The transition-metal-catalyzed denitrogenative transannulation of pyridotriazoles represents an efficient method for the synthesis of fused nitrogen-containing heterocycles. This method is based on the ability of pyridotriazole to exist in an equilibrium with diazo-form A, which can be trapped with Rh(II) to form the reactive pyridyl carbene intermediate B, capable of reacting with terminal alkynes to produce valuable indolizines (Scheme 1). 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. In addition, the reaction was limited to aryl alkynes only (eqn (1)). 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. 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 and aliphatic alkynes now become competent reaction partners (eqn (2)).
The above-mentioned transannulation reaction of pyrido-
triazoles \(1\) (eqn (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 reac-
tions 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.

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)\(_4\)PF\(_6\) catalyst turned out to be even more efficient in
the formation of \(3a\) (entry 4). Finally, a further 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.

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

\(^{a}\) Isolated yields.
upon reaction with pyridotriazole triazoles produced the corresponding indolizines. Thus, the reaction of pyridotriazole with the alkyne over the nitrile group. Cu-catalyzed transannulation showed a strong preference for electron donating substituents at alkynes bearing electron-neutral, electron withdrawing and heteroaromatic alkyynes such as 3-thienyl acetylene and enyne. 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 alkyynes bearing electron-neutral, electron withdrawing and electron donating substituents at ortho-, meta- and para-positions produced the corresponding indolizines in high yields upon reaction with pyridotriazole 1a (Table 2, entries 1–10). Heteroaromatic alkyynes 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 alkyynes 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, 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). Interestingly, even a non-substituted pyridotriazole (R1 = H) reacted with phenylacetylene to form indolizine 3x in a moderate yield. Noteworthily, trialkysilyl-substituted alkyynes 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 acetylde 4, which would react with the z-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 alkyne group at the carbene C-atom of C would form the propargyl intermediate D. The latter would undergo cyclization via a nucleophilic attack of the pyridine nitrogen at the triple bond activated by the electrophilic Cu-species to produce the triazolyl-copper intermediate G. Also, one cannot exclude the formation of propargyl (E) or allenic (F) intermediates upon protiode metallation of D. Cycloisomerization of E and F would form intermediate G. A subsequent protiode metallation of G would lead to the indolizine 3.

In order to verify a potential involvement of Cu-acetylde 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)2PF6 (entry 2) and HF6[NEt4] (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, and potentially to shift the equilibrium of the pyridotriazole towards the reactive z-imino diazo compound A. Although more detailed studies are required to elucidate the exact mechanism of this transformation, based on literature data 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.

Acknowledgements

The support of the National Institutes of Health (GM 64444) and National Science Foundation (CHE-1401722) is gratefully acknowledged. We also thank Dr. S. Chuprakov for initial experiments.
Notes and references


3 For a recent review on rearrangement of 1,2,3-triazoles, see: V. Bakulev, W. Dehaen and T. B. Beryozkina, Thermal Rearrangements and Transformations of 1,2,3-Triazoles, Top. Heterocycl. Chem., 2015, 40, 1.

4 For selected recent reviews on bioactive indolizines, see: (a) V. Sharma and V. Kumar, Med. Chem. Res., 2014, 23, 3593; (b) G. S. Singh and E. E. Mmatli, J. Org. Chem., 2011, 46, 5237.


11 See ESI† for detailed optimization studies.

12 The 7-Cl-substituted isomer of 1a produced a complex mixture of products even at a lower temperature.

13 For a review on the metal carbene migratory insertion, see: Y. Xia, Y. Zhang and J. Wang, ACS Catal., 2013, 3, 2586.

14 For activation of copper acetylide with electrophilic copper species, see: B. T. Worrell, J. A. Malik and V. V. Fokin, Science, 2013, 340, 457.


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 HPF6 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.

