Pd-Catalyzed Suzuki Cross-Coupling Reaction of Bromostilbene: Insights on the Nature of the Boron Species

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Sais e ésteres derivados de ácidos aril borônicos podem ser usados na reação de acoplamento Suzuki com (*E*)-bromoestilbeno usando uma mistura Pd(OAc)$_2$/PPh$_3$ como precursor catalítico. Enquanto que a adição de uma base como KOH é necessária para a reação de acoplamento com ácido borônico ou seu éster derivado do pinacol, o uso de um aril borato de sódio permite que a reação seja realizada na ausência de base. A comparação entre os diferentes compostos organoboro *via* reações competitivas e análise por espectrometria de massas com ionização por "electrospray" mostram que a base inicialmente reage com o ácido ou éster aril borônico para formar um aril borato que é a espécie envolvida na reação de transmetalação com o catalisador de paládio.

Arylboronate esters and arylborate salts can be used as partner for the Suzuki reaction of (*E*)-bromostilbene in the presence of Pd(OAc)$_2$/PPh$_3$ as catalyst precursor. While KOH is necessary for the coupling reaction with arylboronic acids and pinacol esters, aryl borate sodium salt can be used in a base-free protocol. The comparison between the three organoboron compounds using competitive experiments and electrospray ionization mass spectrometry analysis supports the proposition that the base initially reacts with the arylboronic acid or ester to form an arylborate species which undergoes the transmetallation process with the palladium catalyst.

Keywords: cross-coupling reactions, Suzuki reaction, palladium, ESI, organoboron species

Introduction

The palladium-catalyzed Suzuki cross-coupling reaction is one of the most efficient methods for the construction of C-C bonds and has found widespread use in organic synthesis.[1-3] The Suzuki reaction is also nowadays of great industrial significance since many products (drugs, materials, optical devices etc) commercialized or in the development phase have carbon-carbon bonds which can be assembled by catalytic cross-coupling reactions.[4] The use of boron compounds in the coupling reaction presents several advantages such as stability to heat, oxygen, and water, flexibility towards functional groups and commercial availability. We have recently applied the Suzuki reaction at room temperature for the synthesis of tri- and tetrasubstituted olefins in high yields and regioselectivities.[5] Arylboronic acids were used as boron partner, KOH as base and a mixture of Pd(OAc)$_2$/

PPh$_3$ as catalyst precursor. Herein we wish to report our first results in terms of the competitive experiments and electrospray ionization mass spectrometry applied to investigate the nature of the boron species involved in this catalytic cross-coupling reaction. In addition we would like to show that arylboronate esters and arylborate salts can also be used for the Suzuki cross-coupling reaction with (*E*)-bromostilbene in the presence of Pd(OAc)$_2$/PPh$_3$ as catalyst precursor.

Results and Discussion

First, we have compared the different sources of boron on the Pd-catalyzed coupling with (*E*)-bromostilbene (Table 1). We have used the optimized reaction conditions for the coupling of (*E*)-stilbene with phenylboronic acid that afford the coupling product in quantitative yield after one hour at room temperature (Table 1, entry 1).[5] In the absence of base only 1% of triphenylethylene was detected after 24 h (Table 1, entry 2). In general boronate esters
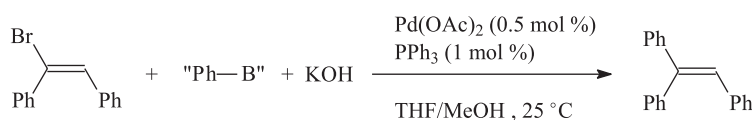
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are less reactive then the corresponding boronic acids.[6] Therefore, when using phenylboronic pinacol ester as the boron containing coupling partner, longer reaction time was necessary to achieve complete conversion to the coupling product (Table 2, entry 3), and no coupling product was observed in a base-free protocol (Table 2, entry 4). Potassium organotrifluoroborates have been used as an alternative to boronic acids and boronate esters,[7] and, more recently, aryl trihydroxyborate salts were isolated and employed in a base-free Suzuki cross-coupling reaction with aryl halides.[8] In order to investigate the role of the base we also used sodium trihydroxyphenylborate for the coupling with (*E*)-bromostilbene and in this case the coupling reaction occurs even in the absence of a base (Table 1, entry 6).

The reactivity of different arylboronic acids for the coupling with (*E*)-bromostilbene was evaluated by competitive experiments. Thus, the reaction of (*E*)-bromostilbene with the different boronic acids was monitored and the relative reactivity were determined at low conversion (*ca.*20%). A plot of the relative reactivity of substituted aryl boronic acids against the s constant shows that the relative reactivity is sensitive to the electronic effect of the substituents on the aryl boronic acids (Figure 1). Aryl boronic acids containing electron-donating groups in the para position are more reactive and the correlation yields a value of $\rho = -0.71$. The trend follows those obtained for the Pd-catalyzed Suzuki cross-coupling of arylboronic acids with vinyl bromide,[9] however the effect is less pronounced ($\rho =$

-0.71 for the (*E*)-bromostilbene against $\rho = -1.26$ for vinyl bromide). The Hammet correlation observed in our case can be explained by the enhancement of the nucleophilicity of the organic moiety when the electron-donating ability of the para-substituent increases. The mechanism of the transmetalation step is less understood then the one for oxidative addition and reductive elimination. Two processes have been proposed for the cross-coupling reaction of organoboron compounds in alkaline solution as summarized by Miyaura: *i*) base reacts with the organoboron reagent, forming a more reactive "ate" complex for arylation of Ar-Pd-X or *ii*) exchange between Ar-Pd-X and a base (R'O-) generating a alkoxo- or hydroxo-Pd(II) complex, that undergoes transmetalation with organoboronic acids without the aid of a base.[10] Since that, by increasing the nucleophilicity of the organic moiety both processes should be facilitated we can not distinguish which process is predominant only by competitive studies. However, kinetic studies were used to propose that the base binds to the boronic acid, forming $[ArB(OH)_3]^-$ species, with the latter becoming the reactive species.[11] Recently, theoretical studies strongly suggest that an organoborate $[ArB(OH)_3]^-$ is involved in the transmetalation step.[12-14] The fact that trihydroxy-arylborates can be applied for the base-free Suzuki reaction with aryl halides is a strong experimental evidence.[8] Our results for the different boron species in the presence and absence of base (see Table 1) also goes in the same direction and our next step was to identify

Table 1. Pd-catalyzed Suzuki cross-coupling reaction of (*E*)-bromostilbene with phenylboron compounds[a]

Entry	PhB	KOH/equiv.	time/h	Yield/(%)[b]
1	PhB(OH)$_2$	2	1	100
2	PhB(OH)$_2$	0	24	1
3	Ph—B (pinacol ester)	2	1	31
		2	24	100
4	Ph—B (pinacol ester)	0	24	0
5	[PhB(OH)$_3$]$^-$Na$^+$	2	24	100
6	[PhB(OH)$_3$]$^-$Na$^+$	0	24	86

[a]Reaction conditions: (*E*)-bromostilbene (0.25 mmol), organoboron (0.3 mmol), KOH when used (0.5 mmol), Pd(OAc)$_2$ (1.25 μmol), PPh$_3$ (2.5 μmol), MeOH (1.5 mL), THF (1.5 mL), 25 °C. [b]GC yields.

the boron species present during the coupling reaction.

Electrospray ionization mass spectrometry (ESI-MS) is a powerful tool in the identification of organometallic reaction intermediates and has been applied to the detection of intermediates in palladium-catalyzed cross coupling reactions.[15-22] However, these studies are essentially focused on the identification of palladium intermediates. Thus, we applied the ESI-MS in the negative mode to detect the boron species in the coupling reaction with (*E*)-bromostilbene.[23]

Solutions of the reaction mixture in methanol were monitored by high resolution ESI-MS-(-) (Table 2), which showed the presence of $[PhB(OCH_3)_3]^-$ and a potassium bound dimer $[PhB(OCH_3)_3]_2^- K^+$ (ratio 1:2 = 7:1). Similar dimers $\{[ArBF_3]_2^- K^+\}$ have been observed for the ESI-MS-(-) analysis of potassium aryltri-fluoroborate solutions.[21] Although these analyses

indicate the presence of borate species, it is unlikely to have a methylated borate species under the reaction conditions. In fact, it has been shown that dilution of the reaction mixture with methanol can produce methylated ions in the ESI experiments for the detection
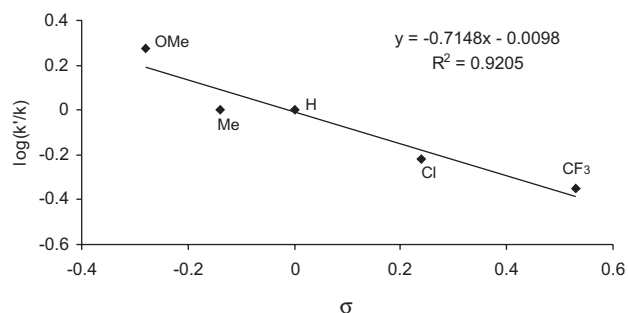

Figure 1. Effects of substituents on aryl boronic acids p-$XC_6H_4B(OH)_2$ (X = MeO, Me, H, Cl and CF_3).

Table 2. ESI-negative mode analysis of the Pd-catalyzed Suzuki cross-coupling reaction of (*E*)-bromostilbene with different organoboron compounds[a]

Organoboron	Species detected during the reaction		Species detected after complete conversion	

[a]Reaction conditions: (*E*)-bromostilbene (0.25 mmol), organoboron (0.3 mmol), KOH when used (0.5 mmol), Pd(OAc)$_2$ (1.25 µmol), PPh$_3$ (2.5 µmol), MeOH (1.5 mL), THF (1.5 mL), 25 °C.

of intermediates in the Pd-catalyzed oxidative self-coupling of arylboronic acids.[16] Similarly, when the sample was diluted with ethanol we obtained the corresponding triethoxyphenylborate anion. On the other hand, when the reaction was diluted in a (water/acetonitrile) mixture an anion with molecular formula $C_{12}H_{11}B_2O_3$ and the phenylboronate anion $[PhB(OH)O]^-$ were observed (ratio 3:4 = 9:1). ESI-MS-MS-(-) analysis of the anion with molecular formula $C_{12}H_{11}B_2O_3$ showed as only fragmentation phenyl-boronate anion $[PhB(OH)O]^-$ with elimination of neutral OBPh moiety from the molecular ion. We proposed the mixed borate-boronate-containing dimer structure (see Table 2). At the end of the reaction bromide, borate $[(CH_3O)_4B]^-$ and dimer $[(CH_3O)_4B]_2^-$ K^+ were observed. Next we examined the reaction coupling of (*E*)-bromostilbene with phenylboronic pinacol ester. It is important to note that under the optimized conditions (see Table 1) the cross-coupling reaction of (*E*)-bromostilbene with phenylboronic pinacol ester gave similar results to those obtained for the coupling reaction with phenylboronic acid. The ESI-MS-(-) experiments showed only one anionic species during the reaction, the borate $[(pinacol)BPhOH]^-$, and the borate $[(pinacol)_2B]^-$ with bromide anion at the end of the reaction. We also investigated, by ESI-MS-(-), the reaction of phenylboronic acid (or phenylboronic pinacol ester) with KOH in a MeOH/THF mixture. In both cases (phenylboronic acid or phenylboronic pinacol ester) the structures are the same as those observed during the cross-coupling reaction. Finally we investigated the coupling reaction with sodium trihydroxyphenylborate in the absence of KOH and the same species that those obtained with $PhB(OH)_2$ + KOH were observed. The only difference in this case is that the dimer observed $[PhB(OCH_3)_3]_2^-$ Na^+ has a sodium cation instead of potassium. These findings support the proposition that the base initially reacts with the arylboronic acid to form an arylborate species that undergoes the transmetallation process with the palladium catalyst. Under optimized conditions two equivalents of base are necessary and this can be rationalized by taking to account that a second equivalent is used to neutralize the boronic species formed in the transmetalation step giving tetra-hydroxyborate and bromide as included in the general accepted catalytic cycle (Scheme 1.)

In summary, we have shown that arylboronate esters and arylborate salts can also be used for the Suzuki reaction with (*E*)-bromostilbene in the presence of $Pd(OAc)_2/PPh_3$ as catalyst precursor. While KOH is necessary for the
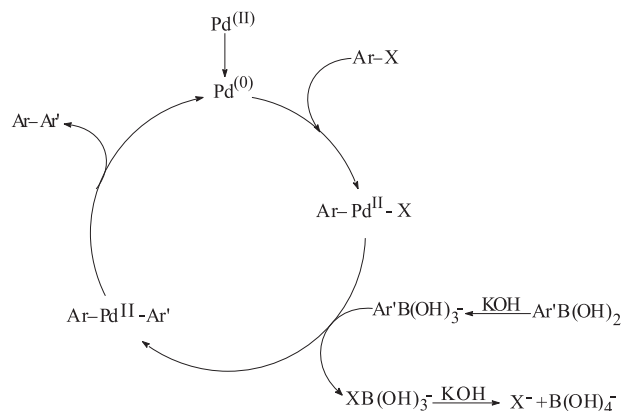
Scheme 1. Catalytic cycle for the Suzuki coupling of (*E*)-bromostilbene with arylboronic acids.

coupling reaction with arylboronic acids and pinacol esters, aryl borate sodium salt can be used in a base-free protocol. The comparison between the three organoboron compounds using competitive experiments and electro-spray ionization mass spectrometry analysis supports the proposition that the base initially reacts with the arylboronic acid to form arylborate species which undergoes the transmetallation process with the palladium catalyst. Further studies to determine catalytic inter-mediates and the mechanism are currently under investigation in our group.

Experimental

General experimental procedures

All reactions were carried out under argon atmosphere in oven dried resealable Schlenk tube. (*E*)-bromostilbene,[5] arylboronic acids,[24] pinacol phenylboronate ester and sodium trihydroxyphenylborate[8] were prepared according to the previously published procedure. Other chemical were purchased from commercial sources. Methanol and tetrahydrofuran were degassed and dried. Other chemicals were used without purification. NMR spectra were recorded on a Varian XL300 spectrometer. Infrared spectra were performed in a Shimadzu FTIR-8300 spectrometer. Mass spectra were obtained on a GC/MS Shimadzu QP-5050 (EI, 70 eV). Gas chromatography analyses were performed on a HP column DB-17 GC with a FID and 30 meter capillary column with a dimethylsiloxane stationary phase. ESI-MS-(-) experiment were performed on a Q-Tof (Micromass) mass spectrometer. The ESI-MS and ESI-MS-MS mass spectra were acquired using an ESI capillary voltage of 3 kV and a cone voltage of 10 V. The sample (10 µL aliquots of reaction mixture added to 0.5-1 mL of methanol or acetonitrile:water (1:1) giving boron concentration of 1-3

µmol L^{-1}) introduction was performed using a syringe pump set to 5 µL min^{-1}. [PhB(OCH$_3$)$_3$]$^-$, C$_9$H$_{14}$BO$_3$: 181.1049 (Calc. 181.1036). [PhB(OCH$_3$)$_3$]$_2^-$ K$^+$, C$_{18}$H$_{28}$B$_2$KO$_6$: 401.1635 (Calc. 401.1709). C$_{12}$H$_{11}$B$_2$O$_3$: 225.0884 (Calc. 225.0894). [PhB(OH)O]$^-$, C$_6$H$_6$BO$_2$: 121.0471(Calc. 121.0461). [(CH$_3$O)$_4$B]$^-$, C$_4$H$_{12}$BO$_4$: 135.0841 (Calc. 135.0829). [(CH$_3$O)$_4$B]$_2^-$ K$^+$, C$_8$H$_{24}$B$_2$KO$_8$: 309.1239 (Calc. 309.1294). [(pinacol)BPhOH]$^-$, C$_{12}$H$_{18}$BO$_3$: 221.1342 (Calc. 221.1349). [(pinacol)$_2$B]$^-$, C$_{12}$H$_{24}$BO$_4$: 243.1731 (Calc. 243.1768). [PhB(OCH$_3$)$_3$]$_2^-$ Na$^+$, C$_{18}$H$_{28}$B$_2$O$_6$Na: 385.2007 (Calc. 385.1977).

Cross-coupling reactions

The Suzuki coupling reactions of (*E*)-bromostilbene with organoboron compounds were carried out using the procedure already described for the coupling with phenylboronic acid.[5]

Effect of substituents: Suzuki reaction with bromostilbene and arylboronic acid

An oven-dried resealable Schlenk flask was evacuated and back-filled with argon and charged with (*E*)-bromostilbene (6.5 mg, 0.025 mmol), aryl boronic acids (0.025 mmol of each one, phenylboronic acid, 4-methylphenylboronic acid, 4-methoxyphenylboronic acid), tetradecane (10 mg), methanol (1.5 mL), THF (1.5 mL), KOH (2.8 mg 0.05 mmol), and a Pd(OAc)$_2$/PPh$_3$ (5.7 mL of a 2.2 mmol mL Pd solution in THF/methanol) were added. The reaction mixture was stirred at room temperature (25 ºC) for 10 minutes (*ca.* 20% conversion). The reaction profile was monitored by GC and the quantification was calculated using an internal standard (tetradecane). The same procedure was carried out using phenylboronic acid, 4-chlorophenylboronic acid, 4-trifluoromethyl-phenylboronic acid (0.025 mmol of each one).

Acknowledgments

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