# Entropy-Controlled Asymmetric Synthesis. How Differential Activation Entropy Is Induced in Chiral Tethered Reactions
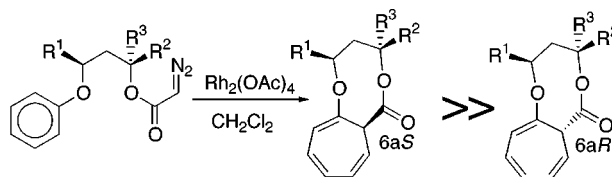
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**ABSTRACT**



Kinetic measurements to determine effective molarities of intramolecular reactions using 2,4-pentanediol and related tethers showed that methyl groups on the tether accelerate the major diastereomeric process but decelerate the minor process. The efficient promotion of stereocontrol is suggested to be due to chiral perturbation of the reaction rate through the entropy term. The conformation of the encounter complex of the reagent and reactant moieties was deduced by stereochemical analysis of the intramolecular adducts.

The reaction using a chiral 2,4-pentanediol tether between prochiral reactant and reagent moieties (PD-tethered reaction) is a versatile and practical method for asymmetric syntheses.[1] The stereochemistries of the products are strictly controlled by only the two small methyl groups (and even by a single methyl group in some cases[1c,2]) on the flexible tether irrespective of the reaction type, rate, or conditions. Recently, we have shown that one of the PD-tethered reactions m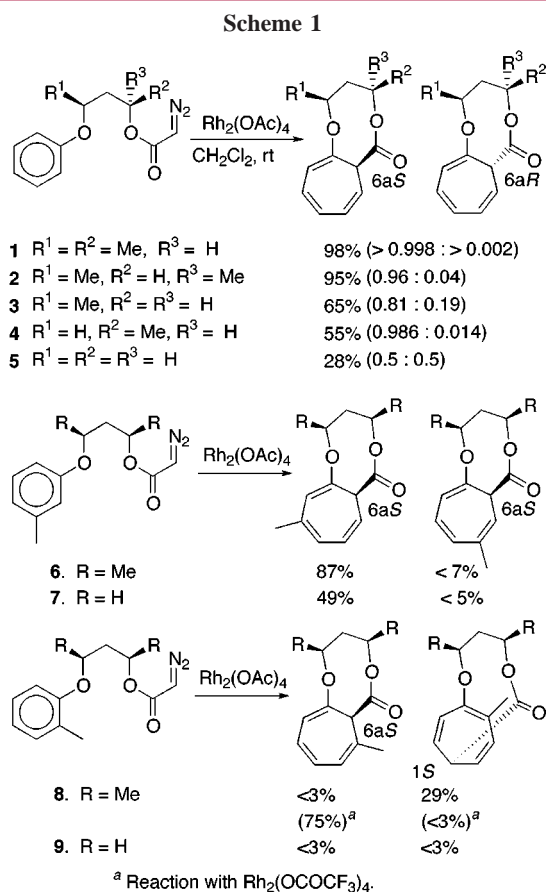aintains its stereoselectivity over a wide range of reaction temperatures (185−423 K) and concluded that the differential activation free energy ($\Delta\Delta G^{\ddagger}$) of the two diastereomeric processes controlled by the PD tether consists mostly of the differential activation entropy ($\Delta\Delta S^{\ddagger}$).[2] Thus, entropy-controlled asymmetric synthesis (ECAS) has been proposed to have high potential for stereocontrol with a simple reaction design. In this communication, we report kinetic and stereochemical studies on a PD-tethered reaction to clarify how the chiralities on the tether induce sufficient stereochemical control.

Alkyl substitution as the chiral origin to control asymmetric synthesis usually affects the reaction by differential retardation between the two diastereomeric processes by steric repulsion or structural strain in the two transition states. However, when the perturbation of the reaction rate by the alkyl substituent is induced in an entropy term, an increase in the reaction rate is also possible through an increase in the frequency factor of the reaction. Thus, we determined the effect of the methyl groups on the PD tether upon the intramolecular reaction rate.

(1) (a) Sugimura, T.; Yoshikawa, M.; Futagawa, T.; Tai, A. *Tetrahedron* **1990**, *46*, 5955−5966. Sugimura, T.; Yoshikawa, M.; Mizuguchi, M.; Tai, A. *Chem. Lett.* **1999**, 831−832. (b) Underiner, T. L.; Paquette, L. A. *J. Org. Chem.* **1992**, *57*, 5438−5446. Sugimura, T.; Iguchi, H.; Tsuchida, R.; Tai, A.; Nishiyama, N.; Hakushi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1007−1013. (c) Sugimura, T.; Nishiyama, N.; Tai, A. *Tetrahedron: Asymmetry* **1993**, *4*, 43−44. (d) Sugimura, T.; Yamada, H.; Inoue, S.; Tai, A. *Tetrahedron: Asymmetry* **1997**, *8*, 649−655. Sugimura, T.; Inoue, S.; Tai, A. *Tetrahedron Lett.* **1998**, *39*, 6487−6490. (e) Mori, A.; Sugimura, T.; Tai, A. *Tetrahedron: Asymmetry* **1997**, *8*, 661−664. (f) Sugimura, T.; Nagano, S.; Tai, A. *Chem. Lett.* **1998**, 45−46. (g) Yamaguchi, K.; Sugimura, T.; Nishida, F.; Tai, A. *Tetrahedron Lett.* **1998**, *39*, 4521−4524.
(2) Sugimura, T.; Tei, T.; Mori, A.; Okuyama, T.; Tai, A. *J. Am. Chem. Soc.* **2000**, *122*, 2128−2129.

The reaction employed for the present study is the $Rh_2$-$(OAc)_4$-catalyzed reaction of the diazo ester and the phenyl group tethered by PD (**1** in Scheme 1), where two pairs of

**Scheme 1**



**1** $R^1 = R^2 = Me$, $R^3 = H$    98% (> 0.998 : > 0.002)
**2** $R^1 = Me$, $R^2 = H$, $R^3 = Me$    95% (0.96 : 0.04)
**3** $R^1 = Me$, $R^2 = R^3 = H$    65% (0.81 : 0.19)
**4** $R^1 = H$, $R^2 = Me$, $R^3 = H$    55% (0.986 : 0.014)
**5** $R^1 = R^2 = R^3 = H$    28% (0.5 : 0.5)

**6**. R = Me    87%    < 7%
**7**. R = H    49%    < 5%

**8**. R = Me    <3%    29%
     (75%)[a]    (<3%)[a]
**9**. R = H    <3%    <3%

[a] Reaction with $Rh_2(OCOCF_3)_4$.

adjacent reaction sites of the 1,2-positions in the phenyl group are differentiated by the carbenoid to result in a diastereo-merically pure cycloheptatriene via the norcaradiene inter-mediate.[1f] The high diastereomeric excess (de) of the product was further shown in the present study to be over 99.6% de (at room temperature).[3] With substrates **2**−**4** having a different tether, the reaction selectivities were moderate to very high (see Scheme 1), and the major products had the same 6a$S$ stereochemistry as that of **1**.[4,5,6] Good regiocontrol

(3) The high de was maintained in the temperature range between −15 and 60 °C (CHCl₃).

(4) Structures of the minor products were not identified in all reactions. Values of the de of the major products were determined by GLC with achiral and chiral columns after treatments of the reaction mixtures with lithium aluminum hydride and acetic anhydride/pyridine. Reference samples were prepared through epimerization of the isolated major products followed by the above conversion. The selectivities shown in Table 1 might be underestimated because of intermolecular reactions. See the Supporting Information for the experimental details.

(5) For reviews, see the following: (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919−939. (b) Davis, H. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; pp 1031−1067. (c) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−935.

(6) For the intramolecular reactions, see the following: (a) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385−5453. (b) Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193−6196. (c) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493−4494. (d) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **1998**, *63*, 3717−3721.

(>90%) was observed with *m*-tolyl derivatives **6** and **7** in addition to the stereocontrol (>99.6% de) with chiral **6**. The reactions of *o*-tolyl derivatives **8** and **9** were sluggish. The achiral substrate **9** was converted to a mixture of products which mostly retained the *o*-tolyl group, while **8** gave an unexpected adduct at the 4,5-position by using $Rh_2(OAc)_4$ (>80% de). When **8** was treated with $Rh_2(OCOCF_3)_4$,[7] the product was sharply switched to the regular adduct at the 1,2-position (>99.6% de).

The relative rates for the intramolecular and the intermo-lecular additions of the rhodium carbenoids produced in situ were determined by the reaction of the substrate in the presence of benzene (at $20 \pm 1$ °C). The reaction resulted in both the intra- and intermolecular additions to give the corresponding cycloheptatrienes, the ratio of which was determined by $^1$H NMR. The relative rates calculated from the ratios at various concentrations of benzene were con-verted to the effective molarities compared with isopropoxy-benzene as a reference substrate (Table 1).[8]

**Table 1.** Effective Molarities of the Reaction of **1**−**8** with $Rh_2(OAc)_4$ and Perturbation Factors $\alpha$ for the Major Isomers

| substrate | effective molarity/M | $\alpha_{6aS}$ | $\alpha_{6aS}/\alpha_{6aR}$ |
|---|---|---|---|
| **1** | $0.64 \pm 0.06$ | 130 | >500 |
| **2** | $0.31 \pm 0.03$ | 62 | 24 |
| **3** | $0.044 \pm 0.001$ | 8.8 | 4.2 |
| **4** | $0.049 \pm 0.011$ | 9.8 | 70 |
| **5** | $0.010 \pm 0.001$ | 1[a] | |
| **6** | $1.23 \pm 0.15$ | 129 | >500 |
| **7** | $0.019 \pm 0.002$ | 1[a] | |
| **8** | $0.013 \pm 0.003$ | 1.4[b] | >9[b] |

[a] The reactions of **5** and **7** were used as the standard achiral reactions ($k_{6aS} = k_{6aR}$) for **1**−**4** and **6** and **8**, respectively. [b] $\alpha_{1S}$ and $\alpha_{1S}/\alpha_{1R}$ for **8**.

The reactions of the PD-tethered substrates, **1** and **2**, are faster than those of **3** and **4** having a singly methylated tether, which are faster than that of the achiral substrate **5** having no methyl group. That is, each methyl substitution on the tether enhances the reaction rate by 1 order of magnitude. The low effective molarity of **5** is ascribed to the entropy loss during the formation of an eight-membered ring from the flexible tether.[9] Acceleration of the intramolecular reaction to give the major 6a$S$-stereoisomer by methyl

(7) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669−8680. Padwa, A.; Austin, D. J.; Hornbuckle, S. F. *J. Org. Chem.* **1996**, *61*, 63−72.

(8) The reactivity ratio of isopropoxybenzene and benzene was inde-pendently determined from the reaction with ethyl diazoacetate ($9.3 \pm 0.9$).

(9) (a) Issacs, N. *Physical Organic Chemistry*; Longman Scientific & Technical: Essex, 1995; pp 643−677. (b) Winnik, M. A. *Chem. Rev.* **1981**, *81*, 491−524.

(10) Entropy-driving acceleration of the intramolecular reaction by the methyl substitution is known as the Thorpe−Ingold effect. See the following: (a) Kirby, A. J. In *Advances in Physical Organic Chemistry*; Gold, V., Bethell, D., Eds.; Academic Press: London, 1980; Vol. 17, pp 183−278. (b) De Tar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505−4512. (c) Jager, J.; Graafland, T.; Schenk, H.; Kirby, A. J.; Engberts, J. B. F. *J. Am. Chem. Soc.* **1984**, *106*, 139−143. (d) Sternbach, D. D.; Rossana, D. M.; Ohan, K. D. *Tetrahedron Lett.* **1985**, *26*, 591−594.

substitution on the tether is characteristic of chiral perturbation through the entropy term.[10] Reactions with *m*-tolyl substrates being faster than those with phenyl substrates (**6** vs **1** and **7** vs **5**) indicates that the rate-determining step of each overall reaction is the addition step following the conformational change of the tether part to achieve the encounter complex both for the chiral and achiral tethers; the more electron-rich tolyl group should have a higher activity toward rhodium carbenoid addition.

The role of the methyl groups as the chiral source becomes clearer by the introduction of a chiral perturbation factor, $\alpha$. The two diastereomeric reaction rates, $k_{6aS}$ and $k_{6aR}$, can be expressed by the unperturbed achiral reaction rate $k$ of **5** (or **7**) and chiral perturbation factors, $\alpha_{6aS}$ and $\alpha_{6aR}$. That is, $k_{6aS} = \alpha_{6aS}k/2$, $k_{6aR} = \alpha_{6aR}k/2$, and the stereoselectivity $k_{6aS}/k_{6aR} = \alpha_{6aS}/\alpha_{6aR}$. In energy terms, $\alpha$ corresponds to $\delta\Delta G^{\ddagger}$ comprising $\delta\Delta H^{\ddagger}$ and $\delta\Delta S^{\ddagger}$ terms.[11]

$$\ln k_{6aS} = \ln \frac{\alpha_{6aS}k}{2} = \frac{-(\Delta H^{\ddagger} + \delta\Delta H^{\ddagger}_{6aS})}{RT} + \frac{(\Delta S^{\ddagger} + \delta\Delta S^{\ddagger}_{6aS})}{R} + \ln \frac{k_B T}{2h}$$

$$\ln k_{6aR} = \ln \frac{\alpha_{6aR}k}{2} = \frac{-(\Delta H^{\ddagger} + \delta\Delta H^{\ddagger}_{6aR})}{RT} + \frac{(\Delta S^{\ddagger} + \delta\Delta S^{\ddagger}_{6aR})}{R} + \ln \frac{k_B T}{2h}$$

The chiral perturbation factors $\alpha_{6aS}$ for **1**−**4**, **6**, and **8** are given in Table 1. In the reaction of **1**, $\alpha_{6aS}$ corresponds to a 130-fold acceleration, which translates to an increase in activation entropy $\delta\Delta S^{\ddagger}_{6aS}$ of 10 cal mol$^{-1}$K$^{-1}$. Considering the magnitude of the stereoselectivity ($\alpha_{6aS}/\alpha_{6aR} > 500$), the $\alpha_{6aR}$ value must be less than unity. That is, the methyl group reduces the production rate of the 6aR-adduct through the minor diastereomeric process, in contrast to its acceleration of the major process.

Since $\delta\Delta S^{\ddagger}_{6aS}$ for the chiral tethered reactions is expected to be induced during the formation of the cyclic conformation of a medium ring, the chiral fate of the reactions should be determined at this stage prior to the start of the addition reaction. That is, the chiralities on the tether control the preequilibrium constants, $K_{6aS}$ and $K_{6aR}$, for the formation of the encounter complexes of the rhodium carbenoid and the reaction site of the aromatic group. The chiral perturbation in entropy brings about a sufficient difference in $K_{6aS}$ and $K_{6aR}$, and the difference is carried over to the product ratio through the rate-determining steps.[12]
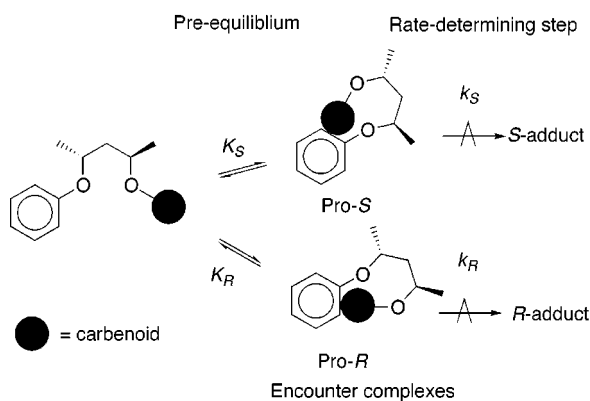


Selected possible structures of the encounter complex in the reaction of **5** are illustrated in Figure 1. Since the free
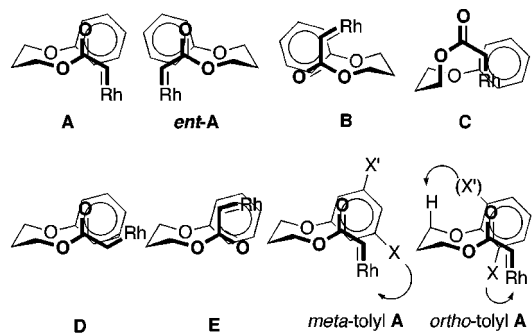


**Figure 1.** Possible encounter complexes to give the intramolecular adducts. Arrows indicate steric interactions (X or X' = methyl).

energy differences among them caused by methyl substitution on the tether should be due to the entropy term, simple MO calculations cannot provide useful information. For example, the two methyl groups of the substrate **2** take the axial and equatorial positions both in **A** and ***ent*-A**. However, analysis of the regio- and stereochemical outcomes indicates the encounter complex in the present reaction to be **A**.

The stereochemical outcomes of **1**−**4** exclude processes through encounter complexes such as ***ent*-A** and **C**. The carbenoids having *s-cis* conformations,[13] **D** and **E**, can also be excluded because the lactone ring in the adduct has a *trans* fusion. The regioselectivity of *m*-tolyl substrates, **6** and **7**, can be explained by steric repulsion during the ensuing addition from both **A** and **B**.

The encounter complex **B** is finally excluded by the results with *o*-tolyl substrates, **8** and **9**. The methyl group at the X'-position causes steric repulsion with the tether proton in both **A** and **B**. Then, the rhodium carbenoid is forced to approach the sterically congested position (X = Me) in **A**, whereas there is no steric barrier in **B**. Since the reactions of **8** and **9** were both sluggish, **B** can be ruled out. The anomalous and selective reaction of **8** is also rationalized with **A**. The addition of the carbenoid generated with Rh$_2$-(OAc)$_4$ occurs at the 4,5-position avoiding the steric barrier,

(11) The concept of the chiral perturbation factor is useful for understanding of the stereocontrol mechanism of other asymmetric syntheses. For example, the linear relationship between the differential activation enthalpy ($\Delta\Delta H^{\ddagger}$) and entropy ($\Delta\Delta S^{\ddagger}$) could not be understood simply as difference in the activation parameters, $\Delta H^{\ddagger}_R - \Delta H^{\ddagger}_S$ and $\Delta S^{\ddagger}_R - \Delta S^{\ddagger}_S$. By introduction of the chiral perturbations factors, $\alpha_R$ and $\alpha_S$, they are translated to $\delta\Delta H^{\ddagger}_R - \delta\Delta H^{\ddagger}_S$ and $\delta\Delta S^{\ddagger}_R - \delta\Delta S^{\ddagger}_S$, respectively. When the chiral perturbation mechanism is similar among the reactions, $\delta\Delta S^{\ddagger}$ and $\delta\Delta H^{\ddagger}$ show the isokinetic relation, and thus those differences, $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$, should have a linear relationship. For the recent experimental examples, see the following: (a) Gallicchio, E.; Kubo, M. M.; Lecy, R. M. *J. Am. Chem. Soc.* **1998**, *120*, 4526−4527. (b) Inoue, Y.; Ikeda, H.; Kaneda, M.; Sumimura, T.; Everitt, S. R. L.; Wada, T. *J. Am. Chem. Soc.* **2000**, *122*, 406−407.
(12) A similar explanation for the reaction rate using "critical distance" in nonstereoselective reactions was also reported. Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128−134.
(13) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53−61.

whereas the more reactive carbenoid prepared with $Rh_2(OCOCF_3)_4$ adds to the stereocongested 1,2-position in conformation **A**. Thus, **A** is implicated as the predominant conformation of the encounter complex giving the intramolecular adducts in all the reaction systems employed in the present study.

In conclusion, the opposite effects of the chiral source on the reaction rates of the two diastereomeric processes are found to be an explanation of strict stereocontrol by small methyl groups. This efficient stereocontrol is considered to be the most notable characteristic of ECAS. In biological reactions and template reactions,[14] selectivities controlled by differential activation entropy are rather common. However, most of those reactions differentiate the substrate or its reaction site at the adsorption or incorporation step of the substrate, and a particular combination of the substrate and the "reactor" is necessary. The PD-tethered reaction has a different stereocontrol mechanism, which should be called an "intramolecular enantio-differentiating reaction".[15] This mechanism makes the PD-tethered reaction widely applicable.

So far, we have learned from the PD-tethered reactions that requirements for designing ECAS with versatile applicability are (1) large negative $\Delta S^{\ddagger}$ before chiral perturbation, (2) minimum chiral perturbation, and (3) a relatively fast intrinsic reaction. The chiral fate of such a reaction is determined in the encounter complex, which results in versatile stereocontrol irrespective of the transition state of the intrinsic reaction.

**Supporting Information Available:** Experimental details including spectral data, determination of stereochemical purity, and kinetics determinations. This information is available free of charge via the Internet at http://pubs.acs.org.

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(14) Diederich, F.; Stang, P. J. *Templated Organic Synthesis*; Wiley & Sons: Weinheim, 2000.

(15) Izumi, I.; Tai, A. *Stereo-differentiating Reactions*; Academic Press: New York, 1977.