JOC Article

"Chiral Perturbation Factor" Approach Reveals Importance of Entropy Term in Stereocontrol of the 2,4-Pentanediol-Tethered Reaction

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The stereocontrol mechanism of the 2,4-pentanediol (PD)-tethered reaction was studied in detail using a reaction system consisting of phenyl and rhodium carbenoid moieties. Different tethers were examined to analyze the effects of the methyl groups on the PD tether. Among the reactions with these tethers, the PD tether achieves an unmeasurably high stereoselectivity in a diastereomeric ratio of >500. Another tether showing a high but measurable stereoselectivity in a ratio of 41 is mostly controlled by the entropy term. To clarify the role of the methyl groups on the chiral tethers, which are the origin of the stereocontrol, the "chiral perturbation factor" is introduced. This parameter is defined as the rate of a chiral reaction relative to that of an achiral reference reaction. By analyzing the temperature dependence of the chiral perturbation factors for different chiral-tethered reactions, high potentials of the PD-tethered reaction in its stereocontrol are concluded to be due to the entropy term.

Introduction

The 2,4-pentanediol (PD)-tethered reaction is designed for various asymmetric syntheses requiring different types of stereocontrol.[1] A prochiral reactant linked to the readily available (*R*,*R*)- or (*S*,*S*)-PD through one of the hydroxy groups and a reagent attached to the other hydroxy group in situ or in advance undergo an intramolecular reaction through a medium (8−11-membered) ring state (Figure 1). The two small methyl groups on the long and flexible tether may not be expected to cause notable steric hindrance or structural strain to interfere with the reaction irrespective of its geometric demands, and thus, various combinations of the reactant and reagent moieties are possible. Nine types of various reactions have already been studied, and all of them were found to be highly stereoselective and produce practically single diastereomers.[2,3] In addition, the high stereoselectivities are insensitive to the reaction conditions. Combined with easy removal of the tether from the products, the PD tether has been established to provide a reliable and widely applicable tool for the construction of stereochemically pure units. Some optically active compounds obtained have been used for asymmetric syntheses of natural products.[4]

The stereocontrollability of the PD-tethered reaction was more than expected for the simple and flexible tether. Namely, we already have a solution for a paradox in designing asymmetric syntheses that strict regulation of the reaction transition state to attain the high selectivity tends to limit its range of applicability. This study aims at answering the question why the PD-tethered reaction can achieve both strict stereocontrollability and wide applicability.[5]

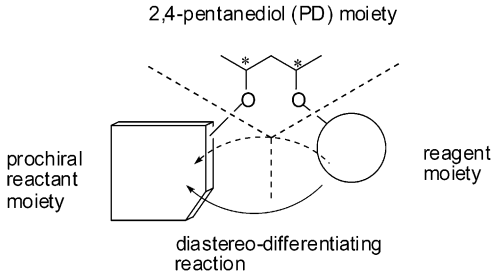

FIGURE 1. Asymmetric synthesis design with a 2,4-pentanediol tether.

A chiral source in a kinetically controlled asymmetric synthesis affects the two stereoisomeric reaction rate constants, k_R and k_S, to different degrees, and the intrinsic selectivity can be expressed by the ratio of the rate constants, k_S/k_R. In general, during the optimization process in terms of the selectivity, one often wonders which value, k_R or k_S, causes the change in k_S/k_R. Since the stereocontrol mechanism of the PD-tethered reactions is believed to be quite different from conventional asymmetric syntheses,[2i] we evaluated the separate effect of

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(1) For a review, see: Sugimura, T. In *Recent Research Developments in Organic Chemistry*; Pandalai, S. G., Ed.: Transworld: Tribundrum, 1998; Vol. 2, pp 47−54.

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TABLE 1. Isolated Yields and Diastereomer Fractions of 2 and Differential Activation Parameters[a] at 20 °C

substrate	isolated yield[b]	fraction[c] (11a*S*)-**2**	fraction[c] (11a*R*)-**2**	k_{11aS}/k_{11aR}	$\Delta\Delta G^{\ddagger}$(kJ mol^{-1})	$\Delta\Delta H^{\ddagger}$(kJ mol^{-1})	$\Delta\Delta S^{\ddagger}$(J T^{-1}mol^{-1})
1a	98%	>0.998	<0.002	>500	>−15		
1b	95%	0.960	0.040	24	−7.8	−5.2 ± 0.8	8.3 ± 2.8
1c	65%	0.81	0.19	4.2	−3.8	−5.8 ± 0.3	−7.8 ± 1.2
1d	55%	0.976	0.024	41	−9.1	0.5 ± 0.8	32.0 ± 2.8
1e	28%	0.5	0.5	1	0	0	0

[a] Calculated from 8 to 12 determinations. See Table S1 (Supporting Information) for individual data. [b] Obtained on a preparative scale. [c] Determined from reactions on an analytical scale.

the chiral source on the reaction rates k_R and k_S in order to elucidate the stereocontrol mechanism of the PD tether.

Results and Discussion

Selectivity of PD-Tethered and Related Reactions. To analyze the stereocontrol mechanism of the PD-tethered reactions, we chose a reaction between a phenyl group and a rhodium carbenoid.[2f,6] The role of the methyl groups in the PD tether as a chiral source was clarified by comparing the reactions of different tethered substrates **1a**−**e**. The carbenoid generated by the treatment of **1** with a proper metal catalyst was expected to add to the phenyl ring to give norcaradiene, which is immediately converted to the chiral cycloheptatriene.[7] To obtain a stereochemically pure product **2**, closely placed intramolecular enantiotopos (or enantioface in this case) should be well differentiated, in addition to the regiocontrol of the addition sites on the phenoxy ring.

The stereochemically pure substrate **1a** was prepared in three steps through the Mitsunobu reaction of (2*R*,4*R*)-2,4-pentanediol (PD) with phenol (99% yield) followed by introduction of a diazo acetate ester (82% for two steps), and the other substrates **1b**−**e** in optically pure form were prepared according to the same method (21−83% for 3−5 steps).[8] The reaction of the substrates **1a**−**e** was carried out in dichloromethane by the addition of catalytic amounts of $Rh_2(OAc)_4$ (30−120 min at rt). No olefinic proton other than those of the expected cycloheptatrienes **2a**−**e** was detected in the product mixture by ^{1}H NMR. The stereochemistries of the major products were assigned as 11a*S* on the basis of NOE experiments. To avoid the fragility of the 7-carboxycycloheptatriene units, diastereomer ratios of **2a**−**d** were determined after the reduction of the reaction mixture to the diols with $LiAlH_4$. It was judged that this conversion does not affect the stereochemical purity of **2** at the 11a-position from the observation that no deuterium was incorporated into the diol in the presence of D_2O. The determined diastereomer ratios of **2a**−**d** do not depend on the reaction time; thus, the present system must consist of kinetically controlled parallel processes of the addition step, and the product ratio, (11a*S*)-**2**/(11a*R*)-**2**, is equal to the intrinsic selectivity, k_{11aS}/k_{11aR}. The results are given in Table 1.

The stereoselectivity of the reaction of the PD-tethered substrate **1a** is very high, and the de (diastereomeric excess) of **2a** produced is over 99.6%. On the other hand, the reaction of **1b**, a diastereomer of **1a**, gives a lower de of 92.0% of **2b**, which should be the result of the mismatching of the two methyl groups in stereocontrol on the basis of the results with the monomethylated substrates; both **1c** and **1d** give the (11a*S*)-rich **2** (62% de of **2c** and 95.2% de of **2d**[9]). The higher selectivity exhibited by **1d** compared to **1c**, as well as the same stereodirection of the chiral tethers of **1a** and **1b**, indicates that the addition is stereocontrolled mainly by the methyl group on the ester side, and the other methyl on the phenoxy side enhances the stereocontrol in **1a** but diminishes it in **1b**.

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(3) For examples of the reactions using other bifunctional chiral auxiliaries as tethers, see: (a) Green, B. S.; Rabinsohn, Y.; Rejto, M. *J. Chem. Soc., Chem. Commun.* **1975**, 313−314. (b) Ukaji, Y.; Sada, K.; Inomata, K. *Chem. Lett.* **1993**, 1227−1230. (c) Lipshutz, B. L.; Liu, Z.; Kayser, F. *Tetrahedron Lett.* **1994**, *35*, 5567−5570. (d) Lipshutz, B. H.; Kayser, F.; Liu, Z. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1842−1844. (e) Koide, N.; Hattori, T.; Miyano, S. *Tetrahedron: Asymmetry* **1994**, *5*, 1899−1994. (f) Lipshutz, B. H.; James, B.; Vance, S.; Carrico, I. *Tetrahedron Lett.* **1997**, *38*, 753−756. (g) Faure, S.; Blanc, S. P. L.; Pica, O.; Pete, J. P. *Tetrahedron Lett.* **1997**, *38*, 1045−1048. (h) Spring, D. R.; Krishnan, S.; Schreiber, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 5656−5657.

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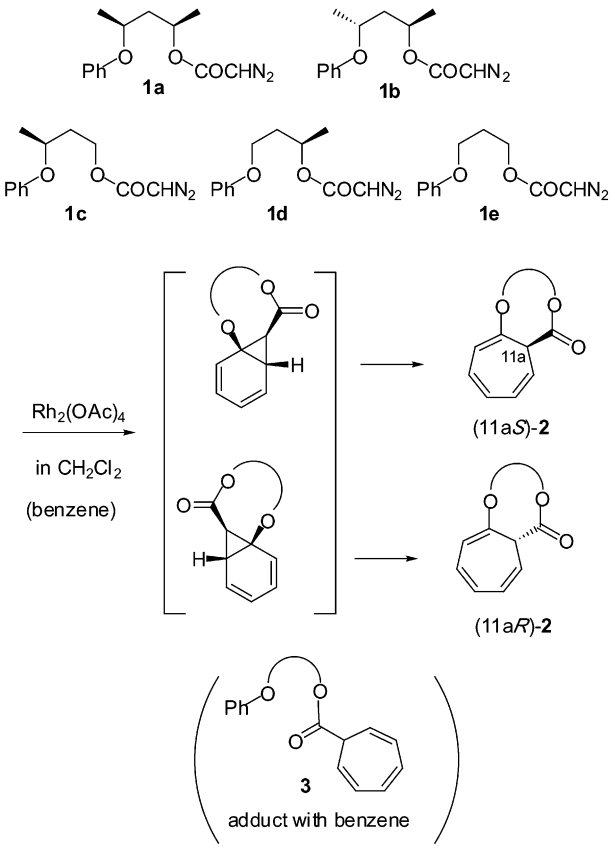
(8) The stereochemistry of the substrate **1b** in the preliminary report (ref 5) should be corrected.

(9) The de of **2d** was refined from reported values[5] by repeated experiments.

SCHEME 1



Temperature Dependence of the Selectivities. The diastereomer ratios of **2a**−**d** were determined in the reaction temperature range of 0−60 °C. The reaction of **1a** gives a >99.6% de over this temperature range, and the temperature dependence cannot be analyzed. The reaction selectivities of the other substrates **1b**−**d** are in the ranges of 90−93% de for **2b**, 54−73% de for **2c**, and 94−95% de for **2d**. From the observed selectivities, the differential activation enthalpies $\Delta\Delta H^{\ddagger}$ ($= \Delta H_{11aS}{}^{\ddagger} - \Delta H_{11aR}{}^{\ddagger}$) and entropies $\Delta\Delta S^{\ddagger}$ ($= \Delta S_{11aS}{}^{\ddagger} - \Delta S_{11aR}{}^{\ddagger}$) were calculated from 8 to 12 independent determinations given in Table S1 (Supporting Information). Table 1 lists the differential activation parameters at 20 °C.

The moderately high selectivity in the reaction of **1b** is mainly governed by $\Delta\Delta H^{\ddagger}$ (ca. 70% of the selectivity). The lower selectivity in the reaction of **1c** is due to the cancellation of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$, even though both absolute values are similar to those for **1b**. In contrast, the reaction of **1d** is well stereocontrolled despite a negligible value of $\Delta\Delta H^{\ddagger}$. In this case, $\Delta\Delta S^{\ddagger}$ governs more than 90% of the selectivity. By this conventional analysis, however, the mechanism causing the differential activation parameters is not clear as to whether the methyl group(s) on the tether lowers the energy barrier for the major process or raises the barrier for the minor process; especially unclear is how the large $\Delta\Delta S^{\ddagger}$ is induced in the reaction of **1d**. The smaller $\Delta\Delta S^{\ddagger}$ in the reactions of **1b** and **1c** cannot necessarily be attributed to the smaller influence on the entropy ($\Delta S^{\ddagger}$) because the methyl group(s) may increase or decrease the activation entropy in the same direction for the two processes. The lack of entropy/enthalpy information about the reaction of the best substrate **1a** in both selectivity and chemical yield is also a problem to be considered. Details of the role of the methyl groups in inducing the selectivity will become much clearer if the differential parameters, $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$, can be divided into the contributions of the chiral source to the major and minor processes.

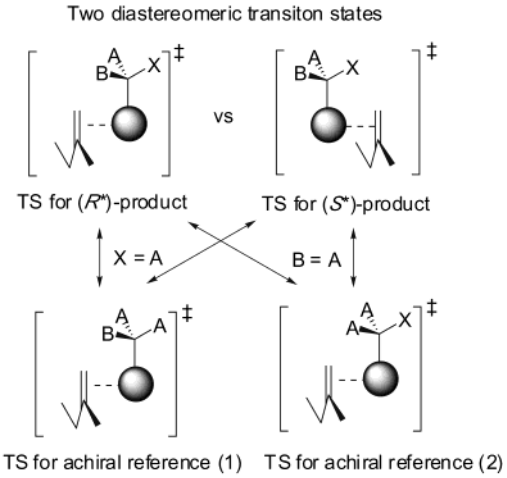


FIGURE 2. Two examples of standardization of asymmetric synthesis. X is a polar group, while A and B are simple alkyl groups.

Definition of Chiral Perturbation Factor. The effects of a chiral source on the reaction rates may be ascribed to several of its functions, but their separation is usually difficult because of the complex multiplicity of the functions governing the free energies of the transition states (schematically expressed in Figure 2, top two). To analyze each function of the chiral source, we introduced an "achiral" reaction as a reference for the two diastereomeric reactions. The reference reaction should be similar to the "chiral" reactions, but has no stereocontrollability by modifying the chiral source to be achiral (e.g., Figure 2, bottom two). The selection of an achiral reaction depends on what kind of function one likes to extract from the effects of the chiral source on the transition states. That is, when a polar group X is replaced by a simple alkyl group A (or B), the electronic or bonding interaction of X with the reagent and/or reactant in the two diastereomeric transition states are removed in making them enantiomeric. By comparing the two rates of the chiral reactions with that of the achiral reference, the selectivity caused by the polar interactions of X can be displayed. On the other hand, when an achiral reaction replacing a simple group B by A (or A by B) is selected, the achiral reference reaction keeps the polar interactions of X, but the interactions cannot be reflected in the stereocontrol. In this case, the difference between A and B in their steric effects can be seen.

The two diastereomeric rate constants, k_R and k_S, for an asymmetric synthesis can be expressed using k of a reference "achiral" reaction as eq 1, where α_R and α_S are the relative rates for the production of the respective stereoisomers. For these parameters, we use the term "chiral perturbation factor", since they are factors expressing rate enhancement or retardation due to a certain chiral origin.

$$k_R = \alpha_R k/2 \text{ and } k_S = \alpha_S k/2 \qquad (1)$$

TABLE 2. Chiral Perturbation Factors and Effective Molarities for Reactions of 1a−e at 20 °C

substrate	k_{11aS}/k_{Bz} (mol dm^{-3})	k_{11aR}/k_{Bz} (mol dm^{-3})	α_{11aS}	α_{11aR}	EM_{11aS} (mol dm^{-3})	EM_{11aR} (mol dm^{-3})
1a	6.4 ± 0.1	<0.013 ± 0.0003	140 ± 3	<0.29 ± 0.01	5.0 ± 0.1	<0.010 ± 0.0002
1b	2.9 ± 0.4	0.12 ± 0.02	64 ± 10	2.7 ± 0.4	2.3 ± 0.3	0.093 ± 0.01
1c	0.54 ± 0.06	0.13 ± 0.01	12 ± 1	2.9 ± 0.3	0.42 ± 0.04	0.10 ± 0.01
1d	0.41 ± 0.02	0.010 ± 0.0005	9.1 ± 0.5	0.22 ± 0.01	0.32 ± 0.02	0.0077 ± 0.0004
1e[a]	0.045 ± 0.008	0.045 ± 0.008	(1)	(1)	0.035 ± 0.006	0.035 ± 0.006

[a] Data for $k/2$.

The temperature dependence of the stereoselectivity k_S/k_R originates from the differential activation enthalpy $\Delta\Delta H^{\ddagger}$ and entropy $\Delta\Delta S^{\ddagger}$ as the difference in the terms for the diastereomeric processes, $\Delta H_S^{\ddagger} - \Delta H_R^{\ddagger}$ and $\Delta S_S^{\ddagger} - \Delta S_R^{\ddagger}$, respectively. These parameters can be expressed according to the chiral perturbation factor approach as the sums of those for the reference reaction ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for $k/2$) and those for the chiral perturbations ($\delta\Delta H^{\ddagger}$ and $\delta\Delta S^{\ddagger}$) by eqs 2 and 3. Accordingly, $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ can be divided into pairs of $\delta\Delta H^{\ddagger}$ and $\delta\Delta S^{\ddagger}$ from the temperature dependence of the α values (eqs 4 and 5). The parameters of $\delta\Delta H^{\ddagger}$ and $\delta\Delta S^{\ddagger}$ indicate a certain effect of the chiral source on each diastereomeric transition state.

$$\Delta H_R^{\ddagger} = \Delta H^{\ddagger} + \delta\Delta H_R^{\ddagger} \text{ and } \Delta H_S^{\ddagger} = \Delta H^{\ddagger} + \delta\Delta H_S^{\ddagger} \quad (2)$$

$$\Delta S_R^{\ddagger} = \Delta S^{\ddagger} + \delta\Delta S_R^{\ddagger} \text{ and } \Delta S_S^{\ddagger} = \Delta S^{\ddagger} + \delta\Delta S_S^{\ddagger} \quad (3)$$

$$\Delta\Delta H^{\ddagger} = \delta\Delta H_S^{\ddagger} - \delta\Delta H_R^{\ddagger} \quad (4)$$

$$\Delta\Delta S^{\ddagger} = \delta\Delta S_S^{\ddagger} - \delta\Delta S_R^{\ddagger} \quad (5)$$

In the chiral perturbation approach to analyzing the stereoselectivity of the PD-tethered reaction, we want to know how the two small methyl groups on the flexible tether can induce a large difference between k_R and k_S. Since a methyl group is the simplest alkyl group, an appropriate reference reaction should be the 1,3-propanediol-tethered reaction (e.g., **1e**), in which the two methyl groups of chiral origin are removed from the PD tether. If we can determine the chiral perturbation factors, α_R (= $2k_R/k$) and α_S (= $2k_S/k$), and their temperature dependence in the tethered reactions, the origin of the unexpectedly high stereocontrollability of the PD-tethered reaction will be disclosed.

Chiral Perturbation Factors in the Reaction of 1. The determination of the chiral perturbation factors, α_{11aS} and α_{11aR}, the reactivities of **1a**−**d** relative to the reference achiral **1e**, requires measurements of their intramolecular reaction rates for the rhodium carbenoid produced in situ by the catalysis. However, such measurements are practically impossible, since the formation of the carbenoid is a rate-limiting step.[10] As an alternative, we evaluated the relative rates of the intramolecular addition in comparison with the intermolecular reference. The carbenoids produced from **1a**−**e** are expected to have approximately the same reactivity toward an external aromatic compound coexisting in the reaction mixture.[11] Benzene was chosen as such a reference compound to simplify the ^{1}H NMR analysis of the product mixture and was used in different concentrations. The ratio of the major intramolecular adduct (11a*S*)-**2** and the intermolecular adduct **3** of benzene was determined (±<3%). From the product ratio of **2**/**3**, the value of k_{intra}/k_{Bz} wascalculated according to eq 6.

$$\frac{[\mathbf{2}]}{[\mathbf{3}]} = \frac{k_{intra}}{k_{Bz}[\text{benzene}]} \quad (6)$$

The relative rate obtained for the major product (k_{11aS}/k_{Bz}) was converted to those for the minor intramolecular adduct (k_{11aR}/k_{Bz}) using the diastereomer ratio (Table S2, Supporting Information). By standardization of these values with that of the achiral reaction of **1e**, the chiral perturbation factors for **1a**−**d** were calculated (Table 2). The effective molarities (EM)[12] for each of the diastereomeric reactions were also obtained using isopropoxybenzene (for **1a**−**c**) or ethoxybenzene (for **1d**,**e**) as the standard substrate.

The low EM for **1e** is reasonable as a reaction of the eight-membered ring formation from a flexible substrate.[13] The total EM ($EM_{11aS} + EM_{11aR}$) increases with methyl substitutions, and the highest value for **1a** (5 mol/dm^3) corresponds to almost neat conditions. Such accelerations are known as the Thorpe−Ingold effect; a methyl substitution on the linear substrate accelerates its cyclization in an entropy term.[14] However, the acceleration effects are much different between the two diastereomeric processes.

The degree of acceleration by the methyl substitution for each diastereomeric process is easy to visualize from the α values. That is, a single methyl group (**1c** and **1d**) increases the intramolecular reaction by ca. 10 times for the major 11a*S* product, irrespective of the position of the methyl substitution. In contrast, the values for the minor process, k_{11aR}, depend on its position: acceleration by the methyl group on the phenoxy side (**1c**), and deceleration by the one on the ester side (**1d**). Although

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(11) If a rhodium carbenoid having a smaller ester part has a larger activity towards benzene, the α values obtained for **1a**,**b**,**d** by this method are slightly overestimated.

(12) Effective molarities (EM) are calculated from the relative rates measured with benzene as the reference by correction for the appropriate reference of isopropoxybenzene at the 1,2-position for **1a**−**c** and ethoxybenezene at the same position for **1d**,**e**. For the regioselectivity of the diazo ester addition to substituted benzenes, see: Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873−876.

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TABLE 3. Thermodynamic Parameters for α_{11aS} and α_{11aR}

	major process		minor process	
substrate	$\delta\Delta H^{\ddagger}_{11aS}$ (kJ/mol[1])	$\delta\Delta S^{\ddagger}_{11aS}$ (J T^{-1} mol^{-1})	$\delta\Delta H^{\ddagger}_{11aR}$ (kJ/mol[1])	$\delta\Delta S^{\ddagger}_{11aR}$ (J T^{-1} mol^{-1})
1a	-4.5 ± 0.4	24.4 ± 1.5	$\delta\Delta G^{\ddagger} > 3.3$	
1b	-1.2 ± 0.4	28.9 ± 1.5	4.0 ± 0.8	20.7 ± 2.8
1c	-3.4 ± 0.4	6.6 ± 1.5	2.4 ± 0.4	14.4 ± 1.5
1d	-0.9 ± 0.4	14.0 ± 1.5	-1.4 ± 0.8	-18.0 ± 2.8

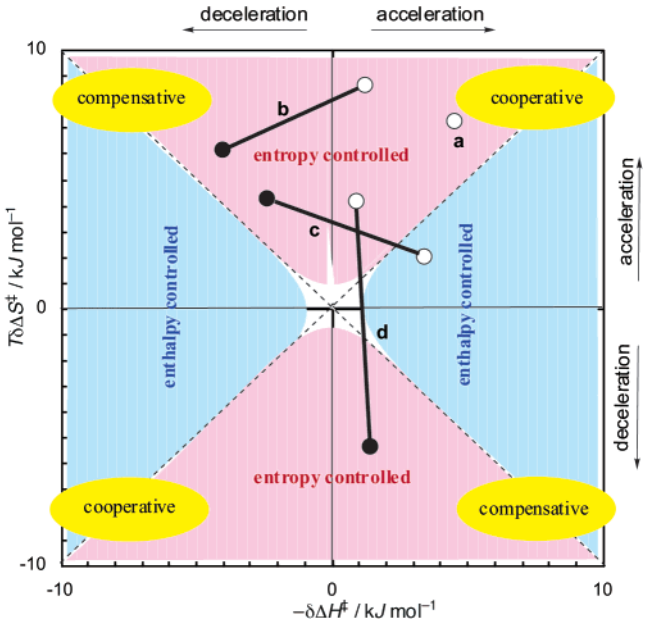

FIGURE 3. Enthalpy and entropy plots for chiral perturbation factors for 11a*S* (open circles) and 11a*R* products (solid circles) of the reaction of **1a**−**d**.

the anti-Thorpe−Ingold effect on the formation of (11a*R*)-**2d** may be explainable by steric repulsion caused by the methyl group, it does not seem to be large on the basis of the molecular model examination.

For **1a** and **1b** having two methyl groups on the tether, the values of α_{11aS} are as large as 140 and 64, respectively. However, the values of α_{11aR} are small, and again, one of them is smaller than unity: $\alpha_{11aR} < 0.29$ for the reaction of **1a**. These results indicate that the Thorpe−Ingold effect is operative in the major process (and thus, in the total reaction), but not in the minor one. The degrees of acceleration and deceleration for the individual diastereomeric processes observed for **1a** and **1b** are compatible with the results of the singly methylated substrates **1c** and **1d**. The cooperation of the moderately high stereocontrollability of the respective methyl groups may result in a very high stereocontrollability of one of the diastereomers of the doubly methylated tether (PD tether) as observed for **1a**.

Thermodynamic Parameters for the Chiral Perturbation Factors. The relative production rates of **2**/**3** were measured in the temperature range of 0−60 °C (Table S3, Supporting Information) and converted to the chiral perturbation factors, α. The perturbation enthalpy ($\delta\Delta H^{\ddagger}$) and entropy ($\delta\Delta S^{\ddagger}$) are calculated from α (Table 3). These values are plotted in Figure 3 to show the contributions of the enthalpy and entropy terms to the chiral perturbation factors. The negative perturbation enthalpy ($-\delta\Delta H^{\ddagger}$) is taken as the abscissa to show the positive value as acceleration. This energy map of the chiral perturbations illustrates the role of the methyl groups in the stereocontrol.

The reactions of **1c** and **1d** controlled by the single methyl group show contrasting positions on this map. For **1d**, the map indicates that the small $\Delta\Delta H^{\ddagger}$ is due to the low level of the perturbation enthalpies ($\delta\Delta H^{\ddagger}$) in both of the diastereomeric processes. The methyl group in **1d** affects the reaction mostly in the entropy term, and the high stereocontrollability originates from acceleration of the one process by the positive perturbation entropy ($\delta\Delta S_{11aS}^{\ddagger}$) and deceleration of the other by the negative perturbation entropy ($\delta\Delta S_{11aR}^{\ddagger}$). In the major process to give (11a*S*)-**2d**, the poor efficiency of the intramolecular reaction of **1e** (EM = 0.035 M) due to the large negative $\Delta S^{\ddagger}$ can be improved by the methyl substitution according to the Thorpe−Ingold effect. However, the minor process to give (11a*R*)-**2d** shows a further decrease in $\Delta S^{\ddagger}$, and as a result, the reaction is highly stereocontrolled by the entropy term.

On the other hand, the methyl group of **1c** perturbs the reaction in the enthalpy term; both perturbation enthalpies are large and in the opposite sign. The negative $\delta\Delta H_{11aS}^{\ddagger}$ may be due to the electron-donating effect of the methyl group to the phenyl ring, while the positive $\delta\Delta H_{11aR}^{\ddagger}$ can be caused by the steric repulsion. The perturbation entropies have the same sign and cancel each other, though their absolute values are comparable to those of **1d**. The lower selectivity with **1c** is mainly due to the compensation of the perturbation enthalpy ($\delta\Delta H_{11aR}^{\ddagger}$) and entropy ($\delta\Delta S_{11aR}^{\ddagger}$) in the minor process. As a result, the selectivity is controlled both by the enthalpy and entropy terms, but there is no relation between the perturbation enthalpy and entropy; thus, these terms must be independently caused by different mechanisms.[15]

For the doubly methylated **1b**, the minor process has an energy profile similar to that of **1c**, but both energy terms are larger. The perturbation entropy of the major process of **1b** is 2-fold larger than that of **1d** and is even larger than that of **1a**. The small $\Delta\Delta S^{\ddagger}$ in **1b** is not due to small perturbation entropies but the result of the cancellation of the large perturbation entropies of the same sign. For **1a**, the stereoselectivity is too high to quantitatively determine the temperature dependence, but the major process is found to be accelerated by both the enthalpy and entropy terms.

As an overall view of the map, the contributions of the entropy terms are more than 50% of the chiral perturbations, except for the major process of **1c** and the undetermined minor process of **1a**. How can $\delta\Delta S^{\ddagger}$ be induced in the PD-tethered reactions? The origin should be in the cyclization process that produces the encounter complexes of the reactant moiety at the reaction sites with the reagent moiety. Thus, the chiral fate of the PD-

(15) If the chiral perturbation mechanism is similar among the reactions, $\delta\Delta S^{\ddagger}$ and $\delta\Delta H^{\ddagger}$ should show the isokinetic relation in both of the processes, and thus those differences, $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$, also have a linear relationship. For examples of an isokinetic relationship (or compensation) in differential activation enthalpy ($\Delta\Delta H^{\ddagger}$) and entropy ($\Delta\Delta S^{\ddagger}$), see: (a) Gallicchio, E.; Kubo, M. M.; Levy, 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. Also see: (c) Ottosson, J.; Rotticci-Mulder, J. C.; Rotticci, D.; Hult, H. *Protein. Sci.* **2001**, *10*, 1769−1774.

tethered reaction should be predetermined during the formation of the encounter complexes. The methyl groups on the tether stereocontrol the process to achieve the encounter states, and the difference in the encounter states is carried over to the product ratio.

Conclusions

From analysis of the newly introduced chiral perturbation factor, we have concluded that the methyl groups on the PD tether control the stereochemistry in the entropy term. Entropy control of an asymmetric synthesis is a new concept of reaction design and can be achieved with small a perturbation enthalpy and with sufficient difference in the frequency factors.[16] The differential frequency factor can be caused either by enantiodifferentiating fixation of the reactant before the formation of the encounter complex or by placement of the reagent in the chiral circumstances to regulate the reactant approach to the reaction site. The selectivity of such a reaction has less temperature dependence, and thus, it is apparently entropy controlled; however, in general, only a specific reactant can be applied to each reaction system, as is the case in biological reactions and some templated reactions.[17] The chiral-tethered reaction is an exception due to its characteristic stereocontrol mechanism; the chiral source straightforwardly regulates the relative geometry of the reactant and the reagent moieties.

Experimental Section

Preparation of Substrates 1a−e. A phenyl group was introduced to the optically active tether part by the Mitsunobu reaction. Stereochemically pure (2*R*,4*R*)-2,4-pentanediol, (2*S*,4*S*)-2,4-pentanediol, (3*R*)-1-benzoyloxy-3-butanol, and (3*R*)-3-(2-tetrahydropylanyloxy)-1-butanol and achiral 1,3-propanediol were converted to the corresponding monophenyl ethers under the complete stereoinversion (69−99% yield). After the deprotection (for **1c** and **1d**) or the inversion of the remaining hydroxy group (for **1b**), a diazo acetate group was introduced at the other hydroxy group of the tether to give **1** (60−80% yield for two steps).

Preparation of 2. To a solution of $Rh_2(OAc)_4$ (ca. 30 mg) in CH_2Cl_2 (80 mL) was added dropwise a solution of **1** (1−2 g) in CH_2Cl_2 (80−160 mL) in 3 h at room temperature. The mixture was concentrated and then purified by column chromatography on silica gel (elution with 20% ethyl acetate in hexane) to give **2**. The isolated yields of **2** are given in Table 1. Stereochemistries of **2** were determined by NOE experiments.

Determination of Stereoselectivity. To a solution of **1** (ca. 20 mg) in dichloromethane (5 mL) was added a catalytic amount of $Rh_2(OAc)_4$ under a nitrogen atmosphere at a constant temperature controlled within ±1 °C. The reaction at 60 °C was carried out in a flask sealed with a septum cap. The reaction at 0 °C takes 1−2 h to consume the reactant as determined by TLC analysis, while the reaction at 60 °C was complete within 1 min. The reaction mixture was concentrated under vacuum and immediately dissolved in dry ether (1 mL). This solution was added to a suspension of $LiAlH_4$ (ca. 30 mg) in ether (3 mL) at 0 °C. The obtained diols were employed for analysis. Authentic samples for both diastereomers of the diols were prepared through the methanolysis of **2a−d** ($MeOH/K_2CO_3$/rt) with accompanying epimerization at the α-position of the carbonyl group. Reducing the methyl esters with $LiAlH_4$ afforded 1:1 diastereomeric mixtures of the diols. The diols were converted to diacetates (acetic anhydride/pyridine) and analyzed by capillary GLC (OV-1, 25 m) under the baseline separations.

The obtained diastereomer ratios of **2** were confirmed to be equal to the reaction selectivity, k_R/k_S, by the following experiments. The epimerization during the reaction was discarded because elongation of the reaction time did not evidently affect to the product ratio. Only in the reactions at 60 °C did values of the de become 1−2% lower, after 3.5 h of standing under the reaction conditions, than those obtained just after completion of the reaction at 5 min. The possible epimerization of **2** during the transformation to the diols was discarded by the experiment in the presence of D_2O. When D_2O was added before the concentration of the rhodium-catalyzed reaction of **1**, the obtained diol did not contain any detectable deuterium (by ^1H NMR analysis), and thus the epimerization of **2** through the enolate was determined to be negligible during this transformation procedure.

Determination of the Relative Reaction Rate of 1. The adducts **3a−e** were prepared from the $Rh_2(OAc)_4$-catalyzed reaction of **1a−e** in benzene. When the reaction of **1** was carried out in a mixture of benzene and dichloromethane, a mixture of **2** and **3** was obtained. The reactions at 20 °C were performed with concentrations of **1** at 9.15 mM and benzene at 0.38, 0.56, 1.12, 1.61, and 2.81 M. The reactions at the other temperatures of 0, 40, and 60 °C were studied with benzene at 1.6 M (for **1a**,**b**) or 0.4 M (for **1c−e**). The ratio of (11a*S*)-**2** to **3** was determined by taking the integration of the α-protons of the ester groups on ^1H NMR.

The relative reactivity between benzene and alkoxybenzene at the 1,2-position to the rhodium carbenoid addition was determined by the reaction of a mixture of benzene and alkoxybenzene with ethyl diazoacetate. The product ratios and regioselectivities were determined by the ^1H NMR analysis.

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Supporting Information Available: Details of the syntheses of **1**, spectral data of all new compounds, and data for the selectivity and kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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