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Copper-Catalyzed Diastereo- and Enantioselective Desymmetrization of Cyclopropenes: Synthesis of Cyclopropylboronates

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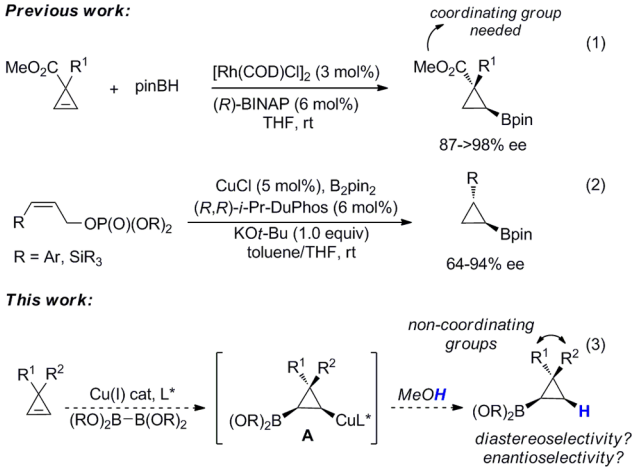
Supporting Information

ABSTRACT: A novel Cu-catalyzed diastereo- and enantioselective desymmetrization of cyclopropenes to afford nonracemic cyclopropylboronates is described. Trapping the cyclopropylcopper intermediate with electrophilic amines allows for the synthesis of cyclopropylaminoboronic esters and demonstrates the potential of the approach for the synthesis of functionalized cyclopropanes.

Cyclopropanes are an important class of compounds widely present in biologically active natural products and pharmaceuticals.[1] In recent years, cyclopropylboronates have gained increasing attention as useful building blocks for the synthesis of functionalized cyclopropanes. In particular, they are suitable partners for metal-catalyzed cross-coupling reactions allowing the synthesis of interesting intermediates such as arylcyclopropanes,[2] cyclopropylketones,[3] or vinylcyclopropanes.[4] Although there are a number of methods available for the synthesis of racemic cyclopropylboronic esters,[5] the preparation of enantiomerically enriched derivatives remains a distinct challenge. The classic approach for the synthesis of optically active cyclopropylboronates requires the use of stoichiometric amounts of chiral auxiliaries on the boron atom.[6,5d,g] There are only two approaches that take advantage of the use of asymmetric transition-metal catalysis (Scheme 1).[7,8] In an elegant study, Gevorgyan et al. described the Rh-catalyzed asymmetric hydroboration of cyclopropenes (Scheme 1, eq 1).[7] They prepared cyclopropylboronates with high levels of diastereo- and enantioselectivity, although a coordinating group (CO_2Me) was necessary to achieve those levels of stereocontrol. More recently, Ito and Sawamura reported the transformation of (*Z*)-3-silyl- and aryl-allylic phosphates to nonracemic 1,2-disubstituted cyclopropylboronates through a Cu(I)-catalyzed reaction with a diboron compound (Scheme 1, eq 2).[8]

Recently, we have been involved in the development of different Cu-catalyzed borylation reactions.[9] Logically, we were intrigued by the possibility of synthesizing enantioenriched cyclopropylboronates from cyclopropenes using a chiral copper(I) boryl complex, ideally without the help of a coordinating group (Scheme 1, eq 3).[10] Along with the importance of the products, there were three additional factors that made this project challenging and interesting: First, Cu-catalyzed asymmetric hydroborations of nonpolarized alkenes have so far been limited to aryl-substituted olefins.[11] Second, despite the excellent work on diastereoselective functionalization of cyclopropenes using copper,[12] there are no reports on Cu-catalyzed enantioselective desymmetrizations of these intermediates. Moreover, most of the diastereoselective Cu-catalyzed carbometalations of cyclopropenes require the presence of a directing group to control the stereoselectivity.[12,13] Third, trapping the cyclopropylcopper intermediate **A** generated through this approach (Scheme 1, eq 3) with electrophiles other than a proton would allow access to highly functionalized cyclopropylboronates that would be difficult to synthesize by known methods. This last feature highlights the synthetic potential of Cu-catalyzed borylations and is in contrast to other metal-catalyzed hydroborations where the C−B bond is formed through a reductive elimination step.[14] Herein, we describe the first Cu-catalyzed enantioselective desymmetrization of cyclopropenes to produce cyclopropylboronates with high diastereo- and enantioselectivity and without the need of a directing group. Additionally, we have shown that racemic cyclopropylcopper intermediates related to **A** can react with electrophilic amines to give unprecedented cyclopropylaminoboronates with high levels of diastereoselectivity.

Scheme 1. Metal-Catalyzed Synthesis of Nonracemic Cyclopropylboronates



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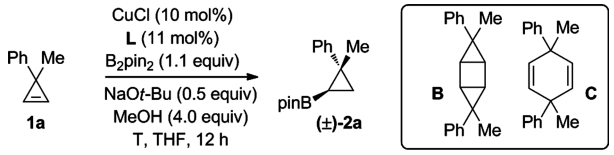
We began by examining the reactivity of cyclopropene **1a** under Cu-catalyzed borylation conditions, using achiral phosphine ligands (Table 1). In the presence of CuCl (10 mol %), xantphos (11 mol %), B_2pin_2 (1.1 equiv), NaO*t*-Bu (0.5 equiv), and MeOH[15] (4 equiv) in THF, we observed the formation of cyclopropylboronate (±)-**2a** with excellent diastereoselectivity (entry 1, Table 1). However, the yields were consistently low due to formation of variable quantities of an inseparable mixture of dimers **B** and **C**. This problem was not completely unexpected since dimerization is one of the most common undesired pathways in transition-metal-catalyzed reactions with cyclopropenes.[13b] Trying to minimize the formation of these dimeric structures therefore became one of the major challenges of this project.[16] The yield of (±)-**2a** increased when we carried out the reaction at lower temperature (entry 2, Table 1), but significant amounts of **B** and **C** were still produced. After extensive experimentation,[17] we observed that addition of cyclopropene **1a** and MeOH to a −78 °C solution of the preformed xantphos−copper−boryl complex, followed by warming to −20 °C, afforded (±)-**2a**[7] in excellent yield as a single diastereomer.

Table 1. Effect of the Ligand and Temperature on the Diastereoselective Hydroboration of Cyclopropenes

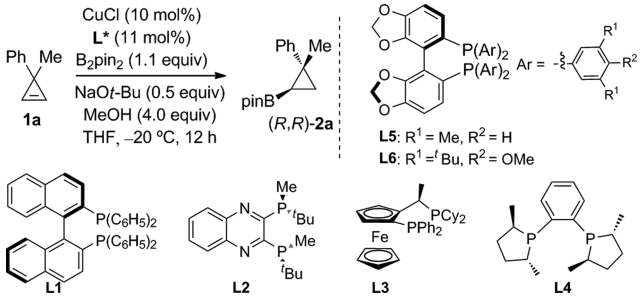


entry[a]	L	*T* (°C)	dr[b]	yield (%)[c]
1	xantphos	23	95:5	40
2	xantphos	−20	≥98:2	60
3[d]	***xantphos***	***−20***	***≥98:2***	***90***

[a]Reaction conditions: **1a** (0.2 mmol), B_2pin_2 (0.22 mmol), NaO*t*-Bu (0.1 mmol), CuCl (10 mol %), xantphos (11 mol %), MeOH (0.8 mmol), THF (0.33 M). [b]Determined by ^{1}H NMR analysis. [c]Yield of isolated (±)-**2a**. [d]Cyclopropane **1a** and MeOH were added at −78 °C; the reaction mixture was then warmed up to −20 °C.

Once we minimized the dimerization pathway for the diastereoselective Cu-catalyzed hydroboration, we looked at the possibility of developing an asymmetric variant (Table 2). We started testing several commercially available phosphines with different steric and electronic properties using the conditions previously optimized for xantphos (entries 1−6, Table 2).[17] We soon realized that the yields and stereoselectivities were highly dependent on the ligand. (*R*)-DTBM-Segphos **L6** was superior to other chiral ligands affording cyclopropane (*R*,*R*)-**2a** in 71% yield and 92:8 enantiomeric ratio. However, we found that these values were poorly reproducible with enantiomeric ratios varying inconsistently from 85:15 to 92:8. Trying to solve this problem, we searched for a different Cu source.[17] A first attempt using $[Cu(CH_3CN)_4]PF_6$ (entry 7, Table 2) afforded (*R*,*R*)-**2a** with high diastereoselectivity but only moderate yield and enantioselectivity. Gratifyingly, when acetonitrile was removed *in vacuo* after phosphine−copper complex formation (entry 8, Table 2), the desired compound was consistently obtained in high yield with excellent diastereo- and enantioselectivity (dr = 97:3, er = 95:5). This result significantly improves upon the 58% ee found in the Rh-catalyzed hydroboration of **1a**.[7] The use of 5 mol % of $[Cu(CH_3CN)_4]PF_6$ resulted in a lower yield and enantioselectivity (entry 9, Table 2).

Table 2. Effect of the Ligand and Copper Source on the Enantioselective Hydroboration of Cyclopropenes



entry[a,b]	Cu(I)	L*	dr[c]	er[d]	yield[e] (%)
1	CuCl	**L1**	96:4	78:22	49
2	CuCl	**L2**	70:30	77:23	70
3	CuCl	**L3**	91:9	42:58	65
4	CuCl	**L4**	95:5	60:40	15
5	CuCl	**L5**	94:6	82:18	70
6	CuCl	**L6**	≥98:2	92:8	71
7	$[Cu(CH_3CN)_4]PF_6$	**L6**	96:4	82:18	58
8[f]	***$[Cu(CH_3CN)_4]PF_6$***	***L6***	***97:3***	***95:5***	***74***
9[g]	$[Cu(CH_3CN)_4]PF_6$	**L6**	95:5	90:10	50
10	–	**L6**	–	–	0

[a]Reaction conditions: **1a** (0.2 mmol), B_2pin_2 (0.22 mmol), NaO*t*-Bu (0.1 mmol), Cu(I) (10 mol %), **L** (11 mol %), MeOH (0.8 mmol), THF (0.33 M). [b]Cyclopropane **1a** and MeOH were added at −78 °C; the reaction mixture was then warmed up to −20 °C. [c]Determined by ^{1}H NMR analysis. [d]er determined by chiral SFC. [e]Yield of isolated (*R*,*R*)-**2a**. [f]CH_3CN was removed *in vacuo* after phosphine−copper complex formation. [g]5% of $[Cu(CH_3CN)_4]PF_6$ was used.

To rule out a possible organocatalytic activation of B_2pin_2,[18] we carried out the reaction in the absence of a Cu salt (entry 10, Table 2). Under these conditions, formation of (*R*,*R*)-**2a** was not observed.

Next, we applied the Cu-catalyzed hydroboration conditions to different (3,3-disubstituted)-cyclopropenes (Table 3). In some cases, the reaction was carried out at either −50 or −78 °C to optimize the enantiomeric ratio. Compounds bearing an electron-rich aromatic substituent afforded the corresponding cyclopropylboronates [(*R*,*R*)-**2b**−**2d**] with similar efficiency to model (*R*,*R*)-**2a** (dr up to ≥98:2, er up to 96:4). Cyclopropenes with electron-deficient aryl groups underwent hydroboration with good yields and high diastereoselectivities although slightly lower enantiomeric ratios [(*R*,*R*)-**2e**−**2f**]. Moreover, substitution at the *meta* position of the aryl group also seemed to affect the enantioselectivity [(*R*,*R*)-**2g**]. Compounds (*R*,*R*)-**2h** and (*R*,*R*)-**2i**, with a thiophene and a furan ring, respectively, were also prepared with good yields and high enantioselectivities. Starting from dideuterated **1a** (**1a**-*d2*), compound (*R*,*R*,*R*)-**2j** with three contiguous stereocenters was successfully obtained. Additionally, coordinating groups (CH_2OMe) were also compatible with the hydroboration conditions and compound (*R*,*S*)-**2k** was obtained with excellent results (er = 96.5:3.5, dr ≥ 98:2).[19]

Cyclopropane (*R*,*R*)-**2l**, bearing a spiro-quaternary stereocenter, was also prepared with high levels of stereocontrol. Gratifyingly, bulkier groups on the cyclopropene (R^2 = *i*-Pr, (*R*,*R*)-**2m**) maintained high levels of enantiocontrol although the diastereoselectivity was moderately decreased (80:20 vs 97:3). Similarly, cyclopropane (*R*,*S*)-**2n** bearing two alkyl groups (R^1 =

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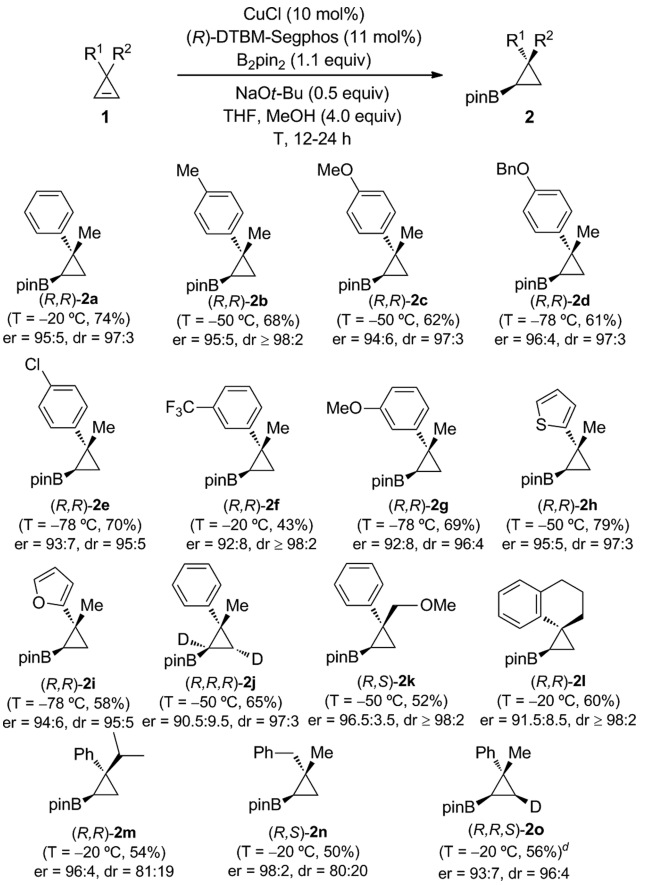
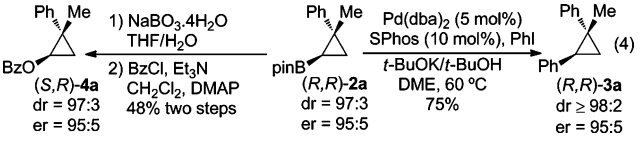
Table 3. Substrate Scope[a,b,c]



[a]Reaction conditions: **1** (0.2 mmol), B_2pin_2 (0.22 mmol), NaO*t*-Bu (0.1 mmol), CuCl (10 mol %), (*R*)-DTBM-Segphos (11 mol %), MeOH (0.8 mmol), THF (0.33 M). [b]Yield of isolated **2**. [c]er determined by chiral SFC; dr determined by ^{1}H NMR analysis. [d]MeOD (0.8 mmol) instead of MeOH was used.

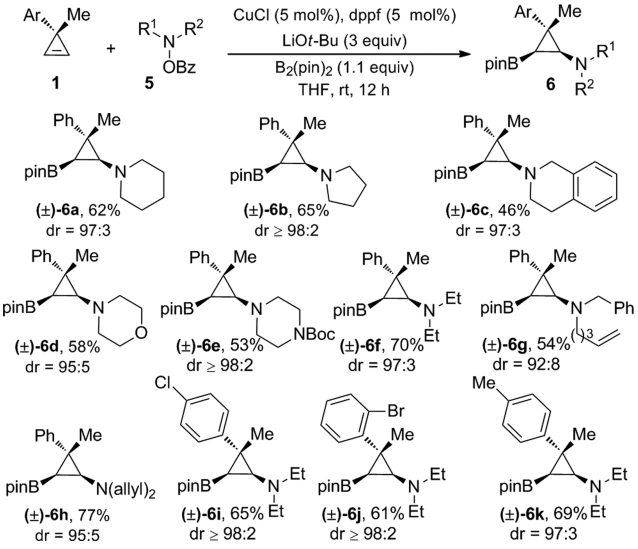
Bn, R^2 = Me) was successfully obtained with somewhat lower diastereoselectivity than (*R,R*)-**2a** but with excellent enantioselectivity (er = 98:2).[20] Finally, in the presence of MeOD, compound (*R,R,S*)-**2o** was obtained in good yield and high stereoselectivity (er = 93:7, dr = 96:4, >98% D incorporation). This experiment demonstrates the *syn* insertion of the cyclopropene in the copper–boryl complex and reveals the configurational stability of the cyclopropylcopper intermediate **A** (Scheme 1, eq 3). Overall, the results described in Table 3 suggest that the stereoselectivity is mostly controlled by steric factors.[21]

To demonstrate the versatility of the cyclopropylboronate species, (*R,R*)-**2a** was easily transformed into cyclopropane (*R,R*)-**3a** through a Suzuki–Miyaura coupling with iodobenzene (eq 4).[22] Aditionally, cyclopropanol derivative (*S,R*)-**4a** was prepared through an oxidation–benzoylation sequence.



Finally, we wanted to explore the trapping of **A** with electrophiles other than a proton. We focused on the use of *O*-benzoyl-*N,N*-dialkylhydroxylamines[23] due to the importance of cyclopropylamines in biologically active compounds. The products would be cyclopropylaminoboronates (**6**) with three contiguous stereocenters, which would be difficult to obtain by known methods. We started our study using achiral phosphines. Unfortunately, the conditions found for the diastereoselective hydroboration of cyclopropene **1a**[17] (entry 3, Table 1) were not optimal for the aminoboration reaction.[24] After significant optimization, we were pleased to find that a CuCl/dppf catalyst system (5 mol %) and LiO*t*-Bu in THF afforded cyclopropylaminoboronates (±)-**6** in good yields and excellent diastereomeric ratios (Table 4). Interestingly, the reactions were carried

Table 4. Copper-Catalyzed Aminoboration[a,b,c]



[a]Reaction conditions: **1** (0.4 mmol), B_2pin_2 (0.44 mmol), R_2NOBz (0.6 mmol), LiO*t*-Bu (1.2 mmol), CuCl (5 mol %), dppf (5 mol %), THF (0.2 M). [b]Determined by ^{1}H NMR analysis. [c]Yield of isolated **6**.

out at rt without observing significant amounts of dimerization products **B** and **C**. These conditions worked well for a variety of *O*-benzoyl-*N,N*-dialkylhydroxylamines. Piperidine, pyrrolidine, tetrahydroisoquinoline, morpholine, and piperazine derivatives ((±)-**6a**–**6e**, Table 4) were easily prepared using the conditions described above. In all cases, a cyclopropane with the methyl, nitrogen, and boron substituents in a *syn* orientation was obtained with high diastereoselectivity.[25] Cyclopropylaminoboronates bearing an acyclic *N,N*-dialkyl amine moiety were also successfully obtained through this method ((±)-**6f**–**6h**, Table 4). Additionally, we performed the reaction with cyclopropenes bearing different substituents on the aromatic ring, obtaining the desired compounds in good yields as nearly single diastereomers ((±)-**6i**–**6k**, Table 4). Unfortunately, none of the chiral phosphines used in the optimization of (*R,R*)-**2a** were compatible with the aminoboration conditions. In all cases, we obtained inseparable mixtures of the desired compounds and unknown byproducts with diastereomeric ratios significantly lower than in the case with dppf.[17]

In summary, we describe here the first diastereo- and enantioselective Cu-catalyzed hydroboration of cyclopropenes. This method allows for the synthesis of enantiomerically enriched cyclopropylboronates with a quaternary stereocenter and represents the first enantioselective Cu-catalyzed desymmetrization of cyclopropenes. Our approach nicely complements the few existing methods to synthesize nonracemic cyclopropylboronates and gives new insights into the enantioselective metal-catalyzed desymmetrization of cyclopropenes. Additionally, the

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capture of the cyclopropylcopper intermediate with electrophilic amines highlights the synthetic potential of this approach and opens a new way to synthesize functionalized cyclopropanes. Further applications toward the enantioselective synthesis of cyclopropylaminoboronates as well as functionalization of cyclopropenes with different electrophiles are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and crystallographic CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

†L.A. and M.G.-C. contributed equally.

Notes

The authors declare no competing financial interest.

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(16) We believe **B** is formed through a Cu-catalyzed formal [2 + 2] cycloaddition. **C** could be formed from **B** through an electrocyclic ring opening.

(17) For a full account on all the ligands used and other parameters see the Supporting Information.

(18) Selected examples of organocatalyzed activation of diboron compounds: (a) Lee, K.-s.; Zhugralin, A.; Hoveyda, A. *J. Am. Chem. Soc.* **2009**, *131*, 7253. (b) Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5130. (c) Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 7158. (d) Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 8277.

(19) Unfortunately, cyclopropenes bearing a carbomethoxy group (R^2 = CO_2Me instead of Me) afforded a complex mixture of compounds.

(20) The absolute configuration of (*R*,*R*)-**2e** was established from single crystal X-ray crystallography of a *p*-nitrobenzoate derived by oxidation of the C−B bond followed by benzoylation. The absolute configuration of the other cyclopropylboronates was assigned by analogy. The relative stereochemistry of compound (*R*,*R*)-**2l** was assigned by single crystal X-ray crystallography.

(21) Proposed transition-state models to explain the observed stereoselectivity are included in the Supporting Information.

(22) For Suzuki−Miyaura couplings of cyclopropylboronates, see: Pietruszka, J.; Witt, A.; Freig, W. *Eur. J. Org. Chem.* **2003**, 3219. See also reference 8a.

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(25) The relative configuration of (±)-**6a** was established by single crystal X-ray crystallography.