

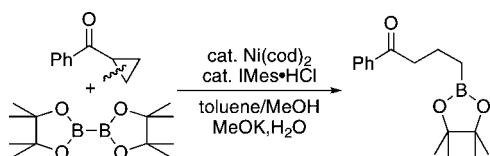
## Nickel-Catalyzed Borylation of Aryl Cyclopropyl Ketones with Bis(pinacolato)diboron to Synthesize 4-Oxoalkylboronates

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Aryl cyclopropyl ketones undergo nickel-catalyzed borylative ring opening with bis(pinacolato)diboron to yield 4-oxoalkylboronates.

Organoboron compounds are extremely important reagents in organic synthesis.<sup>1</sup> Transition metal-catalyzed borylation of unsaturated C–C bonds is one of the most powerful methods to synthesize organoboron reagents.<sup>2</sup> Although many examples of borylation of unsaturated C–C bonds catalyzed by Pt,<sup>3</sup> Pd,<sup>4</sup> Rh,<sup>5</sup> Cu,<sup>6</sup> and Au<sup>7</sup> are known, there are few examples of borylation catalyzed by nickel complexes.<sup>8</sup>

Recently, we reported nickel-catalyzed  $\beta$ -borylation of  $\alpha,\beta$ -unsaturated esters and amides and the borylative ring-opening reaction of vinylcyclopropanes.<sup>9</sup> In the course of these studies, we found another borylative reaction. Here we report nickel-catalyzed borylative ring-opening reactions of aryl cyclopropyl ketones with bis(pinacolato)diboron yielding synthetically useful 4-oxoalkylboronates.<sup>10</sup>

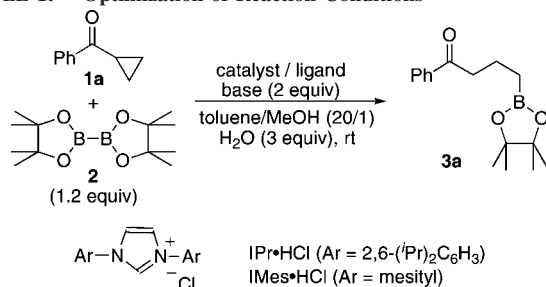
(1) (a) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: London, UK, 1988. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (c) Davison, M.; Hughes, A. K.; Marder, T. B.; Wade, K. *Contemporary Boron Chemistry*; RSC: Cambridge, UK, 2000. (d) Hall, D. G. *Boronic Acids*; Wiley-VCH: Weinheim, Germany, 2005.

(2) Pioneering work: Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018–11019.

(3) (a) Iverson, C. N.; Smith, M. R., III. *Organometallics* **1997**, *16*, 2757–2759. (b) Lawson, Y. G.; Lesley, M. J. G.; Marder, T. B.; Norman, N. C.; Rice, C. R. *Chem. Commun.* **1997**, 2051–2052. (c) Marder, T. B.; Norman, N. C.; Rice, C. R. *Tetrahedron Lett.* **1998**, *39*, 155–158. (d) Ali, H. A.; Goldberg, I.; Srebnik, M. *Organometallics* **2001**, *20*, 3962–3965. (e) Bell, N. J.; Cox, A. J.; Cameron, N. R.; Evans, J. S. O.; Marder, T. B.; Duin, M. A.; Elsevier, C. J.; Baucherel, X.; Tulloch, A. A. D.; Toozee, R. P. *Chem. Commun.* **2004**, 1854–1855.

(4) (a) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328–16329. (b) Sebelius, S.; Olsson, V. J.; Szabó, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 10478–10479. (c) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766–8773.

TABLE 1. Optimization of Reaction Conditions



entry	catalyst (mol %)	ligand (mol %)	base	yield (%) <sup>a</sup>
1	Ni(cod) <sub>2</sub> (10)	PCy <sub>3</sub> (20)	NaOH	47
2	Ni(cod) <sub>2</sub> (10)	P <sup>t</sup> Bu <sub>3</sub> (20)	NaOH	18
3	Ni(cod) <sub>2</sub> (10)	IPr·HCl (12)	NaOH	30
4	Ni(cod) <sub>2</sub> (10)	IMes·HCl (12)	NaOH	49
5	Pd(OAc) <sub>2</sub> (10)	PCy <sub>3</sub> (20)	NaOH	33 <sup>b</sup>
6	Pd(OAc) <sub>2</sub> (10)	IMes·HCl (12)	NaOH	27 <sup>b</sup>
7	Ni(cod) <sub>2</sub> (10)	IMes·HCl (12)	NaOH	77 <sup>c</sup>
8	Ni(cod) <sub>2</sub> (10)	IMes·HCl (12)	MeOK	88 <sup>c</sup>
9	Ni(cod) <sub>2</sub> (5)	IMes·HCl (6)	MeOK	92 <sup>c,d</sup>

<sup>a</sup> NMR yields. <sup>b</sup> Toluene/MeOH (30/1) and 1.5 equiv of diboron were used. <sup>c</sup> Toluene/MeOH (15/1) and 1.5 equiv of diboron were used. <sup>d</sup> At 50 °C and isolated yield.

According to our previous reports,<sup>9</sup> we first attempted the borylative ring-opening reaction by using the previous standard conditions. However, the attempt failed to attain high yield. Specifically, treatment of cyclopropyl phenyl ketone (**1a**) with bis(pinacolato)diboron (**2**) in the presence of a nickel/tricyclohexylphosphine catalyst, sodium hydroxide, and H<sub>2</sub>O in toluene/MeOH afforded the corresponding 4-oxoalkylboronate **3a** in 47% yield (Table 1, entry 1). Tri-*tert*-butylphosphine was inferior to tricyclohexylphosphine (entry 2). When we applied *N*-heterocyclic carbene ligands to this reaction, the results were improved. Among the carbene ligands, IMes·HCl<sup>11</sup> showed the highest activity (entry 4). Interestingly, palladium catalysis also effected the ring-opening reaction, albeit in lower yields (entries 5 and 6).

A higher concentration and an increased amount of diboron enhanced the reaction (entry 7, 77% yield). To optimize this transformation, we next investigated the effects of the bases. After extensive investigations, we found that metal alkoxides were effective. Thus, a high yield was observed with potassium

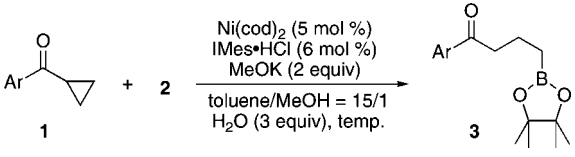
(5) (a) Dai, C.; Robins, E. G.; Scott, A. J.; Clegg, W.; Yufit, D. S.; Howard, J. A. K.; Marder, T. B. *Chem. Commun.* **1998**, 1983–1984. (b) Nguyen, P.; Coapes, R. B.; Woodward, A. D.; Taylor, N. J.; Burke, J. M.; Howard, J. A. K.; Marder, T. B. *J. Organomet. Chem.* **2002**, *652*, 77–85. (c) Kabalka, G. W.; Das, B. C.; Das, S. *Tetrahedron Lett.* **2002**, *43*, 2323–2325. (d) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702–8703.

(6) (a) Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821–6825. (b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47–53. (c) Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887–4889. (d) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034–16035.

(7) Baker, R. T.; Nguyen, P.; Marder, T. B.; Wescott, S. A. *Angew. Chem., Int. Ed.* **1995**, *34*, 1336–1338.

(8) Nickel-catalyzed reactions of diborons are rare: (a) Beletskaya, I.; Moberg, C. *Chem. Rev.* **1999**, *99*, 3435–3462. (b) Yu, C.-M.; Youn, J.; Yoon, S.-K.; Hong, Y.-T. *Org. Lett.* **2005**, *7*, 4507–4510. (c) Cho, H. Y.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 16140–16141.

TABLE 2. Scope of Cyclopropyl Ketones



entry	Ar	product	temp (°C)	yield (%) <sup>a</sup>
1	4-MeC <sub>6</sub> H <sub>4</sub> ( <b>1b</b> )	<b>3b</b>	50	79
2	4-MeOC <sub>6</sub> H <sub>4</sub> ( <b>1c</b> )	<b>3c</b>	40	88
3	4-FC <sub>6</sub> H <sub>4</sub> ( <b>1d</b> )	<b>3d</b>	50	79
4	2-naphthyl ( <b>1e</b> )	<b>3e</b>	50	95
5	2-furyl ( <b>1f</b> )	<b>3f</b>	40	54 <sup>b</sup>
6	2-MeC <sub>6</sub> H <sub>4</sub> ( <b>1g</b> )	<b>3g</b>	70	16 <sup>b,c</sup>

<sup>a</sup> Isolated yields. <sup>b</sup> 10 mol % of Ni(cod)<sub>2</sub> and 12 mol % of IMes·HCl were used. <sup>c</sup> NMR yields.

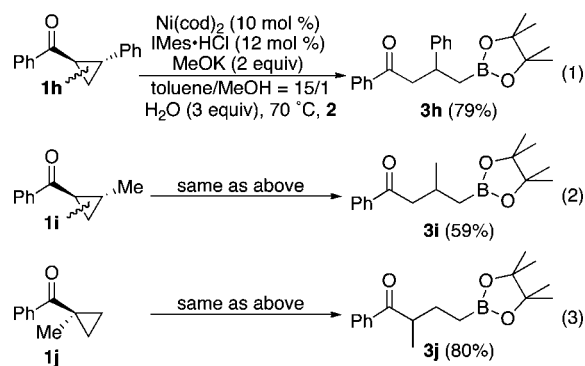
methoxide (entry 8). Moreover, the reaction proceeded smoothly at 50 °C and gave product **3a** in 92% isolated yield, even if an amount of the catalyst was reduced to 5 mol % (entry 9).<sup>12</sup>

Having optimum conditions in hand, a borylative opening reaction was carried out with various aryl cyclopropyl ketones. The reactions of **1b** and **1c** with **2** gave **3b** and **3c** in 79% and 88% yields, respectively (Table 2, entries 1 and 2). The borylation reaction of **1c** required a slightly lower temperature since **3c** was unstable at 50 °C or higher. Fluorine-containing **1d** and 2-naphthyl ketone **1e** were converted to the desired products **3d** and **3e** in 79% and 95% yields, respectively (entries 3 and 4). In addition, heterocyclic compound **1f** can be employed to afford **3f** in moderate yield (entry 5). Probably because the methyl group of **1g** blocks interaction between **1g** and active nickel species, the reaction of **1g** was sluggish to afford **3g** in only 16% yield (entry 6). Unfortunately, the product was not obtained with alkyl cyclopropyl ketones under this catalytic system (vide infra).

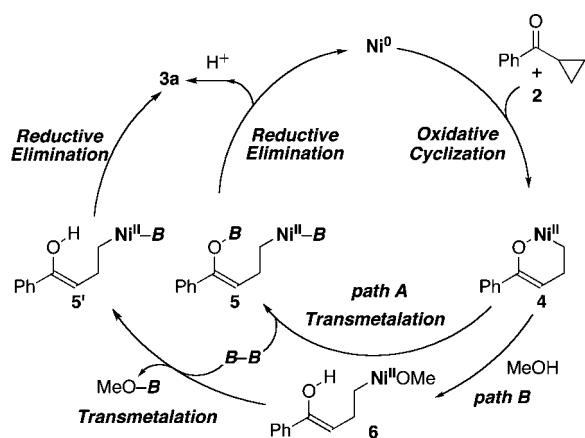
We also investigated the borylative reaction of aryl cyclopropyl ketones having an additional substituent on the cyclopropane ring. There are two C–C bonds that may be cleaved in 1,2-disubstituted cyclopropyl ketones **1h** and **1i**. Fortunately, the reactions of *trans*-1-benzoyl-2-phenylcyclopropane (**1h**) and *trans*-1-benzoyl-2-methylcyclopropane (**1i**) led to **3h** and **3i** as sole products in 79% and 59% yields, respectively (Scheme 1, eqs 1 and 2). It showed that the cleavage of the C–C bond took place selectively on the less sterically hindered side. Furthermore, 1-methylcyclopropyl phenyl ketone (**1j**) also underwent this transformation in high yield (Scheme 1, eq 3).

On the basis of our studies on nickel-catalyzed borylation,<sup>9</sup> we assume the reaction mechanism as follows (Scheme 2). Formation of oxanickelacycle intermediate **4** would occur by oxidative cyclization of cyclopropyl ketone to nickel(0), which was reported by the groups of Ogoshi and Kurosawa<sup>13</sup> and Montgomery.<sup>14</sup> In this step, Lewis acidic bis(pinacolato)diboron

SCHEME 1. Reaction of Disubstituted Cyclopropanes



SCHEME 2. Plausible Mechanism



might activate the cyclopropyl ketone and promote oxidative cyclization. Transmetalation would then take place to give alkylnickel intermediate **5** bearing a boron enolate moiety (path A). Reductive elimination produces the boron enolate of **3a**, which is protonated in situ to afford **3a**, with regeneration of the initial nickel(0) complex. The reaction required base, which would activate the boron species.<sup>15</sup> The roles of MeOH and H<sub>2</sub>O are not clear at this point according to this mechanism.<sup>16</sup>

Another mechanism (path B) that involves a formation of alkoxy nickel intermediate **6** by protonolysis of **4** with MeOH may operate.<sup>17</sup> In this mechanism, transmetalation between **6** and diboron **2** easily occurred to provide alkylnickel intermediate **5'** (path B).<sup>18</sup>

In the cases of alkyl cyclopropyl ketones, oxidative cyclization to nickel(0) would be sluggish, because alkyl cyclopropyl ketones are electron rich compared to aryl cyclopropyl ketones. Furthermore, oxanickelacycle generated from alkyl cyclopropyl ketone with nickel(0) would be less stable than that generated from aryl cyclopropyl ketones.

Finally, we subjected 4-oxoalkylboronates to the Suzuki–Miyaura cross coupling reaction (Scheme 3). After conversion of **3a** to trifluoroborate **3k** in 92% yield, **3k** reacted with 4-bromoanisole in the presence of 5 mol % of Pd(OAc)<sub>2</sub>, 10 mol % of RuPhos (2-dicyclohexylphosphino-2',6'-diisopropoxy-

(9) (a) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 5031–5033. (b) Sumida, Y.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 4677–4679.

(10) (a) Knochel, P. *J. Am. Chem. Soc.* **1990**, *112*, 7431–7433. (b) Molander, G. A.; Bobbitt, K. L.; Murray, C. K. *J. Am. Chem. Soc.* **1992**, *114*, 2759–2760. (c) Pereira, S.; Srebnik, M. *Tetrahedron Lett.* **1995**, *36*, 1805–1808. (d) Lopez-Ruiz, H.; Zard, S. Z. *Chem. Commun.* **2001**, 2618–2619.

(11) (a) Arduengo, A. J., III.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523–14534. (b) Jafarpour, L.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2000**, *606*, 49–54.

(12) A 78% isolated yield of **3a** was obtained in larger scale (5 mmol of **1a**).

(13) Ogoshi, S.; Nagata, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 5350–5351.

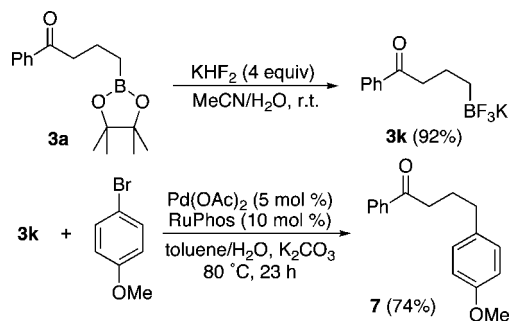
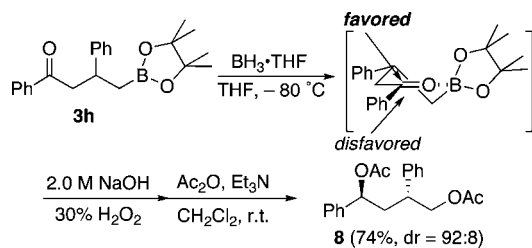
(14) Liu, L.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 5348–5349.

(15) When only 10 mol % of MeOK was used to generate carbene ligand, an 11% NMR yield of **3a** was observed.

(16) When MeOH was not used, the yield of **3a** was only 33% (NMR yield).

(17) Mannathan, S.; Jegannathan, M.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2192–2195.

(18) (a) Dible, B. R.; Sigman, M. S.; Arif, A. M. *Inorg. Chem.* **2005**, *44*, 3774–3776. (b) Lee, C. H.; Laitar, D. S.; Mueller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 13802–13803.

**SCHEME 3. Application of 3a to Suzuki–Miyaura Cross Coupling**

**SCHEME 4. Diastereoselective Reduction of 3h**


1,1'-biphenyl), and  $K_2CO_3$  in toluene/ $H_2O$  at  $80\text{ }^\circ\text{C}$ <sup>19</sup> to provide the corresponding product **7** in 74% yield.

Molander et al. developed highly diastereoselective reduction of 2-substituted-4-oxoalkylboronates, wherein intramolecular coordination of the carbonyl oxygen to the boronate ester plays a key role.<sup>10b</sup> The procedure was applicable to the reduction of **3h**. Treatment of boronate **3h** with  $BH_3\cdot THF$  as a reductant followed by oxidation and esterification afforded the corresponding diester **8** in 74% yield with good diastereoselectivity (Scheme 4).

In summary, we have developed a new borylation reaction under nickel catalysis by using aryl cyclopropyl ketones as substrates, which allows the synthesis of functionalized alkylboronates for synthetic use.

**Experimental Section**

**Typical Procedure for Borylative Ring Opening.**  $Ni(cod)_2$  (2.8 mg, 0.010 mmol),  $IMes\cdot HCl$  (8.2 mg, 0.012 mmol), and  $MeOK$  (28 mg, 0.4 mmol) were placed in a 20-mL reaction flask under argon. After toluene (0.5 mL) was added, the resulting suspension was stirred for 10 min at room temperature. Cyclopropyl ketone **1a** (29 mg, 0.20 mmol) and bis(pinacolato)diboron (**2**, 76 mg, 0.30 mmol) in toluene (1.0 mL) were then added. Methanol (0.10 mL) and  $H_2O$  (10  $\mu\text{L}$ ) were added, and the mixture was allowed to warm to  $50\text{ }^\circ\text{C}$  and stirred for 5 h. The reaction mixture was filtered by alumina (Wako, activated), followed by concentration in vacuo to afford an oil. The crude oil was purified on silica gel (Kanto Chemical, silica gel 60N, hexane/ethyl acetate = 5:1) by using a dry ice/acetone-jacketed chromatographic column to yield **3a** (51 mg, 0.18 mmol) in 92% yield.

**1-Phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-butanone (3a):** IR (neat) 2978, 2935, 1684, 1373, 1317, 1145, 691  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $CDCl_3$ )  $\delta$  0.89 (t,  $J = 8.0$  Hz, 2H), 1.25 (s, 12H), 1.86 (tt,  $J = 8.0, 7.5$  Hz, 2H), 2.98 (t,  $J = 7.5$  Hz, 2H), 7.45 (dd,  $J = 8.0, 7.5$  Hz, 2H), 7.54 (dd,  $J = 8.0, 7.5$  Hz, 1H), 7.97 (dd,  $J = 8.0, 7.5$  Hz, 2H);  $^{13}\text{C NMR}$  ( $CDCl_3$ )  $\delta$  19.3, 24.8, 40.9, 83.1, 128.1, 128.5, 132.8, 137.1, 200.6. The signal for the carbon that is attached to the boron atom was not observed. Found: C, 70.19; H, 8.65. Calcd for  $C_{16}H_{23}O_3B$ : C, 70.09; H, 8.45.

**Acknowledgment.** This work was supported by Grants-in-Aid for Scientific Research and Global COE Research Programs from JSPS.

**Supporting Information Available:** NMR spectra of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(19) Molander, G. A.; Petrillo, D. E. *Org. Lett.* **2008**, *10*, 1795–1798.