



Rapid Interception of $C_n F_{2n+1}(O)SO^{\circ}$ Radical with Copper-Based Carbene: A Novel Access to Perfluoroalkanesulfinate Ester

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Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday

Abstract: In this communication, an unprecedented interception of $C_nF_{2n+1}(O)SO^*$ radical with a copper-based carbene has been established. Distinguished by wide substrate scopes and mild reaction conditions, this novel radical–carbene coupling reaction (RCC reaction) provides a fundamentally different and mechanistically interesting strategy for the synthesis of perfluoroalkanesulfinate esters.



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Organofluorine compounds are widely used in agrochemistry, medicine, and material sciences^[1] since they often possess a variety of remarkable physicochemical and biological properties,^[2] such as solubility, lipophilicity as well as catabolic stability. $^{\mbox{\tiny [2f,3]}}$ However, the utility of trifluoromethanesulfinate esters has not been rigorously explored because of their synthetic inaccessibility and instability. At a first glance, Langlois reagent (CF₃SO₂Na), a commercially available, inexpensive, and stable compound, appears to be a straightforward strategy for generating trifluoromethanesulfinate esters. In practice, however, the strong propensity of CF₃SO₂Na to decompose with release of SO₂ has rendered it mostly a classic trifluoromethylation realkenes,^[4] alkynes^[5] and agent for (hetero)arenes^[6] (Scheme 1 a).

Traditional trifluoromethanesulfinyl oxylation methods, which are essentially ionic processes,^[7] are often limited in substrate scope, require hazardous reagents and harsh conditions, and inevitably generate large amounts of toxic halide byproducts.^[7b,d-g] To the best of our knowledge, there has not been any published study on radical trifluoromethanesulfinyl oxylation reaction. Similar to radicals, metal carbenes are also highly reactive and synthetically versatile species.^[8] Radical–carbene coupling (RCC) is considered a promising and mechanistically interesting strategy for the synthesis of polyfunctionalized molecules considering that both of them have low concentrations in the reaction system. Recently, we reported the direct cou-

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Scheme 1. Synthetic use of Langlois reagent (CF₃SO₂Na).

pling of α -aminoalkyl radicals and metal carbenes to generate β -ester- γ -amino ketones^[9a,b] and indoles.^[9c] We also developed a RCC method that allowed the efficient preparation of isoxazolines from Cu-based carbenes and nitroso radicals under mild conditions.^[9d] These results prompt us to speculate, as illustrated in Scheme 1 b, that the CF₃(O)SO[•] radical II, generated by the single-electron oxidation of Langlois reagent, could be rapidly intercepted by a highly active metal carbene prior to its imminent decomposition (Scheme 1a) to form intermediate III, which could then be further converted to various trifluoromethanesulfinate esters via protonolysis (Scheme 1b).

To test our hypothesis, we first performed a pilot coupling reaction of α -diazoacetophenone **1**a, which served as a carbene precursor, with CF₃SO₂Na 2a for the formation of trifluoromethanesulfinate ester 3a. Considering that the metal carbene plays a critical role in ensuring the successful capture of CF₃(O)SO[•] radical, we screened a variety of transition-metal catalysts containing Cu, Co, or Fe (for more details, see Supporting Information (SI), Table S1, entries 1–11). To our delight, running the coupling reaction at 60° C for 1 h with Cu(OAc)₂, which is commercially available and inexpensive, led to the best result and provided 3a, which was isolated in 75% yield (Table 1, entry 1). Unsurprisingly, little product was formed when no oxidant was used (Table 1, entry 5). However, product 3 a was isolated in 38% yield even in the absence of Cu(OAc)₂ (Table 1, entry 4), suggesting that CF₃(O)SO[•] could also be intercepted by the free carbene. Other oxidants, including di-tertbutyl peroxide (DTBP), K₂S₂O₈, H₂O₂, benzoperoxide (BPO), and tert-butyl peroxybenzoate (TBPB), were all found to be significantly less effective than TBHP in promoting the generation of 3 a (for more details, see SI, Table S1, entries 14-19). Finally, we evaluated several commonly used organic solvents, such as pe-

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Table 1. Optimization of the reaction conditions. ^[a]				
	0 N ₂ + F ₃ (O ≝ C ^{∕S} ∖ONa -	catalyst, oxidant solvent 60 °C, 1 h	
1	a	2a		3a
Entry	Catalyst	Oxidant	Solvent	Isolated yield [%]
1	Cu(OAc) ₂	TBHP	EA	75
2	Co(acac) ₂	TBHP	EA	42
3	FeSO₄·7H₂O	TBHP	EA	36
4	none	TBHP	EA	38
5	Cu(OAc) ₂	none	EA	< 5
6	Cu(OAc) ₂	DTBP	EA	< 5
7	Cu(OAc) ₂	H_2O_2	EA	39
8	Cu(OAc) ₂	TBHP	PE	44
9	Cu(OAc) ₂	TBHP	CHCl ₂ CH ₂ Cl	66
10	Cu(OAc) ₂	TBHP	MeNO ₂	67
11	Cu(OAc) ₂	TBHP	MeCN	49
12	Cu(OAc) ₂	TBHP	DCE	69
13	Cu(OAc) ₂	TBHP	CCI ₃ CH ₃	40

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.6 mmol, 3.0 equiv), catalyst (0.02 mmol, 10 mol%), oxidant (1.0 mmol, 5.0 equiv), and solvent (2.0 mL) for 1 h under air. EA=ethyl acetate, PE=petroleum ether, DCE=1,2-dichloroethane, TBHP=*tert*-butyl hydroperoxide.

troleum ether (PE), $CHCl_2CH_2CI$, $MeNO_2$, MeCN, 1,2-dichloroethane (DCE) and CCl_3CH_3 . The results indicated that substituting ethyl acetate (EA) with any of these solvents would cause the reaction efficiency to decrease slightly (Table 1, entries 8– 13).

With the optimal conditions in hand, we began to explore the substrate scope of the reaction by first testing a series of α -diazo ketones (Scheme 2). We found that both electron-donating and electron-withdrawing groups were tolerated on the benzene ring of 1 a, affording the corresponding products 3 a-3s in moderate to good yields. Satisfyingly, halogens (F, Cl, and Br) and hydroxyl were also well tolerated at the para- and meta-positions, which opens possibilities for further chemical modifications. It is noteworthy that the trifluoromethanesulfinyl oxylation of ortho-methyl aryldiazoketone into the desired product **3r** was not significantly affected by its apparent steric hindrance (73% yield). The coupling reaction was shown to be also compatible with aryl carbenes bearing a naphthalene or thiophene moiety, as demonstrated by the synthesis of 3s and 3t in 52% and 63% yields, respectively. Moreover, alkyl-substituted α -diazo ketones were also suitable reactants for this transformation (3 u and 3 v). Notably, the exact structure of trifluoromethanesulfinate ester 3a was unambiguously determined by X-ray diffraction (Scheme 2).

Next, we investigated whether we could expand the scope of the coupling reaction to include diazo esters from phenols and alcohols (Scheme 3). In all cases, the reactants were well tolerated and converted to the corresponding α -trifluoromethanesulfinate ester products 3a'-3f' in moderate to good yields. Notably, diazo esters carrying an acetyl (Ac) or *tert*-butoxycarbonyl (Boc) protected amino group on the aromatic ring could withstand the oxidation and furnish the desired products 3e' and 3f', albeit at slightly reduced yields of 41% and 48%, respectively.



Scheme 2. Scope of α -diazo ketones. Reaction conditions: 1 (0.2 mmol, 1.0 equiv), 2a (0.6 mmol, 3.0 equiv), Cu(OAc)₂ (0.02 mmol, 10 mol%), TBHP (1.0 mmol, 5.0 equiv, 70% in water), and EA (2.0 mL) for 1 h under air. Yields of isolated products are given.



Scheme 3. Scope of diazo esters. Reaction conditions: 1' (0.2 mmol, 1.0 equiv), **2a** (0.6 mmol, 3.0 equiv), $Cu(OAc)_2$ (0.02 mmol, 10 mol%), TBHP (1.0 mmol, 5.0 equiv, 70% in water), and EA (2.0 mL) for 1 h under air. Yields of isolated products are given.

To further enhance the utility of this methodology, $C_nF_{2n+1}SO_2Na$ substrates of various lengths were also examined (Scheme 4). As expected, all substrates could competently

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Scheme 4. Scope of $C_nF_{2n+1}SO_2Na$. Reaction conditions: **1 a** (0.2 mmol, 1.0 equiv), **2** (0.6 mmol, 3.0 equiv), Cu(OAc)₂ (0.02 mmol, 10 mol%), TBHP (1.0 mmol, 5.0 equiv, 70% in water), and EA (2.0 mL) for 1 h under air. Yields of isolated products are given.

couple with **1a**, enabling the preparation of a wide range of agrochemically and/or pharmaceutically relevant α -perfluoroal-kanesulfinate ketones (**4a**–**4d**) that could not be synthesized by other methods.

Subsequently, we conducted a series of mechanistic studies. First, the inclusion of 1,1-diphenylethylene **6** in the coupling reaction of **1a** and **2a** led to the identification and isolation of two radical adducts **7** and **8** (the yields of **7** and **8** were based upon **6**), providing convincing evidence for the two key intermediates $CF_3(O)SO^{\circ}$ and CF_3° (Scheme 5a). At the same time,



Scheme 5. Probe for the possible mechanism.

the desired product **3a** can be also isolated in 60% yield (the yield of **3a** was based upon **1a**). In addition, the generation of **3a** was completely suppressed in the presence of the radical inhibitor 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO, Scheme 5 b).^[10] Altogether, these results indicated that $C_n F_{2n+1}(O)SO$ was trapped rapidly by a copper-based carbene before it could decompose and release SO_2 .

Based upon findings from the above experiments and literature reports,^[4c,6b,d,11] we proposed a plausible reaction mechanism shown in Scheme 6. The catalytic cycle begins with TBHPpromoted single-electron oxidation of CF_3SO_2Na into $CF_3(O)SO$. **A**, which is immediately trapped by the copper-based carbene **B** to afford an organocopper intermediate **C**. Finally, **C** undergoes protonolysis to deliver the desired perfluoroalkanesulfinate esters in satisfactory yields.

In conclusion, we have successfully developed a novel strategy for the synthesis of perfluoroalkanesulfinates esters from α -diazo compounds and sodium perfluoroalkanesulfinate. Mechanistic studies indicated that the coupling reaction involved the rapid interception of $C_n F_{2n+1}(O)SO^*$ radical with a

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Scheme 6. Proposed reaction mechanism.

copper-based carbene, followed by protonolysis process. We are currently striving to achieve the construction of other fluorine-containing compounds through RCC.

Experimental Section

Diazo compounds (0.2 mmol), $C_nF_{2n+1}SO_2Na$ (0.6 mmol), and $Cu(OAc)_2$ (0.02 mmol) were added to a test tube charged with a stirring bar. Ethyl acetate (2.0 mL) and TBHP (1.0 mmol, 70% in water) were added using a syringe. The reaction mixture was heated at 60°C for 1 h, which was then quenched with saturated Na_2SO_3 solution and extracted with ethyl acetate (3×3.0 mL). The organic layers were combined and dried over anhydrous MgSO₄. Removal of the organic solvent followed by purification by flash column chromatography (PE/EA) afforded the desired products.

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Conflict of interest

The authors declare no conflict of interest.

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copper-based carbene, a fundamentally different and mechanistically interesting synthetic strategy for perfluoroalkanesulfinate esters has been developed. This novel radical-carbene coupling re-

erational simplicity, leading to a variety of perfluoroalkanesulfinate esters in satisfactory yields.

Radical Reactions

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Rapid Interception of $C_n F_{2n+1}(O)SO$. Radical with Copper-Based Carbene: A Novel Access to Perfluoroalkanesulfinate Ester