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Copper-Catalyzed Enantiotopic-Group-Selective Allylation of *gem*-Diborylalkanes

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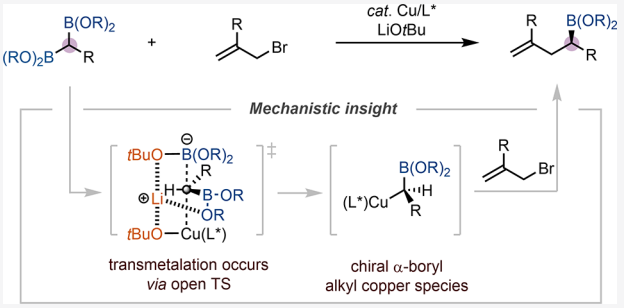
ABSTRACT: We report a copper-catalyzed enantiotopic-group-selective allylation of *gem*-diborylalkanes with allyl bromides. The combination of copper(I) bromide and H_8−BINOL derived phosphoramidite ligand proved to be the most effective catalytic system to provide various enantioenriched homoallylic boronate esters, containing a boron-substituted stereogenic center that is solely derived from *gem*-diborylalkanes, in good yields with high enantiomeric ratios under mild conditions. Experimental and theoretical studies have been conducted to elucidate the reaction mechanism, revealing how the enatiotopic-group-selective transmetalation of *gem*-diborylalkanes with chiral copper complex occurs to generate chiral α-borylalkyl-copper species for the first time. Additional synthetic applications to the synthesis of various chiral building blocks are also included.



INTRODUCTION

The development of an efficient catalytic reaction for preparing enantioenriched organoboron compounds received considerable attention over the past decades because they can serve as versatile intermediates in the synthesis of a range of natural products and pharmaceuticals.[1] Thus, various enantioselective approaches to accessing these compounds have been reported including hydrogenation of vinyl boronates, hydroboration, conjugate addition, allylic borylation, and cross-couplings.[2] Recently, copper-catalyzed enantiotopic-group-selective couplings of *gem*-diborylalkanes with suitable electrophiles emerged as a powerful complementary strategy to afford enantioenriched organoborons.[3,4] In these processes, chiral α-borylalkyl-copper species, generated by enantiotopic-group-selective transmetalation of *gem*-diborylalkanes with copper catalysts that carry chiral phosphine ligands could readily react with electrophiles including carbonyls and imines (Scheme 1a). However, a mechanistic understanding of the enantiotopic-group-selective transmetalation of *gem*-diborylalkanes with chiral copper complex has thus far been elusive. Furthermore, this protocol is restricted primarily to C═O or C═N electrophiles, and the reaction with other electrophiles such as allylic functionalities has rarely been reported.[5]

In our continuing explorations of catalytic enantiotopic-group-selective coupling of *gem*-diborylalkanes,[3,6] we recently disclosed the copper-catalyzed chemo- and regioselective coupling of *gem*-diborylalkanes with allyl chlorides.[5a] Subsequently, Hoveyda[5b] and Fu[5c] independently reported enantioselective variants of similar reactions employing diborylmethane as a nucleophile in the presence of chiral copper/NHC catalytic system. Niu reported an alternative strategy for the enantioselective coupling of diborylmethane with allylic electrophiles in the presence of iridium and silver as cocatalysts.[5d] These processes showed limited scope with respect to *gem*-diborylalkanes, and only diborylmethane was employed as the coupling reagent. In addition, the reactions delivered homoallylic boronate esters, bearing a carbon stereogenic center solely derived from allylic electrophiles but not from nucleophiles, namely, *gem*-diborylalkanes. Therefore, the discovery of a more broadly applicable catalytic system that expands the scope of reactants with regard to the *gem*-diborylalkanes is desirable but has remained an unmatched challenge thus far.

Herein, we describe an enantiotopic-group-selective coupling of *gem*-diborylalkanes with allylic electrophiles catalyzed by copper (Scheme 1c). This method provides homoallylic boronate esters that contain a boron-substituted carbon stereogenic center derived from prochiral *gem*-diborylalkanes with high enantiomeric purity. Extensive experimental and computational studies provide the first mechanistic insight into how the enantiotopic-group-selective transmetalation of *gem*-

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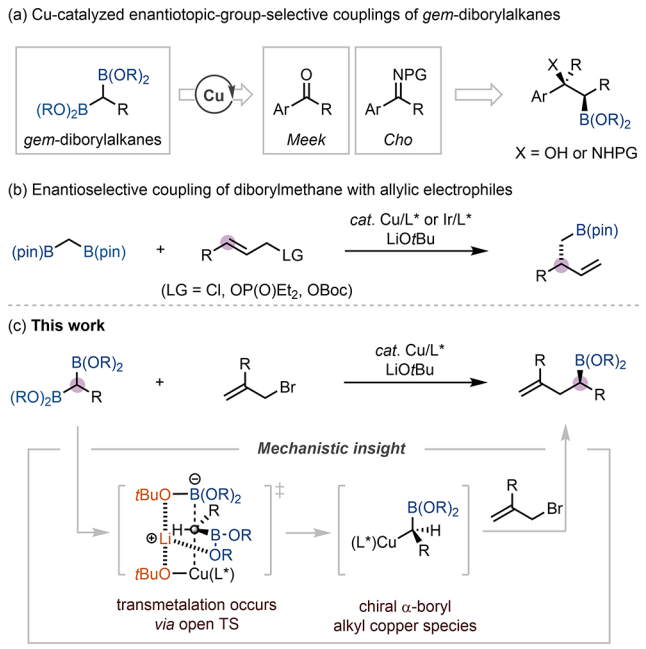
Scheme 1. Copper-Catalyzed Enantioselective Coupling of *gem*-Diborylalkanes with Allylic Electrophiles



diborylalkanes with chiral copper catalyst proceeds. Further synthetic transformations of the obtained enantioenriched homoallylic boronate esters are also demonstrated.

RESULTS AND DISCUSSIONS

Optimization Studies. We tested the reaction of 2-benzylallylic electrophiles (**1**) and *gem*-diborylethane bearing a pinacolato moiety (**2a**) in the presence of CuBr as a catalyst, (*R*)-BINOL-derived phosphoramidite as a ligand (**L1**), and LiO*t*Bu as a base. Although no reaction took place when 2-benzylallyl acetate (**1a**) was employed as an electrophile (Table 1, entry 1), the reactions of **2a** with *tert*-butyl-(2-benzylallyl)carbonate (**1b**) or diethyl-(2-benzylallyl)-phosphate (**1c**) afforded desired allylation product **3a** in low to high yields (entries 2 and 3) with poor enantiomeric ratios (er). The er of **3a** was increased up to 70:30 when (2-(chloromethyl)allyl)benzene (**1d**) was used as an electrophile (entry 4), and (2-(bromomethyl)allyl)benzene (**1e**) gave **3a** with a slightly higher er (entry 5).[7] Next, we surveyed the effect of an amino group of (*R*)-BINOL-derived phosphoramidite ligands (**L2**−**L4**) and found them to have negligible or negative effects on the er (entries 6−8). Pleasingly, subjecting the (*R*)-H_8−BINOL-based phosphoramidite (**L5**) as a ligand afforded **3a** in good yield with 95:5 er (entry 9). Spirobiindanediol (**L6**) or TADDOL-derived phosphoramidte (**L7**) ligand displayed lower efficiencies (entries 10 and 11). To improve the enantioselectivity further, substituent effects of boronate ester were subsequently examined. While *gem*-diborylalkane containing 1,3-propanediolato group(**2b**) showed low efficiency and selectivity (entry 12), the employment of *gem*-diborylalkane having neopentylglycolato group (**2c**) delivered **3c** in good yields with the highest er (entry 13) found in this series. Increasing the reaction temperature to 50 °C shortened the reaction time (12 h), even though **3c** was obtained in a slightly decreased er (entry 14). Using NaO*t*Bu (entry 15) or KO*t*Bu (entry 16) instead of LiO*t*Bu gave **3c** in low to poor er, probably because of the competitive S_N2 reaction of **1e** with in situ generated α-borylcarbanion.[8] The absolute stereochemistry of the major enantiomer of **3c** was determined as *S* after oxidation of B(nep) to a known compound.[9]

Substrate Scope. With the optimized conditions in hand, the scope of allyl bromides was explored using **2c** as a coupling reagent (Table 2a). Allyl bromides bearing methyl-, hexyl-, and cyclohexyl group as a substituent at C2-position furnished **3c**−**3f** in good yields and er. Substrates containing an ester, a protected amine, a *tert*-butyldimethylsilyl (TBS)-protected ether or a trimethylsilyl (TMS) group resulted in the formation of **3g**−**3j** with good to high selectivity. Furthermore, 4- bromo-2-(bromomethyl)but-1-ene was successfully reacted with **2c**, leaving the bromo group intact (**3k**) for further elaborations. Reactions of allyl bromides bearing alkenyl moiety smoothly underwent the allylation, affording **3l** and **3m** in good efficiency. Whereas CuH-catalyzed coupling of alkenes with allylic electrophiles has been well-established,[10] the reaction scope is rather limited especially for substrates containing additional alkene substituent because of competitive hydrocupration. Therefore, our developed protocol offers an attractive alternative to CuH-catalyzed allylation of alkenes. Various C2-aryl-substituted allyl bromides bearing electronically neutral, donating, or withdrawing substituents led to products **3n**−**3r** in good yields with high er. Naphthyl- and heteroaryl-containing 3-bromoprop-1-ene readily engaged in the reaction leading to **3s** and **3t**. 2-Bromo-substituted and simple allyl bromides also underwent the allylation, delivering **3u** and **3v**. Next, we investigated the scope of *gem*-diborylalkanes under the standard reaction conditions. Reactions of *gem*-diborylpropane and *gem*-diboryl-3-phenylpropane with **1e** yielded **4a** and **4b** in good to moderate yields with good er. *gem*-Diborylalkanes bearing a TBS-protected alcohol and alkenes led to **4c**−**4e** in good efficiencies. 2-Bromo-substituted and simple allyl bromides also proceeded to complete the coupling with various *gem*-diborylalkanes to give corresponding products **4f**−**4i**. Interestingly, the reaction of 2-phenylallyl bromide and complex *gem*-diborylalkanes containing pinacolato groups, derived from lithocholic acid and liquid crystal,[11] furnished **4j** and **4k** in good yields with high stereoselectivity.

Mechanistic Studies. To understand how the enantiotopic-group-selective transmetalation occurs between *gem*-diborylalkanes and copper catalyst, we performed quantum mechanical calculations based on density functional theory (DFT). The theoretical investigation utilizes *gem*-diborylalkane **2c** as a representative substrate, **L5** as the ligand bound to copper, and LiO*t*Bu as the base. Figure 1 shows the calculated free energy profile of the enantiotopic-group-selective transmetalation to furnish chiral copper species **C**. The reaction model starts from CuO*t*Bu, which is formed by ligand exchange of CuBr. Once *t*BuO−Cu(**L5**) is formed to accommodate the *gem*-diborylalkane substrate, two mechanistic scenarios of transmetalation can be imagined. One involves the assistance of LiO*t*Bu as marked in blue and red trajectories, while the other excludes participation of the base as shown in the black dotted line. Our calculations indicate that LiO*t*Bu renders the transmetalation much more viable. As illustrated in Figure 1, LiO*t*Bu first binds to the *t*BuO−Cu(**L5**) intermediate to form a cyclic Lewis acid−base pair, **A**, which can act as a bridge during the C−B bond cleavage and Cu−C bond formation between the copper complex and **2c** when traversing what could be best characterized as an open

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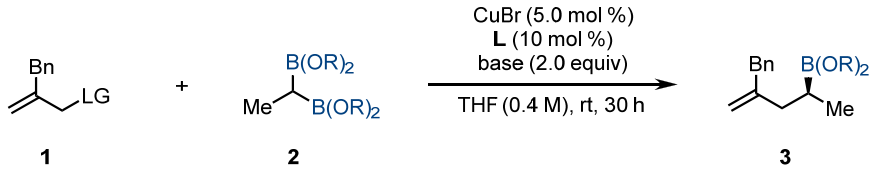
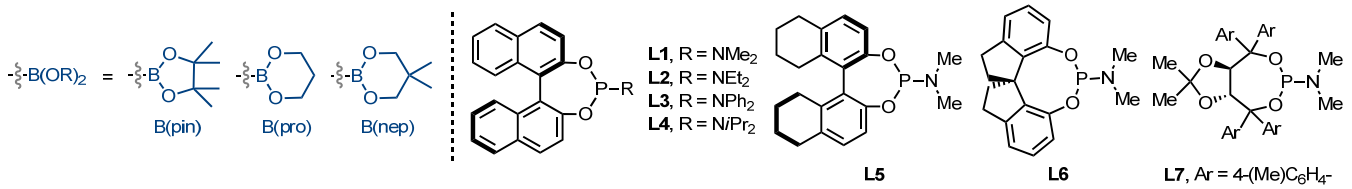
Table 1. Evaluation of Reaction Conditions[a]



entry	LG	B(OR)$_2$	base	ligand	yield (%)[b]	er[c]
1	OAc (**1a**)	B(pin) (**2a**)	LiO*t*Bu	**L1**	<1 (**3a**)	-
2	OBoc (**1b**)	B(pin) (**2a**)	LiO*t*Bu	**L1**	26 (**3a**)	53:47
3	OP(O)(OEt)$_2$ (**1c**)	B(pin) (**2a**)	LiO*t*Bu	**L1**	94 (**3a**)	66:34
4	Cl (**1d**)	B(pin) (**2a**)	LiO*t*Bu	**L1**	94 (**3a**)	70:30
5	Br (**1e**)	B(pin) (**2a**)	LiO*t*Bu	**L1**	93 (**3a**)	84:16
6	Br (**1e**)	B(pin) (**2a**)	LiO*t*Bu	**L2**	93 (**3a**)	84:16
7	Br (**1e**)	B(pin) (**2a**)	LiO*t*Bu	**L3**	62 (**3a**)	63:37
8	Br (**1e**)	B(pin) (**2a**)	LiO*t*Bu	**L4**	38 (**3a**)	70:30
9	Br (**1e**)	B(pin) (**2a**)	LiO*t*Bu	**L5**	92 (**3a**)	95:5
10	Br (**1e**)	B(pin) (**2a**)	LiO*t*Bu	**L6**	32 (**3a**)	60:40
11	Br (**1e**)	B(pin) (**2a**)	LiO*t*Bu	**L7**	58 (**3a**)	61:39
12	Br (**1e**)	B(pro) (**2b**)	LiO*t*Bu	**L5**	34 (**3b**)	87:13
13	Br (**1e**)	B(nep) (**2c**)	LiO*t*Bu	**L5**	92 (**3c**)	97:3
14[d]	Br (**1e**)	B(nep) (**2c**)	LiO*t*Bu	**L5**	94 (**3c**)	92:8
15	Br (**1e**)	B(nep) (**2c**)	NaO*t*Bu	**L5**	89 (**3c**)	86:14
16	Br (**1e**)	B(nep) (**2c**)	KO*t*Bu	**L5**	80 (**3c**)	51:49



[a]The reaction was performed on 0.20 mmol scale with CuBr (5.0 mol %), ligand (10 mol %), and base (2.0 equiv) in THF at room temperature for 30 h. [b]The yield of **3** was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c]Enantiomeric ratios (er) were determined by HPLC. [d]The reaction was conducted at 50 °C for 12 h.

transition state, ^{S}**A-TS** and ^{R}**A-TS**, at 27.4 and 29.0 kcal/mol, respectively. If LiO*t*Bu is not added, then the closed transition state, ^{S}**A-TS′**, must be utilized giving rise to a notably higher barrier of 31.7 kcal/mol. Note that the association of LiO*t*Bu to the catalyst is modeled considering the presence of (LiO*t*Bu)$_4$, a cubane-type cluster, often adopted in quantum chemical modeling of reactions with the metal alkoxide bases.[12]

The energy difference between ^{S}**A-TS** and ^{R}**A-TS** is responsible for the observed product selectivity and was further investigated using the distortion−interaction analysis as summarized in Figure 2.[13] Starting from the fully relaxed structures of **2c** and **A** as the reference state, the energies required to distort the structures to what is found in the transition state are calculated separately. These calculations afford the distortion energy. On letting these two distorted fragments interact with each other, the transition state energies can be reached. As illustrated in Figure 2a, the *gem*-diborylalkane substrate must undergo a substantial structural change, accounting for 34.9 and 35.9 kcal/mol in ^{S}**A-TS** and ^{R}**A-TS**, respectively. In comparison, copper complex **A** has to undergo only a minor distortion to reach the transition state structure worth 15.7 and 7.6 kcal/mol, respectively. The interaction energies are −73.6 and −65.8 kcal/mol to afford the final electronic transition state energies of −23.0 and −22.3 kcal/mol, respectively, giving preference to ^{S}**A-TS**. As the distortion−interaction analysis reveals, the interaction energy difference is the most important factor determining the enantioselectivity. This inequality of interaction energy is easily understood considering the structural difference between the two transition states.

Figure 2b,c illustrates the structures of the two transition states and reveals that in ^{S}**A-TS** the **2c** substrate orientation avoids unfavorable steric interactions with the copper complex, because the sterically demanding portion of **2c** points away from the **L5** ligand. In contrast, the methyl functionality of the B(nep) group points directly at **L5** in ^{R}**A-TS** and does not allow **2c** substrate to approach the Cu-center as closely as in ^{S}**A-TS**, reflected in a C−Cu distance of 2.56 Å in ^{R}**A-TS**, which is 0.29 Å longer than 2.27 Å found in ^{S}**A-TS**. This structural difference explains the weaker interaction energy found for ^{R}**A-TS**, as discussed above. This rationale is also in line with the

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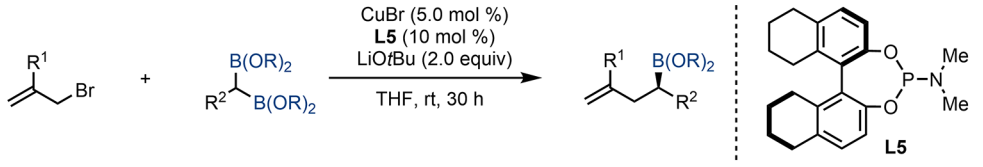
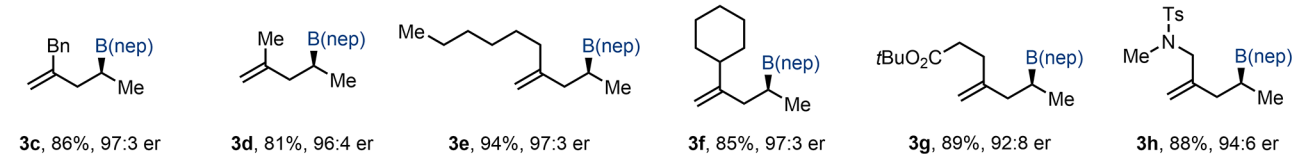
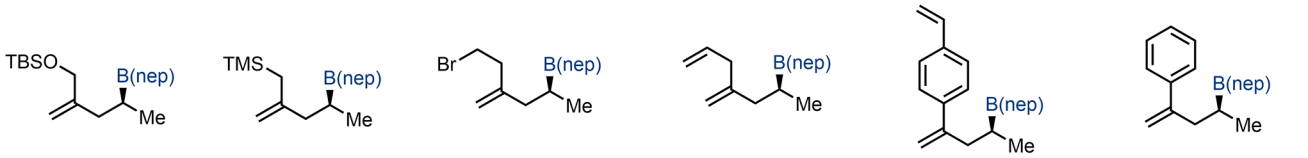
Table 2. Substrate Scope of Allyl Bromides and *gem*-Diborylalkanes[a,b]



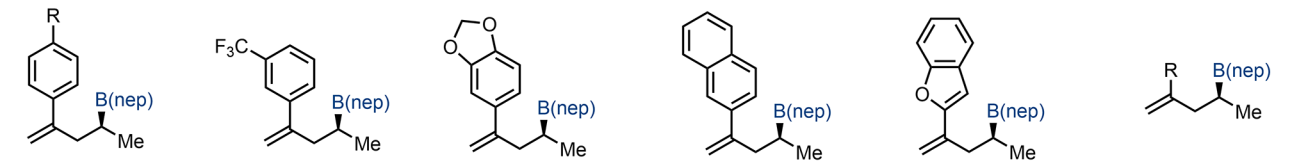
(a) scope of allyl bromides



3c, 86%, 97:3 er; **3d**, 81%, 96:4 er; **3e**, 94%, 97:3 er; **3f**, 85%, 97:3 er; **3g**, 89%, 92:8 er; **3h**, 88%, 94:6 er

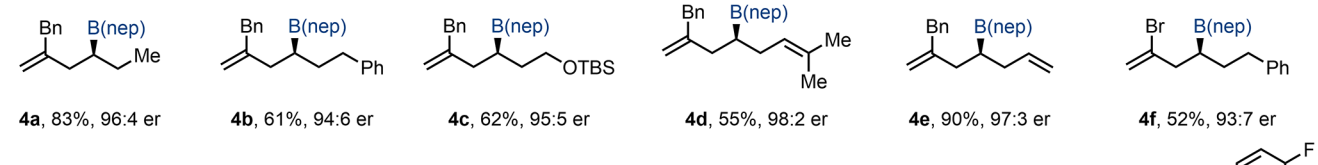


3i, 93%, 96:4 er; **3j**, 71%, 93:7 er; **3k**, 92%, 94:6 er; **3l**, 87%, 94:6 er; **3m**, 95%, 97:3 er; **3n**, 90%, 95:5 er

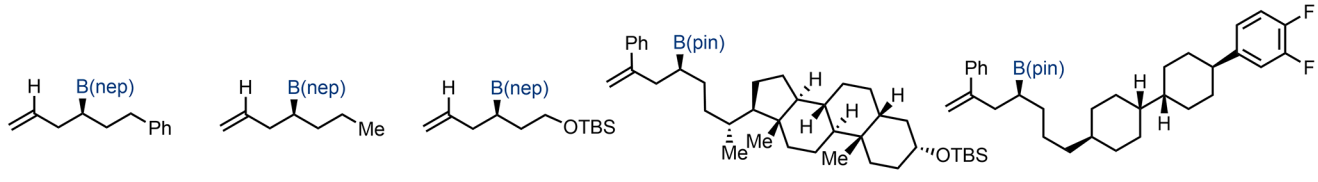


3o, R = OMe, 94%, 95:5 er
3p, R = Cl, 90%, 97:3 er; **3q**, 98%, 96:4 er; **3r**, 60%, 98:2 er; **3s**, 81%, 97:3 er; **3t**, 66%[c], 93:7 er; **3u**, R = Br, 77%, 96:4 er
3v, R = H, 91%, 95:5 er

(b) scope of *gem*-diborylalkanes



4a, 83%, 96:4 er; **4b**, 61%, 94:6 er; **4c**, 62%, 95:5 er; **4d**, 55%, 98:2 er; **4e**, 90%, 97:3 er; **4f**, 52%, 93:7 er



4g, 73%, 95:5 er; **4h**, 51%, 96:4 er; **4i**, 66%, 93:7 er; **4j**, 51%[c], 12:1 dr; **4k**, 78%, 95:5 er

[a]The reaction was performed on 0.2 mmol scale with CuBr (5.0 mol %), **L5** (10 mol %), and LiO*t*Bu (2.0 equiv) in THF at room temperature for 30 h. In all cases, isolated yields are indicated. [b]Enantiomeric ratios (er) were determined by HPLC. [c]Isolated yield after oxidation of boron group is given.

experimental observation that sterically bulkier B(pin) and B(nep) (Table 1, entries 9 and 13) show a better er than the less-bulky B(pro) (Table 1, entry 12). Note that the solution phase free energies were estimated to be +24.4 and +25.9 kcal/mol, respectively. Thus, the entropy and solvation energies increase the preference for ^{S}**A-TS** over ^{R}**A-TS**, slightly.

In order to find additional support for the proposed transmetalation event between *gem*-diborylalkane and the chiral copper species, we performed the allylation reaction by subjecting isotopically chiral (*S*)-^{10}B-**5**, prepared by a known literature procedure,[6a] in the presence of (*R*)-**L5** or (*S*)-**L5**, as summarized in Scheme 2. When (*S*)-^{10}B-**5** and allyl bromide were treated in the presence of CuBr, (*R*)-**L5**, and LiO*t*Bu in THF, coupled product (*S*)-**6** was obtained in 92:8 er. Mass spectral analysis of the isotope pattern showed that the ^{10}B(pin)-containing (*S*)-**6** remained in excess quantities after the transformation.[14] Conversely, the treatment of (*S*)-**L5** instead of (*R*)-**L5** as a ligand under the reaction conditions gave the product (*R*)-**6** in 8:92 er. The boron isotope distribution found in (*R*)-**6** is consistent with the natural distribution, showing an excess of ^{11}B.[9] On the basis of the assumption that the C−C bond forming process takes place with retention of configuration at the carbon of chiral *α*-borylalkyl-copper, the observed isotopic composition of the product suggests that the transmetalation between (*S*)-^{10}B-**5** and chiral copper species occurs in a stereoinvertive fashion, which is in good agreement with our DFT calculations.

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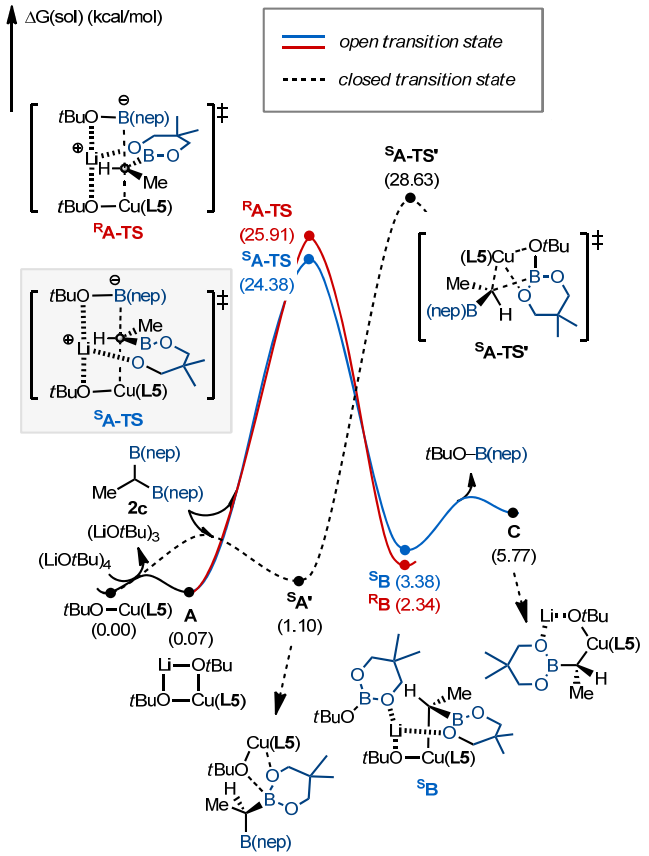


Figure 1. Free energy profile of the reaction mechanism. Dotted traces represent relatively unfavored reaction pathways. Geometry optimization, vibration, and solvation energy calculations were conducted with B3LYP-D3/LACVP** level of theory. Single-point energies were re-evaluated with B3LYP-D3/cc-pVTZ(-f) level of theory.

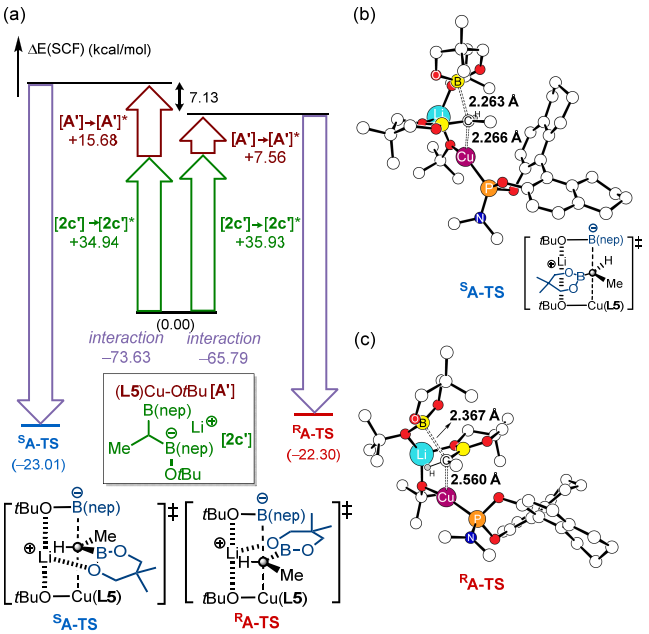
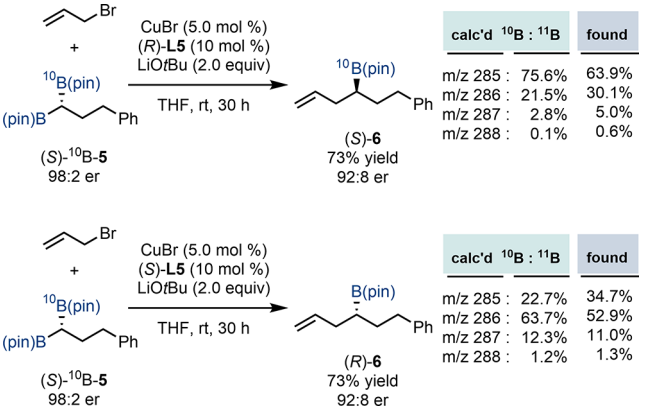


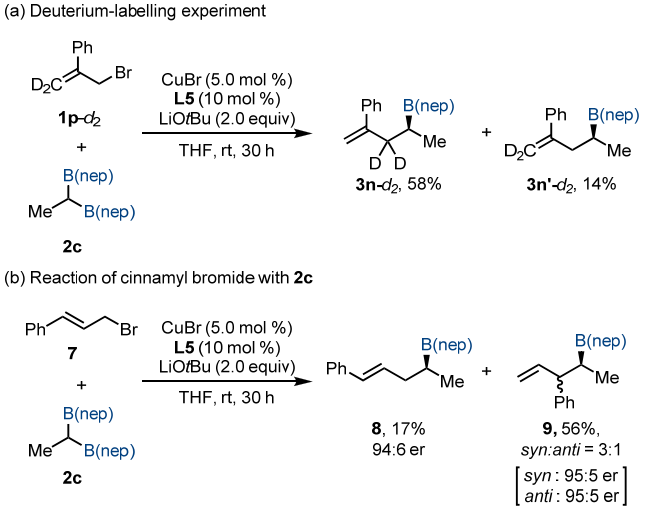
Figure 2. (a) Distortion−interaction analysis diagram for ^{S}**A-TS** and ^{R}**A-TS**. Asterisk indicates distorted fragments. Optimized structures for (b) ^{S}**A-TS** and (c) ^{R}**A-TS**. Unimportant hydrogen atoms are omitted for clarity.

Scheme 2. Mass Spectral Analysis of the Reaction Using Isotopically Enantioenriched *gem*-Diborylalkane (*S*)-^{10}B-5 with Allyl Bromide



After the enantiotopic-group-selective transmetalation occurs, subsequent dissociation of *t*BuO−B(nep) and LiO*t*Bu from **B** gives chiral *α*-borylalkyl-copper intermediate **C** located at −8.1 kcal/mol. To gain further insight for C−C bond formation of chiral copper intermediate **C** with allyl bromide, we performed the reaction by treatment of deuterated 2-phenyl allyl bromide **1p**-d_2 or cinnamyl bromide **7**. When deuterated **1p**-d_2 and **2c** were used as substrates under the standard reaction conditions, a 4:1 mixture of **3n**-d_2 and **3n′**-d_2 was produced (Scheme 3a). Furthermore, using **7** and **2c** as

Scheme 3. Experiments to Examine the Origin of Regioselectivity



substrates also gave the products **8** and **9** with ratios of 3:1 (Scheme 3b) with good optical purity. These experimental results suggested that both S_N2' and S_N2-like processes could be involved at the C−C bond formation event by the attack of the chiral *α*-borylalkyl-copper species **C** to the 3- or 1-position of the allyl bromide.[15]

Synthetic Applications. The enantioenriched homoallylic boronate esters that we obtained could be transformed into other enantioenriched building blocks by further elaborations (Scheme 4a). Oxidation of the boron group of **4g** gave homoallylic alcohol **10**. Product **3c** underwent one-carbon homologation with $ClCH_2Li$, affording *γ*-alkenyl boronate

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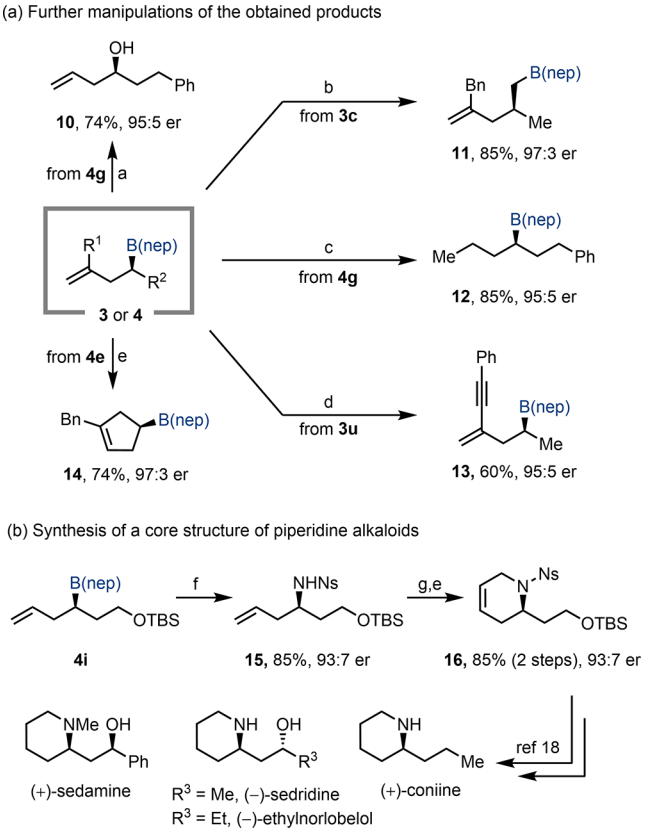
Scheme 4. Synthetic Utility[a]



[a]Reaction conditions: (a) $NaBO_3{\cdot}4H_2O$, THF/H_2O, rt, 3 h. (b) $LiCH_2Cl$, THF, −78 °C to rt, 3 h. (c) $TsNHNH_2$, NaOAc, THF/H_2O, 80 °C, 24 h. (d) *cat.* $Pd(OAc)_2$, phenylacetylene, THF, 70 °C, 24 h. (e) *cat.* Grubbs II, CH_2Cl_2, 50 °C, 6 h. (f) H_2N-DABCO, KO*t*Bu, THF, 80 °C, 1 h, then 2-NO_2−$C_6H_4SO_2Cl$, Et_3N, 0 °C to rt, 1 h. (g) K_2CO_3, allyl bromide, MeCN, 50 °C, 24 h.

ester **11**. Enantioenriched secondary alkylboronate ester **12** could be efficiently synthesized by the reduction of alkene with $TsNHNH_2$ and NaOAc. Sonogashira cross-coupling of **3u** with phenylacetylene yielded 1,3-enyne **13**. Ring-closing metathesis of **4e** using the second generation Grubbs catalyst furnished enantioenriched cyclic homoallyl boronates **14**.

The utility of the enantioenriched homoallylic boronate ester could also be demonstrated by the synthesis of a chiral piperidine derivative, which presents a ubiquitous core structure in myriad piperidine alkaloids (Scheme 4b).[16] After achieving stereospecific amination of B(nep) moiety with H_2N-DABCO under the reaction conditions developed by Liu and co-workers,[17] nosyl protection of the amine group afforded enantioenriched homoallylic amine **15** in good yield without erosion of er. Subsequent N-alkylation of **15** with allyl bromide and ring-closing metathesis yielded enantioenriched cyclic homo homoallylic amine **16**, which can be readily converted to piperidine alkaloids such as (+)-sedamine, (−)-sedridine, (−)-ehtylnorlobelol, and (+)-coniine by known procedures.[18]

CONCLUSION

We have developed a copper-catalyzed enantiotopic-group-selective allylation of *gem*-diborylalkanes with various allyl bromides. The substrate scope is very broad, and a range of *gem*-diborylalkanes and allyl bromides undergoes the coupling, thereby providing various enantioenriched homoallylic boronate esters in good yields with good to high enantiopurity. We also demonstrate that *gem*-diborylalkanes derived from complex molecules can be used to carry out allylations with good stereoselectivity. Combining experimental and theoretical studies, the mechanism is revealed for the enantiotopic-group-selective transmetalation between *gem*-diborylalkanes and chiral copper complex to generate a chiral α-borylalkyl-copper species, which subsequently undergoes C−C bond formation with allyl bromides. Further studies to develop enantio- and diastereoselective versions of the reaction coupling *gem*-diborylalkanes with allylic electrophiles are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11750.

Experimental procedures, characterization data, ^1H NMR, ^{13}C NMR, and HPLC spectra for new compounds. Cartesian coordinates of DFT-optimized structures, calculations, and computational details (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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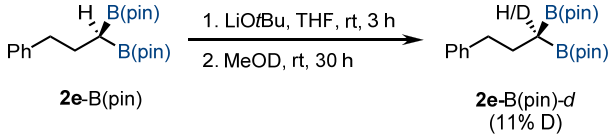

2e-B(pin) **2e**-B(pin)-*d* (11% D)

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