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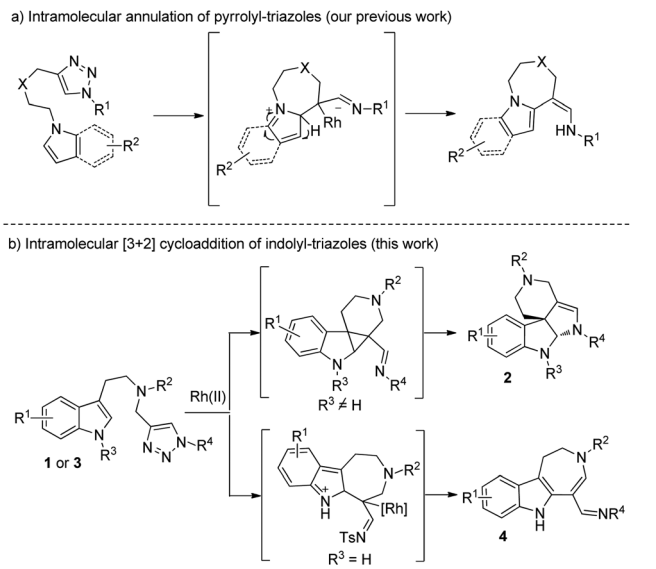
Rh(II)-catalyzed divergent synthesis of polycyclic indolines and azepino[4,5-*b*]indoles through intramolecular [3 + 2] cycloaddition and C–H functionalization of indoles with *N*-sulfonyl 1,2,3-triazoles is described. The reaction pathways are controlled by the substituent type of indole.

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 indoline[2] and azepino[4,5-*b*]indole[3] 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 catalyst[6] and undergo various interesting and useful transformations, such as cyclopropanation,[7] transannulation,[8] C–H bond insertion,[9] X–H (X = heteroatoms) bond insertions[10] 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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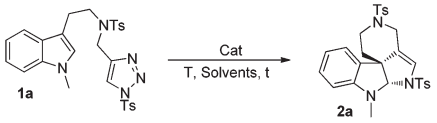
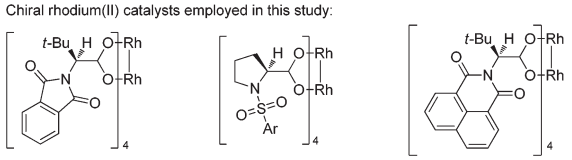
Table 1 Optimization of the reaction conditions of rhodium-catalyzed tandem reaction of **1a**



Entry[a]	Cat.	T (°C)	Solvent	Time	Yield[b] (%) **2a**
1	$Rh_2(Piv)_4$	60	DCM	3 h	26
2	$Rh_2(Piv)_4$	Rt	DCM	24 h	21
3	$Rh_2(Piv)_4$	80	DCM	3 h	30
4	$Rh_2(Piv)_4$	80	DCE	3 h	8[d]
5	$Rh_2(Piv)_4$	110	DCE	3 h	Trace[d]
6	$Rh_2(Oct)_4$	80	DCM	3 h	41
7	$Rh_2(Oct)_4$	120	DCE	3 h	Trace[d]
8	$Rh_2(esp)_2$	80	DCM	3 h	35
9	$Rh_2(OAc)_4$	80	DCM	3 h	13[d]
10	Rh_2(*S*-PTTL)$_4$	75	DCM	3 h	75
11	Rh_2(*S*-NTTL)$_4$	75	DCM	3 h	71
12	Rh_2*S*-DOSP)$_4$	75	DCM	3 h	28
13	Rh_2*S*-TBSP)$_4$	75	DCM	3 h	48
14[c]	Rh_2(*S*-PTTL)$_4$	75	Cyclohexane	3 h	65
15[c]	**Rh_2(*S*-PTTL)$_4$**	**75**	**Cyclohexane : DCM = 5 : 1**	**3 h**	**77 (67)**[e]
16[f]	—	75	DCM	3 h	—

[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 ^{1}H 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:



Rh_2(*S*-PTTL)$_4$ Ar = (4-$C_{12}H_{25}$)C_6H_4, Rh_2(*S*-DOSP) Ar = (*t*-Bu)C_6H_4, Rh_2(*S*-TBSP) Rh_2(*S*-NTTL)$_4$

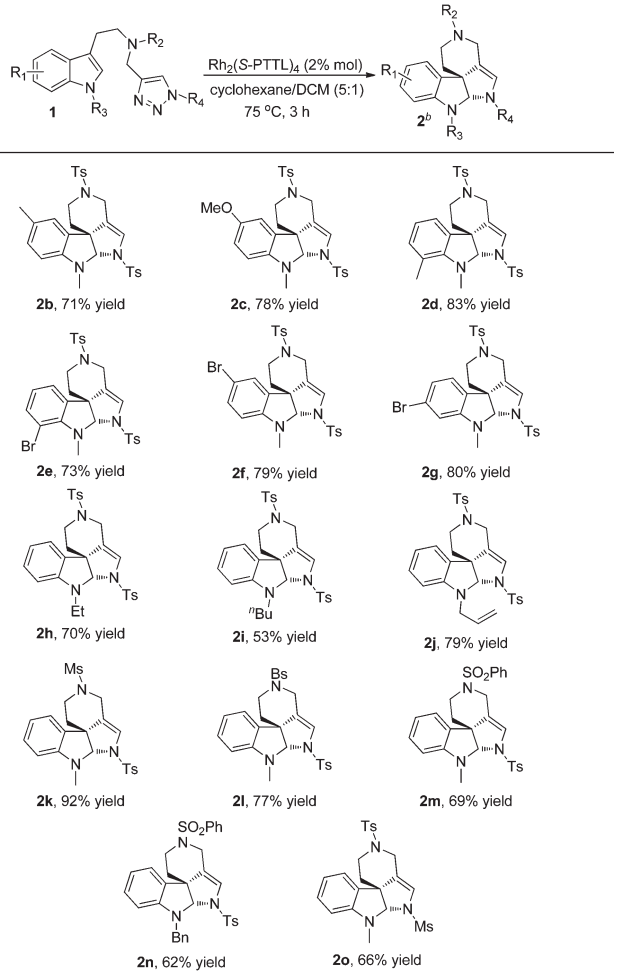
derivatives **4** after C–H functionalization. The structures of **2a** and **4a** were unambiguously determined by X-ray diffraction.[12]

To optimize the reaction conditions, we started to screen different Rh(II) complexes, temperature as well as solvents, using **1a** as the model substrate. As can be seen from Table 1, when the reaction was catalyzed by $Rh_2(Piv)_4$ (2 mol%) in DCM (dichloromethane) for 3 h at different temperatures, the corresponding product **2a** was obtained in 21–30% yields (Table 1, entries 1–3). On changing the solvent to DCE and performing the reaction at 80 °C, the yield of **2a** was only 8%, and by further increasing the reaction temperature to 110 °C, the reaction was very complex with no desired product detected (Table 1, entries 4–5). Other achiral dirhodium tetracarboxylates were also investigated, and all of these catalysts turned out to be of poor efficiency to this reaction (Table 1, entries 6–9). Then, we tried several chiral dirhodium complexes, which were proved to give better results than achiral catalysts in some reported cases.[11a,8h] To our delight, when Rh_2(*S*-PTTL)$_4$ was employed as a catalyst, the yield of **2a** increased to 75% (Table 1, entry 10). Other chiral rhodium catalysts such as Rh_2(*S*-NTTL), Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-TBSP)$_4$ were found less effective than Rh_2(*S*-PTTL)$_4$, affording the desired product **2a** in 28–71% yields, respectively (Table 1, entries 11–13). Next, solvent effects were tested and it was found that using a mixed solvent of cyclohexane and DCM (5 : 1) would benefit the formation of **2a** (77%) (Table 1, entries 14 and 15). The reaction did not take place without a catalyst under otherwise identical standard reaction conditions (Table 1, entry 16). In addition, the reaction of **1a** could also run at a gram scale and the corresponding product of **2a** was obtained in 67% yield (Table 1, entry 15).

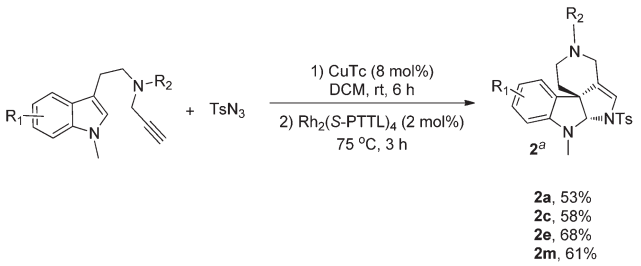
With the optimized reaction conditions in hand, we next investigated the scope and limitations of this reaction and the results are summarized in Table 2. As for substrates **1b–1g**, the reactions proceeded smoothly to afford the corresponding products **2b–2g** in good yields, and the electronic properties of the substituents on indole didn't have significant influence on the reaction outcomes. When indole was protected by ethyl, *n*-butyl or allyl groups (R^3), the corresponding products **2h–2j** were obtained in 53–79% yields. Other sulfonyl substituents (R^2) were also well tolerated and the desired products **2k–2n** were delivered in 62–92% yields. Moreover, changing the protecting group of triazole (R^4) instead of Ts, such as Ms, the reaction also went on well to give **2o** in 66% yield.

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]

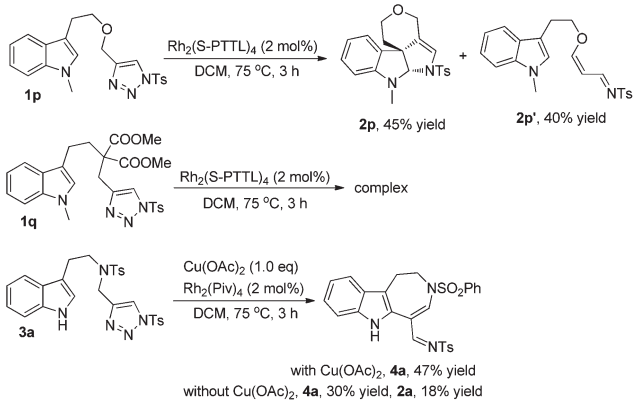


[a] Reaction conditions: 0.2 mmol of **1** and Rh_2(*S*-PTTL)$_4$ (2 mol%) were stirred in dry solvent (cyclohexane : DCM = 5 : 1) in a 10 ml sealed tube. [b] Yields of isolated products.



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) Rh(II) (2 mol%) was added and the reaction mixture was heated at 75 °C for 3 h. [a]Isolated 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 formed, then Rh_2(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.



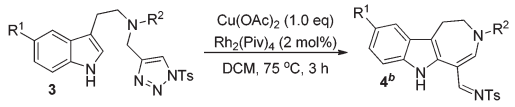
Scheme 3 Further substrate scope study.

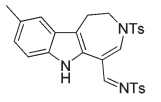
To extend the substrate scope, we also examined other types of indolyltriazoles. As can be seen from Scheme 3, when oxygen tethered tryptopholtriazole **1p** was treated with Rh_2(*S*-PTTL)$_4$ in DCM at 75 °C for 3 h, the desired spiro derivative **2p** was obtained in 45% yield as well as the acrolein 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 ^{1}H NMR of the crude reaction mixture. Interestingly, when indoly-triazole **3a** with a free NH group (R^3 = 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 $Cu(OAc)_2$ was added to the reaction mixture. In comparison, the reaction gave both **4a** and **2a** in 30% and 18% yields without $Cu(OAc)_2$, indicating that the copper salt plays an important role in controlling the reaction selectivity.

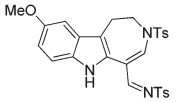
The formation of **4a** stimulated our interest to further investigate the scope and limitations of this reaction. After screening the reaction conditions, it was found that using 2 mol% $Rh_2(Piv)_4$ and 1.0 eq. $Cu(OAc)_2$ as additives, the reaction gave the best results (for more information, please 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]

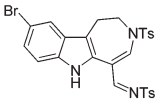
A plausible mechanism is outlined in Scheme 4. Initially, denitrogenation of **1** in the presence of a Rh(II) complex gives an azavinyl carbine intermediate **A**. According to Davies's report,[7f] if the indole substrate is protected by an alkyl group, then the cyclopropanation of the indole double 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

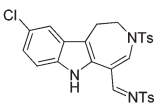
Table 3 Scope of the reaction for the synthesis of **4**[a]



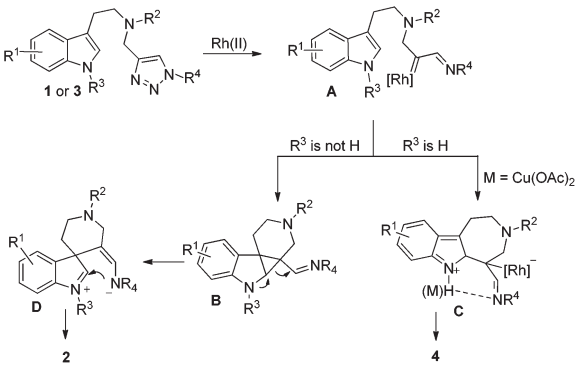

4b, 43% yield


4c, 32% yield


4d, 26% yield


4e, 20% yield

[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 $Cu(OAc)_2$ 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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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.†