

## RESEARCH ARTICLE

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# Divergent synthesis of indole-fused polycycles via Rh(II)-catalyzed intramolecular [3 + 2] cycloaddition and C–H functionalization of indolyltriazoles†

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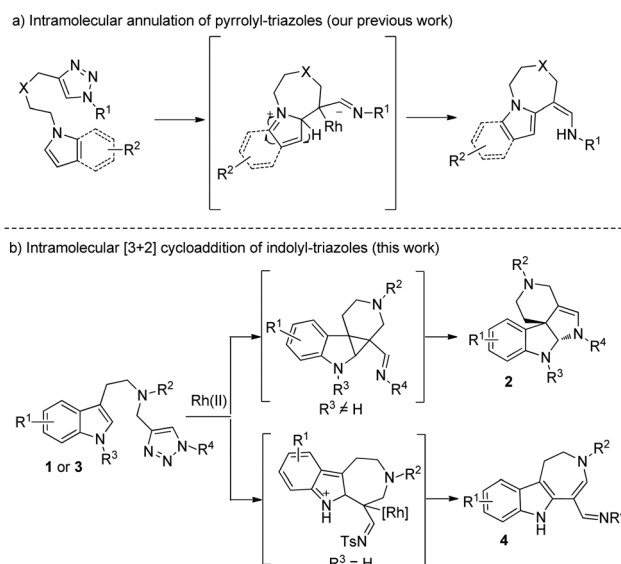
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Rh(II)-catalyzed divergent synthesis of polycyclic indolines and azepino[4,5-*b*]indoles through intramolecular [3 + 2] cycloaddition and C–H functionalization of indoles with *N*-sulfonyl 1,2,3-triazoles is described. The reaction pathways are controlled by the substituent type of indole.

Indole derivatives present a key structural motif in many natural products and medicinal molecules, which exhibit a wide range of promising biological activities.<sup>1</sup> In particular, indole-fused *N*-heterocycles, such as indoline<sup>2</sup> and azepino[4,5-*b*]indole<sup>3</sup> derivatives, are most attractive due to their wide existence in a number of natural products and pharmaceutical reagents. Thus, many synthetic methods have been developed to construct these compounds in recent years.<sup>4</sup> Because a sequential reaction to synthesize such a complex and useful motif is of great importance, we herein disclose a divergent synthesis of polycyclic indolines and azepino[4,5-*b*]indoles from readily available indolyltriazoles. The reaction pathways are switchable according to different substituents at the indole N1 position: if the nitrogen is protected, the reaction goes through a formal [3 + 2] cycloaddition to yield polycyclic indolines **2**, while for the non-protected indole substrate, the reaction delivers azepino[4,5-*b*]indoles **3** via C–H functionalization.

*N*-Sulfonyl-1,2,3-triazoles, which can be simply prepared from terminal alkynes by copper-catalyzed 1,3-dipolar cycloaddition with *N*-sulfonyl azides, have recently attracted much attention.<sup>5</sup> As reported by Fokin, Gevorgyan, Murakami and Davies, *N*-sulfonyl triazoles, as precursors of  $\alpha$ -imino metal carbenes, can be effectively decomposed in the presence of a suitable metal catalyst<sup>6</sup> and undergo various interesting and useful transformations, such as cyclopropanation,<sup>7</sup> transannulation,<sup>8</sup> C–H bond insertion,<sup>9</sup> X–H (X = heteroatoms) bond insertions<sup>10</sup> and other novel reactions based on the inherent

properties of metal carbenes.<sup>11</sup> Previously, we<sup>9b</sup> also developed an intramolecular annulation of 1-sulfonyl-1,2,3-triazoles with pyrroles and indoles to construct indole fused azepine derivatives (Scheme 1a). To continue our research interest in indole chemistry, we envisaged that 4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide **1a** could either undergo intramolecular [3 + 2] cycloaddition/ring expansion or C–H functionalization in the presence of a dirhodium complex (Scheme 1b). To our delight, indoline derivatives **2** were obtained after treatment of **1** ( $R^3$  is not H) with the rhodium catalyst. Moreover, for non-protected substrates ( $R^3 = H$ ), the reaction gave the desired azepine

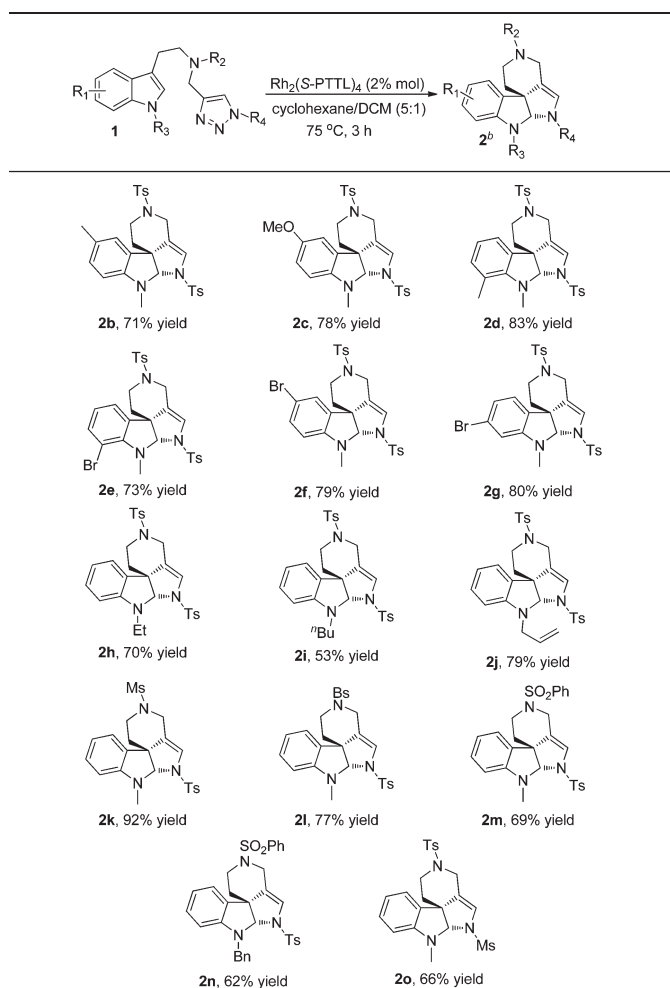


Scheme 1 Previous work and this work.

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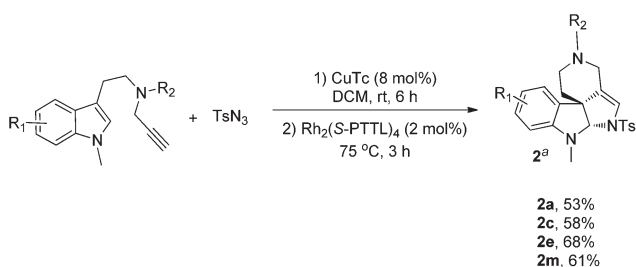
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data of new compounds. CCDC 1018373 and 1018374. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5qo00216h



Table 2 Scope of the reaction for the synthesis of **2**<sup>a</sup>

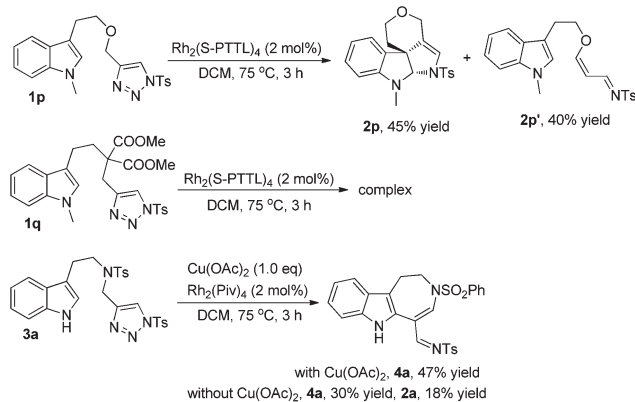
<sup>a</sup> Reaction conditions: 0.2 mmol of **1** and Rh<sub>2</sub>(S-PTTL)<sub>4</sub> (2 mol%) were stirred in dry solvent (cyclohexane : DCM = 5 : 1) in a 10 ml sealed tube.

<sup>b</sup> Yields of isolated products.



**Scheme 2** One-pot synthesis of polycyclic pyrroloindolines. Reaction conditions: (1) alkyne (0.2 mmol), TsN<sub>3</sub> (0.2 mmol) and CuTc (8 mol%) were stirred in 2 mL of DCM at rt for 6 h. (2) Rh<sub>2</sub>(S-PTTL)<sub>4</sub> (2 mol%) was added and the reaction mixture was heated at 75 °C for 3 h. <sup>a</sup>Isolated yield.

alkyne (Scheme 2). On treatment of alkynes (0.2 mmol) with TsN<sub>3</sub> (0.2 mmol) in the presence of CuTc (0.016 mmol) in DCM (2.0 mL) at rt under Ar, a triazole intermediate was



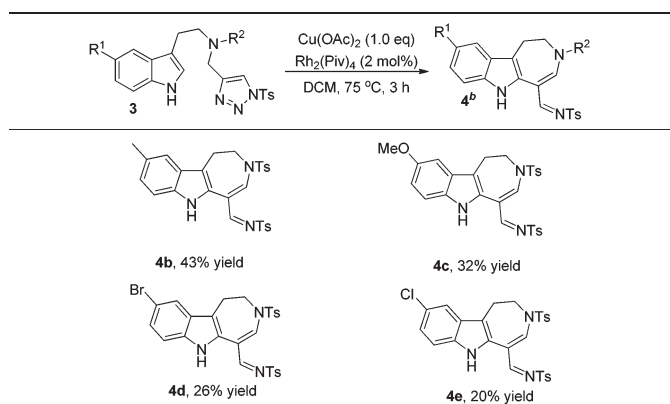
Scheme 3 Further substrate scope study.

formed, then Rh<sub>2</sub>(S-PTTL)<sub>4</sub> was added under Ar and the reaction was heated for 3 h at 75 °C. After completion, the reaction mixture was directly subjected to flash column chromatography to give the products **2a**, **2b**, **2e** and **2m** in moderate yields.

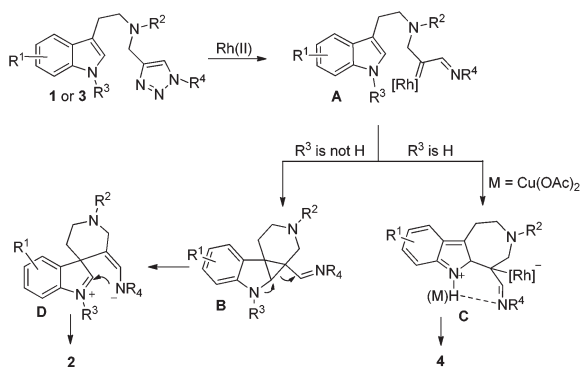
To extend the substrate scope, we also examined other types of indolyltriazoles. As can be seen from Scheme 3, when oxygen tethered tryptopholtriazole **1p** was treated with Rh<sub>2</sub>(S-PTTL)<sub>4</sub> in DCM at 75 °C for 3 h, the desired spiro derivative **2p** was obtained in 45% yield as well as the acrolein imine byproduct **2p'** derived from β-H elimination in 40% yield. However, when substrate **1q** with a *gem*-diester linker was treated under the standard reaction conditions, the reaction became very complex and no desired product was observed as tested by <sup>1</sup>H NMR of the crude reaction mixture. Interestingly, when indolyl-triazole **3a** with a free NH group (R<sup>3</sup> = H) was employed as the substrate, the reaction gave azepine derivative **4a** in 47% yield upon heating in DCM at 75 °C for 3 h when 1.0 eq. of Cu(OAc)<sub>2</sub> was added to the reaction mixture. In comparison, the reaction gave both **4a** and **2a** in 30% and 18% yields without Cu(OAc)<sub>2</sub>, indicating that the copper salt plays an important role in controlling the reaction selectivity.

The formation of **4a** stimulated our interest to further investigate the scope and limitations of this reaction. After screening the reaction conditions, it was found that using 2 mol% Rh<sub>2</sub>(Piv)<sub>4</sub> and 1.0 eq. Cu(OAc)<sub>2</sub> as additives, the reaction gave the best results (for more information, please see Table S1 in the ESI<sup>†</sup>). As can be seen from Table 3, the corresponding azepine derivatives **4b–4e** could be obtained in 20–43% yields. The relatively low yield of the reaction might be due to the instability of the products.<sup>13</sup>

A plausible mechanism is outlined in Scheme 4. Initially, denitrogenation of **1** in the presence of a Rh(II) complex gives an azavinyl carbene intermediate **A**. According to Davies's report,<sup>7f</sup> if the indole substrate is protected by an alkyl group, then the cyclopropanation of the indole double bond by rhodium carbene takes place to yield intermediate **B**, which then undergoes ring expansion to give intermediate **D**. After ring closure, the final product **2** is obtained. On the other

**Table 3** Scope of the reaction for the synthesis of **4**<sup>a</sup>

<sup>a</sup> Reaction conditions: triazole (0.2 mmol), Cu (OAc) (0.2 mmol) and Rh(II) (0.2 mol%) were added to a flask, then DCM was added under Ar and the reaction mixture was heated at 75 °C for 3 h. <sup>b</sup> Isolated yield.

**Scheme 4** A proposed mechanism.

hand, if  $\text{R}^3$  is a proton, a Friedel–Crafts reaction occurs, giving product **4** instead *via* intermediate **C**. Intramolecular H bonding may exist between the indole N–H and the imine group, which could stabilize intermediate **C**, therefore, the formation of **4** is more favored than **2**. When  $\text{Cu}(\text{OAc})_2$  is added to the reaction system, the interaction between copper and imine is even more stronger than the H bonding to stabilize intermediate **C**, giving higher selectivity.

In summary, we have developed a novel and effective method to synthesize a series of polycyclic pyrroloindolines and azepino[4,5-*b*]indoles *via* rhodium(II) catalyzed intramolecular [3 + 2] cycloaddition or C–H functionalization of indolyltriazoles. The reaction pathways are dependent on the substituents at the indole N1 position: when  $\text{R}^3$  is an alkyl group, the reaction delivers pyrroloindolines, while non-protected substrates result in azepino[4,5-*b*]indoles. Further investigations to extend the substrate scope as well as to examine the mechanistic details more extensively are currently underway in our laboratory.

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- 12 The crystal data of **2a** and **4a** have been deposited in CCDC with numbers 1018373 and 1018374.
- 13 The deprotection of Bn or allyl groups of **2n** and **2j** under various conditions turned out to be unsuccessful, the formation of a complex product mixture indicated that the corresponding products might be unstable. For more details, please see the ESI.†

