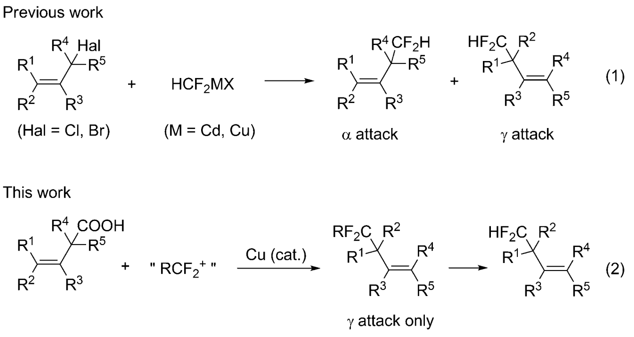
DOI: 10.1002/anie.201206556

Synthetic Methods

Copper-Catalyzed Difluoromethylation of β,γ-Unsaturated Carboxylic Acids: An Efficient Allylic Difluoromethylation**

*Zhengbiao He, Mingyou Hu, Tao Luo, Lingchun Li, and Jinbo Hu**

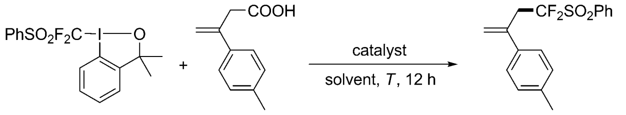
The difluoromethyl group (CF_2H) is an intriguing structural motif, which has great potential for many applications in life-science-related fields.[1–5] It has been realized that the CF_2H group can act as lipophilic hydrogen-bond donors and as a bioisostere of alcohols and thiols.[1–4] In this context, the development of efficient methods for the incorporation of the CF_2H group into organic molecules has attracted much attention.[1,2,6–9] Recently, transition-metal-mediated or transition-metal-catalyzed difluoromethylation (or difluoroalkylation) of aryl halides and aryl boronic acids to construct C_{sp^2}–CF_2H (or C_{sp^2}–CF_2R) bonds have been intensively studied.[6–9] Baran and co-workers also reported an elegant process for the direct difluoromethylation of arenes by a free radical process.[10] However, the transition-metal-mediated or transition-metal-catalyzed difluoromethylation and difluoroalkylation for the construction of allylic C_{sp^3}–CF_2H (or allylic C_{sp^3}–CF_2R) bonds are scarce. Previously, Burton and Hartgraves reported the difluoromethylations of allyl halides using either a difluoromethyl cadmium or copper reagent.[11,12] However, the regioselectivity of these reactions was not well controlled, and in many cases, both α-attack and γ-attack products were obtained [Scheme 1, Eq. (1)]. Herein, we disclose a new catalytic protocol for the regiospecific construction of allylic C_{sp^3}–CF_2H (or allylic C_{sp^3}–CF_2R) bonds by copper-catalyzed decarboxylative difluoromethylation of β,γ-unsaturated carboxylic acids [Scheme 1, Eq. (2)].



Scheme 1. Allylic difluoromethylations.

Recently, we discovered the copper-catalyzed decarboxylative fluoroalkylation of α,β-unsaturated carboxylic acids, a method which provides a powerful tool for vinylic di- and trifluoromethylations.[13] We envisaged that this decarboxylative fluoroalkylation strategy might be also used to tackle the challenging allylic difluoromethylation problem when the β,γ-unsaturated carboxylic acids are used as substrates. With this consideration in mind, we chose the reaction between the I(III)-CF_2SO_2Ph reagent **1**[14] and 3-(*p*-tolyl)-3-butenoic acid (**2a**) as a model reaction to survey the reaction conditions. As shown in Table 1, selection of the proper Lewis acid catalyst, solvent, and temperature was found to be crucial for the reaction. In the absence of a Lewis acid, the desired decarboxylative fluoroalkylation reaction could hardly proceed (entry 21). While $Ni(OAc)_2·4H_2O$ and $Pd(OAc)_2$ were

Table 1: Survey of reaction conditions.



1 (1.0 equiv) **2a** **3a**

Entry	Equiv. **2a**	Solvent[a]	Catalyst (equiv)	T [°C]	Yield [%][b]
1	2.0	dioxane	CuCl (0.25)	70	21
2	2.0	THF	CuCl (0.25)	70	18
3	2.0	CH_3CN	CuCl (0.25)	70	33
4	2.0	CCl_4	CuCl (0.25)	70	33
5	2.0	DCE	CuCl (0.25)	70	30
6	2.0	H_2O/DME (1:4)	CuCl (0.25)	70	52
7	2.0	H_2O/THF (1:4)	CuCl (0.25)	70	48
8	2.0	H_2O/CH_3CN (1:4)	CuCl (0.25)	70	42
9	2.0	H_2O/DMF (1:4)	CuCl (0.25)	70	53
10	2.0	H_2O/dioxane (1:4)	CuCl (0.25)	70	55
11	2.0	H_2O/dioxane (1:4)	$Ni(OAc)_2·4H_2O$ (0.25)	70	0
12	2.0	H_2O/dioxane (1:4)	$Zn(OAc)_2·2H_2O$ (0.25)	70	46
13	2.0	H_2O/dioxane (1:4)	$Pd(OAc)_2$ (0.25)	70	0
14	2.0	H_2O/dioxane (1:4)	$Cu(OAc)_2·H_2O$ (0.25)	70	51
15	2.0	H_2O/dioxane (1:4)	$CuCl_2·2H_2O$ (0.25)	70	62
16	1.0	H_2O/dioxane (1:4)	$CuCl_2·2H_2O$ (0.25)	70	40
17	0.5	H_2O/dioxane (1:4)	$CuCl_2·2H_2O$ (0.25)	70	20
18	2.0	H_2O/dioxane (1:4)	$CuCl_2·2H_2O$ (0.06)	70	75
19	2.0	H_2O/dioxane (1:4)	$CuCl_2·2H_2O$ (0.03)	90	80
20	2.25	H_2O/dioxane (1:4)	$CuCl_2·2H_2O$ (0.016)	90	85
21	2.25	H_2O/dioxane (1:4)	–	90	trace

[a] The data within the parentheses refer to the volume ratio. [b] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. DCE = 1,2-dichloroethane, DME = 1,2-dimethoxyethane, DMF = *N,N*-dimethylformamide.

---

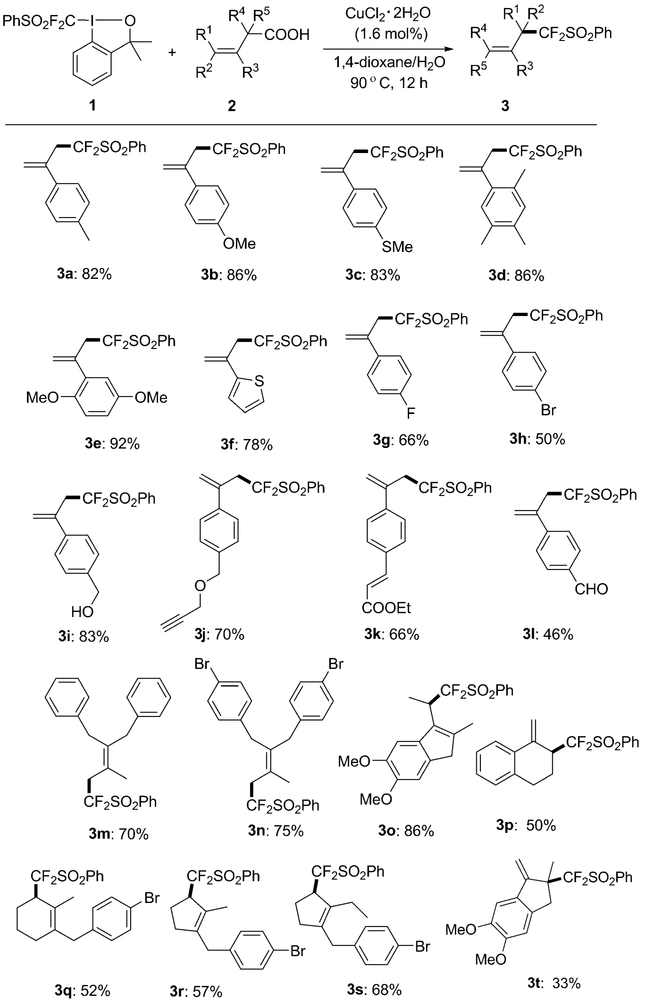
[*] Dr. Z. He, M. Hu, T. Luo, L. Li, Prof. Dr. J. Hu
Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Ling-Ling Road, Shanghai, 200032 (China)
E-mail: jinbohu@sioc.ac.cn

[**] Support of our work by the National Basic Research Program of China (2012CB215500 and 2012CB821600) and the National Natural Science Foundation of China (20825209, 20832008) is gratefully acknowledged. Professor Kuo-Wei Huang is thanked for helpful discussions.

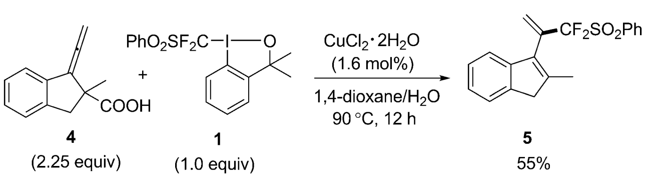
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201206556.

unable to promote the present C–CF_2SO_2Ph bond formation (entries 11 and 13), other Lewis acids such as CuCl, $Zn(OAc)_2{\cdot}2H_2O$, $Cu(OAc)_2{\cdot}2H_2O$, and $CuCl_2{\cdot}2H_2O$ catalyzed the reaction (entries 1–10, 12, and 15–20).[15] It is particularly interesting that the addition of water as a cosolvent can significantly increase the product yield (entries 1–3, 7, 8, and 10). Finally, the optimal yield (85%) of the product **3a** was obtained when **1** and **2a** (molar ratio 1:2.25) were stirred in H_2O/1,4-dioxane (1:4 v/v) in the presence of $CuCl_2{\cdot}2H_2O$ (1.6 mol%) at 90°C for 12 hours (entry 20). It is noteworthy to mention that the reaction is not sensitive to air, thus simplifying the reaction.

By using the optimized reaction conditions (Table 1, entry 20), we examined the substrate scope of the present decarboxylative fluoroalkylation reaction. The results are summarized in Scheme 2. The reaction proved to be general and amenable to a wide range of structurally diverse substrates (**2a**–**t**), and the desired products **3a**–**t** were produced in satisfactory yields. In particular, we found that the relatively electron-rich β,γ-unsaturated carboxylic acids **2a**–**e** and **2i** reacted with **1** to give the corresponding products **3a**–**e** and **3i** in high yields, and the reactions with carboxylic acids bearing an electron-withdrawing group gave lower yields (**3h** and **3l**). Many synthetically important functional groups, including bromine, hydroxy, alkynyl, and ester groups, are well tolerated in the reaction. Notably, the aldehyde group, which is usually fragile under oxidative conditions, remained intact in the reaction. To our delight, alkyl-substituted β,γ-unsaturated acids (**2m,n**) and cyclic substrates (**2p**–**t**) were also found to react smoothly with **1** to give the corresponding products in satisfactory yields. To our surprise and delight, the allenoic acid **4** could also react smoothly with **1** using our method to afford the (penylsufonyl)difluoromethylated product **5** in 55% yield (Scheme 3).

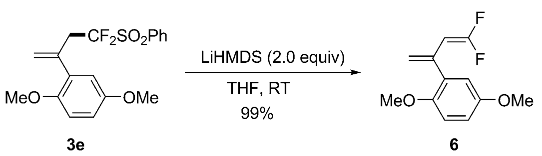


Scheme 2. (Phenylsufonyl)difluoromethylation of the β,γ-unsaturated acids **2** with **1**. Reaction conditions: **1** (0.8 mmol), **2** (1.8 mmol), $CuCl_2{\cdot}2H_2O$ (0.0125 mmol ca. 1.6 mol%), 1,4-dioxane (4 mL), and H_2O (1 mL) were stirred at 90°C for 12 h. Yield is that of the isolated compound.



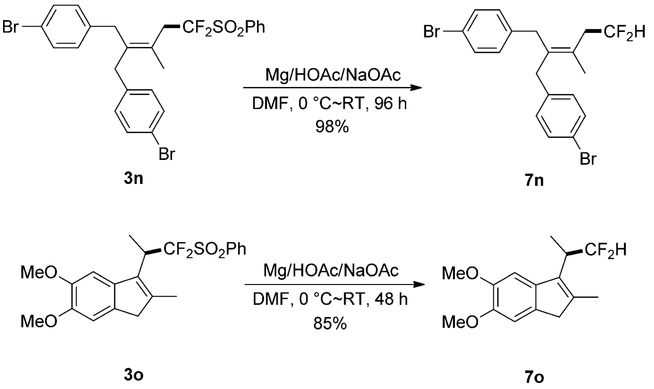
Scheme 3. (Phenylsufonyl)difluoromethylation of allenoic acid **4**.

Since the (phenylsulfonyl)difluoromethyl group is a versatile functionality that can be readily transformed into other highly useful functionalities such as difluoromethylidene (=CF_2) and difluoromethyl (CF_2H),[16,17] the present synthetic method opens up new avenues for the synthesis of a wide range of difluorinated compounds. For instance, when we treated the product **3e** with lithium hexamethyldisilazide (LiHMDS) in THF at room temperature, the 3-substituted *gem*-difluoro-1,3-butadiene **6** was produced in nearly quantitative yield (Scheme 4). Furthermore, upon reductive desulfonylation with our previously developed Mg/HOAc/NaOAc system in DMF solution at room temperature,[18] the compounds **3n** and **3o** were smoothly transformed into the corresponding difluoromethylated products **7n** and **7o** in 98% and 85% yield, respectively (Scheme 5).



Scheme 4. Conversion of **3e** into the gem-difluoroolefine **6**.

In summary, we have developed a new strategy for regiospecific allylic difluoromethylations. Lewis acid-catalyzed decarboxylative fluoroalkylations of the β,γ-unsaturated carboxylic acids **2** with the I(III)-CF_2SO_2Ph reagent **1** gives the corresponding (phenylsulfonyl)difluoromethylated products **3** in high yields. The products can be additionally transformed into allylic CF_2H-substituted products by reductive desulfonylation. Furthermore, an allenoic acid also reacted smoothly with **1** in moderate yield to construct



Scheme 5. Reductive desulfonylation.

C(vinyl)−CF$_2$SO$_2$Ph bonds under our reaction conditions. This decarboxylative difluoromethylation has a wide substrate scope and shows good functional-group tolerance, and promises to find many applications in life-science-related fields. Further investigations into the reaction mechanism and the application of the current strategy in other fluoroalkylations, as well as fluorinations are currently underway in our laboratory.

Experimental Section

Typical procedure for difluoromethylation of the β,γ-unsaturated carboxylic acids **2** with the reagent **1**. The reagent **1** (362 mg, 0.8 mmol, 1.0 equiv), **2n** (986 mg, 1.8 mmol, 2.25 equiv), and CuCl$_2$·2H$_2$O (2.0 mg, 0.0125 mmol, 1.6 mol %) were added to a reaction flask equipped with a magnetic stirring bar and a reflux condenser. 1,4-Dioxane (4 mL) and H$_2$O (1 mL) were then added to the reaction mixture, which was heated to 90 °C and stirred for 12 h. The reaction mixture was then cooled to ambient temperature and extracted with diethylether (15 mL × 3), and dried over MgSO$_4$. After filtration and and removal of solvent under vacuum, the residue was purified by silica gel chromatography (petroleum ether/EtOAc 20:1) to provide the pure product **3n** (350 mg, 75 % yield).

Typical procedure for reductive desulfonylation of **3**. A HOAc/NaOAc (1:1) buffer solution (4 mL; 8 mol L^{-1}) was added to a 50 mL Schlenk flask containing the sulfone compound **3n** (166 mg, 0.285 mmol) in 4 mL DMF at room temperature. Magnesium turnings (288 mg, 12 mmol) were then added in portions at 0 °C. The reaction mixture was stirred at room temperature for 96 h, and then 30 mL water were added. The solution mixture was extracted with Et$_2$O (20 mL × 3), and the combined organic phase was washed with saturated NaHCO$_3$ solution and brine, and then dried over MgSO$_4$. After the removal of the ethyl ether, the crude residue was purified by silica gel column chromatography (petroleum ether/EtOAc 30:1) to give the product **7n** (124 mg, 98 % yield).

Received: August 14, 2012

Keywords: allylic compounds · copper · homogenous catalysis · fluorine · synthetic methods

---

[1] For a recent review on difluoromethylation reactions, see: J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465, and references therein.

[2] For recent examples of difluoromethylations, see: a) Y. Zhao, W. Huang, J. Zheng, J. Hu, *Org. Lett.* **2011**, *13*, 5342; b) A. A. Tyutyunov, V. E. Boyko, S. M. Igoumnov, *Fluorine Notes* **2011**, *78*, 1; c) F. Wang, W. Huang, J. Hu, *Chin. J. Chem.* **2011**, *29*, 2717; d) K. Fuchibe, Y. Koseki, T. Aono, H. Sasagawa, J. Ichikawa, *J. Fluorine Chem.* **2012**, *133*, 52; e) G. K. S. Prakash, Z. Zhang, F. Wang, C. Ni, G. A. Olah, *J. Fluorine Chem.* **2011**, *132*, 792; f) Y. Zhao, B. Gao, J. Hu, *J. Am. Chem. Soc.* **2012**, *134*, 5790; g) T. Iida, R. Hashimoto, K. Aikawa, S. Ito, K. Mikami, *Angew. Chem.* **2012**, *124*, 9673; *Angew. Chem. Int. Ed.* **2012**, *51*, 9535.

[3] J. A. Erickson, J. I. Mcloughlin, *J. Org. Chem.* **1995**, *60*, 1626.

[4] N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529.

[5] For a recent example of CF$_2$H-containing drug candidates, see: G. W. Rewcastle, et al., *J. Med. Chem.* **2011**, *54*, 7105.

[6] a) K. Fujikawa, Y. Fujioka, A. Kobayashi, H. Amii, *Org. Lett.* **2011**, *13*, 5560; b) K. Fujikawa, A. Kobayashi, H. Amii, *Synthesis* **2012**, *44*, 3015.

[7] P. S. Fier, J. F. Harting, *J. Am. Chem. Soc.* **2012**, *134*, 5524.

[8] Q.-Q. Qing, Q.-L. Shen, L. Lu, *J. Am. Chem. Soc.* **2012**, *134*, 6548.

[9] Z. Feng, F. Chen, X. Zhang, *Org. Lett.* **2012**, *14*, 1938.

[10] Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 1494.

[11] G. A. Hartgraves, D. J. Burton, *J. Fluorine Chem.* **1988**, *39*, 425.

[12] G. A. Hartgraves, D. J. Burton, *J. Fluorine Chem.* **2007**, *128*, 1198.

[13] Z. He, T. Luo, M. Hu, Y. Cao, J. Hu, *Angew. Chem.* **2012**, *124*, 4010; *Angew. Chem. Int. Ed.* **2012**, *51*, 3944.

[14] W. Zhang, J. Zhu, J. Hu, *Tetrahedron Lett.* **2008**, *49*, 5006.

[15] We found that the CuF$_2$·2H$_2$O/TMEDA catalyst system (as used in Ref. [12]) was less efficient than CuCl$_2$ for the current reaction. When we used CuF$_2$·2H$_2$O (20 mol %) as the catalyst and TMEDA (25 mol %) as ligand, H$_2$O (4 mL) and DCE (3 mL) as solvent, and **2a** (2.25 equiv) and **1** (1.0 equiv) as reactants, at 80 °C for 12 h; the yield of the product **3a** was only 58 %. When we used CuF$_2$ (20 mol %) as the catalyst and TMEDA (25 mol %) as ligand, H$_2$O (1 mL) and 1,4-dioxane (4 mL) as solvent, and **2a** (2.25 equiv) and **1** (1.0 equiv) as reactants, at 90 °C for 12 h, the yield of **3a** was only 49 %.

[16] J. Hu, *J. Fluorine Chem.* **2009**, *130*, 1130.

[17] G. K. S. Prakash, J. Hu, *Acc. Chem. Res.* **2007**, *40*, 921.

[18] C. Ni, J. Hu, *Tetrahedron Lett.* **2005**, *46*, 8273.