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Rh-Catalyzed Reactions of 3-Diazoindolin-2-imines: Synthesis of Pyridoindoles and Tetrahydrofuropyrroloindoles

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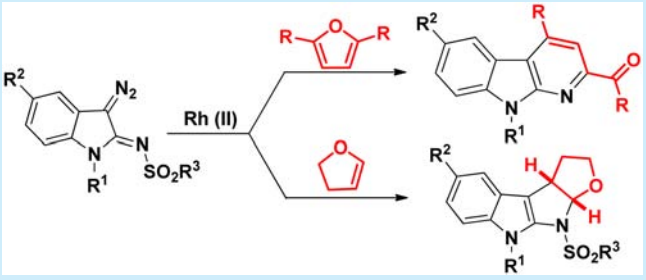
Supporting Information

ABSTRACT: The rhodium-catalyzed reactions of 3-diazoindolin-2-imines with furans and dihydrofuran furnished 9*H*-pyrido[2,3-*b*]indoles and tetrahydrofuro[3′,2′:4,5]pyrrolo[2,3-*b*]indoles, respectively. A cascade reaction mechanism involving an α-imino rhodium carbene intermediate is proposed. The starting materials are readily available, and the procedure is facile and efficient.

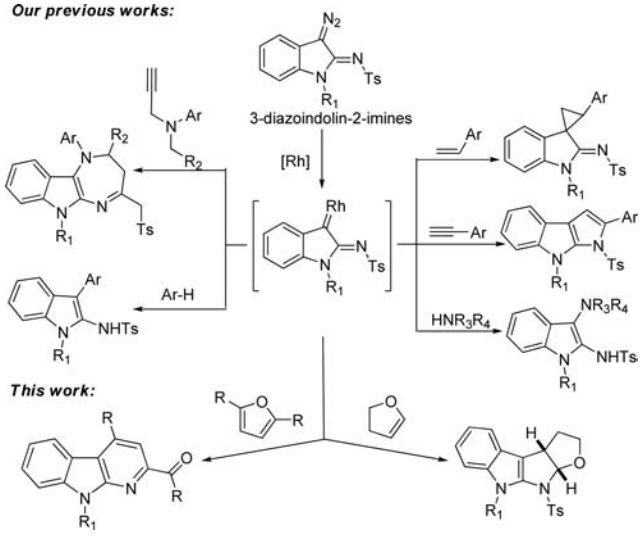


Indole and its derivatives are important scaffolds in naturally occurring compounds,[1] pharmaceuticals,[2] and optoelectronics materials.[3] Their unique functions and structural diversities provide inspiration in the discovery of modern synthetic methods, including the construction of indole skeletons and the functionalization of indole rings.[4]

Recently, α-imino rhodium carbene is becoming an increasingly valuable intermediate in organic synthesis because of the easy formation from 1-sulfonyl-1,2,3-trazole and various effective transformations to a broad range of organic compounds.[5] Fokin,[6] Gevorgyan,[7] Murakami,[8] Davies,[9] Sarpong,[10] Shi,[11] and other groups[12] have made significant contributions in this chemistry. Inspired by the vivid reactivity of α-imino rhodium carbenes and attracted by the importance of indole ring systems, we recently demonstrated a class of indole-embedded α-imino rhodium carbenes in situ generated from 3-diazoindolin-2-imines in the presence of a rhodium catalyst.[13] Upon these specific rhodium carbenes, a series of reactions had been realized, such as arylation, cyclopropanation, N−H insertion, and transannulation (Scheme 1).[13] These transformations furnished a variety of indole derivatives. In continuation of our study on this chemistry, we herein report a rhodium-catalyzed synthesis of 9*H*-pyrido[2,3-*b*]indoles and tetrahydrofuro[3′,2′:4,5]pyrrolo[2,3-*b*]indoles from 3-diazoindolin-2-imines via an indole-embedded α-imino rhodium carbene intermediate.

Our initial trial was conducted between 3-diazo-indolin-2-imine (**1a**) and 2,5-dimethylfuran (**2a**, 2 equiv) in the presence of $Rh_2(Oct)_4$ (1 mol %) in dichloroethane (DCE) at 80 °C for 3 h. After workup, 9*H*-pyrido[2,3-*b*]indole (**3a**) and dihydrofuro[3′,2′:4,5]pyrrolo[2,3-*b*]indole (**4**) were isolated in 36% and 9% yields, respectively (Scheme 2). The structure of **3a** was established by the single crystal analysis of its analog **3d**.[16] Further investigation demonstrated that **4** was unstable and could be converted into **3a** with or without a rhodium catalyst.

Scheme 1. Preparation of Indole Derivations via α-Imino Rhodium Carbenes



In consideration of the importance of 9*H*-pyrido[2,3-*b*]indoles, also called α-carboline, in pharmaceuticals[14] and optoelectronics materials,[15] we optimized the reaction conditions for the preparation of **3a** (Table S1; see Supporting Information). The highest yield (64%) and the best selectivity were approached when the reaction was carried out in DCE at 80 °C for 8 h (Table S1, entry 16).

Subsequently, we evaluated the effectiveness of the sulfonyl group on 3-diazoindolin-2-imines **1** (Scheme 3). Reactions were conducted under standard reaction conditions except for the reaction time which was determined by thin layer

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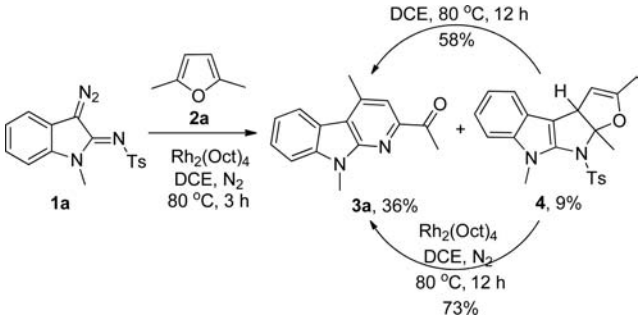
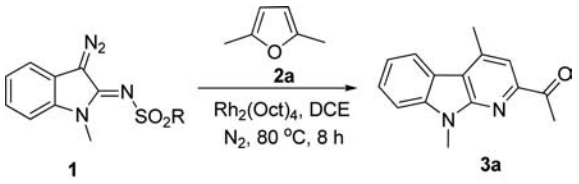
Scheme 2. Formation and Conversion of 3a and 4



Scheme 3. Scope of Sulfonyl of 3-Diazo-indolin-2-imines



	yield of **3a**
1a: R = Tol	64%
1b: R = Ph	65%
1c: R = *p*-FC_6H_4	61%
1d: R = *p*-ClC_6H_4	57% (12 h)
1e: R = 2-naphthyl	51%
1f: R = Me	26% (20 h)

chromatography. A slightly higher yield was observed for *N*-benzenesulfonyl 3-diazoindolin-2-imine **1b**, while *p*-fluorobenzenesulfonyl (**1c**), *p*-chlorobenzenesulfonyl (**1d**), 2-naphthalenesulfonyl (**1e**), and methanesulfonyl substituted 3-diazoindolin-2-imines (**1f**) afforded **3a** in decreased yields.

With the optimized reaction conditions in hand, we tested the substrate scope of this transformation. First, we investigated the scope of 3-diazoindolin-2-imines, and the results are summarized in Figure 1. The substituent on the 1-position of 3-diazoindolin-2-imines could be ethyl (**1g**), isopropyl (**1h**), allyl (**1i**), phenyl (**1j**), benzyl (**1k**), and H (**1l**). Thus, the corresponding products **3b**−**g** were obtained in yields varying from 40% to 55%. The substituent on the 5-position of 3-diazoindolin-2-imine could be either an electron-donating group, such as OMe (**1m**) and Me (**1n**), or an electron-withdrawing group, such as F (**1o**), Cl (**1p**), and Br (**1q**). In these cases, the reaction furnished the corresponding products **3h**−**n** in 68%−86% yields.

The scope of furans was also studied. Furan (**2b**) furnished **3o**−**s** in 33%−48% yields, while 2,5-diphenylfuran (**2c**) provided **3t** and **3u** in 47% and 49% yields, respectively (Figure 2). For the unsymmetrical furans, such as 2-methylfuran (**2d**), 2-ethylfuran (**2e**), 2-methyl-5-benzylfuran (**2g**), and 3-methylfuran (**2h**), the desired products **3va** (38%), **3wa** (40%), **3ya** (27%), and **3z** (8%) were selectively yielded, while their isomers **3vb**, **3wb**, and **3yb** were determined to be trace by ^{1}H NMR (Scheme 4). In the case where 2-methyl-5-phenylfuran (**2f**) was used as a substrate, the desired products **3xa** and **3xb** were isolated in 18% yield for each.

Based on these results, we proposed a possible mechanism for the formation of **3** and **4** (Scheme 5). In the presence of a rhodium(II) catalyst, **1a** is converted into rhodium carbene **A**. Then, **2** nucleophilically attacks the electron-deficient rhodium carbene through two possible pathways. In path A, the attack

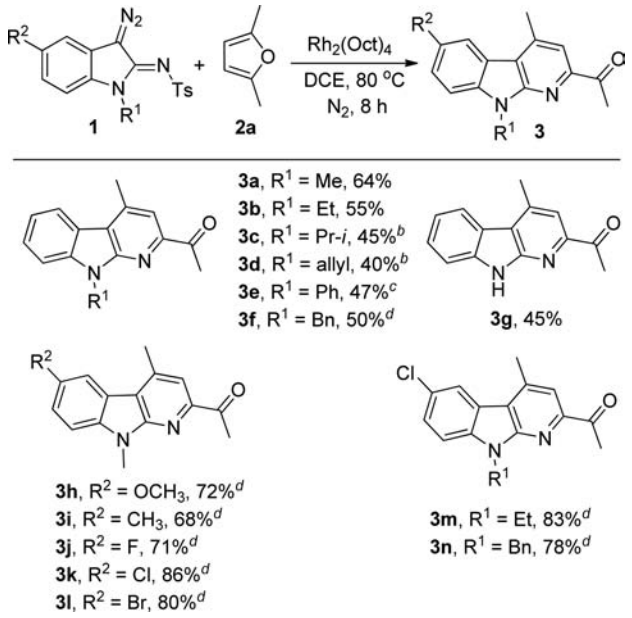


Figure 1. Scope of 3-Diazoindolin-2-imines.[a] [a] Reaction conditions: **1** (0.2 mmol), **2a** (2 mmol), $Rh_2(Oct)_4$ (0.002 mmol), DCE (2 mL), N_2, 80 °C, 8 h. Isolated yield. [b] 18 h. [c] 10 h. [d] 24 h.

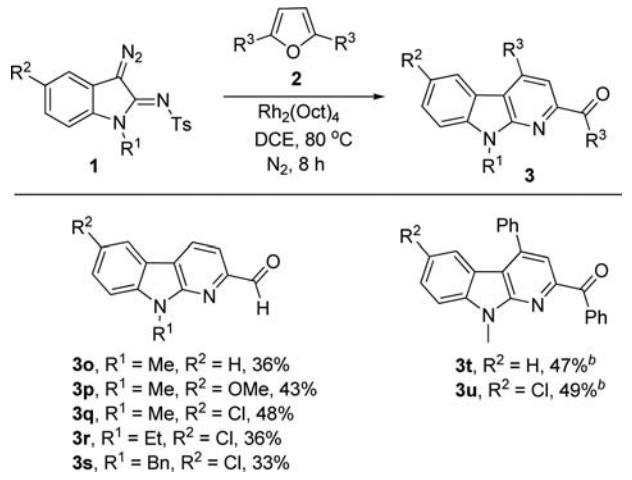


Figure 2. Scope of furans.[a] [a] Reaction conditions: **1** (0.2 mmol), **2** (2 mmol), $Rh_2(Oct)_4$ (0.002 mmol), DCE (2 mL), N_2, 80 °C, 8 h; Isolated yield. [b] 30 h.

occurs at the 2-position of furan to form intermediate **B**, which undergoes a sequential ring-opening, 6π-electron ring closure (6π-ERC) and E_2 elimination to afford **3**. In path B, the attack occurs at the 3-position of furan to generate intermediate **E**, which undergoes an intramoleclular nucleophilic addition to afford **4**. **4** is unstable and can rearrange to **3** through a three-membered ring intermediate **G**. For the monosubstituted furans **2d**, **2e**, and **2h**, Path A seems possible. However, for 2,5-disubstituted furans, Path B should be more likely due to the steric effect.

The reactions between **3** and dihydrofuran (**5**) were also studied. In the presence of a rhodium catalyst, **3a** reacted with **5** in DCE at 80 °C for 4 h to provide tetrahydrofuro[3′,2′:4,5]-pyrrolo[2,3-*b*]indole **6a** (Figure 3) in 43% yield. The optimized reaction conditions were established when the reaction of **1a** with **5** (2 equiv) was performed in the presence of $Rh_2(Oct)_4$

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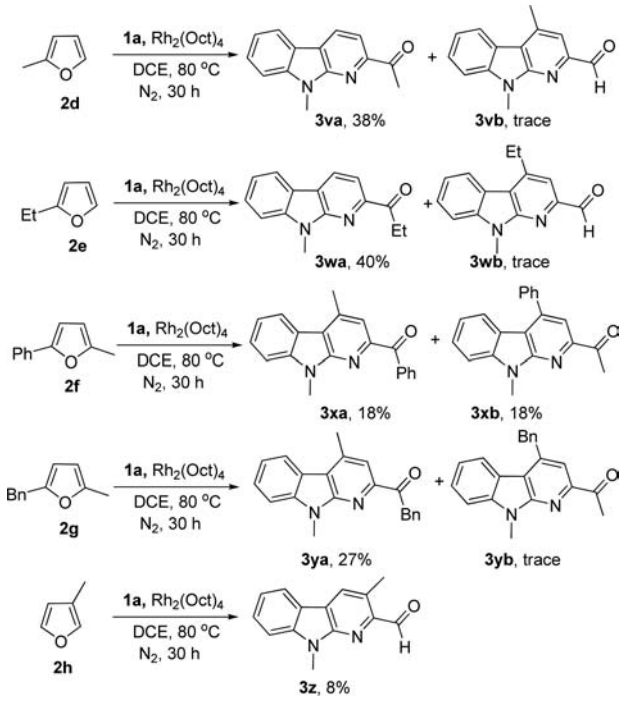
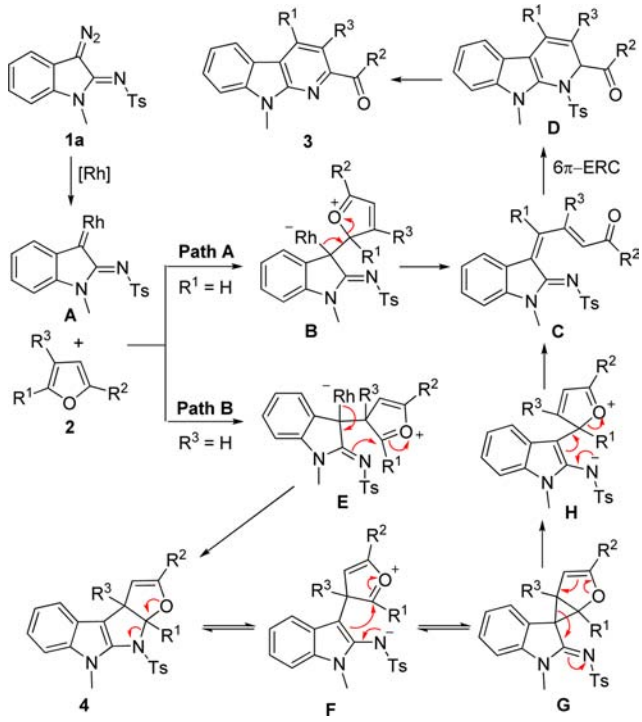
Scheme 4. Reaction of 1a with Asymmetrical Furans



Scheme 5. Possible Mechanism for the Formation of 3 and 4



(1 mol %) in chloroform (2 mL) at 80 °C for 3 h (Table S2, entry 2; see Supporting Information).

Under the optimized reaction conditions, we tested the substrate diversity (Figure 3). Altering the substituent on the 1-position of 3-diazoindolin-2-imines from methyl (**1a**) to ethyl (**1g**), allyl (**1i**), benzyl (**1k**), and phenyl (**1j**) led to the formation of the corresponding products **6b**–**e** in 54%–62% yields. The structure of **6c** was determined by its single crystal analysis.[16] The highest yield (70%) was observed for **6f** in the

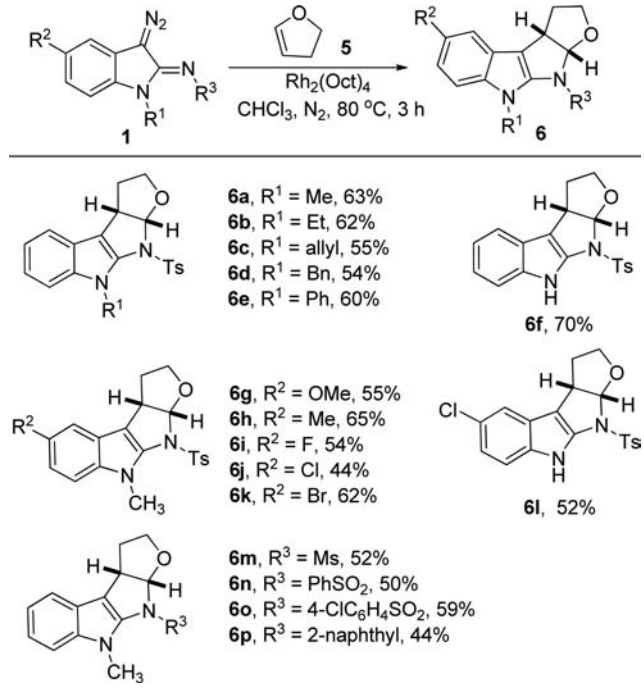
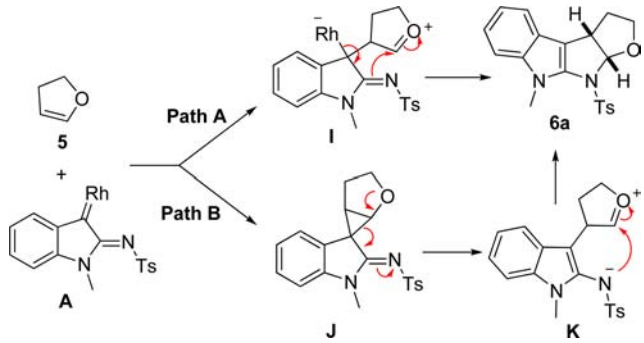


Figure 3. Scope of 3-diazoindolin-2-imines for preparation of **6**. Reaction conditions: **1** (0.2 mmol), **5** (0.4 mmol), $Rh_2(Oct)_4$ (0.002 mmol), $CHCl_3$ (2 mL), N_2, 80 °C, 3 h. Isolated yield.

case where 1-unsubstituted 3-diazoindolin-2-imine **1l** was used as the substrate. The 5-substituted 3-diazoindolin-2-imines furnished the corresponding products **6g**–**l** in 44%–65% yields. The sulfonyl group on 3-diazoindolin-2-imines **1** could be methanesulfonyl (**1f**), benzenesulfonyl (**1b**), *p*-chlorobenzenesulfonyl (**1d**), and naphthalenesulfonyl (**1e**). In these cases, the desired products **6m**–**p** were obtained in 44%–59% yields.

A possible mechanism for the formation of **6a** is illustrated in Scheme 6. Compound **6a** might be formed through two

Scheme 6. Possible Mechanism for Formation of 6a



possible paths. In path A, nucleophilic addition of dihydrofuran to the in situ generated rhodium carbene **A** forms intermediate **I**, which undergoes an intramolecular nucleophilic addition to afford **6a**. Alternatively, the cyclopropanation of rhodium carbine occurs to form intermediate **J**, which undergoes a rearrangement to give **6a** (path B).

In summary, we have developed a rhodium-catalyzed synthesis of 9*H*-pyrido[2,3-*b*]indoles and tetrahydrofuro-[3′,2′:4,5]pyrrolo[2,3-*b*]indoles by the reactions of 3-diazoindolin-2-imines with furans and dihydrofuran, respectively. These transformations proceeded through an indole-embedded

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α-imino rhodium carbene intermediate. The cascade mechanism for the formation of 9*H*-pyrido[2,3-*b*]indoles includes nucleophilic addition of furan to rhodium carbene, 6π-electron ring closure, and elimination−aromatization. Studies on the synthetic applications of this methodology and further exploration of the chemistry of 3-diazoindolin-2-imines are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01943.

Experimental procedures and characterization data for all new compounds (PDF)
Crystallographic information for compound **3d** (CIF)
Crystallographic information for compound **6c** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(16) CCDC 1408514 (**3d**) and CCDC 1408515 (**6c**) contain supplementary crystallographic data for this paper.

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