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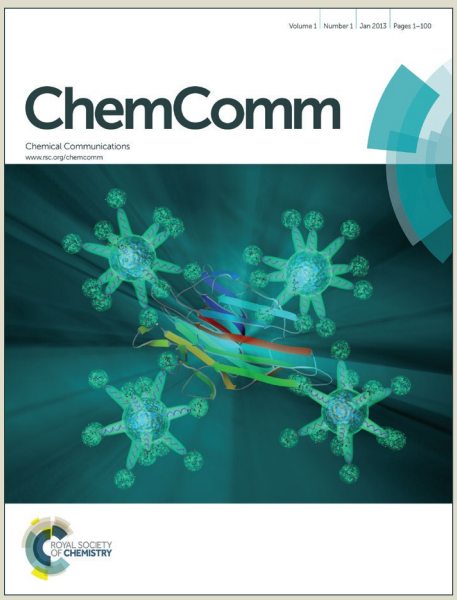

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Copper-catalyzed regio- and enantioselective aminoboration of alkylidenecyclopropanes: synthesis of cyclopropane-containing β-aminoalkylboranes†

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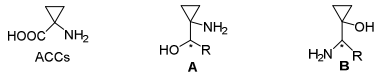
A Cu-catalyzed regio- and enantioselective aminoboration of alkylidenecyclopropanes (ACPs) with bis(pinacolato)-diboron (B_2pin_2) and hydroxylamines has been described in this paper, affording the corresponding cyclopropane-containing β-aminoalkylboranes in good yields under mild conditions. Moreover, a catalytic asymmetric variant of this transformation has been also realized by using a copper complex with a (*S*)-BINAP ligand along with further transformations of the product to give cyclopropane-containing 1,2-aminoalcohols.

Cyclopropane-containing aminoacids, ACCs, are commonly occurring structural motifs in many biologically active natural products and pharmaceuticals (Scheme 1).[1] For example, *Phytotoxin* is a natural product which plays an important role in the jasmonic acid, ethylene and auxin signalling pathways.[2] As the existence of ACCs in many biologically molecules, the synthesis of ACCs and their derivatives have been well studied over the last few decades.[3] Compared with ACCs, although cyclopropane-containing aminoalcohols **A** are not popular subunits in natural products, some molecules having such structural motifs are of great importance in pharmaceuticals (Scheme 1). For instance, *Spirocyclopropylquinolone derivative* was found to be a DNA gyrase inhibitor.[4] Moreover, (*S*)-*Cleonin*, which contains another type of cyclopropane-containing aminoalcohol **B** as a subunit, is an important subunit of *Cleomycin*, an antitumor agent belongs to the family of *bleomycin-phleomycin* antibiotics (Scheme 1).[5] *Bremazocine* is a kappa-opioid receptor agonist with potent analgesic and diuretic activities.[6] Thus far, the synthetic method of cyclopropane-containing aminoalcohols has not been well studied as that of ACCs. Recently, Hirano and Miura described an elegant Cu-catalyzed highly regio- and stereoselective aminoboration of 1-methylenecyclopropanes to obtain (borylmethyl)cyclopropylamines in good yields, which can be easily transformed into aminoalcohols **A** after oxidation (Scheme 2, previous work).[7] In 2001, Kulinkovich reported the synthesis of aminoalcohols **B** from *N*-benzyl α-amino acid ethyl esters by Kulinkovich reaction.[8] In the same year, Taddei explored a six-step synthesis of (*S*)-*Cleonin* from (*R*)-*Serine*.[9] To the best of our knowledge, catalytic asymmetric synthesis of enantiomerically enriched aminoalcohol **B** has never been reported before. Thus, the development of robust methods for the construction of aminoalcohol **B**, especially asymmetric variant, is highly desirable.



Scheme 1 Cyclopropane-containing aminoalcohol and aminoacids

Copper-catalyzed regio- and enantioselective aminoboration reaction of alkenes with diboron reagents and hydroxylamines has received significant attention as an important and powerful strategy to install both boron and amino groups during the C-N bond forming process.[10] The formation of organoborons constitutes an important class of compounds in organic synthesis as they are suitable partners for metal-catalyzed cross-coupling reactions.[11] In addition, this methodology has been applied to a formal regio- and enantioselective hydroamination of styrenes by replacement of diboron reagent with appropriate hydride source.[12] We envisaged that this method, when applied to alkylidenecyclopropanes (ACPs), would allow the generation of a broad range of cyclopropane-containing β-aminoalkylboranes, which can be easily converted into cyclopropane-containing 1,2-aminoalcohols **B** by oxidation. Alkylidenecyclopropanes, as highly strained but readily accessible molecules, are useful building block in organic synthesis.[13] These compounds are attractive starting materials

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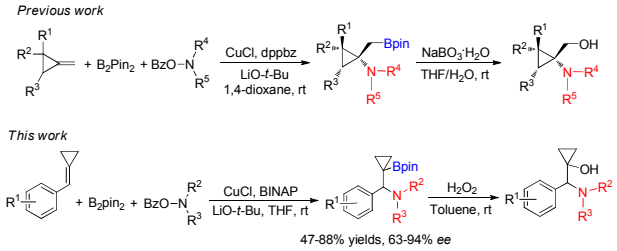
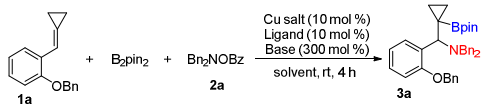
for the synthesis of 1,2-aminoalcohols **B**. Herein, we wish to report a Cu-catalyzed regio- and enantioselective aminoboration of ACPs with bis(pinacolato)-diboron (B_2pin_2) and hydroxylamines to afford the corresponding aminoborated products in good yields with good functional group tolerance and up to 94% ee value under mild conditions (Scheme 2, this work).



Scheme 2 Aminoboroation of ACPs

Our initial investigations focus on the aminoboration reaction of ACP **1a** with *O*-benzoyl-*N*,*N*-dibenzyl-hydroxylamine **2a** and pinB-Bpin using the conditions previously developed for the aminoboration of styrenes[10a] and the results are summarized in Table 1. First, we examined the ligand effect, dppbz, which exhibited the best performance in the previous aminoboration reactions, did not provide the product at all (Table 1, entry 1). To our delight, **1a** underwent the aminoboration reaction in the presence of CuCl/PPh_3 catalytic system using LiO-*t*-Bu as a base in THF at room temperature, giving the desired product **3a** in 78% yield as a single regioisomer (Table 1, entry 2). The adjacent phenyl group can stabilize the Cu-C bond in the intermediate formed in the reaction of borylcopper intermediate with ACP, controlling the regioselectivity.[14] None of **3a** was obtained in the absence of CuCl (Table 1, entry 3). This reaction only afforded **3a** in 52% yield if without PPh_3 ligand (Table 1, entry 4). Dppe and IPr·HCl did not promote the reaction to give the desired product **3a** (Table 1, entries 5 and 10). The reaction went smoothly when DPE-phos, BINAP, phen (phenanthroline), or dppb were used as the ligand and BINAP gave the best result (Table 1, entries 6-9). The examination of solvent effects revealed that THF gave **3a** in the highest yield (Table 1, entries 11-13). CuI, $CuCl_2$, $[Cu(CH_3CN)_4]BF_4$ or $Cu(OAc)_2$ did not give better results than CuCl (Table 1, entries 14-17). Replacement of LiO-*t*-Bu with NaO-*t*-Bu or KO-*t*-Bu impaired the reaction outcomes (Table 1, entries 18 and 19). On the basis of above results, the reactions should be performed at room temperature in the presence of CuCl/BINAP catalytic system using LiO-*t*-Bu as a base in THF.

Table 1 Optimization of the reaction conditions



entry[a]	Cu salt	ligand	base	solvent	yield[b] (%)
1	CuCl	dppbz	LiO-*t*-Bu	THF	0
2	CuCl	PPh_3	LiO-*t*-Bu	THF	78
3	-	PPh_3	LiO-*t*-Bu	THF	0
4	CuCl	-	LiO-*t*-Bu	THF	52
5	CuCl	dppe	LiO-*t*-Bu	THF	0
6	CuCl	DPE-phos	LiO-*t*-Bu	THF	83
7	***CuCl***	***BINAP***	***LiO-t-Bu***	***THF***	***87 (85)***
8	CuCl	dppb	LiO-*t*-Bu	THF	78
9	CuCl	phenanthroline	LiO-*t*-Bu	THF	75
10	CuCl	IPr·HCl	LiO-*t*-Bu	THF	0
11	CuCl	BINAP	LiO-*t*-Bu	Toluene	81
12	CuCl	BINAP	LiO-*t*-Bu	DCM	53
13	CuCl	BINAP	LiO-*t*-Bu	CH_3CN	73
14	CuI	BINAP	LiO-*t*-Bu	THF	85
15	$CuCl_2$	BINAP	LiO-*t*-Bu	THF	83
16	$[Cu(CH_3CN)_4]BF_4$	BINAP	LiO-*t*-Bu	THF	84
17	$Cu(OAc)_2$	BINAP	LiO-*t*-Bu	THF	80
18	CuCl	BINAP	NaO-*t*-Bu	THF	40
19	CuCl	BINAP	KO-*t*-Bu	THF	23

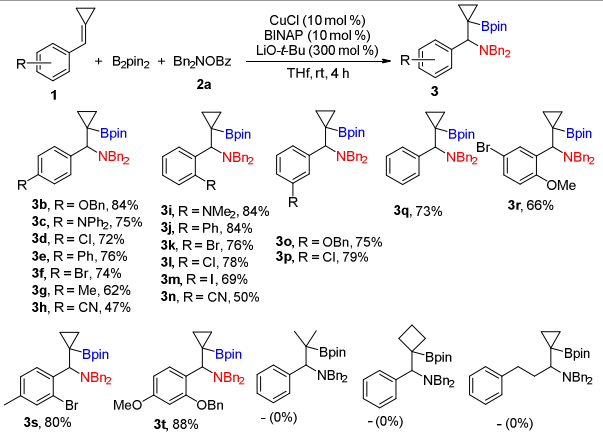
[a] Reaction conditions: **1a** (0.10 mmol, 1.0 eq), B_2pin_2 (0.15 mmol, 1.5 eq), **2a** (0.15 mmol, 1.5 eq), THF (1.5 mL). [b] Yield of **3a** was determined by ^1H NMR analysis with 1,3,5-trimethoxylbenzene as an internal standard. Yield in the parentheses was the isolated yield.

Under the optimized conditions, we next surveyed a range of substrates **1** for this reaction and the results are shown in Table 2. We first examined the electronic effect at the *para*-position of the benzene ring in ACPs **1**. As for substrates **1b**-**1f**, the reactions all proceeded smoothly to give the desired products **3b**-**3f** in good yields regardless of whether they had an electronic-rich or electronic-poor aromatic ring. When R was a Me or CN group, the desired products **3g** and **3h** were given in lower yields (62% and 47% respectively). The *ortho*- and *meta*-substituted substrates were also well tolerated under the standard reaction conditions, providing the desired products **3i**-**3p** in good yields. Substrate bearing a cyano group at the benzene ring suffered lower yield. Non-substituted and disubstituted substrates **1q**-**1t** could also underwent the reaction efficiently to give the desired products **3q**-**3t** in good yields. The structures of **3j** and **3q** have been unambiguously confirmed by single crystal X-ray analyses and their CIF data and ORTEP drawings are presented in the Supporting Information. It should be noted that using (2-methylprop-1-en-1-yl)benzene or alkylidenecyclobutane as substrates, no desired product was obtained under the standard conditions, suggesting that the strained small ring played important role in this Cu-catalyzed aminoboration reaction, suggesting that the driving force may be the release of the ring strain. In addition, the alkyl-substituted substrate failed to give the desired product.

We next examined the scope of hydroxylamines **2** and the results are shown in Table 3. Replacement of one benzyl group of **2a** by a methyl group delivered the desired product **3u** in 55% yield.[15] Allyl-substituted amine **2c** could also react with **1a** and **1j** smoothly to provide the corresponding products **3v** and **3w** in good yields. Benzyl and allyl-substituted amine **2d** was also a good partner to afford the desired products **3x** and **3y** in

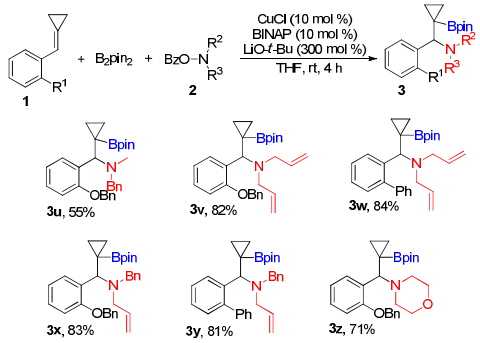
83% and 81% yields, respectively. Hydroxylamine derived from morpholine could be used as well, giving the desired product **3z** in 71% yield, suggesting a broad substrate scope of this reaction.

Table 2 Reaction Scope: Synthesis of cyclopropane-containing β-aminoalkylboranes[a, b]



[a] Reaction conditions: **1** (0.10 mmol, 1.0 eq), B_2pin_2 (0.15 mmol, 1.5 eq), **2a** (0.15 mmol, 1.5 eq), THF (1.5 mL). [b] Isolated yields

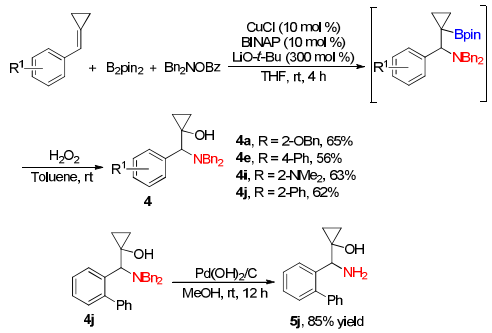
Table 3 Reaction Scope: Synthesis of cyclopropane-containing β-aminoalkylboranes[a, b]



[a] Reaction conditions: **1** (0.10 mmol, 1.0 eq), **2** (0.15 mmol, 1.5 eq), B_2pin_2 (0.15 mmol, 1.5 eq), THF (1.5 mL), r.t. [b] Isolated yield.

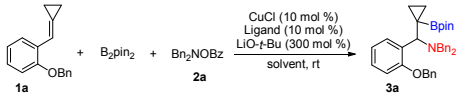
To demonstrate the synthetic utility of the present aminoboration in the construction of aminoalcohol **B**, a sequential aminoboration/oxidation process has been examined. As shown in Scheme 3, aminoboration followed by oxidation with H_2O_2 in toluene afforded the corresponding 1,2-aminoalcohol derivatives **4** in 56-65% yields. After debenzylation of **4j** in the presence of $Pd(OH)_2/C$ under H_2, cyclopropane-containing 1,2-aminoalcohol **5j** was obtained in 85% yield.

Scheme 3 Sequential aminoboration/oxidation[a, b]

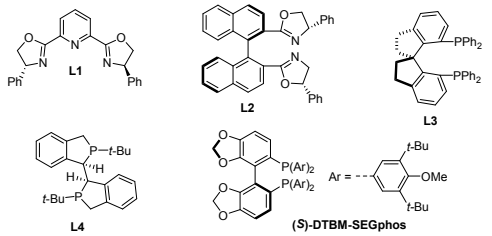


[a] Reaction conditions: **1** (0.20 mmol, 1.0 eq), B_2pin_2 (0.30 mmol, 1.5 eq), **2a** (0.30 mmol, 1.5 eq), THF (3.0 mL), H_2O_2 (0.5 mL), **4j** (0.2 mmol), $Pd(OH)_2/C$ (10 mg), MeOH (2 mL) [b] Isolated yields.

Table 4 Optimization of catalytic enantioselective aminoboration reaction



entry[a]	ligand	solvent	yield[b] (%)	ee[c] (%)
1	**(*S*)-BINAP**	THF	87	88
2	**(*R*)-xyl-BINAP**	THF	83	45
3	**L1**	THF	36	rac
4	**L2**	THF	49	rac
5	**L3**	THF	65	rac
6	**L4**	THF	0	-
7	**(*S*)-DTBM-SEGphos**	THF	65	rac
8	***(S)-BINAP***	*CH_3CN*	*73*	*93*
9	**(*S*)-BINAP**	toluene	81	79
10	**(*S*)-BINAP**	dioxane	77	83

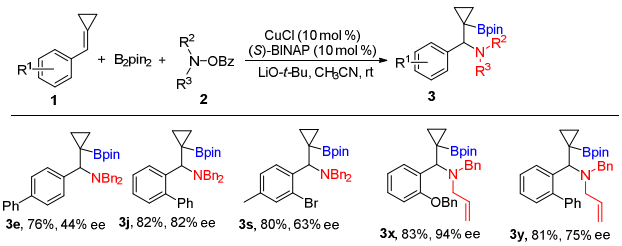


[a] Reaction conditions: **1a** (0.10 mmol, 1.0 eq), B_2pin_2 (0.15 mmol, 1.5 eq), **2a** (0.15 mmol, 1.5 eq), THF (1.5 mL). [b] Isolated yields. [c] ee was determined by chiral HPLC analysis.

Finally, we investigated the possibility of developing an asymmetric variant of this reaction. We began testing several commercially available chiral phosphines with different steric and electronic properties using the conditions optimized for *rac*-BINAP. (*S*)-BINAP is first examined because *rac*-BINAP performed very well for the synthesis of cyclopropane-containing β-aminoalkylboranes. To our delight, **3a** was obtained in 87% yield along with 88% *ee* in the presence of (*S*)-BINAP (Table 4, entry1). While the more sterically hindered ligand, (*R*)-xyl-BINAP, afforded **3a** in 83% yield along with 45% *ee* (Table 4, entry 2). Chiral bis(oxazoline) ligands (**L1** and **L2**) and chiral spiro-diphosphine (**L3**) afforded racemic product (Table 4, entries 3-5). The use of DUAN-phos did not give the desired product (Table 4, entry 6). (*S*)-DTBM-SEGphos, demonstrating the best performance in the asymmetric hydroamination reaction of styrenes, also afforded the racemic product (Table 4, entry 7). Moreover, the screening of

solvents revealed that conducting the reaction in CH_3CN provided the best outcome: 73% yield and 93% *ee* value (Table 4, entries 8-10). Having established the optimal reaction conditions, we next turned our attention to the other substrates and the results are shown in Scheme 4. The corresponding products **3e**, **3j**, **3s**, **3x** and **3y** were obtained in > 76% yields along with 44%-94% *ee* values. We successfully achieved the asymmetric version of this interesting aminoboration reaction.

Scheme 4 Catalytic enantioselective aminoboration[a, b, c]



[a] Reaction conditions: **1** (0.10 mmol, 1.0 eq), B_2pin_2 (0.15 mmol, 1.5 eq), **2** (0.15 mmol, 1.5 eq), CH_3CN (1.5 mL). [b] Isolated yields. [c] ee was determined by chiral HPLC analysis.

In summary, we have developed a Cu-catalyzed aminoboration of alkylidenecyclopropanes (ACPs) with diboron reagent and hydroxylamines to afford the corresponding cyclopropane-containing β-aminoalkylboranes in moderate to good yields under mild conditions. Moreover, a catalytic asymmetric variant of this transformation was also realized by using a copper complex with a chiral (*S*)-BINAP ligand. Further transformation of the product afforded cyclopropane-containing 1,2-aminoalcohol in good yield. The potential utilization and extension of the scope of this new synthetic methodology are currently under investigation.

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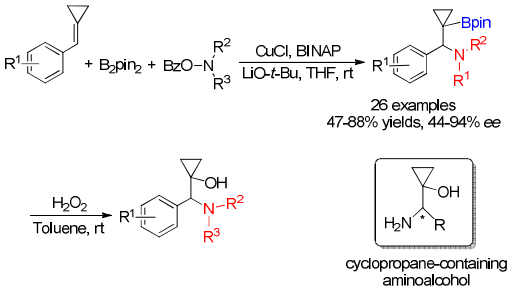
15 This compound is quite labile since it will quickly decompose during the workup process.

Graphical Abstract

Copper-catalyzed regio- and enantioselective aminoboration of alkylidenecyclopropanes: synthesis of cyclopropane-containing β-aminoalkylboranes



A Cu-catalyzed aminoboration of alkylidenecyclopropanes with B_2pin_2 and hydroxylamines produced cyclopropane-containing β-aminoalkylboranes in moderate to good yields.

*Han-Chun Jiang, Xiang-Ying Tang, and Min Shi**