Cu(II) Catalyzed Unsymmetrical Di-oxidation of *gem*-Difluoroalkenes to Generate α,α-Difluorinated-α-Phenoxyketones, an Unstudied Substructure

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Abstract: A Cu-based catalyst system convergently couples *gem*-difluoroalkenes with phenols under aerobic conditions to deliver α,α-difluorinated-α-phenoxy ketones, an unstudied hybrid fluorinated functional group. Composed of α,α-difluorinated ketone and α,α-difluorinated ether moieties, these have only once been previously reported as a synthetic intermediate en route to pharmacologically active compounds. Computational predictions and later experimental corroboration suggest that the sp^3-hybridized hydrate adduct of the phenoxy-substituted fluorinated ketone is energetically accessible. The more facile conversion between ketone and hydrate forms suggest that covalent inhibition of proteases and other enzymes may be possible. Further functionalization of the ketone group enables access to other useful fluorinated functional groups.

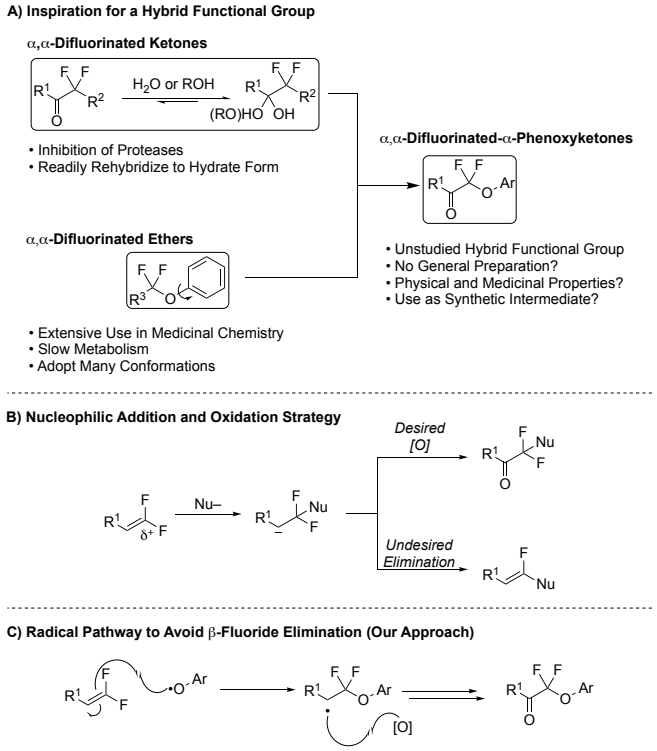
Introduction

Fluorinated organic compounds are of great importance in many fields such as medicine, agrochemistry, and material science[1–10]. Among all the fluorinated building blocks, α,α-difluoroketones are important substructures for medicinal chemistry, as well as synthons for accessing other fluorinated substructures.[11] This group readily rehybridizes from an sp^2-hybridized keto form to an sp^3-hybridzed form, which can interact with aspartyl proteases through noncovalent hydrogen-bonding interactions, with serine proteases through reversible covalent interactions by forming stable tetrahedral adducts,[12–14] and also with non-protease targets.[15,16] Therefore, this substructure has drawn significant attention of synthetic and medicinal chemists.[17] Separately, α,α-difluoroalkyl ethers display a wide range of applications in pharmaceuticals,[18] agrochemicals[19] and material chemistry.[20,21] For example, α,α-difluoroalkyl ethers can enhance metabolic stability[18] and control molecular conformation.[22,23] Due to the small rotational barrier around the ArO–CF_2R bond, difluorinated phenyl ethers can access a wide range of conformers versus the parent alkyl-aryl ethers that preferentially reside in the plane of the arene,[23] and versus trifluoromethyl-aryl ethers that reside orthogonally to the plane of the arene.[24] Interestingly, despite the individual significance of the α,α-difluoroketone and α,α-difluoroalkyl ethers components, the hybrid α,α-difluorinated-α-phenoxy-ketone functional group has only been reported once as a synthetic intermediate (Scheme 1A);[25] the lack of synthetic strategies for accessing α,α-difluorinated-α-phenoxy ketones precludes evaluation of the properties of the functional group, and also impedes its use in medicinal chemistry and chemical biology. Herein, we report the synthesis and physicochemical characterization of the α,α-difluorinated-α-phenoxy-ketone functional group, and predict its utility (computationally and experimentally) in biological and medicinal chemistry.

Results and Discussion

To access α,α-difluorinated-α-phenoxy-ketones, we envisioned exploiting the unique reactivity of readily available *gem*-difluorinated alkenes,[26–28] specifically a sequence involving nucleophilic attack of the electrophilic difluorinated center and subsequent oxidation (Scheme 1B). However, transition metal-catalyzed reactions of *gem*-difluoroalkenes typically proceed through β-fluoro anionic or β-fluoro metal intermediates that are both prone to undergo β-fluoride elimination and generate monofluoroalkene products; in contrast, “fluorine-retentive” catalytic functionalization reactions of *gem*-difluorinated alkenes[29] are rare.[30–32] To overcome the challenge of β-fluoride elimination, we hypothesized that radical (one-electron) functionalization of the *gem*-difluorinated alkene would avoid anionic intermediates and subsequent β-fluoride elimination. Applied to the preparation of α,α-difluorinated-α-phenoxy ketones, addition of a phenoxy radical to the *gem*-difluorinated alkene

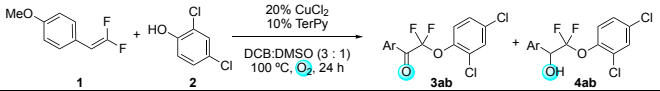
would provide a α,α-difluorinated-α-phenoxy radical, which might be trapped under oxidative conditions to deliver the unsymmetrically dioxygenated target substructure (Scheme 1C).



Scheme 1. Construction of α,α-difluorinated-α-phenoxy ketones by Cu-catalyzed oxidation of *gem*-difluoroalkenes.

Routine synthetic optimization identified an optimal Cu-based catalyst system for reacting *gem*-difluoroalkenes with phenols to produce α,α-difluorinated-α-phenoxy ketone **3ab** selectively, while avoiding formation of a related alcohol-containing side product **4ab**. Notably, the combination of 20% $CuCl_2$ and 10% 2,2',6',2"-terpyridine in a mixed solvent system of DCB/DMSO (1:1) under O_2 at 100 °C afforded the desired ketone product in in 87% yield (Table 1, entry 1; See Supporting Information for more optimization details). Interestingly, these oxidative Cu(II)-catalyzed oxidative conditions delivered the ketone-derived product, in contrast to a recently published Co(II/III)-based oxidative system that delivered alcohol-derived products (e.g. **4ab**, entry 2).[33] Further, use of CuCl instead of $CuCl_2$ lowered the conversion of substrates and delivered lower yield of ketone (entry 3). Replacement of terpyridine with bipyridine or phenanthroline provided lower yield of the desired product (entries 4 and 5). Reactions run with lower loadings of $CuCl_2$ (10%) reduced the yield of ketone product, whereas an increase in ligand (20%), suppressed formation of the desired ketone product (entries 6 and 7). Use of DCB alone in place of DCB:DMSO delivered low conversion and yield of **3ab**, possibly due to the low solubility of O_2 in the aromatic solvent (entry 8).[34,35] However, use of DMSO alone provided no yield of anticipated product (entry 9). Elevating or lowering the reaction temperature lowered the yield of desired product (10 and 11), though elevated temparatures were beneficial for certain substrates (see Tables 2–3). Finally, O_2 served as an essential oxidant for this reaction, as no product formed under an atmosphere of N_2 (entry 12), though under an atmosphere of air, a low yield of desired product was obtained along with the undesired secondary alcohol.

Table 1: Optimization of reaction conditions for the synthesis of α,α-difluorinated-α-phenoxy-ketone.[a]



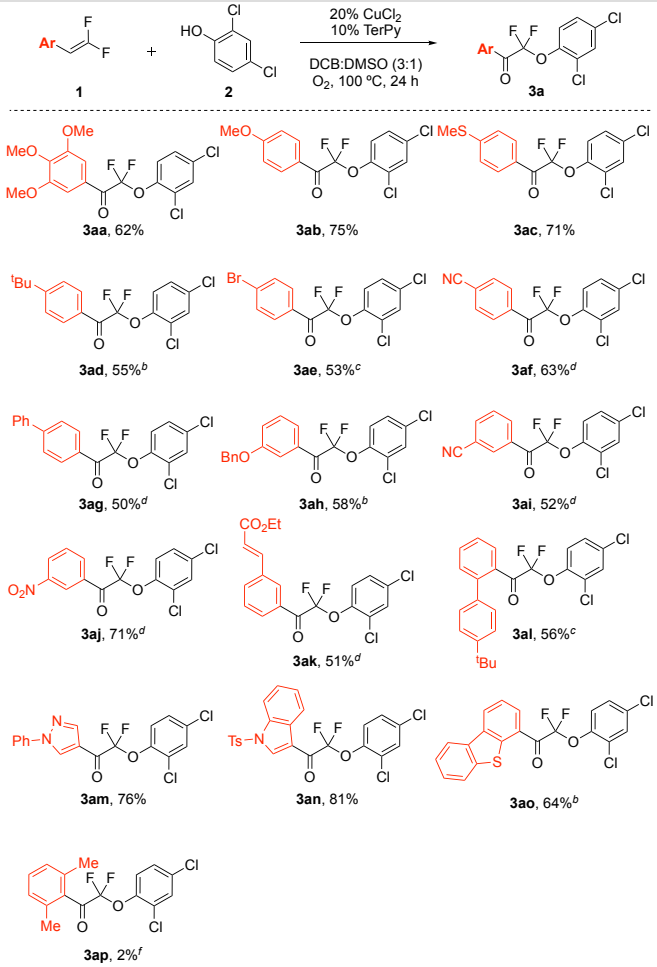
Entry	Deviation from the original condition	Conversion (%)	Yield[b] (%)	
			3ab	**4ab**
1	None	100	87	-
2	$Co(acac)_2$ instead of $CuCl_2$	100	3	70
3	CuCl instead of $CuCl_2$	100	73	-
4	Bipyridine instead of Terpyridine	100	78	-
5	1,10-Phenanthroline instead of Terpyridine	100	68	-
6	10% $CuCl_2$ instead of 20% $CuCl_2$	100	77	-
7	20% Terpyridine instead of 10% Terpyridine	100	81	-
8	Using DCB as only solvent	100	30	-
9	Using DMSO as only solvent	33	2	-
10	80 °C instead of 100 °C	31	30	-
11	120 °C instead of 100 °C	100	77	-
12	Reaction under N_2 atmosphere instead of O_2 atmosphere	6	-	-
13	Reaction under air atmosphere instead of O_2 atmosphere	69	34	10

[a] Standard conditions: **1** (1.0 equiv., 0.10 mmol), **2** (3.0 equiv., 0.30 mmol), DCB (0.30 mL), DMSO (0.10 mL), 24 h under an atmosphere of O_2. [b] Determined by ^{19}F NMR analysis of the crude reaction mixture using α,α,α-trifluorotoluene (TFT) as a standard.

The generality and scope of the developed protocol were explored utilizing a wide range of electron-rich and -deficient *gem*-difluoroalkenes (**1**) and phenols (**2**), which generally afforded the corresponding α,α-difluorinated-α-phenoxyketones **3** in good to high yields (Tables 2–3). Numerous substituents like OR (R = alkyl), SMe, alkyl, and halogen group on the *gem*-difluoroalkene ring were compatible under standard conditions (Table 2, **3aa**–**3ap**). Remarkably, an *ortho*-substituted *gem*-difluoroalkene also provided the corresponding α,α-difluorinated-α-phenoxyketones in good yield (Table 2, **3al**); whereas a bis-*ortho*-substituted *gem*-difluoroalkene only afforded trace amount of product (**3ap**), possibly due to the steric hindrance exerted by two *ortho* methyl groups. Importantly, *gem*-difluoroalkenes (**1**) bearing heteroaromatic groups, such as 3-pyrazolyl and 3-indolyl were tolerated under optimal conditions, with reactions affording the corresponding products in high yields (Table 2, **3am**, **3an**). In addition, an extended heteroaromatic, dibenzothiophene, also afforded the corresponding α,α-difluorinated-α-phenoxyketones

3ao in 64% yield. Of note, reactions of *gem*-difluoroalkenes bearing electron-withdrawing substituents required higher temperatures to increase the yield, which might implicate an electron-deficient intermediate (radical or cation) at the benzylic position (Table 2, **3ad**-**3ag**).

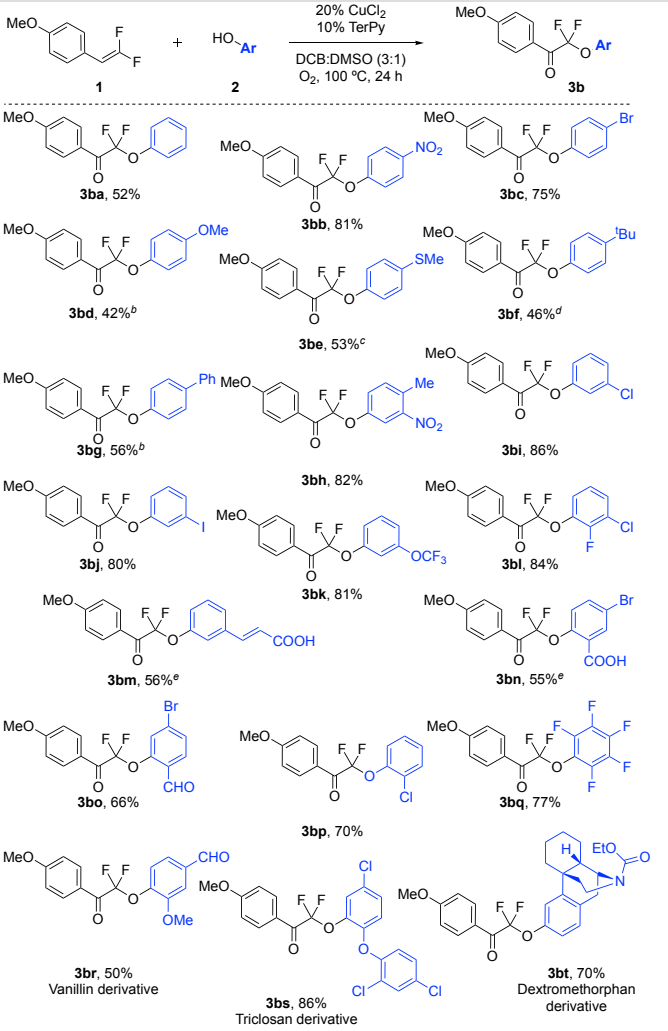
Table 2: Scope of *gem*-difluoroalkenes.[a]



[a] Standard conditions: **1** (1.0 equiv., 1.0 mmol), **2** (3.0 equiv., 3.0 mmol), DCB (3.0 mL), DMSO (1.0 mL), $CuCl_2$ (20 mol%, 0.20 mmol) and terpyridine (10 mol%, 0.10 mmol) at 100 °C for 24 h under an atmosphere of O_2. Yields of isolated material represent the average of 2 runs. [b] DCB (4.0 mL), 120 °C, 60 h, sealed tube. [c] DCB (4.0 mL), 120 °C, 30 h. [d] DCB (4.0 mL), 140 °C, 60 h, sealed tube. [e] DCB (4.0 mL), 140 °C, 30 h. [f] Yield determined by ^{19}F NMR.

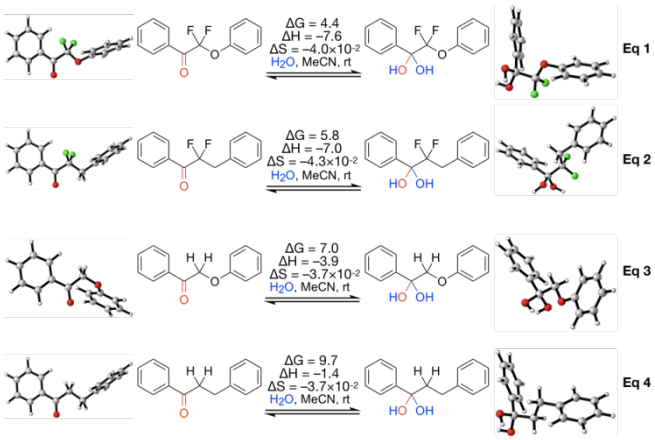
A variety of phenols were successfully coupled to deliver α,α-difluorinated-α-phenoxyketones compounds in good to excellent yields (Table 3). Synthetically useful functional groups, such as halogens, ethers, esters, carboxylic acids, aldehydes, carbamates, and NO_2 groups, were well tolerated under the optimized conditions (Table 3, **3ba**–**3bt**). Phenols bearing an electron donating group (-OMe) at the *para* position required higher temperature (140 °C) to achieve synthetically useful conversion and yield (Table 3, **3bd**). Furthermore, phenols bearing a free acid group also yielded the corresponding α,α-difluorinated-α-phenoxyketones (Table 3, **3bm** and **3bn)** in excellent yield using K_2CO_3 as an additive. Moreover, a phenol bearing a redox-sensitive aldehyde group reacted to deliver product **3bo** in excellent yield (Table 3). Of note, phenols bearing free amino groups did not react to yield the corresponding α,α-difluorinated-α-phenoxyketones. A number of biologically active phenols, such as vanillin (flavoring agent), triclosan (antimicrobial agent), or a dextromethorphan derivative (cough suppressant), were coupled with a *gem*-difluoroalkene to yield the corresponding α,α-difluorinated-α-phenoxyketones in moderate to good yields (Table 3, **3br**–**3bt**).

Table 3: Scope of phenols.[a]



[a] Standard conditions: **1** (1.0 equiv., 1.0 mmol), **2** (3.0 equiv., 3.0 mmol), DCB (3.0 mL), DMSO (1.0 mL), $CuCl_2$ (20 mol%, 0.20 mmol) and terpyridine (10 mol%, 0.10 mmol) at 100 °C for 24 h under an atmosphere of O_2. Yields of isolated material represent the average of 2 runs. [b] DCB (4.0 mL), 140 °C, 30 h. [c] DCB (4.0 mL), 140 °C, 60 h, sealed tube. [d] A trace amount of dimerised phenol was observed as an impurity observed. [e] K_2CO_3 (20 mol%, 0.20 mmol) has been used as an additive.

To gain insight into the medicinal chemistry potential for this under-studied fluorinated substructure, we computed the ketone-hydrate equilibria using density functional theory (DFT) at the PBE[36]/6-31G*[37] level of theory and SMD solvation corrections[38] in water as implemented in Gaussian 16,[39] and compared a range of difluorinated vs. nonfluorinated substrucutres as well as phenyl ether vs. benzyl substitutions (Scheme 2). Conformational searches were performed using the Schrödinger Macromodel software package.[36]



Scheme 2. Reversible formation of geminal diols from fluorinated and nonfluorinated phenoxyketones. ΔG and ΔH in kcal mol^{-1} and ΔS in kcal mol^{-1} K^{-1}).

The ketone is typically favoured over the hydrate by ~4.4–9.7 kcal mol^{-1}. Notably, within this series the novel α,α-difluorinated-α-phenoxy ketone substructure shows the lowest barrier to forming the hydrate (4.4 kcal mol^{-1}, eq. 1). Four factors appear to govern the equilibria.

1. Notably within this series, the hydrate form is always enthalpically favoured (–1.4 to –7.6 kcal mol^{-1}), though the magnitude of this driving force is overcome by the entropic penalty of losing water (–3.7 to –4.3 x 10^{-2} kcal mol^{-1} K^{-1}). Increasing the temperature pushes the equilibrium towards the ketone. For example, DFT analysis of **3aj** and **3bi** confirmed that raising the temperature from rt to 100 °C increased the favourability of the ketone by ~3 kcal mol^{-1} (Tables 2 and 3, respectively; See Supporting Information).

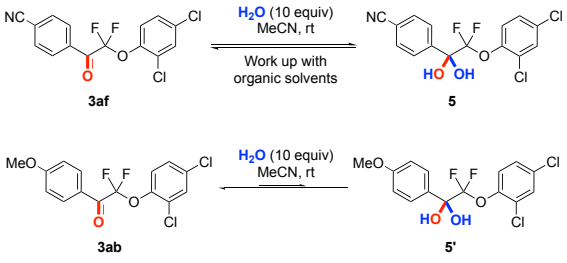
2. The geminal fluorines significantly increase the favourability of the hydrates, as has been previously established experimentally.[13] Going from the hydrocarbon analogue to the fluorinated compound (eq. 3 to eq. 1), the preference for the hydrate increased by 2.6 kcal mol^{-1}. Similarly, for the ether-derived analogs, going from the hydrocarbon to the analogous fluorinated compound (eq. 4 to eq. 2), the favourability of the hydrate increased by 3.9 kcal mol^{-1} (Scheme 2).

3. Replacing the methylene linker with the ether oxygen atom decreased the favourability of the ketone. In the fluorocarbon case (eq. 2 to eq. 1), the favourability decreased by 1.4 kcal mol^{-1}, while in the hydrocarbon case (eq. 4 to eq. 3), the favourability decreased by 2.7 kcal mol^{-1} (Scheme 2).

4. Electron withdrawing groups on the ketone moiety reduced the favourability of the ketone. For example, the addition of NO_2 to the phenone moiety on **3aj** reduced the favourability of the ketone by 2.7 kcal mol^{-1} (See Supporting Information). In contrast, the addition of a methoxy group on the phenone moiety of **3bi** increased the favourability of the ketone by 1.8 kcal mol^{-1} (See Supporting Information).

The ketone possessed fewer conformations in general than the hydrate, but the hydrate was more rigid with a higher energy barrier for conversion between conformations. For both the ketone and hydrate forms (eq. 1, Scheme 2), the most stable conformation exhibited double anomeric donation of both ether oxygen lone pairs into the adjacent σ*$_{CF}$ orbitals. The aryl ketone was planar, and the aryl ether typically resided orthogonal to the ketone. The torsional rotational barrier around the carbonyl carbon and the α-CF_2 group was 3.8 kcal mol^{-1} (See Supporting Information). In contrast, the hydrate tolerated a wider range of conformations. As found in spiroketal natural products, both hydrate hydroxyl groups were oriented *anti* to each other, presumably to maximize the hyperconjugative stabilization of the hydrate oxygen lone pairs. The increase in hybridization from the ketone to the hydrate increased the torsional rotational barrier to 5.2 kcal mol^{-1} (See Supporting Information). These results suggest that the α,α-difluorinated-α-phenoxyketone can readily adopt several conformations, but upon facile rehybridization to the sp^3 form, the substructure should become more rigid in an enzyme's active site.

In support of these computational findings, ketones bearing electron-deficient moieties experimentally rehybridize to form hydrates (**5**) more readily relative to ketones bearing electron-donating moieties (Scheme 3). Specifically, when dissolved in MeCN with H_2O (10 equiv.), a difluorinated ketone bearing an electron withdrawing group (**3af**: ^{19}F NMR δ –74.0 ppm; ^{13}C NMR δ 181.1 ppm; IR 1476 cm^{-1}) readily formed an sp^3-hybridized hydrate (**5**: ^{19}F NMR δ –87.0 ppm; ^{13}C NMR δ 93.8 ppm). This experimental observation matches computational predictions of **3aj**, in which the ketone is energetically preferred by 1.7 kcal mol^{-1} at rt (See Supporting Information). Experimentally, this hydration process was reversible, as extraction of such electron-deficient difluorinated geminal diol (e.g. **5**) into organic solvent (DCM or EtOAc), and evaporation regenerated the corresponding α,α-difluorinated-α-phenoxyketone **3aj**. Notably, the ^{19}F NMR spectra of products bearing either neutral or electron-rich ketone moieties did not show the diol form, as supported by the DFT computations.

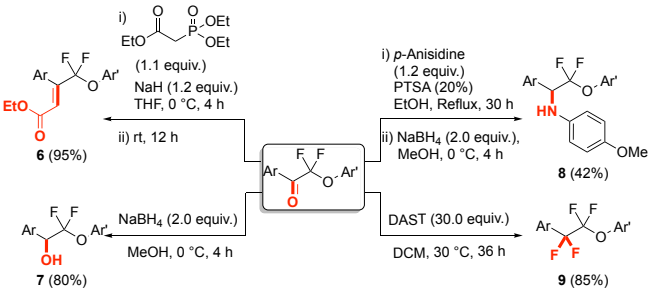


Scheme 3. Ketone moeities bearing electron-withdrawing groups readily form the hydrate as observed by ^{19}F NMR, while ketones bearing electronically neutral or rich rings do not readily form hydrates.

These computations help quantitatively explain the known biological and medical chemistry of fluorinated ketones and suggest strategies for encouraging formation of the sp^3-hybridized form. In the context of drug/probe design, the entropic reluctance to rehybridize to the hydrate form might be readily offset by strong ligand-binding interactions that present a nucleophilic residue (or water) towards the ketone, which promotes the enthalpically favoured rehybridization. Such reversible rehybridization has

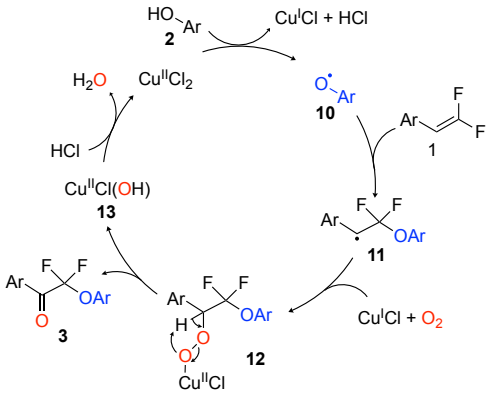
been exploited to engage biological targets *via* reversible covalent interactions (e.g. with serine proteases) or by intricate hydrogen-bonding networks (e.g. aspartate proteases).[12–14] Moreover, the new computations suggest that increasing the electron-withdrawing character of around the ketone, either by introduction of an O-atom at the α-position and/or an electron-withdrawing group off the non-fluorinated side of the ketone, can further push the equilibrium toward the sp^3-hybrized form.

In addition to this potential to inhibit enzymes, the α,α-difluorinated-α-phenoxyketone substructure (**3**) can also serve as a synthetic intermediate for generating various fluorinated substructures (Scheme 4). This group readily participates in Horner-Wadsworth Emmons olefination, reduction, reductive amination, and deoxyfluorination reactions to deliver corresponding difluoroalkyl-substituted acrylates (**6**), alcohols (**7**), amines (**8**), and tetrafluoroethanes (**9**) in good to excellent yields. Thus, the intermediate α,α-difluorinated-α-phenoxyketone can serve synthetically useful for accessing other important substructures.



Scheme 4. Potential applications α,α-difluorinated-α-phenoxyketones.

Literature reports support a plausible mechanism involving radical intermediates (Scheme 5).[40,41] Initial reaction of phenol and $Cu^{II}Cl_2$ generates phenoxy radical **10**.[42] Addition of radical **10** to *gem*-difluoroalkene **1** produces benzylic radical **11**. This regioselective attack of the radical to the difluorinated position is consistent with other radical functionalization reactions of alkenes.[27,28,33,43–45] Trapping of radical **11** with $Cu^{I}Cl$ and molecular oxygen affords peroxo intermediate **12**. Concerted elimination of Cu^{II} oxide **12** might afford product **3** and $Cu^{I}Cl(OH)$ **13**,[40,41,46,47] which could react with HCl to regenerate the active catalyst $Cu^{II}Cl_2$. Critically, by invoking radicals, this reaction sequence avoids β-fluoro anionic or β-fluoro metal intermediates that are prone to eliminate and generate monofluorinated products.



Scheme 5. Plausible mechanism.

Conclusion

In summary, we developed a copper-catalyzed difunctionalization reaction of *gem*-difluoroalkene by readily available phenols and O_2 to furnish an array of synthetically important α,α-difluorinated-α-phenoxyketones. The mild reaction conditions tolerate many useful functional groups and afforded the products in good yields. In addition, the α,α-difluorinated-α-phenoxyketones can also serve as substrates for further synthetic elaboration in reductive amination, reduction, halogenation, and C–C bond-forming reactions to deliver a broad set of products. Computational studies predict that the sp^2-hybridized α,α-difluorinated-α-phenoxyketone substructure can rehybridize to the tetrahedral hydrate. The introduction of additional electron-withdrawing groups enables the enthalpic driving forces to counteract the entropic cost of the bimolecular hydration (ketone + H_2O) encourage this rehybridization. This lowered energy of the hydrate should enable use of these substructures for future biomedical applications, specifically towards covalent inhibition of proteases or other enzymes with nucleophilic residues at the binding site.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: difunctionalization • hybrid functional group • fluorine retention • rehybridization • DFT study

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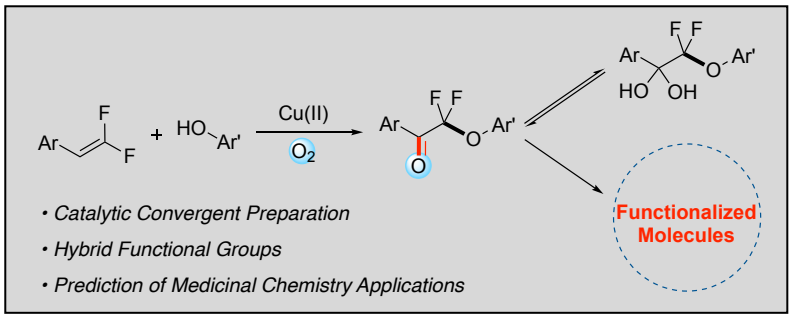
Entry for the Table of Contents



A Cu-catalyzed reaction of *gem*-difluoroalkenes, phenols, and molecular oxygen generate an array of α,α-difluorinated-α-phenoxy ketones, an unstudied functional group. These α,α-difluorinated-α-phenoxy ketones are highly prone to rehybrize to form sp^3-hybrized hydrates as predicted by computational studies, and confirmed by experimental observations. Additionally, the α,α-difluorinated-α-phenoxy ketones can be functionalized to deliver a number of useful substructures.

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