Asymmetric Construction of a $SeCF_3$-Substituted Stereocenter by CuH-Catalyzed Hydroboration of 1-$SeCF_3$-Alkenes

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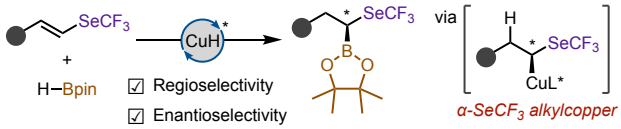
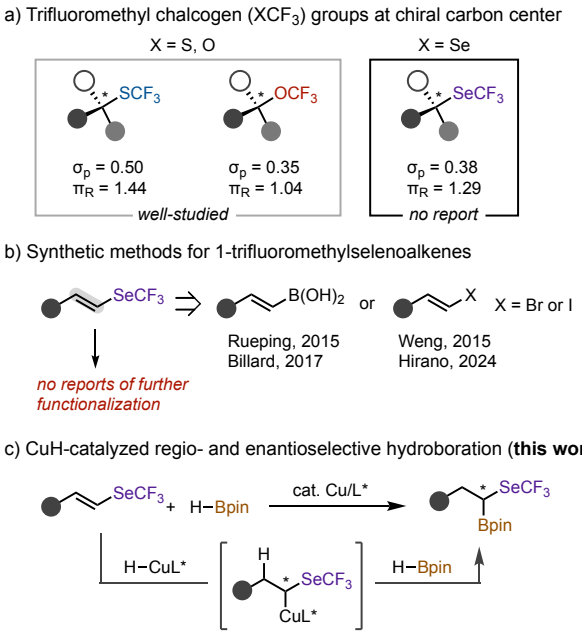
Supporting Information Placeholder



ABSTRACT: A copper hydride (CuH)-catalyzed regio- and enantioselective hydroboration of 1-trifluoromethylseleno ($SeCF_3$)-alkenes with H–Bpin has been developed. The regio- and enantioselective hydrocupration of an *in situ* generated CuH species is followed by a boration reaction to successfully construct a $SeCF_3$- and Bpin-substituted chiral carbon center. The key to success is the appropriate choice of *t*Bu-modified biphosphine ligands, which enables an overwhelmingly high reaction efficiency.

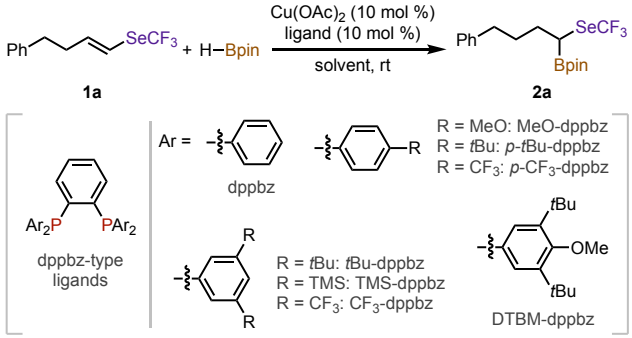
Due to the remarkable effects of fluorine atoms, organofluorine compounds have become staples in the field of pharmaceutical and pesticide development.[1] Among them, trifluoromethyl chalcogen XCF_3 (X = O, S, or Se) groups show great promise in medicinal chemistry. The introduction of these functional groups into parent molecules can significantly enhance biological activities such as metabolic stability and cell membrane permeability.[2] Over the past decades, numerous OCF_3-[2c] and SCF_3-containing[2a,2b,3] compounds have been synthesized, and their biological properties were extensively studied. However, the chemistry of trifluoromethylseleno ($SeCF_3$) compounds remains largely unexplored (Scheme 1a),[4] despite their comparable lipophilicity (Hansch parameter, π_R = 1.29)[4b] to that of SCF_3 (π_R = 1.44) and OCF_3 (π_R = 1.04).[5] Given that compounds containing selenium atoms typically exhibit antimicrobial and antioxidant properties,[6] advancement of $SeCF_3$ chemistry holds the promise of making substantial contributions to innovative drug design. Recently, there have been successive reports on the synthesis of optically active SCF_3- [7] and OCF_3-containing[8] compounds. In contrast, the synthesis of enantioenriched chiral $SeCF_3$ compounds remains largely elusive. Meanwhile, C(sp^2)–$SeCF_3$ compounds are relatively easy to synthesize, and several examples of the synthesis of 1-trifluoromethylselenoalkenes, which have a $SeCF_3$ group on the alkene moiety, have been reported using alkenyl boronic acids[9] or alkenyl halides[10] as starting materials (Scheme 1b). We have also developed modular synthesis of 1-trifluoromethylselenoalkenes using stable and commercially available Se powder.[10b] However, to date, there is no example of functionalization of the C=C bond in $SeCF_3$-alkenes. Herein, we report a copper hydride (CuH)-catalyzed regioselective and enantioselective hydroboration of 1-trifluoromethylselenoalkenes with pinacolborane (H–Bpin; Scheme1c). Our blueprint is shown in Scheme 1c. The starting $SeCF_3$-alkene undergoes regio- and enantioselective insertion into *in situ* generated chiral CuH species[11] to form an α-$SeCF_3$ alkylcopper intermediate. A subsequent stereospecific boration reaction with H–Bpin enables the asymmetric construction of a $SeCF_3$- and Bpin-substituted chiral carbon center. Such a chiral building block with $SeCF_3$ and Bpin in a *gem* relationship is disclosed for the first time.

Scheme 1. Synthetic Approach to $SeCF_3$-Containing Compounds



We have recently achieved related synthesis of SCF_3-substituted alkylboronates using a 1-trifluoromethylthioalkene as a starting platform,[12] where the choice of ligand had a significant impact on reaction efficiency. Therefore, we initially investigated ligand effects for the non-enantioselective hydroboration of 1-trifluoromethylselenoalkene **1a** (Table 1). In the presence of the $Cu(OAc)_2$ precatalyst and bis(diphenylphosphino)benzene (dppbz) ligand, the reaction of compound **1a** with H–Bpin gave the desired hydroborated product **2a** in 13% ^{1}H nuclear magnetic resonance (NMR) yield (entry 1). The yield was poor, but the reaction dominantly gave product **2a** with a high regioselectivity. Inspired by the previous hydroboration of SCF_3-substituted alkenes,[12] we then tested modified dppbz-type ligands. In the case of SCF_3-alkenes, the favorable dispersion interaction between the remote *t*Bu group on the ligand and the SCF_3 group facilitated the hydrocupration step. A similar effect was observed even with $SeCF_3$-alkene. While para-substituted dppbz ligands led to decreased yields (entries 2-4), the use of *t*Bu-dppbz dramatically improved the product yield (entry 5). On the other hand, other meta-substituted dppbz ligands, including TMS-, CF_3-, and DTBM-dppbz, resulted in lower yields (entries 6-8). When tetrahydrofuran (THF) or *N,N*-dimethylformamide (DMF) was used as the solvent, product **2a** was obtained in similarly high yields. We selected toluene as the optimal solvent due to better reproducibility. Additional observations are noted: other common mono- and bidentate phosphine ligands decreased the yield. While *t*Bu modification improved the reaction efficiency also in other ligand skeletons, none surpassed the performance of *t*Bu-dppbz. Other Cu salts and solvents were also tested, but all resulted in lower yields (see the Supporting Information for more details).

Table 1. Optimization Studies for CuH-Catalyzed Regioselective Hydroboration of Compound 1a with H–Bpin[a]

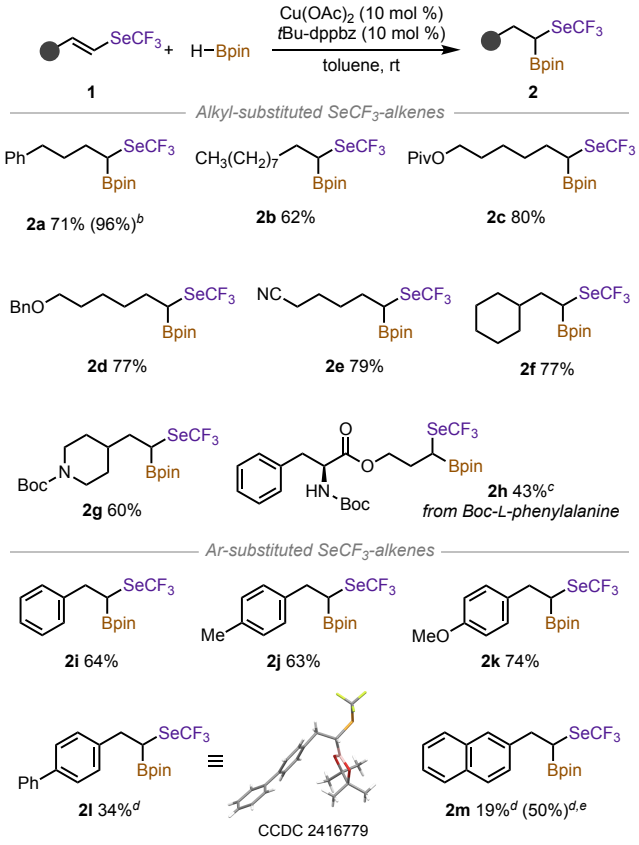


entry	ligand	solvent	yield (%)[b]
1	dppbz	toluene	13
2	MeO-dppbz	toluene	1
3	*p*-*t*Bu-dppbz	toluene	2
4	*p*-CF_3-dppbz	toluene	2
5	*t*Bu-dppbz	toluene	88 (71)
6	TMS-dppbz	toluene	22
7	CF_3-dppbz	toluene	12
8	DTBM-dppbz	toluene	64
9	*t*Bu-dppbz	THF	81
10	*t*Bu-dppbz	DMF	89

[a]Conditions: compound **1a** (0.20 mmol), H–Bpin (0.70 mmol), $Cu(OAc)_2$ (0.020 mmol), ligand (0.020 mmol), solvent (0.30 mL), room temperature, 18 h, and N_2. [b] Estimated by ^{1}H NMR. The isolated yield is given in parentheses.

After establishing the optimal reaction conditions (entry 5 in Table 1), we examined the scope of 1-trifluoromethylselenoalkenes **1** (Scheme 2). In addition to compound **1a**, various alkyl-substituted $SeCF_3$-alkenes were applicable. The substrate **1b** with longer alkyl chain was also coupled with H–Bpin to yield the corresponding hydroborated product **2b** in 62% yield. The reaction with substrates bearing ester (**2c**), benzyl ether (**2d**), and nitrile (**2e**) groups at the terminus of the alkyl chain was also possible. The cyclohexyl- and piperidyl-substituted 1-trifluoromethylselenoalkenes (**1f** and **1g**) could be successfully employed to provide products **2f** and **2g** in 77 and 60%, respectively. Using a substrate derived from Boc-protected *L*-phenylalanine, product **2h** was obtained in a moderate yield without erosion of the enantiopurity of the amino acid framework. In addition, the reaction with aryl-conjugated $SeCF_3$-alkenes was possible to give the desired products with high regioselectivity (**2i**-**2k**). In cases of biphenyl- and naphthyl-substituted alkenes, the use of DMF as a reaction solvent instead of toluene was necessary to obtain the hydroborated products in acceptable yields (**2l** and **2m**). The structure of **2l** was confirmed by X-ray analysis of single crystals (CCDC 2416779). Unfortunately, the reaction with electron-deficient aromatic- or heteroaromatic-ring-substituted $SeCF_3$-alkenes was unsuccessful: both conversion and regioselectivity of the reaction were decreased (see the Supporting Information for details).

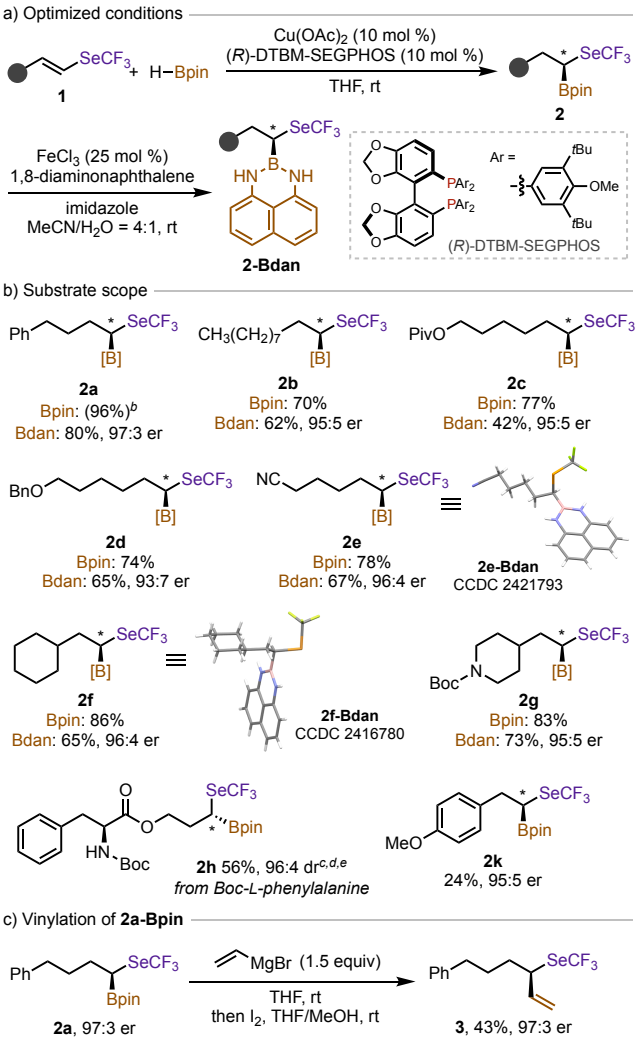
Scheme 2. Products of CuH-Catalyzed Regioselective Hydroboration of 1-Trifluoromethylselenoalkenes 1 with H–Bpin[a]



[a]Conditions: compound **1** (0.20 mmol), H–Bpin (0.70 mmol), $Cu(OAc)_2$ (0.020 mmol), *t*Bu-dppbz (0.020 mmol), toluene (0.30 mL), room temperature, 18 h, and N_2. Isolated yields are shown. [b] On a 1.0 mmol scale. [c] From compound (*Z*)-**1h**. [d] In DMF (0.30 mL). [e] Estimated by ^1H NMR.

We next moved our attention to the asymmetric synthesis using a chiral biphosphine ligand instead of *t*Bu-dppbz (Scheme 3a). After intensive ligand screening, we found that (*R*)-DTBM-SEGPHOS efficiently provided the desired hydroborated products with high enantioselectivity. The enantiomeric ratio of the product was estimated by chiral high-performance liquid chromatography (HPLC) analysis of **2-Bdan** after derivatization using the reported transesterification method.[13] The Bdan derivatives, being more ultraviolet (UV)-detectable and polar, allowed for the easier separation of

Scheme 3. CuH-Catalyzed Regio- and Enantioselective Hydroboration of 1-Trifluoromethylselenoalkenes 1[a]



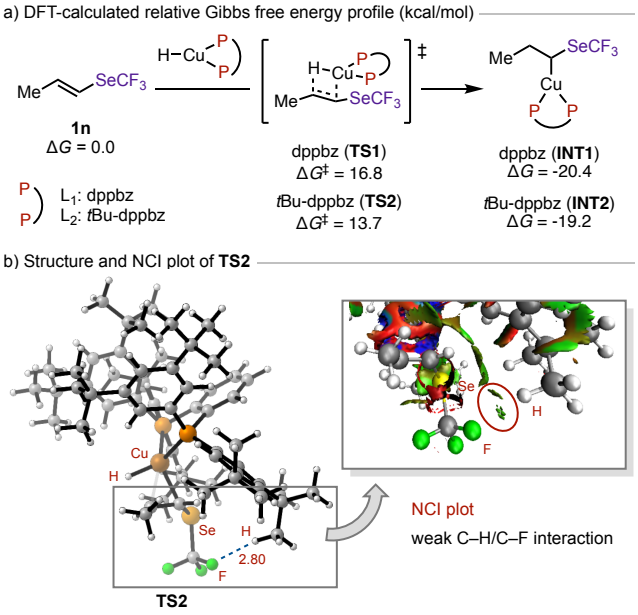
[a]Conditions: compound **1** (0.20 mmol), H–Bpin (0.70 mmol), $Cu(OAc)_2$ (0.020 mmol), (*R*)-DTBM-SEGPHOS (0.020 mmol), THF (0.30 mL), room temperature, 4 h, and N_2. Isolated yields are shown. [b] On a 1.0 mmol scale. [c] From compound (*Z*)-**1h**. [d] Using (*S*)-DTBM-SEGPHOS. [e] The stereoselectivity was estimated by the ratio of its diastereomeric signals on $^{19}F\{^1H\}$ NMR.

enantiomers on a chiral stationary phase. The substrate scope is shown in Scheme 3b, including the isolated yields of all Bpin products, along with the overall isolated yields and enantiomeric ratios after their derivatization to Bdan forms. $SeCF_3$ alkenes, including those with primary alkyl groups and some common functional groups, yielded the desired hydroborated products in good yields with high enantioselectivity (**2a**–**2e**). The substrate bearing a sterically demanding cyclohexyl substituent was converted to product **2f** in 86% yield and successfully transformed into compound **2f-Bdan** with a 96:4 enantiomeric ratio (er). Similarly, piperidyl-substituted substrates **2g** and **2g-Bdan** were obtained in high yields with 95:5 er. The reaction with compound (*Z*)-**1h**, derived from Boc-protected *L*-phenylalanine, produced product **2h** in a moderate yield with a 96:4 diastereomeric ratio (dr). In the reaction with compound **1h**, a match-mismatch phenomenon was observed; using (*R*)-DTBM-SEGPHOS lowered the diastereoselectivity to 87:13 (Scheme S4 of the Supporting Information). On the

other hand, when using Ar-conjugated $SeCF_3$-alkene **1k**, the desired product **2k** was obtained in an only 24% yield but with high enantioselectivity (95:5 er). The absolute configurations of compounds **2e-Bdan** and **2f-Bdan** were confirmed to be *S* by X-ray crystallographic analysis (CCDC 2421793 and CCDC 2416780), and the configurations of other compounds were assigned by analogy. Furthermore, it was confirmed that, even when compound (*Z*)-**1f** was used, compound (*S*)-**2f-Bdan** was obtained as the major enantiomer (84:16 er; Scheme S3 of the Supporting Information). The Bpin moiety of enantioenriched compound **2a** could successfully react with a vinyl Grignard reagent to give the corresponding vinylation product **3** with high stereochemical fidelity (Scheme 3c).[14] Unfortunately, other transformations, including cross-coupling-type reactions, remained unsuccessful (see the Supporting Information for details).

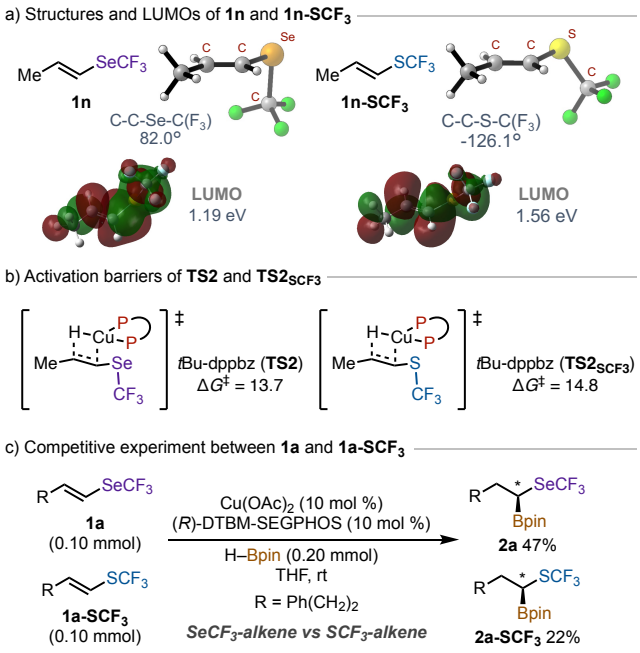
Our preliminary calculations shed light on why the *t*Bu substituent on the phosphine ligand was effective for the hydrocupration of $SeCF_3$-substituted alkenes (Scheme 4). All geometries of intermediates and transition states were optimized by density functional theory (DFT) calculations using the Gaussian 16 program.[15] The long-range and dispersion corrected ωB97X-D functional[16] with a standard 6-31G(d) basis set (LanL2DZ basis set for Cu and Se) was employed for geometry optimizations in THF using the SMD solvation model.[17] Single-point energies were calculated using the 6-311+G(d,p) basis set (SDD basis set for Cu and Se) in THF. A modeled substrate **1n** was used for the calculations. The relative Gibbs free energy of the hydrocupration step was calculated using dppbz and *t*Bu-dppbz ligands (Scheme 4a). In the case of the simple dppbz ligand, the hydrocupration of compound **1n** proceeds through a four-membered transition state **TS1** to form the alkylcopper intermediate **INT1**, with an activation barrier of 16.8 kcal/mol. On the other hand, with the *t*Bu-dppbz ligand, the reaction proceeds via transition state **TS2** to form intermediate **INT2**, with an activation barrier of 13.7 kcal/mol. The structure of transition state **TS2** is shown in Scheme 4b, where the F atom of the $SeCF_3$ group and the H atom of *t*Bu on the ligand are in close proximity (2.80 Å). The non-covalent interaction (NCI) plot of transition state **TS2** reveals a C–H/C–F interaction between the $SeCF_3$ group and the *t*Bu group. Importantly, it is suggested that favorable dispersion interactions contribute to the stabilization of transition state **TS2**, thereby accelerating the reaction.[18]

Scheme 4. DFT Calculations for Hydrocupration of Compound 1n with dppbz and *t*Bu-dppbz Ligands



Finally, we investigated the origin of the high reactivity of $SeCF_3$-substituted alkenes through control experiments using the corresponding SCF_3-alkene. The optimized structure of $SeCF_3$-alkene **1n**, obtained using DFT calculations, is shown in Scheme 5a. The C=C bond and the Se–C(F_3) bond adopt a perpendicular configuration with a dihedral angle of 82.0°. In contrast, the corresponding SCF_3-alkene **1n-SCF₃** has a C–C–S–C(F_3) dihedral angle of -126.1°. In addition, the calculated lowest unoccupied molecular orbital (LUMO) of compound **1n** is significantly localized on the $SeCF_3$ unit. The LUMO level is 1.19 eV, indicating higher electrophilicity compared to **1n-SCF₃** (1.56 eV). These results suggest that the high reactivity of $SeCF_3$-alkenes is attributed to effective overlap between the π* orbital of the alkene and the σ* orbital of the Se–C(F_3) bond. Thus, $SeCF_3$-alkenes are expected to exhibit higher reactivity compared to SCF_3-alkenes. Theoretical calculations also indicate that the activation barrier for the hydrocupration of $SeCF_3$-alkene is lower than that of SCF_3-alkene (Scheme 5b; 13.7 versus 14.8 kcal/mol).[19] Indeed, when a competitive experiment was conducted using 1 equiv of H–Bpin with **1a** and **1a-SCF₃**, product **2a** was preferentially obtained (Schemes 5c and Table S11 of the Supporting Information). Moreover, kinetic studies of the reaction with $SeCF_3$- and SCF_3-alkenes further support the higher reactivity of $SeCF_3$-alkenes (Figure S5 of the Supporting Information).

Scheme 5. Comparison of $SeCF_3$- and SCF_3-Substituted Alkenes in Structure and Reactivity



In summary, we have developed a CuH-catalyzed regio- and enantioselective hydroboration of 1-trifuoromethylselenoalkenes with H–Bpin. The appropriate copper catalyst enables the asymmetric construction of a chiral carbon center substituted with $SeCF_3$ and Bpin. Our preliminary calculation studies suggest that the *t*Bu substituent of the ligands facilitates the reaction through favorable interaction with the $SeCF_3$ group. Moreover, experimental and computational comparison studies with $SeCF_3$- and SCF_3-alkenes uncover the origin of the higher reactivity of $SeCF_3$-alkene. More detailed mechanistic studies and additional synthetic applications of $SeCF_3$-substituted alkenes are ongoing in our laboratory.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are openly available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.xxxx.

Experimental procedures and characterization data for products, ^{1}H, $^{13}C\{^{1}H\}$, $^{19}F\{^{1}H\}$, and ^{11}B NMR spectra, HPLC spectra, Oak Ridge Thermal Ellipsoid Plot (ORTEP) drawing, detailed optimization studies, control experiments, and DFT studies (PDF)

Accession Code

Deposition numbers CCDC 2416779–2416780 and 2421793 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformations-zentrum Karlsruche Access Structure service.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Swallow, S. In *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*; Gouverneur, V. Müller, K., Eds.; Imperial College Press: London, U.K., 2012; p 141. (b) Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007**, *317*, 1881–1886. (c) O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev.* **2008**, *37*, 308–319. (d) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359. (e) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II–III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422–518. (f) Ogawa, Y.; Tokunaga, E.; Kobayashi, O.; Hirai, K.; Shibata, N. Current Contributions of Organofluorine Compounds to the Agrochemical Industry. *iScience* **2020**, *23*, 101467. (g) Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633–10640. (h) Johnson, B. M.; Shu, Y.-Z.; Zhuo, X.; Meanwell, N. A. Metabolic and Pharmaceutical Aspects of Fluorinated Compounds. *J. Med. Chem.* **2020**, *63*, 6315–6386.

(2) (a) Xu, X.-H.; Matsuzaki, K.; Shibata, N. Synthetic Methods for Compounds Having CF_3–S Units on Carbon by Trifluoromethylation, Trifluoromethylthiolation, Triflylation, and Related Reactions. *Chem. Rev.* **2015**, *115*, 731–764. (b) Barata-Vallejo, S.; Bonesi, S.; Postigo, A. Late stage trifluoromethylthiolation strategies for organic compounds. *Org. Biomol. Chem.* **2016**, *14*, 7150–7182. (c) Ghiazza, C.; Billard, T. Tlili, A. Merging Visible-Light Catalysis for the Direct Late-Stage Group-16–Trifluoromethyl Bond Formation. *Chem. Eur. J.* **2019**, *25*, 6482–6495.

(3) (a) Barthelemy, A.-L.; Magnier, E.; Dagousset, G. Direct Trifluoromethylthiolation Reactions Involving Radical Processes. *Synthesis* **2018**, *50*, 4765–4776. (b) Huang, Y.; Zhang, M.; Lin, Q.; Weng, Z. [(bpy)CuSCF$_3$]: A Practical and Efficient Reagent for the Construction of C–SCF$_3$ Bonds. *Synlett* **2021**, *32*, 109–118.

(4) (a) Wang, Y.; Ye, Z.; Zhang, H.; Yuan, Z. Recent Advances in the Development of Direct Trifluoromethylselenolation Reagents and Methods. *Adv. Synth. Catal.* **2021**, *363*, 1835–1854. (b) Yang, X.-H.; Chang, D.; Zhao, R.; Shi, L. Recent Advances and Uses of (Me$_4$N)XCF$_3$ (X=S, Se) in the Synthesis of Trifluoromethylthiolated and Trifluoromethylselenolated Compounds. *Asian J. Org. Chem.* **2021**, *10*, 61–73. (c) Wang, H.-N.; Dong, J.-Y.; Shi, J. Zhang, C.-P. Trifluoromethylselenolation reactions using the versatile [Me$_4$N][SeCF$_3$] reagent. *Tetrahedron* **2021**, *99*, 132476. (d) Cao, Y.; Xu, N.-Y.; Issakhov, A.; Ebadi, A. G.; Poor Heravi, M. R.; Vessally, E. Recent advances in direct trifluoromethylselenolation of C–H bonds. *J. Fluorine Chem.* **2021**, *252*, 109901. (e) Gao, Y.; Xiao, R.; Zhang, S.; Wang, Y.; Yuan, Z. Direct Trifluoromethylselenolation and Fluoroalkylselenolation of C–H Bonds: Recent Advances in Reagents Development and Reactions. *Eur. J. Org. Chem.* **2023**, *26*, e202300668.

(5) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. Aromatic substituent constants for structure-activity correlations. *J. Med. Chem.* **1973**, *16*, 1207–1216.

(6) For a recent review, see: Morán-Serradilla, C.; Plano, D.; Sanmartín, C.; Sharma, A. K. Selenization of Small Molecule Drugs: A New Player on the Board. *J. Med. Chem.* **2024**, *67*, 7759–7787.

(7) (a) Wang, Q.; Nilsson, T.; Eriksson, L.; Szabó, K. J. Sulfenofunctionalization of Chiral α-Trifluoromethyl Allylboronic Acids: Asymmetric Synthesis of SCF$_3$, SCF$_2$R, SCN and SAr Compounds. *Angew. Chem. Int. Ed.* **2022**, *61*, e202210509. (b) Zhang, W.; Tian, Y.; Liu, X.-D.; Luan, C.; Liu, J.-R.; Gu, Q.-S.; Li, Z.-L.; Liu, X.-Y. Copper-Catalyzed Enantioselective C(sp^3)–SCF$_3$ Coupling of Carbon-Centered Benzyl Radicals with (Me$_4$N)SCF$_3$. *Angew. Chem. Int. Ed.* **2024**, *63*, e202319850. (c) Hu, D.-D.; Nie, T.-M.; Xiao, X.; Li, K.; Li, Y.-B.; Gao, Q.; Bi, Y.-X.; Wang, X.-S. Enantioselective Construction of C–SCF$_3$ Stereocenters via Nickel Catalyzed Asymmetric Negishi Coupling Reaction. *Angew. Chem. Int. Ed.* **2024**, *63*, e202400308.

(8) Hardy, M. A.; Chachignon, H.; Cahard, D. Advances in Asymmetric Di-and Trifluoromethylthiolation, and Di- and Trifluoromethoxylation Reactions. *Asian J. Org. Chem.* **2019**, *8*, 591–609.

(9) (a) Lefebvre, Q.; Pluta, R.; Rueping, M. Copper catalyzed oxidative coupling reactions for trifluoromethylselenolations – synthesis of R-SeCF$_3$ compounds using air stable tetramethylammonium trifluoromethylselenate. *Chem. Commun.* **2015**, *51*, 4394–4397. (b) Glenadel, Q.; Ghiazza, C.; Tlili, A.; Billard, T. Copper-Catalyzed Direct Trifluoro- and Perfluoroalkylselenolations of Boronic Acids with a Shelf-Stable Family of Reagents. *Adv. Synth. Catal.* **2017**, *359*, 3414–3420.

(10) (a) Wu, C.; Huang, Y.; Chen, Z.; Weng, Z. Synthesis of vinyl trifluoromethyl selenoethers. *Tetrahedron Lett.* **2015**, *56*, 3838–3841. (b) Matsui, H.; Kojima, Y.; Hirano, K. Facile preparation of SeCF$_3$-substituted alkenes from alkenyl iodides and selenium powder. *Chem. Lett.* **2024**, *53*, upae076.

(11) For pioneering studies on CuH species, see (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. Selective hydride-mediated conjugate reduction of *α,β*-unsaturated carbonyl compounds using [(Ph$_3$P)CuH]$_6$. *J. Am. Chem. Soc.* **1988**, *110*, 291–293. (b) Ito, H.; Ishizuka, T.; Arimoto, K.; Miura, K.; Hosomi, A. Generation of a reducing reagent from Copper(I) salt and hydrosilane. New practical method for conjugate reduction. *Tetrahedron Lett.* **1997**, *38*, 8887–8890. For recent examples, see (c) Romero, E. A.; Olsen, P. M.; Jazzar, R.; Soleilhavoup, M.; Gembicky, M.; Bertrand, G. Spectroscopic Evidence for a Monomeric Copper(I) Hydride and Crystallographic Characterization of a Monomeric Silver(I) Hydride. *Angew. Chem. Int. Ed.* **2017**, *56*, 4024–4027. (d) Xi, Y.; Hartwig, J. F. Mechanistic Studies of Copper-Catalyzed Asymmetric Hydroboration of Alkenes. *J. Am. Chem. Soc.* **2017**, *139*, 12758–12772. (e) Jang, W. J.; Song, S. M.; Moon, J. H.; Lee, J. Y.; Yun, J. Copper-Catalyzed Enantioselective Hydroboration of Unactivated 1,1-Disubstituted Alkenes. *J. Am. Chem. Soc.* **2017**, *139*, 13660-13663. (f) Speelman, A. L.; Tran, B. L.; Erickson, J. D.; Vasiliu, M.; Dixon, D. A.; Bullock, R. M. Accelerating the insertion reactions of (NHC)Cu–H *via* remote ligand functionalization. *Chem. Sci.* **2021**, *12*, 11495–11505. (g) Carroll, T. G.; Ryan, D. E.; Erickson, J. D.; Bullock, R. M.; Tran, B. L. Isolation of a Cu–H Monomer Enabled by Remote Steric Substitution of a *N*-Heterocyclic Carbene Ligand: Stoichiometric Insertion and Catalytic Hydroboration of Internal Alkenes. *J. Am. Chem. Soc.* **2022**, *144*, 13865–13873. (h) Kutateladze, D. A.; Mai, B. K.; Dong, Y.; Zhang, Y.; Liu, P.; Buchwald, S. L. Stereoselective Synthesis of Trisubstituted Alkenes via Copper Hydride-Catalyzed Alkyne Hydroalkylation. *J. Am. Chem. Soc.* **2023**, *145*, 17557–17563.

(12) Kojima, Y.; Nishii, Y.; Hirano, K. Asymmetric Synthesis of SCF$_3$-Substituted Alkylboronates by Copper-Catalyzed Hydroboration of 1-Trifluoromethylthioalkenes. *Angew. Chem., Int. Ed.* **2024**, *63*, e202403337.

(13) (a) Noguchi, H.; Hojo, K.; Suginome, M. Boron-Masking Strategy for the Selective Synthesis of Oligoarenes via Iterative Suzuki–Miyaura Coupling. *J. Am. Chem. Soc.* **2007**, *129*, 758–759. (b) Wood, J. L.; Marciasini, L. D. Vaultier, M.; Pucheault, M. Iron Catalysis and Water: A Synergy for Refunctionalization of Boron. *Synlett* **2014**, *25*, 551–555.

(14) Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. Enantioselective Construction of Quaternary Stereogenic Centers from Tertiary Boronic Esters: Methodology and Applications. *Angew. Chem. Int. Ed.* **2011**, *50*, 3760–3763.

(15) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16*; Gaussian, Inc., Wallingford CT, 2016.

(16) Chai, J.-D.; Head-Gordon, M. Long-range corrected hybrid density functionals with damped atom-atom dispersion corrections. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615–6620.

(17) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

(18) An observed C–H/C–F interaction may contribute to the regioselectivity of the reaction. While the reaction of compound **1a** proceeded with complete regioselectivity, the regioselectivity for the corresponding SeMe-alkene **1a-SeMe** was slightly decreased (14:1 rr; Scheme S5 of the Supporting Information).

(19) Also in the hydrocupration transition state **TS2**, the σ* orbital of Se–C(F$_3$) is critical. NBO calculations revealed a 14.4 kcal/mol donation from σ of the Cu–C bond to σ* of Se–C(F$_3$), further contributing to the high reactivity.