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Cleavage of C−N Bonds in Aniline Derivatives on a Ruthenium Center and Its Relevance to Catalytic C−C Bond Formation

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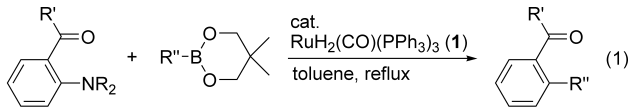
Transition-metal-catalyzed formation of C−C bonds via selective cleavage of unreactive bonds has been one of the most extensively studied areas in organic chemistry because it leads to unique organic transformations that are hard to achieve by other methods.[1] C−N bonds are one of the most abundant and unreactive bonds in organic molecules.[2−7] In particular, aromatic C−N bonds in anilines are considerably inert, and not only catalytic transformations involving their selective cleavage[2,3] but also observations of such cleavage itself are still rare.[4−6]

Recently, we reported the first catalytic C−C bond formation via cleavage of unactivated aromatic C−N bonds in aniline derivatives (eq 1):[2]



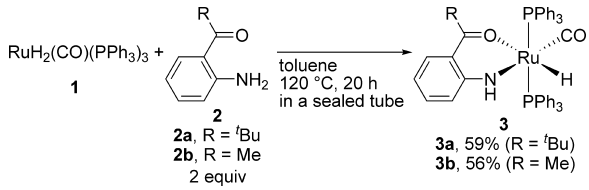
(1)

NR_2 = NH_2, NHMe, NMe_2 etc

o-Acylanilines were used as substrates, and the coupling reactions with various organoboronic acid esters (organoboronates) proceeded using $RuH_2(CO)(PPh_3)_3$ (**1**) as a catalyst. In connection with a similar C−O bond functionalization,[1m,o] we proposed a catalytic cycle involving (1) oxidative addition to the C−N bond, (2) transmetalation between the ruthenium amide complex and an organoboronate, and (3) reductive elimination to form the C−C bond. However, the proposed mechanism included rarely observed steps. For example, there has been only one report on the observation of direct cleavage of unactivated aromatic C−N bonds on a transition-metal center, which was described by Wolczanski and coworkers using a tantalum(III) complex and aniline derivatives.[4] Intrigued by the fact that even free aniline derivative **2a** is applicable to our reaction, we decided to explore the reactivity of this substrate with ruthenium catalyst **1**. Here we report that the C−N bonds of primary aromatic amines can be cleaved on the ruthenium center and that coupling products can be obtained via C−N bond cleavage.

When ruthenium complex **1** was allowed to react with 2 equiv of **2a** in toluene at 120 °C for 20 h, amido hydrido complex **3a** became the predominant ruthenium species and was isolated in 59% yield (Scheme 1). *o*-Acetylaniline (**2b**) also led to the formation of the corresponding

Scheme 1. Cleavage of N−H Bonds on a Ruthenium Center



complex **3b**, which was similarly isolated in 56% yield. The molecular structure of **3b** was confirmed by X-ray crystallography (Figure 1a). Complex **3b** possesses a (2-acetylphenyl)amide ligand that forms a six-membered chelate, and the nitrogen atom of the amide is located cis to the hydride ligand.[8]

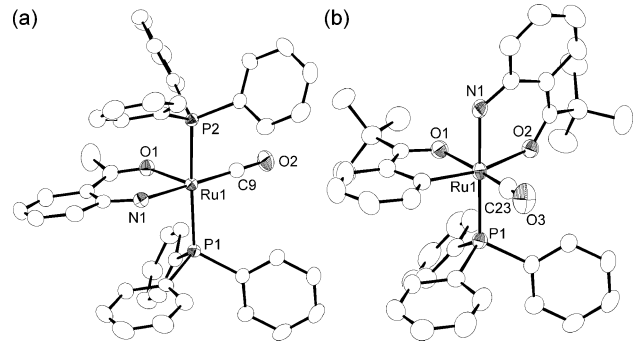
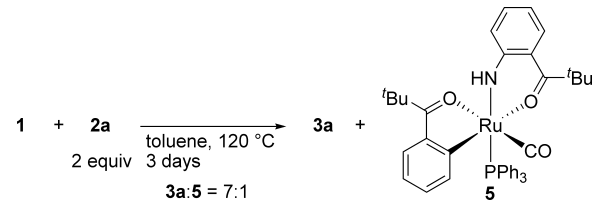


Figure 1. ORTEP drawings of (a) amido hydrido complex **3b** and (b) aryl complex **5**. Hydrogen atoms have been omitted for clarity.

Use of an activated ruthenium complex formulated as "$Ru(CO)(PPh_3)_3$" (**4**),[9] which was generated by a reaction of **1** with 10 equiv of trimethylvinylsilane, enabled the formation of **3a** at room temperature. When the reaction of **4** with **2a** was monitored by ^{31}P NMR spectroscopy, **3a** became the only phosphine ruthenium complex within 1 h. Formation of an amido hydrido ruthenium complex by the reaction of trimethylphosphine complexes with aniline was reported by Hartwig, Andersen, and Bergman.[10]

Reaction of **1** with **2a** was monitored further, and after 3 days, a ∼7:1 mixture of **3a** and arylruthenium complex **5** was obtained; from this mixture, **5** was isolated in 6% yield (Scheme 2). The molecular structure

Scheme 2. Cleavage of a C−N Bond on a Ruthenium Center



of **5** was established by X-ray analysis (Figure 1b). Complex **5** possesses two chelating ligands originating from **2a**, (2-pivaloylphenyl)amide and 2-pivaloylphenyl groups. The latter forms a five-membered chelate and is presumably generated via C−N bond cleavage by the ruthenium center. This result presents the first observation of unactivated aromatic C−N bond cleavage on a late-transition-metal center.

Addition of olefins dramatically increased the rate of the C−N bond cleavage and the yield of **5**. When the reaction of **1** with **2a** was carried out in the presence of trimethylvinylsilane (**6**) at 120 °C, **5** became the only ruthenium species observed by ^{31}P NMR spectroscopy (96% yield by ^{1}H NMR spectroscopy) and was isolated in 56% yield (run 1 in eq 2).

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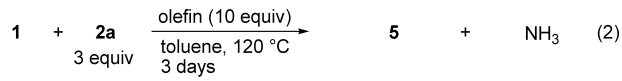
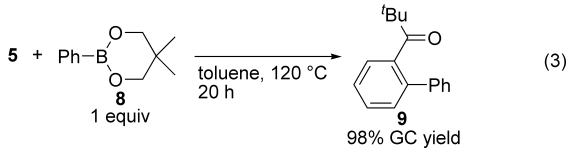
Use of 3,3-dimethyl-1-butene (**7**) as an additive also accelerated the formation of **5** (run 2). In addition to **5**, ammonia was formed in both runs.[11,12] The formation of ammonia suggests that the olefins do not directly activate the C−N bond by covalently forming a bond with the nitrogen atom but simply facilitate the bond cleavage, probably through coordination.

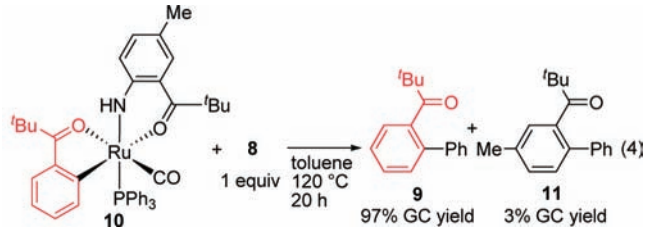


run	olefin	NMR yield	yield[11]
1	CH_2=$CHSiMe_3$ (**6**)	96%	43%
2	CH_2=CH^tBu (**7**)	90%	55%

With complex **5** formed via C−N bond cleavage in hand, we examined whether **5** can be used for C−C bond formation upon treatment with organoboronates. Stoichiometric reaction of **5** with phenylboronate **8** at 120 °C actually provided the ortho phenylation product **9** in 98% GC yield (eq 3):

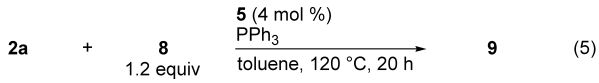


To further confirm the coupling product obtained via C−N bond cleavage, it was necessary to determine which ligand, the amide or the aryl group, in **5** was used for the C−C bond formation. For this purpose, complex **10** was prepared to differentiate the two aryl rings.[13] The reaction of **10** with **8** afforded **9** in 97% GC yield, with only 3% of the methyl-substituted product **11** (eq 4):



This result clearly shows that the product was primarily produced by coupling between the organoboronate and the aryl group formed by the C−N bond cleavage.

Finally, the catalytic activity of **5** toward coupling of aniline **2a** with **8** was examined in the absence or presence of additional PPh_3 (eq 5):



	PPh_3	Ru/PPh_3	GC yield
run 1	0 mol %	1:1	27%
run 2	4 mol %	1:2	49%
run 3	8 mol %	1:3	66%
run 4	12 mol %	1:4	65%

The reaction carried out in the absence of PPh_3 provided **9** in only 27% yield. The addition of PPh_3 increased the yield, and use of 2 equiv of PPh_3 (3:1 Ru/PPh_3) afforded **9** in 66% yield (run 3). Further addition of PPh_3 did not affect the yield (run 4). The 3:1 ratio of Ru/PPh_3 used in run 3 represents the original catalyst system and is probably needed to stabilize an unsaturated low-valent ruthenium intermediate generated after C−C bond formation.

In summary, we have examined the reactivity of 2-acylanilines **2** toward ruthenium complexes. Although the reactive NH_2 group easily led to the formation of amido hydrido complex **3**, the C−N bond was eventually cleaved on the ruthenium center. This is the first observation of cleavage of unactivated aromatic C−N bonds on late-transition-metal centers. Dramatic improvement of the rate of C−N bond cleavage was achieved using olefins as additives. The couplings of boronate **8** with the carbon fragments of **5** and **10** formed via C−N bond cleavage proceeded in high yield. Therefore, we believe that the proposed catalytic cycle (an oxidative addition/transmetalation/reductive elimination pathway) for our catalytic functionalization of C−N bonds described in eq 1 is quite reasonable. Further studies concerning the mechanisms of the catalytic reaction are currently underway.

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Supporting Information Available: Experimental procedures, characterization data, and CIF files for **3b**, **5**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For catalytic functionalization via cleavage of unreactive C−H bonds, see: (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev* **2002**, *102*, 1731. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (d) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. For C−C bonds, see: (e) Murakami, M.; Ito, Y. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; pp 99−129. (f) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (g) Jun, C.-H.; Park, J.-W. *Top. Organomet. Chem.* **2007**, *24*, 117. For C−F bonds, see: (h) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373. (i) Ishii, Y.; Chatani, N.; Yorimitsu, S.; Murai, S. *Chem. Lett.* **1998**, 157. (j) Saeki, T.; Takashima, Y.; Tamao, K. *Synlett* **2005**, 1771. (k) Korn, T. J.; Schade, M. A.; Wirth, S.; Knochel, P. *Org. Lett.* **2006**, *8*, 725. For C−O bonds, see: (l) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246. (m) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706. (n) Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428. (o) Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516.

(2) Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098.

(3) For studies of catalytic reactions involving cleavage of activated aromatic C−N bonds, see: (a) Wenkert, E.; Han, A.-L.; Jenny, C.-J. *J. Chem. Soc., Chem. Commun.* **1988**, 975. (b) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046. (c) Saeki, T.; Son, E.-C.; Tamao, K. *Org. Lett.* **2004**, *6*, 617. (d) Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. *Chem. Rev.* **2006**, *106*, 4622.

(4) Bonnano, J. B.; Henry, T. P.; Neithamer, D. R.; Wolczanski, P. T.; Lobkovsky, E. B. *J. Am. Chem. Soc.* **1996**, *118*, 5132.

(5) For cleavage of an aromatic C−N bond from a (*N*-silyl)arylamido molybdenum complex, see: Cameron, T. M.; Abboud, K. A.; Boncella, J. M. *Chem. Commun.* **2001**, 1224.

(6) Functionalization of aromatic C−N bonds using stoichiometric amounts of Pd complexes has been reported, but the mechanism is unclear. See: Akiyama, F.; Miyazaki, H.; Kaneda, K.; Teranishi, S.; Fujiwara, Y.; Abe, M.; Taniguchi, H. *J. Org. Chem.* **1980**, *45*, 2359.

(7) Cleavage of unactivated aliphatic C−N bonds on transition metals has been reported: (a) Takano, K.; Inagaki, A.; Akita, M. *Chem. Lett.* **2006**, *35*, 434. (b) Burling, S.; Mahon, M. F.; Powell, R. E.; Whittlesey, M. K.; Williams, J. M. J. *J. Am. Chem. Soc.* **2006**, *128*, 13702. (c) Caddick, S.; Cloke, F. G. N.; Hitchcock, P. B.; de K. Lewis, A. K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5824.

(8) The (2-acylphenyl)amido ligand on **3** rapidly exchanges with free substrate **2** at 120 °C in toluene. See the Supporting Information for datails.

(9) (a) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62. (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. Also see footnote 9 in ref 1o.

(10) Hartwig, J. F.; Andersen, R. A.; Bergman, R. G. *Organometallics* **1991**, *10*, 1875.

(11) Ammonia was quantified by the indophenols-blue method: Weatherburn, M. W. *Anal. Chem.* **1967**, *39*, 971.

(12) In view of the formation of ammonia, we believe that complex **5** was formed by oxidative addition to the C−N bond of **2a**, followed by exchange of an NH_2 group with another equivalent of **2a**.

(13) See the Supporting Information for details.

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