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Article

Rhodium(III)-catalyzed selective access to isoindolinones via formal [4 + 1] annulation of arylamides and propargyl alcohols

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ABSTRACT

A mild and efficient oxidative synthesis of isoindolinones has been realized by Rh(III)-catalyzed C–H activation of benzamides and [4 + 1] coupling with propargyl alcohols. This coupling system proceeds with broad substrate scope and mild conditions and provides a new approach to access the useful skeleton of γ-lactams with a stereogenic center.

1. Introduction

N-Heterocyclic motifs are widely embedded in structurally complex biologically active natural products or pharmaceuticals. In this context, the development of efficient methods that deliver complex molecules containing *N*-heterocycle scaffolds has been of continuing interest. In recent years, transition metal-catalyzed direct C–H activation and sequential annulation with unsaturated bonds has been identified as an environment-friendly and atom-economic approach in the construction of an array of functionalized heterocyclic molecules [1–10]. Among such transition metal-catalyzed systems, Cp*Rh(III)-catalyzed annulation reactions using alkynes have emerged as useful and efficient strategies to form diverse *N*-heterocyclic compounds. In these systems, the alkynes mostly serve as a C_2 synthon, especially in the construction of six-membered rings, which may restrict the synthetic utility [11–29]. To grapple with this limitation [30–32], Chang's [33] and our group [34] had independently developed Rh(III)-catalyzed coupling of arylnitrones with internal alkynes to produce indoline derivatives (Scheme 1, Eq. (1)). In 2013, our group also reported a Rh(III)-catalyzed synthesis of isochroman-1-one via C–H activation and sequential insertion into the triple bond of propargyl alcohols, where the resulting aryl-Rh species is prone to insert into the 2-position of the propargyl alcohol as a result of the electronical effect of the aryl group (Scheme 1, Eq. (2)) [35]. In light of this work, We reasoned that the regioselective of the migratory insertion of the Rh-Ar group may be switched when using a propargyl alcohol with an alkyl terminus. Consequently, the resulting intermediate could deliver a ketenol intermediate, whose high reactivity may allow eventual formation of a five-membered lactam though subsequent annulation [36].

N-substituted isoindolinones as an important class of heterocycles are widely present in many bioactive natural prod-

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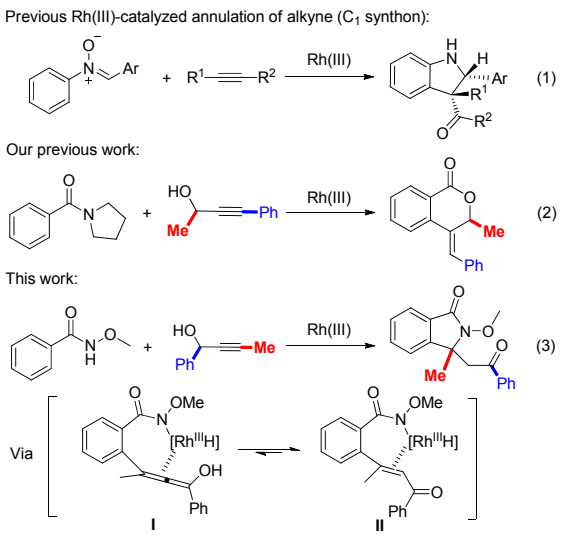


Scheme 1. Rh(III)-catalyzed annulation with alkynes.

ucts and drug candidates [37–40]. The development of highly efficient approach to access isoindolinone derivatives has always been of ongoing interest in organic synthesis [41–44]. Although Rh(III)-catalyzed C–H functionalization has been developed in the construction of isoindolinone cores, reactive and explosive diazo compounds have been typically used [45–50]. Thus alternatives to access these isoindolinone skeletons from more simple and easy handling starting materials are still highly desirable. We now report a Rh(III)-catalyzed regioselective [4 + 1] annulation of *N*-methoxybenzamides with easily available propargyl alcohols to construct various *N*-substituted isoindolinones [51].

2. Experimental

2.1. General

Unless otherwise noted, all reactions were carried out in flame-dried pressure tubes with a Teflon screw cap under air atmosphere. Anhydrous solvents were purified and dried by standard procedures. All commercially available reagents were used as received. ^{1}H and ^{13}C NMR spectra were recorded using $CDCl_3$ as a solvent on a 400 MHz spectrometer at 25 °C. The chemical shift is given in dimensionless δ values and is frequency referenced relative to $SiMe_4$ in ^{1}H and ^{13}C NMR spectroscopy. High-resolution mass spectra were obtained on an Agilent Q-TOF 6540 spectrometer. All other solvents were obtained from commercial sources and were used as received. The *N*-methoxy amides **1** and propargyl alcohols **2** were prepared following a published procedure [50,52–53].

2.2. General procedure for the synthesis of compounds *3* and *4*

Amides (0.2 mmol), propargyl alcohols (0.3 mmol), $[Cp^*RhCl_2]_2$ (2.5–4 mol%), AgOAc (10–16 mol%), Ag_2CO_3 (1.5 equiv.) and MeCN (2 mL) were charged into a pressure tube with a stir bar. The reaction mixture was stirred under air atmosphere at 30 °C for 24 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel chromatography using PE/EA to afford the product.

2.3. Spectral data for products

3a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.78 (m, 3H), 7.56–7.47 (m, 3H), 7.43–7.36 (m, 3H), 4.05 (s, 3H), 3.71 (d, J = 16.9 Hz, 1H), 3.37 (d, J = 16.9 Hz, 1H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 164.8, 146.5, 137.0, 133.2, 132.1, 129.0, 128.5, 128.4, 127.9, 123.6, 122.5, 65.2, 64.6, 44.4, 23.9.

3b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.4 Hz, 1H), 7.78 (d, J = 8.9 Hz, 2H), 7.54–7.52 (m, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.4 Hz, 1H), 6.85 (d, J = 8.9 Hz, 2H), 4.06 (s, 3H), 3.83 (s, 3H), 3.64 (d, J = 16.6 Hz, 1H), 3.31 (d, J = 16.6 Hz, 1H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 164.7, 163.6, 146.6, 132.1, 130.3, 130.1, 129.0, 128.4, 123.6, 122.6, 113.7, 65.2, 64.8, 55.4, 44.1, 23.9.

3c. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 7.4 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.50–7.49 (m, 2H), 7.46–7.41 (m, 1H), 4.05 (s, 3H), 3.68 (d, J = 16.8 Hz, 1H), 3.42 (d, J = 16.8 Hz, 1H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 164.8, 146.1, 139.6, 134.4 (q, $J_{C\text{-}F}$ = 32.7 Hz), 132.3, 129.1, 128.6, 128.2,125.6 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.7, 123.4 (q, $J_{C\text{-}F}$ = 272.7 Hz), 122.2, 65.3, 64.5, 44.6, 24.0. HRMS calc. for $C_{19}H_{17}F_3NO_3(M+H)^+$: 364.1155; Found: 364.1157.

3d. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.84 (m, 3H), 7.62–7.54 (m, 5H), 7.53–7.47 (m, 1H), 7.47–7.35 (m, 4H), 4.07 (s, 3H), 3.74 (d, J = 16.8 Hz, 1H), 3.41 (d, J = 16.8 Hz, 1H), 1.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 164.8, 146.5, 145.8, 139.5, 135.6, 132.1, 129.0, 128.9, 128.5, 128.4, 128.2, 127.13, 127.08, 123.6, 122.4, 65.2, 64.6, 44.3, 23.9. HRMS calc. for $C_{24}H_{22}NO_3(M+H)^+$: 372.1594; Found: 372.1596.

3e. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.3 Hz, 1H), 7.70 (d, J = 7.8 Hz, 2H), 7.56–7.44 (m, 2H), 7.41 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 7.7 Hz, 2H), 4.05 (s, 3H), 3.67 (d, J = 16.8 Hz, 1H), 3.34 (d, J = 16.8 Hz, 1H), 2.36 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 164.7, 146.6, 144.1, 134.5, 132.1, 129.2, 129.0, 128.4, 128.0, 123.6, 122.5, 65.2, 64.7, 44.2, 23.9, 21.6. HRMS calc. for $C_{19}H_{20}NO_3(M+H)^+$: 310.1438; Found: 310.1440.

3f. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 7.5 Hz, 1H), 7.48 (t, J = 7.3 Hz, 1H), 7.43–7.39 (m, 3H), 4.05 (s, 3H), 3.70 (d, J = 16.9 Hz, 1H), 3.33 (d, J = 16.9 Hz, 1H), 1.81 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 164.8, 157.0, 146.7, 134.5, 132.1, 129.0, 128.4, 127.9, 125.5, 123.6, 122.5, 65.2, 64.7, 44.3, 35.1, 31.0, 23.8. HRMS calc. for $C_{22}H_{26}NO_3(M+H)^+$: 352.1907; Found: 352.1909.

3g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.81 (m, 3H), 7.55–7.45 (m, 2H), 7.41 (t, J = 6.3 Hz, 1H), 7.06–7.02 (m, 2H), 4.05 (s, 3H), 3.64 (d, J = 16.7 Hz, 1H), 3.36 (d, J = 16.7 Hz, 1H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 165.7 (d, $J_{C\text{-}F}$ = 255.4 Hz), 164.7, 146.3, 133.4 (d, $J_{C\text{-}F}$ = 2.9 Hz), 132.2, 130.6 (d, $J_{C\text{-}F}$ = 9.4 Hz), 129.0, 128.5, 123.6, 122.4, 115.6 (d, $J_{C\text{-}F}$ = 22.0 Hz), 65.2, 64.6, 44.3, 23.9. HRMS calc. for $C_{18}H_{17}FNO_3(M+H)^+$: 314.1287; Found: 314.1290.

3h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.50–7.47 (m, 2H), 7.43–7.40 (m, 1H), 7.34 (d, J = 8.4 Hz, 2H), 4.04 (s, 3H), 3.63 (d, J = 16.8 Hz, 1H), 3.35 (d,

J = 16.8 Hz, 1H), 1.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 194.9, 164.8, 146.2, 139.7, 135.3, 132.2, 129.3, 129.0, 128.8, 128.5, 123.6, 122.3, 65.2, 64.5, 44.3, 23.9. HRMS calc. for $C_{18}H_{17}ClNO_3(M+H)^+$: 330.0891; Found: 330.0894.

3i. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.82 (d, *J* = 7.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.52–7.49 (m, 4H), 7.45–7.40 (m, 1H), 4.04 (s, 3H), 3.63 (d, *J* = 16.8 Hz, 1H), 3.34 (d, *J* = 16.8 Hz, 1H), 1.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 195.1, 164.8, 146.2, 135.7, 132.2, 131.8, 129.4, 129.0, 128.5, 128.5, 123.7, 122.3, 65.3, 64.5, 44.3, 23.9. HRMS calc. for $C_{18}H_{17}BrNO_3(M+H)^+$: 374.0386; Found: 374.0389.

3j. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.30 (s, 1H), 7.92–7.78 (m, 5H), 7.60–7.38 (m, 5H), 4.08 (s, 3H), 3.84 (d, *J* = 16.8 Hz, 1H), 3.51 (d, *J* = 16.8 Hz, 1H), 1.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 196.0, 164.8, 146.6, 135.5, 134.3, 132.3, 132.1, 129.7, 129.5, 129.0, 128.6, 128.4 (two signals overlapped), 127.7, 126.8, 123.6, 123.4, 122.5, 65.3, 64.7, 44.5, 23.9. HRMS calc. for $C_{22}H_{20}NO_3(M+H)^+$: 346.1438; Found: 346.1439.

3k. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.84 (d, *J* = 6.3 Hz, 1H), 7.67–7.38 (m, 5H), 7.37–7.24 (m, 2H), 4.07 (s, 3H), 3.71 (d, *J* = 16.9 Hz, 1H), 3.36 (d, *J* = 16.9 Hz, 1H), 2.35 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 196.4, 164.9, 146.6, 138.4, 137.1, 134.1, 132.2, 129.1, 128.49, 128.46, 128.45, 125.2, 123.7, 122.6, 65.3, 64.7, 44.6, 23.9, 21.3. HRMS calc. for $C_{19}H_{20}NO_3(M+H)^+$: 310.1438; Found: 310.1439.

3l. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.82 (d, *J* = 7.4 Hz, 1H), 7.76 (s, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.50–7.40 (m, 4H), 7.32 (t, *J* = 7.9 Hz, 1H), 4.05 (s, 3H), 3.65 (d, *J* = 16.9 Hz, 1H), 3.36 (d, *J* = 16.9 Hz, 1H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 194.8, 164.8, 146.2, 138.4, 134.9, 133.1, 132.2, 129.9, 129.0, 128.5, 128.0, 126.0, 123.7, 122.3, 65.3, 64.5, 44.4, 24.0. HRMS calc. for $C_{18}H_{17}ClNO_3(M+H)^+$: 330.0891; Found: 330.0894.

3m. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.82 (d, *J* = 7.5 Hz, 1H), 7.54–7.51 (m, 1H), 7.46–7.41 (m, 2H), 7.31–7.21 (m, 3H), 7.04 (d, *J* = 6.7 Hz, 2H), 4.03 (s, 3H), 3.59 (d, *J* = 15.6 Hz, 1H), 3.52 (d, *J* = 15.6 Hz, 1H), 3.11 (d, *J* = 16.3 Hz, 1H), 2.88 (d, *J* = 16.3 Hz, 1H), 1.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 204.1, 164.6, 146.3, 133.3, 132.3, 129.4, 128.8, 128.7, 128.5, 127.1, 123.7, 122.0, 65.2, 64.4, 51.1, 47.6, 23.7. HRMS calc. for $C_{19}H_{20}NO_3(M+H)^+$: 310.1438; Found: 310.1440.

3n. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.81–7.79 (m, 3H), 7.52 (t, *J* = 7.1 Hz, 1H), 7.47–7.38 (m, 4H), 7.32 (d, *J* = 7.1 Hz, 1H), 4.06 (s, 3H), 3.75–3.61 (m, 2H), 1.62–1.55 (m, 1H), 0.67–0.62 (m, 2H), 0.52–0.41 (m, 1H), 0.07–0.02 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 195.6, 165.1, 142.9, 137.2, 133.2, 131.5, 130.3, 128.51, 128.49, 127.9, 123.6, 122.5, 67.1, 64.6, 41.8, 18.4, 2.9, 1.3. HRMS calc. for $C_{20}H_{20}NO_3(M+H)^+$: 322.1438; Found: 322.1439.

3o. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.87 (d, *J* = 7.3 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.50–7.44 (m, 4H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 2H), 7.18–7.11 (m, 1H), 7.05 (d, *J* = 7.2 Hz, 2H), 4.10 (s, 3H), 3.72 (d, *J* = 16.9 Hz, 1H), 3.50 (d, *J* = 16.9 Hz, 1H), 2.68–2.60 (m, 1H), 2.54–2.39 (m, 2H), 2.06–1.99 (td, *J* = 12.8, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 195.8, 166.0, 144.4, 140.9, 137.0, 133.2, 132.3, 130.0, 128.5 (two signals overlapped), 128.4, 128. 1, 127.8, 125.9, 123.7, 122.3, 67.6, 64.7, 43.9, 37.7, 29.3. HRMS calc. for $C_{25}H_{24}NO_3(M+H)^+$: 386.1751; Found: 386.1751.

3p. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.83 (d, *J* = 7.1 Hz, 1H), 7.61 (t, *J* = 6.9 Hz, 1H), 7.54–7.38 (m, 4H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.10–7.01 (m, 1H), 4.05 (s, 3H), 3.73 (d, *J* = 17.1 Hz, 1H), 3.45 (d, *J* = 17.3 Hz, 1H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 194.4 (d, $J_{C\text{-}F}$ = 3.9 Hz), 164.9, 161.4 (d, $J_{C\text{-}F}$ = 253.6 Hz), 146.4, 134.6 (d, $J_{C\text{-}F}$ = 9.1 Hz), 132.1, 130.4 (d, $J_{C\text{-}F}$ = 2.4 Hz), 129.2, 128.4, 125.9 (d, $J_{C\text{-}F}$ = 13.0 Hz), 124.5 (d, $J_{C\text{-}F}$ = 3.4 Hz), 123.7, 121.9, 116.5 (d, $J_{C\text{-}F}$ = 23.9 Hz), 65.2, 64.5, 48.8 (d, $J_{C\text{-}F}$ = 7.8 Hz), 24.5. HRMS calc. for $C_{18}H_{17}FNO_3(M+H)^+$: 314.1187; Found: 314.1189.

3q. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.82 (d, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 4.8 Hz, 1H), 7.56 (d, *J* = 3.6 Hz, 1H), 7.53–7.47 (m, 2H), 7.45–7.39 (m, 1H), 7.05 (t, *J* = 4.4 Hz, 1H), 4.07 (s, 3H), 3.60 (d, *J* = 16.1 Hz, 1H), 3.29 (d, *J* = 16.1 Hz, 1H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 189.0, 164.7, 146.3, 144.4, 134.3, 132.3, 132.2, 128.8, 128.5, 128.2, 123.7, 122.6, 65.3, 64.7, 45.4, 23.7. HRMS calc. for $C_{16}H_{16}NO_3S(M+H)^+$: 302.0845; Found: 302.0846.

4a. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.89–7.76 (m, 3H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.31 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.11 (td, *J* = 8.9, 2.3 Hz, 1H), 4.04 (s, 3H), 3.74 (d, *J* = 17.3 Hz, 1H), 3.37 (d, *J* = 17.3 Hz, 1H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 195.8, 165.4 (d, $J_{C\text{-}F}$ = 250.0 Hz), 164.0, 149.0 (d, $J_{C\text{-}F}$ = 9.6 Hz), 136.8, 133.4, 128. 6, 127.9, 125.9 (d, $J_{C\text{-}F}$ = 9.6 Hz), 125.0 (d, $J_{C\text{-}F}$ = 2.4 Hz), 116.1 (d, $J_{C\text{-}F}$ = 23.3 Hz), 110.5 (d, $J_{C\text{-}F}$ = 24.7 Hz), 65.5, 64.4 (d, $J_{C\text{-}F}$ = 2.5 Hz), 44.3, 23.8.

4b. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.83 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.60–7.50 (m, 2H), 7.43–7.39 (m, 3H), 4.04 (s, 3H), 3.73 (d, *J* = 17.3 Hz, 1H), 3.39 (d, *J* = 17.3 Hz, 1H), 1.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 195.7, 163.9, 148.1, 138.5, 136.7, 133.4, 129.0, 128.6, 127.9, 127.6, 124.9, 123.2, 65.3, 64.4, 44.1, 23.9.

4c. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.82 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 1.0 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.58–7.50 (m, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 4.04 (s, 3H), 3.72 (d, *J* = 17.3 Hz, 1H), 3.39 (d, *J* = 17.3 Hz, 1H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 195.6, 164.0, 148.2, 136.7, 133.4, 131.9, 128.6, 128.1, 127.8, 126.8, 126.0, 125.1, 65.3, 64.3, 44.0, 23.9.

4d. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.79 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.30 (s, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 4.04 (s, 3H), 3.68 (d, *J* = 16.8 Hz, 1H), 3.36 (d, *J* = 16.8 Hz, 1H), 2.36 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 196.2, 165.1, 146.8, 142.9, 137.1, 133.2, 129.3, 128.5, 127.9, 126.2, 123.5, 123.0, 65.2, 64.5, 44.5, 23.9, 22.0.

4e. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.42 (d, *J* = 1.1 Hz, 1H), 8.32 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 4.08 (s, 3H), 3.78 (d, *J* = 17.5 Hz, 1H), 3.55 (d, *J* = 17.6 Hz, 1H), 1.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 195.2, 162.4, 150.4, 147.5, 136.4, 135.2, 133.7, 128.8, 127.9, 124.7, 124.1, 118.0, 65.3, 64.6, 43.5, 24.2.

4f. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.89 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 2H), 7.71 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.54–7.47 (m, 3H), 7.45–7.35 (m, 5H), 4.09 (s, 3H), 3.76 (d, *J* = 16.7 Hz, 1H), 3.41 (d, *J* = 16.7 Hz, 1H), 1.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 196.2, 164.7, 147.1, 145.4, 140.3, 137.1, 133.2, 128.8, 128.5, 128.0, 127.9, 127.8, 127.6, 127.4, 124.0, 121.4, 65.3, 64.8, 44.5, 23.9.

4g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.6 Hz, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.02 (s, 1H), 6.92 (d, J = 8.3 Hz, 1H), 4.03 (s, 3H), 3.79 (s, 3H), 3.69 (d, J = 16.8 Hz, 1H), 3.34 (d, J = 16.8 Hz, 1H), 1.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 165.3, 163.1, 148.9 137.1, 133.2, 128.5, 127.9, 125.2, 121.1, 114.8, 107.8, 65.3, 64.6, 55.5, 44.6, 23.8.

4h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.6 Hz, 2H), 7.51 (t, J = 7.2 Hz, 1H), 7.43–7.28 (m, 4H), 7.15 (d, J = 7.1 Hz, 1H), 4.03 (s, 3H), 3.65 (d, J = 16.7 Hz, 1H), 3.38 (d, J = 16.7 Hz, 1H), 2.71 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 166.2, 147.2, 137.8, 137.2, 133.1, 131.6, 130.3, 128.5, 127.9, 126.0, 119.6, 65.1, 63.8, 44.4, 24.2, 17.3.

4i. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.86–7.78 (m, 3H), 7.66–7.59 (m, 2H), 7.57–7.45 (m, 2H), 7.36 (t, J = 7.6 Hz, 2H), 4.09 (s, 3H), 3.75 (d, J = 16.7 Hz, 1H), 3.43 (d, J = 16.7 Hz, 1H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 166.7, 147.1, 137.1, 133.2, 133.0, 133.0, 129.1, 128.5, 128.1, 128.1, 127.9, 126.7, 124.1, 122.8, 119.4, 65.3, 64.3, 44.3, 23.7.

4j. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.5 Hz, 2H), 7.52 (t, J = 7.1 Hz, 1H), 7.47–7.31 (m, 5H), 4.03 (s, 3H), 3.68 (d, J = 17.1 Hz, 1H), 3.40 (d, J = 17.1 Hz, 1H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 163.1, 149.1, 136.9, 133.4, 132.9, 131.5, 130.1, 128.7, 127.9, 125.5, 120.9, 65.2, 63.6, 44.2, 24.2. HRMS calc. for $C_{18}H_{17}ClNO_3(M+H)^+$: 330.0891; Found: 330.0892.

4k. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.7 Hz, 2H), 7.55–7.36 (m, 4H), 7.30 (d, J = 7.6 Hz, 1H), 7.04 (t, J = 8.7 Hz, 1H), 4.02 (s, 3H), 3.68 (d, J = 17.1 Hz, 1H), 3.43 (d, J = 17.1 Hz, 1H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 162.2 (d, J_{C-F} = 2.0 Hz), 158.6 (d, J_{C-F} = 260.8 Hz), 149.1 (d, J_{C-F} = 2.6 Hz), 136.8, 134.0 (d, J_{C-F} = 7.7 Hz), 133.3, 128.6, 127.8, 118.3 (d, J_{C-F} = 4.1 Hz), 116.5 (d, J_{C-F} = 13.3 Hz), 115.8 (d, J_{C-F} = 19.3 Hz), 65.2, 64.2, 44.0, 24.3. HRMS calc. for $C_{18}H_{17}FNO_3(M+H)^+$: 314.1187; Found: 314.1187.

4l. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.7 Hz, 2H), 7.51 (t, J = 7.3 Hz, 1H), 7.45–7.36 (m, 3H), 7.05 (d, J = 7.6 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 3.62 (d, J = 16.6 Hz, 1H), 3.36 (d, J = 16.6 Hz, 1H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 164.5, 157.2, 149.2, 137.1, 133.8, 133.1, 128.5, 127.9, 115.9, 114.3, 110.6, 65.1, 63.8, 55.8, 44.3, 24.1. HRMS calc. for $C_{19}H_{20}NO_4(M+H)^+$: 326.1387; Found: 326.1389.

4m. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.5 Hz, 2H), 7.63 (s, 1H), 7.51 (t, J = 7.4 Hz, 1H), 7.42–7.36 (m, 3H), 7.29 (d, J = 7.8 Hz, 1H), 4.04 (s, 3H), 3.68 (d, J = 16.9 Hz, 1H), 3.35 (d, J = 16.8 Hz, 1H), 2.38 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 165.0, 143.8, 138.5, 137.0, 133.2, 133.0, 129.0, 128.5, 127.9, 123.8, 122.3, 65.2, 64.5, 44.5, 24.0, 21.3.

4n. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.4 Hz, 2H), 7.62 (d, J = 4.8 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 7.27–7.26 (m, 1H), 4.08 (s, 3H), 3.87 (d, J = 17.4 Hz, 1H), 3.21 (d, J = 17.4 Hz, 1H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 162.7, 156.8, 136.8, 134.6, 133.5, 130.8, 128.7, 127.9, 123.3, 65.7, 65.7, 45.7, 22.7. HRMS calc. for $C_{16}H_{16}NO_3S$ $(M+H)^+$: 302.0845; Found: 302.0846.

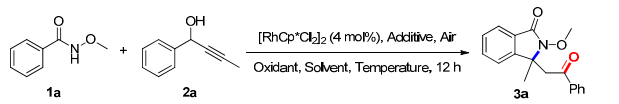
4o. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.80 (m, 3H), 7.56–7.47 (m, 3H), 7.44–7.38 (m, 3H), 4.42–4.34 (m, 1H), 4.25–4.17 (m, 1H), 3.72 (d, J = 16.9 Hz, 1H), 3.34 (d, J = 16.9 Hz, 1H), 1.81 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 165.0, 146.6, 137.0, 133.2, 132.0, 129.1, 128.5, 128.4, 127.9, 123.6, 122.5, 73.2, 64.6, 44.6, 23.8, 14.0. HRMS calc. for $C_{19}H_{20}NO_3(M+H)^+$: 310.1438; Found: 310.1438.

3. Results and discussion

The coupling of *N*-methoxybenzamide (**1a**) with propargyl alcohol (**2a**) was selected as a model reaction for screening of the reaction parameters (Table 1). The initial reaction of **1a** with **2a** was carried out in the presence of 4 mol% of $[RhCp^*Cl_2]_2$ as the catalyst at 60 °C in MeCN. Traces of desired product **3a** were detected using AgOAc as an oxidant, while the yield of **3a** was dramatically improved to 64% when Ag_2CO_3 was used (Table 1, entries 1 and 2). Lowering the reaction temperature to 30 °C afforded **3a** in 73% yield (Table 1, entry 3), but lowering the amount of Ag_2CO_3 to 1 equiv. resulted in a slightly lower yield (Table 1, entry 4). Screening of the solvent gave MeCN as an optimal medium (Table 1, entries 5–9). With K_2CO_3 or HOAc being an additive, the yields of the desired product were decreased to 63% or 54%, respectively (Table 1, entries 10 and 11). To our delight, introduction of AgOAc (16 mol%) as an additive gave **3a** in 76% yield (Table 1, entry 12). Switching the air atmosphere to O_2 atmosphere resulted in an inferior result (Table 1, entry 13). A similar yield was still obtainable when the catalyst loading was lowered to 2.5 mol% (Table 1, entry 14).

With the optimized reaction conditions established, we next investigated the scope and generality of the propargyl alcohols in this catalytic system (Table 2, entries 1–17). Fortunately, various propargyl alcohols bearing both electron-donating (**3b**, **3e**, **3f**, **3k**) and -withdrawing (**3c**, **3d**) as well as halogen (**3g**,

Table 1
Optimization of reaction conditions.



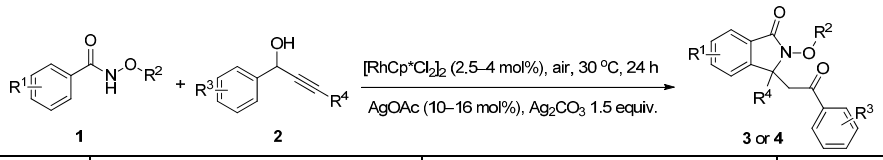
Entry	Solvent	T (°C)	Oxidant (equiv.)	Additive (equiv.)	Yield [a] (%)
1	MeCN	60	AgOAc (2)	—	trace
2	MeCN	60	Ag_2CO_3 (1.5)	—	64
3	MeCN	30	Ag_2CO_3 (1.5)	—	73
4	MeCN	30	Ag_2CO_3 (1)	—	71
5	DCE	30	Ag_2CO_3 (1.5)	—	30
6	Acetone	30	Ag_2CO_3 (1.5)	—	72
7	$PhCH_3$	30	Ag_2CO_3 (1.5)	—	21
8	Dioxane	30	Ag_2CO_3 (1.5)	—	trace
9	DMF	30	Ag_2CO_3 (1.5)	—	trace
10	MeCN	30	Ag_2CO_3 (1.5)	K_2CO_3 (1)	63
11	MeCN	30	Ag_2CO_3 (1.5)	HOAc (1)	54
12	MeCN	30	Ag_2CO_3 (1.5)	AgOAc (0.16)	76
13 [b]	MeCN	30	Ag_2CO_3 (1.5)	AgOAc (0.16)	69
14 [c]	MeCN	30	Ag_2CO_3 (1.5)	AgOAc (0.10)	79

Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), oxidant and additives, solvent (2 mL), 12 h, sealed tube under air. [a] Yield of isolated product. [b] Reaction was performed under 1 atm of O_2. [c] $[Cp^*RhCl_2]_2$ (2.5 mol%) was used.

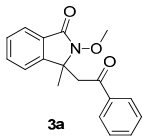
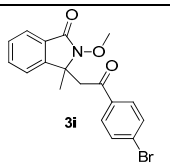
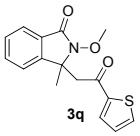
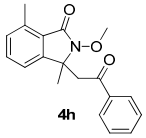
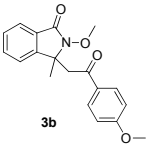
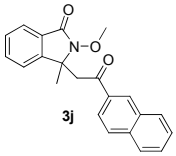
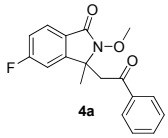
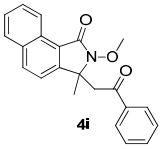
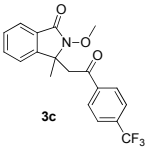
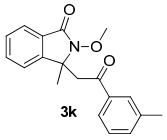
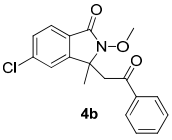
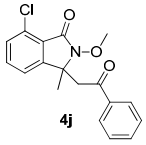
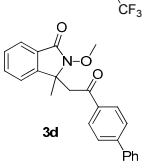
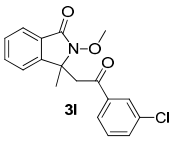
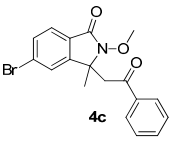
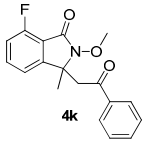
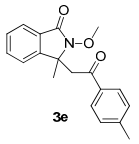
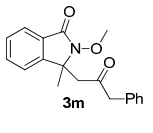
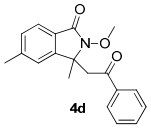
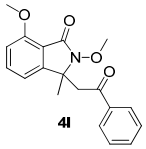
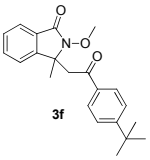
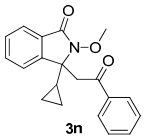
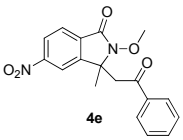
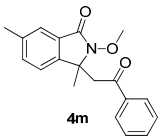
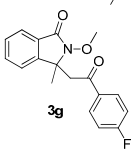
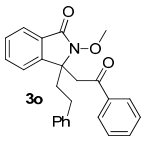
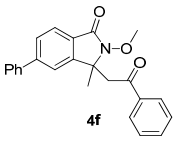
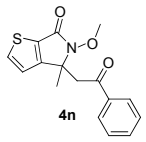
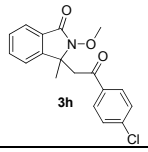
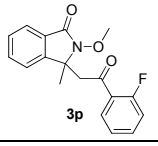
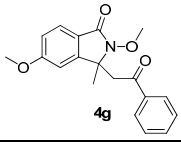
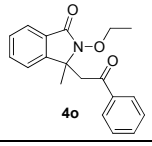
3h, **3i**, **3l**) substituents at the *meta* or *para* positions of the benzene ring of the propargyl alcohol are all compatible. However, introduction a fluorine atom into the *ortho* position of benzene ring caused a lower reactivity (**3p**). In addition to the benzene ring of the propargyl alcohol, a naphthalene ring (**3j**), a thiophene ring (**3q**) and a benzyl group (**3m**) on the 1-position all resulted in good yields of the desired products. Besides methyl group, cyclopropyl (**3n**) and phenylethyl (**3o**) substituted propargyl alcohols could also undergo this annulation smoothly in moderate to high yields.

The substrate scope of the *N*-methoxybenzamides was next explored under modified conditions (Table 2, entries 18–32). In general, *N*-methoxybenzamides bearing different electron-donating and -withdrawing groups at the *ortho* and *para*

Table 2
Scope of substrates.



1 2 3 or 4

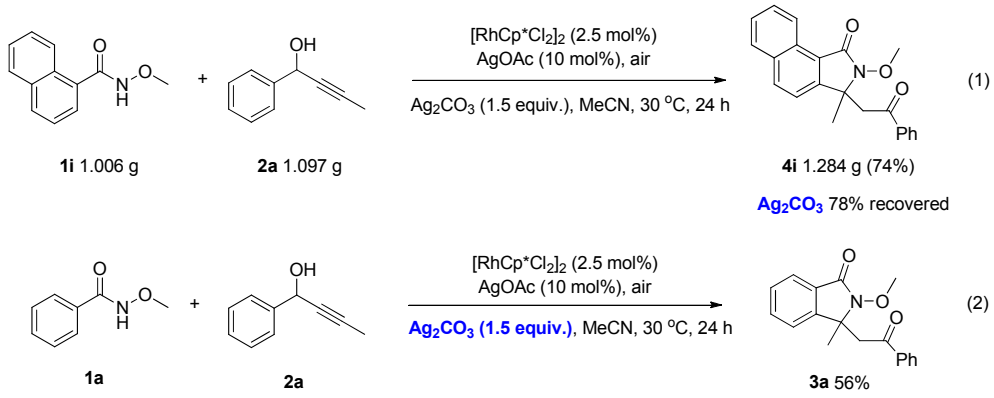
Entry	Product	Yield[c] (%)	Entry	Product	Yield[c] (%)	Entry	Product	Yield[c] (%)	Entry	Product	Yield[c] (%)
1[a]	 **3a**	79	9[a]	 **3i**	74	17[a]	 **3q**	53	25[b]	 **4h**	80
2[a]	 **3b**	47	10[a]	 **3j**	71	18[b]	 **4a**	68	26[b]	 **4i**	81
3[a]	 **3c**	70	11[a]	 **3k**	67	19[b]	 **4b**	60	27[b]	 **4j**	48
4[a]	 **3d**	76	12[a]	 **3l**	66	20[b]	 **4c**	51	28[b]	 **4k**	78
5[a]	 **3e**	73	13[a]	 **3m**	56	21[b]	 **4d**	68	29[b]	 **4l**	66
6[a]	 **3f**	66	14[a]	 **3n**	33	22[b]	 **4e**	25	30[b]	 **4m**	66
7[a]	 **3g**	65	15[a]	 **3o**	83	23[b]	 **4f**	62	31[b]	 **4n**	69
8[a]	 **3h**	75	16[a]	 **3p**	27	24[b]	 **4g**	64	32[b]	 **4o**	74

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), AgOAc (10 mol%), Ag_2CO_3 (1.5 equiv.) in MeCN (2 mL), 30 °C, 24 h, sealed tube under air. [b] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), AgOAc (16 mol%), Ag_2CO_3 (1.5 equiv.) in MeCN (2 mL), 30 °C, 24 h, sealed tube under air. [c] Isolated yield after column chromatography.

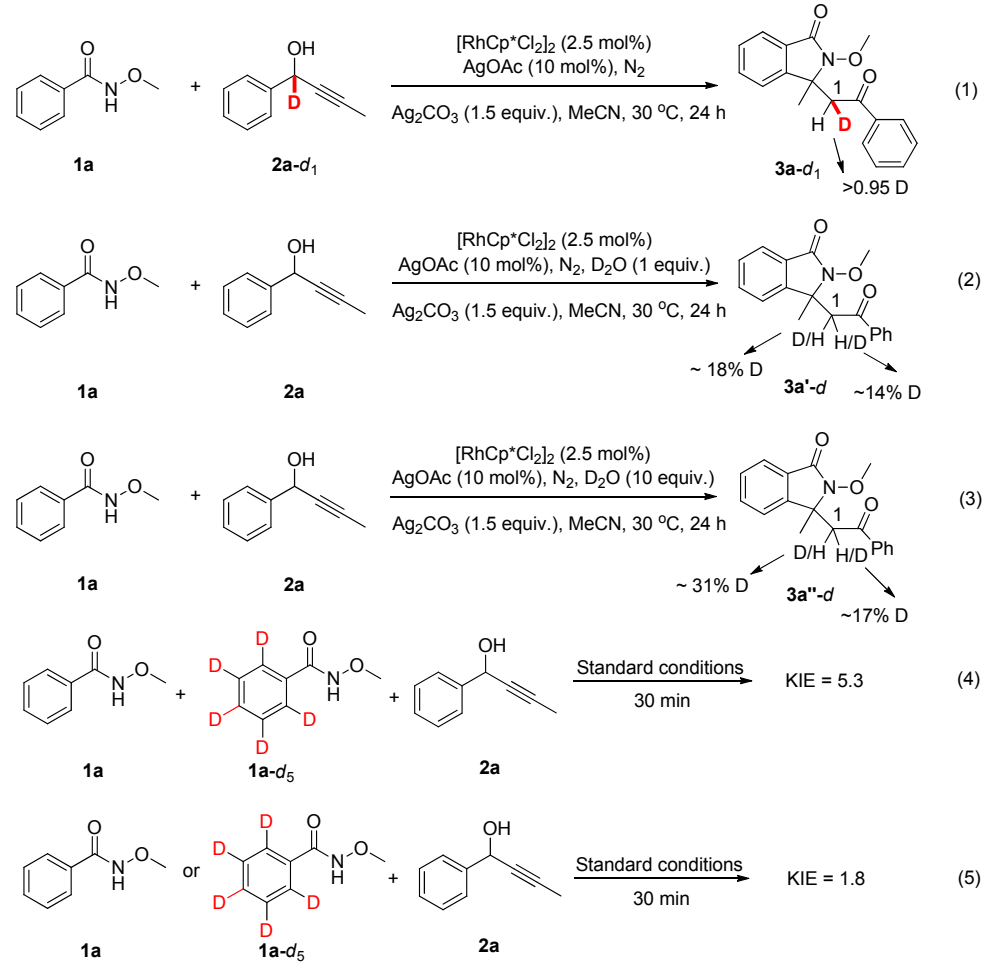
positions all coupled smoothly with propargyl alcohol **2a**, and the desired cyclization products were isolated in moderate to good yields (**4a**–**4d**, **4f**–**4l**). However, 4-nitro-substituted benzamide exhibited lower reactivity (**4e**). The C–H activation of *meta*-methyl substituted substrate occurred selectively at the less hindered position to give product **4m** in 66% yield. Furthermore, the substrate is not limited to *N*-methoxybenzamide; both the thiophene ring (**4n**) and *N*-ethoxybenzamides (**4o**) also coupled in good yields.

To demonstrate the synthetic utility of the reaction, a gram scale reaction between **1i** and **2a** has been performed (Scheme 2), and the desired product **4i** was isolated in good yield (75%) even with a reduced catalyst loading. It should be noted that Ag_2CO_3 as the oxidant could be recovered effectively (78% recovery), and oxidation using the recycled Ag_2CO_3 resulted in isolation of the product **3a** in 56% yield.

Several deuterated experiments have been carried out to probe the reaction mechanism. Treatment of **1a** with **2a**-d_1 under the standard conditions provided **3a**-d_1 with deuterium essentially at the C-1 position (Scheme 3, Eq. (1)). Moreover,



Scheme 2. Gram-scale preparation of **4i**.



Scheme 3. Mechanism study experiments.

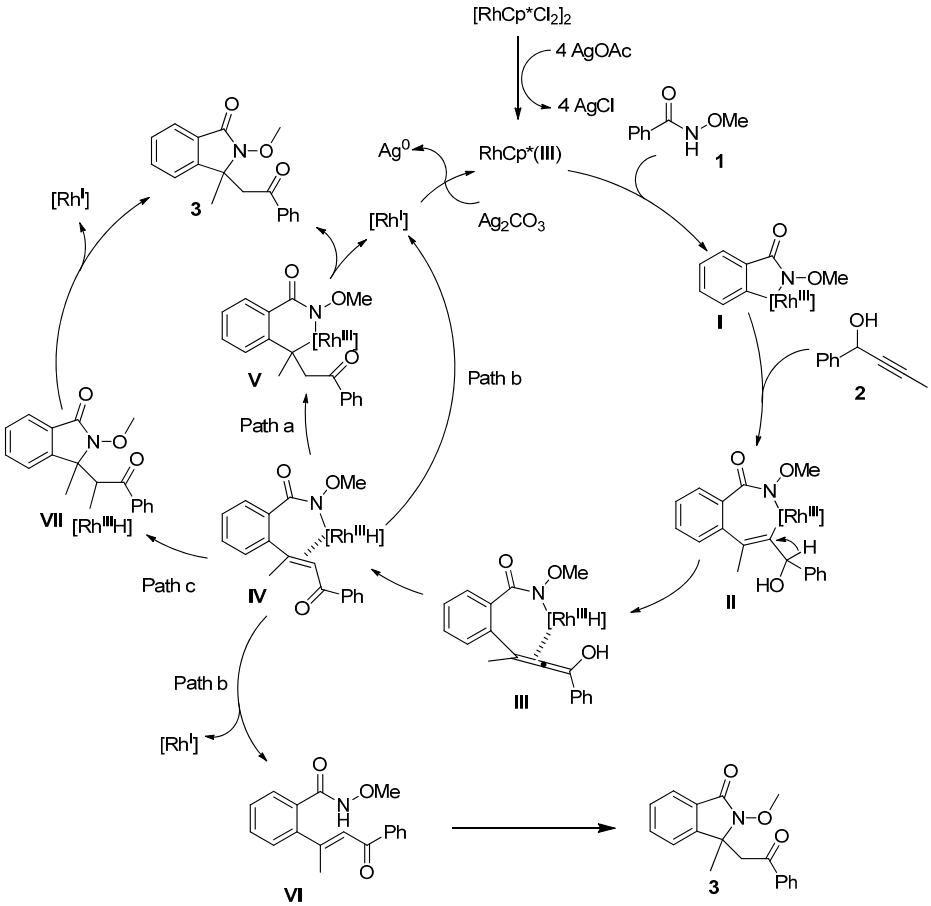
H/D exchange was observed at the C-1 position of **3a** when D_2O was introduced into the catalytic system, indicative of the irreversibility of a *β*-H elimination process under the catalytic conditions (Scheme 3, Eqs. (2) and (3)). A significant kinetic isotope effect (k_H/k_D = 5.3) was observed from an intermolecular competitive coupling using an equivalent molar mixture of **1a** and **1a**-d_5 (Scheme 3, Eq. (4)). In addition, two parallel reactions using **1a** and **1a**-d_5, a KIE value of 1.8 was obtained on the basis of ^{1}H NMR analysis (Scheme 3, Eq. (5)). These results suggest that C–H activation is probably involved in the turnover-limiting step.

On the base of previous work and our preliminary mechanistic experiments, three plausible pathways are proposed in Scheme 4. Initially, an active catalyst Cp*Rh^{III} is likely generated by anion exchange with AgOAc, followed by directed C–H activation of *N*-methoxybenzamides **1** to give intermediate **I**. Subsequent regioselective insertion of the propargyl alcohol gives a seven-membered rhodacycle **II**, which then undergoes *β*-H elimination and tautomerization to give an intermediate **IV**.

Following the formation of **IV**, several pathways may be possible. In path a, the C=C bond in **IV** inserts into the Rh–H bond to give an alkyl intermediate **V**, which undergoes reductive elimination to yield product **3** together with formation of a Rh^I species. Alternatively, intermediate **IV** might also undergo reductive elimination to form intermediate **VI** (path b), followed by aza-Michael addition to give the final product [12]. The intermediate **IV** might also directly undergo Rh–N bond insertion into the C=C bond to give the intermediate **VII**, which releases the final product **3** by reductive elimination. Finally, the Rh^I species could be reoxidized by Ag_2CO_3 to complete the catalytic cycle. Based on our H/D exchange studies, path b seems less likely. This is because if the path b is a primary pathway, we would expect loss of level of deuteration in the product when **2a**-d_1 was used as a result of exchange of the labile N-*H* proton in intermediate **VI** with adventitious water in the solvent or the added (deuterated) water (Scheme 3, Eq. (1)). Furthermore, with introduction of 10 equiv. D_2O, the degree of deuteration at the methylene position is expected to be markedly increased (Scheme 3, Eqs. (2) and (3)). Although paths a and c cannot be distinguished at this stage, on the basis of generally higher tendency of migratory insertion of a hydride group then other groups, we tentatively prefer pathway a.

4. Conclusions

A highly efficient Rh-catalyzed annulation of *N*-methoxybenzamide and propargyl alcohol via C–H activation has been disclosed, leading to the efficient synthesis of a series of *N*-substituted isoindolinones bearing a stereogenic center. The catalytic reaction features mild reaction conditions, good func-



Scheme 4. Proposed mechanism for the synthesis of isoindolinone.

tion group toleration, and high reaction efficiency. Moreover, this protocol endows alkyne with an unusual role of C_1 synthon, and this method may find applications in the formation of related complex molecules.

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Graphical Abstract

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Rhodium(III)-catalyzed selective access to isoindolinones via formal [4 + 1] annulation of arylamides and propargyl alcohols

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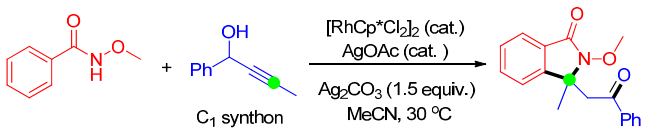

A mild and efficient oxidative synthesis of isoindolinones has been realized by Rh(III)-catalyzed C–H activation of benzamides and [4 + 1] coupling with propargyl alcohols. This coupling system proceeds with broad substrate scope and mild conditions and provides a new approach to access the useful skeleton of γ-lactams with a stereogenic center.

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三价铑催化*N*-甲氧基苯甲酰胺与炔丙醇[4 + 1]环化合成异吲哚啉酮

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摘要: 含N杂环结构广泛存在于具有生物活性的药物或天然产物骨架中. 本文开发了一个高效合成含N杂环骨架的方法, 这类方法在近年来一直是研究热点. 在最近几年, 过渡金属催化C–H键活化并随后与不饱和键发生环化反应被认为是一种环境友好且原子经济性高的构建功能化杂环的方法. 在这些金属催化的体系中, 三价铑催化与炔烃的环化反应体系, 被认为是一种高效且有实际意义的合成含N杂环的体系. 在这类体系, 特别是构建六元环的体系中, 炔烃通常作为一个C_2合成子被广泛应用. 为了克服这一局限性, Chang课题组和本课题组分别独立报道了通过三价铑催化, 炔烃与芳烃硝酮偶联合成吲哚啉化合物, 其中炔烃作为一个C_1合成子参与反应. 另一方面, 本课题组还报道了炔丙醇与吡咯烷苯甲酰胺通过C–H键活化合成1-异色满酮结构, 其中由于电子效应, 芳基-铑物种对于炔烃的插入是在炔烃的2位. 基于上述工作, 本文希望通过置换炔丙醇中芳基与烷基的位置, 使芳基-铑物种对于炔烃插入的方向发生改变, 进而生成联烯中间体, 然后发生环化反应生成五元环内酰胺结构.

异吲哚啉酮骨架结构也是一类重要的含N杂环结构, 广泛存在于多种天然产物及药物分子中, 其合成方法受到广泛关注. 尽管此前已有三价铑催化C–H官能团化的方法来构建异吲哚啉酮骨架结构, 但通常需要活性极高或易爆的化合物作为反应底物. 因此, 本文报道一类以简单的炔丙醇与*N*-甲氧基苯甲酰胺作为起始原料, 通过一步[4 + 1]环化合成异吲哚啉酮骨架结构. 本文完成了32个不同官能团取代的异吲哚啉酮骨架结构的合成, 反应均可以以中等到良好的收率得到目标产物. 另外还进行了放大实验, 结果表明可以以克级规模制备异吲哚啉酮化合物, 反应剩余的Ag_2CO_3以及生成的单质银可以回收(收率78%). 总之, 我们将*N*-甲氧基苯甲酰胺与炔丙醇在三价铑催化作用下通过C–H键活化的方法环化高效合成*N*-取代的异吲哚啉酮骨架结构, 且该骨架结构含有一个手性中心. 催化体系温和, 官能团容忍度好.

关键词: 铑; 碳氢活化; [4 + 1]环化; 炔丙醇; 异吲哚啉酮

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