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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 intra-molecular [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-1H-indol-3-yl)ethyl)-N-((1-tosyl-1H-1,2,3-triazol-4-yl)methyl)benzenesulfonamide 1a could either undergo intramolecular [3 + 2] cyclo-addition/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 (R³ is not H) with the rhodium catalyst. Moreover, for non-protected substrates (R³ = H), the reaction gave the desired azepine

a) Intramolecular annulation of pyrrolyl-triazoles (our previous work)

$$\begin{array}{c}
N \\
N \\
N \\
R^{1}
\end{array}$$

$$\begin{array}{c}
X \\
N \\
N \\
R^{2}
\end{array}$$

$$\begin{array}{c}
X \\
N \\
N \\
N \\
R^{1}
\end{array}$$

b) Intramolecular [3+2] cycloaddition of indolyl-triazoles (this work)

$$R^{1} \xrightarrow{|| \cdot ||} N^{-R^{2}} \xrightarrow{Rh(||)} R^{1} \xrightarrow{|| \cdot ||} R^{1} \xrightarrow{|| \cdot ||}$$

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_2S -DOSP) ₄	75	DCM	3 h	28
13	Rh_2S -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 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:

$$Rh_{2}(S-PTTL)_{4} \qquad Ar = (4-C_{12}H_{25})C_{6}H_{4}, Rh_{2}(S-DOSP) \qquad Rh_{2}(S-NTTL)_{4}$$

$$Ar = (t-Bu)(C_{6}H_{4}, Rh_{2}(S-DOSP) \qquad Rh_{2}(S-NTTL)_{4}$$

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 Rh₂(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 Rh₂(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 Rh₂(S-NTTL), Rh₂(S-DOSP)₄ and Rh₂(S-TBSP)₄ were found less effective than Rh₂(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 (R³), the corresponding products 2h-2j were obtained in 53-79% yields. Other sulfonyl substituents (R²) were also well tolerated and the desired products 2k-2n were delivered in 62-92% yields. Moreover, changing the protecting group of triazole (R4) instead of Ts, such as Ms, the reaction also went on well to give 20 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. alsolated 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 Rh₂(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 Rh₂(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 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 $\mathbf{1}$ in the presence of a Rh(π) complex gives an azavinyl carbine intermediate \mathbf{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 \mathbf{B} , which then undergoes ring expansion to give intermediate \mathbf{D} . After ring closure, the final product $\mathbf{2}$ 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(π) (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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