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Synthesis of Unsymmetrical Biaryl Ketones *via* Palladium-Catalyzed Carbonylative Cross-Coupling Reaction of Arylboronic Acids with Iodoarenes

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Summary: Arylboronic acids selectively react with atmospheric pressure of carbon monoxide and aryl iodides in the presence of palladium catalyst and an appropriate base to provide unsymmetrical biaryl ketones in high yields.

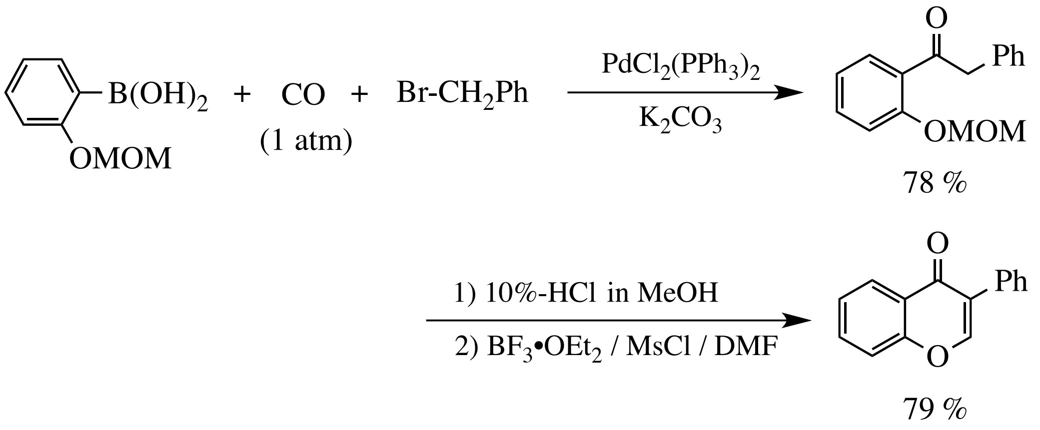
Although palladium-catalyzed three component cross-coupling reaction of arylmetal reagents with carbon monoxide and aryl halides or triflates is an attractive route for the synthesis of unsymmetrical biaryl ketones,[1] application of the protocol to aryl electrophiles having strong electron-withdrawing groups is severely limited due to accompanying directly coupled products.[2] Namely, a part of arylpalladium(II) complex, generated by oxidative addition of palladium(0) species to electrophile, undergoes transmetalation of aryl group on metal prior to CO insertion into aryl-palladium bond in the catalytic cycle. One of general approach to supress the side-reaction is use of pressurized CO which accelerates the CO insertion step and its utility was demonstrated by Stille[1d] in the reaction of aryltin derivatives with aryl triflates. Control of transmetalation rate can be considered as an alternative approach for the selective carbonylation, however, only few attempts have been made. Recently, we reported the palladium-catalyzed cross-coupling reaction of organoboron compounds with organic electrophiles.[3] In this study, it was found that base is indispensable for successful transmetalation from boron to palladium and a nature of the base employed markedly affects the rate of the step. Here, we wish to disclose the palladium-catalyzed carbonylative cross-coupling reaction of arylboronic acids with aryl iodides, which selectively proceeds in the presence of an appropriate base even under atmospheric pressure of CO (eq. 1).

$$\mathrm{Ar^1\text{-}B(OH)_2} \quad + \quad \underset{(1\ \mathrm{atm})}{\mathrm{CO}} \quad + \quad \mathrm{I\text{-}Ar^2} \quad \xrightarrow[\text{base}]{\text{Pd-catalyst}} \quad \mathrm{Ar^1\text{-}CO\text{-}Ar^2} \qquad (1)$$

In order to examine the influence of bases in the carbonylative cross-coupling of arylboron compounds, 4-iodoacetophenone (1.0 mmol) was initially chosen as an aryl electrophile and was allowed to react with phenylboronic acid (1.1 mmol) at 80 。C for 5h with use of PdCl2(PPh3)2 (0.03 mmol), anisole (6 ml), and various bases (3.0 mmol) under atmospheric pressure of carbon monoxide. As shown in Table 1, ratio of carbonylated and directly coupled products was significantly affected by base employed. Among the bases we examined, powdered K2CO3 is most effective and 84 % yield of 4-acetylbenzophenone was obtained along with 11 % yield of 4-acetylbiphenyl. On the other hand, K3PO4,3b Cs2CO3,4 and Tl2CO3,5 which are successfully utilized in the direct coupling reactions of organoboron derivatives and are considered to accelerate the transmetalation step greatly, tend to give direct coupling product (23-24 %). These facts strongly support our hypothesis, that is selective carbonylative cross-coupling of arylboron compounds in the presence of a suitable base under 1 atm of CO. The following observations are worth to note. (1) As catalyst, not only PdCl2(PPh3)2, but also Pd(PPh3)4, PdCl2(dppf), and even ligandless palladium complex catalyze the present reaction effectively. (2) The yield of ketone is influenced by solvent. Conducting the reaction in polar solvent, DMF, in place of anisole dramatically decreased the yield to 9 % without accompanying any coupling products, while starting iodide was completely consumed. It is assumed that carboxylic acid derivatives are formed by nucleophilic attack of base to arylpalladium(II) iodide or acyl iodide caused by reductive elimination of the intermediate under the reaction conditions. (3) Efficiency of the carbonylative coupling depends on leaving group of electrophiles. 4-Bromoacetophenone converted carbonylative and direct coupling products in a ratio of 1:1.6 (4) The reaction is specific with boronic acid derivatives. Use of boronic ester or 9-BBN derivatives did no give any good results at all.

In Table 2 are summarized the representative results of the three component cross-coupling reaction between arylboronic acids, carbon monoxide, and aryl iodides. Although nitro substituent on aromatic ring of aryl iodide has a strong tendency to cause direct coupling reaction and, indeed, carbonylative coupling of triphenylalane with p-iodonitrobenzene only affords 41 % yield of p-nitrobenzophenone under atmospheric pressure of CO,1b similar reaction of phenylboronic acid proceeds selectively to achieve 89 % yield. Aryl iodides having electron-donating groups and heteroaromatic iodides are also smoothly carbonylated and couple with various arylboron compounds to give corresponding ketones in good to excellent yields. When 1,4-diiodobenzene was allowed to react with two equivalents of p-tolylboronic acid, carbonylative coupling occurred at two iodide positions and afforded diketone in 82 % yield. In the case of the coupling between sterically hindered substrates, longer reaction was required to obtain satisfactory yield of the desired ketones.

On further study, it was found that the present method was also applicable for the synthesis of aryl benzyl ketones. For example, carbonylative cross-coupling of benzyl bromide (1.0 mmol) with 2-methoxymethoxyphenylboronic acid (1.1 mmol) proceeds under the same reaction conditions used in the reaction of aryl iodides without any difficulties to give the corresponding ketone in 78 % yield. Ketone thus obtained is a useful synthetic intermediate and is converted to isoflavone (79 %) by the reported procedure7 (eq. 2).



(2)

We previously reported the palladium-catalyzed carbonylative cross-coupling reaction of 9-alkyl-9-BBN derivatives with aryl, benzyl, 1-alkenyl, and saturated alkyl halides.8 The present study can make it possible to apply the method for arylboron derivatives.

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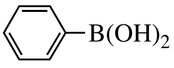
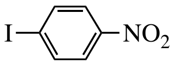
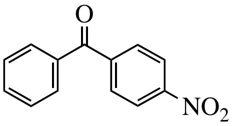
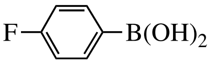
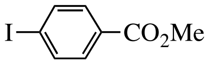
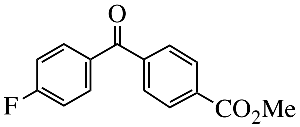
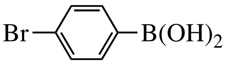
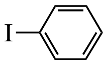
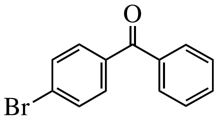
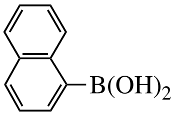
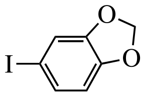
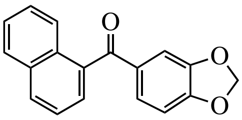
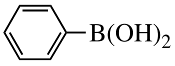
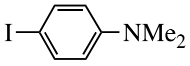
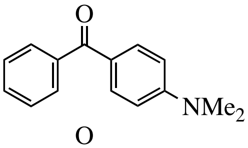
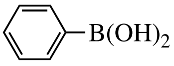
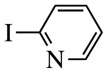
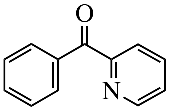
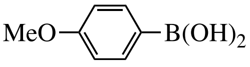
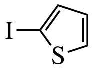
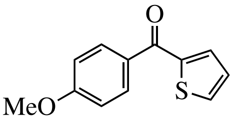
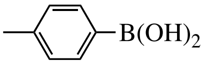
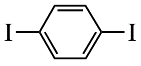
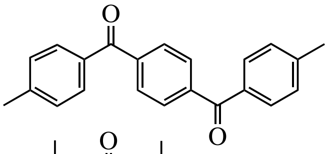
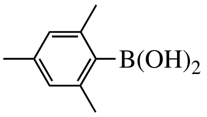
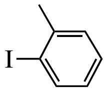
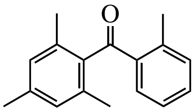
Table 1. Effect of Bases in the Carbonylative Cross-Coupling Reaction of Phenylboronic Acid with 4-Acetyliodobenzene[a)]

base	K_2CO_3	Cs_2CO_3	K_3PO_4	Tl_2CO_3
yield / %[b)] (carbonylative / direct)	84 / 11	69 / 23	43 / 23	38 / 24

a) All reactions were carried out at 80 °C for 5 h in anisole (6 ml) using phenylboronic acid (1.1 mmol), 4-acetyliodobenzene (1.0 mmol), $PdCl_2(PPh_3)_2$ (0.03 mmol), and base (3.0 mmol) under 1 atm of CO.
b) GLC yields based on 4-acetyliodobenzene.

Table 2. Carbonylative Cross-Coupling Reaction of Various Arylboronic Acids with Aryl Iodides[a)]

entry	borane	iodide	product	yield / %[b)]
1				89[c)]
2				76
3				86
4				86
5				89
6				66
7				87
8				82[d)]
9				63[e)]

a) All reactions were carried out at 80 °C under CO (1 atm) for 5 h, by using of arylboronic acids (1.1 mmol), aryl iodides (1.0 mmol), $PdCl_2(PPh_3)_2$ (0.03 mmol), K_2CO_3 (3.0 mmol), and anisole (6 ml).
b) Isolated yields based on aryl iodides employed. c) $PdCl_2(CH_3CN)_2$ was used as catalyst.
d) 2.2 equivs of *p*-tolylboronic acid was employed. e) The reaction was conducted for 24 h.