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# Aryl Radical Activation of C–O Bonds: Copper-Catalyzed Deoxygenative Difluoromethylation of Alcohols

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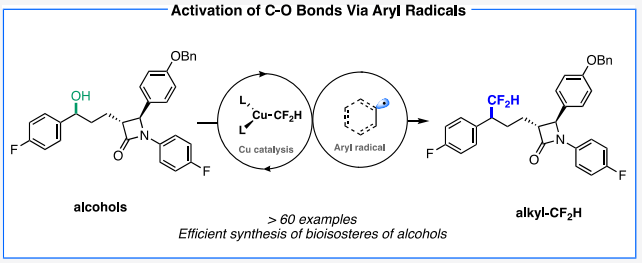
**ABSTRACT:** Given their ubiquity in natural products and pharmaceuticals, alcohols represent one of the most attractive starting materials for the construction of C–C bonds. We report herein the first catalytic strategy to harness the reactivity of aryl radicals for the activation of C–O bonds in alcohol-derived xanthate esters, allowing for the discovery of the first catalytic deoxygenative difluoromethylation reaction. Under copper-catalyzed conditions, a wide variety of alkyl xanthate esters, readily synthesized from alcohol feedstocks, were activated by catalytically generated aryl radicals and were converted to the alkyl-difluoromethane products via alkyl radical intermediates. This scalable protocol exhibits a broad substrate scope and functional group tolerance, enabling late-stage modification of complex pharmaceutical agents. A one-pot protocol has been developed that allows for the direct use of free alcohols without purification of the xanthate esters. Mechanistic studies are consistent with the hypothesis of aryl radicals being formed and initiating the cleavage of the C–O bonds of xanthate esters, to generate alkyl radicals as the key intermediates. This aryl radical activation approach represents a new strategy for the activation of alcohols as cross-coupling partners.




## INTRODUCTION

The development of transition metal-catalyzed cross-coupling reactions for the construction of C–C bonds continues to be a central topic in the field of synthetic organic chemistry.[1] In this area, the identification of stable, easily handled, yet reactive alkyl electrophiles as well as novel activation modes that can engage new coupling partners in these reactions remains an important goal. Recent years have witnessed continuous efforts devoted to the use of alcohols and their derivatives as coupling partners,[2] largely owing to the fact that alcohols are among the most naturally abundant organic compounds and are ubiquitous in bioactive molecules. In particular, the activation of alcohol-based C–O bonds for the construction of C–C bonds via the formation of alkyl radical intermediates offers a promising yet challenging opportunity for the diversification of alcohol feedstocks. For instance, pioneering work by Overman,[3] MacMillan,[4] Gong,[5] and Shu[6] has shown that alkyl oxalates, readily synthesized from alcohols, could be engaged as radical fragments in Ni catalysis or metallophotoredox catalysis. Li et al. have reported an electrochemically enabled, nickel-catalyzed protocol that can directly use free alcohols in the coupling reactions with aryl bromides.[7] The Diao group has very recently discovered that a dihydropyridine-derived auxiliary could activate the anomeric C–O bonds of carbohydrates for the synthesis of aryl glycosides via the formation of glycosyl radical intermediates.[8] In spite of these breakthroughs, the discovery of new activation modes that can engage easily accessed alcohol derivatives in C–C bond-forming coupling reactions remains highly desirable.

Alkyl xanthate esters, which are bench-stable and can be readily prepared from the corresponding alcohols, have been widely used in Barton-McCombie deoxygenation reactions.[9] Despite the well-known formation of alkyl radicals as key intermediates in these reactions, to date, there were very few examples that could engage xanthate esters in cross-couplings. Molander has nicely shown that O-benzyl xanthates could be activated by photogenerated *sec*-butyl radicals and readily participated in Ni-catalyzed coupling reactions.[10] Very recently, the Rousseaux group reported that nickel alone could also catalyze the cross-couplings of finely tuned carbamothioates with aryl halides.[11] These two neat methods allowed for the construction of $Csp^3$–$Csp^2$ bonds using alcohol-derived xanthate analogues although only derivatives of primary benzylic alcohols or tertiary 1-phenylcyclopropanols were amenable with the reaction conditions. In addition, Altman[12] and Cook[13] have shown that in the presence of superstoichiometric amounts of copper(0) or copper(III) complexes, respectively, xanthate esters could be efficiently converted to alkyl-trifluoromethanes. These elegant approaches could provide easy access to trifluoromethylated

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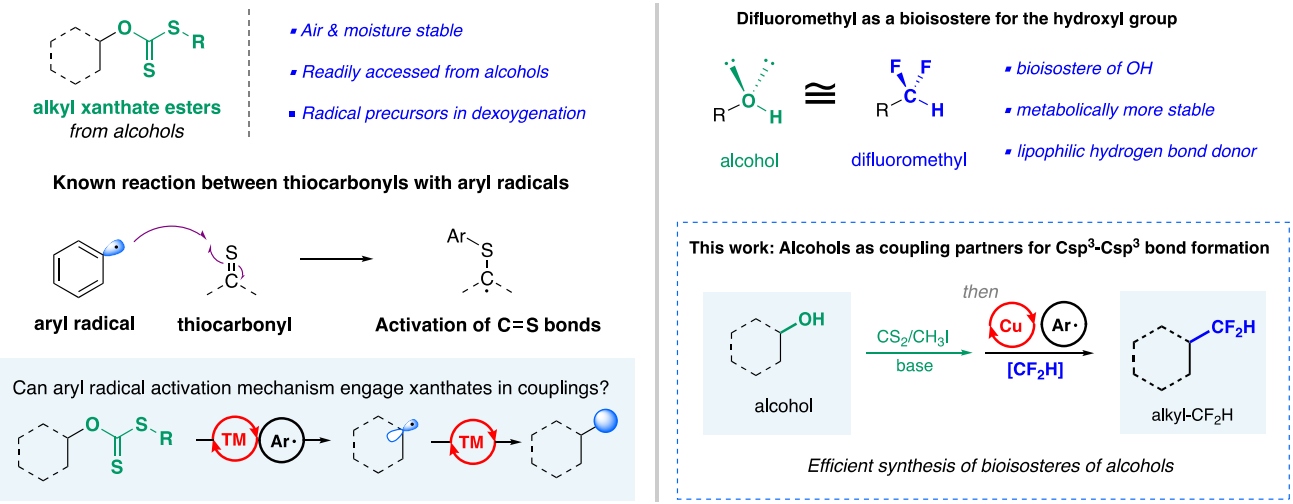


**Figure 1.** A new aryl radical activation/copper capture mechanism could engage alkyl xanthate esters in transition metal-catalyzed cross-coupling reactions and allow for the development of a copper-catalyzed deoxygenative difluoromethylation reaction for the rapid synthesis of bioisosteres of alcohols. TM: transition metals.

products from alcohols although the high loading of copper and a special copper(III) complex[14] could dampen the generality of these methods. Therefore, new catalytic strategies that employ alkyl xanthate esters as coupling partners for the construction of C−C bonds could offer new opportunities for the functionalization of alcohols and the late-stage modification of pharmaceutical agents. Herein, we report a unique aryl radical activation/copper capture mechanism for the catalytic conversion of alkyl xanthate esters to their corresponding alkyl-difluoromethanes (Figure 1).

The difluoromethyl ($CF_2H$) group has received increasing attention in medicinal chemistry community due to its unique hydrogen-bonding ability.[15] Recent work has shown that, depending on the attached functional groups, $CF_2H$ groups can act as hydrogen-bond donors on a scale comparable to (in most cases, weaker than) that of hydroxyl groups.[16] Therefore, $CF_2H$ groups can be considered as lipophilic bioisosteres of alcohols, replacing the hydroxyl groups of the parent drug candidates to modify their pharmacokinetic and pharmacodynamic profiles.

For instance, Burton has successfully used this bioisosteric replacement approach in the development of a DAF-12 receptor antagonist: compared to the parent hydroxyl-containing molecule, the $CF_2H$ analogue exhibited improved *in vivo* activity, retained the antagonist activity, and was devoid of residual agonist activity.[17] However, as traditional difluoromethylation reactions required $CF_2H$ groups to be installed at a very early stage of the synthesis, development of a $CF_2H$ analogue of an alcohol typically required lengthy denovo synthesis. Thus, the direct conversion of a hydroxy group into a $CF_2H$ group at a late stage could be a highly desirable approach to the rapid evaluation of bioisosteres of drug candidates and the synthesis of previously difficult-to-access $CF_2H$ molecules as potent medicines. To this end, the Xiao group has recently reported an ingenious copper-mediated dehydroxylative difluoromethylation reaction although the requirement of superstoichiometric amounts of copper(I) salts and the limitation to only primary alcohols might prevent a wide application of this method.[18]

## RESULTS AND DISCUSSION

**Hypothesis.** Our recent work on the carbo-difluoromethylation of alkenes as well as early work by Goossen[19] has shown that aryl radicals could be generated from the reactions between aryl diazonium salts and $[Cu^{I}-CF_2H]$ species. Given the precedented reactions between aryl radicals and thiocarbonyl groups,[2e,20] we questioned whether *in situ* generated aryl radicals could activate xanthate esters in a fashion similar to how stannyl,[9b] silyl,[21] or ethyl radicals[22] activate them in Barton-McCombie-type reactions in which alkyl radicals were formed via the cleavage of the C−O bonds of xanthate esters. We expect that the alkyl radicals could then engage in our recently discovered copper-$CF_2H$ capture/reductive elimination mechanism to afford alkyl-difluoromethanes.[23] It is worth noting that despite a diverse range of synthetic transformations that involved aryl radical intermediates, the use of aryl radicals for the activation of functional groups has remained an untapped field in organic synthesis.[24] Therefore, we anticipated that the successful execution of this concept would not only provide a general platform to engage xanthate esters in coupling reactions and catalytically access alkyl-difluoromethanes from alcohols but also open a new avenue for the development of novel synthetic transformations that can manipulate the reactivity of aryl radicals.

Our proposed mechanism for the aryl radical-activated, copper-catalyzed deoxygenative difluoromethylation protocol is outlined in Figure 2. The transmetalation from a nucleophilic $CF_2H$ reagent, $(DMPU)_2Zn(CF_2H)_2$ (i.e., Vicic-Mikami reagent) **1**,[25] to a copper(I) catalyst **2** could generate a reactive $[Cu^{I}-CF_2H]$ species **3**.[19,25b,26] This species **3** should undergo a single electron transfer with an aryl diazonium salt **4** to give an aryl radical **5** and a $[Cu^{II}-CF_2H]$ complex **6**. We hypothesized that this aryl radical **5** would attack the C=S $\pi$ bond of an alcohol 7-derived xanthate ester **8** to form a radical intermediate **9**. The ensuing homolytic cleavage of the C−O bond of **9** and the concurrent formation of a new C=O $\pi$ bond could generate an alkyl radical **10** and a *S*-aryl dithiocarbonate **11**. Facile oxidative trapping of the alkyl radical **10** by the $[Cu^{II}-CF_2H]$ intermediate **6** would then furnish a formally alkyl-copper(III) complex **12**.[27] Reductive elimination of **12** would afford the alkyl-difluoromethane


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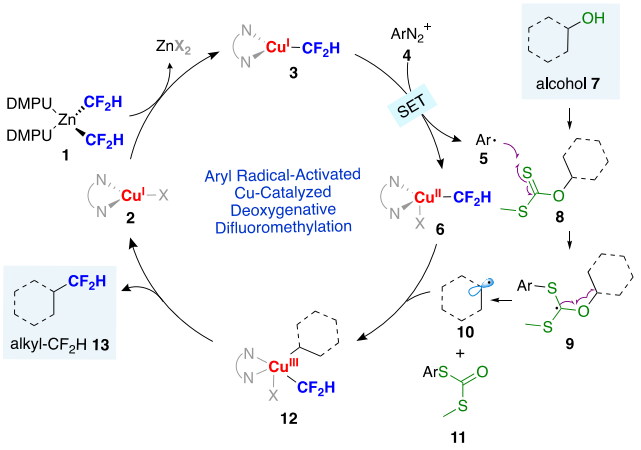
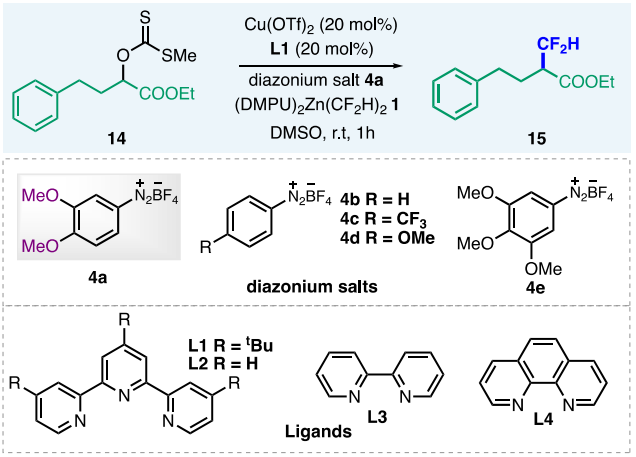



**Figure 2.** Proposed catalytic cycle for the aryl radical-activated, copper-catalyzed deoxygenative difluoromethylation reaction.

product **13** and regenerate the $Cu^{I}$ catalyst **2**,[28] effectively closing the catalytic cycle. We realized that this proposed catalytic cycle would pose two major challenges: (i) the potential binding of sulfur atoms in xanthate esters with copper catalysts could inhibit the reactivity, and (ii) the high reactivity of aryl diazonium salts and aryl radicals could lead to undesired side reactions. We reasoned that these challenges could be circumvented by modifying the binding environment of copper catalysts and tuning the electronic properties of diazonium salts.

**Reaction Optimization.** To test this hypothesis, a xanthate ester **14**, easily synthesized from the corresponding alcohol on a gram scale, was used as the model substrate. After exposing **14** to a variety of conditions, we were pleased to find that in the presence of catalytic amounts of $Cu(OTf)_2$, tri*tert*-butyl-terpyridine **L1** and $(DMPU)_2Zn(CF_2H)_2$ **1**, along with a diazonium salt **4a**, **14** could be selectively converted to the corresponding difluoromethylated product **15** in an 89% yield at room temperature (Table 1, **entry 1** and SI). Consistent with our hypothesis, the ligands played a vital role in this reaction; the use of bidentate ligands had a deleterious effect on the reactions, and the use of other tridentate ligands led to diminished yields (**entries 2−4**). Although the unique role of terpyridine in this reaction remains unclear, it is likely that the tridentate ligand could help to stabilize the [Cu−$CF_2H$] species, thus preventing other unproductive pathways.[29] The choice of a diazonium salt **4a** bearing electron-donating groups was another crucial factor to the success of this reaction (**entries 5−8**). Lower yields were attained when less electron-rich aryl diazonium salts were used. The use of a trimethoxy substituted diazonium salt **4e** led to a decreased yield, largely due to its moderate solubility in DMSO. It is noteworthy that **4a** could be easily prepared from the inexpensive aniline (~ $0.4/g) on a decagram scale and be stored in a −20 °C freezer for at least 3 months without noticeable decomposition. Other copper(I) and copper(II) salts could also be used (**entries 9−10**), albeit with lower efficiency. We postulated that copper(II) salts were reduced *in situ* by the zinc reagents to form the reactive copper(I) catalysts. Of all solvents screened, DMSO was found to be the optimal solvent and the addition of other cosolvents led to diminished yields (**entries 11−12**). Control experiments showed that no products were formed in the absence of either copper catalysts or diazonium salts (**entry 13**).

**Table 1. Reaction Optimization**[a]




| entry | variation from standard conditions | yield (%)[b] |
|---|---|---|
| **1** | **None** | **89** |
| 2 | **L2** instead of **L1** | 76 |
| 3 | **L3** instead of **L1** | 14 |
| 4 | **L4** instead of **L1** | 16 |
| 5 | **4b** instead of **4a** | 42 |
| 6 | **4c** instead of **4a** | 24 |
| 7 | **4d** instead of **4a** | 69 |
| 8 | **4e** instead of **4a** | 20 |
| 9 | $[Cu(OTf)]_2{\cdot}C_6H_6$ instead of $Cu(OTf)_2$ | 46 |
| 10 | $Cu(OAc)_2$ instead of $Cu(OTf)_2$ | 48 |
| 11 | DMSO: THF (2:1) | 54 |
| 12 | DMSO: ACN (2:1) | 32 |
| 13 | no $Cu(OTf)_2$ or no **4a** | N.D. |

[a]Reactions were conducted with **14** (0.1 mmol, 1.0 equiv), diazonium salt (0.2 mmol, 2.0 equiv), **1** (0.12 mmol, 1.2 equiv), $Cu(OTf)_2$ (20 mol %), and ligand (20 mol %) in DMSO (0.6 mL) at RT. [b]Yields were determined by $^{19}F$ NMR using 1-fluoro-3-nitrobenzene as the internal standard.

**Substrate Scope.** We then explored the scope of this deoxygenative difluoromethylation reaction (Table 2). Common functional groups, including esters (**15−17**), nitriles (**18**), imides (**19**), amides (**20, 21**), and carbamates (**34**), were well-tolerated under the reaction conditions. Alkenes (**22−23**) and terminal alkynes (**24**) were also tolerated under the standard conditions, despite their tendency to react with carbon-centered radicals, highlighting the selectivity of aryl radials toward the C=S bonds. Interestingly, despite the reactions between aryl radicals with xanthate groups, this transformation was tolerant of thioesters (**25**). Nitrogen containing heterocycles, which are core structures in drug synthesis, including piperidine (**26**), morpholine (**27−29**), pyrrolidine (**30**), azepane (**31**), tetrahydroisoquinoline (**32**), azetidine (**33**), and piperazine (**34**), were all accommodated in this protocol. Moreover, this system could be applied to the difluoromethylation of secondary benzylic and heterobenzylic alcohols (**35−39**), complementing our previously developed decarboxylative[23b] and deaminative difluoromethylation protocols,[23c] in which the scope of secondary benzylic carboxylic acids or secondary benzylic pyridinium salts was limited. The scalability of this reaction was demonstrated through the gram scale synthesis of compound **15**.

Xanthate esters derived from primary alcohols were also evaluated in this difluoromethylation protocol. Phenyl alcohols


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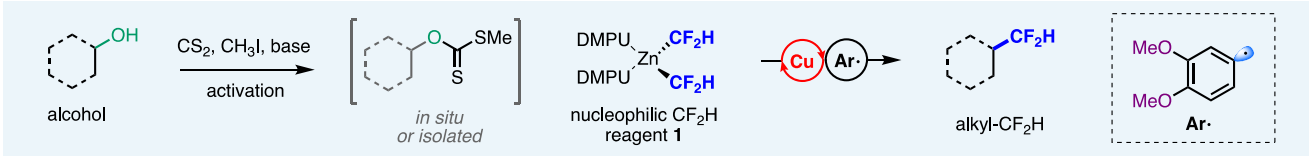
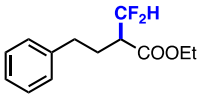
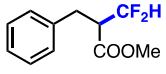
**Table 2. Substrate Scope of the Aryl Radical-Activated, Copper-Catalyzed Deoxygenative Difluoromethylation**[a]

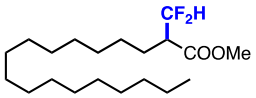


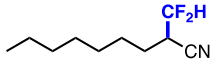
**15**, 86%



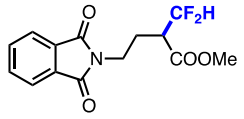
**16**, 82%



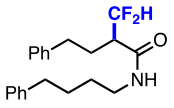
**17**, 65%



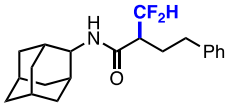
**18**, 56%



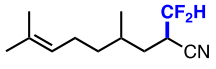
**19,** 55%



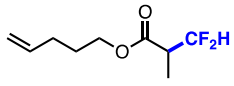
**20,** 62%



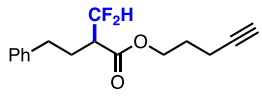
**21**, 62%



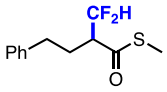
**22,** 54%, *d.r.* = 1.3:1



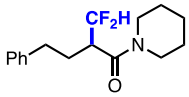
**23**, 52%[c]



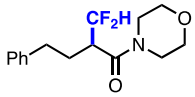
**24**, 46%



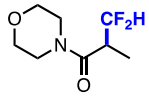
**25**, 62%



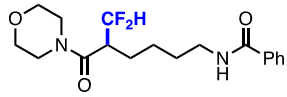
**26**, 66%



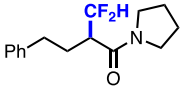
**27**, 70%



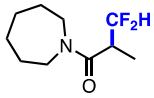
**28**, 56%



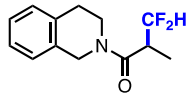
**29**, 64%



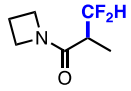
**30**, 54%



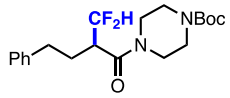
**31**, 66%
*one-pot*: 62%[b]



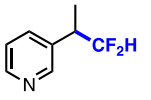
**32**, 60%



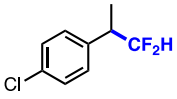
**33,** 74%



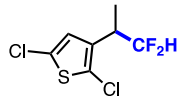
**34,** 36%



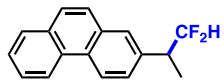
**35**, 43%[c]



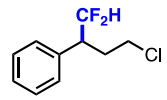
**36**, 65%
*one-pot*: 45%[b]



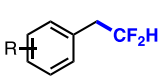
**37**, 67%



**38,** 66%

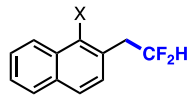


**39**, 55%

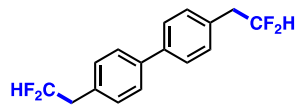


**40**, R = H, 72%[c]
**41**, R = 4-Ph, 91%
*one-pot*: 83%[b]
**42**, R = 3-OPh, 65%
*one-pot*: 52%[b]
**43**, R = 4-I, 56%[c]
**44**, R = 4-CHO, 93%[c]

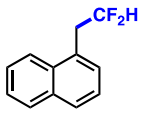
**45**, R = 2,6-$Cl_2$, 83%
*one-pot*: 67%[b]
**46**, R = 3,5-$F_2$, 72%[c]
**47**, R = 3,5-$(CF_3)_2$, 86%[c]
**48**, R = 3,4,5-$(OMe)_3$, 84%
**49**, R = 4-Bpin, 40%



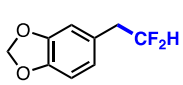
**50**, X = H, 91%
**51**, X = Br, 61%



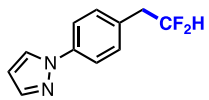
**52**, 50%



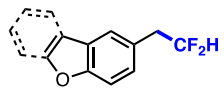
**53**, 64%



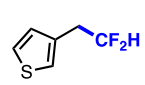
**54**, 67%



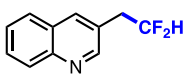
**55**, 85%



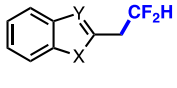
**56**, from benzofuran, 74%
**57,** from dibenzofuran, 76%



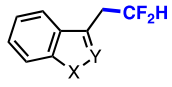
**58**, 71%[c]



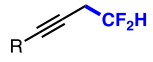
**59**, 65%



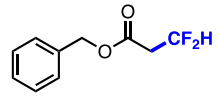
**60**, X = S, Y = CH, 71%
**61**, X = O, Y = CH, 75%
**62**, X = S, Y = N, 75% (64%[b])
**63**, X = O, Y = N, 60%



**64**, X = S, Y = CH, 70%
**65**, X = $NCH_3$, Y = N, 54%



**66,** R = $NPhthCH_2$, 68%
**67,** R = Ph, 71%[c]



**68**, 20%[c]

[a]Unless otherwise noted, reactions were run with 0.25 mmol of xanthate esters, 0.5 mmol of diazonium salt (2.0 equiv), 0.3 mmol of **1** (1.2 equiv), **L1** (20 mol %) and $Cu(OTf)_2$ (20 mol %) in 1.5 mL of DMSO at RT. Isolated yields based on xanthate esters. [b]Reactions were run with 0.25 mmol of alcohols. Isolated yields based on alcohols. [c]Yield was determined by $^{19}F$ NMR due to the volatility of the product.



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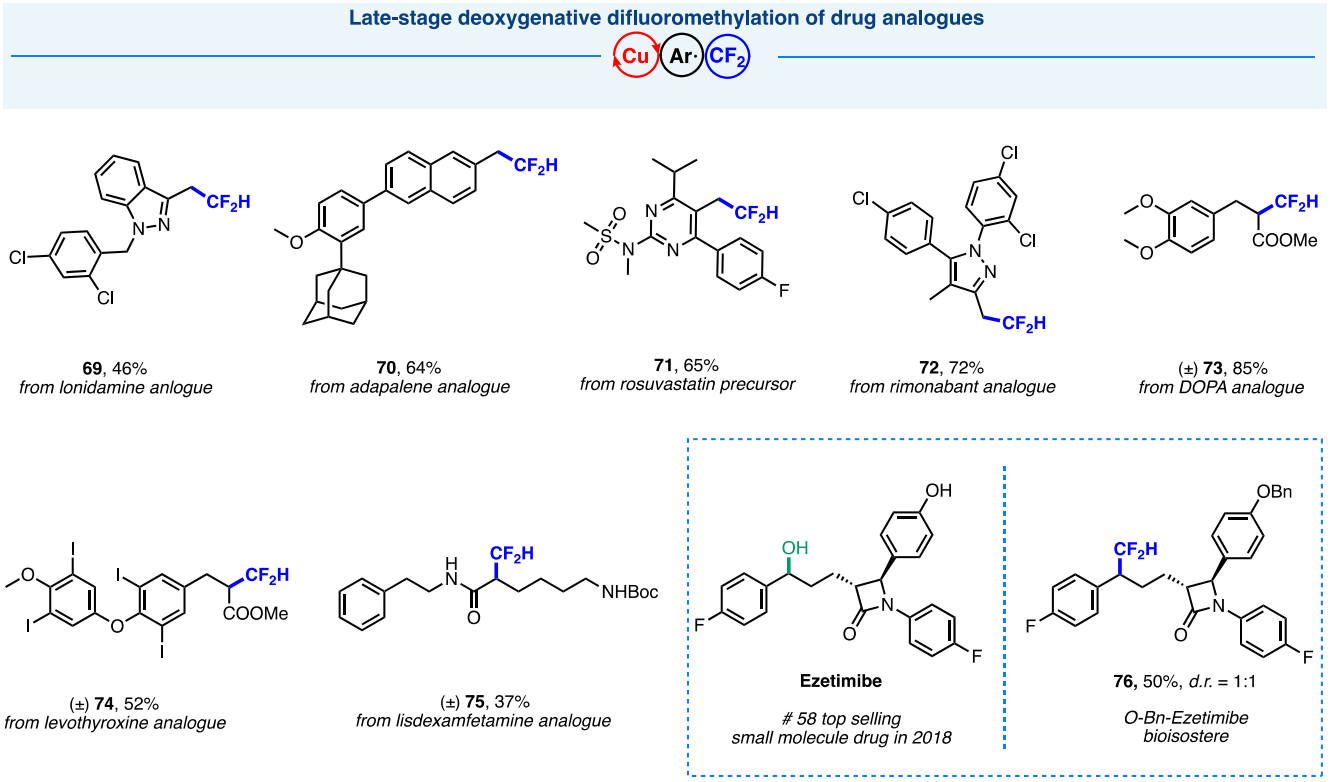


**Figure 3.** Copper-catalyzed late-stage deoxygenative difluoromethylation of pharmaceutical derivatives. See Supporting Information for detailed experimental conditions.

were generally competent, with a diverse range of electron-withdrawing, electron-donating, and electron-neutral functional groups tolerated on the aryl rings (**40**–**49**). Steric hindrance had little effect on the reactivity and a good yield was observed for a 2,6-dichloro substituted substrate (**45**). Notably, the compatibility of aryl bromides (**51**) and iodides (**43**) with this reaction could allow for the further diversification of the products. The aldehyde group, which could be problematic under nucleophilic difluoromethylation conditions, was compatible with this protocol (**44**). A boronic ester was tolerated under the copper-catalyzed mild conditions, albeit in a moderate yield (**49**). A substrate that contained two hydroxyl groups was doubly difluoromethylated (**52**). In addition, different heterocycles including dioxole (**54**), pyrazole (**55**), furan (**56**), were tolerated on the phenyl rings. Furthermore, this method was applied to the difluoromethylation of a diverse range of heterobenzylic (**58**–**65**) and propargylic alcohols (**66** and **67**), affording the $CF_2H$ derivatives of thiophene, quinoline, benzofuran, benzothiazole and indazole. Finally, this protocol could also be extended to a nonbenzylic primary alcohol (**68**), albeit in a fair yield.

**Limitations.** Although diazonium salts were required for all the difluoromethylation reactions shown in Table 1, xanthate esters derived from allylic alcohols could be converted to the corresponding allyl-difluoromethanes in the absence of diazonium salts (Figure S1). The similar reactivity has also been reported by Mikami for the copper-catalyzed difluoromethylation of allyl carbonates in which the formation of $\pi$-allyl copper(III) species has been proposed.[30] We expected that such intermediates were also formed between the reactions of $[Cu^{I}–CF_2H]$ with the allylic xanthate esters, which reductively eliminated to form allyl-difluoromethanes. Similarly, secondary propargylic xanthate esters were converted to difluoromethylated allenes when no diazoniums salts were used (Figure S2). Copper-catalyzed difluoromethylation of conjugated propargyl bromides has been recently reported by Shen using a silver-difluoromethyl reagent.[31] Finally, a limitation of this protocol is its incompatibility with xanthate esters derived from cyclic alcohols (see Figure S3 for a list of unsuccessful substrates). Nonetheless, this complements our previously reported decarboxylative difluoromethylation reactions[23b] in which the cyclic carboxylic acids were more competent than the acyclic counterparts.

**One-Pot Deoxygenative Difluoromethylation.** An ideal deoxygenative difluoromethylation reaction would obviate the need to separate the xanthate intermediates and directly use alcohols in the reactions. Therefore, to further facilitate the broader application of this method in the field of medicinal chemistry, we developed conditions for the one-pot conversion of alcohols to the difluoromethylated products. Specifically, substrates that did not contain base-sensitive functional groups could be readily converted to their xanthate esters in a biphasic $NaOH/CS_2$ system within a few minutes. After the completion of the reactions, the aqueous layers could be easily removed by simple pipetting, and the crude xanthate esters were used in the next step without further purification. The generality of this one-pot procedure has been evaluated on different alcohols (**31**, **36**, **41**, **42**, **45**, **62**), including primary, secondary, and heterobenzylic alcohols, all of which were converted to the corresponding $CF_2H$ products in workable yields.

**Late-Stage Difluoromethylation of Pharmaceuticals.** Hydroxyl groups are ubiquitous in pharmaceuticals and can also be easily transformed from other functional groups. We anticipated that this deoxygenative difluoromethylation


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method could offer a general strategy for the rapid synthesis of $CF_2H$ analogues of pharmaceutical agents. Therefore, we performed a series of late-stage modifications on medicinally relevant molecules (Figure 3). The xanthate esters of derivatives of lonidamine, an antispermatogenic and anticancer agent,[32] as well as adapalene, a topical retinoid for the treatment of acne,[33] were converted to their $CF_2H$ analogues (**69** and **70**) in 46% and 64% yield, respectively. The difluoromethylation of a precursor to rosuvastatin, a medicine used to lower cholesterol,[34] allowed for the incorporation of a $CF_2H$ group on the sterically hindered heterobenzylic position of a pyrimidine ring in a 65% yield (**71**). The analogue of rimonabant, an anorectic antiobesity drug,[35] was converted to the $CF_2H$ analogue in a 72% yield, with three aryl chloride bonds remaining unaffected (**72**).

In addition, the $CF_2H$ analogue of the protected DOPA (**73**), an amino acid made as part of the human biology and used in the clinical treatment of Parkinson's disease,[36] could be synthesized in an 85% yield from its xanthate ester. Levothyroxine, one of the top-selling drugs for the treatment of thyroid hormone deficiency and thyroid tumors,[37] was converted to its $CF_2H$ analogue (**74**) via the xanthate intermediate in a 52% yield. It is worth noting that the tolerance of multiple aryl iodides on electron-rich phenyl rings further highlighted the mild conditions of this copper-catalyzed protocol. Moreover, an analogue of lisdexamfetamine, one of the most prescribed medications in the United States for treating attention deficit hyperactivity disorder and binge eating disorder,[38] was converted to its $CF_2H$ analogue (**75**) in a synthetically useful yield.

Finally, we aimed to synthesize the $CF_2H$ bioisostere of ezetimibe, one of the top-selling pharmaceuticals to treat high blood cholesterol.[39] A main metabolic pathway of ezetimibe involves the oxidation of its benzylic hydroxyl group to form the ketone metabolite.[40] We expected that the replacement of the benzylic hydroxyl group with a $CF_2H$ group should block such a metabolic pathway while partially retaining the original hydrogen-bonding ability. To our delight, the xanthate ester of the benzyl-protected ezetimibe was converted to the difluoromethylated product (**76**) under the standard conditions in a 50% yield. These examples further highlighted the potential of this copper-catalyzed protocol for the rapid synthesis of $CF_2H$-containing pharmaceuticals.

**Mechanistic Studies.** Mechanistic experiments were conducted to shed light on this deoxygenative difluoromethylation reaction. The addition of a radical-trapping reagent TEMPO (2 equiv) to the difluoromethylation of **14** led to a suppression of the formation of **15**, while the generation of an aryl-TEMPO adduct (**77**) was detected by GC. **77** was also formed when the reactions were conducted without the xanthate esters, supporting the notion that aryl radicals were formed in the reactions between aryl diazonium salts and [Cu−$CF_2H$] species (Figure 4A). In addition, to establish the involvement of alkyl radicals in these reactions, we conducted the difluoromethylation of a cyclopropyl-bearing substrate (**78**). The difluoromethylation of this radical clock substrate afforded the unrearranged product (**79**), along with the ring-opened product (**80**), consistent with the hypothesis that short-lived alkyl radicals were involved in the reactions (Figure 4B). More importantly, this result ruled out the alternative pathway which involved the direct nucleophilic substitution of a [$Cu^I$−$CF_2H$] species with the xanthate ester via a $S_N2$ mechanism.

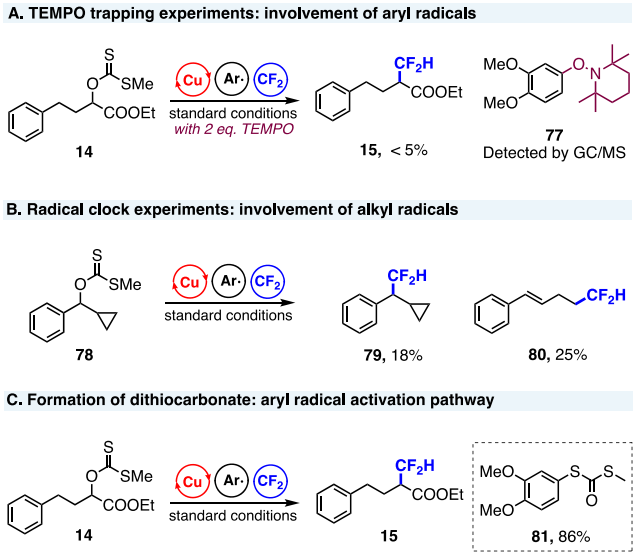


**Figure 4.** Mechanistic studies supported the proposed aryl radical activation mechanism.

Moreover, the proposed mechanism in Figure 2 was further supported by the detection of the *S*-aryl dithiocarbonate side product (**81**) in all the difluoromethylation reactions (Figure 4C). We were able to isolate this compound, the structure of which was unambiguously confirmed by NMR. The isolation of **81**, together with the fact that no difluoromethylated products were formed in the absence of diazonium salts, supported the postulation that aryl radicals were the key to the activation of xanthate esters.

## CONCLUSION

The Barton-McCombie reaction has taught the synthetic community that the formation of alkyl xanthate esters is an efficient strategy for the activation of alcohols via radical intermediates. However, the synthetic utility of xanthates has been significantly limited to the deoxygenation reactions, largely due to the lack of suitable activation modes that could engage them in transition metal-catalyzed coupling reactions. Due to the high reactivity of aryl radicals, they have been widely used in organic synthesis as building blocks for the installation of aryl groups. However, the synthetic utility of aryl radicals as reagents for the activation of functional groups remains an underexplored yet highly promising approach in synthetic organic chemistry.

By tuning the electronic properties of aryl diazonium salts, we disclose herein a unique aryl radical activation approach to engage alcohol-derived xanthate esters in cross-coupling reactions via copper catalysis, allowing for the discovery of the first catalytic deoxygenative difluoromethylation reaction. Mechanistic studies were consistent with an aryl radical activation pathway. Despite the current limitations and the additional work required to extend the scope of alcohols beyond ones bearing radical stabilizing groups, we expect that this protocol could find its wide application in the pharmaceutical industry for the rapid construction of $CF_2H$-containig drug candidates. Furthermore, this unique aryl radical activation approach should inspire novel C−C and C−heteroatom bond-forming reactions using xanthate esters as coupling partners as well as transformations that could


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manipulate the reactivity of aryl radicals. These studies are currently ongoing in our laboratories.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04254.

General information, experimental details, characterizations of new compounds, and NMR spectra (PDF)

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### Author Contributions

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### Notes

The authors declare no competing financial interest.

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