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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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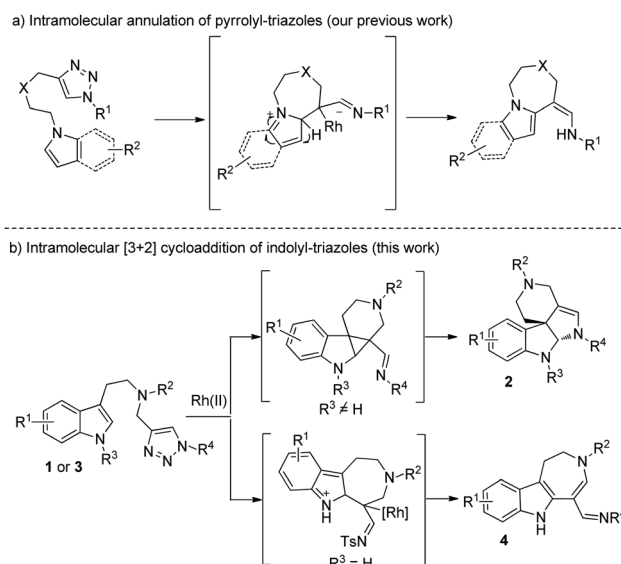
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Rh(II)-catalyzed divergent synthesis of polycyclic indolines and azepino[4,5-*b*]indoles through intramolecular [3 + 2] cycloaddition and C–H functionalization of indoles with *N*-sulfonyl 1,2,3-triazoles is described. The reaction pathways are controlled 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.¹ In particular, indole-fused *N*-heterocycles, such as indoline² and azepino[4,5-*b*]indole³ 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.⁴ 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.⁵ As reported by Fokin, Gevorgyan, Murakami and Davies, *N*-sulfonyl triazoles, as precursors of α -imino metal carbenes, can be effectively decomposed in the presence of a suitable metal catalyst⁶ and undergo various interesting and useful transformations, such as cyclopropanation,⁷ transannulation,⁸ C–H bond insertion,⁹ X–H (X = heteroatoms) bond insertions¹⁰ and other novel reactions based on the inherent

properties of metal carbenes.¹¹ Previously, we^{9b} 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.

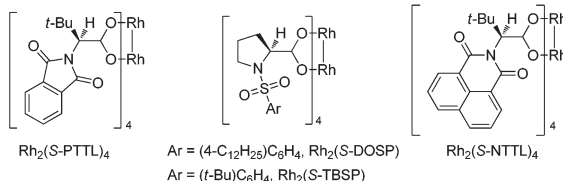
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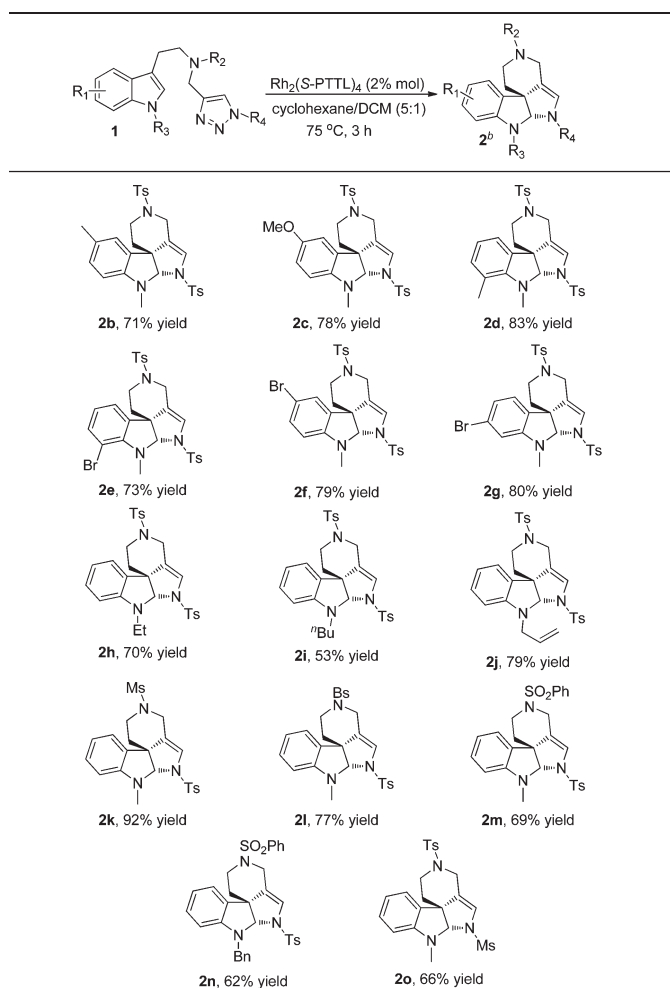
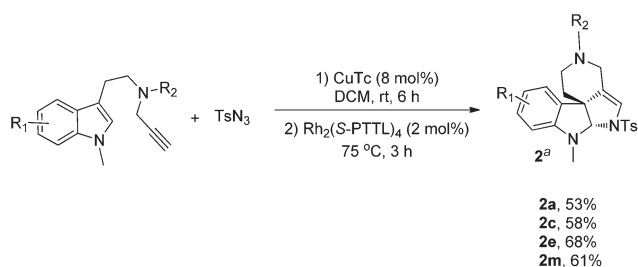
Chemical reaction scheme showing the cyclization of compound **1a** to compound **2a**. Compound **1a** is a 1-methyl-2-(2-(4-(tosyloxymethyl)phenyl)vinyl)indole. It reacts with a catalyst (Cat) under conditions of temperature (T), solvents, and time (t) to form compound **2a**, which is a 1-methyl-2-(4-(tosyloxymethyl)phenyl)-1,2,3,4-tetrahydroindole. The reaction involves the cyclization of the indole ring and the formation of a new C-C bond between the indole C2 and the phenyl ring.

^a Reaction conditions: **1a** (0.2 mmol), and Rh cat. (2 mol%) were stirred in 2 ml of solvent. ^b Yields of isolated product. ^c The solvent was 6 ml. ^d Tested by ¹H NMR. ^e 2.0 mmol scale, 1.1 g of **1a** (67% yield). ^f When the reaction was conducted without a catalyst, no reaction took place.

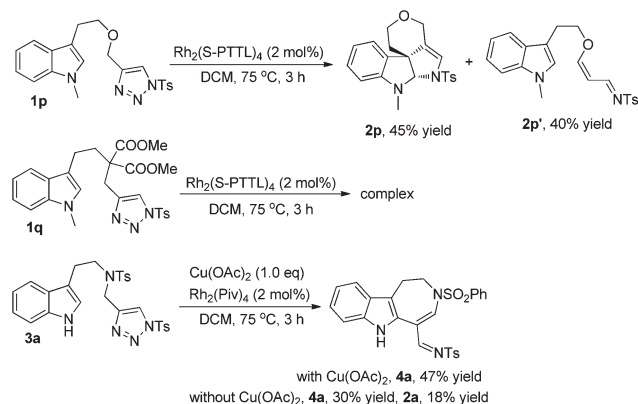
Chiral rhodium(II) catalysts employed in this study:



As a further study of the cycloaddition reaction, we next conducted a one-pot synthesis of the products **2** from terminal

Table 2 Scope of the reaction for the synthesis of **2**^a^a Reaction conditions: 0.2 mmol of **1** and $\text{Rh}_2(\text{S-PTTL})_4$ (2 mol%) were stirred in dry solvent (cyclohexane : DCM = 5 : 1) in a 10 ml sealed tube.^b Yields of isolated products.**Scheme 2** One-pot synthesis of polycyclic pyrroloindolines. Reaction conditions: (1) alkyne (0.2 mmol), TsN_3 (0.2 mmol) and CuTc (8 mol%) were stirred in 2 mL of DCM at rt for 6 h. (2) $\text{Rh}_2(\text{S-PTTL})_4$ (2 mol%) was added and the reaction mixture was heated at 75 °C for 3 h. ^aIsolated yield.

alkyne (Scheme 2). On treatment of alkynes (0.2 mmol) with TsN_3 (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 $\text{Rh}_2(\text{S-PTTL})_4$ 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.

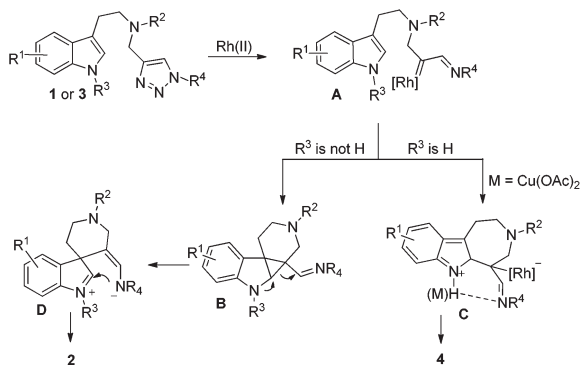
To extend the substrate scope, we also examined other types of indolyltriazoles. As can be seen from Scheme 3, when oxygen tethered tryptopholtriazole **1p** was treated with $\text{Rh}_2(\text{S-PTTL})_4$ in DCM at 75 °C for 3 h, the desired spiro derivative **2p** was obtained in 45% yield as well 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 ^1H NMR of the crude reaction mixture. Interestingly, when indolyl-triazole **3a** with a free NH group ($\text{R}^3 = \text{H}$) 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 $\text{Cu}(\text{OAc})_2$ was added to the reaction mixture. In comparison, the reaction gave both **4a** and **2a** in 30% and 18% yields without $\text{Cu}(\text{OAc})_2$, 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% $\text{Rh}_2(\text{Piv})_4$ and 1.0 eq. $\text{Cu}(\text{OAc})_2$ as additives, the reaction gave the best results (for more information, please see Table S1 in the ESI†). 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.¹³

A plausible mechanism is outlined in Scheme 4. Initially, denitrogenation of **1** in the presence of a $\text{Rh}(\text{II})$ complex gives an azavinyl carbene intermediate **A**. According to Davies's report,²⁷ 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**^a

^a 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. ^b Isolated yield.

**Scheme 4** A proposed mechanism.

hand, if 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 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.†

