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SITE-SELECTIVE INTRODUCTION OF AN ENAMIDO GROUP AT THE C(3)-POSITION OF INDOLES

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Abstract – An enamido group is introduced site-selectively at the C(3)-position of indoles by the rhodium(II)-catalyzed reaction with *N*-sulfonyl-1,2,3-triazoles. Formally, an α-imino rhodium carbene complex is inserted into the C(3)-H bond of an indole.

Indoles are privileged structural motifs found in a myriad of natural products and pharmaceuticals.[1] Numerous methods have been developed for the functionalization of indole skeletons.[2] Among them, a C-H bond functionalization using metal carbene complexes has received much attention in recent years.[3] On the other hand, *N*-sulfonyl-1,2,3-triazoles have emerged as convenient precursors for the generation of α-imino metal carbene complexes.[4] The complexes contain an electrophilic carbene carbon and a nucleophilic imino nitrogen in the molecule. They can trigger a variety of synthetically useful transformations, including not only typical carbene reactions such as cyclopropanation[5] and X-H bond insertion (X = carbon,[6] oxygen,[7] nitrogen[8]) but also carbene-induced reactions such as [3+2] annulation,[9] ring expansion,[10] and others.[11] Davies and co-workers have demonstrated an excellent method for the functionalization of indole skeletons using α-imino rhodium carbene complexes generated from *N*-sulfonyl-1,2,3-triazoles; 1,3-disubstituted indoles undergo [3+2] annulation reaction in an enantioselective manner to afford pyrroloindolines (Figure 1(a)).[12,13] This fascinating result led us to

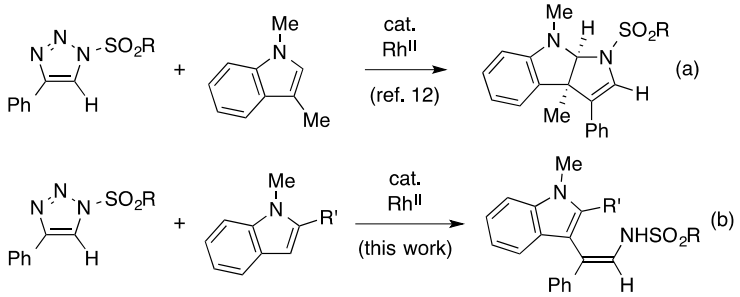
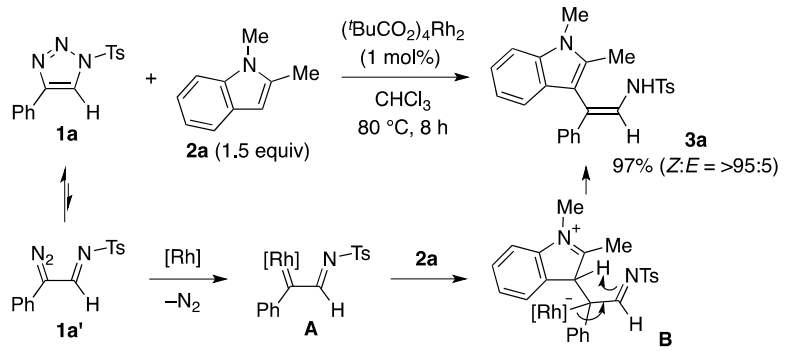


Figure 1. Rh(II)-catalyzed reaction of indoles with *N*-sulfonyl-1,2,3-triazoles

examine the rhodium(II)-catalyzed reaction of indole derivatives having C(3)-H bonds. Now, we report a rhodium(II)-catalyzed reaction of 1,2-disubstituted indoles and 1-monosubstituted indoles with *N*-sulfonyl-1,2,3-triazoles. The presence of the C(3)-H bond shifts the [3+2] annulation pathway to 1,3-insertion of α-imino rhodium carbene complexes into the C(3)-H bond, leading to the formation of β-(3-indolyl)sulfonylenamides with the high (*Z*)-selectivities (Figure 1(b)).

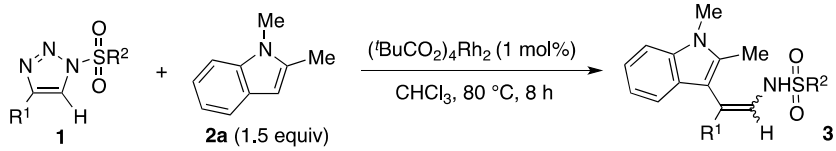
Initially, 4-phenyl-1-tosyl-1,2,3-triazole (**1a**) was prepared from phenylacetylene and tosyl azide according to the authentic procedure using a copper(I) catalyst.[14] When the triazole **1a** (0.2 mmol) was treated with 1,2-dimethyl-1*H*-indole (**2a**, 0.3 mmol) in the presence of (^{t}BuCO$_2$)$_4$Rh$_2$ (1 mol%) in chloroform (2 mL) at 80 °C, **1a** was completely consumed within 8 hours. Chromatographic purification afforded β-(3-indolyl)sulfonylenamide **3a** in 97% isolated yield with the *Z*/*E* ratio of >95:5 (Scheme 1). The configuration of the double bond of **3a** was confirmed as *Z* by an NOE study. Unlike the cases with 1,3-disubstituted indoles, no annulation product was formed.[15] We propose the following mechanism for the production of **3a**. α-Diazo imine **1a'** is generated from the triazole **1a** by a ring-chain tautomerization through equilibrium. The transient **1a'** is trapped by a rhodium(II) catalyst to furnish α-imino carbene complex **A**. Nucleophilic addition of the indole **2a** at the C(3)-position to the electrophilic carbene of **A** gives the zwitterionic intermediate **B**. The anionic rhodium of **B** releases an electron pair, which flows onto the imino nitrogen. Since there is a hydrogen atom at the C(3)-position, the imino nitrogen acts as a base to pick up the hydrogen rather than undergoes nucleophilic attack onto the C(2)-carbon atom, furnishing (*Z*)-isomer of **3a**.



Scheme 1. Reaction of 1,2-dimethyl-1*H*-indole (**2a**) with triazole **1a**

1,2-Dimethyl-1*H*-indole (**2a**) was reacted with various triazoles **1** (Table 1). Triazoles **1b**−**e** possessing aryl and heteroaryl groups at the C(4)-position all reacted well to afford the corresponding products **3b**−**e** in yields ranging from 90% to 95% with high (*Z*)-selectivities (entries 1–4). The reaction of the alkyl-substituted triazoles **1f**−**h** gave the products **3f**−**h**, albeit in moderate yields (entries 5–7).[7] Aryl group as well as alkyl group were compatible for the R^2 substituent on the sulfonyl group to afford the products **3i**−**m** in high yields (entries 8–12).

Table 1. Rh(II)-catalyzed reaction of 1,2-dimethyl-1*H*-indole (**2a**) with various triazoles **1**[a]

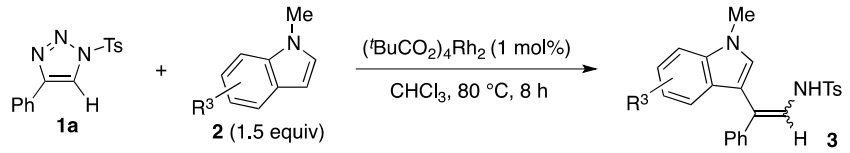


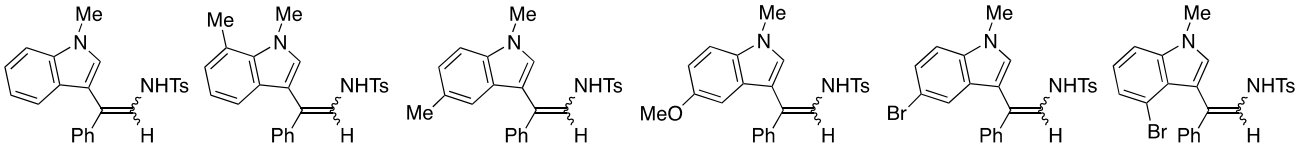
Entry	1	R^1	R^2	3	Yield[b]	*Z*/*E*[c]	Entry	1	R^1	R^2	3	Yield[b]	*Z*/*E*[c]
1	**1b**	*p*-Tol-	*p*-Tol-	**3b**	95%	>95:5	7	**1h**	$BzO(CH_2)_4$-	*p*-Tol-	**3h**	57%[d]	>95:5
2	**1c**	*p*-MeO-C_6H_4-	*p*-Tol-	**3c**	96%	>95:5	8	**1i**	Ph-	*p*-MeO-C_6H_4-	**3i**	98%	>95:5
3	**1d**	*p*-CF_3-C_6H_4-	*p*-Tol-	**3d**	90%	>95:5	9	**1j**	Ph-	*p*-CF_3-C_6H_4-	**3j**	98%	>95:5
4	**1e**	3-Thienyl-	*p*-Tol-	**3e**	95%	>95:5	10	**1k**	Ph-	*o*-Tol-	**3k**	80%	95:5
5	**1f**	*n*Pr-	*p*-Tol-	**3f**	65%	>95:5	11	**1l**	Ph-	*n*Bu-	**3l**	95%	>95:5
6	**1g**	*i*Bu-	*p*-Tol-	**3g**	61%[d]	94:6	12	**1m**	Ph-	Me-	**3m**	95%	>95:5

[a] Reaction conducted on a 0.2 mmol scale. [b] Isolated yield (average of two runs). [c] The ratio determined by ^{1}H NMR. [d] **2a** (1.0 mmol, 5.0 equiv) in $CHCl_3$ (0.5 mL) in the presence of $(^tBuCO_2)_4Rh_2$ (5 mol%).

Next, the use of 1-methyl-1*H*-indole and its derivatives was examined. The C-H bond functionalization took place site-selectively at the C(3)-position, and the corresponding products **3n**−**s** were obtained in excellent yields (Table 2). In these cases, however, the lower (*Z*)-selectivities (*Z*:*E* = 82:18~88:12) were observed except **3s**, which was ascribed to isomerization of the initially formed (*Z*)-isomer to the (*E*)-isomer occurring during the course of the reaction. In fact, when the reaction of **1a** with 1-methyl-1*H*-indole was monitored by ^{1}H NMR, the gradual isomerization from (*Z*)-**3n** to (*E*)-**3n** was observed [96:4 (1 h), 83:17 (4 h), 80:20 (8 h)].

Table 2. Rh(II)-catalyzed reaction of various 1-methyl-1*H*-indoles **2** with triazole **1a**[a]

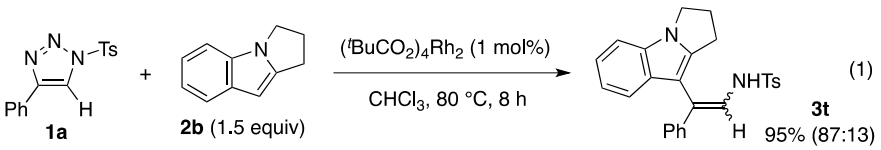




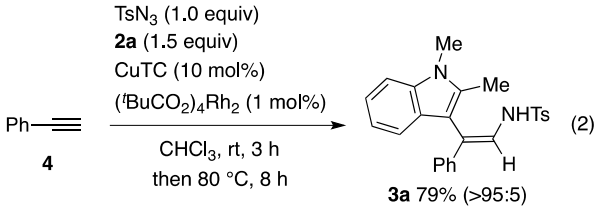
3n 97% (83:17) [98% (87:13)][b] | **3o** 96% (88:12) | **3p** 98% (84:16) | **3q** 96% (82:18) | **3r** 98% (83:17) | **3s** 97% (>95:5)

[a] The reaction conditions were the same as those in Table 1. Isolated yield (average of two runs). The *Z*:*E* ratio determined by ^{1}H NMR. [b] In parentheses on a 2.0 mmol scale of **1a**.

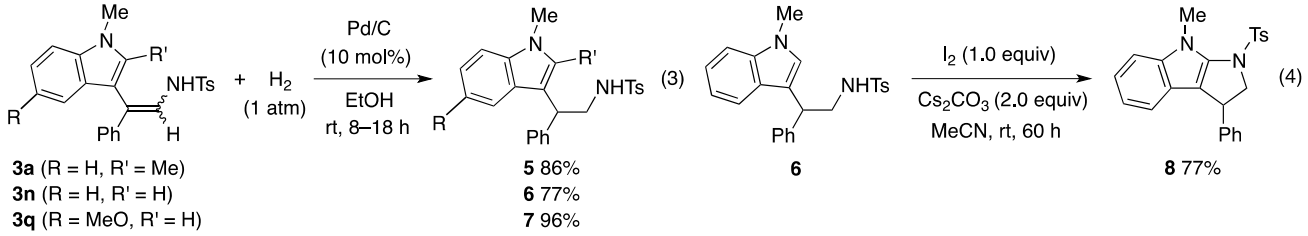
Fused indole **2b** with N(1)-to-C(2) was also suitable substrate, giving the product **3t** in 95% yield with the *Z*/*E* ratio of 87:13 (Eq 1).



An all-in-one-pot procedure was also carried out to demonstrate the practical convenience of the present method (Eq 2). Phenylacetylene (**4**), tosyl azide, 1,2-dimethyl-1*H*-indole (**2a)**, copper(I) and rhodium(II) catalysts, and chloroform were put in a reaction vessel, and the mixture was stirred at room temperature. After 3 hours, **4** and tosyl azide were both consumed to generate the triazole **1a**. Then, the reaction mixture was stirred at 80 °C for 8 hours, and the following chromatographic purification afforded the product **3a** in 79% yield.



The synthetic utility of the products **3** was exemplified by further transformations. The carbon–carbon double bond of **3a**, **3n**, and **3q** was successfully reduced, giving tryptamine derivatives **5**, **6**, and **7** in good yields when a simple hydrogenation reaction using palladium on charcoal was applied (Eq 3). Furthermore, treatment of **6** with iodine (1.0 equiv) caused electrophilic cyclization to afford fused indole derivative **8** in 77% yield (Eq 4).[16]



In summary, a regioselective C-H bond functionalization of 1,2-disubstituted- and 1-monosubstituted indoles by α-imino rhodium carbene complexes is reported. The product selectivity is significantly affected by the substitution pattern at the C(3)-position of the indoles. The resulting products are useful intermediates for the synthesis of tryptamine derivatives.

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