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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:** The cross-coupling reaction between arylboronic acids, carbon monoxide (1 atm), and aryl iodides in the presence of palladium catalyst and base provided unsymmetrical biaryl ketones in high yields. The choice of a suitable base and solvent was essential to achieve selective formation of the unsymmetrical biaryl ketone without a biaryl by-product.

Although the palladium-catalyzed three-component cross-coupling reaction between arylmetal reagents, carbon monoxide, and aryl halides or triflates is an attractive route for the synthesis of unsymmetrical biaryl ketones,[1] the application of the protocol to aryl electrophiles having electron-withdrawing groups is severely limited due to the side reaction forming biaryls.[2] Namely, the presence of an electron-withdrawing group acts to retard the insertion of carbon monoxide into the ArPdX intermediates, and it reversely accelerates the rate of transmetallation to generate the Ar-Pd-Ar' species. The use of higher pressure of carbon monoxide has been a general method for suppressing such a side reaction, and its utility was amply demonstrated in the reaction of aryltin derivatives with aryl triflates.[1d] Another efficient procedure involves the control of the rate of transmetallation between the ArPdX intermediates and organometallics to be sufficiently slower than the rate of carbon monoxide insertion; however, it may usually require a change of metal reagents.

We have reported previously the palladium-catalyzed cross-coupling reaction of organoboron compounds with organic electrophiles.[3] The reactions were induced by suitable bases and the properties of the bases markedly affected the rate of the transmetallation from boron to the RPdX complex. Herein, we wish to report that the palladium-catalyzed carbonylative cross-coupling reaction of arylboronic acids with aryl iodides is substantially controlled by choosing an appropriate base and a solvent to permit the selective coupling even under an atmospheric pressure of carbon monoxide (Eq. 1).

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

The preliminary results for the cross-coupling of *p*-iodotoluene with phenylboronic acid under atmospheric pressure of carbon monoxide indicated that most representative palladium complexes such as $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $PdCl_2(dppf)$, and $PdCl_2(PhCN)_2$ catalyzed the reaction effectively. The yields of 4-methylbenzophenone were mostly influenced by the solvents employed. The best results were obtained using dioxane or anisole, but polar solvents such as DMF resulted in extremely low yields while iodotoluene was completely consumed. In polar solvents, the formation of *p*-toluic acid was a predominant process as a result of the nucleophilic attack of the base on the *p*-toluoylpalladium(II) iodide intermediate or toluoyl iodide generated by its reductive elimination. The use of boronic acids was essential since the 1,3-propanediol and dibutyl esters of phenylboronic acid or 9-phenyl-9-BBN did not produce any good results.

In order to examine the effect of bases on the selective formation of biaryl ketone, *p*-iodoacetophenone was initially chosen, and its reaction with phenylboronic acid (1.1 equivs) in anisole in the presence of $PdCl_2(PPh_3)_2$ (3 mol %) and various bases (3 equivs) was carried out for 5 h at 80 °C under atmospheric pressure of carbon monoxide (Table 1).

Table 1. Effects of Bases on the Carbonylative and Direct Coupling Selectivity in the Reaction of Phenylboronic Acid with *p*-Iodoacetophenone under CO (1 atm)[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 |

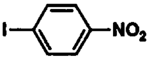
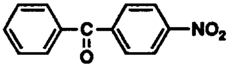
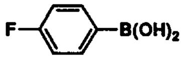
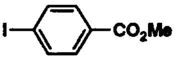
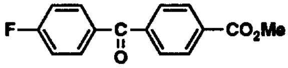
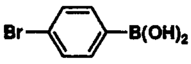
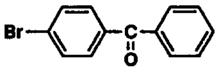
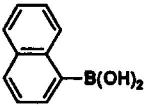
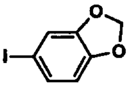
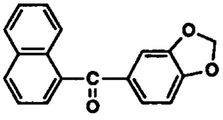
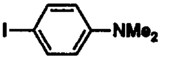
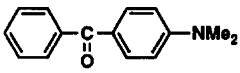
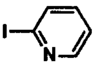
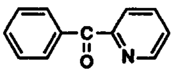
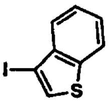
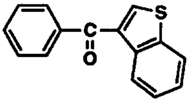
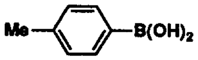
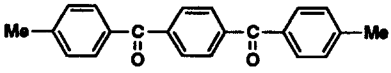
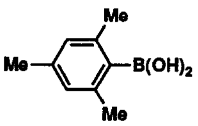
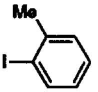
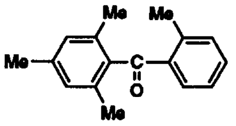
a) All reactions were carried out at 80 °C for 5 h in anisole (6 ml) using phenylboronic acid (1.1 mmol), *p*-iodoacetophenone (1.0 mmol), $PdCl_2(PPh_3)_2$ (0.03 mmol), and base (3.0 mmol) under CO (1 atm).
b) GLC yields based on *p*-iodoacetophenone.

Although the complete control of selectivity was unsuccessful, potassium carbonate suspended in anisole was recognized to be most effective in preventing the formation of undesirable biaryl by-product: an 84% yield of 4-acetylbenzophenone was obtained along with an 11% yield of 4-acetylbiphenyl. $K_3PO_4$,[3b] $Cs_2CO_3$,[4] and $Tl_2CO_3$[5] tend to produce a direct coupling product (23-24 %) due to their higher ability to accelerate the rate of transmetallation. This selectivity can be also affected by the haloarenes employed, and better selectivity was always provided by iodoarenes rather than bromoarenes.[6] For example, the reaction of *p*-bromoacetophenone with phenylboronic acid under the best conditions produced both products in a ratio of 1:1.

In Table 2, the representative results of the present three-component cross-coupling reaction between arylboronic acids, carbon monoxide, and aryl iodoarenes are summarized. Although the nitro group is a synthetically useful functionality, its substitution on haloarenes has a strong tendency to produce direct coupling products. Under atmospheric pressure of carbon monoxide, the reaction of triphenylalane with *p*-iodonitrobenzene was reported to provide only a 41% yield of *p*-nitrobenzophenone[1b] with contamination of *p*-nitrobipenyl in 55% yield, and a similar reaction with tributyltin hydride resulted in only a 9% yield of *p*-nitorobenzaldehyde accompanying an 84% yield of nitrobenzene.[1d] In contrast, the carbonylative coupling of phenylboronic acid with *p*-iodonitrobenzene and methyl *p*-iodobenzoate gave 89 and 76 % yields of ketones, respectively, with less than 10% of accompanying direct coupling products (entries 1 and 2). Aryl iodides having electron-donating groups and heteroaromatic iodides were also carbonylated and coupled with various arylboronic acids without any difficulty (entries 3-7). It is interesting to note that the coupling with the C-I bond is reasonably faster than with other halogen bonds, allowing the synthesis of ketones substituted with fluorine or bromine (entries 2 and 3). 1,4-Diiodobenzene readily underwent the double carbonylative couplings with two equivs of *p*-tolylboronic acid to provide a diketone in 82% yield (entry 8). A more sterically hindered combination of mesitylboronic acid and *o*-tolyl iodide required a longer reaction time to obtain a satisfactory yield (entry 9).

The present procedure can be applicable to the synthesis of aryl benzyl ketones. For example, the carbonylative cross-coupling of benzyl bromide (1.0 mmol) with 2-(methoxymethoxy)phenylboronic acid

Table 2. Synthesis of Biaryl Ketones[a]

| entry | borane | iodide | product | yield / %[b] |
|---|---|---|---|---|
| 1 | $PhB(OH)_2$ |  |  | 89[c] |
| 2 |  |  |  | 76 |
| 3 |  | PhI |  | 86 |
| 4 |  |  |  | 86 |
| 5 | $PhB(OH)_2$ |  |  | 89 |
| 6 | $PhB(OH)_2$ |  |  | 66 |
| 7 | $PhB(OH)_2$ |  |  | 89 |
| 8 |  |  |  | 82[d] |
| 9 |  |  |  | 63[e] |

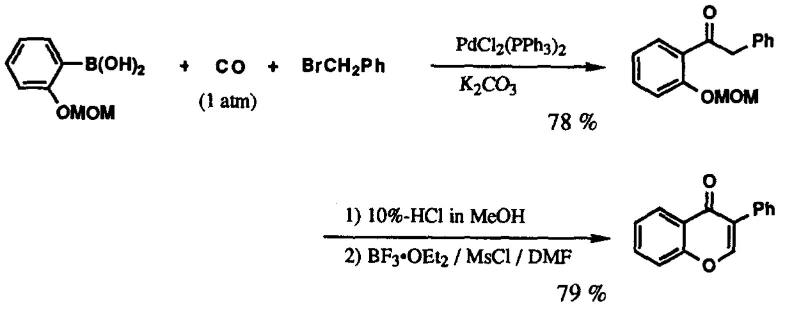
a) All syntheses were carried out by the following representative procedure, unless otherwise noted. To the flask equipped with a reflux condenser and a balloon charged with carbon monoxide were added iodoarene (1.0 mmol), arylboronic acid (1.1 mmol), $PdCl_2(PPh_3)_2$ (0.03 mmol), $K_2CO_3$ (3 mmol), and anisole (6 ml). The flask was flushed with 1 atm of carbon monoxide, and the resulting mixture was then stirred for 5 h at 80 °C. After the usual work-up, the product was isolated by chromatography over silica gel.

b) Isolated yields based on iodoarenes. c) $PdCl_2(CH_3CN)_2$ (0.03 mmol) was used as a catalyst.

d) *p*-Tolylboronic acid (2.2 mmol) and $K_2CO_3$ (6 mmol) were used.

e) The reaction was conducted for 24 h.

(1.1 mmol) readily proceeded under similar reaction conditions to give the corresponding ketone in 78 % yield. The ketone thus obtained is a useful synthetic intermediate which is readily converted to isoflavone (79 %) by a reported procedure[7] (Eq. 2). However, a similar carbonylative coupling reaction of arylboronic acids with allylic halides failed.



(2)

We previously reported the palladium-catalyzed carbonylative cross-coupling reaction of 9-alkyl-9-BBN derivatives[8] with aryl, benzyl, 1-alkenyl, and alkyl halides. The present study can make it possible for the extension of such coupling reactions to the synthesis of aryl ketones. Arylboronic acids are isolable and storable without special precautions because they are thermally stable, inert to water and oxygen. The conditions for the coupling are mild and arylboronic acids are highly tolerant of many functional groups, so that applications for variously functionalized biaryl ketones are anticipated.

## References and Notes

1. (a) Bumagin, N. A.; Bumagina, I. G.; Kashin, A. N.; Beletskaya, I. P. *Dokl. Akad. Nauk SSR* **1981**, *261*, 1141-1145. (b) Bumagin, N. A.; Ponomaryov, A. B.; Beletskaya, I. P. *Tetrahedron Lett.* **1985**, *26*, 4819-4822. (c) Kikukawa, K.; Idemoto, T.; Katsuyama, A.; Kono, K.; Wada, F.; Matsuda, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1511-1514. (d) Echavarrene, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557-1565. (e) Hatanaka, Y.; Hiyama, T. *Chem. Lett.* **1989**, 2049-2052. (f) Hatanaka, Y.; Hiyama, T. *Synlett.* **1991**, 845-853.
2. Hartly, F. R. *The Chemistry of Metal-Carbon Bond*; Patai, S., Ed.; Wiley: New York, 1985.
3. (a) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972-980. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314-321.
4. Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett.* **1992**, 207-210.
5. Satoh, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 14050-1408.
6. It has been reported that the ratio of carbonylated and direct couplings is highly dependent on the halogen ligands used for haloarenes: Stang, P. T.; Zhong, Z.; Arif, A. M. *Organometallics* **1992**, *11*, 1017-1025.
7. Bass, R. J.; *J. Chem. Soc., Chem. Commun.* **1976**, 78-79.
8. (a) Ishiyama, T.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1999-2001. (b) Ishiyama, T.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1991**, *32*, 6923-6926.

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