γ-Butyrolactone Synthesis via Catalytic Asymmetric Cyclocarbonylation

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SUPPLEMENTARY MATERIAL

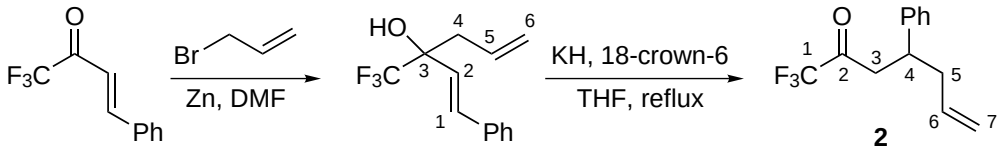
General. All experiments were performed under a nitrogen or argon atmosphere in oven-dried glassware using a Vacuum Atmospheres dry box or by using standard Schlenk techniques. Solvents used as reaction media were distilled immediately before use. Diethyl ether, THF, benzene and toluene were distilled from Na/benzophenone ketyl. Pentane and CCl_4 were distilled from CaH_2. Carbon monoxide of 2.3 grade (99.3%) was purchased from Boc. Gases, New Jersey. (EBTHI)$TiMe_2$ was prepared from (EBTHI)$TiCl_2$ following the reported[1] procedure. (*R R*)- and (*S S*)-(EBTHI)$TiMe_2$ were prepared from (*R R*)- and (*S S*)-(EBTHI)$TiCl_2$ respectively.[2] PMe_3 was purchased from Aldrich as 1M solution in toluene. Substrates of entries 1,2, 11, and 5-9 in Table 1 were prepared as described in our previous work.[3] Enone **3**[4] and substrates of entries 3[5],4[5] and 12[5] in Table 1 were prepared by allylation of appropriate α,β-unsaturated ketone with appropriate allyltrimethylsilane and $TiCl_4$. Substrate in entry 10[6a] was prepared from corresponding primary alcohol[6b] through PCC oxidation[3] in 35% yield. For the preparation of substrates in entries 13 and 14 see reference 7. (*S*)-(+)-2,2,2-Trifluoro-1-(9-anthryl) ethanol and 1,1,1-trifluoro-4-phenyl-3-butene-3-one were purchased from Acros chemical and Aldrich respectively. Potassium Hydride was purchased from Aldrich as 35% suspension in mineral oil. Required amount of suspension was washed with pentane and dried under vacuum prior to use. Commercially available Zn-dust was activated by washing with dilute aqueous HCl and then dried under vacuum. Substrate enals and enones were passed through a plug of alumina (freshly activated by heating at 200°C under vacuum for overnight) prior to use. Lactone products in entry 10, 12, and minor diastereomeric products of entries 3, 4 were not reported earlier. All other lactone products were reported earlier.[3,7]

^{1}H and ^{13}C NMR spectra were recorded on a DPX 250 (250 MHz ^{1}H, 63 MHz ^{13}C) spectrometer in deuterated solvents using the solvent carbon or residual protons ($CHCl_3$: 7.24 ppm ^{1}H, 77.23ppm ^{13}C, C_6D_5H: 7.15ppm ^{1}H) as an internal reference. For the determination of enantiomeric ratio in lactone products (Table 1, entries 7-14), CCl_4 was used as solvent and in those cases C_6D_6 was used (in a Wilmad co-axial insert) to lock the sample externally. NMR solvents were dried over 4Å molecular sieves or by passing through a short column of activated alumina. Chemical shifts (δ) are given in parts per million down from tetramethylsilane (TMS). Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), hex (hextet), hept (heptet), m (multiplet), coupling constants (J) are reported in Hz. Data are reported as follows: δ (multiplicity, J, integration, probable assignment). Infrared spectra recorded on a Perkin-Elmer 1760X FTIR spectrometer. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67-100%), m (medium, 40-67%), w (20-40%), and br (broad). Optical rotations were measured with a JASCO model DIP-370 digital polarimeter. Elemental analysis were performed by Oneida Research Services, Inc., Whitesboro, New York.

Analytical thin layer chromatography (TLC) was performed on Scientific Adsorbent Company Inc. silica gel plate. Components were visualized by illumination with long wave ultraviolet light, exposure to iodine vapor, or by standing with one of the following reagents (followed by heating): p-anisaldehyde (or vanillin) in ethanol/sulfuric acid; 7% phosphomolybdic acid in ethanol; 0.04 M ammonium molybdate in 10% sulfuric acid. Solvents for extraction and chromatography were reagent grade and used as received. Flash column chromatography was performed by method of Still[8] using Scientific Adsorbent Company Inc. silica gel (32-63 μm). Brine refers to a saturated aqueous solution of NaCl. NH_4Cl and $NaHCO_3$ refer to aqueous solutions unless otherwise specified.

Specific Procedures:

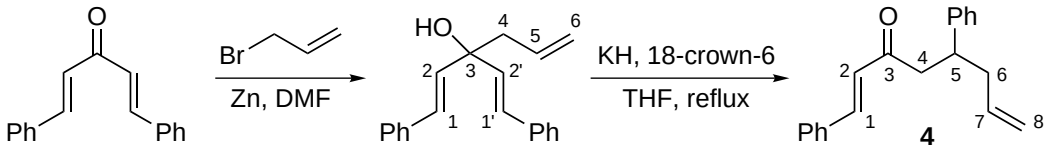
New Organic Substrates:



4-Phenyl-1,1,1-trifluoro-6-hepten-2-one (2):

Allyl bromide (3 g, 0.025 mol) was added dropwise to a mixture of Zn dust (1.62 g, 0.025 mol) and 1,1,1-trifluoro-4-phenyl-3-buten-2-one (4 g, 0.02 mol) in 50 mL of DMF with stirring at room temperature. Mixture was further stirred for 12 h at room temperature. The gray reaction mixture was then quenched via portion-wise addition of saturated aqueous NH_4Cl (50 mL) and extracted with diethyl ether (3 x 50 mL). The combined ethereal extracts were washed with 1N HCl (2 x 25 mL), water, brine, dried ($MgSO_4$), filtered and concentrated to give 4.59 g crude oil of 1-phenyl-3-trifluoromethyl-1,5-hexadien-3-ol. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.45 (s, 1H, O<u>H</u>), 2.63 (d, J=7.7 Hz, 2H, H_4), 5.22 (m, 2H, H_6), 5.77 (m, 1H, H_5), 6.2 (d, J=15Hz, 1H, H_2), 6.86 (d, J=15Hz, 1H, H_1), 7.29-7.43 (m, 5H, <u>H</u>-Ph); ^{13}C NMR (63 MHz, $CDCl_3$): δ 39.43, 74.97, 75.41, 121.19, 124.57, 126.77, 128.31, 128.62, 130.25, 133.21, 135.58. IR (neat): 3392 (w), 1495 (m), 1280 (s), 1149 (s), 1090 (m), 946 (m), 829 (w), 751 (m), 695 (m), 664 (m). This crude product was subjected to next step without further purification. The crude alcohol (4.59g, 0.019 mol) was added dropwise to a suspension of KH (3.43g of 35% suspension in mineral oil, 0.03 mol, 1.5 equiv.) in THF (200 mL) with stirring at room temperature. To the resulting yellow mixture was then added 4.22g of 18-crown-6 (0.016 mol, 0.8 equiv.) and the reaction was refluxed for 1h. After cooling to -78 ^{o}C, reaction mixture was quenched via rapid injection of 10 mL of absolute MeOH. The resulting mixture was quickly partitioned between saturated NH_4Cl (100 mL) and Et_2O (100 mL) and extracted with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated to give a brown oil which was distilled under vacuum to give the titled compound as a colorless oil. Yield. 2.3g (overall 48%). b.p. 77 ^{o}C / 5 mm, TLC (silica gel, 10: 1 hexane : Et_2O, R_f 0.5). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.40 (m, 2H, H_5), 2.98-3.15 (m, 2H, H_3), 3.35 (pent,

J=7.1Hz, 1H, H_4), 5.04 (m, 2H, H_7), 5.60 (m, 1H, H_6), 7.15-7.29 (m, 5H, H-Ph); ^{13}C NMR (63 MHz, $CDCl_3$): δ 39.28, 40.59, 41.93, 113.23, 117.55, 126.89, 127.26, 128.63, 135.31, 142.67, 190.36; IR (neat): 1765 (s), 1642 (w), 1495 (m), 1455 (m), 1285 (m), 1208 (s), 1146 (s), 1008 (m), 922 (w), 762 (m), 701 (s).

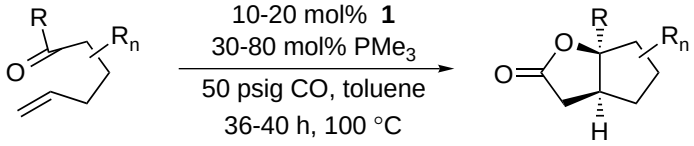


1,5-Diphenyl-1,7-octadien-3-one (4):

Allyl bromide (7.56 g, 0.062 mol) was added dropwise to a mixture of Zn dust (4 g, 0.062 mol) and dibenzylidene acetone (11.7 g, 0.05 mol) in 200 mL of DMF with stirring at room temperature. Mixture was further stirred for 12 h at room temperature. The gray reaction mixture was then quenched via portionwise addition of saturated aqueous NH_4Cl (100 mL) and extracted with diethyl ether (3 x 100 mL). The combined ethereal extracts were washed with 1N HCl (2 x 50 mL), water, brine, dried ($MgSO_4$), filtered and concentrated to give 8.3 g crude gummy oil of 3-benzylidene-1-phenyl-1,5-hexadien-3-ol which was used for the next step without further purification. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.10 (s, 1H, O<u>H</u>), 2.59 (d, J=7.5 Hz, 2H, H_4), 5.23 (m, 2H, H_6), 5.88 (m, 1H, H_5), 6.38 (d, J=15.2Hz, 2H, H_2 and H_2'), 6.71 (d, J=15.1Hz, 2H, H_1 and H_1'), 7.20-7.43 (m, 10H, <u>H</u>-Ph); ^{13}C NMR (63 MHz, $CDCl_3$): δ 46.36, 74.59, 119.93, 126.49, 127.59, 128.54, 128.71, 132.84, 133.61, 136.69. IR (neat): 3417 (w), 2718 (w), 2075 (w), 969 (s), 839 (w), 753 (w), 694 (s), 630 (w). The solution of crude alcohol (8.3g, 0.03 mol) in 10 mL THF was added dropwise to a suspension of KH (4.45g of 35% suspension in mineral oil, 0.039 mol, 1.3 equiv.) in THF (200 mL) with stirring at room temperature. To the resulting yellow mixture was then added 3.96g of 18-crown-6 (0.015 mol, 0.5 equiv.) and the reaction was refluxed for 1h. After cooling to -78 ^{o}C, reaction mixture was quenched via a rapid injection of 20 mL of absolute MeOH. The resulting mixture was quickly partitioned between saturated NH_4Cl (200 mL) and Et_2O (200 mL) and extracted with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated to give a brown residue which was purified by flash column chromatography (10% ethyl acetate in hexane) to get the titled compound as a white solid. Yield 6.38g

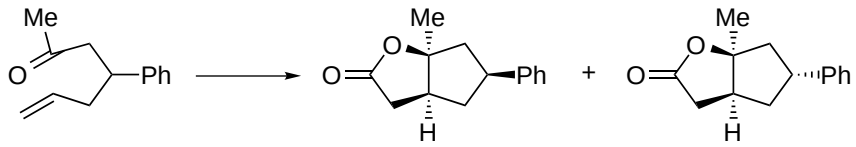
(overall 77%). m.p. 70-71 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.43 (t, J=7.4 Hz, 2H, H_6), 2.96 (dd, J=7.5, 1.2 Hz, 2H, H_4), 3.38 (pent, J=7.1Hz, 1H, H_5), 4.97 (m, 2H, H_8), 5.67 (m, 1H, H_7), 6.63 (d, J=16.3Hz, 1H, H_2), 7.20-7.35 (m, 9H, H_1 and H-Phs), 7.45 (m, 3H, H-Ph); ^{13}C NMR (63 MHz, $CDCl_3$): δ 40.56, 40.92, 46.82, 116.69, 126.29, 127.44, 128.15, 128.33, 128.78, 130.31, 134.34, 136.11, 142.39, 144.44, 198.79; IR ($CHCl_3$): 3050 (w), 2994 (w), 2717 (w), 2084 (w), 1664 (s), 1612 (s), 1550 (m), 1497 (w), 1012 (w), 952 (m), 865 (m), 674 (w), 601 (m); Anal Calcd for $C_{20}H_{20}O$: C, 86.91; H, 7.29; Found: C, 86.56; H, 7.29

General procedure for the synthesis of lactones:



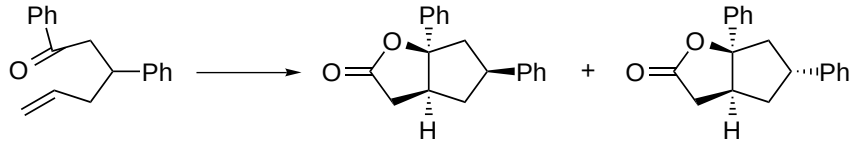
A dry Fisher-Porter bottle was charged with substrate (enal or enone), (EBTHI)$TiMe_2$, PMe_3 and toluene (25 mL), inside a nitrogen or argon filled glove box. The bottle was removed from the glove box, attached to a Schlenk line, then evacuated and backfilled with 50 psig of CO. The reaction was heated at 100 °C for 36-40 h. It was cooled to room temperature and CO pressure was cautiously released inside a fume hood. The reaction mixture was filtered through a pad of silica gel, washed with diethyl ether, concentrated under reduced pressure and purified by flash column chromatography.

All reactions were performed using 0.5-2.0 mmol of the substrate. Yields are average of two to three runs. Spectroscopic data for lactone products of entries 7-9, 11, 13, 14 in Table 1 are identical to that previously reported for the same compounds.[3b,7] Lactones of entries 5 and 6 were obtained as single diastereomer and both ^{1}H NMR and ^{13}C NMR signals are identical to those of major diastereomers previously obtained in stoichiometric reactions.[3b] Although the diastereomeric ratios of lactones in entries 1 and 2 are different from those obtained in stoichiometric reactions run previously, the major diastereomers produced in both catalytic and stoichiometric reaction are same (with the catalytic reactions exhibiting superior selectivity).



Cis-hexahydro-6a-methyl-5-phenyl-2H-cyclopenta [b] furan-2-one (Table 1, entry 3):

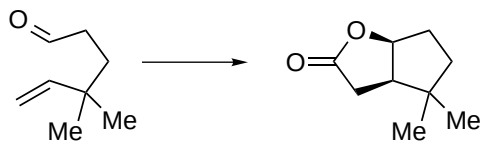
Following above procedure compound lactone was synthesized in 73% yield and isolated as 8.5:1 (major:minor) mixture of diastereomers. The major diastereomer (with phenyl group at *endo* position) was earlier reported by Buchwald for a stoichiometric transformation.[7] ^{1}H NMR (250 MHz, $CDCl_3$): δ major. 1.53 (s, 3H), 1.62 (m, 1H), 2.20 (t, J=12.4Hz, 1H), 2.41 (m, 4H), 2.86 (dd, J=8.8, 18.2Hz, 1H), 3.11 (m, 1H), 7.25 (m, 5H); minor δ 1.57 (s, 3H), 1.72 (m, 1H), 2.00 (m, 1H), 2.40 (m, 3H, obscured by major diastereomer), 2.65 (m, 1H), 3.00 (dd, J=8.8, 18.2Hz, 1H), 3.28 (m, 1H), 7.25 (m, 5H, obscured by major diastereomer); ^{13}C NMR (63 MHz, $CDCl_3$): δ major 26.98, 35.56, 42.02, 44.47, 45.29, 47.55, 94.25, 126.99, 127.35, 128.96, 142.86, 176.82; minor. δ 25.84, 37.54, 42.41, 43.07, 43.52, 47.34, 95.22, 126.98, 127.66, 128.60, 142.73, 177.50; IR (neat): 3050 (w), 2962 (m), 2893 (m), 1768 (s), 1421 (m), 1382 (m), 1272 (s), 1225 (s), 1194 (s), 1150 (s), 950 (s), 861 (w), 819 (w), 675 (w), 595 (w).



Cis-hexahydro-6a-phenyl-5-phenyl-2H-cyclopenta [b] furan-2-one (Table 1, entry 4):

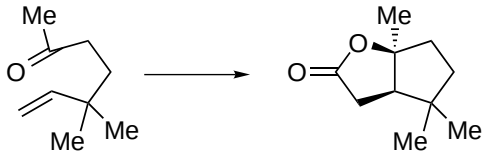
Following the above mentioned procedure the desired lactone product was synthesized in 76% yield and isolated as 19:1 (major:minor) mixture of diastereomers. The major diastereomer (with *endo*-phenyl group on cyclopentane ring) was earlier reported by Buchwald.[7] ^{1}H NMR (250 MHz, $CDCl_3$): δ major. 1.83 (q, J=12.4Hz, 1H), 2.4-2.8 (m, 5H), 2.97 (m, 1H), 3.53 (m, 1H), 7.35 (m, 10H); minor δ 3.90 (m, 1H), all other signals are obscured by major diastereomer), ^{13}C NMR (63 MHz, $CDCl_3$): δ major 34.12, 41.26, 45.99, 48.55, 49.56, 96.19, 123.87, 126.77, 126.92, 127.69, 128.65, 128.72, 142.15, 143.86, 176.39; minor. δ 29.98, 31.32, 36.12, 42.50, 43.10, 97.38, 124.46, 127.68, 128.60, other signals are obscured by major diastereomer; IR

($CHCl_3$): 3052 (w), 2962 (m), 1775 (s), 1526 (w), 1487 (w), 1256 (m), 1191 (s), 1122 (s), 1035 (m), 954 (m), 861 (m), 788 (m), 701 (s), 629 (w).



Cis-hexahydro-4a, 4a-dimethyl-2H-cyclopenta [b] furan-2-one (Table 1, entry 10):

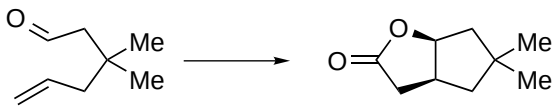
Following the above mentioned procedure the desired lactone product was synthesized in 86% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.00 (s, 6H), 1.46 (m, 1H), 1.64 (m, 1H), 1.93 (m, 1H), 2.10 (m, 1H), 2.49 (m, 2H), 2.59 (m, 1H), 5.04 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.92, 28.85, 30.55, 30.86, 38.07, 40.57, 48.79, 86.55, 177.52. IR ($CHCl_3$): 3010 (w), 2342 (m), 1770 (s), 1650 (w), 1540 (w), 1457 (m), 1189 (s), 997 (m), 754 (m); Anal Calcd for $C_9H_{14}O_2$: C, 70.03; H, 9.22; Found: C, 69.94; H, 9.02. When (*S*,*S*)-**1** was used as catalyst, the product was found to be 89% ee as determined by ^{1}H NMR analysis in the presence of the Pirkle chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl) ethanol (*vide infra*). $[\alpha]_D^{25}$ = -18.21° (*c* 0.527, CH_2Cl_2).



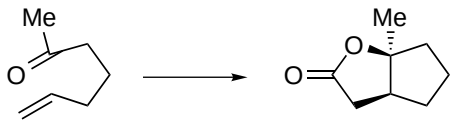
Cis-hexahydro-6a-methyl-4a, 4a-dimethyl-2H-cyclopenta [b] furan-2-one (Table 1, entry 12):

Following the above mentioned procedure the desired lactone product was synthesized in 88% yield . ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.98 (s, 3H), 1.03 (s, 3H), 1.49 (s, 3H), 1.51 (m, 1H), 1.63 (m, 1H), 1.87 (m, 1H), 2.08 (m, 2H), 2.50 (dd, J = 2.7Hz, 1H), 2.67 (dd, J = 9.8Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.21, 26.87, 29.65, 31.26, 37.35, 39.30, 41.41, 54.55, 95.97, 177.00. . IR ($CHCl_3$): 2929 (w), 2362 (m), 2339 (m), 1772 (s), 1636 (w), 1559 (w), 1494 (m), 1000 (s), 795 (m); Anal Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58; Found: C, 71.16; H, 9.56. When (*S*,*S*)-**1** was used as catalyst, the product was found to be 90% ee as determined by ^{1}H

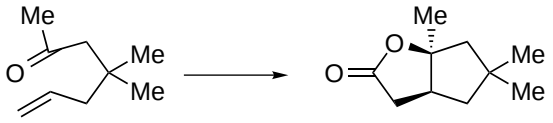
NMR analysis in the presence of the Pirkle chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl) ethanol. $[\alpha]_D^{25}$ = -18.9° (*c* 0.058, CH_2Cl_2).



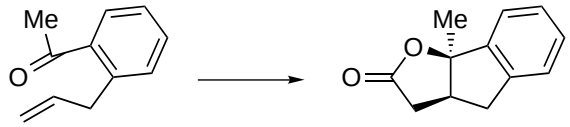
(Table 1, entry 9): Following the above mentioned procedure the desired lactone product was synthesized in 87% yield. When (*S*,*S*)-**1** was used as catalyst, the product was found to be 58% ee as determined by ^{1}H NMR analysis in the presence of the Pirkle chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl) ethanol. $[\alpha]_D^{25}$ = -32.79° (*c* 1.97, CH_2Cl_2). When (*R*,*R*)-**1** was used as catalyst, the product was found to be 60% ee. $[\alpha]_D^{25}$ = +32.81° (*c* 1.28, CH_2Cl_2). The ^{1}H NMR matched the published spectrum.[3b]



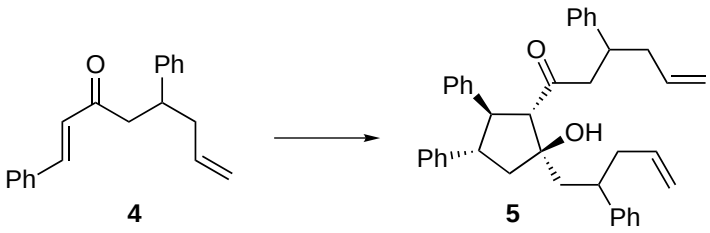
(Table 1, entry 11): Following the above mentioned procedure the desired lactone product was synthesized in 80% yield. When (*S*,*S*)-**1** was used as catalyst, the product was found to be 90% ee as determined by ^{1}H NMR analysis in the presence of the Pirkle chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl) ethanol). $[\alpha]_D^{25}$ = -23.12° (*c* 0.71, CH_2Cl_2). When (*R*,*R*)-**1** was used as catalyst, the product was found to be 89% ee. $[\alpha]_D^{25}$ = +23.03° (*c* 0.68, CH_2Cl_2). The ^{1}H NMR matched the published spectrum.[3b]



(Table 1, entry 13): Following the above mentioned procedure the desired lactone product was synthesized in 93% yield. When (*S*,*S*)-**1** was used as catalyst, the product was found to be 58% ee as determined by ^{1}H NMR analysis in the presence of the Pirkle chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl) ethanol. $[\alpha]_D^{25}$ = -9.42° (*c* 0.138, CH_2Cl_2). The ^{1}H NMR matched the published spectrum.[7a]



(Table 1, entry 14): Following the above mentioned procedure the desired lactone product was synthesized in 96% yield. When (*S*,*S*)-**1** was used as catalyst, the product was found to be 38% ee as determined by ^{1}H NMR analysis in the presence of the Pirkle chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl) ethanol. $[\alpha]_D^{25}$ = -10° (*c* 0.53, CH_2Cl_2). The ^{1}H NMR matched the published spectrum.[7]

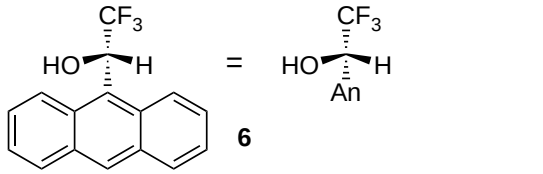


Preparation of cyclopentanol derivative 5:

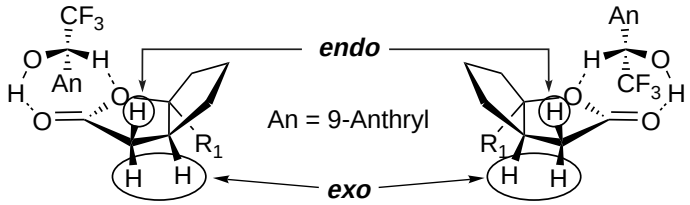
Procedure was same as for the preparation of lactones. Reaction is stoichiometric with respect titanium. Using 10 mol% of (EBTHI)$TiMe_2$ less than 10% conversion occurred. In a stoichiometric reaction using 55.2 mg (0.2 mmol) of enone **4**, 68.4 mg (0.2 mmol) of (EBTHI)$TiMe_2$, compound **5** was obtained as a colorless thick oil . Yield. 93.5 mg (84%), TLC (silica gel, 20% ethyl acetate in hexane, R_f=0.3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.20 (m, 4H), 2.53 (m, 8H), 3.13 (m, 2H), 3.33 (m, 2H), 4.89 (m, 4H), 5.56 (m, 2H), 6.65 (m, 4H), 7.06-7.24 (m, 16H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 40.13, 40.51, 40.59, 44.89, 44.96, 45.07, 46.85, 46.97, 47.33, 48.92, 49.16, 116.58, 126.23, 126.32, 127.29, 127.41, 127.75, 128.33, 128.65, 128.73. 135.99, 136.04, 140.75, 140.84, 140.90, 143.86, 144.04, 207.89. IR (neat): 3697 (w), 3028 (w), 2914 (br), 1711 (s), 1641(m), 1550 (m), 1530 (w), 1494 (m), 1248 (m), 917 (s), 858 (w), 761 (s), 701 (s); Anal Calcd for $C_{40}H_{42}O_2$: C, 86.60; H, 7.63; Found: C, 86.62; H, 7.73

Assignment of absolute configuration and determination of enantiomeric composition of lactones:

Determination of both absolute configuration and enantiomeric composition is based on Pirkle's method.[9] In the presence of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl) ethanol (**6**), separate ^{1}H NMR signals are observed for each enantiomeric lactone in a given product mixture, and the enantiomeric ratio is readily determined from the integration of these signals. Enantiomeric configuration can be assigned on the basis of Pirkle's model for the preferred solvation complexes **A** and **B** (Figure) formed from interaction of **6** with the (1*S*,5*S*) and (1*R*,5*R*) antipodes of the lactone product.[10]

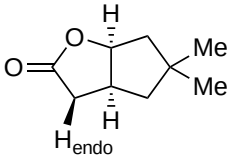
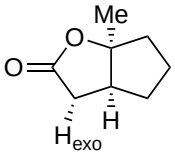


(S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol



A (1*S*, 5*S*)
exo upfield
endo downfield

B (1*R*, 5*R*)
exo downfield
endo upfield

Product **A** (1*S*, 5*S*)	^{1}H signal	catalyst antipode	major signal shift (Δδ)	configuration assignment
	H_{endo}	(*S*,*S*)-**1**	downfield (+.04)	**A** (1*S*, 5*S*)
		(*R*,*R*)-**1**	upfield (-.04)	**B** (1*R*, 5*R*)
	H_{exo}	(*S*,*S*)-**1**	upfield (-.03)	**A** (1*S*, 5*S*)
		(*R*,*R*)-**1**	downfield (+.03)	**B** (1*R*, 5*R*)

Substituents on the exo (convex) and endo (concave) face of lactone will experience different anisotropic effects producing a relative upfield shift for substituents *syn* to the anthracene moiety in the solvate complexes **A** and **B**. An upfield shift of the exo proton signals of the (1*S*,5*S*) lactone enantiomer (relative to the corresponding signals of its enantiomer) is predicted on the basis of the exo-oriented anthracene moiety in **A**.

Likewise, the endo-oriented anthracene moiety in **B** suggests a relative upfield shift of the endo proton signals of the (1*R*,5*R*) lactone enantiomer. In a typical experiment, ^{1}H NMR spectrum was recorded for a sample prepared by dissolving 0.03 mmol of lactone in 0.5 mL saturated solution (at 25 ^{o}C) of **6** in CCl_4. C_6D_6 (in a Wilmad co-axial insert) used for external locking as well as internal reference (C_6D_5H, δ 7.15).[11]

References

(1) Sturla, S.J.; Buchwald, S. L. *J. Org. Chem* **1999**, *64*, 5547.

(2) Chin, B.; Buchwald, S. L. *J. Org. Chem* **1996**, *61*, 5650.

(3) (a) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc*. **1995**, *117*, 6787. (b) Crowe, W. E.; Vu, A. T. *J. Am. Chem. Soc*. **1996**, *118*, 1557.

(4) Majetich, G.; Casares, A.; Chapman, D.; Behnke, M. *J. Org. Chem*. **1986**, *51*, 1745

(5) (a) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc*. **1977**, *99*, 1673. (b) Sakurai, H.; Hosomi, A.; Hayashi, J. *Organic Synthesis*; Wiley & Sons: New York, **1990**; Collect. Vol. *VII*, 443.

(6) (a) Formanek, K.; Aune, J. P.; Jouffret, M.; Metzger, J. *Nouv. J. Chim*. **1979**, *3(5)*, 311. (b) Weber, W. P.; Carr, S. A.; *J. Org. Chem*. **1985**, *50*, 2782

(7) (a) Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 5818. (b) Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1997**, *119*, 4424.

(8) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.

(9) Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem*. **1977**, *42*, 384.

(10) Formation of the solvate complexes is rapidly reversible on the NMR time scale and a single, signal-averaged set of peaks is observed for each lactone enantiomer.

(11) Interaction of the chiral solvating agent with lactone substrates is both temperature and concentration dependent. Thus, absolute chemicals shifts vary from run to run for a particular substrate. The degree of splitting ($\delta\Delta$) remains fairly consistent, however, and both splitting direction (upfield or downfield) and signal ratio are entirely reproducible.