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Cross-Coupling

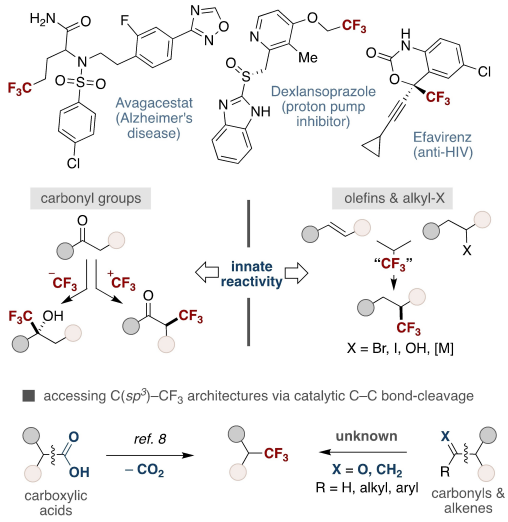
Trifluoromethylation of Carbonyl and Unactivated Olefin Derivatives by C(sp^3)–C Bond Cleavage

*Fei Cong, Riccardo S. Mega, Jinhong Chen, Craig S. Day, and Ruben Martin**

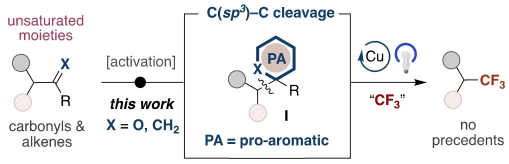
Abstract: Herein, we report a Cu-mediated trifluoromethylation of carbonyl-type compounds and unactivated olefins enabled by visible-light irradiation via σ C(sp^3)–C bond-functionalization. The reaction is distinguished by its modularity, mild conditions and wide scope—even in the context of late-stage functionalization—thus offering a complementary approach en route to valuable C(sp^3)–CF_3 architectures from easily accessible precursors.

The incorporation of trifluoromethyl (CF_3) moieties into saturated hydrocarbon skeletons has received considerable echo in pharmaceuticals and agrochemicals owing to their ability to modulate lipophilicity, permeability, metabolic stability and protein-drug interactions.[1] At present, techniques that allow access to C(sp^3)–CF_3 architectures primarily leverage the innate reactivity of unsaturated compounds,[2] prefunctionalized alkyl (pseudo)halides,[3] organometallics,[4] activated aliphatic alcohols[5] or C(sp^3)–H sites[6] via one- or two-electron pathways (Scheme 1).[7]

Despite the advances realized, the means to enable a trifluoromethylation event via functionalization of aliphatic C(sp^3)–C bonds still constitutes a largely unexplored scenario, with remarkable exceptions being described in elegant decarboxylative couplings (Scheme 1, *bottom*)[8] or ring-opening of cycloalkanols.[9] This paucity is likely due to the inertness of the C(sp^3)–C bond, the directionality of the orbitals along the C–C axis and the kinetic preference for C(sp^3)–H activation.[10] Given that an increase of sp^3 character in drug candidates improves several molecular attributes that contribute to clinical success,[11] the design of a new trifluoromethylation blueprint via C(sp^3)–C cleavage might hold promise to streamline the access to valuable C(sp^3)-architectures in the drug discovery pipeline from readily available precursors.[12]



Scheme 1. C(sp^3)-trifluoromethylation events.



Scheme 2. C(sp^3)–CF_3 architectures via C(sp^3)–C cleavage.

Prompted by the prevalence of carbonyl motifs and unactivated olefins in biologically-relevant molecules, we wondered whether we could reverse the innate reactivity of these building blocks with CF_3 sources by promoting a C(sp^3)–CF_3 bond-formation via α C(sp^3)–C cleavage instead (Scheme 1, *bottom*). If successful, we recognized that such a technique would not only offer an opportunity to improve our knowledge in retrosynthetic analysis by formally masking a CF_3 group with an unsaturated carbonyl or olefin backbone, but also a worthwhile endeavor for chemical invention in both trifluoromethylation events[7] and in the C–C bond-cleavage arena.[10] Driven by our interest in activating strong σ-bonds,[13] Luo's work,[14] and others,[15c–d] we hypothesized that the conversion of a carbonyl compound or an olefin into a pro-aromatic precursor (**I**) might set the basis for enabling a homolytic cleavage of the adjacent α C–C bond via photoinduced single-

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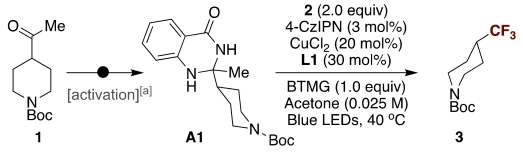
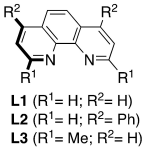
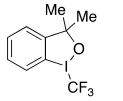
Table 1: Optimization of the reaction conditions. **A1** (0.05 mmol), **2** (0.1 mmol), $CuCl_2$ (20 mol%), **L1** (30 mol%), 4-CzIPN (3 mol%), BTMG (0.05 mmol), in Acetone (0.025 M) at 40 °C under 450 nm blue LED irradiation for 16 h. ^{19}F NMR yields using $PhCF_3$ as internal standard based on **A1**. [a] **1** (1.05 equiv), 2-aminobenzamide (1.0 equiv), I_2 (5 mol%) in DMF (0.67 M) at 80 °C. [b] Isolated yield. BTMG = 2-*tert*-Butyl-1,1,3,3-tetramethylguanidine.



entry	deviation standard conditions	3 (%)
1	none	78 (75)[b]
2	**L2** instead of **L1**	70
3	**L3** instead of **L1**	36
4	no **L1**	51
5	using $CuBr_2$	58
6	using CuCN	35
7	using DMF instead of Acetone	64
8	using CH_3CN instead of Acetone	29
9	no BTMG	28
10	DIPEA instead of BTMG	trace
11	no $CuCl_2$	0
12	no 4-CzIPN or in the darkness	0



L1 (R^1= H; R^2= H)
L2 (R^1= H; R^2= Ph)
L3 (R^1= Me; R^2= H)



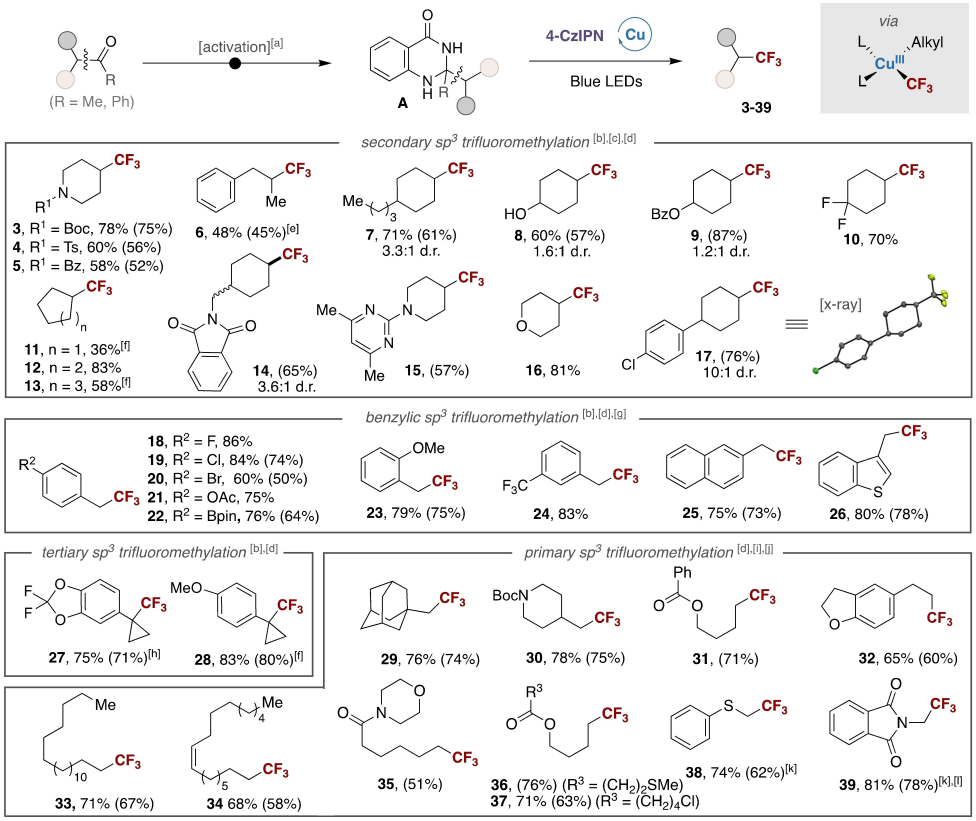
2

electron transfer (Scheme 2).[15] The subsequent open-shell intermediate might then be interfaced with an appropriate metal complex bearing the CF_3 fragment,[16] thus leading to the targeted C(sp^3)–CF_3 architecture upon reductive elimination. Herein, we describe the successful realization of this goal. This protocol is distinguished by its mild conditions, exquisite chemoselectivity profile and wide substrate scope, including particularly challenging substrate combinations.

We began our investigation by evaluating the trifluoromethylation of dihydroquinazolinone **A1** (E_{ox} = +1.21 V vs SCE)[17]—easily accessed by simple condensation of **1** and 2-aminobenzamide—with Togni's reagent **2** (Table 1). After some optimization,[17] a protocol consisting of **2**, $CuCl_2$, 1,10-phenanthroline (**L1**), 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (BTMG) and 4-CzIPN under blue light-emitting diodes (LEDs) irradiation in acetone afforded **3** in 75 % isolated yield. Ligands and copper sources other than **L1** and $CuCl_2$ resulted in lower yields of **3** (entries 1–6). Similarly, a deleterious effect was found when employing DMF or CH_3CN instead of acetone due to competitive trifluoromethylation of the solvent (entries 7 and 8).[18] As shown in entry 9, BTMG was important for success, probably due to its role as proton acceptor to deprotonate $[\mathbf{A1}]^{\bullet+}$ arising from single-electron transfer,[19] thus setting the scene for a site-selective homolytic C–C bond-fragmentation via aromatization. Traces of **3**, if any, where observed when using DIPEA, probably due to competitive quenching of the photoexcited state of 4CzIPN* (E_{red} = +1.35 V vs SCE)[20] by DIPEA (E_{ox} = +0.86 V vs SCE).[21] As expected, control experiments revealed that $CuCl_2$, 4-CzIPN and light were necessary for the reaction to occur (entries 11–12); note, however, that moderate yields were found in the absence of **L1** (entry 4).

Next, we turned our attention to exploring the generality of our Cu-catalyzed trifluoromethylation of dihydroquinazolinones. As shown in Scheme 3, our protocol could be applied with ease to a wide number of differently substituted precursors. For example, our method could be applied independently on whether electron-rich or electron-deficient arenes were utilized en route to the corresponding products containing a trifluoromethyl moiety at benzylic positions (**18**–**26**). Even tertiary reaction sites could trigger the targeted C(sp^3)–CF_3 bond-forming reaction (**27**, **28**). Importantly, our method could be implemented with less-activated radical precursors resulting in the incorporation of the trifluoromethyl fragment at *unactivated* secondary cyclic or acyclic sp^3 sites (**3**–**17**). The chemoselectivity of our reaction is illustrated by the compatibility with amide (**5**, **14**), alcohols (**8**), tertiary amines (**15**), chlorine (**17**, **19**),[22] and benzylic sites (**6**, **15**, **17**). Even substrates containing heterocyclic motifs do not interfere with productive trifluoromethylation (**15**, **26**). Minor modifications of the reaction conditions were made to improve the yields in certain cases, such as for **11**, **13** or **28** where KF was added to inhibit F-elimination from the corresponding $CuCF_3$ complexes generated in situ.[23] Although the results of Scheme 3 tacitly illustrated the viability for incorporating C(sp^3)–CF_3 motifs at benzylic or secondary alkyl sp^3 sites, it was unclear whether our trifluoromethylation could be enabled via the intermediacy of primary alkyl radicals, the least stable, yet most reactive, open-shell species in the sp^3 alkyl series.[24] Indeed, the optimized conditions in Table 1 failed to provide even traces of the C(sp^3)–CF_3 architectures from dihydroquinazolinones possessing primary alkyl fragments susceptible to C(sp^3)–C cleavage.[17] Notably, a protocol based on $Cu(CF_3)_3$(bpy) was particularly suited for our purposes,[3d] resulting in a broadly applicable method that allows for incorporating the trifluoromethyl motif into *unactivated* primary alkyl sp^3 sites (**29**–**39**). Critical for success was the inclusion of both **2** and BTMG, probably by facilitating the regeneration of $Cu(CF_3)_3$(bpy) and/or $Cu(CF_3)_2$(bpy) in situ.[6e,19] As for secondary and benzylic substrates, the reaction turned out to be widely applicable and compounds possessing an alkene (**34**), chlorine (**37**) or thioether (**36**, **38**) did not interfere with productive trifluoromethylation at the primary alkyl sp^3 site. While a priori one might argue that the presence of tertiary sp^3 alkyl or α-heteroatom C–H sites might be detrimental for the reaction due to competitive hydrogen-atom transfer at such activated positions,[25] this was not the case (**29**, **32**, **38**, **39**).

Encouraged by the results of Scheme 3, we wondered whether our C–C bond cleavage protocol could be extended beyond dihydroquinazolinones derived from ketone precursors. To this end, we turned our attention to the utilization of Hantzsch esters, easily obtained in one step from the corresponding aliphatic aldehydes.[26] After some experimentation,[17] we found that a combination of $Cu(CF_3)_3$(bpy), $K_2S_2O_8$, $NaHCO_3$ and 4-CzIPN under blue LED irradiation in MeCN at 40 °C delivered

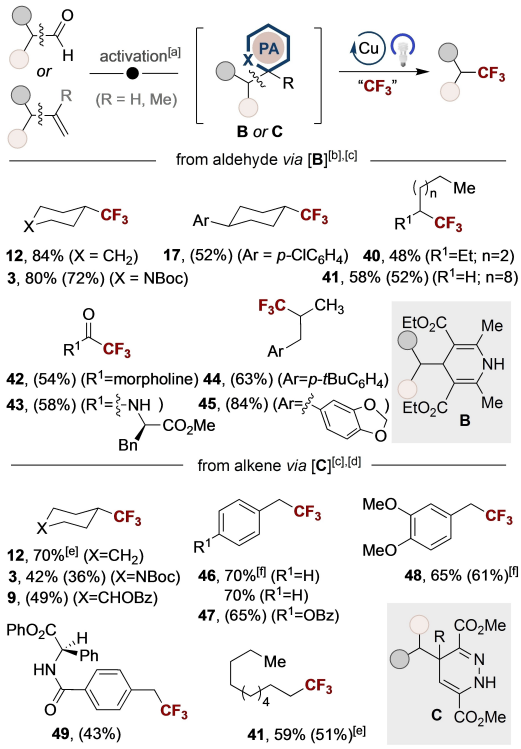


Scheme 3. Scope of trifluoromethylation of alkyl ketones. Conditions: [a] **A**: Ketone (1.05 equiv), aminobenzamide (1.0 equiv), I_2 (5 mol%) in DMF (0.67 M) at 80 °C, see Supporting Information for characterization data of **A**. [b] **A** (0.20 mmol), **2** (0.40 mmol), $CuCl_2$ (20 mol%), 4-CzIPN (3 mol%), under 450 nm blue LED irradiation, R = Me. [c] Using: **L1** (30 mol%), BTMG (1.0 equiv), in acetone (0.025 M). [d] Yields are reported on the basis of ^{19}F NMR analysis using $PhCF_3$ as internal standard; Isolated yields are in parentheses, thus showing how the volatility of some products affects the yield loss. [e] R = Ph. [f] Using **L2** (30 mol%), KH_2PO_4 (2.0 equiv), KF (2.0 equiv) in DMF (0.02 M). [g] Using di(pyridin-2-yl) methanone (30 mol%), KH_2PO_4 (2.0 equiv) in DMF (0.02 M), R = Me. [h] Using **L2** (30 mol%), BTMG (1.0 equiv) in DMF (0.02 M). [i] **A** (0.20 mmol), $Cu(CF_3)_3bpy$ (0.20 mmol), 4-CzIPN (3 mol%) under 450 nm blue LED irradiation, R = Ph. [j] Using **2** (0.30 mmol), BTMG (1.0 equiv) in DMF (0.02 M). [k] Using $K_2S_2O_8$ (1.5 equiv), KH_2PO_4 (2.0 equiv) in CH_3CN (0.025 M). [l] R = Me.

the targeted products in good yields. At present, we believe that the inclusion of $K_2S_2O_8$ most likely facilitates either oxidation of the Hantzsch ester or enables access to Cu^{II} species from the corresponding Cu^{I} analogues.[6b,27] As shown in Scheme 4, a wide range of Hantzsch esters could be employed as substrates en route to the corresponding trifluoromethylated products at cyclic secondary positions (**12**, **3**, **17**), acyclic secondary sp^3 sites (**40**, **44**, **45**) or even at *unactivated* primary alkyl sp^3 sites (**41**). Unlike the utilization of dihydroquinazolinones, this strategy could be utilized to build up trifluoroacetamide substrates via the intermediacy of acyl radical intermediates (**42**, **43**).[28]

Aiming at pushing the boundaries of a method that leverages pro-aromatic compounds as vehicles to enable $C(sp^3)$–CF_3 via $C(sp^3)$–C cleavage, we next focused our attention on the utilization of *unactivated* alkenes as radical precursors. If successful, such a technique would enable a trifluoromethylation event at a sp^3 site with a formal loss of the olefinic site, thus complementing existing methodologies that incorporate the trifluoromethyl moiety across the sp^2 C=C moiety.[2b–e] Among other conceivable scenarios, we wondered whether we could utilize 1,4-dihydropyridazines as radical precursors,[14] as these compounds are easily accessed in one step by simple exposure of *unactivated* alkenes to 1,2,4,5-tetrazines driven by extrusion of nitrogen gas. Gratifyingly, a protocol based on $Cu(CF_3)_3(bpy)$ under 370 nm irradiation was suited for this endeavor, hence delivering the $C(sp^3)$–CF_3 backbone in good yields (Scheme 4, *bottom*).[17] Notably, this strategy allowed the incorporation of the CF_3 fragment at both benzylic moieties (**46**–**49**) or at *unactivated* secondary/primary alkyl sites (**12**, **3**, **9** and **41**).

To further highlight the utility of this protocol, we targeted ketones, aldehydes and alkenes stemming from a range of advanced synthetic intermediates and compounds with biological relevance (Scheme 5). As shown, our protocol could tolerate a wide range of functional groups and heterocyclic motifs, enabling the installation of the $C(sp^3)$–CF_3 architecture on functionalized molecules with ease and good yields. Compounds possessing ketones (**50**, **56**, **60**), esters (**51**, **53**, **54**, **56**–**59**, **64**–**66**),[22] amides (**51**, **55**, **58**, **59**, **65**), halides (**53**, **56**, **58**, **63**, **65**),



Scheme 4. Aliphatic aldehydes or alkenes as precursors. Conditions: [a] **B**: Aldehyde (1.0 equiv), Bu_4NHSO_4 (12 mol%), ethyl 3-aminocrotonate (1.0 equiv), ethyl acetoacetate (1.0 equiv) in ethylene glycol (2.5 M) at 80 °C; **C**: Alkene (1.0 equiv), dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (1.05 equiv) in DCM (0.2 M); see Supporting Information for characterization data of **B** and **C**. [b] **B** (0.20–0.30 mmol), $Cu(CF_3)_3bpy$ (0.20 mmol), $K_2S_2O_8$ (0.30 mmol), 4-CzIPN (3 mol%), $NaHCO_3$ (0.40 mmol) in CH_3CN (0.02 M) at 40 °C under 450 nm blue LED irradiation. [c] Yields are reported on the basis of ^{19}F NMR analysis using $PhCF_3$ as internal standard; Isolated yields are in parentheses, thus showing how the volatility of some products affects the yield loss. [d] **C** (0.20–0.30 mmol), $Cu(CF_3)_3bpy$ (0.2 mmol) at 35 °C under irradiation of 370 nm LEDs, R = Me. [e] **C** (0.30 mmol), $Cu(CF_3)_3bpy$ (0.2 mmol), **2** (0.5 equiv) and BTMG (0.5 equiv). [f] R = H.

free alcohols (**52**) or amines (**58**, **63**) that might be vulnerable to oxidation underwent chemoselective sp^3 trifluoromethylation. Moreover, nitrogen- and oxygen-containing heterocycles (**51**, **53**–**55**, **57**–**59**, **61**, **63**, **66**) could be employed as substrates, thus holding promise for the implementation of this technology in medicinal chemistry programs. Particularly noteworthy are examples bearing benzylic and allylic C(sp^3)–H sites that might a priori be susceptible for C–H trifluoromethylation (**50**, **51**, **54**, **56**–**58**, **61**, **63**–**65**).[6a,b] While one might argue that the presence of internal alkenes or α,β-unsaturated ketones might interfere with productive C(sp^3)–CF_3 bond-formation by competitive addition of the intermediate open-shell species arising from C–C bond-cleavage to the corresponding π-bonds, this was not the case and **54**, **58**, **62** and **66** could be all obtained in moderate yields. Taken together, the examples illustrated in Scheme 5 showcase the versatility and potential application profile that this technique might have for forging C(sp^3)–CF_3 architectures from simple, yet easily accessible, precursors.

Furthermore, the results shown in Scheme 6 illustrate the synthetic value of our protocol. Interestingly, **19**, **12** and **48** were all within reach from the corresponding ketone (**67**), aldehyde (**68**) and olefin (**69**) without the need for isolating the pro-aromatic precursors **A17**, **B1** and **C7** (*top*).[17] Although in unoptimized yields, these results show that telescoping the formation of the latter is an alternative for forging C(sp^3)–CF_3 architectures from a diverse set of readily available, unsaturated precursors in a one-pot operation. More importantly, **72** was within reach via sequential, yet site-selective, trifluoromethylation of **70** possessing both a ketone and an olefin backbone via C(sp^3)–C bond-cleavage (*bottom*). Putting everything into perspective, the results of Schemes 3 to 6 stand as a testament to the impact that our technology might have to rapidly and reliably access libraries of trifluoromethylated aliphatic compounds of interest in drug discovery.

In summary, we have developed a de novo trifluoromethylation of ketones, aldehydes and *unactivated* alkenes via C(sp^3)–C cleavage driven by the propensity of pro-aromatic precursors to generate open-shell species. This method is characterized by its excellent chemoselectivity profile and wide substrate scope. We believe this technique complements existing protocols in the sp^3 trifluoromethylation arena, and streamlines the access to compounds of utmost significance in both academic and industrial laboratories from simple, yet readily available, precursors. Further extensions to other related processes are underway in our laboratories.

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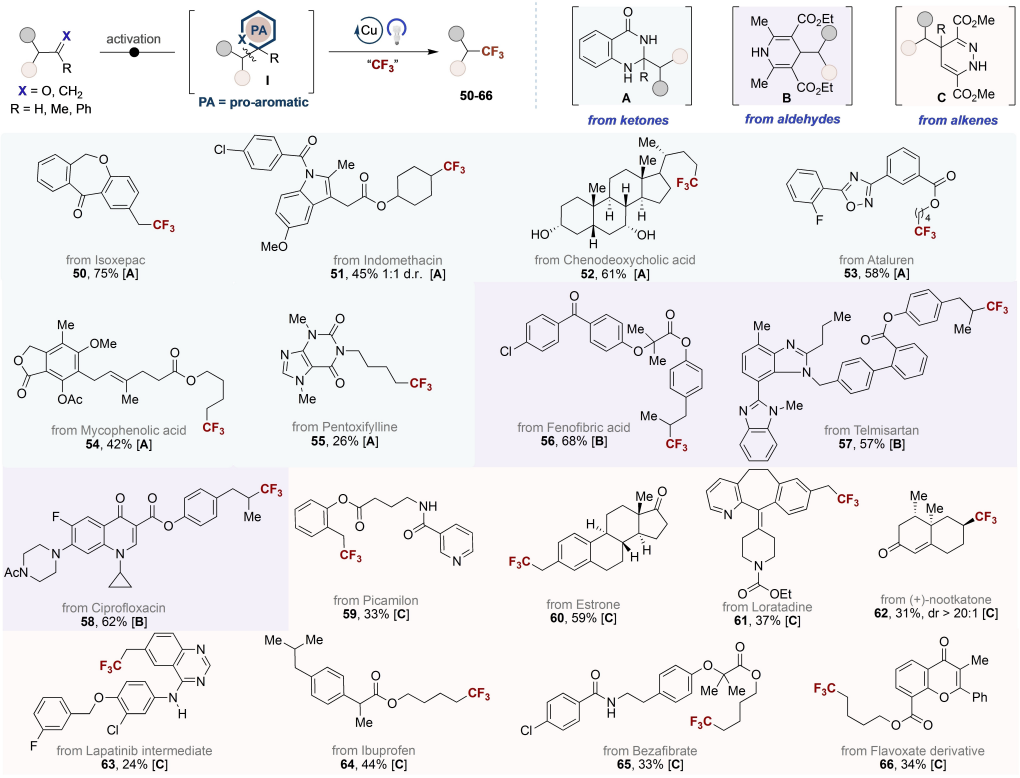
Conflict of Interest

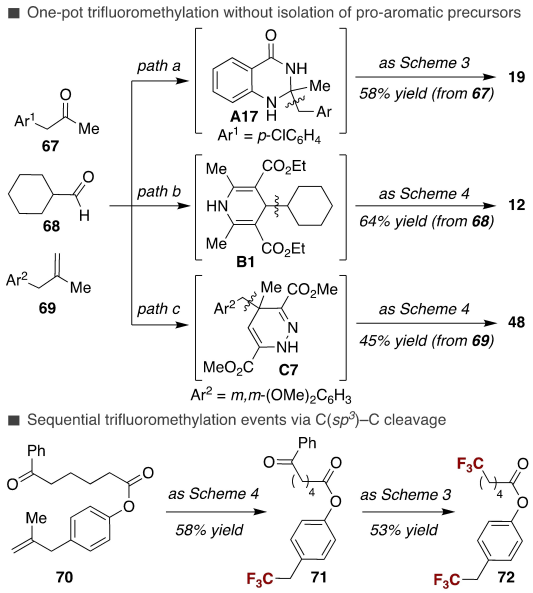
The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.



Scheme 5. Late-stage trifluoromethylation of natural products and medicinal agents. Conditions: **A** (0.20 mmol), $Cu(CF_3)_3bpy$ (0.20 mmol), **2** (0.30 mmol), 4-CzIPN (3 mol%), BTMG (0.20 mmol) in DMF (0.02 M); **B** (0.30 mmol), $Cu(CF_3)_3bpy$ (0.20 mmol), $K_2S_2O_8$ (0.45 mmol), 4-CzIPN (3 mol%), $NaHCO_3$ (0.60 mmol) in CH_3CN (0.02 M); **C** (0.30 mmol), $Cu(CF_3)_3bpy$ (0.20 mmol) at 35 °C under 370 nm irradiation. See Supporting Information for characterization data of **A**–**C**.



Scheme 6. Synthetic applicability. Conditions: *path a:* using **67** (1.05 equiv), aminobenzamide (1.0 equiv), I_2 (5 mol%) in DMF (0.67 M) at 80 °C; *path b:* using **68** (1.0 equiv), Bu_4NHSO_4 (12 mol%), ethyl 3-aminocrotonate (1.0 equiv), ethyl acetoacetate (1.0 equiv) in ethylene glycol (2.5 M) at 80 °C; *path c*: using **69** (1.0 equiv), dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (1.05 equiv) in DCM (0.2 M) at r.t.

Keywords: C–C Bond Cleavage · Cross-Coupling · Pro-Aromatic Precursors · Radical Intermediates · Trifluoromethylation

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