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Synthesis of *gem*-Difluoroalkenes by Copper-catalyzed Regioselective Hydrodefluorination of 1-Trifluoromethylalkenes

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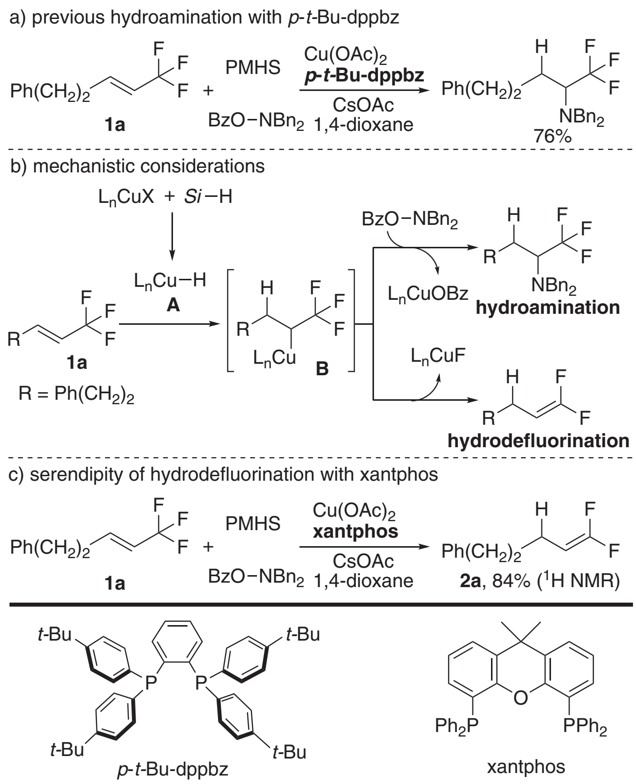
A copper-catalyzed regioselective hydrodefluorination of 1-trifluoromethylalkenes with hydrosilanes has been developed. The copper catalysis is compatible with several functional groups, including alkyl chloride, ether, ester, nitrile, and imide moieties, to form the corresponding *gem*-difluoroalkenes in good yields. Additionally, asymmetric induction is also possible by using the chiral DTBM-SEGPHOS ligand, and *gem*-difluoroalkene with point chirality at the allylic position is obtained with high enantioselectivity.

Keywords: Copper | *gem*-Difluoroalkenes | Fluorine

Because of uniquely high electron-withdrawing nature, *gem*-difluoroalkenes are isosteres of the carbonyl group[1] and thus frequently observed in pharmaceuticals and agrochemicals.[2] Additionally, they are good building blocks for functionalized mono-fluoroalkenes, which can work as the biologically important amide isostere,[3] via metal-catalyzed site-selective defluorofunctionalizations.[4] The *gem*-difluoroalkenes are generally prepared by the Wittig-type reaction of carbonyl compounds with difluoromethylenation reagents.[5] Moreover, some research groups have recently developed more convergent coupling-type processes with some CF_2 carbene precursors or CF_3CH carbene equivalents.[6] However, despite the aforementioned certain advances, there still remains a need for efficient chemical synthesis of *gem*-difluoroalkenes owing to their ubiquity in fields of organic chemistry and medicinal chemistry.

Meanwhile, we recently developed the Cu/*p*-*t*-Bu-dppbz-catalyzed regioselective net-hydroamination[7,8] of 1-trifluoromethylalkene **1a** with polymethylhydrosiloxane (PMHS) and the hydroxylamine derivative (Scheme 1a).[9] Following our mechanistic considerations, **1a** undergoes the insertion into in-situ generated copper hydride species **A**[10] to form the α-CF_3 alkylcopper intermediate **B**. Subsequent electrophilic amination with the hydroxylamine delivers the corresponding hydroaminated product. In spite of the possibility of β-F elimination from **B**,[4,11] the *p*-*t*-Bu-dppbz ligand selectively promoted the net-hydroamination reaction (Scheme 1b). During the optimization studies on this chemistry, we serendipitously found the significant ligand effect of xantphos: even in the presence of hydroxylamine, the hydrodefluorinated product, namely *gem*-difluoroalkene **2a**, was formed exclusively (Scheme 1c). The unique propensity with xantphos toward the β-F elimination prompted us to further investigate this reaction. Herein, we wish to report a Cu/xantphos-catalyzed hydrodefluorination of 1-trifluoromethylalkenes with the hydrosilane to afford the *gem*-difluoroalkenes. The copper catalysis is tolerated with several functional groups, and the corresponding *gem*-difluoroalkenes are obtained in good yields with high regioselectivity. Additionally, by the judicious choice of supporting ligand, the asymmetric induction is also possible. The related boryl-,[12]

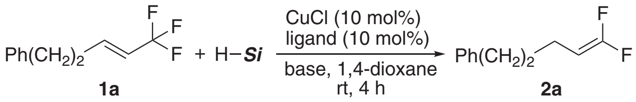


Scheme 1. Copper-catalyzed reductive functionalization of 1-trifluoromethylalkene **1a**. a) Hydroamination with *p*-*t*-Bu-dppbz ligand, b) mechanistic considerations, and c) serendipity of hydrodefluorination with xantphos ligand.

silyl,[13] alkyl-,[14] and aryldefluorination[15] reactions of 1-trifluoromethylalkenes were reported by several groups, but the reductive defluorination process still remains underdeveloped.[16]

Inspired by our initial finding (Scheme 1c), our optimization studies commenced with 1-trifluoromethylalkene **1a**, PMHS, and CuCl/xantphos catalyst in 1,4-dioxane solvent, and some bases were initially screened (Table 1). As shown in Scheme 1c, CsOAc was a good base, giving the *gem*-difluoroalkene **2a** in 75% ^1H NMR yield (Entry 1). Consistent with our previous observation[9] and recent mechanistic insight[11b] that smaller alkali metal cations can accelerate the β-F elimination process, lithium and sodium alkoxide bases also worked well, and the targeted **2a** was obtained in yields comparable to that with CsOAc (Entries 2–5). In particular, NaO-*t*-Bu and NaOTMS showed better performance to deliver **2a** in 87% and 92% isolated yields, respectively (Entries 4 and 5). Other weaker non-alkoxide bases such as KOPiv resulted in no formation of **2a** (data not shown), suggesting that relatively strong bases are necessary in the

Table 1. Optimization studies for regioselective hydrodefluorination of 1-trifluoromethylalkene **1a**.[a]

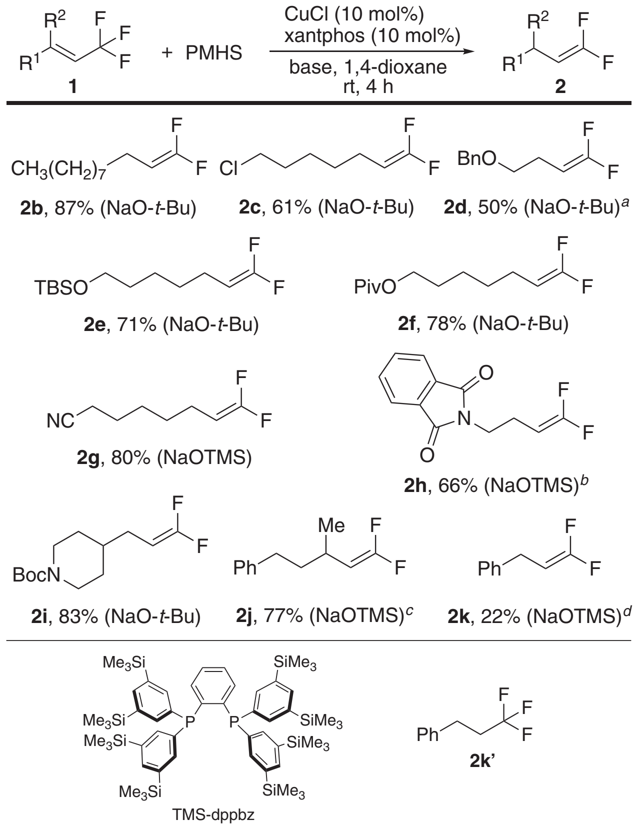


Entry	H–***Si***	Ligand	Base	Yield[b]/%
1	PMHS	xantphos	CsOAc	75
2	PMHS	xantphos	LiO-*t*-Bu	72
3	PMHS	xantphos	LiOTMS	78
4	**PMHS**	**xantphos**	**NaO-*t*-Bu**	**95 (87)**
5	**PMHS**	**xantphos**	**NaOTMS**	**>99 (92)**
6	PMHS	dppbz	NaOTMS	13
7	PMHS	dppe	NaOTMS	21
8	PMHS	dppf	NaOTMS	45
9	PMHS	DPEPhos	NaOTMS	57
10	PMHS	*rac*-BINAP	NaOTMS	59
11[c]	PMHS	PPh_3	NaOTMS	43
12	$(EtO)_2MeSiH$	xantphos	NaOTMS	38
13[d]	Ph_2SiH_2	xantphos	NaOTMS	99

[a]Conditions: CuCl (0.025 mmol), ligand (0.025 mmol), **1a** (0.25 mmol), H–***Si*** (0.75 mmol based on H–Si), base (0.50 mmol), 1,4-dioxane (1.5 mL), rt, 4 h, N_2. [b]Estimated by ^{1}H NMR with CH_2Br_2 as the internal standard. Isolated yields are in parentheses but somewhat lower than the ^{1}H NMR yield because of the volatility of **2a**. [c]With 0.050 mmol of PPh_3. [d]With 0.50 mmol of Ph_2SiH_2.

reaction. The effect of xantphos was critical: some other common phosphine ligands also promoted the reaction but with much lower efficiency (Entries 6–11). We next examined other hydrosilanes. Among them, Ph_2SiH_2 also gave an almost quantitative yield (Entry 13), but from the viewpoints of stability and cost, we identified PMHS to be the best hydride source.

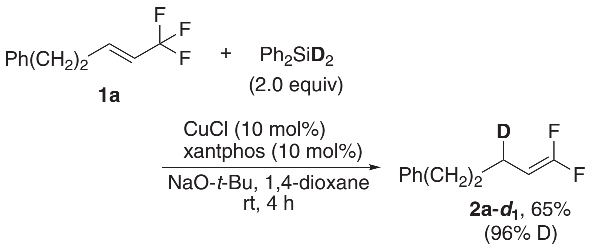
With the optimal conditions in hand, we then investigated the scope of 1-trifluoromethylalkenes **1**. The products **2** obtained are illustrated in Scheme 2, in which the best basic additive (NaO-*t*-Bu or NaOTMS) was dependent on the substrate structure and functional group. The simple aliphatic **1b** was expectedly converted to the *gem*-difluoroalkene **2b** in a good yield. The copper catalysis was compatible with alkyl chloride (**2c**), benzyl ether (**2d**), and silyl ether (**2e**) moieties. The carbonyl functions such as ester (**2f**) and nitrile (**2g**) were also tolerated under the standard conditions. Moreover, the substrates with protected nitrogen groups underwent the hydrodefluorination smoothly to form the corresponding functionalized *gem*-difluoroalkenes **2h** and **2i** in acceptable yields. Particularly notable is the successful conversion of trisubstituted alkene (**2j**) with the aid of TMS-dppbz ligand instead of xantphos, thus giving a chance of asymmetric induction by an appropriate chiral ligand (vide infra).[17] On the other hand, the Ph-conjugated **1k** resulted in a low yield of the corresponding *gem*-difluoroalkene **2k** and competitive formation of the reduced byproduct **2k′**. This is probably because the regioselectivity in the insertion into the copper hydride (Scheme 1b) is not controlled. The Ph-vinyl conjugation increases the coefficient of the LUMO at the carbon α to CF_3, thus competitively forming the regioisomeric β-CF_3 alkylcopper intermediate. A similar trend was observed also in our previous work.[9]



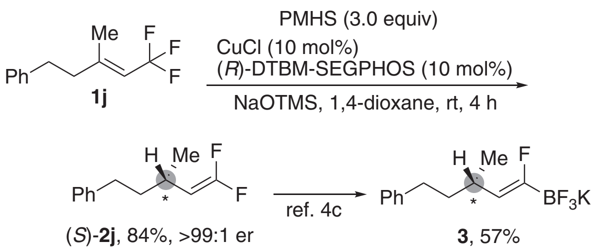
Scheme 2. *gem*-Difluoroalkene products **2** by Cu-catalyzed hydrodefluorination of 1-trifluoromethylalkenes **1**. Conditions: CuCl (0.025 mmol), xantphos (0.025 mmol), **1** (0.25 mmol), PMHS (0.75 mmol based on H–Si), base (0.50 mmol), 1,4-dioxane (1.5 mL), rt, 4 h, N_2. Isolated yields are shown. The base used (NaO-*t*-Bu or NaOTMS) is given in parentheses. [a]With PMHS (0.38 mmol based on H–Si). [b]At 50 °C. [c]With TMS-dppbz ligand instead of xantphos. [d]From a 9:1 *E*/*Z* mixture of **1k**. ^{1}H NMR yield. The reduced byproduct **2k′** was also formed in 3% ^{1}H NMR yield.

As a mechanistic probe, we subsequently performed the reaction of **1a** with the Ph_2SiD_2 instead of PMHS under otherwise identical conditions (eq 1). Expectedly, the deuterium atom was selectively incorporated at the allylic position, and the corresponding **2a-*d*$_1$** was obtained in a good yield with 96% D content. This result not only supports our initial hypothesis (Scheme 1b) but also provides access to deuterium-labeled *gem*-difluoroalkenes, which can find applications in biological labeling studies and drug discovery.[18] Finally, we attempted to apply chiral bisphosphine ligands for the asymmetric synthesis of **2j** (eq 2). Gratifyingly, the (*R*)-DTBM-SEGPHOS ligand was found to be promising to produce the enantioenriched (*S*)-**2j** in 84% yield with >99:1 enantiomeric ratio (er).[19] The product could also be transformed to the borylalkene **3**[20] under the reported conditions,[4c] which should be a useful chiral building block for various chiral fluoroalkenes.

In conclusion, we have developed a copper/xantphos-catalyzed hydrodefluorination of 1-trifluoromethylalkenes with hydrosilanes to form the corresponding *gem*-difluoroalkenes in good yields with high regioselectivity. The copper catalysis can also provide an avenue to deuterium-labeled as well as the enantioenriched *gem*-difluoroalkenes, which are of potent interest in medicinal and pharmaceutical chemistry. Ongoing work seeks to elucidate the origin of uniquely high β-F elimination performance with xantphos and develop related copper-catalyzed reductive transformations of 1-trifluoromethylalkenes.



(1)



(2)

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References and Notes

1 a) C. Leriche, X. He, C. T. Chang, H. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 6348. b) G. Magueur, B. Crousse, M. Ourévitch, D. Bonnet-Delpon, J.-P. Bégué, *J. Fluorine Chem.* **2006**, *127*, 637. c) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529.

2 a) W. R. Moore, G. L. Schatzman, E. T. Jarvi, R. S. Gross, J. R. McCarthy, *J. Am. Chem. Soc.* **1992**, *114*, 360. b) Y. Pan, J. Qiu, R. B. Silverman, *J. Med. Chem.* **2003**, *46*, 5292. c) P. M. Weintraub, A. K. Holland, C. A. Gates, W. R. Moore, R. J. Resvick, P. Bey, N. P. Peet, *Bioorg. Med. Chem.* **2003**, *11*, 427. d) J.-M. Altenburger, G. Y. Lassalle, M. Matrougui, D. Galtier, J.-C. Jetha, Z. Bocskei, C. N. Berry, C. Lunven, J. Lorrain, J.-P. Herault, P. Schaeffer, S. E. O'Connor, J.-M. Herbert, *Bioorg. Med. Chem.* **2004**, *12*, 1713. e) S. Messaoudi, B. Tréguier, A. Hamze, O. Provot, J.-F. Peyrat, J. R. De Losada, J.-M. Liu, J. Bignon, J. Wdzieczak-Bakala, S. Thoret, J. Dubois, J.-D. Brion, M. Alami, *J. Med. Chem.* **2009**, *52*, 4538.

3 a) S. Couve-Bonnaire, D. Cahard, X. Pannecoucke, *Org. Biomol. Chem.* **2007**, *5*, 1151. b) T. Taguchi, H. Yanai, In *Fluorine in Medicinal Chemistry and Chemical Biology*; I. Ojima, Ed.; Blackwell Publishing Inc.: Malden, 2009; pp 257.

4 a) H. Sakaguchi, Y. Uetake, M. Ohashi, T. Niwa, S. Ogoshi, T. Hosoya, *J. Am. Chem. Soc.* **2017**, *139*, 12855. b) R. Kojima, K. Kubota, H. Ito, *Chem. Commun.* **2017**, *53*, 10688. c) H. Ito, T. Seo, R. Kojima, K. Kubota, *Chem. Lett.* **2018**, *47*, 1330. d) D.-H. Tan, E. Lin, W.-W. Ji, Y.-F. Zeng, W.-X. Fan, Q. Li, H. Gao, H. Wang, *Adv. Synth. Catal.* **2018**, *360*, 1032.

5 For a review: a) C. Ni, J. Hu, *Synthesis* **2014**, *46*, 842. Selected examples: b) S. A. Fuqua, W. G. Duncan, R. M. Silverstein, *J. Org. Chem.* **1965**, *30*, 1027. c) Y. Zhao, W. Huang, L. Zhu, J. Hu, *Org. Lett.* **2010**, *12*, 1444. d) C. S. Thomoson, H. Martinez, W. R. Dolbier, Jr., *J. Fluorine Chem.* **2013**, *150*, 53.

6 a) V. G. Nenajdenko, G. N. Varseev, V. N. Korotchenko, A. V. Shastin, E. S. Balenkova, *J. Fluorine Chem.* **2003**, *124*, 115. b) M. Hu, Z. He, B. Gao, L. Li, C. Ni, J. Hu, *J. Am. Chem. Soc.* **2013**, *135*, 17032. c) M. Hu, C. Ni, L. Li, Y. Han, J. Hu, *J. Am. Chem. Soc.* **2015**, *137*, 14496. d) J. Zheng, J.-H. Lin, L.-Y. Yu, Y. Wei, X. Zheng, J.-C. Xiao, *Org. Lett.* **2015**, *17*, 6150. e) Z. Zhang, Q. Zhou, W. Yu, T. Li, G. Wu, Y. Zhang, J. Wang, *Org. Lett.* **2015**, *17*, 2474. f) Z. Zhang, W. Yu, C. Wu, C. Wang, Y. Zhang, J. Wang, *Angew. Chem., Int. Ed.* **2016**, *55*, 273. g) Y. Ma, B. R. P. Reddy, X. Bi, *Org. Lett.* **2019**, *21*, 9860.

7 For contributions from our group, see: a) Y. Miki, K. Hirano, T. Satoh, M. Miura, *Angew. Chem., Int. Ed.* **2013**, *52*, 10830. b) Y. Miki, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2014**, *16*, 1498. c) D. Nishikawa, K. Hirano, M. Miura, *J. Am. Chem. Soc.* **2015**, *137*, 15620. d) D. Nishikawa, R. Sakae, Y. Miki, K. Hirano, M. Miura, *J. Org. Chem.* **2016**, *81*, 12128. e) T. Takata, D. Nishikawa, K. Hirano, M. Miura, *Chem.—Eur. J.* **2018**, *24*, 10975.

8 For contributions from the Buchwald research group, see: a) S. Zhu, N. Niljianskul, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 15746. b) S. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2014**, *136*, 15913. c) N. Niljianskul, S. Zhu, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2015**, *54*, 1638. d) S.-L. Shi, S. L. Buchwald, *Nat. Chem.* **2015**, *7*, 38. e) Y. Yang, S.-L. Shi, D. Niu, P. Liu, S. L. Buchwald, *Science* **2015**, *349*, 62. f) D. Niu, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 9716. g) H. Wang, J. C. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **2017**, *139*, 8428. h) Y. Zhou, O. D. Engl, J. S. Bandar, E. D. Chant, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2018**, *57*, 6672. i) S. Guo, J. C. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **2018**, *140*, 15976.

9 T. Takata, K. Hirano, M. Miura, *Org. Lett.* **2019**, *21*, 4284.

10 For a review on Cu-H species, see: C. Deutsch, N. Krause, B. H. Lipshutz, *Chem. Rev.* **2008**, *108*, 2916.

11 For recent detailed mechanistic studies, see: a) N. O. Andrella, N. Xu, B. M. Gabidullin, C. Ehm, R. T. Baker, *J. Am. Chem. Soc.* **2019**, *141*, 11506. b) P. H. S. Paioti, J. del Pozo, M. S. Mikus, J. Lee, M. J. Koh, F. Romiti, S. Torker, A. H. Hoveyda, *J. Am. Chem. Soc.* **2019**, *141*, 19917.

12 a) R. Corberán, N. W. Mszar, A. H. Hoveyda, *Angew. Chem., Int. Ed.* **2011**, *50*, 7079. b) R. Kojima, S. Akiyama, H. Ito, *Angew. Chem., Int. Ed.* **2018**, *57*, 7196. c) Y. Liu, Y. Zhou, Y. Zhao, J. Qu, *Org. Lett.* **2017**, *19*, 946.

13 H. Sakaguchi, M. Ohashi, S. Ogoshi, *Angew. Chem., Int. Ed.* **2018**, *57*, 328.

14 For recent selected examples, see: a) S. B. Lang, R. J. Wiles, C. B. Kelly, G. A. Molander, *Angew. Chem., Int. Ed.* **2017**,

56, 15073. b) Y. Lan, F. Yang, C. Wang, *ACS Catal.* **2018**, *8*, 9245. c) X. Lu, X.-X. Wang, T.-J. Gong, J.-J. Pi, S.-J. He, Y. Fu, *Chem. Sci.* **2019**, *10*, 809. d) D. Ding, Y. Lan, Z. Lin, C. Wang, *Org. Lett.* **2019**, *21*, 2723.

15 a) T. Miura, Y. Ito, M. Murakami, *Chem. Lett.* **2008**, *37*, 1006. b) Y. Huang, T. Hayashi, *J. Am. Chem. Soc.* **2016**, *138*, 12340.

16 During the preparation of this manuscript, Norton reported the related nickel-catalyzed hydrodefluorination of CF_3-substituted alkenes, but the substrate scope was limited to the Ar-conjugated systems. C. Yao, S. Wang, J. Norton, M. Hammond, *J. Am. Chem. Soc.* **2020**, *142*, 4793.

17 The higher performance of TMS-dppbz was unique to the trisubstituted **1j**. For example, the reaction of **1a** with TMS-dppbz under otherwise identical conditions provided **2a** in only 58% NMR yield (vs. Entry 5 in Table 1).

18 a) T. G. Gant, *J. Med. Chem.* **2014**, *57*, 3595. b) J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, *Angew. Chem., Int. Ed.* **2018**, *57*, 1758. c) T. Pirali, M. Serafini, S. Cargnin, A. A. Genazzani, *J. Med. Chem.* **2019**, *62*, 5276.

19 See the Supporting Information for optimization studies on asymmetric catalysis.

20 The absolute configuration of (*S*)-**2j** and **3** was determined by the specific rotation after the derivatization into the known product. See the Supporting Information for details.