

Copper-Catalyzed Reductive Trifluoromethylation of Alkyl lodides with Togni's Reagent

Yanchi Chen, Guobin Ma,* and Hegui Gong*®

School of Materials Science and Engineering, Center for Supramolecular Chemistry and Catalysis and Department of Chemistry, Shanghai University, 99 Shang-Da Road, Shanghai 200444, China

Supporting Information

ABSTRACT: This work illustrates a reductive cross-electrophile coupling protocol for trifluoromethylation of alkyl iodides under Cucatalyzed/Ni-promoted reaction conditions. The use of diboron esters as the terminal reductant allows the effective generation of the alkyl– CF_3 products with excellent functional group tolerance and broad substrate scope. A mechanism involving a reaction of alkyl–Cu with Togni's reagent was proposed.



odulation of organic compounds with fluorine to Lachieve optimal properties for use in medicinal, agricultural, and materials science is one of the very important tasks in synthetic organic chemistry.¹ As such, development of new synthetic methods for introduction of a trifluoromethyl group into an organic scaffold is noted.¹⁻¹¹ Trifluoromethylation of unactivated alkyl groups, in particular, is less studied, as compared to that of arenes and activated alkyl counterparts, e.g., benzyl, allyl, and α -carbonyl groups.⁴⁻⁶ Although a seminal work shows that the CuCF₃ complex displays good reactivities with aryl halides and benzylic or allylic halides, the preparation of alkyl-CF₃ compounds from the reaction of XCF₂CO₂Me with unactivated alkyl halides in the presence of stoichiometric amounts of CuI, CdI, and KF was only moderately efficient at high temperature (Scheme 1).^{7,8} Li recently developed an elegant protocol for trifluoromethylation of primary and secondary alkyl acids and alkyl halides using a stoichiometric Bpy-Cu(CF₃)₃ reagent.⁹ A proposed mechanism involves oxidative generation of an alkyl radical followed

Scheme 1. Methods for Trifluoromethylation of Unactivated Alkyl Groups

alkyl or CF3 nucleophile



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by trifluoromethylation with an in situ generated Bpy– $Cu(CF_3)_2$ intermediate. Likewise, MacMillan disclosed a photoredox/Cu-catalyzed oxidative decarboxylation/trifluoromethylation of alkyl acids with Togni's reagent I. The reaction was proposed to involve a reaction of alkyl– Cu^{II} intermediate with CF_3 electrophiles.¹⁰ On the other hand, Fu demonstrated that primary and secondary alkylboronic acids were effectively converted into the alkyl– CF_3 products upon treatment with TMS– CF_3 in the presence of excess Ag^+ oxidant. The reaction was characterized by using a catalytic amount of Cu^I salts.¹¹

In connection with our interests in the development of cross-electrophile coupling methods to create diverse types of C-C bonds,¹² we envision that the reaction between an alkyl electrophile and an electrophilic CF₃ species may provide an alternative means for the synthesis of alkyl-CF₃ compounds, which averts the preparation of alkyl nucleophiles under mild catalytic and easy-to-operate conditions. Herein, we report our realization of such a method using a Cu-catalyzed/Nipromoted reductive coupling of alkyl iodides with Togni's reagent II. The reaction features the use of diboron as the terminal reductant under mild conditions, which is distinctive from the metal reductant predominating in the field of crosselectrophile coupling.¹³ The trifluoromethylation products are obtained in moderate to excellent yields with excellent functional group tolerance. Our preliminary mechanistic studies excluded the participation of L_n-Cu(CF₃)₃ or Cu-CF₃ as the authentic trifluoromethylation agents. To the best of our knowledge, this work represents one of the first catalytic processes for cross-electrophile trifluoromethylation of alkyl electrophiles.

We began our examination with the reaction of 1a and Togni's reagent II. After extensive exploration of the reaction conditions, we identified that the use of CuCl/L1 as the catalyst, 15 mol % of NiCl₂glyme as the promoter, 2-

Received: June 27, 2018

pyrrolidinone as the additive, $B_2(nep)_2/LiOMe$ as the terminal reductant, and DMF as the solvent provided the trifluoromethylation product **2a** in an optimal 79% isolated yield (Table 1, entry 1).¹⁴ Slow addition of Togni's reagent via a

Table 1. Optimization for the Trifluoromethylation of 1 with Togni's Reagent II^a



^{*a*}Standard conditions: **1a** (0.3 mmol, 1 equiv), Togni's reagent (0.36 mmol, 1.2 equiv), CuCl (20 mol %), NiCl₂glyme (15 mol %), ligand (35 mol %), B₂(nep)₂ (2 equiv), MeOLi (2.5 equiv), 2-pyrrolidinone (0.5 equiv), and DMF (2 mL). Togni's reagent II was added dropwise over 40 min using a syringe pump. ^{*b*}NMR yield using benzotrifluoride as the internal reference. ^cIsolated yield. ^{*d*}Not detected.

syringe pump was crucial for the optimal yield. Control experiments indicated that without NiCl₂glyme the yield decreased to 44% along with 30% of recovered **1a** (entry 2). Increasing the loading of CuCl to 35% in the absence of Ni salt provided **2a** in a poor yield (entry 3). The use of NiCl₂glyme in the absence of CuCl did not result in detectable **2a**, wherein 40% of recovered **1a** along with 21% of the hydro-dehalogenation product was obtained (entry 4).¹⁴ These results indicate that the reaction was a Cu-catalyzed process. With no B₂(nep)₂ or LiOMe, **1a** remained intact (entries 6 and 7). Other ligands **L2–L16** were inferior (see Table 1). In addition, other trifluoromethylation agents, e.g., Togni's reagent I, Umemoto's, and Ruppert reagents were not or less efficient (entries 8–10). Finally, amplification of the reaction to a 1.5 mmol scale provided **2a** in 73% yield (entry 11).

Next, the trifluoromethylation strategy was extended to a variety of secondary alkyl iodides (Figure 1). Cyclic four-, five-, and six-membered rings were suited, which delivered the coupling products 2b-2k in moderate to good yields. A nitrogen-bridged bicyclo-substrate also provided 2i in 75%



Figure 1. Trifluoromethylation of secondary alkyl iodides with Togni's reagent II. "Reaction conditions as in Table 1, entry 1. ^bIsolated yield unless otherwise noted. 'NMR yield using benzotrifluoride as the internal reference. TBDPS = *t*-butyldiphenylsilyl.

yield. The acyclic alkyl iodides were competent, generating 2l– 2r in moderate and synthetically useful yields. The more sterically hindered 9-iodoheptadecane, on the other hand, displayed low efficiency for the formation of 2s. The reaction conditions also showcased excellent functional group compatibility, including Boc, aryl bromide, secondary amine, phthalimide, ester, acetal, silyl, thiophenyl, and furyl groups.

A survey of the competence of the primary alkyl iodides was also performed under the optimized reaction conditions (Figure 2). In general, their coupling efficiencies were found to be lower than those of the secondary iodides. The esters and



Figure 2. Trifluoromethylation of primary alkyl iodides with Togni's reagent II. "Reaction conditions as in Table 1, entry 1. ^bIsolated yield.

ether-tethered alkyl iodides provided 3a-3g in moderate to good yields. Of note is the tolerance of free amine and bromo groups, as evident in 3d and 3g, respectively. The latter offers opportunities for further functionalization of the product. The indole and amine-decorated alkyl iodides were able to generate 3i-3n in moderate to good yields, wherein the amino-acidderived products 3l-3n were obtained in about 60% yield. By comparison, the present method is much more effective than an early fluoride-mediated catalyst free alkyl trifluoromethylation approach for the coupling of TMSCF₃ with limited scope of primary alkyl iodides.¹⁵

To understand the details of the present reductive trifluoromethylation work, we first examined whether alkyl radicals were involved. Treatment of (iodomethyl)-cyclopropane with Togni's reagent II under the standard conditions gave a ring-opened product in 20% yield (eq 1),



suggesting the radical nature of the alkyl groups in the reaction. Furthermore, the nitrogen-tethered alkyl iodide 4a containing a terminal alkene was subjected to the standard reaction conditions. The cyclization/trifluoromethylation product 5a was obtained in good yield, wherein the linear trifluoromethylation product 5a' was not detected (eq 2). In addition, exposure of 1a to Togni's reagent in the presence of TEMPO generated a CF₃-TEMPO product in a 27% yield (eq 3). This result suggests that the CF₃ radicals may also be involved in the coupling process. A mechanism pertaining to in situ generation of organoboron/Suzuki coupling can be ruled out since the reaction of the alkyl–Bnep 6 with Togni's reagent II under the standard reaction conditions in the absence of B₂(nep)₂ did not lead to 2a. Instead, 6 was primarily recovered (eq 4).



The coupling of a Phen– Cu^{1} – CF_{3} species with 1a under the standard reaction conditions or without B₂(nep)₂/LiOMe did not yield 2a (eq 5). Likewise, formation of 2a from the



reaction of 1a with Phen–Cu^{III}– $(CF_3)_3$ was not observed (eq 5). These results suggest that both Cu^I– CF_3 and Cu^{III}– $(CF_3)_3$ are not the catalytic intermediates involved in the reaction.

The role of Ni was also considered. First, the control experiment in Table 1, entry 2, indicated that the reaction of

1a with Togni's reagent II generated 10% of alkyl–Bnep product 6 when Ni was not added. Without the Ni salt, but with 35% of CuCl, the yield for 2a decreased to 31%, whereas the yield for 6 increased to 37% (Table 1, entry 3 and Table S1).¹⁴ With the Ni salt, such a product was not detected, regardless of the presence of CuCl (Table S1).¹⁴ Furthermore, without Togni's reagent II and Ni, cyclization/borylation of 4a predominated, producing 7 in 74% yield (eq 6).^{13,16} However, use of NiCl₂glyme in the absence of CuCl did not yield detectable 7.¹⁴ These results suggest that Ni can at least inhibit the alkyl borylation process.¹³



The collective studies rendered us to propose a catalytic process, as shown in Scheme 2. The conversion of $(L_n)Cu^I$ salt





(A) to L_nCu^I -Bnep (B) in the presence of $B_2(nep)_2/LiOMe$ is followed by oxidative addition of R¹-I. As a result, the R¹-may arise from iodine abstraction giving an alkyl radical and a $(L_n)Cu^{II}$ -Bnep(I) intermediate (C) in a cage followed by rapid combination of these two species. Reductive elimination of Bnep-I from complex (D) produces $R^1-(L_n)Cu^I$ (E), which reacts with Togni's reagent to give the product accompanied by $(L_n)Cu^{T}$ species (A).¹⁷ Similarly, this process may involve generation of the CF_3 radicals, as evident in eq 3. Reductive elimination of alkyl-Bnep from complex D is possible. However, it should be a slow process, as compared to the formation of complex E and subsequent trifluoromethylation. Without Togni's reagent, reversible formation of complex D from oxidative addition of Bnep-I with complex **E** may ultimately result in alkyl-B(nep) as the major product. Alternatively, a mechanism involving reaction of an alkyl radical with Cu^{II} -CF₃ as proposed by Li cannot be excluded, although generation of Cu^{II} – CF_3 in this novel catalytic system is not straightforward.^{9,18,19}

In summary, we have disclosed a mild, Cu-catalyzed, and Nipromoted trifluoromethylation protocol for the effective formation of alkyl– CF_3 compounds. The reaction tolerates a wide range of functional groups, including free amines, and displays broad substrate scope. A preliminary mechanistic study appears to support that both alkyl and CF_3 radicals are invovled in the catalytic process. The reaction of an alkyl–Cu complex with Togni's reagent may be the key to explaining the trifluoromethyl transformation. However, considerable mechansitic studies are required to understand this novel catalytic process.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b02005.

Detailed experimental procedures and characterization of new compounds (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: hegui_gong@shu.edu.cn. *E-mail: ma_guobin@shu.edu.cn. ORCID ©

Hegui Gong: 0000-0001-6534-5569 Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support was provided by the Chinese NSF (Nos. 21372151 and 21572127).

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