

Supporting Information

The Sonogashira Coupling of Aryl Halides Catalyzed by Palladium on Charcoal

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General. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification including, acetone, dichloromethane, diethylether, di(ethylene glycol) dibutyl ether, diisopropilamine, n-hexane, methanol, PPh_3 , CuI , $\text{Pd}(\text{OAc})_2$, 2-bromopyridine, 3-bromopyridine, 3-bromotoluene, 4-bromotoluene, 3-butyn-1-ol, 2-methyl-3-butyn-2-ol, 1-hexyne, MgSO_4 . Dioxane, N,N-dimethylacetamide (DMA), toluene and distilled water were purged with argon prior to use. SELCAT Q6 Pd/C contains 10 wt% Pd. All reactions were performed under an atmosphere of argon. Analytical thin-layer chromatography (TLC) was performed on pre-coated plastic TLC plates with 0.25mm silica gel. Visualization was performed with a 254 nm UV lamp. Silica gel column chromatography was carried out with Flash silica gel (0.040 – 0.063 mm). All melting point values are uncorrected. The ^1H and ^{13}C NMR spectra were recorded in CDCl_3 . Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards: chloroform (δ 7.26 for ^1H , δ 77.00 for ^{13}C). Coupling constants (J) are reported in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad singlet), dd (doublet doublet). Gas chromatographic measurements were performed with a 10 m x 0.25 mm column with 0.12 μm CP-SIL 5CB coating, using H_2 carrier gas. Combination gas chromatography and low resolution mass spectrometry was obtained on a 30 m x 0.25 mm column with 0.25 μm RH-5 MS+ coating, He carrier gas coupled with a mass spectrometer (Ion source: EI+, 70eV, 250°C; interface: 250°C). In the GC measurements di(ethylene glycol) dibutyl ether (40 μl per reaction) was used as internal standard.

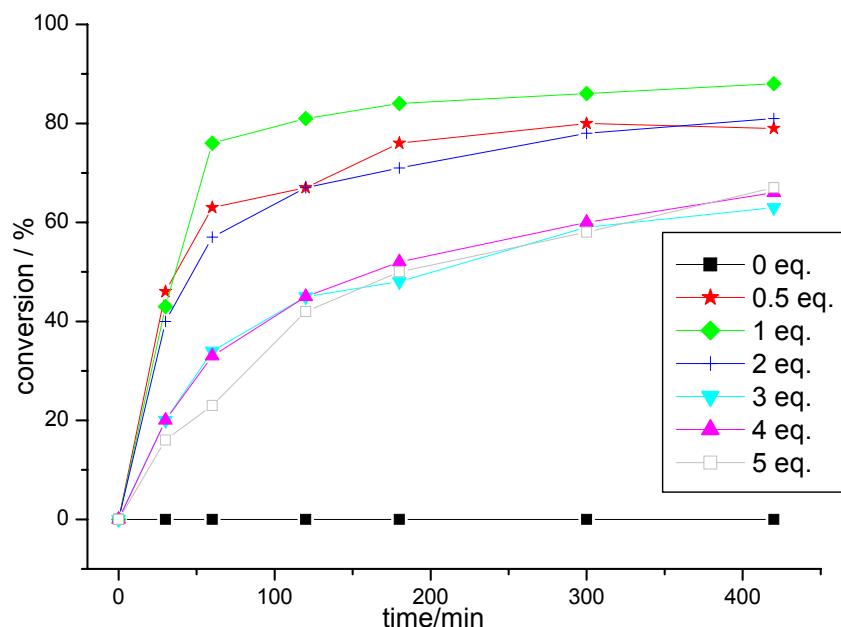
Synthetic procedures.

General procedure for the examination of solvent dependence of the conversion in Sonogashira coupling reactions: A dry Schlenk-flask was charged with 25.6 mg Pd/C (0.025 mmol Pd, 5%), 9.6 mg (0.05 mmol, 10%) CuI , 13.1 mg (0.05 mmol, 10%) PPh_3 and 1ml solvent or solvent mixture. After the addition of 0.5 mmol aryl halide, 105 μl (75 mg, 0.75 mmol) diisopropylamine and 0.64 mmol acetylene the reaction mixture was purged with argon, sealed and stirred at 80°C for 24 hours. Samples were taken by syringe after 24 hours, and analyzed by GC after dilution with methanol.

General procedure for examination of the effect of palladium to ligand ratio on the Sonogashira coupling using charcoal supported catalyst: A dry Schlenk-flask was charged with 25.6 mg Pd/C (0.025 mmol Pd, 5%), 4.8 mg (0.025 mmol, 5%) CuI and the appropriate amount of PPh₃ (Table 1.), followed by 0.950 ml DMA and 0.050 ml distilled water. After the addition of 48 μ l (79 mg, 0.5 mmol) 2-bromopyridine, 105 μ l (75 mg, 0.75 mmol) diisopropylamine and 100 μ l (87 mg, 1.03 mmol) 2-methyl-3-butyn-2-ol the reaction mixture was purged with argon and after sealing stirred at 80°C. The samples taken from the reaction mixture during the process were diluted with methanol and analyzed by GC. Results are summarized in Graph S1.

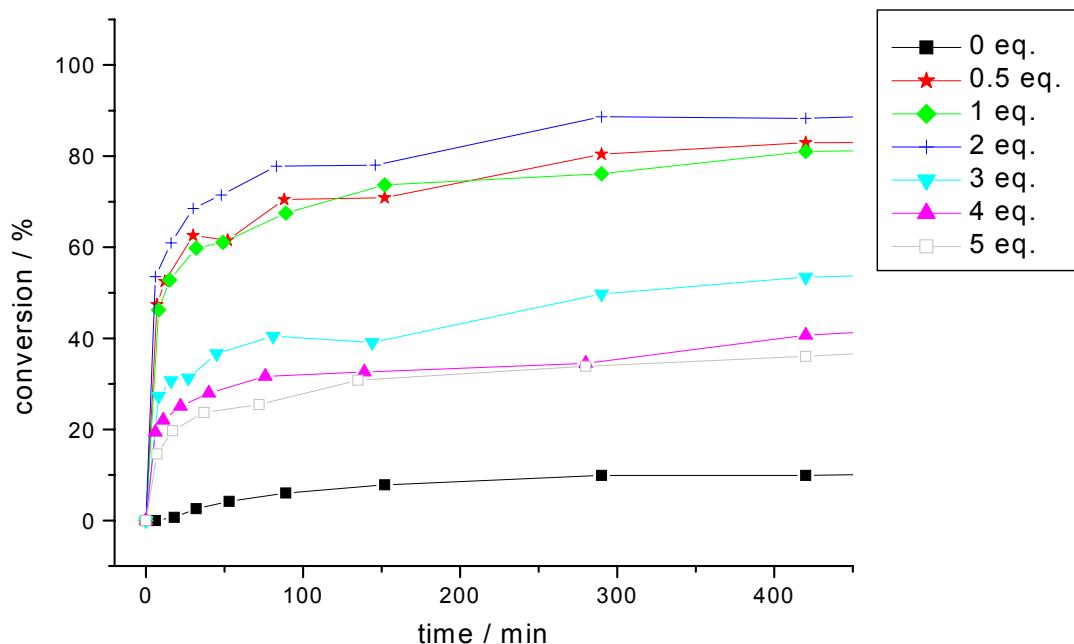
Equivalent	mg	mmol	mol%
0	0	0	0
0.5	3.3	0.0125	2.5
1	6.6	0.025	5
2	13.1	0.05	10
3	19.7	0.075	15
4	26.2	0.1	20
5	32.8	0.125	25

Table S1. The amount of PPh₃ used in the coupling reactions



Graph S1. Time – conversion curves of the Pd/C catalyzed reactions run at different PPh₃:Pd ratios

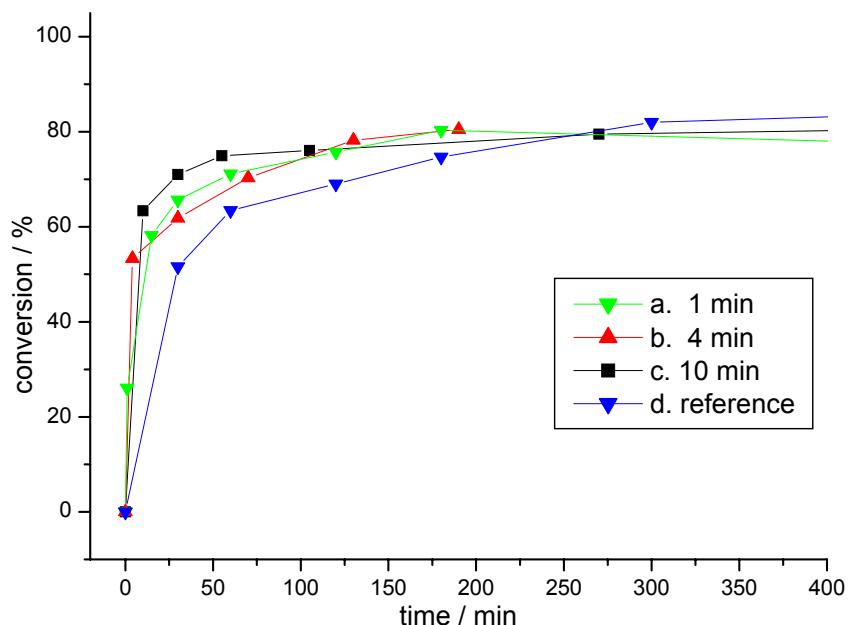
General procedure for examination of the effect of palladium to ligand ratio on Sonogashira coupling using $\text{Pd}(\text{OAc})_2$ catalyst: A dry Schlenk-flask was charged with 5.6 mg $\text{Pd}(\text{OAc})_2$ (0.025 mmol, 5%), 4.8 mg (0.025 mmol, 5%) CuI and the appropriate amount of PPh_3 (Table 1.), followed by 0.950 ml DMA and 0.050 ml distilled water. After the addition of 48 μl (79 mg, 0.5 mmol) 2-bromopyridine, 105 μl (75 mg, 0.75 mmol) diisopropylamine and 100 μl (87 mg, 1.03 mmol) 2-methyl-3-butyn-2-ol the reaction mixture was purged with argon and after sealing stirred at 80°C. The samples taken from the reaction mixture during the process were diluted with methanol and analyzed by GC. Results are summarized in Graph S2.



Graph S2. Time - conversion curves of the $\text{Pd}(\text{OAc})_2$ catalyzed reactions run at different $\text{PPh}_3:\text{Pd}$ ratios

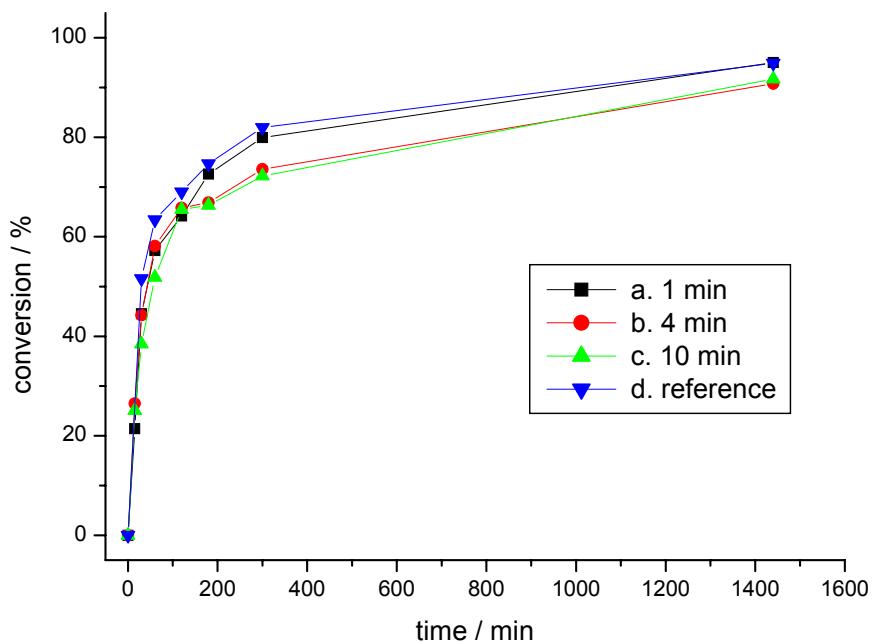
General procedure for the phase separation reactions: Four Schlenk-flasks were charged with 51.2 mg Pd/C (0.05 mmol Pd, 5%), 9.6 mg (0.05 mmol, 5%) CuI and 13.1 mg (0.1 mmol, 10%) PPh_3 , followed by 1.900 ml DMA and 0.100 ml distilled water. After the addition of 96 μl (158 mg, 1 mmol) 2-bromopyridine, 210 μl (150 mg, 1.5 mmol) diisopropylamine and 200 μl (174 mg, 2.06 mmol) 2-methyl-3-butyn-2-ol the reaction mixture was purged with argon and after sealing stirred at 70°C. Three of the reaction mixtures were filtered hot after 1, 4 and 10 minutes respectively

under argon atmosphere into clean, flame dried Schlenk-flasks, which were preheated in a 70°C oil bath and after sealing the reactions were continued at this temperature. The samples taken from the reaction mixtures during the process were diluted with methanol and analyzed by GC. Results are summarized in Graph S3.



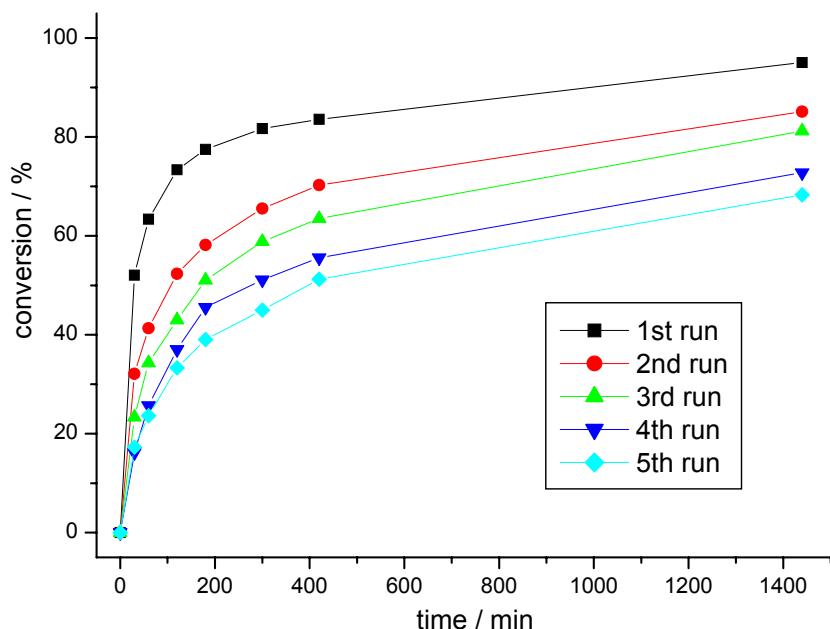
Graph S3. Time – conversion curves of the reactions from which Pd/C was removed: a: the charcoal was filtered after 1 minute reaction time and the first sample was taken from the homogeneous system at 4 minutes. b: the charcoal was filtered after 4 minutes and the first sample was taken from the homogeneous system at 7 minutes. c: the charcoal was filtered after 10 minutes and the first sample was taken from the homogeneous system at 13 minutes. d: the charcoal was not separated (heterogeneous conditions).

To 25.6 mg aliquots of the charcoal separated in the previous experiments, 4.8 mg (0.025 mmol, 5%) CuI and 13.1 mg (0.1 mmol, 10%) PPh₃, 0.950 ml DMA, 0.050 ml distilled water, 0.048 ml (0.079 g, 0.5 mmol) 2-bromopyridine 105 µl (75 mg, 0.75 mmol) diisopropylamine and 100 µl (868 mg, 1.03 mmol) 2-methyl-3-butyn-2-ol was added. The reaction mixtures were purged with argon, sealed and stirred at 70°C. The samples taken from the reaction mixtures during the process were diluted with methanol and analyzed by GC. Results are summarized in Graph S4.



Graph S4. Time – conversion curves of the reactions using the charcoal separated from the previous experiments at different reaction times. a: the charcoal was separated after 1 minute reaction time; b: the charcoal was separated after 4 minute reaction time; c: the charcoal was separated after 10 minute reaction time; d: reaction with “fresh” Pd/C catalyst (reference).

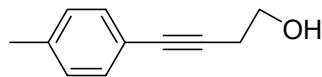
General procedure for Pd/C recycling experiments: A dry Schlenk-flask was charged with 51.2 mg Pd/C (0.05 mmol Pd, 5%), 9.6 mg (0.05 mmol, 5%) CuI and 13.1 mg (0.1 mmol, 10%) PPh_3 , followed by 0.950 ml DMA and 0.05 ml water. After the addition of 96 μl (158 mg, 1mmol) 2-bromopyridine, 210 μl (150 mg, 1.5 mmol) diisopropylamine and 200 μl (174 mg, 2.06 mmol) 2-methyl-3-butyn-2-ol the reaction mixture were purged with argon, sealed and stirred at 70°C. The samples taken from the reaction mixture during the process were diluted with methanol and analyzed by GC. After 24 hours the reaction was cooled to ambient temperature, the charcoal was filtered, washed with distilled water, acetone and dichloromethane and dried in an oven at 100°C for 5 hours. The recovered catalyst was reused four more times using the same ratio of the reaction components. Results are summarized on Graph S5.



Graph S5. Time – conversion curves of the subsequent reactions using the same solid supported catalyst.

General procedure for the preparative scale Sonogashira coupling reactions: A dry Schlenk-flask was charged with 0.512 g Pd/C (0.5 mmol Pd), 0.192 g (1 mmol, 10%) CuI and 0.262 g (1 mmol, 10%) PPh₃, followed by 9.5 ml DMA and 0.5 ml distilled water. After the addition of 10 mmol aryl halide, 2.1 ml (1.50 g, 15 mmol) diisopropylamine and 12.8 mmol acetylene the reaction mixture was purged with argon and it was stirred until completion (by GC) at 80°C. If the conversion did not reach 90% in 24 hours, then another 6 mmol of the acetylene was added and the reaction was continued for a maximum of 24 hours. After cooling to ambient temperature the charcoal was filtered off and the solution was diluted with water, and the aqueous phase was extracted with diethyl ether. The organic phases were combined and dried over MgSO₄. After removal of the solvents in vacuum the crude products were purified by column chromatography on silica gel using hexane/acetone mixtures as eluent.

Physical Characterization Data. Synthesis of acetylene derivatives were performed by the methods described above. All reactions were carried out on a 10 mmol scale. References are supplied for previously reported compounds.

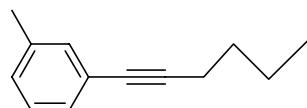


4a¹: Yield: 736 mg (4.6mmol, 46%), yellow crystalline solid. mp.: 22°C.

¹H NMR (CDCl₃; 250MHz): δ 7.20 (d, 2H, *J*=8.1 Hz), 6.97 (d, 2H, *J*=7.9 Hz), 3.68 (t, 2H, *J*=6.5 Hz), 2.643 (br s, 1H), 2.55 (t, 2H, *J*=6.3 Hz), 2.21 (s, 3H).

¹³C NMR (CDCl₃, 62.5 MHz): δ 138.3, 131.9, 129.4, 120.7, 86.2, 82.8, 61.5, 24.1, 21.8.

GC-MS (EI, 70eV) m/z for C₁₁H₁₂O (% relative intensity, ion): 160(24, [M]⁺), 142(4), 130(66), 129(100), 128(92), 115(76), 102(12), 91(7), 77(27).

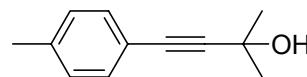


4b²: Yield: 533 mg (3.1mmol, 31%), yellow oil.

¹H NMR (CDCl₃; 250MHz): δ 7.20 (d, 2H, *J*=8.3 Hz), 6.99 (d, 2H, *J*=8.0 Hz), 2.31 (t, 2H, *J*=6.9 Hz), 2.2 (s, 3H), 1.53-1.19 (m, 4H), 0.86 (t, 3H, *J*=7.3 Hz).

¹³C NMR (CDCl₃, 62.5 MHz): δ 137.7, 131.8, 129.3, 121.4, 89.9, 80.9, 31.3, 22.4, 21, 7, 19.5, 14.5.

GC-MS (EI, 70eV) m/z for C₁₃H₁₆ (% relative intensity, ion): 173(3), 172(4, [M]⁺), 171(6), 157(27), 143(47), 142(42), 129(100), 128(60), 115(36), 103(5), 91(4), 77(39).

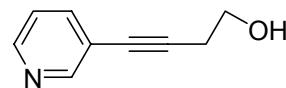


4c³: Yield: 877 mg (5.1mmol, 51%), yellow crystalline solid. mp.: 43°C.

¹H NMR (CDCl₃; 250MHz): δ 7.20 (d, 2H, *J*=8.0 Hz), 6.95 (d, 2H, *J*=8.0 Hz), 2.86 (br s, 1H), 2.20 (s, 3H), 1.50 (s, 6H).

¹³C NMR (CDCl₃, 62.5 MHz): δ 138.0, 131.4, 128.8, 119.6, 93.2, 82.0, 65.4, 31.3, 21.2.

GC-MS (EI, 70eV) m/z for C₁₂H₁₄O (% relative intensity, ion): 175(10, [M+1]⁺), 173(20, [M-1]⁺), 160(22), 159(100), 156(13), 141(20), 131(41), 128(25), 117(32), 91(14), 79(29).

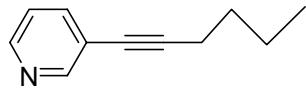


5a⁴: Yield 1132 mg (7.7mmol, 77%), yellow oil.

¹H NMR (CDCl₃; 250MHz): δ 8.53 (d, 1H, *J*=2.0 Hz), 8.37 (d, 1H, *J* = 4.9 Hz), 7.60 (d, 1H, *J* = 7.8 Hz), 7.16-7.10 (m, 1H), 4.19 (br s, 1H), 3.75 (t, 2H, *J*=6.6 Hz), 2.62 (t, 2H, *J*=6.5 Hz).

¹³C NMR (CDCl₃, 62.5 MHz): δ 151.8, 147.5, 138.7, 128.3, 122.9, 91.1, 78.1, 60.4, 23.6.

GC-MS (EI, 70eV) m/z for C₉H₉NO (% relative intensity, ion): 148(14, [M+1]⁺), 147(71, [M]⁺), 146(16, [M-1]⁺), 130(7), 129(14), 118(26), 117(100), 116(67), 101(4), 90(53), 89(61), 79(4).

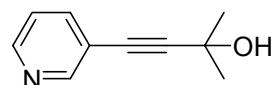


5b⁵: Yield: 1288 mg (8.1mmol, 81%), yellow oil.

¹H NMR (CDCl₃; 250MHz): δ 8.62 (d, 1H, *J*=2.1 Hz), 8.47 (d, 1H, *J* = 4.89 Hz), 7.67 (d, 1H, *J* = 7.9 Hz), 7.23-7.17 (m, 1H), 2.43 (t, 2H, *J* = 6.91 Hz), 1.63-1.43 (m, 4H), 0.95 (t, 3H, *J*=7.2 Hz).

¹³C NMR (CDCl₃, 62.5 MHz): δ 152.3, 147.9, 138.4, 122.9, 121.2, 94.1, 77.6, 30.6, 22.0, 19.1, 13.6.

GC-MS (EI, 70eV) m/z for C₁₁H₁₃N (% relative intensity, ion): 160(8, [M+1]⁺), 159(21, [M]⁺), 144(100), 131(14), 130(50), 117(51), 116(69), 103(16), 89(27).

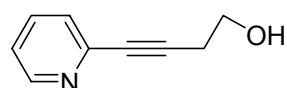


5c⁶: Yield: 1111 mg (6.9mmol, 69%), yellow crystalline solid. mp.:53°C.

¹H NMR (CDCl₃; 250MHz): δ 8.68 (d, 1H, *J*=1.3 Hz), 8.40 (d, 1H, *J* = 4.9 Hz), 7.62 (d, 1H, *J* = 7.9 Hz), 7.28-7.14 (m, 1H), 5.29 (br s, 1H), 1.54 (s, 6H).

¹³C NMR (CDCl₃, 62.5 MHz): δ 151.6, 147.6, 138.8, 123.1, 120.3, 98.6, 77.9, 64.6, 31.2.

GC-MS (EI, 70eV) m/z for C₁₀H₁₁NO (% relative intensity, ion): 161(9, [M]⁺), 160(7, [M-1]⁺), 147(6), 146(98), 130(14), 118(36), 117(19), 104(63), 103(24), 91(12).

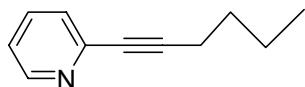


10a⁷: Yield: 853 mg (5.8mmol, 58%), yellow oil.

¹H NMR (CDCl₃; 250MHz): δ 8.42 (d, 1H, *J*= 4.9 Hz), 7.55 (t, 1H, *J*= 7.7 Hz), 7.29 (d, 1H, *J*= 7.8 Hz), 7.14-7.08(m, 1H), 4.60 (br s, 1H), 3.79 (t, 2H, *J*=6.6 Hz), 2.63 (t, 2H, *J*=6.6 Hz).

¹³C NMR (CDCl₃, 62.5 MHz): δ 149.2, 143.1, 136.2, 126.6, 122.4, 88.4, 81.0, 60.2, 23.5.

GC-MS (EI, 70eV) m/z for C₉H₉NO (% relative intensity, ion): 147(3, [M]⁺), 146(2, [M-1]⁺), 130(6), 129(6), 118(27), 117(100), 116(18), 90(38), 89(38), 78(12).

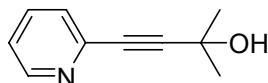


10b⁸: Yield: 986 mg (6.2mmol, 62%) from **6** or 858 mg (5.4 mmol, 54%) for **8**, yellow oil.

¹H NMR (CDCl₃; 250MHz): δ 8.45 (d, 1H, *J*=4.9 Hz), 7.52 (t, 1H, *J*= 7.7 Hz), 7.27 (d, 1H, *J*= 7.8 Hz), 7.11-7.06 (m, 1H), 2.36 (t, 2H, *J*= 7.1 Hz), 1.57-1.35 (m, 4H), 0.86 (t, 3H, *J*=7.2 Hz).

¹³C NMR (CDCl₃, 62.5 MHz): δ 148.8, 142.9, 154.0, 125.7, 121.2, 90.2, 79.3, 29.4, 21.0, 18.0, 12.6.

GC-MS (EI, 70eV) m/z for C₁₁H₁₃N (% relative intensity, ion): 159(41, [M]⁺), 158(59, [M-1]⁺), 144(52), 131(37), 130(100), 118(23), 117(70)116(26), 103(17), 90(32), 89(34), 78(30).

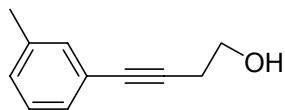


10c⁶: Yield: 1046 mg (6.5mmol, 65%) from **6** and 820 mg (5.1 mmol, 51%) from **8**, yellow crystalline solid. m.p.: 61°C.

¹H NMR (CDCl₃; 250MHz): δ 8.47 (d, 1H, *J*= 4.6 Hz), 7.53 (t, 1H, *J*= 7.7 Hz), 7.28 (d, 1H, *J*= 7.8 Hz), 7.14-7.08(m, 1H), 4.71(br s, 1H), 1.57(s, 6H).

¹³C NMR (CDCl₃, 62.5 MHz): δ 148.5, 141.9, 135.3, 126.1, 121.8, 94.0, 79.9, 63.9, 30.2.

GC-MS (EI, 70eV) m/z for C₁₀H₁₁NO (% relative intensity, ion): 162(2, [M+1]⁺), 161(2, [M]⁺), 160(5, [M-1]⁺), 147(17), 146(100), 118(58), 117(25), 104(80), 103(13), 90(8), 78(53).

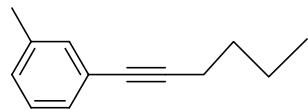


11a⁹: Yield: 704 mg (4.4 mmol, 44%), yellow oil.

¹H NMR (CDCl₃; 250MHz): δ 7.20-6.99 (m, 4H), 3.70 (t, 2H, *J*=6.5 Hz), 2.58 (t, 2H, *J*=6.3 Hz), 2.28 (br s, 1H), 2.22 (s, 3H).

¹³C NMR (CDCl₃, 62.5 MHz): δ 137.8, 132.2, 128.7, 128.6, 128.1, 123.0, 85.9, 82.4, 61.1, 23.7, 21.1.

GC-MS (EI, 70eV) m/z for C₁₁H₁₂O (% relative intensity, ion): 160(22, [M]⁺), 141(5), 130(67), 129(100), 158(90), 115(88), 102(13), 91(7), 77(57).

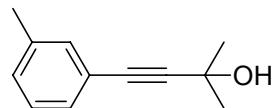


11b¹⁰: Yield: 447 mg (2.6 mmol, 26%), yellow oil.

¹H NMR (CDCl₃; 250MHz): δ 7.14-6.96 (m, 4H), 2.31 (t, 2H, *J*=7.0 Hz), 2.21 (s, 3H), 1.53-1.35 (m, 4H), 0.86 (t, 3H, *J*=7.2 Hz).

¹³C NMR (CDCl₃, 62.5 MHz): δ 137.7, 132.1, 128.6, 128.3, 128.0, 123.9, 89.9, 80.7, 30.8, 22.00, 21.1, 19.1, 13.7.

GC-MS (EI, 70eV) m/z for C₁₃H₁₆ (% relative intensity, ion): 172(34, [M]⁺), 158(11), 157(65), 143(70), 142(56), 129(100), 128(63), 115(41), 103(4), 101(6), 91(1), 77(20).



11c³: Yield: 835 mg (4.8mmol, 48%), yellow oil.

¹H NMR (CDCl₃; 250MHz): δ 7.14-6.98 (m, 4H), 2.50 (br s, 1H), 2.20 (s, 3H), 1.57 (s, 6H).

¹³C NMR (CDCl₃, 62.5 MHz): δ 137.8, 132.1, 129.0, 128.6, 128.0, 122.5, 93.5, 82.1, 65.4, 31.4, 21.0.

GC-MS (EI, 70eV) m/z for C₁₂H₁₄O (% relative intensity, ion): 174(30, [M]⁺), 173(15), 160(25), 159(100), 143(14), 141(14), 131(17), 116(23), 115(43), 91(13), 79(33).

References

- [1] Collins, C. J.; Hanack, M.; Stutz, H.; Auchter, G.; Schoberth, W. *J. Org. Chem.* **1983**, *48*, 5260-5268.
- [2] Sato, H.; Isono, N.; Miyoshi, I.; Mori, M. *Tetrahedron* **1996**, *52*, 8143-8158.
- [3] Dolog, L.; Koerner, B.; Heinze, J.; Yang, J. *Liebigs Ann. Org. Bioorg. Chem.* **1995**, *9*, 1663-1672.
- [4] Glase, S. A.; Akunne, H. C.; Heffner, T. G.; Jaen, J. C.; MacKenzie, R. G. *J. Med. Chem.* **1996**, *39*, 3179-3187.
- [5] Abele, E.; Abele, R.; Gaukhman, A.; Lukevics, E. *Chem. Heterocycl. Comp.* **1998**, *34*, 518-521.
- [6] Rodriguez, J. G.; Martin-Villamil, R.; Cano, F. H.; Fonseca, I. *J. Chem. Soc. Perkin Trans. 1* **1997**, *5*, 709-714.
- [7] Lautens, M.; Yoshida, M. *Org. Lett.* **2002**, *4*, 123-125.
- [8] Sato, N.; Hayakawa, A.; Takeuchi, R. *J. Heterocycl. Chem.* **1990**, *27*, 503-506
- [9] Prestwich, G. D.; Eng, W.; Deaton, E.; Wichern, D. *J. Chem. Ecology* **1984**, *10*, 1201-1217.
- [10] Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412-420.