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Rhodium-Catalysed [4+2] Annulation of Aromatic Oximes with Terminal Alkenes by C–H/N–O Functionalization towards 3,4-Dihydroisoquinolines

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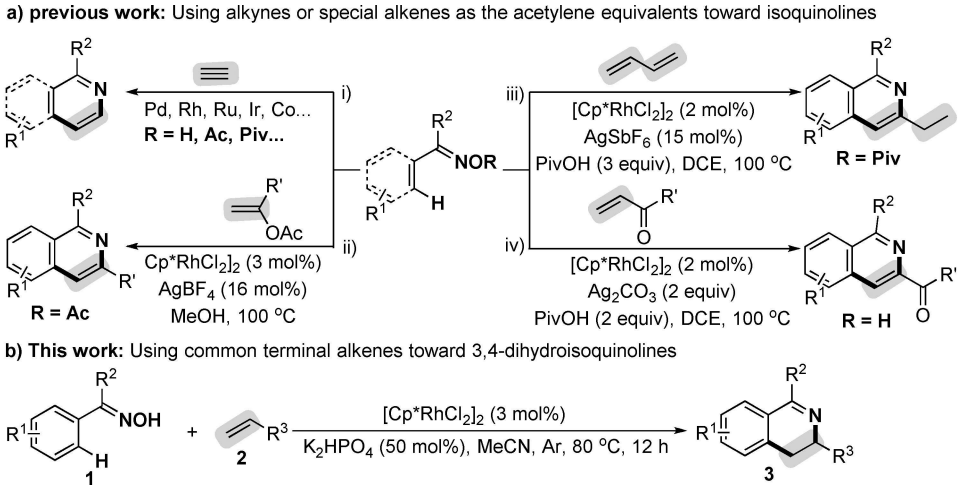
Abstract: Rhodium (Rh)-catalysed [4+2] annulation of aromatic oximes with common terminal alkenes for the synthesis of 3,4-dihydroisoquinolines is presented. Through the cooperation of a Rh (III) catalyst and a catalytic amount of K_2HPO_4 base, the reaction enables the formation of two new bonds, a C(sp^2)–C(sp^3) bond and a C(sp^3)–N bond, in a single reaction via functionalization of both the C–H and N–O bonds and provides a practical method to produce 3,4-dihydroisoquinolines with exquisite selectivity and excellent compatibility of functional groups.

Keywords: alkenes; oximes; rhodium; annulation; dihydroisoquinolines

Isoquinolines are structural motifs present in many biologically active natural products, pharmaceuticals, and functional materials.[1] Accordingly, considerable effort has been devoted to developing increasingly efficient methods for the construction of such isoquinoline molecular scaffolds, especially through intramolecular cyclization or intermolecular annulation reactions.[2,3] Despite substantial progress in the field, the development of highly atom-economic, sustainable routes that can achieve C–H functionalization under external-oxidizing-reagent-free conditions that release nontoxic waste products (e.g., H_2O) remains a challenging area.[4] In recent years, transition-metal-catalysed intermolecular annulation of aromatic oximes and their derivatives (often esters) with unsaturated hydrocarbons (e.g., alkynes, allenes, alkenes, ketenes) have proved to be promising platforms for the preparation of nitrogen-containing heterocycles, wherein the N–O bond in aromatic oximes serves as the internal oxidative chelation group to selectively achieve *ortho*-C(sp^2)–H functionalization.[3–6] While the annulation of aromatic oximes with internal alkynes has been thoroughly investigated for the preparation of 3,4-disubstituted isoquinolines (Scheme 1a–i),[3,5] similar versions with alkenes are rare.[6] Moreover, these transformations focus on special alkenes, including vinyl acetates,[6a] 1,3-dienes[6b] and electron-poor alkenes,[6c] which serve as convenient acetylene equivalents for the synthesis of 3-substituted isoquinolines. Examples that utilize common terminal alkenes as reaction partners towards 3,4-dihydroisoquinolines have not been reported. In 2015, the group of Yu/Cheng[6a] reported the first rhodium-catalysed sequential oxidative C–H activation/annulation of aromatic oxime esters with vinyl acetates leading to 3-substituted or non-C3-substituted isoquinolines (Scheme 1a–ii). The group of Glorius[6b] has developed a PivOH-promoted Rh(III)-catalysed redox-neutral C–H activation/cyclization/isomerization strategy for achieving [4+2] annulation of aromatic oxime esters and diverse 1,3-dienes towards 3-alkyl-substituted isoquinolines (Scheme 1a–iii). Cui and co-workers[6c] have expanded the PivOH-promoted Rh(III)-catalysed redox-neutral C–H activation strategy to include annulation of aromatic oximes with electron-poor alkenes, such as vinyl aldehydes, ketones, esters and amides (Scheme 1a–iv). Thus, it would be desirable to develop general routes for direct annulation of



Scheme 1. [4 + 2] Annulation of Aromatic Oximes.

aromatic oximes with common olefins for targeting diverse isoquinolines and the construction of their derivatives.

Herein, we report a rhodium(III)-catalysed oxidative [4 + 2] annulation of aromatic oximes with terminal alkenes using an internal oxidative strategy for producing 3,4-dihydroisoquinolines, in which both the C–H and N–O bonds are functionalized in a single reaction to form two new bonds, a C(sp^2)–C(sp^3) bond and a C(sp^3)–N bond (Scheme 1b). This method represents the first example of directly utilizing aromatic oximes and common terminal alkenes to achieve [4 + 2] annulation and assembly of 3,4-dihydroisoquinoline frameworks.

Experimentation started by investigating the optimal reaction conditions for the annulation between 1-(*p*-tolyl)ethan-1-one oxime (**1a**) and 1-methoxy-4-vinylbenzene (**2a**) by means of $[Cp^*RhCl_2]_2$ catalyst (Table 1). Treatment of oxime **1a** with alkene **2a** using optimized parameters (3 mol% of $[Cp^*RhCl_2]_2$ and 50 mol% of K_2HPO_4 in MeCN under argon atmosphere at 80 °C for 12 h) resulted in the desired product **3aa** with a 70% yield (entry 1). The reaction is scalable, with a 65% yield at the 1 mmol scale of **1a** (entry 1). These results show that both $[Cp^*RhCl_2]_2$ and a base (e.g., K_2HPO_4) are crucial because omission of each results in no reaction occurring (entries 2 and 4). A higher loading (5 mol%) of $[Cp^*RhCl_2]_2$ had no obvious improvement on the yield (entry 3). The amount of K_2HPO_4 base was examined, and the experiments reveal 50 mol% of K_2HPO_4 as the best option (entries 1, 5 and 6). Several other bases, including K_3PO_4, CsF, K_2CO_3, Ag_2CO_3 and $AgSbF_6$, exhibited reactivity (entries 7–11), but they were all inferior to K_2HPO_4. Brief screening of the effect of solvents (e.g., 1,4-dioxane, MeOH) and reaction temperatures indicated that the reaction in MeCN at 80 °C gave the best results (entry 1 versus entries 12–15). However, replacement of argon by air had a deleterious effect (entry 16).

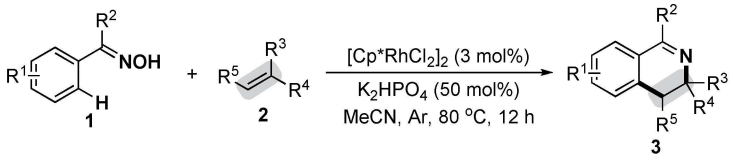
Table 1. Optimization of the Reaction Conditions[a].

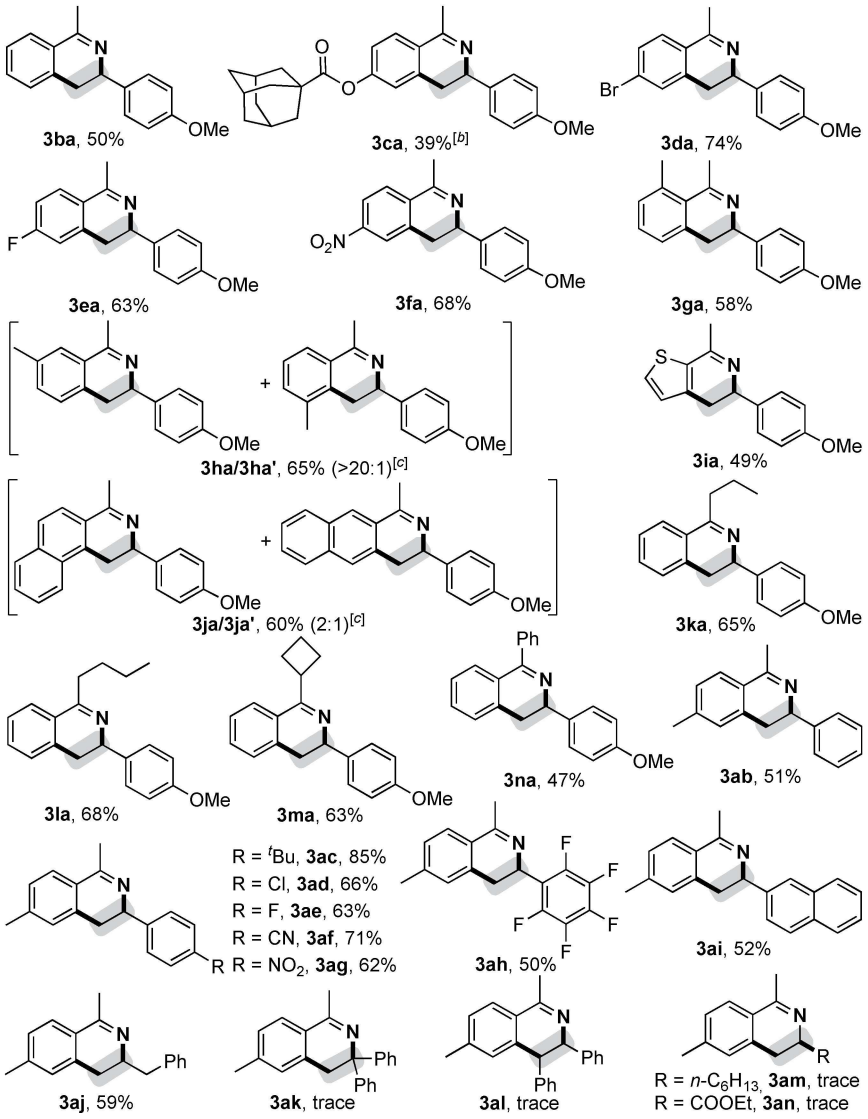
Entry	Variation from the standard conditions	Yield [%][b]
1	none	70/65[c]
2	without $[Cp^*RhCl_2]_2$	0
3	$[Cp^*RhCl_2]_2$ (5 mol%)	71
4	without K_2HPO_4	trace
5	K_2HPO_4 (20 mol%)	39
6	K_2HPO_4 (100 mol%)	49
7	K_3PO_4 instead of K_2HPO_4	67
8	CsF instead of K_2HPO_4	27
9	K_2CO_3 instead of K_2HPO_4	56
10	Ag_2CO_3 instead of K_2HPO_4	45
11	$AgSbF_6$ instead of K_2HPO_4	5
12	1,4-dioxane instead of MeCN	16
13	MeOH instead of MeCN	7
14	at 60 °C	62
15	at 100 °C	37
16[d]	air instead of argon	37

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (3 mol%), K_2HPO_4 (50 mol%), MeCN (2 mL), argon, 80 °C and 12 h.
[b] Isolated yield.
[c] **1a** (1 mmol), MeCN (4 mL) and 36 h.
[d] Oxime **1a** was recovered in 53% yield.

Under the optimal reaction conditions, the [4 + 2] annulation of various aromatic oximes **1** with terminal alkenes **2** is performed efficiently in moderate to good yields (Table 2). The optimal conditions were also found to be compatible with a wide array of aromatic

Table 2. Variations of the aromatic oximes (**1**) and alkenes (**2**)[a].





[a] Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), $[Cp^*RhCl_2]_2$ (3 mol%), K_2HPO_4 (50 mol%), MeCN (2 mL), argon, 80 °C, and 12 h.

[b] The reaction was performed by directly using three components, including 1-methoxy-4-vinylbenzene **1a**, (*E*)-1-(4-hydroxyphenyl)ethan-1-one oxime, adamantane-1-carboxylic acid because 4-(1-(hydroxyimino)ethyl)phenyl-adamantane-1-carboxylate is not stable.

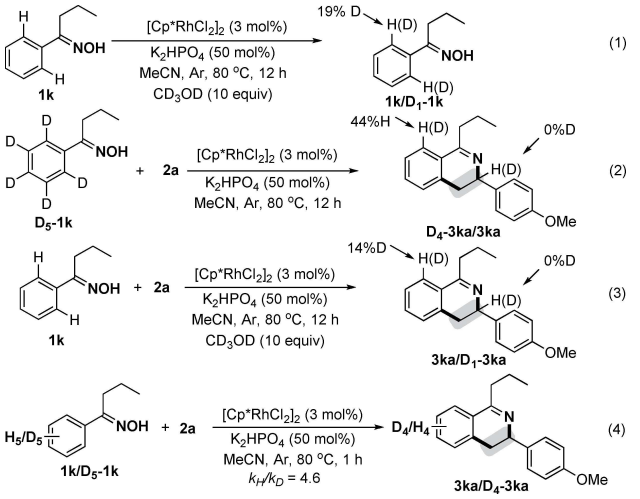
[c] Ratio of the regioselective isomers is given in the parentheses.

oximes **1b**–**m**. Using 1-phenylethan-1-one oxime **1b** reacted with alkene **2a**, $[Cp^*RhCl_2]_2$ and K_2HPO_4 afforded **3ba** with a 50% yield. A variety of aromatic oximes **1c**–**h**, possessing an adamantane-1-carboxylate, a Br, a F, a NO_2 or a Me group, on the aromatic ring were tolerated by the reaction system (**3ca**–**ha**), and the steric properties of each aromatic oxime affected the reactivity. While the bulky *p*-adamantane-1-carboxylate-containing aromatic oxime **1c** was converted to **3ca** in a lower yield, oximes **1d**–**f** bearing a

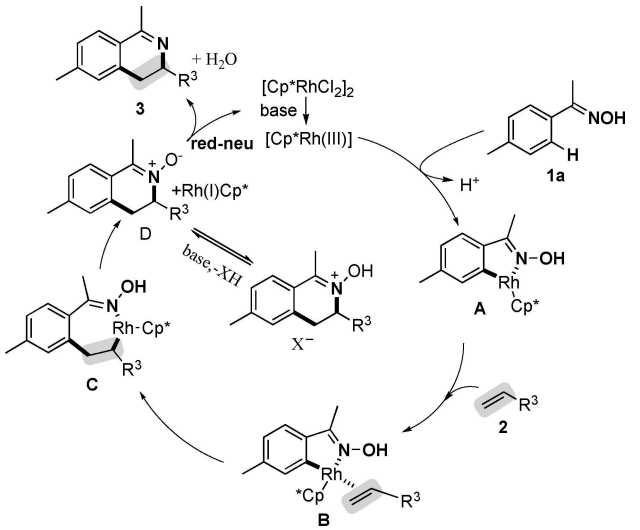
weak (Br, F) or a strong (NO_2) electron-withdrawing group produce **3da–fa** in good yields. Using *o*-Me-substituted oxime **1g** delivered **3ga** with lower yields. For the *m*-Me-substituted oxime **1h**, the annulation occurred regiospecifically at the lower steric effect position, giving 3-(4-methoxyphenyl)-1,7-dimethyl-3,4 dihydroiso-quinoline **3ha** with a 65% yield, with >20:1 regioselectivity. The annulation protocol was applicable to the heteroaromatic oxime 1-(thiophen-2-yl)ethan-1-one, oxime **1i**, resulting in a product containing two different heteroatoms, **3ia**. 1-(Naphthalen-2-yl)ethan-1-one, oxime **1j**, was a suitable substrate for accessing a mixture of two regioselective isomers **3ja/3ja′**. Several functionalized oximes, 1-phenylbutan-1-one (oxime **1k**), 1-phenylpentan-1-one (oxime **1m**), cyclobutyl(phenyl)methanone (oxime **1n**) and diphenylmethanone (oxime **1o**), successfully performed the annulation reaction (**3ka–oa**). Oxime ethers and esters, such as 1-(*p*-tolyl)ethan-1-one *O*-methyl oxime and 1-(*p*-tolyl)ethan-1-one *O*-acetyl oxime, were tested under the optimal conditions, and the results showed that they had no reactivity.

Furthermore, a wide range of aromatic and aliphatic terminal alkenes **2b–n** are amenable to the annulation protocol (**3ab–an**). Using styrene (**2b**) enabled the formation of **3ab** with a moderate yield. Several aryl alkenes bearing a substituent, such as ^{t}Bu, Cl, F, CN and NO_2, on the aryl ring were consistent with the optimal conditions, giving **3ac–ag** in moderate to good yields. It is notable that 1,2,3,4,5-pentafluoro-6-vinylbenzene (**2h**) is viable for accomplishing the annulation reaction (**3ah**). Both 2-vinylnaphthalene (**2i**) and allylbenzene (**2j**) also underwent the reaction smoothly to give the corresponding products **3ai–aj** in moderate yields. Unfortunately, other alkenes, including 1,1-diphenylethene (**2k**), 1,2-diphenylethene (**2l**), alkyl olefin **2m** and acrylate **2n**, were inert (**3ak–an**).

To elucidate the mechanism, control experiments were carried out (Scheme 2). Competition experiments and the line Hammett analysis plot support the reactive order of electron-withdrawing styrene > electron-rich styrene (see the Supporting Information). Furthermore, significant H/D exchanges could be detected in the reactions of **1k**/CD_3OD without **2a** [eq (1) in Scheme 2]. We also conducted the reaction of **[D_5]-1k** with **2a** under standard reaction conditions, the existence of 44% H/D exchange in product **3ka/[D_4]-3ka** [eq (2) in Scheme 2] was observed. In addition, react **1k**/CD_3OD with **2a** under standard reaction conditions; the existence of 14% H/D exchange in product **3ka/[D_1]-3ka** [eq (3) in Scheme 2] was observed. These observations were, hence, indicative of a reversible C–H bond metalation step by an alkene-coordinated ruthenium complex, likely proceeding through base assistance. A kinetic isotope effect (KIE) experiment was carried out [eq (4) in Scheme 2], which provided a large primary KIE value (4.6). The



Scheme 2. Kinetic Experiment.



Scheme 3. Possible pathways.

results support that C(sp^2)–H bond cleavage is the rate-determining step.

Consequently, the following mechanism for the Rh (III)-catalysed [4+2] annulation protocol is proposed on the basis of our current results and the results of previously reported studies (Scheme 3).[2,4–7] Initially, activation of the $[Cp^*RhCl_2]_2$ species with the aid of a base forms the active [Cp*Rh(III)] species,[5–7] which subsequently undergoes insertion at the C(sp^2)–H bond in aromatic oxime **1a** to generate the Cp^*Rh^{III} complex **A**. Coordination of the Cp^*Rh^{III} complex **A** with alkene **2** followed by insertion across the C=C bond to produce the seven-membered rhodacycle **C**. The intermediate **C** possibly undergoes reductive elimination to give the intermediate **D**[5a,7] and a Rh^I species.[5a,7] Finally, the cleavage of the N–O bond of the intermediate **D** by the Rh(I) species releases

expected dihydroisoquinoline **3**, the active Rh(III) species and H_2O. Notably, use of the external oxidant (e.g., air) might not conducive to the formation of the active [Cp*Rh(III)] species.

In summary, we have reported the first acid-free, Rh(III)-catalysed, redox-neutral [4+2] annulation of aromatic oximes using common terminal alkenes for producing 3,4-dihydroisoquinolines. By cooperative Rh catalysis of a catalytic amount of K_2HPO_4 base, this two-component reaction enables annulation of various functionalized aromatic oximes with readily available common alkenes in moderate to good yields with excellent selectivity. The valuable 3,4-dihydroisoquinolines assembled using this method represents examples of the potential for simple bases to activate the Rh catalyst and allow the practical functionalization of oximes and alkenes.

Experimental Section

General Considerations

The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solvents on an NMR spectrometer using TMS as the internal standard. LRMS was performed on a GC-MS instrument. HRMS was measured on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry.

Typical Experimental Procedures

Typical Experimental Procedure for the Rh(III)-catalyzed redox-neutral [4+2] annulation of aromatic oximes (2) with common terminal alkenes (2): To a Schlenk tube were added oxmines **1** (0.1 mmol), aromatic alkenes **2** (0.15 mmol), $[Cp^*RhCl_2]_2$ (3 mol%), K_2HPO_4 (50 mol%), and MeCN (2 mL). Then the mixture was stirred under argon at 80 °C (oil bath temperature) for 12 h until consumption of starting material as monitored by TLC and/or GC-MS analysis. After the reaction was finished, the reaction extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with saturated NaCl solution (3 × 5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20:1) to afford the desired products **3**.

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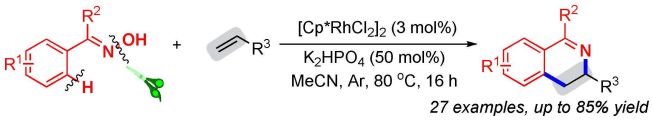

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