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Author(s)	Saha, Priya; Jin, Mingoo; Huang, Dennis Chung-Yang
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Defluorinative C–O Coupling between Trifluoromethylarenes and Alcohols via Copper Photoredox Catalysis

Priya Saha,[a] Mingoo Jin,[a,b] and Dennis Chung-Yang Huang*[a]

[a] P. Saha, Prof. Dr. M. Jin, Prof. Dr. D. C.-Y. Huang
Institute for Chemical Reaction Design and Discovery (WPI-ICReDD)
Hokkaido University
Kita 21, Nishi 10, Kita-ku, Sapporo, Hokkaido 001-0021, Japan
dcyhuang@icredd.hokudai.ac.jp

[b] Prof. Dr. M. Jin
List Sustainable Digital Transformation Catalyst Collaboration Research Platform, Institute for Chemical Reaction Design and Discovery (ICReDD List-PF)
Hokkaido University
Kita 21, Nishi 10, Kita-ku, Sapporo, Hokkaido 001-0021, Japan

Abstract: Fluorine-containing compounds have shown unparalleled impacts in the realm of functional molecules, and the ability to prepare novel structures has been crucial in unlocking new properties for applications in pharmaceutical and materials science. Herein, we report a copper-catalyzed, photoinduced defluorinative C–O coupling between trifluoromethylarenes and alcohols. This method allows for direct access to a wide selection of difluorobenzylether ($ArCF_2OR$) molecules, including a compound displaying liquid crystal behavior. Through slight modification of the protocol, we were able to generate $ArCF_2I$ products, another class of synthetically useful fluorine-bearing molecules. Mechanistic investigations first suggested that $ArCF_2I$ can serve as a reservoir to steadily supply the key $ArCF_2\bullet$ radical species. Furthermore, experimental evidence supported a mechanism consisting of two collaborative cycles: C–F activation operated by a homoleptic Cu(I) coordinated by two bisphosphine ligands as the photocatalyst and C–O coupling promoted by a Cu(I) ligated by a single bisphosphine ligand. The critical roles of the two salt additives, lithium iodide and zinc acetate, in orchestrating the two cycles were also elucidated. This dual-role copper catalyst demonstrates the power of base metal photoredox catalysis in achieving both substrate activation and chemical bond formation via a single catalytic system.

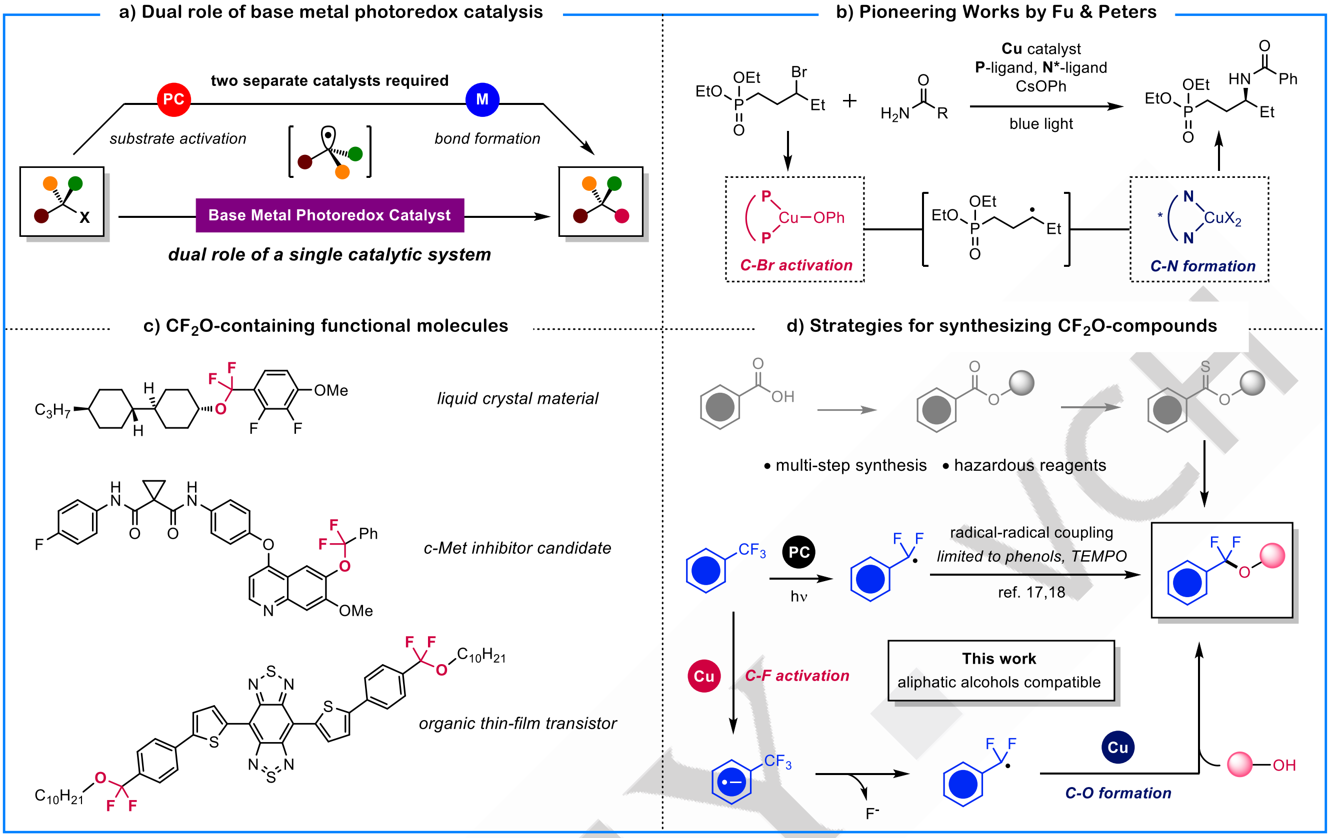
Introduction

Base metal catalysis has in recent years emerged as a prominent force in synthetic organic chemistry.[1] Due to their low cost and versatile ability to engage in single-electron processes, numerous new catalytic systems implementing these earth-abundant metals have been developed to innovate the conventional approaches in activating and forging chemical bonds. Particularly in the realm of photoredox catalysis, base metals[2] are playing an increasingly crucial role in replacing the established catalysts derived from precious metals[3] and organic dyes[4]. One additional advantage is the straightforward tuneability: Coordination of ligands to these metal centers can easily occur in the reactions to generate the active species *in situ*, unlike organic or precious metal photocatalysts that typically required preparations in separate steps. Compatibility with a broad range of ligand classes further allows for rapid screening to attain the desired reactivity and selectivity. Moreover, the flexible coordination field around the metals frequently allows them to participate in the established metal-mediated process (e.g. cross-coupling cycles) in addition to the photoredox activation (Scheme 1a). In other words, these metal catalysts are able to serve dual role in facilitating both photoinduced substrate activation and thermal bond-forming event.[5] This attribute thus allows for the design of sophisticated reaction scheme based on a single catalytic system.

Among the first-row metals, copper has emerged as a powerful choice for photoredox catalysis.[6] Its ability to operate between Cu(I)/(II)/(III) oxidation states enables the design of catalytic cycles for both substrate activation and bond construction through radical pathways. The reactivity of copper catalysts can also be easily tuned via the formation of homoleptic or heteroleptic complexes bearing P-, N- or O-ligands. Recently, particular success has been achieved in C–heteroatom bond formation. As a representative example, the Fu and Peters groups have in the past decade developed a series of photoinduced, copper-catalyzed cross-coupling reactions with alkyl- and aryl halides to forge C–N,[7] C–O,[8] C–S,[9] and C–CN[10] bonds (Scheme 1b). The dual role of these copper catalysts, namely in mediating both the photoredox and cross-coupling processes, represents an evident advantage over the traditional Ir-, Ru-, and organic dye-derived catalysts, which are in general solely effective in substrate activation. This merit thus prompted us to explore the utility of copper photoredox catalysis in C–heteroatom bond formation with challenging while valuable electrophiles.

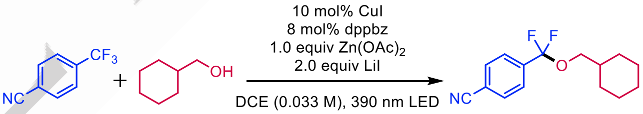
In this regard, C–F activation of trifluoromethyl ($–CF_3$) motifs poses an intriguing challenge. Due to their unique molecular properties, $–CF_3$ groups have been widely implemented in bioactive compounds as a strategy to modulate the efficacy, bioavailability, or metabolic stability of these molecules.[11] Recently, in the effort to expand the chemical space of fluorinated compounds and to search for superior functional molecules, attention has been shifted to difluormethylene ($–CF_2–$) moieties, where the majority of works centers on CF_2-groups bound to a hydrogen or a carbon center.[12] By contrast, CF_2–heteroatom

Scheme 1. Base Metal Photoredox Catalysis for C–F Functionalization.



motifs are less explored but have shown promises in limited cases for pharmaceuticals and functional materials. For example, difluoroalkylether (R^1–CF_2O–R^2) structures can be found in liquid crystal materials[13] and anti-cancer drug candidates[14] (Scheme 1c). Moreover, CF_2O-moieties have been proposed to grant access to unique molecular conformations through anomeric effect.[15] Established protocols to construct these moieties mainly rely on the fluorination of carbonyl derivatives such as thionoesters (Scheme 1d). Although advances have been made to replace the hazardous reagents for this transformation, the requirement to prepare the substrates in multi-step synthesis remains a disadvantage.[16] Conversely, a direct defluorinative C–O coupling between trifluoromethyl compounds and alcohols represents a convergent and step-economical strategy that combines two readily available starting materials (Scheme 1d). One hurdle in this approach is the necessity to cleave the extremely strong C–F bonds. Furthermore, after the initial substitution, over-defluorination can potentially occur due to the lower C–F bond strength of the product as compared to that of the starting material. If these challenges can be properly addressed, a selective coupling between trifluoromethyl compounds and alcohols should serve as an attractive pathway to preparing difluoroalkylether structures.

Table 1. Optimization Studies



1a **2a** **3a**

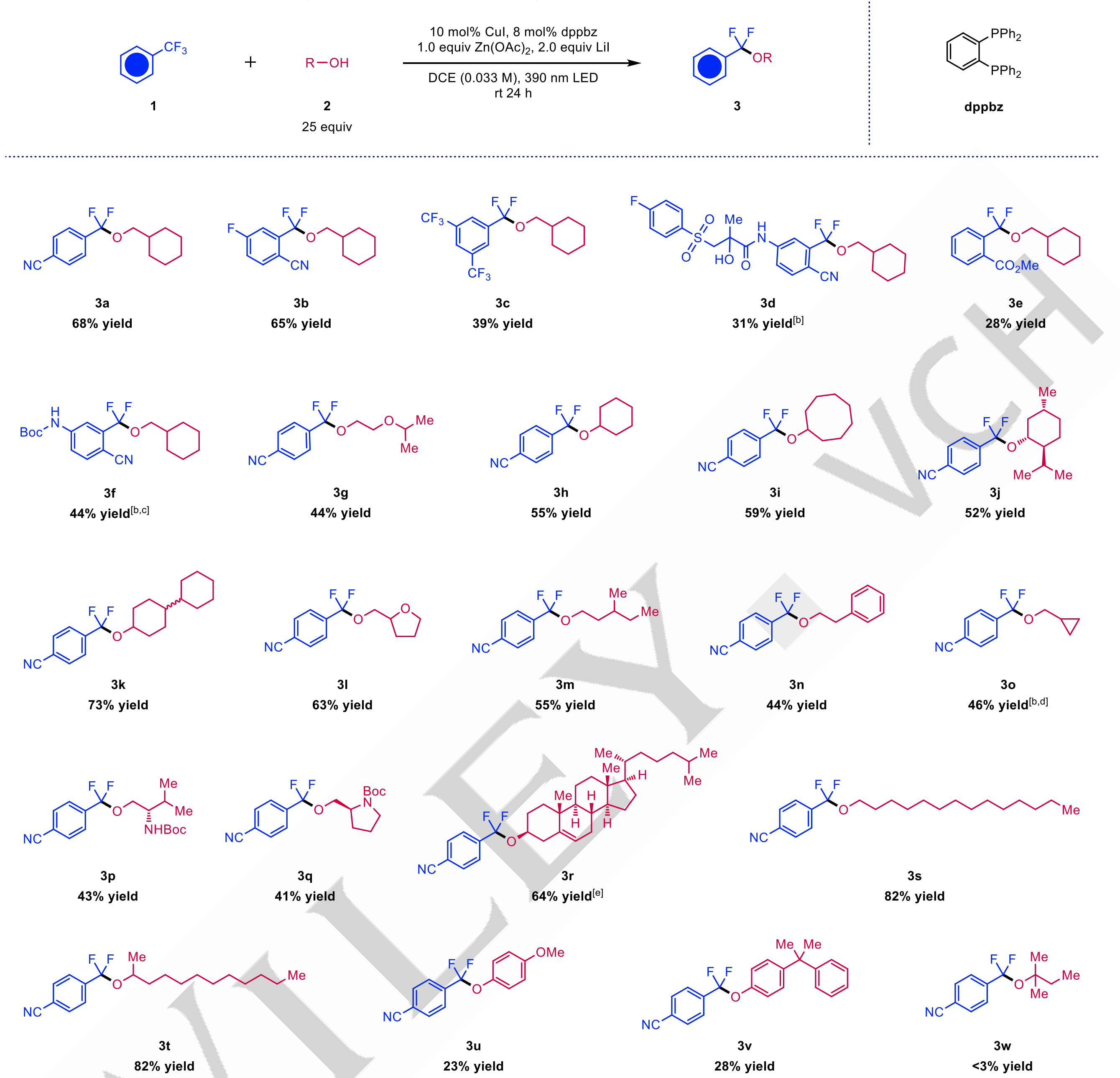
25 equiv *standard conditions*

entry[a]	deviations from *standard conditions*	yield
1	none	71%
2	(*R*)-Tol-BINAP instead of dppbz	12%
3	(*S*)-DTBM-SEGPHOS instead of dppbz	6%
4	DavePhos instead of dppbz	3%
5	Xantphos instead of dppbz	<3%
6	no LiI	<3%
7	no $Zn(OAc)_2$	<3%
8	5 equiv instead of 25 equiv of **2a**	49%
9	440-nm instead of 390-nm LED	32%
10	no CuI/dppbz	<3%
11	no light at rt or 80 °C	<3%
12	under air	<3%

[a] Reactions were carried out using 0.1 mmol of **1a**, and yields were determined by ^{19}F-NMR analysis of the crude mixture with (trifluoromethoxy)benzene as the standard.

In 2023, the Xu group reported a photoredox protocol to convert C–F bonds of trifluoromethylarenes into C–heteroatom structures.[17] C–O coupling was achieved using this protocol, but the scope is only limited to electron-rich phenols (Scheme 1d). Presumably, this mechanism relies on the coupling between the difluorobenzylic (Ar^1–CF_2•) and the phenoxy (Ar^2–O•) radicals, which renders the reaction efficiency susceptible to the nature of alcohol partners. Along the same line, in 2024 Nishimoto, Yasuda, and coworkers presented a defluorinative C–O coupling of

Scheme 2. Substrate Scope of Copper-catalyzed Defluorinative C–O Coupling Reactions[a].



[a] Reactions were carried out using 0.50 mmol of **1**, and yields are the average of two runs. [b] One run. [c] 0.25 mmol scale. [d] Yields were determined by 19F-NMR analysis of the crude mixture with (trifluoromethoxy)benzene as the standard. [e] 12.5 equiv alcohol used.

perfluoroalkylarenes, where 2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO), a stable radical, is the sole coupling partners.[18] We envision that by implementing copper photoredox catalysis, the C–O coupling mediated by a cross-coupling cycle will enjoy an expanded scope to include aliphatic alcohols. Very recently, Han, Xie, and coworkers communicated a defluorinative C–N coupling method enabled by a photoactive copper catalyst.[19] However, the requirement for a carbazole-ligated copper photocatalyst severely limits the scope of nitrogen nucleophiles.

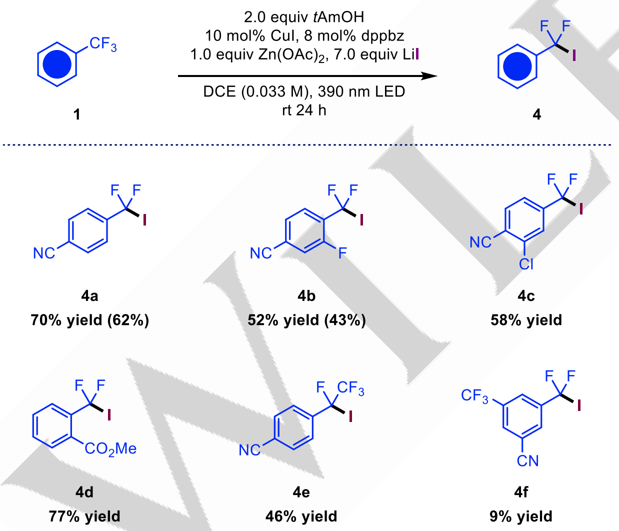
In this work, we present a photoinduced, Cu-catalyzed defluorinative C–O coupling of trifluoromethylarenes. A wide range of aliphatic alcohols can be successfully coupled to afford new CF_2O-compounds, including one displaying liquid crystal behavior. The dual-role copper catalyst enables C–F activation and C–O coupling under the same catalytic system, where a homoleptic Cu-bisphosphine complex is proposed to serve as the photocatalyst.

Results and Discussion

Optimization Studies

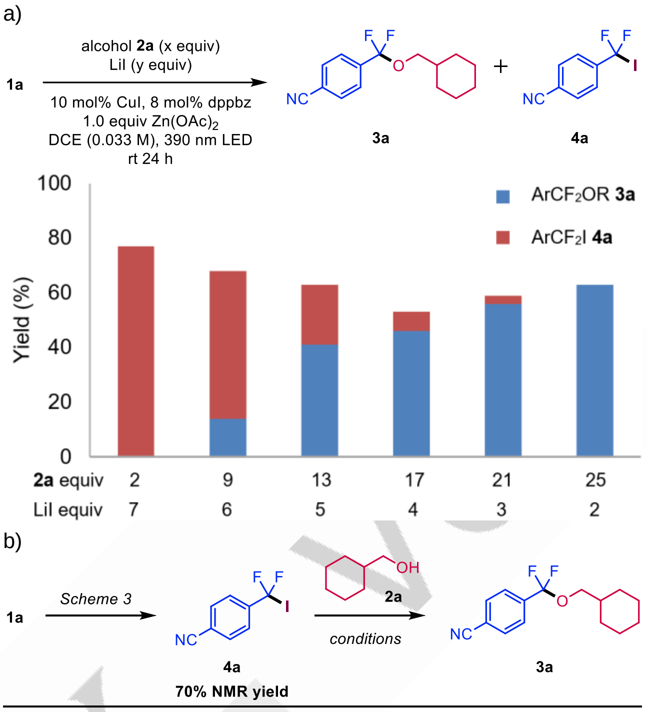
At the outset, two complications can potentially challenge the successful development of a Cu-catalyzed C–O coupling of trifluoromethylarenes. First, reduction of $ArCF_3$ compounds typically requires a fairly reducing photocatalyst, and it was not clear whether a copper species complexed with a suitable ligand could be identified. Second, the mesolytic cleavage of the reduced trifluoromethylarene (ArCF$_3^{\bullet-}$) may not be entirely favorable, and the equilibrium can lie at the ArCF$_3^{\bullet-}$ side. Proper fluorophilic metal ions may be necessary for fluoride trapping while avoiding over-defluorination. With the above considerations in mind, we commenced the optimization by examining conditions effective for the coupling between *p*-(trifluoromethyl)benzonitrile (**1a**) and cyclohexanemethanol (**2a**) (Table 1). In this process, we identified 1,2-bis(diphenylphosphino)benzene (dppbz) as a uniquely suitable ligand for this transformation, whereas other phosphine- or nitrogen-based ligands afforded no or diminished reactivity (entries 2-5; see SI for complete ligand screening). Furthermore, two salt additives, lithium iodide (LiI) and zinc acetate (Zn(OAc)$_2$), were found to be crucial in this protocol (entries 6-7; see SI for other salt additives). A high loading of the alcohol coupling partner is necessary to achieve satisfactory yields (entry 8; see SI for more studies). When a 440-nm instead of 390-nm LED lamp was used as the light source, a decreased yield was observed (entry 9). The essential role of copper, dppbz, and light was demonstrated in the control experiments, and performing the reaction under air resulted in no formation of the desired product (entries 10-12). Thus, by using 10 mol% CuI, 8 mol% dppbz, 1.0 equiv Zn(OAc)$_2$, 2.0 equiv LiI in dichloroethane (DCE) under 390-nm irradiation for 24 h, the desired ether product **3a** can be obtained in 71% yield.

Scheme 3. Substrate Scope of Copper-catalyzed ArCF$_2$I Formation[a].



[a] Reactions were carried out using 0.25 mmol of **1**, and yields were determined by ^{19}F-NMR analysis of the crude mixture with (trifluoromethoxy)benzene as the standard (isolated yields shown in parentheses).

Scheme 4. Studies of ArCF$_2$I.



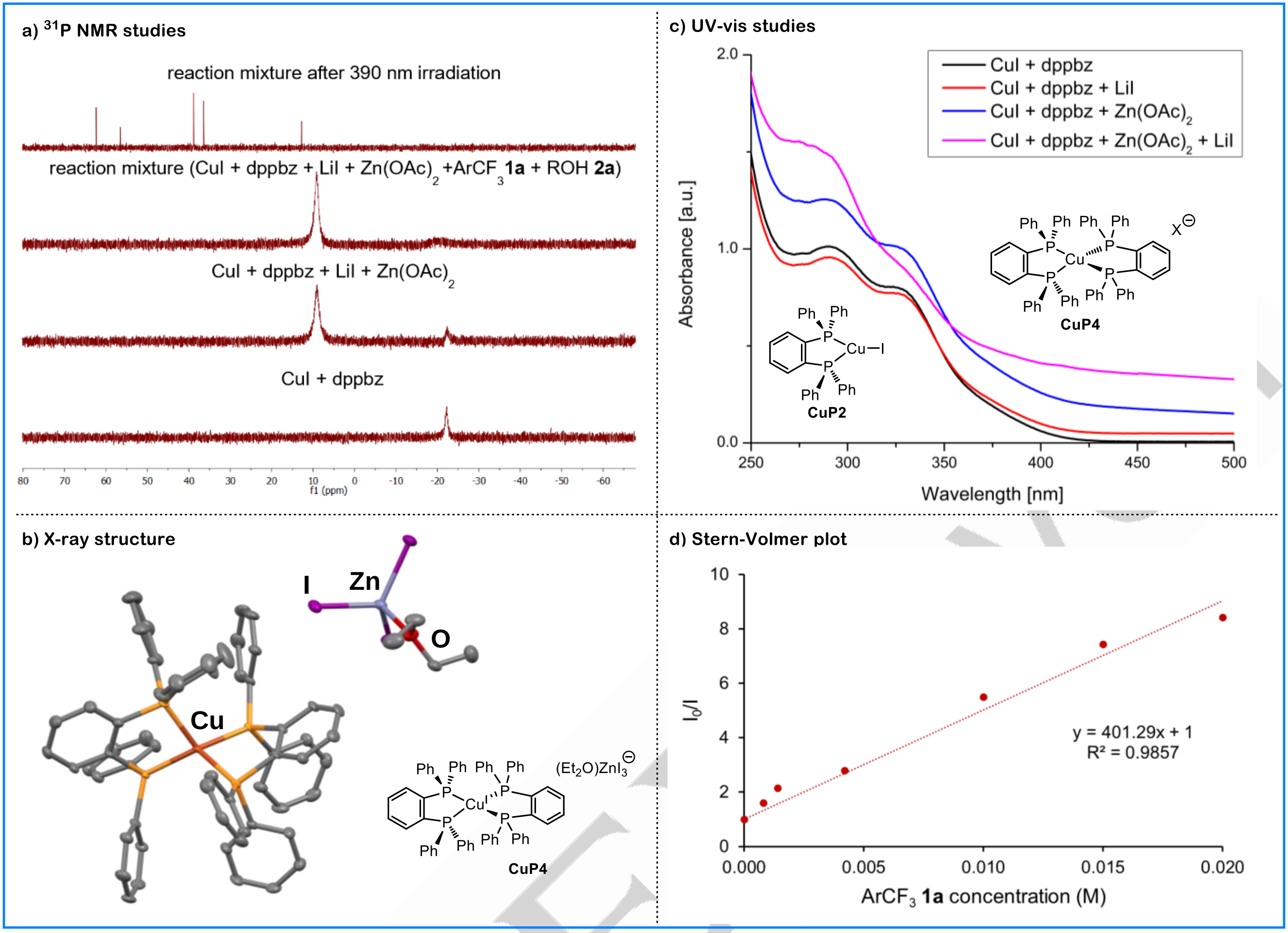
4a → **3a** conditions	**3a** yield (2-step)
dark or 390 nm	<3%
CuI, dppbz, dark or 390 nm	<3%
CuI, dppbz, Zn(OAc)$_2$, dark	<3%
CuI, dppbz, Zn(OAc)$_2$, 390 nm	53%

Synthetic Scope

With the optimized conditions in hand, we next explored the scope of copper-catalyzed defluorinative C–O coupling reactions (Scheme 2). Except for volatile compounds, all products were isolated using typical column chromatography procedure. Various electron-deficient trifluoromethylarenes can be employed in this protocol, including an anti-cancer agent, bicalutamide (**3a-f**). Excitingly, examination of the alcohol scope revealed that a wide range of 1° and 2° aliphatic alcohols can be applied to afford the ArCF$_2$OR products in decent efficiency. Naturally occurring alcohols such as menthol (**3j**) and cholesterol (**3r**) as well as amino alcohols (**3p**, **3q**) are all suitable coupling partners. On the other hand, phenolic ethers could be synthesized using this method, albeit in lower yields (**3u**, **3v**). A limitation of this protocol is 3° alcohol, presumably due to unfavorable steric interactions during the coupling step (**3w**).

During the isolation of ArCF$_2$OR products, we identified an intriguing byproduct, ArCF$_2$I, which represents a rarely studied compound class but can potentially serve as a strategic intermediate for selective mono-functionalization of trifluoromethyl compounds and also as halogen bond donors in bioactive molecules.[20] Regarding ArCF$_2$X, most studies focus on ArCF$_2$Cl/Br, and to the best of our knowledge, only one very recent report demonstrates a direct defluorinative iodination from ArCF$_3$ compounds via ArCF$_2$-carbanion intermediate[21]. To this end, we decided to optimize the conditions for this attractive transformation. Gratifyingly, by slightly modifying the protocol, namely increasing the loading of LiI to 7.0 equiv and applying 2.0 equiv of the non-coupling *tert*-amyl alcohol, iodide **4a** could be produced in 70% NMR yield (Scheme 3). Despite the instability of -CF$_2$I groups, we were able to isolate and fully characterize **4a** and **4b**. This method thus provides a protocol to synthesize these

Scheme 5. Mechanistic Investigations of $(dppbz)_2CuI$ (**CuP4**).



a) ^{31}P NMR studies

b) X-ray structure

c) UV-vis studies

d) Stern-Volmer plot

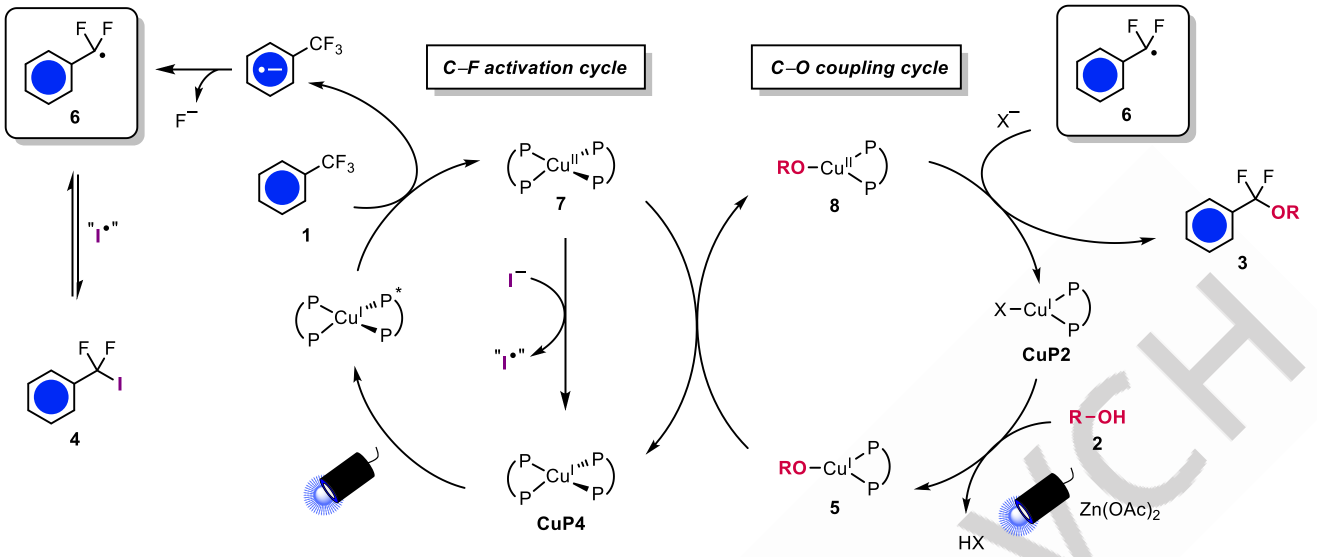
underexplored moieties for future exploration of their utility. Notably, different $ArCF_3$ scopes were observed for $ArCF_2OR$ and $ArCF_2I$ generation. For instance, substrates giving rise to **4b**, **4c**, and **4e** were not suitable for $ArCF_2OR$ formation, which may be due to increased steric hinderance that hampers the C–O coupling.

Mechanistic Considerations

We first aimed to elucidate the role of $ArCF_2I$ in this protocol. As shown in Scheme 4a, generations of $ArCF_2I$ and $ArCF_2OR$ appear to be competitive processes, whereby increasing the loading of alcohol **2a**, $ArCF_2OR$ **3a** was obtained in higher yields with concurrent decrease of $ArCF_2I$ **4a** formation. Furthermore, we first prepared **4a** following the protocol established in Scheme 3, and to the reaction crude was added alcohol **2a** along with other reaction components (Scheme 4b). It was found that only when fresh CuI, dppbz, and $Zn(OAc)_2$ were supplemented and the reaction was irradiated, could **3a** be produced. This observation thus excludes a simple S_N2-type mechanism between $ArCF_2I$ and alcohol. Together with the difference in substrate scopes observed for the two product classes (Scheme 2 and 3, *vide supra*), these outcomes are consistent with the mechanism where $ArCF_2I$ and $ArCF_2OR$ originate from a common intermediate, plausibly a difluorobenzylic ($ArCF_2$•) radical. We propose that $ArCF_2I$ can serve as a reservoir to steadily release the transient $ArCF_2$• radical to the catalytic cycle, thus maintaining the overall reaction efficiency. The involvement of $ArCF_2$• intermediate is supported by TEMPO inhibition and alkene trapping experiments (see SI for details).

To gain further insights on the active copper catalyst, we next carried out a series of ^{31}P NMR studies (Scheme 5a). Upon mixing CuI and dppbz in DCE, a peak at -22 ppm corresponding to (dppbz)CuI (**CuP2**) was formed. When $ArCF_3$ **1a**, alcohol **2a**, LiI, or $Zn(OAc)_2$ was added, no change in the spectrum was observed (see SI for details). However, in the presence of both LiI and $Zn(OAc)_2$, a new peak at +9 ppm appeared. The same peak was also observed as the major species in the reaction mixture prior to the irradiation. Through X-ray diffraction and mass spectroscopy analyses, we were able to confirm the identity of this new species to be a homoleptic copper complex ligated with two dppbz ligands (**CuP4**) (Scheme 5b). Importantly, in the crystal structure of **CuP4**, a counterion bearing ZnI_3^- was observed, which helps explain the necessity of Zn^{2+} and I^- in coverting **CuP2** to **CuP4**. Independent preparation of **CuP4** was successfully achieved by mixing CuI and dppbz in a 1:2 ratio (see SI for details). The above observations were corroborated by UV-vis spectroscopic studies, where the addition of both $Zn(OAc)_2$ and LiI caused an increase in the absorbance at wavelength >400 nm (Scheme 5c). This bathochromically shifted band originated

Scheme 7. Proposed Mechanism of Copper-catalyzed Defluorinative C–O Coupling Reactions.



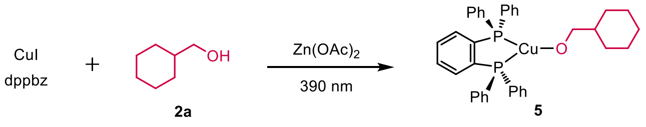
from **CuP4** suggests its key role in responding to the 390-nm photoexcitation employed in this protocol.

We then tested the possibility of **CuP4** serving as the photocatalyst in our protocol via fluorescence quenching experiments in the presence of potential quenchers (Scheme 5d). As can be seen in the Stern-Volmer plot, a linear relationship was observed with respect to the concentration of **1a**, which suggests that the excited **CuP4** can undergo an oxidative quenching by ArCF$_3$. **CuP4**(BF$_4$) has been prepared and examined in the literature as a photoactive complex with the estimated E$_{1/2}$(Cu$^{II/I*}$) = -2.19 V vs. SCE, but despite being a potent photoreductant, this and other homoleptic Cu(I) complexed with two bisphosphine ligands have not received much attention as photocatalysts in synthetic organic chemistry. [2c,22] On the other hand, quenching was also observed with iodide ions, albeit at higher concentration range as compared to **1a**, and the fitting line shows a concave upward curve, which can result from a concurrent dynamic and static quenching due to the ligation of iodide ions (see SI for details).[23] Based on these observations, we propose that upon photoexcitation, **CuP4** undergoes a single-electron transfer to reduce ArCF$_3$ **1a**. Cyclic voltammetry measurements showed that in the presence of LiI and Zn(OAc)$_2$, the reduction of **1a** becomes more favorable (E$_{1/2}$(**1a**/**1a**$^{•-}$) = -1.92 V → -1.84 V vs. SCE), presumably due to the coordination of cations to the substrate, which was demonstrated through NMR studies (see SI for details). Both Li$^+$ and Zn^{2+} can additionally form the corresponding fluoride complex to drive the equilibrium of the mesolytic cleavage.

We next turned our attention to the C–O formation step. As suggested by the studies of ArCF$_2$I→ArCF$_2$OR conversion (Scheme 4b), Cu/dppbz, Zn(OAc)$_2$, and light are all critical for C–O coupling. ^{31}P NMR experiment showed that mixing CuI/dppbz (1:1), Zn(OAc)$_2$, and alcohol **2a** yielded only **CuP2** (see SI for details). Upon irradiation of this mixture, formation of the copper-alkoxide complex **5** was confirmed by mass spectroscopy and ^{31}P NMR analyses (Scheme 6 and see SI for details). Efforts to cleanly generate and isolate this complex from **CuP2** have not been successful. We note that in the absence of a strong base, the substitution of the Cu–I to Cu–OR is challenging and may be the root for a large excess of alcohols required in this protocol. Nevertheless, this result in combination with the studies on ArCF$_2$I→ArCF$_2$OR conversion supports the involvement of copper catalyst in C–O bond formation.

Summarizing the outcomes of our investigations, we propose the following mechanism consisting of two cycles: C–F activation and C–O coupling (Scheme 7). In the presence of LiI and Zn(OAc)$_2$, **CuP4** is formed as the predominant species. Upon photoexcitation, **CuP4*** undergoes a single-electron transfer to ArCF$_3$ **1** to yield the radical anion, and the subsequent mesolytic cleavage generates the ArCF$_2$• intermediate **6**. On the other hand, under irradiation, **CuP2** would react with alcohol **2** in the presence of Zn(OAc)$_2$ to generate the copper-alkoxide species **5**. At the intersection of two cycles, **5** and **7** may undergo electron transfer to form Cu^{II}-alkoxide **8** while regenerating **CuP4** (E$_{1/2}$(**CuP4**/**7**) = +1.10 V vs. SCE, see SI and reference[22d] for details).[7e] **6** and **8** can then react with each other to afford the desired ArCF$_2$OR product **3**, presumably via an outer sphere mechanism due to the steric preference.[24] In the presence of high concentration of iodide, **7** can alternatively oxidize I$^-$ to I$^•$, which may exist in the form of I$_2$$^{•-}$ or metal iodide.[23] This I$^•$ equivalent in turn reacts with **6** to form ArCF$_2$I **4**, which we hypothesize serves as a reservoir to store and steadily supply the transient radical species **6**. This dual-cycle mechanism is operated by two distinct copper species: **CuP4** as the photocatalyst for C–F activation and **CuP2** as the cross-coupling catalyst for C–O bond formation. Crucially, by implementing two salt additives to mediate the precise balance, a single Cu-dppbz system gives rise to two synergistic catalytic species that fulfill the dual role in this transformation.

Scheme 6. Formation of Copper-alkoxide Complex **5**.



[M+H]$^+$ m/z = 623.1688

Liquid Crystal Molecule

Finally, we proceeded to examine the potential of our new CF_2O-molecules as liquid crystal materials. Kirsch and coworkers have demonstrated that CF_2O-bridges can contribute to larger nematic phase range and clearing temperature as well as lower rotational viscosity.[13] By applying our defluorinative C–O coupling, we were able to bypass the length synthetic route typically required to prepare these derivatives and instead directly construct the CF_2O-linkers by combining readily available trifluoromethylarenes and alcohols. As a representative example, we prepared compound **3x** in one step by coupling $ArCF_3$ **1a** and *trans*-4-(*trans*-4-propylcyclohexyl)cyclohexanol **2x** (Figure 1a).[25] **3x** is a crystalline solid material, and a single crystal suitable for XRD analysis was obtained to reveal a solid-state structure with the intermolecular packing via CH–π interaction between the cyclohexyl group and phenylene moiety (Figure 1b, see Figure S20 and Table S18 in SI). When the amorphous powder of **3x** was observed under cross-polarized microscopy, we were pleased to find that it underwent thermotropic phase transition at 140 °C, displaying liquid crystal behavior (Figure 1c). This proof-of-concept experiment thus showcases the power of our method to rapidly prepare novel liquid crystal materials for future applications.

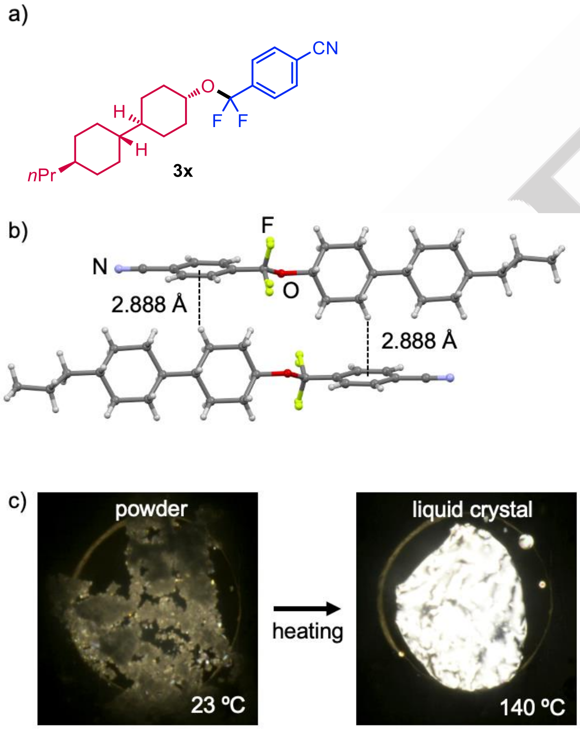


Figure 1. a) Molecular and b) X-ray single crystal structures of **3x**, and c) cross-polarized microscopy images of **3x** recorded at different temperatures.

Conclusion

In this work, we developed a defluorinative C–O coupling between trifluoromethylarenes and alcohols by means of copper photoredox catalysis. This method represents a convergent synthesis for an underexplored motif, difluorobenzylether ($ArCF_2OR$), from two readily available coupling partners. As compared to previous reports that are limited to phenols and TEMPO, a wide collection of aliphatic alcohols can be implemented in this method to afford attractive $ArCF_2OR$ products. A derivative displaying liquid crystal property was prepared using this step-economical methodology. Furthermore, by slightly modifying the conditions, we were able to switch to the production of $ArCF_2I$ compounds, another class of CF_2-containing moiety with high potential.

Mechanistic studies led us to propose a unique mechanism comprising two catalytic cycles. The Cu-dppbz combination generates *in situ* two catalytically active species, **CuP4** and **CuP2**, where **CuP4** serves as a rare case of homoleptic Cu-bisphosphine photocatalyst to promote C–F activation and **CuP2** acts as the cross-coupling catalyst for C–O formation. The synergy between the two catalytic cycles is mediated by two salt additives, LiI and $Zn(OAc)_2$. Additionally, $ArCF_2I$ generated from the C–F activation cycle can serve as a reservoir to store and replenish $ArCF_2$• to the C–O coupling cycle. The interplay between all reaction components then ensures successful formation of the desired products. Further explorations of these new $ArCF_2OR$ and $ArCF_2I$ compounds as well as applications of this Cu-photoredox catalytic system are currently underway.

Acknowledgements

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Keywords: C–F activation • C–O coupling • copper catalysis • liquid crystals • photocatalysis

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[26] Deposition numbers 2382839 (for **3x**), and 2382840 (for **CuP4**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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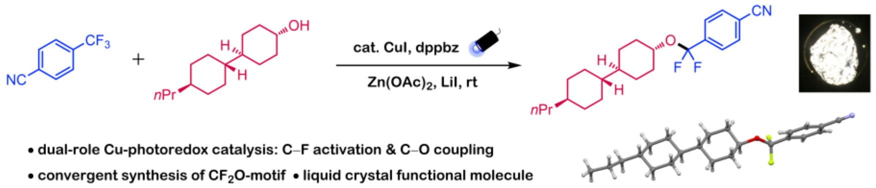

CF_2O-compounds are prepared via photoinduced, Cu-catalyzed defluorinative coupling between readily available trifluoromethylarenes and alcohols. A molecule displaying liquid crystal property was synthesized through this convergent and step-economical method. Mechanistic studies suggested that a homoleptic Cu-bisphosphine complex serves as the photocatalyst, and the two salt additives are crucial in orchestrating this dual-cycle system.

Institute and/or researcher Twitter usernames: @DCYHuang, @MingooJin, @ICReDDconnect