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# Copper-catalyzed Conjugate Additions of Alkylboranes to Aryl $\alpha,\beta$-Unsaturated Ketones

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Conjugate addition of alkylboron compounds (alkyl-9-BBN) to aryl $\alpha,\beta$-unsaturated ketones proceeded in the presence of a catalytic amount (10 mol %) of [(IPr)CuCl] and *t*-BuOK. The alkylboranes are available through alkene hydroboration, and thus the overall process represents a reductive conjugate addition of alkenes to enone derivatives. A variety of functional groups are tolerated in both the alkenes and the $\alpha,\beta$-unsaturated ketones.

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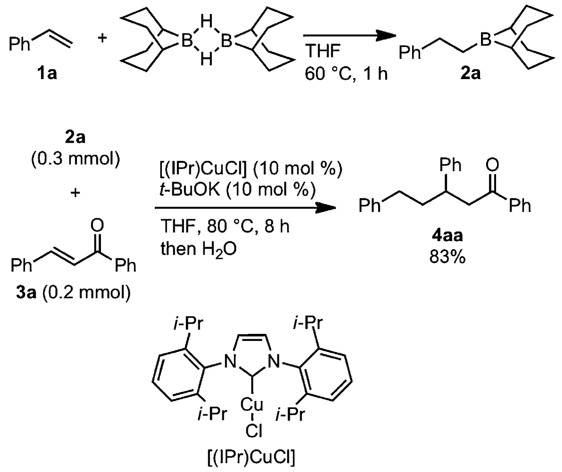
Transition-metal (Rh, Pd, Ni, etc.)-catalyzed conjugate additions of organoboron compounds to $\alpha,\beta$-unsaturated carbonyl compounds are useful carbon–carbon bond formation methods because of their broad substrate scope, functional group compatibility and applicability to asymmetric reactions.[1–4] Unfortunately however, the organoboron reagents that are generally usable for these methods are limited to aryl-, alkenyl-, and allylboron compounds, and the reactions of alkylboron derivatives are relatively unexplored.[2–7]

In this context, we reported recently that conjugate addition of alkylboron compounds (alkyl-9-BBN) to imidazol-2-yl $\alpha,\beta$-unsaturated ketones proceeded in the presence of a catalytic amount (10 mol %) of a Cu/*N*-heterocyclic carbene (NHC) and *t*-BuOK.[8,9] Here we report that the copper-catalyzed conjugate addition of alkylboranes has been expanded to the reaction with aryl $\alpha,\beta$-unsaturated ketones.[10–12] The wide and easy availability of alkylboranes via the established alkene hydroboration is an attractive feature of this transformation and thus the overall process represents a reductive conjugate addition of alkenes to enone derivatives. A variety of functional groups are tolerated in both the alkenes and the $\alpha,\beta$-unsaturated ketones.

Specifically, alkylborane **2a** in THF solution was prepared via hydroboration of styrene (**1a**) with 9-borabicyclo[3.3.1]-nonane dimer [9-BBN-H]$_2$ (**1a**/B 1.05:1) at 60 °C (Scheme 1). Subsequently, the resulting THF solution of **2a** (0.3 mmol) was added to a THF solution of [(IPr)CuCl][13] (10 mol %) and *t*-BuOK (10 mol %). Chalcone (**3a**) (0.2 mmol) was then added to the mixture, which was heated at 80 °C for 8 h. After hydrolytic workup, the conjugate addition product **4aa** was obtained in 83% isolated yield.[14]

Several observations concerning the optimum reaction conditions are to be noted (Scheme 1). Unlike the conjugate addition of alkylboranes to imidazol-2-yl $\alpha,\beta$-unsaturated ketones, IPr ligand was effective for the present protocol. While SIPr was as effective as IPr (80% yield), other NHC ligands such as IMes and ICy resulted in no reactions under otherwise identical conditions.[13] The reaction without a ligand afforded a complex mixture with no addition product. The use of Cu(O*t*-Bu)/IPr instead of [(IPr)CuCl]/*t*-BuOK was also effective to produce **3aa** in 85%, suggesting that KCl present in the optimal conditions is not essential for the catalysis. No reaction occurred when [(IPr)CuCl]/*t*-BuOK was omitted.[15] Alkyl $\alpha,\beta$-unsaturated ketones did not afford the corresponding products under similar reaction conditions: the lower reactivity of the alkyl ketones would be attributed to their lower electrophilicity.[16]



**Scheme 1.** Cu-catalyzed conjugate addition of alkylborane.

Various alkenes **1** and aryl $\alpha,\beta$-unsaturated ketones **3** were subjected to the reductive conjugate addition protocol (Table 1).[17] Functional groups such as ester, acetal, silyl ether, methoxy, trifluoromethyl, phthalimide, bromo, and amido moieties were tolerated in the reaction (Entries 2–11). Both alkyl- and aryl substituents were compatible at the $\beta$-position in the $\alpha,\beta$-unsaturated ketones. The substrate **3k** bearing a 2-thienyl group at the $\beta$-position underwent the conjugate addition (Entry 11). The substitution of the aromatic ring of the aryl ketone with either MeO or CF$_3$ groups caused only marginal and capricious effects on the reactivity (Entries 5 and 6). The 2-furyl ketone substrate **3g** surved as a substrate (Entry 7).

The tolerance of the reaction toward steric demand in alkylboranes **2** and $\alpha,\beta$-unsaturated ketones **3** is also shown in Table 1. The sterically more demanding alkylborane **2e**, which was derived from a terminal alkene **1e** with a tertiary alkyl substituent, underwent coupling with **3i** to afford the corresponding product **4ei** in good yield (Entry 9). The reaction of the $\beta$-branched alkylborane **2h**, which was prepared from $\alpha$-methylstyrene **1h**, also proceeded smoothly to produce **4ha** as a mixture of diastereomers (79:21) (Entry 12). No reaction occurred with secondary alkylboranes (data not shown). A sterically more demanding $\gamma$-alkyl substituent such as an cyclohexyl group was tolerated (Entry 3).

In summary, the scope of the copper-catalyzed conjugate addition of alkylboranes (alkyl-9-BBN) has been expanded toward aryl $\alpha,\beta$-unsaturated ketones. The alkylboranes are easily and widely available through alkene hydroboration and thus the overall process represents a reductive conjugate addition of alkenes to enone derivatives. A variety of functional groups

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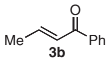
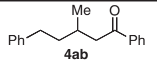
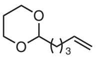
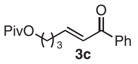
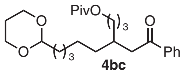
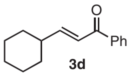
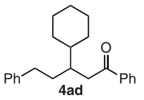
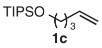
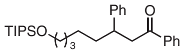
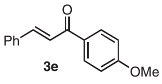
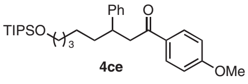
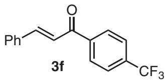
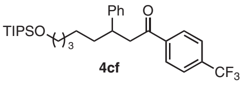
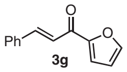
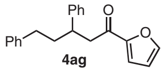
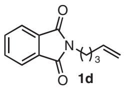
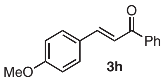
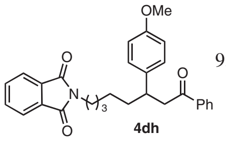
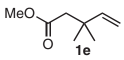
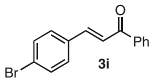
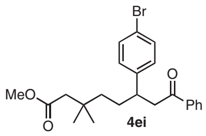
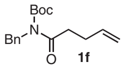
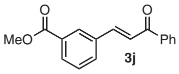
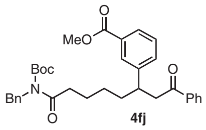
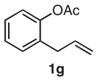
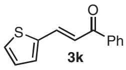
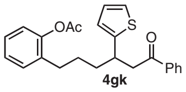
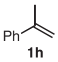
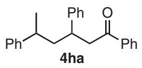
are tolerated in both the alkenes and the $\alpha,\beta$-unsaturated ketones.

**Table 1.** Substrate scope of the Cu-catalyzed conjugate addition of alkylboranes[a]

| Entry | Alkene | Ketone | Product | Yield/%[b] |
|---|---|---|---|---|
| 1 | **1a** |  **3b** |  **4ab** | 73 |
| 2 |  **1b** |  **3c** |  **4bc** | 69 |
| 3 | **1a** |  **3d** |  **4ad** | 62[c] |
| 4 |  **1c** | **3a** |  **4ca** | 84 |
| 5 | **1c** |  **3e** |  **4ce** | 93[d] |
| 6 | **1c** |  **3f** |  **4cf** | 82 |
| 7 | **1a** |  **3g** |  **4ag** | 78 |
| 8 |  **1d** |  **3h** |  **4dh** | 93 |
| 9 |  **1e** |  **3i** |  **4ei** | 74 |
| 10 |  **1f** |  **3j** |  **4fj** | 71 |
| 11 |  **1g** |  **3k** |  **4gk** | 75[d] |
| 12 |  **1h** | **3a** |  **4ha** | 74[e] |

[a]The reaction was carried out with **3** (0.4 mmol, $E/Z > 99:1$), alkylborane **2** (Entries 1–3, 0.6 mmol; Entries 4–12, 0.48 mmol), [(IPr)CuCl] (10 mol %) and *t*-BuOK (10 mol %) in THF (0.8 mL) at 80 °C for 8 h. Alkylborane **2** was prepared in advance from **1**. [b]Isolated yield based on **3**. [c]NMR yield. [d]The isolated product was contaminated with a trace amount of an unidentified material. [e]Diastereomer ratio 79:21.

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13 IPr: 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene; SIPr: 1,3-Bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene; IMes: 1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; ICy: 1,3-Dicyclohexylimidazol-2-ylidene; For reviews on *N*-heterocyclic carbenes (NHCs), see: a) *N-Heterocyclic Carbenes in Transition Metal Catalysis* in *Topics in Organometallic Chemistry*, ed. by F. Glorius, Springer, Heidelberg, **2007**, Vol. 21. doi:10.1007/978-3-540-36930-1 b) *N-Heterocyclic Carbenes in Synthesis*, ed. by S. P. Nolan, Wiley-VCH, Weinheim, **2006**. c) W. A. Herrmann, *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. d) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612.

14 When the catalytic conjugate addition was quenched with $D_2O$ instead of $H_2O$, 77% deuterium was incorporated at the $\alpha$-position of **4aa**. This suggests that the product of the catalytic reaction is in a form of an enolate, but the attempted enolate trap with aldehydes was unsuccessful.

15 The reaction between **2a** and **3a** in the presence of the radical inhibitor, TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) under otherwise identical conditions afforded **3aa** in 83% yield. Thus, the radical mechanism should be ruled out. For a conjugate addition of trialkylboranes to $\alpha,\beta$-unsaturated aldehydes and ketones under radical conditions, see: H. C. Brown, G. W. Kabalka, *J. Am. Chem. Soc.* **1970**, *92*, 714.

16 A reaction mechanism should include the formation of alkylcopper(I) species through B/Cu transmetalation between an alkylborane and a copper(I) alkoxide and subsequent conjugate addtion of the alkylcopper(I) species to an enone. See, refs. 8, 10a, and 10d.

17 Typical experimental procedure for the copper-catalyzed conjugate addition (Table 1, Entry 10): In a glove box, $(9\text{-BBN-H})_2$ (58.6 mg, 0.24 mmol), alkene **1f** (145.5 mg, 0.504 mmol), and THF (0.20 mL) were placed in a vial containing a magnetic stirring bar. Then, the vial was sealed with a cap equipped with a Teflon-coated silicon rubber septum. The vial was removed from the glove box. The mixture was stirred at 60 °C for 1 h to prepare alkylborane **2f**. Also in the glove box, [(IPr)CuCl] (19.5 mg, 0.04 mmol), *t*-BuOK (4.5 mg, 0.04 mmol), and THF (0.20 mL) were placed in another vial and the vial was sealed with a cap equipped with a Teflon-coated silicon rubber septum. After the vial was removed from the glove box, the mixture was stirred at 25 °C for 1 h. Next, the alkylborane was transferred to the vial containing a Cu–IPr complex. Finally, aryl $\alpha,\beta$-unsaturated ketone **3j** (106.5 mg, 0.40 mmol) in THF (0.4 mL) was added. After 8 h stirring at 80 °C, $H_2O$ was added to the reaction mixture. Then, the mixture was diluted and extracted with EtOAc (2 mL × 3). The combined organic layer was dried over $MgSO_4$. Then, the drying agent was removed by filtration, and the resulting solution was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (5–15% EtOAc/hexanes) to afford **4fj** in 71% yield (158.4 mg, 0.284 mmol). White solid. $R_f$ 0.3 (20% EtOAc/hexanes). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.11–1.31 (m, 2H), 1.38 (s, 9H), 1.53–1.85 (m, 4H), 2.82 (t, $J = 7.5$ Hz, 2H), 3.27–3.30 (m, 2H), 3.40 (m, 1H), 3.91 (s, 3H), 4.84 (s, 2H), 7.20–7.26 (m, 5H), 7.35 (m, 1H), 7.41–7.46 (m, 3H), 7.54 (m, 1H), 7.84–7.91 (m, 4H). $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ 24.92, 26.99, 27.72, 36.11, 38.02, 40.82, 45.48, 47.15, 51.97, 83.03, 127.07, 127.51, 127.69, 128.07, 128.30, 128.40, 128.52, 128.60, 130.36, 132.79, 133.08, 137.10, 138.41, 145.28, 153.16, 167.31, 176.10, 198.79. Mp 102.1–103.5 °C. Anal. Calcd for $C_{34}H_{39}NO_6$: C, 73.23; H, 7.05%. Found: C, 73.40; H, 7.30%.