Diels-Alder Reactions of Hexafluoro-2-butyne with 2-Heterosubstituted furans: A Facile and General Synthesis of 1,4-Disubstituted 2,3-Di(trifluoromethyl)benzenes

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Supporting Information

General Spectroscopic and Experimental Data

The NMR spectra were obtained on Varian UP-300, Varian M-300, Bruker AMX-400, and Varian U-400 magnetic resonance spectrometer (300/400MHz for ^{1}H and 75/100MHz for ^{13}C) with deuteriochloroform as solvent and internal standard unless otherwise indicated. The chemical shifts are given in delta (δ) values and the coupling constants (J) in Hertz (Hz). Infrared spectra were recorded on Nicolet 5SX and Nicolet Magna-IR 750 spectrometer. Mass spectra were acquired on a Joel JMS-SX-102 spectrometer. Elemental analysis was performed by Robertson Microlit Laboratories, Inc., Madison, New Jersey. All manipulations were performed under nitrogen atmosphere unless otherwise mentioned. All solvents and reagents were purified when necessary using standard procedures. Flash column chromatography was performed on silica gel 60 (Merck, 230-400 mesh) using the indicated solvent. For routine aqueous workup, the reaction mixture was partitioned between water and EtOAc, and the organic layer was washed with brine and dried over $MgSO_4$.

General procedure for the Diels-Alder reactions of hexafluoro-2-butyne with 2-heterosubstituted furans: Hexafluoro-2-butyne **2** (1.7 g, 10.5 mmol) was condensed to a 60 mL pressure tube by a dry ice/acetone cooling bath. A solution of 2-heterosubstituted furan in dry benzene (15 mL) was slowly added through a septum. The pressure tube was then capped and heated in a 82 ^{o}C oil bath for 5 h. After cooled to rt, the reaction mixture was concentrated, and the residue was either distilled, crystallized or purified by flash chromatography when necessary.

2,3-Di(trifluoromethyl)-1-methoxy-7-oxabicyclo[2.2.1]hepta-2,5-diene (3b)

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (s, 3H), 5.47 (brs, 1H), 7.04 (d, J = 5.4Hz, 1H), 7.27 (dd, J = 5.4, 2.0Hz, 1H). MS (APCI) m/e 259 $(M-1)^-$. IR(neat) 1702 (w), 1453 (m), 1344 (s) cm^{-1}. Anal. calcd for $C_9H_6O_2F_6$: C, 41.55; H, 2.33. Found: C, 41.65; H, 2.38.

2,3-Di(trifluoromethyl)-1-trimethylsilyloxy-7-oxabicyclo[2.2.1]hepta-2,5-diene (3c)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 9H), 5.39 (brs, 1H), 6.93 (d, J = 5.4Hz, 1H), 7.19 (dd, J = 5.4, 2.1Hz, 1H). MS (APCI) m/e 317 $(M-1)^-$, 245 $[M-Si(CH_3)_3]^-$. IR(neat) 2966 (w), 1349 (s), 1288 (s), 1145 (s) cm^{-1}. Anal. calcd for $C_{11}H_{12}F_6O_2Si$: C, 41.50; H, 3.80. Found: C, 41.55; H, 3.88.

2,3-Di(trifluoromethyl)-1-methoxycarboxy-7-oxabicyclo[2.2.1]hepta-2,5-diene (3d)

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 5.59 (brs, 1H), 7.20 (d, J = 5.4Hz, 1H), 7.27 (dd, J = 5.4, 2.1Hz, 1H). MS (APCI) m/e 322 $(M+NH_4)^+$, 303 $(M-1)^-$. IR(neat) 1784 (s), 1278 (s), 1237 (s), 1180 (s), 1148 (s) cm^{-1}. Anal. calcd for $C_{10}H_6F_6O_4$: C, 39.49; H, 1.99. Found: C, 39.68; H, 2.08.

2,3-Di(trifluoromethyl)-1-trimethylacetoxy-7-oxabicyclo[2.2.1]hepta-2,5-diene (3e)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 5.57 (brs, 1H), 7.17 (d, J = 5.4 Hz, 1H), 7.24 (dd, J = 5.4, 2.0Hz, 1H). MS (APCI) m/e 348 $(M+NH_4)^+$, 329 $(M-1)^-$. IR(neat) 2980 (m), 1773 (s), 1344 (s), 1288 (s), 1148 (s) cm^{-1}. Anal. calcd for $C_{13}H_{12}F_6O_3$: C, 47.28; H, 3.66. Found: C, 47.12; H, 3.68.

2,3-Di(trifluoromethyl)-1-tributylstannyl-7-oxabicyclo[2.2.1]hepta-2,5-diene (3f)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2Hz, 9H), 1.07 (t, J = 7.2Hz, 6H), 1.32 (m, 6H), 1.53 (m, 6H), 5.65 (m, 1H), 7.21 (dd, J = 5.0, 1.7 Hz, 1H), 7.25 (d, J = 5.0Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 15.9, 30.3, 31.9, 50.9, 87.8, 145.3, 153.1. MS (APCI) m/e 518 $(M-1)^-$. IR(neat) 2959 (s), 1465 (w), 1285 (s) cm^{-1}. Anal. calcd for $C_{20}H_{30}F_6OSn$: C, 46.27; H, 5.82. Found: C, 46.50; H, 5.87.

4-(t-Butoxycarbamyl-2,3-di(trifluoromethylphenol (6a)

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.42 (s, 9H), 7.27 (d, J = 9.0Hz, 1H), 7.38 (d, J = 9.0Hz, 1H), 8.97 (brs, 1H), 11.10 (brs, 1H). MS (ESI) m/e 363 $(M+NH_4)^+$; 344 $(M-1)^-$. IR(KBr) 3330 (s), 1650 (s), 1520 (s), 1300 (s), 1130 (s) cm^{-1}. Anal. calcd for $C_{13}H_{13}F_6NO_3$: C, 45.23; H, 3.80; N, 4.06. Found: C, 45.17; H, 3.77; N, 3.81.

4-Methoxy-2,3-di(trifluoromethylphenol (6b)

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 5.90 (q, J = 7.1Hz, 1H), 7.17 (d, J = 9.5Hz, 1H), 7.20 (d, J = 9.5Hz, 1H). MS (APCI) m/e 259 $(M-1)^-$. IR(neat) 1702 (w), 1453 (m), 1344 (s), 1143 (s) cm^{-1}. Anal. calcd for $C_9H_6O_2F_6$: C, 41.55; H, 2.33. Found: C, 41.45; H, 2.28.

4-Trimethylsilyloxy-2,3-di(trifluoromethylphenol (6c)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 9H), 5.91 (q, J = 7.5Hz, 1H), 6.98 (d, J = 9.1Hz, 1H), 7.07 (d, J = 9.1Hz, 1H). MS (APCI) m/e 317 $(M-1)^-$, 245 $[M-Si(CH_3)_3]^-$. IR(neat) 2966 (w), 1349 (s), 1288 (s), 1145 (s) cm^{-1}. Anal. calcd for $C_{11}H_{12}F_6O_2Si$: C, 41.50; H, 3.80. Found: C, 41.35; H, 3.78.

4-iodo-2,3-di(trifluoromethyl)phenol (7)

A solution of **6a** (3.32 g, 9.6 mmol) in a mixture of DMSO (50 mL) and 30% H_2SO_4 (50 mL) was heated at 50 ^oC for 2 h. The resulting clear solution was cooled to 0 ^oC and a solution of $NaNO_2$ (994 mg, 14.4 mmol) in H_2O (5 mL) was added. The reaction mixture was stirred at 0 ^oC for 1 h, after which a solution of NaI (4.3 g, 28.8 mmol) in H_2O (5 mL) was added. After stirring at room temperature for 1 h, another batch of NaI (4.3 g) in H_2O (5mL) was then added. The reaction mixture was stirred for another hour. EtOAc was added and the mixture was washed sequentially with brine, 10% $NaHSO_3$ and water. The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (20% EtOAc in hexane) to give **7** as white solid (3.29 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.9 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 6.20 (q, J = 6.5 Hz, 1H). MS (APCI) m/e 355$(M-1)^-$. IR (KBr):

3356 (m), 1584 (w), 1148 (s) cm^{-1}. Anal. calcd for $C_8H_3F_6IO$: C, 26.99; H, 0.85. Found: C, 26.87; H, 0.88.

4-(E-2'-Ethoxycarbonylvinyl)-2,3-di(trifluoromethyl)phenol (8a)

A 100 mL RB flask was charged with **7** (2.0 g, 5.6 mmol), $Pd_2(dba)_3$ (260 mg, 0.28 mmol) and tri(o-tolyl)phosphine (260 mg, 0.84 mmol). After purged with nitrogen, anhydrous DMF (40mL), ethyl acrylate (1.69 g, 16.8 mmol) and triethylamine (2.34 mL, 16.8 mmol) were added under nitrogen. The black reaction mixture was purged with nitrogen again, and was heated at 70°C for 15 h. After cooled to rt, the reaction mixture was partitioned between brine and EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and concentrated. The residual oil was separated by flash chromatography to give **8a** (1.68 g, 91%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, J = 7.1Hz, 3H), 4.28 (q, J = 7.1Hz, 2H), 6.20 (d, J = 15.6Hz, 1H), 6.55 (q, J = 5.8Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.8Hz, 1H), 7.95 (dq, J =15.6, 4.4Hz, 1H). MS (APCI) m/e 346 $(M+NH_4)^+$, 327 $(M-1)^-$. IR(KBr) 3304 (m), 1687 (s), 1638 (s), 1445 (s), 1321 (s) cm^{-1}. Anal. calcd for $C_{13}H_{10}F_6O_3$: C, 47.57; H, 3.07. Found: C, 47.60; H, 3.08.

4-(2'-Furyl)-2,3-di(trifluoromethyl)phenol (8b)

A pressure tube was charged with **7** (200 mg, 0.56 mmol), $Pd_2(dba)_3$ (26 mg, 0.028 mmol) and tri(o-tolyl)phosphine (26 mg, 0.084 mmol), and was purged with nitrogen. Anhydreous DMF (6 mL), tributylstannylfuran (400 mg, 1.12 mmol) and triethylamine (234 μL, 1.68 mmol) were then added. The dark red solution was purged with nitrogen again, capped, and was heated at 70 °C for 4 hours. After cooled to rt, the reaction mixture was partitioned between brine and EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and concentrated. The residual oil was separated by flash chromatography on silica gel (25% EtOAc in hexane) to give **8b** (160 mg, 96%). ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (m, 1H), 6.47 (d, J = 1.3Hz, 2H), 7.20 (d, J = 8.8Hz, 1H), 7.52 (t, J = 1.4 Hz, 1H), 7.61 (d, J = 8.8Hz, 1H). MS (APCI) m/e 295 $(M-1)^-$. IR(KBr) 3401 (m), 1311 (s), 1150 (s) cm^{-1}. Anal. calcd for $C_{12}H_6F_6O_2$: C, 48.67; H, 2.04. Found: C, 48.87; H, 2.14.

4-Phenyl-2,3-di(trifluoromethyl)phenol (8c)

A pressure tube was charged with **7** (200 mg, 0.56 mmol), $Pd_2(dba)_3$ (26 mg, 0.028 mmol), tri(o-tolyl)phosphine (26 mg, 0.084 mmol), phenylboronic acid (137 mg, 1.12 mmol) and K_3PO_4 (237 mg, 1.12 mmol), and was purged with nitrogen. Anhydreous DME (7 mL) was then added. The reaction mixture was purged with nitrogen again, capped, and was heated at 80 ^oC for 6 hours. After cooled to rt, the mixture was partitioned between brine and EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and concentrated. The residual oil was separated by flash chromatography on silica gel (25% EtOAc in hexane) to give **8c** (73 mg, 42%). ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (brs, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.25 – 7.30 (m, 2H), 7.37 – 7.44 (m, 4H). MS (APCI) m/e 305 $(M-1)^-$. IR(KBr) 3505 (s), 1607 (w), 1480 (s), 1254 (s) cm^{-1}. Anal. calcd for $C_{14}H_8F_6O$: C, 54.92; H, 2.63. Found: C, 55.06; H, 2.48. **An alternative procedure for preparation of 8c:** A pressure tube was charged with **7** (200 mg, 0.56 mmol), $Pd_2(dba)_3$ (26 mg, 0.028 mmol), 2-dicyclohexylphosphanyl-2'-dimethylaminobiphenyl (22 mg, 0.056 mmol), phenylboronic acid (137 mg, 1.12 mmol) and K_3PO_4 (237 mg, 1.12 mmol), and was purged with nitrogen. Anhydreous DME (7 mL) was then added. The reaction mixture was purged with nitrogen again, capped, and was heated at 80 ^oC for 3 hours. After cooled to rt, the mixture was partitioned between brine and EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and concentrated. The residual oil was separated by flash chromatography on silica gel (25% EtOAc in hexane) to give **8c** (105 mg, 61%).

4-(5'-Acetylthiophen-2-yl)-2,3-di(trifluoromethyl)phenol (8d)

A pressure tube was charged with **7** (200 mg, 0.56 mmol), $Pd_2(dba)_3$ (26 mg, 0.028 mmol), 2-dicyclohexylphosphanyl-2'-dimethylaminobiphenyl (22 mg, 0.056 mmol), 5-acetylthiophene-2-boronic acid (190 mg, 1.12 mmol) and K_3PO_4 (237 mg, 1.12 mmol), and was purged with nitrogen. Anhydreous DME (7 mL) was then added. The reaction mixture was purged with nitrogen again, capped, and was heated at 80 ^oC for 3 hours. After cooled to rt, the mixture was partitioned between brine and EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and concentrated. The residual oil was separated by flash chromatography on silica gel (35% EtOAc in hexane) to give **8d** (188

mg, 94%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.56 (s, 3H), 7.18 (d, J = 4.0Hz, 1H), 7.37 (d, J = 8.6Hz, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 4.0Hz, 1H), 11.62 (brs, 1H). MS (APCI) m/e 355 $(M+1)^+$, 353 $(M-1)^-$. IR(KBr) 3077 (m), 1636 (s), 1433 (s), 1303 (s), 1170 (s) cm^{-1}. Anal. calcd for $C_{14}H_8F_6O_2S$: C, 47.46; H, 2.28. Found: C, 47.27; H, 2.20.

4-(E-2'-Ethoxycarbonylvinyl)-2,3-di(trifluoromethyl)phenyl trifluoromethane-sulfonate (9)

To a solution of **8a** (10.0 g, 30.5 mmol) in anhydrous pyridine (80 mL) at 0 ^oC was slowly added triflic anhydride (10.33 g, 36.6 mmol) within 10 min. The red solution was stirred at 0^oC for 2 hours, and at rt for 30 min. Ether (200 mL) and hexane (200 mL) were added, and the mixture was sequentially washed with 8% aq. HCl (500 mL), 1% HCl (500 mL) and water (500 mL). The organic phase was dried over $MgSO_4$, filtered through a short pad of silica gel and concentrated to give **9** (13.69 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, J = 7.1Hz, 3H), 4.30 (q, J = 7.1Hz, 2H), 6.30 (d, J =15.6Hz, 1H), 7.67 (d, J = 8.8Hz, 1H),7.82 (d, 8.8Hz, 1H), 7.96 (dq, J = 15.6, 4.2Hz, 1H). MS (APCI) m/e 478 $(M+NH_4)^+$. IR(KBr) 1723 (s), 1435 (s), 1317 (s), 1183 (s) cm^{-1}. Anal. calcd for $C_{14}H_9F_6O_5S$: C, 36.53; H, 1.97. Found: C, 36.73; H, 2.06.

4-(E-2'-Ethoxycarbonylvinyl)-2,3-di(trifluoromethyl)biphenyl (10a)

A pressure tube was charged with $Pd_2(dba)_3$ (26 mg, 0.028 mmol), tri(o-tolyl)phosphine (26 mg, 0.084 mmol), phenylboronic acid (137 mg, 1.12 mmol) and K_3PO_4 (237 mg, 1.12 mmol), and was purged with nitrogen. Anhydrous DME (5 mL), **9** (258 mg, 0.56 mmol) in DME (2 mL) were then added. The reaction mixture was purged with nitrogen again, capped, and was heated at 80 ^oC for 5 hours. After cooled to rt, the mixture was partitioned between brine and EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and concentrated. The residual oil was separated by flash chromatography on silica gel (11% EtOAc in hexane) to give **10a** (245 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, J = 7.2Hz, 3H), 4.30 (q, J = 7.1Hz, 2H), 6.35 (d, J = 15.6Hz, 1H), 7.32 – 7.36 (m, 2H), 7.40 – 7.46 (m, 3H), 7.53 (d, J = 8.2Hz, 1H), 7.73 (d, J = 8.2Hz, 1H), 8.07 (dq, J = 15.6, 4.0Hz, 1H). MS (APCI) m/e 406 $(M+NH_4)^+$. IR(KBr) 1714 (s), 1643

(w), 1316 (s), 1176 (s) cm^{-1}. Anal. calcd for $C_{19}H_{14}F_6O_2$: C, 58.77; H, 3.63. Found: C, 58.97; H, 3.44.

4-(E-2'-Ethoxycarbonylvinyl)-1-(2'-furyl)-2,3-di(trifluoromethyl)benzene (10b)

A pressure tube was charged with $Pd_2(dba)_3$ (26 mg, 0.028 mmol), tri(o-tolyl)phosphine (26 mg, 0.084 mmol), and was purged with nitrogen. Anhydrous DMF (4 mL), **9** (258 mg, 0.56 mmol) in DMF (2 mL), tributylstannylfuran (353 μL, 1.12 mmol) and triethylamine (234 μL, 1.12 mmol) were successively added. The reaction mixture was purged with nitrogen again, capped, and was heated at 80 ^oC for 2 hours. After cooled to rt, the mixture was partitioned between brine and EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and concentrated. The residual oil was separated by flash chromatography on silica gel (15% EtOAc in hexane) to give **10b** (198 mg, 93%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, J = 7.1Hz, 3H), 4.30 (q, J = 7.1Hz, 2H), 6.35 (d, J =15.6Hz, 1H), 6.53 (dd, J = 3.4, 1.7Hz, 1H), 6.66 (d, J = 3.1Hz, 1H), 7.58 (s, 1H), 7.73 (Abd, J = 8.4Hz, 1H), 7.78 (Abd, J = 8.2Hz, 1H), 8.03 (dq, J = 15.8, 4.0Hz, 1H). MS (APCI) m/e 396 $(M+NH_4)^+$. IR(KBr) 1712 (s), 1640 (w), 1316 (s), 1165 (s) cm^{-1}. Anal. calcd for $C_{17}H_{12}F_6O_3$: C, 53.98; H, 3.20. Found: C, 53.96; H, 3.03.

(±)-(1R, 2S, 3R, 4R)-2,3-Di(trifluoromethyl)-1-trimethylsilyloxy-7-oxabicyclo[2.2.1]heptane (11)

To a solution of **3c** (1.50 g, 5.2 mmol) in EtOAc (25 mL) was added 10% Pd/C (200 mg) under nitrogen. The suspension was purged with hydrogen, and was stirred at rt under hydrogen (balloon) for 15 hours. The reaction mixture was filtered through a short pad of silica ge and concentrated. The residual liquid was distilled on Kugelrohr to give **11** (1.43 g, 94%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 9H), 1.69 (tdd, J = 12.8, 5.1, 1.8Hz, 1H), 2.04 (m, 1H), 2.16 (m, 1H), 2.33 (ddd, J = 12.9, 8.8, 4.4Hz, 1H), 2.79 (dqd, J = 12.5, 10.6, 2.3Hz, 1H), 3.22 (dqdd, J =12.5, 10.6, 5.1, 1.7Hz, 1H), 4.53 (t, J = 5.2Hz, 1H). MS (APCI) m/e 312 (90%), 342 (100%). IR(neat) 2964 (w), 1379 (m), 1150 (s) cm^{-1}. Anal. calcd for $C_{11}H_{16}F_6O_2Si$: C, 40.99; H, 5.36. Found: C, 41.15; H, 5.42.

(±)-(2S, 3R, 4R)-2,3-Di(trifluoromethyl)-4-hydroxycyclohexanone (12)

To a solution of **11** (400 mg, 1.24 mmol) in THF (5 mL) was added 10% HCl (0.2 mL) at rt. This solution was stirred at rt for 10 min. Ether was added, and the mixture was washed with diluted $NaHCO_3$ and water. The ether solution was dried (Na_2SO_4), filtered and concentrated. The residual oil was distilled on Kugelrohr to give **12** (248 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 – 2.26 (m, 2H), 2.50 (m, 1H), 2.74 (m, 1H), 3.34 (m, 1H), 3.93 (qd, J 9.0, 5.0Hz, 1H), 4.61 (q, J = 3.0Hz, 1H). MS (APCI) m/e 285 $(M+Cl)^-$. IR(neat) 2964 (w), 1740 (s), 1301 (m), 1178 (s) cm^-. Anal. calcd for $C_8H_8F_6O_2$: C, 38.41; H, 3.22. Found: C, 38.55; H, 3.18.