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Control of Product Selectivity by a Styrene Additive in Ruthenium-Catalyzed C−H Arylation

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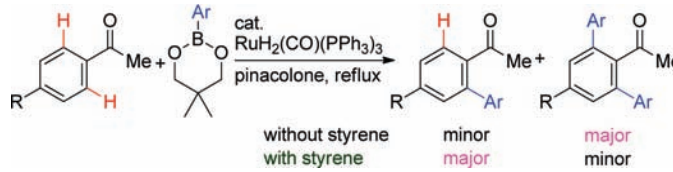
ABSTRACT



A unique effect of styrene additive on product selectivity was observed for $RuH_2(CO)(PPh_3)_3$-catalyzed C−H arylation of acetophenone derivatives bearing two ortho C−H bonds. Without styrene, the C−H arylation with arylboronates gives diarylation products as the major products throughout the reaction, but the use of styrene as an additive switches the product selectivity and leads to selective formation of monoarylation products.

Direct catalytic arylation of aromatic C−H bonds has been one of the most intensively studied areas in organometallic chemistry in recent years[1] because it provides convenient routes to biaryl frameworks, found in many biologically active molecules[2] and organic electronic and photonic materials.[3] Due to the ubiquitous nature of C−H bonds, achievement of high regioselectivity in arylation is important as a practical tool in synthesis. Chelation-assisted control of regiochemistry in C−H bond cleavage has been employed to achieve high ortho selectivity in many C−H functionalizations,[4] and a number of arylation methods have been developed for arenes with various directing groups.[1,4]

One of the challenges in the chelation-assisted C−H arylations is to prepare both mono- and diarylation products selectively from substrates with two ortho hydrogens. When the second arylation is not so fast, the product selectivity can be controlled by changing the stoichiometry or the reaction time.[5] The monoarylation product should be obtained by reducing the amount of the arylating agent or the reaction time, while the diarylation product should become the major product by applying more forcing reaction conditions. However, in some C−H arylations, the second arylation is so fast that the diarylation products start to form even at low conversion of the substrate. To obtain the monoarylation

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(2) (a) Bringmann, G.; Irmer, A. *Phytochem. Rev.* **2008**, *7*, 499. (b) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (c) Chang, J.; Reiner, J.; Xie, J. *Chem. Rev.* **2005**, *105*, 4581. (d) Feliu, L.; Planas, M. *Int. J. Pept. Res. Ther.* **2005**, *11*, 53. (e) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145. (f) Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443. (g) Quideau, S.; Feldman, K. S. *Chem. Rev.* **1996**, *96*, 475.

(3) (a) Berresheim, A. J.; Müller, M.; Müllen, K. *Chem. Rev.* **1999**, *99*, 1747. (b) Schmidt-Mende, L.; Fechtenkötter, A.; Müllen, K.; Moons, E.; Friend, R. H.; MacKenzie, J. D. *Science* **2001**, *293*, 1119. (c) Li, C.; Liu, M.; Pschirer, N. G.; Baumgarten, M.; Müllen, K. *Chem. Rev.* **2010**, DOI: 10.1021/cr1000052z.

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(5) (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740. (b) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579. (c) Oi, S.; Funayama, R.; Hattori, T.; Inoue, T. *Tetrahedron* **2008**, *64*, 6051. (d) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837.

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products in these cases, approaches other than the adjustment of the stoichiometry or the reaction time need to be applied.

Two strategies have been reported to form monoarylation products selectively using the catalyst systems where fast generation of the diarylation products occurs (Figure 1).[6,7]

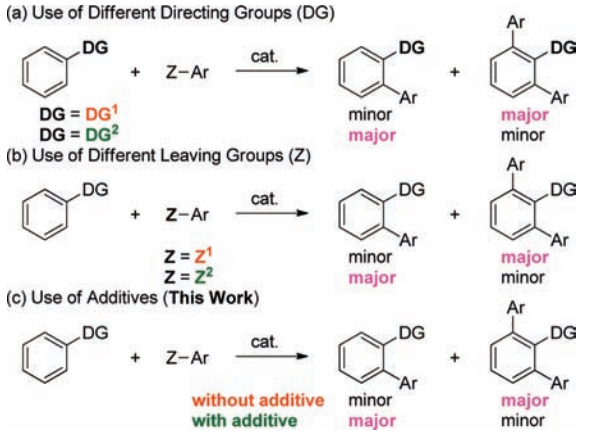


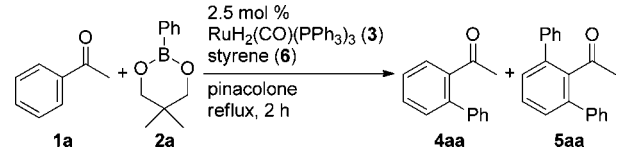
Figure 1. Strategies to control mono-/diarylation selectivity other than changing the stoichiometry or the reaction time.

One is the use of a different directing group to slow the second arylation (Figure 1a),[6] while the other is to employ a different leaving group to control the reactivity of the arylating agent (Figure 1b).[7] In these reactions, the monoarylation products were obtained essentially by changing the substrates. We envisioned that, if simple additives can control the mono-/diarylation product selectivity, monoarylation products would be selectively obtained without altering the structures of the substrates (Figure 1c).

In this paper, we describe that the use of styrene as an additive in ruthenium-catalyzed arylation of aromatic ketones[8b] effectively switches the product selectivity. Monoarylation products are obtained as major products[7a,9] in the presence of styrene, while diarylation occurs rapidly without the additive.

Previously, our group reported a ruthenium-catalyzed C−H arylation of aromatic ketones with organoboronates.[8] In this reaction, aryl groups are introduced selectively at the ortho positions to the acyl group, but when acetophenone was used as a substrate, diarylation products are formed as major products throughout the reaction, even at low conversion. For example, when the reaction of acetophenone (**1a**) with an equimolar amount of phenylboronate **2a** was performed with 2.5 mol % of $RuH_2(CO)(PPh_3)_3$ (**3**) in refluxing pinacolone[8b] for 2 h, mono- and diarylation products, **4aa** and **5aa**, were obtained in 12% and 58% yields, respectively, based on **2a**[10] (Table 1, entry 1). Increasing the amount of

Table 1. Effect of Styrene (**6**) as an Additive on the Product Selectivity[a]



			yields (based on **2a**)[b]	
entry	**1a**	**6**	**4aa**	**5aa**
1	1 mmol	0 mmol	12%	58%
2	3 mmol	0 mmol	15%	64%
3	1 mmol	1 mmol	28%	16%
4	3 mmol	1 mmol	56% (0.56 mmol)	17% (0.09 mmol)
5	5 mmol	1 mmol	58%	16%
6	3 mmol	0.1 mmol	34%	58%
7	3 mmol	3 mmol	55%	8%
8	3 mmol	5 mmol	55%	9%

[a] Reaction conditions: **1a** (1−5 mmol), **2a** (1 mmol), **6** (0.1−5 mmol), pinacolone (1 mL), reflux, 2 h. [b] GC yields based on **2a**.

1a to 3 equiv had little effect on the mono-/diarylation product ratio (entry 2).

Styrene was then examined as an additive for the C−H arylation. We speculated that styrene would slow the second C−H functionalization based on the result that the C−H alkylation of **1a** with styrene catalyzed by **3** afforded only the monoalkylation product, while the reaction with many other olefins such as vinylsilanes also provides dialkylation products.[11] In fact, when the C−H arylation under the conditions for entry 1 of Table 1 was carried out in the presence of 1 equiv of styrene (**6**), reversal of the mono-/diarylation selectivity was observed and **4aa** became the major product (Table 1, entry 3). In this case, the use of 3 equiv of **1a** improved the mono-/diarylation product ratio, and **4aa** was obtained in 56% yield (entry 4). Further increase of **1a** to 5 equiv had little impact on the product yields (entry 5). Reduction of the amount of **6** to 10 mol % resulted in significant lowering of the mono- to diarylation selectivity (entry 6). On the other hand, an increase of the amount of **6** to 3 or 5 equiv did not improve the yield of **4aa** (entries 7 and 8). GC analyses of the reaction mixtures obtained using **6** showed that the coupling of **1a** with **6** proceeded as a side reaction. This observation suggests that an excess amount of **6** is necessary to maintain the presence of **6** during the

(6) (a) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783. (b) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113. (c) Oi, S.; Sasamoto, H.; Funayama, R.; Inoue, Y. *Chem. Lett.* **2008**, *37*, 994. (d) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275.

(7) (a) Gürbüz, N.; Özdemir, I.; Çetinkaya, B. *Tetrahedron Lett.* **2005**, *46*, 2273. (b) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123. (c) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. (d) Ackermann, L.; Born, R.; Vicente, R. *ChemSusChem* **2009**, *3*, 546.

(8) (a) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. (b) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936.

(9) For synthesis of monoarylated aromatic ketones by ortho C−H arylation, see: Gandeepan, P.; Parthasarathy, K.; Cheng, C.-H. *J. Am. Chem. Soc.* **2010**, *132*, 8569. See also ref 7a.

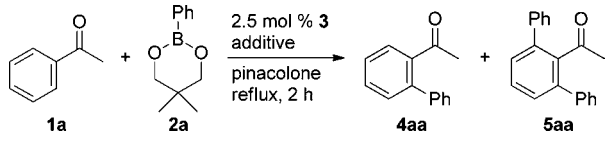
(10) Yields of **4** and **5** described in this paper are calculated based on the amounts of arylboronates **2**, which were used as limiting reagents.

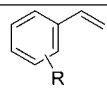
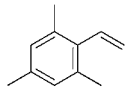
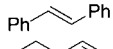
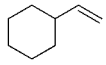
(11) (a) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62. (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826.

reaction, but a too large excess of **6** may promote the C−H/olefin coupling to give the alkylation product.[12] From these results, we decided to conduct further examination under the reaction conditions for entry 4.

Investigation of the olefin additive was next performed (Table 2). First, styrenes with several electron-donating and

Table 2. Screening of Olefin Additives[a]



entry	additive	yields[b] 4aa	yields[b] 5aa	selectivity to 4aa[c]
1	 R = H	56%	15%	79%
2	R = 2-OMe	55%	16%	77%
3	R = 2-Me	51%	18%	74%
4	R = 2-CF_3	53%	13%	80%
5	R = 4-OMe	46%	23%	67%
6	R = 4-Me	48%	14%	77%
7	R = 4-F	48%	18%	73%
8	R = 4-CF_3	48%	13%	79%
9		15%	57%	21%
10		38%	38%	50%
11		34%	48%	41%
12		36%	38%	49%
13		17%	62%	22%
14		12%	50%	19%

[a] Reaction conditions: **1a** (3 mmol), **2a** (1 mmol), additive (1 mmol), pinacolone (1 mL), reflux, 2 h. [b] GC yields based on **2a**. [c] (Yield of **4aa**)/(yield of **4aa** + **5aa**) × 100%.

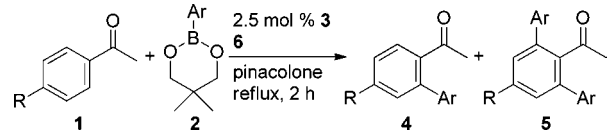
-withdrawing groups at the 2- or 4-position of the benzene ring were used as additives for the reaction of **1a** with **2a** (entries 1−8). In general, comparable results to that with **6** were obtained, but in most cases, slight lowering of the selectivity or the yield was observed. Only with CF_3-substituted styrenes, the arylation proceeded with similar selectivity, but the yield of **4aa** was somewhat decreased (entries 4 and 8). The use of a more sterically hindered olefin, 2,4,6-trimethylstyrene, gave a similar result to that obtained without any additive (entry 9). Introduction of substituents on the vinyl group of styrene also considerably reduced the selectivity to **4aa** (entries 10−12). Aliphatic olefins such as vinylcyclohexane and cyclohexene showed selectivity similar

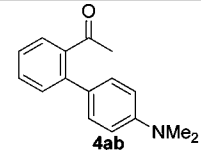
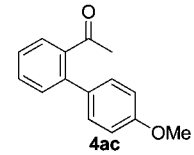
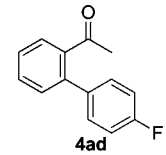
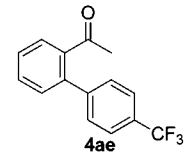
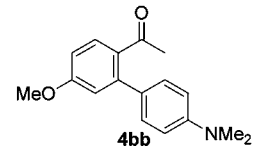
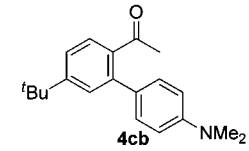
(12) On the basis of GC analyses, more than 10% of **6** was used for the C−H alkylation for entries 3−8 of Table 1.

to the reaction with no additive (entries 13 and 14). Therefore, simple styrene (**6**) was found to be the best additive among the olefins screened and used for the following investigation.

Then the reaction of **1a** was performed with several arylboronates, and in all cases, the product selectivity was switched by the addition of **6** to give monoarylation product **4a** as major products (Table 3, entries 1−8). Whether **6** was

Table 3. Screenings of Acetophenones and Arylboronates[a]



entry	1	2	6 (mmol)	4	yield of 4 (%)[b]	yield of 5 (%)[b]
1	**1a**	**2b**	1	 **4ab**	78 (71)	(11)
2	**1a**	**2b**	0		(23)	(62)
3	**1a**	**2c**	1	 **4ac**	(62)	(18)
4	**1a**	**2c**	0		(21)	(72)
5	**1a**	**2d**	1	 **4ad**	41	11
6	**1a**	**2d**	0		15	47
7	**1a**	**2e**	1	 **4ae**	33	11
8	**1a**	**2e**	0		11	37
9	**1b**	**2b**	1	 **4bb**	65 (56)	–[c]
10	**1c**	**2b**	1	 **4cb**	83 (71)	–[c]

[a] Reaction conditions: **1** (3 mmol), **2** (1 mmol), **6** (0 or 1 mmol), pinacolone (1 mL), reflux, 2 h. [b] GC yields based on **2**. Values in parentheses are isolated yields. [c] Not determined.

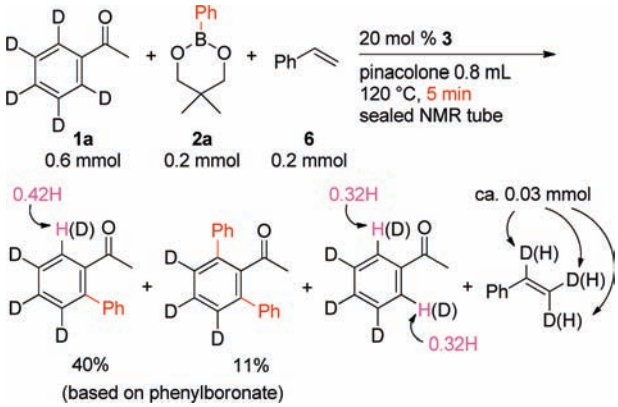
added or not, the use of arylboronates bearing electron-donating groups such as $-NMe_2$ and $-OMe$ groups offered high combined yields of **4a** and **5a** (entries 1−4). In the presence of **6**, monoarylation occurred mainly, and **4ab** and

4ac were isolated in 71% and 62% yields, respectively (entries 1 and 3). Arylboronates with electron-withdrawing groups gave relatively lower yields, probably due to the inherent instability toward deboronation (entries 5−8).

The selective monoarylation was also conducted for substituted acetophenones (entries 9 and 10). The coupling reactions of *p*-methoxy- (**1b**) and *p*-*tert*-butylacetophenones (**1c**) with arylboronate **2b** afforded monoarylation products in 65% and 83% yields.

To investigate the role of **6**, a deuterium-labeling study was carried out using acetophenone-d_5 (**1a**-d_5) (Scheme 1).

Scheme 1. Deuterium-Labeling Experiment Using **1a**-d_5



When the coupling of **1a**-d_5 with arylboronate **2a** using **6** in refluxing pinacolone was carried out for 5 min, mono- and diarylation products were obtained in 40% and 11% yields, and partial H/D exchange between **1a**-d_5 and **6** was observed. The ^{2}H NMR spectrum of the mixture showed partial deuteration of three vinylic protons of **6**. Incorporation of protons at the ortho positions of acetophenone was also indicated by ^{1}H NMR analysis. This result suggests the presence of an intermediate in which both **1a** and **6** are present on a ruthenium center and an equilibrium where C−H oxidative addition, hydroruthenation of **6**, and β-hydride elimination occur rapidly.

Although the role of **6** is still unclear, a possible explanation is shown in Figure 2. Reductive elimination to form a biaryl framework (step a) may be facilitated by coordination of π-acid such as **6**. If the reductive elimination occurs when **6** is on the metal, the intermediate formed after the reductive elimination still bears **6** on the metal center. In the absence

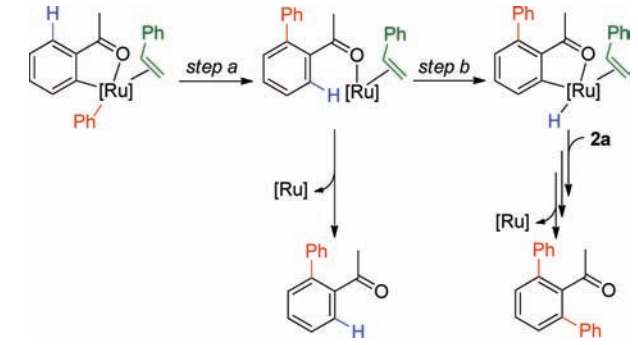


Figure 2. Proposed role of styrene (**6**) in determining the mono-/diarylation selectivity.

of **6**, the following oxidative addition is considered to be faster than the ketone dissociation, based on the fact that diarylation products are formed more than monoarylation products throughout the reaction.[13] However, the presence of **6** on the metal would retard the C−H oxidative addition due to the reduced electron density of the ruthenium center. As a result, the immediate oxidative addition may become slower than the dissociation of the ketone to provide the monoarylation product mainly.

In summary, the mono-/diarylation selectivitity in a ruthenium-catalyzed arylation of aromatic ketone was controlled by the use of styrene as an additive. In the presence of styrene, monoarylation products are formed as major products, while without the additive, diarylation occurs mainly throughout the reaction. Particularly, the reaction of relatively electron-rich arylboronates provided the monoarylation products in high yields.

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Supporting Information Available: Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The C−H arylation of the monoarylation product is much slower than the diarylation of acetophenone in the absence of styrene. Therefore, it is likely that most of the diarylation product is formed directly from acetophenone without dissociating from the ruthenium center as the monoarylation product.