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Cu-catalyzed transannulation reaction of pyridotriazoles with terminal alkynes under aerobic conditions: efficient synthesis of indolizines†

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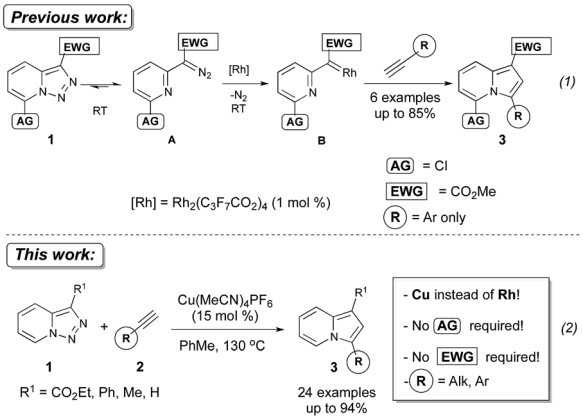
A Cu(I)-catalyzed denitrogenative transannulation reaction of pyridotriazoles with terminal alkynes en route to indolizines was developed. Compared to the previously reported Rh-catalyzed transannulation reaction, this Cu-catalyzed method features aerobic conditions and a much broader scope of pyridotriazoles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

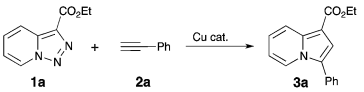
The transition-metal-catalyzed denitrogenative transannulation of pyridotriazoles represents an efficient method for the synthesis of fused nitrogen-containing heterocycles.[1] This method is based on the ability of pyridotriazole to exist in an equilibrium with diazo-form **A**,[2,3] which can be trapped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

Thus, a Cl substituent at the C-7 position (AG, activating group) and an electron withdrawing ester group (EWG) at the C-3 position of the pyridotriazoles were requisite to facilitate the formation of a sufficient amount of the 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 (eqn (1)).[1a] Herein, we report the first general and efficient Cu-catalyzed transannulation of pyridotriazoles **1** with terminal alkynes **2** to form indolizines **3** (eqn (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 a cheap Cu-catalyst and efficiently operates under aerobic conditions. It is also more general demonstrating a much broader reaction scope, as unactivated pyridotriazoles **1** and aliphatic alkynes **2** now become competent reaction partners (eqn (2)).



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

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 (1 M) 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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† Electronic supplementary information (ESI) available: Experimental procedures and characterization for new compounds are provided. See DOI: 10.1039/c4sc03358b

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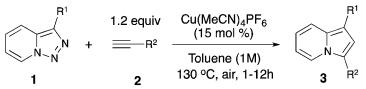
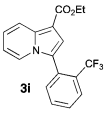
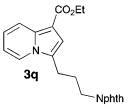
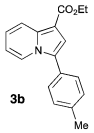
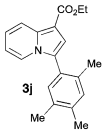
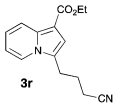
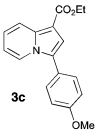
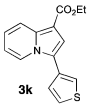
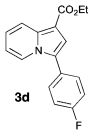
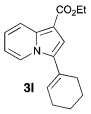
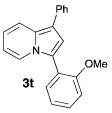
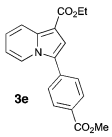
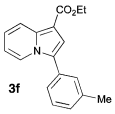
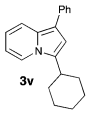
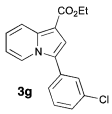
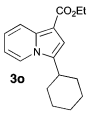
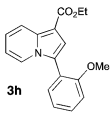
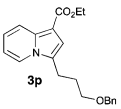
Table 2 Scope of the Cu-catalyzed transannulation reaction of pyridotriazoles with alkynes[a]



Entry	Product	Yield, %	Entry	Product	Yield, %	Entry	Product	Yield, %
1	3a	70	9	 3i	78	17	 3q	82
2	 3b	74	10	 3j	75	18	 3r	66
3	 3c	65	11	 3k	33	19	3s	77
4	 3d	70	12	 3l	67	20	 3t	80
5	 3e	48	13	3m	68	21	3u	67
6	 3f	57	14	3n	82	22	 3v	50
7	 3g	60	15	 3o	83	23	3w	41
8	 3h	94	16	 3p	53	24	3x	54

[a] Isolated yields.

The above-mentioned transannulation reaction of pyridotriazoles **1** (eqn (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 a Rh-catalyst,[8] which is one of the most expensive and rare metals used in catalysis. Naturally, the development of alternative catalysts for transannulation reactions of triazoles would dramatically increase the 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 the potential employment of copper catalysts.[10] To ensure sufficient amounts of the 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 yields (entries 2 and 3).[11] Delightfully, the more electrophilic $Cu(MeCN)_4PF_6$ catalyst turned out to be even more efficient in the formation of **3a** (entry 4). Finally, after optimization of the temperature (entries 5, 6), a virtually quantitative yield of **3a** was achieved (entry 6). Moreover, we were pleased to find that this reaction works equally efficiently under aerobic conditions

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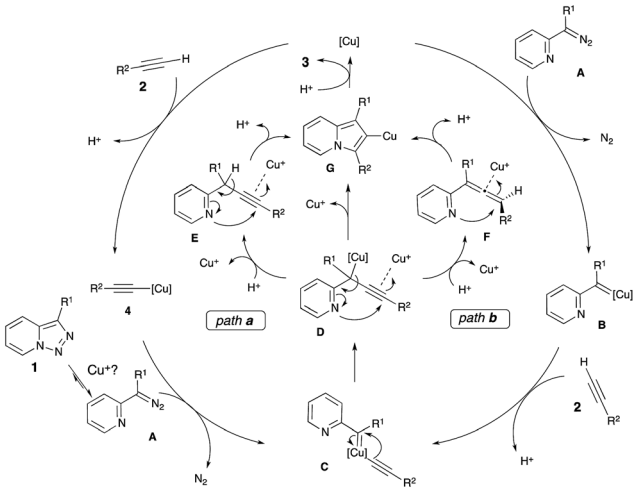
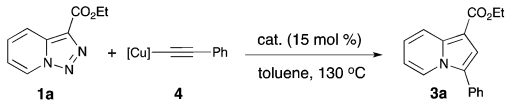


Scheme 2 Proposed mechanism for the Cu-catalyzed transannulation reaction of pyridotriazoles with alkynes.



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 Reactions of the Cu-acetylide with triazole **1a**.

(entry 7). 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 the optimized conditions in hand, 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*-positions produced the corresponding indolizines **3** in high yields upon reaction with pyridotriazole **1a** (Table 2, entries 1–10).[12] Heteroaromatic alkynes such as 3-thienyl acetylene and enyne led to the indolizines **3k**, **l** in reasonable yields (entries 11 and 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 and 17). Moreover, while our group previously reported the Rh-catalyzed transannulation reaction of pyridotriazoles with nitriles,[1a] the Cu-catalyzed transannulation showed a strong preference for the alkyne over the nitrile group. Thus, the reaction of pyridotriazole **1a** with 5-hexynenitrile furnished indolizine **3r** with the nitrile group staying intact (entry 18). Notably, pyridotriazoles which did not contain electron withdrawing groups at the 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 a moderate yield. Noteworthily, trialkylsilyl-substituted alkynes were either unstable (TMS, TES) or stayed intact (TIPS) under the reaction conditions.

We envisioned 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 the 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 the 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 the electrophilic Cu-species[14] to produce the triazolyl-copper intermediate **G**. Also, one cannot exclude the 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**.

In order to verify a potential involvement of 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 an 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 the exact mechanism of this transformation, based on literature data[20,21] and the above-mentioned observations, it is believed that the reaction most likely proceeds *via* path **a** (Scheme 2).

Conclusions

We have developed a 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 a cheap Cu-catalyst and aerobic conditions, but also a much broader scope of multi-substituted indolizines that now can be accessed from unactivated pyridotriazoles and diverse terminal alkynes.

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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 ESI† for details.

17 It is believed that HPF_6 liberates catalytic amounts of an 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 and 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.