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Access to Isoquinolines and Isoquinolin-3-ols via Rh(III)-Catalyzed Coupling/Cyclization Cascade Reaction of Arylimidates and Diazo Compounds

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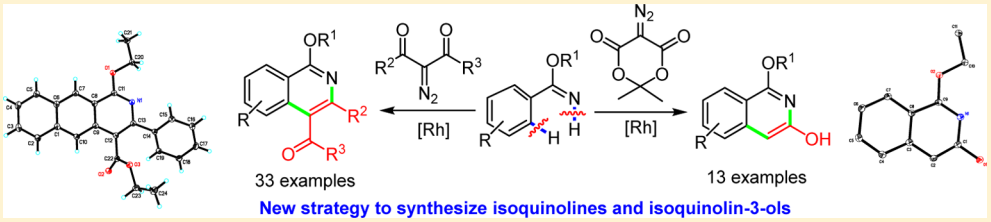
Supporting Information



ABSTRACT: A Rh(III)-catalyzed coupling/cyclization cascade reaction is described, which involves arylimidates and diazo compounds and proceeds via intermolecular C−C bond formation and subsequent intramolecular C−N bond formation. Mechanistic investigation revealed that the reaction is a two-step process: the initial Rh(III)-catalyzed coupling/cyclization proceeds very fast and the following dehydration is rather slow. The reaction provides a direct approach to isoquinolines and isoquinolin-3-ols without any oxidants.

Chemists continue to develop novel methods[1] to synthesize isoquinoline and its derivatives because of their diverse applications in organic synthesis,[2] biopharmaceutical preparation,[3] and materials science.[4] For example, plicamine alkaloids such as (+)-plicamine and (+)-plicane involve the construction of an isoquinoline motif in their synthesis,[5a,b] whereas dinapsoline is a drug developed for the treatment of the Parkinson disease as a agonist at the dopamine receptor (Figure 1).[5c] Moreover, the specific iridium isoquinoline complex, tris(1-phenylisoquinolinato-C^2,N)iridium(III) (Ir(piq)$_3$), could be used as red-emissive material in OLEDs and exhibits high electroluminescence efficiency (Figure 1).[4] However, most existing synthetic methods for isoquinoline and its derivatives have important drawbacks, including limited substrate scope, multiple steps, or harsh reaction conditions.[6] A promising alternative is transition-metal-catalyzed cyclization of *o*-halobenzimines with unsaturated C−C compounds, but this requires preactivating C−X reagents as substrates.[7]

Cp*Rh(III)-catalyzed C−H activation/cyclization has recently emerged as a versatile, step-economic approach for building diverse carbon- and heterocycles via formation of carbon−carbon and carbon−heteroatom bonds.[8] In particular, dehydrogenative coupling/cyclization reactions involving alkynes are useful for creating N-heterocycles.[9] However, these processes often require stoichiometric amounts of external oxidants and severe reaction conditions; in addition, they show low atom efficiency because they lead to side reactions [Scheme 1, eq 1]. Redox-neutral C−H activation/cyclization has emerged as an attractive strategy for building N-heterocycles that avoids the need for external oxidants.[10] Nevertheless, this approach still requires prefunctionalized substrates containing oxidizing directing groups, and it shows low atom economy since the oxidizing moieties cannot be incorporated into the desired products [Scheme 1, eq 2].

Efforts are still needed to develop more efficient reactions to construct isoquinolines from readily available substrates. Following Yu's pioneering work of diazomalonates in Rh(III)-catalyzed C−H activation,[11] Glorius reported an excellent synthesis in 2013 for multisubstituted isoquinoline and pyridine *N*-oxides from oximes and diazo compounds.[12] Although there was one example involving a benzimidate to react with ethyl diazoacetoacetate in this work, investigations on the applicability and mechanism of such a transformation are still urgently needed. We recently achieved the Rh(III)-catalyzed C−H activation of benzamides, followed by intermolecular cyclization with diazo compounds via C−C/C−O bond formation, generating various isocoumarins and α-pyrones under mild conditions.[13] As part of our continuing efforts to construct heterocycles,[14] we now report an oxidant-free, rhodium-catalyzed coupling/cyclization cascade reaction involving readily available arylimidates and diazo compounds that efficiently synthesizes diverse substituted isoquinolines and isoquinolin-3-ols [Scheme 1, eq 3]. Choosing arylimidate and a diazo compound as substrates not only circumvents the use of a stoichiometric oxidant or halogen compounds but also gives environmentally harmless N_2 as the only byproduct.

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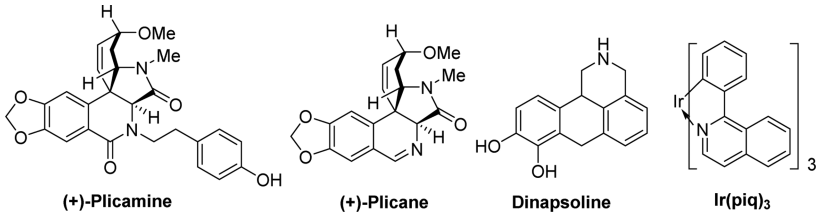
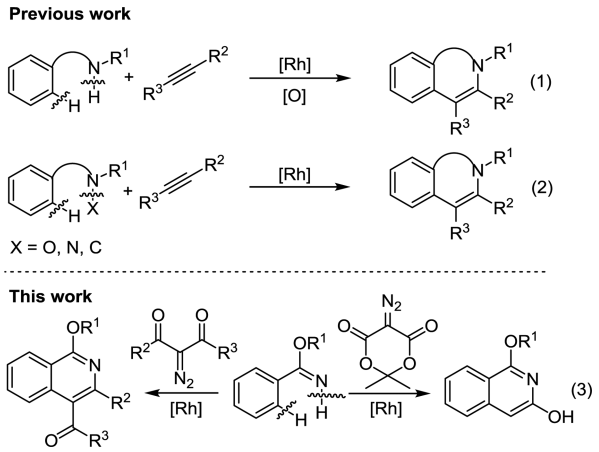


Figure 1. Some useful compounds containing isoquinoline moieties.

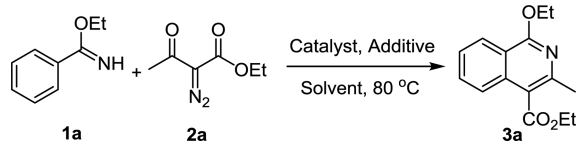
Scheme 1. Strategies for Synthesizing Isoquinoline Derivatives via a Rh(III)-Catalyzed C−H bond Coupling/Cyclization Cascade



Ethyl benzimidate (**1a**) and ethyl 2-diazo-3-oxobutanoate (**2a**) were initially selected as model substrates and 1,2-DCE as the solvent to investigate the cascade reaction (Table 1). Using $Cp^*Rh(OAc)_2$ or Cp^*RhCl_2 as the catalyst led to trace amounts of **3a** (entries 1−3), while using $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ generated **3a** in 67% yield (entry 4). Other catalysts, such as $[RuCl_2(p\text{-cymene})]_2$ and $Pd(OAc)_2$ proved ineffective (entries 5−6). Screening solvents showed 1,2-DCE to be the best choice, while other solvents such as THF, EtOH, and DMF performed well (entries 7−11). When 1,2-DCE was used as the solvent, attempts to add additives such as AcOH, AcONa, or AcOK decreased the yield to different extents (entries 12−14). Changing the ratio of **1a**:**2a** from 1:1 to 1:1.2 substantially improved the yield to 82% (entry 15), while decreasing it further to 1:1.5 did not affect the reaction obviously (entry 16). Raising the temperature increased the yield to 80%, while lowering it decreased the yield sharply (entries 17 and 18). We were pleased to obtain a good yield in the scaled-up experiment (entry 19).

Using the optimized reaction conditions (Table 1, entry 15), we explored the scope of substituted arylimidates (Table 2). Simple benzimidates or ethyl benzimidates substituted with electron-donating or -withdrawing groups at the *para* position smoothly underwent coupling/cyclization, affording multi-substituted isoquinolines **3b−i** in good to excellent yields (73−95%). However, *ortho*-F-substituted ethyl benzimidate gave the desired product **3j** in only 32% yield. We have tried other imidate substrates bearing ortho groups, such as *ortho*-Me or *ortho*-Br substituted ethyl benzimidates, but failed to afford the desired products. Ethyl benzimidate substituted with F or Me at the *meta* position reacted well with **2a**, giving the corresponding product **3k** in 79% yield and **3l** in 60% yield. These results indicate that steric hindrance at the benzene ring

Table 1. Optimization Studies for the Coupling/Cyclization Cascade Reaction of Benzimidate and Diazo Compounds[a]



entry	catalyst	solvent	ratio (**1a**/**2a**)	yield (%)[b]
1[c]	$[Cp^*RhCl_2]_2$	DCE	1/1	trace
2	$[Cp^*RhCl_2]_2$	DCE	1/1	trace
3	$Cp^*Rh(OAc)_2$	DCE	1/1	trace
4	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	DCE	1/1	67
5	$[RuCl_2(p\text{-cymene})]_2$	DCE	1/1	0
6	$Pd(OAc)_2$	DCE	1/1	0
7	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	THF	1/1	65
8	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	EtOH	1/1	65
9	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	DMF	1/1	58
10	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	toluene	1/1	23
11	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	H_2O	1/1	0
12[d]	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	DCE	1/1	61
13[e]	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	DCE	1/1	16
14[f]	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	DCE	1/1	13
15	$\mathbf{[Cp^*Rh(CH_3CN)_3](SbF_6)_2}$	**DCE**	**1/1.2**	**82 (78)**
16	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	DCE	1/1.5	81
17[g]	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	DCE	1/1.2	80
18[h]	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	DCE	1/1.2	44
19[i]	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	DCE	1/1.2	70 (68)

[a]Reaction conditions: **1a** (0.20 mmol), **2a**, catalyst (0.005 mmol, 2.5 mol %), additive (0.02 mmol, 0.1 equiv), solvent (2.0 mL), 80 °C, 5 h, under N_2, unless otherwise noted. [b]Determined by ^1H NMR using $PhSiMe_3$ as the internal standard. The yields in parentheses are isolated yields. [c]0.02 mmol of $AgSbF_6$. [d]0.02 mmol of AcOH was added. [e]0.02 mmol of AcONa was added. [f]0.02 mmol of AcOK was added. [g]At 100 °C was added. [h]At 60 °C. [i]The reaction was scaled up to 1.0 g (7 mmol) of **1a** with 1.0% catalyst loading.

can inhibit the coupling/cyclization process, which was confirmed by the failure of *ortho*-Me-substituted ethyl benzimidate to react. Substrates bearing two substituents at the *meta* positions of the benzene ring reacted smoothly with **2a** to furnish **3m** and **3n** in good yields. Moreover, 3,4-disubstituted derivatives also worked well in this transformation, affording products **3o−q** in good to excellent yields and high regioselectivities. Notably, 3,4-methylenedioxy benzimidate reacted smoothly with **2a** to produce the major product **3r** with inverted regioselectivity. Naphthalene and heterocyclic derivatives were also well tolerated in this transformation, affording the corresponding products **3s** and **3t** in good to excellent yields.

Subsequently, we explored the scope of diazo compounds **2** that can react with ethyl benzimidate **1a** (Table 3). Various 2-diazo-3-oxobutanoates bearing a range of alkyl groups

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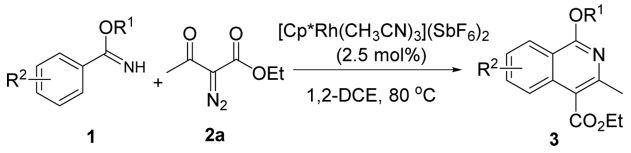
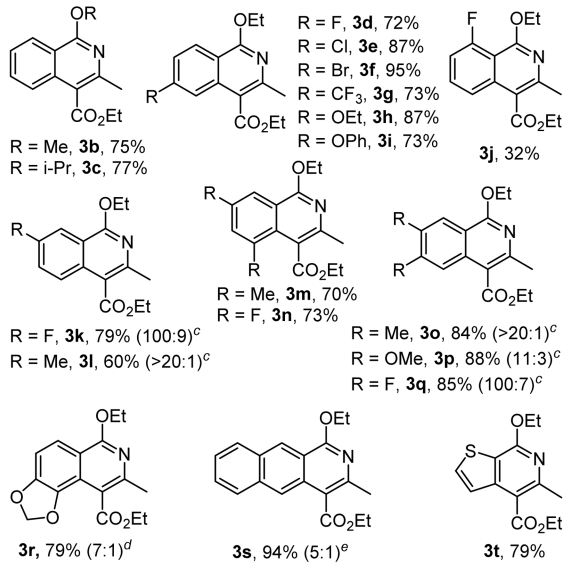
Table 2. Rh(III)-Catalyzed Coupling/Cyclization Cascade Reaction of Arylimidates 1 and Ethyl 2-Diazo-3-oxobutanoate 2a[a,b]



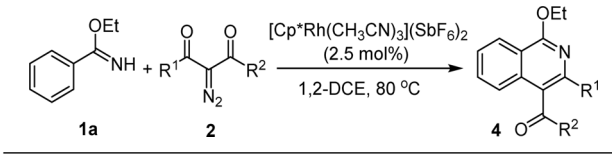


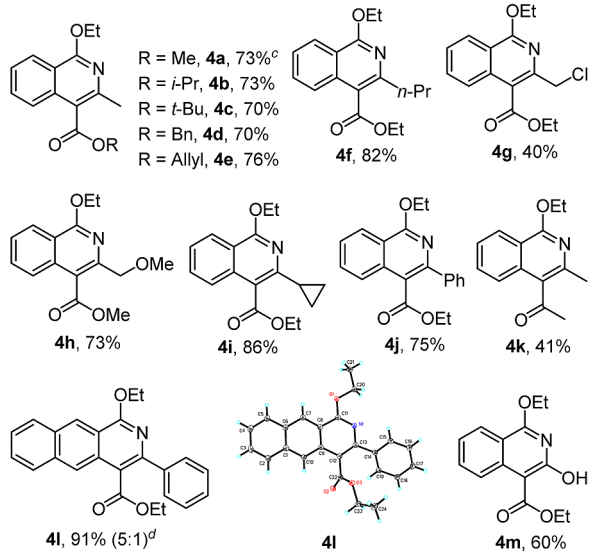
[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.24 mmol), [Cp*Rh-$(CH_3CN)_3$]$(SbF_6)_2$ (0.005 mmol, 2.5 mol %), 1,2-DCE (2.0 mL), 80 °C, 5 h, under N_2. [b]Isolated yields. [c]Regioselectivity occurred at the 6 and 2 positions of the benzimidate ring, defined as **3**/**3′**. [d]Regioselectivity occurred at the 2 and 6 positions of the benzimidate ring, defined as **3**/**3′**. [e]Regioselectivity occurred at the 3 and 1 positions of the naphthimidate ring, defined as **3**/**3′**.

performed well in this reaction, producing **4a**–**e** in moderate to good yields (70–76%). The scaled-up reaction for **4a** also gave a 64% yield. Other diazo substrates bearing alkyl groups such as *n*-propyl, chloromethyl, methoxymethyl, cyclopropyl, or phenyl afforded the corresponding products **4f**–**j** in good yields (73–86%), except for **4g** in a low yield of 40%. Interestingly, **1a** underwent coupling/cyclization with 3-diazopentane-2,4-dione to afford the corresponding product **4k**, albeit in relatively low yield. Treating ethyl 2-naphthimidate with ethyl 2-diazo-3-oxo-3-phenylpropanoate under standard conditions gave products **4l** and **4l′** in 91% yield with a regioselectivity of 5:1. The structure of **4l** was confirmed by NMR and single-crystal X-ray diffraction analysis. Moreover, diazo diethyl malonate reacted well with **1a** under the optimal conditions to give substituted 3-hydroxyisoquinoline **4m** in moderate 60% yield.

After we obtained these satisfactory results, we sought to test whether diazotized Meldrum's acid could be applied in the coupling/cyclization cascade reaction. To our delight, ethyl benzimidate **1a** reacted smoothly with **5**, giving the cyclic product 1-ethoxyisoquinolin-3-ol **6a** in 66% yield. The scaled-up reaction for **6a** also gave a similar 67% yield. The structure of **6a** was unambiguously assigned by X-ray crystallography.[15] We next probed the versatility of the transformation using various arylimidates **1** (Table 4). Ethyl benzimidates substituted with a broad range of electron-donating or -withdrawing groups at the *para* position underwent the coupling/cyclization

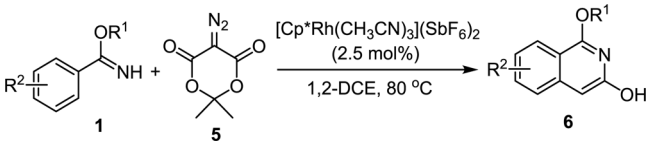
Table 3. Rh(III)-Catalyzed Coupling/Cyclization Cascade Reaction of Ethyl Benzimidate 1a and Diazo Compounds 2[a,b]

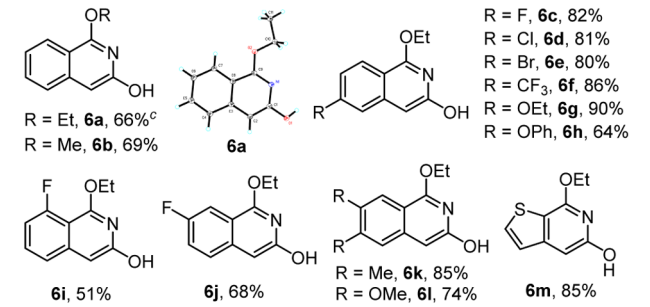




[a]Reaction conditions: **1a** (0.20 mmol), **2** (0.24 mmol), [Cp*Rh-$(CH_3CN)_3$]$(SbF_6)_2$ (0.005 mmol, 2.5 mol %), 1,2-DCE (2.0 mL), 80 °C, 5 h, under N_2. [b]Isolated yields. [c]The scaled-up reaction of **1a** (8.0 mmol) and methyl 2-diazo-3-oxobutanoate (9.6 mmol) was performed using 2.5 mol % catalyst at 80 °C for 5 h, and a 64% yield of **4a** was obtained. [d]The regioselectivity occurring at the 3 and 1 positions of the naphthimidate ring (defined as **4**/**4′**) is shown in the parentheses.

Table 4. Rh(III)-Catalyzed Coupling/Cyclization Cascade Reaction of Arylimidates 1 and Diazotized Meldrum's Acid 5[a,b]





[a]Reaction conditions: **1** (0.20 mmol), **5** (0.24 mmol), [Cp*Rh-$(CH_3CN)_3$]$(SbF_6)_2$ (0.005 mmol, 2.5 mol %), 1,2-DCE (2.0 mL), 80 °C, 12 h, under N_2. [b]Isolated yields. [c]The scaled-up reaction of **1a** (8.0 mmol) and **5** (9.6 mmol) was performed using 2.5 mol % catalyst at 80 °C for 12 h, and a 67% yield of **6a** was obtained.

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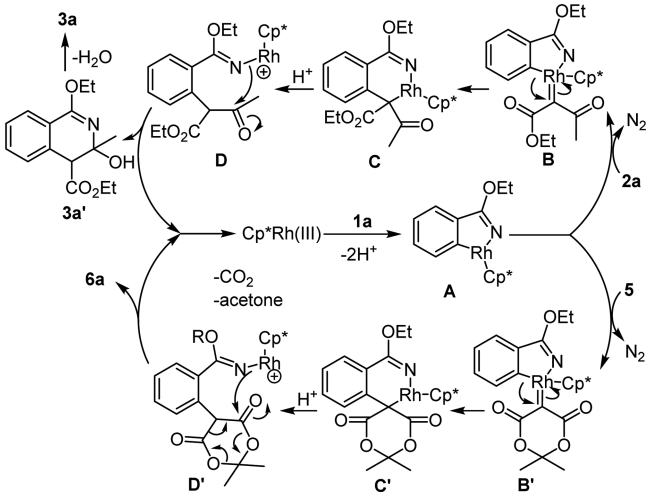
cascade to provide **3b–i** in 64–90% yields. The reaction producing **6i** from the *ortho*-F substrate showed a lower yield (51%) than the reaction producing **6j** from the *meta*-F substrate (68%), suggesting a steric effect. Products **6k** and **6l** were obtained from 3,4-disubstituted benzimidates in good yields and excellent regioselectivities. The heterocyclic substrate ethyl thiophene-2-carbimidate reacted smoothly, affording the corresponding product **6m** in 85% yield.

To gain the insights for the reaction mechanism, we tried to detect the reaction intermediates in this catalytic reaction. When **1a** was treated with the catalyst under typical conditions, the rhodacyclic intermediate **A** generated and was detected by ESI-HRMS analysis ($[M + H]^+$ calcd: 386.0991, found: 386.0990, experimental isotopic distribution matched the theoretical isotopic distribution; see Supporting Information). Moreover, when **1a** reacted with **2a** under the standard conditions, all **1a** transformed to the intermediate **3a′** in 73% isolated yield only after 3 min, which consumed hours to fully convert to **3a** after dehydration. This result illustrates that the reaction is a two-step process, with the initial Rh(III)-catalyzed coupling/cyclization proceeding very fast and the subsequent dehydration being a slow step. Finally, the reaction of **2a** with equal amounts of **1a** and deuterated substrate **1a–d_5** was explored under standard conditions for 1.5 min, and a significant KIE value of 3.5 was observed, which indicated C–H cleavage may be involved as the rate-determining step in the initial reaction to afford the intermediate **3a′**.

On the basis of these experimental investigations and literature precedents,[11,12] we propose a plausible mechanism for the coupling/cyclization cascade (Scheme 2). The reaction

Scheme 2. Plausible Reaction Mechanism for the Rh(III)-Catalyzed Coupling/Cyclization Cascade Reaction of Ethyl Benzimidate 1a and Diazo Compounds



starts with cyclorhodiation of **1a** to afford five-membered cyclic intermediate **A**, followed by the formation of the Rh(III)-carbene species **B** (or **B′**). Then, migration insertion of carbene into the Rh–C bond gives the six-membered rhodacyclic intermediate **C** (or **C′**). Protonolysis of **C** generates intermediate **D**, and the following addition affords the intermediate **3a′**, which undergoes the slow dehydration step to give the desired product **3a**. Similarly, intermediate **D′**, produced from **C′**, undergoes successive addition/elimination/decarboxylation to afford 1-ethoxyisoquinolin-3-ol **6a** and the active Cp*Rh(III) species with extrusion of acetone and CO_2.

In summary, we have developed an oxidant-free, Rh(III)-catalyzed coupling/cyclization cascade reaction that directly synthesizes diverse isoquinolines and isoquinolin-3-ols via C–H activation. In this strategy, diazo compounds serve as efficient coupling/cyclization partners, leading the arylimidate to undergo intermolecular C–C bond formation, followed by intramolecular C–N bond formation. Surprisingly, the reaction is a two-step process, and the initial Rh(III)-catalyzed coupling/cyclization accomplishes very fast while the final dehydration is rather slow. The protocol may inspire the use of a coupling/cyclization cascade reaction involving C–H activation in the construction of heterocycles in a variety of future applications.

EXPERIMENTAL SECTION

All manipulations were carried out under a nitrogen atmosphere using standard Schlenk techniques, unless otherwise stated. Solvents were dehydrated and distilled under nitrogen. Benzimidates[15] and diazo compounds[16,17] were prepared according to the literature methods. Chemical shifts (δ, ppm) in the ^{1}H NMR spectra were recorded using TMS as the internal standard. Chemical shifts in ^{13}C {^{1}H} NMR spectra were internally referenced to $CHCl_3$ (δ = 77.16 ppm) or DMSO (δ = 39.52 ppm).

Typical Procedure for the Synthesis of Isoquinolines (3 or 4). To a mixture of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (4.1 mg, 0.005 mmol, 2.5 mol %) and 1,2-dichloroethane (2 mL) at room temperature were added benzimidates **1** (0.20 mmol) and diazo compounds **2** (0.24 mmol). The reaction mixture was stirred at 80 °C for 5 h, and the progress was monitored using TLC detection. After completion of the present reaction, the solvent was evaporated under reduced pressure and the residue was passed through flash column chromatography on silica gel to afford the desired products **3** or **4**.

Typical Procedure for the Synthesis of Isoquinolin-3-ols (6). To a mixture of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (4.1 mg, 0.005 mmol, 2.5 mol %) and 1,2-dichloroethane (2 mL) at room temperature were added benzimidates **1** (0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol). The reaction mixture was stirred at 80 °C for 12 h, and the progress was monitored using TLC detection. After completion of the present reaction, the solvent was evaporated under reduced pressure and the residue was passed through flash column chromatography on silica gel to afford the desired products **6**.

Detection of Intermediate A. To a mixture of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (4.1 mg, 0.005 mmol, 2.5 mol %) and 1, 2-dichloroethane (2 mL) at room temperature were added benzimidates **1** (0.20 mmol). The reaction mixture was stirred at 80 °C for 20 min, and then a small amount was taken to perform the ESI-HRMS analysis. HRMS (ESI, TOF) calcd for $C_{19}H_{25}NO$ $[M + H]^+$: 386.0991, found: 386.0990.

*Ethyl 1-Ethoxy-3-methylisoquinoline-4-carboxylate (**3a**).* The compound was prepared from ethyl benzimidate **1a** (29.8 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate (37.4 mg, 0.24 mmol) following the general procedure. The product **3a** was obtained in 78% yield (40 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.45 (t, J = 7.2 Hz, 3H), 1.49 (t, J = 7.0 Hz, 3H), 2.60 (s, 1H), 4.49 (q, J = 7.2 Hz, 2H), 4.59 (q, J = 7.1 Hz, 2H), 7.45–7.49 (m, 1H), 7.45–7.49 (m, 1H), 7.63–7.67 (m, 1H), 7.88 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.5, 14.6, 23.4, 61.3, 62.4, 117.1, 117.7, 123.7, 124.4, 126.0, 131.2, 135.9, 149.0, 160.5, 169.2; HRMS (EI, TOF) calcd for $C_{15}H_{17}NO_3^+$ $[M]^+$: 259.1208, found: 259.1206.

*Ethyl 1-Methoxy-3-methylisoquinoline-4-carboxylate (**3b**).* The compound was prepared from methyl benzimidate (27.0 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3b** was obtained in 75% yield (37 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz,

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$CDCl_3$, 25 °C) δ 1.45 (t, J = 7.2 Hz, 3H), 2.62 (s, 3H), 4.13 (s, 3H), 4.49 (q, J = 7.2 Hz, 2H), 7.46−7.50 (m, 1H), 7.63−7.67 (m, 1H), 7.88 (d, J = 8.5 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.5, 23.4, 54.0, 61.4, 117.4, 117.6, 123.7, 124.3, 126.1, 131.3, 135.8, 148.9, 160.7, 169.1; HRMS (EI, TOF) calcd for $C_{14}H_{15}NO_3^+$ $[M]^+$: 245.1052, found: 245.1051.

*Ethyl 1-Isopropoxy-3-methylisoquinoline-4-carboxylate (**3c**).* The compound was prepared from isopropyl benzimidate (32.6 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3c** was obtained in 77% yield (42 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.43−1.46 (m, 9H), 2.60 (s, 3H), 4.48 (q, J = 7.2 Hz, 2H), 5.58−6.67 (m, 1H), 7.43−7.47 (m, 1H), 7.61−7.66 (m, 1H), 7.87 (d, J = 8.5 Hz, 1H), 8.22−8.24 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.5, 22.1, 23.5, 61.3, 68.9, 116.7, 118.0, 123.6, 124.5, 125.9, 131.1, 135.9, 149.1, 160.0, 169.2; HRMS (EI, TOF) calcd for $C_{16}H_{19}NO_3^+$ $[M]^+$: 273.1365, found: 273.1366.

*Ethyl 1-Ethoxy-6-fluoro-3-methylisoquinoline-4-carboxylate (**3d**).* The compound was prepared from ethyl 4-fluorobenzimidate (33.4 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3d** was obtained in 72% yield (40 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 54−55 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.45 (t, J = 7.1 Hz, 3H), 1.48 (t, J = 7.1 Hz, 3H), 2.61 (s, 3H), 4.49 (q, J = 7.2 Hz, 2H), 4.57 (q, J = 7.1 Hz, 2H), 7.17−7.22 (m, 1H), 7.59 (dd, J_1 = 2.4 Hz, J_2 = 11.0 Hz, 1H), 8.24 (dd, J_1 = 6.1 Hz, J_2 = 9.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.5, 14.6, 23.8, 61.4, 62.5, 108.4 (d, J = 23.4 Hz), 114.6, 115.7 (d, J = 24.8 Hz), 116.5 (d, J = 4.5 Hz), 127.4 (d, J = 10.1 Hz), 137.9 (d, J = 10.9 Hz), 151.3, 160.3, 164.1 (d, J = 250.7 Hz), 168.7; ^{19}F NMR (376.5 MHz, $CDCl_3$, 25 °C): δ = −106.6; HRMS (ESI, TOF) calcd for $C_{15}H_{17}NO_3F$, $[M + H]^+$: 278.1192, found: 278.1189.

*Ethyl 6-Chloro-1-ethoxy-3-methylisoquinoline-4-carboxylate (**3e**).* The compound was prepared from ethyl 4-chlorobenzimidate (36.7 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3e** was obtained in 87% yield (51 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 83−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.45 (t, J = 7.2 Hz, 3H), 1.47 (t, J = 7.1 Hz, 3H), 2.60 (s, 3H), 4.49 (q, J = 7.2 Hz, 2H), 4.57 (q, J = 7.1 Hz, 2H), 7.49 (dd, J_1 = 1.9 Hz, J_2 = 8.8 Hz, 1H), 7.92 (d, J = 1.8 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.5, 14.6, 23.7, 61.5, 62.6, 115.9, 116.1, 123.1, 126.1, 126.8, 136.9, 137.8, 151.1, 160.4, 168.5; HRMS (ESI, TOF) calcd for $C_{15}H_{17}NO_3Cl$, $[M + H]^+$: 294.0897, found: 294.0898.

*Ethyl 6-Bromo-1-ethoxy-3-methylisoquinoline-4-carboxylate (**3f**).* The compound was prepared from ethyl 4-bromobenzimidate (45.6 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3f** was obtained in 95% yield (64 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 73−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.45 (t, J = 7.2 Hz, 3H), 1.47 (t, J = 7.1 Hz, 3H), 2.60 (s, 3H), 4.49 (q, J = 7.1 Hz, 2H), 4.56 (q, J = 7.1 Hz, 2H), 7.53 (dd, J_1 = 1.8 Hz, J_2 = 8.8 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 8.10 (d, J = 1.7 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.4, 14.6, 23.7, 61.5, 62.6, 115.9, 116.1, 126.1, 126.3, 126.5, 129.4, 137.1, 151.0, 160.4, 168.5; HRMS (ESI, TOF) calcd for $C_{15}H_{17}NO_3Br$, $[M + H]^+$: 338.0392, found: 338.0386.

*Ethyl 1-Ethoxy-3-methyl-6-(trifluoromethyl)isoquinoline-4-carboxylate (**3g**).* The compound was prepared from ethyl 4-(trifluoromethyl)benzimidate (43.5 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3g** was obtained in 73% yield (48 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 74−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.46 (t, J = 7.2 Hz, 3H), 1.50 (t, J = 7.1 Hz, 3H), 2.65 (s, 3H), 4.52 (q, J = 7.1 Hz, 2H), 4.61 (q, J = 7.1 Hz, 2H), 7.64 (dd, J_1 = 1.6 Hz, J_2 = 8.7 Hz, 1H), 8.26 (s, 1H), 8.35 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.4, 14.6, 23.7, 61.6, 62.9, 117.0, 119.0, 121.7 (q, J = 4.4 Hz), 121.8 (q, J = 3.1 Hz), 124.0 (q, J = 272.8 Hz), 125.7, 132.7 (q, J = 32.2 Hz), 135.4, 151.5, 160.3, 168.3; ^{19}F NMR (376.5 MHz, $CDCl_3$, 25 °C): δ = −63.0; HRMS (ESI, TOF) calcd for $C_{16}H_{17}NO_3F_3$, $[M + H]^+$: 328.1161, found: 328.1159.

*Ethyl 1,6-Diethoxy-3-methylisoquinoline-4-carboxylate (**3h**).* The compound was prepared from ethyl 4-ethoxybenzimidate (38.6 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3h** was obtained in 87% yield (53 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 59−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.42−1.48 (m, 9H), 2.59 (s, 3H), 4.12 (q, J = 7.0 Hz, 2H), 4.48 (q, J = 7.1 Hz, 2H), 4.55 (q, J = 7.1 Hz, 2H), 7.06 (dd, J_1 = 2.4 Hz, J_2 = 9.0 Hz, 1H), 7.24 (d, J = 2.3 Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.5, 14.7, 14.8, 23.7, 61.1, 62.2, 63.6, 103.6, 112.4, 116.3, 117.9, 126.1, 138.0, 150.3, 160.4, 161.2, 169.3; HRMS (ESI, TOF) calcd for $C_{17}H_{22}NO_4$, $[M + H]^+$: 304.1549, found: 304.1542.

*Ethyl 1-Ethoxy-3-methyl-6-phenoxyisoquinoline-4-carboxylate (**3i**).* The compound was prepared from ethyl [1,1′-biphenyl]-4-carbimidate (48.2 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3i** was obtained in 73% yield (51 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.26 (t, J = 7.1 Hz, 3H), 1.47 (t, J = 7.0 Hz, 3H), 2.58 (s, 3H), 4.33 (q, J = 7.1 Hz, 2H), 4.57 (q, J = 7.1 Hz, 2H), 7.08−7.10 (m, 2H), 7.16−7.19 (m, 2H), 7.32 (d, J = 2.3 Hz, 1H), 7.36−7.40 (m, 2H), 8.21 (d, J = 9.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.3, 14.6, 23.5, 61.2, 62.3, 109.6, 113.7, 116.5, 118.6, 120.2, 124.4, 126.7, 130.1, 137.7, 150.6, 155.9, 160.1, 160.4, 168.9; HRMS (ESI, TOF) calcd for $C_{21}H_{22}NO_4$, $[M + H]^+$: 352.1549, found: 352.1554.

*Ethyl 1-Ethoxy-8-fluoro-3-methylisoquinoline-4-carboxylate (**3j**).* The compound was prepared from ethyl 2-fluorobenzimidate (33.4 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3j** was obtained in 32% yield (17 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.44 (t, J = 7.1 Hz, 3H), 1.49 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 4.49 (q, J = 7.1 Hz, 2H), 4.59 (q, J = 7.0 Hz, 2H), 7.09−7.14 (m, 1H), 7.53−7.61 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.4, 14.6, 23.2, 61.5, 62.8, 108.1 (d, J = 12.2 Hz), 112.0 (d, J = 22.0 Hz), 116.8 (d, J = 2.9 Hz), 119.5 (d, J = 4.6 Hz), 131.6 (d, J = 9.2 Hz), 138.5, 149.6, 159.4 (d, J = 5.7 Hz), 159.9 (d, J = 260.8 Hz), 169.1; ^{19}F NMR (376.5 MHz, $CDCl_3$, 25 °C): δ = −107.9; HRMS (ESI, TOF) calcd for $C_{15}H_{17}NO_3F$, $[M + H]^+$: 278.1192, found: 278.1189.

*Ethyl 1-Ethoxy-7-fluoro-3-methylisoquinoline-4-carboxylate (**3k**) and Ethyl 1-Ethoxy-5-fluoro-3-methylisoquinoline-4-carboxylate (**3k′**).* The compounds were prepared from ethyl 3-fluorobenzimidate (33.4 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The products **3k** and **3k′** were obtained in 79% yield (44 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). The two compounds had the same R_f values, and they were obtained as an inseparable mixture with a ratio of 100:9 (**3k**:**3k′**, NMR ratio). The following ^{1}H NMR data are not complete due to overlapping of some of the peaks. ^{1}H NMR for **3k** (400 MHz, $CDCl_3$, 25 °C): δ 1.41 (t, J = 7.2 Hz, 3H), 1.48 (t, J = 7.1 Hz, 3H), 2.52 (s, 3H), 4.46 (q, J = 7.1 Hz, 2H), 4.57 (q, J = 7.1 Hz, 2H), 7.29−7.34 (m, 1H), 7.37−7.43 (m, 1H), 8.03 (dd, J_1 = 0.9 Hz J_2 = 8.2 Hz); ^{1}H NMR for **3k′** (400 MHz, $CDCl_3$, 25 °C): δ 1.41 (t, J = 7.2 Hz, 3H), 1.48 (t, J = 7.1 Hz, 3H), 2.60 (s, 3H), 4.46 (q, J = 7.1 Hz, 2H), 4.57 (q, J = 7.1 Hz, 2H), 7.37−7.43 (m, 1H), 7.84 (dd, J_1 = 2.8 Hz, J_2 = 9.2 Hz), 7.92 (dd, J_1 = 5.2 Hz J_2 = 9.2 Hz). The following ^{13}C NMR data show all the peaks of compounds **3k** and **3k′**. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 14.2, 14.4, 14.6, 22.1, 23.4, 61.4, 61.8, 62.6, 108.4 (d, J = 22.1 Hz), 113.7, 115.8 (d, J = 20.6 Hz), 119.3 (d, J = 4.8 Hz), 120.5 (d, J = 4.2 Hz), 121.0 (d, J = 24.6 Hz), 125.6 (d, J = 14.9 Hz), 126.1 (d, J = 8.1 Hz), 126.5, 147.5, 156.7 (d, J = 251.5 Hz), 159.7 (d, J = 4.2 Hz),

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168.9, 169.9; ^{19}F NMR for **3k** (376.5 MHz, $CDCl_3$, 25 °C): δ = −116.2; ^{19}F NMR for **3k′** (376.5 MHz, $CDCl_3$, 25 °C): δ = −113.6; HRMS (ESI, TOF) calcd for $C_{15}H_{17}FNO_3$, $[M + H]^+$: 278.1192, found: 278.1191.

*Ethyl 1-Ethoxy-3,7-dimethylisoquinoline-4-carboxylate (**3l**).* The compound was prepared from ethyl 3-methylbenzimidate (32.6 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3l** was obtained in 60% yield (33 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.44 (t, J = 7.1 Hz, 3H), 1.49 (t, J = 7.1 Hz, 3H), 2.49 (s, 3H), 2.59 (s, 3H), 4.48 (q, J = 7.1 Hz, 2H), 4.57 (q, J = 7.1 Hz, 2H), 7.48 (dd, J_1 = 1.6 Hz J_2 = 8.6 Hz, 1H), 7.79 (d, J = 8.6 Hz, 1H), 8.01 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.5, 14.7, 21.7, 23.3, 61.2, 62.3, 116.9, 117.8, 123.3, 123.6, 133.2, 134.0, 135.9, 148.0, 160.1, 169.3; HRMS (ESI, TOF) calcd for $C_{16}H_{20}NO_3$, $[M + H]^+$: 274.1443, found: 274.1439.

*Ethyl 1-Ethoxy-3,5,7-trimethylisoquinoline-4-carboxylate (**3m**).* The compound was prepared from ethyl 3,5-dimethylbenzimidate (35.4 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3m** was obtained in 70% yield (38 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.42 (t, J = 7.2 Hz, 3H), 1.48 (t, J = 7.1 Hz, 3H), 2.44 (s, 3H), 2.49 (s, 3H), 2.52 (s, 3H), 4.43 (q, J = 7.2 Hz, 2H), 4.54 (q, J = 7.1 Hz, 2H), 7.28 (s, 1H), 7.94 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.2, 14.7, 20.8, 21.5, 22.4, 61.6, 62.2, 117.4, 118.5, 121.8, 132.0, 132.3, 135.6, 135.7, 145.9, 160.3, 172.1; HRMS (ESI, TOF) calcd for $C_{17}H_{22}NO_3$, $[M + H]^+$: 288.1600, found: 288.1592.

*Ethyl 1-Ethoxy-5,7-difluoro-3-methylisoquinoline-4-carboxylate (**3n**).* The compound was prepared from ethyl 3,5-difluorobenzimidate (37.0 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3n** was obtained in 73% yield (43 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 60−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.41 (t, J = 7.1 Hz, 3H), 1.48 (t, J = 7.1 Hz, 3H), 2.50 (s, 3H), 4.45 (q, J = 7.2 Hz, 2H), 4.56 (q, J = 7.1 Hz, 2H), 7.12−7.17 (m, 1H), 7.67−7.70 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.2, 14.5, 22.0, 61.9, 62.9, 105.0 (dd, J_1 = 4.5 Hz, J_2 = 22.1 Hz), 107.0 (dd, J_1 = 24.4 Hz, J_2 = 28.5 Hz), 113.6, 119.1 (dd, J_1 = 6.4 Hz, J_2 = 9.8 Hz), 122.7 (dd, J_1 = 2.0 Hz, J_2 = 14.7 Hz), 146.9 (d, J = 2.7 Hz), 157.2 (dd, J_1 = 12.1 Hz, J_2 = 242.0 Hz), 159.2 (dd, J_1 = 4.8 Hz, J_2 = 4.8 Hz), 159.7 (dd, J_1 = 11.8 Hz, J_2 = 234.9 Hz), 169.5; ^{19}F NMR (376.5 MHz, $CDCl_3$, 25 °C): δ −111.6 (d, J = 6.9 Hz), −110.7 (d, J = 6.9 Hz); HRMS (EI, TOF) calcd for $C_{15}H_{15}NO_3F_2^+$ $[M]^+$: 295.1020, found: 295.1019.

*Ethyl 1-Ethoxy-3,6,7-trimethylisoquinoline-4-carboxylate (**3o**).* The compound was prepared from ethyl 3,4-dimethylbenzimidate (35.4 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3o** was obtained in 84% yield (48 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 84−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.44 (t, J = 7.2 Hz, 3H), 1.48 (t, J = 7.0 Hz, 3H), 2.397 (s, 3H), 2.401 (s, 3H), 2.57 (s, 3H), 4.49 (q, J = 7.2 Hz, 2H), 4.56 (q, J = 7.1 Hz, 2H), 7.62 (s, 1H), 7.96 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.5, 14.7, 20.2, 20.9, 23.4, 61.1, 62.1, 116.3, 116.5, 123.5, 123.8, 134.6, 135.7, 141.4, 147.9, 160.0, 169.4; HRMS (ESI, TOF) calcd for $C_{17}H_{22}NO_3$, $[M + H]^+$: 288.1600, found: 288.1596.

*Ethyl 1-Ethoxy-6,7-dimethoxy-3-methylisoquinoline-4-carboxylate (**3p**) and Ethyl 1-Ethoxy-5,6-dimethoxy-3-methylisoquinoline-4-carboxylate (**3p′**).* The compounds were prepared from ethyl 3-fluorobenzimidate (41.8 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The products **3p** and **3p′** were obtained in 69% yield (44 mg) and 19% yield (12 mg) respectively as white solids after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). For product **3p**, Mp: 109−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.46 (t, J = 7.1 Hz, 3H), 1.49 (t, J = 7.0 Hz, 3H), 2.60 (s, 3H), 3.99 (s, 3H), 4.01 (s, 3H), 4.49 (q, J = 7.1 Hz, 2H), 4.58 (q, J = 7.1 Hz, 2H), 7.34 (s, 1H), 7.48 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.5, 14.8, 23.7, 56.0, 56.1, 61.1, 62.2, 102.9, 103.3, 112.4, 115.8, 132.5, 148.5, 149.0, 153.2, 159.4, 169.4; HRMS (ESI, TOF) calcd for $C_{17}H_{22}NO_5$, $[M + H]^+$: 320.1498, found: 320.1486. For product **3p′**, Mp: 85.2−87.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.40 (t, J = 7.2 Hz, 3H), 1.46 (t, J = 7.0 Hz, 3H), 2.47 (s, 3H), 3.82 (s, 3H), 3.99 (s, 3H), 4.34−4.50 (m, 2H), 4.54 (q, J = 7.1 Hz, 2H), 7.20 (d, J = 9.1 Hz, 1H), 8.00 (d, J = 9.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.3, 14.7, 22.0, 56.4, 61.26, 61.31, 62.2, 113.3, 113.5, 115.0, 121.3, 141.0, 146.7, 153.0, 159.9, 171.1; HRMS (ESI, TOF) calcd for $C_{17}H_{22}NO_5$, $[M + H]^+$: 320.1498, found: 320.1502.

*Ethyl 1-Ethoxy-6,7-difluoro-3-methylisoquinoline-4-carboxylate (**3q**) and Ethyl 1-Ethoxy-5,6-difluoro-3-methylisoquinoline-4-carboxylate (**3q′**).* The compounds were prepared from ethyl 3,4-difluorobenzimidate (37.0 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The products **3q** and **3q′** were obtained in 85% yield (50 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). The two compounds had the same R_f values, and they were obtained as an inseparable mixture with a ratio of 100:7 (**3q**:**3q′**, NMR ratio). The following ^{1}H NMR data are not complete due to overlapping of some of the peaks. ^{1}H NMR for **3q** (400 MHz, $CDCl_3$, 25 °C): δ 1.42 (t, J = 7.2 Hz, 3H), 1.47 (t, J = 7.1 Hz, 3H), 2.52 (s, 3H), 4.46 (q, J = 7.2 Hz, 2H), 4.56 (q, J = 7.1 Hz, 2H), 7.25−7.32 (m, 1H), 8.00−8.04 (m, 1H); ^{1}H NMR for **3q′** (400 MHz, $CDCl_3$, 25 °C): δ 1.42 (t, J = 7.2 Hz, 3H), 1.47 (t, J = 7.1 Hz, 3H), 2.61 (s, 3H), 4.46 (q, J = 7.2 Hz, 2H), 4.56 (q, J = 7.1 Hz, 2H), 7.78 (dd, J_1 = 7.6 Hz, J_2 = 12.2 Hz, 1H), 7.95 (dd, J_1 = 7.5 Hz, J_2 = 10.5 Hz, 1H). The following ^{13}C NMR data show all the peaks of compounds **3q** and **3q′**. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 14.2, 14.4, 14.5, 22.2, 23.8, 61.5, 62.0, 62.8, 111.3 (d, J = 19.5 Hz), 113.6 (d, J = 5.4 Hz), 115.0 (J = 1.9 Hz), 116.2, 116.4, 121.7 (dd, J_1 = 5.1 Hz, J_2 = 8.1 Hz), 127.1 (dd, J_1 = 2.5 Hz, J_2 = 11.3 Hz), 143.6 (J_1 = 13.5 Hz, J_2 = 252.2 Hz), 149.0, 150.8 (J_1 = 12.2 Hz, J_2 = 252.1 Hz), 159.5 (d, J = 3.4 Hz), 168.5, 169.4; ^{19}F NMR for **3q** (376.5 MHz, $CDCl_3$, 25 °C): δ = −143.4 (d, J = 18.4 Hz), −133.3 (d, J = 18.6 Hz); ^{19}F NMR for **3q′** (376.5 MHz, $CDCl_3$, 25 °C): δ = −136.4 (d, J = 20.7 Hz), −129.6 (d, J = 21.0 Hz); HRMS (ESI, TOF) calcd for $C_{15}H_{16}NO_3F_2$, $[M + H]^+$: 296.1098, found: 296.1087.

*Ethyl 6-Ethoxy-8-methyl-[1,3]dioxolo[4,5-f]isoquinoline-9-carboxylate (**3r**) and Ethyl 5-Ethoxy-7-methyl-[1,3]dioxolo[4,5-g]isoquinoline-8-carboxylate (**3r′**).* The compound was prepared from ethyl benzo[*d*][1,3]dioxole-5-carbimidate (38.6 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The products **3r** and **3r′** were obtained in 69% yield (42 mg) and 10% yield (6 mg) respectively as white solids after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). For product **3r**, Mp: 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.39 (t, J = 7.2 Hz, 3H), 1.46 (t, J = 7.1 Hz, 3H), 2.49 (s, 3H), 4.42 (q, J = 7.2 Hz, 2H), 4.54 (q, J = 7.1 Hz, 2H), 6.12 (s, 1H), 7.18 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.3, 14.6, 22.2, 61.6, 62.4, 102.1, 109.7, 113.0, 113.9, 119.7, 121.1, 139.5, 147.5, 148.3, 160.1, 169.6; HRMS (EI, TOF) calcd for $C_{16}H_{17}NO_5$, $[M + H]^+$: 303.1107, found: 303.1108. For product **3r′**, Mp: 106.7−109.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.44 (t, J = 7.2 Hz, 3H), 1.46 (t, J = 7.1 Hz, 3H), 2.55 (s, 3H), 4.47 (q, J = 7.1 Hz, 2H), 4.53 (q, J = 7.1 Hz, 2H), 6.06 (s, 2H), 7.24 (s, 1H), 7.51 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.5, 14.7, 23.4, 61.3, 62.2, 101.1, 101.2, 101.7, 113.7, 134.0, 147.3, 148.2, 151.7, 159.7, 169.4; HRMS (EI, TOF) calcd for $C_{16}H_{17}NO_5$, $[M + H]^+$: 303.1107, found: 303.1108.

*Ethyl 1-Ethoxy-3-methylbenzo[g]isoquinoline-4-carboxylate (**3s**) and Ethyl 4-Ethoxy-2-methylbenzo[f]isoquinoline-1-carboxylate (**3s′**).* The compounds were prepared from ethyl 2-naphthimidate (39.8 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The products **3s** and **3s′** were obtained in 94% yield (58 mg) as a light yellow solid after column chromatography (eluent = petroleum ether/ethyl acetate

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100:3 v/v). The two compounds had the same R_f values, and they were obtained as an inseparable mixture with a ratio of 5:1 (**3s**:**3s**′, NMR ratio). The following ^{1}H NMR data are not complete due to overlapping of some of the peaks. ^{1}H NMR for **3s** (400 MHz, $CDCl_3$, 25 °C): δ 1.48 (t, J = 7.2 Hz, 3H), 1.54 (t, J = 7.1 Hz, 3H), 2.63 (s, 3H), 4.56 (q, J = 7.2 Hz, 2H), 4.64 (q, J = 7.1 Hz, 2H), 7.43−7.47 (m, 1H), 7.49−7.53 (m, 1H), 7.94 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 8.39 (s, 1H), 8.83 (s, 1H); ^{1}H NMR for **3s**′ (400 MHz, $CDCl_3$, 25 °C): δ 1.38 (t, J = 7.2 Hz, 3H), 1.50 (t, J = 7.0 Hz, 3H), 2.63 (s, 3H), 4.52−4.61 (m, 4H), 7.51−7.56 (m, 1H), 7.59−7.63 (m, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.86−7.88 (m, 1H), 8.16 (d, J = 8.9 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H). The following ^{13}C NMR data show all the peaks of compounds **3s** and **3s**′. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 14.1, 14.5, 14.6, 14.7, 22.8, 23.6, 61.3, 61.9, 62.6, 1 15.4, 116.2, 117.1, 117.8, 121.1, 122.2, 124.6, 125.6, 125.8, 126.3, 127.5, 127.6, 128.1, 129.0, 131.3, 131.9, 134.0, 134.7, 134.9, 147.8, 149.2, 160.3, 160.9, 169.4, 172.3; HRMS (ESI, TOF) calcd for $C_{19}H_{20}NO_3$, $[M + H]^+$: 310.1143, found: 310.1145.

*Ethyl 7-Ethoxy-5-methylthieno[2,3-c]pyridine-4-carboxylate (**3t**).* The compound was prepared from ethyl thiophene-2-carbimidate (31.0 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate **2a** (37.4 mg, 0.24 mmol) following the general procedure. The product **3t** was obtained in 79% yield (42 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 62−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.45 (t, J = 7.2 Hz, 3H), 1.47 (t, J = 7.1 Hz, 3H), 2.76 (s, 3H), 4.45 (q, J = 7.2 Hz, 2H), 4.61 (q, J = 7.1 Hz, 2H), 7.64 (d, J = 5.4 Hz, 1H), 7.76 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.2, 44.8, 63.4, 127.5, 127.9, 128.3, 128.5, 128.7, 131.4, 138.5, 161.8, 162.1; HRMS (EI, TOF) calcd for $C_{13}H_{15}NO_3S^+$ $[M]^+$: 265.0773, found: 265.0772.

*Methyl 1-Ethoxy-3-methylisoquinoline-4-carboxylate (**4a**).* The compound was prepared from ethyl benzimidate **1a** (29.8 mg, 0.20 mmol) and methyl 2-diazo-3-oxobutanoate (34.1 mg, 0.24 mmol) following the general procedure. The product **4a** was obtained in 73% yield (36 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.49 (t, J = 7.1 Hz, 3H), 2.59 (s, 3H), 4.01 (s, 3H), 4.59 (q, J = 7.1 Hz, 2H), 7.46−7.50 (m, 1H), 7.63−7.67 (m, 1H), 7.86 (d, J = 8.5 Hz, 1H), 8.25 (dd, J_1 = 0.4 Hz, J_2 = 8.3 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.7, 23.6, 52.3, 62.4, 116.8, 117.7, 123.8, 124.4, 126.1, 131.3, 135.9, 149.4, 160.6, 169.7; HRMS (EI, TOF) calcd for $C_{14}H_{15}NO_3^+$ $[M]^+$: 245.1052, found: 245.1051.

*Isopropyl 1-Ethoxy-3-methylisoquinoline-4-carboxylate (**4b**).* The compound was prepared from ethyl benzimidate **1a** (29.8 mg, 0.20 mmol) and isopropyl 2-diazo-3-oxobutanoate (40.8 mg, 0.24 mmol) following the general procedure. The product **4b** was obtained in 73% yield (40 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.43 (s, 3H), 1.44 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H), 2.60 (s, 1H), 4.58 (q, J = 7.1 Hz, 2H), 5.36−5.45 (m, 1H), 7.45−7.49 (m, 1H), 7.62−7.67 (m, 1H), 7.86 (d, J = 8.4 Hz, 1H), 8.24 (dd, J_1 = 0.4 Hz, J_2 = 8.3 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.6, 22.1, 23.3, 62.3, 69.0, 117.5, 117.7, 123.6, 124.4, 126.0, 131.2, 135.8, 148.5, 160.4, 168.7; HRMS (ESI, TOF) calcd for $C_{16}H_{20}NO_3$, $[M + H]^+$: 274.1443, found: 274.1440.

*tert-Butyl 1-Ethoxy-3-methylisoquinoline-4-carboxylate (**4c**).* The compound was prepared from ethyl benzimidate **1a** (29.8 mg, 0.20 mmol) and *tert*-butyl 2-diazo-3-oxobutanoate (44.2 mg, 0.24 mmol) following the general procedure. The product **4c** was obtained in 70% yield (40 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.43 (s, 3H), 1.44 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H), 1.67 (s, 9H), 2.60 (s, 1H), 4.57 (q, J = 7.1 Hz, 2H), 7.44−7.48 (m, 1H), 7.62−7.66 (m, 1H), 7.85 (d, J = 8.5 Hz, 1H), 8.22−8.24 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.7, 23.1, 28.5, 62.5, 82.1 117.7, 118.7, 123.5, 124.3, 125.9, 131.1, 135.7, 147.7, 160.1, 168.6; HRMS (ESI, TOF) calcd for $C_{17}H_{22}NO_3$, $[M + H]^+$: 288.1600, found: 288.1601.

*Benzyl 1-Ethoxy-3-methylisoquinoline-4-carboxylate (**4d**).* The compound was prepared from ethyl benzimidate **1a** (29.8 mg, 0.20 mmol) and benzyl 2-diazo-3-oxobutanoate (52.4 mg, 0.24 mmol) following the general procedure. The product **4d** was obtained in 70% yield (45 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.47 (t, J = 7.1 Hz, 3H), 2.56 (s, 3H), 4.57 (q, J = 7.1 Hz, 2H), 5.46 (s, 2H), 7.31−7.41 (m, 3H), 7.43−7.49 (m, 3H), 7.58−7.62 (m, 1H), 7.84 (d, J = 8.4 Hz, 1H), 8.23 (dd, J_1 = 0.5 Hz, J_2 = 8.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.6, 23.5, 62.4, 67.2, 116.7, 117.6, 123.7, 124.3, 126.0, 128.5, 128.7, 128.8, 131.2, 135.8, 135.9, 149.3, 160.5, 169.0; HRMS (ESI, TOF) calcd for $C_{20}H_{20}NO_3$, $[M + H]^+$: 322.1443, found: 322.1435.

*Allyl 1-Ethoxy-3-methylisoquinoline-4-carboxylate (**4e**).* The compound was prepared from ethyl benzimidate **1a** (29.8 mg, 0.20 mmol) and allyl 2-diazo-3-oxobutanoate (40.3 mg, 0.24 mmol) following the general procedure. The product **4e** was obtained in 76% yield (41 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.49 (t, J = 7.1 Hz, 3H), 2.61 (s, 3H), 4.58 (q, J = 7.1 Hz, 2H), 4.93 (td, J_1 = 1.2 Hz, J_2= 7.1 Hz, 1H), 5.31−5.34 (m, 1H), 5.43−5.48 (m, 1H), 6.04−6.14 (m, 1H), 7.45−7.49 (m, 1H), 7.62−7.67 (m, 1H), 7.89 (d, J = 8.5 Hz, 1H), 8.24 (dd, J_1 = 0.3 Hz, J_2 = 8.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.6, 23.5, 62.4, 66.0, 116.7, 117.7, 119.2, 123.7, 124.4, 126.0, 131.2, 132.0, 135.9, 149.4, 160.6, 168.8; HRMS (ESI, TOF) calcd for $C_{16}H_{18}NO_3$, $[M + H]^+$: 272.1287, found: 272.1276.

*Ethyl 1-Ethoxy-3-propylisoquinoline-4-carboxylate (**4f**).* The compound was prepared from ethyl benzimidate **1a** (29.8 mg, 0.20 mmol) and ethyl 2-diazo-3-oxohexanoate (44.2 mg, 0.24 mmol) following the general procedure. The product **4f** was obtained in 82% yield (47 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 0.98 (t, J = 7.4 Hz, 3H), 1.44 (t, J = 7.2 Hz, 3H), 1.48 (t, J = 7.1 Hz, 3H), 1.78−1.88 (m, 1H), 4.49 (q, J = 7.1 Hz, 2H), 4.59 (q, J = 7.1 Hz, 2H), 7.45−7.49 (m, 1H), 7.62−7.66 (m, 1H), 7.81 (d, J = 8.4 Hz, 1H), 8.24 (dd, J_1 = 0.4 Hz, J_2 = 8.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.2, 14.5, 14.7, 22.9, 38.4, 61.3, 62.3, 117.3, 117.7, 123.8, 124.3, 126.0, 131.1, 135.8, 152.2, 160.5, 169.3; HRMS (ESI, TOF) calcd for $C_{17}H_{22}NO_3$, $[M + H]^+$: 288.1600, found: 288.1607.

*Ethyl 3-(Chloromethyl)-1-ethoxyisoquinoline-4-carboxylate (**4g**).* The compound was prepared from ethyl benzimidate **1a** (29.8 mg, 0.20 mmol) and ethyl 4-chloro-2-diazo-3-oxobutanoate (44.2 mg, 0.24 mmol) following the general procedure. The product **4g** was obtained in 40% yield (23 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.48 (t, J = 7.2 Hz, 3H), 1.51 (t, J = 7.1 Hz, 3H), 4.54 (q, J = 7.2 Hz, 2H), 4.64 (q, J = 7.1 Hz, 2H), 4.82 (s, 2H), 7.55−7.59 (m, 1H), 7.69−7.73 (m, 1H), 8.02 (d, J = 8.5 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.4, 14.6, 46.0, 61.9, 62.9, 118.3, 119.0, 124.5, 124.7, 127.5, 131.6, 135.7, 147.1, 161.2, 167.8; HRMS (ESI, TOF) calcd for $C_{15}H_{17}NO_3Cl$, $[M + H]^+$: 294.0897, found: 294.0899.

*Methyl 1-Ethoxy-3-(methoxymethyl)isoquinoline-4-carboxylate (**4h**).* The compound was prepared from ethyl benzimidate **1a** (29.8 mg, 0.20 mmol) and methyl 2-diazo-4-methoxy-3-oxobutanoate (41.3 mg, 0.24 mmol) following the general procedure. The product **4h** was obtained in 73% yield (40 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.49 (t, J = 7.1 Hz, 3H), 1.51 (t, J = 7.1 Hz, 3H), 3.40 (s, 3H), 3.99 (s, 3H), 4.61 (q, J = 7.1 Hz, 2H), 4.69 (s, 2H), 7.51−7.55 (m, 1H), 7.66−7.70 (m, 1H), 7.89 (d, J = 8.5 Hz, 1H), 8.27 (dd, J_1 = 0.4 Hz, J_2 = 8.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.6, 52.4, 58.8, 62.6, 74.9, 117.5, 118.5, 123.9, 124.4, 126.9, 131.3, 135.6, 148.2, 160.7, 169.1; HRMS (ESI, TOF) calcd for $C_{15}H_{18}NO_4$, $[M + H]^+$: 276.1236, found: 276.1239.

*Methyl 1-Ethoxy-3-(methoxymethyl)isoquinoline-4-carboxylate (**4i**).* The compound was prepared from ethyl benzimidate **1a** (29.8 mg, 0.20 mmol) and ethyl 3-cyclopropyl-2-diazo-3-oxopropanoate (43.7 mg, 0.24 mmol) following the general procedure. The product **4i** was obtained in 86% yield (49 mg) as a colorless oil after column

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chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 0.93−0.97 (m, 2H), 1.19−1.22 (m, 2H), 1.43−1.47 (m, 2H), 1.44 (t, J = 7.2 Hz, 3H), 1.46 (t, J = 7.1 Hz, 3H), 2.25−2.31 (m, 1H), 4.47−4.54 (m, 1H), 7.40−7.44 (m, 1H), 7.60−7.64 (m, 1H), 7.81 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ ; HRMS (ESI, TOF) calcd for $C_{17}H_{20}NO_3$, $[M + H]^+$: 286.1443, found: 286.1442.

Ethyl 1-Ethoxy-3-phenylisoquinoline-4-carboxylate (4j). The compound was prepared from ethyl benzimidate **1a** (29.8 mg, 0.20 mmol) and ethyl 2-diazo-3-oxo-3-phenylpropanoate (52.4 mg, 0.24 mmol) following the general procedure. The product **4j** was obtained in 75% yield (48 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 70−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.01 (t, J = 7.1 Hz, 3H), 1.51 (t, J = 7.1 Hz, 3H), 4.19 (q, J = 7.2 Hz, 2H), 4.67 (q, J = 7.1 Hz, 2H), 7.38−7.46 (m, 3H), 7.53−7.57 (m, 1H), 7.69−7.73 (m, 3H), 8.01 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 13.8, 14.7, 61.5, 62.6, 117.5, 118.1, 124.1, 124.5, 126.9, 128.3, 128.5, 128.9, 131.5, 135.9, 140.7, 149.5, 160.5, 169.5; HRMS (ESI, TOF) calcd for $C_{20}H_{20}NO_3$, $[M + H]^+$: 322.1443, found: 322.1443.

1-(1-Ethoxy-3-methylisoquinolin-4-yl)ethan-1-one (4k). The compound was prepared from ethyl benzimidate **1a** (29.8 mg, 0.20 mmol) and 3-diazopentane-2,4-dione (30.3 mg, 0.24 mmol) following the general procedure. The product **4k** was obtained in 41% yield (19 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.49 (t, J = 7.1 Hz, 3H), 2.50 (s, 3H), 2.62 (s, 3H), 4.58 (q, J = 7.1 Hz, 2H), 7.46−7.51 (m, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.62−7.66 (m, 1H), 7.56 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.7, 22.7, 33.1, 62.3, 117.8, 123.0, 124.6, 125.9, 126.1, 131.2, 134.8, 144.8, 160.1, 206.6; HRMS (ESI, TOF) calcd for $C_{14}H_{16}NO_2$, $[M + H]^+$: 230.1181, found: 230.1178.

Ethyl 1-Ethoxy-3-phenylbenzo[g]isoquinoline-4-carboxylate (4l) and Ethyl 4-Ethoxy-2-phenylbenzo[f]isoquinoline-1-carboxylate (4l′). The compounds were prepared from ethyl 2-naphthimidate (39.8 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate (52.4 mg, 0.24 mmol) following the general procedure. The products **4l** and **4l′** were obtained in 91% yield (68 mg) as a light yellow solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). The two compounds had the same R_f values, and they were obtained as an inseparable mixture with a ratio of 20:3 (**4l**: **4l′**, NMR ratio). The following ^{1}H NMR data are not complete due to overlapping of some of the peaks. ^{1}H NMR for **4l** (400 MHz, $CDCl_3$, 25 °C): δ 1.03 (t, J = 7.2 Hz, 3H), 1.58 (t, J = 7.1 Hz, 3H), 4.25 (q, J = 7.1 Hz, 2H), 4.74 (q, J = 7.1 Hz, 2H), 7.39−7.58 (m, 5H), 7.77−7.79 (m, 2H), 8.00 (d, J = 8.3 Hz, 1H), 8.05 (d, J = 8.3 Hz, 1H), 8.55 (s, 1H), 8.92 (s, 1H); ^{1}H NMR for **4l′** (400 MHz, $CDCl_3$, 25 °C): δ 1.10 (t, J = 7.2 Hz, 3H), 1.51 (t, J = 7.1 Hz, 3H), 4.25 (q, J = 7.1 Hz, 2H), 4.64 (q, J = 7.1 Hz, 2H), 7.39−7.58 (m, 5H), 7.63−7.67 (m, 2H), 7.84 (d, J = 8.9 Hz, 1H), 7.91−7.93 (m, 1H), 8.25 (d, J = 8.9 Hz, 1H), 8.37 (d, J = 8.6 Hz, 1H). The following ^{13}C NMR data show all the peaks of compounds **4l** and **4l′**. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 13.7, 13.8, 14.7, 61.5, 61.9, 62.7, 62.8, 116.2, 116.8, 117.3, 118.4, 121.1, 122.8, 124.8, 125.7, 126.2, 126.5, 127.8, 127.9, 128.1, 128.48, 128.50, 128.6, 128.9, 129.1, 129.2, 131.8, 131.9, 134.0, 134.9, 135.0, 140.6, 140.8, 148.2, 150.7, 160.4, 161.1, 169.7, 171.7; HRMS (ESI, TOF) calcd for $C_{24}H_{22}NO_3$, $[M + H]^+$: 372.1600, found: 372.1602.

Ethyl 1-Ethoxy-3-hydroxyisoquinoline-4-carboxylate (4m). The compound was prepared from ethyl benzimidate **1a** (29.8 mg, 0.20 mmol) and diethyl 2-diazomalonate (44.7 mg, 0.24 mmol) following the general procedure. The product **4m** was obtained in 60% yield (31.3 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ1.51 (t, J = 7.1 Hz, 3H), 1.54 (t, J = 7.2 Hz, 3H), 4.56 (q, J = 7.1 Hz, 2H), 4.66 (q, J = 7.1 Hz, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.76−7.70 (m, 1H), 8.25 (d, J = 8.8 Hz, 1H), 8.69 (d, J = 8.2 Hz, 1H), 13.45 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.51, 14.52, 62.1, 63.7, 91.9, 116.3, 123.9, 124.6, 125.3, 132.7, 137.6, 165.0, 167.6, 172.6; HRMS (EI, TOF) calcd for $C_{14}H_{15}NO_4$, $[M]^+$: 261.1101, found: 261.1100.

1-Ethoxyisoquinolin-3-ol (6a). The compound was prepared from ethyl benzimidate (29.8 mg, 0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol) following the general procedure. The product **6a** was obtained in 66% yield (25 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 96−99 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 1.41 (t, J = 7.1 Hz, 3H), 4.47 (q, J = 7.0 Hz, 2H), 6.42 (s, 1H), 7.23−7.27 (m, 1H), 7.52−7.56 (m, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.99 (d, J = 8.3 Hz, 1H), 6.42 (s, 1H), 10.35 (s, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO, 25 °C) δ 14.7, 62.9, 92.8, 115.7, 123.4, 124.6, 125.2, 131.1, 141.6, 156.9, 160.6; HRMS (EI, TOF) calcd for $C_{11}H_{11}NO_2^+$ $[M]^+$: 189.0790, found: 189.0789.

1-Methoxyisoquinolin-3-ol (6b). The compound was prepared from methyl benzimidate (27.0 mg, 0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol) following the general procedure. The product **6b** was obtained in 69% yield (24 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 137−139 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 4.02 (s, 3H), 6.43 (s, 1H), 7.23−7.28 (m, 1H), 7.52−7.56 (m, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.99 (d, J = 8.3 Hz, 1H), 10.39 (s, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO, 25 °C) δ 53.7, 92.4, 113.9, 122.9, 123.6, 124.8, 130.7, 141.1, 158.3, 159.9; HRMS (ESI, TOF) calcd for $C_{10}H_{10}NO_2$, $[M + H]^+$: 176.0712, found: 176.0702.

1-Ethoxy-6-fluoroisoquinolin-3-ol (6c). The compound was prepared from ethyl 4-fluorobenzimidate (33.4 mg, 0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol) following the general procedure. The product **6c** was obtained in 82% yield (34 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 117−118 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 1.40 (t, J = 7.1 Hz, 3H), 4.46 (q, J = 7.0 Hz, 2H), 6.42 (s, 1H), 7.06−7.11 (m, 1H), 7.38 (dd, J_1 = 2.5 Hz, J_2 = 10.7 Hz, 1H), 8.03 (dd, J_1 = 6.0 Hz, J_2 = 9.1 Hz, 1H), 10.53 (s, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO, 25 °C) δ 14.4, 61.9, 92.3 (d, J = 4.6 Hz), 108.1 (d, J = 21.4 Hz), 111.2, 112.5 (d, J = 25.4 Hz), 127.2 (d, J = 10.4 Hz), 142.9 (d, J = 11.2 Hz), 159.4, 159.6, 163.4 (d, J = 247.7 Hz); ^{19}F NMR (376.5 MHz, d_6-DMSO, 25 °C): δ = −109.0; HRMS (ESI, TOF) calcd for $C_{11}H_{11}NO_2F$, $[M + H]^+$: 208.0774, found: 208.0771.

1-Ethoxy-6-chloroisoquinolin-3-ol (6d). The compound was prepared from ethyl 4-fluorobenzimidate (36.7 mg, 0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol) following the general procedure. The product **6d** was obtained in 81% yield (36 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 139−141 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 1.41 (t, J = 7.1 Hz, 3H), 4.46 (q, J = 7.1 Hz, 2H), 6.42 (s, 1H), 7.21 (dd, J_1 = 2.1 Hz, J_2 = 8.8 Hz, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.96 (d, J = 8.8 Hz, 1H), 10.58 (s, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO, 25 °C) δ 14.4, 62.0, 91.8, 112.3, 123.1, 123.4, 126.0, 125.7, 142.1, 159.4, 159.6; HRMS (ESI, TOF) calcd for $C_{11}H_{11}NO_2Cl$, $[M + H]^+$: 224.0478, found: 224.0471.

1-Ethoxy-6-bromoisoquinolin-3-ol (6e). The compound was prepared from ethyl 4-bromobenzimidate (45.6 mg, 0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol) following the general procedure. The product **6e** was obtained in 80% yield (43 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 140−142 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 1.40 (t, J = 7.0 Hz, 3H), 4.46 (q, J = 7.0 Hz, 2H), 6.41 (s, 1H), 7.33 (dd, J_1 = 2.8 Hz, J_2 = 8.4 Hz, 1H), 7.87−7.89 (m, 2H), 10.59 (s, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO, 25 °C) δ 14.4, 62.0, 91.6, 112.5, 124.9, 125.7, 126.0, 126.6, 142.4, 159.3, 159.7; HRMS (ESI, TOF) calcd for $C_{11}H_{11}NO_2Br$, $[M + H]^+$: 267.9973, found: 267.9977.

1-Ethoxy-6-(trifluoromethyl)isoquinolin-3-ol (6f). The compound was prepared from ethyl 4-(trifluoromethyl)benzimidate (43.4 mg, 0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol) following the general procedure. The product **6f** was obtained in 86% yield (44 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 108−109 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 1.43 (t, J = 7.0 Hz, 3H), 4.50 (q, J =

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7.0 Hz, 2H), 6.63 (s, 1H), 7.47 (dd, J_1 = 1.7 Hz, J_2 = 8.7 Hz, 1H), 8.10 (s, 1H), 8.16−8.19 (m, 1H), 10.76 (s, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO, 25 °C) δ 14.4, 62.2, 93.1, 115.1, 117.8 (q, J = 3.1 Hz), 122.5 (q, J = 4.4 Hz), 124.1 (q, J = 272.8 Hz), 125.5, 130.7 (q, J = 31.5 Hz), 140.4, 159.6; ^{19}F NMR (376.5 MHz, d_6-DMSO, 25 °C): δ = −61.7; HRMS (ESI, TOF) calcd for $C_{12}H_9NO_2F_3$, $[M + H]^+$: 256.0585, found: 256.0576.

*1,6-Diethoxyisoquinolin-3-ol (**6g**).* The compound was prepared from ethyl 4-ethoxybenzimidate (38.6 mg, 0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol) following the general procedure. The product **6g** was obtained in 90% yield (42 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 131−134 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 1.35 (t, J = 7.0 Hz, 3H), 1.39 (t, J = 7.0 Hz, 3H), 4.08 (q, J = 7.0 Hz, 2H), 4.43 (q, J = 7.0 Hz, 2H), 6.33 (s, 1H), 6.83 (dd, J_1 = 2.4 Hz, J_2 = 9.1 Hz, 1H), 6.97 (d, J = 2.4 Hz, 2H), 7.86 (q, J = 9.1 Hz, 2H), 10.22 (s, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO, 25 °C) δ 14.6, 61.6, 63.3, 92.2, 103.9, 109.0, 115.2, 125.5, 143.3, 158.9, 159.5, 160.3; HRMS (ESI, TOF) calcd for $C_{13}H_{16}NO_3$, $[M + H]^+$: 234.1130, found: 234.1129.

*1-Ethoxy-6-phenoxyisoquinolin-3-ol (**6h**).* The compound was prepared from ethyl 4-phenoxybenzimidate (48.2 mg, 0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol) following the general procedure. The product **6h** was obtained in 64% yield (36 mg) as a light yellow solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 121−123 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 1.40 (t, J = 7.0 Hz, 3H), 4.46 (q, J = 7.0 Hz, 2H), 6.31 (s, 1H), 6.4−6.99 (m, 2H), 7.10−7.12 (m, 2H), 7.21 (t, J = 7.4 Hz, 1H), 7.42−7.46 (m, 2H), 8.00 (d, J = 8.9 Hz, 1H), 10.36 (s, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO, 25 °C) δ 14.5, 61.7, 92.1, 109.7, 110.3, 115.6, 119.7, 124.3, 126.4, 130.2, 142.8, 155.5, 159.0, 159.1, 159.5; HRMS (ESI, TOF) calcd for $C_{17}H_{16}NO_3$, $[M + H]^+$: 282.1130, found: 282.1128.

*1-Ethoxy-8-fluoroisoquinolin-3-ol (**6i**).* The compound was prepared from ethyl 2-fluorobenzimidate (33.4 mg, 0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol) following the general procedure. The product **6i** was obtained in 51% yield (21 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 87−89 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 1.39 (t, J = 7.0 Hz, 3H), 4.46 (q, J = 7.0 Hz, 2H), 6.46 (d, J = 2.2 Hz, 1H), 6.95 (dd, J_1 = 7.6 Hz, J_2 = 12.3 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.45−7.50 (m, 1H), 10.59 (s, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO, 25 °C) δ 14.4, 62.0, 92.3 (d, J = 2.8 Hz), 104.2 (d, J = 12.4 Hz), 108.1 (d, J = 21.5 Hz), 120.9 (d, J = 4.3 Hz), 131.1 (d, J = 9.5 Hz), 144.0 (d, J = 2.8 Hz), 158.7 (d, J = 5.8 Hz), 158.8, 159.0 (d, J = 257.4 Hz); ^{19}F NMR (376.5 MHz, d_6-DMSO, 25 °C): δ = −109.7; HRMS (ESI, TOF) calcd for $C_{11}H_{11}NO_2F$, $[M + H]^+$: 208.0774, found: 208.0770.

*1-Ethoxy-7-fluoroisoquinolin-3-ol (**6j**).* The compound was prepared from ethyl 2-fluorobenzimidate (33.4 mg, 0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol) following the general procedure. The product **6j** was obtained in 68% yield (28 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 129−132 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 1.41 (t, J = 7.1 Hz, 3H), 4.48 (q, J = 7.1 Hz, 2H), 6.45 (d, J = 0.5 Hz, 1H), 7.19−7.24 (m, 1H), 7.37−7.42 (m, 1H), 7.82 (d, J = 8.4 Hz, 1H), 10.72 (s, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO, 25 °C) δ 14.4, 62.2, 84.8 (d, J = 4.3 Hz), 114.3 (d, J = 8.6 Hz), 115.5 (d, J = 6.4 Hz), 120.0 (d, J = 3.8 Hz), 122.3 (d, J = 7.5 Hz), 131.1 (d, J = 18.2 Hz), 156.2 (d, J = 247.1 Hz), 159.0, 159.6 (d, J = 4.3 Hz); ^{19}F NMR (376.5 MHz, d_6-DMSO, 25 °C): δ = −124.5; HRMS (ESI, TOF) calcd for $C_{11}H_{11}NO_2F$, $[M + H]^+$: 208.0774, found: 208.0765.

*1-Ethoxy-6,7-dimethylisoquinolin-3-ol (**6k**).* The compound was prepared from ethyl 3,4-dimethylbenzimidate (35.4 mg, 0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol) following the general procedure. The product **6k** was obtained in 85% yield (37 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 155−157 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 1.40 (t, J = 7.1 Hz, 3H), 4.44 (q, J = 7.1 Hz, 2H), 6.30 (s, 1H), 7.35 (s, 1H), 7.73 (s, 1H), 10.09 (s, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO, 25 °C) δ 14.6, 19.6, 20.0, 61.5, 91.5, 112.7, 122.9, 124.3, 132.0, 139.9, 140.5, 157.6, 158.9; HRMS (ESI, TOF) calcd for $C_{13}H_{16}NO_2$, $[M + H]^+$: 218.1181, found: 218.1184.

*1-Ethoxy-6,7-dimethoxyisoquinolin-3-ol (**6l**).* The compound was prepared from ethyl 3,4-dimethoxybenzimidate (35.4 mg, 0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol) following the general procedure. The product **6l** was obtained in 74% yield (37 mg) as a light yellow solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 158−160 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 1.40 (t, J = 7.0 Hz, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 4.45 (q, J = 7.0 Hz, 2H), 6.35 (s, 1H), 7.03 (s, 1H), 7.23 (s, 1H), 9.99 (s, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO, 25 °C) δ 14.6, 55.4, 55.5, 61.4, 92.1, 102.2, 104.0, 108.0, 137.7, 146.8, 153.1, 157.3, 158.1; HRMS (ESI, TOF) calcd for $C_{13}H_{16}NO_4$, $[M + H]^+$: 250.1079, found: 250.1071.

*7-Ethoxythieno[2,3-c]pyridin-5-ol (**6m**).* The compound was prepared from ethyl thiophene-2-carbimidate (31.0 mg, 0.20 mmol) and diazotized Meldum's acid (39.9 mg, 0.24 mmol) following the general procedure. The product **6m** was obtained in 85% yield (33 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 113−115 °C; ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 1.36 (t, J = 7.1 Hz, 3H), 4.45 (q, J = 7.1 Hz, 2H), 6.59 (s, J = 7.1 Hz, 1H), 7.28 (d, J = 5.3 Hz, 1H), 7.89 (d, J = 5.3 Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (100.6 MHz, d_6-DMSO, 25 °C) δ 14.6, 61.6, 93.1, 112.9, 123.0, 133.0, 150.8, 156.1, 159.6; HRMS (ESI, TOF) calcd for $C_9H_{10}NO_2S$, $[M + H]^+$: 196.0432, found: 196.0426.

Procedure for the Synthesis of the Undehydrated Product 3a′. To a mixture of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (4.1 mg, 0.005 mmol, 2.5 mol %) and 1,2-dichloroethane (2 mL) at room temperature were added benzimidates **1** (0.20 mmol) and diazo compounds **2** (0.24 mmol). The reaction mixture was stirred at 80 °C. After 3 min, the solvent was evaporated under reduced pressure and the residue passed through flash column chromatography on silica gel to afford the undehydrated product **3a′** (40.4 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.19 (t, J = 7.1 Hz, 2.64H), 1.31 (t, J = 7.2 Hz, 0.58H), 1.34 (s, 2.68H), 1.39 (t, J = 7.1 Hz, 3H), 1.44 (s, 0.61H), 3.78 (s, 0.79H), 3.91 (s, 0.88H), 4.07 (s, 0.18H), 4.10 (q, J = 7.1 Hz, 1.67H), 4.25−4.37 (m, 2.43H), 7.23 (d, J = 7.4 Hz, 0.18 H), 7.31−7.45 (m, 2.92H), 7.73−7.76 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 14.1, 14.3, 25.3, 28.0, 53.6, 54.9, 61.21, 61.25, 61.8, 86.0, 86.4, 124.1, 124.2, 125.4, 125.6, 127.1, 127.9, 128.5, 128.6, 131.4, 131.6, 135.4, 135.6, 157.6, 158.8, 170.9, 171.2. HRMS (EI, TOF) calcd for $C_{15}H_{19}NO_4^+$ $[M]^+$: 277.1314, found: 277.1313.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00264.

Copies of ^{1}H NMR and ^{13}C NMR spectra for products **3a−t**, **4a−m**, and **6a−m**; the ESI-HRMS spectra and the simulated HRMS spectra of intermediate **A** (PDF)

X-ray crystallographic data for **4l** (CIF)

X-ray crystallographic data for **6a** (CIF)

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Notes

The authors declare no competing financial interest.

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