Tin-Free and Catalytic Radical Cyclizations

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Supporting Information

Contents:

I. Synthesis of Dienes	S-1
II. Cyclization of Dienes	S-4
III. Stereochemical proofs of cyclic products	S-5
IV. Bibliography	S-7
V. Analytical Data	S-8

General. ^1H NMR and ^{13}C NMR spectra were recorded at ambient temperature at 400 MHz and 100 or 75 MHz, respectively, using a Bruker DRX400 or DRX 300 spectrometer. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Infrared (IR) spectra were obtained using a Perkin Elmer 2000 FT-IR spectrometer. High resolution mass spectra were acquired on a JOEL JMS-HX110 HF mass spectrometers, and were obtained by peak matching. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Fisher silica gel (SiO_2) 60 (230–400 mesh). Preparative reverse phase (RP) HPLC was performed on a Grace Vydac C18 Protein & Peptide column with a Waters 600 Controller; fractions were detected with a Waters 2487 Dual λ Absorbance Detector (218 and 254 nm). $\text{CpCr}(\text{CO})_3\text{H}$ was stored and manipulated in an inert nitrogen atmosphere dry box ($\text{O}_2 < 1$ ppm). Reaction mixtures involving $\text{CpCr}(\text{CO})_3\text{H}$ were prepared in the drybox. High pressure reactions were carried out in a Fisher-Porter bottle equipped with a pressure gauge, gas inlet, and pressure release valve. All reactions were carried out under an atmosphere of nitrogen in glassware that had been flame-dried under a stream of nitrogen. Deuterated benzene (C_6D_6) was purified by vacuum transfer from sodium-benzophenone ketyl. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. THF, Et_2O , toluene, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs.¹

I. Synthesis of Diene Substrates

A. Diene Substrate (4) Synthetic Scheme.

Alkene (S2). To a cooled (0 °C) solution of PPh₃ (3.68 g, 14.0 mmol) and imidazole (1.27 g, 18.7 mmol) in 26 mL of 3:1 Et₂O/CH₃CN was added iodine (3.56 g, 14.0 mmol).² After 20 min at 0 °C, a solution of alcohol **S1**³ in 5 mL of 3:1 Et₂O/CH₃CN was added dropwise over 10 min. The mixture was warmed to 22 °C for 12 h. Pentane was added to precipitate triphenylphosphine oxide and the solution was filtered through a pad of silica gel and concentrated *in vacuo*.⁴ Purification by flash chromatography (2:98–5:95 EtOAc/hexanes) afforded the product as a colorless oil (3.26 g, 91%): ¹H NMR (400 MHz, CDCl₃) δ 7.16–7.40 (m, 10H), 6.03 (t, *J* = 7.6, 1H), 3.15 (t, *J* = 7.0, 1H), 2.21 (q, *J* = 7.2, 2H), 1.97 (quintet, *J* = 7.2, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 144.4, 143.7, 141.2, 131.2, 129.6, 129.5, 128.7, 128.5, 128.4, 35.2, 32.0, 7.2; IR (thin film) 3018, 2937, 1594, 1440 cm⁻¹; HRMS (FAB) *m/z* calcd for C₁₇H₁₇I (M⁺) 348.0375, found 348.0380.

Amine (S3). To a cooled (–78 °C) solution of diisopropylamine (2.62 mL, 18.7 mmol) in 75 mL of THF was added cold (–78 °C) *n*-BuLi (12 mL, 18 mmol, 1.5 M in hexanes). The mixture was stirred at 0 °C for 30 min and was again cooled to –78 °C. A solution of methyl 3-(dimethylamino)propionate (2.47 mL, 17.2 mmol) in 40 mL of THF was cooled to –78 °C and added to the reaction mixture by cannula over 3 min. After 45 min, a solution of cold (–78 °C) alkyl iodide **S2** (5.00 g, 14.4 mmol) and HMPA (3.00 mL, 17.2 mmol) in 40 mL of THF was added to the reaction mixture dropwise by cannula.⁵ After 12 h at 22 °C, 20 mL of saturated aqueous NH₄Cl was added. The reaction mixture was extracted with EtOAc (50 mL). The organic layer was washed with H₂O (1 × 30 mL), saturated aqueous LiCl (2 × 30 mL), dried (Na₂SO₄), and concentrated *in vacuo*. The product was isolated by flash chromatography (20:79:1 – 79:20:1 EtOAc/hexanes/Et₃N) as a colorless oil (5.05 g, 87%): ¹H NMR (400 MHz, CDCl₃) δ 7.06–7.30 (m, 10H), 5.96 (t, *J* = 7.6, 1H), 3.60 (s, 3H), 2.54 (m, 1H), 2.47 (m, 1H), 2.10 (s, 6H), 2.04 (m, 3H), 1.48 (m, 1H), 1.35 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.9, 141.7, 140.9, 139.1, 128.9, 128.3, 127.1, 127.0, 126.2, 125.9, 125.8, 61.0, 50.5, 44.7, 43.4, 29.4, 28.6, 26.7; IR (thin film) 2945, 1735, 1443, 1262 cm⁻¹; HRMS (FAB) *m/z* calcd for C₂₃H₃₀NO₂ (M + H)⁺ 352.2277, found 352.2268.

Diene (S4). To a solution of ester **S3** (4.378 g, 12.45 mmol) in 120 mL of THF was added iodomethane (1.55 mL, 25.9 mmol, filtered through basic alumina).⁶ After 12 h at 22 °C, the solution was concentrated *in vacuo* to provide a yellow solid. To a solution of this residue in benzene (100 mL) was added DBN (3.02 mL, 25.3 mmol).⁷ After 12 h at 22 °C, H₂O was added and the reaction mixture was extracted with pentane (3 × 50 mL). The combined organic layers were washed with H₂O, brine, dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash chromatography (10:89:1–30:69:1 EtOAc/hexanes/Et₃N) provided the product as a colorless oil (2.12 g, 56%): ¹H NMR (400 MHz, C₆D₆) δ 7.29 (m, 2H), 7.06–7.17 (m, 8H), 6.10 (m, 1H), 6.03 (t, *J* = 7.6, 1H), 5.13 (dd, *J* = 2.8, 1.2, 1H), 3.36 (s, 3H), 2.23 (t, *J* = 7.6, 2H), 2.09 (q, *J* = 7.6, 2H), 1.54 (quintet, *J* = 7.6, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.0, 144.1, 143.4, 141.7, 141.5, 131.2, 130.7, 129.5, 129.4, 128.5, 128.21, 128.16, 126.1, 53.1, 32.8, 30.6, 30.1; IR (thin film) 2945, 1720, 1628, 1439 cm⁻¹. HRMS (FAB) *m/z* calcd for C₂₁H₂₃O₂ (M+H)⁺ 307.1698, found 307.1702.

B. Diene Substrate (13) Synthetic Scheme.

Alkene (12). To a cooled (0 °C) solution of dimethyl malonate (5.00 mL, 43.6 mmol) in 125 mL of THF was added NaH (0.900 g, 35.8 mmol, 95%).⁸ The mixture was stirred at 0 °C for 2 h. The reaction mixture was added with a cannula to a 0 °C solution of 3-bromo-1,1-diphenyl-1-propene **S4**⁹ (7.87 g, 28.8 mmol) in 45 mL of THF. After 30 min at 22 °C, the reaction mixture was treated with saturated aqueous NH₄Cl (60 mL), extracted with EtOAc (2 × 100 mL), dried (Na₂SO₄), and concentrated *in vacuo*. The product was isolated by flash chromatography (4:1 hexanes/EtOAc) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.30–7.34 (m, 4H), 7.13–7.24 (m, 6H), 5.97 (t, *J* = 7.6, 1H), 3.69 (s, 6H), 3.46 (t, *J* = 7.6, 1H), 2.72 (t, *J* = 7.6, 2H); ¹H NMR (400 MHz, C₆D₆) δ 7.25–7.26 (d, 2H), 7.02–7.13 (m, 8H), 6.11 (t, *J* = 7.4, 1H), 3.42 (t, *J* = 7.4, 1H), 3.21 (s, 6H), 2.88 (t, *J* = 7.4, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 169.6, 144.9, 142.6, 139.7, 130.1, 128.7, 128.5, 127.8, 127.7, 124.6, 52.9, 52.2, 29.3; IR (thin film) 3026, 2955, 1740, 1494, 1440, 1342, 1234, 1158 cm⁻¹; HRMS (FAB) *m/z* calcd for C₂₀H₂₀O₄ (M⁺) 324.1362, found 324.1373.

Diene (13). To a cooled (0 °C) solution of dimethyl 2-(3,3-diphenylallyl)malonate (2.6 g, 8.0 mmol) in 80 mL of THF was added NaH (0.22 g, 8.7 mmol, 95%). After 2 h at 22 °C, the reaction mixture was cooled to 0 °C and 2-bromomethylacrylic acid (1.0 mL, 8.1 mmol, 97%) was added. The solution was heated to reflux. After

6 h, the reaction mixture was cooled (22 °C) and treated with saturated aqueous NH_4Cl (40 mL), and extracted with EtOAc (2×75 mL). The combined organic layers were dried (Na_2SO_4), and concentrated *in vacuo*. The product was isolated by flash chromatography (5:1 hexanes/EtOAc) as a white solid (2.8 g, 83%): ^1H NMR (400 MHz, CDCl_3) δ 7.28–7.36 (m, 3H), 7.10–7.23 (m, 6H), 6.16 (s, 1H), 5.91 (t, $J = 7.2$, 1H), 5.51 (s, 1H), 3.65, (s, 3H), 3.64 (s, 6H), 3.01 (s, 2H), 2.73 (d, $J = 7.2$, 2H); ^1H NMR (400 MHz, C_6D_6) δ 7.34 (d, $J = 6.8$, 2H), 6.95–7.09 (m, 8H), 6.25 (t, $J = 7.2$, 1H), 6.12 (s, 1H), 5.36 (s, 1H), 3.31 (s, 6H), 3.30 (s, 2H), 3.26 (s, 3H), 3.06 (d, $J = 7.2$, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.4, 167.6, 145.5, 143.0, 139.7, 135.9, 130.2, 129.7, 128.6, 128.5, 127.9, 127.7, 123.1, 58.1, 52.8, 52.3, 34.4, 33.0; IR (thin film) 2953, 1732, 1441, 1288, 1200, 1155 cm^{-1} ; HRMS (FAB) m/z calcd for $\text{C}_{25}\text{H}_{26}\text{O}_6$ ($\text{M} + \text{H}$) $^+$ 423.1807, found 423.1817.

II. Cyclization of Diene Substrates

General Procedure for $\text{CpCr}(\text{CO})_3\text{H}$ -Mediated Cyclization: $\text{CpCr}(\text{CO})_3\text{H}$ was synthesized according to published procedures¹⁰ and sublimed prior to use. A stock solution of $\text{CpCr}(\text{CO})_3\text{H}$ in C_6D_6 (0.02–0.04 M) was stirred under 30 psi of H_2 . After 30 min, a solution of diene substrate and hexamethylcyclotrisiloxane in C_6D_6 (0.13 M in substrate) was added to the reaction mixture. The reaction mixture was pressurized to 30 psi of H_2 . After NMR analysis indicated that the starting material was consumed, the reaction mixture was filtered through a silica plug and concentrated *in vacuo*. NMR concentrations were determined from integration vs the hexamethylcyclotrisiloxane standard.

Carbocycle (9). The standard cyclization procedure was followed with diene **4** (0.328 g, 1.07 mmol) and $\text{CpCr}(\text{CO})_3\text{H}$ (3.6 mL, 0.071 mmol, 0.020 M) and heated to 50 °C for 4 d. ^1H NMR spectroscopic analysis of the unpurified product showed **9** (62%) as a pair of diastereomers in an 62:38 ratio of diastereomers, hydrogenation product **6** (26%) and isomerization product **10** (12%). Purification by flash chromatography did not adequately separate the products. The products were separable in small amounts by preparative RP-HPLC.

Major 1,2-trans isomer (9a): ^1H NMR (400 MHz, CDCl_3) δ 7.07–7.35 (m, 10H), 3.70 (d, $J = 11.6$, 1H), 3.41 (td, $J = 11.6$, 7.6, 1H), 3.20 (s, 3H), 2.17 (m, 1H), 1.57–1.77 (m, 4H), 1.30 (m, 1H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.7, 146.4, 144.4, 129.8, 129.7, 129.5, 129.0, 127.6, 127.4, 56.1, 52.7, 51.8, 42.9, 32.2, 31.0, 23.3, 18.2; IR (thin film) 3026, 2945, 1724, 1494, 1252 cm^{-1} ; HRMS (FAB) m/z calcd. $\text{C}_{21}\text{H}_{24}\text{O}_2$ for (M^+) 308.1776, found 308.1776.

Minor 1,2-cis isomer (9b): ^1H NMR (400 MHz, CDCl_3) δ 7.19–7.31 (m, 8H), 7.09 (m, 2H), 3.97 (d, $J = 11.6$, 1H), 3.49 (s, 3H), 2.72 (ddd, $J = 11.4$, 10.3, 7.0, 1H), 2.16 (m, 1H), 1.72 (m, 2H), 1.50–1.63 (m, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.8, 145.8, 144.3, 128.8, 128.7, 128.5, 128.3, 126.7, 126.4, 55.2, 52.1, 51.6, 42.1, 34.0, 26.3, 23.4; IR (thin film) 3026, 2946, 1721, 1595, 1448 cm^{-1} ; HRMS (FAB) m/z calcd. $\text{C}_{21}\text{H}_{24}\text{O}_2$ for (M^+) 308.1776, found 308.1771.

Hydrogenation Product (6). ^1H NMR (400 MHz, CDCl_3) δ 7.15–7.37 (m, 10H), 6.05 (t, $J = 7.6$, 1H), 3.65 (s, 3H), 2.40 (sextet, $J = 7.0$, 1H), 2.11 (q, $J = 7.6$, 2H), 1.65 (m, 1H), 1.42 (m, 3H), 1.12 (d, $J = 6.8$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 178.5, 144.0, 143.2, 141.5, 131.2, 130.8, 129.5, 129.4, 128.5, 128.21, 128.16, 52.8, 40.6, 34.7, 30.9, 28.9, 18.4; IR (thin film) 3025, 2937, 1734, 1440 cm^{-1} ; HRMS (FAB) m/z calcd. $\text{C}_{21}\text{H}_{24}\text{O}_2$ for (M^+) 308.1776, found 308.1779.

Isomerization Product (10). ^1H NMR (400 MHz, CDCl_3) δ 7.18–7.36 (m, 10H), 6.76 (m, 1H), 6.10 (t, $J = 7.2$, 1H), 3.75 (s, 3H), 2.30 (m, 4H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.5, 142.9, 142.5, 141.6, 140.1, 129.9, 128.4, 128.2, 127.3, 127.2, 51.8, 29.1, 28.9, 12.6; IR (thin film) 3018, 2944, 1712, 1440, 1263 cm^{-1} ; HRMS (FAB) m/z calcd. $\text{C}_{21}\text{H}_{24}\text{O}_2$ for ($\text{M} + \text{H}$) $^+$ 307.1698, found 307.1688.

Carbocycle (14). The standard cyclization procedure (0.30 M in substrate **14**) was followed with diene **12** (0.189 g, 0.447 mmol) and $\text{CpCr}(\text{CO})_3\text{H}$ (0.75 mL, 0.030 mmol, 0.040 M) and heated to 50 $^\circ\text{C}$ for 1.5 d. ^1H NMR spectroscopic analysis of the unpurified product showed **14** (>95%) as a 1:1 mixture of diastereomers. Purification by flash chromatography did not adequately separate the products. The products were separable in small amounts by preparative RP-HPLC.

1,2-trans isomer (14a): ^1H NMR (400 MHz, C_6D_6) δ 7.27 (d, $J = 7.2$, 2H), 7.20 (d, $J = 7.2$, 2H), 6.87–7.07 (m, 6H), 3.93 (m, 1H), 3.67 (d, $J = 11.6$, 1H), 3.28 (s, 3H), 3.24 (s, 3H), 3.21 (d, $J = 14$, 1H), 2.96 (s, 3H), 2.81 (dd, $J = 14$, 6.8, 1H), 2.73 (d, $J = 14$, 1H), 2.14 (dd, $J = 14$, 12.8, 1H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.9, 173.0, 172.8, 144.3, 142.5, 129.1, 128.6, 128.6, 127.9, 126.9, 126.8, 57.7, 54.1, 53.3, 52.1, 51.0, 48.2, 39.4, 17.6; IR (thin film) 2953, 1738, 1732, 1494, 1454, 1435, 1264, 1247 cm^{-1} ; HRMS (FAB) m/z calcd for $\text{C}_{25}\text{H}_{28}\text{O}_2$ (M^+) 425.1964, found 425.1981.

1,2-cis isomer (9b): ^1H NMR (400 MHz, CDCl_3) δ 7.09–7.25 (m, 10H), 3.88 (d, $J = 11.2$, 1H), 3.71 (s, 3H), 3.67 (s, 1H), 3.65 (s, 3H), 2.98 (m, 1H), 2.95 (d, $J = 14.4$, 1H), 2.23–2.34 (m, 2H), 2.20 (d, $J = 14.4$, 1H), 0.75 (s, 3H); ^1H NMR (400 MHz, C_6D_6) δ 7.30 (d, $J = 7.2$, 2H), 7.20 (d, $J = 7.2$, 2H), 6.93–7.08 (m, 6H), 4.23 (d, $J = 11.6$, 1H), 3.34 (s, 3H), 3.31 (s, 3H), 3.31 (d, $J = 14$, 1H), 3.26 (s, 3H), 3.10 (m, 1H), 2.72 (m, 2H), 2.37 (d, $J = 14$, 1H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3 , distinctive peaks) δ 176.2, 173.7, 172.1, 144.5, 143.4, 128.8, 128.4, 127.8, 126.7, 126.5, 57.5, 54.2, 53.5, 53.0, 52.8, 52.2, 51.6, 47.8, 41.0, 24.9, 17.5; IR (thin film) 2953, 1738, 1732, 1599, 1495, 1453, 1435, 1265 cm^{-1} ; HRMS (FAB) m/z calcd for $\text{C}_{25}\text{H}_{28}\text{O}_2$ (M^+) 425.1964, found 425.1957.

III. Stereochemical proofs of cyclic products

A. The stereochemistry of cyclopentane **9** was determined by analysis of nOe data:

Relevant DPGSE-nOe data (mixing time 0.5 s): (the peaks in the ^1H NMR spectra were assigned using $^1\text{H}/^1\text{H}$ COSY, ^1H NMR chemical shifts, and ^1H NMR coupling constants)

Cyclopentane 9a (1,2-trans, major)

nOe experiments were performed for major **9a** using a pure sample of the isomer in CDCl_3

H^A irradiated: Me (3.3%)

Me irradiated: **H^A** (1.75%), Ph (0.61%), **H^B** (0.3%)

Note: The observation of a large nOe enhancement between **H^A** and Me suggests a 1,2-trans configuration.¹¹

Cyclopentane 9b (1,2-cis, minor)

nOe experiments were performed for minor **9b** using a pure sample of the isomer in CDCl_3

H^B irradiated: Me (2.3%)

Me irradiated: **H^B** (1.3%)

Note: The observation of large nOe enhancements between **H^B** and Me suggests a 1,2-cis configuration.¹¹

B. The stereochemistry of cyclopentane **14** was determined by analysis of nOe data:

Relevant DPGFSE-nOe data (mixing time 2.0 s): (the peaks in the ^1H NMR spectra were assigned using $^1\text{H}/^1\text{H}$ COSY, ^1H NMR chemical shifts, and ^1H NMR coupling constants)

Cyclopentane 14a (1,2-trans, major)

nOe experiments were performed for major **14a** using a pure sample of the isomer in CDCl_3

Me irradiated: H^{D} (1.6%), H^{F} (1.6%), Ph (1.0%)

H^P irradiated: Me (3.1%), H^{C} (3.6%)

Note: The observation of nOe between Me and Ph along with Me and H^{D} suggests a 1,2-trans configuration.¹¹

minor, **14b**

Cyclopentane **14b** (1,2-cis, minor)

nOe experiments were performed for minor **14b** using a pure sample of the isomer in C_6D_6

Me irradiated: H^{E} (1.4%), H^{B} (1.4%)

H^E irradiated: Me (3.0%), H^{B} (0.9%)

H^B irradiated: H^{E} (1.4%), Ph (7.7%)

Note: The observation of nOe between Me and H^{E} along with a large nOe enhancement between Me and H^{E} suggests a 1,2-cis configuration.¹¹

IV. Bibliography

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V. Analytical Data

A. ^1H NMR spectra of unpurified isomer ratios

B. ^1H and ^{13}C NMR spectra of selected compounds