JOC*Note*

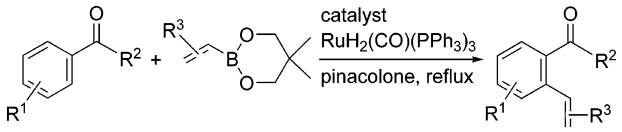
Regioselective Alkenylation of Aromatic Ketones with Alkenylboronates Using a $RuH_2(CO)(PPh_3)_3$ Catalyst via Carbon−Hydrogen Bond Cleavage

Satoshi Ueno,‡ Naoto Chatani,‡ and Fumitoshi Kakiuchi*,†

Department of Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan, and Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

kakiuchi@chem.keio.ac.jp

Received February 1, 2007



The ruthenium-catalyzed alkenylation of C−H bonds with alkenylboronates has been explored for a series of aromatic ketones. The coupling reaction of pivalophenone (**1**) with 2-isopropenyl-5,5-dimethyl[1,3,2]dioxaborinane (**2**) gave the corresponding isopropenylation product in 73% yield. In the case of the reaction of a sterically congested alkenylboronate, such as 2-methylpropenylboronate (**8**), the yield was decreased slightly. When β-styrylboronates were used, the corresponding coupling products were obtained in good yields. The reaction of acetophenone with α-styrylboronate afforded the corresponding 1:1 coupling product, exclusively.

In recent years, considerable attention has been directed toward the selective functionalization of unreactive carbon−hydrogen bonds with the aid of a transition metal catalyst.[1] To date, several types of transformations of C−H bonds have been reported. Among these, C−C bond formations such as alkylation,[2] alkenylation,[3] acylation,[4] and arylation[5−7] have widely been studied. In these reactions, three types of protocols have been published. The first is the addition of C−H bonds to C−C multiple bonds;[2−4] the second involves coupling with organohalides;[5] and the third involves coupling using organometallic compounds.[6,7] The former two protocols have been the subject of extensive investigations. The third has great potential as a synthetic tool, but this is still at a primitive stage of development. Only two types of coupling reagents have appeared in the literature.[6,7] For example, Oi and co-workers reported the ruthenium-catalyzed ortho selective arylation of arylpyridines with arylstannanes.[6a] We subsequently reported the $RuH_2(CO)(PPh_3)_3$-catalyzed arylation of aromatic ketones with arylboronates.[7a,b] To explore the synthetic utility of our protocol of C−H/organoboronate coupling to a variety of organoboronates, we examined the ruthenium-catalyzed alkylation of aromatic ketones using alkenylboronates. We wish to report a new aspect of the regioselective alkenylation of aromatic ketones with alkenylboronates via cleavage of C−H bonds using $RuH_2(CO)(PPh_3)_3$ as a catalyst.

In our previous studies, which focused on the ruthenium-catalyzed arylation of aromatic ketones with arylboronates (Ar−$B(OR)_2$), the use of the acceptor of the H−$B(OR)_2$ species was found to be essential for attaining high yields in the coupling reaction. To this end, we discovered that pinacolone can function as an efficient acceptor of the $HB(OR)_2$ species. As a result of this finding, pinacolone was used as a solvent in this study.

† Keio University.

‡ Osaka University.

(1) (a) Kakiuchi, F.; Murai, S. In *Topics in Organometallic Chemistry*; Murai S., Ed.; Springer-Verlag: Berlin, 1999; Vol. 3, pp 47−79. (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826−834. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1770. (d) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507−514. (e) Miura, M.; Nomura, M. In *Cross-Coupling Reactions*; Springer: Berlin, 2002; pp 211−241. (f) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077−1101. (g) Kakiuchi, F.; Chatani, S. In *Topics in Organometallic Chemistry*; Bruneau, C., Dixneuf, P. H., Eds.; Springer-Verlag: Berlin, 2004; Vol. 11, pp 45−79. (h) Godula, K.; Sames, D. *Science* **2006**, *312*, 67−72.

(2) (a) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778−779. (b) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529−531. (c) Lim, Y.-G.; Kim, Y. H.; Kang, J.-B. *J. Chem. Soc., Chem. Commun.* **1994**, 2267−2268. (d) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62−83. (e) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *J. Am. Chem. Soc.* **1998**, *120*, 4228−4229. (f) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616−6623. (g) Harris, P. W. R.; Rickard, C. E. F.; Woodgate, P. D. *J. Organomet. Chem.* **2000**, *601*, 172−190. (h) Gupta, S. K.; Weber, W. P. *Macromolecules* **2002**, *35*, 3369−3373. (i) Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192−7193.

(3) (a) Hong, P.; Cho, B.-R.; Yamazaki, H. *Chem. Lett.* **1979**, 339−342. (b) Dürr, U.; Kisch, H. *Synlett* **1997**, 1335−1341. (c) Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 681−682. (d) Harris, P. W. R.; Rickard, C. E. F.; Woodgate, P. D. *J. Organomet. Chem.* **1999**, *589*, 168−179. (e) Satoh, T.; Nishinaka, Y.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 615−616. (f) Lim, Y. G.; Lee, K. H.; Koo, B. T.; Kang, J.-B. *Tetrahedron Lett.* **2001**, *42*, 7609−7612. (g) Kakiuchi, K.; Uetsuhara, T.; Tanaka, Y.; Chatani, N.; Murai, S. *J. Mol. Catal. A* **2002**, *182*−*183*, 511−514. (h) Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J. B.; Jun, C. H. *Org. Lett.* **2003**, *5*, 2759−2761. (i) Tsukada, N.; Mitsuboshi, T.; Setoguchi, H.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12102−12103. (j) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202−209.

(4) (a) Hong, P.; Yamazaki, H. *Chem. Lett.* **1979**, 1335−1336. (b) Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S *J. Am. Chem. Soc.* **1992**, *114*, 5888−5890. (c) Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493−494. (d) Szewczyk, J. W.; Zuckerman, R. L.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 216−219. (e) Asaumi, T.; Matsuo, T.; Fukuyama, T.; Ie, Y.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 4433−4440. (f) Chatani, N.; Uemura, T.; Asaumi, T.; Ie, Y.; Kakiuchi, F.; Murai, S. *Can. J. Chem.* **2005**, *83*, 755−763.

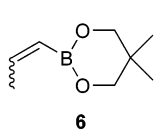
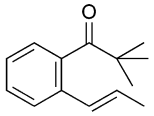
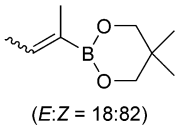
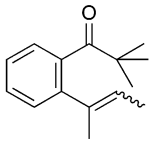
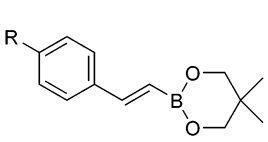
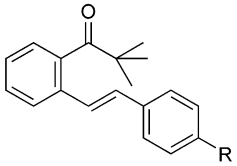
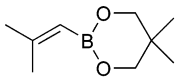
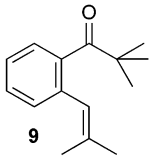
(5) (a) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1985**, *286*, C13−C16. (b) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023−1025. (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740−1742. (d) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579−2581. (e) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112−114. (f) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330−7331. (g) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050−8057.

(6) (a) Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998**, 2439−2440. (b) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78−79.

(7) (a) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698−1699. (b) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936−5945. (c) Park, Y. J.; Jo, E-A.; Jun, C.-H. *Chem. Commun.* **2005**, 1185−1187. (d) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634−12635. (e) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220−14221.

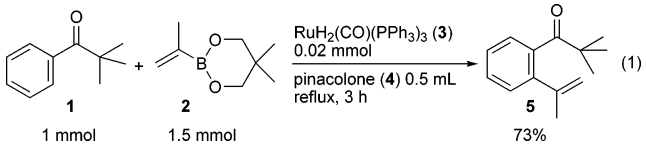
10.1021/jo070182g CCC: $37.00
Published on Web 04/04/2007

TABLE 1. Ruthenium-Catalyzed Alkenylation of Pivalophenone (1) with Alkenylboronates via C−H Bond Cleavage[a]

entry	alkenylboronate	product	yield[b,c]
1[d]	 **6** (*E*:*Z* = 39:61)	 **7** *E*-isomer only	58%
2	 (*E*:*Z* = 18:82)		54% (*E*:*Z* = 65:35)
3		 R = H	61%
4		R = CH_3	56%
5		R = OCH_3	68%
6		R = CF_3	48%
7[d]	 **8**	 **9**	37%
8[e]	**8**	**9**	70%[f]

[a] Reaction conditions: pivalophenone (**1**) (1 mmol), alkenylboronate (1.2 mmol), $RuH_2(CO)(PPh_3)_3$ (**3**) (0.02 mmol), pinacolone (0.5 mL), reflux, 20 h. [b] Isolated yield. [c] The values in parentheses are the yields at 5 mol % catalyst loading. [d] Alkenylboronate (1.5 mmol) was used. [e] Reaction conditions: **1** (2 mmol), **8** (1 mmol), **3** (0.02 mmol), toluene (0.5 mL), reflux, 3 h. [f] Based on **8**.

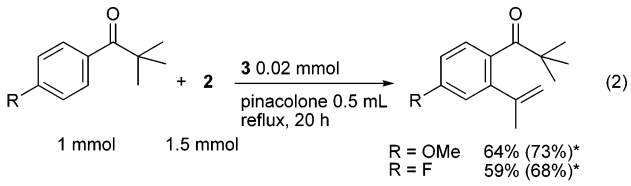
The reaction of pivalophenone (**1**) with 2-isopropenyl-5,5-dimethyl[1,3,2]dioxaborinane (**2**) was initially examined using $RuH_2(CO)(PPh_3)_3$ (**3**) as a catalyst in refluxing pinacolone **4** (eq 1). The expected propenylation reaction occurred ortho to the pivaloyl group to give product **5** in 73% yield. In the case of the C−H/acetylene coupling (addition of C−H bonds to acetylenes), only internal acetylenes can be used as the substrate because terminal acetylenes are prone to dimerize under these reaction conditions, and as a result, alkenylation products, such as **5**, cannot be obtained. Thus, the present alkenylation of aromatic ketones using alkenylboronates provides a complementary protocol to C−H/acetylene coupling.



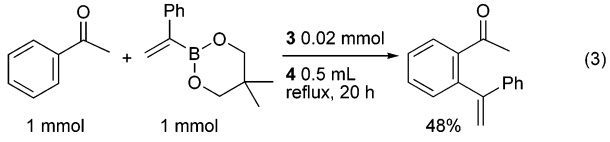
(1)

Alkenylboronate **2** has two different reaction sites. One is the C−B bond, and the other is the C−C double bond. In the case of the reaction of eq 1, the alkenylation product was formed via C−H/C−B coupling. This coupling mode contracts with the addition of the C−H bond to the C−C double bond in **2**, in the case of the reaction using isopropenyltrimethylsilane, where the addition of the C−H bond across the C−C double bonds gave the corresponding alkylation product exclusively.[2b,d]

Several alkenylboronates can be applied to the present new alkenylation reaction. The results for the reaction using **1** are listed in Table 1. The reaction with 1-propenylboronate (**6**), which was used as a mixture of *E*- and *Z*-isomers (*E*:*Z* = 39:61), afforded the coupling product **7** in 58% yield as a single isomer (entry 1). To obtain information concerning the reaction pathway of the stereochemical isomerization of the double bond, the following two control experiments were conducted. When a pinacolone solution of **6** was refluxed in the absence of ruthenium catalyst **3**, no change in the stereochemistry of **6** was observed even after 20 h. In the second experiment, a solution of **6** was heated at 60 °C for 5 min in the presence of catalyst **3**. In this case, the *Z*-isomer of **6** was completely converted to the corresponding *E*-isomer. Thus, the ruthenium catalyst also participated in the isomerization of the stereochemistry of the alkenylboronate **6**. The reaction of 2-butenylboronate (*E*:*Z* = 18:82) gave a mixture of *E*- and *Z*-isomers in the ratio of 65:35 (entry 2). Several styrylboronates having electron-donating or -withdrawing groups can also be used in this coupling reaction (runs 3−6). In these cases, (*E*)-β-styryl derivatives were obtained as a sole product. Oi and co-workers reported that the alkenylation of aryloxazolines with (*E*)-β-styrylbromide using $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ catalyst provided a mixture of stereo- and regioisomers via β-hydride elimination from the styryl−ruthenium intermediate.[6] Interestingly, however, in our case, no isomerization of the stereo- and regiochemistry was observed, although the reaction proceeded through a similar styryl−ruthenium intermediate. From these results, we propose that C−C bond formation, that is, the reductive elimination step, is faster than the β-hydride elimination from the styryl−ruthenium intermediate. In the case of a sterically congested alkenylboronate, such as 2-methyl-1-propenylboronate **8**, the product yield was decreased to 37% (entry 7). When the coupling reaction of **1** (2 equiv) with **8** (1 equiv) was carried out in refluxing toluene, **9** was obtained in 70% yield (0.7 mmol) based on **8** (entry 8). In this case, **1** functioned also as an acceptor of the H−B(OR)$_2$ species. These results suggest that the choice of the acceptor of the H−B(OR)$_2$ species and the steric congestion of the alkenylboronate affect the yields of the alkenylation products. Presently, it is not certain why **1** has high activity as an acceptor of the H−B(OR)$_2$ species, and the reason of the different activity between **1** and **4** as the acceptor must await further study.



(2)



(3)

Reactions of *p*-methoxy- and *p*-fluoropivalophenones provided the corresponding coupling products in 64 and 59% yields,

respectively (eq 2). A higher reaction temperature (140 °C) improved the yields, slightly, to 73 and 68%, respectively. The coupling reaction of acetophenone with α-styrylboronate provided the monoalkenylation product as the sole product (eq 3).

In summary, our results concerning the ruthenium-catalyzed coupling of aromatic ketones with alkenylboronates are presented herein. Several alkenylboronates can be used in this coupling reaction. The electronic nature of the substituent on the benzene ring in styrylboronates did not substantially affect the reactivity. In these cases, C−C bond formation took place between the ortho C−H bonds in aromatic ketones and the C−B bonds in the alkenylboronates.

Experimental Section

General Procedure. The apparatus used, which consisted of a 10 mL two-necked flask equipped with a reflux condenser and a magnetic stirring bar, was flame-dried and then cooled to room temperature under a flow of nitrogen. $RuH_2(CO)(PPh_3)_3$ (0.02 mmol), pinacolone (0.5 mL), aromatic ketones (1.0 mmol), and alkenylboronates (1.2 mmol) were placed in the flask. The resulting mixture was refluxed under a nitrogen atmosphere. The progress of the reaction was monitored by a GC analysis, and the product was isolated and purified by alumina (Merck, aluminum oxide 90 active basic (0.063−0.200 mm)) and/or silica gel (Merck, silica gel 60 (230−400 mesh ASTM)) column chromatography. Further purification of the product was preformed by GPC.

2,2-Dimethyl-1-(2-propenylphenyl)propan-1-one. Following the general procedure above, the crude product was purified by chromatography on basic aluminum oxide (hexane/EtOAc = 10:1): R_f = 0.44 (hexane/EtOAc = 5:1); bp 125 °C/1.0 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9H, C(C*H*$_3$)$_3$), 1.83−1.86 (m, 3H, =CC*H*$_3$), 6.08−6.21 (m, 1H, =C*H*CH$_3$), 6.25 (d, J = 16.2 Hz, 1H, C=C*H*Ar), 7.06−7.33 (m, 3H, Ar*H*), 7.49 (d, J = 7.8 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 18.79, 27.33, 45.17, 124.61, 125.59, 125.77, 128.33, 128.42, 128.47, 134.31, 139.49, 215.22; IR (KBr, cm^{-1}) 2966 w, 1690 s, 1481 m, 1461 w, 1446 w, 1394 w, 1365 w, 1268 w, 1185 w, 963 s, 946 w, 752 w; MS *m*/*z* (% relative intensity) 202 (M^+, 10), 146 (12), 145 (100), 117 (65), 116 (11), 115 (47), 91 (20), 57 (12), 51 (12). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97%. Found: C, 82.84; H, 8.83%.

2,2-Dimethyl-1-(2-styrylphenyl)propan-1-one. Following the general procedure above, the crude product was purified by chromatography on basic aluminum oxide (hexane/EtOAc = 10:1): mp 70−72 °C; R_f = 0.42 (hexane/EtOAc = 5:1); ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 9H, C(C*H*$_3$)$_3$), 6.94 (d, J = 16.2 Hz, 1H, =C*H*), 7.03 (d, J = 16.2 Hz, 1H, C*H*=), 7.14 (d, J = 6.8 Hz, 1H, Ar*H*), 7.22−7.46 (m, 7H, Ar*H*), 7.69 (d, J = 6.8 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 27.39, 45.29, 124.87, 125.58, 125.67, 126.51, 126.57, 127.86, 128.62, 128.67, 130.97, 133.70, 136.83, 140.34, 215.18; IR (KBr, cm^{-1}) 2964 w, 2868 w, 1685 s, 1496 m, 1478 w, 1461 w, 1449 w, 1363 w, 1271 w, 1195 w, 1184 w, 963 s, 945 w, 767 s, 749 w, 734 w, 694 m, 681 w, 669 w, 655 w, 531 w; MS *m*/*z* (% relative intensity) 264 (M^+, 11), 208 (16), 207 (100), 179 (28), 178 (46), 57 (16), 51 (12). Anal. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63%. Found: C, 86.17; H, 7.62%.

Acknowledgment. This work was supported, in part, by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology, Japan. F.K. thanks Tokuyama Science Foundation and The Science Research Promotion Fund of The Promotion and Mutual Aid Corporation for Private Schools of Japan, and S.U. acknowledges Research Fellowships of J.S.P.S. for Young Scientist.

Supporting Information Available: General experimental procedures and characterization data (^{1}H NMR, ^{13}C NMR, IR, R_f, mp, GC−MS analyses, elemental analyses) for all compounds and copies of ^{1}H NMR and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070182G