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Highly Enantioselective Palladium-Catalyzed Ene-type Cyclization of the 1,6-Enyne

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General:

^1H NMR and ^{13}C NMR spectra were measured on a Varian GEMINI 300 (300 MHz) spectrometers. Chemical shift of ^1H NMR were expressed in parts per million downfield from tetramethylsilane as an internal standard ($\delta = 0$) in $CDCl_3$, unless otherwise noted. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard ($\delta = 77.1$) in $CDCl_3$, unless otherwise noted. IR spectra were measured on a JASCO FT/IR-5000 spectrometer. Optical rotations were measured on a JASCO DIP-370. Capillary gas chromatographic analyses (GC) were conducted on a Shimadzu GC-14B instrument equipped with FID detector by using N_2 (75 kPa) as a carrier gas; Peak area were calculated by a Shimadzu C-R6A as an automatic integrator; Chiral column was CP-Cyclodextrin-β-2,3,6-M-19 (i.d. 0.25 mm x 25 m; CHROMPACK; GL Sciences Inc.); Split ratio was 100:1. Analytical thin layer chromatography (TLC) were performed on a glass plates (Merck Kieselgal 60 F_{254}, layer thickness 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid. Column chromatography was performed on KANTO Silica Gel 60N (spherical, neutral). All experiments were carried out under argon atmosphere otherwise noted.

Materials:

$Pd(OAc)_2$ was purchased from Wako Pure Chemical Industries, Ltd. $[Pd_2(dba)_3]\cdot CHCl_3$ was purchased from Kanto chemical Co., Inc. $Pd(OCOCF_3)_2$ and $[(MeCN)_4Pd](BF_4)_2$ were purchased from Aldrich Chemical Co.

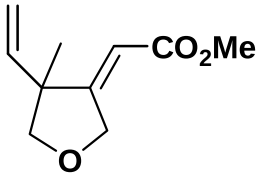
General procedure for Pd-catalyzed Ene-type cyclization of 1 under “*less polar conditions*”.

To a pyrex test tube thoroughly-degassed C_6D_6 (2.0 mL) was injected under argon. $Pd(OCOCF_3)_2$ (8.3 mg, 0.025 mmol) and (*R*)-BINAP (31.1 mg, 0.050 mmol) were added, and this suspension was stirred at room temperature for 5-10 min at which time the solution become clear. Then **1** (91.1 mg, 0.500 mmol) was added, the tube was tightened with a screw cap. The mixture was stirred at 100 C. The crude was checked by ^1H NMR (C_6D_6), and purified by short column chromatography (neutral-silica-gel, pentane/ether=100/3) to afford 93% *ee* of (*S*)-**2** ($[\alpha]_D^{29}$ = + 37.6 (*c* = 0.586 in $CHCl_3$): chiral GC column; CP-Cyclodextrin-β-2,3,6-M-19 [0.25 mm x 25 m, CHROMPACK, GL Sciences Inc.]; t_R = 31.8 min (*R*) and 33.7 min (*S*)) in quantitative yield.

General procedure for Pd-catalyzed Ene-type cyclization of 1 under *“polar conditions”*.

To a pyrex test tube thoroughly-degassed DMSO (1.2 mL) was injected under argon. $[(MeCN)_4Pd](BF_4)_2$ (6.7 mg, 0.015 mmol) and (*S*)-xylyl-SEGPHOS (21.7 mg, 0.030 mmol) were added, and this suspension was stirred at room temperature for 5-10 min at which time the solution become clear. Then **1** (54.7 mg, 0.300 mmol) was added, the tube was tightened with a screw cap. The mixture was stirred at 80 C. The crude was diluted with water, extracted with ether and concentrated after filtration. Then the concentrate was purified by short column chromatography (neutral-silica-gel, pentane/ether=100/3) to afford 96% *ee* of (*R*)-**2** ($[\alpha]_D^{30}$ = -39.4 (*c* = 0.250 in $CHCl_3$)) in quantitative yield.

(4-Methyl-4-vinyldihydrofuran-3-ylidene)-acetic acid methyl ester (**2**).



^1H NMR (300 MHz, $CDCl_3$)
δ 1.26 (s, 3H), 3.62 (d, *J* = 8.7 Hz, 1H), 3.69 (s, 3H), 3.72 (d, *J* = 9.0 Hz, 1H), 4.77 (dd, *J* = 17.7, 2.4 Hz, 1H), 4.91 (dd, *J* = 17.7, 2.4 Hz, 1H), 5.16 (d, *J* = 11.1 Hz, 1H), 5.17 (d, *J* = 17.7 Hz, 1H), 5.63 (t, *J* = 2.4 Hz, 1H), 5.79 (dd, *J* = 17.7, 10.5 Hz, 1H).

^{1}H NMR (300 MHz, C_6D_6)

δ 0.930 (s, 3H), 3.35 (d, *J* = 8.4 Hz, 1H), 3.35 (s, 3H), 3.45 (d, *J* = 8.4 Hz, 1H), 4.89 (d, *J* = 10.5 Hz, 1H), 4.90 (d, *J* = 17.4 Hz, 1H), 5.16 (dd, *J* = 17.7, 2.4 Hz, 1H), 5.08 (dd, *J* = 18.0, 2.7 Hz, 1H), 5.63 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.63 (t, *J* = 2.4 Hz, 1H).

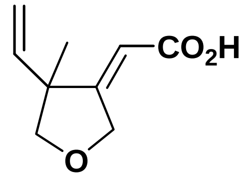
^{13}C NMR (75 MHz, $CDCl_3$)

δ 22.2, 50.7, 51.4, 72.2, 78.3, 111.0, 114.9, 140.7, 166.8, 169.4.

IR (neat)

2934, 2848, 1717, 1667, 1437, 1354, 1224, 1168, 1065, 1021, 930 cm^{-1}.

(4-Methyl-4-vinyldihydrofuran-3-ylidene)-acetic acid.



To a solution of **2** (938 mg, 5.15 mmol) in ethanol was added 30% KOH aq. (7 mL) and the mixture was stirred at room temperature for 3 h (monitored by TLC). The reaction mixture was acidified (pH = 2) by addition of 2 *N* HCl at 0 C, and added large amount of NaCl, then extracted with Et_2O. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate. After evaporation under reduced pressure to give the titled compound (801 mg, 92.5%).

^{1}H NMR (300 MHz, $CDCl_3$)
δ 1.29 (s, 3H), 3.66 (d, *J* = 8.7 Hz, 1H), 3.76 (d, *J* = 8.4 Hz, 1H), 4.73 (dd, *J* = 18.0, 2.7 Hz, 1H), 4.93 (dd, *J* = 18.0, 3.0 Hz, 1H), 5.18 (d, *J* = 3.0 Hz, 1H), 5.23 (d, *J* = 3.0 Hz, 1H), 5.65 (t, *J* = 2.4 Hz, 1H), 5.81 (dd, *J* = 17.4, 10.5 Hz, 1H).

This derived-carboxylic acid was crystallized as a diastereomeric salt of (*S*)-1-phenylehtylamine in a Et_2O-CH_2Cl_2 mixture at room temperature. Crystal data for this salt in X-ray analysis : formula $(C_9H_{12}O_3)_2 \cdot C_8H_{11}N$.