Copper-Catalyzed Difluoromethylation of Alkyl Halides Enabled by Aryl Radical Activation of Carbon–Halogen Bonds

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ABSTRACT: The engagement of unactivated alkyl halides in copper-catalyzed cross-coupling reactions has been historically challenging, due to their low reduction potential and the slow oxidative addition of copper(I) catalysts. In this work, we report a novel strategy that leverages the halogen abstraction ability of aryl radicals, thereby engaging a diverse range of alkyl iodides in copper-catalyzed Negishi–type cross-coupling reactions at room temperature. Specifically, aryl radicals generated via copper catalysis efficiently initiate the cleavage of the carbon–iodide bonds of alkyl iodides. The alkyl radicals thus generated enter the copper catalytic cycles to couple with a difluoromethyl zinc reagent, thus furnishing the alkyl difluoromethane products. This unprecedented Negishi–type difluoromethylation approach has been applied to the late-stage modification of densely functionalized pharmaceutical agents and natural products.

INTRODUCTION

The efficient development of new medicines that treat and prevent diseases plays a vital role to improve the quality of human life. Seminal work by Lovering has shown that increasing fraction of sp^3 hybridized carbons correlates with the clinical success of drug candidates.[1, 2] Therefore, the selective construction of sp^3-enriched centers is among the most important reactions. In the arsenal of organic chemists, transition metal-catalyzed cross-coupling of unactivated alkyl halides with organometallic reagents remains one of the most straightforward and modular approaches to the connection of sp^3-hybridized carbons.[3-6] Tremendous progress has been made in this area through the use of palladium,[7-10] and, more recently, nickel catalysts.[11-15]

On the other hand, copper catalysts represent appealing alternatives to their palladium and nickel counterparts.[16-24] As copper is one of the most abundant transition metals in Earth's crust, it is much less expensive and more globally available than Pd and Ni [*e.g.,* $Cu(OAc)_2$ < \$1/g, $Ni(OAc)_2$ ca. \$10/g, and $Pd(OAc)_2$ ca. \$80/g].[25] In addition, being an essential trace element vital to the health of humans and other living organisms,[26-29] copper salts typically have low toxicity and little environmental impact, as indicated by the higher permitted daily exposure values (Cu 3400 µg, Ni 220 µg, and Pd 100 µg).[30]

Despite these prominent economic and environmental features, the engagement of unactivated haloalkanes in copper-catalyzed cross-coupling reactions remains challenging. The main difficulty associated with such processes has been attributed to the sluggish two-electron oxidative addition of copper(I) complexes. In addition, the low reduction potential of unactivated alkyl halides (E_{red} < –2V vs SCE) hinders the direct single electron transfer (SET) from Cu^I catalysts. By contrast, the capture of alkyl radicals by Cu^{II} species and the ensuing reductive elimination of the organocopper(III) complexes can proceed efficiently (**Figure 1a**).

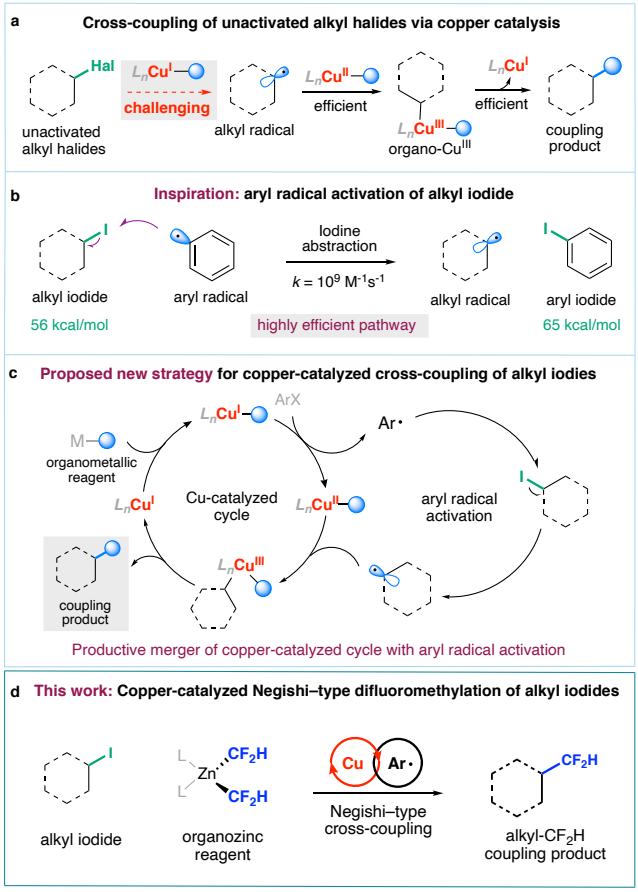


Figure 1. The aryl radical activation pathway can enable a new approach for copper-catalyzed cross-coupling of unactivated alkyl halides. Ar·, aryl radical.

Given the efficiency of the radical capture and reductive elimination steps, strategies relying on the formation of alkyl radicals have been recently applied to engage alkyl halides in copper catalysis. Thus, Fu and Peters have developed photoinduced approaches to the generation of excited-state Cu-nucleophile species, which could reduce alkyl halides via SET pathways.[31-35] The MacMillan group has pioneered the use of silyl radicals, generated via photoredox catalysis, for the activation of alkyl halides in copper catalysis.[36-38] More recently,

Leonori discovered that α-aminoalkyl radicals could enable efficient copper-catalyzed amination of alkyl iodides.[39, 40] Despite these advances, a general activation mode that can allow for the coupling of unactivated alkyl halides with mild organometallic reagents, *e.g.,* alkylzinc reagents, via copper catalysis remains highly desirable.

It is well-precedented that aryl radicals are capable of abstracting iodine atoms from alkyl iodides to form alkyl radicals and aryl iodides with a rate constant of $k = 10^9$ $M^{-1}s^{-1}$ (**Figure 1b**).[41] The iodine abstraction step is expected to be irreversible (rate constant of the reverse reaction $k < 10^2$ $M^{-1}s^{-1}$)[42] due to the difference in the bond dissociation energy (BDE) of the C(sp^2)–I bonds (BDE of iodobenzene = 65 kcal/mol) and C(sp^3)–I bonds (BDE of isopropyl iodide = 56 kcal/mol).[43] The high reactivity and irreversibility of the iodine abstraction step should outcompete other unwanted pathways of the aryl radicals, including the direct capture of aryl radicals by copper catalysts ($k \approx 10^8$ $M^{-1}s^{-1}$).[44] Nonetheless, such a reactivity has received little attention in synthetic applications.[45-47] We hypothesize that various alkyl iodides could be converted to alkyl radicals for copper catalysis via the use of the transient aryl radicals that could be readily generated via copper-catalyzed pathways, *e.g.,* from arenediazonium salts. The SET to arenediazonium salts is a unique reactivity of Cu^I complexes and has been widely involved in transformations of arenediazonium salts, including Sandmeyer reaction and Meerwein arylation.[48] We postulate that such a productive merger of copper catalysis with aryl radical activation could provide a new strategy for the coupling of unactivated alkyl iodides with mild organometallic reagents (**Figure 1c**). As a proof of concept, in this work, we have exploited this new strategy to deliver a general approach to the difluoromethylation of alkyl iodides via a copper-catalyzed Negishi–type cross-coupling reaction (**Figure 1d**).

The incorporation of difluoromethyl (CF_2H) groups into organic molecules has recently received increasing attention largely owing to their unique hydrogen bonding ability.[49-57] Due to the highly polarized C–H bond of the CF_2H group—induced by the electron-withdrawing fluorine atoms—it can act as a lipophilic hydrogen bond donor. Recent studies showed that the hydrogen bonding ability of the CF_2H group was comparable to that of hydroxyl, thiol, and amine groups.[58, 59] Therefore, the installation of CF_2H groups has become a commonly used tactic in medicinal chemistry to modulate the lipophilicity and metabolic stability of lead drug candidates.[60]

One of the most straightforward approaches to the synthesis of CF_2H-containing compounds is the direct difluoromethylation of the corresponding organohalides. Although transition metal catalysis has received great success in the difluoromethylation of aryl halides,[61-69] the analogous reaction with unactivated alkyl halides remains a formidable challenge. Prakash has reported a nucleophilic substitution approach to the conversion of primary alkyl halides to their corresponding difluoromethyl phenyl sulfones, which were then transformed to the alkyl difluoromethanes using the sodium/mercury amalgam reduction.[70] Very recently, the Shen group has reported an elegant Pd-catalyzed approach for the difluoromethylation of primary alkyl halides with $TMSCF_2H$ as the CF_2H source along with stoichiometric copper iodide.[71] Nonetheless, the limitation to primary alkyl halides and the use of large quantity of copper salts might dampen the synthetic utilities of these methods. Given the known iodine abstraction ability of aryl radicals, we questioned whether the aryl radical activation approach could be applied to enable a catalytic CF_2H-installation protocol with significant utility to medicinal chemistry. We disclose herein the successful execution of this strategy and report a broadly applicable protocol for the catalytic conversion of alkyl iodides to alkyl difluoromethanes.

RESULTS AND DISCUSSION

The proposed mechanism for the aryl radical-enabled, copper-catalyzed difluoromethylation of alkyl iodides is outlined in **Figure 2**. We reason that the transmetallation of a Cu^I catalyst **1** with a zinc-difluoromethyl reagent, $(DMPU)_2Zn(CF_2H)_2$ **2**, *i.e.,* Vicic-Mikami reagent,[62, 64] could form a Cu^I–CF_2H species **3**. Notably, a hectogram synthesis of **2** has been recently reported by Pfizer.[72] Our previous work has suggested that Cu^I–CF_2H species **3** was a strong reductant (cal'd $E_{red} = -1.2$ V vs SCE).[73-75] Therefore, we anticipate that **3** could undergo a SET event with a diazonium salt **4** to form an aryl radical intermediate **5**, with the concurrent formation of a Cu^{II}–CF_2H complex **6**.[76-78] The former should efficiently abstract an iodine atom from an alkyl iodide **7** to form an alkyl radical **8** and an aryl iodide **9**. Oxidative capture of **8** by the Cu^{II}–CF_2H species **6** would furnish a high-valent organocopper(III) complex **10**,[79] which should undergo reductive elimination to afford the alkyl difluoromethane coupling product **11**.[80-82] This reductive elimination step would regenerate the starting Cu^I catalysts and close the catalytic cycle.

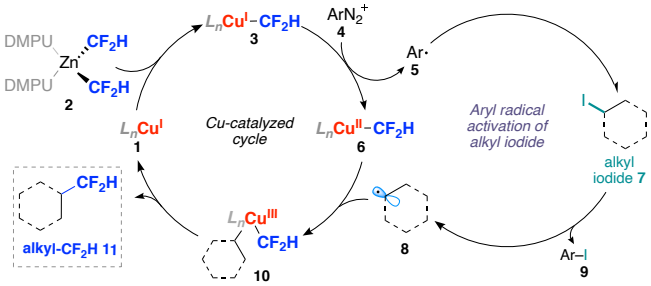


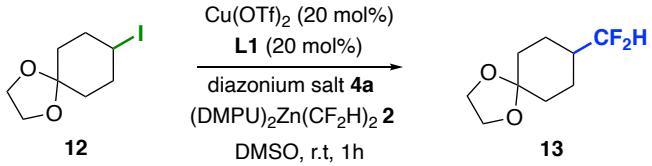
Figure 2. Proposed catalytic cycle for the aryl radical-enabled, copper-catalyzed coupling of alkyl iodides with CF_2H groups.

Reaction Optimization.

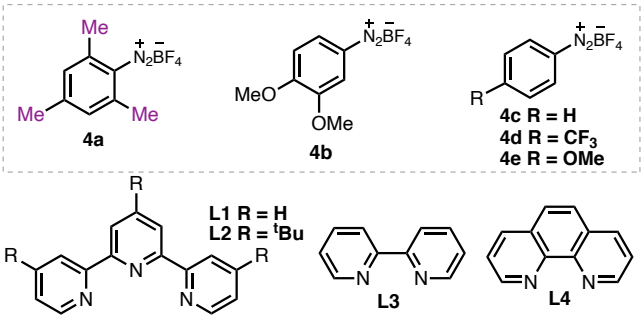
This hypothesis was then tested on a model substrate **12** with a various combinations of different copper sources, ligands and arenediazonium salts (**Table 1**). We were delighted to find that when 2,4,6-trimethylbenzene diazonium salt **4a** was used, **12** could efficiently couple with the difluoromethylzinc reagent **2** under copper-catalyzed conditions, affording the desired alkyl difluoromethane product **13** at room temperature (**entry 1**). The use of a sterically hindered and electron-rich diazonium salt **4a** was crucial to the success of this reaction (**entry 2** to **5**). We reason that the electron-rich and sterically hindered aryl rings stabilized the aryl radicals, thereby preventing other undesired pathways. It is worth noting that **4a** could be easily synthesized from the corresponding aniline (ca. \$0.3/g) on a decagram scale and be stored in a –20°C freezer for at least a month without noticeable decomposition. Tridentate nitrogen ligand, terpyridine **L1**, was found to be beneficial for this reaction, while other bidentate ligands such as bipyridine **L3** or phenanthroline **L4** was less efficient (**entry 6** to **8**). We

attribute this efficiency to the stabilization of the intermediate [Cu–CF_2H] species by tridentate ligands.

Table 1. Reaction optimization[a]



entry	Variation from standard	Yield[b]
1	**None**	**90%** (99%[c])
2	**4b** instead of **4a**	85%
3	**4c** instead of **4a**	68%
4	**4d** instead of **4a**	25%
5	**4e** instead of **4a**	82%
6	**L2** instead of **L1**	78%
7	**L3** instead of **L1**	27%
8	**L4** instead of **L1**	17%
9	$[Cu(OTf)]_2 \cdot C_6H_6$ instead of	80%
10	$Cu(acac)_2$ instead of $Cu(OTf)_2$	78%
11	open to air	86%
12	**4a** (1.5 equiv.)	74% (83%[c])
13	**4a** (2.0 equiv.)	84% (92%[c])
14	no $Cu(OTf)_2$	N.D.
15	no **4a**	N.D. (<5%[c])



[a]Reactions were conducted with **12** (0.1 mmol, 1.0 equiv.), diazonium salt (0.25 mmol, 2.5 equiv.), **1** (0.15 mmol, 1.5 equiv.) $Cu(OTf)_2$ (20 mol%), and ligand (20 mol%) in DMSO (0.6 mL) at R.T. [b]Yields were determined by ^{19}F NMR using 1-fluoro-3-nitrobenzene as the internal standard. [c]Conversion of **12**, determined by GC using 1-fluoro-3-nitrobenzene as the internal standard. N.D., not detected.

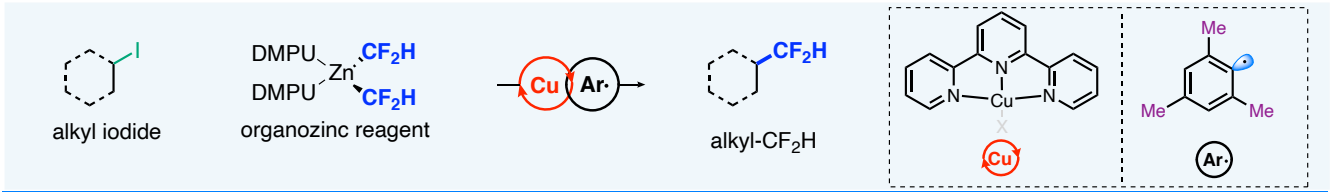
Other copper(I) and copper(II) salts could also be used as the catalysts (**entry 9** and **10**). Notably, the use of less air-sensitive copper(II) catalysts allowed the reaction to be set up under an air atmosphere affording **13** in a similar yield (**entry 11**). The copper(II) salts were expected to be reduced *in situ* by the organozinc reagents to form the active copper(I) catalysts. Moreover, the loading of the diazonium salts could be reduced while the desired product was formed in good yields (**entry 12** and **13**), although our later study revealed that unreacted alkyl iodides occasionally complicated the purification of difluoromethylated products. Therefore, 2.5 equiv. of **4a** was used in the entire study to ensure the full consumption of the alkyl iodides. Finally, control experiments have shown that no desired products were formed in the absence of either the diazonium salt or the copper catalyst (**entry 14** and **15**). The alkyl iodide remained intact when the diazonium salt was omitted in the reaction, consistent with the argument that copper catalysts alone were not reactive toward unactivated alkyl iodides.

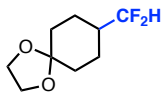
Substrate Scope

With the optimized conditions in hand, we then evaluated the group tolerance of this aryl radical activation strategy (**Table 2**). A broad range of secondary alkyl iodides appended to a variety of rings (cyclobutane, cyclopentane, cyclohexane, piperidine, 1,3-dioxane, azetidine, and azepane) afforded the corresponding CF_2H products in good to excellent yields (**13** to **24**, 50% to 90% yield). Functional groups including acetal, carbamate, ester, and even tertiary amine could be tolerated under the reaction conditions. A high diastereoselectivity was observed for the difluoromethylation of the alkyl iodide derived from menthol (**18,** *d.r.* = 16:1), presumably induced by the interaction between the bulky isopropyl group and the copper(II) complex during the radical recombination step. Acyclic secondary alkyl iodides, some of which contained reactive hydrogen atoms that were prone to β-hydride elimination reactions, were successfully difluoromethylated (**25** to **28**, 60 to 77% yield). By contrast, previously reported decarboxylative and deaminative difluoromethylation reactions were incapable of installing CF_2H groups at acyclic alkyl sites.[73, 74]

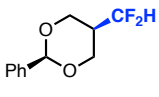
Next, the compatibility of primary alkyl iodides has been evaluated. Substrates that contain diverse functional groups, such as silyl ether, sulfonamide, imide, perfluoroalkyl, and the base-labile Fmoc group, were found to give good to excellent yields of the desired products (**29** to **35,** 56% to 88% yield). Alkyl and aryl bromides were accommodated under the reaction conditions (**36** and **37,** 67% and 82% yield, respectively), providing potential opportunities for the diversification of the difluoromethylated products. A substrate that contained an aryl iodide moiety could be selectively activated at the C(sp^3) site with 1.3 equiv. of diazonium salt being employed (**38**, 59% yield); the use of more diazonium salts led to the protodeiodination of the aryl iodide group, indicating a competing iodine abstraction from the aryl ring ($k = 9 \times 10^7$ $M^{-1}s^{-1}$).[83, 84] Notably, unprotected phenol and aldehyde groups, which were typically problematic in cross-coupling reactions involving reactive organometallic reagents, did not interfere the difluoromethylation reactions (**39** and **40**, 92 and 91% yield, respectively). An electron-rich aromatic ring, which was prone to arylation with aryl radicals in the Gomberg–Bachmann reaction,[85] was well tolerated (**41**, 85% yield). Substrates that contained potential nucleophiles, such as unprotected indole and terminal alkyne, which were known to react with alkyl iodides under related conditions[35, 39], could furnish the desired products in reasonable yields (**42** and **43**, 49% and 42%, respectively). Difluoromethylation of alkyl iodides that consisted of pharmaceutically relevant heterocycles, including thiophene, oxazole, thiazole, and pyridine, was accomplished in generally good efficiency. (**44** to **47,** 46% to 69% yield). Finally, the scalability of this protocol has been demonstrated with the synthesis of compound **32** in a 5 mmol scale (65% yield).

Table 2. Substrate Scope of the Aryl Radical-Enabled, Copper-Catalyzed Difluoromethylation of Alkyl Iodides[a]

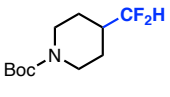




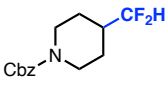
13, 90%[b]



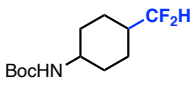
14, 78%, *d.r.* = 3:1[c] (54% major isomer)



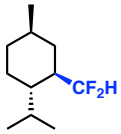
15, 65%



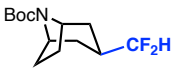
16, 82%



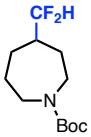
17, 73% *d.r.* = 1:1



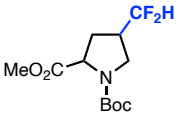
18, 51%[b], *d.r.* = 16:1



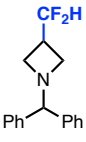
19, 80%, *d.r.* = 5:1[c] (62% major isomer)



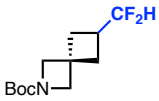
20, 79%



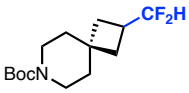
21, 54%, *d.r.* = 2.1:1



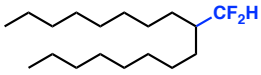
22, 50%



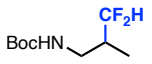
23, 51%



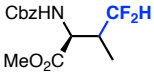
24, 52%



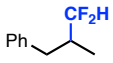
25, 60%



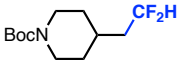
26, 77%



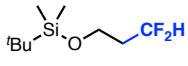
27, 70%, *d.r.* = 1.2:1



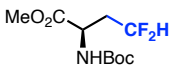
28, 62%[b]



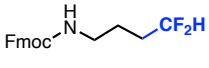
29, 88%



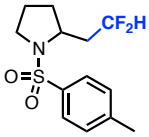
30, 84%[b]



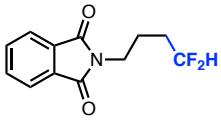
31, 69%



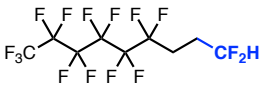
32, 77%, 65% (5 mmol)



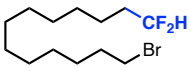
33, 75%



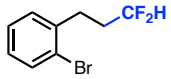
34, 76%



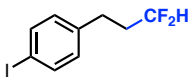
35, 56%[b]



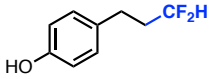
36, 67%



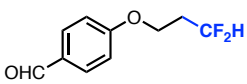
37, 82%



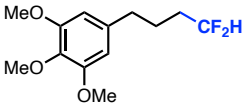
38, 59%



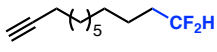
39, 92%



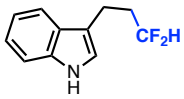
40, 91%[b]



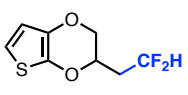
41, 85%



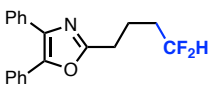
42, 49%



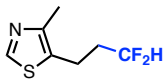
43, 42%



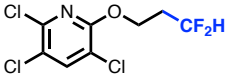
44, 69%



45, 68%



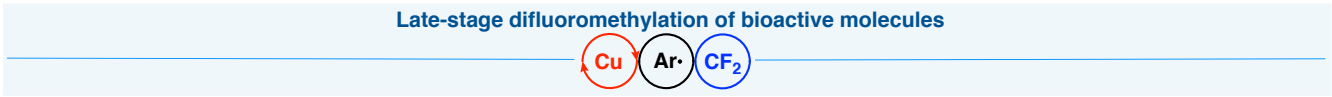
46, 46%[b]

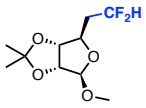


47, 66%

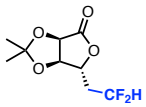
[a]Reactions were run with 0.25 mmol of alkyl iodides, 0.625 mmol of **4a** (2.5 equiv.), 0.375 mmol of **1** (1.5 equiv.), **L1** (20 mol %) and $Cu(OTf)_2$ (20 mol %) in 1.5 mL of DMSO at r.t. under Ar. Isolated yields were reported. [b]Yield determined by ^{19}F NMR due to the volatility of the product. [c]Yield and diastereoselectivity determined by ^{19}F NMR of the crude reaction mixture. Isolated yield of the major isomer shown in parenthesis.

Table 3. Copper-Catalyzed Late-Stage Difluoromethylation of Complex Bio-Relevant Molecules[a]

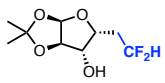




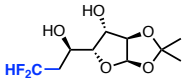
48, 73%
from D-ribofuranoside



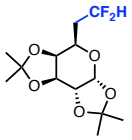
49, 67%
from D-ribonic lactone



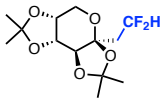
50, 72%
from D-xylofuranose



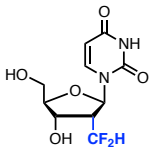
51, 62%
from D-glucofuranose



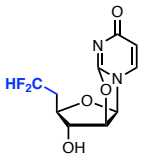
52, 51%
from D-galactopyranose



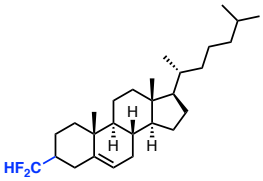
53, 69%
from D-fructopyranose



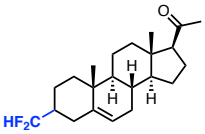
54, 58%, single isomer
from uridine



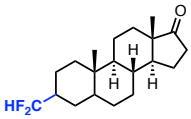
55, 40%
from cyclouridine



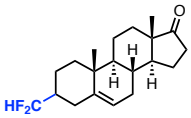
56, 43%, *d.r.* = 1.4:1
from cholesterol



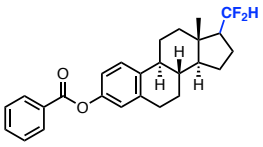
57, 55%, *d.r.* = 1.4:1
from pregnenolone



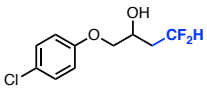
58, 54%, *d.r.* = 3.0:1
from epiandrosterone



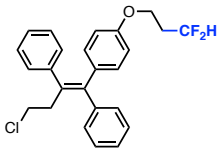
59, 61%, *d.r.* = 1.6:1
from DHEA



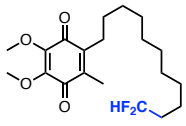
60, 54%, *d.r.* = 2.4:1
from estradiol benzoate



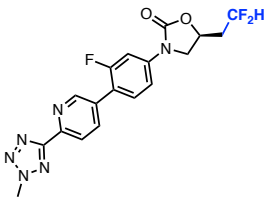
61, 64%
from chlorphensin



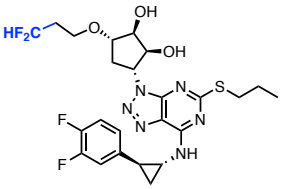
62, 72%
from ospemifene



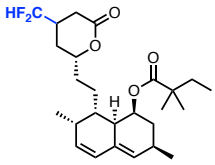
63, 71%
from idebenone



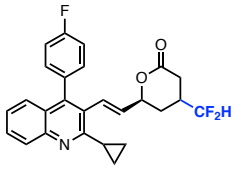
64, 65%
from tedizolid



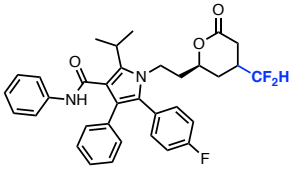
65, 65%
from ticagrelor



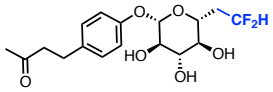
66, 61%
from simvastatin



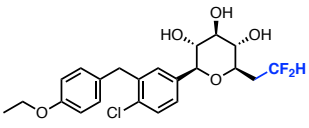
67, 74%, *d.r.* = 1.4:1
from pitavastatin



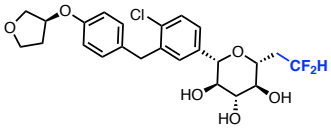
68, 67%, *d.r.* = 1.6:1
from atorvastatin



69, 64%
from raspberry ketone glucoside



70, 58%
from dapagliflozin



71, 60%
from empagliflozin

[a]Reactions were run with 0.25 mmol of alkyl iodides, 0.625 mmol of diazonium salt (2.5 equiv.), 0.375 mmol of **1** (1.5 equiv.), **L1** (20 mol %) and $Cu(OTf)_2$ (20 mol %) in 1.5 mL of DMSO at r.t. under Ar. Isolated yields were reporte

Late-Stage Difluoromethylation of Bioactive Molecules

Alkyl iodides could be easily synthesized via Appel iodination reactions from alcohols, which are ubiquitous in natural products and pharmaceutical agents, such as carbohydrates, nucleosides, steroids, and glycosides. Thus, the synthetic utility of this difluoromethylation protocol was further highlighted by the late-stage functionalization of a large variety of alkyl halides derived from complex bio-relevant molecules (**Table 3**). Alkyl iodides prepared from a group of commercially available monosaccharides (ribose, xylose, glucose, galactose, and fructose), some of which contained unprotected hydroxyl groups, could readily couple with the CF_2H groups to afford the desired difluoromethylated carbohydrates (**48** to **53**, 51 to 73% yield). Additionally, fluorine-containing nucleosides have shown desired properties as antiviral and antitumor agents, but their preparation usually required multi-step synthesis.[86, 87] Gratifyingly, with our protocol, two CF_2H-derivatives of uridine, a pyrimidine nucleoside, could be straightforwardly synthesized from the corresponding alkyl iodide precursors (**54** and **55,** 58 and 40% yield, respectively). It is worthy of mention that compound **54** was previously prepared via a 7-step procedure, which involved tedious protection/deprotection steps as well as a preparative HPLC separation of the diastereomers.[88] Moreover, a diverse range of steroids, including cholesterol, pregnenolone, androsterone, DHEA, and estradiol, were converted to their CF_2H analogues in useful to good yields (**56** to **60**, 43% to 61% yield).

In addition to natural-occurring compounds, pharmaceutical agents such as chlorphenesin, a muscle relaxant,[89] and ospemifene, a selective estrogen receptor modulator,[90] were successfully converted to their difluoromethylated analogues (**61** and **62**, 64% and 72% yield, respectively). These two examples demonstrated the compatibility of aryl and alkyl chloride bonds with this approach. Idebenone, a benzoquinone-containing molecule that was originally designed for the treatment of cognitive defects,[91] could be difluoromethylated with the benzoquinone group unaffected (**63,** 71% yield). Tedizolid, an antibiotic that incorporated a tetrazole, a pyridine, and an oxazolidone ring,[92] was transformed in good efficiency (**64**, 65% yield). Ticagrelor, a top-selling blood thinner[93] that consisted of a diol, a thioether, a secondary amine and a triazolo[4,5,-*d*]pyrimidine scaffold, was converted to its CF_2H analogue in a 65% yield (**65**). Three cholesterol-lowering statins, including simvastatin, pitavastatin, and atorvastatin, all produced the desired CF_2H products in good yields (**66** to **68,** 61% to 74% yield). It is noteworthy that the stereoisomers of these CF_2H-lactones could be easily separated via silica column chromatography, thus potentially enabling structure-activity relationship studies. Finally, this protocol was applied to the difluoromethylation of glucoside compounds, including raspberry ketone glucoside (**69,** 64% yield), dapagliflozin (**70,** 58% yield) and empagliflozin (**71,** 60% yield), the latter two of which were among the top-selling pharmaceuticals in 2020 for the treatment of diabetes.[94] The tolerance of unprotected triol groups further highlighted the mild conditions of the aryl radical activation strategy. Considering that CF_2H groups could serve as the bioisoteres of hydroxyl groups, this difluoromethylation approach should enable the rapid synthesis and evaluation of bioisoteres of drug candidates.

Mechanistic Studies.

To further shed light on this aryl radical-enabled, copper-catalyzed protocol, we conducted several mechanistic studies to support the proposed catalytic cycle (**Figure 3**). The coupling of a cyclopropyl-containing alkyl iodide **72** under the standard conditions afforded mainly the ring-opened product **73**, with trace amounts of unrearranged product **74**. This result supports the presence of alkyl radicals in the reactions (**Figure 3a**).

Moreover, the addition of TEMPO (2 equiv.), a radical trapping agent, to the coupling of **12** led to the suppression of the formation of **13**, while the TEMPO adduct **75** was isolated in a 55% yield (**Figure 3b**). The formation of **75** further supports the involvement of an alkyl radical intermediate. More importantly, the failure of TEMPO to directly trap the aryl radical was consistent with the high reaction rate of the iodine abstraction step. Finally, GC analysis of the reaction mixture demonstrated that iodomesitylene **76** was formed in a nearly quantitative yield, in agreement with the aryl radical abstracting an iodine atom from an alkyl iodide (**Figure 3c**).

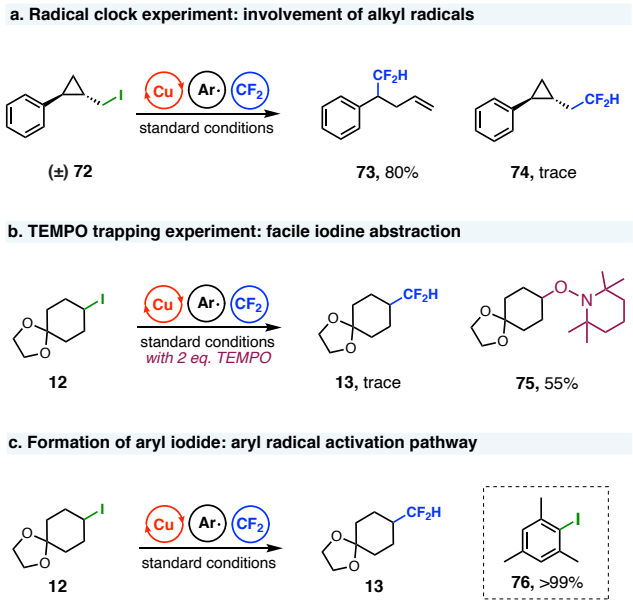


Figure 3. Mechanistic studies support the proposed aryl radical activation mechanism.

Overall, these mechanistic studies support the hypothetical mechanism in which the iodine abstraction from an alkyl iodide by an aryl radical was involved. In addition, the successful execution of the aryl radical activation strategy could be attributed to the fast iodine abstraction by aryl radicals. More thorough mechanistic studies are currently ongoing in our laboratory to better understand this aryl radical activation strategy.

CONCLUSION

To conclude, the century-old Sandmeyer reactions have taught the synthetic community one of the simplest ways of generating of aryl radicals. However, the reactivity of aryl radicals that received attention in synthetic chemistry was limited to either nucleophilic substitutions or the addition to unsaturated bonds. We report herein an aryl radical activation strategy that harnesses the halogen abstraction ability of aryl radicals, thus allowing unactivated alkyl iodides to participate in copper-catalyzed Negishi–type cross-coupling reactions. This aryl radical-enabled difluoromethylation reaction demonstrated high functional group tolerance and empowered late-stage modification of complex bioactive molecules. Mechanistic studies indicated that the rapid iodine atom abstraction by aryl radicals contributed the success of this strategy. Given the rich medicinal potential of CF_2H groups and the broad availability of alkyl halides, we anticipate that this protocol will find wide application in drug development. Most important, we expect that this aryl radical activation strategy will be a general paradigm to the development of a diverse range of C–C and C–heteroatom bond-forming reactions.

Acknowledgements

W.L. acknowledges financial support from the University of Cincinnati. NMR experiments were performed using a Bruker AVANCE NEO 400 MHz NMR spectrometer (funded by NSF-MRI grant CHE-1726092).

Keywords: Difluoromethylation • Copper Catalysis • Aryl Radical • Cross Coupling• Alkyl Halides

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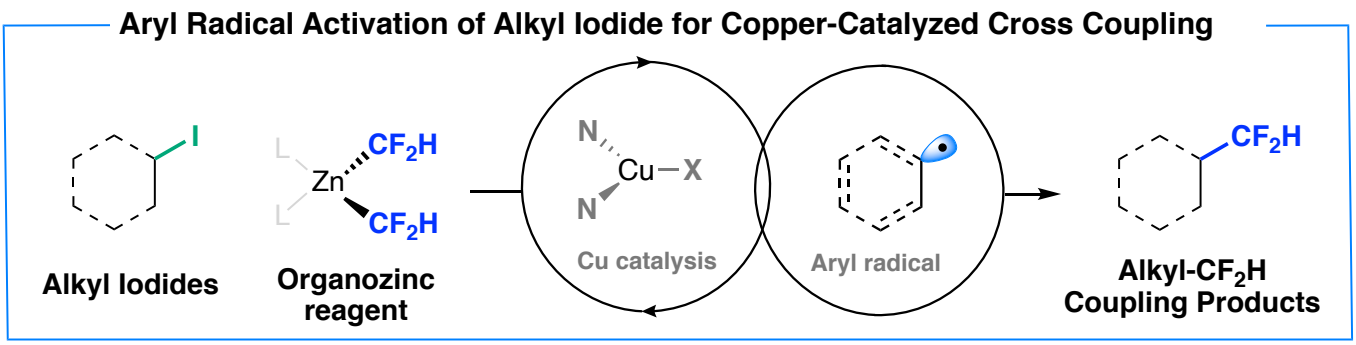
Aryl Radical Activation of Alkyl Iodide for Copper-Catalyzed Cross Coupling
I
Alkyl Iodides
Zn
CF2H
CF2H
Organozinc reagent
N
Cu—X
N
Cu catalysis
Aryl radical
CF2H
Alkyl-CF2H Coupling Products