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 methods1 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-C2,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 σ-halobenzenimines 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 benzamidate to react with ethyl diazoacetate 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 N2 as the only byproduct.
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_2CN)_3](SbF_6)_2 generated 3a in 67% yield (entry 4). Other catalysts, such as [RuCl_3(p-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-Zr 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 can inhibit the coupling/cyclization process, which was confirmed by the failure of ortho-Br-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-diazoo-3-oxobutanoates bearing a range of alkyl groups...
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 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. The regioselectivity occurring at the 3 and 1 positions of the naphthimidate ring (defined as 3/3′) is shown in the parentheses.

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

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<td>3/3′</td>
</tr>
<tr>
<td>F</td>
<td>73</td>
<td>3/3′</td>
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</tbody>
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Table 3. Rh(III)-Catalyzed Coupling/Cyclization Cascade Reaction of Ethyl Benzimidate 1a and Diazotized Meldrum’s Acid 5

<table>
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Table 4. Rh(III)-Catalyzed Coupling/Cyclization Cascade Reaction of Arylimidates 1 and Diazotized Meldrum’s Acid 5

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<th>Regioselectivity</th>
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<td>F</td>
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Note: For the reaction conditions and isolated yields, refer to the table captions.
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 benzimidazoles in good yields and excellent regioselectivities. The heterocyclic substrate ethyl thiophene-2-carboximide 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 rhodacylic intermediate A generated and was detected by ESI-HRMS analysis ([M + H]+ calced: 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−d5, 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 starts with cyclorhodation 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-ethoxysouqinolin-3-ol 6a and the active Cp*Rh(III) species with extrusion of acetone and CO2.

In summary, we have developed an oxidant-free, Rh(III)-catalyzed coupling/cyclization cascade reaction that directly synthesizes diverse isouquinolines and isouquinolin-3-ols via C−H activation. In this strategy, diazo compounds serve as efficient coupling/cyclization partners, leading the arylimidate to undergo intramolecular 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 dehydrogenation 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. Benzimidazoles14 and diazo compounds16,17 were prepared according to the literature methods. Chemical shifts (δ, ppm) in the 1H NMR spectra were recorded using TMS as the internal standard. Chemical shifts in 13C (1H) NMR spectra were internally referenced to CHCl3 (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(CH3CN)2][SbF6]2 (4.1 mg, 0.005 mmol, 2.5 mol%) and 1,2-dichloroethane (2 mL) at room temperature were added benzimidate 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(CH3CN)2][SbF6]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 solution 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(CH3CN)2][SbF6]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 Cp*RhH2NO [M + H]+: 386.0991, found: 386.0990.

**Ethyl 1-Ethoxy-3-methylisouquinoline-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). 1H NMR (400 MHz, CDCl3, 25 °C) δ 1.45 (t, J = 7.2 Hz, 3H), 1.49 (t, J = 7.0 Hz, 2H), 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), 7.89 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H). 13C NMR (100.6 MHz, CDCl3, 25 °C) δ 14.5, 14.6, 23.4, 61.3, 62.4, 111.7, 117.7, 123.7, 124.4, 126.0, 131.2, 135.9, 149.0, 160.5, 169.2; HRMS (EI, TOF) calcd for C15H17NO3 [M]+: 259.1208, found: 259.1206.

**Ethyl 1-Methoxy-3-methylisouquinoline-4-carboxylate (3b).** The compound was prepared from methyl benzimidate (27.6 mg, 0.20 mmol) and ethyl 2-diazo-3-oxobutanoate 6a (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). 1H NMR (400 MHz, CDCl3, 25 °C) δ 1.45 (t, J = 7.2 Hz, 3H), 1.49 (t, J = 7.0 Hz, 2H), 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), 7.89 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H). 13C NMR (100.6 MHz, CDCl3, 25 °C) δ 14.5, 14.6, 23.4, 61.3, 62.4, 111.7, 117.7, 123.7, 124.4, 126.0, 131.2, 135.9, 149.0, 160.5, 169.2; HRMS (EI, TOF) calcd for C15H17NO3 [M]+: 259.1208, found: 259.1206.
Ethyl 1-Ethoxy-6-fluoro-3-methylisoquinoline-4-carboxylate (3e). The compound was prepared from ethyl 4-ethoxybenzimidate (33.4 mg, 0.20 mmol) and ethyl 2-diazoo-3-oxobutanoate 2a (37.4 mg, 0.24 mmol) following the general procedure. The product 3e was obtained in 87% yield (53 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 54–55 °C; 1H NMR (400 MHz, CDCl3, 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), 7.30 (s, 1H), 7.99 (d, J = 7.1 Hz, 2H), 7.47 (d, J = 7.1 Hz, 2H), 1.80 (d, J = 3.6 Hz, 2H), 4.54 (q, J = 2.4 Hz, J = 9.1 Hz, 1H); 13C NMR (100.6 MHz, CDCl3, 25 °C) δ 14.5, 23.4, 61.5, 62.6, 108.4 (d, J = 23.8 Hz), 116.4, 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; 19F NMR (376.5 MHz, CDCl3, 25 °C) δ = −106.6; HRMS (ESI, TOF) calcd for C18H16NO3F [M + H]+: 325.1354, found: 325.1354.

Ethyl 1-Ethoxy-6-fluoro-3-methylisoquinoline-4-carboxylate (3h). The compound was prepared from ethyl 2-fluorobenzimidate (33.4 mg, 0.20 mmol) and ethyl 2-diazoo-3-oxobutanoate 2a (37.4 mg, 0.24 mmol) following the general procedure. The product 3h was obtained in 71% yield (51 mg) as a colorless solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 55–56 °C; 1H NMR (400 MHz, CDCl3, 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), 7.30 (s, 1H), 7.99 (d, J = 7.1 Hz, 2H), 7.47 (d, J = 7.1 Hz, 2H), 7.34 (m, 1H), 7.37–7.71 (m, 2H), 7.59 (d, J = 2.4 Hz, J = 11.0 Hz, 1H), 8.24 (dd, J = 6.1 Hz, J = 9.1 Hz, 1H); 13C NMR (100.6 MHz, CDCl3, 25 °C) δ 14.5, 14.6, 23.8, 61.4, 62.5, 108.4 (d, J = 23.8 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; 19F NMR (376.5 MHz, CDCl3, 25 °C) δ = −106.6; HRMS (ESI, TOF) calcd for C18H16NO3F [M + H]+: 325.1354, found: 325.1354.
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168.9, 169.9; ²³F NMR for 3k (376.5 MHz, CDCl₃, 25 °C): δ = −116.2; ²³F NMR for 3k (376.5 MHz, CDCl₃, 25 °C): δ = −113.6; HRMS (ESI, TOF) calc for C₁₇H₂₂NO₃ [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). ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.24 (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, J₁ = 1.9 Hz, J₂ = 6.8 Hz, 1H), 7.79 (d, J = 8.6 Hz, 1H), 8.01 (s, 1H); ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): δ 14.5, 14.7, 21.7, 23.3, 61.2, 62.3, 116.9, 117.8, 123.3, 123.6, 132.0, 153.9, 148.0, 160.1, 160.9, 169.3; HRMS (ESI, TOF) calc for C₁₇H₂₂NO₃ [M + H⁺]: 274.1443, found: 274.1439.

**Ethyl 1-Ethoxy-3,7-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).

1H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.24 (t, J = 7.2 Hz, 3H), 1.48 (t, J = 7.1 Hz, 3H), 2.44 (s, 3H), 2.59 (s, 3H), 4.45 (q, J = 7.2 Hz, 2H), 4.54 (q, J = 7.1 Hz, 2H), 7.28 (s, 1H), 7.94 (s, 1H); ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): δ 14.2, 14.7, 20.8, 21.5, 22.4, 61.6, 62.2, 117.4, 121.8, 131.8, 132.3, 135.6, 135.7, 145.9, 160.3, 172.1; HRMS (ESI, TOF) calc for C₁₅H₁₆NO₃ [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).

1H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.24, 14.4, 14.5, 22.5, 61.0, 62.0, 62.8, 111.3, 113.6 (d, J = 5.4 Hz), 110.9 (J = 1.9 Hz), 116.2, 116.4, 121.7 (dd, J = 5.1 Hz, J = 8.1 Hz), 127.1 (dd, J = 2.5 Hz, J = 11.3 Hz), 143.6 (J = 13.5 Hz, J = 25.2 Hz), 149.0, 150.8 (J = 12.2 Hz, J = 25.1 Hz), 159.5 (d, J = 3.4 Hz), 168.5, 169.4; ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): δ = −134.3 (d, J = 18.4 Hz), −133.3 (d, J = 18.6 Hz); ²³F NMR for 3q (376.5 MHz, CDCl₃, 25 °C): δ = −136.4 (d, J = 20.7 Hz), −129.6 (d, J = 21.0 Hz); HRMS (ESI, TOF) calc for C₁₅H₁₄F₂NO₃ [M + H⁺]: 296.1089, found: 296.1087.

**Ethyl 1-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 (3f).** The compound was prepared from ethyl benzo[d][1,3]dioxole-5-carboximide (38.6 mg, 0.22 mmol) and ethyl 2-diazo-3-oxobutanoate (2a (37.4 mg, 0.24 mmol) following the general procedure. The products 3r and 3f 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; ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.39 (t, J = 7.3 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); ¹³C NMR (100.6 MHz, CDCl₃, 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) calc for C₁₅H₁₄F₂NO₃ [M + H⁺]: 303.1107, found: 303.1108. For product 3f, Mp: 106–107.9 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.44 (t, J = 7.3 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); ¹¹C NMR (100.6 MHz, CDCl₃, 25 °C): δ 14.5, 14.7, 23.4, 61.3, 62.2, 101.1, 101.2, 113.7, 134.0, 147.3, 148.2, 151.7, 159.7, 169.4; HRMS (EI, TOF) calc for C₁₆H₁₃NO₄ [M + H⁺]: 313.1007, found: 313.1008.
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The compound was prepared from ethyl benzimidate 1a (29.8 mg, 0.20 mmol) and ethyl 2-diazoo-3-oxobutanoate (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). 1H NMR (400 MHz, CDCl₃, 25 °C) δ 1.49 (t, J = 7.1 Hz, 3H), 2.59 (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 = 0.4 Hz, J = 8.3 Hz, 1H); 13C NMR (100.6 MHz, CDCl₃, 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) calcld for C₆H₄NO₃⁺ [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 isopropyl 2-diazoo-3-oxobutanoate (40.8 mg, 0.24 mmol) following the general procedure. The product 4g was obtained in 73% yield (46 mg) as a colorless oil after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). 1H NMR (400 MHz, CDCl₃, 25 °C) δ 1.45 (t, J = 7.1 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), 7.64–7.67 (m, 1H), 7.75–7.59 (m, 1H), 7.69–7.73 (m, 1H), 8.02 (d, J = 8.5 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H); 13C NMR (100.6 MHz, CDCl₃, 25 °C) δ 14.4, 14.6, 60.9, 62.9, 118.3, 119.0, 124.5, 127.5, 131.6, 135.7, 147.1, 161.2, 167.8; HRMS (ESI, TOF) calcld for C₁₅H₁₈NO₄⁺[M + Na]+: 354.0897, found: 354.0895.

**Note**

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chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v).
\(^1H\) 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).
\(^13C\) NMR (100.6 MHz, CDCl\(_3\), 25 °C) δ 13.7, 13.8, 14.1, 14.2, 14.8, 15.0, 16.0, 161.4, 169.7, 171.7; HRMS (ESI, TOF) calc for C\(_9\)H\(_{12}\)NO\(_2\) [M + H]: 172.1046, found: 172.1048.

1-Ethoxy-3-ethynylbenzofuran-4-carboxylate (4l). The compound was prepared from ethyl benzimidate 1a (29.8 mg, 0.20 mmol) and ethyl diazoacetate (33.4 mg, 0.20 mmol) following the general procedure. The product 4l was obtained in 41% yield (84 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 112–115 °C; \(^1H\) NMR (400 MHz, d-DMF, 25 °C) δ 1.10 (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 = 7.2 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); \(^13C\) NMR (100.6 MHz, CDCl\(_3\), 25 °C) δ 13.7, 13.8, 14.1, 14.2, 14.8, 15.0, 161.4, 169.7, 171.7; HRMS (ESI, TOF) calc for C\(_9\)H\(_{12}\)NO\(_2\) [M + H]: 172.1046, found: 172.1048.

1-Methoxy-3-ethynylbenzofuran-4-carboxylate (4c). The compound was prepared from ethyl benzimidate 1a (29.8 mg, 0.20 mmol) and ethyl diazoacetate (33.4 mg, 0.20 mmol) following the general procedure. The product 4c was obtained in 81% yield (84 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 112–115 °C; \(^1H\) NMR (400 MHz, d-DMF, 25 °C) δ 1.10 (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 = 7.2 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); \(^13C\) NMR (100.6 MHz, CDCl\(_3\), 25 °C) δ 13.7, 13.8, 14.1, 14.2, 14.8, 15.0, 161.4, 169.7, 171.7; HRMS (ESI, TOF) calc for C\(_9\)H\(_{12}\)NO\(_2\) [M + H]: 172.1046, found: 172.1048.

1-Ethoxy-3-ethylselenoquinoline-4-carboxylate (4d). The compound was prepared from ethyl benzimidate 1a (29.8 mg, 0.20 mmol) and ethyl diazoacetate (33.4 mg, 0.20 mmol) following the general procedure. The product 4d was obtained in 81% yield (84 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 112–115 °C; \(^1H\) NMR (400 MHz, d-DMF, 25 °C) δ 1.10 (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 = 7.2 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); \(^13C\) NMR (100.6 MHz, CDCl\(_3\), 25 °C) δ 13.7, 13.8, 14.1, 14.2, 14.8, 15.0, 161.4, 169.7, 171.7; HRMS (ESI, TOF) calc for C\(_9\)H\(_{12}\)NO\(_2\) [M + H]: 172.1046, found: 172.1048.

1-Ethoxy-3-methylselenoquinoline-4-carboxylate (4e). The compound was prepared from ethyl benzimidate 1a (29.8 mg, 0.20 mmol) and ethyl diazoacetate (33.4 mg, 0.20 mmol) following the general procedure. The product 4e was obtained in 81% yield (84 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:3 v/v). Mp: 112–115 °C; \(^1H\) NMR (400 MHz, d-DMF, 25 °C) δ 1.10 (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 = 7.2 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); \(^13C\) NMR (100.6 MHz, CDCl\(_3\), 25 °C) δ 13.7, 13.8, 14.1, 14.2, 14.8, 15.0, 161.4, 169.7, 171.7; HRMS (ESI, TOF) calc for C\(_9\)H\(_{12}\)NO\(_2\) [M + H]: 172.1046, found: 172.1048.
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7.0 Hz, 2H), 6.63 (s, 1H), 7.47 (dd, J = 1.7 Hz, J = 8.7 Hz, 1H), 8.10 (s, 1H), 8.16−8.19 (m, 1H), 10.76 (s, 1H); 13C NMR (100.6 MHz, d4-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, 1H), 140.4, 159.6; 19F NMR (376.5 MHz, d4-DMSO, 25 °C): δ = −61.7; HRMS (ESI, TOF) calc for C13H10NO2F3, [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 was obtained in 74% yield (37 mg) as a white solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 155−157 °C; 1H NMR (400 MHz, d4-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); 13C NMR (100.6 MHz, d4-DMSO, 25 °C) δ 14.6, 19.6, 20.0, 61.5, 91.5, 112.7, 122.9, 124.3, 132.0, 133.9, 140.5, 157.6, 158.9; HRMS (ESI, TOF) calc for C13H12NO2: [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 85% yield (33 mg) as a light yellow solid after column chromatography (eluent = petroleum ether/ethyl acetate 100:8 v/v). Mp: 113−115 °C; 1H NMR (400 MHz, d4-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); 13C NMR (100.6 MHz, d4-DMSO, 25 °C) δ 14.6, 61.5, 93.1, 112.9, 123.0, 133.0, 150.8, 156.1, 159.6; HRMS (ESI, TOF) calc for C13H12NO2S, [M + H]+: 216.0432, found: 216.0426.

Procedure for the Synthesis of the Dehydrated Product 3a. To a mixture of [Cp*Rh(C6H5CN)]2(SbF6)2 (4.1 mg, 0.005 mmol, 2.5 mol%) and 1,2-dichloroethane (2 mL) at room temperature were added benzimidazoles 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 dehydrated product 3a (40.4 mg, 82%).

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 1H NMR and 13C 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 4I (CIF)

X-ray crystallographic data for 6a (CIF)

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Notes
The authors declare no competing financial interest.

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