Communication

# Rh(III)-Catalyzed Synthesis of Multisubstituted Isoquinoline and Pyridine N-Oxides from Oximes and Diazo Compounds

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# Rh(III)-Catalyzed Synthesis of Multisubstituted Isoquinoline and Pyridine *N*-Oxides from Oximes and Diazo Compounds

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Supporting Information Placeholder

**ABSTRACT:** Multisubstituted isoquinoline and pyridine *N*-oxides have been prepared by Rh(III)-catalyzed cyclization of oximes and diazo compounds *via* aryl and vinylic C-H activation. This intermolecular annulation procedure involving tandem C-H activation, cyclization and condensation steps, proceeds under mild conditions, obviates the use of oxidants, releases $N_2$ and $H_2O$ as the byproducts, and displays a broad scope with respect to the substituents.

Isoquinoline and pyridine *N*-oxides are commonly occurring structural motifs not only found in numerous pharmaceuticals, biologically active compounds[1] and chiral ligands[2] but are also widely used as powerful intermediates in the functionalization of isoquinolines and pyridines.[3] Traditional methods have been reported for the *N*-oxidation of isoquinoline and pyridine by different oxidants such as *m*CPBA, $H_2O_2$, $CF_3CO_3H$, $MeReO_3/H_2O_2$.[3] However, their parent heterocycles need to be prepared in advance and suffer from the potential overoxidation of the functionalized substituents. Electrophilic cyclizations of oximes are available methods for the preparation of isoquinoline and pyridine *N*-oxides.[4] Shin et al. reported that Ag- or Au-catalyzed cyclization of 2-alkynylbenzaldoxime derivatives to the corresponding isoquinoline *N*-oxides (Figure 1, a).[5] Nakamura et al. demonstrated the Cu(I)-catalyzed synthesis of multisubstituted pyridine *N*-oxides from (*E*)-*O*-propargylic *α,β*-unsaturated oximes (Figure 1, b).[6] However, a general method on the intermolecular cyclization selectively accessing isoquinoline and pyridine *N*-oxides has not been developed.

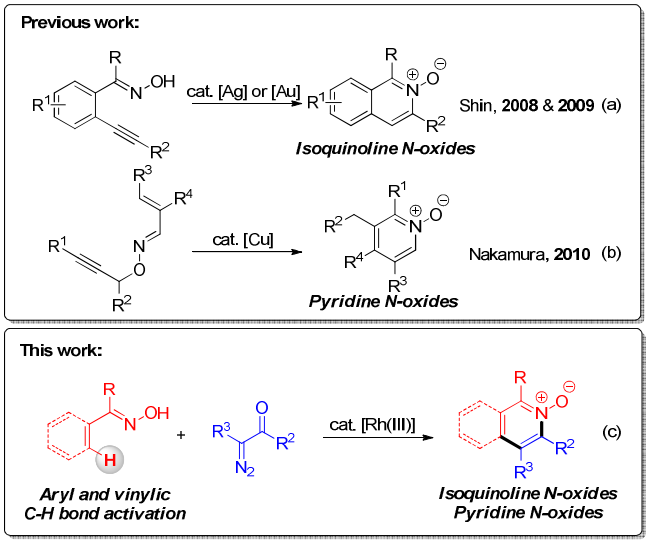
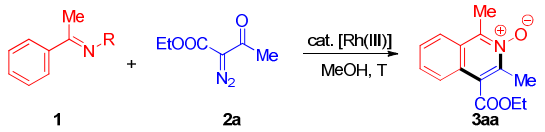



**Figure 1.** Cyclization of oximes to isoquinoline and pyridine *N*-oxides.

Direct C-H activation has advantages over traditional protocols based on substrate preactivation[7] and rhodium complexes such as Wilkinson's catalyst $(RhCl(PPh_3)_3)$,[8] $Rh_2(OAc)_4$[9] and $[(Cp^*RhCl_2)_2]$[10, 11] are particularly promising catalysts in this transformation. Rh(II)-catalyzed C-H activation with diazo compounds is a powerful method to construct C-C bonds.[9] Although carbenoid insertion into alkyl C-H bonds is well established,[12] the intermolecular aromatic C-H bond coupling has limited precedent in the literature[13] and alkenyl C-H activation is unprecedented due to the preferred cyclopropanation[14] and allylic C-H activation process.[15] Significant progress was made by Yu in 2012, who first developed chelation-assisted Rh(III)-catalyzed intermolecular cross-coupling of diazomalonates with arene C-H bonds.[16] Very recently, Rovis et al. also uncovered the cyclization of benzamides and donor/acceptor diazo compounds to construct *γ*-lactams *via* Rh(III)-catalyzed C-H activation.[17] It's noted that insertion of carbenoids into vinylic C-H bonds is still unsolved and such a useful coupling is worth further exploration. Herein, we report the Rh(III)-catalyzed cyclization of oximes with a class of diazo compounds containing carbonyl groups, affording the corresponding polysubstituted isoquinoline and pyridine *N*-oxides regioselectively (Figure 1, c).

The initial experiments were performed with *O*-boc oxime ester and ethyl diazoacetoacetate (**2a**) in the presence of 2.5 mol% $[(Cp^*RhCl_2)_2]$ and 15.0 mol% AgOAc as the catalytic system, at 60 °C under an Ar atmosphere in methanol. This set of conditions indeed afforded the desired product **3aa** in 19% yield after 12 h

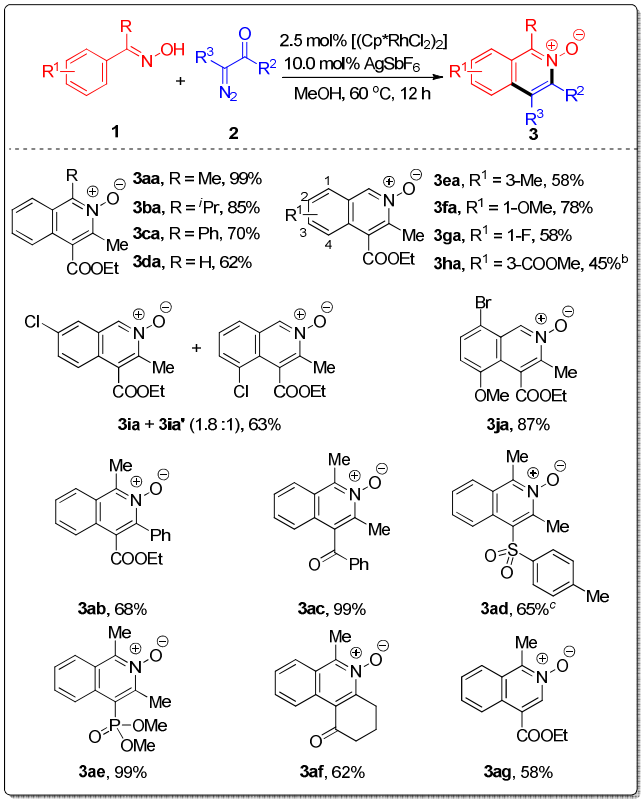
**Table 1.** Reaction Development.[a]




| entry | R | catalyst system (mol%) | T (°C) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | OBoc | $[(Cp^*RhCl_2)_2]$ (2.5) + AgOAc (15.0) | 60 | 19 |
| 2 | OPiv | $[(Cp^*RhCl_2)_2]$ (2.5) + AgOAc (15.0) | 60 | 34 |
| 3 | OPiv | $[(Cp^*RhCl_2)_2]$ (2.5) + $AgSbF_6$ (10.0) | 60 | 76 |
| 4 | OAc | $[(Cp^*RhCl_2)_2]$ (2.5) + $AgSbF_6$ (10.0) | 60 | 99 |
| **5** | **OH (1a)** | **$[(Cp^*RhCl_2)_2]$ (2.5) + $AgSbF_6$ (10.0)** | **60** | **99** |
| 6 | OH (**1a**) | $[(Cp^*RhCl_2)_2]$ (1.0) + $AgSbF_6$ (4.0) | 60 | 92 |
| 7 | OH (**1a**) | $[(Cp^*RhCl_2)_2]$ (2.5) + $AgSbF_6$ (10.0) | rt | 69 |
| 8 | OH (**1a**) | $AgSbF_6$ (10.0) | 60 | 0 |

[a] Conditions: **1** (0.20 mmol), **2a** (0.24 mmol), 2.5 mol% $[(Cp^*RhCl_2)_2]$, 10 mol% $AgSbF_6$, MeOH(1.0 mL), 12 h, under Ar. [b] Isolated yield.

**Table 2.** Rh(III)-catalyzed isoquinoline *N*-oxide formation.[a]

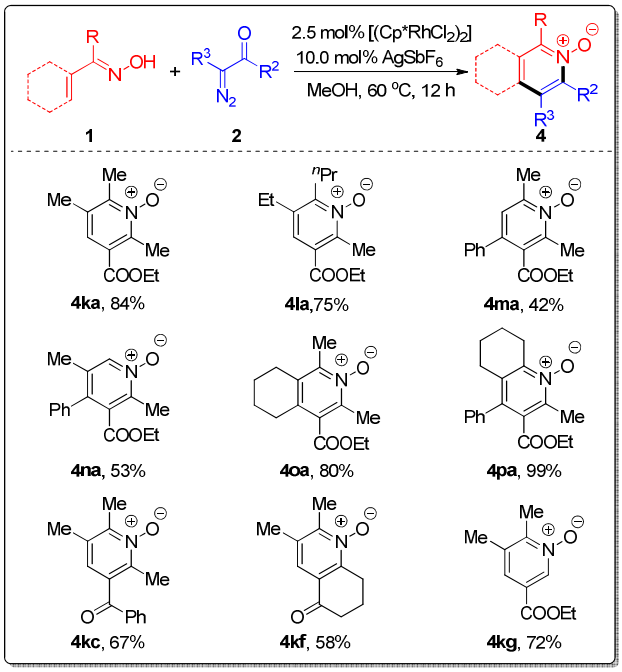



[a] Conditions: **1** (0.20 mmol), **2** (0.24 mmol), 2.5 mol% $[Cp^*RhCl_2]_2$, 10.0 mol% $AgSbF_6$ in MeOH (1.0 mL) at 60 °C, 12 h, under Ar; isolated yield. [b] Using 5.0 mol% $[Cp^*RhCl_2]_2$, 20.0 mol% $AgSbF_6$, at 100 °C. [c] At 100 °C.

without an additional oxidant (Table 1, entry 1). By using the *O*-pivaloyl derivative as substrate, the yield could be improved to 34% (entry 2). The isolated yield of **3aa** was dramatically increased to 76% yield using $AgSbF_6$ as halogen scavenger (entry 3). When choosing *O*-acetyl derivative as substrate, 99% yield of cyclization product was isolated (entry 4). Interestingly, the simplest substrate acetophenone oxime (**1a**) also gave the product **3aa** in 99% yield (entry 5). A slightly reduced yield was obtained with lower catalyst loading (entry 6) and reactions at room temperature became sluggish (entry 7). Control reactions confirmed that the transformation does not occur in the absence of the $[(Cp^*RhCl_2)_2]$ (entry 8).

With the optimized conditions in hand, we examined the scope of this C-H activation and cyclization process (Table 2). We were pleased to find other ketoximes **1b** and **1c** derived from isobutyrophenone and benzophenone afforded the 1,3,4-trisubstituted isoquinoline *N*-oxides **3ba** and **3ca** in good yield. Aldoxime **1d** was also suitable for this transformation and gave the desired product **3da** in 62% yield. The aldoxime substrates were found to be tolerant of methyl (**1e**), methoxy (**1f**) and fluoro (**1g**) substitution at the *ortho* or *para* position giving the corresponding *N*-oxides **3ea-3ga** in 58-78% yield. However, electron-deficient groups such as aldoxime **1h** with ester group at *para* position led to a dramatically decreased conversion. The reaction of *meta*-chloro-substituted oxime **1i** produced separable regioisomeric products **3ia** and **3ia'** in 63% total yield with a ratio of 1.8:1 based on NMR analysis of the crude mixture. This reaction was also applicable to multisubstituted aldoximes such as **1j**, which was converted into compound **3ja** in 87% yield. The scope of other diazo compounds was also investigated with acetophenone oxime (**1a**) as partners. The diazo substrates **2b-2g**

**Table 3.** Rh(III)-catalyzed pyridine *N*-oxide formation.[a]

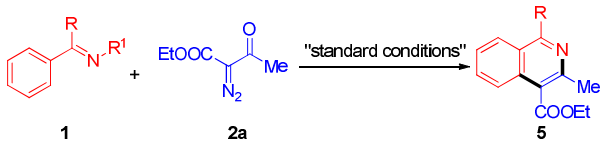



[a] Conditions: **1** (0.20 mmol), **2** (0.24 mmol), 2.5 mol% $[Cp^*RhCl_2]_2$, 10.0 mol% $AgSbF_6$ in MeOH (1.0 mL) at 60 °C, 12 h, under Ar; isolated yield.

bearing substituents such as phenyl, ketone, dimethyl phosphonate, phenylsulfone gave the corresponding products in 58-99% yield. Among them, the unsymmetrical diketone diazo substrate **2c** underwent the desired reaction to only give one regioisomer of the product **3ac** in 99% yield. Interestingly, ethyl 2-diazo-3-oxopropanoate (**2g**) can also react with **1a**, giving the disubstituted product **3ag** in 58% yield.

This cyclization was also extended to pyridine *N*-oxide synthesis by utilizing *α,β*-unsaturated oximes and diazo compounds as starting materials (Table 2). In the case of the 3-methylbut-3-en-2-one oxime (**1k**) and ethyl diazoacetoacetate (**2a**), we were delighted to get 2,3,5,6-tetrasubstituted pyridine *N*-oxide **4ma** in 84% yield under standard conditions. A variety of *α,β*-unsaturated oximes **1l-1p** were tolerated in the reaction, affording the products with multisubstituents at each position on the pyridine ring. Other diazo compounds such as 2-diazo-1-phenylbutane-1,3-dione (**2c**), 2-diazocyclohexane-1,3-dione (**2f**) and ethyl 2-diazo-3-oxopropanoate (**2g**) reacted smoothly with the 3-methylbut-3-en-2-one oxime (**1k**) giving the cyclization products in 58-72% yield.

Rh(III)-catalyzed cyclization of oxime derivatives with alkynes represents a useful tool in isoquinoline and pyridine synthesis.[18] However, the reactions with unsymmetrical and electron-deficient alkynes suffer from low regioselectivities and reactivities. Surprisingly, the reaction of acetophenone *O*-methyl oxime (**1q**) and **2a** under our standard conditions afforded isoquinoline **5qa** with *N*-*O* bond cleavage, albeit only in 28% isolated yield. While oxime ether was not a viable substrate for the intermolecular cyclization,




R = Me, $R^1$ = OMe, **1q** R = Me, **5qa**, 28%

R = Ph, $R^1$ = H, **1r** R = Ph, **5ra**, 88%

R = OEt, $R^1$ = H, **1s** R = OEt, **5sa**, 95%

**Figure 2.** Rh(III)-catalyzed isoquinoline formation.

we found that diphenylmethanimine (**1r**) could be employed in this isoquinoline formation, giving the corresponding product in 88% yield. Additionally, the use of ethyl benzimidate (**1s**) as a substrate allowed the formation of **5sa** in excellent yield.[19] The findings that this class of diazo compounds can act as equivalents of electron-deficient alkynes in Rh(III)-catalyzed isoquinoline synthesis greatly enriches the diversity of synthetic applications (Figure 2).

*N*-oxides are useful synthetic intermediates since they exhibit different reactivity and regioselectivity compared with the parent heterocycles (Figure 3). For example, reaction of **3da** was carried out in THF in the presence of TMSCN and DBU to give the cyanoisoquinolines **6** in good yield.[20] Generation of imidoyl chloride from *N*-methylacetamide and its in situ reaction with **3da** gave 1-aminoisoquinoline amide **7** in 83% yield.[21] **3da** was smoothly alkenylated at the 1-position with acrylate in 66% yield by palladium-catalyzed C-H activation using *N*-oxide as internal oxidant.[22] Based on Fagnou's method, palladium-catalyzed regioselective direct arylation of **3da** also occurred and gave the product **9** in moderate yield.[23]

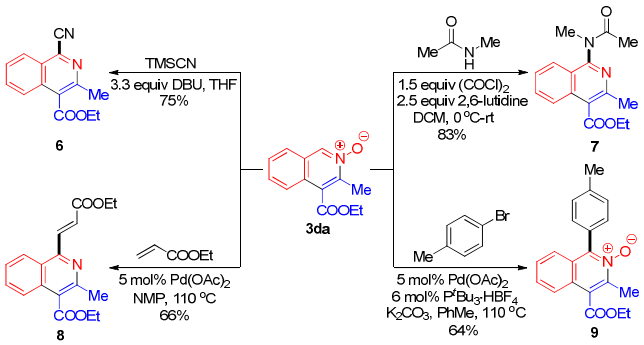
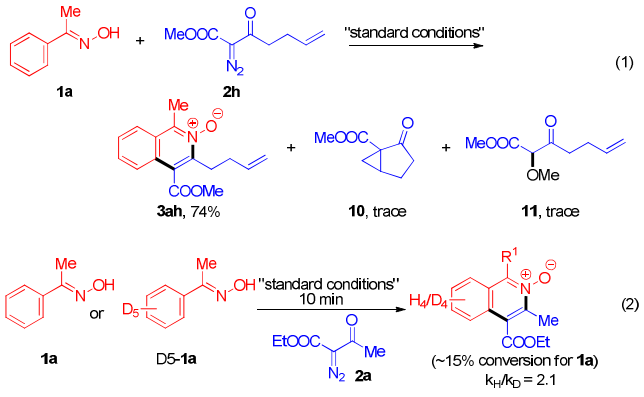



**Figure 3.** Synthetic transformation of isoquinoline *N*-oxide.

Diazo compound **2h** was an efficient substrate for the synthesis of cyclopropane **10** in the presence of $Rh_2(OAc)_4$ as the catalyst.[24] However, when **2h** was employed in standard conditions with acetophenone oxime (**1a**), the *N*-oxide **3ah** was still obtained in 74% isolated yield and the byproducts **10** and **11** were only in trace amount (eq 1). These result indicated that C-H metalation step is much faster than Rh-carbene formation in our catalytic system. Meanwhile, the C-H bond cleavage process is involved in the rate-determining step, since a notable primary kinetic isotope effect (KIE) of $k_H/k_D$ = 2.1 was revealed in two parallel experiments (eq 2).[25] On the basis of above results, we proposed the coordination of the substrate **1** to a [$Rh^{III}$Cp*] species as the key step for the regioselective C-H bond cleavage to afford **A**. This rhodacycle can coordinate one equivalent of diazo compound **2** to give intermediate **B** via Rh-carbene formation pathway.[26] Subsequently, protonolysis of **B** delivers the alkylated intermediate **C**. Then enol intermediate **D** is generated in situ by tautomerization



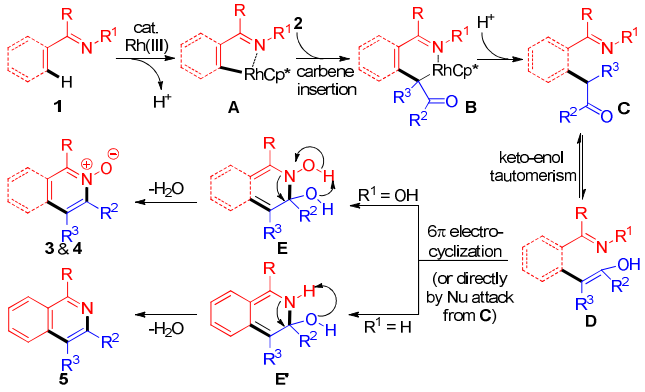




**Figure 4.** Proposed reaction pathway.

of carbonyl intermediate **C**. When using oxime and imine as substrates, the formed enol species can selectively undergo 6π electrocyclization[27] and elimination of water to give products **3-5**. An alternative process involving nucleophilic attack by the nitrogen atom in **C** on the carbonyl group to form **E** and **E'** directly may not be ruled out at the present stage.

In summary, we have developed the first example of Rh-catalyzed isoquinoline and pyridine *N*-oxide synthesis in which the aryl and vinylic C-H activation serves as the cyclization initiating event. This intermolecular annulation procedure involving tandem C-H activation, cyclization and condensation steps, proceeds under mild conditions, obviates the need for oxidants, releases $H_2O$ and $N_2$ as byproducts, and displays a broad scope with respect to the substituents. This method also provides direct access to isoquinolines, which cannot be synthesized efficiently by previous methods. Due to these advantages, this reaction should be of synthetic value.

## ASSOCIATED CONTENT

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

## AUTHOR INFORMATION

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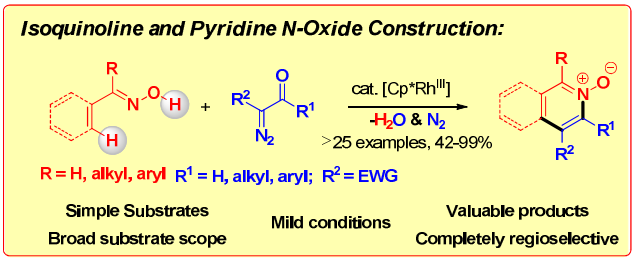
Isoquinoline and Pyridine N-Oxide Construction:
cat. [Cp*Rh^III]
-H2O & N2
>25 examples, 42-99%
R = H, alkyl, aryl R1 = H, alkyl, aryl; R2 = EWG
Simple Substrates
Broad substrate scope
Mild conditions
Valuable products
Completely regioselective