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Rhodium-Catalyzed C=N Bond Formation through a Rebound Hydrolysis Mechanism and Application in β -Lactam Synthesis

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Supporting Information

ABSTRACT: A rhodium-catalyzed reaction of *N*-hydroxyanilines with diazo compounds to produce α -imino esters was developed. Distinct from the commonly accepted 1,2-H transfer for normal X–H insertion reactions, density functional theory calculations indicate that this transformation



proceeds via a novel rebound hydrolysis mechanism. Furthermore, a three-component reaction was explored to synthesize highly functionalized β -lactams in good yields and diastereoselectivities.

T ransition-metal-catalyzed carbene transfer represents a powerful tool for constructing various carbon-carbon and carbon-heteroatom bonds in organic synthesis.¹ Typically, the catalytic carbene insertion into X-H bonds (X = N, O, S, Si, B, etc.), simplified as X-H insertion reactions (XHI), has been broadly utilized to form C-X bonds.² The commonly accepted mechanism for XHI reactions proceeds stepwise (the Si-H bond and B-H bond insertion reactions generally undergo a concerted mechanism), namely, the nucleophilic attack of the heteroatom to electrophilic metal-carbene provides the key ylide intermediate, which undergoes 1,2-proton transfer from X to C to form the C-X single bond (Scheme 1a).

To develop novel metal-carbene mediated transformations,³ recently, we reported a rhodium-catalyzed selective N²alkylation of benzotriazoles with diazo compounds.^{3b} Quantum mechanical calculations disclose that the reaction involves a 1,3-proton transfer from N¹ to C of ¹H-benzotriazole to form N^2-C single bond. Herein, we wish to report another novel formal XHI reaction with an unprecedented reaction mechanism. We found that the reaction of N-hydroxyaniline (an amphiphilic nucleophile with O and N nucleophilic properties⁴) with rhodium-carbene intermediates produced imines rather than N-H/O-H insertion products (Scheme 1b). Density functional theory (DFT) calculations indicate that C-N bonding proceeds through the nucleophilic addition of nitrogen atom to rhodium carbene. However, the 1,2-proton transfer from N to C does not occur, but the leaving of hydroxy anion does occur. This anion conversely abstracts the hydrogen from nitrogen and releases a molecule of H₂O to form the C=N double bond. This addition-leavingabstraction process, namely a "rebound hydrolysis" mecha-

Scheme 1. Previous Reports and Our Work



nism, is distinct from the common XHI reactions for C-X single bond formation.

On the other hand, α -imino esters are key building blocks in organic synthesis with diverse applications.⁵ Although numerous methods exist, there are still limitations in preparing such motifs. Using metal–carbene as key intermediates, in 2005, the Hu group described a rhodium catalyzed three-

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component reaction of α -diazoesters, anilines, and azodicarboxylates to produce α -imino esters.⁶ Later, the Doyle group⁷ reported the preparation of α -imino esters from donor/ acceptor dirhodium carbenes with azides. Just recently, the Fürstner group developed an efficient protocol by catalytic metathesis of azobenzenes using a half-sandwich rhodium catalyst under blue LED irradiation.⁸ Compared with azides and azobenzenes, *N*-hydroxyanilines have many advantages such as stability, safety, and ready availability. We then sought to test *N*-hydroxyanilines as the nitrogen sources to prepare α imino esters. The initial investigation started from the reaction of *N*-hydroxyaniline (1a) with diazoacetate (2a) under rhodium catalysis at room temperature (Table 1). We found

Fable 1. Optimization	of	the I	Reaction	Conditions ^a
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H N Ph ^{´ N} \OH	+ Ph CO ₂ Me	Catalyst (1 mol %) Solvent, rt		Ph Ph CO ₂ Me
1a	2a			3a
entry	[Rh]	solvent	time (h)	yield (%) ^b
1	[Cp*RhCl ₂] ₂	DCM	0.5	73
2	$[Rh(COD)Cl]_2$	DCM	0.5	trace
3	$Rh_2(esp)_2$	DCM	0.5	94
4	$Rh_2(OPiv)_4$	DCM	0.5	87
5	$Rh_2(Oct)_4$	DCM	0.5	35
6	$Rh_2(OAc)_4$	DCM	2	94
7	$Rh_2(esp)_2$	DCE	0.5	90
8	$Rh_2(esp)_2$	CHCl ₃	0.5	87
9	$Rh_2(esp)_2$	THF	0.5	84
10	$Rh_2(esp)_2$	MeCN	0.5	68
11	$Rh_2(esp)_2$	toluene	0.5	78
12	$Rh_2(esp)_2$	DMF	0.5	83

^aStandard reaction conditions: 1a (0.2 mmol), 2a (0.24 mmol), rhodium catalyst (1 mol %), CH_2Cl_2 (4 mL). The mixture was stirred at rt. ^bIsolated yields.



that the use of 1 mol % of $[Cp*RhCl_2]_2$ furnished 3a in 73% yield (entry 1), whereas $[Rh(COD)Cl]_2$ can not catalyze this reaction (entry 2). To our delight, the use of $Rh_2(esp)_2$ or $Rh_2(OAc)_4$ as the catalyst delivered 3a in 94% yield under very mild conditions (entries 3 and 6), and longer reaction time was required for $Rh_2(OAc)_4$. $Rh_2(OPiv)_4$ also exhibited good catalytic reactivity, providing 3a in 87% yield (entry 4). In contrast, $Rh_2(Oct)_4$ was less effective and only gave 35% yield (entry 5). Next, other solvents were screened, and it was found that DCM still was the best choice (entries 7–12).

With the established optimal reaction conditions, we next investigated the substrate scope for imine formation (Scheme 2). First, the scope of *N*-hydroxyanilines (1) was evaluated, and it was found that *N*-hydroxyanilines bearing either electron-donating or electron-withdrawing substituents were all amenable to the reaction, providing imines (3b-h) in excellent yields (85-95%). Typically, the sterically hindered imine **3h**, which could not be obtained via catalytic metathesis of azobenzene,⁷ was obtained in 85% yield via this approach. For the scope of diazo compounds, the phenyl ring of the diazo substrates bearing either electron-donating or electron-with-

Scheme 2. Substrate Scope^{*a*,*b*}



^{*a*}Standard reaction conditions: 1 (0.2 mmol), 2 (0.24 mmol), and $Rh_2(esp)_2$ (1 mol %) in CH_2Cl_2 (4 mL); the mixture was stirred at rt for 30 min. ^{*b*}Isolated yields. ^{*c*}The reaction was performed at 80 °C for 6 h. ^{*d*}The reaction was performed at 80 °C for 1 h.

drawing groups was tolerated, furnishing the desired imines (3i-3k) in excellent yields. Other types of diazo compounds such as dimethyl 2-diazomalonate, enol diazoacetate, α -phenyl trifluoromethyl, and phosphonate diazos were all amenable to this reaction, affording the desired products (3m-3p) in good yields. Notably, the donor-donor diazo compounds also reacted well, leading to moderate yields of desired imines (3q-3t).

To better understand the reaction mechanism, DFT calculations were conducted (Figure 1). The initial processes should be the formation of active rhodium carbene (INT1) between $Rh_2(OAc)_4$ and 2a (Supplementary Figure 1), followed by the nucleophilic attack of N atom in 1a to INT1, which is barrierless and exergonic by 21.0 kcal/mol (Supplementary Figure 1). Next, the ammonium ylide 1-INT2 undergoes direct decomposition with 9.8 kcal/mol barrier (1-TS2), giving an iminium/hydroxy ion pair (1-INT3).⁹ The geometries show that with the forming of iminium ion, the N-O bond (1.47 Å in 1-INT2, 1.97 Å in 1-TS2, and 2.05 Å in 1-INT3) and Rh-C bond (2.35 Å in 1-INT2, 3.05 Å in 1-TS2 and 3.24 Å in 1-INT3) are elongating, indicating the dissociation of hydroxy anion and $Rh_2(OAc)_4$. Finally, the hydroxy anion rebounds and abstracts the hydrogen in the iminium ion moiety of 1-INT3 with only 0.3 kcal/mol barrier (1-TS3) to yield imine 4a.¹⁰ For 1-TS3, the distance of O···H decreases slightly to 1.96 Å, and the geometry is still close to 1-INT3, which is consistent with Hammond's postulate.¹¹ Two other possible pathways involving the commonly proposed N-H insertion into the Rh carbene were also considered.¹² As shown by the blue line, the ion pair intermediate 1-INT3 may undergo H₂O-catalyzed [1,2]-H shift after the dissociation of $Rh_2(OAc)_4$ via transition state 2-TS3 with 10.0 kcal/mol barrier and give the N-H insertion product 2-INT4

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Figure 1. Free energy profile of dirhodium(II) complex catalyzed C=N bond formation. Free energies and enthalpies (in parentheses) are given in kcal/mol; atomic distances are in Å.

irreversibly.¹³ Furthermore, the elimination of H₂O from 2-INT4 to produce 4a requires 40.4 kcal/mol (2-TS4), which is energetically infeasible at room temperature. As shown by the red line, the ammonium ylide 1-INT2 may transform into the enol 3-INT3 via H₂O-catalyzed [1,4]-H shift (3-TS2) and is endergonic by 12.1 kcal/mol. The following H₂O-catalyzed [1,3]-H shift of 3-INT3 with 9.2 kcal/mol barrier (3-TS3) leads to the N–H insertion product 2-INT4.¹⁴ Both of two N–H insertion pathways were calculated to have higher energy barriers than the rebound hydrolysis mechanism.

Next, following Doyle's procedure,⁷ the one-pot reaction of *N*-hydroxyaniline **1a** and diazoaceate **2a** and **4a** to synthesize β -lactam was examined. We found that $Rh_2(esp)_2$ cannot achieve the Staudinger cyclization; thus, $Rh_2(OAc)_4$ (1 mol %) was used and delivered lactam **5a** in 83% yield with excellent diastereoselectivity (>20:1 dr) (Scheme 3). The reaction



involves the rhodium-catalyzed imine formation and Wolff rearrangement¹⁵ to afford imine and ketene intermediates, respectively. Then, the thermal Staudinger cyclization¹⁶ of imine with ketene occurs to form lactam **5a**.

We next extended this three-component reaction to a range of substrates (Scheme 4). First, the scope of aniline has been examined, and we found the anilines containing various electron-donating and electron-withdrawing groups were all tolerated in this reaction, providing the corresponding β - Scheme 4. Substrate Scope for Rhodium-Catalyzed Lactam Formation a,b



^{*a*}Reactions were carried out with 1 (0.2 mmol), 2 (0.24 mmol), 4 (0.36 mmol), and $Rh_2(OAc)_4$ (1 mol %) in CH_2Cl_2 (4 mL) at rt for 3 h. ^{*b*}Isolated yields. ^{*c*}80 °C for 2 h. ^{*d*}80 °C for 7 h.

lactams (5a-5h) in good yields with excellent dr ratio (>20:1). Next, the scope of diazo substrates 2 was evaluated. We found that various donor-acceptor diazo compounds were tolerated, affording the desired lactams in good yields (5i-5o). Acceptor-acceptor diazo compound was also amenable to the reaction and afforded 5p in 52% yield. Then, the scope of diazo compounds 4 for the ketene formation was finally disclosed, and the corresponding lactams were isolated in

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moderate yields (5q-5s). The structures of 5q and 5s were determined by X-ray diffraction.

In summary, we demonstrated a novel rhodium-catalyzed C=N bond formation from the reaction of *N*-hydroxyanilines with carbene precursors. DFT calculations indicate that this transformation occurs through a "rebound hydrolysis" mechanism. Moreover, based on the novel imine formation, a three-component reaction to prepare fully substituted β -lactams was developed. The reaction proceeds through rhodium-catalyzed imine formation, Wolff rearrangement, and Staudinger reaction to deliver the final products in high efficiency.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b01312.

Experimental procedures, characterizing data, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1860109–1860110 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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