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Enantioselective Conjugate Addition of Alkylboranes Catalyzed by a Copper–*N*-Heterocyclic Carbene Complex

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Supporting Information

ABSTRACT: The first catalytic enantioselective conjugate addition of alkylboron compounds has been achieved. Reactions between alkylboranes and imidazol-2-yl α,β-unsaturated ketones proceeded with high enantioselectivity under the influence of a Cu(I) catalyst system, prepared in situ from CuCl, a new chiral imidazolium salt as a precursor for the *N*-heterocyclic carbene ligand, and PhOK. Alkylboranes are widely obtained via alkene hydroboration. A variety of functional groups are tolerated in alkylboranes and α,β-unsaturated ketones.

Enantioselective conjugate additions of organometallic reagents to α,β-unsaturated carbonyl compounds under the influence of chiral transition metal catalysts are efficient and versatile methods for asymmetric C–C bond formation.[1] In recent decades, reactions using organoboron compounds as organometallic reagents for conjugate additions have achieved remarkable development, given their broad substrate scope and functional group compatibility.[2−5] Unfortunately, usable organoboron reagents are limited to aryl-, alkenyl-, and allylborons; the methodology has not yet been expanded to the use of alkylborons.[6,7]

Here we report enantioselective conjugate addition of alkylboranes (alkyl-9-BBN) to imidazol-2-yl α,β-unsaturated ketones catalyzed by a Cu(I) complex with a chiral *N*-heterocyclic carbene (NHC) ligand.[6−10] To our knowledge, this protocol is the first transition-metal-catalyzed enantioselective conjugate addition of alkylborons. Alkylboranes are widely obtainable through alkene hydroboration. A variety of functional groups are tolerated in alkylboranes and α,β-unsaturated ketones. The 2-acylimidazolyl moiety can be transformed into various carboxylic functional groups.[11,12]

After our preliminary research with achiral NHC–Cu catalysts,[6c,d] various chiral NHC ligands were examined for catalytic activity and enantiocontrol in the copper-catalyzed conjugate addition of the alkylborane **2a**, which was prepared from styrene (**1a**), to the *trans*-cinnamyl 1-methylimidazol-2-yl ketone **3a** (Table 1, entries 1–9).[13,14] Copper–NHC catalysts were prepared in situ from imidazolium salts (**L1**–**L8**), CuCl, and *t*-BuOK. The ring-saturated NHC ligand (**L1**)[15] with stereogenic C centers in the ring did not form an active catalyst (with *t*-BuOK) (entry 1). The *N*-substituted NHC ligand (**L2**)[16] with a hydroxyalkyl arm involving a stereogenic center induced slight catalytic activity and enantioselectivity (entry 2), but further investigation based on hydroxylated ligands was not fruitful. The ring-unsaturated C_2-symmetric NHC ligand (**L3**)[17] having 1-(1-naphthyl)ethyl groups at both N atoms imparted moderate yields and enantioselectivities (46%, 41% ee in THF; 62%, 43% ee in toluene) (entries 3 and 4).

Based on the results in the preliminary ligand screening, we investigated various ring-unsaturated C_2-symmetric NHC ligands, featuring stereogenic centers at the positions α to the N atoms, in toluene at 35–60 °C (Table 1, entries 5–9). To our disappointment, replacing the Me group of **L3** with an Et group decreased the enantioselectivity (entry 5). Introducing the adamantyl (**L5**)[18] or mesityl (**L6**)[19] group instead of the naphthyl substituents in **L3** resulted in loss of enantiocontrol or complete inhibition of the reaction, respectively (entries 6 and 7). These results imply that introducing steric hindrance in close proximity to the α-stereogenic center of *N*-substituents is unfavorable. This prompted us to prepare a new NHC ligand, in which steric hindrance is introduced at some distance from the stereogenic center rather than within proximity. We successfully improved the product yield (68%) and enantioselectivity (59% ee) using the ligand (**L7**) with 3,5-di-*tert*-butyl-4-methoxyphenyl (DTBM) substituents at 40 °C (entry 8). Replacing the Me groups of **L7** with Et groups resulted in almost total loss of the enantiocontrol, indicating that the enantiocontrol relies on the subtle balance of steric hindrance associated with the substituents at the stereogenic centers (entry 9).

Accordingly, we conducted substrate modification at the imidazolyl moiety of an enone with the CuCl–**L7** catalyst system. As a result, the 1-methylbenzimidazol-2-yl ketone **3b** was found to be more reactive than the 1-methylimidazolyl ketone **3a**, giving the corresponding conjugate addition product **4ab** in higher yield (76%) with higher enantioselectivity (76% ee) (Table 1, entry 10).

Next, the effect of a base was examined in the reaction between **2a** and **3b** with the CuCl–**L7** catalyst system in toluene at 25 °C with a constant reaction time of 48 h (Table 1, entries 11–14).[20] Changing the alkoxide base from *t*-BuOK to the smaller MeOK markedly increased the rate of substrate conversion, but this change did not improve the enantioselection (from 11% yield, 76% ee to 54% yield, 75% ee) (entries 11 and 12). Further screening on the different types of bases showed PhOK to be optimal, affording the conjugate addition product **4ab** in 93% yield with an enantiomeric excess as high as 85% ee (entry 13). The Cu loading could be reduced to 5 mol % in a slightly decreased yield with the high enantioselectivity unchanged (89%, 85% ee, data not shown

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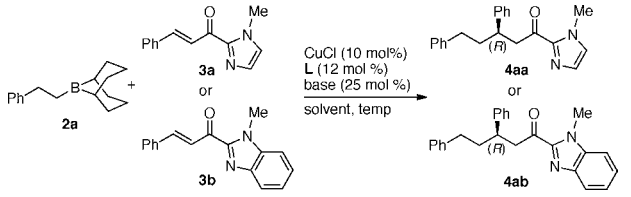
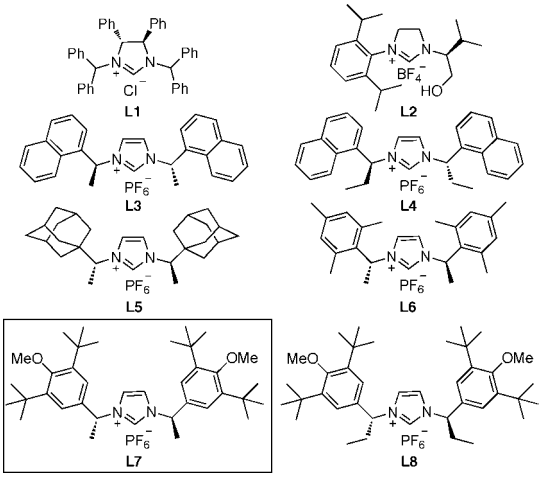
Table 1. Copper-Catalyzed Conjugate Additions of Alkylborane 2a under Various Conditions[a]



entry	SM	L	base	solvent	temp (°C)	yield (%)[b]	ee (%)[c]
1	**3a**	**L1**	*t*-BuOK	THF	80	0	–
2	**3a**	**L2**	*t*-BuOK	THF	80	24	30
3	**3a**	**L3**	*t*-BuOK	THF	80	46	41(S)
4	**3a**	**L3**	*t*-BuOK	tol	80	62	43(S)
5	**3a**	**L4**	*t*-BuOK	tol	60	41	7(S)
6	**3a**	**L5**	*t*-BuOK	tol	60	36	2
7	**3a**	**L6**	*t*-BuOK	tol	60	0	–
8	**3a**	**L7**	*t*-BuOK	tol	40	68	59
9	**3a**	**L8**	*t*-BuOK	tol	35	68	6
10	**3b**	**L7**	*t*-BuOK	tol	40	76	76
11	**3b**	**L7**	*t*-BuOK	tol	25	11	76
12	**3b**	**L7**	MeOK	tol	25	54	75
13	**3b**	**L7**	PhOK	tol	25	93	85
14	**3b**	**L7**	2,6-Me_2-C_6H_3OK	tol	25	12	51
15	**3b**	**L7**	PhOK	mes	25	85	87

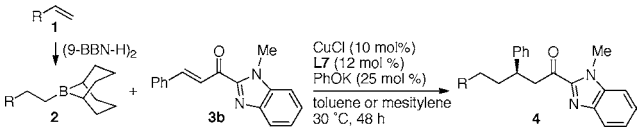


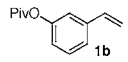
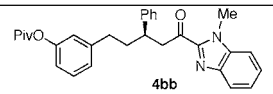
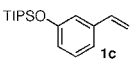
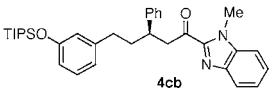
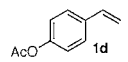
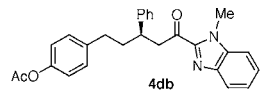
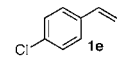
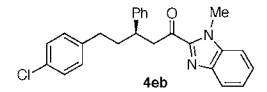
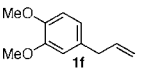
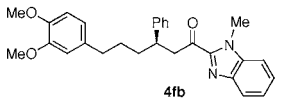
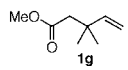
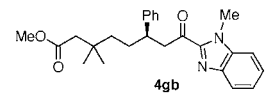
[a]Reaction was carried out with **3** (0.15 mmol), **2a** (0.18 mmol), CuCl (10 mol %), **L1**–**8** (12 mol %), and a base (25 mol %) in THF (0.3 mL), mesitylene (1.0 mL), or toluene (0.6 mL) for 12 h (entries 1–8) or 48 h (entries 9–15). Alkylborane **2** was prepared in advance by hydroboration of **1** with the 9-BBN dimer at 60 °C for 1 h and used without purification. [b]Yield of the isolated product. [c]Enantiomeric excess determined by HPLC analysis.

in Table 1). A higher enantioselectivity (87% ee) for **4ab** was obtained when the reaction was conducted in mesitylene (entry 15). Bulkier alkoxide base 2,6-Me_2-C_6H_3OK was much less effective (entry 14), and other ArOK bases with varying electronic nature did not lead to improvement in both reactivity and enantioselectivity (see Supporting Information).

Various terminal alkenes were subjected to 9-BBN-hydroboration and were used for conjugate addition of the *trans*-cinnamyl 1-methylbenzimidazolyl ketone **3b** with the CuCl/**L7**/PhOK catalyst system (Table 2). Alkenes having functional groups such as ester, silyloxy, chloro, or methoxy moieties on the aromatic ring were compatible with the protocol (entries

Table 2. Scope of Alkenes (Alkylboranes)[a]



entry	alkene	product	yield (%)[b]	ee (%)[c]
1			93	92
2			91	87
3			71	90
4			84	85
5			57	86
6[d]			73	84

[a]Reaction was carried out with **3b** (0.15 mmol), **2** (0.18 mmol), CuCl (10 mol %), **L7** (12 mol %), and PhOK (25 mol %) in toluene (0.6 mL; entries 1 and 6) or mesitylene (1.0 mL; entries 2–5) at 30 °C for 48 h. Alkylborane **2** was prepared in advance by hydroboration of **1** with the 9-BBN dimer at 60 °C for 1 h and used without purification. [b]Yield of the isolated product. [c]Enantiomeric excess determined by HPLC analysis. [d]Reaction was carried out at 25 °C.

1–5). An ester moiety at the terminal of the aliphatic chain (entry 6) was also tolerated in the reaction.

The reaction of the alkylboranes, which were prepared from styrene or allylbenzene derivatives, proceeded with high enantioselectivities (Table 2, entries 1–5). The sterically more demanding alkylborane **2g**, which was derived from the terminal alkene **1g** with a tertiary alkyl substituent, served as a suitable substrate to afford the corresponding product **4gb** (entry 6).

The scope of imidazolyl α,β-unsaturated ketone derivatives (**3**) is shown in Table 3.[21] The methoxy group was tolerated as a *para*-substituent on the aromatic ring at the β-position (61% yield, 93% ee, entry 1).[22] The ketone **3d**, bearing a 2-thienyl group at the β-position, also underwent conjugate addition in 80% yield with 91% ee (entry 2).

Alkyl groups were also acceptable as a β-substituent of the α,β-unsaturated ketones (Table 3, entries 3–6). α,β-Unsaturated ketones with a Me group at the β-position reacted with high enantioselectivities (entries 3–5): the 4,5,6,7-tetrahydrobenzimidazolyl substrate was used in this case because the corresponding benzimidazolyl α,β-unsaturated ketone was unstable. The reaction of the ketone having an Et group as the β-substituent gave a slightly decreased product yield and enantioselectivity (entry 6).

The conjugate addition product **4ab** (87% ee) could be readily converted into the corresponding methyl ester **5ab** through treatment with MeOTf in MeCN followed by the

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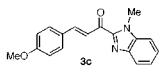
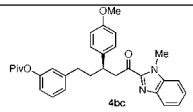
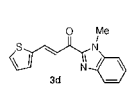
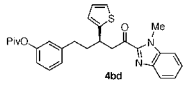
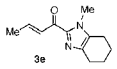
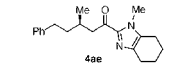
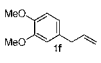
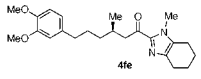
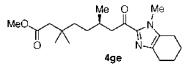
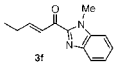
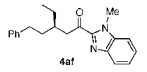
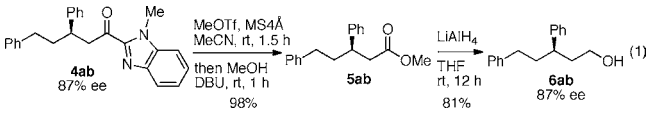
Table 3. Scope of Imidazolyl α,β-Unsaturated Ketones[a]

entry	alkene	substrate	product	yield (%)[b]	ee (%)[c]
1	 1b	 3c	 4bc	61	93
2[d]	1b	 3d	 4bd	80	91
3	 1a	 3e	 4ae	85	80
4	 1f	3e	 4fe	86	82
5[d]	 1g	3e	 4ge	82	83
6	1a	 3f	 4af	64	77

[a]Reaction was carried out with **3** (0.15 mmol), **2** (0.18 mmol), CuCl (10 mol %), **L7** (12 mol %), and PhOK (25 mol %) in toluene (0.6 mL; entries 3–5), mesitylene (1.0 mL; entries 1 and 6) or a toluene/mesitylene 1:1 mixture (1.0 mL; entry 2) at 30 °C for 48 h. Alkylborane **2** was prepared in advance by hydroboration of **1** with the 9-BBN dimer at 60 °C for 1 h and used without purification. [b]Yield of the isolated product. [c]Enantiomeric excess determined by HPLC analysis. [d]Reaction was carried out at 25 °C.

addition of MeOH and DBU (eq 1).[11,12] The absolute configuration of **4ab** was determined to be *R* by the optical rotation of **6ab** (87% ee) obtained by reduction with $LiAlH_4$.[23]



A possible catalytic cycle for the present copper catalysis is illustrated in Figure 1. Initially, the reaction of CuCl, **L7**, and PhOK forms a phenoxycopper complex (**A**). B/Cu transmetalation between **A** and alkylborane **2** forms an alkylcopper(I) species (**B**) and phenoxyborane (9-BBN-OPh).[10] The alkylcopper(I) species **B** forms a π-complex (**C**) with enone **3**. Then, with the assistance of Lewis acidic activation with

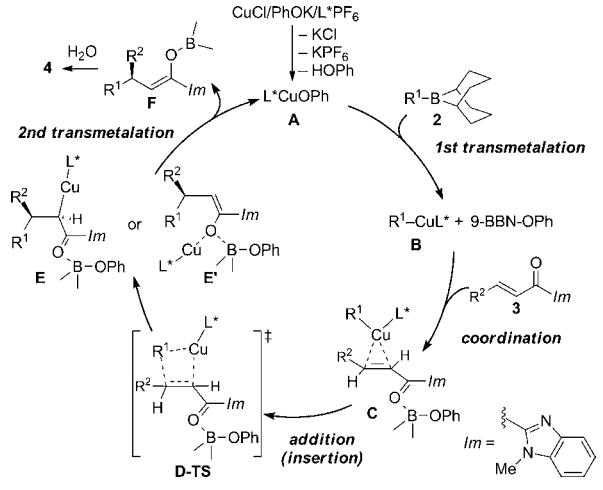


Figure 1. Possible catalytic cycle.

phenoxyborane, alkyl–Cu addition across the C–C double bond occurs to form a *C*-copper enolate (**E**) or an *O*-copper enolate (**E′**).[10b,24] Finally, the second B/Cu transmetalation releases a boron enolate (**F**), regenerating the phenoxycopper(I) complex **A** for the next catalytic cycle.[25,26]

According to the proposed catalytic cycle, the superiority of PhOK over *t*-BuOK and MeOK in promoting the reaction may be ascribed to the higher Lewis acidity of phenoxyborane over the alkoxyboranes for activating the enone toward organocopper addition (**D-TS**).[10b] In addition, the compactness of phenoxyborane relative to *tert*-butoxyborane may also contribute to the smooth catalyst turnover because the second transmetalation step (from **E**/**E′** to **A** and **F**) is sensitive to steric effects. Similarly, the increase in product yield upon replacing *t*-BuOK with MeOK can be explained by the steric effect in the second transmetalation.

Models (**D-TS-1** and **D-TS-2**) for enantiodiscrimination based on the proposed catalytic cycle are depicted in Figure 2.

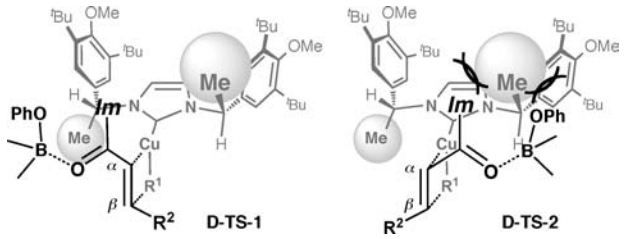


Figure 2. Models for enantiodiscrimination.

The models involve two additional assumptions: first, the NHC–Cu coordination axis is coplanar with the developing Cu–C(α) and C(R^1)–C(β) σ-bonds in **D-TS**, and second, the substituents at the stereogenic centers in **L7** are arranged such that the aryl groups are placed away from the enone-coordinated Cu-atom and hence the two methyl groups constitute a C_2-type quadrant around the copper center (the first and third quadrants being sterically more demanding). According to these assumptions, the imidazolylcarbonyl group and the *O*-bound 9-BBN-OPh moieties should encounter larger steric repulsion with the chiral ligand in **D-TS-2**, which leads to the minor enantiomer, than in **D-TS-1**. On the other hand, the β-substituent (R^2) of the enone should have less steric interactions with the chiral ligand in both TSs than the imidazolylcarbonyl moiety has. These considerations are consistent with the experimental observations that the sterically more demanding imidazolyl groups (e.g., **3a** vs **3b**) induced higher enantioselectivities while the steric demand of the β-substituent have less impact on the enantiocontrol.

In summary, we demonstrated the enantioselective conjugate addition of alkylborons (alkyl-9-BBN) to imidazol-2-yl α,β-unsaturated ketones catalyzed by a copper(I)–chiral *N*-heterocyclic carbene (NHC) complex. This is the first catalytic enantioselective conjugate addition of alkylboron derivatives. The chiral NHC–Cu catalysis allowed versatile and enantiocontrolled sp^3-alkylation at the β-position of α,β-unsaturated carbonyl compounds. The availability of alkylboranes through *in situ* alkene hydroboration and the broad functional group compatibility in both alkenes and α,β-unsaturated ketones are attractive features from a synthetic viewpoint. The 2-acylimidazolyl moiety can be transformed into various carboxylic functional groups.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) Use of Li or Na alkoxides resulted in no reaction.

(21) Imidazolyl α,β-unsaturated ketones in the Z-configuration were difficult to prepare.

(22) Imidazolyl α,β-unsaturated ketones, with an electron-deficient group such as p-CF_3 group on the aromatic ring at the β-position, were not suitable for the reaction due to their low solubilities.

(23) Conjugate addition product **4ae** (80% ee) was also converted into the corresponding methyl ester **5ae** (80% ee) in 95% yield under the same reaction conditions. The absolute configuration of **4ae** was determined to be *R* by the optical rotation of **5ae**. Absolute configurations of the other products were assigned on the basis of analogy in the optical rotations of **4ab** and **4ae**.

(24) Our attempts to detect possible reaction intermediates such as Cu or B enolates (**E**/**E**′, **F**) by *in situ* NMR observations were unsuccessful. In addition, quenching the reaction with D_2O resulted in no deuterium incorporation. A source of the proton is not clear at present.

(25) According to this mechanism, the phenoxyborane participates in the second B/Cu transmetalation. This may also contribute to smooth catalyst turnover. Nevertheless, a possibility of direct formation of the alkylcopper(I) species **B** through B/Cu transmetalation between Cu enolates (**E**/**E**′) and alkylborane **2** is not ruled out.

(26) Coordination of the imidazolyl group to Cu may be possible, but the resulting complex should be a nonproductive species.