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# A $RuH_2(CO)(PPh_3)_3$-Catalyzed Regioselective Arylation of Aromatic Ketones with Arylboronates via Carbon−Hydrogen Bond Cleavage

Fumitoshi Kakiuchi,*[,†,‡] Yusuke Matsuura,[†] Shintaro Kan,[†] and Naoto Chatani[†]

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

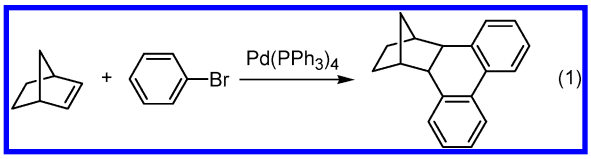
Received November 4, 2004; E-mail: kakiuchi@chem.eng.osaka-u.ac.jp.

***Abstract:*** When the reaction of aromatic ketones with arylboronates (arylboronic acid esters) using $RuH_2(CO)(PPh_3)_3$ (**3**) as a catalyst was conducted in toluene, the corresponding arylation product was obtained in moderate yields. In this case, a nearly equivalent amount of a benzyl alcohol derived from a reduction of an aromatic ketone was also formed. The use of aliphatic ketones, such as pinacolone and acetone, as an additive or a solvent dramatically suppressed the reduction of the aromatic ketones and, as a result, ortho-arylation products were obtained in high yield based on the aromatic ketones. In these reactions, the aliphatic ketone functioned as a scavenger of ortho-hydrogens of the aromatic ketones and the $B(OR)_2$ moiety of the arylboron compound (HB species). A variety of aromatic ketones, such as acetophenones, acetonaphthones, tetralones, and benzosuberone, could also be used in this coupling reaction. Several arylboronates containing electron-donating ($NMe_2$, OMe, and Me) and -withdrawing ($CF_3$ and F) groups were also applicable to this coupling reaction. Intermolecular competitive reaction using pivalophenone-$d_0$ and -$d_5$ and intramolecular competitive reaction using pivalophenone-$d_1$ were carried out using **3** as a catalyst. The $k_H/k_D$ value for the intermolecular competitive reaction was substantially different, compared with intramolecular competitive reaction. This strongly suggests the production of an intermediate where the ketone carbonyl is coordinated to the ruthenium involved in this catalytic reaction. $^1H$ and $^{11}B$ NMR studies using 2′-methylacetophenone, phenylboronate (**2**), and pinacolone (**6**) indicate that **6** functions effectively as a scavenger of the HB species.

## Introduction

The development of highly efficient, selective catalytic reactions involving C−H bond cleavage has been a subject of considerable interest in organic and organometallic chemistry. During the past decade, a variety of reactions that involve C−H bond transformations have been developed.[1,2] Among these, the catalytic conversion of C−H bonds to C−C bonds is one of the most useful transformations, because of the importance of C−C bond formation in organic synthesis. To date, several different types of transition-metal-catalyzed C−C bond formation have been reported, involving alkylation with olefins,[3−5] alkenylation with acetylenes,[6,7] carbonylation with olefins and carbon monoxide,[8] and the hydroacylation of olefins and acetylenes.[9] These reactions involve the addition of C−H bonds to C−C multiple bonds. In the case of the arylation of C−H bonds, this approach is not applicable. Such a reaction usually requires the coupling of C−H bonds with Ar−X bonds. To date, several examples of the arylation of C−H bonds in arenes using aryl halides or aryl pseudo-halides have been reported.[10−18]

The first example of this type of reaction was reported by Chiusoli in 1985[10] and involved the reaction of bromobenzene with norbornene using $Pd(PPh_3)_4$ as a catalyst to give 1,2,3,4,-4a,12b-hexahydro-1,4-methanotriphenylene (eq 1). de Meijere



(1)

subsequently reported a similar biarylation reaction in which aryl halides were reacted with norbornene using a palladium catalyst.[11] Since these pioneering studies, several studies with respect to catalytic arylations of C−H bonds have been reported.[12−18] In 1997, Miura achieved an important advance in this area.[12] When the reactions of aromatic carbonyl compounds such as ketones,[12d] amides,[12e] and aldehydes[12d] with aryl halides were carried out with the aid of a palladium complex as the catalyst, C−C bond formation took place between the α carbon of the carbonyl functionality and the ortho carbon in

† Osaka University.
‡ PRESTO.

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the benzene ring toward the carbonyl group. In this case, the coordination of the carbonyl group to palladium was important for the success of this regioselective arylation. They also reported the arylation of phenols,[12a−c] naphthols,[12b] and arylmethanols.[12f] Dyker reported that the palladium-catalyzed arylation of $sp^3$ C−H bonds proceeded via a similar reaction pathway. In their studies, the palladium-catalyzed reaction of 1-*tert*-butyl-2-iodobenzene gave the cyclization product, i.e., 7,7-dimethylbicyclo[4.2.0]octa-1,3,5-triene.[13] Sames recently reported on the phenylation of alkane segments using $Ph_2Si(OH)Me$ with the aid of $Pd(OAc)_2/Cu(OAc)_2$/benzoquinone.[14] In this case, the palladium(II) species functioned as a catalyst. Oi reported that, in the case of the arylation of 2-arylpyridines and arylimines with aryl halides, $RuCl_2(PPh_3)_3$ exhibited good catalytic activity.[15] They proposed that a Ru(IV) species derived from an oxidative addition of an aryl halide to the Ru(II) species served as the catalytically active species. In 2003, Bedford reported that the $RhCl(PPh_3)_3$-catalyzed arylation of phenols with aryl halides can be achieved using phosphinite ($PR_2(OAr)$) as a cocatalyst.[16] The important points of this reaction are the exchange of phenols with the arylated phenoxy moiety on the phosphinite and the generation of electrophilic Rh(III) species via the oxidative addition of aryl halides to the Rh(I) complex. Sharp reported that the arylation of 3-carbethoxyfuran and 3-carbomethoxythiophene with an aryl bromide proceeded at the 2-position.[17] The arylation of thiazole with an aryl iodide using $PdCl_2(PPh_3)_2$/CuI as a catalyst was reported by Mori.[18] In all of these reactions mentioned above, C−H bond cleavage took place via an electrophilic substitution pathway. Thus, Ar−M−X species which were formed by the oxidative addition of aryl halides or pseudo-halides to the corresponding low-valent transition-metal complex functioned as an electrophile. The hydrogens of the ortho C−H bonds should be removed as protons.

Another type of catalytic arylation of C−H bonds has recently been reported by Oi[19] and by us.[20] Oi found that the rhodium-catalyzed reaction of arylpyridines with tetraaryltins gave the ortho arylation product. In this case, the use of a halogenated solvent such as 1,1,2,2-tetrachloroethane is important for this reaction to proceed effectively. While the reaction pathway has not been elucidated, they proposed that the initial step in this reaction appeared to involve the oxidation of the rhodium(I)


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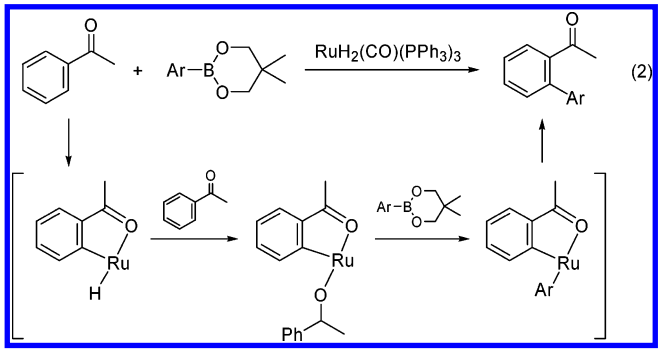
species to the corresponding rhodium(III) species by the halogenated solvent. Thus, the C−H bond cleavage step would proceed via an electrophilic substitution reaction.[21] This is unique in the arylation of C−H bonds, but its applicability is restricted. Recently, we reported on the ruthenium-catalyzed arylation of ortho C−H bonds in aromatic ketones with arylboronates (arylboronic acid esters), in which ortho arylation products were obtained in good yields (eq 2).[20] In this arylation



(2)

reaction, a nearly equivalent amount of alcohol derived from the reduction of the starting ketone was obtained as a byproduct. This suggests that the hydrogen of the ortho C−H bond is removed as a hydride and is then transferred to the ketone carbonyl. From this observation, we proposed that the C−H bond was cleaved via an oxidative addition to a ruthenium(0) species to give an aryl−Ru−H species. Thus, the mechanism of the C−H bond cleavage step in our coupling reaction appears to be different from the other precedent examples.

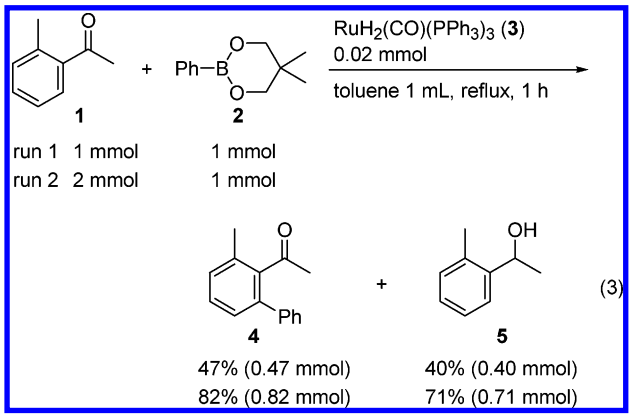
In our arylation reaction, one of the most important steps is the generation of a ruthenium−alkoxy (Ru−OR) species, a key intermediate in the transmetalation which appeared to be formed by the addition of a Ru−H species to a carbonyl group in aromatic ketones. For each molecule of arylation product formed, one molecule of the aromatic ketones should be reduced to a benzyl alcohol derivative. Therefore, the reduction of one molecule of the ketone to the corresponding alcohol is an inevitable side reaction. This reduction is the most serious, open issue of our arylation protocol, and a variety of efforts have been made to suppress this side reaction. We found that some aliphatic ketones, such as pinacolone and acetone, could effectively function as an acceptor of the hydrogen of the ortho C−H bond in aromatic ketones and the $B(OR)_2$ moiety of arylboronates $Ar-B(OR)_2$ (hereafter abbreviated as HB species), thus suppressing the reduction of the aromatic ketones.

In this paper, we report that the ruthenium-catalyzed arylation of aromatic ketones with arylboronates in the presence of an aliphatic ketone as an acceptor of HB species gives an ortho-arylated aromatic ketone in high yield, based on the aromatic ketone. A plausible reaction pathway for this arylation reaction is proposed.

## Results and Discussion

When the reaction of aromatic ketones with arylboronates ($Ar-B(OR)_2$) was conducted in refluxing toluene with the aid of $RuH_2(CO)(PPh_3)_3$ as a catalyst, the ortho-arylation of the aromatic ketone occurred via C−H bond cleavage. In addition to the arylation product, this coupling reaction gave the benzyl alcohol, formed by the addition of the HB species to the carbonyl group of the aromatic ketone. To suppress this undesired reduction of aromatic ketones, the reaction was carried out in the presence of an aliphatic ketone, which was employed as a scavenger of the HB species. Among the aliphatic ketones examined, pinacolone (3,3-dimethyl-2-butanone) showed the highest activity for the C−H/$ArB(OR)_2$ coupling in many cases. In some cases, acetone could also be used as a scavenger of the HB species. This arylation reaction using arylborons can be applied to a variety of combinations of aromatic ketones and arylboronates. In many cases, the corresponding ortho-arylation products were obtained in high to excellent yields based on the aromatic ketones. The importance of the coordination of ketone carbonyl to the ruthenium center was revealed by means of inter- and intramolecular competitive reactions using deuterium-labeled pivalophenones. The formation of $^tBu(Me)CH(OB(OR)_2)$ by addition of the HB species to pinacolone was verified by $^1H$ and $^{11}B$ NMR and GC/MS spectroscopy.

**Reactions of 2′-Methylacetophenone with Phenylboron Compounds: Optimization of Reaction Conditions.** The reaction of 2′-methylacetophenone (**1**) with 5,5-dimethyl-2-phenyl[1,3,2]dioxaborinane (**2**) was carried out in refluxing toluene using $RuH_2(CO)(PPh_3)_3$ (**3**) as a catalyst (run 1 in eq 3). When 1 equiv of ketone was used, the corresponding ortho-



(3)

phenylation product **4** was obtained in 47% yield (0.47 mmol) (run 1 in eq 3). In this case, a nearly equivalent amount (40% yield, 0.4 mmol)) of (2-methylphenyl)ethyl alcohol (**5**), a reduction product of **1**, which was formed by a hydrolysis of 5,5-dimethyl-2-(1-*o*-tolylethoxy)[1,3,2]dioxaborinane during the workup, was obtained as a byproduct. When a 2-fold excess of ketone **1** was used, **4** was obtained in 82% yield, based on phenylboronate **2** (run 2 in eq 3).

The catalytic activities of some ruthenium and rhodium complexes were investigated under the same reaction conditions as used in run 2 in eq 3. When the reaction of **1** with **2** was conducted in refluxing toluene for 20 h using a ruthenium complex such as $Ru(CO)_2(PPh_3)_3$, $Ru(CO)_3(PPh_3)_2$, $RuHCl(CO)(PPh_3)_3$, and $RuHCl(CO)(PPh_3)_3$/CsF, coupling product **4** was obtained in 33%, 19%, 0%, and 29% yields, respectively. For the present phenylation reaction, $(\eta^5\text{-}C_5Me_5)Rh(C_2H_3SiMe_3)_2$, which showed catalytic activity for the alkylation of aromatic ketones with olefins,[4f] was ineffective as a catalyst. Among the complexes screened, $RuH_2(CO)(PPh_3)_3$ (**3**) exhibited the highest activity. Therefore, **3** was used in the coupling reaction described below.

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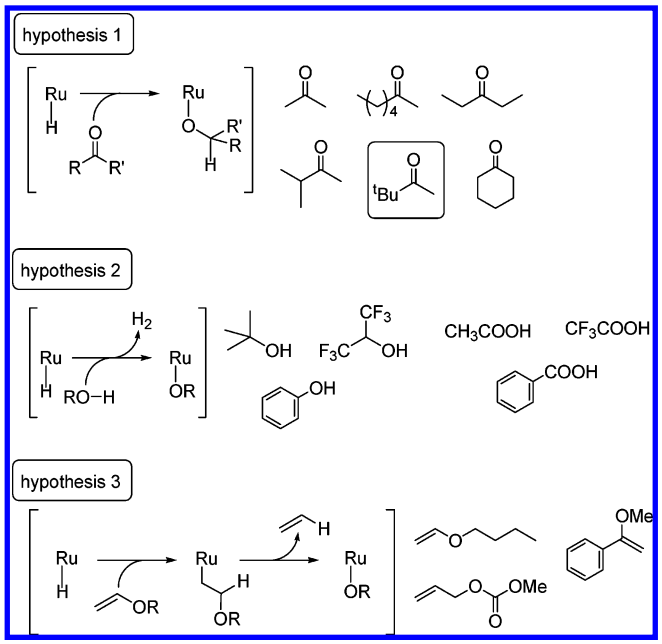
***Scheme 1.*** Hypotheses for Conversion of a Ru−H Bond to a Ru−OR Bond




In this phenylation, the formation of benzyl alcohol **5** is an inevitable side reaction under the reaction conditions shown in eq 3. This suggests that the addition of the Ru−H bond to the carbonyl group in the aromatic ketone is a key step in this coupling reaction. Thus, the generation of a ruthenium−alkoxide (Ru−OR) species is essential in the transmetalation step. We propose that, in place of the reduction of aromatic ketones with the Ru−H species, the following three protocols appeared to be effective for the conversion of the Ru−H to the Ru−OR species: (i) the addition of the Ru−H to a carbonyl group in aliphatic ketones (hypothesis 1 in Scheme 1),[22] (ii) protonation of the Ru−H species with alcohols or carboxylic acids (hypothesis 2 in Scheme 1),[23] and (iii) a $\beta$-alkoxy elimination[24] from the $\beta$-alkoxy(ethyl)ruthenium intermediate formed by the hydroruthenation to a vinyl ether or allyl carbonate (hypothesis 3 in Scheme 1).

We verified the possibility of hypothesis 1 using several aliphatic ketones, such as 3,3-dimethyl-2-butanone (pinacolone) (**6**), acetone, 2-heptanone, 3-pentanone, 3-methyl-2-butanone, and cyclohexanone (Table 1). The findings show that pinacolone **6** exhibited the highest activity for the coupling reaction. Acetone could also be used as a scavenger of the HB species, but its efficiency and generality were slightly lower than those of **6**. These ketones have large p$K_E$ values (pinacolone, p$K_E$ = 8.76; acetone, p$K_E$ = 8.33), indicating a large contribution by the keto form.[25] Thus, these ketones can potentially function as

***Table 1.*** Screening of Aliphatic Ketone as a Scavenger

| | | | % yield[b] | |
|---|---|---|---|---|
| run | aliphatic ketone | p$K_E$[a] value | **4**[c] | **8**[d] |
| 1 | pinacolone (**6**) | 8.76 | 67 | 72 |
| 2 | acetone | 8.33 | 65 | 61 |
| 3 | 2-heptanone[e] | 7.51 | 17 | 10 |
| 4 | 3-pentanone | 7.43 | 7 | 37 |
| 5 | 3-methyl-2-butanone | 7.33 | 29 | 15 |
| 6 | cyclohexanone | 6.38 | 13 | NR |
| 7[f] | 6 | 8.76 | 64[g] | 66[g] |
| 8[h] | 6 | 8.76 | 85[g] | 76[g] |
| 9[i] | 6 | 8.76 | 81[g] | − |

[a] From ref 25. [b] GC yield. [c] Reaction conditions: 2′-methylacetophenone **1** (1 mmol), phenylboronate **2** (1 mmol), toluene (1 mL), aliphatic ketone (2 mmol), $RuH_2(CO)(PPh_3)_3$ (**3**) (0.02 mmol), reflux or 110 °C (sealed tube), 20 h. [d] Reaction conditions: pivalophenone **7** (1 mmol), **2** (1 mmol), pinacolone **6** (0.5 mL, 4 mmol), **3** (0.02 mmol), reflux or 110 °C (sealed tube), 20 h. [e] The value of the p$K_E$ for 2-butanone is used, neglecting the effect of the alkyl chain length. [f] **6** (0.5 mL). [g] Isolated yield. [h] **6** (1 mL). [i] **6** (2 mL).

good acceptors of Ru−H species. Though the ability of the HB species to serve as a scavenger was not certainly consistent with the order of the p$K_E$ values, the higher contribution of the keto form appeared to be suitable for the addition of the Ru−H species to the carbonyl group to give the Ru−OR species. The activity of aliphatic ketones as a scavenger was also examined using 2,2-dimethylpropiophenone (pivalophenone) (**7**). When the reaction was conducted in pinacolone or acetone, the coupling product **8** was obtained in high yields as well as the reaction of **1**. On the basis of hypothesis 2, we examined the protonation of the Ru−H bond with an alcohol or a carboxylic acid[23] such as *tert*-butyl alcohol, hexafluoro-2-propanol, phenol, acetic acid, trifluoroacetic acid, and benzoic acid. Unfortunately, no reaction or a substantial decrease in yield was observed. We also investigated the possibility of $\beta$-alkoxy elimination (hypothesis 3 in Scheme 1). When the arylation was conducted in the presence of vinyl alcohols or allyl methyl carbonate, no improvement in activity was observed. On the basis of these results, we employed pinacolone **6** as the scavenger of the HB species.

**Screening of Phenylboron Compounds.** In transition-metal-catalyzed coupling reactions using organoboron compounds such as the Suzuki−Miyaura coupling, the substituent on the boron atom influences the reactivity and stability of the boron compounds.[26] To determine the optimal substituent on the boron atom, the coupling reaction of **1** with several phenylboron compounds was examined (Table 2). When the reaction of **1** with **2** was carried out in refluxing pinacolone, **4** was obtained in 85% isolated yield (run 1). In the case of the reaction with phenylboronic acid, a trace amount of **4** was obtained (run 2). When the reaction was conducted in the presence of potassium fluoride,[27] the yield was improved to 26% (run 3), but ketone **1** was recovered only in 34% yield. This suggests that ketone **1** also functioned as a scavenger of the HB species. Reactions using 2-phenyl[1,3,2]dioxaborolane **9** (run 4), 4,4,5,5-tetramethyl-2-phenyl[1,3,2]dioxaborolane **10** (run 5), and 2-phenyl[1,3,2]dioxaborinane **11** (run 6), gave **4** in 60%, 46%, and 62% yields, respectively. Phenylboronate **2** had the highest phenylating ability among the phenylboron compounds screened.

(22) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; Chapter 2. (b) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; Chapter 1. (c) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis*; VCH: Weinheim, 1993. (d) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(23) (a) Field, L. D.; Hambley, T. W.; Yau, B. C. K. *Inorg. Chem.* **1994**, *33*, 2009−2017. (b) Osakada, K.; Ohshiro, K.; Yamamoto, A. *Organometallics* **1991**, *10*, 404−410.

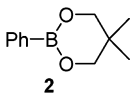
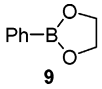
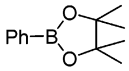
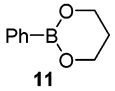
(24) (a) Ito, H.; Nakamura, T.; Taguchi, T.; Hanazawa, Y. *Tetrahedron* **1995**, *51*, 4507−4518. (b) Bedjeguelal, K.; Bolitt, V.; Sinou, D. *Synlett* **1999**, 762. (c) Hara, R.; Ura, Y.; Huo, S.; Kasai, K.; Suzuki, N.; Takahasahi, T. *Inorg. Chim. Acta* **2000**, *300*−*302*, 741−748.

(25) Keeffe, J. R.; Kresge, A. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1990**, *112*, 4862−4868.

(26) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695.

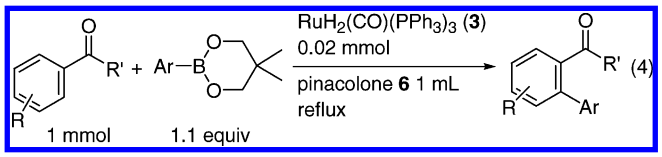
(27) Wright, S. W.; Hangeman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095−6097.

***Table 2.*** Screening of Phenylboronates[a]

| run | Ph−B(OR)$_2$ | yield of **4** | recovery of **1** |
|---|---|---|---|
| 1 |  **2** | 85% | trace |
| 2 | Ph−B(OH)$_2$ | trace | >95% |
| 3 | Ph−B(OH)$_2$[b] | 26% | 34% |
| 4 |  **9** | 60% | 6% |
| 5 |  **10** | 46% | 25% |
| 6 |  **11** | 62% | 7% |

[a] Reaction conditions: 2′-methylacetophenone **1** (1 mmol), phenylboronate (1.1 mmol), pinacolone (**6**) (1.0 mL), $RuH_2(CO)(PPh_3)_3$ (**3**) (0.02 mmol), reflux, 1 h. [b] KF (1 mmol) was added.

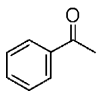
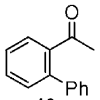
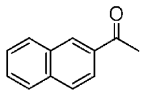
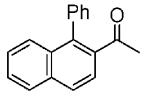
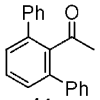
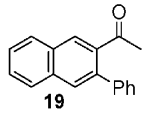
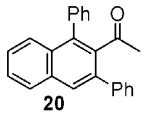
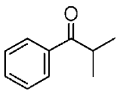
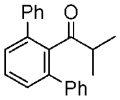
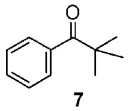
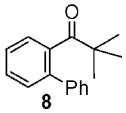
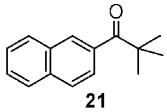
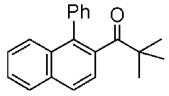
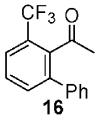
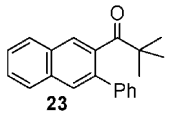
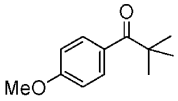
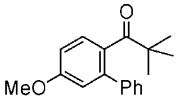
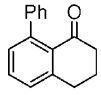
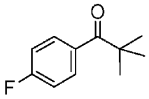
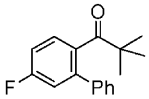
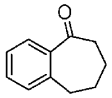
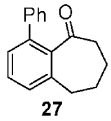
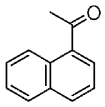
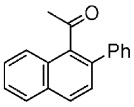
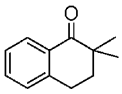
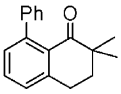
After further optimization of the reaction conditions, we adopted 2 mol % $RuH_2(CO)(PPh_3)_3$ (**3**), aromatic ketone (1 mmol), and arylboronates (1.1 equiv) in refluxing pinacolone (**6**) (1 mL) as the standard reaction conditions (eq 4).




**Phenylation Reactions of Various Aromatic Ketones.** The applicability of aromatic ketones for use in this arylation reaction was examined using phenylboronate **2** (Table 3). In the case of the reaction of acetophenone **12** using equimolar amount of **2** in refluxing pinacolone, a mixture of mono- and diphenylation products was obtained in 17% (**13**, 0.17 mmol) and 39% (**14**, 0.39 mmol) yields based on **12**, respectively (run 1). When an excess amount (2.2 mmol) of **2** was used in the coupling reaction of **12**, diphenylation product **14** was formed in 89% yield along with a 3% yield of **13** (run 2). In the reaction of 2-methyl-1-phenylpropan-1-one, the 1:2 coupling product was also formed as the major product (run 3). A similar product selectivity was observed in the ruthenium-catalyzed reactions of aromatic ketones,[3a−c] esters,[3d] and nitriles[3g] with olefins. It has been proposed that these alkylation reactions proceed without the dissociation of the 1:1 coupling product from the ruthenium center. These observations provide for a scenario in which the second C−C bond formation takes place without the dissociation of the 1:1 coupling product from the ruthenium. When an aromatic ketone with a sterically hindered *tert*-butyl group on the carbonyl group was used, product selectivity was dramatically changed. In the case of pivalophenone (**7**), the corresponding mono phenylation product **8** was obtained in 76% yield as the sole product (run 4). The large steric repulsion between the *tert*-butyl group and the ortho phenyl group introduced at the ortho position inhibited the second C−H bond cleavage. The reaction of 2′-α,α,α-trifluoromethylacetophenone (**15**) gave the coupling product **16** in 61% yield (run 5). In this case, **15** and **16** were reduced to some extent. Our proposed explanation for this is that the electron-withdrawing $CF_3$ group increases the electrophilicity of the carbonyl group in the starting material **15** and in the coupling product **16**. The methoxy and fluoro groups at the 4′-position in the aromatic ring remained intact in the coupling products (runs 6 and 7). These results suggest that the electronic nature of the substituent on the aromatic ring does not exert a large affect on the reactivity of these ketones. Naphthalene derivatives can also be used in this reaction. The reaction of 1-acetonaphthone with **2** gave the expected 2-phenyl-1-acetonaphthone in 78% yield (run 8). In the case of the reaction of 2-acetonaphthone (**17**) using 1.1 equiv of **2**, 1-phenyl- (**18**), 3-phenyl- (**19**), and 1,3-diphenylacetonaphthones (**20**) were obtained in 5% (0.05 mmol), 46% (0.46 mmol), and 16% (0.16 mmol) yields, respectively (run 9). When 2 equiv of **2** was used for this coupling reaction, the reaction afforded a mixture of **19** and **20** in 12% and 55% yields, respectively (run 10). It is noteworthy that C−C bond formation also took place at the *β*-position, although in the alkylation of **17** with triethoxyvinylsilane, C−C bond formation occurs only at the α position. To determine the relative reactivity of these two C−H bonds, 2-pivalonaphthone (**21**) was used in this coupling reaction because the pivaloyl group suppressed the second C−H bond cleavage or C−C bond formation. Thus, in this case, the mono coupling product was obtained exclusively. In this case, α- and *β*-phenylation products (**22** and **23**, respectively) were obtained in 17% and 64% yields, respectively (run 11). We attribute this regioselectivity to steric repulsion between the ruthenium center and the hydrogen at the peri-position (the 8-position) or among the phenyl group and the ruthenium atom and the hydrogen at the 8-position, which would disturb C−C bond formation at the 1-position (Figure 1). Fused aromatic ketones, i.e., α-tetralone **24**, 1-benzosuberone **26**, and 2,2-dimethyl-α-tetralone, exhibited a high reactivity. The reaction of ketone **24** gave the phenylation product **25** in 92% yield. In this case, **24** was recovered in 6% yield. Among the aromatic ketones examined, 1-benzosuberone (**26**) showed the highest reactivity. The reaction of **26** with **2** gave the phenylation product **27** in 98% yield. The reaction of 2,2-dimethyl-α-tetralone also gave the coupling product in 91% yield, but a prolonged reaction period (20 h) was required to attain this high yield. This suggests that steric congestion around the carbonyl group retarded the reactivity of the ketone substantially.

**Reaction of 1-Benzosuberone 26 with Arylboronates.** The applicability of arylboronates was examined using ketone **26**, which exhibited the highest reactivity. Some selected results are listed in Table 4. The reaction with arylboronates containing an electron-donating group such as methoxy and *N*,*N*-dimethylamino groups gave the corresponding arylation products in 88% and 84% yields, respectively (runs 1 and 2 in Table 4). Reactions with *p*-fluoro- and *p*-trifluoromethylphenylboronates also provided arylation products in good yields (75% and 84% yields, respectively). These results indicate that the electronic nature of the substituent on the aromatic ring does not greatly affect reactivity. In the case of reactions with sterically hindered arylboronates, it would appear that the reactivity of the boronates is low. Interestingly, however, coupling reactions using 2-tolyl-

***Table 3.*** Aromatic Ketone Generality[a]

| run | ketone | time | product | yield[b] | run | ketone | time | product | yield[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1[c] |  **12** | 2 h |  **13** | 17% (0.17 mmol) | 9 |  **17** | 20 h |  **18** | 5% (0.05 mmol) |
| | | |  **14** | 39% (0.39 mmol) | | | |  **19** | 46% (0.46 mmol) |
| 2[d] | **12** | 1 h | **14** | 89% | | | |  **20** | 16% (0.16 mmol) |
| 3[e] |  | 1 h |  | 70% | 10[f] | **17** | 1 h | **19** | 12% |
| | | | | | | | | **20** | 55% |
| 4 |  **7** | 1 h |  **8** | 76% | 11 |  **21** | 2 h |  **22** | 17%[g] |
| 5 |  **15** | 2 h |  **16** | 61% | | | |  **23** | 64%[g] |
| 6 |  | 1 h |  | 81% | 12[h] |  **24** | 4 h |  **25** | 92% |
| 7 |  | 1 h |  | 78% | 13[i] |  **26** | 4 h |  **27** | 98% |
| 8 |  | 3 h |  | 78% | 14[h] |  | 24 h |  | 91% |

[a] Reaction conditions: aromatic ketone (1 mmol), phenylboronate (**2**) (1.1 mmol), $RuH_2(CO)(PPh_3)_3$ (**3**) (0.02 mmol), pinacolone (1.0 mL, 8 mmol), reflux. [b] Isolated yield. [c] **2** (1 mmol). [d] **2** (2.2 mmol). [e] **2** (2 mmol), pinacolone (0.5 mL). [f] **2** (2 mmol). [g] Products **22** and **23** were isolated in 81% yield as a mixture with a ratio of 21:79, respectively. [h] **2** (1.5 mmol), pinacolone (0.5 mL). [i] **2** (1.2 mmol), pinacolone (0.5 mL).

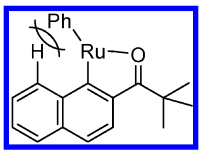
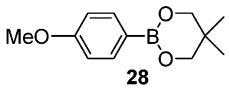
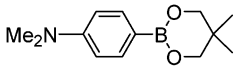
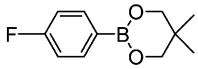
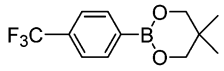
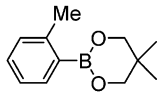
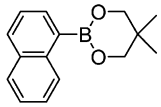



***Figure 1.*** Steric repulsion between the peri-hydrogen and the ruthenium complex.

(run 5) and 1-naphthylboronates (run 6) afforded the corresponding arylation product in 96% and 92% yields, respectively. The reason for the high yields of these reactions is not clear at present, but steric congestion around the biaryl framework in the coupling products appears to prevent the Ru−H species from attacking at the carbonyl group. Thus, the reduction of the coupling product was effectively suppressed by the bulky biaryl framework. Unfortunately, however, the highly hindered 2,4,6-trimethylphenylboronate was inactive under these reaction conditions.

**Elucidation of Precoordination of the Ketone Carbonyl to the Ruthenium Center: Competitive Reactions Using Deuterium-Labeled Pivalophenones.** In our previous study concerning the alkylation of C−H bonds in aromatic ketones and esters with olefins (C−H/olefin coupling), we proposed that the carbonyl group coordinates to the ruthenium based on deuterium-labeling experiments using acetophenone-$d_5$ (**12**-$d_5$)[3c] and methyl benzoate-$d_5$ (**29**-$d_5$).[3i] These deuterium-labeling experiments indicated that the H/D exchange occurred between the ortho positions of **12**-$d_5$ and **29**-$d_5$ and at the vinylic positions of triethoxyvinylsilane. The regioselectivity of the H/D exchange was consistent with the regioselectivity of the C−C bond formation in the products. From these observations, in the case of the $RuH_2(CO)(PPh_3)_3$-catalyzed C−H/olefin coupling, the precoordination of the carbonyl group would be predicted to be involved prior to the C−H bond cleavage.

***Table 4.*** Reaction of 1-Benzosuberone **26** with Arylboronates[a]

| run | boronate | yield[b] |
|---|---|---|
| 1 |  **28** | 88% |
| 2 |  | 84% |
| 3 |  | 75% |
| 4 |  | 84% |
| 5 |  | 96% |
| 6 |  | 92% |

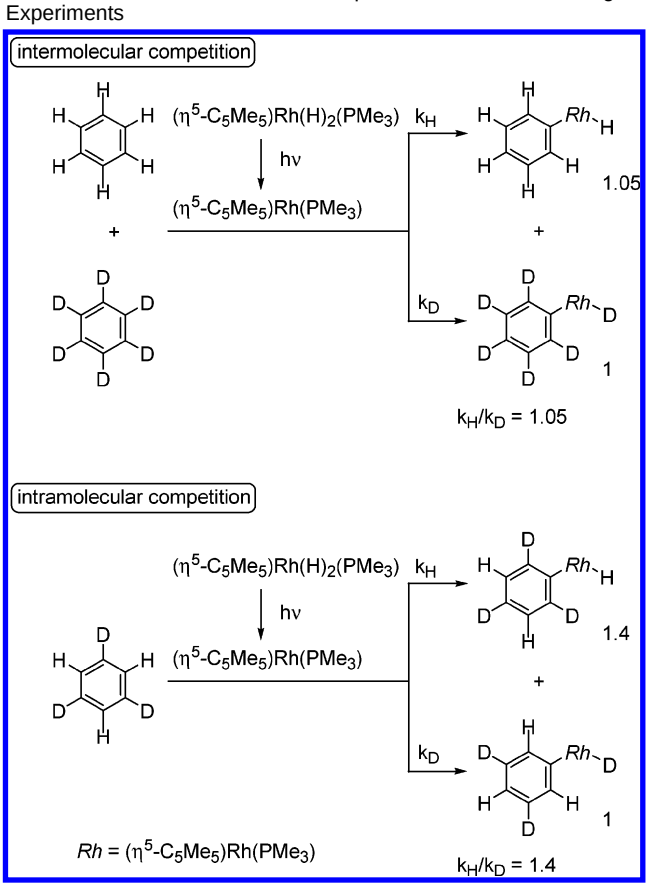
[a] Reaction conditions: 1-benzosuberone **26** (1 mmol), boronate (1.2 mmol), $RuH_2(CO)(PPh_3)_3$ (**3**) (0.02 mmol), pinacolone (0.5 mL, 4 mmol), reflux, 1 h. [b] Isolated yield.

On the contrary, Brookhart found that, in the case of ($\eta^5$-$C_5Me_5$)Rh($C_2H_3SiMe_3$)$_2$-catalyzed reaction of **12**-$d_5$ with trimethylvinylsilane, the H/D exchange occurred at the para- and the meta-positions but not at the ortho-position and that C−C bond formation took place at the ortho-position.[4f] On the basis of these results, they proposed that C−H (or C−D) bond cleavage proceeded without the coordination of the carbonyl and that the coordination of the ketone carbonyl to the rhodium participated in the C−C bond formation step, i.e., in the reductive elimination step and not in the C−H bond cleavage step.

The results of our and Brookhart's deuterium-labeling experiments described above indicate that the regioselectivity of C−C bond formation in the product does not always provide accurate information with respect to the role of the directing group in the catalytic cycle. To reveal the role of the ketone carbonyl in the present arylation reaction, we applied the Jones' protocol of deuterium-labeling experiments[28] to our reaction. The outline of Jones' protocol is illustrated in Scheme 2 along with their experimentally derived $k_H/k_D$ values. Jones postulated the $\eta^2$-arene complex as the intermediate prior to C−H bond cleavage on the basis of these deuterium-labeling competitive reactions on the basis of the observation of substantially different $k_H/k_D$ values in intermolecular competitive reactions of $C_6H_6$ and $C_6D_6$ with ($\eta^5$-$C_5Me_5$)Rh($PMe_3$), compared with the intramolecular competitive reaction of 1,3,5-$C_6D_3H_3$ with ($\eta^5$-$C_5Me_5$)Rh($PMe_3$).

We modified these inter- and intramolecular competitive reactions using deuterium-labeled pivalophenones. Our hypothesis is as follows. If, in the present coupling reaction of aromatic ketones with arylboronates, C−H bond cleavage proceeds without coordination of the ketone carbonyl group, the values

***Scheme 2.*** Jones' Protocol for Competitive Deuterium-Labeling Experiments

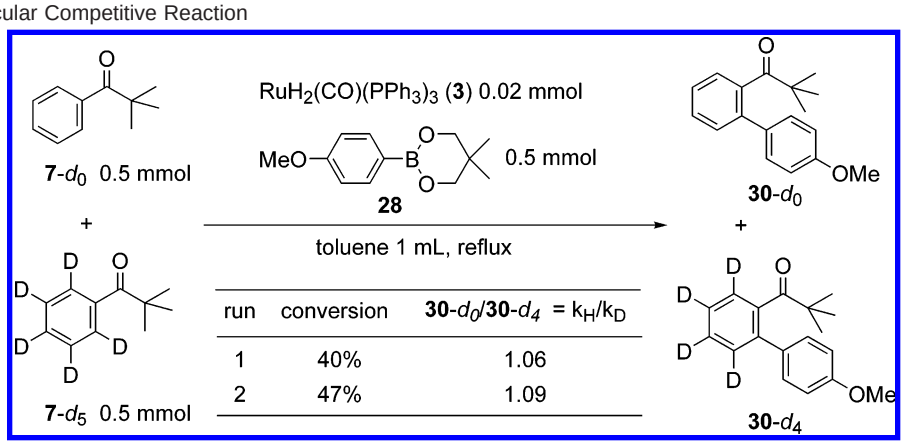



for $k_H/k_D$ in both the inter- and intramolecular competitive reactions should be nearly the same. On the other hand, if the present reaction involves the coordination of the ketone carbonyl to the ruthenium prior to C−H bond cleavage, the $k_H/k_D$ values in these labeling experiments should be different.

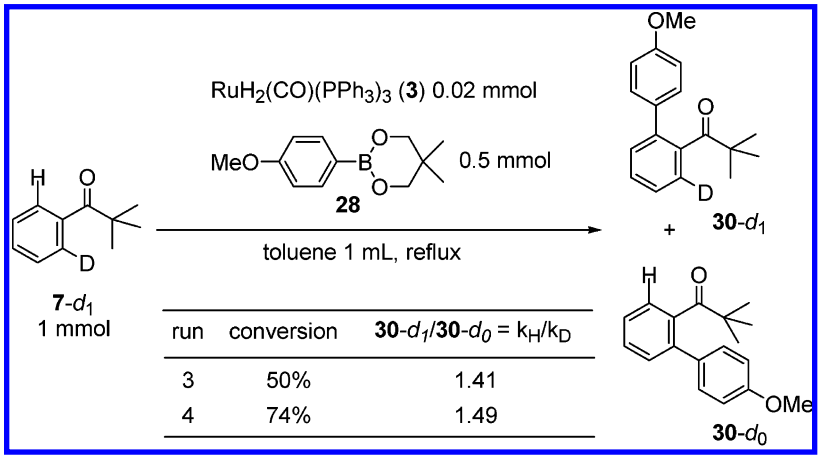
On the basis of our hypothesis, we examined both inter- (Scheme 3) and intramolecular (Scheme 4) competitive reactions. The reactions of **7**-$d_0$ and **7**-$d_5$ with *p*-methoxyphenylboronate (**28**) were conducted under the reaction conditions shown in Scheme 3. The reactions were stopped at 40% and 47% conversions (runs 1 and 2, respectively). In the case of run 1, the coupling products **30**-$d_0$ and **30**-$d_4$ were obtained in 40% total yield based on **28**. The $^1$H NMR and the GC/MS spectra of the products indicated that the arylation products **30**-$d_0$ and **30**-$d_4$ were obtained in almost the same ratio (**30**-$d_0$/**30**-$d_4$ = 1.06). This ratio indicates a ratio of $k_H/k_D$, i.e., a kinetic isotope effect (KIE) = 1.06. In the case of run 2, a similar value of $k_H/k_D$, i.e., KIE = 1.09, was observed. The intramolecular competitive reactions were examined using 2′-deuteriopivalophenone (**7**-$d_1$) (runs 3 and 4 in Scheme 4). In the case of run 3, the reaction of **7**-$d_1$ with **28** gave **30**-$d_1$ and **30**-$d_0$ in 50% total yield based on **28**. The ratio of **30**-$d_1$ and **30**-$d_0$, indicative of the KIE ($k_H/k_D$), was found to be 1.41. When the reaction was stopped at 74% conversion (run 4), the KIE value ($k_H/k_D$ = 1.49) was almost the same as that in run 3. Thus, these $k_H/k_D$ values were different between the inter- (Scheme 3) and intramolecular (Scheme 4) competitive reactions. These observations indicate that an intermediate such as **I** or **II** in Figure 2 is produced prior to C−H bond cleavage. On the basis of the basicity of the ketone carbonyl oxygen compared with the $\pi$-electrons of the benzene ring and the regioselectivity

(28) (a) Jones, W. D.; Feher, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 4814−4819. (b) Jones, W. D.; Feher, F. J. *Acc. Chem. Res.* **1989**, *22*, 91−100.

***Scheme 3.*** Intermolecular Competitive Reaction




***Scheme 4.*** Intramolecular Competitive Reaction




of C−C bond formation, the coordination of the carbonyl group (intermediate I)[4e,l−n,29] is more plausible compared with the $\eta^2$-arene complex (intermediate **II**).[30]

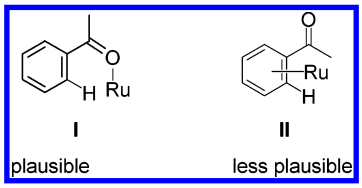
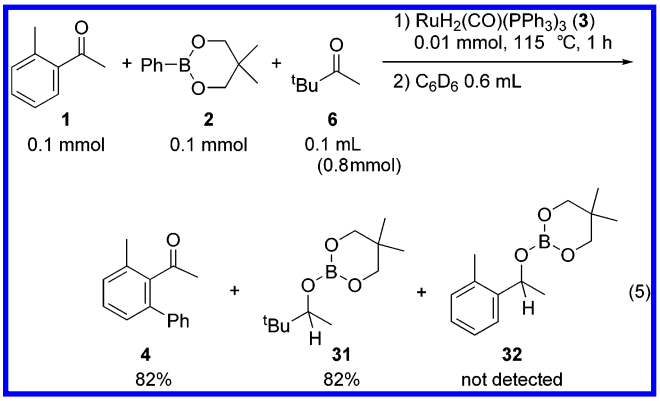



***Figure 2.***

**Plausible Pathway for the Reduction of Pinacolone.** In the present arylation reaction, pinacolone **6** appeared to be key for suppressing the reduction of aromatic ketones. Thus, **6** served as an effective scavenger of the HB species. To confirm that **6**, in fact, functioned as a scavenger of the HB species, we carried out the reaction of **1** (0.1 mmol) with **2** (0.1 mmol) in pinacolone **6** (0.1 mL, 0.8 mmol) using catalyst **3** (0.01 mmol) at 115 °C in an NMR tube (eq 5). After 1 h, 0.6 mL of benzene-$d_6$ was added to the reaction mixture, and $^1$H and $^{11}$B NMR spectra of the reaction mixture were then collected. The $^1$H NMR spectrum indicated that phenylation product **4** was formed in 82% yield, **1** in 18% yield, and trialkoxyborane **31** was formed in 82% yield. No formation of **32** derived from the reduction of **1** by



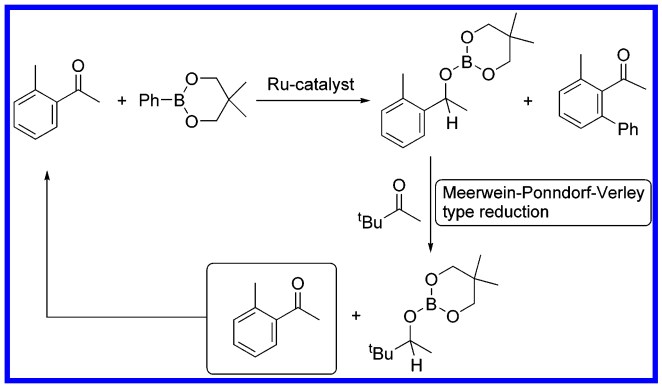

the HB species was observed. The $^{11}$B NMR spectrum of the reaction mixture indicated that the signal for **2** at $\delta$ 26.5 had completely disappeared and a new signal appeared at $\delta$ 17.5, which is close to a chemical shift of B(OMe)$_3$ ($\delta$ 18.2). This $^{11}$B NMR spectrum indicated that a trialkoxyborane species was formed during this reaction. The GC/MS spectrum showed a base peak ($m/z$ = 199) consistent with $M^+$ − Me ($C_{11}H_{23}BO_3$ − $CH_3$). These observations indicate that pinacolone **6** effectively functioned as an acceptor of the H and B($OCH_2C(CH_3)_2$-$CH_2O$) moieties (the HB species).

To contradict the possibility that reduction product **31** was formed by the transfer hydroboration from **32** to pinacolone (Scheme 5), i.e., Meerwein−Ponndorf−Verley-type reduction,

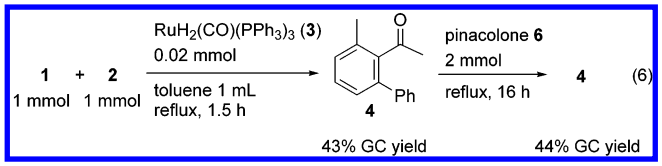
(29) (a) McGuiggan, M. F.; Pignolet, L. H. *Inorg. Chem.* **1982**, *21*, 2523−2526. (b) Munshi, P.; Samanta, R.; Kumar, L. G. *J. Organomet. Chem.* **1999**, *586*, 176−183. (b) Chandra, M.; Sahay, A. N.: Pandey, D. S.; Puerta, M. C.; Valerga, P. *J. Organomet. Chem.* **2002**, *648*, 39−48.

(30) (a) Sweet, J. R.; Graham, W. A. G. *Organometallics* **1983**, *2*, 135−140. (b) Hackett, M.; Ibers, J. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1988**, *110*, 1436−1448. (c) Cordon, R.; Taube, H. *J. Am. Chem. Soc.* **1987**, *109*, 8101−8102.

*Scheme 5*




we examined the following control experiment. When the reaction of **1** with **2** was carried out in refluxing toluene for 1.5 h, a mixture of phenylation product **4** and reduction product **32** was obtained (eq 6). Then, to the reaction mixture was added




pinacolone **6** at the same temperature, and the resulting reaction mixture was further refluxed for 16 h. The GC analysis of the reaction mixture indicated that conversion of **32** to **31** did not occur. This observation suggests that **31** is formed by the reduction of **6** with the HB species directly.

**A Plausible Reaction Pathway.** On the basis of the deuterium-labeling results and the NMR studies of the $RuH_2(CO)(PPh_3)_3$-catalyzed arylation of aromatic ketones with arylboron compounds, we propose the reaction pathway illustrated in Figure 3. The reaction starts with the coordination of the ketone carbonyl to intermediate **B**, as confirmed by the deuterium-labeling experiments (Schemes 3 and 4), followed by cleavage of C−H bonds to give the ortho-metalated ruthenacycle **C**. The addition of the Ru−H in **C** to the carbonyl group in pinacolone **6** leads to alkoxy−ruthenium intermediate **D**. Transmetalation between alkoxy−ruthenium intermediate **D** and **2** affords the diaryl ruthenium intermediate **E** and trialkoxyborane **31**, which was detected by $^1H$ and $^{11}B$ NMR and GC/MS spectroscopy (eq 5). A reductive elimination, forming a C−C bond from **E** provides the coupling product and regenerates the active species **A**.

## Conclusion

The reaction of aromatic ketones with arylboronates was conducted in refluxing pinacolone **6** with the aid of $RuH_2(CO)(PPh_3)_3$ (**3**) as a catalyst to give the ortho arylation products in good to excellent yields. This arylation of aromatic ketones exclusively occurred at the position ortho to the carbonyl group. The use of aliphatic ketones, especially pinacolone, as the acceptor of the HB species is quite effective for suppressing the undesired reduction of aromatic ketones. The substituent on the boron atom in phenylboron compounds influences its reactivity. Phenylboronate **2** derived from phenylboronic acid and 2,2-dimethyl-1,3-propanediol showed the highest reactivity among the phenylboron compounds screened. The present arylation can be applied to various combinations of aromatic ketones (e.g., acetophenones, acetonaphthones, and fused-aromatic ketones) and arylboronates. Fused aromatic ketones such as α-tetralones and 1-benzosuberone showed a high reactivity for this arylation reaction. The electronic nature of the substituent on the benzene ring in the arylboronates did not greatly affect the reactivity. The kinetic isotope effects for the intermolecular competitive reactions ($k_H/k_D$ = 1.06 and 1.09) was different from that for the intramolecular one ($k_H/k_D$ = 1.41 and 1.49). These results indicate that the ketone carbonyl group coordinates to the ruthenium prior to C−H bond cleavage. $^1H$ and $^{11}B$ NMR studies using **1** and **2** indicated that pinacolone **6** effectively functioned as an acceptor of H and $B(OCH_2C(CH_3)_2CH_2O)$ moiety (HB species). The catalytic arylation of aromatic ketones via C−H bond cleavage using arylboron compounds described here provides new opportunities for preparing a variety of biaryl compounds. We anticipate that this type of coupling reaction using organometalloid and organometallic reagents and involving C−H bond cleavage will become a powerful new synthetic protocol in organic synthesis.

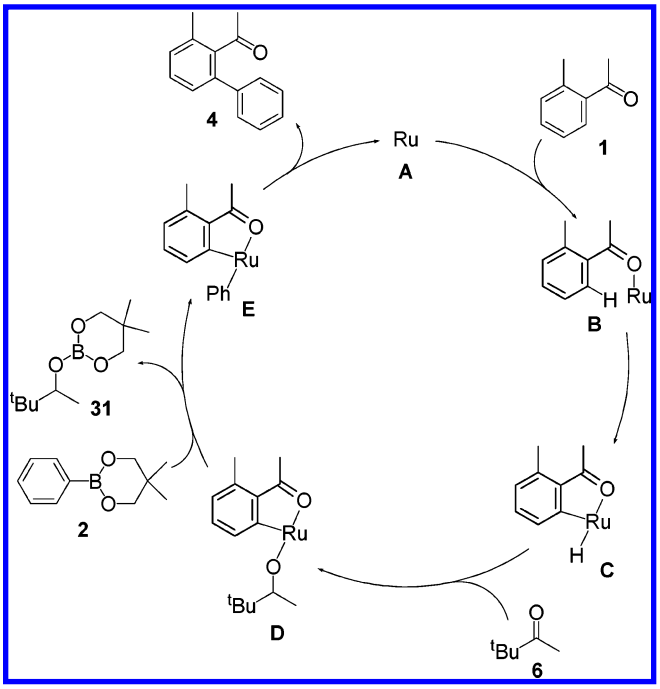



***Figure 3.*** A proposed reaction pathway.

## Experimental Section

**General Information.** $^1H$ NMR and $^{13}C$ NMR were recorded on a JEOL JNM-EX270 spectrometer operating at 270 and 67.5 MHz, respectively. $^{11}B$ NMR was recorded on a JEOL ECP-400 spectrometer operating at 128 MHz. $^1H$ and $^{13}C$ NMR signals are quoted relative to internal $CHCl_3$ ($\delta$ = 7.26 and 77.0) or tetramethylsilane. $^{11}B$ NMR signals are quoted relative to $BF_3$. $^1H$ NMR data are reported as follows: chemical shift in ppm ($\delta$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet, br = broad), coupling constant (Hz), relative intensity. $^{13}C$ NMR data are reported as follows: chemical shift in ppm ($\delta$). IR spectra were measured on a Hitachi 270-50 infrared spectrometer. GC/MS analyses were performed on a Shimadzu GCMS QP-5000 gas chromatography mass spectrometer.

**GC Analysis.** Conditions for the GC analysis were as follows: Shimadzu GC-14A (equipped with CBP-10 25 m × 0.2 mm); initial temperature, 70 or 120 °C; final temperature, 250 °C; rate, 10 °C/min; injection temperature, 250 °C; detector temperature, 250 °C.

**Solvents and Materials.** Toluene was distilled under nitrogen over $CaH_2$. Aliphatic and aromatic ketones were distilled under nitrogen over $CaSO_4$. $RuH_2(CO)(PPh_3)_3$ was prepared by previously described method.[3c]

**General Procedure.** The apparatus used in the reactions consisted of a 10-mL two-necked flask equipped with a reflux condenser connected to a nitrogen line, a rubber septum, and a magnetic stirring bar. The flask was flame-dried under a stream of nitrogen. The ruthenium complex (0.02 mmol), 1 mL of pinacolone, aromatic ketone (1 mmol), and arylboronic acid ester (1−1.5 mmol) were then placed in the flask. The resulting mixture was refluxed under a nitrogen atmosphere. The progress of the reaction was monitored by GC analysis and the product was isolated and purified by alumina and/or silica gel column chromatography.

**Intermolecular Deuterium-Labeling Experiment Using Pivalophenone-$d_0$ (7) and Pivalophenone-$d_5$ (7-$d_5$).** The apparatus consisted of a 10-mL two-necked flask equipped with a reflux condenser connected to a nitrogen line, a rubber septum, and a magnetic stirring bar. The flask was flame-dried under a stream of nitrogen. The ruthenium complex (0.02 mmol), 1 mL of toluene, pivalophenone (**7**) (0.5 mmol), pivalophenone-$d_5$ (**7**-$d_5$) (0.5 mmol), and *p*-methoxyphenylboronate **28** (0.5 mmol) were then placed in the flask. The resulting mixture was refluxed under a nitrogen atmosphere for 15 min. The reaction mixture was analyzed by GC and GC/MS, and the ratio of the **30**-$d_0$ and **30**-$d_4$ in the reaction mixture was determined by GC/MS[31] and $^1$H NMR spectrometry. The products and the starting materials were isolated and purified by alumina and silica gel column chromatography.

**Intramolecular Deuterium-Labeling Experiment using Pivalophenone-$d_1$ (7-$d_1$).** The apparatus consisted of 10-mL two-necked flask equipped with a reflux condenser connected to a nitrogen line, a rubber septum, and a magnetic stirring bar. The flask was flame dried under a stream of nitrogen. The ruthenium complex (0.02 mmol), 1 mL of toluene, pivalophenone-$d_1$ (1 mmol), and *p*-methoxyphenylboronate **28** (0.5 mmol) were then placed in the flask. The resulting mixture was refluxed under a nitrogen atmosphere for 15 min. The reaction mixture was analyzed by GC and GC/MS, and the ratio of the **30**-$d_0$ and **30**-$d_1$ in the reaction mixture was determined by GC/MS[31] and $^1$H NMR spectrometry. The products and the starting materials were isolated and purified by alumina and silica gel column chromatography.

**Confirmation of the Direct Reduction of Pinacolone with HB Species.** The apparatus consisted of 10-mL two-necked flask equipped with a reflux condenser connected to a nitrogen line, a rubber septum, and a magnetic stirring bar. The flask was flame-dried under a stream of nitrogen. The ruthenium complex (0.02 mmol), 1 mL of toluene, 2′-methylacetophenone (**1**) (1 mmol), and phenylboronate **2** (1 mmol) were then placed in the flask. The resulting mixture was refluxed under a nitrogen atmosphere for 1.5 h. The reaction mixture was analyzed by GC. To the reaction mixture, pinacolone (2 mmol) was carefully added at the same temperature using a syringe. The resulting reaction mixture was refluxed for 16 h further, and the reaction mixture was analyzed by GC.

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**Supporting Information Available:** Physical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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