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

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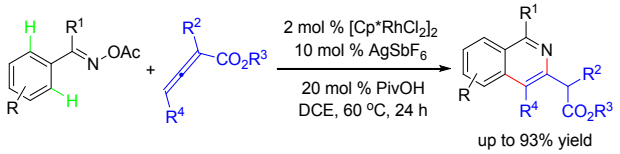
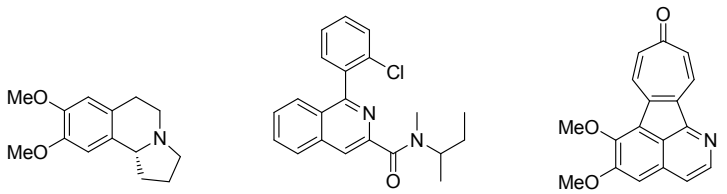


ABSTRACT: Rhodium(III)-catalyzed annulation of acetophenone *O*-acetyl oximes with allenoates was achieved, affording isoquinolines in good to excellent yields with high regioselectivities under redox-neutral conditions. Allenoates acted as the C2 synthons in the annulation reaction. The present synthetic 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 cyctotoxic activity, PK 11195[1c] can be used as an inhibitor of [^{3}H]MeTRH, and Pareitropone[1d] is the most potent anticancer agent among the relatively small family of tropoloiso-quinoline alkaloids (Scheme 1). Considerable efforts 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

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



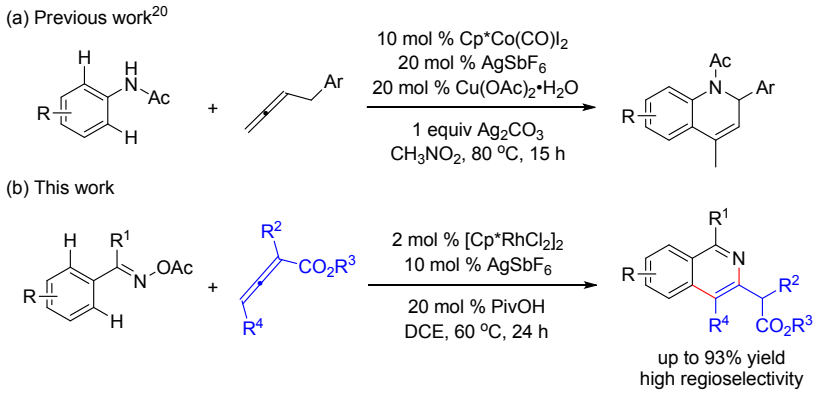
(*R*)-(+)-Crispine A[1b] PK 11195[1c] Pareitropone[1d]

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

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



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

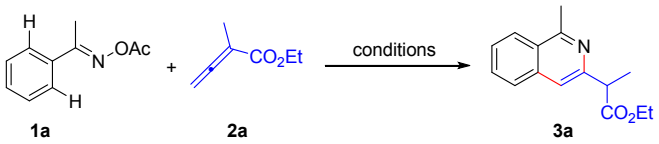
Mn/Ag catalyzed C–H activation of ketimines with allenes for the synthesis of polycyclic products.[11d] Pyrimidine-directed, Mn-catalyzed 1,2-diheteroarylation of allenes formed bicyclic and tricyclic heterocycles.[12] Transition-metal-catalyzed C–H annulation of arylamides with allenes have been well 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) salt Ag_2CO_3 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 % $RhCl_3 \cdot 3H_2O$/8 mol % $AgSbF_6$ 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 % $[Cp^*RhCl_2]_2$/8 mol % $AgSbF_6$ led to

Table 1. Optimiation of Reaction Conditions[a]



1a 2a 3a

entry	[Ag] (mol %)	PivOH (mol %)	Temp (°C)	yield[b] (%)
1[c]	$AgSbF_6$ (8)	20	60	0
2	$AgSbF_6$ (8)	20	60	66
3	$AgPF_6$ (8)	20	60	40
4	$AgBF_4$ (8)	20	60	51
5	$AgSbF_6$ (9)	20	60	87
6	$AgSbF_6$ (10)	20	60	91
7	$AgSbF_6$ (11)	20	60	90
8	$AgSbF_6$ (10)	30	60	90
9	$AgSbF_6$ (10)	10	60	88
10[d]	$AgSbF_6$ (10)	20	60	92 (86)[e]
11	$AgSbF_6$ (10)	20	50	83
12	$AgSbF_6$ (10)	20	70	92
13[f]	$AgSbF_6$ (10)	20	60	0
14		20	60	0
15	$AgSbF_6$ (10)		60	86

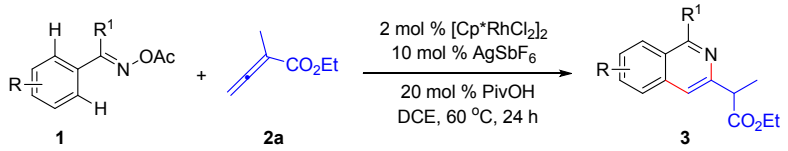
[a] Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[Cp^*RhCl_2]_2$ (2 mol %), DCE (2 mL), 0.1 MPa N_2, 60 °C, 24 h. [b] Determined by ^1H NMR analysis with 1,3,5-trimethyloxylbenzene as the internal standard. [c] $RhCl_3 \cdot 3H_2O$ (2 mol %) [d] **1a** (0.3 mmol), **2a** (0.6 mmol), DCE (3 mL). [e] Isolated yield given in parentheses. [f] Without $[Cp^*RhCl_2]_2$。

isoquinoline derivative **3a** in 66% yield by ^{1}H NMR determination (Table 1, entry 2). Both silver salts $AgPF_6$ and $AgBF_4$ were less effective than $AgSbF_6$ (Table 1, entries 3 and 4). Use of 10 mol % $AgSbF_6$ 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 ^{o}C diminished the yield to 83%, and elevating the temperature to 70 ^{o}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 $[Cp^*RhCl_2]_2$ or $AgSbF_6$ (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 % $Cp^*Co(CO)I_2$ as the catalyst, but the reaction did not occur.

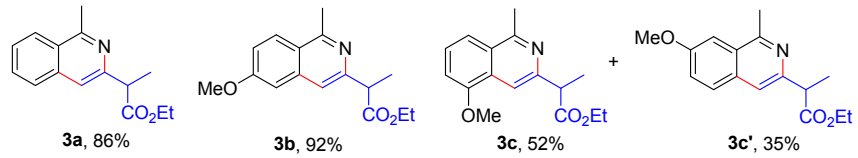
Under the optimized conditions, the scope of *O*-acetyl oximes **1** was investigated (Table 2). The substituted acetophenone *O*-acetyl oximes also efficiently reacted with **2a** to form the target products of type **3**. The *para*-methoxy substituent on the aryl ring of acetophenone *O*-acetyl oxime **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 ^{o}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

Table 2. Scope of *O*-Acetyl Oximes 1[a]



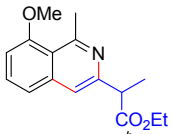
1 **2a** **3**

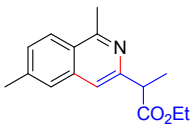

3a, 86%

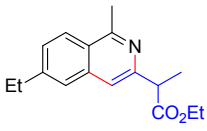
3b, 92%

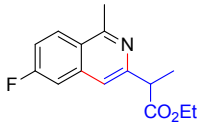
3c, 52%

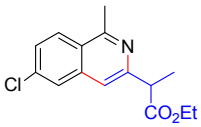
3c', 35%

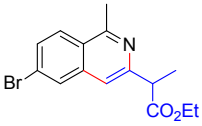

3d, 43%[b]

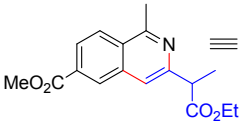

3e, 88%

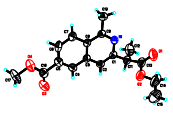

3f, 90%

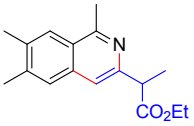

3g, 62%[c]

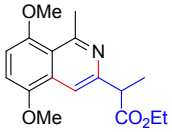

3h, 64%[c]

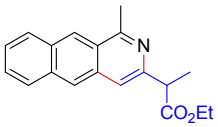

3i, 64%[c]

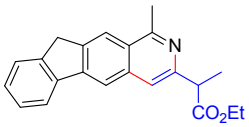

3j, 51%[c]

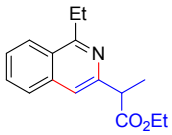

X-ray structure of **3j**

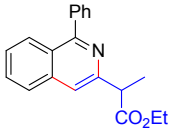

3k, 84%

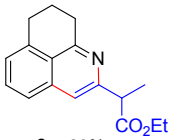

3l, 69%

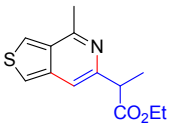

3m, 80%

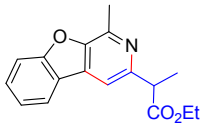

3n, 80%

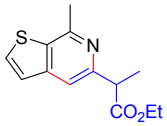

3o, 78%


3p, 68%


3q, 83%


3r, 79%


3s, 0%

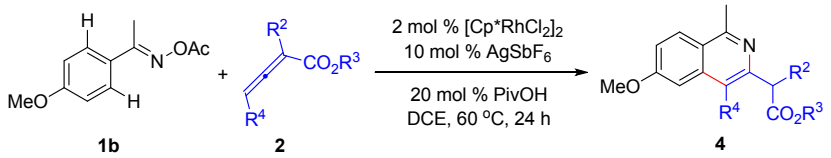

3t, 0%

[a] Conditions: **1** (0.3 mmol), **2a** (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] 80 °C. [c] $[Cp^*RhCl_2]_2$ (0.012 mmol), $AgSbF_6$ (0.06 mmol).

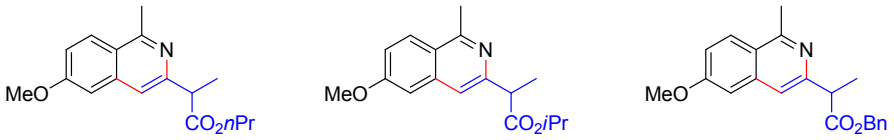
electron-withdrawing groups such as F and CO_2Me remarkably reduced the product yields of **3g** (62%) and **3j** (51%), respectively. The negative impact from the *ortho*-substituent was also observed that 2,5-dimethoxy-acetophenone *O*-acetyl oxime (**1l**) reacted with **2a** to give **3l** (69%), while its 3,4-dimethyl-substituted analog **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 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*-NO_2, *p*-CN, and *p*-CF_3-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-1H-indol-3-yl)ethanone *O*-acetyl oximes could not react with **2a** under the same conditions either.

Table 3. Scope of Allenoates 2[a]

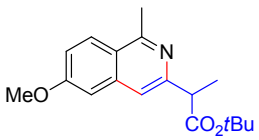


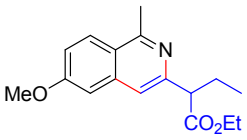
1b **2** **4**

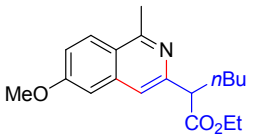

4a, 93%

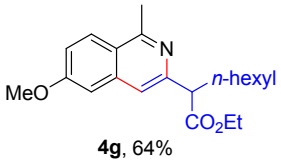
4b, 90%

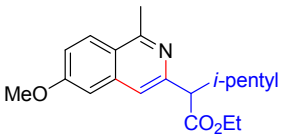
4c, 91%

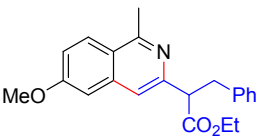

4d, 81%

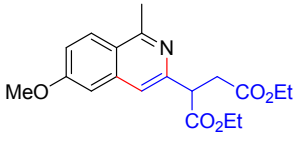

4e, 78%

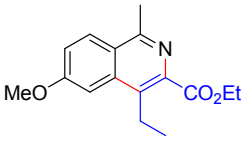

4f, 79%

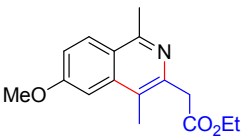

4g, 64%

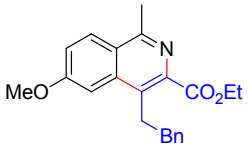

4h, 57%

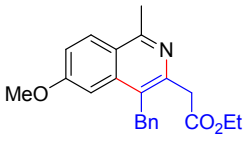

4i, 86%

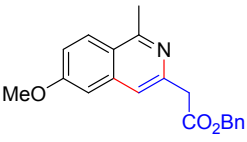

4j, 78%

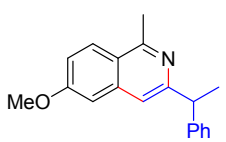

4k, 50%

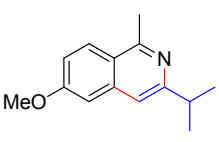

4k', 43%

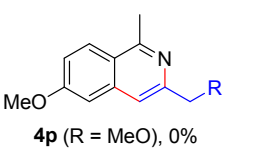

4l, 84%


4l', 14%


4m, 44%[b]


4n, 47%[b]

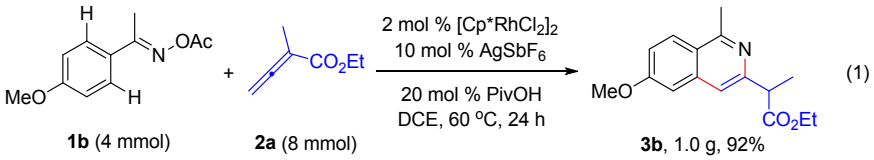

4o, 0%

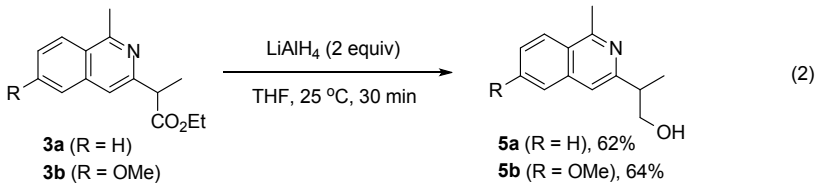

4p (R = MeO), 0%
4q (R = cyclohexyl), 0%

[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).

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-d** efficiently underwent to afford the corresponding isoquinoline products **4a-d** (81-93%), respectively, 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, implicating that a terminal ester group is also a crucial functionality in the allene-type substatrates **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-p** under the stated conditions.

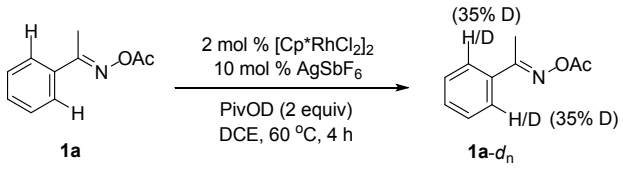




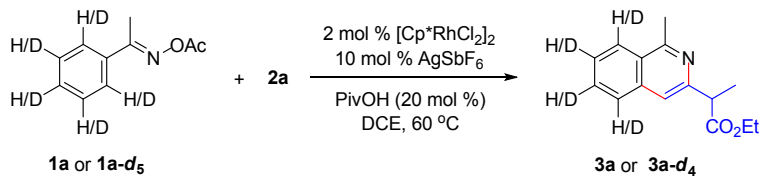
To demonstrate the utility of the synthetic protocol, a gram-scale reaction of oxime **1b** and allenoate **2a** was performed, affording the target product **3b** in 92% yield (eq 1). Chemoselective reduction of isoquinolines **3a** and **3b** was readily conducted to give the corresponding alcohols **5a** (62%) and **5b** (64%), respectively (eq 2).

Scheme 3. Mechanism Studies.

(a) H/D exchange



(b) KIE studies

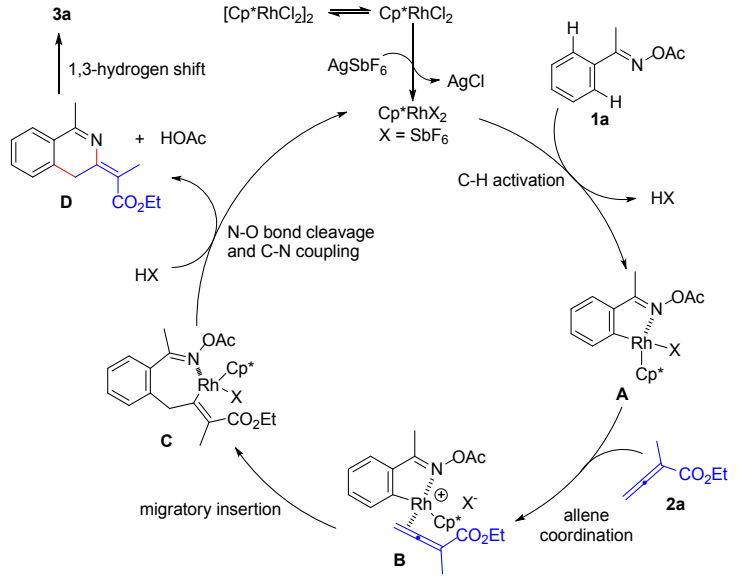


time (min)	5	10	15	
yield of **3a**	26.7%	32.1%	36.1%	k_H/k_D = 3.2
yield of **3a-*d*$_4$**	8.5%	9.9%	11.3%	

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 (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.

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

Scheme 4. Proposed Reaction Mechanism



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 accompolish 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 $CDCl_3$ ($\delta(^{1}H)$, 7.26 ppm and $\delta(^{13}C)$, 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), $NH_2OH·HCl$ (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 cooled 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_2O (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; m.p. 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; m.p. 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 ylied (31 mmol) and CH_3I (5.7 g, 40 mmol) in 50 mL chloroform was stirred at reflux for 25 h. After cooled to ambient temperature, the mixture was evaporated all the volatiles under reduced pressure. 50 mL CH_2Cl_2 and Et_3N (6.3 g, 62 mmol) were then added with stirring, and 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 evaporated 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. The filtrate was evaporated all the volatiles under reduced pressure and 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; colourless 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 $C_8H_{12}O_2$ $[M+H]^+$: 141.0916; Found: 141.0915.

*Isopropyl 2-methylbuta-2,3-dienoate (**2c**)***:*** 2.8 g, 67% yield; colourless 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). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 214.0, 167.1, 95.8, 77.7, 68.3, 21.8, 14.8. HRMS (EI) calcd for $C_8H_{12}O_2$ $[M+H]^+$: 141.0916; Found: 141.0913.

*tert-Butyl 2-methylbuta-2,3-dienoate (**2e**)***:*** 1.6 g, 52% yield; colourless 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). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 214.0, 167.0, 96.9, 80.9, 77.4, 28.2, 14.8. HRMS (EI) calcd for $C_9H_{14}O_2$ $[M+H]^+$: 155.1072; Found: 155.1073.

A 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 cooled to ambient temperature, the mixture was evaporated all the volatiles 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; colourless 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). $^{13}C\{^1H\}$ 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. ^1H 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), 2.94 (s, 3 H), 1.60 (d, J = 7.2 Hz, 3 H), 1.19 (t, J = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ 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; colourless oil. ^1H 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). $^{13}C\{^1H\}$ 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; colourless oil. ^1H 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). $^{13}C\{^1H\}$ 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; colourless 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;

colourless 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; colourless 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; m.p. 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; colourless 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; colourless 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; m.p. 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; colourless 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; colourless 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; m.p. 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 $C_{13}H_{15}NO_2S$ $[M+H]^+$: 250.0902; Found: 250.0903.

*Propyl 2-(6-methoxy-1-methylisoquinolin-3-yl)propanoate (**4a**)***:*** 80 mg, 93% yield; colourless 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. ^1H 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). $^{13}C\{^1H\}$ 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; colourless oil. ^1H 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). $^{13}C\{^1H\}$ 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, 66.4, 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; colourless oil. ^1H 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). $^{13}C\{^1H\}$ 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. ^1H 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). $^{13}C\{^1H\}$ 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. ^1H 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). $^{13}C\{^1H\}$ 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. ^1H 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). $^{13}C\{^1H\}$ 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; colourless 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). $^{13}C\{^1H\}$ 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; m.p. 77-79 °C. ^1H 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). $^{13}C\{^1H\}$ 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; m.p. 83-85 °C. ^1H 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). $^{13}C\{^1H\}$ 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; m.p. 90-92 °C. ^1H 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). $^{13}C\{^1H\}$ 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; m.p. 76-78°C. ^1H 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). $^{13}C\{^1H\}$ 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; m.p. 68-70 °C. ^1H 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). $^{13}C\{^1H\}$ 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; m.p. 104-106 °C. ^1H 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). $^{13}C\{^1H\}$ 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 cooled to ambient temperature, the mixture was evaporated all the volatiles 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%).

A 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_2Cl_2 (3×10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated all the volatiles 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; colourless 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). $^{13}C\{^1H\}$ 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; m.p. 110-112 °C. ^1H 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). $^{13}C\{^1H\}$ 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 cooled to ambient temperature, the mixture was evaporated all the volatiles 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 ^1H 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 evaporated all the volatiles 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 min, 10 min, and 15 min.

ASSOCIATED CONTENT

Supporting Information Available

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jo-2018-03092p.

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

Crystal data for compound **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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