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Asymmetric Synthesis

Asymmetric Synthesis of SCF_3-Substituted Alkylboronates by Copper-Catalyzed Hydroboration of 1-Trifluoromethylthioalkenes

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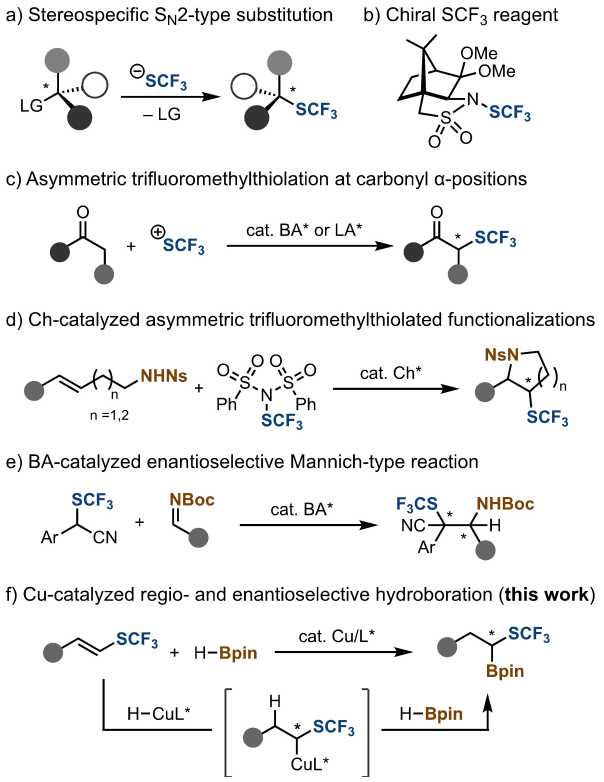
Abstract: A synthetic method for preparation of optically active trifluoromethylthio (SCF_3) compounds by a copper-catalyzed regio- and enantioselective hydroboration of 1-trifluoromethylthioalkenes with H-Bpin has been developed. The enantioselective hydrocupration of an in situ generated CuH species and subsequent boration reaction generate a chiral SCF_3-containing alkylboronate, of which Bpin moiety can be further transformed to deliver various optically active SCF_3 molecules. Computational studies suggest that the SCF_3 group successfully controls the regioselectivity in the reaction.

Organo-fluorine compounds are frequently found in medicinal chemistry and agrochemistry because the introduction of fluorine atom into organic molecules improves their bioavailability such as lipophilicity and metabolic stability.[1] To date, more than 20 % of pharmaceuticals and 40 % of agrochemicals have the fluorine atom in their frameworks, and numerous synthetic methods for a variety of fluorinated molecules have been intensively studied. Among them, a trifluoromethylthio (SCF_3) group is promising thanks to its high electron-withdrawing property[2] and lipophilicity.[3] Although several SCF_3-containing compounds have been synthesized in the past decade,[4] the synthesis of C_{sp3}-SCF_3 compounds, especially catalytic asymmetric version, is still underdeveloped.[5] For the synthesis of optically active SCF_3 compounds, stereospecific S_N2-type trifluoromethylthiolation on chiral carbon center was reported (Scheme 1a).[6] Also, a chiral trifluoromethylthiolation reagent was developed by Shen to achieve the asymmetric trifluoromethylthiolation of cyclic β-ketoesters



Scheme 1. Stoichiometric or catalytic asymmetric construction of SCF_3-substituted stereocenters.

(Scheme 1b).[7] However, in these cases, preparation of a stoichiometric amount of chiral starting materials or reagents was basically required. Recently, catalytic S_N2-type substitution of racemic propargyl substrates using chiral Cu catalysts has also been reported.[8] On the other hand, catalytic asymmetric trifluoromethylthiolation reactions at the α-position of carbonyl or nitrile compounds were successfully explored using chiral Brønsted or Lewis acids (BA or LA; Scheme 1c).[5a,9] In addition, several asymmetric trifluoromethylthiolated functionalizations have been achieved using optically active chalcogenide (Ch) catalysts (Scheme 1d).[10] Meanwhile, a building block approach is also a powerful and practical method to construct a chiral carbon center bearing the SCF_3 group.[11] Zhao group has developed the chiral BA-catalyzed enantioselective Mannich-type reaction of SCF_3-substituted benzylic cyanide as the starting building block (Scheme 1e).[11c] Despite the aforementioned certain efforts, there still remains structural limitations in the synthesis of chiral SCF_3-containing com-

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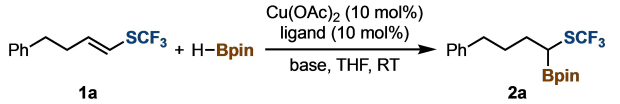
pounds, and expansion of their chemical space is highly desired. Herein, we report a copper-catalyzed regio- and enantioselective hydroboration of 1-trifluoromethylthioalkenes with pinacolborane (H-Bpin; Scheme 1f). The SCF_3-substituted alkenes were easy to access from the corresponding alkenyl halides by using the literature methods.[12] The alkene moiety undergoes the regio- and enantioselective insertion into in situ generated CuH species[13] to form an optically active α-SCF_3 alkylcopper intermediate. Subsequent boration reaction with H-Bpin provides the Bpin-substituted SCF_3 compound in an enantioenriched form. Moreover, the Bpin moiety in the product could be easily transformed to various useful functional groups. To the best of our knowledge, such a chiral platform containing SCF_3 and Bpin functions in the *gem*-relationship is disclosed for the first time. During the preparation of this manuscript, Liu and co-workers reported an enantioconvergent coupling reaction of benzyl halides and $[Me_4N][SCF_3]$ in the presence of copper catalyst with N,N,P-type tridentate ligand.[14] However, the carbon radical-based strategy still required the use of benzyl halides to only construct the aryl- and SCF_3-substituted chiral carbon center. Thus, it is complementary to our method, which gives an alkyl-substituted chiral center.

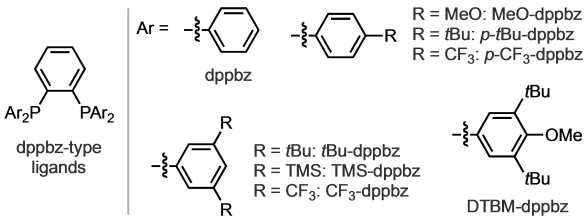
We commenced optimization studies for nonenantioselective conditions using 1-trifluoromethylthioalkene **1a** as a model substrate with achiral biphosphine ligands (Table 1). In the presence of $Cu(OAc)_2$ catalyst and bis(diphenylphosphino)benzene (dppbz) ligand, treatment of **1a** with H-Bpin in THF solvent at room temperature afforded the desired hydroborated product **2a** in 9 % ^{1}H NMR yield. The yield was poor, but the high regioselectivity was observed. Inspired by the previously reported positive effects of substituents at remote positions in the biphosphine ligand to improve reaction efficiency,[15] we then tested several modified dppbz ligands (entries 2–8). As expected, bulky substituents at meta-positions on phenyl ring accelerated the desired hydroboration reaction. In particular, *t*Bu-dppbz showed high performance to yield **2a** in 99 % yield (entry 5). On the other hand, other common bidentate and monodentate phosphine ligands showed relatively poor activity (see the Supporting Information for more detailed ligand screening). Although the desired product was obtained in only 37 % with DTBM-dppbz (entry 8), an improvement of the reaction efficiency by the addition of some bases was observed. For example, LiOAc could accelerate the reaction (entry 9), while an alkoxide base diminished the yield (entry 10). Acetate-type bases bearing other alkali metal cations were also effective (entries 11–13). Among them, CsOAc was best and increased the yield to 91 % (entry 13). In cases of cesium carbonate and fluoride bases, the reaction yields were slightly decreased (entries 14 and 15). On the other hand, under the *t*Bu-dppbz-mediated conditions, CsOAc gave the negligible impact on the yield of **2a** (entry 16). CsOAc may play an important role in the initial formation step of the active CuH species. Actually, the acceleration of the initial reaction rate was observed in detailed kinetic studies (Figure S3).

Table 1: Optimization studies for copper-catalyzed regioselective hydroboration of 1-trifluoromethylthioalkene **1a** with H-Bpin.[a]

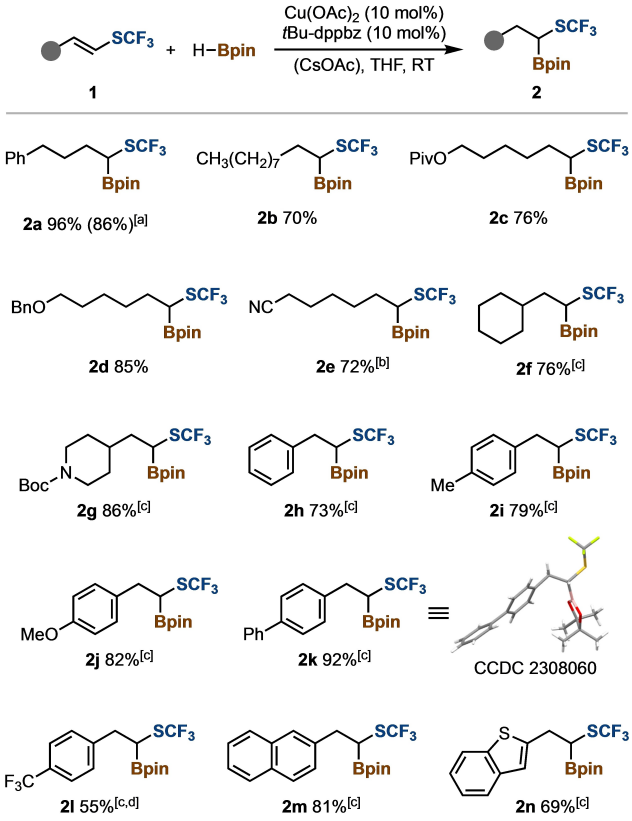


entry	ligand	base	yield (%)[b]
1	dppbz		9
2	MeO-dppbz		trace
3	*p*-*t*Bu-dppbz		8
4	*p*-CF_3-dppbz		0
5	*t*Bu-dppbz		99 (96)
6	TMS-dppbz		73
7	CF_3-dppbz		49
8	DTBM-dppbz		37
9	DTBM-dppbz	LiOAc	83
10	DTBM-dppbz	LiO*t*Bu	15
11	DTBM-dppbz	NaOAc	57
12	DTBM-dppbz	KOAc	89
13	DTBM-dppbz	CsOAc	91
14	DTBM-dppbz	Cs_2CO_3	67
15	DTBM-dppbz	CsF	69
16	*t*Bu-dppbz	CsOAc	97

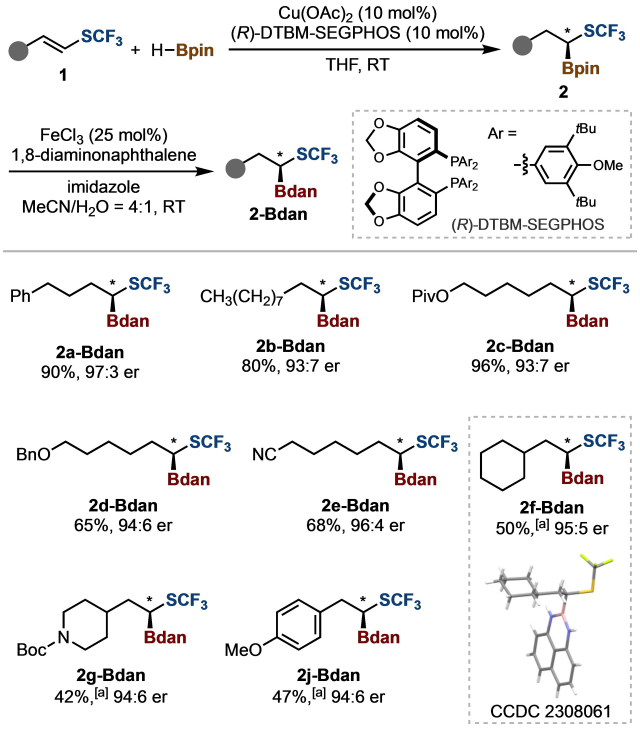
[a] Conditions: **1a** (0.20 mmol), H-Bpin (0.70 mmol), $Cu(OAc)_2$ (0.020 mmol), ligand (0.020 mmol), base (0.40 mmol), THF (0.30 mL), RT, 4 h, N_2. [b] Estimated by ^{1}H NMR. Isolated yield is given in parentheses.



Under the optimal reaction conditions (entry 5 in Table 1), the generality of the reaction was examined (Scheme 2). The primary alkyl-substituted 1-trifluoromethylthioalkene **1b** also reacted with H-Bpin efficiently to afford the corresponding hydroborated product **2b** in 70 % yield. The reaction conditions were tolerant of various functional groups, including ester (**2c**), ether (**2d**), and nitrile (**2e**). In cases of secondary alkyl substituted 1-trifluoromethylthioalkenes **1f** and **1g**, the addition of CsOAc was necessary to obtain the satisfactory conversion probably due to their steric bulkiness. In addition, aryl-conjugated substrates could be successfully employed in the presence of CsOAc base. Both electron-rich and -neutral substrates were coupled with H-Bpin in good yields (**2h**–**2k**). Although the substrate with an electron-deficient aromatic ring gave a mixture of regioisomers, the target product was isolated in an acceptable yield (**2l**). The reaction with naphthalene- and benzothiophen-conjugated substrates was also possible (**2m** and **2n**). The hydroboration of **1a** could also be scaled up to form **2a** in 86 % yield even on a 1.0 mmol scale. The regioselectivity of the hydroboration reaction was confirmed by the X-ray analysis of **2k** (CCDC 2308060).



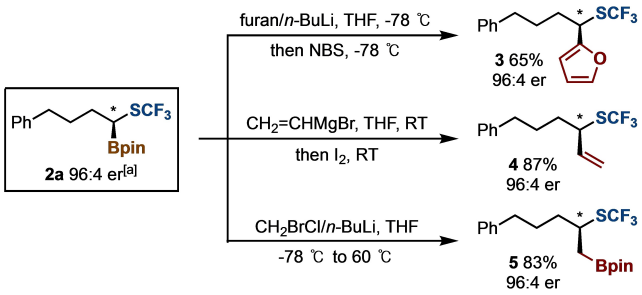
Scheme 2. Products of Cu-catalyzed regioselective hydroboration of 1-trifluoromethylalkenes **1** with H-Bpin. Conditions: **1** (0.20 mmol), H-Bpin (0.70 mmol), $Cu(OAc)_2$ (0.020 mmol), *t*Bu-dppbz (0.020 mmol), THF (0.30 mL), RT, 4–18 h. Isolated yields are shown. [a] On a 1.0 mmol scale. [b] In toluene (0.30 mL). [c] With CsOAc (0.40 mmol). [d] The regioisomeric ratio (rr) was 2.8 : 1. The regioisomer was detected as the simple CF_3-substituted styrene by the elimination process of SCF_3 group (see the Supporting Information for details).



Scheme 3. Cu-catalyzed regio- and enantioselective hydroboration of 1-trifluoromethylthioalkenes **1**. Conditions: **1** (0.20 mmol), H-Bpin (0.70 mmol), $Cu(OAc)_2$ (0.020 mmol), (*R*)-DTBM-SEGPHOS (0.020 mmol), THF (0.30 mL), RT, 4–18 h. Isolated yields are shown. [a] With CsOAc (0.40 mmol).

Encouraged by the successful results mentioned above, we then examined the enantioselective conditions using a chiral biphosphine ligand (Scheme 3). After intensive ligand screening, we found that the replacement of *t*Bu-dppbz with (*R*)-DTBM-SEGPHOS gave the hydroborated product **2a** in a high yield with high enantioselectivity (see the Supporting Information for detailed ligand screening and other optimization studies). The enantiomeric ratio was estimated by HPLC analysis of **2a-Bdan** after derivatization using the reported Bpin to Bdan transesterification.[16] The enantioselective reaction conditions were also compatible with aliphatic 1-trifluoromethylthioalkenes bearing some common functional groups (**2b-Bdan**–**2e-Bdan**). Similar to nonenantioselective conditions, the addition of CsOAc as an external base was necessary for the secondary alkyl-substituted (**2f-Bdan** and **2g-Bdan**) and aryl-conjugated (**2j-Bdan**) SCF_3-alkenes. However, the yields still remained only moderate even in the presence of CsOAc likely due to steric repulsions between the bulky DTBM-SEGPHOS ligand and the substituent at the β-position of SCF_3 group. We confirmed that CsOAc gave no effect on the enantioselectivity (Table S6). The absolute configuration of **2f-Bdan** was confirmed to be *S* by the X-ray analysis (CCDC 2308061), and those of other compounds were assigned by analogy.

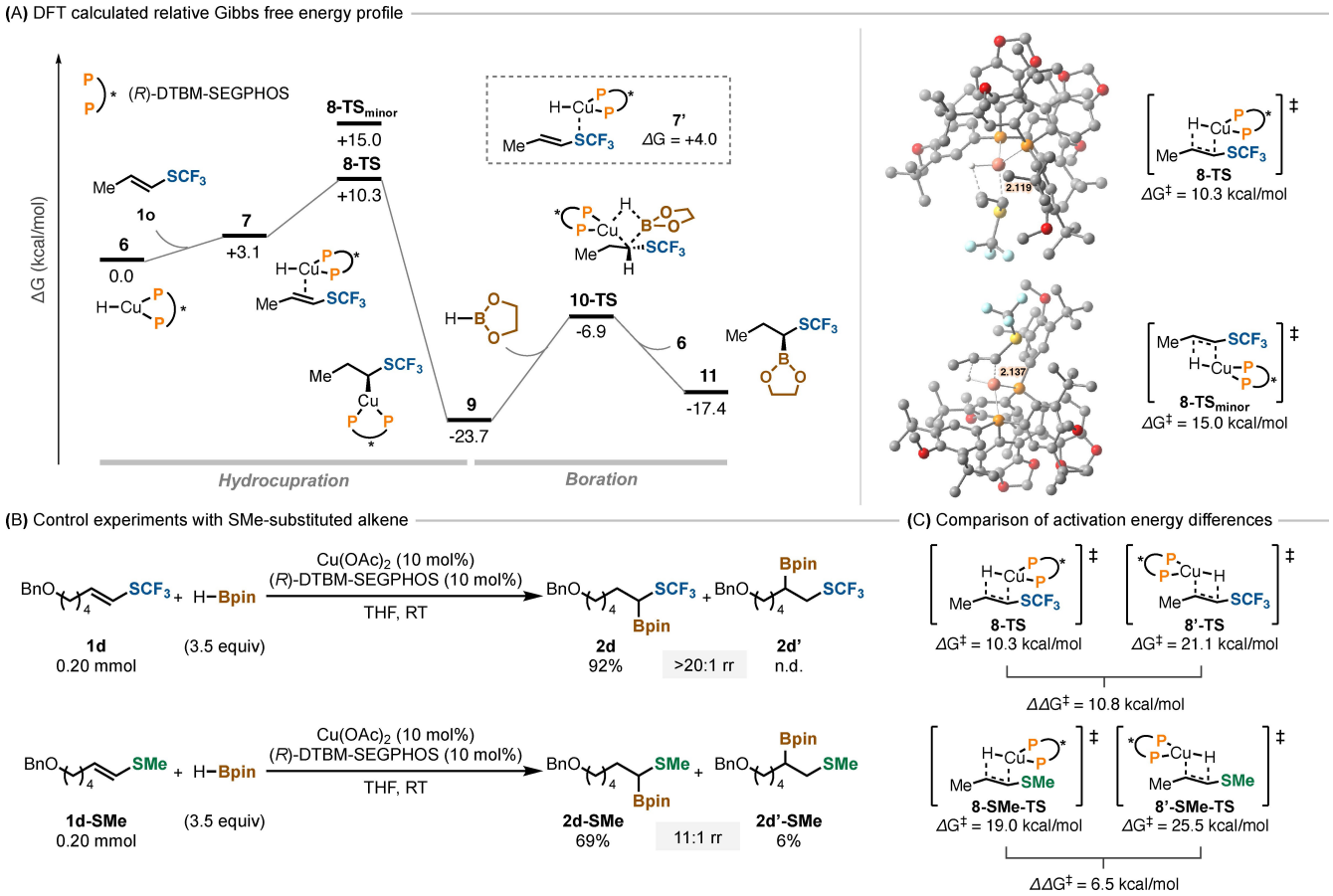
The Bpin moiety of the product obtained in the enantioselective reaction easily underwent various chemical transformations to produce the functionalized SCF_3-containing molecules with high stereochemical fidelity (Scheme 4). For example, the hydroborated product **2a** successfully reacted with furanyllithium and vinyl Grignard reagent to furnish the corresponding furanylation[17] and vinylation[18] products, respectively, without any erosion of enantiomeric ratio. In addition, a homologation reaction of **2a** was also possible to yield the one carbon elongated product **5** with high enantiospecificity.[19] Thus, the chiral α-



Scheme 4. Stereospecific transformations of Bpin moiety in **2a**. See the Supporting Information for more detailed conditions. [a] Estimated by HPLC analysis of **2a-Bdan** after derivatization.

SCF_3 alkylboronates **2** would be valuable platforms for versatile optically active SCF_3 molecules. Unfortunately, attempts to apply cross-coupling-type transformations remained unsuccessful (see the Supporting Information for details).

Finally, we investigated the mechanism of hydroboration reaction through a combination of control experiments and density functional theory (DFT) calculations (Scheme 5). All calculations were carried out using Gaussian 16 program.[20] The long-range and dispersion corrected ωB97X-D function[21] was employed for geometry optimizations and single-point energy calculations. Geometries of intermediates and transition states were optimized with a standard 6-31G(d) basis set (LanL2DZ basis set for Cu). Single-point energy calculations were performed using the 6-311+G(d,p) basis set (SDD basis set for Cu) in THF using the SMD solvation model.[22] In the case of *t*Bu-dppbz ligand, an activation energy of the hydrocupration transition was lower than that of simple dppbz ligand (Scheme S4; $\Delta G^{\ddagger}=12.0$ and 16.0 kcal/mol, respectively, with respect to the monomeric CuH). The results indicate some favorable dispersion interaction[23] between *t*Bu substituents of ligand and substrate, including a C–H/C–F interaction with SCF_3 group. However, since both activation barriers are relatively small, the possibility that *t*Bu substituent promotes other steps, such as the generation of active CuH species, cannot be excluded. We also calculated the relative Gibbs free energies of each intermediate and transition state, giving (*S*)- or (*R*)-enantiomer, respectively, in the asymmetric hydroboration of 1-trifluoromethylthioalkene **1o** with the (*R*)-DTBM-SEGPHOS ligand (Scheme 5A). The dimeric CuH species is generally thermodynamically stable than monomeric CuH **6**,[23d,24] expecting that the reaction was initiated by the coordination of substrate **1o** to the active **6** in equilibrium. Actually, a clear linear effect of enantiomer excess (ee) between ligand and product was observed (Figure S4), supporting the identification of monomeric CuH as the real active species. The relative Gibbs energy of Cu(η^2-alkene) complex **7** was +3.1 kcal/mol with respect to **6**, and it is more favorable than the other possible Cu complex **7'**, in which the SCF_3 group of **1o** coordinates to the Cu center. As reported by Hartwig and co-workers in their computational study of the copper-catalyzed hydroboration of simple olefin substrates, the boration step is stereospecific with retention of configuration.[24b] Therefore, the enantioselectivity of the reaction is considered to be determined in the hydrocupration of alkene moiety. In the transition state **8-TS**, the distance between Cu and C at α-



Scheme 5. Mechanistic investigations; (A) DFT calculated relative Gibbs free energy profile of the asymmetric hydroboration of 1-trifluoromethylthioalkene **1o** with Cu–H catalyst at ωB97X-D/6-311+G(d,p)&SDD/SMD(THF)//ωB97X-D/6-31G(d)&LanL2DZ, (B) control experiments with corresponding SMe-substituted alkene, (C) comparison of activation free energy differences between transition states leading to regioisomers.

position of the SCF_3 group was 2.119 Å. In contrast, the longer atomic distance (2.137 Å) was observed in **8-TS$_{minor}$** that leads to the minor enantiomer. Also, the activation energy of **8-TS** was 4.7 kcal/mol lower than **8-TS$_{minor}$**. The enantioselective hydrocupration forms α-SCF_3 alkylcopper intermediate **9**, which then undergoes the stereoretentive boration reaction through transition state **10-TS**. In the boration step, monomeric CuH **6** is regenerated and the desired product **11** is obtained. The stereochemistry of **11** is consistent with the absolute configuration confirmed by X-ray analysis. The overall Gibbs energy change of the reaction is −17.4 kcal/mol, indicating an exergonic process, which is the driving force of the reaction. In addition, the effect of fluorine atom on regioselectivity was evaluated by the reaction with the corresponding SMe-alkene (Scheme 5B). While the hydroboration reaction of **1d** proceeded with excellent regioselectivity, the reaction with the corresponding SMe-substituted alkene **1d-SMe** under otherwise identical conditions gave an 11 : 1 mixture of regioisomers.[25] As shown in Scheme 5C, these results can also be explained by DFT calculations. The energy difference between the regioisomeric transition states **8-TS** and **8′-TS** was 10.8 kcal/mol. On the other hand, in the case of SMe-alkene **1o-SMe**, the energy difference between the corresponding transition states (**8-SMe-TS** and **8'-SMe-TS**) is smaller ($\Delta\Delta G^{\ddagger}$ = 6.5 kcal/mol). These results suggest that the high electronegativity of the fluorine atom in **1** effectively decreases the activation barrier in the α-insertion process to deliver the α-SCF_3 alkylboronate with high regioselectivity.

In conclusion, we have developed a Cu-catalyzed regio- and enantioselective hydroboration of 1-trifluoromethylthioalkenes. Appropriate chiral copper catalysts can successfully construct the *gem*-Bpin- and SCF_3-substituted chiral carbon center. Several stereospecific transformations of Bpin moiety in the product demonstrate the high synthetic potential that successfully expands the chemical space of chiral SCF_3-containing molecules. Furthermore, we investigate the regioselectivity and enantioselectivity of the reaction by using theoretical calculation analysis and obtain some important findings that SCF_3 successfully controls the regioselectivity. Additional synthetic applications of SCF_3-substituted alkenes are currently under investigation in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: asymmetric catalysis · copper · fluorine molecule · hydrofunctionalization · trifluoromethylthio group

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Communications

Asymmetric Synthesis

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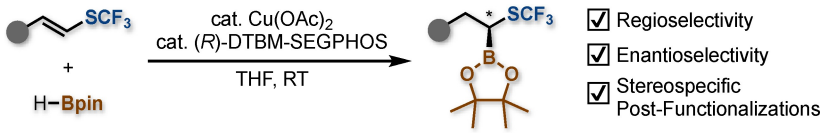
Asymmetric Synthesis of SCF_3-Substituted Alkylboronates by Copper-Catalyzed Hydroboration of 1-Trifluoromethylthioalkenes



A copper-catalyzed regio- and enantioselective hydroboration of 1-trifluoromethylthio(SCF_3)-alkenes with H-Bpin has been developed. The enantioselective hydrocupration and subsequent boration reaction generate a chiral SCF_3-containing alkylboronate, of which Bpin moiety can be further transformed to deliver various optically active SCF_3 molecules. Computational studies suggest that SCF_3 group successfully controls the regioselectivity.