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Ruthenium-Catalyzed Functionalization of Aryl Carbon−Oxygen Bonds in Aromatic Ethers with Organoboron Compounds

Fumitoshi Kakiuchi,*,†,‡ Mayumi Usui,† Satoshi Ueno,† Naoto Chatani,† and Shinji Murai†

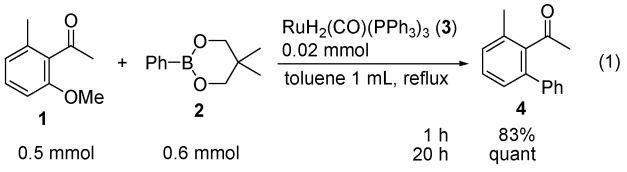
Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan, and PRESTO, JST, 4-1-8 Honcho Kawaguchi, Saitama, Japan

Received October 30, 2003; E-mail: kakiuchi@chem.eng.osaka-u.ac.jp

The development of catalytic methods involving the cleavage of unreactive bonds such as carbon−hydrogen,[1] carbon−carbon,[2] and carbon−fluorine[3] bonds has been a highly attractive research area in organic and organometallic chemistry. In addition to the above bonds, the aryl carbon−oxygen bond in aryl ethers (Ar−OR) is also unreactive because of its large bond dissociation energy (ca. 100 kcal/mol).[4] For the cleavage of aryl C−O bonds by low-valent transition metal complexes, the presence of a strong electron-withdrawing group, such as CF_3SO_2, near a phenolic oxygen is typically required. Thus, the cleavage of aryl C−O bonds is generally difficult without assistance from a strong electron-withdrawing group.

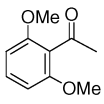
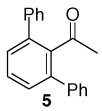
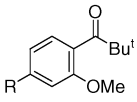
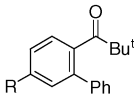
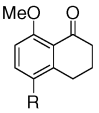
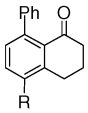
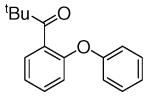
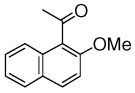
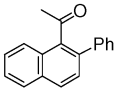
In 1979, Wenkert reported that the nickel-catalyzed reaction of aryl methyl ethers with Grignard reagents resulted in the production of alkylated arenes.[5] To the best of our knowledge, this is the only example of a transition metal-catalyzed reaction involving an aryl C−O (Ar−OR) bond cleavage.[6] However, only a limited number of examples have been examined for this reaction. In this Communication, we describe a ruthenium-catalyzed reaction of aromatic ethers with organoboronic acid esters (organoboronates) via aryl C−O bond cleavage by means of chelation assistance.

As part of an ongoing program in chelation-assisted reactions of aromatic ketones with arylboronates,[7] we discovered a unique protocol for the conversion of aryl C−O bonds to C−C bonds with the aid of $RuH_2(CO)(PPh_3)_3$. The reaction of 2′-methoxy-6′-methylacetophenone (**1**) with 5,5-dimethyl-2-phenyl-[1,3,2]dioxaborinane (**2**) was carried out in the presence of $RuH_2(CO)(PPh_3)_3$ (**3**) as a catalyst. The ortho phenylated product **4** was obtained in quantitative yield in 20 h (eq 1). To the best of our knowledge, this reaction is the first example of the efficient catalytic conversion of Ar−OR bonds in aryl ethers to C−C bonds via an oxidative addition to the ruthenium complex. This result motivated us to examine this coupling reaction more extensively.



Among complexes such as $RuH_2(CO)(PPh_3)_3$ (**3**), $Ru_3(CO)_{12}$, $Ru(CO)_2(PPh_3)_3$, $RuHCl(CO)(PPh_3)_3$, and $Cp^*Rh(C_2H_3SiMe_3)_2$, **3** showed the highest catalytic activity, but the activity of the others was poor (less than 10% yield). A substituent on the boron atom affects the reactivity of the phenylboronates. Because boronate **2** exhibited the highest reactivity among the phenylboronates screened [e.g., Ph-B$(OR)_2$, where $(OR)_2$ = OCH_2CH_2O (72%), $OCH(CH_3)CH(CH_3)O$ (57%), $OC(CH_3)_2C(CH_3)_2O$ (42%), $O(CH_2)_3O$ (62%), $OCH(CH_3)CH_2CH(CH_3)O$ (76%), or $OCH_2C(CH_3)_2CH_2O$ (**2**) (83%)], **2** was chosen for the coupling reactions described here.

Table 1. Ruthenium-Catalyzed Phenylation of Aromatic Ketones with Phenylboronate 2 via a Carbon−Oxygen Bond Cleavage[a]

run	ketone	time, h	product	Yield[b]
1[c]		1	 **5**	96%
2	 R = H (**6**)	20	 **7**	92%
3	R = OMe	20		76%
4	 R = H	20		55%
5	R = OMe	3		75%
6		20	**7**	60%
7		1		84%

[a] Reaction conditions: ketone (0.5 mmol), phenylboronate **2** (0.6 mmol), $RuH_2(CO)(PPh_3)_3$ (**3**) (0.02 mmol), and toluene 1 mL, reflux. [b] Isolated yield. [c] 1.2 mmol of **2** was used.

Several aromatic ketones having alkoxy groups at the ortho position can be used in this coupling reaction. Some selected results are shown in Table 1. The reaction of 2′,6′-dimethoxyacetophenone with **2** gave the corresponding 1:2 coupling product **5** in 96% yield (run 1). The use of 2′-methoxypivalophenone (**6**) resulted in the formation of the monophenylated product as the major end product (run 2). In this case, two reaction sites are possible. One is a C−O bond and the other a C−H bond.[7] The coupling reaction proceeded only at the C−O bond. In the case of the reaction of 2′,4′-dimethoxypivalophenone, phenylation occurred exclusively at the position ortho to the pivaloyl group, and the para MeO group remained intact (run 3). Fused aromatic ketones can also be used. In the case of 6-methoxy-α-tetralone, the phenylation product was obtained in 55% yield (run 4). The reaction of 3,6-dimethoxy-α-tetralone took place only at the 6-position (run 5). There are two different aryl C−O bonds in 2′-phenoxypivalophenone (run 6). The phenylation took place only at the benzene ring containing the pivaloyl group, giving **7** in 60% yield. In the case of runs 3, 5, and

† Osaka University.
‡ PRESTO, JST.

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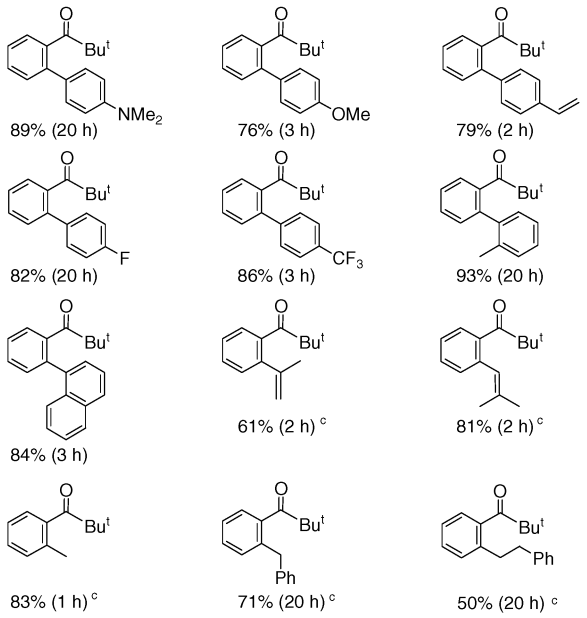
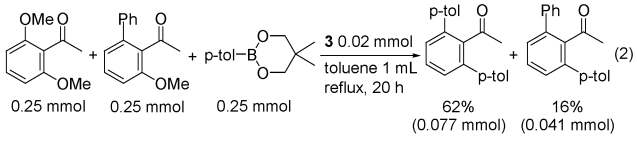
Table 2. Ruthenium-Catalyzed Coupling Reaction of 6 with Several Organoboronates[a,b]



[a] Reaction conditions: ketone **6** (0.5 mmol), organoboronate (0.6 mmol), $RuH_2(CO)(PPh_3)_3$ (**3**) (0.02 mmol), and toluene 1 mL, reflux. [b] Isolated yield. [c] Ketone **6** (0.5 mmol), organoboronate (1 mmol), **3** (0.05 mmol), and xylene 1 mL, reflux.

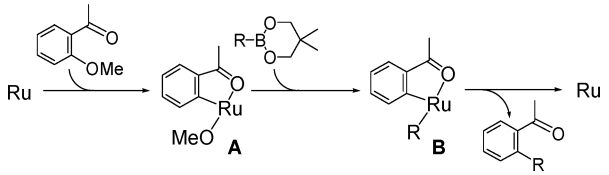
6, phenylation took place predominantly at the position ortho to the carbonyl group. In addition, no reaction occurred in the case of the reaction of anisole with the phenylboronate. These results strongly suggest that the coordination of the carbonyl group to the ruthenium is essential for the C−O bond cleavage to occur. The reaction with 1-naphthylboronate afforded the corresponding coupling product in 84% yield (run 7).

The reaction of 2′,6′-dimethoxyacetophenone gave **5** as a major product. From this product selectivity, we proposed that the second C−O bond cleavage took place without dissociation of the 1:1 coupling product from the ruthenium center.[8] To confirm this possibility, a competitive reaction of 2′,6′-dimethoxyacetophenone and 2′-methoxy-6′-phenylacetophenone with *p*-tolylboronate was performed (eq 2). This reaction gave 2′,6′-di(tolyl)acetophenone as a major product (62% yield based on the boronate). This result suggests that a major portion of **5** is formed without dissociation of the 1:1 coupling product.



A variety of organoboronates involving aryl, alkenyl, and alkylboronates can be used in this reaction. Some selected results are listed in Table 2. This coupling reaction is tolerant of both electron-donating and -withdrawing substituents such as NMe_2, OMe, vinyl, F, CF_3, and Me. In the case of the *p*-styrylboronate, two reaction sites are available. One is the Ar−B moiety and the other the vinyl moiey.[1c,8] Interestingly, aryl C−O/ArB$(OR)_2$ coupling occurred exclusively. It appears that the aryl C−O/ArB$(OR)_2$ coupling proceeds readily compared to C−H/olefin coupling.

Scheme 1. A Possible Reaction Pathway



A naphthalene derivative is also applicable. Alkenylation using alkenylboronates provided styrene derivatives in high yields. The reactions with 2-propenyl- and 2-methyl-1-propenylboronates gave the alkenylation products in 61% and 81% yields, respectively. Reactions using alkylboronates such as methyl-, benzyl-, and phenethylboronates afford the alkylation product. In the cases of alkenylation and alkylation, a higher loading of the catalyst and a higher reaction temperature were required to attain a high yield.

Although the mechanism for this reaction has not been elucidated, we speculate that this coupling reaction proceeds via the pathway shown in Scheme 1. The ortho C−O bond can be cleaved by the ruthenium complex to give (aryl)(methoxy)ruthenium intermediate **A**. A transmetalation between the organoboronates and intermediate **A** would result in the formation of (diorgano)ruthenium complex **B**. Reductive elimination from **B** provides the coupling product with the active catalyst species being regenerated.

In summary, this paper has presented our results concerning the cleavage of unreactive aryl C−O (Ar−OR) bonds in aromatic ethers by means of chelation assistance and catalytic conversion of these C−O bonds to C−C bonds using organoboron compounds. These results lead to the conclusion that otherwise unreactive aryl C−O bonds can be used in organic synthesis without transformation to $Ar-OSO_2CF_3$ bonds. We are currently broadening the scope of this reaction in an attempt to elucidate the pathway of this reaction.

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

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