Synthesis of α-Trifluoromethylamines by Cu-Catalyzed Regio- and Enantioselective Hydroamination of 1-Trifluoromethylalkenes

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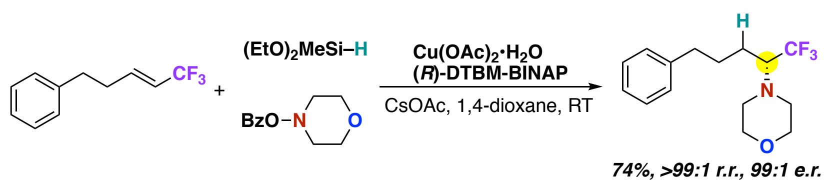
Supporting Information Placeholder

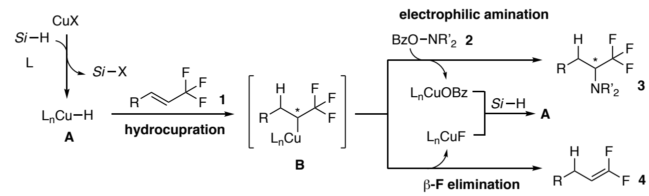


ABSTRACT: A copper-catalyzed regioselective net hydroamination of 1-trifluoromethylalkenes with hydrosilanes and hydroxylamines has been developed. The judicious choice of ligand and additive suppresses the conceivable but undesired β-F elimination of an α-CF_3-substituted organocopper intermediate, leading to targeted α-trifluoromethylamines in good yields with excellent regioselectivity. Additionally, with an appropriate chiral bisphosphine ligand the enantioselective reaction is also possible to deliver optically active α-trifluoromethylamines of high potential in medicinal and pharmaceutical chemistry.

The introduction of fluorine into organic molecules can increase the lipophilicity and metabolic stability, and organofluorine compounds thus have received significant attention in the design of new drug candidates and agrochemicals.[1] Among them, α-trifluoromethylamines are proposed to be amide isosteres and frequently occur in biologically active compounds.[2] Thus, the development of their efficient synthetic methods, particularly catalytic asymmetric synthesis, has been a long-standing topic in the synthetic community. The most common approaches to the above α-trifluoromethylamine structure include the reduction[3] or carbon nucleophile addition[4] of trifluoromethyl-substituted imines and nucleophilic trifluoromethylation[5] of simple imines.[6] Herein, we report an alternative strategy using a 1-trifluoromethylalkene as a starting platform: A copper-catalyzed regio- and enantioselective hydroamination[7] of trifluoromethylalkenes with hydrosilanes and hydroxylamines is described. The copper catalysis relies on an umpolung, electrophilic amination strategy[8] and thus delivers the α-trifluoromethylamines with excellent regioselectivity, which can be difficult to achieve under conventional nucleophilic hydroamination catalysis due to the Michael acceptor nature of trifluoromethylalkene. Additionally, the asymmetric catalysis ligated with an appropriate chiral bisphosphine enables the enantioselective synthesis of chiral alkyl-substituted α-trifluoromethylamines, which are still challenging by means of reported methods.[9]

Our working scenario is shown in Scheme 1, which is based on the recent success of net hydroamination of relatively electronically neutral alkenes, originally and independently developed by our group[10] and the Buchwald research group.[11] A L_nCu-H species **A**, which is initially generated from a Cu salt, ancillary ligand, and hydrosilane,[12] undergoes the hydrocupration with the 1-trifluoromethylalkene **1** to form the organocopper intermediate **B**; where the CF_3 group works as the strong electron-withdrawing group, and thus **B** would be formed as the preferable regioisomer.[13] Subsequent electrophilic amination with the hydroxylamine derivative **2** occurs to deliver the desired α-trifluoromethylamine **3** regioselectively.[14] The concurrently formed L_nCuOBz is converted to the starting copper hydride **A** with the second hydrosilane to complete the catalytic cycle. If the enantioselectivity is also controlled by an appropriate chiral ligand in the insertion step (**A** to **B**), then the stereodefined α-CF_3-substituted organocopper is formed, leading to the corresponding optically active **3** catalytically through the stereoretentive electrophilic amination.[15] However, the intermediate **B** contains the fluorine atom at position β to Cu and thus can easily decompose via β-F elimination to afford the undesired *gem*-difluoroalkene **4**. Actually, such an elementary step is reported in several transition-metal-catalyzed reactions with fluoroalkene substrates.[13,16] Therefore, suppression of the undesired β-F elimination is the most important and challenging task for the development of regio- and stereoselective net hydroamination of 1-trifluoromethylalkene.

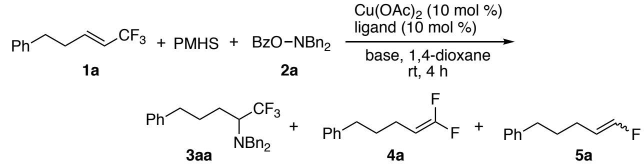
Scheme 1. Working Hypothesis: Net Hydroamination versus Hydrodefluorination of 1-Trifluoromethylalkene 1[a]



[a]Bz = benzoyl, L = ligand.

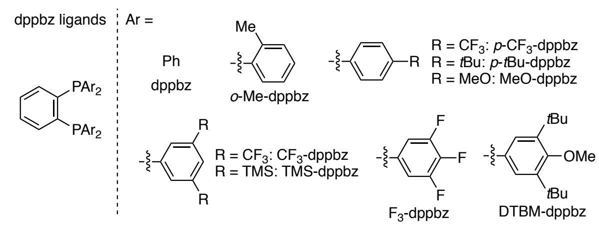
On the basis of the aforementioned hypothesis, we began our optimization studies by using 1-trifluoromethylalkene **1a** (0.25 mmol), *N,N*-dibenzylhydroxylamine **2a** (1.5 equiv), and polymethylhydrosiloxane (PMHS) to identify the appropriate ligand in the presence of $Cu(OAc)_2$ catalyst and CsOAc base (Table 1). An initial experiment with 1,2-bis(diphenylphosphino)benzene (dppbz) afforded the targeted α-trifluoromethylamine **3aa** regioselectively, but expectedly the *gem*-difluoroalkene **4a** was preferably formed (entry 1). Notably, the substituent on the phosphorus of dppbz ligand gave a significant impact on the product selectivity. While the electron-withdrawing CF_3-, *p*-CF_3-, and F_3-dppbzs resulted in almost no conversion (entries 2–4), electron-donating substituents at the meta- or para-position suppressed the undesired β-F elimination to furnish the desired **3aa** with better chemoselectivity (entries 5–8). Particularly, the para-*tert*-butyl-substituted *p*-*t*Bu-dppbz ligand proved to be best, delivering **3aa** in 76% ^{1}H NMR yield, albeit with 10% concomitant formation of the over-reduced monofluoroalkene **5a** (entry 8).[16c] On the other hand, the more sterically hindered *o*-Me-dppbz showed no activity (entry 9), thus suggesting the important role of remote steric hindrance in the chemoselective net hydroamination of **1a**.[17] Additionally, the effect of the base was critical: Weaker acetate bases such as LiOAc and NaOAc gave poor conversion (entries 10 and 11) whereas the defluorinated **4a** was predominantly formed with LiO*t*Bu and NaO*t*Bu (entries 12 and 13), which are usually optimal bases in our previous net hydroamination of alkenes.[10] The observed trend apparently indicates that the Lewis acidic alkali cations with smaller ionic radius promoted the undesired β-F elimination because of their higher fluorine affinity, as illustrated in Figure 1.[18] On the other hand, no reaction occurred without any external bases (entry 14); the exact reason was not clear, but in our catalyst system with the *p*-*t*Bu-dppbz ligand, the external base might be essential for generation of the copper hydride species. After additional fine-tuning, we finally obtained the desired **3aa** in 85% ^{1}H NMR yield (70% isolated yield) with $Cu(OAc)_2$•H_2O/*p*-*t*Bu-dppbz catalyst, CsOAc base, and $(EtO)_2MeSiH$ (entry 15).[19] The reaction could also be conducted on a 1.0 mmol scale, thus indicating the good reproducibility of this process.

Table 1. Optimization Studies for Copper-Catalyzed Regioselective Net Hydroamination of 1-Trifluoromethylalkene 1a with *N,N*-Dibenzylhydroxylamine 2a[a]



entry	ligand	base	yield (%)[b] 3aa	4a	5a
1	dppbz	CsOAc	29	35	0
2	CF_3-dppbz	CsOAc	0	0	0
3	*p*-CF_3-dppbz	CsOAc	0	0	0
4	F_3-dppbz	CsOAc	0	0	0
5	DTBM-dppbz	CsOAc	68	0	20
6	TMS-dppbz	CsOAc	71	0	11
7	MeO-dppbz	CsOAc	36	0	0
8	*p*-*t*Bu-dppbz	CsOAc	76	0	<10
9	*o*-Me-dppbz	CsOAc	0	0	0
10	*p*-*t*Bu-dppbz	LiOAc	0	0	0
11	*p*-*t*Bu-dppbz	NaOAc	0	0	0
12	*p*-*t*Bu-dppbz	LiO*t*Bu	34	37	0
13	*p*-*t*Bu-dppbz	NaO*t*Bu	10	36	0
14	*p*-*t*Bu-dppbz	none	0	0	0
15[c]	*p*-*t*Bu-dppbz	CsOAc	85 (70, 61[d])	0	0

[a] Conditions: **1a** (0.25 mmol), **2a** (0.38 mmol), PMHS (0.75 mmol based on Si–H), $Cu(OAc)_2$ (0.025 mmol), ligand (0.025 mmol), base (0.50 mmol), and 1,4-dioxane (1.5 mL), rt, 4 h, N_2. [b] Estimated by ^{1}H NMR. Isolated yield in parentheses. [c] With $Cu(OAc)_2$•H_2O and $(EtO)_2MeSiH$ instead of $Cu(OAc)_2$ and PMHS. [d] On a 1.0 mmol scale. Bn = benzyl, Bz = benzoyl.



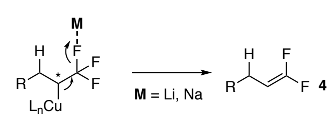
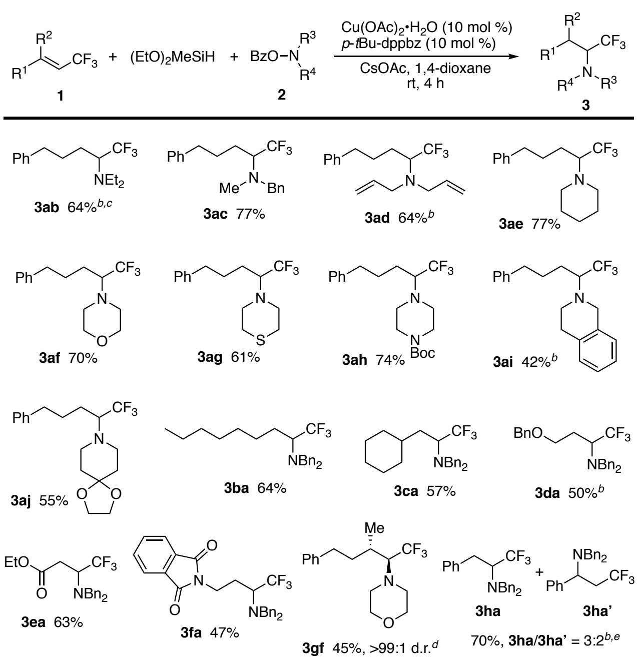


Figure 1. Possible mechanism of undesired β-F elimination promoted by Lewis acidic metals.

With the optimal conditions in hand (Table 1, entry 15), we examined the substrate scope of the catalytic hydroamination (Scheme 2). In addition to **2a**, some acyclic hydroxylamines bearing *N,N*-diethyl, *N*-benzyl-*N*-methyl, and *N,N*-diallyl groups could be coupled with **1a** to form the corresponding α-trifluoromethylamines **3ab**–**3ad** in good yields as the single regioisomers. In the case of **3ad**, the CF_3-substituted alkene moiety was preferably hydroaminated over the allylic system.[11g] The copper catalysis was also compatible with cyclic amines, including piperidine, morpholine, thiomorpholine, Boc-protected piperazine, and tetrahydroisoquinoline (**3ae**–**3ai**). The acetal-protected piperidone could also be employed (**3aj**); the protecting group of which can be readily removed to form the corresponding NH_2 amine.[20] The reactions of several 1-trifluoromethylalkenes **1** with **2a** were also performed. The aliphatic primary and secondary alkyl-substituted substrates underwent the regioselective hydroamination to afford the corresponding amines **3ba** and **3ca** in acceptable yields. Additionally, the ether, ester, and phthalimide functional groups were tolerated under the standard conditions (**3da**–**3fa**). Notably, the reaction system also accommodated the trisubstituted 1-trifluoromethylalkene to deliver **3gf** as the single diastereomer.[21] On the other hand, the styrenyl-type substrate gave a 3:2 regiomixture of **3ha** and **3ha**', which can be attributed to the competitive Ph-vinyl conjugation[22] in the hydrocupration step (**A** to **B** in Scheme 1). In some cases, the yield of the desired **3** was relatively low; no full conversion of **1** was observed, and sometimes simply reduced trifluoromethylalkanes were also detected as the side products.

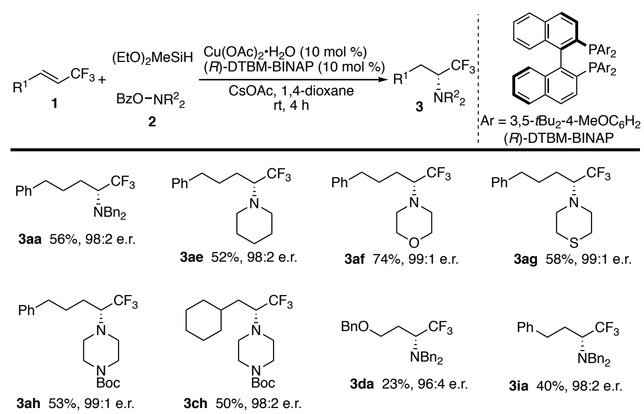
Scheme 2. Copper-Catalyzed Regioselective Net Hydroamination of Various 1-Trifluoromethylalkenes 1 and Hydroxylamines 2*a*



*a*Conditions: **1** (0.25 mmol), **2** (0.38 mmol), $(EtO)_2MeSiH$ (0.75 mmol), $Cu(OAc)_2$•H_2O (0.025 mmol), *p*-*t*Bu-dppbz (0.025 mmol), CsOAc (0.50 mmol), 1,4-dioxane (1.5 mL), rt, 4 h, N_2. Yields of isolated products are given. *b* With PMHS instead of $(EtO)_2MeSiH$. *c* Without CsOAc. *d* With TMS-dppbz instead of *p*-*t*Bu-dppbz. *e* Starting from 9:1 *E/Z* mixture. Boc = *tert*-butoxycarbonyl.

As mentioned in Scheme 1, an appropriate chiral bisphosphine ligand can successfully induce the enantioselectivity. After the extensive screening (see the Supporting Information for detail), we were pleased to find that the $Cu(OAc)_2$•H_2O/(*R*)-DTBM-BINAP complex catalyzed the enantioselective hydroamination of **1a** with **2a** to provide the enantioenriched **3aa** in 56% yield with a 98:2 enantiomeric ratio (e.r.; Scheme 3). The observed high stereoinduction and acceptable reactivity were unique to the (*R*)-DTBM-BINAP; attempts to apply related (*R*)-DTBM-SEGPHOS and (*R*)-DTBM-MeO-BIPHEP remained unsuccessful. Regardless of steric and electronic nature of hydroxylamine used, the $Cu(OAc)_2$•H_2O/(*R*)-DTBM-BINAP asymmetric catalysis uniformly produced the corresponding optically active α-trifluoromethylamines **3ae**–**3ah** with excellent enantioselectivity (98:2–99:1 e.r.). Other 1-trifluoromethylalkenes **1c** and **1d** were also successfully converted to the chiral amines **3ch** and **3da** with 98:2 and 96:4 e.r., respectively. The absolute configuration was assigned to be *R* by the preparation of known compound **3ia** (40%, 98:2 e.r.) under the present $Cu(OAc)_2$•H_2O/(*R*)-DTBM-BINAP catalysis (see the Supporting Information for details).

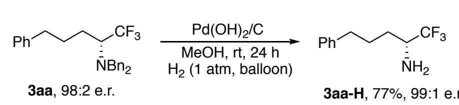
Scheme 3. Copper-Catalyzed Regio- and Enantioselective Net Hydroamination of 1-Trifluoromethylalkenes 1 and Hydroxylamines 2*a*



*a*Conditions: **1** (0.25 mmol), **2** (0.38 mmol), $(EtO)_2MeSiH$ (0.75 mmol), $Cu(OAc)_2$•H_2O (0.025 mmol), (*R*)-DTBM-BINAP (0.025 mmol), CsOAc (0.50 mmol), and 1,4-dioxane (1.5 mL), rt, 4 h, N_2.

Finally, we derivatized the optically active *N,N*-dibenzylamine **3aa** (Scheme 4). The hydrogenolysis of benzyl protection readily afforded the corresponding primary amine **3aa-H** in 77% yield without loss of enantiomeric excess. The product obtained can be an important building block for more complicated and chiral CF_3-containing amino compounds.

Scheme 4. Derivatization of Optically Active 3aa



In conclusion, we have developed an umpolung-enabled copper-catalyzed regio- and enantioselective net hydroamination of 1-trifluoromethylalkenes with hydrosilanes and hydroxylamines. By the judicious choice of an ancillary ligand and additive, the undesired β-F elimination process is effectively suppressed to deliver the optically active α-trifluoromethylamines of great interest in medicinal application. In particular, the copper catalysis successfully produces the alkyl-substituted α-trifluoromethylamines, which are still challenging by means of reported methods, and thus complements the precedented strategies.[9] The newly developed protocol, particularly for the generation of stereodefined α-CF_3-substituted organocopper species, will find wide applications in further development of related copper-catalyzed multicomponent coupling reactions with 1-trifluoromethylalkenes for the synthesis of versatile CF_3-containing complex molecules, which are of great importance in medicinal and pharmaceutical research fields.

ASSOCIATED CONTENT

Supporting Information

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

^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(19) See the Supporting Information for more detailed optimization studies. We do not have an explanation for the exact reason why *p-t*Bu-dppbz effectively suppressed the undesired β-F elimination, but one possibility is the attractive London dispersion, which can accelerate the reaction of organocopper intermediate with the hydroxylamine, see: (a) Liptrot, D. J.; Power, P. P. *Nat. Rev. Chem.* **2017**, *1*, 0004. (b) Lu, G.; Liu, R. Y.; Yang, Y.; Fang, C.; Lambrecht, D. S.; Buchwald, S. L.; Liu, P. *J. Am. Chem. Soc.* **2017**, *139*, 16548.

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