PMHS Mediated Couplings of Alkynes or Benzothiazoles with Various Electrophiles: Application to the Synthesis of (–)-Akolactone A

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Methods and Materials

Reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere, unless otherwise noted. All commercial reagents were used without purification unless otherwise noted. CuCl^{I} was prepared by reduction of CuCl_2 with Na_2SO_3 . All solvents were reagent grade. THF as freshly distilled from sodium/benzophenone under nitrogen. Except as otherwise indicated, all reactions were magnetically stirred and monitored by thin layer chromatography with 0.25-mm ultra pure silica gel 60 Å TLC plates or capillary GC with a fused silica column. Flash chromatography was performed with silica gel 60 Å (particle size 230-400 Mesh ASTM). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Proton and carbon NMR chemical shifts are reported relative to the residue peaks of solvent chloroform (δ 7.24 for ^1H and δ 77.0 for ^{13}C).

Copper (I) thiophene-2-carboxylate (CuTC).² 2-Thiophene carboxylic acid (100 g, 780 mmol), Cu_2O (28 g, 196 mmol), and toluene (300 mL) were added to a 500 mL three-neck round bottom flask. The flask was outfitted with a Dean-Stark trap and condenser. The mixture was then allowed to reflux for 3 days with azeotropic removal of water. The yellow-brown suspension was then cooled to $\sim 60^\circ\text{C}$ and the product were collected on a glass-sintered funnel (D-frit). Under a stream of nitrogen, the filter cake was washed with MeOH (300 mL), then with Et_2O until the filtrate was colorless and then with hexanes (75 mL). The product was dried under a flow of N_2 and then was transferred to a flask and dried under vacuum. The procedure afforded CuTC (70 g, 94%) as a light brown powder.

Representative PMHS/CsF mediated Sonogashira coupling of vinyl or aryl halides. 2-Methyl-6-phenyl-hex-5-en-3-yn-2-ol (2)

(Table 2, entry 1). To a solution of 2-methyl-3-butyn-2-ol (1) (0.10 mL, 1.0 mmol), and PMHS (0.24 mL, 4 mmol) in 30 mL of THF/NMP (1:1) was added CsF (1.52 g, 10.0 mmol). After the initial reaction subsided (~ 1 min) CuTC (380 mg, 2.0 mmol), *E*- β -bromostyrene (0.2795 g, 1.5 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (70 mg, 0.10 mmol) were added. This mixture was stirred at room temperature until complete by TLC analysis (90/10 hexane/EtOAc). Once complete (2 h), the reaction was diluted with Et_2O and then washed with sat. aq. NH_4OH . The phases were then separated and the combined organics

were washed with H₂O (2x), brine (2x), dried (MgSO₄), filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 80/20) to afford 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**2**) (184 mg, 99%) as a yellow oil.

1-iodo-dodeca-1,11-diene (4). Under an Ar atmosphere, TMSCl (15.3 mL, 120 mmol) was added to a suspension of CrCl₃ (0.6334 g, 4 mmol), Zn (7.84 g, 120 mmol), and NaI (3.0 g, 20 mmol) in dioxane (100 mL) at 25 °C. After the reaction was stirred for 40 min, a solution of 10-undecenal (4.16 mL, 20 mmol) and CHI₃ (15.75 g, 40 mmol) in dioxane (50 mL) was added at 25 °C via a syringe pump over 24 hours. After the addition the mixture became very thick. The reaction was quenched by the addition of water. The reaction was then extracted with hexanes (5x). The combined organics were washed with brine, dried over MgSO₄, filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel; hexanes) to afford *E*-1-iodo-1,11-dodecadiene³ (**4**) (4.35 g, 75%, *E/Z* 98/2) as an oil and *E*-1-chloro-1,11-dodecadiene (trace by GC/MS).

Representative PMHS/CsF mediated Sonogashira coupling of vinyl or aryl halides. Hexadeca-5(*E*),15-dien-3-yn-2-ol (5) (Table 2, entry 2). The representative PMHS/CsF mediated coupling conditions for aryl halides were applied to 3-butyne-2-ol (**3**) (0.16 mL, 2.0 mmol) and *E*-1-iodo-1,11-dodecadiene (**4**) (0.8766 g, 3.0 mmol). After reacting at room temperature for 5 h, column chromatography (silica gel; hexane/EtOAc 80/20) afforded hexadeca-5(*E*),15-dien-3-yn-2-ol⁴ (**5**) (431 mg, 92%) as a yellow oil.

1-[4-(3-Hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (6) (Table 2, entry 3). The representative PMHS/CsF mediated coupling conditions for aryl halides were applied to 2-methyl-3-butyne-2-ol (**1**) (0.10 mL, 1.0 mmol) and *p*-iodoacetophenone (0.3691 g, 1.5 mmol). After reacting at room temperature for 5 h, column chromatography (silica gel; hexanes/EtOAc 75/25) afforded 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone⁵ (**6**) (175 mg, 86%) as an oil.

1-[4-(3-Hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (6) (Table 2, entry 4). The representative PMHS/CsF mediated coupling conditions for aryl halides were applied to 2-methyl-3-butyne-2-ol (**1**) (0.10 mL, 1.0 mmol) and *p*-bromoacetophenone (0.2986 g, 1.5 mmol). After reacting at room temperature for 5 h, column chromatography (silica gel; hexanes/EtOAc 75/25) afforded 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone⁵ (**6**) (162 mg, 80%) as an oil.

Representative procedure for the formation of aryl nonaflates.

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (8).

To a solution of *p*-hydroxyacetophenone (6.81 g, 50 mmol) and Et₃N (8.36 mL, 60 mmol) in CH₂Cl₂ (300 mL) at room temperature was added 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonyl fluoride (10.8 mL, 60 mmol) in a dropwise fashion. The resulting solution was stirred at room temperature for 10 h. Once complete the reaction was washed with H₂O (2x), brine (2x), dried (Na₂SO₄), filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 80/20) to afford 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**8**) (19.62 g, 94%) as a white solid: mp 42 °C (lit.⁶ 41–42).

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 4-methoxy-phenyl ester (18).

The representative procedure for the formation of aryl nonaflates was applied to *p*-methoxyphenol (1.24 g, 10 mmol). After complete reaction (2 h), column chromatography (silica gel; pentane/EtOAc 95/5) afforded 3.28 g (81%) of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-methoxy-phenyl ester (**18**) as a clear oil.⁷

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 4-bromo-phenyl ester (21).

The representative procedure for the formation of aryl nonaflates was applied to *p*-bromophenol (3.46 g, 20 mmol). After complete reaction (12 h), column chromatography afforded (silica gel; hexane/EtOAc 90/10) 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-bromo-phenyl ester (**21**) (4.61 g, 51%) as a clear oil. IR (neat) 1176 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.15–7.19 (m, 2 H), 7.55–7.60 (m, 2 H); ¹³C (125 MHz, CDCl₃) δ 109.9, 114.9, 115.9, 118.2, 122.0, 123.1, 133.4, 148.8; HRMS (EI) *m/z* 453.8921 [(M⁺), calcd. for C₁₀H₄BrF₉O₃S 453.8927].

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 4-(nonafluorobutane-1-sulfonyloxy)-phenyl ester (23).

The representative procedure for the formation of aryl nonaflates was applied to hydroquinone (1.10 g, 10 mmol). After complete reaction (18 h), column chromatography afforded (silica gel; hexane/EtOAc 90/10) 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-(nonafluorobutane-1-sulfonyloxy)-phenyl ester (**23**) (6.41 g, 95%) as a purple solid: mp 66–67 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.39 (s, 4 H); ^{13}C (75 MHz, CDCl_3) δ 123.4, 148.6; HRMS (EI) m/z 673.9162 [M^+], calcd. for $\text{C}_{14}\text{H}_4\text{F}_{18}\text{O}_6\text{S}_2$ 673.9167].

Trifluoromethanesulfonic acid 4-acetyl-phenyl ester (25). Tf_2O (5.61 mL, 33.3 mmol) was slowly added to a solution of 4-hydroxyacetophenone (4.08 g, 30 mmol) in 15 mL of pyridine at 0 °C. This mixture was then allowed to warm to 25 °C and

stir for 1 day. The resulting mixture was poured into water and extracted with Et_2O . The organics were washed with water, 10% HCl, water, brine, dried (MgSO_4), filtered and concentrated. The resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 95/5) to afford 5.60 g (70 %) of trifluoromethanesulfonic acid 4-acetyl-phenyl ester⁸ (**25**) as a colorless liquid.

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid cyclohex-1-enyl ester (26).

A solution of $n\text{-BuLi}$ (13.13 mL of a 1.6 M solution in hexanes, 21 mmol) was added at –78 °C to a solution of $i\text{-Pr}_2\text{NH}$ (2.94 mL, 21 mmol) in THF (300 mL). After 1 h at –78 °C, cyclohexanone (2.07 mL, 20 mmol) was added and stirring continued for 1 h –78 °C. Neat NfF (7.2 mL, 40 mmol) was added dropwise at –78 °C. After the addition, the reaction was allowed to warm to room temperature over 8 h. The reaction was then poured into a sat. aq. solution of NH_4Cl . The aqueous phase was extracted with EtOAc and the combined organics were dried (MgSO_4), filtered, and concentrated. The resulting residue was purified by distillation (120 °C at 18 mmHg) to afford 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid cyclohex-1-enyl ester (**26**) (6.49 g, 86%) as a clear liquid.⁹

Representative PMHS/CsF mediated coupling of aryl or vinyl nonaflates. 1-(4-Phenylethynyl-phenyl)-ethanone (9) (Table 3,

entry 1). To a solution of phenylacetylene (**7**) (0.11 mL, 1.0 mmol) and

PMHS (0.12 mL, 2 mmol) in 30 mL of NMP was added CsF (0.7595 g, 5.0 mmol). After the initial reaction subsided (~1 min), CuCl (5 mg, 0.05 mmol), 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**8**) (0.6273 g, 1.5 mmol) and PdCl₂(PPh₃)₂ (0.0350 g, 0.05 mmol) were added. This mixture was stirred at room temperature until complete by TLC analysis (90/10 hexane/EtOAc). Once complete (4 h), the reaction was diluted with Et₂O and then washed with sat. aq. NH₄Cl. The phases were then separated and the combined organics were washed with H₂O (2x), brine (2x), dried (MgSO₄), filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 90:10) to afford 1-(4-phenylethynyl-phenyl)-ethanone (**9**) (210 mg, 95%) as a light yellow solid: mp 95 °C, (lit.¹⁰ 94–96).

1-[4-(3-Hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (6) (Table 3, entry 2).

The representative PMHS/CsF conditions for the coupling of aryl nonaflates were applied to 2-methyl-3-butyn-2-ol (**1**) (0.10 mL,

1.0 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**8**) (0.6273 g, 1.5 mmol). After reacting at room temperature for 5 h, column chromatography (silica gel; hexanes/EtOAc 75/25) afforded 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone⁵ (**6**) (190 mg, 94%) as an oil.

1-[4-(3-Hydroxy-but-1-ynyl)-phenyl]-ethanone (10) (Table 3,

entry 3). The representative PMHS/CsF conditions for the coupling of aryl nonaflates were applied to 3-butyn-2-ol (**3**) (0.08 mL, 1.0 mmol) and

1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**8**) (0.6273 g, 1.5 mmol). After reacting at room temperature for 5 h, column chromatography (silica gel; hexanes/EtOAc 70/30) afforded 1-[4-(3-hydroxy-but-1-ynyl)-phenyl]-ethanone (**10**) (158 mg, 84%) as a yellow solid: mp 56–57 °C. IR (KBr) 3452 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.55 (d, *J* = 6.6 Hz, 3 H), 2.55 (s, 3 H), 3.24 (br s, 1 H), 4.77 (q, *J* = 6.31 Hz, 1 H), 7.40–7.47 (m, 2 H), 7.80–7.87 (m, 2 H); ¹³C (75 MHz, CDCl₃) δ 24.0, 26.5, 58.4,

82.8, 94.5, 127.5, 128.0, 131.6, 136.0, 197.6; HRMS (EI) m/z 188.0837 [M^+], calcd. for $C_{12}H_{12}O_2$ 188.0834].

1-[4-(5-Hydroxy-pent-1-ynyl)-phenyl]-ethanone (12) (Table 3, entry 4). The representative PMHS/CsF conditions for the coupling of aryl nonaflates were applied to 4-pentyn-2-ol (**11**) (0.10 mL, 1.0 mmol) and

1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**8**) (0.6273 g, 1.5 mmol). After reacting at room temperature for 6 h, column chromatography (silica gel; hexane/EtOAc 70:30) afforded 1-[4-(3-hydroxy-but-1-ynyl)-phenyl]-ethanone (**12**) (175 mg, 87%) as an orange oil. IR (neat) 3426, 1687 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 1.86 (quint, J = 6.6 Hz, 2 H), 2.40 (br s, 1 H), 2.57 (m, 5 H), 3.80 (t, J = 6.18 Hz, 2 H), 7.43 (d, J = 8.24 Hz, 2 H), 7.85 (d, J = 8.17 Hz, 2 H); ^{13}C (75 MHz, $CDCl_3$) δ 15.9, 26.5, 31.1, 61.3, 80.3, 93.3, 128.1, 128.8, 131.5, 135.5, 197.5; HRMS (EI) m/z 202.0994 [M^+], calcd. for $C_{13}H_{14}O_2$ 202.0987].

1-(4-Pent-1-ynyl-phenyl)-ethanone (14) (Table 3, entry 5).

The representative PMHS/CsF conditions for the coupling of aryl nonaflates were applied to 1-pentyne (**13**) (0.10 mL, 1.0 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**8**) (0.6273 g, 1.5 mmol). After reacting at room temperature for 8 h, column chromatography (silica gel; hexane/EtOAc 90:10) afforded of 1-(4-pent-1-ynyl-phenyl)-ethanone¹¹ (**14**) (145 mg, 77%) as a light yellow oil.

1-(4-Octadec-1-ynyl-phenyl)-ethanone (16) (Table 3, entry 6). The representative PMHS/CsF conditions for the coupling of aryl nonaflates were applied to 1-octadecyne (**15**) (0.2505 g, 1.0 mmol) and

1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**8**) (0.6273 g, 1.5 mmol). After reacting at room temperature for 8 h, column chromatography (silica gel; hexanes/EtOAc 90/10) afforded 1-(4-octadec-1-ynyl-phenyl)-ethanone (**16**) (349 mg, 94%) as an oil. IR (neat) 1691 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.0 Hz, 3 H), 1.15–1.51 (m, 26 H), 1.53–1.72 (m, 2 H), 2.40 (t, J = 7.0 Hz, 3 H),

2.56 (s, 3 H), 7.43 (m, 2 H), 7.85 (m, 2 H); ^{13}C (75 MHz, CDCl_3) δ 14.1, 22.7, 28.4, 28.9, 29.4, 29.6, 29.6, 29.7, 29.7, 29.7, 31.9, 36.1, 74.2, 146.7; HRMS (EI) m/z 368.3079 $[(\text{M}^+)]$, calcd. for $\text{C}_{26}\text{H}_{40}\text{O}$ 368.3073].

4-(4-Methoxy-phenyl)-2-phenyl-but-3-yn-2-ol (19) (Table 3, entry 7). The representative PMHS/CsF conditions for the coupling of aryl nonaflates were applied to 2-phenyl-but-3-yn-2-ol (**17**) (146 mg, 1.0 mmol) and

1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-methoxy-phenyl ester (**18**) (488 mg, 1.5 mmol). After reacting at room temperature for 7 h, column chromatography (silica gel; hexane/EtOAc 80/20) 4-(4-methoxy-phenyl)-2-phenyl-but-3-yn-2-ol (**19**) (130 mg, 52%) as an oil. IR (neat) 3372 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.79 (s, 6 H), 2.96 (br s, 1 H), 3.82 (s, 1 H), 6.87 (d, $J = 8.9\text{ Hz}$, 2 H), 7.27–7.50 (m, 4 H), 7.74 (d, $J = 8.9\text{ Hz}$, 2 H); ^{13}C (75 MHz, CDCl_3) δ 33.3, 55.2, 70.3, 84.7, 91.1, 113.8, 114.6, 124.9, 127.6, 128.2, 133.1, 145.8, 159.6; HRMS (EI) m/z 252.1153 $[(\text{M}^+)]$, calcd. for $\text{C}_{17}\text{H}_{16}\text{O}_2$ 252.1150].

1-(4-Bromo-phenyl)-3-methyl-pent-1-yn-3-ol (22) (Table 3, entry 8). The representative PMHS/CsF conditions for the coupling of aryl nonaflates were applied to 3-methyl-pent-1-yn-3-ol (**20**) (0.23 mL, 2.0 mmol) and

1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-bromo-phenyl ester (**21**) (1.09 g, 3.0 mmol). After reacting at room temperature for 6 h, column chromatography (silica gel; hexane/EtOAc 80/20) afforded 1-(4-bromo-phenyl)-3-methyl-pent-1-yn-3-ol (**22**) (379 mg, 75%) as an oil. IR (neat) 3372 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.09 (t, $J = 7.4\text{ Hz}$, 3 H), 1.55 (s, 3 H), 1.77 (m, 2 H), 2.09 (br s, 1 H), 7.24–7.28 (m, 2 H), 7.40–7.44 (m, 2 H); ^{13}C (125 MHz, CDCl_3) δ 9.0, 29.2, 36.6, 69.1, 82.3, 93.8, 121.8, 122.4, 131.5, 133.1; HRMS (EI) m/z 252.0150 $[(\text{M}^+)]$, calcd. for $\text{C}_{12}\text{H}_{13}\text{BrO}$ 252.0154].

1-[4-(3-Hydroxy-3-methyl-pent-1-ynyl)-phenyl]-3-methyl-pent-1-yn-3-ol (24) (Table 3, entry 9). The representative PMHS/CsF conditions for the coupling of aryl nonaflates were applied to 3-

methyl-pent-1-yn-3-ol (**20**) (0.24 mL, 2.1 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-(nonafluorobutane-1-sulfonyloxy)-phenyl ester (**23**) (0.6743 g, 1.0 mmol). After reacting at room

temperature for 6 h, column chromatography (silica gel; hexane/EtOAc 80/20) afforded 1-[4-(3-hydroxy-3-methyl-pent-1-ynyl)-phenyl]-3-methyl-pent-1-yn-3-ol (**24**) (202 mg, 75%) as a yellow solid: mp 100 °C; IR (KBr) 3367 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.09 (t, *J* = 7.4 Hz, 6 H), 1.55 (s, 6 H), 1.77 (m, 4 H), 2.15 (br s, 2 H), 7.33 (s, 4 H); ¹³C (125 MHz, CDCl₃) δ 8.9, 29.2, 36.6, 69.1, 83.0, 94.4, 122.6, 131.5; HRMS (EI) *m/z* 270.1620 [(M⁺), calcd. for C₁₈H₂₂O₂ 270.1615].

1-[4-(3-Hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (6)

(Table 3, entry 10). The representative PMHS/CsF conditions for the coupling of aryl nonaflates were applied to 2-methyl-3-butyn-2-ol (**1**) (0.20 mL, 2.0 mmol) and trifluoromethanesulfonic acid 4-acetyl-phenyl ester (**25**) (0.8046 g, 3.0 mmol). After reacting at room temperature for 5 h, column chromatography (silica gel; hexanes/EtOAc 75/25) afforded 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (**6**) (340 mg, 84%) as an oil. For spectroscopic data see above.

4-Cyclohex-1-enyl-but-3-yn-2-ol (27) (Table 3, entry 11).

The representative PMHS/CsF conditions for the coupling of aryl nonaflates were applied to 3-butyn-2-ol (**3**) (0.16 mL, 2.0 mmol), CuTC (38 mg, 0.20 mmol), and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid cyclohex-1-enyl ester (**26**) (1.14 g, 3.0 mmol) in THF/NMP (1:1; 30 mL). After reacting at room temperature for 5 h, column chromatography (silica gel; hexane/EtOAc 90:10) afforded 4-cyclohex-1-enyl-but-3-yn-2-ol (**27**) (360 mg, 85%) as an oil.¹²

1-(4-Ethynyl-phenyl)-ethanone (28).

A 25 mL flask was charged with ground potassium carbonate (0.1380 g, 1.0 mmol) and 18-crown-6 (0.0530 g, 0.20 mmol) and then purged with nitrogen. To the flask was added the 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (**6**) (See Table 3, entry 2 for preparation) (0.1700 g, 0.95 mmol) in toluene (8 mL + 2 mL wash) and the suspension was heated to 120 °C. The mixture was vigorously stirred under a stream of nitrogen until completion. Water (20 mL) was added and the mixture poured into a separatory funnel containing ethyl acetate (10 mL). The layers were separated and the

aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography (silica gel; hexanes/EtOAc 90/10) to afford 1-(4-ethynyl-phenyl)-ethanone¹³ (**28**) (107 mg, 78%) as an oil.

1-[4-(4-Methoxy-phenylethynyl)-phenyl]-ethanone (29). The representative PMHS/CsF conditions for the coupling of aryl nonaflates were applied to 1-(4-ethynyl-phenyl)-ethanone (**28**) (0.1440 g, 1.0 mmol)

and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-methoxy-phenyl ester (**18**) (0.4875 g, 1.5 mmol). After reacting at room temperature for 6 h, column chromatography (silica gel; hexanes/EtOAc 80/20) afforded 1-[4-(4-methoxy-phenylethynyl)-phenyl]-ethanone⁶ (**29**) (225 mg, 91%) as an oil.

Polymethyl(3-hydroxy-3-methyl-1-butynyl)siloxane (30). CsF (304 mg, 2.0 mmol) was dissolved in THF/NMP (10 mL; 1:1). 2-Methyl-3-butyn-2-ol (**1**) (0.10 mL, 1.0 mmol) and PMHS (0.09 mL, 1.5 mmol) and were added successively. Once

the initial reaction had subsided (foaming and gas evolution), the mixture was washed with water (3x) and extracted with ether (4x). The organic layer was dried (MgSO_4), filtered, and concentrated to afford **30** (143 mg, 99%) of a white solid: decomp 175–181 °C. ¹H NMR (300 MHz, CDCl_3) δ 0.01–0.24 (m), 1.43 (s), 2.70 (br s); ¹³C NMR (75 MHz, CDCl_3) δ 0.8, 1.5, 31.3, 64.9, 85.7, 110.8.

Polymethyl(1-octadecynyl)siloxane (31). CsF (304 mg, 2.0 mmol) was dissolved in THF/NMP (10 mL; 1:1). 1-Octadecyne (**15**) (251 mg, 1 mmol) and PMHS (0.09 mL, 1 mmol) and were added successively. Once the initial reaction had subsided (foaming and gas evolution), the mixture was washed

with water (3x) and extracted with ether (4x). The organic layer was dried (MgSO_4), filtered, and concentrated to afford **31** (305 mg, 97%) of a white solid: decomp 295 °C. ¹H NMR (300 MHz, CDCl_3) δ 0.00–0.30 (m), 0.90 (t, J = 5.6 Hz), 1.20–1.60 (m), 2.20 (td, J = 2.5, 7.0 Hz); ¹³C NMR (75 MHz, CDCl_3) δ 0.9, 1.6, 14.1, 19.9, 22.7, 28.7, 28.8, 29.1, 29.4, 29.5, 29.6, 29.7, 29.7, 32.0, 84.2, 107.7.

Reaction of 30 with TBAF. TBAF (5 mL as a 1 M solution in THF) was added to a solution of alkynyl siloxane **30** (143 mg, 1.0 mmol) in THF (5 mL). The reaction was stirred at 25 °C for 12 h. ¹H NMR analysis indicated complete removal of the silyl group.

The mixture was washed with water (3x) and extracted with ether (4x). The organic layer was dried (MgSO₄), filtered, and concentrated and filtering passed through a plug of silica to afford 2-methyl-3-butyn-2-ol (**1**) (83 mg, 99%) as a clear liquid.

Reaction of 31 with TBAF. TBAF (5 mL as a 1 M solution in THF) was added to a solution of alkynyl siloxane **30** (305 mg, 1.0 mmol) in THF (5 mL).

The reaction was stirred at 25 °C for 12 h. ¹H NMR analysis indicated complete removal of the silyl group. The mixture was washed with water (3x) and extracted with ether (4x). The organic layer was dried (MgSO₄), filtered, and concentrated and filtering passed through a plug of silica to afford 1-octadecyne (**15**) (247 mg, 97%) as an oil.

Coupling of 30. The representative PMHS/CsF conditions for the coupling of aryl nonaflates were applied to alkynyl siloxane **30** (301 mg, 1 mmol) and (*E*)-β-bromostryene (0.2745 g, 1.5 mmol). After reacting at room temperature for 8 h,

column chromatography (silica gel; hexanes/EtOAc 90/10) afforded **2** (85 mg, 46%) as an oil.

Coupling of 31. The representative PMHS/CsF conditions for the coupling of aryl nonaflates were applied to alkynyl siloxane **31** (305 mg, 1 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-

phenyl ester (**8**) (0.6273 g, 1.5 mmol). After reacting at room temperature for 8 h, column chromatography (silica gel; hexanes/EtOAc 90/10) afforded 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**16**) (158 mg, 43%) as an oil.

Representative PMHS/CsF mediated coupling with acyl chlorides.
4-Hydroxy-4-methyl-1-phenyl-pent-2-yn-1-one (32) (Table 4, entry 1). To 30 mL of NMP was added CsF (1.52 g, 10.0 mmol), 2-methyl-3-butyn-2-ol

(**1**) (0.20 mL, 2.0 mmol) and PMHS (0.24 mL, 4.0 mmol). After the initial reaction subsided, CuCl (40 mg, 0.4 mmol) was added followed by benzoyl chloride (0.26 mL, 2.2 mmol). The reaction was then heated to ~80 °C for 5 h. Once complete, the reaction was diluted with water and then extracted with ether (2x). The combined organics were dried (MgSO₄), filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 90/10) to afford 4-hydroxy-4-methyl-1-phenyl-pent-2-yn-1-one¹⁴ (**32**) (173 mg, 46%) as a yellow oil.

1,3-Diphenyl-propynone (33) (Table 4, entry 2). The representative conditions for the PMHS/CsF mediated coupling of acyl chlorides were applied to phenyl acetylene (**7**) (0.22 mL, 2.0 mmol) and benzoyl chloride (**36**) (0.26 mL, 2.2 mmol). After complete reaction (5 h), column chromatography (silica gel; hexane/EtOAc 95/5) afforded 1,3-diphenyl-propynone¹⁵ (**33**) (275 mg, 67%) as an oil.

1-(4-Methoxy-phenyl)-3-phenyl-propynone (34) (Table 4, entry 3). The representative conditions for the PMHS/CsF mediated coupling of acyl chlorides were applied to phenyl acetylene (**7**) (0.22 mL, 2.0 mmol) and 4-methoxybenzoyl chloride (0.30 mL, 2.2 mmol). After complete reaction (7 h), column chromatography, (silica gel; hexane/EtOAc 90/10) afforded 1-(4-methoxy-phenyl)-3-phenyl-propynone (**34**) (324 mg, 69%) as a white crystalline solid: mp 90–92 °C (lit.¹⁶ 92).

Representative PMHS/CsF mediated coupling of benzothiazole.

1-(4-Benzothiazol-2-yl-phenyl)-ethanone (35). To a solution of NMP (20 mL) was added CsF (760 mg, 5.0 mmol), benzothiazole (0.22 mL, 2.0 mmol), PMHS (0.24 mL, 4.0 mmol), CuCl (5.0 mg, 0.05 mmol), 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**8**) (418 mg, 1.0 mmol), and PdCl₂(PPh₃)₂ (35 mg, 0.05 mmol). This mixture was then allowed to stir for 17 h at room temperature. The reaction was then washed with H₂O (20 mL) and separated. The organics were washed with brine, dried (MgSO₄), filtered, and concentrated. The resulting residue diluted with a minimum amount of EtOH/PhCH₃ (5/2) and cooled to –5 °C to promote

crystallization. The solid was then dried under vacuum to afford 1-(4-benzothiazol-2-yl-phenyl)-ethanone (**35**) (146 mg, 58%) as an off white solid: mp 181 °C (lit.¹⁷ 182–183).

2-Phenyl-benzothiazole (36). The representative conditions for the PMHS/CsF mediated coupling of benzothiazole were applied to iodobenzene (0.11 mL, 1.0 mmol).

After complete reaction (14 h), recrystallization from EtOH/H₂O (2:1) afforded 2-phenyl-benzothiazole (**36**) (110 mg, 52%) as an off white solid: mp 112 °C (lit.¹⁷ 113–113.5).

1-Iodo-tetradec-1-ene (39). Super-hydride[®] (51.45 mL of a 1M THF solution, 51.45 mmol) was added dropwise to a foil wrapped flask containing a solution of Cp₂ZrCl₂ (15.04 g, 51.45 mmol) in THF (120 mL) . After 1 h, 1-tetradecyne (5.0 g,

25.73 mmol) in THF (150 mL) was added dropwise and stirring continued for 4 h. The reaction was then cooled to 0 °C and a solution of I₂ (6.53 g, 25.73 mmol) in CH₂Cl₂ (~200 mL) was added dropwise until a brown-orange color persisted. The mixture was diluted with CH₂Cl₂ (~100 mL) and washed with aq. sat. Na₂S₂O₃. The phases were separated and the combined organics were dried (MgSO₄), filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel; hexane) to afford 1-iodo-tetradec-1-ene (**39**) (7.95 g, 96%) as a light yellow oil. IR (neat) 2939, 1466 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.90 (t, *J* = 6.32 Hz, 3 H), 1.10–1.50 (m, 20 H), 2.06 (q, *J* = 7.07 Hz, 2 H), 5.99 (d, *J* = 14.35 Hz, 1 H), 6.53 (dt, *J* = 7.14, 14.28 Hz, 1 H); ¹³C (75 MHz, CDCl₃) δ 14.1, 22.7, 28.4, 28.9, 29.4, 29.5, 29.6, 29.7, 29.7, 29.7, 31.9, 36.1, 74.2, 146.7; HRMS (EI) *m/z* 322.1158 [(M⁺), calcd. for C₁₄H₂₇I 322.1156].

(*R*)-(-)-3-butyn-2-ol ((-)-3). TBAF (36.35 mL as a 1 M solution in THF) was added to a 0 °C solution of (*R*)-4-trimethylsilyl-3-butyn-2-ol¹⁸ (4.31 g, 30.3 mmol) in Et₂O (40 mL). The reaction was allowed to warm to room temperature and stir for 2

h. The reaction was then quenched by the addition of sat. aqueous NH₄Cl. The phases were separated and the organics dried over MgSO₄. The Et₂O was distilled off at atmospheric pressure (40 °C). With the majority of the Et₂O removed the remaining material was distilled at 110 °C to afford (*R*)-3-butyn-2-ol ((-)-

3) as a 0.49 M solution in THF as judged by ^1H NMR (68% yield). This solution was used as is in the next step.

(*R*)-(+)-Octadec-5-en-3-yn-2-ol (38). The representative PMHS/CsF mediated coupling conditions of vinyl halides were applied to (*R*)-3-butyne-2-ol ((-)-**3**) (24.49 mL of 0.49 M solution in THF, 12.0 mmol), 1-iodo-tetradec-1-ene (**39**)

(5.80 g, 18 mmol). After 7 h the reaction was judged complete by TLC analysis (hexanes/EtOAc 90/10). After workup as described above, the resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 90/10) to afford (*R*)-octadec-5-en-3-yn-2-ol (**38**) (2.80 g, 88%) as an off white solid: mp 32–34 °C; $[\alpha]_{\text{D}}^{23} +12.8$, (c 0.392, CHCl_3); IR (neat) 3200 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.88 (t, J = 6.11 Hz, 3 H), 1.05–1.41 (m, 20 H), 1.45 (d, J = 6.52 Hz, 3 H), 2.08 (q, J = 6.80 Hz, 2 H), 2.50 (br s, 1 H), 4.62 (q, J = 5.56 Hz, 1 H), 5.47 (d, J = 15.86 Hz, 1 H), 6.13 (dt, J = 7.07, 14.50 Hz, 1 H); ^{13}C (75 MHz, CDCl_3) δ 14.0, 22.6, 24.3, 28.6, 29.0, 29.3, 29.4, 29.5, 29.6, 29.6, 31.9, 33.0, 58.6, 82.7, 89.4, 108.72, 145.3; HRMS (EI) m/z 264.2453 [M^+], calcd. for $\text{C}_{18}\text{H}_{32}\text{O}$ 264.2456].

(-)-Akolactone A (37). Under an Ar atmosphere, (*R*)-octadec-5-en-3-yn-2-ol (**38**) (1.06 g, 4 mmol), Pd_2dba_3 (146.4 mg, 0.16 mmol) and dppb (136.4 mg, 0.32 mmol), were added to an oven dried stainless steel autoclave. Degassed (~2 h with

N_2) CH_2Cl_2 (40 mL) was added and the autoclave was sealed in under an Ar atmosphere. The vessel was purged 6x with CO (200 psi each time). It was then charged with CO (600 psi) and then H_2 (200 psi). The vessel was placed in oil bath and the internal temperature was maintained at 95 °C for 48 h. The reaction vessel was cooled to room temperature before opening. Once opened, the reaction was concentrated and the resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 92/8) to afford (-)-akolactone A (or 5-methyl-3-tetradec-1-enyl-5H-furan-2-one)¹⁹ (**37**) (1.02 g, 88%) as a clear oil. $[\alpha]_{\text{D}}^{23} -12.7$ (c 0.4, CHCl_3) (lit. -13.2 (c 0.1, CHCl_3)); IR (neat) 1767, 1662 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.87 (t, J = 7.1 Hz, 3 H), 1.16–1.36 (br s, 18 H), 1.42 (m, 5 H), 2.16 (q, J = 6.9 Hz, 2 H), 5.02 (qd, J = 1.7, 7.4 Hz, 1 H), 6.09 (d, J = 17.23 Hz, 1 H), 6.79 (dt, J = 7.1, 15.8 Hz, 1 H), 7.03 (d, J = 1.80 Hz, 1 H); ^{13}C (75 MHz,

CDCI₃) δ 14.0, 19.1, 22.6, 28.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 33.4, 76.9, 118.2, 129.3, 138.7, 146.8, 171.9; HRMS (EI) m/z 292.2402 [(M⁺), calcd. for C₁₉H₃₂O₂ 292.2403].

Alkyne homocoupling under "classic" Sonogashira coupling conditions.

1-[4-(3-Hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (40). 2-Methyl-3-butyn-2-ol (**1**) (0.10 mL, 1.0 mmol), CuI (0.010 g, 0.05 mmol), PdCl₂(PPh₃)₂ (0.0350 g, 0.05 mmol), Et₃N (0.28 mL, 2 mmol), and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**8**) (0.6273 g, 1.5 mmol) were all added to 10 mL of THF and stirred until complete by TLC analysis. Once complete (6 h), the reaction was concentrated and purified by column chromatography (silica gel; hexanes/EtOAc 70/30) to afford 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (**6**) (97 mg, 48%) as an oil and 2,7-dimethylocta-3,5-diyne-2,7-diol (**40**) (64 mg, 39%) as a white solid: mp 130 °C (lit.²⁰ 129–132).

Preparation of 2,7-diphenylocta-3,5-diyne-2,7-diol (41).

The "classic" Sonogashira conditions shown above were applied to 2-phenyl-3-butyn-2-ol (**17**) (0.1462 g, 1.0 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-methoxy-phenyl ester (**18**) (0.4875 g, 1.5 mmol). After complete reaction (11 h), column chromatography (silica gel; hexanes/EtOAc 80/20) afforded 2,7-diphenylocta-3,5-diyne-2,7-diol (**41**) (134 mg, 46%) as a white solid: mp 133 °C (lit.²⁰ 132–134).

ReactIR™ Study. CsF (15.19 g, 100 mmol) was added to a vigorously stirred solution of the alkyne (50 mmol) in NMP (50 mL). An initial IR spectrum was obtained. PMHS (6 mL, 100 mmol) was added dropwise at a rate that kept the reaction under control (~17 min). Data collection began immediately upon the first addition of PMHS and continued at 45 second intervals for 5.5 hours.

References

- (1) Keller, R. N.; Wycoff, H. D. *Inorg,Synth.* **1946**, *2*, 1–4.

- (2) This procedure was provided by Williams, D. R., Indiana University, personal communication, 2002. The Williams' preparation is a modification of the preparation reported by Liebeskind (Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749).
- (3) For a prior preparation and spectroscopic data see: Richecoeur, A. M. E.; Sweeney, J. B. *Tetrahedron* **2000**, *56*, 389–395.
- (4) For a prior preparation and spectroscopic data see: Liao, B.; Negishi, E. *Heterocycles* **2000**, *52*, 1241–1249.
- (5) For a prior preparation and spectroscopic data see: Hundertmark, T.; Littke, A. L.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729–1731.
- (6) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.-I.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780-1787 and references therein.
- (7) For a prior preparation and spectroscopic data see: Subramanian, L.R.; Martinez, A.G.; Fernandez, A.H.; Alvarez, R.M. *Synthesis* **1984**, 481-485.
- (8) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266–3270.
- (9) Lyapkalo, I. M.; Webel, M.; Reißig, H.-U. *Eur. J. Org. Chem.* **2002**, 1015–1025.
- (10) For a prior preparation and spectroscopic data see: Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017–8028.
- (11) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417–10418.
- (12) For a prior preparation and spectroscopic data see: Clark, D. L.; Chou, W.-N.; White, J. B. *J. Org. Chem.* **1990**, *55*, 3975–3977.
- (13) Havens, S. J.; Hergenrother, P. M. *J. Org. Chem.* **1985**, *50*, 1763–1765.

- (14) For a prior preparation and spectroscopic data: Saimoto, H.; Yasui, M.; Ohrai, S.-i.; Oikawa, H.; Yokoyama, K.; Shigemasa, Y. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 279–284.
- (15) For a prior preparation and spectroscopic data see: Chowdhury, C.; Kundu, N. G. *Tetrahedron* **1999**, *55*, 7011–7016.
- (16) For a prior preparation and spectroscopic data see: Nozaki, K.; Sato, N.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 2679–2681.
- (17) For a prior preparation and spectroscopic data see: Perry, R. J.; Wilson, B. D. *Organometallics* **1994**, *13*, 3346–3350.
- (18) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 3369–3372.
- (19) Chen, I.-S.; Lai-Yaun, I.-L.; Duh, C.-Y.; Tsai, I.-L. *Phytochemistry* **1998**, *49*, 745–750.
- (20) Raj, C. P.; Braverman, S. *Synth. Commun.* **1999**, *29*, 2629–2637

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