Supporting Information for
Accessing 4-Oxy-Substituted Isoquinolinones via C–H Activation and Regioselective Migratory Insertion with Electronically Biased Ynol Ethers

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**General Information**

THF was obtained from the Innovative Technologies PureSolv MD 5 solvent purification system and kept under dry argon or nitrogen atmosphere. All other solvents were obtained from commercial suppliers. Reagents were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, Acros Organics, and TCI and used as received. Reactions were run in dry solvents, with a magnetic stir bar, capped with a rubber septum, and under a nitrogen atmosphere unless otherwise indicated. Heated reactions were performed in temperature controlled oil baths. Thin-layer chromatography was carried out on EMD Millipore 60 silica gel plates visualized by UV-light (254 nm /365 nm) and treatment with KMnO$_4$ stain followed by gentle heating utilizing a heat gun. Work-up procedures were completed in ambient conditions. Flash chromatography was performed on RediSep Rf Gold high performance silica gel cartridges (12-40 gram). $^1$H and $^{13}$C NMR spectra were recorded with Bruker NMR spectrometer (500 MHz). $^1$H NMR spectra were referenced to CDCl$_3$ (7.26 ppm), and reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, qt = quartet of triplets, br s = broad singlet, m = multiplet). Chemical shifts of the $^{13}$C NMR spectra were referenced to CDCl$_3$ (77.2 ppm) and DMSO (39.5 ppm). Mass spectral data were obtained from the Central Analytical Laboratory at the University of Colorado at Boulder.

**Solvent Screening Procedure:**

To a 5 mL round bottomed flask N-(pivalyloxy)benzamide (22.1 mg, 0.10 mmol, 1.0 eq), NaOAc (2.0 mg, 0.025 mmol, 0.25 eq.), and (Cp*RhCl)$_2$ (1.6 mg, 0.0025 mmol, 0.025 eq.) were added. The flask was place under a nitrogen atmosphere by evacuation and refill (3x) and then the appropriate solvent (0.4 mL) was added and the flask was heated to 30 °C. Then, a 0.3 M solution of 1-(phenoxy)hexyne in the appropriate solvent was prepared and was added in 3 aliquots over 2 hours (1-(phenoxy)hexyne = 20.9 mg, 0.12 mmol, 1.2 eq.). The reaction mixtures were left to stir for an additional 2 h after the final aliquot was added to the round bottomed flask. The reaction mixtures were then concentrated under reduced pressure and 2,4,5-trichloropyrimidine (0.0262 mmol) was added as an internal NMR standard to determine yields.

**Additive Screening Procedure:** To a 5 mL round bottomed flask N-(pivalyloxy)benzamide (22.1 mg, 0.1 mmol, 1.0 eq), the appropriate additive (0.025 mmol, 0.25 eq.) and (Cp*RhCl)$_2$ (1.6 mg, 0.0025 mmol, 0.025 eq.) were added. The flask was place under a nitrogen atmosphere by evacuation and refill (3x) and then the 1,2-dichloroethane (0.4 mL) was added and the flask was heated to 30 °C. Then, a 0.3 M solution of 1-(phenoxy)hexyne in the 1,2-dichloroethane was prepared and was added in 3 aliquots over 2 hours bringing to total volume to 0.4 mL (1-(phenoxy)hexyne = 20.9 mg, 0.12 mmol, 1.2 eq.). The reaction mixtures were left to stir for an additional 2 h after the final aliquot was added to the round bottomed flask. The reaction mixtures were then concentrated under reduced pressure and 2,4,5-trichloropyrimidine (0.0262 mmol) was added as an internal NMR standard to determine yields.
**Catalyst Loading Screening Procedure:** To a 5 mL round bottomed flask N-(pivalyloxy)benzamide (22.1 mg, 0.1 mmol, 1.0 eq), NH₄OAc (7.5 mg, 0.025 mmol, 0.25 eq.) and (Cp*RhCl₂)₂ (0.625 mol% - 10 mol%). were added. The flask was place under a nitrogen by evacuation and refill (3x) atmosphere and then the 1,2-dichloroethane (0.4 mL) was added and the flask was heated to 30 °C. Then, a 0.3 M solution of 1-(phenoxy)hexyne in the 1,2-dichloroethane was prepared and was added in 3 aliquots over 2 hours bringing the total volume to 0.4 mL (1-(phenoxy)hexyne = 20.9 mg, 0.12 mmol, 1.2 eq.). The reaction mixes were left to stir for an additional 2 h after final aliquot was added to the round bottomed flask. The reaction mixtures were then concentrated under reduced pressure and 2,4,5-trichloropyrimidine (0.0262 mmol) was added as an internal NMR standard to determine yields.

**Table S1: Optimization of Reagents**

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### Table S2: Additive Loading Optimization

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### Table S3: Catalyst Loading Optimization

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**Compounds 1h-i, 1b-g and 1k were prepare according to literature procedure and matched characterization values.

Synthesis of Alkylated Ynol Ethers (2)

The corresponding dichlorovinyl ether (1.0 eq.) was added to a multi-neck flask. The flask was placed under a nitrogen atmosphere by evacuation and refill (3x) and THF (0.1 M) was added. The round bottomed flask was cooled to -78 °C, and nBuLi (2.2 eq.) was added dropwise. The reaction mixture was warmed to -40 °C for 1 h, and then cooled to -78 °C. Then the alkylhalide (0.93 eq.) was added and warmed to room temperature over 2-8 h (Note: For iodobutane as the electrophile HMPA (2.2 eq.) was added first to the flask, and the reaction mixture was stirred for 30 min at -78 °C. Then, iodobutane was added.). The reaction was quenched with 40 mL of sat. NH₄Cl, washed twice with water and once with brine. The organic layer was dried over Na₂SO₄. The crude product was concentrated under reduced pressure and purified by flash chromatography (Hexanes, 1.5 min. retention time). Products were verified by ¹H, and ¹³C NMR. Isolated yields are reported below. Mass spectral analysis was attempted on all compounds via HR- and LR-LCMS however the mass of the ynol ethers were not observed, likely due to poor ionization. This ionization issue is in agreement with other low molecular weight ynol ethers. However, the ¹H-NMR and ¹³C-NMR spectra as well as the products obtained from the annulation of these compounds gives strong evidence for their synthesis.

1-(neopentyloxy)hex-1-yne (2b): Molecular formula: C₁₁H₂₀O. 10.9 mmol scale, pale-yellow oil, (0.972 g, 5.8 mmol, 53% yield).

¹H NMR (500 MHz, Chloroform-d) δ 3.70 (s, 2H), 2.13 (t, J = 6.7 Hz, 2H), 1.43 (m, 4H), 0.97 (s, 9H), 0.92 (t, J = 7.1 Hz, 3H).

¹³C NMR (126 MHz, Chloroform-d) δ 84.5, 36.6, 31.9, 29.7, 28.0, 21.9, 18.6, 16.9, 13.7.

1-(neopentyloxy)prop-1-yne (2c): Molecular formula: C₈H₁₄O. 10 mmol scale, pale yellow oil, (0.462 g, 3.7 mmol, 37% yield).

¹H NMR (500 MHz, Chloroform-d) δ 3.70 (s, 2H), 1.74 (s, 3H), 0.97 (s, 9H).

¹³C NMR (126 MHz, Chloroform-d) δ 88.6, 88.3, 32.2, 31.1, 25.9, 1.5.
1-isobutoxyhex-1-yne (2d): Molecular formula: C_{10}H_{18}O. 8.6 mmol scale, pale-Yellow oil, (0.806 g, 5.2 mmol, 59% yield).

^1^H NMR (500 MHz, Chloroform-d) δ 3.76 (d, J = 6.8 Hz, 2H), 2.13 (t, J = 6.7 Hz, 2H), 2.06 (qt, J = 6.7, 6.7 Hz, 1H), 1.43 (m, 4H), 1.0 (d, J = 6.8, 6H), 0.92 (t, J = 7.1 Hz, 3H).

^13^C NMR (126 MHz, Chloroform-d) δ 90.0, 84.4, 36.6, 31.9, 28.0, 21.9, 18.5, 16.9, 13.6.

Synthesis of Ynol ethers 2e and 2i

(2e) (ethoxyethynyl)trimethylsilane: Molecular formula: C_{7}H_{14}OSi. A 250-mL, oven dried, two neck flask was place under a nitrogen atmosphere by evacuation and refill (3x). Diisopropyl amine (1.8 mL, 17.5 mmol, 3.5 eq.) and THF (100 mL) were then added. The flask was cooled to 0 °C and 2.5 M n-BuLi (7.0 mL, 17.5 mmol, 3.5 eq.) was added slowly to form lithium diisopropyl amide in-situ. The reaction was stirred at 0 °C for 1 h. Chloroacetaldehyde dimethyl acetal (0.82 mL, 5.5 mmol, 1.0 eq.) was added over 10 min. and the reaction was stirred for 2 hours at 0 °C. Next, the TMS-Cl (1.26 mL, 10 mmol, 2.0 eq.) was added, and the reaction was stirred for an additional hour at 0 °C. The reaction was quenched by adding saturated, aqueous NH_{4}Cl, which was extracted with EtOAc. The combined organics were washed with brine, dried over anhydrous Na_{2}SO_{4}, and concentrated under reduced pressure. The crude product was purified via flash chromatography (Hexanes, retention time 1.5 min) to provide a colorless oil, (0.284 g, 2.0 mmol, 18% yield).

^1^H NMR (500 MHz, Chloroform-d) δ 4.15 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 H, 3H), 0.15, (s, 9H).

^13^C NMR (126 MHz, Chloroform-d) δ 109.5, 74.8, 36.8, 14.2, 0.69

Mass spectral analysis was attempted on all compounds via HR- and LR-LCMS however the mass of the ynol ethers were not observed, likely due to poor ionization. This ionization issue is in agreeance with other low molecular weight ynol ethers. However, the ^1^H-NMR and ^13^C-NMR spectra as well as the products obtained from the annulation of these compounds gives strong evidence for their synthesis.
(2i) 3-methoxyprop-2-yn-1-yl acetate: Molecular formula: C₆H₈O₃. 1. A 250-mL, oven dried, two neck flask was placed completely under a nitrogen atmosphere by evacuating and refilling (3x). Diisopropyl amine (8.3 mL, 59.5 mmol, 3.5 eq.) and THF (130 mL) were added. The flask was cooled to 0 °C and 2.5 M nBuLi (20.4 mL, 51 mmol, 3.0 eq.) was added slowly to form lithium diisopropyl amide in-situ. The reaction was stirred at 0 °C for 1 hour. The chloroacetaldehyde dimethyl acetal (1.93 mL, 17 mmol, 1.0 eq.) was added over 10 min. and the reaction was stirred for 2 hours at 0 °C. Next, paraformaldehyde (2.0 g, 68 mmol, 4.0 eq.) was added, and the reaction was stirred for an addition hour at 0 °C. The reaction was quenched by adding saturated, aqueous NH₄Cl. The solution was washed with brine and extracted three times with EtOAc. The solution was evaporated close to dryness under reduced pressure (minimum pressure = 100 mbar).

2. The crude product was dissolved in dry CH₂Cl₂ (30 mL). Triethylamine (8.2 mL, 59.5 mmol, 3.5 eq.) was added and the reaction mixtures was allowed to stir at room temperature for 10 min. Then a single crystal of DMAP and acetyl chloride (2.4 mL, 34 mmol, 2.0 eq.) were added and the reaction mixture stirred at room temperature for 30 min. The mixture was washed with brine and dried over anhydrous Na₂SO₄, and the concentrated under reduced pressure. The crude product was purified by flash chromatography (Gradient: 25-50% EtOAc in Hexanes, retention time 5.0 min.) to give a colorless oil (686 mg, 5.4 mmol, 46% yield).

(ethoxyethynyl)trimethylsilane:

1H NMR (500 MHz, Chloroform-d) δ 4.70 (s, 2H), 3.92 (s, 3H), 2.10 (s, 3H).

13C NMR (126 MHz, Chloroform-d) δ 170.5, 96.3, 65.8, 52.6, 32.1, 20.9.⁸

Mass spectral analysis was attempted on all compounds via HR- and LR-LCMS however the mass of the ynol ethers were not observed, likely due to poor ionization. This ionization issue is in agreeance with other low molecular weight ynol ethers.⁹ However, the ¹H-NMR and ¹³C-NMR spectra as well as the products obtained from the annulation of these compounds gives strong evidence for their synthesis.
References:
10) Austin, W. F.; Zhang, Y; Danheiser, R. L. *Tetrahedron*, 2008, 64, 915-925
(3ab)
3ag 1H-NMR:

Internal Standard

Aromatic region 3ag 1H-NMR:
Aromatic region 3ah $^1$H-NMR:

3ah crude $^1$H-NMR:

Internal Standard

N $\text{H}_2$O
N$\text{Pe}$
O
O
A
O
N
N
Cl
Cl
Cl
Cl

Internal Standard

Aromatic region 3ah $^1$H-NMR:
(3db)