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Rhodium-Catalyzed Direct Vinylene Annulation of 2-Aryloxazoline and Cascade Ring-Opening Using Vinyl Selenone

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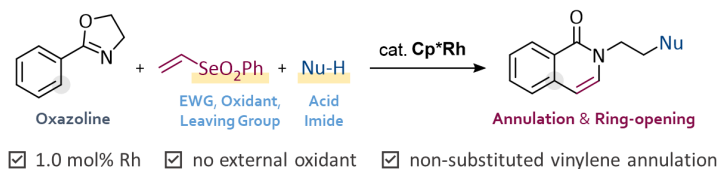
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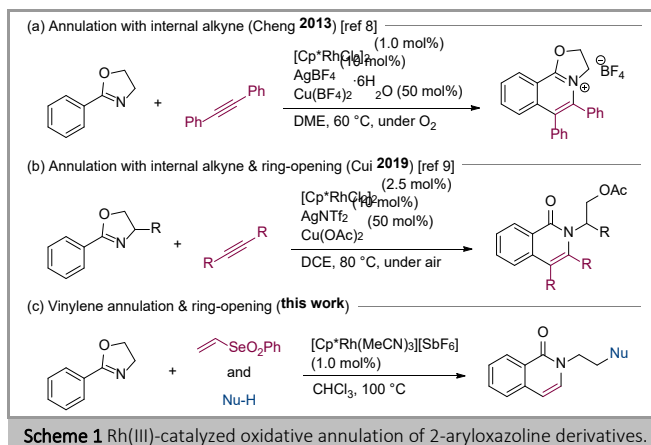
Abstract Over the past two decades, transition-metal-catalyzed C–H activation and the subsequent oxidative cyclization with alkynes or their surrogates has emerged as a powerful synthetic tool for fused heteroaromatics. We herein report a Rh(III)-catalyzed annulation and ring-opening cascade reaction with 2-aryloxazolines. By utilizing vinyl selenone as an oxidizing acetylene surrogate, the target three-component coupling products were obtained in high yields without using a stoichiometric amount of external oxidant.

Key words C–H activation; oxazoline; annulation; rhodium, vinyl selenone

Oxazoline (also known as 4,5-dihydroxazole) derivatives are frequently found in natural products¹ and synthetic functional molecules such as chiral ligand,² polymer,³ glycosyl donor,⁴ etc. In the organic chemistry field, oxazolines have been utilized as directing groups because of their rigid structure and chemical stability. In particular, oxazoline-directed lithiation of aromatic substrates has been a promising synthetic tool over past 50 years.⁵ Recently, transition-metal-catalyzed C–H activation strategy has attracted significant research interest,⁶ and numerous direct bond forming reactions have been developed adopting oxazoline directing groups.⁷

In 2013, Cheng reported an efficient synthetic method of polycyclic pyridinium salts from a series of N-heterocycles through Rh(III)-catalyzed C–H activation and subsequent oxidative annulation with alkynes.⁸ They demonstrated that 2-phenyloxazoline can be coupled with diphenylacetylene in the presence of $\text{Cu}(\text{BF}_4)_2$ oxidant while maintaining its oxazoline ring skeleton (Scheme 1a). A contrasting outcome was obtained in a recent work by Cui, where the oxazoline ring-opening was achieved by nucleophilic attack of acetate anion derived from $\text{Cu}(\text{OAc})_2$ (Scheme 1b).⁹ Afterward, a few rare examples of Rh(III)-catalyzed tandem annulation/ring-opening reactions

were developed adopting iodonium ylides or α -diazo carbonyl compounds as the coupling partners.¹⁰

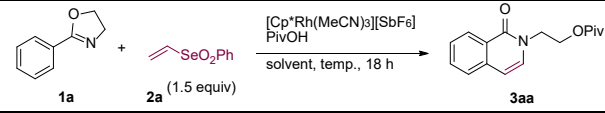


Our group recently focus on the development of catalytic C–H activation and direct vinylene annulation reactions.¹¹ Vinylene carbonate¹² and vinyl selenone¹³ are particularly useful “vinylene transfer” reagents since their oxidized nature enable us to avoid using stoichiometric external oxidants. In 2023, we reported that vinyl selenone exhibited higher productivity for the isoquinoline synthesis by vinylene annulation of imine derivatives, probably because of its enhanced Michael acceptor character.^{11e} In this work, we developed a Rh(III)-catalyzed three-component reaction of 2-aryloxazolines, vinyl selenone, and external nucleophiles via oxazoline ring-opening (Scheme 1c). This transformation achieves challenging formal acetylene annulation with 1.0 mol% Rh catalyst to construct isoquinolone scaffolds.

As an initial study, we examined the vinylene annulation of oxazoline **1a** with vinyl selenone **2a** as a model reaction (Table 1, see the SI for additional data). The corresponding product **3aa** was obtained in 24% yield using 6.0 mol%

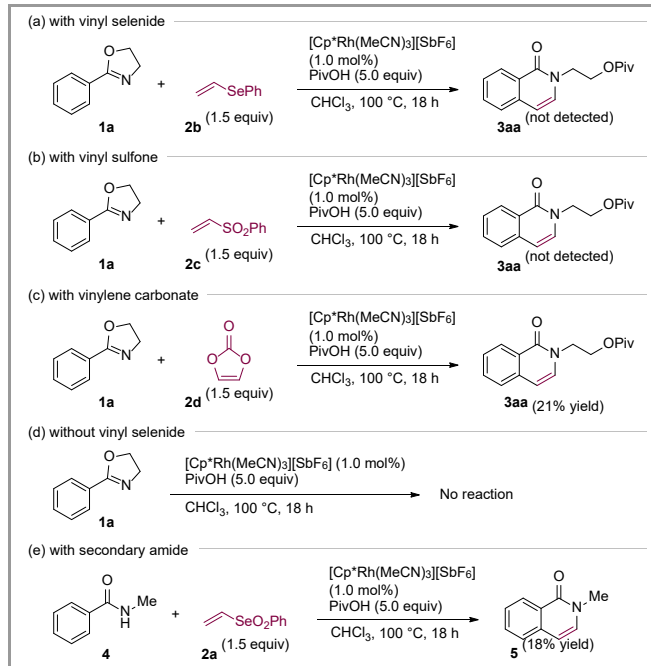
[Cp*Rh(MeCN)₃][SbF₆]₂ catalyst and 1.2 equiv pivalic acid (PivOH) in toluene solvent (entry 1). PivOH herein acted as a nucleophile to convert the oxazoline ring to the isoquinolinone scaffold. The structure of **3aa** was unambiguously confirmed by an X-ray crystallographic analysis (CCDC 2302556). After screening the solvents (entries 2–6), CHCl₃ gave the highest 44% product yield (entry 4). The productivity was further improved with increased temperature and amount of PivOH (entry 7), and the Rh catalyst loading could be decreased to 1.0 mol% without affecting the yield of **3aa** (entry 8). NaOPiv was not a suitable promoter for this transformation (entry 9). The highest yield 74% was obtained when the reaction was conducted at 100 °C (entries 10,11). It is notable that the present system does not require any external oxidant to achieve the formal oxidative annulation. We assume the leaving Se(IV) fragment acted as two electron oxidant within the catalytic cycle; however, the resulting Se(II) species was not determined yet.

Table 1 Optimization of reaction conditions ^a

				
entry	Rh cat.	PivOH	conditions	yield ^b
1	6.0 mol%	1.2 eq.	toluene, 80 °C	24%
2	6.0 mol%	1.2 eq.	PhCl, 80 °C	21%
3	6.0 mol%	1.2 eq.	THF, 80 °C	27%
4	6.0 mol%	1.2 eq.	CHCl ₃ , 80 °C	44%
5	6.0 mol%	1.2 eq.	MeCN, 80 °C	30%
6	6.0 mol%	1.2 eq.	<i>t</i> -AmOH, 80 °C	35%
7	3.0 mol%	5.0 eq.	CHCl ₃ , 120 °C	64%
8	1.0 mol%	5.0 eq.	CHCl ₃ , 120 °C	68%
9	1.0 mol%	NaOPiv (5.0 eq.)	CHCl ₃ , 120 °C	n.d.
10	1.0 mol%	5.0 eq.	CHCl ₃ , 100 °C	74%
11	1.0 mol%	5.0 eq.	CHCl ₃ , 80 °C	72%

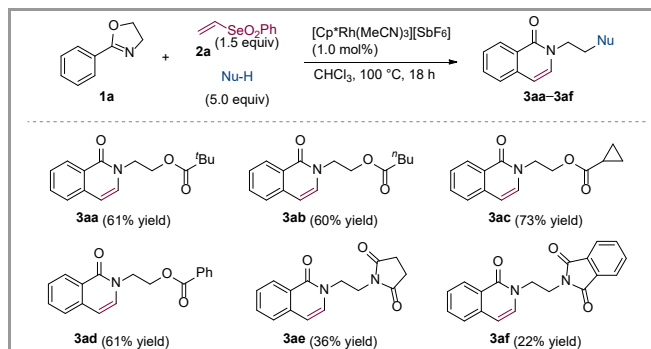
^a Standard conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), [Cp*Rh(MeCN)₃][SbF₆]₂, and PivOH in solvent (1.0 mL) was heated for 18 h. ^b Estimated by NMR analyses. n.d. = not detected.

We then examined several vinyl compounds under the standard reaction conditions. Vinyl selenide **2b** and vinyl sulfone **2c** did not produce the coupling product (Scheme 2a and 2b). Vinylene carbonate (**2d**) was not an effective coupling partner in this case, affording **3aa** in 21% yield (Scheme 2c). These results would highlight the significance of selenonyl group for facilitating the annulation reaction after oxazoline-directed C–H activation. Oxazoline **1a** was fully recovered under the standard reaction conditions in the absence of selenone **2a** (Scheme 2d). This clearly shows that the oxazoline ring would not open simply heating with PivOH, and thus we assume the corresponding pyridinium species should form in prior to the ring-opening event (see below). In addition, a secondary amide **4** was converted to the annulation product **5** only in low yield (Scheme 2e).



Scheme 2 Reaction with other vinyl reagents and control experiment.

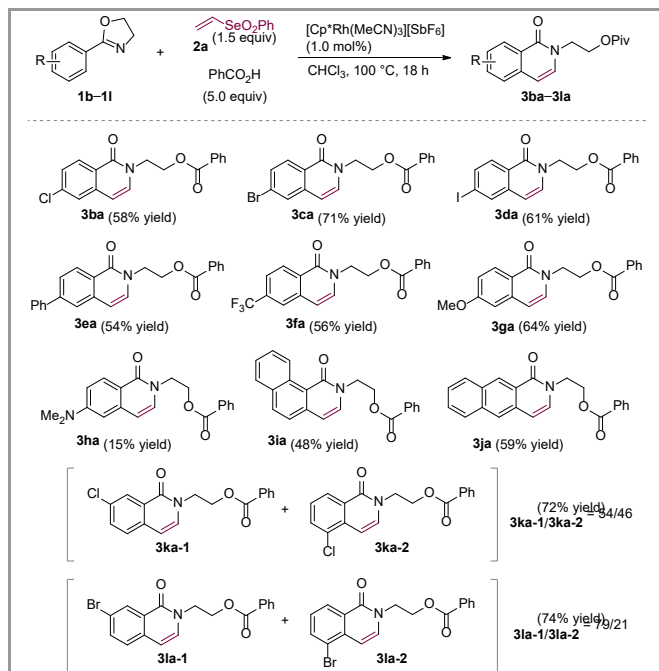
Next, the scope and limitation of the established reaction system was evaluated (Scheme 3). With regards to the nucleophile, both aliphatic and aromatic acids were applicable, affording the corresponding products **3aa–3ad** in 60–73% isolated yields. Interestingly, succinimide and phthalimide could be adopted as nitrogen nucleophiles to give **3ae** (36%) and **3af** (22%), respectively. We also tested several other nitrogen (carboxamide, sulfonamide) and sulfur (thiol) nucleophiles, but these were not suitable reactants for this system (not shown).



Scheme 3 Substrate scope for nucleophiles.

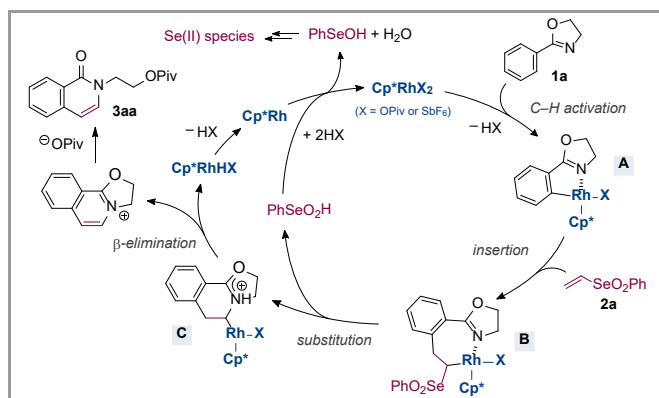
A series of substituted 2-aryloxazolines were then examined adopting benzoic acid as the nucleophile (Scheme 4). To our delight, chloro (**3ba**), bromo (**3ca**), and iodo (**3da**) functionalities remained untouched during the reaction, which would be beneficial for post-functionalization of the isoquinolinone scaffold. Phenyl (**1e**), CF₃ (**1f**), and OMe (**1g**) groups were tolerated to give the corresponding coupling products in 54–64% yields, whereas a strong electron donating NMe₂ (**1h**) substituent significantly retarded the reaction, and most of the starting material was recovered. 1-Naphtyloxazoline **1i** was also applicable to the developed catalytic system. For the reaction of 2-naphtyloxazoline **1j**, a sterically more accessible site was selectively annulated to produce **3ja** as a single isomer. However,

m-Cl (**1k**) and *m*-Br (**1l**) oxazolines afforded mixture of isomers in high total yields.



Scheme 4 Substrate scope for the oxazolines.

According to literatures,^{8,9,14} we would like to propose a mechanism for the coupling reaction of **1a** with **2a** and PivOH as shown in Scheme 5. A catalytically active Rh(III) species, which is assumed as $[\text{Cp}^*\text{Rh}(\text{OPiv})]^+$, undergoes directing-group-assisted C–H bond activation to form a rhodacycle intermediate **A**. Vinyl selenone **2a** coordinates to the metal and inserted into the Rh–C bond (**A**→**B**). The subsequent nucleophilic substitution takes place at the carbon atom adjacent to Rh (**B**→**C**), liberating a benzeneseleninic acid (PhSeO_2H) molecule. β -Hydrogen elimination would produce an oxazolium salt intermediate, which is further converted to the ring-opening product **3aa** by the nucleophilic attack of a pivalate anion. The concurrently formed Rh(III) hydride species may undergo reductive elimination to give a Rh(I) species. We believe this is oxidized by Se(IV) to regenerate the catalytically active Rh(III) complex. In our previous report, the resulting Se(II) was almost quantitatively recovered as diphenyl diselenide,^{11e} but in the present reaction, the fate of selenium content has not been determined.



Scheme 5 A proposed reaction mechanism.

In summary, we have developed a Rh(III)-catalyzed annulation and ring-opening cascade reaction with 2-aryloxazolines, vinyl selenone, and external nucleophiles. This transformation achieves challenging formal acetylene annulation which does not require a stoichiometric amount of metal salts as external oxidant. The use of vinyl selenone was important to facilitate the oxazoline ring-opening process and to obtain the target three-component coupling products in high yields. It is notable that the present reaction can involve nitrogen nucleophiles (such as succinimide; and phthalimide), while further optimization should be conducted to improve the productivity.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

References and Notes

General Procedure for the Rh-catalyzed Oxidative Annulation: To an oven-dried 10 mL screw-top tube were added **1** (0.2 mmol), phenyl vinyl selenone **2a** (64.5 mg, 0.3 mmol), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]_2$ (1.7 mg, 1.0 mol%), nucleophile (1.0 mmol). The tube was filled with N_2 , and CHCl_3 (2.0 mL) was added via syringe. The mixture was heated at 100 °C with an oil bath for 18 h. The resulting suspension was filtered through a pad of Celite eluting with CHCl_3 . The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography and, if indicated, GPC to give **3**.

2-(1-oxisoquinolin-2(1*H*)-yl)ethyl pivalate (**3aa**)

Purified by silica gel column chromatography (hexane/EtOAc = 2/1) as pale-yellow solid (33.2 mg, 61% yield), m.p. 108.3–110.3 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.43 (dt, J = 0.6, 8.0 Hz, 1H), 7.67–7.62 (m, 1H), 7.53–7.47 (m, 2H), 7.05 (d, J = 7.4 Hz, 1H), 6.48 (d, J = 7.3 Hz, 1H), 4.42 (t, J = 5.3 Hz, 2H), 4.27 (t, J = 5.3 Hz, 2H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 178.2, 162.2, 137.1, 132.4, 132.3, 127.8, 126.9, 126.2, 125.9, 105.7, 62.3, 48.4, 38.8, 27.2; HRMS (APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_3$ 274.1438; Found 274.1434.

For other compounds, see the Supporting Information.

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