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# Copper-Catalyzed Diboration of Ketones: Facile Synthesis of Tertiary α-Hydroxyboronate Esters

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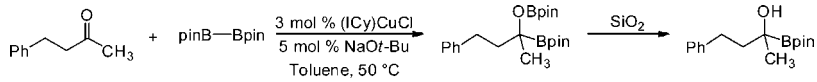
## ABSTRACT




**The diboration of ketones with the (ICy)CuO*t*-Bu catalyst was developed to provide access to tertiary α-hydroxyboronate esters. The (ICy)CuO*t*-Bu catalyst was generated in situ with (ICy)CuCl and NaO*t*-Bu to afford a more efficient catalyst than the preformed (ICy)CuO*t*-Bu. These conditions result in the diboration of various ketones in toluene at 50 °C in 2−22 h. Treatment of the resulting products with silica gel affords the corresponding α-hydroxyboronate esters.**

The versatility of the carbon−boron bond in synthesis has resulted in an emergence of interest in transformations that incorporate boron substituents with high regio- and stereoselectivity.[1−3] Traditional reactions used to introduce boron substituents into substrates include hydroboration and diboration of alkenes and alkynes,[4−6] Miyaura borylation reactions,[7] addition of organometallic reagents to trialkyl borates,[8,9] and C−H borylation reactions.[10−14]

The incorporation of boron substituents alpha to heteroatoms, however, has received limited attention even though the resulting compounds are known to have synthetic and pharmaceutical applications.[15−20] Baker and co-workers developed the rhodium-catalyzed diboration of thiocarbonyls[21] to form α-thiolboronate esters and the platinum-catalyzed diboration of aromatic aldimines to generate α-aminoboronate esters,[22] which are known pharmacophores with serine protease inhibition.[17,18,23−25]

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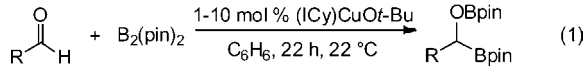
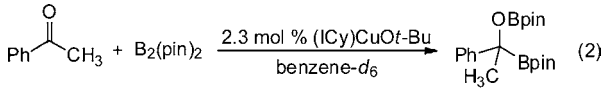
Until recently, however, the diboration of carbonyls was unknown. In 2006, Sadighi and co-workers found that a copper complex [(ICy)CuO*t*-Bu; ICy = *N*,*N*-dicyclohexylimidazolyl] efficiently catalyzed the diboration of aldehydes at ambient temperature (eq 1).[26,27] A subsequent report by Ellman and co-workers demonstrated that Sadighi's catalyst could be used in combination with a chiral auxiliary to achieve the asymmetric diboration of *tert*-butanesulfinylaldimines.[28] Ellman also demonstrated the synthetic utility of this transformation in the synthesis of the boropeptide Bortezomib, an FDA-approved treatment of multiple myeloma and mantle cell lymphoma.[23] Although these reactions represent an elegent solution for the synthesis of α-amino- and hydroxyboronate esters, there are no known general methods for the synthesis of tertiary α-hydroxyboronate esters from ketones. Development of such a method would allow access to new potential pharmacophores and valuable precursors in organic synthesis. We report herein the first example of the diboration of ketones, providing optimized reaction conditions for the formation of the corresponding α-hydroxyboronate esters under mild reaction conditions.[29,30]



(1)

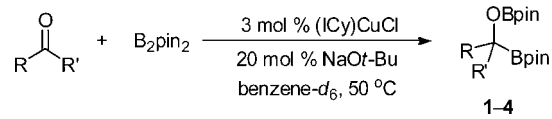
Initial experiments probed the reactivity of the (ICy)CuO*t*-Bu catalyst developed by Sadighi in the diboration of acetophenone. Under these conditions, the catalyst system was much less efficient with ketones than those reported for the diboration of aldehydes, providing 90% conversion after 70 h at 70 °C (as compared to 22 h at 22 °C with aldehydes).[26] Various additives were explored in an effort to increase catalyst turnover. Because the catalyst is highly sensitive to moisture, it was postulated that adventitious water may result in the loss of catalyst activity. Addition of common drying agents (entries 2−4, Table 1) did not improve catalyst turnover, and 3 Å molecular sieves and $MgSO_4$ shut down the reaction completely. The return of catalyst activity in the case of $K_2CO_3$ prompted the examination of additional bases as additives (entries 4−6). Although most bases resulted in lower conversion than (ICy)CuO*t*-Bu alone, sodium bicarbonate provided an increased catalyst efficiency. Continued optimization, however, did not result in full conversion to **1**.



(2)

**1**

Further reaction optimization revealed conditions that achieved full conversion of acetophenone to **1** (eq 3). Relying on studies reported by Nolan and co-workers in the copper-catalyzed hydrosilylation of ketones,[31] the in situ generation of (ICy)CuO*t*-Bu was explored. The active catalyst could be generated in situ from the (ICy)CuCl species in the presence of sodium *tert*-butoxide (eq 3). Using these conditions (50 °C, 3 mol % (ICy)CuCl, 20 mol % NaO*t*-Bu) the reactions were monitored by $^1$H NMR spectroscopy.[32] The in situ generated catalyst increased the reaction rate and resulted in complete conversion and high yields of the corresponding diboration products **1**−**4** (Table 2).



(3)

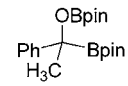
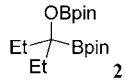
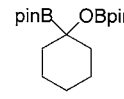
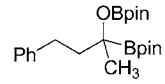
**1**–**4**

**Table 1.** Effect of Additives on Acetophenone Diboration (eq 2)

| entry | additive | temp, °C | time, h | % conversion[a] |
|---|---|---|---|---|
| 1 | none | 70 | 68 | 90 |
| 2 | 3 Å mol sieves[b] | 70 | 20 | 0 |
| 3 | $MgSO_4$ | 50 | 20 | 0 |
| 4 | $K_2CO_3$ | 50 | 68 | 59 |
| 5 | $NaO_2CCH_3$ | 50 | 68 | 46 |
| 6 | $NaHCO_3$ | 50 | 68 | 85 |
| 7 | none | 50 | 68 | 71 |

[a] Reaction progress monitored by $^1$H NMR spectroscopy, using a 10 s relaxation delay to ensure integral integrity. [b] Crushed, activated 3 Å molecular sieves.

**Table 2.** Diboration Reactions of Simple Ketones (eq 3)

| entry | product | time, h | yield (%)[a] |
|---|---|---|---|
| 1 |  **1** | 22 | 80 |
| 2 |  **2** | 20 | 92 |
| 3 |  **3** | 20 | 97 |
| 4 |  **4** | 2.5 | 90 |

[a] As determined by $^1$H NMR spectroscopic analysis of the product relative to an internal standard ($PhSiMe_3$) and with a 10 s relaxation delay to ensure integral integrity. See the Supporting Information for details.

Control experiments were conducted to probe the increase in catalyst activity resulting from in situ formation of (ICy)CuO*t*-Bu. Addition of 20 mol % of NaO*t*-Bu to

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(27) Laitar, D. S.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 17196–17197.
(28) Beenen, M. A.; An, C.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6910–6911.
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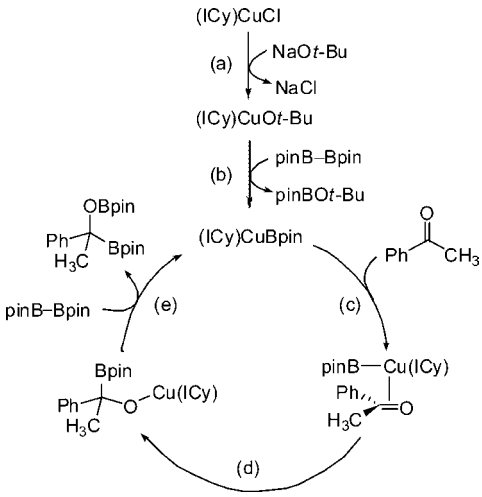
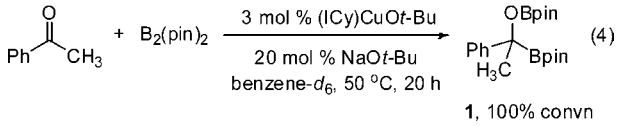
(ICy)CuO*t*-Bu provided an increased reaction rate over reactions involving (ICy)CuO*t*-Bu alone (eq 4). Our current hypothesis is that the added base can coordinate to the diboron reagent and increase the rate of $\sigma$-bond metathesis in the regeneration of the active copper-boryl species (see Scheme 1, step e).[33] In the absence of the base additive, slow

**Scheme 1.** Proposed Catalytic Cycle[33]

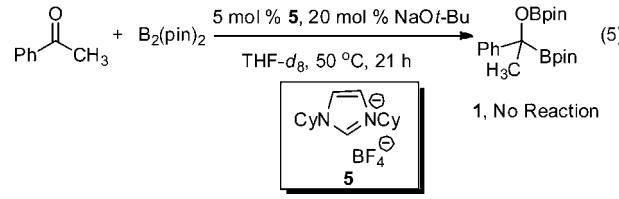



catalyst degradation takes place, resulting in deactivation of the catalyst over the course of the reaction.




The catalytic cycle of the diboration reaction is believed to be similar to the calculated mechanism reported by Marder and Lin in the copper-catalyzed diboration of aldehydes (Scheme 1).[33] The only expected difference from the calculated catalytic cycle is in the formation of (ICy)CuO*t*-Bu from the precatalyst (ICy)CuCl (step a). The formation of the copper-boryl species proceeds by $\sigma$-bond metathesis (step b), followed by coordination of the ketone (step c). The coordinated ketone can undergo migratory insertion (step d) to form the copper alkoxide, which will react with $B_2pin_2$ through $\sigma$-bond metathesis (step e) to regenerate the active copper-boryl catalyst.

An alternative metal-free mechanism was considered. Hoveyda and co-workers recently reported the metal-free 1,4-diboration of enones.[34] Under their reaction conditions (catalytic *N*-heterocyclic carbene with $B_2pin_2$) the NHC activates $B_2pin_2$ by coordination to one Lewis acidic boron. The activated diboron reagent then adds to the unsaturated alkene. To rule out dissociation of the NHC from (ICy)CuCl under our reaction conditions, a control experiment was conducted under Hoveyda's metal-free conditions. Under these conditions, no diboration was observed, discounting a metal-free mechanism.




Tertiary α-hydroxyboronate esters could be isolated by selective cleavage of the O−B bond of the diboration products (eq 6). Diboration reactions were run using 1−3 mmol of ketone, 3 mol % of (ICy)CuCl, and 5 mol % of NaO*t*-Bu in toluene at 50 °C for 3−22 h. Selective protonolysis of the O−B bond in the presence of the C−B bond was achieved upon purification by silica gel chromatography to provide α-hydroxyboronate esters **6**−**12** (Table 3). In the case of diboration product **1**, however, treatment

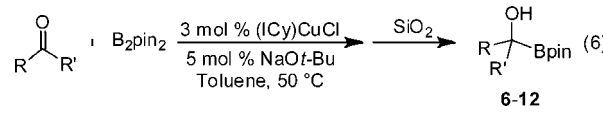
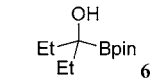
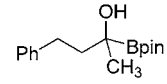
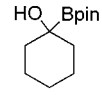
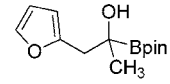
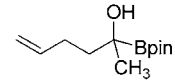
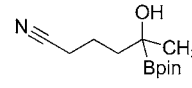
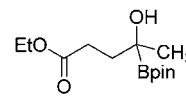



**Table 3.** Isolation of α-Hydroxyboronate Esters (eq 6)

| entry | product | time, h | yield (%) |
|---|---|---|---|
| 1 |  **6** | 17 | 52 |
| 2 |  **7** | 3 | 81 |
| 3 |  **8** | 22 | 74 |
| 4 |  **9** | 2 | 87 |
| 5 |  **10** | 6 | 74 |
| 6 |  **11** | 5 | 55 |
| 7 |  **12** | 2.5 | 55 |

(30) Carmés, L.; Carreaux, F.; Carboni, B.; Mortier, J. *Tetrahedron Lett.* **1998**, *39*, 555–556.

(31) Díez-González, S.; Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *J. Org. Chem.* **2005**, *70*, 4784–4796.

(32) Reactions were conducted in resealable J. Young tubes and heated to 50 °C in an oil bath. Due to the small reation scale, 20 mol % of NaO*t*-Bu was required to allow the solid to be weighed out accurately. Reactions on larger scale utilize 5 mol % of NaO*t*-Bu.

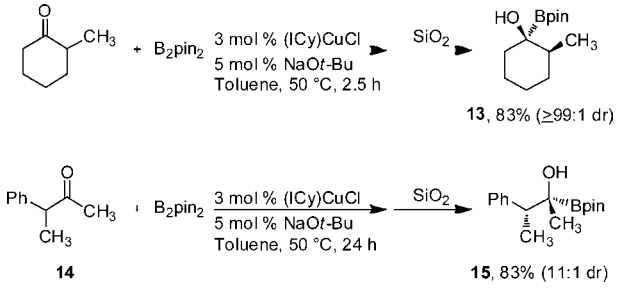
(33) Zhao, H.; Dang, L.; Marder, T. B.; Lin, Z. *J. Am. Chem. Soc.* **2008**, *130*, 5586–5594.

with silica gel resulted in decomposition rather than formation of the corresponding α-hydroxyboronate ester. The facile decomposition of **1** is consistent with studies reported by Sadighi that show analogous decomposition of benzaldehyde-derived diboration products.[26] Sadighi attributed the decomposition to an oxygen-mediated process. Attempts to purify **1** by silica gel chromatography in the absence of oxygen (in an inert atmosphere glovebox), however, still resulted in decomposition rather than selective O−B bond cleavage.

The optimized conditions for the diboration reaction were compatible with a variety of ketones. Cyclic and dialkyl ketones provided moderate to high yields at 50 °C (Table 3, entries 1−3). The presence of several functional groups was also tolerated under the optimized reaction conditions, providing selective diboration of the ketone in the presence of a furan (entry 4), alkene (entry 5), ester (entry 6), and nitrile (entry 7). Isolation of α-hydroxyboronate esters **11** and **12** required purification with Davisil grade silica gel to prevent acid-mediated decomposition of the these functionalized products.

Diboration of chiral ketones was examined, resulting in diastereoselective formation of the corresponding α-hydroxyboronate esters. 2-Methylcyclohexanone was subjected to the optimized reaction conditions to provide **13** in ≥99:1 diastereoselectivity (Scheme 2).[35] Acyclic ketone **14** was also found to react with high diastereoselectivity (11:1 dr) in the formation of **15**.[35−38]

**Scheme 2.** Diastereoselective Diboration of Ketones




The high diastereoselectivities observed for these substrates likely result from the extensive steric congestion required in the migratory insertion of the carbonyl into the Cu−Bpin bond (Figure 1).[33] The steric congestion imposed by the Bpin substituent increases the selectivity that would normally be observed for Felkin−Anh-controlled addition to carbonyl compounds.[39,40] The ability to control the facial selectivity of diboration with pendant substituents in chiral ketones is consistent with the asymmetric induction observed by Ellman and co-workers in the diboration of *tert*-butanesulfinylaldimines.[28]

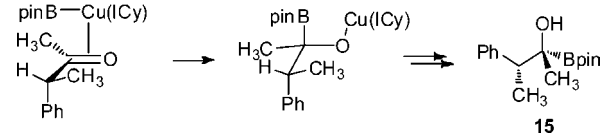



**Figure 1.** Source of diastereoselecive diboration reactions.

In summary, optimized reaction conditions were developed that provide high-yielding diboration of ketones. In situ formation of (ICy)CuO*t*-Bu provides convenient reaction conditions to achieve high catalyst efficiency. Diboration of several functionalized ketones provided selective reaction at the ketone in moderate to high yields. High diastereoselectivity was also observed in the diboration of chiral ketones.

**Acknowledgment.** This research was supported by a Research Corporation for Science Advancement Cottrell College Science Award (7339), a Research Corporation for Science Advancement and M. J. Murdock Charitable Trust Department Development Grant, and Western Washington University. C.M.M. thanks the American Chemical Society Division of Organic Chemistry for a Summer Undergraduate Research Fellowship. The authors thank Charles Wandler for assistance with NMR spectrometry and Dr. John Greaves (University of California, Irvine) for assistance with mass spectrometry.

**Supporting Information Available:** Experimental procedures and spectroscopic and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100468F

(34) Lee, K.-S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253–7255.
(35) Diastereomeric ratios determined by GC analysis. See the Supporting Information for details on establishing the relative stereochemistry.
(36) Typical diastereoselectivities of hydride additions to **14** range from 1.5:1 to 6:1 except in the case of L-Selectride (>99:1 dr).
(37) Kruger, D.; Sopchik, A. E.; Kingsbury, C. A. *J. Org. Chem.* **1984**, *49*, 778–788.
(38) Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 4475–4476.
(39) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199–2204.
(40) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, *17*, 155–158.