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Temperature-Effected Tuning of Enantioselectivity in Asymmetric Catalysis

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Abstract: Asymmetric desymmetrization in chiral organotin-catalyzed reaction of 2-substituted 1,3-propanediol with phenyl isocyanate exhibits a linear variation of %ee depending on the reaction temperature and, thus, the chirality sense is inverted from one enantiomer at higher temperature to the other at lower temperature.

Asymmetric reaction plays a central role in organic synthesis.[1] In particular, its catalytic version is among the most important in terms of proliferation of chirality.[2] In these reactions, one of the enantiomers should be produced predominantly over the other. However, the activation free energies leading to both enantiomers are not so much different and, hence, lowering the reaction temperature is commonly invoked for compensating such disadvantage. With decrease of the reaction temperature, the portion of one product enantiomer monotonously increases due to the enhanced bias of Boltzman distribution of the activated complexes in the transition state. Despite a considerable number of diastereoselective reactions conflicting with this protocol,[3] only a few examples of enantioselective reactions are known which exhibit the reversed enantioselectivity vs. temperature relationship. The chirality sense was found to be inverted by changing the reaction temperature in photochemical isomerization of cyclooctene in the presence of chiral sensitizer.[4] With respect to asymmetric catalysis, alcohol addition to ketenes catalyzed by chiral alkaloids exhibited the temperature-dependent inversion of the chirality sense, for which different reaction mechanisms at higher and lower temperatures were put forth.[5] More recently, the increase of %ee with increasing reaction temperature was reported in Rh(I) complex-catalyzed hydrogenation of unsaturated amino acids,[6] asymmetric addition of diethylzinc to benzaldehyde,[7] asymmetric borane reduction of ketones,[8] and Nickel-catalyzed ring-opening of oxabicycloalkenes.[9] Nevertheless, the switching of enantioselectivity has been shown only in one case[6b] where change of the reaction path was suggested to be responsible for this switching. Here we disclose the asymmetric catalysis that distinctly exhibits the inversion of enantioselectivity depending on the reaction temperature.

In the context of our studies on organotin-catalyzed carbamate synthesis,[10,11] we have employed chiral tin catalysts of C_2 symmetry, **1a**[12] and **1b**,[13] in the desymmetrization reaction (eq 1). When 2-benzyl-1,3-propanediol (**2a**) (0.5 mmol) was treated with phenyl isocyanate (**3**) (1.0 mmol) in the presence of (*R*)-**1a** (0.05 mmol) in THF (5 mL) at 0 °C for 4 h, (*S*)-monocarbamate **4a** (32% ee)[14] was obtained in 85% chemical yield together with dicarbamate **5** (8%). As shown in Figure 1 (line 1), upon decreasing of the reaction temperature, the %ee decreased and became zero at around -47 °C. Below this critical temperature, the major enantiomer turned to be (*R*)-**4a**, %ee of which reached to 24% (37% chemical yield together with 12% of **5**) at -78 °C after 5 h. The profile of the temperature dependence was completely inverted by use of (*S*)-**1a** (line 2). Obviously, the reaction is totally controlled by the chiral catalyst. Employment of 2-trimethylsilylmethyl-1,3-

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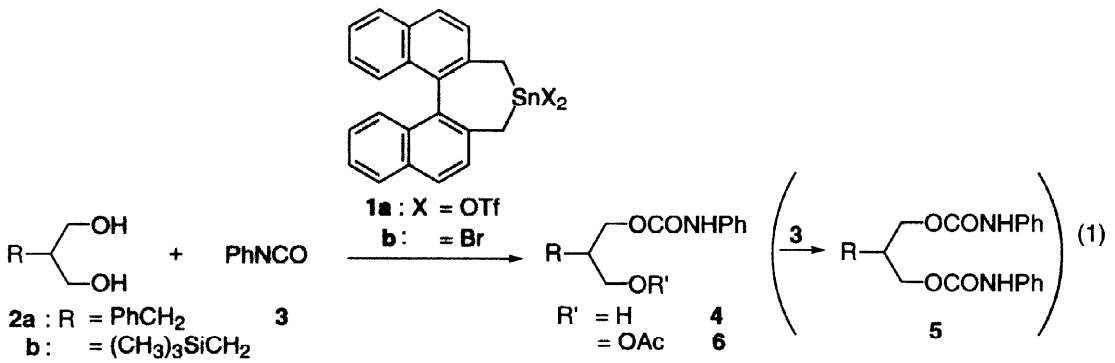


propanediol (**2b**) led to essentially the same feature with somewhat lower critical temperature (ca. -51 ℃) (lines 3,4). Reaction catalyzed by dibromide **1b** proceeded analogously, giving rise to the critical temperature around -82 °C (lines 5,6). Notably, only low yields of **4a** were obtained in the absence of catalyst (< 1%) or by AgOTf alone (15%) at -78 ℃ after 5 h, indicating that the organotin catalysts serve as the real active species.

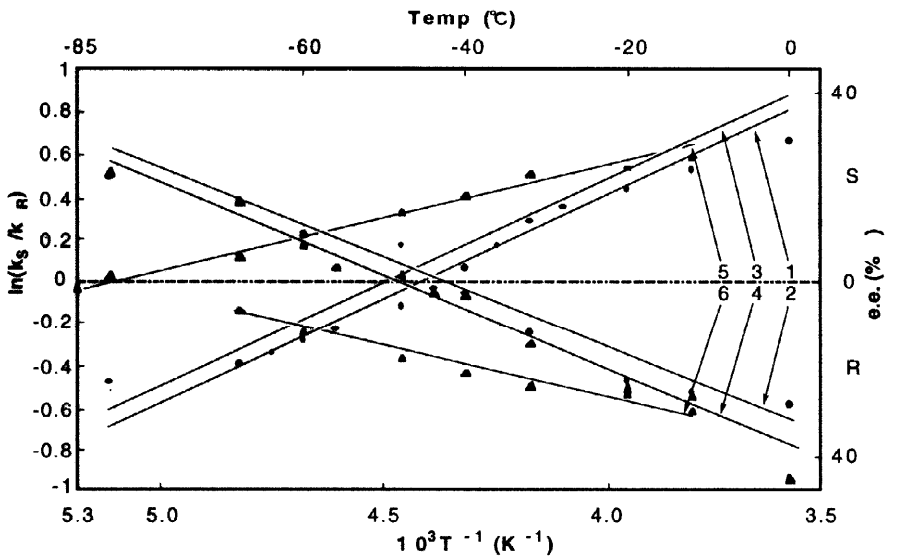


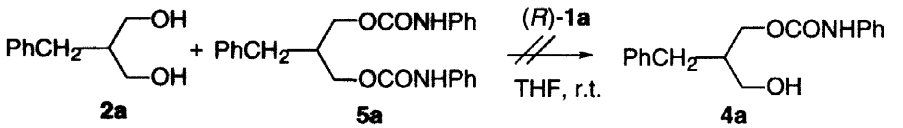
Figure 1. Temperature dependence of enantioselectivity of reaction 1. (1) **2a**/(*R*)-**1a** (correlation coefficient 0.978), (2) **2a**/(*S*)-**1a** (correlation coefficient 0.972), (3) **2b**/(*R*)-**1a** (correlation coefficient 0.981), (4) **2b**/(*S*)-**1a** (correlation coefficient 0.971), (5) **2a**/(*R*)-**1b** (correlation coefficient 0.995), (6) **2a**/(*S*)-**1b** (correlation coefficient 0.984).

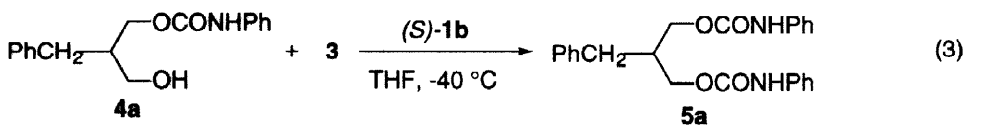
The kinetic control of the reaction 1 was exemplified by the time-dependence of the %ee in the reaction between **2b** and **3**, which proved to remain constant during the reaction time from 0.5 to 5 h both at 0 and -78 °C: with (*S*)-**1a** catalyst at 0 °C, 42.3 ± 0.9% ee; with (*R*)-**1a** catalyst at -78 °C, 24.0 ± 0.1% ee.

Treatment of *rac*-**4a** with a catalytic amount of (*R*)-**1a** in THF at -60°C for 5 h gave rise to no asymmetric induction. Analogously, treatment of (*S*)-**4a** (30% ee) with the racemic catalyst led to the recovery of (*S*)-**4a** without any variation of the %ee. Apparently, the asymmetric induction in reaction 1 is not ascribed to intra- or intermolecular transcarbamoylation of **4a** itself.

Next, an equimolar mixture of diol **2a** and dicarbamate **5a** was stirred in the presence of (*R*)-**1a** (0.1 equiv) in THF at room temperature (eq 2). No disproportionation occurred, negating the equilibrium process

to arrive at **4a**. Finally, (*R,S*)-**4a** was treated with **3** in the presence of (*S*)-**1b** in THF at -40 °C for 5 h to give a 68% yield of **5a** (eq 3). Unreacted **4a** that had been recovered from the reaction mixture (31%) was found to be completely racemic. Consequently, it is reasonably postulated for reaction 1 that kinetic resolution of the monocarbamate in the second step leading to **5** does not cause the asymmetric induction. These results lead us to conclude that the desymmetrization originates from discrimination between the two enantiotopic hydroxy groups in **2** by the chiral tin catalysts.





^{1}H and ^{13}C NMR spectra of **1b** gave rise to no change even if the temperature was lowered from 25 °C to -78 °C. Addition of **2a** or **3** to **1b** also induced no change. Possibly, the temperature dependence of enantioselectivity cannot be attributed to the structural change of the catalyst. Moreover, it can be said that the interaction between the catalyst and **2a** or **3** is very weak.

Conceivably, the reaction proceeds through the successive coordination of **2** and **3** followed by interaction of these two components on the tin template. It is theoretically possible that the temperature-dependent reversal of enantioselectivity might occur in such a multi-step process due to the shift of the rate-determining step depending on the reaction temperature.[15] To check if this is the case in our reaction, we examined the influence of the ratio of **2**:**3** on %ee. In the reaction of **2a** catalyzed by (*R*)-**1a**, no appreciable fluctuation of %ee was observed upon variation of the **2**:**3** ratio from 5:1 to 1:5; for example, 27.9 ± 1.3 %ee at -10 °C and 23.4 ± 1.8 %ee at -78 °C. This implies that the shift of the rate-determining step is not plausible.

As is evident from the correlation coefficient values in Fig. 1, the linear relationship of %ee vs. reaction temperature indicates that a single mechanism operates in the whole temperature range. The activation parameters for reaction 1 can be obtained from the Arrehnius and Eyring equations.[3c,4b] As given in Table 1, the $\Delta\Delta S^{\neq}_{S\text{-}R}$ values are large and, accordingly, the relative frequency factors A_S/A_R greatly deviate from zero, that is, the entropy term contributes to $\Delta\Delta G^{\neq}$ to more extent than usual. Possibly, the weak acidity of organotin catalyst is responsible for this anomaly. Due to the weak interaction between the catalyst and the diol or isocyanate, the enthalpy term associated with coordination bond formation may only play a moderate part. Instead, the significance of the entropy factor rises to a degree comparable to the enthalpy factor.

Table 1. Activation Parameters for Reaction 1

1	2	$\Delta\Delta H^{\neq}_{S\text{-}R}$ (kcal/mol)	$\Delta\Delta S^{\neq}_{S\text{-}R}$ (cal/mol K)	A_S/A_R
(*R*)-**1a**	**2a**	+1.67	+7.35	40.42
(*S*)-**1a**	**2a**	-1.59	-7.04	0.029
(*R*)-**1a**	**2b**	+1.94	+8.75	81.74
(*S*)-**1a**	**2b**	-1.86	-8.35	0.015
(*R*)-**1b**	**2a**	+0.86	+4.47	9.51
(*S*)-**1b**	**2a**	-0.88	-4.59	0.099

In summary, we have shown the explicit asymmetric tuning in the intermolecular reaction in contrast to the preceding intramolecular photochemical protocol. More importantly from the synthetic point of view, both

enantiomers may be accessible, in principle, from a single chiral catalyst by changing the reaction temperature. This reaction is totally different from the precedent ones. Namely, the alkaloid-catalyzed reaction showed saturated curves and, hence, the increase of %ee's stops above a certain temperature[5] while a considerable bias to one enantiomer (68% ee for the (*S*)-isomer and only 6 %ee for the (*R*)-counterpart) appeared in the Rh(I)-catalyzed hydrogenation.[6b] The linearity observed in this study is of great promise for arriving at both enantiomers with high optical purity if the catalyst is suitably designed.

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