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α-Amidino Rhodium Carbenes: Key Intermediates for the Preparation of (*E*)-2-Aminomethylene-3-oxoindoles and Pyranoindoles

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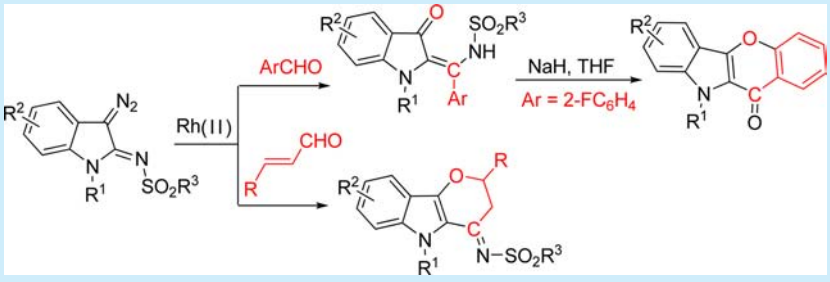
Supporting Information

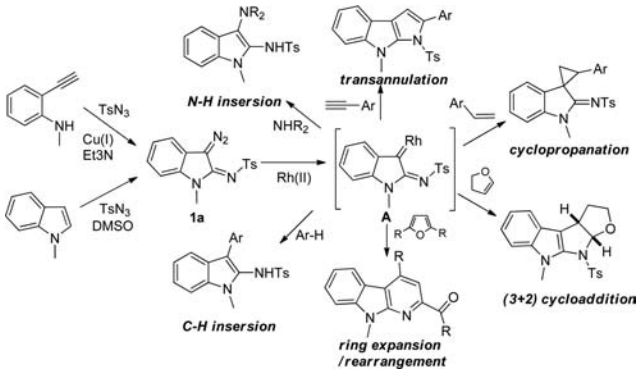


ABSTRACT: Rhodium-catalyzed reactions of 3-diazoindolin-2-imines with aromatic aldehydes and α,β-unsaturated aldehydes respectively furnished (*E*)-2-aminomethylene-3-oxoindoles and pyranoindoles in moderate to excellent yields with nice functional group tolerance. The reaction proceeds in a cascade involving α-amidino rhodium carbene as the key intermediate.

The indole scaffold with functional groups widely exists in natural products[1] and pharmaceutical compounds.[2] Their particular bioactive functions and structural diversities have attracted much attention from organic chemists who wish to develop the construction[3] and functionalization[4] of the indole skeleton.

The rhodium(II)-catalyzed denitrogenative transformation of 1-sulfonyl-1,2,3-triazoles has rapidly become a useful synthetic strategy for the preparation of various nitrogen-containing cyclic and acyclic compounds.[5] Several research groups have made significant contribution to this field, such as Fokin,[6] Gevorgyan,[7] Murakami,[8] Davies,[9] Sarpong,[10] Shi,[11] and so on. In 2014, our group developed two different methods to prepare 3-diazoindolin-2-imines **1** which could undergo rhodium(II)-catalyzed denitrogenative transformation through α-amidino rhodium carbene intermediate **A**.[12] As shown in Scheme 1, a series of typical reactions, such as transannulation, cyclopropanation, (3 + 2) cycloaddition, ring expansion/rearrangement, C−H insertion, and N−H insertion, had been realized through this α-amidino rhodium carbene. As a result, a number of indole-containing compounds have been synthesized.[13]

Scheme 1. Preparation of 3-Diazoindolin-2-imines and their Rhodium-Catalyzed Reactions



In our continuing research on the chemistry of 3-diazoindolin-2-imines in the presence of rhodium catalyst, we wonder whether the carbonyl oxygen could serve as the nucleophile to trap the electron deficient α-amidino rhodium carbene intermediate. The first trial was conducted between 3-diazoindolin-2-imine (**1a**) and 2-fluorobenzaldehyde (**2a**, 4.5 equiv) in the presence of $Rh_2(TFA)_4$ (rhodium(II) trifluoroacetate dimer) and 4 Å molecular sieves (MS) in dichloromethane (DCM) at 100 °C. After 4 h, **1a** was completely consumed and **3a** was isolated in 59% yield. The structure of **3a** was confirmed by ^1H NMR, ^{13}C NMR, HRMS, and the single crystal analysis of its analogues (**3o** and **3t**).[14] The carbonyl carbon of 2-fluorobenzaldehyde was inserted into the C−N bond of amidine in the starting material **1a**. Delighted by this result, we screened the reaction conditions, including catalyst, solvent, reaction temperature, and time. Results were listed in Table 1. By screening other Rh(II) catalysts, $Rh_2(HFB)_4$ (rhodium(II) heptafluorobutyrate dimer) was found to be optimal (Table 1, entries 1−6). No reaction occurred either with Cu(II) or Ag(I) as the catalyst (Table 1, entries 7 and 8). As to the various solvents tested, polar aprotic solvents (CH_3CN and DMSO) were not suitable in comparison with DCE, DCM, toluene, and $CHCl_3$. Among these, DCM provided **3a** in the highest yield (Table 1, entries 2, 9−13).

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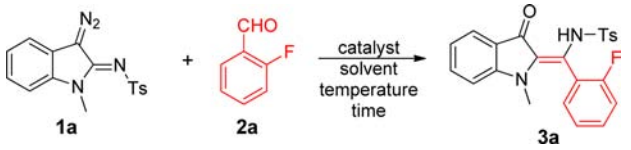
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	time (h)	yields (%)[b]
1	$Rh_2(TFA)_4$	DCM	100	4	59
2	$Rh_2(HFB)_4$	DCM	100	4	67
3	Rh_2(s-DOSP)$_4$	DCM	100	4	trace
4	$Rh_2(OAc)_4$	DCM	100	4	36
5	$Rh_2(Oct)_4$	DCM	100	4	trace
6	$Rh_2(esp)_2$	DCM	100	4	trace
7	$Cu(OTf)_2$	DCM	100	4	trace
8	AgOTf	DCM	100	4	trace
9	$Rh_2(HFB)_4$	DCE	100	4	51
10	$Rh_2(HFB)_4$	$CHCl_3$	100	4	40
11	$Rh_2(HFB)_4$	toluene	100	4	27
12	$Rh_2(HFB)_4$	CH_3CN	100	4	trace
13	$Rh_2(HFB)_4$	DMSO	100	4	trace
14	$Rh_2(HFB)_4$	DCM	100	4	42[c]
15	$Rh_2(HFB)_4$	DCM	rt	4	33
16	$Rh_2(HFB)_4$	DCM	40	4	56
17	$Rh_2(HFB)_4$	DCM	120	4	46
18	$Rh_2(HFB)_4$	DCM	100	2	35
19	$Rh_2(HFB)_4$	DCM	100	5	66

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.9 mmol), catalyst (0.005 mmol), solvent (2 mL), 4 Å MS (20 mg). [b]Isolated yields. [c]Without 4 Å MS.

Without 4 Å MS, a dramatically decreased yield was observed (Table 1, entry 14). Finally, we screened the reaction temperature and time. The optimal reaction temperature and time were found to be 100 °C and 4 h, respectively (Table 1, entries 2, 16−19).

With the optimized reaction conditions (Table 1, entry 2), we tested the substrate scope of this transformation. First, we investigated the scope of aromatic aldehydes (**2**) (Figure 1). As shown in Figure 1, when 3-diazoindolin-2-imine (**1a**) reacted with benzaldehydes with various substituents, corresponding

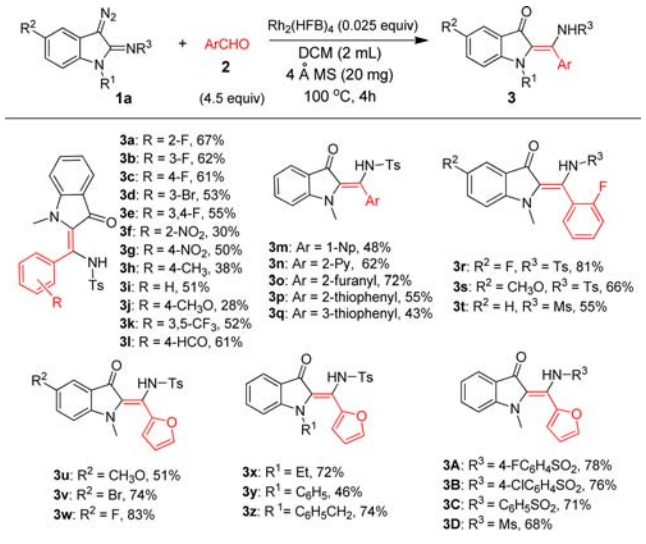


Figure 1. Scope of aryl aldehyde.

products (**3a−l**) were smoothly obtained in yields ranging from 27% to 67%. With the electron withdrawing group occupying the phenyl ring of benzaldehyde, corresponding products were isolated in higher yields in comparison with those with electron-donating groups. 2-Nitrobenzaldehyde provided **3f** in 30% yield because of the steric hindrance. 4-Methylbenzaldehyde and 4-methoxybenzaldehyde afforded **3h** and **3j** in 38% and 28% yields, respectively. It is noticeable that terephthaldehyde worked well and provided **3l** in 61% yield with the reservation of one unreacted formyl group. When 1-naphthaldehyde and pyrene-2-carbaldehyde reacted, **3m** and **3n** were obtained in 48% and 62% yields, respectively. When fural (**2b**), 2- or 3-formyl thiophenes were used as substrates, **3o**, **3p**, and **3q** were respectively obtained in 72%, 55%, and 43% yields.

Subsequently, a variety of 3-diazoindolin-2-imines (**1**) were subjected to the rhodium-catalyzed reaction with *o*-fluoroaldehyde (**2a**) under the same reaction conditions. The substituent on the 5-position of indole skeleton could be altered from electron withdrawing (F) to electron donating (CH_3O). Thus, **3r** and **3s** were isolated in 81% and 66% yields, respectively. This situation was also observed for the series of **3u**, **3v**, and **3w**. Higher yields were observed for those with electron withdrawing groups, such as bromo (**3v**, 74%) and fluoro (**3w**, 83%). The substituent on the 1-position of indole skeleton could be altered from methyl (**3o**), ethyl (**3x**), phenyl (**3y**), and benzyl (**3z**). When 1-position of indole was hydrogen, the reaction did not occur. Both arenesulfonyl and alkenesulfonyl in 3-diazo-indolin-2-imines worked well for this reaction. Thus, compounds **3A−D** were prepared in moderate yields ranging from 68% to 78%.

The reactions between **1** and acrylaldehydes (**4**) were also investigated. In the presence of $Rh_2(TFA)_4$ and 4 Å MS, **1a** reacted with (*E*)-but-2-enal (**4a**) in toluene at 60 °C. After 3 h, pyranoindole (**5a**) was isolated in 34% yield (Figure 2). The

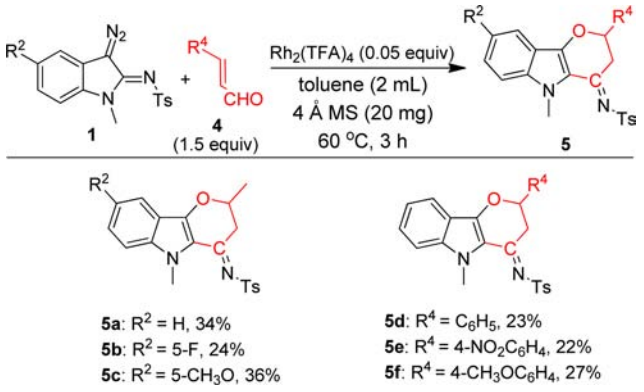


Figure 2. Rh-catalyzed reactions between 3-diazoindolin-2-imines **1** and acrylaldehydes **4**.

structure of **5a** was confirmed by its single crystal analysis.[14] Unfortunately, the yield of **5a** could not be raised anymore although many efforts had been made, such as changing catalyst, solvent, temperature, and time (Table S1). We even tried to change the substrate (Figure 2). Altering the substituent on the 5-position of indole in 3-diazoindolin-2-imines (**1**), **5b** (5-F) and **5c** (5-MeO) were obtained in 24% and 36% yields, respectively. When *E*-cinnamaldehyde (**4b**) reacted with **1a**, **5d** was isolated in 23% only. Poor yields were also observed for those cinnamaldehydes either with electron

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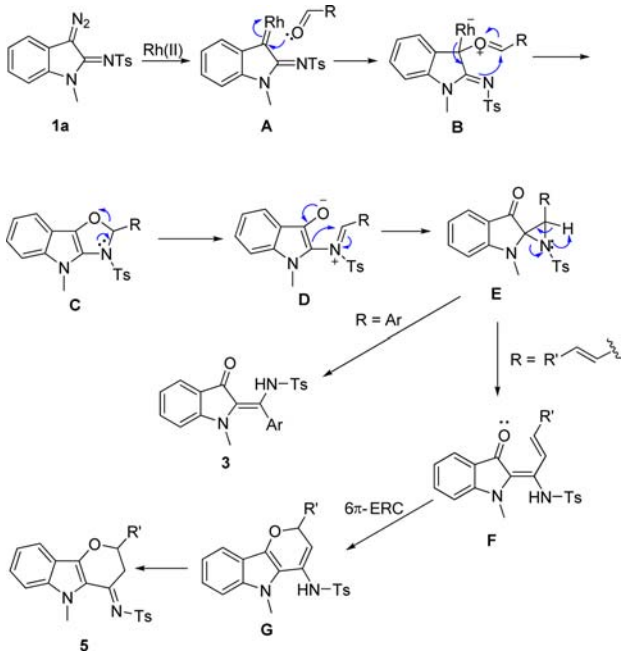
withdrawing (4-NO_2, **5e**) or with electron donating (4-MeO, **5f**) on the phenyl ring of *E*-cinnamaldehyde.

On the basis of the above findings, we proposed a possible mechanism for the formation of **3** and **5** (Scheme 2). In the presence of a rhodium(II) catalyst, **1a** is converted into α-amidino rhodium carbene **A**. Then, the oxygen of aldehyde nucleophilically attacks the electron-deficient rhodium carbene to form adduct **B**. Followed by a sequential electron movement, oxazoline ring **C** is formed. **C** is unstable and the C−O bond is selectively cleaved due to the higher electronegativity of oxygen and the higher electron-donating ability of nitrogen.[15] It provides the zwitterionic intermediate **D**. Subsequently, the enolate moiety of **D** intramolecularly attacks the electron deficient iminium moiety to give the aziridine ring **E**. Finally, when the nucleophile is aryl aldehyde, **E** undergoes a ring-opening to afford 2-aminomethylene-3-oxoindoles with C=C double bond in *E*-configuration because of the intramolecular hydrogen bonding between carbonyl oxygen and NH of sulfonamide in product **3**. When the nucleophile is acrylaldehyde **4**, **E** opens to form intermediate **F** which may undergo 6π-electron ring closure (6π-ERC) and tautoumerism to afford **5**.

Scheme 2. Proposed Mechanism for the Formation of 3 and 5



The synthetic utility of 2-aminomethylene-3-oxoindoles (**3**) was shown by their further transformations. When **3a** reacted with sodium hydride (NaH), a product **6a** with bright blue fluorescence was obtained in 93% yield (Figure 3). The structure of **6a** contained chromeno[3,2-*b*]indol-11-oneskeleton which was already known.[16] A similar reaction could be conducted with **3r**, **3s**, and **3t**. Excellent yields were observed for these base-induced reactions.

A possible mechanism for the formation of **6a** is illustrated in Scheme 3. Irreversible deprotonation of **3a** in the presence of NaH provides phenolic anion **H** as a strong nucleophile. Subsequently, a nucleophilic aromatic substitution (S_NAr) occurs intramolecularly and provides intermediate **I**. Finally, hydrolysis of **I** furnishes chromeno[3,2-*b*]indol-11-one (**6a**) in excellent yield.

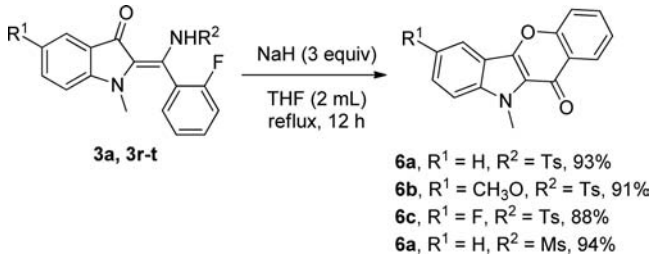
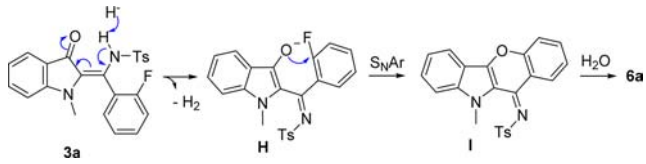


Figure 3. Preparation of benzopyranoindoles **6**.

Scheme 3. Proposed Mechanism for the Formation of 6



In summary, we have developed the syntheses of (*E*)-2-aminomethylene-3-oxoindoles and pyranoindoles from the reactions of 3-diazoindolin-2-imines with aromatic aldehydes and α,β-unsaturated aldehydes, respectively. In the presence of sodium hydride, the prepared (*E*)-2-aminomethylene-3-oxoindoles could be further derived into chromeno[3,2-*b*]indol-11-ones in excellent yields. The synthesized heterocycles with an indole skeleton may find applications in medicinal chemistry. Further exploration of the chemistry of 3-diazoindolin-2-imines is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01728.

Experimental procedures and characterization data for all new compounds (PDF)

Crystallographic information file for compounds **3o** (CIF)

Crystallographic information file for compounds **3t** (CIF)

Crystallographic information file for compounds **5a** (CIF)

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Notes

The authors declare no competing financial interest.

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