Enhancement of Enantioselectivity by THF in Asymmetric Mo-Catalyzed Olefin Metathesis. Catalytic Enantioselective Synthesis of Cyclic Tertiary Ethers and Spirocycles

Xin Teng,* Dustin R. Cefalo,* Richard R. Schrock,# Amir H. Hoveyda*,*

Department of Chemistry, Merkert Chemistry Center, Boston College

Chestnut Hill, Massachusetts 02467

Department of Chemistry, Massachusetts Institute of Technology

Cambridge, Massachusetts 02139

Supporting Information

4-But-3-enyl-4-methoxymethoxy-cyclopentene (4). IR (neat): 3056(w), 2930(m), 2817(w), 1646(w), 1445(w), 1149(m), 1099(m), 1036(s), 910(m), 677(w) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 5.85 (ddt, J = 16.8, 10.0, 6.4 Hz, 1H, $\text{CH}_2=\text{CH}$), 5.67 (brs, 2H, $\text{CH}=\text{CH}$), 5.03 (ddt, J = 17.6, 1.6, 1.6 Hz, 1H, $\text{CH}_2=\text{CH}$), 4.94 (ddt, J = 10.0, 1.6, 1.6 Hz, 1H, $\text{CH}_2=\text{CH}$), 4.67 (s, 2H, OCH_2O), 3.37 (s, 3H, CH_3O), 2.61 (brd, J = 16.0 Hz, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 2.37 (brd, J = 16.0 Hz, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 2.24-2.10 (m, 2H, $\text{CH}_2=\text{CHCH}_2$), 1.84-1.75 (m, 2H, $\text{CH}_2\text{CH}_2\text{CO}$); ^{13}C NMR (100MHz, CDCl_3): δ 138.9, 128.7, 114.2, 91.9, 86.4, 55.5, 43.9, 39.1, 28.7; Anal. calcd for $\text{C}_{11}\text{H}_{18}\text{O}_2$: C, 72.49; H, 9.95. Found: C, 72.32; H, 9.66.

(1-But-3-enyl-cyclopent-3-enyloxy)-tert-butyl-dimethyl-silane (7). IR (neat): 3063(w), 2949(s), 2930(s), 2855(m), 1640(w), 1469(w), 1249(s), 1073(s), 834(s), 778(s), 671(w) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 5.85 (ddt, J = 16.8, 10.0, 6.4 Hz, 1H, $\text{CH}_2=\text{CH}$), 5.64 (brs, 2H, $\text{CH}=\text{CH}$), 5.01 (ddt, J = 17.6, 1.2, 1.2 Hz, 1H, $\text{CH}_2=\text{CH}$), 4.92 (ddt, J = 10.0, 1.2, 1.2 Hz, 1H, $\text{CH}_2=\text{CH}$), 2.48-2.35 (m, 4H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 2.21-2.13 (m, 2H, $\text{CH}_2=\text{CHCH}_2$), 1.73-1.65 (m, 2H, $\text{CH}_2\text{CH}_2\text{CO}$), 0.85 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.03(s, 6H, SiCH_3); ^{13}C NMR (100MHz, CDCl_3): δ 139.4, 128.8, 113.8, 83.4, 46.9, 42.5, 29.1, 25.9, 25.7, -2.9, -2.9; Anal. calcd for $\text{C}_{15}\text{H}_{28}\text{OSi}$: C, 71.36; H, 11.18. Found: C, 71.10; H, 10.98.

4-But-3-enyl-4-methoxy-cyclopentene (9). IR (neat): 3056(m), 2930(s), 2823(m), 1646(w), 1457(m), 1319(m), 1249(m), 1086(s), 910(m), 683(m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 5.85 (ddt, J = 16.8, 10.4, 6.8 Hz, 1H, $\text{CH}_2=\text{CH}$), 5.65 (brs, 2H, $\text{CH}=\text{CH}$), 5.03

(ddt, $J = 16.8, 1.2, 1.2$ Hz, 1H, $\text{CH}_2=\text{CH}$), 4.94 (ddt, $J = 10.0, 2.0, 1.2$ Hz, 1H, $\text{CH}_2=\text{CH}$), 3.15 (s, 3H, CH_3O), 2.51 (brd, $J = 16.0$ Hz, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 2.30 (brd, $J = 16.0$ Hz, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 2.16-2.00 (m, 2H, $\text{CH}_2=\text{CHCH}_2$), 1.78-1.66 (m, 2H, $\text{CH}_2\text{CH}_2\text{CO}$); ^{13}C NMR (100MHz, CDCl_3): δ 138.9, 128.6, 114.1, 85.4, 50.0, 42.5, 37.5, 28.4; Anal. calcd for $\text{C}_{10}\text{H}_{16}\text{O}$: C, 78.90; H, 10.59. Found: C, 78.99; H, 10.57.

(1-But-3-enyl-cyclopent-3-enyloxymethyl)-Benzene (11). IR (neat): 3061(w), 2924(m), 2859(m), 1640(w), 1456(m), 1319(w), 1242(w), 1093(m), 1064(m), 909(m), 737(m), 701(m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.40-7.18 (m, 5H, C_6H_5), 5.88 (ddt, $J = 17.2, 10.4, 6.8$ Hz, 1H, $\text{CH}_2=\text{CH}$), 5.70 (brs, 2H, $\text{CH}=\text{CH}$), 5.04 (ddt, $J = 17.2, 1.6, 1.6$ Hz, 1H, $\text{CH}_2=\text{CH}$), 4.95 (ddt, $J = 10.0, 2.0, 1.2$ Hz, 1H, $\text{CH}_2=\text{CH}$), 4.37 (s, 2H, $\text{C}_6\text{H}_5\text{CH}_2$), 2.63 (brd, $J = 16.0$ Hz, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 2.41 (brd, $J = 16.0$ Hz, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 2.26-2.16 (m, 2H, $\text{CH}_2=\text{CHCH}_2$), 1.90-1.81 (m, 2H, $\text{CH}_2\text{CH}_2\text{CO}$); ^{13}C NMR (100MHz, CDCl_3): δ 139.7, 139.0, 128.7, 128.3, 128.2, 127.1, 114.1, 85.8, 64.7, 43.1, 38.6, 28.5; Anal. calcd for $\text{C}_{16}\text{H}_{20}\text{O}$: C, 84.16; H, 8.83. Found: C, 84.51; H, 8.36. Enantiopurity of **12** was determined by its conversion into the corresponding tertiary alcohol, followed by GLC analysis.

(S)-1-Allyl-cyclohex-3-enol (alcohol derived from deprotection of 12). To a solution of sodium (21 mg, 0.88 mmol) in liquid NH_3 (3 mL) at -50°C , was added **12** (50 mg, 0.22 mmol) in THF (0.25 mL). The mixture was stirred for 1h and then treated with solid NH_4Cl until the solution became colorless. The NH_3 was allowed to evaporate at ambient temperature and water was added. The aqueous solution was extracted with Et_2O (3 x 5 mL), dried over MgSO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (pentane-diethyl ether, 15:1) to give pure **31** (26 mg, 85%) as an oil. IR (neat): 3402(m), 3074(m), 3024(m), 2924(m), 2848(m), 1646(w), 1432(w), 1042(w), 922(w), 740(w), 658(w) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 5.92 (ddt, $J = 18.0, 10.4, 7.6$ Hz, 1H, $\text{CH}_2=\text{CH}$), 5.76-5.68(m, 1H, $\text{CH}=\text{CH}$), 5.63-5.56 (m, 1H, $\text{CH}=\text{CH}$), 5.17 (ddt, $J = 10.4, 2.0, 0.8$ Hz, 1H, $\text{CH}_2=\text{CH}$), 5.13 (ddt, $J = 17.6, 2.4, 1.2$ Hz, 1H, $\text{CH}_2=\text{CH}$), 2.29 (ddt, $J = 14.0, 7.6, 1.2$ Hz, 1H, $\text{CH}_2=\text{CHCH}_2$), 2.24 (dddd, $J = 14.0, 7.2, 2.4, 1.2$ Hz, 1H, $\text{CH}_2=\text{CHCH}_2$), 2.22-1.95(m, 4H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 1.65-1.55 (m, 2H, CCH_2CH_2); ^{13}C NMR (100MHz, CDCl_3): δ 133.6, 126.5, 124.4, 118.8, 69.8, 45.4, 37.8, 33.0, 22.7; GC (CDGTA: column temperature = 80°C (isothermal), injector and detector temperature = 250°C , inlet pressure = 15 psi): t_r (major) = 25.1 min, t_r (minor) = 26.1 min.

4-Allyloxy-4-(2-methyl-allyl)-cyclopentene (15). IR (neat): 3062(w), 2917(s), 2848(m), 1650(w), 1432(m), 1320(m), 1256(m), 1092(s), 922(m), 897(m), 677(m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 5.91 (ddt, $J = 17.2, 10.4, 5.2$ Hz, 1H, $\text{CH}_2=\text{CH}$), 5.65 (brs, 2H, $\text{CH}=\text{CH}$), 5.27 (ddt, $J = 17.2, 2.0, 2.0$ Hz, 1H, $\text{CH}_2=\text{CH}$), 5.09 (ddt, $J = 10.4, 2.0, 1.6$ Hz, 1H, $\text{CH}_2=\text{CH}$), 4.87-4.82 (m, 1H, $\text{CH}_2=\text{C}$), 4.80-4.76 (m, 1H, $\text{CH}_2=\text{C}$), 3.87 (dt, $J = 5.6, 1.6$

Hz, 2H, CH₂O), 2.53 (brd, $J = 16.0$ Hz, 2H, CH₂CH=CHCH₂), 2.43 (brd, $J = 16.0$ Hz, 2H, CH₂CH=CHCH₂), 2.42 (s, 2H, CCH₂C), 1.81 (s, 3H, CCH₃); ¹³C NMR (100MHz, CDCl₃): δ 143.1, 135.9, 128.7, 115.4, 113.6, 85.9, 63.8, 46.3, 42.9, 24.1; Anal. calcd for C₁₂H₁₈O: C, 80.85; H, 10.18. Found: C, 80.58; H, 9.97.

4-Allyloxy-4-(2-methyl-but-2-enyl)-cyclopentene (inseparable *E/Z* mixture 19). (*E*)-isomer: ¹H NMR (400 MHz, CDCl₃): δ = 5.90 (ddt, $J = 17.2, 10.4, 4.8$ Hz, 1H, CH₂=CH), 5.64 (brs, 2H, CH=CH), 5.31-5.23 (m, 1H, CH₃C=CHCH₃), 5.26 (ddt, $J = 17.2, 1.6, 1.6$ Hz, 1H, CH₂=CH), 5.09 (ddt, $J = 10.8, 1.6, 1.6$ Hz, 1H, CH₂=CH), 3.86 (dt, $J = 5.2, 1.6$ Hz, 2H, CH₂O), 2.47 (brd, $J = 16.0$ Hz, 2H, CH₂CH=CHCH₂), 2.40 (brd, $J = 16.0$ Hz, 2H, CH₂CH=CHCH₂), 2.36 (s, 2H, CCH₂C), 1.69 (t, $J = 1.2$ Hz, 3H, CH₃C=CHCH₃), 1.60 (dq, $J = 6.4, 0.8$ Hz, 3H, CH₃C=CHCH₃); ¹³C NMR (100MHz, CDCl₃): δ 136.0, 133.3, 128.7, 122.2, 115.3, 86.5, 63.8, 48.2, 42.7, 17.1, 13.5; Anal. calcd for C₁₃H₂₀O: C, 81.20; H, 10.48. Found: C, 81.48; H, 10.35.

(*Z*)-isomer: ¹H NMR (400 MHz, CDCl₃): δ = 5.65 (brs, 2H, CH=CH), 5.37 (q, $J = 6.8$ Hz, 1H, CH₃C=CHCH₃), 3.89 (dt, $J = 5.2, 1.6$ Hz, 2H, CH₂O), 1.80 (dq, $J = 1.6, 1.6$ Hz, 3H, CH₃C=CHCH₃), 1.54 (dq, $J = 6.8, 0.8$ Hz, 3H, CH₃C=CHCH₃); ¹³C NMR (100MHz, CDCl₃): δ 135.9, 133.9, 128.8, 122.1, 115.4, 87.0, 64.0, 42.6, 39.1, 25.2, 13.8.

4-Allyloxy-4-(3-methyl-but-3-enyl)-cyclopentene (20). IR (neat): 3056(w), 2974(w), 2924(s), 2854(m), 1652(m), 1457(m), 1319(w), 1243(w), 1130(w), 1080(m), 929(m), 885(m), 671(m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 5.92 (ddt, $J = 17.6, 10.4, 5.2$ Hz, 1H, CH₂=CH), 5.66 (brs, 2H, CH=CH), 5.28 (ddt, $J = 17.2, 1.6, 1.6$ Hz, 1H, CH₂=CH), 5.10 (ddt, $J = 10.4, 1.6, 1.6$ Hz, 1H, CH₂=CH), 4.69 (brs, 2H, C=CH₂), 3.84 (dt, $J = 5.2, 1.2$ Hz, 2H, CH₂O), 2.54 (brd, $J = 16.0$ Hz, 2H, CH₂CH=CHCH₂), 2.35 (brd, $J = 16.0$ Hz, 2H, CH₂CH=CHCH₂), 2.14-2.05 (m, 2H, CH₂=CCH₂), 1.85-1.77 (m, 2H, CH₂=CCH₂CH₂), 1.75 (s, 3H, CH₃); ¹³C NMR (100MHz, CDCl₃): δ 146.3, 135.9, 128.7, 115.5, 109.3, 85.7, 63.7, 43.1, 37.3, 32.2, 22.8; Anal. calcd for C₁₃H₂₀O: C, 81.20; H, 10.48. Found: C, 81.41; H, 10.32.

{1-[2-(1-Allyloxy-cyclopent-3-enyl)-ethyl]-vinyl}-trimethyl-silane (22). IR (neat): 3056(w), 2955(s), 2936(m), 2854(m), 1646(w), 1426(w), 1243(s), 1073(m), 916(m), 841(s), 759(m), 677(w) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 5.91 (ddt, $J = 17.2, 10.4, 5.2$ Hz, 1H, CH₂=CH), 5.66 (brs, 2H, CH=CH), 5.58 (dt, $J = 3.2, 1.6$ Hz, 1H, CH₂=C), 5.32 (dt, $J = 2.8, 0.8$ Hz, 1H, CH₂=C), 5.27 (ddt, $J = 17.2, 1.6, 1.6$ Hz, 1H, CH₂=CH), 5.11 (ddt, $J = 10.4, 1.6, 1.6$ Hz, 1H, CH₂=CH), 3.84 (dt, $J = 5.2, 1.6$ Hz, 2H, CH₂O), 2.55 (brd, $J = 15.6$ Hz, 2H, CH₂CH=CHCH₂), 2.35 (brd, $J = 16.0$ Hz, 2H, CH₂CH=CHCH₂), 2.26-2.16 (m, 2H, CH₂=CCH₂), 1.80-1.74 (m, 2H, CH₂CH₂CO) 0.09 (s, 9H, Si(CH₃)₃); ¹³C NMR (100MHz,

CDCl_3): δ 152.5, 135.9, 128.7, 123.6, 115.5, 85.8, 63.6, 43.2, 38.6, 30.0, -1.5; Anal. calcd for $\text{C}_{15}\text{H}_{26}\text{OSi}$: C, 71.93; H, 10.46. Found: C, 72.22; H, 10.36.

(E)-4-Allyloxy-4-(4-methyl-hex-4-enyl)-cyclopentene (26). IR (neat): 3056(w), 2987(w), 2930(m), 2861(m), 1646(w), 1464(w), 1382(w), 1319(w), 1237(w), 1130(w), 1080(m), 922(m), 671(m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 5.91 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H, $\text{CH}_2=\text{CH}$), 5.65 (brs, 2H, $\text{CH}=\text{CH}$), 5.27 (ddt, J = 17.2, 2.0, 2.0 Hz, 1H, $\text{CH}_2=\text{CH}$), 5.24-5.17 (m, 1H, $\text{CH}_3\text{C}=\text{CHCH}_3$), 5.10 (ddt, J = 10.4, 2.0, 1.6 Hz, 1H, $\text{CH}_2=\text{CH}$), 3.82 (dt, J = 5.2, 1.6 Hz, 2H, CH_2O), 2.51 (brd, J = 16.0 Hz, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 2.31 (brd, J = 16.0 Hz, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 1.98 (t, J = 7.2 Hz, 2H, CH_3CCH_2), 1.65-1.36 (m, 7H, $\text{CH}_2\text{CH}_2\text{O}$, $\text{CH}_3\text{CH}=\text{C}$), 1.59 (s, 3H, CH_3CCH_2); ^{13}C NMR (100MHz, CDCl_3): δ 136.0, 135.8, 128.7, 118.4, 115.5, 85.8, 63.7, 43.1, 40.0, 38.7, 22.3, 15.5, 13.3; Anal. calcd. for $\text{C}_{15}\text{H}_{24}\text{O}$: C, 81.76; H, 10.98. Found: C, 81.83; H, 11.16.

Proof of absolute stereochemistry. The stereochemical identity of spirocycle **16**, **21**, **23** and **27** are by inference, based on the previously published results.⁴ The stereochemical identity of **8** was determined by comparison of the optical rotations of the compound prepared. Thus, as illustrated in Scheme 1, removal of the TBS group of **8** with TBAF/THF, followed by allylation of resulting *tert*-alcohol gave triene **31** in 88% yield. Subsequent Ru-catalyzed¹ RCM of **31** afforded (*R*)-**29**. The stereochemical identity of **8** was then established by comparison the optical rotations of (*R*)-**29** with (*S*)-**29** derived from **22** (see Scheme 1).

Scheme 1. Proof of absolute stereochemistry of spirocycle **8**

The identity of the major enantiomer of **29**, obtained from spirocycle **23** (see Table 2, text) was correlated with an authentic sample obtained from (*S*)-**8**.

1) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(S)-1-Oxa-spiro[5.5]undeca-3,8-diene (29). IR (neat): 3018(m), 2911(s), 2936(m), 1659(m), 1432(m), 1193(m), 1099(s), 1020(m), 834(m), 759(m), 652(m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 5.80-5.67 (m, 3H, olefin-H), 5.62-5.55 (m, 1H, olefin-H), 4.22-3.90 (m, 2H, CH_2O), 2.25-1.85 (m, 7H, allylic-H, $\text{CCH}_2\text{CH}_2\text{CH}=\text{CH}$) 1.55 (dt, J = 13.2, 7.2 Hz, 1H, $\text{CCH}_2\text{CH}_2\text{CH}=\text{CH}$); ^{13}C NMR (100MHz, CDCl_3): δ 126.5, 125.4, 124.1, 122.7, 69.7, 60.8, 35.7, 33.9, 30.7, 22.8; Anal. calcd. for $\text{C}_{10}\text{H}_{14}\text{O}$: C, 79.96; H, 9.39. Found: C, 79.82; H, 9.21.

Representative results of catalyst screening for cyclopentenyl substrate (4):

Table 1. Chiral catalyst screening

catalyst	% ee
(S)-17	-28
(S)-24	<5
(S)-28	<5
(R)-3	45
(R)-6	72
(R)-33	11

(R)-34 NO REACTION

Representative GLC traces for determination of optical purity:

authentic racemic

reaction without THF (78% ee)

reaction with 2 equiv THF (85% ee)

reaction with 10 equiv THF (92% ee)

reaction with in situ catalyst (90% ee)

authentic racemic

reaction without THF (58% ee)

reaction with 10 equiv THF (96% ee)

reaction with in situ catalyst (90% ee)

authentic racemic

reaction without THF (79% ee)

reaction with 10 equiv THF (90% ee)

authentic racemic

asymmetric reaction (80% ee)

authentic racemic

from asymmetric reaction (83% ee)