Unsymmetrical coupling of 1-chloroalkynes and terminal alkynes under experimental Sonogashira conditions

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SUPPORTING INFORMATION

General Methods
Chemicals were purchased from Sigma-Aldrich, Merck, Acros, and GFS Chemicals and were used as received. Dry THF was obtained from a Solvent Purification System, Innovative Technology, Inc. All reactions were carried out under an inert atmosphere of argon, and the solvents were degassed with a sonicator under argon atmosphere prior to use. Purification of products was carried out by flash chromatography on silica gel (ROCC 40–63 micron). Thin-layer chromatography (TLC) was carried out using aluminum sheets pre-coated with silica gel 60F (Merck 5554). The plates were inspected under UV light. NMR spectra were recorded on a 500-MHz Bruker instrument with cryoprobe using the residual solvent as the internal standard. All chemical shifts are quoted on the $\delta$ scale (ppm) and are referenced to the solvent residual signal (CDCl$_3$: 7.26 and 77.16 for $^1$H and $^{13}$C, respectively). All coupling constants ($J$) are expressed in Hz. Gas chromatography (GC) mass spectra (MS) were recorded on an Agilent 6890A (G1530A) gas chromatograph coupled with an Agilent mass selective detector 5973Network. High resolution mass spectra (HR-MS) were obtained on a Bruker MicrOTOF-QII-system with electrospray ionization (ESP) source. Melting points were determined using a Stuart SMP 40 automatic melting point machine and are uncorrected. Elemental analyses were obtained at Department of Chemistry, University of Copenhagen.
Synthesis

4-[(Trimethylsilyl)buta-1,3-diy-1-yl]benzonitrile (2). To a solution of 1 (50 mg, 0.31 mmol) in degassed THF (5 mL) and diisopropylamine (1 mL) was added PdCl₂(PPh₃)₂ (11 mg, 0.016 mmol) and CuI (3 mg, 0.016 mmol) and trimethylsilylacetylene (91 mg, 0.93 mmol). After 2 h of stirring at rt, the reaction mixture was separated between CH₂Cl₂ (25 mL) and saturated aqueous ammonium chloride (25 mL). The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Flash column chromatography (SiO₂, CH₂Cl₂:heptane 1:1) gave 2 as a white solid (52 mg, 75%). MP: 145 – 147 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.61 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 0.24 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 133.24, 132.22, 126.60, 118.32, 112.69, 93.87, 87.12, 78.35, 74.57, -0.36. MS (GC-MS): m/z = 223.1 [M⁺].


4-(Phenylbuta-1,3-diy-1-yl)benzonitrile (3). To a solution of 1 (50 mg, 0.31 mmol) in degassed THF (5 mL) and diisopropylamine (1 mL) was added PdCl₂(PPh₃)₂ (11 mg, 0.016 mmol), CuI (3 mg, 0.016 mmol) and phenylacetylene (95 mg, 0.93 mmol). After 2 h of stirring at rt, the reaction mixture was separated between CH₂Cl₂ (25 mL) and saturated aqueous ammonium chloride (25 mL). The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Flash column chromatography (SiO₂, CH₂Cl₂:heptane 1:1) gave 3 as a yellow powder (51 mg, 72%). MP: 200 – 202 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.63 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 6.9 Hz, 2H), 0.24 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 133.06, 132.78, 132.25, 129.88, 128.70, 126.99, 121.32, 118.40, 112.52, 84.09, 79.45, 78.30, 73.37. MS (GC-MS): m/z = 227.1 [M⁺].

4-[(4-Methoxyphenyl)buta-1,3-diy-1-yl]benzonitrile (4). To a solution of 1 (50 mg, 0.31 mmol) in degassed THF (5 mL) and diisopropylamine (1 mL) was added PdCl$_2$(PPh$_3$)$_2$ (11 mg, 0.016 mmol) and CuI (3 mg, 0.016 mmol) and $p$-methoxyphenylacetylene (123 mg, 0.93 mmol). After 3 h of stirring at rt, the reaction mixture was separated between CH$_2$Cl$_2$ (25 mL) and saturated aqueous ammonium chloride (25 mL). The organic phase was washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. Flash column chromatography (SiO$_2$, CH$_2$Cl$_2$:heptane 3:2) gave 4 as an off-white powder (46 mg, 58%). MP: 234 – 237 °C (decomp.). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.62 (d, $J$ = 8.6 Hz, 2H), 7.58 (d, $J$ = 8.6 Hz, 2H), 7.49 (d, $J$ = 8.9 Hz, 2H), 6.87 (d, $J$ = 8.9 Hz, 2H), 3.84 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 160.92, 134.47, 132.97, 132.22, 127.25, 118.46, 114.43, 113.17, 112.28, 84.52, 79.06, 78.69, 72.34, 55.55. MS (GC-MS): $m/z$ = 257.2 [M$^+$]. HR-MS (ESP+): $m/z$ = 258.0909 [M+H$^+$] (calcd. for C$_{18}$H$_{12}$NO$: 258.0913$).

4-[(4-Nitrophenyl)buta-1,3-diy-1-yl]benzonitrile (5). To a solution of 1 (50 mg, 0.31 mmol) in degassed THF (5 mL) and diisopropylamine (1 mL) was added PdCl$_2$(PPh$_3$)$_2$ (11 mg, 0.016 mmol), CuI (3 mg, 0.016 mmol) and 1-ethynyl-4-nitrobenzene (118 mg, 0.80 mmol). After 3 h of stirring at rt, the reaction mixture was separated between CH$_2$Cl$_2$ (25 mL) and saturated aqueous ammonium chloride (25 mL). The organic phase was washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. Flash column chromatography (SiO$_2$, CH$_2$Cl$_2$) gave 5 as a yellow solid (49 mg, 58%). MP: 246 – 248 °C. $^1$H NMR (500 MHz, Acetone-$d_6$) $\delta$ 8.32 (d, $J$ = 9.0 Hz, 2H), 7.91 (d, $J$ = 9.0 Hz, 2H), 7.89 (d, $J$ = 8.7 Hz, 2H), 7.84 (d, $J$ = 8.7 Hz, 2H). $^{13}$C NMR (126 MHz, Acetone-$d_6$) $\delta$ 149.10, 134.60, 134.17, 133.43, 128.35, 126.36, 124.76, 118.66, 114.11, 82.58, 81.91, 77.74, 76.98. MS (GC-MS): $m/z$ = 272.1 [M$^+$]. HR-MS (ESP+): $m/z$ = 273.0660 [M+H$^+$] (calcd. for C$_{17}$H$_9$N$_2$O$_2^+$: 273.0659).
Trimethyl(phenylbuta-1,3-diyn-1-yl)disilane (9). General procedure: Chloroalkyne 8 (100 mg, 0.732 mmol) was dissolved in THF (10 mL) and diisopropylamine (2 mL). To the solution was added the palladium catalyst (1-5 %), CuI (5-10 %) and trimethylsilylacetylene (1-3 equiv.). After stirring the mixture at rt for the desired reaction time (3-24 h), saturated aqueous NH₄Cl (25 mL) was added, and the mixture was extracted with CH₂Cl₂ (50 mL), washed with brine (25 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was analyzed by GC-MS. An analytical sample of 9 was obtained by flash column chromatography (SiO₂, CH₂Cl₂:heptane 1:9) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.52 – 7.45 (m, 2H), 7.37 – 7.29 (m, 3H), 0.23 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 132.82, 129.47, 128.56, 121.53, 90.79, 87.95, 77.37, 74.27, -0.23. MS (GC-MS): m/z = 198.1 [M⁺].

For an alternative synthesis, see for example: Gung, B. W.; Kumi, G. J. Org. Chem. 1990, 55, 1311.

[(4-Bromophenyl)buta-1,3-diyn-1-yl]trimethylsilane (14). Compound 13 (116 mg, 0.54 mmol) was dissolved in THF (10 mL) and diisopropylamine (2 mL). PdCl₂(PPPh₃)₂ (19 mg, 0.027 mmol), CuI (5 mg, 0.03 mmol) and trimethylsilylacetylene (58 mg, 0.59 mmol) were added and the mixture was stirred for 3 h. Saturated aqueous NH₄Cl was added, and the mixture was extracted with CH₂Cl₂, washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Flash column chromatography (SiO₂, heptanes) gave 14 as a white solid (94 mg, 63%). MP: 75.2 – 76.6 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.45 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 0.23 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 134.14, 131.92, 123.98, 120.51, 91.67, 87.68, 75.68, 75.39, -0.28. MS (GC-MS): m/z = 276.1 [M⁺].

GC-MS of the crude reaction mixture showed minor quantities of compounds 15 and 16:

1-Chloro-1-octyne (20). To a solution of 1-octyne (2.10 g, 19.0 mmol) in THF (20 mL) at 0 °C was added n-BuLi (8.0 mL, 2.5 M in hexanes, 20 mmol). A solution of benzenesulfonyl chloride (4.00 g, 22.6 mmol) in THF (6 mL) was added while the temperature was kept at 0 °C. After the addition, the temperature was slowly raised to 35 °C and kept there for 1 h. Water (40 mL) was added, and the mixture was cooled to rt, extracted with pentane (5 x 25 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was dissolved in pentane and passed through a plug of SiO₂ with heptane to give 20 (1.87 g, 68%) as a colorless oil. \( \delta \) H NMR (500 MHz, CDCl₃) \( \delta \) 2.16 (t, \( J = 7.1 \) Hz, 2H), 1.54 – 1.44 (m, 3H), 1.42 – 1.22 (m, 6H), 0.89 (t, \( J = 7.1 \) Hz, 3H). \( ^{13} \)C NMR (126 MHz, CDCl₃) \( \delta \) 69.92, 57.02, 31.44, 28.62, 28.47, 22.69, 18.89, 14.22. MS (GC-MS) \( m/z \) = 115.2 [M-CH₂CH₃]⁺.

Competition experiment. Chloroalkyne 1 (118 mg, 0.732 mmol) and 4-bromobenzonitrile (6) (133 mg, 0.732 mmol) were dissolved in THF (10 mL) and diisopropylamine (2 mL). To the solution was added PdCl$_2$(PPh$_3$)$_2$ (26 mg, 0.037 mmol), CuI (7 mg, 0.04 mmol) and trimethylsilylacetylene (ca. 72 mg, ca. 0.73 mmol). After stirring the mixture at rt for 2 h, saturated aqueous NH$_4$Cl (25 mL) was added, and the mixture was extracted with CH$_2$Cl$_2$ (50 mL), washed with brine (25 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was analyzed by GC-MS.
**Competition experiments.** Chloroalkyne 8 (100 mg, 0.732 mmol) and the desired aryl- or vinyl halide (0.732 mmol) were dissolved in THF (10 mL) and diisopropylamine (2 mL). To the solution was added PdCl$_2$(PPh$_3$)$_2$ (26 mg, 0.037 mmol), CuI (7 mg, 0.04 mmol) and trimethylsilylacetylene (ca. 72 mg, ca. 0.73 mmol). After stirring the mixture at rt for 2 h, saturated aqueous NH$_4$Cl (25 mL) was added, and the mixture was extracted with CH$_2$Cl$_2$ (50 mL), washed with brine (25 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was analyzed by GC-MS.

![Retention time graph](image)

Total ion count from competition experiment, $X = \text{Br}$. 

**Chemical structures:**
- **8:** Chloroalkyne with Ph-X (X = Br or I)
- **9-12:** Products from reaction with PdCl$_2$(PPh$_3$)$_2$, CuI, i-Pr$_2$NH, THF, and trimethylsilylacetylene.
- **13-16:** Products from reaction with PdCl$_2$(PPh$_3$)$_2$, CuI, i-Pr$_2$NH, THF, and Br or I.

**Legend:**
- Ph: Phenyl
- Cl: Chlorine
- SiMe$_3$: Trimethylsilyl
- PdCl$_2$(PPh$_3$)$_2$: Palladium(II) chloride (dichloro)diphenyltriphosphine adduct
- CuI: Cuprous iodide
- i-Pr$_2$NH: Diisopropylamine
- THF: Tetrahydrofuran
- **17:** Product from reaction with PdCl$_2$(PPh$_3$)$_2$, CuI, i-Pr$_2$NH, THF, and Br.
- **18:** Product from reaction with PdCl$_2$(PPh$_3$)$_2$, CuI, i-Pr$_2$NH, THF, and I.
Total ion count from competition experiment, $X = I$.

Total ion count from competition experiment. * Neighbor peaks are assigned to *cis/trans-*isomers.
**Competition experiment.** Chloroalkyne 20 (106 mg, 0.732 mmol) and bromobenzene (115 mg, 0.732 mmol) or iodobenzene (149 mg, 0.732 mmol) was dissolved in THF (10 mL) and diisopropylamine (2 mL). To the solution was added PdCl$_2$(PPh$_3$)$_2$ (26 mg, 0.037 mmol), CuI (7 mg, 0.04 mmol), and trimethylsilylacetylene (ca. 72 mg, 0.732 mmol). After stirring the mixture at rt for 2 h, saturated aqueous NH$_4$Cl (25 mL) was added, and the mixture was extracted with CH$_2$Cl$_2$ (50 mL), washed with brine (25 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was analyzed by GC-MS.
Comparison of Compound Ratios Obtained by GC-MS and $^1$H-NMR Spectroscopy

Pure compounds were mixed in CDCl$_3$ and ratios between the compounds were estimated by GC-MS and $^1$H-NMR (500 MHz) analysis.

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Comparison of GC-MS Ratios to Ratios Based on Balanced-out Amounts

=>$>$ too low intensity of arylhalides in GC-MS
Validation of GC-MS Ratios Between 9 and 11 Obtained in Optimization Experiments

Comparison of GC-MS ratios to ratios based on balanced-out amounts

Area Percent Report

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Misc: ALS Vial: 6 Sample Multiplier: 1
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Sum of corrected areas: 1319672307


Abundance

Time→

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TIC: 8176.D\data.ms

(μmol) Molar ratio GC-MS

| 5.0 mg (25.2) | 36.2 | 35.7 |
| 9.0 mg (44.5) | 63.8 | 64.3 |
Validation of GC-MS Ratios Between 9 and 11 Obtained in Optimization Experiments

Comparison of GC-MS ratios to ratios based on balanced-out amounts

Area Percent Report

Validation of GC-MS Ratios Between 9 and 11 Obtained in Optimization Experiments

Comparison of GC-MS ratios to ratios based on balanced-out amounts
Comparison of Pd Catalysts by TLC Analysis

- **TLC analysis after 2 h (shown to the left below):**
  With PdCl$_2$(PPh$_3$)$_2$, the reaction is complete. With Pd(PPh$_3$)$_4$ or PdCl$_2$(PPh$_3$)$_2$ + 2 equiv. PPh$_3$, only starting material (8) is visible.

- **TLC analysis after 17 h (shown to the right below):**
  With Pd(PPh$_3$)$_4$, the reaction seems almost complete. With PdCl$_2$(PPh$_3$)$_2$ + 2 equiv. PPh$_3$, the reaction is not complete.

Eluent: 10% CH$_2$Cl$_2$ in heptane
$^1$H NMR Spectrum of Compound 2

$^{13}$C NMR Spectrum of Compound 2
$^1$H NMR Spectrum of Compound 3

$^{13}$C NMR Spectrum of Compound 3
$^1$H NMR Spectrum of Compound 4

$^{13}$C NMR Spectrum of Compound 4
$^1$H NMR Spectrum of Compound 5

$^{13}$C NMR Spectrum of Compound 5
$^1$H NMR Spectrum of Compound 14

$^{13}$C NMR Spectrum of Compound 14
$^1$H NMR Spectrum of Compound 20

$^{13}$C NMR Spectrum of Compound 20
Mass Spectra of Compound 14 and of the By-products 15 and 16 (Crude Reaction Mixture):

**MS Spectrum of Compound 14 (m/z 276 M⁺)**

- 200.0
- 233.0
- 261.1

**MS Spectrum of Compound 15 (m/z 358 M⁺)**

- 200.1
- 230.0
- 254.0
- 281.0
- 307.8
- 339.9
- 359.9
MS Spectrum of Compound 16 (m/z 294 M+)

![MS Spectrum of Compound 16](image)
Mass Spectra Used in Analysis of GC-MS Data (Competition Experiments)

MS Spectrum of Compound 2 ($m/z$ 223 $M^+$)

MS Spectrum of Compound 9 ($m/z$ 198 $M^+$)
MS Spectrum of Compound 10 (m/z 174 M⁺)

MS Spectrum of Compound 11 (m/z 202 M⁺)
MS Spectrum of Compound 12 (m/z 178 M⁺)
MS Spectrum of Compound 18 (m/z 200 M⁺)

MS Spectrum of Compound 18* (m/z 200 M⁺)
MS Spectrum of Compound 21 ($m/z$ 191 [M-CH$_3$]$^{+}$+)

MS Spectrum of Compound 22 ($m/z$ 189 [M-CH$_2$CH$_3$]$^{+}$+)
MS Spectrum of Compound 23 ($m/z$ 186 M⁺)

MS Spectrum of PPh₃ ($m/z$ 262 M⁺)