A rhodium-catalysed Sonogashira-type coupling exploiting C-S functionalisation: Orthogonality with palladium-catalysed variants

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Electronic Supporting Information

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1 General Experimental Considerations

Reactions were performed under an inert atmosphere of nitrogen, using anhydrous solvent unless otherwise stated. All glassware was oven dried at >80 °C, and allowed to cool to room temperature under a positive nitrogen pressure. Reactions were monitored by TLC until deemed complete using aluminum backed silica plates. Plates were visualized under ultraviolet light and/or by staining with KMnO₄. Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Acros Organics Ltd., Lancaster Synthesis Ltd, or Strem Chemicals Inc. and were used as supplied unless otherwise stated. Ortho-xylene (<0.003% H₂O) was purchased from Sigma-Aldrich Chemical Co. Ltd. Anhydrous acetonitrile, diethylether, dichloromethane, toluene and tetrahydrofuran were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Acetone was distilled from Drierite®. Petrol refers to the fractions obtained between 30 °C and 40 °C. Ether refers to diethyl ether. Flash chromatography was carried out using matrix 60 silica.

¹H NMR spectra were obtained on a Bruker DQX-400 (400 MHz) spectrometer using the residual solvent as an internal standard. ¹³C NMR spectra were obtained on a Bruker DQX-400 (101 MHz) spectrometer using the solvent as an internal standard. Chemical shifts were reported in parts per million (ppm) with the multiplicities of the spectra reported as following: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Low-resolution ESI mass spectra were recorded on a Fisons Platform spectrometer. High-resolution ESI mass spectrometry measurements were recorded on a Bruker Daltronics microTOF (ESI) spectrometer by the internal service at the Department of Organic Chemistry, University of Oxford. Infra-red spectra were recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer. Melting points were determined using a Stuart Scientific Melting Point Apparatus SMP1.
2 General Procedures

Formation of ethynyl compounds via rhodium-catalysis

General procedure A

[Rh(nbd)$_2$].BF$_4$ (2.8 mg, 0.0075 mmol) and dcpe (3.2 mg, 0.0075 mmol) were dissolved in DCE (2 mL). H$_2$ gas was bubbled through the solution for 2 mins, and the solution was purged with N$_2$ gas for a further 30 secs. This was transferred via cannula to a mixture of aryl sulfide (0.15 mmol), alkyne (0.30 mmol), copper bromide (42 mg, 0.3 mmol) and silver carbonate (41 mg, 0.15 mmol). The reaction mixture was heated to 80 °C until completion, and allowed to cool to room temperature. The mixture was concentrated in vacuo and purified by flash chromatography to yield the product. (nbd = norbornadiene; dcpe = bis(dicyclohexylphosphino)ethane)

General procedure B

[Rh(nbd)$_2$].BF$_4$ (2.8 mg, 0.0075 mmol) and dcpe (3.2 mg, 0.0075 mmol) were dissolved in DCE (2 mL). H$_2$ gas was bubbled through the solution for 2 mins, and the solution was purged with N$_2$ gas for a further 30 secs. This was transferred via cannula to a mixture of aryl sulfide (0.15 mmol), alkyne (0.30 mmol), copper bromide (84 mg, 0.60 mmol) and potassium carbonate (40 mg, 0.30 mmol). The reaction mixture was heated to 80 °C until completion, and allowed to cool to room temperature. The mixture was concentrated in vacuo and purified by flash chromatography to yield the product. (nbd = norbornadiene; dcpe = bis(dicyclohexylphosphino)ethane)

Hydroacylation-Sonogashira cascade

General procedure C

[Rh(nbd)$_2$].BF$_4$ (5.6 mg, 0.015 mmol) and dcpe (6.3 mg, 0.015 mmol) were dissolved in DCE (2 mL). H$_2$ gas was bubbled through the solution for 2 mins, and the solution was purged with N$_2$ gas for a further 30 secs. This was transferred via cannula to a
mixture of aldehyde (0.30 mmol), alkyne (0.45 mmol) and stirred at room temperature until starting material was consumed. This was then transferred to a mixture containing copper bromide (86 mg, 0.60 mmol), silver carbonate (83 mg, 0.30 mmol) and the appropriate alkyne (0.60 mmol). The reaction mixture was stirred and heated to 80 °C until completion, and allowed to cool to room temperature. The mixture was concentrated in vacuo and purified by flash chromatography to yield the product. (nbd = norbornadiene; dcpe = bis(dicyclohexylphosphino)ethane)

**General procedure D**

[Rh(nbd)2].BF4 (5.6 mg, 0.015 mmol) and dcpe (6.3 mg, 0.015 mmol) were dissolved in DCE (2 mL). H2 gas was bubbled through the solution for 2 mins, and the solution was purged with N2 gas for a further 30 secs. This was transferred via cannula to a mixture of aldehyde (0.30 mmol), alkyne (0.45 mmol) and stirred at room temperature until starting material was consumed. This was then transferred to a mixture containing copper bromide (172 mg, 1.2 mmol), potassium carbonate (80 mg, 0.60 mmol) and the appropriate alkyne (0.60 mmol). The reaction mixture was stirred and heated to 80 °C until completion, and allowed to cool to room temperature. The mixture was concentrated in vacuo and purified by flash chromatography to yield the product. (nbd = norbornadiene; dcpe = bis(dicyclohexylphosphino)ethane)
3 Characterisation of Compounds

3.1 Sonogashira-type coupling products

1-(2-(Phenylethynyl)phenyl)ethanone, 3a

Prepared following general procedure A using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and phenylacetylene (33 μL, 0.30 mmol). After 16 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5% ether in petrol), to yield the product as a dark yellow oil (31 mg, 95%); $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.79 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.66 (dd, $J = 7.5, 1.0$ Hz, 1H), 7.60-7.57 (m, 2H), 7.50 (td, $J = 7.5, 1.5$ Hz, 1H), 7.44-7.39 (m, 4H), 2.83 (s, 3H); $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 200.4, 140.8, 133.9, 131.6, 131.4, 128.82, 128.75, 128.5, 128.3, 122.9, 121.7, 95.1, 88.6, 30.0; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1681, 755; Data consistent with the literature.$^1$

1-(2-((4-Methoxyphenyl)ethynyl)phenyl)ethanone, 3b

Prepared following general procedure A using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and 4-ethynylanisole (39 μL, 0.30 mmol). After 16 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5% ether in petrol), to yield the product as a bright yellow oil (34 mg, 92%); $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.68 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.54 (dd, $J = 8.0,
1.0 Hz, 1H), 7.43-7.37 (m, 3H), 7.30 (td, J = 7.5, 1.5 Hz, 1H), 6.84-6.81 (m, 2H), 3.76 (s, 3H), 2.72 (s, 3H); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 200.6, 160.1, 140.6, 133.7, 133.1, 131.3, 128.7, 127.9, 122.1, 115.0, 114.2, 95.3, 87.4, 55.4, 30.1; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2212, 1979, 1510, 1247; MS (ESI\(^+\)) m/z (rel intensity) 273 [100, (M+Na)\(^+\)].

Data consistent with the literature.\(^{ii}\)

**1-(2-((4-Bromophenyl)ethynyl)phenyl)ethanone, 3c**

![Chemical Structure Image]

Prepared following general procedure A using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and 1-bromo-ethynyl-benzene (54 mg, 0.30 mmol). After 16 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (70% toluene in petrol), to yield the product as a yellow oil, (39 mg, 89%); preparation following general procedure B gave yellow oil, (33 mg, 75%). \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.69 (dd, \(J = 7.5, 1.0\) Hz, 1H), 7.56-7.54 (dd, \(J = 7.5, 1.0\) Hz, 1H), 7.44-7.39 (m, 3H), 7.36-7.32 (m, 3H), 2.69 (s, 3H); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 200.0, 140.6, 134.0, 133.0, 131.8, 131.4, 128.9, 128.5, 123.1, 121.9, 121.4, 93.7, 89.6, 29.8; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2360, 1686, 1491, 823, 761; MS (ESI\(^+\)) m/z (rel intensity) 321 [100, (M+Na)\(^+\)], 323 [97, (M+Na)\(^+\)], 299 [40, (M+H)\(^+\)]; HRMS (ESI\(^+\)) 299.0070 ([M+H]\(^+\), \(C_{16}H_{12}OBr\)) requires 299.0065.

**1-(2-((3,5-Bis(trifluoromethyl)phenyl)ethynyl)phenyl)ethanone, 3d**

![Chemical Structure Image]
Prepared following general procedure A using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and (3-5-trifuroro)-1-ethynyl-benzene (53 μL, 0.30 mmol). After 8 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5% ether in petrol), to yield the product as a white solid, (50 mg, 96%); M.p: 72 °C; $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.91 (s, 2H), 7.76 (s, 1H), 7.74 (dd, $J = 7.5$, 1.0 Hz, 1H), 7.61 (dd, $J = 7.5$, 1.0 Hz, 1H), 7.47 (td, $J = 7.5$, 1.5 Hz, 1H), 7.41 (td, $J = 7.5$, 1.5 Hz, 1H); $^{13}$C NMR (126 MHz; CDCl$_3$): $\delta$ 199.1, 140.5, 134.5, 132.1 (q, $J = 33.5$ Hz), 131.6, 131.4 (q, $J = 3.5$ Hz), 129.20, 129.1, 125.4, 122.9 (q, $J = 272.0$ Hz), 122.0 (heptet, $J = 3.5$ Hz), 20.4, 91.8, 90.9, 29.3; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1691,1377, 1131; HRMS (Fl$^+$) 358.0630 [(M)$^+$, C$_{18}$H$_{10}$OF$_6$ requires 358.063).

1-(2-(Thiophen-3-ylethynyl)phenyl)ethanone, 3e

Prepared following general procedure B using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and 3-ethynylthiophene (30 μL, 0.30 mmol). After 16 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (50% toluene in petrol), to yield the product as a dark yellow oil, (23 mg, 70%); $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.68 (dd, $J = 8.0$, 1.0 Hz, 1H), 7.55 (dd, $J = 8.0$, 1.0 Hz, 1H), 7.50 (dd, $J = 3.0$, 1.0 Hz, 1H), 7.41 (td, $J = 7.5$, 1.5 Hz, 1H), 7.33 (td, $J = 7.5$, 1.0 Hz, 1H), 7.26 (dd, $J = 5.0$, 3.0 Hz, 1H), 7.15 (dd, $J = 5.0$, 1.0 Hz, 1H), 2.71 (s, 3H); $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 200.3, 140.7, 133.8, 131.3, 129.6, 129.2, 128.8, 128.2, 125.7, 122.0, 121.7, 90.3, 88.1, 30.0; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1672, 1283, 700; MS (ESI$^+$) m/z (rel intensity) 249 [100, (M+Na)$^+$]; HRMS (ESI$^+$) 226.0460 ([M+H]$^+$, C$_{14}$H$_{10}$OS requires 226.0452).

1-(2-(Dec-1-yn-1-yl)phenyl)ethanone, 3f
Prepared following general procedure A using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and 1-octyne (44 μL, 0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (50% toluene in petrol), to yield the product as a pail yellow oil, (17 mg, 45%); \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.59 (dd, \(J = 7.5, 1.0\) Hz, 1H), 7.41 (d, \(J = 7.5\) Hz, 1H), 7.33 (td, \(J = 7.5, 1.0\) Hz, 1H), 7.25 (td, \(J = 7.5, 1.0\) Hz, 1H), 2.65 (s, 3H), 2.39 (t, \(J = 7.0\) Hz, 2H), 1.55 (dt, \(J = 15.0, 7.5\) Hz, 3H), 1.42-1.35 (m, 3H), 1.26-1.23 (m, 4H), 0.83 (t, \(J = 7.0\) Hz, 3H); \(^13\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 201.2, 141.1, 134.0, 131.1, 128.3, 127.6, 122.5, 97.0, 79.7, 31.4, 30.2, 28.7, 28.5, 22.6, 19.8, 14.1; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2926, 1711, 756; MS (ESI\(^+\)) \(m/z\) (rel intensity) 229 [70, (M+Na)\(^+\)].

Data consistent with the literature.\(^{iii}\)

\(\quad\) (2-(Oct-1-yn-1-yl)phenyl)(phenyl)methanone, 3g

Prepared following general procedure B using (2-(methylthio)phenyl)(phenyl)methanone (44 mg, 0.15 mmol) and 1-octyne (44 μL, 0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (1% EtOAc in petrol), to yield the product as a yellow oil, (39 mg, 90%); \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.74 (dd, \(J = 8.5, 1.0\) Hz, 2H), 7.48 (tt, \(J = 7.5, 1.5\) Hz, 1H), 7.41-7.27 (m, 6H), 2.02 (t, \(J = 6.5\) Hz, 2H), 1.18-1.05 (m, 8H), 0.78 (t, \(J = 7.0\) Hz, 3H); \(^13\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 197.4, 141.8, 137.4, 133.0, 132.6, 130.2, 130.1, 130.0, 128.3, 128.1, 127.4, 122.5, 96.7, 78.6, 31.3, 28.4, 28.2, 22.5, 19.3, 14.1; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2929, 1666, 1287, 755, 703; MS
(ESI⁺) m/z (rel intensity) 313 [100, (M+Na)⁺], 291 [65, (M+H)⁺]; HRMS (ESI⁺) 291.17439 ((M+Na)⁺, C₂₁H₂₂O requires 291.17434).

1-(2-(3,3-Dimethylbut-1-yn-1-yl)phenyl)ethanone, 3h

![Chemical structure](image)

Prepared following general procedure A using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and 3,3-dimethyl-1-butyn (25 mg, 0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (50% toluene in petrol), to yield the product as a pail yellow oil, (22 mg, 73%); ¹H NMR (400 MHz; CDCl₃): δ 7.66 (dd, J = 8.0, 1.0 Hz, 1H), 7.47 (dd, J = 7.5, 1.0 Hz, 1H), 7.39 (td, J = 7.5, 1.5 Hz, 1H), 7.31 (td, J = 7.5, 1.5 Hz, 1H), 2.74 (s, 3H), 1.33 (s, 9H); ¹³C NMR (101 MHz; CDCl₃): δ 201.3, 141.1, 133.8, 131.1, 128.3, 127.6, 122.4, 104.7, 78.5, 30.7, 30.3, 28.3; νmax (film)/cm⁻¹ 2967, 1684, 1278, 759; MS (ESI⁺) m/z (rel intensity) 223 [90, (M+Na)⁺].

Data consistent with the literature.iv

1-(2-(Cyclohexylethynyl)phenyl)ethanone, 3i

![Chemical structure](image)

Prepared following general procedure B using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and cyclohexylacetylene (30 μL, 0.30 mmol). After 16 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (50% toluene in petrol), to yield the product as a dark yellow oil, (16 mg, 50%); ¹H NMR (400 MHz; CDCl₃): δ 7.59 (dd, J = 7.5, 1.0 Hz, 1H),
7.41 (dd, J = 7.5, 1.0 Hz, 1H), 7.32 (td, J = 7.5, 1.5 Hz, 1H), 7.25 (td, J = 7.5, 1.5 Hz, 1H), 2.64 (s, 3H), 2.60-2.53 (m, 1H), 1.85-1.82 (m, 2H), 1.72-1.65 (m, 2H), 1.54-1.44 (m, 4H), 1.29-1.26 (m, 2H); $^{13}$C NMR (101 MHz; CDCl$_3$): δ 201.3, 141.1, 134.0, 131.1, 128.3, 127.5, 122.5, 100.9, 79.7, 32.4, 30.3, 30.0, 29.7, 25.9, 25.0; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2927, 2362, 1703, 1647, 1448, 756; m/z (rel intensity) 267 [100, (M+H)$^+$].

1-(2-{(Triisopropylsilyl)ethynyl}phenyl)ethanone, 3j

![Structural formula of 3j](image)

Prepared following general procedure B using 1-(2-{methylthio}phenyl)ethanone (25 mg, 0.15 mmol) and (triisopropylsilyl)-acetylene (67 μL, 0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5% ether in petrol), to yield the product as a pail yellow oil, (43 mg, 96%); using procedure A also gave colourless oil, (42 mg, 94%); $^1$H NMR (400 MHz; CDCl$_3$): δ 7.68 (dd, J = 7.5, 1.5 Hz, 1H), 7.58 (dd, J = 7.5, 1.0 Hz, 1H), 7.42 (td, J = 7.5, 1.5 Hz, 1H), 7.37 (td, J = 7.5, 1.5 Hz, 1H), 2.78 (s, 3H), 1.12-1.15 (m, 21H); $^{13}$C NMR (101 MHz; CDCl$_3$): δ 200.8, 141.4, 134.8, 131.0, 128.44, 128.26, 121.8, 105.6, 98.2, 30.3, 18.7, 11.4; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2942, 2864, 2153, 1685; MS (ESI$^+$) m/z (rel intensity) 323 [100, (M+Na)$^+$], 301 [45, (M+H)$^+$]; HRMS (ESI$^+$) 323.17988 ((M+Na)$^+$, C$_{19}$H$_{28}$NaOSi requires 323.18016).

1-{5-Methoxy-2-(phenylethynyl)phenyl}ethanone, 3k

![Structural formula of 3k](image)
Prepared following general procedure B using 1-(5-methoxy-2-\((methylthio)\)phenyl)ethanone (29 mg, 0.15 mmol) and phenylacetylene (33 μL, 0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (0.5% ether in toluene), to yield the product as a yellow oil, (28.9 mg, 77%), using general procedure A also gave desired product (mg, 76%); \(^1\)H NMR (400 MHz; CDCl\(_3\)): δ 7.48 (d, \(J = 8.5\) Hz, 1H), 7.46-7.43 (m, 2H), 7.27-7.20 (m, 3H), 7.20 (d, \(J = 3.0\) Hz, 1H), 6.94 (dd, \(J = 8.5, 3.0\) Hz, 1H), 3.79 (s, 3H), 2.75 (s, 3H); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): δ 200.4, 159.5, 142.3, 135.4, 131.3, 128.5, 124.6, 123.2, 118.0, 114.0, 113.1, 93.8, 88.5, 55.6, 30.3; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1679, 1223, 822, 756; \(m/z\) (rel intensity) 273 [100, (M+Na)]\(^+\), 351 [45, (M+H)]\(^+\); HRMS (ESI\(^+\)) 251.10654 ((M+H), \(C_{17}H_{15}O_2\) requires 251.10666).

1-(2-\((\text{Phenylethynyl})\)-4-(trifluoromethyl)phenyl)nonan-1-one, 3l

\[
\text{Ph} \\
\begin{array}{c}
\text{F}_3\text{C} \\
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\begin{array}{c}
\text{O} \\
\begin{array}{c}
\text{Me} \\
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\]

Prepared following general procedure A using [Rh(nbd)\(_2\)].BF\(_4\) (5.6 mg, 0.015 mmol), dcpe (6.4 mg, 0.015 mmol), 1-(2-\((methylthio)\)-4-(trifluoromethyl)phenyl)nonan-1-one (40 mg, 0.12 mmol) and phenylacetylene (30 μL, 0.24 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5-30% CH\(_2\)Cl\(_2\) in petrol), to yield the product as a yellow oil, (46 mg, 91%); \(^1\)H NMR (500 MHz; CDCl\(_3\)): δ 7.79 (s, 1H), 7.64 (d, \(J = 8.0\) Hz, 1H), 7.55 (dd, \(J = 8.0, 1.0\) Hz, 1H), 7.47-7.45 (m, 2H), 7.33-7.29 (m, 3H), 3.07 (t, \(J = 7.5\) Hz, 2H), 1.67 (quintet, \(J = 7.5\) Hz, 2H), 1.30-1.12 (m, 10H), 0.78 (t, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (126 MHz; CDCl\(_3\)): δ 203.2, 144.5, 132.7 (q, \(J = 33\) Hz), 131.7, 130.4 (q, \(J = 3.5\) Hz), 129.3, 128.6, 128.50, 124.8 (q, \(J = 3.5\) Hz), 123.3 (q, \(J = 273\) Hz), 122.2, 121.9, 96.0, 86.7, 42.4, 31.8, 29.42, 29.34, 29.17, 24.3, 22.7, 14.1; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2926,
1689, 1336, 1130, 755; m/z (rel intensity) 409 [100, (M+Na)^+], 387 [40, (M+H)^+]; 
HRMS (ESI^+) 387.19268 ((M+H)^+, C_{24}H_{26}O_2F_3 requires 387.19303).

1-(2-(Phenylethynyl)-5-(trifluoromethyl)phenyl)nonan-1-one, 3m

![Chemical structure of 3m](image)

Prepared following general procedure A using [Rh(nbd)_2].BF_4 (2.1 mg, 0.0055 mmol), dcpe (2.3 mg, 0.0055 mmol), 1-(2-(methylthio)-5-(trifluoromethyl)phenyl)nonan-1-one (35 mg, 0.11 mmol) and phenylacetylene (25 μL, 0.22 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5% CH_2Cl_2 in petrol), to yield the product as a yellow oil, (37 mg, 89%), using general procedure B also gave desired product (32 mg, 76%); ^1H NMR (400 MHz; CDCl_3): δ 7.83 (s, 1H), 7.66-7.60 (m, 2H), 7.49-7.46 (m, 2H), 7.34-7.30 (m, 3H), 3.09 (t, J = 7.5 Hz, 2H), 1.68 (dt, J = 15.0, 7.5 Hz, 2H), 1.32-1.15 (m, 10H), 0.78 (t, J = 7.0 Hz, 3H); ^13C NMR (101 MHz; CDCl_3): δ 202.4, 141.8, 134.2, 131.7, 130.2 (q, J = 33 Hz), 129.3, 128.6, 127.2 (q, J = 3.5 Hz), 125.2 (q, J = 3.5 Hz), 124.8, 122.2, 120.8 (q, J = 273 Hz), 97.1, 87.1, 42.3, 31.8, 29.42, 29.34, 29.17, 24.3, 22.7, 14.1; ν_{max} (film)/cm^{-1} 2926, 1688, 1127; m/z (rel intensity) 409 [100, (M+Na)^+], 387 [50, (M+H)^+]; HRMS (ESI^+) 387.19280 ((M+H)^+, C_{24}H_{26}O_2F_3 requires 387.19303).

1-(2-Fluoro-6-(phenylethynyl)phenyl)nonan-1-one, 3n

![Chemical structure of 3n](image)

Prepared following general procedure B using 1-(2-fluoro-6-(methylthio)phenyl)nonan-1-one (42 mg, 0.15 mmol) and phenylacetylene (33 μL,
0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (45% ether in petrol), to yield the product as a yellow oil, (45 mg, 91%); $^{1}$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.42-7.40 (m, 2H), 7.29-7.26 (m, 5H), 7.00 (ddd, $J = 9.5$, 7.5, 2.0 Hz, 1H), 2.86 (t, $J = 7.5$ Hz, 2H), 1.66 (quintet, $J = 7.5$ Hz, 2H), 1.32-1.27 (m, 2H), 1.22-1.13 (m, 8H), 0.78 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (126 MHz; CDCl$_3$): $\delta$ 202.2, 158.7 (d, $J = 273.0$ Hz), 131.89 (d, $J = 20.0$ Hz), 131.71, 130.7 (d, $J = 8.5$ Hz), 128.9, 128.5 (d, $J = 3.0$ Hz), 128.43, 122.4, 122.14 (d, $J = 6.0$ Hz), 116.0 (d, $J = 22.0$ Hz), 94.2, 85.86 (d, $J = 3.0$ Hz), 44.49, 31.8, 29.43, 29.23, 29.16, 23.8, 22.7, 14.1; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2925, 1705, 755; m/z (rel intensity) 359 [100, (M+Na)$^+$], 337 [75, (M+H)$^+$]; HRMS (ESI$^+$) 337.19589 ((M+H)$^+$, C$_{23}$H$_{26}$O requires 337.19622).

1-(4-Bromo-2-(phenylethynyl)phenyl)nonan-1-one, 3o

![Chemical structure](image)

Prepared following general procedure B using [Rh(nbd)$_2$].BF$_4$ (1.9 mg, 0.005 mmol), dcpp (2.1 mg, 0.005 mmol), 1-(4-bromo-2-(methylthio)phenyl)nonan-1-one (35 mg, 0.10 mmol) and phenylacetylene (22 μL, 0.20 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (20% toluene in petrol), to yield the product as a yellow oil, (38 mg, 97%). $^{1}$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.77 (d, $J = 1.5$ Hz, 1H), 7.54-7.52 (m, 4H), 7.39-7.36 (m, 3H), 3.12 (t, $J = 7.5$ Hz, 2H), 1.73 (dt, $J = 15.0$, 7.5 Hz, 2H), 1.34-1.22 (m, 10H), 0.86 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (126 MHz; CDCl$_3$): $\delta$ 202.6, 139.9, 136.2, 131.6, 131.5, 129.8, 129.1, 128.5, 125.3, 123.2, 122.4, 95.8, 87.0, 42.2, 31.8, 29.44, 29.37, 29.19, 24.5, 22.7, 14.1; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2924, 1685, 755, 689; HRMS (ESI$^+$) 397.11600 ((M+H)$^+$, C$_{23}$H$_{26}$O$_7$Br requires 397.11615).

1-(4-Oxo-4-(2-(phenylethynyl)phenyl)butyl)indolin-2-one, 3p
Prepared following general procedure B using 1-(4-(2-(methylthio)phenyl)-4-oxobutyl)indolin-2-one (49 mg, 0.15 mmol) and phenylacetylene (33 μL, 0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (45% ether in petrol), to yield the product as a yellow oil, (50 mg, 89%); ^1H NMR (400 MHz; CDCl\textsubscript{3}): δ 7.60 (dd, J = 7.5, 1.0 Hz, 1H), 7.55 (dd, J = 7.5, 1.0 Hz, 1H), 7.45-7.43 (m, 2H), 7.39 (td, J = 7.5, 1.5 Hz, 1H), 7.32 (td, J = 7.5, 1.5 Hz, 1H), 7.29-7.26 (m, 3H), 7.18-7.12 (m, 2H), 6.95-6.90 (m, 2H), 3.73 (t, J = 7.5 Hz, 2H), 3.39 (s, 2H), 3.19 (t, J = 7.0 Hz, 2H), 2.07 (quintet, J = 7.0 Hz, 2H); ^13C NMR (101 MHz; CDCl\textsubscript{3}): δ 202.1, 175.1, 144.5, 140.8, 133.9, 131.6, 131.2, 128.8, 128.6, 128.4, 128.3, 128.0, 124.6, 124.4, 122.8, 122.2, 121.3, 108.6, 94.7, 88.2, 39.3, 38.9, 35.8, 22.1; \nu\textsubscript{max} (film)/cm\textsuperscript{-1} 1708, 1614, 753; m/z (rel intensity) 402 [100, (M+Na)^+] , 380 [80, (M+H)^+]; HRMS (ESI\textsuperscript{+}) 380.16440 ((M+H)^+, C\textsubscript{26}H\textsubscript{22}O\textsubscript{2}N requires 380.16451).
3.2 Tandem hydroaclyation/sonogashira coupling products

\((E)-3\text{-}(4\text{-Fluorophenyl})\text{-}1\text{-}(2\text{-}((4\text{-fluorophenyl})\text{ethynyl})\text{phenyl})\text{prop-2-en-1-one, 9a}\)

Prepared following general procedure C using 2-(methylthio)benzaldehyde (38 mg, 0.30 mmol) and 1-ethynyl-4-fluorobenzene (52 μL, 0.45 mmol) for 30 mins, followed by 1-ethynyl-4-fluorobenzene (69 μL, 0.60 mmol) for 6 h. The mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5% ether in petrol), to yield the product as a pale yellow solid, (78 mg, 76%); M.p: 102 °C; $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.70-7.62 (m, 3H), 7.59-7.56 (m, 2H), 7.50 (td, $J = 7.5, 1.5$ Hz, 1H), 7.47-7.43 (m, 2H), 7.35-7.31 (m, 2H), 7.07-7.03 (m, 2H), 6.94-6.89 (m, 2H); $^{13}$C NMR (126 MHz; CDCl$_3$): $\delta$ 193.4, 164.1 (d, $J = 250.0$ Hz), 162.7 (d, $J = 250.0$ Hz), 143.0, 141.8, 133.4 (d, $J = 8.5$ Hz), 133.1, 131.1 (d, $J = 3.0$ Hz), 130.96, 130.4 (d, $J = 8.5$ Hz), 128.8, 128.5, 125.5 (d, $J = 3.0$ Hz), 121.4, 118.8 (d, $J = 3.0$ Hz), 116.1 (d, $J = 22.0$ Hz), 115.7 (d, $J = 22.0$ Hz), 94.3, 87.7; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1665, 1597, 1507, 1231, 832; m/z (rel intensity) 345 [100, (M+H)$^+$]; HRMS (ESI$^+$) 345.10854 ((M+H)$^+$, $C_{23}H_{15}$OF$_2$ requires 345.10855). 

Data consistent with the literature.$^v$

\((E)-3\text{-}(2\text{-Chlorophenyl})\text{-}1\text{-}(2\text{-}((4\text{-fluorophenyl})\text{ethynyl})\text{phenyl})\text{prop-2-en-1-one, 9b}\)

S15
Prepared following general procedure D using 2-(methylthio)benzaldehyde (38 mg, 0.30 mmol) and 1-chloro-2-ethynylbenzene (55 μL, 0.45 mmol) for 30 mins, followed by 1-ethynyl-4-fluorobenzene (69 μL, 0.60 mmol) for 6 h. The mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5% ether in petrol), to yield the product as a yellow oil, (95 mg, 88%); \( ^1 \text{H} \) NMR (400 MHz; CDCl\(_3\)): \( \delta \) 8.02 (d, \( J = 16.0 \) Hz, 1H), 7.64-7.53 (m, 3H), 7.46-7.31 (m, 4H), 7.31-7.23 (m, 2H), 7.21 (td, \( J = 7.5, 1.5 \) Hz, 1H), 7.10 (t, \( J = 8.0 \) Hz, 1H), 6.88-6.81 (m, 2H); \( ^{13} \text{C} \) NMR (101 MHz; CDCl\(_3\)): \( \delta \) 193.3, 162.7 (d, \( J = 250.0 \) Hz), 141.6, 140.0, 135.5, 133.50 (d, \( J = 8.5 \) Hz), 133.19, 133.15, 131.26, 131.08, 130.3, 128.9, 128.5, 128.2, 127.8, 127.1, 121.5, 118.83 (d, \( J = 3.0 \) Hz), 115.6 (d, \( J = 22.0 \) Hz), 94.5, 87.8; \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1662, 1597, 1506, 754; m/z (rel intensity) 383 [100, (M+Na)+]; HRMS (ESI\(^+\)) 361.07917 ((M+H)+, C\(_{23}\)H\(_{15}\)O\(_3\)F requires 361.07900).

\((E)\)-3-(3,5-Bis(trifluoromethyl)phenyl)-1-(2-(phenylethynyl)phenyl)prop-2-en-1-one, 9c

Prepared following general procedure D using 2-(methylthio)benzaldehyde (38 mg, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) for 10 mins, followed by phenylacetylene (66 μL, 0.60 mmol) for 6 h. The mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (20% CH\(_2\)Cl\(_2\) in petrol), to yield the product as a pale yellow solid, (97 mg, 73%); M.p: 85 °C; \( ^1 \text{H} \) NMR (400 MHz; CDCl\(_3\)): \( \delta \) 7.88 (s, 2H), 7.74 (s, 1H), 7.70-7.65 (m, 3H), 7.61-7.57 (m, 1H), 7.46 (td, \( J = 7.5, 1.5 \) Hz, 1H), 7.40-7.36 (td, \( J = 7.5, 1.5 \) Hz, 1H), 7.28-7.25 (m, 2H), 7.21-7.17 (m, 1H), 7.14-7.10 (m, 2H); \( ^{13} \text{C} \) NMR (101 MHz; CDCl\(_3\)): \( \delta \) 192.4, 141.1, 139.6, 137.2, 133.4, 132.4 (q, \( J = 33.0 \) Hz), 131.6, 131.3,
129.06, 129.00, 128.95, 128.37, 127.8 (br), 123.3 (quintet, $J = 3.5$ Hz), 123.0 (q, $J = 273$ Hz), 122.2, 121.8, 96.3, 87.9; $v_{\text{max}}$ (film)/cm$^{-1}$ 1665, 1129; HRMS (FI$^+$) 444.0952 ((M)$^+$, C$_{25}$H$_{14}$F$_6$O requires 444.0949).

(E)-1-(2-(3,3-Dimethylbut-1-yn-1-yl)phenyl)-4,4-dimethylpent-2-en-1-one, 9d

Prepared following general procedure C using 2-(methylthio)benzaldehyde (38 mg, 0.30 mmol) and 3,3-dimethylbut-1-yne (55 μL, 0.45 mmol) for 4 h, followed by 3,3-dimethylbut-1-yne (74 μL, 0.60 mmol) for 24 h. The mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (45% ether in petrol), to yield the product as a yellow oil, (55 mg, 64%); $^1$H NMR (400 MHz; CDCl$_3$): δ 7.42 (d, $J = 0.5$ Hz, 1H), 7.40-7.28 (m, $J = 1.5$ Hz, 3H), 6.78 (d, $J = 16.0$ Hz, 1H), 6.57 (d, $J = 16.0$ Hz, 1H), 6.27 (s, 3H), 5.11(s, 3H); $^{13}$C NMR (101 MHz; CDCl$_3$): δ 196.3, 159.7, 142.6, 133.0, 129.9, 127.7, 127.4, 125.1, 121.8, 104.0, 77.5, 34.1, 30.8, 28.7, 28.2; $v_{\text{max}}$ (film)/cm$^{-1}$ 2963, 1658, 1615, 1300, 753; $m/z$ (rel intensity) 269 [100, (M+H)$^+$]; HRMS (ESI$^+$) 269.18998 ((M+H)$^+$, C$_{19}$H$_{25}$O requires 269.18999).

(E)-3-Cyclohexyl-1-(2-(phenylethynyl)-5-(trifluoromethyl)phenyl)prop-2-en-1-one, 9e

Prepared following general procedure D using 2-(methylthio)-5-(trifluoromethyl)benzaldehyde (66 mg, 0.30 mmol) and ethynylcyclohexane (59 μL, 0.45 mmol) for 1h, followed by phenylacetylene (66 μL, 0.60 mmol) for 24 h. The
mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (20% toluene in petrol), to yield the product as a yellow oil, (92 mg, 87%); \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.72 (s, 1H), 7.64-7.61 (m, 2H), 7.43-7.39 (m, 2H), 7.32-7.26 (m, 3H), 6.80 (dd, \(J = 16.0, 6.5\) Hz, 1H), 6.65 (dd, \(J = 16.0, 1.5\) Hz, 1H), 2.16-2.08 (m, 1H), 1.70-1.57 (m, 5H), 1.21-1.04 (m, 5H); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 193.5, 156.6, 142.5, 133.4, 131.7, 130.1 (q, \(J = 33.0\) Hz), 129.2, 128.4, 126.8 (q, \(J = 3.0\) Hz), 126.7, 125.5 (q, \(J = 3\) Hz), 125.0, 123.6 (q, \(J = 272.0\) Hz), 122.3, 97.3, 86.7, 41.0, 31.6, 25.9, 25.7; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2926, 1663, 1617,1334, 1126; HRMS (FI\(^+\)) 382.1553 ((M)\(^+\), \(C_{24}H_{21}O\) requires 382.1544).

\((E)\)-1-(4-Bromo-2-(phenylethynyl)phenyl)non-2-en-1-one, 9f

\[
\begin{align*}
\text{Br} & \quad \equiv \\
\text{O} & \quad \text{Me}
\end{align*}
\]

Prepared following general procedure D using 4-bromo-2-(methylthio)benzaldehyde (69 mg, 0.30 mmol) and 1-octyne (66 \(\mu\)L, 0.45 mmol) for 30 mins, followed by Phenylacetylene (66 \(\mu\)L, 0.60 mmol) for 24 h. The mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (30% toluene in petrol), to yield the product as a yellow oil, (65 mg, 55%); \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.75 (d, \(J = 12.0\) Hz, 1H), 7.52 (dd, \(J = 8.5, 2.0\) Hz, 1H), 7.48-7.41 (m, 3H), 7.37-7.33 (m, 3H), 6.91 (dt, \(J = 15.5, 7.0\) Hz, 1H), 6.75 (dt, \(J = 15.5, 1.5\) Hz, 1H), 2.29-2.24 (m, 2H), 1.43 (quintet, \(J = 7.0\) Hz, 2H), 1.31-1.18 (m, 8H), 0.85 (t, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 193.5, 151.4, 140.6, 135.5, 131.6, 131.4, 130.0, 129.3, 129.0, 128.4, 124.7, 123.4, 122.5, 96.1, 86.5, 32.9, 31.6, 29.0, 28.0, 22.5, 14.1; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2926, 16662, 1616; HRMS (FI\(^+\)) 394.0928 ((M)\(^+\), \(C_{23}H_{23}\)\(^{79}\)BrO requires 394.0932).

\((E)\)-1-(4-Bromo-2-((2-chlorophenyl)ethynyl)phenyl)-7-iodohept-2-en-1-one, 9g

S18
[Rh(nbd)$_2$]BF$_4$ (5.6 mg, 0.015 mmol) and dcpe (6.3 mg, 0.015 mmol) were dissolved in DCE (2 mL). H$_2$ gas was bubbled through the solution for 2 mins, and the solution was purged with N$_2$ gas for a further 30 secs. This was transferred via cannula to a mixture of 4-bromo-2-(methylthio)benzaldehyde (69 mg, 0.30 mmol), 6-iodohex-1-yne (52 μL, 0.45 mmol) and stirred at room temperature for 1 h. This was then transferred to a mixture containing copper iodide (86 mg, 0.60 mmol), silver carbonate (83 mg, 0.30 mmol) and 1-chloro-2-ethynylbenzene (73 μL, 0.60 mmol). The reaction mixture was stirred and heated to 80 °C for 24 h, and then allowed to cool to room temperature and the crude product was purified by column chromatography (50% toluene in petrol), to yield the product as a colourless oil, (97 mg, 63%); $^1$H NMR (400 MHz; CDCl$_3$): δ 7.72 (d, $J = 2.0$ Hz, 1H), 7.48 (dd, $J = 8.5$, 2.0 Hz, 1H), 7.43 (dd, $J = 7.5$, 2.0 Hz, 1H), 7.37-7.34 (m, 2H), 7.25-7.16 (m, 2H), 6.79 (dt, $J = 15.5$, 6.5 Hz, 1H), 6.70 (d, $J = 15.5$ Hz, 1H), 3.01 (t, $J = 7.0$ Hz, 2H), 2.22 (q, $J = 7.0$ Hz, 2H), 1.71 (quintet, $J = 7.5$ Hz, 2H), 1.48 (quintet, $J = 7.5$ Hz, 2H); $^{13}$C NMR (101 MHz; CDCl$_3$): δ 193.1, 150.2, 140.4, 136.0, 135.8, 133.4, 131.9, 130.0, 129.94, 129.86, 129.5, 126.6, 124.8, 122.9, 122.4, 92.7, 91.2, 32.8, 31.7, 28.9, 6.1; ν$_{\text{max}}$ (film)/cm$^{-1}$ 1659, 1616, 1577, 755; HRMS (Fl$^+$) 527.9152 ((M)$^+$, C$_{21}$H$_{17}$Br$_3$ClO requires 527.9175).
3.3 Miscellaneous further reactions

1-(4-Bromo-2-(phenylethynyl)phenyl)ethan-1-one, 3q

Prepared following general procedure B using 1-(4-bromo-2-(methylthio)phenyl)ethan-1-one (74 mg, 0.30 mmol) and phenylacetylene (66 μL, 0.45 mmol) for 24 h. The mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5% Et₂O in petrol), to yield the product as a colourless oil (72 mg, 80%); ¹H NMR (400 MHz; CDCl₃): δ 7.79 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.57-7.52 (m, 3H), 7.40-7.37 (m, 3H), 2.78 (s, 3H); ¹³C NMR (101 MHz; CDCl₃): δ 199.2, 139.3, 136.5, 131.8, 131.6, 130.4, 129.3, 128.7, 126.1, 123.8, 122.5, 96.6, 87.4, 30.1; ν_max (film)/cm⁻¹ 3060, 2925, 2853, 2215, 1683, 1578, 1492, 1268, 1090, 881; m/z (rel intensity) 299 [100, (M+H)⁺], 300 [97, (M+H)⁺]; HRMS (ESI⁺) 320.9886 ((M+Na)⁺, C₁₆H₁₁Br₂O₂³Na² requires 320.9886).

1-(4-((4-Fluorophenyl)ethynyl)-2-(methylthio)phenyl)ethanone, 6

Diisopropylamine (4.0 mL) was added to a mixture of 1-(4-bromo-2-(methylthio)phenyl)ethanone (100 mg, 0.41 mmol), 1-ethynyl-4-fluorobenzene (57 μL, 0.50 mmol), palladium acetate (1.9 mg, 0.0082 mmol), triphenylphosphine (4.3 mg, 0.0164 mmol) and copper iodide (3.2 mg, 0.0164 mmol) in an inert atmosphere. This was heated to 75 °C and stirred for 2 h. The mixture was allowed to cool to room temperature, dried under vacuo and the crude product was purified by column chromatography (1% EtOAc in petrol), to yield the product as white needles (34 mg, 92%); M.p: 125 °C; ¹H NMR (400 MHz; CDCl₃): δ 7.83 (d, J = 8.0 Hz, 1H), 7.57-7.52 (m,
2H), 7.41 (d, J = 1.0 Hz, 1H), 7.31 (dd, J = 8.0, 1.5 Hz, 1H), 7.10-7.04 (m, 2H), 2.62 (s, 3H), 2.47 (s, 3H); 13C NMR (101 MHz; CDCl3): δ 198.2, 162.9 (d, J = 250.0 Hz), 143.3, 133.8 (d, J = 8.0 Hz), 133.2, 131.1, 127.45, 127.39, 126.3, 118.6 (d, J = 3.0 Hz), 115.9 (d, J = 22.0 Hz), 91.4, 88.2, 28.1, 15.9; νmax (film)/cm⁻¹ 1668, 1584, 835; m/z (rel intensity) 307 [100, (M+Na)⁺], 285[30, (M+H)⁺]; HRMS (ESI⁺) 307.05601 ((M+Na)⁺, C₁₇H₁₃O²⁺Na²⁻ requires 307.05634).

1-(4-((4-Fluorophenyl)ethynyl)-2-(phenylethynyl)phenyl)ethanone, 7

Prepared following general procedure B using 1-(4-((4-fluorophenyl)ethynyl)-2-(methylthio)phenyl)ethanone (30 mg, 0.11 mmol) and phenylacetylene (24 μL, 0.22 mmol). After 4 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (40% CH₂Cl₂ in petrol), to yield the product as a white solid, (31 mg, 83%); Alternatively, diisopropylamine (4.0 mL) was added to a mixture of 1-(4-((4-fluorophenyl)ethynyl)-2-(methylthio)phenyl)ethanone (50 mg, 0.17 mmol), 1-ethynyl-4-fluorobenzene (24 μL, 0.204 mmol), palladium acetate (1.0 mg, 0.0034 mmol), triphenylphosphine (1.7 mg, 0.0068 mmol) and copper iodide (1.7 mg, 0.0068 mmol) in an inert atmosphere. This was heated to 75 °C and stirred for 2 h. The mixture was allowed to cool to room temperature, dried under vacuo and the crude product was purified by column chromatography (1% EtOAc in petrol), to yield the product as white solid (47 mg, 81%); M.p: 65 °C; 1H NMR (400 MHz; CDCl₃): δ 7.79 (d, J = 1.5 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.58-7.50 (m, 5H), 7.40-7.37 (m, J = 2.0 Hz, 3H), 7.10-7.05 (m, 2H), 2.81 (s, 3H); 13C NMR (101 MHz; CDCl₃): δ 199.4, 162.6 (d, J = 250.0 Hz), 139.5, 136.8, 133.8
(d, J = 8.0 Hz), 131.6, 131.0, 129.09, 129.02, 128.6, 126.7, 122.7, 122.3, 118.7 (d, J = 3.0 Hz), 115.8 (d, J = 22.0 Hz), 95.7, 91.6, 87.9, 87.5, 30.0; ν_{\text{max}} (film)/\text{cm}^{-1} 1680, 753; HRMS (Fl') 338.1112 ([M]^{+}, C_{24}H_{15}OF requires 338.1107).

**tert-Butyl 2-(4-methoxyphenyl)-5-[2-(phenylethynyl)-5-(trifluoromethyl)phenyl]-1H-pyrrole-1-carboxylate, 11**

![Chemical structure image]

An oven-dried microwave vial was charged with [Rh(nbd)₂]BF₄ (7.5 mg, 0.02 mmol), and dcppe (8.5 mg, 0.02 mmol). Once under an inert atmosphere, they were dissolved in 1,2-DCE (1.0 mL). Hydrogen gas was bubbled through the solution at room temperature for 1-2 mins in order to generate the active catalyst species. The hydrogen gas was purged using nitrogen gas, and this was bubbled through the catalyst to dryness. The dry catalyst was dissolved in acetone (88 μL, 1.0 M with respect to aldehyde minus the volume or mass of both aldehyde and alkyne) and this was transferred to a nitrogen-filled microwave vial containing 2-(methylthio)-5-(trifluoromethyl)benzaldehyde (44 mg, 0.20 mmol) and tert-butyl [1-(4-methoxyphenyl)prop-2-yn-1-yl]carbamate (67.9 mg, 0.26 mmol). After 2 mins at room temperature the reaction mixture was transferred to silver carbonate (55.0 mg, 0.20 mmol), copper bromide (114.8 mg, 0.8 mmol) and phenylacetylene (44 μL, 0.40 mmol) using 1,2-DCE (0.5 mL). After stirring for 16 h at 80 °C the reaction was filtered through a plug of silica and stirred with CH₂Cl₂ (3 mL) and p-TSA (57 mg, 0.30 mmol) at room temperature for a further 3 h. The crude product was purified by column chromatography (5-10% Et₂O in petrol) to afford pyrrole 9 as an off white solid (56 mg, 54%). ¹H NMR (400 MHz, CDCl₃): δ 7.74-7.72 (m, 1H), 7.67 (app dt, J 8.0, 1.0 Hz, 1H), 7.61-7.59 (m, 1H), 7.44-7.41 (m, 2H), 7.36-7.32 (m, 5H), 6.96-6.94 (m,
2H), 6.34 (d, J = 3.5 Hz, 1H), 6.26 (d, J = 3.5 Hz, 1H), 3.88 (s, 3H), 1.10 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 159.1, 149.2, 138.7, 136.5, 132.4 (q, J = 36.0 Hz), 131.9, 131.5, 130.5, 130.0, 128.7, 127.6 (q, J = 200.5 Hz), 127.3, 126.1 (q, J = 3.5 Hz), 123.9 (q, J = 3.5 Hz), 122.6, 114.6, 113.7, 113.2, 112.5, 94.9, 87.3, 83.7, 55.3, 27.0; $^{19}$F NMR (377 MHz, CDCl$_3$, $^1$H decoupled): δ -62.1; IR: $\nu_{\text{max}}$(neat)/cm$^{-1}$ 2980, 2838, 1745, 1581, 1325, 1248, 1172, 1097, 991; LRMS (ESI?): m/z 540 ([M+Na]$^+$, 100%), 518 ([M+H]$^+$, 40%); HRMS (ESI$^+$) found 540.17474 [M+Na]$^+$ requires 540.17570; mp: 136-137 °C (Et$_2$O/petrol).

(E)-(4-(3,5-Bis(trifluoromethyl)styryl)-2-(o-tolyl)-1,2-dihyronaphthalen-1-yl)(4-fluorophenyl)methanone, 13

![Chemical Structure](image)

Prepared following general procedure D using 2-(methylthio)benzaldehyde (38 mg, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) for 10 mins, followed by 4-fluorophenylacetylene (66 μL, 0.60 mmol) for 6 h. The mixture was allowed to cool to room temperature and the crude product was filtered through a plug of silica then dried in vacuo. To this was added copper triflate (12 mg, 0.030 mmol), 1-methyl-2-vinylbenzene (58 μL, 0.45 mmol), DCE (2 mL) and stirred under nitrogen at 80 °C for 5 mins. The mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (20% toluene in petrol), to yield the product as an amorphous solid, (106 mg, 61%); $^1$H NMR (400 MHz; CDCl$_3$): δ 7.92 (dd, J = 9.0, 5.5 Hz, 2H), 7.87 (s, 2H), 7.75 (1H, s), 7.51 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.24-6.98 (m, 9H), 6.93 (d, J = 7.5 Hz, 1H), 6.26 (d, J = 4.0 Hz, 1H), 5.14 (d, J = 10.0 Hz, 1H), 4.56 (dd, J = 10.0, 4.0 Hz, 1H), 2.37 (s, 3H); $^{13}$C NMR (101 MHz; CDCl$_3$): δ 200.1, 165.9 (d, J$_{CF}$ = 250 Hz), 140.3, 139.6, 135.9, 134.9, 134.2 (d, J$_{CF}$ = 3 Hz), 134.0, 133.4, 132.2 (q, J$_{CF}$ = 33 Hz), 131.8, 131.2 (d, J$_{CF}$ = 9 Hz), 131.0, 130.5, 128.5, 128.0 (2C), 127.8, 127.4, 127.1, 126.5, 126.3, 124.7, 123.5
(q, J_CF = 273 Hz), 121.0 (sept. J_CF = 4 Hz), 116.0 (d, J_CF = 21 Hz), 52.3, 39.8, 20.1; ν_{max} (film)/cm\(^{-1}\) 1681, 1277, 1130, 751; HRMS (ESI\(^{+}\)) found 581.1710 [M+H\(^{+}\)], C\(_{34}\)H\(_{24}\)F\(_7\)O\(^{+}\) requires 581.1710.
3.4 Starting material synthesis

4-Bromo-2-(methylthio)benzaldehyde, 8a

To a stirred suspension of sodium thiomethoxide (345.2 g, 4.9 mmol) in DMF (25 mL) was added 4-bromo-2-fluorobenzaldehyde (1.0 g, 4.9 mmol) over 30 mins at -45 °C. After the addition was complete, the solution was stirred for a further 3 h at -45 °C, then stirred at room temperature overnight. The reaction was then quenched with water and the precipitate was filtered off to yield the product as white needles (747 mg, 66%); M.p: 78 °C; $^1$H NMR (400 MHz; CDCl$_3$): δ 10.13 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.38-7.35 (m, 2H), 2.46 (s, 3H); $^{13}$C NMR (101 MHz; CDCl$_3$): δ 190.3, 145.5, 134.6, 131.3, 129.7, 127.8, 127.5, 15.4; ν$_{\text{max}}$ (film)/cm$^{-1}$ 2920, 2825, 2776, 2733, 1680, 1570, 1534, 1455, 1255, 1194, 1083, 847, 799; HRMS (EI) 229.9398 ([M]+, C$_8$H$_7$OBr$_7^9$S requires 229.9401).

1-(2-(Methylthio)-5-(trifluoromethyl)phenyl)nonan-1-one, 1m

To a solution of 2-(methylthio)-5-(trifluoromethyl)benzaldehyde (45 mg, 0.35 mmol) and [Rh(Bn-(p-F))(dtmp)].Bar$^4$ (2.7 mg, 0.002) in acetone (0.25 mL) was added 1-octene (47 μL, 0.30 mmol). This was stirred at 55 °C for 4 h, and allowed to cool to room temperature. The mixture was concentrated in vacuo and purified by flash chromatography (5% ether in petrol) to yield the ketone as a yellow oil (116 mg, 97%); $^1$H NMR (400 MHz; CDCl$_3$): δ 7.93 (d, J = 1.0 Hz, 1H), 7.57 (dd, J = 8.5, 1.5 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 2.89 (t, J = 7.5 Hz, 2H), 1.66 (quintet, J = 7.5 Hz, 2H), 1.66 (quintet, J = 7.5 Hz, 2H); $^{13}$C NMR (101 MHz; CDCl$_3$): δ 200.5, 147.5, 134.3, 128.1 (q, J
= 3.5 Hz), 126.6 (q, J = 3.5 Hz), 126.5 (q, J = 33.0 Hz), 125.18, 123.8 (q, J = 271.5 Hz),
39.9, 31.8, 29.43, 29.24, 22.7, 15.9, 14.1; \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1674, 1116,

2-Fluoro-6-(methylthio)benzaldehyde

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\begin{align*}
\text{MeS} & \quad \text{O} \\
\text{F} & \\
\end{align*}
\]

To a stirred suspension of sodium thiomethoxide (494 mg, 7.0 mmol) in DMF (25 mL) was added 2,6-difluorobenzaldehyde (1.0 g, 7.0 mmol) over 30 mins at -45 °C. After the addition was complete, the solution was stirred for a further 3 h at -45 °C. The reaction was then quenched with water and the precipitate was filtered off to yield the product as pale yellow needles (786 mg, 66%); \(^1\)H NMR (400 MHz; CDCl\(_3\)): \( \delta \) 10.48 (d, \( J = 5.0 \) Hz, 1H), 7.52-7.45 (m, 1H), 6.91-6.86 (m, 1H), 2.46-2.45 (m, 3H); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \( \delta \) 187.2 (d, \( J = 11.0 \) Hz), 166.6 (d, \( J = 259.0 \) Hz), 146.1, 135.05 (d, \( J = 11.0 \) Hz), 120.6 (d, \( J = 8.0 \) Hz), 119.8 (d, \( J = 3.5 \) Hz), 110.9 (d, \( J = 22.0 \) Hz), 15.4; \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1672, 773; \( m/z \) (rel intensity) 193 [100, (M+Na)], HRMS (ESI\(^+\)) 171.02744 ((M+H))\(^+\), \( C_8 H_8 OFS \) requires 171.02744.

1-(2-Fluoro-6-(methylthio)phenyl)nonan-1-one, 1n

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\begin{align*}
\text{MeS} & \quad \text{O} \\
\text{F} & \quad \text{Me} \\
\end{align*}
\]

To a solution of 2-fluoro-6-(methylthio)benzaldehyde (85 mg, 0.50 mmol) and [Rh(Bn-(p-F))(dtmp)].BAR\(^f\) (70 mg, 0.025 mmol) in acetone (0.25 mL) was added 1-octene (118 \( \mu \)L, 0.75 mmol). This was stirred at 55 °C for 4 h, and allowed to cool to room temperature. The mixture was concentrated in vacuo and purified by flash chromatography (5% ether in petrol) to yield the ketone as a colourless oil (64 mg, 46%); \(^1\)H NMR (400 MHz; CDCl\(_3\)): \( \delta \) 7.31 (td, \( J = 8.0, 6.0 \) Hz, 1H), 7.07 (d, \( J = 8.0 \) Hz, 1H), 6.88 (ddd, \( J = 9.5, 8.5, 1.0 \) Hz, 1H), 2.84 (td, \( J = 7.5, 2.0 \) Hz, 2H), 2.43 (s, 3H), 1.70 (quintet, \( J = 7.5 \) Hz, 2H), 1.36-1.25 (m, 10H), 0.86 (t, \( J = 7.0 \) Hz, 3H); \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \( \delta \) 202.3, 156.8 (d, \( J = 249.0 \) Hz), 139.7 (d, \( J = 4.0 \) Hz), 131.2 (d, \( J = 9.0 \) Hz).
Hz), 128.2 (d, J = 18.0 Hz), 122.4 (d, J = 3.0 Hz), 112.4 (d, J = 22.0 Hz), 44.61, 44.57, 31.9, 29.4, 29.2, 23.8, 22.7, 16.9, 14.1; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1687, 1447, 894, 777;

1-(4-Bromo-2-(methylthio)phenyl)ethanone, 5

To a stirred suspension of sodium thiomethoxide (323 mg, 4.6 mmol) in DMF (25 mL) was added 1-(4-bromo-2-fluorophenyl)ethanone (1.0 g, 4.6 mmol) over 30 mins at -45 °C. After the addition was complete, the solution was stirred for a further 3 h at -45 °C. The reaction was then quenched with water and the precipitate was filtered off to yield the product as a white solid (913 mg, 81%); $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.70 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 1.5 Hz, 1H), 7.32 (dd, J = 8.5, 2.0 Hz, 1H), 2.59 (s, 3H), 2.43 (s, 3H); $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 197.9, 145.4, 132.5, 132.4, 127.8, 127.5, 126.4, 28.1. 16.0 $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1739, 1663, 788; m/z (rel intensity) 267 [50, (M+Na)$^+$]; HRMS (ESI$^+$) 244.96303 ((M+H)$^+$, C$_9$H$_{10}$O$_7$BrS requires 244.96303).

1-(5-Methoxy-2-(methylthio)phenyl)ethanone, 1k

To a stirred suspension of sodium thiomethoxide (282 mg, 4.0 mmol) in DMF (25 mL) was added 1-(2-bromo-5-methoxyphenyl)ethanone (1.0 g, 3.36 mmol) over 30 mins at 0 °C. After the addition was complete, the solution was stirred for a further 3 h at r.t. The reaction was then quenched with water and the precipitate was filtered off to yield the product as pale yellow needles (481 mg, 73%); $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.31-7.27 (m, 2H), 7.07 (dd, J = 8.5, 2.5 Hz, 1H), 2.68 (s, 3H), 2.44 (s, 3H); $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 199.5, 156.6, 137.1, 131.8, 127.7, 118.0, 116.0, 55.6, 28.7, 16.9; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1659; m/z (rel intensity) 219 [100, (M+Na)$^+$], HRMS (ESI$^+$) 197.0636 ((M+H)$^+$, C$_{10}$H$_{13}$O$_2$S requires 197.0639).
4 References


5 NMR Spectra

![NMR Spectra Image]

S29
S33
TIPS

Me

S38