DOI: 10.1002/ejoc.200900234

Introduction of Allyl and Prenyl Side-Chains into Aromatic Systems by Suzuki Cross-Coupling Reactions

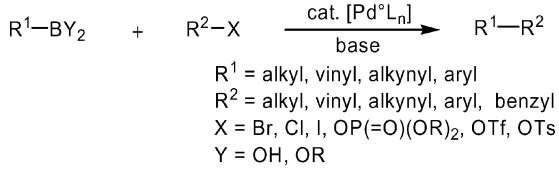
Darío C. Gerbino,[a,b] Sandra D. Mandolesi,[a] Hans-Günther Schmalz,*[c] and Julio C. Podestá*[a,b]

Keywords: Cross-coupling / Boron / Borates / Arenes

This paper reports some studies aiming at the developement of a general protocol useful for the synthesis of allyl- and prenylaromatic compounds. The first part deals with the preparation of boron reagents like arylboronic acids and their pinacol esters as well as of pinacol allyl- and prenylboronates. The second part of the paper is devoted to the use of these boron reagents in Suzuki–Miyaura cross-coupling reactions leading to allylation and prenylation of aromatic compounds. Of the six methods studied, the most promising results were obtained by using the $Pd_2(dba)_3$-catalyzed reactions of arylboronic acids with allyl and prenyl bromides, that lead to the products of cross coupling in high yields (average 87%), and the reactions of aryl trifluoroborates with allyl and prenyl bromides catalyzed by $Pd(OAc)_2$ that lead to the products of coupling in all cases in high yields (average 82%).

Introduction

The selective formation of new carbon–carbon bonds is frequently a key step in the synthesis of molecules of high added value, like fine chemicals, as well as in the preparation of conventional and special polymers. Cross-coupling reactions catalysed by metal complexes could undoubtedly be included among the most powerful and versatile synthetic methods for achieving these transformations.[1] During the last 30 years, the development of a wide variety of cross-coupling methods has facilitated the synthesis of carbon–carbon bonds between unsaturated species, notably sp and sp^2 moieties, like vinyl, alkynyl and phenyl groups. Of the coupling reactions catalysed by palladium, the Suzuki–Miyaura reaction, that is, the reaction between organoboron compounds and organic electrophiles, for example, vinyl, alkynyl, aryl and benzyl halides and triflates, catalysed by palladium complexes (Scheme 1) is one of the most useful for making carbon–carbon bonds.[2] The first example of this protocol was reported by Suzuki and coworkers in 1979.[3]



Scheme 1. Suzuki–Miyaura reaction.

Some of the advantages of this reaction are the availability of a wide variety of reagents, mild reaction conditions, the compatibility of boron derivatives with a wide range of functional groups and their lower toxicity compared with other organometallic derivatives, for example, organotin compounds. In addition, inorganic boron byproducts have a low environmental impact, minimal toxicity and can be removed by very simple procedures.

On the other hand, taking into account the fact that allylation and prenylation reactions are useful tools for the introduction of chains containing carbon–carbon double bonds leading to fragments that in many cases are part of natural products,[4,5] it would certainly be of interest to find more general techniques for carrying out these reactions. Although successful allylation and prenylation reactions of a wide variety of organic substrates by cross-coupling reactions have been reported,[5a,5b,6] in most cases the protocols of these reactions could only be applied with excellent yields to particular systems and not in general. Also, surprisingly, the nature of the organoboron coupling partners has been little studied. Owing to the importance of these reactions in synthetic applications, we considered it of interest to carry out a study to establish both the conditions and methods needed to develop a protocol that could be applied successfully to the allylation and prenylation of a wide number of organic substrates.

[a] Departmento de Química, Universidad Nacional del Sur,
Av. Alem 1253, 8000 Bahía Blanca, Argentina
Fax: +54-291-4595187
E-mail: jpodesta@criba.edu.ar
[b] CONICET,
Av. Rivadavia 1917, 1033 Buenos Aires, Argentina
[c] Department Chemie, Universität zu Köln,
Greinstrasse 4, 50939 Köln, Germany
Fax: +49-221-4703064

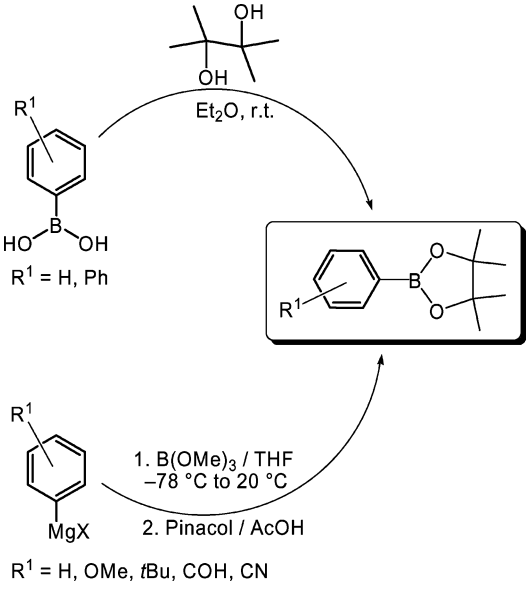
Results and Discussion

The paper is organized into two parts: the first deals with the preparation of boron reagents and the second is devoted to Suzuki–Miyaura cross-coupling reactions.

Synthesis of Boron Reagents

Preparation of Phenylboronic Acids and Pinacol Phenylboronates

The arylboronic esters and acids used in these studies were prepared following various procedures. Thus, pinacol arylboronic esters were obtained in high yields from commercially available boronic acids and pinacol at room temperature (Scheme 2). This synthetic route involves no chromatography. A cheaper route, which allows preparations on a multigram scale, makes use of functionalized arylmagnesium reagents in the presence of trimethyl borate and pinacol (Scheme 2, Table 1). This simple method enabled us to obtain the corresponding boronic esters in very good yields. In those cases in which the presence of sensitive functional groups prevented the generation of the corresponding Grignard reagents (see Table 1, entries 4 and 5), we used *i*PrMgCl in THF at –20 °C.[7]

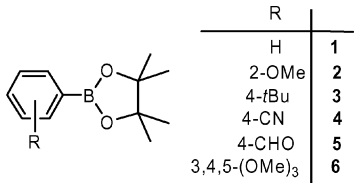


Scheme 2. Synthesis of pinacol arylboronates.

In 1995, Miyaura and co-workers found a direct procedure for the synthesis of boronic esters from commercially available bis(pinacolato)diboron and aryl halides through a palladium-catalysed cross-coupling reaction (Scheme 3).[8]

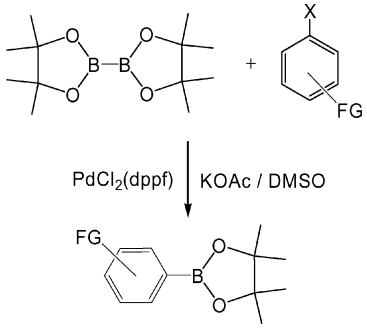
We have extended this procedure to substrates containing other functional groups. Thus, the reactions between bis(pinacolato)diboron and aryl halides using [$PdCl_2$(dppf)] as catalyst in the presence of KOAc in DMSO at 80 °C (Scheme 3) led to the corresponding products in high yields, as shown in Table 2.

Table 1. Synthesis of pinacol arylboronates by reaction of arylmagnesium reagents with trimethyl borate in the presence of pinacol.[a]



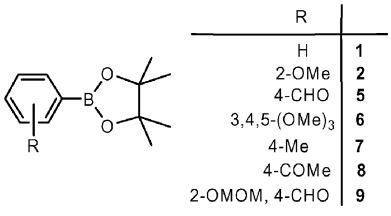
Entry	Grignard Reagent	Product	% Yield[b]
1	C_6H_5MgBr	**1**	82
2	2-$MeOC_6H_4MgBr$	**2**	85
3	4-$tBuC_6H_4MgBr$	**3**	76
4	4-NCC_6H_4MgBr	**4**	83[c]
5	4-$OHCC_6H_4MgBr$	**5**	81[c]
6	3,4,5-$MeOC_6H_2MgBr$	**6**	80

[a] Reactions were carried out in THF using arylmagnesium bromide (1.0 equiv.), trimethyl borate (1.0 equiv.) and pinacol (1.0 equiv.). [b] Yields of analytically pure products. [c] The Grignard reagents were prepared by the reactions of *i*PrMgCl (1.1 equiv.) with 4-bromobenzonitrile (**4**) and 4-iodobenzaldehyde (**5**) at –20 °C; see ref.[7].



Scheme 3. Synthesis of arylboronic esters using bis(pinacolato)diboron.

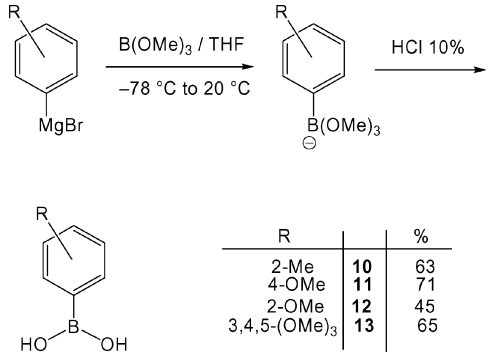
Table 2. Cross-coupling of bis(pinacolato)diboron with haloarenes.[a]



Entry	Halide	Product	Time [h]	% Yield[b]
1	C_6H_5Br	**1**	2	90
2	2-$MeOC_6H_4I$	**2**	10	80
3	4-$IBuC_6H_4CHO$	**5**	2	86
4	3,4,5$(MeO)_3C_6H_2Br$	**6**	24	85
5	4-MeC_6H_4I	**7**	14	89
6	4-IC_6H_4COMe	**8**	2	80
7	2-Br-3-$OMOMC_6H_3$-CHO	**9**	24	68[c]

[a] Reactions were carried out at 80 °C in DMSO using bis(pinacolato)diboron (1.1 equiv.), aryl halide (1.0 equiv.), [$PdCl_2$(dppf)] (3 mol-%) and KOAc (3 equiv.). [b] Isolated product yields. [c] The reaction was carried out in DMF.

We prepared a series of arylboronic acids by the reaction of arylmagnesium bromides with trimethyl borate. The results obtained by using this simple method are summarized in Scheme 4.



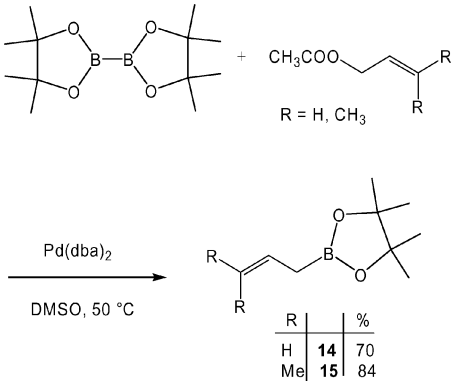
R		%
2-Me	**10**	63
4-OMe	**11**	71
2-OMe	**12**	45
3,4,5-(OMe)$_3$	**13**	65

Scheme 4. Synthesis of arylboronic acids.

Preparation of Pinacol Allyl- and Prenylboronates

Allylboron compounds are valuable reagents in organic synthesis. Their diastereoselective addition to carbon–oxygen and carbon–nitrogen double bonds provides homoallylic alcohols and amines via a chair-like six-membered cyclic transition state.[9] Allylboron reagents are now accessible by various methods, including the transmetallation of allyllithiums or -magnesiums with boron,[10] the coupling of 1-alkenyl halides with borylmethylzinc reagents,[11] the reaction of halomethylboronates with vinyllithiums,[12] the monohydroboration of 1,2- or 1,3-dienes[13] and the one-carbon homologation of L-alkenylboronates.[14]

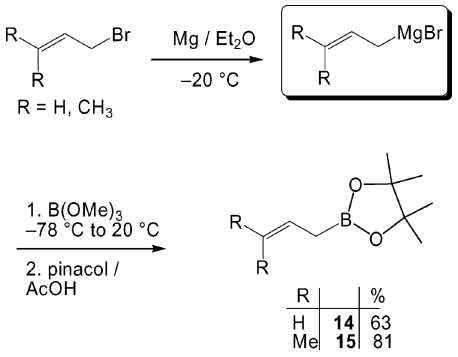
We were able to efficiently synthesize allylboronates stereoselectively by the reaction of bis(pinacolato)diboron and allyl acetates at 50 °C in DMSO in the presence of [Pd(dba)$_2$] (Scheme 5).[15] This reaction proceeded smoothly under neutral conditions. Allyl and prenyl acetates provided the corresponding boronic esters in very good yields. All attempts at the borylation of 3-methyl-2-butenyl acetate were unsuccessful, however, the corresponding tertiary allyl acetate can be used for the same purpose. Note that allylboronic ester **14** is commercially available.



R		%
H	**14**	70
Me	**15**	84

Scheme 5. Synthesis of pinacol allyl- and prenylboronates using bis(pinacolato)diboron.

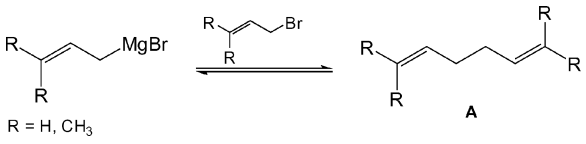
We also synthesized allylboronates by using Grignard reagents and trimethyl borate (Scheme 6). The allylmagnesium bromides were prepared by direct reaction between the metal and the allyl or prenyl bromide. Diethyl ether is the solvent most commonly used in this preparation. The main problem in this reaction is to minimize the coupling of the Grignard reagent with unused halide.[16]



R		%
H	**14**	63
Me	**15**	81

Scheme 6. Synthesis of pinacol allyl- and prenylboronates using Grignard reagents and trimethyl borate.

Different studies have indicated that this coupling can be minimized by increasing the time of addition of the bromide, increasing the ratio of solvent/bromide and by using 20–30 mesh magnesium turnings prepared just prior to use.[17] We found that working at a low temperature (–20 °C) reduces the amount of homocoupling product **A** (Scheme 7), that is, the equilibrium lies on the left side of the equation.

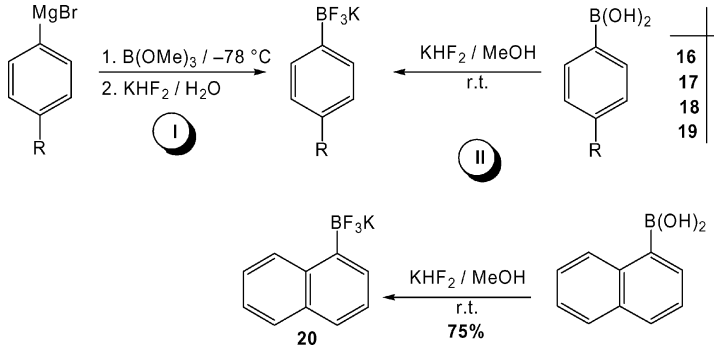


Scheme 7. Homocoupling of allyl and prenyl Grignard reagents.

Preparation of Potassium Aryltrifluoroborates

Vedejs et al. have reported the easy preparation of potassium aryltrifluoroborates from the corresponding boronic acids; such species are very stable, water resistant and easily isolated.[18a] We prepared a series of aryltrifluoroborates from arylboronic acids with aqueous KHF_2 at room temperature and also by the addition of arylmagnesium bromide to trimethyl borate followed by the in situ treatment of the resulting boronic ester with KHF_2 (Scheme 8).

As shown in Scheme 8, both methods lead to the corresponding organotrifluoroborates in similar yields. These salts are monomeric crystalline solids, which are readily isolated and indefinitely stable in air. Potassium organotrifluoroborates have been used in palladium-catalysed cross-coupling reactions. Thus, potassium aryl- and 1-alkenyltrifluoroborates couple with arenediazonium tetrafluoroborates and diaryliodonium salts.[18b–18d]



	R	Yield I	Yield II
16	H	82%	85%
17	OMe	81%	85%
18	Ph	–	84%
19	*t*Bu	65%	70%

Scheme 8. Synthesis of aryltrifluoroborates.

Suzuki–Miyaura Cross-Coupling Reactions

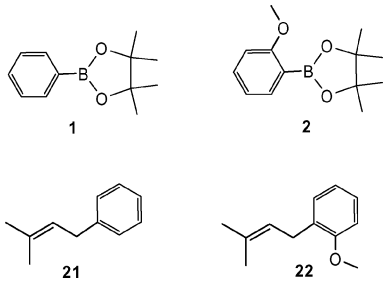
Although the Suzuki cross-coupling reaction is one of the most useful methods to have been developed for the synthesis of carbon skeletons, there are still improvements that could be made to render it even more effective. Considerable effort has been made to develop metal/ligand catalytic systems that facilitate the cross-coupling and expand its scope.[19] The Suzuki method was initially used for $C(sp^2)$–$C(sp^2)$ coupling[20] and later it was extended to accommodate carbon atoms in other hybridizations, for example, sp^3.[21] A recent major improvement of the Suzuki cross-coupling reaction is the introduction of phosphane-free catalytic systems.[22]

To study the insertion of prenyl and allyl side-chains into aromatic systems by aryl–allyl coupling, we carried out the reactions under different conditions. Thus, we investigated the prenylation of several arylboronic esters with prenyl bromide in the presence of palladium catalysts such as $[PdCl_2(dppf)]$, $[PdCl_2(PPh_3)_2]$ and $[Pd_2(dba)_3]$. The results are summarized in Table 3.

When arylboronic esters **1** and **2** (entries 1 and 5, respectively) activated with *s*BuLi in THF at –78 °C in the presence of $[PdCl_2(dppf)]$ as catalyst were allowed to react with prenyl bromide, prenylated products were obtained in moderate yields. On the other hand, when the reaction between arylboronic ester **1** and prenyl bromide was carried out in the presence of THF/2 M K_2CO_3 (aq.) and $[PdCl_2(PPh_3)_2]$, no cross-coupling product was obtained and the starting substrates were recovered (entry 2). As shown in entry 3 (Table 3), cross-coupling product **21** can be prepared in good yield in toluene solution by using $[Pd_2(dba)_3]$ as a phosphane-free catalyst in the presence of suspended potassium carbonate. The reaction between arylboronic ester **1** and prenyl bromide carried out in 1,4-dioxane in the presence of $[PdCl_2(dppf)]$ and K_3PO_4 led to product **21** in low yield (entry 4).

We carried out the allylation and prenylation of different aryl halides using allyl and prenylboronic esters in the presence of various palladium catalysts. Thus, the reaction of activated allyl- and prenylboronic esters (*s*BuLi/THF at –78 °C) with aryl iodides in the presence of $[PdCl_2(dppf)]$ and KOAc led to the corresponding allylated and prenylated products in moderate yields (Table 4, entries 1 and 8).

Table 3. Prenylation of arylboronic esters with prenyl bromide.



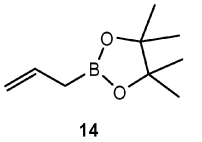
Entry	Boronic ester	Method[a]	Time [h]	% Yield[b]
1	**1**	A	48	51
2	**1**	B	48	–[c]
3	**1**	C	24	56
4	**1**	D	48	35[c]
5	**2**	A	24	60
6	**2**	C	24	58[d]

[a] Method A: reactions were carried out at 80 °C in THF using 1.1 equiv. of activated boronic ester [*s*BuLi (1 equiv.), THF, at –78 °C], prenyl bromide (1.0 equiv.), $[PdCl_2(dppf)]$ (5 mol-%) and KOAc (3 equiv.). Method B: the reaction was carried out at 80 °C in THF/2M K_2CO_3 (aq.) (4:1, v/v) using boronic ester (1.5 equiv.), prenyl bromide (1.0 equiv.) and $[PdCl_2(PPh_3)_2]$ (5 mol-%). Method C: reactions were carried out at 110 °C in toluene using boronic ester (1.5 equiv.), prenyl bromide (1 equiv.), $[Pd_2(dba)_3]$ (7 mol-%) and K_2CO_3 (9 equiv.). Method D: the reaction was carried out in 1,4-dioxane using boronic ester (1.2 equiv.), prenyl bromide (1.0 equiv.), $[PdCl_2(dppf)]$ (3 mol-%), dppf (3 mol-%) and K_3PO_4 (3 equiv.). [b] Isolated product yields unless otherwise stated. [c] Boronic ester was recovered in this case. [d] GC yield.

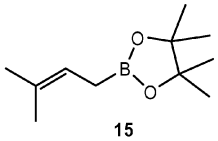
The reactions between allyl- and prenylboronic esters and various aryl halides (entries 2–4, 9 and 10) in the presence of $[PdCl_2(PPh_3)_2]$ [THF/2 M K_2CO_3 (aq.)] gave the corresponding allylated and prenylated compounds in good-to-moderate yields. On the other hand, when allyl- and prenylboronic esters were treated with aryl halides in the presence of $[Pd(PPh_3)_4]$ and CsF in THF, the cross-coupled products were obtained in good-to-very-good-yields (entries 5–7 and 11). The presence of CsF[5a] appears to be crucial for the success of the coupling reaction.[5b]

We studied the scope of these Suzuki–Miyaura cross-couplings with more complex structures (Scheme 9). Several reaction conditions were explored and the best results for

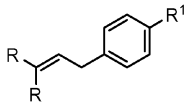
Table 4. Palladium-catalysed cross-coupling of allyl- and prenylboronates with haloarenes.



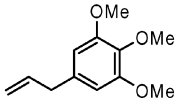
14



15



	R	R	R^1
23	H	H	H
24	H	H	Me
25	H	H	Me-C=O
26	H	H	OMe
28	Me	Me	OMe



27

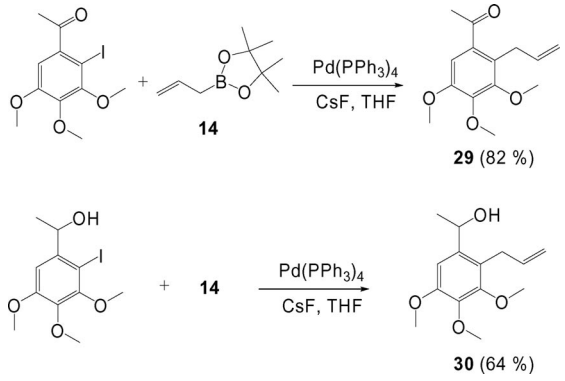
Entry	Boronate	Aryl halide	Method[a] (time [h])	Product (% yield)[b]
1	**14**	Ph-I	A (24)	**23** (40)
2	**14**	Ph-I	B (48)	**21** (47)
3	**14**	4-MeC_6H_4I	B (48)	**24** (35)
4	**14**	4-IC_6H_4COPh	B (48)	**25** (90)[c]
5	**14**	4-I-C_6H_4COPh	C (24)	**25** (89)[c]
6	**14**	4-$MeOC_6H_4I$	C (24)	**26** (45)
7	**14**	3,4,5-$(MeO)_3C_6H_2Br$	C (24)	**27** (75)
8	**15**	PhI	A (24)	**21** (41)
9	**15**	PhI	B (48)	**21** (43)
10	**15**	2-$MeOC_6H_4I$	B (48)	**22** (49)[c]
11	**15**	4-$MeOC_6H_4I$	C (24)	**28** (60)[c]

[a] Method A: reactions were carried out at 80 °C in THF using 1.1 equiv. of activated boronic ester [*s*BuLi (1 equiv.), THF at –78 °C], aryl halide (1 equiv.), [$PdCl_2$(dppf)] (3 mol-%) and KOAc (3 equiv.). Method B: reactions were carried out at 80 °C in THF/2 M K_2CO_3 (aq.) (4:1, v/v) using boronic ester (1.5 equiv.), aryl halide (1.0 equiv.), [$PdCl_2(PPh_3)_2$] (5 mol-%). Method C: reactions were carried out at 85 °C in THF with allylboronic esters (1.5 equiv.), aryl halide (1 equiv.), [$Pd(PPh_3)_4$] (7 mol-%) and CsF (4 equiv.). [b] Isolated product yields unless otherwise stated. [c] GC yields.

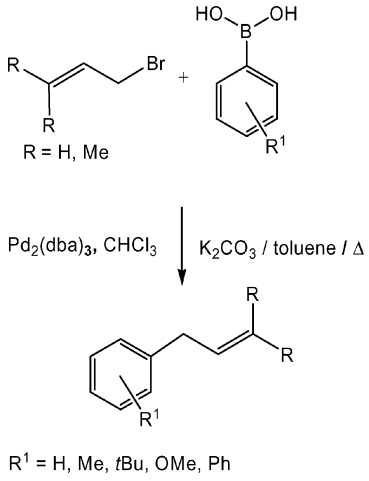
the allylations were obtained by using allylboronic ester **14** in the presence of [$Pd(PPh_3)_4$] and CsF. As shown in Scheme 9, this reaction is tolerated by various functional groups, such as OMe, COMe and OH, and sterically hindered aromatic halides, leading to the cross-coupled products in very good yields.

We have also studied the Suzuki–Miyaura cross-coupling reactions of arylboronic acids with allyl and prenyl bromides. The reactions catalysed by [$Pd_2(dba)_3$] were carried out in toluene in the presence of suspended potassium carbonate and gave the coupling products in very good yields (Scheme 10). The work-up was easy and involved filtration and evaporation. Additional treatment with hydrogen peroxide allowed elimination of traces of the arylboronic acids introduced in excess.[23] The results obtained are summarized in Table 5. The progress of the reactions was followed by GC–MS and TLC. The products were isolated by column chromatography on silica gel.

Phenylboronic acid (Table 5, entries 1 and 2), 4-biphenylboronic acid (entries 3 and 4) and 1- and 2-naphthylboronics acids (entries 13–16) are commercially available. On the other hand, 4-methoxyphenylboronic acid (entries 5 and 6), 2-methylphenylboronic acid (entries 7 and 8), 4-*tert*-butylphenylboronic acid (entries 9 and 10) and 3,4,5-trimethoxyphenylboronic acid (entries 11 and 12) were prepared from the reaction of the corresponding aryl Grignard reagents with trimethyl borate (see the Exptl. Sect.).



Scheme 9. Cross-coupling reactions between pinacol allylboronate (**14**) and some complex haloarenes.



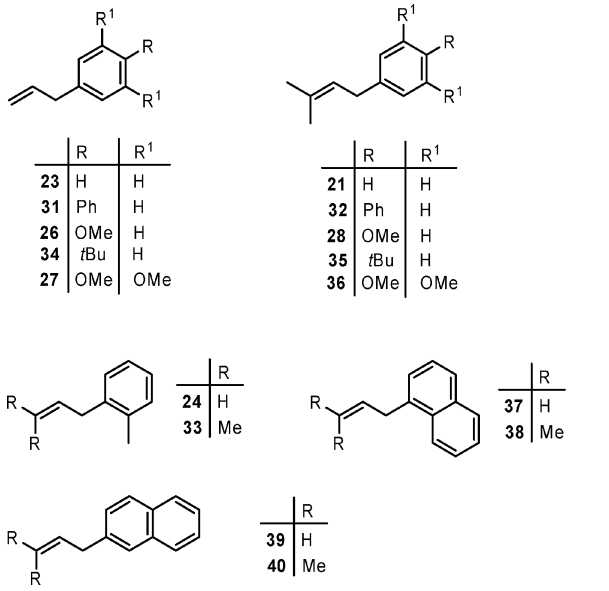
Scheme 10. Cross-coupling reactions between arylboronic acids and allyl and prenyl bromides.

We also carried out a study of the behaviour of aryltrifluoroborates in Suzuki–Miyaura cross-coupling reactions (Scheme 11). Of the catalytic systems examined, the best results were obtained by using 5 mol-% $Pd(OAc)_2$ in 1,4-dioxane at 100 °C under argon.

To test the efficiency and scope of the method, we applied this catalytic system to the reaction of allyl and prenyl halides. In all cases the cross-coupled products were obtained in very good yields. The results are summarized in Table 6.

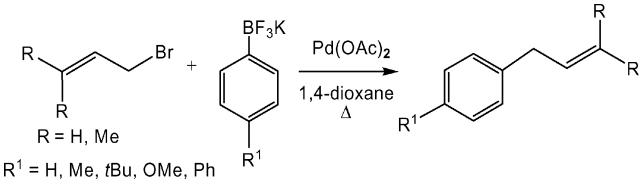
By using this synthetic strategy it was possible to increase the nucleophilic characteristics of the organoboron reagents by making the latter more reactive than the corresponding organoboronic acids, thus leading to shorter reaction times (6–12 h). Owing to the increase in reactivity it is not necessary to use any base or special ligand. Note that when we

Table 5. Palladium-catalysed cross-coupling reactions between arylboronic acids and allyl and prenyl bromides.[a]



Entry	Arylboronic acid	Alkenyl halide	Product	% Yield[b]
1	phenylboronic	Allyl Br	**23**	91
2	phenylboronic	Prenyl Br	**21**	89
3	4-biphenylboronic	Allyl Br	**31**	95
4	4-biphenylboronic	Prenyl Br	**32**	82
5	**10**	Allyl Br	**24**	88
6	**10**	Prenyl Br	**33**	90
7	**11**	Allyl Br	**26**	92
8	**11**	Prenyl Br	**28**	87
9	4-*tert*-butylphenylboronic	Allyl Br	**34**	84
10	4-*tert*-butylphenylboronic	Prenyl Br	**35**	81
11	**13**	Allyl Br	**27**	89
12	**13**	Prenyl Br	**36**	79
13	1-naphthylboronic	Allyl Br	**37**	85
14	1-naphthylboronic	Prenyl Br	**38**	83
15	2-naphthylboronic	Allyl Br	**39**	91
16	2-naphthylboronic	Prenyl Br	**40**	80

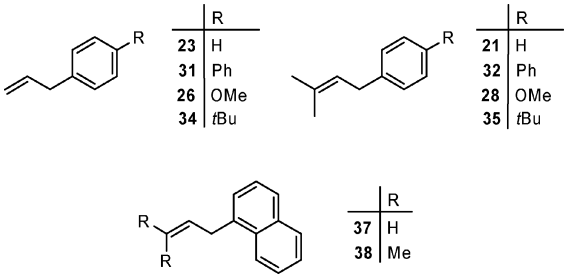
[a] The mixtures of boronic acid (1.5 equiv.), allyl or prenyl bromides (1 equiv.), $[Pd_2(dba)_3]$ (7 mol-%) and K_2CO_3 (9 equiv.) in toluene were heated at 110 °C for 15 h in the case of the allylations and for 17 h in the case of the prenylations. [b] Yields of isolated products.



Scheme 11. Cross-coupling reaction between potassium aryltrifluoroborate and allyl and prenyl bromides.

carried out these reactions at room temperature, no cross-coupled products were obtained and the starting material was recovered. Another important feature of this method is the use of $Pd(OAc)_2$ instead of other more unstable complex palladium catalysts.

Table 6. Palladium-catalysed cross-coupling reactions of potassium aryltrifluoroborates and allyl and prenyl bromides.[a]



Entry	Potassium aryltrifluoroborate	Alkenyl halide	Product	% Yield[b]
1	**16**	Allyl Br	**23**	96[c]
2	**16**	Prenyl Br	**21**	95[c]
3	**17**	Allyl Br	**26**	85
4	**17**	Prenyl Br	**28**	87
5	**18**	Allyl Br	**31**	72
6	**18**	Prenyl Br	**32**	65
7	**19**	Allyl Br	**34**	84
8	**19**	Prenyl Br	**35**	71
9	**20**	Allyl Br	**37**	85
10	**20**	Prenyl Br	**38**	83[c]

[a] The mixtures of potassium aryltrifluoroborates (1.2 equiv.), allyl or prenyl bromides (1 equiv.) and $Pd(OAc)_2$ (5 mol-%) in 1,4-dioxane were heated at 100 °C for 6 h in the case of the allylations and for 12 h in the case of the prenylations. [b] Isolated product yields unless otherwise stated. [c] Yields determined by GC.

Conclusions

We have studied several methods for carrying out Suzuki–Miyaura cross-coupling reactions and, in particular, the nature of the organoboron coupling partners. From these studies, it is possible to conclude that apparently the more advantageous method is the one that employs aryltrifluoroborates. The main advantages of this protocol are 1) it is not necessary to use any base or special ligand, 2) no secondary reaction products like reduction or homocoupling products are formed, 3) the use of the palladium catalyst $Pd(OAc)_2$, which is more stable than the normally used complex palladium catalysts and 4) the easy preparation and handling of reagents.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded with Bruker 250 and 300 instruments and are referenced to the non-deuteriated impurities of the used solvents ($CDCl_3$, CD_3OD, $[D_6]DMSO$) as the internal standard. IR spectra were recorded with a Perkin–Elmer Paragon 1000 FT-IR spectrometer using the ATR technique. Gas chromatography (GC) and low-resolution mass spectra (EI, 70 eV) were recorded with an Agilent HP 6890 apparatus with a flame-ionization detector (FID) and mass detector (MSD) 5937 N. High-resolution mass spectra (HRMS) were recorded with a Finnigan MAT 900S spectrometer in EI or ESI mode. Analytical thin-layer chromatography (TLC) was performed on silica-coated alumina

plates. Flash chromatography was performed on silica gel 60 (230–400 mesh). Melting points were determined in open capillary tubes with a Büchi melting point apparatus model B-545 and are uncorrected. Reagents were analytical reagent grade and were used without further purification unless otherwise noted. THF and toluene were freshly distilled from sodium benzophenone ketyl, and dichloromethane was distilled from CaH_2. All reactions with organometallic reagents were carried out under dry argon in oven-dried glassware using Schlenk techniques. Solvents and solutions were added by syringe through rubber septa.

Synthesis of Pinacol Arylboronates Using Grignard Reagents: All the reactions were carried out by the same procedure. One experiment is described in detail to illustrate the method used.

Magnesium turnings (0.098 g, 4 mmol) and a small crystal of iodine were introduced into a three-necked flask under argon and then a solution of 5-bromo-1,2,3-trimethoxybenzene (1.0 g, 4 mmol) in dry THF (5 mL) was slowly added. After the addition was complete, the reaction mixture was heated at reflux for 40 min. The flask was cooled to –78 °C and a solution of trimethyl borate (0.41 g, 4 mmol) in dry THF (12 mL) was added and the mixture was allowed to warm to 25 °C and was stirred overnight. Then a solution of pinacol (0.47 g, 4 mmol) in dry THF (3 mL) was added followed after 15 min by glacial acetic acid (1.5 mL). The mixture was kept at room temperature for 4 h and then was decomposed by the addition of an aqueous saturated solution of NH_4Cl. The organic layer was separated and the aqueous layer extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine and dried with $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel; pinacol 3,4,5-trimethoxyphenylboronate (**6**; 0.94 g, 3.2 mmol, 80%) was eluted with ethyl acetate/*n*-hexane (2:98) to give a white solid; m.p. 105–107 °C. ^{1}H NMR ($CDCl_3$): δ = 1.35 (s, 12 H), 3.89 (s, 3 H), 3.92 (s, 6 H), 7.05 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.73, 56.02, 60.65, 83.75, 111.18, 141.02, 152.77 ppm. MS: (EI, 70 eV): *m*/*z* (%) = 294 (100) $[M]^+$, 279 (33), 251 (8), 209 (10), 194 (35), 179 (13), 151 (8), 136 (12), 59 (6), 41 (9). HRMS (EI): calcd. for $C_{15}H_{23}BO_5$ 294.1639; found 294.1648.

4,4,5,5-Tetramethyl-2-(3-methylbut-2-enyl)-1,3,2-dioxaborolane (15): ^{1}H NMR ($CDCl_3$): δ = 1.23 (s, 12 H), 1.56 (s, 3 H), 1.58 (d, *J* = 7.0 Hz, 2 H), 1.65 (d, *J* = 1.5 Hz, 3 H), 5.22 (tq, *J* = 7.0, 1.5 Hz, 1 H) ppm. ^{13}C NMR: ($CDCl_3$): δ = 17.64, 24.75, 25.71, 83.11, 118.56, 131.42 ppm. MS (EI, 70 eV): *m*/*z* (%) = 196 (79) $[M]^+$, 181 (38), 139 (93), 123 (19), 101 (63), 84 (100), 69 (89), 41 (49). HRMS (EI): calcd. for $C_{11}H_{21}BO_2$ 196.1635; found 196.1640.

Palladium-Catalysed Cross-Coupling Reaction of Bis(pinacolato)diboron with Haloarenes: All the reactions were carried out by the same procedure. One experiment is described in detail to illustrate the methods used. A Schlenk flask was charged with $[PdCl_2(dppf)]$ (0.020 g, 3 mol-%), KOAc (0.20 g, 2.04 mmol) and bis(pinacolato) diboron (0.20 g, 0.79 mmol) under argon. Dry DMSO (4 mL) and 2-bromo-3-(methoxymethoxy)benzaldehyde (0.17 g, 0.71 mmol) were then added. After being stirred at 80 °C for an appropriate period of time (monitoring by GC), the product was extracted with benzene, washed with water and dried with anhydrous $MgSO_4$. The solvent was eliminated under reduced pressure. The product was purified by column chromatography on silica gel (EtOAc/cyclohexane, 2:98), to afford boronate **9** (0.14 g, 0.48 mmol, 68%) as a yellowish liquid. ^{1}H NMR ($CDCl_3$): δ = 1.46 (s, 12 H), 3.48 (s, 3 H), 5.20 (s, 2 H), 7.28–7.46 (m, 3 H), 9.93 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.76, 56.03, 75.01, 84.18, 94.11, 119.54, 125.70, 130.74, 192.91 ppm. MS (EI, 70 eV): *m*/*z* (%) = 292 (2) $[M]^+$, 277 (10), 247 (35), 234, (15), 205 (68), 189 (25), 176 (51), 162 (42), 146 (67), 133 (21), 120 (20), 102 (19), 83 (21), 77 (15), 57 (29), 45 (100). HRMS (EI): calcd. for $C_{15}H_{21}BO_5$ 292.1482; found 292.1490.

Palladium-Catalysed Cross-Coupling Reaction of Arylboronic Esters with Allyl and Prenyl Bromides: All the reactions were carried out by the same procedure. One experiment is described in detail to illustrate the methods used. A solution of *s*BuLi (0.9 mL, 0.98 mmol, 1.1 M in *n*-hexane) was added dropwise to a solution of boronate **1** (0.20 g, 0.98 mmol) in dry THF (14 mL) with the internal temperature being kept at –78 °C. The mixture was stirred under argon and warmed to room temperature. Then $[PdCl_2(dppf)]$ (0.040 g, 5 mol-%) and KOAc (0.29 g, 2.94 mmol) were added, the mixture was stirred for 2 min and prenyl bromide (0.11 mL, 0.94 mmol) was added. The mixture was then heated at reflux overnight under argon. The progress of the reaction was monitored by GC. Column chromatography on silica gel (EtOAc/cyclohexane, 2:98) gave prenylbenzene (**21**) (0.058 g, 0.40 mmol, 41%) as a colourless liquid. ^{1}H NMR ($CDCl_3$): δ = 1.72 (s, 3 H), 1.76 (s, 3 H), 2.97 (d, *J* = 6.9 Hz, 2 H), 5.37 (t, *J* = 6.9 Hz, 1 H), 6.92–7.08 (m, 5 H) ppm. ^{13}C NMR: ($CDCl_3$): δ = 17.76, 25.55, 33.52, 120.86, 126.10, 127.80, 128.65, 131.10, 140.80 ppm. MS (EI, 70 eV): *m*/*z* (%) = 146 (55) $[M]^+$, 131 (100), 116 (14), 103 (7), 91 (48), 77 (11), 65 (11), 51 (7), 39 (9). HRMS (EI): calcd. for $C_{11}H_{14}$ 146.1096; found 146.1085.

2-Prenylanisole (22): A mixture of $[Pd_2(dba)_3]$ (0.041 g, 7 mol-%), prenyl bromide (0.097 g, 0.65 mmol), K_2CO_3 (1.06 g, 7.69 mmol) and boronate **2** (0.20 g, 0.85 mmol) in dry toluene (14 mL) was heated at refluxed under argon for 24 h with monitoring by GC. Water (20 mL) was added and the mixture was extracted three times with Et_2O. The combined organic layers were washed with water and brine and dried with $MgSO_4$. The solvent was eliminated under reduced pressure. The product was purified by column chromatography on silica gel (EtOAc/cyclohexane, 5:95), to afford **22** (0.072 g, 0.41 mmol, 48%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.74 (s, 3 H), 1.77 (s, 3 H), 3.12 (d, *J* = 6.8 Hz, 2 H), 3.75 (s, 3 H), 5.19 (t, *J* = 6.8 Hz, 1 H), 6.81–7.01 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.69, 25.57, 25.82, 55.94, 112.25, 121.59, 122.86, 127.85, 128.90, 129.86, 131.15, 156.66 ppm. MS (EI, 70 eV): *m*/*z* (%) = 176 (81) $[M]^+$, 161 (100), 145 (16), 133 (16), 121 (32), 107 (13), 91 (45), 77 (13), 65 (12), 51 (10), 39 (11). HRMS (EI): calcd. for $C_{12}H_{16}O$ 176.1201 found 176.1210.

1-(2-Allyl-3,4,5-trimethoxyphenyl)ethanone (29): ^{1}H NMR ($CDCl_3$): δ = 2.49 (s, 3 H), 3.55 (d, *J* = 6.7 Hz, 2 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 3.88 (s, 3 H), 4.85–4.95 (m, 2 H), 5.92 (ddt, *J* = 16.8, 10.2, 6.7 Hz, 1 H), 6.89 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.69, 30.67, 56.10, 59.75, 60.70, 106.57, 114.31, 131.63, 136.94, 146.56, 149.95, 150.77, 201.18 ppm. MS (EI, 70 eV): *m*/*z* (%) = 250 (24) $[M]^+$, 235 (100), 220 (18), 204 (39), 191 (12), 176 (11), 161 (10), 147 (8), 133 (8), 115 (9), 103 (8), 91 (10), 77 (9), 65 (5), 43 (45). HRMS (EI): calcd. for $C_{14}H_{18}O_4$ 250.1205 found 250.1211.

1-(2-Allyl-3,4,5-trimethoxyphenyl)ethanol (30): ^{1}H NMR ($CDCl_3$): δ = 1.55 (d, 3 H), 3.37 (d, *J* = 6.7 Hz, 2 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 4.96–5.05 (m, 3 H), 5.85 (ddt, *J* = 16.8 Hz, 10.2, 6.7, 1 H), 6.45 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.65, 29.53, 59.75, 59.93, 60.61, 69.80, 109.29, 114.29, 125.67, 136.95, 137.19, 141.42, 151.63, 151.84 ppm. MS (EI, 70 eV): *m*/*z* (%) = 252 (69) $[M]^+$, 237 (45), 234 (55), 219 (100), 209 (23), 204 (24), 188 (70), 176 (21), 161 (24), 147 (21), 131 (25), 115 (21), 103 (20), 91 (38), 77 (26), 65 (17), 53 (9), 43 (55). HRMS (EI): calcd. for $C_{14}H_{20}O_4$ 252.1362; found 252.1354.

Palladium-Catalysed Cross-Coupling Reactions of Arylboronic Acids with Allyl and Prenyl Bromides: All the reactions were carried out by the same procedure. One experiment is described in detail to illustrate the methods used. $[Pd_2(dba)_3]$ (0.054 g, 7 mol-%), allyl bromide (0.090 g, 0.75 mmol), K_2CO_3 (0.93 g, 9 equiv.), 4-biphenylboronic acid (0.20 g, 1 mmol) and dry toluene (14 mL) were placed in a two-necked round-bottom flask under argon. The reaction mixture was heated at reflux for 15 h, monitoring by GC. Then hydrogen peroxide (10 mL) was added, the mixture was stirred at room temperature for 30 min and the toluene layer was separated. The aqueous layer was extracted three times with Et_2O. The combined organic extracts were washed with brine and dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (EtOAc/cyclohexane, 4:96) to give 4-allylbiphenyl (**31**) (0.138 g, 0.71 mmol, 95%) as a brown oil. ^{1}H NMR ($CDCl_3$): δ = 3.28 (d, J = 6.8 Hz, 2 H), 4.96–4.99 (m, 1 H), 5.95 (ddt, J = 16.8, 10.2, 6.8 Hz, 1 H), 7.09–7.46 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 39.22, 115.75, 126.81, 127.29, 127.48, 128.25, 128.88, 136.15, 137.65, 139.96, 145.60 ppm. MS (EI, 70 eV): *m/z* (%) = 194 (100) $[M]^+$, 178 (34), 165 (36), 152 (20), 128 (5), 115 (19), 91 (5), 78 (11), 63 (5), 51 (6), 39 (14). HRMS (EI): calcd. for $C_{15}H_{14}$ 194.1096; found 194.1087.

4-Prenylbiphenyl (32): ^{1}H NMR ($CDCl_3$): δ = 1.74 (s, 3 H), 1.76 (s, 3 H), 3.05 (d, J = 6.7 Hz, 2 H), 5.25 (t, J = 6.7 Hz, 1 H), 7.06–7.48 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.76, 25.65, 33.44, 120.68, 126.81, 127.02, 127.29, 128.88, 131.10, 136.17, 139.96, 141.95 ppm. MS (EI, 70 eV): *m/z* (%) = 222 (100) $[M]^+$, 207 (44), 192 (17), 179 (39), 165 (34), 152 (17), 129 (8), 115 (7), 91 (5), 78 (7), 63 (5), 56 (4), 41 (8). HRMS (EI): calcd. for $C_{17}H_{18}$ 222.1409; found 222.1415.

Palladium-Catalysed Cross-Coupling Reactions of Potassium Aryltrifluoroborates and Allyl and Prenyl Bromides: All the reactions were carried out by the same procedure. One experiment is described in detail to illustrate the methods used. A Schlenk flask was charged with $Pd(OAc)_2$ (0.010 g, 5 mol-%), allyl bromide (0.13 g, 1.08 mmol), potassium naphthalenetrifluoroborate (0.26 g, 1.29 mmol) and dry 1,4-dioxane (3 mL). The reaction mixture was heated at 100 °C for 6 h and the progress of the reaction was monitored by GC. The crude product was diluted with water (10 mL) and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine and dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (*n*-hexane), to afford 1-allylnaphthalene (**37**; 0.15 g, 0.92 mmol, 85%) as an oily liquid. ^{1}H NMR ($CDCl_3$): δ = 3.81 (d, J = 6.3 Hz, 2 H), 5.05–5.10 (m, 2 H), 6.16–6.60 (m, 1 H), 7.31 (d, J = 6.9 Hz, 1 H), 7.37 (d, J = 7.2 Hz, 1 H), 7.42–7.51 (m, 2 H), 7.70 (d, J = 6.9 Hz, 1 H), 7.83 (t, J = 7.7 Hz, 1 H), 8.02 (d, J = 8.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 35.45, 114.38, 122.19, 123.68, 123.77, 123.96, 124.44, 125.13, 126.86, 130.16, 132.01, 133.17, 135.15 ppm. MS (EI, 70 eV): *m/z* (%) = 168 (100) $[M]^+$, 167 (95), 153 (90), 141 (32), 128 (15), 115 (37), 102 (8), 83 (10), 63 (10), 51 (9), 39 (12). HRMS (EI): calcd. for $C_{13}H_{12}$ 168.0939; found 168.0931.

Acknowledgments

This work was supported by Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) (PIP 6095), Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT) (BID 1728/OC-AR PICT N°2467), the Universidad Nacional del Sur (Bahía Blanca, Argentina), the Deutsche Forschungsgemeinschaft (DFG), and the Fonds der Chemischen Industrie (Germany). A travel grant to J. C. P. from the Alexander von Humboldt Foundation and fellowships to D. C. G. and S. D. M. for short stays in Germany from Secretaria de Ciencia y Tecnica (SECyT) (Argentina) and Deutscher Akademischer Austauschdienst (DAAD) (Germany) are acknowledged.

[1] a) A. Suzuki, *The Suzuki Reaction with Arylboron Compounds in Arene Chemistry*, in: *Modern Arene Chemistry* (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**, p. 53; b) F. Diederich, P. J. Stang (Eds.), *Metal-catalyzed Cross-coupling Reactions*, Wiley-VCH, Weinheim, **1997**; c) J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, **1995**.

[2] a) A. Suzuki, *Acc. Chem. Res.* **1982**, *15*, 178; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

[3] a) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437; b) N. Miyaura, A. Suzuki, *J. Chem. Soc., Chem. Commun.* **1979**, 866.

[4] a) G. E. Keck, E. J. Enholm, J. B. Yates, *Tetrahedron* **1985**, *41*, 4079; b) V. Farina, *Pure Appl. Chem.* **1996**, *68*, 73; c) S. D. Goldberg, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2002**, *41*, 807.

[5] a) D. Bouyssi, V. Gerusz, G. Balme, *Eur. J. Org. Chem.* **2002**, 2445; b) S. Kotha, M. Behera, V. R. Shah, *Synlett* **2005**, *12*, 1877; c) S. W. Wright, D. L. Hageman, L. D. McClure, *J. Org. Chem.* **1994**, *59*, 6095.

[6] a) Y. Yamamoto, M. Takahashi, N. Miyaura, *Synlett* **2002**, 1473; b) M. Stefinovic, V. Snieckus, *J. Org. Chem.* **1998**, *63*, 2808; c) S. J. Miller, H. E. Blackwell, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, *118*, 9606; d) A. Okada, T. Ohshima, M. Shibasaki, *Tetrahedron Lett.* **2001**, *42*, 8023; see also ref.[4].

[7] W. Dohle, F. Kopp, G. Cahierz, P. Knochel, *Synlett* **2001**, *12*, 1901.

[8] T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508.

[9] a) M. Vaultier, B. Carboni, *Comprehensive Organometallic Chemistry II* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon Press, Oxford, **1995**, vol. 11, p. 191; b) W. R. Roush, *Comprehensive Organic Synthesis* (Ed.: B. M. Trost), Pergamon Press, Oxford, **1991**, vol. 2, p. 1.

[10] a) E. J. Corey, C.-M. Yu, S. S. Kim, *J. Am. Chem. Soc.* **1989**, *111*, 5495; b) P. G. M. Wuts, S. S. Bigelow, *J. Org. Chem.* **1982**, *47*, 2498; c) R. W. Hoffmann, B. Kemper, *Tetrahedron Lett.* **1982**, *23*, 845.

[11] a) T. Watanabe, N. Miyaura, A. Suzuki, *J. Organomet. Chem.* **1993**, *444*, C1; b) R. W. Hoffmann, T. Sander, A. Hense, *Liebigs Ann. Chem.* **1993**, 771.

[12] a) V. Nyzam, C. Belaud, J. Villieras, *Tetrahedron Lett.* **1993**, *34*, 6899; b) R. W. Hoffmann, G. Niel, *Liebigs Ann. Chem.* **1991**, 1195.

[13] a) K. K. Wang, C. Liu, Y. Gu, F. N. Burnett, P. D. Sattsangi, *J. Org. Chem.* **1991**, *56*, 1914; b) M. Satoh, Y. Nomoto, N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1989**, *30*, 3789.

[14] a) M. Sato, Y. Yamamoto, S. Hara, A. Suzuki, *Tetrahedron Lett.* **1993**, *34*, 7071; b) D. S. Matteson, D. Majumdar, *Organometallics* **1983**, *2*, 1529.

[15] T. Ishiyama, T. A. Ahiko, N. Miyaura, *Tetrahedron Lett.* **1996**, *37*, 6889.

[16] W. G. Young, A. N. Prater, S. Winstein, *J. Am. Chem. Soc.* **1933**, *55*, 4908.

[17] a) R. A. Benkeser, *Synthesis* **1971**, 347; b) J. E. Nordlander, W. G. Young, J. D. Roberts, *J. Am. Chem. Soc.* **1961**, *83*, 494.

[18] a) E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin, M. R. Schrimpf, *J. Org. Chem.* **1995**, 60; b) S. Darses, G. Michaud, J.-P. Genêt, *Eur. J. Org. Chem.* **1999**, 1875; c) S. Darses, G. Michaud, J.-P. Genêt, *Tetrahedron Lett.* **1998**, *39*, 5045; d) S. Darses, G. Michaud, J.-P. Genêt, J.-L. Brayer, J.-P. Demoute, *Tetrahedron Lett.* **1997**, *38*, 4393.

[19] a) J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9550; b) A. F. Littke, D. Chaoyang, G. C. Fu, *J. Am. Chem.*

Soc. **2000**, *122*, 4020; c) R. B. Bedford, C. S. J. Cazin, *Chem. Commun.* **2001**, 1540.
[20] N. Miyaura, T. Yanagi, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513.
[21] a) N. Miyaura, H. Suginome, A. Suzuki, *Tetrahedron Lett.* **1984**, *25*, 761; b) T. Ishiyama, S. Abe, N. Miyaura, A. Suzuki, *Chem. Lett.* **1992**, 691; c) T. Ohe, N. Miyaura, A. Suzuki, *J. Org. Chem.* **1993**, *58*,2201; d) T. Moriya, T. Furuuchi, N. Miyaura, A. Suzuki, *Tetrahedron* **1994**, *50*, 7961.
[22] T. I. Wallow, B. M. Novak, *J. Org. Chem.* **1994**, *59*, 5034.
[23] M. M. Manas, F. Pajuelo, R. Pleixats, *J. Org. Chem.* **1995**, *60*, 2396.

Received: March 4, 2009
Published Online: July 6, 2009

