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# Rh-Catalyzed Transannulation of Pyridotriazoles with Alkynes and Nitriles**

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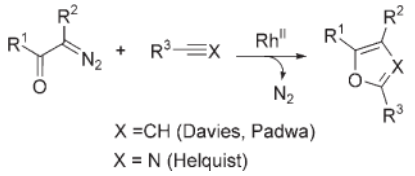
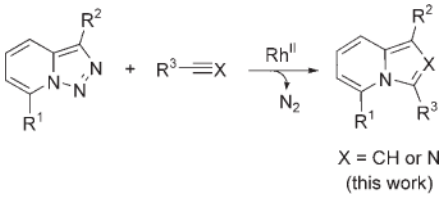
**Keywords**

annulation; nitrogen heterocycles; rhodium; synthetic methods; triazoles

Transition-metal-catalyzed annulations are widely used in the synthesis of heterocyclic compounds.[1] One of the most efficient methods for the construction of five-membered oxygen-containing heterocycles involves the annulation of diazocarbonyl compounds with alkynes and nitriles. Thus, Davies et al.[2] and Padwa et al.[3] have employed this method[4] for the synthesis of furans (X = CH), and Helquist et al.[5] for the preparation of oxazoles (X = N) [Eq. (1)]. In contrast, analogous transformations of α-imino diazo compounds, which may lead to the formation of pyrrole and imidazole rings, are unknown. Herein we report an efficient, direct, Rh-catalyzed transannulation of pyridotriazoles with alkynes and nitriles that leads to indolizines (X= CH) and imidazopyridines (X = N), respectively [Eq. (2)].




(1)




(2)

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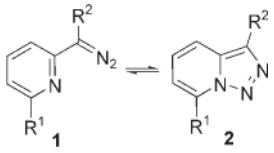
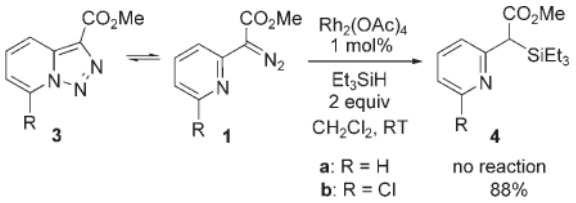
It has been shown that 2-pyridyl diazo compounds **1**[6] transform into their cyclic triazole form **2**[7] upon storage [Eq. (3)], and it is also known that some of these cyclic triazoles can still undergo transformations that are characteristic of diazo compounds.[8] This phenomenon has been attributed to the closed/open form equilibrium of N-fused triazoles in solution,[9] which can produce trace to significant amounts of **1**. The position of this equilibrium depends on the temperature and the substitution pattern of the triazole.[9b] Thus, introduction of a halogen substituent at C7 ($R^1$ = Cl) shifts the equilibrium to the left, which has been explained in terms of nonbonding repulsion between the lone pair of the halogen and that of the nitrogen in the *peri* position.[10]



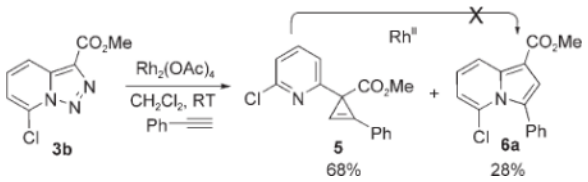
(3)

To evaluate the feasibility of using triazoles as precursors of Rh carbenoids we investigated the reaction of triazoles **3a** and **3b** with triethylsilane in the presence of a catalytic amount of rhodium(II) acetate, which is a method developed by Doyle and coworkers[11] for the efficient trapping of Rh carbenoids [Eq. (4)]. Not surprisingly, pyridotriazoles **3a** and **3b** behave differently under these reaction conditions. Thus, while the 7-H derivative **3a** remains unaffected, the 7-chloro-substituted compound **3b** is smoothly converted into **4**, which is the product of carbenoid insertion into the Si–H bond. These experiments clearly indicate that 7-halo-substituted pyridotriazoles can indeed serve as convenient precursors of Rh carbenoids.




(4)

Next, to test our hypothesis regarding the annulation of α-imino diazo compounds with alkynes to form a pyrrole ring, we treated triazole **3b** with phenylacetylene in the presence of rhodium(II) acetate. This reaction proceeded smoothly to produce a mixture of cyclopropene **5** and indolizine **6a** with yields of 68% and 28% of isolated product, respectively [Eq. (5)]. Surprisingly, cyclopropene **5** does not undergo further isomerization into indolizine **6a** under these reaction conditions.[12] The ratio of these products remained constant throughout the course of the reaction, thereby suggesting an independent path for the formation of **6a**.




(5)

We found, however, that the selectivity of the transannulation (**6** over **5**) could be dramatically improved by using rhodium(II) heptafluorobutyrate as catalyst.[13] Thus, transannulation of **3b** with a series of aryl and alkenyl alkynes[14] proceeded highly chemoselectively (90:10 to 95:5 vs. cyclopropene) to produce indolizines **6**[15] in good yields (Table 1). Electron-rich, electron-deficient, and sterically hindered aryl alkynes were nearly equally effective in this reaction.

Inspired by the successful formation of an N-fused pyrrole ring from the transannulation of triazoles with alkynes, we examined the formation of an N-fused imidazole ring in the reaction of **3** with nitriles and found that pyridotriazoles **3** react smoothly with a variety of aryl, alkyl, and alkenyl nitriles in the presence of $Rh_2(OAc)_4$ (1 mol%) in toluene at 60°C (Table 2) to afford N-fused imidazopyridines **7** in reasonable to high yields.

Both 3-carbomethoxy-(Table 2, entries 1–9) and 3-aryl-(Table 2, entry 10) pyridotriazoles are equally efficient in this reaction. Moreover, 7-bromo-(Table 2, entry 11) and even 7-methoxy-substituted (Table 2, entry 12) triazoles proved to be good substrates for this transannulation reaction.

We propose the following mechanism for this novel Rh-catalyzed transformation (Scheme 1). First, pyridotriazole **3** undergoes closed/open form equilibrium[9] to produce small amounts of diazo compound **1** which, upon reaction with rhodium(II) carboxylate, generates the Rh-carbenoid species **I**. A direct nucleophilic attack[18] of alkyne or nitrile **8** on species **I** produces ylide species **II**, according to path A, which then cyclizes to form **6** or **7** via cyclic zwitterion **III**. Alternatively (path B), [2+2] cycloaddition of **I** and **8** leads to metallacyclobutene **IV**, which can also be formed by cyclization of **II**.[19] Rhodacycle **IV** then undergoes metathesis to produce Rh carbenoid **V** which, upon 6π-electrocyclization and subsequent reductive elimination, furnishes product **6** or **7**. [2+1] Cycloaddition of **I** with **8** (path C) accounts for the formation of cyclopropene **5** in the presence of rhodium(II) acetate [see Eq. (5)]. As discussed above, **5** does not transform into heterocycle **6** under these reaction conditions.[12]

In summary, we have developed an efficient Rh-catalyzed transannulation of pyridotriazoles for the formation of pyrrolo- and imidazopyridines, which are important fused heterocyclic scaffolds.[20] We have also demonstrated that some of these pyridotriazoles can serve as stable[13] and convenient[21] precursors of Rh carbenoids.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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12. For a related transformation of 3-carbonyl cyclopropenes into furans, see refs. [2a] and [3a].
13. See the Supporting Information for details.
14. The use of aliphatic alkynes resulted in sluggish and incomplete reactions.
15. Halo-substituted N-fused heterocycles can be further functionalized by cross-coupling reactions.[16] We have also found that the chloride in **6a** can be quantitatively removed by treatment with $PdCl_2/HSiEt_3$.[17]
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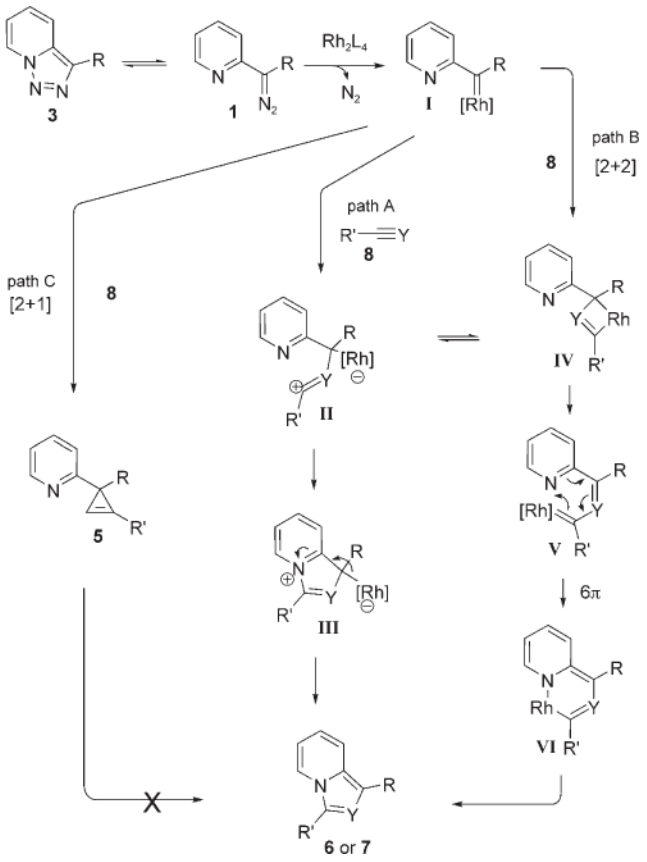
21. The use of **3** does not require special slow-addition techniques as the concentration of **1** in the reaction mixture is always low.[9]

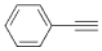
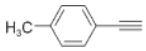
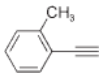
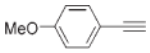
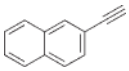
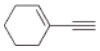
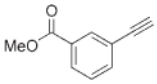



**Scheme 1.**

Plausible mechanisms for the Rh-catalyzed transannulation of pyridotriazoles with alkynes and nitriles. Y=N, CR″.

## Table 1

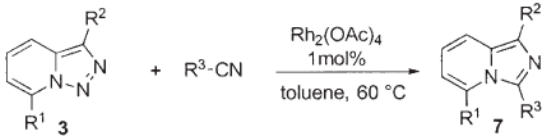
Rhodium(II)-catalyzed transannulation of triazole **3b** with alkynes.

| Entry | Alkyne | Product | Yield [%][a] |
|---|---|---|---|
| 1 |  | **6a** | 78 |
| 2 |  | **6b** | 80 |
| 3 |  | **6c** | 73 |
| 4 |  | **6d** | 85 |
| 5 |  | **6e** | 70 |
| 6 |  | **6f** | 65 |
| 7 |  | **6g** | 57 |

[a]Yield of isolated product. Indolizines **6** were accompanied by 5–10% of the corresponding cyclopropenes **5**; these compounds were readily separable by column chromatography.

**Table 2**

Rhodium(II)-catalyzed transannulation of triazoles with nitriles.




| Entry | $R^1$ | $R^2$ | Triazole | $R^3$ | Product | Yield [%][a] |
|---|---|---|---|---|---|---|
| 1 | Cl | $CO_2Me$ | **3b** | *p*-Tol | **7a** | 89 |
| 2 | Cl | $CO_2Me$ | **3b** | Ph | **7b** | 83 |
| 3 | Cl | $CO_2Me$ | **3b** | *p*-Me(O)C$C_6H_4$ | **7c** | 54 |
| 4 | Cl | $CO_2Me$ | **3b** | Bn | **7d** | 63 |
| 5 | Cl | $CO_2Me$ | **3b** | *n*Pr | **7e** | 75 |
| 6 | Cl | $CO_2Me$ | **3b** | *c*Pr | **7f** | 74 |
| 7 | Cl | $CO_2Me$ | **3b** | *t*Bu | **7g** | 69 |
| 8 | Cl | $CO_2Me$ | **3b** |  | **7h** | 66 |
| 9 | Cl | $CO_2Me$ | **3b** | $CH_2SiMe_3$ | **7i** | 70 |
| 10 | Cl | *p*-$CF_3C_6H_4$ | **3c** | Ph | **7j** | 82 |
| 11 | Br | *p*-$CF_3C_6H_4$ | **3d** | *p*-Tol | **7k** | 73 |
| 12 | OMe | *p*-$CF_3C_6H_4$ | **3e** | *n*Pr | **7l** | 51 |

[a]Yield of isolated product.

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