as a brown oil which slowly crystallized (0.418 g, 80% yield) and was clean enough for being used in the next step.



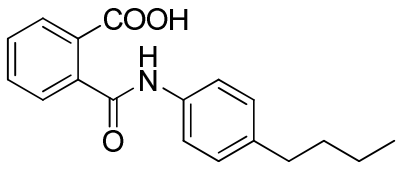
(3-(2-Aminoethyl)phenyl)methanol 12. Commercially available methyl 3-toluate (2 g, 13.32 mmol, 1 eq) was dissolved in CCl_4 (15 mL) and treated with freshly crystallized NBS (2.37 g, 13.32 mmol, 1 eq) and benzoyl peroxide (32 mg, 0.133 mmol, 0.01 eq). The stirred mixture was heated to reflux and irradiated with visible light for 3 h. After cooling down to R.T., succinimide was filtered off (washing the filter with CCl_4), and the filtrate was evaporated giving a colorless liquid containing product **10**[S31] in mixture with a minor amount of starting material and bis-bromination product. The crude product **10** was dissolved in a mixture of MeOH (20 mL) and H_2O (4.5 mL), and KCN (1.04 g, 15.98 mmol, 1.2 eq) was added. The mixture was heated to reflux and stirred for 5 h, then it was poured in H_2O (40 mL) and extracted with AcOEt (3 × 50 mL). The combined organic phases were dried with Na_2SO_4 and evaporated. Purification by flash chromatography (9:1 and 8:2 hexane/AcOEt) gave nitrile **11**[S31] as an oil (1 g, 58% yield over two steps). A solution of **11** (0.764 g, 4.36 mmol, 1 eq) in Et_2O (9 mL) was added dropwise to a stirred suspension of $AlCl_3$ / $LiAlH_4$ in THF [just prepared by adding a solution of $AlCl_3$ (1.28 g, 9.6 mmol, 2.2 eq) in 15 mL of THF to a suspension of $LiAlH_4$ (0.364 g, 9.6 mmol, 2.2 mL) in 10 mL of THF]. The resulting suspension was stirred overnight at R.T. and then quenched with H_2O (6.5 mL) and 3 M H_2SO_4 (13 mL). The resulting mixture was extracted with Et_2O (3 × 20 mL). The aqueous phase was brought to pH ~ 12 by adding solid KOH, then it was diluted with H_2O (30 mL) and extracted with AcOEt (5 × 30 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to give aminoalcohol **12**[S32] (0.548 g, 83% yield) as a colorless oil, which was used without further purification.



(4-(2-Aminoethyl)phenyl)methanol 15. Compound **15** was prepared by a procedure identical to that described above for aminoalcohol **12**: commercial methyl 4-toluate was converted into nitrile **14**[S33] via bromide **13**[S33] (53% yield over two steps). Compound **14** was reduced with $AlCl_3$ / $LiAlH_4$ in 78% yield to give aminoalcohol **15**.[S34]

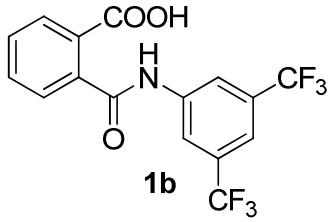
4.6.3.2 Preparation of the phthalic acid mono-amides 1a-b.

General Procedure. The chosen amine (1 eq) was added to a stirred 1.44 M solution of phthalic anhydride (1 eq, typical scale: 15 g) in $CHCl_3$: a white precipitate soon began to form. The mixture was heated to reflux and stirred for 3 h, then it was cooled down with an ice bath. The precipitate was collected on a Buchner funnel and washed on the filter with 6:1 $CHCl_3$ / hexane until the red impurities had disappeared. The product was dried under high vacuum.



1a

2-(4-Butylphenylcarbamoyl)benzoic acid 1a. The product, a white solid, was prepared according to the General Procedure starting from 15 g of phthalic anhydride and 15.58 g of 97% 4-butylaniline. Yield: 28.2 g (94%); m.p. = 163-166 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.98 (s, 1H), 10.24 (s, 1H), 7.88 (dd, ^3J(H,H) = 6.8 Hz, ^4J(H,H) = 1.0 Hz, 1H), 7.68-7.53 (m, 5H), 7.15 (d, ^3J(H,H) = 8.4 Hz, 2H), 2.55 (t, ^3J(H,H) = 7.6 Hz, 2H), 1.55 (m, 2H), 1.32 (m, 2H), 0.91 (t, J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 167.5, 167.1, 139.0, 137.3, 131.6, 130.0, 129.5, 129.3, 128.3, 127.8, 119.5, 34.3, 33.3, 21.7, 13.8; IR (KBr): ν = 3325.6, 2922.6, 1723.1, 1636.3, 1577.5, 1245.8, 645.1 cm^{-1}; MS (ESI+): *m*/*z* 320.1 [M + Na]$^+$ (calcd. for $C_{18}H_{19}NO_3Na$: 320.1); elemental analysis (%): C 73.06, H 6.37, N 4.69 (calcd. for $C_{18}H_{19}NO_3$: C 72.71, H 6.44, N 4.71).

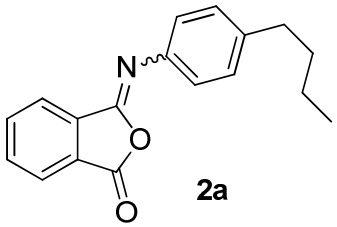


1b

2-(3,5-Bis(trifluoromethyl)phenylcarbamoyl)benzoic acid 1b. The product, a white solid, was prepared according to the General Procedure starting from 3.14 g of phthalic anhydride and 5 g of 3,5-bis(trifluoromethyl)aniline. Yield: 7.82 g (98%); m.p. = 190-192 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 13.17 (br s, 1H), 10.98 (s, 1H), 8.37 (s, 2H), 7.94 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.7 Hz, 1H), 7.78 (s, 1H), 7.70 (td, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.3 Hz, 1H), 7.65-7.61 (m, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 168.3, 167.1, 141.2, 137.9, 131.9, 130.8 (q, ^2J(C,F) = 32.9 Hz), 129.9, 129.7, 129.7, 127.7, 123.2 (q, ^1J(C,F) = 272.6 Hz), 119.0 (d, ^3J(C,F) = 3.5 Hz), 116.0 (m); ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = -57.7 (s); IR (KBr): ν = 3286.1, 3114.5, 1702.8, 1671.0, 1278.6, 703.9 cm^{-1}; MS (FAB+): *m*/*z* 378.0 [M + H]$^+$ (calcd. for $C_{16}H_{10}F_6NO_3$: 378.1) and 400.0 [M + Na]$^+$

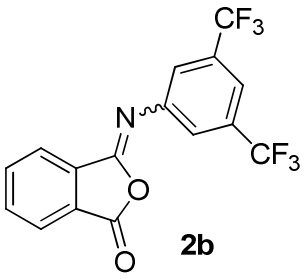
(calcd. for $C_{16}H_9F_6NO_3Na$: 400.0); elemental analysis (%): C 50.93, H 2.28, N 3.70 (calcd. for $C_{16}H_9F_6NO_3$: C 50.94, H 2.40, N 3.71.

4.6.3.3 Preparation of the phthalisoimides 2a-b.



2a

3-(4-Butylphenylimino)isobenzofuran-1(3*H*)-one 2a. A literature procedure for preparing this class of compounds was followed:[S35] trifluoroacetic anhydride (2.1 mL, 15.13 mmol, 1.5 eq) was added dropwise to a stirred solution of acid **1a** (3 g, 10.09 mmol, 1 eq) and TEA (4.2 mL, 30.27 mmol, 3 eq) in dioxane (45 mL) kept at 0 °C with an ice bath. After 5 min the yellow solution was allowed to reach R.T. and stirred for 15 min, then it was poured in cold H_2O (120 mL). A pale yellow, light precipitate formed, which was filtered on Buchner and washed with some H_2O. The product was dried for 20 min on the filter and then for one night under high vacuum. A pale yellow solid was obtained. Yield: 2.72 g (97%); m.p. = 58-61 °C; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.11 (d, ^3J(H,H) = 7.6 Hz, 1H), δ 8.00 (d, ^3J(H,H) = 7.6 Hz, 1H), δ 7.90 (t, ^3J(H,H) = 7.6 Hz, 1H), 7.80 (t, ^3J(H,H) = 7.6 Hz, 1H), 7.41 (d, ^3J(H,H) = 8.2 Hz, 2H), 7.28 (d, ^3J(H,H) = 8.2 Hz, 2H), 2.69 (t, ^3J(H,H) = 7.8 Hz, 2H), 1.68 (m, 2H), 1.43 (m, 2H), 1.00 (t, *J*(H,H) = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 165.5, 147.2, 142.2, 142.1, 137.8, 136.0, 133.6, 129.5, 128.2, 125.7, 125.1, 124.0, 35.8, 34.2, 22.9, 14.3; IR (KBr): ν = 2956.3, 2855.1, 1791.6, 1689.3, 915.1, cm^{-1}; MS (ESI+): *m*/*z* 280.3 $[M + H]^+$ (calcd. for $C_{18}H_{18}NO_2$: 280.1); elemental analysis (%): C 77.33, H 6.32, N 4.97 (calcd. for $C_{18}H_{17}NO_2$: C 77.40, H 6.13, N 5.01).



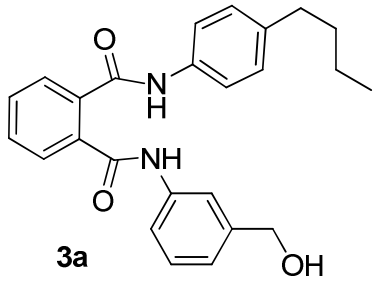
2b

3-(3,5-Bis(trifluoromethyl)phenylimino)isobenzofuran-1(3*H*)-one 2b. Trifluoroacetic anhydride (0.276 mL, 1.988 mmol, 1.5 eq) was added dropwise to a stirred solution of acid **1b** (0.5 g, 1.325 mmol, 1 eq) and TEA (0.185 mL, 1.325 mmol, 1 eq) in THF (6 mL) kept at 0 °C with an ice bath. After 5 min the solution was allowed to reach R.T. and stirred for 10 min. A second portion of TEA (0.37 mL, 3.976 mmol, 2 eq) was added dropwise, and the solution was stirred for 20 min at R.T.. The volatiles were removed at rotavapor and the product was purified by flash chromatography through a short pad of silica (1:1 hexane/DCM). Compound **2b** was obtained as a white solid. Yield: 471 mg

(99%); m.p. = 127-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, ^{3}J(H,H) = 7.6 Hz, 1H), 8.06 (d, ^{3}J(H,H) = 7.6 Hz, 1H), 7.97 (td, ^{3}J(H,H) = 7.6 Hz, ^{4}J(H,H) = 0.9 Hz, 1H), 7.90 (td, ^{3}J(H,H) = 7.6 Hz, ^{4}J(H,H) = 0.7 Hz, 1H), 7.82 (s, 2H), 7.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4, 150.7, 146.5, 136.7, 136.5, 134.7, 132.7 (q, ^{2}J(C,F) = 33.5 Hz), 128.3, 126.2, 124.5, 124.5, 123.9 (q, ^{1}J(C,F) = 272.2 Hz), 119.9 (m); ^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.2; IR (film): ν = 3083.6, 3042.2, 1827.2, 1796.4, 1700.9, 1279.5, 1118.5 cm^{-1}; MS (FAB+): *m*/*z* 360.0 $[M + H]^+$ (calcd. for $C_{16}H_8F_6NO_2$: 360.0); elemental analysis (%): C 53.35, H 1.88, N 3.90 (calcd. for $C_{16}H_7F_6NO_2$: C 53.50, H 1.96, N 3.90).

4.6.3.4 Preparation of the alcohols 3a-i

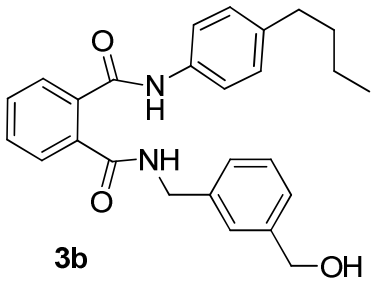
General Procedure. Phthalisoimide **2a** or **2b** (1 eq) was added to the stirred 0.11 M solution of the chosen aminoalcohol (1.2 eq) in THF. The mixture was stirred overnight at R.T.. Two alternative workup procedures were followed depending on whether the product precipitated or not. **Workup 1 (soluble product):** the mixture was diluted with AcOEt (triple volume with respect to THF) and washed three times with 1 M HCl. The organic phase was dried with Na_2SO_4 and evaporated. The product was purified by column chromatography. **Workup 2 (insoluble product):** the precipitated product was collected by filtration on a Buchner funnel and washed on the filter with little amounts of 1:1 Et_2O / hexane until the yellow impurities had disappeared. The product obtained with this workup procedure did not need a chromatographic purification.



3a

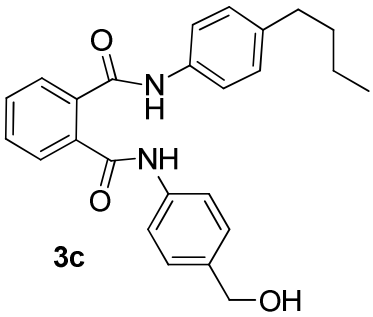
***N*^{1}-(4-Butylphenyl)-*N*^{2}-(3-(hydroxymethyl)phenyl)phthalamide 3a.** The product was prepared according to the General Procedure – Workup 1 starting from 2 g of phthalisoimide **2a** and 1.09 g of 97% 3-aminobenzyl alcohol. Purification by flash chromatography (8:2 and then 7:3 DCM/AcOEt) gave the product as a white solid. Yield: 1.9 g (66%); m.p. = 110-115 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = 7.74-7.71 (m, 2H), δ 7.67 (s, 1H), 7.64-7.61 (m, 2H), 7.52-7.53 (m, 3H), 7.31 (t, ^{3}J(H,H) = 7.8 Hz, 1H), 7.15 (m, 3H), 4.59 (s, 2H), 2.60 (t, ^{3}J(H,H) = 7.7 Hz, 2H), 1.60 (m, 2H), 1.37 (m, 2H), 0.95 (t, ^{3}J(H,H) = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 169.6, 169.5, 143.6, 140.4, 139.9, 137.6, 137.5, 137.4, 131.4, 131.4, 129.8, 129.7, 129.1, 124.1, 122.1, 120.8, 120.5, 65.1, 36.1, 34.9, 23.3, 14.3; IR (KBr): ν = 3247.5, 2926.5, 2856.1, 1646.9, 1541.8, 1325.8, 828.3 cm^{-1}; MS (ESI+): *m*/*z*

425.4 $[M + Na]^+$ (calcd. for $C_{25}H_{26}N_2O_3Na$: 425.2); elemental analysis (%): C 75.04, H 6.47, N 6.94 (calcd. for $C_{25}H_{26}N_2O_3$: C 74.60, H 6.51, N 6.96).



3b

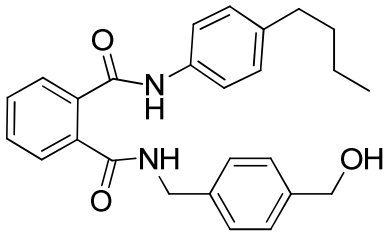
***N*^{1}-(4-Butylphenyl)-*N*^{2}-(3-(hydroxymethyl)benzyl)phthalamide 3b.** The product, a white solid, was prepared according to the General Procedure – Workup 2 starting from 0.5 g of phthalisoimide **2a** and 0.3 g of aminoalcohol **7**. Yield: 0.61 g (82%); m.p. = 150-154 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 10.27 (s, 1H), 8.92 (t, ^3J(H,H) = 5.9 Hz, 1H), 7.62-7.54 (m, 4H), 7.61 (d, ^3J(H,H) = 8.3 Hz, 2H), 7.31 (s, 1H), 7.26-7.18 (m, 3H), 7.14 (d, ^3J(H,H) = 8.3 Hz, 2H), 5.15 (t, ^3J(H,H) = 5.7 Hz, 1H), 4.49 (d, ^3J(H,H) = 5.7 Hz, 2H), 4.42 (d, ^3J(H,H) = 5.9 Hz, 2H), 2.55 (t, ^3J(H,H) = 7.4 Hz, 2H), 1.55 (m, 2H), 1.31 (m, 2H), 0.90 (t, ^3J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 167.7, 166.8, 142.4, 139.1, 137.2, 137.1, 137.1, 135.8, 129.5, 129.3, 128.2, 127.8, 127.7, 127.5, 125.4, 125.2, 124.7, 119.5, 62.8, 42.5, 34.2, 33.2, 21.6, 13.7; IR (KBr): ν = 3451.0, 3280.3, 2925.5, 1646.9, 1543.7, 1330.6, 830.2 cm^{-1}; MS (ESI+): *m*/*z* 439.4 $[M + Na]^+$ (calcd. for $C_{26}H_{28}N_2O_3Na$: 439.2); elemental analysis (%): C 74.77, H 6.61, N 6.63 (calcd. for $C_{26}H_{28}N_2O_3$: C 74.97, H 6.78, N 6.73).



3c

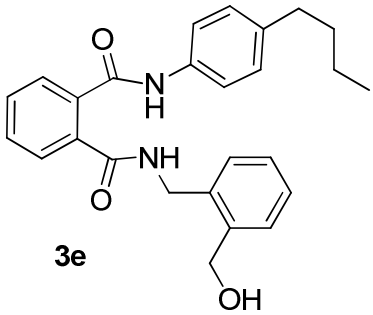
***N*^{1}-(4-Butylphenyl)-*N*^{2}-(4-(hydroxymethyl)phenyl)phthalamide 3c.** The product was prepared according to the General Procedure – Workup 1 starting from 0.246 g of phthalisoimide **2a** and 0.130 g of 4-aminobenzyl alcohol. Purification by flash chromatography (8:2 and then 6:4 DCM/AcOEt) gave the product as a white solid. Yield: 0.254 g (75%); m.p. = 88-93 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 10.38 (s, 1H), 10.33 (s, 1H), 7.68-7.58 (m, 8H), 7.26 (d, ^3J(H,H) = 8.4 Hz, 2H), 7.13 (d, ^3J(H,H) = 8.4 Hz, 2H), 5.11 (t, ^3J(H,H) = 5.7 Hz, 1H), 4.45 (d, ^3J(H,H) = 5.7 Hz, 2H), 2.54 (t, ^3J(H,H) = 7.5 Hz, 2H), 1.54 (m, 2H), 1.30 (m, 2H), 0.90 (t, ^3J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (100

MHz, [D_6]DMSO): δ = 166.6, 166.6, 138.0, 137.6, 137.4, 137.1, 136.8, 136.8, 129.6, 128.3, 127.8, 127.7, 119.6, 119.3, 62.6, 34.3, 33.2, 21.6, 13.8; IR (KBr): ν = 3368.1, 3245.6, 2926.5, 1646.9, 1603.5, 1540.8, 1514.8, 1326.8, 827.3 cm^{-1}; MS (ESI+): *m*/*z* 425.3 $[M + Na]^+$ (calcd. for $C_{25}H_{26}N_2O_3Na$: 425.2); elemental analysis (%):C 74.30, H 6.42, N 6.89 (calcd. for $C_{25}H_{26}N_2O_3$: C 74.60, H 6.51, N 6.96).



3d

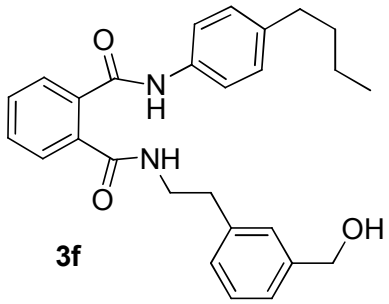
***N*^{1}-(4-Butylphenyl)-*N*^{2}-(4-(hydroxymethyl)benzyl)phthalamide 3d.** The product, a white solid, was prepared according to the General Procedure – Workup 1 starting from 0.613 g of phthalisoimide **2a** and 0.301 g of aminoalcohol **8**. Purification by flash chromatography (98:2, then 96:4 and 95:5 DCM/MeOH) gave the product as a white solid. Yield: 0.816 g (89%); m.p. = 163-167 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 10.24 (s, 1H), 8.86 (t, ^3J(H,H) = 6.0 Hz, 1H), 7.61-7.53 (m, 6H), 7.30 (d, ^3J(H,H) = 8.1 Hz, 2H), 7.22 (d, ^3J(H,H) = 8.1 Hz, 2H), 7.15 (d, ^3J(H,H) = 8.4 Hz, 2H), 5.11 (t, ^3J(H,H) = 5.7 Hz, 1H), 4.46 (d, ^3J(H,H) = 5.7 Hz, 2H), 4.41 (d, ^3J(H,H) = 6.0 Hz, 2H), 2.56 (t, ^3J(H,H) = 7.5 Hz, 2H), 1.55 (m, 2H), 1.31 (m, 2H), 0.91 (t, ^3J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 167.8, 166.9, 140.9, 137.7, 137.2, 137.2, 135.9, 129.6, 129.4, 128.3, 127.7, 127.6, 126.9, 126.3, 119.5, 62.7, 42.3, 34.3, 33.3, 21.7, 13.8; IR (KBr): ν = 3490.5, 3229.2, 2927.4, 1629.6, 1541.8, 1321.9, 724.1 cm^{-1}; MS (ESI+): *m*/*z* 439.3 $[M + Na]^+$ (calcd. for $C_{26}H_{28}N_2O_3Na$: 439.2); elemental analysis (%): C 74.72, H 6.62, N 6.44 (calcd. for $C_{26}H_{28}N_2O_3$: C 74.97, H 6.78, N 6.73).



3e

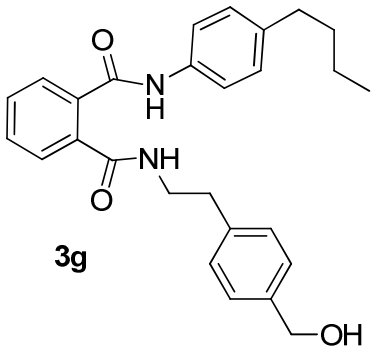
***N*^{1}-(4-Butylphenyl)-*N*^{2}-(2-(hydroxymethyl)benzyl)phthalamide 3e.** The product, a white solid, was prepared according to the General Procedure – Workup 2 starting from 1.06 g of phthalisoimide **2a** and 1.28 g of aminoalcohol **9**. Yield: 1.27 g (80%); m.p. = 145-147 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 10.25 (s, 1H), 8.77 (t, ^3J(H,H) = 5.6 Hz, 1H), 7.62-7.54 (m, 6H), 7.38 (m, 2H), 7.21 (td, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 1.2 Hz, 1H), 7.15 (td, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 1.4 Hz, 1H), 7.14

(d, ^3J(H,H) = 8.4 Hz, 2H), 5.13 (t, ^3J(H,H) = 5.4 Hz, 1H), 4.59 (d, ^3J(H,H) = 5.4 Hz, 2H), 4.47 (d, ^3J(H,H) = 5.6 Hz, 2H), 2.55 (t, ^3J(H,H) = 7.5 Hz, 2H), 1.55 (m, 2H), 1.31 (m, 2H), 0.90 (t, ^3J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 167.7, 166.9, 139.4, 137.2, 137.2, 137.1, 136.4, 135.9, 129.6, 129.4, 128.3, 127.7, 127.6, 127.2, 127.1, 126.7, 126.4, 119.6, 60.7, 39.6, 34.3, 33.3, 21.6, 13.8; IR (KBr): ν = 3433.6, 3244.6, 2927.4, 1645.9, 1605.5, 1542.8, 1326.8, 825.4 cm^{-1}; MS (ESI+): *m*/*z* 439.3 [M + Na]$^+$ (calcd. for $C_{26}H_{28}N_2O_3Na$: 439.2); elemental analysis (%): C 75.23, H 6.50, N 6.69 (calcd. for $C_{26}H_{28}N_2O_3$: C 74.97, H 6.78, N 6.73).



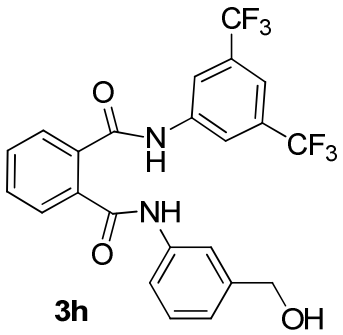
3f

***N*^{1}-(4-Butylphenyl)-*N*^{2}-(3-(hydroxymethyl)phenethyl)phthalamide 3f.** The product, a white solid, was prepared according to the General Procedure – Workup 1 starting from 1.012 g of phthalisoimide **2a** and 0.548 g of aminoalcohol **12**. Purification by flash chromatography (6:4, then 1:1 and 4:6 DCM/AcOEt) gave the product as a white solid. Yield: 1.28 g (82%); m.p. = 146 °C; ^{1}H NMR (400 MHz, CD$_3$OD): δ = 7.67 (dd, ^3J(H,H) = 6.8 Hz, ^4J(H,H) = 1.6 Hz, 1H), 7.60-7.50 (m, 3H), 7.57 (d, ^3J(H,H) = 8.4 Hz, 2H), 7.27-7.24 (m, 2H), 7.21-7.15 (m, 2H), 7.18 (d, ^3J(H,H) = 8.4 Hz, 2H), 4.59 (s, 2H), 3.57 (t, ^3J(H,H) = 7.6 Hz, 2H), 2.89 (t, ^3J(H,H) = 7.6 Hz, 2H), 2.62 (t, ^3J(H,H) = 7.6 Hz, 2H), 1.62 (m, 2H), 1.37 (m, 2H), 0.96 (t, ^3J(H,H) = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CD$_3$OD): δ = 171.4, 169.7, 142.9, 140.7, 140.4, 137.7, 137.6, 137.0, 131.3, 131.3, 129.7, 129.6, 129.1, 128.9, 128.9, 128.6, 126.1, 121.9, 65.3, 42.7, 36.4, 36.1, 35.1, 23.3, 14.3; IR (KBr): ν = 3448.1, 3250.4, 2928.4, 1647.8, 1623.8, 1546.6, 1332.6, 821.5 cm^{-1}; MS (ESI+): *m*/*z* 453.4 [M + Na]$^+$ (calcd. for $C_{27}H_{30}N_2O_3Na$: 453.2); elemental analysis (%): C 75.32, H 6.86, N 6.37 (calcd. for $C_{27}H_{30}N_2O_3$: C 75.32, H 7.02, N 6.51).



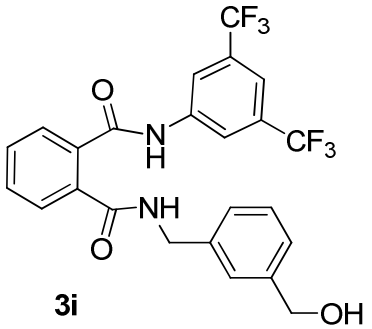
3g

***N*^{1}-(4-Butylphenyl)-*N*^{2}-(4-(hydroxymethyl)phenethyl)phthalamide 3g.** The product, a white solid, was prepared according to the General Procedure – Workup 1 starting from 1.524 g of phthalisoimide **2a** and 0.825 g of aminoalcohol **15**. Purification by flash chromatography (6:4 and then 1:1 DCM/AcOEt) gave the product as a white solid. Yield: 1.79 g (76%); m.p. = 120-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.18 (s, 1H), 7.74 (d, ^3J(H,H) = 7.5 Hz, 1H), 7.56 (d, ^3J(H,H) = 8.3 Hz, 2H), 7.48-7.38 (m, 3H), 7.20 (d, ^3J(H,H) = 8.0 Hz, 2H), 7.16 (d, ^3J(H,H) = 8.3 Hz, 2H), 7.11 (d, ^3J(H,H) = 8.0 Hz, 2H), 6.57 (br s, 1H), 4.57 (s, 2H), 3.63 (q, ^3J(H,H) = 7.0 Hz, 2H), 2.82 (t, ^3J(H,H) = 7.0 Hz, 2H), 2.59 (t, ^3J(H,H) = 7.7 Hz, 2H), 1.59 (m, 2H), 1.35 (m, 2H), 0.92 (t, ^3J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 166.9, 139.4, 139.4, 138.0, 136.0, 134.9, 134.7, 130.5, 130.3, 129.3, 129.0, 129.0, 127.9, 127.4, 120.4, 65.0, 41.5, 35.3, 35.2, 33.9, 22.5, 14.1; IR (KBr): ν = 3264.9, 2926.5, 1637.3, 1594.8, 1513.8, 1326.9, 829.4 cm^{-1}; MS (ESI+): *m*/*z* 453.4 $[M + Na]^+$ (calcd. for $C_{27}H_{30}N_2O_3Na$: 453.2); elemental analysis (%): C 74.99, H 6.96, N 6.36 (calcd. for $C_{27}H_{30}N_2O_3$: C 75.32, H 7.02, N 6.51).



3h

***N*^{1}-(3,5-Bis(trifluoromethyl)phenyl)-*N*^{2}-(3-(hydroxymethyl)phenyl)phthalamide 3h.** The product was prepared according to the General Procedure – Workup 1 starting from 0.429 g of phthalisoimide **2b** and 0.182 g of 97% 3-aminobenzyl alcohol. Purification by flash chromatography (8:2 and then 6:4 DCM/AcOEt) gave the product as a white solid. Yield: 0.456 g (79%); m.p. = 187-190 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = 8.30 (s, 2H), 7.76 (m, 2H), 7.66 (m, 4H), 7.54 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.31 (t, ^3J(H,H) = 7.8 Hz, 1H), 7.14 (d, ^3J(H,H) = 7.8 Hz, 1H), 4.59 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 170.1, 169.6, 143.6, 142.1, 139.8, 137.4, 136.8, 133.1 (q, ^2J(C,F) = 33.2 Hz), 131.9, 131.5, 129.8, 129.1, 129.0, 124.7 (q, ^1J(C,F) = 272.0 Hz), 124.2, 120.8, 120.4, 117.8, 65.1; ^{19}F NMR (282 MHz, CD_3OD): δ = -62.0 (s); IR (KBr): ν = 3452.9, 3262.9, 3089.4, 1647.9, 1559.2, 1277.6, 840.8 cm^{-1}; MS (ESI+): *m*/*z* 505.1 $[M + Na]^+$ (calcd. for $C_{23}H_{16}F_6N_2O_3Na$: 505.1); elemental analysis (%): C 57.02, H 3.20, N 5.78 (calcd. for $C_{23}H_{16}F_6N_2O_3$: C 57.27, H 3.34, N 5.81).



3i

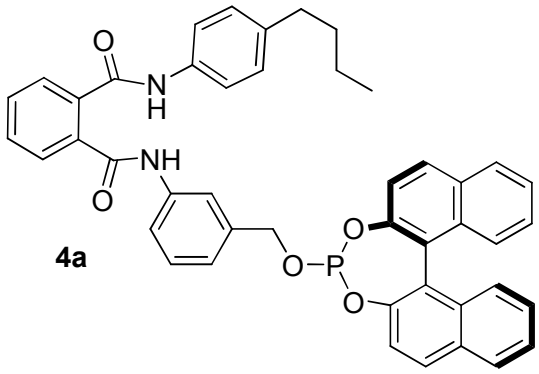
***N*^{1}-(3,5-Bis(trifluoromethyl)phenyl)-*N*^{2}-(3-(hydroxymethyl)benzyl)phthalamide 3i.** The product, a pale yellow solid, was prepared according to the General Procedure – Workup 1 starting from 0.400 g of phthalisoimide **2b** and 0.184 g of aminoalcohol **7**. Yield: 0.495 g (90%); m.p. = 175-177 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = 8.31 (s, 2H), 7.57 (s, 1H), 7.50-7.43 (m, 4H), 7.41 (s, 1H), 7.32-7.22 (m, 3H), 4.59 (s, 2H), 4.54 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 171.0, 170.2, 143.0, 142.2, 140.0, 137.0, 136.6, 133.0 (q, ^2J(C,F) = 33.0 Hz), 131.7, 131.4, 129.5, 129.0, 129.0, 127.7, 127.3, 126.9, 124.7 (q, ^1J(C,F) = 270.3 Hz), 120.7, 117.7, 65.1, 44.7; ^{19}F NMR (282 MHz, CD_3OD): δ = -62.0 (s); IR (KBr): ν = 3394.1, 3273.6, 3084.6, 1635.3, 1592.9, 1280.5, 840.8 cm^{-1}; MS (ESI+): *m*/*z* 519.2 $[M + Na]^+$ (calcd. for $C_{24}H_{18}F_6N_2O_3Na$: 519.1); elemental analysis (%): C 57.81, H 3.58, N 5.41 (calcd. for $C_{24}H_{18}F_6N_2O_3$: C 58.07, H 3.65, N 5.64).

4.6.3.5 Synthesis of phosphites 4a-i (PhthalaPhos ligands).

Two alternative, slightly different procedures were followed depending on whether the starting alcohol was soluble in THF or not.

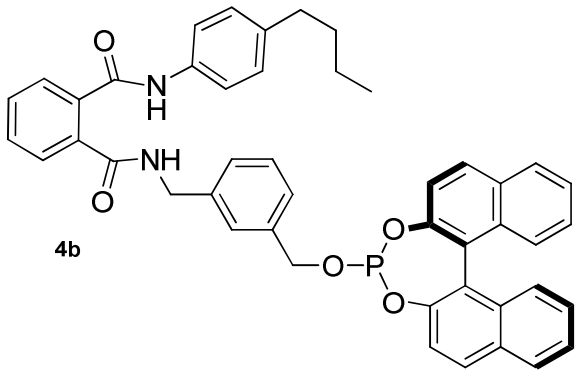
General Procedure 1. (*S*)-BINOL-PCl (1 eq, typical scale: 0.3 g) was added to a stirred 0.1 M solution of the selected alcohol (1 eq) and Et_3N (3 eq) in THF. The obtained mixture was stirred overnight and then filtered through a pad of celite (washing with THF). The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel.

General Procedure 2. (*S*)-BINOL-PCl (1 eq, typical scale: 0.3 g) was added to a stirred suspension of the selected alcohol (1 eq) and Et_3N (3 eq) in 6:4 THF/DCM (conc. ~ 0.1 M). The obtained mixture was stirred overnight and then Et_2O (half volume with respect to the THF/DCM mixture) was added. The mixture was filtered through a pad of celite (washing with THF), the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel.



4a

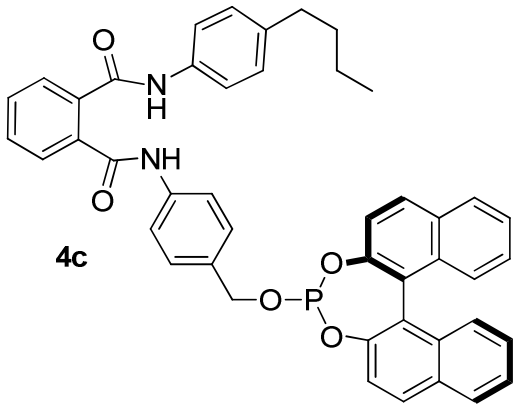
***N*^{1}-(4-Butylphenyl)-*N*^{2}-(3-(((11b*S*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)methyl)phenyl)phthalamide 4a.** The product, a white solid, was prepared according to the General Procedure 1 starting from 0.314 g of (*S*)-BINOL-PCl and 0.36 g of alcohol **3a** in the presence of 0.375 mL of TEA. Yield: 0.473 g (74%); m.p. = 114-121 °C; $[\alpha]^{19}_{D}$ = + 277.6 (*c* = 1.0 in DCM); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.40 (s, 1H), 9.02 (s, 1H), 8.04 (d, ^3J(H,H) = 8.8 Hz, 1H), 8.00 (d, ^3J(H,H) = 8.4 Hz, 1H), 7.93 (d, ^3J(H,H) = 8.8 Hz, 1H), 7.92 (d, ^3J(H,H) = 8.2 Hz, 1H), 7.59-7.56 (m, 3H), 7.53-7.42 (m, 6H), 7.39-7.27 (m, 7H), 7.23 (t, ^3J(H,H) = 8.0 Hz, 1H), 7.04 (d, ^3J(H,H) = 8.4 Hz, 2H), 7.00 (d, ^3J(H,H) = 8.0 Hz, 1H), 4.92 (dd, ^2J(H,H) = 12.3 Hz, ^3J(H,P) = 8.0 Hz, 1H), 4.70 (dd, ^2J(H,H) = 12.3 Hz, ^3J(H,P) = 8.0 Hz, 1H), 2.53 (t, ^3J(H,H) = 7.8 Hz, 2H), 1.54 (m, 2H), 1.33 (m, 2H), 0.92 (t, ^3J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 167.9, 149.2, 148.1, 139.8, 139.0, 138.5, 136.3, 135.7, 135.6, 133.3, 133.1, 132.2, 131.7, 131.1, 131.0, 130.9, 129.5, 129.3, 129.1, 129.1, 128.8, 127.4, 127.0, 126.9, 125.8, 125.6, 124.1, 123.2, 122.5, 122.3, 121.6, 120.8, 120.4, 119.8, 67.2 (d, ^2J(C,P) = 5.6 Hz), 35.6, 34.3, 23.0, 14.3; ^{31}P NMR (162 MHz, CD_2Cl_2): δ = 141.3 (s). IR (film): ν = 3238.9, 3060.5, 2954.4, 1639.2, 1541.8, 1230.3, 823.5 cm^{-1}; HRMS (ESI+): *m*/*z* 739.23323 $[M + Na]^+$ (calcd. for $C_{45}H_{37}N_2O_5PNa$: 739.23469).



4b

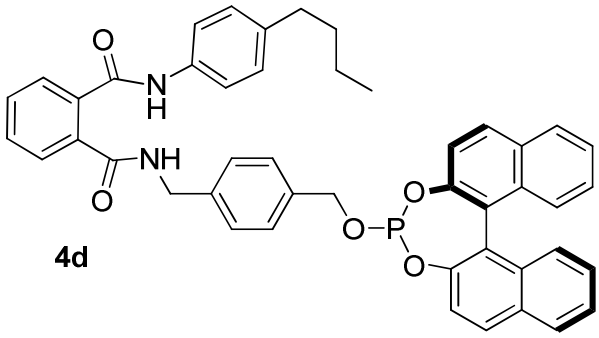
***N*^{1}-(4-Butylphenyl)-*N*^{2}-(3-(((11b*S*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)methyl)benzyl)phthalamide 4b.** The product, a white solid, was prepared according to the General Procedure 2 starting from 0.337 g of (*S*)-BINOL-PCl and 0.40 g of alcohol **3b** in the presence of 0.40 mL of TEA. Yield: 0.475 g (67%); m.p. = 139-145 °C; $[\alpha]^{23}_{D}$ = + 120.1 (*c* = 1.0 in DCM); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.80 (s, 1H), 8.06 (d, ^3J(H,H) = 8.8 Hz, 1H), 8.01 (d, ^3J(H,H) = 8.2 Hz,

1H), 7.95 (d, ^{3}J(H,H) = 9.0 Hz, 1H), 7.92 (d, ^{3}J(H,H) = 7.8 Hz, 1H), 7.79 (d, ^{3}J(H,H) = 7.1 Hz, 1H), 7.62 (dd, ^{3}J(H,H) = 7.4 Hz, ^{4}J(H,H) = 1.5 Hz, 1H), 7.58-7.43 (m, 7H), 7.39-7.20 (m, 9H), 7.15 (d, ^{3}J(H,H) = 8.3 Hz, 2H), 6.89 (t, ^{3}J(H,H) = 6.0 Hz, 1H), 4.91 (dd, ^{2}J(H,H) = 12.3 Hz, ^{3}J(H,P) = 8.0 Hz, 1H), 4.71 (dd, ^{2}J(H,H) = 12.3 Hz, ^{3}J(H,P) = 8.2 Hz, 1H), 4.60 (d, ^{3}J(H,H) = 6.0 Hz, 2H), 2.62 (t, ^{3}J(H,H) = 7.8 Hz, 2H), 1.62 (m, 2H), 1.39 (m, 2H), 0.97 (t, ^{3}J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 170.0, 167.3, 149.2, 148.1, 139.7, 139.1, 138.2, 136.6, 135.7, 135.0, 133.4, 133.1, 132.2, 131.7, 131.0, 130.8, 130.8, 129.4, 129.1, 129.0, 128.9, 128.7, 127.3, 126.8, 126.8, 125.7, 125.5, 124.6, 124.0, 123.1, 122.4, 122.2, 120.7, 120.3, 119.7, 67.1 (d, ^{2}J(C,P) = 5.7 Hz), 44.3, 35.5, 34.2, 22.9, 14.3; ^{31}P NMR (162 MHz, CD_2Cl_2): δ = 141.8 (s). IR (film): ν = 3243.7, 3058.6, 2954.4, 1635.3, 1538.9, 1230.0, 825.4 cm^{-1}; HRMS (ESI+): *m*/*z* 753.24782 $[M + Na]^+$ (calcd. for $C_{46}H_{39}N_2O_5PNa$: 753.24888).



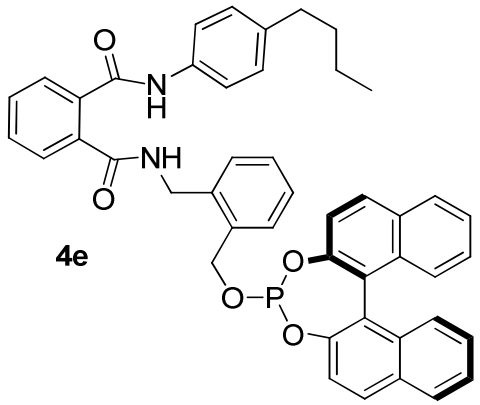
4c

***N*^{1}-(4-Butylphenyl)-*N*^{2}-(4-(((11b*S*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)methyl)phenyl)phthalamide 4c.** The product, a white solid, was prepared according to the General Procedure 1 starting from 0.174 g of (*S*)-BINOL-PCl and 0.200 g of alcohol **3c** in the presence of 0.208 mL of TEA. Yield: 0.219 g (62%); m.p. = 150-159 °C; $[\alpha]^{18}_{D}$ = + 209.1 (*c* = 0.8 in DCM); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.96 (s, 1H), 8.53 (s, 1H), 8.06 (d, ^{3}J(H,H) = 8.8 Hz, 1H), 8.01, (d, ^{3}J(H,H) = 8.2 Hz, 1H), 7.97 (d, ^{3}J(H,H) = 8.6 Hz, 2H), 7.78 (m, 1H), 7.72 (m, 1H), 7.65 (d, ^{3}J(H,H) = 8.2 Hz, 2H), 7.60-7.46 (m, 7H), 7.39-7.29 (m, 7H), 7.18 (d, ^{3}J(H,H) = 8.3 Hz, 2H), 5.00 (dd, ^{2}J(H,H) = 12.1 Hz, ^{3}J(H,P) = 8.0 Hz, 1H), 4.78 (dd, ^{2}J(H,H) = 12.1 Hz, ^{3}J(H,P) = 8.3 Hz, 1H), 2.61 (t, ^{3}J(H,H) = 7.8 Hz, 2H), 1.60 (m, 2H), 1.37 (m, 2H), 0.95 (t, ^{3}J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 168.2, 168.0, 149.3, 148.2, 139.2, 136.8, 135.6, 135.5, 133.4, 133.1, 132.2, 131.7, 131.0, 130.7, 130.3, 130.2, 129.0, 128.8, 128.5, 127.3, 126.8, 125.7, 125.5, 124.7, 124.6, 123.2, 122.4, 122.2, 120.6, 120.5, 67.1 (d, ^{2}J(C,P) = 4.6 Hz), 35.6, 34.2, 22.9, 14.3; ^{31}P NMR (162 MHz, CD_2Cl_2): δ = 141.8 (s). IR (film): ν = 3240.1, 3059.1, 2954.4, 1639.2, 1541.8, 1230.0, 823.5 cm^{-1}; HRMS (ESI+): *m*/*z* 739.23437 $[M + Na]^+$ (calcd. for $C_{45}H_{37}N_2O_5PNa$: 739.23323).



4d

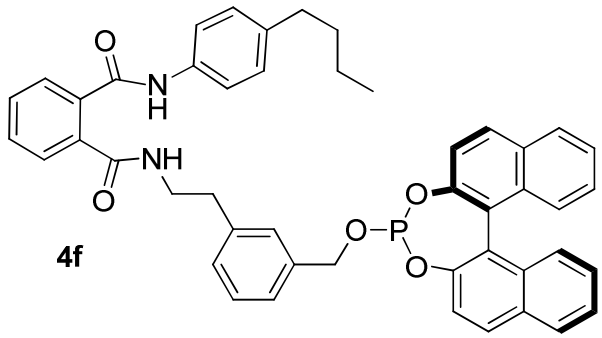
***N*^{1}-(4-Butylphenyl)-*N*^{2}-(4-(((11b*S*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)methyl)benzyl)phthalamide 4d.** The product, a white solid, was prepared according to the General Procedure 1 starting from 0.278 g of (*S*)-BINOL-PCl and 0.30 g of alcohol **3d** in the presence of 0.30 mL of TEA. Yield: 0.342 g (65%); m.p. = 110-130 °C; $[\alpha]^{18}_{D}$ = + 239.6 (*c* = 0.93 in DCM); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.88 (s, 1H), 8.06 (d, ^3J(H,H) = 8.8 Hz, 1H), 8.01 (d, ^3J(H,H) = 8.3 Hz, 1H), 7.97 (d, ^3J(H,H) = 8.7 Hz, 2H), 7.80 (d, ^3J(H,H) = 7.0 Hz, 1H), 7.62-7.46 (m, 8H), 7.39-7.30 (m, 7H), 7.20 (d, ^3J(H,H) = 7.4 Hz, 2H), 7.18 (d, ^3J(H,H) = 7.4 Hz, 2H), 6.88 (t, ^3J(H,H) = 5.9 Hz, 1H), 4.97 (dd, ^2J(H,H) = 12.2 Hz, ^3J(H,P) = 8.0 Hz, 1H), 4.76 (dd, ^2J(H,H) = 12.2 Hz, ^3J(H,P) = 8.2 Hz, 1H), 4.60 (d, ^3J(H,H) = 5.9 Hz, 2H), 2.61 (t, ^3J(H,H) = 7.6 Hz, 2H), 1.61 (m, 2H), 1.37 (m, 2H), 0.95 (t, ^3J(H,H) = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 170.0, 167.4, 149.3, 148.1, 139.7, 138.7, 137.0, 136.6, 135.7, 135.0, 133.4, 133.1, 132.2, 131.7, 131.1, 130.8, 130.7, 130.6, 129.2, 129.1, 129.0, 129.0, 128.5, 128.4, 128.3, 127.3, 126.9, 126.9, 125.7, 125.6, 124.6, 123.2, 122.3, 122.1, 120.8, 67.0 (d, ^2J(C,P) = 5.7 Hz), 44.2, 35.6, 34.3, 22.9, 14.3; ^{31}P NMR (162 MHz, CD_2Cl_2): δ = 141.6 (s). IR (film): ν = 3259.1, 3058.6, 2954.4, 1637.3, 1540.8, 1230.0, 824.4 cm^{-1}; HRMS (ESI+): *m*/*z* 753.24963 $[M + Na]^+$ (calcd. for $C_{46}H_{39}N_2O_5PNa$: 753.24888).



4e

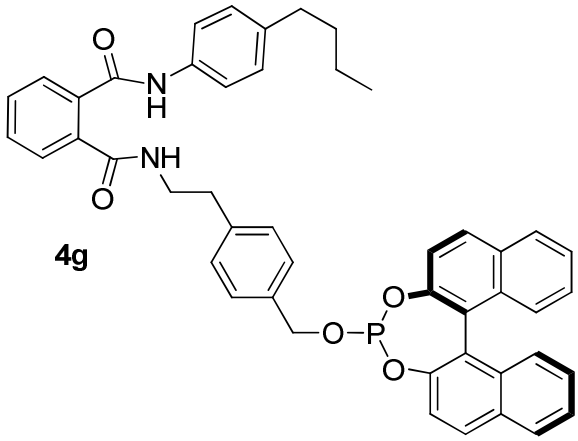
***N*^{1}-(4-Butylphenyl)-*N*^{2}-(2-(((11b*S*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)methyl)benzyl)phthalamide 4e.** The product, a white solid, was prepared according to the General Procedure 2 starting from 0.287 g of (*S*)-BINOL-PCl and 0.340 g of alcohol **3e** in the presence of 0.342 mL of TEA. Yield: 0.412 g (69%); m.p. = 115-122 °C; $[\alpha]^{20}_{D}$ = + 313.5 (*c* = 0.87 in DCM); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.91 (s, 1H), 8.04 (d, ^3J(H,H) = 8.8 Hz, 1H), 8.00 (d,

^{3}J(H,H) = 8.2 Hz, 1H), 7.89 (d, ^{3}J(H,H) = 8.8 Hz, 1H), 7.88 (d, ^{3}J(H,H) = 8.0 Hz, 1H), 7.70 (d, ^{3}J(H,H) = 7.7 Hz, 1H), 7.52-7.38 (m, 7H), 7.34-7.20 (m, 10H), 7.16 (d, ^{3}J(H,H) = 8.3 Hz, 2H), 6.76 (t, ^{3}J(H,H) = 5.4 Hz, 1H), 5.13 (dd, ^{2}J(H,H) = 12.1 Hz, ^{3}J(H,P) = 7.8 Hz, 1H), 4.98 (dd, ^{2}J(H,H) = 12.1 Hz, ^{3}J(H,P) = 8.4 Hz, 1H), 4.61 (dd, ^{2}J(H,H) = 14.7 Hz, ^{3}J(H,P) = 5.9 Hz, 1H), 4.53 (dd, ^{2}J(H,H) = 14.7 Hz, ^{3}J(H,P) = 5.7 Hz, 1H), 2.63 (t, ^{3}J(H,H) = 7.8 Hz, 2H), 1.64 (m, 2H), 1.40 (m, 2H), 0.98 (t, ^{3}J(H,H) = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.6, 166.8, 148.9, 147.8, 139.7, 137.3, 136.5, 135.7, 135.6, 134.7, 133.3, 133.0, 132.2, 131.6, 131.1, 130.8, 130.7, 130.4, 130.2, 129.7, 129.6, 129.3, 129.0, 128.9, 128.5, 128.3, 127.3, 127.3, 126.9, 126.9, 125.8, 125.6, 124.5, 123.2, 122.2, 122.0, 121.9, 120.6, 65.6 (d, ^{2}J(C,P) = 9.3 Hz), 41.9, 35.6, 34.3, 22.9, 14.3; ^{31}P NMR (162 MHz, CD_2Cl_2): δ = 144.0 (s). IR (film): ν = 3245.6, 3058.8, 2954.4, 1636.3, 1541.8, 1230.0, 824.4 cm^{-1}; HRMS (ESI+): *m*/*z* 753.24983 $[M + Na]^+$ (calcd. for $C_{46}H_{39}N_2O_5PNa$: 753.24888).



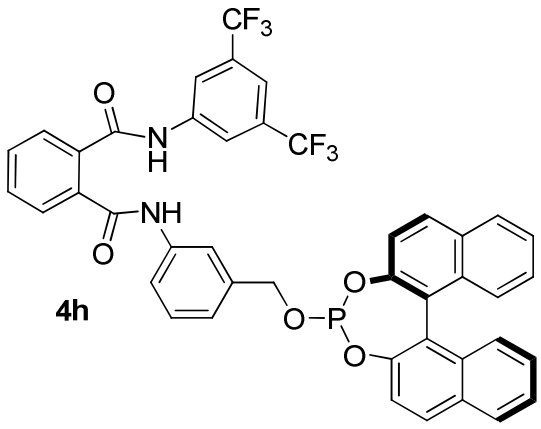
4f

***N*^{1}-(4-Butylphenyl)-*N*^{2}-(3-(((11b*S*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)methyl)phenethyl)phthalamide 4f.** The product, a white solid, was prepared according to the General Procedure 1 starting from 0.137 g of (*S*)-BINOL-PCl and 0.390 g of alcohol **3f** in the presence of 0.163 mL of TEA. Yield: 0.183 g (63%); m.p. = 105-116 °C; $[\alpha]^{20}_{D}$ = + 201.7 (*c* = 0.8 in DCM); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.21 (s, 1H), 8.06 (d, ^{3}J(H,H) = 8.8 Hz, 1H), 8.01 (d, ^{3}J(H,H) = 8.3 Hz, 1H), 7.96 (d, ^{3}J(H,H) = 8.7 Hz, 2H), 7.73 (d, ^{3}J(H,H) = 7.4 Hz, 1H), 7.58 (d, ^{3}J(H,H) = 8.8 Hz, 1H), 7.57 (d, ^{3}J(H,H) = 8.1 Hz, 2H), 7.52-7.28 (m, 11H), 7.19-7.17 (m, 5H), 6.55 (bs, 1H), 5.00 (dd, ^{2}J(H,H) = 12.2 Hz, ^{3}J(H,P) = 7.9 Hz, 1H), 4.80 (dd, ^{2}J(H,H) = 12.2 Hz, ^{3}J(H,P) = 8.4 Hz, 1H), 3.64 (m, 2H), 2.88 (t, ^{3}J(H,P) = 7.1 Hz, 2H), 2.62 (t, ^{3}J(H,P) = 7.6 Hz, 2H), 1.63 (m, 2H), 1.38 (m, 2H), 0.96 (t, ^{3}J(H,P) = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 170.3, 167.1, 149.2, 148.1, 139.9, 139.6, 138.1, 136.8, 135.6, 135.4, 133.4, 133.1, 132.2, 131.7, 131.1, 130.8, 130.4, 129.3, 129.2, 129.1, 129.0, 128.6, 128.2, 127.3, 126.9, 126.3, 125.7, 125.6, 124.6, 123.2, 122.4, 122.1, 120.7, 67.2 (d, ^{2}J(C,P) = 4.6 Hz), 41.8, 35.8, 35.6, 34.3, 22.9, 14.3; ^{31}P NMR (162 MHz, CD_2Cl_2): δ = 142.2 (s). IR (film): ν = 3240.6, 3058.5, 2954.4, 1636.3, 1541.8, 1230.0, 825.4 cm^{-1}; HRMS (ESI+): *m*/*z* 745.28262 $[M + H]^+$ (calcd. for $C_{47}H_{42}N_2O_5P$: 745.28259) and 767.26300 $[M + Na]^+$ (calcd. for $C_{47}H_{41}N_2O_5PNa$: 767.26453).



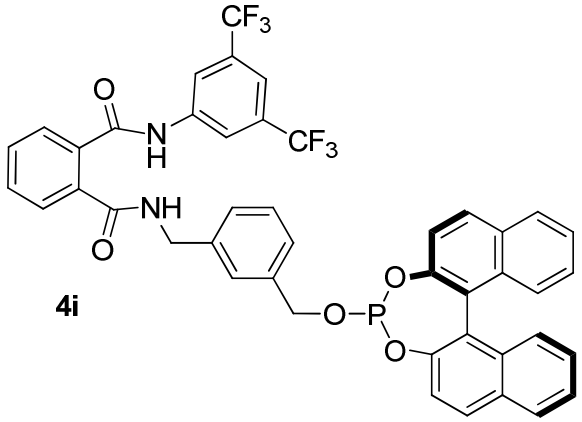
4g

***N*^{1}-(4-Butylphenyl)-*N*^{2}-(4-(((11b*S*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)methyl)phenethyl)phthalamide 4g.** The product, a white solid, was prepared according to the General Procedure 2 starting from 0.275 g of (*S*)-BINOL-PCl and 0.338 g of alcohol **3g** in the presence of 0.328 mL of TEA. Yield: 0.415 g (71%); m.p. = 109-117 °C; $[\alpha]^{20}_D$ = + 248.8 (*c* = 0.8 in DCM); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.22 (s, 1H), 8.06 (d, ^3J(H,P) = 8.8 Hz, 1H), 8.01 (d, ^3J(H,P) = 8.3 Hz, 1H), 7.96 (d, ^3J(H,P) = 9.0 Hz, 2H), 7.74 (d, ^3J(H,P) = 7.4 Hz, 1H), 7.58 (m, 3H), 7.52-7.29 (m, 10H), 7.23 (m, 4H), 7.19 (d, ^3J(H,P) = 8.5 Hz, 2H), 6.62 (t, ^3J(H,P) = 5.6 Hz, 1H), 4.98 (dd, ^2J(H,H) = 12.1 Hz, ^3J(H,P) = 8.0 Hz, 1H), 4.77 (dd, ^2J(H,H) = 12.1 Hz, ^3J(H,P) = 8.2 Hz, 1H), 3.65 (q, ^3J (H,H) = 6 Hz, 2H), 2.89 (t, ^3J(H,P) = 7.1 Hz, 2H), 2.63 (t, ^3J(H,P) = 7.6 Hz, 2H), 1.63 (m, 2H), 1.39 (m, 2H), 0.97 (t, ^3J(H,P) = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 170.2, 167.5, 149.3, 148.1, 139.8, 139.4, 137.0, 135.9, 135.7, 135.4, 133.4, 133.1, 132.2, 131.7, 131.1, 130.8, 130.5, 130.2, 129.4, 129.1, 129.0, 129.0, 128.4, 128.1, 127.3, 126.9, 126.9, 125.7, 125.6, 124.6, 123.2, 122.4, 122.1, 120.7, 67.2 (d, ^2J(C,P) = 4.8 Hz), 41.8, 35.6, 35.5, 34.3, 22.9, 14.4; ^{31}P NMR (162 MHz, CD_2Cl_2): δ = 141.9 (s). IR (film): ν = 3252.4, 3073.0, 2954.3, 1635.3, 1540.8, 1230.0, 823.5 cm^{-1}; HRMS (ESI+): *m*/*z* 767.26494 $[M + Na]^+$ (calcd. for $C_{47}H_{41}N_2O_5PNa$: 767.26453).



4h

***N*^{1}-(3,5-Bis(trifluoromethyl)phenyl)-*N*^{2}-(3-(((11b*S*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)methyl)phenyl)phthalamide 4h.** The product, a white solid, was prepared according to the General Procedure 1 starting from 0.168 g of (*S*)-BINOL-PCl and 0.230 g of alcohol **3h** in the presence of 0.2 mL of TEA. Yield: 0.296 g (78%); m.p. = 165-176 °C; $[\alpha]^{21}_D$ = + 216.7 (*c* = 0.75 in DCM); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 10.53 (s, 1H), 9.16 (s, 1H), 8.07 (s, 2H), 7.96 (d, ^3J(H,H) = 8.8 Hz, 1H), 7.92 (d, ^3J(H,H) = 8.2 Hz, 1H), 7.85 (d, ^3J(H,H) = 8.7 Hz, 1H), 7.83 (d, ^3J(H,H) = 7.5 Hz, 1H), 7.63 (s, 1H), 7.45 (d, ^3J(H,H) = 8.8 Hz, 1H), 7.42-7.34 (m, 4H), 7.31-7.15 (m, 6H), 7.04 (m, 1H), 6.96 (d, ^3J(H,H) = 7.7 Hz, 2H), 6.89 (m, 2H), 4.87 (dd, ^2J(H,H) = 12.4 Hz, ^3J(H,P) = 8.1 Hz, 1H), 4.69 (dd, ^2J(H,H) = 12.4 Hz, ^3J(H,P) = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 168.7, 168.4, 149.1, 148.0, 140.6, 138.7, 138.5, 135.7, 134.8, 133.3, 133.1, 132.2, 132.1 (q, ^2J(C,F) = 33.3 Hz), 131.6, 131.2, 131.0, 130.8, 130.7, 129.6, 129.0, 128.9, 128.5, 128.0, 127.3, 127.3, 126.9, 126.8, 125.7, 125.5, 124.6, 124.5, 123.7 (q, ^1J(C,F) = 272.6 Hz), 123.1, 122.3, 122.0, 120.4, 119.9, 119.4, 117.8, 66.9 (d, ^2J(C,P) = 6.7 Hz); ^{31}P NMR (162 MHz, CD_2Cl_2): δ = 141.0 (s); ^{19}F NMR (282 MHz, CD_2Cl_2): δ = -62.2 (s); IR (film): ν = 3220.4, 1638.2, 1380.8, 1276.0, 1230.0, 823.5 cm^{-1}; HRMS (ESI+): *m*/*z* 819.14729 $[M + Na]^+$ (calcd. for $C_{43}H_{27}F_6N_2O_5PNa$: 819.14540).



4i

***N*^{1}-(3,5-bis(trifluoromethyl)phenyl)-*N*^{2}-(3-(((11b*S*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)methyl)benzyl)phthalamide 4i.** The product, a white solid, was prepared according to the General Procedure 1 starting from 0.234 g of (*S*)-BINOL-PCl and 0.330 g of alcohol **3i** in the presence of 0.279 mL of TEA. Yield: 0.413 g (76%); m.p. = 138-145 °C; $[\alpha]^{21}_D$ = + 229.8 (*c* = 0.95 in DCM); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 10.81 (s, 1H), 8.16 (s, 2H), 8.02 (d, ^3J(H,H) = 8.8 Hz, 1H), 7.98 (d, ^3J(H,H) = 8.2 Hz, 1H), 7.92 (d, ^3J(H,H) = 8.8 Hz, 1H), 7.90 (d, ^3J(H,H) = 8.1 Hz, 1H), 7.54-7.25 (m, 12H), 7.22-7.16 (m, 2H), 6.69 (t, ^3J(H,H) = 5.7 Hz, 1H), 5.03 (dd, ^2J(H,H) = 12.3 Hz, ^3J(H,P) = 8.2 Hz, 1H), 4.85 (dd, ^2J(H,H) = 12.3 Hz, ^3J(H,P) = 8.2 Hz, 1H), 4.65 (AB system, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 170.0, 168.8, 149.2, 148.0, 141.2, 139.5, 138.3, 135.1, 134.4, 133.3, 133.1, 132.2, 132.1 (q, ^2J(C,F) = 33.2 Hz), 131.7, 131.1, 130.8, 130.3, 129.4, 129.0, 128.9, 128.4, 128.3, 127.7, 127.6, 127.4, 127.3, 127.3, 127.0, 126.9, 125.8, 125.6, 124.6,

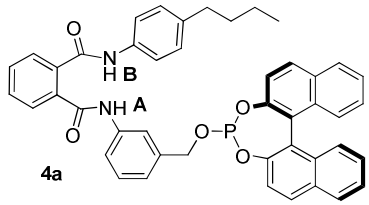
123.8 (q, ^{1}J(C,F) = 272.7 Hz), 123.2, 122.2, 122.0, 119.6, 117.2, 67.1 (d, ^{2}J(C,P) = 6.5 Hz), 44.3; ^{31}P NMR (162 MHz, CD_2Cl_2): δ = 140.6 (s); ^{19}F NMR (282 MHz, CD_2Cl_2): δ = -62.2 (s); IR (film): ν = 3219.2, 1635.3, 1382.7, 1281.0, 1230.0, 823.5 cm^{-1}; HRMS (ESI+): *m*/*z* 833.16280 $[M + Na]^+$ (calcd. for $C_{44}H_{29}F_6N_2O_5PNa$: 833.16105).

4.6.4 NMR studies

4.6.4.1 Concentration dependence of the chemical shift of NH protons of ligand 4a and complex [Rh(4a)$_2$(cod)BF$_4$]

Experimental parameters: T = 298 K; solvent: CD_2Cl_2 (0.8 mL).

Ligand:



Complex [Rh(4a)$_2$(cod)BF$_4$]: prepared in situ from [Rh(cod)$_2$BF$_4$] (1 eq) and **4a** (2.1 eq).

Table 4.9. Concentration dependence of chemical shift of protons NH A and NH B in the free ligand **4a**.

Conc. / mM	**Proton NH A** δ_A / ppm	$\Delta\delta_A = \delta_A - \delta_{A\ 0,3125\ mM}$ / ppm	**Proton NH B** δ_B / ppm	$\Delta\delta_B = \delta_B - \delta_{B\ 0,3125\ mM}$ / ppm
0.3125	8.6540	0.0000	8.3080	0.0000
0.625	8.6620	0.0080	8.3130	0.0050
1.25	8.6740	0.0200	8.3260	0.0180
2.5	8.7060	0.0520	8.3550	0.0470
5	8.7590	0.1050	8.4050	0.0970
10	8.8480	0.1940	8.4870	0.1790
20	9.0064	0.3524	8.6363	0.3283

Table 4.10 Concentration dependence of chemical shift of protons NH A and NH B in the complex [Rh(**4a**)$_2$(cod)BF$_4$].

Conc. / mM	**Proton NH A** δ_A / ppm	$\Delta\delta_A = \delta_A - \delta_{A\ 0,3125\ mM}$ / ppm	**Proton NH B** δ_B / ppm	$\Delta\delta_B = \delta_B - \delta_{B\ 0,3125\ mM}$ / ppm
0.3125	9.6270	0.0000	8.3980	0.0000
0.625	9.6140	-0.0130	8.4450	0.0470
1.25	9.6040	-0.0230	8.5060	0.1080
2.5	9.5990	-0.0280	8.5840	0.1860
5	9.6060	-0.0210	8.6870	0.2890
10	9.6130	-0.0140	8.7890	0.3910
20	9.6570	0.0300	8.9410	0.5430

Note: in all the experiments, the ^{31}P NMR spectra invariably showed a clean doublet signal at δ = 122.0 ppm with $J_{Rh\text{-}P}$ = 257.7 Hz.

Figure 4.6 Concentration dependence of proton NH A in the free ligand **4a** and in complex [Rh(**4a**)$_2$(cod)BF$_4$].

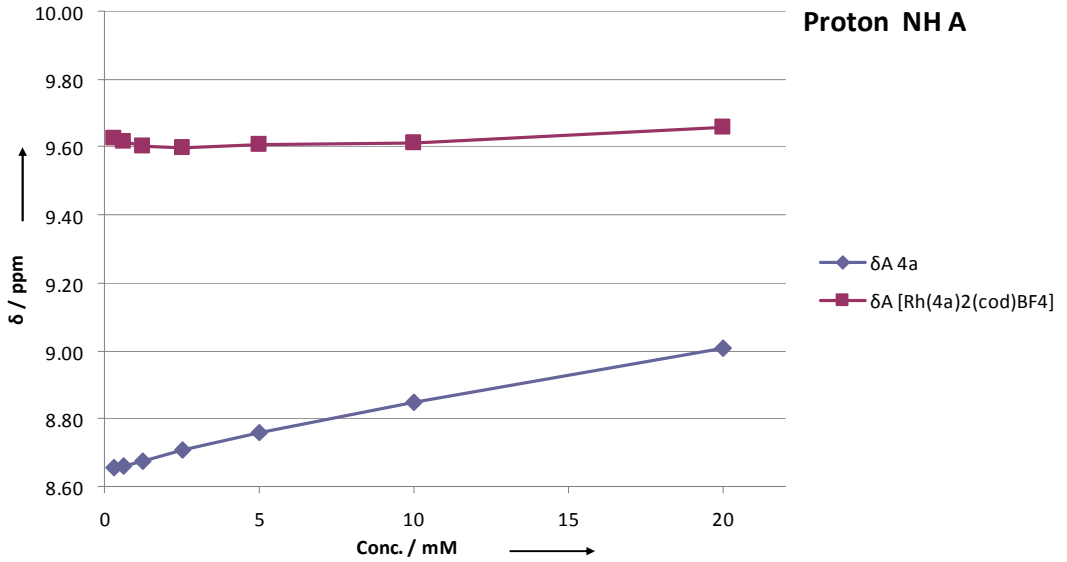
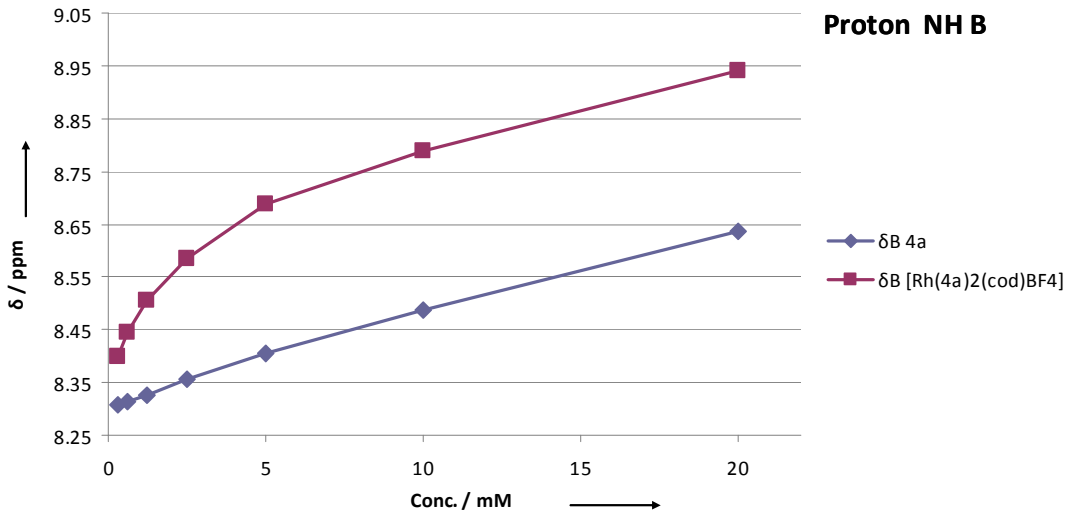


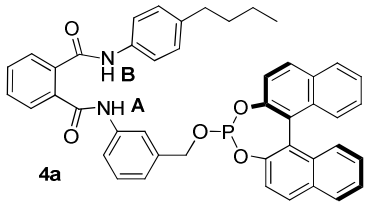
Figure 4.7 Concentration dependence of proton NH B in the free ligand **4a** and in complex [Rh(**4a**)$_2$(cod)BF$_4$].



4.6.4.2 Temperature dependence of the chemical shift of NH protons of ligand 4a and complex [Rh(4a)$_2$(cod)BF$_4$]

Experimental parameters: concentration: 1.2 mM; solvent: CD_2Cl_2 (0.8 mL).

Ligand:



Complex [Rh(4a)$_2$(cod)BF$_4$]: prepared in situ from [Rh(cod)$_2$BF$_4$] (1 eq) and **4a** (2.1 eq).

Table 4.11 Temperature dependence of chemical shift of protons NH A and NH B in the free ligand **4a**.

	Proton NH A		**Proton NH B**	
T (K)	δ_A (ppm)	$\Delta\delta_A$ (ppm) = δ_A - $\delta_{A\ 298\ K}$	δ_B (ppm)	$\Delta\delta_B$ (ppm) = δ_B - $\delta_{B\ 298\ K}$
298	8.6922	0.0000	8.3423	0.0000
288	8.7362	0.0440	8.3739	0.0316
278	8.7902	0.0980	8.4117	0.0694
268	8.8628	0.1706	8.4592	0.1169
258	8.9919	0.2997	8.5459	0.2036
248	9.2746	0.5824	8.7624	0.4201

Table 4.12. Temperature dependence of chemical shift of protons NH A and NH B in complex [Rh(**4a**)$_2$(cod)BF$_4$].

	Proton NH A		**Proton NH B**	
T (K)	δ_A (ppm)	$\Delta\delta_A$ (ppm) = δ_A - $\delta_{A\ 298\ K}$	δ_B (ppm)	$\Delta\delta_B$ (ppm) = δ_B - $\delta_{B\ 298\ K}$
298	9.6060	0.0000	8.4800	0.0000
288	9.7390	0.1330	8.4690	-0.0110
278	9.8770	0.2710	8.4510	-0.0290
268	10.0080	0.4020	8.4320	-0.0480
258	10.1330	0.5270	8.4130	-0.0670
248	10.2490	0.6430	8.3960	-0.0840

Figure 4.8 Temperature dependence of chemical shift of proton NH A in free ligand **4a** and in complex [Rh(**4a**)$_2$(cod)BF$_4$].

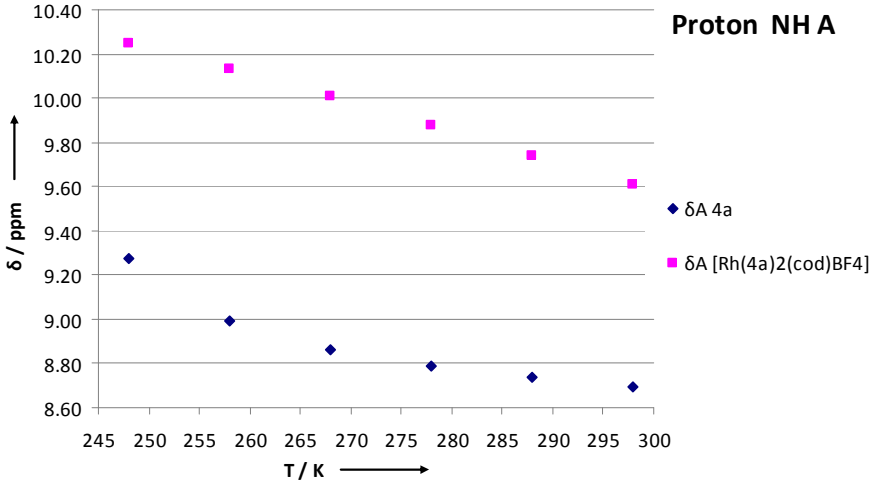
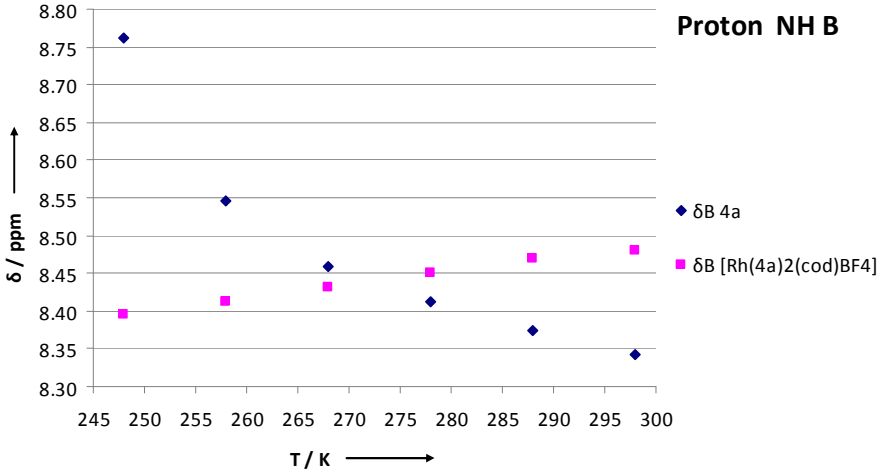


Figure 4.9 Temperature dependence of chemical shift of proton NH B in free ligand **4a** and in complex [Rh(**4a**)$_2$(cod)BF$_4$].



Note: the $\Delta\delta/\Delta T$ values were calculated from the slope of a linear least squares fit to the δ vs. *T* graph obtained for the complex [Rh(**4a**)$_2$(cod)BF$_4$] (Tables S3 and S4), which showed a linear dependence of NH proton chemical shift from temperature. No $\Delta\delta/\Delta T$ calculation was carried out for the free ligand **4a**, whose NH protons did not show a linear temperature dependence of chemical shift.

Table 4.13 Determination of $\Delta\delta/\Delta T$ values of protons NH A and NH B in complex [Rh(**4a**)$_2$(cod)BF$_4$].

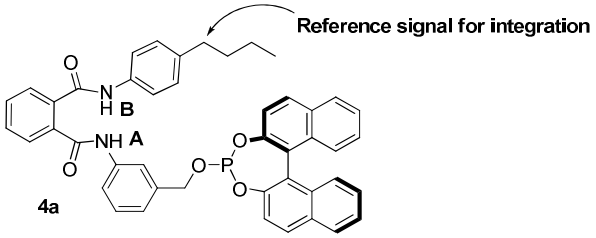
	Proton NH A		**Proton NH B**	
Linear regression of □ vs. T	**Slope** **-0.0129**	**Intercept** 13.4672	**Slope** **0.0017**	**Intercept** 7.9667
Standard error =	0.0002	0.0519	0.0001	0.0171
R^2 =	0.9991	0.0079	0.9948	0.0026
F index =	4641.4392	4.0000	771.8904	4.0000
	0.2929	0.0003	0.0053	0.0000
Δδ / ΔT (ppb K^{-1}) =	**-12.94**		**1.73**	

4.6.4.3 Kinetic study of H/D exchange of NH protons of ligand 4a and complex $[Rh(4a)_2(cod)BF_4]$ in the presence of a large excess of CD_3OD

Experimental parameters: T = 298 K; concentration: 1.2 mM; solvent: CD_2Cl_2 (0.8 mL). Excess of CD_3OD: 513 eq (20 µL, 0.492 mmol).

Abbreviations used in the tables: $\%H_t$ = percent of H still not exchanged ($\%H_t$) for each NH group; $R_{H,t}$ = fraction of unexchanged H ($R_{H,0} = 1$).

Ligand:



Complex $[Rh(4a)_2(cod)BF_4]$: prepared in situ from $[Rh(cod)_2BF_4]$ (1 eq) and **4a** (2.1 eq).

Note: time = 0 was marked when CD_3OD was added. A distinct non-exchanging NMR signal was used as an internal integration reference. Rate constants *k* and corresponding half-lives $t_{1/2}$ were determined from the slope of a linear least squares fit to the graph of $\ln(R_{H,t}) = -kt$. The part of the curve corresponding values of $R_{H,t} < 0.1$ (i.e. $\%H_t < 10\%$) was not computed for the least square fit because, for such low values, the integration error becomes significant.

Table 4.14 H/D exchange of the NH protons of ligand **4a** (1.2 mM CD_2Cl_2 solution).

	Proton NH A			**Proton NH B**		
t (min)	$\%H_t$	$R_{H,t}$	$\ln(R_{H,t})$	$\%H_t$	$R_{H,t}$	$\ln(R_{H,t})$
0.00	100.00	1.0000	0.000	100.00	1.0000	0.000
3.12	77.17	0.7717	-0.259	79.80	0.7980	-0.226
6.99	59.81	0.5981	-0.514	66.18	0.6618	-0.413
10.84	47.53	0.4753	-0.744	53.96	0.5396	-0.617
14.70	39.16	0.3916	-0.937	45.36	0.4536	-0.791
18.55	31.56	0.3156	-1.153	39.07	0.3907	-0.940
22.42	26.66	0.2666	-1.322	33.03	0.3303	-1.108
26.29	21.48	0.2148	-1.538	27.34	0.2734	-1.297
30.14	16.17	0.1617	-1.822	22.50	0.2250	-1.491
34.00	16.86	0.1686	-1.780	20.79	0.2079	-1.571
37.85	12.15	0.1215	-2.108	16.12	0.1612	-1.825
41.72	10.75	0.1075	-2.230	15.96	0.1596	-1.835
49.59	9.57	0.0957	-2.347	11.72	0.1172	-2.144
57.44	7.14	0.0714	-2.640	8.80	0.0880	-2.431
65.30	7.45	0.0745	-2.597	8.49	0.0849	-2.466
73.17	6.05	0.0605	-2.805	6.73	0.0673	-2.699
81.02	5.63	0.0563	-2.876	6.88	0.0688	-2.677
88.89	5.66	0.0566	-2.872	6.60	0.0660	-2.718

96.75	4.85	0.0485	-3.026	5.27	0.0527	-2.944
104.60	5.18	0.0518	-2.960	5.55	0.0555	-2.891
112.47	4.96	0.0496	-3.003	4.82	0.0482	-3.033
120.34	4.67	0.0467	-3.064	5.36	0.0536	-2.925
133.19	4.42	0.0442	-3.120	4.30	0.0430	-3.147
146.05	3.76	0.0376	-3.281	4.53	0.0453	-3.093
158.92	3.63	0.0363	-3.316	3.86	0.0386	-3.254
171.79	4.01	0.0401	-3.217	3.42	0.0342	-3.377
184.65	4.25	0.0425	-3.158	4.98	0.0498	-2.999
202.50	4.26	0.0426	-3.157	3.72	0.0372	-3.290
220.37	3.82	0.0382	-3.265	4.20	0.0420	-3.169
238.22	3.53	0.0353	-3.345	3.45	0.0345	-3.368
256.09	3.67	0.0367	-3.306	3.87	0.0387	-3.251
288.95	3.91	0.0391	-3.242	4.20	0.0420	-3.169
321.80	3.58	0.0358	-3.331	3.34	0.0334	-3.400
354.69	4.06	0.0406	-3.203	3.80	0.0380	-3.271

Table 4.15 H/D exchange of the NH protons of complex [Rh(**4a**)$_2$(cod)BF$_4$] (1.2 mM CD_2Cl_2 solution).

	Proton NH A			**Proton NH B**		
t (min)	$\%H_t$	$R_{H,t}$	ln ($R_{H,t}$)	$\%H_t$	$R_{H,t}$	ln ($R_{H,t}$)
0.00	100.00	1.0000	0.000	100.00	1.0000	0.000
1.75	98.02	0.9802	-0.020	94.33	0.9433	-0.058
4.22	97.70	0.9770	-0.023	89.61	0.8961	-0.110
6.68	90.22	0.9022	-0.103	81.89	0.8189	-0.200
9.17	85.55	0.8555	-0.156	75.32	0.7532	-0.283
11.63	84.70	0.8470	-0.166	71.78	0.7178	-0.332
14.10	78.01	0.7801	-0.248	65.67	0.6567	-0.421
16.58	77.93	0.7793	-0.249	63.55	0.6355	-0.453
19.03	77.07	0.7707	-0.260	62.34	0.6234	-0.473
21.52	75.44	0.7544	-0.282	58.89	0.5889	-0.530
24.00	74.28	0.7428	-0.297	56.38	0.5638	-0.573
26.47	69.11	0.6911	-0.370	50.56	0.5056	-0.682
32.93	63.89	0.6389	-0.448	45.30	0.4530	-0.792
39.42	58.85	0.5885	-0.530	38.68	0.3868	-0.950
45.88	50.06	0.5006	-0.692	30.55	0.3055	-1.186
52.38	47.45	0.4745	-0.746	27.75	0.2775	-1.282
58.88	44.67	0.4467	-0.806	25.62	0.2562	-1.362
70.55	35.28	0.3528	-1.042	17.04	0.1704	-1.769
77.03	32.18	0.3218	-1.134	15.06	0.1506	-1.893
83.50	29.23	0.2923	-1.230	12.69	0.1269	-2.064
89.98	25.66	0.2566	-1.360	11.07	0.1107	-2.201
96.45	23.54	0.2354	-1.446	10.77	0.1077	-2.228
102.92	22.00	0.2200	-1.514	8.04	0.0804	-2.521
114.42	17.02	0.1702	-1.771	6.38	0.0638	-2.752
125.88	14.14	0.1414	-1.956	6.03	0.0603	-2.808
137.37	12.75	0.1275	-2.060	4.66	0.0466	-3.066

148.83	11.73	0.1173	-2.143	4.13	0.0413	-3.187
160.32	10.55	0.1055	-2.249	5.12	0.0512	-2.971
176.78	7.96	0.0796	-2.530	4.84	0.0484	-3.029
193.27	7.33	0.0733	-2.614	4.04	0.0404	-3.208
209.73	6.14	0.0614	-2.791	4.19	0.0419	-3.171
237.12	4.99	0.0499	-2.997	4.78	0.0478	-3.042
268.58	4.82	0.0482	-3.033	5.30	0.0530	-2.938
300.08	5.37	0.0537	-2.925	4.44	0.0444	-3.114
331.57	4.16	0.0416	-3.180	4.65	0.0465	-3.069
363.13	3.41	0.0341	-3.379	3.88	0.0388	-3.251

Figure 4.5 H/D exchange of the NH protons of ligand **4a** and complex [Rh(**4a**)$_2$(cod)BF$_4$]: plot of %H$_t$ vs. time.

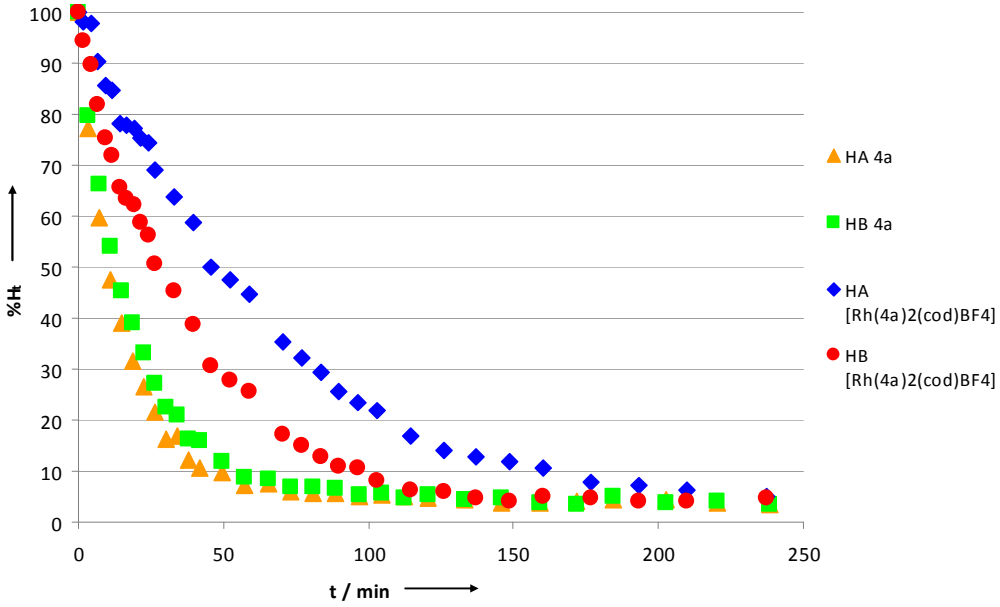


Table 4.16 H/D exchange of the NH protons of ligand **4a** (1.2 mM CD_2Cl_2 solution): kinetic data.

	Proton NH A	
Regression interval =	0 - 41.72 min	
Linear regression of ln ($R_{H,t}$) vs. t	**Slope**	**Intercept**
	-0.0566	0.0000
Standard error =	0.0012	#N/D
R^2 =	0.9949	0.1035
F index =	2145.6915	11.0000
	22.9931	0.1179
***k* (min^{-1}) =**	**0.057**	
$t_{1/2}$ (min) = ln(2) / *k* =	**12.24**	

	Proton NH B	
Regression interval =	0 - 49.59 min	
Linear regression of ln ($R_{H,t}$) vs. t	**Slope**	**Intercept**
	-0.0466	0.0000
Standard error =	0.0009	#N/D
R^2 =	0.9951	0.0930
F index =	2418.1351	12.0000
	20.9011	0.1037
***k* (min^{-1}) =**	**0.047**	
$t_{1/2}$ (min) = ln(2) / *k* =	**14.88**	

Table 4.17 H/D exchange of the NH protons of complex [Rh(**4a**)$_2$(cod)BF$_4$] (1.2 mM CD_2Cl_2 solution): kinetic data.

	Proton NH A	
Regression interval =	0 - 160.32 min	
Linear regression of ln ($R_{H,t}$) vs. t	**Slope**	**Intercept**
	-0.0147	0.0000
Standard error =	0.0001	#N/D
R^2 =	0.9984	0.0445
F index =	17017.5956	27.0000
	33.6475	0.0534
***k* (min^{-1}) =**	**0.015**	
$t_{1/2}$ (min) = ln(2) / *k* =	**47.10**	

	Proton NH B	
Regression interval =	0 - 96.45 min	
Linear regression of ln ($R_{H,t}$) vs. t	**Slope**	**Intercept**
	-0.0243	0.0000
Standard error =	0.0002	#N/D
R^2 =	0.9984	0.0470
F index =	13181.3248	21.0000
	29.1005	0.0464
***k* (min^{-1}) =**	**0.024**	
$t_{1/2}$ (min) = ln(2) / *k* =	**28.47**	

Table 4.18 Effect of an excess of CD_3OD on the chemical shift of NH protons of ligand **4a** and complex [Rh(**4a**)$_2$(cod)BF$_4$].

1.2 mM CD_2Cl_2 solution of		Free ligand **4a**		[Rh(**4a**)$_2$(cod)BF$_4$]	
		NH A	**NH B**	**NH A**	**NH B**
Before CD_3OD addition	□ (ppm) =	8.683	8.333	9.619	8.508
After addition of CD_3OD (513 eq)	□ (ppm) =	9.337	9.075	9.893	9.066
Chemical shift variation	**□□ (ppm) =**	**0.654**	**0.742**	**0.274**	**0.558**

4.6.5 CATALYTIC SCREENING OF THE PHTHALAPHOS LIBRARY

The results of the catalytic screening of the whole PhthalaPhos library (ligands **4a-s**) on substrates **S1**, **S2**, **S3** and **S4** are reported in this section.

General Procedure for asymmetric hydrogenations under atmospheric pressure. Seven oven-dried glass test tubes with stirring bars were employed: in each one the ligand (0.0042 mmol, 0.022 eq) was weighted, then the test tubes were placed in a Schlenk and subjected to three vacuum/nitrogen cycles. A 2.12 mM DCM solution of [Rh(cod)$_2$BF$_4$] (0.9 mL, 0.001909 mmol, 0.01 eq) was added and the mixtures were stirred for 10 min under nitrogen. A 0.1909 M solution of the substrate in DCM (1 mL, 0.1909 mmol, 1 eq) was finally added, followed by 2.1 mL of DCM. The reaction mixtures were subjected to three vacuum/hydrogen cycles and then left stirring overnight at room temperature under 1 bar of hydrogen. Samples were taken for chiral GC analysis (for the GC conditions, see below).

General Procedure for asymmetric hydrogenations under pressure higher than atmospheric. A Parr multireactor was employed, allowing six reactions in parallel under hydrogen pressure. The selected ligands (0.0042 mmol, 0.022 eq) were weighted in special glass vessels. The vessels were purged with nitrogen and a 2.12 mM DCM solution of [Rh(cod)$_2$BF$_4$] (0.9 mL, 0.001909 mmol, 0.01

eq) was added in each of them. After 10 min a 0.1909 M solution of the substrate in DCM (1 mL, 0.1909 mmol, 1 eq) was added followed by 6.1 mL of DCM, and the vessels were placed in the respective autoclaves and purged three times with hydrogen at the selected pressure. The reactions were stirred overnight at R.T. under pressure of hydrogen, and then analysed by chiral GC for conversion and *ee* determination (see below).

GC conditions for conversion and *ee* determination

Methyl 2-acetamidopropanoate P1: capillary column: MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin, 0.25 μm; diameter = 0.25 mm; length = 25 m; carrier: hydrogen; flow: 1 mL/min; oven temperature: 140 °C for 6 min, then a 8 °C/min gradient is applied): $t_{substrate}$ = 3.7 min; t_R = 4.7 min; t_S = 5.3 min.[S36]

***N*-(1-Phenylethyl)acetamide P2:** capillary column: MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin, 0.25 μm; diameter = 0.25 mm; length = 25 m; carrier: hydrogen; flow: 1.3 mL/min; oven temperature: 145 °C for 15 min, then a 8 °C/min gradient is applied; t_R = 12.8 min; t_S = 13.4 min; $t_{substrate}$ = 16.1 min.[S37]

***N*-(1,2,3,4-Tetrahydronaphthalen-1-yl)acetamide P3:** capillary column: MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin, 0.25 μm; diameter = 0.25 mm; length = 25 m; carrier: hydrogen; inlet pressure: 1.15 bar; oven temperature: 160 °C for 13 min, then a 13 °C/min gradient is applied; t_R = 11.5 min; t_S = 12.1 min; $t_{substrate}$ = 15.2 min.[S38]

Methyl 3-acetamido-2-benzylpropanoate P4: capillary column: MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin, 0.25 μm; diameter = 0.25 mm; length = 25 m; carrier: hydrogen; flow: 1.4 mL/min; oven temperature: 170 °C for 30 min, then a 10 °C/min gradient is applied; $t_{(+)}$ = 22.4 min; $t_{(-)}$ = 23.0 min; $t_{substrate}$ = 24.1 min.[S39]

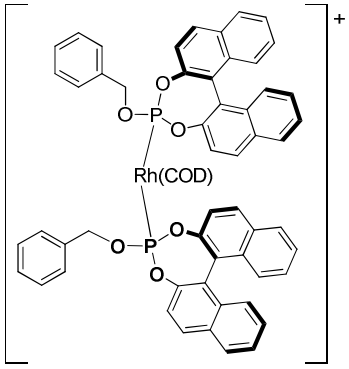
4.6.6 DFT AND MOLECULAR MECHANICS CALCULATIONS

All calculations were run using the Schrödinger suite of programs (http://www.schrodinger.com) through the Maestro graphical interface. The following procedure was implemented to generate starting geometries of the [Rh(**4a**)2(cod)]+ complex for DFT optimization:

4.6.6.1 DFT Rh(cod) phosphite core optimization

The structure of the Rh(cod) phosphite core (Figure 4.6) was optimized at the B3LYP/LACVP level of theory using the Jaguar module.[21] Rhodium was considered as a +1 cation in square planar geometry, coordinated to the cod ligand, and bound to the phosphorous atoms of simplified ligands. The core complex is a closed-shell molecule with a net charge of +1. Default convergence criteria have been employed.

Figure 4.6 Structure of Rh(cod) phosphite core optimized by DFT calculation.



Optimized geometry as XYZ coordinates for Rh(cod) phospite core (distances in Ångstroms)

Rh(COD) phospite core

121
energy: -3635.39774745126 hartrees

O1	-1.8803856334	-5.5528705386	0.1696196923
P2	-3.2302291903	-6.6558832217	-0.0949629230
O3	-2.4471325236	-8.1879879804	0.2674333589
C4	-0.5384778702	-5.8345218335	-0.1956259881
C5	0.1489234315	-6.9111064962	0.3544239580
C6	0.0753431005	-4.9015774923	-1.0572669697
C7	1.4629009000	-7.1988485233	-0.1680993917
C8	1.3754130566	-5.1005422217	-1.4612257860
H9	-0.5010538512	-4.0423364376	-1.3711660938
C10	2.0810541198	-6.2759814084	-1.0808069847
H11	1.8612968390	-4.3841566891	-2.1140461299
C12	-1.6381522664	-8.3133115686	1.4370830607
C13	-2.1610956765	-9.1031164365	2.4868344469
C14	-0.4039879887	-7.6850910194	1.5018660172
C15	-1.4404119355	-9.2377791934	3.6524834126
C16	0.3174986317	-7.7501523981	2.7531526028
C17	-0.2054846758	-8.5499515331	3.8283750126
C18	2.1709377645	-8.3927092706	0.1623645788
C19	3.3779961821	-6.5635956073	-1.5952969354
C20	3.4200565479	-8.6506308185	-0.3677042601
C21	4.0369425991	-7.7251061512	-1.2480511737
H22	1.7087342817	-9.1134311598	0.8250461700
H23	3.9342227455	-9.5713370844	-0.1115849266
H24	3.8332407999	-5.8545671656	-2.2797818352
H25	5.0214511142	-7.9381053516	-1.6510875002
H26	-1.8170977870	-9.8557169647	4.4611115391
H27	-3.1135805638	-9.5995420762	2.3437689504
C28	0.5057428554	-8.6167409806	5.0608653662
C29	1.5123346189	-7.0072835938	2.9922218164
C30	1.6707915882	-7.9017804642	5.2478683633
C31	2.1681582951	-7.0799704370	4.2054893694
H32	3.0704419933	-6.4987250364	4.3646137993
H33	1.9033480310	-6.3664508343	2.2141235400
H34	0.1045708863	-9.2355329607	5.8579568646
H35	2.2014633511	-7.9560030728	6.1923908120
O36	-4.1241193608	-6.1734892706	1.2773679046
C37	-3.6515999757	-5.5308684731	2.5574170334
H38	-3.1425773003	-6.2968816576	3.1459951316
H39	-2.9537782014	-4.7359968615	2.2927119457
C40	-7.3547038365	-4.1770836461	4.2954475516
C41	-6.6642634818	-3.3605107254	3.3891223926
C42	-5.4473037181	-3.7878620843	2.8494115194
C43	-4.9060036151	-5.0344136633	3.2102109395
C44	-5.6031650703	-5.8450375834	4.1221192304
C45	-6.8204219964	-5.4183158479	4.6643638566
H46	-8.2976540263	-3.8445623836	4.7170277307

H47	-7.0711322715	-2.3936451508	3.1108417207
H48	-4.9123605146	-3.1566279792	2.1451577473
H49	-5.1903248615	-6.8091187794	4.4062362437
O50	-3.9011301923	-4.4852108834	-4.1811731114
C51	-5.1307744999	-3.8774066878	-4.7465751347
H52	-4.7212839881	-3.0534467317	-5.3380266576
H53	-5.6122441338	-4.5802429174	-5.4343723203
C54	-7.8670265351	-2.3421494794	-1.7713859458
C55	-8.3568090138	-2.9142425448	-2.9520341939
C56	-7.4673442224	-3.4374488791	-3.8999053507
C57	-6.0804148558	-3.3849641677	-3.6803080448
C58	-5.5950217419	-2.8062428867	-2.4952991209
C59	-6.4842117976	-2.2913459132	-1.5456568993
H60	-8.5546495111	-1.9314418955	-1.0394913316
H61	-9.4253587986	-2.9479583397	-3.1390701788
H62	-7.8532091813	-3.8684595758	-4.8207515338
H63	-4.5245737831	-2.7544056632	-2.3267471304
Rh64	-5.0451830756	-7.0461596095	-1.7716026790
C65	-6.2803665550	-8.1852146901	-3.2507069012
C66	-6.3816828296	-9.6182606148	-2.7703806590
C67	-6.6309046305	-9.7640682869	-1.2474910135
C68	-5.9144131938	-8.7049984227	-0.4214183780
C69	-6.4637525698	-7.4886888203	-0.0205492996
C70	-7.8228957552	-6.9358188822	-0.3903256224
C71	-8.2282871080	-7.1774434894	-1.8653094930
C72	-7.0519758584	-7.0952699017	-2.8277286830
H73	-7.1715767608	-10.1414031404	-3.3336454363
H74	-5.4416087303	-10.1170353274	-3.0313511621
H75	-7.7036950243	-9.7349695389	-1.0294019994
H76	-6.2804278367	-10.7524243343	-0.9302525379
H77	-8.5868761447	-7.3510537866	0.2860935544
H78	-7.8026732489	-5.8574166080	-0.1977909646
H79	-8.7231834815	-8.1482507321	-1.9766937439
H80	-8.9658007071	-6.4206775826	-2.1538356494
H81	-7.0197950574	-6.1919305401	-3.4330175136
H82	-5.7445754752	-8.0710347739	-4.1878021387
H83	-5.9654621583	-6.9620900327	0.7897609960
H84	-5.0103936183	-9.0389652247	0.0851930972
O85	-3.6376608564	-6.9285531541	-5.1328530801
P86	-3.7719224790	-6.0880617261	-3.5711939237
O87	-2.1070666249	-6.0591150680	-3.1197749530
C88	-2.9734638950	-8.1929427453	-5.1221253411
C89	-1.6048726799	-8.2914089918	-4.8573957530
C90	-3.7747656289	-9.3150179683	-5.4366365343
C91	-1.0731577032	-9.6223522549	-4.6671534046
C92	-3.2344250340	-10.5793329500	-5.3889625321
H93	-4.7957558132	-9.1497814306	-5.7590282065
C94	-1.8939224866	-10.7702278544	-4.9531734169
H95	-3.8292252260	-11.4442094894	-5.6644589551
C96	-1.0865287919	-5.9509552201	-4.1127883823
C97	-0.4455471102	-4.6995043666	-4.2167457021
C98	-0.7439479403	-7.0649684643	-4.8655039423
C99	0.6621196743	-4.5798322981	-5.0202656817
C100	0.3998040455	-6.9340351050	-5.7464746150
C101	1.1336154142	-5.6929711612	-5.7690496648
C102	0.2397129831	-9.8510726932	-4.1581540430
C103	-1.3567342031	-12.0778687502	-4.7825948084
C104	0.7213529706	-11.1334645429	-3.9779349325
C105	-0.0745322081	-12.2602718271	-4.3078944818
H106	0.8572180125	-9.0013232404	-3.8951160603
H107	1.7181083694	-11.2810213186	-3.5755413354
H108	-1.9839501292	-12.9312905444	-5.0215068839
H109	0.3238297526	-13.2603101729	-4.1738965722
H110	1.1847278638	-3.6318248192	-5.1010137725
H111	-0.8377178923	-3.8652206508	-3.6521158768
C112	2.3044690906	-5.5786545199	-6.5714689761
C113	0.8415155972	-7.9712447011	-6.6212591313
C114	2.7336207001	-6.6275520073	-7.3566300930

C115	1.9782350657	-7.8257703352	-7.3934978912
H116	2.2920431846	-8.6372583894	-8.0419672228
H117	0.2797933760	-8.8923940289	-6.6816194529
H118	2.8489586197	-4.6391049653	-6.5587566566
H119	3.6295298193	-6.5329586831	-7.9607886249
H120	-6.0988967592	-1.8398273451	-0.6371237072
H121	-7.3479999301	-6.0486954719	5.3727782542

4.6.6.2 Molecular Mechanics calculations of $[Rh(4a)_2(cod)]^+$ complex.

Monte Carlo conformational search of the [Rh(**4a**)$_2$(cod)]+ complex was performed as implemented in the framework of Macromodel version 9.6S19 (AMBER* force field,S20 *in vacuo* condition with ε= 4r). The butyl group of ligand **4a** was not included in the model. The Rh(cod) phosphite core was frozen to the optimized DFT geometry leaving the benzyl groups free to move. For each search, at least 1000 starting structures for each variable torsion angle were generated and minimized until the gradient was less than 0.05 kJ/Å mol using the truncated Newton–Raphson algorithm.[18] Duplicate conformations of ligands and those with an energy greater than 6 kcal/mol above the global minimum were discarded. A number of low energy conformers were identified which, in agreement with the spectroscopic data, are characterized by interligand hydrogen bonding involving proton NH_A, namely: (i) structure-type **I** where the ligands are held together by two hydrogen bonds between proton NH_A of each ligand and the carbonyl of the NH_B-bearing ancillary amide of the other ligand (Figure 4.7); (ii) structure-type **II** with a single hydrogen bond between proton NH_A of one ligand and the carbonyl of the NH_B-bearing amide of the other ligand (Figure 4.8); (iii) structure-type **III**, where only one hydrogen bond connects proton NH_A of one ligand with the carbonyl of the NH_A-bearing amide of the other ligand (Figure 4.9). Obviously, **III** is in equilibrium with the iso-energetic structure where the roles of H-bond donor and acceptor of - NH_ACO- in the two ligands are inverted.

Figure 4.7 Low energy structure-type **I** identified by molecular mechanics calculations.

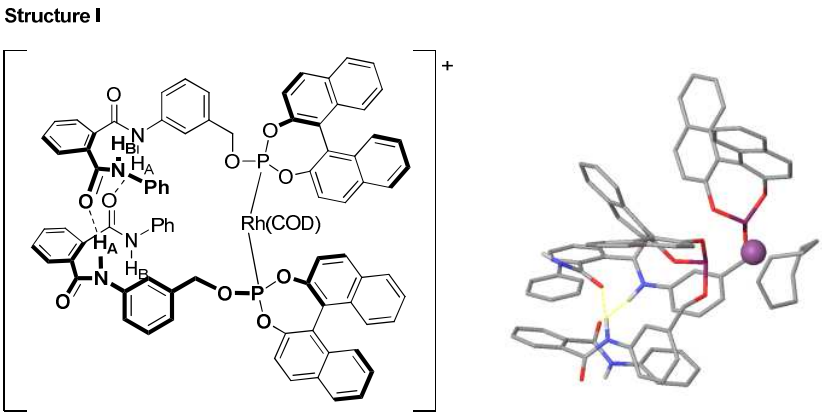


Figure 4.8 Low energy structure-type **II** identified by molecular mechanics calculations.

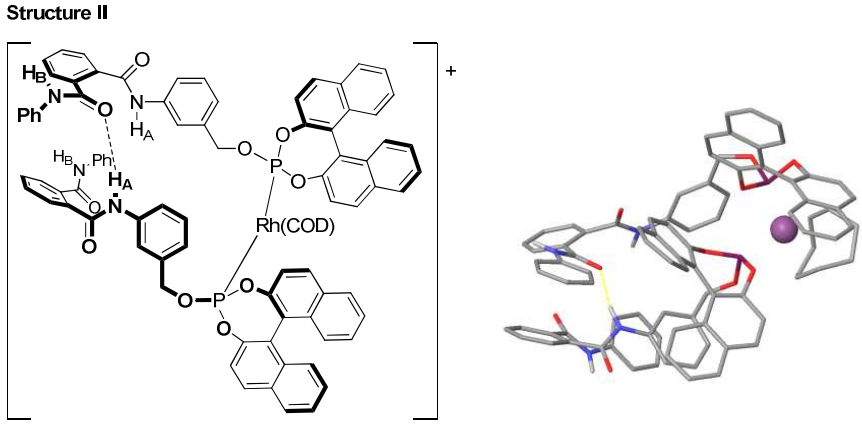
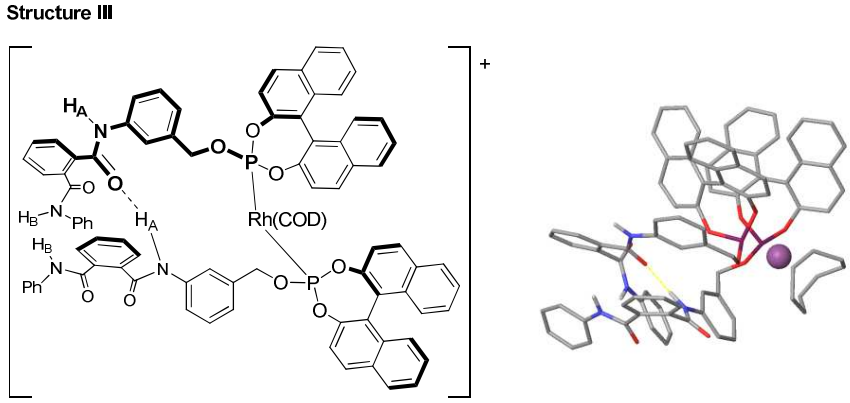


Figure 4.10 Low energy structure-type **III** identified by molecular mechanics calculations.



DFT optimization of structure-types I, II and III obtained from the conformational search. Structure-type **I**, **II** and **III** identified by the above-described conformational search were fully optimized with DFT calculations at the B3LYP/LACVP level of theory using the Jaguar module[SErrore. Il segnalibro non è definito.] and their relative energies are reported in Table S20. The obtained stationary points were confirmed as minima by frequency calculation at the same level of theory.

Table 4.19 Relative energies (kcal/mol) of optimized (B3LYP/LACVP) structure-type **I**, **II** and **III**.

Structure-type	ΔE (kcal/mol)
I	0.00
II	8.50
III	7.45

Optimized geometry as XYZ coordinates of the lowest energy minimum (structure-type **I**) of [Rh(**4a**)$_2$(cod)]$^+$ complex (distances in Ångstroms). The DFT optimized structure is shown in Figure 4.5, see page 187).

Rh(**4a**)$_2$(COD)
177
energy: -5233.98053359893 hartrees

O1	-1.4114873516	-5.6097599810	0.6918941919
P2	-2.6852425090	-6.7611456051	0.2710151962
O3	-1.7250787417	-8.2517033599	0.3566885059
C4	-0.1010432778	-5.6766582168	0.1452629318
C5	0.7446761946	-6.7294934323	0.4753820426
C6	0.3162168903	-4.5805527098	-0.6379192177
C7	2.0352717822	-6.7823033246	-0.1644308930
C8	1.5896327832	-4.5694371240	-1.1609872386
H9	-0.3804566364	-3.7738990282	-0.8144569130
C10	2.4615530445	-5.6791291711	-0.9820477021
H11	1.9225335657	-3.7263469883	-1.7550038900
C12	-0.8118825487	-8.4541976420	1.4385979850
C13	-1.1852077025	-9.4120228221	2.4126465546
C14	0.3564614104	-7.7089817539	1.5292696037
C15	-0.4270325863	-9.5537931835	3.5532662836
C16	1.1423247976	-7.8268719678	2.7399465251
C17	0.7220440927	-8.7390034741	3.7706032781
C18	2.9114780516	-7.9004082433	-0.0290740900
C19	3.7439232813	-5.7248041692	-1.6017955169
C20	4.1454918966	-7.9162366978	-0.6491533481
C21	4.5722761658	-6.8163412319	-1.4377076191
H22	2.5930042131	-8.7519932139	0.5598697375
H23	4.7938675447	-8.7793723699	-0.5376705271
H24	4.0517852043	-4.8853493486	-2.2178563457
H25	5.5454710929	-6.8425752721	-1.9166893362
H26	-0.7112485997	-10.2748048425	4.3134001754
H27	-2.0772390396	-10.0043766659	2.2449637465
C28	1.4483299433	-8.7953700603	4.9959189855
C29	2.2915572346	-7.0187226911	2.9951304641
C30	2.5531134248	-7.9946048714	5.2055932103
C31	2.9777590315	-7.1031444401	4.1901637582
H32	3.8373410441	-6.4641201908	4.3623162198
H33	2.6183524665	-6.3101081356	2.2483714127
H34	1.1124149534	-9.4838834989	5.7657224574
H35	3.0953518183	-8.0434534294	6.1439867258
O36	-3.5486237250	-6.6357085624	1.7523639163
O37	-4.0187176526	-4.0829836152	-3.7467051061
Rh38	-4.5187775557	-6.9590414862	-1.4908912579
C39	-5.6511076043	-7.9464409755	-3.1325986009
C40	-5.6631931545	-9.4407096652	-2.8884440396
C41	-5.8877944381	-9.8401069718	-1.4089118553
C42	-5.2334248526	-8.8748380967	-0.4303853590
C43	-5.8698424073	-7.7792294261	0.1521838625
C44	-7.2828057518	-7.3073127605	-0.1277171486
C45	-7.6661623283	-7.2989334527	-1.6303141769
C46	-6.4943208204	-6.9824424037	-2.5526927636
H47	-6.4272564129	-9.9120326813	-3.5282963684
H48	-4.6987120805	-9.8341427914	-3.2280993783
H49	-6.9584606561	-9.9133169796	-1.1890274543
H50	-5.4727955852	-10.8412908840	-1.2483352126
H51	-7.9996480157	-7.9218066589	0.4398897615
H52	-7.3773203112	-6.2914083946	0.2725100017
H53	-8.1002737855	-8.2625102482	-1.9199358614
H54	-8.4525277711	-6.5530157381	-1.7899074460
H55	-6.5423903916	-6.0156570237	-3.0526665813
H56	-5.1422592395	-7.6560100789	-4.0449886855
H57	-5.4084071447	-7.3471566496	1.0377745781
H58	-4.3046396499	-9.2199324655	0.0211517919
O59	-3.3094786362	-6.2142260137	-4.8535817785
P60	-3.4478959798	-5.6066526758	-3.1980232801
O61	-1.7640040408	-5.4316625010	-2.8227731200
C62	-2.5406412034	-7.3960981432	-5.0491275374
C63	-1.1633446417	-7.4140546360	-4.8268538620
C64	-3.2528440263	-8.5193222994	-5.5306749785

C65	-0.5256257942	-8.7122353877	-4.8227455665
C66	-2.6160257913	-9.7314836269	-5.6599349396
H67	-4.2859746057	-8.3873494441	-5.8291039607
C68	-1.2613198220	-9.8744656982	-5.2489114405
H69	-3.1423670332	-10.5932679406	-6.0573052147
C70	-0.7885714606	-5.1355750169	-3.8215218993
C71	-0.2158539918	-3.8464475360	-3.7766153690
C72	-0.4023261604	-6.1293464983	-4.7116773884
C73	0.8470312038	-3.5625867433	-4.6016295140
C74	0.6871682256	-5.8171749705	-5.6140925525
C75	1.3406009709	-4.5364492304	-5.5127230210
C76	0.8111088653	-8.8999363777	-4.3622017886
C77	-0.6266927177	-11.1489618732	-5.2436811450
C78	1.3893298234	-10.1549378544	-4.3453115758
C79	0.6724266130	-11.2907722235	-4.8018485362
H80	1.3681398974	-8.0428800016	-4.0034453458
H81	2.4017390612	-10.2745466142	-3.9736254838
H82	-1.1927510481	-12.0117497189	-5.5824473076
H83	1.1452032683	-12.2671466084	-4.7921701730
H84	1.3131653771	-2.5828315084	-4.5685878685
H85	-0.5987527665	-3.1076204683	-3.0837499452
C86	2.4558644159	-4.2465541883	-6.3499409025
C87	1.1439319584	-6.7093252961	-6.6305978928
C88	2.9028516369	-5.1591433707	-7.2818303798
C89	2.2238665370	-6.3936935597	-7.4323235907
H90	2.5508028490	-7.0963978227	-8.1919293153
H91	0.6363528671	-7.6516919247	-6.7804686803
H92	2.9417790217	-3.2809486987	-6.2448490989
H93	3.7552649346	-4.9295503346	-7.9125114737
C94	-1.8909563618	-1.2886364328	5.9163551503
N95	-1.9089969358	-2.3365197688	5.0358977122
O96	-2.7296622354	-1.1279918552	6.8406208379
H97	-1.2183780239	-2.3053201117	4.2826049207
C98	1.3920878427	1.5120387400	5.6017759089
C99	0.3756403370	1.5542690380	4.6462725923
C100	-0.7177681542	0.6719144285	4.7096670650
C101	-0.7689722826	-0.2895274711	5.7452658284
C102	0.2393038437	-0.2978768510	6.7231859770
C103	1.3177887030	0.5883567052	6.6516821620
H104	2.2207516746	2.2105669687	5.5440790976
H105	0.4027145227	2.2703415852	3.8337949463
H106	0.1790462500	-1.0170040998	7.5323358841
H107	2.0886190511	0.5629612011	7.4151837082
C108	-1.7321074348	0.7933828478	3.6102246206
N109	-3.0255063710	0.4592301139	3.9243136890
O110	-1.3822963016	1.1747828537	2.4637973019
H111	-3.2392893322	0.2873471037	4.8993619269
C112	-6.2622585959	-0.4243780454	1.3491620119
C113	-5.1987032721	0.3476668719	0.8708469424
C114	-4.1173853573	0.6776917215	1.6963095558
C115	-4.0983212983	0.2128890072	3.0236454702
C116	-5.1712323306	-0.5581384346	3.5108956050
C117	-6.2454592581	-0.8703906125	2.6775913261
H118	-7.0967226540	-0.6695482059	0.7003660355
H119	-5.2053140907	0.7056634700	-0.1537476557
H120	-3.2951796652	1.2716251176	1.3274076774
H121	-5.1536097118	-0.9181814304	4.5357185122
H122	-7.0671852791	-1.4637156122	3.0661124758
C123	-0.5807367159	-0.8340111320	-0.4320556357
N124	-1.5863994857	-1.2991353503	0.3613298959
O125	-0.5254059311	-1.0301414586	-1.6773575539
H126	-1.4527115614	-1.1487306615	1.3606528932
C127	2.3960045180	1.8659347201	1.1904577988
C128	2.1044333578	0.7087728805	1.9141671941
C129	1.1324735018	-0.2150323091	1.4760036464
C130	0.4641961549	0.0297232126	0.2435612023
C131	0.8094152066	1.1755230320	-0.4926960044
C132	1.7414579098	2.1016235325	-0.0207241289

H133	3.1231943480	2.5747293418	1.5722224584
H134	2.5912896075	0.5519874595	2.8702991175
H135	0.3197549595	1.3311122677	-1.4465872000
H136	1.9549895523	2.9954136394	-0.5968302195
C137	0.8177903647	-1.3436907108	2.4118798274
N138	1.8685556139	-1.9413759967	3.0496362333
O139	-0.3699621903	-1.7025045234	2.6791335230
H140	2.8057000760	-1.6492912476	2.8099720928
C141	1.1647239525	-4.5999414205	6.2731808305
C142	2.0276584581	-3.5099830628	6.4374812793
C143	2.2898650852	-2.6491555966	5.3650345411
C144	1.6926220734	-2.8876749265	4.1196002297
C145	0.8772789388	-4.0119285447	3.9366221308
C146	0.6030076499	-4.8538319609	5.0182090025
H147	0.9434520901	-5.2522084150	7.1109717509
H148	2.4818320350	-3.3149834786	7.4035234555
H149	2.9140739751	-1.7733368714	5.5055399756
H150	0.4559887329	-4.2097843737	2.9591162219
H151	-0.0402927677	-5.7140215715	4.8793794689
C152	-2.9382335786	-6.7281741805	3.1297419668
H153	-3.2830680174	-7.6889699404	3.5161305996
H154	-1.8563010336	-6.7464235087	3.0196768743
C155	-3.8690720815	-3.5930917987	5.9322447238
C156	-4.6720999390	-4.7368025763	5.8619810150
C157	-4.4200716321	-5.7445862776	4.9258279779
C158	-3.3514046574	-5.6005498435	4.0254955030
C159	-2.5703759171	-4.4385781489	4.0637982810
C160	-2.8011829424	-3.4373224826	5.0237974093
H161	-4.0416713399	-2.8371745528	6.6837592722
H162	-5.4896271468	-4.8473673738	6.5669443396
H163	-5.0239990831	-6.6471195833	4.9131164815
H164	-1.7570954484	-4.3277377474	3.3572432428
C165	-4.8675809639	-3.1803070522	-2.9033424022
H166	-4.8425816681	-2.2557878986	-3.4819523285
H167	-5.8875097088	-3.5765313079	-2.9059310101
C168	-3.3519595997	-2.7408644307	1.0861325612
C169	-4.4891193244	-3.5079780280	0.8628827836
C170	-4.9928839323	-3.6453776677	-0.4366465080
C171	-4.3445873190	-3.0071385317	-1.5078365114
C172	-3.1947585946	-2.2305173695	-1.2857696689
C173	-2.6960953049	-2.0940358699	0.0189729376
H174	-2.9702762490	-2.6231333545	2.0908912016
H175	-4.9783917545	-3.9939374949	1.6979003660
H176	-5.8969545209	-4.2199796568	-0.6170551545
H177	-2.6931637291	-1.7355761522	-2.1064342667

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"Combinatorial and Supramolecular Approaches to Monodentate Phosphorus-Ligands for Transition Metal Catalyzed Asymmetric Reactions"

SUMMARY

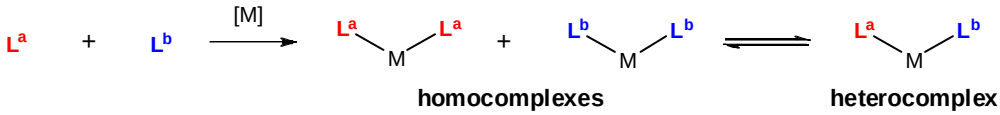
In recent years, monodentate phosphorus ligands (*e.g.* phosphites, phosphonites, phosphoramidites and phosphinamines) have held the stage in asymmetric catalysis.[1] In addition to their outstanding activity and selectivity, comparable or even superior to those of bidentate ligands, the convenient, fast and practical preparation from commercially available materials underlines their potential for industrial applications. Furthermore, the modular nature of all these ligands allows the synthesis of a variety of representatives, thereby making a combinatorial approach possible.[2]

My PhD research project deals with the synthesis of libraries of new chiral monodentate *P*-ligands and their screening in asymmetric transition metal-catalyzed reactions through two innovative approaches:

- ✓ combination of binaphthol-derived phosphites and C_1-symmetric phosphinamines for the selective generation of heteroleptic catalysts in Rh- and Pd-mediated reactions (*Ligand Combination Approach*, *Research line 1*);
- ✓ supramolecular ligand-ligand interactions for highly selective transition metal catalysis (*Supramolecular Approach*, *Research line 2*).

Research line 1

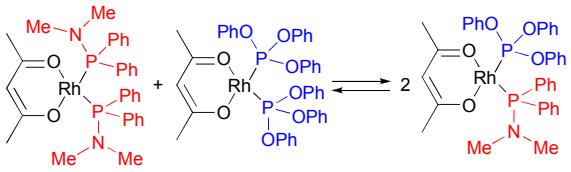
In 2002-3, the groups of Reetz and Feringa independently used a binary mixture of chiral monodentate *P*-ligands in several asymmetric rhodium-catalyzed reactions. By mixing two different ligands (L^a and L^b) in the presence of a transition metal **[M]**, three species can be formed: **[M]**L^aL^a, **[M]**L^bL^b (homocomplexes) and **[M]**L^aL^b (heterocomplex). The heterocomplex is often more reactive and more (regio-, diastereo-, enantio-) selective than either of the two homocomplexes. Moreover, under thermodynamic control the heterocomplex : homocomplexes ratios usually exceed the statistical value (2 :1 :1).



Scheme 1. The concept of using mixtures of chiral monodentate ligands

The ideal case would constitute an equilibrium completely in favor of the heterocomplex **[M]**L^aL^b, because a single well-defined catalyst would then exist in the reaction mixture and the undesired competition of the less selective homocomplexes would be avoided.[3]

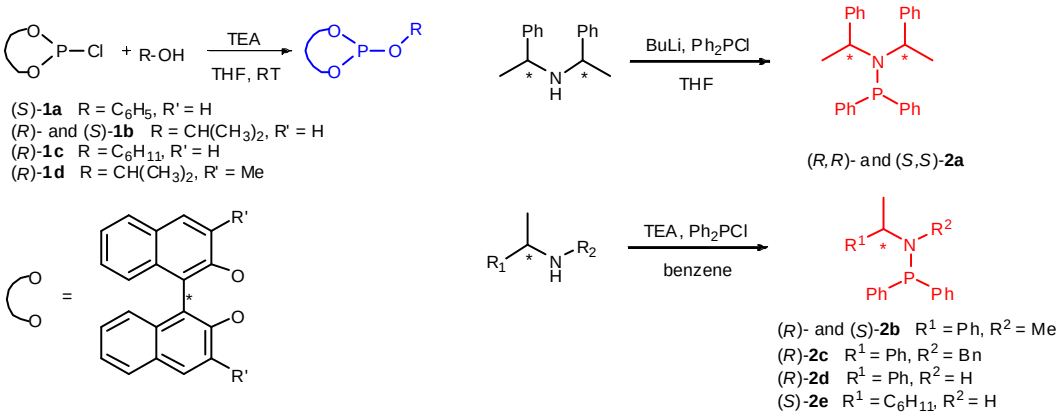
We were intrigued by the remarkable selectivities reported for the mixtures of chiral ligands (binol-derived phosphites, phosphonites and phosphoramidites) with achiral phosphines.[4] In particular, the 1:1 mixture of a chiral phosphite with an achiral phosphine was reported to induce reversal of the enantioselectivity in the Rh-catalysed hydrogenation of *N*-acetamido acrylate (compared to the chiral phosphite alone). The only possible explanation for this peculiar behaviour is the selective formation of the phosphite-phosphine Rh-heterocomplex, favoured by electronically matching one σ-donor ligand (phosphine) and one π-acceptor ligand (phosphite). As enantiomerically pure chiral phosphines are not easy to synthesize, we were wondering whether the phosphine ligands could be substituted by other σ-donor phosphorus ligands still retaining the thermodynamic preference for the formation of the heterocomplex. For this reason, we turned our attention to chiral phosphinamines, which are easy to prepare enantiomerically pure, and have electronic properties similar to those of phosphines.[5] DFT calculations showed that the phosphite-phosphinamine rhodium heterocomplex is more stable than the two homocomplexes by 11.29 kcal/mol (Scheme 2).



Scheme 2 DFT calculations at the B3LYP/SDD level of theory on the isodesmic reaction of phosphite-phosphinamine heterocomplex

We synthesized a library of monodentate chiral phosphites **1a-d** by reacting enantiopure BINOL-PCl with different chiral and achiral alcohols. Monodentate chiral phosphinamines **2a-e** were prepared by reaction of Ph_2PCl with a number of C_2-symmetric secondary amines and C_1-symmetric secondary and primary amines. Complexation studies were performed by means of ^{31}P-NMR, using $Rh(acac)(C_2H_4)_2$ as the rhodium source. When C_1-symmetric phosphinamine ligands were employed, the *cis*-heterocomplexes were formed with selectivity ranging from moderate (70%) to excellent (≥ 99%).

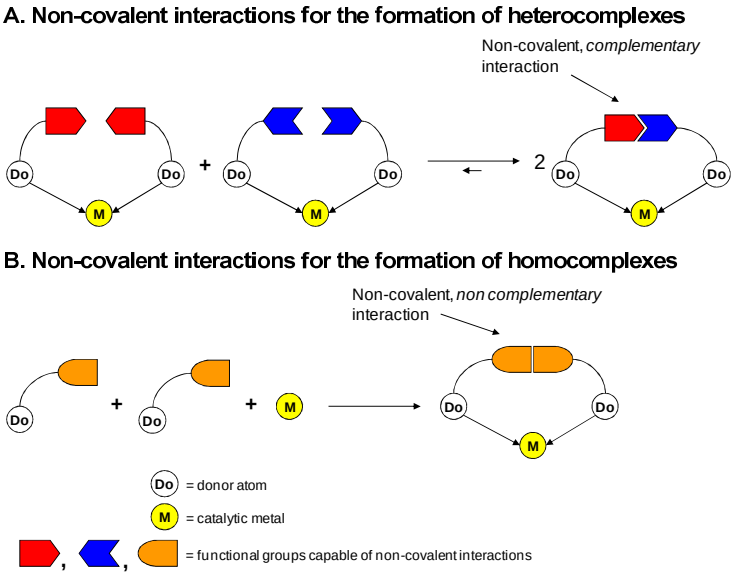
The homo- and heterocombinations of phosphites and C_1-symmetric phosphinamines were then screened in the rhodium-catalyzed hydrogenation of methyl 2-acetamidoacrylate. Remarkably, the 1:1 combination of a BINOL-derived phosphite and a phosphinamine induced reversal of the enantioselectivity, compared both to the phosphite and the phosphinamine alone. This heterocombination induced a peculiar stereochemical outcome also in the palladium-catalyzed asymmetric allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate.



Scheme 3. Synthesis of binaphthol monodentate phosphites and *C-1/C-2*-symmetric monodentate aminophosphines.

Research line 2

In recent years, *non-covalent* interactions appeared as a clever way to achieve the exclusive formation of the heteroleptic complexes from mixtures of monodentate ligands.[6] To this end, *supramolecular ligands* capable of *complementary interactions* (Scheme 3 A) are required, so that attractive interactions take place only between different ligands.

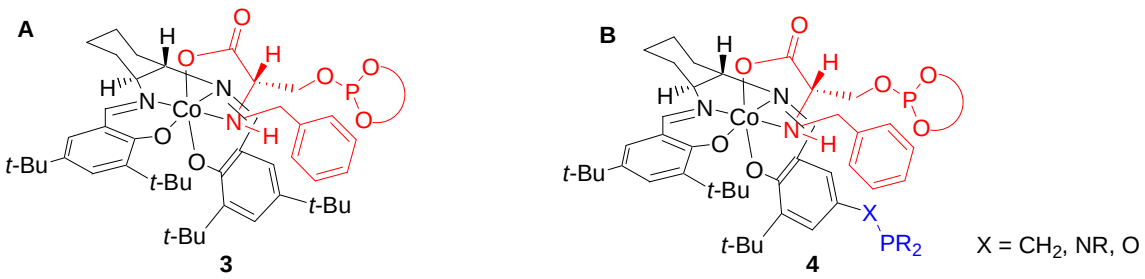


Scheme 3 Schematic representation of supramolecular bidentate ligands formed by complementary (A) and non-complementary interactions (B).

The heterocomplexes formed in this way are expected to have reduced degrees of freedom[7] compared to the complexes of normal monodentate ligands, and thus supramolecular ligands somehow resemble traditional bidentate ligands. According to this analogy, they are often referred to as *supramolecular*

bidentate ligands or *self-assembled ligands*, thanks to their ability to spontaneously form bidentate systems in solution. These terms also apply to those supramolecular ligands that are only capable of *non-complementary* interactions (Scheme 3 B):[6] indeed these systems are still capable of forming rigid and conformationally restricted complexes, although they cannot selectively form heterocomplexes when used in a mixture, which quite reduces their "combinatorial appeal".

Prompted by the studies of Prof. Reek and co-workers on the synthesis of supramolecular bidentate heterocomplexes through complementary interactions (*e.g.* coordinative bondings)[8] and by the efficient resolution strategy of racemic *N*-benzyl α-amino acids (*N*-Bn-AA) by liquid-liquid extraction using a chiral salen–cobalt(III) complex as enantioselective receptor, accomplished in our laboratories,[9] we decided to use the salen-cobalt(III)-*N*-benzyl-L-serine complex as a chiral platform for the preparation of new families of supramolecular mono- and bi-dentate P-ligands (Scheme 4 A and B).[10]



Scheme 4 (A) Monodentate (salen)cobalt(III)(*N*-Bn-Ser) phosphites, (B) Bidentate hybrid P-ligands suitable for the formation of transition metal-catalysts by the supramolecular approach.

The salen-cobalt(III)-*N*-Bn-AA complexes, in fact, possess a rigid framework with the salen ligand in a cis-β-folded arrangement around the octahedral cobalt ion. The remaining two *cis* coordination sites are occupied by the *N*-benzyl α-amino acid, which is thus accommodated in the “binding pocket” of the chiral cobalt complex. [9b]

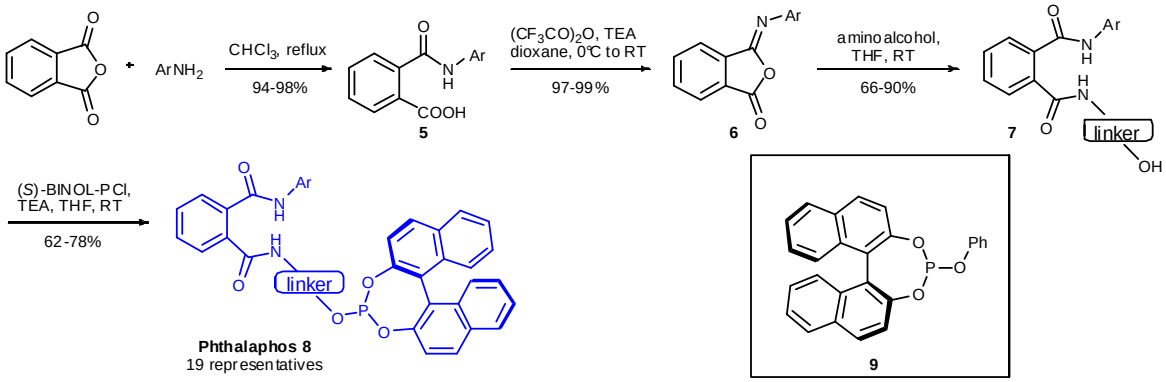
Ligands **3** were synthesized in good yields starting from the symmetrical tetra-*t*-butyl-salen which was transformed into the corresponding cobalt(III) acetate complex, and the acetate ion was exchanged with *N*-benzyl-L-serine. In the case of symmetric salen backbone, the complex was obtained pure in high yield and the phosphite moieties were then introduced by reaction with different diol-derived chlorophosphite. In the case of the supramolecular bidentate ligands **4,** the unsymmetrical hydroxymethyl-containing salen afforded the corresponding cobalt(III) acetate complex as a mixture of two inseparable diastereoisomers.

Complexation of monodentate ligands **3** to rhodium(I) was studied by ^{31}P-NMR spectroscopy, which showed the formation of the desired Rh-complexes. The reactivity of supramolecular monodentate P-

ligands was investigated in two Pd-catalyzed-allylic alkylation on (*E*)-1,3-diphenylallyl acetate and Pd-catalized desymmetrization of meso-cyclopenten-2-ene-1,4-diol biscarbamate.

We are now exploring new synthetic pathways to obtain the unsymmetrical (*S*,*S*)-salen-ligand and the corresponding unsymmetrical (*S*,*S*)-salen-cobalt(III)-*N*-Bn-L-serine bidentate P-ligand in a pure diastereoisomeric fashion.

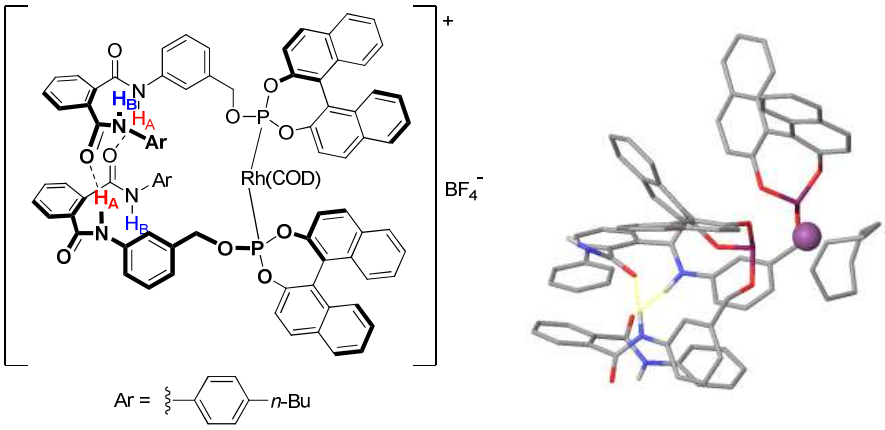
We have also investigated the design and synthesis of a novel class of chiral monodentate phosphite ligands, named *PhthalaPhos*, which contain a phthalic acid primary diamide moiety. Such phthalamidic group displays both donor and acceptor hydrogen bonding properties that, in principle, can give rise to supramolecular interactions both between the ligands and with the reaction substrate (Scheme 6).[11]



Scheme 5 Synthetic pathway for *PhthalaPhos* ligands

The pre-catalytic Rh complex of one of these ligands was fully characterized and studied by NMR, IR and mass spectroscopy, which confirmed the presence of hydrogen bonds between the coordinated ligands, and the formation of a supramolecular bidentate ligand.

The catalytic properties of these new ligands were assessed in the rhodium-catalyzed hydrogenation of benchmark olefins (*e.g.* methyl 2-acetoamidoacrylate and *N*-(1-phenylvinyl)acetamide), taking the known phosphite **9** as a touchstone. Four ligands gave *e.e.* values higher than 97% with methyl 2-acetoamidoacrylate as substrate, and six reached the same level of performance with *N*-(1-phenylvinyl)acetamide. Remarkably, the reference ligand **9**, featuring the same BINOL phosphite moiety, gave only 84% and 90% *e.e.* respectively for the same substrates, thus suggesting that the phthalimide residue significantly influences the catalytic properties of these ligands.



Scheme 6. Supramolecular bidentate precatalyst [Rh(**4a**)$_2$(cod)]$^+$ and DFT calculated structure. Heteroatoms (N, O, P, Rh) are shown in black, carbon atoms in gray, and amide hydrogen atoms in light gray. For clarity, all hydrogen atoms bound to carbon are omitted.

Evaluation of the catalytic properties of the Phthalaphos ligands were also extended to the Rh-catalyzed hydrogenation of more challenging substrates of potential industrial interest, such as *N*-(3,4-dihydronaphthalen-1-yl)acetamide and (*E*)-methyl 2-(acetamidomethyl)-3-phenylacrylate. The results of this screening were quite variegated both in terms of activity and enantioselectivity, but the employment of a Phthalaphos ligand gave the highest *e.e.* value ever obtained on *N*-(3,4-dihydronaphthalen-1-yl)acetamide with phosphite ligands and the highest *e.e.* value ever obtained with (*E*)-methyl 2-(acetamidomethyl)-3-phenylacrylate.

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