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Communication

Metallaphotoredox Perfluoroalkylation of Organobromides

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ABSTRACT: Ruppert–Prakash type reagents ($TMSCF_3$, $TMSC_2F_5$, and $TMSC_3F_7$) are readily available, air-stable, and easy-to-handle fluoroalkyl sources. Herein, we describe a mild, copper-catalyzed cross-coupling of these fluoroalkyl nucleophiles with aryl and alkyl bromides to produce a diverse array of trifluoromethyl, pentafluoroethyl, and heptafluoropropyl adducts. This light-mediated transformation proceeds via a silyl-radical-mediated halogen atom abstraction pathway, which enables perfluoroalkylation of a broad range of organobromides of variable steric and electronic demand. The utility of the method is demonstrated through the late-stage functionalization of several drug analogues.

It is well understood that the incorporation of a fluoroalkyl group into a drug molecule can confer significant advantages, including enhanced protein binding selectivity, improved membrane permeability, and protection against *in vivo* metabolism.[1] While the trifluoromethyl (CF_3) group has been a major focus of medicinal chemistry, the relatively underexplored pentafluoroethyl (C_2F_5) moiety also possesses some distinct characteristics, such as increased steric demand, electronegativity, and lipophilicity,[2] that render it an attractive alternative to the trifluoromethyl group. The potential utility of the C_2F_5 moiety is exemplified by its inclusion in many bioactive molecules, including the angiotensin II receptor antagonist DuP 532,[3] the antibreast cancer drug Fulvestrant,[4] and the antihypertensive K^+ channel opener KC-515 (Figure 1).[5,6]

Modern approaches to the direct, selective introduction of small perfluoroalkyl groups into organic molecules typically involve transition-metal-mediated cross-coupling of organohalides with appropriate perfluoroalkyl reagents.[7] While Ni- and Pd-based strategies are hindered by the high kinetic barrier to reductive elimination,[8] Cu complexes have been shown to undergo facile reductive elimination of electronegative coupling partners from the high-valent metal center.[9] This observation has inspired extensive efforts to develop protocols to achieve direct, copper-mediated perfluoroalkylation with haloarenes. However, the diminished capacity of Cu(I) to undergo oxidative addition with organohalides limits the utility of these methods, which are typically narrow in substrate scope and require high catalyst loadings,[10,11] expensive copper-based perfluoroalkyl reagents,[12,13] and elevated temperatures. Although they do not readily undergo two-electron oxidative addition with organohalides, copper salts can efficiently trap carbon-centered radicals,[14] providing an alternate route to copper oxidative insertion via an open-shell mechanism. We recently harnessed this reactivity to develop a silyl radical-mediated halogen abstraction-radical capture (HARC) system.[15,16] According to this dual copper-photoredox catalytic pathway, aryl and alkyl bromides are converted to intermediate radical species capable of forming aryl-Cu(III)-CF_3 and alkyl-Cu(III)-CF_3 complexes.[17] These complexes readily undergo reductive elimination to afford the desired trifluoromethyl adducts.[15a,b] Recently, we sought to employ this general activation strategy, along with well-established aerobic copper chemistry, as a means to use perfluoroalkyl nucleophiles as coupling partners with a diverse range of organic bromides.

Trifluoromethyltrimethylsilane ($TMSCF_3$) and its homologues $TMSC_2F_5$ and $TMSC_3F_7$—collectively known as the Ruppert–Prakash type reagents—are the most widely used perfluoroalkyl nucleophiles due to their commercial availability, bench stability, and operational convenience.[18] Although it is possible to perfluoroalkylate aryl iodides using the Ruppert–Prakash reagents activated by fluoride anion,[11] there are currently no general methods that directly employ these nucleophiles for the functionalization of more stable and readily accessible organobromides. We speculated that our recently developed HARC trifluoromethylation protocol might be expanded to accommodate nucleophilic Ruppert–Prakash type reagents, providing a unified approach for the direct introduction of CF_3, C_2F_5, and C_3F_7 groups to a diverse array of aryl and alkyl frameworks. Herein, we disclose the successful implementation of this strategy and present a mild, convenient, and broadly applicable metallaphotoredox-catalyzed perfluoroalkylation of organobromides.

A proposed mechanism for the oxidative trifluoromethylation of organobromides is illustrated in Figure 2. Upon irradiation with visible light, excitation of photocatalyst [Ir(F-mppy)$_2$(phen)](PF$_6$) (**1**) to the long-lived triplet $^*Ir^{III}$ complex **2** is expected. Given the oxidation potentials of the excited state **2** ($E_{1/2}^{red}[^*Ir^{III}/Ir^{II}]$ = +0.83 V vs SCE in MeCN)[19] and aminosilane **4** (E_{pa} [**4**/**4**$^{+\bullet}$] = +0.66 V vs SCE in MeCN),[20] we assume that a rapid SET event would generate a

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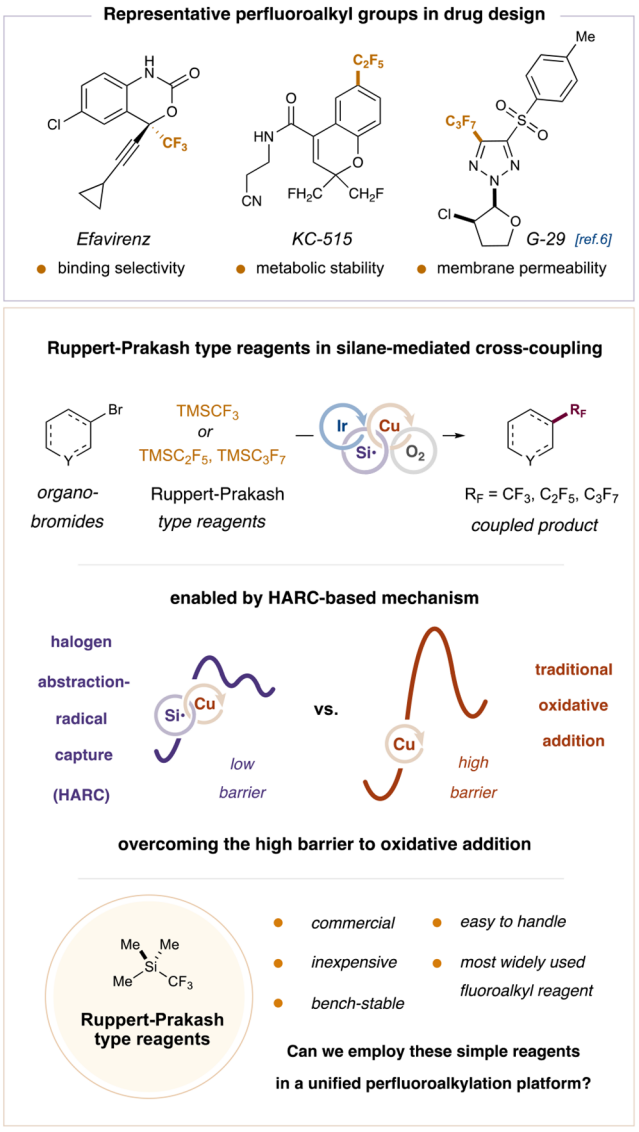

Figure 1. Unified perfluoroalkylation of organobromides.

silicon-centered radical (**5**) after deprotonation by a suitable base and subsequent aza-radical Brook rearrangement. The nucleophilic silyl radical **5** can then abstract a bromine atom from organobromide **6** to form open-shell radical intermediate **7**. Concurrently, Cu(I) species **8** would undergo ligand exchange with the nucleophilic trifluoromethyl source, likely in a base-mediated process, thereby generating ligated Cu(I)–CF_3 complex **9**, which can be subsequently oxidized by a terminal oxidant. The resultant Cu(II) species **10** can rapidly capture radical **7** to generate transient formal Cu(III)–CF_3 complex **11**, which would be expected to undergo facile reductive elimination to afford product **12** and regenerate the Cu(I) catalyst. Oxidative turnover of the photocatalytic cycle returns Ir(II) complex **3** to the ground-state photocatalyst **1**.

At the outset, we evaluated the trifluoromethylation of aryl bromide **13** with the nucleophilic $TMSCF_3$ reagent. Following an extensive survey of supersilane derivatives, catalysts, and ligands (see Supporting Information (SI) for details), we ultimately identified the optimized conditions outlined in Table 1, entry 1. Thus, the aminosilane reagent **4** facilitates formation of the desired product in 87% yield using a combination of photocatalyst **1** (0.5 mol %), 4,4′-dimethyl-2,2′-bipyridine ligand (25 mol %), and copper(I) bromide (20 mol %). The low oxidation potential of organosilane **4** permits generation of a silyl radical by photocatalyst **1** via SET under mild conditions; accordingly, this procedure can tolerate sensitive functional groups, such as aniline and tertiary alkyl amine, that are traditionally susceptible to oxidation. Interestingly, other silane reagents previously used in photoredox cross-electrophile couplings (including supersilanol and supersilane)[21] were ineffective (entries 2 and 3). Conveniently, the optimal conditions employ air as an oxidant, obviating the need for rigorous deoxygenation. Control experiments revealed that iridium photocatalyst, light, silane reagent, ligand, air, and copper catalyst were all necessary for product formation (entries 4–10).

With optimized conditions in hand, we turned our attention to evaluating the scope of the aryl trifluoromethylation. As shown in Table 2, *para*- and *meta*-substituted aryl bromides bearing sulfone and nitrile groups generated trifluoromethyl adducts in high yields (**16** and **17**, 82% and 78% yield). Notably, the efficiency of the reaction was not impeded by the installation of *ortho* substituents on the aryl ring (**18** and **19**, 70% and 65% yield). Additionally, aryl bromides with fused cyclic motifs afforded the desired trifluoromethylarenes with good efficiency (**20** and **21**, 68% and 72% yield). Heteroaryl bromides were readily accommodated in the transformation: pyridine-derived substrates were functionalized in good yields (**22**–**24**, 65–78% yield), and multiple-nitrogen-bearing heteroarenes, such as pyrazines, quinoxalines, and pyrimidines, were readily converted into the corresponding trifluoromethylarenes (**25**–**27**, 66–80% yield). Five-membered heteroaryl bromides, including benzimidazoles, thiazoles, and benzothiazoles, were also found to serve as competent coupling partners (**28**–**30**, 65–73% yield). Consistent with the modular radical activation paradigm, we expected aliphatic bromides to be an amenable substrate class. Gratifyingly, trifluoromethylation of primary alkyl bromides was successfully achieved (**31**, 84% yield), while secondary cyclic alkyl bromides were likewise converted to their trifluoromethyl congeners in good yields (**32** and **33**, 75% and 68% yield). This broad substrate scope validates the utility of this transformation as a means to gain rapid access to analogs of drug-like molecules.

Given the value of the C_2F_5 group in medicinal chemistry,[2] we next investigated the extension of this reaction to the pentafluoroethylation of bromoarenes using the $TMSC_2F_5$ reagent. In initial experiments using the representative aryl bromide **13**, the desired C_2F_5-bearing product was produced in only 48% yield (see Supporting Information for details). Changing the photocatalyst to the more reducing [Ir(ppy)$_2$bpy](PF$_6$) (**15**) and prolonging the reaction time led to an increase in the overall reaction efficiency (68% yield). Interestingly, performing the reaction in the Integrated Photoreactor,[22] which precisely controls light intensity and stirring rate, allowed further optimization to a reproducible 85% assay yield. This optimization of stirring rate and light intensity curtailed the formation of aryl radical-derived side products, including those generated through dehalogenation and copper-mediated aryl dimerization.

With optimal conditions for the pentafluoroethylation in hand, we next examined the scope with respect to the aryl bromide component. As shown in Table 2, *para*-substituted bromoarenes containing nitrile and amide groups generated the corresponding pentafluoroethyl adducts in good to excellent yields (**34** and **35**, 84% and 75% yield). As a useful

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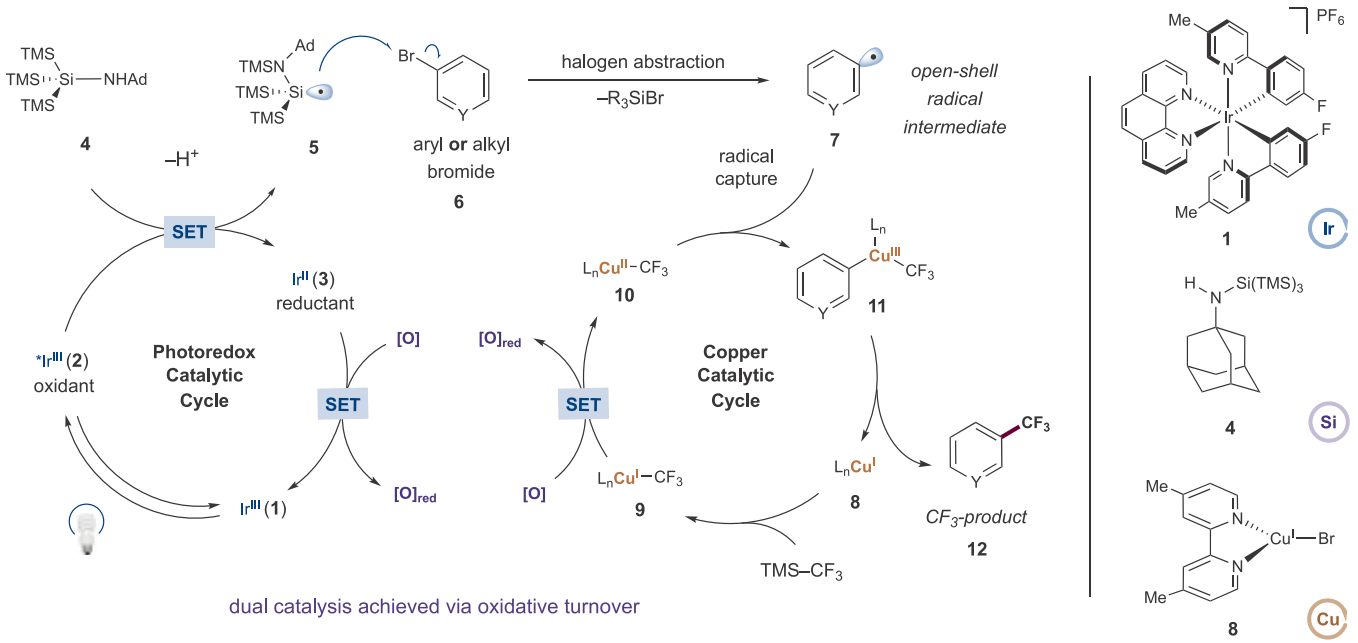
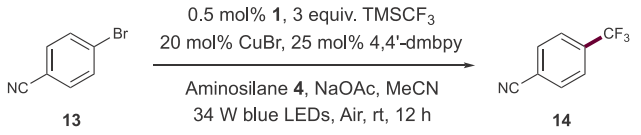


Figure 2. Proposed mechanism for the copper-catalyzed perfluoroalkylation of organobromides

Table 1. Control Reactions of Optimized Conditions[a]



13 14

entry	deviations	yield[b]
1	none	87%
2	TMS_3SiH instead of **4**	15%
3	TMS_3SiOH instead of **4**	35%
4	no silane source	0%
5	no CuBr	0%
6	no ligand	0%
7	no light	0%
8	no photocatalyst	0%
9	N_2 sparge	0%
10	no base	38%

[a]Performed with aminosilane reagent **4** (1.8 equiv), NaOAc (4 equiv), aryl bromide **13** (0.1 mmol), and $TMSCF_3$ (3 equiv) in MeCN (0.1 M). [b]Yields determined by ^{19}F NMR analysis using 1,4-difluorobenzene as internal standard. See SI for more details.

demonstration of the mild conditions and broad functional group tolerance of this new coupling procedure, we found that aryl electrophiles bearing tertiary alkylamine groups, namely morpholine and piperazine motifs, generate the desired products, **36** and **37**, in good yields (65% and 70%). *Ortho*-substitution on the aryl coupling partner was well accommodated, furnishing adducts **38** and **39** in 70% and 66% yield, respectively. Moreover, aryl bromides with fused cyclic motifs were converted to pentafluoroethylarenes **40** and **41** in good yields (68% and 70%). With respect to heteroaryl bromide substrates, we observed that pyridine-derived substrates—motifs commonly found in drug scaffolds—were readily accommodated (**42**–**46**, 63–82% yield). Multinitrogen-containing heterocycles, such as pyrimidines, pyrazines, and quinoxalines, participated in good yields (**47**–**49**, 62–66% yield). A wide range of five-membered heteroaryl bromides, including pyrazoles, indazoles, benzimidazoles, thiazoles, and benzothiazoles, underwent pentafluoroethylation in useful to good yields (**50**–**54**, 48–65% yield). Notably, primary and secondary alkyl bromides proved to be suitable substrates for the pentafluoroethylation protocol (**55**–**57**, 45–83% yield). Last, as a demonstration that this method can be extended to the installation of longer-chain perfluoroalkyl groups, heptafluoropropylation can also be accomplished using this new protocol to provide the corresponding perfluoropropylarene in useful efficiencies (**58**, 52% yield; see Figure S13 for additional heptafluoropropylated substrates). These results represent a novel and straightforward way to introduce varied perfluoroalkyl groups onto a diverse range of carbon electrophiles.

Given the pharmaceutical relevance of the CF_3 and C_2F_5 functional motifs, we further sought to showcase our novel procedure by selectively appending CF_3 and C_2F_5 groups onto several medicinal scaffolds. As shown in Table 3, aryl bromide progenitors of sulfadimethoxine, indometacin, dramamine II, rupatadine, etoricoxib, and a purine nucleoside were subjected to our standard trifluoromethylation conditions, generating the corresponding trifluoromethylated derivatives **59**–**64** (48–80% yield). Pentafluoroethylation of these complex medicinal agents similarly delivered the desired adducts **65**–**70** with good efficiency (48–76% yield). These results further highlight the real-world utility of this new perfluoroalkylation technology, and its ability to tolerate a wide range of medicinally relevant functional groups including sulfonamides, nitrogen heterocycles, styrenes, aryl chlorides, and tertiary amines.[23]

In summary, we have developed a novel procedure by which to achieve nucleophilic perfluoroalkylation of a variety of aryl, heteroaryl, and alkyl bromides. This reaction circumvents the need for substrates to undergo challenging Cu-mediated oxidative additions by employing a silyl radical-mediated halogen abstraction-radical capture (HARC) pathway and common Ruppert–Prakash type nucleophiles as a convenient source of the perfluoroalkyl group. Given its operational simplicity and broad applicability to pharmaceutically relevant

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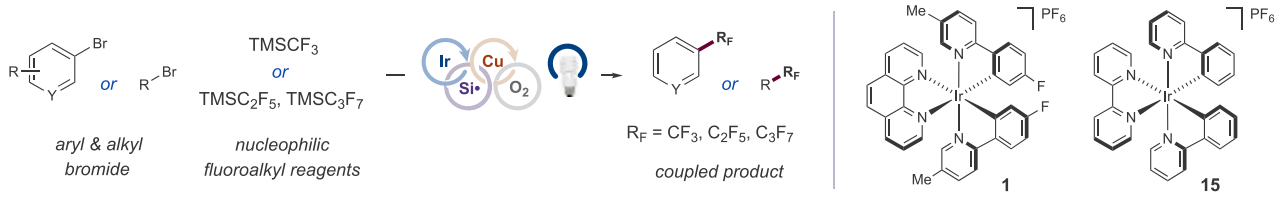
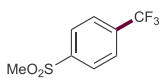
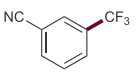
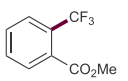
Table 2. Scope Evaluation of Silane-Mediated Perfluoroalkylation of Alkyl and Aryl Bromides

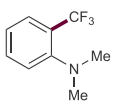


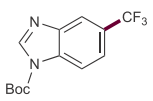
trifluoromethylation[a]


16, 82% yield

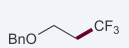

17, 78% yield

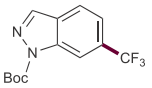

18, 70% yield

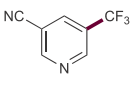

19, 65% yield[d]

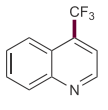

20, 68% yield

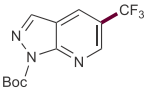
alkyl bromides

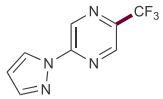

31, 84% yield[g]

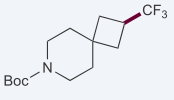

21, 72% yield

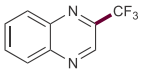

22, 70% yield

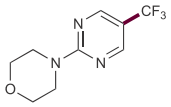

23, 78% yield

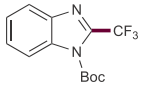

24, 65% yield

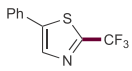

25, 66% yield[e]

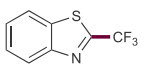

32, 75% yield[g]

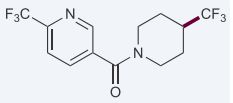

26, 80% yield[e]


27, 68% yield

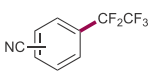

28, 65% yield[f]

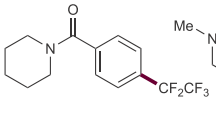

29, 68% yield[f]

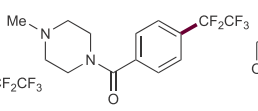

30, 73% yield[f]

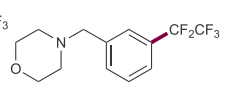

33, 68% yield[g]

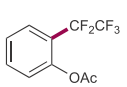
pentafluoroethylation[b]


34, (*p*-CN) 84% yield
38, (*o*-CN) 70% yield

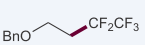

35, 75% yield

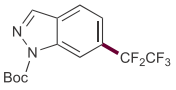

36, 65% yield

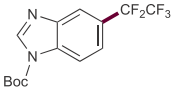

37, 70% yield

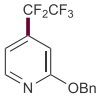

39, 66% yield

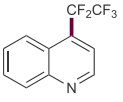
alkyl bromides

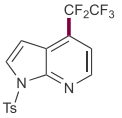

55, 83% yield[g]

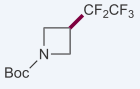

40, 68% yield

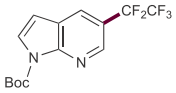

41, 70% yield

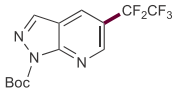

42, 82% yield

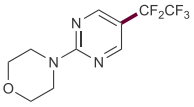

43, 70% yield

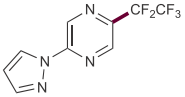

44, 63% yield

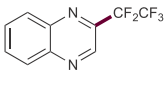

56, 72% yield[g]

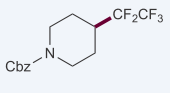

45, 64% yield

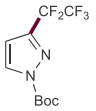

46, 63% yield

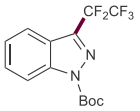

47, 62% yield[e]

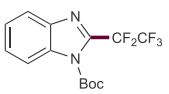

48, 65% yield


49, 66% yield


57, 45% yield[g]


50, 50% yield[d]


51, 48% yield


52, 64% yield

53, 65% yield

54, 62% yield[f]

heptafluoropropylation[c]

58, 52% yield

[a]Performed with photocatalyst **1** (0.5 mol %), CuBr (20 mol %), 4,4′-dimethyl-2,2′-bipyridine (25 mol %), aminosilane **4** (1.8 equiv), NaOAc (4 equiv), aryl or alkyl bromide (0.5 mmol), and $TMSCF_3$ (3 equiv) in MeCN (0.2 M). Yields isolated unless otherwise noted. [b]Performed with photocatalyst **15** (0.5 mol %), CuBr (20 mol %), 4,4′-dimethyl-2,2′-bipyridine (25 mol %), aminosilane **4** (1.8 equiv), NaOAc (4 equiv), aryl or alkyl bromide (0.5 mmol), and $TMSC_2F_5$ (3 equiv) in MeCN (0.2 M). [c]Performed with photocatalyst **15** (0.5 mol %), $[Cu(MeCN)_4]BF_4$ (20 mol %), 4,4′-dimethyl-2,2′-bipyridine (25 mol %), aminosilane **4** (1.8 equiv), NaOAc (4 equiv), pyridine (2.0 equiv), aryl bromide (0.5 mmol), and $TMSC_3F_7$ (3 equiv) in MeCN (0.2 M). [d]Yields determined by ^{19}F NMR using 1,4-difluorobenzene as internal standard. [e]25 mol % 4,4′-dimethoxy-2,2′-bipyridine as ligand. [f]25 mol % 1,10-phenanthroline as ligand. [g]25 mol % 2,2′-bipyridine as ligand. See SI for full experimental details.

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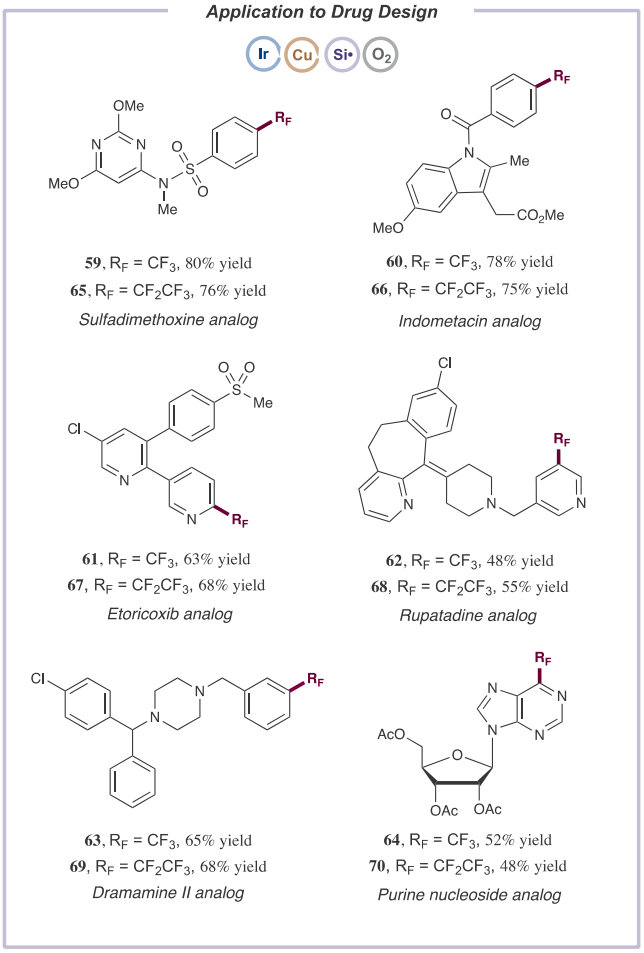
Table 3. Application to Late-Stage Functionalization[a]



[a]All yields are isolated yields. See SI for experimental details.

scaffolds, we expect this method to be widely adopted within the synthetic and medicinal chemistry communities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09977.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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