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Grau de Química

Treball Final de Grau

P-Stereogenic ligands. Bibliographic and experimental studies.
Lligands P-estereogènics. Estudi bibliogràfic i experimental.

Helena Solé Àvila

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Dans la vie, rien n'est à craindre, tout est à comprendre. C'est maintenant le moment de comprendre davantage, afin de craindre moins.

Marie Curie

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REPORT

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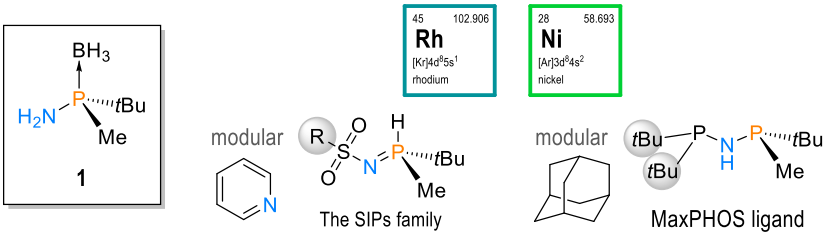
1. SUMMARY

The synthesis of chiral compounds has long been a primary goal in the field of catalytic asymmetric synthesis. The breakthrough of chiral ligands, able to induce excellent enantioselectivities in many processes, is in line with the measures taken to minimize the environmental risks in organic synthesis. Among them, P*-stereogenic phosphine ligands are proficient in inducing chirality to produce optically active compounds in a straightforward and atom-economic pathway.

On this matter, our group has synthesized building block **1**. This P-stereogenic aminophosphane is prone to providing air-stable chiral ligands by means of a NH/PH tautomeric equilibrium. The MaxPHOS ligand and the Secondary Iminophosphorane family of ligands (SIPs) are great examples of its versatility.

In this work, novel ligands for asymmetric catalysis have been developed starting from privileged intermediate **1**. The inspection of the recent literature assisted on the election of the appropriate modulation while conceiving these ligands.

Afterwards, the scope of application has been considered in the design of the respective catalysts. Thereby, their rhodium complexes have been prepared, whereas the incorporation of an inexpensive transition-metal, nickel, has been assessed.



Keywords: chiral ligands, P-stereogenic, asymmetric catalysis

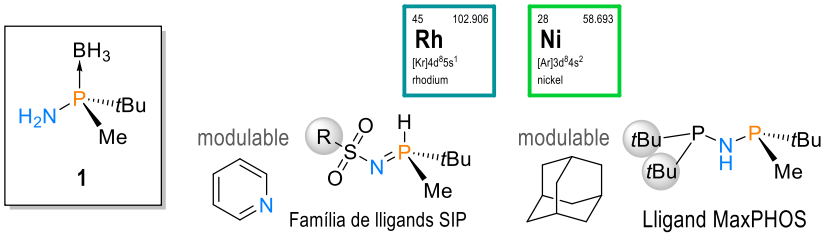
2. RESUM

La síntesi de compostos quirals és un dels objectius principals en el camp de la síntesi asimètrica catalítica. L'avanç que han suposat els lligands quirals, capaços d'induir excel·lents enantioselectivitats en molts processos, s'ajusta a les mesures adoptades per minimitzar els riscos ambientals en síntesi orgànica. Entre ells, les fosfines P-estereogèniques com a lligands són hàbils en induir quiralitat en la producció de compostos òpticament actius mitjançant una via directa i econòmica.

En aquesta direcció, el nostre grup ha sintetitzat el compost **1**. Aquesta aminofosfina P-estereogènica proporciona lligands quirals estables a l'aire mitjançant un equilibri tautomèric NH/PH. El lligand MaxPHOS i la família de lligands SIP són bons exemples de la seva versatilitat.

En aquest treball, s'han dissenyat nous lligands per a la catàlisi asimètrica amb els avantatges que proporciona l'intermedi **1**. La inspecció de la literatura recent va ajudar a l'elecció de la modulació adequada durant el disseny d'aquests lligands.

Posteriorment, s'ha considerat el seu abast d'aplicació en el desenvolupament dels respectius catalitzadors. Per això, s'han preparat els seus complexos de rodi, mentre que s'ha valorat la incorporació d'un metall de transició més econòmic, el níquel.



Paraules clau: lligands quirals, P-estereogènic, catàlisi asimètrica

3. INTRODUCTION

3.1. ASYMMETRIC SYNTHESIS

Nowadays the widespread requirement for chiral compounds in optically active forms is in accordance with the rising interest to the minimization of human and ecological risks, a new viewpoint aimed to make the improvement compatible with environmental sustainability and savings of natural resources.[1] 'Green chemistry' was coined to define the design of new chemicals and processes that reduce or eliminate the use and generation of hazardous substances.[2,3]

In this regard, catalysis has become a useful tool to implement the green chemistry principles. Furthermore, catalytic asymmetric synthesis is one of the most efficient methods to furnish chiral compounds.[4] Among various asymmetric catalyses, great emphasis has been placed on transition-metal-catalysed reactions over the years; many catalyst systems of this kind have been developed and some have been successfully applied to the manufacturing of useful optically active compounds.[5]

Chirality transfer from the catalyst to the product constitutes one of the most general and appealing strategies in terms of atom economy and eco-friendly considerations.[6] Both enantioselectivity (*i.e.* enantiomeric excess [ee]), and catalytic efficiency are highly dependent on chiral ligands and metal centres.[7–9] Therefore, the design and synthesis of new chiral ligands is a very important research subject in this field.

Chiral phosphorous ligands remain a common target for the achievement of high activity and selectivity in asymmetric catalysis.[10] Consequently, much research effort has been devoted to developing a wide array of efficient phosphine ligands for a range of catalytic processes. The enantiomeric outcome of these ligands mainly arises from having stereogenic elements on the backbone. Nevertheless, chirality can also be located at the phosphorous atom.[11] This family of ligands are known as P-stereogenic or P-chirogenic, *i.e.*, those that contain phosphorus atoms bound to four different substituents.

Their ability of introducing chirality into many production processes has been remarkably developed in the asymmetric hydrogenation field. It is one of the most common, reliable, and

ecologically friendly industrial operations for the preparation of chiral compounds, such as drugs and crop-protecting chemicals. Research efforts in both academia and industry over the last decades[12,13] have enabled the development of myriad chiral transition metal-based coordination compounds, with rhodium in the lead, and mostly phosphorus-containing derivatives as ligands.[14] It is now amongst the most well-established transformations in asymmetric synthesis.

3.2. OVERVIEW OF P-STEREOGENIC LIGANDS REPORTED BY THE GROUP

Dedicated to the progress of asymmetric synthesis, our group has worked on the development of a large variety of chiral ligands for the past decade.

The exploration of new effective chiral ligands has been focused on enantiomerically pure phosphines and diphosphines containing stereogenic phosphorus centres, which have long been considered powerful structures for metal-based asymmetric homogeneous catalysis.

In particular, our approaches involve the preparation of optically pure aminophosphane-boranes and phosphinous acid-boranes through asymmetric synthesis in high yields. Their most characteristic feature is that they bear two different sized groups at the P atom, being the *tert*-butylmethyl combination the most successful until this date.

These P-stereogenic synthons proved to be suitable for the preparation of many significant ligands such as MaxPHOS, an excellent ligand for Rh-catalysed enantioselective hydrogenation[15] and asymmetric Pauson-Khand reactions;[16] the P-stereogenic Secondary Iminophosphoranes (SIPs) family, effective in [2+2+2] Rh-catalysed cycloadditions,[17] and more recently, the MaxPHOX ligands, an oxazoline-based line applied to the Ir-catalysed hydrogenation of imines[18,19] and cyclic enamides[20] (Figure 1).

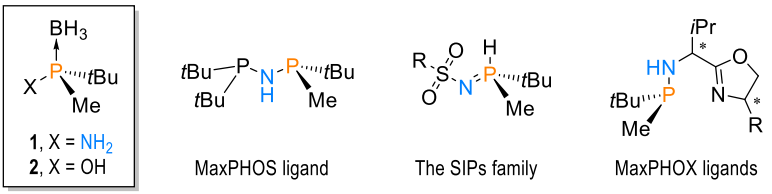


Figure 1. Outline of the aminophosphane-based ligands developed by the group.

Herein, we further research in ligand development, together with the application of our ligand toolbox for the preparation of optically pure valuable products.

4. OBJECTIVES

The aim of this work is to innovate in structural modifications of both MaxPHOS and SIPs ligands with the purpose of enhancing the previous results in asymmetric catalysis.

To do so, the first objective was to conduct a bibliographic research focused on the ligand structure. It is of great importance to evaluate which backbones have been the most successful in enantioselective hydrogenation. The effectiveness of a bulkier phosphine substituent, such as adamantyl, will be analysed, as it is considered a promising candidate to be incorporated into the MaxPHOS ligand scaffold.

On the other hand, with the aim of expanding the range of metals with a greener approach, another bibliographic objective was to study the coordination chemistry of nickel (0) with P-stereogenic ligands. Nickel could serve as an inexpensive alternative to precious metals, such as rhodium and iridium, in catalytic transformations.

The second objective was the synthesis of the adamantane containing analogue of the MaxPHOS ligand and determine its efficiency in asymmetric hydrogenation with challenging substrates.

Furthermore, fine-tuning the SIP ligand would modulate both its selectivity and coordination modes. Therefore, the preparation of novel SIP ligands became the third objective, along with exploring the synthesis of their corresponding nickel complexes.

5. RETROSPECTIVE IN CATALYST DESIGN FOR ASYMMETRIC SYNTHESIS

5.1. CHIRAL DIPHOSPHINE LIGANDS IN Rh-CATALYSED ASYMMETRIC HYDROGENATION

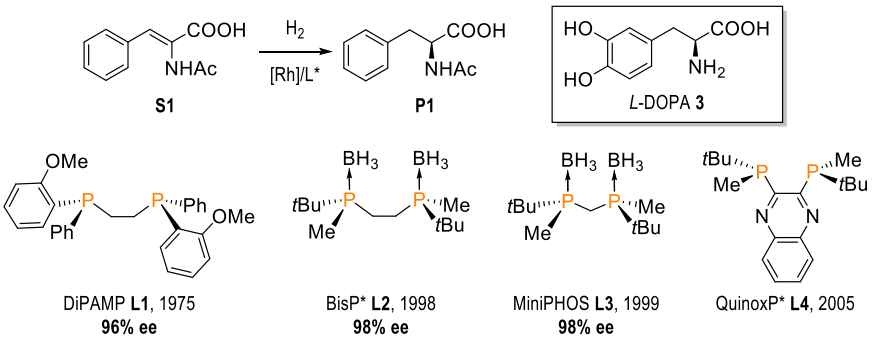
The key element of asymmetric synthesis is asymmetric induction, which can be internal, relayed or external. In the latter, chirality is generally introduced at the transition state by a catalyst bearing a chiral ligand. The structure of the chiral ligand and, in particular, chiral diphosphines play a critical role.[21] This was first illustrated by Knowles and co-workers who reported the ligand DiPAMP (Scheme 1).[22] It is the most well-known P-stereogenic diphosphine, and gave

outstanding enantioselectivities in a model reaction for the efficient synthesis of *L*-DOPA, a drug for Parkinson's treatment,[23] and many other substrates.[24,25] This work is considered a milestone in the field of enantioselective homogeneous catalysis.[26] William S. Knowles was awarded, together with Ryoji Noyori and Barry Sharpless, the Nobel Prize in Chemistry in 2001 for his work on asymmetric catalysis.[21]

In 1998, Imamoto *et al.* developed a new class of P-chirogenic phosphines, named BisP*,[27] inspired in the backbone structure of DiPAMP. A key characteristic of these ligands is that they bear two different-sized alkyl groups attached to the P atom, a methyl and a bulky alkyl group. Upon coordination to transition metals, they form five-membered C_2-symmetric rings. This strong steric dissymmetry was revealed to be exceptionally beneficial for hydrogenation reactions. The downside is that due to their trialkyl nature, the ligands are very electron-donating and therefore extremely sensitive to oxidation, hence protection with borane is necessary.

Encouraged by the exciting results of BisP* ligands, a simplified structure was created, the methylene-bridged analogues, which were called MiniPHOS (Scheme 1).[28] Ever since, the MiniPHOS analogues have found extensive application in many asymmetric catalytic reactions.[29–31] Among them, they were active towards Rh-catalysed hydrogenation of model compounds, achieving excellent enantiomeric excesses of the hydrogenated products.[32]

Following up on this, in 2005 a more rigid type of diphosphines denominated QuinoxP* was designed (Scheme 1).[33,34] Great enantioselectivities were obtained in the asymmetric hydrogenation of commonly employed substrates. Remarkably, the QuinoxP* analogues were air-stable, presumably due to the significant electron-withdrawing character of the quinoxaline backbone, which reduces the electron density at the phosphorus atoms.



Scheme 1. P-Stereogenic diphosphine ligands and their application in the synthesis of *L*-DOPA.

5.2. THE ADAMANTYL MOIETY IN ASYMMETRIC HYDROGENATION

The term 'diamondoid' originated from the early attempts to synthesize diamonds carried out by Decker in 1924.[35] It was used again in the 1930s in synthetic approaches towards this type of compounds.[36] The structure of the smallest diamondoid, adamantane (ADH),[37] was first discovered as a natural constituent of fossil fuel. The compound was finally synthetized by Prelog in 1941,[38,39] however it was not until 20 years later that a more effective synthesis was reported.[40]

This adamantane robust synthesis triggered great interest, especially in the 1960s, and pave the way to the incorporation of different functional groups to the ADH core. Since then, the adamantane scaffold has shown broad application range, including medicinal chemistry and drug development.[41,42] Notably within the context of this work, its application to ligand design and asymmetric hydrogenation reactions mediated by their catalytic systems are highlighted.

5.2.1. The influence of the adamantane group in diphosphine ligands

Fine-tuning the catalytic activity of a given organometallic catalyst by changing its structural and chemical features, has become an essential strategy in ligand design. In this regard, adamantane offers special properties such as inert hydrocarbon reactivity, rigidity, symmetry, and steric hindrance. Therefore, the adamantyl substituent (Ad) has become rather conventional in organometallic catalysis, exhibiting a great deal of success across several reaction types.[43] Adamantane is believed to play a crucial role at various key stages of the catalytic cycle, on account of its large steric bulk and electron-donating abilities.

The adamantane analogues of BisP*[27,32] and QuinoxP*[44] (Figure 2) proved to be very effective in Rh-catalysed asymmetric hydrogenation, furnishing the hydrogenated product of the methyl ester of *L*-DOPA's model substrate in up to >99.9% ee. However, the adamantyl analogue of MiniPHOS found its application in asymmetric conjugate additions,[45] substantiating the broad range of applications of the adamantane moiety.

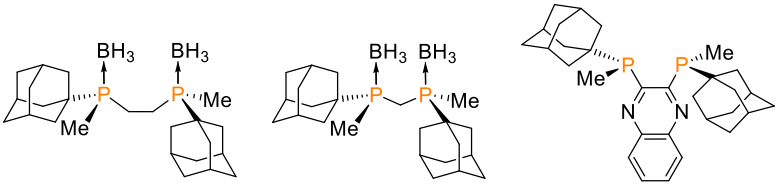


Figure 2. Adamantane containing diphosphine ligands for asymmetric synthesis.

5.2.2. Study of ligand symmetry and hindrance

Detailed mechanistic studies of the elementary steps in asymmetric hydrogenation have given rise to a practical predictive model, based on quadrant diagrams, which has been used to enlighten the performance of ligands.

The previously presented diphosphine ligands are examples of C_2-symmetry, being the most studied systems.[24,46] A key factor that arouse the use of such ligands with C_2-symmetry was the reduced number of intermediates and transition states during the catalytic cycles, that simplified their study. In fact, their excellent catalytic results created a trend,[26] delaying the widespread development of less symmetric analogues, C_1-symmetrical diphosphine ligands and their corresponding catalysts (Figure 3).[47–49] These contemporary C_1-symmetric ligands enable to control the coordination mode by changing the steric and electronic properties of the phosphino moiety in a modular approach. Moreover, a wider range of ligand possibilities is allowed since each phosphorus atom can be modified independently.[50,51]

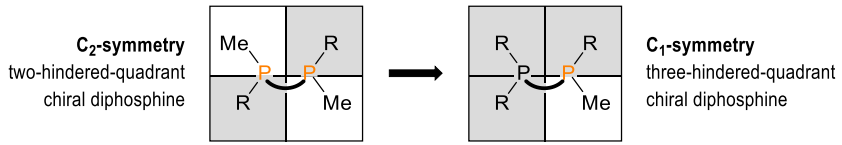
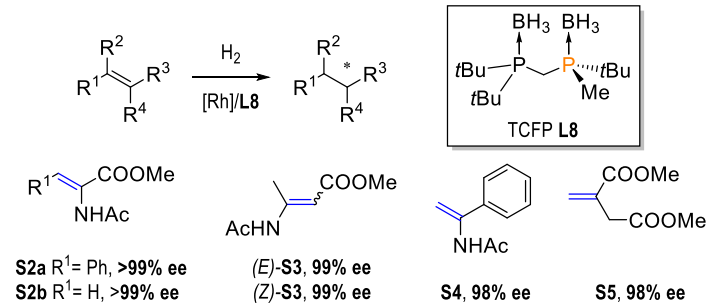


Figure 3. Quadrant diagrams for diphosphine ligands.

The use of C_1-symmetry with a three-hindered-quadrant P-chirogenic diphosphine ligand was first demonstrated by the TrichickenfootPHOS (TCFP) ligand **L8**,[52,53] which improved the enantioselectivities obtained by other C_2-symmetric ligands (Figure 4),[54] and has been applied to a broad range of substrates.[55–57]



S2a R^1= Ph, **>99% ee** (*E*)-**S3**, **99% ee**
S2b R^1= H, **>99% ee** (*Z*)-**S3**, **99% ee** **S4**, **98% ee** **S5**, **98% ee**

Figure 4. **L8** and its performance on the Rh-catalysed hydrogenation of functionalized alkenes.

The complex was also tested for the enantioselective hydrogenation of an intermediate towards the synthesis of pregabalin,[58] a pharmaceutical used to treat epilepsy and neuropathic pain,[59] and its performance was impressive. Despite that, **L8** oxidises in air and also requires chiral HPLC separation in its synthetic approach, fact that limits large scale production.

Recently, the adamantyl substituent has been studied by computational design and experimental evaluations in C_1-symmetric three-hindered-quadrant P* diphosphine ligands.[60] This strategy demonstrated that its introduction generates great enantioselectivities.

In the mechanism of Rh-catalysed asymmetric hydrogenation of olefins,[61] the sterically demanding adamantyl groups cause heavy steric hindrance to the substrate when it approaches the metal centre. Consequently, the substrate, with its double bond and an additional donor atom, is directed to the open quadrant (Figure 5) and chelates to the rhodium atom during the catalytic cycle. Thereby, the asymmetry of the phosphorous atom controls the preferable side of the double bond plane and the chirality is induced.[62]

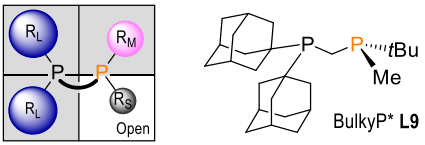


Figure 5. Quadrant diagram for the enantioselection imposed by the BulkyP* ligand.

These mechanistic studies lead to the production of the BulkyP* ligand **L9** (Figure 5).[63] It has become the latest breakthrough in the field, providing excellent enantioselectivities for the asymmetric hydrogenation of a wide range of compounds (Figure 6). In addition, it is synthesized as a crystalline solid that can be readily handled in air. If we compare the bulkiness of the phosphorous substituents in quadrants, it can be observed that the adamantane moieties form an effective shield and, consequently, the phosphorous atom is protected.

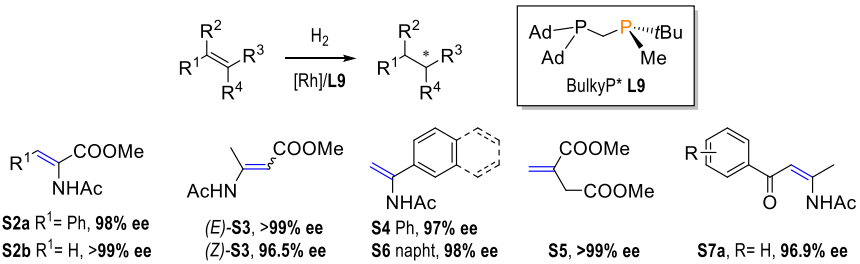


Figure 6. Hydrogenation of functionalized alkenes with the Rh(I) complex of **L9**.

5.3. OTHER Ni-BASED *P,N* AND *P,O* CATALYSTS FOR ASYMMETRIC SYNTHESIS

Even though these diphosphine containing transition-metal catalysts are routinely used in the preparation of chiral fine chemicals, the availability of even more active and selective ligands can allow lower generation of metal residues and organic solvent wastes.

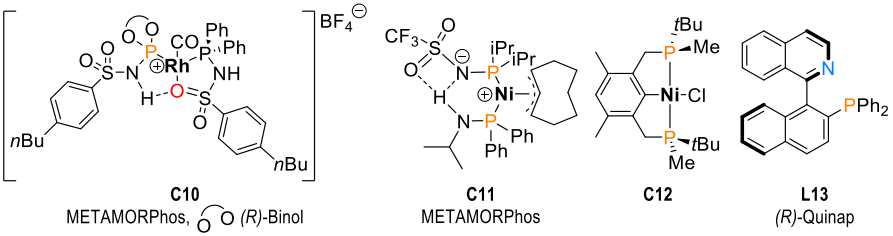
In this context, some novelty in the field consists in the use of heterodonor ligands with P and other coordinating atoms, such as N or O. Other promising approaches concern the use of more economical metals as substitutes to precious metals to implement in a 'greener' direction. Nickel stands out particularly for generating highly active catalysts for many transformations.[64]

A great example are the METAMORPhos bidentate ligands. They exhibit interesting coordination behaviour, as they coordinate in P and P,O chelating forms. This heterobidentate adaptative character showed excellent activity and selectivity (up to 99% ee) in the hydrogenation of **S2b** with the *P,O* coordinated catalysts **C10** (Figure 7).[65] Nonetheless, METAMORPhos can also chelate through the P atoms to act as a pincer ligand in the presence of a nickel precatalyst and generate complex **C11**, which is highly selective for the dimerization of ethylene to 1-butene.[66]

This kind of catalysts has received widespread attention over the last few years. A Ni-*P,C,P*-chelated pincer chiral catalyst **C12**, possessing P-stereogenic centres, has been recently applied to the asymmetric aza-Michael reactions with unprecedented results.[67]

The presence of nickel as an economical and effective transition-metal can also be found in combination with *P,N*-chelating pyridine-containing ligands, such as the Quinap ligand **L13**. A highly reactive azanickelacycle can be generated providing a new synthetic route in enantioselective annulation reactions.[68]

This high selectivity for many diverse asymmetric reactions is noteworthy, considering the market demand for such products. Thus, these outstanding results may perpetuate interest in the development of new generations of nickel catalysts.



C10 METAMORPhos, O O *(R)*-Binol **C11** METAMORPhos **C12** **L13** *(R)*-Quinap

Figure 7. Examples on several selective heterobidentate ligands and their corresponding Ni catalysts.

6. P-STEREOGENIC AMINOPHOSPHANES AS CHIRAL LIGANDS

6.1. NOVEL P-STEREOGENIC BUILDING BLOCK FOR LIGAND SYNTHESIS

Chiral phosphines have made a critical contribution to the achievement of high activity and selectivity in asymmetric catalysis through the years. Among these, P-stereogenic electron-rich alkylphosphines are highly proficient in many industrially relevant processes.[69]

The design of P-chirogenic synthons has become a common objective in the field. In this direction, our group has developed a novel building block: the borane-protected *tert*-butylmethylphosphanamine **1** (Figure 8). Compound **1** has the peculiarity of functioning either as an electrophilic synthon at the P atom or as a nucleophile at the appended nitrogen. Moreover, both enantiomers can be prepared in an optically pure form on a multigram scale in a three-step synthesis starting from cis-1-amino-2-indanol.[70–73] Inspired in Imamoto's work,[33] the ligands including a *tert*-butylmethylphosphine moiety are of great interest since a large steric bias is provided between the two substituents. Combined with a rigid backbone, appears to be fundamental to promote high selectivity in asymmetric catalysis.[74]

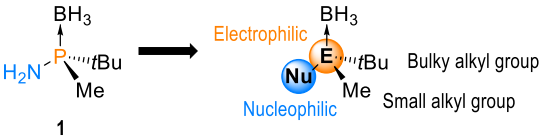
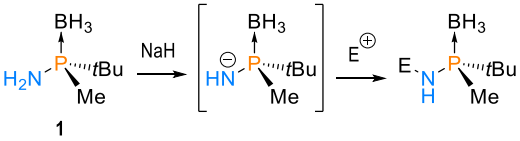


Figure 8. Characteristics of the amino P*-synthon.

Former members of the group noticed right away that the amino group in **1** in its neutral form was not nucleophilic enough due to the delocalization of the nitrogen's lone pair into the phosphorus atom. However, its anion can be generated by deprotonation with a strong base, which followed by treatment with electrophiles, yields the substituted aminophosphine (Scheme 2).



Scheme 2. Reaction of **1** with electrophiles.

This reactivity of the amino group has permitted further functionalization of the building block, emerging as a privileged intermediate for the construction of chiral ligands. As a result, we can have access to novel structures that preserve the original P-centred chirality.

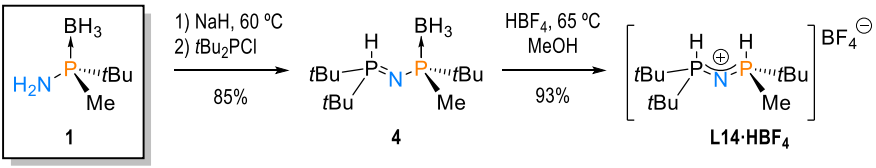
6.2. TAKING ADVANTAGE OF NH/PH TAUTOMERISM

Protection of the phosphorus free electron pair with a BH_3 unit is a recurring strategy in the synthesis of P-stereogenic compounds to deal with the important drawback of their sensitivity to oxidation.[76] However, metal complexation to achieve the corresponding catalyst requires a prior deprotection or isolation step, as only the free phosphine is capable to do so. Unfortunately, such procedure is not ideal for routine screening and scale-up.

For this reason, two different types of P-stereogenic ligands bearing building block **1** were synthesized by the group to overcome this limitation and provide air-stable ligands.

6.2.1. MaxPHOS ligand

The potential of the P-stereogenic aminophosphane **1** was first demonstrated by the synthesis of the ligand MaxPHOS (Scheme 3).[77] When *t*Bu$_2$PCl was used as the electrophile the monoprotected iminophosphorane **4** was obtained. The exclusive presence of **4** as its P-H tautomer prevented the oxidation at the phosphorus atom, that in combination with the bulky *tert*-butyl groups on the P atom makes this aminophosphane not as likely to undergo hydrolysis.[78]



Scheme 3. Synthesis of the MaxPHOS salt **L14·HBF$_4$**.

Protonation turned **4** into the MaxPHOS·HBF$_4$ salt **L14·HBF4**, a unique air-stable crystalline solid becoming an excellent precursor for metal coordination. The existence of the NH bridge between the two P-centres in **L14·HBF$_4$** allows the NH/PH tautomerism to take place. The overall positive charge is distributed on both P atoms, thus, leading to the stable PH form (Figure 9), which was confirmed by X-ray.[15] In contrast, deprotonation of the salt with *n*-BuLi under anhydrous conditions furnished an air-sensitive free ligand **L14**, where de NH tautomer was predominant.

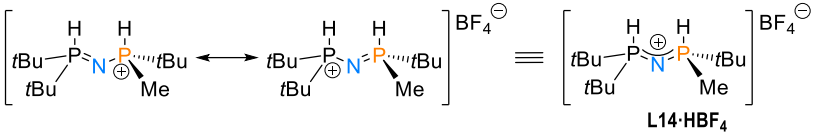
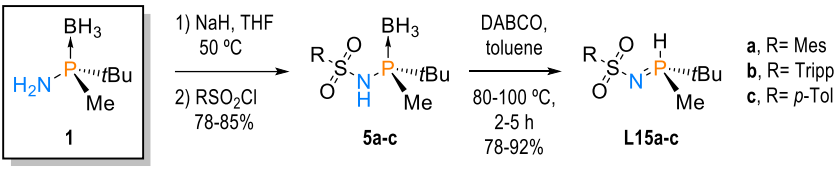


Figure 9. Resonance descriptors of MaxPHOS·HBF_4.

6.2.2. P-Stereogenic Secondary Iminophosphorane ligands (SIPs)

The privileged intermediate **1** was also considered to be highly suitable for the synthesis of electron-rich P*-sulfonyl iminophosphorane ligands (SIP) because it could benefit from NH/PH tautomerism. Starting from **1**, anion formation with sodium hydride and subsequent reaction with sulfonylchlorides provided the corresponding borane-protected phosphinosulfonamides **5** (Scheme 4).[17] It is noteworthy that bulky sulfonylchlorides provided the desired products in high yields. The treatment with amine allows the deprotection of the borane group, readily affording the phosphino arylsulfonamides in excellent yields.



Scheme 4. Synthesis of SIP ligands.

In contrast with other similar ligands reported[65,79] where the prevailing form was the N-H tautomer, removal of the borane group furnishes the secondary iminophosphorane form as the practically exclusive tautomer found in solution. This behaviour can be explained by the relative basicity of the phosphorus lone pair. The formation of the PH form is favoured by the presence of electron-rich substituents that increase the basic character of the lone pair at the P atom.[80] In the same manner, electron-withdrawing groups, such as sulfonyls, at the nitrogen add to the acidity of the NH group, again favouring the P-H tautomer (Figure 10).

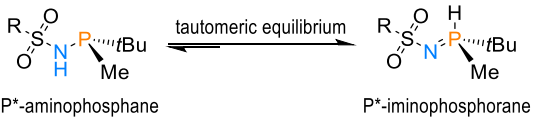


Figure 10. Aminophosphane/SIP tautomerism.

Although SIP ligands reported by the group are configurationally stable as the iminophosphorane, the tautomeric equilibrium is shifted towards the phosphinosulfonamide in presence of a metal source. Consequently, they become *P,O*-ligands for asymmetric catalysis allowing coordination through the phosphorus and the oxygen donor atoms.

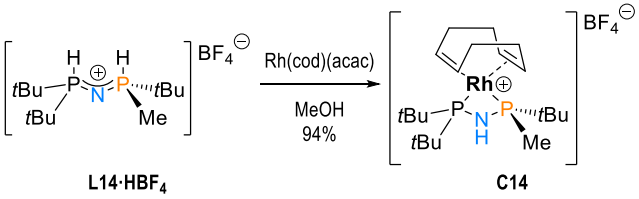
6.3. CATIONIC RHODIUM (I) COMPLEXES IN ASYMMETRIC CATALYSIS

Chiral rhodium complexes perform exceptionally well as catalysts in terms of efficiency, enantioselectivity and substrate scope.[81] Various of these complexes can be obtained from enantiopure phosphorus ligands, and many have enabled the asymmetric synthesis of chiral pharmaceutical targets, agrochemicals, advanced materials or fragrances.

Besides, rhodium catalysts are very stable towards air and moisture, which simplifies reaction setups.[82] Therefore, Rh(I) precursors were chosen for the complexation of the MaxPHOS and SIP ligands in order to find notable applications in asymmetric catalysis.

6.3.1. Asymmetric hydrogenation

MaxPHOS ligand **L14** is a nitrogen-containing analogue of the TrichickenfootPHOS (TCFP) ligand **L8** reported by Hoge *et al.*; one of the most efficient ligands ever developed for asymmetric hydrogenation reactions.[52,54] Taking this into consideration, the MaxPHOS salt **L14·HBF$_4$** became an excellent precursor for Rh coordination with the purpose of succeeding in asymmetric hydrogenations. Thus, the corresponding cationic rhodium complex, Rh-MaxPHOS **C14**, was produced by reaction with Rh(cod)(acac) in high yield (Scheme 5).



L14·HBF$_4$ **C14**

Scheme 5. Coordination of the MaxPHOS ligand to Rh(I), synthesis of Rh-MaxPHOS.

The asymmetric hydrogenation of functionalized olefins at mild hydrogen pressure provided complete stereocontrol even at S/C = 10,000,[15] turning catalyst **C14** into a top performer (Figure 11). Excellent conversions and enantioselectivities were also achieved for many α-dehydroamino acids, tolerating assorted group functionalities, and other miscellaneous substrates.

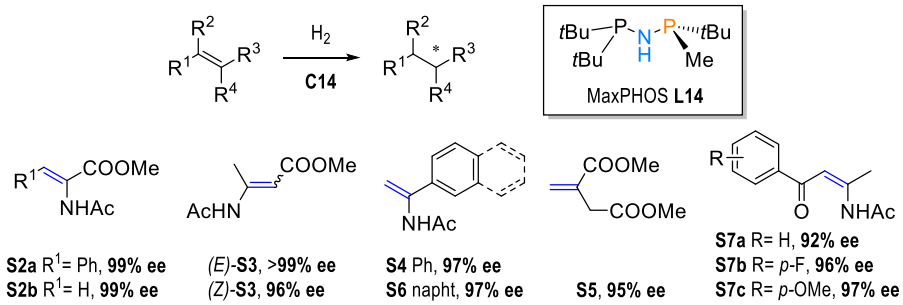
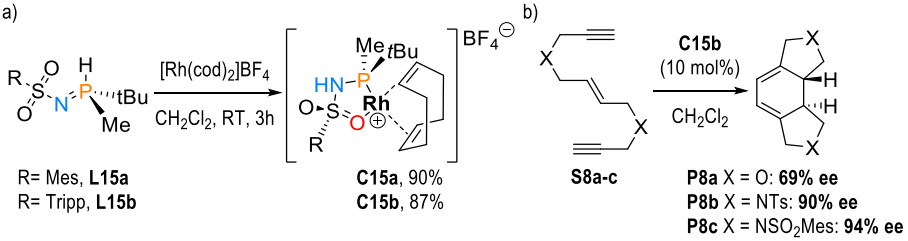


Figure 11. Hydrogenation of functionalized alkenes with Rh-MaxPHOS **C14**.

6.3.2. [2+2+2] Cycloadditions

The [2+2+2] cycloaddition is an appealing and atom-efficient reaction, useful to produce six-membered carbocycles, such as benzenes and cyclohexadienes, or heterocycles, such as pyridines and pyrimidines. It involves the formation of several C–C bonds in a single step, being remarkable in terms of synthetic power and scope.[83]

Our group reported that Rh-SIP complexes were active catalysts in the asymmetric [2+2+2] intramolecular cycloaddition of terminal enediynes (Scheme 6).[17] The reaction between **L15a** and **b** with $[Rh(cod)_2]BF_4$ in CH_2Cl_2 afforded complexes **C15a** and **b**. X-ray analysis showed that the ligand coordinates to rhodium through the P atom and one of the O atoms of the sulfone group, acting as a bidentate *P,O*-ligand. The chiral *tert*-butylmethylphosphino moiety strongly attached to the rhodium centre and the hemilabile sulfonyl group, were key in providing good results in this type of cyclization. In addition, the bulkier Tripp group, was more selective than the mesityl complex **C15a**. Both excellent activities and enantioselectivities were obtained.

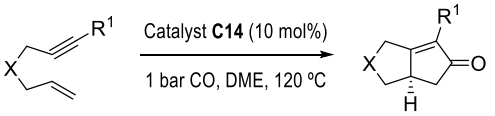


Scheme 6. a) Coordination of the SIP ligands to Rh(I). b) [2+2+2] Intramolecular cycloaddition of terminal enediynes catalysed by Rh-SIP complex **C15b**.

6.3.3. The Pauson-Khand reaction and related [2+2+1] cycloadditions

The Pauson-Khand reaction (PKR), formally a [2+2+1] cycloaddition involving an alkene, an alkyne and carbon monoxide is one of the most efficient methods for the construction of cyclopentanic compounds. With the advantageous many years of experience in the PKR,[84–87] and the aim of further exploring the potential of the MaxPHOS ligand in asymmetric catalysis, Rh-MaxPHOS **C14** was applied to the intermolecular asymmetric Pauson-Khand reaction.

The reaction was conducted using DME and low CO pressure, affording the PK-adducts in good yields and satisfactory enantioselectivities (Scheme 7).[16] Therefore, it was revealed that other ligand backbones such as P*-ligands are a possible alternative to BINAP-type ligands.[88]

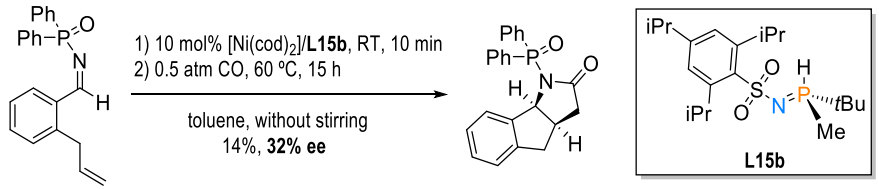


S9a-f
X = NTs, O, $C(CO_2Et)_2$
R^1= H, Ph, Me

up to 6 examples
67-86% ee

Scheme 7. Intramolecular asymmetric Pauson−Khand catalysed by Rh-MaxPHOS complex **C14**.

But MaxPHOS ligand was not lone in finding an application in the [2+2+1] cycloadditions reactions. Ogoshi and co-workers have recently applied the SIP ligand **L15b** in a nickel(0)-catalysed asymmetric [2+2+1] carbonylative cycloaddition (Scheme 8).[89] The active ligand-metal species were conveniently generated *in situ* by reacting **L15b** with $Ni(cod)_2$ in toluene followed by pressurizing with CO, and heating at 60 ºC for 15 h. Ligand **L15b** was capable of inducing enantioselectivity in the final product.



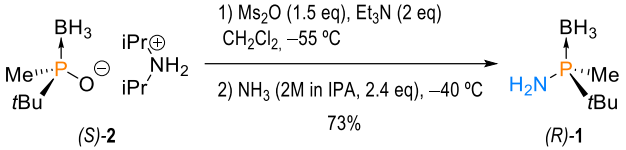
S10 **P10**

Scheme 8. Nickel(0)-catalysed asymmetric [2+2+1] carbonylative cycloaddition with SIP ligand **L15b**.

7. RESULTS AND DISCUSSION

7.1. BUILDING BLOCK *(R)-tert*-butylmethyl-phosphanamine

The first step for the preparation of P*-aminophosphane ligands was the synthesis of privileged intermediate **1**. In Scheme 9 its synthesis from optically pure diisopropylammonium *(S)-tert*-butylmethylphosphinite borane **2**, accessible in multigram scale in our laboratory, is outlined. Compound *(S)*-**2**, cannot undergo an S_N2 reaction because of the hydroxyl not being a good leaving group. However, upon activation with Ms_2O in basic conditions, a nucleophilic substitution with ammonia at the P atom is feasible and building block *(R)*-**1** is obtained. The total outcome of this reaction is an inversion of the configuration at the P* centre.



Scheme 9. Synthesis of *(R)-tert*-butylmethyl-phosphanamine **1**.

The reaction had an added difficulty given that it was very sensitive to temperature variations and dependent to the solvent used. The intermediate P-OMs was found to racemize, hence optimal conditions of low temperature and CH_2Cl_2 were fundamental aspects to develop the synthesis of **1** in either configuration.

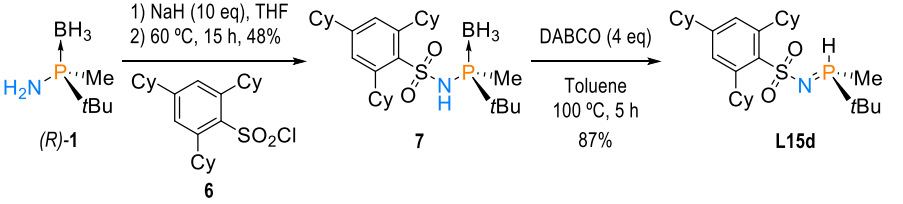
7.2. DESIGN OF NOVEL SIP LIGANDS AND CATALYSTS

7.2.1. Introduction of bulkiness and first attempts to Ni coordination

SIP's newest interest falls on nickel (0) catalysis. We envisioned the existence of a Ni^0-SIP catalyst that would generate the active ligand-metal specie for the [2+2+1] cycloaddition reaction, hence our rising interest of elucidating its structure, along with designing new profitable analogues of the SIP family of ligands.

Regarding to the ligand structure, the addition of bulkier groups at the sulfonyl moiety is expected to potentially improve the enantioselectivity of the aforementioned cycloaddition reaction. Therefore, following previous work of Dr. Salomó, a new SIP ligand was designed bearing three cyclohexyl groups in the sulfonyl moiety.

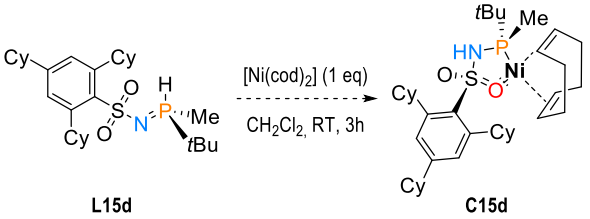
Upon deprotonation with NaH, our building block *(R)*-**1**, prepared in high amounts in our laboratory, was accessible to react with sulfonyl chloride **6**. Compound **6** acted as an electrophile, to successfully synthesise the borane protected SIP novel ligand. This bulkier analogue can be easily deprotected in the presence of an excess of DABCO to afford ligand SIP **L15d** in good yields (Scheme 10).



Scheme 10. Synthesis of novel SIP ligand **L15d**.

With the deprotected ligand in hand, complexation with nickel was attempted in the presence of $Ni(cod)_2$ in CH_2Cl_2 (Scheme 11). The manifestation of a main product in the reaction mixture was determined by ^{31}P-NMR, considering that the ligand **L15d** signal of 22.7 ppm was shifted to 74.2 ppm, a reasonable value for **C15d**. However, the existence of complex **C15d** could not be confirmed because the product was found to degrade in solution and consequently showed very broad signals in the ^{1}H-NMR. This behaviour is comparable to other Ni^0 complexes,[90] apart from **C15d**'s deterioration being faster, in only a few hours.

With the aim of elucidating its structure, the formation of crystals for X-ray determination was sought via crystallization by liquid-liquid diffusion, but the presence of the alkyl cyclohexyl groups became an inconvenience and no crystals were obtained.



Scheme 11. Complexation trial for **L15d** in the presence of Ni^0 and proposed structure for **C15d**.

7.2.2. Exploring a divergent coordination mode

Former work of Dr. Prades disclosed the possibility of modifying SIP's coordination modes. By introducing a pyridine-2-sulfonyl group, the pyridine nitrogen could also coordinate to the metal centre, creating a 6-membered chelate ring, represented in Figure 12.

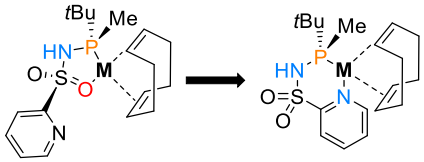
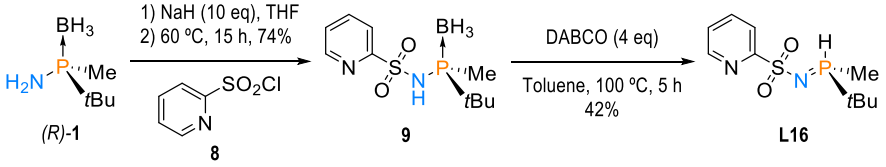


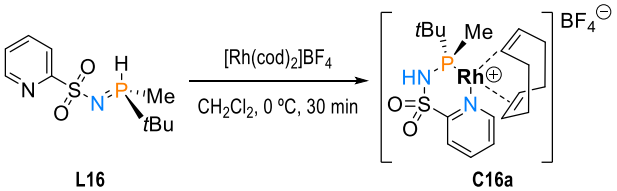
Figure 12. Switching the coordination modes for SIP ligands.

Building block's *(R)*-**1** anion was generated in the presence of sodium hydride and compound **8** was introduced as the electrophile, yielding the borane protected pyridine SIP ligand. Deprotection with DABCO was conducted straightaway and **L16** was obtained in moderate yields due to the similar polarity of the product and the DABCO·BH_3 adduct that interfered in the purification step (Scheme 12).



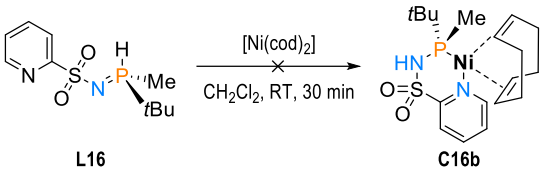
Scheme 12. Incorporation of the pyridine moiety in the SIP ligand **L16**.

Reaction of SIP ligand **L16** with $[Rh(cod)_2]BF_4$ in dichloromethane at 0 ºC allowed the generation of catalyst **C16a** in only 30 min (Scheme 13). Its structure was confirmed by Dr. Prades, who succeeded in growing crystals suitable for X-ray analysis of cationic complex **C16a**. Its structure showed that the ligand coordinates to the metal centre through the P* atom and the nitrogen of the pyridine. This novel catalyst is yet to find an application for asymmetric catalysis.



Scheme 13. Preparation of the cationic Rh(I) complex of SIP ligand **L16**.

On the other hand, the synthesis of the corresponding Ni complex was ineffective because the product was very air-sensitive and degradation lead to a black solution of unidentifiable compounds (Scheme 14).

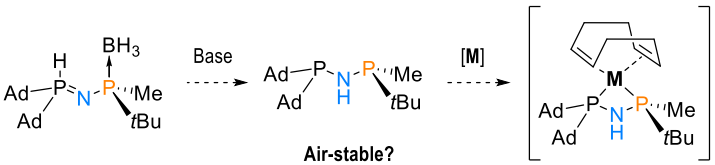


Scheme 14. Complexation trial for **L16** in the presence of Ni^0 and proposed structure for **C16b**.

7.3. INTRODUCING THE MAdPHOS LIGAND

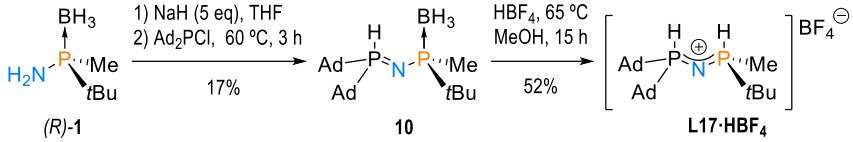
Having attested the great potential and applications of the MaxPHOS salt due to the NH/PH tautomeric equilibrium, it is indeed unfortunate that the neutral ligand, in which the NH form predominates, is an air-sensitive compound.[15] Given that adamantyl's ability to stabilize phosphines has been recently demonstrated in the literature,[60,91] we considered it a promising candidate to improve the MaxPHOS ligand **L14**. Introducing adamantyl, a bulkier substituent than *tert*-butyl, could generate an even more hindered P atom.

The main purpose of this new strategy is to be able to generate a stable adamantyl-based MaxPHOS analogue. Supposing it could be easily deprotected and isolated, the absence of byproducts such as pyrrolidine·BH_3 or acid would enable coordination to other metals such as palladium, copper or nickel, that otherwise are deteriorated (Scheme 15).



Scheme 15. Synthesis of MaxPHOS-Ad complexes for asymmetric catalysis.

For this purpose, optically pure *(R)*-**1** reacted with Ad_2PCl to provide diphosphanamine **15** (Scheme 16). The P-H tautomer of compound **10** was isolated by chromatography and turned out to be noticeably less polar than the borane protected MaxPHOS **4**. The reaction resulted in low yields since unreacted starting material was also present in the reaction mixture. It was hypothesized that the deprotonation of *(R)*-**1** was not complete.

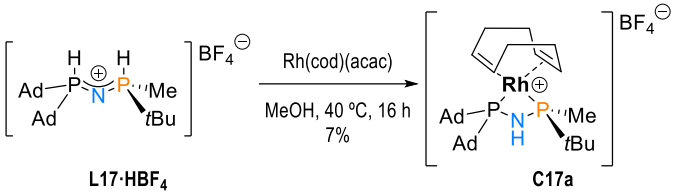


Scheme 16. Preparation of the MaxPHOS-Ad salt **L17·HBF$_4$**.

In the same fashion as the MaxPHOS salt, removal of the borane moiety with HBF_4 in MeOH at 65 ºC provided the air-stable phosphonium salt **L17·HBF$_4$** in 52% yield. The two protons are located on both P atoms and show high coupling constants ($J_{H\text{-}P}$ = 452 Hz and $J_{H\text{-}P}$ = 476 Hz). It is worth remarking that, even though the product is a salt, the adamantane substituents reduce its polarity and **L17·HBF$_4$** can be purified by column chromatography. This consideration is opposed to the nature of **L14·HBF$_4$**, that even though it can be produced in a scale-up strategy, it does not tolerate this purification step.

Nevertheless, **L17·HBF$_4$** was obtained as white solid and, with analogy to the MaxPHOS salt, was denominated as the MAdPHOS salt regarding the Ad groups.

Afterwards, the synthesis of the corresponding Rh(I) complex was conducted. The MAdPHOS salt **L17·HBF$_4$** reacted with Rh(cod)(acac) in MeOH at 40 ºC to obtain the corresponding complex **C17a** (Scheme 17). Precipitation was induced in the presence of pentane, though an impurity was detected in the ^{31}P-NMR and an added purification step will be required, such as recrystallization.

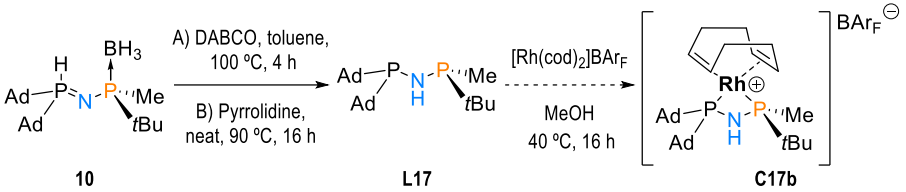


Scheme 17. Preparation of the Rh-MAdPHOS complex **C17a**.

7.3.1. Some insights into the MAdPHOS neutral ligand

Exploring the possibilities of the neutral MAdPHOS's stability due to the shield effect of adamantane, the borane protected diphosphanamine **10** was attempted to deprotect by means of DABCO, but the free ligand was not obtained (Scheme 18A). It might be due to the steric hindrance of both the ligand and the base, but most importantly to the fact that the P atoms retain more electron density by the large adamantane alkyl groups. Consequently, the P-BH_3 bond is stronger and the unpaired electrons of the nitrogen of DABCO are unable to coordinate to BH_3.

To reduce the bulkiness of the base, pyrrolidine was proposed to substitute DABCO. Reaction of pyrrolidine with **10** at 90 ºC for 16 h led to the identification of the characteristic signals in the ^{31}P-NMR among the products, which encouraged further investigation in this route. Uncertain about the stability of the product, it was immediately complexed with Rh(I) to generate an awaited stable catalyst in an NMR tube test. However, coordination led to such a mixture that in combination with low quantities resulted in an inaccessible purification. Further efforts will be invested in the development of this pathway (Scheme 18).



Scheme 18. Investigation on the synthesis of the neutral MAdPHOS ligand **L17**.

7.3.2. Future work

Once Rh-MAdPHOS complex **C17a** is synthesized and isolated, the performance of a preliminary test would be the next step to examine its efficiency in asymmetric hydrogenation. Methyl *(Z)*-α-acetamidocinnamate **S2b** would be the first compound to put to the test (Figure 13). Not only due to its usefulness for comparison with MaxPHOS ligand, **S2b** is also an outstanding precursor for the synthesis of α-amino acids. If successful, future perspectives would include testing other substrates in order to improve MaxPHOS' results.

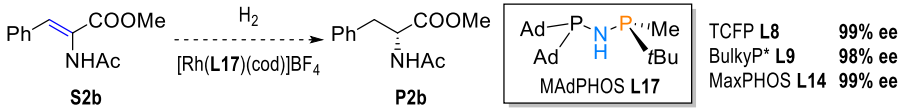


Figure 13. Asymmetric hydrogenation test of the MAdPHOS ligand.

8. EXPERIMENTAL SECTION

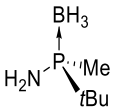
8.1. MATERIALS AND METHODS

Unless otherwise noted, air and moisture sensitive reactions were carried out in oven-dried (55 ºC) glassware capped with a rubber septum under a positive pressure of nitrogen. Air and moisture sensitive reagents, solvents, and solutions were transferred via syringe or stainless-steel cannula under a dry nitrogen atmosphere. Commercial reagents and solvents were used as received without further purification unless otherwise noted. Anhydrous and degassed dichloromethane, tetrahydrofuran and diethyl ether were taken from a solvent purification system (SPS PS-MD-3). Silica gel chromatography was performed using an automated chromatography system (PuriFlash® 430, Interchim). ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer of the Centres Científics i Tecnològics de la Universitat de Barcelona. Chemical shifts (δ) were referenced to internal solvent resonances and reported relative to TMS (tetramethylsilane). The coupling constants (J) are reported in Hertz (Hz). High resolution ESI-MS spectra were recorded in an LC/MSD-TOF G1969A (Agilent Technologies) of the Centres Científics i Tecnològics de la Universitat de Barcelona. IR spectra were measured in a Thermo Nicolet 6700 FT-IR spectrometer using an ATR system, of the Department of Organic Chemistry in the Universitat de Barcelona.

8.2. PREPARATION OF BORANE COMPLEX OF *(R)-tert*-BUTYLMETHYL-PHOSPHANAMINE, 1

In a 50 mL two-neck round-bottom flask equipped with a stirring bar and a thermometer was placed a solution of diisopropylammonium *(S)-tert*-butyl(methyl)phosphinite borane **2** (1.2 g, 6.4 mmol) in anhydrous CH_2Cl_2 (15 mL) under N_2. The reaction mixture was cooled to −55 ºC and Et_3N (1.8 mL, 1 mmol, 2.0 eq) was added dropwise. In a 25 mL pear-shaped flask was prepared a suspension of Ms_2O (1.1 g, 6.4 mmol, 1.5 eq) in CH_2Cl_2 (6 mL) at RT. The Ms_2O solution was added dropwise to the solution of **2**. The mixture was stirred for 1 h. Then, NH_3 (2 M in IPA, 7.7 mL, 15 mmol, 2.4 eq) was added dropwise. After another hour, the solution was quenched with H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with toluene (3 x

20 mL). The organic layers were combined, washed with 5% NaCl (3 x 15 mL) and dried over $MgSO_4$ to afford the desired product as a white paste. The paste was partially dissolved in heptane at reflux temperature (5 mL). The suspension was hot filtered and washed with heptane (10 mL). The resulting suspension was stirred at 0 ºC for 1 h, was filtered and washed with cold heptane (5 mL) to afford *(R)*-**1** (615 mg, 73%, 99% ee) as a white solid. The analytical data for this compound were in excellent agreement with the reported data.[73]

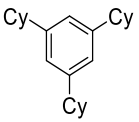


White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76 (s, 2H), 1.35 (d, J = 9 Hz, 3H), 1.14 (d, J = 14 Hz, 9H), 0.47 (ddd, J = 189, 94, 16 Hz, 3H) ppm. GC analysis: Beta-Dex 120 (30 m x 0.25 mm x 0.25 mm, Supelco®), 130°C, t*S* = 18.7 min, t*R* = 19.2 min.

8.3. SYNTHESIS OF SULFONYL CHLORIDES

8.3.1. Synthesis of 1,3,5-tricyclohexylbenzene

A 50 mL Schenk was charged with cyclohexylbromide (5.4 mL, 43.7 mmol, 4 eq) and benzene (1 mL, 11.3 mmol) under N_2, and the mixture was cooled to −35 °C. $AlCl_3$ (2.9 g, 21.9 mmol, 2 eq) was added in small portions over 2 h. Then, the reaction temperature was raised to 0 °C over 2 h. Afterwards, the reaction was carefully quenched by addition of water. The product was extracted with CH_2Cl_2 and dried over $MgSO_4$. The sample was purified by column chromatography with hexanes to give a colourless oil (3.5 g) in 98% yield. The analytical data for this compound were in excellent agreement with the reported data.[92]

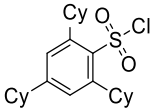


Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 3H), 2.52 – 2.40 (m, 3H), 2.16 (m, 2H), 1.93 – 1.78 (m, 14H), 1.74 (m, 4H), 1.46 – 1.31 (m, 15H), 1.31 – 1.18 (m, 4H) ppm.

8.3.2. Synthesis of 2,4,6-tricyclohexylbenzenesulfonyl chloride, 6

The purified product 1,3,5-tricyclohexylbenzene was dissolved in $CHCl_3$ (21 mL) and cooled to −20 °C in a 250 mL two-neck round-bottom flask. Then, $ClSO_3H$ (21 mL) was added over 2 h and the solution was stirred for an additional hour. At −20 °C, water was added dropwise to quench the chlorosulfonic acid. After heating the reaction mixture to room temperature, it was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. A first fraction from crystallization from CH_2Cl_2/hexanes yielded 0.76

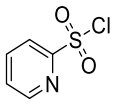
g (16 %) pure product. The analytical data for this compound were in excellent agreement with the reported data.[93]



Black solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (s, 2H), 3.89 – 3.74 (m, 1H), 2.64 – 2.42 (m, 2H), 1.97 – 1.72 (m, 16H), 1.53 – 1.33 (m, 14H) ppm.

8.3.3. Synthesis of 2-pyridylsulfonyl chloride, 8

In a two-neck round-bottom flask, 2-mercaptopyridine (0.75 g, 6.75 mmol) was dissolved in HCl 3 M (19.5 mL) and cooled in an ice bath. NaClO (bleach solution, 90 mL) was added over 30 min to the reaction mixture by means of a dropping funnel. The resulting mixture was stirred for 15 min at 0 °C before it was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated to afford 2-pyridylsulfonyl chloride **8** as a pale yellow oil (1.10 g, 91% yield). The compound is relatively unstable at room temperature. The analytical data for this compound were in excellent agreement with the reported data.[94]



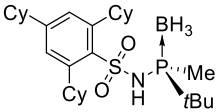
Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (ddd, J = 5, 2, 1 Hz, 1H), 8.12 (dt, J = 8, 1 Hz, 1H), 8.06 (td, J = 8, 2 Hz, 1H), 7.69 (ddd, J = 8, 5, 1 Hz, 1H) ppm.

8.4. General Method 1: synthesis of borane-protected phosphinosulfonamides

In a 50 mL two-neck round-bottom flask, equipped with a stirring bar and a condenser, a solution of NaH (60% in oil, 10 eq) in cyclohexane (5 mL) was prepared at RT under N_2. The suspension was decanted for 10 min and cyclohexane was removed by cannula three times. Anhydrous THF (2 mL) was added and the suspension was heated to 60 ºC. Then, the aminophosphane *(R)*-**1** (1 eq) was added in THF (1 mL) and the mixture was stirred during 45 minutes at 60 ºC. The corresponding sulfonyl chloride (1.2 eq) was added dropwise. The reaction was easily followed by TLC. After 15 hours, the crude was cooled to 0 ºC and water was slowly added. The aqueous phase was washed with CH_2Cl_2 and acidified with HCl 3 M. The crude was extracted with CH_2Cl_2 and the combined organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated under vacuum.

8.4.1. Synthesis of borane-protected *(R)*-N-(*tert*-butyl(methyl)phosphino)-2,4,6-tris(cyclohexyl)benzenesulfonamide, 7

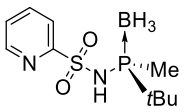
Compound **7** was prepared in accordance with GM1. Purification by column chromatography through silica gel (hexanes/EtOAc, gradient) yielded 50.8 mg (48%) of **7** as white solid.



White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, J = 1 Hz, 2H), 5.02 (d, J = 9 Hz, 1H), 3.75 – 3.60 (m, 2H), 2.55 – 2.44 (m, 1H), 1.84 (dt, J = 20, 13 Hz, 15H), 1.74 (d, J = 9 Hz, 3H), 1.69 – 1.32 (m, 15H), 1.28 (d, J = 16 Hz, 9H), 1.15 – 0.08 (m, 3H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 82.4 (s) ppm.

8.4.2. Synthesis of borane-protected *(R)*-N-(*tert*-butyl(methyl)phosphino)-2-pyridinesulfonamide, 9

Compound **9** was prepared in accordance with GM1. Purification by column chromatography through silica gel (hexanes/EtOAc, gradient) yielded 233 mg (74%) of **9** as pale yellow solid.



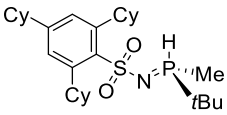
Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 – 8.70 (m, 1H), 8.03 (d, J = 8 Hz, 1H), 7.94 (td, J = 8, 2 Hz, 1H), 7.58 – 7.51 (m, 1H), 1.69 (d, J = 9 Hz, 3H), 1.24 (d, J = 16 Hz, 9H), 0.68 – 0.08 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.9 (C), 150.0 (CH), 138.3 (CH), 127.3 (CH), 121.8 (CH), 31.7 (d, $^{1}J_{CP}$ = 33 Hz, C), 24.8 (d, $^{2}J_{CP}$ = 4 Hz, $3CH_3$), 7.7 (d, $^{1}J_{CP}$ = 36 Hz, CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 84.2 (d, J = 90 Hz) ppm. IR: 2972, 2386, 1392, 896 cm^{-1}. HRMS-ESI+: m/z calcd. for $C_{10}H_{21}BN_2O_2PS$: 275.1148, found 275.1155.

8.5. General Method 2: removal of the borane group

In a 50 mL round-bottom flask equipped with a magnetic stirrer and a condenser, a solution of the corresponding sulfonyl chloride and 4 equivalents of DABCO in toluene (0.08 M) were heated at 100 ºC during 5 h. The reaction was easily followed by TLC. Then, the crude was cooled to room temperature and concentrated under vacuum.

8.5.1. Synthesis of *(R)*-N-(*tert*-butyl(methyl)phosphoranilidene)-2,4,6-tris(cyclohexyl)benzenesulfonamide, L15d

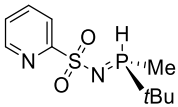
Ligand **L15d** was prepared consonantly to GM2. The resulting crude was easily purified by column chromatography through silica gel (hexanes/EtOAc, gradient) yielding 29 mg (58%) of **L15d** as white solid.



White solid. $[\alpha]_D^{25}$ +23.21 (*c* 0.015, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.03 (s, 2H), 6.53 (dq, J = 452, 4 Hz, 1H), 4.17 – 4.01 (m, 2H), 2.54 – 2.36 (m, 1H), 1.94 – 1.65 (m, 15H), 1.61 (dd, J = 13, 4 Hz, 3H), 1.52 – 1.25 (m, 15H), 1.21 (d, J = 18 Hz, 9H) ppm. ^{13}C NMR (101 MHz, CDCl3): δ 148.2 (C), 145.9 (C), 138.0 (d, J = 3 Hz, C), 123.1 (CH), 43.5 (CH), 39.0 (CH), 28.4 (d, $^1J_{CP}$ = 74 Hz, C), 26.2 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 25.1 (CH_2), 22.9 (d, $^2J_{CP}$ = 2 Hz, $3CH_3$), 6.4 (d, $^1J_{CP}$ = 58.9 Hz, CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.7 (s) ppm.

8.5.2. Synthesis of *(R)*-N-(*tert*-butyl(methyl)phosphoranilidene)-2-pyridenesulfonamide, L16

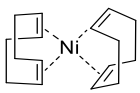
Ligand **L16** was synthesised according to GM2. The resulting crude was purified by column chromatography through silica gel (hexanes/EtOAc, gradient) yielding 55 mg (42%) of **L16** as a pale yellow solid.



Pale yellow solid. ^1H NMR (400Hz, $CDCl_3$): δ 8.51 (ddd, J = 5, 2, 1 Hz, 1H), 7.93 (dt, J = 8, 1 Hz, 1H), 7.75 (td, J = 8, 2 Hz, 1H), 7.30 (ddd, J = 8, 5, 1 Hz, 1H), 6.77 (dq, J = 470, 4 Hz, 1H), 1.75 (dd, J = 13, 5 Hz, 3H), 1.17 (d, J = 18 Hz, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.8 (C), 152.4 (CH), 141.5 (CH), 129.5 (CH), 123.6 (CH), 35.0 (d, $^1J_{CP}$ = 37 Hz, C), 25.5 (d, $^2J_{CP}$ = 7 Hz, $3CH_3$), 9.0 (d, $^1J_{CP}$ = 36 Hz, CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 30.9 (s) ppm. IR: 2969, 2361, 1324, 1152, cm^{-1}.

8.6. SYNTHESIS OF $Ni(cod)_2$

A 100 mL Schlenk was charged with a stirring bar and $NiCl_2(pyridine)_4$ (1.24 g, 2.8 mmol). The flask was evacuated and refilled with nitrogen three times. 1,5-Cyclooctadiene (1 mL, 8.3 mmol, 3 eq) and THF (6 mL) were introduced via syringes. Na (in small pieces, 0.13 g) was added quickly and the mixture was stirred vigorously at room temperature for 16 h. Anhydrous MeOH (15 mL) was added to induce the precipitation of $Ni(cod)_2$. MeOH (15 mL) was added again to rinse the crystals, and the upper layer was removed by syringe 4 times. The $Ni(cod)_2$ (0.3 g, 39%) was dried overnight under vacuum and stored in the dry glovebox's freezer at −26 ºC. The analytical data for this compound were in excellent agreement with the reported data.[95]

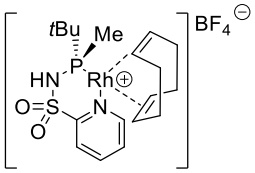


Yellow solid. ^1H NMR (400 MHz, C_6D_6): δ 4.31 (br, 4H), 2.08 (br, 8H) ppm.

8.7. $[Rh(L16)(cod)]BF_4$, C15a

A 25 mL Schlenk was purged and charged with a stirring bar and a solution of $[Rh(cod)_2]BF_4$ (86 mg, 0.21 mmol, 1 eq) in CH_2Cl_2 (1 mL) was added. A solution of **L16** (55 mg, 0.21 mmol, 1

eq) in CH_2Cl_2 (1 mL) was added at 0 ºC and the mixture was stirred for 30 min and concentrated under vacuum. The resulting crude was digested in hexane affording the corresponding complex as an orange solid.



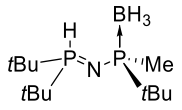
Orange solid. ^{1}H NMR (400Hz, $CDCl_3$): δ 8.93 (d, J = 5 Hz, 1H), 8.33 – 8.18 (m, 2H), 7.85 (ddd, J = 7, 5, 2 Hz, 1H), 5.57 (d, J = 3 Hz, 1H), 5.24 (s, 1H), 4.83 (s, 1H), 4.19 – 4.04 (m, 2H), 1.44 (d, J = 7 Hz, 3H), 0.98 (d, J = 16 Hz, 9H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 65.0 (d, J = 140 Hz) ppm. IR: 2954, 2341, 1244, 1147 cm^{-1}.

8.8. General Method 3: Synthesis of monoborane diphosphanamine ligands

In a 50 mL two-neck round-bottom flask equipped with a stirring bar and a condenser, was prepared a suspension of NaH (60% in oil, 240 mg, 6 mmol, 5 eq) in cyclohexane (10 mL) at RT under N_2. The suspension was decanted for 10 min and cyclohexane was removed by cannula three times. Anhydrous THF (4 mL) was added and the suspension was heated to 60 ºC. Then, a solution of **1** (160 mg, 1.2 mmol, 1 eq) in anhydrous THF (1 mL) was added dropwise and the mixture was stirred for 1 h and 30 min at 60 ºC. Afterwards, the corresponding dialkyl chlorophosphane (1.1 eq) was added and the mixture was stirred at 60 ºC for 3 h. Later, the mixture was cooled to RT, then to 0 ºC with an ice-bath and cold H_2O (5 mL) followed by a saturated solution of NH_4Cl (5 mL) were added to dissolve all solids. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and were concentrated under reduced pressure to provide the corresponding monoborane aminodiphosphane.

8.8.1. Monoborane complex of *(R)*-(*tert*-butylmethylphosphino)-(di-*tert*-butylphosphino)amine, 4

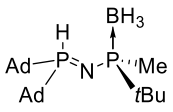
Compound **4** was prepared according to GM3, yielding 352 mg (106%) of **5** as white solid. The product was used without further purification. The analytical data for this compound were in excellent agreement with the reported data.[77]



White solid. ^{1}H NMR (400Hz, $CDCl_3$): δ 6.22 (d, J = 413 Hz, 1H), 1.26 (d, J = 7 Hz, 9H), 1.24 (dd, J = 6, 3H), 1.21 (d, J = 12 Hz, 9H), 1.13 (d, J = 14 Hz, 9H), 0.65 – 0.02 (m, 3H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 63.7 (dd, J = 83 Hz), 42.8 (d, J = 5 Hz) ppm.

8.8.2. Monoborane complex of *(R)*-(*tert*-butylmethylphosphino)-(diadamantylphosphino)amine, 10

Compound **10** was prepared according to GM3, yielding 40.9 mg (17%) of **10** as white solid.



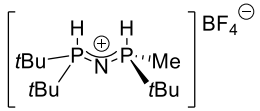
White solid. ^{1}H NMR (400Hz, $CDCl_3$): δ 5.83 (dd, J = 411, 4 Hz, 1H), 2.07 – 1.91 (m, 18H), 1.80 – 1.68 (m, 12H), 1.23 (d, J = 9 Hz, 3H), 1.14 (d, J = 14 Hz, 9H), 0.65 – 0.02 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 37.5 (d, $^{2}J_{CP}$ = 6 Hz, CH), 36.5 (CH_2), 31.5 (dd, J_{CP} = 50, 8 Hz, C), 27.7 (dd, J_{CP} = 10, 4 Hz, C), 25.1 (d, $^{2}J_{CP}$ = 3 Hz, $3CH_3$), 14.9 (d, $^{1}J_{CP}$ = 38 Hz, CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 63.4 (dd, J = 165, 77 Hz), 36.86 (d, J = 9 Hz) ppm. IR: 2899, 2849, 2365, 1185, 875 cm^{-1}. HRMS-ESI+: m/z calcd. for $C_{25}H_{47}BNP_2$: 434.3271, found 434.3277.

8.9. General Method 4: Tetrafluoroborate salt of diphosphanamine ligands

In a 50 mL round-bottom flask, aqueous HBF_4 (48%, 2 eq) was added to a solution of the corresponding diphosphanamine borane complex in anhydrous MeOH (0.05 M) at room temperature. The mixture was stirred for 15 h at 65 ºC, and the solvent was then removed under vacuum. At this point, aqueous saturated solution of $NaHCO_3$ (5 mL) and EtOAc (5 mL) were added and the mixture was stirred for 15 min. The aqueous layer was washed with EtOAc (3 x 5 mL), and the combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum to provide the desired tetrafluoroborate salt.

8.9.1. Tetrafluoroborate salt of *(R)*-(*tert*-butylmethylphosphino)(di-*tert*-butylphosphino)amine, L14·HBF$_4$

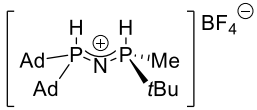
Ligand **L14·HBF$_4$** was prepared in accordance with GM4 yielding 244.4 mg (58%) of **L14·HBF$_4$** as a white solid. The analytical data for this compound were in excellent agreement with the reported data.[77]



White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (dd, J = 479, 4 Hz, 1H), 6.66 (dd, J = 461, 7 Hz, 1H), 1.79 (dd, J = 13, 4 Hz, 3H), 1.33 (d, J = 17 Hz, 9H), 1.30 (d, J = 17 Hz, 9H), 1.24 (d, J = 18 Hz, 9H) ppm.

8.9.2. Tetrafluoroborate salt of *(R)*-(*tert*-butylmethylphosphino)-(diadamantylphosphino)amine, L17·HBF$_4$

Ligand **L17·HBF$_4$** was prepared in accordance with GM4. The resulting crude was easily purified by chromatography through silica gel (CH_2Cl_2/MeOH, gradient) yielding 23.8 mg (52%) of **L17·HBF$_4$** as white solid.



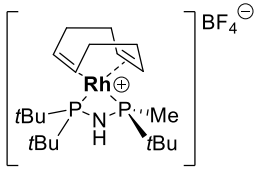
White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (dq, J = 476, 4 Hz, 1H), 6.10 (dd, J = 452, 7 Hz, 1H), 2.11 – 1.88 (m, 18H), 1.84 – 1.69 (m, 12H), 1.25 (d, J = 18 Hz, 9H), 1.15 (d, J = 15 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 39.1 (d, $^1J_{CP}$ = 60 Hz, C), 36.8 (d, $^2J_{CP}$ = 15 Hz, CH_2), 36.1 (CH_2), 29.9 (d, $^1J_{CP}$ = 51 Hz, C), 27.4 (d, $^3J_{CP}$ = 11 Hz, CH), 23.7 (d, $^2J_{CP}$ = 2 Hz, $3CH_3$), 7.84 (d, $^1J_{CP}$ = 60 Hz, CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 39.5 (d, J = 36 Hz), 34.9 (d, J = 36 Hz) ppm. IR: 2903, 2848, 1736, 1045 cm^{-1}.

8.10. General Method 5: Synthesis of Rh diphosphanamine complexes

A 5 mL round-bottom flask equipped with a magnetic stirring bar and purged with N_2 was charged with [Rh(cod)(acac)] (1 eq). A solution of the corresponding salt of the ligand (1 eq) in anhydrous MeOH (2 mL) was slowly added. The resulting solution was stirred at 40 ºC for 16 h. At this point, MeOH was evaporated under vacuum and the resulting solid was further digested with Et_2O (3 x 3 mL) to provide the desired complex.

8.10.1. [Rh(L14)(cod)]BF$_4$, C14

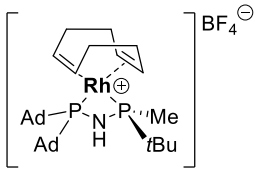
Catalyst **C14** was prepared following GM5, yielding 53 mg (29%) of **C14** as an orange solid. The analytical data for this compound were in excellent agreement with the reported data.[77]



Orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.54 (m, 2H), 5.39 (br, 1H), 5.10 (br, 2H), 2.55 – 2.34 (m, 4H), 2.31 – 2.10 (m, 4H), 1.77 (dd, J = 8, 1 Hz, 3H), 1.39 (d, J = 15 Hz, 9H), 1.38 (d, J = 15 Hz, 8H), 1.21 (d, J = 16 Hz, 9H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 69.9 (dd, J = 128, 49 Hz), 47.67 (dd, J = 129, 49 Hz). HRMS-ESI+: m/z calcd. for $C_{13}H_{31}NP_2Rh$: 366.0981, found 366.0978.

8.10.2. [Rh(L17)(cod)]BF$_4$, C17a

Catalyst **C15** was prepared following GM5, yielding 2 mg (7%) of **C15** as an orange solid.



Yellow solid. ^{31}P NMR (162 MHz, $CDCl_3$): δ 60.3 (dd, J = 127, 47 Hz), 46.9 (dd, J = 128, 47 Hz) ppm. IR: 2901, 2850, 1736, 1011 cm^{-1}. HRMS-ESI+: m/z calcd. for $C_{25}H_{43}NP_2Rh$: 522.1920, found 522.1917.

9. CONCLUSIONS

The main aim of this work was the design of novel P-stereogenic ligands for catalytic asymmetric synthesis. The MAdPHOS ligand, bearing the bulkier adamantane groups, was successfully synthesized as a promising ligand for the Rh-catalysed enantioselective hydrogenation. Moreover, the synthetic route has proven to be very versatile and opens new doors to further modulate the MaxPHOS ligand.

Evaluation of the recent literature was key to determine the rising competences of the adamantane moiety. In this sense, different approaches are being tested to obtain the neutral MAdPHOS ligand and determine whether it could be air-stable.

On the other hand, a unique SIP *P,N*-chelating ligand and the corresponding Rh-catalyst were prepared, and its catalytic potential will be further studied. Unfortunately, SIP did not tolerate Ni^0 as desired, whose chemistry was found to be very sensitive to moisture and air.

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11. ACRONYMS

acac	Acetylacetone
Ad	Adamantyl
ADH	Adamantane
BAr_F	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
cod	1,5-Cyclooctadiene
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
δ	Chemical shift
E	Electrophile
ee	Enantiomeric excess
eq	Equivalent(s)
ESI	Electrospray ionization
IPA	2-Propanol
iPr	Isopropyl
HRMS	High resolution mass spectrometry
IR	Infrared spectroscopy
M	Metal
Mes	2,4,6-Trimethylphenyl
m/z	Mass-to-charge ratio
NMR	Nuclear magnetic resonance
Nu	Nucleophile
P*	P-stereogenic
PKR	Pauson-Khand Reaction
p-Tol	*p*-Toluenesulfonyl
S/C	Substrate/Catalyst
SIP	Secondary Iminophosphorane
S_N2	Secondary nucleophilic substitution
THF	Tetrahydrofuran
Tripp	2,4,6-Tris(isopropyl)phenyl