SUPPORTING INFORMATION

Title: Enantioselective Mukaiyama-Aldol Reaction of Pyruvates and 1-Phenyl-1-trimethylsilyloxyethene Catalyzed by Lanthanide/Pybox Complexes
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Ref. No.: O200600716
1. General Experimental Details

General methods and materials: $^1$H- and $^{13}$C-NMR spectra were recorded at 300 and 75 MHz respectively. Dichloromethane was the hydrocarbon-stabilized Aldrich ACS grade, distilled from calcium hydride and used immediately; lanthanide triflates were Aldrich ACS reagents; powdered molecular sieves 4 Å was Aldrich reagent heated under vacuum at 300 °C for 5 hours and kept in sealed vials in a dryer. 1-Phenyl-1-trimethylsilyloxyethylene (1), methyl and ethyl pyruvates (2a,b) were Aldrich commercial products. (4’S,5’S)-2,6-bis[4’-(triisopropylsilyl)oxymethyl-5’-phenyl-1’,3’-oxazolin-2’-yl]pyridine (3) was prepared as previously described [1].

Diphenylmethyl pyruvate (2c): It was prepared following the literature method [2], except phthalic anhydride was used instead of benzoic anhydride, because the better chromatographic separation (no overlap with residual anhydride - silicagel, 3 cm l, 1.5 cm diameter, cyclohexane/ethyl acetate 90:10 as eluant) allows to isolate 2c without carbonyl contaminants.

General procedure for the Mukaiyama-aldol reaction between 1 and 2a-c: Pyruvic ester (2a-c) (0.33 mmol), pybox (3) (0.024 g, 0.033 mmol), the lanthanide triflate (0.03 mmol) and MS (about 0.040 g) were added to anhydrous CH$_2$Cl$_2$ (0.5 mL) at ambient temperature in a rubber septum sealed vial, the mixture was stirred 10 minutes and then cooled at –50 °C [the La(III)-catalyzed reactions were kept in a thermostated water bath at 20 °C]. Phenyl-1-trimethylsilyloxyethylene (1, 80 µL, 0.4 mmol) was added with a microsyringe and stirring was continued at –50 °C for the time reported in Table 1. The reaction was warmed to room temperature, few drops of trifluoroacetic acid were added to the mixture, and, after about one hour stirring, TLC shows the formation of 4. The product was separated by column chromatography (silicagel, 30 cm l, 1.5 cm diameter, cyclohexane/ethyl acetate 80:20 as eluant), and submitted to HPLC analysis using a Chiralcel OD column with hexane/2-propanol [96:4] as eluant (1.0 mL/min).

(+)-(S)-Ethyl 2-hydroxy-2-methyl-4-oxo-4-phenyl butanoate (S)-4a: Prepared in accordance to the general procedure. The ee was determined by HPLC with a Chiralcel OD column: (S)-4a rt = 15 min, (R)-4a rt = 13.5 min; [α]$_D$ + 45.9 (85% ee) (c = 0.37, CHCl$_3$); IR (neat) 3501 ($\nu$ O-H), 1732 ($\nu$ C=O), 1682 ($\nu$ C=O) cm$^{-1}$; 1H-NMR (CDCl$_3$), $\delta$: 7.96 (dd, $J = 7.5$, 1.5, 2H, ortho aromatic protons), 7.61 (tt, $J = 7.5$, 1.5, 1H, para aromatic protons), 7.50 (t, $J = 7.5$, 2H, meta aromatic protons), 7.50 (t, $J = 7.5$, 2H, ometa aromatic protons), 7.50 (t, $J = 7.5$, 2H, meta aromatic protons), 3.99 (br s, 1H, OH), 4.25 (q, $J = 7$, 2H, OCH$_2$), 3.68 (d, $J = 17.6$ Hz, 1H, CH$_2$), 3.36 (d, J = 17.6 Hz, 1H, CH$_2$), 1.53 (s, 3H, Me), 1.28 (t, 3H, CH$_2$C$_3$H$_7$); $^{13}$C-NMR (CDCl$_3$), $\delta$: 198.7, 175.8, 136.3, 133.5, 128.6, 128.0, 72.5, 61.6, 47.8, 26.3, 14.0. Elemental analysis calcd (%) for C$_{13}$H$_{16}$O$_4$ (236.26): C 66.01, H 6.83; found: C 66.18, H 6.91.

(+)-(S)-Methyl 2-hydroxy-2-methyl-4-oxo-4-phenyl butanoate (S)-4b: Prepared in accordance to the general procedure. The ee was determined by HPLC with a Chiralcel OD column: (S)-4b rt = 21.5 min, (R)-4b rt = 17.5 min; [α]$_D$ + 73.5, (for 85% ee), (c = 1.0, CHCl$_3$); lit.: [α]$_D$ + 84.4 (c = 3.5, CHCl$_3$) for (S) 99% ee [3], [α]$_D$ - 86.7 (c = 1.0, CHCl$_3$) for (R) 98% ee [4]; IR (neat) 3502 ($\nu$ O-H), 1739 ($\nu$ C=O), 1683 ($\nu$ C=O) cm$^{-1}$; 1H-NMR (CDCl$_3$), $\delta$: 7.94-7.43 (m, 5H, Aromatic protons), 3.99 (br s, 1H, OH), 3.75 (s, 3H, OMe), 3.65 (d, J = 17.7 Hz, 1H, CH$_2$), 3.34 (d, J = 17.7 Hz, 1H, CH$_2$), 1.50 (s, 3H, Me); $^{13}$C-NMR (CDCl$_3$), $\delta$: 198.8, 176.3, 136.2, 133.7, 128.6, 128.1, 72.6, 52.7, 47.9, 26.4; (see identical NMR in ref. 3).
(+)-(S)-Diphenylmethyl 2-hydroxy-2-methyl-4-oxo-4-phenyl butanoate (S)-4c: Prepared in accordance to the general procedure. White crystals m.p. 80-81°C (cyclohexane/pentane). The ee was determined by HPLC with a Chiralcel OD column: (S)-4c rt = 25 min, (R)-4c rt = 22 min; [α]D + 14.4 (for 99.5% ee) (c = 2.35, CHCl3) IR (nujol mull) 3571 (νO-H), 1738 (νC=O), 1683 (νC=O) cm⁻¹; ¹H-NMR (CDCl₃), δ: 7.9-7.2 (m, 15H, aromatic protons), 6.94 (s, 1H, CHPh₂), 3.77 (d, J = 17.7 Hz, 1H, CHH), 3.36 (d, J = 17.7 Hz, 1H, CHH), 1.55 (s, 3H, Me); ¹³C-NMR (CDCl₃), δ: 198.3, 174.3, 139.0, 138.9, 135.8, 133.2, 128.1, 128.9, 127.9, 127.6, 127.5, 127.4, 126.7, 126.6, 77.6, 72.4, 47.3, 25.7. Elemental analysis calcd (%) for C₂₄H₂₂O₄ (374.44): C 76.98, H 5.92; found: C 77.15, H 5.87.

Transesterification of 4b,c to 4a: A sample of 4b or 4c (0.020 g) obtained from the Sc(III)-catalyzed reactions (Table 1 – entries 1b,c) was dissolved in methanol (2 mL) and a few mg of K₂CO₃ were added. The stirred mixture was monitored by TLC that showed the development of 4a within few minutes. When nearly all starting product was consumed, methanol was evaporated and the residue was column chromatographed (silicagel, cyclohexane/ethyl acetate 80:20). The fraction containing 4a was submitted to HPLC that showed an enantiomeric composition of (S)-4a (major enantiomer) and (R)-4a (minor enantiomer) identical to those of the starting products.

2. NMR Spectra

Figure A. $^1$H-NMR Spectrum of 4a.
Figure B. $^1\text{H}$-NMR Spectrum of 4a.
Figure C. $^1$H-NMR Spectrum of 4c.
Figure D. $^{13}$C-NMR Spectrum of 4c.
Figure a. Chromatogram of 4a from the Lu(III)-catalyzed M.A. reaction between 1 and 2a in Table 1, entry 2a.
Figure b. Chromatogram of 4a from the La(III)-catalyzed M.A. reaction between 1 and 2a in Table 1, entry 7a.
Figure c. Chromatogram of 4b from the Lu(III)-catalyzed M.A. reaction between 1 and 2b in Table 1, entry 2b.
Figure d. Chromatogram of 4c from the Lu(III)-catalyzed M.A. reaction between 1 and 2c in Table 1, entry 2c.
Figure e. Chromatogram of the transesterification of 4a to 4b, interrupted at about 80% completion.
Figure f. Chromatogram of the transesterification of 4c to 4b, interrupted at about 80% completion, the shoulder at 21.5 is due to diphenylcarbinol. The $^1$HNMR spectrum of the reaction mixture consists of 4b, 4c and diphenylcarbinol.