PERKIN 1 COMMUNICATION

Dramatic temperature effect in asymmetric catalysis in the enantioselective addition of diethylzinc to aldehydes

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The enantioselectivity of the addition of diethylzinc to aryl aldehydes catalysed by (*S*)-2-(3-methyl-2-pyridyl)-3,5-di-*tert*-butylphenol have been found to depend heavily on temperature with the inversion temperatures affected by the *para*-substituents of aryl aldehydes.

Temperature serves as a convenient experimental tool to probe mechanisms and also provides a practical approach to maximize selectivity in chemical processes especially in asymmetric catalysis. Abrupt maxima (or minima) in plots of ln (*R*/*S*) *vs.* 1/*T* due to two intercepting linear regions are known as nonlinear temperature behavior and have generated much recent theoretical interest.[1] The temperature at the maximum is the so-called "inversion temperature". One interpretation of such a phenomenon is a shift in the rate-determining step of the reaction with the change of temperature. A maximum in such a plot for the osmium tetroxide asymmetric dihydroxylation of olefins has been interpreted as evidence for a non-concerted pathway.[2] Practically, the increase of temperature with a resultant faster reaction rate and more selective chemical conversion would be most desirable. One recent example is the asymmetric catalytic hydrogenation to yield L-Dopa [(−)-L-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid].[3] In our continuing studies on the enantioselective addition of diethylzinc to aryl aldehydes[3] catalyzed by (*S*)-2-(3-methyl-2-pyridyl)-3,5-di-*tert*-butylphenol (**1**),[4,5] we have found a dramatic temperature effect on the enantiomeric excess (ee) of the 1-phenylpropanols formed and that the inversion temperatures of aryl aldehydes depend on the *para*-substituents.

The results of the enantioselective catalytic addition of diethylzinc to aromatic aldehydes **2a**–**c** [eqn. (1)] catalysed by 5 mol% of **1** (optical purity >99.5%) from −23 °C to 25 °C[6] are summarized in Table 1 and the plots of ln (*R*/*S*) of the alcohols **3a**–**c** *vs.* 1/*T* are shown in Fig. 1. The reactions were conducted in toluene under N_2 within 48 h to give high yields of alcohols **3a**–**c** with moderate to high enantioselectivity. The yields were slightly lower at −23 °C due to slower reactions. The homogeneity of the reaction was maintained throughout by visual judgement. The ee of **3b** increased from −23 °C and reached a maximum at around −4 °C before it sharply dropped to near zero (Table 1 and Fig. 1). Therefore, an inversion temperature occurred at −4 °C. Most noticeably, when the temperature of the reaction with benzaldehyde was raised from 0 to 15 °C, the ee of 75% fell very rapidly to 3%. A 15 degree change in temperature marks the difference between high or low enantioselectivity. To the best of our knowledge, this is the sharpest temperature effect on ee ever reported.[1] Similar, though less prominent, effects were observed for *p*-chlorobenzaldehyde **2a** and *p*-methoxybenzaldehyde **2c**. Neither the catalyst **1** nor the alcohol **3b** underwent any racemization in either acidic (1 M HCl in MeOH) or in alkaline conditions (1 M NaOH in MeOH) at room temperature for 24 h. This temperature effect therefore originated from the asymmetric ethylation.

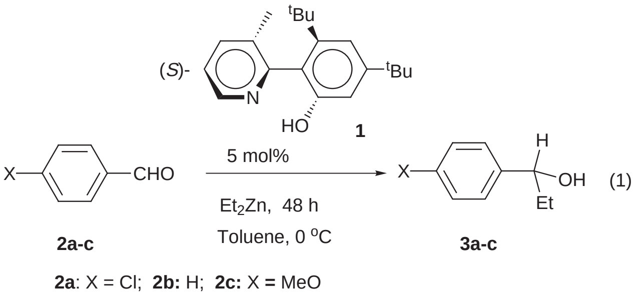

Table 1 Temperature effect on the enantioselectivity of (*R*)-**3a**–**c** (ees were determined on a Daicel OD column)

	3a (X = Cl)		**3b** (X = H)		**3c** (X = OMe)	
T/°C	% ee (*R*)	Yield (%)	% ee (*R*)	Yield (%)	% ee (*R*)	Yield (%)
−23	52	64	35	45	45	60
−15	59	78	61	67	66	74
−8	66	83	77	79	74	80
−4	75	85	84	87	77	83
0	80	97	75	90	66	96
4	72	88	42	90	60	87
8	48	89	17	85	35	91
15	33	88	3	86	30	90
25	24	89	1	85	3	88

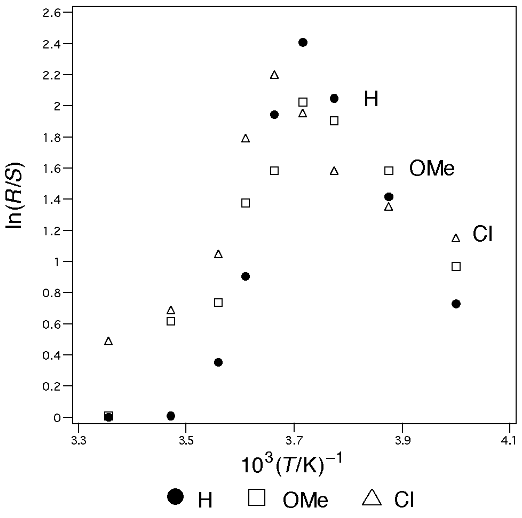

Fig. 1

The inversion temperature of the more electron-deficient and more reactive *p*-chlorobenzaldehyde[5] occurred at 0 °C while those of benzaldehyde and *p*-methoxybenzaldehyde appeared at −4 °C, which suggests that the more reactive the substrate, the higher the inversion temperature. The reactivity pattern suggested that the more reactive substrate gave the more stereoselective products as reported earlier.[5]

The origin of this temperature effect remains unclear. The possible temperature-dependent competing reactions between the monomeric and dimeric zinc species[7] as the active catalyst might account for the inversion temperature. Alternatively, the inversion temperature might be caused by the change in activation energy between the diastereoselective binding of aldehydes to organozinc species and the alkylation step, which has been exemplified by Halpern in the olefin binding and hydrogenation steps with a rhodium complex in the case of asymmetric hydrogenation.[3] Detailed explanations must await further mechanistic and kinetic experiments since exchanges among the oragnozinc intermediates may be possible and further complicate the mechanistic scheme.[1d]

In conclusion, a dramatic temperature effect in the enantioselective addition of diethylzinc to aryl aldehydes is observed. In asymmetric catalysis, careful variations in temperature for achieving highest ee is encouraged otherwise less satisfactory results or even the wrong conclusion about a catalyst may be drawn.

Experimental

The addition reaction of Et_2Zn to benzaldehyde in toluene at −23 °C is described as a typical example. To a solution of (*S*)-(+)-**1** (5 mg, 0.017 mmol) in dry toluene (2 mL) at −78 °C under N_2, Et_2Zn (1 M in hexane, 0.68 mL, 0.68 mmol) was added. The mixture was stirred for 10 min. Benzaldehyde (**2b**) (0.034 ml, 0.34 mmol) was then added. The reaction mixture was then immediately placed in a CCl_4–dry ice bath (−23 °C) and stirred for 48 h under N_2. Saturated aqueous NH_4Cl (5 mL) was added and the mixture was extracted with Et_2O (10 mL × 3). The extracts were washed with brine and dried over $MgSO_4$. Purification by column chromatography on silica gel with a mixture of hexane–EtOAc (4:1) as the eluent afforded 1-phenylpropan-1-ol (**3b**)[5] (20 mg, 45%) as a colorless liquid; 35% ee by HPLC analysis (Daicel OD chiral column). The (*S*)-(+)-**1** was recovered in 80% yield without the loss of optical purity.

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