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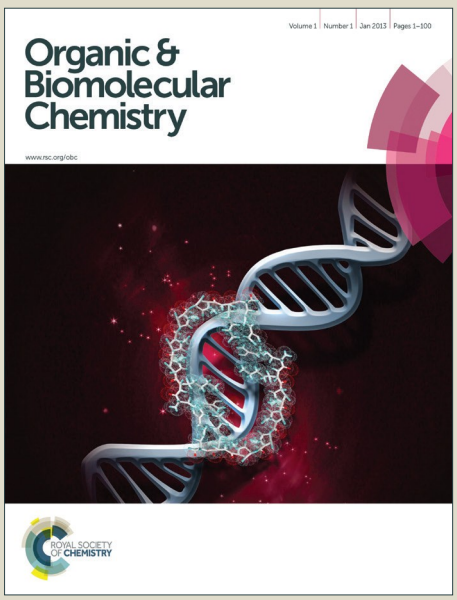

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Rh(III)-catalyzed C–H activation/cyclization of oximes with alkenes for regioselective synthesis of isoquinolines

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A Rh(III)-catalyzed C–H activation/cyclization of oximes and alkenes for facile and regioselective access to isoquinolines has been developed. This protocol is featured with mild reaction conditions and easy accessible starting materials, and has been applied to concise synthesis of Moxaverine. Kinetic isotope effect study was conducted and a plausible mechanism was proposed.

Isoquinoline represents an important class of structural motifs existing in numerous pharmaceuticals, natural products and ligands.[1] Therefore, various methods have been developed for accessing those compounds.[2] In recent years, the transition-metal-catalyzed C–H activation/cyclization of aryl oximes, imines, azides with internal alkynes has been explored for the achievement of isoquinolines (Fig 1a).[3] However, these protocols suffer from difficult regiocontrol. Recently, Glorius (Fig 1b) and Cheng (Fig 1c) have independently found that 1,3-dienes and geminal-substituted vinyl acetate could serve as cyclization partners in Rh(III)-catalysis for regioselective synthesis of isoquinolines.[4] Despite these advances, the development of general and efficient method for the construction of these compounds, especially with good regioselectivity and broad functional group tolerance, still remains important and interesting, since various privileged biologically interesting isoquinolines bear functional groups like ketone.

Recently, Rovis reported Rh(III)-catalyzed C–H activation/cyclization of oxime esters and alkenes for accessing pyridines,[5] indicating that alkenes act as a coupling component in the cyclization process and could probably be applied to isoquinoline synthesis. In continuation of our interests in Rh(III)-catalyzed C–H functionalization for biologically interesting small molecule synthesis.[6] Herein, we would like to report a Rh(III)-catalyzed C–H activation/cyclization of oximes with alkenes for regioselective synthesis of isoquinolines,

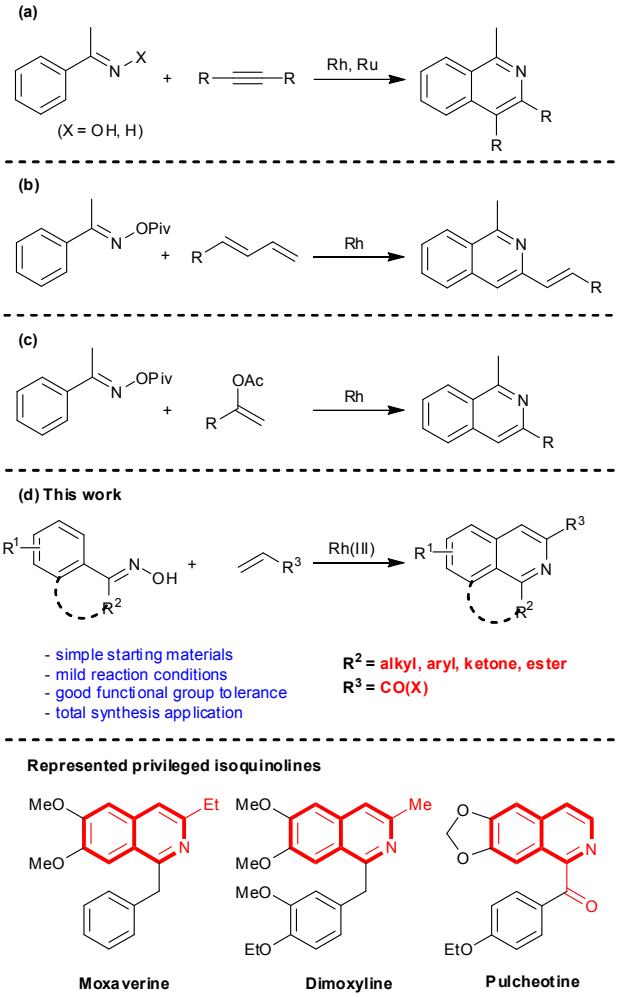

Fig. 1 Rh(III)-catalyzed regioselective isoquinoline synthesis.

and its application in total synthesis of Moxaverine (Fig. 1d).

We commenced our study by investigating oxime **1a** and acrolein **2a**, with $[Cp^*RhCl_2]_2$ as catalyst and the addition of PivOH at room temperature in the solvent of CH_3CN. With the addition of 2 equivalent amount of CsOAc, we were pleased to

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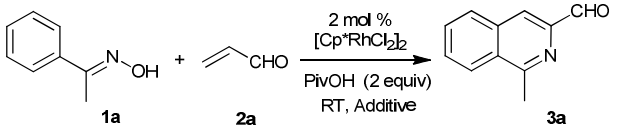
find that the isoquinoline product **3a** was formed and isolated in 43% yield (Table 1, entry 1). The formation of **3a** indicated a C–H activation/cyclization occurring in the process. This encouraged us to further screen the additives, and $Cu(OAc)_2$ was found inferior to shut down the reactivity (entry 2). We next turn to screen the silver salts and found that AgOAc was optimal to increase the yield to 57% (entry 3). The use of $AgBF_4$ and Ag_2O were found to further improve the yield (entries 4 and 5). Gratifyingly, the addition of Ag_2CO_3 as additive was superior, leading to a dramatic improvement of the yield to 84% (entry 6).[7] Control reaction showed that the removement of PivOH would completely shut down the reactivity, demonstrating the importance of PivOH (entry 7). The solvent screening showed that DCE, MeOH and THF were not effective, resulting trace product formation (entries 8-10). Other oximes such as *O*-methyl oxime **4** and *O*-pivaloyl oxime **5** were also tested and found not applicable in this protocol (Fig. 2).

Table 1. Optimization of reaction conditions.[a]



entry	additive	solvent	yield (%)[b]
1	CsOAc (2 equiv)	CH_3CN	43
2	$Cu(OAc)_2$ (2 equiv)	CH_3CN	trace
3	AgOAc (2 equiv)	CH_3CN	57
4	$AgBF_4$ (2 equiv)	CH_3CN	60
5	Ag_2O (2 equiv)	CH_3CN	69
6	Ag_2CO_3 (2 equiv)	CH_3CN	84
7[c]	Ag_2CO_3 (2 equiv)	CH_3CN	trace
8	Ag_2CO_3 (2 equiv)	DCE	trace
9	Ag_2CO_3 (2 equiv)	MeOH	trace
10	Ag_2CO_3 (2 equiv)	THF	trace

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $[Cp^*RhCl_2]_2$ (2 mol %), PivOH (0.4 mmol), solvent (1 mL), RT, 18 h. [b]Yields of isolated product. [c]Without PivOH.

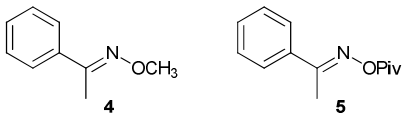
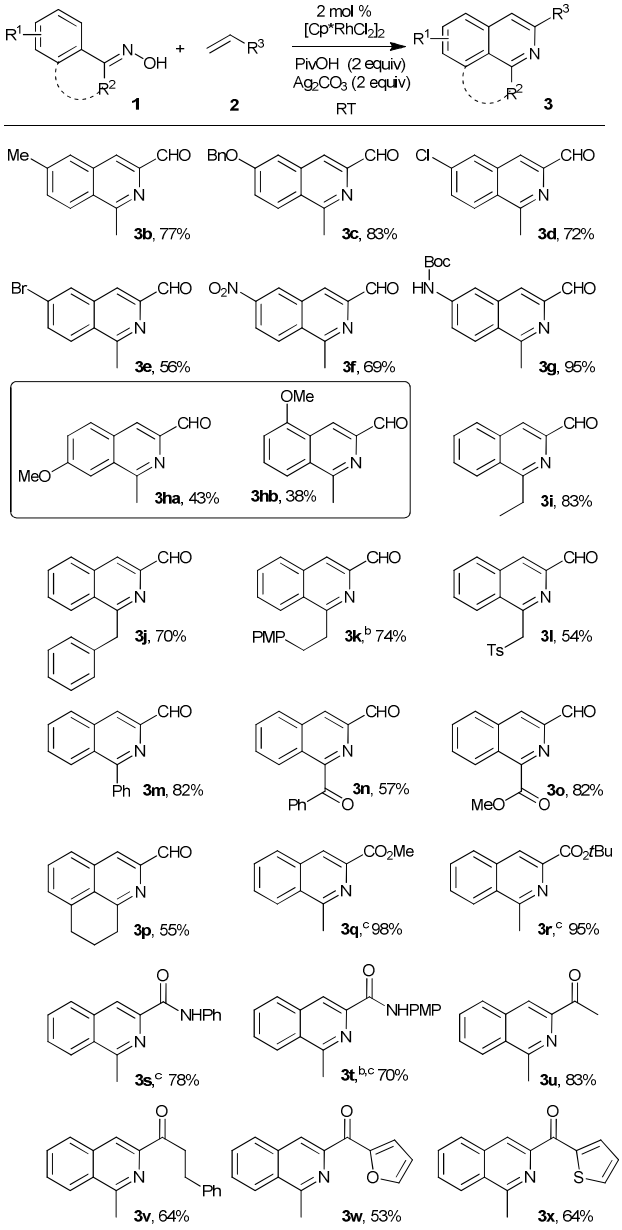


Fig. 2 Other screened oximes without reactivity.

With the optimized reaction condition in hand, we next investigated the generality of the reaction (Scheme 1). Various aromatic oximes with valuable functional groups on the aromatic ring, such as methyl, benzyloxy, chloro, bromo, nitro, amino, could react smoothly with acrolein **2a** to afford the corresponding products (**3b**-**3g**) in moderate to excellent yields (56%-95%), thus offering ample opportunity for further derivation. Additionally, when a *meta* substituted oxime **1h** was used, the reaction afforded a separatable mixture of isoquinoline products **3ha** and **3hb**. When the substitution is varied on the methyl group, a variety of functional groups were tolerated in this process. For example, the groups like ethyl, benzyl, sulfone, phenyl, were well applicable in this cyclization to furnish the structural different isoquinolines (**3i**-**3m**). Interestingly, the ketone and ester substituted oximes were also applicable in this process to furnish the products in good yields (**3n** and **3o**). It should be noted that **3j** and **3n** are the core structures of Moxaverine and Pulcheotine to demonstrate the synthetic utility. Moreover, the bicyclic oxime **1p** could also proceed well to deliver tricyclic product in moderate yield (**3p**, 55%). Next, we test the substrate scope of alkenes. The acrylates and acryl amides could proceed well in this process to generate the products in moderate to excellent yields (**3q**-**3t**) under a slightly modified reaction condition. Furthermore, a variety of vinyl ketones were also tested and found tolerable in this process to furnish the isoquinolines (**3u**-**3x**), with the valuable substitution like furan and thiophene. Considering the wealth of isoquinoline in natural products and

Scheme 1. Variation of Oximes.[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), $(Cp^*RhCl_2)_2$ (2 mol %), PivOH (0.4 mmol), CH_3CN (1 mL), RT, 18 h, yields of isolated products. [b]PMP = *para*-methoxyphenyl. [c]Run at 76 °C.

pharmaceuticals, this method provides a direct approach toward the achievement of these heterocycles from readily available starting materials under mild reaction conditions.

Next, the synthetic utility of this protocol was further demonstrated by concise synthesis of Moxaverine, a drug used to treat functional gastrointestinal disorders (Fig. 3).[8] Initially, the simple phenylacetic acid was converted to phenylacetyl chloride, which underwent a Friedel-Crafts reaction with 1,2-dimethoxybenzene to afford **6**. **6** was then converted to oxime **7** and subject to the standard reaction condition with methyl vinyl ketone to deliver isoquinoline **8**. The next transformation of ketone to tosyl hydrazone and a following DIBAL-reduction finally furnished Moxaverine in 65% yield.

To gain insight to the reaction mechanism, kinetic isotope effect (KIE) study was conducted (Fig. 4), and a large primary KIE value (2.8) was obtained, suggesting that C−H bond cleavage occurs during the rate-determing step.

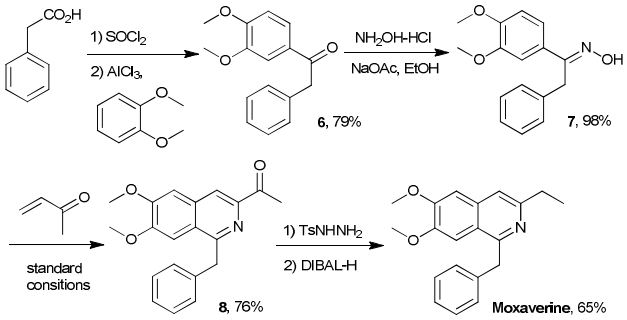


Fig. 3 Concise synthesis of Moxaverine.

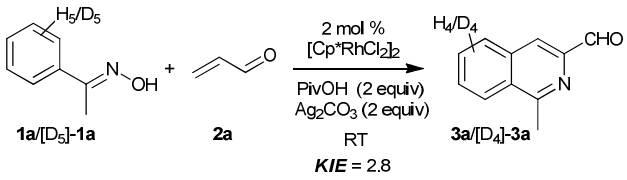


Fig. 4 KIE study.

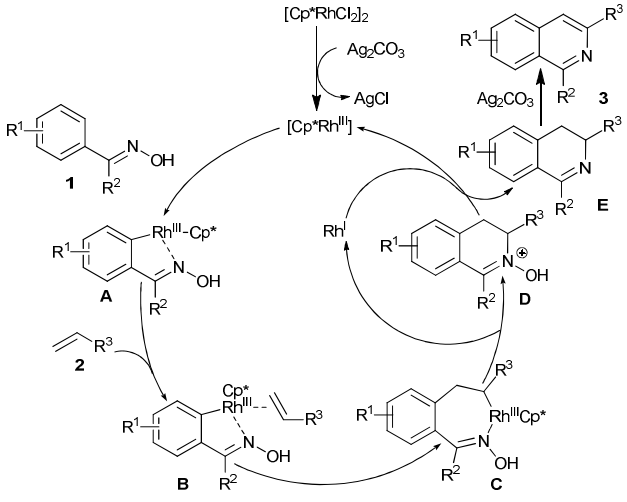


Fig. 5 Proposed reaction mechanism.

Based on the experiments and literature precedents,[9] a plausible mechanism is proposed in Fig. 4. The initial [Cp*Rh^{III}] was generated from $[Cp^*RhCl_2]_2$ and Ag_2CO_3, and reacted with oxime **1** with a C−H activation/cyclorhodation step to afford intermediate **A**, which is coordinated with alkenes **2** to form complex **B**. The sequential regioselective insertion of alkene from **B** led to intermediate **C**, and a redox-neutral cyclization furnished **D** and Rh(I). The reduction of **D** by Rh(I) regenerates [Cp*Rh^{III}] catalyst to enable the catalytic cycle and also delivers dihydroisoquinoline species **E**. Finally, the oxidation of **E** by Ag_2CO_3 delivered the aromatic isoquinoline products **3**, thus the amount of Ag_2CO_3 should be equivalent.

In summary, a Rh(III)-catalyzed C−H activation/cyclization of oximes and alkenes has been developed for regioselective synthesis of isoquinolines. The protocol is featured with broad substrate scope and mild reaction conditions, and also applied to concise synthesis of Moxaverine. Furthermore, kinetic effect study was conducted and a plausible mechanism was proposed.

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