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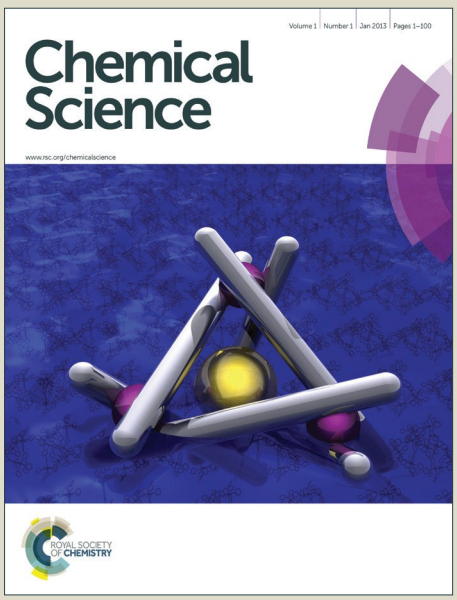

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Cu-Catalyzed Transannulation Reaction of Pyridotriazoles with Terminal Alkynes under Aerobic Conditions: Efficient Synthesis of Indolizines†

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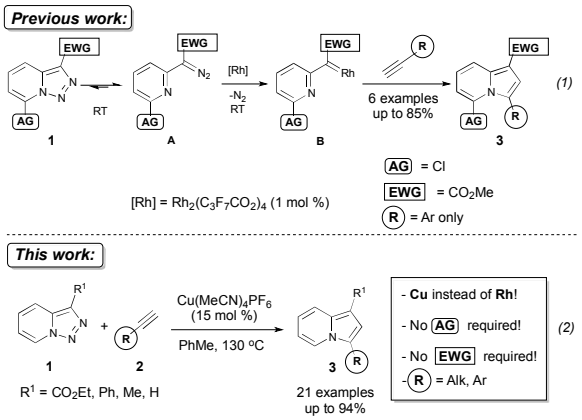
The Cu(I)-catalyzed denitrogenative transannulation reaction of pyridotriazoles with terminal alkynes en route to indolizines was developed. Compared to the previously reported Rh-catalyzed transannulation reaction, this Cu-catalyzed method features aerobic conditions and much broader scope of pyridotriazoles and alkynes.

Transition-metal-catalyzed denitrogenative transannulation of pyridotriazoles represent an efficient method for the synthesis of fused nitrogen-containing heterocycles.[1] This method is based on the ability of pyridotriazole **1** to exist in the equilibrium with diazo-form **A**,[2,3] which can be trapped with Rh(II) to form the reactive pyridyl carbene intermediate **B**, capable to react with terminal alkynes[1a] to produce valuable indolizines **3** (Scheme 1).[4,5] However, this transannulation reaction has several shortcomings.



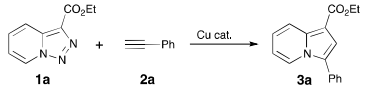
Scheme 1 Metal-catalyzed transannulation reactions of pyridotriazoles with terminal alkynes.

Thus, Cl substituent at C-7 position (AG, activating group) and electronwithdrawing ester group (EWG) at C-3 position of pyridotriazoles were requisite to facilitate the formation of a sufficient amount of an open-form of triazole **A** even at room temperature and subsequently generate indolizines **3**.[2,3,6] In addition, the reaction was limited to aryl alkynes only (eq. 1).[1a]

Herein, we report the first general and efficient Cu-catalyzed transannulation of pyridotriazoles **1** with terminal alkynes **2** to form indolizines **3** (eq. 2). This newly developed method features several important advantages over the previously reported Rh-catalyzed protocol.[1a] Thus, it is highly practical as it employs cheap Cu-catalyst and efficiently operates un-der aerobic conditions. It is also more general demonstrating a much broader reaction scope, as unactivated pyridotriazoles **1** and aliphatic alkynes **2** now became competent reaction partners (eq. 2).

The abovementioned transannulation reaction of pyridotriazoles **1** (eq. 1),[1] as well as the further developed and widely used transannulation reactions of *N*-sulfonyl 1,2,3-triazoles,[7] require the use of Rh-catalyst,[8] which is one of the

Table 1 Optimization of the Cu-transannulation reaction conditions.[a]



Entry	Catalyst, mol %	T (°C)	Yield[b]
1	CuCl, 15%	100	N.R.
2	CuOTf•0.5C_6H_6, 15%	100	38%
3	$Cu(OTf)_2$, 15%	100	25%
4	$Cu(MeCN)_4PF_6$, 15%	100	50%
5[c]	$Cu(MeCN)_4PF_6$, 15%	120	96%
6[c]	$Cu(MeCN)_4PF_6$, 15%	130	99%
7[d,e]	$Cu(MeCN)_4PF_6$, 15%	130	99%
8	No catalyst	100	N.R.
9	$Rh_2(hfb)_4$, 1%	100	N.R.[f]

[a]Triazole (1 equiv), Alkyne (3 equiv), Cu cat. (15 mol %), toluene (1M) in a Wheaton V-vial capped with a mininert syringe valve. [b]GC/MS yields are given. [c]1.2 equiv of alkyne was used. [d]In air with 1.2 equiv of alkyne. [e]Lower catalyst loading led to decreased reaction yields.[11] [f]Polymerization of the alkyne was observed; hfb = heptafluorobutyrate.

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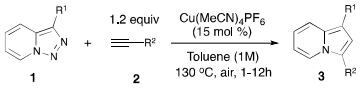
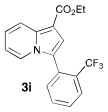
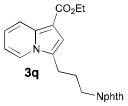
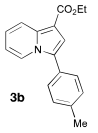
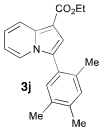
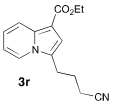
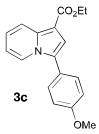
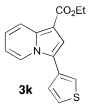
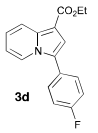
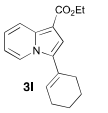
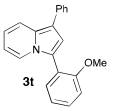
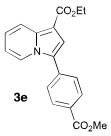
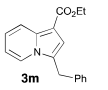
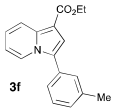
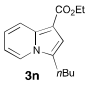
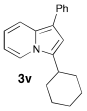
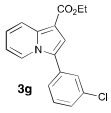
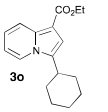
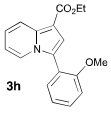
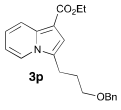
Table 2 Scope of the Cu-catalyzed transannulation reaction of pyridotriazoles with alkynes.[a]



1 2 3

Entry	Product	Yield, %	Entry	Product	Yield, %	Entry	Product	Yield, %
1		70%	9		78%	17		82%
2		74%	10		75%	18		66%
3		65%	11		33%	19		77%
4		70%	12		67%	20		80%
5		48%	13		68%	21		67%
6		57%	14		82%	22		50%
7		60%	15		83%	23		41%
8		94%	16		53%	24		54%

[a] Isolated yields.

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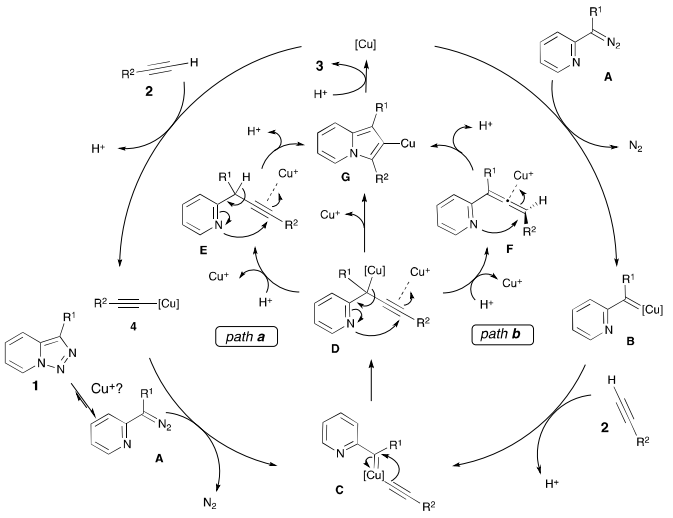
most expensive and rare metals used in catalysis. Naturally, the development of alternative catalysts for transannulation reactions of triazoles would dramatically increase a synthetic applicability of this methodology.[9] Accordingly, aiming at the discovery of a cheaper catalyst and at expanding the scope of transannulation reactions of pyridotriazoles, we turned our attention to potential employment of copper catalysts.[10] To ensure sufficient amounts of an open-form **A** of the unactivated pyridotriazole, we tested the potential transannulation reaction at elevated temperatures.[3] Thus, we tested various copper catalysts in the reaction of unactivated pyridotriazole **1a** with phenylacetylene **2a** (Table 1). While CuCl was found to be inefficient (entry 1), the use of Cu(I) and Cu(II) triflates led to the formation of the corresponding indolizine **3a** in moderate yield (entries 2, 3).[11] Delightfully, more electrophilic $Cu(MeCN)_4PF_6$ catalyst turned out to be even more efficient for the formation of **3a** (entry 4). Finally, after optimization of temperature (entries 5, 6), virtually quantitative yield of **1a** was achieved (entry 7). Moreover, we were pleased to find that this reaction works equally efficient under aerobic conditions (entry 9). As expected, under thermal conditions no reaction occurred (entry 8). Moreover, it was found that $Rh_2(hfb)_4$ is not a capable catalyst for this reaction (entry 9).

Having in hands the optimized conditions, we investigated the scope of this Cu–catalyzed transannulation reaction of pyridotriazoles with terminal alkynes (Table 2). A variety of aryl alkynes bearing electron-neutral, electron withdrawing, and electron donating substituents at *ortho*-, *meta*- and *para*-position produced the corresponding indolizines **3** in high yields upon the reaction with pyridotriazole **1a** (Table 2, entries 1-10).[12] Heteroaromatic alkynes, such as 3-thienyl acetylene, and enyne led to indolizines **3k-l** in reasonable yields (entries 11,12). We were pleased to find that in contrast to the previously reported Rh-catalyzed reaction, aliphatic alkynes were also competent reactants. Thus, benzyl-, *n*-butyl, and *c*-hexyl acetylenes reacted smoothly to produce the corresponding indolizines in good yields (entries 13-15). To our delight, functional groups including benzyloxy- and *N*-phthalimido were perfectly tolerated under the reaction conditions (entries 16,17). Moreover, while our group previously reported the Rh-catalyzed transannulation reaction of pyridotriazoles with nitriles,[1a] the Cu-catalyzed transannulation showed strong preference for the alkyne- over the nitrile group. Thus, the reaction of pyridotriazole **1a** with 5-hexynenitrile furnished indolizine **3r** with nitrile group stayed intact (entry 18). Notably, pyridotriazoles which did not contain electron withdrawing groups at C-3 position were found to be reactive substrates as well. Hence, the indolizines derived from 3-phenyl and 3-methyl pyridotriazoles were produced in reasonable yields (entries 19-23). Remarkably, even a non-substituted pyridotriazole (R^1 = H) reacted with phenylacetylene to form indolizine **3x** in moderate yield. Noteworthy, trialkylsilyl-substituted alkynes were either unstable (TMS, TES) or stayed intact (TIPS) under the reaction conditions.

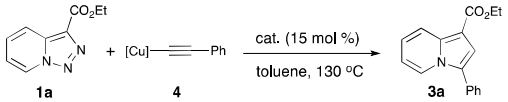
We envision two alternative pathways for this Cu-catalyzed transannulation reaction (Scheme 2). First, the copper catalyst can react with the terminal alkyne **2** to form copper acetylide **4**, which would react with α-imino diazo compound **A** to generate the Cu-carbene complex **C** (path **a**). Alternatively, the copper carbene **C** can be formed via the reaction of alkyne **2** with copper carbene **B**, which is produced from the diazo compound **A** and Cu-catalyst (path **b**). Next, migratory insertion of the alkynyl group at the carbene C-atom of **C** would form the propargyl intermediate **D**.[13] The latter would undergo cyclization via a nucleophilic attack of the pyridine nitrogen at the triple bond activated by electrophilic Cu-species[14] to produce a triazolyl-copper intermediate **G**. Also, one cannot exclude formation of propargylic (**E**) or allenic (**F**) intermediates upon protiodemetalation of **D**. Cycloisomerization of **E** and **F** would form intermediate **G**.[15] A subsequent protiodemetalation of **G** would lead to the indolizine **3**.



Scheme 2 Proposed mechanism for the Cu-catalyzed transannulation reaction of pyridotriazoles with alkynes.

In order to verify a potential involvement of the Cu-acetylide **4** in this transformation, we performed several test-experiments. First, it was found that the reaction of pyridotriazole **1a** with **4** did not produce indolizine **3a** (Scheme

3, entry 1). However, the reaction of **1a** with **4** can be catalyzed by both $Cu(MeCN)_4PF_6$ (entry 2)[16] and $HPF_{6(aq.)}$ (entry 3). This observation suggests that the presence of electrophilic Cu-species is required to activate the alkyne during the cyclization of **D** into **G**,[17,18] and potentially to shift the equilibrium of the pyridotriazole towards the reactive α-imino diazo compound **A**.[19] Although more detailed studies are required to elucidate



Entry	cat.	yield of 3a
1	none	No reaction
2	$Cu(MeCN)_4PF_6$	42%
3	HPF_6 (55% in H_2O)	51%

Scheme 3 The reactions of Cu-acetylide with triazole **1a**.

the exact mechanism for this transformation, based on literature data[20,21] and the mentioned above observations, it is believed that the reaction most likely proceeds via the path **a** (Scheme 2).

Conclusions

We have developed practical and efficient copper-catalyzed denitrogenative transannulation reaction of pyridotriazoles with terminal alkynes into indolizines. Compared to the known Rh-catalyzed transannulation reaction, this newly developed method features not only the use of cheap Cu-catalyst and aerobic conditions, but also much broader scope of multisubstituted indolizines that now can be accessed from unactivated pyridotriazoles and diverse terminal alkynes.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization for new compounds are provided. See DOI: 10.1039/b000000x/

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16 Apparently, in this case, intermediate **G** was quenched by an eventual proton source, which was supported by deuterium labeling studies. See Electronic Supporting Information for details.

17 It is believed that HPF_6 liberates catalytic amounts of electrophilic Cu-species by protonation of copper acetylide **4** (Scheme 3, entry 3).

18 For selected recent reviews on the formation of heterocycles via attack of nucleophiles at the metal-activated triple bond, see: (a) B. Godoi, R. E. Schumacher and G. Zeni, *Chem. Rev*., 2011, **111**, 2937; (b) A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084, and references therein. For a selected recent example, see: (c) C. He, J. Hao, H. Xu, Y. Mo, H. Liu, J. Han and A. Lei, *Chem. Commun.*, 2012, **48**, 11073.

19 B. Chattopadhyay and V. Gevorgyan, *Org. Lett.*, 2011, **13**, 3746.

20 For the Cu-catalyzed reactions of diazo compounds with alkynes, see: (a) A. Suárez and G. Fu, *Angew. Chem., Int. Ed.*, 2004, **43**, 3580; (b) L. Zhou, J. Ma, Y. Zhang and J. Wang, *Tetrahedron Lett.*, 2011, **52**, 5484; (c) Q. Xiao, Y. Xia, H. Li, Y. Zhamg and J. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 1114; (d) L. Zhou, Y. Shi, Q. Xiao, Y. Liu, F. Ye, Y. Zhang and J. Wang, *Org. Lett.*, 2011, **13**, 968; (e) F. Ye, Y. Shi, L. Zhou, Q. Xiao, Y. Zhang and J. Wang, *Org. Lett.*, 2011, **13**, 5020; (f) F. Ye, X. Ma, Q. Xiao, H. Li, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2012, **134**, 5742; (g) F. Ye, M. L. Hossain, Y. Xu, X. Ma, Q. Xiao, Y. Zhang and J. Wang, *Chem.–Asian J.*, 2013, **8**, 1404; (h) M. L. Hossain, F. Ye, Y. Zhang, J. Wang, *Tetrahedron*, 2014, **70**, 6957; (i) M. L. Hossain, F. Ye, Z. Liu, Y. Xia, L. Zhou, Y. Zhang and J. Wang, *J. Org. Chem.*, 2014, **79**, 8689.

21 For computational studies of the Cu-catalyzed cross-coupling reaction of diazo compounds with alkynes, see: T. Wang, M. Wang, S. Fang and J. Liu, *Organometallics*, 2014, **33**, 3941.