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Ruthenium-Catalyzed Carbon−Carbon Bond Formation via the Cleavage of an Unreactive Aryl Carbon−Nitrogen Bond in Aniline Derivatives with Organoboronates

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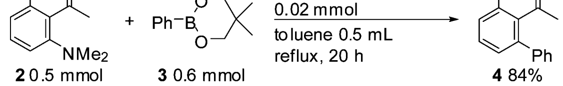
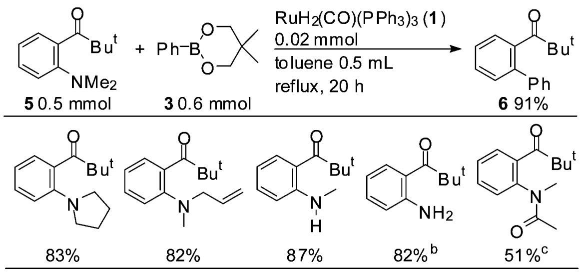
The catalytic functionalization of unreactive bonds such as carbon−hydrogen,[1] carbon−carbon,[2] carbon−fluorine,[3] and carbon−oxygen[4] bonds has become an interesting research subject in modern organic synthesis. In addition to these reactions, the functionalization of aryl carbon−nitrogen bonds in aniline derivatives is also challenging because, to date, only one example of the oxidative addition of an aryl C−N bond in anilines to a transition metal has been reported.[5,6] For the functionalization of aryl C−N bonds, the bonds are usually activated by conversion to diazonium salts ($Ar-N_2X$),[7] ammonium salts,[8] triazenes,[9] and imidazoles.[10] However, to the best of our knowledge, the catalytic functionalization of unreactive aryl C−N bonds in aniline derivatives has not yet been achieved. Herein, we describe the first example of catalytic C−C bond formation via the cleavage of aryl C−N bonds in anilines.

In our continuous studies of the catalytic functionalization of unreactive carbon bonds such as C−H and C−O bonds, we found that $RuH_2(CO)(PPh_3)_3$ (**1**) can function as an excellent catalyst, and the use of a chelation assistance protocol is highly efficient for attaining the cleavage of these bonds.[1a,4b,d,11] Therefore, the reaction of 2′-*N*,*N*-dimethylamino-6′-methylacetophenone (**2**) with 5,5-dimethyl-2-phenyl[1,3,2]dioxaborinane (**3**) was examined using **1** as a catalyst (eq 1). We were pleased to find that the expected ortho phenylation via aryl C−N bond cleavage took place to give 2′-methyl-6′-phenylacetophenone (**4**) in 84% yield.[12] This result provides the following notable features: (1) this is the first example of the catalytic functionalization of aryl C−N bonds in anilines via an oxidative addition of a C−N bond to a low-valent transition metal; (2) this coupling reaction proceeds through a transmetalation between a ruthenium−amide complex and an organoboron compound.



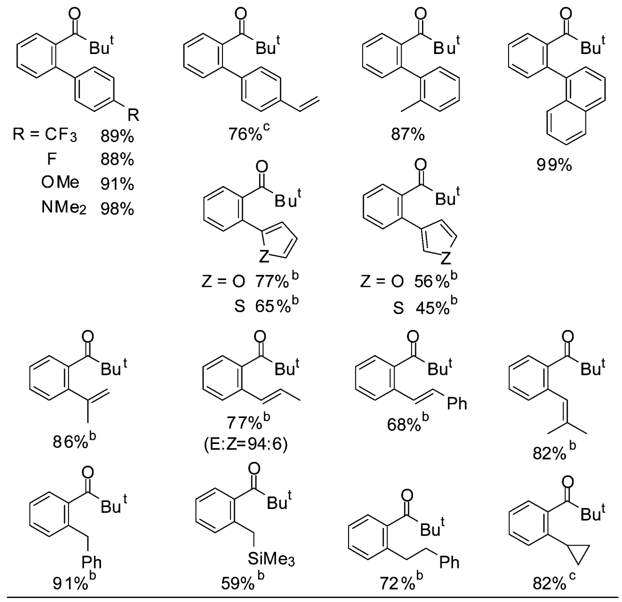
2 0.5 mmol **3** 0.6 mmol **4** 84% (1)

Scheme 1. The Phenylation of a Variety of C−N Bonds[a]



[a] Isolated yields. [b] Phenylboronate **3** (1.0 mmol) and catalyst **1** (0.04mmol). [c] Phenylboronate **3** (1.5 mmol) and catalyst **1** (0.06 mmol).

Table 1. The Coupling Reaction of *N*,*N*-Dimethylaminopivalophenone (**5**) with Various Organoboronates[a]



[a] Conditions: $RuH_2(CO)(PPh_3)_3$ **1** (0.02 mmol), toluene (0.5 mL), arylamine **5** (0.5 mmol), organoboronate (0.6 mmol), reflux, 20 h. [b] Conditions: **1** (0.04 mmol), organoboronate (1.0 mmol). [c] Conditions: **1** (0.06 mmol), organoboronates (1.5 mmol).

When this coupling reaction was carried out using 2′-*N*,*N*-dimethylaminoacetophenone, the phenylation took place at both $C-NMe_2$ and C−H bonds. To suppress this undesired phenylation at the C−H bond, pivalophenone derivatives were employed. Several amino groups such as $-NMe_2$, $-N(CH_2)_4$, −NMe(allyl), −NHMe, and $-NH_2$ are applicable to this aryl $C-N/RB(OR')_2$ coupling (Scheme 1). The substituent on the nitrogen atom does not have a significant effect on the yields of the coupling products except for the −NMeAc group. Interestingly, a free N−H group (NHMe and NH_2) does not disturb this coupling reaction. In the case of the reaction of an NMeAc derivative, the reactivity of the ketone was decreased. Coupling product **6** was obtained in 51% yield under conditions of 12 mol % of catalyst loading.

Several organoboronates involving aryl, heteroaryl, alkenyl, and alkylboronates can be used in this reaction. Some selected results are listed in Table 1. In the case of 4-styrylboronate, the yield was decreased slightly due to the polymerization of some of the 4-styrylboronate during the reaction. The reaction using sterically demanding arylboronates such as 2-tolyl- and 1-naphthylboronates

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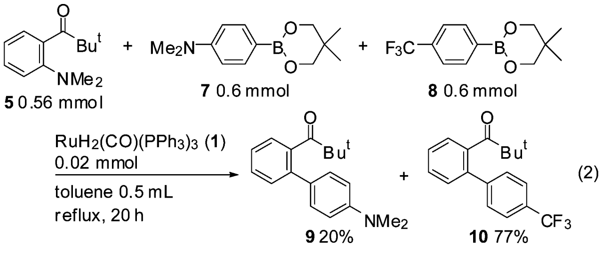
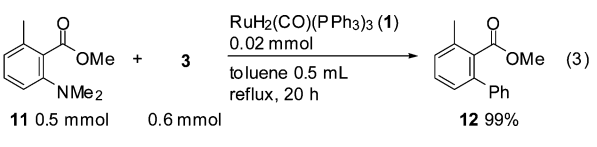
afforded the coupling products in 87 and 99% isolated yields, respectively. When the coupling reaction with heteroarylboronates was carried out in the presence of 8 mol % of catalyst, the corresponding coupling products were obtained in 45−77% yields. The reaction using 1-propenylboronate (*E*:*Z* = 5:95) afforded 2′-(1-*E*-propenyl)pivalophenone as a major product (*E*:*Z* = 94:6). When (*Z*)-1-propenylboronate was heated at 60 °C for 30 min in the presence of RuH$_2$(CO)(PPh$_3$)$_3$ catalyst, isomerization of (*Z*)-1-propenylboronate (*E*:*Z* = 5:95) to the corresponding *E*-isomer (*E*:*Z* = 95:5) occurred. This suggests that the *E*-propenylation product was formed after the isomerization of the propenylboronate. Alkylboronates, such as benzyl, trimethylsilylmethyl, β-phenethyl, and cyclopropylboronates, can be used in this reaction. It is noteworthy that, in the case of the reaction of β-phenethylboronate, the α-phenethyl product, which could be formed via β-hydride elimination from the β-phenethylruthenium intermediate followed by the re-insertion of the double bond in styrene into the Ru−H bond, was not formed, and that the cyclopropyl group can be introduced on the aromatic ring without ring opening of the cyclopropyl ring, which is usually reactive toward low-valent transition metals.

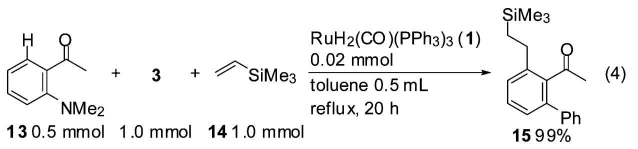
To obtain information with respect to the transmetalation process, we carried out a competitive reaction using 2′-aminopivalophenone **5**, 4-*N*,*N*-dimethylaminophenylboronate **7**, and 4-trifluoromethylphenylboronate **8** (eq 2). After heating for 20 h, the coupling product **10** derived from **8** was obtained as the major product. This indicates that an electron-withdrawing group improves the reactivity of the arylboronate. These electronic effects of the arylboron compounds are consistent with the results of the palladium-catalyzed cross-coupling reaction of propargylic carbonates with arylboron compounds.[13] In their study of this reaction, these workers reported that transmetalation between the palladium−alkoxy species and arylboron compounds proceeded through the coordination of the alkoxy oxygen to the boron atom. We propose, on the basis of their studies, that the transmetalation between the Ru−NMe$_2$ species and Ar−B(OR)$_2$ takes place via the coordination of the amino group to the boron atom. The low reactivity of *N*-methyl-*N*-(2-pivaloylphenyl)acetamide, in which the electron density on the nitrogen atom is slightly lower than those of other amino groups (Scheme 1), is consistent with this proposed mechanism of the transmetalation step.



In place of aromatic ketones, aromatic esters **11** can also be used in this reaction. The phenylation occurred efficiently at the C−N bond to give the phenylation product **12** in 99% isolated yield (eq 3). We reported the Ru$_3$(CO)$_{12}$-catalyzed cross-coupling reaction of esters with organoboron compounds via pyridyl-group-directed acyl carbon−oxygen bond cleavage leading to ketones.[14] However, in the present reaction, the ester group remained intact in the coupling product.



The ruthenium-catalyzed chemoselective sequential C−C bond formation using 2′-*N*,*N*-dimethylaminoacetophenone (**13**) with **3** and trimethylvinylsilane (**14**) gave **15** as the sole product (eq 4).[15] Phenylation at the C−N bond with **3** and alkylation at the C−H bond with **14** took place to give product **15** in 99% isolated yield.



In summary, we discovered the ruthenium-catalyzed C−C bond formation via the unreactive aryl C−N bond cleavage in aniline derivatives with organoboronates. This reaction includes two important elementary steps: one is oxidative addition of an unreactive aryl C−N bond to the late transition-metal complex and the other is transmetalation between the Ru−NR$_2$ species and organoboronates. Further studies to address the scope and limitation of this reaction and the reaction pathway are currently in progress.

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Supporting Information Available: Experimental procedures and spectral analyses of all products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826−834. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1770. (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077−1101. (d) Godula, K.; Sames, D. *Science* **2006**, *312*, 67−68.

(2) For reviews, see: (a) Murakami, M.; Ito, Y. In *Topics in Organometallic Chemistry*; Murai, S., Ed.; Springer: Berlin, Germany, 1999; pp 97−130. (b) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610−618.

(3) (a) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373−431. (b) Ishii, Y.; Chatani, N.; Yorimitsu, S.; Murai, S. *Chem. Lett.* **1998**, 157−158. (c) Saeki, T.; Takashima, Y.; Tamao, K. *Synlett* **2005**, *11*, 1771−1774. (d) Korn, T. J.; Schade, M. A.; Wirth, S.; Knochel, P. *Org. Lett.* **2006**, *8*, 725−728.

(4) (a) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246−2247. (b) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706−2707. (c) Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428−2432. (d) Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516−16517.

(5) An oxidative addition of aryl C−N bonds in anilines to Ta(OSiBu^t)$_3$ has been reported. Bonanno, J. B.; Henry, T. P.; Neithamer, D. R.; Wolczanski, P. T.; Lobkovsky, E. B. *J. Am. Chem. Soc.* **1996**, *118*, 5132−5133.

(6) For several examples with respect to cleavage of alkyl C−N bonds with low-valent transition-metal complexes, see: (a) Cotton, F. A.; Daniels, L. M.; Murillo, C. A.; Wang, X. *Inorg. Chem.* **1997**, *36*, 96−901. (b) Ozerov, O. V.; Guo, C.; Papkov, V. A.; Foxman, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 4792−4793. (c) Burling, S.; Mahon, M. F.; Powell, R. E.; Whittlesey, M. K.; Williams, J. M. J. *J. Am. Chem. Soc.* **2006**, *128*, 13702−13703.

(7) Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. *Chem. Rev.* **2006**, *106*, 4622−4643.

(8) (a) Wenkert, E.; Han, A.-L.; Jenny, C.-J. *J. Chem. Soc., Chem. Commun.* **1988**, 975−976. (b) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046−6047.

(9) Saeki, T.; Son, E.-C.; Tamao, K. *Org. Lett.* **2004**, *6*, 617−619.

(10) Liu, J.; Robins, M. J. *Org. Lett.* **2004**, *6*, 3421−3423.

(11) (a) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698−1697. (b) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936−5945.

(12) A formation of boronamide species (Me$_2$NB(OCH$_2$C(Me$_2$)CH$_2$O)) was confirmed by the ^{11}B NMR spectrum (δ 20.2 ppm). Suginome, M.; Uehlin, L.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 13196−13197.

(13) Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, 149−151.

(14) Tatamidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 5615−5621.

(15) A similar sequential alkyl−aryl coupling was reported using 2-methoxyacetophenone, arylboronates, and vinylsilanes. See ref 4d.

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