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Aminotrifluoromethylation of Olefins via Cyclic Amine Formation: Mechanistic Study and Application to Synthesis of Trifluoromethylated Pyrrolidines

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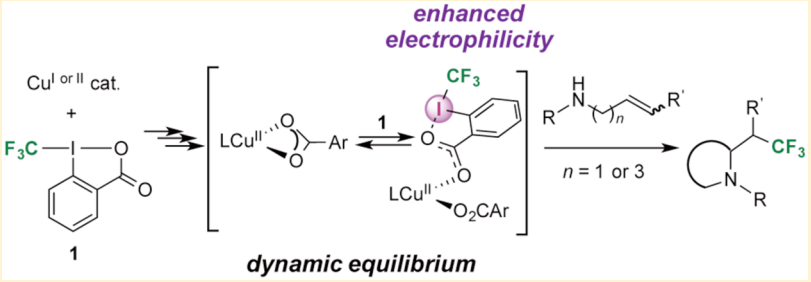
Supporting Information



ABSTRACT: We examined the mechanism of our previously reported aminotrifluoromethylation reaction, which proceeds via intramolecular cyclization of alkenylamines in the presence of the combination of copper catalyst and Togni reagent (**1**). Kinetic studies revealed that the initial rate of the reaction was first order with respect to Togni reagent and CuI, as well as the substrate. Changes of the ^{19}F NMR chemical shift of Togni reagent during the reaction suggested the existence of a dynamic equilibrium involving coordination of not only Togni reagent, but also the substrate amine and the product aziridine to copper. ESI-MS analysis provided evidence of involvement of reactive Cu(II) intermediates in the catalytic cycle. Overall, our results indicate that the reaction proceeds at the hypervalent iodine moiety of Togni reagent, which is activated by Cu(II) species acting as a Lewis acid catalyst. On the basis of these mechanistic considerations, we developed an efficient synthesis of trifluoromethylated pyrrolidine derivatives. This transformation exhibited a remarkable rate enhancement upon addition of Et_3N.

INTRODUCTION

Trifluoromethylated compounds have attracted much attention as candidate agrochemicals and pharmaceuticals because of their unique biological activities, high hydrophobicity, lipophilicity, and metabolic stability.[1,2] Trifluoromethylated cyclic amines are especially important, not only as core structures of bioactive compounds,[3] but also as potential synthetic precursors of β-trifluoromethylated alkylamine derivatives.[4] Thus, efficient and convenient synthetic methods to access these compounds are desirable.

Catalytic trifluoromethylations have been well studied in the past decade.[5] In 1989, Chen and Wu reported the first copper-catalyzed trifluoromethylation with 2,2-difluoro-2-(fluorosufonyl)acetate (DFSA).[6a,b] Amii[6c] and Inoue[6d] independently developed the efficient catalytic trifluoromethylation of aromatic compounds with trialkyltrifluoromethylsilane in 2009,[6] and various types of aromatic trifluoromethylation have since been reported.[5] In 2011, Hartwig isolated a Cu–CF_3-diamine complex and demonstrated its reactivity for aromatic trifluoromethylation.[7,8] After the establishment of trifluoromethylation of aromatic compounds, C_{sp3}–CF_3 bond-forming reactions emerged as the next focus of research.[5] In 2011, Buchwald,[9a] Liu,[9b] and Wang[9c] independently reported Cu-catalyzed deprotonative trifluoromethylation of olefins by using electrophilic trifluoromethylating reagents such as Togni reagent and Umemoto reagent. Qing achieved the reaction with the combination of Ruppert–Prakash reagent (CF_3SiMe_3) and oxidant in 2012.[9d] We and Gouverneur also independently reported the reaction of allylsilanes with Togni reagent to afford trifluoromethylated exomethylenes, trisubstituted alkenes, and vinylsilane derivatives, which are synthetically important building blocks.[10] Difunctionalization of olefins via trifluoromethylation is an important goal in this field, because this approach offers direct access to synthetically significant compounds.[5,10−19] In 2012, catalytic oxytrifluoromethylation of styrene derivatives with Togni reagent was independently reported by us[11a] and Szabó,[11b] enabling direct introduction of both 2-iodobenzoate and trifluoromethyl groups. Buchwald developed intramolecular oxytrifluoromethylation leading to

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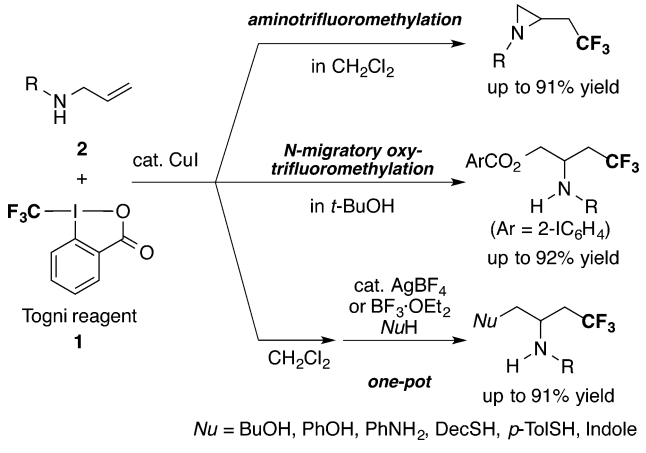
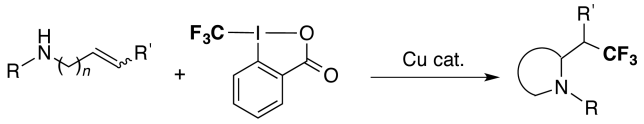
cyclic ethers or lactones, and also reported an asymmetric version of the reaction.[11c,d] Synthetically useful intra- and intermolecular oxytrifluoromethylations have also been developed.[12] The first example of catalytic carbotrifluoromethylation was reported by Liu in 2012.[13] The reaction proceeded under oxidative trifluoromethylation conditions using CF_3SiMe_3 and Pd(II) catalyst, affording trifluoromethylated oxindoles from α,β-unsaturated amides. In 2013, we developed a copper-catalyzed electrophilic carbotrifluoromethylation of simple olefins, through which both carbo- and heterocycles such as indane, tetralin, indoline, and tetrahydroquinoline were successfully constructed.[14a,b] Trifluoromethylated oxindole synthesis by electrophilic carbotrifluoromethylation has been extensively studied and achieved under various reaction conditions.[14−16] However, despite the rapid progress of difunctionalizing trifluoromethylations,[17] aminotrifluoromethylation is still rare.[18,19] Akita and Cho independently achieved aminotrifluoromethylation by using Ru-bipyridyl complexes as photoredox catalysts. Akita developed a Ritter-type reaction of styrene derivatives with Umemoto reagent,[19b] and Cho demonstrated the perfluoroalkylation of *N*-allylanilines with perfluoroalkyl iodide, providing trifluoromethylated aziridines in up to 65% yield.[19c] At around the same time, we independently reported an efficient aminotrifluoromethylation of alkenylamines with the combination of Togni reagent **1** and CuI as a catalyst; this provided a method for selective and high-yielding synthesis of trifluoromethylated aziridines (Scheme 1).[19a] In the same report, we showed that selective synthesis of

Scheme 1. Cu-Catalyzed Aminotrifluoromethylation of Allylamines 2 with Togni Reagent 1 to Obtain β-Trifluoromethyl Amines



N-migratory oxytrifluoromethylation products could also be achieved by solvent switching. Furthermore, we successfully transformed the in situ-generated aziridine to various β-trifluoromethylated amines via Lewis acid-catalyzed ring opening with various nucleophiles, such as *n*-BuOH, PhOH, $PhNH_2$, DecSH, *p*-TolSH, and indole. Although this method is an efficient and convenient strategy for preparing β-trifluoromethyl amines, the reaction mechanism remained unclear. We also reported in the same paper that the reaction conditions were applicable to the synthesis of trifluoromethylated pyrrolidines, albeit with limited substrate scope. Here, we present a mechanistic study of our aminotrifluoromethylation and we also describe an extension of the substrate scope to enable synthesis of trifluoromethylated pyrrolidines (Scheme 2).

Scheme 2. This Work

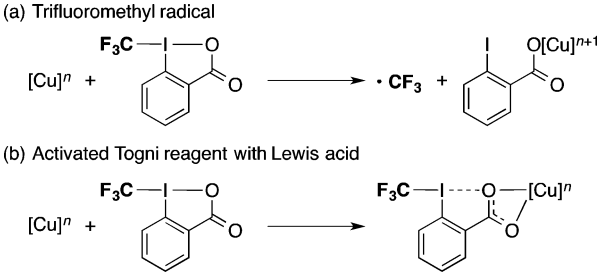


· Mechanistic studies including kinetics, NMR, and ESI-MS analyses
· Efficient trifluoromethylated pyrrolidine synthesis

RESULTS AND DISCUSSION

Mechanistic Study. To our knowledge, two types of possible key reactive species have been proposed in related work on Cu-catalyzed trifluoromethylations of olefins with Togni reagent **1** (Scheme 3). One of the proposed mechanisms

Scheme 3. Proposed Key Intermediates



requires generation of trifluoromethyl radical as a key intermediate, which either reacts directly with olefins or is a precursor of Cu−CF_3 species.[20] The other proposed mechanism involves activated Togni regent as the reactive species, in which the electrophilicity of the hypervalent iodine is enhanced by copper as a Lewis acid. The latter is based on Togni's originally proposed mechanism of trifluoromethylation of alcohols in the presence of zinc salts.[21] However, there is no decisive evidence regarding the mechanism of Cu-catalyzed olefin trifluoromethylation. In this context, we first planned to identify the reactive species of the aminotrifluoromethylation.[19a] As shown in Scheme 3(a), highly reactive free CF_3 radical could be generated by the reaction of Togni reagent **1** with Cu(I) salt. If the resulting CF_3 radical plays a major role in the aminotrifluoromethylation reaction, preincubation of copper salt with **1** in the absence of the substrate should have negative effects on the reaction. Therefore, the influence of pretreatment of the copper salt with Togni reagent **1** on the reaction was examined (Scheme 4, Figure 1). Less reactive allylamine bearing an ethylbenzoate group **2** was selected as a model substrate for the study. In procedure A, CuI was pretreated with Togni reagent **1** in CH_2Cl_2 at 40 °C for 30 min, and the substrate was then added to the mixture. In procedure B, substrate and Togni reagent **1** were mixed first, and then CuI was added. No conversion was observed when a mixture of substrate and Togni reagent **1** was simply warmed to 40 °C without the copper catalyst. Under these conditions, we traced the formation of the trifluoromethylated aziridine **3** and *N*-migratory oxytrifluoromethylated product **4**. It was found that not only did the reaction rate increase, but also the product selectivity of **3** was improved by the pretreatment. These

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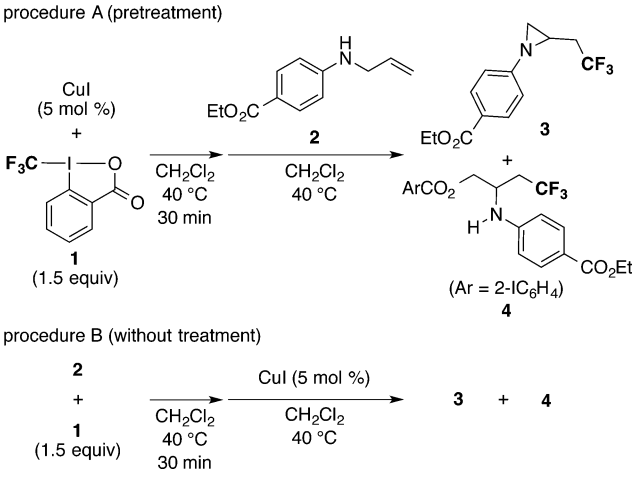
Scheme 4. Procedures for Aminotrifluoromethylation



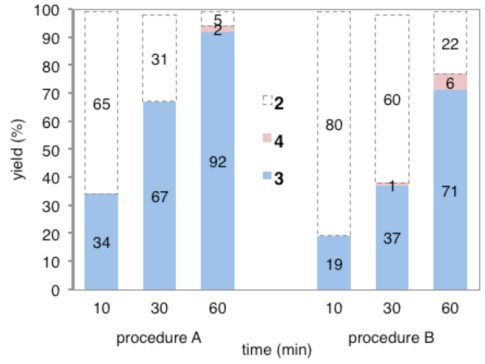


Figure 1. Effect of preactivation of Cu catalyst with Togni reagent **1** on the reaction of allylamine **2**.

observations suggested formation of a reactive species during the pretreatment of CuI with **1** (Figure 1). Thus, using procedure A, we conducted a kinetic study of the reaction, and the yield of aziridine **3** was plotted against the reaction time (Figure 2, blue line; 0.20 M). An induction period was observed at the initial stage of the reaction, despite the preactivation of CuI. We speculated that low solubility of copper species caused the induction period, and the substrate amine possibly

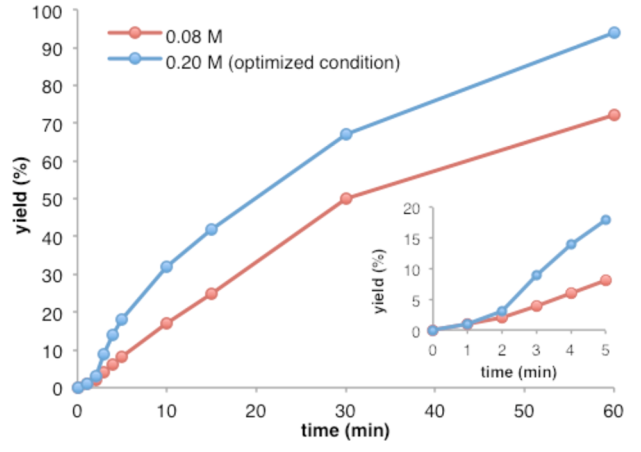


Figure 2. Reaction rate under the previously reported optimized conditions for aminotrifluoromethylation (blue) and under the diluted condition used for kinetic study (red).

increased the solubility by coordination, thereby accelerating the reaction.[22] Indeed, a dilute condition (0.08 M) showed an almost linear time course at the initial stage of the reaction. Therefore, further investigation of the kinetics was performed under a dilute condition (Figures 3–5). The dependence of the

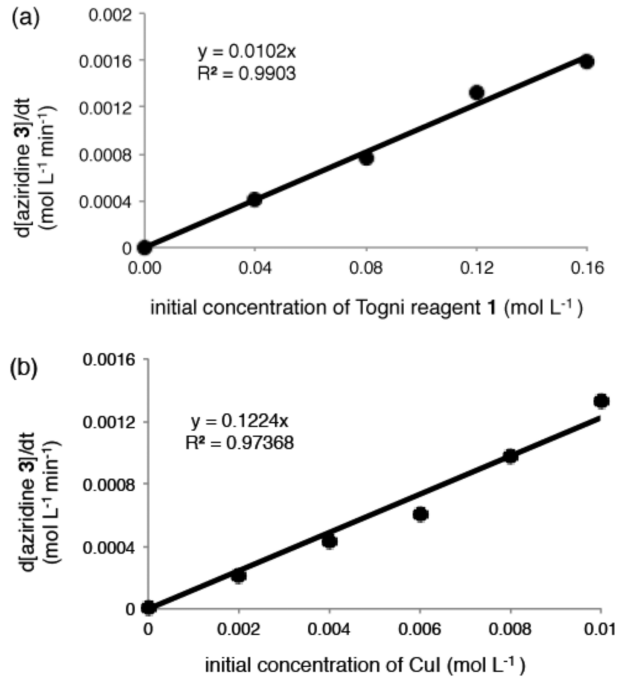


Figure 3. Plots of d[aziridine **3**]/d*t* vs initial concentration of (a) Togni reagent **1** and (b) CuI.

initial rate on the concentrations of Togni reagent **1**, CuI, and allylamine **2** was examined (Figures 3 and 4).[23] As shown in

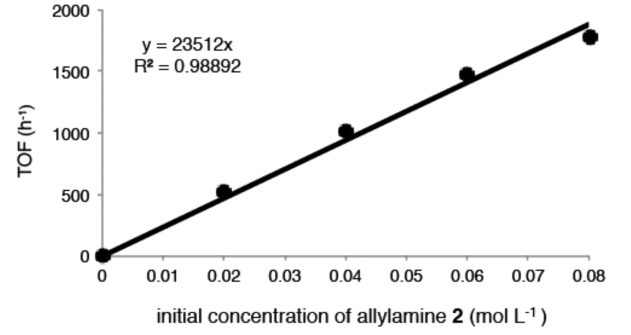


Figure 4. Plot of turnover frequency (TOF) vs initial concentration of allylamine **2**.

Figure 3, first-order relationships of the initial rates with the concentrations of both Togni reagent **1** and CuI were observed. Furthermore, the turnover frequency (TOF) of the catalyst was found to depend on the initial concentration of allylamine **2** with a first-order relationship (Figure 4). These observations suggested that not only Togni reagent **1** and the reactive copper species, but also the substrate are involved in the turnover-limiting step. The possibility of product inhibition was also investigated by external addition of aziridine **3** to the reaction mixture (Figure 5). The rate of conversion of starting material **2** decreased with increasing amount of externally added aziridine **3**, and the plot showed an inverse first-order

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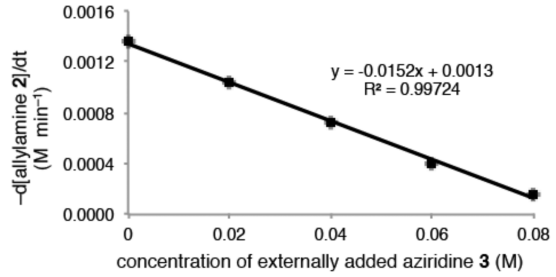


Figure 5. Product inhibition.

relationship. Thus, aziridine **3** probably inhibits the reaction by coordination to a copper center of an intermediate in the catalytic cycle.

Next, we attempted to identify the reactive copper species generated by preincubation of Togni reagent **1** and CuI. The mixture of CuI and Togni reagent **1** showed a green color regardless of the solvent. Fortunately, green crystals of **5a** generated from the reaction mixture of CuI and Togni reagent **1** in MeOH were successfully isolated, and the crystal structure was solved by X-ray single-crystal analysis.[24] No trifluoromethyl group was contained in the complex **5a**, and it was found to be a Cu(II) dimer bridged by four 2-iodobenzoates with two solvent molecules as additional ligands (Figure 6).[25] This result

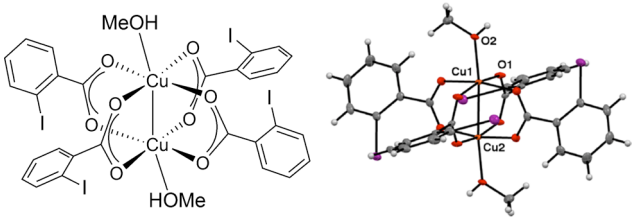
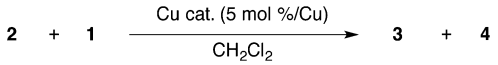


Figure 6. Structure of $Cu_2(O_2CAr)_4$·2MeOH (**5a**) (Ar = 2-IC_6H_4) Thermal ellipsoids are shown at 50% probability in the X-ray crystal structure. Selected bond lengths (Å): Cu1−O1, 1.986(2); Cu1−Cu2, 2.6040(6); Cu1−O2, 2.111(2).

suggested that Togni reagent **1** can oxidize Cu(I) to Cu(II) species under the reaction conditions. Having the copper complex **5a** in hand, we examined its catalytic reactivity in the aminotrifluoromethylation (Table 1). According to procedure A shown in Scheme 4, allylamine **2** was reacted with Togni reagent **1** in the presence of **5a** in CH_2Cl_2 at 40 °C for 1 h.

Table 1. Aminotrifluoromethylation with Cu(II)-2-Iodobenzoate Complexes As the Precursor



entry[a]	Cu cat.	yield (%)[b] 3	4	recovery of 2 (%)[b]
1	CuI	92[d]	2	5
2	$Cu_2(O_2CAr)_4$·2MeOH (**5a**)	66	4	29
3[c]	$Cu_2(O_2CAr)_4$·2MeOH (**5a**)	71	16	13
4	$Cu_2(O_2CAr)_4$·2THF (**5b**)	14	7	70
5	CuI + MeOH (20 mol %)	64	10	25

[a]Reactions were conducted on 0.25 mmol scale for 1 h according to procedure A in Scheme 4. [b]Yields were determined by ^{1}H NMR analysis with dibromomethane as an internal standard. [c]The reaction was conducted for 3 h. [d]Isolated yield.

Complex **5a** provided the desired aziridine **3** in 66% yield, despite slow conversion (entry 2) compared to the reaction with CuI (entry 1). Extension of the reaction time increased the amount of *N*-migratory oxytrifluoromethylated product **4** (entry 3). In order to investigate the influence of the coordinating solvent, $Cu_2(O_2CAr)_4$·2THF (**5b**) was employed in the reaction (entry 4). The THF complex **5b** provided the desired products **3** and **4** in only 14 and 7% yield, respectively.[26] Furthermore, catalytic amount of MeOH was externally added to the reaction using CuI, and the rate was found to be decreased to the similar level of the reaction using **5a** (entries 2 and 5) indicating the coordinating solvent decreases the catalytic reactivity. These data suggest that the Cu(II) 2-iodobenzoate species[27] dominantly catalyzes the aminotrifluoromethylation reaction with the pretreatment procedure.[28]

The trifluoromethyl group in the reaction mixture was then traced by means of ^{19}F NMR spectroscopy. First, CuI and complex **5a** were each reacted with Togni reagent **1** in CD_2Cl_2, and the ^{19}F NMR spectra were compared (Figure 7). The ^{19}F

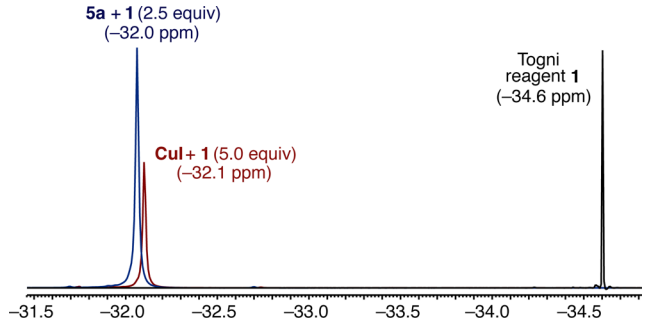


Figure 7. ^{19}F NMR analysis of the mixtures of Cu precursors and Togni reagent in CD_2Cl_2.

NMR signal derived from Togni reagent **1** (−34.6 ppm) was shifted to lower magnetic field after addition of the copper salt, and the two mixtures gave almost the same chemical shifts (−32 ppm).[29] Notably, the signal of Togni reagent **1** itself completely disappeared, despite its excess amount. This can be explained in terms of rapid ligand exchange of intermediates. Only CuI as the precursor gave signals with low intensity at −25.9 and −3.4 ppm that should be derived from side-products generated during the oxidation of CuI.[30] For further comparison of the mixtures, ESI-MS spectra were obtained (Figure 8). We found that the ESI-MS spectra obtained from the two mixtures were almost identical, which indicated that the same intermediates were formed from the different copper precursors by reaction with Togni reagent **1**. In addition to the signal corresponding to the Togni reagent, several signals derived from copper species were observed by ESI-MS analysis, although a single major signal was observed in the ^{19}F NMR spectra of the mixtures, which suggested the existence of rapid equilibria between the various copper complexes. The intense signals of copper-containing species were assigned as described in Figure 9.[31−33] ESI-MS signals of copper species were easily distinguished because of the unique isotope pattern of copper. The strongest signal **A** was assigned as a cationic monomeric copper species with Togni reagent **1**, and an Na^+ adduct of neutral diiodobenzoate complex **B**, a potential parent compound of **A**, was also detected as a weak signal. Signal **C**

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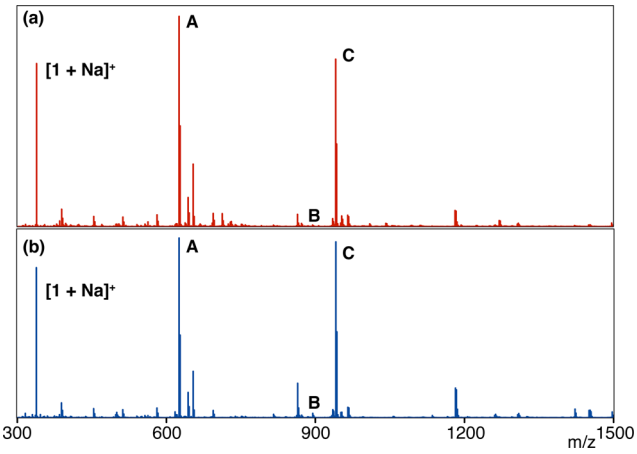

Figure 8. ESI-MS analysis of mixtures of Cu catalysts and Togni reagent **1** in MeOH (a: CuI + **1**, b: **5a** + **1**).

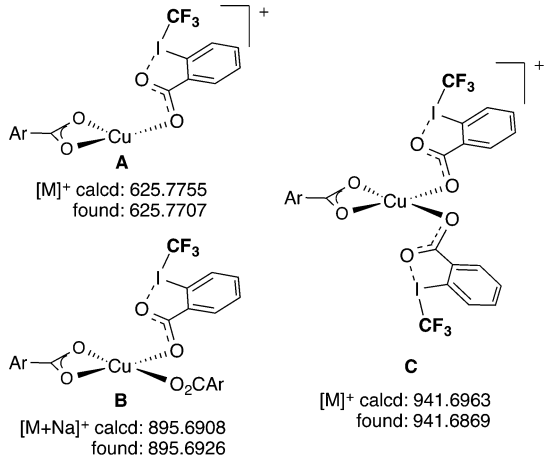

Figure 9. Possible structures of the copper species detected by ESI-MS analysis in the mixtures of copper precursors and Togni reagent (Ar = 2-IC_6H_4).

was characterized as a cationic copper species involving two Togni reagent molecules.

Next, the substrate allylamine **2** was added to the equilibrated mixture of Togni reagent **1** and **5a**, and the mixture was monitored using ^{19}F NMR (Figure 10). As presented in Figure 7, a signal derived from the reactive species formed from **5a** with Togni reagent **1** was detected at −32.0 ppm. As soon as the substrate **2** was added to the reaction mixture, the ^{19}F NMR signal shifted to −34.0 ppm, and a broad signal, probably derived from aziridine **3**, was detected at −64.9 to −65.0 ppm. As the reaction proceeded, the signal at −34.0 ppm gradually shifted to lower magnetic field and its intensity decreased. On the other hand, the signal of aziridine **3** increased as the other major signal at ca. −33 to −34 ppm decreased. After overnight reaction, a very tiny signal was detected at −33.6 ppm and the signal derived from the aziridine was slightly shifted to lower magnetic field.[34] In addition, a signal at −63.6 ppm derived from the *N*-migratory oxytrifluoromethylation product was detected. These observations help us to understand the dynamic equilibrium during the reaction. The chemical shift changes observed for the first and second ^{19}F NMR signals can be explained in terms of coordination of the starting material **2** and the product aziridine **3** to the copper center coordinating Togni reagent **1**, respectively.[35]

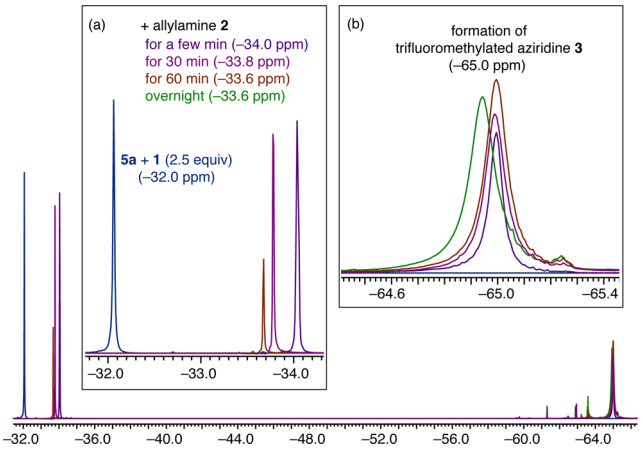

Figure 10. ^{19}F NMR traces of the reaction of allylamine **2** with Togni reagent **1** by using Cu catalyst **5a** in CD_2Cl_2. Expanded views from (a) −34.7 to −31.7 ppm and (b) −65.4 to −64.5 ppm are shown in the boxes.

The results of the above mechanistic studies led us to the following conclusions. The Cu(II) species generated by oxidation of CuI with Togni reagent **1** serves as a Lewis acid catalyst, and the desired reaction involves rapid equilibria that include product inhibition. A plausible catalytic cycle is shown in Figure 11. CuI is first oxidized by Togni reagent **1** to provide

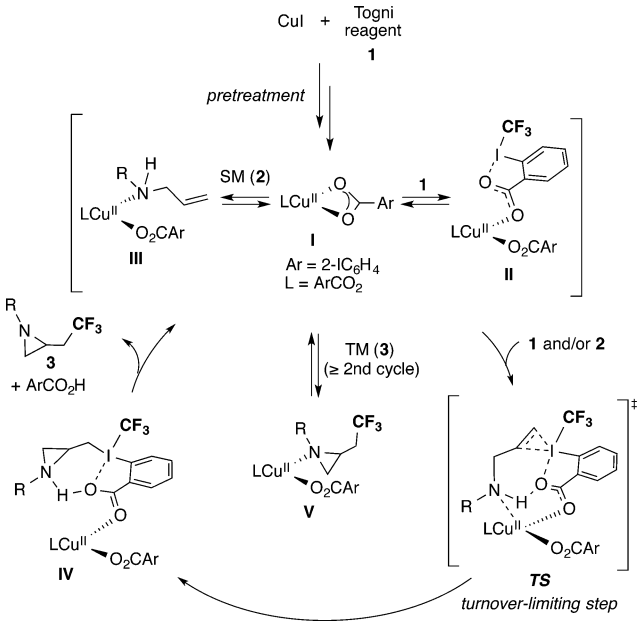

Figure 11. Proposed catalytic cycle.

Cu(II) species during the pretreatment. Although CF_3 radical would be cogenerated by this oxidation step, it is likely to be decomposed in the absence of the substrate.[35] The Lewis-acidic Cu(II) species forms an intermediate **I**, detected as a fragment ion by ESI-MS analysis.[36] The O−I bond of Togni reagent **1** is activated by the Cu(II) species and the electrophilicity of the hypervalent iodine is enhanced by formation of intermediate **II**. This intermediate **II** is in equilibrium with intermediates **I** and also **III** in the presence of allylamine **2**. Intermediates **II** or **III** reacts with nucleophilic allylamine **2** or Togni reagent **1** on the activated hypervalent iodine moiety, respectively. We consid-

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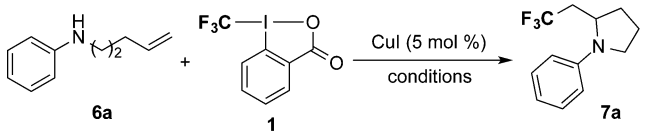
ered this step to be the turnover-limiting step, based on the first-order kinetic relationships of Togni reagent, CuI, and allylamine (Figures 3 and 4). The transformation of intermediate **I** to **IV**[37] should be affected by the concentrations of copper catalyst, Togni reagent **1**, and allylamine **2** because of the rapid equilibriums. Intermediate **I** is regenerated via ligand coupling[38] with formation of the desired aziridine **3** and 2-iodobenzoic acid. After the second cycle, aziridine can inhibit the reaction by coordination to the copper center.

Application to Synthesis of Trifluoromethylated Pyrrolidines. In our previous report on aminotrifluoromethylation, we demonstrated that this reaction was applicable to the systhesis of not only trifluoromethylated aziridines, but also pyrrolidines.[19a] Recently, Tan and Liu reported an intramolecular aminotrifluoromethylation with five-membered ring formation, in which 10−50 mol % of CuI and higher temperature were required.[39] They also noted that our previously reported conditions for aminotrifluoromethylation (with CuI, in *t*-BuOH (0.2 M)) provided better results for some of their substrates. However, in some cases poor results were obtained. For instance, when *N*-(4-pentenyl)aniline **6a** was employed as a substrate, the desired pyrrolidine **7a** was obtained in only 38% yield due to formation of uncyclized byproducts (Scheme 5). On the basis of the present

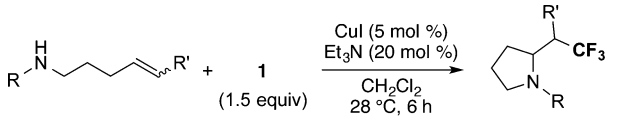
Scheme 5. Pyrrolidine Ring Formation by Aminotrifluoromethylation of Alkenylamine 6a with Togni Reagent 1

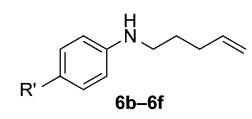
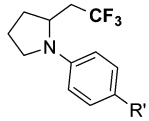
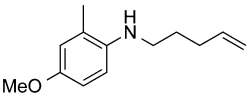
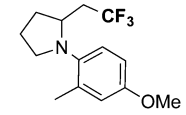
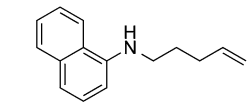
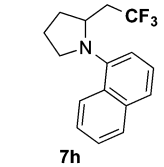
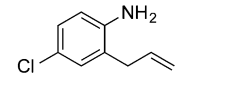
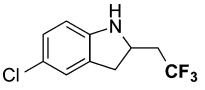
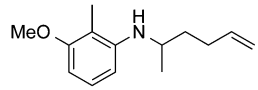
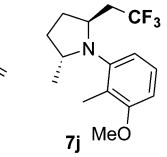
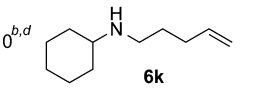
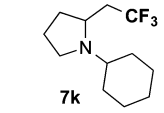
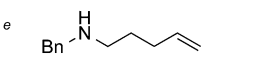
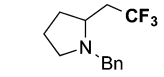
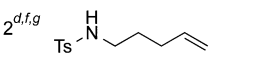
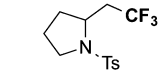
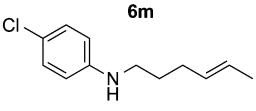
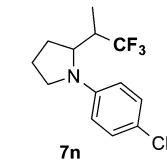
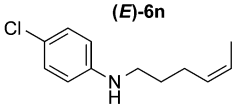


t-BuOH (0.2 M), 40 °C, 6 h	without additive	38%
	with 20 mol % of Et_3N	73%
CH_2Cl_2 (0.4 M), 28 °C, 12 h	without additive	31%
	with 20 mo l% of Et_3N	89%

mechanistic findings, we speculated that protonation of the substrate amine by the coexisting 2-iodobenzoic acid prevents nucleophilic C−N bond formation. Thus, trapping the acid with an appropriate base should accelerate the ring formation and improve the yield of the desired product. We conducted additive screening, and found that Et_3N as a cocatalyst dramatically improved the reaction, affording **7a** in 73% yield.[40] After further optimization, the reaction in CH_2Cl_2 (0.4 M) was found to give the best result under mild conditions, and the desired pyrrolidine **7a** was obtained in 89% yield.[41] We then examined the substrate scope of the reaction under the optimized conditions (Table 2). Both electron-rich and deficient aniline tolerated available for the reaction (entries 1−5). Alkenylamine **6b** bearing a 4-methoxy group on the aromatic ring showed high reactivity, as did **6a**, although the yield was slightly decreased due to competing trifluoromethylation of the aromatic ring (entry 1). Halogen groups are completely tolerated under these conditions, and the desired product was obtained in 72−78% yield (entries 2−5). 2-Me-4-MeO-phenyl substrate **6g** provided the desired product **7g** in 82% yield (entry 6). Naphthylamine **6h** afforded the corresponding pyrrolidine **7h** in 42% yield (entry 7). The *o*-allylaniline **6i** efficiently gave the indoline derivative **7i** in 82% yield under the conditions with Et_3N (entry 8). In addition, the catalyst loading could be reduced to 1 mol % without decrease

Table 2. Substrate Scope for Synthesis of Trifluoromethylated Pyrrolidines



entry[a]	substrate	product	isolated yield
1			R' = OMe (**7b**) 81%
2			R' = F (**7c**) 72%
3			R' = Cl (**7d**) 78%
4			R' = Br (**7e**) 76%
5	**6b–6f**	**7b–7f**	R' = I (**7f**) 74%
6			82%
	6g	**7g**	
7			42%
	6h	**7h**	
8[b]			80% (58%) 81%[c]
	6i	**7i**	
9[b]			55% *trans/cis* = 64/36
	6j	**7j**	
10[b,d]			45%
	6k	**7k**	
11[e]			56% (17%)
	6l	**7l**	
12[d,f,g]			81% 80%[h]
	6m	**7m**	
13			43% *anti/syn* = 50/50
	(*E*)-6n		
14			40% *anti/syn* = 50/50
	(*Z*)-6n	**7n**	

[a]Reactions were conducted under the optimal conditions described in Scheme 5. The yields without Et_3N are shown in parentheses. [b]The reaction was conducted at 40 °C. [c]1 mol % of CuI was used. [d]*t*-BuOH was used as the solvent. [e]The reaction was conducted for 3 h. [f]The reaction was conducted at 75 °C for 24 h. [g]Without Et_3N. [h]0.3 mol % of CuI was used.

of the yield. Alkenylamine **6j**, possessing a methyl side chain, could also be employed in the reaction (entry 9). The desired product **7j** was obtained in 55% yield (*trans/cis* = 64/36).

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Aliphatic substrates bearing cyclohexyl (**6k**) and benzyl (**6l**) groups afforded the desired products **7k** and **7l** in 45% and 56% yields, respectively (entries 10 and 11). In the case of the much less nucleophilic tosylated alkenylamine **6m**, the reaction proceeded at 75 °C in *t*-BuOH to afford the desired product **7m** in 81% yield (entry 12). Furthermore, with 0.3 mol % catalyst, the cyclized product was obtained in 80% yield. The internal alkenylamine **6n** also showed high reactivity under these conditions (entries 13 and 14). The desired pyrrolidine **7n** was obtained in 43% and 40% yields from (*E*)-**6n** and (*Z*)-**6n**, respectively, albeit with no diastereoselectivity.[42]

CONCLUSION

In conclusion, we examined the mechanism of our aminotrifluoromethylation reaction, which provides various trifluoromethylated cyclic amines, by means of kinetic studies, NMR and ESI-MS analyses. In our aminotrifluoromethylation conditions, Cu(II) complex generated by oxidation of CuI during the pretreatment plays major role. Several Cu(II) species are in rapid dynamic equilibrium through ligand exchanges. The turnover limiting step of this reaction involves copper, Togni reagent **1**, and allylamine. Cu(II) ion serves as a Lewis acid catalyst to activate Togni reagent and enhances the electrophilicity of its hypervalent iodine. In addition, use of triethylamine as a cocatalyst improved the yield of the aminotrifluoromethylation in the synthesis of trifluoromethylated pyrrolidines. The substrate scope of this reaction is broad, including internal alkenylamines, and catalytic efficiency is excellent. We expect that this reaction will prove useful in synthetic organic and medicinal chemistry.

ASSOCIATED CONTENT

Supporting Information

Additional results, experimental details, procedures, spectra for characterization of new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(22) Solubility of CuI and also $Cu_2(O_2CAr)_4{\cdot}2MeOH$ is low, and thus complexation with substrates was expected to affect the reactivity by increasing the solubility.

(23) Almost no byproduct was detected under the conditions used. For experimental procedure, see Supporting Information.

(24) For details of the preparation, see Supporting Information.

(25) Chen and Xi reported that Togni reagent **1** and CuCl provided the dimeric Cu complex **5a**. See: Cai, S.; Chen, C.; Sun, Z.; Xi, C. *Chem. Commn.* **2013**, *49*, 4552.

(26) Use of THF as the solvent completely stopped the reaction. Details were reported in our previous work (Supporting Information of ref 19a)

(27) Magnetic susceptibility of the diluted solution of the mixture of the Cu precursors and **1**, roughly estimated by the Evans method based on ^{1}H NMR spectra, was 1.4−1.5 μ_B. The result supported the generation of Cu(II) species in the solution phase, but not Cu(III) species. For details, see Supporting Information. Original papers on the Evans method, see: (a) Grant, D. H. *J. Chem. Educ.* **1995**, *72*, 39. (b) Evans, D. F.; Franzakerley, G. V.; Philips, P. R. F. *J. Chem. Soc. A* **1971**, 1931. (c) Crawford, T. H.; Swanson, J. *J. Chem. Educ.* **1971**, *48*, 328. (d) Evans, D. F. *J. Chem. Soc.* **1951**, 2003.

(28) Upon generation of Cu(II) species from CuI and **1** during the preincubation, CF_3 radical should also be generated, but in the absence of substrate it is likely to decompose. Further discussions are described in Supporting Information.

(29) Weakly coordinating MeOH derived from **5a** may affect the chemical shift and also the reactivity of the catalyst due to its participation in the dynamic equilibrium.

(30) The small signals at −25.9 ppm and −3.4 ppm were assigned to CF_3Cu and CF_3I according to reference 7e and Naumann, D.; Heisen, H. H.; Lehmann, E. *J. Fluorine Chem.* **1976**, *8*, 243. A spectrum is shown in the Supporting Information.

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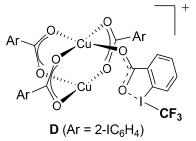
(31) The structure was decided by analogy with the X-ray single-crystal structure of $[Zn(\mathbf{1})_2(4\text{-}NO_2C_6H_4CH_2OH)_2(H_2O)_2](NTf_2)_2$ reported by Togni. For details, see ref 21a.

(32) DFT calculation of Togni reagent indicated that the carbonyl oxygen makes a major electronic contribution to the HOMO. Thus we show the structures with carbonyl coordination. For details, see Supporting Information.

(33) A dimeric Cu species (m/z = 1182.5563) was also detected and assigned as complex **D** shown below. The complex is also a potential reactive species, but the monomeric species were considered as the major catalytically active species on cycle for the reasons discussed in the text.



D (Ar = 2-IC_6H_4)

$[M]^+$ calcd: 1182.5563
found: 1182.5531

(34) At the late stage of the reaction, increased acidity due to 2-iodobenzoic acid production may affect the chemical shift of the signal derived from the aziridine **3**.

(35) The presented data suggested the Cu(II) species as a Lewis acid catalyst mainly contributed in the reaction with the pretreated CuI. If CF_3 radical was generated by the oxidation of CuI in the presence of the substrate, it may partly contribute to the production of **3**. Further discussion is shown in Supporting Information.

(36) ESI-MS of the reaction mixture and assignment of the signals are described in Supporting Information; a Cu species coordinating Togni reagent **1**, the substrate, and/or the aziridine was detected.

(37) In the conversion from **TS** to **IV**, C−I and C−N bond formation may proceed either in concerted or stepwise mechanism via cation intermediate formation.

(38) Selected paper, see: Ochiai, M.; Kitagawa, Y.; Toyonari, M. *ARKIVOC* **2003**, *vi*, 43.

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(40) In the absence of Et_3N, several unidentified products were also obtained in addition to the uncyclized allylic and hydrotrifluoromethylation products.[41] Et_3N improved the product selectivity of the reaction.

(41) For details of additive screening and optimization, see Supporting Information.

(42) The stereochemical outcome may suggest the stepwise mechanism for the pyrrolidine formation.

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