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Palladium Catalyzed, Equilibrium Addition of Acidic OH Bonds to Dienes

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General comments. All reactions were performed under a nitrogen atmosphere with standard Schlenk and drybox techniques. Toluene was distilled from sodium and benzophenone under nitrogen. Dienes, phenols, acids, ligands, $[Pd(allyl)Cl]_2$ and $Pd(PPh_3)_4$ were purchased from commercial sources and were used without further purification. NMR spectra were recorded on Bruker DPX 400 and 500 MHz instruments. Elemental analyses were performed by Robertson Microlit Laboratories, Madison, NJ. Activity coefficient for 1,3-cyclohexadiene and 4-*tert*-butylphenol in toluene were calculated to be 1.11±0.04 and 1.95±0.15 by the UNIFAC method.[1] The activity coefficient of cyclohex-2'-enyl-4-*tert*-butylphenyl ether was assumed to be similar to that of diphenyl ether in toluene, which was calculated by the Chao-Seader method,[2] to be 1.01±0.01.

General Procedure for the 1, 2-addition of phenols and carboxylic acids to dienes (Table 2 and 3). In a drybox, diene (4.00 mmol) and phenol or carboxylic acid (1.00 mmol) were added to a suspension of $Pd(PPh_3)_4$ (11.7 mg, 10.0 μmol) in toluene (0.50 mL) in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was then stirred at room temperature for 24 h unless otherwise stated. After the reaction, the reaction mixture was adsorbed onto silica gel and purified by flash column chromatography.

Cyclohex-2′-enyl-phenyl ether (Table 2, Entry 1).[3] The general procedure was followed with cyclohexadiene (381 μl, 4.00 mmol) and phenol (94.1 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (0.5% EtOAc in hexane) to give 124 mg (71%) of the ether product: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.64 (m, 1H), 1.78-2.07 (m, 4H), 2.13 (m, 1H), 4.79 (m, 1H), 5.87 (m, 1H), 5.96 (ddt, *J* = 10.0, 3.5, 1.0 Hz, 1H), 6.92 (m, 3H), 7.26 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 19.0, 25.1, 28.3, 70.7, 115.8, 120.6, 126.4, 129.4, 132.0, 157.8.

Cyclohex-2′-enyl-4-*tert*-butylphenyl ether (Table 2, Entry 2).[4] The general procedure was followed with cyclohexadiene (381 μl, 4.00 mmol) and 4-*tert*-butylphenol (150.2 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (0.5% EtOAc in hexane) to give

168 mg (73%) of the ether product: ^{1}H NMR (400 MHz, CDCl$_3$, TMS) δ 1.29 (s, 9H), 1.63 (m, 1H), 1.76-2.24 (m, 5H), 4.77 (m, 1H), 5.87 (m, 1H), 5.96 (ddt, *J* = 10.1, 3.6, 1.0 Hz, 1H), 6.86 (m, 2H), 7.29 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 19.0, 25.1, 28.3, 31.5, 34.0, 70.7, 115.2, 126.2, 126.6, 131.9, 143.2, 155.5.

Cyclohex-2′-enyl-3,5-dimethylphenyl ether (Table 2, Entry 3).[4] The general procedure was followed with cyclohexadiene (381 μl, 4.00 mmol) and 3,5-dimethylphenol (122.1 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (0.5% EtOAc in hexane) to give 145 mg (72%) of the ether product: ^{1}H NMR (400 MHz, CDCl$_3$, TMS) δ 1.63 (m, 1H), 1.77-2.22 (m, 5H), 2.28 (s, 6H), 4.77 (m, 1H), 5.86 (m, 1H), 5.95 (m, 1H), 6.56 (s, 2H), 6.58 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 19.0, 21.4, 25.1, 28.3, 70.5, 113.5, 122.3, 126.5, 131.9, 139.2, 157.8.

Cyclohex-2′-enyl-2-isopropylphenyl ether (Table 2, Entry 4). The general procedure was followed with cyclohexadiene (381 μl, 4.00 mmol) and 2-isopropylphenol (136 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (0.5% EtOAc in hexane) to give 130.9 mg (61%) of the ether product: ^{1}H NMR (400 MHz, CDCl$_3$, TMS) δ 1.20 (d, *J* = 7.0 Hz, 3H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.65 (m, 1H), 1.79-2.22 (m, 5H), 3.34 (septet, *J* = 7.0 Hz, 1H), 4.78 (m, 1H), 5.89 (m, 1H), 5.94 (m, 1H), 6.90 (m, 2H), 7.12 (dt, *J* = 7.9, 1.6 Hz, 1H), 7.21 (dd, *J* = 7.4, 1.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 19.1, 22.7, 22.7, 25.2, 26.8, 28.6, 70.9, 112.8, 120.4, 126.2, 126.3, 126.7, 131.6, 138.0, 155.0. Anal. Calcd for $C_{16}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.50; H, 9.36.

Cyclohex-2′-enyl-4-methoxyphenyl ether (Table 2, Entry 5).[3] The general procedure was followed with cyclohexadiene (381 μl, 4.00 mmol) and 4-methoxyphenol (124 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (1% EtOAc in hexane) to give 138 mg (67%) of the ether product: ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.61 (m, 1H), 1.77-2.18 (m, 5H), 3.76 (s, 3H), 4.67 (m, 1H), 5.86 (m, 1H), 5.96 (ddt, *J* = 10.0, 3.6, 1.1 Hz, 1H), 6.83 (m, 2H), 6.88 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 18.9, 25.1, 28.3, 55.6, 71.8, 114.6, 117.3, 126.6, 131.9, 151.7, 153.8.

Cyclohex-2′-enyl-3,4-methylenedioxyphenyl ether (Table 2, Entry 6).[5] The general procedure was followed with cyclohexadiene (381 μl, 4.00 mmol) and sesamol (138 mg, 1.00 mmol), and the reaction solution was heated at 50 °C for 24 h. The reaction mixture was purified by flash column chromatography (0.5% EtOAc in hexane) to give 116 mg (53%) of the ether product: ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.62 (m, 1H), 1.76-2.18 (m, 5H), 4.63 (m, 1H), 5.86 (m, 1H), 5.91 (s, 2H), 5.96 (m, 1H), 6.37 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.69 (d, *J* = 8.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz,

$CDCl_3$) δ 18.9, 25.1, 28.2, 72.2, 99.6, 101.1, 107.9, 108.0, 126.4, 132.1, 141.6, 148.2, 153.1.

Cyclohex-2′-enyl-4-fluorophenyl ether (Table 2, Entry 7).[3] The general procedure was followed with $Pd(PPh_3)_4$ (23.1 mg, 20.0 μmol), cyclohexadiene (381 μl, 4.00 mmol) and 4-fluorophenol (112 mg, 1.00 mmol), and the reaction solution was heated at 50 °C for 24 h. The reaction mixture was purified by flash column chromatography (0.5% EtOAc in hexane) to give 120 mg (62%) of the ether product: ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.63 (m, 1H), 1.77-2.22 (m, 5H), 4.70 (m, 1H), 5.86 (m, 1H), 5.97 (m, 1H), 6.89 (m, 2H), 6.96 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 18.9, 25.1, 28.2, 71.7, 115.7 (d, *J* = 23 Hz), 117.1 (d, *J* = 8.1 Hz), 126.1, 132.3, 153.8, 157.2 (d, *J* = 238 Hz).

Cyclohex-2′-enyl-4-chlorophenyl ether (Table 2, Entry 8).[4] The general procedure was followed with $Pd(PPh_3)_4$ (23.1 mg, 20.0 μmol), cyclohexadiene (381 μl, 4.00 mmol) and 4-chlorophenol (129 mg, 1.00 mmol), and the reaction solution was heated at 50 °C for 24 h. The reaction mixture was purified by flash column chromatography (1% EtOAc in hexane) to give 118 mg (57%) of the ether product: ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.64 (m, 1H), 1.77-2.23 (m, 5H), 4.74 (m, 1H), 5.84 (m, 1H), 5.99 (ddt, *J* = 10.1, 3.6, 1.3 Hz, 1H), 6.85 (m, 2H), 7.21 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 18.9, 25.1, 28.1, 71.2, 117.1, 125.3, 125.8, 129.3, 132.5, 156.4.

Cyclohex-2′-enyl-3-trifluoromethylphenyl ether (Table 2, Entry 9). The general procedure was followed with $Pd(PPh_3)_4$ (23.1 mg, 20.0 μmol), cyclohexadiene (381 μl, 4.00 mmol) and 3-trifluoromethylphenol (162 mg, 1.00 mmol), and the reaction solution was heated at 50 ˚C for 18 h. The reaction mixture was purified by flash column chromatography (0.5% EtOAc in hexane) to give 107 mg (44%) of the ether product: ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.66 (m, 1H), 1.78-2.22 (m, 5H), 4.83 (m, 1H), 5.85 (m, 1H), 6.00 (ddt, *J* = 10.1, 3.6, 1.1 Hz, 1H), 7.08 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.13-7.21 (m, 2H), 7.36 (t, *J* = 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 18.8, 25.0, 28.1, 71.1, 112.6 (q, *J* = 4.1 Hz), 117.2 (q, *J* = 3.9 Hz), 119.1 (d, *J* = 1.6 Hz), 124.0 (q, *J* = 272 Hz), 125.5, 130.0, 131.8 (q, *J* = 32.2 Hz), 132.8, 157.9, Anal. Calcd for $C_{13}H_{13}F_2O$: C, 64.46; H, 5.41. Found: C, 64.29; H, 5.38.

Cyclohex-2′-enyl-3-methyl carboxylate phenyl ether (Table 2, Entry 10). The general procedure was followed with $Pd(PPh_3)_4$ (57.8 mg, 50.0 μmol), toluene 1.00 mL, cyclohexadiene (381 μl, 4.00 mmol) and 3-methyl hydroxybenzoate (152 mg, 1.00 mmol), and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was purified by flash column chromatography (1.0% EtOAc in hexane) to give 109 mg (47%) of the ether product:

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.66 (m, 1H), 1.78-2.21 (m, 5H), 3.91 (s, 3H), 4.86 (m, 1H), 5.86 (m, 1H), 5.99 (ddt, *J* = 10.1, 3.6, 1.0 Hz, 1H), 7.12 (ddd, *J* = 8.3, 2.7, 0.9 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.57-7.65 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.9, 25.0, 28.1, 52.1, 71.0, 115.9, 121.2, 121.8, 125.8, 129.4, 131.4, 132.5, 157.8, 167.0, Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.54; H, 7.09.

Cyclohex-2′-enyl benzoate (Table 2, Entry 11).[6] The general procedure was followed with $Pd(PPh_3)_4$ (11.6 mg, 10.0 μmol), cyclohexadiene (381 μl, 4.00 mmol) and benzoic acid (122 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (2% EtOAc in hexane) to give 101 mg (50%) of the ester product: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.71 (m, 1H), 1.77-2.22 (m, 5H), 5.51 (m, 1H), 5.84 (m, 1H), 6.02 (m, 1H), 7.43 (m, 2H), 7.54 (m, 1H), 8.06 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.9, 24.9, 28.4, 68.6, 125.7, 128.2, 129.6, 130.8, 132.7, 132.8, 166.2.

Cyclohex-2’-enyl acetate (Table 2, Entry 12).[7] The general procedure was followed with $Pd(PPh_3)_4$ (23.1 mg, 20.0 μmol), toluene 1.00 mL, cyclohexadiene (762 μl, 8.00 mmol) and acetic acid (123 mg, 2.05 mmol), and the reaction solution was stirred at room temperature for 48 h. The yield (52%) was determined by GC analysis with dodecane as internal standard. 1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.55-2.18 (m, 6H), 2.05 (s, 3H), 5.26 (m, 1H), 5.71 (m, 1H), 5.96 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 18.8, 21.3, 24.7, 28.2, 68.0, 125.6, 132.6, 170.7.

1′-Methylbut-2*(E)*′-enyl-4-*tert*-butylphenyl ether (Table 3, Entry 1). The general procedure was followed with $Pd(PPh_3)_4$ (11.6 mg, 10.0 μmol), *trans*-1,3-pentadiene (399 μl, 4.00 mmol) and 4-*tert*-butylphenol (150 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (0.5% EtOAc in hexane) to give 138 mg (63%) of the ether product (*E*:*Z* = 88:12): ^1H NMR (400 MHz, $CDCl_3$, TMS) of the major isomer δ 1.29 (s, 9H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.69 (d, *J* = 6.7 Hz, 3H), 4.72 (m, 1H), 5.55 (m, 1H), 5.70 (m, 1H), 6.82 (m, 2H), 7.26 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 17.7, 21.6, 31.5, 34.0, 74.2, 115.3, 126.1, 127.0, 132.5, 143.1, 155.8, Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.34; H, 10.08.

1′, 2′-Dimethylbut-2*(E)*′-enyl-4-*tert*-butylphenyl ether (Table 3, Entry 2). The general procedure was followed with $Pd(PPh_3)_4$ (11.6 mg, 10.0 μmol), *trans*-3-methyl-1,3-pentadiene (450 μl, 4.00 mmol) and 4-*tert*-butylphenol (150 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (0.25% EtOAc in hexane) to give 137 mg (59%) of the ether product (*E:Z* = 89:11): ^1H NMR (400 MHz, $CDCl_3$, TMS) of the major isomer δ 1.28 (s, 9H), 1.39 (d, *J* = 6.6Hz, 3H), 1.60 (d, *J* = 7.6 Hz, 3H), 1.61 (s, 3H), 4.63 (q, *J* = 6.6 Hz, 1H), 5.54 (m, 1H), 6.81 (m, 2H), 7.23 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 11.1, 13.1, 20.6, 31.5, 34.0, 78.8, 115.3, 120.7, 126.0, 136.5, 142.9, 156.0, Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.70; H, 10.43.

1′,2′-Dimethoxy-1′-methylprop-2′-enyl-4-*tert*-butylphenyl ether (Table 3, Entry 3). The general procedure was followed with $Pd(PPh_3)_4$ (57.8 mg, 50.0 μmol), 2,3-dimethoxy-1,3-butadiene (243 μl, 2.00 mmol) and 4-*tert*-butylphenol (150 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (1.0% EtOAc in hexane) to give 162 mg (62%) of the ether product: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.29 (s, 9H), 1.50 (s, 3H), 3.34 (s, 3H), 3.60 (s, 3H), 4.23 (d, *J* = 2.2 Hz, 1H), 4.77 (d, *J* = 2.2Hz, 1H), 7.05 (m, 2H), 7.26 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 23.2, 31.5, 34.1, 49.9, 55.2, 83.8, 102.1, 120.3, 125.8, 145.3, 152.0, 161.0, Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.88; H, 9.24.

1′-Methylbut-2*(E)*′-enyl benzoate (Table 3, Entry 4).[8] The general procedure was followed with $Pd(PPh_3)_4$ (23.1 mg, 20.0 μmol), *trans*-1,3-pentadiene (798 μl, 8.00 mmol) and benzoic acid (122 mg, 1.00 mmol), and the reaction solution was heated at 50 °C for 24 h. The reaction mixture was purified by flash column chromatography (0.5% EtOAc in hexane) to give 78.0 mg (41%) of the ester product (*E*:*Z* =

85:15): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) of the major isomer δ 1.42 (d, *J* = 6.2 Hz, 3H), 1.71 (d, *J* = 6.7 Hz, 3H), 5.52-5.65 (m, 1H), 5.57 (m, 1H), 5.81 (m, 1H), 7.42 (m, 2H), 7.54 (m, 1H), 8.05 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 17.7, 20.5, 71.7, 128.2, 128.2, 129.5, 130.8, 130.8, 132.7, 165.9.

Reaction of Cyclohexadiene with 4-*tert*-butyl-PhOD. The general procedure was followed with deuterio-4-*tert*-butylphenol (151.2 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography. The isolated product in a mixture of $CDCl_3$ (1.0 μl) and $CHCl_3$ (0.70 mL) was evaluated by ^{2}H NMR spectroscopy. Resonances at 1.92, 1.99 and 2.10 ppm were observed in an approximate ratio of 2:1:1. The resonance at 1.92 corresponds to two overlapping signals from material with the phenoxy and deuterium located 1,2 syn and 1,2 anti.

This material was then hydrogenated. The cyclohex-2′-enyl-4-*tert*-butylphenyl ether-d_1 (100 mg, 0.43 mmol) was added to a suspension of 10 % palladium on carbon in methanol (3.00 mL). This material was stirred under an ambient pressure of hydrogen gas for 16 h. The hydrogenated product was isolated by flash column chromatography, eluting with 0.5% EtOAc in hexane. A solution of the isolated product in $CDCl_3$ (1.0 μl) and $CHCl_3$ (0.70 mL) was evaluated by ^{2}H NMR spectroscopy. Resonances at 1.33, 1.53, 1.59 and 2.03 ppm were observed in an approximate ratio of 1:1:1:1. According to the assigned ^{1}H NMR spectrum of cyclohexanol,[9] the resonances at 1.53 and 1.59 correspond to the products with the phenoxy and deuterium located 1,4 anti and 1,2 syn, while the most upfield and downfield signals correspond to the products with the phenoxy and deuterium located 1,4 syn and 1,2 anti respectively.

Chemical Labeling, Substitution Reactions for Reversible C-O Bond Cleavage. In a dry box, cyclohex-2′-enyl-4-*tert*-butylphenyl ether (9.2 mg, 40 μmol or 46.1 mg, 0.20 mmol) and phenol (33.9 mg, 0.36 mmol or 19.1 mg, 0.20 mmol) were added to a suspension of $Pd(PPh_3)_4$ (4.6 mg, 4.0 μmol) in toluene 0.20 mL in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred at room temperature, and the yields of cyclohex-2′-enyl-4-*tert*-butylphenyl ether and cyclohex-2′-enylphenyl ether were measured by GC analysis at various reaction times. The yields as a function of time are shown in Figure S1.

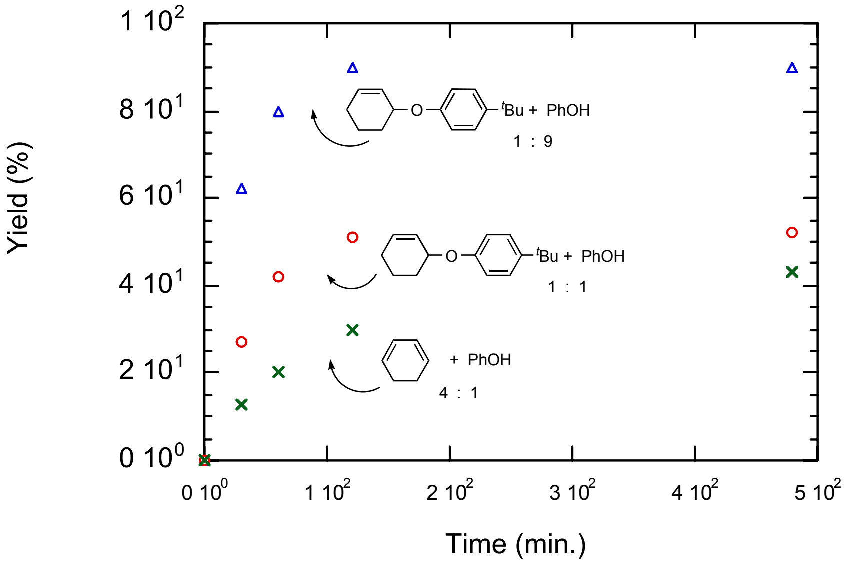

Figure S1. Comparison of the rate of exchange between the phenoxy group of the allylic ether and free phenol with the rate of addition of phenol to cyclohexadiene.

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