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

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General:

$^1$H NMR and $^{13}$C NMR spectra were measured on a Varian GEMINI 300 (300 MHz) spectrometers. Chemical shift of $^1$H 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-\(\beta\)-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, KMnO₄ 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. [Pd₂(dba)₃]·CHCl₃ was purchased from Kanto chemical Co., Inc. Pd(OCOCF₃)₂ and [(MeCN)₄Pd](BF₄)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 C₆D₆ (2.0 mL) was injected under argon. Pd(OCOCF₃)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 became 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 (C₆D₆), and purified by short column chromatography (neutral-silica-gel, pentane/ether=100/3) to afford 93% ee of (S)-2 ([α]D²⁹ = +37.6 (c = 0.586 in CHCl₃): chiral GC column; CP-Cyclodextrin-β-2,3,6-M-19 [0.25 mm x 25 m, CHROMPACK, GL Sciences Inc.]; tᵣ = 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. \([(\text{MeCN})_4\text{Pd}(\text{BF}_4)_2\) (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 became 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 ([α]_D^{30} = -39.4 (c = 0.250 in CHCl_3)) in quantitative yield.

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

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\text{CO}_2\text{Me}
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^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\(_6\)D\(_6\))
\[\delta 0.930 (s, 3H), 3.35 (d, J = 8.4 \text{ Hz}, 1H), 3.35 (s, 3H), 3.45 (d, J = 8.4 \text{ Hz}, 1H), 4.89 (d, J = 10.5 \text{ Hz}, 1H), 4.90 (d, J = 17.4 \text{ Hz}, 1H), 5.16 (dd, J = 17.7, 2.4 \text{ Hz}, 1H), 5.08 (dd, J = 18.0, 2.7 \text{ Hz}, 1H), 5.63 (dd, J = 17.4, 10.8 \text{ Hz}, 1H), 5.63 (t, J = 2.4 \text{ Hz}, 1H).\]

\(^{13}\)C NMR (75 MHz, CDCl\(_3\))
\[\delta 22.2, 50.7, 51.4, 72.2, 78.3, 111.0, 114.9, 140.7, 166.8, 169.4.\]

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\(_2\)O. 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$_3$)

$\delta$ 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-phenylethylamine in a Et$_2$O-CH$_2$Cl$_2$ mixture at room temperature. Crystal data for this salt in X-ray analysis: formula (C$_9$H$_{12}$O$_3$)$_2$·C$_8$H$_{12}$N.