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Temperature-Independent Stereocontrolled [2+2] Cycloaddition. Potential of the 2,4-Pentanediol Tether in Asymmetric Reactions as a Differential Activation Entropy Promoter

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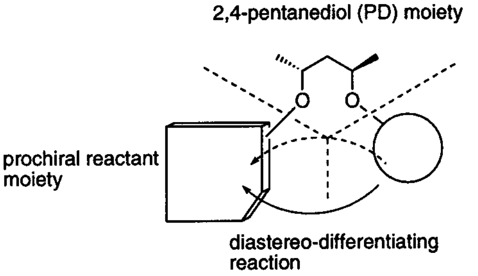
We have been studying asymmetric reactions using optically active 2,4-pentanediol (PD)[1] as a chiral tether between a prochiral reactant and a reagent.[2] A variety of reactant−reagent combinations have resulted in high diastereodifferentiation to give products easily with over 99% diastereomeric excess (de) without detailed optimization of the reaction conditions, and after the reaction, the tether part can be removed from the product without epimerization. The excellent ability and the wide applicability of the PD-tethered reaction is thus established as a handy stereocontroller for asymmetric reactions.[3,4] However, the stereocontrol mechanisms for these reactions were not readily comprehensible. The chiral tether part has only two small methyl groups and leads to a flexible medium ring (8- to 10-membered ring) in the transition states, where the methyl groups are not expected to cause enough steric repulsion nor structural strain to perform strict stereocontrol. Thus, we assume that the chiral fate of the reaction is prearranged in the ground state.



In this communication, we report that a PD-tethered [2+2] cycloaddition of an olefin and a ketene could perform strict diastereodifferentiation in the temperature range as wide as 195−423 K. Similar tethers having a single chiral center showed varied diastereodifferentiating abilities, which had almost no temperature dependencies in the same wide range. The present results suggest the potential of the PD tether to induce sufficient differential activation entropy and reveal a new aspect for designing asymmetric reactions.

The Eyring treatment[5] of the reaction rates of independent parallel processes to give respective stereoisomers in asymmetric reaction provides a differential activation enthalpy ($\Delta\Delta H^{\ddagger}$) and entropy ($\Delta\Delta S^{\ddagger}$) as shown in eq 1.[6] Most known asymmetric

$$\ln\frac{k_R}{k_S} = \frac{-(\Delta H^{\ddagger}_R - \Delta H^{\ddagger}_S)}{RT} + \frac{(\Delta S^{\ddagger}_R - \Delta S^{\ddagger}_S)}{R} = \frac{-\Delta\Delta H^{\ddagger}}{RT} + \frac{\Delta\Delta S^{\ddagger}}{R} \qquad (1)$$

reactions have been designed to induce sufficient $\Delta\Delta H^{\ddagger}$ by steric repulsion, structural strain, or electronic interaction in the transition states. As a result, these reactions have a temperature-dependence of stereodifferentiation and are performed at low temperatures so that the reactions can proceed with better stereocontrol although the temperature must also be high enough to achieve a practical rate of reaction. An entropy-controlled asymmetric reaction having sufficient $\Delta\Delta S^{\ddagger}$ is preferable from a synthetic viewpoint. Reactions of varied reagent−reactant combinations can then be performed to keep the stereocontrol high enough, independent of the reaction temperature, and thus, optimization for each reaction system is not necessary.

To investigate the potential of PD-tethered reactions which may have sufficient $\Delta\Delta S^{\ddagger}$, the diastereodifferentiating ability over a wide range of temperatures should be studied to minimize the uncertainties due to the extrapolation of the experimental data to $1/T$ (K^{-1}) = 0. In this context, the thermal [2+2] cycloaddition of an olefin with a ketene was selected, since the addition is rapid and a ketene can be readily generated by a photochemical method from a diazo carbonyl compound through the Wolff rearrangement.[7−9] The substrate **1a** was prepared from (2*R*,4*R*)-PD by the reported method,[2e] and photolyzed in pentane (≤293 K) or decane (≥296 K) solution with a low-pressure mercury lamp in a temperature range of 195−423 K (by 10−23 K steps). The majority of the carbene generated by photoirradiation was trapped by the solvent, but the expected [2+2] cycloadduct was also produced (10−33% isolated yield).[10−12] At all temperatures, the adduct was the

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(3) Since the latest mechanistic study of the Lewis acid promoted diastereodifferentiating nucleophilic addition to a PD acetal suggested an $\mathrm{S_N1}$-like mechanism, some of the reactions of PD acetals might also be classified into the group of PD tethered reactions. Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998−10999.

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(10) The stereochemical purities were determined by GLC equipped with FID or MS. Four more isomeric adducts, 1,2-trans-adducts and 2-keto-adducts, are possible besides **3**. Analyses of the reaction mixtures and those after solvolysis indicated that formation of the isomers of **2** is below the detection limit (<0.5%) except for **3d** and **3c**. The de and isolated yield of **2** (and **3**) were somewhat affected by the solvent used, photoirradiation time, and the irradiation wavelength. See the Supporting Information for the details.

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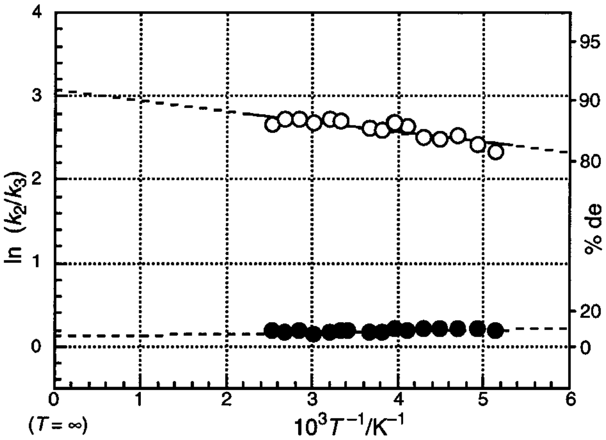
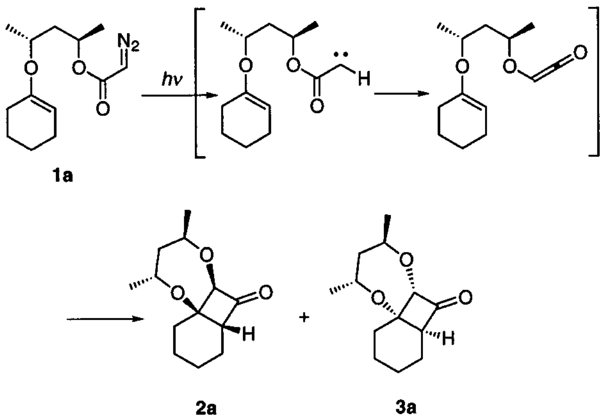


Figure 1. Plots of ln(k_2/k_3) as a function of $1/T$ for the reactions of **1c** (○) and **1d** (●). The abscissa is extended to $T = \infty$ to show the intercepts. Differential activation parameters are $\Delta\Delta H^{\ddagger} = 0.23 \pm 0.05$ kcal mol^{-1} and $\Delta\Delta S^{\ddagger} = 6.00 \pm 0.02$ cal mol^{-1} K^{-1} for **1c** and $\Delta\Delta H^{\ddagger} = -0.03 \pm 0.01$ kcal mol^{-1} and $\Delta\Delta S^{\ddagger} = 0.26 \pm 0.04$ cal mol^{-1} K^{-1} for **1d**.

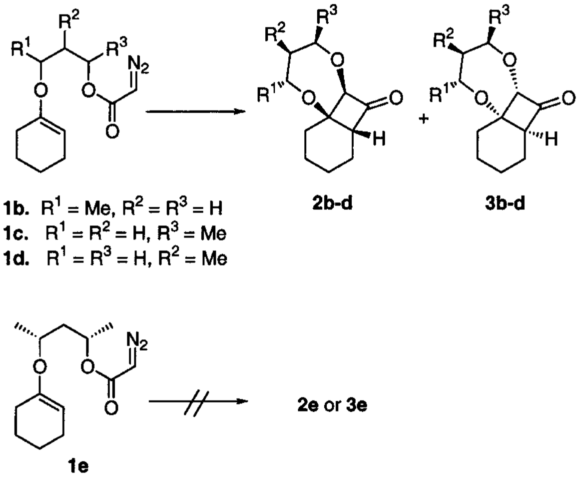
Scheme 1



(1*R*,6*R*)-isomer **2a** and none of the diastereomer **3a** was detected (<0.5% of **2a**). Thus, the stereocontrol with the PD tether was shown to be rigorous between the temperature of 195 and 423 K. The ratio of $k_2/k_3 > 200$ (> 99% de) at 423 K translates to $\Delta\Delta G^{\ddagger} > 4.4$ kcal mol^{-1}, the origin of which is difficult to explain with only $\Delta\Delta H^{\ddagger}$ for such a rapid reaction.

The stereocontrol ability of each chirality on the PD tether was examined using substrates **1b**−**d** (racemic mixtures) having a methyl group at different positions on the tether moiety. Photolysis of **1b** again yielded a single diastereomer of **2b** from 195 to 400 K (4−14% isolated yield). In the cases of **1c** and **1d**, a mixture of **2** and **3** was obtained (4−16% and 3−8% isolated yields, respectively). The de values of **2c** only varied from 84% to 88%, and those for **2d** (or **3d**) varied from 10% to 11%. That is, the ratios of diastereomers **2**/**3** in the reactions of **1c** and **1d** were almost unchanged in the temperature range twice as wide as in Kelvin. Plots of the ln(k_2/k_3) as a function of $1/T$ are shown in Figure 1. The "flat" temperature dependency observed in this wide range of temperature is unprecedented, and clearly demonstrates that the reaction is stereocontrolled by the differential activation entropy, $\Delta\Delta S^{\ddagger}$.[13]

Scheme 2



Since the direction controlled by the methyl chiralities in **1b** and **1c** was the same as that of **1a**, the two methyl groups in **1a** can be considered to work cooperatively to differentiate the diastereoface. On the contrary, the two methyl groups of **1e** were expected to compete with each other in the stereocontrol due to the entropy factors. When **1e** was photolyzed in the same temperature range, the [2+2] addition was sluggish and the adducts were not observed (<3%). The two methyl groups must interfere with the attacks on the respective stereofaces to retard the [2+2] addition itself independent of temperature.

In the present study, the PD-tethered [2+2] addition was proven to have rigorous diastereodifferentiation (>99% de) over a wide range of temperature, and the reason for the stereocontrol was shown to be the differential activation entropy, $\Delta\Delta S^{\ddagger}$. The effective induction of $\Delta\Delta S^{\ddagger}$ with the PD tether can be explained as follows. Formation of a medium ring from a flexible substrate requires a great loss of entropy, the degree of which largely depends on the conformational property of the substrate.[14] The PD-tethered reaction starts with the encounter of the reagent and reactant moieties, and the accompanying large entropy loss would result in enough difference in entropy between the two diastereomeric encounter states from the influence of the chiralities on the tether. This difference is carried over to the transition states to give $\Delta\Delta S^{\ddagger}$.[6,15] The differentiated face of the olefin in **1a** was *si,re* as was the case for the metal-catalyzed carbenoid addition of **1a**[2e] and other related reactions.[2a,b] Thus, all the PD-tethered reactions might also have a large enough $\Delta\Delta S^{\ddagger}$ and be stereocontrolled by the differential activation entropy. This prediction is very compatible with the fact that the stereocontrol ability of PD tether does not depend on the reaction types or rates. The success of the PD tethered reaction as a versatile stereocontroller indicates that an entropy-controlled asymmetric reaction can perform high stereodifferentiation with a much simpler reaction design than the conventional asymmetric reactions of enthalpy control, and provides a new principle for the design of asymmetric reactions.

Supporting Information Available: Experimental details and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The structure of the adduct **2a**−**c** were fully identified. The stereochemistries of **2d** and **3d** were not determined. See the Supporting Information for the details.

(12) The ketene generated through the base-promoted 1,2-elimination from a corresponding substrate also produced only **2a**. See the Supporting Information for the details.

(13) Contributions of $\Delta\Delta H^{\ddagger}$ to ln(k_2/k_3) at 300 K are only −15% for **1c** and 27% for **1d**. In **1c**, stereodirections of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ are opposite, and thus, the result is also regarded as the stereoselectivity caused by $\Delta\Delta S^{\ddagger}$, which is reduced 12% by $\Delta\Delta H^{\ddagger}$.

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(15) If the conformational equilibration of the tether part is slower than the [2+2] addition, the de is also independent of the reaction temperature. This anti-Curtin−Hammett explanation also leads to the same conclusion that the chiral fate of the reaction is prearranged in the ground state. For kinetic data for intermolecular ketene [2+2] additions, see: Issacs, N. S.; Stanbury, P. *J. Chem. Soc., Perkin Trans. 2* **1973**, 166−169.