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Copper- and Iron-Catalyzed Decarboxylative Tri- and Difluoromethylation of α,*β*-Unsaturated Carboxylic Acids with CF_3SO_2Na and $(CF_2HSO_2)_2Zn$ via a Radical Process

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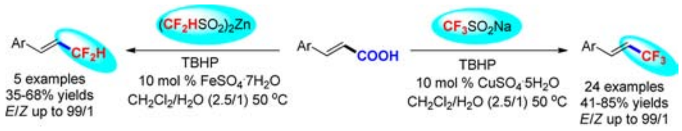
ABSTRACT



A copper-catalyzed decarboxylative trifluoromethylation of various α,*β*-unsaturated carboxylic acids by using a stable and inexpensive solid, sodium trifluoromethanesulfinate (CF_3SO_2Na, Langlois reagent), was developed. In addition, an iron-catalyzed difluoromethylation of aryl-substituted acrylic acids by using zinc difluoromethanesulfinate (DFMS, $(CF_2HSO_2)_2Zn$, 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 $C_{vinyl}{-}CF_3$ bonds have been developed by Buchwald,[4] Hu,[5] Liu,[6] and Shen[7] 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 (CF_3SO_2Na, Langlois reagent). In addition, an iron-catalyzed difluoromethylation of α,*β*-unsaturated carboxylic acid by using zinc difluoromethanesulfinate (DFMS, $(CF_2HSO_2)_2Zn$, Baran reagent) via a similar radical process is also achieved.

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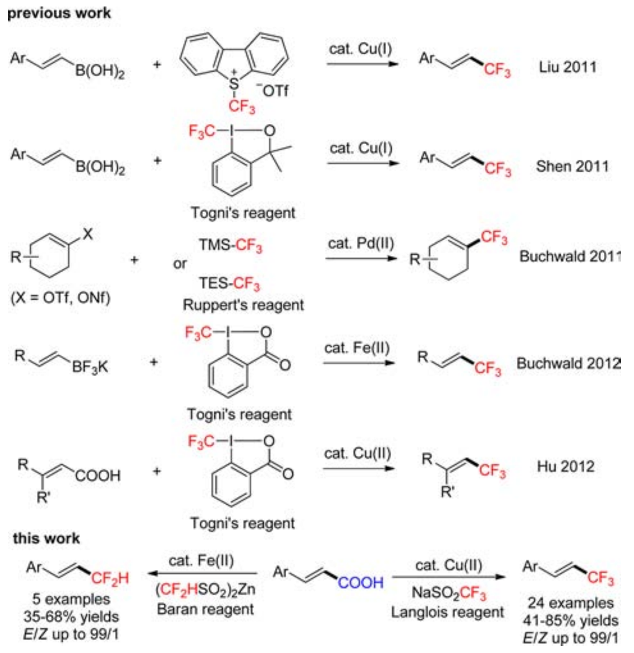
The Langlois reagent was first developed in the 1980s, for use as an electrophilic trifluoromethyl radical in the addition of electron-rich double bonds and arenes.[8] In 2011, Baran et al. reported a very efficient trifluoromethylation of heterocycles by using the inexpensive and benchtop stable solid 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 Liu[14] et al.[15] over the past several years. Very recently, we reported the first example of decarboxylative olefination of various sp^3 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 $C_{vinyl}{-}CF_3$/$C_{vinyl}{-}CF_2H$ bonds could be constructed by a similar radical addition−elimination reaction of α,β-unsaturated carboxylic acids with a tri- and difluoromethyl radical. Fortunately, an economical, convenient, and selective access to a variety of tri- and difluoromethyl-substituted (*E*)-alkenes has been developed.

Scheme 1. Formation of $C_{vinyl}{-}CF_3$/$C_{vinyl}{-}CF_2H$ 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 $CuSO_4\cdot 5H_2O$ was more efficient than copper(II) salts such as $Cu(OTf)_2$, $Cu(OAc)_2$, $Cu(acac)_2$, CuO, $CuCl_2$, CuF_2, $CuBr_2$, $Cu(OAc)_2\cdot H_2O$, etc. (entries 1−5). Other copper(I) salts such as CuCl, CuBr, CuI, Cu_2O, and $(PPh_3)_2CuNO_3$ and other metal salts such as $Fe(OAc)_2$, $Mn(OAc)_2\cdot 4H_2O$, $Co(OAc)_2\cdot 4H_2O$, 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 % $CuSO_4\cdot 5H_2O$. 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 CH_2Cl_2/H_2O was proven to be more efficient than others such as CH_3CN/H_2O, *t*BuOH/H_2O, acetone/H_2O, 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), H_2O_2, $K_2S_2O_8$, 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

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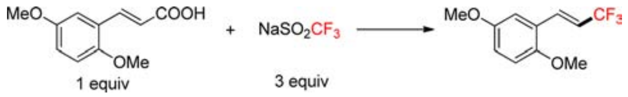
Table 1. Modification of the Typical Reaction Conditions[a]

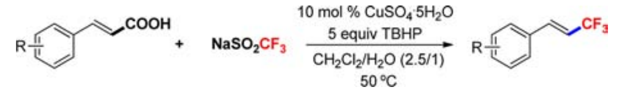


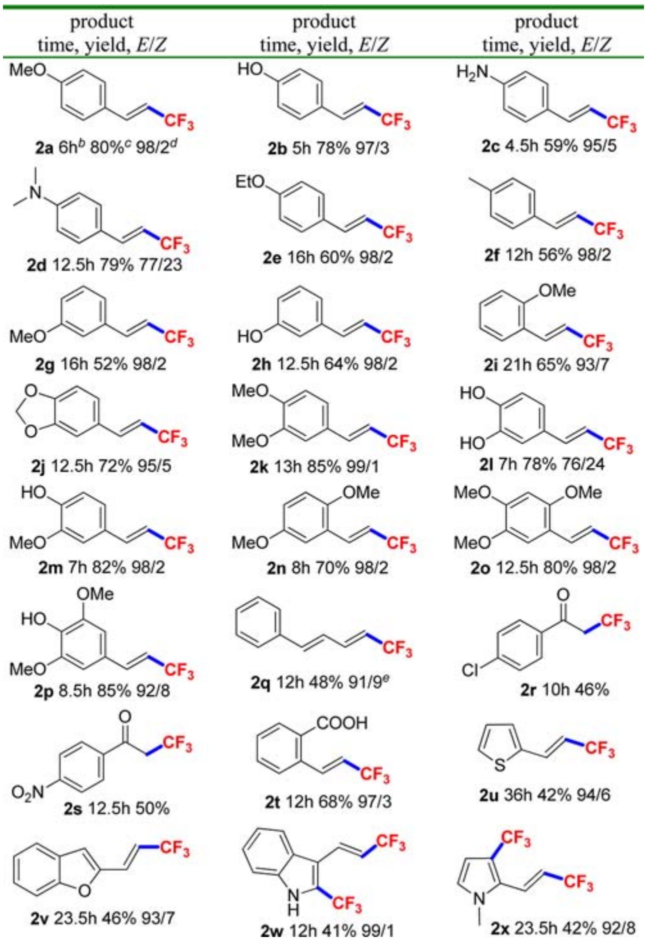
entry	catalyst (mol %)	radical initiator (equiv)	solvent (v/v, V)	yield (%)[b]
1	_	TBHP (5)	CH_2Cl_2/H_2O (2.5/1, 3.5 mL)	_
2	$Cu(OTf)_2$ (10)	TBHP (5)	CH_2Cl_2/H_2O (2.5/1, 3.5 mL)	56
3	$CuSO_4 \cdot 5H_2O$ (10)	TBHP (5)	CH_2Cl_2/H_2O (2.5/1, 3.5 mL)	66
4	$Cu(acac)_2$ (10)	TBHP (5)	CH_2Cl_2/H_2O (2.5/1, 3.5 mL)	54
5	$Cu(OAc)_2$ (10)	TBHP (5)	CH_2Cl_2/H_2O (2.5/1, 3.5 mL)	52
6	$CuSO_4 \cdot 5H_2O$ (5)	TBHP (5)	CH_2Cl_2/H_2O (2.5/1, 3.5 mL)	54
7	$CuSO_4 \cdot 5H_2O$ (15)	TBHP (5)	CH_2Cl_2/H_2O (2.5/1, 3.5 mL)	47
8	$CuSO_4 \cdot 5H_2O$ (10)	TBHP (5)	CH_3CN/H_2O (2.5/1, 3.5 mL)	60
9	$CuSO_4 \cdot 5H_2O$ (10)	TBHP (5)	Acetone/H_2O (2.5/1, 3.5 mL)	59
10	$CuSO_4 \cdot 5H_2O$ (10)	TBHP (3)	CH_2Cl_2/H_2O (2.5/1, 3.5 mL)	32
11[c]	$CuSO_4 \cdot 5H_2O$ (10)	TBHP (5)	CH_2Cl_2/H_2O (2.5/1, 3.5 mL)	45
12[d]	$CuSO_4 \cdot 5H_2O$ (10)	TBHP (5)	CH_2Cl_2/H_2O (2.5/1, 3.5 mL)	40

[a] Reaction conditions: 2,5-dimethoxycinnamic acid (0.5 mmol), $NaSO_2CF_3$ (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 $NaSO_2CF_3$ with cinnamic acids bearing electron-donating groups such as OMe, OH, NH_2, NMe_2, 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 (2*E*,4*E*)-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)-3,3,3-trifluoropropan-1-one (**2r**) and 1-(4-nitrophenyl)-3,3,3-trifluoropropan-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 $NaSO_2CF_3$ under these conditions.

Table 2. Copper-Catalyzed Decarboxylative Trifluoromethylation of Cinnamic Acids with Sodium Trifluoromethanesulfinate[a]





product time, yield, *E*/*Z*	product time, yield, *E*/*Z*	product time, yield, *E*/*Z*
2a 6h[b] 80%[c] 98/2[d]	**2b** 5h 78% 97/3	**2c** 4.5h 59% 95/5
2d 12.5h 79% 77/23	**2e** 16h 60% 98/2	**2f** 12h 56% 98/2
2g 16h 52% 98/2	**2h** 12.5h 64% 98/2	**2i** 21h 65% 93/7
2j 12.5h 72% 95/5	**2k** 13h 85% 99/1	**2l** 7h 78% 76/24
2m 7h 82% 98/2	**2n** 8h 70% 98/2	**2o** 12.5h 80% 98/2
2p 8.5h 85% 92/8	**2q** 12h 48% 91/9[e]	**2r** 10h 46%
2s 12.5h 50%	**2t** 12h 68% 97/3	**2u** 36h 42% 94/6
2v 23.5h 46% 93/7	**2w** 12h 41% 99/1	**2x** 23.5h 42% 92/8

[a] Reaction conditions: cinnamic acid (0.5 mmol), $NaSO_2CF_3$ (1.5 mmol), $CuSO_4 \cdot 5H_2O$ (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] Reaction time, indicated by TLC. [c] Isolated yields. [d] Ratio of *E*/*Z* was determined by ^{19}F 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 CO_2 to form a series of difluoromethyl-substituted alkenes. Fotunately, iron-catalyzed decarboxylative difluoromethylation of electron-rich aryl-substituted acrylic acids by using DFMS ($(CF_2HSO_2)_2Zn$, Baran reagent) via a similar radical process is also achieved,

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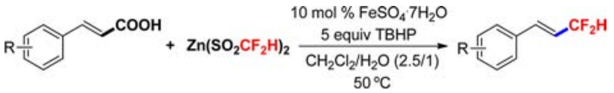
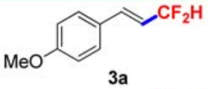
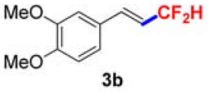
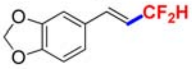
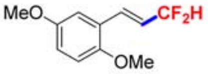
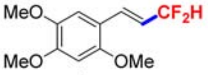
which has never been reported before.[17] Under the typical reaction conditions, various difluoromethyl-substituted (*E*)-alkenes have been selectively isolated in relatively low to moderate yields (Table 3, entries 1−5). Electron-deficient aryl-substituted acrylic acids gave very low yields of the desired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

Table 3. Iron-Catalyzed Decarboxylative Difluoromethylation of Cinnamic Acids with Zinc Difluoromethanesulfinate[a]

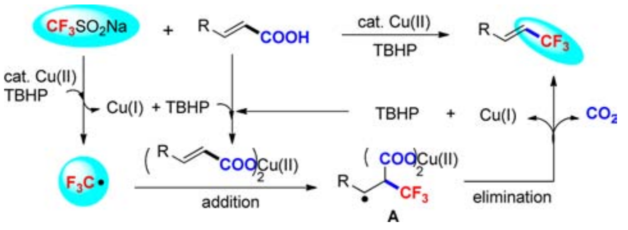


entry	product	*t* (h)	yield (%)[b]	*E*/*Z*[c]
1	 **3a**	6	68	99/1
2	 **3b**	22	60	95/5
3	 **3c**	22	42	99/1
4	 **3d**	22	40	99/1
5	 **3e**	22	35	99/1

[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 ^{19}F 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 $NaSO_2CF_3$ 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 reaction[19] 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, $NaSO_2CF_3$. This method provides a useful and practical strategy for stereospecific synthesis of CF_3-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 electron-rich aryl-substituted acrylic acids is also developed by using DFMS in a similar radical process, which can be used to stereospecifically prepare HCF_2-substituted *E*-alkenes. This system provides a novel pathway for the construction of $C_{vinyl}-CF_3/C_{vinyl}-CF_2$ 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.

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The authors declare no competing financial interest.