Copper(I)-Catalyzed Direct C-H Trifluoromethylation of Imidazoheterocycles with Togni's Reagent

Ruonan Wang, Jingcai Wang, Qingxuan Tang, Xin Zhao, Junfeng Wang, Yuting Leng, Yangjie Wu, Junbiao Chang, Yusheng Wu, Zhaoda Zhang, Shiwei Wang

PII: S0040-4039(19)30038-3
DOI: https://doi.org/10.1016/j.tetlet.2019.01.026
Reference: TETL 50559

To appear in: *Tetrahedron Letters*

Received Date: 25 November 2018
Revised Date: 12 January 2019
Accepted Date: 14 January 2019

Please cite this article as: Wang, R., Wang, J., Tang, Q., Zhao, X., Wang, J., Leng, Y., Wu, Y., Chang, J., Wu, Y., Zhang, Z., Wang, S., Copper(I)-Catalyzed Direct C-H Trifluoromethylation of Imidazoheterocycles with Togni's Reagent, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.01.026

Copper(I)-Catalyzed Direct C-H Trifluoromethylation of Imidazoheterocycles with Togni's Reagent

Ruonan Wang,[1] Jingcai Wang,[1] Qingxuan Tang,[1] Xin Zhao,[1] Junfeng Wang,[2] Yuting Leng,[1,2]* Yangjie Wu,[1]* Junbiao Chang,[1] Yusheng Wu,[1,4] Zhaoda Zhang,[2] Shiwei Wang[3]

1 College of Chemistry and Molecular Engineering, Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, Collaborative Innovation Center of New Drug Research and Safety Evaluation, Zhengzhou University, Zhengzhou 450001, People's Republic of China

2 Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, 149, 13th St., Suite 2301, Charlestown, MA 02129, USA

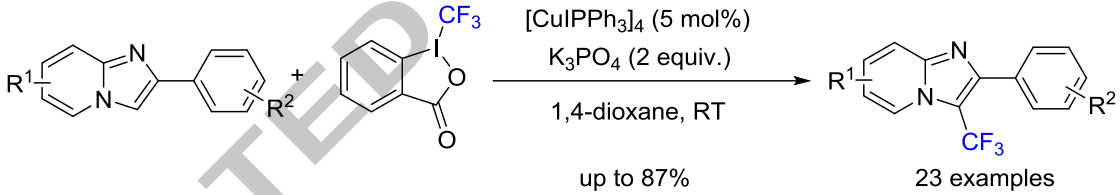
3 School of Mechanics and Engineering Science, Zhengzhou University, Zhengzhou, Henan 450001, People's Republic of China

4 Tetranov Biopharm LLC, Zhengzhou 450052, People's Republic of China

Corresponding Email address: yutingleng@zzu.edu.cn; wyj@zzu.edu.cn.

ABSTRACT

A mild and efficient trifluoromethylation of imidazopyridines with Togni's reagent in the presence of inexpensive base has been realized at room temperature. This methodology has several advantages: (1) using efficient copper(I) as catalyst and inexpensive K_3PO_4 as base, (2) no additional oxidants required for this reaction. (3) good functional group tolerance. An array of trifluoromethylated imidazopyridines with broad functionalities were obtained in acceptable yields.



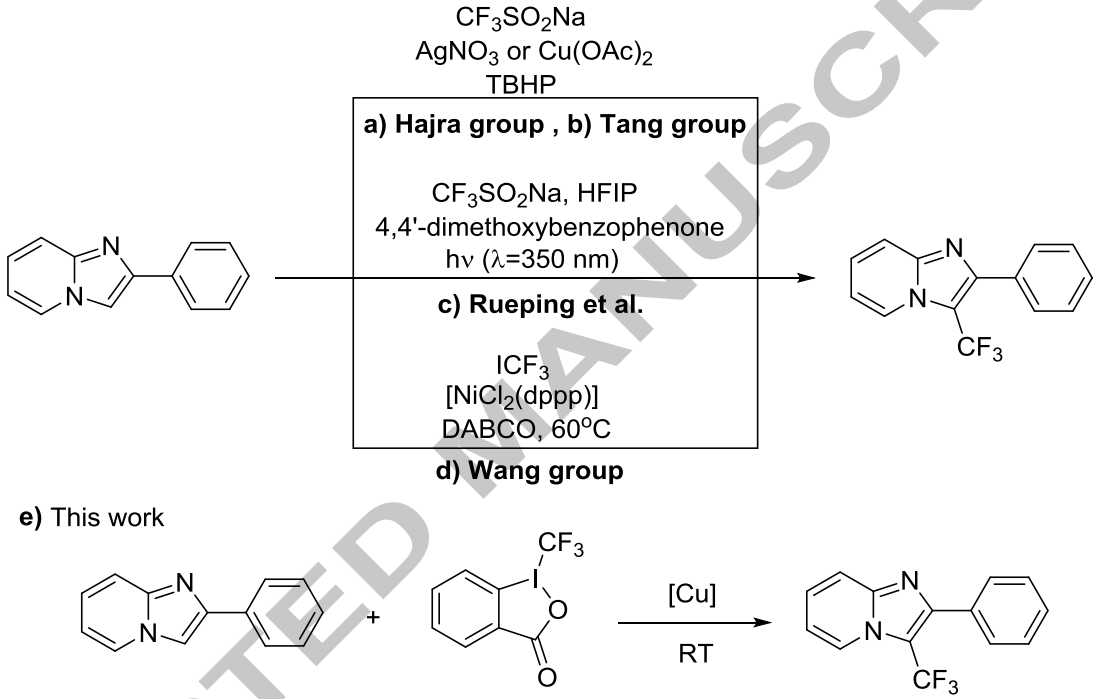
Keywords: Imidazopyridines; Togni's Reagent; Copper; Trifluoromethylation

Introduction

Imidazopyridine and its derivatives exist in a variety of natural products and have attracted much attention due to their important biological activities and broad utilization in the pharmaceutical industry.[1] Many commercialized drugs contain this pyridine core such as alpidem, zolpidem, necopidem, minodronic acid,[2] saripidem,[3] olprinone, zolimidine, etc. What's more, imidazopyridines are core ligands in the field of electronic devices and abnormal N-heterocyclic carbenes.[4] Therefore, a number of efficient processes have been developed for the synthesis and functionalization of imidazo[1,2-a]pyridines.[5]

The introduction of a trifluoromethyl group into organic molecules can bring unique alteration of their physical, chemical, and biological properties such as permeability, bioavailability, and metabolic stability.[6] Therefore, significant attention has been paid to the developments of versatile and efficacious methodologies to incorporate the trifluoromethyl group into target molecules in the area of organofluorine chemistry.[7] Recently, transition-metal-mediated or -catalyzed trifluoromethylation reactions have been developed intensively to synthesize various CF_3-containing compounds.[8] Accordingly, a few methods have been reported for the trifluoromethylation of imidazo[1,2-a]pyridine and its derivatives. In 2015, Hajra and Tang groups reported two methods for the trifluoromethylation of

imidazopyridines, using Langlois' reagent ($NaSO_2CF_3$) in the presence of TBHP as CF_3 radical source and $AgNO_3$ or $Cu(OAc)_2$ as catalyst, respectively.[9,10] Then photoorganocatalysed trifluoromethylation of (hetero)aromatics was performed by Rueping et al.[11] Thereafter, Wang group developed the trifluoromethylation of imidazo[1,2-a]pyridine with iodotrifluoromethane (CF_3I) as the CF_3 source at 60 °C .[12] Although great progress has been achieved, milder strategies for the trifluoromethylation are still valuable to be developed in simple catalytic reaction system. Herein, we report a copper-catalyzed trifluoromethylation of imidazopyridines with Togni's reagent as a trifluoromethylating reagent in the presence of inexpensive base K_3PO_4 at room temperature under air.



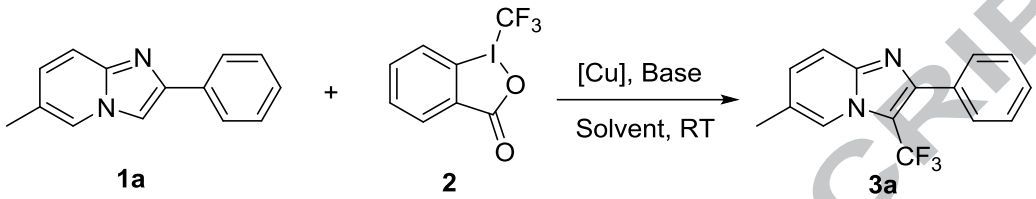
Scheme 1 Previous examples and current goals to realize the trifluoromethylation of imidazopyridines

Results and Discussion

To optimize the reaction system, we examined the reaction of 6-methyl-2-phenylimidazo[1,2-a]pyridine **1a** with Togni's reagent **2** under various conditions, and the results are summarized in **Table 1**. We initiated the trifluoromethylation of 6-methyl-2-phenylimidazo[1,2-a]pyridine **1a** (0.20 mmol) with Togni's reagent (0.30 mmol) **2** in the presence of 10 mol% of CuI and 15 equivalents of NaOH at room temperature in DCM for 6 h, the desired product 6-methyl-2-phenyl-3-(trifluoromethyl)imidazo[1,2-a]pyridine **3a** was isolated in 43 % yield (**entry 1**). With the same conditions, we screened various solvents, including EA, 1,4-dioxane, and DMSO (**entries 2-4**). Among these solvents, 1,4-dioxane was the best one, affording the desired product in 61% yield (**entry 3**). To improve the efficiency, different Cu catalysts such as CuBr, CuCN, $[CuIPPh_3]_4$, CuOAc, and $Cu(CH_3CN)_4PF_6$ were also examined (**entries 5-9**). Of these catalysts, $[CuIPPh_3]_4$ was the most effective (**entry 7**). It was found that **3a** was obtained in only 39% yield in the absence of Cu catalyst (**entry 10**). Next, when we decreased the amount of NaOH to 2 equivalents, the reaction gave **3a** in 58% yield (**entry 11**). Under the same conditions, reaction was performed with other bases such as Cs_2CO_3, Na_2CO_3, $NaHCO_3$, LiOH, K_3PO_4 and NaH (**entries 12-17**), among these bases **3a** was isolated in good

yield (79%) with K_3PO_4 (**entry 16**). The yield of the desired product was dropped by increasing or decreasing the amount of base (**entries 18-19**).Decreasing the amount of $[CuIPPh_3]_4$ led to a decrease in the yield (**entry 20-21**). Only 6% yield of the product was obtained in the absence of $[CuIPPh_3]_4$ (**entry 22**). This result revealed that copper catalyst is necessary for our reaction system.

Table 1. Optimization of the reaction conditions [a]



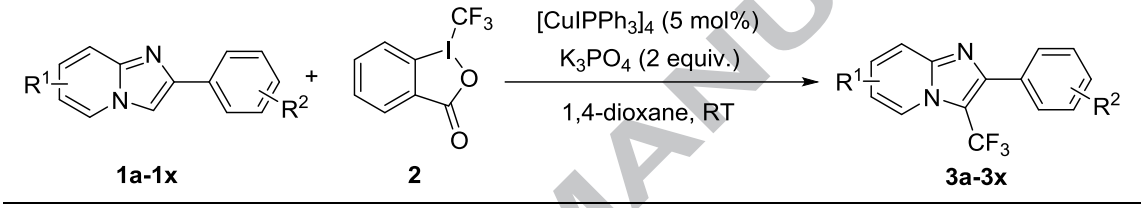
Entry	Catalyst(mol %)	Base (equiv.)	Solvent	Yield (%)[b]
1	CuI (10)	NaOH (15)	DCM	43
2	CuI (10)	NaOH (15)	EA	34
3	CuI (10)	NaOH (15)	1,4-dioxane	61
4	CuI (10)	NaOH (15)	DMSO	56
5	CuBr (10)	NaOH (15)	1,4-dioxane	59
6	CuCN (10)	NaOH (15)	1,4-dioxane	63
7	$[CuIPPh_3]_4$ (5)	NaOH (15)	1,4-dioxane	67
8	CuOAc (10)	NaOH (15)	1,4-dioxane	48
9	$Cu(CH_3CN)_4PF_6$ (10)	NaOH (15)	1,4-dioxane	52
10	none	NaOH (15)	1,4-dioxane	39
11	$[CuIPPh_3]_4$ (5)	NaOH (2)	1,4-dioxane	58
12	$[CuIPPh_3]_4$ (5)	Cs_2CO_3 (2)	1,4-dioxane	71
13	$[CuIPPh_3]_4$ (5)	Na_2CO_3 (2)	1,4-dioxane	65
14	$[CuIPPh_3]_4$ (5)	$NaHCO_3$ (2)	1,4-dioxane	59
15	$[CuIPPh_3]_4$ (5)	LiOH (2)	1,4-dioxane	62
16	$[CuIPPh_3]_4$ (5)	K_3PO_4 (2)	1,4-dioxane	79
17	$[CuIPPh_3]_4$ (5)	NaH (2)	1,4-dioxane	70
18	$[CuIPPh_3]_4$ (5)	K_3PO_4 (3)	1,4-dioxane	67
19	$[CuIPPh_3]_4$ (5)	K_3PO_4 (1)	1,4-dioxane	60
20	[CuIPPh3]4 (2.5)	K3PO4 (2)	1,4-dioxane	55
21	[CuIPPh3]4 (1)	K3PO4 (2)	1,4-dioxane	24
22	none	K_3PO_4 (2)	1,4-dioxane	6

[a] Reaction conditions: 6-methyl-2-phenylimidazo[1,2-a]pyridine **1a** (0.2 mmol, 1.0 equiv.), Togni's reagent **2** (0.3 mmol, 1.5 equiv.), catalyst, base, and solvent (1.5 mL) at room temperature for 6 h. [b] Isolated yield.

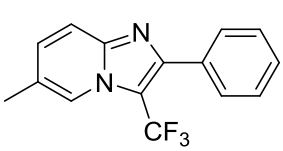
With the optimized reaction conditions in hand (**Table 1, entry 16**), we set out to investigate the substrate scope of this trifluoromethylation reaction to show the generality of this methodology (**Table 2**). First, imidazo[1,2-a]pyridines substrates bearing methyl group at different positions efficiently reacted with trifluoromethylating agent under the standard conditions to give the corresponding trifluoromethylated products in good yield (**3a-3c**). To our delight, both electron-donating groups, such as methyl, methoxy, methylthio, and

electron-withdrawing groups, such as trifluoromethyl, cyano, fluoro, chloro, bromo, on the phenyl ring at the 4-position of imidazopyridines were compatible to this reaction system in satisfactory yields (**3e-3i** and **3k-3m**). The imidazopyridines with *meta*-substituents on the phenyl ring underwent the reaction successfully to give the corresponding trifluoromethylated products in modest to good yields (**3n-3p**). Interestingly, 7-methoxy-2-phenylimidazo[1,2-a]pyridine **1q** provided the corresponding product **3q** in a higher yield than the product **3r** afforded from 6-methoxy-2-phenylimidazo[1,2-a]pyridine **1r**. The imidazopyridines bearing bromo, chloro on the pyridine ring smoothly reacted to give the desired products (**3s** and **3t**). In addition, 2-(thiophen-2-yl)imidazo[1,2-a]pyridine and 2-phenylimidazo[1,2-a]pyrimidine also reacted well to afford the corresponding products in good yields. Finally, the C-2 alkyl-substituted imidazo[1,2-a]pyridine and simple imidazo[1,2-a]pyridine were also investigated under the standard conditions affording the desired products in the yield of 47% and trace respectively (**3w** and **3x**)

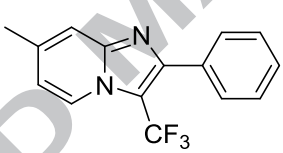
Table 2. The scope of imidazo[1,2-a]pyridines[a,b]



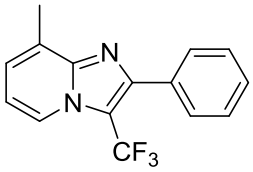
1a-1x **2** **3a-3x**



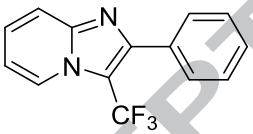
3a, 79%



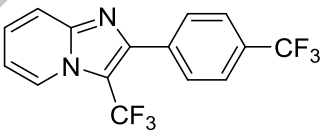
3b, 87%



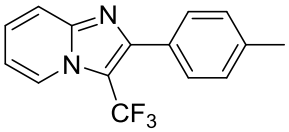
3c, 80%



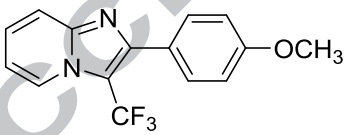
3d, 77%



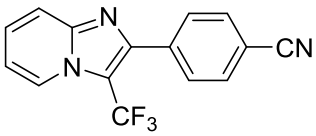
3e, 70%



3f, 84%

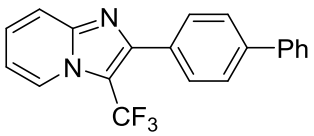


3g, 83%

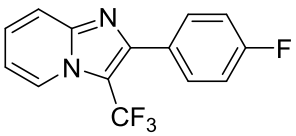


3h, 71%

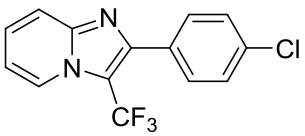
3i, 56%



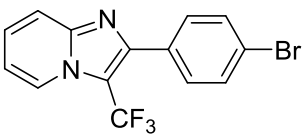
3j, 70%



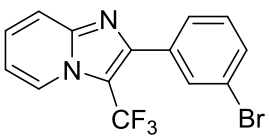
3k, 80%



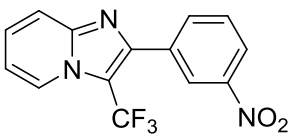
3l, 76%



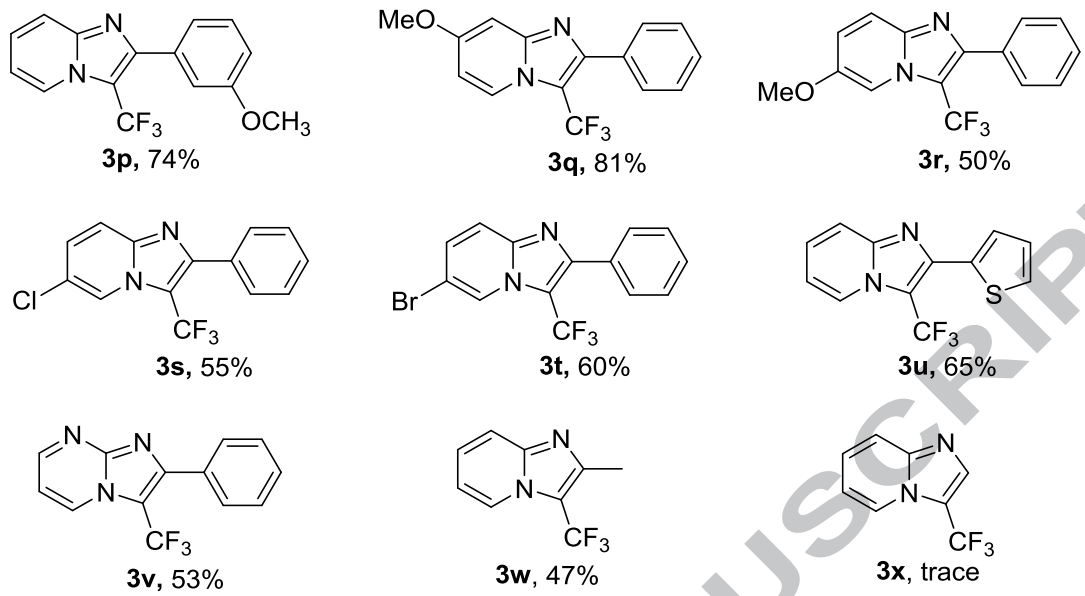
3m, 74%



3n, 68%

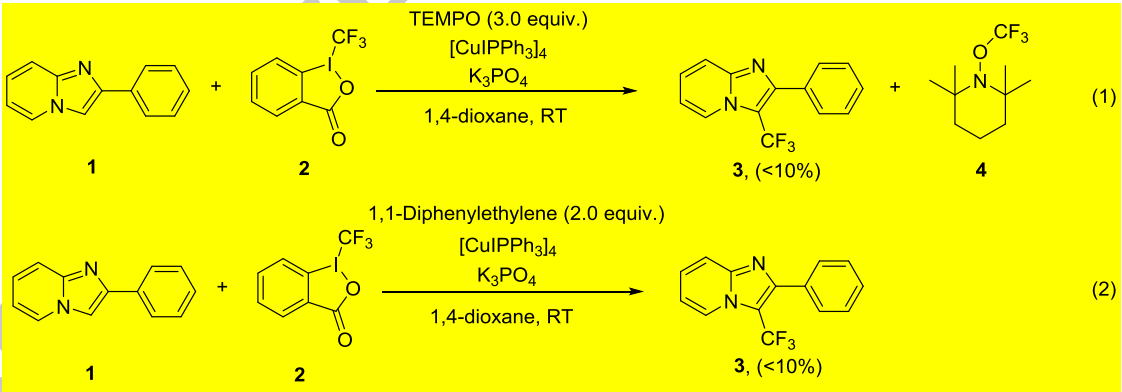


3o, 47%



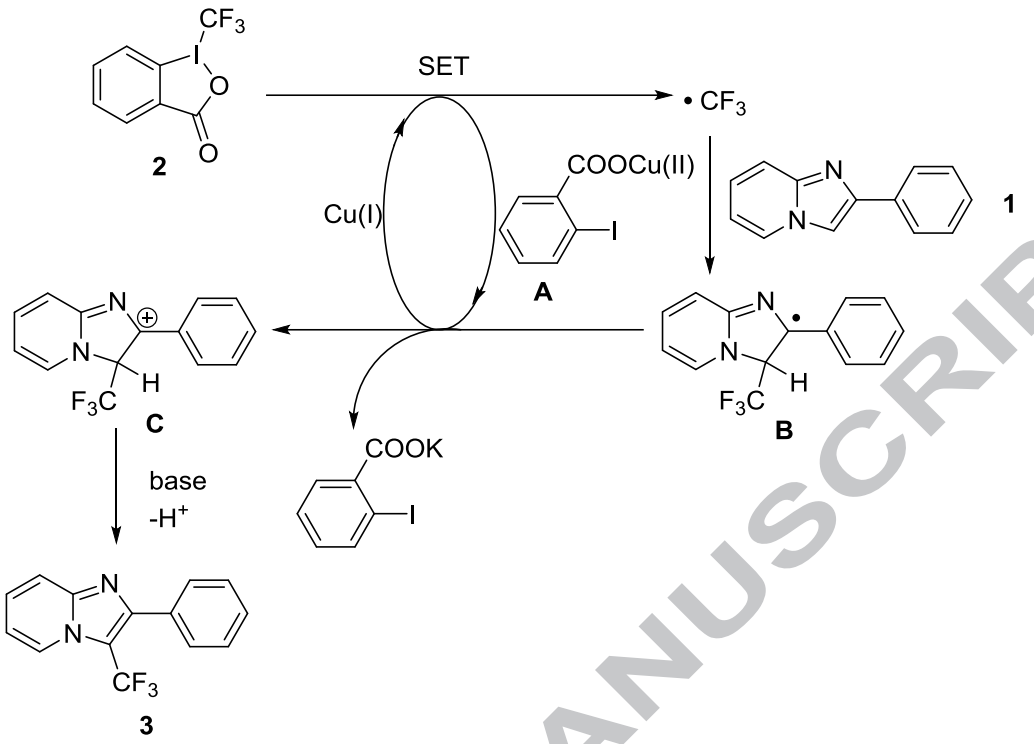
[a] Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), Togni's reagent **2** (0.3 mmol, 1.5 equiv.), $[CuIPPh_3]_4$ (5 mol%), K_3PO_4 (2 equiv.), and 1,4-dioxane (1.5 mL) at room temperature for 6 h. [b] Isolated yield.

To gain insight into the reaction mechanism, two control experiments were performed under the optimized conditions (**Scheme 2**). When the radical scavengers TEMPO and 1,1-diphenylethylene were added separately to the trifluoromethylation reaction mixture, only a small amount of product was isolated, and ^{19}F NMR analysis showed that the compound **4** was produced (**Scheme 2, eqs 1 and 2**). These results suggested that this reaction possibly involve a radical pathway.



Scheme 2. Controlled Experiments

On the basis of above control experiments and previous reports[13,14], a plausible mechanism for this reaction is outlined in **Scheme 3**. First, the CF_3 radical and Cu(II) intermediate **A** are generated by a single-electron transfer (SET) from Cu(I) to **2**. Subsequently, the CF_3 radical reacts with the imidazopyridine **1** to form the radical intermediate **B**. The oxidation of **B** by Cu(II) intermediate **A** results in a cationic intermediate **C**, accompanied by the regeneration of Cu(I) catalyst. Finally, trifluoromethylated imidazopyridine **3** are generated from cationic intermediate **C** via the base-promoted deprotonation.



Scheme 3. Plausible mechanism.

Conclusions

In summary, we have developed an efficient copper-catalyzed trifluoromethylation of imidazopyridines with Togni reagent as a trifluoromethylating reagent at room temperature. Mechanistic investigations suggested that this reaction possibly involve a radical pathway. Clean reaction, ease of product isolation, mild reaction conditions, the use of inexpensive reagent and a simple experimental procedure are the notable advantages of the method and these features will make this procedure practical and synthetically useful. Further investigation on the application of this synthetic methodology is currently underway.

Acknowledgements

We gratefully acknowledge National Science Foundation of China(51603192, 21172200) and Natural Science Foundation of Henan Province (182300410211) for financial support of this research.

References

1. (a) Baviskar, A. T.; Amrutkar, S. M.; Trivedi, N.; Chaudhary, V.; Nayak, A.; Guchhait, S. K.; Banerjee, U. C.; Bharatam, P. V.; Kundu, C. N. *ACS Med. Chem. Lett*., **2015**, *6*, 481; (b) Stasyuk, A. J.; Banasiewicz, M.; Cyrański M. K.; Gryko, D. T.; *J. Org. Chem.*, **2012**, *77*, 5552.
2. (a) Langer, S. Z.; Arbilla, S.; Benavides, J.; Scatton, B. *Adv. Biochem. Psychopharmacol*. **1990**, *46*, 61; (b) Mizushige, K.; Ueda, T.; Yukiiri, K.; Suzuki, H. *Cardiovasc. Drugs Rev*. **2002**, *20*, 163.
3. (a) Almirante, L.; Polo, L.; Mugnaini, A.; Provinciali, E.; Rugarli, P.; Biancotti, A.; Gamba, A.; Murmann, W.; *J. Med. Chem*. **1965**, *8*, 305. (b) Ma, G. Z.; Leng, Y. T.; Wu, Y. S., Wu, Y. J. *Tetrahedron*, **2013**, *69*, 902.
4. Wan, J.; Zheng, C.-J.; Fung, M.-K.; Liu, X.-K.; Lee, C.-S.; Zhang, X.-H. *J. Mater. Chem.* **2012**, *22*, 4502.

5. (a) Bagdi, A. K.; Santra, S.; Monir, K.; Hajra, A. *Chem. Commun*., **2015**, *51*, 1555; (b) Wang, H.; Xu, W.; Xin, L.; Liu, W.; Wang, Z.; Xu, K.; *J. Org. Chem*., **2016**, *81*, 3681; (c) Wu, S.-S.; Feng, C.-T.; Hu, D.; Huang, Y.-K.; Li, Z.; Luoa, Z.-G.; Mac, Si.-T. *Org. Biomol. Chem*., **2017**, *15*, 1680.
6. (a) Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed*. **2005**, *44*, 214; (b) Schlosser, M. *Angew. Chem. Int. Ed*. **2006**, *45*, 5432; (c) Mller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881; (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320.
7. (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320; (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881; (c) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed*. **2013**, *52*, 8214; (d) Alonso, C.; Martínez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847.
8. (a) Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.;. Liu, L. *J. Am. Chem. Soc*. **2011**, *133*, 15300; (b) Dai, J.-J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z.-J.; Lu, X.; Liu, L.; Fu, Y. *J. Am. Chem. Soc*. **2013**, *135*, 8436; (c) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev*. **2015**, *115*, 2, 650; (d) Alonso, C.; Martínez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847; (e) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem. Int. Ed*. **2012**, *51*, 5048; (f) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. - Asian J*. **2012**, *7*, 1744; (g) Chu, L.-L.; Qing, F.-L. *J. Am. Chem. Soc*. **2012**, *134*, 1298; (h) Mu, X.; Chen, S.; Zhen, X.; Liu, G. *Chem. - Eur. J*. **2011**, *17*, 6039.
9. Monir, K.; Bagdi, A. K.; Ghosh, M.; Hajra, A. *J. Org. Chem*. **2015**, *80*, 1332.
10. Ji, X.-M.; Wei, L.; Chen, F.; Tang, R.- Y. *RSC Adv*. **2015**, *5*, 29766.
11. Lefebvre, Q.; Hoffmann, N.; Rueping, M. *Chem. Commun.*, **2016**, *52*, 2493.
12. Wu, Y.; Zhang, H.-R.; Jin, R.-X.; Lan, Q.; Wang, X.-S. *Adv. Synth. Catal.* **2016**, *358*, 3528.
13. (a) Kuninobu, Y.; Nishi, M.; Kanai, M. *Org. Biomol. Chem*. **2016**, *14*, 8092; (b) Zhang, Y.; Guo, D. M.; Ye, S. Y.; Liu, Z. C.; Zhu, G. G. *Org. Lett.*, **2017**, *19*, 1302.
14. Gao, X. Y.; Geng, Y.; Han, S. J.; Liang, A. P.; Li, J. Y.; Zou D.P.; Wu, Y. S.; Wu, Y. J. *Org. Lett*. **2018**, *20*, 3732.

Supplementary Material

Supplementary data associated with this article can be found in the online version.

1. Cu(I)-catalyzed trifluoromethylation of imidazoheterocycles with Togni's Reagent.
2. Simple imidazoheterocycles to trifluoromethylation product at room condition.
3. Clean reaction, ease of product isolation and a simple experimental procedure.

Graphical Abstract.

Copper(I)-Catalyzed Direct C-H Trifluoromethylation of Imidazoheterocycles with Togni's Reagent

Ruonan Wang, Jingcai Wang , Qingxuan Tang, Xin Zhao, Junfeng Wang, Yuting Leng,* Yangjie Wu,* Junbiao Chang, Yusheng Wu, Zhaoda Zhang, Shiwei Wang

A mild and efficient copper-catalyzed trifluoromethylation of imidazopyridines with Togni's reagent as a trifluoromethylating reagent in the presence of inexpensive base K_3PO_4 has been realized at room temperature. An array of trifluoromethylated imidazopyridines with broad