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Copper- and Iron-Catalyzed Decarboxylative Tri- and Difluoromethylation of α , β -Unsaturated Carboxylic Acids with CF₃SO₂Na and (CF₂HSO₂)₂Zn via a Radical Process

Zejiang Li, Zili Cui, and Zhong-Quan Liu*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou Gansu 730000, P. R. China

liuzhq@lzu.edu.cn

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A copper-catalyzed decarboxylative trifluoromethylation of various α , β -unsaturated carboxylic acids by using a stable and inexpensive solid, sodium trifluoromethanesulfinate (CF₃SO₂Na, Langlois reagent), was developed. In addition, an iron-catalyzed difluoromethylation of aryl-substituted acrylic acids by using zinc difluoromethanesulfinate (DFMS, (CF₂HSO₂)₂Zn, Baran reagent) via a similar radical process was also achieved.

The introduction of fluorinated moieties into organic molecules such as pharmaceuticals and agrochemicals can often change their chemical and biological properties.¹ Hence, the fluorination and trifluoromethylation reactions have drawn much attention recently.² In the past several years, strategies for trifluoromethylations of arenes have been well established.³ However, only a few approaches to the synthesis of C_{vinyl} -CF₃ bonds have been developed by Buchwald,⁴ Hu,⁵ Liu,⁶ and Shen⁷ et al. (Scheme 1). It is seen from Scheme 1 that most of these systems suffer from using expensive and relatively unstable trifluoromethylating reagents. Herein, we wish to report a copper-catalyzed

decarboxylic trifluoromethylation of α , β -unsaturated carboxylic acid by using a stable and inexpensive solid, sodium trifluoromethanesulfinate (CF₃SO₂Na, Langlois reagent). In addition, an iron-catalyzed difluoromethylation of α , β -unsaturated carboxylic acid by using zinc difluoromethanesulfinate (DFMS, (CF₂HSO₂)₂Zn, Baran reagent) via a similar radical process is also achieved.

^{(1) (}a) Organofluorine Compounds: Chemistry and Applications; Hiyama, T.; Springer: New York, 2000. (b) Kirsch, P. Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications; Wiley-VCH: Weinheim, 2004. (c) Fluorine in Medicinal Chemistry and Chemical Biology; Ojima, I., Ed.; Wiley-Blackwell: Chichester, 2009.

^{(2) (}a) Umemoto, T. Chem. Rev. **1996**, *96*, 1757. (b) Prakash, G. K. S.; Yudin, A. K. Chem. Rev. **1997**, *97*, 757. (c) Singh, R. P.; Shreeve, J. M. Tetrahedron **2000**, *56*, 7613. (d) Ma, J.-A.; Cahard, D. Chem. Rev. **2004**, *104*, 6119. (e) Ma, J.-A.; Cahard, D. J. Fluorine Chem. **2007**, *128*, 975. (f) Müller, K.; Faeh, C.; Diederich, F. Science **2007**, *317*, 1881. (g) Prakash, G. K. S.; Hu, J. Acc. Chem. Res. **2007**, *40*, 921. (h) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Chem. Soc. Rev. **2008**, *37*, 320. (i) Hu, J.; Zhang, W.; Wang, F. Chem. Commun. **2009**, 7465.

⁽³⁾ For selected reviews, see: (a) Tomashenko, O. A.; Grushin, V. V. Chem. Rev. 2011, 111, 4475. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. Nature 2011, 473, 470. (c) Besset, T.; Schneider, C.; Cahard, D. Angew. Chem., Int. Ed. 2012, 51, 5048. (d) Studer, A. Angew. Chem., Int. Ed. **2012**, *51*, 8950. For selected recent examples, see: (a) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. Science 2010, 328, 1679. (b) Wang, X.; Truesdale, L.; Yu, J.-Q. J. Am. Chem. Soc. 2010, 132, 3648. (c) Chu, L.; Qing, F.-L. Org. Lett. 2010, 12, 5060. (d) Zhang, C.-P.; Wang, Z.-L.; Chen, Q.-Y.; Zhang, C.-T.; Gu, Y.-C.; Xiao, J.-C. Angew. Chem., Int. Ed. 2011, 50, 1896. (e) Parsons, A. T.; Buchwald, S. L. Angew. Chem., Int. Ed. 2011, 50, 9120. (f) Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. J. Am. Chem. Soc. 2011, 133, 15300. (g) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. J. Am. Chem. Soc. 2011, 133, 16410. (h) Kawai, H.; Furukawa, T.; Nomura, Y.; Tokunaga, E.; Shibata, N. Org. Lett. 2011, 13, 3596. (i) Ye, Y.; Sanford, M. S. J. Am. Chem. Soc. 2012, 134, 9034. (j) Chu, L.; Qing, F. L. J. Am. Chem. Soc. 2012, 134, 1298. (k) Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. Angew. Chem., Int. Ed. 2012, 51, 536. (1) Liu, T.; Shao, X.; Wu, Y.; Shen, Q. Angew. Chem., Int. Ed. 2012, 51, 540.

The Langlois reagent was first developed in the 1980s, for use as an electrophilic trifluoromethyl radical in the addition of electron-rich double bonds and arenes.⁸ In 2011, Baran et al. reported a very efficient trifluoromethylation of heterocycles by using the inexpensive and benchtop stable solid CF_3SO_2Na .⁹ They also developed a direct radical difluoromethylation of heteroarenes by using DFMS.¹⁰ Very recently, Sanford reported a copper-mediated trifluoromethylation of aryl boronic acids by using the Langlois reagent.¹¹ However, to the best of our knowledge, no examples of metal-catalyzed direct formation of C_{vinyl} – CF_3 bonds by using Langlois' reagent as well as C_{vinyl} – CF_2H bond formation using DFMS have been reported.

On the other hand, a series of decarboxylative C–C bond formation reactions have been developed by Myers,¹² Goossen,¹³ and Liu¹⁴ et al.¹⁵ over the past several years. Very recently, we reported the first example of decarboxylative olefination of various sp³ C–H bonds via radical addition–elimination reactions of vinylic carboxylic acids with alcohols, ethers, and hydrocarbons.¹⁶ Of particular interest in the radical processes, we began to wonder whether C_{vinyl} –CF₃/ C_{vinyl} –CF₂H bonds could be constructed by a similar radical addition–elimination reaction of α , β -unsaturated carboxylic acids with a triand difluoromethyl radical. Fortunately, an economical, convenient, and selective access to a variety of

(4) (a) Cho, E. J.; Buchwald, S. L. Org. Lett. **2011**, *13*, 6552. (b) Parsons, A. T.; Senecal, T. D.; Buchwald, S. L. Angew. Chem., Int. Ed. **2012**, *51*, 2947.

(5) He, Z.; Luo, T.; Hu, M.; Cao, Y.; Hu, J. Angew. Chem., Int. Ed. 2012, 51, 3944.

(6) Xu, J.; Luo, D. F.; Xiao, B.; Liu, Z. J.; Gong, T. J.; Fu, Y.; Liu, L. Chem. Commun. **2011**, 4300.

(7) Liu, T.; Shen, Q. Org. Lett. 2011, 13, 2342.

(8) (a) Tordeux, M.; Langlois, B. R.; Wakselman, C. J. Org. Chem. **1989**, *54*, 2452. (b) Langlois, B. R.; Laurent, E.; Roidot, N. Tetrahedron Lett. **1991**, *32*, 7525. (c) Billard, T.; Langlois, B. R. Tetrahedron **1999**, *55*, 8065. (d) Tommasino, J. B.; Brondex, A.; Médebielle, M.; Thomalla, M.; Langlois, B. R.; Billard, T. Synlett **2002**, 1697.

(9) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411.

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

(11) Ye, Y.; Künzi, S. A.; Sanford, M. S. Org. Lett. 2012, 14, 4979.

(12) (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. J. Am. Chem. Soc. 2002, 124, 11250. (b) Tanaka, D.; Myers, A. G. Org. Lett. 2004, 6, 433

(13) (a) Goossen, L. J.; Deng, G.; Levy, L. M. Science 2006, 313, 662.
(b) Goossen, L. J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. J. Am. Chem. Soc. 2007, 129, 4824. (c) Goossen, L. J.; Goossen, K.; Rodríguez, N.; Blanchot, M.; Linder, C.; Zimmermann, B. Pure Appl. Chem. 2008, 80, 1725. (d) Rodríguez, N.; Goossen, L. J. Chem. Soc. Rev. 2011, 40, 5030. (e) Dzik, W. I.; Lange, P. P.; Goossen, L. J. Chem. Sci. 2012, 3, 2671.

(14) (a) Zhang, S.-L.; Fu, Y.; Shang, R.; Guo, Q.-X.; Liu, L. J. Am. Chem. Soc. 2010, 132, 638. (b) Shang, R.; Ji, D.-S.; Chu, L.; Fu, Y.; Liu, L. Angew. Chem., Int. Ed. 2011, 50, 4470. (c) Shang, R.; Liu, L. Sci. China Chem. 2011, 54, 1670.

(15) For selected examples, see: (a) Cornella, J.; Lu, P.; Larrosa, I. Org. Lett. 2009, 11, 5506. (b) Jana, R.; Trivedi, R.; Tunge, J. A. Org. Lett. 2009, 11, 3434. (c) Torregrosa, R. R. P.; Ariyarathna, Y.; Chattopadhyay, K.; Tunge, J. A. J. Am. Chem. Soc. 2010, 132, 9280. (d) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. Org. Lett. 2010, 12, 592. (e) Zhang, F.; Greaney, M. F. Angew. Chem., Int. Ed. 2010, 49, 2768. (f) Hu, P.; Shang, Y.; Su, W. Angew. Chem., Int. Ed. 2012, 51, 5945. (g) Fang, P.; Li, M.; Ge, H. J. Am. Chem. Soc. 2010, 132, 11898.

(16) Cui, Z.; Shang, X.; Shao, X. F.; Liu, Z. Q. Chem. Sci. 2012, 3, 2853.

tri- and difluoromethyl-substituted (*E*)-alkenes has been developed.

Scheme 1. Formation of Cvinyl-CF3/Cvinyl-CF2H Bonds



Initially, we chose 2,5-dimethoxycinnamic acid as the model substrate to optimize suitable conditions for this reaction (Table 1; see also the Supporting Information (SI)). It was found that the catalyst and radical initiator greatly effect reaction efficiency. The CuSO₄·5H₂O was more efficient than copper(II) salts such as Cu(OTf)₂, Cu(OAc)₂, Cu- $(acac)_2$, CuO, CuCl₂, CuF₂, CuBr₂, Cu(OAc)₂·H₂O, etc. (entries 1-5). Other copper(I) salts such as CuCl, CuBr, CuI, Cu₂O, and (PPh₃)₂CuNO₃ and other metal salts such as Fe(OAc)₂, Mn(OAc)₂·4H₂O, Co(OAc)₂·4H₂O, etc. are less effective than $CuSO_4 \cdot 5H_2O$ (see the SI). The desired product was isolated in 66% yield by using 10 mol % CuSO₄·5H₂O. However, addition of 5 mol % and 15 mol % catalysts led to generation of the product in 54% and 47% yields, respectively (entries 6 and 7). A mixed solvent of CH₂Cl₂/H₂O was proven to be more efficient than others such as CH₃CN/H₂O, tBuOH/H₂O, acetone/H₂O, AcOH/ H_2O , etc. (entries 8 and 9). The yield decreased to 32%when 3 equiv of TBHP as the radical initiator were used (entry 10). Other radical initiators such as di-tert-butyl peroxide (DTBP), dicumyl peroxide (DCP), H₂O₂, K₂S₂O₈, and benzoyl peroxide (BPO) were found to be less efficient than TBHP (see the SI). The desired product was obtained in 45% and 40% yields at 25 and 80 °C, respectively (entries 11 and 12). It is worth noting that (E)-1,4-dimethoxy-2-(3,3,3-trifluoroprop-1-en-1-yl)benzene was obtained as the major product and the ratio of E/Z was up to 98/2.

To examine the scope of this system, the decarboxylative coupling reactions of various cinnamic acids with sodium

Table 1. Modification of the Typical Reaction Conditions^a

radical catalyst initiator solvent	eld (%) ^b
catalyst initiator solvent	eld (%) ^b
	eld (%) ^o
entry (mol %) (equiv) (v/v, V) yi	_
1 _ TBHP (5) CH_2Cl_2/H_2O	
(2.5/1, 3.5 mL)	
$2 \qquad Cu(OTf)_2 (10) \qquad TBHP (5) CH_2 Cl_2 / H_2 O$	56
(2.5/1, 3.5 mL)	
3 $CuSO_4 \cdot 5H_2O(10)$ TBHP (5) CH_2Cl_2/H_2O	66
(2.5/1, 3.5 mL)	
4 $\operatorname{Cu}(\operatorname{acac})_2(10)$ TBHP (5) $\operatorname{CH}_2\operatorname{Cl}_2/\operatorname{H}_2O$	54
(2.5/1, 3.5 mL)	
5 $\operatorname{Cu}(\operatorname{OAc})_2(10)$ TBHP (5) $\operatorname{CH}_2\operatorname{Cl}_2/\operatorname{H}_2\operatorname{O}$	52
(2.5/1, 3.5 mL)	
$6 \qquad \text{CuSO}_4 \cdot 5\text{H}_2\text{O}(5) \qquad \text{TBHP}(5) \qquad \text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	54
(2.5/1, 3.5 mL)	
7 $\operatorname{CuSO}_4 \cdot 5\operatorname{H}_2O(15)$ TBHP(5) $\operatorname{CH}_2\operatorname{Cl}_2/\operatorname{H}_2O$	47
(2.5/1, 3.5 mL)	
8 $\operatorname{CuSO}_4 \cdot 5\operatorname{H}_2O(10)$ TBHP(5) $\operatorname{CH}_3CN/\operatorname{H}_2O$	60
(2.5/1, 3.5 mL)	-
9 $\operatorname{CuSO}_4 \cdot \operatorname{5H}_2 \operatorname{O}(10)$ TBHP (5) Acetone/H ₂ O	59
(2.5/1, 3.5 mL)	00
10 $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}(10)$ $\text{TBHP}(3)$ $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	32
(2.5/1, 3.5 mL)	45
$11 \bigcup U = \bigcup U_4 \cdot \partial \Pi_2 \cup (10) I = D = \Pi P (\partial) \bigcup \Pi_2 \bigcup U_2 / \Pi_2 \cup U_2 / \Pi_2 \cup (2 \cdot 5/1 - 2 \cdot 5 \cdot m \cdot 1))$	40
(2.5/1, 5.5 IIL) 19 ^d CuSO 5H O (10) TBHP (5) CH Cl /U O	40
(2.5/1, 3.5 mL)	τU

^{*a*} Reaction conditions: 2,5-dimethoxycinnamic acid (0.5 mmol), NaSO₂CF₃ (1.5 mmol), TBHP (70% aqueous), 2.5 h. ^{*b*} Isolated yields. ^{*c*} The reaction was conducted at 25 °C. ^{*d*} The reaction was conducted at 80 °C.

trifluoromethanesulfinate were studied (Table 2). The coupling reaction of NaSO2CF3 with cinnamic acids bearing electron-donating groups such as OMe, OH, NH₂, NMe₂, and OEt afforded the corresponding products in moderate to high yields (2a-2e). p-Methylcinnamic acid gave 2f in 56% yield. In addition, meta- and ortho-substituted cinnamic acids also gave moderate yields of the products (2g, 2h, and 2i), which indicated that the steric effect in the aromatic core is not pronounced. Moreover, the desired products were isolated in good to high yields by using highly substituted aryl acrylic acids (2j-2p). It is noteworthy that (2E, 4E)-5-phenylpenta-2,4-dienoic acid could also generate the desired product 2q in 48% yield under the reaction conditions. Interestingly, 4-chloro- and 4-nitrocinnamic acids gave 1-(4-chlorophenyl)-3,3,3trifluoropropan-1-one (2r) and 1-(4-nitrophenyl)-3,3,3trifluoropropan-1-one (2s), respectively. Surprisingly, (E)-2-(2-carboxyvinyl)benzoic acid gave the desired product 2t in 68% yield, and no ketones were observed. It is also worth noting that heteroarene substituted acrylic acids also gave the desired products (2u and 2v). A N-heteroarene such as indole and N-methyl pyrrole substituted acrylic acids gave bis-trifluoromethylated product 2w and 2x in 41% and 42% yield, respectively. No products were obtained by coupling (*E*)-3-(pyridine-3-yl)acrylic acid with NaSO₂CF₃ under these conditions.





^{*a*} Reaction conditions: cinnamic acid (0.5 mmol), NaSO₂CF₃ (1.5 mmol), CuSO₄•5H₂O (0.05 mmol), TBHP (2.5 mmol, 70% aqueous), CH₂Cl₂/H₂O (v/v = 2.5/1, 3.5 mL), 50 °C. ^{*b*} Reaction time, indicated by TLC. ^{*c*} Isolated yields. ^{*d*} Ratio of E/Z was determined by ¹⁹F NMR of the crude product mixture. ^{*e*} Ratio of (E,E)/(E,Z).

Inspired by Baran's work,¹⁰ we began to wonder whether other radicals such as a difluoromethyl radical could also add to the α,β -unsaturated carboxylic acids followed by elimination of CO₂ to form a series of difluoromethylsubstituted alkenes. Fotunately, iron-catalyzed decarboxylative difluoromethylation of electron-rich arylsubstituted acrylic acids by using DFMS ((CF₂HSO₂)₂Zn, Baran reagent) via a similar radical process is also achieved,

^{(17) (}a) Prakash, G. K. S.; Ganesh, S. K.; Jones, J. P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 12090. (b) He, Z.; Hu, M.; Luo, T.; Li, L.; Hu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11545.

which has never been reported before.¹⁷ Under the typical reaction conditions, various difluoromethyl-substituted (*E*)-alkenes have been selectively isolated in relatively low to moderate yields (Table 3, entries 1-5). Electron-deficient aryl-substituted acrylic acids gave very low yields of the desired products under these conditions.

Table 3. Iron-Catalyzed Decarboxylative Difluoromethylationof Cinnamic Acids with Zinc Difluoromethanesulfinate^a



^{*a*} Reaction conditions: cinnamic acid (0.5 mmol), $Zn(SO_2CF_2H)_2$ (1.5 mmol), $FeSO_4 \cdot 7H_2O$ (0.05 mmol), TBHP (2.5 mmol, 70% aqueous), CH_2Cl_2/H_2O (v/v = 2.5/1, 3.5 mL), 50 °C. ^{*b*} Isolated yields. ^{*c*} Ratio of E/Z was determined by ¹⁹F NMR of the crude product mixture.

A plausible mechanism that is consistent with our previous work and the literature precedent^{16,18} is depicted in Scheme 2. The trifluoromethyl radical will be generated by the reaction of *tert*-butyl peroxide with NaSO₂CF₃ and Cu(II).⁸ Reaction of the acrylic acid with Cu(I) reduced from the former step would generate a salt of Cu(II) carboxylate in the presence of TBHP. Addition of the trifluoromethyl radical at the α -position of the double bond in cupric cinnamate would give radical **A**, which then proceeds via an elimination of carbon dioxide and Cu(I) to generate the product. Oxidation of Cu(I) by the hydroxyl radical in the presence of cinnamic acid would regenerate the cupric cinnamate. Another possible process similar to the Kharasch–Sosnovsky reaction¹⁹ involving a Cu(III) intermediate cannot be ruled out at this time.

Scheme 2. Possible Mechanism



In conclusion, we report a convenient copper(II)catalyzed trifluoromethylation reaction of various acrylic acids with a stable solid, NaSO₂CF₃. This method provides a useful and practical strategy for stereospecific synthesis of CF₃-substituted *E*-alkenes. Various arenes, including indoles and divinyl carboxyl acids, are compatible with this decarboxylative C-C bond formating reaction. Furthermore, an iron-catalyzed difluoromethylation of electronrich aryl-substituted acrylic acids is also developed by using DFMS in a similar radical process, which can be used to stereospecifically prepare HCF2-substituted E-alkenes. This system provides a novel pathway for the construction of Cvinyl-CF3/Cvinyl-CF2 bonds via a radical addition-elimination process. This method is limited to aryl-substituted acrylic acid substrates. Alkyl-substituted acrylic acids failed to give the desired products which might be due to the stability of the radical intermediate. Further investigation of this procedure focusing on this disadvantage is underway in our laboratory.

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Supporting Information Available. Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

^{(18) (}a) Russell, G. A.; Ngoviwatchai, P. J. Org. Chem. **1989**, 54, 1836. (b) Xiang, J.; Fuchs, P. L. J. Am. Soc. Chem. **1996**, 118, 11986.

⁽¹⁹⁾ Kharasch, M. S.; Sosnovsky, G. J. Am. Soc. Chem. **1958**, 80, 756.

The authors declare no competing financial interest.