

Article

Rh-Catalyzed Cascade C-H Activation/Annulation of *N*-Hydroxybenzamides and Propargylic Acetates for Modular Access to Isoquinolones

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Abstract: A sequential Rh(III)-catalyzed C-H activation/annulation of *N*-hydroxybenzamides with propargylic acetates leading to the formation of NH-free isoquinolones is described. This reaction proceeds through a sequential C-H activation/alkyne insertion/intramolecular annulation/N-O bond cleavage procedure, affording a broad spectrum of products with diverse substituents in moderate-to-excellent yields. Notably, this protocol features the simultaneous formation of two new C-C/C-N bonds and one heterocycle in one pot with the release of water as the sole byproduct.

Keywords: C-H activation; isoquinolones; *N*-hydroxybenzamides; propargylic acetates



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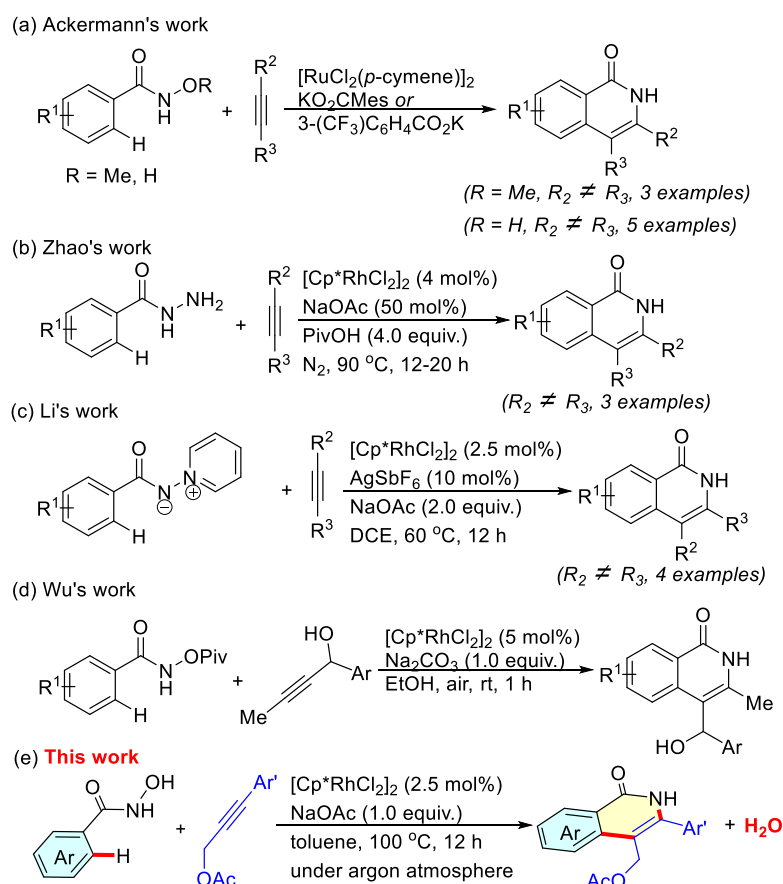
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1. Introduction

Isoquinolone is a ubiquitous, structural motif that presents in various natural products, conjugated materials, and pharmaceuticals with a wide range of biological activities [1–4]. Meanwhile, isoquinolone derivatives, as versatile intermediates, provide wide access to a large variety of chemical molecules and drug structures in various organic transformations [5–7]. In this regard, the formation of isoquinolone derivatives has gained significant attention among synthetic and medicinal chemists [8–14]. Traditional methods to access these valuable derivatives involve the Bischler-Napieralski and Pictet-Spengler reactions [15,16], but they often suffer from the need for pre-activated substrates and harsh reaction conditions, which restrict their regioselectivity. Consequently, the development of efficient and atom/step-economical synthetic methods to construct these structures has attracted considerable attention from synthetic chemists.

In the last few decades, transition-metal-catalyzed C-H activation/annulations have been recognized as a powerful and straightforward approach for the synthesis of *N*-heterocycles and, therefore, have attracted increasing attention [17–20]. Recently, the transition-metal-catalyzed oxidative cyclization of *N*-substituted benzamides with symmetrical alkynes or diazos via C-H bond activation has been an efficient method for constructing *N*-protected isoquinolone derivatives [21–28]. Meanwhile, many other substrates bearing the *N*-directing group have also been used to construct an isoquinolone scaffold through the C-H activation/annulation strategy [29–31]. Despite these achievements, directing access to NH-free isoquinolone scaffolds via cascade C-H activation/annulation has attracted our great interest [32]. Ackermann reported the preparations of isoquinolone derivatives by Ru-catalyzed C-H functionalization/annulation of *N*-methoxybenzamides or *N*-hydroxybenzamides with

alkynes in water in the presence of MesCO₂K or 3-(CF₃)C₆H₄CO₂K as the cocatalytic additive (Scheme 1a) [33,34]. Later, a Rh(III)-catalyzed synthesis of isoquinolones via C-H activation/annulation of benzoylhydrazines and alkynes was further developed (Scheme 1b) [35]. In addition, Li described a highly efficient synthesis pathway by the reaction of iminopyridinium ylides with alkynes for the formation of an isoquinolone skeleton (Scheme 1c) [36]. Very recently, Wu disclosed a robust and convenient rhodium-catalyzed regioselective C-H activation/[4 + 2] annulation using propargyl alcohols as two-carbon synthons to construct 3-methylisoquinolones (Scheme 1d) [37]. Among the limited successful procedures with unsymmetric alkynes serving as the coupling partners, it is desirable to explore a new pathway for furnishing greater structural diversity of NH-free isoquinolone derivatives. We herein describe a novel rhodium(III)-catalyzed cascade C-H activation/annulation of *N*-hydroxybenzamides and propargylic acetates to generate NH-free 3-aryisoquinolones, releasing H₂O as the sole byproduct (Scheme 1e).



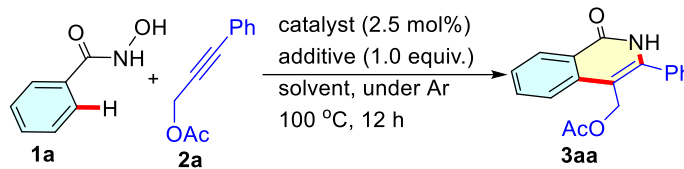
Scheme 1. Synthesis of NH-free isoquinolones via C-H activation/annulation strategy.

2. Results and Discussion

Our study commenced with the reaction between *N*-hydroxybenzamide (**1a**) and 3-phenylprop-2-yn-1-yl acetate (**2a**) in the presence of [Cp * RhCl₂]₂ as catalyst (Table 1, entry 5). For experimental condition screening, the catalyst precursor [Cp * RhCl₂]₂ was fixed at 2.5 mol%, and, with addition of chloride abstracting reagent NaOAc (1.0 equiv.), the [4 + 2] annulated product **3aa** was isolated in 84% yield after 12 h at 100 °C in toluene (Table 1, entry 5). The reaction was then performed in the presence of other transition metal catalysts, but none of them was as effective as [Cp * RhCl₂]₂ (Table 1, entries 1–4). Changing the catalyst loading failed to improve the reaction yield (Table 1, entries 6, 7). Investigation of the additive showed that NaOAc was the best choice (Table 1, entries 8–17). In addition, either decreasing or increasing the loading of additive did not improve this transformation (Table 1, entries 19, 20). Furthermore, several common organic solvents were investigated,

and the results indicated that toluene favored this transformation (Table 1, entries 21–26). There was no extra benefit to the product yield at elevated reaction temperature and reaction time (Table 1, entries 27–30). Finally, we chose the reaction conditions of entry 5 as the optimal conditions.

Table 1. Optimization of the reaction conditions ^a.

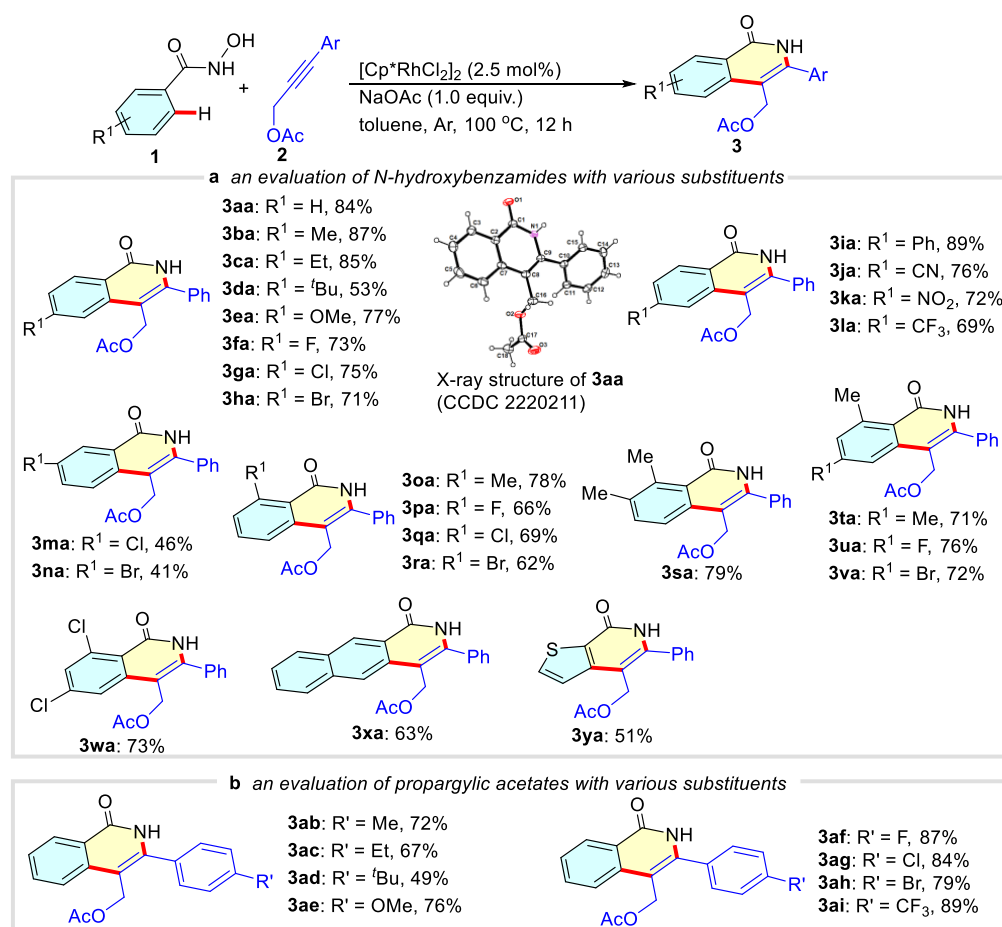
				
Entry	Catalyst	Additive	Solvent	Yield (%) ^b
1	Pd(PPh ₃) ₄	NaOAc	toluene	0
2	Pd(OAc) ₂	NaOAc	toluene	trace
3	[RuCl ₂ (<i>p</i> -cymene)] ₂	NaOAc	toluene	37
4	[Cp * RhCl ₂] ₂	NaOAc	toluene	65
5	[Cp * RhCl ₂] ₂	NaOAc	toluene	84
6 ^c	[Cp * RhCl ₂] ₂	NaOAc	toluene	46
7 ^d	[Cp * RhCl ₂] ₂	NaOAc	toluene	71
8	[Cp * RhCl ₂] ₂	CsOAc	toluene	52
9	[Cp * RhCl ₂] ₂	AgOAc	toluene	41
10	[Cp * RhCl ₂] ₂	NaHCO ₃	toluene	67
11	[Cp * RhCl ₂] ₂	Na ₂ CO ₃	toluene	63
12	[Cp * RhCl ₂] ₂	KHCO ₃	toluene	61
13	[Cp * RhCl ₂] ₂	K ₂ CO ₃	toluene	30
14	[Cp * RhCl ₂] ₂	Et ₃ N	toluene	64
15	[Cp * RhCl ₂] ₂	AgSbF ₆	toluene	29
16	[Cp * RhCl ₂] ₂	AgNTf ₂	toluene	17
17	[Cp * RhCl ₂] ₂	Cs ₂ CO ₃	MeOH	48
18	[Cp * RhCl ₂] ₂	-	toluene	0
19 ^e	[Cp * RhCl ₂] ₂	NaOAc	toluene	62
20 ^f	[Cp * RhCl ₂] ₂	NaOAc	toluene	80
21	[Cp * RhCl ₂] ₂	NaOAc	DCE	62
22	[Cp * RhCl ₂] ₂	NaOAc	MeCN	43
23	[Cp * RhCl ₂] ₂	NaOAc	DMF	54
24	[Cp * RhCl ₂] ₂	NaOAc	THF	67
25	[Cp * RhCl ₂] ₂	NaOAc	1,4-dioxane	59
26	[Cp * RhCl ₂] ₂	NaOAc	<i>o</i> -xylene	60
27 ^g	[Cp * RhCl ₂] ₂	NaOAc	toluene	61
28 ^h	[Cp * RhCl ₂] ₂	NaOAc	toluene	84
29 ⁱ	[Cp * RhCl ₂] ₂	NaOAc	toluene	50
30 ^j	[Cp * RhCl ₂] ₂	NaOAc	toluene	83

^a Reaction conditions: *N*-hydroxybenzamide **1a** (0.2 mmol), 3-phenylprop-2-yn-1-yl acetate **2a** (0.2 mmol), catalyst (2.5 mol%), and additive (0.2 mmol) in solvent at 100 °C for 12 h under argon atmosphere. ^b Isolated yields.

^c The amount of catalyst was 1 mol%. ^d The amount of catalyst was 5 mol%. ^e The amount of additive was 0.5 equivalent. ^f The amount of additive was 1.5 equivalent. ^g At 80 °C. ^h At reflux. ⁱ For 5 h. ^j For 15 h.

With the establishment of the optimum conditions, we first investigated the scope and generality of *N*-hydroxybenzamide substrates (Scheme 2a). It was found that a variety of substituted *N*-hydroxybenzamides reacted smoothly with 3-phenylprop-2-yn-1-yl acetate **2a** to produce the corresponding isoquinolones in 41–89% yields. In general, *N*-hydroxybenzamides with either electron-donating (e.g., -Me, -Et, -^{*t*}Bu, -OMe) or electron-withdrawing (e.g., -F, -Cl, -Br) groups at the *para* position of the benzene ring worked well with **2a** to afford the corresponding products **3ba–3ha** in 53–87% yields. Notably, various functional groups, including phenyl and even strong electron-withdrawing substituents -CN, -NO₂, and -CF₃, were tolerated well to supply the desired products **3ia–3la** in 69–89% yields. Furthermore, *meta*- and *ortho*-substituted substrates were also

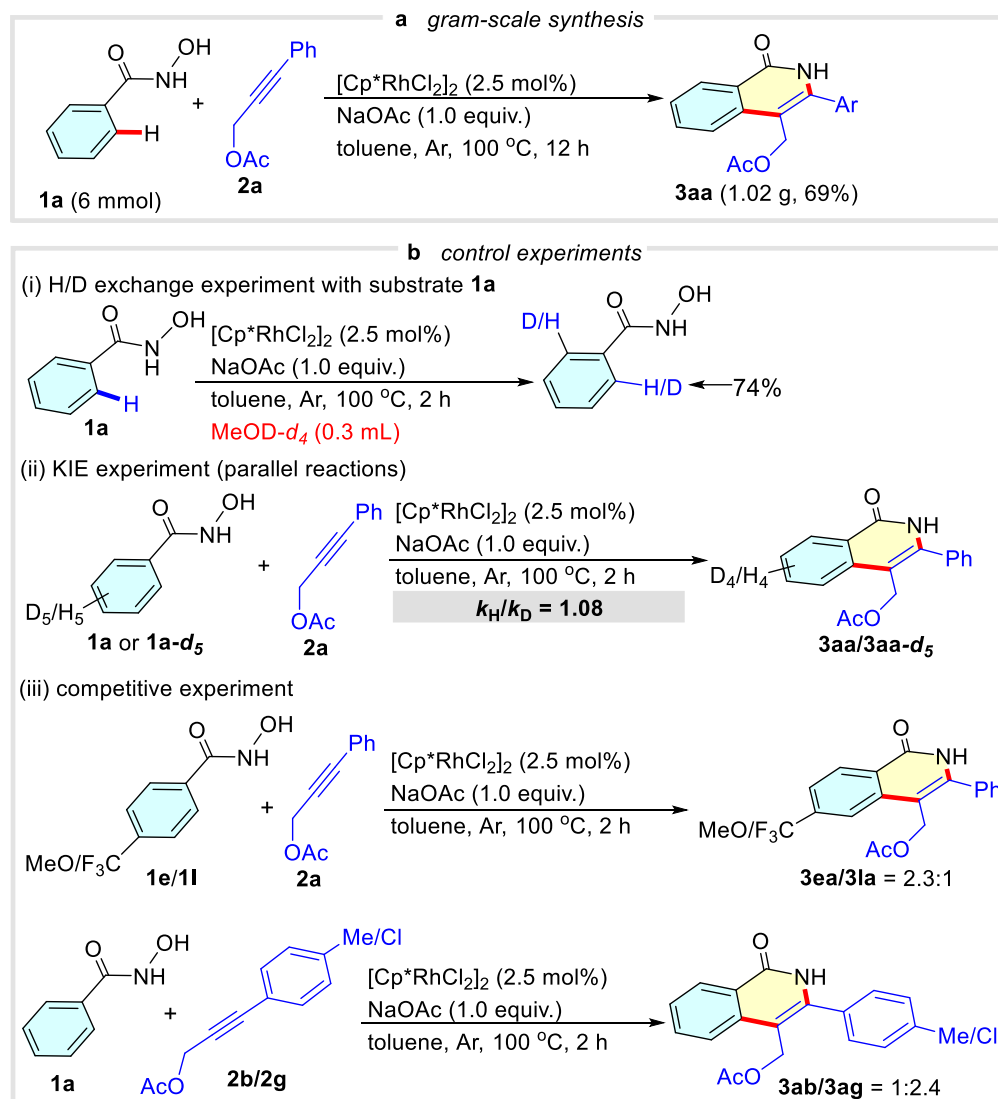
tolerated regardless of the electronic property on the benzene ring, providing the desired isoquinolones **3ma–3ra** in 41–78% yields. In addition, disubstituted *N*-hydroxybenzamides were also reactive to produce the corresponding products in 71–79% yields (products **3sa–3wa**). Moreover, this transformation was further extended to *N*-hydroxy-2-naphthamide and *N*-hydroxythiophene-2-carboxamide substrates, giving the corresponding products **3xa** and **3ya** in 63% and 51% yields, respectively. Subsequently, we probed the scope of this transformation, employing propargylic acetates **2** bearing diverse substituents at the *para* position of the benzene ring and leading to the corresponding products **3ab–3ai** in 49–89% yields (Scheme 2b). Encouragingly, the halo groups on either benzamide, as well as on the propargylic acetates moiety, were well tolerated to produce the target products, which may have potential applications in organic synthesis by further functionalization through Pd-catalyzed coupling reactions.



Scheme 2. Substrate scope. Reaction conditions: *N*-hydroxybenzamides **1** (0.2 mmol), propargylic acetates **2** (0.2 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (2.5 mol%), and NaOAc (0.2 mmol) in toluene at 100 °C for 12 h under argon atmosphere. Isolated yields were reported.

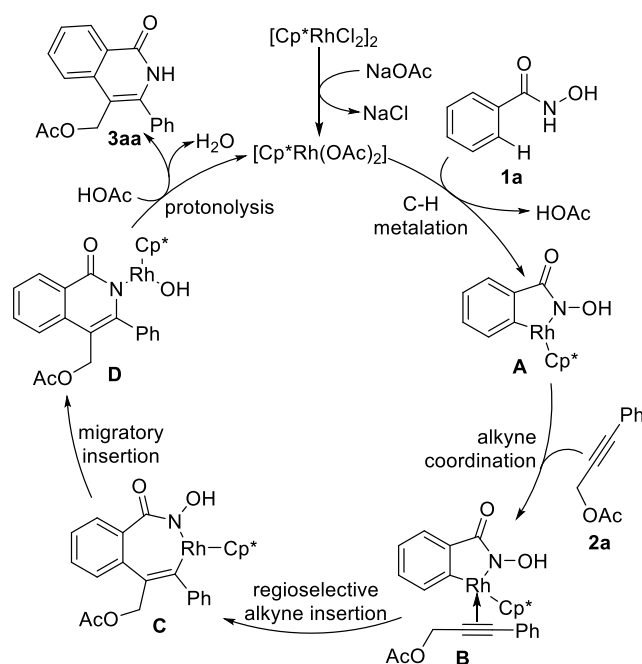
To further prove the robustness and the general utility of this protocol, we carried out the reaction of *N*-hydroxybenzamide **1a** and 3-phenylprop-2-yn-1-yl acetate **2a** in gram-scale synthesis under the standard condition. This transformation was easily scaled up to 6 mmol (scaled up to 30 times), producing the desired product **3aa** in 69% yield (Scheme 3a). Subsequently, insights into this cascade C-H activation/annulation were gained by performing control experiments to clarify the reaction mechanism. Treating *N*-hydroxybenzamide **1a** with methanol-*d*₄ under standard conditions for 2 h, a 74% deuterium was detected on the *ortho* C-H bond (Scheme 3b(i)), which indicated that the C-H activation process might be the reversible step. Next, a kinetic isotope effect (KIE) value of 1.08 was measured from two parallel reactions of *N*-hydroxybenzamide **1a** or **1a-d**₅ with propargylic acetate

2a for 2 h under the standard conditions (Scheme 3b(ii)). The intermolecular competitive experiment of *para*-methoxyl- and *para*-trifluoromethyl-substituted *N*-hydroxybenzamide showed that the electron-donating group facilitated the reaction step, implying that C(*sp*²)-H bond cleavage might be the limiting step (Scheme 3b(iii)). As for the distinct propargylic acetates **2b** and **2g**, the electron-deficient propargylic acetate **2g** delivered the product in a higher yield.



Scheme 3. Gram-scale synthesis and control experiments.

On the basis of the above control experiments and relevant reports [33,36,38], a plausible mechanism for the Rh-catalyzed cascade C-H activation/annulation for the formation of NH-free isoquinolones is proposed in Scheme 4. Initially, the active catalyst was generated via ligand exchange, which mediated a facile C-H metalation process to give the five-membered rhodacycle **A**. Subsequent coordination of the alkyne to the rhodium center followed by the 1,2-insertion of the alkyne afforded the seven-membered rhodacycle **C**. Then, the metal migration and C-N bond formation of intermediate **C** afforded the intermediate **D**, which underwent the protonation to generate the desired product **3aa** along with the release of a molecule of water.



Scheme 4. Proposed mechanism for the formation of NH-free isoquinolones.

3. Materials and Methods

The detailed procedures for the synthesis and characterization of the products are given in Appendix A.

4. Conclusions

In conclusion, we developed an efficient and practical method to construct NH-free isoquinolones via Rh(III)-catalyzed C-H activation/annulation of *N*-hydroxybenzamides and propargylic acetates. A variety of *N*-hydroxybenzamides with a diverse array of substituents, irrespective of their electronic and steric nature, were tolerated well under the optimal conditions. Generation of H₂O as the only byproduct makes this 100% carbon-efficient process attractive for the synthesis of isoquinolone derivatives. Moreover, the synthetic utility and practicability of the developed methodology in gram-scale synthesis were validated.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules27238553/s1>, Characterization data for product **3**, including ¹H- and ¹³C-NMR spectroscopies, are available online. CCDC 2220211 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; fax: +44-1223-336033.

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Data Availability Statement: The data presented in this study are available in this article.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A. Experimental Section

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All cascade reactions were performed in a resealable screw-capped Schlenk flask (approx. 15 mL volume) in the presence of a Teflon-coated magnetic stirrer bar (4 mm × 10 mm). Reactions were monitored by using thin-layer chromatography (TLC) on commercial silica gel plates (GF 254). Visualization of the developed plates was performed under UV lights (GF 254 nm). Flash column chromatography was performed on silica gel (200–300 mesh). ¹H NMR spectra were recorded on a 500 MHz spectrometer, and ¹³C NMR spectra were recorded on a 125 MHz spectrometer (Supplementary Materials: ¹H NMR and ¹³C NMR). Chemical shifts were expressed in parts per million (δ), and the signals were reported as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), and m (multiplet), and coupling constants (J) were given in Hz. Chemical shifts as internal standards were referenced to CDCl₃ (δ = 7.26 for ¹H and δ = 77.16 for ¹³C NMR) as internal standard. HRMS analysis with a quadrupole time-of-flight mass spectrometer yielded ion mass/charge (*m/z*) ratios in atomic mass units. The melting points were measured using SGWX-4 melting point apparatus and were not corrected. The X-ray source used for the single-crystal X-ray diffraction analysis of compound **3aa** was Mo Kα (λ = 0.71073 Å), and the thermal ellipsoid was drawn at the 30% probability level (Supplementary Materials: X-ray crystal data).

General procedure for the synthesis of isoquinolones 3 (product **3aa** as an example). *N*-Hydroxybenzamides **1a** (27.4 mg, 0.2 mmol), [Cp * RhCl₂]₂ (3.1 mg, 2.5 mol%), and NaOAc (16.4 mg, 0.2 mmol) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tube was evacuated and flushed with argon for three cycles. Propargylic acetates **2a** (34.8 mg, 0.2 mmol) and toluene (2 mL) were then added, and the tube was placed into a preheated oil bath (100 °C) and stirred for 12 h. After the completion of the reaction, the reaction tube was allowed to cool to room temperature, extracted with CH₂Cl₂ (3 × 10 mL), and washed with brine. The organic layers were combined, dried over Na₂SO₄, filtered, and then evaporated under vacuum. The residue was purified using flash column chromatography with a silica gel (200–300 mesh) and using ethyl acetate and petroleum ether as the elution solvent to give desired product **3**.

(1-Oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3aa**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 84% yield (49 mg); mp 163–164 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.58 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 7.82–7.75 (m, 2H), 7.58–7.47 (m, 6H), 4.97 (s, 2H), 2.03 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 170.9, 162.2, 143.2, 137.5, 133.9, 133.4, 129.9, 129.8, 128.9, 127.5, 127.0, 125.8, 124.1, 106.8, 60.7, 21.2; HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₈H₁₆NO₃ 294.1125; Found 294.1127.

(6-Methyl-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ba**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 87% yield (53 mg); mp 166–167 °C; ¹H NMR (500 MHz, CDCl₃) δ 9.52 (s, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 7.52–7.47 (m, 6H), 7.36 (d, *J* = 8.0 Hz, 1H), 5.13 (s, 2H), 2.53 (s, 3H), 2.12 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.4, 163.1, 144.4, 142.4, 142.3, 138.0, 134.3, 130.3, 129.3, 128.9, 128.3, 123.6, 108.0, 61.2, 22.7, 21.5; HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₉H₁₈NO₃ 308.1281; Found 308.1283.

(6-Ethyl-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ca**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 85% yield (54 mg); mp 172–173 °C; ¹H NMR (500 MHz, CDCl₃) δ 9.76 (s, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 7.50–7.48 (m, 6H), 7.39 (d, *J* = 8.0 Hz, 1H), 5.15 (s, 2H), 2.82 (q, *J* = 7.5, 2H), 2.12 (s, 3H), 1.31 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.4, 163.3, 150.5, 142.4, 138.1, 134.3, 130.3, 129.4, 129.3, 128.4, 127.8, 123.8, 122.4, 108.2, 61.2, 29.9, 21.5, 15.8; HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₀H₂₀NO₃ 322.1438; Found 322.1430.

(6-(*tert*-Butyl)-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3da**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 53% yield (37 mg); mp 174–175 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.68 (s, 1H), 8.38 (d, J = 8.5 Hz, 1H), 7.74–7.68 (m, 1H), 7.64–7.57 (m, 1H), 7.54–7.47 (m, 5H), 5.21 (s, 2H), 2.10 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.3, 162.7, 157.3, 141.9, 137.6, 134.5, 130.3, 129.5, 129.2, 128.1, 125.4, 123.6, 120.1, 108.6, 61.0, 35.9, 31.5, 21.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{24}\text{NO}_3$ 350.1751; Found 350.1759.

(6-Methoxy-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ea**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 77% yield (49 mg); mp 172–173 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.62 (s, 1H), 8.32 (d, J = 10.0 Hz, 1H), 7.51 (s, 5H), 7.14–7.05 (m, 2H), 5.14 (s, 2H), 3.92 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4, 164.1, 162.4, 142.8, 140.0, 134.4, 130.4, 130.4, 129.5, 129.2, 119.6, 116.1, 108.1, 105.9, 61.0, 55.9, 21.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_4$ 324.1230; Found 324.1228.

(6-Fluoro-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3fa**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 73% yield (45 mg); mp 161–162 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.00 (s, 1H), 8.42 (m, 1H), 7.53–7.47 (m, 6H), 7.35 (dd, J = 10.5 Hz, 2.0 Hz, 1H), 5.07 (s, 2H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.3, 166.4 (d, $J_{\text{C-F}}$ = 250.1 Hz), 162.4, 143.6, 140.6 (d, $J_{\text{C-F}}$ = 9.9 Hz), 133.7, 131.5 (d, $J_{\text{C-F}}$ = 10.1 Hz), 130.4, 129.2 (d, $J_{\text{C-F}}$ = 26.2 Hz), 115.9 (d, $J_{\text{C-F}}$ = 23.1 Hz), 115.6, 109.4, 109.2, 60.8, 21.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{15}\text{FNO}_3$ 312.1030; Found 312.1022.

(6-Chloro-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ga**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 75% yield (49 mg); mp 174–175 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.37 (s, 1H), 8.38 (d, J = 2.0 Hz, 1H), 7.70–7.64 (m, 2H), 7.54–7.48 (m, 5H), 5.13 (s, 2H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.3, 161.9, 142.4, 136.3, 134.1, 133.9, 133.5, 130.6, 129.5, 129.2, 127.8, 127.1, 125.7, 108.1, 60.8, 21.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{15}\text{ClNO}_3$ 328.0735; Found 328.0727.

(6-Bromo-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ha**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 71% yield (52 mg); mp 164–165 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.20 (s, 1H), 8.26 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.64 (dd, J = 8.5, 2.0 Hz, 1H), 7.56–7.46 (m, 5H), 5.08 (s, 2H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.3, 162.5, 143.4, 139.5, 133.9, 130.7, 130.7, 130.0, 129.5, 129.2, 129.2, 126.8, 124.6, 107.5, 60.8, 21.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{15}\text{BrNO}_3$ 372.0230; Found 372.0235.

(1-Oxo-3,6-diphenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ia**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 89% yield (65 mg); mp 181–182 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.68 (s, 1H), 8.52 (d, J = 8 Hz, 1H), 7.92 (s, 1H), 7.80 (dd, J = 8.5, 1 Hz, 1H), 7.68 (d, J = 5.0 Hz, 2H), 7.49–7.55 (m, 7H), 7.44 (m, 1H), 5.21 (s, 2H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4, 163.1, 146.4, 142.8, 140.6, 138.3, 134.3, 130.4, 129.5, 129.4, 129.4, 129.2, 128.8, 127.9, 126.5, 124.7, 122.1, 108.5, 61.1, 21.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{20}\text{NO}_3$ 370.1438; Found 370.1439.

(6-Cyano-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ja**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 76% yield (48 mg); mp 205–206 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.42 (s, 1H), 8.50 (d, J = 8.0 Hz, 1H), 8.05 (s, 1H), 7.74 (dd, J = 8.0, 1 Hz, 1H), 7.59–7.52 (m, 6H), 5.12 (s, 2H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.1, 161.8, 144.1, 138.2, 133.5, 131.0, 129.5, 129.4, 129.2, 129.1, 128.9, 128.4, 118.6, 117.3, 107.6, 60.6, 21.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_3$ 319.1077; Found 319.1079.

(6-Nitro-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ka**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a yellow solid in 72% yield (48 mg); mp 191–192 °C; ^1H NMR (500 MHz, CDCl_3) δ 10.16

(s, 1H), 8.61 (s, 1H), 8.54 (d, $J = 9.0$ Hz, 1H), 8.39–8.21 (m, 1H), 7.60–7.50 (m, 5H), 5.19 (s, 2H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.1, 161.9, 151.3, 144.4, 138.9, 133.4, 131.0, 130.4, 129.6, 129.5, 129.2, 120.9, 119.8, 108.5, 60.7, 21.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_5$ 339.0975; Found 339.0971.

(1-Oxo-3-phenyl-6-(trifluoromethyl)-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3la**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 69% yield (50 mg); mp 193–194 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.40 (s, 1H), 8.53 (d, $J = 8.0$ Hz, 1H), 7.99 (s, 1H), 7.74 (d, $J = 8.5$ Hz, 1H), 7.57–7.53 (m, 3H), 7.52–7.48 (m, 2H), 5.16 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.0, 162.5, 143.7, 137.9, 135.1 (q, $J_{\text{C-F}} = 32.5$ Hz), 133.4, 130.4, 129.3, 129.1, 127.7, 125.18 (q, $J_{\text{C-F}} = 271.3$ Hz), 123.0, 122.8, 121.1, 108.1, 60.6, 21.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{15}\text{F}_3\text{NO}_3$ 362.0999; Found 362.1007.

(7-Chloro-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ma**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 46% yield (30 mg); mp 177–178 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.11 (s, 1H), 8.39 (d, $J = 2.0$ Hz, 1H), 7.70 (dd, $J = 10.0, 5.0$ Hz, 1H), 7.66 (d, $J = 10.0$ Hz, 1H), 7.57–7.51 (m, 3H), 7.49 (dd, $J = 5.0, 1.5$ Hz, 2H), 5.12 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.3, 161.9, 142.3, 136.3, 134.1, 133.9, 133.6, 130.6, 129.5, 129.2, 127.8, 127.1, 125.7, 108.1, 60.8, 21.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{15}\text{ClNO}_3$ 328.0735; Found 328.0741.

(7-Bromo-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3na**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 41% yield (30 mg); mp 172–173 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.77 (s, 1H), 8.50 (s, 1H), 7.82 (dd, $J = 5.0, 1.5$ Hz, 1H), 7.58 (d, $J = 10.0$ Hz, 1H), 7.56–7.47 (m, 5H), 5.12 (s, 2H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.0, 161.6, 142.4, 136.6, 136.5, 133.8, 130.8, 130.5, 129.3, 129.0, 127.2, 125.6, 121.2, 107.9, 60.6, 21.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{15}\text{BrNO}_3$ 372.0230; Found 372.0231.

(8-Methyl-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3oa**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 78% yield (48 mg); mp 182–183 °C; ^1H NMR (500 MHz, CDCl_3) δ 10.77 (s, 1H), 7.56–7.48 (m, 7H), 7.24 (d, $J = 7.0$ Hz, 1H), 5.13 (s, 2H), 2.76 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.5, 164.8, 142.8, 139.7, 134.1, 132.7, 130.2, 130.0, 129.6, 129.1, 124.2, 121.7, 108.0, 61.7, 24.3, 21.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_3$ 308.1281; Found 308.1286.

(8-Fluoro-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3pa**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a brownish yellow solid in 66% yield (41 mg); mp 164–165 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.45 (s, 1H), 7.70–7.66 (m, 1H), 7.53–7.49 (m, 5H), 7.47 (d, $J = 5.0$ Hz, 1H), 7.17 (dd, $J = 15.0$ Hz, 5.0 Hz, 1H), 5.11 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.3, 163.3 (d, $J_{\text{C-F}} = 262.5$ Hz), 160.6, 143.6, 140.8, 134.6 (d, $J_{\text{C-F}} = 10.0$ Hz), 133.7, 130.6, 129.5, 129.3 (d, $J_{\text{C-F}} = 7.5$ Hz), 119.7 (d, $J_{\text{C-F}} = 5.0$ Hz), 115.1 (d, $J_{\text{C-F}} = 5.0$ Hz), 114.2 (d, $J_{\text{C-F}} = 21.2$ Hz), 107.5, 61.3, 21.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{15}\text{FNO}_3$ 312.1030; Found 312.1031.

(8-Chloro-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3qa**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a brownish yellow solid in 69% yield (45 mg); mp 171–172 °C; ^1H NMR (500 MHz, CDCl_3) δ 10.28 (s, 1H), 7.60–7.49 (m, 8H), 5.11 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4, 161.8, 143.8, 141.1, 136.4, 133.6, 133.2, 130.5, 130.4, 129.4, 129.4, 122.8, 122.4, 107.6, 61.4, 21.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{15}\text{ClNO}_3$ 328.0735; Found 328.0744.

(8-Bromo-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ra**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a brownish yellow solid in 62% yield (46 mg); mp 168–169 °C; ^1H NMR (500 MHz, CDCl_3) δ 10.21 (s, 1H), 7.76 (d, $J = 7.5$, 1H), 7.64 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.55–7.50 (m, 5H), 7.47 (t, $J = 8.0$ Hz, 1H), 5.10 (s, 2H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4, 161.8, 143.6, 141.1, 134.3, 133.7, 133.3, 130.4, 129.4, 123.8, 123.5, 123.3, 107.7, 61.4, 21.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{15}\text{BrNO}_3$ 372.0230; Found 372.0237.

(7,8-Dimethyl-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3sa**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 79% yield (51 mg); mp 198–199 °C; ^1H NMR (500 MHz, CDCl_3) δ 10.14 (s, 1H), 7.56–7.46 (m, 6H), 7.42 (d, J = 8.3 Hz, 1H), 5.12 (s, 2H), 2.78 (s, 3H), 2.42 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.5, 164.7, 141.6, 140.8, 137.8, 136.6, 135.3, 134.2, 130.0, 129.5, 129.2, 124.2, 120.9, 107.9, 61.7, 21.5, 21.4, 18.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_3$ 322.1438; Found 322.1444.

(6,8-Dimethyl-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ta**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a light yellow solid in 71% yield (45 mg); mp 214–215 °C; ^1H NMR (500 MHz, CDCl_3) δ 10.75 (s, 1H), 7.56–7.45 (m, 5H), 7.28 (s, 1H), 7.07 (s, 1H), 5.10 (s, 2H), 2.71 (s, 3H), 2.44 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.6, 164.7, 143.1, 142.9, 142.6, 139.8, 134.3, 131.8, 129.9, 129.6, 129.1, 121.9, 121.6, 107.7, 61.8, 24.1, 22.4, 21.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_3$ 322.1438; Found 322.1437.

(6-Fluoro-8-methyl-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ua**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 76% yield (49 mg); mp 182–183 °C; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.43 (s, 1H), 7.53–7.48 (m, 3H), 7.48–7.39 (m, 2H), 7.30 (d, J = 10.0 Hz, 1H), 7.19 (d, J = 10.0 Hz, 1H), 4.88 (s, 2H), 2.84 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 170.4, 164.1 (d, J = 247.2 Hz), 162.5, 145.8 (d, J = 1.0 Hz), 144.2, 141.9 (d, J = 10.5 Hz), 133.1, 129.6, 129.2, 128.4, 120.6, 117.1 (d, J = 27.5 Hz), 107.0, 106.8, 106.0 (d, J = 5.0 Hz), 60.6, 23.7, 20.8; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{17}\text{FNO}_3$ 326.1187; Found 326.1179.

(6-Bromo-8-methyl-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3va**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 72% yield (55 mg); mp 180–181 °C; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.49 (s, 1H), 7.69 (s, 1H), 7.50 (s, 4H), 7.42 (d, J = 5.0 Hz, 2H), 4.88 (s, 2H), 2.80 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 170.8, 162.7, 144.7, 144.2, 140.9, 133.5, 132.1, 130.1, 129.7, 128.9, 126.8, 124.4, 123.0, 105.9, 60.8, 23.7, 21.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{17}\text{BrNO}_3$ 386.0386; Found 386.0377.

(6,8-Dichloro-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3wa**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 73% yield (53 mg); mp 217–218 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.74 (s, 1H), 7.57–7.25 (m, 7H), 5.05 (s, 2H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.2, 161.0, 144.8, 141.9, 139.3, 137.6, 133.3, 130.8, 130.3, 129.5, 129.2, 122.6, 120.9, 107.0, 61.2, 21.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{14}\text{Cl}_2\text{NO}_3$ 362.0345; Found 362.0339.

(1-Oxo-3-phenyl-1,2-dihydrobenzo[*g*]isoquinolin-4-yl)methyl acetate (**3xa**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a yellow solid in 63% yield (43 mg); mp 185–186 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.24 (s, 1H), 9.03 (s, 1H), 8.15 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.66–7.60 (m, 1H), 7.59–7.50 (m, 6H), 5.26 (s, 2H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.6, 163.7, 141.1, 136.2, 134.6, 133.5, 131.9, 130.3, 129.8, 129.4, 129.3, 128.9, 128.6, 126.8, 124.1, 122.6, 108.2, 61.5, 21.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{18}\text{NO}_3$ 344.1281; Found 344.1277.

(7-Oxo-5-phenyl-6,7-dihydrothieno [2,3-*c*]pyridin-4-yl)methyl acetate (**3ya**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 51% yield (30 mg); mp 158–159 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.64 (s, 1H), 7.80 (d, J = 5.0 Hz, 1H), 7.53–7.51 (m, 5H), 7.38 (d, J = 5.0 Hz, 1H), 5.13 (s, 2H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.0, 158.9, 147.1, 142.8, 134.4, 133.1, 130.1, 129.1, 129.0, 124.4, 123.5, 108.0, 61.2, 21.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{14}\text{NO}_3\text{S}$ 300.0689; Found 300.0684.

(1-Oxo-3-(*p*-tolyl)-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ab**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 72% yield (44 mg); mp 163–164 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.67 (s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 7.76–7.68 (m, 2H), 7.54–7.51 (m, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 5.15 (s, 2H), 2.43 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4,

163.2, 142.5, 140.5, 138.0, 133.6, 131.3, 130.0, 129.2, 128.3, 127.1, 125.8, 123.8, 108.1, 61.2, 21.8, 21.5; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{19}H_{18}NO_3$ 308.1281; Found 308.1279.

(3-(4-Ethylphenyl)-1-oxo-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ac**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 67% yield (43 mg); mp 165–166 °C; 1H NMR (500 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.38 (d, J = 8.0 Hz, 1H), 7.76–7.68 (m, 2H), 7.51 (m, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 5.17 (s, 2H), 2.73 (q, J = 5.0 Hz, 2H), 2.11 (s, 3H), 1.30 (t, J = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 163.5, 146.6, 142.7, 138.1, 133.6, 131.5, 129.4, 128.8, 128.3, 127.1, 125.8, 123.7, 108.0, 61.3, 29.1, 21.5, 15.7; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{20}H_{20}NO_3$ 322.1438; Found 322.1436.

(3-(4-(tert-Butyl)phenyl)-1-oxo-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ad**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 49% yield (34 mg); mp 171–172 °C; 1H NMR (500 MHz, $CDCl_3$) δ 8.42 (dd, J = 10.0, 5.0 Hz, 1H), 7.75–7.74 (m, 1H), 7.69 (d, J = 5.0 Hz, 1H), 7.53–7.51 (m, 3H), 7.43 (dd, J = 5.0, 2.0 Hz, 2H), 5.18 (s, 2H), 2.13 (s, 3H), 1.38 (s, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 162.9, 153.6, 142.4, 138.0, 133.7, 131.3, 129.0, 128.3, 127.2, 126.4, 125.9, 123.8, 108.0, 61.3, 35.3, 31.6, 21.5; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{22}H_{24}NO_3$ 350.1751; Found 350.1754.

(3-(4-Methoxyphenyl)-1-oxo-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ae**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 76% yield (49 mg); mp 174–175 °C; 1H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.45 (d, J = 7.5 Hz, 1H), 7.77–7.68 (m, 2H), 7.56–7.50 (m, 1H), 7.42 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 8.5 Hz, 2H), 5.16 (s, 2H), 3.88 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 163.0, 161.2, 142.0, 138.0, 133.7, 130.6, 128.3, 127.2, 126.5, 125.8, 123.8, 114.9, 108.1, 61.3, 55.8, 21.4; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{19}H_{18}NO_4$ 324.1230; Found 324.1225.

(3-(4-Fluorophenyl)-1-oxo-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3af**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 87% yield (54 mg); mp 193–194 °C; 1H NMR (500 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.78–7.70 (m, 2H), 7.59–7.47 (m, 3H), 7.22 (dd, J = 8.5, 8.5 Hz, 2H), 5.14 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 164.1 (d, J = 243.8 Hz), 163.4, 141.2, 137.5, 133.5, 131.4 (d, J = 8.8 Hz), 123.0, 128.0, 127.2, 125.6, 123.6, 116.2 (d, J = 21.2 Hz), 108.4, 60.8, 21.2; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{18}H_{15}FNO_3$ 312.1030; Found 312.1021.

(3-(4-Chlorophenyl)-1-oxo-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ag**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 84% yield (55 mg); mp 184–185 °C; 1H NMR (500 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.78–7.70 (m, 2H), 7.57–7.47 (m, 5H), 5.13 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 163.6, 141.3, 137.8, 136.6, 133.8, 132.5, 131.0, 129.5, 128.2, 127.5, 125.8, 123.9, 108.7, 60.9, 21.4; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{18}H_{15}ClNO_3$ 328.0735; Found 328.0736.

(3-(4-Bromophenyl)-1-oxo-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ah**). This compound was purified by column chromatography (ethyl acetate/petroleum ether = 1:6) to provide a white solid in 79% yield (58 mg); mp 178–179 °C; 1H NMR (500 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.76 (dd, J = 7.5, 7.5 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.56 (dd, 7.5, 7.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 5.13 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 163.6, 141.3, 137.8, 133.8, 132.9, 132.5, 131.2, 128.3, 127.5, 125.8, 124.9, 123.9, 108.7, 60.9, 21.4; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{18}H_{15}BrNO_3$ 372.0230; Found 372.0225.

(1-Oxo-3-(4-(trifluoromethyl)phenyl)-1,2-dihydroisoquinolin-4-yl)methyl acetate (**3ai**). This compound was purified by column chromatography (EtOAc/petroleum ether = 1:6) to provide a white solid in 89% yield (64 mg); mp 195–196 °C; 1H NMR (500 MHz, $CDCl_3$) δ 10.87 (s, 1H), 8.32–8.29 (m, 1H), 7.81–7.69 (m, 6H), 7.59–7.57 (m, 1H), 5.14 (s, 2H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 163.5, 141.0, 137.6, 137.5, 133.9, 132.1 (q, J = 32.5 Hz),

130.2, 128.2, 127.7, 126.2, 125.9, 124.2 (q, $J = 276.3$ Hz), 108.9, 60.5, 21.2; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{19}H_{15}F_3NO_3$ 362.0999; Found 362.0992.

References

1. Brookings, D.; Davenport, R.J.; Davis, J.; Galvin, F.C.A.; Lloyd, S.; Mack, S.R.; Owens, R.; Sabin, V.; Wynn, J. Novel nucleotide triphosphates as potent P_2Y_2 agonists. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 562–565. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Kiselev, E.; Sooryakumar, D.; Agama, K.; Cushman, M.; Pommier, Y. Optimization of the Lactam Side Chain of 7-Azaindenoisoquinoline Topoisomerase I Inhibitors and Mechanism of Action Studies in Cancer Cells. *J. Med. Chem.* **2014**, *57*, 1289–1298. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Bentley, K.W. β -Phenylethylamines and the isoquinoline alkaloids. *Nat. Prod. Rep.* **2006**, *23*, 444–463. [\[CrossRef\]](#)
4. Bhadra, K.; Kumar, G.S. Isoquinoline Alkaloids and their Binding with DNA: Calorimetry and Thermal Analysis Applications. *Mini-Rev. Med. Chem.* **2010**, *10*, 1235–1247. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Khadka, D.B.; Yang, S.H.; Cho, S.H.; Zhao, C.; Cho, W.-J. Synthesis of 12-oxobenzo[c]phenanthridinones and 4-substituted 3-arylisoquinolones via Vilsmeier–Haack reaction. *Tetrahedron* **2012**, *68*, 250–261. [\[CrossRef\]](#)
6. Malkov, A.V.; Westwater, M.-M.; Gutnov, A.; Ramírez-López, P.; Friscourt, F.; Kadlíková, A.; Hodačová, J.; Rankovic, Z.; Kotora, M.; Kočovský, P. New pyridine N -oxides as chiral organocatalysts in the asymmetric allylation of aromatic aldehydes. *Tetrahedron* **2008**, *64*, 11335–11348. [\[CrossRef\]](#)
7. Thoi, V.S.; Kornienko, N.; Margarit, C.G.; Yang, P.; Chang, C.J. Visible-Light Photoredox Catalysis: Selective Reduction of Carbon Dioxide to Carbon Monoxide by a Nickel N -Heterocyclic Carbene–Isoquinoline Complex. *J. Am. Chem. Soc.* **2013**, *135*, 14413–14424. [\[CrossRef\]](#)
8. Yu, D.-G.; Azambuja, F.; Glorius, F. α -MsO/TsO/Cl Ketones as Oxidized Alkyne Equivalents: Redox-Neutral Rhodium(III)-Catalyzed C–H Activation for the Synthesis of N -Heterocycles. *Angew. Chem. Int. Ed.* **2014**, *53*, 2754–2758. [\[CrossRef\]](#)
9. Fang, Z.; Zheng, S.-C.; Guo, Z.; Guo, J.-Y.; Tan, B.; Liu, X.-Y. Asymmetric Synthesis of Axially Chiral Isoquinolones: Nickel-Catalyzed Denitrogenative Transannulation. *Angew. Chem. Int. Ed.* **2015**, *54*, 9528–9532. [\[CrossRef\]](#)
10. Wu, J.-Q.; Zhang, S.-S.; Gao, H.; Qi, Z.; Zhou, C.-J.; Ji, W.-W.; Liu, Y.; Chen, Y.; Li, Q.; Li, X.; et al. Experimental and Theoretical Studies on Rhodium-Catalyzed Coupling of Benzamides with 2,2-Difluorovinyl Tosylate: Diverse Synthesis of Fluorinated Heterocycles. *J. Am. Chem. Soc.* **2017**, *139*, 3537–3545. [\[CrossRef\]](#)
11. Huang, J.-R.; Bolm, C. Microwave-Assisted Synthesis of Heterocycles by Rhodium(III)-Catalyzed Annulation of N -Methoxyamides with α -Chloroaldehydes. *Angew. Chem. Int. Ed.* **2017**, *56*, 15921–15925. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Xu, Y.; Zheng, G.; Yang, X.; Li, X. Rhodium(III)-catalyzed chemodivergent annulations between N -methoxybenzamides and sulfoxonium ylides via C–H activation. *Chem. Commun.* **2018**, *54*, 670–673. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Mei, R.; Fang, X.; He, L.; Sun, J.; Zou, L.; Ma, W.; Ackermann, L. Cobalt/electro-catalyzed oxidative allene annulation by electro-removable hydrazides. *Chem. Commun.* **2020**, *56*, 1393–1396. [\[CrossRef\]](#)
14. Zhang, L.-B.; Geng, R.-S.; Wang, Z.-C.; Ren, G.-Y.; Wen, L.-R.; Li, M. Electrochemical intramolecular C–H/ N -H functionalization for the synthesis of isoxazolidine-fused isoquinolin-1(2H)-ones. *Green Chem.* **2020**, *22*, 16–21. [\[CrossRef\]](#)
15. Alvarez-Builla, J.; Vaquero, J.J.; Barluenga, J. *Modern Heterocyclic Chemistry*; Wiley-VCH: Weinheim, Germany, 2011.
16. Glushkov, V.A.; Shklyayev, Y.V. Synthesis of 1(2H)-Isoquinolones. *Chem. Heterocycl. Compd.* **2001**, *37*, 663–687. [\[CrossRef\]](#)
17. Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. Transition metal-catalyzed C–H bond functionalizations by the use of diverse directing groups. *Org. Chem. Front.* **2015**, *2*, 1107–1295. [\[CrossRef\]](#)
18. Zhang, J.; Lu, X.; Shen, C.; Xu, L.; Ding, L.; Zhong, G. Recent advances in chelation-assisted site- and stereoselective alkenyl C–H functionalization. *Chem. Soc. Rev.* **2021**, *50*, 3263–3314. [\[CrossRef\]](#)
19. Kumar, S.; Nunewar, S.; Oluguttula, S.; Nanduri, S.; Kanchupalli, V. Recent advances in Rh(III)/Ir(III)-catalyzed C–H functionalization/annulation via carbene migratory insertion. *Org. Biomol. Chem.* **2021**, *19*, 1438–1458. [\[CrossRef\]](#)
20. Liu, J.; Xiao, X.; Lai, Y.; Zhang, Z. Recent advances in transition metal-catalyzed heteroannulative difunctionalization of alkenes via C–H activation for the synthesis of heterocycles. *Org. Chem. Front.* **2022**, *9*, 2256–2279. [\[CrossRef\]](#)
21. Subhedar, D.D.; Mishra, A.A.; Bhanage, B.M. N -Methoxybenzamide: A Versatile Directing Group for Palladium-, Rhodium- and Ruthenium-Catalyzed C–H Bond Activations. *Adv. Synth. Catal.* **2019**, *361*, 4149–4195. [\[CrossRef\]](#)
22. Hao, X.-Q.; Du, C.; Zhu, X.; Li, P.-X.; Zhang, J.-H.; Niu, J.-L.; Song, M.-P. Cobalt(II)-Catalyzed Decarboxylative C–H Activation/Annulation Cascades: Regioselective Access to Isoquinolones and Isoindolinones. *Org. Lett.* **2016**, *18*, 3610–3613. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Shi, L.; Yu, K.; Wang, B. Regioselective synthesis of multisubstituted isoquinolones and pyridones via Rh(III)-catalyzed annulation reactions. *Chem. Commun.* **2015**, *51*, 17277–17280. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Manoharan, R.; Jegannathan, M. Cobalt-catalyzed cyclization of benzamides with alkynes: A facile route to isoquinolones with hydrogen evolution. *Org. Biomol. Chem.* **2018**, *16*, 8384–8389. [\[CrossRef\]](#)
25. Lin, C.; Shen, L. Co-catalyzed *ortho*-C–H functionalization/annulation of arenes and alkenes with alkynylsilanes: Access to isoquinolone and pyridine motifs. *RSC Adv.* **2019**, *9*, 30650–30654. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Thorat, V.H.; Aman, H.; Tsai, Y.-L.; Pallikonda, G.; Chuang, G.J.; Hsieh, J.-C. Cobalt-catalyzed coupling reactions of 2-halobenzamides with alkynes: Investigation of ligand-controlled dual pathways. *Org. Chem. Front.* **2021**, *8*, 6419–6426. [\[CrossRef\]](#)

27. Allu, S.; Swamy, K.C.K. Ruthenium-Catalyzed Synthesis of Isoquinolones with 8-Aminoquinoline as a Bidentate Directing Group in C–H Functionalization. *J. Org. Chem.* **2014**, *79*, 3963–3972. [[CrossRef](#)] [[PubMed](#)]
28. Chen, Z.-W.; Zhu, Y.-Z.; Ou, J.-W.; Wang, Y.-P.; Zheng, J.-Y. Metal-Free Iodine(III)-Promoted Synthesis of Isoquinolones. *J. Org. Chem.* **2014**, *79*, 10988–10998. [[CrossRef](#)]
29. Cera, G.; Haven, T.; Ackermann, L. Iron-catalyzed C–H/N–H activation by triazole guidance: Versatile alkyne annulation. *Chem. Commun.* **2017**, *53*, 6460–6463. [[CrossRef](#)]
30. Xu, F.; Zhu, W.-J.; Wang, J.; Ma, Q.; Shen, L.-J. Rhodium-catalyzed synthesis of substituted isoquinolones via a selective decarbonylation/alkyne insertion cascade of phthalimides. *Org. Biomol. Chem.* **2020**, *18*, 8219–8223. [[CrossRef](#)]
31. He, Y.; Liao, X.-Z.; Dong, L.; Chen, F.-E. Rh(III)-Catalyzed three-component cascade annulation to produce the *N*-oxopropyl chain of isoquinolone derivatives. *Org. Biomol. Chem.* **2021**, *19*, 561–567. [[CrossRef](#)]
32. Zhao, Y.; Shi, C.; Su, X.; Xia, W. Synthesis of isoquinolones by visible-light-induced deaminative [4+2] annulation reactions. *Chem. Commun.* **2020**, *56*, 5259–5262. [[CrossRef](#)] [[PubMed](#)]
33. Ackermann, L.; Fenner, S. Ruthenium-Catalyzed C–H/N–O Bond Functionalization: Green Isoquinolone Syntheses in Water. *Org. Lett.* **2011**, *13*, 6548–6551. [[CrossRef](#)] [[PubMed](#)]
34. Yang, F.; Ackermann, L. Dehydrative C–H/N–OH Functionalizations in H₂O by Ruthenium(II) Catalysis: Subtle Effect of Carboxylate Ligands and Mechanistic Insight. *J. Org. Chem.* **2014**, *79*, 12070–12082. [[CrossRef](#)]
35. Yu, B.; Chen, Y.; Hong, M.; Duan, P.; Gan, S.; Chao, H.; Zhao, Z.; Zhao, J. Rhodium-catalyzed C–H activation of hydrazines leads to isoquinolones with tunable aggregation-induced emission properties. *Chem. Commun.* **2015**, *51*, 14365–14368. [[CrossRef](#)] [[PubMed](#)]
36. Li, X.; Zhang, R.; Qi, Y.; Zhao, Q.; Yao, T. Rhodium(III)-catalyzed C–H activation/annulation of *N*-iminopyridinium ylides with alkynes and diazo compounds. *Org. Chem. Front.* **2021**, *8*, 1190–1196. [[CrossRef](#)]
37. Meng, H.; Xu, H.; Zhou, Z.; Tang, Z.; Li, Y.; Zhou, Y.; Yi, W.; Wu, X. Recyclable rhodium-catalyzed C–H activation/[4 + 2] annulation with unconventional regioselectivity at ambient temperature: Experimental development and mechanistic insight. *Green Chem.* **2022**, *24*, 7012–7021. [[CrossRef](#)]
38. Fukui, Y.; Liu, P.; Liu, Q.; He, Z.-T.; Wu, N.-Y.; Tian, P.; Lin, G.-Q. Tunable Arylative Cyclization of 1,6-Enynes Triggered by Rhodium(III)-Catalyzed C–H Activation. *J. Am. Chem. Soc.* **2014**, *136*, 15607–15614. [[CrossRef](#)]