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Stereospecific Synthesis of Cyclobutylboronates through Copper(I)-Catalyzed Reaction of Homoallylic Sulfonates and a Diboron Derivative

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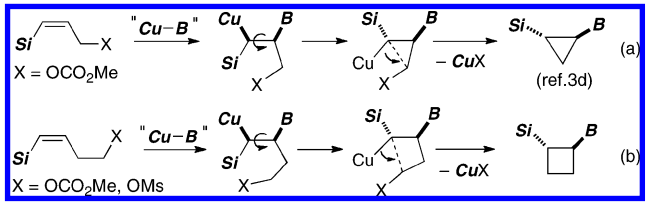
Cyclobutanes have received considerable attention as prevalent structures in natural products and as versatile synthetic intermediates.[1] However, synthetic methods for cyclobutanes with multiple stereocenters are relatively less developed than those for other ring systems. [2 + 2] Photocycloadditions are the most widely used and reliable method for stereoselective cyclobutane synthesis; however, high regio- and stereoselectivity is almost limited to the enone−alkene reactions.[1] Cyclobutylboronates with stereodefined structures are expected to be a promising synthetic intermediate because they have high configurational stability and many stereospecific transformations of C−B bonds exist. However, highly general methods for the stereoselective synthesis of such compounds have been scarcely reported.[2] Herein, we describe a novel catalytic protocol for accessing *cis*- and *trans*-1-silyl-2-borylcyclobutanes as well as 1-aryl-2-borylcyclobutanes. The synthetic utility of the compounds is also demonstrated by their stereospecific derivatization.

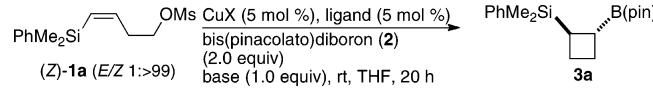
During the course of our studies on copper(I)/diboron catalytic reactions,[3,4] we reported the enantio- and stereoselective reaction that produces *trans*-1-silyl-2-borylcyclopropane compounds (Scheme 1a).[3d] The reaction mechanism involves intramolecular ring closing of the organocopper intermediate formed by the reaction between a borylcopper intermediate and a carbonate derivative of a 3-silyl-substituted allylic alcohol. The starting point of this investigation was to determine whether 1,2-bimetallic cyclobutanes could be obtained by the reaction of 4-silyl-3-buten-1-ol derivatives (Scheme 1b). This was anticipated to be more challenging because it involves the kinetically unfavorable closure of a four-membered ring.[5] To the best of our knowledge, no transition-metal-catalyzed reaction involving such ring closures has been reported. The initial attempts using a carbonate derivative (Scheme 1b, X = OCO_2Me) with copper(I)/diboron systems gave no desired products.

Scheme 1. Copper(I)-Catalyzed Small-Ring Formation



Extensive optimization of leaving groups, copper catalysts, ligands, and additives was performed to ascertain the conditions under which the four-membered-ring formation reaction would proceed. The result of this optimization led the reaction of (*Z*)-4-(dimethylphenylsilyl)buten-3-yl methanesulfonate [(*Z*)-**1a**] with 2.0 equiv of bis(pinacolato)diboron (**2**) in the presence of 5 mol % CuCl, 5 mol % dppp, and 1.0 equiv of K(O-*t*-Bu)/THF for 20 h at room temperature, which afforded the desired *trans*-1-silyl-2-borylcyclobutane (*trans*-**3a**) in high yield with excellent diastereoselectivity (93%, trans/cis >99:1) (Table 1, entry 1).[6] The reaction with a lower catalyst loading (1 mol %) or a smaller amount of diboron (1.2 equiv) also resulted in good yields (entry 2, 83%; entry 3, 95%) with excellent selectivities (trans/cis >99:1). Use of CuI instead of CuCl gave a comparable yield and selectivity (entry 4). The copper(I) salt,[7] a phosphine ligand, and the base [K(O-*t*-Bu)] are essential for the reaction (entries 5−7). The reaction with K_2CO_3 as the base resulted in a poor yield (entry 8). A slightly lower yield was observed when dppe rather than dppp was used (entry 9). The use of dppb, dppf, Xantphos, and PPh_3 resulted in moderate to low yields (entries 10−13). We could not find side products that occurred from the regioisomeric Cu−B insertion in any case.

Table 1. Reaction of Methanesulfonate **1** with Diboron **2** Using Various Cu(I) Catalysts[a]



entry	CuX	ligand	base	yield (%)[b]	dr (trans/cis)[c]
1	CuCl	dppp	K(O-*t*-Bu)	93	>99:1
2[d]	CuCl	dppp	K(O-*t*-Bu)	83	>99:1
3[e]	CuCl	dppp	K(O-*t*-Bu)	95	>99:1
4	CuI	dppp	K(O-*t*-Bu)	97	>99:1
5	none	dppp	K(O-*t*-Bu)	0	−
6	CuCl	none	K(O-*t*-Bu)	2	−
7	CuCl	dppp	none	0	−
8	CuCl	dppp	K_2CO_3	5	−
9	CuCl	dppe	K(O-*t*-Bu)	86	>98:2
10	CuCl	dppb	K(O-*t*-Bu)	47	>98:2
11	CuCl	dppf	K(O-*t*-Bu)	63	15:1
12	CuCl	Xantphos	K(O-*t*-Bu)	40	>98:2
13	CuCl	PPh_3	K(O-*t*-Bu)	15	>98:2

[a] Reaction conditions: sulfonate **1** (0.5 mmol), **2** (1.0 mmol), CuCl (0.025 mmol), ligand (0.025 mmol), and K(O-*t*-Bu)/THF (1.0 M, 0.5 mL) at room temperature. [b] Determined by GC analysis. [c] Determined by GC analysis. [d] Using 1 mol % CuCl and dppp. [e] Using 1.2 equiv of **2**; the isolated yield was 74%.

As summarized in Table 2, this reaction proceeds with various (*E*)- and (*Z*)-homoallylic sulfonates in a stereospecific manner with high fidelity in the transfer of stereochemical infomation. This is in stark contrast to our previous results for cyclopropylboronate formation, where only *trans*-cyclopropane derivatives were obtained as the major products, irrespective of the configuration (*E* or *Z*) of the starting allylic carbonates.[3d] (*E*)-4-(Dimethylphenylsilyl)buten-

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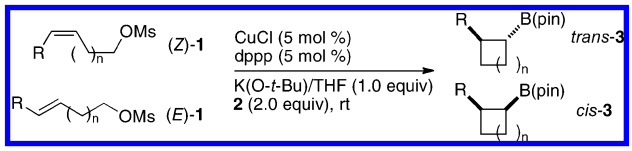
Table 2. Stereospecific Formation of Cycloalkylboronates[a]



entry	substrate	time(h)	product	yield(%)[b]	dr[c] trans/cis
1	PhMe$_2$Si, OMs	20	PhMe$_2$Si, B(pin)	76	5:95
	(*E*)-**1a** (*E*/*Z* 95:5)		*cis*-**3a**		
2	Me$_3$Si, OMs	22	Me$_3$Si, B(pin)	74	99:1
	(*Z*)-**1b** (*E*/*Z* 1:>99)		*trans*-**3b**		
3	Me$_3$Si, OMs	24	Me$_3$Si, B(pin)	69	3:97
	(*E*)-**1b** (*E*/*Z* 96:4)		*cis*-**3b**		
4[d]	BnMe$_2$Si, OMs	29	BnMe$_2$Si, B(pin)	80	96:4
	(*Z*)-**1c** (*E*/*Z* 3:97)		*trans*-**3c**		
5[d]	BnMe$_2$Si, OMs	48	BnMe$_2$Si, B(pin)	81	4:96
	(*E*)-**1c** (*E*/*Z* 96:4)		*cis*-**3c**		
	X, OMs		X, B(pin)		
6[e,g]	X = H, (*Z*)-**1d** (*E*/*Z* 4:96)	23	X = H, *trans*-**3d**	89	95:5
7[e,f,g]	X = CH$_3$, (*Z*)-**1e** (*E*/*Z* 13:87)	50	X = CH$_3$, *trans*-**3e**	76	88:12
8[e,f,g,h]	X = CF$_3$, (*Z*)-**1f** (*E*/*Z* 12:88)	59	X = CF$_3$, *trans*-**3f**	28	94:6
	X, OMs		X, B(pin)		
9[e,g]	X = H, (*E*)-**1d** (*E*/*Z* 97:3)	22	X = H, *cis*-**3d**	63	6:94
10[e,f,g]	X = CH$_3$, (*E*)-**1e** (*E*/*Z* >99:1)	56	X = CH$_3$, *cis*-**3e**	70	4:96
11[e,f,g]	X = CF$_3$, (*E*)-**1f** (*E*/*Z* >99:1)	39	X = CF$_3$, *cis*-**3f**	39	5:95
12[e,f,g]	X = OCH$_3$, (*E*)-**1g** (*E*/*Z* 97:3)	67	X = OCH$_3$, *cis*-**3g**	60	3:97
13	*n*-Bu, OMs	20	*n*-Bu, B(pin)	0	–
	(*Z*)-**1h** (*E*/*Z* 1:>99)		*trans*-**3h**		
14[e,g]	PhMe$_2$Si, OMs	28	PhMe$_2$Si, B(pin)	68	97:3
	(*Z*)-**1i** (*E*/*Z* 1:99)		*trans*-**3i**		
15[e]	PhMe$_2$Si, OMs	21.5	PhMe$_2$Si, B(pin)	78	6:94
	(*E*)-**1i** (*E*/*Z* 95:5)		*cis*-**3i**		
16[g]	PhMe$_2$Si, OMs	96	PhMe$_2$Si, B(pin)	trace	–
	(*Z*)-**1j** (*E*/*Z* 3:97)		*trans*-**3j**		
17[g]	PhMe$_2$Si, OMs	97	PhMe$_2$Si, B(pin)	trace	–
	(*E*)-**1j** (*E*/*Z* 96:4)		*cis*-**3j**		

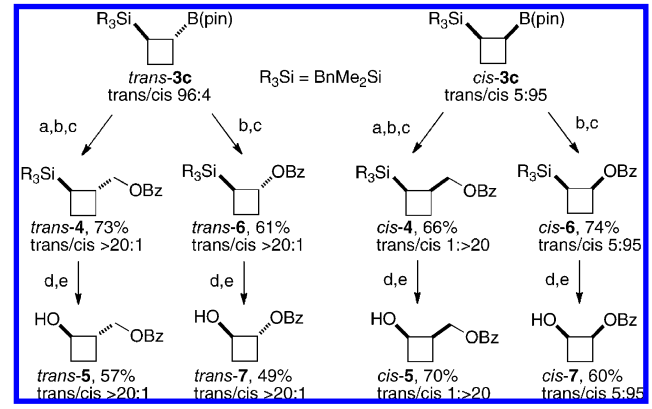
[a] Conditions: **1** (0.5 mmol), **2** (1.0 mmol), CuCl (0.025 mmol), dppp (0.025 mmol), and K(O-*t*-Bu)/THF (1.0 M, 0.5 mL). [b] Isolated yield. [c] Determined by GC analysis. [d] Run on a 3 mmol scale. [e] NMR yield. [f] Using 10 mol % catalyst. [g] Using CuI instead of CuCl. [h] Run on a 0.25 mmol scale.

3-yl methanesulfonate [(*E*)-**1a**, *E*/*Z* 95:5] was efficiently converted to *cis*-1-silyl-2-borylcyclobutane (*cis*-**3a**) in high yield with high diastereoselectivity (99% NMR yield, 76% isolated yield, trans/cis 5:95) (entry 1). The reaction of trimethylsilyl and benzyldimethylsilyl derivatives afforded the corresponding products with very high fidelity in the transfer of stereochemical information (entries 2−5).

Substrates with an aryl group instead of the silyl group were also converted into the corresponding cyclobutanes with a high degree of stereospecificity (entries 6−12). The reaction of (*Z*)-4-phenylbuten-3-yl methanesulfonate [(*Z*)-**1d**] gave *trans*-**3d** in 89% NMR yield and 51% isolated yield. Substituting an electron-donating methyl group at the para position did not greatly affect the product yield (*trans*-**3e**, 76%, entry 7), but para substitution of an electron-withdrawing CF_3 group resulted in a poor yield (28%) and the formation of many side products. (*E*)-Configured homoallyl compounds showed a similar trend in yield (entries 9−11), but the more strongly electron-donating *p*-MeO group resulted in a moderate yield (60%, entry 12). As expected on the basis of the requirement that the alkene substrates should have a low LUMO level for the borylcupration process, an alkyl-substituted compound [(*Z*)-**1h**] remained intact (entry 13).[8] The reactions with (*Z*)- and (*E*)-**1i** afforded five-membered-ring products, *trans*- and *cis*-1-silyl-2-borylcyclopentanes, in good yields with high stereospecificity (entries 14 and 15). In the case of the six-membered-ring version, however, only trace amounts of the products were detected (entries 16 and 17). Side products originating from the regioisomeric insertion could not be detected in the reactions shown in Table 2.

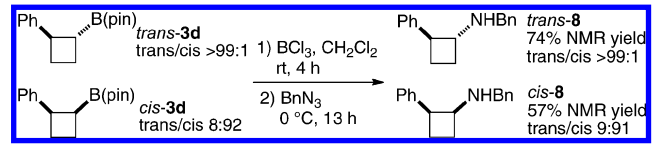
Stereospecific H_2O_2 oxidation of the B−C bonds in the above products afforded the corresponding *trans*- and *cis*-cyclobutanols with high diastereomeric purity. Other derivatization examples are also shown in Schemes 2 and 3. One-carbon homologation of *trans*- and *cis*-**3c**[9] and subsequent oxidation and esterification afforded *trans*- and *cis*-**4**, respectively. Oxidation of the Si−C bonds of the isomers of **4** gave *trans*- and *cis*-**5** with excellent diastereomeric purities (Scheme 2).[10] Monobenzoate derivatives of 1,2-butandiol (*trans* and *cis*-**7**) were also synthesized by oxidation of the B−C bonds of *trans*- and *cis*-**3c** followed by benzoate protection and subsequent Si−C bond oxidation. The cyclobutylamine derivatives *trans*- and *cis*-**8** were also obtained without detectable erosion of diastereomeric purity from *trans*- and *cis*-**3d**, respectively (Scheme 3).[11]

Scheme 2. Stereospecific Derivatization of Cyclobutylboronates[a]



[a] Conditions: (a) $LiCH_2Cl$, THF, −78°C to rt, 3−5 h; (b) H_2O_2, NaOH(aq), THF, 0 °C, 2−3 h; (c) PhCOCl, pyridine, CH_2Cl_2, 0 °C, 3.5−4 h; (d) TBAF, THF, rt, 30 min; (e) H_2O_2, $KHCO_3$, MeOH, rt, 30 min. The yields of *trans*- and *cis*-**7** were determined by ^{1}H NMR spectroscopy.

Scheme 3. Stereoselective Synthesis of *trans*- and *cis*-2-Phenylcyclobutylamines



A proposed mechanism is depicted in Figure 1.[3,4,8] This reaction is initiated by the generation of borylcopper(I) intermediate **B** through the σ-bond metathesis reaction between diboron and species **A** formed by the reaction of CuCl, K(O-*t*-Bu), and dppp. Insertion of the double bond in **1** into the Cu−B

bond produces **C**, in which the Cu−C bond is stabilized by the electronic effect of the adjacent silyl- or aryl- group (R^1 or R^2). These effects would be responsible for the high insertion regioselectivities.[8] Alkyl-substituted starting compounds cannot undergo this step because of the high alkene LUMO level and the lack of the electronic effect in **C**. Ring closure then proceeds through alkoxycuprate **D**, which is formed by coordination of K(O-*t*-Bu) to **C** and would facilitate the intramolecular nucleophilic substitution.[12] The poor product yields observed for the aryl substrate bearing an electron-withdrawing group could be attributed to low intermediate nucleophilicity in this ring-closing step. The stereochemical outcome suggests that the intramolecular substitution proceeds with retention of the configuration on the carbon atom at the copper center. We thus speculate that the ring-closing step proceeds through Cu(III) metallacycle structure **E**. This explains the significant drop in the yield of **3j** ($n = 3$), as the formation of seven-membered Cu(III) metallacycle would be unfavorable in comparison with five- and six-membered ones ($n = 1, 2$). The catalytic cycle is closed by the formation of **3** and potassium methanesulfonate accompanied by the regeneration of **A**.

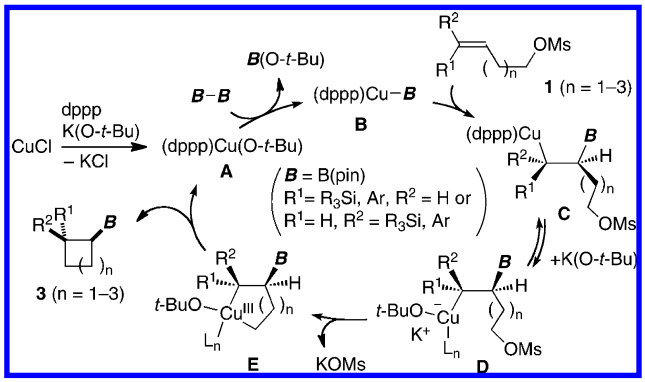


Figure 1. Proposed mechanism for the copper(I)-catalyzed ring formation.

In summary, we have developed a copper(I)-catalyzed reaction that produces 1,2-disubstituted cyclobutanes, which are useful synthetic building blocks for the preparation of cyclobutane derivatives. The reaction proceeds in a stereospecific manner, with (*Z*)- and (*E*)- homoallylic sulfonates being converted to the trans and cis products, respectively. The development of enantioselective versions of this reaction with chiral ligands is currently under investigation.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449–1484. (b) Namyslo, J.; Kaufmann, D. *Chem. Rev.* **2003**, *103*, 1485–1538.

(2) For examples of the syntheses of cyclobutylboron compounds, see: (a) Brener, L.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2702–2704. (b) Hollis, W. G., Jr.; Lappenbusch, W. C.; Everberg, K. A.; Woleban, C. M. *Tetrahedron Lett.* **1993**, *34*, 7517–7520. (c) Gridnev, I. D.; Meller, A. *J. Org. Chem.* **1998**, *63*, 3599–3606. (d) Man, H. W.; Hiscox, W. C.; Matteson, D. S. *Org. Lett.* **1999**, *1*, 379–381.

(3) (a) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034–16035. (b) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856–14857. (c) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774–15775. (d) Ito, H.; Kosaka, Y.; Nonoyama, K.; Sasaki, Y.; Sawamura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7424–7427. (e) Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821–6825. (f) Sasaki, Y.; Zhong, C.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 1226–1227.

(4) For selected other publications on copper(I)-catalyzed reactions with diboron, see: (a) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, *29*, 982–983. (b) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036–11037. (c) Lee, J.; Yun, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 145–147. (d) Lillo, V.; Prieto, A.; Bonet, A.; Díaz-Requejo, M. M.; Ramírez, J.; Pérez, P. J.; Fernández, E. *Organometallics* **2009**, *28*, 659–662.

(5) (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; p 542. (b) Knipe, A. C.; Stirling, C. J. M. *J. Chem. Soc. B* **1968**, 67–71.

(6) This is the first example of 1-silyl-2-borylcyclobutanes. All of the products (*trans*- and *cis*-**3a**−**i**) of the copper(I)-catalyzed reaction are new compounds.

(7) For a metal-free reaction, see: Lee, K. S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253–7255.

(8) The highly reactive and regioselective feature observed in the reaction of the silyl substrates is due to the α-stabilization effect of the silyl groups. See: (a) Brinkman, E. A.; Berger, S.; Brauman, J. I. *J. Am. Chem. Soc.* **1994**, *116*, 8304–8310. Also see ref 3d. For a similar effect in the borylation of alkenylboronates, see: (b) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160–3161. For aryl substrates, the electron-withdrawing effect of the aryl groups on the alkene π system is important. (c) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *Organometallics* **2006**, *25*, 2405–2408. (d) Dang, L.; Zhao, H. T.; Lin, Z. Y.; Marder, T. B. *Organometallics* **2007**, *26*, 2824–2832.

(9) Brown, H. C.; Singh, S. M.; Rangaishenvi, M. V. *J. Org. Chem.* **1986**, *51*, 3150–3155.

(10) Miura, K.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *Org. Lett.* **2000**, *2*, 385–388.

(11) Hupe, E.; Marek, I.; Knochel, P. *Org. Lett.* **2002**, *4*, 2861–2863.

(12) Using an excess amount of *tert*-butoxide with respect to the copper(I) salt was crucial for ensuring ring closure. The reaction of (*Z*)-**1a** and **2** in the presence of CuCl (110 mol %), K(O-*t*-Bu) (100 mol %), and dppp (10 mol %) in THF was very slow, despite the presence of a large amount of copper(I), and afforded *trans*-**3a** in yields of 7% after 3 h and 10% after 20 h. Conversely, a similar reaction with CuCl (110 mol %), excess K(O-*t*-Bu) (150 mol %), and dppp (10 mol %) went to completion smoothly within 3 h, affording *trans*-**3a** with a yield of 97%. It is known that the formation of borylcopper(I) intermediates and their addition to activated alkenes proceeds without excess base, which suggests that K(O-*t*-Bu) most probably affects the cyclization step (see refs 3d and 8).

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