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Copper(II)-catalyzed trifluoromethylation of *N*-aryl imines†

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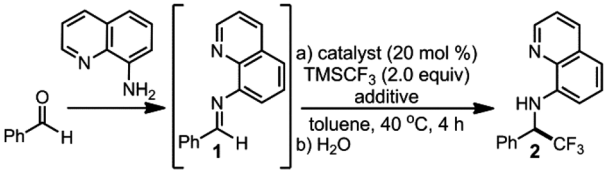
Methods for imine trifluoromethylation are of great importance because amines with trifluoromethylated stereogenic centers are useful building blocks for synthetic chemistry and drug discovery. Herein, we describe a new copper(II)-catalyzed imine trifluoromethylation method without the use of Lewis base activators, presumably through cooperative activation.

Trifluoromethylated heterocycles and amines with trifluoromethylated stereogenic centers are important building blocks for organic synthesis and pharmaceutical research because of their unique lipophilic and metabolic properties applicable to drug discovery.[1] There has recently been a tremendous amount of progress in the trifluoromethylation of aromatics and heterocycles.[2] Likewise, a method for direct trifluoromethylation of imines would be a convenient means to access amines with trifluoromethylated stereogenic centers. While methods for aldehyde and ketone trifluoromethylation with nucleophilic Ruppert–Prakash reagent ($TMSCF_3$) are well-established,[3] general and selective catalytic methods for trifluoromethylation of imines are yet to be discovered.[4] One probable reason is that the kinetic inertness of the C=N bond and the relatively low energy of the Si–N bond render the catalytic cycle sluggish. Despite these obstacles, Olah, Prakash, Dolbier, Mukaiyama, Dilman, and others reported the trifluoromethylation of activated *N*-sulfonyl and *N*-sulfinyl imines;[5] Blazejewski, Olah, and Prakash discovered the *N*-aryl imine trifluoromethylation with fluoride or *tert*-butoxide-based activators;[6] and Dilman and Hu recently disclosed a method for *N*-alkyl imine trifluoromethylation mediated by HF.[7] Nonetheless, methods for *N*-aryl and alkyl imine trifluoromethylation without the use of fluoride or strong basic activators remain highly desirable. Herein, we report a copper(II)-catalyzed *N*-aryl imine trifluoromethylation without the use of Lewis base activators, presumably through cooperative activation.

We selected an 8-aminoquinoline derived *N*-aryl imine **1** (generated *in situ*) as a model substrate during catalyst discovery for imine trifluoromethylation (Table 1). When KF was applied to activate $TMSCF_3$ under an argon atmosphere without any copper catalyst, significant conversion of **1** was not observed (entry 1). CuI and $CuBr_2$ were subsequently determined to ineffectively promote the desired reaction (entries 2 and 3). Interestingly, CuOAc promotes the trifluoromethylation of **1** at 40 °C (entry 4, 35% conversion, 23% yield), and $Cu(OAc)_2$ catalyzes this reaction to efficiently deliver **2** (full conversion, 65% yield). After exploration of the counterion effect with a variety of copper(II) salts, we determined that

Table 1 Catalyst discovery for *N*-aryl imine trifluoromethylation



Entry[a]	Catalyst	Additive (equiv.)	Conversion[b]	Yield[c]
1	None	KF (3.0)	<5%	NA
2	CuI	KF (3.0)	<5%	NA
3	$CuBr_2$	KF (3.0)	<5%	NA
4	CuOAc	KF (3.0)	35%	23%
5	$Cu(OAc)_2$	KF (3.0)	>95%	65%
6	$Cu(TFA)_2$	KF (3.0)	43%	24%
7	$Cu(OTf)_2$	KF (3.0)	<5%	NA
8	$CuSO_4$	KF (3.0)	<5%	NA
9	$Cu(OAc)_2$	LiOAc (1.0)	>95%	78%
10	$Cu(OAc)_2$	None	>95%	81%

[a] Reactions were carried out under argon at 40 °C, and the imine was generated *in situ* by stirring benzaldehyde and 8-aminoquinoline in toluene in the presence of 4 Å molecular sieves at RT for 1 h. [b] Conversions (from **1** to **2**) were determined by ^1H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield over two steps. TFA = trifluoroacetate, OTf = trifluoromethanesulfonate, TMS = trimethylsilyl.

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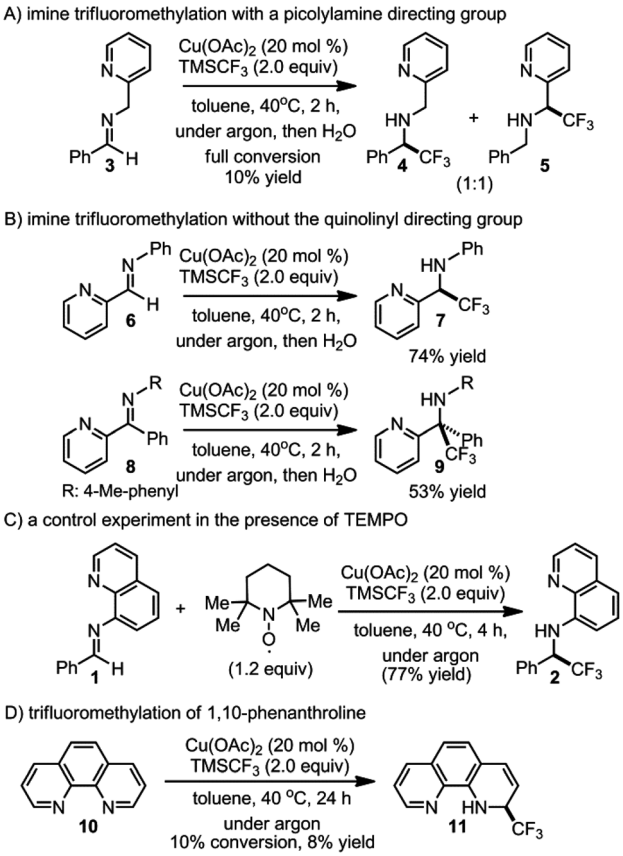
$Cu(OAc)_2$ is superior to $Cu(TFA)_2$, $Cu(OTf)_2$, and $CuSO_4$ (entries 6–8). We subsequently replaced the activator KF (3.0 equiv.) with LiOAc (1.0 equiv.) and achieved a greater isolated yield (entry 9, 78% yield). Surprisingly, we discovered that $Cu(OAc)_2$ alone catalyzes efficient imine trifluoromethylation even in the absence of any activator (entry 10, 81% yield).

We subsequently applied the optimized catalytic system to a variety of *N*-aryl imines, and discovered that a variety of aromatic imines with different electronic and steric properties are generally good substrates (Table 2, entries 1–9). We also determined that furyl and pyridyl imines can participate in this reaction with decent yields (entries 10–12). Further exploration revealed that aliphatic and alkenyl imines, such as cyclohexyl, iso-butyl, and cinnamyl imines, can also undergo the copper-catalyzed trifluoromethylation (entries 13–15).

It is mechanistically intriguing that $Cu(OAc)_2$ is effective to promote the *N*-aryl imine trifluoromethylation and that the catalytic cycle turns over in the absence of any fluoride-based activator. Additionally, the 8-aminoquinolinyl group proves uniquely effective whereas imines derived from other isomeric aminoquinolines suffer from low reactivity.[8] In order to probe for a possible mechanism, we carried out a few control experiments (Scheme 1A–D). First, we replaced the model substrate with a picolylamine-derived imine **3** and discovered that $Cu(OAc)_2$ rapidly decomposed and isomerized imine **3**. As a result, two isomeric trifluoromethylation products **4** and **5** were isolated with low yield (Scheme 1A, *ca.* 1 : 1, full conversion, 10% yield). We subsequently inspected imines derived from other branched picolylamines; however, none of them delivered the desired trifluoromethylation products.[9] Nonetheless, aniline-derived aldimine **6** and ketoimine **8** with an *ortho*-pyridyl moiety can undergo the smooth reaction to afford **7** and **9** respectively (Scheme 1B). These results suggest that an *N*,*N*-bi-dentate directing group is crucial for the copper-catalyzed imine trifluoromethylation.

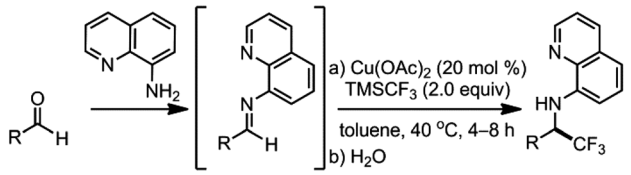


Scheme 1 Experiments to probe for mechanistic insight of $Cu(OAc)_2$-catalyzed imine trifluoromethylation.

When a stoichiometric amount of TEMPO was applied to the standard condition, **2** was still isolated with good yield (77%). Concordantly, we did not detect any TEMPO–CF_3 adduct (Scheme 1C).[10] This result indicates that the CF_3 radical is unlikely to be involved in this reaction. Since copper salts are necessary for the CF_3 group transfer (Table 1, entry 1), an alternative mechanism might involve internal nucleophilic CF_3 addition (likely from a "Cu(II)–CF_3" complex) to the C=N bond.[11] It is known that the C=N bond within 1,10-phenanthroline **10** is labile to nucleophilic addition;[12] therefore, we subjected **10** to the standard reaction condition and managed to isolate the trifluoromethylation product 1,2-dihydrophenanthroline **11** after 24 h albeit with low yield (Scheme 1D, 10% conversion with the recovery of **10**).

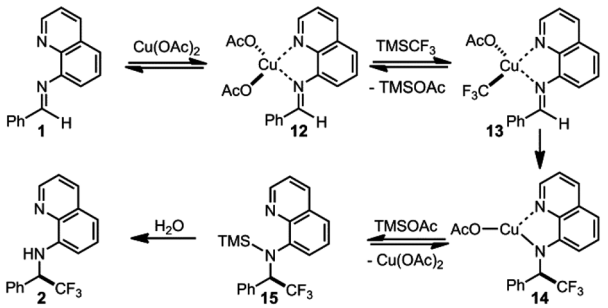
Based on the collective mechanistic evidence, we propose a working hypothesis that best corroborates the experimental data (Scheme 2): since copper(II) is able to coordinate with *N*,*N*-bi-dentate ligands and generate the tetrahedral complex **12**, the acetate ligand may be activated by the imine **1** to

Table 2 Substrate scope for $Cu(OAc)_2$-catalyzed *N*-aryl imine trifluoromethylation



Entry[a]	R	Yield[b]
1	Phenyl	81%
2	3-Cl-phenyl	70%
3	4-F-phenyl	71%
4	4-Cl-phenyl	78%
5	4-NO_2-phenyl	72%
6	4-Br-phenyl	71%
7	4-Me-phenyl	67%
8	4-MeO-phenyl	69%
9	3,4-$(Me)_2$-phenyl	63%
10	2-Furyl	61%
11	3-Pyridyl	72%
12	2-Pyridyl	61%
13	Cyclohexyl	62%
14	iso-Butyl	47%
15	Cinnamyl	53%

[a] Reactions were carried out under argon at 40 °C, imines were formed *in situ* by mixing the aldehyde and 8-aminoquinoline at RT for 1–12 h in the presence of 4 Å molecular sieves. [b] Isolated yield over two steps.



Scheme 2 Mechanistic working hypothesis for copper(II)-catalyzed imine trifluoromethylation.

release the CF_3 group from $TMSCF_3$ through a hypervalent silicon species.[5] Through this anionic metathesis process, a $Cu(CF_3)(OAc)$(imine) intermediate **13** may be subsequently generated. The coordination of imine **1** to the Lewis acid copper(II) presumably polarizes the C=N bond and renders it more labile to nucleophilic addition; concordantly, the Lewis base imine ligand may further enhance the nucleophilicity of the CF_3 group. Cooperative CF_3 group transfer will convert **13** to **14**, and the *in situ*-generated TMSOAc presumably interacts with **14** to furnish silylation product **15** and regenerate $Cu(OAc)_2$. The labile Si–N bond in **15** can then readily undergo hydrolysis upon workup to afford **2**.

In conclusion, we have discovered a new copper(II)-catalyzed *N*-aryl imine trifluoromethylation without the use of fluoride or HF-based activators. This method readily converts a variety of *N*-aryl imines to corresponding amines with trifluoromethylated stereogenic centers. Our current efforts are focused on understanding the mechanistic details of these new reactions and their application in medicinal agent synthesis.

Acknowledgements

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