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Palladium-catalyzed cross-coupling of aryl chlorides with alkenylboronic acids with low *E*/*Z* isomerization

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ABSTRACT

Using a bulky electron-rich monodentate benzoferrocenyl phosphine as supporting ligand, an efficient protocol for stereoselective palladium-catalyzed Suzuki–Miyaura cross-coupling of aryl chlorides with alkenylboronic acids was uncovered. Using this protocol, both *trans*- and *cis*-alkenylboronic acids can be coupled with high stereoselectivity giving the corresponding vinylarenes in good to quantitative yields. Electron-poor and -rich aryl chlorides including highly hindered ones are all suitable substrates for the reaction.

1. Introduction

The palladium-catalyzed Suzuki–Miyaura cross-coupling is one of the most useful carbon–carbon bond formation reactions and has found wide applications in the synthesis of bioactive complex molecules.[1] In this reaction, various aryl and vinyl halides or triflates can be coupled with a wide range of aryl and alkenylboronic acids; and the reaction is tolerant of certain functional groups such as ketone, aldehyde, cyanide, and amide. Before late 1990s, aryl and vinyl bromides, iodides, and triflates were generally used as the electrophilic reaction partner of the transformation, and the more available and less expensive aryl chlorides were not viable substrates. This challenge has been overcome by Fu and Buchwald and their co-workers and other research groups through the use of electron-rich and bulky phosphine- and carbene-based ligands.[2] These ligands can form highly active mono-coordinated unsaturated organometallic species with palladium (0), which can activate the Ar–Cl bond toward cross-coupling reactions. Now, both electron-rich and -poor aryl chlorides can be coupled with various arylboronic acids to form biaryls including highly hindered ones with high efficiency. However, despite these achievements in the area, the cross-coupling of aryl chlorides with alkenylboronic acids remains challenging. Because of the lower reactivity of aryl chlorides compared with bromides and iodides and problems associated with alkenylboronic acids, under certain reported conditions that were used to activate aryl chlorides toward palladium-catalyzed cross-coupling reactions, mixtures of *E*- and *Z*-isomers of vinyl arenes were obtained even though sterically pure alkenylboronic acids were used.[2d] This problem has been partially solved by Nolan and Andrus and their co-workers using bulky *N*-heterocyclic carbenes as the supporting ligand. Under their conditions, electron-poor and -rich aryl chlorides were successfully coupled with *trans*-2-phenylvinylboronic acid with negligible isomerization.[3] However, in their reports, only one vinylboronic acid was tested, and the *trans*-stilbene products are significantly more stable than their *cis*-isomers. Recently, Denmark and his co-worker used alkenylsilanolates instead of boronic acids to couple with aryl chlorides to give vinyl arenes; under their conditions, excellent chemical yields (87–98%) and stereoselectivities (98.6–99.9%) were obtained for more than 20 substrate combinations.[4] However, compared with alkenylboronic acids, alkenylsilanolates are sensitive to moisture and are less compatible with polar functional groups. Moreover, many alkenylboronic acids are commercially available while alkenylsilanolates are not. As a result, the coupling of alkenylboronic acids with aryl chlorides to form vinylarenes with high stereoselectivity and broader substrate scope is still highly desired.

Recently, we reported the synthesis and characterization of several monodentate benzoferrocenyl phosphine ligands, which include **1** and **2** (Fig. 1), and their application in allylic alkylation.[5] In the X-ray determined single crystal structure of **1**, we noticed that the lone pair on the phosphorus atom points to the *endo* face of benzoferrocene. We therefore reasoned that coordination of this

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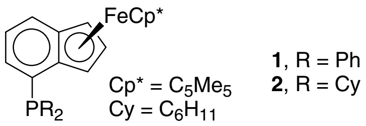


Figure 1.

class of ligands with palladium would produce mono-coordinated unsaturated organometallic species. Because benzoferrocene, like ferrocene,[6] is electron-rich, these ligands might represent a new class of bulky electron-rich ligands, and therefore should be useful for Suzuki–Miyaura coupling of aryl chlorides with alkenylboronic acids. Our studies showed that this was indeed the case and more significantly, the reactions were stereoselective for both *trans*- and *cis*-alkenylboronic acids. Here we report our results.

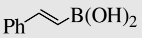
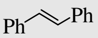
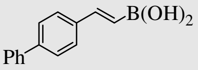
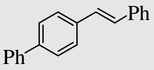
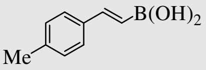
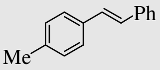
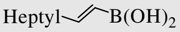
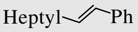
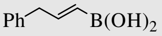
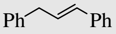
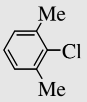
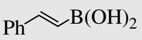
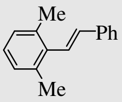
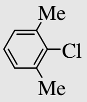
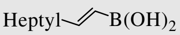
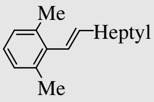
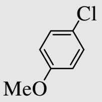
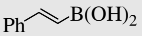
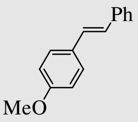
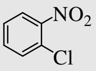
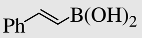
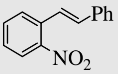
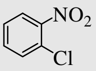
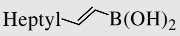
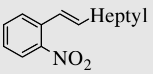
2. Results and discussion

Because ligand **2** is more electron-rich and sterically hindered than **1** and several other ligands we prepared, it was expected to be most active for activating aryl chlorides. This was indeed the case as we demonstrated earlier,[5b] and therefore **2** was chosen for the current study. Thus, using **2** as ligand, chlorobenzene was reacted with *trans*-2-phenylvinylboronic acid in refluxing 1,4-dioxane in the presence of the pre-catalyst $Pd_2(dba)_3$ and the base Cs_2CO_3. Within 1 h, 86% conversion was achieved as indicated by GC–MS. After 24 h, an isolated yield of 90% of stilbene was obtained. The reaction was 100% stereoselective, only *trans* product was formed; no *cis* isomer could be detected by analyzing the crude reaction mixture with GC–MS, NMR, and TLC (Table 1, entry 1).

Encouraged by these results, we next studied the generality of this reaction. Under the same conditions, the coupling between chlorobenzene and substituted phenylvinylboronic acids gave lower but still good yields (entries 2 and 3). The reactions gave better results for 2-alkyl substituted alkenylboronic acids than for 2-aryl substituted ones; both examples of the former shown in Table 1 gave 92% yield within 1 h (entries 4 and 5). Significantly, in all cases, high stereoselectivity was achieved as indicated by ^1H NMR and GC. The lowest *trans* selectivity was 98% (entry 5); others were virtually completely stereoselective (entries 2–4).

It is well-known that Suzuki–Miyaura coupling is sensitive to steric hindrance. In addition, electron-rich chloroarenes are more difficult substrates than electron-poor ones.[2d,3a] Accordingly, we challenged our coupling protocol with the highly hindered and electron-rich 2-chloro-1,3-dimethylbenzene (entries 6 and 7). The reactions proceeded with similar efficiency as those with

Table 1
Palladium-catalyzed cross-coupling of aryl chlorides with *trans*-alkenylboronic acids

Entry	Ar–Cl	Boronic acid	Product	Yield[a] (%)	*E*/*Z*[b]
1	Ph–Cl			90[c]	>99:1
2	Ph–Cl			74[c]	>99:1
3	Ph–Cl			60[c]	>99:1
4	Ph–Cl			92	>99:1
5	Ph–Cl			92	98:1
6				84	>99:1
7				90	>99:1
8				60[c]	>99:1
9				99	>99:1
10				97	>99:1

Reaction conditions: aryl chloride, 1 equiv; boronic acid, 1 equiv; $Pd_2(dba)_3$, 1.5 mol %; **2**, 3.6 mol %; Cs_2CO_3, 2 equiv; 1,4-dioxane; reflux; 1 h.

[a] Isolated yield.

[b] Determined by ^1H NMR analyses; results were close to those from GC analyses.

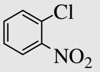
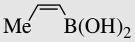
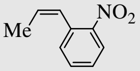
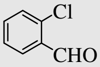
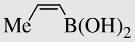
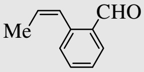
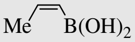
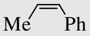
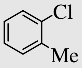
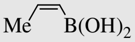
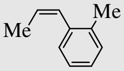
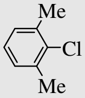
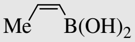
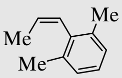
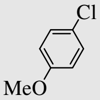
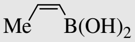
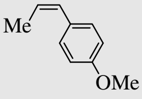
[c] Yield after 24 h.

electron-neutral and unhindered chloroarenes; within 1 h, excellent isolated yields of *trans*-alkenes were obtained. With the even more electron-rich 4-chloroanisole as substrate, although the reaction was slower, useful results were still obtained. When coupling with *trans*-2-phenylvinylboronic acid, 60% yield was obtained after 24 h; and despite the long reaction time, only *trans* product was isolated (entry 8). For electron-poor chloroarenes, the reactions were very fast. For example, when 1-chloro-2-nitrobenzene was coupled with 2-phenyl and alkyl substituted vinyl boronic acids, the reactions only took 1 h to complete and quantitative isolated yields were obtained (entries 9 and 10). Significantly, in both cases, no *cis*-stereoisomer was detected in the crude reaction mixture.

We next extended the substrate scope to *cis*-alkenylboronic acid. Under similar conditions described above, coupling of *cis*-propenylboronic acid with electron-rich and -poor aryl chlorides all gave *cis*-vinyl arene products with high selectivity (Table 2). We first tested to use a 1:1 ratio of aryl chloride and boronic acid for the reaction, but GC–MS showed that the former could not be consumed completely even after long reaction time. However, when the amount of aryl chlorides was reduced to 0.5 equiv, the reactions were complete within 1 h when electron-poor chloroarenes were used (entries 1 and 2). With electron-neutral and -rich chloroarenes, the conversions were also high (entries 3–6). In all reaction products, there were some *trans*-vinyl arenes (8–20%, see Table 2) as indicated by GC–MS and ^{1}H NMR (see Supplementary data); we believe that this was mostly resulted from the *trans*-boronic acid (~7% indicated by ^{1}H NMR, see Supplementary data) impurity contained in the starting *cis*-boronic acid, which was purchased from Aldrich. In addition, *cis*-vinyl arenes generally have higher boiling points than their *trans*-isomers, and the products are volatile under vacuum. As a result, the actual selectivity for the reaction is higher than that shown in Table 2. The yields of the reaction ranged from good to excellent depending on the nature of aryl chloride substrate. When electron-poor ones were used, excellent isolated yields were obtained (entries 1 and 2). With electron-neutral ones, yields were not reduced significantly (entries 3 and 4). However, the reaction is sensitive to steric hindrance, with 2-chloro-1,3-dimethylbenzene as substrate, the yield was reduced to 62% (entry 5). Finally, when the more electron-rich 4-chloroanisole was used, the reaction was sluggish but still useful. After 24 h, good yields and stereoselectivity were obtained (entry 6).

Table 2

Palladium-catalyzed cross-coupling of aryl chlorides with *cis*-alkenylboronic acids

Entry	Ar–Cl	Boronic acid	Product	Yield[a] (%)	Z/E[b]
1				95	92:8
2				85	90:10
3	Ph–Cl			81	80:20
4				83	88:12
5				62	89:11
6				58[c]	80:20

Reaction conditions: aryl chloride, 0.5 equiv; boronic acid, 1 equiv; $Pd_2(dba)_3$, 1.5 mol %; **2**, 3.6 mol %; Cs_2CO_3, 2 equiv; 1,4-dioxane; reflux; 1 h.

[a] Isolated yield.

[b] Determined by ^{1}H NMR analyses; results were close to those from GC analyses. Because the starting boronic acid contains ~7% *E*-isomer as estimated by ^{1}H NMR (see Supplementary data) and generally *Z*-products have lower boiling points than *E*-products, the actual selectivity is higher than shown.

[c] Yield after 24 h.

The use of Suzuki–Miyaura coupling to synthesize *cis*-vinylarenes is particularly significant. To our best knowledge, there is only one report that described coupling aryl iodides with *cis*-alkenylboronates in the presence of NaOEt to give *cis* products with high selectivity (>84% to >98%).[8] No such precedents involving coupling aryl iodides, bromides, and chlorides stereoselectively with *cis*-alkenylboronic acids could be found in literature. This may be attributed to the ability of Pd(II) to isomerize *cis*-vinylarenes under certain conditions.[7]

3. Conclusion

In conclusion, we have uncovered a catalytic protocol for the synthesis of both *cis*- and *trans*-vinylarenes with low *E*/*Z* isomerization using Suzuki–Miyaura coupling. Considering the highly functional group tolerance and other advantages of this important carbon–carbon bond formation reaction,[1d] our protocol will find useful in organic synthesis.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.050.

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