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A Ruthenium-Catalyzed Reaction of Aromatic Ketones with Arylboronates: A New Method for the Arylation of Aromatic Compounds via C−H Bond Cleavage

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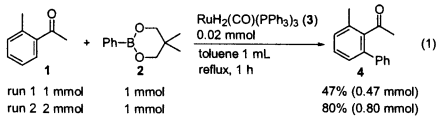
Among carbon−carbon bond forming reactions, the catalytic addition of C−H bonds to C−C multiple bonds has recently been a subject of considerable interest[1−6] because the direct use of unreactive C−H bonds for organic synthesis represents a powerful and relatively straightforward protocol. In previous studies, we reported that various aromatic compounds that contain appropriate directing groups can be used for transition-metal-catalyzed C−H/olefin,[1,3] C−H/acetylene,[1,4] and C−H/CO/olefin[5] couplings which permit the site-selective alkylation, alkenylation, and acylation of aromatic rings. In the case of the arylation of aromatic rings, however, these procedures cannot be employed. In this communication, we report on the ruthenium-catalyzed arylation of aromatic ketones with arylboron compounds, which represents a new catalytic reaction involving C−H bond cleavage.

Several research groups have recently reported on the electrophilic arylation of aromatic compounds via the use of transition metal catalysts.[7] In these cases, Ar−M−X (X = halogen) species participate in a C−H bond cleavage step. Thus, it is necessary for the C−H bond to be cleaved in an electrophilic fashion. The protocol described herein involves the oxidative addition of a C−H bond in aromatic ketones to a ruthenium(0) center, which is different from previously reported arylation procedures.[7]

The reaction of 2′-methylacetophenone (**1**) with phenylboronate **2** (5,5-dimethyl-2-phenyl-[1,3,2]dioxa-borinane) was carried out in the presence of $RuH_2(CO)(PPh_3)_3$ (**3**) as the catalyst in refluxing toluene (eq 1). When 1 equiv of ketone was used, the corresponding phenylation product **4** was obtained in 47% yield (eq 1, run 1). The use of 2 equiv of **1** improved the product yield based on **2** to 80% (eq 1, run 2).



Several other organometallic reagents, for example, phenylboronic acid, phenylboronic acid anhydride, sodium tetraphenylborate, and tetraphenyltin, were also examined. Of the reagents screened, phenylboronic acid showed reactivity, albeit in low efficiency as compared to **2**. Because arylboronates are usually easily handled, and readily prepared by the condensation of arylboronic acids with dioles, and are stable under ambient conditions,[8] arylboronates were chosen for the coupling reactions described here.

The applicability of several aromatic ketones was examined (Table 1). The reaction of acetophenone with **2** yielded the corresponding 1:1 and 1:2 coupling products in 7% (0.07 mmol) and 60% (0.30 mmol) yields, respectively (entry 1). In this case, the 1:2 coupling product was obtained as the major component. In the case of the reaction of isopropylphenyl ketone, the corresponding 1:2 coupling product was formed in 76% yield (entry 2). In the case of a bulky aromatic ketone, that is, *tert*-butylphenyl ketone (**5**), the 1:1 coupling product was obtained exclusively in 95% yield (entry 3). This selectivity can be explained by steric repulsion between the *tert*-butyl group and the introduced ortho phenyl group, because the same product selectivity in the ruthenium-catalyzed C−H/olefin coupling has also been reported.[1,3b] The presence of a methoxy group on the aromatic ring had no significant effect on reactivity (entry 4). In the case of the reaction of aromatic ketones containing a fluoro group, the fluoro group was retained in the coupling product (entry 5). The presence of a strong electron-withdrawing CF_3 group had no effect on reactivity (entry 6). The phenylation product was obtained in 90% yield. A phenyl group can be efficiently introduced in the naphthalene ring (entry 7). Although α-tetralone showed a higher reactivity than that of benzosuberone (**6**) in the case of the ruthenium-catalyzed C−H/olefin coupling, the reactivity of α-tetralone (56% yield for 20 h, entry 8) for this phenylation reaction was low as compared to benzosuberone (75% yield for 3 h, entry 9).

The reaction was then run using a variety of arylboronates, and some selected results are listed in Table 2. When *p*-*N*,*N*-dimethylaminophenylboronate was used, the product yield was decreased

Table 1. Products of the Ruthenium-Catalyzed Arylation of Several Aromatic Ketones with Phenylboronate **2**[a]

entry	ketone	time, h	product	Yield[b]
1	R = Me	1		60% (0.30)[c,d]
2	R = ^{i}Pr	1		76% (0.38)[c,e]
3	R = H	1		95%
4	R = OMe	1		78%
5	R = F	2		88%
6		1		90%
7		1		75%
8		20		56%
9	**6**	3		75%

[a] Reaction conditions: ketone (2 mmol), phenylboronate **2** (1 mmol), $RuH_2(CO)(PPh_3)_3$ (**3**) (0.02 mmol), toluene 1 mL, reflux. [b] Based on **2**. [c] The values in parentheses are mmols of products. [d] The corresponding 1:1 coupling product was also obtained in 7% yield. [e] The corresponding 1:1 coupling product was also obtained in 9% yield.

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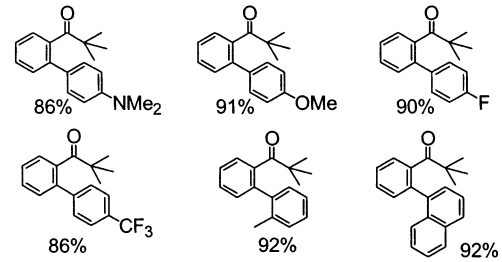
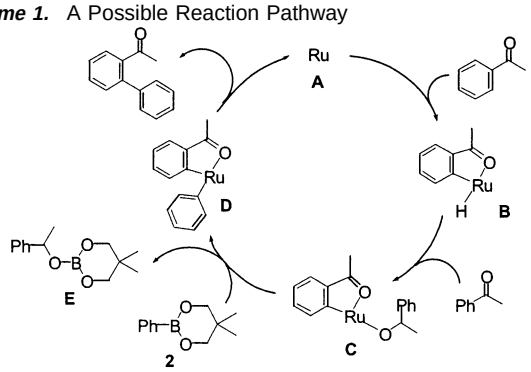
Table 2. Products of Reaction of the Ketone **5** with a Variety of Arylboronates[a]



[a] Reaction conditions: ketone (**5**) (2 mmol), arylboronate (1 mmol), $RuH_2(CO)(PPh_3)_3$ (**3**) (0.02 mmol), toluene 1 mL, reflux, 1 h.

Scheme 1. A Possible Reaction Pathway



slightly to 86%. Both electron-donating (Me_2N and MeO) and electron-withdrawing (F and CF_3) groups had no significant effect on reactivity, and the corresponding biaryl compounds were obtained in high yields in each case. Even when slightly sterically congested arylboronates (*o*-tolyl- and α-naphthylboronates) were used in this coupling reaction, the expected biaryl compounds were obtained in high yields.

An NMR experiment was run to obtain information concerning the transmetalation step. The reaction of ketone **5** (0.2 mmol) with the phenylboronate **2** (0.1 mmol) was carried out in the presence of catalyst **3** (0.01 mmol) in toluene-d_8 at 115 °C. After the mixture was heated for 1 h, the ^{11}B NMR spectrum of the reaction mixture showed that the signal of **2** (δ 26.15) had completely disappeared and that a new signal appeared at 17.14 ppm which can be assigned to a trialkoxyborane species.[9] The GC-MS spectrum of the reaction mixture was also consistent with the formation of the trialkoxyborane (2-(2,2-dimethyl-1-phenyl-propoxy)-5,5-dimethyl-[1,3,2]-dioxa-borinane).[10]

From these observations, we speculate that this coupling reaction proceeds via a pathway shown in Scheme 1. The ortho C−H bond is cleaved by ruthenium(0) complex **A**[11,12] to give the ortho metalated intermediate **B**. The addition of a Ru−H bond in **B** to the ketone carbonyl group leads to the production of an (alkoxy)-ruthenium intermediate **C**. A transmetalation between the phenylboronate and intermediate **C** results in the formation of the (diaryl)ruthenium complex **D**[7c] and the trialkoxyborane (borinate) **E**. Reductive elimination leading to C−C bond formation then provides the arylation product and the regeneration of the active catalyst species **A**.

Oi and co-workers reported on the rhodium-catalyzed arylation of phenylpyridines with tetraaryltin compounds.[13] In this case, the use of halogenated hydrocarbon solvents such as 1,1,2,2-tetrachloroethane is essential for attaining a catalytic reaction. The initial step of this reaction appears to involve the oxidation of the rhodium(I) species to the corresponding rhodium(III) species with the halogenated solvent.[14] Thus, the C−H bond cleavage step would proceed via an electrophilic substitution reaction.[14]

The ruthenium-catalyzed ortho arylation of aromatic ketones with arylboronates provides a new approach to C−C bond formation via a novel transmetalation pathway and provides a new protocol for the synthesis of biaryl compounds. To the best of our knowledge, this reaction is the first example of the catalytic coupling of C−H bonds with organometallic compounds via the oxidative addition of C−H bonds. We are currently broadening the scope of this reaction and attempting to elucidate the reaction pathway of this process.

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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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