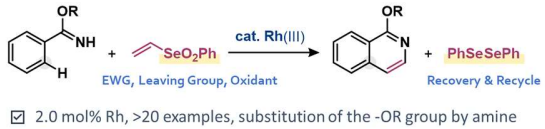
Rhodium-Catalyzed Isoquinoline Synthesis Using Vinyl Selenone as Oxidizing Acetylene Surrogate

Ayumi Inami,[†] Yuji Nishii,*[,†] Koji Hirano, [†,‡] and Masahiro Miura*[,‡]

[†] Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

[‡] Innovative Catalysis Science Division, Institute for Open and Transdisciplinary Research Initiatives (ICS-OTRI), Osaka University, Suita, Osaka 565-0871, Japan

Supporting Information Placeholder

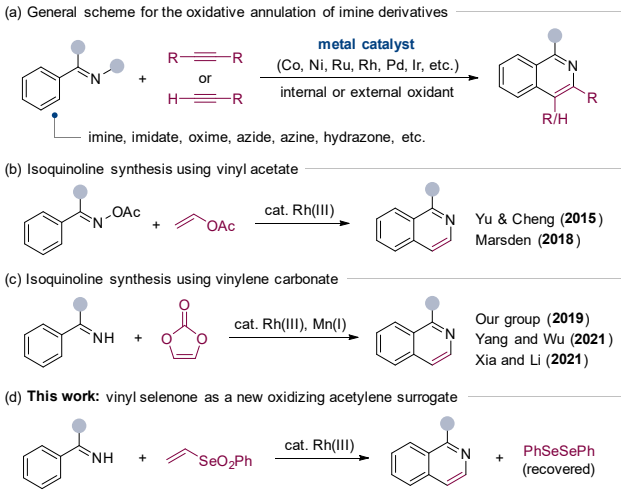


ABSTRACT: Isoquinoline is a privileged structure in many bioactive compounds and valuable ligands. Transition-metal-catalyzed oxidative annulation of imine derivatives has become a promising synthetic method; however, catalytic synthesis of 3,4-nonsubstituted isoquinolines by formal acetylene annulation has been scarce to date. Herein, we introduce vinyl selenone as an effective acetylene surrogate for the Rh-catalyzed annulative coupling under mild conditions. The Se fragment can be recovered as diselenide and recycled. The product can readily be converted to 1-aminoisoquinolines.

Isoquinoline derivatives are among the most important class of N-heterocyclic compounds with variable medicinal applications including antimicrobial, antiviral, anesthetics, enzyme inhibitors, vasodilators, neurochemical agent, etc.[1] The naturally occurring isoquinolines constitute a large family of isoquinoline alkaloids.[2] Functionalized isoquinolines have also been a key motif in chiral ligands for asymmetric synthesis.[3] These important applications have motivated chemists to develop efficient and practical synthetic methods for isoquinoline derivatives. Over the past two decades, catalytic intermolecular oxidative annulation of imine derivatives with alkynes (or surrogate such as sulfur ylides, α-diazocarbonyl compounds, etc.) through C–H activation has been a powerful synthetic tool because of its operational simplicity, step-efficiency, and broad substrate scope (Scheme 1a).[4] Transition-metal complexes of Co, Ni, Ru, Rh, Pd, and Ir have been mainly utilized as catalysts. These reaction systems are particularly effective for the synthesis of 3,4-disubstituted and 3-monosubstituted isoquinoline derivatives.

In sharp contrast, catalytic synthesis of 3,4-nonsubstituted isoquinolines by formal acetylene annulation[5] has been scarce to date. As a seminal work, Yu and Cheng developed a Rh-catalyzed coupling reaction of *O*-acetyl oximes with vinyl acetate in 2015 (Scheme 1b).[6] Marsden, who used vinyl acetate firstly for the Rh-catalyzed annulation chemistry in 2014,[7] also reported a coupling reaction of oximes in 2018.[8] Recently, our group utilized vinylene carbonate as an oxidizing acetylene surrogate[9] to the synthesis of vinylene-fused N-heterocyclic compounds (Scheme 1c). [9a] Thereafter, Yang and Wu reported the catalytic reaction of amidines with vinylene carbonate to give 1-aminoisoquinolines.[10a] Xia and Li developed a similar reaction system using Mn catalyst.[10b] These methods, however, require excess vinyl reagent, high catalyst loading, and/or increased reaction temperature yet with relatively narrow substrate scope.

Scheme 1. Isoquinoline Synthesis by Catalytic Annulation of Imine Derivatives

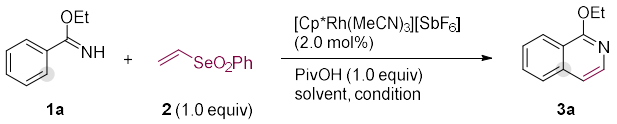


To address these issues, we envisioned using vinyl selenone as a new vinylene transfer reagent for the annulative coupling reactions (Scheme 1d). Vinyl selenones show unique reactivity among common vinyl compounds because the selenonyl moiety acts as a strong electron-withdrawing group to facilitate Michael addition and as a leaving group to accept another nucleo-

phile.[11] These properties are particularly advantageous for multiple-bond forming reactions. Moreover, the leaving seleninic acid may act as a terminal oxidant to ensure the catalyst turnover.[12] Herein, we report a Rh-catalyzed isoquinoline synthesis adopting 1.0 equiv phenyl vinyl selenone **2** as an oxidizing acetylene surrogate. This catalytic system offers efficient synthesis of functionalized 3,4-nonsubstituted isoquinolines under mild reaction conditions. The selenium content was readily recovered as neutral diphenyl diselenide, minimizing unwanted selenium waste.

As an initial attempt, we examined the coupling reaction of benzimidate **1a** with phenyl vinyl selenone (**2**) in the presence of 2.0 mol% $[Cp^*Rh(MeCN)_3][SbF_6]_2$ catalyst in ^{t}AmOH solvent, and the target product **3a** was obtained in 21% yield (Scheme 2, entry 1). The productivity was significantly improved by using PivOH as an additive (entry 2), whereas PivOK was not a suitable promoter for this transformation (entry 3). The product **3a** was not obtained without the Rh catalyst (entry 4). After further optimization, ethereal solvents were found to be optimal to achieve quantitative conversion (entries 5–7). This reaction was successfully conducted in 1.0 mmol scale to afford **3a** in 70% isolated yield (entry 8). The catalyst loading and the reaction temperature could respectively be decreased to 1.0 mol% and 60 °C (entry 9). Other metal complexes were less effective to give **3a** in fairly low yields (entries 10–12).

Scheme 2. Optimization Study [a]

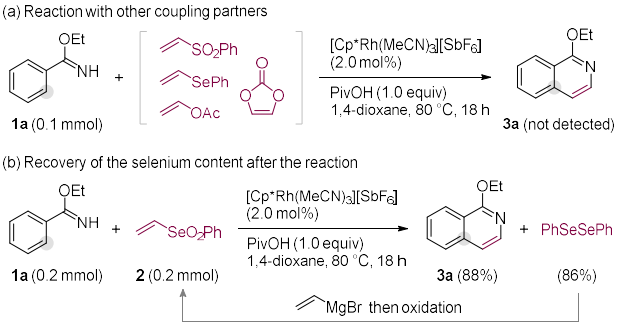


entry	deviation	solvent	condition	yield [b]
1	without PivOH	^{t}AmOH	80 °C, 16 h	21%
2	--	^{t}AmOH	80 °C, 16 h	74%
3	PivOK instead of PivOH	^{t}AmOH	80 °C, 16 h	n.d.
4	without Rh catalyst	^{t}AmOH	80 °C, 16 h	n.d.
5	--	toluene	80 °C, 16 h	66%
6	--	DCE	80 °C, 16 h	88%
7	--	1,4-dioxane	80 °C, 16 h	99%
8	1.0 mmol scale	1,4-dioxane	80 °C, 16 h	(70%)
9	1.0 mol% Rh catalyst	THF	60 °C, 24 h	93%
10 [c]	$[Ru(p\text{-cymene})Cl_2]_2$ catalyst	THF	60 °C, 24 h	11%
11 [c]	$Cp^*CoI_2(CO)$ catalyst	THF	60 °C, 24 h	14%
12 [c]	$[Cp^*IrCl_2]_2$ catalyst	THF	60 °C, 24 h	25%

[a] Standard conditions: **1a** (0.1 mmol), **2** (0.1 mmol), PivOH (0.1 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (2.0 mol %) in solvent (1.0 mL). [b] Determined by NMR analysis. Isolated yield in parentheses. [c] With 2.0 mol% (as metal) catalyst and 10 mol% $AgSbF_6$.

We also examined several other coupling partners: vinyl sulfone, vinyl selenide, vinyl acetate, and vinylene carbonate, but the target product **3a** was not detected (Scheme 3a). This result clearly highlighted exceptional activity of the selenium reagent for the annulative coupling. Interestingly, under the optimized reaction conditions, diphenyl diselenide was isolated in high yield (86% recovery of Se) along with **3a** (88% yield) (Scheme 3b). This outcome indicates that Se(IV) species formed in the cyclization step would be a terminal two electron oxidant to regenerate catalytically active Rh(III) species (see below). In addition, because the vinyl selenone **2** was readily prepared from diphenyl diselenide through vinylation and oxidation,[13] the developed synthetic method can minimize the overall selenium waste.

Scheme 3. Control Experiments

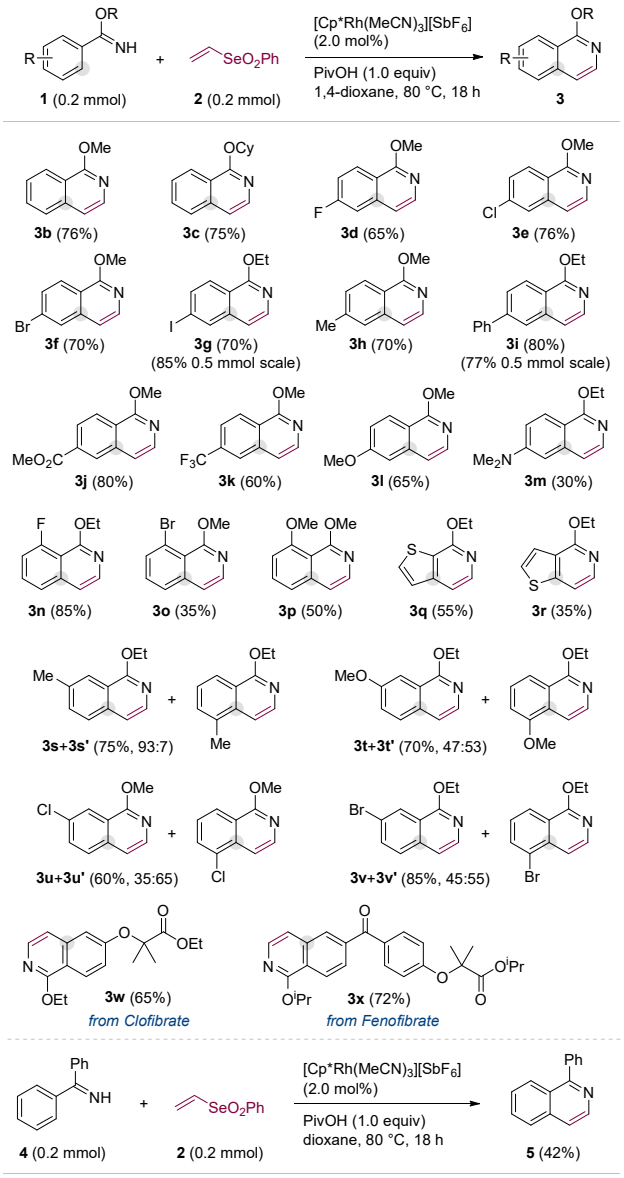


We then evaluated the scope and limitations of the catalytic reaction system (Scheme 4). The alkyl substituent within the directing group can be methyl (**1b**) and cyclohexyl (**1c**) as well. Various functionalities such as halogen (**1d**–**1g**, **1n**, **1o**), aryl (**1i**), ester (**1j**), trifluoromethyl (**1k**), alkoxy (**1l**, **1p**), and amine (**1m**) groups were readily tolerated under the standard reaction conditions to give the corresponding isoquinolines in moderate to high yields. The structures of **3l** (CCDC 2247087) and **3p** (CCDC 2247088) were unambiguously determined by X-ray crystallographic analyses. This method was also applicable to the synthesis of thienopyridine derivatives (**3q**, **3r**). For the reaction of *m*-Me benzimidate **1s**, the sterically more accessible site was preferentially annulated to give C7-substituted isoquinoline **3s**, whereas *m*-OMe benzimidate **1t** afforded almost 1:1 mixture of two isomers. Unexpectedly, in the case of *m*-Cl benzimidate **1u**, a sterically congested isomer **3u'** was obtained as the major product (**3u**:**3u'** = 35:65). A similar trend was observed for *m*-Br benzimidate **1v**: C5-substituted isoquinoline **3v'** was obtained slightly more than **3v** even with the steric bulkiness of Br group (**3v**:**3v'** = 45:55).[14] Isoquinolines derived from clofibrate (**3w**) and fenofibrate (**3x**) could be efficiently synthesized. The established reaction conditions can be applied to the vinylene annulation of benzophenone imine (**4**) to give 1-phenylisoquinoline (**5**) in 42% yield. The previous method using vinylene carbonate required 2.0 equiv of **4**, increased catalyst loading (5.0 mol% Rh), and higher temperature (120 °C) to achieve comparable productivity (65% yield of **5**). We examined several benzamidine derivatives, but the corresponding 1-aminoisoquinolines were not obtained (not shown).

According to literature information,[15] we would like to propose a reaction mechanism for the catalytic annulation of **1a** with **2** as shown in Scheme 5. A catalytically active Rh(III) species triggers directing-group-assisted C–H activation to give an intermediate **A**. This is converted to a seven-membered complex **B** via coordination and migratory insertion of **2** to the Rh–C bond. Intramolecular nucleophilic substitution takes place at the carbon atom adjacent to Rh to form an intermediate **C**, liberating a benzeneseleninic acid ($PhSeO_2H$) molecule. The target product **3a** would be obtained through the subsequent β-hydrogen elimination. As an alternative pathway for the pyridine ring formation, β-hydrogen elimination, electrocyclization, and α-selenation cannot be ruled out while the reaction outcome is the same. The liberated Rh(III) hydride species may undergo

reductive elimination to form Rh(I) complex, which would be oxidized by Se(IV) to close the catalytic cycle. Eventually, the Se(II) species were converted to diphenyl diselenide (Scheme 3b).

Scheme 4. Substrate Scope [a]

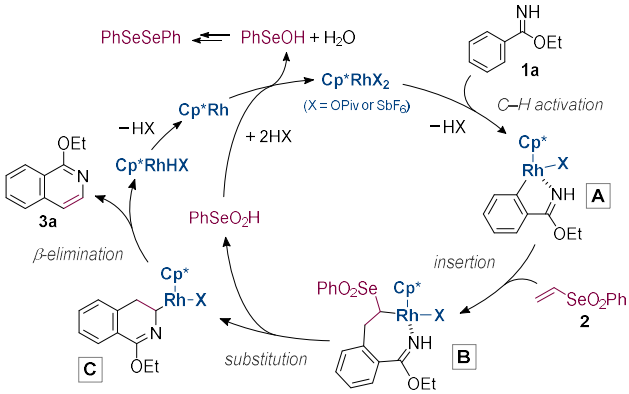


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), PivOH (0.2 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (2.0 mol %) in 1,4-dioxane (2.0 mL).

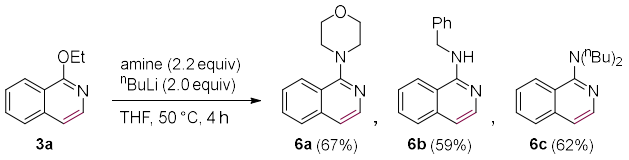
1-Alkoxyisoquinolines have become more readily available by the catalytic oxidative annulation of imidate derivatives; however, their synthetic utility has been scarcely investigated. To our delight, the coupling product **3a** was successfully converted to 1-aminoisoquinolines upon treatment with lithium amide reagents formed in situ (Scheme 6).[16] The corresponding substitution products **6a**–**6c** were obtained in good yields. This would be an alternative synthetic method for medicinally valuable 3,4-unsubstituted aminoisoquinoline compounds.

In summary, we have introduced vinyl selenone **2** as an effective acetylene surrogate for the metal-catalyzed annulative coupling reaction. A series of 3,4-unsubstituted isoquinoline derivatives were successfully synthesized under mild reaction conditions with low catalyst loading. The Se fragment was recovered as the corresponding diselenide and can be recycled, minimizing unwanted selenium waste. As demonstrated in 1-aminoisoquinoline synthesis, the coupling products would be versatile precursors of various 1-substituted isoquinoline derivatives.

Scheme 5. Proposed Reaction Mechanism



Scheme 6. Synthetic Application



ASSOCIATED CONTENT

Data Availability

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and product identification data, ORTEP drawings, and copy of ^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ NMR spectra (PDF)

Accession Codes

CCDC 2247087 and 2247088 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

Yuji Nishii – *Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan*; orcid.org/0000-0002-6824-0639; Email: y_nishii@chem.eng.osaka-u.ac.jp.

Masahiro Miura – *Innovative Catalysis Science Division, Institute for Open and Transdisciplinary Research Initiatives (ICS-OTRI), Osaka University, Suita, Osaka 565-0871, Japan*; orcid.org/0000-0001-8288-6439; Email: miura@chem.eng.osaka-u.ac.jp.

Authors

Ayumi Inami – *Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan.*

Koji Hirano − *Department of Applied Chemistry, Graduate School of Engineering and Innovative Catalysis Science Division, Institute for Open and Transdisciplinary Research Initiatives (ICS-OTRI), Osaka University, Suita, Osaka 565-0871, Japan;* orcid.org/ 0000-0001-9752-1985..

Notes

The authors declare no competing financial interest.

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