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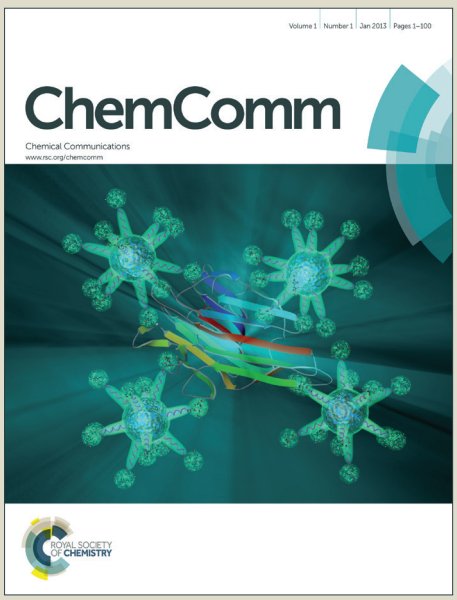

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Cu-Catalyzed Transannulation Reaction of Pyridotriazoles: General Access to Fused Polycyclic Indolizines

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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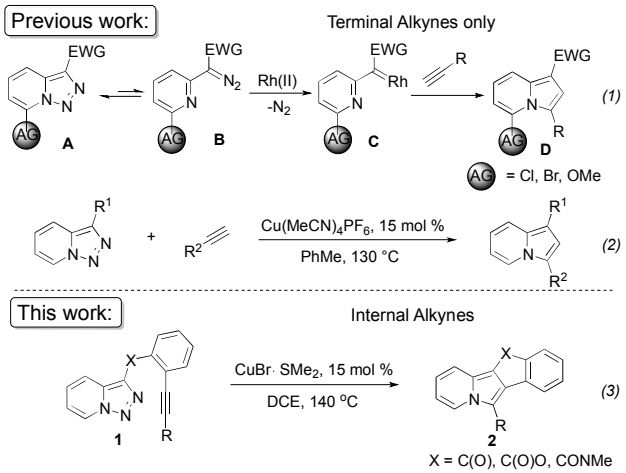
An efficient intramolecular transannulation reaction of pyridotriazoles with internal alkynes en route to various fused polycyclic indolizines has been developed. For the first time it was shown that in addition to the well-established Rh- or Cu-catalyzed carbene mechanism, the transannulation reaction could also follow a Lewis acid-mediated electrophilic pathway.

Transition metal-catalyzed denitrogenative transannulation of triazoles[1-4] represents a powerful tool for synthesis of nitrogen-containing heterocycles. Previously, our group developed the transannulation reaction of pyridotriazoles proceeding via the reaction of rhodium carbene intermediate **C** with alkynes.[2a] It was shown that Cl, Br, or OMe substituents at C7 (AG = activating group) were requisite for efficient formation of the cyclization product (eq. 1). Recently, we reported the Cu-catalyzed version of this reaction, which addressed the above mentioned limitations (eq. 2).[2d] Despite a much broader reaction scope and employment of cheap copper catalyst, this transformation was still limited to terminal alkynes, which precluded the possibility of an intramolecular transannulation reaction toward valuable fused *N*-heterocycles.[5] Herein, we report the first general and efficient Cu-catalyzed intramolecular transannulation of pyridotriazoles with tethered internal alkynes to produce a wide range of fused polycyclic indolizines (eq. 3).

Aiming at the development of efficient intramolecular transannulation reaction, an extensive screening of various transition metal catalysts was performed.[6] It was found that this reaction could efficiently be accomplished in the present of Cu-catalyst. Thus, pyridotriazole **1aa** was converted to the desired tetracyclic δ-valerolactone-fused indolizine product in 83% yield employing 15 mol % of CuBr•SMe in dichloroethane (Table 1, entry 1). This transformation appeared to be quite general with respect to arylalkyne moiety (entries 1-10). Thus, a variety of tethered internal arylalkynes bearing electron-neutral, electron-withdrawing, and electron-donating substituents at *ortho*-, *meta*- and *para*-positions participated well in this transannulation reaction toward fused indolizine **2**. It was also found that this reaction is not limited to aryl alkynes. Thus, alkenyl (**ak**), as well as alkyl (**al**) alkynes, could also be utilized in this transformation to produce the corresponding indolizines. Moreover, an electron-deficient alkyne **2am** was found to be a competent substrate, as well. Notably, the reaction of alkynyl pyridotriazole bearing a silyl substituent proceeded smoothly to afford 3-TBS-indolizine **2an** in good yield, which upon desilylation offers an access to C3-nonsubstituted indolizine.



Scheme 1 Transannulation reactions of pyridotriazoles.

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†Electronic Supplementary Information (ESI) available: Experimental procedures and characterization for new compounds are provided.
See DOI: 10.1039/x0xx00000x

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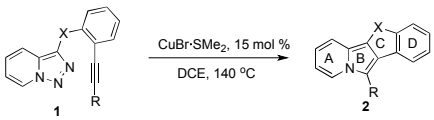
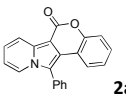
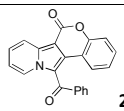
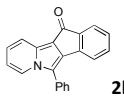
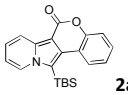
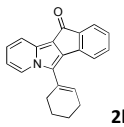
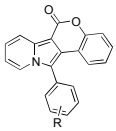
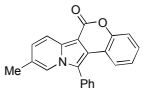
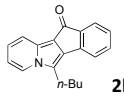
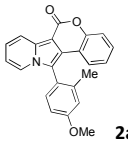
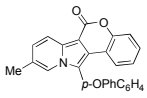
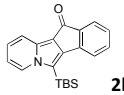
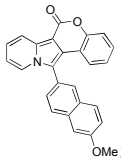
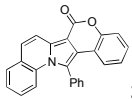
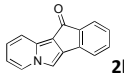
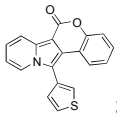
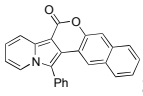
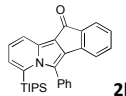
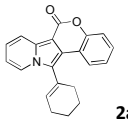
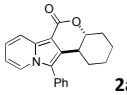
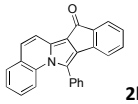
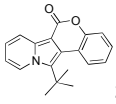
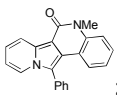
Table 1 Scope of copper catalyzed transannulation reaction of pyridotriazoles. – synthesis of 3-5 cyclic Indolizines.[a,b]



Entry	Product	Yield, %	Entry	Product	Yield, %	Entry	Product	Yield, %
1	 **2aa**	83	13	 **2am**	50	21	 **2ba**	91
2	**2ab**, R = *p*-Me	75						
3	**2ac**, R = *p*-OMe	85	14	 **2an**	67[c]	22	 **2bb**	87
4	**2ad**, R = *p*-CF_3	80						
5	 **2ae**, R = *p*-F	73						
6	**2af**, R = *p*-C(O)Me	78	15	 **2ao**	78	23	 **2bc**	73
7	**2ag**, R = *m*-Cl	58						
8	 **2ah**	76	16	 **2ap**	71	24	 **2bd**	90
9	 **2ai**	81	17	 **2aq**	60[d]	25	 **2be**	23
10	 **2aj**	64	18	 **2ar**	68	26	 **2bf**	95
11	 **2ak**	47	19	 **2as**	60	27	 **2bg**	85
12	 **2al**	41	20	 **2at**	52	28	 **2bh**	40 (84[e])

[a] Conditions: pyridotriazole **1** (0.20 mmol) and CuBr•SMe_2 (15 mol %) were heated in 2 mL of dry DCE at 140 °C until completion (in general, 24 h for entries 1-20, 27; 2 h for entries 21-26, 28). [b] Isolated yields. [c] 5 mol % $[Rh^*CpCl_2]_2$ in 2 mL of dry mesitylene at 140 °C. [d] Performed at 180 °C in PhCl. [e] 1.0 mol % $Rh_2(esp)_2$ in 2 mL of dry Toluene at 120 °C.

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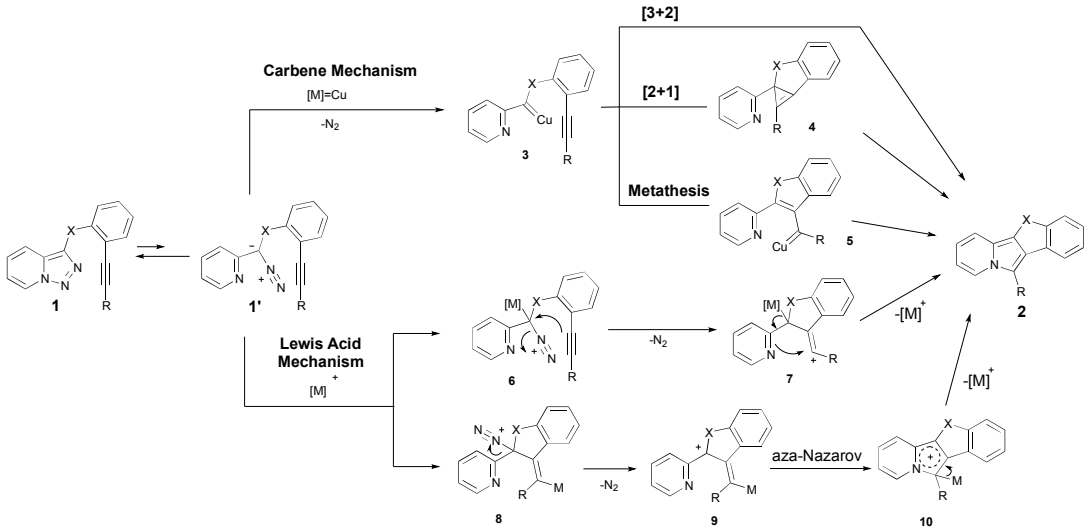
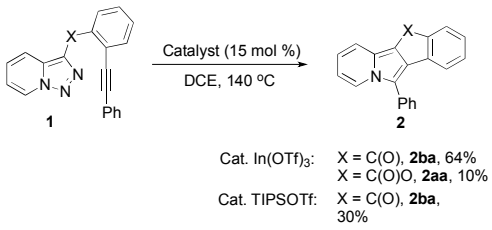
Next, the scope of rings A and D was examined (Table 1, entries 15-19). To our delight, substituents at ring A (**2ao**, **2ap**) were tolerated under these reaction conditions, which for the first time, enabled the synthesis of C6-substituted indolizines in a selective manner.[7] Notably, the reaction proceeded smoothly to construct pentacyclic fused systems **2aq** and **2ar**. In addition, tetracyclic indolizine with non-aromatic ring D (**2as**) could also be produced in good yield. Moreover, pyridotriazole processing an amide tether underwent transannulation reaction to afford the corresponding lactam-fused product **2at**, albeit in a moderate yield.[8]

After developing the transannulation reaction to form 6-membered C ring, we turned our attention to the construction of a 5-membered ring (Table 1, entries 21-28). We were pleased to find that, aryl (**2ba**), alkenyl (**2bb**), alkyl (**2bc**) and silyl (**2bd**) group at the alkyne moiety were all perfectly compatible under these reaction conditions to efficiently afford the corresponding indanone-fused indolizines. Surprisingly, terminal alkyne could also be utilized to produce **2be**, although in a low yield. Remarkably, 1,3-strained C3,5-disubstituted fused indolizines **2bf**, **2bg**[9] were efficiently constructed by this method. In addition to the above-mentioned indanone-fused indolizines, a tricyclic γ-butyrolactone-fused indolizine **2bh** could also be obtained albeit in moderate yield.



Scheme 2 Proposed mechanism for the copper catalyzed transannulation reaction of pyridotriazoles.



Scheme 3. Lewis acid - catalyzed transannulation reaction of pyridotriazoles.

Naturally, after establishing the scope of this intramolecular transannulation reaction, we were eager to clarify the reaction pathway (Scheme 2). Apparently, the pyridotriazole **1** exists in equilibrium with the diazo form **1'**, which can react with copper catalyst to generate copper carbene intermediate **3**.[10] Next, a direct [3+2] cyclization would lead to the indolizine product **2**.[2a] Alternatively, a [2+1] cycloaddition would produce a cyclopropene intermediate **4**, which would then isomerize into indolizine **2**.[2b] Also, one cannot exclude the carbene-alkyne metathesis pathway[3m] involving a newly formed copper carbene intermediate **5**. During optimization, we unexpectedly found that Lewis acids, such as $In(OTf)_3$ or TIPSOTf, could also catalyze this transformation (Scheme 3). Based on this observation, we envisioned an alternative Lewis acid activation pathway, according to which, the diazo form **1'** can be metallated to produced intermediate **6**, which would then undergo a denitrogenative cyclization to form a cationic intermediate **7**. A subsequent cyclization and a metal loss of the latter would form the fused indolizine product **2**. Also, the reaction could be triggered by a nucleophilic attack of the diazo carbon at the Lewis acid-activated triple bond to form intermediate **8**. The latter, upon exclusion of dinitrogen, aza-Nazarov cyclization,[11] and a metal loss, would be converted into indolizine **2**.

In summary, we developed an efficient copper catalyzed intramolecular transannulation reaction of pyridotriazoles with internal alkynes. This first intramolecular transannulation reaction of pyridotriazoles provides expeditious and general access to various tri-, tetra-, and pentacyclic fused indolizines, including C6-substituted fused indolizines that cannot be synthesized selectively via known cycloaddition methods. For the first time it was shown that this reaction could also be triggered by Lewis acids.

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Acknowledgements

The support of the National Science Foundation (CHE-1362541) is gratefully acknowledged.

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6 See Supporting Information for details.

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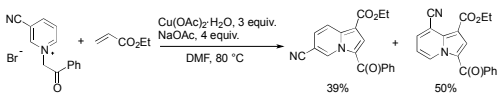
However, cyclization of *meta*-substituted pyridinium salt is not selective.[7b]



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DOI: 10.1039/C5CC07598J

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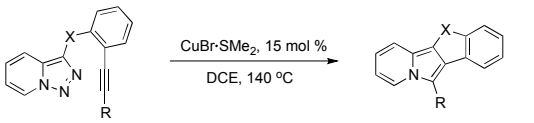

X = C(O), C(O)O, CONMe

An efficient intramolecular transannulation reaction of pyridotriazoles with internal alkynes en route to various fused polycyclic indolizines has been developed. For the first time it was shown that in addition to the well-established Rh- or Cu-catalyzed carbene mechanism, the transannulation reaction could also follow a Lewis acid-mediated electrophilic pathway.