Copper-Catalyzed Regio- and Enantioselective Hydroallylation of 1-Trifluoromethylalkenes: Effect of Crown Ether

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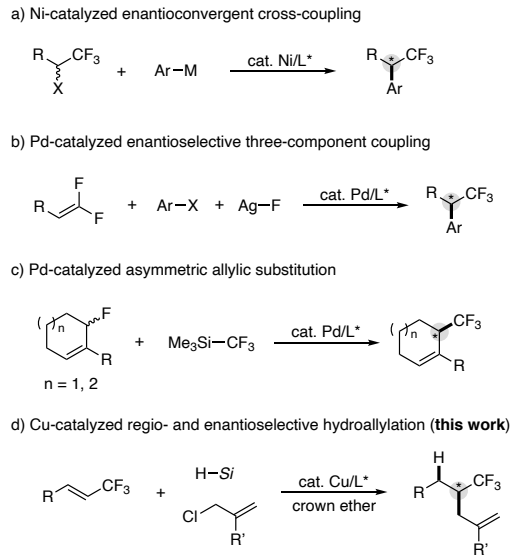
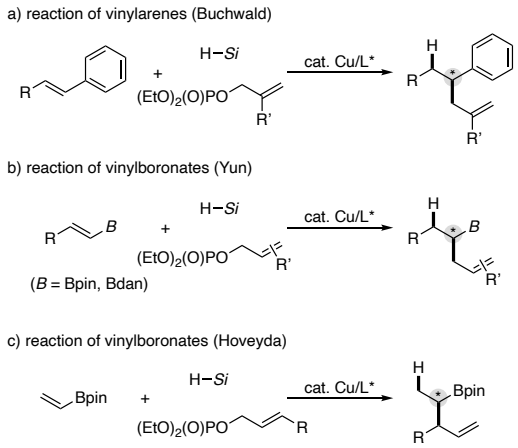
ABSTRACT: A Cu-catalyzed regio- and enantioselective hydroallylation of 1-trifluoromethylalkenes with hydrosilanes and allylic chlorides has been developed. An *in situ* generated CuH species undergoes the hydrocupration regio- and enantioselectively to form a chiral α-CF_3 alkylcopper intermediate, which then leads to the optically active hydroallylated product. The key to success is the use of not only an appropriate chiral bisphosphine ligand but also 18-crown-6 to suppress the otherwise predominant β-F elimination from the α-CF_3 alkylcopper intermediate. The asymmetric Cu catalysis successfully constructs the nonbenzylic and nonallylic CF_3-substituted C_{sp3} chiral center, which is difficult to operate by other means.

Due to their unique nature that increases the lipophilicity, metabolic stability, and bioavailability, fluorinated molecules have received significant attention in the design of pharmaceutical agents and agrochemicals.[1] In particular, the trifluoromethyl (CF_3) group widely occurrs in biologically active compounds.[2] Accordingly, synthetic chemists have developed numerous strategies for the preparation of CF_3-containing organic molecules.[3] However, in comparison to Ar-CF_3 and alkenyl-CF_3, the synthesis of C_{sp3}–CF_3 molecules, in particular, their enantioenriched forms, still remains underdeveloped. While several chiral α-CF_3 alcohols[4]/amines[5] and related α-CF_3 carbonyls[6] are relatively easily prepared by the stereoselective trifluoromethylation of carbonyls/imines or reduction and addition reactions of trifluoromethylated carbonyl/imines, the construction of the point chirality at a position α to CF_3 without any proximal heteroatoms is a formidable challenge. Limited successful examples include the Ni-catalyzed enantioconvergent cross-coupling reaction of racemic CF_3-substituted secondary alkyl halides with organometallic reagents (Scheme 1a),[7] the Pd-catalyzed enantioselective three-component coupling reaction of *gem*-difluoroalkenes, aryl halides, and AgF (Scheme 1b),[8] and the Pd-catalyzed asymmetric allylic substitution of allylic fluorides with trifluoromethylsilanes (Scheme 1c).[9] Herein, we report a totally different approach to optically active C_{sp3}–CF_3 molecules using 1-trifluoromethylalkene as the starting platform: a Cu-catalyzed regio- and enantioselective hydroallylation of 1-trifluoromethylalkenes with hydrosilanes and allylic chlorides is described (Scheme 1d). The asymmetric Cu catalysis can construct the nonbenzylic and nonallylic CF_3-substituted chiral center, which is difficult to operate by other means. Although there are some examples of copper hydride catalyzed regio- and enantioselective hydroallylation of vinylarenes and vinylboronates, which were originally developed by Buchwald (Scheme 2a),[10] Yun (Scheme 2b),[11] and Hoveyda (Scheme 2c),[12] the application of 1-trifluoromethylalkenes remains elusive. Related stereoselective hydrogenation[13] and Michael addition[14] have been reported, but the applicable substrates were restricted to highly electron deficient CF_3-substituted acrylic acids and nitroalkenes. Additionally, the critical effect of the crown ether is found to suppress the competitive β-F elimination from an α-CF_3 organocopper intermediate.

Scheme 1. Catalytic Asymmetric Construction of CF_3-Substituted Stereocenters without Any Proximal Heteroatoms

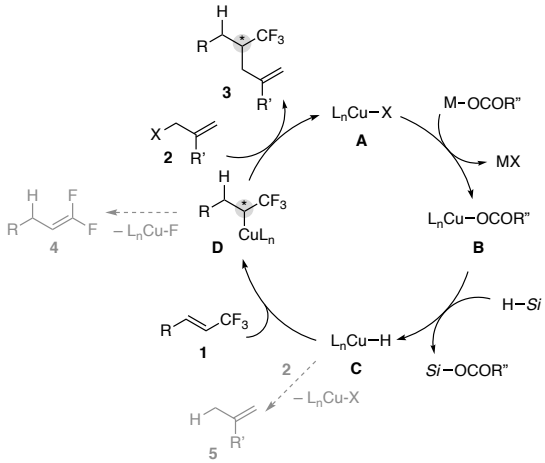


Scheme 2. Reported Examples of Copper Hydride Catalyzed Regio- and Enantioselective Hydroallylation of Alkenes



Our blueprint for the asymmetric synthesis of C_{sp3}–CF_3 molecules by an enantioselective Cu-catalyzed hydroallylation is shown in Scheme 3, the scenario of which is based on the recent progress of CuH-catalyzed[15] stereoselective hydrofunctionalization of alkenes developed by our group,[16] Yun,[11,17] Buchwald,[10,18] and others.[19] The *in situ* formed ligand-coordinated copper complex L_nCu-X (**A**) undergoes a salt metathesis with the acetate-type external base MOCOR" to form the copper acetate species L_nCu-OCOR" (**B**). Subsequent σ-bond metathesis with the hydrosilane generates the active copper hydride **C**. With guidance by the strong electron-withdrawing nature of the CF_3 group, the double-bond moiety of 1-trifluoromethylalkene **1** inserts the Cu–H bond regioselectively to furnish the α-CF_3 alkylcopper intermediate **D**. The desired hydroallylated product **3** and starting copper salt **A** then follow from electrophilic trapping with the allylic electrophile **2** to complete the catalytic cycle. If the enantioselectivity and the regioselectivity are successfully controlled in the insertion step by a judicious choice of the ancillary chiral ligand (**C** to **D**), the optically active α-CF_3 alkylcopper is formed, en route to the enantioenriched product via a stereospecific allylation. However, there are several issues to overcome in the aforementioned reaction design. First, the copper hydride **C** should react with the 1-trifluoromethylalkene **1** in preference to the alkene moiety of allyl electrophile **2** to avoid the formation of the reduced byproduct **5**. Moreover, suitable conditions including the ligand and external base should be identified to suppress the formation of *gem*-difluoroalkene **4** through the conceivably competitive β-F elimination from the α-CF_3 alkylcopper **D**, which is frequently observed in the metal-catalyzed reactions of 1-trifluoromethylalkenes with some nucleophiles.[20,21]

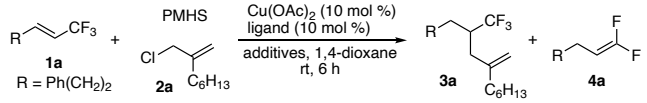
Scheme 3. Working Hypothesis and Conceivable Side Reactions in Copper-Catalyzed Regio- and Enantioselective Hydroallylation of 1-Trifluoromethylalkene 1 with Hydrosilane and Allylic Electrophile 2



Our optimization studies commenced with the trifluoromethylalkene **1a** and allylic chloride **2a** for the development of nonenantioselective hydroallylation conditions. In an early experiment, on the basis of our previous work,[16c] treatment of **1a** with **2a** (2.0 equiv) and polymethylhydrosiloxane (PMHS; 3.0 equiv) in the presence of the $Cu(OAc)_2$ catalyst, the bis(diphenylphosphino)benzene (dppbz) ligand, and the cesium pivalate base in 1,4-dioxane at room temperature afforded the desired hydroallylated product **3a** regioselectively in 34% yield. However, as mentioned in Scheme 3, the *gem*-difluoroalkene **4a** was also observed in 30% yield (Table 1, entry 1). Inspired by the preliminary result and the previously observed positive effect of substituents at the remote position in the bisphosphine ligands to suppress the β-F elimination,[16c] we then tested several modified dppbz-type ligands. Although the electron-withdrawing substituents completely shut down the conversion of **1a** (entry 2), the introduction of electron-donating groups at the remote meta and/or para positions generally increased the hydroallylation selectivity over the hydrodefluorination except for the *t*Bu-dppbz ligand (entries 3–7). In particular, the MeO-dppbz ligand furnished the desired **3a** in 80% yield without any detection of **4a** (entry 6). On the other hand, the *o*-methyl-substituted *o*-Me-dppbz resulted in no reaction because of steric factors (entry 8). The judicious choice of exter-

nal base was critical: the related CsOAc also promoted the reaction (entry 9), but the sluggish conversion was observed with the less basic KOAc and NaOAc (entry 10). Moreover, the more basic LiO*t*Bu and NaO*t*Bu, which are frequently employed in related Cu-catalyzed hydrofunctionalizations of alkenes,[15-19] mainly formed the *gem*-difluoroalkene **4a** (entries 11 and 12). This is probably because of the higher affinity of Li and Na cations to the fluorine atom[22] to accelerate the β-F elimination.[21b] Finally, an increase in the amount of PMHS to 4.0 equiv further improved the yield of **3a** to 94% (90% isolated yield; entry 13). As shown in entries 4 and 5, TMS-dppbz and *t*Bu-dppbz also gave a high conversion of **1a** but with a low product selectivity. To increase the selectivity for **3a**, we added 18-crown-6 because it can accommodate the Cs cation to suppress the undesired interaction between the Lewis acidic Cs cation and the Lewis basic fluorine atom in the α-CF_3 alkylcopper intermediate **D** for the β-F elimination (Figure 1)[23] Gratifyingly, the chemoselectivity was dramatically changed, and the desired **3a** was obtained in 85% and 99% yields (entries 14 and 15, respectively). However, the positive effect was somewhat unique, and 18-crown-6 was detrimental to the optimal $Cu(OAc)_2$/MeO-dppbz-catalyzed conditions (entry 16). Additional observations in the optimization studies are to be noted. Other common monodentate and bidentate phosphine ligands showed much poorer performance; some other ethereal solvents and hydrosilanes also promoted the reaction, but the combination of 1,4-dioxane and PMHS proved to be best from the viewpoint of cost and performance. The chloride leaving group was the key to success, and the corresponding allylic bromide, acetate, carbonate, and phosphate did not form the hydroallylated product at all; the allylic bromide was too reactive and was rapidly consumed by a direct reduction with the copper hydride (reaction of **C** with **2** to **5** in Scheme 3), whereas other allylic alcohol derivatives only gave the *gem*-difluoroalkene **4** probably because of less reactivity with the α-CF_3 alkylcopper intermediate (reaction of **D** with **2** to give **3** in Scheme 3). Thus, the reactivity balance of the allylic electrophile is also of great importance (see the Supporting Information for more detailed optimization studies and control experiments with only two reaction components).

Table 1. Optimization Studies for Copper-Catalyzed Regioselective Hydroallylation of 1-Trifluoromethylalkene 1a with PMHS and Allyl Chloride 2a[a]



entry	ligand	additives	yield (%)[b]	
			3a	**4a**
1	dppbz	CsOPiv	34	30
2	CF_3-dppbz, *p*-CF_3-dppbz, or F_3-dppbz	CsOPiv	0	0
3	DTBM-dppbz	CsOPiv	76	13
4	TMS-dppbz	CsOPiv	58	30
5	*t*Bu-dppbz	CsOPiv	0	78
6	MeO-dppbz	CsOPiv	80	0
7	*p*-*t*Bu-dppbz	CsOPiv	43	24
8	*o*-Me-dppbz	CsOPiv	0	0
9	MeO-dppbz	CsOAc	67	0
10	MeO-dppbz	KOAc or NaOAc	~10	trace
11	MeO-dppbz	LiO*t*Bu	4	34
12	MeO-dppbz	NaO*t*Bu	20	44
13[c]	MeO-dppbz	CsOPiv	94 (90)	0
14	TMS-dppbz	CsOPiv, 18-crown-6	85	9
15	*t*Bu-dppbz	CsOPiv, 18-crown-6	99 (93)	0
16[c]	MeO-dppbz	CsOPiv, 18-crown-6	51	11

[a]Conditions unless specific otherwise: **1a** (0.25 mmol), PMHS (0.75 mmol based on Si–H), **2a** (0.50 mmol), $Cu(OAc)_2$ (0.025 mmol), ligand (0.025 mmol), additives (0.50 mmol), 1,4-dioxane (1.5 mL), rt, 6 h, N_2. [b] Estimated by ^{1}H NMR. Isolated yields are given in parentheses. [c] With 1.0 mmol of PMHS based on Si–H.

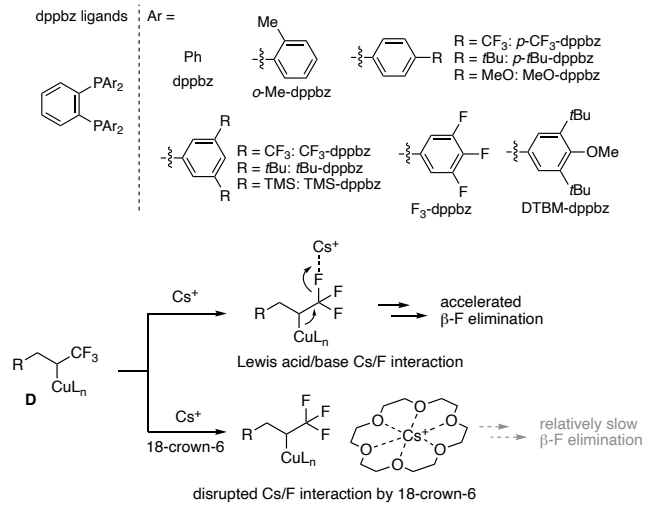


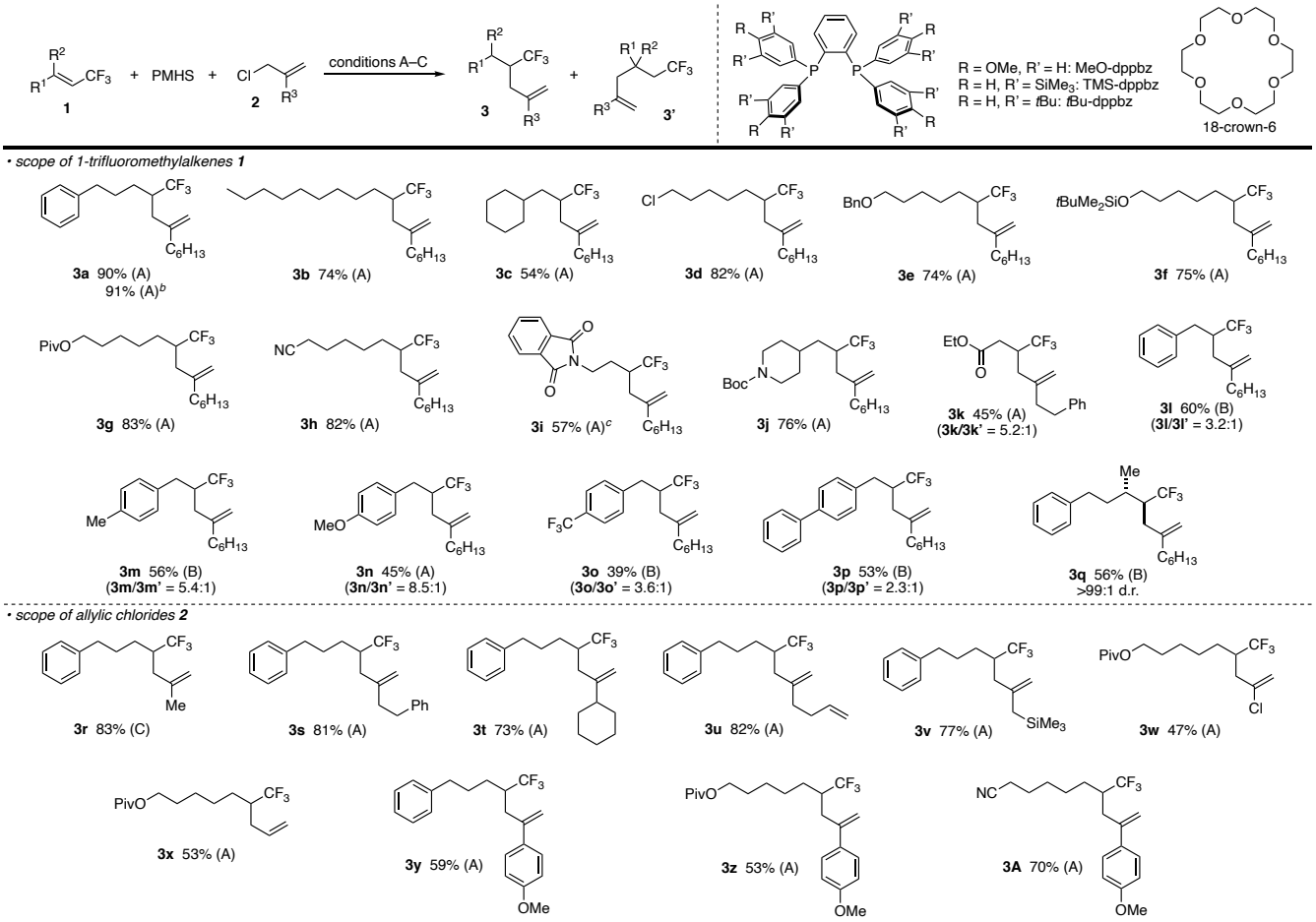
Figure 1. Possible mechanism of the undesired β-F elimination promoted by Cs cation and role of 18-crown-6.

We then examined the substrate scope of the Cu-catalyzed hydroallylation (Scheme 4). The crown-ether-free, MeO-dppbz-promoted conditions (conditions A) were generally successfully applied, but in some specific cases the crown-ether-assisted, TMS-dppbz- and *t*Bu-dppbz-ligated Cu catalysis (conditions B and C, respectively) showed better performance. In addition to the model substrate (**1a**), the primary and secondary alkyl-substituted 1-trifluoromethylalknenes were successfully coupled with **2a** to form the corresponding hydroallylated products **3b**, **c** in 74% and 54% yields, respectively. The reaction conditions were also compatible with several common functional groups, including the alkyl chloride, benzyl ether, silyl ether, ester, nitrile, phthalimide, and Boc-protected amine (**3d**–**j**). The ester-conjugated substrate **1k** also participated in the reaction to give **3k** as the major regioisomer. In the cases of styrenyl-type

substances **1l**–**p**, mixtures of regioisomers were generally formed, probably due to the aryl-vinyl conjugation[24] being competitive with the electron-withdrawing nature of the CF_3 group in the insertion step (**C** to **D** in Scheme 3), but the desired products could be isolated in synthetically useful yields by chromatographic purification (**3l**–**p**). As a general trend, the introduction of electron-donating groups increased the regioselectivity.[25] It is noteworthy that the trisubstituted alkene **1q** was selectively converted to **3q** with high regio- and diastereoselectivity.[26] The reaction could also be performed on a 1.0 mmol scale without any erosion of yield and selectivity (**3a**), thus indicating the good reproducibility.

The scope of allylic chlorides **2** was also broad: the methyl-, phenethyl-, and cyclohexyl-substituted **2b**–**d** underwent the reaction smoothly to furnish **3r**–**t** in 73–81% yields. The copper-catalyzed conditions tolerated the isolated terminal alkene and allylsilane functions (**3u**, **v**), which can be useful synthetic handles for further manipulations. Notably, the reaction with **2g** selectively occurred at the allyl position to afford **3w** with the vinyl chloride left intact. Additionally, the parent allyl chloride (**2h**) and aryl-substituted allyl chloride **2i** were accommodated under the standard conditions to deliver the corresponding **3x**–**z**, and **3A** in good yields.

Scheme 4. Products of Cu-Catalyzed Regioselective Hydroallylation of 1-Trifluoromethylalkenes 1 with PMHS and Allylic Chlorides 2[a]



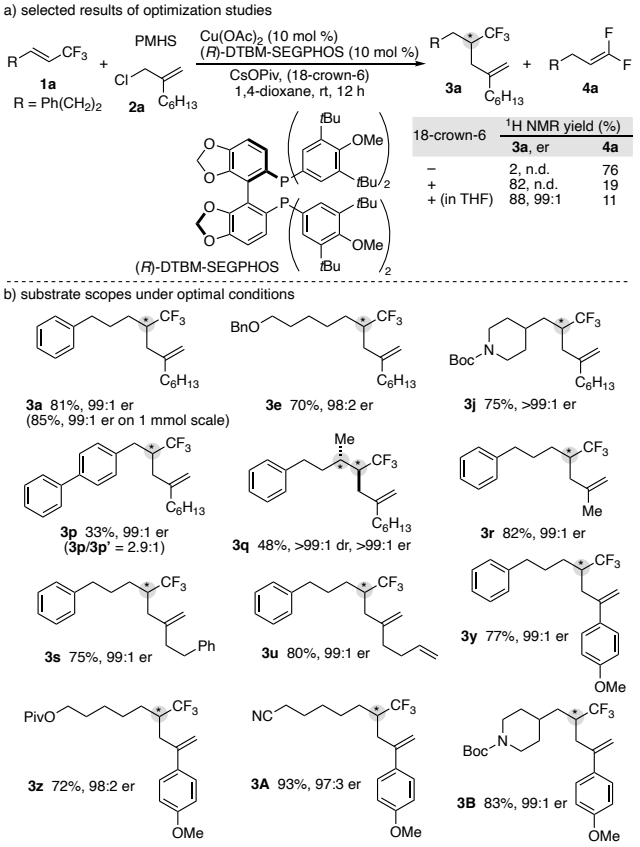
[a]Conditions A: **1** (0.25 mmol), PMHS (1.0 mmol of PMHS based on Si–H), **2** (0.50 mmol), CsOPiv (0.50 mmol), $Cu(OAc)_2$ (0.025 mmol), MeO-dppbz (0.025 mmol), 1,4-dioxane (1.5 mL), rt, 6 h. Conditions B: **1** (0.25 mmol), PMHS (0.75 mmol of PMHS based on Si–H), **2** (0.50 mmol), CsOPiv (0.50 mmol), 18-crown-6 (0.50 mmol), $Cu(OAc)_2$ (0.025 mmol), TMS-dppbz (0.025 mmol), 1,4-dioxane (1.5 mL), rt, 6 h; Conditions C. **1** (0.25 mmol), PMHS (0.75 mmol of PMHS based on Si–H), **2** (0.50 mmol), CsOPiv (0.50 mmol), 18-crown-6 (0.50 mmol), $Cu(OAc)_2$ (0.025 mmol), *t*Bu-dppbz (0.025 mmol), 1,4-dioxane (1.5 mL), rt, 6 h. Isolated yields of pure regioisomers are shown. The conditions employed (A, B, or C) are given in parentheses. The dr was determined by ^{1}H NMR in the crude product. [b]On a 1.0 mmol scale. [c]With $(EtO)_3SiH$ (0.75 mmol) instead of PMHS.

We next moved our attention to the development of asymmetric catalysis. Unfortunately, the simple replacement of the MeO-dppbz ligand with chiral bisphosphine ligands was detrimental as far as we tested. For example, the reaction of **1a** with PMHS and **2a** in the presence of the $Cu(OAc)_2$/(*R*)-DTBM-SEGPHOS catalyst and CsOPiv base dominantly produced the *gem*-difluoroalkene **4a** in 76% yield. The targeted **3a** was formed only in 2% yield (Scheme 5a; see the Supporting Information for more details). However, similar to the

cases of TMS- and *t*Bu-dppbz ligands (entries 14 and 15 in Table 1), the addition of 18-crown-6 dramatically improved the chemoselectivity to form **3a** in 82% yield. Additional fine tunings proved THF to be a somewhat better solvent, and the enantioenriched hydroallylated product was finally obtained in 88% yield with 99:1 enantiomeric ratio (er). Under the optimal 18-crown-6-assisted enantioselective conditions, various combinations of 1-trifluoromethylalkenes **1** and allylic chlorides **2** were successfully employed (Scheme 5b). A benzyl ether (**3e**), Boc-protected amine (**3j, 3B**), isolated terminal alkene (**3u**), ester (**3z**), and nitrile (**3A**) were equally tolerated to give the corresponding hydroallylated products with 97:3 to 99:1 er.

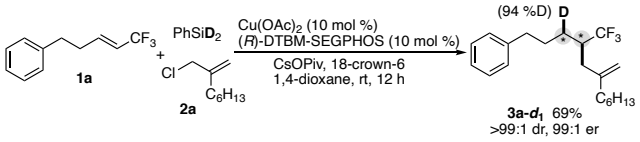
As same under the nonenantioselective conditions in Scheme 4, the aryl-conjugated system **1p** afforded a mixture of regioisomers **3p** and **3p'**, but the desired isomer was successfully isolated with high enantiopurity (**3p**; 99:1 er). Particularly notable is the successful control of both diastereoselectivity and enantioselectivity in the production of **3q**. The enantioselective reaction could also be conducted on a 1.0 mmol scale without any drop in the yield and enantioselectivity (**3a**). Furthermore, an asymmetric catalysis with Ph_2SiD_2 successfully synthesized the deuterium-labeled chiral CF_3-substituted molecule **3a**-d_1 (Scheme 6), which has applications in biological labeling studies and drug discovery.[27] Additionally, the result can also support the mechanistic hypothesis in Scheme 3, in which the copper hydride species **A** is formed from the hydrosilane and the hydride is finally transferred to the product **3** via the alkyl copper intermediate **D**.

Scheme 5. Copper-Catalyzed Regio- and Enantioselective Hydroallylation of 1-Trifluoromethylalkenes 1[a]



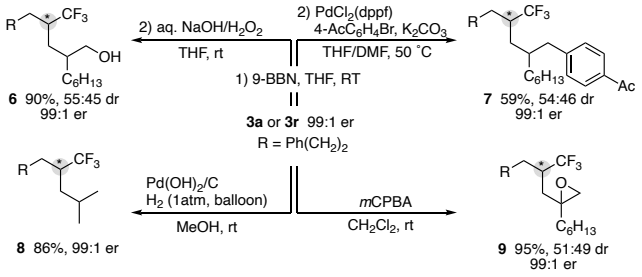
[a]Optimal conditions: **1** (0.25 mmol), **2** (0.50 mmol), PMHS (0.75 mmol based on Si–H), 18-crown-6 (0.63 mmol), $Cu(OAc)_2$ (0.025 mmol), (*R*)-DTBM-SEGPHOS (0.025 mmol), CsOPiv (0.50 mmol), THF (1.5 mL), rt, 12 h, N_2. Isolated yields of pure regioisomers are shown. The enantiomeric ratio (er) was determined by HPLC analysis on a chiral stationary phase.

Scheme 6. Synthesis of Deuterium-Labeled Chiral 3a-d_1



The allylic function in the optically active **3a**, **r** could be readily derivatized (Scheme 7). A regioselective hydroboration with 9-BBN was followed by an oxidation with aqueous H_2O_2 to form the chiral alcohol **6** in 90% yield. A Suzuki-Miyaura coupling of the same alkylborane intermediate was also possible, delivering **7** in 59% overall yield. Additionally, the chiral alkane **8** and epoxide **9** were obtained in high yields by the standard hydrogenation and epoxidation reactions, respectively. All transformations proceeded without any erosion of enantiomeric excess.

Scheme 7. Derivatizations of 3a, r[a]



[a]See the Supporting Information for detailed conditions.

To get some insight into the allylation process (**D** and **2** to **A** and **3** in Scheme 3), the regioisomeric allyl chlorides 3-chlorobut-1-ene (**2j**) and 1-chlorobut-2-ene (**2j'**) were tested under the nonenantioselective conditions using MeO-dppbz (Scheme 8a). The branched **2j** reacted with **1a** to deliver a mixture of linear **3C** and branched **3C'** in favor of linear **3C**. On the other hand, the linear **2j'** also formed a regioisomeric mixture, but the **3C**/**3C'** ratio was reversed; the branched **3C'** was mainly observed. The replacement of MeO-dppbz with TMS-dppbz and *t*Bu-dppbz, in conjunction with 18-crown-6, also resulted in similar trends (see the Supporting Information for details). These phenomena suggest that the S_N2'-type addition-elimination-type mechanism[28] is mainly operating, while the formation of π-allyl- or π-en-σ-yl copper species[29] is competitively involved, particularly in a case of sterically congested allylic chloride such as **2j'** (Scheme 8b). The different *E:Z* ratios of the starting **2j'** (*E:Z* = 5:1) and the linear product **3C** (*E:Z* > 20:1) can also support involvement of the π-allyl- or π-en-σ-yl copper intermediate and its rapid *E:Z* (*syn/anti*) isomerization. Actually, the more hindered prenyl chloride (**2k**) and cinnamyl chloride (**2l**) gave the corresponding liner hydroallylated products (**3D**, **E**, respectively) exclusively (Scheme 8c), probably via the formation of π-allyl- or π-en-σ-yl copper then reductive elimination at the more sterically accessible position.[30] Attempts to control the regioselectivity in the allylation step are still ongoing.

Finally, we examined the effects of KOPiv and KOPiv/18-crown-6 on the initial reaction rate of hydrodefluorination of **1a** with $(MeO)_2MeSiH$ to **4a** under stoichiometric conditions using 1.0 equiv of $Cu(OAc)_2$ and TMS-dppbz (Figure 2).[31] In comparison to the parent conditions without any additives, the addition of KOPiv increased the initial rate by 1.57 times, thus indicating the alkali cation accelerated β-F elimination from the α-CF_3 alkylcopper (Figure 1, top). On the other hand, when the combination of KOPiv and 18-crown-6 was used, relatively moderate acceleration (1.22 times) was observed. The result is consistent with our assumption that 18-crown-6 disrupts the interaction of the alkali cation and fluorine atom to decrease the rate of the β-F elimination (Figure 1, bottom).

Scheme 8. Reactions with 1- or 3-Substituted Allyl Chlorides 2

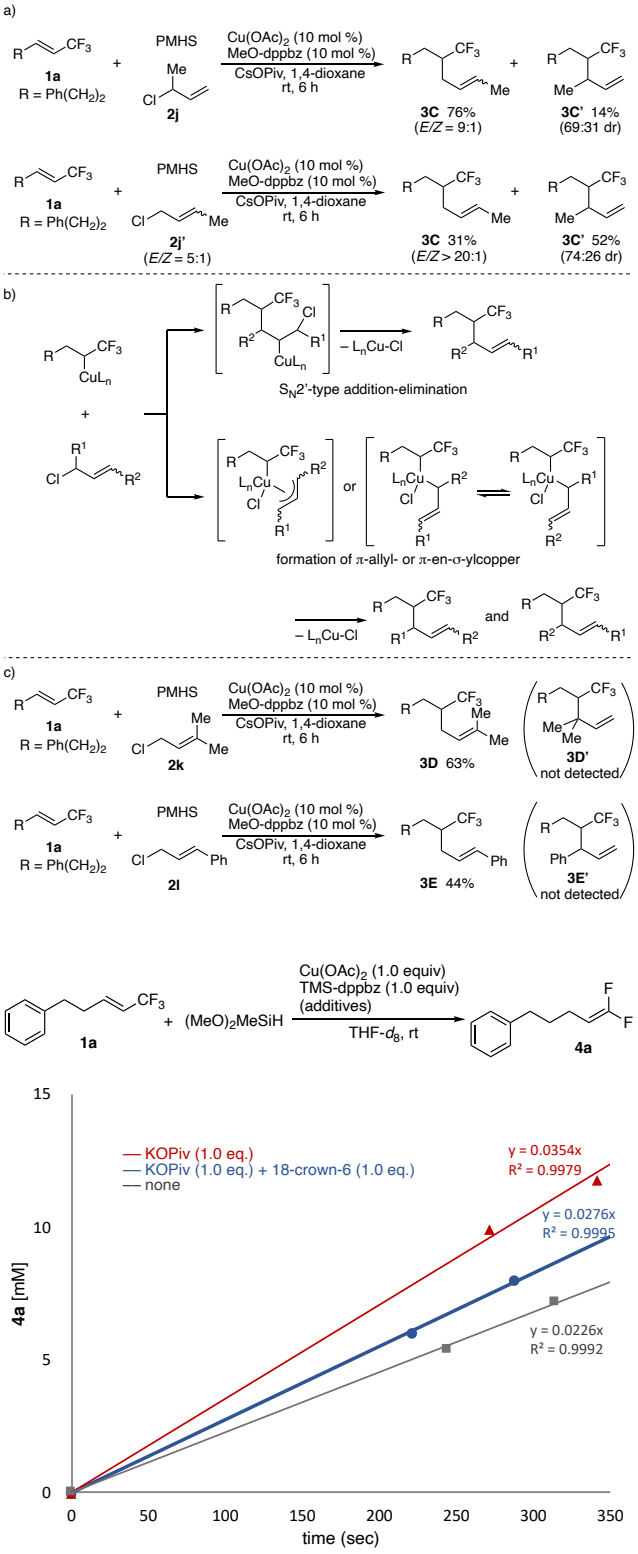


Figure 2. Effects of additives on the initial reaction rate in the hydrodefluorination of **1a** with $(MeO)_2MeSiH$.

In conclusion, we have developed a CuH-catalyzed regio- and enantioselective hydroallylation of 1-trifluoromethylalkenes. The key to success is the combined use of 18-crown-ether and CsOPiv base to suppress the otherwise predominant β-F elimination from an α-CF_3 organocopper intermediate. The asymmetric Cu

catalysis successfully controls the point chirality at the position α to CF_3 even in the absence of any proximal directing heteroatoms. The present strategy can provide a new repertoire of CF_3-containing chiral molecules, which have high potential in medicinal and pharmaceutical chemistry. Elucidation of the detailed mechanism and further development of related enantioselective hydrofunctionalization reactions are currently underway in our laboratory.

ASSOCIATED CONTENT

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Complete contact information is available at: https://pubs.acs.org/10.1021/xxxx.

Notes

The authors declare no competing financial interest.

Supporting Information

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

^1H, $^{13}C\{^1H\}$, and $^{19}F\{^1H\}$ NMR spectra, detailed optimization studies, experimental procedures, control experiments with two-components, and kinetic experiments (PDF)

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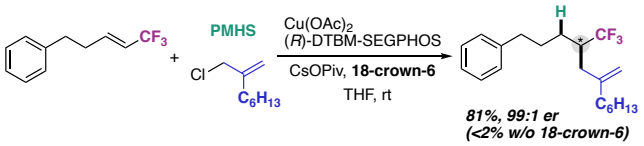
(31) In the kinetic experiments, we chose $(MeO)_2MeSiH$, TMS-dppbz, and KOPiv as the optimal hydrosilane, ligand, and base, respectively, because other combinations provided a heterogeneous system and thus irreproducible results. See the Supporting Information for details.



81%, 99:1 er
(<2% w/o 18-crown-6)