An *In Situ* Approach to Nickel-Catalyzed Cycloadditions

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SUPPORTING INFORMATION

Table of Contents

General Considerations	S2
Experimental Details and Analytical Data	S2
References	S4
¹ H and ¹³ C NMR Spectra of compounds 2 - 10	S5

General Experimental:

All reactions were conducted under an atmosphere of N₂. Toluene and hexanes were dried over neutral alumina under N₂ using a Grubbs type solvent purification system. Ni(acac)₂ and *n*-BuLi (2.5 M in hexanes) were purchased from Aldrich Chemical Company and was used without further purification. IPr·HCl and SIPr·HCl was synthesized according to the procedure reported by Herrmann.¹ Anhydrous acetonitrile was purchased from the Acros chemical company. *o*-Tolunitrile and benzonitrile were purchased from the Aldrich Chemical Company and were distilled from CaH₂ prior to use. Diynes 2,2-di-*n*-but-2-ynyl-malonic acid dimethyl ester (**1**),² *N,N*-di-2-butynyl-*p*-toluenesulfonamide,³ and 1-but-2-ynyloxy-but-2-yne,⁴ were prepared according to literature procedures. 3,9-Dodecadiyne was purchased from GFS.

¹H and ¹³C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 300 and 75 MHz, respectively unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ¹H and to the center line of a triplet at 77.23 ppm for ¹³C. The abbreviations s, d, t, q, and m stand for singlet, doublet, triplet, quartet, and multiplet in that order. All ¹³C NMR spectra were proton decoupled. Gas Chromatographies were performed on an Alient 6890 gas chromatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 °C; temperature ramp rate 50 °C/min.; final temperature: 300 °C held for 7 minutes; detector temperature: 250 °C.

General Procedure for the [2+2+2] Cycloaddition of Diynes and Nitriles. Method (a): To a stirring suspension of Ni(acac)₂ and IPr·HCl in hexanes was added *n*-BuLi (2.5 M in hexanes) dropwise at room temperature. The resulting suspension was stirred for an additional 5 min. at which time a solution of diyne (~ 0.2 M in toluene) was added followed by the nitrile. The reaction mixture was stirred at room temperature until no starting diyne was detected by TLC analysis (~ 30 min.). The reaction mixture was then quenched by the addition of 5 drops of MeOH and concentrated in vacuo. The residue was purified by flash column chromatography to yield the desired pyridine. Method (b): To a stirring suspension of Ni(acac)₂ and SIPr·HCl in benzene was added *n*-BuLi (2.5 M in hexanes) dropwise at room temperature. The resulting suspension was stirred for an additional 5 min. at which time a solution of diyne (0.3 M in benzene) was added followed by the nitrile (0.3 M in benzene). The reaction mixture was stirred at room temperature until no starting diyne was detected by TLC analysis (~ 30 min.). The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography to yield the desired pyridine.

Preparation of 2,3,6-Trimethyl pyridine 2. Method **b** of the general procedure was used with diyne **1** (42.5 mg, 0.18 mmol), acetonitrile (8.2 mg, 0.20 mmol), Ni(acac)₂ (2.3 mg, 0.009 mmol), SIPr·HCl (7.7 mg, 0.018 mmol), *n*-BuLi (18 μL, 0.045 mmol), and 0.6 mL benzene. The reaction mixture was purified by flash column chromatography eluting with 25% EtOAc/hexanes to yield title compound **2** (33.5 mg, 67%) as a white solid. ¹H NMR (CDCl₃) δ 2.16 (s, 3H), 2.41 (s, 3H), 2.46 (s, 3H), 3.55 (s, 4H) and 3.78 (s, 6H); ¹³C NMR (CDCl₃) δ 15.2, 21.8, 22.2, 39.1, 40.0, 53.3, 59.6, 124.7, 131.4, 148.4, 149.7, 154.9 and 172.0.

Preparation of 2-*tert*-Butyl-3,6-dimethyl pyridine 3. Method **a** of the general procedure was used with diyne **1** (135.0 mg, 0.5741 mmol, 0.2588 M in toluene), *t*-Butyl nitrile (61.9 mg, 0.600 mmol), Ni(acac)₂ (7.3 mg, 0.028 mmol), IPr·HCl (24.3 mg, .0573 mmol), *n*-BuLi (57 μL, 0.14 mmol), and 3.47 mL hexanes. The reaction mixture was purified by flash column chromatography eluting with 25% EtOAc/hexanes to yield title compound **3** (96.5 mg, 53%) as a pale yellow oil. ¹H NMR (CDCl₃) δ 1.40 (s, 9H), 2.35 (s, 3H), 2.37 (s, 3H) 3.52 (s, 2H), 3.53 (s, 2H) and 3.77 (s, 6H); ¹³C NMR (CDCl₃) δ 17.5, 22.1, 30.4, 38.6, 39.1, 40.5, 53.3, 59.5, 124.3, 130.8, 148.3, 150.0, 163.5 and 172.3.

Preparation of 3,6-Dimethyl-2-phenyl pyridine 4. Method **b** of the general procedure was used with diyne **1** (34.8 mg, 0.15 mmol), benzonitrile (16.5 mg, 0.165 mmol), Ni(acac)₂ (2.1 mg, 0.008 mmol), SiPr-HCl (6.8 mg, 0.016 mmol), *n*-BuLi (16 μ L, 0.04 mmol), and 0.5 mL benzene. The reaction mixture was purified by flash column chromatography eluting with 50% EtOAc/hexanes to yield title compound **4** (42.7 mg, 85%) as a white solid. ¹H NMR (CDCl₃) δ 2.19 (s, 3H), 2.48 (s, 3H), 3.60 (s, 2H), 3.63 (s, 2H), 3.80 (s, 6H) and 7.34-7.43 (m, 5H); ¹³C NMR (CDCl₃) δ 16.3, 22.0, 39.3, 40.3, 53.3, 59.5, 124.3, 127.7, 128.2, 129.2, 132.5, 140.8, 149.4, 150.5, 157.1 and 172.0

Preparation of 3,6-Dimethyl-2-o-tolyl pyridine 5. Method **a** of the general procedure was used with diyne **1** (135.0 mg, 0.5741 mmol, 0.2551 M in toluene), *o*-tolunitrile (70.3 mg, 0.600 mmol), Ni(acac)₂ (7.3 mg, 0.028 mmol), IPr-HCl (24.3 mg, 0.0573 mmol), *n*-BuLi (57 μ L, 0.14 mmol), and 3.47 mL hexanes. The reaction mixture was purified by flash column chromatography eluting with 25% EtOAc/hexanes to yield title compound **5** (161.5 mg, 80%) as a white solid. ¹H NMR (CDCl₃) δ 1.98 (s, 3H), 2.08 (s, 3H), 2.48 (s, 3H), 3.62 (s, 2H), 3.66 (s, 2H), 3.82 (s, 6H) and 7.24-7.28 (m, 4H); ¹³C NMR (CDCl₃) δ 15.4, 19.7, 22.0, 39.4, 40.2, 53.4, 59.5, 124.9, 125.8, 127.8, 129.0, 130.3, 132.5, 135.9, 140.4, 148.9, 150.4, 157.7 and 172.1.

Preparation of 3,6-Dimethyl-2-naphthalene-1-yl pyridine 6. Method **a** of the general procedure was used with diyne **1** (135.0 mg, 0.5741 mmol, 0.2563 M in toluene), 1-cyanonaphthalene (91.9 mg, 0.600 mmol, 1.3 M in toluene), Ni(acac)₂ (7.3 mg, 0.028 mmol), IPr-HCl (24.3 mg, 0.0573 mmol), *n*-BuLi (57 μ L, 0.14 mmol), and 3.05 mL hexanes. The reaction mixture was purified by flash column chromatography eluting with 25% EtOAc/Hexanes to yield title compound **6** (206.8 mg, 92%) as a white solid. ¹H NMR (CDCl₃) δ 1.94 (s, 3H), 2.51 (s, 3H), 3.66 (s, 2H), 3.72 (s, 2H), 3.84 (s, 6H), 7.39-7.56 (m, 5H) 7.86-7.90 (m, 2H); ¹³C NMR (CDCl₃) δ 15.8, 22.1, 39.5, 40.3, 53.5, 59.5, 125.2, 125.8, 125.9, 126.3, 126.8, 128.2, 128.4, 131.9, 132.9, 133.9, 138.6, 149.0, 150.7, 156.6 and 172.2.

Preparation of 1,4-Diethyl-3-phenyl-5,6,7,8-tetrahydro isoquinoline 7. Method **b** of the general procedure was used with 3,9-dodecadiyne (30.6 mg, 0.19 mmol), benzonitrile (21.6 mg, 0.21 mmol), Ni(acac)₂ (2.6 mg, 0.01 mmol), SiPr-HCl (8.2 mg, 0.019 mmol), *n*-BuLi (20 μ L, 0.05 mmol), and 0.6 mL benzene. The reaction mixture was purified by flash column chromatography eluting with 25% EtOAc/hexanes to yield title compound **7** (43.4 mg, 87%) as a white solid. ¹H NMR (CDCl₃) δ 1.02 (t, 3H, *J* = 7 Hz), 1.27 (t, 3H, *J* = 7 Hz), 1.85 (m, 4H), 2.72 (q, 4H, *J* = 7 Hz), 2.80 (m, 4H) and 7.37-7.43 (m, 5H); ¹³C NMR (CDCl₃) δ 13.5, 14.4, 21.9, 22.7, 26.1, 26.6, 28.4, 127.3, 128.2, 128.9, 129.7, 132.6, 142.3, 144.7, 155.6 and 158.4.

Preparation of 3,6-Dimethyl-2-o-tolyl pyridine 8. Method **a** of the general procedure was used with *N,N*-di-2-butynyl-*p*-toluenesulfonamide (135.0 mg, 0.4908 mmol, 0.2226 M in toluene), benzonitrile (53.1 mg, 0.515 mmol), Ni(acac)₂ (6.3 mg, 0.025 mmol), IPr-HCl (20.9 mg, 0.0491 mmol), *n*-BuLi (49 μ L, 0.12 mmol), and 2.65 mL hexanes. The reaction mixture was purified by flash column chromatography eluting with 25% EtOAc/hexanes to yield title compound **8** (140.9 mg, 76%) as a white solid. ¹H NMR (CDCl₃) δ 2.15 (s, 3H), 2.44 (s, 6H), 4.63 (s, 2H), 4.66 (s, 2H), 7.34-7.43 (m, 7H) and 7.83 (d, 2H, *J* = 8 Hz); ¹³C NMR (CDCl₃) δ 16.2, 21.8, 22.0, 53.0, 53.7, 123.1, 127.8, 128.2, 128.5, 129.2, 130.2, 133.9, 140.1, 144.2, 145.9, 149.6 and 158.1.

Preparation of 3,6-Dimethyl-2-phenyl pyridine 9. Method **b** of the general procedure was used with 1-but-2-ynyloxy-but-2-yne (27.1 mg, 0.22 mmol), benzonitrile (24.7 mg, 0.24 mmol), Ni(acac)₂ (2.8 mg, 0.011 mmol), SIPr·HCl (9.4 mg, 0.022 mmol), *n*-BuLi (22 μ L, 0.055 mmol), and 0.7 mL benzene. The reaction mixture was purified by flash column chromatography eluting with 25% EtOAc/hexanes to yield title compound **9** (44.5 mg, 89%) as a white solid. ¹H NMR (CDCl₃) δ 2.19 (s, 3H), 2.48 (s, 3H), 5.14 (s, 2H), 5.19 (s, 2H) and 7.40-7.50 (m, 5H); ¹³C NMR (CDCl₃) δ 16.4, 22.3, 73.2, 73.7, 121.9, 128.0, 128.4, 129.3, 131.8, 140.4, 149.0 and 157.7

Preparation of 1,4-Dimethyl-3-oxo-3,5-dihydro-7H-cyclopenta[c]pyran-6,6-dicarboxylic acid dimethyl ester 10. To a stirring suspension of Ni(acac)₂ (29.0 mg, 0.0113 mmol) and IPr·HCl (96.0 mg, 0.226 mmol) in 2.38 mL hexanes was added *n*-BuLi (226 μ L, 2.5 M in hexanes) dropwise at room temperature. The resulting mixture was added to a two-necked flask containing a stirring solution of diyne **1** (133.3 mg, 0.5645 mmol) in 3.04 mL toluene under a balloon of CO₂ at 60 °C. The reaction mixture was stirred at 60 °C until no starting diyne was observed by TLC analysis (~ 30 min.). The reaction mixture was then quenched by the addition of 2 drops of MeOH and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography eluting with 35% EtOAc/hexanes to yield title compound **10** (92 mg, 58%) as a white solid. ¹H NMR (300 MHz, CDCl₃, ppm): δ 3.72 (s, 6H), 3.28 (s, 2H), 3.22 (s, 2H), 2.11 (s, 3H), 1.94 (s, 3H); ¹³C {¹H} NMR (75 MHz, CDCl₃, ppm): δ 170.7, 164.3, 155.0, 151.8, 115.9, 115.5, 59.4, 53.2, 38.6, 35.4, 17.4, 12.7.

References

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¹H NMR spectrum of **2** in CDCl₃

^{13}C NMR spectrum of **2** in CDCl_3

¹H NMR spectrum of **3** in CDCl₃

¹H NMR spectrum of **4** in CDCl₃

¹H NMR spectrum of **5** in CDCl₃

^{13}C NMR spectrum of **5** in CDCl_3

^{13}C NMR spectrum of **6** in CDCl_3

^{13}C NMR spectrum of **7** in CDCl_3

^1H NMR spectrum of **8** in CDCl_3

^{13}C NMR spectrum of **8** in CDCl_3

¹H NMR spectrum of **9** in CDCl₃

^{13}C NMR spectrum of **9** in CDCl_3

¹H NMR spectrum of **10** in CDCl₃