THÈSE

présentée en vue de l'obtention du grade de

DOCTEUR DE L'UNIVERSITE DE STRASBOURG

Par

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NEW METHODOLOGIES IN ORGANOMETALLIC CHEMISTRY: APPLICATION TO THE SYNTHESIS OF MANDELATE DERIVATIVES, PROPARGYLIC ALCOHOLS AND *P*-CHIROGENIC PHOSPHINAMIDES

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A mamma, papà e Silvia,

A Sylvain,

AVANT-PROPOS

Le travail présenté dans ce manuscrit a été réalisé durant la période Janvier 2007-Février 2010 et a été mené en coopération entre Laboratoire de Stéréochimie de l'Université de Strasbourg sous la direction du Pr. Françoise Colobert, et dans le laboratoire de NovAlix-Pharma à Illkirch sous la direction du Dr. Alain Wagner. Je tiens à les remercier pour m'avoir accueillie dans leurs respectives équipes ainsi que pour l'intérêt qu'ils ont montré envers le sujet de recherche et la confiance qui m'ont accordé tout au long de ces trois années. Mes plus vifs remerciements vont au Professeur Colobert plus particulièrement pour l'encadrement et les conseils qu'elle a su m'adresser. Son dévouement au travail et son enthousiasme pour la recherche ont été pour moi un vrai repère dans les moments difficiles de la thèse. Je la remercie encore pour la patience dont elle a fait preuve durant les corrections de ce manuscrit.

Aux membres du jury, Madame Elisabet Duñach (Directeur de Recherche à l'Université de Nice) et Messieurs Dominique Matt (Directeur de Recherche à l'Université de Strasbourg), Sylvain Jugè (Professeur à l'Université de Bourgogne) et Philippe Gros (Directeur de Recherche à l'Université Henry Poincarè de Nancy) j'adresse mes plus sincères remerciements pour l'honneur qu'ils m'ont fait en acceptant de juger ce travail.

J'adresse mes remerciements à Novalyst en la personne du Dr Stephan Jenn pour avoir accepté de me faire confiance en finançant ma thèse, et l'équipe des docteurs ainsi que des techniciens pour leur accueil chaleureux et leur disponibilité.

Je remercie également les Dr. Sabine Choppin, Dr. Fréderic Leroux et Dr. Gilles Hanquet pour leur disponibilité et les discussion scientifiques enrichissantes.
Je remercie Mlle Coraline Egloff et M. Antoine Renier pour avoir collaboré à une partie de mon travail de thèse.

Un grand merci à Michel Schmitt pour sa bonne humeur et les innombrables spectres RMN du phosphore. Merci aussi à M. Didier Boettger, vrai pilier des laboratoires du R2, pour ses dépannages techniques et Mme Bouchra El Fahssi pour son assistance dans la «paperasse française». Je remercie chaleureusement Mesdames Agnès Schmitt et Arlette Klein pour leur immense disponibilité et pour avoir toujours su être a l'écoute de mes petites préoccupations.
Un énorme merci a tous mes amis et collègues de laboratoire: Marie, qui nous a fait toujours bien rigoler lors de ses «petites casses quotidiennes», Nicolas, vrai disc-jockey du labo, Guillaume et Elena, les deux new-entries du labo. Je remercie également Florence (vrai concentré de sympathie et bonne humeur), Charlotte, Juan, Timo, Mariam et Maggy. Merci encore aux cousins du R4 Julien et Maida pour les rigolades entre une RMN et une autre et les échanges scientifiques (qui aurait dit qu'une balle de foot aurait pu intéresser des chimistes!!!) et culinaires. Merci aussi à Alex, Laure, Thibaut et Camille.
Merci à Don Antoine, David, Juan-Jo, Damien et Christophe les post-docs les plus sympas et doués jamais connu!

Je remercie tous mes amis españols: Leticia, qui a été une vraie référence dés mon arrivée au labo, Mercedes, collègue et amie avec qui j'ai partagé les derniers mois de thèse…je voudrais lui dire que moi aussi j'aime beaucoup son «Estyle», Luisito, que j'admire beaucoup pour toutes ses «batailles», Vicky, a qui je dois les moments les plus heureux de cette expérience, Rafa y Rafeta, because two is better than one!
A Laurence, la thésarde parfaite, merci pour sa gentillesse et disponibilité et à Pasquale, que je remercie également en étant le seul italien que j'ai pu côtoyer ici à Strasbourg, un grand merci et toutes mes félicitations pour ce beau couple que vous êtes!
A mes plus chères copines qui la chimie m'a donné la chance de rencontrer Pauline et Carolina je voulais dire merci, même si ça ne suffira pas, pour tout ce qu'elles ont fait pour moi.
Merci à Esther et Joseph pour leur amitié sincère et pour les nombreuses soirée libanaises délicieusement préparées par leurs soins. Merci à Cynthia et Mathieu pour tous les bons moments passés ensemble.

Parmi les «non chimistes» je remercie les amis de la vallée du Florival Jean et Nico pour les petites soirées strasbourgeoises très agréables. Un grand merci à Emanuela, ma copine de toujours qui n'a pas manqué d'être présente et disponible à tout moment.

Merci a mes amis de l'Unibas que je n'oublierai jamais Daniela, Lidia, Laura, Maria Vittoria, Pasquale, Francesco, Nadia et Maria Teresa.

Enfin je remercie sincèrement toute ma famille qui m'a beaucoup soutenue durant ces longs mois de séparation, et Odile et Jean Baptiste qui m'ont chaleureusement accueillie dans la leur. Je ne pourrai pas terminer ici sans remercier Sylvain qui a toujours été présent pour me soutenir et qui m'a supporté durant la période difficile de la rédaction.

Merci infiniment à tous, vous avez tous contribué a ce que cette expérience strasbourgeoise soit vraiment inoubliable.

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General Introduction for Chapters 1 and 2

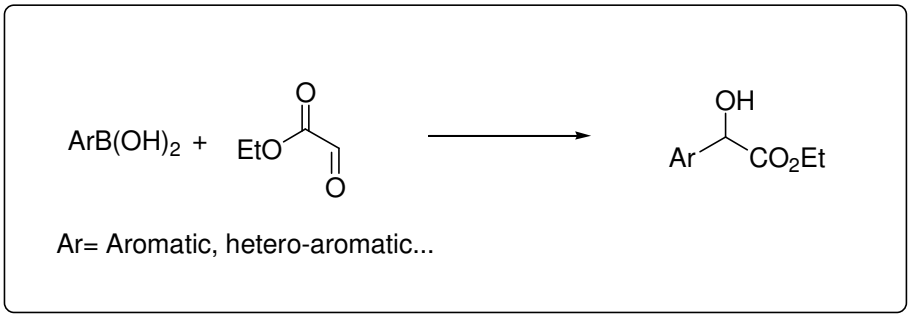
Organometallic reagents are of increasing importance not only for organometallic chemists but also in organic chemistry and pharmaceutical synthesis and to access organic materials. The usefulness of organomagnesium and organolithium compounds is taken for granted, but their high nucleophilicity and basicity sometimes preclude their use in many reactions with sensitive functional groups. Thus, for decades, chemists have looked for more selective organometallics, which tolerate a wider range of functionalities, such as Zn, Si, B, and Sn for carbon-carbon bond formation. Among them, organoboranes and organostannanes have emerged as reagents of choice in various transition-metalcatalyzed reactions. However, there are still drawbacks in the use of organostannanes because of their toxicity which strongly limits its use in synthesis.

On the other hand, organoboranes have played an important role in the development of modern organic catalytic and asymmetric synthesis. Since the discovery of the Suzuki-Miyaura reaction, organoboranes have emerged as reagents of choice in transition-metal-catalyzed reactions, particularly with palladium catalysts, allowing straightforward formation of carbon-carbon bonds. This reaction is now one of the most frequently used transition-metal-catalyzed reactions either in academic institutions or in industry. Since that date, numerous publications and patents on this topic have been reported in the literature. The efficacy of boron in many asymmetric processes may be rationalized in part by its relatively small size which allows any chiral ligand to exert more influence on the transition state, and in part for the high Lewis acidity which enable it to the coordination with several heteroatoms. Additionally, organoboron reagents feature a very low toxicity, which makes these compounds environmentally friendly compared to other organometallic reagents, particularly organostannanes.

Among every possible organic transformation, the use of organoboranes in the nucleophilic addition to carbonyl compounds to generate secondary and tertiary alcohols, has attracted, more recently, increasing attention and represent an active and challenging subject in organometallic chemistry. In particular, focusing on the addition of organoboron compounds to aldehydes, a limited number of reports can be found in the literature comparing to other reactions. Since our major objectives is to find new synthetic methodologies in this field, we will describe in the next pages our efforts to achieve them.

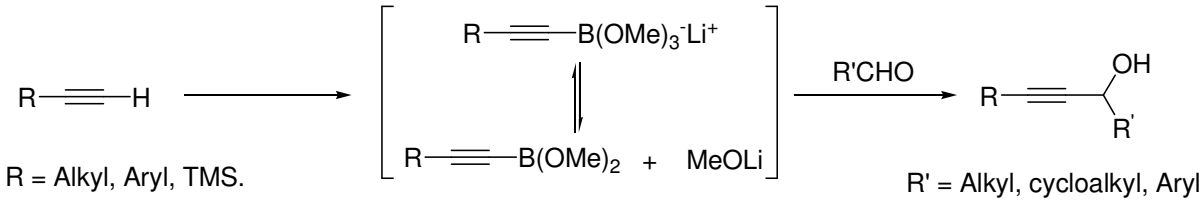
In the first two parts of this manuscript we will focus on the addition of organoborane to aldehydes. Two synthetic methodologies have been optimized for the synthesis of α-hydroxy esters and secondary propargylic alcohols, important intermediates for the synthesis of biologically active compounds.

Particularly, in the first chapter, we will discuss about the palladium-catalyzed addition of arylboronic acids to ethylglyoxylate and all the data of this subject will be presented in form of article already published in the previous years.



In the last part of the first chapter we will briefly introduce our preliminary results concerning the stereoselective coupling. Two strategies based either on introducing chiral ligand on the catalyst or chiral inducer on the glyoxylate have been explored. Since this part of the study deals with unpublished results, it will be inserted as enclosure to the end of Chapter 1.

In the second chapter, we will displace our attention on the addition of lithium alkynyl trimethoxy borates to aldehydes. Since this part of the work has been recently published, we will include the original article.



Chapter 1

Suzuki-Miyaura coupling reaction of boronic acids and ethyl glyoxylate: synthetic access to mandelate derivatives

1.1 Purposes

The transition metal catalyzed addition of boronic acids to aldehydes is a new and relatively undiscovered method of C-C bond formation mainly applied to the synthesis of diarylmethanols, important synthons for the synthesis of biologically active compounds. Since the purpose of this work was to find new developments of this reaction, we will present a new approach toward the synthesis of mandelate derivatives by a palladium-catalyzed addition of boronic acids to glyoxylates. Within this first chapter we will briefly retrace the history of this reaction since its discovery in 1998 by Miyaura and throughout the rhodium and palladium catalysis. Afterward, we will introduce our results in racemic and stereoselective coupling.

1.2 Bibliographic recall

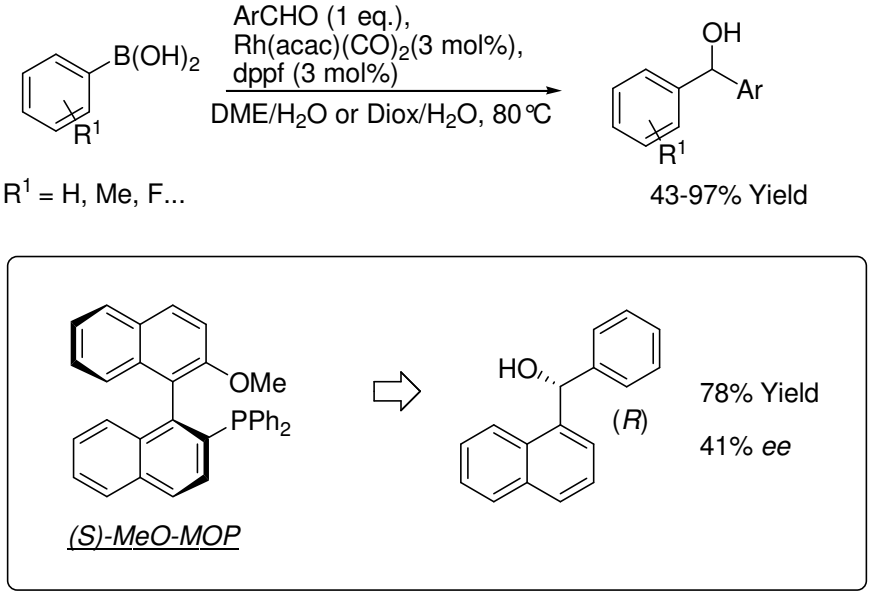
1.2.1 Rhodium catalyzed addition of boronic acids to aldehydes

1.2.1.1 Non stereoselective methods

In 1998, Miyaura reported the first Rh-catalyzed addition of aryl and alkenylboronic acids to aldehydes, which marked an important step of transition metal-catalyzed reactions.[1] The reaction was carried out with [Rh(acac)$(CO)_2$] and a phosphane ligand (dppp and dppf are the best ligands and ensure the formation of a complex catalyst having a large P-Rh-P angle) in an aqueous solvent and worked well with both electron rich and electron poor aromatic aldehydes with aryl boronic acids (Scheme 1.1).

Moreover, they examined the asymmetric version of this protocol: (R)-(+)-(1-naphthyl)(phenyl)methanol was formed preferentially by using a chiral monodentate ligand, the (*S*)-MeO-MOP.

[1] Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 3279-3281



Scheme 1.1: First Rhodium-catalyzed addition of arylboronic acids and aldehydes

Because the insertion of aldehydes into the carbon-metal bond was very rare in transition metal chemistry, they tried to give some explanation of experimental data by formulating a possible catalytic cycle. In this case the transmetalation step involves a Rh^{I} species and the boronic acid forming an $ArylRh^{I}$ complex that could active the aldehyde for the next insertion into the carbon-metal bond. Water is responsible of the elimination step and restores the catalytic turnover (Figure 1.1).

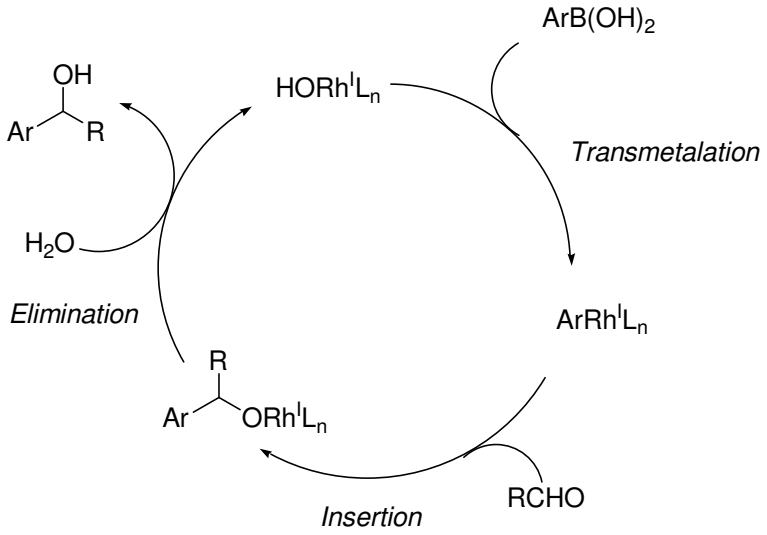
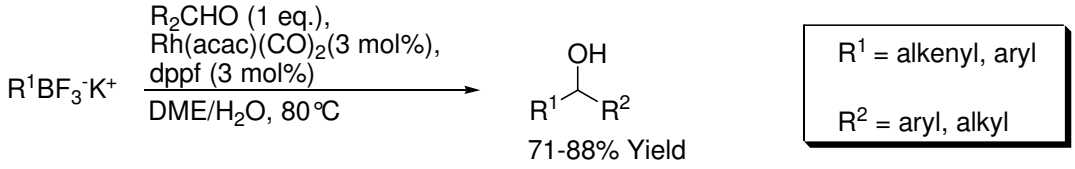


Figure 1.1: Catalytic cycle of the addition reaction.

The effectiveness of this catalytic system, formed by $Rh(acac)(CO)_2$ and bisphosphine ligands as dppf or dppb, was also proved in the addition of potassium alkenyl- and aryltrifluoroborates to aldehydes (Scheme 1.2).[2]

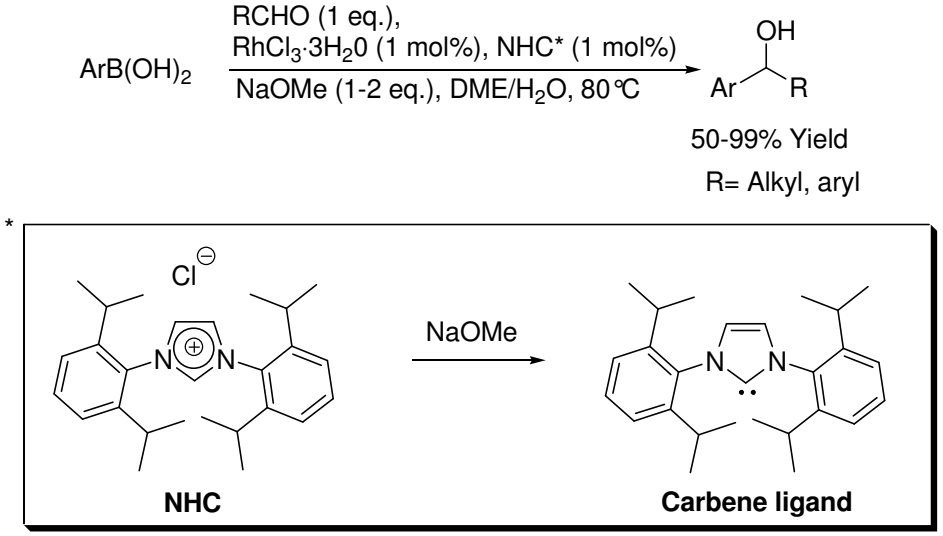


Scheme 1.2: Rhodium-catalyzed addition of potassium alkenyl- and aryltrifluoroborates to aldehydes

Subsequently, the same group showed that bulky, monodentate phosphines such as $P(t\text{-}Bu)_3$ and PCy_3 showed a better catalytic activity than bisphosphines[3].

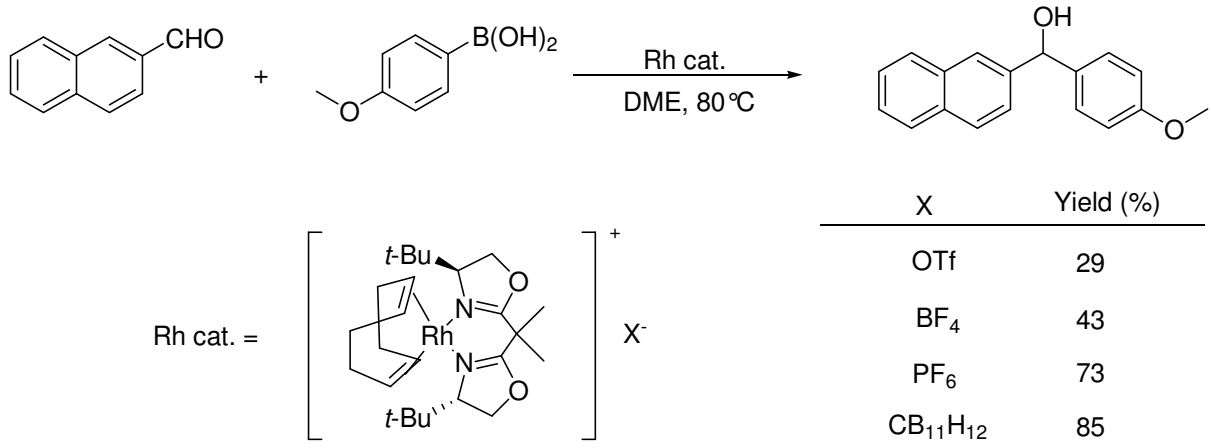
Few years later, in 2001, Fürstner et al[4] introduced a new catalytic system for this reaction based on a rhodium catalyst and N-heterocyclic carbenes (NHCs) ligands, opening new perspectives for further works.[5] NHCs exhibit a great σ-electron donating ability which produce stronger bonds with the majority of metals when compared to phosphine ligands and can be considered as a better choice of expensive and air-sensitive $P(t\text{-}Bu)_3$ and PCy_3. After showing that unsaturated and in situ prepared carbenes (a strong base can easily deprotect the precursor imidazolium salt) gave the best results, they evaluated a wide scope of the arylation of aryl and alkyl aldehydes and the results showed that the reaction was compatible with sensitive functional groups onto carbonyl compounds (Scheme 1.3).

[2]Batey R., A.; Thadani, A. N.; Smil, D. V. *Org. Lett.*, **1999**, *1*, 1683–1686
[3]Sakai, M.; Ueda, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 4450–4452
[4]Fürstner, A.; Krause, H. *Adv. Synth. Catal.* **2001**, *343*, 343–350
[5] (a) Focken, T.; Rudolph, J.; Bolm, C. *Synthesis* **2005**, *3*, 429–436; (b) Özdemir, I.; Demir, S.; Çetinkaya, B.; Çetinkaya, E. *J organomet. Chem.* **2005**, *690*, 5849-5855; (c) Chen, J.; Zhang, X.; Feng, Q.; Luo, M. *J. Organomet. Chem.* **2006**, *691*, 470–474; (d) Yan, C.; Zeng, X.; Zhang, W.; Luo, M *J. Organomet. Chem.* **2006**, *691*, 3391-3396; (e) Gois, P. M. P.; Trindade, A. F.; Veiros, L. F.; André, V.; Duarte, M. T.; Afonso, C. A. M.; Caddick, S.; Cloke, F. G. N. *Angew. Chem. Int. Ed.* **2007**, *46*, 5750–5753; (f) Türkmen, H.; Denizalti, S.; Özdemir, I.; Çetinkaya, E.; Çetinkaya, B. *J organomet. Chem.* **2008**, *6930*, 425-434 ; (g) Trinidade, A. F.; Gois, P. M. P.; Veiros, L. F.; André, V.; Duarte, M. T.; Afonso, C. A. M.; Caddick, S.; Cloke, F. G. N. *J. Org. Chem.* **2008**, *73*, 4076-4086.



Scheme 1.3: NHCs in rhodium-catalyzed addition of boronic acids to aldehydes.

At the same time, Frost's team demonstrated that cationic rhodium complexes based on bis oxazolines ligands revealed to be equally effective for the reaction between aromatic boronic acids and aldehydes.[6] Furthermore, they carried out a study on the counterion effect on the final yields, showing that weakly coordinating ions provide more active catalyst.

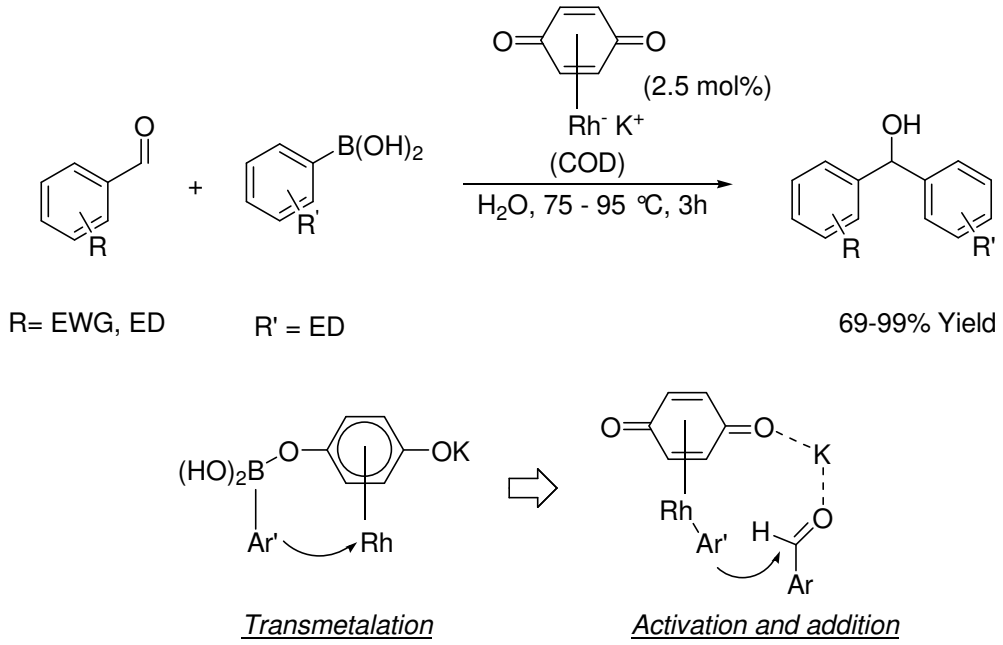


X	Yield (%)
OTf	29
BF_4	43
PF_6	73
$CB_{11}H_{12}$	85

Scheme 1.4: NHCs in rhodium-catalyzed addition of boronic acids to aldehydes

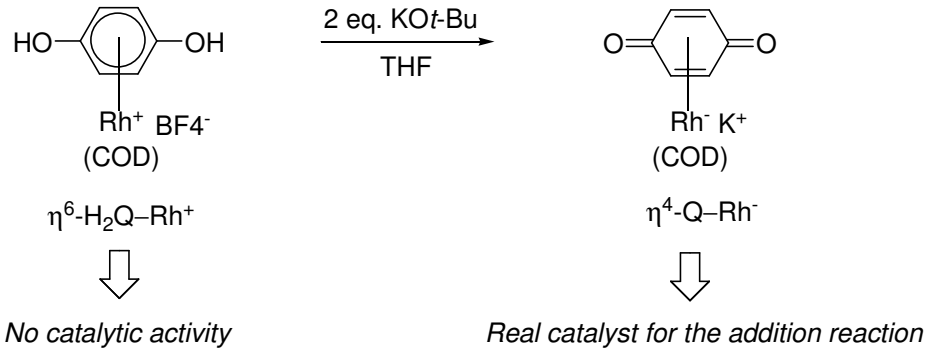
In 2005, Sweigart[7] presented the catalytic arylation of aromatic adehydes by using an anionic π-bonded rhodium η^4-quinonoid complex as catalyst. The ligand has a double role: it acts to activate the aldehydes by interaction between the alkali metal (K^+or Li^+) and the carbonyl oxygen, and works as a base by binding to the boron via the quinonoid oxygens so that assisting the transmetalation step and placing the transition metal near to the transferring groups as shown in the Scheme 1.5.

[6] Moreau, C.; Weller, A. S.; Frost, C. G. *Tetrahedron Lett.* **2001**, *42*, 6957–6960
[7] Son, S. U.; Kim, S. B.; Reingold, J. A.; Carpenter, G. B.; Sweigart, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 12238-12239



Scheme 1.5: Rh-quinonoid complex in catalytic arylation of aldehydes.

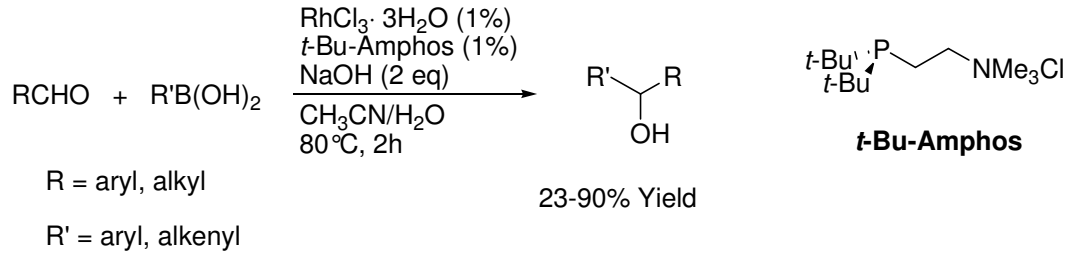
The catalytic activity of the rhodium quinonoid complex took advantage of the key chemical property displayed by quinone ring system, the facile deprotonation of the –OH group implies the electron transfer to the metal center and changes in the hapticity of the quinonoid ring. Particularly, only anionic Rh-η^4-quinone complexes will show a catalytic activity (Scheme 1.6).



Scheme 1.6: η^4- vs -η^6-Rh-quinonoid complex.

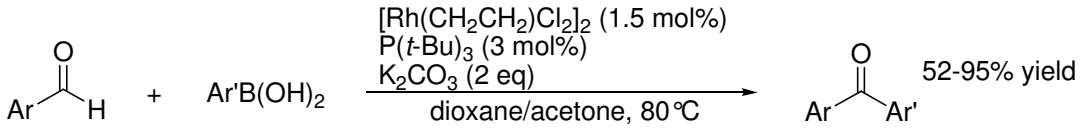
Concerning the coupling between aldehydes and boronic acids promoted by sterically demanding alkylphosphines and a Rh complex,[3] Shaughenessy and Huang reported the arylation and alkenylation of aldehydes, realized with a highly recyclable complex catalyst, *t*-Bu-Amphos-$RhCl_3 \cdot H_2O$, in water (Scheme 1.7). The catalyst proved to be highly performing even after nine reaction cycles.[8]

[8] Huang, R.; Shaughnessy, K. *Chem. Comm.* **2005**, 4484-4486



Scheme 1.7: Recyclable Rh-t-BuAmphos complex for the boronic acid addition to aldehydes

A truly original application of the catalytic addition of boronic acids to aldehydes is presented by Genet's team in 2007, and concerns the synthesis of benzophenones units by direct rhodium catalyzed cross coupling reactions of aromatic aldehydes with arylboronic acids *via* a formal aldehyde C-H bond activation.[9] Various diarylketones have been synthesized in high yields under mild reaction conditions and sensitive functional groups on the aromatic rings are well tolerated (Scheme 1.8).



Scheme 1.8: Synthesis of diarylketones by tandem rhodium-catalyzed addition-oxidation

According to the authors, the reaction would occur through a tandem process involving the classical aldehyde cross coupling followed by an unusual carbinol oxidation promoted by hydride elimination (Figure 1.2). Here, the inorganic base and acetone play a key role: the former is responsible of the regeneration of the alkoxo-rhodium intermediate thus favouring its entry in the second catalytic cycle while the latter, is considered like the hydride acceptor required for the regeneration of the Rh-X intermediate.

[9] Mora, G.; Darses, S.; Genet J. -P. *Adv. Synth. Catal.* **2007**, *349*, 1180-1184

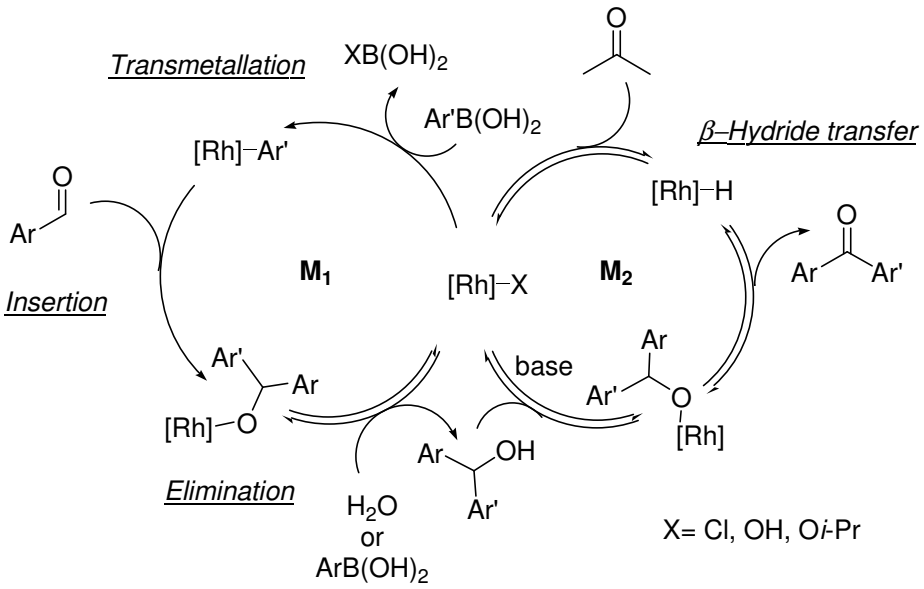
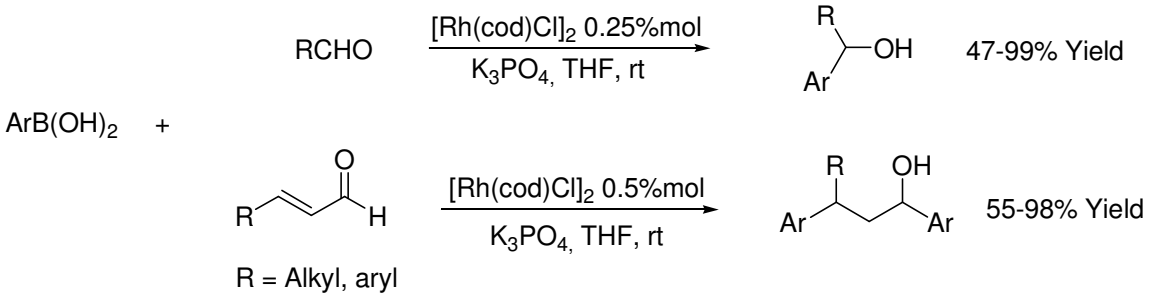


Figure 1.2: Catalytic cycle for Addition-Oxidation

Diene ligands, such as cyclooctadiene, demonstrated to be efficient in the addition of aryl and alkenylboronic acids with a wide series of aliphatic and aromatic aldehydes.[10] A tandem reactions occurs with α,β-unsaturated aldehydes leading to the adduct deriving from sequential 1,4- and 1,2-addition (Scheme 1.9).



Scheme 1.9: Diene ligands in rhodium catalyzed 1,4 and 1,2 addition of boronic acid to aldehydes

1.2.1.2 Stereoselective methods

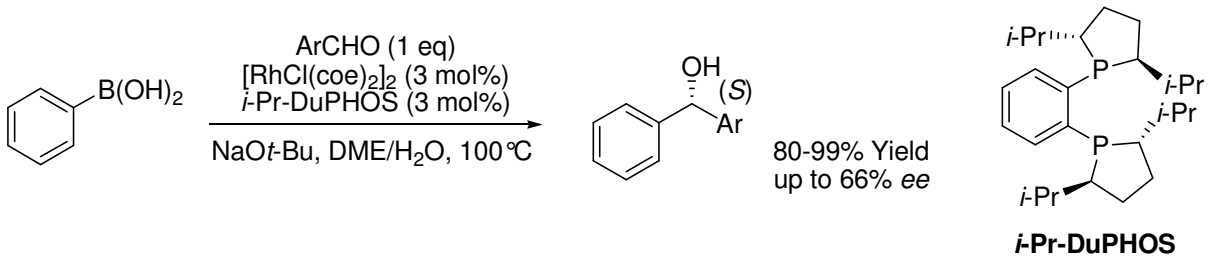
Despite the increasing number of reports about the catalytic cross coupling of boronic acids and aldehydes, only rare and unsuccessful examples for asymmetric synthesis of optically active diarylmethanols has been reported.[11] However, in 2006, Aoyama and coworkers[12] presented the asymmetric synthesis of diarylmethanols by rhodium catalyzed arylation of aldehydes (Scheme 1.10). After ligand and pre-catalyst complexes screening, they found that i-Pr-DuPHOS/ $[RhCl(coe)_2]_2$ was the best catalytic system for a wide panel of electron rich and poor aromatic aldehydes. Furthermore, the steric hindrance on the aromatic ring of the

[10] Xing, C. -H.; Liu, T. -P.; Zheng, J. R., Ng, J.; Esposito, M.; Hu, Q. -S. *Tetrahedron Lett.* **2009**, *50*, 4953-4957

[11] (a) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851; (b) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138-4140

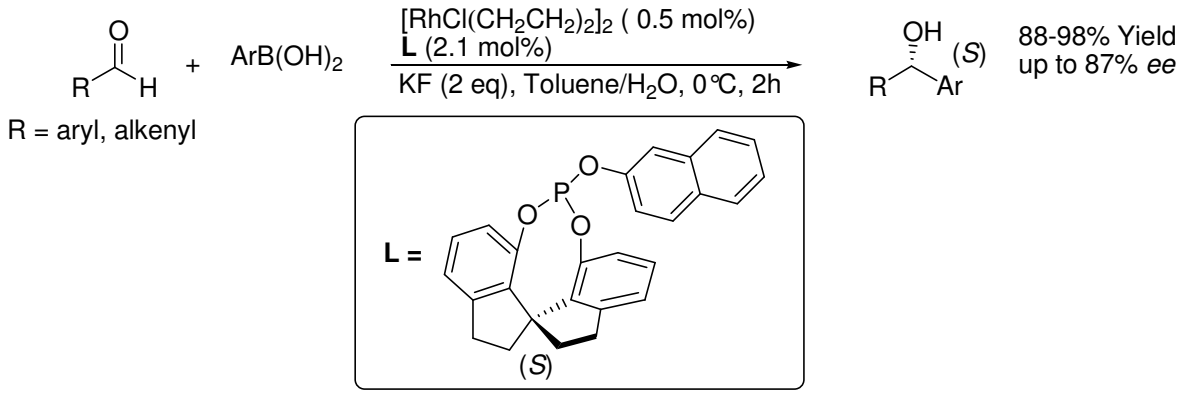
[12] Suzuki, K.; Kondo, K.; Aoyama, T. *Synthesis* **2005**, *8*, 1360-1364

aldehyde seems to be an important factor to achieve high ee values by means of a better asymmetric induction.



Scheme 1.10: Enantioselective rhodium-catalyzed arylation of aromatic aldehydes

Better results were obtained by Zhou[13] in the enantioselective rhodium-catalyzed addition of arylboronic acids to aldehydes by using chiral spiro monophosphite ligands that allowed the synthesis of diarylmethanols in high yields and up to 87% *ee*. A rigid spiro phosphite with a large dihedral angle is responsible of the high stereocontrol (Scheme 1.11).



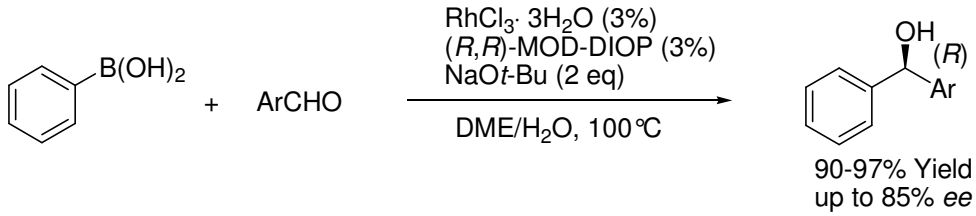
Scheme 1.11: Chiral spiro momophosphites in enantioselective addition of boronic acid to aryl and alkenyl aldehydes.

Basing on the concept of conformational control, previously developed on chiral P,N-ligand mimicking axial chirality,[14] Aoyama *et al.* reported the enantioselective synthesis of diarylmethanols by using a novel chiral hemilabile ligand bearing both diarylphosphino and diarylphosphinoyl groups (Scheme 1.12).[15]

[13] Duan, H. F.; Xie, J. H.; Shi, W. J.; Zhang, Q.; Zhou, Q. L. *Org. Lett.* **2006**, *8*, 1479-1481

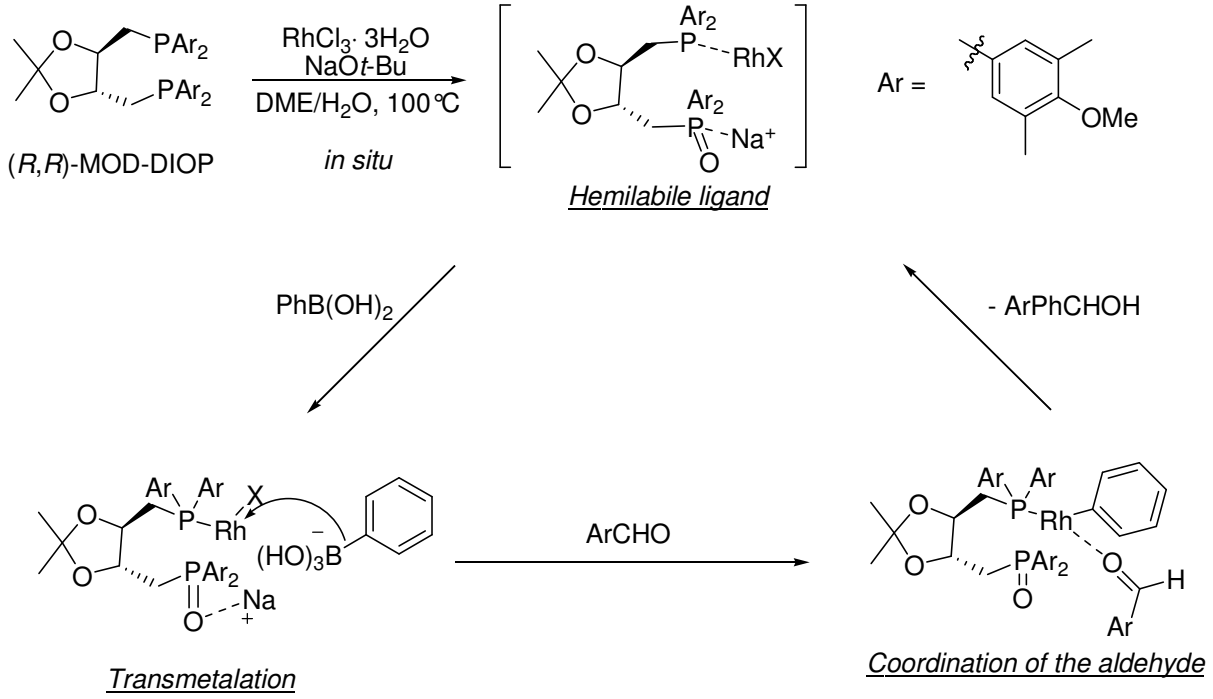
[14] (a) Arao, T.; Kondo, K.; Aoyama, T *Tetrahedron Lett.* **2006**, *47*, 1417-1420 (b) Horibe, H.; Fukuda, K.; Kondo, Okuno, H.; K.; Okuno, H.; Murakami, Y.; Aoyama, T. *Tetrahedron* **2004**, *60*, 10701-10709; (c) Horibe, H.; Kazuta, K.; Kondo, K.; Okuno, H.; Fujita, H.; Murakami, Y.; Aoyama, T. *Synlett* **2003**, 2047-2051; (d) Kondo, K.; Kazuta, K.; Fujita, H.; Sakamoto, Y.; Murakami, Y.*Tetrahedron* **2002**, *58*, 5209-5214

[15] Arao, T.; Suzuki, K.; Kondo, K.; Aoyama, T. *Synthesis* **2006**, *22*, 3809-3814



Scheme 1.12 New hemilabile phosphine ligand in asymmetric synthesis of diarylmethanols

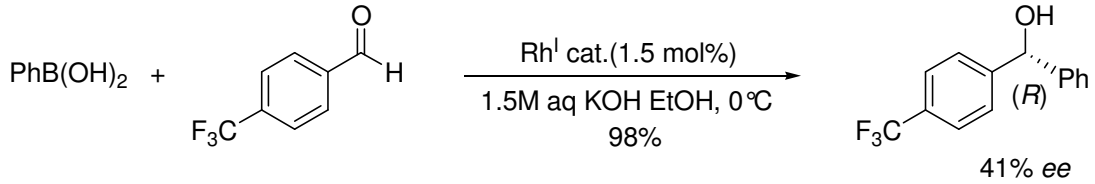
In their previous reports, the authors underlined how a chiral carbon center on the ligand could induce a preferred conformation which is fixed by formation of a chelate structure chiral phosphine-metal complex. In the present context, the catalyst complex can activate, with their soft (PAr_2) and hard($P(=O)Ar_2$) coordinating centers, soft (Rh^{I}) and hard (Na^{+}) metals respectively, thus favouring the transmetalation of the rhodium complex with the boronic acid and the enantiodiscriminating insertion of the aldehyde in the metal-carbon bond as depicted in the Scheme 1.14. The conformational fixation of soft metal-hard metal-hemilabile ligand complex recovers the concept of conformational control, allowing the creation of a favourable reaction environment. High enantioselectivity are reached in reason of the stereogenic carbons near the phosphorus atoms.



Scheme 1.13: Conformational fixation of soft metal-hard metal-hemilabile ligand complex

Finally, with new C_2-symmetric diene ligands, synthetized from the bicyclo[2.2.1] heptadiene in a work realized by Van der Eycken,[16] the catalytic addition of phenyl boronic acid to *p*-trifluoromethylbenzaldehyde proceeds smoothly allowing the synthesis of corresponding alcohol in high yields but poor *ee* although a better compatibility for α,β-unsaturated ketones (Scheme 1.14).

[16] Noël, T.; Vandyck, K.; Van der Eycken, J. *Tetrahedron* **2007**, *63*, 12961-12967



Scheme 1.14: C_2-symmetric bicyclo[2.2.1] heptadiene ligands in asymmetric addition of phenylboronic acid to aldehydes

The synthetic route toward enantiomerically pure 2,5-diisobutyl bicyclo[2.2.1] heptadiene rhodium catalyst, which proved to be the best among various analogues, is shown in Figure 1.3. Starting from the norbornadiene the authors synthesized the diene ligands in four steps.

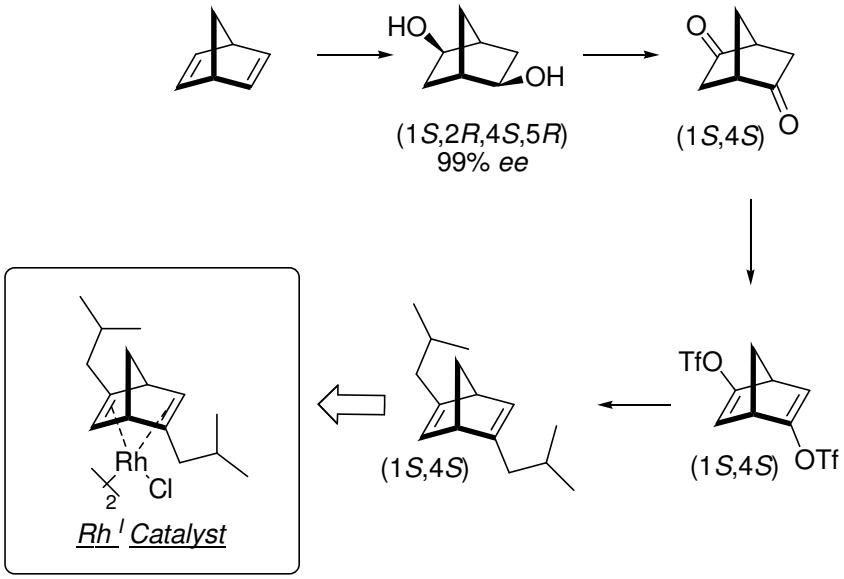
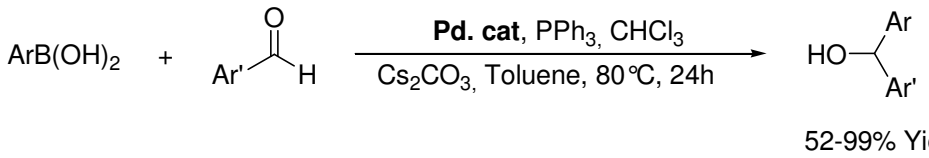


Figure 1.3: Synthesis of enantiomerically pure 2,5-diisobutyl bicyclo[2.2.1] heptadiene ligand

1.2.2 Palladium catalyzed addition of boronic acids to aldehydes

1.1.2.1 Non-stereoselective methods

Although many examples were founded for the rhodium catalyzed addition of boronic acids to aldehydes, cheaper palladium catalysis has recently attracted more and more attention.
In 2005, Ohta reported the addition of aryl boronic acids to aromatic aldehydes in presence of a palladium catalyst, a phosphine ligand and catalytic amounts of chloroform (Scheme 1.15).[17]



Scheme 1.15: Palladium catalyzed addition of boronic acids to aldehydes in presence of chloroform.

[17] Yamamoto, T.; Ohta, T.; Ito, Y. *Org. Lett.* **2005**, *7*, 4153–4155

Electronic effects of aromatic substituents on the reagents have shown a remarkable influence on the course of the reaction. Electron-rich aldehydes and electron-poor aromatic boronic acids are the most disadvantaged substrates but the overall results are good with yields up to 99% (Table 1.1).

entry	*ArB(OH)$_2$*	*aldehyde*	*yield(%)*
1	PhB(OH)$_2$	*p*-CF$_3$C$_6$H$_4$CHO	99
2	PhB(OH)$_2$	*p*-MeOC$_6$H$_4$CHO	56
3	*p*-FC$_6$H$_4$B(OH)$_2$	2-naphtaldehyde	52
4	*p*-FC$_6$H$_4$B(OH)$_2$	*p*-CNC$_6$H$_4$CHO	75
5	*p*-CNC$_6$H$_4$B(OH)$_2$	2-naphtaldehyde	<1

Table 1.1: Influence of aromatic substituents.

In a succeeding work the same authors extended this procedure to α,β-unsaturated aldehydes, ketones and nitriles.[18] According to the authors, chloroform seems to be capital for the reaction, maybe for its coordination to the metal center, affording a Palladium (II) intermediate considered as a starter of the catalytic cycle (Figure 1.4). It has been proposed that the oxidative addition of chloroform to the pre-catalyst produces a dichloromethyl-coordinating palladium(II) intermediate which gives a hydroxyl palladium(II) species by counterion exchange. The transmetalation with the arylboronic acid occurs to generate an arylpalladium(II) intermediate. The following insertion of the aldehyde into the carbon-metal bond produces the corresponding palladium alkoxide and the final hydrolysis gives the diarylmethanol and the hydroxyl palladium(II) species, thus retrieving the catalytic cycle.

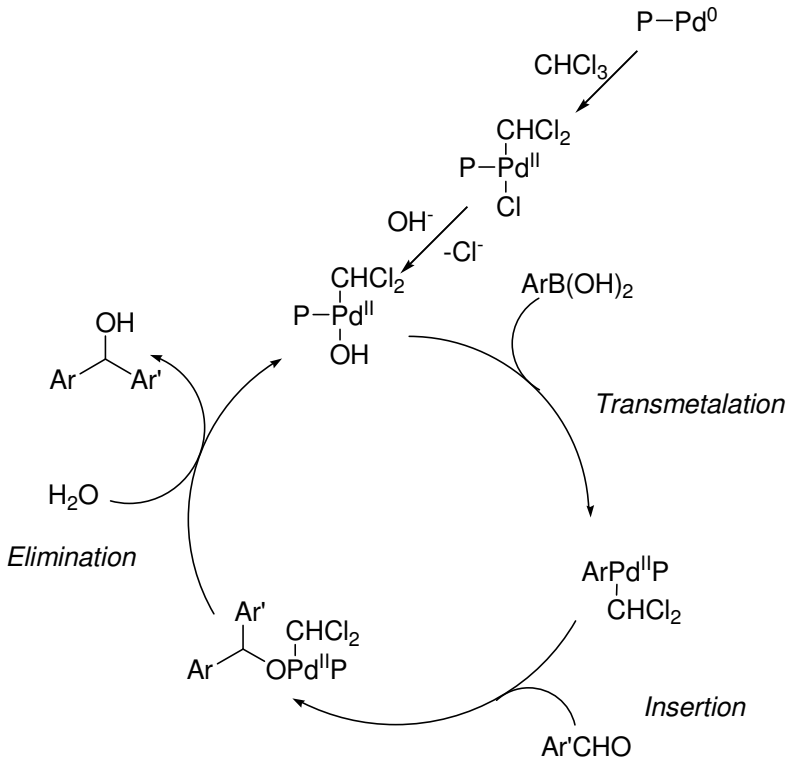
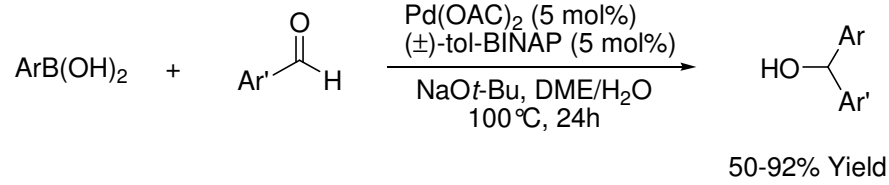


Figure 1.4: Hypothetical catalytic cycle for thePd-catalyzed addition

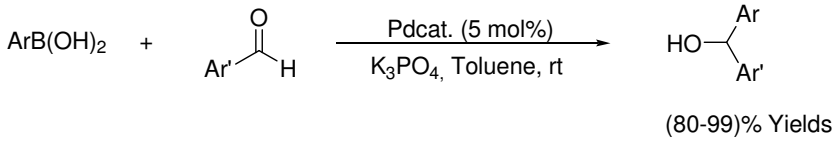
[18] Yamamoto, T.; Iikuka, M.; Takenaka, H.; Ohta, T.; Ito, Y. *J Organomet. Chem.* **2009**, 694, 1325-1332

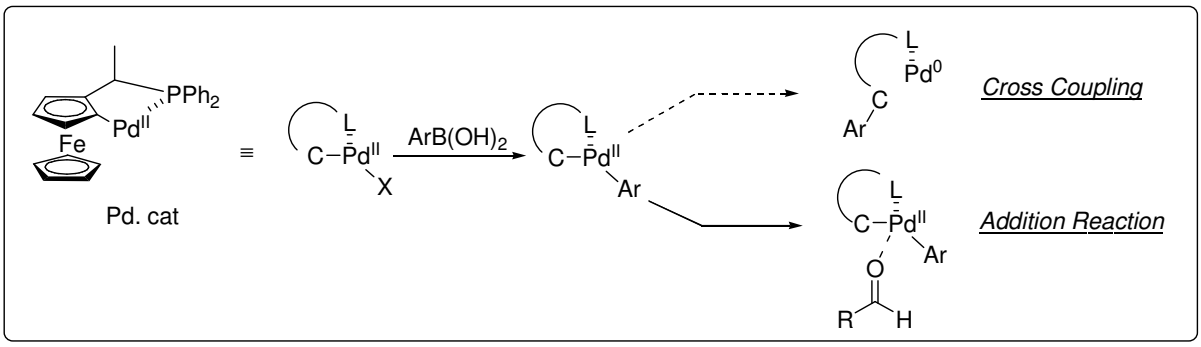
Shortly afterward, Aoyama and coworkers reported a chloroform free Pd-catalytic system for the synthesis of diarylmethanols.[19] The inexpensive palladium acetate and racemic BINAP in presence of a strong base in aqueous solvent are the optimized conditions for the reaction between aromatic aldehydes and boronic acids (Scheme 1.16).



Scheme 1.16: $Pd(OAc)_2$-BINAP catalyzed arylation of aromatic aldehydes

In 2007, Hu showed that an anionic four electron donor-based ferrocenyl phosphapalladacycle, easily synthesized from cheap and air/moisture stable precursors, can catalyze the addition of arylboronic acids with aromatic and aliphatic aldehydes. [20] It was well established that Pd(II) center in palladacycle, originated after the transmetalation step, could act as a Lewis acid (Scheme 1.17). According to the authors, the coordination of the aldehyde will occur preferentially instead of the reductive elimination allowing to a Pd(0) complex as in a classic cross coupling reaction mechanism. The examined palladacycles have proved to be highly efficient catalyst for 1,2 or 1,4 addition to aldehydes, α,β-unsaturated ketones and α-ketoesters.





Scheme 1.17: Palladacycles as good catalyst for the addition of boronic acids to aldehydes

In a second paper about the palladium catalyzed addition of boronic acid and aldehydes, Hu recurs to the palladacycles by making some theoretical considerations about the addition mechanism.[21] In the course of this study the authors have shown that palladacyles are able to distinguish between a cross coupling and an organometallic addition reactions just by

[19] Suzuki, K.; Arao, T.; Ishii, Y.; Maeda, Y.; Kondo, K.; Aoyama, T *Tetrahedron Lett.* **2006**, *47*, 5789-5792
[20] He, P.; Lu, Y.; Dong, C. G.; Hu, Q. S. *Org. Lett.* **2007**, *9*, 343-346.
[21] He, P.; Lu, Y.; Hu Q.-S. *Tetrahedron Lett.* **2007**, *48*, 5283-5288

controlling the reductive elimination process, making them the ideal candidates for that purposes (Figure 1.5).

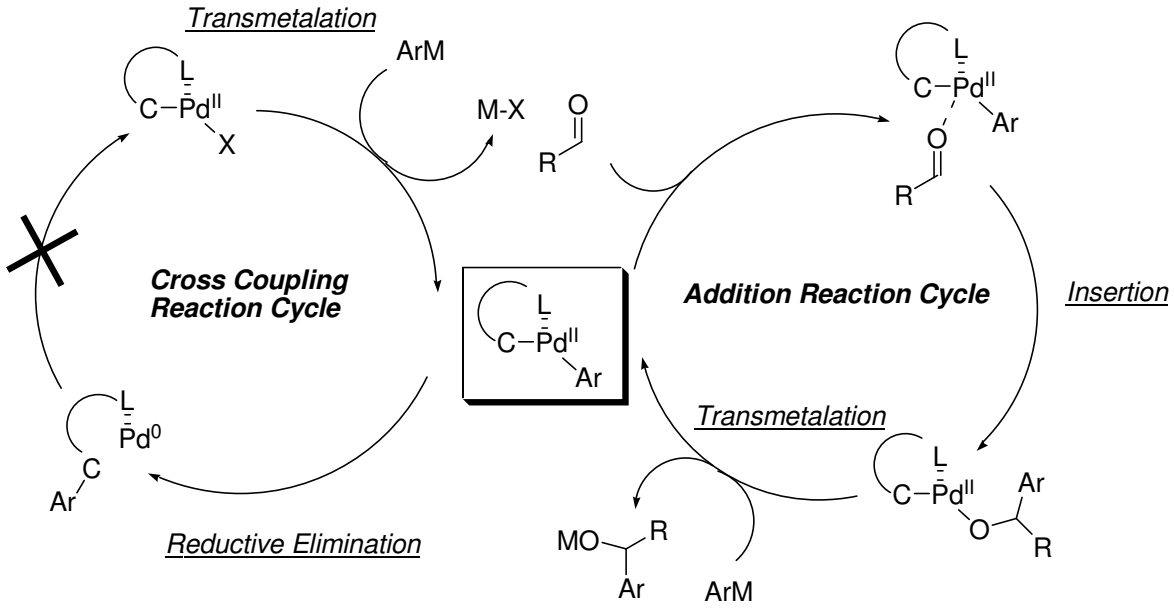
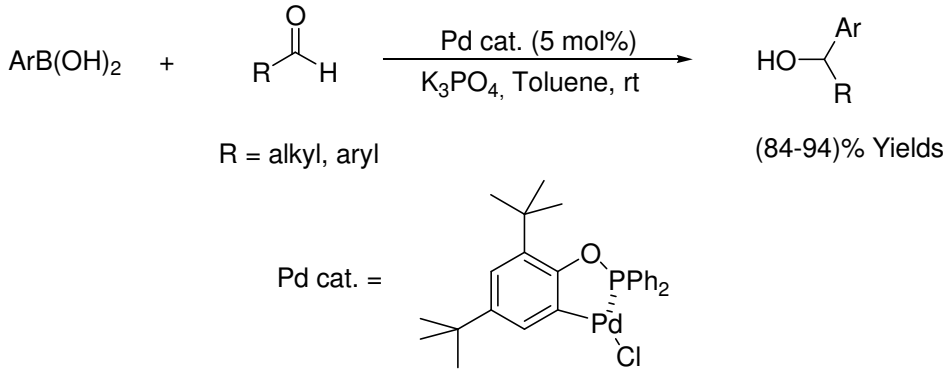


Figure 1.5: Cross-coupling vs addition with palladacycle catalysts

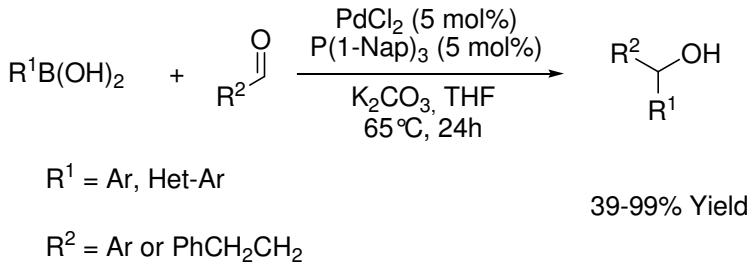
A series of phosphinite- and phosphite-based palladacycles were employed with success in the addition of arylboronic acids to aldehydes, α,β-unsaturated ketones, α-ketoesters and aldimines (Scheme 1.18).



Scheme 1.18: Phosphinite- and phosphite-based palladacycles in the addition of arylboronic acids to aldehydes

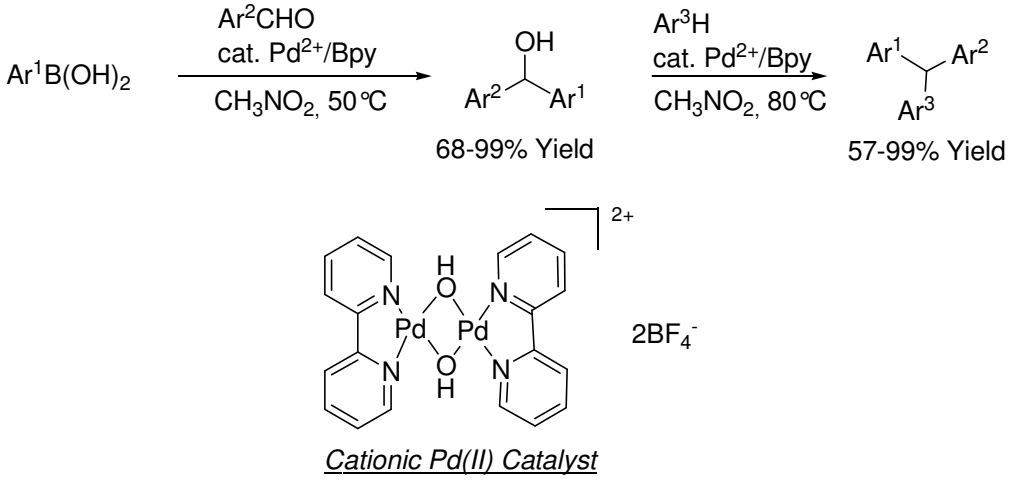
A simple catalytic system based on palladium dichloride and trinaphtylphosphine is described by Wu as efficient for the addition of aryl- and heteroaryl boronic acids to a wide range of aromatic and aliphatic aldehydes with high compatibility for hindered or sensitive substituent on the aromatic moiety (Scheme 1.18).[22] By the way, this transformation provides highly functionalized secondary alcohols in good to excellent yields under simple reaction conditions and any restriction for air or moisture.

[22] Qin, C.; Wu, H.; Cheng, J.; Liu, M.; Zhang, W.; Su, W.; Ding, J.; *J.Org. Chem.* **2007**, *72*, 4102-4107



Scheme 1.18: $PdCl_2$ and $P(1\text{-}Nap)_3$ in catalytic arylation and heteroarylation of aldehydes

Due to their high Lewis acidity and the existence of free coordination sites, also cationic palladium(II) complexes stabilized by appropriate ligands, can be considered as good catalyst system for the activation of carbon-heteroatom multiple bond. Indeed, Lu and Lin[23] described the one-pot synthesis of triarylmethanes starting from arylboronic acids, aldehydes and electron-rich arenes based on the initial formation of the diarylmethanol followed by the addition of the desired arene leading to the triarylmethane in which every aromatic ring has diverse electronic properties (Scheme 1.19). Lower yields of diarylmethanols are observed with electron-rich aromatic aldehydes.



Scheme 1.19 Cationic Pd(II)/bipyridine catalyzed addition of arylboronic acids to aldehydes one-pot to triarylmethanes

The reaction is catalyzed by a cationic Pd(II)/bipyridine complex (Figure 1.6). It has been proposed that while the addition of a boronic acid to an aldehyde follow the classic mechanism leading to the secondary alcohol after a transmetalation between the boronic acid and the palladium catalyst followed by the insertion of the aldehyde and elimination of the corresponding diarylmethanol. This latter, in presence of a Pd(II) species which exhibit good Lewis acidity properties, can be activated, thus favouring the addition of electron-rich arenes leading to triarylmethanes.

[23] Lin, S.; Lu, X. *J. Org. Chem.* **2007**, *72*, 9757-9760

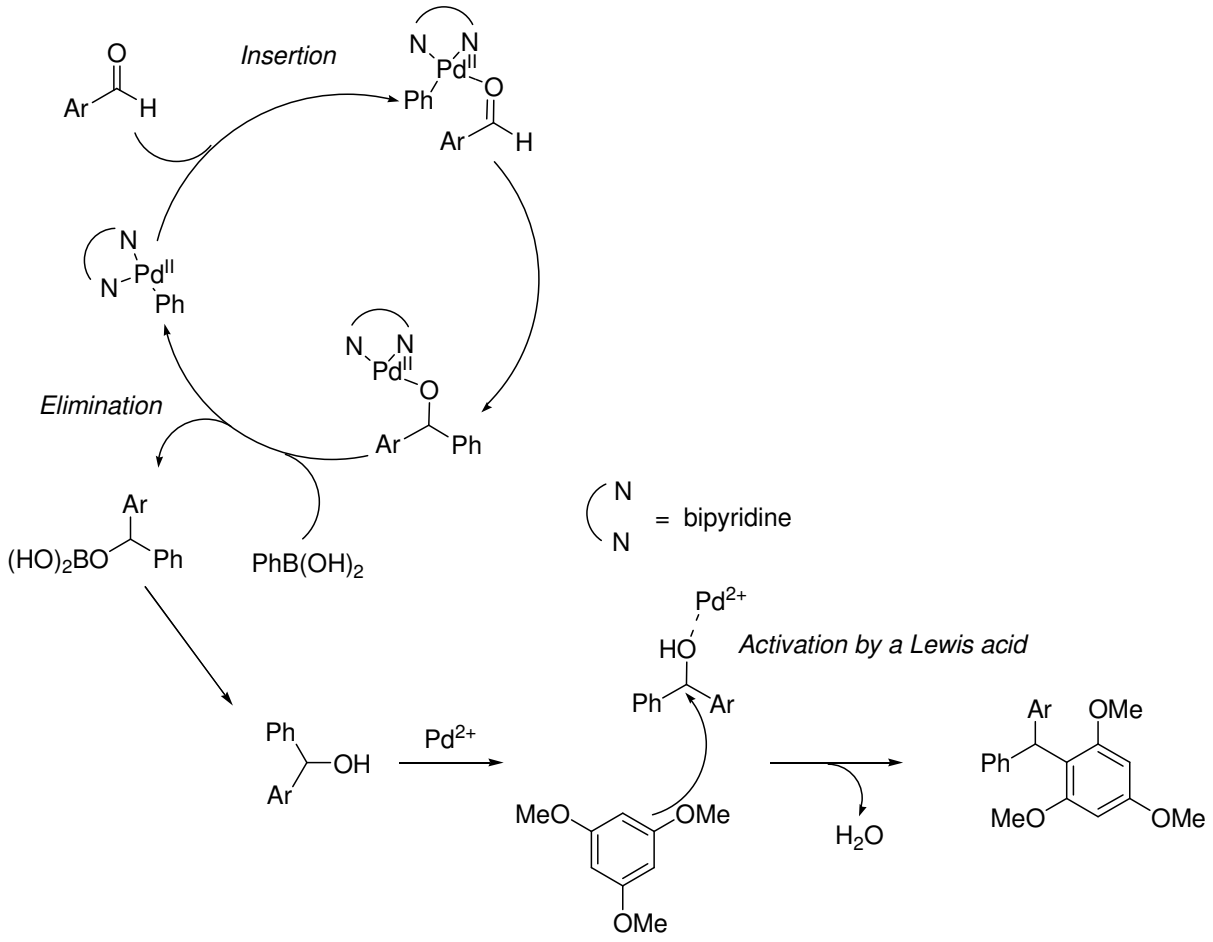
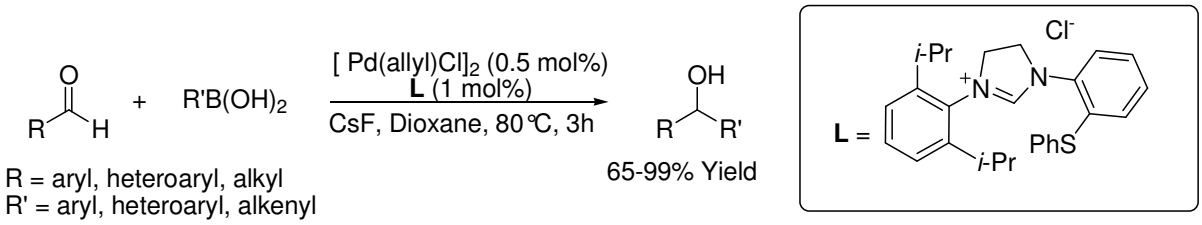


Figure 1.6: Proposed mechanism for the one-pot process

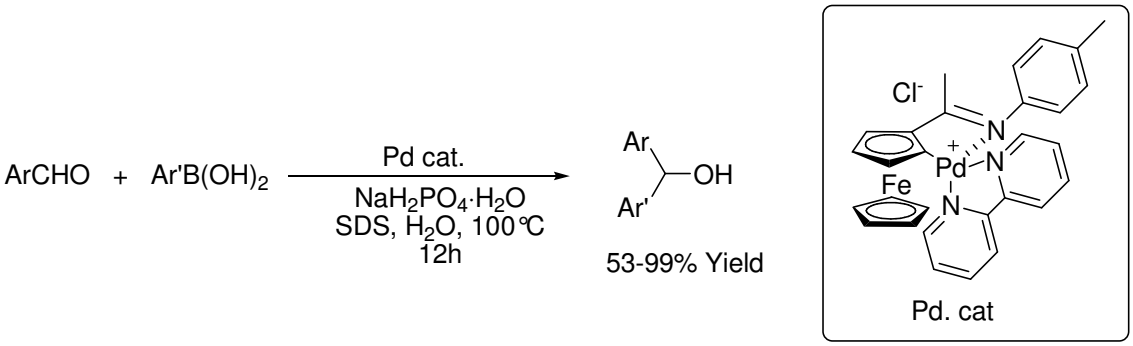
Imidazolium ligands, that have been successfully used in the rhodium catalyzed addition of boronic acid to aldehydes, turned to be useful even with a palladium catalyst. Shirai showed that a palladium/thioether-imidazolinium chloride is highly performing in the reaction between constraining substrates.[24] Indeed, electron-rich, -deficient and sterically hindered aryl- and heteroarylboronic acids as well as aromatic and aliphatic hindered aldehydes have been easily converted in the corresponding secondary alcohols with high yields (Scheme 1.20).



Scheme 1.20: Palladium/thioether-imidazolinium chloride as catalyst for the addition of boronic acid to aromatic and aliphatic hindered aldehydes

[24] Shirai, R.; Shimazawa, R.; Kuriyama, M. *J. Org. Chem.* **2008**,*73*, 1597-1600

Finally, Wu et al, described the synthesis of few phosphine-free ferrocenylimino palladacycles and their application to the coupling between boronic acids and aldehydes.[25] The study revealed that this kind of cationic complexes are excellent catalyst for the reaction and the activity can be enhanced by using a weak acid as additive, an anionic surfactant such as sodium dodecyl sulfonate (SDS) and neat water as solvent (Scheme 1.20).

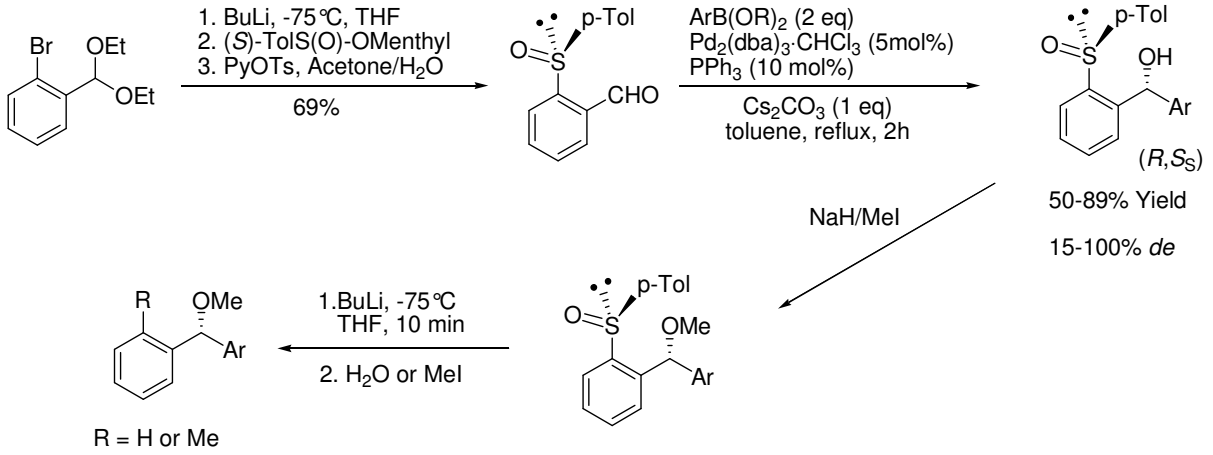


Scheme 1.20: Phosphine-free ferrocenylimino palladacycles in synthesis of diarylmethanols

1.2.2.2 Stereoselective methods

With the aim to develop a stereoselective method for this catalytic transformation, our group presented the first diastereoselective palladium-catalyzed addition of boronic acids to enantiopure aromatic sulfinylaldehydes,[26] prepared in a two-step sequence from commercially available compounds. From commercial 2-bromobenzaldehyde diethyl acetal after the exchange bromine-lithium, trap with enantiopure (S_S)-menthylsulfinate and final hydrolysis, the (S_S)-2-*p*-tolylbenzaldehyde was recovered in acceptable yield. The coupling reaction between the prepared aldehydes and few electron-rich and -poor arylboronic acids, realized following the Ohta conditions,[17] afforded the corresponding diarylmethanols in high yields and moderate to excellent diastereoisomeric ratios depending on the steric hindrance around the reacting boron center. Enantiopures diarylmethanols have been recovered after sulfur-lithium exchange in high yields and without any loss of chirality (Scheme 1.21).

[25] Yu, A.; Cheng, B.; Wu, Y.; Wei, K. *Tetrahedron Lett.* **2008**, *49*, 5405-5407
[26] Novodomskà, A.; Dudičovà, M.; Leroux, F. R.; Colobert, F. *Tetrahedron: Asymm.* **2007**, *18*, 1628-1634

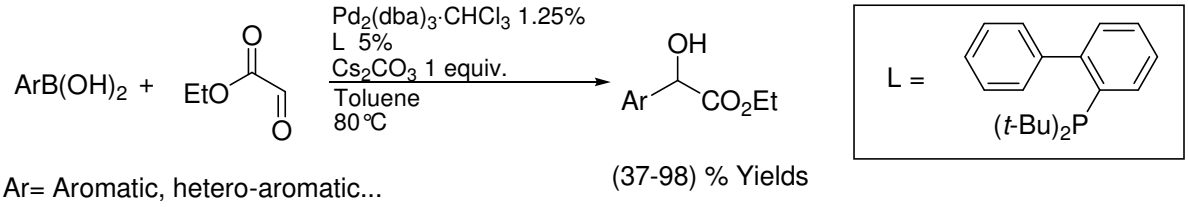


Scheme 1.21: Diastereoselective palladium-catalyzed addition of boronic acids to enantiopure aromatic sulfinylaldimine

1.3 Suzuki–Miyaura coupling reaction of boronic acids and ethyl glyoxylate: synthetic access to mandelate derivatives

1.3.1 Synopsis

In the next section we will introduce our contribution in the field of palladium catalyzed addition of boronic acid to aldehydes. In particular, the coupling of ethyl glyoxylate with arylboronic acids under the reaction conditions first reported by Ohta[17] opening the access to α-hydroxy benzoic esters, also known as mandelic acid derivatives. Due to their versatile functional groups, which may be easily transformed, mandelic esters are important synthetic building blocks in preparative organic chemistry.



Ar= Aromatic, hetero-aromatic...

(37-98) % Yields

Our work is concentrated on the optimization of the reaction conditions and was especially oriented toward the best catalytic system. The reaction scope was also explored by using differently substituted arylboronic acids. These results will be inserted as a publication: Notar Francesco, I.; Wagner, A.; Colobert, F. *Eur. J. Org. Chem.* **2008**, 5692–5695.

1.3.2 Article

DOI: 10.1002/ejoc.200800881

Suzuki–Miyaura Coupling Reaction of Boronic Acids and Ethyl Glyoxylate: Synthetic Access to Mandelate Derivatives

Irene Notar Francesco,[a,b] Alain Wagner,*[b] and Françoise Colobert*[a]

Keywords: C–C coupling / Boronic acids / Boron / Glyoxylates / Palladium

The palladium-catalyzed coupling reaction of arylboronic acids with ethyl glyoxylate provides a straightforward method for the synthesis of mandelic esters. $Pd_2(dba)_3{\cdot}CHCl_3$ in combination with 2-di-*tert*-butylphosphanylbiphenyl as the catalytic system and Cs_2CO_3 as the base were used. The reaction tolerates a wide range of functionalized boronic acids. Mandelic esters were isolated in good-to-excellent yields with a variety of neutral, slightly electron-rich, and slightly electron-poor substituents.

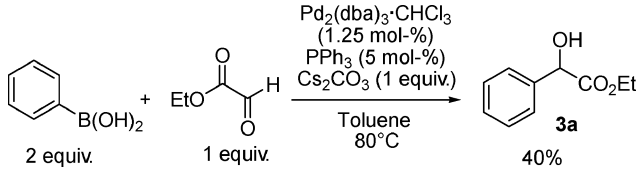
Introduction

As a result of their high stability, easy handling, and nontoxicity, organoboronic acids are useful reagents for carbon–carbon bond formation reactions with various electrophiles in the presence of transition metals.[1] Recently, more attention has been directed to the addition of a metal–carbon bond to electrophiles bearing a carbon–heteroatom double bond. Particularly, the addition of organometallic reagents to aldehydes remains an attractive topic, especially for the asymmetric issue of the products, and it is relatively undiscovered if we consider the limited examples in which transition metals are used. In 1998, Miyaura and coworkers reported that 1,2-addition of phenylboronic acid to aldehydes was catalyzed by a rhodium(I) complex.[2] In the following years, different procedures using Rh catalysts were developed.[3] In comparison to Rh catalysts, Pd catalysts for the 1,2-addition of arylboronic acids to aldehydes are relatively rare. Ohta described addition reactions of arylboronic acids to aromatic aldehydes catalyzed by Pd/PPh_3 complexes in the presence of chloroform.[4] Kondo and Aoyama reported the $Pd(OAc)_2$/tol-binap complex as a chloroform-free catalyst.[5] Hu proposed anionic palladacycles for the 1,2-addition of arylboronic acids to aromatic and aliphatic aldehydes at room temperature.[6] More recently, Shirai and Kuriyama described efficient 1,2-addition reactions of aryl-, heteroaryl-, and alkenylboronic acids to aromatic, heteroaromatic, and aliphatic aldehydes catalyzed by a palladium/thioether–imidazolinium chloride system.[7] In connection with a project devoted to extend new developments around the Suzuki coupling reaction,[8] we recently described the first stereoselective application of Pd-catalyzed addition of boronic acids to aldehydes for the synthesis of pure chiral carbinols.[9]

Herein we report a new catalytic system for the Pd-catalyzed coupling reaction of arylboronic acids and ethyl glyoxylate to give an original method for the preparation of α-hydroxy esters. Indeed, mandelate derivatives are important synthetic building blocks in preparative organic chemistry owing to their versatile functional groups, which may be easily transformed into other functionalities, for example, diols, halo or amino derivatives, and epoxides. This methodology provides an efficient strategy for the addition of organometallic compounds to highly functionalized glyoxylates under mild conditions.

Results and Discussion

Our first experiment was performed by the addition of phenylboronic acid (2 equiv.) to ethyl glyoxylate (1 equiv.) by using the conditions already described,[4,9] that is, $Pd_2(dba)_3{\cdot}CHCl_3$ (1.25 mol-%), triphenylphosphane (5 mol-%), and Cs_2CO_3 (1 equiv.) in toluene at 80 °C, and we obtained ethyl mandelate **3a** as the cross-coupling product in only 40% yield (Scheme 1).



Scheme 1. Initial coupling experiment.

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Because ligands always play important roles in metal-catalyzed chemistry, we then turned our attention to the effect of ligands. We screened a wide range of mono- and bidentate ligands (Figure 1).

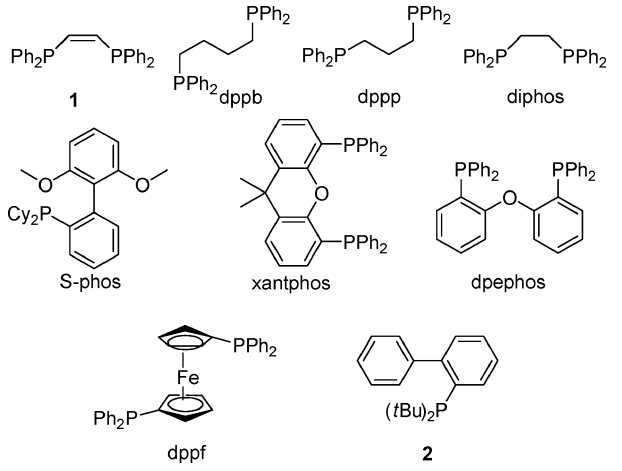
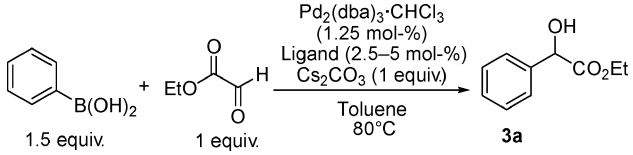


Figure 1. Tested phosphane ligands in Pd-catalyzed addition of phenylboronic acid to ethyl glyoxylate.

Through the screening process (Table 1), it was observed that electronic effects and steric hindrance played important roles in this system. Among various bidentate phosphanes with large bite angles and rigid or nonrigid skeletons (Table 1, entries 2–7), only diphos exhibited average catalytic activity (Table 1, entry 2). The dppp and dppb ligands (Table 1, entries 4 and 5), in which the phosphorus atoms are 1,3- and 1,4-positioned, respectively, have no catalytic activity. Furthermore, more-rigid biphosphanes **1** or dpephos as well as xantphos (Figure 1; Table 1, entries 3, 6, 7) were ineffective. To our delight, biarylphosphane ligands gave the desired product with isolated yields of 55% for S-phos[10] and 78% for 2-di-*tert*-butylphosphanylbiphenyl (**2**) (Table 1, entries 8 and 9) in reaction times of 7 and 8 h,

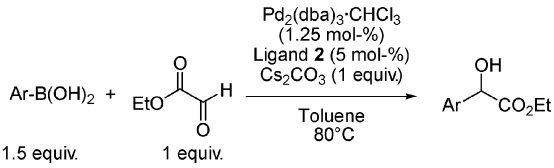
Table 1. Ligand effects in Pd-catalyzed addition of phenylboronic acid to ethyl glyoxylate.

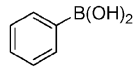
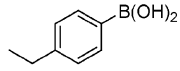
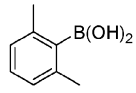
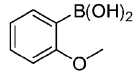
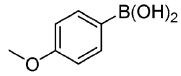
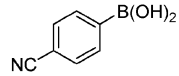
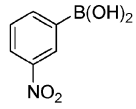
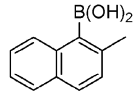
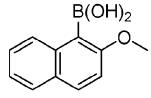
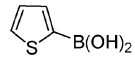
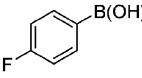
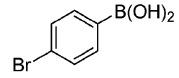
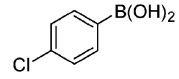
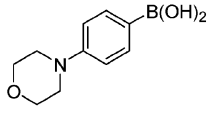
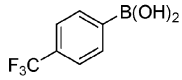


Entry	Ligand	Time [h]	Yield [%][c]
1	PPh_3[a]	24	40
2	diphos[b]	18	51
3	ligand **1**[b]	24	Trace
4	dppb[b]	27	0
5	dppp[b]	27	0
6	dpephos[b]	24	0
7	xantphos[b]	24	0
8	S-phos[a]	7	55
9	ligand **2**[a]	8	78
10	dppf[b]	30	0

[a] Reactions were carried out by using 5 mol-% ligand. [b] Reactions were carried out by using 2.5 mol-% ligand. [c] Isolated yields.

Table 2. Palladium-catalyzed addition of boronic acids to ethyl glyoxylate.[a]



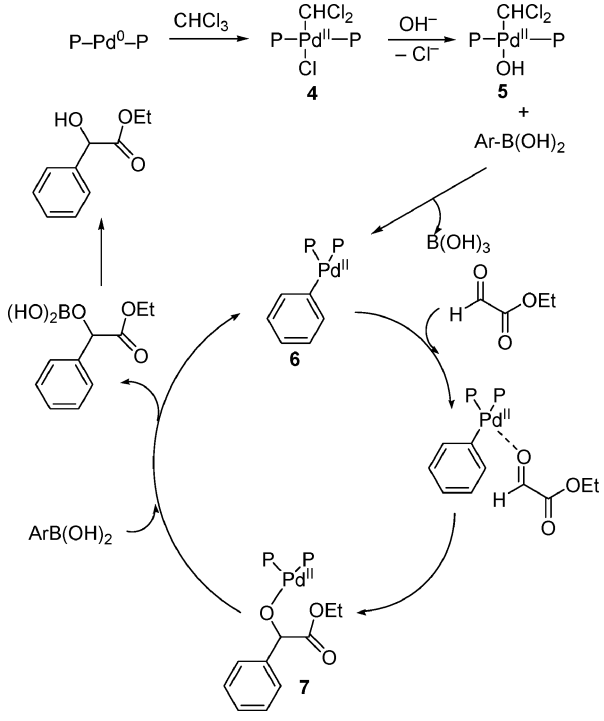
Entry	Ar-B(OH)$_2$	Product	Time [h]	Yield [%][b]
1		**3a**	8	78
2		**3b**	9	83
3		**3c**	13	89
4		**3d**	8	87
5		**3e**	8	85
6		**3f**	23	37
7		**3g**	16	48
8		**4h**	18	41
9		**3i**	16	73
10		**3j**	16	98
11		**3k**	7	74
12		**3l**	7	79
13		**3m**	7	68
14		**3n**	7	87
15		**3o**	8	69

[a] The reactions were carried out with ethyl glyoxylate (solution in toluene, 50%) (1 mmol), boronic acid (1.5 mmol), Cs_2CO_3 (1 mmol), $Pd_2(dba)_3$·$CHCl_3$ (0.0125 mmol), and 2-di-*tert*-butylphosphanylbiphenyl (0.05 mmol) in dry toluene (3 mL) at 80 °C. [b] After column chromatography with unmetalated silica (see Supporting Information).

and we succeeded to decrease the amount of boronic acid involved in this reaction from 2 to 1.5 equiv. Bidentate phosphanes with large bite angles such as dppf (Table 1, entry 10), which was an excellent ligand in Rh-catalyzed additions of boronic acids to aldehydes,[2b] was completely ineffective under our reaction conditions.

To investigate the scope and limitations of this coupling reaction, we subjected various arylboronic acids bearing different electron-donating and electron-withdrawing substituents in the *ortho*, *meta*, and *para* positions of the phenyl ring to the optimized catalytic system [i.e., $Pd_2(dba)_3$·$CHCl_3$ (1.25 mol-%), 2-di-*tert*-butylphosphanylbiphenyl (5 mol-%); Table 2].

We observed a high difference in the yields among phenyl boronic acids having electron-donating or electron-withdrawing groups. Nonactivated boronic acids with electron-withdrawing substituents in the *para* and *meta* positions (Table 2, entries 6 and 7) showed lower reactivities. However, in the case of the *p*-fluoro-, *p*-bromo-, *p*-chloro-, and *p*-trifluoromethylphenylboronic acids (Table 2, entries 11–13, 15), the corresponding ethyl mandelates were obtained in good yields, and these new compounds with strong withdrawing character should be very active for further reactions. However, we observed high yields for the reaction with aryl boronic acids having electron-donor substituents (Table 2, entries 2–5, 9, 14). Additionally electron-donor substituents in the *ortho* position (Table 2, entries 3, 4, 9) had no influence on the yield, which indicates that the reaction does not suffer from steric hindrance around the reacting center. Surprisingly, the mandelate derivative obtained from 2-methylnaphthylboronic acid was formed in a poor yield of 41% (Table 2, entry 8). The palladium-catalyzed coupling reaction of ethyl glyoxylate with electron-rich thiophene boronic acid gave the corresponding coupling product in quantitative yield (Table 2, entry 10).



Scheme 2. Proposed mechanism for the addition of arylboronic acids to ethyl glyoxylate.

We propose a possible catalytic cycle of this reaction that shows that cationic Pd^{II} complexes are excellent catalysts for the addition of arylboronic acids to carbon–heteroatom multiple bonds owing to their high Lewis acidity and the existence of a vacant coordination site.[4,11] At first, oxidative addition of chloroform to phosphane-coordinated with Pd^0 would give chloromethyl-coordinated Pd^{II} intermediate **4**, which produces hydroxyl Pd^{II} species **5** by counteranion exchange. Therefore, transmetalation between the arylboronic acid and hydroxyl Pd^{II} species **5** occurs to generate aryl Pd^{II} intermediate **6** and after coordination of **6** to an aldehyde functionality, the insertion of the aldehyde into the carbon–palladium bond occurs to give palladium alkoxide **7**. Palladium alkoxide **7** is then hydrolyzed to give the corresponding alcohol and aryl Pd^{II} intermediate **6** is recovered (Scheme 2).

Conclusions

Efficient palladium-catalyzed addition of arylboronic acids to ethyl glyoxylate was realized by using the catalytic system of $Pd_2(dba)_3$·$CHCl_3$/2-di-*tert*-butylphosphanylbiphenyl to afford differently substituted mandelic ester derivatives in excellent yields. Further investigations on an asymmetric version of this reaction are underway.

Experimental Section

General Procedure for Coupling of Boronic Acids and Ethyl Glyoxylate: To a suspension of boronic acid (1.5 mmol) and Cs_2CO_3 (1 mmol, 326 mg) in dry toluene (3 mL) was added $Pd_2(dba)_3$·$CHCl_3$ (0.0125 mmol, 13 mg), 2-di-*tert*-butylphosphanylbiphenyl (0.05 mmol, 15 mg) and ethyl glyoxylate (1 mmol) under an atmosphere of argon at room temperature. The temperature was increased to 80 °C, and the mixture was stirred for 7–24 h. The reaction was quenched with water (10 mL), and the resulting mixture was extracted with dichloromethane (3 × 15 mL). The combined organic phase was dried with sodium sulfate, filtered, and concentrated under vacuum. The resulting crude mixture was purified by flash chromatography with unmetalated silica (cyclohexane/EtOAc).

Supporting Information (see footnote on the first page of this article): Experimental procedures and details of compound characterization.

Acknowledgments

We are grateful to Novalyst Discovery (www.Novalyst.com) for financial support.

[1] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; b) A. Suzuki, *J. Organomet. Chem.* **1998**, *576*, 147–168; c) B. Cornlis, W. A. Herrmann in *Applied Homogeneous Catalysis with Organometallic Compounds*, VCH, New York, **1996**; d) M.

Beller in *Transition Metals for Organic Synthesis-Building Blocks and Fine Chemicals*, Wiley-VCH, New York, **1998**.

[2] a) M. Sakai, M. Ueda, N. Miyaura, *Angew. Chem. Int. Ed.* **1998**, *37*, 3279–3281; b) M. Sakai, M. Ueda, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 4450–4452.

[3] a) A. Fürstner, H. Krause, *Adv. Synth. Catal.* **2001**, *343*, 343–350; b) C. Moreau, A. S. Weller, C. G. Frost, *Tetrahedron Lett.* **2001**, *42*, 6957–6960; c) C. Bolm, J. Rudolph, *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851; d) I. Ozdemir, S. Demir, B. Cetinkaya, *J. Mol. Catal. A* **2004**, *215*, 45–48; e) T. Focken, J. Rudolph, C. Bolm, *Synthesis* **2005**, *3*, 429–436; f) S. U. Son, S. B. Kim, J. A. Reingold, G. B. Carpenter, D. A. Sweigart, *J. Am. Chem. Soc.* **2005**, *127*, 12238–12239; g) T. Focken, J. Rudolph, C. Bolm, *Synthesis* **2005**, 429–436; h) K. Suzuki, S. Ishii, K. Kondo, T. Aoyama, *Synlett* **2006**, 648–650; i) P. Wu, H. L. Wu, B. J. Uang, *J. Org. Chem.* **2006**, *71*, 833–835; j) J. Chen, X. Zhang, Q. Feng, M. Luo, *J. Organomet. Chem.* **2006**, *691*, 470–474; k) H. F. Duan, J. H. Xie, W. J. Shi, Q. Zhang, Q. L. Zhou, *Org. Lett.* **2006**, *8*, 1479–1481; l) P. M. P. Gois, A. F. Trindade, L. F. Veiros, V. André, M. T. Duarte, C. A. M. Afonso, S. Caddick, F. G. N. Cloke, *Angew. Chem. Int. Ed.* **2007**, *46*, 5750–5753.

[4] T. Yamamoto, T. Ohta, Y. Ito, *Org. Lett.* **2005**, *7*, 4153–4155.

[5] K. Suzuki, T. Arao, S. Ishii, Y. Maeda, K. Kondo, T. Aoyama, *Tetrahedron Lett.* **2006**, *47*, 5789–5792.

[6] P. He, Y. Lu, C. G. Dong, Q. S. Hu, *Org. Lett.* **2007**, *9*, 343–346.

[7] R. Shirai, R. Shimazawa, M. Kuriyama, *J. Org. Chem.* **2008**, *73*, 1597–1600.

[8] a) A.-S. Castanet, F. Colobert, T. Schlama, *Org. Lett.* **2000**, *2*, 3559–3561; b) A.-S. Castanet, F. Colobert, T. Schlama, *J. Mol. Catal. A* **2002**, *182–183*, 481–487; c) A.-S. Castanet, F. Colobert, P.-E. Broutin, M. Obringer, *Tetrahedron: Asymmetry* **2002**, *13*, 659–665; d) P.-E. Broutin, F. Colobert, *Org. Lett.* **2003**, *5*, 3281–3284; e) P.-E. Broutin, I. Cerna, M. Campaniello, F. Leroux, F. Colobert, *Org. Lett.* **2004**, *6*, 4419–4422; f) F. Colobert, A.-S. Castanet, O. Abillard, *Eur. J. Org. Chem.* **2005**, 3334–3341; g) P.-E. Broutin, F. Colobert, *Eur. J. Org. Chem.* **2005**, 1113–1128; h) P.-E. Broutin, F. F. Colobert, *Org. Lett.* **2005**, *7*, 3737–3740; i) G. Hernandez-Torres, S. Choppin, F. Colobert, *Eur. J. Org. Chem.* **2006**, 1455–1467.

[9] A. Novodomska, M. Dudicova, F. R. Leroux, F. Colobert, *Tetrahedron: Asymmetry* **2007**, *18*, 1628–1634.

[10] a) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871–1876; b) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, ASAP article.

[11] a) B. Zhao, X. Lu, *Org. Lett.* **2006**, *8*, 5987–5990; b) G. Liu, X. Lu, *J. Am. Chem. Soc.* **2006**, *128*, 16504–16505; c) S. Lin, X. Lu, *J. Org. Chem.* **2007**, *72*, 9757–9760.

Received: September 10, 2008
Published Online: October 29, 2008

1.3.3 Experimental part

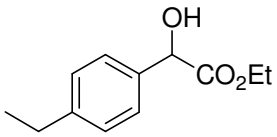
1.3.3.1 General Experimental Procedures.

Toluene was freshly distilled from sodium under Argon. All the phosphines as well as $Pd_2(dba)_3{\cdot}CHCl_3$ were purchased from Strem Chemicals and stored under Argon. Boronic acids were purchased from Aldrich, across and Alfa Aesar. Ethyl glyoxylate was used like a commercially available 50% solution in toluene (Fluka). All the reactions were performed under Argon atmosphere. Thin-layer chromatography (TLC) was carried out on Aluminum plates silica gel 60 F_{254} purchased by Merck. Columns chromatography were performed with unmetalled silica gel which was prepared according to literature[27].
^1H- and ^{13}C- NMR spectra were recorded in $CDCl_3$ at room temperature on a Bruker 300 MHz spectrometer. All chemical shifts (δ) are quoted in parts per million (ppm). The coupling constants are given in Hertz (Hz). Resonance patterns are reported with the following notations: br (broad), s (singulet), d (doublet), t (triplet), q (quartet), m (multiplet). Mass spectra were recorded by HRMS by electrospray ionization method obtained with a microTOF LC Brucker Daltonics microTOF LC from Brucker Daltonics apparatus.

1.3.3.2 General Procedure for Coupling of Boronic acids and Ethyl Glyoxylate.

To a suspension of boronic acid (1.5 mmol) and Cs_2CO_3 (1 mmol, 326 mg) in dry toluene (3ml) were added under Argon, $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0125 mmol, 13 mg), di-tert-butylphosphino biphenyl (0.05 mmol, 15 mg) and the Ethyl Glyoxylate (0.5 mmol). Temperature was increased to 80°C for 7-24 h. The reactions were quenched with water (10 ml) and resulting mixtures were extracted with dichloromethane (3x15 ml). Combined organic phases are dried over sodium sulfate, filtered and concentrated under vacuum. Resulting crude mixtures were purified by flash chromatography using unmetalled silica (Cyclohexane/EtOAc).

1.3.3.3 Characterization data for compounds 4b-4o



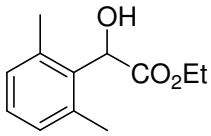
Ethyl 2-(4-ethylphenyl)-2-hydroxyacetate (**4b**): Yield 83%, pale yellow oil.

^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 12 Hz, 2H, C-*H* arom.), 7.19 (d, *J* = 12,3 Hz, 2H, C-*H* arom.), 5.13 (s, 1H, OH-C-*H*), 4.36-4.10 (m, 2H, -CO_2-CH_2-), 3.43 (br s, 1H, -O*H*), 2.65 (q, J = 11.4 Hz, 2H, Ph-CH_2-CH_3), 1,23 (t, J = 11.5 Hz, 3H, -C*H3*), 1.24 (t, J = 10.5 Hz, 3H, -CH_3) ppm

[27] Hubbard, J. S.; Harris, T. M. *J. Org. Chem*. **1981**, *46*, 2566-2570

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.79, 144.50, 135.70, 128.05, 126.50, 72.74, 62.12, 28.53, 15.43, 14.02 ppm

HMRS (ESI^+) calcd for $C_{12}H_{16}O_3$ (M + Li^+) 215.1254, found 215.1239.

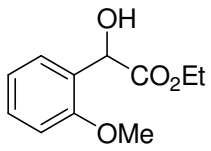


Ethyl 2-hydroxy-2-(2,6-dimethylphenyl)acetate (**4c**): Yield 89%, yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.00 (m, 3H, C-*H* arom.), 5.57 (d, J = 2.7 Hz, 1H, *H*-C-OH), 4.31-4.15 (m, 2H, -CO_2-CH_2-), 3.27 (d, *J* = 2.7 Hz, 1H, -O*H*), 2.37 (s, 6H, 2 -CH_3), 1,22 (t, *J* = 7.2 Hz, 3H, -CO_2-CH_2-CH_3) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.74, 137.32, 134.32, 129.00, 128.21, 69.27,62.20, 20.06, 14.01 ppm

HMRS (ESI^+) calcd for $C_{12}H_{16}O_3$ (M + Li^+) 215.1254, found 215.1239.

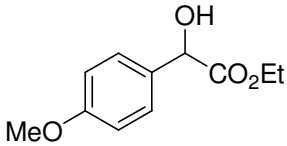


Ethyl 2-hydroxy-2-(2-methoxyphenyl)acetate (**4d**): Yield 87%, yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.25 (m, 2H, C-*H* arom.), 6.99-6.89 (m, 2H, C-*H* arom.), 5.27 (s, 1H, *H*-C-OH), 4.27-4.16 (m, 2H, -CO_2-CH_2-), 3.83 (s, 3H, OCH_3), 3.54 (br s, 1H, -O*H*), 1,21 (t, *J* = 6.9 Hz, 3H, -CO_2-CH_2-CH_3)ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.71, 157.16, 129.42, 127.17, 120.83, 111.11, 70.26, 61.71, 55.49, 14.08 ppm

HMRS (ESI^+) calcd for $C_{11}H_{14}O_4$ (M + Li^+) 217.1047, found 217.1018.

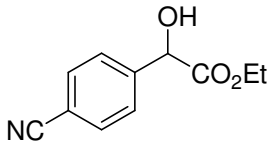


Ethyl 2-hydroxy-2-(4-methoxyphenyl)acetate (**4e**): Yield 85%, yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 12.6 Hz, 2H, C-*H* arom.), 6.89 (d, *J* = 13.2 Hz, 2H, C-*H* arom.), 5.12 (d, J = 8.4 Hz, 1H, *H*-C-OH), 4.35-4.08 (m, 2H, -CO_2-CH_2-), 3.80 (s, 3H, OCH_3), 3.43 (d, *J* = 2.7 Hz, 1H, -O*H*), 1,22 (t, *J* = 10.8 Hz, 3H, -CO_2-CH_2-CH_3) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.85, 159.64, 130.61, 127.75, 113.95, 72.45, 62.11, 55.25, 14.03 ppm

HMRS (ESI$^+$) calcd for $C_{11}H_{14}O_4$ (M + Li^+) 217.1047, found 217.1052.

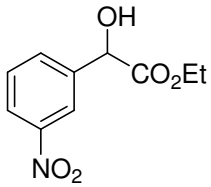


Ethyl 2-(4-cyanophenyl)-2-hydroxyacetate (**4f**): Yield 85%, yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H, C-*H* arom.), 7.60 (d, *J* = 8.4 Hz, 2H, C-*H* arom.), 5.22 (s, 1H, *H*-C-OH), 4.34-4.12 (m, 2H, -CO_2-CH_2-), 3.62 (br s, 1H, -O*H*), 1,24 (t, *J* = 7.2 Hz, 3H, -CO_2-CH_2-CH_3) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.51, 143.31, 132.29, 127.19, 118.51, 112.22, 72.14, 62.88, 13.98.

HMRS (ESI$^+$) calcd for $C_{11}H_{11}NO_3$ (M + Li^+) 212.0894, found 212.0873.

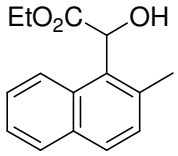


Ethyl 2-(3-nitrophenyl)-2-hydroxyacetate (**4g**): Yield 48%, pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (t, *J* = 1.8 Hz, 1H, C-*H* arom.), 8.21-8.17 (m, 1H, C-*H* arom.), 7.81 (d, *J* = 7.8 Hz, 1H, C-*H* arom.), 7.55 (t, *J* = 7.8 Hz, 1H, C-*H* arom.), 5.28 (s, 1H, *H*-C-OH), 4.36-4.16 (m, 2H, -CO_2-CH_2-), 3.66 (br s, 1H, -O*H*), 1,25 (t, *J* = 7.2 Hz, 3H, -CO_2-CH_2-CH_3) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.52, 140.35, 129.45, 123.30, 121.63, 71.80, 62.94, 14.01.

HMRS (ESI$^+$) calcd for $C_{11}H_{11}NO_5$ (M + Li^+) 232.0792, found 232.0809.

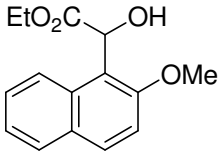


Ethyl 2-hydroxy-2-(2-methylnaphthalen-1-yl)acetate (**4h**): Yield 41%, white crystals (mp = 89.4-90.8).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.1 Hz, 1H, C-*H* arom.), 7.83-7.73 (m, 2H, C-*H* arom.), 7.50-7.39 (m, 2H, C-*H* arom.), 7.31 (d, *J* = 8.4 Hz, 1H, C-*H* arom.), 5.94 (s, 1H, *H*-C-OH), 4.28-4.09 (m, 2H, -CO_2-CH_2-), 3.49 (br s, 1H, -O*H*), 2.61 (s, 3H, CH_3), 1,10 (t, *J* = 7.2 Hz, 3H, -CO_2-CH_2-CH_3) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.04, 135.43, 132.92, 131.64, 130.46, 129.24, 128.98, 128.58, 126.43, 124.81, 123.79, 69.07, 62.16, 20.47, 13.93 ppm

HMRS (ESI$^+$) calcd for $C_{15}H_{16}O_3$ (M + Li^+) 251.1254, found 251.1233.

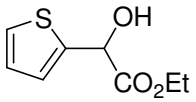


Ethyl 2-hydroxy-2-(2-methoxynaphthalen-1-yl)acetate (**4i**): Yield 73%, white crystals (mp = 91.7-93.3).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.7 Hz, 1H, C-*H* arom.), 7.86 (d, *J* = 9.3 Hz, 1H, C-*H* arom.), 7.81 (d, *J* = 8.1 Hz, 1H, C-*H* arom.), 7.54-7.48 (m, 1H, C-*H* arom.), 7.37 (t, *J* = 7.8 Hz, 1H, C-*H* arom.), 7.28 (d, *J* = 9 Hz, 1H, C-*H* arom.), 6.02(s, 1H, *H*-C-OH), 4.29-4.14 (m, 2H, -CO_2-CH_2-), 3.95 (s, 3H, OCH_3), 3.72 (br s, 1H, -O*H*), 1,15 (t, *J* = 7.2 Hz, 3H, -CO_2-CH_2-CH_3) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 176.68, 155.19, 132.58, 130.82, 129.42, 128.62, 127.25, 123.75, 122.66, 119.72, 113.41, 66.28, 56.69, 14.09 ppm

HMRS (ESI$^+$) calcd for $C_{15}H_{16}O_4$ (M + Li^+) 267.1203, found 267.1170.

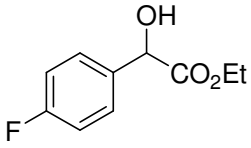


Ethyl 2-hydroxy-2-(thiophen-2-yl)acetate (**4j**): Yield 98%, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.27 (m, 1H, C-*H* arom.), 7.11 (t, *J* = 0.9 Hz, 1H, C-*H* arom.), 7.01-6.98 (m, 1H, C-*H* arom.), 5.41 (d, J = 6 Hz, 1H, *H*-C-OH), 4.35-4.24 (m, 2H, -CO_2-CH_2-), 3.47 (d, *J* = 2.7 Hz, 1H, -O*H*), 1,30 (t, *J* = 7.2 Hz, 3H, -CO_2-CH_2-CH_3) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.47, 141.54, 126.92, 125.64, 125.28, 69.09, 62.57, 14.04 ppm

HMRS (ESI$^+$) calcd for $C_8H_{10}O_3S$ (M + Li^+) 193.0511, found 193.0543.

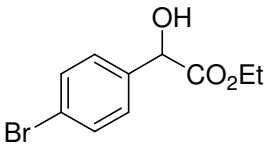


Ethyl 2-(4-fluorophenyl)-2-hydroxyacetate (**4k**): Yield 74%, colorless needles (mp = 63.7-67.5).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2H, C-*H* arom.), 7.08-7.02 (m, 2H, C-*H* arom.), 5.14 (s, 1H, OH-C-*H*), 4.32-4.12 (m, 2H, -CO_2-CH_2-), 3.51 (br s, 1H, -O*H*), 1,23 (t, J = 6 Hz, 3H, -CH_3) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.49, 162.7 (d, $^{1}J_{C\text{-}F}$= 122,62 Hz), 134.19 (d, $^{4}J_{C\text{-}F}$= 1.4 Hz), 128.24 (d, $^{2}J_{C\text{-}F}$= 8.2 Hz), 115.45 (d, $^{3}J_{C\text{-}F}$= 21.6 Hz), 72.162, 62.37, 14.00 ppm

HMRS (ESI$^+$) calcd for $C_{11}H_{11}FO_3$ (M + Li^+) 205.0897, found 205.0896.

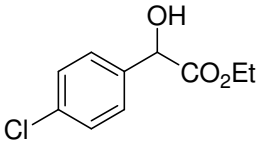


Ethyl 2-(4-bromophenyl)-2-hydroxyacetate (**4l**): Yield 79%, white solid (mp = 69.4-73.2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 2H, C-*H* arom.), 7.23 (d, *J* = 8.4 Hz, 2H, C-*H* arom.), 5.04 (s, 1H, OH-C-*H*), 4.24-4.04 (m, 2H, -CO_2-CH_2-), 3.36 (br s, 1H, -O*H*), 1,15 (t, J = 6.9 Hz, 3H, -C*H3*), 1.24 (t, J = 10.5 Hz, 3H, -CH_3) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.21, 137.36, 131.66, 128.19, 122.42, 72.21, 62.51, 14.01 ppm

HMRS (ESI$^+$) calcd for $C_{10}H_{11}BrO_3$ (M + Li^+) 265.0046, found 265.0015.

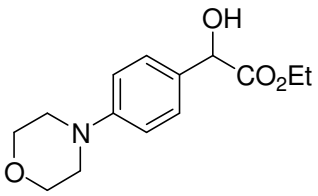


Ethyl 2-(4-chlorophenyl)-2-hydroxyacetate (**4m**): Yield 68%, colorless needles (mp = 62.8-64.7).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.31 (m, 4H, C-*H* arom.), 5.13 (s, 1H, OH-C-*H*), 4.31-4.12 (m, 2H, -CO_2-CH_2-), 3.54 (br s, 1H, -O*H*), 1,22 (t, J = 7.2 Hz, 3H, -CH_3) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.23, 136.82, 134.19, 127.84, 72.14, 62.41, 13.97 ppm

HMRS (ESI^+) calcd for $C_{10}H_{11}ClO_3$ ($M + Li^+$) 265.0551, found 265.0573.

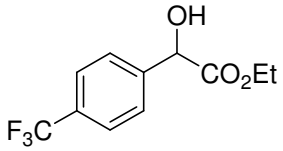


Ethyl 2-hydroxy-2-(4-morpholinophenyl)acetate (**4n**): Yield 87% , white solid (mp = 109.5-112.2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.7 Hz, 2H, C-*H* arom.), 6.89 (d, *J* = 8.7 Hz, 2H, C-*H* arom.), 5.08 (d, J = 5.7 Hz, 1H, *H*-C-OH), 4.32-4.11 (m, 2H, -CO_2-C*H_2*-), 3.85 (t, *J* = 4.8 Hz, 4H, O-C*H_2*-CH_2-N), 3.35 (d, *J* = 6 Hz, 1H, -O*H*), 3.16 (t, *J* = 4.8 Hz, 4H, O-CH_2-C*H_2*-N) 1,23 (t, *J* = 7.2 Hz, 3H, -CO_2-CH_2-C*H_3*) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.85, 151.23, 129.70, 127.50, 115.43, 72.496, 66.791, 61.99, 49.03, 14.04 ppm

HMRS (ESI^+) calcd for $C_{14}H_{19}NO_4$ ($M + Li^+$) 272.1492, found 272.1523.



Ethyl 2-(4-(trifluoromethyl)phenyl)-2-hydroxyacetate (**4o**): Yield 69%, white solid (mp = 84.1-87.6).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.4 Hz, 2H, C-*H* arom.), 7.75 (d, *J* = 8.7 Hz, 2H, C-*H* arom.), 5.22 (d, J = 2.7 Hz, 1H, *H*-C-OH), 4.32-4.16 (m, 2H, -CO_2-C*H_2*-), 3.55 (d, *J* = 4.8 Hz, 1H, -O*H*), 1,24 (t, *J* = 7.2 Hz, 3H, -CO_2-CH_2-C*H_3*) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.94, 142.16, 130.76 (q, $^2J_{C\text{-}F}$= 32.25 Hz), 126.82, 125.44 (q, $^3J_{C\text{-}F}$= 5.62 Hz), 123.98 (q, $^1J_{C\text{-}F}$= 270.37 Hz, -*C*F_3), 72.25, 62.66, 13.96 ppm

HMRS (ESI^+) calcd for $C_{11}H_{11}F_3O_3$ ($M + Li^+$) 255.0815, found 255.0921.

1.4 Enclosure

1.4.1 Stereoselective approaches to the synthesis of chiral non racemic mandelate derivatives.

In order to extend our methodology to the synthesis of chiral non racemic mandelates, two stereoselective strategies based either on introducing chiral ligand on the catalyst or chiral inducer on the glyoxylate moiety have been explored.

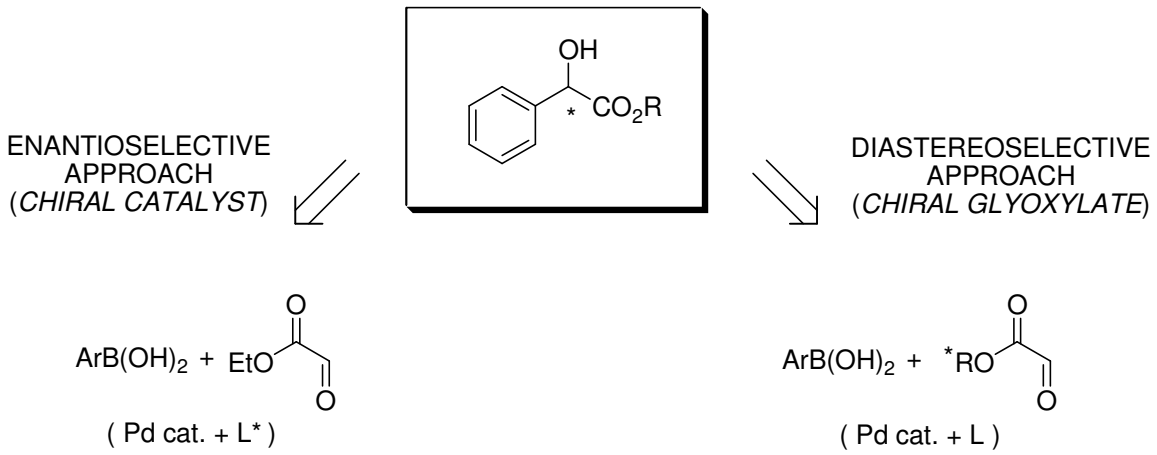
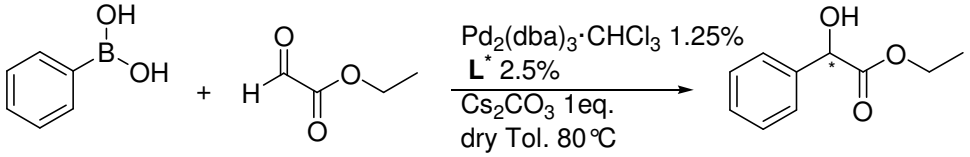
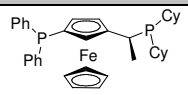
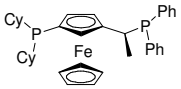
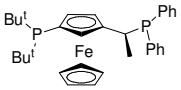
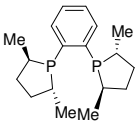
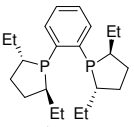
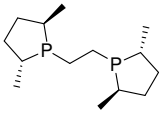
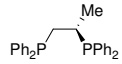
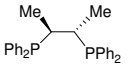
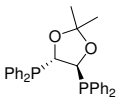
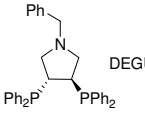
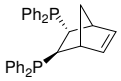
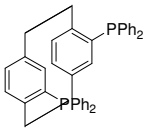
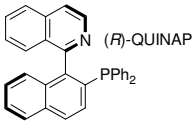
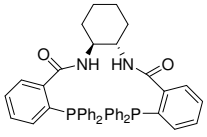


Figure 1.7 Enantio- and diastereoselective approaches.

In the "chiral catalyst" approach, a large number of chiral mono- and bis-phosphines have been tested in a model reaction between phenylboronic acid and ethyl glyoxylate under the reaction conditions optimized for the racemic coupling. Indeed, phenylboronic acid have been subjected to react with ethyl glyoxylate in presence of $Pd_2(dba)_3$·chloroform adduct and a chiral phosphine ligand in toluene at 80°C. The results are summarized in the Table 1.2. We observed that ferrocenylphosphines, which belong to the class of the *Josiphos* type diphosphines (entries 1-2-3), showed good catalytic activity but only poor chiral induction. Methyl-, Ethyl-DUPHOS (entries 4 and 5) and non aromatic bis-phospholane ligand (*R*,*R*)-Me-BPE (entry 6) were almost equally effective and afforded ethyl mandelate in low average ee. With 1,2 bis-diarylphosphines (entries 7 to 11), the results revealed big differences in term of both reactivity and asymmetric induction, suggesting that the chemical "environment" around the P atoms is also an important factor in catalysis. While (*S*,*S*)-Chiraphos displayed a good catalytic activity affording the coupling product in high yield and slightly better *ee* (entry 8), with (*R*)-Prophos, which have the same structure unless a methyl group and consequently only one stereogenic center, no coupling product was obtained (entry 7). 1,3-dioxolane bisphosphine as the DIOP (entry 9) afforded the ethyl mandelate in 62% yield but as racemic mixture. (+)-NorPhos (entry 11), a highly rigid 1,2-bisphosphine ligand having a norbornene structure, gave the ethyl mandelate in 65% yield and 32% ee, which is the best result in term of enantiomeric excess altogether. (S)-Phanephos, a [2,2]-paracyclophanic structured bisphosphine , displayed only moderate yields and poor enantioselectivity of the final ester (entry 13). Atropoisomeric monophosphines as QUINAP (entry 14) as well as

diarylphosphines derived from chiral 1,2 diamino cyclohexane (entry 15), N-protected pyrolidine (entry 10) and linear 1,3 diarylphosphine (entry 12) were totally ineffective.



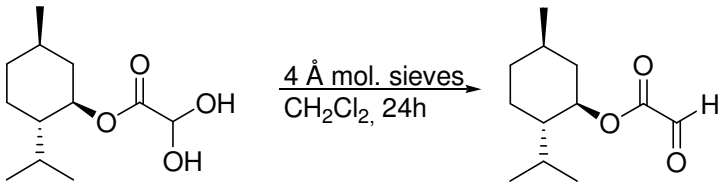
entry	*Ligand* (L*)	*Time*	*Yield*[a](%)	$[\alpha]_D$	*ee*[b] *(%)*	*Abs conf.*
1	 (S)-JOSIPHOS	16h	91	+3.8 °	3	*S*
2		24h	55	+12,8°	10	S
3		25h	63	+17.3°	13.5	*S*
4	 (*R*,*R*)Me-DuPHOS	7h	62	- 4,5°	3.5	*R*
5	 (*S*,*S*)-Et-DuPHOS	15h	69	+7.1°	5.5	*S*
6	 (*R*,*R*)-Me-BPE	14h	73	-7.3°	5.7	*R*
7	 (*R*)-PROPHOS	25h	0	--	--	--
8	 (*S*,*S*)-CHIRAPHOS	7h	86	-23,4°	18	*R*
9	 *S*-DIOP	16h	62	+0.8°	--	*S*
10	 DEGU-PHOS	23h	0	--	--	--
11	 (+)-NORPHOS	13h	65	-41.7°	32	*R*
12	 (2*R*,4*R*)-BDPP	27h	traces	--	--	--
13	 (+)-S-PHANEPHOS	14h	43	+10.9°	8.5	*S*
14	 (*R*)-QUINAP	32h	traces	--	--	--
15	 *(R,R)*-TROST LIGAND	18	0	--	--	--

[a] Yields after chromatography. [b] Calculated from $[\alpha]_D$ value by comparison with enantiomerically pure sample of ethyl mandelate.

Table 1.2: Chiral ligands screening in enantioselective palladium catalyzed addition of phenylboronic acid to ethyl glyoxylate.

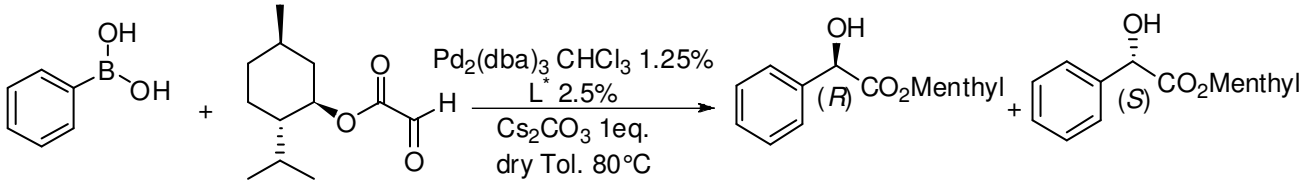
In order to improve the enantioselectivity, we tried to optimize the reaction conditions by changing solvent or base and lowering temperature, by keeping as tag reaction the enantioselective coupling between phenylboronic acid and ethyl glyoxylate, using $Pd_2(dba)_3{\cdot}CHCl_3$ and (*R*,*R*)-(+)-NorPhos as catalytic system and Cs_2CO_3 as inorganic base. To our delight, when the reaction was carried out at lower temperatures, higher yields were achieved (60 and 50°C giving respectively 77 and 72% yields) and only a small improvement of the ee from 32 to 33%. However, under 50°C no reaction occurred as well as when the reaction is performed in polar oxygenated solvents such as dioxane, THF or DME. The inorganic base seems also to be important. Indeed, when we used K_3PO_4, the yields and the ee dropped to 51 and 6% respectively. With K_2CO_3 and CsF the reaction didn't work at all.

Thus, we decided to explore the diastereoselective approach performing the coupling reaction by using the commercial (-)-menthyl glyoxylate hydrated as electrophilic counterpart under the reaction conditions optimized for the racemic coupling.
The free menthyl glyoxylate was recovered after treatment of a solution of his hydrated form with molecular sieves in dichloromethane at room temperature for 24 hours (Scheme 1.22).



Scheme 1.22: Dehydration of commercial (-)-menthylglyoxylate

When the (-)-menthyl glyoxylate is employed in the reaction with phenylboronic acid in presence of the triphenylphosphine and $Pd_2(dba)_3{\cdot}CHCl_3$, the hydroxy ester was isolated with excellent yield but no selectivity (Table 1.3, entry 1). In order to improve and enhance the asymmetric induction, we decided to use a combination of chiral inducer and chiral catalyst (Table 1.2, entries 2 to 6). We selected few phoshine ligands that have been used in the case of the enantioselective approach. Surprisingly, (*S*,*S*)-DIOP and (*R*,*R*)-Me-BPE didn't conduct to any coupling product whereas they showed a good catalytic activity in the previous case (Table 1.2, entries 2-3). With (*R*,*R*)-Me-Duphos, the diastereoisomeric (S)-menthyl mandelates was obtained in low yield and only 10% *de* (Table 1.2, entry 4). With (*R*,*R*)-NorPhos and (*S*,S)-Chiraphos better yields of final product were observed in lower reaction time but, unfortunately they did not bring any noticeable improvement of the diastereoisomeric excess which didn't exceed 30% for the (S)-mandelate (Table 1.2, entries 5-6).



Entry	*Ligand*	*Time* (h)	*Yield*[a] *(%)*	*dr*[b] *[(S):(R)]*
1	PPh_3	2,5	84	50:50
2	(*S*,*S*)-Me-BPE	16	0	--
3	(*S*,*S*)-DIOP	13	0	--
4	(*R*,*R*)Me-DUPHOS	17	19	55:45
5	(*S*,*S*)-CHIRAPHOS	5	58	65:35
6	(*R*)-(+)-NORPHOS	4	51	60:40

a. Yields after chromatography. b Calculated from ^{1}H-NMR spectra of the crude

Table 1.3: Diastereoselective addition of phenylboronic acid to (-)-menthyl glyoxylate.

After some considerations on the structure of the used chiral inducer, we envisioned that a phenyl group at the 8 position could result in a better diastereofacial selectivity by directing the approach of the nucleophile to the less hindered face of the glyoxylate, leading to higher diastereoisomeric ratios as depicted in Figure 1.8.

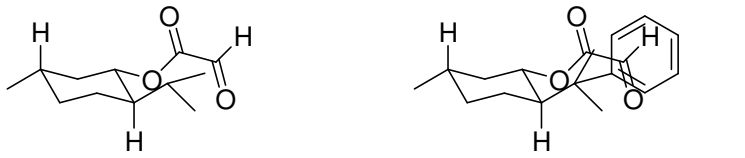
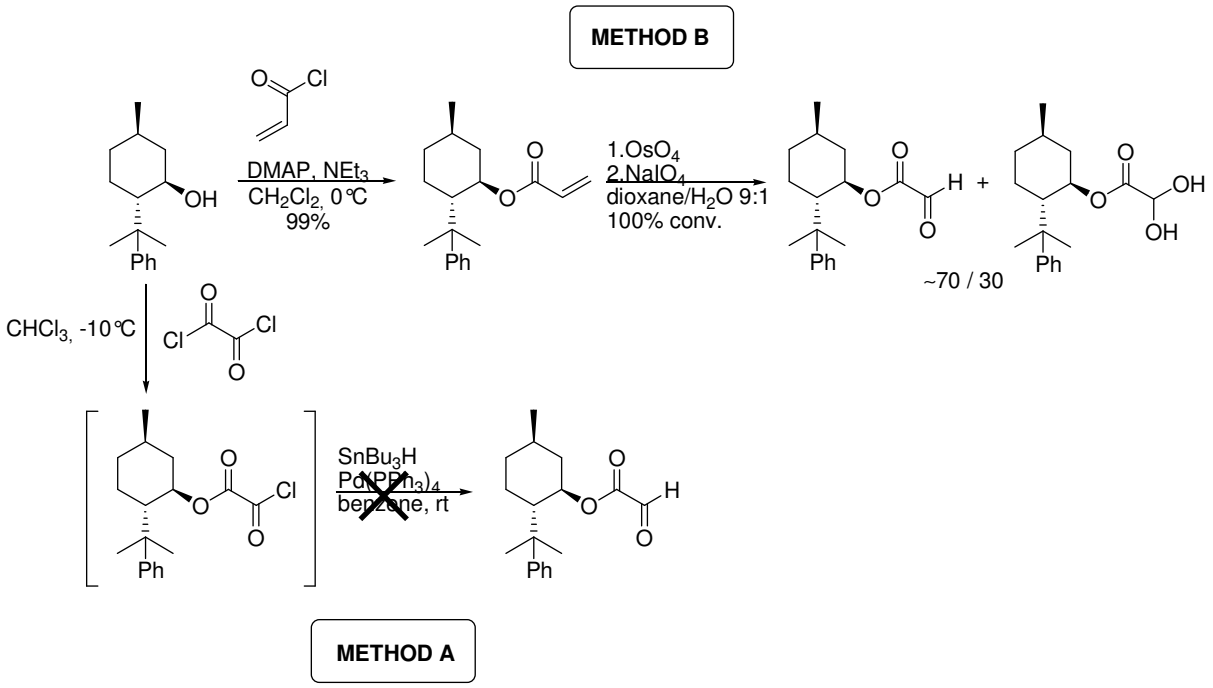


Figure 1.8: 8-Phenylmenthyl glyoxylate vs menthyl glyoxylate

The enantiopure (-)-8-phenyl menthol has been synthesized by a known procedure starting from the (*R*)-(+)-pulegone,[28] and it has been employed in the synthesis of the corresponding glyoxylate. Two different methods have been applied as shown in the Scheme 1.23. In the Method A, previously described by Rodriguez-Borges[29], the chiral carbinol reacted with the oxalyl chloride and the corresponding glyoxylic chloride product is immediately employed for the following coupling using the tributyltin hydride in presence of a palladium catalyst, in benzene at room temperature. Nevertheless, no reaction occurred and the starting alcohol was completely recovered. Alternatively, according the Method B described by Whitsell[30] we synthesized the acrylic ester of the (-)-8-phenyl menthol in high yields starting from the acrylic chloride, catalytic amounts of DMAP and triethylamine at 0°C. On the corresponding

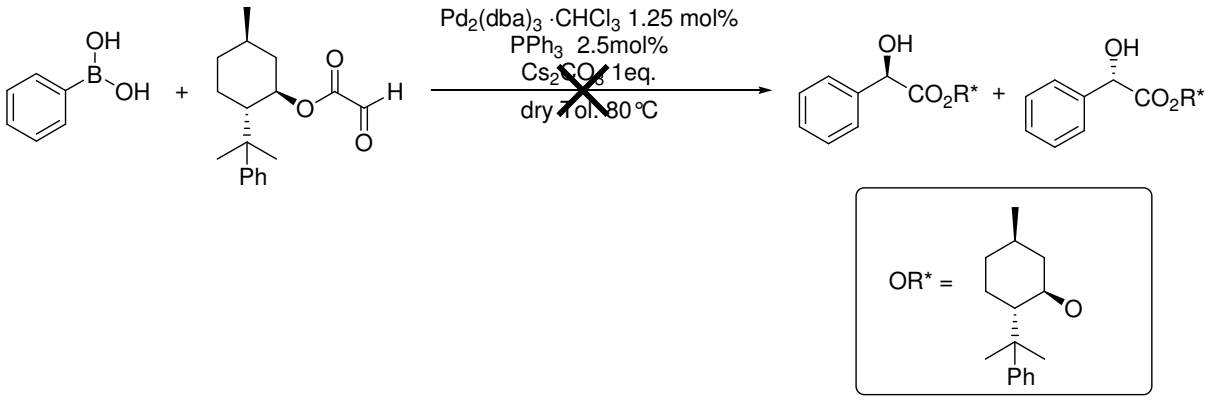
[28] (a) Poyin, P.; Dumas F.; Maddaluno, J. *Synth. Commun.* **1990**, *20*, 2805-2807. (b) Ort, O. *Org. Synth.* 1987, *65*, 203.
[29] Blanco, J. M.; Caamano, O.; Fernandez, F.; Garcia-Mera, X.; Lopez, C.; Rodriguez-Borges, J. E.; Hergueta, A. R. *Synthesis* **1998**,*11*, 1590-1592.
[30] Whitsell, J.; Liu, C.-L.; Buchanan, C. M.; Chen, H. -H.; Minton, M. A. *J. Org. Chem*. **1986**, *51*, 551-553.

acrylic ester we performed the oxidation of the double bond by osmium tetroxide in aqueous solvent, followed by the oxidative cleavage of the diol intermediate which resulted in a complicated mixture of the 8-phenyl menthyl glyoxylate and his hydrated form (in 70:30 ratio), and few other unidentified byproducts (Scheme 1.23).



Scheme 1.23: Synthesis of enantiopure 8-phenyl menthyl glyoxylate.

Although every possible attempts to purified the synthesized glyoxylate, no clean product was ever obtained. However, we performed the coupling reaction with phenylboronic acid starting from the not completely purified 8-phenyl menthyl glyoxylate under the reaction conditions already employed for the menthyl glyoxylate using the triphenylphosphine as ligand (Scheme 1.24). Unfortunately, under these conditions, no reaction occurred.



Scheme 1.24: Palladium-catalyzed addition of phenylboronic acid to 8-phenylmenthyl glyoxylate.

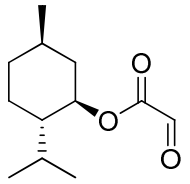
A change of ligand with 2-di-*tert*-butylphosphanylbiphenyl, the best ligand in the case of the coupling between arylboronic acids and achiral ethylglyoxylate, did not bring any noticeable improvements.

1.4.2 Conclusions

Two different approaches have been investigated for the synthesis of chiral mandelates based to the Pd-catalyzed addition of boronic acid to glyoxylates. In the "chiral catalyst" approach, a large number of chiral mono- and bis-phosphines with differents electronic and steric properties have been tested in the coupling of phenylboronic acid and ethyl glyoxylate under the reaction conditions optimized for the racemic coupling. A 32% ee on the ethyl mandelate was the best results achieved employing a rigid 1,2-bisphosphine ligand having a norbornene structure (NorPhos). A diastereoselective approach involving the enantiopure (-)-menthyl glyoxylate or (-)-8-phenyl menthyl glyoxylate as electophilic counterparts, was explored as well. In the former case we observed that the menthyl group alone is not sufficient to ensure a satisfactory facial control and the coupling of phenylboronic acid and (-)-menthyl glyoxylate provided racemic adducts in presence of an achiral phosphine ligand and up to 30% de when the reaction was performed with a chiral phosphine. Under the hypothesis that a phenyl group in 8-position on the menthyl moiety could result in a better diastereofacial selectivity we tried to synthesize the corresponding glyoxylate. However, every attempts to isolate pure (-)-8-phenyl menthyl glyoxylate failed. The coupling reaction with the arylboronic acid was then tested with a not completely clean product but no addition adduct was ever isolated.

1.4.3 Experimental part

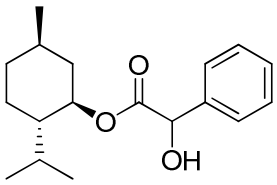
1.4.3.1 General experimental procedures and compound characterization.



(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-oxoacetate[29]

Isolated in quantitative yield as a colorless oil after dehydration, over 4 Å molecular sieves in a dichloromethane solution of its commercially available hydrated glyoxylate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73 (d, *J*= 6.9 Hz, 3H, *Me i*-Pr menthyl), 0.84 (d, *J*= 6.9 Hz, 3H, *Me i*-Pr menthyl), 0.85 (d, *J*= 7 Hz, 3H, *Me*CH menthyl), 0.80-1.09 (m, 3H, menthyl), 1.43-1.60 (m, 2H, menthyl), 1.54-1.63 (m, 2H, menthyl), 1.83(dsept, ^3J= 7 Hz, $^4J_{ax\text{-}ax}$= 2.8 Hz, 1H, MeC*H i*-Pr menthyl), 1.91-2.00 (m, 2H, menthyl), 4.94 (dt, $^3J_{ax\text{-}ax}$= 10.8 Hz, $^4J_{ax\text{-}ax}$= 4.5 Hz, 1H, C*H*OC(O)), 9.47(s, 1H, C(O)*H*) ppm.



(R)- and (S)-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) 2-hydroxy-2-phenylacetate[31]

To a suspension of boronic acid (1.5 mmol) and Cs_2CO_3 (1 mmol, 326 mg) in dry toluene (3ml) were added under Argon, $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0125 mmol, 13 mg), the desired phosphine (0.05 mmol). A solution of menthyl glyoxylate (0.5 mmol) in toluene (1mL) was then added by cannula and the temperature was increased to 80°C. The reactions was monitored by TLC until starting material disappearance and quenched with water (10 ml). The resulting mixture was extracted with dichloromethane (3x15 ml). Combined organic phases are dried over sodium sulfate, filtered and concentrated under vacuum. Resulting crude mixtures were purified by flash chromatography using unmetalled silica (Cyclohexane/Et_2O 4:1)

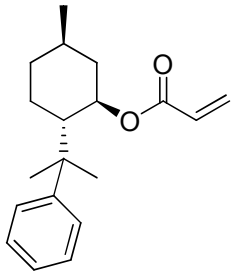
(1S,2R,3S)-Menthyl (S)-Mandelate, major diastereomer.

^{1}H NMR ($CDCl_3$, 300MHz)δ 0.78 (3H, d, *J* = 6.9, *Me i*-Pr), 0.80 (m, 1H, menthyl), 0.82 (d, *J* = 6.9, 3H, *Me i*-Pr), 0.90 (d, *J*= 7 Hz, 3H, *Me*CH) 1.04 (m, 2H, menthyl), 1.38 (m, 2H, menthyl), 1.69 (m, 3H, menthyl), 1.85 (dsept, ^3J= 7 Hz, $^4J_{ax\text{-}ax}$= 2.8 Hz, 1H, MeC*H i*-Pr), 3.58 (d, *J* = 6.0, 1H, O*H*), 4.77 (dt, $^3J_{ax\text{-}ax}$= 10.7 Hz, $^4J_{ax\text{-}ax}$= 4.4 Hz, 1H, C*H*OC(O)), 5.13 (d, *J* = 6.0, 1H,C*H*OH), 7.34 (5H, m) ppm.

Mixture of diastereomers: (R) and *(S)-mandelate.*

^{1}H NMR ($CDCl_3$, 300MHz)δ 0.39 (d, *J* = 6.9, 3H,*Me i*-Pr, minor), 0.58 (d, *J* = 6.9, 3H,*Me i*-Pr, minor), 0.78 (d, *J* = 6.9, 3H,*Me i*-Pr, major),0.80 (d, *J*= 6.9 Hz, 3H,*Me i*-Pr, major), 0.90 (d, *J*= 7 Hz, 3H, *Me*CH, major), 0.91 (d, *J*= 6.4 Hz, 3H, *Me*CH, minor), 1.22-2.04 (m, 9H, menthyl, major + minor), 3.58 (d, *J* = 6.0 Hz, 1H, O*H*, major), 3.73 (d, *J* = 5.5 Hz, 1H, O*H*, minor), 4.65 (dt, $^3J_{ax\text{-}ax}$= 10.9 Hz, $^4J_{ax\text{-}ax}$= 4.4 Hz, 1H, C*H*OC(O), minor), 4.77 (dt, $^3J_{ax\text{-}ax}$= 10.7 Hz, $^4J_{ax\text{-}ax}$= 4.4 Hz, 1H, C*H*OC(O), major), 5.10 (d, *J* = 5.5, 1H,C*H*OH minor), 5.13 (d, *J* = 6.0, 1H,C*H*OH, major) and 7.34 (m, 5H major + minor) ppm.

[31] (a) Janison, M. M.; Turner, E. E. *J. Chem. Soc.* **1942**, 611-612; (b) Whitsell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548-3551

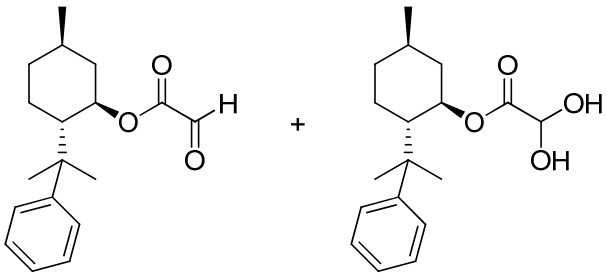


(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl acrylate[30]

To a solution of (-)-8-phenylmenthol (2.5 g, 10.8 mmol), 4-(dimethylamino)pyridine (0.2 g, 1.52 mmol) and triethylamine (2.2 g, 21.6 mmol) in 100 mL of dichloromethane at 0°C, was slowly added 1.96 g (21.6 mmol) of acryloyl chloride. The mixture was stirred at 0 °C for 1.5 h and then 20 mL of saturated $NaHCO_3$, solution was added. The organic layers were separated and the aqueous layer was extracted with dichloromethane (3 x 40 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was filtered through a short column of silica gel (Cyclohexane/EtOAc 9:1) to yield 2.80 g (99%) of acrylate.

^{1}H NMR ($CDCl_3$, 300MHz) δ 0.97 (d, *J*= 7.5 Hz, 3 H, *Me i*-Pr), 1.01-1.32 (m, 3H, menthyl) 1.23 (s, 3 H, *Me* 8-Ph-*i*-Pr) 1.33 (s, 3 H, *Me* 8-Ph-*i*-Pr), 1.45-1.71 (m, 3H, menthyl), 1.88-1.95 (m, 1H, menthyl), 2.04 (td, $^3J_{ax\text{-}ax}$= 10.8 Hz, $^4J_{ax\text{-}ax}$= 4.3 Hz, 1H, menthyl), 4.86 (dt, $^3J_{ax\text{-}ax}$= 10.8 Hz, $^4J_{ax\text{-}ax}$= 4.2 Hz, 1H, C*H*OC(O)), 5.52-5.63 (m, 2 H, HC=CH_2), 5.97-6.06 (m, 1 H, *H*C=CH_2), 7.08-7.28 (m, *5* H, C*H* aromatic) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.8 (*C*H_3), 25.4 (*C*H_3), 26.6 (*C*H_2), 27.5 (*C*H_3), 31.3 (C*H*), 34.6 (*C*H_2), 39.7 (*C* quat.), 41.6 (*C*H_2), 50.5 (*C* quat.), 74.6 C*H*), 124,9 (C*H* arom.), 125.4 (2xC*H* arom.), 127.9 (2xC*H* arom.), 128.9 (C*H* vinyl), 129.9 (CH_2 vinyl), 151.6 (*C* quat. arom.), 165.4 (*C* quat. C=O) ppm.



(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-oxoacetate and its hydrated form[29]

Method A[29]

A solution of (-)-8-phenyl menthol (1 mmol) in anhydrous $CHCl_3$(10 mL) was slowly added, over 2 hours, to a solution of oxalyl chloride in anhydrous $CHCl_3$ (3 mL). The mixture was stirred at room temperature for 2 hours and then the solvent and the excess of oxalyl chloride were removed on the rotary evaporator. The crude alkoxy oxalyl chloride, isolated

as colorless oil, was dissolved in anhydrous benzene (10 mL) and to this solution it has been sequentially added $Pd(PPh_3)_4$ (5 mg, 4% mol) and Bu_3SnH (0.3 g, 1. 02 mmol). The resulting mixture was stirred for 3 hours at room temperature, then diluted with anhydrous $CHCl_3$ (3 mL) and refluxed for 1 hour. The solvent was evaporated in vacuo and the oily residue was analyzed by ^{1}H NMR revealing the only presence of the starting chiral alcohol.

Method B[30]

To a solution of 0.735 g of (1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl acrylate in 3 ml of water and 9 ml of dioxane, 0.01 g of osmium tetroxide was added and the resulting dark brown mixture was stirred at room temperature for 5 minutes. A total of 1.11 g of sodium periodate was added in small portion over a period of 30 minutes. The colour of the solution changed to pale brown and this mixture was stirred for additional 2 hours. After extraction with diethyl ether, drying over $MgSO_4$ and concentration of the organic phases in vacuo the glyoxylate and its hydrate were isolated as brown viscous oil.

^{1}H NMR ($CDCl_3$, 300MHz) δ 0.85 (d, *J* = 7.5 Hz, 3 H, *Me i*-Pr), 0.98-1.18 (m, 2H, menthyl) 1.30 (s, 3 H, *Me* 8-Ph-*i*-Pr), 1.38 (s, 3 H, *Me* 8-Ph-*i*-Pr), 1.40-1.77 (m, 7H, menthyl), 2.01 (td, $^3J_{ax\text{-}ax}$= 10.7 Hz, $^4J_{ax\text{-}ax}$= 4.4 Hz, 1H, menthyl), 4.87 (dt, $^3J_{ax\text{-}ax}$= 10.7 Hz, $^4J_{ax\text{-}ax}$= 4.4 Hz, 1H, C*H*OC(O) menthyl), 7.09-7.15 (m, *1* H, C*H* aromatic), 7. 23-7.29 (m, *4* H, C*H* aromatic) ppm.

[15] Noël, T.; Vandyck, K.; Van der Eycken, J. *Tetrahedron* **2007**, *63*, 12961-12967

[16] Xing, C. -H.; Liu, T. -P.; Zheng, J. R., Ng, J.; Esposito, M.; Hu, Q. -S. *Tetrahedron Lett.* **2009**, *50*, 4953-4957

[17] Yamamoto, T.; Ohta, T.; Ito, Y. *Org. Lett.* **2005**, *7*, 4153–4155

[18] Yamamoto, T.; Iikuka, M.; Takenaka, H.; Ohta, T.; Ito, Y. *J Organomet. Chem.* **2009**, 694, 1325-1332

[19] Suzuki, K.; Arao, T.; Ishii, Y.; Maeda, Y.; Kondo, K.; Aoyama, T *Tetrahedron Lett.* **2006**, *47*, 5789-5792

[20] He, P.; Lu, Y.; Dong, C. G.; Hu, Q. S. *Org. Lett.* **2007**, *9*, 343-346.

[21] He, P.; Lu, Y.; Hu Q.-S. *Tetrahedron Lett.* **2007**, *48*, 5283-5288

[22] Qin, C.; Wu, H.; Cheng, J.; Liu, M.; Zhang, W.; Su, W.; Ding, J.; *J.Org. Chem.* **2007**, *72*, 4102-4107

[23] Lin, S.; Lu, X. *J. Org. Chem.* **2007**, *72*, 9757-9760

[24] Shirai, R.; Shimazawa, R.; Kuriyama, M. *J. Org. Chem.* **2008**,*73*, 1597-1600

[25] Yu, A.; Cheng, B.; Wu, Y.; Wei, K. *Tetrahedron Lett.* **2008**, *49*, 5405-5407

[26] Novodomskà, A.; Dudičovà, M.; Leroux, F. R.; Colobert, F. *Tetrahedron: Asymm.* **2007**, *18*, 1628-1634

[27] Hubbard, J. S.; Harris, T. M. *J. Org. Chem*. **1981**, *46*, 2566-2570

[28] (a) Poyin, P.; Dumas F.; Maddaluno, J. *Synth. Commun.* **1990**, *20*, 2805-2807. (b) Ort, O. *Org. Synth.* 1987, *65*, 203.

[29] Blanco, J. M.; Caamano, O.; Fernandez, F.; Garcia-Mera, X.; Lopez, C.; Rodriguez-Borges, J. E.; Hergueta, A. R. *Synthesis* **1998**,*11*, 1590-1592

[30] Whitsell, J.; Liu, C.-L.; Buchanan, C. M.; Chen, H. -H.; Minton, M. A. *J. Org. Chem*. **1986**, *51*, 551-553.

[31] (a) Janison, M. M.; Turner, E. E. *J. Chem. Soc.* **1942**, 611-612; (b) Whitsell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548-3551

Chapter 2

Chemoselective addition of in situ prepared lithium alkynyl borates to aldehydes: a practical and transition metal free approach toward the synthesis of propargylic alcohols

2.1 Purposes

In the first chapter of this manuscript we discussed about the use of aryl and alkenyl boronic acids in catalytic transformations more specifically oriented toward the synthesis of diarylcarbinols and mandelate derivatives. While alkyl, allyl and arylborates have been extensively studied over the past few years, the scientific production about the use of alkynyl borates is still limited to some examples, individually treated in the following section. By the way, aimed to find new reactions involving lithium alkynyl-trialkyl borates, we will present the use of such nucleophilic compounds in the addition to aldehydes as a highly chemoselective method applied to the synthesis of propargylic alcohols.

2.2 Bibliographic recall

Aimed to give a specific overview to alkynyl borates, various examples are presented. Particularly, we will focus on

1. the use of alkynyl-trialkyl borates by showing our previous contribution to the understanding of their chemistry.

2. the use of other alkynylborates in the enantioselective or racemic addition to carbonyl compounds that is schematically shown below (Figure 2.1).

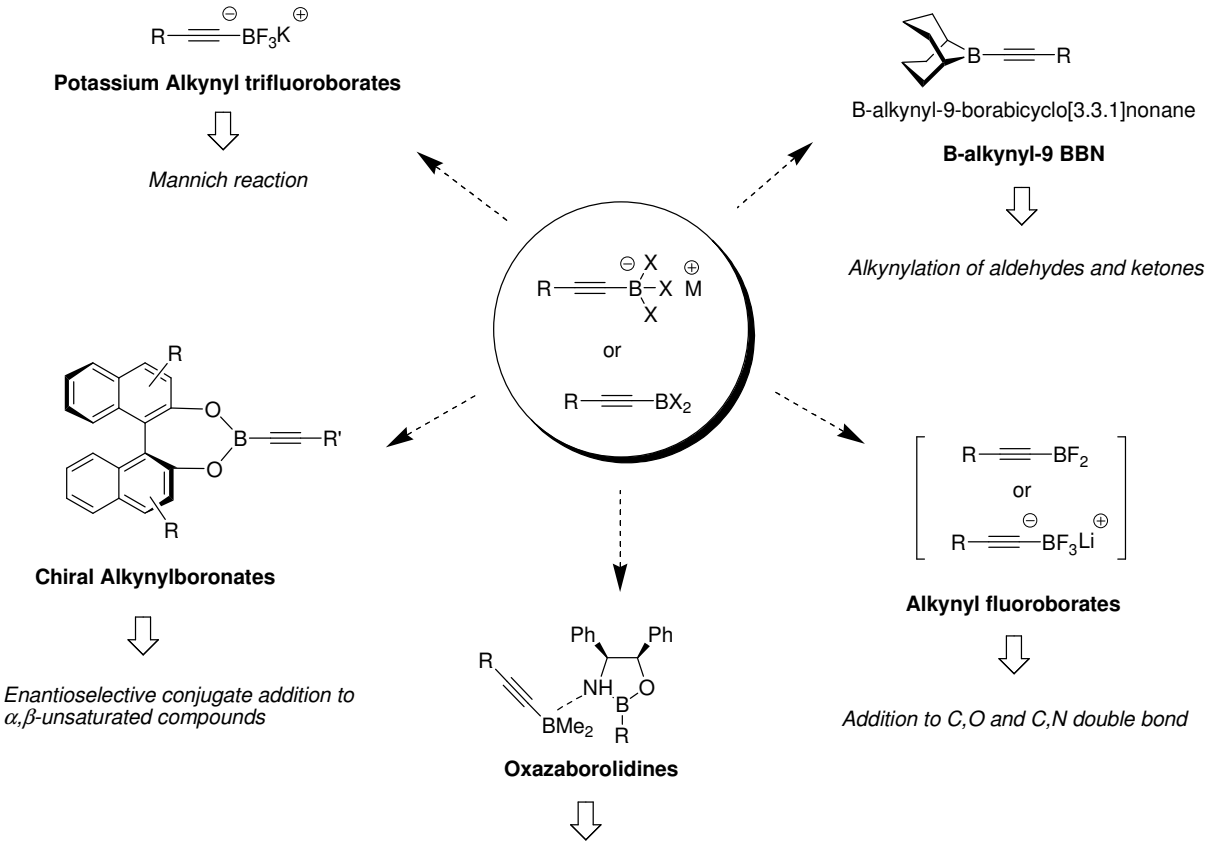
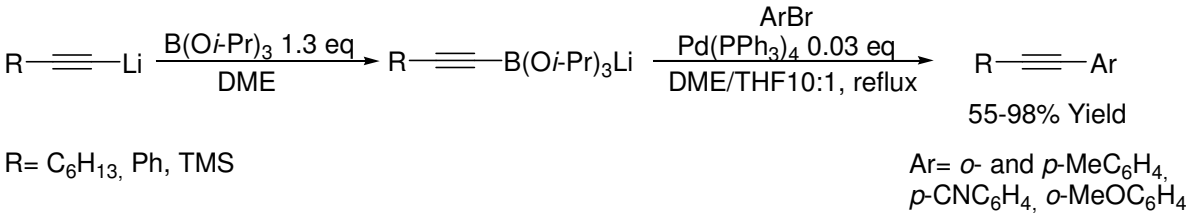


Figure 2.1: Alkynylborates in addition to carbonylic compounds

2.2.1 Lithium Alkynyl-trialkyl borates.

Since their synthesis reported by Brown in 1988,[1] lithium alkynyl-triisopropyl borates and their trivalent analogues have been relatively little explored. More recently our research group reported the use of such interesting lithiated intermediate as valid organometallic components in palladium catalyzed cross coupling reactions.

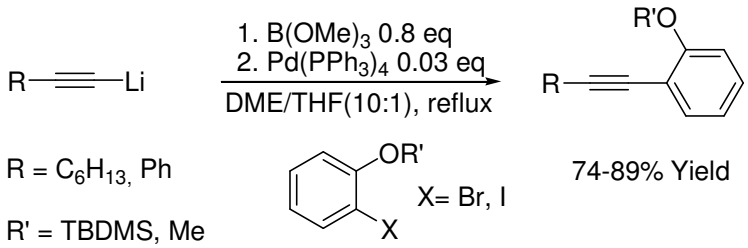
Particularly, such organoboron compounds have been employed in the Suzuki-Miyaura coupling with aryl and vinyl bromides (Scheme 2.1).[2] The reaction proved to be efficient also in case of non activate aryl bromides and represents a valid alternative to known and largely used methods (Sonogashira, Stille, Negishi…). Moreover, the nucleophilic lithium alkynyl-trialkyl borate is generated *in situ* in order to prevent any possible hydrolysis of this highly sensitive starting material.



[1] Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.*, **1988**, *29*, 2631-2634
[2] Castanet, A. -S.; Colobert, F.; Schlama, T. *Org. Lett.*, **2000**, *2*, 3559-3561

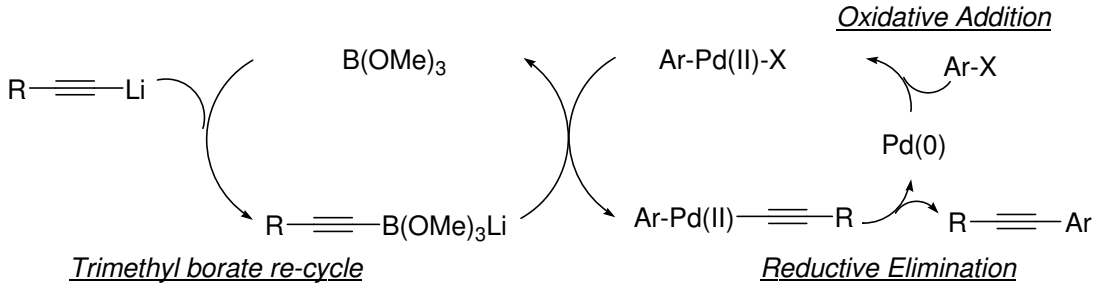
Scheme 2.1: Palladium catalyzed alkynylation of arylbromides.

In 2005, we reported the efficient coupling of acetylenic boronic esters and *ortho*-substituted aryl bromides and iodides (Scheme 2.2).[3]



Scheme 2.2: Suzuki-Miyaura cross-coupling of o-bromoanisoles

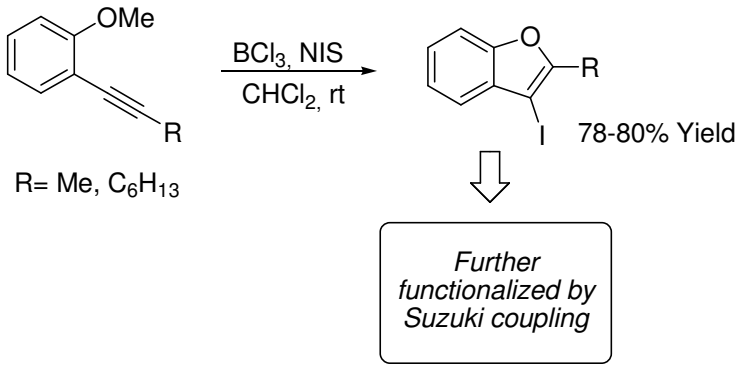
After ^{11}B NMR studies on the course of the reaction, a possible catalytic cycle involving a regeneration of the trimethylborate has been proposed as in the Scheme 2.3. Actually, ^{11}B NMR spectra showed the disappearance of the trimethyl borate signal in favour of the corresponding alkynylborate and again the appearance of the former signal once the reaction proceeds. That means trimethyl borate could be used in substoichiometric amounts.



Scheme 2.3: Catalytic cycle of sp-sp^2 coupling

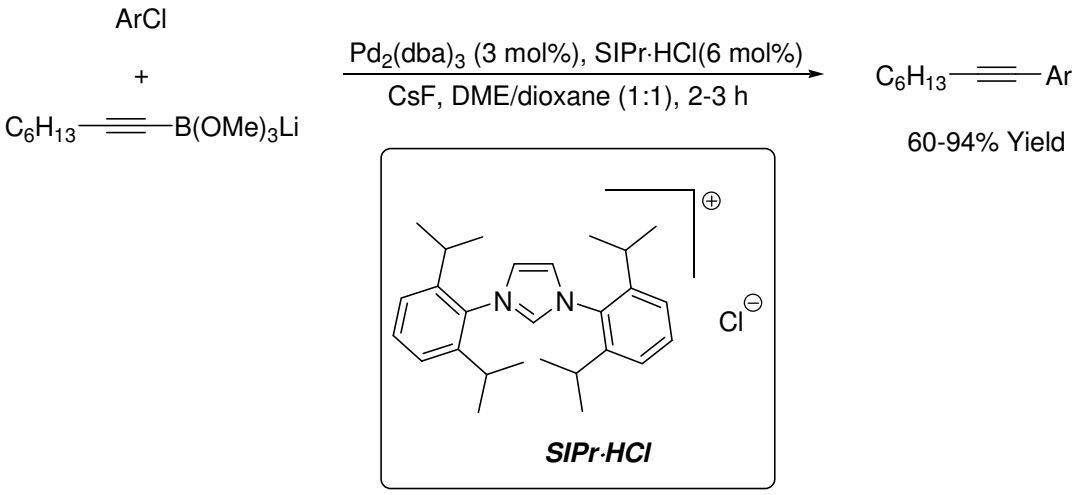
Additionally, the cross coupling products, the *ortho*-alkynyl anisoles are suitable intermediates in the synthesis of benzofuranes and have been employed in the 5-endo-dig-iodocyclisation in presence of BCl_3 and *N*-iodosuccinimide (NIS) (Scheme 2.4).

[3] Colobert, F.; Castanet, A. -S.; Abillard, O. *Eur. J. Org. Chem.* **2005**, 3334-3341



Scheme 2.4: 5-Endo-dig-iodocyclisation of o-alkynylanisoles

Further studies on the reaction allowed to realize the cross coupling of a terminal alkyne with aryl chlorides, typically weak substrates in other similar transition metal catalyzed reactions.[4] A change in the catalytic system toward cationic imidazolium ligands (NHC) and $Pd_2(dba)_3$ and the presence of a fluorinated inorganic base ensure high yields with differently substituted chloroarenes (Scheme 2.5).



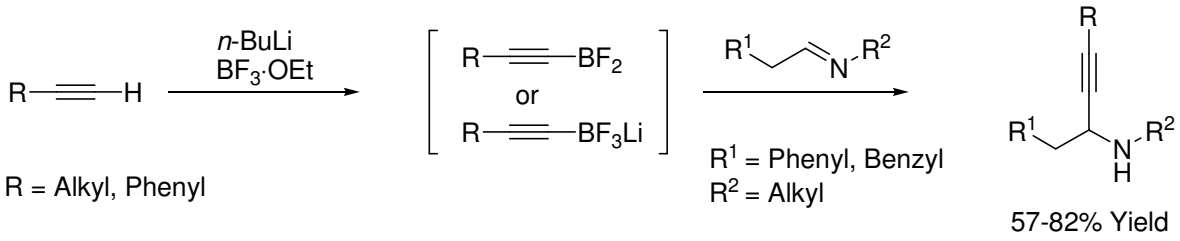
Scheme 2.5: Suzuki-Miyaura Coupling between lithium alkynyl-trimethyl borates and aryl chlorides

Particularly, alkynyl borates in their trivalent or tetravalent form have been employed in several organic transformation such as the 1,2- or 1,4 addition to C,O and C,N douple bonds. The products of the alkynylation reactions, propargilyc alcohols and amines or amides are versatiles synthetic intermediates in the preparative chemistry and frequent structural motifs in many biologically active compounds.

[4] Colobert, F.; Castanet, A. -S.; Abillard, O. *Eur. J. Org. Chem.* **2006**, 1450-1454

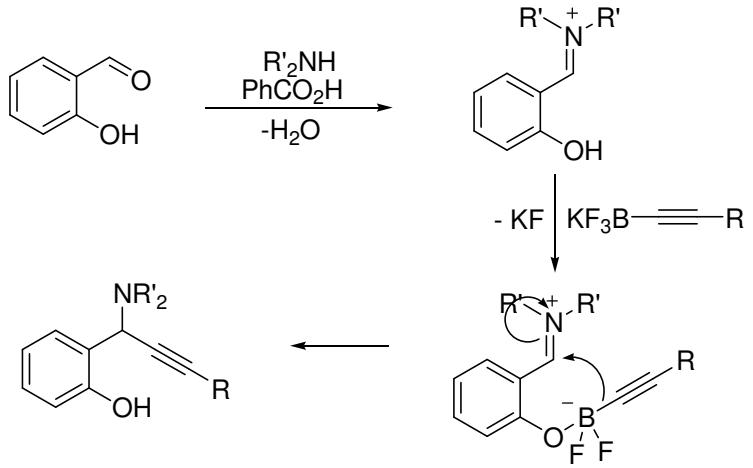
2.2.2 Fluoroalkynylborates in 1,2-addition reactions.

In 1984, Akiba[5] reported the synthesis of propargylic amines by alkynylation of aldimines by using alkynyl borates prepared in situ from lithium acetylides and boron trifluoride etherate. The corresponding adducts were obtained in good yields (Scheme 2.6).



Scheme 2.6 Fluoroalkynyl borates in 1,2 addition to non activated imines

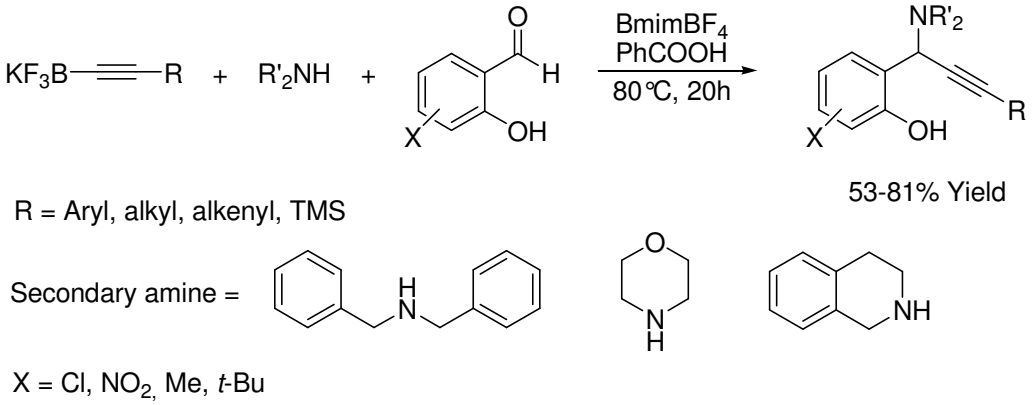
In 2004, Kabalka presented an application of the Petasis reaction using potassium trifluoro alkynyl borate in ionic liquids.[6] The reaction is a modern variation of the Mannich reaction involving a carbonyl compound, an amine and an organoborane. Among the solvents tested in the conditions optimization, it has been observed that ionic liquid such as butylmethylimidazolium tetrafluoroborate or hexafluorophosphate (respectively $BmimBF_4$ and $BmimPF_6$) considerably increased the yields of the final propargylamine compared to classic solvents as THF, 1,4-dioxane and acetonitrile. Interestingly, the addition of one equivalent of benzoic acid showed beneficial effects maybe because it catalyzes the initial condensation of the aldehyde with the secondary amine leading to the iminium ion, which then reacted more efficiently with the borate as depicted in the Scheme 2.7. The hydroxyl group of the salicylaldehyde turns to be useful for anchoring the organometallic reagent by coordination of the oxygen to the boron.



Scheme 2.7: Mannich reaction with organoboron compound

[5] Wada, M.; Sakurai, Y.; Akiba, K. *Tetraherdon Lett.* **1984**, *25*,1083-84
[6] Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetraherdon Lett.*, **2004**, *45*, 729-731

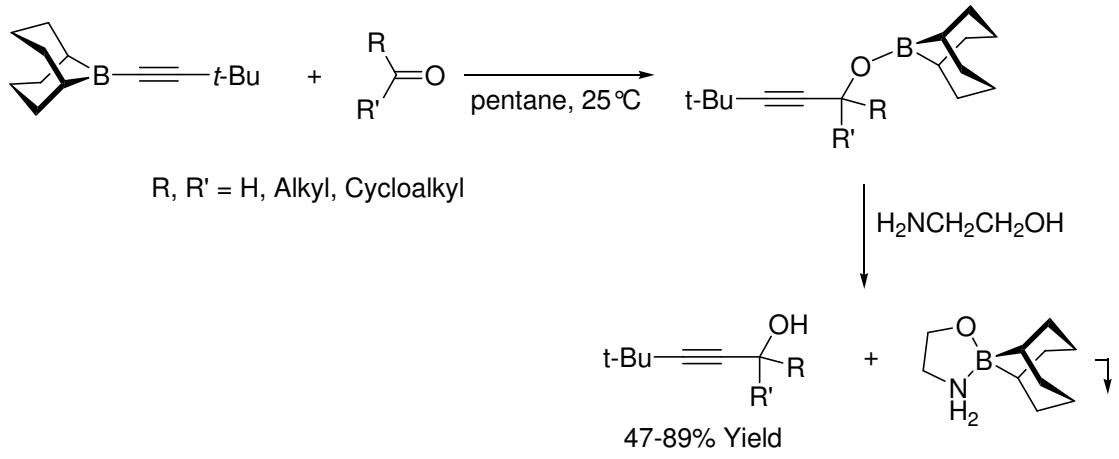
The authors then investigated on the scope of the reaction with aliphatic and aromatic potassium alkynyltrifluoroborates and few secondary amines were isolated with good overall results (Scheme 2.8).



Scheme 2.8: Three component Petasis reaction

2.2.3 B-1-alkynyl-9-borabicyclo[3.3.1]nonane in 1,2-addition reactions.

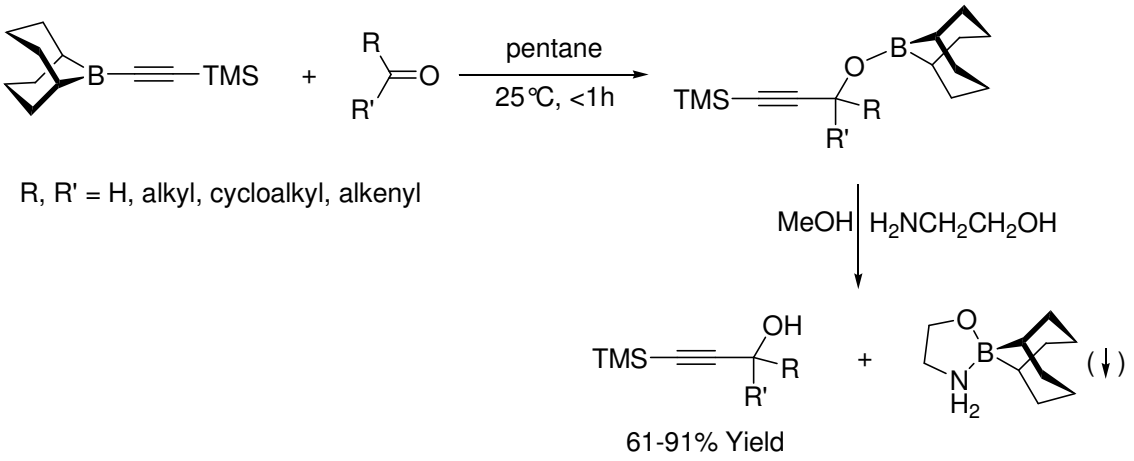
In 1985, Brown and Molander[7] published the 1,2 addition of B-1-alkynyl-9-borabicyclo[3.3.1]nonane (also known as B-alkynyl-9-BBN compounds) to aldehydes and ketones (Scheme 2.9). The mildness of the boron reagents ensure good yields of the propargylic alcohols and the use of the ethanolamine as additive is responsible of the formation of 9-BBN-ethanolamine adduct. Once the adduct is filtered off, the final alcohol is recovered without any further purification.



Scheme 2.9: B-alkynyl-9-BBN in addition to ketones and aldehydes

[7]Brown, H.; Molander, G. A.; Singh, S. M.; Racherla, U. S.; *J. Org. Chem* **1985**, *50*, 1577-1582

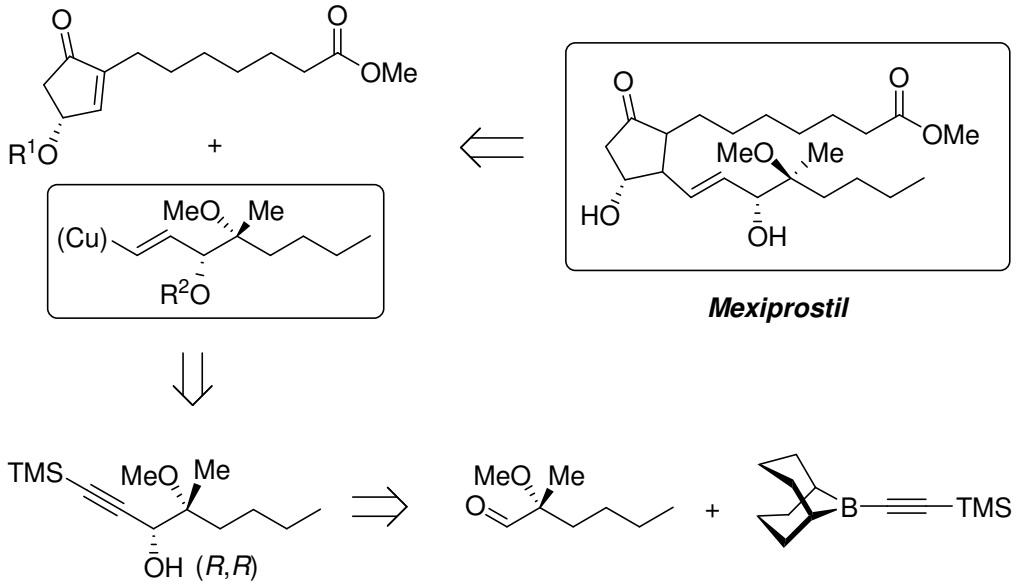
Following the Brown's works, few years later, Evans and coworkers[8] reported the synthesis of TMS-protected propargylic alcohols by reaction between a carbonyl derivative and B-[2-(trimethylsilyl)ethynyl]-9-BBN (Scheme 2.10).



Scheme 2.10: B-[2-(trimethylsilyl)ethynyl]-9-BBN in addition to ketones and aldehydes

Good results in the corresponding propargylic carbinols, with yields up to 91%, encouraged them to apply this methodology to the total synthesis of mexiprostil, a gastroprotective drug (Scheme 2.11).

In the first part of the synthesis, the stereogenic center near the triple bond is formed by a diastereoselective addition of B-[2-(trimethylsilyl)ethynyl]-9-BBN to the chiral (R)-2-methoxy-2-methyl-hexanal affording the two diastereoisomeric adducts in 5:1 ratio. Unfortunately, the desired diastereoisomer was the minor one. The propargylic alcohol is then transformed in alkenylcuprate which reacted with the cyclopentenone in the 1,4 addition thus forming the lower side chain of the Mexiprostil.

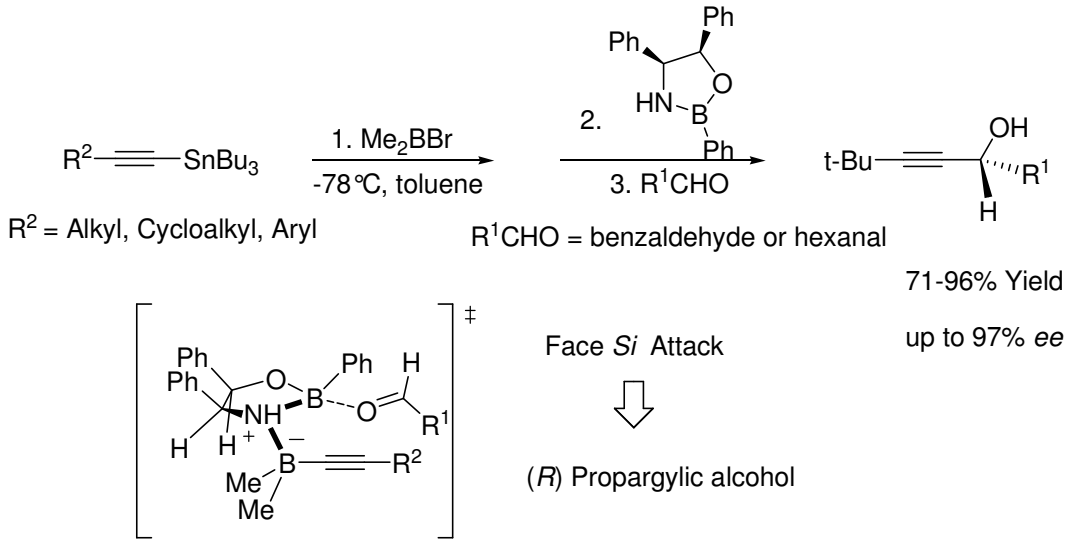


Scheme 2.11: Retrosynthetic analysis of mexiprostil

[8]Evans, J. C.; Goralski, C. T.; Hasha, L. D. *J. Org. Chem* **1992**, *57*, 2941-2943

2.2.4 Chiral oxazaborolidines in 1,2-addition reactions.

In 1994, Corey introduced the oxazaborolidines as catalysts for the enantioselective alkynylation of aldehydes by using an alkynylborate generated in situ from the corresponding alkynylstannane.[9] Alkyl and aryl aldehydes are equally effective leading to high yields and enantioselectivities (Scheme 2.12). The chiral oxazaborolidine could direct the nucleophile approach by offering its two coordinating groups and the chiral environment ensure a good facial selectivity. Indeed, the amino and borane groups are coordinated to the alkynyl borate and the oxygen of the aldehyde respectively in the transition-state assembly. The loss of the just formed propargylic alcohol as borate derivatives release the free oxazaborolidine for repetition of the catalytic cycle.

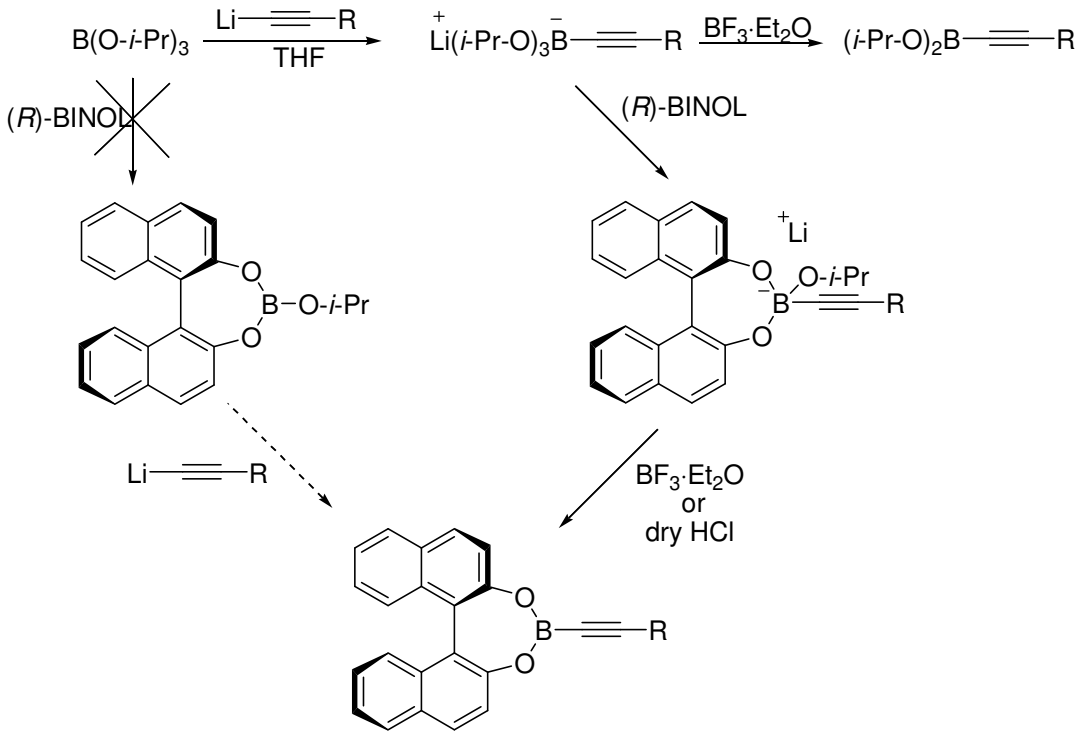


Scheme 2.12: Enantioselective conjugate addition of alkynyl borates to enones

2.2.5 Chiral alkynylboronates in conjugated addition to enone and acylimines: stoichiometric and catalytic processes.

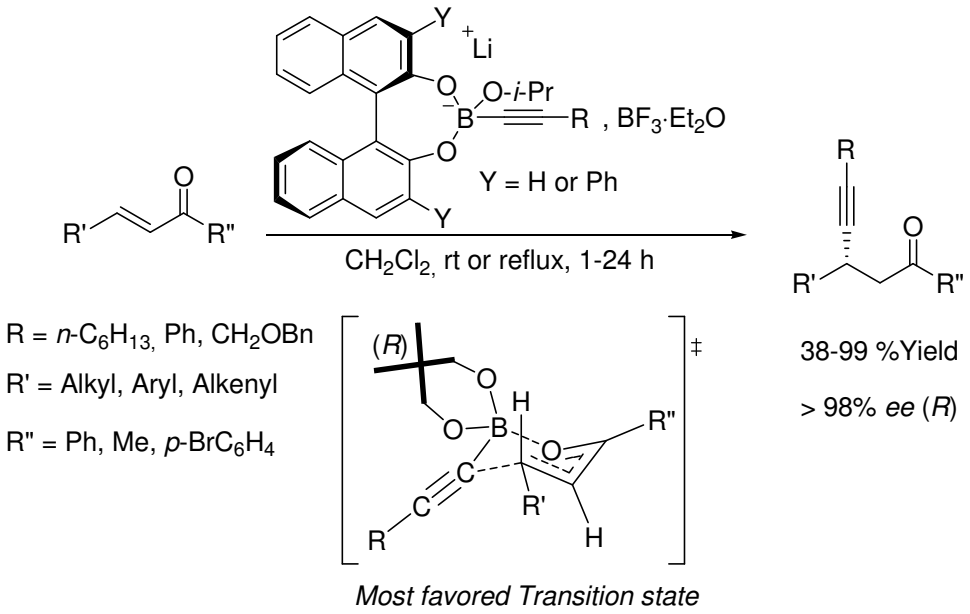
Chiral BINOL-derived borates have been synthesized by Chong and Taylor and used in the conjugate addition to enones.[10] The most straightforward route to alkynylborates is to add the alkynyllithium to the binaphtyl isopropylborate but every attempts of preparation of mixed borate resulted in boron bridged trimers of binaphtol. Alternatively, the enantiopure alkynyl borates has been prepared by initial addition of the desired alkynyl lithium to triisopropyl borate and transesterification with (R)-BINOL (Scheme 2.13). The chiral lithium alkynylborate is then treated with a Lewis or Brønsted acid to generate the reactive trivalent (R)-binaphtyl alkynylborate.

[9] Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc* **1994**, *116*, 3151-52
[10] Chong, M. J.; Shen, L.; Taylor, N. J. *J. Am. Chem. Soc.* **2000**, *122*, 1822-23



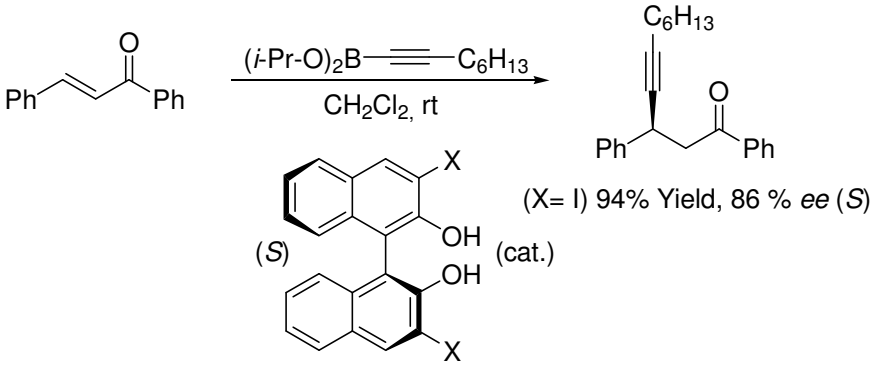
Scheme 2.13: Synthesis of (R)-binaphtyl alkynylborate

The reaction proceeds smoothly with almost all α,β-unsaturated ketones with yields, ranging from 38 to 99 %. Alkyl groups in β position of the enone displays more important steric effects than the aromatic groups; consequently, selectivities increased with the size of the substituent leading to ee >98% for R' = *t*-Bu. Additionally, substituents in 3,3' positions of the BINOL moiety seem to play an important role in the chiral induction since when Y = H, a drop in the ee's values is observed. A cyclic six membered chair-transition state is invoked to predict the stereochemistry of the conjugate addition (Scheme 2.14). The model is consistent with the observed dependence on the size and the electronic properties of the β-substituent of the enone and also with the fact that only enones capable to achieve a *s*-cis configuration are effective.



Scheme 2.14: Enantioselective 1,4-adition of (R)-binaphtylalkynyl borates to enones

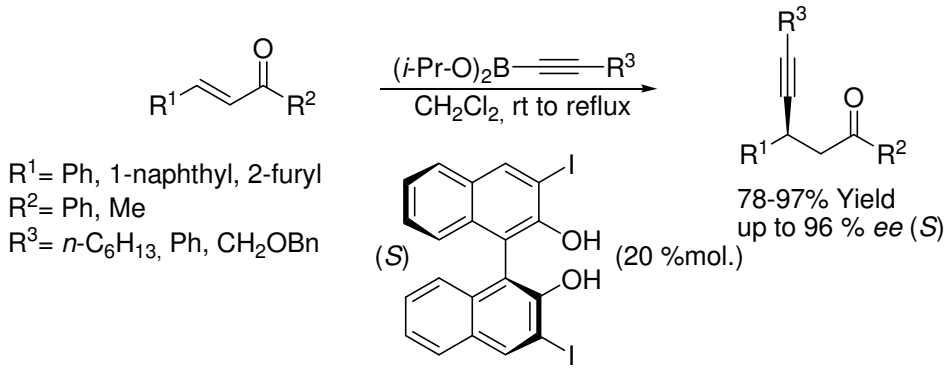
Few years later, Chong and Wu reported the first example of catalytic asymmetric alkynylation of enones introducing a new paradigm for the use of organoboranes in organic transformation.[11] Hence, while few boron nucleophiles have been used as catalyst in other asymmetric reactions, the authors introduced the new concept of "echangeable" chiral diol on the alkynylborate. Few chiral binaphtols have been tested in the alkynylation of chalcone. Particularly, 3,3'-disubstituted with electron-withdrawing groups (I, CF_3, $(CF_3)_2C_6H_3$) allowed to reach the best results in term of yields and enantioselectivities (Scheme 2.15). With (S)-3,3'diidobinaphtol, the 1,4 addition adduct was isolated in 94% yield and 86% *ee*, results comparable to that observed for stoichiometric reaction.



Scheme 2.15: Catalytic enantioselective 1,4-addition of alkynylborates to enones: effect of the 3,3' substituents

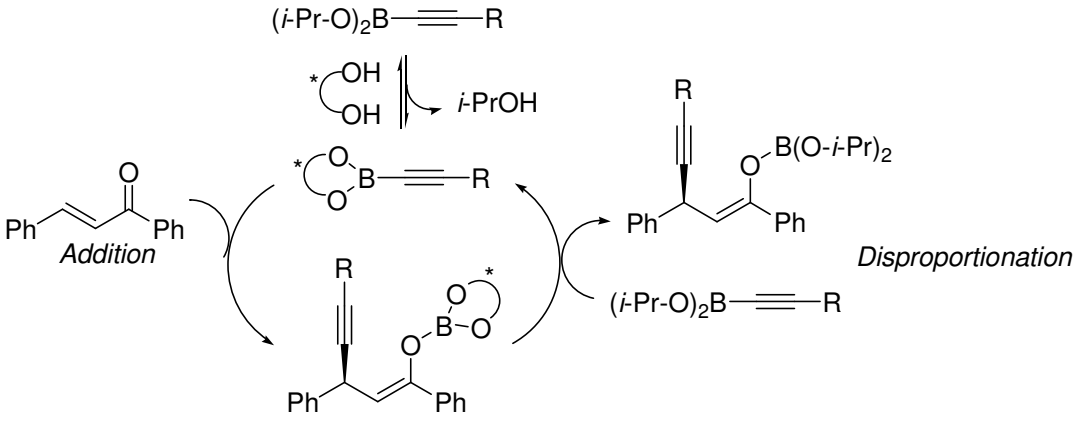
The 3,3'-diiodobinaphtol has been used as chiral ligand in the alkynylation of a wide range of enones with excellent results in term of yields and enantioselectivities (Scheme 2.16).

[11] Chong, M. J.; Wu, R. T. . *J. Am. Chem. Soc*. **2006**, *127*, 3244-45



Scheme 2.16: Catalytic enantioselective 1,4-addition of alkynylborates to enones

In the catalytic cycle proposed by the authors and displayed in the Scheme 2.17, the reaction is catalytic in binaphthol only if the chiral diol could be liberated from the addition adduct by an exchange/disproportionation with the achiral alkynyl borate. Additionally, while the achiral borate is totally ineffective compared to its chiral analogue, this is clearly an example of ligand-accelerated catalysis, which is a quite rare phenomenon with boron reagents.

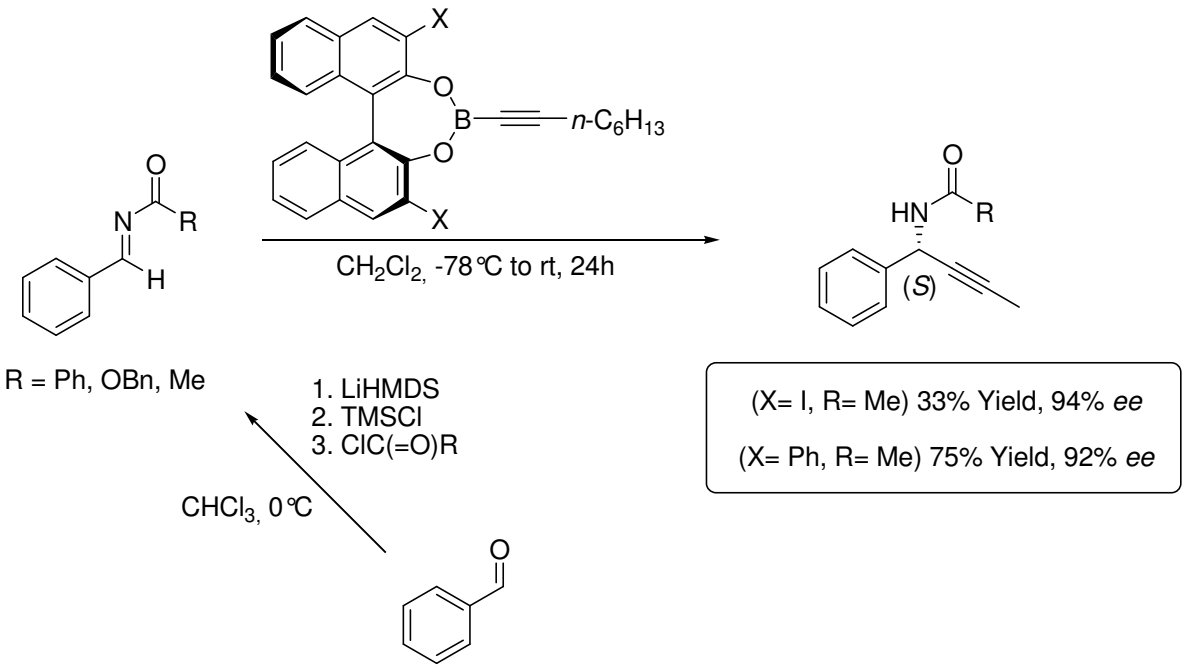


Scheme 2.17: Mechanism of the conjugate addition using catalytic amounts of chiral ligand

One possible explanation of this behaviour is offered by Goodman and Pellegrinet in a publication about theoretical studies on the asymmetric conjugate addition of alkynyl borates to enones.[12] Theoretical calculation revealed that the reactivity of the different components in the Scheme 2.17 is finely balanced. Particularly, the reactivity of the achiral alkynyl borate is shared between the chiral borate, which is more reactive towards the enones, and the addition product, which reacts in the disproportionation step. Firstly, the lack of reactivity is explained by taking into account the dihedral C-O-B-C angle which is 180° for the diisopropyl alkynyl borate and 147° for the (S)-binaphtyl-alkynyl borate. The twisted structure is responsible of the ability of the coordination of the oxygen of the enone to the vacant boron orbital and electron-withdrawing groups in 3 and 3' positions of the aromatic system enhanced the Lewis acid character of the boron atom.

[12]Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc*. **2006**, *128*, 3116-17

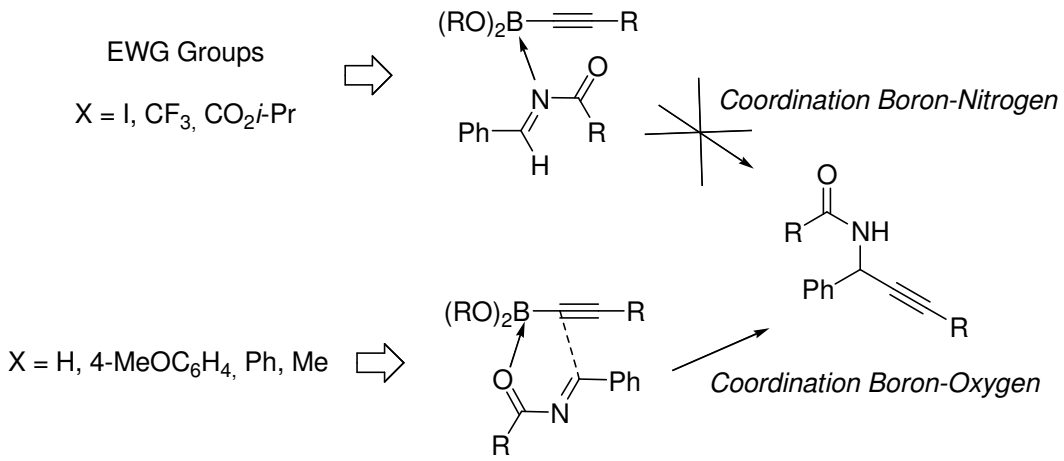
The efficiency of 3,3'-disubstituted-2,2'-binaphtyl-alkynyl borates has been demonstrated once again by Chong and Wu in the reaction with activated acylimines affording chiral propargylamides, useful intermediates in the synthesis of many natural product and biologically active molecules.[13] In the first part of their work they reported the stoichiometric reaction of acyl benzaldimines, prepared according the Kupfer's method, with chiral alkynyl borates 3,3'-binaphtol-derived. It was observed that, the electronic properties of the X substituent have a strong influence on the course of the reaction. While the enantioselectivity remains good, the yields decreased with the increase of electron-withdrawing character of the X group (Scheme 2.18.



Scheme 2.18: Alkynylation of N-acylbenzaldimine with chiral alkynyl borates

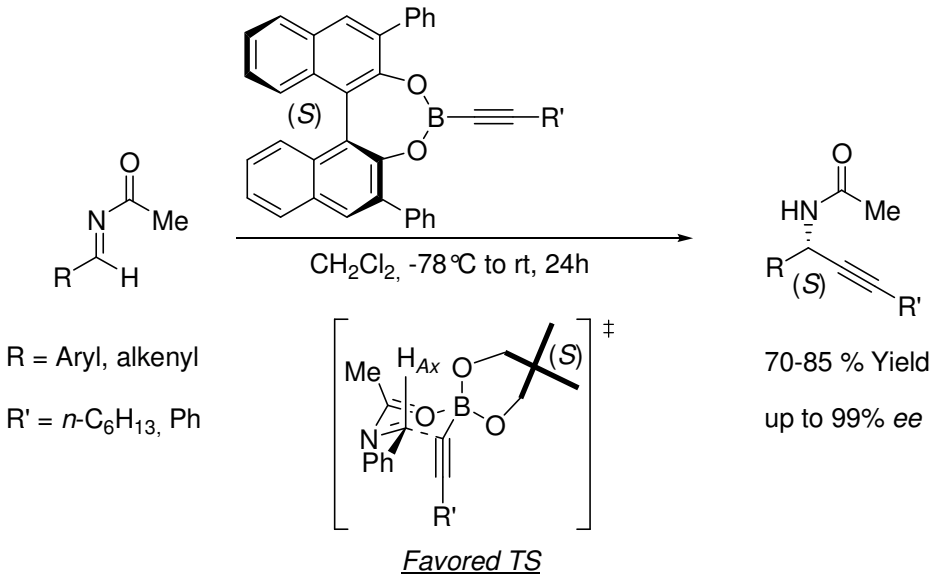
This result can be rationalized by recognizing that strong electron-withdrawing group onto the binaphtyl rings would increase the Lewis acidity of boron thus favouring the coordination of the nitrogen of the acylimine instead of the oxygen atom, responsible of a correct delivery of the alkynyl group via 1,4-fashion (Scheme 2.19). The displacement of the coordination provides a negative impact on the addition reaction, leading poor yields.

[13]Chong, M. J.; Wu, R. T. *Org Lett* **2006**, *8*, 15-18



Scheme 2.19: Nitrogen vs Oxygen Coordination

Alkynylation of various N-acylimines using the 3,3'-diphenylnaphtyl alkynylborate proceeded smoothly giving final propargylamides in high yields and excellent *ee*. The stereochemical outcomes are consistent with a cyclic six-membered chair transition state in which aryl group occupies the pseudo-equatorial position. Non bonding interaction between the 3-substituent on the naphtyl moiety and the axial imine hydrogen presumably favors the transition state structure shown in the Scheme 2.20

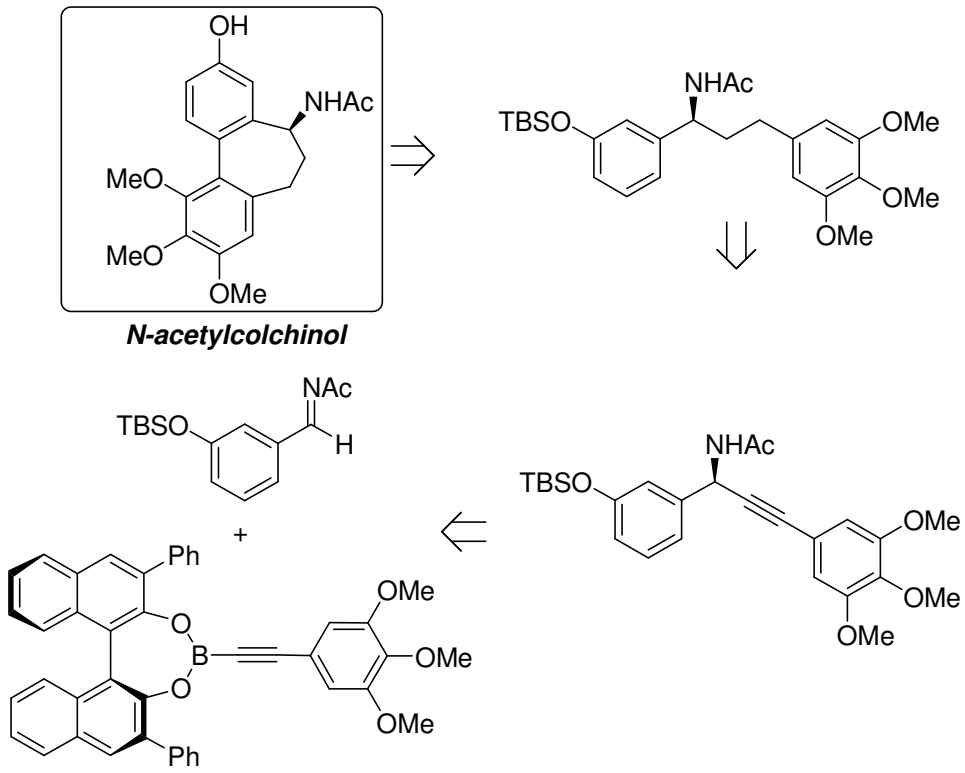


Scheme 2.20: Enantioselective alkynylation of N-acylbenzaldimines

This methodology was successfully applied to the total synthesis of the (-)-N-acetylcolchinol[14], a vascular targeting agent, developed for the treatment of solid tumors, previously isolated after degradation of natural colchicine. The synthesis starts with the addition of an (*R*)-3,3'-diphenyl-2,2'-binaphthyl alkynylborate to the TBS protected 3-hydroxybenzaldehyde N-acetylimine providing the corresponding (*R*)-propargylamide in 72%

[14] (±)-N-acetylcolchinol has been prepared according the method described in: Sawer, J. S.; Macdonald, T. L. Tetrahedron Lett. **1988**, *29*, 4839-4842. (-)-N-acetylcolchinol has been obtained only by degradation of natural colchicine.

yield and 94% *ee*. The hydrogenation of the triple bond followed by a cyclization of the saturated amide gave the final product with high purity degree (*Scheme 2.21*).

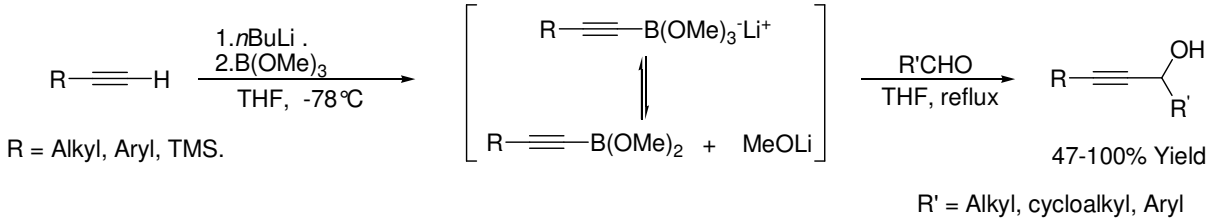


Scheme 2.21: Retrosynthetic analysis for N-acetylcolchinol

2.3 Chemoselective addition of in situ prepared lithium alkynyl borates to aldehydes: a practical and transition metal free approach toward the synthesis of propargylic alcohols

2.3.1 Synopsis

In the following section we will present our results concerning the addition of alkynylborates to aldehydes. In the course of our studies we find out that lithium alkynyl-trimethyl borates, generated in situ as non isolable intermediates, are efficient nucleophilic reagents and react smoothly with a large number of aldehydes providing the corresponding secondary propargylic alcohols in high yields.



These results are the subject of a publication that will be inserted as is: Notar Francesco I.; Renier A.; Wagner A.; Colobert F. *Tetrahedron Letters*, **2010**, *51*, 1386-1389.

2.3.2 Article

Tetrahedron Letters 51 (2010) 1386–1389

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Chemoselective addition of in situ prepared lithium alkynyl borates to aldehydes: a practical and transition metal free approach toward the synthesis of propargylic alcohols

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ARTICLE INFO

Article history:
Received 23 November 2009
Revised 21 December 2009
Accepted 6 January 2010
Available online 11 January 2010

Keywords:
Lithium alkynyl borate
Aldehyde
Propargylic alcohol

ABSTRACT

A convenient synthesis of functionalized propargylic alcohols arising from the 1,2-addition of lithium alkynyl-trimethyl borate onto aldehydes under transition metal free mild conditions is reported. The reaction tolerates a wide range of functional groups, is highly chemoselective and the propargylic alcohols are isolated in good to excellent yields.

1. Introduction

Propargylic alcohols are versatile building blocks in the synthesis of many natural products and pharmaceuticals.[1,2] Over the past few decades many methods to obtain propargylic alcohols have been presented. Most of them involved alkynylmetals in nucleophilic addition to carbonyl compounds. The alkynyl lithium or magnesium reagents generally employed in such processes are typically prepared from acetylene derivatives and organolithium[3] or organomagnesium[4] bases. However such strong basic and nucleophile reagents are often incompatible with a large range of functional groups. Recent efforts on this subject have led to the use of less reactive but highly efficient alkynylmetals involving metal species such as Cs,[5] Zn,[6] In,[7] Rh,[8] Ag,[9] Cu,[10] Ga,[11] Ce,[12] V,[13] B,[14] and Ti,[15] to a large extent in catalytic enantioselective procedures with aldehydes and ketones.

Although many significant results have been achieved in this field, the development of new procedures, allowing for a better compatibility between the reactivity of nucleophilic species and the substitution pattern of carbonyl compounds and alkynes, have still a considerable interest.

Because of their mildness, large availability, and ready preparation,[16] alkynyl borates have been extensively used in organic synthesis. We recently described their use in Pd-catalyzed Suzuki coupling with aromatic halides.[17–19] They also have been successfully used in the addition to aldehydes and ketones as isolated B-alkynyl-9-BBN derivatives.[14]

In this Letter, we describe the use of in situ prepared lithium alkynyltrimethyl borate in the metal-free 1,2-addition to aldehydes as an efficient and selective straightforward way to synthesize propargylic alcohols. This reaction is in agreement of functional-group tolerance, environmental sustainability, and economy, factors that are in constant demand nowadays. Processes that do not require any transition metal catalyst are of great interest because it avoids the elimination of traces of metal in the final compound.

2. Results and discussion

In an initial approach we chose to study the reaction of 1-octyne with benzaldehyde. Hence, the metallation of 1-octyne with 1 equiv of BuLi in THF at −78 °C during 1 h afforded the lithium 1-octynyl intermediate which was treated with 1.35 equiv of trimethylborate in THF at −78 °C. Two hours are normally sufficient to convert the alkynyl lithium in alkynyl borate derivative as confirmed by ^{11}B NMR[20] spectra. Addition by cannula of the in situ prepared lithium octynyl trimethyl borate to the aldehyde in THF at room temperature afforded after 1 h at reflux the desired coupling product in 98% yield. In the same reaction conditions methyl benzoate is completely unreactive in evidence of absence of lithium 1-octynyl intermediate (Scheme 1).

Further investigations showed that oxygenated, polar solvents such as THF and DME, which are equally effective in terms of

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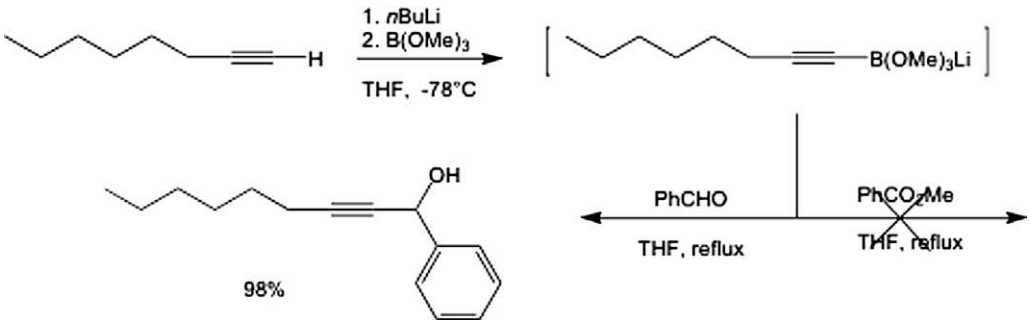
doi:10.1016/j.tetlet.2010.01.011



Scheme 1. Differences in the chemical behavior of lithium alkynyl borate with respect to benzaldehyde and benzoic ester.

conversion rates and reaction times, are the most suitable to our purposes. In a typical experiment a solution of lithium alkynyl-trimethyl borate, formed in situ after the addition of $B(OMe)_3$ on the corresponding alkynyl lithium at −78 °C in THF, is added to a solution of the desired aldehyde at room temperature. The temperature is increased to reflux and the aldehyde consumption is monitored by TLC (1–4 h are normally sufficient). This protocol was also demonstrated to work among different alkyne species and a wide series of aldehyde partners. Results obtained with 1-octyne are listed in Table 1.[21]

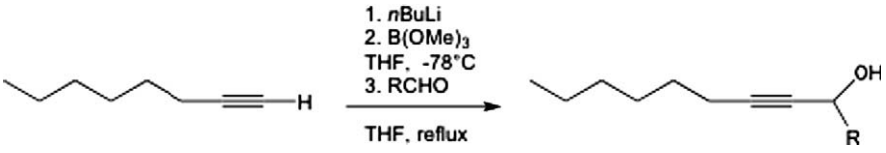
Good to excellent results were obtained in the coupling reaction between lithium octynyl trimethyl borate and aliphatic or aromatic aldehydes. Coupling with activated aromatic aldehydes in the presence of electron-withdrawing substituents on the aromatic moiety led in high yields to the corresponding propargylic alcohols (Table 1, entries 5–8). In cases of entries 6 and 8, 3 equiv of alkynyl borate salt has been used because no reaction occurred under normal conditions. One explanation could be the coordination of the oxygens of the nitro- or ester groups to the boron species. Very interesting are the cases in entries 7 and 8 showing that when the 4-acetyl- and 4-methylcarboxylate-benzaldehyde are used, the coupling reaction occurred exclusively on the aldehyde giving in good yield the corresponding products as a proof of the complete chemoselectivity of this method. We also performed the addition with aromatic aldehydes substituted in *ortho* or *para* position with halide atom (Table 1, entries 9 and 10) giving in satisfactory yields the related propargylic alcohols. In accordance with literature observations, with an electron-donating substituent on the aromatic ring (Table 1, entry 11), only 47% yield of the isolated adduct was obtained as expected in reason of a lower reactivity of the aldehyde toward the carbonyl addition. It has to be noticed that aromatic aldehydes bearing electron-donating substituent are rarely used in those kind of organic processes.

In order to evaluate the scope of the reaction also in regard to the electronic properties of the starting alkyne further tests have been performed. The results with phenylacetylene in association with several aldehydes are presented in Table 2.

In a general extent we observed that phenylacetylene gave good to excellent results with various aldehydes suggesting that electronic properties of the borate intermediate also play a key role. The *i*-butyraldehyde gave the best result (Table 2, entry 2) among the aliphatic aldehydes that have been used (Table 2, entries 1–4). With aromatic aldehydes excellent results were obtained and, to our delight, with electron-donating groups such as a methoxy on the phenyl ring (Table 2, entries 10 and 11) 75% and 98% yields were achieved for *ortho* and *para* position, respectively, despite to their inactivating function. On the contrary the 4-cyano benzaldehyde (Table 2, entry 6) gave only 65% yield. Aromatic aldehydes with halogenated substituent also showed a great reactivity, allowing high yields (Table 3, entries 7–9) especially in the case of a fluorine which gave the addition product in nearly quantitative yield.

The case of TMS substituent, that turns to be useful for further functionalization, was also explored (Table 3) but we observed the

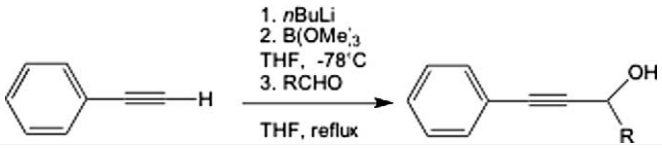
Table 1
1,2-Addition of in situ formed lithium 1-octynyl-trimethyl borate to aliphatic and aromatic aldehydes[a]



Entry	R	Yield[b] (%)
1	C_6H_5	98
2	*n*-C_5H_{11}	65
3	*i*-Pr	65
4	*t*-Bu	99
5	*p*-(CN)C_6H_4	97
6	*p*-(NO_2)C_6H_4[c]	62
7	*p*-(COMe)C_6H_4	68
8	*p*-(CO_2Me)C_6H_4[c]	75
9	*p*-(Br)C_6H_4	61
10	*o*-(F)C_6H_4	68
11	*p*-(OMe)C_6H_4	47

[a] Unless otherwise stated, reactions were run under argon by using a commercially available 1.6 M *n*BuLi solution in hexane with the following molar ratios: 1-octyne/*n*BuLi/$B(OMe)_3$/aldehyde = 1.3:1.3:1.35:1.
[b] Isolated yields after chromatography.
[c] 3 equiv of lithium octynyl trimethyl borate.

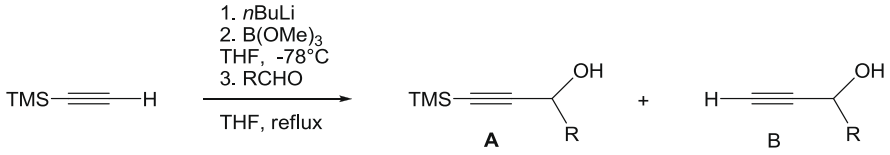
Table 2
1,2-Addition of in situ formed lithium phenylethynyl-trimethyl borate to aliphatic and aromatic aldehydes[a]



Entry	R	Yield[b] (%)
1	*n*-C_5H_{11}	77
2	*i*-Pr	91
3	*t*-Bu	87
4	Cyclohexyl	71
5	C_6H_5	88
6	*p*-(CN)C_6H_4	65
7	*o*-(F)C_6H_4	95
8	*o*-(Cl)C_6H_4	65
9	*p*-(Br)C_6H_4	71
10	*o*-(OMe)C_6H_4	75
11	*p*-(OMe)C_6H_4	98

[a] Unless otherwise stated, reactions were run under argon by using a commercially available 1.6 M *n*BuLi solution in hexane with the following molar ratios: phenyl acetylene/*n*BuLi/$B(OMe)_3$/aldehyde = 1.3:1.3:1.35:1.
[b] Isolated yields after chromatography.

Table 3
1,2-Addition of in situ formed lithium trimethylsilylethynyl-trimethyl borate to aliphatic and aromatic aldehydes[a]



Entry	R	Yield[b] (%) **A** (**A** + **B**)[c]
1	*t*-Bu	89 (95)[c]
2	1-Pentenyl	87
3	C_6H_5	54
4	*p*-(OMe)C_6H_4	56
5	*mm'p*-$(OMe)_3C_6H_2$	(81)[c]
6	*p*-(CO_2Me)C_6H_4	43 (83)[c,d]
7	*p*-(COMe)C_6H_4	48 (99)[c]

[a] Unless otherwise stated, reactions were run under argon by using a commercially available 1.6 M *n*BuLi solution in hexane with the following molar ratios: TMS-acetylene/*n*BuLi/$B(OMe)_3$/aldehyde = 1.3:1.3:1.35:1.
[b] Isolated yields after chromatography.
[c] Yield of compound **A** + **B**.
[d] 3 equiv of lithium octynyl trimethyl borate.

formation of a product which corresponds to the deprotected propargylic alcohol. Excellent yields were reached with aliphatic aldehydes as pivalaldehyde and *n*-hexanal with only 6% of the deprotected triple bond in the case of pivalaldehyde (Table 3, entries 1 and 2). Benzaldehyde and *p*-anisaldehyde are quite equally effective giving 54% and 56%, respectively, of the propargylic alcohol (Table 3, entries 3 and 4). Surprisingly with 3,4,5-trimethoxybenzaldehyde, 81% of the byproduct without TMS was obtained and when the 4-acetyl and the 4-methylcarboxylate benzaldehyde are used, an equal mixture of coupling products with and without TMS is obtained in excellent yields (Table 3, entries 6 and 7). The deprotection of the triple bond is probably caused by two different factors. The excess of the lithiated ate complex, as well as the hydrolysis during the work up, could affect the amount of the deprotected alcohol as confirmed by TLC. Such process seems to be independent from the electronic properties of starting materials.

In summary a new, practical, and efficient reaction involving lithium alkynyltrimethyl borate in the 1,2-addition to aldehydes is presented. This novel process constitutes a straightforward and chemoselective protocol to functionalized propargylic alcohols from simple and cheap precursors. Further studies on an asymmetric version are currently under investigation.

References and notes

1. Stang, P. J.; Diederich, F. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995.
2. Brandsma, L. In *Preparative Acetylene Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988.
3. Wakefield, B. J. In *Organolithium Methods*; Academic: London, 1988; p 32. Chapter 3.
4. Wakefield, B. J. In *Organomagnesium Methods in Organic Synthesis*; Academic: London, 1988; pp 46–48. Chapter 3.
5. Tzalis, D.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1463.
6. Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.
7. (a) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363; (b) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760.
8. Dhondi, P. K.; Chisholm, J. D. *Org. Lett.* **2006**, *8*, 67.
9. Yao, X.; Li, C.-J. *Org. Lett.* **2005**, *7*, 4395.
10. Asano, Y.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2007**, *9*, 3901.
11. Jia, X.; Yang, H.; Fang, L.; Zhu, C. *Tetrahedron Lett.* **2008**, *49*, 1370.
12. Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.
13. Hirao, T.; Misu, D.; Agawa, T. *Tetrahedron Lett.* **1986**, *27*, 933.

14. (a) Brown, H. C.; Molander, G. A.; Singh, S.; Racherla, U. S. *J. Org. Chem.* **1985**, *50*, 1577; (b) Lewis, M.-D.; Duffy, J.-P.; Heck, J.-V.; Menes, R. *Tetrahedron Lett.* **1988**, *19*, 2279; (c) Evans, J.-C.; Goralsky, C.-T.; Hasha, D.-L. *J. Org. Chem.* **1992**, *57*, 2941.
15. (a) Li, H.; Huang, Y.; Jin, W.; Xue, F.; Wan, B. *Tetrahedron Lett.* **2008**, *49*, 1686; (b) Kamble, R. M.; Singh, V. K. *Tetrahedron Lett.* **2003**, *44*, 5347; (c) Chen, Z.-C.; Hui, X.-P.; Yin, C.; Huang, L.-N.; Xu, P.-F.; Yu, X.-X.; Cheng, S.-Y. *J. Mol. Catal. A* **2007**, *269*, 179.
16. Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1991**, *29*, 2631.
17. Castanet, A. S.; Colobert, F.; Schlama, T. *Org. Lett.* **2000**, *2*, 3559.
18. Colobert, F.; Castanet, A. S.; Abillard, O. *Eur. J. Org. Chem.* **2005**, 3334.
19. Hernandez Torres, G.; Choppin, S.; Colobert, F. *Eur. J. Org. Chem.* **2006**, 1450.
20. $[B(OMe)_3]$: ^{11}B NMR ($CDCl_3$, 400 MHz, 25 °C) δ 19.7 ppm [lithiated 1-octynyl-trimethyl borate]: ^{11}B NMR ($CDCl_3$, 400 MHz, 25 °C) δ 4.3 ppm.
21. Preparation of lithiated 1-octynyl-trimethyl borate and 1,2-addition to pivalaldehyde (Table 1, entry 4): A solution of *n*-butyllithium (1.6 M in hexane, 1.3 mmol, 800 μL) was slowly added to a solution of 1-octyne (1.3 mmol, 192 μL) in THF (7 mL). After 1 h at −78 °C, trimethyl borate (1.35 mmol, 150 μL) was slowly added and the mixture was stirred for further 2 h. The temperature was raised up to 20 °C during 20 min and the solution was added by cannula to a solution of pivalaldehyde (1 mmol, 110 μL) in THF (1 mL). The reaction was heated under reflux until complete disappearance of the starting aldehyde (TLC) and allowed to cool to room temperature. After the addition of water (15 mL) and extraction with ethyl acetate (3 × 15 mL), the combined organic phases were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent = cyclohexane/ethyl acetate 98:2). Yield 99%.

2.3.3 Experimental part

2.3.3.1 General experimental procedures

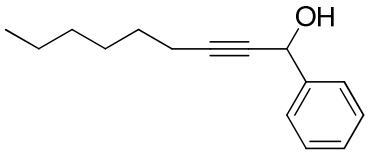
All the solvents used were dried and freshly distilled in argon atmosphere. Tetrahydrofuran and dimethoxyethane were distilled under sodium and benzophenone. Trimethylborate was distilled under sodium prior to use. All the aldehydes were distilled just before use. All the reactions were performed under argon atmosphere and in flamed under high vacuum flasks. Thin-layer chromatography (TLC) was carried out on aluminum plates silica gel 60 F_{254} purchased from Merck. Chromatography columns were performed with Merck silica gel Si 60 (40-63µm). ^{1}H,^{13}C (NMR) spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts are reported in δ units, parts per million (ppm) from tetramethylsilane and were measured relative to the signals for residual chloroform (7.26 ppm for proton and 77.00 for carbon NMR spectra). Coupling constants *J* are given in Hz. Coupling patterns are abbreviated as, for example, br (broad) s (singlet), d (doublet), t (triplet) and m (multiplet).

Mass spectra were recorded by HRMS by electrospray ionization method obtained with a microTOF LC Brucker Daltonics microTOF LC from Brucker Daltonics apparatus.

2.3.3.2 Representative procedure for coupling of lithium alkynyl-trimethyl borate and aldehydes

Preparation of lithiated 1-octynyl-trimethyl borate and 1,2-addition to pivalaldehyde (Table 1, entry 4): A solution of n-butyllithium (1.6 M in hexane, 1.3 mmol, 800 µL) was slowly added to a solution of 1-octyne (1.3 mmol, 192 µL) in THF (7 mL). After 1 h at -78 °C, trimethyl borate (1.35 mmol, 150 µL) was slowly added and the mixture was stirred for further 2 h. The temperature was raised up to 20 °C during 20 min and the solution was added by cannula to a solution of pivalaldehyde (1 mmol, 110 µL) in THF (1 mL). The reaction was heated under reflux until complete disappearance of the starting aldehyde (TLC) and allowed to cool to room temperature. After the addition of water (15 mL) and extraction with ethyl acetate (3x15 mL), the combined organic phases were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent = cyclohexane/ethyl acetate 98:2). Colourless oil, yield 99%.

2.3.3.3 Caracterization of substrates

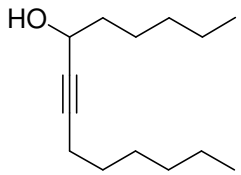


1-Phenylnon-2-yn-1-ol[15]

98 % yield, light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, ^{3}J= 7.0 Hz, 3H, CH_3), 1.23-1.35 (m, 4H, 2xCH_2), 1.36-1.44 (m, 2H, CH_2), 1.51-1.57 (m, 2H, CH_2), 2.07 (br s, 1H, O*H*), 2.25-2.29 (m, 2H, CH_2), 5.45 (br s, 1H, HO-C*H*), 7.29-7.56 (m, 5H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (*C*H_3), 18.8 (*C*H_2), 22.5 (*C*H_2), 28.49 (*C*H_2), 28.52 (*C*H_2), 31.3(H_2*C*-C≡C), 64.7 (*C*≡C), 79.9 (C≡*C*), 87.7 (H*C*-OH), 126.6 (*C*H arom), 128.1(*C*H arom), 128.5 (*C*H arom), 141.2 (*C* quat. arom) ppm.

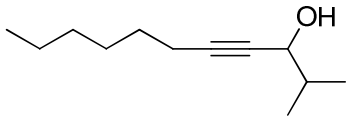


Tetradec-7-yn-6-ol[16]

65 % yield, colourless oil

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 6 H, 2 x CH_3), 1.28–1.49 (m, 18 H, 9 x CH_2), 1.61–1.70 (m, 2 H, CH_2), 1.77 (s, 1 H, O*H*), 2.19 (td, ^{3}J = 6.9 Hz, ^{4}J = 1.8 Hz, 2 H, CH_2), 4.34 (br t, *J* = 6.3 Hz, 1 H, C*H*OH) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (*C*H_3), 14.1 (CH_3), 18.7 (*C*H_2), 22.5 (*C*H_2), 22.6 (*C*H_2), 25.2 (*C*H_2), 28.5 (*C*H_2), 28.6 (*C*H_2), 29.2 (*C*H_2), 29.7 (*C*H_2), 31.3(H_2*C*-C≡C), 31.8 (HC-*C*H_2), 38.2 (C≡C), 62.8 (C*H*–OH), 85.5 (*C*≡C) ppm.



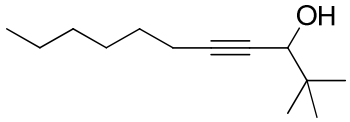
2-Methylundec-4-yn-3-ol[17]

[15] Egi, M.; Yamaguchi, Y.; Fujiwara, N.; Akai S. *Org. Lett*. **2008**, *10*, 1867-1870
[16] Ariza, X.; Fernàndez N.; Garcia, J.; Lopez, M.; Monserrat, L.; Ortiz, J. *Synthesis* **2004**, *1*, 128-134
[17] *Bull. Soc. Chim. Fr.* **1995**, *132*, 739-753

65 % yield, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 0.88 (t, ^3J = 7 Hz, 3H, CH_3) 0.97 (d, ^3J = 6 Hz, 3H, CH_3 *i*-Pr), 0.99 (d, ^3J = 6 Hz, 3H, CH_3 *i*-Pr), 1.17–1.52 (m, 8 H, 4x CH_2), 1.68 (br s, 1 H, O*H*), 1.85 (m, 1 H, C*H* *i*-Pr), 2.20 (dt, ^3J = 7.1 Hz, ^4J = 1.8 Hz, 2 H, CH_2), 4.15 (br s, 1H, C*H*OH) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) : δ = 14.0 (*C*H_3), 15.3 (2x*C*H_3, *i*-Pr) 19.5 (CH_2), 22.5 (*C*H_2), 28.2 (*C*H_2), 29.0 (*C*H_2), 31.0 (H_2C-C≡C), 34.8 (*C*H, *i*-Pr), 71.6 (*C*HOH), 80.1 (C≡C), 83.9 (C≡C) ppm.



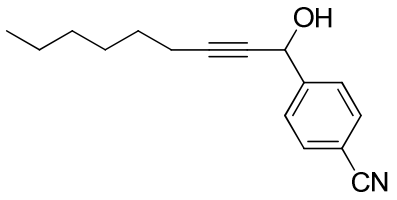
2,2-Dimethylundec-4-yn-3-ol

99 % yield, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 0.87 (t, ^3J = 6.9 Hz, 3 H, CH_3), 0.96 (s, 9 H, 3 x CH_3, *t*-Bu), 1.28–1.49 (m, 8 H, 4 x CH_2), 1.66 (s, 1 H, O*H*), 2.19 (td, ^3J = 7.2 Hz, ^4J = 1.8 Hz, 2 H, CH_2), 3.97 (br s, 1 H, C*H*OH) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) : δ 14.0 (CH_3), 18.6 (CH_2), 22.5 (CH_2), 25.3 (3 x CH_3, *t*-Bu), 28.5 (CH_2), 28.7 (CH_2), 31.3 (H_2C-C≡C), 35.8 (*C* quat, *t*-Bu), 71.6 (*C*H–OH), 79.8 (C≡C), 86.2 (C≡C) ppm.

Anal. calcd for $C_{13}H_{24}O$: C 79.58, H 12.32; found: C 79.71, H 12.14.



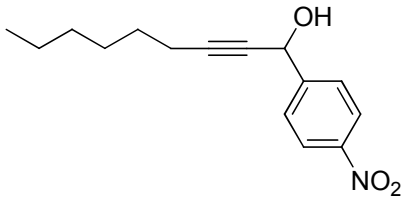
4-(1-Hydroxynon-2-ynyl)benzonitrile[18]

97 % yield, brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 0.88 (t, ^3J = 6.7 Hz, 3 H, CH_3), 1.25–1.55 (m, 8 H, 4 x CH_2), 2.26 (td, ^3J= 7.1 Hz, ^4J = 1.8 Hz, 2 H, CH_2), 2.39 (br s, 1 H, O*H*), 5.49 (br s, 1 H, C*H*OH), 7.70 (m, 4 H, 4 x C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (*C*H_3), 18.7 (*C*H_2), 22.5 (*C*H_2), 28.4 (*C*H_2), 28.5 (*C*H_2), 31.2 (H_2C-C≡C), 63.9 (*C*H–OH), 79.0 (C≡*C*), 88.8 (*C*≡C), 113.3 (*C* quat, arom), 118.7 (*C* quat, *C*≡N), 127.2 (*C*H arom), 130.1 (*C*H arom), 146.3 (*C* quat, arom) ppm.

[18] Sakai, N.; Kanada, R.; Hirasawa, M.; Konakahara, T. *Tetrahedron* **2005**, *61*, 9298-9304

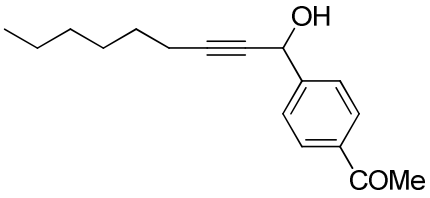


1-(4-Nitrophenyl)non-2-yn-1-ol[19]

62 % yield, brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (t, ^{3}J = 7 Hz, 3 H, CH_3), 1.18–1.35 (m, 6 H, 3 x CH_2), 1.41–1.51 (m, 2 H, CH_2), 2.19 (td, ^{3}J = 7.1 Hz, ^{4}J = 2.1 Hz, 2 H, CH_2), 2.54 (s, 1 H, O*H*), 5.46 (d, ^{4}J= 2.2Hz, 1 H, C*H*OH), 7.63 (d, 2 H, ^{3}J = 9 Hz, 2 x CH arom), 8.15 (d, 2 H, ^{3}J = 9 Hz, 2 x CH arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (*C*H_3), 18.5 (*C*H_2), 22.9 (*C*H_2), 27.9 (*C*H_2), 28.8 (*C*H_2), 31.5 (H_2*C*-C≡C), 64.8 (*C*H–OH), 78.3 (C≡*C*), 88.3 (*C*≡C), 114.3 (*C* quat, arom), 125.2 (*C*H arom), 132.4 (*C*H arom), 148.6 (*C* quat, arom) ppm.



1-(4-(1-Hydroxynon-2-ynyl)phenyl)ethanone

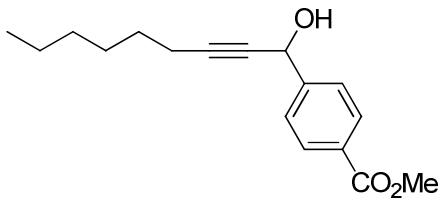
68 % yield, yiellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 0.88 (t, ^{3}J = 6.7 Hz, 3 H, CH_3), 0.90–1.57 (m, 8 H, 4 x CH_2), 2.15 (br s, 1 H, O*H*), 2.26 (td, ^{3}J = 7 Hz, ^{4}J = 2.1 Hz, 2^{3}H, CH_2), 2.54 (s, 3 H, (O=C)CH_3), 5.45 (br s, 1 H, C*H*OH), 7.63 (d, 2 H, ^{3}J = 8.1 Hz, 2 x CH arom), 8.03 (d, 2 H, ^{3}J = 8.4 Hz, 2 x CH arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) : δ 13.0 (*C*H_3), 18.1 (*C*H_2), 22.7 (*C*H_2), 25.8 ((O=C)*C*H_3), 29.4 (*C*H_2), 30.2 (*C*H_2), 30.9 (H_2*C*-C≡C), 67.2 (*C*H–OH), 78.7 (C≡*C*), 87.4 (*C*≡C), 125.7 (*C*H arom), 127.8 (*C*H arom), 135.8 (*C* quat, arom), 145.3 (*C* quat, arom), 194.8 (*C* quat, *C*=O) ppm.

Anal. calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58; found: C, 79.15; H, 8.64.

[19] Morrill, C.; Beutner, G. L.; Grubbs, R; H. *J. Org. Chem* **2006**, *71*, 7813-7825

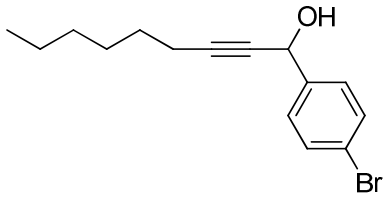


Methyl 4-(1-hydroxynon-2-ynyl)benzoate[20]

75 % yield, colourless oil.

^{1}H NMR (300 MHz, CDCl,) δ0.88 (t, ^{3}J = 6.7 Hz, 3 H, CH_3), 1.00-1.70 (m, 8 H, 4 x CH_2), 2.24 (td, ^{3}J = 7.1 Hz, ^{4}J = 2.0 Hz, 2 H, CH_2), 2.15 (br s, 1 H, O*H*), 3.91 (s, 3 H, OCH_3), 5.49 (br s, 1 H, C*H*OH), 7.60 (d, 2 H, ^{3}J = 8.1 Hz, 2 x CH arom), 8.02 (d, 2 H, ^{3}J = 8.3 Hz, 2 x CH arom).

^{13}C NMR (250 MHz, $CDCl_3$) δ 13.65 (*C*H_3), 18.52 (*C*H_3), 22.22 (*C*H_2), 28.27 (*C*H_2), 31.02 (H_2*C*-C≡C), 51.74 (*C*H_2), 63.82(O*C*H_3) ,79.5 (*C*H–OH) (*C*≡C), 87.53 (*C*≡C), 126.22(*C*H arom), 129.35(*C* quat, arom), 129.46 (*C*H arom), 146.41 (*C* quat, arom), 166.70 (C(O) quat.)



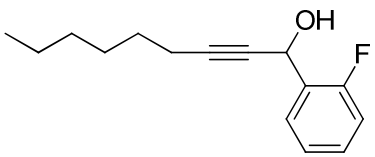
1-(4-Bromophenyl)non-2-yn-1-ol

61 % yield, brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.27–1.55 (m, 8 H, 4 x CH_2), 2.24 (td, ^{3}J = 7.2 Hz, ^{4}J = 2.1 Hz, 2 H, CH_2), 2.65 (br s, 1 H, OH), 5.37 (br s, 1 H, C*H*OH), 7.38 (d, ^{3}J = 8.4 Hz, 2 H, 2 x CH arom), 7.47 (d, ^{3}J = 8.4 Hz, 2 H, 2 x CH arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) : δ 14.1 (*C*H_3), 18.4 (*C*H_2), 22.6 (*C*H_2), 28.6 (*C*H_2), 28.8 (*C*H_2), 31.3 (H_2*C*-C≡C), 64.0 (*C*H–OH), 79.6 (*C*≡C), 88.0 (C≡*C*), 122.1 (*C* quat, arom), 128.4 (2 x *C*H arom), 131.1 (2 x *C*H arom), 140.3 (*C* quat, arom) ppm.

Anal. calcd for $C_{15}H_{19}BrO$: C, 61.03; H, 6.49; found: C, 61.01; H, 6.53.



[20] Walba, D. M.; Razavi, H. A.; Clark, N. A.; Parmar, D. S. *J. Am. Chem.Soc.* **1988**, *110*, 8686-8691

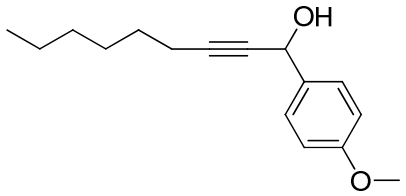
1-(2-Fluorophenyl)non-2-yn-1-ol

68 % yield, brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, ^3J = 6.6 Hz, 3 H, CH_3), 1.28-1.56 (m, 8 H, 4 x CH_2), 2.26 (td, ^3J = 6.9 Hz, ^4J = 1.8 Hz, 2 H, CH_2), 2.58 (br s, 1 H, O*H*), 5.73 (br s, 1 H, C*H*OH), 7.01-7.08 (m, 1 H, C*H* arom), 7.13-7.18 (m, 1 H, CH arom), 7.25–7.30 (m, 1 H, C*H* arom), 7.66 (td, ^3J = 7.5 Hz, $^5J_{HF}$ = 2.1 Hz, 1 H, CH arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (*C*H_3), 18.8 (*C*H_2), 22.2 (*C*H_2), 22.5 (*C*H_2), 28.5 (*C*H_2), 31.3 (H_2*C*-C≡C), 59.1 (d, $^3J_{CF}$= 5.4 Hz, 1C, *C*HOH), 78.9 (C≡*C*), 87.7 (*C*≡C), 115.8 (d,$^2J_{CF}$= 20 Hz, 1C, *C*H arom), 124.5 (d,$^3J_{CF}$= 3.8 Hz, 1C, *C*H arom), 128.3 (d,$^2J_{CF}$= 13 Hz, 1C, *C* quat. arom), 129.9 (d,$^3J_{CF}$= 3.8 Hz, 1C, *C*H arom), 130.7 (d,$^4J_{CF}$= 8.3 Hz, 1C, *C*H arom) 160.2 (d, $^1J_{CF}$ = 246.5 Hz, *C*F arom.) ppm.

Anal. calcd for $C_{15}H_{19}FO$: C, 76.89; H, 8.17; found: C, 76.95; H, 8.23.

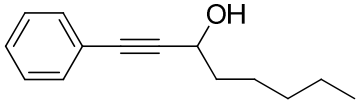


1-(4-methoxyphenyl)non-2-yn-1-ol[21]

47 % yield, brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, ^3J = 6.6 Hz, 3 H, CH_3), 1.26–1.42 (m, 8 H, 4 x CH_2), 2.26 (td, ^3J = 7.2 Hz, ^4J = 2.1 Hz, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 5.40 (br s, 1 H, C*H*OH), 6.89 (d, ^3J = 9.0 Hz, 2 H, 2 x CH arom), 7.46 (d, ^3J = 8.7 Hz, 2 H, 2 x CH arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) : δ 14.0 (*C*H_3), 18.9 (*C*H_2), 19.7 (*C*H_2), 22.5 (*C*H_2), 28.6 (*C*H_2), 32.5 (H_2*C*-C≡C), 55.3 (O*C*H_3), 64.4 (*C*HOH), 80.2 (C≡*C*), 87.4 (*C*≡C), 113.8 (2 x *C*H arom), 128.0 (2 x *C*H arom), 133.8 (*C* quat arom), 159.5 (*C* quat arom) ppm.



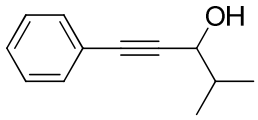
1-Phenyloct-1-yn-3-ol[22]

77 % yield, colourless oil.

[21] Morrill, C.; Beutner, G. L.; Grubbs R. H. *J. Org. Chem*. **2006**, *71*, 7813-7825
[22] Pacheco, C.; Gouverneur, V. *Org. Lett.* **2005**, *7*, 1267-1270

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, ^3J= 6.8 Hz, 3H, CH_3), 1.26–1.57 (m, 6H, 3xCH_2), 1.72–1.87 (m, 2H, CH_2), 3.07 (s, 1H, O*H*), 4.59 (t, ^3J= 6.6 Hz, 1H, C*H*OH), 7.28–7.34 (m, 3H, C*H* arom), 7.39–7.45 (m, 2H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (*C*H_3), 19.9 (*C*H_2), 22.5 (*C*H_2), 31.5 (*C*H_2), 31.3(HC*C*H_2), 64.7(C*H*OH), 79.9 (C≡*C*), 87.7(*C*≡C), 126.6 (2 x *C*H arom), 128.1(*C*H arom), 128.5 (2 x *C*H arom), 141.2 (*C* quat. arom) ppm.

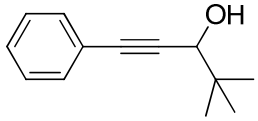


4-Methyl-1-phenylpent-1-yn-3-ol[23]

91 % yield, pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, ^3J = 6.8 Hz, 3H, CH_3 *i*-Pr), 1.07 (d, ^3J= 6.6 Hz, 3H, CH_3 *i*-Pr), 1.91–2.03 (m, 1H, C*H* *i*-Pr), 3.03 (s, 1H, O*H*), 4.38 (d, ^3J= 5.6 Hz, 1H, C*H*OH), 7.28–7.44 (m, 5H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5 (*C*H_3 *i*-Pr), 18.2 (*C*H_3 *i*-Pr) , 34.7(*C*H *i*-Pr), 68.3 (*C*HOH), 85.5 (C≡*C*), 88.8 (*C*≡C), 122.7 (*C* quat arom), 128.2 (2 x *C*H arom), 128.3 (2 x *C*H arom), 131.6 (*C* quat arom) ppm.

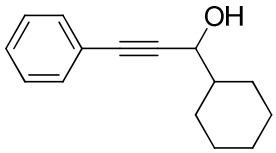


4,4-Dimethyl-1-phenylpent-1-yn-3-ol[23]

87 % yield, Pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9 H, 3 x CH_3, *t*-Bu), 1.88 (d, ^3J = 5.6 Hz, 1H, O*H*), 4.24 (d, ^3J = 5.6 Hz, 1H, C*H*OH), 7.28–7.47 (m, 5H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4 (3 x CH_3, *t*-Bu), 36.1 (*C* quat, *t*-Bu), 71.9 (*C*HOH), 85.7 (C≡*C*), 88.9 (*C*≡C), 122.8 (*C*H arom), 128.32 (2 x *C*H arom), 128.3 (2 x *C*H arom), 131.7(*C* quat arom) ppm.



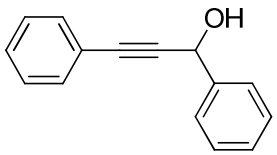
[23] Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem*. **2003**, *68*, 3702-3705

1-Cyclohexyl-3-phenylprop-2-yn-1-ol[24]

71 % yield, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19–1.43 (m, 4H, 2 x CH_2), 1.61–1.97 (m, 6H, 3 x CH_2), 3.73–3.77 (m, 1H, C*H*), 4.37 (d, ^3J= 6 Hz, 1H, C*H*OH), 7.28–7.33 (m, 3H, C*H* arom), 7.41–7.49 (m, 2H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8 (*C*H_2), 26.3 (*C*H_2), 28.1 (*C*H_2), 28.6 (*C*H_2), 44.2 (*C*H), 67.5 (*C*HOH), 85.5 (C≡*C*), 89.2 (*C*≡C), 122.6 (*C*H arom), 128.1 (2 x *C*H arom), 128.2 (2 x *C*H arom), 131.5 (*C* quat arom) ppm.

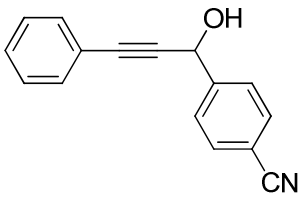


1,3-diphenylprop-2-yn-1-ol[25]

88 % yield, brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18 (s, 1 H, O*H*), 5.75 (s, 1 H, C*H*OH), 7.36–7.46 (m, 6 H, C*H* arom), 7.54–7.57 (m, 2 H, C*H* arom), 7.69 (d, ^3J = 6.6 Hz, 2 H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 65.0 (*C*HOH), 86.7(C≡*C*), 89.1 (*C*≡C), 122.6 (*C* quat arom), 126.5 (*C*H arom), 127.7 (*C*H arom), 128.4 (*C*H arom), 128.7 (*C*H arom), 129.0 (*C*H arom), 131.9 (*C*H arom), 140.8 (*C* quat arom) ppm.



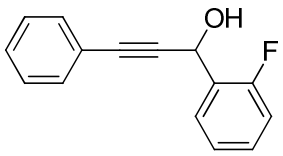
4-(1-Hydroxy-3-phenylprop-2-ynyl)benzonitrile[18]

65 % yield, orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.19 (s, 1H, O*H*), 5.71 (s, 1 H, C*H*OH), 7.27–7.32 (m, 3H, C*H* arom), 7.41–7.42 (m, 2H, C*H* arom), 7.61 (d, ^3J=8.0 Hz, 2H, C*H* arom), 7.68 (d, ^3J=8.0Hz, 2H, C*H* arom) ppm.

[24] Yao, X.; Li, C. -J. *Org. Lett.* **2005**, *7*, 4395-4398
[25] Pilcher, A. S.; DeShong, Ph. *J. Org. Chem*. **1996**, *61*, 6901-6905

^{13}C NMR (75 MHz, $CDCl_3$) δ 64.0 (*C*HOH), 87.2 (C≡*C*), 87.5 (*C*≡C), 111.7 (*C*≡N), 118.5 (*C* quat arom), 121.7 (*C* quat arom), 127.1 (*C*H arom), 128.3 (*C*H arom), 128.8 (*C*H arom), 131.6 (*C*H arom), 132.3 (*C*H arom), 145.6 (*C* quat arom) ppm.

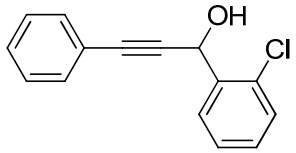


1-(2-Fluorophenyl)-3-phenylprop-2-yn-1-ol[24]

95 % yield, brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (s, 1 H, O*H*), 5.99 (s, 1 H, C*H*OH), 7.06-7.13 (m, 1 H, C*H* arom), 7.17-7.22 (m, 1 H, C*H* arom), 7.30-7.35 (m, 4 H, C*H* arom), 7.47-7.50 (m, 2 H, C*H* arom), 7.75 (m, 1H, C*H* arom)) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 59.4 (d, $^{3}J_{CF}$= 5.4 Hz, 1C, *C*HOH), 86.5(C≡*C*), 87.9 (*C*≡C), 115.6 (d,$^{2}J_{CF}$= 20 Hz, 1C, *C*H arom) 122.5 (*C* quat. arom), 124.6 (d,$^{3}J_{CF}$= 3.8 Hz, 1C, *C*H arom), 128.1 (d,$^{2}J_{CF}$= 13 Hz, 1C, *C* quat. arom), 128.4 (*C*H arom), 128.5 (2 x *C*H arom), 128.7 (d,$^{3}J_{CF}$= 3.8 Hz, 1C, *C*H arom), 130.4 (d,$^{4}J_{CF}$= 8.3 Hz, 1C, *C*H arom), 132.2 (2 x *C*H arom), 160.2 (d, $^{1}J_{CF}$ = 246.8 Hz, 1C, *C*F) ppm.

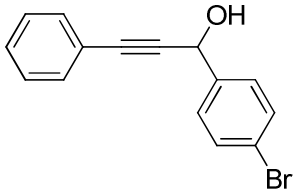


1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-ol[24]

65 % yield, brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (s, 1 H, O*H*), 6.06 (s, 1 H, C*H*OH), 7.28–7.50 (m, 6 H, C*H* arom), 7.48–7.51 (m, 2 H, C*H* arom), 7.85 (dd, ^{3}J = 7.2 Hz, ^{4}J = 2.1 Hz, 1 H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) : δ 62.4 (*C*–OH), 86.7 (C≡*C*), 87.8 (C≡*C*), 122.4 (*C* quat arom), 127.3, 128.4 (*C*H arom), 128.5 (*C*H arom), 128.8 (*C*H arom), 129.1 (*C*H arom), 132.5 (*C*H arom), 138.0 (*C* quat arom), 143.8 (*C* quat arom) ppm.

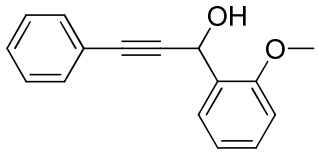


1-(4-Bromophenyl)-3-phenylprop-2-yn-1-ol[24]

71 % yield, brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 1 H, O*H*), 5.64 (s, 1 H, C*H*OH), 7.31–7.52 (m, 9 H, 9 x C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 64.4 (*C*–OH), 87.0 (*C*≡C), 88.3 (C≡*C*), 122.2 (*C* quat arom), 122.4 (*C* quat arom), 128.4 (*C*H arom), 128.5 (*C*H arom), 128.7 (*C*H arom), 128.8 (*C*H arom), 131.3 (*C*H arom), 132.1 (*C*H arom), 139.7 (*C* quat arom) ppm.

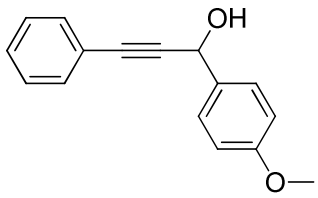


1-(2-Methoxyphenyl)-3-phenylprop-2-yn-1-ol[20]

75 % yield, brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 1 H, O*H*), 3.92 (s, 3 H, OCH_3), 5.95 (s, 1 H, C*H*OH), 6.94 (dd, ^{3}J = 8.7 Hz, ^{4}J = 0.6 Hz, 1 H, C*H* arom), 7.02 (td, ^{3}J = 7.5 Hz, ^{4}J = 1.2 Hz, 1 H, C*H* arom), 7.31–7.34 (m, 4 H, C*H* arom), 7.48–7.51 (m, 2 H, C*H* arom), 7.66 (dd, ^{3}J = 7.5 Hz, ^{4}J = 0.9 Hz, 1 H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 55.7 (O-*C*H_3), 61.5 (*C*HOH), 86.1 (*C*≡C), 88.6 (C≡*C*), 111.0 (*C*H arom), 121.3 (*C*H arom), 122.7 (*C* quat arom), 126.5 (*C* quat arom), 127.9 (*C*H arom), 128.3 (*C*H arom), 128.5 (*C*H arom), 128.7 (*C*H arom), 132.2 (*C*H arom), 156.9 (*C* quat arom) ppm.



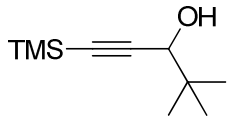
1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol[26]

98 % yield, brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ2.33 (s, 1 H, O*H*), 3.82 (s, 3 H, OCH_3), 5.65 (s, 1 H, C*H*OH), 6.93 (d, ^{3}J = 6.0 Hz, 2 H, C*H* arom), 7.31–7.57 (m, 7 H, C*H* arom) ppm.

[26] Lettan II, R. B.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 3227-3230

^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4 (O*C*H_3), 64.7 (*C*HOH), 86.5(*C*≡C), 89.0 (C≡*C*), 114.0, 122.5(*C* quat arom), 128.3 (*C*H arom), 128.6 (*C*H arom), 128.8 (*C*H arom), 133.0 (*C*H arom), 136.8 (*C* quat arom), 159.7 (*C* quat arom) ppm.

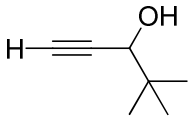


4,4-Dimethyl-1-(trimethylsilyl)pent-1-yn-3-ol[27]

89 % yield, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.102 (s, 9 H, 3 x C*H*$_3$ TMS), 0.919 (s, 9 H, 3 x C*H*$_3$ *t*-Bu), 1.67 *(*br s, 1 H*,* O*H*), 3.92 (s, 1 H, C*H*OH) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ -0.139 (*C*H$_3$ TMS), 25.3 (*C*H$_3$ *t*-Bu), 35.8 (*C* quat *t*-Bu), 71.8 (*C*HOH), 90.3 (*C*≡C), 105.6 (C≡*C*) ppm.

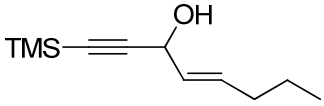


4,4-Dimethylpent-1-yn-3-ol[28]

6 % yield, colourless oil.

^{1}H NMR (300 MHz, CDCl3) δ 1.03 (s, 9 H, 3 x C*H*$_3$ *t*-Bu), 2.02 *(*br s, 1 H*,* O*H*), 2.48 (s, 1H, C≡C*H*), 4.04 (br s, 1 H, C*H*OH) ppm.

^{13}C NMR (75 MHz, CDCl3) δ 25.0 (*C*H$_3$ *t*-Bu), 35.4 (*C* quat *t*-Bu), 70.9 (*C*HOH), 73.6 (C≡*C*H), 83.6 (*C*≡CH).



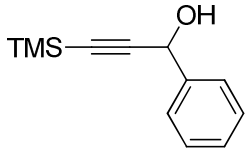
(E)-1-(Trimethylsilyl)oct-4-en-1-yn-3-ol[29]

87 % yield, pale yellow oil.

[27] Evans, J. C.; Goralski, C. T.; Hasha, L. D. *J. Org. Chem* **1992**, *57*, 2941-2943
[28] Nielsen, T. E.; Tanner, D. *J. Org. Chem*. **2002**, *67*, 6366-6371
[29] Allevi, P.; Ciuffreda, P.; Anastasia, M. *Tetrahedron: Asym*. **1997**, *8*, 93-100

^{1}H NMR (300 MHz, CDCl3) δ^{1}H NMR (300 MHz, $CDCl_3$) δ0.17 (s, 9 H, 3 x C*H*$_3$ TMS), 0.90 (t, *J*= 7 Hz, 3H, C*H*$_3$), 1.36–1.46 (m, 2H, C*H*$_2$), 2.03 (q, ^{3}*J*= 7.2 Hz, 2H, C*H*$_2$), 2.21 *(*br s, 1 H*,* O*H*), 4.80 (d, ^{3}*J*= 6.2 Hz, 1 H, C*H*OH), 5.57(dd, ^{3}*J* = 6.2 Hz, $^3J_{trans}$ = 15 Hz, 1 H, =C*H*(CHOH)), 5.82-5.89 (m,1H, =C*H*(CH_2))ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ-0.13 (*C*H_3 TMS), 13.7 (*C*H_3), 22.1 (*C*H_2), 35.8 (*C*H_2), 63.3 (*C*HOH), 90.5 (*C*≡C), 105.1 (C≡*C*), 128.9 (=*C*$CHCH_2$), 133.9 (=*C*HCHOH) ppm.

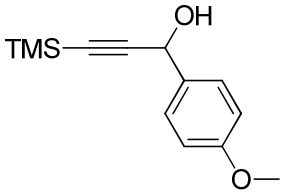


1-Phenyl-3-(trimethylsilyl)prop-2-yn-1-ol[30]

54 % yield, brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ0.23 (s, 9H, 3 x C*H*$_3$TMS), 2.46 (s, 1H, O*H*), 5.46 (s, 1 H, C*H*OH) 7.34–7.42 (m, 3H, C*H* arom), 7.57 (m, 2H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ0.23 (*C*H_3TMS) , 65.0 (*C*HOH), 91.6 (*C*≡C), 105.1 (C≡*C*), 127.1 (*C*H arom), 128.4 (*C*H arom), 128.6 (*C*H arom), 140.4 (*C* quat arom)



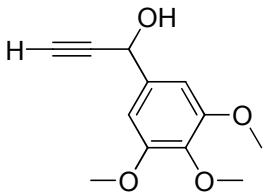
1-(4-Methoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-ol[31]

56 % yield, brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ0.21 (s, 9H, 3 x C*H*$_3$ TMS), 2.30 (s, 1H, O*H*), 3.81 (s, 3 H, OC*H*$_3$), 5.40 (s, 1H, C*H*OH), 6.90 (d, ^{3}*J* = 8.7 Hz, 2H, C*H* arom), 7.47 (d, ^{3}*J* = 8.7 Hz, 2H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ-0.2 (*C*H_3TMS), 55.3 (OCH_3), 64.6 (*C*HOH), 91.3 (*C*≡C), 105.3 (C≡*C*), 128.2 (*C*H arom), 132.7 (*C*H arom), 139.2 (*C* quat arom), 159.8 (*C* quat arom) ppm.

[30] Shintani, R.; Okamoto, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 2872-2873
[31] Shi Shun, A. L. K.; Chernick, E. T.; Eisler, S.; Tykwinski, R. R. J. Org. Chem. 2003, 68, 1339-1347

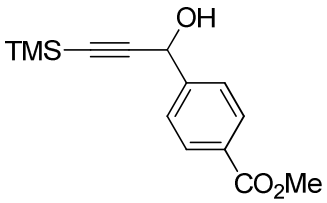


1-(3,4,5-Trimethoxyphenyl)prop-2-yn-1-ol[32]

81 % yield, yellow solid.

^{1}H NMR (300 MHz/CDCl3) δ 2.25 (s, 1H, O*H*), 2.69 (d, 1H, ^{4}J = 2.2 Hz, C≡C*H*), 3.84 (s, 3H, OCH_3), 3.87 (s, 6H, 2 x OCH_3), 5.40 (d, ^{4}J= 2.1 Hz, C*H*OH), 6.79 (s, 2H, C*H* arom) ppm.

^{13}C NMR (75 MHz) δ 56.15 (2 x O*C*H_3) , 60.87 (*C*HOH), 64.50 (O*C*H_3), 74.85 (*C*≡CH), 83.49 (HC≡*C*) , 103.64 (*C*H arom), 135.74 (*C* quat arom), 137.98 (*C* quat arom), 153.35 (*C* quat arom) ppm.



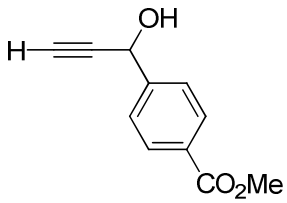
Methyl 4-(1-hydroxy-3-(trimethylsilyl)prop-2-ynyl)benzoate

43 % yield, pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 0.19 (s, 9H, 3 x CH_3 TMS), 2.15 (br s, 1 H, O*H*), 3.91 (s, 3 H, OCH_3), 5.49 (s, 1 H, C*H*OH), 7.60 (d, 2 H, ^{3}J = 8.2 Hz, 2 x CH arom), 8.03 (d, 2 H, ^{3}J = 8.4 Hz, 2 x C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) : δ -0.2 (*C*H_3TMS), 52.2 (O*C*H_3), 64.4 (*C*HOH), 90.0 (C≡*C*), 104.5 (*C*≡C), 126.6 (*C*H arom), 128.8 (*C* quat, arom), 129.9 (*C*H arom), 145.3 (*C* quat, arom), 166.9 (*C* quat, *C*=O) ppm.

Anal. calcd for $C_{14}H_{18}O_3Si$: C 64.09, H 6.91; found: C 64.12, H 6.87.



Methyl 4-(1-hydroxyprop-2-ynyl)benzoate

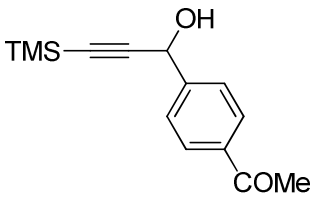
[32] Sibelle, L.; Bernardes, C.; Kato,M. J.; Albuquerque, S.; Carvalho, I. *Bioorg. Med. Chem*. **2006**, *14*, 7075-7082

40 % yield, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (br s, 1 H, O*H*), 2.70 (d, ^{3}J= 2.2 Hz, 1H, *H*≡C), 5.52 (d, ^{4}J= 2.2 Hz, 1H, C*H*OH), 7.62 (d, 2 H, ^{3}J = 8.4 Hz, 2 x CH arom), 8.04 (d, 2 H, ^{3}J= 8.4 Hz, 2 x C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 52.3 (O*C*H_3), 63.9 (*C*HOH), 75.4 (C≡*C*H), 83.0 (*C*≡CH), 126.5 (*C*H arom), 130.0 (*C*H arom), 130.2 (*C* quat, arom), 144.8 (*C* quat, arom), 166.8 (*C* quat, *C*=O) ppm.

Anal. calcd for $C_{11}H_{10}O_3$: C 69.46, H 5.30; found: C 69.48, H 5.21.



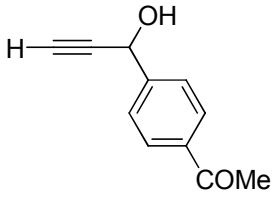
1-(4-(1-Hhydroxy-3-(trimethylsilyl)prop-2-ynyl)phenyl)ethanone

48 % yield, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 9H, 3 x CH_3 TMS), 1.95 (br s, 1 H, O*H*), 2.61 (s, 3 H, (O=C)CH_3), 5.51 (s, 1 H, C*H*OH), 7.64 (d, 2 H, ^{3}J= 8.4 Hz, 2 x CH arom), 7.97 (d, 2 H, ^{3}J = 8.4 Hz, 2 x CH arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 0.1 (*C*H_3TMS), 26.4 ((O=C)*C*H_3), 66.2 (*C*HOH), 79.9 (C≡*C*), 93.4 (*C*≡C), 126.5 (*C*H arom), 129.0 (*C*H arom), 135.8 (*C* quat, arom), 146.8 (*C* quat, arom), 195.3 (*C* quat, *C*=O) ppm.

Anal. calcd for $C_{14}H_{18}O_2Si$: C 68.25, H 7.36; found: C 68.29, H 7.29.



1-(4-(1-Hydroxyprop-2-ynyl)phenyl)ethanone

51 % yield, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (br s, 1 H, O*H*), 2.74 (s, 3 H, (O=C)CH_3), 2.88 (d, ^{4}J= 2.2 Hz, 1H, *H*≡C), 5.85 (d, ^{4}J= 2.2 Hz, 1H, C*H*OH), 7.69 (d, ^{3}J = 8.4 Hz, 2 H,2 x CH arom), 8.01 (d, ^{3}J = 8.4 Hz, 2 H,2 x CH arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8 ((O=C)*C*H$_3$), 67.1 (*C*HOH), 77.2 (C≡*C*H), 95.7 (*C*≡C), 126.9 (*C*H arom), 128.7 (*C*H arom), 136.3 (*C* quat, arom), 146.3 (*C* quat, arom), 195.5 (*C* quat, *C*=O) ppm

Anal. calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79; found: C, 75.89; H, 5.63.

[21] Morrill, C.; Beutner, G. L.; Grubbs R. H. *J. Org. Chem*. **2006**, *71*, 7813-7825

[22] Pacheco, C.; Gouverneur, V. *Org. Lett.* **2005**, *7*, 1267-1270

[23] Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem*. **2003**, *68*, 3702-3705

[24] Yao, X.; Li, C. -J. *Org. Lett.* **2005**, *7*, 4395-4398

[25] Pilcher, A. S.; DeShong, Ph. *J. Org. Chem*. **1996**, *61*, 6901-6905

[26] Lettan II, R. B.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 3227-3230

[27] Evans, J. C.; Goralski, C. T.; Hasha, L. D. *J. Org. Chem* **1992**, *57*, 2941-2943

[28] Nielsen, T. E.; Tanner, D. *J. Org. Chem*. **2002**, *67*, 6366-6371

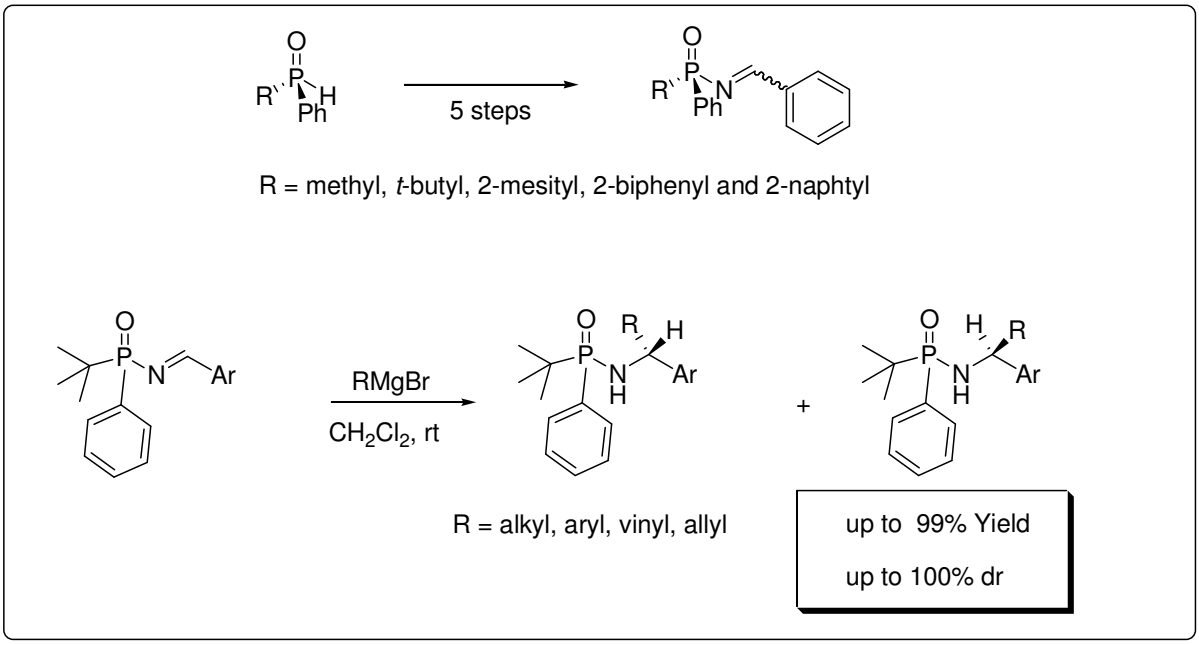
[29] Allevi, P.; Ciuffreda, P.; Anastasia, M. *Tetrahedron: Asym*. **1997**, *8*, 93-100

[30] Shintani, R.; Okamoto, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 2872-2873

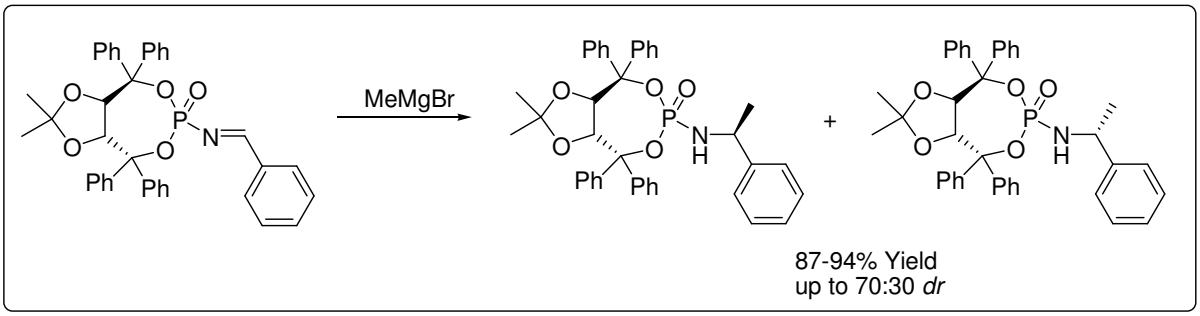
[31] Shi Shun, A. L. K.; Chernick, E. T.; Eisler, S.; Tykwinski, R. R. J. Org. Chem. 2003, 68, 1339-1347

[32] Sibelle, L.; Bernardes, C.; Kato, M. J.; Albuquerque, S.; Carvalho, I. *Bioorg. Med. Chem*. **2006**, *14*, 7075-7082

sulfinimines represent the most direct and reliable method for the asymmetric construction of diverse amine derivatives having a nitrogen attached to a stereogenic center. More recently *N*-phosphinoylimines have begun to draw the attention of synthetic chemistry for their good reactivity, easy preparation and purification. The attractiveness of this imine includes the fact that, like sulfinylimines, they can be chiral by introduction of a chirogenic phosphorous atom or by a chiral auxiliary directly linked to the P atom. This chemistry is completely unexplored if we consider the scarce scientific production about chiral *N*-phosphinoylimines. Under the purpose to bring new developments in this field ranging from the synthesis of *P*-chirogenic and chiral *N*-phosphynoylimines to their use in stereoselective reactions. Particularly, we will introduce the synthesis of several *P*-chirogenic *N*-phosphinoylaldimines and their use in diastereoselective addition of organometallic reagents. Since a part of this work has been recently published, we will attach the corresponding publications. We will disclose supplementary results in a report that will be submitted afterwards.



Secondarily, we will describe the synthesis of a new chiral enantiopure TADDOL-derived *N*-phosphorylbenzaldimine and its application to the nucleophilic addition of a Grignard reagent. Since this part of the study deals with unpublished results, it will be inserted as enclosure at the end of Chapter 3.



Chapter 3

New *P*-chirogenic and chiral *N*-phosphinoylimines in stereoselective addition of organometallic reagents.

3.1 Purposes

N-Phosphinoylimines have recently begun to attract significant attention from synthetic chemists for the preparation of nitrogen-containing molecules. Aimed to discover some interesting topic in the almost totally unexplored field of *P*-chirogenic phosphinoylimines, within this chapter, we want to give an account of our research about the synthesis and the enantioselective addition of organometallic reagents to new chiral TADDOL-derived and *P*-chirogenic *N*-phosphinoyl aldimines. Starting with a brief description of the chemical and synthetic background of this emerging class of reactive intermediates throughout their synthesis and application in organic chemistry, we will focus on the stereoselective additions of organometallic reagents to *N*-phosphinoylimines. Out of the bibliographic context, we will present the results achieved in this field.

3.2 Bibliographic recall

Among imines with electron-withdrawing groups on the nitrogen, *N*-Phosphinoylimines have recently emerged in the literature for the preparation of nitrogen-containing molecules. Compared to sulfonylimines, phosphinoylimines can be more easily isolated, purified and stored. Additionally, phosphinoylimines are usually preferred to other activated imines for the deprotection in mild conditions of the addition adducts, phosphonamides or phosphinamides. Several methods have been developed for their synthesis and they are employed in many synthetic transformation, from nucleophilic addition to cycloaddition and pericyclic reactions (Figure 3.1).[1] Racemic *P*,*P*-diphenyl- or *P*,*P*-diethoxy-*N*-phosphinoylimines are among the most used but rare examples of P-chirogenic phosphinoylimines exists.

[1] Weinreb S. M.; Orr, R. K. *Synthesis* **2005**, *8*, 1205-1227.

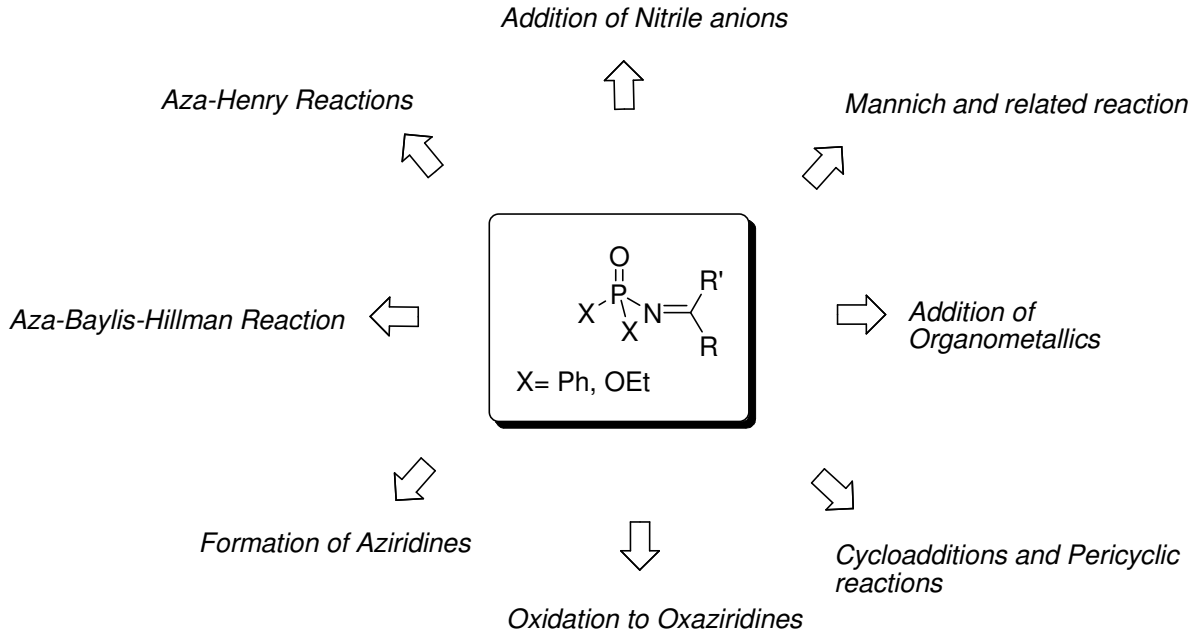
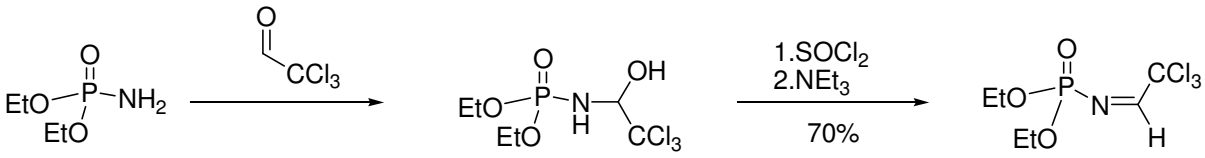


Figure 3.1: Synthetic applications of N-phosphinoylimines.

3.2.1 Synthesis of *N*-phosphinoylimines

3.2.1.1 Achiral *N*-phosphinoylimines

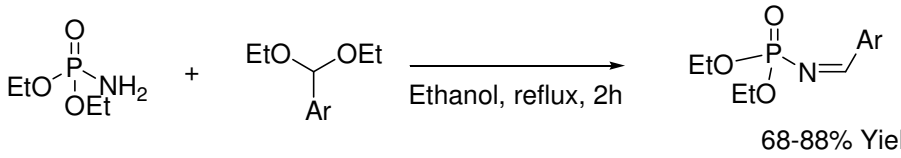
Several general methods are currently available for the preparation of achiral N-phosphinoyl imines. Due to the differences of the methodologies employed for their synthesis, we distinguished the *P*,*P*-diphenyl- and P,P-diethoxy-*N*-phosphinoylimines.
Indeed, *P*,*P*-diethoxy-*N*-phosphinoylimines can be synthesized by direct condensation of a non-enolizable, highly electrophilic aldehyde or ketone with commercially available diethylphosphoramidate, followed by dehydration (Scheme 3.1). Hexafluoroacetones and methyl trifluoropyruvate undergo similar reactions to produce corresponding *N*-phosphinoylimines in good overall yields.[1]



Scheme 3.1:Synthesis of P,P-diethoxy-N-phosphinoylimines

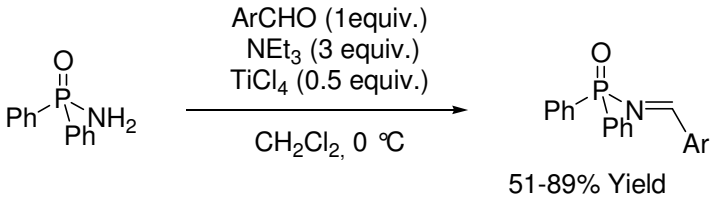
Alternatively, the access to these compounds is possible by thermic condensation, in refluxing ethanol, of aromatic acetals with diethylphosphoramidate which gave the

corresponding imines in good yields and reasonable reaction times (Scheme 3.2).[2] However, the reaction doesn't work with aliphatic acetals.



Scheme 3.2:Condensation between diethylphosphoramidate and acetals

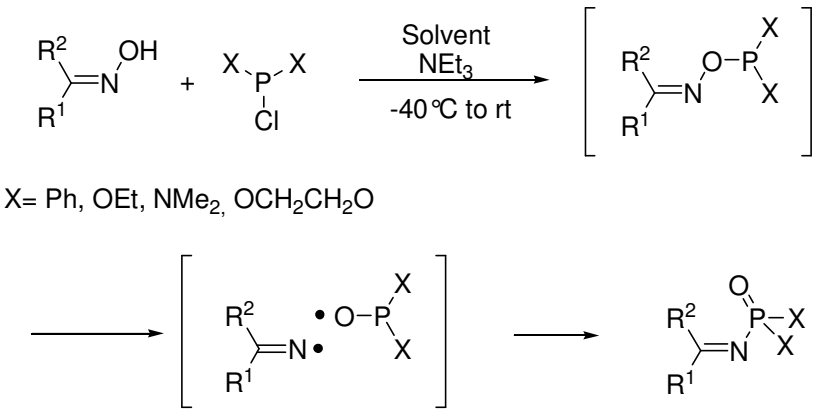
Concerning *P*,*P*-diphenyl-*N*-phosphinoylimines, more largely used compared to their phosphonate analogues, more recent synthetic methods have been found in literature.
A first procedure involves the condensation of aromatic aldehydes with diphenylphosphinamide under $TiCl_4/NEt_3$ catalysis (Scheme 3.3) at 0°C.[3] Here, $TiCl_4$ has the double function of dehydrating agent and activator of the aldehyde through the coordination with the carbonyl oxygen. Corresponding imines are recovered in good to excellent yields. Aliphatic aldehydes and ketones are not good substrates for this reaction.



Scheme 3.3: $TiCl_4/NEt_3$ catalysis

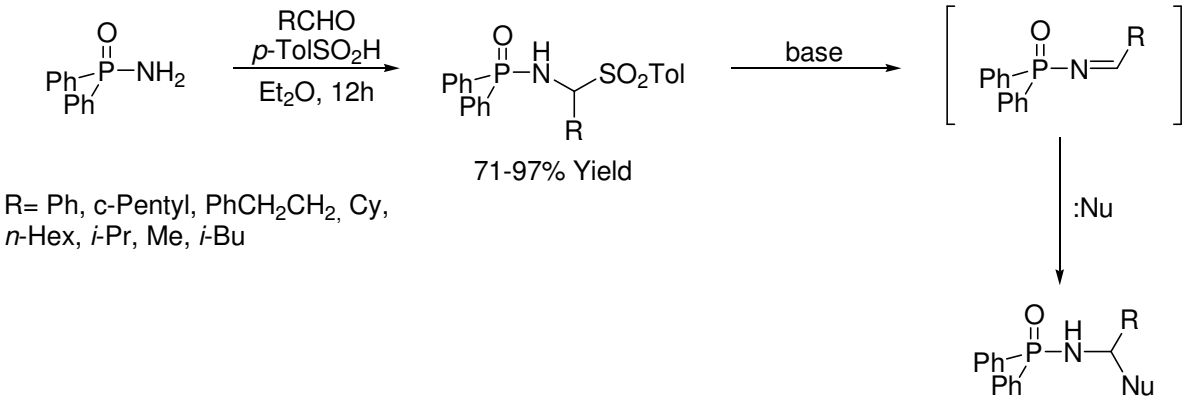
The most widely used method for the synthesis of N-phosphinoylimines involves the treatment of an oxime with a trivalent phosphorous compound. The reaction, first discovered by Krugjyak in 1968,[1,4] proceeds according to a radical mechanism, later clarified by Hudson and coworkers.[5] Thus, an oxime reacts with a chlorophosphine at low temperature (typically -40°C) in presence of triethylamine, in solvent such as dichloromethane, diethylether or toluene, followed by warming to room temperature, affording to *N*-phosphinoylimines in good results (Scheme 3.4).

[2] Zwierzac, A.; Napieraj, A.; *Tetrahedron* **1996**, *52*, 8789-8793
[3](a) Jennings, W. B.; Lovely, C. J.; *Tetrahedron Lett.***1988**, *29*, 3725-3728; (b) Jennings, W. B.; Lovely, C. J.; *Tetrahedron* **1991**, *47*, 5561-5567
[4] Krugjlyak, Y. L.; Leiboskaya, G. A.; Sretenkaya, I. I.; Sheluchenko, V. V.; Martynov, I. V. *Gen.C hem. USSR (Eng. Transl.)* **1968**, *38*, 908-912
[5] Brown, C.; Hudson, R. F.; Maron, A.; Record, K. A. F. *J. Chem. Soc., Chem. Comm.* **1976**, 663-670.



Scheme 3.4: Radical mechanism for the synthesis of aldimine and ketimines

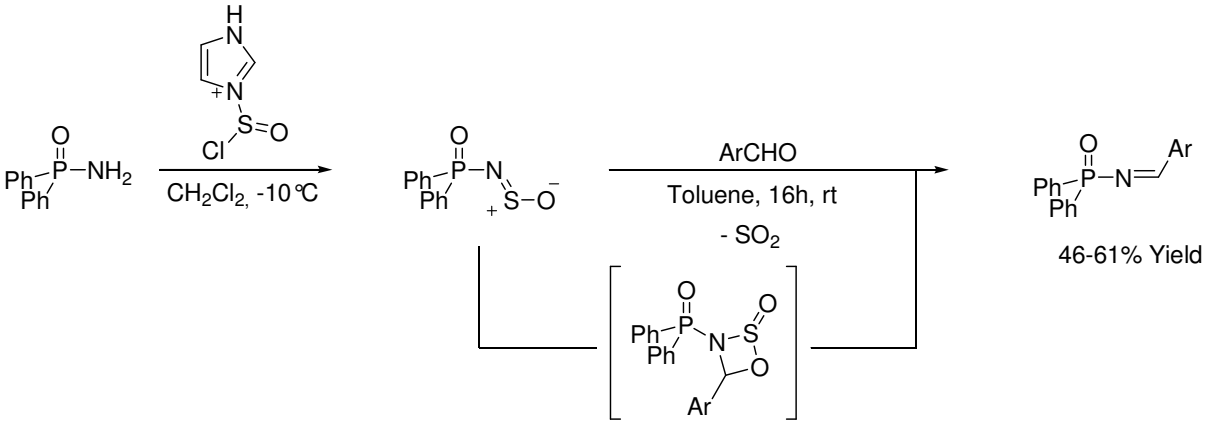
From the mechanistic point of view, after the nucleophilic substitution to the P atom, the corresponding intermediate undergoes homolytic dissociation of the P-O bond upon warming. Recombination of the radical species lead to the *N*-phosphinoylimine. This transformation showed a more general application field, since it has been used for the preparation of a variety of imines from both aliphatic and aromatic ketones and aromatic aldehydes as well as α,β-unsaturated ketones. Among carbonyl compounds, aliphatic aldehydes are the most problematic substrates to employ in such transformation. However, Charette and coworkers, who gave a big contribution to the development and understanding of the chemistry of *P*,*P*-diphenyl-*N*-phosphinoylimines, reported the synthesis of aryl and alkyl aldimines by initial condensation of the starting aldehydes and the diphenylphosphinamide in presence of *p*-tolylsulfinic acid in diethylether, as shown in the Scheme 3.5.[6] At room temperature, the sulfone intermediate, derived from the condensation of the initial amide, the aldehyde and sulfinic acid, slowly precipitate and is recovered in high yields by simple filtration. Treatment of α-tosyl phosphinamide with a strong inorganic base afforded N-phosphinoylimines which were generated *in situ* for the reaction with various nucleophiles.



Scheme 3.5: Synthesis of alkyl diphenylphosphinoylbenzaldimines

[6] Côté, A.; Boezio A. A.; Charette, A. B. *Proc. Natl. Acad.Sci. U. S. A.* **2004**, *101*, 5405-5410

Inspired by the Kresze reaction[7], which is the condensation of aldehydes and *N*-sulfinylamine in presence of a Lewis acid to generate *N*-tosylimines, the same authors described a new approach for the synthesis of *P*,*P*-diphenyl-*N*-phosphinoylimines (Scheme 3.6).[8] Thus, such imines were synthesized by the reaction of in situ generated *P*,*P*-diphenyl *N*-sulfinylphosphoramidate and an aldehyde. The sulfinylphosphoramidate is prepared from diphenylphosphinamide and *N*-(chlorosulfinyl)imidazole. Once formed, it reacts with the aldehyde leading to phosphinoylimine after elimination of sulfur dioxide and formation of four membered cyclic intermediate. This methodology was successfully applied to a variety of arylaldehydes with moderate to good yields.



Scheme 3.6: Kresze reaction for N-phosphinoylimines

3.2.1.2 Chiral *P*-chirogenic *N*-phosphinoylimines

Despite the massive use of *N*-phosphinoylimines in asymmetric organic synthesis, achiral *P*,*P*-diphenyl-*N*-phosphinoylimines with chiral auxiliary or reagent are often employed in most of the cases. Nevertheless, few examples of *P*-chirogenic *N*-phosphinoylimines can be founded in literature. In this paragraph we will describe their synthesis starting from commercial sources, specifying the methods employed to get enantiopure imines and we will classify the reactions by the chiral auxiliary used therein.

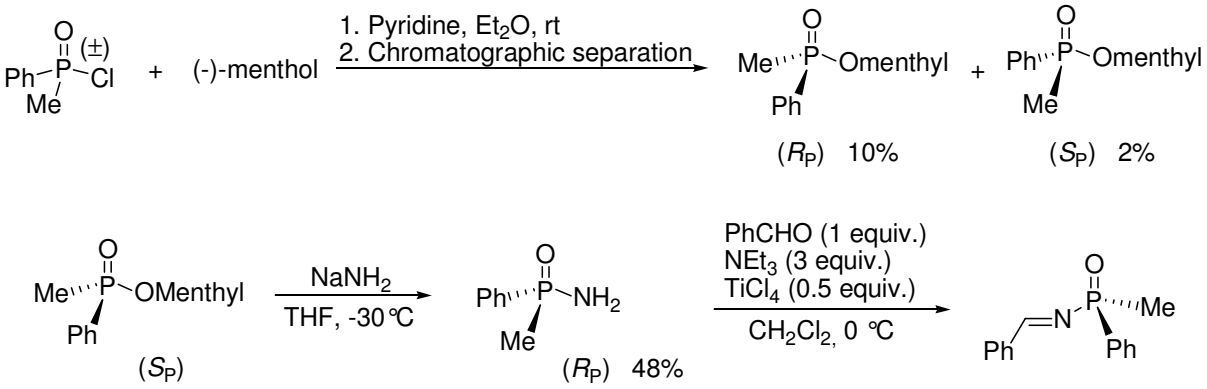
3.2.1.2.1 Use of (-)-menthol

Via racemic phosphinoyl chloride

P-methyl-*P*-phenyl-*N*-phosphinoyl imine have been synthesized starting from the corresponding racemic phosphinic chloride as reported by Harger.[9] This latter reacts with (-)-menthol in presence of pyridine to give the two diastereomeric menthylphosphinates in almost the same ratio. After chromatographic separation, which highly lowered the final

[7] Kresze, G.; Wucherpfennig, W. *Angew. Chem. Int. Ed.* **1967**, *6*, 1431-1434
[8] Lauzon, C.; Desrosiers, J. -N.; Charette, A. B.; *J. Org. Chem*. **2005**, *70*, 10579-10580
[9] Harger, M. J. P. J. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2057-2063

yields,[10] the (S_P)-methylphenylphosphinate was converted in the corresponding enantiopure phosphinamide by amination in THF at low temperature (Scheme 3.7). The methylphenylphosphinoyl benzaldimine was prepared by Royer[11] according to a known method[3].

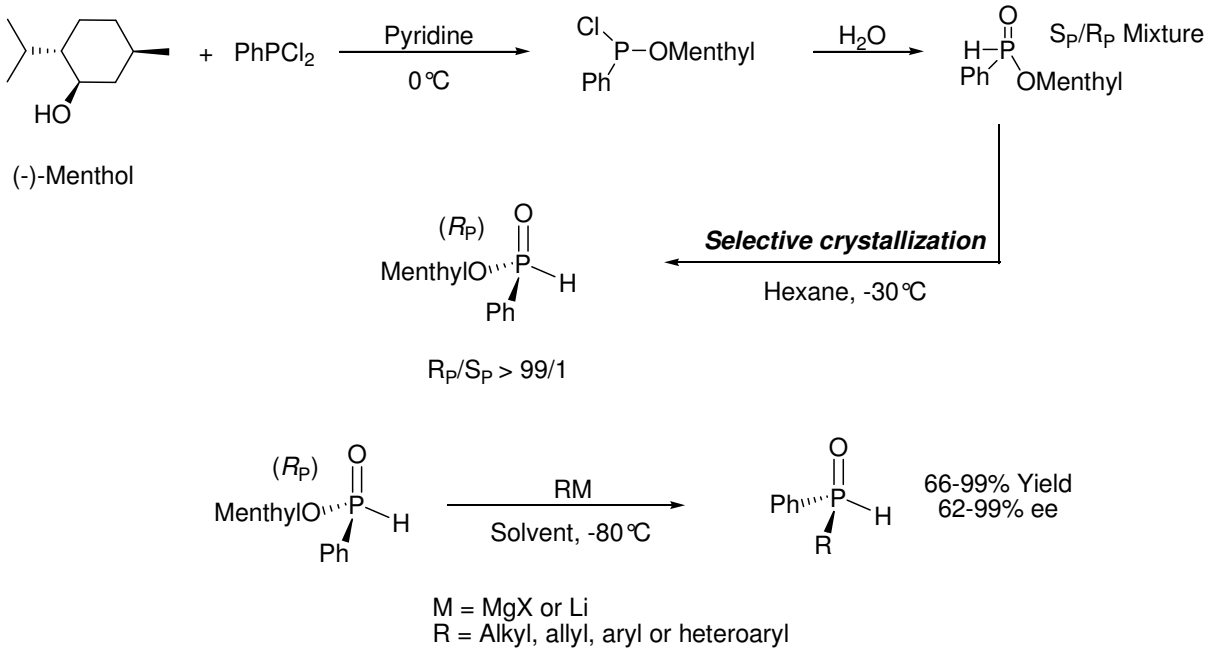


Scheme 3.7: Synthesis of enantiopureP-methyl-P-phenyl-N-phosphinoylaldimines

Via P-chirogenic phosphinoxides (SPOs)

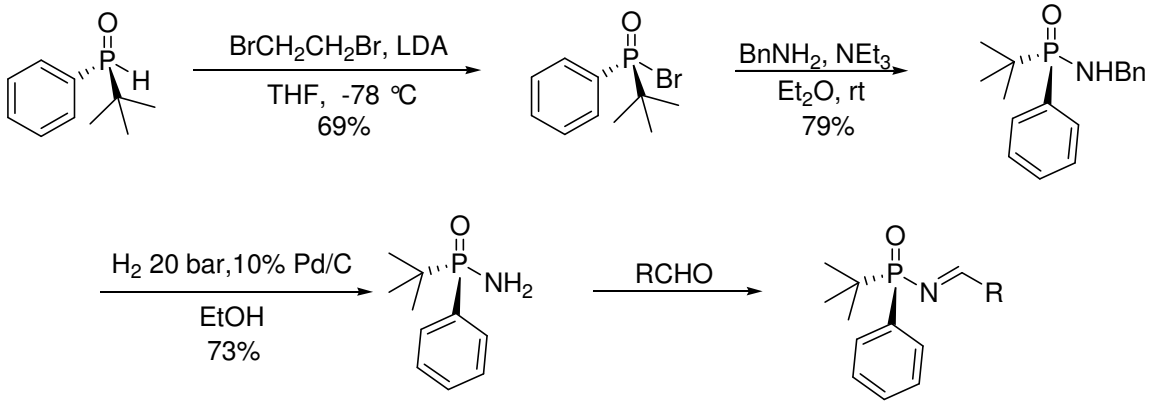
In 2008, Han and coworkers reported the nucleophilic substitution of optically pure H-phosphinate as a general way to prepare chiral, *P*-chirogenic phosphinoxides (SPOs). Optically pure (-)-menthyl (R_P)-phenylphosphinates were obtained, with more of 98% de, from the reaction between $PhPCl_2$ and (L)-(-)-menthol, aqueous treatment and selective crystallization of the diastereomeric mixture in hexane at -30°C. By adding an organolithium or a Grignard reagent to this H-phosphinate at low temperature, in presence of a large excess of the organometallic reagent, in order to prevent any epimerization of the chiral P atom, they synthesized many secondary SPOs in high yields and up to 99% ee[12] (Scheme 3.8).

[10] Nudelman, A.; Cram, D. J. *J. Org. Chem.* **1971**, *36*, 335-337
[11] Benamer, M.; Turcaud, S.; Royer, J. *Tetrahedron Lett.* **2010**, *51*, 645-648.
[12] Xu, Q.; Zhao, C. -Q.; Han, L. -B. *J. Am. Chem. Soc.* **2008**, *130*, 12648-12655



Scheme 3.8: Stereoselective synthesis of secondary SPOs

Optically active phosphinates were also synthesized by Khiar starting from the diacetone-D-glucose (DAG) in 90% de.[13] These chiral secondary phosphine oxides (SPOs) have a large application field in organic chemistry. Their use as ligand in metal-catalyzed reactions has recently inspired a new wave studies on metal-catalyzed asymmetric reactions. On the other hand, SPOs can also be considered as a valid precursors of phosphinoylimines. Indeed, starting from the chiral phosphinoxide a possible route to the N-phosphinoylimine is offered by Yeung and coworkers who synthesized the *P*-t-butyl-*P*-phenylphosphinamides in five steps starting from (-)-*P*-*t*-butyl-*P*-phenylphosphane oxide.[14] Deprotonation of the phosphinoxide with LDA and subsequent addition of 1,2-dibromoethane afforded the bromophosphane. Then nucleophilic substitution with benzylamine and deprotection using H_2, 10% Pd/C in EtOH gave the (-)-*P*-*t*-butyl-*P*-phenyl-*N*-phosphoramidate in 73% yield (Scheme 3.9).



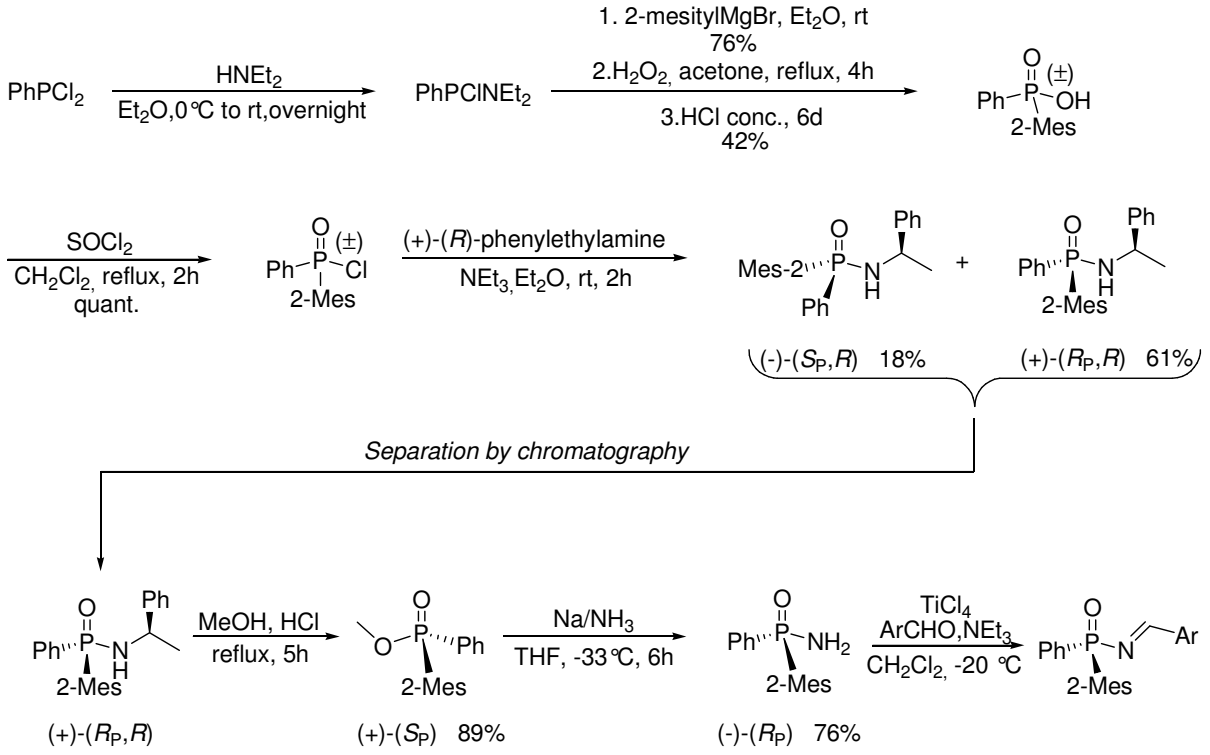
Scheme 3.9: Synthesis of (±)-P-t-butyl-P-phenyl-N-phosphinoyl benzaldimine

[13] Férnandez, I.; Khiar,N.; Roca, A.; Benabra, A.; Alcudia, A.; Espatero, J. L.; Alcudia, F. *Tetrahedron Lett.* **1999**, *40*, 2029-2032
[14] Lam, W.-L.; Haynes, R. K.; Yeung, L.-L.; Chan, W.-K. *Tetrahedron Lett.* **1996**, *37*, 4733-4736.

3.2.1.2.2 Use of (+)-(*R*)-phenylethylamine

Via racemic phosphinoyl chloride

In a similar manner, *P*-2-mesityl-*P*-phenyl-*N*-phosphinoylaldimines have been synthesized by Jennings and coworkers starting from commercial dichlorophenylphosphine in 8 steps.[15] After a nucleophilic substitution by diethylamine to the P atom of the starting chlorophosphine, the addition of 2-mesityl magnesium bromide followed by oxidation promoted by hydrogen peroxide and the treatment with concentrated hydrochloric acid provided racemic *P*-2-mesityl-*P*-phenylphosphinic acid which was transformed into phosphinic chloride. This latter reacts with enantiopure (+)-(*R*)-phenylethylamine leading to two chromatographically separable diastereoisomers in 77:23 ratio [(+)-(R_P,*R*) major,(-)-(S_P,*R*) minor]. Methanolysis of the major phosphinamide, followed by amination with Na/NH_3 provide enantiopure (-)-(R_P)-*P*-2-mesityl-*P*-phenyl phosphinamide with two consecutive formal configurational inversions to the *P* center (Scheme 3.10). The corresponding aldimines were synthetized according to the known method previously developed by the same authors.[3]



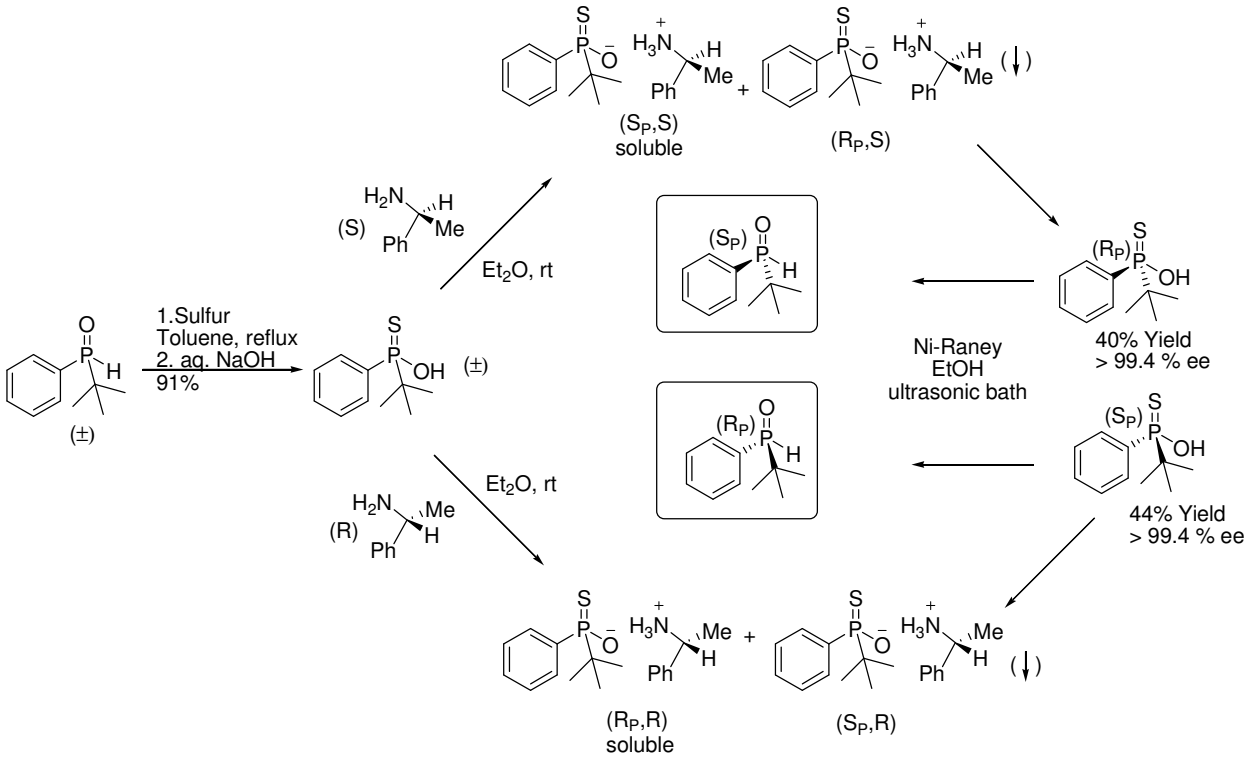
Scheme 3.10: Synthesis of enantiopure P-2-mesityl-P-phenyl phosphinoylaldimines

[15] Harmor, T. A.; Jennings, W. B.; Lovely, C. J.; Reever, K. A. *J. Chem. Soc. Perkin Trans. 2* **1992**, 843-849

Via racemic phosphinoxide

Nucleophilic displacement involving phosphinates are sensitive to the structural variation of groups both attached to the P atom often leading to the epimerization of the chiral phosphorous center and, consequentially, to racemic phosphinoxides. For this reason, resolution of racemic mixture of secondary phosphinoxides is considered as a valid alternative to other synthetic methods. Several examples based on the use of various resolving agent mainly focusing on *t*-BuPhHP=O, have been founded in literature. By distinguishing between resolving agent based on the formation of diastereomeric complexes or salts we selected the most important findings for each class.

In a report of Haynes,[16] racemic *P*-*t*-butyl-*P*-phenylphosphanylthioic acid was prepared from *P*-*t*-butyl-*P*-phenylphosphane oxide and resolved with enantiopure (*R*)- or (*S*)-phenylethylamine. Two diastereomeric salts are formed in ether at room temperature and only one precipitate. After filtration of the crystals, the optical purity is checked by ^{1}H-NMR and the process was repeated until >99.4% optical purity was achieved. The enantiomeric phosphanylthioic acid was recovered after dissolution of the salt in NaOH, removal of chiral amine by extraction with CH_2CH_2, acidification and again extraction. Desufurization by means of Raney nickel under ultrasound irradiation at room temprerature provide the secondary phosphane oxides as shown in the Scheme 3.11.



Scheme 3.11: Resolution of racemic P-t-butyl-P-phenylphosphane oxide by formation of diastereomeric salts

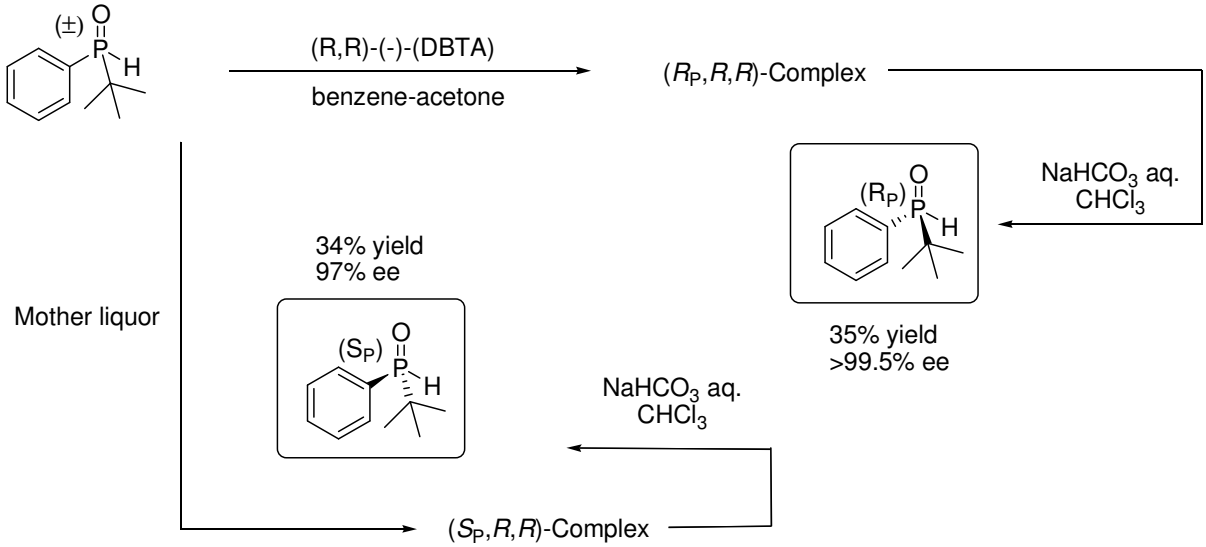
[16] Haynes, R.K.; Au-Yeung, T. -L.; Chan, W. -K.; Lam, W. -L.; Li, Z. -L.; Yeung, L. -L.; Chan, A. S. C.; Li, P.; Koen, M.; Mitchell, C. R.; Vonwiller, C. *Eur. J. Org. Chem.* **2000**, 3205-3216

3.2.1.2.3 Use of other chiral auxiliary

Via racemic phosphinoxide

Despite the above technique is very convenient in term of yields and ee of the resolved phosphinoxide, desulfurization is often problematic and results in a substantial racemization.[17] Resolving agent capable to form more easily cleaved diastereomeric complexes could appear helpful in most of the cases. Few chiral compounds have been used to this purpose.

Very recently Holt and coworkers, reported the resolution of *P*-*t*-butyl-*P*-phenylphosphane oxide using (*R*,*R*)-(-)-dibenzoyltartaric acid (DBTA).[18] The complex formed between the chiral acid and the (*R*)-(+)-*P*-*t*-butyl-*P*-phenylphosphane oxide was not soluble in benzene-acetone and was recovered with > 99.5% ee without any further recrystallization. Liberation of the phosphinoxide from the complex by washing a chloroform solution with aqueous $NaHCO_3$ afforded enantiopure (*R*)-(+)-*P*-*t*-butyl-*P*-phenylphosphane oxide without any loss of ee and 31% yield (Scheme 3.12). Using the same protocol they got the (S)- enantiomer in 31% yield and 97% ee. Interestingly, the complex recovered from the mother solution displayed an excellent optical purity and afforded the (*S*)-(+)-*t*-butyl(phenyl)phosphane oxide in high yield and 97% ee.



Scheme 3.12: Resolution of racemic P-t-butyl-P-phenylphosphane oxide by formation of diastereomeric complexes

[17] (a) Aaron, H.; Shryne, T. M.; Miller, J. I. *J. Am. Chem. Soc.* **1958**, *80*, 107-109; (b) Harger, M. J. P. *J. Chem. Soc. Perkin Transl. 2* **1978**, 326-331.

[18] Holt, J.; Maj, A. M.; Schudde, E. P.; Pietrusiewicz, M; K.; Sieron, L.: Wiekzorek, W.; Jerphagnon, T.; Arends, W. C; E.; hanefeld, U.; Minnaard, A. J *Synthesis* **2009**, *12*, 2061-2065

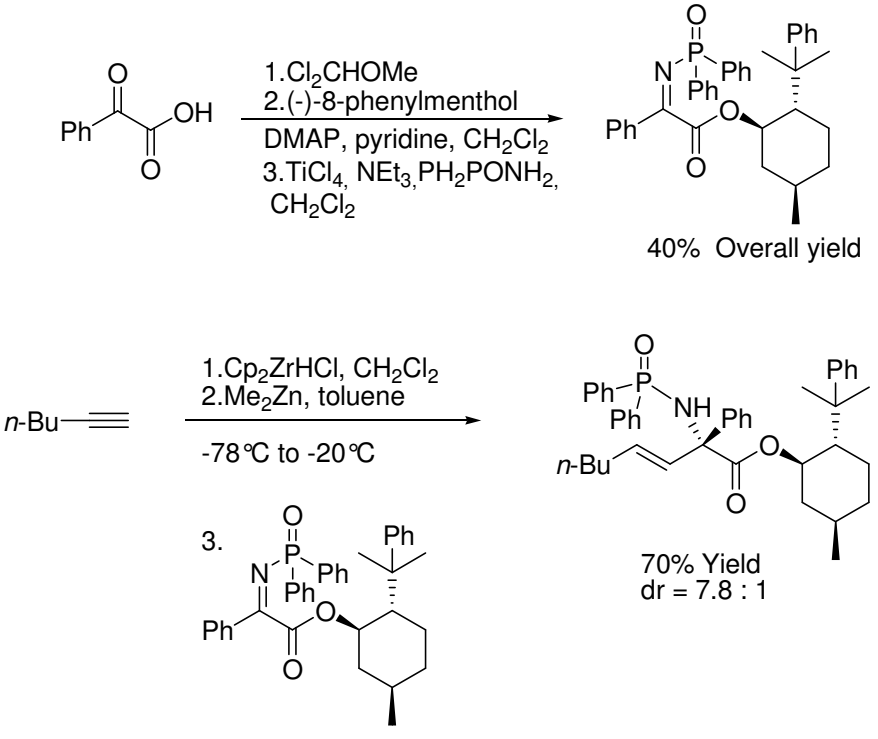
Optically active (+)-2,2'-dihydroxy-1,1'-binaphthol (BINOL) and (+)-mandelic acid[19] have been also used as resolving agents showing less satisfactory results in term of yields and enantiomeric excess of the final phosphinoxide.

3.2.2 Stereoselective addition of nucleophiles to *N*-phosphinoylimines

3.2.2.1 Stereoselective addition of organometallic reagents on *P*,*P*-diphenyl-*N*-phosphinoyl imines

3.2.2.1.1 Chiral auxiliary controlled additions

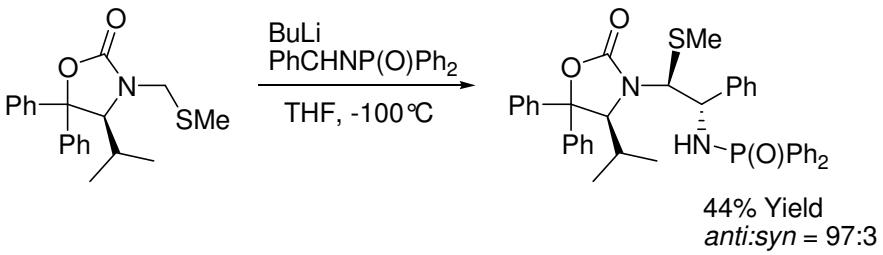
Several groups reported the addition of organometallic reagents to N-phosphinoylimines involving systems with a chiral auxiliary attached to either the nucleophile or the electrophile. For instance Wipf and Stephenson[20] reported the Zr to Zn transmetalation/addition sequence using *N*-phosphinoylimine derived from 8-phenylmenthyl phenylglyoxylate, prepared in three steps from phenylglyoxylic acid in 40% overall yield. Hydrozirconation of alkynes followed by *in situ* transmetalation to dimethylzinc and 1,2-addition to chiral activated *P*,*P*-diphenyl-*N*-phosphinoylimine leads to secondary allylic amides, via a *Si*-face attack of the imine in high overall yield and diastereoselectivity as depicted in Scheme 3.13.



Scheme 3.13: Zr to Zn transmetalation/addition sequence using N-phosphinoylimine derived from 8-phenylmenthyl phenylglyoxylate

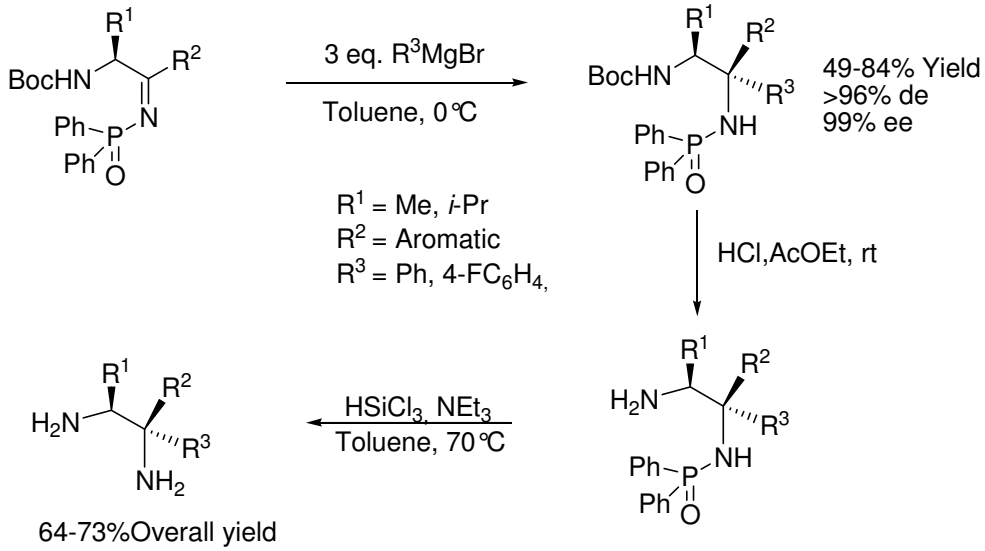
[19] Drabowicz, J.; Łyzwa, P. Omelànczuk, Pietrusiewicz, M. J. K.; Mikołajczyk, M. *Tetrahedron: Asymm.* **1999**, *10*, 2757–2763
[20] Wipf, P.; Stephenson, C. R. *Org. Lett.*, **2003**, *5*, 2449-2452

In 2001, Seebach reported the addition of lithium 4-isopropyl-3-(methylthiomethyl)-5,5-diphenyloxazolidin-2-one to activated imines.[21] The formyl anion equivalent is readily prepared from commercial precursors. The attack of lithiated oxazolidinone on the *P*,*P*-diphenyl-*N*-phosphinoylbenzaldimine resulted in the corresponding *anti*-1,2-amidothioether in 44% yield and 94% diastereomeric excess as shown in Scheme 3.14.



Scheme 3.14: Lithium 4-isopropyl-3-(methylthiomethyl)-5,5-diphenyloxazolidin-2-one addition to P,P-diphenyl-N-phosphinoylbenzaldimine

Another application of the organometallic reagents addition to chiral *N*-phosphinoylimines is given by Kohmura who described the addition of Grignard reagents to *P*,*P*-diphenyl-*N*-phosphinoylimines derived from aminoacids affording chiral 1,2-ethylenediamines in good yields and high diastereoselectivities (Scheme 3.15).[22] The synthesis of optically active ketimines was accomplished starting from the Weinreb amide of *N*-Boc protected valine or alanine, in three steps without any loss of chirality at the stereogenic center, following the method developed by Krugjyak-Hudson.[4,5]



Scheme 3.15: Grignard addition to enantiopure P,P-diphenyl-N-phosphinoyl ketimine derived from aminoacids. Deprotection of the chiral phosphinamide

[21] Gaul,C; Schärer, K.; Seebach, D. *J. Org. Chem.* **2001**, *66,* 3059-3073
[22] Kohmura, Y.; Mase, T. *J. Org. Chem.* **2004**, *69,* 6329-6334

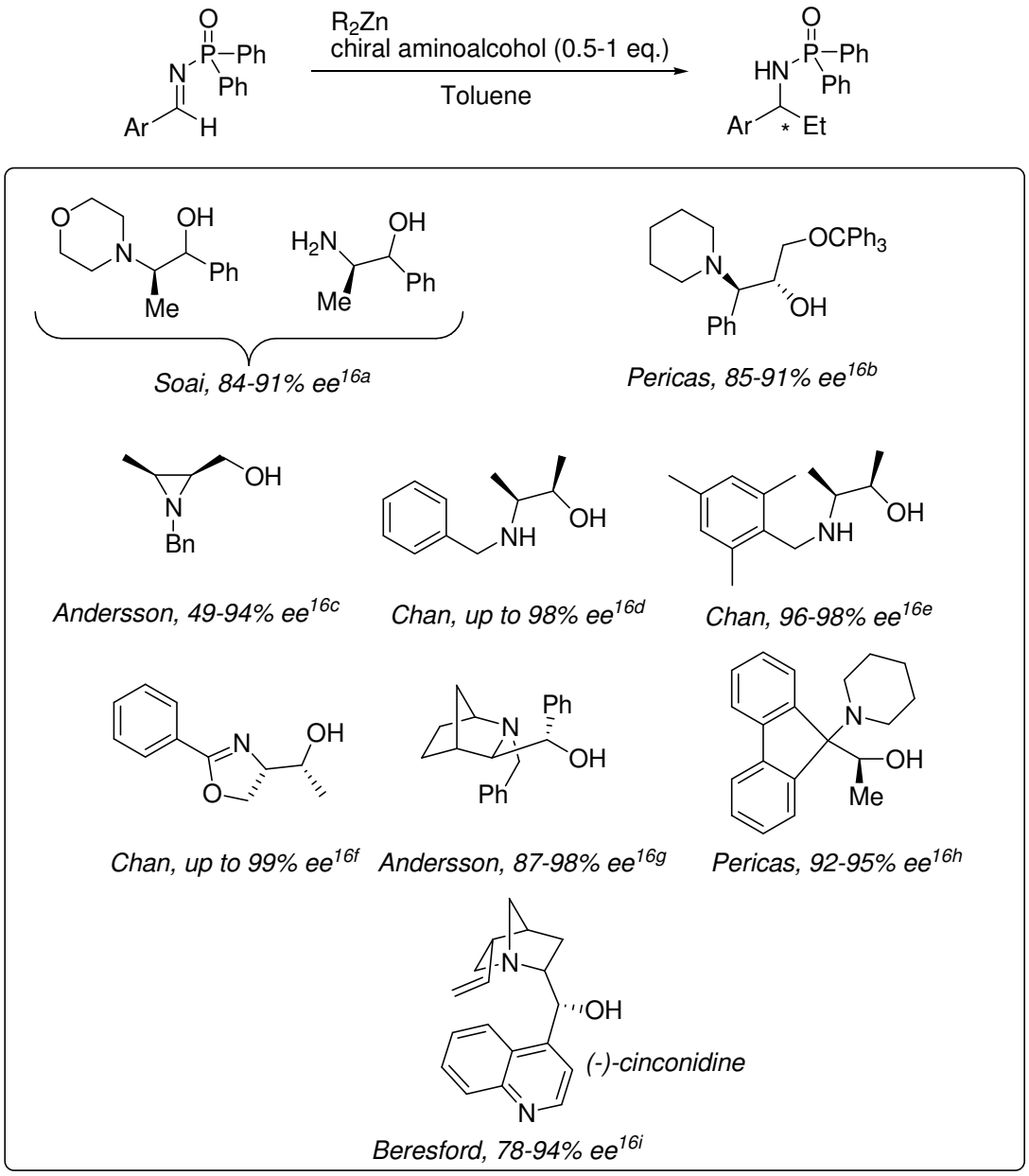
The addition reaction, was carried out in a non-coordinating solvent such as toluene at 0°C, followed by deprotection of the corresponding phosphinamides in acidic conditions in order to remove the Boc-protecting group. Diphenylphosphinoyl group, which resulted stable to acidic conditions, was removed in presence of $HSiCl_3/NEt_3$, affording chiral diamines in good yields and excellent *ee* and *de* values (Scheme 3.15).

3.2.2.1.2 Enantioselective additions promoted by chiral ligands

Organo-zinc and -copper reagents

Due to the importance of chiral amine in the synthesis of pharmaceuticals and natural products, there has been a high interest in the catalytic asymmetric addition of organometallics to activated imines. For the past two decades, the bulk of this research has been devoted to the development of dialkylzinc additions to *N*-phosphinoylimines in the presence of a chiral vicinal amino-alcohol. Due to the poor nucleophilicity of the organometallic reagent, stoichiometric amounts of chiral ligand are required in most of the cases. An overview of most effective aminoalcohols ligands[23] is represented in the Scheme 3.16.

[23] (a) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc. Chem. Comm*. **1992**, 1097; (b) Jimeno, C.; Reddy, K. S.; Sola, L.; Moyano, A.; Pericas, M.; (c) Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem*. **1997**, *62*, 7364; (d) Zhang, X.; Gong, L.; Mi, A.; Lin, W.; Cui, X.; Jiang, Y. -Z.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett*. **2001**, *42*, 6369-6372 (e) Zhang, X.; Lin, W.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y. -Z.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 1399-1402; (f) Zhang, X.;Lin, W.; Gong, L. -Z.; Mi, A.; Cui, X.; Jiang, Y. -Z.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett*. **2002**, *43*, 1535-1540 (g) Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem*. **1998**, *63*, 2530-2535; (h) Jimeno, C.; Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.*, **2000**, *2*, 3157-3159 (i) Beresford, Kenneth J. M. *Tetrahedron Lett.* **2002**, *43*, 7175-7177.



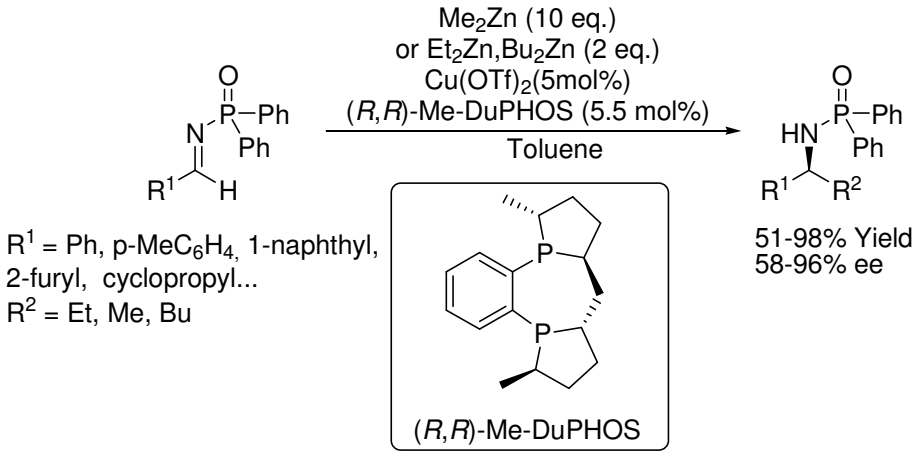
Scheme 3.16: Chiral vicinal amino-alcohol as ligands for the addition of dialkylzinc to N-phosphinoylimines

More recently, few catalytic asymmetric addition reactions were reported, involving the use of more nucleophilic species such as copper-phosphine complexes which promotes the addition of organozinc reagents with high stereocontrol.

Charette reported the first catalytic asymmetric addition of organozinc to *N*-phosphinoyl imines. His alternative approach involved the *in situ* formation of a highly nucleophilic dialkylcuprate(II)phosphine complex to achieve carbon-carbon bond formation with only catalytic amounts of chiral ligand and copper salt.[24] Initially, a variety of chiral mono- and bis-phosphine was screened for the addition to *P*,*P*-diphenyl-*N*-phosphinoylbenzaldimine; the best results were achieved with 5.5 mol% of Me-DuPHOS, 5 mol% of $Cu(OTf)_2$ and two

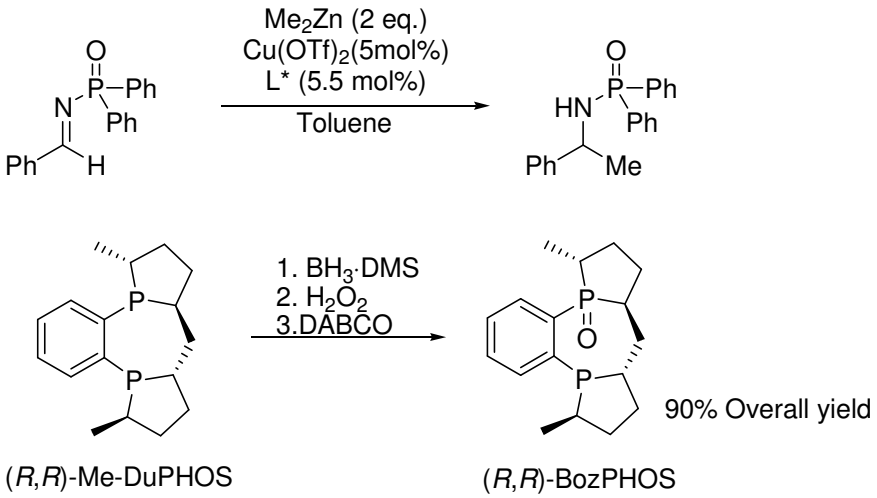
[24]Boezio, A. A.; Charette, A. B. *J. Am. Chem. Soc*. **2003**,*125*, 1692-1693

equivalents of diethylzinc. These reaction conditions have been applied to a large number of aldimines with yields ranging from 51-98% and ee values from 58-96% for the achievement of (S)-phosphinamides as shown in Scheme 3.17. Dimethyl and dibutylzinc were also compatible with these conditions and afforded the adducts in slightly lower yields but high ee.



Scheme 3.17: (R,R)-Me-DuPHOS-Cu(OTF)$_2$ catalyzed asymmetric addition of dialkylzinc to P,P-diphenyl-N-phosphinoylimines

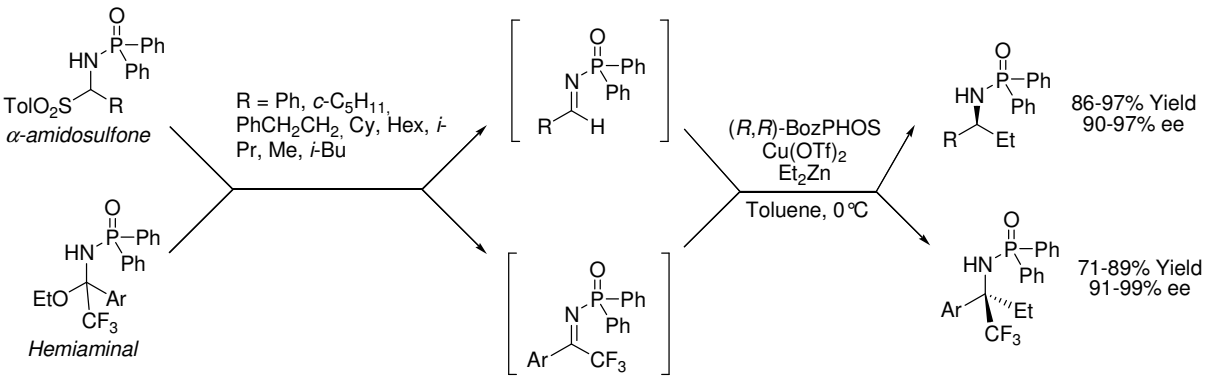
Further works about this subject have clarified that the active chiral ligand is oxidized in situ under the reaction conditions to the monoxide form, named (*R*,*R*)-BozPHOS, which is the actual catalytic species.[25] This ligand was found to be excellent for the addition of dimethylzinc to *N*-phosphinoylimine, which previously had required up to ten equivalent of reagent affording low yields of product.[26] Bisphosphine monoxide ligand BozPHOS, which is synthesized in three steps from the Me-DuPHOS, was found to be an excellent chiral ligand for the reaction, allowing the use of reduced amount of dimethylzinc and affording the addition product in 87% yield and 97% ee (Scheme 3.18).



Scheme 3.18: Synthesis of (R,R)-BozPHOS. Application to the asymmetric addition of Me$_2$Zn

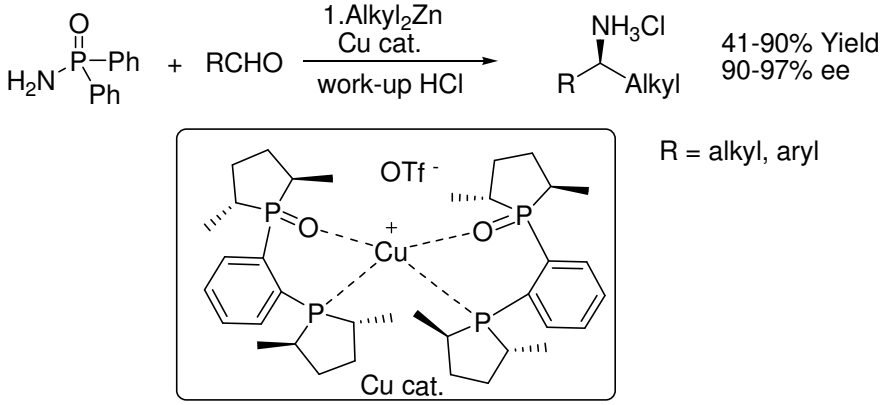
[25] Côtè, A.; Boezio, A. A.; Charette, A. B. *Angew. Chem. Int. Ed.* **2004**, *43*, 6525-6528
[26] Boezio, A. A.; Pytkowicz, J.; Côtè, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**,*125*, 14260-14261

Some years later the same authors, after discovering a valid method for the synthesis of aliphatic *N*-phosphinoylimines, proposed the addition of diethylzinc catalyzed by Cu(I)BozPHOS complex on both *N*-phosphinoylimines derived from aliphatic aldehydes[6] or trifluoromethyl ketimines[27]. These imines have been formed in situ via elimination of the sulfone and the hemiaminal respectively (Scheme 3.19).



Scheme 3.19: Cu(I)BozPHOS complex as catalyst for the addition of diethylzinc to N-phosphinoylimines derived from aliphatic aldehydes and trifluoromethyl ketimines

A multicomponent one-pot procedure for the synthesis of chiral amine involving the formation of the imine, addition of dialkylzinc catalyzed by Cu(I)BozPHOS and deprotection in acidic conditions has also been reported recently.[28] The corresponding chiral amines hydrochlorides are recovered in high yields and ee up to 97% as depicted in Scheme 3.20.



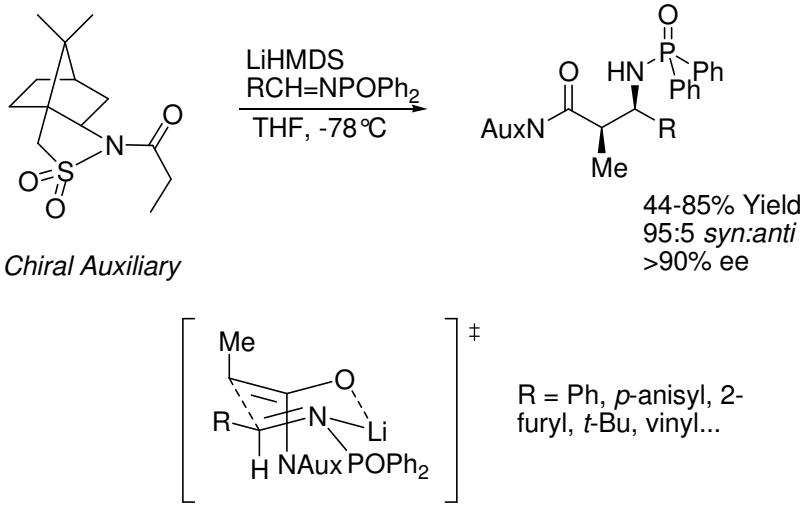
Scheme 3.20:Multicomponent one-pot synthesis of chiral amine by Cu-catalyzed enantioselective addition of dialkylzinc to N-phosphinoylimines.

<u>*Enantioselective metal-catalyzed Mannich type reactions*</u>

In 2000, Sweeney and McLaren disclosed a chiral auxiliary-controlled enolate addition to *N*-phosphinoylimines. For this reaction, an enolate derived from chiral (2*S*)-*N*-propionylcamphorsultame was added to a variety of aromatic, *t*-Bu, and vinyl-substituted *N*-phosphinoylaldimines with good *syn* diastereoselectivity and, excellent enantiocontrol of the

[27] Lauzon, C.; Charette, A. B. *Org. Lett*. **2006**, *8*, 2743-2745
[28] Côté, A.; Charette, A. B. *J. Org. Chem*. **2005**, *70*, 10864-10867

(2*R*,3*S*) product after the removal of the chiral auxiliary.[29] The observed syn selectivity is proposed to be derived via a Zimmermann-Traxler-like transition state with a Z enolate. The major product derived from the attack of the *si* face of the enolate onto the *re* face of the imine as depicted in the Scheme 3.21.

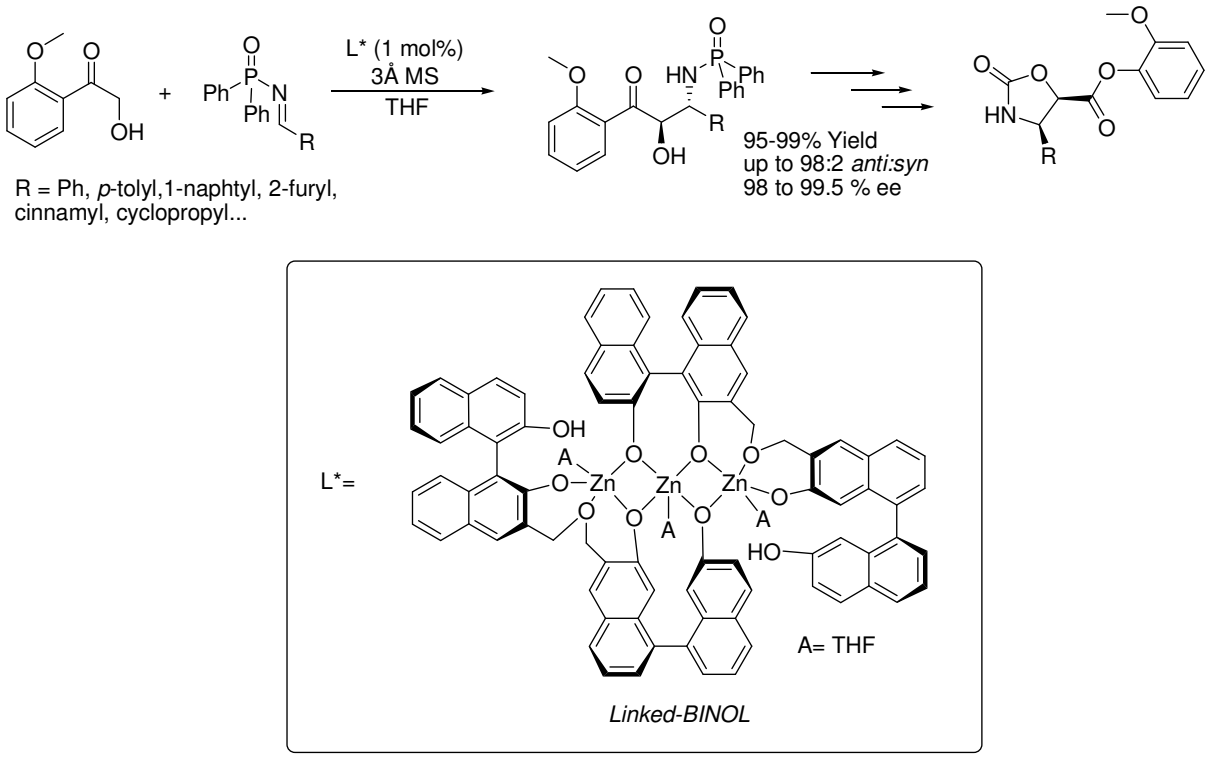


Scheme 3.21: Chiral auxiliary-controlled enolate addition to N-phosphinoylimines

On the other hand, Shibasaki and coworkers proposed the synthesis of Et_2Zn/linked-BINOL complex, which catalyzes Mannich reaction of non-enolizable *N*-phosphinoylaldimines with 2-hydroxy-2'-methoxyacetophenone affording the anti-(2*R*,3*R*)-adduct in high yields and excellent enantioselectivity.[30] The reaction has been extended to a variety of aromatic, α,β-unsaturated and cyclopropyl-substituted imines. The Mannich adduct can be easily transformed to the cyclic carbamate in three steps sequence in 74% yield without any epimerization as depicted in Scheme 3.22 below.

[29] McLaren, A. B.; Sweeney, J. B. *Synthesis* **2000**, 1625-1627

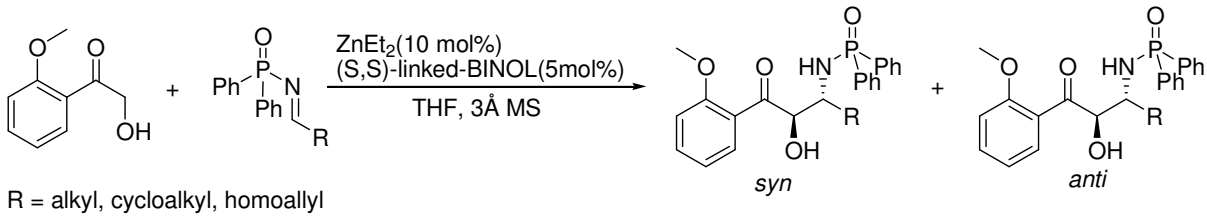
[30] (a) Yoshikawa, N.; Suzuki, T.; Shibasaki, M. *J. Org. Chem.* **2002**, *67*, 2556-2559; (b) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466-2471; (c) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169-2171



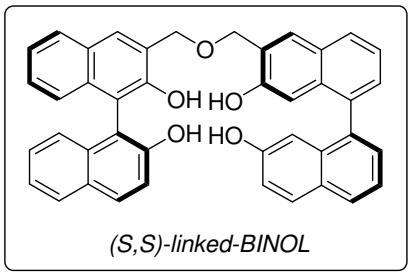
Scheme 3.22: Et_2Zn/linked-BINOL complex as catalyst for Mannich type rection on diphenylphosphinoyl arylimines

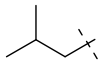
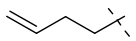
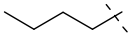
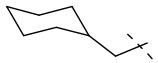
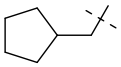
More recently, the same authors reported the use of enolizable *N*-phosphinoylaldimines, derived from alkylaldehydes, in the Mannich reaction with 2-hydroxy-2'-methoxyacetophenone.[31] In contrast to their previous results,[30a] diastereoselectivity was low to modest, although enantioselectivity was high in all of the presented examples, suggesting that diastereoselectivity was strongly dependent on the imine substituent (*syn*/*anti*= 82/18 to 35/65) while the enantioface selection of Zn-enolate generated in situ from α-hydroxy ketone and the Et_2Zn/linked-BINOL complex, is good (Scheme 3.23).

[31] Yamaguchi, A.; Matsunaga, S.; Shibasaki, M.; *Tetrahedron Lett*. **2006**, *47*, 3985-3987



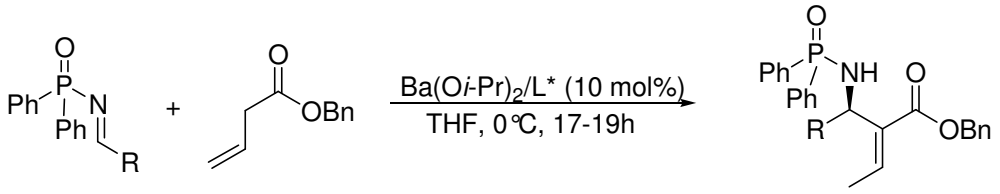
R = alkyl, cycloalkyl, homoallyl



R	Yield%	dr(*syn/anti*)	ee(*syn/anti*)
	92	82/18	98/97
	85	56/44	95/98
	79	65/35	99/99
	77	55/45	90/99
	88	35/65	96/99

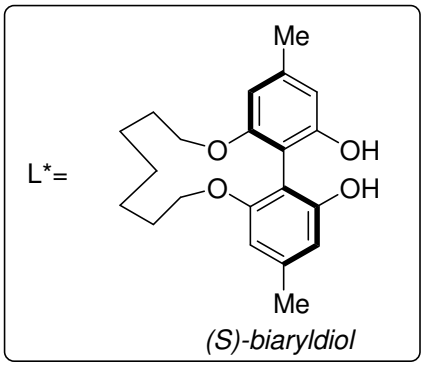
Scheme 3.23: Et_2Zn/linked-BINOL complex as catalyst for Mannich type reaction on N-diphenylphosphinoylalkylimines

The efficacy of the *N*-phosphinoylimines was proved also with barium catalysis of Mannich-type reactions of a β,γ-unsaturated ester providing β-methyl-*aza*-Morita-Baylis-Hillman-type products in good yields and enantioselectivities using Ba(O*i*-Pr)$_2$/biaryldiol complex (Scheme 3.24).[32]



R= aryl, heteroaryl, alkyl

53-88% Yield
up to 80% ee

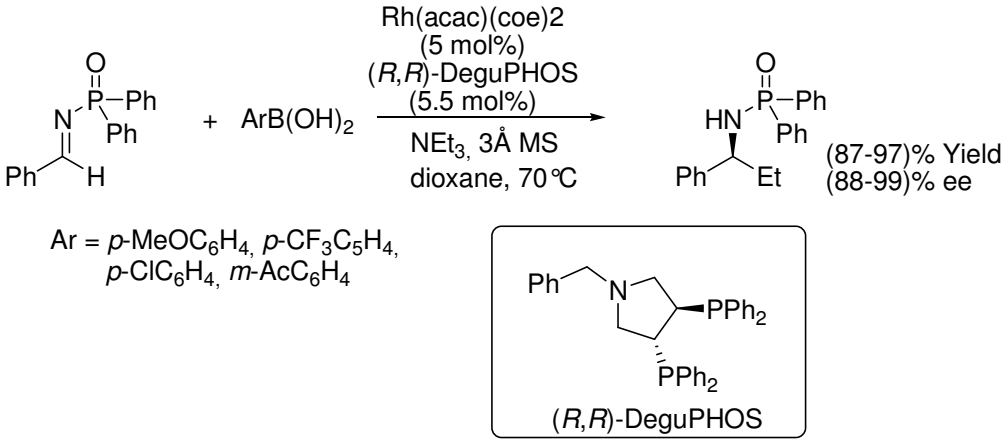


Scheme 3.24: Ba(Oi-Pr)$_2$/biaryldiol complex as catalyst for the Mannich type reaction

[32] Yamaguchi, A.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *Org.Lett*. **2007**, *9*, 3387-3390

Rhodium catalyzed addition of boronic acids

Besides the addition of dialkylzinc, *N*-phosphinoylimines have been employed in the addition of arylboronic acids catalyzed by Rh(I)-(*R*,*R*)-DeguPHOS catalyst complex as reported by Ellman in 2005. This reaction provided chiral amines in high yields and enantioselectivities after deprotection in acidic conditions. The addition of triethylamine and 3Å molecular sieves to the reaction is required to achieve quantitative conversions (Scheme 3.25).[33]

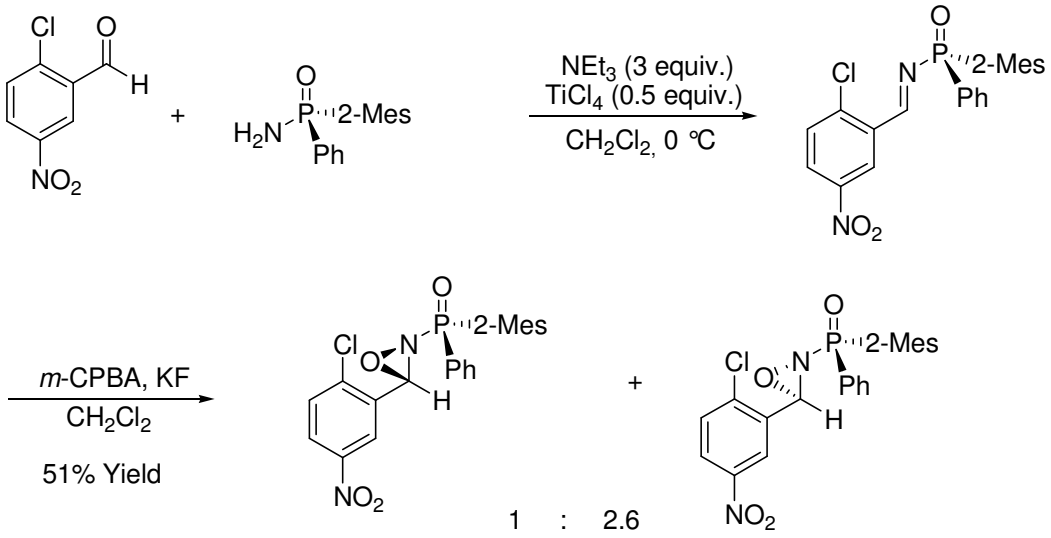


Scheme 3.25: Rhodium catalyzed boronic acid enantioselective addition to N-phosphinoylimines

3.2.2.1.2 *P*-chirogenic phosphinoyl imines: application in organic transformations

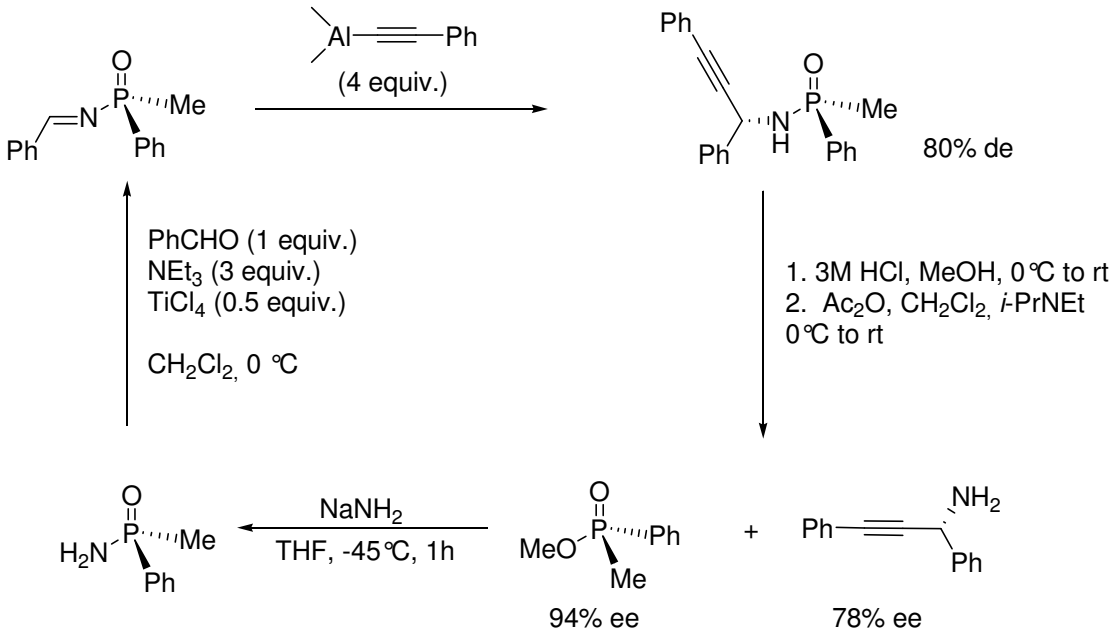
Despite the large number of reports about achiral *N*-phosphinoylimines, only two examples of P-chirogenic *N*-phosphinoylimine can be founded in the literature. In 1994, Jennings and coworkers prepared some chiral, non-racemic oxaziridines for their use in enantioselective oxidations. Condensation of enantiopure *P*-phenyl-*P*-2-mesityl-*N*-phosphinamide (its preparation was previously described in the Scheme 3.10) with 2-chloro-5-nitrobenzaldehyde using $TiCl_4/NEt_3$ as catalyst afforded the corresponding (*E*)-imine.[3,15] Oxidation of this imine then produced the oxaziridine as a 2.6:1 mixture of chromatographically separable oxaziridines. These compounds were then employed as chiral reagents in the enantioselective oxidation of sulfides to chiral sulfoxydes with moderate ee values (Scheme 3.26).[34]

[33] Weix, D. J.; Shi, Y.; Ellman, J. *J. Am. Chem. Soc.* **2005**,*127*, 1092-1093
[34] Jennings, W. B.; Kochanewycz, M. J.; Lovely, C. J.; Boyd, D. R. *J. Chem. Soc., Chem. Comm.* **1994**, 2569-2570



Scheme 3.26: Chiral oxaziridines derived from P-chirogenic phosphinoylimines

Several years later, in concomitance with our report describing the addition of Grignard reagents to a new *P*-chirogenic *N*-phosphinoylimine that will be presented in the following section, Royer reported the synthesis of chiral *P*-methyl-*P*-phenyl-*N*-phosphinoylimines and described their application in the diastereoselective alkynylation with aluminium acetylides. The chiral imines have been prepared according to known methods (see Scheme 3.7)[9,10] and then subjected to the nucleophilic addition of aluminium acetylides providing propargylamines in good yields and diastereoselectivities (Scheme 3.27).[11] Four equivalents of organoaluminium reagent are required for the reaction presumably because of collateral complexation to the oxygen and nitrogen atoms.

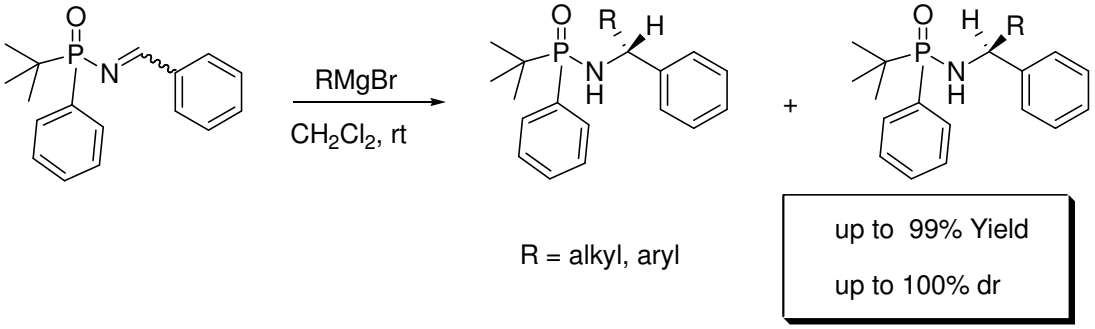


Scheme 3.27 Diastereoselective alkynylation of chiral phosphinoylimines.

3.3 Stereoselective Addition of Grignard Reagents to new *P*-Chirogenic *N*-Phosphinoylimines

3.3.1 Synopsis

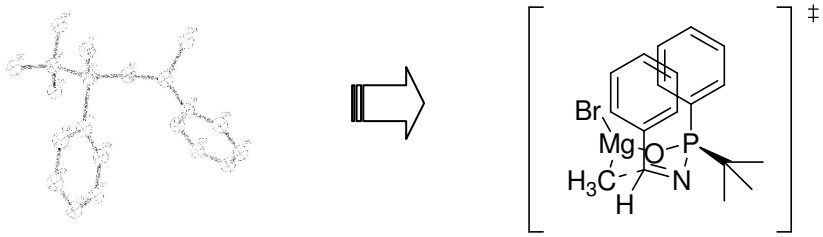
P-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine has been synthesized for the first time and has been engaged with a large number of organomagnesium reagents and afforded the corresponding adducts in excellent yields and moderate to excellent diastereoisomeric ratios.



The optically active phosphinoylimine was obtained as single enantiomer by racemate resolution of his precursor, *t*-butyl-phenyl-phosphane oxide, using (*S*)-(+)-mandelic acid as resolving agent.

Addition of methylmagnesium bromide on the chiral phosphinoyl imine led after chromatographic separation of the two diastereoisomers and crystallization, a single crystal which allowed to determine the absolute configuration (R_P,*R*) of the major diastereoisomer .

Based on this result, we propose a transition state model invoking the coordination of the magnesium atom with the oxygen of the phosphine oxide arranged in a chair-like conformation. This structure could be additionally stabilized by π-stacking interactions between two phenyl ring 1,3-positioned.



3.3.2 Article

Stereoselective addition of Grignard reagents to new *P*-chirogenic *N*-phosphinoylimines†

Irene Notar Francesco,[ab] Alain Wagner*[b] and Françoise Colobert*[a]

Received (in Cambridge, UK) 3rd August 2009, Accepted 27th January 2010
First published as an Advance Article on the web 15th February 2010
DOI: 10.1039/b915781f

The addition of various Grignard reagents to *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine provides a stereoselective method for the synthesis of chiral phosphinoylamines.

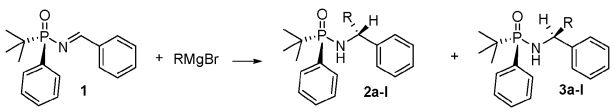
Chiral amines play an important role in biologically active systems[1] and they have been utilized extensively as chiral ligands in asymmetric catalysis.[2] Another class of chiral amines such as chiral phosphinoylamines[3] complement catalysis by chiral amines; they can be seen as analogues of hexamethylphosphoric triamides (HMPA) and used as chiral Lewis basic group.

Stereoselective addition of nucleophiles to imines is a major and efficient methodology for the synthesis of these chiral amines. In particular imines with electron withdrawing groups on the nitrogen atom such as *N*-sulfonyl-, *N*-sulfinyl-, *N*-acylimines have been extensively used in the last decades because of their higher electrophilicity. Therefore chiral versions of such *N*-sulfinylimines with chirality on the sulfur atom enabled them to reach high stereocontrol.[4] In the past few years, *P*,*P*-diaryl *N*-phosphinoylimines have emerged in the literature as good electrophiles in many reactions.[5] To the best of our knowledge, (a) no synthesis of *P*-chirogenic *N*-phosphinoylimine and (b) no diastereoselective addition of nucleophiles on such electrophiles are reported so far in the literature.

Enantioselective addition to achiral *N*-phosphinoylimines using chiral catalysts have been developed, addition of dialkylzinc by Soai[6] and Charette,[7] Mannich-type reactions by Shibasaki[8] and addition of boronic acids by Ellman.[9] To date, although numerous *P*,*P*-diaryl- or *P*,*P*-diethoxy-*N*-phosphinoylimines are used in various reactions, the chirality was so far never introduced on the phosphorus atom of a *N*-phosphinoylimine substrate.

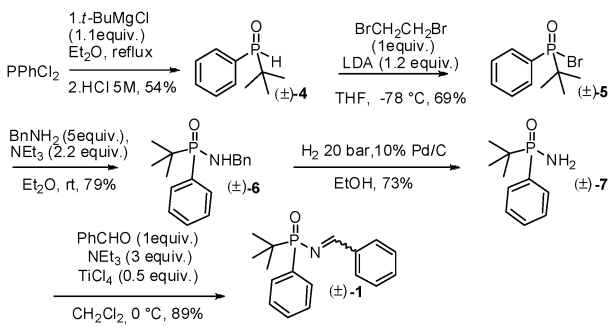
In this communication we report on the first synthesis of *P*-chirogenic *N*-phosphinoyl benzaldimine **1** and the diastereoselective addition of various Grignard reagents to racemic and enantiopure *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoylimines **1** derived from benzaldehyde leading to diastereomerically pure *N*-phosphinoylamines **2** and **3** (Scheme 1).

For the preparation of racemic *P*-*t*-butyl-*P*-phenyl-*N*-phosphoramidates **7**, we followed the reaction sequence



Scheme 1 Addition of Grignard reagents to *P*-chirogenic *N*-phosphinoyl benzaldimine **1**.

described by Yeung *et al*. starting with dichlorophenylphosphine; addition of *t*-butylmagnesium chloride followed by treatment with HCl afforded the (±)-*P*-*t*-butyl-*P*-phenylphosphane oxide **4**.[10] Deprotonation of **4** with LDA and subsequent addition of 1,2-dibromoethane afforded the bromophosphane (±)-**5** in 69% yield. Then nucleophilic substitution with benzylamine was performed in Et_2O and deprotection using H_2, 10% Pd/C in EtOH gave the (±)-*P*-*t*-butyl-*P*-phenyl-*N*-phosphoramidate **7** in 73% yield (Scheme 2).[11]



Scheme 2 Synthesis of (±)-*P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine **1**.

Benzaldehyde was then condensed with **7** under $TiCl_4$/triethylamine catalysis in CH_2Cl_2 to produce the corresponding (±)-*P*-*t*-butyl-*P*-phenyl-*N* phosphinoyl benzaldimine **1** in 89% yield.

At first we studied the effect of different reaction conditions (solvent and temperature) on the outcome of the addition of methylmagnesium bromide on (±)-*P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine **1**. The diastereomeric ratio (dr) determined from ^1H NMR spectra of crude mixture is the ratio of the two pairs of enantiomers **2a–2a′**/**3a–3a′**.

With polar oxygenated solvents like THF or diethyl ether (Table 1, entries 1–3), the stereoselectivities were modest. To perform the reaction in Et_2O, a higher temperature was necessary (10 °C instead of 0 °C in THF) and the conversion was not complete. However in toluene, the selectivity raised up to 80 : 20 at 0 °C (Table 1, entry 5) and the best diastereomeric ratio of 85 : 15 was obtained using CH_2Cl_2 as solvent at 0 °C as well as at 25 °C where the conversion was complete (entries 6–8). When chloroform or dichloroethane were used

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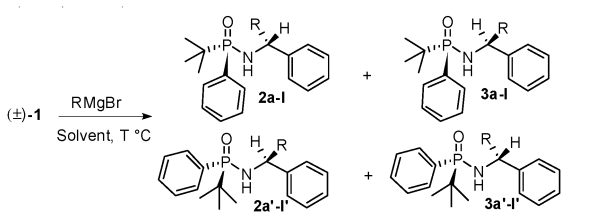
[b] *Université Louis Pasteur, CNRS UMR 7175, 74 route du rhin, 67401, Illkirch, France*

† Electronic supplementary information (ESI) available: Experimental details and NMR spectra. CCDC 743199. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b915781f

Table 1 Optimization of reaction conditions in 1,2-Grignard addition to (±)-**1** (R = Me)



Entry	Solvent	T/°C	Time/h	Conv[a] (%)	dr[a] (%)
1	THF	−10	3	100	60 : 40
2	THF	0	1,5	100	60 : 40
3	Et_2O	10	4	63	55 : 45
4	Toluene	−10	5	47	70 : 30
5[c]	Toluene	0	3	100[b]	80 : 20
6	CH_2Cl_2	0	6	53	85 : 15
7	CH_2Cl_2	0	18	72	85 : 15
8	CH_2Cl_2	rt	3	100[b]	85 : 15
9	$CHCl_3$	rt	5	64	80 : 20
10	$ClCH_2CH_2Cl$	rt	4	90	80 : 20
11	C_6H_5Cl	rt	4	95	70 : 30
12	Heptane	rt	18	100	35 : 65[d]

[a] Determined from ^{1}H NMR spectra of crude mixture. [b] Isolated yield after chromatography: 77% in toluene and 79% in CH_2Cl_2. [c] Run with MeLi instead of MeMgBr. [d] Reversed diastereomeric order.

as solvent, always at 25 °C, the same selectivity as with toluene was obtained (entries 9–10). Moreover the stereoselectivity slightly decreased with chlorobenzene, and more dramatically with n-heptane. Surprisingly, in the latter case with apolar solvent, we observed an inversion of the diastereoselectivity (entries 11 and 12). These results indicate that the presence of a chelating atom such as an oxygen in the solvent (THF, Et_2O) probably disturbs the transition state leading to lower selectivity.

Using these optimized conditions (CH_2Cl_2 at 25 °C, 3–4 h), we studied the addition of various Grignard reagents onto (±)-*P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine **1** (Table 2). Branched and linear aliphatic Grignard reagent were first tested. Diastereomeric ratio of 75 : 25 and 98% yield were obtained in the addition of *i*-propylmagnesium bromide in CH_2Cl_2 at 25 °C. To be sure that CH_2Cl_2 is the best solvent for this diastereoselective addition whatever the Grignard reagent used, we performed in parallel the reaction in toluene and obtained, as expected, a slightly lower selectivity of 70 : 30 (Table 2, entries 3, 4). Using the sterically more hindered *t*-butylmagnesium chloride, we observed only 47% conversion of the phosphinoyl benzaldimine **1** in CH_2Cl_2 at 25 °C and the selectivity decreased to 60 : 40. Heating to reflux completed the reaction but no real improvement of the stereoselectivity was noticed (Table 2, entries 5, 6). With linear aliphatic Grignard reagents such as n-butyl- and n-decylmagnesium bromide, we observed modest selectivity (70 : 30) and high yields in CH_2Cl_2 at 25 °C (Table 2, entries 7, 8). Then we turned our attention to the use of unsaturated Grignard reagents.

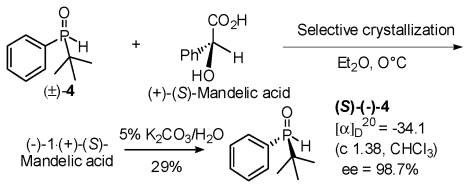
In the addition of vinylmagnesium bromide onto the phosphinoyl benzaldimine **1**, the corresponding amine was obtained in a 60 : 40 diastereomeric ratio (Table 2, entry 9). The use of sterically more hindered 2-methylallylmagnesium chloride allowed us to improve the selectivity to 75 : 25 in CH_2Cl_2 in 85% yield (Table 2, entry 10). Surprisingly, the addition of mesitylmagnesium bromide compared to *p*-methoxy-(60 : 40), *o*-methoxy-(60 : 40) and *o*-methylphenylmagnesium bromide (55 : 45) was totally diastereoselective giving the corresponding amine in 98% yield in CH_2Cl_2 (Table 2, entries 11–14). ^{31}P NMR of the crude product confirmed the orientation of only one diastereomer in the case of entry 14. Furthermore, as expected, the addition of 2,6-dimethylphenylmagnesium bromide gave the corresponding *N*-phosphinoyl amine in high yield (99%) and high selectivity (85 : 15) (Table 2, entry 15). It should be pointed out that the reaction products could always be separated by column chromatography affording diastereomerically pure compounds.

In order to determine the absolute configuration of the major diastereomer we performed the addition of methylmagnesium bromide on the enantiopure *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine (*R*)-(+)-**1**. To obtain the enantiopure (*S*)-(−)-*P*-*t*-butyl-*P*-phenylphosphane oxide **4**, resolution of (±)-*P*-*t*-butyl-*P*-phenylphosphane oxide **4** was performed using an equimolecular amount of (*S*)-(+)-mandelic acid, as described by Mikolajczyk *et al.*,[12] giving after selective crystallization and treatment with K_2CO_3, the enantiopure (*S*)-(−)-*P*-*t*-butyl-*P*-phenylphosphane oxide **4** (Scheme 3).

Table 2 Grignard 1,2-addition to *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine (±)-**1** (scheme to Table 1)

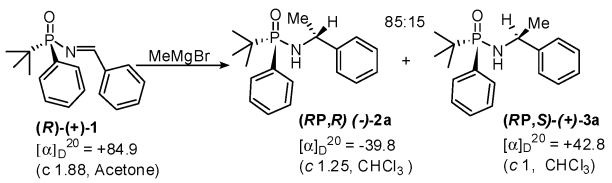
Entry	*R*	Conditions	Conversion[b] (%)	dr[b] (%)	Yield[c] (%)	Products
1	Methyl	Toluene, 0 °C	100	80 : 20	77	**2a–2a′/3a–3a′**
2	Methyl	CH_2Cl_2, 25 °C	100	85 : 15	79	**2a–2a′/3a–3a′**
3	*i*-Propyl	CH_2Cl_2, 25 °C	100	75 : 25	98	**2b–2b′/3b–3b′**
4	*i*-Propyl	Toluene, 0 °C	100	70 : 30	83	**2b–2b′/3b–3b′**
5	*t*-Butyl[f]	CH_2Cl_2, 25 °C[d]	47	60 : 40	29	**2c–2c′/3c–3c′**
6	*t*-Butyl[f]	CH_2Cl_2, reflux	100	65 : 35	90	**2c–2c′/3c–3c′**
7	*n*-Butyl	CH_2Cl_2, 25 °C	100	70 : 30	93	**2d–2d′/3d–3d′**
8	*n*-Decyl	CH_2Cl_2, 25 °C	100	70 : 30	91	**2e–2e′/3e–3e′**
9	Vinyl	CH_2Cl_2, 25 °C	100	60 : 40	67	**2f–2f′/3f–3f′**
10	2-Methylallyl[f]	CH_2Cl_2, 25 °C	100	75 : 25	85	**2g–2g′/3g–3g′**
11	*p*-Methoxyphenyl	CH_2Cl_2, 25 °C	100	60 : 40	97	**2h–2h′/3h–3h′**
12	*o*-Methoxyphenyl	CH_2Cl_2, 25 °C	100	60 : 40	97	**2i–2i′/3i–3i′**
13	*o*-Methylphenyl	CH_2Cl_2, 25 °C	100	55 : 45	95	**2j–2j′/3j–3j′**
14	2-Mesityl	CH_2Cl_2, 25 °C	100	100 : 0[e]	98	**2k–2k′/3k–3k′**
15	2,6-Dimethylphenyl	CH_2Cl_2, 25 °C	100	85 : 15	99	**2l–2l′/3l–3l′**

[a] Until otherwise specified, reactions are complete in 3–4 h. [b] Calculated from crude ^{1}H-NMR spectra. [c] Isolated yield after chromatography. [d] 24 h at room temperature. [e] Calculated from crude ^{31}P-NMR spectra. [f] Use of *t*-butylmagnesium chloride and 2-methylallylmagnesium chloride.



Scheme 3 Racemate resolution of *tert*-butylphenylphosphinoxide **4** with (+)-(*S*)-mandelic acid as chiral solvating agent.

Starting from the enantiopure (*S*)-(−)-*P*-*t*-butyl-*P*-phenylphosphane oxide **4**, the synthesis of the enantiopure benzaldimine (*R*)-(+)-**1** was performed using the same reaction sequence described in Scheme 2. Condensation of methylmagnesium bromide with (*R*)-(+)-**1** in CH_2Cl_2 at 25 °C afforded the two diastereomers **2a** and **3a** in a ratio 85 : 15 (Scheme 4) and after chromatographic separation and crystallization, a single crystal was obtained which allowed us to determine the absolute configuration (*R*P,*R*) of the major diastereomer **2a** (Fig. 1).‡



Scheme 4 Determination of the absolute configuration of the major diastereomer **2a**.

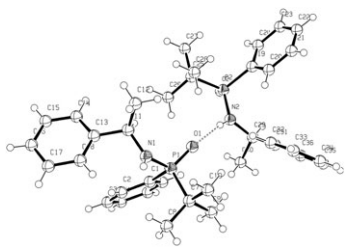
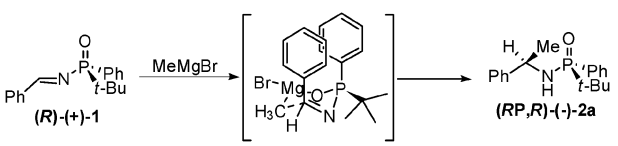


Fig. 1 ORTEP Plot of (*R*P,*R*)-**2a**. Two molecules connected by hydrogen bond are in the asymmetric unit. Ellipsoids at 50% probability.

On the basis of the absolute configuration of the major phosphinoylamine formed (*R*P,*R*)-**(−)-2a**, we propose a transition state model invoking the coordination of the magnesium atom with the oxygen of the phosphine oxide. Grignard reagent would approach from the less hindered *Re* face of the C=N bond developing a six member chair like transition state with the *t*-butyl group in the pseudoequatorial position (Scheme 5). In addition, π stacking between both phenyl groups in 1,3-diaxial positions stabilize this transition state as reported by molecular calculations (AM1) on *cis*-1,3-diarylcyclohexane.[13]



Scheme 5 Proposed transition state model of the addition.

In conclusion, we reported an efficient addition of various Grignard reagents onto *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine in a stereoselective way affording the corresponding diastereomerically pure *P*-chirogenic *N*-phosphinoylamines in excellent yields. This report opens new perspectives in the field of chiral amine synthesis; especially chiral phosphinoylamines that can be used as chiral Lewis basic groups. This original class of chiral inducer should offer interesting alternatives in the field of asymmetric catalysis. Further investigations are currently underway in our laboratory in order to extend the scope of this reaction and to get a better insight into the mechanism.

We are grateful to NovALIX-Pharma contact@alix-pharma.com for financial support. We are indebted to Dr Lydia Brelot (Service de Radiocristallographie, University of Strasbourg, France) for her assistance with the single crystal structure elucidation.

Notes and references

‡ Crystallographic data for (*R*P,*R*)-(+)-**2a**: $C_{18}H_{24}NOP$ M = 301.35, monoclinic, a = 8.6513(4), b = 19.0107(10), c = 10.3315(4) Å, β = 90.445(2)°, U = 1699.14(14) Å^3, T = 173 K, space group $P2_1$, Z = 4, D_x = 1.178 g cm^{-3}, F(000) = 648.0, μ(Mo-Kα) = 0.161 mm^{-1}, R(reflections) = 0.0847 (5724), $wR2$(reflections) = 0.2243 (6945), S = 1.083, Npar = 387 (R_{int} = 0.0539). CCDC number 743199.

1 (*a*) S. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069–1094; (*b*) R. Bloch, *Chem. Rev.*, 1998, **98**, 1407–1438; (*c*) D. Enders and U. Reinhold, *Tetrahedron: Asymmetry*, 1997, **8**, 1895–1946.
2 S. France, D. J. Guerin, S. J. Miller and T. Lectka, *Chem. Rev.*, 2003, **103**, 2985–3012.
3 S. E. Denmark and R. A. Stavenger, *Acc. Chem. Res.*, 2000, **33**, 432–440.
4 J. A. Ellman, T. D. Owens and T. P. Tang, *Acc. Chem. Res.*, 2002, **35**, 984–995; P. Zhou, B.-C. Chen and F. A. Davis, *Tetrahedron*, 2004, **60**, 8003–8030.
5 S. M. Weinreb and R. K. Orr, *Synthesis*, 2005, 1205–1227.
6 (*a*) K. Soai, T. Hatanaka and T. Miyazaka, *J. Chem. Soc., Chem. Commun.*, 1992, 1097–1098; (*b*) T. Hayase, S. Osanai, T. Shibata and K. Soai, *Heterocycles*, 1998, **48**, 139–142; (*c*) T. Hayase, Y. Inoue, T. Shibata and K. Soai, *Tetrahedron: Asymmetry*, 1996, **7**, 2509–2510.
7 (*a*) I. Bonnaventure and A. B. Charette, *J. Org. Chem.*, 2008, **73**, 6330–6340; (*b*) A. A. Boezio, J. Pytkowicz, A. Côté and A. B. Charette, *J. Am. Chem. Soc.*, 2003, **125**, 14260–14261; (*c*) A. Côté, A. A. Boezio and A. B. Charette, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5405–5410; (*d*) J.-N. Desrosiers, A. Côté and A. B. Charette, *Tetrahedron*, 2005, **61**, 6186; (*e*) A. Côté and A. B. Charrette, *J. Org. Chem.*, 2005, **70**, 10864–10867; (*f*) A. A. Boezio and A. B. Charrette, *J. Am. Chem. Soc.*, 2003, **125**, 1692–1693.
8 (*a*) K. Yamada, S. J. Harwood, H. Gröger and M. Shibasaki, *Angew. Chem., Int. Ed.*, 1999, **38**, 3504–3506; (*b*) S. Matsunaga, N. Kumagai, S. Harada and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 4712–4713.
9 D. J. Weix, Y. Shi and J. A. Ellmann, *J. Am. Chem. Soc.*, 2005, **127**, 1092–1093.
10 W.-L. Lam, R. K. Haynes, L.-L. Yeung and W.-K. Chan, *Tetrahedron Lett.*, 1996, **37**, 4733–4736.
11 (*a*) W. B. Jennings and C. J. Lovely, *Tetrahedron Lett.*, 1988, **29**, 3725–3728; (*b*) W. B. Jennings and C. J. Lovely, *Tetrahedron*, 1991, **47**, 5561–5568.
12 J. Drabowicz, P. Lyzwa, J. Omelanczuk, K. M. Pietrusiewicz and M. Mikolajczyk, *Tetrahedron: Asymmetry*, 1999, **10**, 2757–2763.
13 V. E. Williams, R. P. Lemieux and G. R. J. Thatcher, *J. Org. Chem.*, 1996, **61**, 1927–1933.

3.3.3 Experimental part

3.3.3.1 General.

All the solvents used were dried and freshly distilled in argon atmosphere. Tetrahydrofuran and diethylether were distilled under sodium and benzophenone, toluene and heptane were distilled over sodium, dichloromethane and 1,2-dichloroethane were dried with calcium hydride and fractionally distilled. Chlorobenzene was simply dried with activated Linde 4Å molecular sieves.

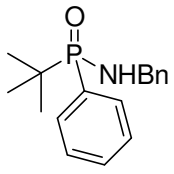
Benzaldehyde, triethylamine and benzylamine were distilled just before use. Palladium on carbon (10%, 50% wet with water for safety) was purchased from Acros and stored in a drying device. Titanium tetrachloride was used like a 1 M solution in dichloromethane. Alkyl- and aryl- magnesium halides solutions were purchased from Aldrich and Acros or prepared just by adding a solution of corresponding organohalide on the activated magnesium and refluxing the resulting solutions for 2h.

All the reactions were performed under argon atmosphere and in flamed under high vacuum flasks. Thin-layer chromatography (TLC) was carried out on aluminum plates silica gel 60 F_{254} purchased from Merck. Chromatography columns were performed with Merck silica gel Si 60 (40-63μm). All hydrogenation reactions were carried out in a 75 ml standard stainless steel autoclave.

Compounds **4** and **5** were prepared according to literature procedure[35].
^{1}H,^{13}C and large band decoupled ^{31}P nuclear magnetic resonance (NMR) spectra were recorded at 300, 75 and 162 MHz, respectively. Chemical shifts are reported in δ units, parts per million (ppm) from tetramethylsilane and were measured relative to the signals for residual chloroform (7.26 ppm for proton and 77.00 for carbon NMR spectra). Coupling constants *J* are given in Hz. Coupling patterns are abbreviated as, for example, br (broad) s (singlet), d (doublet), t (triplet) and m (multiplet).
Mass spectra were recorded by HRMS by electrospray ionization method obtained with a microTOF LC Brucker Daltonics microTOF LC from Brucker Daltonics apparatus.
Melting ranges (m.p.) given were found to be reproducible after resolidification.

3.3.3.2 Preparation of substrates.

(±)-6

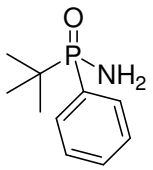


[35] Haynes, R. K.; Au-Yeung, T-L.; Chan, W-K.; Lam, W-L.; Li, Z-Y.; Yeung, L-L.; Chan, A. S. C.; Li, P.; Koen, M.; Mitchell, C. R.; Vonwiller, S. C. *Eur. J. Org. Chem*., **2000**, 3205-3216, and cited references.

To a solution of triethylamine (0.39 mL, 2.8 mmol) and bromide **5** (0.326 g, 1.25 mmol) in Et_2O (10 mL) was added benzylamine (0.687 mL, 6.25 mmol) at room temperature. The mixture was stirred for 16 h and the white precipitate of ammonium bromide was filtered off. The filtrate was then poured into a saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with Et_2O (3x15 mL) and the combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/cyclohexane 4:1) of the crude mixture afforded pure **3** (261 mg, 0.91 mmol, 73% yield) as a white solid. (mp = 148.7-151.3 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.896-7.271(m, 10H, C-*H* arom.), 4.192 (ABd, J_{AB} = 79.3 Hz, $^3J_{P\text{-}H}$ = 3 Hz, 2H, O=P-*CH*$_2$-NH-Ph), 2.967 (br s, 1H, O=P-*NH*-CH_2-Ph), 1.169 (d, $^3J_{P\text{-}H}$ = 15 Hz, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ139.934 (d, $^3J_{P\text{-}C}$ = 7.75 Hz, *C* quat. arom.), 133.792 (d, $^2J_{P\text{-}C}$ = 8.32 Hz, 2 *C*-H arom.), 131.760 (d, $^4J_{P\text{-}C}$ = 2.4 Hz, *C*-H arom.), 128.751 (d, $^1J_{P\text{-}C}$ = 58.72 Hz, *C* quat. arom.),128.582 (s, 2 *C*-H arom.), 128.209 (d, $^3J_{P\text{-}C}$ = 11.62 Hz, 2 *C*-H arom), 127.662 (s, 1 *C*-H arom.), 127.325 (s, 2 *C*-H arom.), 44.376 (d, $^2J_{P\text{-}C}$ = 2.7 Hz, -*C*H_2-), 32.165 (d, $^1J_{P\text{-}C}$ = 89.1 Hz, quat. *t*-Bu.), 24.944 (s, 3 –*C*H_3, *t*-Bu); ^{31}P NMR(162 MHz, $CDCl_3$) δ43.2849. HMRS calculated for $C_{17}H_{22}NNaOP$ 310.1331, found 310.1306.

(*R*)-(-)-**6**: $[\alpha]_D^{20}$ = -7.4° (c 1, MeOH).

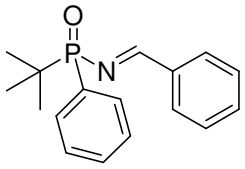
(±)-7



Compound **6** (200 mg, 0.7 mmol), Pd/C (20 mg) and EtOH (5 mL) were placed in the autoclave and flushed three times with hydrogen before pressuring up to 20 Bar. The mixture was stirred at room temperature for 24 h and then depressurized. The solution was filtered through a Celite pad that was thoroughly rinsed with ethanol. The solvent was removed *in vacuo* affording pure phosphinamide **7** (0.135 g, 0.69 mmol, 98 % yield) as a colorless needles. (mp = 128.1-133.5) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.873-7.413 (m, 5H, C-*H* arom.), 2.897 (br s, 2H, -*NH*$_2$) 1.134 (d, $^3J_{P\text{-}H}$ = 15.3 Hz, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.191 (d, $^2J_{P\text{-}C}$ = 8.32 Hz, 2 *C*-H arom.), 131.842 (d, $^4J_{P\text{-}C}$ = 2.48 Hz, *C*-H arom.), 130.04 (d, $^1J_{P\text{-}C}$ = 115.09 Hz, *C* quat. arom.), 128.079 (d, $^3J_{P\text{-}C}$ = 11.55 Hz, 2 *C*-H arom), 32.304 (d, $^1J_{P\text{-}C}$ = 92.25 Hz, quat. *t*-Bu.), 24.672 (s, 3 –*C*H_3, *t*-Bu); ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.5063. HMRS calculated for $C_{10}H_{16}NNaOP$ 220.0862, found 220.0850.

(*R*)-(-)-**7**: $[\alpha]_D^{20}$ = -12.6 (c 1, $CHCl_3$).

(±)-1



To a solution of benzaldehyde (0.08 ml, 0.76 mmol), P-*t*-butyl-P-phenyl phosphinamide (0.150 mg, 0.76 mmol) and triethylamine (0.32 ml, 2.28 mmol) in dichloromethane at 0°C was added $TiCl_4$ (0.38 ml, 0.38 mmol) dropwise. The reaction mixture was allowed to stir for 2 h before the solvent was removed *in vacuo*. The yellow oily solid was diluted with ethyl acetate and the precipitate filtered through Celite. The filtrate was concentrated *in vacuo*. Crude imine was purified by flash-chromatography (EtOAc 100%) affording pure phosphinoyl benzaldimine **1** (162 mg, 75% yield) as a white solid. (mp = 176.3-177.7). ^{1}H NMR (300 MHz, $CDCl_3$) δ9.21 (d, $^3J_{P\text{-}H}$ = 29.7 Hz, 1H, N=C-*H*), 8.01-7.44 (m, 10H, C-*H* arom), 1.19 (d, $^3J_{P\text{-}H}$ = 15.3 Hz, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ174.251 (d, $^2J_{P\text{-}C}$ = 8.1 Hz, 2 *C*-H imine), 136.032 (d, $^3J_{P\text{-}C}$ = 23.25 Hz, *C* quat. arom.), 133.193 (d, $^2J_{P\text{-}C}$ = 14.77 Hz, 2 *C*-H arom.), 132.994 (s, 2 *C*-H arom.), 131.645 (d, $^4J_{P\text{-}C}$ = 2.62 Hz, *C*-H arom.), 130.141 (d, $^1J_{P\text{-}C}$ = 113.02 Hz, *C* quat. arom.), 129.901(s, 1 *C*-H arom.), 128.871 (s, 2 *C*-H arom.), 127.968 (d, $^3J_{P\text{-}C}$ = 11.17 Hz, 2 *C*-H arom), 32.893 (d, $^1J_{P\text{-}C}$ = 88.35 Hz, quat. *t*-Bu.), 24.428 (s, 3 –*C*H_3, *t*-Bu); ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.0214. HMRS calculated for $C_{17}H_{20}NNaOP$ 308.1175 found 308.1154.

(*R*)-(+)-**1**: $[\alpha]_D^{20}$ = +84.9° (c 1.88, Acetone).

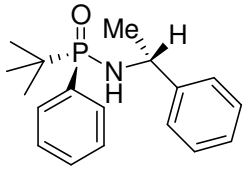
3.3.3.3 1,2 Grignard additions to P-*tert*-butyl-P-phenyl-N-phosphinoyl benzaldimine (1)

Representative procedure

A representative experimental procedure is shown by the synthesis of **2a** and **3a** adducts. Methyl magnesium bromide (3 M solution in diethyl ether, 3 equiv., 0.6 mmol, 200 µL) was added dropwise at 0°C to a solution of **1** (1equiv., 0.2 mmol, 57 mg) in dichloromethane (1.5 mL). The mixture was stirred at room temperature for 3h, then cooled to 0°C, quenched with aqueous $KHSO_4$ (0.5 M, 10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic phases were washed once with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The slightly yellow oily solid was purified by flash chromatography (EtOAc 100%) affording the two diastereoisomers (major/minor = 85 : 15) **2a** and **3a** as colorless solid with 70 and 9% yield respectively.

Characterization data of compunds 2 and 3a-l

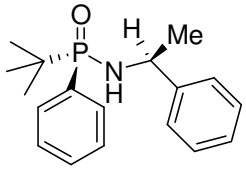
(*R*P,*R*)-(+)-**2a** (Major)



Colorless solid (mp = 164.1-167.6°C). $[\alpha]_D^{20}$ = +42.8 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ7.672-7.206 (m, 10H, C-*H* arom.), 4.274 (brm, 1H, C-*H*), 2.86 (brm, 1H, N-*H*), 1.587 (d, *J* = 6.9 Hz, 1H, H-C-*CH*$_3$), 1.141 (d, $^3J_{PH}$ = 14.7 Hz, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ145.362 (d, $^3J_{P\text{-}C}$ = 7.12 Hz, *C* quat. arom.), 134.024 (d, $^2J_{P\text{-}C}$ = 8.47 Hz, 2 *C*-H arom.), 131.574 (d, $^4J_{P\text{-}C}$ = 2.4 Hz, *C*-H arom.), 129.952 (d, $^1J_{P\text{-}C}$ = 48.37 Hz, *C* quat. arom.), 128.525 (s, 2 *C*-H arom.), 127.869

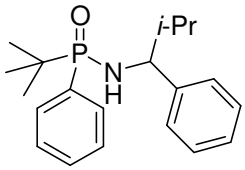
(d, $^{3}J_{P\text{-}C}$ = 11.85 Hz, 2 *C*-H arom), 126.971 (s, 1 *C*-H arom.), 125.765(s, 2 *C*-H arom.), 50.712 (d, $^{2}J_{P\text{-}C}$ = 2.55 Hz, HN-*C*H-), , 32.089 (d, $^{1}J_{P\text{-}C}$ = 88.72 Hz, quat. *t*-Bu.), 24.950 (s, 3 –*C*H_3, *t*-Bu); ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.30. HMRS calculated for $C_{18}H_{24}NNaOP$ 324.1488, found 324.1456.

(R_P,*S*)-(-)-**3a** (Minor)



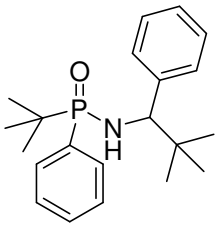
Colorless solid (mp = 151.4-153.8°C). $[\alpha]_D^{20}$= -39.8° (c = 1.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.21 (m, 10H, C-*H* arom.), 4.512 (sestet, $^{2}J_{PH}$ = $^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = $J_{H\text{-}C\text{-}Me}$ = 7.2 Hz, 1H, C-*H*), 2.855 (t, $^{2}J_{PH}$ = $^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 8.7 Hz, 1H, N-*H*), 1.402 (d, *J*= 6.6 Hz, 1H, H-C-*CH*$_3$), 1.085 (d, $^{3}J_{PH}$= 15 Hz, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.514 (d, $^{3}J_{P\text{-}C}$ = 4.27 Hz, *C* quat. arom.), 133.447 (d, $^{2}J_{P\text{-}C}$ = 8.45 Hz, 2 *C*-H arom.), 131.484 (d, $^{4}J_{P\text{-}C}$ = 2.49 Hz, *C*-H arom.) , 131.026 (d, $^{1}J_{P\text{-}C}$ = 115.87 Hz, *C* quat. arom.), 128.492 (s, 2 *C*-H arom.), 127.963 (d, $^{3}J_{P\text{-}C}$ = 11.55 Hz, 2 *C*-H arom), 126.996 (s, 1 *C*-H arom.), 126.185 (s, 2 *C*-H arom.), 49.871(d, $^{2}J_{P\text{-}C}$ = 2.41 Hz, HN-*C*H-), 32.448 (d, $^{1}J_{P\text{-}C}$ = 88.72 Hz, quat. *t*-Bu.), 24.948 (d, $^{3}J_{P\text{-}C}$ = 4.27 Hz, HC-*C*H_3), 24.835; ^{31}P NMR (162 MHz, $CDCl_3$) δ40.5. HMRS calculated for $C_{18}H_{24}NNaOP$ 324.1488, found 324.1461.

Addition of *i*-PrMgBr: **2b-2b'/3b-3b'**



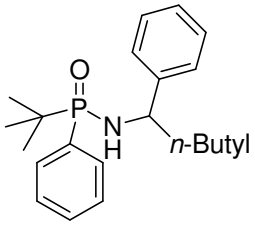
Major/minor = 75 : 25. 98% Yield, white solid (mp = 178.3-182.1°C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.868-7.00 (m, 10H, C-*H* arom. minor + major), 4.126 (brm, 1H, C-*H* major), 3.859 (brm, 1H, C-*H* minor), 3.147 (brm, 1H, N-*H* minor), 3.019 (brm, 1H, N-*H* major), 2.039 (m, 1H, *H*-C(CH_3)$_2$ minor), 1.935(m, 1H, *H*-C(CH_3)$_2$ major),1.143 (d, $^{3}J_{PH}$= 15 Hz, 9H, *t*-Bu minor), 1.02 (d, J = 6.9 Hz, 3H, H-C-*CH*$_3$ minor), 1.015 (d, $^{3}J_{PH}$= 15 Hz, 9H, *t*-Bu major) 0.874 (d, J = 6.9 Hz, 3H, *H*-C-*CH*$_3$ major), 0.814 (d, J = 7.8 Hz, 3H, *H*-C-*CH*$_3$ minor) 0.79 (d, J = 6.6 Hz, 3H, H-C-*CH*$_3$ major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.268, 134.139, 134.021, 132.987, 132.878, 131.457, 131.421, 128.061, 128.018, 127.920, 127.543, 127.386, 127.081, 126.968, 126.757, 60.357, 60.322, 35.913, 35.889, 35.833, 35.667, 35.596, 33.700, 32.498, 24.949, 24.833, 19.288, 19.132, 18.975; ^{31}P NMR (162 MHz, $CDCl_3$) δ41.68 (minor), 40.32 (major). HMRS calculated for $C_{20}H_{28}NNaOP$ 352.1801, found 352.1774.

Addition of *t*-BuMgBr: **2c-2c'/3c-3c'**



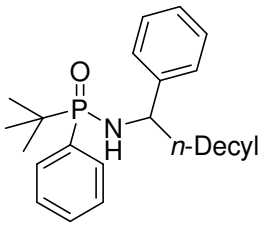
Major/minor = 65 : 35. 90% Yield, pale yellow solid (mp = 198.7-205.7°C). ^{1}H -NMR (300 MHz, $CDCl_3$) δ 7.834-6.924 (m, 10H, C-*H* arom. minor + major), 4.068 (t, $^{3}J_{PH}$ = $^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9.9 Hz, 1H, C-*H* major), 3.782 (t, $^{3}J_{PH}$ = $^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 11.1 Hz, 1H, C-*H* minor), 3.221 (brt, $^{2}J_{PH}$ = $^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 10.8 Hz, 1H, N-*H* minor), 3.063 (brt, $^{2}J_{PH}$ = $^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9.3 Hz, 1H, N-*H* major), 1.078 (d, $^{3}J_{PH}$ = 6.6 Hz, 9H, HC-*tBu* major), 0.859 (m, 27H, 2 *t*-Bu [major + minor] + HC-*tBu* minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.319, 142.293, 142.253, 142.128, 142.102, 134.164, 134.046, 132.607, 132.500, 131.376, 131.343, 131.124, 131.094, 129.714, 129.679, 128.245, 128.092, 127.944, 127.510, 127.487, 127.328, 127.171, 126.703, 126.544, 63.239, 63.200, 62.710, 62.669, 35.677, 35.610, 35.580, 35.544, 34.032, 32.817, 31.491, 31.053, 29.679, 26.940, 24.999, 24.777; ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.31 (minor), 40.28 (major). HMRS calculated for $C_{21}H_{31}NOP$ 344.2138, found 344.2141.

Addition of *n*-BuMgBr: **2d-2d'/3d-3d'**



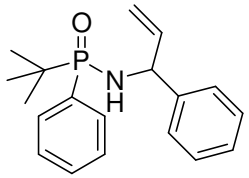
Major/minor = 70: 30. 93% Yield, white solid, (mp = 142.1-146.7 °C). ^{1}H -NMR (300 MHz, $CDCl_3$) δ 7.90-7.08 (m, 10H, C-*H* arom. minor + major), 4.293 (m, 1H, C-*H* major), 4.06 (m, 1H, C-*H* minor), 2.903 (brs, 1H, N-*H* minor + major), 1.845 (m, 4H, H-C-*CH$_2$*-*CH$_2$*- major + minor), 1.239 (m, 2H, -*CH$_2$*-CH_3 major + minor), 1.124 (d, $^{3}J_{PH}$= 15 Hz, *9H*, *t*-Bu minor), 1.046 (d, $^{3}J_{PH}$= 15 Hz, 9H, *t*-Bu major), 0.798 (t, *J* = 7.5 Hz, 3H, -*CH$_3$* minor), 0.75 (t, *J* = 7.2 Hz, 3H, -*CH$_3$* major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.418, 144.371, 144.264, 144.187, 134.128, 134.011, 133.250, 133.139, 131.850, 131.836, 131.455, 131.421, 131.354, 131.319, 130.308, 128.433, 128.369, 128.016, 127.864, 127.690, 127.534, 126.938, 126.865, 126.594, 126.386, 55.083, 55.046, 54.838, 54.805, 39.791, 39.764, 38.925, 38.862, 33.225, 32.607, 32.035, 31.423, 28.126, 28.075, 24.923, 24.836, 22.463, 22.379, 13.906, 13.810; ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.41 (major), 40.07 (minor). HMRS calculated for $C_{21}H_{30}NNaOP$ 366.1957, found 366.1938.

Addition of *n*-Decyl MgBr: **2e-2e'/3e-3e'**



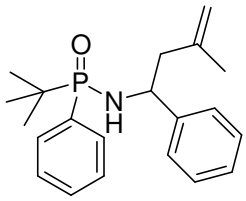
Major/minor = 70 : 30. 91% Yield, white solid, (mp = 237.6-238.9°C). ^{1}H -NMR (300 MHz, $CDCl_3$) δ 7.895-7.075 (m, 10H, C-*H* arom. minor + major), 4.296 (quintet, $^{2}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H} = J_{H\text{-}C\text{-}CH2}$ = 8.1 Hz, 1H, C-*H* major) , 4.053 (quintet, $^{2}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H} = J_{H\text{-}C\text{-}CH2}$ = 9.3 Hz, 1H, C-*H* minor), 2.925 (brt, $^{2}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9.3 Hz, 1H, N-*H* minor), 2.871 (brt, $^{2}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 8.7 Hz, 1H, N-*H* major), 1.820 ,(m, 2H, HC-CH_2- minor + major), 1.181 (m, 16H, 8 -CH_2- minor + major), 1.113 (d, $^{3}J_{PH}$ = 14.7 Hz, *9H*, *t*-Bu minor), 1;035(d, $^{3}J_{PH}$= 14.7 Hz, 9H, *t*-Bu major), 0.859 (t, *J*= 6.6 Hz, 3H, -CH_3 major), 0.853(t, J= 6.6 Hz, 3H, -CH_3 minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.429, 144.384, 134.096, 133.979, 133.240, 133.129, 131.826, 131.386, 131.303, 131.275, 130.296, 128.403, 128.334, 127.990, 127.838, 127.659, 127.503, 126.905, 126.832, 126.563, 126.369, 55.079, 55.047, 54.817, 54.785, 40.045, 40.019, 39.185, 39.122, 33.186, 32.587, 31.996, 31.836, 31.402, 29.659, 29.493, 29.446, 29.376, 29.321, 29.279, 29.231, 25.949, 25.918, 24.901, 24.805, 22.620, 14.064; ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.28 (minor), 41.8 (major). HMRS calculated for $C_{27}H_{42}NNaOP$ 450.2896, found 450.2849.

Addition of Vinyl MgBr: **2f-2f'/3f-3f'**



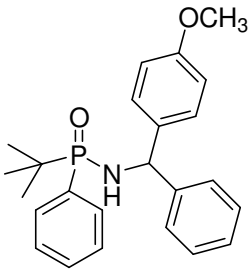
Major/minor = 60 : 40. 67% Yield, white solid, (mp = 116.4-119.8°C).^{1}H -NMR (300 MHz, $CDCl_3$) δ 7.905-7.161 (m, 10H, C-*H* arom. minor + major), 6.137 (m, 1H, *H*-*C*=CH_2 minor), 5.967 (m, 1H, *H*-*C*=CH_2 major), 5.154 (m, 2H, HC=CH_2 major + minor), 4.801 (m, 1H, C-*H* major + minor), 3.009 (brt, $^{2}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9.6 Hz, 1H, N-*H* minor), 2.952 (brt, $^{2}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9.6 Hz, 1H, N-*H* major), 1.156 (d, $^{3}J_{PH}$= 15 Hz, 9H, *t*-Bu minor), 1.115 (d, $^{3}J_{PH}$= 15 Hz, 9H, *t*-Bu major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.702, 142.666, 142.311, 142.227, 140.780, 140.756, 139.822, 139.745, 133.929, 133.842, 133.729, 131.642, 131.608, 131.548, 131.515, 130.571, 129.006, 128.524, 128.492, 127.955, 127.882, 127.800, 127.727, 127.249, 127.135, 126.958, 115.389, 56.382, 56.357, 33.047, 32.960, 31.859, 31.769, 24.968, 24.904,; ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.99 (minor), 41.47 (major). HMRS calculated for $C_{19}H_{24}LiNOP$ 320.1750, found 320.1736.

Addition of 2-Methylallyl MgBr: **2g-2g'/3g-3g'**



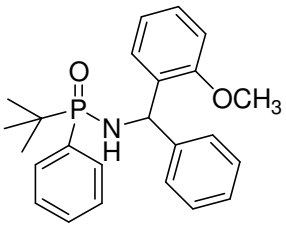
Major/minor = 75 : 25. 85% Yield, white solid, (mp = 129.7-131.2°C). ^{1}H -NMR (300 MHz, $CDCl_3$) δ 7.851-7.132 (m, 10H, C-*H* arom. minor + major), 4.85 (s, 1H, C=*C*-*H* major), 4.796 (s, 1H, C=*C*-*H* major), 4.752 (s, 1H, C=*C*-*H* minor), 4;668 (s, 1H, C=*C*-*H* minor), 4.404 (m, 1H, C-*H* major + minor), 3.141(brt, $^{2}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 7.2 Hz, 1H, N-*H* major), 3.026 (brt, $^{2}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9.6 Hz, 1H, N-*H* minor), 2.605 (m, 2H, -CH_2- major), 2.457 (m, 2H, -CH_2- minor), 1.62 (s, 3H, -CH_3 major) 1.51 (s, 3H, -CH_3 minor), 1.118 (d, $^{3}J_{PH}$= 14.7 Hz, *9H*, *t*-Bu major), 1.061(d, $^{3}J_{PH}$= 14.7 Hz, *9H*, *t*-Bu minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.150, 144.133, 143.781, 143.721, 142.597, 142.435, 133.959, 133.843, 133.198, 133.085, 131.428, 131.393, 131.145, 131.112, 129.910, 128.247, 128.099, 127.973, 127.821, 127.487, 127.330, 126.917, 126.826, 126.608, 126.541, 114.510, 114.181, 52.648, 52.616, 51.857, 51.825, 48.239, 48.160, 48.109, 48.061, 33.291, 32.867, 32.093, 31.695, 24.846, 24.766, 22.365, 22.266; ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.74 (major), 40.03 (minor). HMRS calculated for $C_{21}H_{28}$LiNOP 348.2064, found 348.2030.

Addition of *p*-Anisyl MgBr: **2h-2h'/3h-3h'**



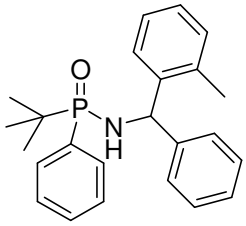
Major/minor = 60 : 40. 97% Yield, pale yellow viscous oil. ^{1}H -NMR (300 MHz, $CDCl_3$) δ 7.694-6.783 (m, 14H, C-*H* arom. minor + major), 5.427 (t, $^{3}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9.9 Hz, 1H, C-*H* major), 5.404 (t, $^{3}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9.9 Hz, 1H, C-*H* minor), 3.786 (s, 3H, -OCH_3 major), 3.767(s, 3H, -OCH_3 minor), 3.266 (brt, $^{2}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9 Hz, 1H, N-*H* minor + major), 1.134 (d, $^{3}J_{PH}$= 15 Hz, 9H, *t*-Bu minor + major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.569, 144.217, 144.199, 133.910, 133.856, 133.753, 131.503, 128.968, 128.712, 128.385, 128.310, 127.825, 127.716, 127.639, 127.460, 127.007, 126.946, 113.760, 113.683, 57.026, 55.234, 32.954, 31.826, 24.939; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.35(minor), 42.18 (major). HMRS calculated for $C_{24}H_{28}$NNaOP 416.1750, found 416.1798.

Addition of *o*-Anisyl MgBr: **2i-2i'/3i-3i'**



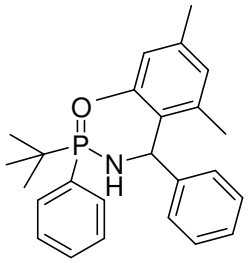
Major/minor = 60 : 40. 97% Yield, white solid, (mp = 148.2-156.3°C). ^{1}H -NMR (300 MHz, $CDCl_3$) δ 7.813-6.869 (m, 14H, C-*H* arom. minor + major), 5.507 (t, $^{3}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 10.2 Hz, 1H, C-*H* minor), 5.436 (t, $^{3}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 10.8 Hz, 1H, C-*H* major), 4.23 (m, 1H, -*NH* minor + major), 3.714 (s, 3H, -O*CH*$_3$ minor), 3.631(s, 3H, -O*CH*$_3$ major), 1.159 (d, *J* = 14.7 Hz, 9H, *t*-Bu major), 1.104 (d, $^{3}J_{PH}$= 15 Hz, 9H, *t*-Bu minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.085, 156.660, 134.123, 134.006, 133.556, 133.443, 131.862, 131.507, 131.283, 129.379, 128.956, 128.505, 128.453, 127.995, 127.928, 127.846, 127.650, 127.495, 127.046, 126.750, 126.463, 120.991, 120.783, 111.602, 111.508, 56.056, 56.030, 55.471, 55.444, 55.417, 55.372, 33.298, 32.722, 32.572, 32.104, 31.527, 24.962, 24.891; ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.65(minor), 41.47 (major). HMRS calculated for $C_{24}H_{28}NNaOP$ 416.1750, found 416.1747.

Addition of *o*-Tolyl MgBr: **2j-2j'/3j-3j'**



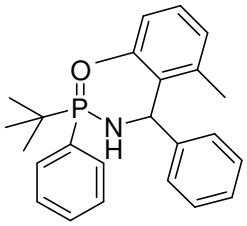
Major/minor = 55 : 45. 95% Yield, white solid, (mp = 161.7-165.3°C). ^{1}H -NMR (300 MHz, $CDCl_3$) δ 7.796-7.023 (m, 14H, C-*H* arom. minor + major), 5.728 (t, $^{3}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9.3 Hz, 1H, C-*H* minor), 5.516 (t, $^{3}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9.6 Hz, 1H, C-*H* major), 3.361 (t, $^{2}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9.3, 1H, -*NH* minor), 3.199 (t, $^{2}J_{PH} = {}^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9.3 Hz, 1H, -*NH* major), 2.157 (s, 3H, -*CH*$_3$ minor), 1.789 (s, 3H, -*CH*$_3$ major), 1.163 (d, $^{3}J_{PH}$ = 14.7 Hz, 9H, *t*-Bu major), 1.092 (d, $^{3}J_{PH}$ = 15 Hz, 9H, *t*-Bu minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.428, 143.395, 143.315, 141.514, 141.471, 141.362, 135.447, 134.053, 133.936, 133.203, 133.091, 131.561, 131.526, 130.694, 130.352, 128.427, 128.401, 128.002, 127.932, 127.849, 127.771, 127.607, 127.106, 127.041, 127.004, 126.868, 126.501, 126.212, 126.066, 54.714, 54.688, 54.223, 54.194, 33.679, 32.752, 32.473, 31.560, 25.010, 24.872, 19.490, 19.100,; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.00(minor), 41.33 (major). HMRS calculated for $C_{24}H_{28}NNaOP$ 400.1801, found 400.1837.

Addition of 2-Mesityl MgBr: **2k-2k'**



Major/minor = 100 : 0. 98% Yield, pale yellow viscous oil. ^{1}H -NMR (300 MHz, $CDCl_3$) δ7.867-7.109 (m, 10H, C-*H* arom), 6.748 (s, 2H, C-*H* arom), 5.823 (t, $^{3}J_{PH}$ = $^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 9.9 Hz, 1H, -*CH*), 3.361 (m, 1H, -*NH*), 2.183 (s, 3H, -CH_3), 2.074 (s, 6H, 2-CH_3), 1.04(d, $^{3}J_{PH}$ = 15 Hz, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.555, 143.455, 137.325, 136.497, 135.766, 133.119, 133.010, 131.612, 131.579, 130.733, 130.163, 129.204, 128.232, 128.093, 126.400, 126.144, 52.820, 52.793, 33.632, 32.433, 24.797, 20.850, 20.666; ^{31}P NMR (162 MHz, $CDCl_3$) δ41.35. HMRS calculated for $C_{26}H_{32}LiNOP$ 412.2377, found 412.2339.

Addition of 2,6-dimethylphenyl MgBr: **2l-2l'/3l-3l'**

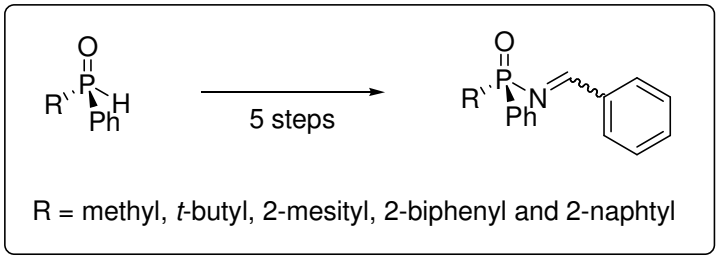


Major/minor = 85 : 15. 99% Yield, pale yellow viscous oil. ^{1}H -NMR (300 MHz, $CDCl_3$) δ7.942-6.997 (m, 13H, C-*H* arom), 5.963 (t, $^{3}J_{PH}$ = $^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 10.8 Hz, 1H, C-*H* major), 5.963 (t, $^{3}J_{PH}$ = $^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 11.1 Hz, 1H, C-*H* minor) 3.625 (t, $^{2}J_{PH}$ = $^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 10.8 Hz, 1H, -*NH* minor), 3.498 (t, $^{2}J_{PH}$ = $^{3}J_{H\text{-}C\text{-}N\text{-}H}$ = 10.8 Hz, 1H, -*NH* major), 2.2 (s, 6H, 2-CH_3 major), 2.2 (s, 6H, 2-CH_3 minor), 1.206 (d, $^{3}J_{PH}$ = 14.7 Hz, 9H, *t*-Bu major), 1.078(d, $^{3}J_{PH}$ = 15 Hz, 9H, *t*-Bu minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.252, 143.154, 140.209, 135.987, 134.247, 134.128, 133.062, 132.953, 131.691, 131.657, 130.678, 129.404, 129.363, 129.155, 128.376, 128.297, 128.151, 127.702, 127.540, 127.243, 127.090, 126.772, 126.517, 126.145, 53.016, 52.990, 33.678, 32.479, 25.130, 24.745, 20.846, 20.778; ^{31}P NMR (162 MHz, $CDCl_3$) δ42.75 (minor), 41;64 (major). HMRS calculated for $C_{25}H_{31}NOP$ 392.2138, found 392.2154.

3.4 Stereoselective addition of Grignard reagents to new *P*-chirogenic *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine: effect of the *P* substituents on the stereoselectivity (to be submitted)

3.4.1 Synopsis

Several phosphinoylimines have been synthesized in five steps starting from the appropriate phosphinoxide, and then subjected to the addition of methylmagnesium bromide giving both diastereoisomers in high yields and promising diastereomeric ratios.



R = methyl, *t*-butyl, 2-mesityl, 2-biphenyl and 2-naphtyl

Indeed, this imine has been engaged in the 1,2 addition of Grignard reagents in order to evaluate the best chiral induction due to the stereogenic phosphorous. The *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoylaldimine, which displayed the best results, have been used as electrophile in the nucleophilic addition of a large number of organomagnesium reagents and afforded the corresponding adducts in excellent yields and moderate to excellent diastereoisomeric ratios.

3.4.2 Article

Introduction

Chiral amines play an important role in biologically active systems.[36] These motifs belong to the most important structural frames in chiral drugs. It is now well established that stereoselective addition of organometallic reagents to imines is one of the most powerful and direct method for the asymmetric construction of amines. In particular imines activated by electron withdrawing groups on the nitrogen atom such as *N*-sulfonyl-, *N*-sulfinyl-, *N*-acylimines have been extensively used in the last decades because of their higher electrophilicity. Chiral *N*-sulfinylimines are doubtless the most widely used in such transformation for their chiral sulfur atom which ensure high stereocontrol.[37] Nevertheless, there still exists some limitations and shortcomings to their use in asymmetric synthesis due to the sensitiveness of the *N*-sulfinyl group to the oxidation and to the action of Brønsted acids or strong Lewis acids ($TiCl_4$)[38] which can cause the racemization of sulfur center and strongly compromise the recovery of the chiral auxiliary at the end of the process. On the other hand, *N*-phosphinoylimines begun to attract more attention from synthetic chemists and have been employed in a wide range of asymmetric transformations with various nucleophiles. Although *P,P*-diphenyl-*N*-phosphinoylimines are by far the most common electrophiles in stereoselective addition of nucleophiles with chiral metal complexes catalysts,[39] rare examples of chiral *N*-phosphinoylimines bearing a *P*-chirogenic center or a chiral auxiliary linked to the P atom can be found in literature. Very recently, Li and coworkers reported the synthesis of chiral C_2-symmetry *N*-phosphinoylimines derived from secondary enantiopure *trans*-cyclohexane-1,2-diamine which were successfully used as electrophiles in a couple of asymmetric reactions such as aza-Darzens,[40] aza-Henry[41] and Mannich reactions,[42] additions of Grignard reagents[43] and various enolates[44] with excellents results in term of yields and diastereomeric excess of the final products. In 1994, Jennings reported the synthesis of *P*-2-mesityl-*P*-phenyl-*N*-phosphinoylbenzaldimine and the oxidation of the C,N double bond leading to new chiral oxaziridines,[45] important reagents in asymmetric oxidation of prochiral sulfides and olefins. Moreover, two months before the publication of our article, Royer described diastereoselective alkynylation of new *P*-methyl-*P*-phenyl-*N*-phosphinoylbenzaldimine by aluminium acetylides.[46] To the best of our

[36] (a) S. Kobayashi and H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094; (b) R. Bloch, *Chem. Rev.* **1998**, 98, 1407–1438; (c) D. Enders and U. Reinhold, *Tetrahedron: Asymmetry*, **1997**, *8*, 1895–1946.

[37] J. A. Ellman, T. D. Owens and T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984–995; P. Zhou, B.-C. Chen and F. A. Davis, *Tetrahedron* **2004**, *60*, 8003–8030.

[38] (a) Li, G.; Wei, H. Y.; Whittlesey, B.; Batrice, N. N. *J. Org. Chem*. **1999**, *64*, 1061-1064; (b) Wei, H. -X.; Hook, J. D.; Fitzgerald, K. A.; Li, G. *Tetrahetron: Asymmetry* **1999**, *10*, 661-665.

[39] For a recent review see: S. M. Weinreb and R. K. Orr, *Synthesis*, **2005**, 1205–1227.

[40] Kattuboina, A.; Li, G. *Tetrahedron Lett*. **2008**, *49*, 1573-1577

[41] Kattuboina, A.; Kaur, P.; Ai, T.; Li, G. *Chem. Biol. Drug Des.* **2008**, *71*, 216-223

[42] (a) Han, J.; Ai, T.; Li, G. *Synthesis* **2008**, 2519-2526; (b) Han, J.; Ai, T.; Nguyen, T. Li, G. Chem. Biol. Drug Des. **2008**, *72*, 120-126; (c) Ai, T.; Han, J.; Chen, Z. -X.; Li, G. *Chem. Biol. Drug Des*. **2009**, *73*, 203-208

[43] Kattuboina, A.; Kaur, P.; Nguyen, T.; Li, G. *Tetrahedron Lett.* **2008**, *49*, 3772-3724

[44] (a) Chen, Z. -X.; Ai, T.; Kaur, P.; Li, G. *Tetrahedron Lett.* **2009**, *50*, 1079-1081; (b) Kaur, P.; Nguyen, T.; Li, G. *Eur. J. Org. Chem*. **2009**, 212-216; (c) Ai, T.; Li, G. *Bioorg. Med. Chem. Lett.* **2009**, *9*, 3967-3969

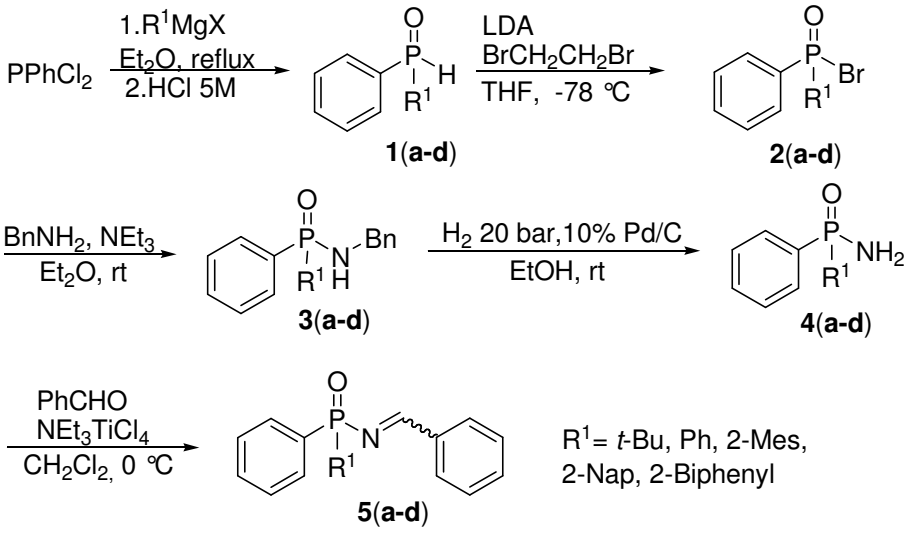
[45] Jennings, W. B.; Kochanewycz, M. J.; Lovely, C. J.; Boyd, D. R. *J. Chem. Soc., Chem. Comm.* **1994**, 2569-2570

[46] Benamer, M.; Turcaud, S.; Royer, J. *Tetrahedron Lett.* **2010**, *51*, 645-648.

knowledge these are the only examples of asymmetric transformation involving chiral or *P*-chirogenic *N*-phosphinoylimines described to date. Recently we reported the synthesis of *P*-chirogenic *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine which was successfully applied to the diastereoselective addition of various Grignard reagents with encouraging levels of stereoselection.[47] We now report a full account of our results concerning the synthesis of both *P*-chirogenic *P*-*P*-diaryl- and *P*-alkyl-*P*-aryl-*N*- phosphinoylimines as well as their use in diastereoselective 1,2-addition of Grignard reagents.

Results and Discussion

The synthesis of a series of racemic *P*-phenyl-*P*-aryl- and *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine was realized in five steps starting from commercially available phenyldichlorophosphine. Indeed, following the general reaction sequence described by Yeung et al. for the preparation of the *P*-*t*-butyl-*P*-phenylphosphinamide, dichlorophenylphosphine was treated with a Grignard reagent followed by treatment with HCl which afforded the corresponding secondary phosphane oxide **1**(**a-d**). The phosphane oxides were then deprotonated with LDA and trapped by 1,2-dibromoethane to afford the bromophosphane **2**(**a-d**). Then, a nucleophilic substitution to the phosphorous center with benzylamine was performed in Et_2O at room temperature. Debenzylation of the secondary phosphinamides **3**(**a-d**) carried out in autoclave with H_2 at 20 Bar and 10% Pd/C in EtOH gave the phosphinamides **4**(**a-d**). Benzaldehyde was then condensed with **4**(**a-d**) under $TiCl_4$/triethylamine catalysis in CH_2Cl_2 to produce the corresponding *N*-phosphinoyl benzaldimines **5**(**a-d**) (Scheme 1). All the results are summarized in Table 1.

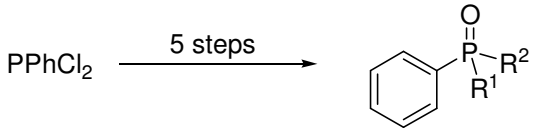


*Scheme 1: Synthesis of P-chirogenic N-phosphinoylimines **5(a-d)***

Secondary phosphinoxides in entries 1, 6 and 11 are synthesized in good to excellent yields from phenyldichlorophosphine by addition of the desired Grignard reagent. 3 equivalents of

[47] Notar Francesco, I.; Wagner, A.; Colobert, F. *Chem. Comm*. **2010**, *46*, 2139–2141

freshly prepared *t*-BuMgCl are necessary for the phosphinoxide **1a** whereas only 1.1 equivalents of organometallic reagent for **1b** and **1c** which have been isolated in almost quantitative yield. Surprisingly, the addition of 2-naphtylmagnesium bromide to the chlorophosphine failed and the *P*-phenyl-*P*-2-naphtylphosphane oxide **1d** (entry 16) was prepared in moderate yields by addition of the organolithiated compound to a diastereoisomeric mixture of (-)-menthyl phenylphosphinate, according to the procedure developed by Han[48] and coworkers. Bromophosphane oxides **2**(**a-c**) are obtained in moderate to good yields from phosphinoxides except **2b** which was isolated in very low yields due to the formation of a byproduct, the diphosphane probably originated from a side reaction of the lithiated phosphinoxide with the bromophosphane formed. Benzylphosphinamides **3**(**a**-**d**) and phosphinamides **4**(**a**-**d**) are then recovered in high yields after a nucleophilic substitution to the P atom (entries 3, 8, 13 and 18) and a catalytic debenzylation (entries 4, 9, 14 and 19).



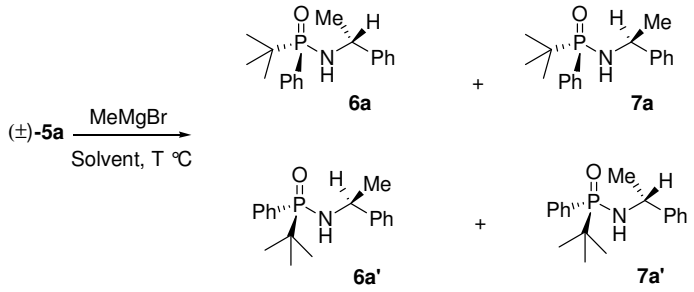
Entry	*R¹*	*R²*	*Product*	*yield (%)*[a]
1		H[b]	**1a**	54
2		Br[c]	**2a**	69
3		NHBn[e]	**3a**	79
4		NH_2[f]	**4a**	73
5		imine[i]	**5a**	89
6		H[g]	**1b**	97
7		Br[c]	**2b**	12[d]
8		NHBn[e]	**3b**	73
9		NH_2[f]	**4b**	97
10		imine[i]	**5b**	59
11		H[g]	**1c**	98
12		Br[c]	**2c**	47
13		NHBn[e]	**3c**	93
14		NH_2[f]	**4c**	98
15		imine[i]	**5c**	67
16		H[h]	**1d**	41
17		Br[c]	**2d**	54
18		NHBn[e]	**3d**	71
19		NH_2[f]	**4d**	96
20		imine[i]	**5d**	61

[a]Isolated yields after chromatography. [b](3 eq) RMgX, (1 eq) PCl_2Ph, Et_2O, reflux, 16h. [c](1.2 eq) LDA, (1 eq) $BrCH_2CH_2Br$, THF, -78°C, 3h. [d]Byproduct (diphosphane) isolated in 32% yield. [e](5 eq) $PhCH_2NH_2$, (2.2 eq) NEt_3, Et_2O, rt. [f]H_2 (20 Bar), 10% Pd/C, EtOH, rt. [g](1.1 eq) RMgX, (1 eq) PCl_2Ph, Et_2O, reflux, 16h. [h]Synthesized from diastereoisomeric mixture of menthyl phenylphosphinate (See supporting information). [i](1 eq) PhCHO, (3 eq) NEt_3, (0.5) eq) $TiCl_4$, CH_2Cl_2, 0°C, rt

*Table 1: Synthesis of P-chirogenic N-phosphinoylimines **5(a-d)** and precursors **1-4(a-d)***

[48] Xu, Q.; Zhao, C. -Q.; Han, L. -B. *J. Am. Chem. Soc.* **2008**, *130*, 12648-12655

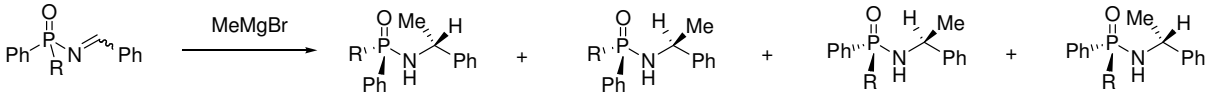
These imines were then subjected to the addition of methylmagnesium bromide in order to compare the different level of diastereoselection exerted by the adjacent *P*-chirogenic center. In our previous report we identified two different reaction conditions (dichloromethane, rt or toluene at 0°C) which allowed to isolate the addition adducts of methylmagnesium bromide to *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine in high yields and satisfactory diastereomeric ratios (Scheme 2).

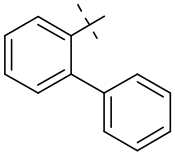
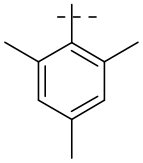
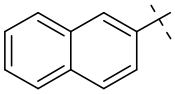


Solvent	T	t	yield	dr (**6a**-**6a'**/**7a**-**7a'**)
CH_2Cl_2	rt	3h	79	85:15
Toluene	0°C	3h	77	80:20

*Scheme 2: Methylmagnesium bromide addition to racemic P-t-butyl-P-phenyl-N-phosphinoyl benzaldimine **5a***

Indeed, we decided to apply these two different conditions to the imines **5**(**b-d**). The results are summarized in Table 2. It has been observed that *P*,*P*-diaryl-*N*-phosphinoylimines (Table 2, entries 1 to 6) displayed a good reactivity and chiral induction affording the corresponding addition products in excellent yields and moderate to good diastereoisomeric ratios although to less extent compared to imine **5a**. By the way, the steric hindrance of the aryl moiety seems to be a key factor in the diastereoselective process.



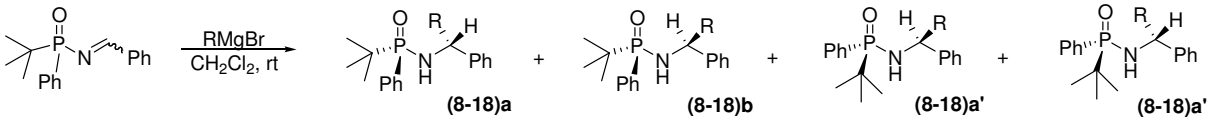
Entry	*R*	*Imine*	*Conditions*	*dr*[d]	*Yield (%)*[a,b]	*Products*
1		**5b**	CH_2Cl_2, rt	65:35	89	(**6b**-**6b'**)/(**7b**-**7b'**)
2			Toluene, 0°C	75:25	83	(**6b**-**6b'**)/(**7b**-**7b'**)
3		**5c**	CH_2Cl_2, rt	70:30	79	(**6c**-**6c'**)/(**7c**-**7c'**)
4			Toluene, 0°C	75:25	95	(**6c**-**6c'**)/(**7c**-**7c'**)
5		**5d**	CH_2Cl_2, rt	55:45	81	(**6d**-**6d'**)/(**7d**-**7d'**)
6			Toluene, 0°C	60:40	85	(**6d**-**6d'**)/(**7d**-**7d'**)
7	Methyl	**5e**[c]	CH_2Cl_2, rt	70:30	91	(**6e**-**6e'**)/(**7e**-**7e'**)

[a]Overall yields of the four stereoisomers. [b]Yield after chromatography.[c]**5e** was synthesized according to the procedure reported by Jennings[49].[d]Determined by ^{1}H- or ^{31}P NMR of crude

[49] Harmor, T. A.; Jennings, W. B.; Lovely, C. J.; Reever, K. A. *J. Chem. Soc. Perkin Trans. 2* **1992**, 843-849

*Table 2: 1,2-addition of methylmagnesium bromide to racemic P-t-butyl-P-phenyl-N-phosphinoyl benzaldimine **5(b-e)**.*

For instance, imine **5c**, bearing a 2-mesityl group highly hindered on the *oo'p* positions, provided the addition products in 70:30 diastereomeric ratio (Table 2, entry 3) when the reaction is carried out in dichloromethane at room temperature and 75:25 in toluene at 0°C (Table 2, entries 3 and 4). With less hindered aryl groups such as 2-biphenyl and 2-naphtyl lower diastereosomeric ratios have been observed in the addition adducts (Table 2, entries 1 and 5 respectively) when the reaction is carried out in toluene at 0°C. Curiously, in contrast with what we observed in the case of *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine (Scheme 2), we noticed an inversion of the diastereoselectivity when *P*,*P*-diarylphosphinoylimines are employed and the toluene seems to be here the best solvent at 0°C (Table 2, entries 2 and 6). The 1,2 addition of MeMgBr was explored as well on the imine **5e**, which is easily prepared from the corresponding commercially available *P*-methyl-*P*-phenylphosphinyl chloride as previously reported by Jennings and coworkers[49] and taken up by Royer.[46] The addition reaction was carried out in dichloromethane at room temperature and provided the adducts in 91% yields and 70:30 diastereomeric ratios (Table 2, entry 7). These results encouraged us to explore the scope of the addition of other Grignard reagents to *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoylbenzaldimines **5a**. Thus, this imine has been used in association with a large number of organomagnesium reagents and the corresponding adducts were isolated in excellent yields and moderate to excellent diastereomeric ratios.



Entry	*R*	*Ar*	*Imine*	*Conditions*	*dr*[b]	*Yield*[c] *(%)*	*Products*
1	*i*-propyl	Ph	**5a**	CH_2Cl_2, 25 °C	75 : 25	98	**8**(**a**-**a'**)/(**b**-**b'**)
2	*i*-propyl	Ph	**5a**	Toluene, 0 °C	70 : 30	83	**8**(**a**-**a'**)/(**b**-**b'**)
3	*t*-butyl[f]	Ph	**5a**	CH_2Cl_2, 25 °C[d,e]	60 : 40	29	**9**(**a**-**a'**)/(**b**-**b'**)
4	*t*-butyl[f]	Ph	**5a**	CH_2Cl_2, reflux	65 : 35	90	**9**(**a**-**a'**)/(**b**-**b'**)
5	*n*-butyl	Ph	**5a**	CH_2Cl_2, 25 °C	70 : 30	93	**10**(**a**-**a'**)/(**b**-**b'**)
6	*n*-decyl	Ph	**5a**	CH_2Cl_2, 25 °C	70 : 30	91	**11**(**a**-**a'**)/(**b**-**b'**)
7	vinyl	Ph	**5a**	CH_2Cl_2, 25 °C	60 : 40	67	**12**(**a**-**a'**)/(**b**-**b'**)
8	2-methylallyl[f]	Ph	**5a**	CH_2Cl_2, 25 °C	75 : 25	85	**13**(**a**-**a'**)/(**b**-**b'**)
9	*p*-methoxyphenyl	Ph	**5a**	CH_2Cl_2, 25 °C	60 : 40	97	**14**(**a**-**a'**)/(**b**-**b'**)
10	*o*-methoxyphenyl	Ph	**5a**	CH_2Cl_2, 25 °C	60 : 40	97	**15**(**a**-**a'**)/(**b**-**b'**)
11	*o*-methylphenyl	Ph	**5a**	CH_2Cl_2, 25 °C	55 : 45	95	**16**(**a**-**a'**)/(**b**-**b'**)
12	2-mesityl	Ph	**5a**	CH_2Cl_2, 25 °C	100 : 0[g]	98	**17**(**a**-**a'**)/(**b**-**b'**)
13	2,6-dimethylphenyl	Ph	**5a**	CH_2Cl_2, 25 °C	85 : 15	99	**18**(**a**-**a'**)/(**b**-**b'**)

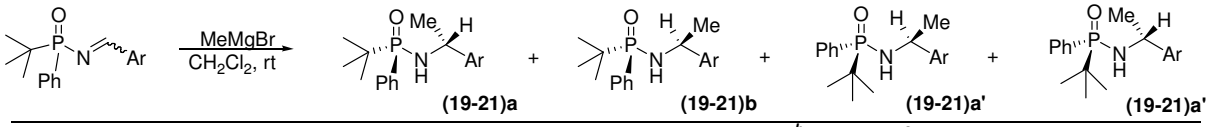
[a] Until otherwise specified, reactions are complete in 3–4 h. [b] Calculated from crude ^{1}H-NMR spectra. [c] Isolated yield after chromatography. [d] 24 h at room temperature. [e] 47% conversion was observed at room temperature. [f] Use of t-butylmagnesium chloride and 2-methylallylmagnesium chloride.[g] Calculated from crude ^{31}P-NMR spectra.

*Table 3: Grignard 1,2 addition to racemic P-t-butyl-P-phenyl-N-phosphinoyl benzaldimine **5a***

Branched and linear aliphatic Grignard reagent were first tested onto *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine **5a**. Diastereomeric ratio of 75 : 25 and 98% yield were obtained in the addition of *i*-propylmagnesium bromide in CH_2Cl_2 at room temperature. To be sure that CH_2Cl_2 is the best solvent for this diastereoselective addition whatever the Grignard reagent used, we performed in parallel the reaction in toluene and obtained, as expected, a slightly

lower selectivity of 70 : 30 (Table 3, entries 1 and 2). Using the sterically more hindered *t*-butylmagnesium chloride, we observed only 47% conversion of the phosphinoyl benzaldimine **5e** in CH_2Cl_2 at 25°C and the selectivity decreased to 60 : 40. Heating to reflux completed the reaction but no real improvement of the stereoselectivity was noticed (Table 3, entries 3 and 4). With linear aliphatic Grignard reagents such as n-butyl- and n-decylmagnesium bromide, we observed modest selectivity (70 : 30) and high yields in CH_2Cl_2 at 25 °C (Table 3, entries 5 and 6). Then, we turned our attention to the use of unsaturated Grignard reagents. In the addition of vinylmagnesium bromide onto the phosphinoyl benzaldimine **5a** the corresponding phosphinamide was obtained in a 60 : 40 diastereomeric ratio (Table 3, entry 7). The use of sterically more hindered 2-methylallylmagnesium chloride allowed us to improve the selectivity to 75 : 25 in CH_2Cl_2 in 85% yield (Table 3, entry 8). Surprisingly, the addition of mesitylmagnesium bromide compared to p-methoxy-(60 : 40), o-methoxy-(60 : 40) and *o*-methylphenylmagnesium bromide (55 : 45) resulted completely diastereospecific giving the corresponding amine in 98% yield in CH_2Cl_2 (Table 3, entries 9 to 12). ^{31}P NMR of the crude product confirmed the obtention of only one diastereomer in the case of entry 12. Furthermore, as expected, the addition of 2,6-dimethylphenylmagnesium bromide gave the corresponding N-phosphinoyl amine in high yield and selectivity (Table 2, entry 13).

Aromatic imines derived from pentafluoro-, 4-cyano- and 3,4,5-trimethoxybenzaldehyde were also tested and displayed a reduced diastereoselectivity in the addition of methylmagnesium bromide compared to the benzaldimine (Table 4). Particularly, pentafluorophenyl- and *m,m',p*-methoxyphenyl groups showed a comparable dr values (Table 4, entries 2 and 3) but with 4-cyanophenyl the diastereomeric ratio drop to 55:45 (Table 4, entry 4) suggesting that both electronic and steric effects could disturb the correct arrangement of the molecules in a rigid trasition state, essential for reaching high selectivities. While aromatic aldehydes are good reagent in the preparation of *N*-phosphinoylimines, every attempts to synthesize *P-t*-butyl-*P*-phenyl-*N*-phosphinoylimines starting from aliphatic aldehydes failed with the present method and those commonly used.

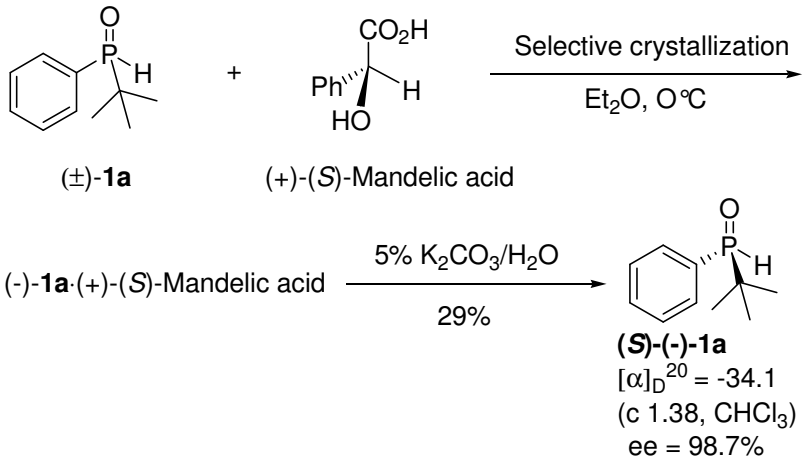


Entry	*Ar*	*Imine*	*Conditions*	*dr*[b]	*Yield*[c] *(%)*	*Products*
1	Ph	**5a**	CH_2Cl_2, 25 °C	85 : 15	79	(**6a**-**7a**)/(**6a'**-**7a'**)
2	C_6F_5	**5f**	CH_2Cl_2, 25 °C	75 : 25	75	**19**(**a**-**b**)/(**a'**-**b'**)
3	*mm'p*-$(OMe)_3$-C_6H_2	**5g**	CH_2Cl_2, 25 °C	70 : 30	81	**20**(**a**-**b**)/(**a'**-**b'**)
4	*p*-CN-C_6H_4	**5h**	CH_2Cl_2, 25 °C	55 : 45	88	**21**(**a**-**b**)/(**a'**-**b'**)

[a] Until otherwise specified, reactions are complete in 3–4 h. [b] Calculated from crude ^1H-NMR spectra. [c] Isolated yield after chromatography.

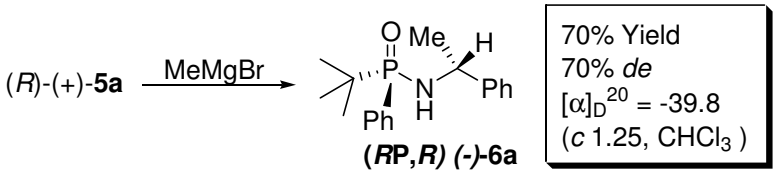
Table 4: Grignard 1,2 addition to racemic P-t-butyl-P-phenyl-N-phosphinoyl benzaldimine **5a**

For a better understanding of the chiral induction, we decided to prepare an enantiopure imine and to determine the absolute configuration of the major diastereomer afforded by the addition of methylmagnesium bromide. Thus, (*R*)-(+)-*P-t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine **5a** was synthesized starting from (*S*)-(−)-*P-t*-butyl-*P*-phenylphosphane oxide according to the reaction sequence shown in Scheme 1. The optically active phosphane oxide **1a** was obtained as single enantiomer by resolution of diastereomeric complex with (*S*)-(+)-mandelic acid and treatment with aqueous potassium carbonate (Scheme 3).



*Scheme 3. Racemate resolution of tert-butylphenylphosphinoxide **1a** with (+)-(S)-mandelic acid as chiral solvating agent.*

Addition of methylmagnesium bromide on the enantiopure phosphinoyl imine **5a** led, after chromatographic separation, to the major diastereoisomer in 70% yield and 70% diastereomeric excess (Table 4, entry 1; Scheme 2).



Scheme 4. Determination of the absolute configuration of the major diastereomer **6a**.

Crystallization in Hexane/CH_2Cl_2 provided a single crystal which allowed to determine the absolute configuration of the two stereocenters by RX crystallography (Figure 1). Interestingly, it has been observed that in the crystal unity the single molecules of (-)-**8a** are linked by intermolecular hydrogen bond between the P=O (acceptor) and the N-H (donor) groups.

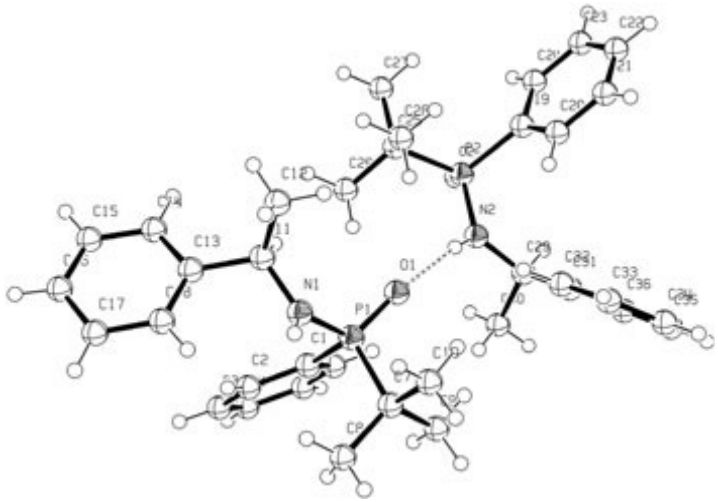


*Figure 1: ORTEP Plot of (RP,R)-**2a.** Hydrogen atoms are omitted for clarity. Hydrogen bond between O1 and N2.*

Taking into account the absolute configuration (*R*P,*R*) of the major diastereoisomer, we proposed a transition state model invoking the coordination of the magnesium atom with the oxygen of the phosphine oxide arranged in a chair-like conformation in which the hindered t-Bu group occupy the equatorial position and phenyl groups are both in axial position. This structure could be further stabilized by π-stacking interactions between two phenyl ring 1,3-positioned[50] (Figure 2).

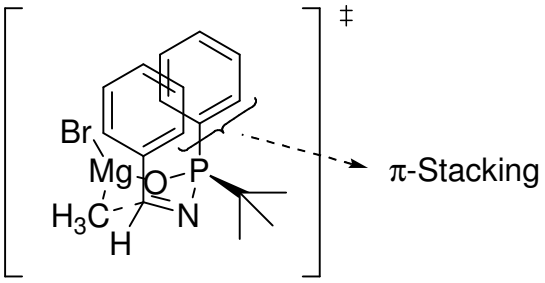
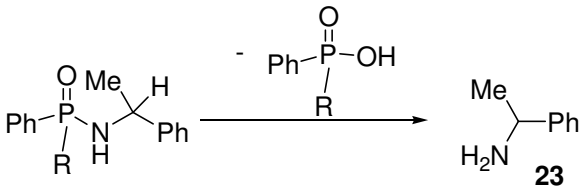


Figure 2: Proposed transition state model of the addition.

Phosphinamides are generally highly reactive in the cleavage reaction of phosphinoyl group providing deprotected amines in high yields under mild acidic conditions. In our case, this behaviour is confirmed for amides bearing two aromatic groups on the P atom, that allow to recover the free amine after 18-24h in 1,5M HCl in MeOH followed by a basic work-up in 57 and 68% yields from phosphinamides **6**-**7b** and **6**-**7c** (as mixture of enantiomers) respectively (Table 5, entries 1, 2). By contrast, *P*-*t*-butyl-*P*-phenyl phosphinamides were completely unreactive under these conditions and this fact was the subject of a systematic study. We observed in few cases (hard conditions like high acid concentration and high temperature) that the cleavage of the P-N bond took place, as confirmed by the phosphinic acid recovered after an acidic work-up, but the free amine has never been isolated (Table 5, entries 3, 4). It is noteworthy that we observed the deprotection of phosphinamides **6**-**7e** derived from the *P*-methyl-*P*-phenyl-*N*-phosphinoylimine **5e**. The cleavage is complete in 2h at room temperature in a slightly acidic water-methanol solution and provide the methylbenzylamine **23** in high yield (Table 5, entry 5).



entry	*R*		*Conditions*	*Yield (%)*
1	2-biphenyl	(**6b**-**6b'**)/(**7b**-**7b'**)	1. 1.5 M HCl in MeOH, 18h, rt; 2. NaOH aq.	57
2	2-mesityl	(**6c**-**6c'**)/(**7c**-**7c'**)	1. 1.5 M HCl in MeOH, 18h, rt; 2. NaOH aq.	68
3	*t*-butyl	(**6a**-**6a'**)/(**7a**-**7a'**)	1. 2N HCl in 35%Dioxane-H_20, 110°C, 24h; 2. NaOH aq.	0
4	*t*-butyl	(**6a**-**6a'**)/(**7a**-**7a'**)	conc. HCl, 90°C, 5h; 2. NaOH aq.	0
5	methyl	(**6e**-**6e'**)/(**7e**-**7e'**)	1. 3M M HCl in MeOH (1:5), 2h, rt; 2. NaOH aq	85

Table 5: Cleavage tests

[50] Williams, V. E.; Lemieux R. P., Thatcher, G. R. J. *J. Org. Chem*. **1996**, *61*, 1927-1933.

Conclusions

In conclusion, we reported an efficient stereoselective addition of various Grignard reagents onto new *P*-chirogenic *P,P*-diaryl and *P*-alkyl-*P*-phenyl *N*-phosphinoyl benzaldimine affording the corresponding N-phosphinoylamines in excellent yields and moderate to excellent stereoselectivities. Initial results of the stereoselective addition of Grignard reagents towards the synthesized activated imines were quite encouraging suggesting that this new class of compounds deserve to be further explored. This original class of chiral inducer could offer interesting alternatives in the field of asymmetric catalysis and also new alternative to the widely used sulfinylimines. Further investigations concerning the design of other interesting synthetic routes involving these P-chirogenic compounds are currently underway in our laboratory.

Aknowledgement
We are grateful to NovALIX-Pharma (contact@alixpharma. com) for financial support. We are indebted to Dr Lydia Brelot (Service de Radiocristallographie, University of Strasbourg, France) for her assistance with the single crystal structure elucidation.

3.5.3 Experimental part

General.

All the solvents used were dried and freshly distilled in argon atmosphere. Toluene was distilled over sodium, dichloromethane was dried with calcium hydride and fractionally distilled.

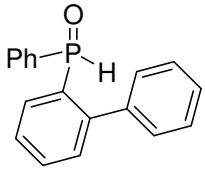
Benzaldehyde, triethylamine and benzylamine were distilled prior to using. Palladium on carbon (10%, 50% wet with water for safety) was purchased from Acros and stored in a drying device. Titanium tetrachloride was used like a 1 M solution in dichloromethane. Alkyl- and aryl- magnesium halides solutions were purchased from Aldrich and Acros or prepared just by adding a solution of corresponding organohalide in dry diethylether on the activated magnesium and refluxing the resulting solutions for 2h.

All the reactions were performed under argon atmosphere and in flamed under high vacuum flasks. Thin-layer chromatography (TLC) was carried out on aluminum plates silica gel 60 F_{254} purchased from Merck. Chromatography columns were performed with Merck silica gel Si 60 (40-63µm). All hydrogenation reactions were carried out in a 75 ml standard stainless steel autoclave.
^{1}H,^{13}C and large band decoupled ^{31}P nuclear magnetic resonance (NMR) spectra were recorded at 300, 75 and 162 MHz, respectively. Chemical shifts are reported in δ units, parts per million (ppm) from tetramethylsilane and were measured relative to the signals for residual chloroform (7.26 ppm for proton and 77.00 for carbon NMR spectra). Coupling constants *J* are given in Hz. Coupling patterns are abbreviated as, for example, br (broad) s (singlet), d (doublet), t (triplet) and m (multiplet).
Mass spectra were recorded by HRMS by electrospray ionization method obtained with a microTOF LC Brucker Daltonics microTOF LC from Brucker Daltonics apparatus.
Melting ranges (m.p.) given were found to be reproducible after resolidification.

General experimental procedure for the preparation of (±)-1b and (±)-1c

A solution of the desired Grignard reagent (1.1 eq) was added dropwise to the dichlorophenylphosphine (1 eq) in dry diethyl ether at 0°C under Argon. After the addition the resulting suspension was heated under reflux overnight. The mixture was cooled at 0°C, poured into ice and treated with HCl (5M). The organic phase was separated and the acidic water layer was extracted with dichloromethane (3x15 mL) affording the crude phosphinoxide which was purified by chromatography (Cyclohexane/EtOAc 7:3)

(±)-1b



97% Yield. White solid (mp = 154.4-155.8°C)

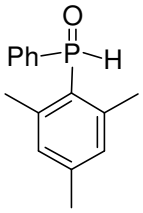
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.28 (m, 10H, C*H* arom), 7.30-7.36 (m, 1H, C*H* arom), 7.41-7.54 (m, 1H, C*H* arom), 7.80 (d, $^{1}J_{PH}$= 492.6 Hz, 1H, P*H*), 7.88 (dd, $^{2}J_{PH}$= 13.7 Hz, ^{3}J= 7.5Hz, 1H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 127.5 (d, $^{2}J_{PC}$= 11.8 Hz, *C*H), 128.0 (*C*H), 128.2 (*C*H), 128.4 (d, $^{2}J_{PC}$= 12.9 Hz, *C*H), 129.4 (*C*H), 130.1 (d, $^{1}J_{PC}$= 108 Hz, *C* quat.), 130.4 (d, $^{3}J_{PC}$= 11.5 Hz, *C*H), 130.6 (d, $^{3}J_{PC}$= 9 Hz, *C*H), 131.6 (d, $^{1}J_{PC}$= 97.5 Hz, *C* quat.), 131.9 (d, $^{4}J_{PC}$= 1.9 Hz, *C*H), 132.3 (d, $^{4}J_{PC}$= 1.4 Hz, *C*H), 132.7(d, $^{3}J_{PC}$= 10.7Hz, *C*H), 139.2 (d, $^{3}J_{PC}$= 5.2 Hz, *C* quat.), 145.9 (d, $^{2}J_{PC}$= 10.4 Hz, *C* quat.) ppm.

^{31}P NMR(162 MHz, $CDCl_3$) δ 18.44 ppm.

Anal. calcd for $C_{18}H_{15}OP$: C, 77.69; H, 5.43; found: C, 76.54; H, 5.96.

(±)-1c[12]



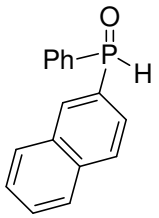
98% Yield. White crystalline solid

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3H, *p* -C*H*$_3$ Mes), 2.38 (s, 6H, *oo'*-C*H*$_3$ Mes), 6.80 (d, $^{4}J_{PH}$= 3.8 Hz, 2H, C*H* arom Mes), 7.41-7.51 (m, 3H, C*H* arom), 7.58-7.65 (m, 2H, C*H* arom), 8.55 (d, $^{1}J_{PH}$= 483.2 Hz, 1H, P*H*) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (*p* -C*H*$_3$), 21.5(d, $^{2}J_{PC}$= 8.2 Hz, *oo'*-C*H*$_3$), 125.0 (d, $^{1}J_{PC}$= 102.9 Hz, *C* quat.), 128.0 (d,$^{2}J_{PC}$=12.6 Hz, *C*H), 130.3 (d, $^{3}J_{PC}$= 10.4 Hz, *C*H), 130.4 (d, $^{3}J_{PC}$= 11.3 Hz, *C*H), 131.9 (d, $^{4}J_{PC}$= 2.5 Hz, *C*H), 132.2 (d, $^{1}J_{PC}$= 99.1 Hz, *C* quat.), 142.1 (d, $^{2}J_{PC}$= 9.9 Hz, *C* quat.), 142.8 (d, $^{4}J_{PC}$= 1.6 Hz, *C* quat.) ppm.

^{31}P NMR(162 MHz, $CDCl_3$) δ 9.87 ppm.

Preparation of (±)-1d[12]



To a Schlenk tube containing 2-naphtyllithium (12.8 mmol, 1.2 eq) solution in THF, was

slowly added menthylphosphinate (3 g, 10.7 mmol, 1 eq) of as 1M solution in THF at -78°C under argon for 5h and then quenched with 1mL of saturated NH_4Cl solution, and slowly warmed to room temperature. The resulting solution was poured into a separation funnel and diluted with water. A first extraction with hexane allowed to remove the menthol, then the aqueous phase was extracted twice (10 mL) with chloroform. The combined organic phases were dried under $MgSO_4$, filtered and concentrated under vacuum to give the crude *P*-naphtyl-*P*-phenyl- phosphinoxide as a colourless oil. Column chromatography in Cyclohexane/AcOEt 1:1 gave the pure product in 41% as white crystalline solid (1.31 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.62 (m, 6H, C*H*), 7.69-7.76 (m, 3H, C*H*), 7.84-7.92 (m, 3H, C*H*), 8.19 (d, $^1J_{PH}$= 480.9 Hz, 1H, P*H*), 8.34 (d, $^3J_{PH}$= 15.6 Hz, 1H, C*H*) ppm.

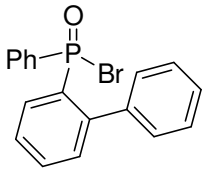
^{13}C NMR (75 MHz, $CDCl_3$) δ 125.02, 125.18, 127.2, 127.74, 127.99, 128.46, 128.81, 128.84, 128.86, 128.98, 129.03, 129.03, 129.09, 130.72, 130.87, 132.26, 132.47, 132.59, 132.63, 132.78, 132. 92, 135.09, 135.12 ppm.

^{31}P NMR(162 MHz, $CDCl_3$) δ 12.37 ppm.

General experimental procedure for the preparation of (±)-2(b-d)

To a solution of phosphinoxide in THF (10mL/mmol) kept at -78°C was added by cannula LDA (1.2 eq. in 8mL/mmol of THF). The resulting yellow to dark brown solution was stirred for 1h at the same temperature. 1,2 dibromoethane was then added dropwise and the mixture was stirred for further 1h at -78°C. The reaction was quenched with saturated NH_4Cl aq. The organic layer was separated and the aqueous phase was washed with diethyl ether (3x30mL). The combined organic phases were were dried under $MgSO_4$, filtered and concentrated under vacuum to give the crude bromophosphinoxide as a orange oil wich was purified by chromatography (cyclohexane/EtOAc 1:1).

(±)-2b



12% Yield. White solid (mp = 146.8-149.2°C)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.29 (m, 10H, C*H*), 7.33-7.39 (m, 1H, C*H*), 7.44-7.52 (m, 1H, C*H*), 7.88 (dd, $^2J_{PH}$= 13.9 Hz, ^3J= 7.5Hz, 1H, C*H*) ppm.

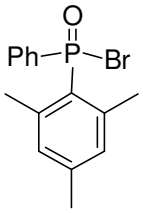
^{13}C NMR (75 MHz, $CDCl_3$) δ 127.5 (d, $^2J_{PC}$= 11.8 Hz, *C*H), 128.0 (*C*H), 128.2 (*C*H), 128.4 (d, $^2J_{PC}$= 12.7 Hz, *C*H), 129.4 (*C*H), 129.6 (d, $^1J_{PC}$= 106.4 Hz, *C* quat.), 130.4 (d, $^3J_{PC}$= 11.5 Hz, *C*H), 130.6 (d, $^3J_{PC}$= 9 Hz, *C*H), 131.9 (d, $^4J_{PC}$= 1.9 Hz, *C*H), 132.0 (d, $^1J_{PC}$= 101 Hz, *C* quat.), 132.3 (d, $^4J_{PC}$=

1.4 Hz, *C*H), 132.7(d, $^{3}J_{PC}$= 10.7Hz, *C*H), 139.2 (d, $^{3}J_{PC}$= 5.2 Hz, *C* quat.), 145.9 (d, $^{2}J_{PC}$= 10.4 Hz, *C* quat.) ppm.

^{31}P NMR(162 MHz, $CDCl_3$) δ 46.34 ppm.

Anal. calcd for $C_{18}H_{14}BrOP$: C, 60.53; H, 3.95; found: C, 61.45; H, 4.12.

(±)-2c



47% Yield. White solid (mp = 124.6-125.3°C)

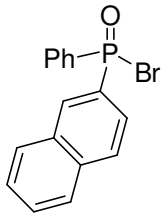
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H, *p* -C*H*$_3$ Mes), 2.40 (s, 6H, *oo'*-C*H*$_3$ Mes), 6.80 (d, $^{4}J_{PH}$= 3.8 Hz, 2H, C*H* arom Mes), 7.41-7.51 (m, 3H, C*H* arom), 7.58-7.65 (m, 2H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2(, *p* -C*H*$_3$), 21.8(d, $^{3}J_{PC}$= 8.3 Hz, *oo'*-C*H*$_3$), 125.3 (d, $^{1}J_{PC}$= 104 Hz, *C* quat.), 128.1 (d, $^{2}J_{PC}$= 12.5 Hz, *C*H), 130.3 (d, $^{3}J_{PC}$= 10.7 Hz, *C*H), 130.4 (d, $^{3}J_{PC}$= 10.9 Hz, *C*H), 132.5 (d, $^{4}J_{PC}$= 2.4 Hz, *C*H), 132.9 (d, $^{1}J_{PC}$= 101 Hz, *C* quat.), 142.1 (d, $^{2}J_{PC}$= 9.9 Hz, *C* quat.), 142.8 (d, $^{4}J_{PC}$= 2 Hz,*C* quat.) ppm.

^{31}P NMR(162 MHz, $CDCl_3$) δ 28.34 ppm.

Anal. calcd for $C_{15}H_{16}BrOP$: C, 55.75; H, 4.99; found: C, 55.12; H, 6.01.

(±)-2d



54% Yield. White solid (mp = 167.3-169.2°C)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.47 (m, 6H, C*H*), 7.63-7.99 (m, 5H, C*H*), 8.37 (d, $^{3}J_{PH}$= 15.6 Hz, 1H, C*H*) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 125.03, 125.26, 127.29, 127.74, 127.86, 128.35, 128.83, 128.85, 128.87, 128.99, 129.11, 129.15, 130.69, 130.89, 130.92, 132.31, 132.52, 132.60, 132.64, 132.71, 132.81, 132. 92, 135.26, 135.28 ppm.

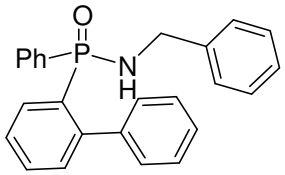
^{31}P NMR(162 MHz, $CDCl_3$) δ 38.57 ppm.

Anal. calcd for $C_{16}H_{12}BrOP$: C, 58.03; H, 3.65; found: C, 58.35; H, 3.98.

General experimental procedure for the preparation of (±)-3(b-d)

To a solution of triethylamine (0.39 mL, 2.8 mmol) and phosphinoylbromide **2**(**b**-**d**) (1.25 mmol) in Et_2O (10 mL) was added benzylamine (0.687 mL, 6.25 mmol) at room temperature. The mixture was stirred for 16 h and the white precipitate of ammonium bromide was filtered off. The filtrate was then poured into a saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with Et_2O (3x15 mL) and the combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/cyclohexane 4:1) of the crude mixture afforded pure **3**(**b**-**d**) as a white solid.

(±)-3b



73% Yield. White solid (mp = 189.3-193.2°C)

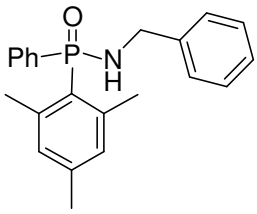
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (AB part of ABX (X=P), J_{AB} = 79.3 Hz, $^3J_{PH}$ = 3 Hz, 2H, *CH*$_2$), 2.99 (br s, 1H, N*H*), 7.15-7.29 (m, 10H, C*H*), 7.32-7.64 (m, 7H, C*H*), 7.88 (dd, $^2J_{PH}$= 13.9 Hz, ^3J= 7.5Hz, 1H, C*H*) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 45.8 (d, $^2J_{PC}$ = 2.6 Hz, *C*H_2), 127.3 (*C*H), 127.5 (d, $^2J_{PC}$= 11.8 Hz, *C*H arom.), 128.0 (*C*H arom.), 128.1 (*C*H arom.), 128.2 (*C*H arom.), 128.4 (d, $^2J_{PC}$= 12.9 Hz, *C*H arom.), 129.4 (*C*H arom.), 128.7 (*C*H arom.), 129.6 (d, $^1J_{PC}$= 108 Hz, *C* quat. arom.), 130.4 (d, $^3J_{PC}$= 11.5 Hz, *C*H arom.), 130.6 (d, $^3J_{PC}$= 9 Hz, *C*H arom.), 130.9 (d, $^1J_{PC}$= 101 Hz, *C* quat. arom.), 131.9 (d, $^4J_{PC}$= 1.9 Hz, *C*H arom.), 132.3 (d, $^4J_{PC}$= 1.4 Hz, *C*H arom.), 132.7 (d, $^3J_{PC}$= 10.7Hz, *C*H arom.), 139.2 (d, $^3J_{PC}$= 5.2 Hz, *C* quat. arom.), 139.7 (d, $^3J_{PC}$ = 7.8 Hz, *C* quat. arom.), 145.9 (d, $^2J_{PC}$= 10.4 Hz, *C* quat. arom.) ppm.

^{31}P NMR(162 MHz, $CDCl_3$) δ 35.12 ppm.

Anal. calcd for $C_{25}H_{22}NOP$: C, 78.31; H, 5.78; N, 3.65; found C, 79.56; H, 5.32; N, 3.08.

(±)-3c



93% Yield. White solid (mp = 178.0-180.3°C)

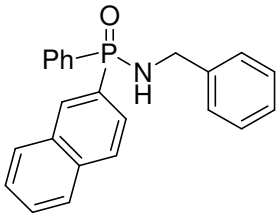
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H, *p* -C*H*$_3$ Mes), 2.47 (s, 6H, *oo'*-C*H*$_3$ Mes), 3.03 (br s, 1H, *NH*), 4.52 (AB part of ABX (X=P), J_{AB} = 79.3 Hz, $^{3}J_{PH}$ = 3.2 Hz, 2H, *CH*$_2$), 6.80 (d, $^{4}J_{PH}$= 4.1 Hz, 2H, C*H* arom Mes), 7.40-7.52 (m, 3H, C*H* arom), 7.56-7.79 (m, 7H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1(*p* -C*H*$_3$ Mes), 21.8(d, $^{3}J_{PC}$= 7.9 Hz, *oo'*-C*H*$_3$ Mes), 44.376 (d, $^{2}J_{PC}$ = 2.7 Hz, *C*H$_2$), 125.0 (d, $^{1}J_{PC}$= 102.9 Hz, *C* quat. arom.), 127.3 (*C*-H arom.), 127.6 (*C*H arom.), 128.0 (d,$^{2}J_{PC}$=12.3 Hz, *C*H), 128.4 (*C*-H arom.), 130.3 (d, $^{3}J_{PC}$= 10.4 Hz, *C*H), 131.6 (d, $^{3}J_{PC}$= 10.9 Hz, *C*H), 131.9 (d, $^{4}J_{PC}$= 2.2 Hz, *C*H), 132.2 (d, $^{1}J_{PC}$= 99.1 Hz, *C* quat. arom.), 139.9 (d, $^{3}J_{PC}$ = 7.5 Hz, *C* quat. arom.), 142.1 (d, $^{2}J_{PC}$= 9.9 Hz, *C* quat. arom.), 143.0 (*C* quat. arom.) ppm.

^{31}P NMR(162 MHz, $CDCl_3$) δ 21.15 ppm.

Anal. calcd for $C_{22}H_{24}NOP$: C, 75.62; H, 6.92; N, 4.01; found C, 75.25; H, 7.01; N, 3.89.

(±)-3d



71% Yield. White solid (mp = 193.5-196.2°C)

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.02 (br s, 1H, *NH*), 4.22 (AB part of ABX (X=P), J_{AB} = 76.5 Hz, $^{3}J_{P\text{-}H}$ = 2.8 Hz, 2H, *CH*$_2$), 7.29-7.57 (m, 11H, C*H*), 7.69-8.01 (m, 5H, C*H*), 8.45 (d, $^{3}J_{PH}$= 15.6 Hz, 1H, C*H*) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 45.14, 125.21, 125.35, 127.32, 127.66, 127.77, 127.92, 128.04, 128.61, 128.70, 129.03, 129.11, 130.12, 130.21, 131.88, 132.39, 132.43, 132.65, 132.69 132.78, 132.92, 135.87, 132.89, 140.41, 140.52 ppm

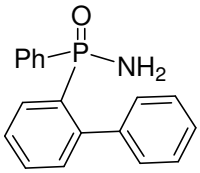
^{31}P NMR(162 MHz, $CDCl_3$) δ 29.81 ppm

Anal. calcd for $C_{23}H_{20}NOP$: C, 77.30; H, 5.64; N, 3.92; found C, 77.15; H, 5.41; N, 3.97.

General experimental procedure for the preparation of (±)-4(b-d)

Phosphinamide **3**(**b-d**) (0.7 mmol), Pd/C (10 mg/(100 mg phosphinamide)) and EtOH (5 mL) were placed in the autoclave and flushed three times with hydrogen before pressuring up to 20 Bar. The mixture was stirred at room temperature for 24 h and then depressurized. The solution was filtered through a Celite pad that was thoroughly washed with ethanol. The solvent was removed *in vacuo* affording pure phosphinamide **4**(**b-d**).

(±)-4b



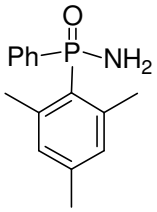
97% Yield. White solid (mp = 179.0-180.5°C)

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73 (br s, 2H, NH_2), 7.21-7.60 (m, 13H, C*H*), 7.84 (ddd, $^{3}J_{PH}$= 14.2 Hz, ^{3}J= 7.8Hz, ^{4}J= 1.3Hz, 1H, C*H*) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 126.8 (d, $^{2}J_{PC}$= 12.9 Hz, *C*H), 127.8 (*C*H), 127.8 (*C*H), 128.1(d, $^{2}J_{PC}$= 12.9 Hz, *C*H), 129.6 (*C*H), 130.9 (d, $^{3}J_{PC}$= 10.7 Hz, *C*H), 131.1 (d, $^{4}J_{PC}$= 1.9 Hz, *C*H), 131.5 (d, $^{4}J_{PC}$= 2.5 Hz, *C*H), 131.7 (d, $^{3}J_{PC}$= 10.2 Hz, *C*H), 132.4 (d, $^{1}J_{PC}$= 104 Hz, *C* quat.), 132.6 (d, $^{3}J_{PC}$= 11 Hz, *C*H), 134.2 (d, $^{1}J_{PC}$= 107 Hz, *C* quat.), 141.0 (d, $^{4}J_{PC}$= 3.6 Hz, *C* quat.) 144.9 (d, $^{2}J_{PC}$= 9.3 Hz, *C* quat.) ppm

^{31}P NMR(162 MHz, $CDCl_3$) δ 35.92 ppm.
Anal. calcd for $C_{18}H_{16}NOP$: C, 73.71; H, 5.50; N, 4.78; found: C, 72.56; H, 5.21; N, 4.36.

(±)-4c



98% Yield. White solid (mp = 143.8-145.2°C)

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H, *p* -CH_3 Mes), 2.48 (s, 6H, *oo'*-CH_3 Mes), 3.07 (br s, 2H, *NH_2*), 6.89 (d, $^{4}J_{PH}$= 3.6 Hz, 2H, C*H* arom Mes), 7.37-7.49 (m, 3H, C*H* arom), 7.67-7.75 (m, 2H, C*H* arom) ppm.

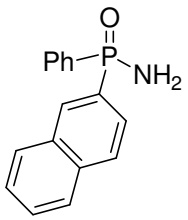
^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (*p* -CH_3), 23.7 (d, $^{3}J_{PC}$= 3 Hz, *oo'*-CH_3), 126.0 (d, $^{1}J_{PC}$= 123.2 Hz, *C* quat.), 128.4 (d, $^{2}J_{PC}$=12.9 Hz, *C*H), 130.2 (d, $^{3}J_{PC}$= 11 Hz, *C*H), 130.9 (d, $^{3}J_{PC}$= 12.3 Hz, *C*H),

131.2 (d, $^{4}J_{PC}$= 2.2 Hz, *C*H), 136.9 (d, $^{1}J_{PC}$= 125.4 Hz, *C* quat.), 141.5 (d, $^{4}J_{PC}$= 2.5 Hz, *C* quat.), 142.9 (d, $^{3}J_{PC}$= 11.3 Hz, *C* quat.) ppm.

^{31}P NMR(162 MHz, $CDCl_3$) δ 25.92 ppm.

Anal. calcd for $C_{15}H_{18}NOP$: C, 69.48; H, 7.00; N, 5.40; found: C, 69.89; H, 7.16; N, 5.23.

(±)-4d



96% Yield. White solid (mp = 177.8-179.0°C)

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (br s, 2H, *NH*$_2$), δ 7.27-7.93 (m, 11H, C*H*), 8.37 (d, $^{3}J_{PH}$= 15.6 Hz, 1H, C*H*)

^{13}C NMR (75 MHz, $CDCl_3$) δ 125.11, 125.34, 127.37, 127.71, 127.84, 128.43, 128.89, 128.91, 128.95, 128.99, 129.13, 129.16, 130.75, 130.92, 130.97, 132.31, 132.52, 132.62, 132.66, 132.71, 133.12, 133.25, 135.89, 135.92

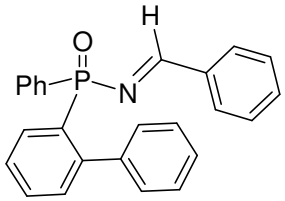
^{31}P NMR(162 MHz, $CDCl_3$) δ 21.89

Anal. calcd for $C_{16}H_{14}NOP$: C, 71.90; H, 5.28; N, 5.24; found: C, 72.05; H, 4.89; N, 4.99.

General experimental procedure for the preparation of (±)-5(b-h)

To a solution of benzaldehyde (1 eq.), the desired phosphinamide (1 eq.) and triethylamine (3 eq.) in dichloromethane at 0°C was added $TiCl_4$ (0.5 eq) dropwise. The reaction mixture was stirred for 2 h before the solvent was removed *in vacuo*. The yellow oily solid was diluted with ethyl acetate and the precipitate filtered through Celite. The filtrate was concentrated *in vacuo*. Crude imine was purified by flash-chromatography (EtOAc 100%) affording pure phosphinoyl benzaldimine.

(±)-5b



59% Yield. White solid (mp = 201.5-202.7°C)

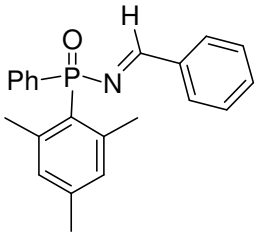
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04-7.06 (m, 4H, C*H*), 7.24-7.44 (m, 7H, C*H*), 7.48-7.53 (m, 3H, C*H*), 7.66-7.76 (m, 5H, C*H*),8.74 (d, $^{3}J_{PH}$= 32.5 Hz, 1H, C*H* imine)

^{13}C NMR (75 MHz, $CDCl_3$) δ 126.75, 126.92, 127.09, 127.52, 127.69, 127.86, 128.01, 128.33, 128.50, 130.14, 130.72, 131.25, 131.69, 131.84, 132.62, 132.73, 132.84, 133.16, 133.30, 134.75, 136.41, 136.75, 141.41, 147.04, 173.80, 173.90 ppm.

^{31}P NMR(162 MHz, $CDCl_3$) δ 25.52.

Anal. calcd for $C_{25}H_{20}NOP$: C, 78.73; H, 5.29; N, 3.67; found: C, 79.01; H, 5.18; N, 3.73.

(±)-5c



67% Yield. White solid (mp = 189.7-193.1°C)

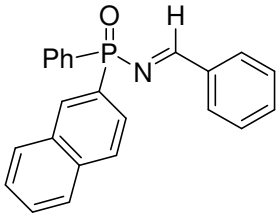
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 3H, *p* -CH_3 Mes), 2.77 (s, 6H, *oo'*-CH_3 Mes), 6.99 (d, $^{4}J_{PH}$= 3.8 Hz, 2H, C*H* arom Mes), 7.33-7.48 (m, 3H, C*H* arom), 7.73-7.77 (m, 2H, C*H* arom), 7.96-8.03 (m, 2H, C*H* arom), 9.65 (d, $^{3}J_{PC}$= 32.6 Hz, 1H, C*H* imine) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2(*p*-CH_3), 23.8 (d, $^{3}J_{PC}$= 3 Hz, *oo'*-CH_3), 125.78, 127.26, 127.38, 127.69, 128.01, 128.33, 128.44, 128.61, 128.84, 130.63, 130.62, 130.72, 130.90, 130.97, 131.01, 131.12, 132.29, 140.66, 143.91, 173.88, 173.99 ppm.

^{31}P NMR(162 MHz, $CDCl_3$) δ 25.92.

Anal. calcd for $C_{22}H_{22}NOP$: C, 76.06; H, 6.38; N, 4.03; found: C, 76.97; H, 6.74; N, 3.93.

(±)-5d



61% Yield. White solid (mp = 206.6-209.1°C)

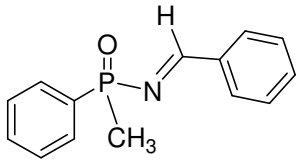
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.61 (m, 11H, C*H*), 7.69-8.01 (m, 5H, C*H*) 8.37 (d, $^{3}J_{PH}$= 15.6 Hz, 1H, C*H*), 9.02 (d, $^{3}J_{PC}$= 32.1 Hz, 1H, C*H* imine) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 125.21, 125.90, 127.35, 127.71, 127.86, 128.02, 128.41, 128.63, 128.71, 128.98, 129.13, 130.24, 131.93, 132.45, 132.66, 132.81, 132.96, 136.20, 140.51 140.57, 172.12, 172.23 ppm.

^{31}P NMR(162 MHz, $CDCl_3$) δ 29.15 ppm

Anal. calcd for $C_{23}H_{18}NOP$: C, 77.74; H, 5.11; N, 3.94; found: C, 76.13; H, 5.99; N, 4.02.

(±)-5e



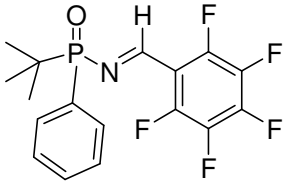
36 % Yield. Colourless oil.[11]

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (d, $^{2}J_{P\text{-}H}$ = 14.4 Hz, 3H, CH_3), 7.52 (m, 6H, C-*H* arom.), 7.94 (m, 4H, C-*H* arom.) 9.19 (d, $^{3}J_{PH}$ = 33.1 Hz, 1H, N=C-*H*), ppm;

^{13}C NMR (100 MHz, $CDCl_3$) δ = 17.3 (d, $^{1}J_{PC}$ = 93.2 Hz, CH_3), 128.7 (d, $^{3}J_{PC}$ = 12.1 Hz, 2 *C*-H arom.), 129.0 (*C*H arom.), 130.2 (*C*H arom.), 131.1 (d, $^{2}J_{PC}$ = 9.2 Hz, *C*H arom.), 132.0 (d, $^{4}J_{PC}$ = 2.6 Hz, *C*H arom.), 133.1 (d, $^{1}J_{PC}$ = 122.1 Hz, *C* quat. arom.), 133.6 (s, 2 *C*H arom.), 135.9 (d, $^{3}J_{PC}$ = 25.3 Hz, *C* quat. arom.), 173.4 (d, $^{3}J_{PC}$ = 8.4 Hz, *C*H imine) ppm

^{31}P NMR (162 MHz, $CDCl_3$) δ = 34.34 ppm

(±)-5f



75% Yield. White solid (mp = 189.3-190.8°C)

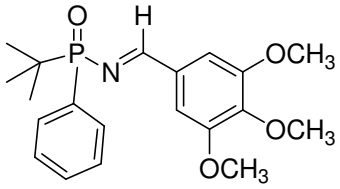
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, $^{3}J_{PH}$ = 15.3 Hz, 9H, 3xCH_3 *t*-Bu), 7.38-7.51 (m, 3H, C-*H* arom), 7.99-8.12 (m, 2H, C-*H* arom) 9.50 (d, $^{3}J_{PH}$ = 29.7 Hz, 1H, C*H* imine) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3(*C*H_3 *t*-Bu), 32.9 (d, $^{1}J_{P\text{-}C}$ = 87.8 Hz, quat. *t*-Bu), 111.1-111.7 (m, *C*F C_6F_5), 128.3 (d, $^{2}J_{P\text{-}C}$ = 11.3 Hz, *C*H arom.), 130.2 (d, $^{1}J_{PC}$ = 112.5 Hz, *C* quat. arom.), 132.1 (d, $^{4}J_{PC}$ = 2.2 Hz, *C*-H arom.), 133.6 (d, $^{3}J_{PC}$ = 7.7 Hz, *C*H arom), 135.7-139.5 (m, *C*F C_6F_5), 145.0-148.5 (m, *C*F C_6F_5), 162.6 (d, $^{2}J_{PC}$ = 4.1 Hz, *C*H imine) ppm.

^{31}P NMR (162 MHz, $CDCl_3$) δ 42.44 ppm.

Anal. calcd for $C_{17}H_{15}F_5NOP$: C, 54.41; H, 4.03; N, 3.73; found: C, 54.36; H, 5.58; N, 3.72.

(±)-5g



81% Yield. White solid (mp = 199.6-201.8°C)

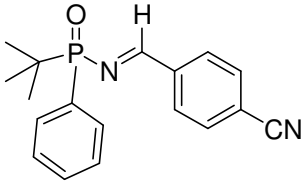
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (d, $^3J_{PH}$ = 14.7Hz, 9H, 3xC*H*$_3$ *t*-Bu), 3.58 (s, 6H, *mm'*-OC*H*$_3$), 4.04 (s, 3H, *p*-OC*H*$_3$), 6.85 (s, 2H, C*H* arom), 7.29-7.48 (m, 3H, C*H* arom), 7.54-8.06 (m, 2H, C-*H* arom) 9.60 (d, $^3J_{PH}$= 29.3 Hz, 1H, C*H* imine) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7 (*C*H$_3$ *t*-Bu), 33.1 (d, $^1J_{PC}$ = 89.2 Hz, quat. *t*-Bu), 55.8 (*mm'*-O*C*H$_3$), 60.5 (*p*-O*C*H$_3$), 107.6 (*C*H arom), 128.1 (d, $^2J_{PC}$ = 11.5 Hz, *C*H arom.), 130.0 (d, $^1J_{PC}$ = 117.3 Hz, *C* quat. arom.), 132.1(d, $^4J_{PC}$ = 2.2 Hz, *C*-H arom.), 132.2 (*C* quat. arom.) 133.6 (d, $^3J_{PC}$ = 7.7 Hz, *C*H arom), 136.8 (d, $^3J_{P\text{-}C}$ = 7.3 Hz, *C* quat. arom.), 151.7 (*C* quat. arom.), 174.6 (d, $^2J_{PC}$ = 7.4 Hz, *C*H imine) ppm.

^{31}P NMR (162 MHz, $CDCl_3$) δ 41.14 ppm.

Anal. calcd for $C_{20}H_{26}NO_4P$: C, 63.99; H, 6.98; N, 3.73; found: C, 63.02; H, 7.066; N, 3.52.

(±)-5h



88% Yield. White solid (mp = 197.7-199.3°C)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, $^3J_{PH}$ = 15.4 Hz, 9H, 3xC*H*$_3$ *t*-Bu), 7.47-7.55 (m, 3H, C*H* arom), 7.80 (d, ^3J= 8.3 Hz, 2H, C*H* arom), 7.93-8.00 (m, 2H, C-*H* arom), 8.08 (d, ^3J= 8.3 Hz, 2H, C*H* arom), 9.24 (d, $^3J_{PH}$= 28.8 Hz, 1H, C*H* imine) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4 (*C*H$_3$ *t*-Bu), 33.5 (d, $^1J_{P\text{-}C}$ = 87 Hz, quat. *t*-Bu), 116.4 (*C* quat, *C*≡N), 128.1 (*C*Harom.), 118.1 (*C* quat. arom.), 128.2 (d, $^2J_{PC}$ = 9 Hz, *C*H arom), 129.7 (*C*H arom), 131.5 (d, $^1J_{PC}$ = 111 Hz, *C* quat. arom.), 131.9 (d, $^4J_{PC}$ = 2.3 Hz, *C*H arom.), 132.3 (d, $^3J_{PC}$ = 7.7 Hz, *C*H arom), 139.0 (*C* quat. arom.), 172.4 (d, $^3J_{PC}$ = 7.5 Hz, *C*H imine) ppm.

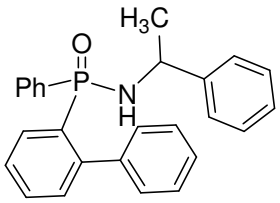
^{31}P NMR (162 MHz, $CDCl_3$) δ 43.49 ppm.

Anal. calcd for $C_{18}H_{19}N_2OP$: C, 69.67; H, 6.17; N, 9.03; found: C, 68.28; H, 6.21; N, 8.72.

General experimental procedure for 1, 2 Grignard additions to N-phosphinoylaldimines 5(b-e)

Methyl magnesium bromide (3 M solution in diethyl ether, 3 equiv., 0.6 mmol, 200 µL) was added dropwise at 0°C to a solution of the desired phosphinamide (1equiv., 0.2 mmol) in dichloromethane (1.5 mL). The mixture was stirred at room temperature for 3h, then cooled to 0°C, quenched with aqueous $KHSO_4$ (0.5 M, 10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic phases were washed once with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue solid was purified by flash chromatography.

(**6b**-**6b'**)/(**7b**-**7b'**)



Major/minor = 65 : 35. 89% Yield. White solid (mp = 211.0-213.1°C)

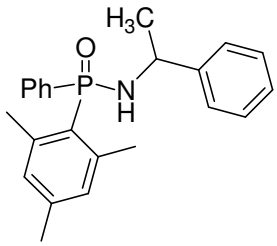
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, ^3J= 6.8 Hz, 1H, HC*CH*$_3$ minor),1.30 (d, ^3J= 6.8 Hz, 1H, HC*CH*$_3$ major), 2.64 (br t, $^2J_{PH}$ = $^3J_{HCNH}$ = 8.3 Hz, 1H, N*H* minor+major), 3.99-4.07 (m, 1H, C*H*NH min), 4.26-4.39 (m, 1H, C*H*NH major), 6.97-7.72 (m, 19H, C*H* arom. minor+major) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1 (d, $^3J_{PC}$ = 4.7 Hz, HC-*C*H$_3$ major), 26.4 (d, $^3J_{PC}$ = 4.5 Hz, HC-*C*H$_3$ minor), 49.7 (HNC*H* minor), 50.7(HNC*H* major), 126.11, 126.67, 126.93, 127.5, 127.78, 128.04, 128.21, 128.43, 129.67, 131.08, 131.42, 131.5, 132.28, 132.34, 133.09, 133.21, 140.89, 131.37, 131.43, 131.51, 132.24, 132.33, 133.18, 133.34, 135.07, 137.01, 138.25, 140.89, 144.9, 144.86, 145.03, 145.27, 145.41 ppm.

^{31}P NMR (162 MHz, $CDCl_3$) δ 25.13 (major), 26.86 (minor).

Anal. calcd for $C_{26}H_{24}NOP$: C, 78.57; H, 6.09; N, 3.52; found: C, 78.46; H, 6.13; N, 3.73.

(**6c**-**6c'**)/(**7c**-**7c'**)



Major/minor = 70 : 30. 79% Yield. White solid (mp = 207.4-209.7°C)

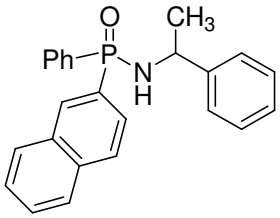
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (d, *J*= 6.8 Hz, 1H, HC*CH*$_3$ minor),1.57 (d, *J*= 6.8 Hz, 1H, HC*CH*$_3$ major), 2.19 (s, 3H, *p* -C*H*$_3$ Mes major), 2.21(s, 3H, *p* -C*H*$_3$ Mes minor), 2.28 (s, 6H, *oo'*-C*H*$_3$ Mes major), 2.39 (s, 6H, *oo'*-C*H*$_3$ Mes minor), 2.99 (br t, $^{2}J_{PH}$ = $^{3}J_{HCNH}$ = 8.3 Hz, 1H, N*H* minor+major), 4.39-4.51 (m, 1H, C*H*NH major), 4.53-4.67 (m, 1H, C*H*NH minor), 6.74 (d, $^{4}J_{PH}$= 3.8 Hz, 2H, C*H* arom Mes, major), 6.82 (d, $^{4}J_{PH}$= 3.8 Hz, 2H, C*H* arom Mes, minor), 7.11-7.16 (m, 5H, C*H* arom major), 7.18-7.38 (m, 11H, C*H* arom major + minor), 7.46-7.54 (m, 2H, C*H* arom minor), 7.57-7.65 (m, 2H, C*H* arom major) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (*p*-*C*H$_3$ Mes, major), 21.1 (*p*-*C*H$_3$ Mes, minor), 23.7 (d, $^{3}J_{PC}$= 3.3 Hz, *oo'*-*C*H$_3$ Mes, major), 23.9 (d, $^{3}J_{PC}$= 3.3 Hz, *oo'*-*C*H$_3$ Mes, minor), 25.7 (d, $^{3}J_{PC}$ = 3.6 Hz, HC*C*H$_3$ major), 25.9 (d, $^{3}J_{PC}$ = 2.9 Hz, HC*C*H$_3$ minor), 50.7 (HNC*H* minor), 51.2 (HNC*H* major), 124.45, 125.89, 126.11, 126.23, 127.04, 127.12, 127.91, 128.18, 128.26, 128.41, 128.53, 128.57, 130.45, 130.62, 130.81, 131.05, 131.06, 131.23, 131.54, 131.56, 135.63, 135.66 135.88, 137.56, 141.28, 141.45, 143.03, 143.22, 143.40, 143.61, 145.13, 145.22, 145.52, 145.65 ppm.

^{31}P NMR (162 MHz, $CDCl_3$) δ 26.95 (major), 27.45 (minor).

Anal. calcd for $C_{23}H_{26}NOP$: C, 76.01; H, 7.21; N, 3.85; found: C, 76.75; H, 7.08; N, 4.07.

(**6d**-**6d'**)/(**7d**-**7d'**)



Major/minor = 55 : 45. 81% Yield. White solid(mp = 204.6-205.9°C)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, ^{3}J= 6.8 Hz, 1H, HC*CH*$_3$ minor),1.29 (d, ^{3}J= 6.8 Hz, 1H, HC*CH*$_3$ major), 2.78 (br t, $^{2}J_{PH}$ = $^{3}J_{HCNH}$ = 8.3 Hz, 1H, N*H* minor+major), 4.01-4.19 (m, 1H, C*H*NH min), 4.21-4.29 (m, 1H, C*H*NH major), 7.12-7.72 (m, 19H, C*H* arom. minor+major), 8.34 (d, $^{3}J_{PH}$= 15.6 Hz, 1H, C*H* minor) 8.37 (d, $^{3}J_{PH}$= 15.6 Hz, 1H, C*H* major),ppm.

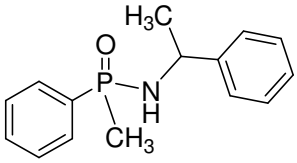
^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3 (d, $^{3}J_{P-C}$ = 4 Hz, HC*C*H$_3$ major), 25.8 (d, $^{3}J_{P-C}$ = 3.7 Hz, HC*C*H$_3$ minor), 49.7 (HNC*H* minor), 50.7(HNC*H* major), 125.04, 125.16, 125.44, 127.22, 127.45,

127.78, 127.96, 128.03, 128.27, 128.53, 128.54, 128.78, 128.89, 129.01, 129.23, 129.72, 129.85, 129.93, 130.04 130.23, 130.38, 130.72, 130.94, 131.76, 131.88, 132.23, 132.40, 132.71, 132.76, 132.93, 135.13, 135.22, 135.35 ppm.

^{31}P NMR (162 MHz, $CDCl_3$) δ 25.13 (major), 26.86 (minor).

Anal. calcd for $C_{24}H_{22}NOP$: C, 77.61; H, 5.97; N, 3.77; found: C, 78.33; H, 5.04; N, 4.06.

(**6e**-**6e'**)/(**7e**-**7e'**)

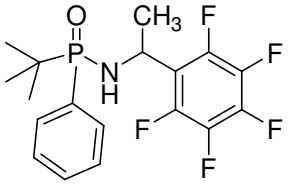


Major/minor = 70 : 30. 91% Yield. White solid

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (d, ^{3}J= 6.8 Hz, 3H, HC*CH*$_3$ minor), 1.54 (d, $^{2}J_{PC}$= 15 Hz, 3H, P-C*H*$_3$ minor) 1.55 (d, ^{3}J= 6.8 Hz, 3H, HC*CH*$_3$ major), 1.63 (d, $^{2}J_{PC}$= 15 Hz, 3H, P-C*H*$_3$ major), 2.30 (br s, 1H, N*H* major), 2.99 (br s, 1H, N*H* minor), 4.19-4.26 (m, 1H, C*H*NH major), 4.50-4.57 (m, 1H, C*H*NH minor), 7.17-7.28 (m, 3H, C*H* arom. minor+major), 7.33-7.41 (m, 3H, C*H* arom. minor+major), 7.46-7.56 (m, 2H, C*H* arom. minor+major), 7.69-7.75 (m, 2H, C*H* arom. major), 7.83-7.88 (m, 2H, C*H* arom. minor) ppm.

^{31}P NMR (162 MHz, $CDCl_3$) δ 29.69 (major), 30.32 (minor).

19(**a**-**b**)/(**a'**-**b'**)



Major/minor = 75 : 25. 75% Yield.

Major (59% yield). Pale yellow solid (mp = 205.4-207.8°C)
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, $^{3}J_{PH}$ = 15.1 Hz, 9H, 3xC*H*$_3$ *t*-Bu), 1.62 (d, ^{3}J= 7 Hz, 1H, HC*CH*$_3$), 3.01 (br t, $^{2}J_{PH}$= $^{3}J_{HCNH}$= 10.2 Hz, 1H, N*H*), 4.64-4.68 (m, 1H, C*H*NH), 7.29-7.35 (m, 2H, C*H* arom), 7.43-7.46 (m, 1H, C*H* arom), 7.57-7.61 (m, 2H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2 (HC*C*H$_3$), 24.8 (*C*H$_3$ *t*-Bu, minor), 32.1(d, $^{1}J_{PC}$ = 89.5 Hz, *C* quat. *t*-Bu), 42.1(*C*HNH), 118.1-118.3 (m, *C*F C_6F_5), 127.9(d, $^{2}J_{PC}$= 11.5 Hz, *C*H arom), 128.8(d, $^{1}J_{PC}$= 117.5 Hz, *C* quat arom), 131.8(*C*H arom), 133.3(d, $^{3}J_{PC}$= 8.5 Hz, *C*H arom), 135.6-136.0 (m, *C*F C_6F_5), 138.3-139.2 (m, *C*F C_6F_5) 145.8-146.2 (m, *C*F C_6F_5) ppm.

^{31}P NMR (162 MHz, $CDCl_3$) δ 42.07

Anal. calcd for $C_{18}H_{19}F_5NOP$: C, 55.25; H, 4.89; F, 24.28; N, 3.58; found: C, 55.34; H, 4.87; N, 3.52.

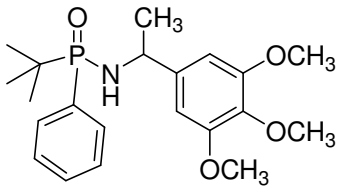
Minor (16% yield). Pale yellow solid(mp = 208.3-209.1°C)
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, $^3J_{PH}$ = 15.1 Hz, 9H, 3xCH_3 *t*-Bu), 1.54 (d, ^3J= 7 Hz, 1H, HCCH_3), 3.40(br t, $^2J_{PH}$= $^3J_{HCNH}$= 10.2 Hz, 1H, N*H*), 4.55-4.68(m, 1H, C*H*NH), 7.24-7.57(m, 3H, C*H* arom), 7.43-7.46(m, 1H, C*H* arom), 7.78-7.85 (m, 2H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6 (d, $^3J_{PC}$= 8.2 Hz, HC*C*H_3), 24.6 (*C*H_3 *t*-Bu, minor), 32.1(d, $^1J_{PC}$ = 88.9 Hz, *C* quat. *t*-Bu), 42.2 (*C*HNH), 118.1-119.2 (m, *C*F C_6F_5), 128.3 (d, $^2J_{PC}$= 11.5 Hz, *C*H arom), 129.3(d, $^1J_{PC}$= 118.6 Hz, *C* quat arom), 131.9(*C*H arom), 133.5(d, $^3J_{PC}$= 8.5 Hz, *C*H arom) 135.7-136.0 (m, *C*F C_6F_5), 131.3-139.6 (m, *C*F C_6F_5) 142.6-146.2 (m, *C*F C_6F_5) ppm.

^{31}P NMR (162 MHz, $CDCl_3$) δ 42.07

Anal. calcd for $C_{18}H_{19}F_5NOP$: C, 55.25; H, 4.89; F, 24.28; N, 3.58; found: C, 55.19; H, 4.73; N, 3.63.

20(**a**-**b**)/(**a'**-**b'**)



Major/minor = 70 : 30. 75% yield.

Major (62% yield). White solid(mp = 199.6-201.1°C)
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (d, $^3J_{PH}$ = 14.7 Hz, 9H, 3xCH_3 *t*-Bu), 1.42 (d, ^3J= 6.8 Hz, 1H, HCCH_3), 2.85 (br s, 1H, N*H*), 3.83 (s, 3H, *p*-OCH_3), 3.87 (s, 6H, *mm'*-OCH_3), 4.41 (br s, 1H, C*H*NH), 6.74 (s, 2H, C*H* arom) 7.48-7.52 (m, 3H, C*H* arom), 7. 78-7.89 (m, 2H, C*H* arom) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3 (d, *J*= 4.1 Hz, HC*C*H_3), 24.8 (*C*H_3 *t*-Bu, minor), 32.2(d, $^1J_{PC}$ = 89.7 Hz, *C* quat. *t*-Bu), 49.7(*C*HNH), 56.2 (*mm'*-O*C*H_3), 60.8 (*p*-O*C*H_3), 103.7 (*C*H arom) 128.1 (d, $^2J_{PC}$= 11.5 Hz, *C*H arom), 130.6 (d, $^1J_{PC}$= 117.5 Hz, *C* quat arom), 131.6 (*C*H arom), 133.6 (d, $^3J_{PC}$= 8.5 Hz, *C*H arom), 137.0 (*C* quat.), 141.1 ($^3J_{P\text{-}C}$ = 6.3 Hz, *C* quat. arom), 153.2 (*C* quat.) ppm

^{31}P NMR (162 MHz, $CDCl_3$) δ 41.75 ppm

Anal. calcd for $C_{21}H_{30}NO_4P$: C, 64.43; H, 7.72; N, 3.58; found: C, 63.66; H, 7.71; N, 3.38.

Minor (19% yield). White solid (mp = 198.2-200.0°C)

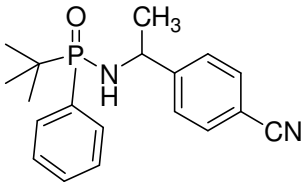
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, $^{3}J_{PH}$ = 14.7 Hz, 9H, 3xC*H*$_3$ *t*-Bu), 1.57 (d, ^{3}J= 6.8 Hz, 1H, HC*CH*$_3$), 2.77 (br t, $^{2}J_{PH}$= $^{3}J_{HCNH}$= 8.9 Hz, 1H, N*H*), 3.77 (s, 6H, *mm'*-OC*H*$_3$), 3.81 (s, 3H, *p*-OC*H*$_3$), 4.64-4.68 (m, 1H, C*H*NH), 6.41 (s, 2H, C*H* arom) 7.29-7.35 (m, 2H, C*H* arom), 7.41-7.46 (m, 1H, C*H* arom), 7.62-7.68 (m, 2H, C*H* arom) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9 (*C*H$_3$ *t*-Bu, minor), 25.7 (HC*C*H$_3$),32.1(d, $^{1}J_{P-C}$ = 89.2 Hz, *C* quat. *t*-Bu), 50.7(*C*HNH), 56.1 (*mm'*-O*C*H$_3$), 60.8 (*p*-O*C*H$_3$), 103.2 (*C*H arom) 127.7(d, $^{2}J_{PC}$= 11.5 Hz, *C*H arom), 129.6 (d, $^{1}J_{PC}$= 117.5 Hz, *C* quat arom), 131.4 (*C*H arom), 133.9 (d, $^{3}J_{PC}$= 8.5 Hz, *C*H arom), 136.9 (*C* quat.), 141.0 ($^{3}J_{PC}$ = 6.3 Hz, *C* quat. arom), 153.2 (*C* quat.) ppm

^{31}P NMR (162 MHz, $CDCl_3$) δ 40.90 ppm

Anal. calcd for $C_{21}H_{30}NO_4P$: C, 64.43; H, 7.72; N, 3.58; found: C, 63.90; H, 7.73; N, 3.41.

21(**a**-**b**)/(**a'**-**b'**)



Major/minor = 70 : 305. 75% yield (mp = 201.7-204.3°C).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, $^{3}J_{PH}$ = 13.4 Hz, 9H, 3xC*H*$_3$ *t*-Bu minor), 1.14 (d, $^{3}J_{PH}$ = 13 Hz, 9H, 3xC*H*$_3$ *t*-Bu major), 1.44 (d, ^{3}J= 6.9 Hz, 1H, HC*CH*$_3$ minor), 1.56 (d, ^{3}J= 6.9 Hz, 1H, HC*CH*$_3$ major), 2.93 (br m, 1H, N*H* major+minor), 4.30-4.51 (m, 1H, CHNH, major+minor), 7.30-7.87 (m, 9H, CH arom major+minor)

^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7 (HC*C*H$_3$ major), 24.8(*C*H$_3$ *t*-Bu, minor) , 24.9(*C*H$_3$ *t*-Bu major) 26.2 (d, $^{3}J_{P-C}$ = 3.7 Hz, HC*C*H$_3$ minor), 32.3 (d, $^{1}J_{P-C}$ = 89.2 Hz, *C* quat. *t*-Bu, major), 32.4 (d, $^{1}J_{P-C}$ = 89.5 Hz, *C* quat. *t*-Bu. major), 49.7 (HNC*H* minor), 50.3(HNC*H* major), 110.8 (C quat *C*≡N major + minor), 118.8, 118.9, 126.1, 126.9, 127.1, 128.1, 128.3, 131.6, 131.7, 131.8, 131.7, 131.8, 132.3, 133.4, 133.5, 133.6, 133.7, 150.7, 150.8, 150.9 ppm.

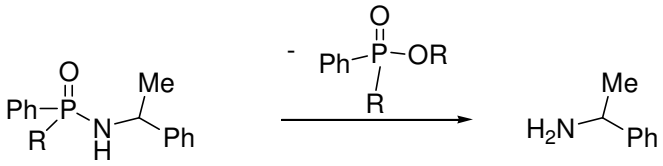
^{31}P NMR (162 MHz, $CDCl_3$) δ 41.15 (major), 42.54 (minor).

Anal. calcd for $C_{19}H_{23}N_2OP$: C, 69.92; H, 7.10; N, 8.58; found: C, 69.76; H, 7.01; N, 8.96.

3.5 Enclosure

3.5.1 Deprotection tests

While *P*,*P*-diphenyl-*N*-phosphinoylamines are known to be easily deprotected under mild conditions such as slightly acidic solutions, we encountered considerable difficulties in the deprotection of *P*-*t*-butyl-*P*-phenyl-*N*-phosphinamide. An overall account of all the attempts realized for the cleavage of the P-N bond is done in the Table 3.1 below.



R= H, Me

Entry	*R*	*Conditions*	*Yield (%)*
1	Ph	1.5 M HCl, MeOH,rt	96
2	*t*-Bu	1.5 M HCl, MeOH, rt	0[a]
3	*t*-Bu	1.5M HCl, MeOH, 60°C microwaves	0[a]
4	*t*-Bu	1.5 M HCl, MeOH, reflux	0[a]
5	*t*-Bu	1.5M HCl, MeOH, 100°C, microwaves	0[a]
6	*t*-Bu	2N HCl, 35:65 Diox-H_2O, 50°C	0[a]
7	*t*-Bu	2N HCl, 35:65 Diox-H_2O, 80°C	--[b,c]
8	*t*-Bu	2N HCl, 35:65 Diox-H_2O, 100°C	--[b,c]
9	Ph	2N HCl, 35:65 Diox-H_2O, 80°C	--[b,c]
10	*t*-Bu	2N HCl, 1:1 Diox-H_2O, 80°C	0[a]
11	*t*-Bu	2N HCl, 70:30 Diox-H_2O, 80°C	0[a]
12	*t*-Bu	HCl conc., rt	0[a]
13	*t*-Bu	HCl conc., 90°C	--[b]
14	*t*-Bu	HCl conc., 80°C microwaves	--[b]
15	*t*-Bu	TFA, MeOH, reflux	0[a]
16	*t*-Bu	TfOH, MeOH, rt	--
17	*t*-Bu	$HSiCl_3$, NEt_3, Toluene, 70°C[d]	--[d]
18	*t*-Bu	$SOCl_2$, 1,2dichloroethane, reflux[e]	--[b,c,e]

Unless otherwise specified, every reaction was treated with 2N HCl aq. and the resulting mixture was extracted with EtOAc. The organic phase, containing the phosphinic acid or methyl ester and/or the unreacted phosphinamide was separated off. The acidic aqueous phase, containing the cleaved amine, was then basified with NaOH until pH=12 and extracted with EtOAc. [a]Starting material recovered after acidic or basic work-up. [b]Degradation of the cleaved amine. [c]Phosphinic acid recovered. [d]Quenched with water. [e]Quenched with aq. $NaHCO_3$

Table 3.1: Cleavage of P-N bond of t-butylpthenylphosphinamide

On the model reaction (Table 3.1, entry 1) the free phenylethylamine is isolated with 96% yields after 16h et room temperature in 1.5M HCl using methanol as solvent. Unfortunately, the cleavage of *P*-*t*-butyl-*P*-phenyl-*N*-phosphinamide under the same acidic conditions didn't take place at rt and reflux (Table 3.1, entries 2 and 4) or by using a microwave source and

heating at 60 or 100°C (Table 3.1, entries 3 and 5). In these cases the starting material has been entirely recovered. In order to increase the temperature, a mixture of dioxane and water was used as solvent at different temperature and positive gradient of dioxane. When the reaction is carried out in a 2N solution of HCl in 35:65 dioxane-water no reaction occurred at 50°C after several hours (Table 3.1, entry 6). By contrast, heating up to 80°C or 100°C, only degradation products were detected by GC and ^{1}H NMR (Table 3.1, entries 7 and 8). Surprisingly, the corresponding phosphinic acid was isolated in high yields after acidic work-up. This fact suggests that the cleavage took place and the free amine underwent to degradation processes in the acidic environment. The case in entry 9 could be useful to explain the reason why the isolation of the free amine is impossible under these conditions. Indeed, the deprotection of *P*,*P*-diphenyl-*N*-phosphinoylamine, seems to be complete in 2 hours. Additional 3 hours under the same conditions caused the degradation of the free amine formed just before. The correspondent phosphinic acid was isolated with 98% after acidic work-up. By rising up the percentage of dioxane in the mixture dioxane-water no noticeable improvements are brought (Table 3.1, entries 10 and 11) and starting materials are entirely recovered after work-up. As expected, using concentrated HCl we observed a complete degradation of the starting phosphinamide at 90 °C (Table 3.1, entry 12) and 80°C under microwaves irradiation (Table 3.1, entry 14). Unfortunately, at room temperature the phosphinamide is not soluble and no reaction occurs (Table 3.1 entry 13). Trifluoroacetic acid, which is a stronger acid than hydrochloric acid, was completely uneffective for the deprotection (Table 3.1, entry 15) whereas triflic acid as well as trichlorosilane, that has been successfully used in the deprotection of chiral 1,2-ethylenediamines,[22] afforded only complicated mixture degradation products (Table 3.1, entries 16 and 17). Finally, the use of thionyl chloride in 1,2-dichloroethane under reflux causes the cleavage of the P-N bond and the corresponding phosphinic acid was isolated in nearly quantitative yield. Nevertheless no amine was found after basic work-up (Table 3.1, entry 18).

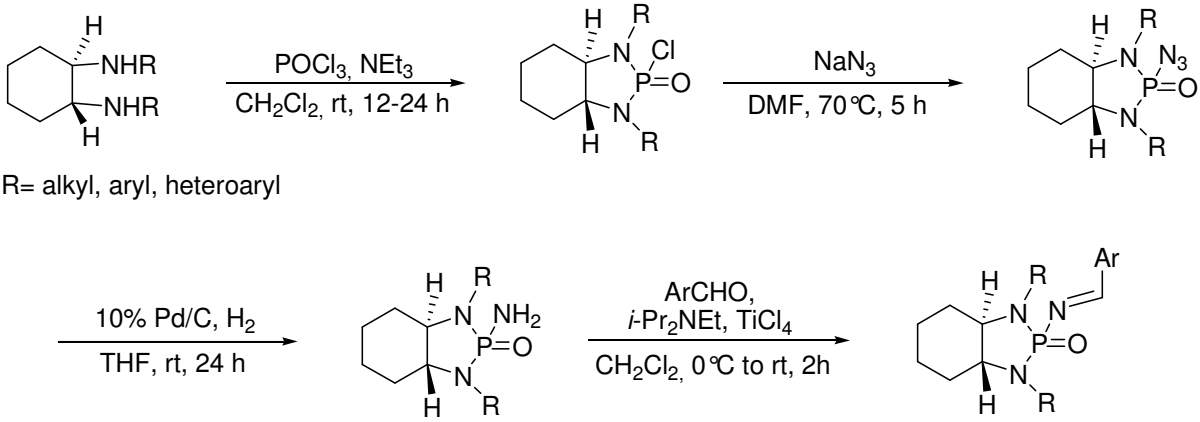
3.5.2 Synthesis of new chiral enantiopure TADDOL-derived *N*-phosphorylbenzaldimine and application to the nucleophilic addition of organometallic reagents.

3.5.2.1 Introduction

In continuation of our studies on the synthesis of new chiral *N*-phosphinoylimines, we developed a synthetic strategy to a new chiral C_2-symmetry TADDOL-derived *N*-phosphorylimine and we tested their effectiveness in the addition of a Grignard reagent. In this paragraph we will describe the results of these studies. Indeed, chiral C_2-symmetry *N*-phosphorylaldimines were already known since several recent reports of Li and coworkers who strongly contribute to develop this completely unexplored chemistry. Starting from the C2-symmetry 1,2 diaminocyclohexane, they accomplished the synthesis of the chiral phosphoramidate[51] in three steps on 40 g scale with consistent chemical yields of more than

[51] (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2581-2627 (b) Denmark, S. E. *Nature* **2006**, *443*, 40-41

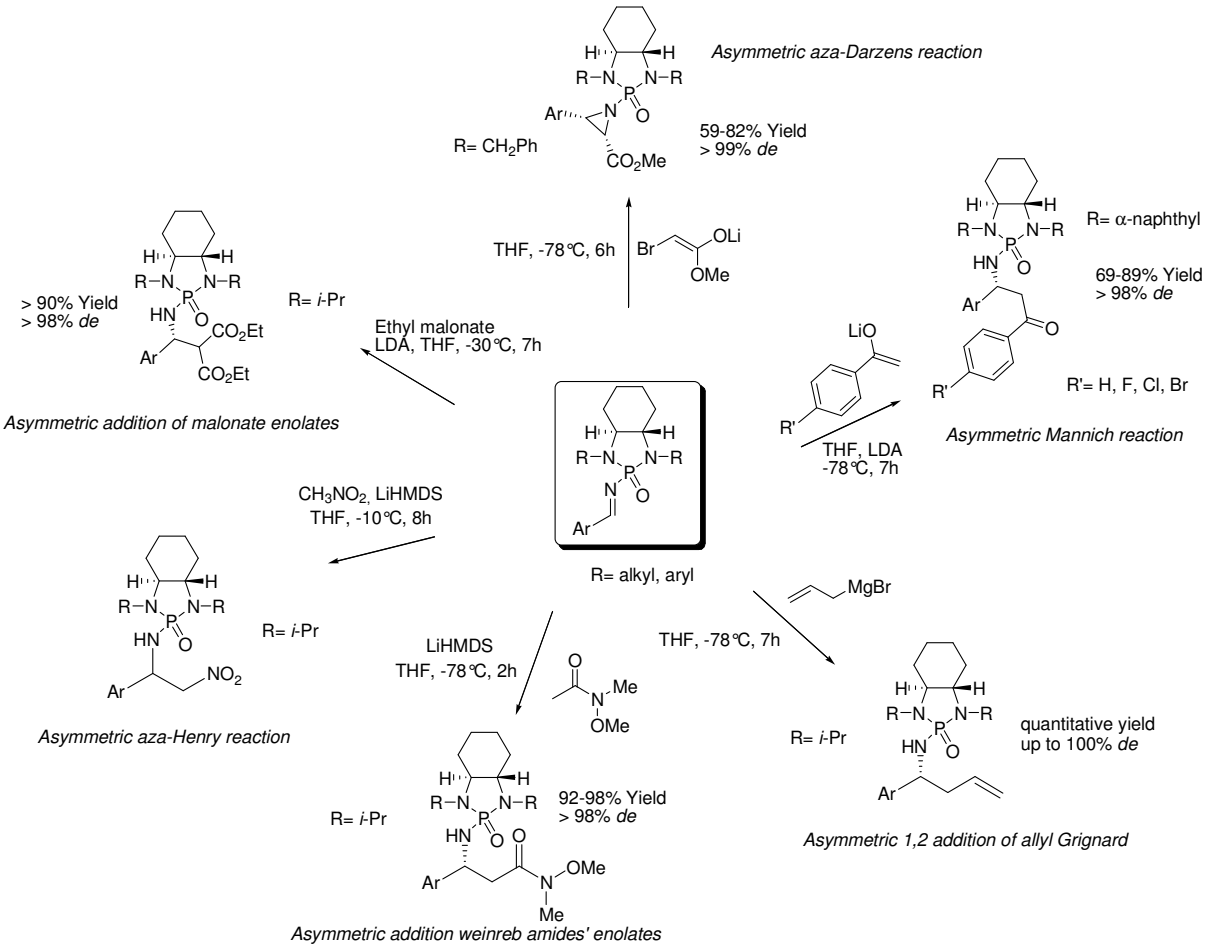
90% and achieved the synthesis corresponding imine according to the method previously developed by Jennings[3](Scheme 3.28).



Scheme 3.28 : Synthesis of chiral C_2 symmetry P-(R,R)- diaminocyclohexyl-N-phosphorylimines

Basing on this chiral C_2 symmetry N-phosphorylimines, they developed many nucleophilic reactions such as asymmetric aza-Darzens reaction, [52] aza-Henry reaction,[53] Mannich reaction,[54] additions of Grignard reagents[55] and addition of various enolates[56] with excellents results in term of yields and diastereomeric excess of final products. A rapid overview of such reactions is done in the Scheme 3.29.

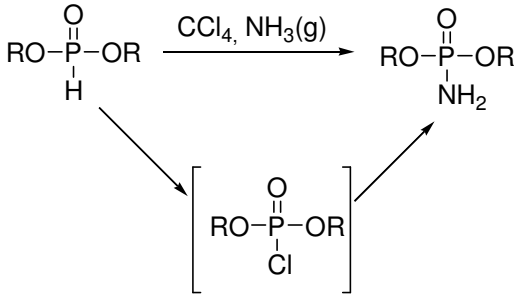
[52] Kattuboina, A.; Li, G. *Tetrahedron Lett*. **2008**, *49*, 1573-1577
[53] Kattuboina, A.; Kaur, P.; Ai, T.; Li, G. *Chem. Biol. Drug Des.* **2008**, *71*, 216-223
[54] (a) Han, J.; Ai, T.; Li, G. *Synthesis* **2008**, 2519-2526; (b) Han, J.; Ai, T.; Nguyen, T. Li, G. Chem. Biol. Drug Des. **2008**, *72*, 120-126; (c) Ai, T.; Han, J.; Chen, Z. -X.; Li, G. *Chem. Biol. Drug Des*. **2009**, *73*, 203-208
[55] Kattuboina, A.; Kaur, P.; Nguyen, T.; Li, G. *Tetrahedron Lett.* **2008**, *49*, 3772-3724
[56] (a) Chen, Z. -X.; Ai, T.; Kaur, P.; Li, G. *Tetrahedron Lett.* **2009**, *50*, 1079-1081; (b) Kaur, P.; Nguyen, T.; Li, G. *Eur. J. Org. Chem*. **2009**, 212-216; (c) Ai, T.; Li, G. *Bioorg. Med. Chem. Lett.* **2009**, *9*, 3967-3969



Scheme 3.29: Survey reactions of P-(R,R)- diaminocyclohexyl-N-phosphorylimine

3.5.2.2 Synthesis of new chiral enantiopure TADDOL-derived *N*-phosphinoylbenzaldimine

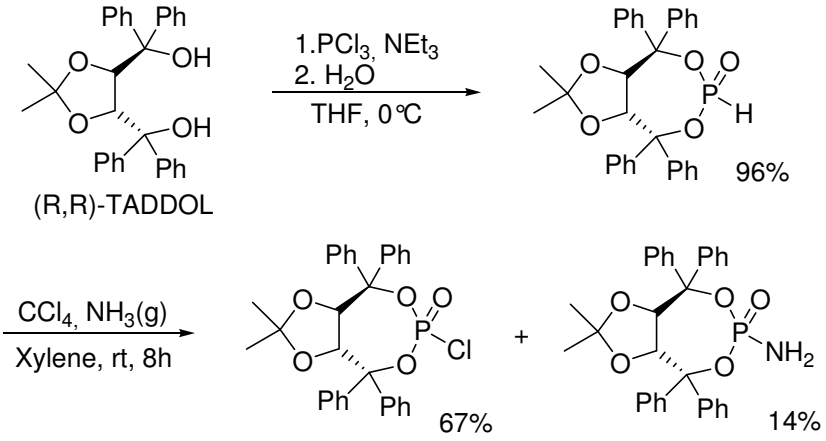
The Atherton-Todd reaction is a synthetically valuable method for the preparation of tetracoordinates phosphorous compounds.[57] The versatility of the reaction results from the fact that the initial products in the reaction are highly reactive chlorophosphates, which are originated from H-phosphinates in presence of carbon tetrachloride and converted *in situ* into their corresponding phosphoramidates in presence of gaseous ammonia (Scheme 3.30).



Scheme 3.30: Atherton-Todd reaction

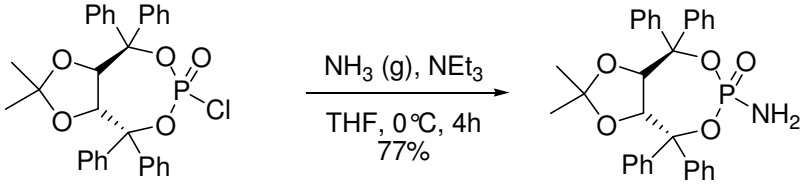
[57] Liu, L.; Li, G.; Zeng, X.; Fu, L.; Cao, R. *J. Heteroatom Chem.* **1996**, *7*, 131-136

Indeed, we prepared a chiral TADDOL-derived phosphoramidate in high yields by using this method. Starting from TADDOL the six membered cyclic H-phosphinate[58] was recovered in 96% by nucleophilic substitution onto the P atom of the phosphorous trichloride. Treatment with carbon tetrachloride under gaseous ammonia flow in xylene at room temperature provided a mixture of phosphoryl chloride in 67% yield and phosphoramidate in only 14% yield.[59]



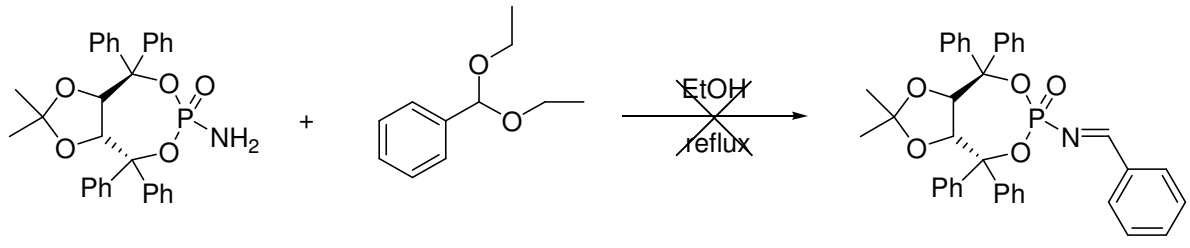
Scheme 3.31: Atherton-Todd reaction applied to chiral TADDOL-derived phosphinate

By using an oxygenated more polar solvent such as THF at 0°C, the phosphoramidate was recovered in better yields starting from the phosphoryl chloride (Scheme 3.32).



Scheme 3.32: Synthesis of chiral TADDOL-derived phosphoramidate

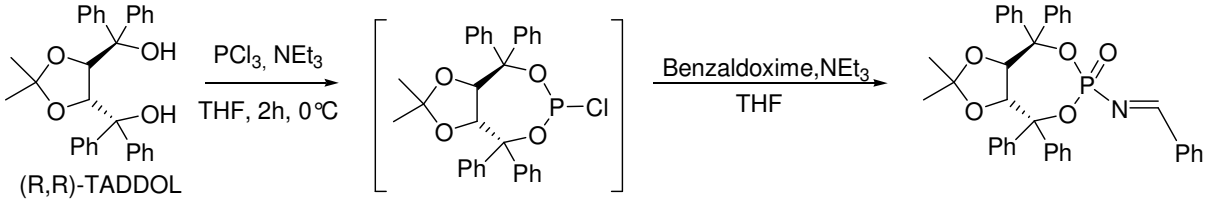
For the synthesis of chiral imine three different methods have been employed. In the first attempt a thermic condensation, in refluxing ethanol, of benzaldehyde diethylacetal with the chiral phosphoramidate has been carried out.[2] Unfortunately the reaction didn't work and the presence of EtOH as solvent allowed to trans-esterification products.

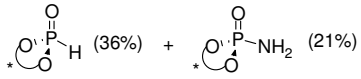
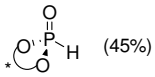
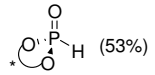


[58] Enders, D.; Tedeschi, L.; Förster, D. *Synthesis* **2006**, 1447-1460
[59] Blum, M. -M.; Löhr, F.; Richardt, A.; Rüterjans, H.; Chen, J. C. -H. *J. Am. Chem. Soc.* **2006**, *128*, 12750-12757

Scheme 3.33: Synthesis of chiral phosphorylimine by condensation of phosphoramidate and benzaldehyde diethylacetal

Alternatively, we decided to use the procedure described by Hudson[5] in which a phosphoryl chloride reacts with an oxime allowing the N-phosphorylimine in high yields after a radical rearrangement. In our case, the phosphoryl chloride intermediate has been formed by reaction of (*R*,*R*)-TADDOL and phosphorous trichloride in THF at 0°C, recovered by filtration under argon and directly used, as THF solution, in the second step. The disappearance of the oxime was monitored by TLC. The results are summarized in the Table 3.2 below.



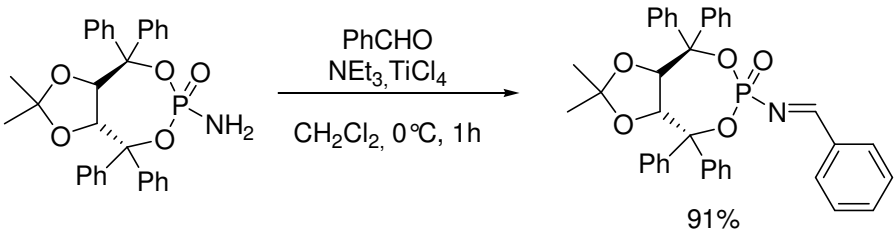
entry	*T (2nd step)*	*t*	*Isolated products (yield)*
1[a]	-30 °C	3h	 (36%) + (21%)
2	-50→20°C	8h	 (45%)
3[b]	-30°C	3.5h	 (53%)

[a]After aqueous work-up. [b]Reversed addition (Oxime solution onto chlorophosphinite).

Table 3.2: Radical reaction onto chiral TADDOL-derived phosphoryl chloride

When the reaction is carried out at -30°C we observed a total consumption of the starting material but the imine presumably formed was hydrolyzed during the work up as well as unreacted phosphoryl chloride which is immediately converted into the H-phosphinate by reacting with water (Table 1, entry 1). Chiral phosphoramidate is recovered in only 21% yield after chromatography. By cooling the reaction mixture at -50°C the reaction didn't take place at all and the H-phosphinate was the major product recovered even after warming to room temperature (Table 1, entry 2). Reversed addition of the oxime to the phosphoryl chloride didn't bring any particular improvements (Table 1, entry 3).

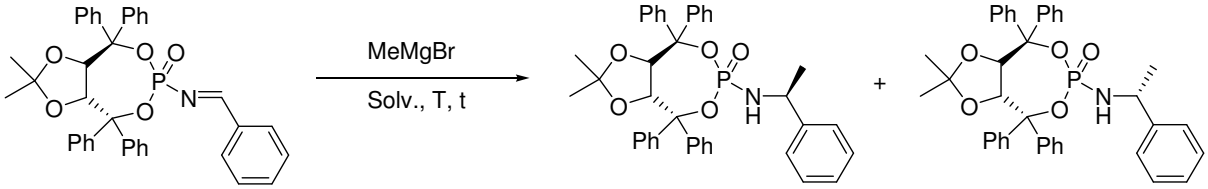
Finally, we decided to apply the method developed by Jennings[3] consisting in a $TiCl_4$ catalysis. Thus, the chiral TADDOL-derived phosphoramidate reacts with benzaldehyde in presence of triethylamine and catalytic amounts of $TiCl_4$ providing the corresponding imine in high yields (Scheme 3.34).



Scheme 3.34: $TiCl_4$/NEt_3 catalysis

3.5.2.3 Grignard additions: preliminary results

The TADDOL-derived *N*-phosphorylbenzaldimine was engaged in the addition of methylmagnesiumbromide under different conditions (solvent and temperature). The results are summarized in the Table 3.3 below.



entry	*Solvent*	*T (°C)*	*t (h)*	*dr*	*Yield (%)*
1	CH_2Cl_2	0	4.5	57:43	89
2	Toluene	0	1h	65:35	94
3	Toluene	-20	5h	65:35	91
4	Toluene	-40	7h	70:30	87

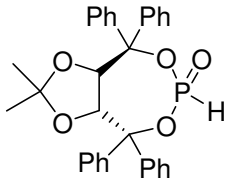
Table 3.3: 1,2 addition of MeMgBr toTADDOL-derived N-phosphorylbenzaldimine

Basing on our previous results on the Grignard reagent additions to the *P*-*t*-butyl-*P*-phenyl-*N*-phopshorylimine (see sections 3.2 and 3.3) we decided to use dichloromethane as solvent at 0°C. Surprisingly, the addition product was recovered in high yields but extremely low diastereomeric ratio (Table 3.3, entry 1) suggesting that the reactivity of this imine highly differs from the previous one. Toluene brought some improvements in yields and diastereomeric excess of addition adducts. At 0°C the reaction is really fast and lead in 1 h to the addition product in high yields and a slightly better dr of 65:35 (Table 3.3, entry 2). Almost the same results are achieved by lowering the temperature from 0 to -20°C hours reaction thus extending reaction times from 1 to 5 hours (Table 3.3, entry 3). At -40°C the addition adduct are isolated in 87% and with a 70:30 diastereomeric ratio after 7 hours (Table 3.3, entry 4).

3.5.2.4 Conclusions

Taking into account our findings in the design of new *P*-chirogenic *N*-phosphinoylimines, in which the differentiation of the two substituent on the P center is at the base of the chiral induction, we introduced a chiral *N*-phosphorylimine in which the source of chirality is originated by a chiral inducer directly linked to the P atom. To this purpose a TADDOL-derived *N*-phosphorylimine was synthesized in few steps with good overall yields. Starting from the (*R*,*R*)-TADDOL and PCl_3, we synthesized the H-phosphinate and the corresponding phosphoramidate was prepared by Aetherton-Todd reaction in presence of CCl_4 and gaseous ammonia. A condensation of benzaldehyde and phosphoramidate under $TiCl_4/NEt_3$ catalysis provided the TADDOL-derived *N*-phosphorylimine. The addition of MeMgBr under different reaction conditions of solvent and temperature was also briefly explored and provided the corresponding adducts in up to 40% de.

3.5.2.5 Experimental part



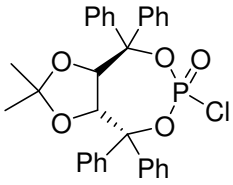
(3R,8R)-2,2-Dimethyl-4,4,8,8-tetraphenylperhydro-6l5-[1,3]dioxolo-[4,5-[1,3,2]dioxaphosphepin-6-one [(R,R)-1][58]

TADDOL (750 mg, 1.61 mmol) was added over 60 min via canula to a solution of PCl_3 (0.195 mL, 2.23 mmol) and Et_3N (0.66 mL) in THF (345 mL) at 0 °C. After 2 h, the precipitated colorless solid was separated by filtration under argon and a previously degassed mixture of H_2O (0.05 mL), Et_3N (0.3 mL) and THF (0.1 mL) was added to the filtrate. After 2 h the precipitated colorless solid was separated off by filtration under argon and the crude product was purified by column chromatography (cyclohexane-Et_2O, 3:2) to give the phosphite (*R*,*R*)-**1** as a colorless solid (780 mg, 95% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.57 (s, 3 H, CC*H*$_3$), 0.76 (s, 3 H, CC*H*$_3$), 5.21 (d, ^3J = 8.2 Hz, 1 H, OC*H*), 5.36 (d, ^3J= 8.0 Hz, 1 H, OCH), 7.08 (d, $^1J_{PH}$ = 726.8 Hz, 1 H, P*H*), 7.25–7.43 (m, 12 H, C*H* arom), 7.57–7.61 (m, 8 H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2(*C*H$_3$), 26.7(*C*H$_3$), 79.8(O*C*H), 80.6(O*C*H), 88.6(Ph-*C*-Ph quat.), 88.7(Ph-*C*-Ph quat.), 114.4(Me-*C*-Me quat.), 126.8(*C*H arom.), 126.9(*C*H arom.), 127.3(*C*H arom.), 127.5(*C*H arom.), 127.9(*C*H arom.), 128.0(*C*H arom.), 128.2(*C*H arom.), 128.3(*C*H arom.), 128.5(*C*H arom.), 128.6(*C*H arom.), 128.7(*C*H arom.), 128.8(*C*H arom.), 138.9(*C* quat arom.), 139.1(*C* quat arom.), 143.2(*C* quat arom.), 143.6(*C* quat arom.) ppm.

^{31}P NMR (162 MHz, CDCl3): δ -3.35 ppm.

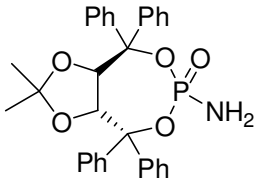


To a stirred solution of TADDOL-derived phosphinoxide (1.46 mmol, 750 mg) in 10 ml of xylene was added tetrachloromethane (1.46 mmol, 0.15 mL). Gaseous ammonia was then passed slowly over 7h at rt. Precipitated ammonium chloride was filtered and washed with xylene. Combined xylene fractions were concentrated in vacuo affording a crude mixture of chlorophosphite and phosphoramidate as white solid. The two products were separated by chromatography:
chlorophosphite (Cyclohexane/EtOAc 4:1): 538.2 mg, 67% yield; phosphoramidate (EtOAc) 105.2 mg, 14% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.58 (s, 3 H, CCH_3), 0.64 (s, 3 H, CCH_3), 5.31 (d, ^{3}J= 7.9 Hz, 1 H, OC*H*), 5.37 (d, ^{3}J= 8.0 Hz, 1 H, OCH), 7.26-7.31 (m, 14 H, C*H* arom), 7.39-7.42 (m, 4 H, C*H* arom), 7.57-7.61 (m, 2 H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 26.5 (CH_3), 26.6 (CH_3), 78.6 (O*C*H), 79.4 (O*C*H), 91.5 (Ph-*C*-Ph quat.), 92.5 (Ph-*C*-Ph quat.), 115.0 (Me-*C*-Me quat.), 126.8 (*C*H arom.), 126.9(*C*H arom.), 127.3(*C*H arom.), 127.5 (*C*H arom.), 128.1 (*C*H arom.), 128.3 (*C*H arom.), 128.4 (*C*H arom.), 128.5 (*C*H arom.), 128.7 (*C*H arom.), 128.8 (*C*H arom.), 128.9 (*C*H arom.), 138.6 (*C* quat arom.), 138.7 (*C* quat arom.), 138.9 (*C* quat arom.), 142.1 (*C* quat arom.) ppm.

^{31}P NMR (162 MHz, $CDCl_3$): δ -9.71.



To a stirred solution of TADDOL-derived chlorophosphite (538.2 mg, 1 mmol) in 10 ml of THF was added triethylamine (0.28 mL, 2 mmol). Gaseous ammonia was then passed slowly over 4h at 0°C in a ice bath. The solvent was then removed and the residue was treated with dichloromethane. The precipitated ammonium chloride was filtered off and the solution was concentrated under reduced pressure affording the crude product as white mousse. Column chromatography (EtOAc) afforded the pure phosphoramidate in 77% yield as white powder (399 mg).

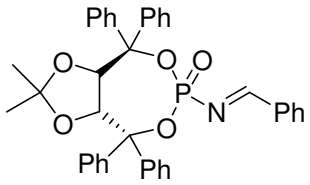
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.64 (s, 3 H, CCH_3), 0.71 (s, 3 H, CCH_3), 2.01 (s, 2H, NH_2), 5.24 (d, $^{3}J_{H-H}$ = 8.1 Hz, 1 H, OC*H*), 5.38 (d, $^{3}J_{H-H}$ = 8.1 Hz, 1 H, OCH), 7.25-7.38 (m, 14 H, C*H* arom), 7.49-7.52 (m, 2H, C*H* arom), 7.57-7.61 (m, 4 H, C*H* arom) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 26.7 (CH_3), 26.6 (CH_3), 79.1 (O*C*H), 79.5 (O*C*H), 86.5 (d, $^{4}J_{PC}$ = 6Hz Ph-*C*-Ph quat.), 88.3 (d, $^{4}J_{PC}$ = 8.5Hz Ph-*C*-Ph quat.), 113. (Me-*C*-Me quat.), 126.8 (*C*H arom.), 126.9 (*C*H arom.), 127.2 (*C*H arom.), 127.6 (*C*H arom.), 128.2 (*C*H arom.), 128.3 (*C*H arom.), 128.4 (*C*H arom.), 128.5 (*C*H arom.), 128.8 (*C*H arom.), 128.9 (*C*H arom.), 138.6 (*C* quat arom.), 138.7 (*C* quat arom.), 138.9 (*C* quat arom.), 142.1 (*C* quat arom.), 143.6 (*C* quat arom.) ppm.

^{31}P NMR (162 MHz, CDCl3): δ -0.24 ppm.

Anal. calcd for $C_{31}H_{30}NO_5P$: C, 70.58; H, 5.73; N, 2.66; found: C, 70.33; H, 5.73; N, 2.57

$[\alpha]_D^{20}$= - 268.5 ° (c 1 $CHCl_3$)



To a solution of benzaldehyde (0.07 mL, 0.57 mmol), TADDOL-derived phosphoramidate (300 mg, 0.57 mmol) and triethylamine (0.32 ml, 2.28 mmol) in dichloromethane at 0°C was added $TiCl_4$ (0.3 ml, 0.3 mmol) dropwise. The reaction mixture was allowed to stir for 2 h before the solvent was removed *in vacuo*. The yellow oily solid was diluted with ethyl acetate and the precipitate filtered through Celite. The filtrate was concentrated *in vacuo*. Crude imine was purified by flash-chromatography (EtOAc 100%) affording pure phosphinoyl benzaldimine (327.9 mg, 91% yield) as a white solid.

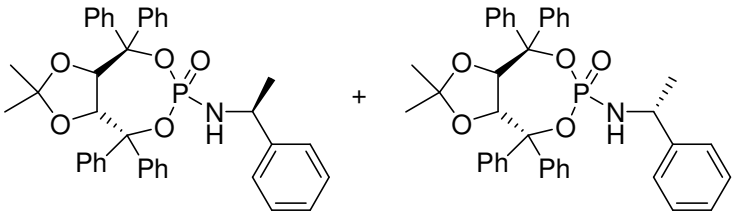
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.41 (s, 3 H, CC*H*$_3$), 0.88 (s, 3 H, CC*H*$_3$), 5.17 (d, ^3J= 8.1 Hz, 1 H, OC*H*), 5.55 (d, ^3J= 8.1 Hz, 1 H, OCH), 6.91-7.55(m, 25 H, C*H* arom), 8.74 (d, $^3J_{PH}$ = 35.6 Hz, 1 H, C*H* imine) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0 (*C*H$_3$), 27.1 (*C*H$_3$), 72.9 (O*C*H), 80.55(O*C*H), 88.1 (Ph-*C*-Ph quat.), 88.3 (Ph-*C*-Ph quat.), 113.4 (Me-*C*-Me quat.), 126.98 (*C*H arom.), 126.9 (*C*H arom.), 127.1 (*C*H arom.), 127.2 (*C*H arom.), 127.4 (*C*H arom.) 127.6 (*C*H arom.), 127.7 (*C*H arom.), 128.0 (*C*H arom.), 128.4 (*C*H arom.), 129.1 (*C*H arom.), 130.4 (*C*H arom.), 133.9 (*C*H arom.), 139.7 (d, $^4J_{PC}$ = 9.3Hz, *C* quat arom.), 140.3 (d, $^4J_{P-C}$ = 6Hz, *C* quat arom.), 143.7 (d, $^3J_{PC}$ = 4.7Hz, *C* quat arom.), 144.1 (*C* quat arom.), 142.1 (*C* quat arom.), 143.6 (*C* quat arom.), 144.1 (*C* quat arom.), 176.0 (d, $^3J_{PC}$ = 6 Hz, 1 H, C*H* imine) ppm.

^{31}P NMR (162 MHz, $CDCl_3$): δ -2.10 ppm.

Anal. calcd for $C_{38}H_{34}NO_5P$: C, 74.13; H, 5.57; N, 2.28; found: C, 74.19; H, 5.43; N, 2.33.

$[\alpha]_D^{20}$= - 189.3 ° (*c* 1 $CHCl_3$)



Methyl magnesium bromide (3 M solution in diethyl ether, 3 equiv., 0.24 mmol, 0.200 mL) was added dropwise at -40°C (acetonitrile-dry ice bath) to a solution of phosphinoyl benzaldimine (1 equiv., 0.08 mmol, 50 mg) in toluene (1.5 mL). The mixture was stirred at room temperature for 3h, then cooled to 0°C, quenched with aqueous $KHSO_4$ (0.5 M, 10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic phases were washed

once with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The slightly yellow oily solid was purified by flash chromatography (EtOAc 100%) affording the two diastereoisomers as white solid with 94% overall yield (dr= 70:30).

^{1}H NMR (300 MHz, CDCl3): δ 0.54(s, 3 H, CC*H*$_3$ Maj), 0.60 (s, 3 H, CC*H*$_3$ min), 0.63(s, 3 H, CC*H*$_3$ Maj), 0.71 (s, 3 H, CC*H*$_3$ min), 1.28 (d, $^3J_{H-H}$ = 7 Hz,3H, CHC*H*$_3$ Maj), 1.46 (d, $^3J_{H-H}$ = 7 Hz,3H, CHC*H*$_3$ min), 3.12 (br t, $^3J_{P-H}$= 11.3 Hz, 1H, N*H* min), 3.47 (br s, 1H, N*H* Maj), 4.01 (sest, J= 7 Hz, C*H*NH Maj), 4.32-4.45 (m, 1H, C*H*NH min), 4.91 (d, $^3J_{H-H}$ = 8.1 Hz, 1 H, OC*H* Maj), 5.12 (d, $^3J_{H-H}$ = 8.1 Hz, 1 H, OC*H* min),5.37 (d, $^3J_{H-H}$ = 8.1 Hz, 1 H, OC*H* Maj), 5.56 (d, $^3J_{H-H}$ = 8.1 Hz, 1 H, OC*H* min), 6.52 (d, *J*= 7.5 Hz, 2H, C*H* arom. min + Maj), 6.90-7.59 (m, 24 H, C*H* arom min + Maj) ppm.

^{31}P NMR (162 MHz, CDCl3): δ -0.28 (Major), -0.32 (minor) ppm.

3.6 References

[1] Weinreb S. M.; Orr, R. K. *Synthesis* **2005**, *8*, 1205–1227.

[2] Zwierzac, A.; Napieraj, A.; *Tetrahedron* **1996**, *52*, 8789-8793.

[3] (a) Jennings, W. B.; Lovely, C. J.; *Tetrahedron Lett.***1988**, *29*, 3725-3728; (b) Jennings, W. B.; Lovely, C. J.; *Tetrahedron* **1991**, *47*, 5561-5567.

[4] Krugjlyak, Y. L.; Leiboskaya, G. A.; Sretenkaya, I. I.; Sheluchenko, V. V.; Martynov, I. V. *Gen.C hem. USSR (Eng. Transl.)* **1968**, *38*, 908-912.

[5] Brown, C.; Hudson, R. F.; Maron, A.; Record, K. A. F. *J. Chem. Soc., Chem. Comm.* **1976**, 663-670.

[6] Côté, A.; Boezio A. A.; Charette, A. B. *Proc. Natl. Acad.Sci. U. S. A.* **2004**, *101*, 5405-5410.

[7] Kresze, G.; Wucherpfennig, W. *Angew. Chem. Int. Ed.* **1967**, *6*, 1431-1434.

[8] Lauzon, C.; Desrosiers, J. -N.; Charette, A. B.; *J. Org. Chem*. **2005**, *70*, 10579-10580.

[9] Harger, M. J. P. J. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2057-2063.

[10] Nudelman, A.; Cram, D. J. *J. Org. Chem.* **1971**, *36*, 335-337.

[11] Benamer, M.; Turcaud, S.; Royer, J. *Tetrahedron Lett.* **2010**, *51*, 645-648.

[12] Xu, Q.; Zhao, C. -Q.; Han, L. -B. *J. Am. Chem. Soc.* **2008**, *130*, 12648-12655.

[13] Férnandez, I.; Khiar,N.; Roca, A.; Benabra, A.; Alcudia, A.; Espatero, J. L.; Alcudia, F. *Tetrahedron Lett.* **1999**, *40*, 2029-2032.

[14] Lam, W.-L.; Haynes, R. K.; Yeung, L.-L.; Chan, W.-K. *Tetrahedron Lett.* **1996**, *37*, 4733-4736.

[15] Harmor, T. A.; Jennings, W. B.; Lovely, C. J.; Reever, K. A. *J. Chem. Soc. Perkin Trans. 2* **1992**, 843-849.

[16] Haynes, R.K.; Au-Yeung, T. -L.; Chan, W. -K.; Lam, W. -L.; Li, Z. -L.; Yeung, L. -L.; Chan, A. S. C.; Li, P.; Koen, M.; Mitchell, C. R.; Vonwiller, C. *Eur. J. Org. Chem.* **2000**, 3205-3216.

[17] (a) Aaron, H.; Shryne, T. M.; Miller, J. I. *J. Am. Chem. Soc.* **1958**, *80*, 107-109; (b) Harger, M. J. P. *J. Chem. Soc. Perkin Transl. 2* **1978**, 326-331.

[18] Holt, J.; Maj, A. M.; Schudde, E. P.; Pietrusiewicz, M; K.; Sieron, L.: Wiekzorek, W.; Jerphagnon, T.; Arends, W. C; E.; hanefeld, U.; Minnaard, A. J *Synthesis* **2009**, *12*, 2061-2065.

[19] Drabowicz, J.; Łyzwa, P. Omelànczuk, Pietrusiewicz, M. J. K.; Mikołajczyk, M. *Tetrahedron: Asymm.* **1999**, *10*, 2757-2763.

[20] Wipf, P.; Stephenson, C. R. *Org. Lett.*, **2003**, *5*, 2449-2452.

[21] Gaul,C; Schärer, K.; Seebach, D. *J. Org. Chem.* **2001**, *66,* 3059-3073.

[22] Kohmura, Y.; Mase, T. *J. Org. Chem.* **2004**, *69,* 6329-6334.

[23] (a) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc. Chem. Comm*. **1992**, 1097; (b) Jimeno, C.; Reddy, K. S.; Sola, L.; Moyano, A.; Pericas, M.; (c) Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem*. **1997**, *62*, 7364; (d) Zhang, X.; Gong, L.; Mi, A.; Lin, W.; Cui, X.; Jiang, Y. -Z.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett*. **2001**, *42*, 6369-6372 (e) Zhang, X.; Lin, W.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y. -Z.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 1399-1402; (f) Zhang, X.;Lin, W.; Gong, L. -Z.; Mi, A.; Cui, X.; Jiang, Y. -Z.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett*. **2002**, *43*, 1535-1540 (g) Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem*. **1998**, *63*, 2530-2535; (h) Jimeno, C.; Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.*, **2000**, *2*, 3157-3159 (i) Beresford, Kenneth J. M. *Tetrahedron Lett.* **2002**, *43*, 7175-7177.

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

[25] Côtè, A.; Boezio, A. A.; Charette, A. B. *Angew. Chem. Int. Ed.* **2004**, *43*, 6525-6528.

[26] Boezio, A. A.; Pytkowicz, J.; Côtè, A.; Charette, A. B. *J. Am. Chem. Soc*. **2003**,*125*, 14260-14261.

[27] Lauzon, C.; Charette, A. B. *Org. Lett*. **2006**, *8*, 2743-2745.

[28] Côtè, A.; Charette, A. B. *J. Org. Chem*. **2005**, *70*, 10864-10867.

[29] McLaren, A. B.; Sweeney, J. B. *Synthesis* **2000**, 1625-1627.

[30] (a) Yoshikawa, N.; Suzuki, T.; Shibasaki, M. *J. Org. Chem*. **2002**, *67*, 2556-2559; (b) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466-2471; (c) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169-2171.

[31] Yamaguchi, A.; Matsunaga, S.; Shibasaki, M.; *Tetrahedron Lett*. **2006**, *47*, 3985-3987

[32] Yamaguchi, A.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *Org.Lett*. **2007**, *9*, 3387-3390.

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

[34] Jennings, W. B.; Kochanewycz, M. J.; Lovely, C. J.; Boyd, D. R. *J. Chem. Soc., Chem. Comm.* **1994**, 2569-2570.

[35] Haynes, R. K.; Au-Yeung, T-L.; Chan, W-K.; Lam, W-L.; Li, Z-Y.; Yeung, L-L.; Chan, A. S. C.; Li, P.; Koen, M.; Mitchell, C. R.; Vonwiller, S. C. *Eur. J. Org. Chem*., **2000**, 3205-3216, and cited references.

[36] (a) S. Kobayashi and H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094; (b) R. Bloch, *Chem. Rev.* **1998**, 98, 1407–1438; (c) D. Enders and U. Reinhold, *Tetrahedron: Asymmetry*, **1997**, *8*, 1895–1946.

[37] J. A. Ellman, T. D. Owens and T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984–995; P. Zhou, B.-C. Chen and F. A. Davis, *Tetrahedron* **2004**, *60*, 8003–8030.

[38] (a) Li, G.; Wei, H. Y.; Whittlesey, B.; Batrice, N. N. *J. Org. Chem*. **1999**, *64*, 1061-1064; (b) Wei, H. -X.; Hook, J. D.; Fitzgerald, K. A.; Li, G. *Tetrahetron: Asymmetry* **1999**, *10*, 661-665.

[39] S. M. Weinreb and R. K. Orr, *Synthesis*, **2005**, 1205–1227.

[40] Kattuboina, A.; Li, G. *Tetrahedron Lett*. **2008**, *49*, 1573-1577.

[41] Kattuboina, A.; Kaur, P.; Ai, T.; Li, G. *Chem. Biol. Drug Des.* **2008**, *71*, 216-223.

[42] (a) Han, J.; Ai, T.; Li, G. *Synthesis* **2008**, 2519-2526; (b) Han, J.; Ai, T.; Nguyen, T. Li, G. Chem. Biol. Drug Des. **2008**, *72*, 120-126; (c) Ai, T.; Han, J.; Chen, Z. -X.; Li, G. *Chem. Biol. Drug Des*. **2009**, *73*, 203-208.

[43] Kattuboina, A.; Kaur, P.; Nguyen, T.; Li, G. *Tetrahedron Lett.* **2008**, *49*, 3772-3724

[44] (a) Chen, Z. -X.; Ai, T.; Kaur, P.; Li, G. *Tetrahedron Lett.* **2009**, *50*, 1079-1081; (b) Kaur, P.; Nguyen, T.; Li, G. *Eur. J. Org. Chem*. **2009**, 212-216; (c) Ai, T.; Li, G. *Bioorg. Med. Chem. Lett.* **2009**, *9*, 3967-3969.

[45] Jennings, W. B.; Kochanewycz, M. J.; Lovely, C. J.; Boyd, D. R. *J. Chem. Soc., Chem. Comm.* **1994**, 2569-2570.

[46] Benamer, M.; Turcaud, S.; Royer, J. *Tetrahedron Lett.* **2010**, *51*, 645-648.

[47] Notar Francesco, I.; Wagner, A.; Colobert, F. *Chem. Comm*. **2010**, *46*, 2139-2141.

[48] Xu, Q.; Zhao, C. -Q.; Han, L. -B. *J. Am. Chem. Soc.* **2008**, *130*, 12648-12655.

[49] Harmor, T. A.; Jennings, W. B.; Lovely, C. J.; Reever, K. A. *J. Chem. Soc. Perkin Trans. 2* **1992**, 843-849.

[50] Williams, V. E.; Lemieux R. P., Thatcher, G. R. J. *J. Org. Chem*. **1996**, *61*, 1927-1933.

[51] (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2581-2627 (b) Denmark, S. E. *Nature* **2006**, *443*, 40-41.

[52] Kattuboina, A.; Li, G. *Tetrahedron Lett*. **2008**, *49*, 1573-1577.

[53] Kattuboina, A.; Kaur, P.; Ai, T.; Li, G. *Chem. Biol. Drug Des.* **2008**, *71*, 216-223

[54] (a) Han, J.; Ai, T.; Li, G. *Synthesis* **2008**, 2519-2526; (b) Han, J.; Ai, T.; Nguyen, T. Li, G. Chem. Biol. Drug Des. **2008**, *72*, 120-126; (c) Ai, T.; Han, J.; Chen, Z. -X.; Li, G. *Chem. Biol. Drug Des*. **2009**, *73*, 203-208.

[55] Kattuboina, A.; Kaur, P.; Nguyen, T.; Li, G. *Tetrahedron Lett.* **2008**, *49*, 3772-3724

[56] (a) Chen, Z. -X.; Ai, T.; Kaur, P.; Li, G. *Tetrahedron Lett.* **2009**, *50*, 1079-1081; (b) Kaur, P.; Nguyen, T.; Li, G. *Eur. J. Org. Chem*. **2009**, 212-216; (c) Ai, T.; Li, G. *Bioorg. Med. Chem. Lett.* **2009**, *9*, 3967-3969.

[57] Liu, L.; Li, G.; Zeng, X.; Fu, L.; Cao, R. *J. Heteroatom Chem.* **1996**, *7*, 131-136

[58] Enders, D.; Tedeschi, L.; Förster, D. *Synthesis* **2006**, 1447-1460.

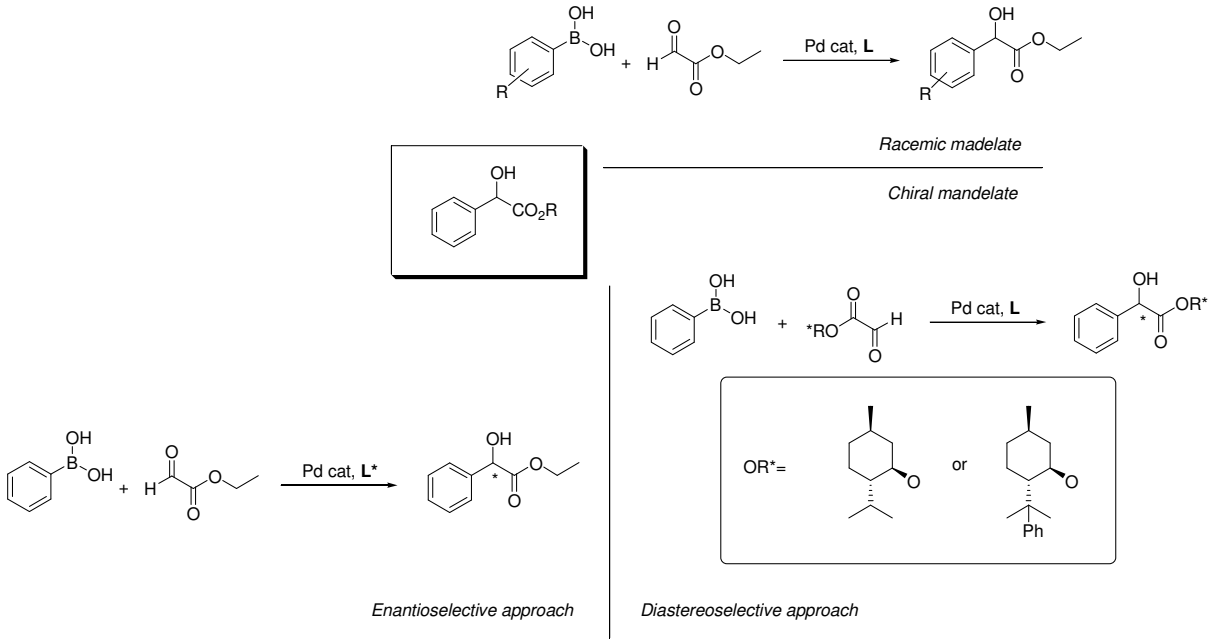
[59] Blum, M. -M.; Löhr, F.; Richardt, A.; Rüterjans, H.; Chen, J. C. -H. *J. Am. Chem. Soc.* **2006**, *128*, 12750-12757.

General conclusions

This work deals with three different organometallic reactions leading to key molecular motifs: mandelic esters, propargylic alcohols and *N*-phosphinamides. The following conclusions seek to take stock of our researches.

1. Synthesis of racemic and chiral functionalized mandelates by Pd-catalyzed coupling of arylboronic acids and glyoxylates.

The asymmetric addition of organometallic reagents to aldehydes remains a prevalent synthetic pathway to provide chiral carbinols. In the last recent years several reports on the development of the transition metals catalyzed additions of boronic acids to aldehydes appeared revealing that Pd-catalysis applied to this reaction is almost unexplored especially if we consider the stereoselective profile. In this context, we aimed to develop a new method to synthesize mandelate derivatives by means of coupling of an arylboronic acid and a glyoxylate derivative. Three different approaches have been attempted as depicted in Scheme 1.



Scheme 1

We started by exploring the achiral approach in which an arylboronic acid reacts with ethylglyoxylate under Pd-catalysis. Several phosphine ligands with different electronic and steric effects have been tested to this purposes. In particular a catalytic system composed by biarylphosphane ligands, 2-di-*tert*-butylphosphanylbiphenyl, and $Pd_2(dba)_3{\cdot}CHCl_3$, gave the desired product with good isolated yields. This optimized calalytic system allow us to evaluate the reaction scope by extending the reaction to arylboronic acids bearing different electron-donating and electron-withdrawing substituents in the *ortho*, *meta*, and *para* positions of the phenyl ring. The study revealed that aromatic boronic acids bearing electron withdrawing substituents, except halides or trifluoromethyl group, showed lower

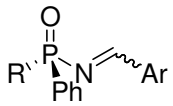
reactivities. However, *ortho* and *para* electron donating substituents led to the corresponding ethyl mandelates in good yields further suggesting that the reaction doesn't suffer the effects of steric hindrance around the reacting center. An hypothesis for a possible mechanism invoking a Pd^{II} complex, acting both in the transmetallation step and as a Lewis acid through its vacant coordination site, was proposed as well.
Since chiral mandelates are very valuable building-blocks in synthetic organic chemistry, we attempted a stereoselective approach to the synthesis of such compounds. Particularly, we explored two different strategies based either on introducing chiral ligand on the catalyst or chiral inducer on the glyoxylate moiety. In the enantioselective approach, a large number of chiral mono- and bis-phosphines with differents electronic and steric properties have been tested in the coupling of phenylboronic acid and ethyl glyoxylate under the reaction conditions optimized for the racemic coupling. A 32% ee on the ethyl mandelate was the best results achieved employing a rigid 1,2-bisphosphine ligand having a norbornene structure (NorPHOS). A diastereoselective approach involving the enantiopure (-)-menthyl glyoxylate or (-)-8-phenyl menthyl glyoxylate as electrophilic counterparts, was explored as well. In the former case we observed that the menthyl group alone is not sufficient to ensure a satisfactory facial control and the coupling of phenylboronic acid and (-)-menthyl glyoxylate provided racemic adducts in presence of an achiral phosphine ligand and up to 30% de when the reaction was performed with a chiral phosphine. Under the hypothesis that a phenyl group in 8-position on the menthyl moiety could result in a better diastereofacial selectivity we tried to synthesize the corresponding glyoxylate. However, every attempts to isolate pure (-)-8-phenyl menthyl glyoxylate failed. The coupling reaction with the arylboronic acid was then tested with a not completely clean product but no addition adduct was ever isolated.

2. Chemoselective addition of in situ prepared lithium alkynyl borates to aldehydes: a practical and transition metal free approach toward the synthesis of propargylic alcohols

Basing on our previous experience with lithium alkynylborate, that have been successfully employed in Pd-catalyzed Suzuki coupling with aromatic halides, we aimed to evaluate their effectiveness in other synthetic transformations. Indeed, we decided to investigate their use as nucleophile in the addition to aldehydes.
In the course of this study we find out that any catalyst was required for this reaction. Thus, lithium alkynyl borate is generated in situ as a non isolable intermediate by treatment of the desired alkyne with butyllithium and trimethylborate. The addition of an aldehyde to the alkynyl borate derivative solution, provides the corresponding propargylic alcohol, after aqueous work-up. Under these conditions, a large number of differently substituted aromatic and aliphatic aldehydes rapidly undergo the addition of various lithium alkynyl borates (alkyl, aryl and TMS) providing the corresponding propargylic alcohols in high yields (Scheme 2).

Chiral N-phosphinoylimines

P-chirogenic

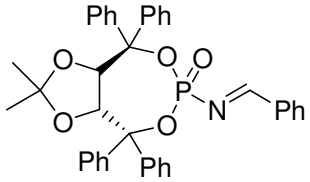


R = methyl, *t*-butyl, 2-mesityl, 2-biphenyl and 2-naphtyl

1,2 Addition of Grignard reagents

Up to 100% de

Chiral auxiliary linked to P atom

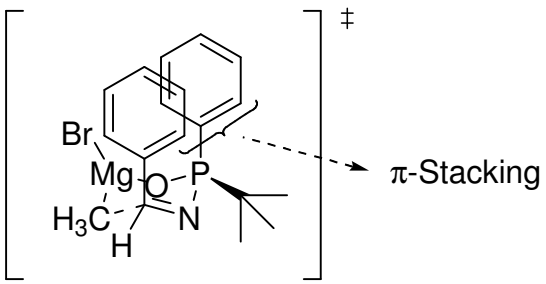


1,2 Addition of Grignard reagents

Up to 40% de

Scheme 3

Therefore, *P*-chirogenic *P*,*P*-diaryl- and *P*-alkyl-*P*-phenyl-*N*-phosphinoylimines have been prepared in a five step sequence reaction starting from the dichlorophenylphosphine. The results of the 1,2-addition of MeMgBr identified the *P*-*t*-butyl-*P*-phenylphosphinoyl group as the best compromise of yield and diastereomeric ratios (85:15) of the products. The addition of a large number of Grignard reagents on *P*-*t*-butyl-*P*-phenylphosphynoylimines provided the corresponding adducts in high yields and moderate to excellent results. For instance, a 100% *de* was presumably observed in case of hindered 2-mesityl group. For a better understanding of the chiral induction, an enantiopure imine has been prepared. The hypothesis of the transition state structure, also supported by the known structure of the major diastereoisomer issued by the addition of methylmagnesium bromide, invoked the coordination of the magnesium atom with the oxygen of the phosphine oxide arranged in a chair-like conformation in which the hindered *t*-Bu group occupy the equatorial position and phenyl groups are both in axial position. This structure could be further stabilized by π-stacking interactions between two phenyl ring in 1,3-position.



Phosphinamides are generally highly reactive in the cleavage reaction of phosphinoyl group roviding deprotected amines in high yields under mild acidic conditions which. In our case, this behaviour is confirmed for amides bearing two aromatic groups on the P atom or for the *P*-methyl-*P*-phenylphosphinamide. By contrast, *P*-*t*-butyl-*P*-phenylphosphinamides resulted to be resistant to mild acidic conditions and seems to undergo degradation process under the effect of stronger acids and other reagents at higher temperature.
Concerning chiral *N*-phosphinoylimines bearing a chiral inducer linked to the phosphorus atom, we synthesized a new TADDOL-derived *N*-phosphorylimine in four steps starting from the phosphorous trichloride with good overall yields. The addition of MeMgBr under different reaction conditions of solvent and temperature was only briefly explored and provided the corresponding adducts in up to 40% *de*.

Outlooks

This work allowed the development of new routes toward few synthetically interesting molecules. However, some aspects of this project deserve to be further investigated. In particular, the Pd-catalyzed coupling of boronic acid and glyoxylates opens new perspectives in the synthesis of chiral mandelates and at the same time represents one of the rare example of palladium catalysis applied to this reaction. Therefore, both the initial results should be completed especially in case of enantioselective coupling by searching for a better phosphine ligand. Moreover, the encouraging results on the nucleophilic addition onto P-chirogenic and chiral *N*-phosphinoylimine suggest to explore other nucleophilic reactions. These topics are currently active in the laboratory demonstrating that this work may open new perspectives in other synthetic fields.

Nouvelles méthodologies en chimie organométallique. Application à la synthèse de dérivés mandéliques, alcools propargyliques et phosphinamides P-chirogéniques.

Introduction Generale

Ce travail se compose de trois différentes parties chacune dédiée à une réaction différente dans le cadre de la chimie organométallique et qui a permis la synthèse d'importants motifs moléculaires tels que esters mandéliques, alcools propargyliques et phosphinamides *P*-chirogéniques.
Dans la première partie nous présenterons une nouvelle méthodologie de synthèse racémique et stéréosélective de derivés de l'acide mandélique par couplage pallado-catalysé entre un acide boronique aromatique et plusieurs esters glyoxyliques.
La seconde partie sera consacrée à l'addition d'alkynylborates de lithium sur des aldéhydes dans le cadre d'une approche hautement chimiosélective vers la synthèse d'alcools propargyliques.
Dans la dernière partie du manuscrit nous introduirons une nouvelle classe de phosphinoylimines chirales et présenterons nos résultats dans l'addition diastéréosélective de réactifs organométalliques.

Chapitre 1: Couplage pallado-catalysé entre un acide boronique et le glyoxylate d'éthyle. Approches énantio- et diastéréosélective de la synthèse d'α-hydroxy esters.

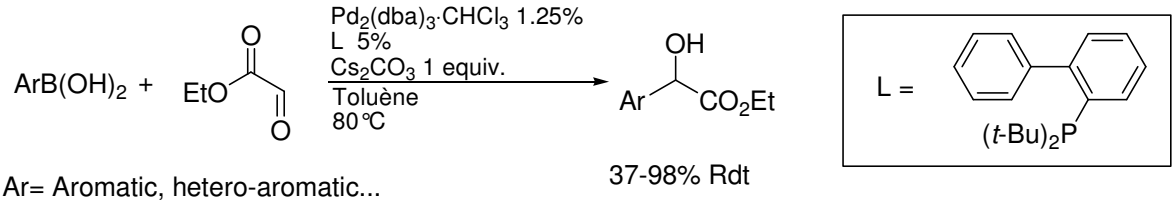
Introduction

L'addition d'acides boroniques sur les aldéhydes représente une méthode relativement peu connue de formation de liaisons carbone-carbone appliquée à la synthèse de diarylmethanols, d'importants intermédiaires moléculaires dans la synthèse de molécules biologiquement actives. A partir du 1998, année dans laquelle Miyaura a publié la première réaction catalysée par un complexe Rh^{I}-phosphine, plusieurs exemples d'addition d'acides boroniques sur les aldéhydes aromatiques ainsi qu'aliphatiques catalysées par des complexes de rhodium ou de palladium en version racémique et stéréosélective peuvent être retrouvés dans la littérature. Cependant, les exemples de catalyse au palladium restent très peu nombreux si comparés aux réactions qui utilisent un catalyseur au rhodium, et se concentrent dans la plupart des cas sur des méthodes de synthèse de carbinols racémiques. La mise au point d'une nouvelle méthodologie autour de cette réaction et dans le cadre de la catalyse au palladium, qui puisse a la fois être applicable aux couplages racémiques et stéréosélectifs a été notre objectif primaire.

Résultats et Discussion

L'addition asymétrique de réactifs organométalliques sur les glyoxylates constitue une méthode alternative pour la synthèse d'α-hydroxy esters, importants intermédiaires synthétiques dans le cadre de la chimie organique préparative. La méthode que nous avons développée permet d'additionner des réactifs organométalliques sur des composés hautement fonctionnalisés, tels que les glyoxylates, dans des conditions douces. Afin de développer de

nouvelles méthodologies autour de la réaction de couplage de Suzuki, on a mis au point un nouveau système catalytique pour le couplage d'un acide boronique avec le glyoxylate d'éthyle.



Ar= Aromatic, hetero-aromatic...

37-98% Rdt

Dans le but d'une possible approche énantiosélective, on a commencé par trouver les meilleures conditions de couplage en racémique. On s'est donc intéressé aux effets du ligand. On a observé que les effets électroniques ainsi que l'encombrement stérique des phosphines jouent un rôle important dans cette réaction. Parmi les phosphines avec un large angle dièdre il y a la Diphos, pour laquelle on retrouve les deux atomes de phosphore en position 1,2, qui donne un rendement modéré de 51 %. Les phosphines plus rigides comme la DPE-Phos et la Xantphos ne montrent pas d'activité catalytique. Les meilleurs résultats sont obtenus avec les biaryl-phosphines. En particulier le 2-di-*tert*-butylphosphanylbiphényle a donné l'ester mandélique avec un très bon rendement sur le produit isolé (78%).

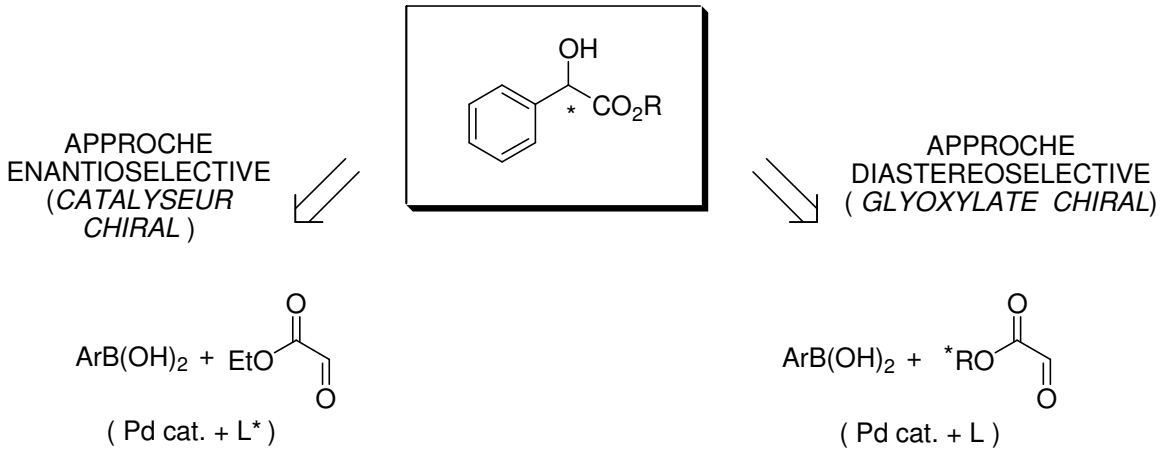
Ces conditions nous ont permis d'évaluer la réactivité de différents acides boroniques. De manière générale on remarque une plus haute réactivité des acides boroniques activés par des substituants électrodonneurs ou halogénés vis-à-vis d'une plus basse réactivité dans les cas des substituants électroattracteurs. La reaction d'addition d'acides boroniques sur le glyoxylate d'éthyle conduit aux derivés mandeliques avec des rendements qui vont de 37 a 98%.

Sur la base des informations sur la nature cationique des complexes de Pd (II) en présence de chloroforme, on a présenté une hypothèse de mécanisme avec un cycle catalytique dans lequel ce complexe joue un rôle fondamental notamment dans l'étape de transmétallation.

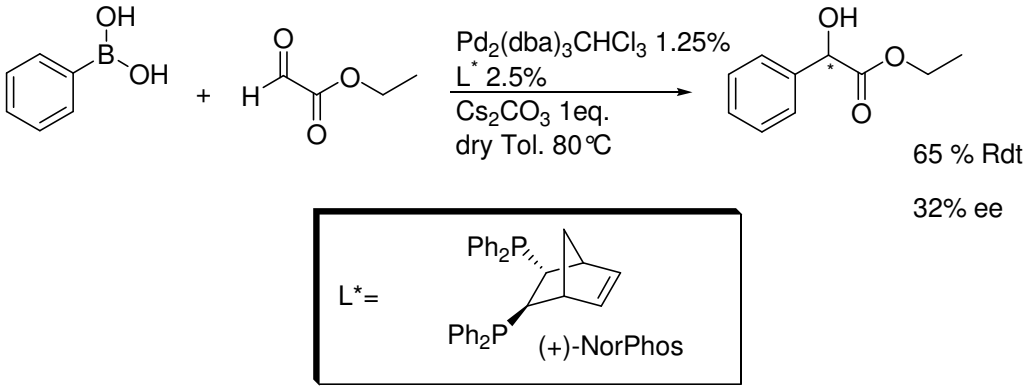
En série stéréosélective on a utilisé deux différentes stratégies:

1. Utilisation d'un ligand de type phosphine chirale.

2. Utilisation d'un glyoxylate chiral derivé du (-)-menthol.



Dans l'approche énantiosélective plusieurs diphosphines chirales ont été testées. Le meilleur résultat en termes d'excès énantiomérique est fourni par la Norphos, un ligand rigide ayant un squelette de type norbornéne qui nous donne 32% d'excès énantiomérique.



N'étant pas satisfait des résultats en catalyse énantiosélective, on a décidé d'utiliser le glyoxylate de menthyle dans le cadre d'une stratégie diastéréosélective. L'utilisation de la triphénylphosphine en qualité de ligand nous donne les produits d'addition correspondants avec un très bon rendement mais un rapport diastéréoisomérique nul. Cependant, le remplacement de la triphenylphosphine par de différents ligands chiraux apporte juste une légère amélioration de la diastéréosélectivité qui, malgré tout, ne dépasse pas les 30%.

Chapitre 2: Additions d'esters alkynylboroniques sur les aldéhydes : synthèses d'alcools propargyliques.

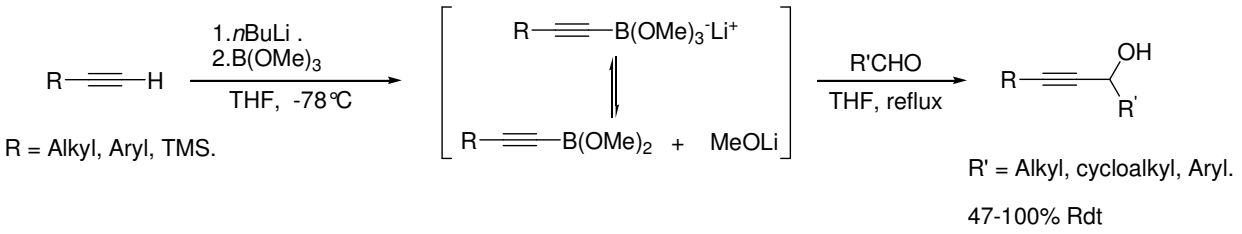
Introduction

Les alkynylmétaux sont connus pour leurs réactions sur les aldéhydes et les cétones pour donner des alcools propargyliques, composés largement utilisés dans la synthèse organique. Cependant, compte tenu des métaux utilisés (Li, Na, K, Mg), leur réactivité est difficilement maîtrisable car ce sont de puissants nucléophiles mais aussi des bases fortes, qui peuvent notamment provoquer des réactions secondaires. Pour remédier à ce problème, on peut utiliser les alkynylboranes, réactifs plus doux ne réagissant pas sur un grand nombre de groupements fonctionnels sensibles. Ce deuxième chapitre de la thèse sera consacré a l'étude de l'addition d'un alkynylborate sous forme de «ate» complexe lithié sur différents aldéhydes.

Résultats et Discussion

Nous nous sommes initialement intéressés au couplage d'un alkynylborane sur des électrophiles tels que les aldéhydes en présence de palladium sur la base de l'expérience acquise au laboratoire en matière de réactivité de ces composés. Les essais préliminaires qu'on a effectué nous ont permis d'affirmer que la catalyse par un métal n'est pas nécessaire. Après optimisation des conditions réactionnelles le protocole suivi consiste à former le «ate» complexe de bore, dans le THF à -78°C, et, *in situ,* ajouter l'aldéhyde, puis remonter la température jusqu'au reflux.
Afin de généraliser les conditions mises au point précédemment, on les a appliqué au couplage de divers alcynes avec un large éventail d'aldéhydes. Les alcools propargyliques

correspondants sont obtenus avec de bons à excellents rendements. L'utilisation du triméthylsylilacétylène a toutefois été problématique dans la récupération de l'alcool propargylique protégé, qui, dans certains cas était mélangé à son analogue privé du groupement silylé qui s'est revelé sensible aux conditions de traitement réactionnel.



Au cours de cette étude nous avons montré que la réaction d'addition d'un alkynylborate lithié formé *in situ* sur les aldehydes était hautement chimiosélective car certains groupements fonctionnels tels que cétones, esters, nitriles se sont révélés inertes.

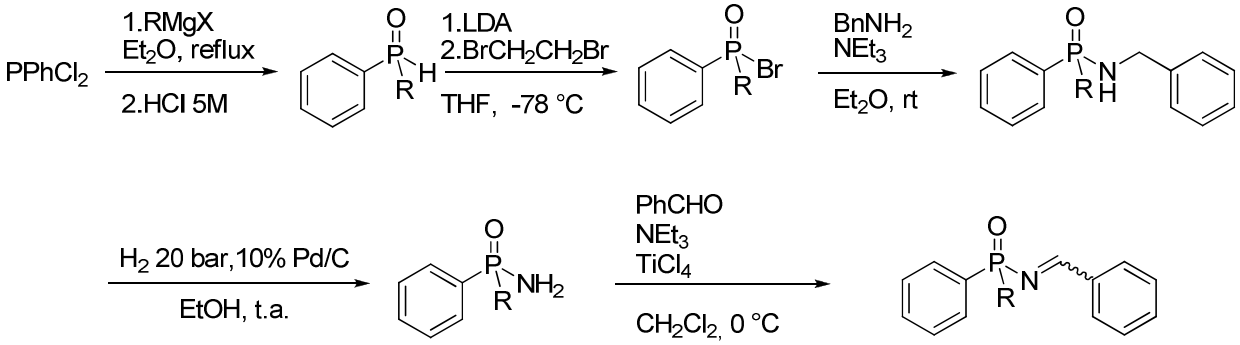
Chapitre 3: Synthèse de phosphinoylimines P-chirogéniques et addition stéréosélective de réactifs organométalliques.

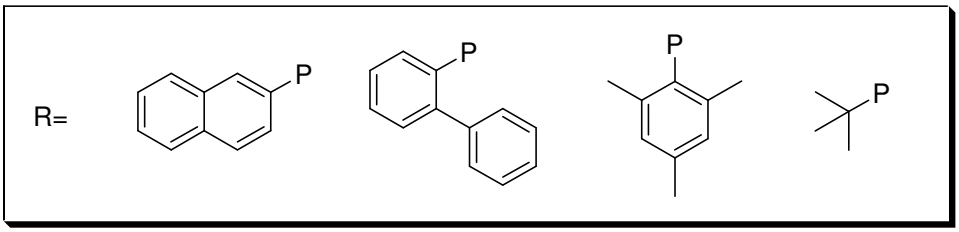
Introduction

L'addition stéréosélective de nucléophiles sur les imines est une méthode efficace de synthèse d'amines chirales. Particulièrement, les imines ayant un groupement électroattracteur sur l'atome d'azote tel que N-sulfonyl-, N-sulfynyl- ou N-acylimines ont été largement utilisées grâce à leur plus grande électrophilicité. Par ailleurs, les *P,P*-diaryl *N*-phosphinoylimines ont plus récemment émergé comme étant de bons électrophiles dans un grand nombre de réactions. Malgré l'utilisation massive des *P,P*-diaryl- or *P,P*-diéthoxy- *N*-phosphinoylimines, il n'existe que deux exemples dans la littérature relatifs à l'introduction de la chiralité sur l'atome de phosphore. Nous avons donc essayé de synthétiser plusieurs imines P-chirogénique et d'évaluer leur degré d'induction asymétrique dans la réaction d'addition de réactifs organométalliques.

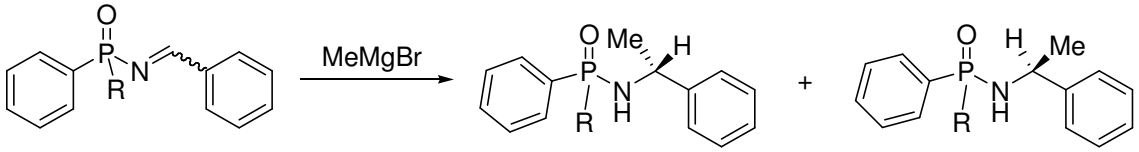
Résultats et Discussion

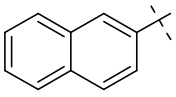
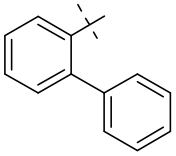
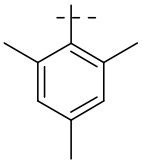
La synthèse d'une série *P*-Phényl-*P*-aryl- and *P*-*t*-butyl-*P*-phényl-*N*-phosphinoyl benzaldimine racémique a été réalisée en cinq étapes en partant de la dichlorophénylphosphine commerciale avec de bons rendements globaux.





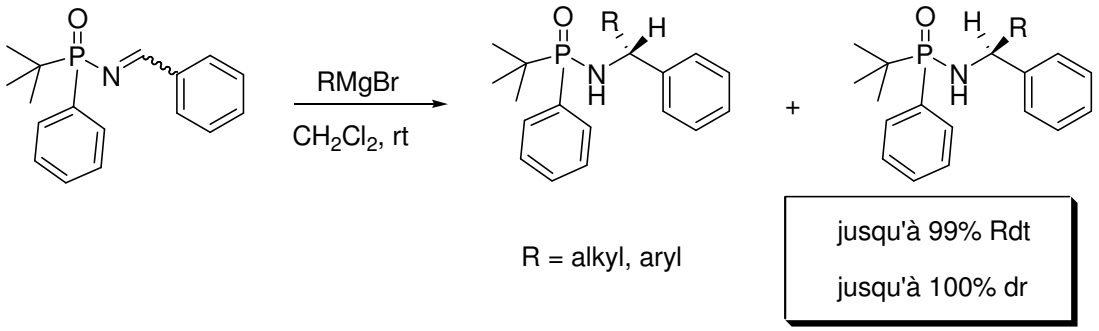
Par ailleurs la P-methyl-P-phenylphosphinoylimine a egalement été synthétisée selon une voie différente. Ces imines ont donc été testées dans l'addition de bromure de méthylmagnesium en utilisant deux différentes conditions réactionnelles. Les deux diastéréomères, chacun étant un mélange racémique, ont été obtenus avec de bons rendements et des rapports diastéréomériques assez prometteurs.



R	*Conditions*	*dr*	*Rendement globale (%)*
	CH_2Cl_2, Ta	55:45	81
	Toluène, 0°C	60:40	85
	CH_2Cl_2, Ta	65:35	89
	Toluène, 0°C	75:25	83
	CH_2Cl_2, Ta	70:30	79
	Toluène, 0°C	75:25	95
	CH_2Cl_2, Ta	85:15	79
	Toluène, 0°C	80:20	77
Methyl	CH_2Cl_2, Ta	70:30	91

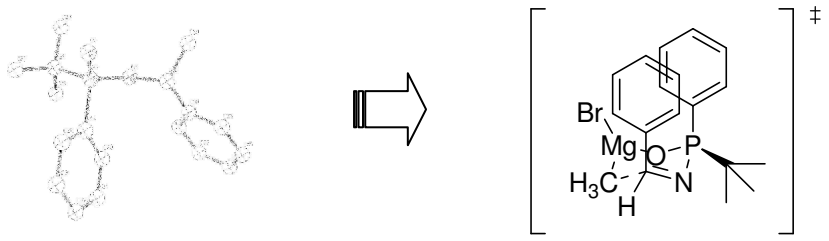
En particulier le cas de la *P*-*t*-butyl-*P*-phenyl-*N*-phosphinoyl benzaldimine nous a semblé un bon point de depart pour des essais supplémentaires. Une première évaluation de l'induction chirale, due au centre stéréogène sur l'atome de phosphore, a été possible par l'addition d'un

réactif organomagnésien à la double liaison C=N de l'imine. Les phosphinamides correspondantes ont été obtenues avec des très bons rendements et de bons à excellents rapports diastéréoisomériques.



Des aldimines dérivées du pentafluoro-, 4-cyano- et 3,4,5-trimethoxybenzaldehyde ont été également synthétisées et testées dans la réaction d'addition de méthyle Grignard mais elles ont montré une diastéréosélectivité réduite si comparées à la benzaldimine correspondante. En particulier, si les rapports diastéréomèriques observés dans le cas des groupements pentafluoro- et 3,4,5-triméthoxyphényle restent plus ou moins en accord avec les données précédentes relative à un groupement phényle simple, dans le cas du groupement 4-cyanophényle la valeur de dr chute drastiquement a 55 :45 ce qui suggère une influence des effets stériques et à la fois électroniques sur l'état de transition dans le processus d'addition. Afin de pouvoir faire des considérations plus précises sur l'état de transition qui nous permettront de connaitre le sens de l'induction asymétrique, une imine énantiopure a été obtenue par résolution cinétique du *tert*-butylphenylphosphinoxyde racémique. L'agent de résolution employé est l'acide (+)-(*S*)-mandélique qui forme un complexe avec le phosphinoxyde en question. Le complexe diastéréomère formé entre l'énantiomère, (+)-(*R*) du phosphinoxyde et le réactif chiral précipite dans l'éther à 0°C. Après filtration, l'énantiomère correspondant est récupéré par traitement d'une solution du complexe avec une solution aqueuse de carbonate de potassium. Le rendement final est de 29% et l'excès énantiomèrique 98.5%. A partir du phosphinoxyde toutes les étapes successives sont stéréospécifiques. L'addition du bromure de méthylmagnesium sur l'imine enantiopure nous a conduit, après séparation chromatographique des deux diastéréomères obtenus et cristallisation, a un monocristal qui nous a permis d'établir la configuration absolue (*R*P,*R*) du diastéréomère majoritaire.

Sur la base de ce résultat, nous avons proposé un état de transition de type chaise qui pourrait être stabilisé par des interactions de type π-stacking entre les deux phényles en position relative 1,3.



Conclusions

En conclusion, deux méthodes alternatives ont été appliquées à la préparation de dérivés mandéliques et alcools propargyliques, deux importants intermédiaires dans la synthèse d'un grand nombre de produits naturels et pharmaceutiques. La synthèse de nouvelles *N*-phosphinoylimines chirales a été effectuée. Les résultats préliminaires de l'addition stéréosélective de réactifs de Grignard sur les imines synthétisées sont encourageants et suggèrent que la réactivité de cette nouvelle classe de composés mérite d'être approfondie ultérieurement.