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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

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 involving tandem C−H activation, cyclization, and condensation steps proceeds under mild conditions, obviates the need for oxidants, releases N_2 and H_2O as the byproducts, and displays a broad substituent scope.

Isoquinoline and pyridine *N*-oxides are commonly occurring structural motifs found in numerous pharmaceuticals, biologically active compounds,[1] and chiral ligands[2] and are 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, and $MeReO_3/H_2O_2$.[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 and co-workers reported the Ag- or Au-catalyzed cyclization of 2-alkynylbenzaldoxime derivatives to the corresponding isoquinoline *N*-oxides (Figure 1a).[5] Nakamura et al.[6] demonstrated the Cu(I)-catalyzed synthesis of multisubstituted pyridine *N*-oxides from (*E*)-*O*-propargylic α,β-unsaturated oximes (Figure 1b). However, a general intermolecular cyclization to give isoquinoline and pyridine *N*-oxides selectively has not been developed.

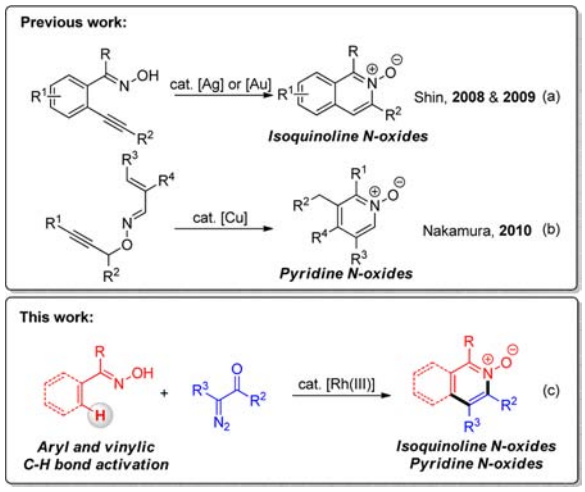

Figure 1. Cyclization of oximes to isoquinoline and pyridine *N*-oxides.

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 for constructing C−C bonds.[9] Although carbenoid insertion into alkyl C−H bonds is well-established,[12] intermolecular aromatic C−H bond coupling has limited precedent in the literature[13] and alkenyl C−H activation is unprecedented because of 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 and co-workers also uncovered the cyclization of benzamides and donor/acceptor diazo compounds to construct γ-lactams via Rh(III)-catalyzed C−H activation.[17] Insertion of carbenoids into vinylic C−H bonds is still unsolved, and such a useful coupling is worth further exploration. Here we report the Rh(III)-catalyzed cyclization of oximes with carbonyl-containing diazo compounds to give the corresponding polysubstituted isoquinoline and pyridine *N*-oxides regioselectively (Figure 1c).

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 without an additional oxidant (Table 1, entry 1). Using the *O*-pivaloyl derivative as the substrate improved the yield to 34% (entry 2). The isolated yield of **3aa** dramatically increased to 76% yield when $AgSbF_6$ was used as a halogen scavenger (entry 3). When the *O*-acetyl derivative was selected as the substrate, a 99% yield of the cyclization product was isolated (entry 4). Interestingly, the simplest substrate, acetophenone oxime (**1a**), also gave **3aa** in 99% yield (entry 5). A slightly reduced yield was obtained with a 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 that ketoximes **1b** and **1c**, derived from isobutyrophenone and benzophenone respectively, afforded

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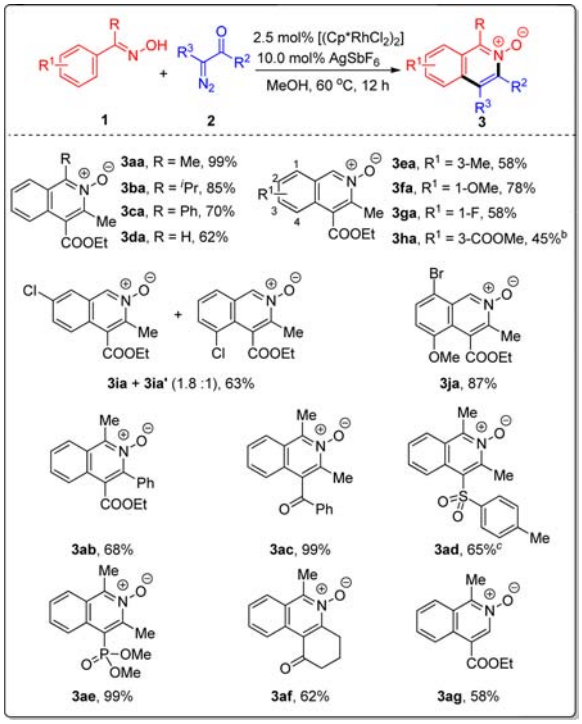
Table 1. Reaction Development[a]

1 2a 3aa

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), $[(Cp^*RhCl_2)_2]$ (2.5 mol %), $AgSbF_6$ (10 mol %), MeOH (1.0 mL), 12 h, under Ar. [b]Isolated yields.

Table 2. Rh(III)-Catalyzed Isoquinoline *N*-Oxide Formation[a]

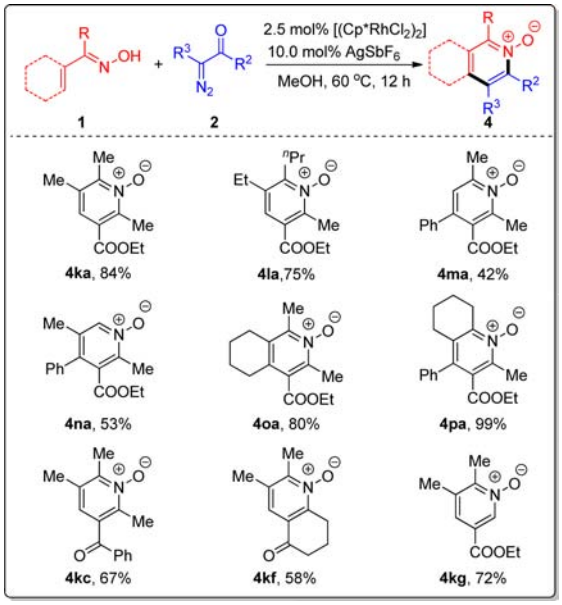


[a]Conditions: **1** (0.20 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10.0 mol %), MeOH (1.0 mL), 60 °C, 12 h, under Ar; isolated yields are shown. [b]Using 5.0 mol % $[Cp^*RhCl_2]_2$ and 20.0 mol % $AgSbF_6$ at 100 °C. [c]At 100 °C.

1,3,4-trisubstituted isoquinoline *N*-oxides **3ba** and **3ca** in good yield. Aldoxime **1d** was also suitable for this transformation, giving 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**–**ga** in 58–78% yield. However, electron-deficient groups such as an ester group at *para* position in aldoxime **1h** led to a dramatically decreased conversion. The reaction of *m*-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 multi-substituted aldoximes such as **1j**, which was converted into compound **3ja** in 87% yield. The scope of other diazo compounds was also investigated with **1a** as the reaction partner. Diazo substrates **2b**–**g** bearing substituents such as phenyl, ketone, dimethyl phosphonate, and phenylsulfone gave the corresponding products in 58–99% yield. Among them, unsymmetrical diketone **2c** underwent the desired reaction to give only one regioisomer of **3ac** in 99% yield. Interestingly, ethyl 2-diazo-3-oxopropanoate (**2g**) reacted with **1a** to give 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 3). In the case of the

Table 3. Rh(III)-Catalyzed Pyridine *N*-Oxide Formation[a]



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

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 **4ka** in 84% yield under the standard conditions. A variety of α,β-unsaturated oximes **1l**–**p** were tolerated in the reaction, affording products with substituents at multiple positions 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 corresponding 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 in only 28% isolated yield. While oxime ether was not a viable substrate for the intermolecular cyclization, 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

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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).

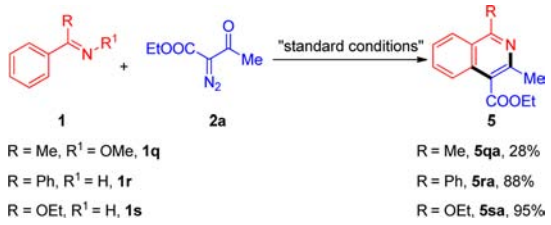

Figure 2. Rh(III)-catalyzed isoquinoline formation.

N-Oxides are useful synthetic intermediates since they exhibit different reactivity and regioselectivity compared with the parent heterocycles (Figure 3). For example, the reaction of **3da** in THF

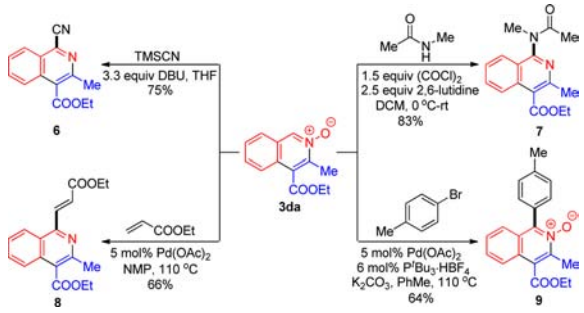

Figure 3. Synthetic transformations of isoquinoline *N*-oxide **3da**.

in the presence of TMSCN and DBU gave the cyanoisoquinoline **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 to give **8** in 66% yield by Pd-catalyzed C−H activation using the *N*-oxide as an internal oxidant.[22] Pd-catalyzed regioselective direct arylation of **3da** by Fagnou's method gave product **9** in moderate yield.[23]

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 under the standard conditions with **1a**, *N*-oxide **3ah** was still obtained in 74% isolated yield with only trace amounts of byproducts **10** and **11** (eq 1). These results indicate that the 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 (k_H/k_D = 2.1) was revealed in two parallel experiments (eq 2).[25] On the basis of the above results, we propose 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** (Figure 4). This rhodacycle can coordinate 1 equiv of diazo compound **2** to give intermediate **B** via the Rh carbene formation

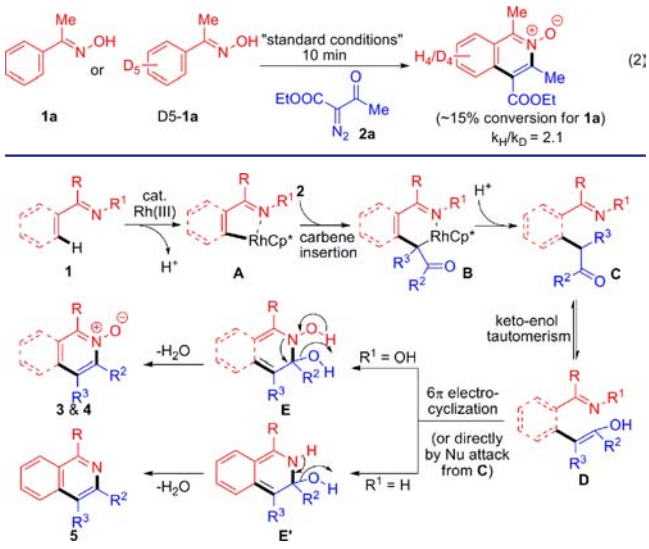

Figure 4. Proposed reaction pathway.

pathway.[26] Subsequently, protonolysis of **B** delivers alkylated intermediate **C**, tautomerization of which generates enol intermediate **D** in situ. With oxime and imine 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 N atom in **C** on the carbonyl group to form **E** and **E′** directly cannot be ruled out at the present stage.

In summary, we have developed the first example of a Rh-catalyzed synthesis of isoquinoline and pyridine *N*-oxides in which 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.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic data. 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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