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Nageswaran Praveenganesh

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Université Joseph Fourier – Grenoble I



THESE

Présentée et soutenue publiquement par

NAGESWARAN PRAVEEN GANESH

pour obtenir le grade de

**DOCTEUR DE L'UNIVERSITE JOSEPH FOURIER
GRENOBLE I**

Spécialité : CHIMIE ORGANIQUE

**PREPARATION AND REACTIVITY OF
FUNCTIONALISED BORONIC ESTERS FROM 4,4,6-
TRIMETHYL-1,3,2-DIOXABORINANE**

Soutenue le 24 Octobre 2008 devant le jury composé de

Pr Olivier Baudoin, UCBL, Lyon,
Dr Frédéric Leroux, CR1, EECPM Strasbourg,
Dr Jacques Einhorn, DR, UJF Grenoble,
Dr Pierre Yves Chavant, UJF Grenoble,

rapporteur
rapporteur
examineur
directeur de thèse

Thèse préparée au sein du Département de Chimie Moléculaire, (équipe SERCO),
Université Joseph Fourier, Grenoble.

RESUME

La thèse porte sur de nouvelles préparations et utilisations en synthèse du 4,4,6-triméthyl-1,3,2-dioxaborinane (MPBH) comme agent d'hydroboration d'alcynes et de borylation d'halogénures d'aryle.

La préparation de MPBH à partir de diverses sources de borane a été mise au point et la stabilité du réactif confirmée.

L'hydroboration d'alcyne terminaux par MPBH, catalysée par le réactif de Schwartz, donne accès à des esters vinylboroniques hautement fonctionnalisés dans des conditions douces. Les produits obtenus sont stables, isolables, stockables. Ces esters vinylboroniques, par transmétallation avec le diméthylzinc et piégeage par une nitronne, conduisent efficacement à des *E*-allyl-hydroxylamines. Les conditions sont compatibles avec de nombreux groupes fonctionnels.

Deux réactions de borylation d'halogénures d'aryle par MPBH ont été ensuite développées. Elles conduisent à d'excellents rendements en esters arylboroniques, stables et faciles à purifier, à partir d'iodures et de bromures. L'efficacité de ces esters boroniques dans des couplages de Suzuki-Miyaura a été vérifiée.

Donc, l'utilisation de MPBH donne accès à des esters vinyl- et aryl-boroniques stables, faciles à purifier et à stocker ; ces esters sont des intermédiaires de synthèse très efficaces.

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General introduction.

Organoboron chemistry has reached a high degree of sophistication in the synthetic applications of triorganylborane R_3B compounds. But the sensitivity of these reagents to radicals, air, etc... has somewhat limited their practical applications. Reversely, organoboronic species $RB(OR')_2$, generally stable, at least to oxygen, received renewed interest when it was shown that they could be submitted to transmetallation reactions allowing transformation of the C-B bond into a C-C bond. The most important example of such process is the famous Suzuki-Miyaura coupling.

In the course of our studies on the vinylation of nitrones, we had found that vinylboronic esters, in the presence of dialkylzincs, could transfer their vinylic chain onto nitrones. We had developed this method with pinacol esters, since these reagents offer two important advantages: they are very easily accessible by hydroboration of 1-alkynes, and they are air- and water- stable, thus can be purified and stored.

But we also found that these pinacolboronic esters were poorly reactive. We couldn't use mild reaction conditions that would have been compatible with sufficient chemoselectivities. Thus, we sought for other vinylboronic esters that would be as stable, as easy to handle, and as accessible as pinacolboronic esters, but that would nevertheless be more reactive. This brought us to study the preparation and use of 4,4,6-trimethyl-1,3,2-dioxaborinane (or **MPBH** for **MethylPentanediolBorane**) in hydroboration. This reagent had been disclosed in 1966 and its stability had been noticed, but has seldom been used ever since.

We describe in the first chapter of this thesis our development of convenient, cost-effective, scalable, fast preparations of MPBH, and in chapter 2 its use in the hydroboration of 1-alkynes catalyzed by Cp_2ZrHCl . This hydroboration is high yielding and chemoselective, allowing the preparation of *E* vinylboronic esters with functionalized side chains under very simple and robust conditions.

In chapter 3 are detailed our studies on the preparation of *N*-hydroxy-allyl-amines by reaction of a vinylboronic ester derived from MPBH, a nitron and dimethylzinc. Compared to our former work on this reaction, new and milder conditions have been found that give access to functionalized *N*-hydroxy-allyl-amines in good yields. We compare the relative reactivity of MPBH and pinacolborane (PinBH) in Zr-catalyzed hydroboration. We compare also the relative reactivities of diversely hindered vinylboronic ester in the reaction with nitrones, and we propose a discussion on the mechanism of the latter reaction.

With MPBH now easily available, it was tempting to use it for the borylation of aryl halides, since this is a very efficient, broad-scope, atom-economic access to the very useful class of arylboronic derivatives. Chapter 4 describes successful borylation of aryl iodides, bromides, triflates and chlorides with MPBH and two different Palladium-based catalytic systems. High yields and selectivities are attained.

In the last chapter, we confirm that the arylboronic esters can be readily used for the Suzuki-Miyaura coupling, which is the principal application of this reagents family.

The present work was partly published in

N. PraveenGanesh, P. Y. Chavant , *Eur. J. Org. Chem.*, **2008**, 4690.

N. PraveenGanesh, S. d'Hondt, P. Y. Chavant , *J. Org. Chem.*, **2007**, 72, 4510.

1 Hydroboration of alkynes

1.1 Bibliographic introduction: preparation of alkenylboronic esters.

Alkenylboranes are interesting synthetic intermediates for two main reasons. First, they can be readily prepared by hydroboration of alkynes. Second, the vinylic group is easily amenable to nucleophilic transfer to various electrophiles.

The direct, uncatalyzed hydroboration of alkynes with borane itself is possible, but the methods suffer drawbacks: high unstability of the trivinylborane intermediates, limited regioselectivity, by-products deriving from double addition. Alternatively, the use of alkylboranes and dialkylboranes has been extensively studied, and high levels of stereoselectivity achieved. But these reagents are very air-sensitive. Thus, in the practice, intermediates are not isolated, and the success of the reaction depends on the total control of all steps of a one-pot, multireaction process. Moreover, in some cases, the alkylboron bonds of the "dummy" substituents on the boron are reactive enough to interfere.

Alkenylboronic esters, from this viewpoint, offer many advantages. Except for catechol derivatives, the cyclic esters derived from a 1,2 or 1,3-diol are stable to air, water, chromatography, making their isolation a simple task. Therefore, it is no more necessary to run all the steps of the process in the same pot, and the formation of by-products can thus be avoided. Moreover, side reactions occurring from the presence of alkoxy groups on the boron atom are virtually impossible.

Alkenylboronic esters are particularly popular as partners in the Suzuki-Miyaura cross coupling reaction for the synthesis of styrenes, dienes and other unsaturated units

present in many natural products.¹ Several methods are available for the synthesis of these alkenyl boronic esters.²

1.1.1 Indirect access: hydroboration with dialkylboranes followed by oxidation.

The historic access to alkenylboronic esters is indirect. It is usually achieved by the hydroboration of an alkyne with a dialkylborane followed by a selective oxidative transformation of the alkylboron bonds into oxygen-boron bonds. Several borane reagents have been explored and used for this purpose (Figure 1).

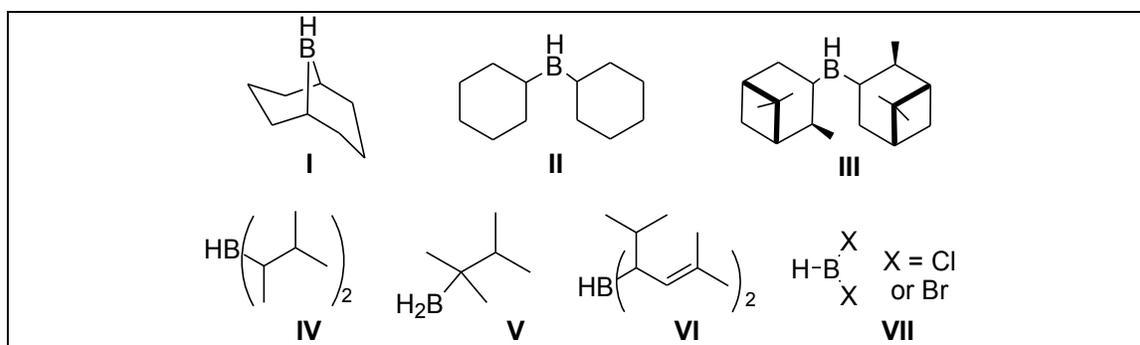


Figure 1: Common hydroborating agents for alkynes

A good example of such a process is the preparation of dienic boronates from both diisopinocampheylborane (IpC₂BH, **III**) and dicyclohexylborane (Cy₂BH, **II**) by Vaultier and Hoffmann^{3,4} (Scheme 1). Dialkylborane reagents like dicyclohexylborane (**II**) react with terminal alkynes to provide dialkylalkenyl boranes in very high regioselectivity. The corresponding alkenylboronic esters may be obtained after an oxidative workup, which is generally performed with a mild and selective oxidant like trimethylamine oxide or acetaldehyde.⁵

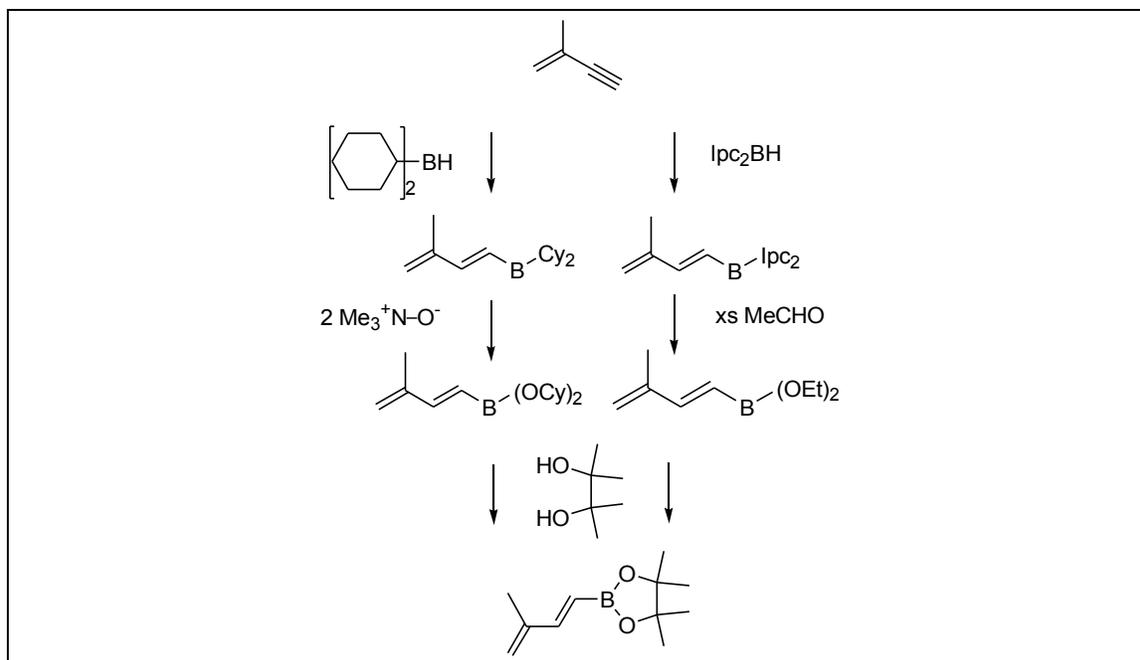
¹ a) H. C. Brown, *Organic Synthesis via Boranes*, Wiley-Interscience, 1975, New York; G. M. L. Cragg, *Organoboranes in Organic Synthesis*, Dekker, New York, 1973. b) N. Miyaura and A. Suzuki, *Chem. Rev.*, **1995**, 95, 2457.

² M. Vaultier and G. Alcaez, in *Science of Synthesis*; D. Kaufmann, Thieme Chemistry; Stuttgart, 2004, Vol. 6, p 721.

³ M. Vaultier, F. Truchet, B. Carboni, R. W. Hoffmann, I. Denne, *Tetrahedron Lett.* **1987**, 28, 4169.

⁴ R. W. Hoffmann, S. Dresely, *Synthesis*, **1988**, 103.

⁵ a) R. Koster, Y. Morita, *Liebigs Ann. Chem.* **1967**, 704, 70. b) J. A. Miller, G. Zweifel, *Synthesis*, **1981**, 288.



Scheme 1: alkenylboronic esters from dialkylboranes

Dihaloboranes like dichloroborane⁶ and dibromoborane⁷ (**VII**, in Figure 1) have been utilized to a lesser extent for the direct hydroboration of alkynes due to the difficulty in handling them. However, other variants like the commercially available Cl_2BH -dioxane complex⁸ or dichloroborane⁹ (generated *in situ* by the reaction of trimethylsilane with boron trichloride) have been used for the regioselective hydroboration of alkynes to yield 1-alkenylboronic acids after hydrolysis. In that case, a simple hydrolysis is sufficient to produce the alkenylboronic acid that is esterified immediately.

1.1.2 Direct hydroboration with dialkoxyboranes.

1.1.2.1 Uncatalyzed hydroborations.

The direct uncatalyzed hydroboration of alkynes by catecholborane¹⁰ (Scheme 2) often requires harsh conditions (70°C) and furthermore, it leads to water-sensitive B-alkyl and B-alkenyl catecholboranes of variable thermal stability. Their transesterification to

⁶ A. Hassner, J. A. Soderquist, *J. Organomet. Chem.* **1977**, 131, C1.

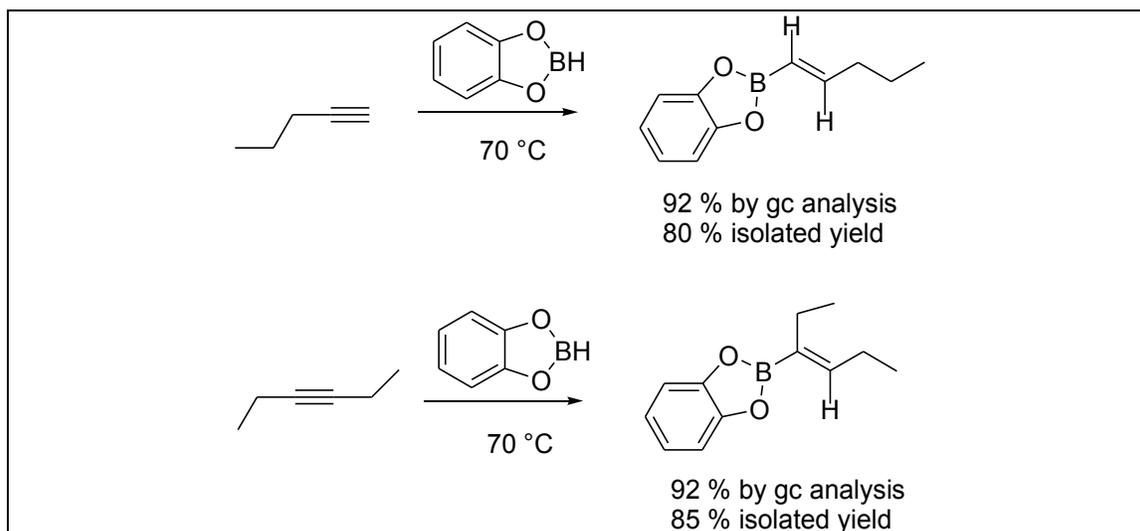
⁷ H. C. Brown, J. B. Campbell, *J. Org. Chem.*, **1980**, 45, 389-395.

⁸ K. V. B. Josyula, P. Gao, C. Hewitt, *Tetrahedron Lett.*, **2003**, 44, 7789.

⁹ R. Soundararajan, D. S. Matteson, *J. Org. Chem.*, **1990**, 55, 2274

¹⁰ a) C. F. Lane, *Tetrahedron*, **1976**, 32, 981. b) H. C. Brown and S. K. Gupta, *J. Am. Chem. Soc.*, **1975**, 97, 5249. c) H. C. Brown and S. K. Gupta, *J. Am. Chem. Soc.*, **1975**, 94, 4370.

more stable boronic esters via intermediate boronic acids is often necessary if further transformations have to be performed. In addition to steric effects, electronic effects are also important in directing the bonding of the B-atom and thus the reaction usually occurs with diminished regioselectivity.



Scheme 2: hydroboration with catecholborane

The uncatalyzed direct hydroboration of alkynes by pinacolborane was first studied by Knochel and coworkers.¹¹ They have observed that the hydroboration of alkynes proceeds in the absence of transition metal catalysts, leading to better regioselectivity and stereoselectivity than catecholborane. Furthermore, in contrast to catecholborane that requires elevated reaction temperatures, the reactions with pinacolborane could be performed at room temperature. The resulting alkenylboronic esters exhibit excellent stability towards aqueous workup and chromatographic separations.

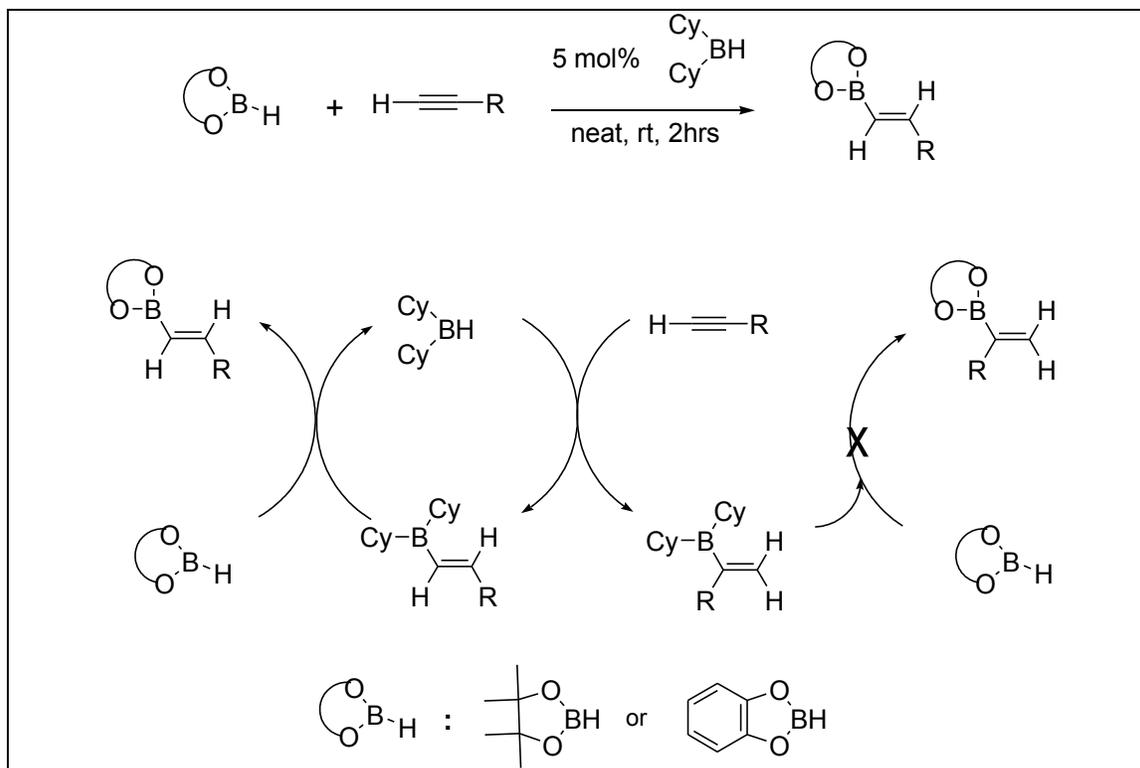
1.1.2.2 Hydroboration catalyzed by boranes.

Nevertheless, Knochel's procedure sometimes suffered from erratic results, and various catalysts were proposed to improve the robustness of the hydroboration. Hoshi and coworkers¹² reported that dicyclohexylborane catalyzes the hydroboration of alkynes

¹¹ C. E. Tucker, J. Davidson, P. Knochel, *J. Org. Chem.* **1992**, 57, 3482.

¹² A) K. Shirakawa, A. Arase, M. Hoshi, *Synthesis*, **2004**, 1814. b) A. Arase, M. Hoshi, A. Mijin, K. Nishi, *Syn. Comm.* **1995**, 25, 1957.

with catecholborane or pinacolborane (Scheme 3). As dialkylboranes are more reactive than dialkoxyboranes, it was suggested that the catalytic process involves the exchange of the resulting alkenyl group with the dialkoxyborane to recycle the dialkylborane.



Scheme 3: Plausible catalytic cycle for dicyclohexylborane-mediated hydroboration:

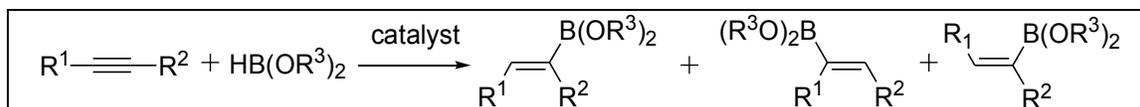
Catalytic amounts of additives like BH_3 -diethylaniline¹³ and dimethylacetamide¹⁴ have been used to accelerate the hydroboration of alkynes by dialkoxyboranes, albeit with moderate selectivity.

1.1.2.3 Transition metal catalyzed hydroborations:

The hydroboration of alkynes was mainly studied with pinacolborane and catecholborane. In the general case it can result in the formation of three possible products (Scheme 4).

¹³ Y. Suseela, A. S. Bhanu Prasad, M. Periasamy, *J. Chem. Soc. Chem. Comm.* **1990**, 6, 446.

¹⁴ C. E. Garrett, G. C. Fu, *J. Org. Chem.*, **1996**, 61, 3224.



Scheme 4

The reactions proceed under mild conditions in the presence of palladium, nickel, rhodium, iridium, zirconium or titanium catalysts.¹⁵ In order for the catalytic process to be useful it must, in some way, complement the known reactions. Thus, in contrast to uncatalyzed reactions, the catalyst can direct the course of the addition of borane to the alkyne triple bond offering a means of changing the regioselectivity. Hydroboration of alkynes catalyzed by transition metals affords vinylboronates in good yields at room temperature. The additions occur regio- and stereoselectivity, leading to anti-Markovnikov *syn* adducts. The commonly employed catalytic systems are briefly discussed in the following sections.

1.1.2.4 Hydroboration catalyzed by late transition metals:

Rhodium and Iridium-catalyzed hydroborations

Hydroboration of thioalkynes by dialkyl- or dialkoxyboranes results in the formation of thioalkenyl boron compounds. Such compounds have several advantages in terms of their practical use for Suzuki cross-coupling reactions with organic halides, since vinylic sulfides can be considered as synthetically equivalent to carbonyls and can be stereospecifically converted to alkenes by nickel-catalyzed coupling reactions with Grignard reagents.¹⁶

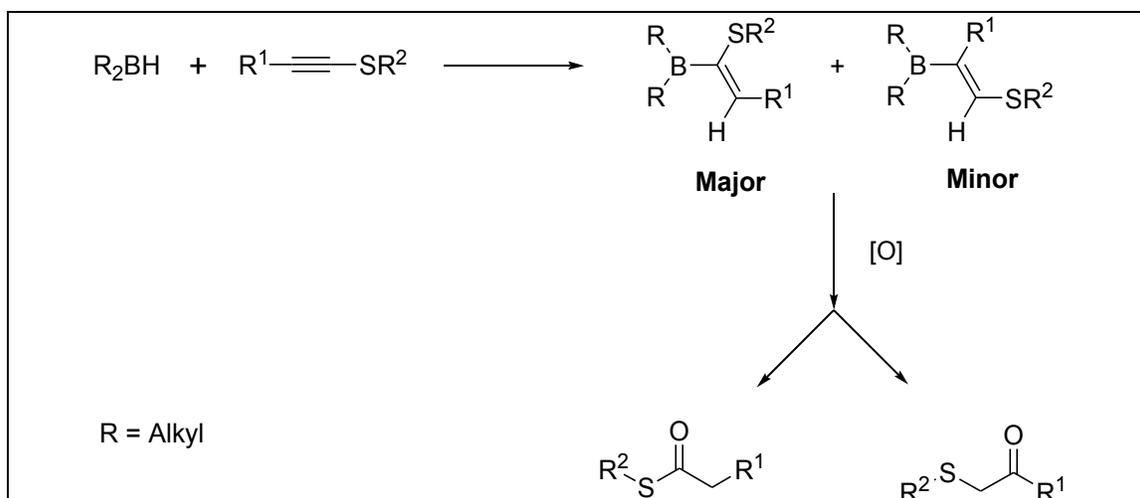
The non-catalyzed hydroboration of thioalkynes by dialkylboranes has been studied by Masuda and co-workers.^{17,18} They have observed a strong preference for placing the boron on the carbon atom carrying the sulfur atom.

¹⁵ I. Beletskaya, A. Pelter, *Tetrahedron* **1997**, 53, 4957.

¹⁶ a) Ishiyama, T., Miyaura, N., Suzuki, A., *Chem. Lett.* **1987**, 25.

¹⁷ M. Hoshi, Y. Masuda, A. Arase, *Bull. Chem. Soc. Jpn.* **1990**, 63, 447.

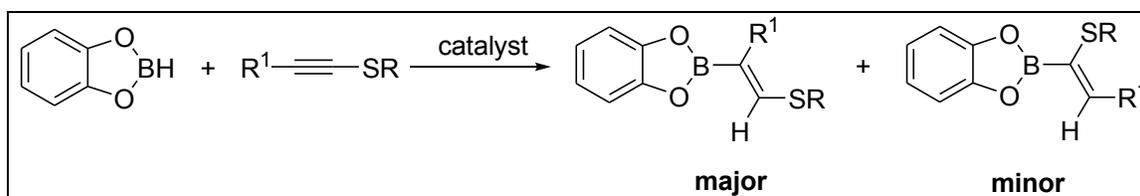
¹⁸ Y. Hoshino, N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1988**, 29, 3983 and references cited therein.



Scheme 5

The regioselectivity of addition is highly dependent upon the substituents on the thioalkyne and on the dialkylborane employed. A complete regioselectivity is generally difficult to achieve.

Suzuki, Miyaura and coworkers¹⁹ have studied the nickel and palladium-catalyzed hydroboration of the same substrates by catecholborane and found a complete reversal of the regiochemical preference, as the boron atom is always located at the β -position relative to the sulfur group (Scheme 6).



Scheme 6: Pd-catalyzed hydroboration of thioalkynes

It was also found that catalysis by rhodium, which has been most commonly applied for the catalytic hydroboration of alkenes,²⁰ was inefficient both in terms of chemical yield and regioselectivity. The results obtained are summarized below.

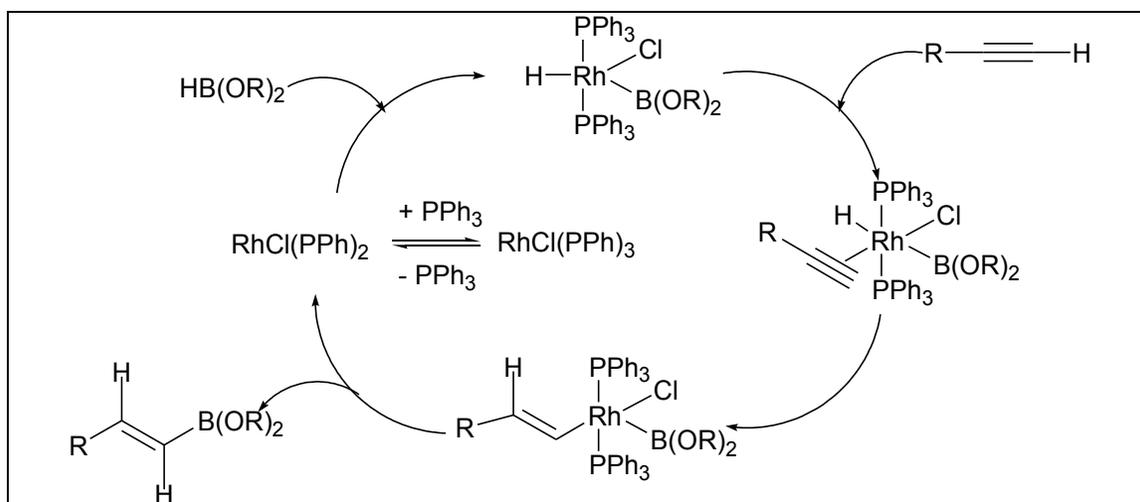
¹⁹ I. D. Gridnev, N. Miyaura, A. Suzuki, *Organometallics* **1993**, 12, 589.

²⁰ Review: K. Burgess, M. J. Ohlmeyer, *Chem. Rev.* **1991**, 91, 1179.

Table 1: Rhodium-catalyzed hydroboration of thioalkynes:

Entry	Catalyst	Ratio (2:3)	% Yield
1.	Rh(PPh ₃) ₃ Cl	58:42	40
2.	Rh(PPh ₃) ₂ Cp	91:9	12
3.	[Rh(C ₂ H ₄) ₂ Cl] ₂	90:10	23
4.	[Rh(COD)(PPh ₃) ₂] ₂ PF ₆	74:26	45

A tentative catalytic cycle has been proposed, similar to that of hydroboration of alkenes by rhodium complexes. The initial step of the catalytic cycle is a ligand displacement reaction, followed by oxidative addition of the metal to B-H bond. Subsequent insertion of the alkyne into the metal hydride bond followed by reductive elimination generates the product and regenerates the catalyst.

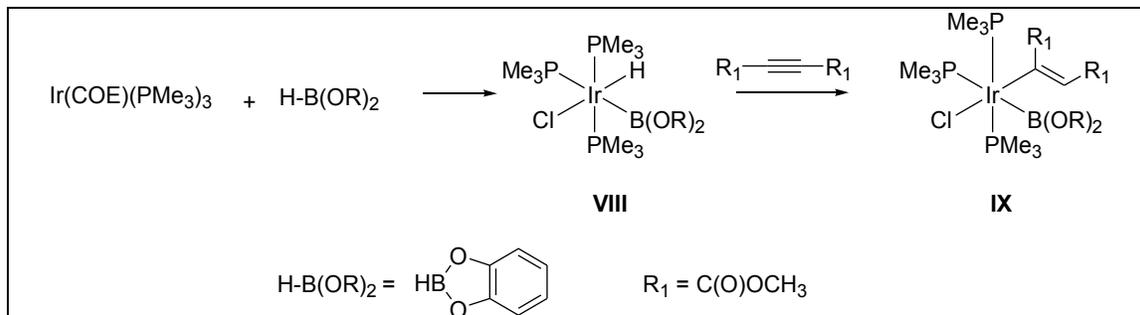
**Scheme 7:** mechanism of Rh-catalyzed hydroboration

The lower yields obtained in these reactions has been attributed to the metal-catalyzed decomposition of catecholborane resulting in the formation of diborane which adds with selectivity that is independent of the catalyst.

A strikingly similar mechanism has been proposed for iridium-catalyzed hydroboration of alkynes²¹ in which the intermediate six-coordinate complex **VIII** has been isolated and its structure determined by single crystal X-ray diffraction. The

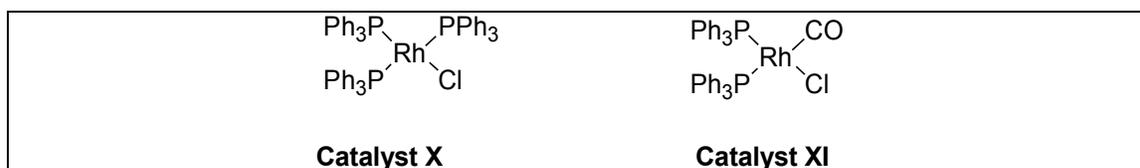
²¹ J R. Knorr and J. S. Merola, *Organometallics*, **1990**, 9, 3008.

subsequent alkyne addition product **IX** has also been observed by NMR spectroscopy (^1H , ^{31}P , ^{13}C). Thus, the alkyne addition proceeded through the formation of an Ir-C bond by Ir-H insertion and not by Ir-B insertion.



Scheme 8

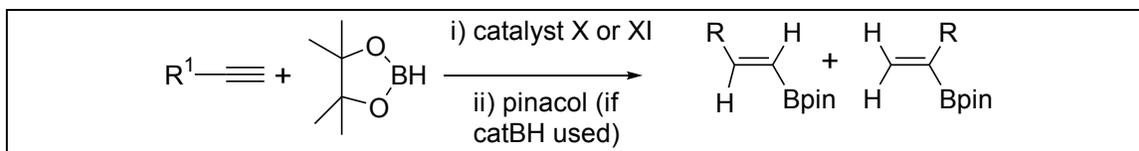
The rhodium-catalyzed hydroboration of alkynes by pinacolborane was studied by Pereira and Srebnik.²² It is widely accepted that pinacolborane results in better regio- and stereoselectivity than catecholborane in hydroboration and that the resulting vinylboronates are insensitive to moisture and chromatography making their isolation a simple affair.



Scheme 9

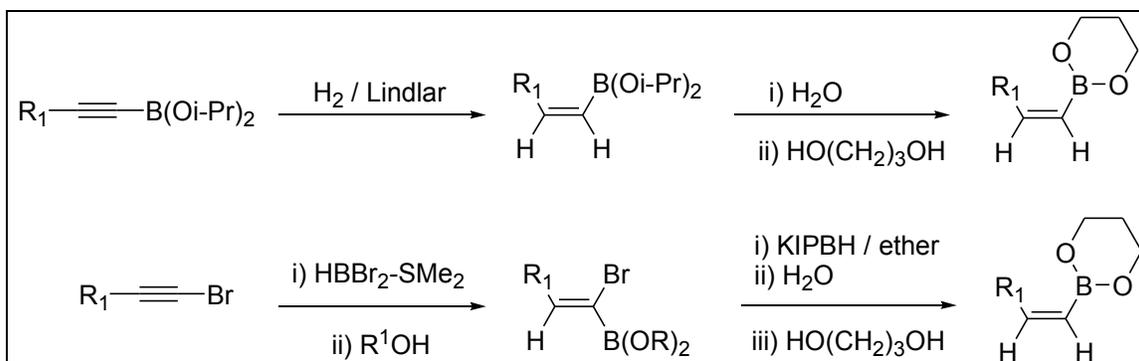
Of the two catalysts examined, catalyst **X** (Wilkinson's catalyst) gave varying amounts of internal hydroboration depending on the steric demand of the substrate. Changing one phosphine group to a CO ligand (catalyst **XI**, $\text{Rh}(\text{CO})(\text{PPh}_3)_2\text{Cl}$) profoundly influenced the ratio of the regioisomers and gave essentially pure anti-Markovnikov products. Unlike catalyzed hydroborations with catecholborane no other products could be detected. The results obtained with various alkynes are tabulated below. These results clearly suggest that fine-tuning of ligand properties could lead to better selectivities in metal-catalyzed hydroborations.

²² S. Pereira; M. Srebnik, *Tetrahedron Lett.*, **1996**, 37, 3283.

**Table 2:** Rhodium Catalyzed Hydroboration with Pinacolborane 11

Entry	R ¹	Catalyst	Ratio (1:2)	% Yield
1.	n-hexyl	X	71:29	99
		XI	99:1	99
2.	phenyl	X	48:52	99
		XI	98:2	99
3.	3-chloropropyl	X	40:60	99
		XI	99:1	99
4.	-CH ₂ OCH ₃	X	30:70	99
		XI	99:1	99

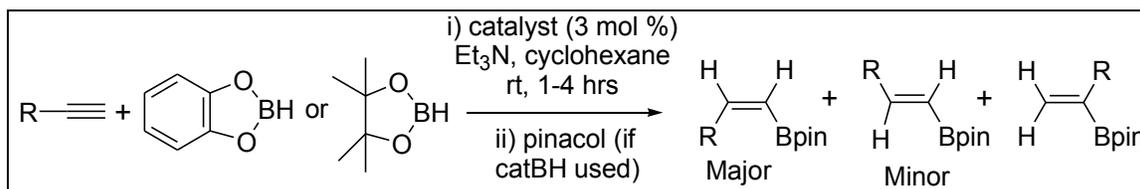
Although *E*-1-alkenylboronates can be accessed by both the catalyzed and uncatalyzed direct hydroboration reaction, the access to *Z*-1-alkenyl boron compounds have been achieved only by indirect methods as outlined below.²³

**Scheme 10**

The *cis* hydroboration of alkynes by catecholborane and pinacolborane in the presence of rhodium and iridium catalysts has been investigated by Yamamoto and

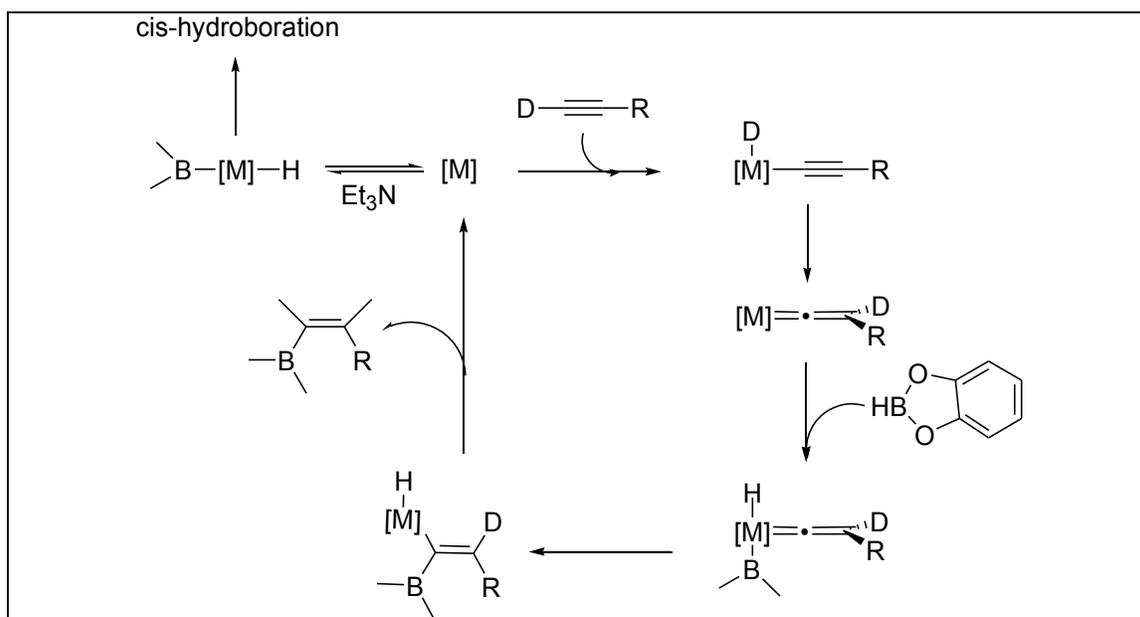
²³ a) M. Srebnik, N. G. Bhat, H. C. Brown, *Tetrahedron Lett.*, **1988**, 29, 2635. b) H. C. Brown, T. Imai, *Organometallics*, **1984**, 3, 1392.

coworkers²⁴ The authors have found that adding stoichiometric quantities of TEA to a Rh-triarylphosphine catalytic system, can bring about a complete reversal of stereoselectivity resulting in the formation of *Z*-1-alkenylboronates. However, an excess of alkyne over the borane reagent was required to attain the desired reversal in addition.



Scheme 11

A completely different catalytic cycle has been proposed for the observed selectivity, on the basis of deuterium labeling experiments (Scheme 12). Thus the formation of a vinylidene intermediate²⁵ has been proposed to account for both the acetylenic hydrogen migration and the anti addition of the B-H bond.

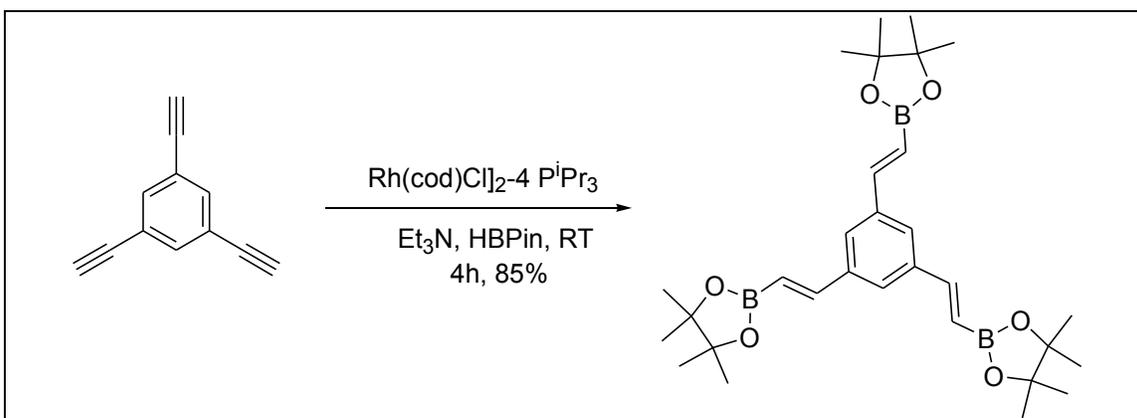


Scheme 12

²⁴ T. Ohmura, Y. Yamamoto, N. Miyaura, *J. Am. Chem. Soc.* **2000**, 122, 4990.

²⁵ For reviews of vinylidene complexes: a) M. I. Bruce, *Chem. Rev.*, **1991**, 91, 197. b) C. Bruneau, P. H. Dixneuf, *Acc. Chem. Res.* **1999**, 32, 311.

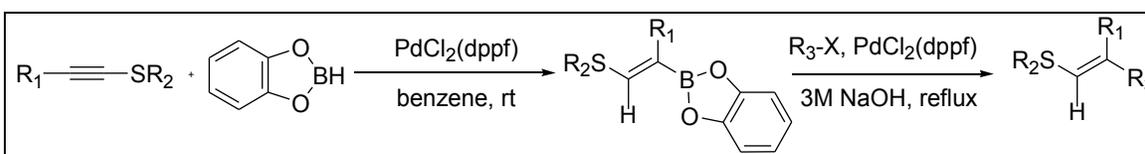
Ko and coworkers²⁶ found that the use of same conditions involving rhodium/trialkyl phosphine catalytic system in the presence of stoichiometric quantities of TEA can lead exclusively to trans hydroboration in substrates containing diynes and triynes. These results clearly indicate that hydroboration of terminal or internal alkynes affords a variable product distribution depending also on the nature of the substrate.



Scheme 13

Palladium and Nickel-catalyzed Hydroborations

Suzuki and coworkers⁹ have studied the hydroboration of thioalkynes catalyzed by Palladium and Nickel complexes. It was observed that palladium-catalyzed hydroborations are slower than nickel-catalyzed reactions and are effective in placing the boron atom β to the sulfur atom, albeit with moderate yields. Nevertheless, palladium catalysts can then be used in a one-pot procedure²⁷ involving first catalytic hydroboration, then coupling of the vinylboronate with unsaturated halides as shown in Scheme 14.



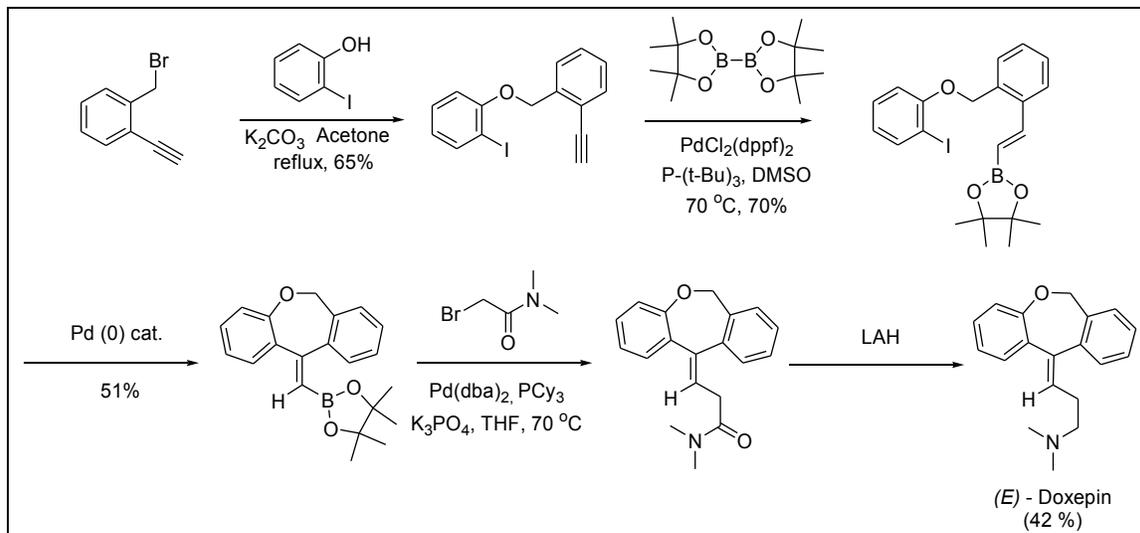
Scheme 14

An application of the preparation of alkenyl boronate by the hydroboration of a terminal alkyne has been utilized in the stereoselective synthesis of *E*-Doxepin (Scheme

²⁶ T. Lee, S. Kim, D. Kim, S. O. Kang, J. Ko, *Organometallics*, **2004**, 23, 4569.

²⁷ I. D. Gridnev, N. Miyaura, A. Suzuki, *J. Org. Chem.*, **1993**, 58, 5351.

),²⁸ an anti-depressant drug. The key step in the synthetic sequence is a tandem hydroboration reaction followed by an intra-molecular carbopalladation to yield the final product in fair yields.

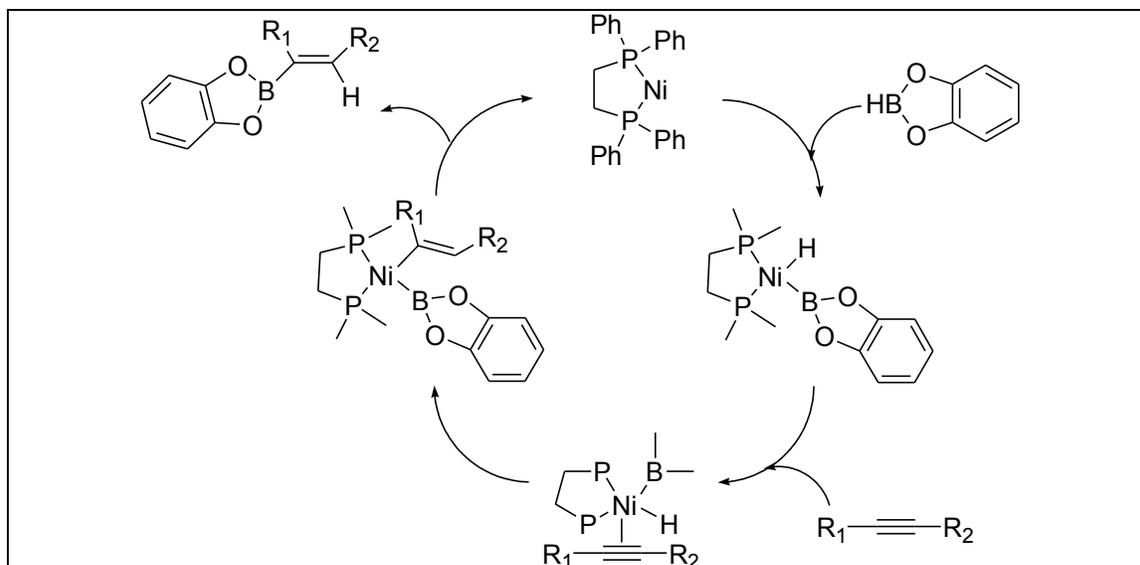


Scheme 15

Contrary to palladium-catalyzed hydroborations, nickel complexes bearing bidentate phosphine ligands were found to be extremely effective in terms of regioselectivity and overall yields.⁹ The efficiency of these bidentate nickel complexes has been attributed to the formation of a saturated five-coordinated species (1) that is unlikely in the case of monodentate phosphine ligands, as those would readily undergo ligand dissociation to form a four-coordinated intermediate. In addition to the electron-rich nature of the bidentate ligands, the formation of such five-coordinate species can be more favored by nickel²⁹ rather than palladium or rhodium. This could explain the superiority of nickel catalysts. The catalytic cycle is developed in Scheme 16.

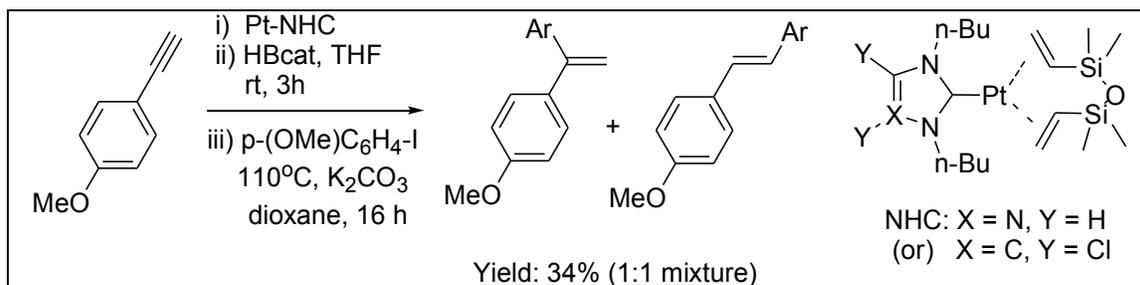
²⁸ C. Xue, S. H. Kung, J. Z. Wu, F. T. Luo., *Tetrahedron*, **2008**, 64, 248.

²⁹ A. Yamamoto, *Organotransition Metal Chemistry*; Wiley Interscience, New York, **1986**, p 201.



Scheme 16

A single example of a platinum-catalyzed hydroboration of alkynes mediated by NHC ligands has been reported by Fernandez and coworkers.³⁰ Although only moderate regio-selectivity has been observed, it is clearly evident that the advantage of using catalysts based on nickel group is the ability to perform a tandem H-B addition/cross coupling reaction with the same catalytic system.



Scheme 17

Hydroboration catalyzed by Early Transition Metals:

Titanium -catalyzed hydroborations:

The catalytic hydroboration of alkynes and alkenes with early transition metal complexes has been investigated by a number of research groups in order to reduce the

³⁰ V. Lillo, J. A. Mata, A. M. Segarra, E. Peris, E. Fernandez, *Chem. Commun.*, **2007**, 2184-2186.

cost of hydroboration catalysts, to complement the selectivity of the late metal systems and to seek new catalytic pathways.^{31,32}

The inherent difficulty associated with many early transition metal catalysts (TiCl_4 , $\text{Ti}(\text{O-Pr})_4$, $\text{Cp}_2\text{Ti}(\text{BH}_4)$) is their ability to decompose catecholborane into diborane and B_2Cat_3 .³³

Thus, it is the diborane formed in these processes that produces the hydroborated products, with selectivities independent of the catalyst and as such the early transition metal complexes are not considered as “true” hydroboration catalysts.

Hartwig and coworkers have studied the catalysis mediated by Titanium complexes³⁴ and of the two titanium complexes examined, it was found that dimethyl titanocene (catalyst **XII**, Figure 2) was found to be an effective catalyst for alkene hydroboration while dicarbonyl titanocene (catalyst **XIII**) gave good selectivities for alkyne hydroboration.



Figure 2

Thus hydroboration of various alkynes by the commercially available dicarbonyl titanocene (catalyst **XIII**), led exclusively to anti-Markovnikov products. The regioselectivities were higher than in uncatalyzed reactions and in reactions catalyzed by Wilkinson’s catalyst. Analysis of the reaction mixtures before oxidative workup revealed neither alkylboranes from multiple hydroborations nor trivinylborane products from uncatalyzed diborane reactions. Thus, the addition of catecholborane to alkynes catalyzed by dicarbonyl titanocene was found to be truly metal-catalyzed.

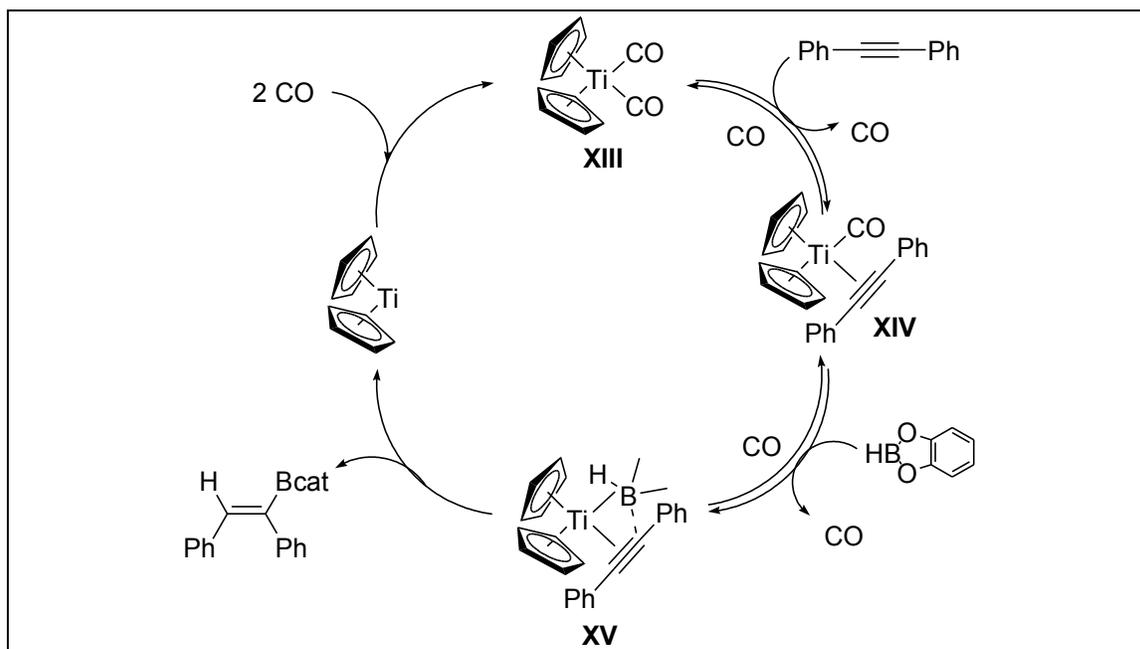
³¹ E. A. Bijpost, R. Duchateau, J. H. Teuben., *J. Mol. Catal. A.: Chem.* **1995**, 95,121.

³² S. Pereira and M. Srebnik, *Organometallics* **1995**, 14, 3127.

³³ a) K. Burgess, M. Jaspars, *Tetrahedron Lett.*, **1993**, 34, 6813. b) K. Burgess, W. A. van der Donk., *Organometallics* **1994**, 13, 3616. c) K. Burgess, W. A. van der Donk., *J. Am. Chem. Soc.* **1994**, 116, 6561

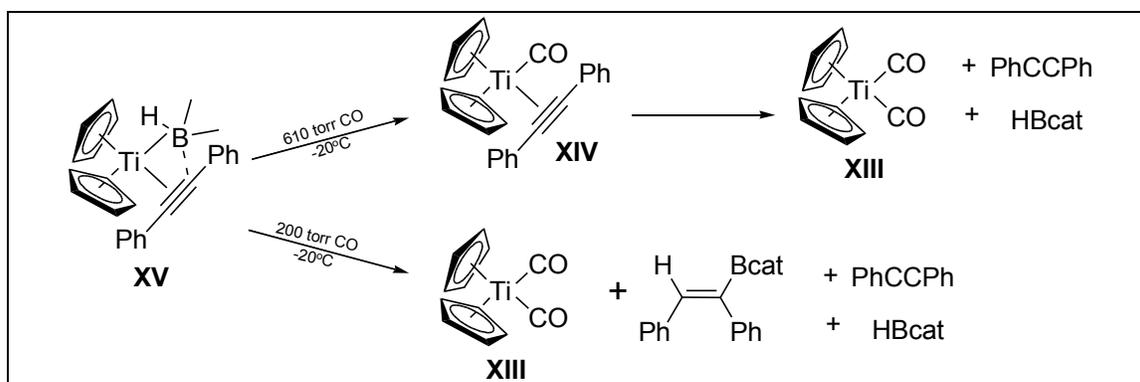
³⁴ a) X. He, J. F. Hartwig, *J. Am. Chem. Soc.*, **1996**, 118, 1696. b) J. F. Hartwig, C. N. Muhoro, *Organometallics*, **2000**, 19, 30.

An interesting mechanism (Scheme 18), involving the reversible formation of a catalytically competent species **XIV** has been proposed and confirmed by the preparation of intermediates **XIV** and **XV** and by subsequent reactions with CO to regenerate the catalyst.



Scheme 18: Proposed catalytic cycle for titanocene-catalyzed hydroboration

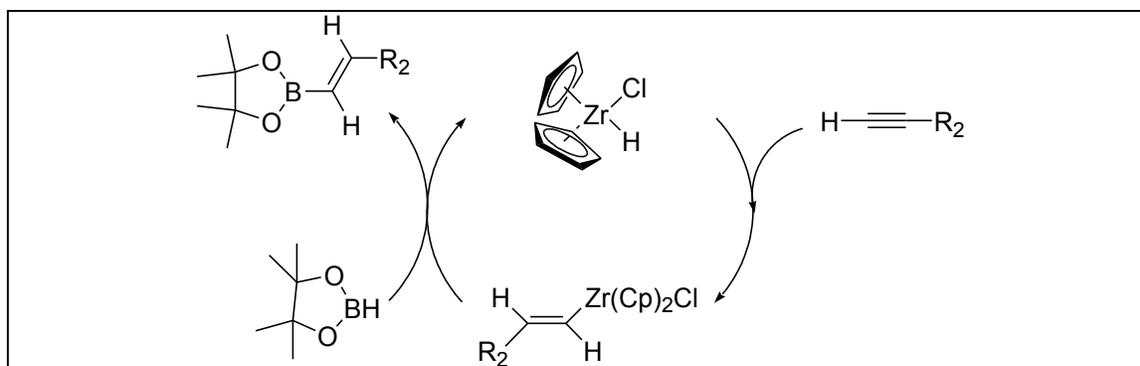
The intermediate alkyne carbonyl complex **XIV** was prepared by the stoichiometric reaction of the alkyne with **XIII** at $-20\text{ }^{\circ}\text{C}$. Subsequent reaction of the alkyne carbonyl complex with CatBH at room temperature resulted in the quantitative formation of the required vinylboronate while at $-30\text{ }^{\circ}\text{C}$ the formation of alkyne borane complex **XV** was observed. This alkyne borane complex **XV** when subjected to an external pressure of CO led to the formation of the required vinylboronate or to the regeneration of the catalyst **XIII**, depending on the external pressure of CO used (Scheme 19).



Scheme 19

Zirconium-catalyzed hydroborations:

The most commonly employed and effective catalyst for the hydroboration of alkynes is Schwartz reagent (Cp_2ZrClH). Pereira and Srebnik¹⁷ have reported that Schwartz's reagent catalyzes the hydroboration of alkynes with pinacolborane at room temperature resulting in highly regioselective *E* addition. The *Z* addition products and other regioisomers were observed, but in negligible quantities. The Zr-mediated hydroboration of alkynes is believed to operate by a pathway (Scheme 20) involving alkyne insertion, transmetalation, and vinyl-hydride exchange, similar to the mechanism of lanthanide catalyzed hydroboration of alkenes.^{11,35}

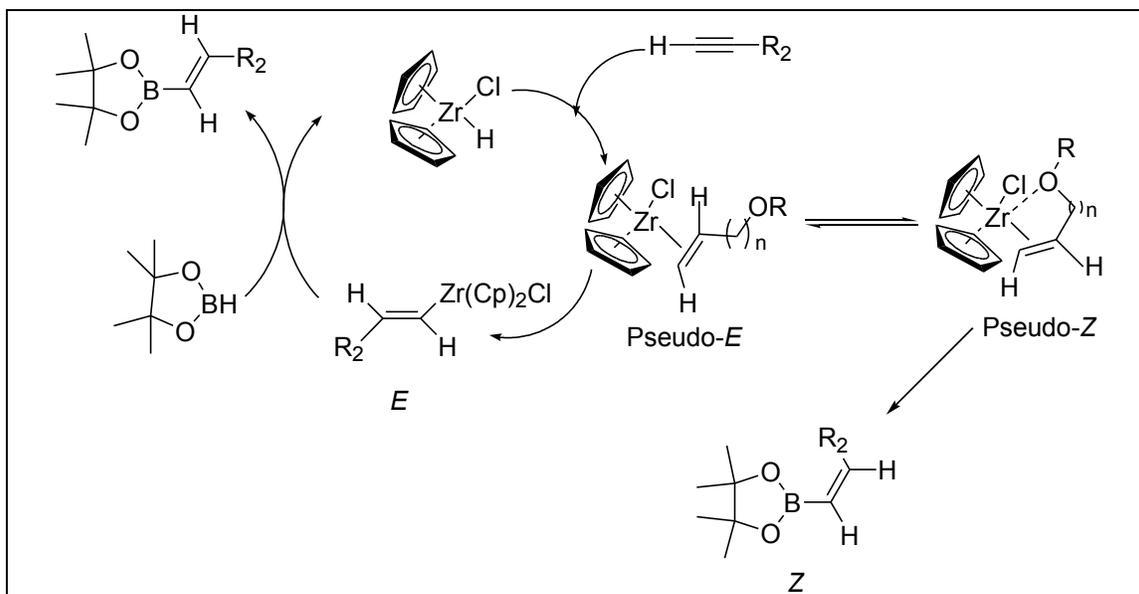


Scheme 20

An additional intermediate step in the catalytic cycle involving the reversible formation of a pseudo-*E* or pseudo-*Z* configuration has been proposed by Wang and

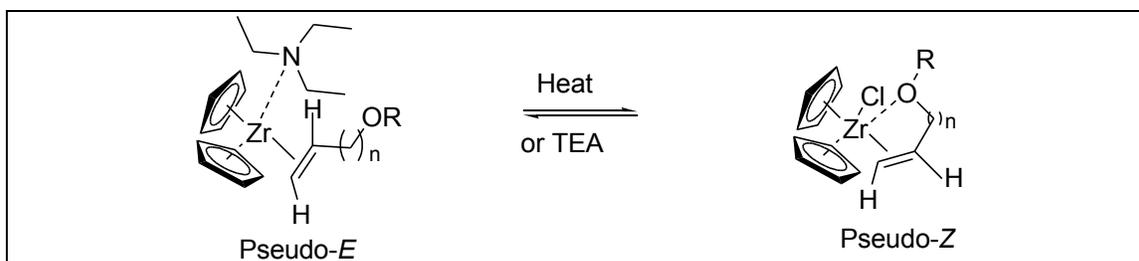
³⁵ K. N. Harrison, T. J. Marks, *J. Am. Chem. Soc.*, **1992**, 114, 9220.

coworkers³⁶ (Scheme 21) to account for the lower selectivities observed especially for oxygen-containing alkynes.



Scheme 21

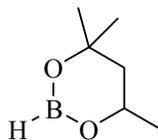
Using additives like TEA in catalytic amounts and performing the reaction at elevated temperatures (60 °C) disrupts the intramolecular O-Zr interaction (Scheme 22) and suppresses the pseudo-Z configuration, resulting in optimal *E* selectivity.



Scheme 22

³⁶ Y. D. Wang, G. Kimball, A. S. Prashad, Y. Wang, *Tetrahedron Lett.*, **2005**, 46, 8777.

1.2 Results and discussion



MPBH (1)

1.2.1 Introduction

4,4,6-trimethyl-1,3,2-dioxaborinane [23894-82-8] (Methylpentanediolborane, MPBH) was first mentioned in 1962,³⁷ but the first complete literature data was reported in 1966³⁸, when Woods and Strong described a preparation and noticed the stability of this reagent. It was then applied to uncatalyzed hydroboration of alkenes³⁹. At the same time, catecholborane was the raising star among these reagents, and it is probably why MPBH was forgotten. Its existence and possible interest is mentioned in reviews⁴⁰ A footnote⁴¹ mentioned in 2000 that it could be prepared “according to Knochel’s method” (see below).

1.2.2 Preparations of MPBH

1.2.2.1 From $BH_3:DMS$

Our first preparation of MPBH was directly inspired by the work of Knochel⁶ and coworkers. The reaction of neat borane/dimethyl sulfide complex with 2-methyl-2,4-pentanediol in dry dichloromethane at 0°C led very efficiently to the formation of MPBH (Scheme 23). ¹¹B and ¹H NMR indicated that the sole impurity was excess $BH_3:DMS$. The product was then distilled (45 °C at 35 mm Hg) to yield MPBH as a colorless liquid

³⁷ R. C. Mehrotra, G. Srivastava, *J. Chem. Soc., Abstracts*, **1962**, 1032

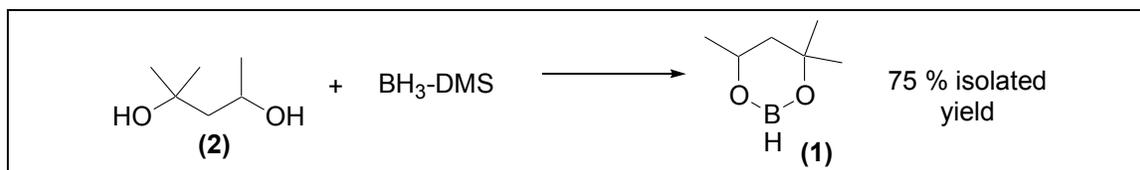
³⁸ W. G. Woods, I. S. Bengelsdorf, D. L. Hunter, *J. Org. Chem.*, **1966**, *31*, 2766. W. G. Woods; P. L. Strong, *J. Am. Chem. Soc.*, **1966**, *88*, 4667.

³⁹ R. H. Fish, *J. Org. Chem.*, **1973**, *38*, 158-159; R. H. Fish, *J. Am. Chem. Soc.*, **1968**, *90*, 4435

⁴⁰ D. Männig, H. Nöth, *Angew. Chem. Int. Ed.*, **1985**, *24*, 878

⁴¹ M. Suginome, T. Matsuda, Y. Ito, *Organometallics*, **2000**, *19*, 4647 (footnote 20).

in 75% isolated yield. The use of commercial solutions of BH_3 in THF led to impure samples.⁴²



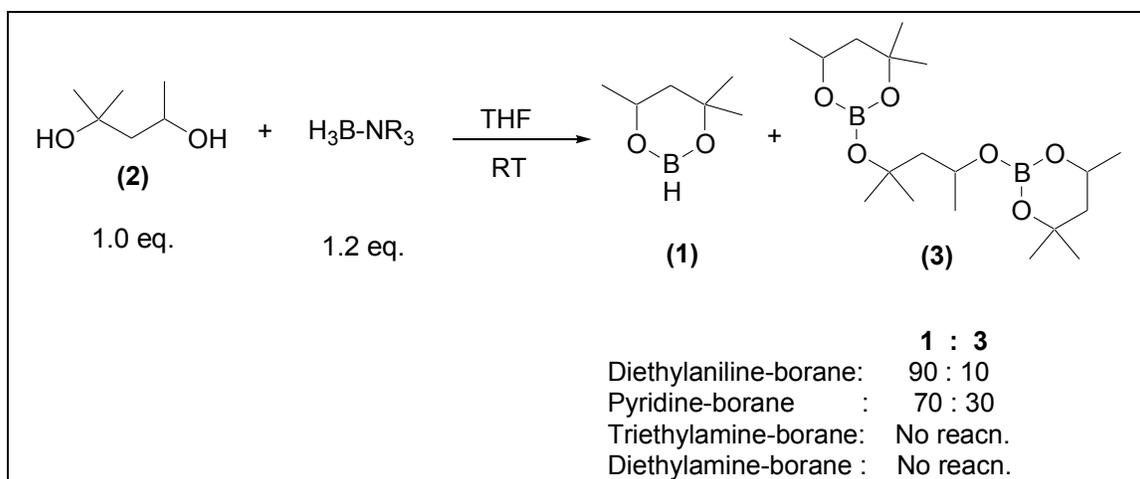
Scheme 23: preparation of MPBH from BH_3 :DMS

1.2.2.2 From amine-borane complexes:

The preparation of MPBH can be achieved using BH_3 -DMS while commercial BH_3 -THF was found to be unsuitable. However, both of these borane sources are unsuitable for large-scale preparation. Disadvantages like low concentration and instability of BH_3 -THF solutions, and the high volatility, flammability and unpleasant odor of DMS are pervasive. On the other hand, amine-borane complexes are free from most of these problems. Hence we studied the use of amine-borane complexes as a source of BH_3 .

The decomplexation of BH_3 from borane-amine complexes is highly dependent on the nature and size of the substituent on the nitrogen. So, we used several commercially available complexes. Reaction of the diol with these borane-amine complexes in THF yielded MPBH and along with it the triester (3) in various proportions determined by ^{11}B NMR.

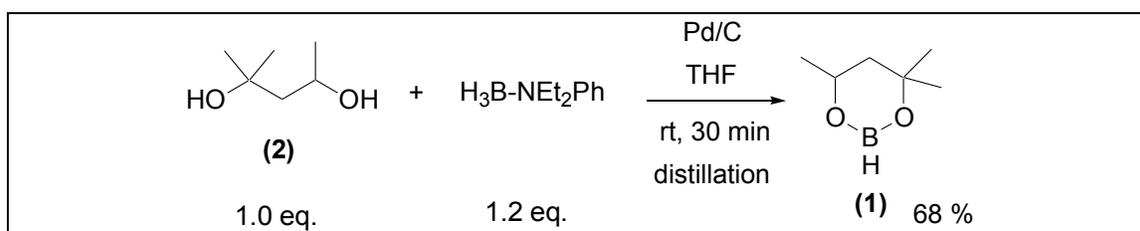
⁴² M. Potyén, K. V. B. Joysula, M. Schuck, S. Lu, P. Gao, C. Hewitt, *Org. Process Res. Dev.* **2007**, *11*, 210.
 b) A mode of deactivation of BH_3 in THF is by conversion of THF to n-butoxyborane. Upon quenching, n-butanol is formed.



Scheme 24: preparation of MPBH from amine-borane complexes

The reaction was very slow for the stable complexes of triethylamine or trimethylamine. The use of diethylaniline borane resulted in complete consumption of the diol in 60 min at ambient temperature. But a mixture of MPBH and the triester (3) was produced in a 90:10 ratio.

The use of Pd/C is known to accelerate the decomplexation and solvolysis of amine boranes in methanol.⁴³ Although $\text{PdCl}_2(\text{TPP})_2$ (as a soluble source of Pd) did not accelerate the reaction and turned black on contact with the borane-amine, the use of 10% Pd/C (5% by weight) resulted in the complete consumption of the diol in 30 min at r.t. in THF. Distillation of the reaction mixture *in vacuo* gave MPBH in 68% yield (Scheme 25). Diethylaniline-borane is considered a safe source of BH_3 for large-scale reactions.⁴⁴



Scheme 25: preparation of MPBH from diethylaniline-borane complexes

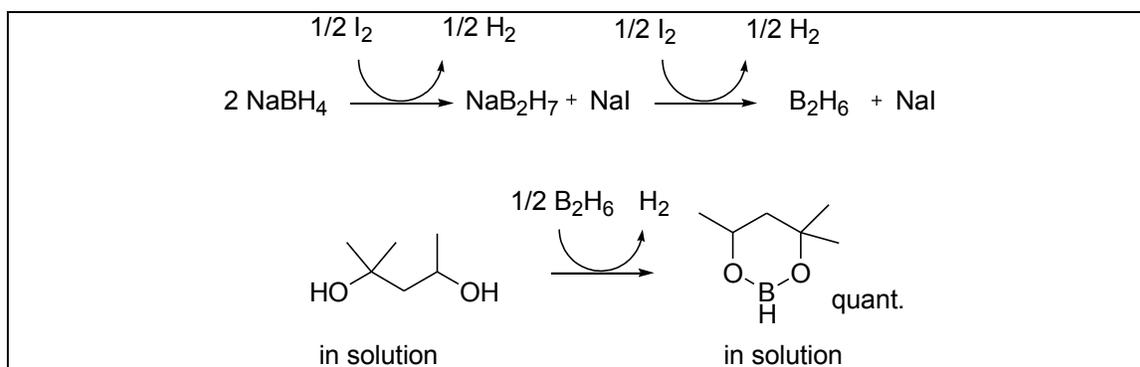
⁴³ M. Couturier, J. L. Tucker, B. M. Andresen, P. Dube, J. T. Negri, *Org. Lett.* **2001**, 3, 465.

⁴⁴ H. S. Wilkinson; G. J. Tanoury; S. A. Wald; C. H. Senanayake, *Org. Process Res. Dev.*, **2002**, 6, 146.

1.2.2.3 From NaBH_4 and I_2

We also investigated a procedure inspired by the work of Suseela and Periasamy,⁴⁵ who showed that B_2H_6 can be conveniently generated from I_2 and NaBH_4 in ether solvents.

Thus, we used a dropwise addition of a solution of I_2 in diglyme into a solution of NaBH_4 in the same solvent to generate a stream of B_2H_6 and H_2 . The gas was diluted with a stream of N_2 and bubbled in a separated flask through a solution of hexyleneglycol in toluene or dichloromethane at $0\text{ }^\circ\text{C}$ (Scheme 26).



Scheme 26

A fast and slightly exothermic reaction was observed and since the first step is the formation of NaB_2H_7 , a brisk evolution of H_2 gas is observed at the initial stages of addition. To obtain a complete conversion of the diol, it was sufficient to generate 1.5 mol eq. of B_2H_6 (from 1.5 eq. of I_2 and 3.0 eq. of NaBH_4). MPBH was obtained in excellent purity, as confirmed by ^1H and ^{11}B NMR of the solution.

1.2.2.4 Improved, scalable preparation from NaBH_4 and methanesulfonic acid:

The need for increasing quantities of MPBH prompted us to design an improved process for its preparation. The preceding procedure (NaBH_4 and I_2) although efficient on a smaller scale was hampered by limited solubility of I_2 in diglyme. It turned out that diborane is much more conveniently generated by the slow addition of MeSO_3H onto NaBH_4 .⁴⁶

⁴⁵ a) Y. Suseela; M. Periasamy, *J. Organomet. Chem.*, **1993**, 450, 47; b) C. Narayana; M. Periasamy, *J. Organomet. Chem.*, **1987**, 323, 145.

⁴⁶ H. G. Weiss; I. Shapiro, *J. Am. Chem. Soc.*, **1959**, 81, 6167.

We could scale this reaction up to 350 mmol of MPBH. Both ^1H and ^{11}B NMR of such DMS-free MPBH solutions indicate excellent purities. Yields are quantitative, thus the solutions are diluted to a known volume and the concentration is calculated on this basis. The standardized toluene, dichloromethane or dioxane solutions of MPBH could be kept for several months at 4 °C without any decomposition as seen by their NMR spectra.

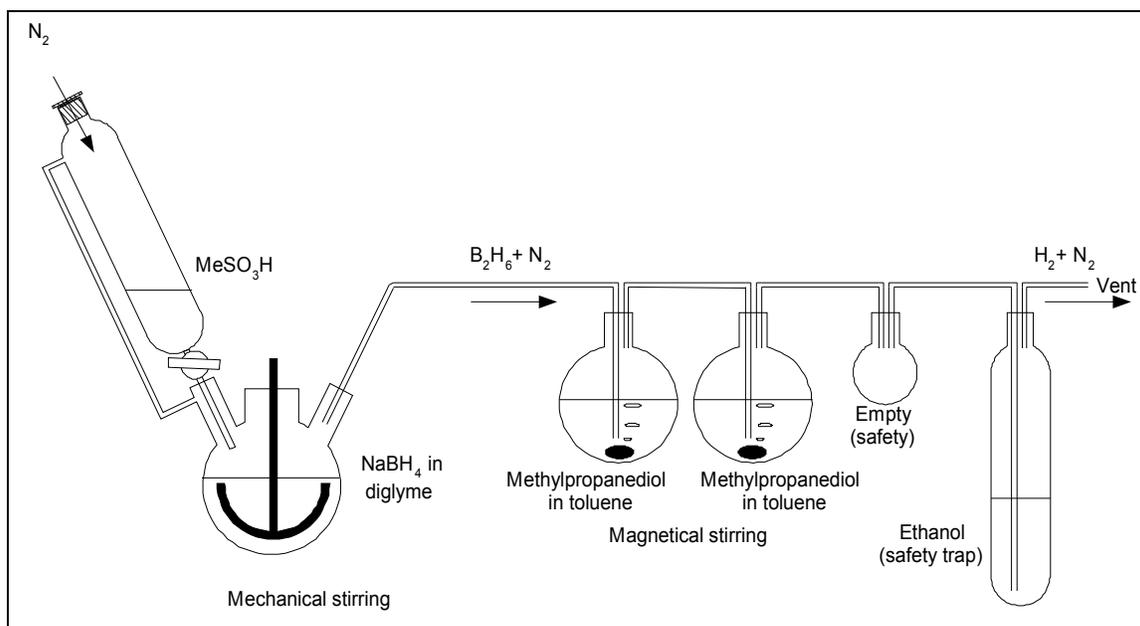


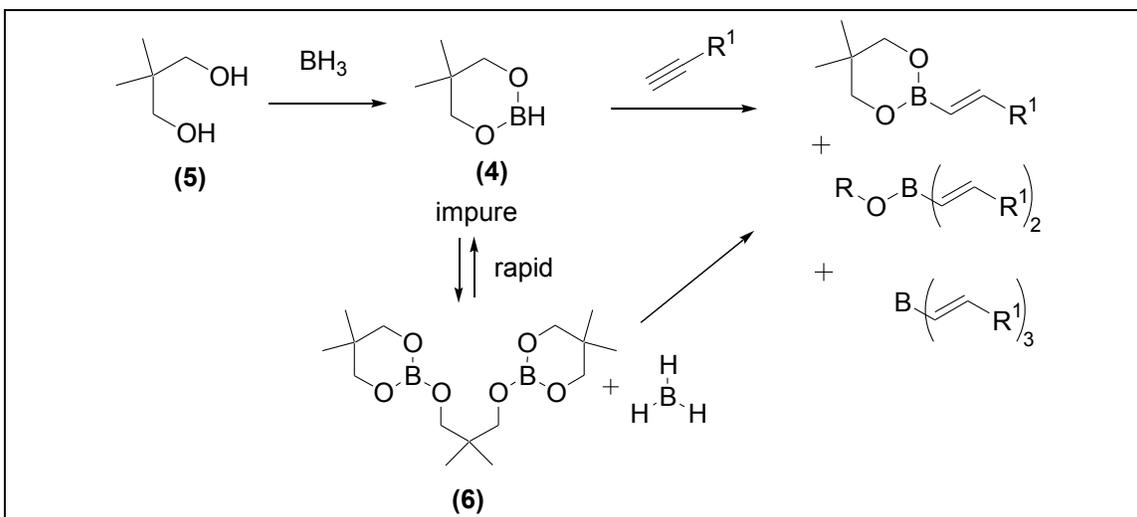
Figure 3: apparatus for large-scale preparation of MPBH

Thus, MPBH is easily accessible from many sources, stable and storable. The dimethylpropanediol, also named hexyleneglycol, is inexpensive (it is a solvent; its price is 10-fold inferior to that of pinacolborane).

1.2.3 Attempted preparation of 5,5-dimethyl-1,3,2-dioxaborinane

We repeatedly attempted to prepare the less hindered 5,5-dimethyl-1,3,2-dioxaborinane from the corresponding diol (2,2-dimethyl-1,3-propanediol, neopentylglycol), but we could obtain only poor yields in borinane samples of low purity. The reaction of either $\text{BH}_3\cdot\text{DMS}$ or B_2H_6 generated *in situ* led to the formation of some required compound as seen by NMR, but also showed a considerable amount of the trialkoxy borane species (^{11}B NMR: 17 ppm).

Further, a distillation of the reaction mixture to obtain the borinane in neat form resulted in extensive decomposition leading to impure material even after distillation.



Scheme 27: disproportionation of 5,5-dimethyl-1,3,2-dioxaborinane

As distillation of the parent borinane led predominantly to decomposition, the reagent was prepared by the BH_3 :DMS method and used as such in solution for the hydroboration of alkynes. The attempts to hydroborate alkynes with these solutions of impure hydroborinane led to a mixture of boronic and borinic species* presumably due to concurrent hydroboration and disproportionation. Rapid distillation of the reaction mixture after completion led to the required alkenylboronate ester but in very low yields.

* ^{11}B -NMR showed several overlapping peaks, ratios could not be determined.

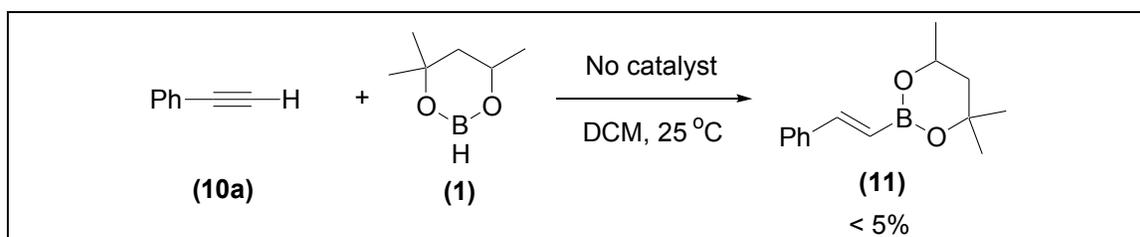
1.3 Hydroboration of Alkynes with MPBH

With an easy and large-scale access to MPBH available, we turned to the hydroboration of alkynes catalyzed by transition metals, with a special interest for the challenging case of alkynes carrying heteroatoms on position 3.

1.3.1 Uncatalyzed hydroboration

Accordingly, we attempted the uncatalyzed hydroboration of phenylacetylene with MPBH. Knochel and coworkers⁶ have reported that the hydroboration of 1-alkynes occurs smoothly with PinBH at room temperature in the absence of any external catalyst. But in a later paper, Srebnik and Pereira observed¹⁷ that in their hands, in the absence of any metal catalyst, the hydroboration of alkynes by pinacolborane afforded 2 % yield of the required product when *in situ* prepared PinBH was used, or 20 % yield when freshly prepared and distilled PinBH was used.

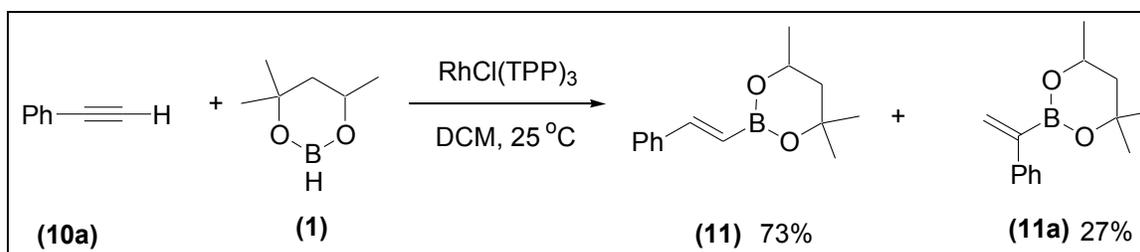
In our case, the reaction of MPBH with phenylacetylene was very sluggish even when 2 equiv. of MPBH was used, leading to less than 5% formation of the required vinylboronate after 24 hrs (Scheme 28).



Scheme 28

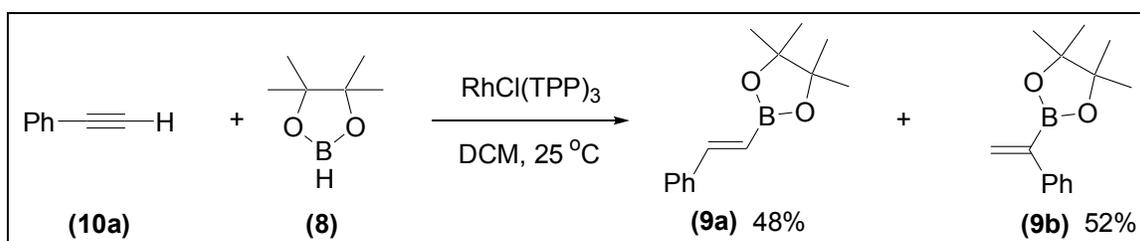
1.3.1.1 Rhodium catalyst

In our essay with MPBH (Scheme 29), the hydroboration of phenylacetylene in the presence of Wilkinson's catalyst led to a mixture of regioisomers, as determined by ¹H NMR.



Scheme 29

In similar conditions, Pereira and Srebnik¹¹ observed a total lack of regioselectivity (Scheme 30).



Scheme 30

1.3.1.2 Zirconocene catalyst

From a practical point of view we preferred Schwartz's reagent as the catalyst. It is commercially available, and easy to handle. It is very regioselective for hydrometallation of 1-alkynes. It is relatively inexpensive, and can be very easily separated from reaction mixtures; thus, it can be used at rather high loading (typically 5 to 10%), which renders the reactions less sensitive to trace contaminants.

The reactions were run in toluene or DCM at room temperature overnight. We first checked that solutions of MPBH prepared from $\text{BH}_3:\text{DMS}$, thus containing about 1 mol. eq. of DMS, and DMS-free solutions prepared from NaBH_4 , led to same results.

When 1-hexyne was added to a solution of MPBH (1M, 1.05 eq., CH_2Cl_2) containing 5 mol% of Cp_2ZrClH , an orange colour developed over time (2 h) then slowly disappeared. After the mixture was stirred for 24 hr at 25°C to ensure completion of the reaction, a simple filtration of the crude material on basic alumina yielded the vinylboronic ester in pure form. In the NMR of the crude, nevertheless, trace amounts of

the *Z* vinylboronic ester isomer were observed (<5%), but were easily removed in the alumina filtration.

In all the cases examined (Table 3), the addition of the alkyne at 0 °C followed by a few hours of stirring at 25 °C, afforded the *E*-alkenyl boronate as the only stereoisomer. We rapidly checked if other Zirconium precatalysts: Cp₂ZrCl₂, ZrCl₄ could be used (the former could have been reduced to Cp₂ZrClH *in situ*), but both were ineffective as a hydroboration catalyst.

We then looked at the hydroboration of various 1-alkynes, with special interest for challenging alkynes carrying heteroatoms on position 3.

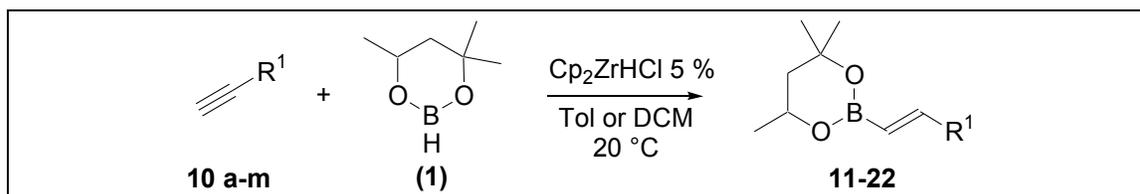
The reaction works well with a variety of alkynes and of particular importance is that only a slight excess of MPBH is required. As illustrated in Table 3, the MPBH/Cp₂ZrClH system hydroborates readily, in moderate to excellent yields and excellent purity, diversely functionalized alkynes, including propargyl chloride^{47,48}, bromide⁴⁹, or protected propionaldehyde⁵⁰. Propargyl alcohol could be used, when protected as an acetate or *tert*-butyl ether (Table 3, entries 7 and 9). Surprisingly, the corresponding benzoate (entry 8) could not be hydroborated, despite repeated attempts. Toluene solutions of MPBH are more easily stored than DCM solutions, but toluene removal can be problematic with volatile vinylboronic esters (entries 5, 6). The electron-poor *t*-butyl propiolate was the major limitation: it reacted very sluggishly at 20 °C (entry 13).

⁴⁷ M. Gravel, B. B. Toure, D. G. Hall, *Org. Prep. Proc. Int.* **2004**, 36, 573.

⁴⁸ M. Lombardo, S. Morganti, M. Tozzi, C. Trombini, *Eur. J. Org. Chem.* **2002**, 2823.

⁴⁹ L. Gaddoni, M. Lombardo, C. Trombini, *Tetrahedron Lett.* 1998, 39, 7571.

⁵⁰ a) C. Rasset-Deloge, M. Vaultier, *Bull. Soc. Chim. Fr.* **1994**, 131, 919. b) A. Kamabuchi, T. Moriya, N. Miyaura, A. Suzuki, *Synth. Commun.* **1993**, 23, 2851.

Table 3: Zirconocene-catalyzed hydroboration with MPBH

entry	R ¹ =	isolated yield	Product No
1	Ph (10a)	93 ^a (79) ^d	(11)
2	<i>n</i> -Bu (10b)	90 ^a	(12)
3	Cyclohexen-1-yl (10c)	66 ^a	(13)
4	(CH ₂) ₃ Cl (10d)	66 ^a	(14)
5	TMS (10e)	61 ^a	(15)
6	CH ₂ OMe (10f)	70 ^b (49 ^a)	(16)
7	CH ₂ OAc (10g)	68 ^b (43 ^a)	(17)
8	CH ₂ OCOPh (10h)	0 ^c	
9	CH ₂ OtBu (10i)	82 ^a	(18)
10	CH ₂ Cl (10j)	68 ^b	(19)
11	CH ₂ Br (10k)	73 ^a	(20)
12	CH(OEt) ₂ (10l)	80 ^a	(21)
13	COOtBu (10m)	19 ^{a,c}	(22)

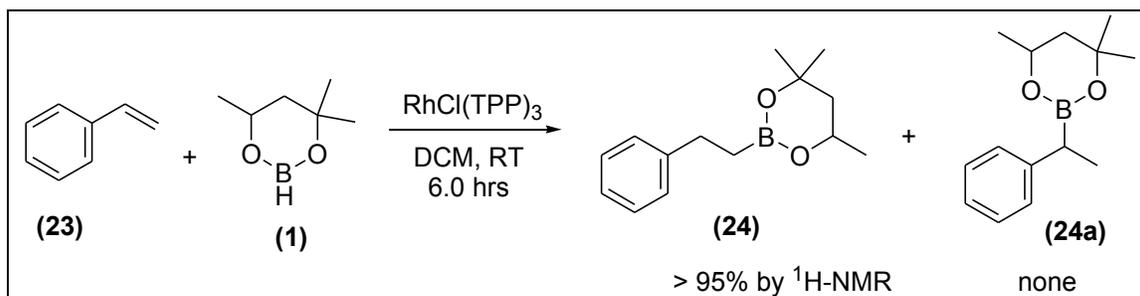
(a) obtained using MPBH in toluene.

(b) obtained using MPBH in DCM.

(c) remainder: starting material.

(d) DCM, 40 °C, 4 hrs.

1.3.1.3 Hydroboration of styrene with Wilkinson's catalyst.



We rapidly checked also the hydroboration of unsubstituted styrene catalyzed by Wilkinson's catalyst.⁵¹ It proceeds under mild conditions to yield exclusively the terminal boronate in quantitative yields. Note that the intermediate σ -borane rhodium complex (from MPBH) has been isolated in 1975 and characterized by ^1H NMR and IR studies.⁵² In another run, reaction catalyzed by $\text{Rh}(\text{COD})\text{Cl}_2$ gave in addition to the linear isomer 12% of the vinylboronate also.

1.3.1.4 Comparison with pinacolborane.

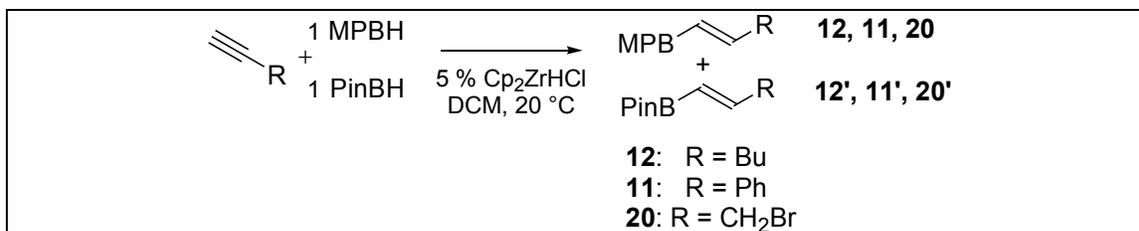
The goal of the present work was to provide a convenient access to vinylboronic esters that would not be pinacol esters, and this is obviously the main difference between MPBH and pinacolborane (PinBH). Nevertheless, it could be interesting to compare the intrinsic reactivity of MPBH and pinacolborane in the Zr-catalyzed hydroboration.

For this study, we used solutions of MPBH and PinBH in DCM , prepared by the NaBH_4/I_2 procedure. We chose to performed competition experiments (Scheme 31): a mixture of one equivalent each of both boranes (MPBH and PinBH) was reacted with the 1-alkyne (1-hexyne or phenylacetylene or propargyl bromide) in the presence of 10 % Cp_2ZrClH , at 20 °C. We monitored by GC (internal standard) the formation of the corresponding vinylboronate **12** (resp. **11** or **20**) and its pinacol-derived isomer **12'** (resp. **11'** or **20'**). This protocol ruled out any experimental bias that could evolve from contaminants in boranes or reagents (that could either poison the catalyst or act as catalysts).⁵³

⁵¹ C. M. Crudden, D. Edwards, *Eur. J. Org. Chem.* **2003**, 4695

⁵² H. Kono, K. Ito, Y. Nagai, *Chem. Lett.*, **1975**, 1095.

⁵³ Hydroboration of 1-alkynes with PinBH is catalyzed by dicyclohexylborane, thus the possibility of catalysis byproducts containing B-H bonds should be considered. Ether and amine ligands affect /...32



Scheme 31: Competition experiments

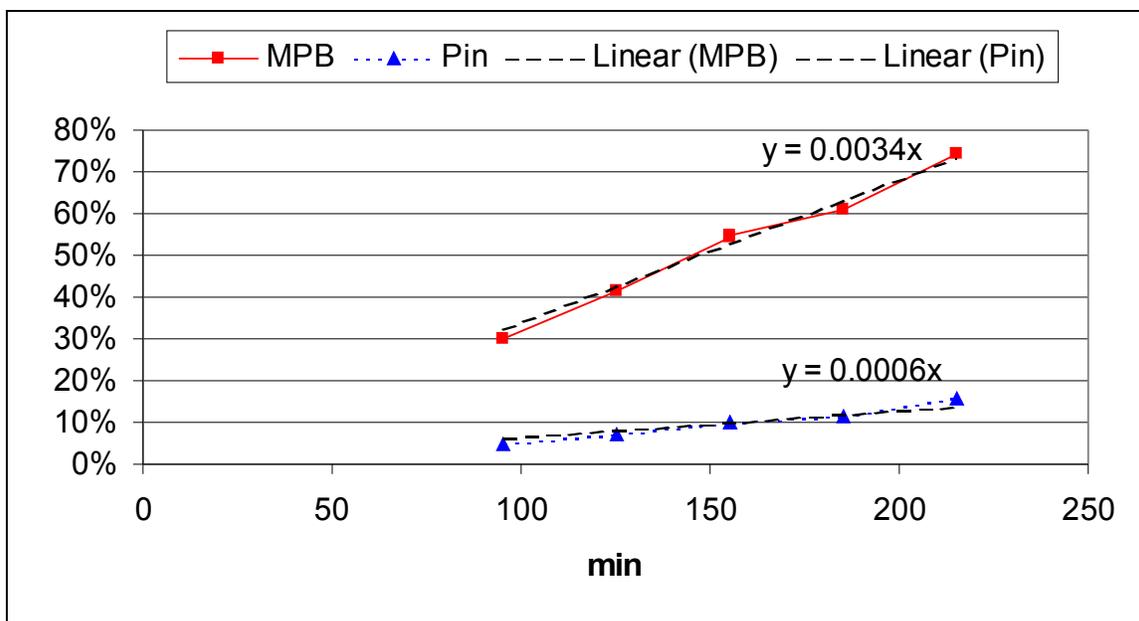


Figure 4. Competitive hydroboration of 1-hexyne by a mixture of PinBH and MPBH: plot of the GC yield in boronic esters.

We found that the curves of formation of all boronates were linear, up to about 40 % conversion of the borane. Rates ratios were estimated from the slopes of the trend lines in this region. In the case of the reactive 1-hexyne (3 eq.), **12** formed 5 times faster than **12'**.

.../31 positively the Cp₂ZrClH catalysis.

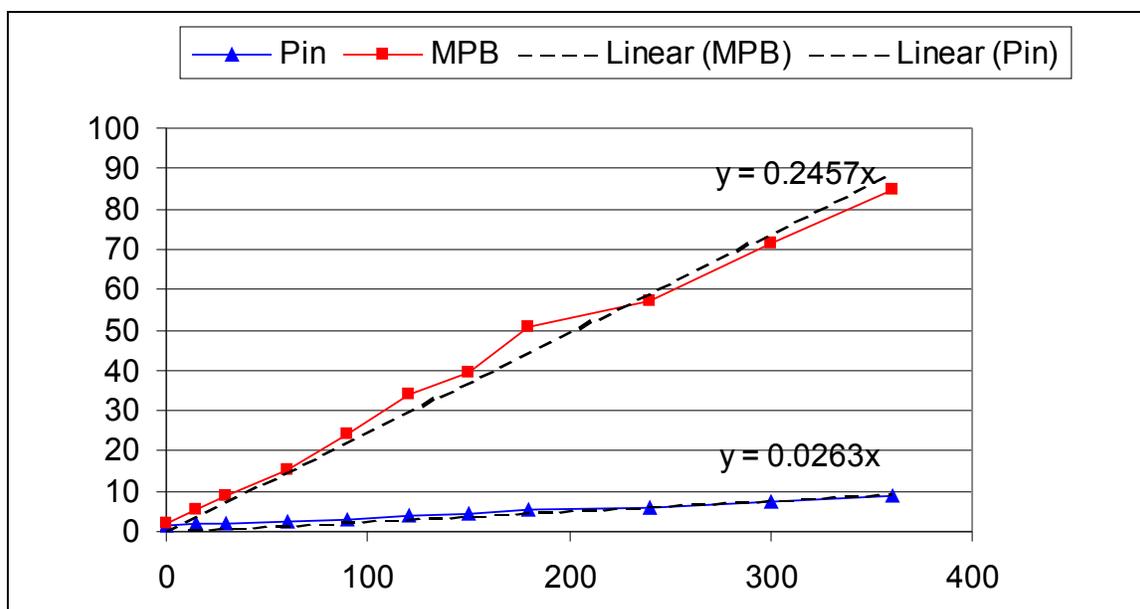


Figure 5: Competitive hydroboration of phenylacetylene by a mixture of PinBH and MPBH: plot of the GC yield in boronic esters.

With phenylacetylene (1 molar equivalent), **11** formed 10 times faster than **11'**. In a separate experiment, we repeated Pereira and Srebnik's¹⁷ preparation of **11'** with our DMS-free solution of PinBH and obtained **11'** in 61 % isolated yield (litt.^{8a} 75 %; our yield in **11** from MPBH 93 %, see Table 3).

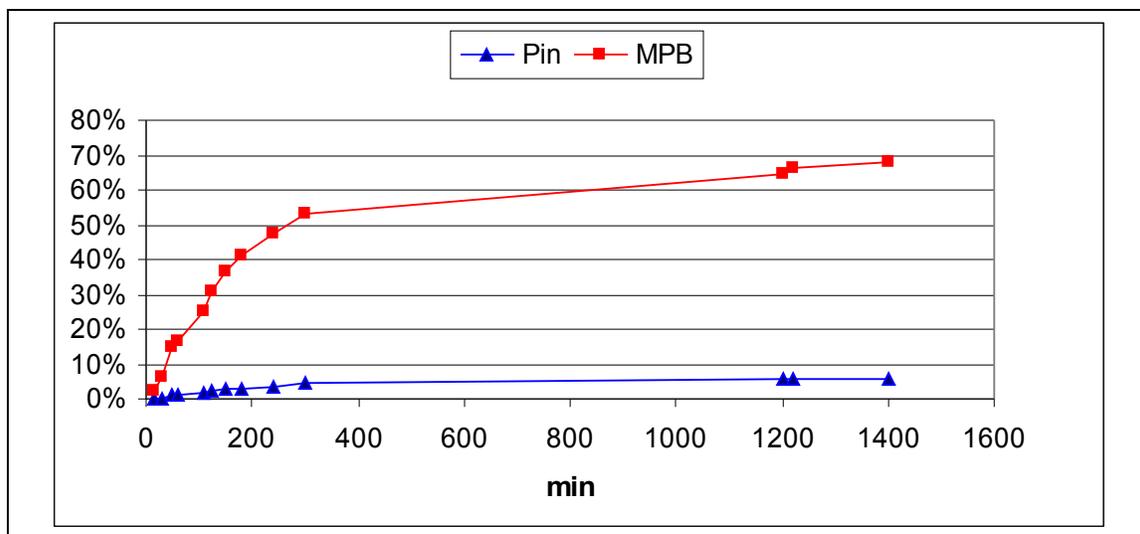


Figure 6: Competitive hydroboration of propargyl bromide by a mixture of PinBH and MPBH: plot of the GC yield in boronic esters.

The largest difference appeared with propargyl bromide. MPBH led to **c** in 73 % isolated yield (5 % cat., Table 3). In the same conditions, no reaction took place between propargyl bromide and DMS-free PinBH (10 % cat.).⁵⁴ We performed a competition experiment (2 equiv. propargyl bromide), and observed evolution of **20** and traces of **20'**, **20** being formed 14 times faster. After 20 hours at 20 °C, the final GC yield was 67 % for **20**, and 5 % for **20'**. Both in phenylacetylene and propargyl bromide competition experiments, the reaction did not proceed further. ¹¹B-NMR showed that both borinanes had disappeared, although they were theoretically in excess over the alkyne. We think that the excess B-H disappears slowly by disproportionation of the reagent leaving esters of boric acid ((RO)₃B) that are difficult to observe by ¹¹B-NMR.

⁵⁴ Hydroboration of propargyl bromide by Cy₂BH: Lombardo, M.; Morganti, S.; Trombini, C. *J. Org. Chem.* **2000**, *65*, 8767. Hydroboration of propargyl chloride with PinBH catalyzed by Cy₂BH: K. Shirakawa, A. Arase, M. Hoshi. *Synthesis* **2004**, 1814

2 Addition of vinylzinc reagents on nitrones

In the course of our studies on nitrones⁵⁵, we were interested in obtaining *E*-allylic *N*-hydroxylamines by the addition of organometallic reagents onto nitrones.

In the past, addition of organolithium or organomagnesium reagents onto C=N⁵⁶ bonds was studied to a much lesser extent than the corresponding addition onto carbonyl functions, the major reason being that imines are less prone to nucleophilic addition and more prone to deprotonation. In recent years, there has been a renewed interest in the addition of organometallics onto C=N double bonds because of both the availability of more selective organotransition reagents, and the use of more reactive C=N species. Among the latter, nitrones appear to be an interesting choice. They are reactive, readily available and stable.

2.1 Bibliographic introduction: nitrones

The chemistry of nitrones⁵⁷ has attracted special attention due to their successful application as building blocks in the synthesis of various natural and biologically active compounds. Nitrones have also been extensively used as spin-traps for the study of radical processes including those that take place in biological systems.⁵⁸

The name nitrone derived from <nitrogen> and <ketone>, indicates a chemical relationship between nitrones and carbonyl compounds as they possess a carbon-nitrogen

⁵⁵ a) J. -N. Denis, S. Tchertchian, A. Tomassini, Y. Vallée, *Tetrahedron Lett.* **1997**, 38, 5503. b) C. Dagonneau, J. -N. Denis, Y. Vallée, *Synlett* **1999**, 5, 602. c) C. Dagonneau, A. Tomassini, J. -N. Denis, Y. Vallée, *Synthesis* **2001**, 150. d) B. Sayah, N. Pelloux-Léon, Y. Vallée, *J. Org. Chem.* **2000**, 65, 2824. e) B. Sayah, N. Pelloux-Léon, A. Milet, J. Pardillos-Guindet, Y. Vallée, *J. Org. Chem.* **2001**, 66, 2522. f) J. Patel, N. Pelloux-Léon, F. Minassian, Y. Vallée, *J. Org. Chem.* **2005**, 70, 9081. g) J. Patel, N. Pelloux-Léon, F. Minassian, Y. Vallée, *Tetrahedron Lett.* **2006**, 47, 5561 h) S. K. Patel; K. Murat; S. Py; Y. Vallee, *Org. Lett.*, **2003**, 5, 4081.

⁵⁶ D. Enders, U. Reinhold, *Tetrahedron: Asymmetry*, **1997**, 8, 1895. b) R. Bloch. *Chem. Rev.* **1998**, 98, 1407.

⁵⁷ E. Breuer. In *Nitrones, Nitronates and Nitroxides*, S. Patai, Z. Rappoport, Eds.; Wiley: Chichester, **1989**, Chapter 3.

⁵⁸ a) R. A. Floyd, *Aging Cell*, **2006**, 5, 51; b) S. T. Caldwell; C. Quin; R. Edge; R. C. Hartley, *Org. Lett.*, **2007**, 9, 3499; c) F. Chalier; M. Hardy; O. Ouari; A. Rockenbauer; P. Tordo, *J. Org. Chem.*, **2007**, 72, 7886.

double bond and a dative nitrogen-oxygen bond. Nitrones are isoelectronic with allyl anions and are stabilized by resonance.

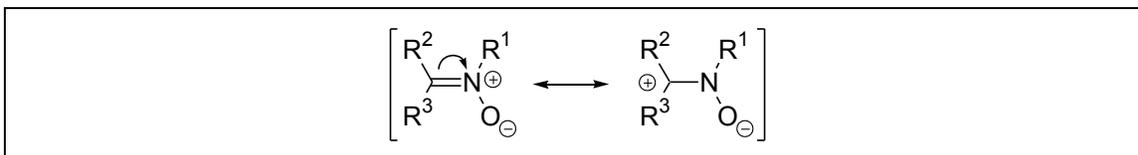


Figure 7

The presence of the electronegative oxygen atom and a positively charged nitrogen atom implies that the carbon-nitrogen bond of nitrones are more polarized than imines, rendering the carbon more electrophilic and thus more reactive. Accordingly, nitrones react with both electrophiles (at the oxygen atom) and with nucleophiles (at the carbon atom). Further, they behave as 1,3-dipoles, and historically the 1,3-dipolar cycloaddition chemistry of nitrones has been the main focus of attention.

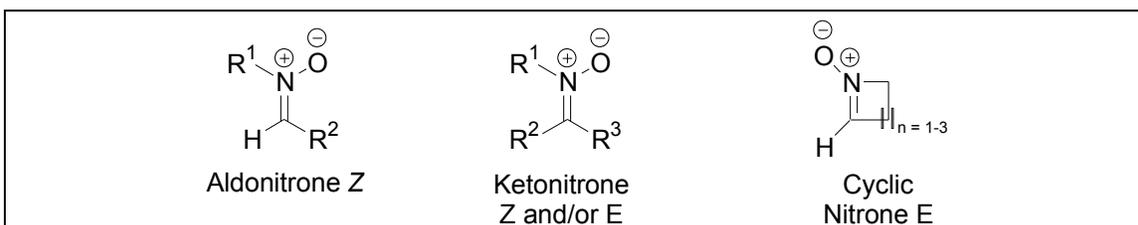


Figure 8

Nitrones⁵⁹ are basically classified as aldonitrones, which are comparable to aldehydes, and ketonitrones, similar to ketones. In general, ketonitrones can exist in *E* or *Z* geometries, the latter having a larger dipole moment. Aldonitrones,^{60,61} without electron-withdrawing groups at the α -position, only exist in the more stable *Z*-form while cyclic aldonitrones exist exclusively in the *E* form.

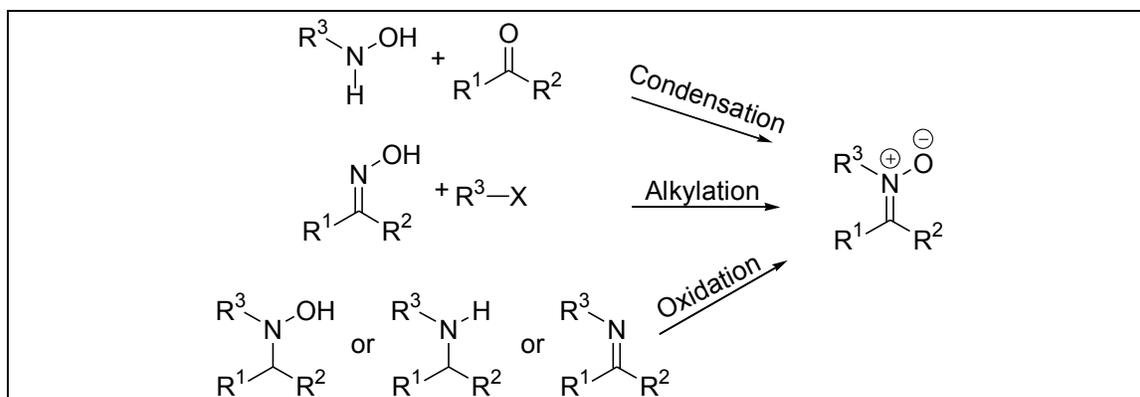
⁵⁹ J. Hamer, A. Malacuso, *Chem. Rev.* **1964**, 64, 473.

⁶⁰ a) Y. Inouye, J. Hara, H. Kakisawa, *Chem. Lett.* **1980**, 1407. b) Y. Inouye, *Bull. Chem. Soc. Jpn.* **1983**, 56, 244.

⁶¹ J. Thesing, V. Sirrenberg, *Chem. Ber.* **1958**, 91, 1978.

2.2 Synthesis of nitrones:

Of the several methods available in the literature⁶² for the access to nitrones, the most commonly utilized are the oxidations involving amines, *N*-hydroxylamines or imines, the condensation of carbonyl compounds with *N*-hydroxylamines and the alkylation of oximes.

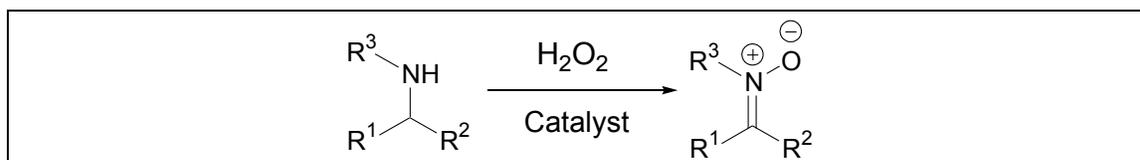


Scheme 32: Various ways to nitrones

2.2.1 Synthesis by Oxidation:

2.2.1.1 Starting from amines:

Treatment of a secondary amine with hydrogen peroxide in the presence of a metal catalyst causes oxidation to nitronium. Of the several catalysts used, sodium tungstate dihydrate⁶³ and methyltrioxorhenium⁶⁴ are the most effective. A safer alternative to the 30 % aqueous hydrogen peroxide is the use of Urea-Hydrogen peroxide complex (UHP).⁶⁵



Scheme 33

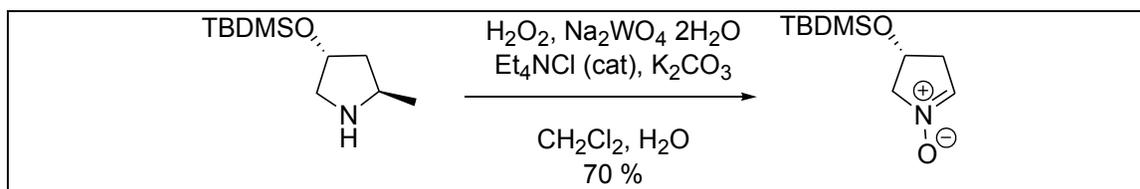
⁶² P. Merino, In *Science of Synthesis*; A. Padwa., Ed.; Georg Thieme Verlag; KG, **2004**, Vol. 27, Chapter 13, p 511-580.

⁶³ S. -I. Murahashi, H. Mitsui, T. Shiota, T. Tsuda, S. Watanabe, *J. Org. Chem.* **1990**, 55, 1736.

⁶⁴ A. Goti, L. Nanelli, *Tetrahedron Lett.* **1996**, 37, 6025.

⁶⁵ E. Mercantoni, M. Petrini, O. Polimanti, *Tetrahedron Lett.* **1995**, 36, 3561.

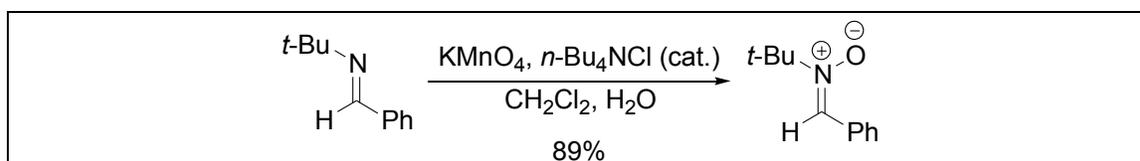
In the case of unsymmetrical amines, the oxidations lead always to a mixture of regioisomers. Conjugated regioisomers are clearly preferred and ketonitrones are formed preferentially over aldonitrones particularly in the case of cyclic compounds. When the reaction is effected with α -aminoacids in the presence of a base, a regioselective oxidation occurs followed by concomitant decarboxylation⁶⁶.



Scheme 34

2.2.1.2 Starting from imines:

The oxidation of imines to nitrones implies the creation of an O-N bond by the delivery of an electron-deficient oxygen atom to the nucleophilic imine nitrogen. Typical oxidizing agents such as molybdenum complexes, oxone, UHP complex, DMDO or peracids afford oxaziridines.⁶⁷ Oxidation of imines to nitrones can be achieved with permanganate ion along with a phase transfer catalyst⁶⁸ (Scheme 35). In the absence of PTC, oxidation of imines to amides becomes an efficient process.



Scheme 35

2.2.1.3 Starting from hydroxylamines:

The oxidation of hydroxylamines is the most effective oxidative route^{69,70} to nitrones and the process is compatible with several protecting groups including silyl

⁶⁶ S. -I. Murahashi, Y. Imada, H. Ohtake, *J. Org. Chem.* **1994**, 59, 6170.

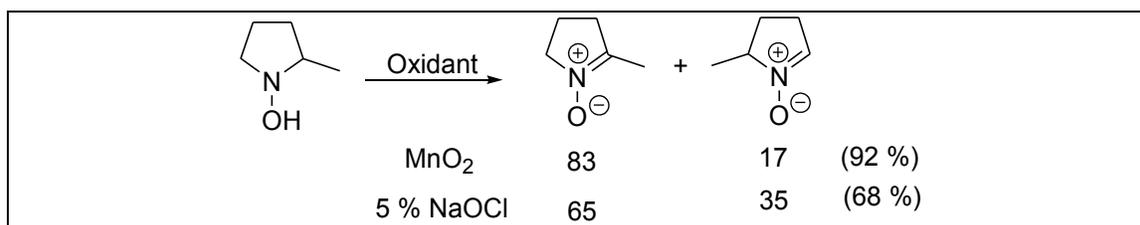
⁶⁷ J. Perrocheau, R. Carrie, *Bull. Soc. Chim. Belg.* **1995**, 104, 463.

⁶⁸ D. Christensen, K. A. Jørgensen, *J. Org. Chem.* **1989**, 54, 126.

⁶⁹ S. Cicchi, A. Goti, A. Brandi, *J. Org. Chem.* **1995**, 60, 4743.

⁷⁰ A. Goti, M. Cacciarini, F. Cordona, A. Brandi, *Tetrahedron Lett.* **1999**, 40, 2853.

ethers. Oxidations using Manganese(IV) oxide⁷¹ are very efficient and versatile⁷², resulting in good regioselectivity in the case non-symmetrical hydroxylamines. Another safe and inexpensive method uses bleach⁷³ (5% sodium hypochlorite) as the oxidant representing an application of green chemistry since the only byproduct of the reaction is an aqueous solution of sodium chloride. Catalytic amounts of tetrapropylammonium perruthenate in the presence of 4-methylmorpholine N-oxide⁷⁴ also affords nitrones in very good yields.



Scheme 36

2.2.2 By the condensation of hydroxylamines with carbonyl compounds:

One of the most useful ways to prepare nitrones is the condensation of carbonyl compounds with a hydroxylamine in the presence of a dehydrating agent. A variety of solvents and desiccants can be used, all leading to similar results. In general, aldehydes are more reactive than ketones.

2.2.2.1 With aldehydes:

Condensation between aldehydes and N-substituted hydroxylamines, such as N-benzyl hydroxylamine, yields the corresponding most stable *Z*-nitrones.⁷⁵ Solvents for condensation include diethyl ether and dichloromethane, at ambient temperature, plus a desiccant such as MgSO₄, CaCl₂ or molecular sieves. The hydrochloride salt of hydroxylamine can also be employed; a stoichiometric quantity of a base is then required.

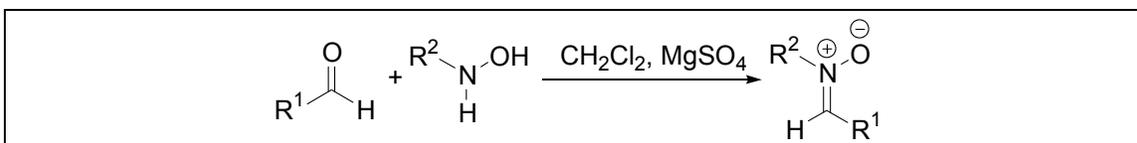
⁷¹ S. Cicchi, M. Marradi, A. Goti, A. Brandi, *Tetrahedron Lett.* **2001**, 42, 6503.

⁷² A. Goti, S. Cicchi, V. Fedi, L. Nannelli, A. Brandi, *J. Org. Chem.* **1997**, 62, 3119.

⁷³ S. Cicchi, M. Corsi, A. Goti, *J. Org. Chem.* **1999**, 64, 7243.

⁷⁴ A. Goti, F. Desarlo, M. Romani, *Tetrahedron Lett.* **1994**, 35, 6571.

⁷⁵ R. F. Borch, M. D. Berstein, H. D. Durst, *J. Am. Chem. Soc.* **1971**, 93, 2897.

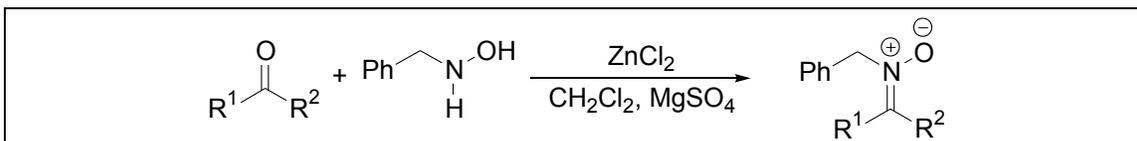


Scheme 37

N-benzylaldonitrones (where $\text{R}^2=\text{Bn}$) are particularly interesting as synthetic intermediates since after reaction of the nitron, easy deprotection of the benzyl group by hydrogenolysis⁷⁶ give access to amines.

2.2.2.2 With ketones:

The condensation of aliphatic ketones with *N*-hydroxylamines may be sluggish and the formed ketonitrones are generally unstable. The reactions are usually favoured by the addition of a Lewis acid, the best results being obtained with anhydrous zinc (II) chloride.⁷⁷ Ketones with electron-withdrawing groups in the α -position⁷⁸ are activated for condensations thus obviating the need for Lewis acids.



Scheme 38

2.2.3 Synthesis from Oximes:

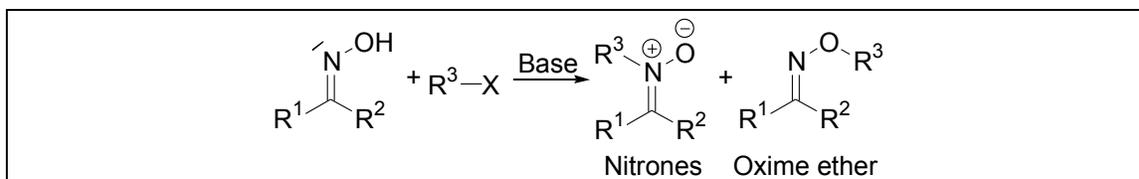
The reaction of an oxime with an alkylating agent represents an useful method of generating nitrones although a mixture of products due to O-Alkylation and N-Alkylation is generally obtained⁷⁹. The chemoselectivity of the reaction is governed by the configuration of the oxime. In case of aldoximes, the *Z*-oxime is more reactive than the *E*-oxime due to unfavourable steric interactions in the latter between the nitrogen lone-pair electrons and the substituent group bonded to the iminium carbon atom.

⁷⁶S. Franco, F. Junquera, F. Merchan, P. Merino, T. Tejero, *Synth. Commun.* **1994**, 24, 2537.

⁷⁷S. Franco, F. Merchan, P. Merino, T. Tejero, *Synth. Commun.* **1995**, 25, 2275.

⁷⁸E. G. Janzen, Y. K. Zhang, M. Arimura, *J. Org. Chem.* **1995**, 60, 5434.

⁷⁹T. Polonski, A. Chimiak, *J. Org. Chem.* **1976**, 41, 2092.



Scheme 39

2.2.4 Reactivity of nitrones

The nitrones present three types of reactivity:

- 1,3-Dipolar cycloaddition – the most commonly studied and used reaction.
- Nitrones are useful for trapping free radicals in the chemical and biological systems. This property of nitrones was studied and developed especially during last years.
- Nitrones are excellent electrophiles, therefore they are widely used in nucleophilic addition. We will detail particularly this reaction which put in motion the polarized character of double bond C=N of nitrones.

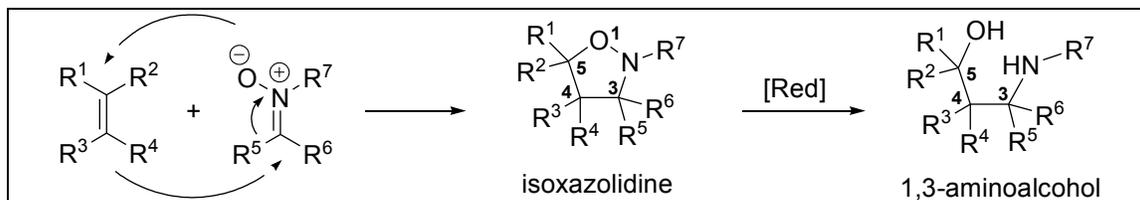
2.2.4.1 1,3-Dipolar cycloaddition

The nitrones are excellent 1,3-dipoles owing to their allylic anion type of structure. They can undergo 1,3-dipolar cycloaddition with a large number of unsaturated compounds (dipolarophiles): alkynes, alkenes, ketenes, ketenimines, nitriles, isocyanates, isothiocyanates, carbodiimides, aziridinium and azetidinium salts, carbon disulfide, thioketenes, sulfenes, phosphoranes, iminophosphoranes and N-suphydryl compounds. The most commonly studied substrates for the cycloaddition reaction with nitrones are alkenes.

The reactions with alkenes allow creation of several adjoining stereogenic centers at the desired molecules (Scheme 40). The relative stereochemistry of C-3 and C-4 is controlled by the *E* or *Z geometry* of the alkene. The configuration of C-5 is governed by facial diastereoselectivity of the cycloaddition reaction known as endo/exo selectivity.

The stereoselectivity of this reaction can be improved by using alkenes or nitrones that already possess a stereocenter (in this case the chirality can be α to the nitrogen atom⁸⁰ or carbon atom⁸¹ of the C=N bond).

This reaction allows the formation of isoxazolidines, useful as synthetic intermediates, and after subsequent ring opening, to the 1,3-aminoalcohols⁸² - precursors of bio-active molecules⁸³, amino acids and amino sugars⁴² (Scheme 40).



Scheme 40

The isoxazolidine ring can be opened (by catalytic hydrogenation with Pd or Ni-Raney or zinc in acidic conditions) with retention of configuration at the stereo centers.

Cycloaddition reactions can also occur in the presence of metallic complexes⁸⁴ ($\text{ZnI}_2/\text{TiCl}(\text{O}i\text{-Pr})_3$, $\text{ZnI}_2/\text{TiCl}(\text{O}i\text{-Pr})_2$) in order to provide a novel diastereoselective version. The intramolecular versions of this cycloaddition has been described in the literature which allows an access to bicyclic products.^{42,85}

2.2.4.2 Radical reactions

Nitrones are used in the chemical and biological systems as trapping agents of free radicals. Addition of these short-lived radicals to nitrones results in formation of more stable nitroxide radical that can be detected by ESR.

⁸⁰ A. Vasella. *Helv. Chim. Acta*, **1977**, *60*, 426 and 1273.

⁸¹ E. G. Baggiolini, J. A. Iacobelli, B. M. Hennesy, A. D. Batcho, U. J. Sereno, M. R. Uskokovic. *J. Org. Chem.* **1986**, *51*, 3098.

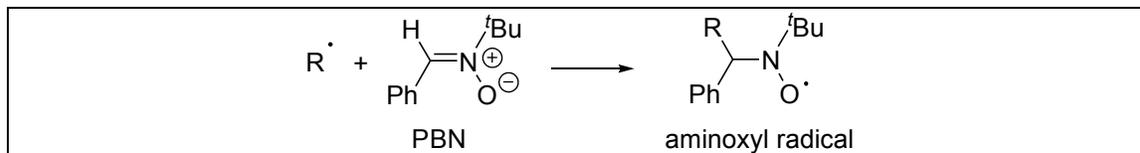
⁸² K. V. Gothelf, K. A. Jorgensen. *Chem. Rev.*, **1998**, *98*, 863.

⁸³ J. C. Rohloff, T.V. Alfredson, M. A. Schwartz. *Tetrahedron Lett.*, **1994**, *35*, 1011.

⁸⁴ S. Kanemasa, T. Uemura, E. Wada, *Tetrahedron Lett.*, **1992**, *33*, 7889.

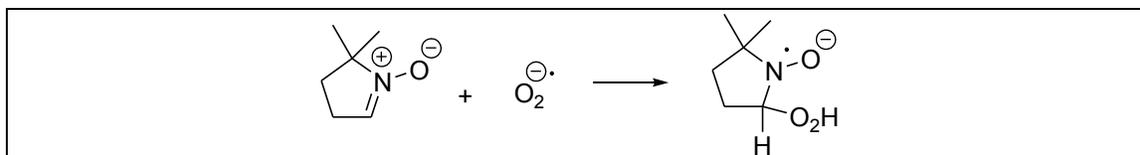
⁸⁵ N. A. Le Bel, J. J. Whang, *J. Am. Chem. Soc.*, **1959**, *81*, 6334.

α -phenyl-*tert*-butylnitron (PBN) is the archetype of such spin-traps. The aminoxyl radical formed after radical trapping was detected and identified by EPR⁸⁶ by its hyperfine coupling constants (Scheme 41).



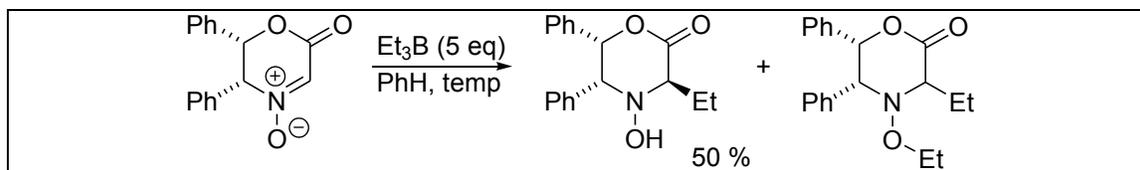
Scheme 41

During oxidative stress in the biological system a superoxide radical ($O_2^{\cdot-}$) is formed. Its presence results in cell death. Several nitron families were tested for *in vivo* superoxide radical trapping activity,⁸⁷ for example 5,5-dimethyl-1-pyrroline-*N*-oxyde (DMPO)⁸⁸ (Scheme 42).



Scheme 42

Recently, Naito and coworkers⁸⁹ demonstrated that radical reaction between nitrones and triethylborane could be used for the formation of the new C-C bond. Later, they developed a novel asymmetric synthesis of α -amino acids by alkyl radical addition to the chiral glyoxylic nitron below (Scheme 43).



Scheme 43

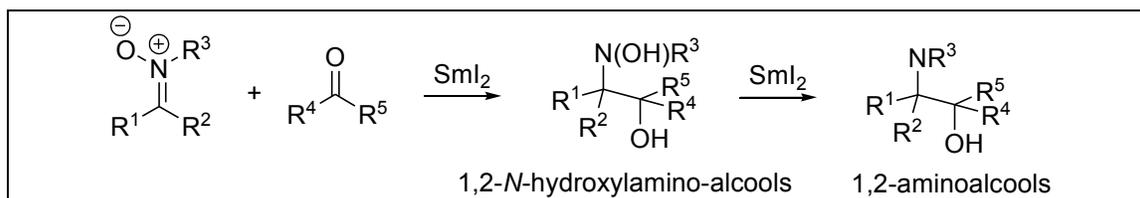
⁸⁶ R. D. Hinton, E.G. Janzen *J. Org. Chem.*, **1992**, *57*, 2646.

⁸⁷ review: R. A. Floyd, *Aging Cell*, **2006**, *5*, 51.

⁸⁸ F. A. Villamena, J.L. Zweier *J. Chem. Soc., Perkin Trans. 2*, **2000**, 1340.

⁸⁹ a) H. Miyabe, M. Ueda, T. Naito *J. Org. Chem.*, **2000**, *65*, 5043; b) M. Ueda, H. Miyabe, M. Teramachi, O. Miyata, T. Naito *Chem. Comm.*, **2003**, 426.

Masson and Py⁹⁰ reported intra- and intermolecular reductive coupling between nitrones and carbonyl compounds. The intermolecular version was chemoselective, giving access to highly substituted vicinal *N*-hydroxylamino-alcohols and amino alcohols (Scheme 44).



Scheme 44: SmI₂-induced reductive heterocoupling

2.2.4.3 Nucleophilic additions

The strong polarization of the C=N bond of nitrones confers them a strong electrophilic character. This makes nitrones much better electrophiles than simple imines.

Organomagnesium and organolithium reagents

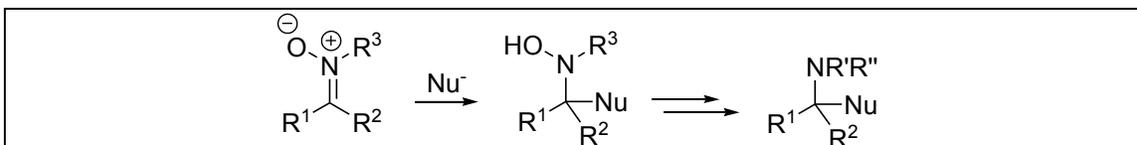
The reaction of organomagnesium or organolithium reagents with nitrones is about as old as the organometallic species themselves⁹¹, and been subject to renewed interest in the last 20 years, mainly with the development of enantiopure nitrones as

⁹⁰ a) G. Masson *PhD thesis*, Joseph Fourier, Grenoble, **2003**. b) G. Masson, S. Py, Y. Vallee *Angew. Chem. Int. Ed.*, **2002**, *41*, 1772.

⁹¹ A. Angeli, L. Alessandri, M. Aiazzi-Mancini *Atti Reale Accad. Lincei (Rome)*, **1911**, *20*, 546. *Chem. Abstr.*, **1911**, *5*, 3403.

substrates.^{35,92} Indeed, recent work has dealt with the addition of alkyl⁹³, aryl,⁹⁴ allyl⁹⁵ and alkynyl⁹⁶ lithium reagents onto nitrones.

These different reactions generally resulted in the corresponding *N*-hydroxylamine that can be transformed in highly functionalized amine derivatives such as α,β -unsaturated γ -amino-esters, α,β -saturated γ -amino-esters, γ -lactams, 2-pyrrolidones, isoxazolidines (Scheme 45).



Scheme 45

Organozinc reagents

The symmetrical organozinc reagents are relatively unreactive species, that are amenable to very selective reactions, and particularly to enantioselective additions. Alkynylzinc reagents have been successfully added to nitrones to yield *N*-hydroxypropargylamines.^{97,98,99} Carreira used zinc triflate and triethylamine to generate

⁹² a) J. Revuelta; S. Cicchi; A. Goti; A. Brandi, *Synthesis*, **2007**, 485; c) P. Merino, *Comptes Rendus Chimie*, **2005**, 8, 775; d) P. Merino; V. Mannucci; T. Tejero, *Tetrahedron*, **2005**, 61, 3335; e) P. Merino Product class 13: nitrones and cyclic analogues. *Science Of Synthesis*; G. Thieme Verlag: New York, 2005, **27**; pp 511-580; f) M. Bonanni; M. Marradi; S. Cicchi; C. Faggi; A. Goti, *Org. Lett.*, **2005**, 7, 319; g) R. Portoles; J. Murga; E. Falomir; M. Carda; S. Uriel; J. A. Marco, *Synlett*, **2002**, 711; h) M. Lombardo; C. Trombini, *Curr. Org. Chem.* **2002**, 6, 695; i) M. Lombardo, C. Trombini *Synthesis*, **2000**, 56, 759; j) A. Dondoni; F. L. Merchan; P. Merino; T. Tejero, *Synth. Commun.*, **1994**, 24, 2551.

⁹³ P. Merino; I. Delso; T. Tejero; F. Cardona; M. Marradi; E. Faggi; C. Parmeggiani; A. Goti, *Eur. J. Org. Chem.*, **2008**, 2929-2947; b) A. Dondoni, D. Perrone, M. Rinaldi, *J. Org. Chem.* **1998**, 63, 9252; c) V. Capriati; S. Florio; R. Luisi; A. Salomone; C. Cuocci, *Org. Lett.*, **2006**, 8, 3923; d) J. Murga; R. Portoles; E. Falomir; M. Carda; J. A. Marco, *Tetrahedron: Asymmetry*, **2005**, 16, 1807; e) Y. Kazuta; H. Abe; A. Matsuda; S. Shuto, *J. Org. Chem.*, **2004**, 69, 9143.

⁹⁴ a) P. Merino; I. Delso; T. Tejero; F. Cardona; A. Goti, *Synlett*, **2007**, 2651. b) A. Dondoni; A. Nuzzi, *J. Org. Chem.*, **2006**, 71, 7574.

⁹⁵ a) H. M. S. Kumar, S. Ajaneyulu, E. J. Reddy, J. S. Yadav, *Tetrahedron Lett.* **2000**, 41, 9311; b) P. Merino; I. Delso; V. Mannucci; T. Tejero, *Tetrahedron Lett.*, **2006**, 47, 3311; c) D. D. Dhavale; S. M. Jachak; N. P. Karche; C. Trombini, *Tetrahedron*, **2004**, 60, 3009.

⁹⁶ a) P. Merino; P. Padar; I. Delso; M. Thirumalaikumar; T. Tejero; L. Kovacs, *Tetrahedron Lett.*, **2006**, 47, 5013. b) C. Pillard; V. Desvergnès; S. Py, *Tetrahedron Lett.*, **2007**, 48, 6209.

⁹⁷ A. Pernet-Poil-Chevrier; F. Cantagrel; K. Le Jeune; C. Philouze; P. Y. Chavant, *Tetrahedron: Asymmetry*, **2006**, 17, 1969.

⁹⁸ F. Cantagrel; S. Pinet; Y. Gimbert; P. Y. Chavant, *Eur. J. Org. Chem.*, **2005**, 2694.

⁹⁹ S. Pinet; S. U. Pandya; P. Y. Chavant; A. Ayling; Y. Vallee, *Org. Lett.*, **2002**, 4, 1463.

alkynylzinc species *in situ* from 1-alkyne, and add these reagents onto nitrones.¹⁰⁰ Inomata¹⁰¹ described an enantioselective addition of alkynylzinc with a tartrate derivative as chiral auxiliary, and extended recently this system to diarylzinc reagents¹⁰² We have already mentioned the our addition of vinylzinc reagents onto nitrones;¹⁰³ an enantioselective version was recently proposed.¹⁰⁴

¹⁰⁰ D. E. Frantz; R. Faessler; E. M. Carreira, *J. Am. Chem. Soc.*, **1999**, *121*, 11245.

¹⁰¹ W. Wei, M. Kobayashi, Y. Ukaji, K. Inomata, *Chem. Lett.*, **2006**, *35*, 176; Y. Ukaji; Y. Kenmoku; K. Inomata, *Tetrahedron: Asymmetry*, **1996**, *7*, 53-56.

¹⁰² W. Wei, Y. Hamamoto, Y. Ukaji, K. Inomata, *Tetrahedron: Asymmetry*, **2008**, *19*, 476.

¹⁰³ S. U. Pandya; S. Pinet; P. Y. Chavant; Y. Vallée, *Eur. J. Org. Chem.*, **2003**, 3621.

¹⁰⁴ S. A. Wang; C. T. Seto, *Org. Lett.*, **2006**, *8*, 3979

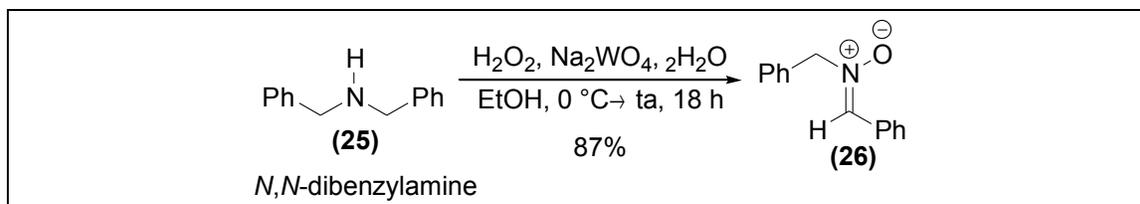
2.3 Results and discussion: dimethylzinc-mediated vinylation of nitrones.

2.3.1 The electrophilic species: Nitrones – Choice and preparation

For this study, we have synthesized different nitrones either by oxidation methods or by condensation of aldehydes with *N*-benzylhydroxylamine as previously described in the bibliographic section.

2.3.1.1 *N*-benzylidene benzylamine *N*-oxide

This nitrone was prepared according to the procedure described by Murahashi and coworkers¹⁰⁵ Oxidation of dibenzylamine **25** with hydrogen peroxide in the presence of a catalytic quantity of sodium tungstate leads to the formation of of *N*-benzylidene benzylamine *N*-oxide **26** (Scheme 46). A series of washings with pentane, precooled to 5 °C, produced the nitrone as a crystalline solid with 87% yield.



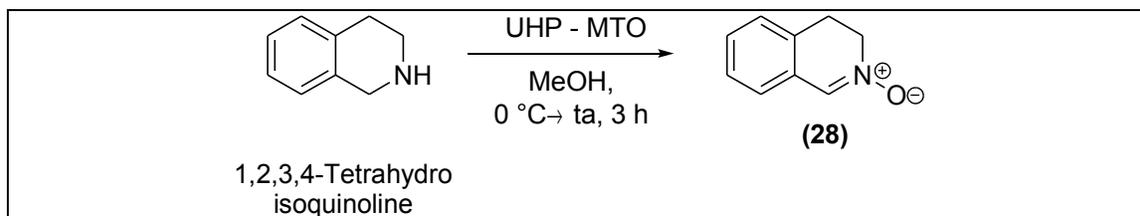
Scheme 46

2.3.1.2 3,4-Dihydroisoquinoline *N*-oxide

Another oxidation protocol was applicable for the synthesis of the cyclic nitrone 3,4-dihydroisoquinoline *N*-oxide **28** from 1,2,3,4-tetrahydroisoquinoline. Oxidation was effected with Urea-Hydrogen peroxide complex and catalytic amounts of

¹⁰⁵ a) S. -I, Murahashi, T. Shiota, Y. Imada, *Org. Synth.* **1998**, 9, 632. b) S. -I, Murahashi, T. Shiota, *Tetrahedron Lett.* **1987**, 28, 6469.

Methyltrioxorhenium (MTO) in methanol¹⁰⁶¹⁰⁷¹⁰⁸ (Scheme 47). Note in that case the regioselectivity of the oxidation.

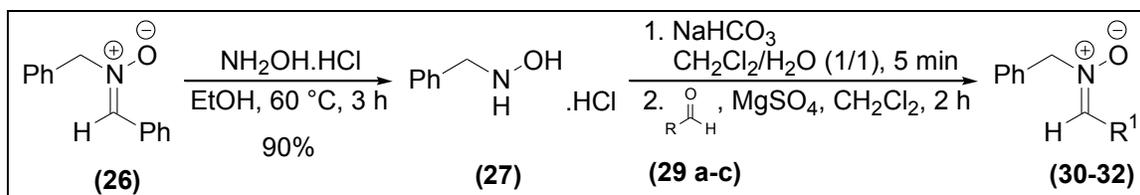


Scheme 47

2.3.1.3 Other nitrones

Three other nitrones were prepared by the condensation of *N*-benzylhydroxylamine **3** with the corresponding aldehydes according to the procedure described by Dondoni (Scheme 48).¹⁰⁹

Although *N*-benzylhydroxylamine is commercially available, for economic reasons, its preparation in the laboratory from nitron **5a** is preferred.



Scheme 48

¹⁰⁶ a) A. Goti; F. Cardona; G. Soldaini, *Org. Synth.* **2004**, *81*, 204; b) A. Goti; L. Nannelli, *Tetrahedron Lett.*, **1996**, *37*, 6025.

¹⁰⁷ J. Einhorn, C. Einhorn, F. Ratajczak, A. Durif, M.T. Averbuch, J.-L. Pierre, *Tetrahedron Lett.* **1998**, *39*, 2565.

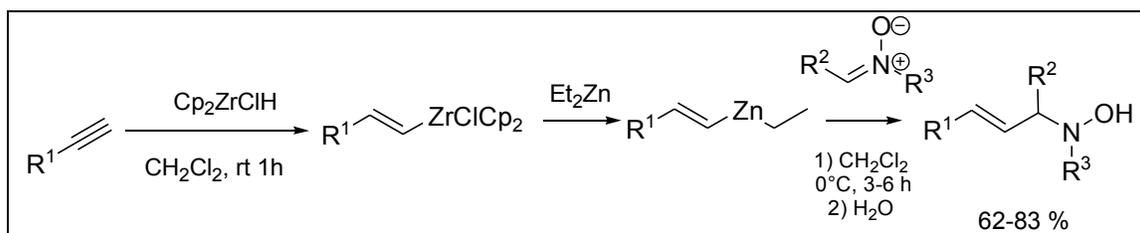
¹⁰⁸ A. Long; S. W. Baldwin, *Tetrahedron Lett.*, **2001**, *42*, 5343.

¹⁰⁹ A. Dondoni; S. Franco; F. Junquera, F. L.; P. Merino; T. Tejero, *Synth. Commun.*, **1994**, *24*, 2537.

In the preceding work of our group, we adapted two preparations of alkenylzinc species, originally used for enantioselective vinylations of aldehydes,¹¹⁰ to the additions onto nitrones. Both methods used dialkylzinc reagents for the transmetallation step of Scheme 49.

2.3.3 Hydrozirconation pathway

In our first study on the vinylation of nitrones, the group had used Wipf's procedure¹¹¹ involving hydrozirconation of alkynes with Schwartz's reagent (Cp_2ZrClH) followed by transmetallation with dialkylzinc to yield pure *E* vinylzinc species. The resulting organometallic reagents add readily onto nitrones, under mild conditions, to give secondary *N*-hydroxylamines in good yields¹¹².



Scheme 50

The use of stoichiometric amounts of Schwartz's reagent restricted its scope to small scale reactions. Thus, we sought an analogous sequence in which the hydrozirconation could be replaced by a hydroboration reaction, which is more robust and economical¹¹³ and would allow greater flexibility.

¹¹⁰ a) Y. K. Chen, A. E. Lurrain, P. J. Walsh, *J. Am. Chem. Soc.* **2002**, 124, 12225. b) A. E. Lurrain, P. J. Walsh, *J. Am. Chem. Soc.* **2003**, 125, 10677. c) A. E. Lurrain, P. J. Carroll, P. J. Walsh, *J. Org. Chem.* **2005**, 70, 1262. d) A. R. Kelly, A. E. Lurrain, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, 125, 14668. e) S. Dahmen, S. Bräse, *Org. Lett.* **2001**, 25, 4119. f) F. Lauterwasser, J. Gall, S. Höfener, S. Bräse, *Adv. Synth. Catal.* **2006**, 348, 2068. g) C. M. Sprout, M. L. Richmond, C. T. Seto, *J. Org. Chem.* **2004**, 69, 6666. h) C. M. Sprout, M. L. Richmond, C. T. Seto, *J. Org. Chem.* **2005**, 70, 7408. i) M. L. Richmond, C. M. Sprout, C. T. Seto, *J. Org. Chem.* **2005**, 70, 8835. j) S. -L. Tseng, T. -K. Yang, *Tetrahedron: Asymmetry* **2005**, 16, 773. k) J. -X. Ji, L. Q. Qiu, C. W. Yip, A. S. C. Chan, *J. Org. Chem.* **2003**, 68, 1589.

¹¹¹ a) P. Wipf, R. L. Nunes, *Tetrahedron* **2004**, 60, 1269. b) P. Wipf, N. Jayasuriya, S. Ribe, *Chirality* **2003**, 15, 208. c) P. Wipf, C. Kendall, *Chem. Eur. J.* **2002**, 8, 1779. d) P. Wipf, S. Ribe, *J. Org. Chem.* **1998**, 63, 6454.

¹¹² S. U. Pandya, C. Garcon, P. Y. Chavant, S. Py, Y. Vallee, *Chem. Commun.* **2001**, 1806.

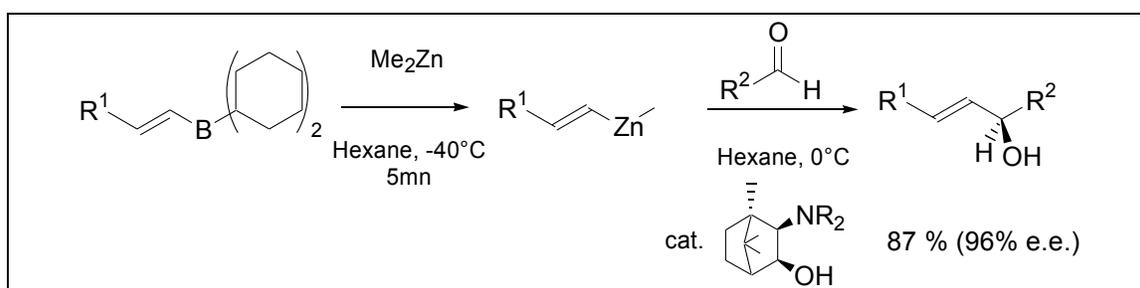
¹¹³ Cp_2ZrClH , Aldrich, 3225 \$/mole; $\text{BH}_3\cdot\text{DMS}$, Aldrich, 95 \$/mole.

2.3.4 Hydroboration pathway

Of the various hydrometallation reactions of alkynes¹¹⁴ leading to stereospecifically defined metallated alkenes, the most general is probably that of a borane with a suitable alkyne.¹¹⁵ Transfer of the alkenyl group from boron to zinc would then give the desired alkenylzinc that could add onto nitrones to give the corresponding *E*-allyl hydroxylamine.

Thus our second procedure was inspired from the work of Oppolzer¹¹⁶ (Scheme 51) and Srebnik,¹¹⁷ (Scheme 52) based on the hydroboration of terminal alkynes followed by *in situ* boron-zinc transmetalation with dialkylzinc. The vinylboranes thus obtained can be added onto aldehydes enantioselectively in the presence of various amino-alcohol catalysts.

Oppolzer et al.:



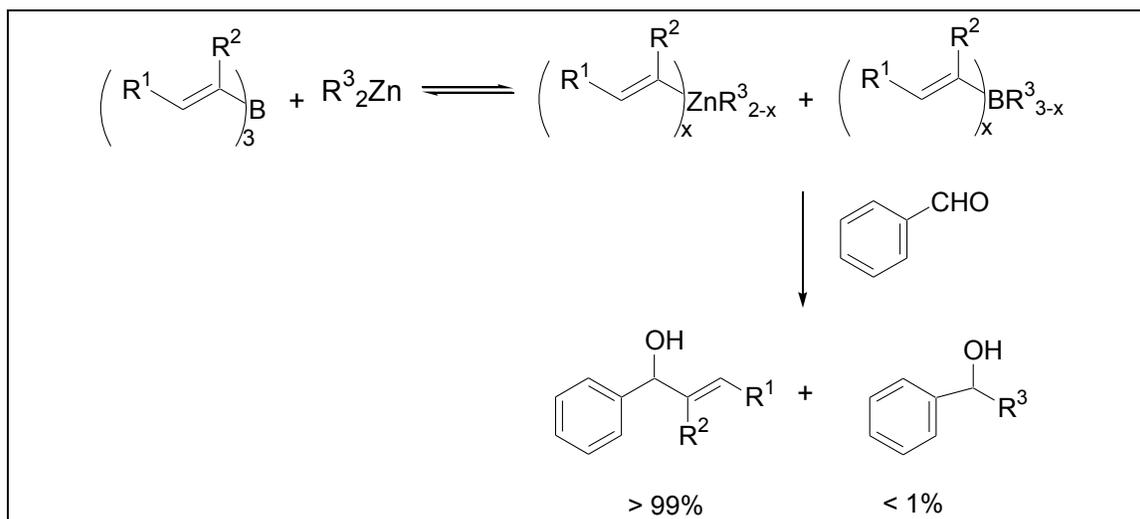
Scheme 51

¹¹⁴ a) **Hydrozirconation:** E. Negishi, T. Takahashi, *Aldrichim. Acta* **1985**, 18, 31. b) **Carboalumination:** R. E. Ireland, P. Wipf, *J. Org. Chem.* **1990**, 55, 1425 and references cited therein. c) **Carbocupration:** M. Gardetta, A. Alexakis, J. F. Normant, *Tetrahedron*, **1985**, 41, 5887. d) **Aluminium, copper, lithium, magnesium, zinc:** J. F. Normant, A. Alexakis, *Synthesis*, **1981**, 841. e) **Vinylboranes:** J. A. Soderquist, J. Vaquer, *Tetrahedron Lett.* **1990**, 31, 4545. f) For a discussion of the merits of various metallated alkenyl species, see: J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*; Univ. Science Books: Mill Valley, **1987**.

¹¹⁵ a) A. Pelter, K. Smith, H. C. Brown, *Borane Reagents*; Academic Press: London, **1988**. b) B. M. Mikhailov, Y. N. Bubnov, *Organoboron Compounds in Organic Synthesis*; Harwood Academic Publishers GmbH: Chur, **1984**.

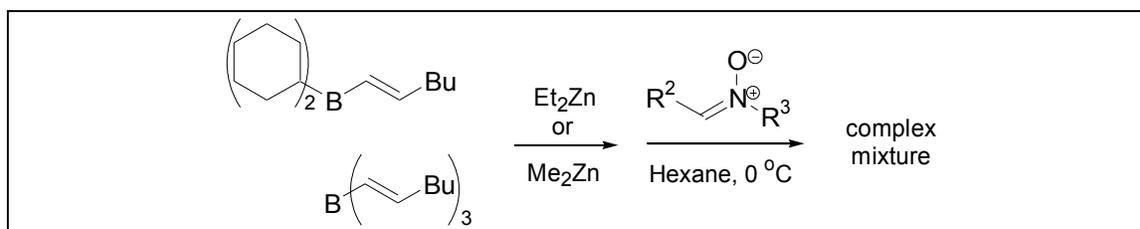
¹¹⁶ a) W. Oppolzer, R. N. Radinov, E. El-Sayed, *J. Org. Chem.* **2001**, 66, 4766. b) W. Oppolzer, R. N. Radinov, *J. Am. Chem. Soc.* **1993**, 115, 1593. c) W. Oppolzer, R. N. Radinov, *Helv. Chim. Acta* **1992**, 75, 170. d) W. Oppolzer, R. N. Radinov, *Tetrahedron Lett.* **1998**, 29, 5645.

¹¹⁷ a) K. A. Agrios, M. Srebnik, *J. Organomet. Chem.* **1993**, 444, 15. b) M. Srebnik, *Tetrahedron Lett.* **1991**, 32, 2449.

Srebnik *et al.*:

Scheme 52

Our attempts to adapt directly Oppolzer's and Srebnik's methods (from dicyclohexyl(vinyl) borane and trivinylborane, respectively) to nitrones led to complex mixture of products. We concluded that the very reactive nitrones reacted unselectively with all carbon-zinc bonds, leading to ethyl and cyclohexyl⁴⁶ adducts as well as vinyl.^{51b} (Scheme 53)



Scheme 53

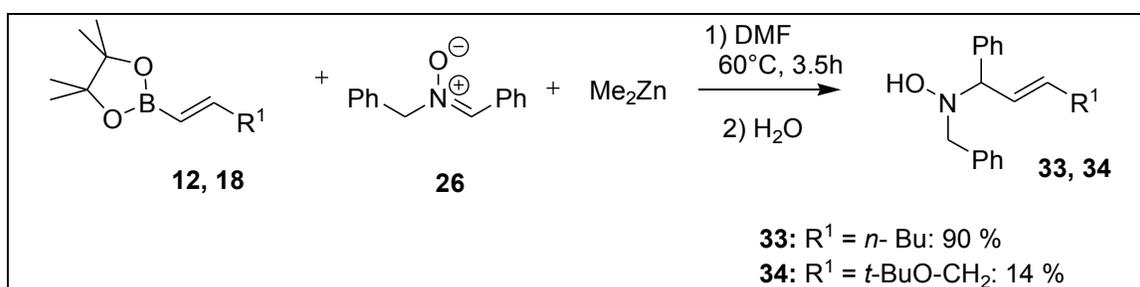
In view of the good stability, mild reactivity and the easy availability of cyclic alkenylboronic esters, we conceived that the generation of alkenylzinc species from them could provide a useful access to allyl-hydroxylamines. However, keeping in mind that the structures of alkenylboronic esters and particularly the nature of the diol¹¹⁸ could have an

¹¹⁸ For a related study on the reactivities of allylboronates with different alcohol moieties to aldehydes, see: a) H. C. Brown, U. S. Racherla, P. J. Pellechia, *J. Org. Chem.* **1990**, 55, 1868. b) S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2006**, 128, 12660. c) T. J. Southwood, M. C. Curry, C. A. Hutton, *Tetrahedron* **2006**, 62, 236.

influence on their reactivities, we have examined the effect of the structure of the alkenylboronic esters on the outcome of the reaction.

2.3.5 The use of alkenylboronic esters from pinacol:

We first considered the use of vinylboronic ester **1**, derived from pinacol. These esters of pinacol were easily and conveniently prepared in pure *trans* form by hydroboration of alkynes with pinacolborane.¹¹⁹ The vinylboronic esters of pinacol, in the presence of dimethylzinc, could transfer selectively the vinyl rest to nitrones to yield *N*-hydroxy-allylamines in fair yields.⁴⁶ (Scheme 54)



Scheme 54

Nevertheless, the pinacolboronate esters reacted sluggishly, and our process required rather harsh conditions (DMF, 60°C). This limited the scope, particularly in terms of functional groups on the vinylboronic ester. For example, the hydroboration step was compatible with a functional group in allylic position,^{17,120,121} and highly functional vinylboronic esters like **1b** (Scheme 54, R¹ = CH₂O^tBu) were readily accessible. But the yield in hydroxylamine adduct was very low in this case.⁴⁶

2.3.6 Boronic esters derived from 2,2-dimethyl-1,3-propanediol:

We next turned to boronic esters derived from 5,5-dimethyl-1,3,2-dioxaborinanes.¹²² The protection of boronic acids with 2,2-dimethylpropane 1,3-diol is a well-known, convenient alternative to the use of pinacol. The corresponding esters can be

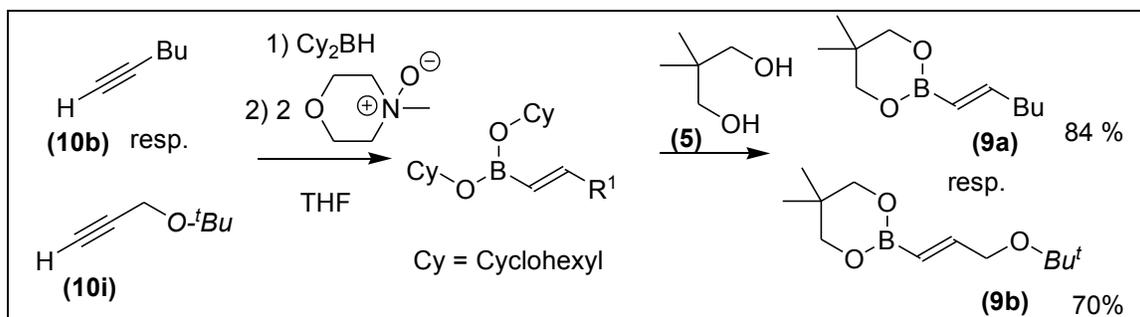
¹¹⁹ a) C. E. Tucker, J. Davidson, P. Knochel, *J. Org. Chem.* **1992**, *57*, 3482; b) T. Ohmura, Y. Yamamoto, N. Miyaura, *J. Am. Chem. Soc.* **2000**, *122*, 4990; c) S. Pereira, M. Srebnik, *Tetrahedron Lett.* **1996**, *37*, 3283.

¹²⁰ C. M. Vogels, S. A. Westcott, *Curr. Org. Chem.* **2005**, *9*, 687.

¹²¹ K. Shirakawa, A. Arase, M. Hoshi, *Synthesis* **2004**, 1814.

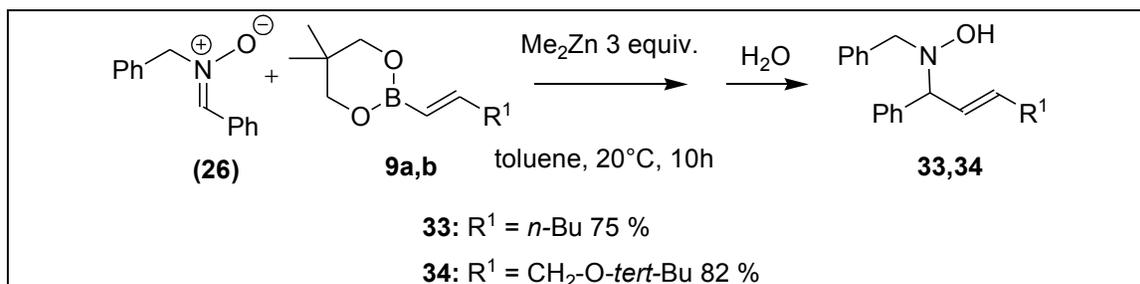
¹²² K. Kobayashi; Nakayama; Mizojiri, *Tetrahedron* **1998**, *54*, 1053.

easily handled and stored. We obtained samples of the vinylboronic esters with the efficient one-pot sequence proposed by Hoffmann and coworkers^{29,29,29,123} starting from dicyclohexylborane (Scheme 55). The 5,5-dimethyl-2-vinyl-1,3,2-dioxaborinanes **4a,b** were purified by flash chromatography. They could be stored in neat form at room temperature.



Scheme 55: Reaction of 5,5-dimethyl-2-vinyl-1,3,2-dioxaborinanes, dimethylzinc and a nitron.

Very interestingly, these boronic esters **4** reacted with nitrones and dimethylzinc to yield *N*-allyl-hydroxylamines at 20°C within 3 hours, provided that 3 molar equiv. of dimethylzinc were used (Scheme 56; vinylboronic esters of pinacol **1** required 60 °C in DMF). The best solvents were toluene and dichloromethane; the reactions were slower in THF.



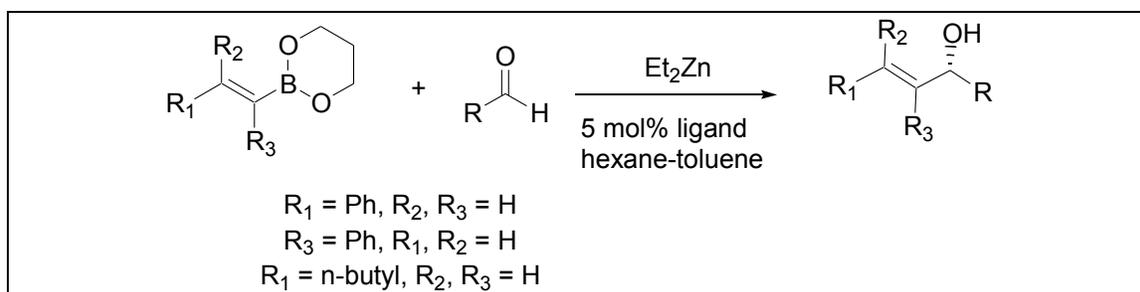
Scheme 56

The increased reactivity of the unhindered boronic esters compared to pinacol esters made it possible to use much milder conditions that were compatible with more

¹²³ R. W. Hoffmann, S. Dresely, *Synthesis* **1988**, 103.

functionalized molecules. The functional pinacol vinylboronate **1b** led mainly to degradation products (14% yield in **3b**, Scheme 54). In the new conditions, the corresponding **4b** produced the addition product in high yield (82%, Scheme 56). Thus, unhindered boronic esters could clearly enlarge the scope of the method, without loss of the practical advantages of using air- and chromatography-stable reagents. But at this stage of the work, we considered that the need to use dicyclohexylborane for the preparation of **4** deeply lowered the practical interest of the reaction with regard to existing methods.⁵¹

Recently, Chai and coworkers¹²⁴ described the transmetallation of unhindered 2-vinyl-1,3-dioxaborinanes with diethylzinc at 20 °C (Scheme 57). An original preparation of vinylzinc species from vinylboronic acids and diethylzinc should also be noted.¹²⁵ In both papers, the vinylboronic species were obtained from Grignard reagents.



Scheme 57

2.3.7 The use of 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinanes:

It would have been much more interesting to prepare the vinylboronic esters by direct hydroboration of alkynes with the corresponding 5,5-dimethyl-1,3,2-dioxaborinane, but we¹²⁶ and others¹²⁷ observed that this preparation was inefficient. The reagent 5,5-dimethyl-1,3,2-dioxaborinane is prone to a fast disproportionation, releasing BH_3 *in situ* (see Scheme 27 page 27). Thus, in the presence of an alkyne, a mixture of hydroboration products was recovered.

¹²⁴ Z. Chai, X. Y. Liu, J. K. Zhang, G. Zhao, *Tetrahedron: Asymmetry* **2007**, 18, 724.

¹²⁵ F. Schmidt, J. Rudolph, C. Bolm, *Synthesis* **2006**, 3625.

¹²⁶ N. PraveenGanesh, S. d'Hondt, P. Y. Chavant, *J. Org. Chem.* **2007**, 72, 4510.

¹²⁷ a) D. S. Matteson, Product subclass 1: Hydroboranes. In *Science of Synthesis*, 2004, Vol. 6, pp 5-79; b) D. J. Pasto, V. Balasubramanian, P. W. Wojtkowski, *Inorg. Chem.* **1969**, 8, 594.

Thus, as neopentylglycol esters could not be considered owing to their instability, we turned to MPB derivatives.

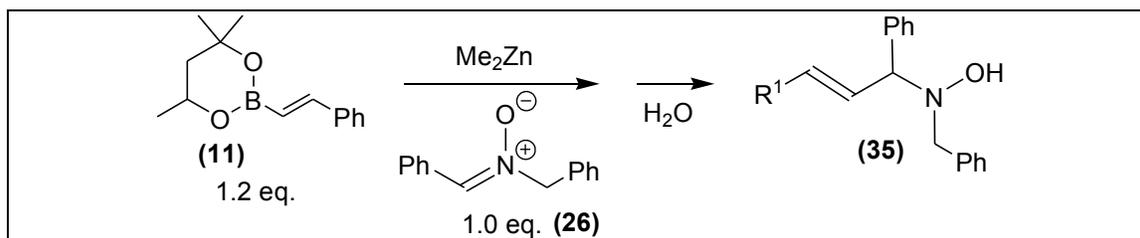
With the method developed in Chapter 2, we have an efficient access to a family of boronic esters that actually are less hindered than pinacol esters. As the steric effect seemed to predominate, we expected that the boronate esters derived from MPBH could be a compromise between the less reactive pinacol esters and the less readily available 2,2-dimethylpropanediol esters, and we submitted the MPB boronic esters to the same reaction.

2.3.8 Optimisation of conditions:

The initial experiments quite clearly revealed that the reactions could be run at lower temperatures and with less dimethylzinc when compared with pinacol boronates. The reaction proceeded to completion in 36 hrs at room temperature. Nevertheless, we found that slightly higher temperatures (40 °C) provided better reactivity, and cleaner reactions without leading to decomposition products.

Our study on the influence of solvent is tabulated below.

Table 4



Entry	Solvent	Time (h)	Dialkylzinc	Vinyl adduct ^a
1.	Toluene	24	3.0 eq.	83%
2.	Toluene	24	2.0 eq	79%
3.	DCM	24	2.0 eq	64%
4.	DMF	24	2.0 eq	68%
5.	CH_3CN	24	2.0 eq	29%

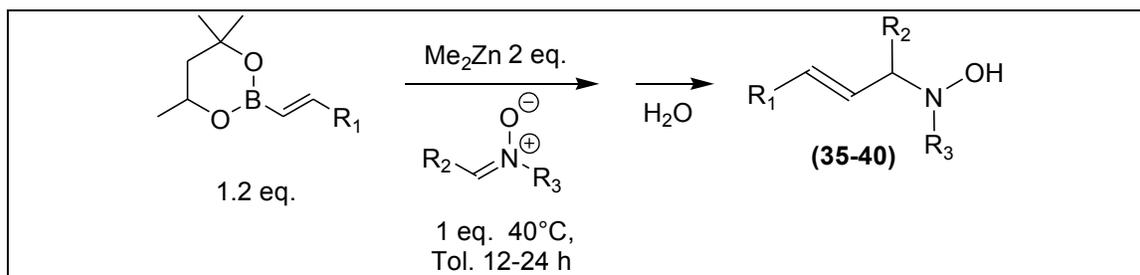
^aIsolated yield

In the case of pinacol boronates, we have already observed the formation of traces of ethyl adducts when diethylzinc was used. Thus we preferred dimethylzinc as the source of alkylzinc. Other zinc salts like ZnF_2 (DMSO, 40 °C, 24 hrs), ZnCl_2 (DMSO, 40 °C, 24 hrs) when used in place of dimethylzinc, did not produce any vinyl adduct.

Of the solvents examined, both toluene and dichloromethane were found suitable while polar solvents like acetonitrile and DMF were less efficient.

We then studied the extension of the reaction to different nitrones and vinyl boronates. (Table 5). The reaction proceeds readily with a variety of functional groups on the vinylic reagents.

Table 5



Entry	R ¹	R ²	R ³	% Yield ^{a,b}	Product No
1	(12)	Ph-CH ₂ -		76	(33)
2	(11)	Ph-CH ₂ -		84	(35)
3	H	Ph-CH ₂ -		77	(36)
4	(13)	Ph-CH ₂ -		60	(37)
5	(11)	Ph-CH ₂ -		64	(39)
6	(11)	Ph-CH ₂ -		67	(40)

a Refers to isolated yields.

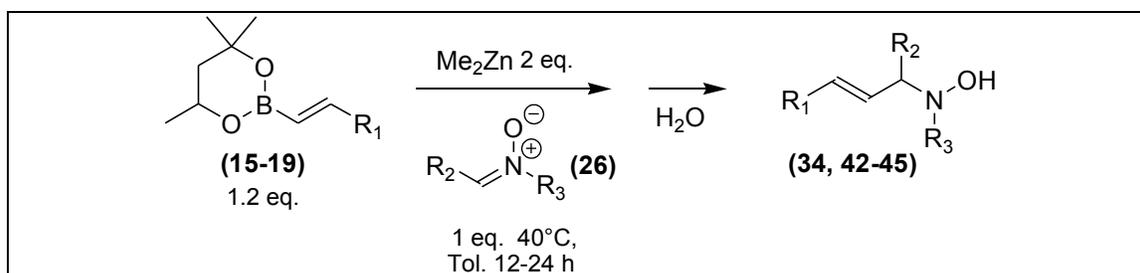
b Reaction conditions: 1.0 eq. of nitronium salt, 1.2 eq. of vinylboronate, 2.0 eq. of DMZ, 24hrs at 40°C

2.3.9 With other functionalized vinyl boronates:

The single major advantage of using vinylboronates derived from MPBH in the above reactions is the better compatibility of various functional groups with the mild reaction conditions. Alkenyl boronates have been scarcely used as alkenyl transfer reagents in the literature.^{55,55}

Our earlier work with pinacolboronates was limited in terms of the functional groups on the alkenyl boronate, because the harsher conditions led to the premature decomposition of the alkenyl zinc species. These limitations were quite clearly overcome under the milder reaction conditions employed.

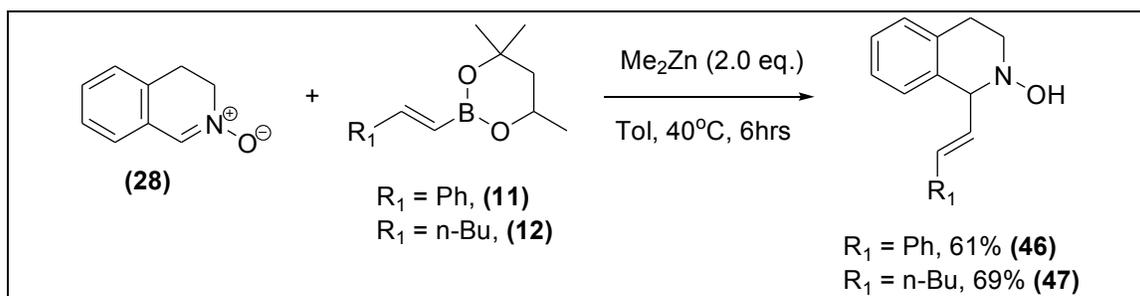
Table 6



Entry	Vinyl Boronate	Nitronium	% Yield ^a	Product No
1	 (18)	 26	80	(34)
2	 (16)	26	75	(42)
3	 (17)	26	63	(43)
4	 (15)	26	60	(44)
5	 (19)	26	31	(45)

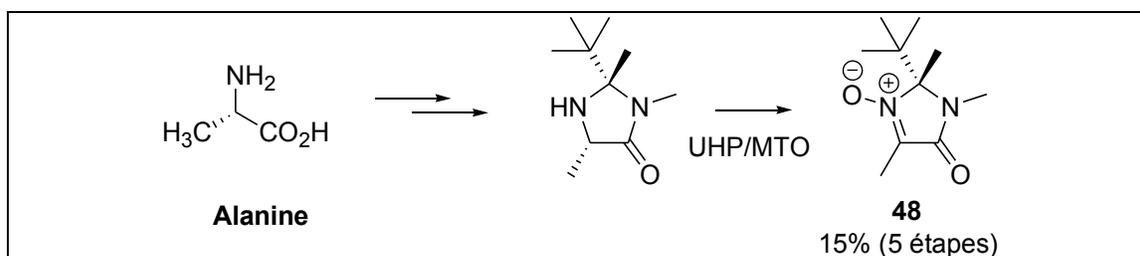
2.3.10 With Cyclic nitrones:

The enantioselective addition of vinylzinc species generated by transmetallation from dialkylalkenylborane reagents to diethylzinc and their subsequent addition onto cyclic nitrones was recently studied by Seto and co-workers.⁴⁶ The cyclic nitron (3,4-dihydroisoquinoline *N*-oxide, reacts faster than the acyclic nitrones (due to the release of steric strain). The reaction of our vinylboronates with 3,4-dihydroisoquinoline *N*-oxide proceeded well (Scheme 58).



Scheme 58

Another cyclic nitron **48**, based on the imidazoline skeleton, is studied in our laboratory for diastereoselective addition of various organometallic reagents¹²⁸ and can be prepared in five steps in 12-15% yield from Alanine⁴⁵ (Scheme 59)

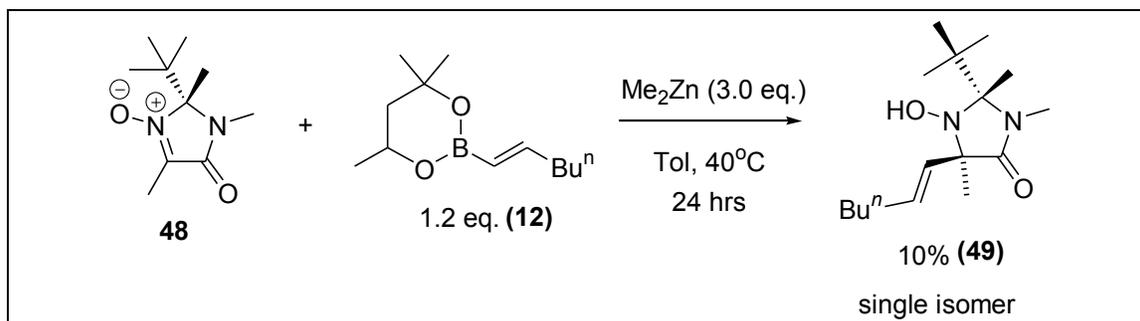


Scheme 59

Addition of a vinylboronate to the cyclic nitron **48** under the new conditions resulted in an incomplete reaction leading to less than 10% of the required hydroxylamine. The ¹H NMR of the reaction mixture revealed that the conversion was very low, but the addition completely diastereoselective. Most of the nitron was recovered unreacted. The sterically hindered nitron is presumably very unreactive

¹²⁸ a) F. Cantagrel, *Préparation et Réactivité de nouvelles Nitrones énantiopures, précurseurs d'acides α-amines*. Thèse Grenoble, **2004**. b) Maryse Thiverny, thèse en cours, Grenoble, **2010**.

towards the addition of vinylzincs. Similar yields were observed with boronate esters derived from pinacolborane (10% yield) and 2,2-dimethylpropanediolborane (14%).⁶⁰

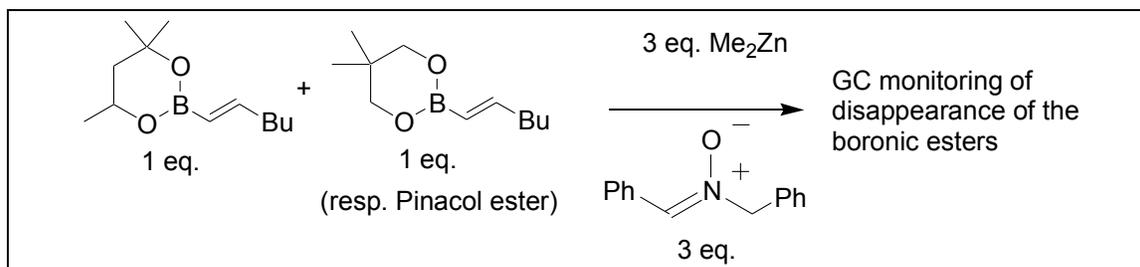


Scheme 60

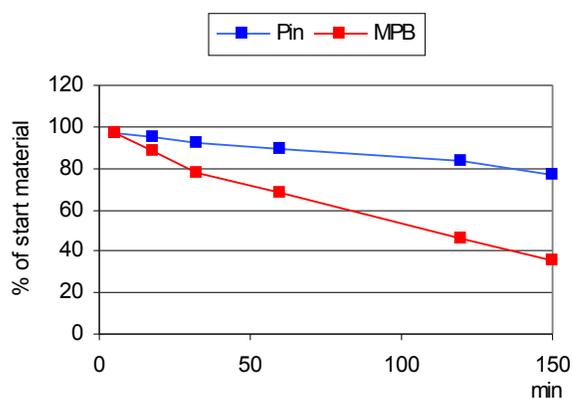
2.3.11 Comparison Experiments:

We have found (§ 1.3) that MPBH reacted faster than pinacolborane in Zr-catalyzed hydroboration. In order to compare accurately the reactivity of the three boronic esters in the present transmetalation-addition sequence, we submitted them to competition experiments: two different vinylboronic esters were put in the same reaction mixtures in the presence of excess dimethylzinc and nitrone. The disappearances of the boronic esters were monitored by gas chromatography and the ratios of the initial speeds were estimated. At $40^\circ C$ pinacol ester reacted 5 times slower than the MPB ester. In turn, MPB ester reacted 4 times slower than the unhindered neopentylglycol ester at $40^\circ C$, and more than 9 times at $60^\circ C$. So, a strong influence of steric factors appears clearly.

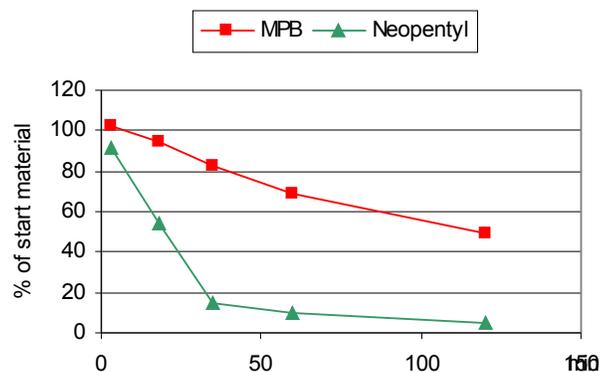
Figure 9: Competition experiments: relative reactivity of pinacol, MPB and neopentylglycol esters in the transmetalation-vinylation.



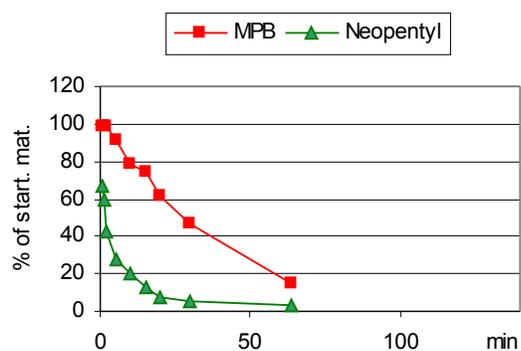
Pin ester/MPB ester at 40°C



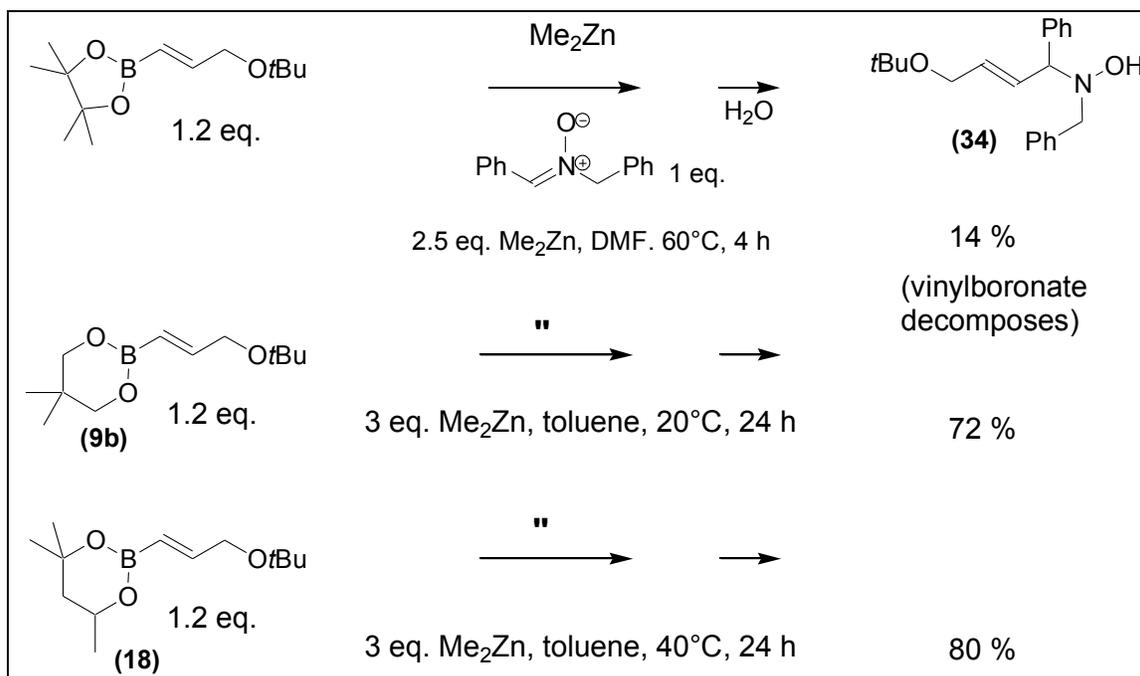
MPB ester/Neopentylglycol ester at 40°C



MPB ester/Neopentylglycol ester at 60°C



The three reactions below are a good summary of our progress in this reaction. Where pinacolboronic esters required harsh conditions that were incompatible with functional groups on the vinyl moiety, less hindered boronic esters combine the advantages of stable and isolable intermediates with a sufficient reactivity. Among these less hindered compounds, MPB esters are readily accessible by alkyne hydroboration.



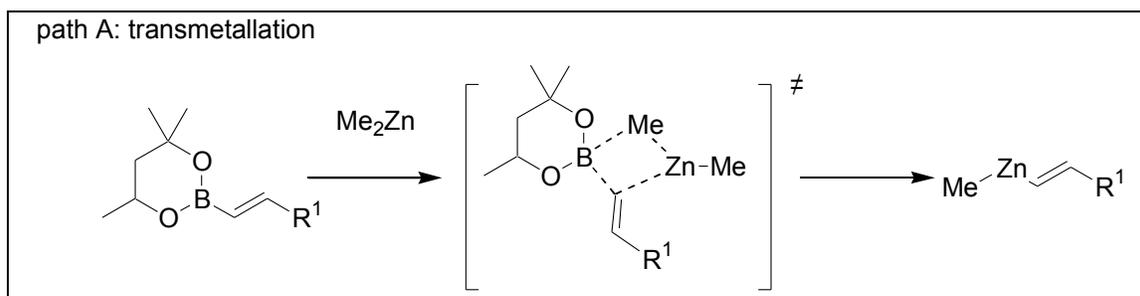
Scheme 61

2.4 Mechanism:

Two possible hypotheses for the mechanism of the reaction can be proposed, which are summarized below.

In the first hypothesis (path A, Scheme 62), a boron-to-zinc transmetallation of the vinyl group would produce a vinyl-methyl-zinc species.

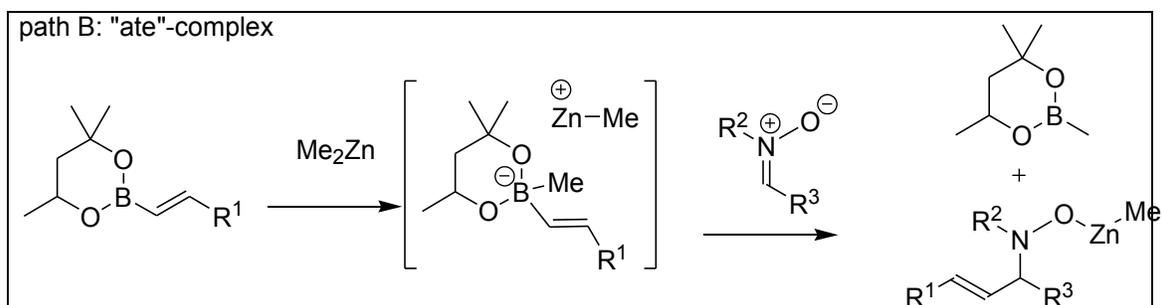
This vinyl-methyl-zinc species would react in a separate step with the nitron to produce the allylic hydroxylamine. It is known that such an organozinc species can selectively transfer the vinyl group to various electrophiles.



Scheme 62: transmetallation hypothesis

The second hypothesis (path B, Scheme 63) involves the formation of a tetracoordinate boronate complex from the boronate ester and dimethylzinc. This anionic boronate complex would react with the nitron and transfer the vinyl group directly from the boron atom. Such reactive species (methyl-vinyl-borate anion) has been widely postulated¹²⁹ in other analogous reactions.

¹²⁹ lithium borates: a) Y. Kobayashi; M. Asano; S. Yoshida; A. Takeuchi, *Org. Lett.*, **2005**, *7*, 1533; b) Y. Kobayashi; A. D. William; R. Mizojiri, *J. Organomet. Chem.*, **2002**, *653*, 91; c) Y. Kobayashi; S. Yoshida; Y. Nakayama, *Eur. J. Org. Chem.*, **2001**, 1873; d) Y. Kobayashi; Y. Nakayama; G. B. Kumar, *Tetrahedron Lett.*, **1998**, *39*, 6337; e) Y. Kobayashi; R. Mizojiri, *Tetrahedron Lett.*, **1996**, *37*, 8531; zinc borates: f) Y. Kobayashi, Y. Tokoro, K. Watatani, *Eur. J. Org. Chem.* **2000**, 3825.



Scheme 63: "ate"-complex hypothesis

We were particularly interested in choosing one hypothesis, since it was important for further development of an enantioselective version of the reaction. If path A is operating, the vinyl zinc reagent could undergo the well-studied¹³⁰ catalytic enantioselective addition reactions of vinylzinc catalyzed by chiral β -aminoalcohols. If path B is at work, a chirality on the dioxaborinane ring could be ultimately transferred to the adduct.

2.4.1 Attempted transmetalation without electrophiles (hypothesis A)

Oppolzer's team observed by 1H NMR that a dicyclohexylvinylborane react within minutes at -65 °C with dimethylzinc to produce a new species quantitatively.¹³¹ They noticed that the zinc reagent decomposed "slowly at 0 °C". Other reports¹³² also showed that vinylzinc species are not stable in the presence of trialkylboranes or dialkylborinates, and that an efficient trapping by an electrophile was required. Vinylboronic esters reacted sluggishly with dimethyl-46 or diethylzinc⁵⁵. Higher temperatures were necessary, and when the intermediate formed it decomposed rapidly to give black metallic Zinc. It should be noted from Chai's⁵⁵ work that dioxaborinanes seemed slightly more stable than dioxaborolanes in the presence of diethylzinc at 0 °C in hexanes. We found that MPB ester and excess dimethylzinc remained essentially unchanged (1H and ^{11}B -NMR) for 12 hrs in toluene at 20 °C, or for 2 hrs at 60 °C. After 12 hrs at 60 °C, Zn^0 was formed and NMR spectra became unreadable.

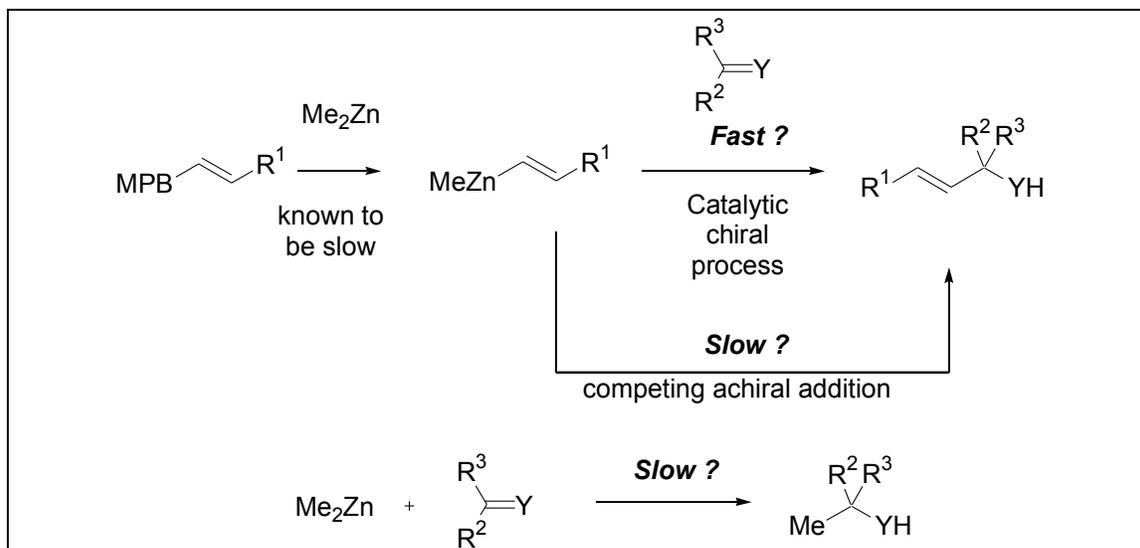
¹³⁰ Recent review: V. Dimitrov, K. Kostova, *Lett. Org. Chem.*, **2006**, 3, 176.

¹³¹ W. Oppolzer, R. N. Radinov, *Helv. Chim. Acta* **1992**, 75, 170.

¹³² a) G. A. Molander, P. W. Zinke, *Organometallics* **1986**, 5, 2161; b) C. Garcia, E. R. Libra, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2003**, 125, 3210.

2.4.2 Additions catalyzed by chiral amino alcohols:

On the basis of hypothesis A, it should be possible to obtain enantioselective additions of vinyl rests on aldehydes, in the presence of chiral enantiopure β -aminoalcohols. But the transmetalation from our vinylboronic ester can only be performed with *in situ* trapping. Thus, the enantioselective process would be successful only if the competing reactions feature favorable kinetics (Scheme 64).



Scheme 64: Requirements for successful enantioselectively catalyzed addition

Interesting results were obtained with nitrones as electrophiles. The preliminary essays in Table 7 indicate that chirality can actually be transferred from the β -aminoalcohol to the product. But since the enantioselective reaction is not fast, competition with the non-catalyzed process severely lowers the e.e.

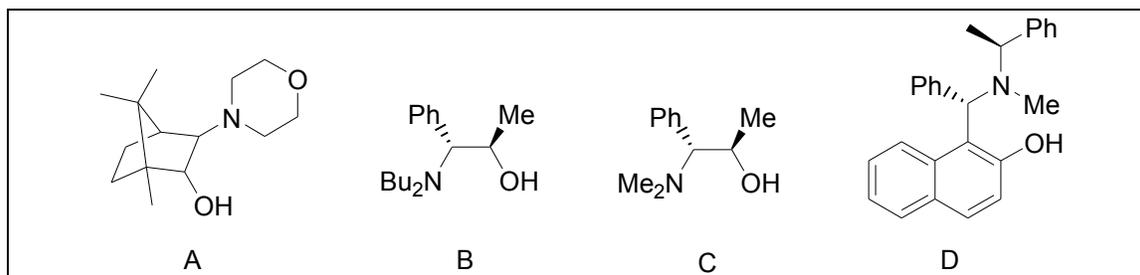
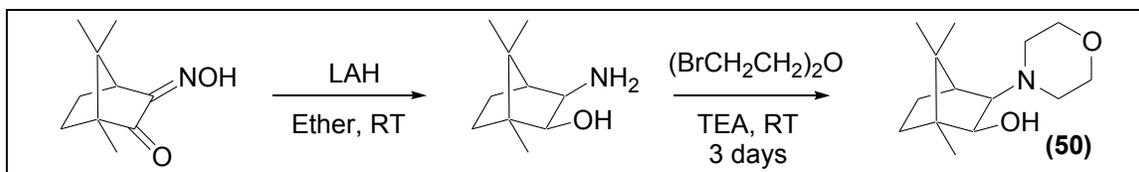
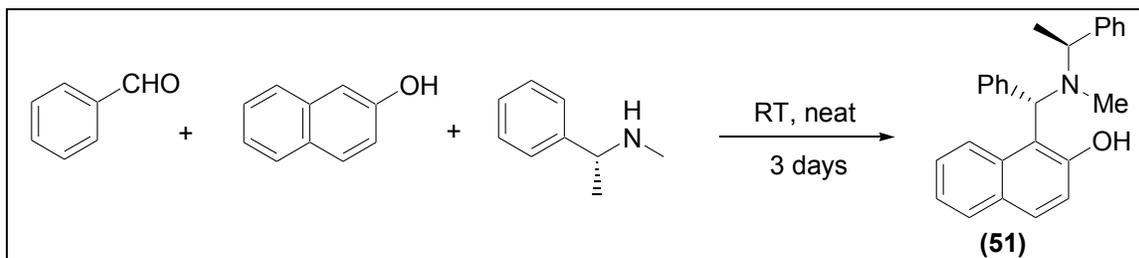


Figure 10: ligands used in table 6

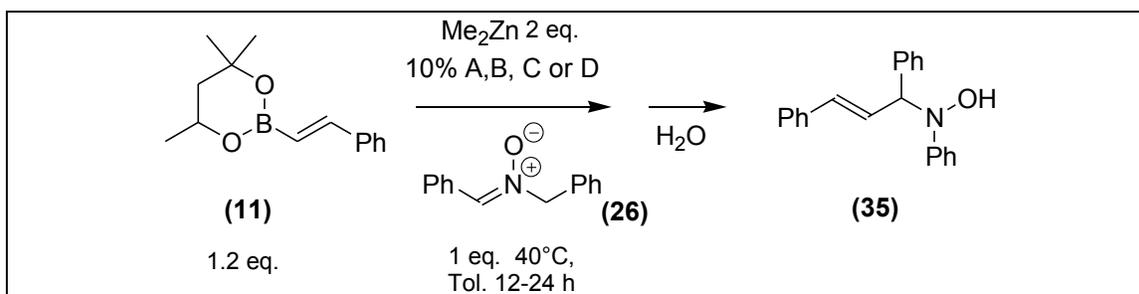


Scheme 65: Preparation of A(50):



Scheme 66: Preparation of D (51):

Table 7: enantioselective vinylation of nitrones



Entry	Catalyst	% ee
1	A	15
2	B	10
3	C	17
4	D	17
5	A	22

% ee were determined by chiral HPLC

Entry 1 commercial sample from Aldrich, Entry 5 Lab sample, recrystallised from MeOH.

2.5 DFT Studies:

We have attempted to gain insight into the mechanism by means of *ab initio* calculations.¹³³ Since the reactions involve organometallic additions, we chose to investigate at the DFT level, as the only way to correctly describe the transition states. Thus, we had to use extremely simplified models, and it was impossible to take steric interactions in accounts. Since we have good clues (previous §) that steric interactions are very important, the following theoretical results should be considered with caution. Figure 11 summarizes these calculations.

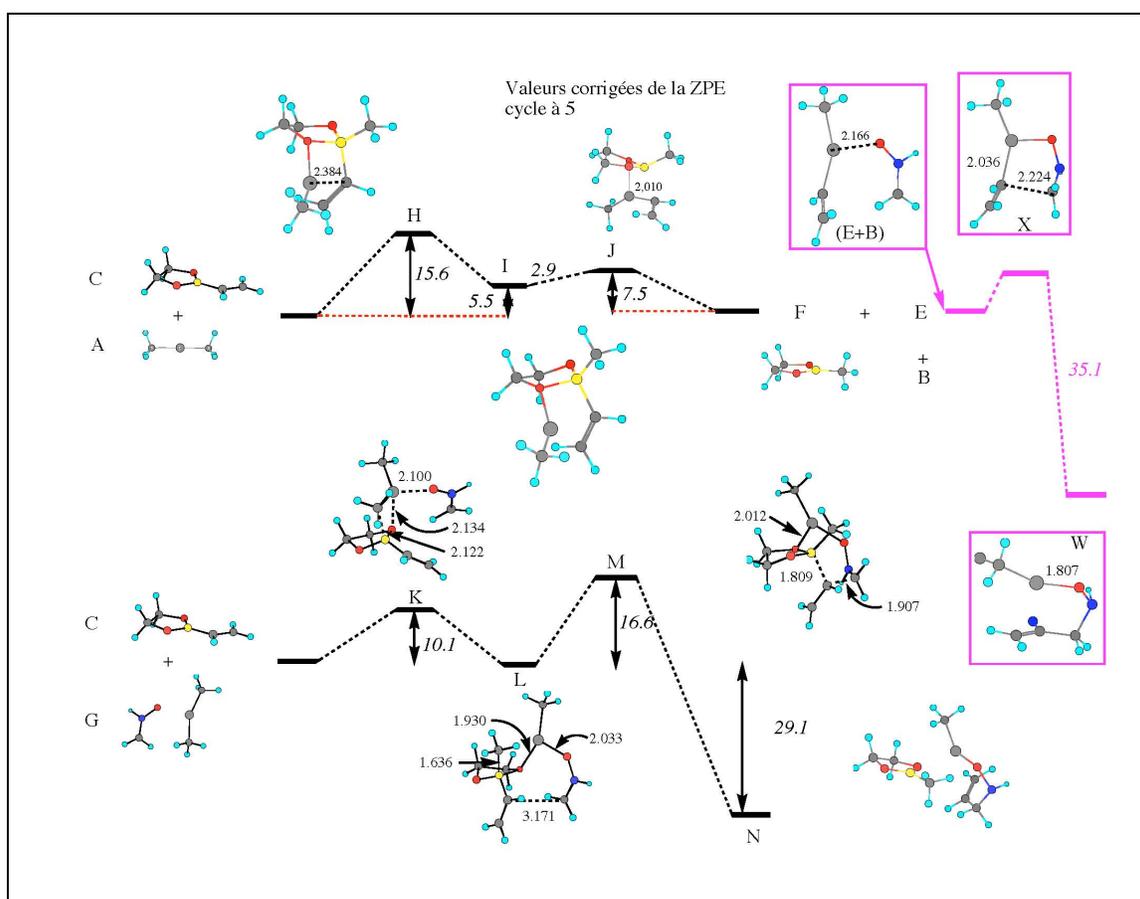


Figure 11 : DFT studies on the hypothetical mechanisms.

¹³³ We gratefully acknowledge Dr Y. Gimbert for carrying out this study.

2.5.1 Pathway A: transmetallation followed by addition

We studied first the vinyl exchange between boronate ester C and dimethylzinc A (pathway A). As the two reagents A and C approach,¹³⁴ an intermediate I is formed which present an hypervalent boron atom bearing vinyl and methyl group transferred from dimethylzinc A. Formation of intermediate I from A and C occurs via the transition state H, requiring an activation energy of 15.6 kcal/mol. This step is endothermic by 5.5 kcal/mol. The B—C(-CH=CH₂) bond in I (1.660 Å) is much longer than the same bond in boronate ester C (1.550 Å). Intermediate I can evolve by the formation of vinylmethylzinc E, requiring a low activation energy of 2.9 kcal/mol. This step is exothermic by 5.5 kcal/mol referring to I, and as a whole, energetically neutral referring to starting reagents A and C. Vinylmethylzinc E and nitron B give a precomplex (E+B) via a barrierless process, the stabilization energetic gain being 2.3 kcal/mol. The formation of the C-C bond yielding W, requires 9.1 kcal/mol (through transition state X) and is strongly exothermic (more than 35 kcal/mol). In conclusion, the rate determinant step of pathway A seems to be the formation of I, corresponding to the methyl transfer on boron atom.

2.5.2 Pathway B: direct addition from a boronate anion.

Alternatively, in the case of pathway 2, dimethylzinc A can be coordinated by nitron B to give, without barrier, the precomplex G. This precomplex, after reaction with vinyl boronate ester C, can be transformed into a three bodies intermediate L, through transition state K, the methyl transfert requiring this time only 10.1 kcal/mol (against 15.6 with dimethylzinc not coordinated initially by nitron). This step is athermic referring to energies of separated starting reagents G and C. At this stage, we can conclude that the methyl transfer from zinc to boron seems to be facilitated when dimethylzinc is initially coordinated by nitron: the activation energy is lower and the transformation is no more endothermic. The next step corresponds to the formation of the C-C bond joining nitron and vinyl group. Energy of the transition state M is located 16.6 kcal/mol above intermediate L, and yield adduct N. This transformation is strongly exothermic by 29.1

¹³⁴ Precomplexation during this approach by interaction of O with Zn atoms, wasn't observed

kcal/mol. By comparison with the transformation (E+B)→W in channel 1, the formation of the C-C bond is more costly in channel 2, 16.6 against 9.1 kcal/mol.

To summarize, the expected rate-determining steps, according to the energetic study presented in Figure 11, are for pathway A the formation of I through H and for the Pathway B the formation of N through M. As soon as these steps are successfully passed the reactions can be considered irreversible.

Nevertheless, at this level of investigation, it was difficult to conclude on the pathway preferentially followed by the reaction. Indeed, if we compare both determinant steps, the energies of activations involved are separated only by 1 kcal/mol. So, the DFT results were submitted to a kinetics analysis by Karoly Wekey and Antoine Menboeuf (Chemistry Institute of Budapest). The detail of their work is beyond the scope and the thesis. To say it shortly, rate constants could be derived from the DFT determination of the transition state. These rate constants were used to build a model of the kinetic behaviour of the reaction *in silico*, and this model predict that in a mixture, most of the molecule will be transformed through pathway A (transmetallation).

Fortunately, this is consistent with the other mechanistic clues we have.

Thus, we can conclude so far that the mechanism of our reaction doesn't involve the formation of a boronate anion (with Zn as counterion), but probably a boron-to-zinc transmetallation as a first, separate step.

2.6 Conclusion:

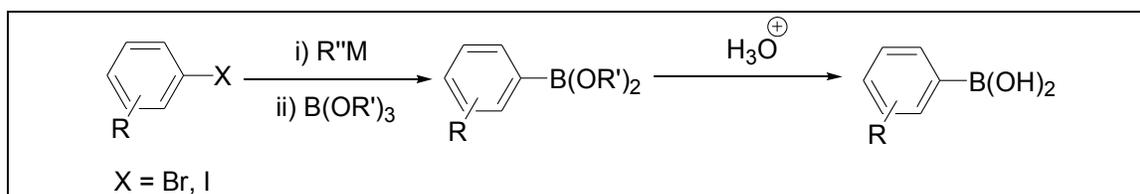
The use of vinylboronates as alkenyl transfer reagents has been amply demonstrated by the addition onto nitrones in this chapter. These esters can be made to react under mild conditions allowing better functional group tolerance and this underscores the flexibility of the reaction. Preliminary results indicate that chirality can be induced by the use of β -aminoalcohols, and this indicates that the reactive species is a vinyl-zinc species. Thus the obvious direction of the future work is the search for the proper β -aminoalcohol allowing a catalytic enantioselective version of this vinylation of nitrones.

3 Preparations and Applications of arylboronic derivatives

3.1 Bibliographic introduction: the preparation of arylboronic esters.

3.1.1 By reaction of aryl metal intermediates with boric esters

The typical preparation of arylboronic acids involves the reaction between a trialkoxyborane and an organometallic (Li or Mg) species, usually prepared from the corresponding aryl halides by magnesium insertion or lithium-halogen exchange.¹³⁵

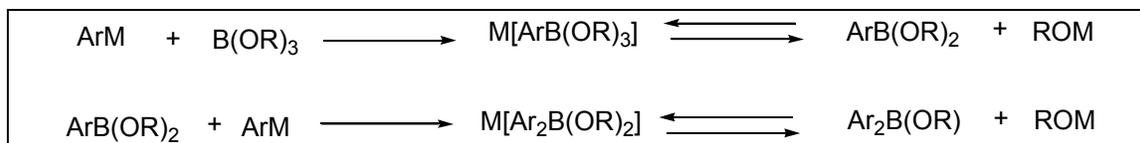


Scheme 67

The boric ester is often trimethylborate, used in large excess. The product may then be contaminated with variable amounts of a borinic ester resulting from a double addition (Scheme 68). The Brown and Cole modification¹³⁶ of the same reaction involved the use of triisopropyl borate to overcome these difficulties. The use of triisopropyl borate results in the precipitation of the magnesium trialkoxyphenylborate salt thereby protecting the desired boronate ester from a second displacement by the Grignard reagent. (Scheme 68)

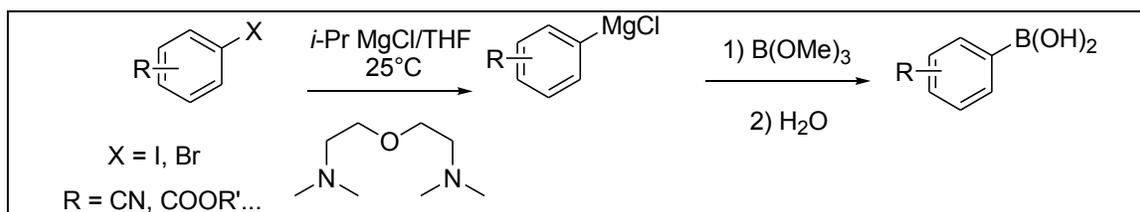
¹³⁵ a) E. Khotinsky, M. Melamed, *Ber.* **1909**, 54, 2784. b) E. Khotinsky, M. Melamed, *Ber.* **1909**, 42, 3090.

¹³⁶ a) H. C. Brown, T. E. Cole, *Organometallics* **1983**, 2, 1316. b) H. C. Brown, M. Srebnik, T. E. Cole, *Organometallics* **1986**, 5, 2300.



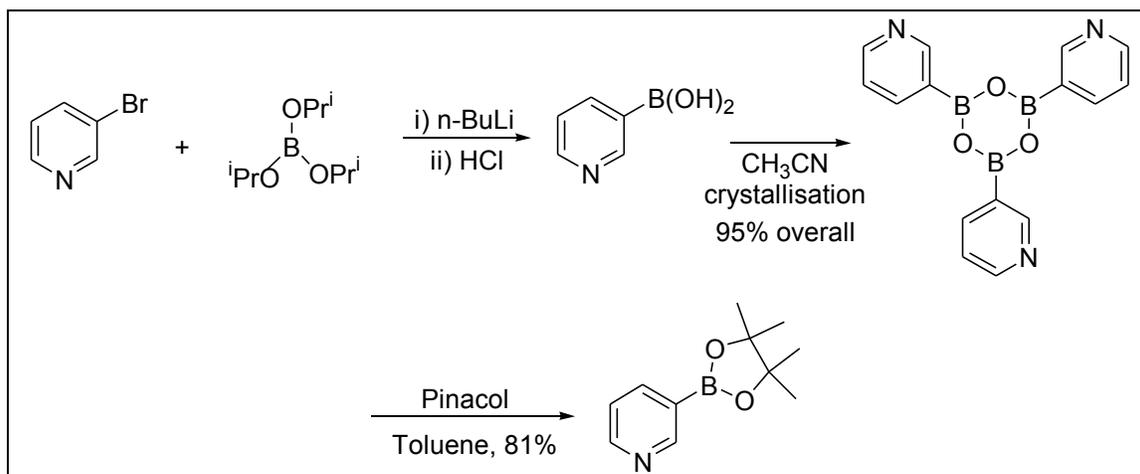
Scheme 68

The organometallic is often prepared by halogen-metal exchange. As a recent example, a variant of the iodine-magnesium exchange disclosed by Knochel and Cahiez¹³⁷ was applied to the preparation of boronic esters (Scheme 69).¹³⁸



Scheme 69

More recently, an *in situ* quench variant whereby triisopropylborate is present prior to the addition of butyl lithium has been shown to produce better yields of aryl and heteroaryl boronic esters compared to the sequential addition procedure¹³⁹ (Scheme 70).



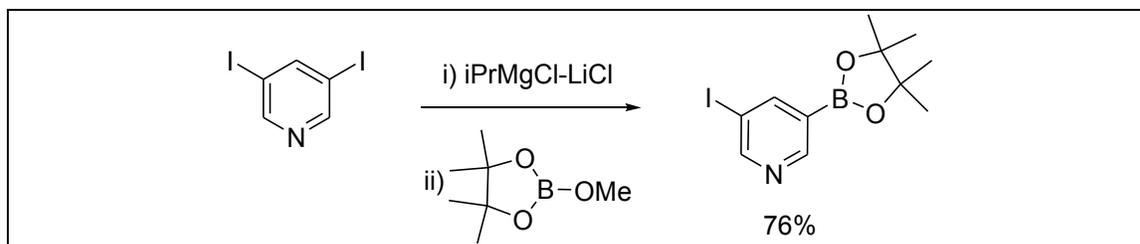
Scheme 70

¹³⁷ L. Boymond, M. Rottlander, G Cahiez, P. Knochel *Angew. Chem. Int. Ed.* **1998**, *37*, 1701.

¹³⁸ X.-j. Wang, X. Sun, L. Zhang, Y. Xu, D. Krishnamurthy, C.H. Senanayake, *Org. Lett.* **2006**, *8*, 305.

¹³⁹ W. Li, D. P. Nelson, M. S. Jensen, R. S. Hoermer, D. Cai, R. D. Larsen, P. J. Reider, *J. Org. Chem.* **2002**, *67*, 5394.

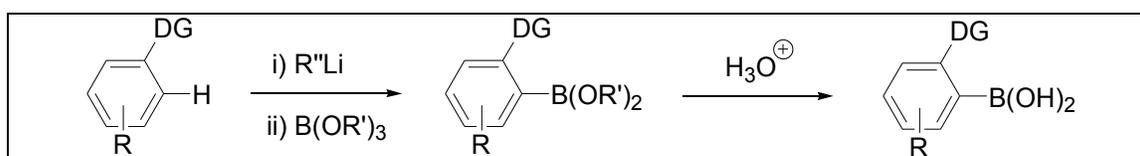
Alternatively, the robust pinacol ester can be obtained directly by the electrophilic quench of the aryllithium intermediate with a pinacol borate ester thereby overcoming the difficulties of functional group tolerance as described by Baron and Knochel.¹⁴⁰ It should also be noted that metallated heterocycles which are intrinsically unstable can be transformed into the corresponding boronate esters in good yields under these mild conditions. (Scheme 71)



Scheme 71

3.1.2 Organometallics obtained by Directed Ortho-metallation Reaction:

The metallation of arenes functionalized with coordinating ortho-directing groups such as amines, ethers, anilides, esters and amides is an easy way to access arylmetal intermediates that can be trapped with borate esters (Scheme 72).^{141,142,143} The nature of the functional group present exerts an important influence on the kinetics of the reaction and follows the order R_2N , F, CF_3 , $<MeO < CH_2RN_2$, $C(O)NR_2$, SO_2NR_2 .¹⁴⁴



Scheme 72

¹⁴⁰ O. Baron, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, 44, 3133.

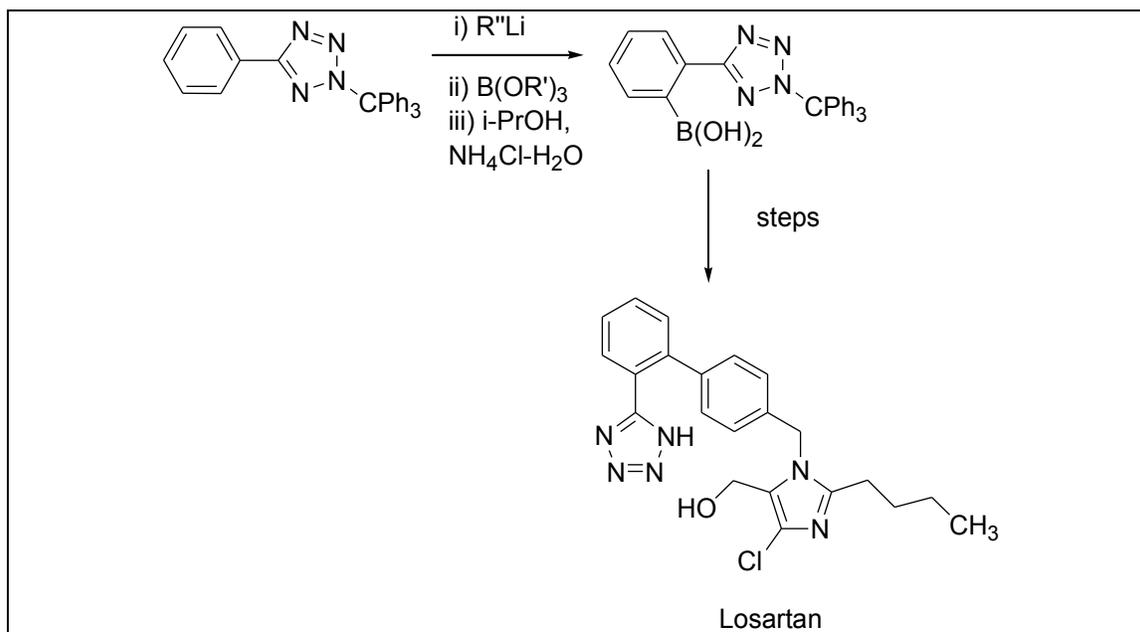
¹⁴¹ G. Marr, R. E. Moore, B. W. Rockett, *J. Organomet. Chem.* **1967**, 7, P11.

¹⁴² R. T. Hawkins, D. B. Stroup, *J. Org. Chem.* **1969**, 34, 1173.

¹⁴³ M. Lauer, G. Wulff, *J. Organomet. Chem.* **1983**, 256, 1.

¹⁴⁴ D. W. Slocum, C. A. Jennings, *J. Org. Chem.* **1976**, 41, 3653.

The protocol¹⁴⁵ involving the use of *sec*-BuLi in the presence of TMEDA in THF at -78 °C is found to be generally applicable for many substrates¹⁴⁶ including the heterocyclic tetrazole intermediate required in the synthesis of the antihypertensive drug Losartan (Scheme 73).¹⁴⁷



Scheme 73

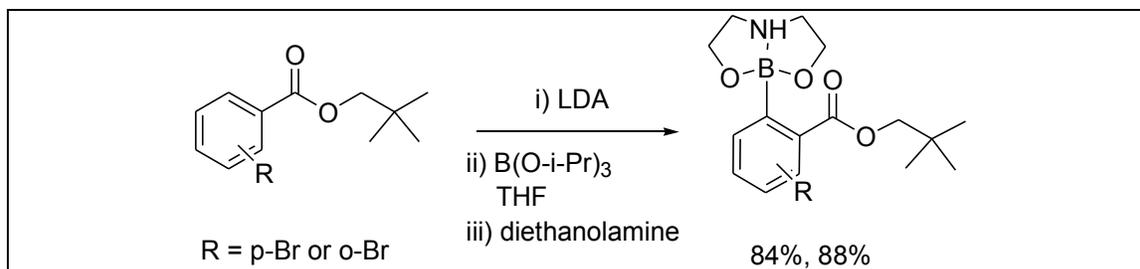
The use of esters as directing groups was found to be problematic in many cases and a modified *in situ* metallation-boronylation procedure employing LDA as a base and neopentyl esters has been developed.¹⁴⁸ LDA was found to be compatible with the borate esters under the conditions employed and its inertness to bromide-substituted ester substrates (Scheme 74) provides another significant advantage over the use of BuLi.

¹⁴⁵ a) M. J. Sharp, V. Snieckus, *Tetrahedron Lett.* **1985**, 49, 5997. b) M. J. Sharp, W. Cheng, V. Snieckus, *Tetrahedron Lett.* **1987**, 28, 5093.

¹⁴⁶ B. I. Alo, A. Kandil, P. A. Patil, M. J. Sharp, M. A. Siddiqui, V. Snieckus, *J. Org. Chem.* **1991**, 96, 3763.

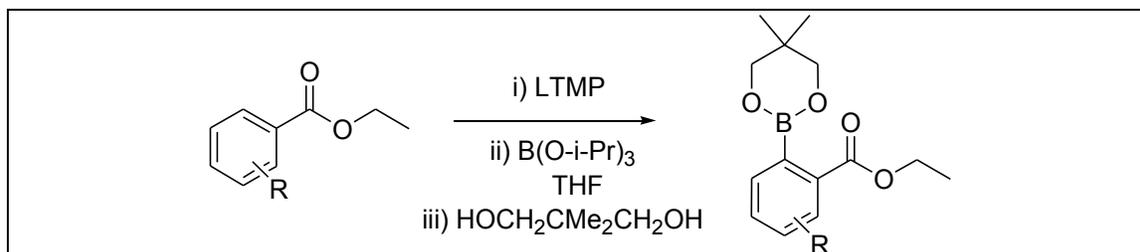
¹⁴⁷ R. D. Larsen, A. O. King, C. Y. Chen, E. G. Corley, B. S. Foster, F. E. Roberts, C. Yang, D. R. Lieberman, R. A. Reamer, D. M. Tschaen, T. R. Verhoeven, P. J. Reider, Y. S. Lo, D. Meloni, J. R. Moore, J. F. Arnett, *J. Org. Chem.* **1994**, 59, 6391.

¹⁴⁸ S. Caron, J. M. Hawkins, *J. Org. Chem.* **1998**, 63, 2054.



Scheme 74

The recent variant of the in situ trapping procedure uses lithium 2,2,6,6-tetramethylpiperidide (LTMP) as a base allowing the presence of other substituents normally incompatible with alkyllithium bases¹⁴⁹. As demonstrated in the particular case of ethyl benzoate (Scheme 75), the use of LTMP was advantageous as LDA failed to metalate this substrate, leading instead to the carboxamide issuing of the addition to the ester.



Scheme 75

3.1.3 By transmetalation of Arylsilanes and stannanes:

One of the earliest methods for preparing aromatic boronic acids involved the reaction between organomercury compounds and boron trichloride¹⁵⁰ or diborane¹⁵¹. Although the reaction provides the corresponding arylboronic acids in good yields after an aqueous workup, this method is unpopular due to safety and environmental reasons.

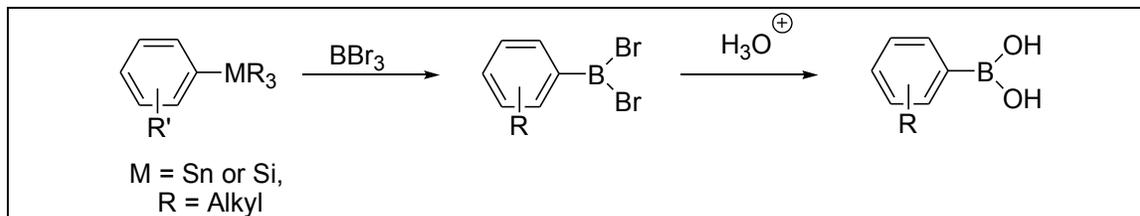
Trialkylaryl silanes and stannanes are more suited for the preparation of arylboronic acids and both can be transmetalated efficiently with a hard boron halide

¹⁴⁹ J. Kristensen, M. Lysen, P. Vedso, M. Begtrup, *Org. Lett.* **2001**, 3, 1435.

¹⁵⁰ (a) A. Michaelis, P. Becker, *Ber.* **1880**, 13, 58. (b) A. Michaelis, P. Becker, *Ber.* **1882**, 15, 180.

¹⁵¹ S. W. Breuer and F. G. Thorpe, *Tetrahedron Lett.* **1974**, 42, 3719.

such as BBr_3 ¹⁵² (Scheme 76). The driving force for this reaction is the higher stability of B-C and Si(Sn)-Br bonds of the product compared to the respective B-Br and Si(Sn)-C bonds of the substrate¹⁵³.



Scheme 76

3.1.4 Direct Boronylation by transition metal-catalyzed Aromatic C-H functionalisation:

In terms of atom economy, the direct boronylation of arenes through a transition metal promoted C-H functionalisation is the best strategy for accessing aryl boronic esters and acids¹⁵⁴. Both diboronyl esters and dialkoxy boranes can act as suitable boron donors^{155,156}. The putative catalytic cycle has been established by the synthesis and characterization of the catalytically important species.^{157,158,159}

3.1.4.1 Iridium catalyzed aromatic borylation:

The first example of aromatic C-H borylation was reported by Marder and co-workers with Ir complexes, while the catalytic reaction was first demonstrated by Smith and coworker. It was found that Ir complexes themselves were not active catalysts, while

¹⁵² W. Haubold, J. Herdtle, W. Gollinger, W. Einholz, *J. Organomet. Chem.* **1986**, 315, 1.

¹⁵³ M. J. Sharp, W. Cheng, V. Snieckus, *Tetrahedron Lett.* **1985**, 49, 5997.

¹⁵⁴ Reviews for C-H activation: a) B. A. Arndtsen, R. G. Bergman, T. A. Mobley, T. H. Peterson, *Acc. Chem. Res.* **1995**, 28, 154. b) G. Dyker, *Angew. Chem. Int. Ed.* **1999**, 38, 1698. c) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, 102, 1731.

¹⁵⁵ Review, T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2003**, 680, 3.

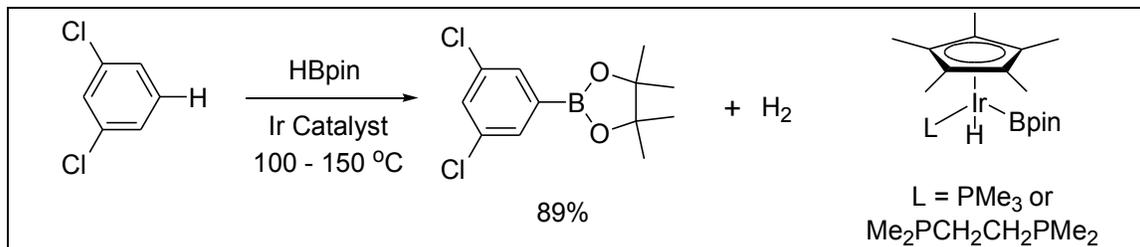
¹⁵⁶ a) T. Ishiyama, N. Miyaura, *J. Organomet. Chem.*, **2000**, 611, 392. b) T. Ishiyama, N. Miyaura, *J. Synth. Org. Chem. Jpn.*, **1999**, 57, 503. c) T. Ishiyama, N. Miyaura, *Chem. Record* **2004**, 3, 271.

¹⁵⁷ P. Nguyen, H. P. Blom, S. A. Wescott, N. J. Taylor, T. B. Marder, *J. Am. Chem. Soc.* **1993**, 115, 9329.

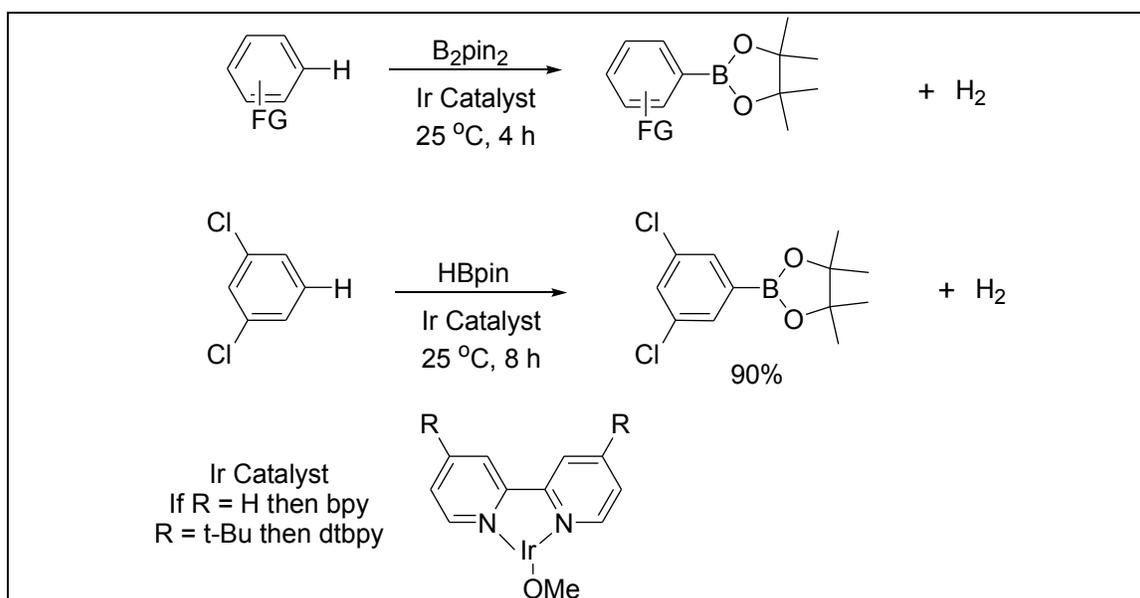
¹⁵⁸ a) K. M. Waltz, J. F. Hartwig, *Science* **1997**, 277, 211. b) K. M. Waltz, C. N. Muhoro, J. F. Hartwig, *Organometallics*, **1999**, 18, 9329.

¹⁵⁹ a) G. J. Irvine, M. J. G. Lesley, T. B. Marder, N. C. Norman, C. R. Rice, E. G. Robins, W. R. Roper, G. R. Whittel, L. J. Wright, *Chem. Rev.* **1998**, 98, 2865. b) For theoretical studies, see W. H. Lam, Z. Y. Lin, *Organometallics*, **2003**, 22, 473.

the addition of an electron donating alkylphosphine like PMe_3 ¹⁶⁰ or a chelating phosphine like dmpe ¹⁶¹ [1,2-bis(dimethylphosphino)ethane] increased the catalyst activity and turnover number significantly. (Scheme 77)



Scheme 77



Scheme 78

In situ prepared Ir complexes with 2,2'-bipyridine (bpy) or 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) ligands have been found to exhibit excellent activity and selectivity with both B_2pin_2 and HBpin for aromatic C-H borylation.¹⁶² The reaction proceeds at room temperature and various functional groups are tolerated (Scheme 78).

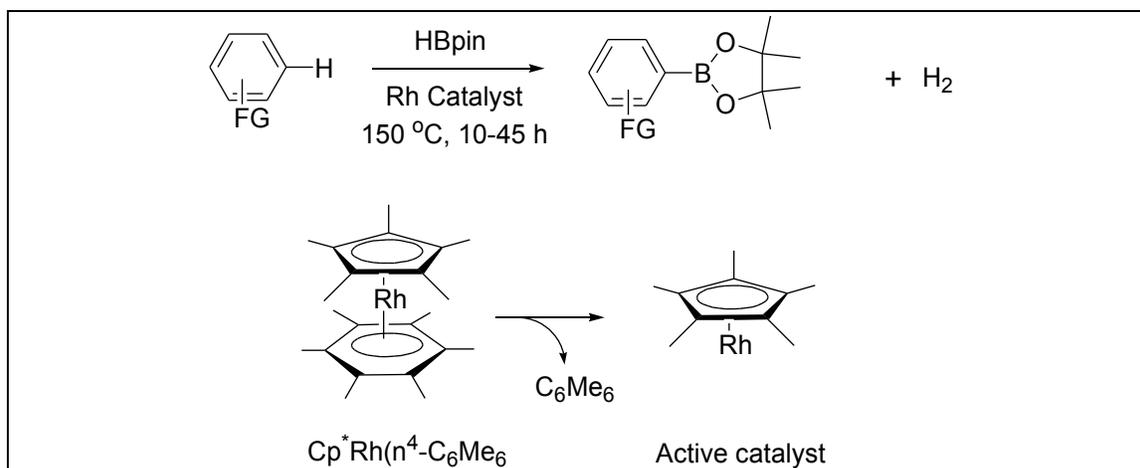
¹⁶⁰ C. N. Iverson, M. R. Smith, III, *J. Am. Chem. Soc.* **1991**, 121, 7696.

¹⁶¹ J. Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, Jr., M. R. Smith, III, *Science* **2002**, 295, 305.

¹⁶² T. Ishiyama; J. Takagi; K. Ishida; N. Miyaoura; N. R. Anastasi; J. F. Hartwig, *J. Am. Chem. Soc.*, **2002**, 124, 390-391.

3.1.4.2 Rhodium catalyzed borylation¹⁶³:

Rhodium complexes like $\text{Cp}^*\text{Rh}(\eta^4\text{-C}_6\text{Me}_6)^{164}$ (Hartwig's catalyst) efficiently catalyze both aliphatic and aromatic C-H borylations. Turnover numbers are high due to the in situ formation of a coordinatively unsaturated species active for oxidative addition. (Scheme 79)



Scheme 79

Although these catalysts provide much higher TON than the corresponding Ir catalysts, they are less selective for alkylarenes and (trihalomethyl)-arenes because rhodium catalysts react at the benzylic C-H bonds and aliphatic C-halogen bonds⁷⁸.

3.1.5 Direct Borylation by Palladium-catalyzed dehaloborylation of aryl halides.

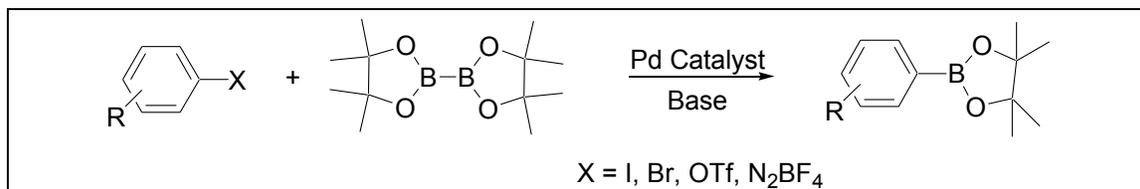
In this thesis, we describe the application of MPBH to the preparation of arylboronic esters. This class of compounds has acquired a huge importance with the development of the Suzuki-Miyaura cross-coupling. Because of this very importance, the literature on the access to these compounds is very large. We will focus particularly on the immediately related preparations from pinacolborane.

¹⁶³ H. Y. Chen, S. Schlecht, T. C. Semple, J. F. Hartwig, *Science* **2000**, 287, 1995.

¹⁶⁴ a) M. K. Tse, J. -Y. Cho, M. R. Smith III, *Org. Lett.* **2001**, 3, 2831. b) J. -Y. Cho, C. N. Iverson, M. R. Smith III. *J. Am. Chem. Soc.* **2000**, 122, 12868.

3.1.5.1 With diboron compounds

A very important breakthrough in the preparation of arylboronic came in 1995 when Miyaura and coworkers found that tetra(alkoxo)diborons such as bis(pinacolato)diboron^{77,165} can act as boron nucleophiles for palladium catalyzed cross-coupling reactions of organic halides¹⁶⁶ and triflates¹⁶⁷. (Scheme 80)



Scheme 80: Borylation of Aryl halides and triflates

The presence of a base such as KOAc is critical for the success of the coupling reactions of diborons. This suggests that the catalytic cycle involves a transmetalation between the diboron compound and the Ar-Pd-OAc intermediate that is generated by displacement of X in Ar-Pd-X with an acetate anion^{80,80} (Scheme 81). Since strong bases such as K₃PO₄ and K₂CO₃ prompt the competitive formation of homocoupling biaryls (35-60% yields), KOAc¹⁶⁸ is recognized to be a suitable base for a wide variety of aromatic substrates, including iodides^{80,169}, bromides^{80,170}, chlorides^{171,172} and triflates^{80,173}.

¹⁶⁵ a) N. Miyaura, in *Catalytic Heterofunctionalisation*, A. Togni, H. Grutzmacher (Eds.), Wiley VCH, Chichester, **2001**, Chapter 1.

¹⁶⁶ a) T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.*, **1995**, 60, 7508. b) T. Ishiyama, K. Ishida, N. Miyaura, *Tetrahedron*, **2001**, 57, 9813.

¹⁶⁷ T. Ishiyama, Y. Itoh, T. Kitano, N. Miyaura, *Tetrahedron Lett.*, **1997**, 38, 3447.

¹⁶⁸ For an interesting computational study on the use of KOAc as the base, see K. L. Billingsley; T. E. Barder; S. L. Buchwald, *Angew. Chem. Int. Ed.*, **2007**, 46, 5359.

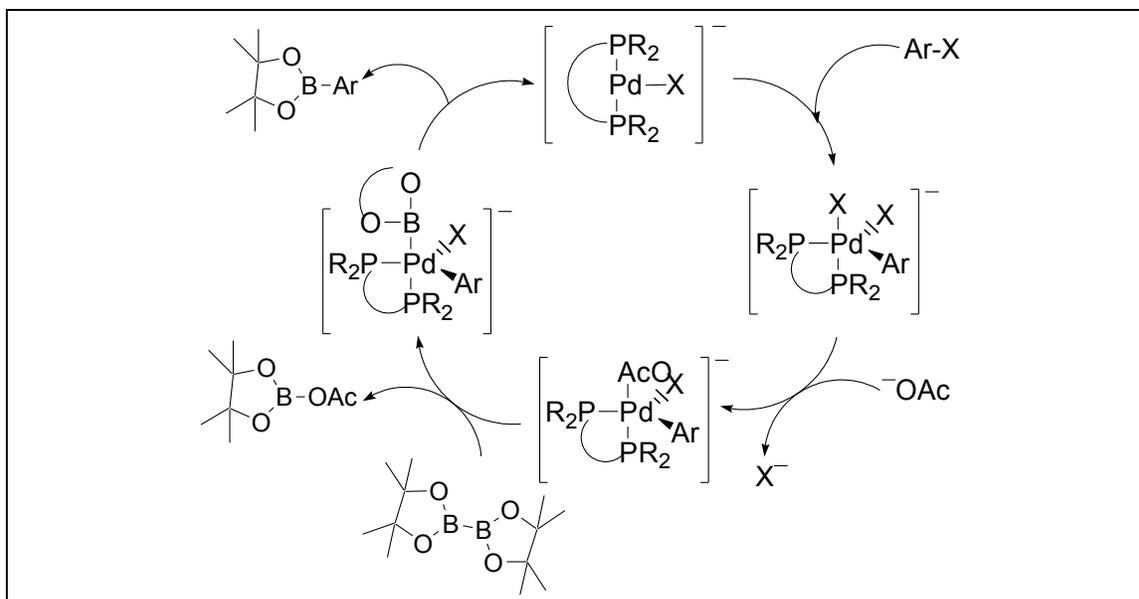
¹⁶⁹ a) S. N. Lin, S. J. Danishefsky, *Angew. Chem. Int. Ed.*, **2001**, 40, 1967. b) M. Kaiser, M. Groll, C. Renner, R. Huber, L. Moroder, *Angew. Chem. Int. Ed.*, **2002**, 41, 780.

¹⁷⁰ a) M. W. Read, J. O. Escobeda, D. M. Willis, P. A. Beck, R. M. Strongin, *Org. Lett.* **2000**, 2, 3201. b) S. Takaoka, K. Nakade, Y. Fukayama, *Tetrahedron Lett.*, **2002**, 43, 6919

¹⁷¹ A. Furstner, G. Seidel, *Org. Lett.*, **2002**, 4, 541.

¹⁷² K. L. Billingsley, T. E. Barder, S. L. Buchwald *Angew. Chem. Int. Ed.*, **2007**, 46, 5359.

¹⁷³ C. F. Nising, U. K. Schmid, M. Neiger, S. Brase, *J. Org. Chem.*, **2004**, 69, 6830.



Scheme 81: Proposed Catalytic Cycle

Although $\text{PdCl}_2(\text{dppf})$ is suitable for representative halides, other catalytic systems (Figure 12) like the electron-donating tricyclohexyl phosphine^{80b} (PCy_3), N-heterocyclic carbenes⁸⁰ (NHC) and bulky biphenyl based phosphine ligands⁸⁰ (XPhos) are advantageous.

They help in achieving high yields within short reaction times for aryl chlorides and electron-rich bromides and triflates (Figure 13). These ligands are also effective for preventing the participation of phosphine-bound aryls, which occurs competitively when PPh_3 and dppf are used as ligands. NHC's¹⁷⁴ in particular, by virtue of their pronounced σ -donor but very weak π -acceptor properties, render the resulting complexes very electron-rich and hence facilitate all kinds of oxidative insertion process.¹⁷⁵

¹⁷⁴ Reviews: a) A. J. Arduengo *Acc. Chem. Res.*, **1999**, 32, 913. b) W. A. Hermann, C. Kocher *Angew. Chem. Int. Ed.* **1997**, 36, 2162. c) D. Bourissou, O. Guerret, F. P. Gabai, G. Bertrand *Chem. Rev.* **2000**, 100, 39.

¹⁷⁵ For applications in cross-coupling reactions, see a) S. Lee, J. F. Hartwig *J. Org. Chem.*, **2001**, 66, 3402. b) J. Cheng, M. L. Trudell *Org. Lett.* **2001**, 3, 1371 and references cited therein. For applications in olefin metathesis, see c) R. H. Grubbs, T. M. Trnka *Acc. Chem. Res.*, **2001**, 34, 18 and references therein.

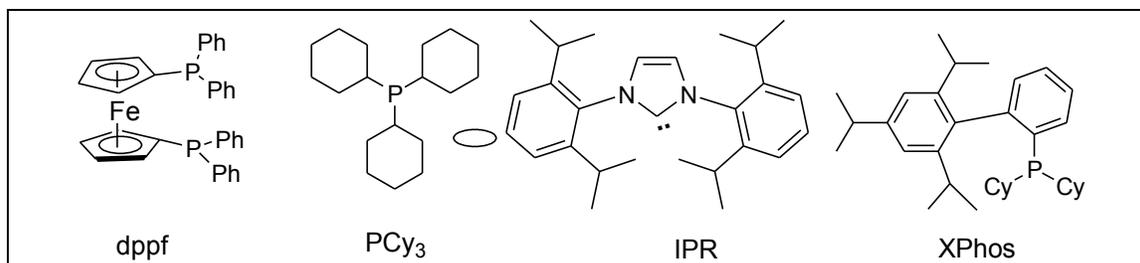


Figure 12: Commonly used ligand systems

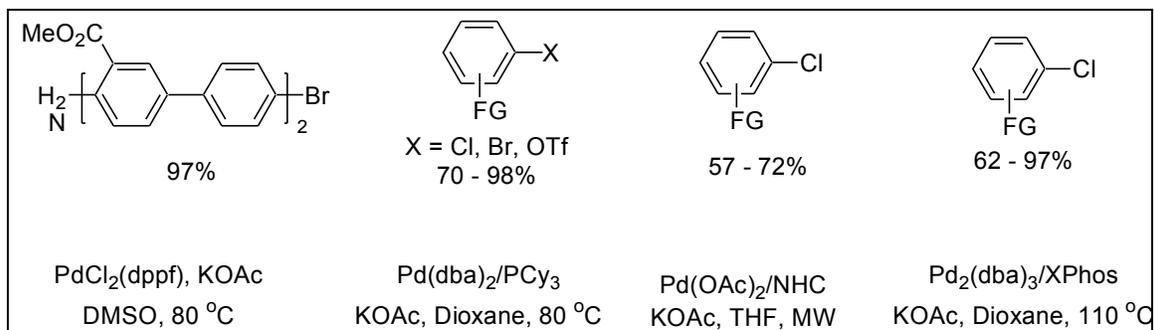


Figure 13: Selected examples of borylation using bis-(pinacolato)-diboron

But despite the obvious appeal of this cross coupling method, the poor accessibility¹⁷⁶ and the high price of the diboronyl reagents restricts its use for large-scale preparations of boronic esters.

¹⁷⁶ a) H. Abu Ali, I. Goldberg, M. Srebnik, *Eur. J. Inorg. Chem.* **2002**, 73. b) X. Liu, *Synlett* **2003**, 2442.

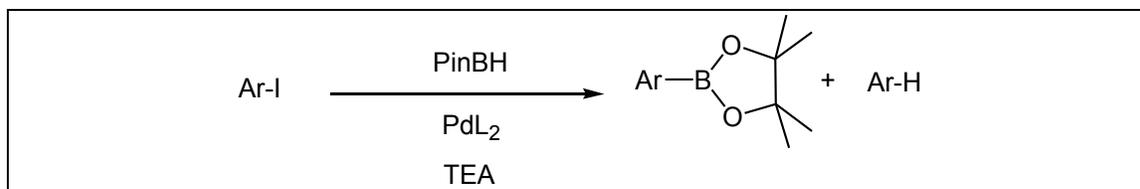
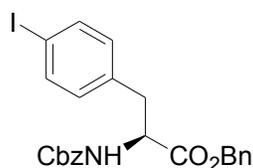


Figure 14

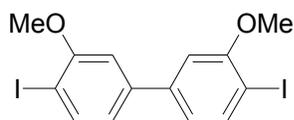
The authors disclosed that the Pd⁰-catalyzed reaction of aryl iodides and bromides Ar-X with pinacolborane (PinBH) can lead mainly to the arylboronic ester Ar-BPin in the presence of triethylamine (TEA). The only byproduct is the hydridehalogenation product Ar-H. Triethylamine is very particular in this reaction. Other amine bases as well as oxygenated bases lead to a poorer Ar-BPin/Ar-H ratio. The reaction can be run indifferently in dioxane, acetonitrile, toluene or dichloroethane. DMF gave much lesser yields and selectivity. The authors proposed PdCl₂dppf as the best precatalyst. PdCl₂TPP₂ was less efficient, leading to a slightly lower Ar-BPin/Ar-H ratio. PdTPP₄ was sluggish, and PdCl₂TPP₂+2 TPP was not reacting at all. The same team extended the method to trifluoromethanesulfonates in a second article.¹⁷⁸ Iodides react at 80°C within less than 6 hrs. Triflates require 6 hrs at 100°C, bromides up to 36 hrs at 100°C. The authors used moderate (1.5 eq.) excess of PinBH, and 3 eq. of TEA, and this stoichiometry became an usual standard in the subsequent work.

Many teams have used these conditions for the preparation of specific targets. Some of these results are gathered below.

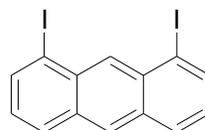
¹⁷⁸ M. Murata, T. Oyama, S. Watanabe, Y. Masuda, *J. Org. Chem.* **2000**, *65*, 164



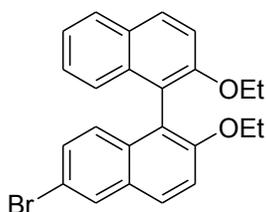
dioxane, 80°C, 27h,
82%¹⁷⁹



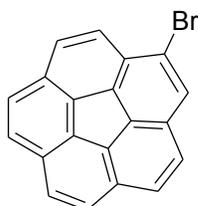
acetonitrile, 80°C, 1.5h,
69%
double borylation^{180, 181}



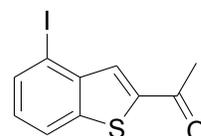
88%
double borylation¹⁸²



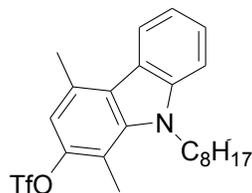
dioxane, reflux, 36 h,
30%¹⁸³



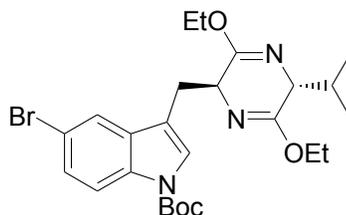
dioxane, 105°C, 24 h,
95%¹⁸⁴



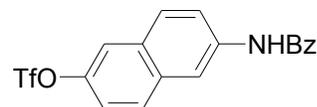
dioxane, 80°C, 74%¹⁸⁵



(CH₂Cl)₂, 80°C, 4 h,
95%¹⁸⁶



5% Pd, toluene, 90°C, 9h,
89%¹⁸⁷



Dioxane, 85 °C, 18 h, 65%¹⁸⁸

¹⁷⁹ H. Nakamura, M. Fujiwara, Y. Yamamoto, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 231.

¹⁸⁰ N. Sakai, D. Gerard, S. Matile, *J. Am. Chem. Soc.* **2001**, *123*, 2517.

¹⁸¹ D. Ronan, D. Jeannerat, A. Pinto, N. Sakai, S. Matile, *New J. Chem.* **2006**, *30*, 168.

¹⁸² S. Saito, H. Yamaguchi, H. Muto, T. Makino, *Tetrahedron Lett.* **2007**, *48*, 7498. The author confirmed us that the base used is TEA.

¹⁸³ L. Ma, P. S. White, W. Lin, *J. Org. Chem.* **2002**, *67*, 7577.

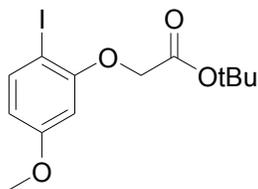
¹⁸⁴ H. A. Wegner, L. T. Scott, A. de Meijere, *J. Org. Chem.* **2003**, *68*, 883.

¹⁸⁵ P.-Y. Michellys, J. D'Arrigo, T. A. Grese, D. S. Karanewsky, M. D. Leibowitz, D. A. Mais, C. M. Mapes, A. Reifel-Miller, D. Rungta, M. F. Boehm, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1593.

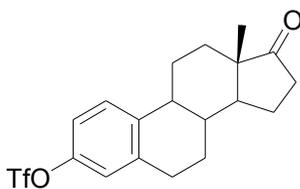
¹⁸⁶ S. Wakim, J. Bouchard, M. Simard, N. Drolet, Y. e. Tao, M. Leclerc, *Chem. mater.* **2004**, *16*, 4386.

¹⁸⁷ M. Okada, I. Sato, S. J. Cho, Y. Suzuki, M. Ojika, D. Dubnau, Y. Sakagami, *Biosci., Biotechnol., Biochem.* **2004**, *68*, 2374.

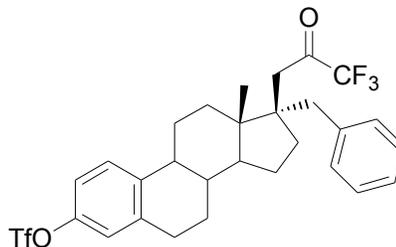
¹⁸⁸ V. K. Tam, Q. i. Liu, Y. Tor, *Chem. Commun.* **2006**, 2684.



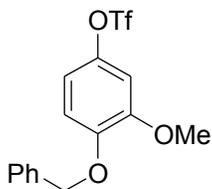
acetonitrile, reflux,
1h, 88%¹⁸⁹



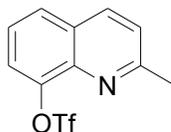
Dioxane, 100°C, 16 h,
78%¹⁹⁰



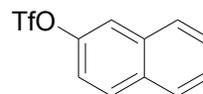
Dioxane, 96°C, 3h, 62%⁸⁶



Dioxane, 80°C, 36 h,
68%¹⁹¹



dioxane, 80°C, 4 h, 63 %⁸⁴



(CH₂Cl)₂, 110°C, 53 %¹⁹²

PdCl₂TPP₂ catalyst

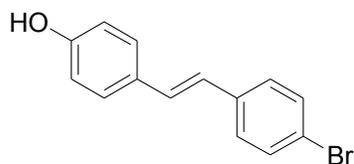
The very common PdCl₂TPP₂ catalyst has also been used for this borylation. The operating conditions are generally taken directly from the original publications. Examples of PdCl₂TPP₂-catalyzed borylation are gathered below:

¹⁸⁹ a) N. Sakai, A. L. Sisson, S. Bhosale, A. Fuerstenberg, N. Banerji, E. Vauthey, S. Matile, *Org. Biomol. Chem.* **2007**, *5*, 2560. b) N. Sakai, A. L. Sisson, T. Burgi, S. Matile, *J. Am. Chem. Soc.* **2007**, *129*, 15758.

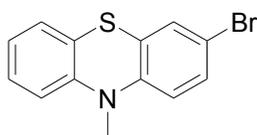
¹⁹⁰ V. Ahmed, Y. Liu, C. Silvestro, S. D. Taylor, *Bioorg. Med. Chem.* **2006**, *14*, 8564.

¹⁹¹ M. Ebisawa, M. Ueno, Y. Oshima, Y. Kondo, *Tetrahedron Lett.* **2007**, *48*, 8918..

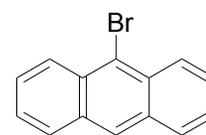
¹⁹² M. A. Brimble, M. Y. H. Lai, *Org. Biomol. Chem.* **2003**, *1*, 2084-.



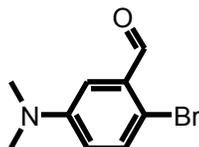
toluene, 90 °C, 17 h ,
48%¹⁹³



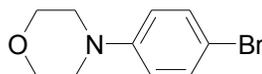
dioxane, reflux, 48 h, 73%¹⁹⁴



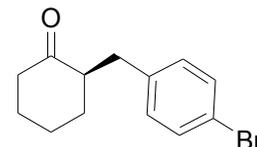
toluene, reflux, 5% Pd, 16 h,
74%¹⁹⁵



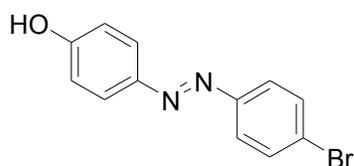
dioxane, 100°C, 3 h, 35%¹⁹⁶



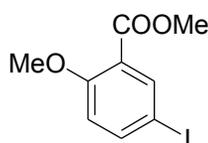
PinBH 1.2 eq., dioxane, reflux,
4h, 84%¹⁹⁷



dioxane, 100°C, 3h, 67%
(17% Ar-H).¹⁹⁸



toluene, 90 °C, 17 h, 48%¹⁹⁹



dioxane, 80 °C, 84%²⁰⁰

¹⁹³T. Takeuchi, K. Akeda, S. Murakami, H. Shinmori, S. Inoue, W.-S. Lee, T. Hishiya, *Org. Biomol. Chem.* **2007**, *5*, 2368.

¹⁹⁴ C. S. Kramer, K. Zeitler, T. J. J. Muller, *Tetrahedron Lett.* **2001**, *42*, 8619.

¹⁹⁵ A. Petitjean, R. G. Khoury, N. Kyritsakas, J.-M. Lehn, *J. Am. Chem. Soc.* **2004**, *126*, 6637.

¹⁹⁶ J. Cody, C. J. Fahmi, *Tetrahedron* **2004**, *60*, 11099.

¹⁹⁷ N. Dodic, F. J. Gellibert, **WO2004013138**.

¹⁹⁸ C. Spino, V. G. Gund, C. Nadeau, *J. Comb. Chem.* **2005**, *7*, 345..

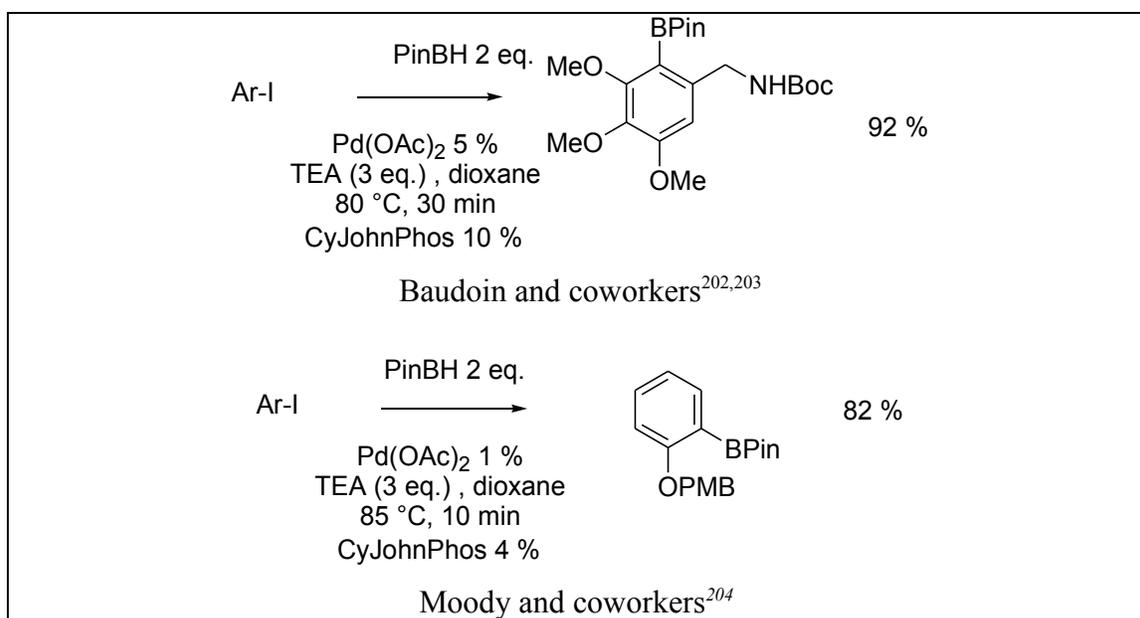
¹⁹⁹ T. Takeuchi, K. Akeda, S. Murakami, H. Shinmori, S. Inoue, W.-S. Lee, T. Hishiya, *Org. Biomol. Chem.* **2007**, *5*, 2368.

²⁰⁰ A. Casimiro-Garcia, A. G. Schultz, *Tetrahedron Lett.* **2006**, *47*, 2739.

CyJohnPhos-based catalysts

In 2000, Baudoin and coworkers²⁰¹ proposed the use of a ligand disclosed by Buchwald (CyJohnPhos), to improve the outcome of the reaction in the case of hindered, *ortho*-substituted substrates. They proved that this catalyst led to a higher borylation/hydrodehalogenation ratio than the dppf-based catalyst. Compared to PdCl₂dppf, the reactions are much faster and a better outcome is met with aryl bromides.

Dramatic reaction rates were achieved with CyJohnPhos-based catalyst, on iodides :



In an interesting comparison²⁰⁵ between the Kumada, Negishi, Stille, and Suzuki-Miyaura reactions in the synthesis of indole alkaloids, a very fast and efficient borylation of 7-bromoindole was described:

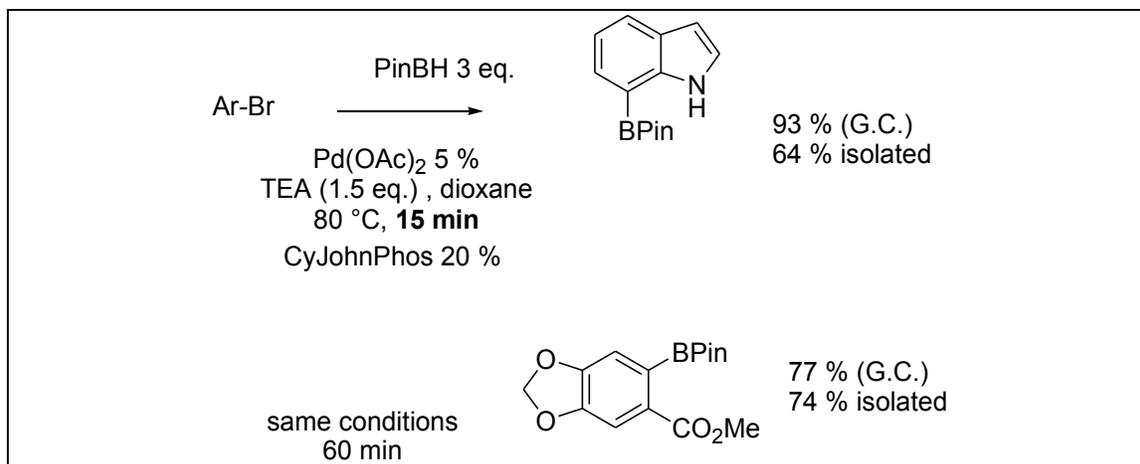
²⁰¹ O. Baudoin, D. Guenard, F. Gueritte, *J. Org. Chem.*, **2000**, *65*, 9268.

²⁰² A. Joncour, A. Decor, S. Thoret, A. Chiaroni, O. Baudoin, *Angew. Chem. Int. Ed.*, **2006**, *45*, 4149.

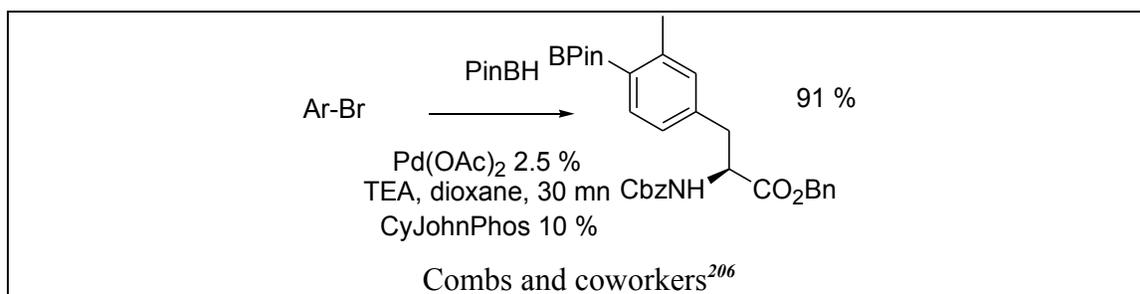
²⁰³ O. Baudoin, A. Decor, M. Cesario, F. Gueritte, *Synlett*, **2003**, 2009.

²⁰⁴ C. Poriel, M. Lachia, C. Wilson, J. R. Davies, C. J. Moody, *J. Org. Chem.*, **2007**, *72*, 2978.

²⁰⁵ U. V. Mentzel, D. Tanner, J. E. Tonder, *J. Org. Chem.*, **2006**, *71*, 5807.



Fast reactions are now reported with aryl bromides as well:

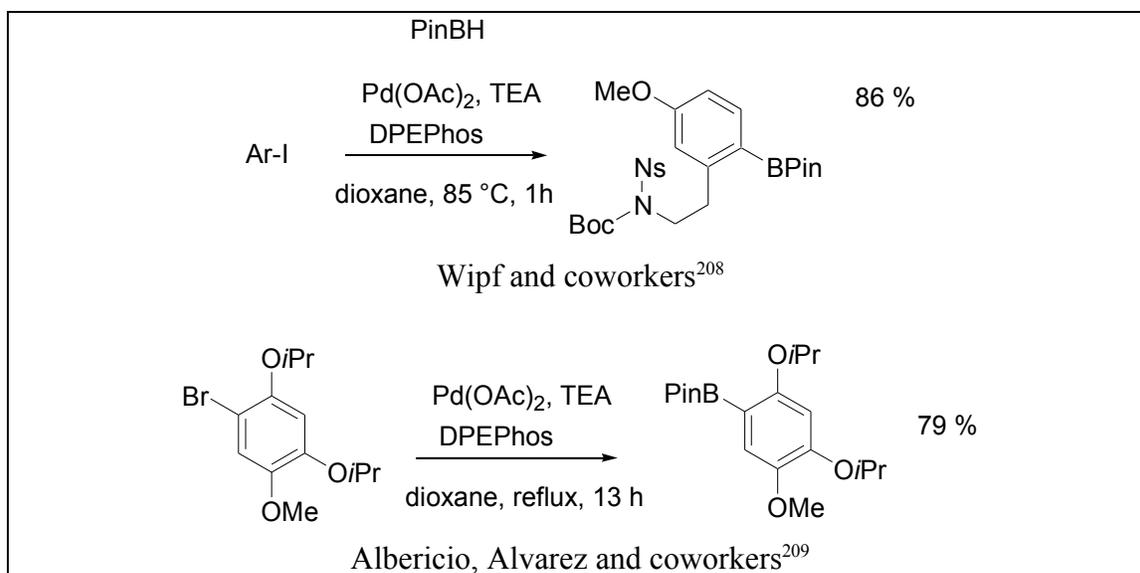


DPEphos-based catalyst

Leroux and Colobert proposed in 2004²⁰⁷ the use of the less expensive and oxidatively stable DPEphos as ligand for the borylation various unactivated and sterically hindered phenyl bromides. These more recent conditions have not been yet much illustrated:

²⁰⁶ A. P. Combs, W. Zhu, M. L. Crawley, B. Glass, P. Polam, R. B. Sparks, D. Modi, A. Takvorian, E. McLaughlin, E. W. Yue, Z. Wasserman, M. Bower, M. Wei, M. Rupal, P. J. Ala, B. M. Reid, E, *J. Med. Chem.*, **2006**, *49*, 3774.

²⁰⁷ P. E. Broutin, I. Cerna, M. Campaniello, F. Leroux, F. Colobert, *Org. Lett.*, **2004**, *6*, 4419.



t-BuDPEphos-based catalyst

In 2006, Murata²¹⁰ proposed a cross between the two former ligands, namely bis(2-di-*tert*-butyl-phosphinophenyl)ether (*t*-BuDPEphos), aiming to solve the problem of the hydrodehalogenation side reaction. They succeeded in bringing the Ar-BPin/Ar-H ratio to 84/16 in the challenging case of 4-bromo-benzoate esters. The same ligand was applied later to a borylation of aryl iodides with MPBH,²¹¹ featuring very high borylation/hydrodehalogenation selectivity. The ligand is not commercial worldwide yet.

Other ligands

Le Floch and coworkers²¹² proposed the precatalyst below to increase the TON of the recently described borylation. Good results were obtained with aryl iodides, providing high yields in boronic esters with 0.005% catalyst (dioxane, 80 °C). Later, the following catalysts^{213,214} allowed TON up to 9000 when the substrate was a reactive bromide.

²⁰⁸ P. Wipf, M. Furegati, *Org. Lett.*, **2006**, *8*, 1901.

²⁰⁹ D. Pla, A. Marchal, C. A. Olsen, F. Albericio, M. Alvarez, *J. Org. Chem.*, **2005**, *70*, 8231.

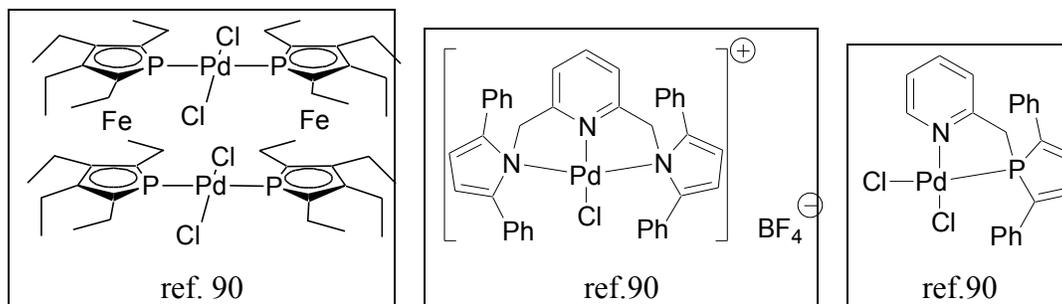
²¹⁰ M. Murata, T. Sambomatsu, S. Watanabe, Y. Masuda, *Synlett*, **2006**, 1867.

²¹¹ M. Murata, T. Oda, S. Watanabe, Y. Masuda, *Synthesis*, **2007**, 351.

²¹² M. Melaimi, F. Mathey, P. Le Floch, *J. Organomet. Chem.*, **2001**, *640*, 197.

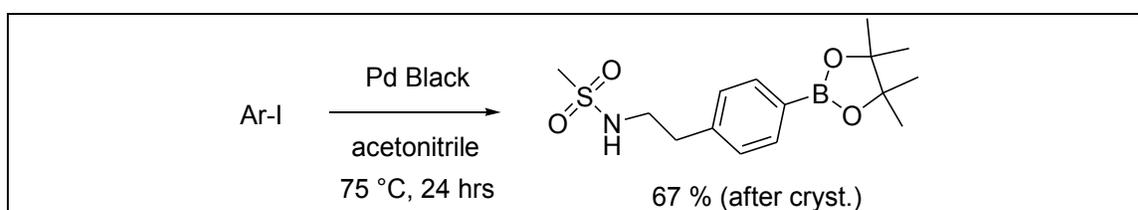
²¹³ C. Thoumazet, M. Melaimi, L. Ricard, P. Le Floch, *Comptes Rendus Chimie*, **2004**, *7*, 823.

²¹⁴ M. Melaimi, C. Thoumazet, L. Ricard, P. Le Floch, *J. Organomet. Chem.*, **2004**, *689*, 2988.



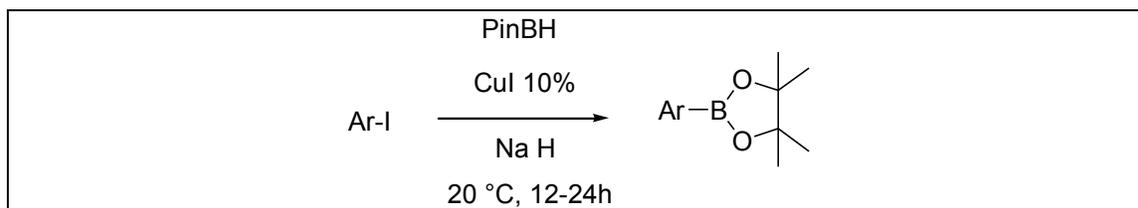
Palladium Black catalyst

In 2007, a 3 mol-scale borylation was described with Pd Black in acetonitrile.²¹⁵



Copper catalysis

D. Ma published in 2006²¹⁶ the borylation of aryl iodides in the presence of catalytic CuI and NaH as the base; the reaction is run at room temperature.



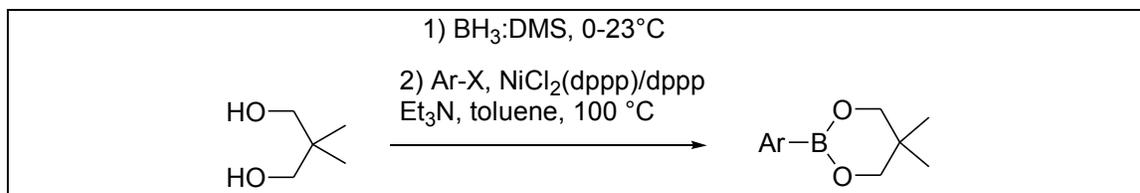
Ni Catalysis

In 2008, a Nickel-catalyzed borylation with an *in situ* prepared solution of neopentylglycolborane has been proposed.²¹⁷

²¹⁵ W. D. Miller, A. H. Fray, J. T. Quatroche, C. D. Sturgill, *Org. Process Res. Dev.*, **2007**, *11*, 359.

²¹⁶ W. Zhu, D. Ma, *Org. Lett.*, **2006**, *8*, 261

²¹⁷ B. M. Rosen; C. Huang; V. Percec, *Org. Lett.*, **2008**, *10*, 2597.

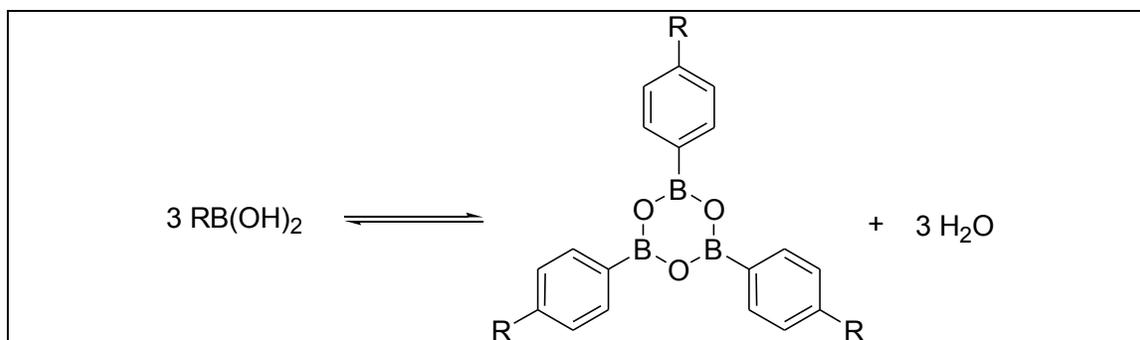


3.1.6 Other Derivatives of Boronic Acid:

For convenience in their purification and characterization, boronic acids are often best handled as ester derivatives, in which the two hydroxyl groups are masked. Likewise, transformation of the hydroxyl groups into other substituents such as halides may also provide the increased reactivity necessary for several synthetic applications.

3.1.6.1 Boroxines

Boroxines are cyclotrimeric anhydrides of boronic acids. They are isoelectronic to benzene and by virtue of the vacant orbital on boron they possess partial aromatic character.²¹⁸ Boroxines are easily produced by the simple dehydration of boronic acids. They are present as a mixture in equilibrium with boronic acids (Scheme 83).



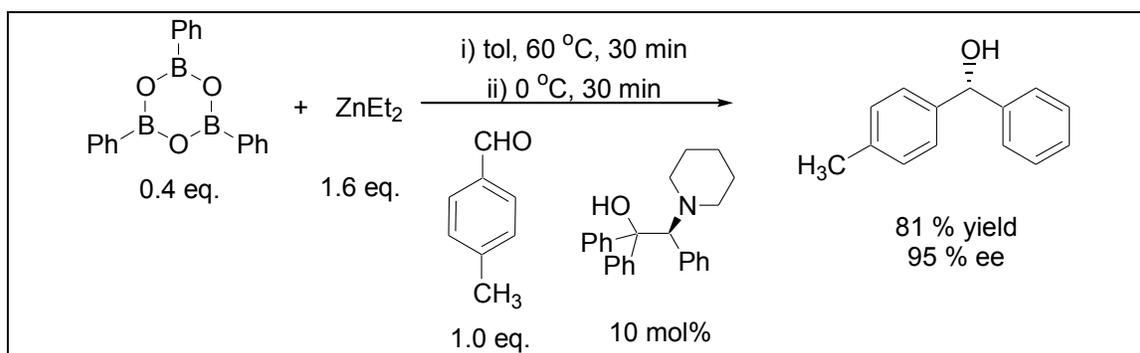
Scheme 83

The significant entropic drive for boroxine formation arises due to the release of three molecules of water and it is usually difficult to determine the concentration of boronic acid versus boroxine in a mixture. Currently there exists no simple assay to assess the amount of boronic acid actually present in equilibrium.

²¹⁸ C. P. Brock, R. P. Minton, K. Niendenzu, *Acta. Crysta.* **1987**, C43, 1775.

Several experimental and theoretical studies²¹⁹ have addressed the nature and the structure of these derivatives; in particular, X-ray crystallographic analysis of triphenylboroxine confirms that it is virtually flat. Boroxines can be employed invariably as substrates in many of the same synthetic transformations known to affect boronic acids, but they are rarely sought as synthetic products.

Triaryl boroxines²²⁰ have been used extensively as aryl transfer reagents in the enantioselective arylation of aldehydes (Scheme 84). They represent the most atom-economical source of aryl groups among the different aryl boron reagents (74% of the molecular weight of triphenylboroxine corresponds to transferable phenyl groups versus 63% for phenylboronic acid and only 51% for dimethyl phenylboronate, the simplest phenyl-boronic ester).



Scheme 84

3.1.6.2 Trifluoroborate salts

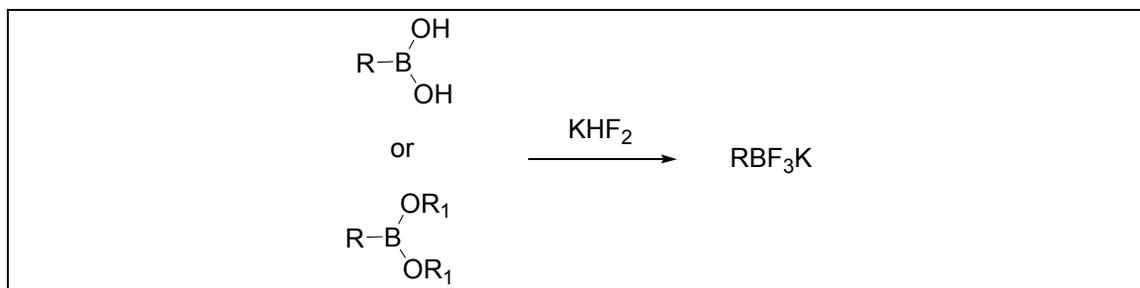
Organotrifluoroborates²²¹ are a new class of air-stable boronic acid derivatives that can be readily prepared according to the procedure of Vedejs and coworkers (Scheme 85).²²² Boronic esters also give the desired salts under similar conditions.

²¹⁹ a) R. F. Porter, S. K. Gupta, *J. Phy. Chem.*, **1964**, 68, 280. b) S. K. Wason, R. F. Porter, *J. Phy. Chem.* **1964**, 68, 1443. c) F. A. Grimm, L. Barton, R. F. Porter, *Inorg. Chem.* **1968**, 7, 1309. d) C. H. Chang, R. F. Porter, S. H. Bauer, *Inorg. Chem.* **1969**, 8, 1689.

²²⁰ A) Z. Chai, X. Liu, X. Wu, G. Zhao, *Tetrahedron: Asymmetry* **2006**, 17, 2442. b) X. Wu, X. Liu, G. Zhao, *Tetrahedron: Asymmetry* **2005**, 16, 2299.

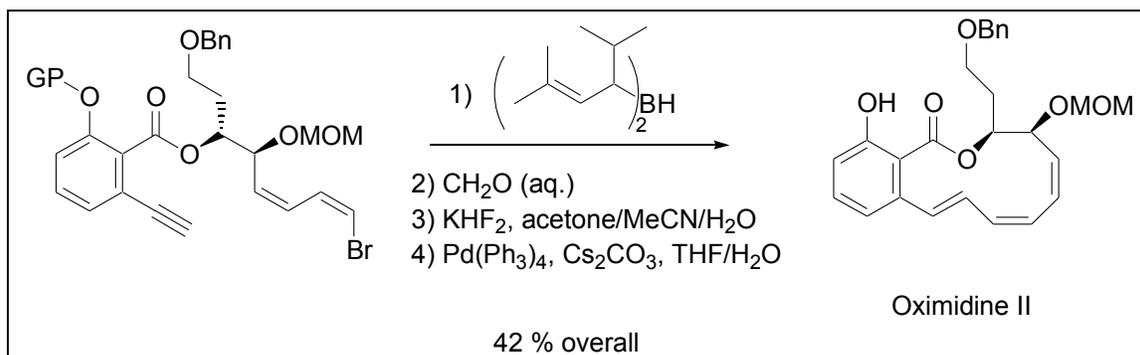
²²¹ a) S. Darses, J. P. Genet, *Chem. Rev.* **2008**, 108, 288-325. b) G. A. Molander; N. Ellis, *Acc. Chem. Res.*, **2007**, 40, 275; c) G. A. Molander, R. Figueroa, *Aldrichim. Acta* **2005**, 38, 49.

²²² a) E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin, M. R. Schrimpf, *J. Org. Chem.* **1995**, 60, 3020. b) E. Vedejs, S. C. Fields, R. Hayashi, S. R. Hitchcock, D. R. Powell, M. R. Schrimpf, *J. Am. Chem. Soc.* **1999**, 121, 2460.



Scheme 85

These crystalline, water-soluble derivatives are easy to handle, highly stable and can be used as substrates in many of the same reaction processes that employ free boronic acids. Their important applications include the Suzuki-Miyaura cross-coupling reaction (Scheme 86),²²³ rhodium catalyzed 1,4-addition (Scheme 87)²²⁴ copper-promoted coupling (Scheme 88)²²⁵ to amines and alcohols and allylation of aldehydes.²²⁶



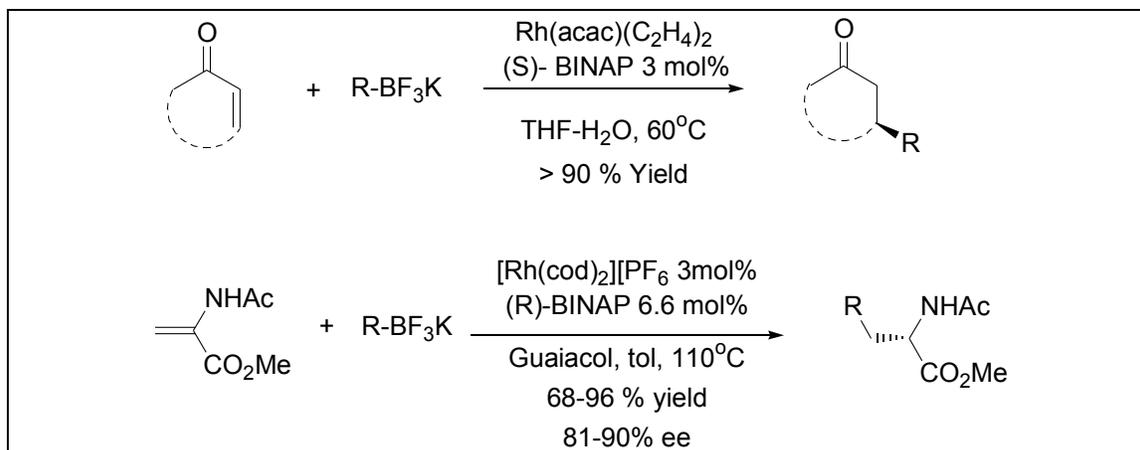
Scheme 86: Formal Total Synthesis of Oximidine using Suzuki coupling

²²³ S. Darses, J. -P. Genet, J. -L. Brayer, J. -P. Demoute, *Tetrahedron Lett.* **1997**, 38, 4393. b) S. Darses, G. Michaud, J. -P. Genet, *Tetrahedron Lett.* **1998**, 39, 5045. c) G. A. Molander, T. Ito, *Org. Lett.* **2001**, 3, 393. d) G. A. Molander, M. R. Rivero, *Org. Lett.* **2002**, 4, 107. e) H. A. Stefani; R. Cella; R. S. Vieira, *Tetrahedron*, **2007**, 63, 3623; f) L. Zhang; T. Meng; J. Wu, *J. Org. Chem.*, **2007**, 72, 9346.

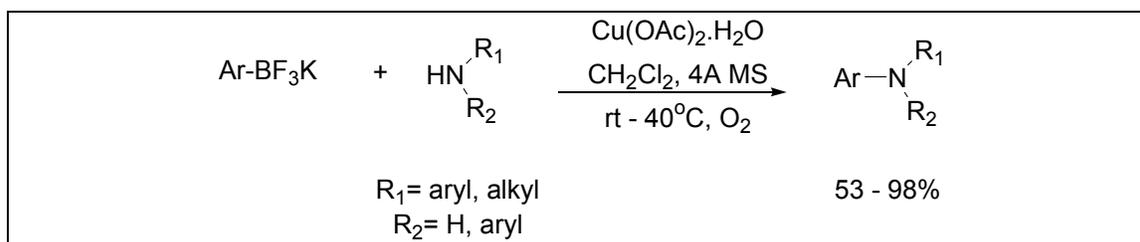
²²⁴ L. Navarre, S. Darses, J. -P. Genet, *Eur. J. Org. Chem.* **2004**, 69-73.

²²⁵ T. D. Quach, R. A. Batey, *Org. Lett.* **2003**, 5, 1381.

²²⁶ A. N. Thadani, R. A. Batey, *Tetrahedron Lett.* **2003**, 44, 8051. b) A. N. Thadani, R. A. Batey, *Org. Lett.* **2002**, 4, 3827.



Scheme 87: Rh-Catalyzed 1,4-Addition

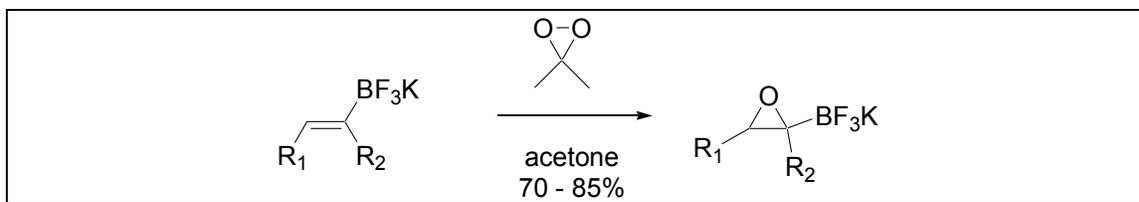


Scheme 88: Cu-Catalyzed Amine synthesis

The tetracoordinate nature of boron in trifluoroborate complexes, fortified by strong boron-fluorine bonds, provides mechanistic inhibition of undesirable reactions typical of trivalent organoborons. Notably, the incompatibility of boron-carbon bonds with several oxidants limits the possibilities to further transform compounds containing a boronic acid (or ester) functionality. Thus, epoxidation²²⁷ of an alkenyltrifluoroborate salt in good yields while preserving the carbon-boron bond intact, serves as a clear testimony of the advantage of using them. The corresponding boronic acids and esters do not lead to the desired epoxide but to the aldehyde resulting from carbon-boron bond oxidation (Scheme 89). It was recently reported that trifluoroborate salts can be conveniently transformed into dichloroboranes by treatment with SiCl_4 in THF.²²⁸

²²⁷ G. A. Molander; M. Ribagorda, *J. Am. Chem. Soc.*, **2003**, *125*, 11148;

²²⁸ B. J. Kim, D. S. Matteson, *Angew. Chem. Int. Ed.* **2004**, *43*, 3056.



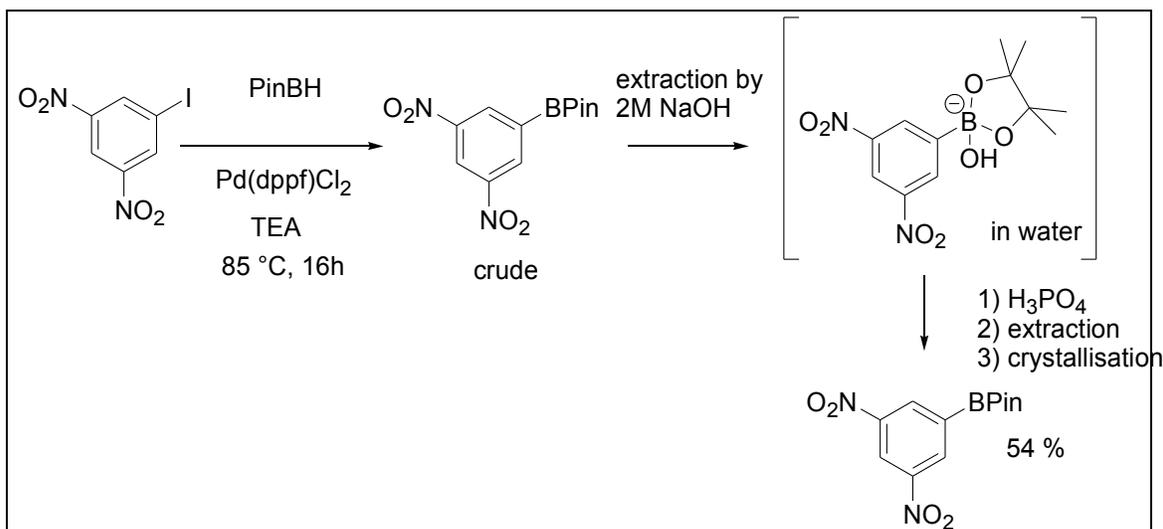
Scheme 89

3.1.6.3 Interconversion of arylboronic species

The formation of a cyclic boronic ester from the boronic acid and a 1,2- or 1,3-diol is a fast, acid or base-catalyzed reaction. The equilibrium is largely in favor of the ester, all the more in the case of pinacol.

Boronic esters can be used as such in Suzuki-Miyaura couplings. Considering the usual conditions of Suzuki reactions, one could suppose that the boronic ester is hydrolysed *in situ*, the acid-ester equilibrium being displaced by the coupling step.

But the occurrence of arylboronate anions is very plausible, as shown for example by the experiment²²⁹ in Scheme 90. These anions could be the active species in the transmetalation step of the Suzuki coupling.

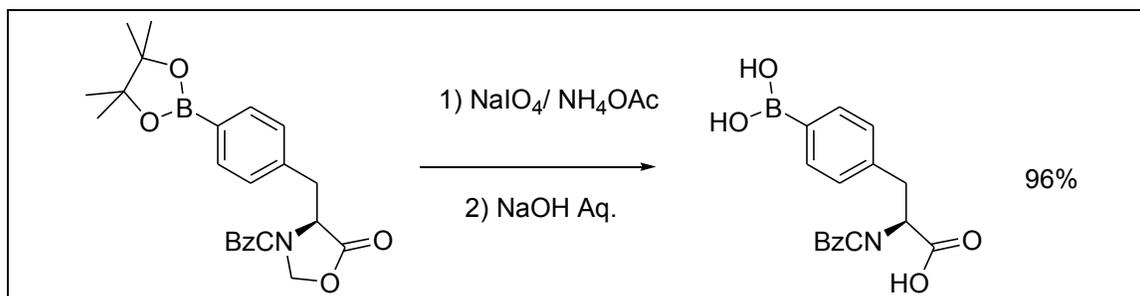


Scheme 90

Nevertheless, mainly for the sake of obtaining solid products for isolation, protocols for the hydrolysis of the boronic esters of pinacol were developed. Several

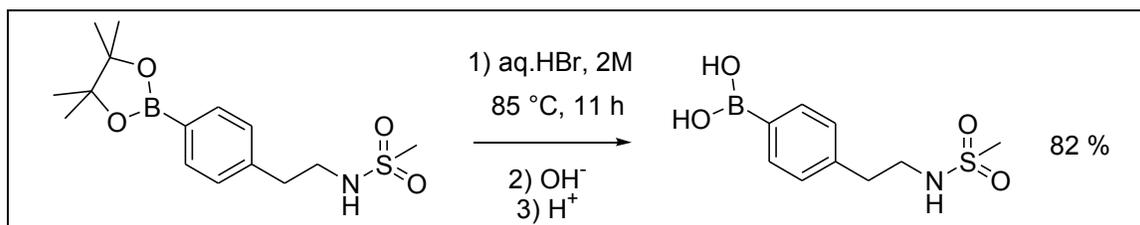
²²⁹ A. Zahn; C. J. Leumann, *Bioorg. Med. Chem.*, **2006**, *14*, 6174

authors use stoichiometric NaIO_4 ,⁸⁵ to drive the equilibrium by degradation of the diol (Scheme 91).



Scheme 91

A large-scale hydrolysis of a boronic ester by aqueous HBr was recently described⁹¹ (Scheme 92). It could be supposed that in such harsh conditions, the evolved pinacol could undergo pinacolic rearrangement, which could once more drive the hydrolysis equilibrium.



Scheme 92

The preparation of trifluoroborates (see above) is mostly conducted from boronic acids. The same products can be made from pinacolboronic esters (typical conditions: KHF_2 , $\text{MeOH-H}_2\text{O}$, 2 h, rt, quant.²³⁰).

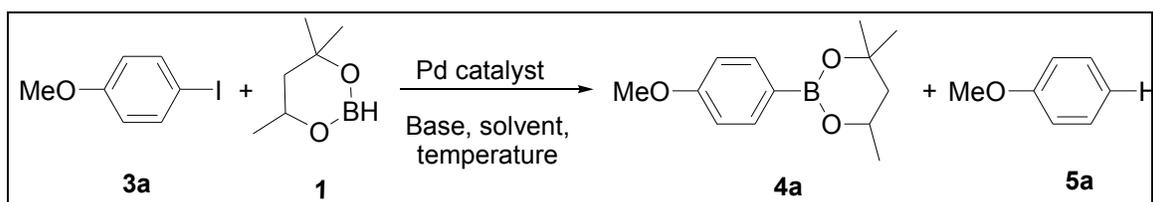
²³⁰ N. Sakai; A. L. Sisson; S. Bhosale; A. Fuerstenberg; N. Banerji et al., *Org. Biomol. Chem.*, **2007**, *5*, 2560.

3.2 Results and discussion

3.2.1 Borylation with $\text{PdCl}_2(\text{TPP})_2$

3.2.1.1 Optimisation of the reaction conditions :

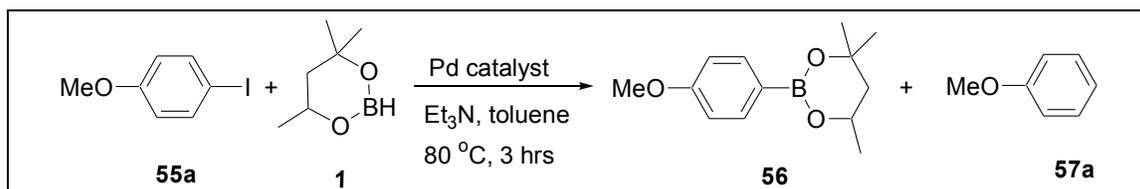
During the course of our initial studies on this reaction, the formation of varying amounts of the reduction product has always been observed by GC analysis. The formation of this reduction product is dependant on the nature of the base, the catalyst used and the nature of the substituent present in the aryl moiety. With the aim of accessing aryl boronates selectively, the influence of various parameters including the nature of catalyst, base and temperature of the reaction on the outcome of the reaction was examined. 4-iodoanisole (**3a**) was chosen as the model substrate (Scheme 93) and the results of the screening are discussed below.



Scheme 93

3.2.1.2 The choice of catalyst:

Then, the influence of the catalyst ligands on the outcome of the reaction was examined. The reaction is effected in toluene in the presence of three equivalents of triethylamine for a period of three hours.

Table 8: Influence of the Catalyst

Entry	Catalyst Used	No. of equivalents	Yield ^a (%)	
			Ar-B(OR) ₂ 56	Ar-H 57a
1	PdCl ₂ (dppf)	0.03	78	20
2	Pd(TPP) ₄	0.03	70	30
3	PdCl ₂ (TPP) ₂	0.03	89	07
4	Pd(OAc) ₂	0.03	40	26
5	Pd ₂ (dba) ₃	0.03	10 ^b	13
	None	0		No trace

^a GC Yields (internal standard) based on (**55a**).

^b Unreacted aryl halide was the major product.

The reaction was efficiently catalyzed by Pd(II) complexes with two phosphine moieties. PdCl₂(dppf), (Table 8, entry 1), which is commonly used in pinacol borylation gave acceptable yields. But the use of PdCl₂(TPP)₂, (Table 8, entry 3) a simple, robust and fully air stable catalyst increased the overall efficiency of the process. The catalyst, resulted in the complete conversion of the aryl halide and minimal formation of the reduced product. Complexes with additional phosphine ligands like Pd(TPP)₄, (table 2, entry 2), led to a slower reaction.

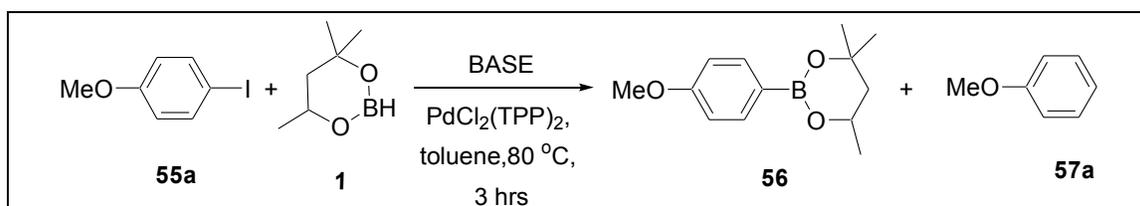
Pd(OAc)₂ (Table 8, entry 4) or Pd₂(dba)₃ (Table 8, entry 5) as catalysts, resulted in the immediate formation of a black precipitate. But the required aryl boronate was formed, albeit to a lesser extent. This encouraged us to try the “ligandless conditions” which has been described recently in the literature for a PinBH borylation reaction.⁹¹ Accordingly, the reaction was tested with 10% Pd/C (3 mol%) as the catalyst under both

conventional heating (in dioxane) and microwave²³¹ heating. Unfortunately, the formation of the reduction product was found to be the major outcome of the reaction.

3.2.1.3 The choice of base:

The role of the base is found to be very crucial in influencing the outcome of the reaction. In the literature, TEA is the only practically utilized base in borylation by PinBH. We checked several amine and oxygenated bases with MPBH.

Table 9: Influence of the Base



Entry	Base used	No. of equivalents	Ar-I 55a	yield ^a (%)	
				Ar-B(OR) ₂ 56	Ar-H 57a
1	K ₃ PO ₄	3.0	-	26 ^b	30
2	KOAc	3.0	-	26	60
3	Et ₃ N	3.0	-	89	07
4	Et ₃ N	10.0	-	72	13
5	ⁿ Bu ₃ N	3.0	36	47	12
6	Pyridine	3.0	49	27	23
7	PhNEt ₂	3.0	72	16	10

^a GC Yields (internal standard) based on 55a. The conversion of the iodide was complete in cases 1 to 4, within 3 hrs.

^b Homocoupled product was formed up to 34%

In this case also, TEA (Table 9, Entry 3) proved to be effective in promoting the reaction. Other bases like ⁿBu₃N (Table 9, entry 5) and pyridine (entry 6) resulted in incomplete reactions.

²³¹ Biotage monomode closed-vessel apparatus, 300 W, 10 min.

As discussed in the preceding chapter, the preparation of MPBH could be achieved using BH_3 -diethylaniline as the boron source.²³² Thus, it would have been advantageous to use the diethylaniline liberated *in situ* as the only base for the borylation. Thus, we added iodoanisole and $\text{PdCl}_2(\text{TPP})_2$ to the reaction mixture resulting from treatment of BH_3 -diethylaniline with hexyleneglycol. No reaction was observed after 6 hrs at 80 °C. At this stage, addition of 3 eq. TEA started the borylation, although at a much lower rate than in the reference run (Table 9, entry 3). The reaction in the presence of oxygenated bases like KOAc or K_3PO_4 proceeds much slower than with TEA. This is presumably due to the non-homogeneity of the reaction mixture. Moreover, the use of KOAc (Entry 1, Table 1) as the base strongly favors the reduction pathway leading to anisole **57a**. The use of a stronger base like K_3PO_4 (Table 9, entry 2) promotes the Suzuki coupling of the formed aryl boronate with the remaining aryl iodide, leading to the formation of the symmetrical biaryl compound.

Thus, TEA is again the base of choice for the borylation with MPBH. The reasons for such a singularity are not obvious. In an attempt to observe a possible intermediate, a mixture of MPBH and TEA in toluene was heated at 80 °C for 4 hrs. We observed only starting materials by ^1H and ^{11}B NMR. The use of a larger amount (10 mol. eq.) of TEA did not change the reaction rate (Table 9, entry 4). Thus TEA is probably not involved in a rate-determining step.

3.2.1.4 Influence of other parameters

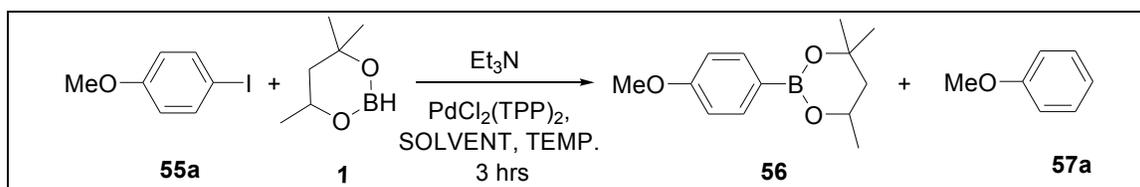
With triethylamine as the base of choice and $\text{PdCl}_2(\text{TPP})_2$ as the source of Pd, the influence of other parameters like nature of the solvent and temperature was briefly examined (Table 10). Of the solvents examined, both toluene and dioxane were found to be equally effective in the reaction (Table 10, entries 1 & 2). Since the stability of MPBH solutions is slightly better in toluene than in dioxane, we chose toluene for subsequent reactions. The use of a polar solvent like DMF (Table 10, entry 3) caused both a low yield and a poor borylation/reduction ratio. Such a trend was attributed earlier to the disproportionation of dialkoxyborane into diborane.⁷ The reaction carried out at a lower

²³² Chapter 1, page 23.

temperature (60 °C, Table 10, entry 4) resulted in the recovery of unreacted starting material. At 90 °C the reduction process begins to predominate (Table 10, entry 4)

We will note here that we also checked the sensitivity of the reaction to contaminants. We had observed that the addition of the MPBH solution was usually followed by a gentle evolution of H₂. So, we could hope that MPBH was scavenging impurities in the reaction mixture, and that this could prevent some catalyst degradation. But when we used undistilled triethylamine in our standard conditions, the reaction was clearly slower than usual, indicating a loss of active catalyst.

Table 10: Influence of solvent & temperature



Entry	Catalyst used	Solvent	Temp (°C)	Yield ^a (in %)		
				Ar-I 55a	Ar- B(OR) ₂ 56	Ar-H 57a
1	PdCl ₂ (TPP) ₂	Toluene	80	<5	89	07
2	PdCl ₂ (TPP) ₂	Dioxane	80	<5	89	07
3	PdCl ₂ (TPP) ₂	DMF	80	<5	40	40
4	PdCl ₂ (TPP) ₂	Toluene	60	75	12	3
5	PdCl ₂ (TPP) ₂	Toluene	90	5	60	30

^a determined by GC (internal standard)

3.2.1.5 Borylation of Aryl iodides and bromides:

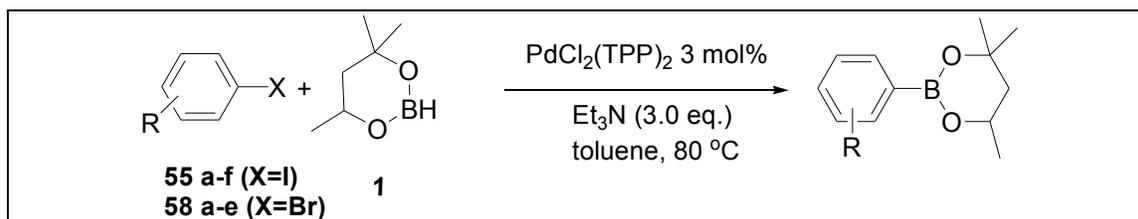
The borylation of various aryl halides in the presence of $\text{PdCl}_2(\text{TPP})_2$ and TEA was carried out to yield the corresponding aryl boronates. The results obtained are summarized in Table 11 (next page).

The reaction works well with both electron-rich and electron-deficient aryl iodides as well as for electron-rich bromides. The analysis of the crude reaction mixture generally showed good conversions for aryl iodides. The present procedure, using MPBH, is tolerant to a variety of common functional groups.

A small amount of reduced by-product was formed in all cases. Separation of this by-product was easily achieved by flash chromatography as the resulting boronates exhibited excellent stability in aqueous workup and chromatography.

Both the yield and product selectivity was found to be dependant on the steric and electronic nature of the aryl halide used. Thus in the case of electron-rich iodides (Table 11, entries 1, 3, 5, 7) the reactions were high yielding with significantly shorter reaction times and better borylation/reduction ratios. These results are comparable to those of Murata in terms of conditions, yield and compatibility with functional groups. We give in Table 12 a selection of examples with either methods.

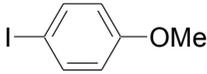
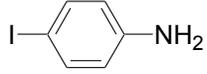
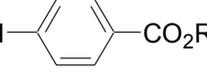
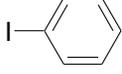
Aryl halides carrying electron-withdrawing groups usually lead to a less favorable borylation/reduction ratio. In such cases, the superiority of the Murata's catalytic system⁹⁰ appeared. The benzoate ester borylated in 68 % isolated yield in the present work, and was obtained in 78 % yield by using t-Bu-DPEphos-based catalyst. The difference was much more significant in the case of 4-Iodonitrobenzene where it was completely reduced in the former case, while in the later system, a 77% yield of the corresponding boronate ester was obtained. The 3-nitro derivative was also found to be mediocre in its reactivity resulting in the formation of the boronate ester only to an extent of 50% leading predominantly to the reduction product.

Table 11: Borylation of aryl iodides and bromides with PdCl₂(TPP)₂

Entry	Aryl Halide	Halide	Time (hr)	% Yield ^b	Prod.No.
1		X = I (55a)	3.0	89	(56)
2		X = Br (58a)	6.0	89	
3		X = I (55b)	3.0	79	(59)
4		X = Br (58b)	6.0	83	
5		X = I (55c)	6.0	85	(60)
6		X = Br (58c)	16.0	71	
7		X = I (55d)	6.0	60	(61)
8		X = Br (58d)	16.0	51	
9		X = I (55i)	16.0	68	(62)
10		X = I (55m)	16.0	73	(62')
11		X = Br (58e)	6.0	60	(63)
12		X = I (55f)	6.0	88	(64)
13		X = I (55g)	16.0	78	(65)

(a) Reaction conditions: Halide (1.0 mmol), MPBH (1.5 mmol), PdCl₂(TPP)₂ (3 mol%) and TEA (3.0 mmol) in toluene (3ml) at 80 °C for the indicated time. (b) Isolated yields are based on aryl halides.

Table 12: Comparison with t-Bu-DPEphos

Entry	Aryl Halide	Product No.	Condition A t-Bu-DPEphos	Condition B PdCl ₂ (TPP) ₂
1		(56)	86	89 (87) ^c
2		(66)	72	71
3		(67)	78	68
4		(68)	93	91 ^d (82)

Cond. A- Aryl halide 1 mmol, MPBH 1.5 mmol, Et₃N 3.0 mmol, PdCl₂(MeCN)₂ 30 μmol, ligand 30 μmol, in toluene (4 ml) at 80 °C for 16 hrs.

Cond. B- Aryl halide 1 mmol, MPBH 1.5 mmol, Et₃N 3.0 mmol, PdCl₂(TPP)₂ 3 mol% in toluene (4 ml) at 80 °C for indicated time.

(c) Isolated Yield in a 10 mmol run using 2 mol% catalyst.

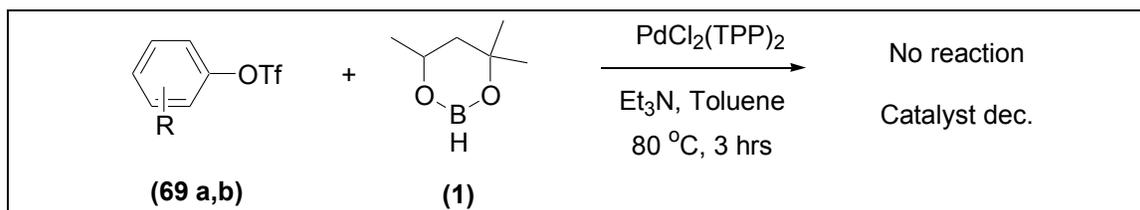
(d) GC Yield, isolated yield given in parenthesis.

3.2.1.6 Borylation of Aryl triflates and chlorides:

The ready availability of triflates from phenols has made their usage widespread in borylation reaction.²³³ Moreover, their reactivity has been described as being intermediate between iodides and bromides.

We attempted to carry out the coupling of aryl triflates with MPBH and PdCl₂(TPP)₂ in the above experimental conditions. The formation of the required aryl boronate was not observed. Instead, in each case, we observed the precipitation of Pd black at an early stage of the reaction.

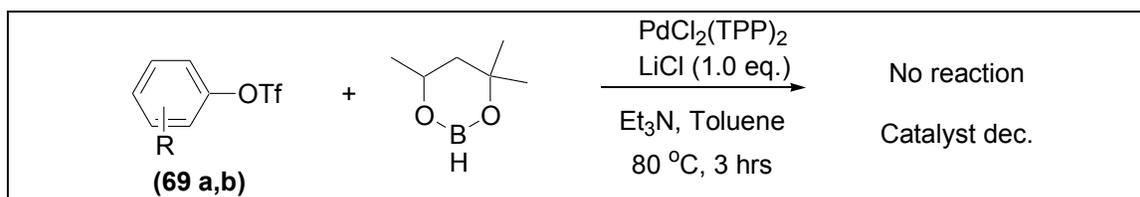
²³³ a) K. Ritter, *Synthesis* **1993**, 735. b) P. J. Stang, M. Hanack, L. R. Subramanian *Synthesis* **1982**, 85. c) M. Rottlander, P. Knochel *J. Org. Chem.* **1998**, 63, 203.

Table 13: attempted borylation of aryl triflates

R	Ar-OTf	Ar-B(OR) ₂	Ar-H
4-Me (69 a)	89%	7%	2%
4-COCH ₃ (69 b)	91%	0	5%

As noted earlier in the literature, the triphenylphosphine ligand can react with triflates to give phosphonium salts and render the Pd inactive.²³⁴ The use of additives like LiCl²³⁵ was known to be effective in preventing such a decomposition of the catalyst.

In our assays with MPBH, neither did the addition of 1.0 eq of LiCl nor a slow addition of the aryl triflate (1 hr via syringe pump)⁸⁰ improved the outcome of the reaction.

**Scheme 94**

²³⁴ A. Jutand, A. Mosleh *Organometallics* **1995**, *14*, 1810.

²³⁵ *Tetrahedron* **1989**, *45*, 6679

3.2.2 Borylation catalyzed by Pd/CyJohnPhos

As already mentioned in the preceding section the use of aryl chlorides²³⁶ or triflates for the borylation reaction is attractive due to the ready availability of these substrates compared to their bromide and iodide counterparts. We thus turned our attention towards the very interesting results obtained by the groups of Buchwald,²³⁷ Baudoin,⁸⁸ and others concerning the use of sterically hindered phosphine ligands for demanding substrates. The dialkylbiaryl phosphine ligands CyJohnPhos and XPhos could be employed to afford highly active catalyst. These ligands possess a fine balance of steric and electronic properties which allow for significantly accelerated oxidative addition while facilitating the other steps (transmetalation, reductive elimination) in the catalytic cycle. The basic phosphine binds tightly to the metal (relative to a triarylphosphine) to prevent precipitation of the catalyst.

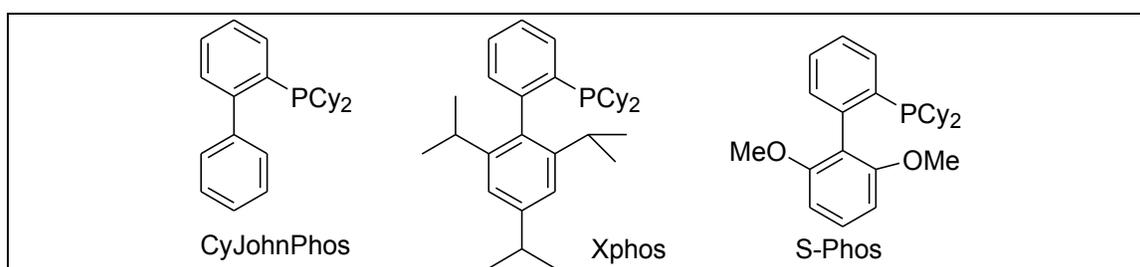


Figure 15: Ligands for Borylation

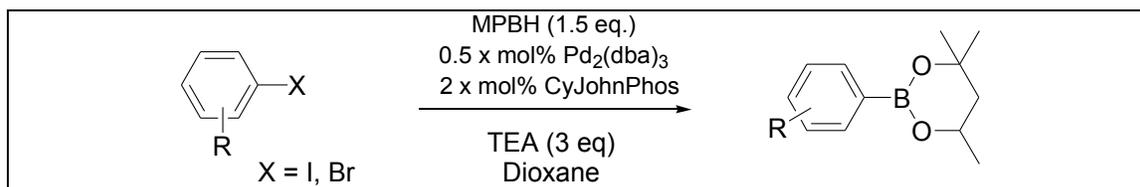
3.2.2.1 Borylation of aryl iodides and bromides

In PdCl₂(TPP)₂-catalyzed coupling of aryl iodides and bromides, Et₃N was shown to be more efficient among the other bases examined and hence was used in this case also without investigating other bases. Toluene and dioxane again were found to be suitable solvents and dioxane was preferred. The optimum temperature for the reaction was very dependent on the electronic nature of the aryl halide or triflate used. Thus in the case of relatively simple electron-rich iodides and bromides the reaction proceeds at room temperature or slightly above with complete conversion of the aryl halide in all cases.

²³⁶ For a review of Pd-catalyzed coupling reactions of aryl chlorides, see A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

²³⁷ K. L. Billingsley, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 5589

Most importantly, the formation of the reduction product was always found to be much less than with the catalytic system used earlier. A very low loading of the catalyst (1%) was enough to bring about an almost quantitative yield of the aryl boronate ester (Table 14, entry 4-7). The process remained efficient at lower levels of catalyst as the boronate ester was produced in 91% yield after 6 h at r.t. when 0.3 mol% Pd was utilized in a 10 mmol scale. (Table 14, entry 2).

Table 14: Borylation with MPBH and CyJohnPhos

Entry	Aryl Halide	Pd (x mol %)	Time (hrs)	Temp °C	Product No.	% Yield ^a	% Redn ^b .
1	(58 a)	0.5	3.0	40	(56)	81	<5
2	(58 b)	0.3	6.0	RT	(59)	91	None
3	(55 h)	0.5	0.5	RT	(66)	79	<3
4	(55 f)	1.0	3.0	RT	(64)	88	<3
5	(55 l)	1.0	16.0	40	(70)	60	ND ^c
6	(55 i)	1.0	3.0	80	(71)	68	30
7	(55 n)	1.0	3.0	80	(72)	52	ND ^c
8	(55 o)	1.0	16.0	40	(73)	60	10
9.	(55 k)	2.0	3.0	80	(74)	54	25

Conditions:- x mol% Pd₂dba₃, (2x mol % Pd), 4x mol% CyJohnPhos, (Pd:Phosphine = 1:2), 1.5 eq. of MPBH, 3.0 eq. of Et₃N, 1,4-dioxane (2.0 ml/mmol halide)

- a) Isolated Yields after column chromatography.
- b) % Yield in reduction product based on halide, was determined from ^1H NMR and in the case of entries 1, 2 and 9 by GC (internal std.).
- c) Was not determined in these cases.

Electron-deficient aryl halides are known to be more challenging substrates for the Pd-catalyzed borylation process and thus the borylation of 3-iodonitrobenzene produced only 60% of the required product in 16 hrs at 40 °C (Table 14, entry 5). The iodo ester **55i** also led to incomplete reactions at r.t. after 24 hrs while increasing the temperature to 80 °C led to the smooth conversion of the aryl halide in less than 3 hrs of reaction time (Table 14, entry 6).

Importantly, this method was also applicable to *ortho*-substituted aryl halides as the borylation of the 2-iodoaniline (Table 14, entry 4) resulted in the corresponding boronate in 88% yield at r.t. The more hindered 2-iodo-*m*-xylene (Table 14, entry 9) resulted in 54% conversion only, with a concomitant formation of the reduction product (<25%). Thus, increasing the steric hindrance in the *ortho* position to the halogen atom substantially affects the efficiency of the borylation. This result is in sharp contrast to the recent work of Buchwald⁸⁰ and coworkers where a similar catalytic system was described, and gave up to 90% of the pinacolboronate ester in the case of 2-bromomesitylene.

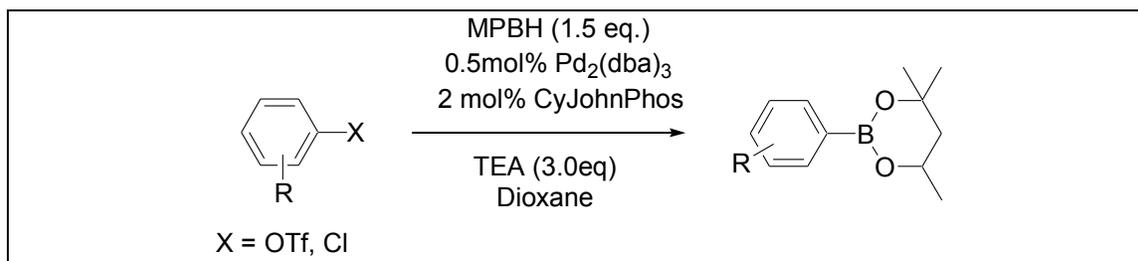
In addition, the heteroaryl iodide (Table 14, entry 8) was also converted in 60% yield at r.t. alongwith 10% of the reduction product. But in this case, the isolation of the corresponding boronate was hampered by the presence of other boron-containing impurities (δ 18 ppm ^{11}B NMR).

3.2.2.2 Borylation of aryl chlorides and triflates

We then turned our attention to the application of aryl chlorides for the palladium-catalyzed borylation using MPBH. The present catalyst system proved to be efficient for the electron-rich aryl chlorides, although a reaction temperature of 100-120°C was required. Thus 4-chloroanisole was successfully converted to its boronate ester in more than 90% yield while the corresponding 2-chloroanisole led to 47 % product formation. 4-Chlorotoluene that can be considered as an electron-neutral aryl halide resulted in 61 %

yield. Electron-poor substrates still remain problematic as in general, the reactions of these substrates resulted in incomplete conversion of the aryl chloride as well in extensive protodeboration.

Aryl triflates are also amenable to borylation in the same conditions although only two representative examples were tried. The reaction was found to work well with both electron-releasing and electron-withdrawing substituents.

Table 15: Borylation of chlorides and triflates

Entry	Aryl Halide	Pd (mol %)	Time (hrs)	Temp °C	% Yield ^a	Product No.
1	(75 a)	1.0	16.0	100	90	(56)
2	(75 b)	2.0	24.0	100	<10	(76)
3	(69 a)	1.0	6.0	80	82	(60)
4	(75 c)	2.0	16.0	80	45	(77)
5	(75 d)	1.0	24.0	100	13	(78)
6	(69 c)	1.0	16.0	80	73	(78)
7	(75 e)	1.0	24.0	80	62	(60)

Conditions-0.5 mol% Pd₂dba₃, 2 mol% CyJohnPhos, (Pd:Phosphine = 1:4), 1.5 eq. of MPBH, 3.0 eq. of Et₃N, 1,4-dioxane (2.0 ml/mmol halide)

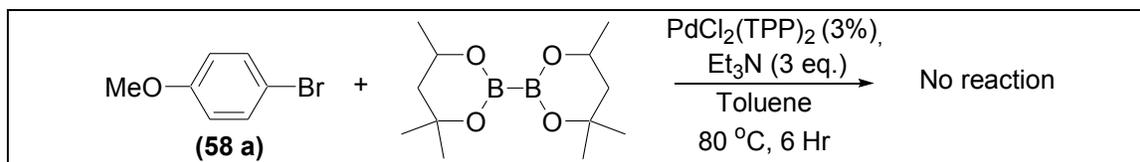
^aIsolated yields after column chromatography.

3.2.3 Borylation with bis(hexyleneglycolato)diboron

As mentioned in the preceding part, the scope of the borylation reaction using $\text{PdCl}_2(\text{TPP})_2$ was limited to electron-rich iodides and bromides and to a larger extent with electron-deficient aryl iodides. Aryl chlorides and triflates were not amenable to borylation with the existing conditions. The choice of aryl chlorides as substrates for cross-coupling reactions is highly desirable as they are less expensive and more readily available than the iodide or bromide counterparts. But the competing reduction of their C-Cl bonds could not be overcome using the present catalytic system. Thus, the borylation of aryl halides, particularly chlorides was examined briefly using commercially available bis(hexyleneglycol)diboron as the source of boron nucleophile.

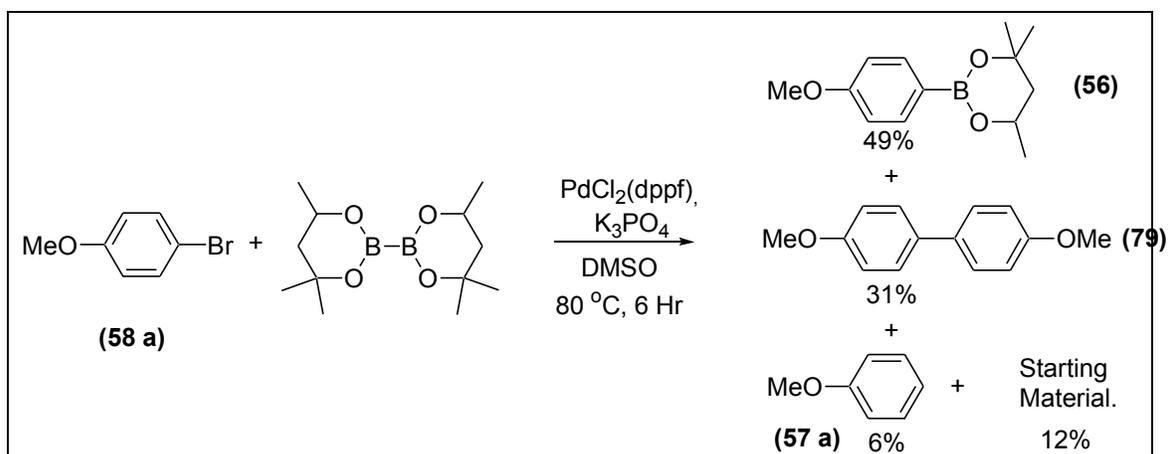
3.2.3.1 Preliminary studies

With this aim, our initial attempts to borylate aryl halides using the diboron compound bis(hexyleneglycolato)diboron ($(\text{MPB})_2$) were based on the conditions developed for borylation using MPBH. But attempted borylation of 4-bromoanisole with $(\text{MPB})_2$ in the presence of $\text{PdCl}_2(\text{TPP})_2$ and TEA using toluene or dioxane as the solvent resulted only in the complete recovery of unreacted aryl halide after 6 hrs at 80 °C (Scheme 95).



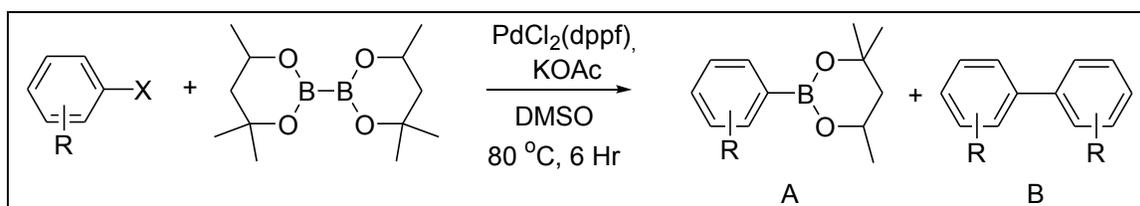
Scheme 95

The use of the much stronger K_3PO_4 base induced the desired borylation reaction but gave in addition, a considerable amount of homo-coupled dimer as already noted (see Table 16).



The literature protocol²³⁸ involving $PdCl_2(dppf)$ and $KOAc$ in $DMSO$, which is the most commonly used condition for borylation with diboron compounds, was found to work well for the representative halides examined.

Table 16: Borylation of representative substrates



Entry	R	X	Time (Hrs)	% Ar-X consumed ^a	A : B ^b
1	2 - OMe	I	16	75	100:0
2	4 - COCH ₃	OTf	6	<99	95:5
3	3 - NO ₂	I	16	<99	95:0
4	4 - COOMe	Br	16	<99	95:5

a) Determined by GC (based on internal standard)

b) Determined by GC and NMR of the crude reaction mixture.

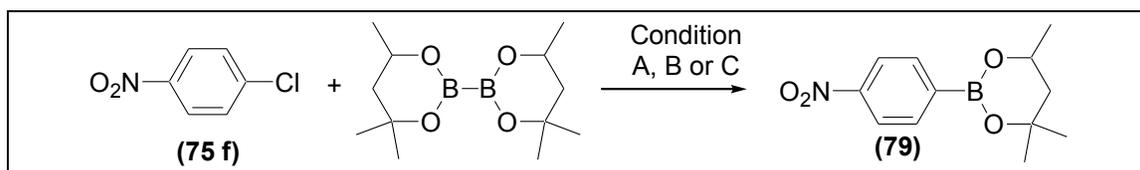
²³⁸ T. Ishiyama; M. Murata; N. Miyaura, *J. Org. Chem.*, **1995**, *60*, 7508.

3.2.3.2 Borylation of Aryl chlorides:

As described in the bibliography, the borylation of aryl chlorides has been achieved by using one of the three ligands like PCy₃, NHC or XPhos along with a suitable Pd source. The high reactivity of these complexes is attributable to the strong electron-donating ability of these ligands and the ready dissociation of the ligand to generate a co-ordinatively unsaturated species.

A screening of representative ligands reported in the literature for borylation reactions of 4-chloronitrobenzene as the model substrate is summarized in Table 17. The catalysts were prepared *in situ* by stirring a mixture of the appropriate Pd source and the phosphine ligand and used directly for the coupling reaction of diboron (1.1 eq.) and chloroarene (1.0 eq.) in the presence of KOAc (3 eq.).

Table 17: Borylation of aryl chlorides

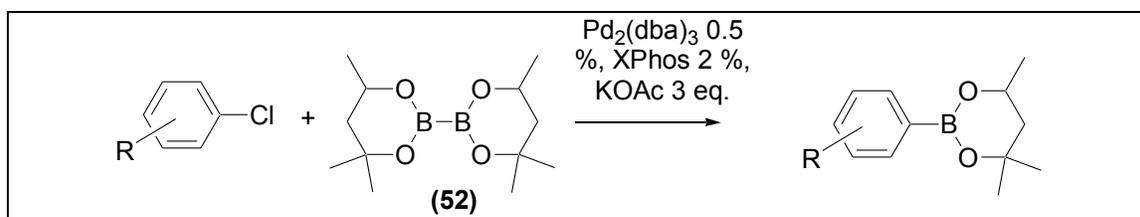


Entry	Conditions	Time (Hrs)	% Aryl chloride conversion ^a	% Yield ^a
1	A: Pd ₂ (dba) ₃ (3 mol%), PCy ₃ (3.6 mol%), KOAc (1.5 eq.)	4	50	50 ^b
2	B: Pd ₂ (dba) ₃ (0.5 mol %), XPhos (2.0 mol %) KOAc (3.0 eq.)	6	< 99	87 ^c
3	C: Pd(OAc) ₂ (3 mol %), NHC (6 mol%), KOAc (2.5 eq.)	6	<10	Traces

a) % conversion determined by GC. b) determined by ¹H NMR of the crude reaction mixture. c) Isolated yield based on the chloroarene.

The catalyst system derived from $\text{Pd}_2(\text{dba})_3$ and XPhos was found to be very efficient when compared to the other two systems examined. The conditions were then extended to both electron-rich and electron-deficient aryl chlorides. The results obtained are tabulated below.

Table 18: Borylation of various aryl chlorides with $(\text{MPB})_2$



Entry	Aryl chloride	Time (Hrs)	%Conversion ^a	%Yield ^b	Product No.
1	(75 a)	16	88	74	(56)
2	(75 d)	6	< 99	92	(78)
3	(75 f)	6	< 99	87	(79)
4	(75 g)	8	60	Traces ^c	
5	(75 h)	6	< 99	79	(80)

^a % conversion of the aryl chloride was determined by GC

^b %Yield refers to the isolated yields after chromatography.

^c dehalogenated product was found to be predominating as seen by ¹H NMR

GC inspection of the crude reaction mixtures showed that the conversion was quantitative in most cases. The reaction was very fast, completing within 6 h for chloroarenes possessing an electron-withdrawing group such as $-\text{NO}_2$ (Table 18, entry 3) and $-\text{COCH}_3$ (Table 18, entry 2). The presence of electron-donating OMe substituent (Table 18, entry 1) slowed down the reaction significantly, thus requiring prolongation of the reaction time to 16 hrs. The reaction is applicable for the borylation of heteroaromatic chloride such as 6-chloroindole (Table 18, entry 5) leading to the corresponding boronate ester in good yields. Surprisingly, the chloroarene with an ortho $-\text{CHO}$ group relative to the halide failed to yield the boronate ester (Table 18, entry 4). Since boronate esters adjacent to a heteroatom are highly susceptible to hydrolytic protodeboration, the coupling reaction often leads to boron-carbon bond cleavage. Such side reaction giving the reduction product of the chloro-arene in small amounts (less than 5%) was also observed in the case of entries 1 and 2.

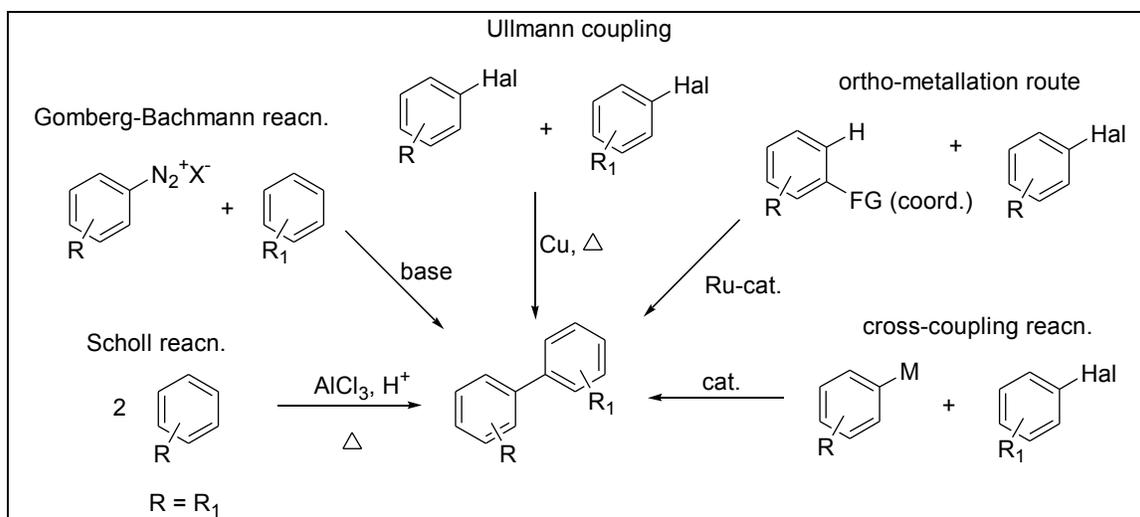
3.3 Suzuki-Miyaura coupling:

3.3.1 Bibliographic Introduction:

Carbon-carbon bonds are the molecular “bricks and mortar” from which diverse architectures in living organisms and man-made materials are constructed. As the field of organic chemistry has evolved, numerous methods for the carbon-carbon bond construction have been developed, ranging from the classical examples, like the Diels-Alder reaction, to more recent metal-catalyzed processes, such as olefin polymerization and metathesis.

Biaryl subunits and their heteroaromatic analogs are abundant in natural and synthetic materials, and controlled methods for linking aromatic rings via C-C sigma bonds have long been pursued by organic chemists (Scheme 97). Activity in this regard intensified in the late 1970's, during which Pd-catalyzed methods for C-C bond construction emerged.²³⁹

²³⁹ F. Diedrich, P. J. Stang, *Metal-catalyzed Cross-coupling Reactions* Wiley-VCH, NewYork, 1988.



Scheme 97: Various accesses to biaryl motif

First disclosed in 1979, the seminal paper of Miyaura, Yamada and Suzuki²⁴⁰ laid the groundwork for what now is arguably the most important and useful transformation for the construction of the carbon-carbon bonds in modern day organic chemistry. Although the original paper reported coupling reactions of alkenyl boronates with alkenyl bromides, throughout the past 25 years contributions from several research groups²⁴¹ have led to vast improvements on what is now known as the Suzuki-Miyaura cross-coupling reaction (Scheme 98). Advances have been made in the way of reaction scope, including the use of aryl chlorides¹⁰⁷ as substrates and the ability to conduct couplings at very low catalyst loadings²⁴² and at room-temperature.²⁴³

²⁴⁰ N. Miyaura, K. Yamada, A. Suzuki *Tetrahedron Lett.*, **1979**, 36, 3437.

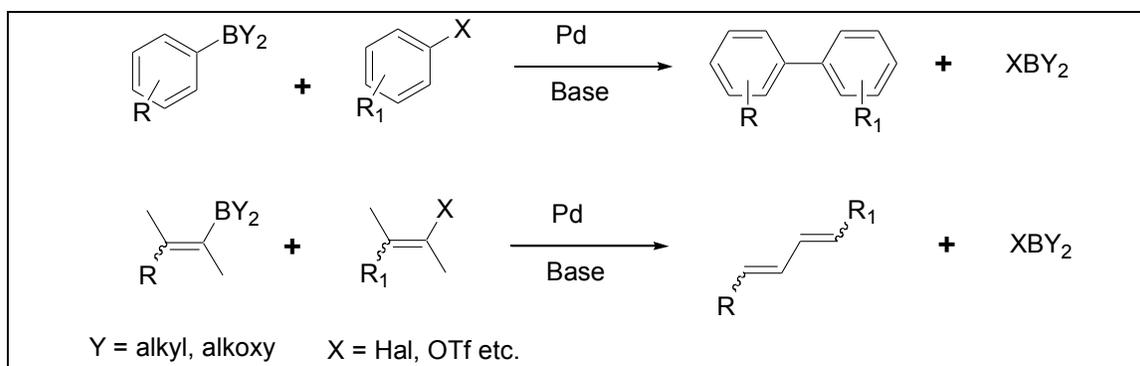
²⁴¹ a) N. Miyaura, A. Suzuki *Chem. Rev.*, **1995**, 95, 2457. b) A. Suzuki *J. Organomet. Chem.*, **1999**, 576, 147. c) N. Miyaura *Top. Curr. Chem.*, **2002**, 219, 11. d) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.*, **2002**, 102, 1359. e) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, 58, 9633.

f) F. Bellina, A. Carpita, R. Rossi *Synthesis* **2004**, 15, 2419.

²⁴² a) J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.*, **1999**, 121, 9550. b) A. Zapf, A. Erhentraut, M. Beller, *Angew. Chem. Int. Ed.*, **2000**, 39, 4153. c) D. A. Alonso, C. Najera, M. C. Pacheo, *J. Org. Chem.*, **2002**, 67, 5588. d) R. B. Bedford, C. S. J. Cazin, S. L. Hazelwood *Angew. Chem. Int. Ed.*, **2002**, 41, 4120. e) R. B. Bedford, S. L. Hazelwood, M. E. Limmert, *Chem. Commun.*, **2002**, 2610. f) R. B. Bedford, S. L. Hazelwood, M. E. Limmert, D. A. Albiison, S. M. Draper, P. N. Scully, S. J. Coles, M. B. Hursthouse, *Chem. Eur. J.*, **2003**, 9, 3216.

²⁴³ a) D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.*, **1998**, 120, 9722. b) D. Zim, A. S. Gruber, G. Ebeling, J. Dupont, A. Monteiro, *Org. Lett.*, **2000**, 2881. c) M. R. Netherton, C. Dai, K. Neuschütz, G. C. Fu, *J. Am. Chem. Soc.*, **2001**, 123, 10099. d) T. J. Colacot, E. S. Gore, A. Kuber, *Organometallics*, **2002**, 21, 3301. e) J. H. Kirchoff, M. R. Netherton, I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.*, **2002**, 124, 13662.

f) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *Angew. Chem. Int. Ed.*, **2003**, 42, 3690. g) O. Navarro, R. A. Kelly, S. P. Nolan, *J. Am. Chem. Soc.*, **2003**, 125, 16194.



Scheme 98: General form of Suzuki-Miyaura coupling reaction

Moreover, it is now possible to couple hindered substrates²⁴⁴ and even asymmetric variations²⁴⁵ have been reported. Improvements in the Suzuki-Miyaura coupling reactions have relied a great deal on the increased stability of the metal catalyst by the use of increasingly efficacious supporting ligands. The most common ligands used today are phosphine-based, although a variety of others,²⁴⁶ including N-heterocyclic carbenes (NHC), have been employed. Also of great importance are the procedures that utilize the so-called ligandless conditions²⁴⁷.

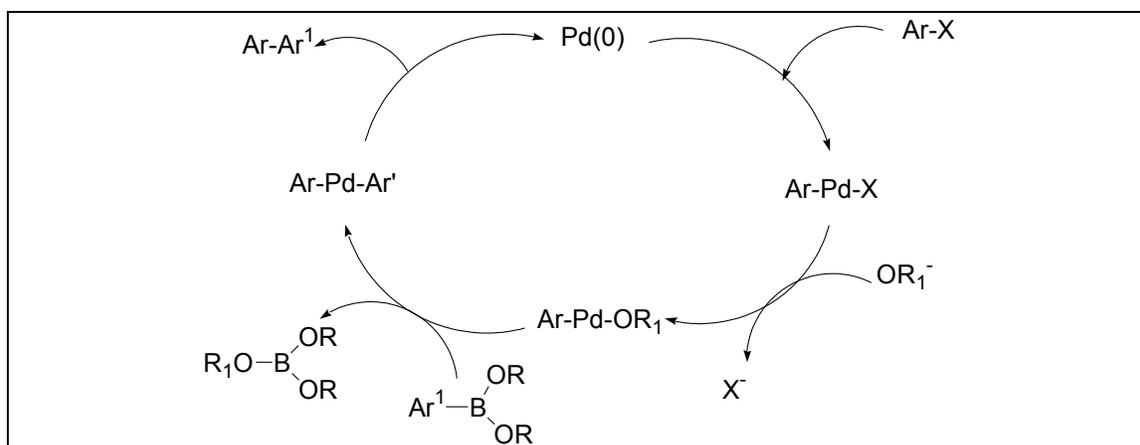
The general catalytic cycle for the Suzuki-Miyaura cross-coupling involves the oxidative addition of the halide to the Pd(0) complex to form the organopalladium halide (R-M-X), and is often the rate-determining step in the catalytic cycle. This step is followed by transmetalation with the organoboron reagent to provide the diorganopalladium (R-M-R') that can undergo a reductive elimination, leading to carbon-carbon bond formation and regeneration of the catalyst. (Scheme 99)

²⁴⁴ G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *J. Am. Chem. Soc.*, **2004**, 126, 15195.

²⁴⁵ a) S. Y. Cho, M. Shibasaki, *Tetrahedron: Asymmetry* **1998**, 9, 3751. b) A. Herrbach, A. Marinetti, O. Baudoin, D. Guenard, F. Gueritte, *J. Org. Chem.*, **2003**, 68, 4897. c) A. S. Castanet, F. Colobert, P. E. Broutin, M. Obringer, *Tetrahedron: Asymmetry* **2002**, 13, 659. d) J. Yin, S. L. Buchwald *J. Am. Chem. Soc.*, **2000**, 122, 12051. e) A. N. Cammidge, K. V. L. Crepy, *Chem. Commun.* **2000**, 1723. f) A. N. Cammidge, K. V. L. Crepy, *Tetrahedron* **2004**, 60, 4377. g) K. Mikami, T. Miyamoto, M. Hatano, *Chem. Commun.* **2004**, 2082.

²⁴⁶ a) V. P. W. Bohm, C. W. K. Gstottmayr, T. Weskamp, A. W. Hermann, *J. Organomet. Chem.*, **2000**, 595, 186. b) M. B. Andrus, C. Song, *Org. Lett.*, **2001**, 3, 3761. c) Y. H. Zhao, Y. Y. Zhou, D. D. Ma, J. P. Liu, T. Y. Zhang, H. B. Zhang, *Org. Biomol. Chem.* **2003**, 1, 1643.

²⁴⁷ a) T. I. Wallow, B. M. Novak, *J. Org. Chem.* **1994**, 59, 5034. b) G. A. Molander, B. J. Biolatto, *J. Org. Chem.* **2003**, 68, 4302 and references cited therein. c) G. W. Kabalka, V. Nambodiri, L. Wang, *Chem. Commun.* **2001**, 775. d) S. Darses, T. Jeffery, J. -P. Genêt, J. -L. Brayer, J. -P. Demoute, *Tetrahedron Lett.* **1996**, 37, 3857.



Scheme 99 General catalytic cycle for a Suzuki-Miyaura cross-coupling

Today, the Suzuki-Miyaura coupling reaction is routinely applied in high-throughput screening for drug-discovery,²⁴⁸ in the final steps of convergent natural product syntheses,²⁴⁹ and in the synthesis of conjugated organic materials (Figure 16).²⁵⁰

²⁴⁸ R. E. Sammelson, M. J. Kurth, *Chem. Rev.* **2001**, 101, 137.

²⁴⁹ S. R. Chemler, S. J. Danishefsky, *Org. Lett.* **2000**, 2, 2695.

²⁵⁰ A. D. Schlüter, *J. Polym. Sci. A.* **2001**, 39, 1533.

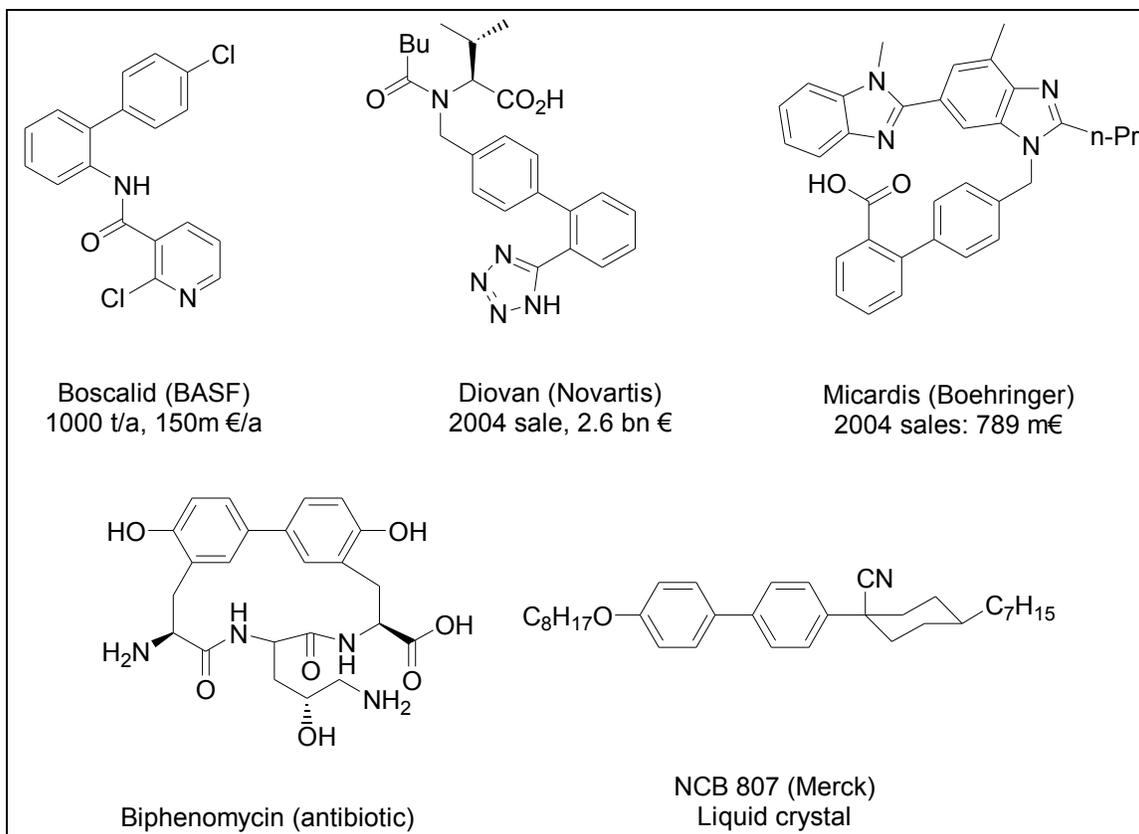


Figure 16: Importance of the biaryl structural motif

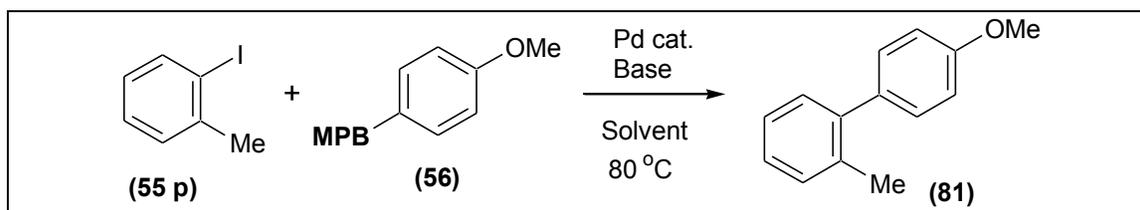
3.3.2 Results and Discussion:

The major application of arylboronate esters is the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction. With an easy access to functionalized boronate esters in hands, we sought to confirm that MPB esters can be efficiently used in the preparation of unsymmetrical biphenyls.

3.3.2.1 Choice of the conditions

The various conditions tested for the coupling of 2-iodotoluene and 4-methoxy phenyl boronic ester are gathered in Table 19.

Table 19: Suzuki-Miyaura cross-coupling reaction of **4a** under various conditions^a:



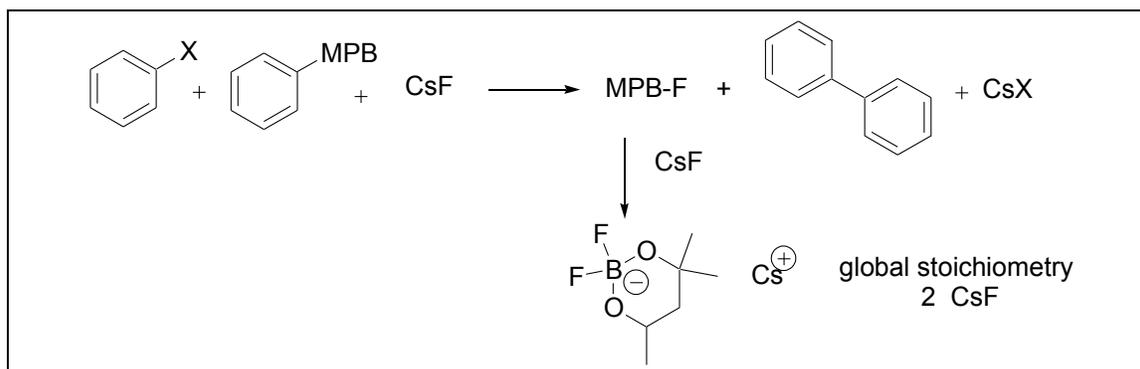
Entry	Catalyst	Base	Solvent	Time (hrs)	Yield (%)
1	PdCl ₂ (TPP) ₂	Et ₃ N	Toluene	16	0
2	PdCl ₂ (TPP) ₂	Et ₃ N	DMF	16	0
3	PdCl ₂ (TPP) ₂	K ₃ PO ₄	DMF	4	90
4	Pd ₂ (dba) ₃	K ₃ PO ₄	DMF	4	84
5	PdCl ₂ (TPP) ₂	CsF (3 eq.)	DMF	0.5	94
6	Pd(TPP) ₄	CsF (3 eq.)	DMF	2	90
7	Pd(OAc) ₂	CsF (3 eq.)	DMF	2	88
8	PdCl ₂ (TPP) ₂	CsF	Toluene	4	<10

(a) Reaction conditions: Aryl boronate (1.0 mmol), aryl iodide (1.0 mmol), base (3.0 mmol), Pd catalyst (3 mol%) in solvent (2 ml) at 80 °C for the given time. Reported yields are determined by GC (internal standard) based on **55p**.

Triethylamine (Table 19, entries 1 & 2) as the base did not produce the desired Suzuki coupling product, which was not surprising as we never observed any

homocoupling product in the borylation reactions. Changing the base from Et_3N to K_3PO_4 (Table 19, entry 3) resulted in quantitative conversion of the starting material in 4.0 hrs.

Finally, the choice of $\text{CsF}^{251,252}$ (Table 19, entry 5) as the base gratifyingly produced the desired biaryl product in excellent yield within 30 min. The time required for the completion of the reaction was considerably reduced upon the addition of 3 mol CsF per mol Ar-X , rather than the stoichiometric 2 mol (Scheme 100). No further enhancement of reaction rate was noted when 4.0 eq. of CsF was used.



Scheme 100: stoichiometry of CsF

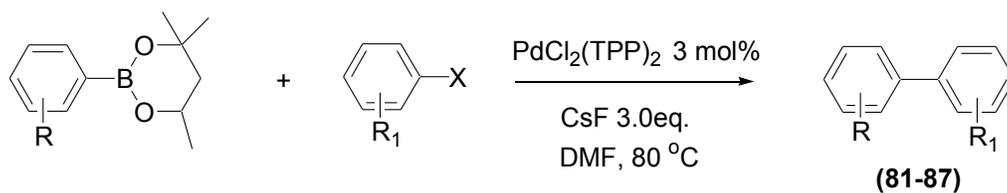
The nature of the Palladium source did not highly influence the outcome of the reaction, as the yields were comparable with various Pd catalysts studied (Table 19, entries 5, 6 & 7). In general, $\text{PdCl}_2(\text{TPP})_2$ (Table 19, entry 5) was found to be a much efficient catalyst offering faster reaction rates and leading to the corresponding boronate esters in high yields. Last, the use of toluene (Table 19, entry 8) as the solvent resulted in poor conversions presumably due to the poor solubility of CsF in toluene.

3.3.2.2 Aryl-Aryl cross coupling reactions:

With the above optimized conditions in hand, we proceeded to examine the cross-coupling reactions of various aryl boronates in order to demonstrate their synthetic utility. The conditions were found to be very general and highly efficient for a variety of aryl iodides, bromides and triflates examined. The results are summarized in Table 20 and show that a variety of substituted biaryls can be obtained in high yields.

²⁵¹ S. W. Wright, D. L. Hageman, L. D. McLure, *J. Org. Chem.* **1994**, *59*, 6095.

²⁵² Other fluoride salts like KF and Bu_4NF were found to be somewhat inferior to CsF in terms of conversion of the starting material within a given time.

Table 20: Examples of Aryl-Aryl cross-coupling:

Entry	R	Aryl halide or Triflate	Time (min)	% Yield ^a	Product No.
1	4-OMe	(58 f)	60	92	(81)
2	4-OMe	(69 a)	60	85	(82)
3	4-OMe	(55 i)	30	92	(83)
4	4-OMe	(55 m)	30	80	(84)
5	4-Me	(55 k)	90	87	(85)
6	4-Me	(69 c)	90	72	(82)
7	2, 4-dimethyl	(55 q)	30	92	(86)
8	2, 4-dimethyl	(58 g)	180	97	(87)

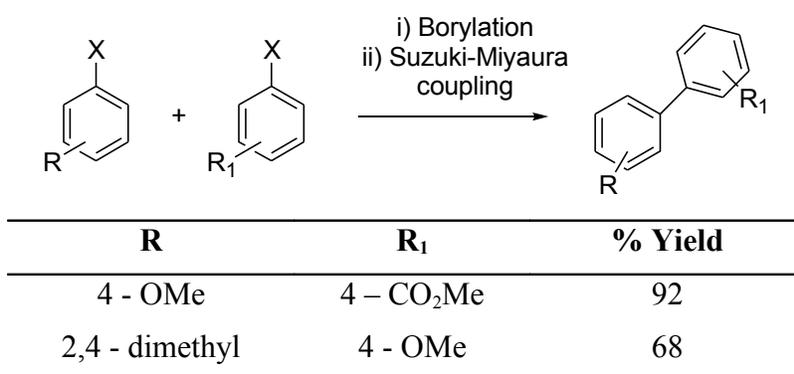
a) Isolated yields. Reaction conditions: aryl boronate (1.0 mmol), aryl halide (or triflate) (1.0 mmol), CsF (3.0 mmol), PdCl₂(TPP)₂ (3 mol%) in DMF (4.0 ml) at 80 °C for given period of time.

b) Yield in 8-benzyloxy-,7-di-p-tolyl-quinoline from 2 eq. of 4. the reaction of single equivalent of the boronic ester was not regioselective.

The reactions were rapid (< 2 h) with both electron-poor and electron rich aryl halides. (Table 20, entries 2 and 3). Hindered aryl boronates are not inhibited from coupling to sterically demanding aryl halides as seen by entries 5 and 7. Heteroaromatic halides can also be cross-coupled with equal efficiency. (Table 20, entry 11).

3.3.2.3 One pot, two steps synthesis of biphenyls:

Since the borylation reaction were high yielding and clean, it was possible to use a “one-pot” reaction protocol^{88,253} combining the borylation and Suzuki-Miyaura steps to synthesize biaryl compounds. Thus in this process, the substrate was subjected to standard Pd-catalyzed borylation conditions with subsequent addition of the second aryl halide. No workup was performed, nor was catalyst added, prior to conducting the second reaction of the sequence.



Scheme 101: One pot-two steps synthesis of Biphenyl

Thus, the borylation of iodides with the standard conditions, was followed by removal of solvent²⁵⁴, then by the addition of a solution of CsF and the second aryl iodide in DMF. It should be noted that the coupling itself was slower than in the two-steps protocol. In both runs, the homocoupling product was not detected (<5%) thus indicating that the conversion of the starting iodide in the borylation reaction was total.

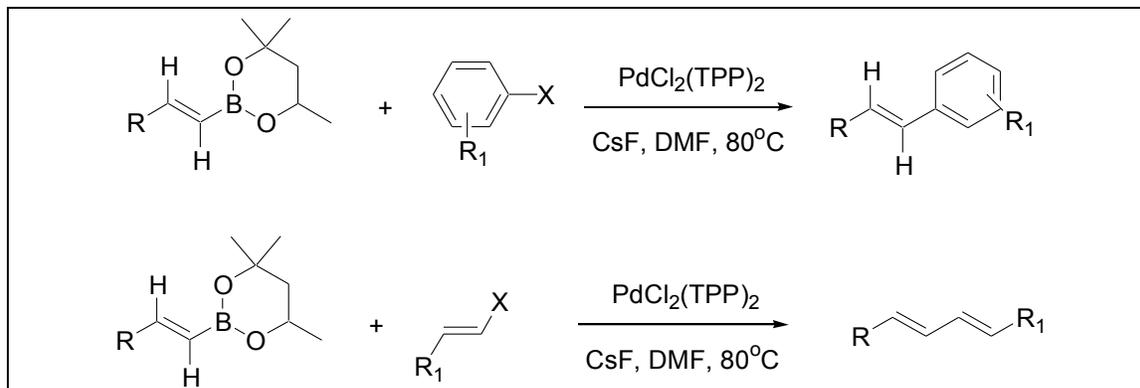
3.3.2.4 Alkenyl-aryl/Alkenyl-alkenyl cross coupling:

In addition to aryl boronates, alkenyl boronates obtained by the hydroboration of alkynes, are also suitable substrates for the cross-coupling processes, providing a route to

²⁵³ A. Giroux, Y. Han, P. Prasit, *Tetrahedron Lett.* **1997**, 38, 3841.

²⁵⁴ Keeping with toluene as the solvent led to decreased yields of coupled materials (data not shown)

conjugated unsaturated arenes²⁵⁵ (Scheme 102). Under the above conditions, without reoptimization, a variety of functional groups are tolerated within both the alkenyl boronate and the aryl halide.



Scheme 102: Coupling of alkenyl boronates

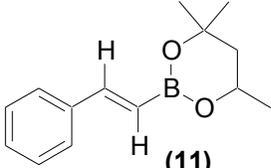
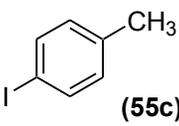
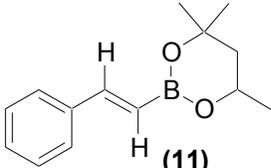
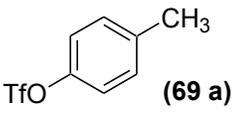
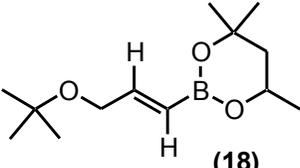
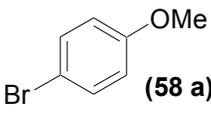
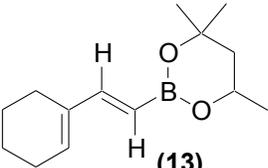
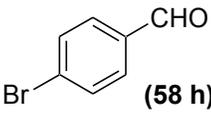
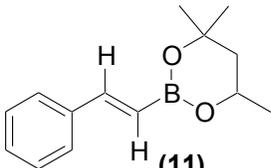
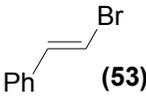
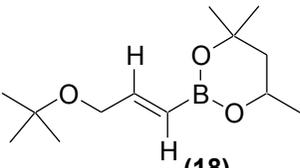
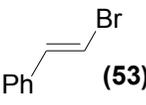
The results are tabulated in Table 21 and, as it is evident from the table, the reaction proceeded with satisfactory yields in most cases. The general order of reactivity of the various electrophiles appears to be I>Br>OTf. Thus, the use of triflate²⁵⁶ (Table 20, entry 2) provided the desired product in lower yields over a longer reaction time as compared to the analogous iodide (Table 20, entry 1). The reaction was incomplete even after prolonged heating (24 hrs, 69%) due to catalyst decomposition precipitating Palladium black.

Various substitution patterns about the alkenyl boronate can also be employed, and α -substituted boronate partner provided the desired product in moderate yield (Table 20, entry 3). Alkenyl bromides can also undergo coupling under identical conditions (entries 5 and 6) resulting in conjugated dienes. The reaction was found to be completely stereospecific with regard to the olefin geometry in all the cases examined.

²⁵⁵ a) G. A. Molander, C. Bernadi *J. Org. Chem.* **2002**, 67, 8416. b) J. Garcia-Fortanet, J. R. Debergh, J. K. Barbander, *Org. Lett.* **2005**, 7, 685.

²⁵⁶ H. Kowalski, R. J. Hinkle, P. J. Stang, *J. Org. Chem.* **1989**, 54, 2783.

Table 21: Examples of Aryl-Alkenyl cross-coupling

Entry	Alkenyl boronate	Aryl Halide	Time (hrs)	% Yield ^a	Product No.
1	 (11)	 (55c)	2	94	(89)
2	 (11)	 (69 a)	6	69	(89)
3	 (18)	 (58 a)	2	58	(90)
4	 (13)	 (58 h)	16	51	(91)
5	 (11)	 (53)	2	93	(92)
6	 (18)	 (53)	6	85	(93)

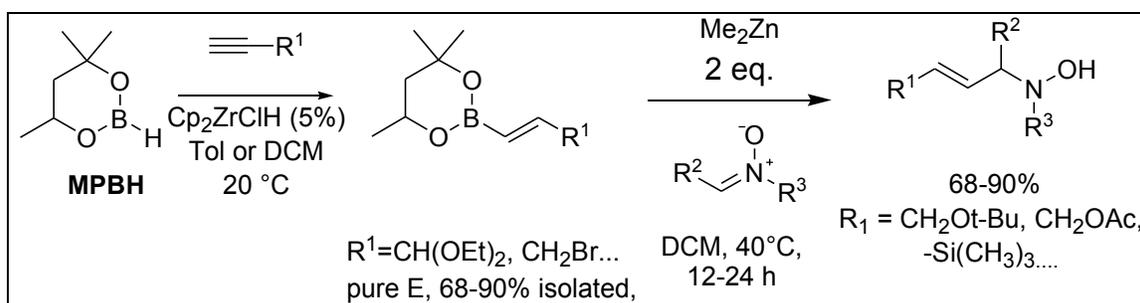
^aIsolated yields after column chromatography.

3.4 Conclusion:

In summary, palladium-catalyzed cross-coupling reactions of aryl and alkenyl boronates with aryl and alkenyl halides have been achieved with good yields. A variety of functional groups were tolerated in the coupling reactions, and even *ortho*, *ortho*-disubstituted aryl halide partners and α -substituted organoboron partners provided the desired cross-coupling products. The aryl or the alkenyl boronate esters have been prepared by metal-catalyzed borylation or hydroboration reactions respectively. The ease of isolation, purification, storage and handling makes them highly attractive intermediates for laboratory and large-scale operations.

4 Conclusions and perspectives

Thus, we have demonstrated that MPBH is an excellent reagent for the hydroboration of alkynes and for the borylation of aryl halides. It is very easily prepared from an inexpensive diol (hexyleneglycol \$0.02/g compared to \$0.50/g for pinacol). Of Carbon-Boron bond-forming reactions examined, MPBH appeared to be superior or equally efficient compared with pinacolborane.

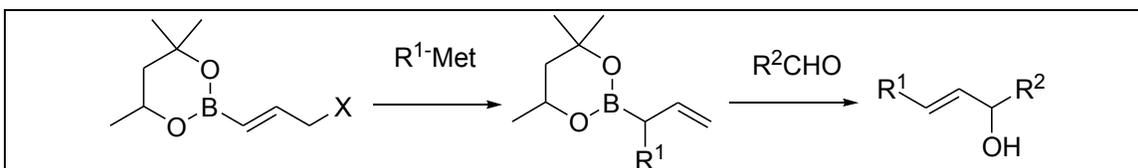


It could obviously be interesting to study the hydroboration of alkenes. In that case, the chiral center of MPBH would cause the occurrence of diastereomers, and this could make attempts towards catalytic enantioselective hydroborations more complex. Thus first focus should be on the normal and achiral anti-Markovnikov hydroboration of terminal alkenes, mainly for the sake of finding application to the MPB-alkyl products.

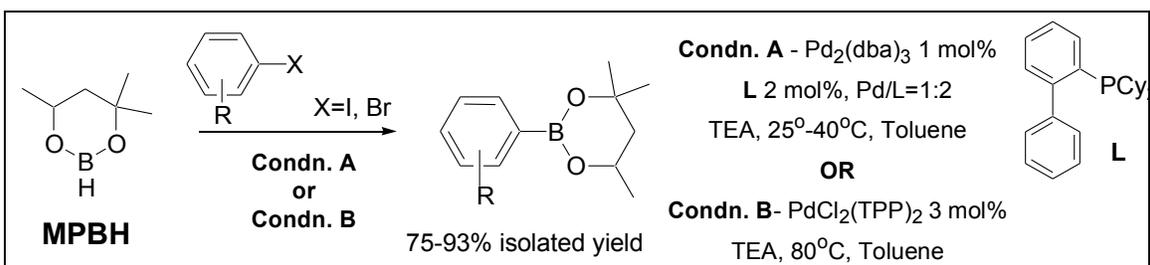
The use of vinylboronates as alkenyl transfer reagents has been amply demonstrated by the addition onto nitrones in the 2nd chapter. These esters can be made to react under mild conditions allowing better functional group tolerance and this underscores the flexibility of the reaction. Preliminary results indicate that chirality can be induced by the use of β -aminoalcohols, and this indicates that the reactive species is a vinyl-zinc species. Thus the obvious direction of the future work is the search for the proper β -aminoalcohol allowing a catalytic enantioselective version of this vinylation of nitrones.

Another outcome of the present work is the easy obtention of vinylboronic esters carrying heteroatoms in allylic position. Addition of properly chosen carbon nucleophiles

on these molecules could lead to new allylboronic esters. Considering the large reactivity of the latter, interesting applications could be proposed.



The palladium-catalyzed borylation of aryl halides and triflates leading to arylboronates opens the access to these highly useful synthetic intermediates in an efficient manner. These arylboronate esters can be utilized without drawback in Suzuki-Miyaura coupling, which is the principal application of this family of reagents.



MPBH appeared to have the almost the same reactivity as PinBH, and so do the arylboronic esters derived from it. Again, the arguments of price and easy preparation speak in favor of MPBH.

It would be now very interesting to challenge PinBH in the Ir-catalyzed Ar-H borylation reaction. This reaction is more subject to steric constraints: its regioselectivity is ruled by bulk, and the organometallic intermediates feature σ -bonded dioxaborinanes. Thus, one could expect that the less hindered MPBH could react faster than PinBH as it was shown in the Zr-catalyzed hydroborations.

Arylboronic acids and (to a much lesser extent esters) have been recently used as aryl transfer reagents. The enantioselective version of this reaction has been extensively studied and applied on an industrial scale using boronic acids as the aryl source. With MPB esters, preliminary studies clearly indicate that boronate esters derived from MPBH can be made to undergo the racemic version of this reaction using CsF, and this will be the subject of further development.

EXPERIMENTAL PART

5 Experimental part

5.1 General

All non-aqueous reactions were performed under a positive pressure of dry argon in oven-dried or flame-dried glassware equipped with a magnetic stir bar. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents.

Dichloromethane (CH_2Cl_2) and Dimethylformamide (DMF), as well as bases such as triethylamine and pyridine, were distilled over calcium hydride. Tetrahydrofuran (THF) was distilled over sodium ketyl and toluene over sodium.

All reagents were purchased from either Aldrich or Acros chemical companies and used without purification unless otherwise stated.

Reactions were monitored by thin layer chromatography (TLC) using commercial aluminium-backed silica gel plates (Merck, Kieselgel 60 F 254). TLC spots were viewed under ultraviolet light and by heating the plate after treatment with either a staining solution of KMnO_4 (300 ml water, 3 g KMnO_4 , 20 g K_2CO_3 , 0.3 g KOH), ninhydrine (200 ml EtOH, 1g ninhydrine), TTC (100ml EtOH, 0.5 g of 2,3,5-triphenyl tetrazolium chloride, then NaOH 1% in water), solution of PMA (5 ml phosphomolybdic acid reagent 20 wt % solution in ethanol, 95 ml EtOH) or DPC staining solution for B containing compounds (1% wt/vol solution of diphenylcarbazone in EtOH).

Product purification by gravity column chromatography was performed using Macherey-Nagel Silica Gel 60 (70-230 mesh) or (40-60 mesh).

Melting points were obtained on a Büchi B35 apparatus and are uncorrected.

Infrared spectra (IR) were obtained either as neat films on sodium chloride discs or in potassium bromide sintered plates. All IR spectra were recorded on a Nicolet Impact-400 Fourier transform infrared spectrometer (FTIR) and the data are reported in reciprocal centimeters (cm^{-1}).

¹H NMR Spectra (300 or 400 MHz) and **¹³C NMR spectra** (75 or 100 MHz) were recorded on either a Bruker Advance300 or Advance400 spectrometers. Chemical shifts are given in ppm (δ) and were referenced to the solvent signal or to TMS used as an internal standard. Multiplicities are declared as follows: *s* (singlet), *br s* (broad singlet), *d* (doublet), *t* (triplet), *q* (quadruplet), *sept* (septet), *dd* (doublet of doublet), *ddd* (doublet of doublet of doublet), *dt* (doublet of triplet), *dq* (doublet of quadruplet), *m* (multiplet), *AB_q* (*AB_q* system). Coupling constants *J* are given in Hertz and are given with 0.5 Hz precision.

Low Resolution Mass Spectra (LRMS) were recorded on a Brücker Esquire 3000 plus (ESI) or a ThermoFinnigan PolarisQ ion-trap spectrometer, using DCI (ammonia/isobutane 63/37).

High Resolution Mass Spectra (HRMS) were recorded on Thermoquest Orbitrap spectrometer at the LCOSB, UMR 7613, Université Pierre et Marie Curie, Paris.

Elemental analysis were performed at the Service d'Analyse Élémentaire du Département de Chimie Moléculaire, Grenoble.

5.2 Preparations of MPBH

5.2.1 Preparation of Neat MPBH from BH₃:DMS55

Caution : Stench! H₂ evolution! A solution of 2-methyl-2,4-pentanediol (10 mmol, 1.18 g) in dry dichloromethane or toluene (2.36 mL) was stirred and cooled to 0 °C. A solution of BH₃:DMS (11 mmol, 10 M in methyl sulfide, Aldrich) was added over 20-30 min to control the brisk evolution of gas. The reaction was stirred for 1 h at 0 °C and was then warmed to 25 °C and stirred for an additional 1 hr until there was no further evolution of gas. The resulting solution was checked by ¹¹B and ¹H NMR; conversion of the diol was quantitative. Distillation under reduced pressure afforded 0.870 gm (68%) yield of 4,4,6-trimethyl-1,3,2-dioxaborinane (**MPBH, 1**), bp 45 °C/35 mmHg.

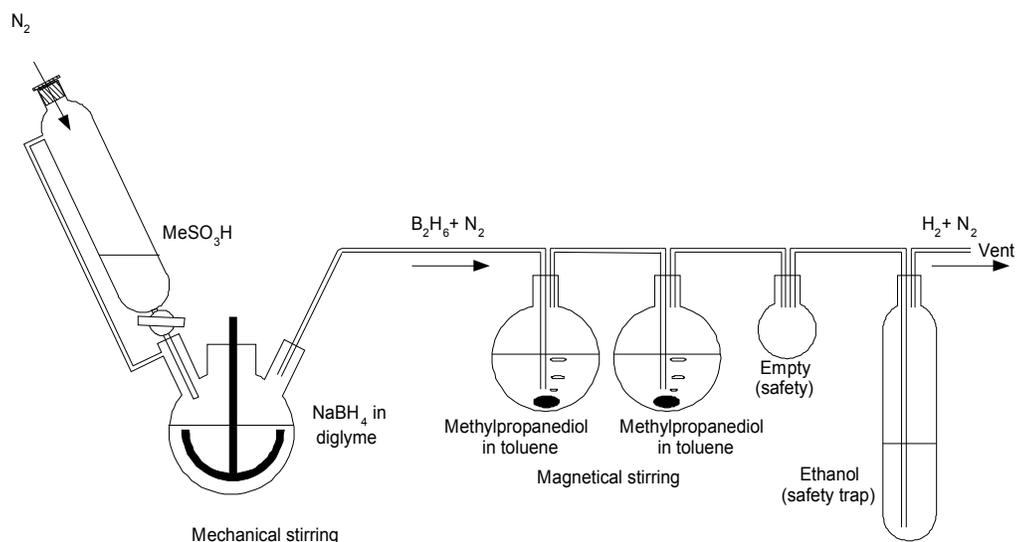
5.2.2 Preparation of MPBH from NaBH₄ and MSA:

Caution: H₂ evolution! Diborane is a toxic and pyrophoric gas. All preparations should be carried out in a well-ventilated fume hood.

50 mmol scale: In a 100-mL two-necked round-bottom flask fitted with a pressure equalizing dropping funnel, an efficient magnetic stirring and a N₂ inlet, NaBH₄ (3.7g, 100 mmol) was suspended in 40 mL of bis(2-methoxy-ethylether) (diglyme). The flask was connected through a double-ended needle to a second 100 mL cylindrical flask containing a magnetically stirred solution of 2-methyl-2,4-pentanediol (5.9 g, 50 mmol) in 45 mL of dry dioxane, cooled to 8-10 °C. The double-ended needle was positioned so that gas evolving from the first flask would bubble through the solution. The second flask was vented through a double-ended needle bubbling into ethanol (to trap the excess diborane). The dropping funnel was loaded with a solution of methanesulphonic acid (9.6 g, 100 mmol) in diglyme (20 mL). This solution was added dropwise over 30-45 min to the NaBH₄ suspension, during which time the temperature increased to 40 °C. The evolved gases were bubbled through the solution of diol in the second flask. All along the process, a small stream of nitrogen (2-5 bubbles per second) was applied through the whole apparatus to ensure complete transfer of the diborane. At the end of addition of methanesulphonic acid, the temperature of the second flask was brought to 20°C, and the stream of N₂ was continued for 1 hr; this step allowed the elimination of excess diborane in the solution of MPBH. The solution was transferred to a volumetric flask and made up to 50 mL, to produce a 1 M solution.

350 mmol scale: A 1 L glass reactor fitted with a pressure equalizing dropping funnel, a mechanical stirring, a thermometer and a reflux condenser surmounted with a N₂ inlet, was charged with powdered NaBH₄ (28.45 g, 730 mmol) and 250 mL of bis(2-methoxy-ethylether) (diglyme). The flask was connected through a double-ended needle (1/8 in. Teflon tube) to a second 500 mL round-bottomed flask containing a solution of 2-methyl-2,4-pentanediol (29.5 g, 250 mmol) in 200 mL of dry toluene, cooled to 8-10 °C. The tube is positioned so that the gases bubble through the solution. The second flask was connected identically to a third 500 mL round-bottomed flask containing another solution of 2-methyl-2,4-pentanediol (14.75 g, 125 mmol) in 200 mL of dry toluene, cooled to 8-

10 °C. The third flask was connected, through a 100 mL empty flask, to a last bubbler containing 100 mL of ethanol (to trap the excess diborane).



The dropping funnel was loaded with a solution of methanesulphonic acid (72 g, 750 mmol) in diglyme (20 mL). This solution was added dropwise over 3 hrs to the NaBH_4 suspension. The gas evolution was fast. The temperature in the generator flask increased slowly up to 40 °C. All along the process, a small stream of nitrogen (2-5 bubbles per second) was applied through the whole apparatus to ensure complete transfer of the diborane. At the end of addition of methanesulphonic acid, the temperature of flasks 2 and 3 was brought to 20°C, and the stream of N_2 was continued for 1.5 hr; this step allowed the elimination of excess diborane in the solution of MPBH. The solutions from flasks 2 and 3 were transferred to 250 mL volumetric flasks and adjusted to produce a 1 M solution and a 0.5 M solution.

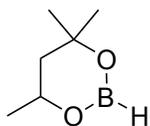
^{11}B - and ^1H -NMR of the solutions indicated that the conversion of diol was quantitative. Thus the molarity of the solution was calculated on this basis. The solution could be kept at 4°C for several months without any change. Storage at room temperature was deleterious.

5.2.3 Preparation from Diethylaniline-borane:

A 100 ml flask equipped with a Claisen-head distillation apparatus, was charged with 300-320 mg of 10 % Pd/C (5% by weight) and anhydrous dioxane (10 ml). The

flask was flushed with nitrogen and freshly distilled 2-methyl-2,4-pentanediol (50 mmol, 6.4 gm) as a solution in dioxane (10 ml) was added. To this mixture was added a solution of diethylaniline borane (60 mmol, 9.78 g) in dioxane (10 ml) at room temperature in 30 min. The reaction mixture was stirred for an additional 30 min at the same temperature. Distillation in vacuo gave MPBH in the neat form. (4.8 g, 75%). B.pt 45 °C/35 mm Hg.

MPBH (4,4,6-trimethyl-1,3,2-dioxaborinane, 1)



¹H NMR (300 MHz, *CDCl*₃) δ ppm 4.16 (dq, *J* = 11.8, 6.2, 3.0 Hz, 1H), 1.76 (ddd, *J* = 13.9, 3.0, 1.7 Hz, 1H), 1.50 (dd, *J* = 13.9, 11.8 Hz, 1H), 1.27 (s, 3H), 1.26 (s, 3H), 1.23 (d, *J* = 6.21 Hz, 3H).

¹³C NMR (75.5 MHz, *CDCl*₃) δ ppm 70.8, 64.6, 46.1, 31.0, 28.1, 22.9.

¹¹B NMR (96 MHz, *CDCl*₃) δ ppm 25.2 (d, *J* = 170 Hz).

IR (neat, cm⁻¹): 2551, 2498.

5.3 Hydroboration of alkynes

5.3.1 General Experimental Procedure for the Hydroboration of Alkynes by MPBH.

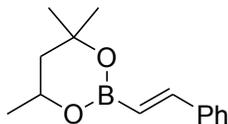
A 5-mL round-bottom flask equipped with a side arm and magnetic stirring was charged with HZrCp_2Cl (0.05 mmol, 13 mg) and dry dichloromethane or toluene (1 mL) under a N_2 atmosphere and cooled to 0°C . Alkyne (1.0 mmol) was then added dropwise, the mixture then was stirred for 2 min, and MPBH (1.1 mmol) was introduced dropwise via a syringe. Stirring was continued for 16 h at 20°C , at which point GC analysis of a reaction aliquot showed completion of reaction. Isolation of the product was achieved by removing volatile matter under reduced pressure followed by flash column chromatography (3% ether in hexane) to provide the desired product as a clear oil.

All products were found to be $> 95\%$ purity by gas chromatography (FID).

The above procedure was also applied for the hydroboration of styrene by changing the catalyst to $(\text{PPh}_3)_3\text{RhCl}$ (0.01 mmol, 9 mg).

5.3.2 Products Description: Vinylboronic Esters

4,4,6-trimethyl-2-styryl-[1,3,2]dioxaborinane (11)



$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 7.5-7.4 (m, 2H), 7.35-7.2 (m, 4H), 6.11 (d, $J = 18.2$ Hz, 1H), 4.26 (dq, $J = 11.7, 6.2, 3.0$ Hz, 1H), 1.80 (dd, $J = 13.8, 3.0$ Hz, 1H), 1.53 (dd, $J = 13.8, 11.7$ Hz, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 1.30 (d, $J = 6.2$ Hz, 3H).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ ppm 146.4, 137.9, 128.3, 128.2, 126.8, 121 (br), 70.7, 64.7, 45.9, 31.2, 28.1, 23.1.

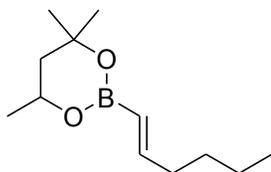
$^{11}\text{B NMR}$ (96 MHz, CDCl_3) δ 25.8 ppm.

IR (cm^{-1}): 3023, 2974, 1624, 1577, 1213, 1162, 993, 750.

LRMS (EI) m/z (%) 230 (100) [M^+], 130(71), 215(69), 229(25), 231(17), 232(3).

HRMS EI m/z calculated for $\text{C}_{14}\text{H}_{19}\text{BO}_2^+$ 230.1473; found 230.1478.

2-hex-1-enyl-4,4,6-trimethyl-[1,3,2]dioxaborinane (12)



^1H NMR (300 MHz, CDCl_3) δ ppm 6.52 (dt, $J = 17.7, 6.4$ Hz, 1H), 5.34 (dt, $J = 17.7, 1.6$ Hz, 1H), 4.20 (dq, $J = 11.8, 6.2, 2.9$ Hz, 1H), 2.12 (m, 2H), 1.77 (dd, $J = 13.9, 2.9$ Hz, 1H), 1.49 (dd, $J = 13.9, 11.8$ Hz, 1H), 1.43-1.30 (m, 4H), 1.29 (s, 6H), 1.26 (d, $J = 6.2$ Hz, 3H), 0.88 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ ppm 150.9, 123.7(br), 70.3, 64.4, 45.9, 35.0, 31.2, 30.5, 28.0, 23.1, 22.2, 13.8.

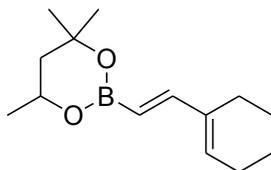
^{11}B NMR (96 MHz, CDCl_3) 25.8 ppm.

IR (cm^{-1}): 2973, 1639, 1388, 1164, 998, 768

LRMS (DCI NH_3 /Isobutane) m/z (%) 228(100) [$\text{M} + \text{NH}_4^+$].

HRMS (DCI NH_3) m/z calculated for $\text{C}_{12}\text{H}_{27}\text{BNO}_2^+$ 228.2129; found 228.2135

2-cyclohexen-1-enyl-4,4,6-trimethyl-[1,3,2]dioxaborinane (13)



^1H NMR (300 MHz, CDCl_3) δ ppm 6.91 (d, $J = 17.6$ Hz, 1H), 5.88 (br. t, $J = 3.2$ Hz, 1H), 5.34 (d, $J = 17.6$ Hz, 1H), 4.20 (dq, $J = 11.8, 6.2, 3.0$ Hz, 1H), 2.18-2.04 (m, 2H), 1.76 (dd, $J = 13.9, 3.0$ Hz, 1H), 1.68-1.53 (m, 4H), 1.47 (dd, $J = 13.9, 11.8$ Hz, 1H), 1.30-1.27 (m, 8H), 1.25 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ ppm 150.1, 137.1(br), 132.4, 117.4, 70.4, 64.5, 45.9, 31.1, 28.0, 25.9, 23.9, 23.1, 22.4, 22.3.

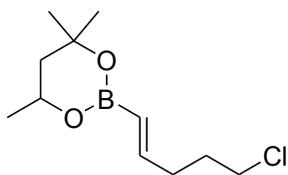
^{11}B NMR (96 MHz, CDCl_3) δ 26.0 ppm.

IR (cm^{-1}): 3018, 2974, 2929, 1634, 1607, 1300, 1162, 997, 795, 771.

LRMS (DCI NH_3 /Isobutane) m/z (%) 235(100) $[\text{M}+\text{H}^+]$, 247(40), 248(23), 250(34), 251(4).

HRMS (DCI NH_3) m/z calculated for $\text{C}_{14}\text{H}_{24}\text{BO}_2$ 235.1864; found 235.1861

2-(5-chloro-pent-1-enyl)-4,4,6-trimethyl-[1,3,2]dioxaborinane (14)



^1H NMR (200 MHz, CDCl_3) δ ppm 6.42 (dt, $J = 17.7, 6.4$ Hz, 1H), 5.33 (dt, $J = 17.7, 1.5$ Hz, 1H), 4.16 (dq, $J = 11.7, 6.2, 3.0$ Hz, 1H), 3.48 (t, $J = 6.7$ Hz, 2H), 2.29-2.13 (tt, $J = 8.1, 6.7$ Hz, 2H), 1.85 (q, $J = 8.1$ Hz, 1H), 1.73 (dd, $J = 13.9, 3.0$ Hz, 1H), 1.44 (dd, $J = 13.9, 11.7$ Hz, 1H), 1.24 (s, 6H), 1.21 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ ppm 148.3, 125.2(br), 70.5, 64.5, 45.9, 44.3, 32.3, 31.2(x2), 28.0, 23.0.

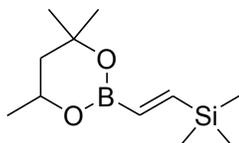
^{11}B NMR (96 MHz, CDCl_3) δ 25.5 ppm.

IR (cm^{-1}): 2970, 2933, 1641, 1392, 1164, 995, 771.

LRMS (DCI NH_3 /Isobutane) m/z (%) 248 (100) $[\text{M}+\text{NH}_4^+]$, 234(11), 236(7).

HRMS (DCI NH_3) m/z calculated for $\text{C}_{11}\text{H}_{24}\text{BClNO}_2$ 248.1583; found 248.1586

4,4,6-trimethyl-2-(2-trimethylsilyl-vinyl)-[1,3,2]dioxaborinane (15)



¹H NMR (300 MHz, *CDCl*₃) δ ppm 7.01 (d, *J* = 21.6 Hz, 1H), 6.18 (d, *J* = 21.6 Hz, 1H), 4.24 (dq, *J* = 11.7, 6.2, 3.0 Hz, 1H), 1.79 (dd, *J* = 13.8, 3.0 Hz, 1H), 1.51 (dd, *J* = 13.8, 11.7 Hz, 1H), 1.32 (s, 3H), 1.31 (s, 3H), 1.29 (d, *J* = 6.2 Hz, 3H), 0.07 (s, 9H).

¹³C NMR (75.5 MHz, *CDCl*₃) δ ppm: 153.3, 142(br), 70.7, 64.7, 45.9, 31.1, 28.0, 26.8, 23.1, -1.6.

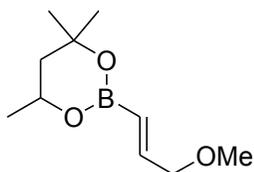
¹¹B NMR (96 MHz, *CDCl*₃) δ 24.6 ppm.

IR (cm⁻¹): 2970, 1592, 1418, 1389, 1018, 862, 1166, 837, 744.

LRMS (DCI NH₃/Isobutane) *m/z* (%) 228(100) [M+NH₄⁺], 209(9), 243(36), 245(12).

HRMS (DCI NH₃) *m/z* calculated for C₁₁H₂₇BNO₂Si = 244.1899; found 244.1909

2-(3-methoxy-propenyl)-4,4,6-trimethyl-[1,3,2]dioxaborinane (16)



¹H NMR (200 MHz, *CDCl*₃) δ ppm 6.46 (dt, *J* = 17.9, 5.1, 1H), 5.52 (dt, *J* = 17.9, 1.3 Hz, 1H), 4.16 (dq, *J* = 11.6, 6.3, 3.0 Hz, 1H), 3.91 (dd, *J* = 5.1, 1.3 Hz, 2H), 3.28 (s, 3H), 1.73 (dd, *J* = 13.8, 3.0 Hz, 1H), 1.43 (dd, *J* = 13.8, 11.6 Hz, 1H), 1.24 (s, 6H), 1.20 (d, *J* = 6.3 Hz, 3H).

¹³C NMR (75.5 MHz, *CDCl*₃) δ ppm 145.5, 126 (br), 74.4, 70.6, 64.6, 58.0, 45.9, 31.1, 28.0, 23.0.

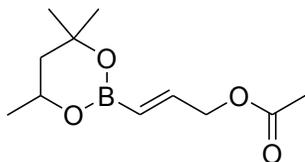
¹¹B NMR (96 MHz, *CDCl*₃) δ 25.5 ppm.

IR (cm⁻¹): 2974, 1644, 1392, 1120, 1001, 768, 620.

LRMS (DCI NH₃/Isobutane) *m/z* (%) 216(100) [M+NH₄⁺], 184(26), 199 (20), 215(36), 217(14).

HRMS (DCI NH₃) *m/z* calculated for C₁₀H₂₃BNO₃⁺ 216.1766, found 216.1708

2-(3-acetoxy-propenyl)-4,4,6-trimethyl-[1,3,2]dioxaborinane (17)



¹H NMR (200 MHz, *CDCl*₃) δ ppm 6.44 (td, *J* = 17.8, 4.9 Hz, 1H), 5.52 (td, *J* = 17.8, 1.7 Hz, 1H), 4.55 (dd, *J* = 4.9, 1.7 Hz, 2H), 4.15 (dq, *J* = 11.6, 6.2, 3.1 Hz, 1H), 2.01 (s, 3H), 1.73 (dd, *J* = 13.9, 3.1 Hz, 1H), 1.42 (dd, *J* = 13.9, 11.6 Hz, 1H), 1.22 (s, 6H), 1.19 (d, *J* = 6.2 Hz, 3H).

¹³C NMR (75.5 MHz, *CDCl*₃) δ ppm 170.4, 142.3, 125(br), 70.7, 65.6, 64.6, 45.8, 31.0, 27.9, 22.9, 20.7.

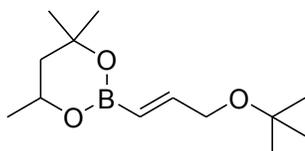
¹¹B NMR (96 MHz, *CDCl*₃) δ 25.6 ppm.

IR (cm⁻¹): 3015, 2975, 2935, 1744, 1163, 993, 768.

LRMS (DCI NH₃/Isobutane) *m/z* (%) 227(100) [M+H⁺], 244(52).

HRMS (DCI NH₃) *m/z* calculated for C₁₁H₂₃BNO₄⁺ 244.1715; found 244.1708

2-(3-tert-butoxy-propenyl)-4,4,6-trimethyl-[1,3,2]dioxaborinane (18)



¹H NMR (300 MHz, *CDCl*₃) δ ppm 6.48 (dt, *J* = 17.8, 4.9 Hz, 1H), 5.52 (dt, *J* = 17.8, 1.2 Hz, 1H), 4.12 (dq, *J* = 12.1, 6.2, 2.9 Hz, 1H), 3.88 (dd, *J* = 4.9, 1.2 Hz, 2H), 1.69 (dd, *J* = 13.9, 2.9 Hz, 1H), 1.39 (dd, *J* = 13.9, 12.1 Hz, 1H), 1.20 (s, 6H), 1.17 (d, *J* = 6.2 Hz, 3H), 1.12 (s, 9H).

¹³C NMR (75.5 MHz, *CDCl*₃) δ ppm 147.3, 123.4(br), 72.8, 70.4, 64.4, 63.9, 45.9, 31.1, 27.9, 27.4 (x3), 23.0.

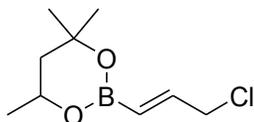
¹¹B NMR (96 MHz, *CDCl*₃) δ 25.4 ppm.

IR (cm⁻¹): 1644, 1391, 997, 768, 620.

LRMS (DCI NH₃/Isobutane) *m/z* (%) 258(100) [M+NH₄⁺], 202(39), 256(11), 257(21), 259(6).

HRMS (ESI) Calcd for C₁₃H₂₅O₃BNa⁺ 263.17890(100), 262.18253(25), 264.18226(14) Found 263.17891(100), 262.18258(25), 264.18213(14).

2-(3-chloro-propenyl)-4,4,6-trimethyl-[1,3,2]dioxaborinane (19)



¹H NMR (200 MHz, CDCl₃). δ ppm 6.52 (dt, *J* = 17.4, 6.3 Hz, 1H), 5.62 (dt, *J* = 17.4, 1.4 Hz, 1H), 4.22 (dq, *J* = 11.5, 6.2, 3.0 Hz, 1H), 4.07 (dd, *J* = 6.3, 1.4 Hz, 2H), 1.80 (dd, *J* = 13.9, 3.0 Hz, 1H), 1.49 (dd, *J* = 13.9, 11.5 Hz, 1H), 1.29 (s, 6H), 1.26 (d, *J* = 6.2 Hz, 3H).

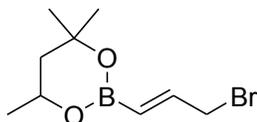
¹³C NMR (75.5 MHz, CDCl₃) δ ppm 143.3, 128.1 (br), 70.8, 64.7, 46.2, 45.8, 31.0, 27.9, 22.9.

¹¹B NMR (96 MHz, CDCl₃) δ 25.3 ppm.

IR (cm⁻¹): 2974, 1641, 1421, 1162, 993, 767.

We could not obtain any coherent mass spectrum for this compound.

2-(3-bromo-propenyl)-4,4,6-trimethyl-[1,3,2]dioxaborinane (20)



¹H NMR (300 MHz, CDCl₃) δ ppm 6.50 (td, *J* = 17.3, 7.2 Hz, 1H), 5.51 (td, *J* = 17.3, 1.1 Hz, 1H), 4.13 (dq, *J* = 11.8, 6.2, 3.0 Hz, 1H), 3.88 (dd, *J* = 7.16, 1.1 Hz, 2H), 1.71 (dd, *J* = 13.9, 3.0 Hz, 1H), 1.41 (dd, *J* = 13.9, 11.8 Hz, 1H), 1.21 (s, 6H), 1.18 (d, *J* = 6.2 Hz, 3H).

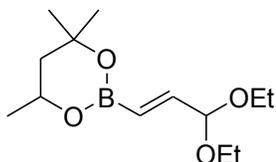
¹³C NMR (75.5 MHz, CDCl₃) δ ppm 143.5, 128.6(br), 70.9, 64.7, 45.8, 34.1, 31.1, 28.0, 23.0.

^{11}B NMR (96 MHz, CDCl_3) δ 25.2 ppm.

IR (cm^{-1}): 2973, 2933, 1634, 1425, 1230, 1196, 1162, 993, 771.

We could not obtain any coherent mass spectrum for this compound.

2-(3,3-diethoxy-propenyl)-4,4,6-trimethyl-[1,3,2]dioxaborinane (21)



^1H NMR (300 MHz, CDCl_3). δ ppm 6.34 (dd, $J = 18.0, 5.0$ Hz, 1H), 5.60 (dd, $J = 18.0, 1.2$ Hz, 1H), 4.78 (dd, $J = 5.0, 1.2$ Hz, 1H), 4.13 (dq, $J = 11.7, 6.2, 3.0$ Hz, 1H), 3.57 (m, 2H), 3.44 (dq, $J = 9.5, 7.1$ Hz, 2H), 1.71 (dd, $J = 13.8, 3.0$ Hz, 1H), 1.40 (dd, $J = 13.8, 11.7$ Hz, 1H), 1.21 (s, 6H), 1.18 (d, $J = 6.2$ Hz, 3H), 1.13 (t, $J = 7.1$ Hz, 6H).

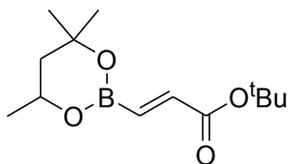
^{13}C NMR (75.5 MHz, CDCl_3) δ ppm 145.2, 126.9(br), 102.4, 70.7, 64.6, 61.0(x2), 45.9, 31.1, 28.0, 23.0, 15.1(x2).

^{11}B NMR (96 MHz, CDCl_3) δ 25.5 ppm.

IR (cm^{-1}): 2971, 2933, 1648, 1421, 1054, 1000, 896, 767.

We could not obtain any consistent mass spectrum for this compound.

3-(4,4,6-trimethyl-[1,3,2]dioxaborinan-2-yl)-acrylic acid tert-butyl ester (22)



^1H NMR (300 MHz, CDCl_3) δ ppm 6.61 (d, $J = 18.0$ Hz, 1H), 6.46 (d, $J = 18.0$ Hz, 1H), 4.24 (dq, $J = 12.3, 6.2, 3.0$ Hz, 1H), 1.82 (dd, $J = 14.0, 3.0$ Hz, 1H), 1.47 (s, 9H), 1.46 (m, 1H), 1.30 (s, 6H), 1.27 (d, $J = 6.19$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ ppm 165.5, 138(br), 137.8, 79.8, 71.0, 64.9, 45.7, 30.9, 27.9(3x), 22.8.

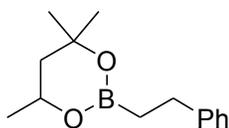
^{11}B NMR (96 MHz, CDCl_3) δ 25.4 ppm.

IR (cm^{-1}): 3046, 2971, 2933, 1714, 1623, 1432, 1150, 1003, 765.

LRMS (DCI NH_3 /Isobutane) m/z (%) 272(57) [$\text{M}+\text{NH}_4^+$], 215(31), 216(100), 217(24), 271(35), 273(7).

HRMS (ESI) Calcd. for $\text{C}_{26}\text{H}_{46}\text{O}_8\text{B}_2\text{Na}^+$ 531.32710(100), 530.33073(50), 532.33054(29) Found 531.32705(100), 530.33071(41), 532.32991(42).

4,4,6-trimethyl-2-phenethyl-[1,3,2]dioxaborinane (24a)



^1H NMR (300 MHz, CDCl_3) δ ppm 7.27-7.08 (m, 5H), 4.13 (dq, $J = 11.7, 6.2, 3.0$ Hz, 1H), 1.71 (dd, $J = 13.9, 3.0$ Hz, 1H), 2.72-2.65 (m, 2H), 1.39 (dd, $J = 13.9, 11.7$ Hz, 1H), 1.24 (s, 3H), 1.23 (s, 3H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.02 (m, 2H).

^{13}C NMR (75.5 MHz, CDCl_3) δ ppm 145.1, 128.0, 127.9, 125.1, 70.4, 64.4, 45.9, 31.1, 30.2, 28.0, 23.1, 17(br).

^{11}B NMR (96 MHz, CDCl_3) δ 29.7 ppm.

IR (cm^{-1}): 3024, 2974, 2933, 1389, 1182, 793, 771, 751.

LRMS (DCI NH_3 /Isobutane) m/z (%) 250(100) [$\text{M}+\text{NH}_4^+$].

HRMS (DCI NH_3) m/z calculated for $\text{C}_{14}\text{H}_{25}\text{BNO}_2^+$ = 250.1973; found 250.1966.

5.4 Addition of vinylzinc reagents on nitrones

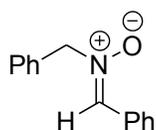
5.4.1 General Procedure for the reaction of vinylboronic esters, dimethylzinc and nitrones

Dimethylzinc (2 M solution in toluene, 0.625 ml, 1.0 mmol, 2.0 equiv.) was added under nitrogen to a mixture of nitron (0.5 mmol) and vinylborane (0.6 mmol) in anhydrous toluene or dichloromethane (0.5 ml). The mixture was stirred at 40 °C for 16

hours. Hydrolysis was performed at 20 °C by the addition of a saturated solution of ammonium chloride (2 ml) and the mixture was extracted with DCM (3 x 5 ml). The collected organic phases were filtered through a pad of silica gel, dried with sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (cyclohexane/EtOAc) to yield the corresponding hydroxylamine. The reaction of *N,N*-dialkylhydroxylamine with triphenyltetrazolium chloride on the TLC plate provided an efficient diagnosis (strong red colour on gentle heating).

5.4.2 Products Description : nitrones

N-Benzylidene-benzylamine *N*-oxide (26)



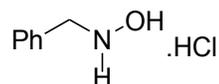
To a stirred solution of *N,N*-dibenzylamine (67.1 g, 0.34 mol) in ethanol (700 mL) was added Na₂WO₄ · 2 H₂O (4.40 g, 13.3 mmol) and the mixture was cooled to 0 °C. Hydrogen peroxide (30% wt, 124.7 g, 1.1 mol) was added dropwise over 2 hours. After addition, the mixture was allowed to warm to room temperature and stirred for 18 hours. The mixture was then concentrated under vacuum. Water was added and the aqueous layer was extracted three times with CH₂Cl₂. The combined organic layers were washed with saturated aqueous Na₂SO₃ solution and dried over anhydrous MgSO₄. The crude product was washed several times with pentane to afford nitrone **5a** (63.7 g, 0.30 mol, 87%) as a yellow solid.

IR (KBr disc): 3080, 3060, 3030, 2990, 2950, 1570, 1450, 1210, 1150 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ 5.06 (s, 2H, CH₂Ph), 7.26-7.47 (m, 9H, H_{arom.}, CH=N), 8.19-8.22 (m, 2H, H_{arom.}).

¹³C NMR (75 MHz, CDCl₃) δ 71.0 (CH₂Ph), 128.8-130.1 (CH_{arom.}), 130.8 (C_{arom.}), 133.2 (C_{arom.}), 134.2 (CH=N).

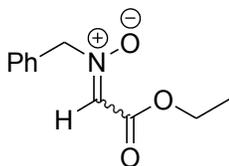
***N*-benzylhydroxylamine hydrochloride (27)**



To a stirred solution of nitrone **28** (45.0 g, 0.21 mol) in EtOH was added hydroxylamine hydrochloride (14.8, 0.21 mol). The mixture was heated to 60 °C and stirred for 3 hours. The mixture was concentrated under vacuum. Et₂O was then added. The solid was washed several times with Et₂O to afford *N*-benzylhydroxylamine hydrochloride **3** (30.2 g, 0.19 mol, 90%) as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 4.41 (s, 2H, CH₂Ph), 7.45-7.56 (m, 5H, H_{arom.}).

***N*-(α-ethoxycarbonyl)methylene benzylamine *N*-oxide (32)**



To a stirred solution of *N*-benzylhydroxylamine **27** (0.80 g, 6.5 mmol) in toluene (15 mL) was added anhydrous MgSO₄ (1.58 g, 13.1 mmol) and ethyl glyoxylate (0.66 g, 6.5 mmol). The mixture was stirred for 2 hours and then filtered over a celite pad and concentrated in vacuo. The crude product was washed several times with pentane to afford nitrone **32** as a mixture of *Z/E* isomers (0.96 g, 4.62 mmol, 71%) as a white solid.

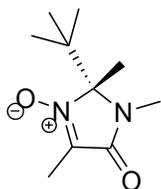
IR (KBr disc): 3120, 3070, 2990, 2980, 2930, 2900, 1710, 1570, 1210 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ 1.26-1.34 (m, 3H, H_{2'}), 4.21-4.30 (m, 2H, H_{1'}), 4.99 and 5.70 (s, 2H, CH₂Ph), 7.04 and 7.20 (m, 1H, H₁), 7.34-7.54 (m, 5H, H_{arom.}).

¹³C NMR (75 MHz, CDCl₃) δ 14.1 (CH₃, C_{2'}), 60.9 and 61.4 (CH₂, C_{1'}), 66.4 and 73.3 (CH₂Ph), 125.1 and 128.8 (CH, C₁), 128.6 and 129.2 (CH_{arom.}), 129.1 (CH_{arom.}), 129.5 and 129.6 (CH_{arom.}), 131.7 (C_{arom.}), 159.9 (C=O).

MS (DCI, NH₃/isobutane): *m/z* 208 [(M+H)⁺] (100%).

(S)-2-tert-Butyl-2,3,5-trimethyl-1-oxy-2,3-dihydro-imidazol-4-one (48)



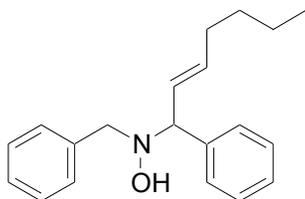
$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 2.90 (s, 3H), 1.90 (s, 3H), 1.50 (s, 3H), 0.90 (s, 9H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 165.3 (C=O), 134.1 (Cq nitrone), 94.5 (Cq aminal), 39.8 (Cq), 29.7 (CH_3 amine), 25.3 (CH_3 t-butyl), 17.6 (CH_3), 7.4 (CH_3).

Rf = 0.24 (Solvent: EtOAc/Cyclohexane : 50/50)

5.4.3 Products Description : *N*-Hydroxy-allyl-amines

N-Benzyl-*N*-(1-phenyl-hept-2-enyl)-hydroxylamine (33)



This compound was prepared according to the General Procedure from *N*-benzylidene-benzylamine *N*-oxide (0.5 mmol, 105 mg) and dioxaborolane (0.6 mmol, 126 mg) in 77% yield (wt. 113 mg). Colourless oil. TLC: Rf = 0.52 (cyclohexane/ethyl acetate, 50:50).

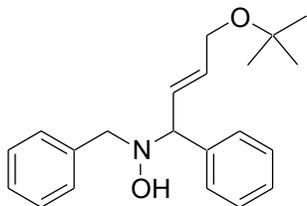
$^1\text{H NMR}$ (200 MHz, CDCl_3/TMS): δ = 0.87 (t, J=6.8 Hz, 3H), 1.20-1.45 (m, 4H), 2.05 (q, J = 6.4 Hz, 2H), 3.68 (d, J = 13.5 Hz, 1H), 3.83 (d, J = 13.5 Hz, 1H), 4.17 (d, J = 7.6 Hz, 1H), 5.19 (s, 1H), 5.64 (dt, J = 6.4, 15.6 Hz, 1H), 5.80 (dd, J = 7.6, 15.6 Hz, 1H), 7.15-7.40 (m, 10H) ppm.

$^{13}\text{C NMR}$ (75 MHz, CDCl_3/TMS): δ = 14.36, 22.71, 29.32, 31.76, 61.50, 75.05, 127.52, 127.60, 128.44, 128.64, 128.91, 129.47(br.), 129.82, 135.23, 138.68, 142.36 ppm.

IR(KBr disc): $\nu = 3553, 3240, 3086, 3061, 2955, 2922, 1591, 1502, 1380, 971, 702 \text{ cm}^{-1}$.

MS (EI, 70 eV): m/z (%) = 295 (2) [M^+], 213 (7), 212 (9), 173 (30), 91 (100)

***N*-Benzyl-*N*-(4-*tert*-butoxy-1-phenyl-but-2-enyl)-hydroxylamine (34)**



Colourless oil. $R_f = 0.3$ (Cyclohexane/ethyl acetate 70:30)

$^1\text{H NMR}$ (400 MHz, CDCl_3/TMS): $\delta = 1.18$ (s, 9H), 3.70-3.90 (m, 2H), 3.91 (dd, $J = 5.5 \text{ Hz}$, $^4J = 1.3 \text{ Hz}$, 2H), 4.28 (d, $J = 8.4 \text{ Hz}$, 1H), 5.78 (dt, $J = 15.5 \text{ Hz}$, $J = 5.5 \text{ Hz}$, 1H), 5.52 (s, OH), 6.00 (ddt, $J = 15.5 \text{ Hz}$, $J = 8.4 \text{ Hz}$, $^4J = 1.3 \text{ Hz}$, 1H), 7.21-7.42 (m, 10H) ppm.

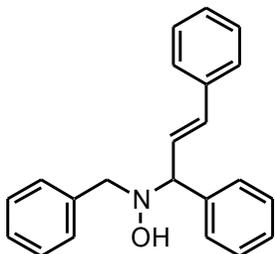
$^{13}\text{C NMR}$ (75 MHz, CDCl_3/TMS): $\delta = 27.58, 61.25, 62.33, 73.23, 74.68, 127.03, 127.30, 128.08, 128.17, 128.51, 129.19, 130.83, 131.84, 138.43, 141.32$ ppm.

IR (film) $\nu = 3383, 3056, 3027, 2972, 2928, 1601, 1495, 1458, 1388, 1359, 1190, 1065, 1021, 969, 745 \text{ cm}^{-1}$.

MS (DCI, $\text{NH}_3/\text{isobutane}$) : m/z 326 ($M+H^+$)

HRMS: calcd. for $\text{C}_{21}\text{H}_{27}\text{O}_2\text{N}_1\text{Na}_1$ 348.1934, found 348.1933.

***N*-Benzyl-*N*-(1,3-diphenyl-allyl)-hydroxylamine (35):**



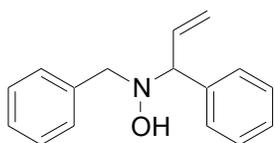
Pale yellow solid. $R_f = 0.5$ (Cyclohexane/ethylacetate, 60:40)

$^1\text{H NMR}$ (300 MHz, CDCl_3/TMS) δ ppm 7.5-7.0 (m, 10H), 6.63 (d, $J = 15.9$ Hz, 1H), 6.53 (dd, $J = 15.9, 7.9$ Hz, 1H), 4.47 (d, $J = 7.9$ Hz, 1H), 3.99 (d, $J = 13.1$ Hz, 1H), 3.84 (d, $J = 13.1$ Hz, 1H), 1.50 (OH).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3/TMS) δ ppm: 62.1, 75.7, 126.5, 127.2, 127.5, 127.7, 128.06, 128.3, 128.5, 128.7, 128.7, 129.3.

HRMS calcd. for $\text{C}_{22}\text{H}_{22}\text{NO}$: 315.1623, found 316.1695.

N-Benzyl-*N*-(1-phenyl-allyl)-hydroxylamine (36)



$^1\text{H NMR}$ (300 MHz, CDCl_3/TMS) δ ppm : 3.70 (d, $J = 13.4$ Hz, 1H), 3.74 (d, $J = 13.4$ Hz, 1H), 4.21 (d, $J = 8.4$ Hz, 1H), 5.17-5.25 (m, 2H), 5.75 (s, OH), 6.12 (ddd, $J = 8.4$ Hz, $^{\text{trans}}J = 17.2$ Hz, $^{\text{cis}}J = 10.2$ Hz, 1H), 7.19-7.39 (m, 10 H).

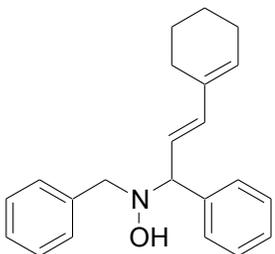
$^{13}\text{C NMR}$ (75 MHz, CDCl_3/TMS) δ ppm : 61.04, 75.29, 117.73, 172.15, 127.41, 128.05, 128.19, 128.55, 129.41, 137.67, 137.98, 140.95.

IR (film) $\nu = 3530, 3058, 3026, 2842, 2359, 1495, 1452, 1027, 926, 764$ cm^{-1} .

MS (DCI, $\text{NH}_3/\text{isobutane}$) $m/z = 240$ (M+H) $^+$

HRMS calcd. for $\text{C}_{16}\text{H}_{18}\text{NO}$ 240.1382, found 240.1381.

N-Benzyl-*N*-(3-cyclohex-1-enyl-1-phenyl-allyl)-hydroxylamine (37)46



Colourless oil. Rf = 0.60 (cyclohexane/ethylacetate, 50:50)

¹H NMR: (300 MHz, CDCl₃/TMS): δ ppm = 1.45-1.55 (m, 4H), 1.95-2.15 (m, 4H), 3.60 (d, J = 13.8 Hz, 1H), 3.86 (d, J = 13.8 Hz, 1H), 4.22 (d, J = 8.7 Hz, 1H), 4.49 (s, OH), 5.65-5.80 (m, 2 H), 6.17 (d, J = 15.8 Hz, 1 H), 7.10-7.44 (m, 10 H).

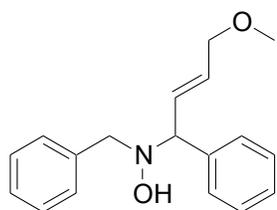
¹³C NMR: (75 MHz, CDCl₃/TMS): δ ppm = 22.53, 22.60, 24.74, 26.01, 61.46, 75.64, 125.17, 127.19, 127.37, 128.01, 128.35, 129.32, 130.16, 135.42, 136.66, 138.70, 142.16 ppm.

IR (film): ν = 3518, 3437, 3216, 3055, 3025, 2922, 2863, 2238, 1957, 1498, 1453, 1022, 971, 905 cm⁻¹

LRMS (CI): m/z (%) = 320 (3), 302 (7), 214 (8), 197 (100).

HRMS calcd. For C₂₂H₂₆NO : 320.2014, found 320.2070.

***N*-Benzyl-*N*-(4-methoxy-1-phenyl-but-2-enyl)-hydroxylamine (42)**

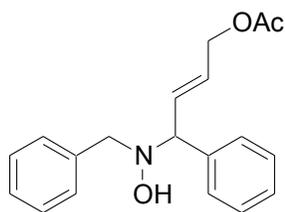


This compound was prepared according to the General Procedure from benzyl(benzylidene)azane oxide (0.5 mmol, 105 mg) and dioxaborolane (0.6 mmol, 126 mg) in 75% yield (wt. 113 mg). Colourless oil. TLC: Rf = 0.4 (cyclohexane/ethyl acetate, 60:40).

¹H NMR (400 MHz, CDCl₃) δ ppm 3.24 (s, 3H), 3.58 (s, OH), 3.70 (d, J = 13.2 Hz, 1H), 3.79 (d, J = 13.2 Hz, 1H), 3.86 (d, J = 5.6 Hz, 2H), 4.24 (d, J = 8.4 Hz, 1H), 5.71 (dt, J = 15.4, 5.6 Hz, 1H), 6.03 (dd, J = 15.4, 8.4 Hz, 1H), 7.40-7.16 (m, 10H).

¹³C NMR (75 MHz, CDCl₃) δ = 27.6, 58.5, 61.9, 73.2, 74.7, 127.8, 128, 128.9, 129.2, 130.1, 130.4, 130.5, 133.3, 138.8, 141.8 ppm.

Acetic acid 4-(benzyl-hydroxy-amino)-4-phenyl-but-2-enyl ester (43)

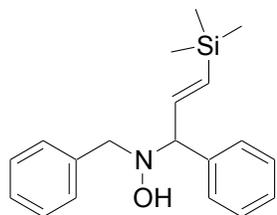


Colourless oil. $R_f = 0.6$ (Cyclohexane/EtOAc 60:40)

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm: 2.06 (s, 3H), 3.82 (d, $J = 13.5$ Hz, 1H), 3.96 (d, $J = 13.5$ Hz, 1H), 4.51 (d, $J = 8.0$ Hz, 1H), 4.55 (dt, $J = 16.0$ Hz, $J = 8.0$ Hz, 2H), 4.65 (br s, OH), 5.85 (d, $J = 16.0$ Hz, 1H), 5.88 (m, 1H), 7.0-7.3 (m, 10H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 20.99, 61.27, 65.21, 71.84, 124.9, 128.4, 128.5, 128.8, 128.9, 135.64, 138.2, 141.2, 170.59.

***N*-Benzyl-*N*-(1-phenyl-3-trimethylsilanyl-allyl)-hydroxylamine (44)**



$^1\text{H NMR}$ (400 MHz, CDCl_3/TMS): $\delta = 0.05$ (s, 9H), 3.72 (d, $J = 13.5$ Hz, 1H), 3.85 (d, $J = 13.5$ Hz, 1H), 4.26 (d, $J = 7.7$ Hz, 1H), 5.3 (Br s, OH), 5.92 (d, $J = 18.6$ Hz, 1H), 6.30 (dd, $J = 18.6$ Hz, $J = 7.7$ Hz, 1H), 7.23-7.42 (m, 11H) ppm.

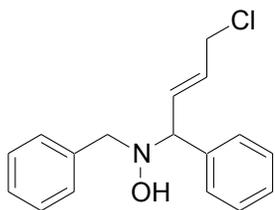
$^{13}\text{C NMR}$ (75 MHz, CDCl_3/TMS): $\delta = -1.14$, 61.40, 77.36, 127.26, 127.45, 128.34, 128.37, 128.65, 129.47, 134.10, 138.33, 141.15, 145.01 ppm.

IR (film) $\nu = 3531, 3026, 2949, 1597, 1491, 1451, 1246, 985, 870, 839, 736$ cm^{-1} .

MS (ESI) : 312 (100) ($\text{M}+\text{H}$) $^+$, 310 (29), 350 (16), ($\text{M}+\text{K}$) $^+$, 334 (14) ($\text{M}+\text{Na}$) $^+$

HRMS calcd. for $\text{C}_{19}\text{H}_{26}\text{O}_1\text{N}_1\text{Si}_1$ 312.1778, found 312.1775.

***N*-Benzyl-*N*-(4-chloro-1-phenyl-but-2-enyl)-hydroxylamine (45)**



¹H NMR (300 MHz, CDCl₃/TMS): δ = 3.71 (d, J = 13.4 Hz, 1H), 3.75 (d, J = 13.4 Hz, 1H), 4.00 (d, J = 6.9 Hz, 2H), 4.25 (d, J = 8.4 Hz, 1H), 5.79 (dt, J = 15.2 Hz, J = 6.9, 1H), 6.09 (dd, J = 15.2 Hz, J = 8.4 Hz, 1H), 7.20-7.36 (m, 10H) ppm.

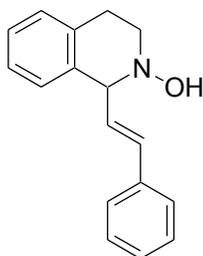
¹³C NMR (75 MHz, CDCl₃/TMS): δ = 44.43, 61.33, 73.60, 127.25, 127.66, 128.06, 128.27, 128.68, 129.07, 129.28, 134.12, 137.87, 140.42 ppm.

IR (film) ν = 3530, 3060, 3027, 2920, 2847, 1495, 1454, 1028, 969, 745, 697 cm⁻¹.

MS (DCI, NH₃/isobutane) m/z = 288 (M+H)⁺

HRMS : A correct HRMS could not be obtained for this sample.

1-Styryl-3,4-dihydro-1H-isoquinolin-2-ol (46)



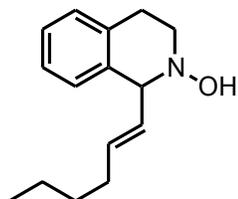
This compound was prepared according to the General Procedure from 1,2,3,4-Tetrahydroisoquinoline-N-oxide and dioxaborinane. Following flash chromatography (cyclohexane/ethyl acetate 1:6), the hydroxylamine was isolated in 62% yield.

¹H NMR (400 MHz, CDCl₃) δ = 2.87-2.92 (m, 1H), 3.08-3.17 (m, 2H), 3.51-3.54 (m, 1H), 4.49 (d, 1H, J = 8.0 Hz), 6.30 (dd, 1H, J = 15.6, 8.0 Hz), 6.72 (d, 1H, J = 15.6 Hz), 7.22-7.12 (m, 4H), 7.38-7.27 (m, 3H), 7.48-7.46 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 136.7, 135.5, 135.3, 133.4, 129.5, 128.7, 128.4, 128.1, 127.9, 127.0, 126.7, 126.2, 71.9, 53.9, 28.6 ppm.

MS: calcd. For $\text{C}_{17}\text{H}_{17}\text{NO}$ $[\text{M}+\text{Na}]$ 274, found 274.

1-Hex-1-enyl-3,4-dihydro-1H-isoquinolin-2-ol (47):



Isolated yield: 66% Colourless oil.

R_f = 0.4 ($\text{CHCl}_3/\text{MeOH}$, 80:20)

^1H NMR (300 MHz, CDCl_3) δ ppm: 0.94 (t, 3H, J = 7.1 Hz), 1.51-1.29 (m, 4H), 2.21-2.14 (m, 2H), 2.96-2.90 (m, 1H), 3.18-3.03 (m, 2H), 3.53-3.49 (m, 1H), 4.27 (d, 1H, J = 6.8 Hz), 5.52 (dd, 1H, J = 15.2, 8.3 Hz), 5.87-5.78 (m, 1H), 7.19-7.10 (m, 4H).

^{13}C NMR (75 MHz, CDCl_3) δ ppm: 13.92, 22.31, 28.28, 31.42, 32.14, 53.45, 71.40, 125.87, 126.55, 127.94, 128.12, 129.73, 133.26, 135.85, 136.98 ppm.

IR (film) ν = 3219, 3068, 3026, 2956, 2929, 2863, 1629, 1464, 752 cm^{-1}

LRMS (CI): m/z (%) = 232 (6), 231 (19), 214 (12), 172 (25), 148(80), 129 (100).

HRMS calcd. For $\text{C}_{15}\text{H}_{21}\text{NO}$ 231.1623, found 231.3334.

5.5 Preparation of aryl boronic derivatives

5.5.1 General Procedure for the borylation of aryl halides with $\text{PdCl}_2(\text{TPP})_2$

In an oven-dried Schlenk tube with N_2 inlet, $\text{PdCl}_2(\text{TPP})_2$ (21 mg, 0.03 mmol) was dissolved in 4.0 mL of toluene. TEA (0.420 mL, 3.0 mmol), the aryl halide (1.0 mmol) and 1.5 mL of a 1M solution of MPBH in dioxane (1.5 mmol) were then added and the reaction mixture stirred for the indicated time at 80 $^\circ\text{C}$. After completion of reaction, the

mixture was diluted with ether and washed once with brine. The organic layer was dried over MgSO_4 and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2 deactivated with 3% Et_3N , eluent pentane-ether) to give the desired aryl boronate.

The same procedure was used on a 10-mmol scale: (Table 2 entry 1): In an oven-dried Schlenk tube with N_2 inlet, $\text{PdCl}_2(\text{TPP})_2$ (140 mg, 0.2 mmol) was dissolved in 40 mL of toluene. TEA (4.20 mL, 3.0 mmol), the 4-iodoanisole (2.30 g, 10 mmol) and 15 mL of a 1M solution of MPBH in dioxane (15 mmol) were then added and the reaction mixture stirred for 3 hrs at 80 °C. The mixture was diluted with 100 mL ether and washed once with 10 mL brine. The organic layer was dried over MgSO_4 and concentrated. The material was purified by Kugelrohr distillation.

5.5.2 General Procedure for the borylation of aryl halides with Pd_2dba_3 and CyJohnPhos

An oven-dried Schlenk tube was charged with $\text{Pd}_2(\text{dba})_3$ (0.5x%, X be) and CyJohnPhos (2x %). The Schlenk tube was capped with a rubber septum and then evacuated and refilled with argon (this sequence was carried out a total of three times). Anhydrous dioxane (0.6 ml) was added via a syringe, through the septum, followed by the addition of the aryl halide (0.5 mmol), triethylamine (152 mg, 1.5 mmol), and MPBH (96 mg, 0.75 mmol) in a sequential manner (aryl halides that were solids were added along with the other solid reagents). The reaction mixture was then heated at the indicated temperature until the aryl halide has been completely consumed as determined by gas chromatography using internal standard. The reaction was allowed to cool to room temperature, and filtered through a thin pad of cellite (eluting with ether). The eluent was concentrated and the crude material so obtained was purified via flash chromatography on silica gel.

5.5.3 General Procedure for the borylation of aryl halides with bis(hexylene glycolato) diboron derivative:

To a 25 ml flask fitted with a septum inlet, a condenser and a magnetic stirring bar was charged with Pd₂(dba)₃ (0.008 g, 0.01 mmol, 1 mol%) and Buchwald's XPhos ligand (0.016 g, 0.04 mmol, 4 mol%), and flushed with nitrogen. Dioxane (4 ml) was added and the resulting mixture was then stirred at room temperature for 10 min. Bis(hexyleneglycolato)diboron (0.279 g, 1.1 mmol), KOAc (0.147 g, 1.5 mmol), and a chloroarene were added successively. After being stirred at 80 °C for an indicated period of time, the reaction mixture was treated with water (5 ml) at room temperature. The product was extracted with benzene, washed with brine, and dried over magnesium sulphate. The solvent was evaporated, and the residue purified by flash column chromatography (silica gel, ca. 10 cm x 2cm, cyclohexane/EtOAc) to give the desired arylboronic ester as a colorless liquid.

5.5.4 General Procedure for Suzuki-Miyaura biaryl coupling

To a mixture of aryl-4,4,6-trimethyl-1,3,2-dioxaborinane 4 (1.0 mmol), aryl halide 3 (1.0 mmol) and PdCl₂(TPP)₂ (0.03 mmol) in 1 mL DMF was added a suspension of CsF (456 mg, 3.0 mmol) in 3.0 mL DMF. The reaction mixture was stirred at 80 °C for 2 hrs or until GC analysis showed completion. The mixture was then diluted with diethyl ether (20 mL) and washed with water. The organic layer was dried over MgSO₄, the solvent removed under vacuum and the residue was purified by flash chromatography (eluent: cyclohexane/ethyl acetate).

5.5.5 One pot Procedure:

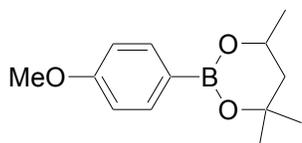
In an oven-dried Schlenk tube with N₂ atmosphere was placed PdCl₂(TPP)₂ (21 mg, 0.03 mmol) in 4.0 mL dioxane. TEA (0.420 mL, 3.0 mmol) was then added and the reaction mixture stirred for 30 min. The aryl iodide (1.0 mmol) and MPBH solution (1M, 1.5 mmol) in dioxane were then successively added and the reaction mixture stirred at 80°C. The reaction was monitored by GC analysis of reaction aliquots. After completion, the solvent was evaporated to dryness and a solution of CsF (5.0 mmol) and the second aryl halide (1.0 mmol) in DMF (4.0 mL) was added. The reaction was stirred at 80°C for

2 hrs. After completion, it was diluted with ether and washed with water. The organic layer was dried over MgSO_4 , the solvent removed under vacuum and the residue was purified by flash chromatography (eluent: cyclohexane/ethyl acetate).

5.5.6 Products Description: Arylboronic esters

In the ^{13}C -NMR spectra, C atoms that are directly bonded to boron remained undetected.

2-(4-Methoxy-phenyl)-4,4,6-trimethyl-[1,3,2]dioxaborinane:90 (56)



^1H NMR (300 MHz, CDCl_3) δ ppm 7.75 (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 4.30 (dq, $J = 11.7, 6.2, 3.0$ Hz, 1H), 3.79 (s, 3H), 1.82 (dd, $J = 13.8, 3.0$ Hz, 1H), 1.55 (dd, $J = 13.8, 11.7$ Hz, 1H), 1.35 (s, 3H), 1.34 (s, 3H), 1.32 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ ppm 161.4(C), 135.3(CH), 112.9(CH), 70.7(C), 64.7(CH), 54.9(CH_3), 46.0(CH_2), 31.2(CH_3), 28.1(CH_3), 23.2(CH_3).

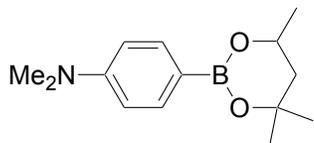
^{11}B NMR (96.3 MHz, CDCl_3) δ ppm 26.8;

I.R. (neat, cm^{-1}) 2969, 2932, 2911, 1606, 1573, 1304, 832;

MS (DCI), 235 (40, $\text{M}+\text{H}^+$), 144 (100) ;

HRMS (APPI-APCI): Calc. for $\text{C}_{13}\text{H}_{19}\text{O}_3^{11}\text{B}$ 234.14218; found 234.14240.

Dimethyl-[4-(4,4,6-trimethyl-[1,3,2]dioxaborinan-2-yl)-phenyl]-amine: (59)



¹H NMR (400 MHz, *CDCl*₃) δ ppm 7.67 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 4.29 (dq, *J* = 11.7, 6.2, 3.0 Hz, 1H), 2.95 (s, 6H), 1.81 (dd, *J* = 13.8, 3.0 Hz, 1H), 1.54 (dd, *J* = 13.8, 11.7 Hz, 1H), 1.34 (s, 3H), 1.32 (s, 3H), 1.31 (d, *J* = 6.2 Hz, 3H).

¹³C NMR (75.5 MHz, *CDCl*₃) δ ppm 152.1(C), 135.0(CH), 111.4(CH), 70.5(C), 64.6(CH), 46.1(CH₂), 40.3(2xCH₃), 31.4(CH₃), 28.2(CH₃), 23.3(CH₃).

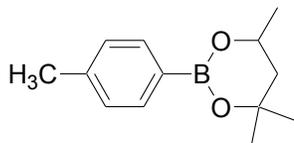
¹¹B NMR (128.4 MHz, *CDCl*₃) δ ppm 26.9;

IR (neat, cm⁻¹) 2970, 2930, 2906, 1605, 1300, 945, 816;

MS (DCI) 248 (M+H⁺);

HRMS (ES): Calc. for C₁₄H₂₃O₂N¹⁰B 247.18527; found 247.18500.

2-(4-Methyl-phenyl)-4,4,6-trimethyl-[1,3,2]dioxaborinane: (60)



¹H NMR (300 MHz, *CDCl*₃) δ ppm 7.70 (d, *J* = 7.7 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 2H), 4.32 (dq, *J* = 11.8, 6.7, 3.0 Hz, 1H), 2.34 (s, 3H), 1.84 (dd, *J* = 13.7, 3.0 Hz, 1H), 1.57 (dd, *J* = 13.7, 11.8 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 3H), 1.33 (d, *J* = 6.7 Hz, 3H);

¹³C NMR (75.5 MHz, *CDCl*₃) δ ppm 140.1(C), 133.8(CH), 128.2(CH), 70.7(C), 64.8(CH), 46.0(CH₂), 31.3(CH₃), 28.1(CH₃), 23.2(CH₃), 21.6(CH₃).

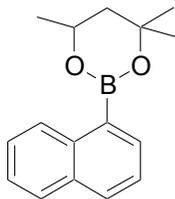
¹¹B NMR (96.3 MHz, *CDCl*₃) δ ppm 27.1;

I.R. (neat, cm⁻¹) 2971, 2932, 2908, 1612, 1406, 815, 766, 724;

MS (DCI) 236 (100, M+NH₄⁺), 144(50);

HRMS (EI) Calc. for C₁₃H₁₉O₂¹¹B 218.1473 found 218.1479.

4,4,6-Trimethyl-2-naphthalen-1-yl-[1,3,2]dioxaborinane (61)



¹H NMR (400 MHz, *CDCl*₃) δ ppm 8.79 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 6.8 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.50-7.38 (m, 1H), 4.42 (dq, *J* = 12.0, 6.2, 3.0 Hz, 1H), 1.88 (dd, *J* = 13.6, 3.0 Hz, 1H), 1.67 (dd, *J* = 13.6, 12.0 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.40 (d, *J* = 6.2 Hz, 3H);

¹³C NMR (100.6 MHz, *CDCl*₃) δ ppm 136.8(C), 134.2(CH), 133.4(C), 130.6(CH), 128.4(CH), 128.4(CH), 125.8(CH), 125.1(CH), 125.0(CH), 71.5(C), 65.3(CH), 46.0(CH₂), 31.4(CH₃), 28.3(CH₃), 23.3(CH₃);

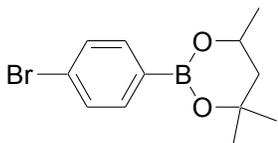
¹¹B NMR (128 MHz, *CDCl*₃) δ ppm 27.8;

IR (neat, cm⁻¹) 3038, 2973, 2926, 1509, 1459, 1303, 804, 779;

MS (DCI) 272 (100, M+NH₄⁺), 271(62), 144(29).

HRMS (APPI-APCI) Calc. for C₁₆H₁₉O₂¹¹B 254.1473 found 254.1463.

2-(4-Bromo-phenyl)-4,4,6-trimethyl-[1,3,2]dioxaborinane: (62)



¹H NMR (400 MHz, *CDCl*₃) δ ppm 7.66 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 4.32 (dq, *J* = 11.7, 6.2, 3.0 Hz, 1H), 1.86 (dd, *J* = 13.9, 3.0 Hz, 1H), 1.57 (dd, *J* = 13.9, 11.7 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 3H), 1.33 (d, *J* = 6.2 Hz, 3H);

¹³C NMR (75.5 MHz, *CDCl*₃) δ ppm 135.4(CH), 133.7(C), 130.6(CH), 125.1(C), 71.2(C), 65.1(CH), 46.0(CH₂), 31.2(CH₃), 28.1(CH₃), 23.1(CH₃);

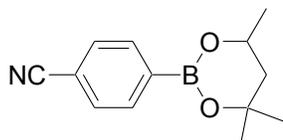
¹¹B NMR (96.3 MHz, *CDCl*₃) δ ppm 26.7;

I.R. (neat, cm^{-1}) 2968, 2928, 2906, 1583, 1403, 1304, 823, 767, 723;

MS (DCI) 284(100, M^+), 283 (27), 282 (98), 281 (29);

HRMS (EI) Calc. for $\text{C}_{12}\text{H}_{16}\text{BrO}_2^{11}\text{B}$ 204.1238 found 204.1235.

4-(4,4,6-Trimethyl-[1,3,2]dioxaborinan-2-yl)-benzonitrile (62')



^1H NMR (300 MHz, CDCl_3) δ ppm 7.88 (d, $J = 7.9$ Hz, 2H), 7.59 (d, $J = 7.9$ Hz, 2H), 4.35 (dq, $J = 11.6, 6.2, 3.0$ Hz, 1H), 1.89 (dd, $J = 14.0, 3.0$ Hz, 1H), 1.59 (dd, $J = 14.0, 11.6$ Hz, 1H), 1.38 (s, 3H), 1.37 (s, 3H), 1.35 (d, $J = 6.2$ Hz, 3H);

^{13}C NMR (75.5 MHz, CDCl_3) δ ppm 134.1(CH), 130.8(CH), 119.2(C), 113.5(C), 71.6(C), 65.3(CH), 45.9(CH_2), 31.1(CH_3), 28.1(CH_3), 23.0(CH_3);

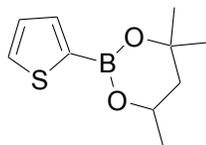
^{11}B NMR (128.4 MHz, CDCl_3) δ ppm 26.3;

IR (neat, cm^{-1}) 2972, 2928, 2226, 1408, 1304, 1164, 834, 768, 738;

MS (DCI) 247 (100, $\text{M}+\text{NH}_4^+$);

HRMS (EI) Calc. for $\text{C}_{13}\text{H}_{16}\text{NO}_2^{11}\text{B}$ 229.1269 found 229.1277.

4,4,6-Trimethyl-2-thiophen-2-yl-[1,3,2]dioxaborinane (63)



^1H NMR (400 MHz, CDCl_3) δ ppm 7.56 (dd, $J = 3.4, 0.9$ Hz, 1H), 7.52 (dd, $J = 4.7, 0.9$ Hz, 1H), 7.13 (dd, $J = 4.7, 3.4$ Hz, 1H), 4.33 (dq, $J = 11.7, 6.2, 3.0$ Hz, 1H), 1.84 (dd, $J = 13.8, 3.0$ Hz, 1H), 1.60 (dd, $J = 13.8, 11.7$ Hz, 1H), 1.36 (s, 6H), 1.33 (d, $J = 6.2$ Hz, 3H);

^{13}C NMR (100.6 MHz, CDCl_3) δ ppm 135.2(CH), 130.8(CH), 127.8(CH), 71.3(C), 65.2(CH), 46.0(CH_2), 31.1(CH_3), 28.0(CH_3), 23.1(CH_3);

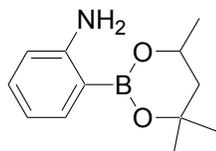
^{11}B NMR (128 MHz, CDCl_3) δ ppm 25.4;

I.R. (neat, cm^{-1}) 2974, 2933, 2913, 1520, 1421, 1283;

MS(DCI) 111 (100), 210 (83, M^+), 211 (64, $\text{M}+\text{H}^+$);

HRMS (ES) Calc. for $\text{C}_{10}\text{H}_{15}\text{O}_2\text{S}^{11}\text{B}$ 210.0880 found 210.0887.

2-(4,4,6-Trimethyl-[1,3,2]dioxaborinan-2-yl)-phenylamine (64)



^1H NMR (400 MHz, CDCl_3) δ ppm 7.68 (dd, $J = 7.9, 1.6$ Hz, 1H) 7.18 (ddd, $J = 8.2, 7.9, 1.6$ Hz, 1H), , 6.71 (td, $J = 8.1, 1.0$ Hz, 1H), 6.65 (d, $J = 8.0$ Hz, 1H), 4.37 (dq, $J = 11.9, 6.2, 3.0$ Hz, 1H), 1.87 (dd, $J = 13.8, 3.0$ Hz, 1H), 1.62 (dd, $J = 13.8, 11.9$ Hz, 1H), 1.39 (s, 3H), 1.38 (s, 3H), 1.35 (d, $J = 6.2$ Hz, 3H);

^{13}C NMR (100.6 MHz, CDCl_3) δ ppm 153.1(C), 136.0(CH), 131.7(CH), 116.9(CH), 115.1(CH), 71.2(C), 65.0(CH), 45.7(CH_2), 31.3(CH_3), 28.1(CH_3), 23.2(CH_3);

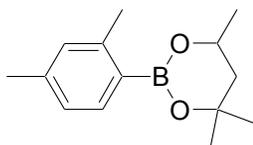
^{11}B NMR (128 MHz, CDCl_3) δ ppm 27.4;

I.R. (neat, cm^{-1}) 3480, 3385, 3019, 2971, 2930, 2909, 1601, 1565, 1451, 755;

MS(DCI) 219 (85, M^+), 220 (100, $\text{M}+\text{H}^+$);

HRMS (ES) calc. for $\text{C}_{12}\text{H}_{19}\text{O}_2\text{N}^{10}\text{B}$ 219.15397; found 219.15371.

2-(2,4-Dimethyl-phenyl)-4,4,6-trimethyl-[1,3,2]dioxaborinane (65)



¹H NMR (300 MHz, *CDCl*₃) δ ppm 7.63 (d, *J* = 8.1 Hz, 1H), 6.97-6.92 (m, 2H), 4.32 (dq, *J* = 11.7, 6.2, 3.0 Hz, 1H), 2.48 (s, 3H), 2.28 (s, 3H), 1.83 (dd, *J* = 13.8, 3.0 Hz, 1H), 1.56 (dd, *J* = 13.7, 11.7 Hz, 1H), 1.35 (s, 6H), 1.32 (d, *J* = 6.2 Hz, 3H);

¹³C NMR (75.5 MHz, *CDCl*₃) δ ppm 143.9(C), 139.5(C), 135.0(CH), 130.8(CH), 125.4(CH), 70.9(CH), 64.9(CH), 46.0(CH₂), 31.4(CH₃), 28.2(CH₃), 23.3(CH₃), 22.3(CH₃), 21.3(CH₃);

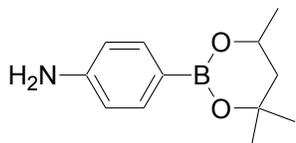
¹¹B NMR (96.3 MHz, *CDCl*₃) δ ppm 27.8;

IR (KBr, cm⁻¹) 2972, 2920, 1610, 1379, 1301;

MS(DCI) 144 (75), 233 (42, M+ H⁺), 250 (100, M+ NH₄⁺);

HRMS (ES) Calc. for C₁₄H₂₁O₂¹¹B 232.1629 found 232.1626.

4-(4,4,6-Trimethyl-[1,3,2]dioxaborinan-2-yl)-phenylamine Erreur : source de la référence non trouvée (66)



¹H NMR (300 MHz, *CDCl*₃) δ ppm 7.61 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 4.29 (dq, *J* = 11.7, 6.2, 3.0 Hz, 1H), 3.72 (s, 2H), 1.81 (dd, *J* = 13.8, 3.0 Hz, 1H), 1.54 (dd, *J* = 13.8, 11.7 Hz, 1H), 1.34 (s, 3H), 1.33 (s, 3H), 1.31 (d, *J* = 6.2 Hz, 3H);

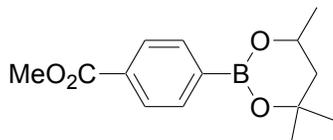
¹³C NMR (100.6 MHz, *CDCl*₃) δ ppm 148.4(C), 135.2(CH), 114.0(CH), 70.5(C), 64.6(CH), 46.0(CH₂), 31.3(CH₃), 28.1(CH₃), 23.2(CH₃);

¹¹B NMR (128 MHz, *CDCl*₃) δ ppm 26.8;

IR (neat, cm⁻¹) 3466, 3377, 3217, 3019, 2971, 2930, 2905, 1623, 1604, 1568, 1301, 828;

MS(DCI) 94 (100), 219 (46, M⁺), 220 (55, M+H⁺).

4-(4,4,6-Trimethyl-[1,3,2]dioxaborinan-2-yl)-benzoic acid methyl ester (67)



¹H NMR (300 MHz, *CDCl*₃) δ ppm 8.00 (d, *J* = 8.1 Hz, 2H), 7.88 (d, *J* = 8.1 Hz, 2H), 4.38 (dq, *J* = 11.5, 6.2, 3.0 Hz, 1H), 3.93 (s, 3H), 1.91 (dd, *J* = 13.9, 3.0 Hz, 1H), 1.62 (dd, *J* = 13.9, 11.5 Hz, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.38 (d, *J* = 6.2 Hz, 3H);

¹³C NMR (75.5 MHz, *CDCl*₃) δ ppm 167.3(C), 133.6(C), 131.4(CH), 128.3(CH), 71.2(C), 65.1(CH), 51.9(CH₃), 45.9(CH₂), 31.1(CH₃), 28.1(CH₃), 23.0(CH₃);

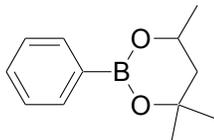
¹¹B NMR (96.3 MHz, *CDCl*₃) δ ppm 27.1;

IR (neat, cm⁻¹) 2971, 2949, 2908, 1725, 1561, 1432, 1166, 766, 711;

MS (ESI) 263 (M+H⁺), 279 (M+Na⁺);

HRMS (APPI-APCI) Calc. for C₁₄H₂₀O₄¹¹B 263.14492 found 263.14503.

2-phenyl-4,4,6-trimethyl-[1,3,2]dioxaborinane:83 (68)



¹H NMR (400 MHz, *CDCl*₃) δ ppm 7.84-7.77 (m, 2H), 7.41-7.27 (m, 3H), 4.30 (dq, *J* = 11.7, 6.2, 3.0 Hz, 1H), 1.80 (dd, *J* = 13.9, 3.0 Hz, 1H), 1.54 (dd, *J* = 13.9, 11.7 Hz, 1H), 1.35 (s, 3H), 1.33 (s, 3H), 1.31 (d, *J* = 6.7 Hz, 3H);

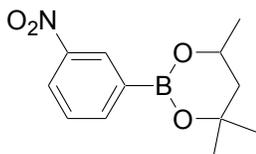
¹³C NMR (100.6 MHz, *CDCl*₃) δ ppm 133.8(C), 130.4(CH), 127.5(CH), 71.0(C), 65.0(CH), 46.1(CH₂), 31.3(CH₃), 28.2(CH₃), 23.3(CH₃);

¹¹B NMR (128 MHz, *CDCl*₃) δ ppm 26.9;

IR (neat, cm⁻¹) 3074, 3050, 2974, 2933, 2912, 1601, 1440, 1304, 768;

MS (DCI) 105 (100), 204 (23, M⁺), 205 (34, M+H⁺).

4,4,6-Trimethyl-2-(3-nitro-phenyl)-[1,3,2]dioxaborinane (70)



¹H NMR (400 MHz, *CDCl*₃) δ ppm 8.62 (d, *J* = 2.5 Hz, 1H), 8.23 (ddd, *J* = 7.7, 2.5, 1.1 Hz, 1H), 8.10 (td, *J* = 7.7, 1.1 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 4.38 (dq, *J* = 11.8, 6.2, 3.0 Hz, 1H), 1.91 (dd, *J* = 13.9, 3.0 Hz, 1H), 1.62 (dd, *J* = 13.9, 11.8 Hz, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 1.37 (d, *J* = 6.2 Hz, 3H);

¹³C NMR (100 MHz, *CDCl*₃) δ ppm 147.8(C), 139.8(CH), 128.4(CH), 128.3(CH), 125.0(CH), 71.7(C), 65.4(CH), 45.9(CH₂), 31.1(CH₃), 28.1(CH₃), 23.0(CH₃);

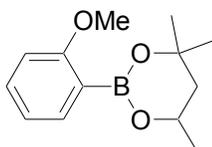
¹¹B NMR (128.4 MHz, *CDCl*₃) δ ppm 26.3;

IR (neat, cm⁻¹) 2972, 2924, 1609, 1528, 1304, 837, 771, 697;

MS (DCI) 250 (90, M+H⁺), 220 (100);

HRMS (EI) Calc. for C₁₂H₁₆NO₄¹¹B 249.1167 found 229.1170.

2-(2-Methoxy-phenyl)-4,4,6-trimethyl-[1,3,2]dioxaborinane (77)



¹H NMR: (400 MHz, *CDCl*₃): δ ppm 1.34 (d, *J* = 6.1 Hz, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.63 (dd, *J* = 7.0, 11.9 Hz, 1H), 1.86 (dd, *J* = 3.1, 7.0 Hz, 1H), 3.80 (s, 3H), 4.38 (br s, 1H), 6.82 (d, *J* = 7.3 Hz, 1H), 6.92 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.59 (d, *J* = 7.3 Hz, 1H).

¹³C NMR: (75 MHz, *CDCl*₃): δ ppm 23.11, 28.07, 31.1, 45.85, 55.70, 65.06, 71.02, 110.80, 120.18, 131.06, 135.38, 163.43.

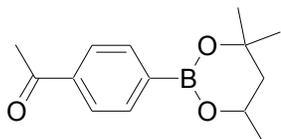
¹¹B NMR (96.3 MHz, *CDCl*₃) δ ppm 26.8;

I.R. (neat, cm⁻¹) 2969, 2932, 2911, 1606, 1573, 1304, 832;

MS (DCI), 235 (40, M+H⁺), 144 (100) ;

HRMS (APPI-APCI): Calc. for C₁₃H₁₉O₃¹¹B 234.14218; found 234.14240.

1-[4-(4,4,6-Trimethyl-[1,3,2]dioxaborinan-2-yl)-phenyl]-ethanone (78)



¹H NMR (400 MHz, CDCl₃): δ ppm 1.36 (d, J = 6.1 Hz, 3H), 1.38 (s, 3H), 1.39 (s, 3H), 1.61 (dd, J = 7.0, 12.2 Hz, 1H), 1.89 (dd, J = 2.8, 6.9 Hz, 1H), 2.61 (s, 3H), 4.36 (br s, 1H), 7.88 (d, J = 8.6 Hz, 2H), 7.90 (d, J = 8.6 Hz, 2H).

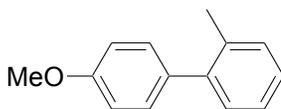
¹³C NMR (75 MHz, CDCl₃): δ ppm 23.1, 26.7, 28.13, 31.17, 45.92, 65.19, 71.33, 127.06, 133.90, 138.28, 198.68.

¹¹B NMR (96 MHz, CDCl₃): δ ppm 26.8

HRMS: m/z calcd for C₁₄H₁₉BO₃: 246.1427; found 246.1417.

5.5.7 Products Description :Suzuki Coupling

4'-Methoxy-2-methyl-biphenyl²⁵⁷ (81)

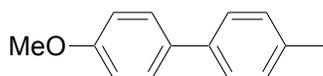


¹H NMR (300 MHz, CDCl₃) δ ppm 7.28-7.18 (m, 6H), 6.97-6.91 (m, 2H), 3.84 (s, 3H), 2.27 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ ppm 14.3, 56.0, 114.6, 127.3, 128.4, 129.7, 136.6, 137.3, 160.9.

²⁵⁷ V. V. Rostovtsev; L. M. Bryman; C. P. Junk; M. A. Harmer; L. G. Carcani, *J. Org. Chem.*, **2008**, 73, 711.

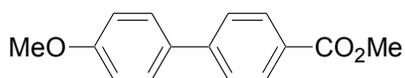
4-Methoxy-4'-methyl-biphenyl²⁵⁸ (82)



¹H NMR (300 MHz, CDCl₃) δ ppm 7.43 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 3.76 (s, 3H), 2.30 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ ppm: 20.9, 56.1, 114.6, 127.3, 128.4, 128.9, 129.7, 136.6, 160.9.

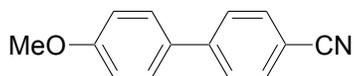
4'-Methoxy-biphenyl-4-carboxylic acid methyl ester²⁵⁹ (83)



¹H NMR (300 MHz, CDCl₃) δ ppm 8.10 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H), 3.89 (s, 3H).

¹³C NMR (75 MHz, CDCl₃/TMS) δ ppm 50.0, 56.2, 114.6, 127.3, 128.9, 130.2, 140.9, 160.9, 167.1.

4'-Methoxy-biphenyl-4-carbonitrile²⁶⁰ (84)



¹H NMR (400 MHz, CDCl₃) δ ppm 7.61-7.51 (m, 4H), 7.44 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.77 (s, 3H).

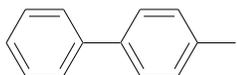
¹³C NMR (75 MHz, CDCl₃/TMS) δ ppm: 56.1, 111.4, 114.6, 116.5, 128.1, 128.4, 128.9, 132.5, 140.9.

²⁵⁸ J. L. Bolliger, O. Blacque, C. M. Frech, *Angew. Chem. Int. Ed.* **2007**, *46*, 6514.

²⁵⁹ S. Teo, Z. Weng, T. S. A. Hor, *Organometallics* **2006**, *25*, 1199.

²⁶⁰ T. J. Korn, M. A. Schade, S. Wirth, P. Knochel, *Org. Lett.* **2006**, *8*, 725.

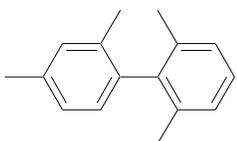
4-Methyl-biphenyl²⁶¹ (



¹H NMR (300 MHz, CDCl₃) δ ppm 8.00 (d, *J* = 7.7 Hz, 1H), 7.64-7.55 (m, 1H), 7.49-7.38 (m, 2H), 7.26 (s, 4H), 2.41 (s, 3H).

¹³C NMR (75MHz, CDCl₃) δ ppm 20.9, 127.3, 127.9, 127.4, 129.0, 129.7, 135.5.

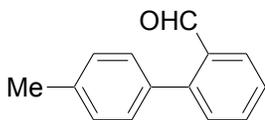
2,4,2',6'-Tetramethyl-biphenyl²⁶² (85)



¹H NMR (300 MHz, CDCl₃) δ ppm 7.20-7.02 (m, 5H), 6.89 (d, *J* = 7.6 Hz, 1H), 2.36 (s, 3H), 1.94 (s, 6H), 1.92 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ ppm: 14.6, 21.2, 126.7, 127.2, 130.4, 134.3, 136.5, 138.0.

4'-Methyl-biphenyl-2-carbaldehyde²⁶³ (86)



¹H NMR (300 MHz, CDCl₃) δ ppm 9.98 (s, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.65-7.55 (m, 1H), 7.49-7.39 (m, 1H), 7.26 (s, 4H), 2.41 (s, 3H).

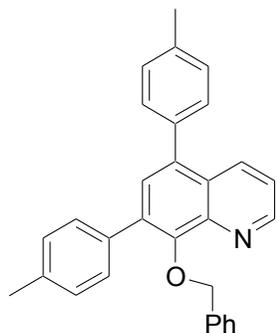
¹³C NMR (75 MHz, CDCl₃) δ ppm: 20.9, 127.3, 127.9, 129.7, 130.2, 133.6, 134.8, 135.6, 136.6, 137.8.

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8-Benzyloxy-5,7-di-p-tolyl-quinoline: (87)



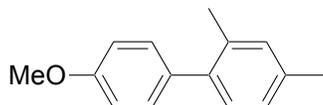
¹H NMR (300 MHz, *CDCl*₃) δ ppm 9.03 (s, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 7.63-7.17 (m, 15H), 5.16 (s, 2H), 2.48-2.45(s, 3H), 2.42 (s, 3H).

¹³C NMR (75.5 MHz, *CDCl*₃) δ ppm 150.7(C), 149.4(CH), 143.2(C), 137.5(CH), 137.3(CH), 137.2(CH), 136.2(CH), 135.9(CH), 135.1(CH), 134.9(C), 134.0(CH), 130.0(CH), 129.8(CH), 129.8(CH), 129.2(CH), 128.9(CH), 128.5(CH), 127.9(CH), 127.5(CH), 127.2(C), 120.8(CH), 76.2(CH₂), 21.3(CH₃), 21.2(CH₃);

IR (neat, cm⁻¹) 3027, 2920, 2854, 1599, 1513, 1447, 1076, 819, 734;

HRMS (ES) Calc. for C₃₀H₂₆ON 416.20089 found 416.20074.

4'-Methoxy-2,4-dimethyl-biphenyl. (88)

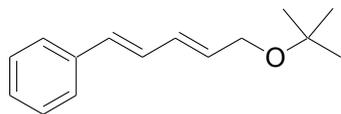


¹H NMR (300 MHz, *CDCl*₃) δ ppm 7.23 (d, *J* = 8.6 Hz, 2H), 7.14-6.99 (m, 3H), 6.93 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 3H), 2.35 (s, 3H), 2.24 (s, 3H);

¹³C NMR (75 MHz, *CDCl*₃) δ ppm: 158.4(C), 138.7(C), 136.5(C), 135.2(C), 134.3(C), 131.1(CH), 130.3(CH), 129.8(CH), 126.5(CH), 113.4(CH), 55.2(CH₃), 21.0(CH₃), 20.4(CH₃);

IR (neat, cm⁻¹) 3031, 2998, 2950, 2917, 1609, 1240, 1040, 815;

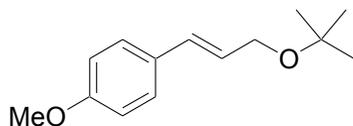
MS (DCI) 213 (100, M+H⁺); **HRMS** (ES) calc. for C₁₅H₁₆O 212.11957 found 212.11961.

***E,E*-(5-*tert*-Butoxy-penta-1,3-dienyl)-benzene (93)**

Colorless waxy solid. $R_f=0.71$ (Cyclohexane/EtOAc 90:10)

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm: 1.17 (s, 9H), 4.24 (d, $J = 12.9$ Hz, 2H), 5.9 (dt, $J = 15.5$ Hz, 6.2 Hz, 1H), 6.36 (dd, $J = 15.1$ Hz, $J = 10.0$ Hz, 1H), 6.51 (d, $J = 15.7$ Hz, 1H), 6.77 (dd, $J = 15.7$ Hz, $J = 10.0$ Hz, 1H), 7.21-7.36 (m, 4H).

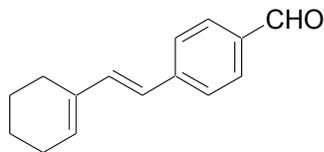
$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm: 27.82, 63.14, 73.81, 26.23, 127.5, 128.6, 131.6, 134.2, 136.9.

***E*-1-(3-*tert*-Butoxy-propenyl)-4-methoxy-benzene (90)**

Colorless solid. $R_f=0.8$ (Cyclohexane/EtOAc 85:15)

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm: 1.16 (s, 9H), 3.77 (s, 3H), 4.14 (d, $J = 13.38$ Hz, 2H), 5.99 (dt, $J = 15.95$ Hz, 5.90 Hz, 1H), 6.48 (d, $J = 15.95$ Hz, 1H), 6.83-7.32 (m, 4H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm: 27.56, 55.20, 61.57, 73.79, 114.25, 127.48, 127.84, 132.75, 159.55.

4-(2-Cyclohex-1-enyl-vinyl)-benzaldehyde (91)

Colorless liquid. $R_f = 0.6$ (Cyclohexane/EtOAc 80:20)

¹H NMR (300MHz, *CDCl*₃) δ ppm: 1.58-1.68 (m, 4H), 2.1-2.56 (m, 4H), 5.90 (t, J = 3.9 Hz, 1H), 6.42 (d, J = 16.2 Hz, 1H), 6.79 (d, J = 16.2 Hz, 1H), 7.52-7.79 (m, 4H), 9.47 (s, 1H).

¹³C NMR (75 MHz, *CDCl*₃) δ ppm: 22.09, 22.73, 24.02, 26.15, 127.53, 127.76, 128.47, 130.02, 134.86, 136.33, 137.55, 191.60.

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