Asymmetric Catalysis

International Edition: DOI: 10.1002/anie.201909712
German Edition: DOI: 10.1002/ange.201909712

Catalytic Asymmetric Conjugate Addition of a Borylalkyl Copper Complex for Chiral Organoboronate Synthesis

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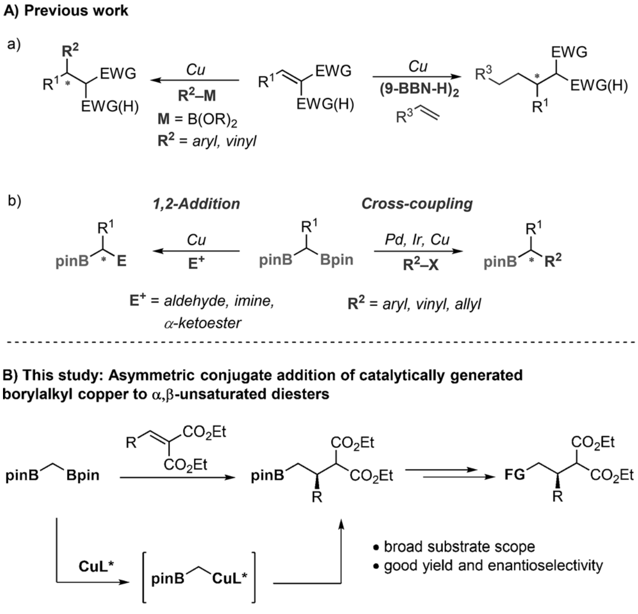
Abstract: *We report the catalytic enantioselective conjugate addition of a borylalkyl copper nucleophile generated in situ from a 1,1-diborylmethane derivative to α,β-unsaturated diesters. In the presence of a chiral N-heterocyclic carbene (NHC)–copper catalyst, this method facilitated the enantioselective incorporation of a CH_2Bpin moiety at the β-position of the diesters to yield β-chiral alkyl boronates in up to 86 % yield with high enantioselectivity. The alkylboron moiety in the resulting chiral diester products was converted into various functional groups by organic transformation of the C−B bond.*

The catalytic asymmetric conjugate addition of organometallic reagents to α,β-unsaturated compounds is one of the key methods for C−C bond formation with the efficient construction of new carbon stereogenic centers.[1] In the past decades, air-sensitive nonstabilized organometallic nucleophiles, such as Grignard reagents,[2] organozinc reagents,[3] organoaluminum reagents,[4] and organozirconium reagents,[5] have been used. However, the use of stoichiometric amounts of these reagents and difficulties in handling them generally limited their synthetic efficiency. Organoboron compounds have drawn attention as alternative reagents owing to their excellent functional-group tolerance, nontoxicity, stability, and easy handling. Nevertheless, their limited use in asymmetric conjugate addition may be attributed to their lower reactivity than that of the aforementioned organometallic reagents. Asymmetric conjugate addition using aryl and alkenyl boronic acid derivatives has been extensively developed with precious transition metals, such as rhodium and palladium catalysts.[6,7] Copper-catalyzed enantioselective conjugate addition has been reported using sp^2-carbon-based nucleophiles, including aryl-,[8a,b] alkenyl-,[8c] and allenylboron reagents[8d] (Scheme 1 A, a). In comparison, the use of alkylboron reagents in asymmetric conjugate addition is extremely rare, with one known report by the Sawamura group involving the copper-catalyzed enantioselective conjugate addition of alkyl-9-BBN, prepared from alkenes and 9-borabicyclo[3.3.1]nonane (9-BBN-H), to unusual imidazolyl α,β-unsaturated ketones for $C(sp^3)-C(sp^3)$ bond formation (Scheme 1 A, a).[9,10] However, this method yielded products with nonfunctional alkyl groups, which limited further transformation of the resulting products.



Scheme 1. Conjugate addition with organoboron reagents and reactions of 1,1-diborylalkanes.

1,1-Diborylalkanes, which contain two boryl groups at the same sp^3-carbon atom, are attractive reagents for stereoselective C−C coupling reactions with diverse electrophiles owing to the retention of a single boryl moiety even after catalytic activation of one of the C−B bonds.[11,12] Since the Shibata group first reported the use of 1,1-diborylalkanes in palladium-catalyzed chemoselective Suzuki coupling,[13] a number of advances with transition-metal catalysts were reported (Scheme 1 A, b): enantioselective Suzuki coupling reactions with aryl and vinyl halides,[14] S_N2'-selective allylic substitution with allylic electrophiles,[15] S_N2 substitution with propagylic electrophiles,[16] and diastereo- and enantioselective 1,2-addition to aldehydes,[17a] α-ketoesters,[17b] and imines.[17c] However, conjugate addition using 1,1-diborylalkanes is unknown and remains unexplored.

We envisioned that copper-catalyzed enantioselective conjugate addition of a 1,1-diborylmethane derivative to α,β-unsaturated carbonyl compounds would provide versatile products carrying a borylmethyl group at the β-position (Scheme 1 B). The resulting chiral alkylboron compounds could be utilized for further stereospecific organic transformations.[18]

To assess the feasibility of the envisioned reaction design, we started our investigation with commercially available diethyl benzylidenemalonate (**1a**) and bis[(pinacolato)boryl]-methane (**2**) in the presence of copper chloride with a chiral

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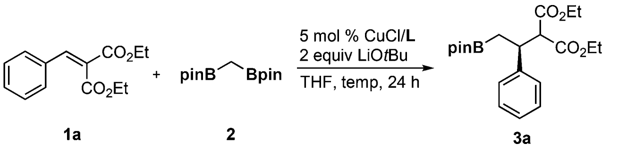
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201909712.

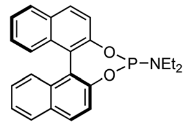
phosphoramidite ligand, as such ligands have proven efficient in copper-catalyzed 1,2-addition reactions with 1,1-diborylalkanes.[17] Under the reaction conditions, the desired product was obtained in 97% yield, but a racemic product was obtained (Table 1, entry 1). The chiral bisphosphine ligand (*R*,*R*)-methyl-Duphos (**L2**) also resulted in a good yield but with 0% *ee* (entry 2). We suspected a possible background reaction for the low *ee* values and found that a severe background reaction even occurred in the absence of a ligand (entry 3). This extremely facile background reaction inhibited asymmetric conversion in the addition reaction; therefore, N-heterocyclic carbene (NHC) ligands, which coordinately tightly to copper, were considered as good ligand candidates.[19]

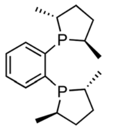
Table 1: Optimization of the reaction conditions.[a]

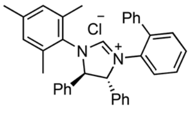


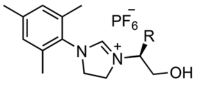
Entry	Ligand [L]	Cu/L ratio	T [°C]	Yield [%][b]	e.r.[c]
1	**L1**	1:1	RT	97	50:50
2	**L2**	1:1	RT	95	50:50
3	–	–	RT	91	–
4	**L3**	1:1	RT	95	50:50
5	**L4**	1:1	RT	74	69:31
6	**L4**	1:2	RT	41	93:7
7	**L4**	1:2	60	86	94:6
8	**L5**	1:2	60	26	86:14
9	**L6**	1:2	60	73	53:47
10	**L7**	1:2	60	49	54:46

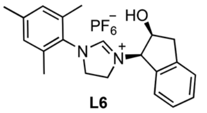
[a] General reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), CuCl (0.025 mmol), ligand (0.025 mmol), LiO*t*Bu (1 mmol), THF (1 mL), room temperature; see the Supporting Information for details. [b] Yield of the isolated product. [c] The enantiomeric ratio was determined by HPLC analysis.

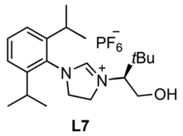

L1


L2


L3

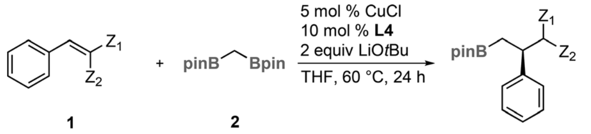

L4, R = *t*Bu
L5, R = Ph


L6


L7

We examined the reactions using copper catalysts with chiral NHC ligands **L3** and **L4** (Table 1, entries 4 and 5), and found that **L4** bearing a hydroxy coordinating substituent[20] yielded promising results with a moderate enantiomeric ratio (69:31). When the molar ratio of copper to ligand was changed to 1:2 to minimize the presence of ligand-free copper catalyst, the yield of the desired product decreased to 41%, but the enantiomeric ratio was greatly improved (entry 6). The results indicated the decreased reactivity of the **L4**–copper complex as compared to the ligand-free copper catalyst and that higher temperatures might be necessary for an efficient reaction (entry 6). When the temperature was increased to 60°C, the product was obtained in increased yield without significantly affecting the enantiomeric ratio (entry 7). We further examined the reaction with various chiral NHC ligands. Changing the R substituent on the alkyl tether of the NHC ligand from *tert*-butyl to phenyl (**L5**) or indanol (**L6**) resulted in lower yields and enantioselectivities (entries 8 and 9). NHC ligand **L7** containing a 2,6-isopropylphenyl group was less efficient than **L4**, resulting in 49% yield and an enantiomeric ratio of 54:46 (entry 10). Therefore, the conditions using **L4** ligand (entry 7) were selected as optimal for the addition reaction.[21] The optimized conditions were then applied to various α,β-unsaturated acceptors (Table 2).[22] A monoester was unreactive, and other diester and dinitrile compounds exhibited decreased enantioselectivity as compared to diethyl diester compounds (entries 2–4).

Table 2: Screening of α,β-unsaturated compounds.[a]

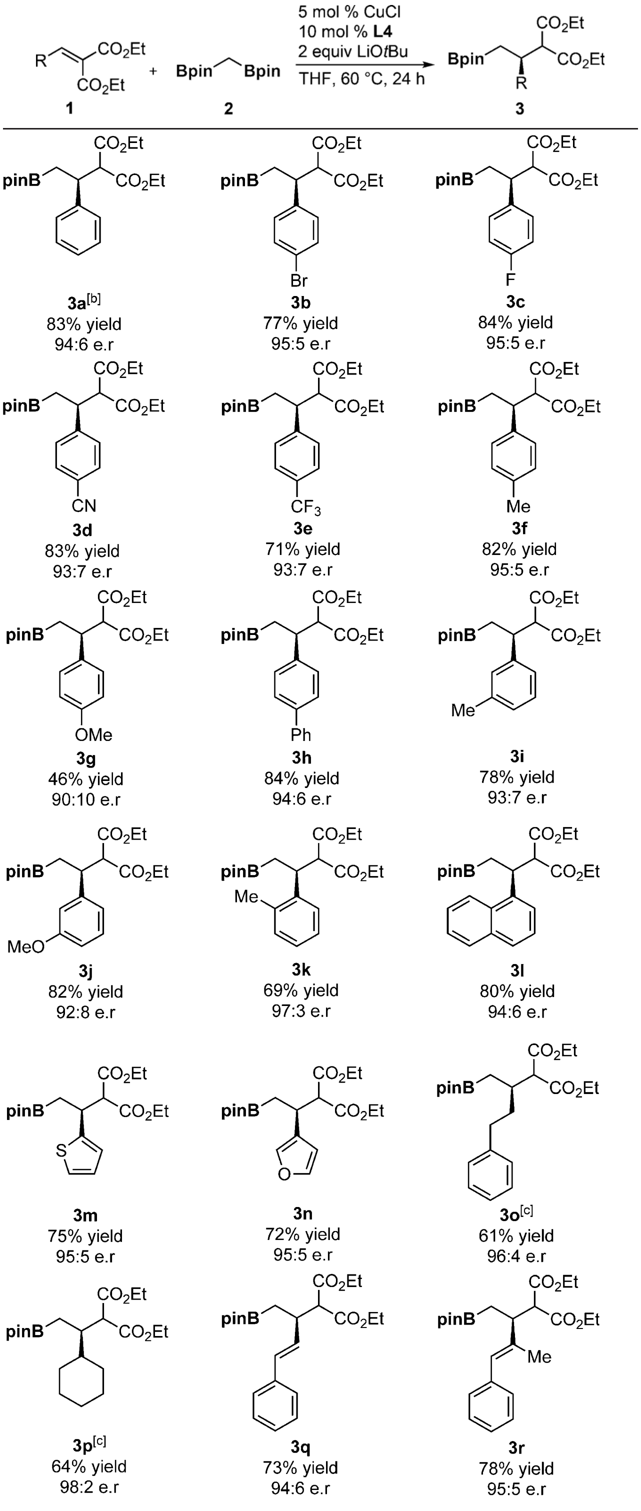


Entry	Substrate (Z^1, Z^2)	Yield [%][b]	e.r.[c]
1	CO_2Et, H	0	–
2	CO_2Me, CO_2Me	84	84:16
3	CO_2tBu, CO_2tBu	58	87:13
4	CN, CN	77	54:46

[a] General reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), CuCl (0.025 mmol), ligand (0.05 mmol), LiO*t*Bu(1 mmol), THF (1 mL), room temperature. [b] Yield of the isolated product. [c] The enantiomeric ratio was determined by HPLC analysis.

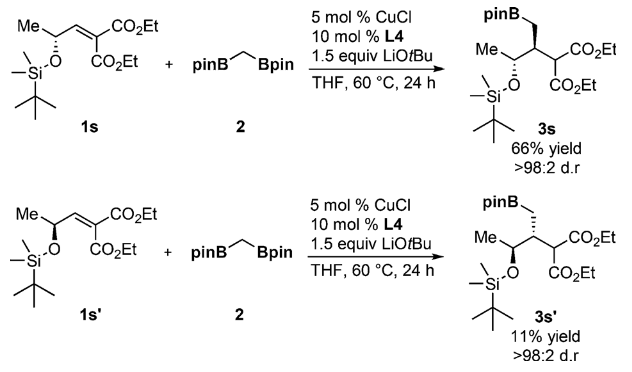
Next, various α,β-unsaturated diethyl diesters **1** with different β-substituents were examined (Table 3).[23] The conjugate addition resulted in the corresponding β-chiral alkylboronate compounds in good yields with high enantioselectivity. Reactions of β-aryl-substituted diesters containing a halogen or an electron-withdrawing or electron-donating group yielded the desired products **3b**–**f** and **3h**. For the less electrophilic diester **1g** containing a strongly electron donating *p*-methoxyphenyl group, decreased yield and enantioselectivity were observed (product **3g**). Diesters containing *meta*- and *ortho*-substituted aryl groups and heteroaryl groups were also tolerated under the optimal reaction conditions (products **3i**–**n**). Besides aryl substituents, diesters with primary and secondary alkyl substituents provided enantiomerically enriched organoboronates **3o** and **3p** in good yields with high enantiomeric ratios. We determined the site selectivity (1,4- vs. 1,6-addition)[24] of the addition with α,β,γ,δ-unsaturated dienoates **1q** and **1r**. Both reactions afforded only the 1,4-addition product **3q** or **3r** in good yield with high enantioselectivity without 1,6-addition. Finally, when the reaction was carried out on a larger scale (3 mmol), reduced amounts of catalyst and ligand resulted in the desired product **3a** without reduction in yield or enantioselectivity.

Table 3: Copper-catalyzed asymmetric conjugate addition of bis[(pinacolato)boryl]methane to α,β-unsaturated diesters.[a]



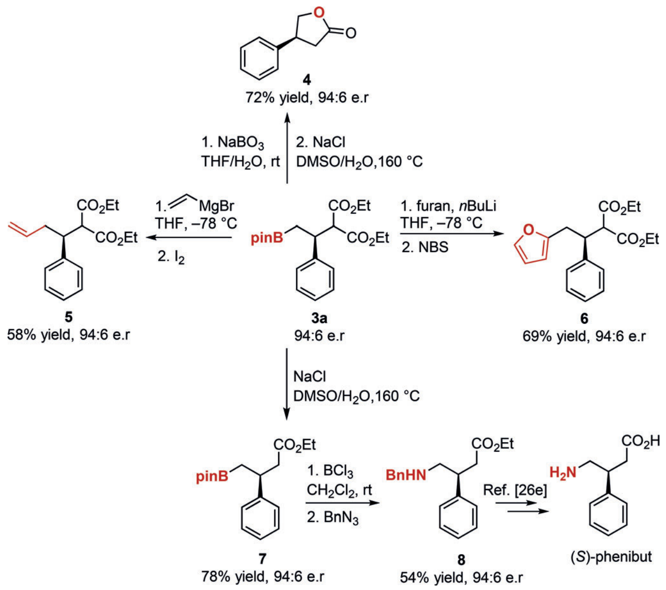
[a] Yields are for the isolated product from reactions on a 0.5 mmol scale. The enantiomeric ratio was determined by HPLC analysis. [b] The reaction was carried out with 2.5 mol% of the copper catalyst and 3.75 mol% of the ligand on a 3 mmol scale. [c] The reaction was carried out with 1.5 equivalents of LiO*t*Bu.

We explored the diastereoselectivity of the catalyst with enantiomerically pure α,β-unsaturated diesters **1s** and **1s′** (Scheme 2). In contrast to the formation of **3s** from **1s** in good yield with excellent diastereoselectivity, the reaction of **1s′** resulted only in the substrate-controlled product **3s′**, the enantiomer of **3s**, in very low yield. The current chiral borylalkyl copper species preferentially approaches the *Re* face of the β-carbon atom of α,β-unsaturated esters; however, steric hindrance between the copper catalyst and the OTBS group of the mismatched substrate **1s′** completely inhibited the synthesis of the other diastereomer.[25]



Scheme 2. Conjugate addition to chiral α,β-unsaturated diesters.

To demonstrate the synthetic applicability of the resulting chiral alkylboron products, we carried out several organic transformations (Scheme 3). Chiral γ-lactone **4** was obtained by intramolecular transesterification of **3a** through oxidation and decarboxylation.[26a] Stereospecific functionalization of the C−B bond to give a C−C bond by metal-free vinylation[26b] and heteroarylation[26c] yielded **5** and **6** without deterioration of enantioselectivity. The Bpin group of **3a** was tolerated



Scheme 3. Transformation of chiral organoboron compounds. Bn = benzyl, DMSO = dimethyl sulfoxide, NBS = *N*-bromosuccinimide.

under decarboxylation conditions, and subsequent amination[26d] of the corresponding product **7** produced benzyl-protected amine **8**, which is a key intermediate[26e] in the synthesis of antianxiety drug (*S*)-phenibut.[27]

In summary, we have described the copper-catalyzed enantioselective conjugate addition of a 1,1-diborylmethane to α,β-unsaturated diesters. Severe background reactions were suppressed by using a chiral N-heterocyclic-carbene–copper catalyst, and the reaction provided a new class of enantiomerically enriched alkylboronates in good yields with high enantioselectivity. Moreover, the versatility of our catalytic method was demonstrated by stereospecific transformation of the resulting chiral organoboron compounds into various organic molecules. Further evaluation of other alkylboron nucleophile candidates is under way.

Acknowledgements

This research was supported by National Research Foundation of Korea (NRF) grants (Nos.2019R1A2C2005706 and 2019R1A4A2001440) funded by the Korean government.

Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · boron · conjugate addition · copper · diborylmethane

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[21] See Table S1 in the Supporting Information for more screening results.

[22] See Tables S1 and S2 in the Supporting Information for more screening results.

[23] Under the current catalytic conditions, branched 1,1-diborylalkanes, such as 1,1-diborylethane, were not reactive (see Table S2).

[24] For selected examples of copper-catalyzed 1,6-conjugate addition reactions, see: a) T. den Hartog, S. R. Harutyunyan, D. Font, A. J. Minnaard, B. L. Feringa, *Angew. Chem. Int. Ed.* **2008**, *47*, 398; *Angew. Chem.* **2008**, *120*, 404; b) H. Hénon, M. Mauduit, A. Alexakis, *Angew. Chem. Int. Ed.* **2008**, *47*, 9122; *Angew. Chem.* **2008**, *120*, 9262; c) Y. Luo, I. D. Roy, A. G. E. Madec, H. W. Lam, *Angew. Chem. Int. Ed.* **2014**, *53*, 4186; *Angew. Chem.* **2014**, *126*, 4270; d) F. Meng, X. Li, S. Torker, Y. Shi, X. Shen, A. H. Hoveyda, *Nature* **2016**, *537*, 387.

[25] See the Supporting Information for stereochemical models.

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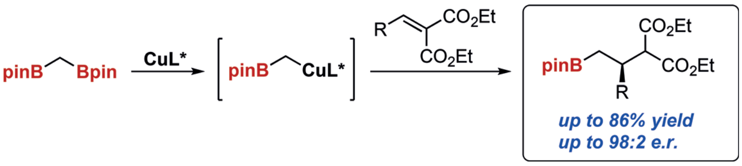
Manuscript received: August 1, 2019
Accepted manuscript online: September 3, 2019
Version of record online: ■■ ■■, ■■■■

Communications

Asymmetric Catalysis



Neat as a new Bpin: Asymmetric catalytic conjugate addition of a borylalkyl copper nucleophile generated in situ from a 1,1-diborylmethane to α,β-unsaturated diesters enabled the enantioselective incorporation of a CH_2Bpin moiety at the β-position of the diesters. The resulting β-chiral alkylboronates were obtained in up to 86% yield with high enantioselectivity (see scheme).