Communication

Copper-Catalyzed Trifluoromethylation of Alkyl Bromides

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Copper-Catalyzed Trifluoromethylation of Alkyl Bromides

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Supporting Information Placeholder

ABSTRACT: Copper oxidative addition into organohalides is a challenging two-electron process. In contrast, formal oxidative addition of copper to Csp^2 carbon–bromine bonds can be accomplished by employing latent silyl radicals under photoredox conditions. This novel paradigm for copper oxidative addition has now been applied to a Cu-catalyzed cross-coupling of Csp^3-bromides. Specifically, a copper/photoredox dual catalytic system for the coupling of alkyl bromides with trifluoromethyl groups is presented. This operationally simple and robust protocol successfully converts a variety of alkyl, allyl, benzyl, and heterobenzyl bromides into the corresponding alkyl trifluoromethanes.

Over the last four decades, a range of novel ligand classes in combination with palladium and nickel salts has enabled the efficient catalytic conversion of C–X bonds into carbon–carbon, –nitrogen, –sulfur, and –oxygen bonds across a vast array of reaction manifolds.[1] In contrast, copper has achieved limited success in analogous transformations, a notable deficiency given its salient potential for economical and operational benefit.[2] Copper's diminished utility arises from an intrinsically high barrier to oxidative addition with both haloarenes and aliphatic halides. This feature necessitates the use of activated aryl bromides and iodides along with elevated temperatures in the former case, while haloalkanes remain effectively inert to almost all forms of catalytic copper insertion.[3] This deficiency is further underscored by the fact that high-valent Cu(III) complexes undergo reductive elimination with electronegative coupling partners (e.g., CF_3, CN, F moieties) at rates that are often superior to Ni and Pd salts.[4]

Recently, we became interested in overcoming the copper oxidative addition problem via the conversion of aryl and alkyl bromides to their aryl- and alkyl-Cu(III) analogs using a halogen-atom abstraction/metal-radical capture mechanism. More specifically, silicon-centered radicals have long been established as potent abstractors of bromine atoms that can rapidly convert organobromides into carbon-centered radicals under mild conditions.[5] In contrast to their limited capacity for oxidative addition, copper salts can efficiently trap carbon-centered radicals at rates approaching diffusion control, thereby allowing copper C–X insertion to be readily accomplished via an alternative open-shell mechanism.[6] Recently, this previously unknown approach has enabled aryl bromides to undergo copper-catalyzed trifluoromethylation at room temperature,[7] a transformation that was generally considered to be challenging given the kinetically high barrier to reductive elimination of aryl–CF_3 products using either nickel or palladium salts.[8] In this disclosure, we elevate this radical capture/copper oxidative addition platform to the implementation of aliphatic bromides, a structural format that has previously been outside the scope of most copper-catalyzed cross-coupling protocols.

Within medicinal chemistry, the introduction of trifluoromethyl groups onto Csp^3-rich scaffolds can often enhance the pharmacokinetic properties of lead candidates in drug discovery, generally via improvements in surface hydrophobicity and/or decreased rates of enzymatic metabolism and clearance.[9] However, the catalytic trifluoromethylation of alkyl halides has historically been challenging, and at the present time substrate tolerance is limited to allylic or benzylic halides.[10] The production of Csp^3–CF_3 bonds has been accomplished using stoichiometric Cu(III)-based reagents, however, only recently have catalytic variants been investigated.[11] Given the success of our copper/aryl halide insertion-trifluoromethylation studies, we questioned whether this open shell cross-coupling mechanism might be translated to all classes of aliphatic bromides, thereby delivering a catalytic CF_3-installation protocol of significant utility to medicinal and process chemists. Herein we disclose the successful execution of these ideals and present a mild, broadly

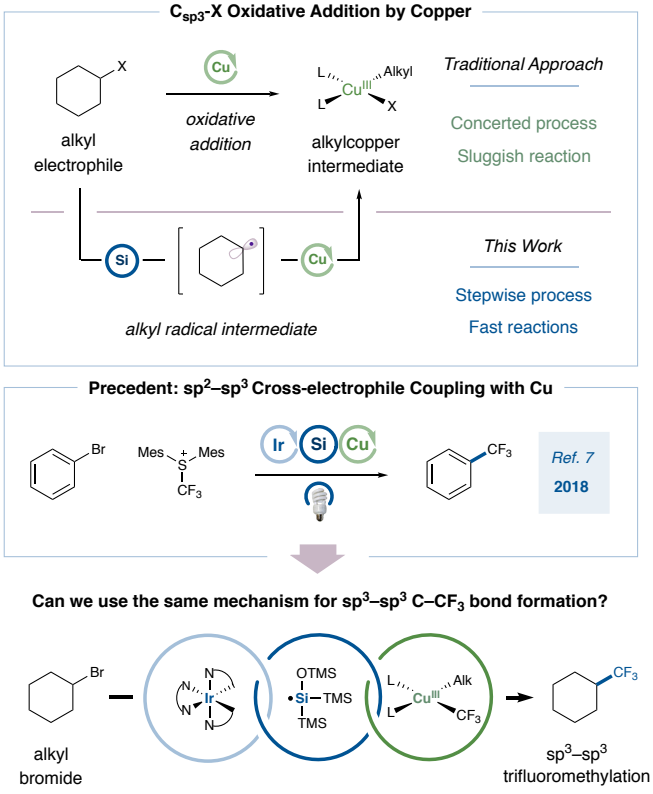


Figure 1. Catalytic trifluoromethylation of alkyl bromides

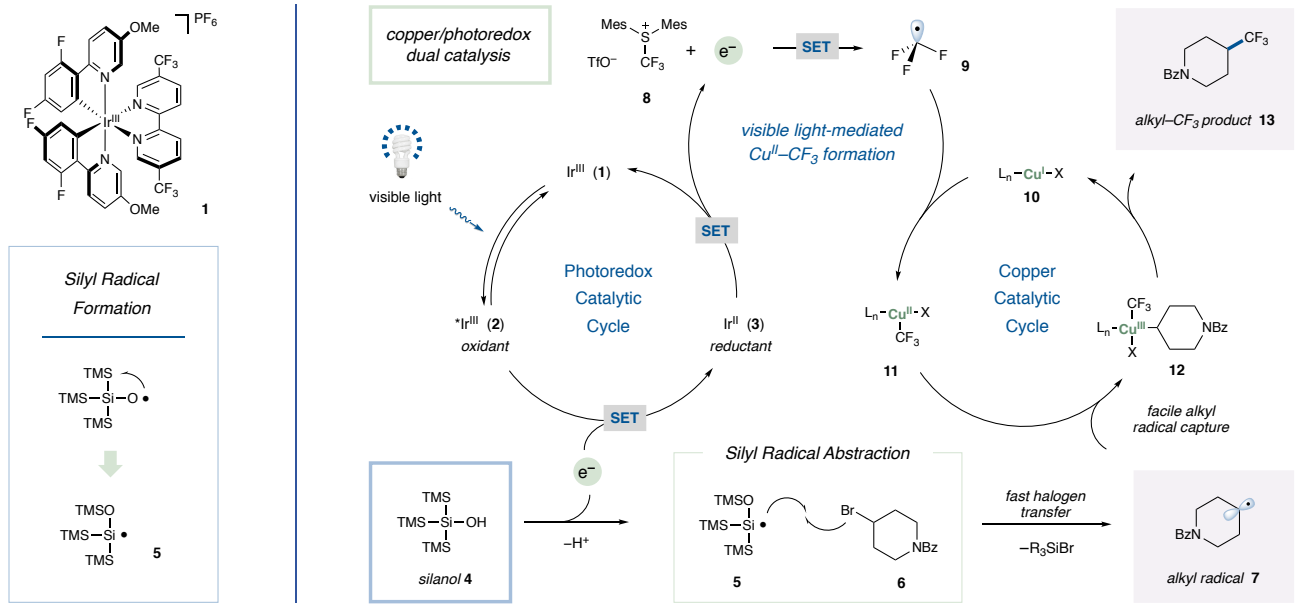


Figure 2. Proposed mechanism for the copper-catalyzed trifluoromethylation of alkyl bromides via metallophotoredox.

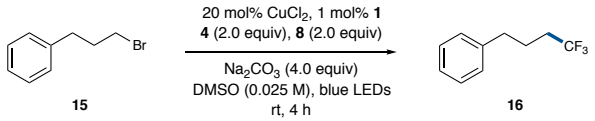
applicable, one-step protocol for the conversion of alkyl bromides into alkyl trifluoromethanes.

We envisioned that a dual copper/photoredox trifluoromethylation mechanism might be initiated by photoexcitation of Ir^{III} photocatalyst **1** with blue LEDs to generate a long-lived Ir^{III} excited state (**2**). Given the relative oxidation potentials of the excited-state Ir^{III} catalyst (**2**, $E_{1/2}^{red}$ [$*Ir^{III}/Ir^{II}$] = +1.60 V vs SCE in MeCN) and tris(trimethylsilyl)silanol (**4**, E_p^{red} [$(TMS)_3SiOH^{+\bullet}/(TMS)_3SiOH$] = +1.54 V vs SCE in MeCN)[7], we assumed that a rapid SET event would generate silicon-centered radical **5** after a deprotonation and radical Brook rearrangement sequence.[12] At this stage, silyl radical **5** was expected to abstract a bromine atom from alkyl bromide **6** at a rate on the order of 10^7 $M^{-1}s^{-1}$ to generate corresponding alkyl radical **7**.[5b] At the same time, single electron transfer between the Ir^{II} reductant (**3**, $E_{1/2}^{red}$ [Ir^{III}/Ir^{II}] = –0.81 V vs SCE in MeCN) and electrophilic trifluoromethylation reagent **8** (E_p^{red} = –0.52 V in MeCN)[7,10g] would regenerate photocatalyst **1** while inducing the production of the trifluoromethyl radical (**9**).[13] Rapid capture of **9** by Cu^I species **10** would produce Cu^{II}–CF_3 adduct **11**. Subsequent combination of this Cu^{II}–CF_3 adduct with alkyl radical **7**, a step that is considered to happen with kinetics approaching diffusion rates, would afford critical alkyl-Cu^{III}-CF_3 species **12**, which upon reductive elimination would afford the desired product **13** and regenerate the Cu^I catalyst.[14]

Initial experiments on a representative alkyl bromide, **15**, revealed that the combination of silanol **4**, trifluoromethylsulfonium salt **8**, photocatalyst **1**, and $CuCl_2$ was highly effective, affording the desired CF_3-bearing product **16** in 94% yield (Table 1, entry 1). In agreement with our previous studies, silanol **4** proved to be superior to tris(trimethylsilyl)silane, presumably due to the feature that supersilane has a weak Si–H bond (BDE = 84 kcal/mol)[15] and can participate in competitive hydrogen-atom transfer to produce protodehalogenated material (entry 2). Notably, the Adachi-Zhang organic photocatalyst, 4CzIPN (**17**), was also highly effective for this transformation (entry 3)[16] While control reactions revealed that the copper catalyst, silanol, blue light, and photocatalyst were all individually necessary (entries 4–7, 0% yield), the omission of base resulted in decreased but measurable product formation (entry 8). Moreover, the use of ligated copper salts led to decreased yields. Lastly, an examination of alternate metal chlorides including Ni, Fe, Co, and Pd salts showed no activity, further highlighting the unique effectiveness of Cu.[17]

With these conditions in hand, we next turned our attention to evaluating the scope of this new alkyl trifluoromethylation reaction. First, with a diverse set of primary alkyl bromides, we determined that excellent functional group compatibility was possible with substrates containing alcohols, esters, amides, and protected amines (Table 2, **18**–**22**, 61–83% yield). Next, secondary cyclic alkyl bromides were converted to their trifluoromethyl congeners in good to excellent yield (**23**–**25**, 52–95% yield), presaging the utility of this transformation for rapid access to analogs of drug-like molecules. The observed lack of diastereoselectivity for cyclobutane adduct **24** is consistent with a carbon-centered, radical-based mechanism. Saturated hetero-cycles such as tetrahydropyrans and piperidines, prevalent moieties in medicinal agents,

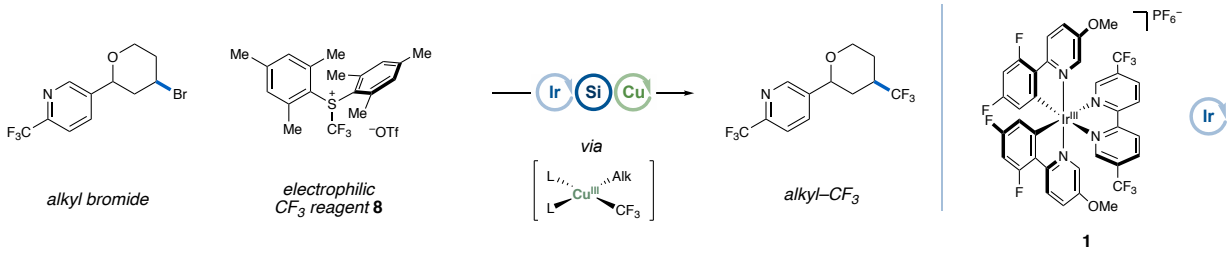
Table 1. Control reactions of optimized conditions[a,b]



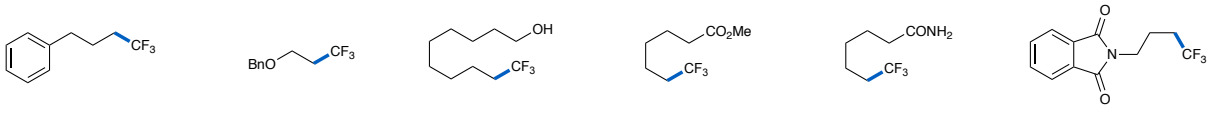
entry	deviation	yield
1	None	94%
2	TMS_3SiH instead of **4**	50%
3	4CzIPN (**17**) instead of **1**	94%
4	no $CuCl_2$	0%
5	no TMS_3SiOH	0%
6	no light	0%
7	no photocatalyst	0%
8	no base	26%

[a]Performed with **15** (0.05 mmol), $CuCl_2$ (20 mol%), **1** or **17** (1 or 5 mol%, respectively), **8** (2 equiv.), $(TMS)_3SiOH$ (2 equiv.), and Na_2CO_3 (4 equiv.) in DMSO (0.025 M) for 4 h at 30 °C. [b]Yields are reported on the basis of ^{19}F NMR analysis using $PhCF_3$ as an internal standard.

Table 2. Scope of the copper-catalyzed trifluoromethylation reaction of alkyl bromides via metallophotoredox[a,b]



Unactivated Alkyl Bromides

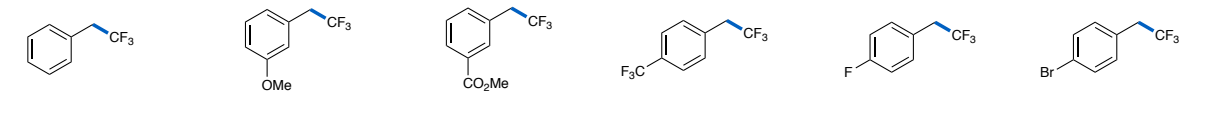


16 90% (42%) yield[c] **18** 61% (59%) yield[c] **19** 81% (69%) yield[c] **20** 83% yield[c] **21** 79% (72%) yield[c] **22** 79% (76%) yield[c]

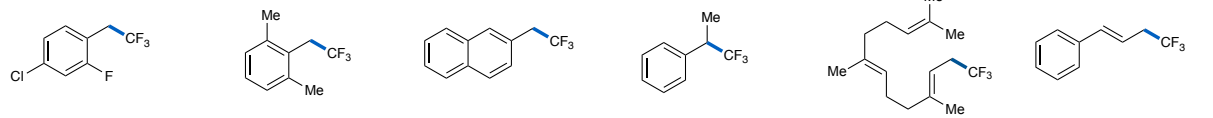
23 76% (63%) yield[c] **24** 95% (80%) yield[c] 1.3:1 d.r. **25** 52% yield[d] **26** 91% yield[c] **27** 89% (81%) yield[c] (±) **28** 61% (52%) yield[c]

13 88% (83%) yield[c] **29** 47% yield[d] (±) **30** 63% yield[c] **31** 74% (44%) yield[c] **32** 43% (35%) yield[c] **33** 70% (37%) yield[c]

Activated Alkyl Bromides

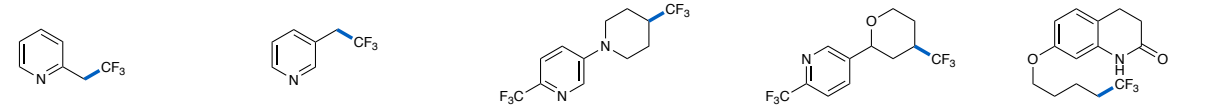


34 87% yield[c] **35** 85% yield[c] **36** 79% yield[c] **37** 54% yield[c] **38** 83% yield[c] **39** 39% yield[e]

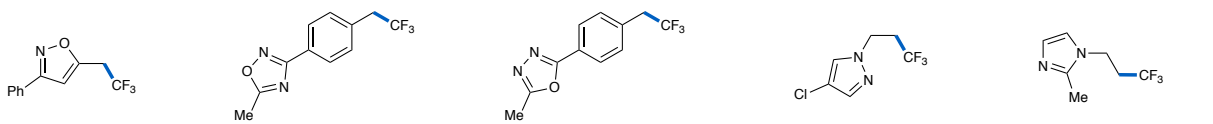


40 71% yield[c] **41** 56% yield[c] **42** 38% (35%) yield[d] (±) **43** 68% yield[d] **44** 81% (70%) yield[d] 2:1 *E*:*Z* **45** 76% yield[d] >20:1 l:b

Heterocycle-Containing Alkyl Bromides



46 72% yield[d] **47** 59% yield[d] **48** 67% (61%) yield[c] (±) **49** 78% (72%) yield[c] 1.7:1 d.r. **50** 74% (69%) yield[c]



51 78% (66%) yield[d] **52** 66% (57%) yield[c] **53** 42% (40%) yield[c] **54** 89% (77%) yield[d] **55** 38% (35%) yield[d]

[a]Performed with $CuCl_2$ (20 mol%), **8** (2 equiv.), **4** (2 equiv.), Na_2CO_3 (4 equiv.), and with either **1** (1 mol%) or **17** (5 mol%) in MeCN or DMSO, respectively (see SI for full experimental details). [b]Due to the volatility of a number of products, yields are reported on the basis of ^{19}F NMR analysis using $PhCF_3$ as an internal standard. Isolated yields are in parentheses. [c]Performed with **17** in DMSO for 1 h. [d]Performed with **1** in MeCN for 4 h. [e]Performed with **17** in DMSO for 30 min.

could also be readily employed (**13**, **26**–**28**, 61–91% yield). Notably, homobenzylic bromides,which are prone to E2 elimination in base-mediated cross- coupling reactions, were well-tolerated using this mild protocol (**30**, 63% yield).[18] Similarly, rigid frameworks such as 2-bromoadamantane and 5-bromo-2-adamantanone readily afforded CF_3-bearing analogs **31** and **32** (74% and 43% yield, respectively).

We next examined activated allylic and benzylic bromides substrates, given the prevalence of benzylic CF_3 substituents in medicinal chemistry. A series of diversely substituted benzyl bromides could be readily functionalized in good yield (**34**–**41**, 39–87% yield). Notably, an alkyl bromide was engaged faster than an aryl bromide (**39**, 39% yield), enabling the possibility of sequential cross-coupling functionalization. We were delighted to find that other activated substrates such as allylic and secondary benzylic bromides were also tolerated (**42**–**45**, 38–81% yield).[19]

Heteroarenes, among the most widely used core structures in pharmaceutical synthesis, were also evaluated as trifluoromethylation substrates.[20] (Bromomethyl)pyridines afforded the corresponding CF_3-adducts in good yield (**46** and **47**, 72% and 59% yield, respectively). Surprisingly, anilines, substrates that can be easily oxidized in photocatalytic SET processes, were competent substrates for trifluoromethyl incorporation (**48**, 67% yield). Heterocycles that are often susceptible to N–O and N–N bond cleavage,[21] such as isoxazoles, oxadiazoles, and pyrazoles, were all accommodated in this new copper-mediated transformation, yielding the corresponding trifluoromethylated adducts (**51**–**54**, 42–89% yield). Moreover, imidazoles such as **55**, which are often problematic in metal-catalyzed protocols, provided a level of efficiency suitable for medicinal chemistry purposes.

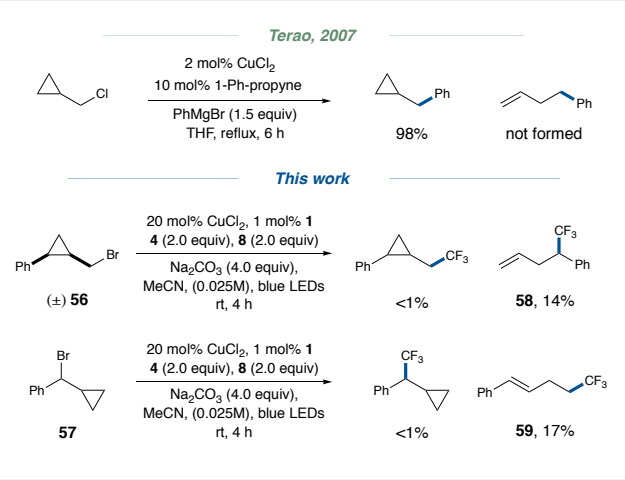


Figure 3. Studies into the proposed open-shell mechanism.

We next sought to establish the intermediacy of alkyl radicals by testing the functionalization of cyclopropyl-bearing substrates **56** and **57** (Figure 3). Cross-coupling of halomethyl cyclopropanes under reducing Grignard conditions is known to proceed without cyclopropane opening. As such, functionalization of these radical clock substrates would enable us to distinguish the mechanistic basis for the current protocol from direct oxidative addition by either low-valent or nanoparticulate copper in solution.[22] Upon exposure of **56** to our standard protocol, we observed the production of **58** in 14% yield. Similarly, cross-coupling of **57** also afforded ring-opened product **59** in 17% yield. These results directly support the presence of discrete alkyl radical intermediates in the reaction, consistent with our proposed mechanism.

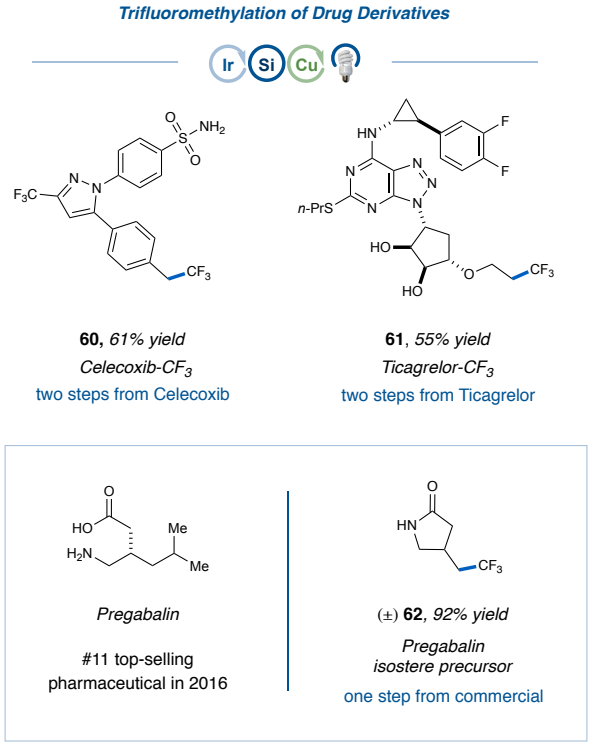


Figure 4. Late-stage trifluoromethylation of medicinal agents.

To demonstrate the utility of this transformation in late-stage functionalization of drug analogs, we next undertook the rapid synthesis of trifluoromethylated celecoxib and ticagrelor derivatives **60** and **61** in 61% and 55% yield, respectively, from the corresponding alkyl bromides. These relatively complex medicinal agents underwent trifluoromethylation using the standard conditions outlined in Table 1, further demonstrating the general utility of this new protocol. Moreover, the trifluoromethyl moiety has also been recognized as an isopropyl group isostere in medicinal chemistry based on their similarities in molecular volume and hydrophobicity.[23] With this goal in mind, we successfully synthesized trifluoromethyl isostere of pregabalin **62** (92% yield, dehydrated, cyclic form) from the commercial precursor bromide. The application of this new trifluoromethylation protocol to a diverse range of medicinally relevant structural classes serves to emphasize the real-world utility and versatility of this new copper-mediated protocol for both early- and late-stage applications.

ASSOCIATED CONTENT

Supporting Information

Experimental setup, optimization details, characterization and spectroscopic data for all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: (link to DOI)

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Notes

The authors declare no competing financial interests.

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