Reinvestigation of the Diastereoselectivity of Kinetic Aldol Condensation of Cyclohexanone Lithium Enolate with Benzaldehyde

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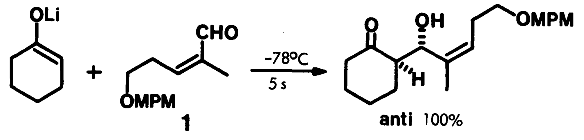
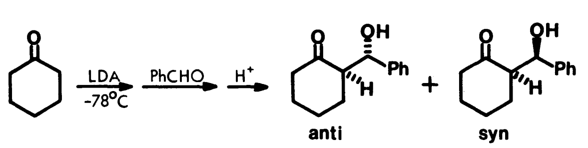
Synopsis. Aldol condensation of cyclohexanone lithium enolate with benzaldehyde has been shown to give a considerably higher stereoselectivity at low temperature than that reported previously.

It has been well-established that the aldol condensations from lithium (*E*)-enolates exhibit rather low anti diastereoselectivity.[1] In particular, lithium enolate of cyclohexanone with benzaldehyde has been recorded to give 1:1[2] anti/syn ratio at −20 °C and 1.1:1[3] even at −72 °C. Accordingly several devices using other metal ions have been developed to improve the selectivity.[2b,4] In connection with our synthetic study on a stereocontrolled construction of hexahydrobenzofuran subunit of the avermectins and the milbemycins, we examined the diastereoselectivity of kinetic aldol condensation of cyclohexanone lithium enolate with α,β-unsaturated aldehyde **1**, and have found that it gives a complete anti selectivity (Eq. 1).[5] These extreme results prompted us to reinvestigate the kinetic aldol reaction of the cyclohexanone lithium enolate with benzaldehyde (Eq. 2).



(1)

As the stereoselectivity might depend strongly on reaction temperature, the temperature of reaction mixture in a flask was controlled carefully and directly monitored by digital thermometer. The anti/syn ratios obtained under various conditions are summarized in Table 1. Contrary to the previous result,[3] considerably high ratios were obtained at low temperature in a short reaction period (entries 1, 3). The apparent ratio (ca. 5:1) at −78 °C is likely to be kinetic at this temperature because equilibration appears to be slow at −78 °C (entry 2), only reasonably rapid at −50 °C (entries 3, 4) and very rapid at −20 °C (entry 5). The temperature of reaction mixture was found to rise by up to 5 °C at the moment benzaldehyde was added to the enolate solution, even though the aldehyde solution was precooled.



(2)

Thus, the rapid equilibration of the lithium ketone enolates requires careful temperature control and short reaction period to get kinetic stereoselectivity in the condensation of cyclohexanone lithium enolate with benzaldehyde, as recognized in the condensations of other ketones such as propiophenone.[3]

Kinetic stereoselectivities with crotonaldehyde, isobutyraldehyde and trans isomer of **1**[5] at −78 °C were also obtained to be 7.0:1,[6] 28:1, and 20:1, respectively, which suggest that steric bulk owing to methyl group at α-position of α,β-unsaturated aldehydes such as **1** would play an important role for high kinetic diastereoselectivity.

Experimental

^{1}H NMR spectra were run for $CDCl_3$ solutions with Me_4Si as the internal standard on Varian XL200 and JEOL FX-90Q spectrometers. Infrared spectra were recorded on a JASCO IRA-2 diffraction grating spectrophotometer. Melting points were measured on a Yanaco MP-S3 hot stage melting point apparatus and were uncorrected. Elemental analyses were performed at Instrumental Analysis Center for Chemistry, Tohoku University. Reaction temperature was measured on a DELTA MC-20R digital thermometer with MC-20R-01 sensor (Pt 100 Ω).

THF was distilled from sodium benzophenone ketyl. Merck silica gel 60 (230—400 mesh) was used for column chromatography. Analytical thin-layer chromatography (TLC) was performed by using plates precoated with Wako silica gel 70 F_{254} (0.25 mm thick). HPLC analysis (column: Develosil 30-3, 15 cm×4 mm; solvent: Et_2O:hexane=3:2, 2 ml min^{-1}) was performed on a GILSON HPLC system (Model 302—802) with GILSON 111B UV detector (254 nm)

Table 1. Diastereoselectivity of Aldol Condensation of Cyclohexanone Lithium Enolate with Benzaldehyde

Entry	Reaction condition[a]	anti : syn	Yield[b]/%
1	−78°C, 3 s	4.7—5.4 : 1[c,d]	68—78
2	−78°C, 30 min	4.3 : 1[d]	87
3	−50°C, 3 s	4.6 : 1[e]	63
4	−50°C, 5 min	1.5 : 1[d]	92
5	−20°C, 3 s	0.7 : 1[e]	65

a) Precooled (−78 °C) benzaldehyde solution was added to enolate solution quickly by syringe or via cannula. b) Cambined isolated yield for anti and syn products. c) The highest and the lowest ratio among four runs. d) Ratio determined by HPLC analysis. e) Ratio determined by ^{1}H NMR spectroscopy.

and Shimadzu Chromatopac C-R3A. All reactions were carried out in a three or two necked 10 ml flask equipped with the sensor of digital thermometer under an argon atmosphere.

General Procedure: A 1.61 M† hexane solution of butyllithium (0.650 ml, 1.05 mmol) was added to a solution of diisopropylamine (0.154 ml, 1.1 mmol) in dry THF (2 ml) at −78 °C and stirred at 0 °C for 10 min. To this LDA solution was added dropwise a solution of cyclohexanone (98 mg, 1.0 mmol) in dry THF (0.5 ml) at −78 °C. After 20 min at this temperature, a cooling bath was replaced to set the solution at a specific temperature. After the temperature became specific, to this solution was added quickly a cold (−78 °C) solution of an aldehyde (0.112 ml, 1.0 mmol) in dry THF (0.5 ml) by a syringe or via a cannula at the temperature. After 3 s, a saturated aqueous NH_4Cl (5 ml) was added and the mixture was warmed up to room temperature, extracted with ether (3×10 ml). The combined organic layer was dried over $MgSO_4$ and concentrated. A diastereomer ratio of the aldol was determined by ^{1}H NMR spectroscopy (relative intensity of carbinol methine proton) or HPLC analysis of crude product. The crude mixture was chromatographed on SiO_2 column with AcOEt/hexane (1:3) as an eluent to give pure aldols from benzaldehyde in the yield shown in Table 1 or a mixture of diastereomers (70% yield) from the other aldehydes.

2-(α-Hydroxybenzyl)cyclohexan-1-one; syn isomer: R_f= 0.42 (AcOEt/hexane=1:2); colorless needles; mp 105—106.5 °C (hexane–ether) (lit, mp 102—103 °C[2b)]); ^{1}H NMR δ=1.31—2.79 (9H, m), 3.00 (1H, d, J=3.3 Hz, OH), 5.38 (1H, m, benzylic CH, collapsed to doublet, J=2.2 Hz, when D_2O added), 7.30 (5H, m); IR (KBr) 3570, 1695, 1500, 1450, 1130, 1060, 985, 700 cm^{-1}; Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.86%, Found: C, 76.26; H, 7.89%. Anti isomer: R_f=0.36 (AcOEt/hexane=1:2); colorless plates; mp 76—77 °C (hexane–ether) (lit, mp 74—75 °C); ^{1}H NMR δ=1.08—2.79 (9H, m), 3.93 (1H, d, J=2.9 Hz, OH), 4.78 (1H, dd, J=2.9 and 8.7 Hz, benzylic CH), 7.31 (5H, m); IR (KBr) 3520, 1685, 1500, 1450, 1130, 1040, 1010, 700 cm^{-1}; Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.86%, Found: C, 76.37; H, 8.16%.

2-(*trans*-1-Hydroxy-2-butenyl)cyclohexan-1-one (7.0:1 anti/syn mixture): colorless oil; ^{1}H NMR δ=1.2—2.2 (6H, m), 1.72 (3H, dd, J=6.3, 1.5 Hz), 2.2—2.6 (3H, m), 3.60 (1H, br, OH), 4.21 (1H, br t, J=8.0 Hz, $\mathrm{C\underline{H}OH}$), 4.49 (syn $\mathrm{C\underline{H}OH}$, br m), 5.46 (1H, ddq, J=15.3, 8.0, 1.5 Hz), 5.72 (1H, dqd, J=15.3, 6.3, 0.7 Hz); IR (film) 3430, 2930, 2860, 1700, 1450, 1310, 1215, 1115, 965 cm^{-1}; MS m/z 169 (M^++1, 20), 151 (34), 135 (50), 98 (100), 83 (63), 70 (100).

2-(1-Hydroxy-2-methylpropyl)cyclohexan-1-one (28:1 anti/syn mixture): colorless oil; ^{1}H NMR δ=0.91 (3H, d, J=6.9 Hz), 1.01 (3H, d, J=6.9 Hz), 1.1—2.2 (7H, m), 2.2—2.6 (3H, m), 3.32 (1H, br d, J=4.5 Hz, OH), 3.56 (1H, br dt, J=7.5, 4.5, 4.0 Hz, $\mathrm{C\underline{H}OH}$), 3.74 (syn $\mathrm{C\underline{H}OH}$, br dd, J=9.5, 2 Hz); IR (film) 3550, 2940, 2860, 1695, 1445, 1395, 1240, 1130, 990, 840 cm^{-1}; MS m/z 170 (M^+, 2), 151 (55), 136 (43), 126 (100), 98 (23).

2-[*trans*-1-Hydroxy-2-methyl-5-(4-methoxybenzyloxy)-2-pentenyl]cyclohexan-1-one (20:1 anti/syn mixture): colorless oil; ^{1}H NMR δ=1.53—2.18 (6H, m), 1.63 (3H, br s), 2.29—2.55 (3H, m), 2.37 (2H, br q, J=6.9 Hz), 3.47 (2H, td, J=6.9, 1.4 Hz), 3.60 (1H, br s, OH), 3.82 (3H, s), 4.20 (1H, d, J=9.2 Hz, $\mathrm{C\underline{H}OH}$), 4.60 (syn $\mathrm{C\underline{H}OH}$, d, J=3 Hz), 4.45 (2H, s), 5.43 (1H, br t, J=6.9 Hz), 6.90 (2H, br d, J=8.8 Hz), 7.27 (2H, br d, J=8.8 Hz); IR (film) 3500, 2940, 2860, 1700, 1610, 1515, 1240, 1090, 1030, 815 cm^{-1}; MS m/z 314 (M^+-H_2O), 234, 178, 137, 136, 122, 121, 108, 99, 98, 83, 70.

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† 1 M=1 mol dm^{-3}.