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

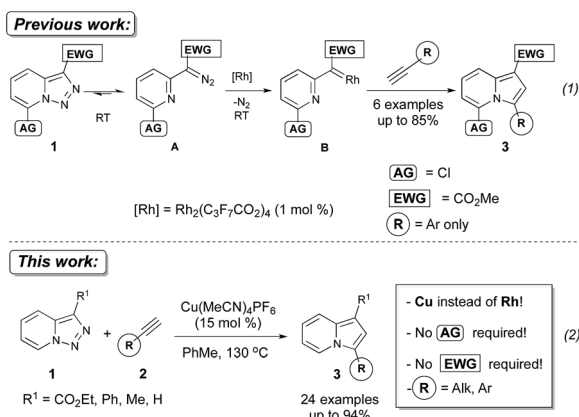
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A Cu(I)-catalyzed denitrogenative transannulation reaction of pyridotriazoles with terminal alkynes en route to indolizines was developed. Compared to the previously reported Rh-catalyzed transannulation reaction, this Cu-catalyzed method features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

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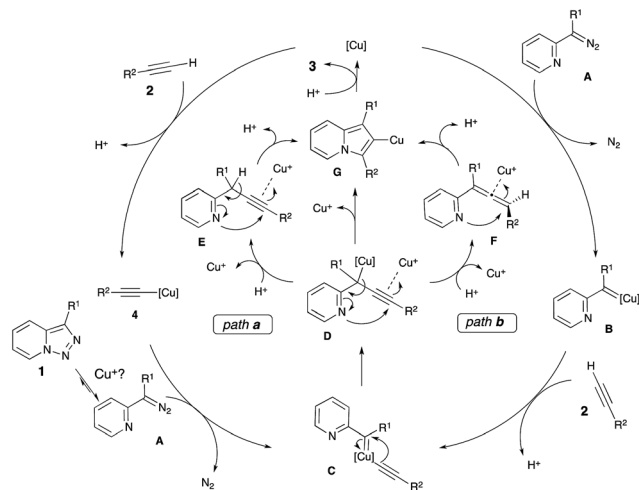
† Electronic supplementary information (ESI) available: Experimental procedures and characterization for new compounds are provided. See DOI: 10.1039/c4sc03358b

Table 1 Optimization of the Cu-transannulation reaction conditions^a

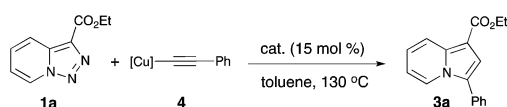
Entry	Catalyst, mol%	T (°C)	Yield ^b
1	CuCl, 15%	100	N.R.
2	CuOTf·0.5C ₆ H ₆ , 15%	100	38%
3	Cu(OTf) ₂ , 15%	100	25%
4	Cu(MeCN) ₄ PF ₆ , 15%	100	50%
5 ^c	Cu(MeCN) ₄ PF ₆ , 15%	120	96%
6 ^c	Cu(MeCN) ₄ PF ₆ , 15%	130	99%
7 ^{d,e}	Cu(MeCN) ₄ PF ₆ , 15%	130	99%
8	No catalyst	100	N.R.
9	Rh ₂ (hfb) ₄ , 1%	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.





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) ₄ PF ₆	42%
3	HPF ₆ (55% in H ₂ O)	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 $\text{Rh}_2(\text{hfb})_4$ 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 ($\text{R}^1 = \text{H}$) reacted with phenylacetylene to form indolizine 3x in a moderate yield. Noteworthy, 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-species¹⁴ to produce the triazolyl-copper intermediate G. Also, one cannot exclude the formation of propargylic (E) or allenic (F) intermediates upon protodemetalation of D. Cycloisomerization of E and F would form intermediate G.¹⁵ A subsequent protodemetalation 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 $\text{Cu}(\text{MeCN})_4\text{PF}_6$ (entry 2)¹⁶ and $\text{HPF}_6(\text{aq.})$ (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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