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Copper-Catalyzed Conjugate Additions of Alkylboranes to Imidazolyl α,*β*-Unsaturated Ketones: Formal Reductive Conjugate Addition of Terminal Alkenes

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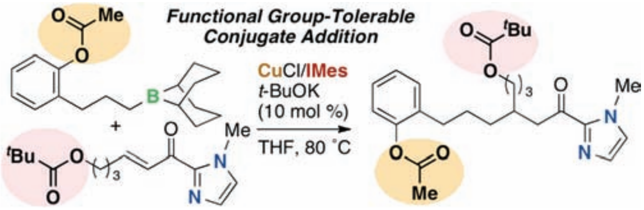
ABSTRACT



Conjugate addition of alkylboron compounds (alkyl-9-BBN) to imidazol-2-yl α,*β*-unsaturated ketones proceeded in the presence of a catalytic amount (10 mol %) of CuCl, 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes), 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 α,*β*-unsaturated ketones. The 2-acylimidazole moiety can easily be converted into the corresponding carboxylic acid, ester, and amide derivatives.

Transition-metal-catalyzed conjugate additions of organometallic reagents to α,*β*-unsaturated carbonyl compounds are important carbon−carbon bond formation methods in view of their broad substrate scope and applicability to asymmetric reactions.[1] In particular, the reactions of organoboron compounds under the influence of transition metal catalysts, such as rhodium, palladium, nickel, etc., have emerged at the frontier of the field given their broad substrate scope and functional group compatibility.[2−5] Unfortunately, however, the organoboron reagents that are usable for these methods are generally limited to aryl-, alkenyl-, and allylboron compounds,[2−5] and the reactions of alkylboron derivatives are rare and underdevel-

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(1) For reviews on transition-metal-catalyzed conjugate additions, see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, *171*, 196. (b) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823. (c) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852. (d) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rossle, M. *Synthesis* **2007**, *1279*, 1300. (e) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295–7306.

(2) For selected references on Rh-catalyzed conjugate additions with aryl- and alkenylboron compounds, see: (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229–4231. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580. (c) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508–11509. For reviews, see: (d) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196. (e) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844.

(3) For selected references on Pd-catalyzed conjugate additions with aryl- and alkenylboron compounds, see: (a) Cho, C. S.; Tanabe, K.; Uemura, S. *Tetrahedron Lett.* **1994**, *35*, 1275–1278. (b) Cho, C. S.; Motofusa, S.; Ohe, K.; Uemura, S.; Shim, S. C. *J. Org. Chem.* **1995**, *60*, 883–888. (c) Cho, C. S.; Motofusa, S.; Ohe, K.; Uemura, S. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2341–2348. (d) Gini, F.; Hessen, B.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 5309–5312. (e) He, P.; Lu, Y.; Dong, C.-G.; Hu, Q.-S. *Org. Lett.* **2007**, *9*, 343–346. (f) Lu, X.; Lin, S. *J. Org. Chem.* **2005**, *70*, 9651–9653. (g) Lin, S.; Lu, X. *Tetrahedron Lett.* **2006**, *47*, 7167–7170. (h) Lin, S.; Lu, X. *Org. Lett.* **2010**, *12*, 2536–2539. (i) Yamamoto, Y.; Nishikata, T.; Miyaura, N. *Pure Appl. Chem.* **2008**, *80*, 807–817, and references therein.

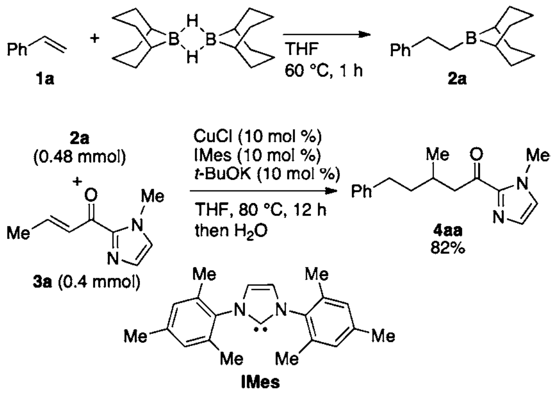
10.1021/ol102819k

oped. Specifically, more than 30 years ago Suzuki et al. reported the copper-mediated conjugate addition of lithium trialkylmethylborates prepared from trialkylboranes and methyllithium to acrylonitrile or ethyl acrylate.[6] Recently, Oshima, Yorimitsu and co-workers reported the nickel-catalyzed conjugate addition of trialkylboranes to α,β-unsaturated esters, but functionalized alkylboranes (alkyl-9-BBN) were only used for the addition to the specific substrate benzyl (*E*)-crotonate. Furthermore, the system required the use of a difficult-to-handle catalyst precursor [Ni(cod)$_2$/P^{t}Bu$_3$] and large excess amounts of alkylboron reagents and base.[7]

Herein, we report a copper-catalyzed conjugate addition of alkylboron compounds (alkyl-9-BBN) to imidazol-2-yl α,β-unsaturated ketones.[8−10] Several aspects of this transformation are noteworthy: (1) Cu, which is relatively abundant in the Earth's crust and thus cheap and environmentally benign, is used as a metal; (2) alkyl-9-BBN reagents are widely available via alkene hydroboration; (3) a variety of functional groups are tolerated in both the alkene and the α,β-unsaturated ketones; and (4) the 2-acylimidazole moiety is a practical equivalent to various carbonyl-based functional groups, such as carboxylic acids, esters, and amides, via the protocols developed by Ohta.[11,12] The overall molecular transformation represents a formal reductive conjugate addition of terminal alkenes to α,β-unsaturated carbonyl compounds.[9,13]

Specifically, alkylborane **2a** in THF solution was prepared via hydroboration of alkene (**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** (0.48 mmol) was added to a brown suspension of CuCl (10 mol %), 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) (10 mol %), and *t*-BuOK (10 mol %). Imidazolyl α,β-unsaturated ketone (**3a**) (0.4 mmol) was then added to the mixture, which was heated at 80 °C for 12 h. After hydrolytic workup, the conjugate addition product **4aa** was obtained in 82% isolated yield.[14] Unlike the copper-catalyzed γ-selective allyl−alkyl coupling between allylic phosphates and alkylboranes,[8a] the present protocol uses alkylboranes directly without converting them into alkylborates.

Scheme 1



Several observations concerning the optimum reaction conditions are to be noted. Ligand screening for the reaction between **2a** and **3a** revealed that *N*-heterocyclic carbene (NHC) ligands were useful, with IMes being most effective. Other NHC ligands such as IPr (27%), SIPr (0%), and SIMes (26%) were less effective.[15,16] The reaction without a ligand

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(4) For Ni-catalyzed conjugate additions with arylboron compounds, see: (a) Shirakawa, E.; Yasuhara, Y.; Hayashi, T. *Chem. Lett.* **2006**, *35*, 768–769.

(5) For conjugate additions with allylboron compounds, see: (a) Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214–2215. (b) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978–4983. (c) Shaghafi, M. B.; Kohn, B. L.; Jarvo, E. R. *Org. Lett.* **2008**, *10*, 4743–4746.

(6) Miyaura, N.; Itoh, M.; Suzuki, A. *Tetrahedron Lett.* **1976**, *255*, 258.

(7) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1541–1544.

(8) For Cu-catalyzed γ-selective and stereospecific allyl−alkyl and allyl−aryl couplings with organoboron compounds, see: (a) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895–2897. (b) Ohmiya, H.; Yokokawa, N.; Sawamura, M. *Org. Lett.* **2010**, *12*, 2438–2440. (c) Whittaker, A. M.; Rucker, R. P.; Lalic, G. *Org. Lett.* **2010**, *12*, 3216–3218.

(9) Knochel *et al.* reported the copper-mediated conjugate addition of dialkylzinc reagents, prepared by a hydroboration/boron−zinc exchange sequence, to ethyl acrylate, but the application to β-substituted α,β-unsaturated esters is underdeveloped while benzylidene malonate has successfully been used. Furthermore, the cumbersome procedure and its low atom efficiency, using a large excess of substrate and reagents, hampers the wide application of this method. See: (a) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229–8243. (b) Hupe, E.; Calaza, M. I.; Knochel, P. *Tetrahedron. Lett.* **2001**, *42*, 8829–8831. (c) Hupe, E.; Calaza, M. I.; Knochel, P. *Chem.*—*Eur. J.* **2003**, *9*, 2789–2796. (d) Hupe, E.; Calaza, M. I.; Knochel, P. *J. Organomet. Chem.* **2003**, *680*, 136–142.

(10) For selected references on Cu-catalyzed enantioselective conjugate additions with alkylmagnesium or alkylzinc reagents, see: (a) Lee, K.-S.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184. (b) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417. (c) Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 9103–9118. (d) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2007**, *129*, 276–277, See also refs 1b and c.

(11) Ohta, S.; Hayakawa, S.; Nishimura, K.; Okamoto, M. *Chem. Pharm. Bull.* **1987**, *35*, 1058–1069.

(12) For examples of the conversion of 2-acylimidazoles to other groups such as carboxylic acids, esters, amides, ketone derivatives, etc., see: (a) Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 3351–3354. (b) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029–10041. (c) Trost, B. M.; Lehr, K.; Michaelis, D. J.; Xu, J.; Buckl, A. K. *J. Am. Chem. Soc.* **2010**, *132*, 8915–8917. (d) Davies, D. H.; Haire, N. A.; Hall, J.; Smith, E. H. *Tetrahedron* **1992**, *48*, 7839–7856. (e) Bakhtiar, C.; Smith, E. H. *J. Chem. Soc., Perkin Trans. 1* **1994**, *239*, 243. (f) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376–1379.

(13) Cu-catalyzed conjugate additions of *alkenyl*metal compounds prepared through carbo- or hydrometalation of terminal alkynes, to α,β-unsaturated carbonyl compounds, have been developed. However, the use of *alkyl*metal compounds generated from alkenes is not well explored. See: (a) Lipshutz, B. H.; Dimock, S. H. *J. Org. Chem.* **1991**, *56*, 5761–5763. (b) Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem.*—*Eur. J.* **2007**, *13*, 9647–9662. (c) Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440–7441.

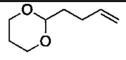
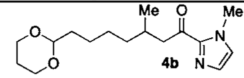
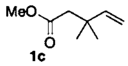
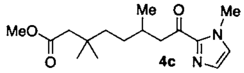
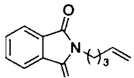
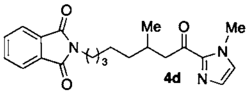
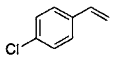
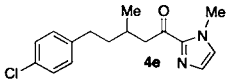
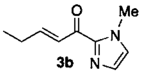
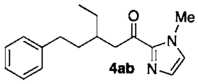
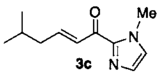
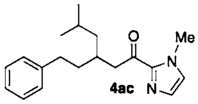
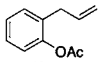
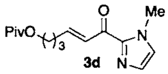
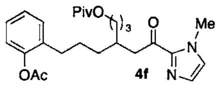
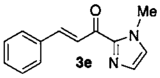
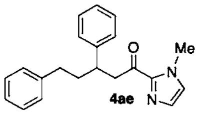
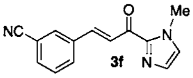
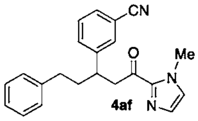
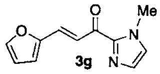
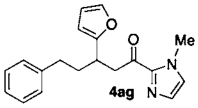
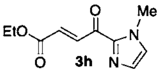
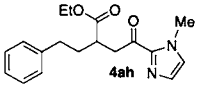
(14) Even when the conjugate addition was quenched with D$_2$O or benzaldehyde instead of H$_2$O, only the protonated product **4aa** was obtained.

(15) IPr: 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene; SIPr: 1,3-Bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene; SIMes: 1,3-Bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene. For reviews on *N*-heterocyclic carbenes (NHCs), see: (a) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Topics in Organometallic Chemistry; Springer: Heidelberg, 2007; Vol. 21. (b) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, 2006. (c) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309. (d) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612–3676.

afforded a complex mixture with no coupling product. The use of Cu(O-*t*-Bu)/IMes instead of CuCl/IMes/*t*-BuOK was also effective, but the yield decreased to 60%, suggesting that KCl present in the optimal conditions is not essential for the catalysis. The reaction with the corresponding α,*β*-unsaturated esters, amides, or aldehydes resulted in the formation of complex mixtures.

Various alkenes (**1**) and imidazolyl α,*β*-unsaturated ketones (**3**) were subjected to the reductive conjugate addition protocol (Table 1). Functional groups such as ester, chloro, cyano, acetal, and phthalimide moieties were compatible with the reaction (entries 1−4 and 7−11). Both alkyl and aryl substituents were tolerated at the *β*-position in the α,*β*-unsaturated ketones. The substrate **3g** bearing a fur-2-yl group at the *β*-position underwent the conjugate addition (entry 10). The alkylation of fumaric acid derivative **3h** occurred with complete regioselectivity at the *β*-position of the 2-acylimidazole moiety (entry 11).

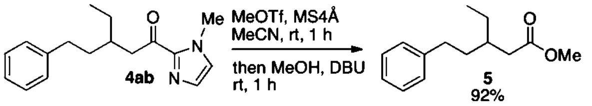
Table 1. Copper-Catalyzed Conjugate Additions[a]

entry	alkene	2-acylimidazole	product	yield (%)[b]
1	 **1b**	**3a**	 **4b**	85
2	 **1c**	**3a**	 **4c**	84
3	 **1d**	**3a**	 **4d**	80
4[c]	 **1e**	**3a**	 **4e**	65
5	**1a**	 **3b**	 **4ab**	75
6[d]	**1a**	 **3c**	 **4ac**	17
7	 **1f**	 **3d**	 **4f**	74
8[e]	**1a**	 **3e**	 **4ae**	80
9[f]	**1a**	 **3f**	 **4af**	75
10[g]	**1a**	 **3g**	 **4ag**	59
11[h]	**1a**	 **3h**	 **4ah**	70

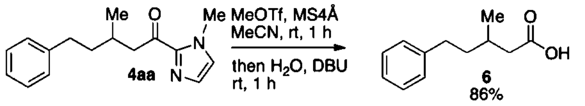
[a] The reaction was carried out with **3** (0.4 mmol, *E*/*Z* > 20:1), alkylborane **2** (0.48 mmol), CuCl (10 mol %), IMes (10 mol %), and *t*-BuOK (10 mol %) in THF (0.8 mL) at 80 °C for 12 h. Alkylborane **2** was prepared in advance by hydroboration of **1** with 9-BBN dimer at 60 °C for 1 h and used without purification. [b] Isolated yield based on **3**. [c] The isolated product was contaminated with a trace amount of an unidentified material. [d] An isomeric mixture was used as a substrate (**3c**, *E*/*Z* 87:13). [e] The reaction was carried out in toluene (0.8 mL) at 80 °C. [f] The reaction was carried out in toluene (1.75 mL) at 80 °C. [g] The reaction was carried out in toluene (0.8 mL) at 100 °C. [h] The reaction was carried out at 60 °C.

The tolerance of the reaction toward steric demand in both the alkylboranes (**2**) and α,*β*-unsaturated ketones (**3**) is also shown in Table 1. The sterically more demanding alkylborane (**2c**), which was derived from a terminal alkene (**1c**) with a tertiary alkyl substituent, served as a coupling partner for **3a** to afford the corresponding product (**4c**) in good yield (entry 2). The use of secondary alkylboranes and *β*-branched alkylboranes resulted in no reaction (data not shown). Although the copper catalysis tolerated an Et group as a *β*-substituent of the α,*β*-unsaturated ketone (**3b**), with the corresponding *i*-Bu-substituted substrate (**3c**), the product yield was low (17%) (entries 5 and 6, respectively).

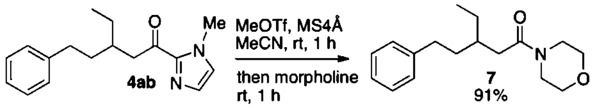
The conjugate addition products with the 2-acylimidazole moiety were readily derivatized into various carbonyl compounds (eqs 1−3).[11,12] The treatment of **4ab** with MeOTf and MS 4 Å in MeCN followed by addition of MeOH and DBU afforded the corresponding methyl ester derivative **5** in 92% yield (eq 1). Using H_2O instead of MeOH under similar conditions, **4aa** was converted into carboxylic acid **6** in 86% yield (eq 2). An amide (**7**) was also obtainable in high yield (91%) by employing morpholine as a nucleophilic reagent (eq 3).



(1)



(2)



(3)

In summary, we have developed a copper-catalyzed conjugate addition of alkylboranes (alkyl-9-BBN) to imidazol-2-yl α,*β*-unsaturated ketones. This transformation has

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(16) For selected references on catalytic reactions with NHC−copper(I) alkoxide systems, see: (a) Diez-González, S.; Nolan, S. P. *Synlett* **2007**, *2158*, 2167. (b) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417–2420. (c) Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2004**, *23*, 1157–1160. (d) Laitar, D. S.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 17196–17197. (e) Mankad, N. P.; Gray, T. G.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 1191–1193. (f) Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 5792–5795. (g) O'Brien, J. M.; Lee, K.-S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630–10633. (h) Lee, K.-S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900. (i) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160–3161. (j) Lee, Y.; Jang, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 18234–18235. (k) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634–10637. (l) Boogaerts, I. I. F.; Fortman, G. C.; Furst, M. R. L.; Cazin, C. S. J.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 8674–8677. (m) Zhang, L.; Cheng, C.; Ohishi, T.; Hou, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 8670–8673. (n) Shintani, R.; Takatsu, K.; Hayashi, T. *Chem. Commun.* **2010**, *46*, 6822–6824.

expanded the scope of transition-metal-catalyzed conjugate additions of organoboron reagents to α,β-unsaturated carbonyl compounds, making versatile sp^3-alkylation at the β-position possible. 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 are tolerated in both the alkenes and the α,β-unsaturated ketones. In addition, the 2-acylimidazole moiety is a practical equivalent to various carbonyl-based functional groups such as carboxylic acid, esters, and amides. Studies on enantioselective conjugate additions using chiral copper catalysts are ongoing in our laboratory.

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Supporting Information Available: Experimental details and characterization data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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