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Preparation of Triazoloindoles via Tandem Copper Catalysis and Their Utility as α-Imino Rhodium Carbene Precursors

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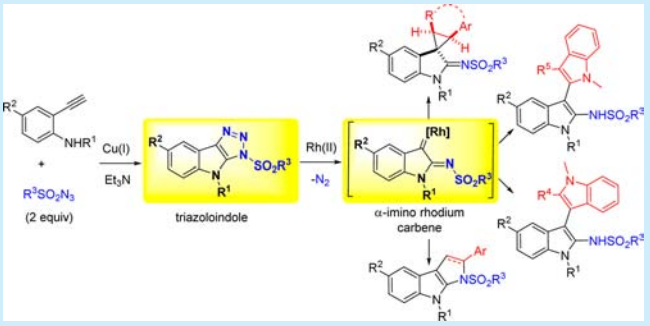
Supporting Information

ABSTRACT: 3-Sulfonyl[1,2,3]triazolo[4,5-*b*]indoles were efficiently prepared via a tandem catalysis process involving intramolecular ligand stabilized CuAAC and Cu-catalyzed C−N coupling. The obtained 3-sulfonyl[1,2,3]triazolo[4,5-*b*]-indoles could be utilized as α-imino rhodium carbene precursors for the construction of a range of valuable indole molecules including pyrrolo[2,3-*b*]indoles, spirocyclopropyl iminoindoles, 2,3-dihydropyrrolo[2,3-*b*]indoles, 3,3′-biindoles, and 2,3′-biindoles.



Indole and its derivatives have attracted much attention because they are impressive structures in tremendous natural products and drugs. As examples, the compounds containing pyrrolo[2,3-*b*]indole,[1a] spirocyclopropyl oxindole,[1b−d] 2,3′-biindole,[1e,f] and 3,3′-biindole substructures[1g,h] possess significant biological activities (Figure 1). A number of methodologies for the construction and functionalization of indole ring have thereafter been disclosed.[2] Among these methods, the transition-metal-catalyzed reactions[2e−g] exhibited more reliable and feasible as compared to the traditional indole synthesis.[2b−d]

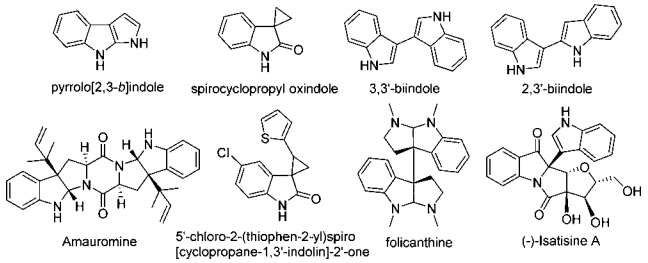


Figure 1. Indole skeletons and bioactive molecules.

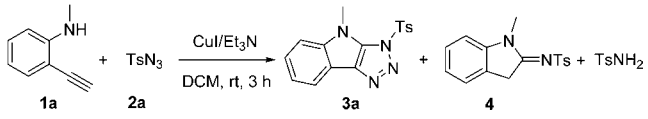
Different from unreactive 1,2,3-triazoles that had been widely used in drug discovery and fluorescent labeling, material science, and supramolecular chemistry,[3] 1-sulfonyl-1,2,3-triazole exhibits a unique role in modern organic synthesis. The weakened N_1-N_2 bond[4] facilitated the formation of α-imino rhodium carbenes and had been successfully applied in many reactions, such as transannulations,[5] ring expansion/rearrangement reactions,[6] cyclopropanations,[7] C−H insertions,[8] and arylations.[9]

Although the chemistry of 1-sulfonyl-1,2,3-triazoles in the presence of rhodium has been very impressive, the preparation of 1-sulfonyl-1,2,3-triazole is deemed challengeable because of the weakened N_1-N_2 bond. Copper-catalyzed azide−alkyne cycloaddition (CuAAC) deserved to be the most reliable and practical way to regioselective formation of 1,4-disubstituted-1,2,3-triazoles,[10] but *N*-sulfonylketenimine intermediates would be formed when sulfonyl azides were used.[11] By fine-tuning the reaction conditions, 1-sulfonyl-1,2,3-triazoles could be produced and isolated. For instance, either facilitating the protonation of 1-sulfonyl-5-copper-1,2,3-triazoles or lowering reaction temperature would produce 1-sulfonyl-1,2,3-triazoles.[12] Moreover, they could be efficiently constructed via intermolecular ligand stabilizations.[13]

Inspired by the preparation of 1-sulfonyl-1,2,3-triazoles using the intermolecular ligand stabilization, we speculated whether the ligand stabilization would be realized intramolecularly. Based on this consideration, we designed *o*-alkynylanilines as substrates. Thus, **1a**, **2a**, and Et_3N were mixed in a 1:1:2.2 ratio and reacted in the presence of CuI in CH_2Cl_2 at rt for 3 h. Triazoloindole **3a** was isolated in 32% yield, while **4** and $TsNH_2$ were formed as well (Scheme 1). This is different from the results obtained by Chang,[14] who obtained **4** as the major product and did not obtain **3a** from his catalytic system.

Delighted by this result, we optimized the reaction conditions (Table S1, Supporting Information). Increasing the amount of TsN_3 would significantly raise the yield of **3a** and

Scheme 1. Formation of 3a via Copper-Catalyzed Cycloaddition of 1a and 2a



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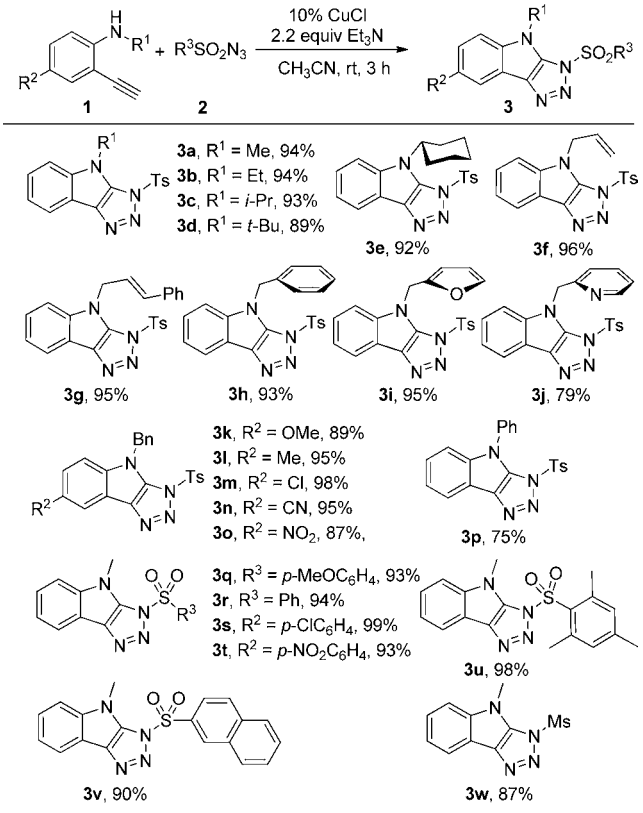
effectively inhibit the formation of **4** (Table S1, entries 1−5, Supporting Information). When 2.2 equiv of **2a** was added to **1a**, the yield reached to 80% and **4** was not detectable by HPLC. CuCl afforded the best yield in comparison with CuI and CuBr (Table S1, entried 5−7, Supporting Information). In a sharp contrast, the reaction efficiency was largely dependent on the solvent. MeCN gave the best yield (Table S1, entries 7−10, 1. By changing the base additive to K_2CO_3, **3a** was isolated in 55% yield (Table S1, entry 11, Supporting Information). In a good accordance with the results obtained by Chang,[14] **4** was formed when 2,6-lutidine was used (Table S1, entry 12, Supporting Information). Both shortening and lengthening the reaction time would decrease the yields (Table S1, entries 13 and 14, Supporting Information). When the reaction was conducted under air, the yield was dramatically decreased to 66% (Table S1, entry 15, Supporting Information). Finally, the optimized reaction conditions were established (Table S1, entry 10, Supporting Information).

With the optimized reaction conditions in hand, we thus tested the substrate scope of 2-ethynylanilines **1** (Scheme 2).

Scheme 2. Preparation of Compounds 3a−w



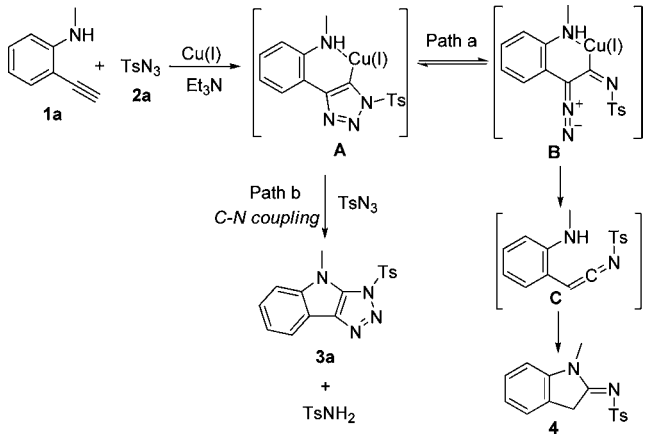
Generally, 2-ethynylanilines with alkyl group on nitrogen gave triazoloindoles **3a−o** in better yields (79−98%) than the one with aryl group on nitrogen (**3p**, 75%). A wide range of alkyl groups on the nitrogen atom of 2-ethynylanilines, such as methyl, ethyl, isopropyl, cyclohexyl, and *tert*-butyl, was suitable for this reaction.

2-Ethynylanilines, with allyl and cinnamyl on nitrogen, afforded **3f** and **3g** in 96% and 95% yields, respectively. 2-Ethynylanilines, with benzyl and 2-furanylmethyl on nitrogen, furnished **3h** and **3i** in yields of 93% and 95%, respectively. 2-Ethynyl-*N*-(pyridin-2-ylmethyl)aniline produced **3j** in 79% yield. Substituents on the benzene ring of 2-ethynylanilines could be altered from electron donating (MeO) to electron withdrawing (Cl, CN, NO_2) without significant substituent effect. Thus, **3k−o** were isolated in yields varying from 87% to 98%. The scope of azides was also investigated. Electronic and steric effects on the benzene ring of azides were not apparent as **3q−v** were obtained in similar yields (90−99%). Finally, MsN_3 was tested. In this case, **3w** was isolated in 87% yield. This protocol was reproducible and scalable. When 5 mmol of **1a** was reacted, 1.46 g of **3a** was isolated by column chromatograph in 89% yield.

In order to understand the mechanism of the present catalysis, we investigated the byproduct of the reaction. For the reaction to give **3t**, 4-nitrobenzenesulfonamide was isolated in 90% yield.

On the basis of these results, a possible mechanism was proposed (Scheme 3). In the presence of Et_3N and CuCl,

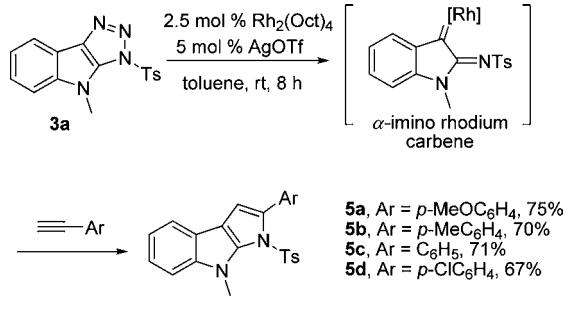
Scheme 3. Proposed Mechanism for the Formation 3a



CuAAC occurs and regioselectively produces **A**. **A** is unstable and equilibrates with its chain form **B** (path a).[4] **B** can undergo denitrogenation and protonation to form **C** and then gives **4**.[14] In the presence of an excess amount of TsN_3, **A** undergoes intramolecular C−N coupling to afford **3a** along with $TsNH_2$ (path b). In path b, TsN_3 not only works as a component but also functions as an oxidant.

Attracted by the wealthy chemistry of α-imino rhodium carbene, we investigated the reactivity of triazoloindoles **3**. Thus, **5a−d** were regioselectively prepared via α-imino rhodium carbene when **3a** reacted with terminal aryl alkynes (Scheme 4). Both electron-rich alkynes and electron-deficient alkynes could work for the reaction. This is slightly different from the previous result obtained through the rhodium-catalyzed transannulation of 1-sulfonyl-1,2,3-triazole with

Scheme 4. Rh-Catalyzed Transannulation of 3a with Alkynes



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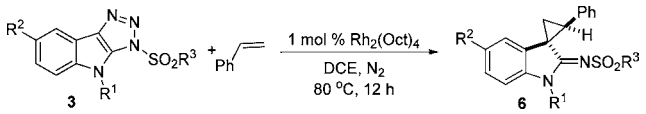
alkyne in which only the electron-rich terminal alkynes were effective.[5d]

The success of the construction of pyrrolo[2,3-*b*]indoles promoted us to further explore other reactivities of **3**. Thus, we tested the cyclopropanation of olefin with **3** in the presence of rhodium catalyst (Tables 1 and 2). When **3a**, **3h**, **3f**, **3m**, **3n**, **3s**, and **3w**, respectively, reacted with styrene in the presence of $Rh_2(Oct)_4$ in 1,2-dichloroethane at 80 °C for 12 h, **6a**−**g** were prepared in excellent yields (89−95%) with high diasterose-lectivities (dr > 95:5). Compound **3f** furnished **6c** in 90% yield, indicating the allyl group remained in the presence of α-imino rhodium carbene. The observed diastereoselectivity was the same as Fokin's work[7] and further confirmed by the single-crystal analysis of **6a**.[15] Reactions of **3** with indene in the presence of rhodium afforded **7** in excellent yields (Table 2). The structure elucidation was based on the single-crystal analysis of **7a**.[15] Substrate scope presented that different substitunt groups on the nitrogen of indole ring did not affect the output of the products. Compounds **7a**−**d** were successfully obtained in 85−97% yields (Table 2, entries 1−4). The sulfonyl group could also be alternated from tosyl to *p*-methoxybenze-nesulfonyl, *p*-chlorobenzenesulfonyl, and 2-naphthlenesulfonyl (Table 2, entries 5−7).

As an exceptional example, electron-rich 1-methoxy-4-vinylbenzene, furnished **8a**−**i** in 74−94% yields instead of obtaining the 3-cyclopropyl-2-iminoindole (Table 3). Oxidation of **8a** with DDQ afforded **5a** (81% yield), indicating that **8** possess the skeleton of 2,3-dihydropyrrolo[2,3-*b*]indole and the reaction was regioselective. Substitunets on the nitrogen of indole could be altered from methyl to ethyl to isopropyl (Table 3, entries 1−3). Substitunts on the phenyl ring of indole could be electron donating (CH_3) (Table 3, entry 4) and electron withdrawing (CN) (Table 3, entry 5). The sulfonyl group could also be altered from *p*-nitrobenzenesulfonyl, *p*-chlorobenzene-sulfonyl, and *p*-methoxybenzenesulfonyl to 2-naphthalenesulfonyl (Table 3, entries 6−9).

Subsequently, we moved our attention to the rhodium-catalyzed arylation[9] of **3** with indoles (Scheme 5). Both electron-donating and electron-withdrawing substituted indoles were investigated, and 3,3′-biindoles **9a**−**h** were isolated in excellent yields (93−99%) with high regioselectivities. For 1,3-dimethyl-1*H*-indole, 2,3′-biindoles **10a**−**f** were prepared in excellent yields (82−94%) (Scheme 6). Their structures were

Table 1. Rh-Catalyzed Cyclopropanation of 3 with Styrene[a]

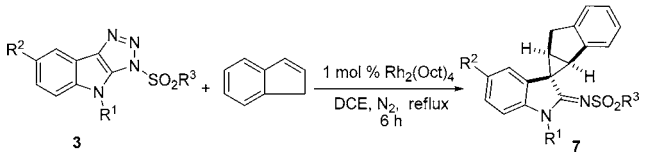


3 6

entry	R^1	R^2	R^3	**6**/yield (%)	dr
1	Me	H	Tol	**6a**/95	>95:5
2	Bn	H	Tol	**6b**/94	>95:5
3	allyl	H	Tol	**6c**/90	>95:5
4	Bn	Cl	Tol	**6d**/93	>95:5
5	Bn	CN	Tol	**6e**/89	>95:5
6	Me	H	*p*-ClC_6H_4	**6f**/93	>95:5
7	Me	H	Me	**6g**/91	>95:5

[a]Reaction conditions: **3** (0.2 mmol), alkene (1.0 mmol), $Rh_2(Oct)_4$ (0.002 mmol), DCE (2 mL), N_2, 80 °C, 12 h. Yield refers to the isolated yield. The dr values are determined from the ^1H NMR spectra of the crude products.

Table 2. Rh-Catalyzed Cyclopropanation of 3 with Indene[a]

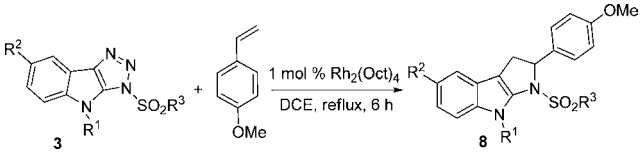


3 7

entry	R^1	R^2	R^3	**7**/yield (%)	dr
1	Me	H	Tol	**7a**/97	>95:5
2	Et	H	Tol	**7b**/93	>95:5
3	*i*-Pr	H	Tol	**7c**/90	>95:5
4	Bn	Me	Tol	**7d**/85	>95:5
5	Me	H	*p*-$MeOC_6H_4$	**7e**/90	>95:5
6	Me	H	*p*-ClC_6H_4	**7f**/88	>95:5
7	Me	H	2-naphthyl	**7g**/83	>95:5

[a]Reaction conditions: **3** (0.2 mmol), alkene (1.0 mmol), $Rh_2(Oct)_4$ (0.002 mmol), DCE (2 mL), N_2, reflux, 6 h.

Table 3. Rh-Catalyzed Cyclization of 3 with 1-Methoxy-4-vinylbenzene[a]

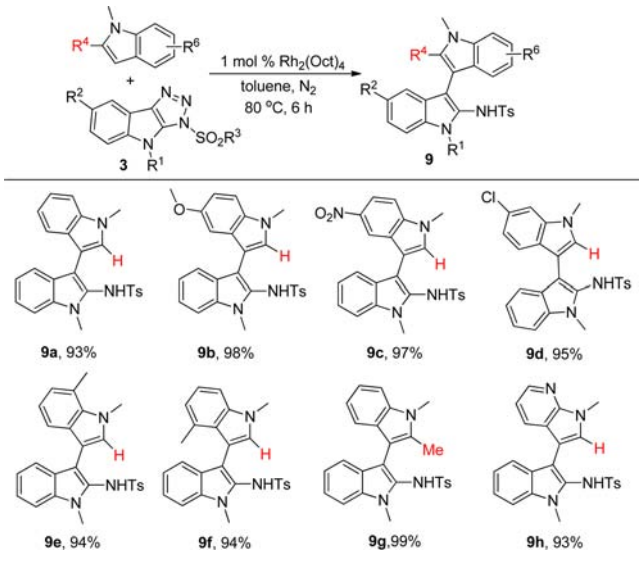


3 8

entry	R^1	R^2	R^3	**8**/yield (%)
1	Me	H	Tol	**8a**/87
2	Et	H	Tol	**8b**/83[b]
3	*i*-Pr	H	Tol	**8c**/89
4	Bn	Me	Tol	**8d**/82
5	Bn	CN	Tol	**8e**/77
6	Me	H	*p*-$NO_2C_6H_4$	**8f**/93
7	Me	H	*p*-ClC_6H_4	**8g**/94
8	Me	H	*p*-$MeOC_6H_4$	**8h**/77
9	Me	H	2-naphthyl	**8i**/74

[a]Reaction conditions: **3** (0.2 mmol), 1-methoxy-4-vinylbenzene (1.0 mmol), $Rh_2(Oct)_4$ (0.002 mmol), DCE (2 mL), reflux, N_2, 6 h. [b]Toluene, reflux, 8 h.

Scheme 5. Rh-Catalyzed Arylation to 3,3′-Biindoles



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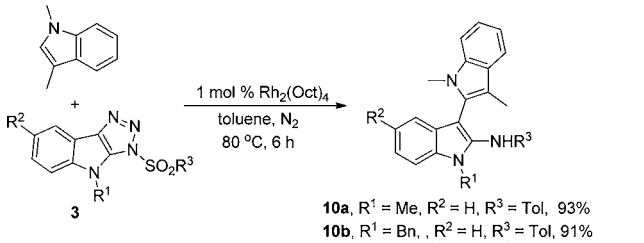
Scheme 6. Rh-Catalyzed Arylation to 2,3′-Biindoles



confirmed by the single-crystal analysis of **10e**.[15] It was noticed that **3j** bearing a pyridinylmethyl group was recovered after it reacted with 1,3-dimethyl-1*H*-indole.

In conclusion, we have developed an efficient method for the preparation of triazoloindoles from *o*-alkynylanilines and sulfonyl azides. Construction of the fragile 1-sulfonyl-1,2,3-triazole ring was realized by stabilizing 5-copper-1,2,3-triazole intermediate through intramolecular coordination. Although triazoloindoles were seldom reported,[16] they presented rich chemistry in the presence of rhodium catalyst because they could be easily transferred into the α-imino rhodium carbene which is embedded in the indole skeleton. Through these distinct α-imino rhodium carbenes, a variety of valuable indole molecules were constructed, including pyrrolo[2,3-*b*]indoles, spirocyclopropyl iminoindoles, 2,3-dihydropyrrolo[2,3-*b*]-indoles, 3,3′-biindoles, and 2,3′-biindoles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) For CIsF of **6a**, **7a**, and **10e**, see the Supporting Information. CCDC 968839 (**6a**), CCDC 968840 (**7a**), and CCDC 968841 (**10e**) contain supplementary crystallographic data and can be obtained from the Cambridge Crystallographic Data Centre.

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