Rhodium(III)-Catalyzed Annulation of Acetophenone *O*-Acetyl Oximes with Allenoates through Arene C−H Activation: An Access to Isoquinolines

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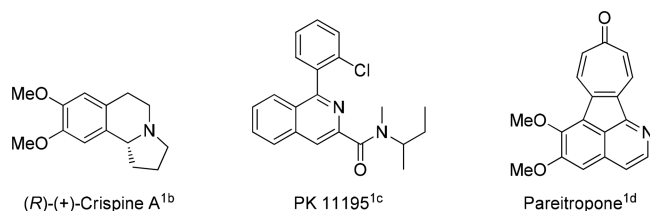
S *Supporting Information*

ABSTRACT: Rhodium(III)-catalyzed annulation of acetophenone *O*-acetyl oximes with allenoates was achieved, affording isoquinolines in good to excellent yields with high regioselectivities under redox-neutral conditions. Allenoates acted as the C2 synthons in the annulation reaction. The present synthetic methodology features good functional group tolerance and avoids metal salts as the external oxidants. The proposed mechanism suggests that the reaction proceeds through arene C−H activation, allene insertion, and C−N coupling.

INTRODUCTION

Isoquinoline motif exists in a variety of biologically active molecules, pharmaceuticals, and functional materials[1a] For example, (*R*)-(+)-Crispine A[1b] shows significant cytotoxic activity, PK 11195[1c] can be used as an inhibitor of [³H]MeTRH, and Pareitropone[1d] is the most potent anticancer agent among the relatively small family of tropoloisoquinoline alkaloids (Scheme 1). Considerable efforts

Scheme 1. Structures of (*R*)-(+)-Crispine A, PK 11195, and Pareitropone

(*R*)-(+)-Crispine A[1b]   PK 11195[1c]   Pareitropone[1d]

have recently been devoted to the synthesis of isoquinolines, and nitrogen-containing directing group-assisted transition-metal-catalyzed C−H activation seems to be a promising route to reach this goal.[2] Among the nitrogen-containing directing groups for C−H activation, oxime ester has been paid much attention due to its ready availability, easy removal, and transformation.[3] In this regard, transition-metal-catalyzed C−H annulation of acetophenone *O*-acetyl oximes with alkynes has been developed to access isoquinolines.[4] However, such a protocol is limited to internal alkynes, and only a few examples using terminal alkynes have been reported.[5] To synthesize

isoquinolines, vinyl acetates,[6a] 1,3-dienes,[6b] and diazo compounds[7] have been explored as the coupling partners to react with acetophenone *O*-acetyl oximes through arene C−H annulation. Although progress has been achieved, more powerful and elegant synthetic methods are strongly desired in this area.

Allenes, which can exhibit high reactivity in comparison to similar alkenes, have been demonstrated as useful building blocks for the construction of complex skeletons.[8] Much attention has been paid to allene-involved, transition-metal-catalyzed C−H transformations. In the relevant catalytic cycle, allene is usually inserted into the metal−carbon bond of an in situ generated organometallic species to form an alkenyl-metal or π-allyl-metal intermediate. Protonation or β-hydride elimination then occurs to give an allylation[9] or allenylation[10] product. Coupling such an intermediate with the nucleophilic atom in the directing group has recently been documented to build a heterocycle. Various nitrogen-containing directing groups have been explored in the C−H annulation with allenes for the synthesis of *N*-heterocycles. Ding[11a] and Cramer[11b,c] et al. reported an imine-directed C−H annulation of ketimines with allenes for the synthesis of 1-aminoindanes, respectively. Wang group realized a Mn/Ag catalyzed C−H activation of ketimines with allenes for the synthesis of polycyclic products.[11d] Pyrimidine-directed, Mn-catalyzed 1,2-diheteroarylation of allenes formed bicyclic and tricyclic heterocycles.[12] Transition-metal-catalyzed C−H annulation of arylamides with allenes have been well explored to produce
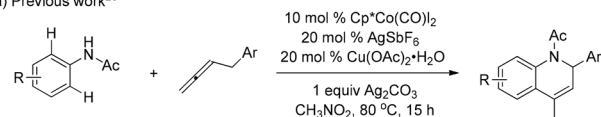
diverse isoquinolones by Rao,[13] Ackermann,[10a,14] Volla,[15] Glorius,[16] Cheng,[17] Ma,[10b,18] and other groups.[19] Cheng et al. recently developed a cobalt(III)-catalyzed oxidative [3 + 3] annulation of anilides with allenes to access 1,2-dihydroquinolines (Scheme 2a).[20] However, this reaction required silver(I)

Scheme 2. Transition-Metal-Catalyzed C−H Activation with Allenes

salt Ag₂CO₃ as the external oxidant. It has been known that the N−O functionality of oximes can act as an internal oxidant in the relevant C−H functionalization reactions,[4,5] and the C=N functionality in the C=N−OR moiety is a potential directing group. During our continuous investigation of C−H activation,[21] we were intrigued by the structural features of *O*-acyl oximes, and reasonably envisioned the direct C−H annulation of aromatic *O*-acyl oximes with allenes. Herein, we disclose a rhodium(III)-catalyzed [4 + 2] annulation of acetophenone *O*-acetyl oximes with allenoates for the synthesis of isoquinoline derivatives under redox-neutral conditions (Scheme 2b).

RESULTS AND DISCUSSION

Initially, the reaction of (*E*)-acetophenone *O*-acetyl oxime (**1a**) with ethyl 2-methylbuta-2,3-dienoate (**2a**) was conducted to screen the reaction conditions (Table 1). With 2 mol % RhCl₃· 3H₂O/8 mol % AgSbF₆ as the catalyst, 20 mol % PivOH as the additive, the reaction of **1a** with **2a** in a 1:2 molar ratio did not occur in 1,2-dichloroethane (DCE) at 60 °C for 24 h under a nitrogen atmosphere (Table 1, entry 1). Changing the catalyst to 2 mol % [Cp*RhCl₂]₂/8 mol % AgSbF₆ led to isoquinoline derivative **3a** in 66% yield by ¹H NMR determination (Table 1, entry 2). Both silver salts AgPF₆ and AgBF₄ were less effective than AgSbF₆ (Table 1, entries 3 and 4). Use of 10 mol % AgSbF₆ improved the product yield to 91% (Table 1, entries 5−7). The highest yield (92%) was reached, and the target product was obtained in 86% isolated yield from a 0.3 mmol-scale reaction (Table 1, entry 10). Lowering the temperature to 50 °C diminished the yield to 83%, and elevating the temperature to 70 °C did not further enhance the product yield (Table 1, entries 11 and 12). The control experiments revealed that the reaction could not occur in the absence of [Cp*RhCl₂]₂ or AgSbF₆ (Table 1, entries 13 and 14). It is noteworthy that the reaction could also occur in the absence of PivOH to give product **3a** in 86% NMR yield (Table 1, entry 15). The reaction of **1a** and **2a** was conducted under the optimal conditions with 2 mol % Cp*Co(CO)I₂ as the catalyst, but the reaction did not occur.
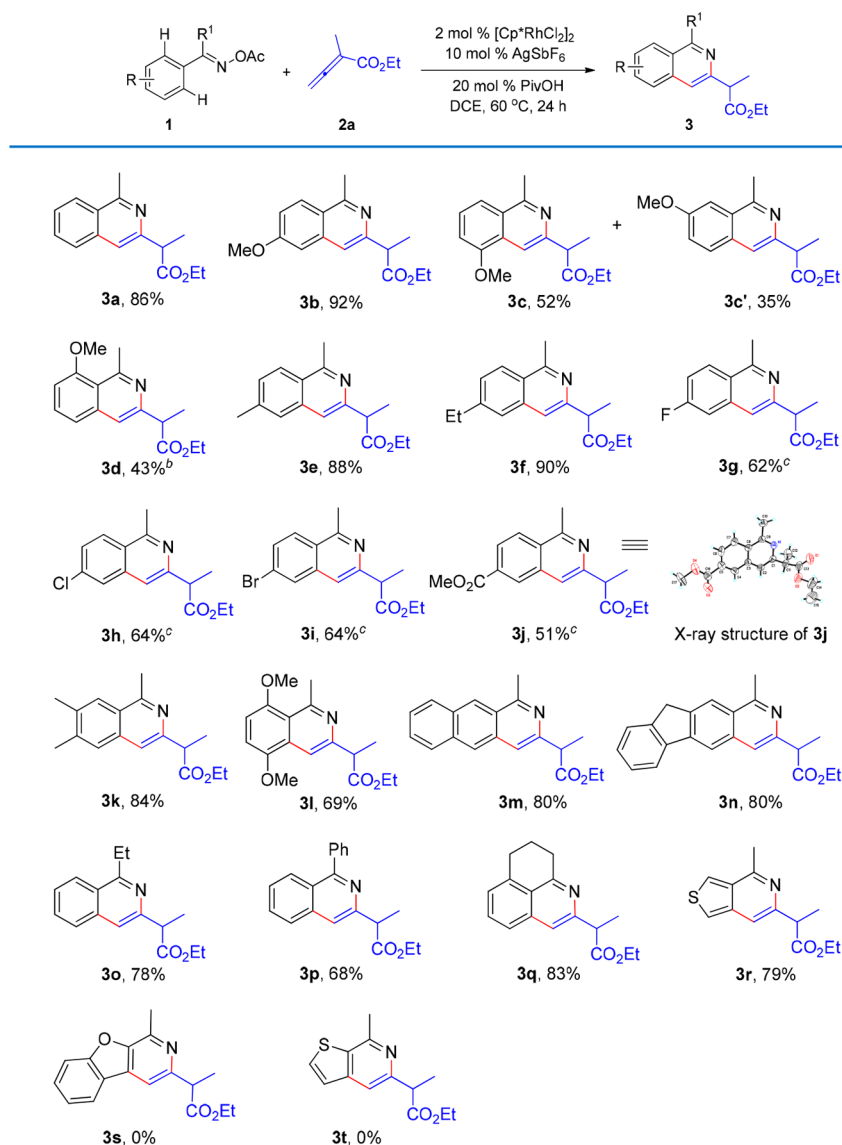
Under the optimized conditions, the scope of *O*-acetyl oximes **1** was investigated (Table 2). The substituted acetophenone *O*-acetyl oximes also efficiently reacted with **2a**

Table 1. Optimization of Reaction Conditions[a]

entry	[Ag] (mol %)	PivOH (mol %)	temp (°C)	yield[b] (%)
1[c]	AgSbF₆ (8)	20	60	0
2	AgSbF₆ (8)	20	60	66
3	AgPF₆ (8)	20	60	40
4	AgBF₄ (8)	20	60	51
5	AgSbF₆ (9)	20	60	87
6	AgSbF₆ (10)	20	60	91
7	AgSbF₆ (11)	20	60	90
8	AgSbF₆ (10)	30	60	90
9	AgSbF₆ (10)	10	60	88
10[d]	AgSbF₆ (10)	20	60	92 (86)[e]
11	AgSbF₆ (10)	20	50	83
12	AgSbF₆ (10)	20	70	92
13[f]	AgSbF₆ (10)	20	60	0
14		20	60	0
15	AgSbF₆ (10)		60	86

[a]Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Cp*RhCl₂]₂ (2 mol %), DCE (2 mL), 0.1 MPa N₂, 60 °C, 24 h. [b]Determined by ¹H NMR analysis with 1,3,5-trimethyloxylbenzene as the internal standard. [c]RhCl₃·3H₂O (2 mol %) [d]**1a** (0.3 mmol), **2a** (0.6 mmol), DCE (3 mL). [e]Isolated yield given in parentheses. [f]Without [Cp*RhCl₂]₂

to form the target products of type **3**. The *para*-methoxy substituent on the aryl ring of acetophenone *O*-acetyl oxime **1b** facilitated formation of **3b** (92%). Due to presence of two different reactive sites on the aryl ring of *meta*-methoxy acetophenone-based oxime substrate **1c**, two isomeric products **3c** (52%) and **3c′** (35%) were generated. However, *ortho*-MeO group exhibited an obvious steric effect on the yield of **3d** (43%), and the reaction had to be performed at an elevated temperature (80 °C). Both 4-methyl and 4-ethyl substituents facilitated the reaction to produce **3e** and **3f** (88−90%), respectively. The halogen substituents F, Cl, and Br deteriorated the reaction efficiency to yield **3g−i** (62−64%). It is noteworthy that electron-withdrawing groups such as F and CO₂Me remarkably reduced the product yields of **3g** (62%) and **3j** (51%), respectively. The negative impact from the *ortho*-substituent was also observed that 2,5-dimethoxy-acetophenone *O*-acetyl oxime (**1l**) reacted with **2a** to give **3l** (69%), while its 3,4-dimethyl-substituted analogue **1k** almost kept the same reactivity as **1a** did, forming **3k** in 84% yield. Both 2-acetonaphthone and 2-acetylfluorene *O*-acetyl oximes (**1m** and **1n**) reacted efficiently with **2a**, yielding **3m** (80%) and **3n** (80%), respectively. Increasing the steric hindrance of the acyl group in the starting ketones, that is, using propiophenone and benzophenone *O*-acetyl oximes **1o** and **1p** as the substrates, led to **3o** and **3p** in 78% and 68% yields, respectively, demonstrating a negative steric effect on the reaction efficiency. Unexpectedly, *α*-tetralone *O*-acetyl oxime **1q** reacted well with **2a** to afford tricyclic isoquinoline **3q** (83%). It should be noted that (*E*)-1-(thiophen-3-yl)ethanone *O*-acetyl oxime (**1r**) also efficiently reacted with **2a** to exclusively produce the corresponding product **3r** (79%). However, both 1-(benzofuran-2-yl)- ethanone and 1-(thiophen-2-yl)ethanone *O*-acetyl oximes **1s** and **1t** did not react with **2a** under the same conditions, which is presumably
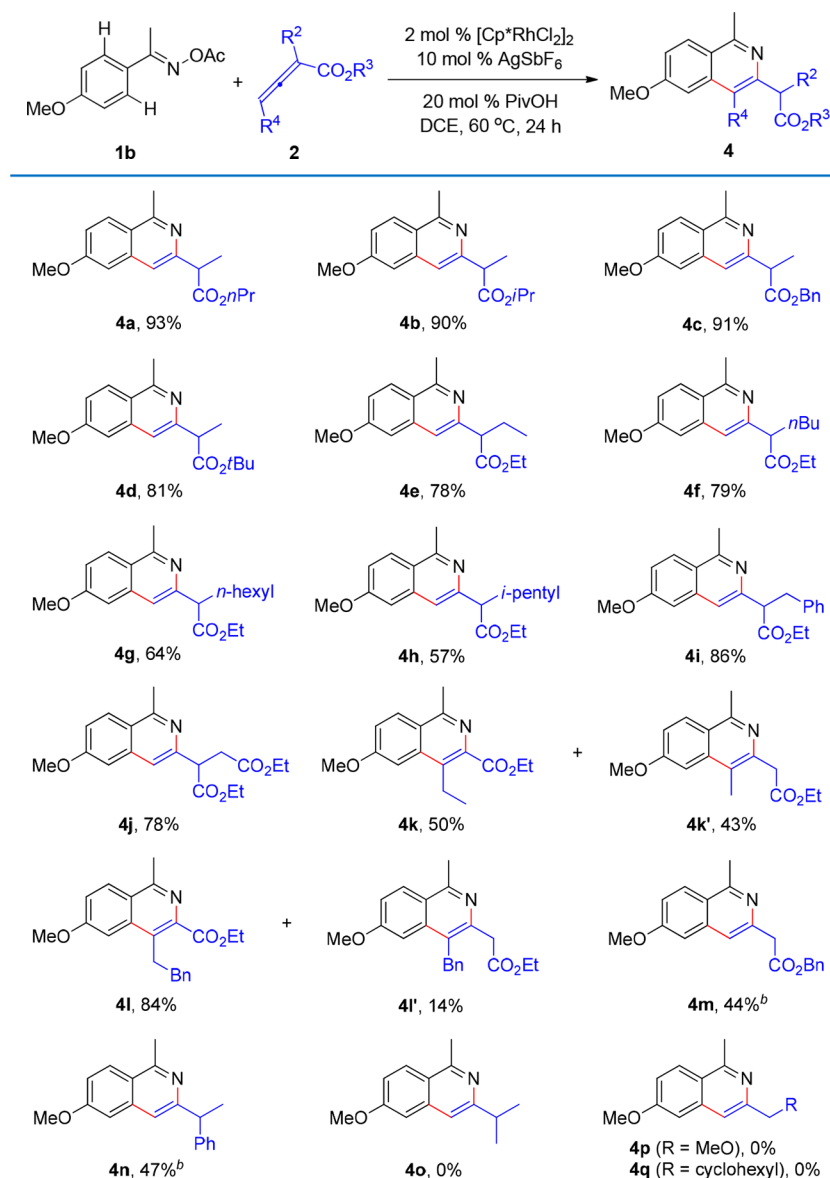
Table 2. Scope of *O*-Acetyl Oximes 1[a]

X-ray structure of 3j

[a]Conditions: **1** (0.3 mmol), **2a** (0.6 mmol), [Cp*RhCl₂]₂ (0.006 mmol), AgSbF₆ (0.03 mmol), PivOH (0.06 mol), DCE (3 mL), 0.1 MPa N₂, 60 °C, 24 h. Yields refer to the isolated products. [b]80 °C. [c][Cp*RhCl₂]₂ (0.012 mmol), AgSbF₆ (0.06 mmol).

attributed to the bidentate coordination of the vicinal N,O or N,S heteroatoms in the oxime substrate **1s** or **1t** to the rhodium atom of the catalyst that inhibits activation of the *ortho*-(hetero)arene C−H bond by the catalyst. The molecular structure of compound **3j** was further confirmed by the X-ray single crystal crystallographic determination (see the Supporting Information for details). It should be noted that in the cases of using *p*-NO₂, *p*-CN, and *p*-CF₃-substituted aryl oxime derivatives as the substrates, the reactions with **2a** could not effectively occur and no target products were obtained. *N*-Hetercycles such as (*E*)-1-(pyridin-4-yl)ethanone and (*E*)-1-(1-benzyl-1*H*-indol- 3-yl)ethanone *O*-acetyl oximes could not react with **2a** under the same conditions either.

Next, the protocol generality was investigated by testing various allenoates **2** as the coupling partners (Table 3). With *para*-methoxy-acetophenone *O*-acetyl oxime **1b** as the substrate, its reactions with *n*-propyl, isopropyl, benzyl, and *tert*-butyl allenoates **2b−e** efficiently underwent to afford the corresponding isoquinoline products **4a−d** (81−93%), re-

spectively, and only *tert*-butyl group exhibited an obvious steric effect. Altering the 2-substituent of allenoates to ethyl, *n*-butyl, *n*-hexyl, or isopentyl diminished the product yields of **4e−h** to 57−79%, demonstrating a negative steric effect in comparison to the formation of **3b** (92%, see Table 2). Ethyl 2-benzylbuta-2,3-dienoate (**2j**) exhibited a good reactivity to **1b**, producing the target product **4i** in 86% yield. Diethyl 2-vinylidenesuccinate (**2k**) also underwent the reaction well with **1b** to form **4j** (78%). Unexpectedly, ethyl penta-2,3-dienoate (**2l**) reacted with **1b** to afford two separable isomers **4k** (50%) and **4k′** (43%), and ethyl 5-phenylpenta-2,3-dienoate (**2m**) behaved the same way to yield separable **4l** (84%) and **4l′** (14%). However, unsubstituted allenoate **2n** only exhibited a poor reactivity to undergo the reaction with **1b**, giving **4m** in 44% yield, while the reaction of **2d** with **1b** formed **4c** in an excellent yield (91%). This result suggests that a 2-substituent is crucial to efficiently execute the desired reaction. Buta-2,3-dien-2-ylbenzene (**2o**) was also tested as the substrate to react with **1b**, generating the target product **4n** in 47% yield,
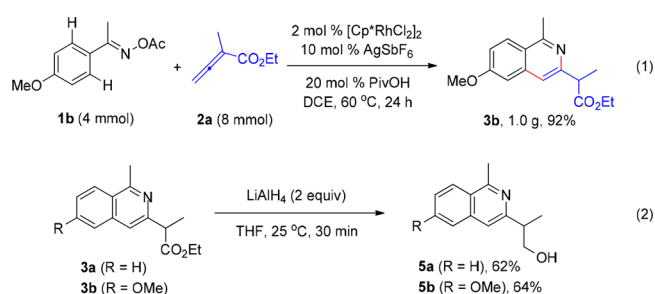
Table 3. Scope of Allenoates 2[a]

4a, 93% **4b**, 90% **4c**, 91%

4d, 81% **4e**, 78% **4f**, 79%

4g, 64% **4h**, 57% **4i**, 86%

4j, 78% **4k**, 50% + **4k'**, 43%

4l, 84% + **4l'**, 14% **4m**, 44%[b]

4n, 47%[b] **4o**, 0% **4p** (R = MeO), 0%
4q (R = cyclohexyl), 0%

[a]Conditions: **1b** (0.3 mmol), **2** (0.6 mmol), [Cp*RhCl$_2$]$_2$ (0.006 mmol), AgSbF$_6$ (0.03 mmol), PivOH (0.06 mol), DCE (3 mL), 0.1 MPa N$_2$, 60 °C, 24 h. Yields refer to the isolated products. [b][Cp*RhCl$_2$]$_2$ (0.012 mmol), AgSbF$_6$ (0.06 mmol).

implicating that a terminal ester group is also a crucial functionality in the allene-type substrates **2**. It is noteworthy that electron-donating group-substituted allenes such as 1,1-dimethylallene, methoxy allene, and cyclohexylallene could not undergo the same type of annulation reactions with **1b** to give the corresponding products **4o−q** under the stated conditions.

To demonstrate the utility of the synthetic protocol, a gram-scale reaction of oxime **1b** and allenoate **2a** was performed, affording the target product **3b** in 92% yield (eq 1). Chemoselective reduction of isoquinolines **3a** and **3b** was readily conducted to give the corresponding alcohols **5a** (62%) and **5b** (64%), respectively (eq 2).
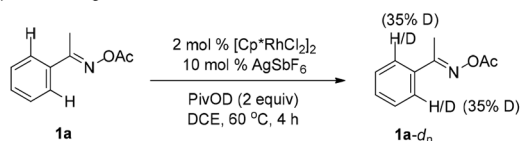
To gain insight into the reaction mechanism, control experiments were carried out. Significant H/D exchange was observed for the *ortho* C−H of the aryl ring in (*E*)-acetophenone *O*-acetyl oxime (**1a**) in the presence of PivOD under the reaction conditions, revealing reversibility of the C−H bond cleavage (Scheme 3a). The kinetic isotope effect
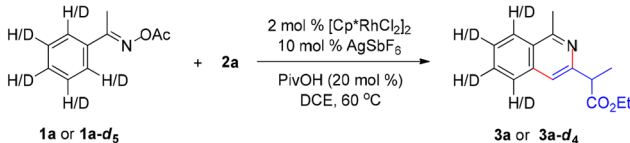

(1)

(2)

(KIE) was measured from the parallel experiments using **1a** and its deuterated form **1a**-d_5 with **2a** as the coupling partner (Scheme 3b). A primary isotope effect was obtained with $k_H/k_D = 3.2$, which suggests that arene C−H bond activation/cleavage is likely involved in the rate-determining step in the overall catalytic cycle.
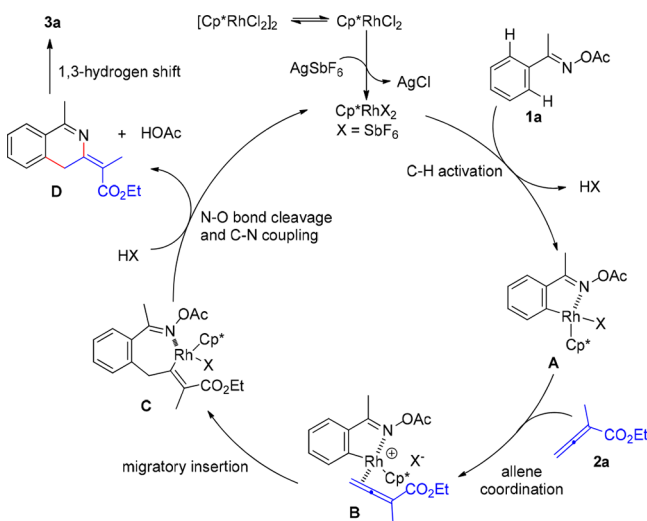
Scheme 3. Mechanism Studies

(a) H/D exchange

(b) KIE studies

time (min)	5	10	15	
yield of 3a	26.7%	32.1%	36.1%	k_H/k_D = 3.2
yield of 3a-d_4	8.5%	9.9%	11.3%	

A plausible mechanism[13−18,24] is proposed in Scheme 4. With the assistance of coordination of the oxime moiety to the

Scheme 4. Proposed Reaction Mechanism

rhodium center, cyclorhodation of **1a** initially occurs to form intermediate **A**. The rhodium center is then coordinated by allenoate **2a** to give Rh(III) cation intermediate **B**. Regioselective migratory insertion of the activated allenoate into the Rh−C(aryl) bond delivers a seven-membered rhodacycle intermediate **C**. Subsequent C−N bond formation and N−O bond cleavage of intermediate **C** affords intermediate **D** and regenerates the catalytically active Rh(III) species, accomplishing a catalytic cycle. Eventually, intermediate **D** undergoes 1,3-hydrogen shift[13,15] to accomplish aromatization, yielding the more stable product **3a**.

In summary, we have successfully realized rhodium(III)-catalyzed C−H annulation of acetophenone O-acetyl oximes with allenoates to efficiently access isoquinoline derivatives under redox-neutral conditions. The [4 + 2] annulation reaction proceeds with high regioselectivities, broad scopes, and avoids metal salts as the external oxidants. The present synthetic protocol provides a convenient and mild route to functionalized isoquinolines.

■ EXPERIMENTAL SECTION

General Considerations. The solvents were dried and distilled prior to use by the literature methods. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a 400 MHz spectrometer, and all chemical shift values refer to δ_{TMS} = 0.00 ppm or CDCl$_3$ (δ(^{1}H), 7.26 ppm and δ(^{13}C), 77.16 ppm). The HRMS analysis was obtained on a GC-TOF mass spectrometer. All the chemical reagents were purchased from commercial sources and used as received unless otherwise indicated. Known compounds **1a** and **1b**,[4b] **1c** and **1d**,[4f] **1e−i**,[4b] **1j**,[22] **1k** and **1m**,[23] **1n**,[24] **1o**,[4b] **1p**,[4f] **1q** and **1r**,[4b] **1t**,[4f] **2a**, **2d**, and **2f−m**,[25] **2n**,[26] and **2o**[25] were prepared by the literature procedures, and their spectroscopic features are in good agreement with those reported in the literatures.

General Procedure for the Synthesis of Acetophenone O-Acetyl Oximes (1). A mixture of the aryl ketone (5 mmol), NH$_2$OH·HCl (521 mg, 7.5 mmol) and pyridine (1.1 mL, 14 mmol) in 2 mL EtOH was stirred at 60 °C for 1 h. After cooling to ambient temperature, the reaction was quenched by water (10 mL). The resultant mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was washed with aqueous 1 N HCl (2 × 10 mL), dried over anhydrous MgSO$_4$, filtered, and evaporated all the volatiles under reduced pressure. The resultant residue was treated with Ac$_2$O (0.9 mL, 10 mmol) and a catalytic amount of 4-dimethylaminopyridine (1.2 mg, 0.01 mmol) in pyridine (2.5 mL) with stirring at ambient temperature for 1 h. The reaction was then quenched by water (10 mL) and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was washed with aqueous 1 N HCl (2 × 10 mL), dried over anhydrous MgSO$_4$, filtered, and evaporated all the volatiles under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/ether = 10:1, v/v) to afford **1**.

(E)-1-(2,5-Dimethoxyphenyl)ethanone O-acetyl oxime (1l). 0.87 g, 74% yield; white solid; mp 76−78 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.89 (m, 2 H), 6.82 (d, J = 8.7 Hz, 1 H), 3.75 (d, J = 5.7 Hz, 6 H), 2.30 (s, 3 H), 2.21 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 168.9, 164.7, 153.4, 151.7, 125.9, 116.4, 115.2, 112.4, 56.1, 55.9, 19.8, 17.7. HRMS (EI) calcd for C$_{12}$H$_{15}$NO$_4$ [M + H]$^+$: 238.1079, found 238.1079.

(E)-1-(Benzofuran-2-yl)ethanone O-acetyl oxime (1s). 0.81 g, 74% yield; white solid; mp 82−84 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.61 (d, J = 7.8 Hz, 1 H), 7.55 (d, J = 8.3 Hz, 1 H), 7.37 (t, J = 7.3 Hz, 1 H), 7.26 (m, 2 H), 2.41 (s, 3 H), 2.29 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 168.3, 155.7, 154.4, 150.0, 127.6, 126.9, 123.5, 121.9, 112.1, 109.9, 19.7, 13.4. HRMS (EI) calcd for C$_{12}$H$_{11}$NO$_3$ [M + H]$^+$: 218.0817, found 218.0819.

General Procedure for the Synthesis of Allenoates (2). A mixture of the corresponding basified yield (31 mmol) and CH$_3$I (5.7 g, 40 mmol) in 50 mL chloroform was stirred at reflux for 25 h. After being cooled to ambient temperature, all the volatiles in the mixture were evaporated under reduced pressure. 50 mL CH$_2$Cl$_2$ and Et$_3$N (6.3 g, 62 mmol) were then added with stirring, followed by slow addition of acetyl chloride (2.9 g, 37 mmol) at 0 °C over half an hour. The reaction mixture was allowed to warm up to ambient temperature and stirred overnight. After evaporating all the volatiles under reduced pressure, the resulting residue was dissolved in 100 mL petroleum ether (60−90 °C), stirred for 2 h, and filtered. All the volatiles in the filtrate were evaporated under reduced pressure, and the filtrate was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/ether = 20:1, v/v) to afford **2**.

Propyl 2-methylbuta-2,3-dienoate (2b). 2.4 g, 57% yield; colorless liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.04 (q, J = 3.2 Hz, 2 H), 4.08 (t, J = 6.7 Hz, 2 H), 1.85 (t, J = 3.2 Hz, 3 H), 1.65 (m, 2 H), 0.92 (t, J = 7.4 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 214.1, 167.7, 95.6, 77.8, 66.6, 22.1, 14.8, 10.4. HRMS (EI) calcd for C$_8$H$_{12}$O$_2$ [M + H]$^+$: 141.0916, found 141.0915.

Isopropyl 2-methylbuta-2,3-dienoate (2c). 2.8 g, 67% yield; colorless liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.00 (m, 3 H), 1.82 (t, J = 3.2 Hz, 3 H), 1.21 (d, J = 6.3 Hz, 6 H). ^{13}C{^{1}H} NMR (100

MHz, CDCl$_3$) δ 214.0, 167.1, 95.8, 77.7, 68.3, 21.8, 14.8. HRMS (EI) calcd for C$_8$H$_{12}$O$_2$ [M + H]$^+$: 141.0916, found 141.0913.

tert-Butyl 2-methylbuta-2,3-dienoate (*2e*). 1.6 g, 52% yield; colorless liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.99 (q, J = 3.2 Hz, 2 H), 1.82 (t, J = 3.2 Hz, 3 H), 1.46 (s, 9 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 214.0, 167.0, 96.9, 80.9, 77.4, 28.2, 14.8. HRMS (EI) calcd for C$_9$H$_{14}$O$_2$ [M + H]$^+$: 155.1072, found 155.1073.

Typical Procedure for the Synthesis of 3 and 4. *Synthesis of Ethyl 2-(1-Methylisoquinolin-3-yl)propanoate (3a).* A mixture of **1a** (53 mg, 0.3 mmol), allenoate **2a** (76 mg, 0.6 mmol), [Cp*RhCl$_2$]$_2$ (3.7 mg, 0.006 mmol), AgSbF$_6$ (10.3 mg, 0.03 mmol), and PivOH (6.1 mg, 0.06 mmol) in 3 mL 1,2-dichloroethane (DCE) was stirred at 60 °C for 24 h under a nitrogen atmosphere. After cooling to ambient temperature, all the volatiles in the mixture were evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/ ethyl acetate = 10:1, v/v) to afford **3a** as a colorless liquid (63 mg, 86%).

Ethyl 2-(1-methylisoquinolin-3-yl)propanoate (3a). 62 mg, 86% yield; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.05 (d, J = 8.3 Hz, 1), 7.74 (d, J = 8.2 Hz, 1 H), 7.61 (t, J = 7.1 Hz, 1 H), 7.52 (m, 1 H), 7.46 (s, 1 H), 4.17 (qd, J = 7.1, 2.3 Hz, 2 H), 4.04 (q, J = 7.2 Hz, 1 H), 2.92 (s, 3 H), 1.62 (d, J = 7.2 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.4, 158.5, 152.6, 136.6, 130.0, 127.3, 126.7, 126.5, 125.6, 116.2, 60.8, 47.8, 22.4, 17.8, 14.2. HRMS (EI) calcd for C$_{15}$H$_{17}$NO$_2$ [M + H]$^+$: 244.1338, found 244.1337.

Ethyl 2-(6-methoxy-1-methylisoquinolin-3-yl)propanoate (3b). 75 mg, 92% yield; pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, J = 9.2 Hz, 1 H), 7.45 (s, 1 H), 7.18 (dd, J = 9.2, 2.5 Hz, 1 H), 7.03 (d, J = 2.4 Hz, 1 H), 4.16 (m, 3 H), 3.91 (s, 3 H), 1.60 (d, J = 7.2 Hz, 3 H), 1.19 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.4, 160.6, 157.8, 153.2, 138.7, 127.4, 122.1, 119.4, 115.6, 104.9, 60.8, 55.4, 47.8, 22.2, 17.8, 14.2. HRMS (EI) calcd for C$_{16}$H$_{19}$NO$_3$ [M + H]$^+$: 274.1443, found 274.1443.

Ethyl 2-(5-methoxy-1-methylisoquinolin-3-yl)propanoate (3c). 43 mg, 52% yield; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86 (s, 1 H), 7.61 (d, J = 8.5 Hz, 1 H), 7.42 (t, J = 8.1 Hz, 1 H), 6.94 (d, J = 7.7 Hz, 1 H), 4.17 (m, 2 H), 4.05 (q, J = 7.2 Hz, 1 H), 3.97 (s, 3 H), 2.91 (s, 3 H), 1.62 (d, J = 7.2 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.4, 157.8, 154.9, 152.3, 129.2, 127.2, 126.6, 117.4, 110.6, 107.3, 60.7, 55.6, 48.0, 22.7, 17.8, 14.2. HRMS (EI) calcd for C$_{16}$H$_{19}$NO$_3$ [M + H]$^+$: 274.1443, found 274.1442.

Ethyl 2-(7-methoxy-1-methylisoquinolin-3-yl)propanoate (3c'). 28 mg, 35% yield; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (d, J = 8.9 Hz, 1 H), 7.40 (s, 1 H), 7.28 (m, 2 H), 4.16 (m, J = 7.1, 3.0 Hz, 2 H), 4.00 (q, J = 7.2 Hz, 1 H), 3.93 (s, 3 H), 2.88 (s, 3 H), 1.60 (d, J = 7.2 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.6, 158.1, 156.7, 150.7, 132.2, 128.9, 127.5, 122.7, 116.0, 103.6, 60.8, 55.5, 47.6, 22.5, 17.9, 14.3. HRMS (EI) calcd for C$_{16}$H$_{19}$NO$_3$ [M + H]$^+$: 274.1443, found 274.1446.

Ethyl 2-(8-methoxy-1-methylisoquinolin-3-yl)propanoate (3d). 35 mg, 43% yield; pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (t, J = 8.0 Hz, 1 H), 7.36 (s, 1 H), 7.29 (d, J = 8.1 Hz, 1 H), 6.83 (d, J = 7.8 Hz, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 3.99 (m, 4 H), 3.07 (s, 3 H), 1.60 (d, J = 7.2 Hz, 3 H), 1.22 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.4, 158.4, 158.2, 152.7, 139.6, 130.3, 119.6, 119.4, 115.8, 106.0, 60.8, 55.5, 47.7, 28.8, 17.7, 14.3. HRMS (EI) calcd for C$_{16}$H$_{19}$NO$_3$ [M + H]$^+$: 274.1443, found 274.1441.

Ethyl 2-(1,6-dimethylisoquinolin-3-yl)propanoate (3e). 68 mg, 88% yield; pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94 (d, J = 8.6 Hz, 1 H), 7.51 (s, 1 H), 7.35 (m, 2 H), 4.17 (m, 2 H), 4.02 (q, J = 7.2 Hz, 1 H), 2.89 (s, 3 H), 2.50 (s, 3 H), 1.61 (d, J = 7.2 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.4, 158.1, 152.6, 140.2, 137.0, 128.9, 126.2, 125.4, 124.9, 115.8, 60.8, 47.8), 22.3, 21.9, 17.8, 14.2. HRMS (EI) calcd for C$_{16}$H$_{19}$NO$_2$ [M + H]$^+$: 258.1494, found 258.1490.

Ethyl 2-(6-ethyl-1-methylisoquinolin-3-yl)propanoate (3f). 73 mg, 90% yield; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97

(d, J = 8.6 Hz, 1 H), 7.53 (s, 1 H,), 7.38 (m, 2 H), 4.17 (m, 2 H), 4.02 (q, J = 7.2 Hz, 1 H), 2.89 (s, 3 H), 2.80 (q, J = 7.6 Hz, 2 H), 1.61 (d, J = 7.2 Hz, 3 H), 1.30 (t, J = 7.6 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.4, 158.0, 152.6, 146.3, 137.0, 127.9, 125.5, 125.1, 124.9, 115.9, 60.7, 47.8, 29.1, 22.3, 17.8, 15.2, 14.2. HRMS (EI) calcd for C$_{17}$H$_{21}$NO$_2$ [M + H]$^+$: 272.1651, found 272.1648.

Ethyl 2-(6-fluoro-1-methylisoquinolin-3-yl)propanoate (3g). 48 mg, 62% yield; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.08 (dd, J = 9.2, 5.5 Hz, 1 H), 7.41 (s, 1 H), 7.35 (dd, J = 9.4, 2.5 Hz, 1 H), 7.28 (td, J = 8.8, 2.9 Hz, 1 H), 4.18 (m, 2 H), 4.01 (q, J = 7.2 Hz, 1 H), 2.91 (s, 3 H), 1.60 (d, J = 7.2 Hz, 3 H), 1.22 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.2, 163.15 (d, J = 251.8 Hz), 158.4 (d, J = 0.9 Hz), 153.8, 138.4 (d, J = 10.3 Hz), 128.7 (d, J = 9.6 Hz), 123.7, 117.0 (d, J = 25.1 Hz), 116.0 (d, J = 5.0 Hz), 110.5 (d, J = 20.5 Hz), 60.9, 47.8, 22.5, 17.7, 14.3. HRMS (EI) calcd for C$_{15}$H$_{16}$FNO$_2$ [M + H]$^+$: 262.1243, found 262.1245.

Ethyl 2-(6-chloro-1-methylisoquinolin-3-yl)propanoate (3h). 53 mg, 64% yield; pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (d, J = 8.9 Hz, 1 H), 7.69 (d, J = 2.1 Hz, 1 H), 7.41 (dd, J = 8.9, 2.1 Hz, 1 H), 7.35 (s, 1 H), 4.16 (m, 2 H), 4.00 (q, J = 7.2 Hz, 1 H), 2.87 (s, 3 H), 1.59 (d, J = 7.2 Hz, 3 H), 1.20 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.1, 158.6, 153.9, 137.6, 136.2, 127.7, 127.4, 126.0, 124.7, 115.5, 60.9, 47.8, 22.4, 17.7, 14.3. HRMS (EI) calcd for C$_{15}$H$_{16}$ClNO$_2$ [M + H]$^+$: 278.0948, found 278.0950.

Ethyl 2-(6-bromo-1-methylisoquinolin-3-yl)propanoate (3i). 61 mg, 64% yield; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91 (dd, J = 5.3, 3.4 Hz, 2 H), 7.59 (dd, J = 9.0, 1.8 Hz, 1 H), 7.36 (s, 1 H), 4.17 (m, 2 H), 4.02 (q, J = 7.2 Hz, 1 H), 2.90 (s, 3 H), 1.60 (d, J = 7.2 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.1, 158.7, 153.9, 137.9, 130.3, 129.4, 127.4, 125.0, 124.8, 115.4, 61.0, 47.9, 22.4, 17.7, 14.3. HRMS (EI) calcd for C$_{15}$H$_{16}$BrNO$_2$ [M + H]$^+$: 322.0443, found 322.0443.

Methyl 3-(1-ethoxy-1-oxopropan-2-yl)-1-methylisoquinoline-6-carboxylate (3j). 46 mg, 51% yield; white solid; mp 70−72 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.49 (s, 1 H), 8.10 (m, 2 H), 7.54 (s, 1 H), 4.17 (q, J = 7.0 Hz, 2 H), 4.03 (m, 4 H), 2.94 (s, 3 H), 1.62 (d, J = 7.2 Hz, 3 H), 1.22 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.1, 166.6, 158.7, 153.6, 136.0, 131.2, 130.1, 128.0, 126.2, 126.0, 117.2, 60.9, 52.6, 47.8, 22.5, 17.7, 14.3. HRMS (EI) calcd for C$_{17}$H$_{19}$NO$_4$ [M + H]$^+$: 302.1392, found 302.1394.

Ethyl 2-(1,6,7-trimethylisoquinolin-3-yl)propanoate (3k). 68 mg, 84% yield; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.78 (s, 1 H), 7.49 (s, 1 H), 7.34 (s, 1 H), 4.17 (m, 2 H), 4.01 (q, J = 7.2 Hz, 1 H), 2.88 (s, 3 H), 2.43 (s, 3 H), 2.41 (s, 3 H), 1.60 (d, J = 7.2 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.5, 157.3, 151.8, 140.2, 136.5, 135.6, 126.7, 125.8, 125.0, 115.3, 60.7, 47.8), 22.3, 20.5, 20.4, 17.8, 14.2. HRMS (EI) calcd for C$_{17}$H$_{21}$NO$_2$ [M + H]$^+$: 272.1651, found 272.1654.

Ethyl 2-(5,8-dimethoxy-1-methylisoquinolin-3-yl)propanoate (3l). 63 mg, 69% yield; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (s, 1 H), 6.81 (d, J = 8.5 Hz, 1 H), 6.69 (d, J = 8.5 Hz, 1 H), 4.16 (q, J = 7.1 Hz, 2 H), 4.02 (q, J = 7.2 Hz, 1 H), 3.89 (d, J = 13.7 Hz, 6 H), 3.06 (s, 3 H), 1.60 (d, J = 7.2 Hz, 3 H), 1.20 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.4, 157.8, 152.6, 151.8, 148.4, 131.3, 119.6, 109.9, 107.4, 105.1, 60.7, 55.8, 55.7, 47.9, 28.6, 17.6, 14.2. HRMS (EI) calcd for C$_{17}$H$_{21}$NO$_4$ [M + H]$^+$: 304.1549, found 304.1549.

Ethyl 2-(1-methylbenzo[g]isoquinolin-3-yl)propanoate (3m). 70 mg, 80% yield; pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.62 (s, 1 H), 8.25 (s, 1 H), 8.02 (d, J = 8.3 Hz, 1 H), 7.94 (d, J = 8.4 Hz, 1 H), 7.49 (m, 3 H), 4.22 (q, J = 7.1 Hz, 2 H), 4.08 (q, J = 7.1 Hz, 1 H), 3.05 (s, 3 H), 1.68 (d, J = 7.2 Hz, 3 H), 1.25 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.5, 160.1, 150.3, 134.0, 132.9, 131.9, 129.1, 127.8, 127.3, 125.8, 125.5, 125.3, 125.0, 115.5, 60.8, 47.7, 22.8, 17.6, 14.3. HRMS (EI) calcd for C$_{19}$H$_{19}$NO$_2$ [M + H]$^+$: 294.1494, found 294.1494.

Ethyl 2-(1-methyl-10H-indeno[1,2-g]isoquinolin-3-yl)-propanoate (3n). 79 mg, 80% yield; pale yellow solid; mp 104−106 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.08 (s, 1 H), 7.99 (s, 1 H),

7.87 (m, 1 H), 7.53 (d, J = 8.4 Hz, 2 H), 7.39 (m, 2 H), 4.22 (m, 2 H), 4.08 (q, J = 7.2 Hz, 1 H), 3.99 (s, 2 H), 2.93 (s, 3 H), 1.67 (d, J = 7.2 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.5, 157.9, 152.0, 144.3, 144.1, 142.0, 140.2, 136.3, 128.5, 127.2, 125.8, 125.4, 121.2, 121.0, 116.8, 116.5, 60.8, 47.7, 36.6, 22.6, 17.8, 14.3. HRMS (EI) calcd for C$_{22}$H$_{21}$NO$_2$ [M + H]$^+$: 332.1651, found 332.1652.

Ethyl 2-(1-ethylisoquinolin-3-yl)propanoate (3o). 60 mg, 78% yield; colorless liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.11 (d, J = 8.3 Hz, 1 H), 7.76 (d, J = 8.2 Hz, 1 H), 7.61 (m, 1 H), 7.52 (m, 1 H), 7.45 (s, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 4.05 (q, J = 7.2 Hz, 1 H), 3.30 (q, J = 7.5 Hz, 2 H), 1.63 (d, J = 7.2 Hz, 3 H), 1.41 (t, J = 7.6 Hz, 3 H), 1.22 (t, J = 7.1 Hz, 3 H).^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.4, 162.9, 152.7, 137.0, 129.8, 127.5, 126.6, 125.6, 125.2, 116.1, 60.7, 47.8, 28.4, 17.7, 14.3, 13.7. HRMS (EI) calcd for C$_{16}$H$_{19}$NO$_2$ [M + H]$^+$: 258.1494, found 258.1496.

Ethyl 2-(1-phenylisoquinolin-3-yl)propanoate (3p). 62 mg, 68% yield; colorless liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.07 (d, J = 8.5 Hz, 1 H), 7.85 (d, J = 8.2 Hz, 1 H), 7.68 (m, 4 H), 7.52 (m, 4 H), 4.21 (m, 3 H), 1.69 (d, J = 7.2 Hz, 3 H), 1.25 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.4, 160.3, 153.0, 139.6, 137.7, 130.2, 130.1, 128.6, 128.4, 127.6, 127.1, 126.9, 125.7, 117.0, 60.9, 47.9, 18.0, 14.3. HRMS (EI) calcd for C$_{20}$H$_{19}$NO$_2$ [M + H]$^+$: 306.1494, found 306.1495.

Ethyl 2-(8,9-dihydro-7H-benzo[de]quinolin-2-yl)propanoate (3q). 67 mg, 83% yield; pale yellow solid; mp 64−66 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 (m, 2 H), 7.42 (s, 1 H), 7.25 (d, J = 6.7 Hz, 1 H), 4.18 (m, 2 H), 4.03 (q, J = 7.2 Hz, 1 H), 3.22 (m, 2 H), 3.07 (t, J = 6.1 Hz, 2 H), 2.16 (m, 2 H), 1.61 (d, J = 7.2 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.4, 160.1, 152.6, 138.7, 136.8, 130.0, 124.6, 124.4, 124.2, 115.8, 60.8, 47.9, 34.4, 30.5, 23.3, 17.8, 14.2. HRMS (EI) calcd for C$_{17}$H$_{19}$NO$_2$ [M + H]$^+$: 270.1494, found 270.1496.

Ethyl 2-(4-methylthieno[3,4-c]pyridin-6-yl)propanoate (3r). 59 mg, 79% yield; pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (s, 1 H), 7.39 (s, 2 H), 4.15 (m, 2 H), 4.01 (q, J = 7.2 Hz, 1 H), 2.80 (s, 3 H), 1.58 (d, J = 7.2 Hz, 3 H), 1.20 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.2, 153.6, 153.0, 148.0, 133.5, 126.3, 122.0, 112.7, 60.9, 48.0, 22.8, 18.0, 14.2. HRMS (EI) calcd for C$_{13}$H$_{15}$NO$_2$S [M + H]$^+$: 250.0902, found 250.0903.

Propyl 2-(6-methoxy-1-methylisoquinolin-3-yl)propanoate (4a). 80 mg, 93% yield; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94 (d, J = 9.2 Hz, 1 H), 7.36 (s, 1 H), 7.14 (dd, J = 9.2, 2.5 Hz, 1 H), 7.00 (d, J = 2.5 Hz, 1 H), 4.07 (m, 2 H), 4.01 (q, J = 7.2 Hz, 1 H), 3.90 (s, 3 H), 2.86 (s, 3 H), 1.60 (m, 5 H), 0.84 (t, J = 7.4 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.5, 160.6, 157.7, 153.3, 138.7, 127.4, 122.1, 119.4, 115.7, 104.9, 66.4, 55.5, 47.8, 22.2, 22.0, 17.8, 10.3. HRMS (EI) calcd for C$_{17}$H$_{21}$NO$_3$ [M + H]$^+$: 288.1600, found 288.1598.

Isopropyl 2-(6-methoxy-1-methylisoquinolin-3-yl)propanoate (4b). 77 mg, 90% yield; pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (d, J = 9.2 Hz, 1 H), 7.36 (s, 1 H), 7.14 (dd, J = 9.2, 2.6 Hz, 1 H), 7.01 (d, J = 2.5 Hz, 1 H), 5.06 (hept, J = 6.3 Hz, 1 H), 3.96 (q, J = 7.2 Hz, 1 H), 3.91 (s, 3 H), 2.86 (s, 3 H), 1.58 (d, J = 7.2 Hz, 3 H), 1.23 (d, J = 6.3 Hz) and 1.16 (d, J = 6.2 Hz) (3:3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.0, 160.6, 157.7, 153.5, 138.7, 127.4, 122.1, 119.4, 115.6, 104.9, 68.0, 55.5, 47.9, 22.3, 21.9, 21.7, 17.9. HRMS (EI) calcd for C$_{17}$H$_{21}$NO$_3$ [M + H]$^+$: 288.1600, found 288.1599.

Benzyl 2-(6-methoxy-1-methylisoquinolin-3-yl)propanoate (4c). 91 mg, 91% yield; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.96 (d, J = 9.2 Hz, 1 H), 7.29 (m, 6 H), 7.16 (dd, J = 9.1, 2.4 Hz, 1 H), 6.96 (d, J = 2.4 Hz, 1 H), 5.19 (m, 2 H), 4.09 (q, J = 7.2 Hz, 1 H), 3.91 (s, 3 H), 2.87 (s, 3 H), 1.64 (d, J = 7.2 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.2, 160.6, 157.8, 153.0, 138.7, 136.3, 128.4, 128.0, 128.0, 127.4, 122.1, 119.4, 115.8, 104.9, 66.6, 55.5, 47.8, 22.3, 17.7. HRMS (EI) calcd for C$_{21}$H$_{21}$NO$_3$ [M + H]$^+$: 336.1600, found 336.1599.

tert-Butyl 2-(6-methoxy-1-methylisoquinolin-3-yl)propanoate (4d). 73 mg, 81% yield; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$)

δ 7.94 (d, J = 9.2 Hz,1 H), 7.35 (s, 1 H), 7.12 (dd, J = 9.2, 2.5 Hz, 1 H), 7.00 (d, J = 2.5 Hz, 1 H), 3.90 (m, 4 H), 2.85 (s, 3 H), 1.54 (d, J = 7.2 Hz, 3 H), 1.42 (s, 9 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 173.8, 160.5, 157.5, 153.8, 138.7, 127.4, 122.0, 119.3, 115.4, 104.8, 80.5, 55.4, 48.6, 28.1, 22.2, 17.9. HRMS (EI) calcd for C$_{18}$H$_{23}$NO$_3$ [M + H]$^+$: 302.1756, found 302.1759.

Ethyl 2-(6-methoxy-1-methylisoquinolin-3-yl)butanoate (4e). 67 mg, 78% yield; pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94 (d, J = 9.2 Hz, 1 H), 7.40 (s, 1 H), 7.13 (dd, J = 9.2, 2.5 Hz, 1 H), 7.01 (d, J = 2.4 Hz, 1 H), 4.16 (m, 2 H), 3.89 (s, 3 H), 3.78 (m, 1 H), 2.86 (s, 3 H), 2.15 and 2.00 (m each, 1:1 H), 1.21 (t, J = 7.1 Hz, 3 H), 0.95 (t, J = 7.4 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 173.9, 160.6, 157.7, 152.0, 138.6, 127.4, 122.2, 119.4, 116.2, 104.8, 60.7, 55.5, 55.4, 26.2, 22.3, 14.3, 12.3. HRMS (EI) calcd for C$_{17}$H$_{21}$NO$_3$ [M + H]$^+$: 288.1600, found 288.1601.

Ethyl 2-(6-methoxy-1-methylisoquinolin-3-yl)hexanoate (4f). 75 mg, 79% yield; yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94 (d, J = 9.2 Hz, 1 H), 7.41 (s, 1 H), 7.13 (dd, J = 9.2, 2.5 Hz, 1 H), 7.01 (d, J = 2.5 Hz, 1 H), 4.15 (m, 2 H), 3.90 (s, 3 H), 3.85 (dd, J = 8.2, 7.1 Hz, 1 H), 2.86 (s, 3 H), 2.13 and 1.96 (m each, 1:1 H), 1.32 (m, 4 H), 1.21 (t, J = 7.1 Hz, 3 H), 0.87 (t, J = 7.0 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.0, 160.6, 157.7, 152.2, 138.6, 127.4, 122.2, 119.4, 116.1, 104.8, 60.7, 55.4, 53.9, 32.7, 30.0, 22.7, 22.3, 14.3, 14.0. HRMS (EI) calcd for C$_{19}$H$_{25}$NO$_3$ [M + H]$^+$: 316.1913, found 316.1911.

Ethyl 2-(6-methoxy-1-methylisoquinolin-3-yl)octanoate (4g). 66 mg, 64% yield; pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (d, J = 9.2 Hz, 1 H), 7.41 (s, 1 H), 7.14 (dd, J = 9.2, 2.4 Hz, 1 H), 7.01 (d, J = 2.4 Hz, 1 H), 4.16 (m, 2 H), 3.91 (s, 3 H), 3.86 (m, 1 H), 2.86 (s, 3 H), 2.12 and 1.95 (m each, 1:1 H), 1.27 (m, 11 H), 0.85 (t, J = 6.8 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.1, 160.6, 157.7, 152.2, 138.7, 127.4, 122.2, 119.4, 116.2, 104.9, 60.7, 55.5, 53.9, 33.0, 31.7, 29.2, 27.7, 22.7, 22.3, 14.3, 14.2. HRMS (EI) calcd for C$_{21}$H$_{29}$NO$_3$ [M + H]$^+$: 344.2226, found 344.2224.

Ethyl 2-(6-methoxy-1-methylisoquinolin-3-yl)-5-methylhexanoate (4h). 57 mg, 57% yield; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (d, J = 9.2 Hz, 1 H), 7.41 (s, 1 H), 7.14 (dd, J = 9.2, 2.5 Hz, 1 H), 7.02 (d, J = 2.5 Hz, 1 H), 4.16 (m, 2 H), 3.91 (s, 3 H), 3.82 (dd, J = 8.3, 6.9 Hz, 1 H), 2.87 (s, 3 H), 2.13, 1.96 (m each, 1:1 H), 1.57 (m, 1 H), 1.22 (m, 5 H), 0.87 (dd, J = 6.6, 5.2 Hz, 6 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 174.1, 160.6, 157.7, 152.2, 138.7, 127.4, 122.2, 119.4, 116.2, 104.9, 60.7, 55.5, 54.2, 36.9, 31.0, 28.1, 22.6, 22.3, 14.3. HRMS (EI) calcd for C$_{20}$H$_{27}$NO$_3$ [M + H]$^+$: 330.2069, found 330.2067.

Ethyl 2-(6-methoxy-1-methylisoquinolin-3-yl)-3-phenylpropanoate (4i). 90 mg, 86% yield; pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, J = 9.2 Hz, 1 H), 7.39 (s, 1 H), 7.23 (m, 4 H), 7.17 (m, 2 H), 7.00 (d, J = 2.5 Hz, 1 H), 4.21 (m, 1 H), 4.10 (m, 2 H), 3.91 (s, 3 H), 3.47 (dd, J = 13.8, 8.9 Hz) and 3.34 (dd, J = 13.8, 6.6 Hz) (1:1 H), 2.90 (s, 3 H), 1.12 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 173.1, 160.6, 157.9, 151.2, 139.5, 138.6, 129.1, 128.3, 127.4, 126.3, 122.2, 119.5, 116.7, 104.9, 60.8, 55.5, 55.4, 38.7, 22.3, 14.1. HRMS (EI) calcd for C$_{22}$H$_{23}$NO$_3$ [M + H]$^+$: 350.1756, found 350.1754.

Diethyl 2-(6-methoxy-1-methylisoquinolin-3-yl)succinate (4j). 81 mg, 78% yield; yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 (d, J = 9.2 Hz, 1 H), 7.35 (s, 1 H), 7.13 (dd, J = 9.2, 2.5 Hz, 1 H), 6.98 (d, J = 2.5 Hz, 1 H), 4.34 (dd, J = 9.4, 5.6 Hz, 1 H), 4.16 (m, 4 H), 3.89 (s, 3 H), 3.26 and 2.92 (m each, 1:1 H), 2.83 (s, 3 H), 1.20 (td, J = 7.1, 4.7 Hz, 6 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 172.6, 171.9, 160.7, 158.1, 150.3, 138.5, 127.3, 122.2, 119.6, 116.8, 104.8, 61.1, 60.6, 55.4, 49.4, 36.8, 22.2, 14.2, 14.1. HRMS (EI) calcd for C$_{19}$H$_{23}$NO$_5$ [M + H]$^+$: 346.1654, found 346.1655.

Ethyl 4-ethyl-6-methoxy-1-methylisoquinoline-3-carboxylate (4k). 41 mg, 50% yield; pale yellow solid; mp 77−79 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.03 (d, J = 9.1 Hz, 1 H), 7.30 (d, J = 2.4 Hz, 1 H), 7.25 (dd, J = 9.1, 2.4 Hz, 1 H), 4.48 (q, J = 7.1 Hz, 2 H), 3.95 (s, 3 H), 3.12 (q, J = 7.5 Hz, 2 H), 2.88 (s, 3 H), 1.43 (t, J = 7.1 Hz, 3 H), 1.35 (t, J = 7.5 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 168.2, 160.9, 156.2, 141.8, 136.9, 131.3, 128.2, 123.7, 119.8, 103.1,

61.7, 55.5, 22.5, 21.8, 15.0, 14.4. HRMS (EI) calcd for $C_{16}H_{19}NO_3$ [M + H]$^+$: 274.1443, found 274.1444.

Ethyl 2-(6-methoxy-1,4-dimethylisoquinolin-3-yl)acetate (4k′). 35 mg, 43% yield; yellow solid; mp 83−85 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98 (dd, J = 8.5, 1.0 Hz, 1 H), 7.16 (m, 2 H), 4.17 (q, J = 7.1 Hz, 2 H), 4.02 (s, 2 H), 3.94 (s, 3 H), 2.84 (s, 3 H), 2.49 (s, 3 H), 1.25 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 171.3, 160.6, 155.3, 144.8, 138.1, 128.0, 123.1, 122.1, 118.4, 102.1, 60.9, 55.4, 42.3, 22.1, 14.3, 14.3. HRMS (EI) calcd for $C_{16}H_{19}NO_3$ [M + H]$^+$: 274.1443, found 274.1442.

Ethyl 6-methoxy-1-methyl-4-phenethylisoquinoline-3-carboxylate (4l). 88 mg, 84% yield; pale yellow solid; mp 90−92 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.03 (d, J = 9.1 Hz, 1 H), 7.26 (m, 7 H), 4.47 (q, J = 7.1 Hz, 2 H), 3.91 (s, 3 H), 3.41 and 3.01 (m each, 2:2 H), 2.90 (s, 3 H), 1.43 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 167.9, 161.0, 156.4, 141.9, 137.1, 129.4, 128.6, 128.4, 128.2, 126.2, 123.7, 120.0, 103.0, 61.7, 55.4, 36.8, 30.6, 22.5, 14.4. HRMS (EI) calcd for $C_{22}H_{23}NO_3$ [M + H]$^+$: 350.1756, found 350.1757.

Ethyl 2-(4-benzyl-6-methoxy-1-methylisoquinolin-3-yl)acetate (4l′). 15 mg, 14% yield; yellow solid; mp 76−78 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, J = 9.1 Hz, 1 H), 7.17 (m, 8 H), 4.38 (s, 2 H), 4.11 (q, J = 7.1 Hz, 2 H), 4.00 (s, 2 H), 3.75 (s, 3 H), 2.90 (s, 3 H), 1.21 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 171.4, 160.7, 156.6, 146.3, 139.6, 138.1, 128.7, 128.2, 128.0, 126.3, 125.1, 122.6, 118.6, 103.0, 61.0, 55.4, 42.2, 34.1, 22.4, 14.3. HRMS (EI) calcd for $C_{22}H_{23}NO_3$ [M + H]$^+$: 350.1756, found 350.1758.

Benzyl 2-(6-methoxy-1-methylisoquinolin-3-yl)acetate (4m). 42 mg, 44% yield; pale yellow solid; mp 68−70 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, J = 9.2 Hz, 1 H), 7.32 (m, 6 H), 7.17 (dd, J = 9.2, 2.5 Hz, 1 H), 6.98 (d, J = 2.5 Hz, 1 H), 5.20 (s, 2 H), 3.97 (s, 2 H), 3.92 (s, 3 H), 2.88 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 171.2, 160.8, 158.0, 147.1, 138.7, 136.1, 128.6, 128.3, 128.2, 127.5, 122.1, 119.6, 118.1, 104.8, 66.7, 55.5, 43.7, 22.3. HRMS (EI) calcd for $C_{20}H_{19}NO_3$ [M + H]$^+$: 322.1443, found 322.1440.

6-Methoxy-1-methyl-3-(1-phenylethyl)isoquinoline (4n). 39 mg, 47% yield; white solid; mp 104−106 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (d, J = 9.1 Hz, 1 H), 7.40 (d, J = 7.4 Hz, 2 H), 7.33 (t, J = 7.6 Hz, 2 H), 7.23 (dd, J = 14.1, 6.8 Hz, 1 H), 7.13 (m, 2 H), 6.94 (d, J = 2.5 Hz, 1 H), 4.42 (q, J = 7.2 Hz, 1 H), 3.89 (s, 3 H), 2.90 (s, 3 H), 1.78 (d, J = 7.2 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 160.5, 158.5, 157.5, 145.5, 138.7, 128.4, 128.1, 127.4, 126.2, 121.8, 119.0, 115.5, 104.8, 55.4, 47.2, 22.5, 21.4. HRMS (EI) calcd for $C_{19}H_{19}NO$ [M + H]$^+$: 278.1545, found 278.1544.

Gram-Scale Preparation of the Target Products. *Synthesis of Ethyl 2-(6-methoxy-1-methylisoquinolin-3-yl)propanoate (3b).* A mixture of **1b** (0.83 g, 4 mmol), allenoate **2a** (1.01 g, 8 mmol), [Cp*RhCl$_2$]$_2$ (49 mg, 0.08 mmol), AgSbF$_6$ (137 mg, 0.4 mmol), and PivOH (81 mg, 0.8 mmol) in 3 mL 1,2-dichloroethane (DCE) was stirred at 60 °C for 24 h under a nitrogen atmosphere. After cooling to ambient temperature, all the volatiles in the mixture were evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/ethyl acetate = 20:1, v/v) to afford **3b** as a pale yellow oil (1.00 g, 92%).

Typical Procedure for the Synthesis of 5. *Synthesis of 2-(1-Methylisoquinolin-3-yl)propan-1-ol (5a).* A mixture of **3a** (73 mg, 0.3 mmol) and LiAlH$_4$ (23 mg, 0.6 mmol) in 2 mL THF was stirred at 25 °C for 30 min under an argon atmosphere. The resulting mixture was poured into ice water (25 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic phase was dried over anhydrous Na$_2$SO$_4$, filtered, and all the volatiles were evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/ethyl acetate = 1:1, v/v) to afford **5a** as a colorless liquid (37 mg, 62%).

2-(1-Methylisoquinolin-3-yl)propan-1-ol (5a). 37 mg, 62% yield; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.06 (d, J = 8.4 Hz, 1 H), 7.74 (d, J = 8.2 Hz, 1 H), 7.64 (m, 1 H), 7.53 (ddd, J = 8.1, 6.9, 1.1 Hz, 1 H), 7.35 (s, 1 H), 3.99 (dd, J = 10.6, 3.6 Hz) and 3.86 (dd, J = 10.6, 6.7 Hz) (1:1 H), 3.16 (m, 1 H), 2.92 (s, 3 H), 1.41 (d, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 157.9, 157.1, 136.8, 130.3, 127.1, 126.6, 126.2, 125.7, 116.0, 68.0, 41.3, 22.5, 17.1. HRMS (EI) calcd for $C_{13}H_{15}NO$ [M + H]$^+$: 202.1232, found 202.1230.

2-(6-Methoxy-1-methylisoquinolin-3-yl)propan-1-ol (5b). 44 mg, 64% yield; white solid; mp 110−112 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (d, J = 9.1 Hz, 1 H), 7.26 (s, 1 H), 7.15 (m, 1 H), 7.00 (d, J = 2.1 Hz, 1 H), 3.97 (m) and 3.83 (dd, J = 10.5, 6.7 Hz) (4:1 H), 3.12 (m, 1 H), 2.86 (s, 3 H), 1.39 (d, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 160.9, 157.8, 157.1, 138.9, 127.5, 121.8, 119.3, 115.4, 104.7, 68.1, 55.5, 41.1, 22.4, 17.1. HRMS (EI) calcd for $C_{14}H_{17}NO_2$ [M + H]$^+$: 232.1338, found 232.1335.

H/D Exchange in Acetophene *O*-Acetyl Oxime (1a). A mixture of **1a** (35 mg, 0.2 mmol), [Cp*RhCl$_2$]$_2$ (2.5 mg, 0.004 mmol), AgSbF$_6$ (6.9 mg, 0.02 mmol), and PivOD (41 mg, 0.4 mmol) in 2 mL 1,2-dichloroethane (DCE) was stirred at 60 °C for 4 h under a nitrogen atmosphere. After cooling to ambient temperature, all the volatiles in the mixture were evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/ethyl acetate = 20:1, v/v). The H/D exchange was determined by ^{1}H NMR analysis.

Kinetic Isotope Effect (KIE) Experiments. The reactions with **1a** or its deuterated form **1a**-d_5 were carried out in a parallel manner under the standard conditions as follows. A mixture of **1a** (35 mg, 0.2 mmol) or **1a**-d_5 (36 mg, 0.2 mmol), **2a** (50 mg, 0.4 mmol), [Cp*RhCl$_2$]$_2$ (2.5 mg, 0.004 mmol), AgSbF$_6$ (6.9 mg, 0.02 mmol), and PivOH (4.1 mg, 0.04 mmol) in 2 mL 1,2-dichloroethane (DCE) was stirred at 60 °C under a nitrogen atmosphere. The reaction was then quenched by water (5 mL), and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried over anhydrous MgSO$_4$, filtered, and all the volatiles were evaporated under reduced pressure, and the resultant residue was subjected to proton NMR analysis with 1,3,5-trimethyloxylbenzene as the internal standard. The k_H/k_D value was calculated according to the yields of **3a** from the reactions at 5, 10, and 15 min.

■ ASSOCIATED CONTENT

ⓢ Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b03092.

> Experimental procedures for the starting materials **1** and **2**, NMR spectra of the substrates and products, and X-ray crystallographic analysis for compound **3j** (PDF)
> Crystal data for compound **3j** (CIF)

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■ REFERENCES

(1) (a) Chrzanowska, M.; Grajewska, A.; Rozwadowska, M. D. Asymmetric Synthesis of Isoquinoline Alkaloids: 2004−2015. *Chem.*

Rev. **2016**, *116*, 12369−12465. (b) Gurram, M.; Gyimóthy, B.; Wang, R. F.; Lam, S. Q.; Ahmed, F.; Herr, R. J. Concise Enantiospecific, Stereoselective Syntheses of (+)-Crispine A and Its (−)-Antipode. *J. Org. Chem.* **2011**, *76*, 1605−1613. (c) Jiang, J.-K.; Thomas, C. J.; Neumann, S.; Lu, X.; Rice, K. C.; Gershengorn, M. C. 1-(Phenyl)isoquinoline Carboxamides: A Novel Class of Subtype Selective Inhibitors of Thyrotropin- Releasing Hormone (TRH) Receptors. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 733−736. (d) Feldman, K. S.; Cutarelli, T. D. Alkynyliodonium Salts in Organic Synthesis. Application to the Total Synthesis of the Tropoloisoquinoline Alkaloid Pareitropone. *J. Am. Chem. Soc.* **2002**, *124*, 11600−11601.

(2) (a) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild Metal-Catalyzed C−H Activation: Examples and Concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900−2936. (b) Ackermann, L. Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C−H/Het−H Bond Functionalizations. *Acc. Chem. Res.* **2014**, *47*, 281−295. (c) He, R. Y.; Huang, Z. T.; Zheng, Q. Y.; Wang, C. Y. Isoquinoline Skeleton Synthesis *via* Chelation-Assisted C−H Activation. *Tetrahedron Lett.* **2014**, *55*, 5705−5713.

(3) (a) Huang, H. W.; Ji, X. C.; Wu, W. Q.; Jiang, H. F. Transition Metal-Catalyzed C−H Functionalization of *N*-Oxyenamine Internal Oxidants. *Chem. Soc. Rev.* **2015**, *44*, 1155−1171. (b) Song, G. Y.; Wang, F.; Li, X. W. C−C, C−O and C−N Bond Formation *via* Rhodium(III)-Catalyzed Oxidative C−H Activation. *Chem. Soc. Rev.* **2012**, *41*, 3651−3678.

(4) (a) Feng, R. K.; Ning, H. Q.; Su, H.; Gao, Y.; Yin, H. T.; Wang, Y. D.; Yang, Z.; Qi, C. Z. Selective Synthesis of Alkynylated Isoquinolines and Biisoquinolines *via* Rh^{III} Catalyzed C−H Activation/1,3-Diyne Strategy. *J. Org. Chem.* **2017**, *82*, 10408−10417. (b) Wang, H.; Koeller, J.; Liu, W. P.; Ackermann, L. Cobalt(III)-Catalyzed C−H/N−O Functionalizations: Isohypsic Access to Isoquinolines. *Chem. - Eur. J.* **2015**, *21*, 15525−15528. (c) Hyster, T. K.; Rovis, T. Pyridine Synthesis from Oximes and Alkynes via Rhodium(III) Catalysis: Cp* and Cp^t Provide Complementary Selectivity. *Chem. Commun.* **2011**, *47*, 11846−11848. (d) Zhang, X. P.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A. Q.; Li, X. W. Synthesis of Isoquinolines *via* Rhodium(III)-Catalyzed Dehydrative C−C and C−N Coupling between Oximines and Alkynes. *Adv. Synth. Catal.* **2011**, *353*, 719−723. (e) Too, P. C.; Chua, S. H.; Wong, S. H.; Chiba, S. Synthesis of Azaheterocycles from Aryl Ketone *O*-Acetyl Oximes and Internal Alkynes by Cu−Rh Bimetallic Relay Catalysts. *J. Org. Chem.* **2011**, *76*, 6159−6168. (f) Too, P. C.; Wang, Y. F.; Chiba, S. Rhodium(III)-Catalyzed Synthesis of Isoquinolines from Aryl Ketone *O*-Acyloxime Derivatives and Internal Alkynes. *Org. Lett.* **2010**, *12*, 5688−5691.

(5) (a) Sun, B.; Yoshino, T.; Kanai, M.; Matsunag, S. Cp*CoIII Catalyzed Site-Selective C−H Activation of Unsymmetrical *O*-Acyl Oximes: Synthesis of Multisubstituted Isoquinolines from Terminal and Internal Alkynes. *Angew. Chem., Int. Ed.* **2015**, *54*, 12968−12972. (b) Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. Ruthenium-Catalyzed Highly Regioselective Cyclization of Ketoximes with Alkynes by C−H Bond Activation: A Practical Route to Synthesize Substituted Isoquinolines. *Org. Lett.* **2012**, *14*, 3032−3035.

(6) (a) Chu, H. K.; Sun, S.; Yu, J.-T.; Cheng, J. Rh-Catalyzed Sequential Oxidative C−H Activation/Annulation with Geminal-Substituted Vinyl Acetates to Access Isoquinolines. *Chem. Commun.* **2015**, *51*, 13327−13329. (b) Zhao, D. B.; Lied, F.; Glorius, F. Rh(III)-Catalyzed C−H Functionalization/Aromatization Cascade with 1,3-Dienes: A Redox-Neutral and Regioselective Access to Isoquinolines. *Chem. Sci.* **2014**, *5*, 2869−2873.

(7) Shi, Z. Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. Rh(III)-Catalyzed Synthesis of Multisubstituted Isoquinoline and Pyridine *N*-Oxides from Oximes and Diazo Compounds. *J. Am. Chem. Soc.* **2013**, *135*, 12204−12207.

(8) (a) Ye, J. T.; Ma, S. M. Palladium-Catalyzed Cyclization Reactions of Allenes in the Presence of Unsaturated Carbon−Carbon Bonds. *Acc. Chem. Res.* **2014**, *47*, 989−1000. (b) Yu, S. C.; Ma, S. M. Allenes in Catalytic Asymmetric Synthesis and Natural Product Syntheses. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074−3112. (c) Ma, S. M.

Electrophilic Addition and Cyclization Reactions of Allenes. *Acc. Chem. Res.* **2009**, *42*, 1679−1688.

(9) Koschker, P.; Breit, B. Branching Out: Rhodium-Catalyzed Allylation with Alkynes and Allenes. *Acc. Chem. Res.* **2016**, *49*, 1524−1536.

(10) (a) Nakanowatari, S.; Ackermann, L. Ruthenium(II)-Catalyzed C−H Functionalizations with Allenes: Versatile Allenylations and Allylations. *Chem. - Eur. J.* **2015**, *21*, 16246−16251. (b) Zeng, R.; Wu, S. Z.; Fu, C. L.; Ma, S. M. Room-Temperature Synthesis of Trisubstituted Allenylsilanes *via* Regioselective C−H Functionalization. *J. Am. Chem. Soc.* **2013**, *135*, 18284−18287.

(11) (a) Lei, C.; Peng, L. J.; Ding, K. Manganese-Catalyzed C−H Annulation of Ketimines with Allenes: Stereoselective Synthesis of 1-Aminoindanes. *Adv. Synth. Catal.* **2018**, *360*, 2952−2958. (b) Tran, D. N.; Cramer, N. Rhodium-Catalyzed Dynamic Kinetic Asymmetric Transformations of Racemic Allenes by the [3 + 2] Annulation of Aryl Ketimines. *Angew. Chem., Int. Ed.* **2013**, *52*, 10630−10634. (c) Tran, D. N.; Cramer, N. *syn*-Selective Rhodium(I)-Catalyzed Allylations of Ketimines Proceeding through a Directed C−H Activation/Allene Addition Sequence. *Angew. Chem., Int. Ed.* **2010**, *49*, 8181−8184. (d) Chen, S.-Y.; Li, Q. J.; Liu, X.-G.; Wu, J. Q.; Zhang, S.-S.; Wang, H. G. Polycyclization Enabled by Relay Catalysis: One-Pot Manganese-Catalyzed C−H Allylation and Silver-Catalyzed Povarov Reaction. *ChemSusChem* **2017**, *10*, 2360−2364.

(12) (a) Chen, S.-Y.; Han, X.-L.; Wu, J.-Q.; Li, Q. J.; Chen, Y. Y.; Wang, H. G. Manganese(I)-Catalyzed Regio- and Stereoselective 1,2-Diheteroarylation of Allenes: Combination of C−H Activation and Smiles Rearrangement. *Angew. Chem., Int. Ed.* **2017**, *56*, 9939−9943. (b) Wang, C. M.; Wang, A.; Rueping, M. Manganese-Catalyzed C−H Functionalizations: Hydroarylations and Alkenylations Involving an Unexpected Heteroaryl Shift. *Angew. Chem., Int. Ed.* **2017**, *56*, 9935−9938.

(13) (a) Lan, T. L.; Wang, L. G.; Rao, Y. Regioselective Annulation of Aryl Sulfonamides with Allenes through Cobalt-Promoted C−H Functionalization. *Org. Lett.* **2017**, *19*, 972−975. (b) Li, T. L.; Zhang, C.; Tan, Y. H.; Pan, W. D.; Rao, Y. Cobalt-Catalyzed C−H Activation and Regioselective Intermolecular Annulation with Allenes. *Org. Chem. Front.* **2017**, *4*, 204−209.

(14) Mo, J. Y.; Müller, T.; Oliveira, J. C. A.; Ackermann, L. 1,4-Iron Migration for Expedient Allene Annulationsthrough Iron-Catalyzed C−H/N−H/C−O/C−H Functionalizations. *Angew. Chem., Int. Ed.* **2018**, *57*, 7719−7723.

(15) (a) Thrimurtulu, N.; Nallagonda, R.; Volla, C. M. R. Cobalt-Catalyzed Aryl C−H Activation and Highly Regioselective Intermolecular Annulation of Sulfonamides with Allenes. *Chem. Commun.* **2017**, *53*, 1872−1875. (b) Thrimurtulu, N.; Dey, A.; Maiti, D.; Volla, C. M. R. Cobalt-Catalyzed sp^2-C−H Activation: Intermolecular Heterocyclization with Allenes at Room Temperature. *Angew. Chem., Int. Ed.* **2016**, *55*, 12361−12365.

(16) Wang, H. G.; Glorius, F. Mild Rhodium(III)-Catalyzed C−H Activation and Intermolecular Annulation with Allenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 7318−7322.

(17) Boobalan, R.; Kuppusamy, R.; Santhoshkumar, R.; Gandeepan, P.; Cheng, C.-H. Access to Isoquinolin-1(2*H*)-ones and Pyridones by Cobalt-Catalyzed Oxidative Annulation of Amides with Allenes. *ChemCatChem* **2017**, *9*, 273−277.

(18) (a) Wu, S. Z.; Zeng, R.; Fu, C. L.; Yu, Y. H.; Zhang, X.; Ma, S. M. Rhodium-Catalyzed C−H Functionalization-Based Approach to Eight-Membered Lactams. *Chem. Sci.* **2015**, *6*, 2275−2285. (b) Zeng, R.; Fu, C. L.; Ma, S. M. Highly Selective Mild Stepwise Allylation of *N*−Methoxybenzamides with Allenes. *J. Am. Chem. Soc.* **2012**, *134*, 9597−9560.

(19) (a) Zhai, S. X.; Qiu, S. X.; Chen, X. M.; Tao, C.; Li, Y.; Cheng, B.; Wang, H. F.; Zhai, H. B. Trifunctionalization of Allenes *via* Cobalt-Catalyzed MHP-Assisted C−H Bond Functionalization and Molecular Oxygen Activation. *ACS Catal.* **2018**, *8*, 6645−6649. (b) Ji, C.; Xu, Q.; Shi, M. Rhodium(III)-Catalyzed Controllable C−H Bond Functionalization of Benzamides and Vinylidenecyclopropanes: A Directing Group Determined Reaction Pathway. *Adv. Synth. Catal.*

2017, *359*, 974−983. (c) Xia, X.-F.; Wang, Y.-Q.; Zhang, L.-L.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. Palladium-Catalyzed C−H Activation and Intermolecular Annulation with Allenes. *Chem. - Eur. J.* **2014**, *20*, 5087−5091.

(20) Kuppusamy, R.; Santhoshkumar, R.; Boobalan, R.; Wu, H.-R.; Cheng, C.-H. Synthesis of 1,2-Dihydroquinolines by Co(III)-Catalyzed [3 + 3] Annulation of Anilides with Benzylallenes. *ACS Catal.* **2018**, *8*, 1880−1883.

(21) (a) Jiang, Q. B.; Guo, T. L.; Wu, K. K.; Yu, Z. K. Rhodium(III)-Catalyzed sp^2 C−H Bond Addition to CF$_3$-Substituted Unsaturated Ketones. *Chem. Commun.* **2016**, *52*, 2913−2915. (b) Yang, X. G.; Liu, Z. Q.; Sun, C. L.; Chen, J. P.; Yu, Z. K. Palladium-Catalyzed Oxidative Cross-Coupling of α-Cyanoketene Dithioacetals with Olefins. *Chem. - Eur. J.* **2015**, *21*, 14085−14094. (c) Yu, H. F.; Jin, W. W.; Sun, C. L.; Chen, J. P.; Du, W. M.; He, S. B.; Yu, Z. K. Palladium-Catalyzed Cross-Coupling of Internal Alkenes with Terminal Alkenes to Functionalized 1,3-Butadienes Using C−H Bond Activation: Efficient Synthesis of Bicyclic Pyridones. *Angew. Chem., Int. Ed.* **2010**, *49*, 5792−5797. (d) Luo, N.; Yu, Z. K. RuCl$_3$·xH$_2$O-Catalyzed Direct Arylation of Arenes with Aryl Chlorides in the Presence of Triphenylphosphine. *Chem. - Eur. J.* **2010**, *16*, 787−791. (e) Jin, W. W.; Yu, Z. K.; He, W.; Ye, W. J.; Xiao, W.-J. Efficient Rh(I)-Catalyzed Direct Arylation and Alkenylation of Arene C−H Bonds *via* Decarbonylation of Benzoic and Cinnamic Anhydrides. *Org. Lett.* **2009**, *11*, 1317−1320. (f) Zhao, X. D.; Yu, Z. K. Rhodium-Catalyzed Regioselective C−H Functionalization *via* Decarbonylation of Acid Chlorides and C−H Bond Activation under Phosphine-Free Conditions. *J. Am. Chem. Soc.* **2008**, *130*, 8136−8137.

(22) Yang, H.-B.; Selander, N. A. Redox-Economical Synthesis of Trifluoromethylated Enamides with the Langlois Reagent. *Org. Biomol. Chem.* **2017**, *15*, 1771−1775.

(23) Zhu, Z. Z.; Tang, X. D.; Li, J. X.; Li, X. W.; Wu, W. Q.; Deng, G. H.; Jiang, H. F. Iron-Catalyzed Synthesis of 2*H*-Imidazoles from Oxime Acetates and Vinyl Azides under Redox-Neutral Conditions. *Org. Lett.* **2017**, *19*, 1370−1373.

(24) Yang, X. F.; Liu, S.; Yu, S. J.; Kong, L. H.; Yu, L.; Li, X. W. Redox-Neutral Access to Isoquinolinones *via* Rhodium(III)-Catalyzed Annulations of O-Pivaloyl Oximes with Ketenes. *Org. Lett.* **2018**, *20*, 2698−2701.

(25) Wang, G.; Liu, X. H.; Chen, Y. S.; Yang, J.; Li, J.; Lin, L. L.; Feng, X. M. Diastereoselective and Enantioselective Alleno-aldol Reaction of Allenoates with Isatins to Synthesis of Carbinol Allenoates Catalyzed by Gold. *ACS Catal.* **2016**, *6*, 2482−2486.

(26) Liu, J. W.; Nie, M.; Zhou, Q. H.; Gao, S.; Jiang, W. H.; Chung, L. W.; Tang, W. J.; Ding, K. L. Enantioselective Palladium-Catalyzed Diboration of 1,1-Disubstituted Allenes. *Chem. Sci.* **2017**, *8*, 5161−5165.