Catalytic Generation of Activated Carboxylates: Stereoselective Synthesis of β -Hydroxyesters from Epoxyaldehydes

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Supporting Information

General Methods. All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry Ar. EtOH, ⁱPrOH, and BnOH were distilled from Na and stored over MS 4A. CH₂Cl₂ was distilled over CaH₂. CH₃CN was distilled from P₂O₅. Thiazolium salts were purified according to a reported protocol.¹ DBU and diisopropylethylamine (DIPEA) were distilled from KOH. Other reagents were used without further purification. Aldehydes were prepared by oxidation of the corresponding alcohols with SO₃•pyr. Epoxides were prepared from allylic alcohols via standard procedures. Thin layer chromatography (TLC) was performed on Merck precoated plates (silica gel 60 F₂₅₄, Art 5715, 0.25 mm) and were visualized by fluorescence quenching under UV light or by staining with phosphomolybdic acid. Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates prepared from Merck Kieselgel 60 PF₂₅₄ (Art 7747). Column chromatography was performed on E. Merck Silica Gel 60 (230–400 Mesh) using a forced flow of 0.5–1.0 bar. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) were measured on a Varian Unity 400 spectrometer. Chemical shifts are expressed in parts per million (PPM) downfield from internal tetramethylsilane (δ = 0) and coupling constants are reported as Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on a JASCO FT/IR-430 spectrophotometer and are reported as wavenumbers (cm⁻¹). Unpurified reaction mixtures were analyzed by gas chromatography (GC) at 115 °C on a J&W DB-5 column using H₂ as the carrier gas.

(1) Stetter H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639–647.

Preparation of Catalyst 1. To 2,3-dimethylthiazole (1.15 g, 10.0 mmol, 1.00 equiv) in 5 mL CH₃CN was added BnCl (1.27 g, 10.0 mmol, 1.0 equiv) dropwise over 10 min. The solution was warmed to reflux for 24 h. Following cooling to rt and gentle scraping with a spatula, a white precipitate formed, which was collected by filtration and washed with cold CH₃CN. Vacuum drying gave **1** (1.95 g, 66%) as a white solid. This catalyst was stored at rt in a dessicator for several months without decomposition or loss of catalytic activity.

¹H NMR (400 Mhz, CDCl₃) δ 11.9 (s, 1H) δ 7.35 (s, 5H), 6.11 (s, 2H), 2.47 (s, 3H), 2.37 (s, 3H)

¹³C NMR (100 Mhz, CDCl₃) δ 158.4, 141.9, 133.2, 132.2, 129.6, 129.5, 128.4, 57.5, 12.8, 12.3

IR (KBr) ν 3413, 3072, 1773, 1637, 1590, 1446, 1397, 1213, 1118, 1066, 816, 761, 712 cm⁻¹

MP: 56-58°C

EI-MS: 204 (M-Cl)

This salt has been previously described and utilized for catalytic reactions.²

(2) Castells, J.; Lopex-Calahorra, F.; Bassedas, M.; Urrios, P. *Synthesis* **1988**, 314–315.

Representative procedure for the oxidation of epoxyalcohols to epoxyaldehydes.

***trans*-2-methyl-3-phenyloxirane-2-carbaldehyde (2).** To the epoxyalcohol (1.0 g, 6.1mmol, 1.0 equiv) in 63 ml of a 4:1 CH₂Cl₂/DMSO solution in an ice bath was added NEt₃ (4.16 mL, 0.030 mol, 4.9 equiv) and solid SO₃.pyridine complex (3.4 g, 2.1mmol, 3.5 equiv). The mixture was stirred 30 min at 0°C and then warmed to rt and stirred for an additional 90 min. The resulting yellow solution was treated with NaHCO₃ (20 mL) and extracted with 2:1 hexane/ether (2 x 30 mL). The organic extracts were washed with brine, dried with Na₂SO₄ and concentrated under reduced pressure. The product was purified by flash chromatography (hexane/EtOAc, 3:1) to give epoxyaldehyde **2** (0.92 g, 93% yield).

¹H NMR (CDCl₃, 400 MHz) δ 9.11 (s, 1H), 7.29-7.42 (m, 5H), 4.31 (s, 1H), 1.22 (s, 1H)

¹³C NMR (CDCl₃, 100 MHz) δ 199.3, 133.1, 128.6, 128.5 126.7, 65.1, 60.6, 9.3

IR (thin film) ν 3435, 3064, 2975, 1726, 1681, 1496, 1453, 1299, 1241, 1072, 1014 889, 849, 742, 700 cm⁻¹

The physical properties and an alternative synthesis of this epoxide in both racemic and enantiomerically enriched has been previously described.³

(3) Hayashi, M.; Terashima, S.; Koga, K. *Tetrahedron* **1981**, 37, 2797–2803.

General Procedure for Catalytic Esterifications.

anti-Ethyl 3-hydroxy-2-methyl-3-phenylpropanoate (4). To catalyst **1** (13.3 mg, 0.055 mmol, 0.010 equiv) was added aldehyde **2** (80 mg, 0.49 mmol, 1.00 equiv) in CH₂Cl₂ (1 mL) at rt. To this suspension was added EtOH (86 mL, 1.47 mmol, 3.0 equiv) and DIPEA (6.9 mL, 0.040 mmol, 0.08 equiv). The resulting yellow solution was warmed to 30 °C and stirred 15 h. The reaction mixture was treated with sat. aq. NH₄Cl (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 3:1) to afford ester **4** (81 mg, 84%). The diastereoselectivity of the reaction was determined by GC analysis of the crude reaction mixture (see general information) at 115 °C.

¹H NMR (CDCl₃, 400 MHz) δ 7.26–7.37 (m, 5H), 4.74 (dd, 1H, *J* = 8.4Hz, 4.3Hz), 4.18 (q, 2H, *J* = 7Hz), 3.11 (d, 1H, *J* = 4.3Hz), 2.76–2.81 (m, 1H), 1.25 (t, 3H, *J* = 7.0 Hz), 1.01 (d, 3H, *J* = 7.0 Hz)

¹³C NMR (CDCl₃, 100 MHz) δ 176.1, 141.8, 128.6, 128.2, 126.8, 76.5, 60.9, 47.3, 14.7, 14.3

IR (thin film) ν 3491, 2981, 1724, 1455, 1376, 1251, 1181, 1034 cm⁻¹
Other physical properties were identical to those previously reported.⁴

(4) Marcantoni, E.; Alessandrini, S.; Malavolta, M.; Bartoli, G.; Bellucci, M. C.; Sambri, L.; Dalpozzo, R. *J. Org. Chem.* **1999**, *64*, 1986–1992.

anti-Benzyl 3-hydroxy-2-methyl-3-phenylpropanoate (5). Prepared according to the general procedure using 3 equiv of BnOH. The product was isolated in 89% yield by column chromatography (4:1 hexane/EtOAc).

¹H NMR (CDCl₃, 400 MHz) δ 7.26–7.39 (m, 10H), 5.11 minor, 5.18 major (s, 2H), 4.77–4.80 (m, 1H), 2.95 minor, 3.04 major (d, 1H *J* = 4.6Hz), 2.89(m, 1H), 1.04 major, 1.18 minor (d, 3H, *J* = 7.0 Hz)

¹³C NMR (CDCl₃, 100 MHz) δ 175.8, 141.7, 135.9, 128.7, 128.6, 128.4, 128.3, 128.2, 126.8, 76.5, 66.6, 47.4, 14.6

IR (thin film) ν 3471, 3063, 3031, 2976, 2883, 1728, 1455, 1385, 1265, 1167, 1049 cm⁻¹
Other physical properties were identical to those previously reported.⁵

anti-Isopropyl 3-hydroxy-2-methyl-3-phenylpropanoate (6). Prepared according to the general procedure using 3 equiv of ⁱPrOH. The product was isolated in 80% yield by column chromatography (3:1 hexane/EtOAc).

¹H NMR (CDCl₃, 400 MHz) δ 7.37–7.24 (m, 5H), 5.05 (sept, 1H, *J* = 6.3Hz), 4.74 (dd, 1 H, *J* = 4.3 Hz, 8.1Hz), 3.10 (d, 1H, *J* = 4.3 Hz), 2.79–2.73 (m, 1 H), 1.24 (d, 3H, *J* = 6.3 Hz), 1.21 (d, 3H, *J* = 6.3 Hz), 1.03 (d, 3H, *J* = 7.2 Hz)

¹³C NMR (CDCl₃, 100 MHz) δ 175.7, 141.9, 128.7, 128.2, 126.8, 76.5, 68.4, 47.4, 21.9, 14.8

IR (thin film) ν 3526, 3055, 2984, 2939, 1724, 1454, 1377, 1265, 1184, 1107 cm⁻¹
Other physical properties were identical to those previously reported.⁶

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- (5) Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, 66, 3483–3491.
(6) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, 51, 3027–3037.

***anti-d³*-Methyl-3-hydroxy-2-deuterio-2-methyl-3-phenylpropanoate (7).** Prepared according to the general procedure using 3 equiv CD₃OD. ¹H and 2D NMR analysis of the isolated product indicated ~50% deuterium incorporation. The mixture of deuterated and non-deuterated products were isolated in 81% yield by column chromatography (3:1 hexane/EtOAc).

¹H NMR (CDCl₃, 400 MHz) δ 7.22–7.38 (m, 5H), 4.74 (d, 1H, *J* = 7.8 Hz), 2.97 (s, 1H), 2.82 (dt, 1H, *J* = 15.8, 7.1 Hz), 1.00 (d, 3H, *J* = 7.1 Hz)

¹³C NMR (CDCl₃, 100 MHz) δ 176.5, 141.7, 128.7, 128.3, 126.9, 76.6, 76.5, 47.3, 14.7

IR (thin film) ν 3502, 3426, 3055, 2982, 2982, 2936, 1732, 1457, 1377, 1305, 1266, 1197, 1087 cm⁻¹

EI-MS: 197 (H, M⁺); 198 (D, M⁺)

Other physical properties were identical to those previously reported.⁷

Ethyl 3-hydroxy-3-phenylpropanoate (9). Prepared according to the general reaction procedure from the epoxyaldehyde⁸ in 84% yield by column chromatography (3:1 hexane/EtOAc).

¹H NMR (CDCl₃, 400 MHz) δ 7.26–7.39 (m, 5H), 5.14 (m, 1H), 4.18 (q, 2H, *J* = 7.0 Hz), 3.33 (s, 1H), 2.72 (m, 2H), 1.27 (t, 3H, *J* = 7.0 Hz)

¹³C NMR (CDCl₃, 100 MHz) δ 172.6, 142.7, 128.7, 127.9, 125.9, 70.5, 61.1, 43.5, 14.3

IR (thin film) ν 3479, 3062, 3032, 2982, 2931, 1725, 1453, 1373, 1267, 1060 cm⁻¹

Other physical properties were identical to those previously reported.⁹

(7) Marcantoni, E.; Alessandrini, S.; Malavolta, M.; Bartoli, G.; Bellucci, M. C.; Sambri, L.; Dalpozzo, R. *J. Org. Chem.* **1999**, *64*, 1986–1992.

(8) Yadav, V.; Kapoor, K. K. *Tetrahedron* **1995**, *51*, 8573–8584.

(9) Manzocchi, A.; Casati, R.; Fiecchi, A.; Santaniello, E. *J. Chem. Soc. Perkins Trans. I* **1987**, 2753.

2-methyl-3-cyclohexyloxirane-2-carbaldehyde (10). Prepared from the corresponding alcohol according to the general procedure for the oxidation of epoxyalcohols to the aldehydes in 89% yield. Isolated as a 4:1 ratio of trans:cis epoxide stereoisomers.

¹H NMR (CDCl₃, 400 MHz) δ 9.36* (s, 1H), 8.79 (s, 1H), 2.82 (d, 1H, *J* = 8.8 Hz), 2.78* (d, 1H, *J* = 8.8 Hz), 2.10–1.50 (m, 5H), 1.38 (s, 1H), 1.31–1.03 (m, 6H) *indicates minor diastereomer

¹³C NMR (CDCl₃, 100 MHz) δ 200.9, 200.4, 70.3, 64.1, 62.4, 37.2, 37.1, 31.1, 30.9, 29.1, 28.6, 26.1, 25.5, 16.2, 10.2

IR (thin film) ν 2931, 2854, 2255, 1726, 1450, 1389, 1266, 1077, 1011, 910, 733 cm⁻¹

ESI-MS: 169 (M+H), 191 (M+Na)

Anti-methyl 3-cyclohexyl-3-hydroxy-2-methylpropanoate (11). Prepared according to the general procedure from the corresponding epoxyaldehyde with the exception that DBU (8 mol %) and MeOH (3 equiv) were employed. The product was isolated in 82% yield.

¹H NMR (CDCl₃, 400 MHz) δ 3.71 (s, 3H), 3.37 (dd, 1H, *J* = 12.9, 6.0 Hz), 2.72 (quint, 1H, *J* = 7.0 Hz), 2.50 (d, 1H, *J* = 6 Hz), 1.89–1.50 (m, 6H), 1.41–1.02 (m, 8H)

¹³C NMR (CDCl₃, 100 MHz) δ 177.2, 77.9, 51.9, 42.0, 41.2, 30.2, 27.2, 26.6, 26.2, 15.1

IR (thin film) ν 3525, 3054, 2985, 2929, 2854, 1728, 1450, 1265, 1199, 1173, 1104 cm⁻¹

ESI-MS: 223.1 (M+Na); 423.2 (2M+Na)

Other physical properties were identical to those previously reported.¹⁰

(9) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1983**, *40*, 2309–2315.

(S)-Ethyl 3-hydroxy-3,7-dimethyloct-6-enoate (13). Prepared according to the general reaction procedure from the corresponding epoxyaldehyde¹¹ in 85% yield. The use of 1 equiv EtOH afforded the product in 66% yield.

$[\alpha]_D^{20}$ (*c* 1.40, CHCl₃) = -1.9

¹H NMR (CDCl₃, 400 MHz) δ 5.07–5.11(m, 1H), 4.18 (q, 2H, *J* = 7.0 Hz), 3.55 (s, 1H), 2.52 (q, 2H, *J* = 15.5 Hz), 2.06 (m, 2H), 1.68 (s, 3H), 1.61(s, 3H), 1.51–1.59 (m, 2H), 1.28 (t, 3H, *J* = 7 Hz), 1.25 (s, 3H)

¹³C NMR (CDCl₃, 100 MHz) δ 173.3, 132.0, 124.3, 71.1, 60.8, 45.0, 42.0, 26.8, 25.9, 22.9, 17.8, 14.4

IR (thin film) ν 3504, 3054, 2985, 2929, 2873, 1717, 1436, 1265, 1187, 1031 cm⁻¹
Other physical properties were identical to those previously reported.¹²

(11) Narco, K.; Baltas, M.; Escudier, J.-M.; Gorrichon, L. *Tetrahedron* **1996**, 52, 9047–9056.

(12) Marotta, E.; Foresti, E.; Marcelli, T.; Peri, F.; Righi, P.; Scardovi, N.; Rosini, G. *Org. Lett.* **2002**, 4, 4451–4453.

3-Phenyl-1-tosylaziridin-2-carbaldehyde (14). To the 3-phenyl-1-tosylaziridin-2-yl)methanol¹³ (0.35 g, 1.20 mmol, 1.00 equiv) in 13 ml of a 4:1 CH₂Cl₂/DMSO solution in an ice bath was added NEt₃ (0.81 mL, 5.67 mmol, 4.9 equiv) and solid SO₃.pyridine complex (640 mg, 4.1mmol, 3.5 equiv). The mixture was stirred 30 min at 0°C and then warmed to rt and stirred for an additional 90 min. The resulting yellow solution was treated with NaHCO₃ (20 mL) and extracted with 2:1 hexane/ether (2 x 30 mL). The organic extracts were washed with brine, dried with Na₂SO₄ and concentrated under reduced pressure. The product was purified by flash chromatography (hexane/EtOAc, 3:1) to give 3-phenyl-1-tosylaziridin-2-carbaldehyde (0.15 g, 43% yield).

¹H NMR (CDCl₃, 400 MHz) δ 9.76 (d, 1H, *J* = 7 Hz), 7.86 (d, 2H, *J* = 8.3 Hz), 7.34-7.17 (m, 7H), 4.52 (d, 1H, *J* = 3.7 Hz), 3.29 (dd, 1H, *J* = 3.7, 7 Hz), 2.43 (s, 3H)

¹³C NMR (CDCl₃, 100 MHz) δ 193.0, 145.3, 135.7, 132.9, 130.1, 129.3, 129.0, 127.8, 126.6, 55.6, 47.3, 21.9

IR (thin film) ν 3292, 3065, 3035, 2924, 2869, 2256, 1919, 1803, 1720, 1597, 1331, 1161, 1091, 910, 862 cm⁻¹

Ethyl 3-(4-methylphenylsulfonamido)-3-phenylpropanoate (15). Prepared according to the general reaction procedure from the corresponding aziridinyaldehyde (see below) in 53% unoptimized yield.

¹H NMR (CDCl₃, 400 MHz) δ 7.58-7.60 (m, 2H), 7.12-7.26 (m, 5H), 7.08-7.11 (m, 2H), 5.78 (d, 1H, *J* = 7.8 Hz), 4.71(q, 1H, *J* = 7.5Hz), 3.96-4.02 (m, 2H), 2.81 (dd, 1H, *J* = 15.9 Hz, 6.3 Hz), 2.72 (dd, 1H, *J* = 15.9 Hz, 6.3 Hz), 2.36 (s, 3H), 1.11 (t, 3H, *J* = 7.2 Hz).

¹³C NMR (CDCl₃, 100 MHz) δ 170.8, 143.4, 139.5, 137.6, 129.6, 128.7, 127.9, 127.3, 126.6, 61.1, 54.5, 41.5, 21.7, 14.2

IR (thin film) ν 3293, 3055, 2986, 1727, 1420, 1331, 1265, 1161, 1092 cm⁻¹

Other physical properties were identical to those previously reported.¹⁴

(13) Ali, S. I.; Nikalje, M. D.; Sudalai, A. *Org. Lett.* 1999, 1, 705–707.

(14) Molander, G. A.; Stengel, P. J. *Tetrahedron* **1997**, 53, 8887–8912.

Deuterium labeling studies at 40% completion. To catalyst **1** (13.3 mg, 0.055 mmol, 0.010 equiv) was added aldehyde **2** (80 mg, 0.49 mmol, 1.00 equiv) in CH₂Cl₂ (1 mL) at rt. To this suspension was added CD₃OD (60 mL, 1.47 mmol, 3.0 equiv) and DIPEA (6.9 mL, 0.040 mmol, 0.08 equiv). The resulting yellow solution was warmed to 30 °C and stirred 30 min. The reaction mixture was treated with sat. aq. NH₄Cl (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 3:1) to afford ester **7** (40 mg, 41%) and recovered aldehyde **1** (26.2 mg, 33%).

The following observations were made:

- (1) The conversion of the reaction was determined by GC analysis of the crude reaction mixture to be ~40% (see general information).
- (2) ¹H and ²D NMR analysis of the recovered aldehyde indicated no deuterium incorporation into the recovered starting material.
- (3) ¹H and ²D NMR analysis of ester **7** indicated ~50% deuterium incorporation into the α-position of the product.

Control Reaction: Resubjection of the ester product to the reaction conditions. In order to confirm that deuterium incorporation did not occur directly on the product ester under these reaction conditions, the following experiment was performed: Ester **4** (57 mg, 0.27 mmol, 1.0 equiv, 13:1 dr) in 0.6 mL CH₂Cl₂ was treated with CD₃OD (22.2 mL, 0.54 mmol, 2.0 equiv) followed by thiazolium salt **1** (10 mol %) and DIPEA (8 mol %). The resulting yellow solution was stirred 6 h at 30 °C, followed by usual workup. The ester was recovered in quantitative yield. Capillary GC analysis of the unpurified ester revealed no change in the ratio of diastereomers. Analysis by ¹H and ²D NMR reveal no indication of deuterium incorporation.