Entropy-Driven Asymmetric Synthesis with Chiral Tethers

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Dedicated to Professor Yoshikazu Sugihara on the occasion of his 60th birthday

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The 2,4-pentanediol (PD)-tethered reaction is a stereocontrolled reaction having versatile applicability. When reactant and reagent elements are connected through a PD tether prior to their reaction, stereochemical purity of the product is very high for nine different types of reactions so far studied. Selectivity of one of the reactions shows temperature independency over a wide range from –78 to 150 °C, which indicates that the stereocontrol is driven by the entropy term. The strict stereocontrol of this reaction at high temperatures can be extended to vapor phase reactions performed above 250 °C. To understand how the two methyl groups on the PD tether stereocontrol the reaction, a new parameter, a chiral perturbation factor, is introduced. By this analysis, it is disclosed that the methyl groups promote an activation entropy change for both the diastereomeric processes, and the strict stereocontrol is achieved when the changes have opposite signs.

1. Introduction

Mechanisms of unimolecular and intramolecular reactions regarding their selectivities are often discussed separately from those of bimolecular and intermolecular reactions.[1] The uniqueness of the former reactions sometimes brings about wonderful benefits inaccessible with the latter to synthetic organic chemists, who like to perform exclusive formation of a desired product. A representative example is a series of reactions demonstrated by Breslow over 20 years ago; called biomimetic reaction.[2] With a pre-formed complex connecting two rigid parts of a reactant and a reagent through a covalent bond, the reaction site in the reagent piece can reach certain sites of the reactant piece to result in highly regio- and stereoselective formation of the product due to the strict restriction of the complex geometry. Because there is no chance for production of other stereoisomers unless intermolecular reactions take place, these reactions are even not classified as stereodifferentiating reactions, but the stereochemical fate of the reactions is predetermined at the formation step of the reactant/substrate complexes. In 1986, we started a new series of asymmetric syntheses consisting of intramolecular reactions using 2,4-pentanediol (PD), a widely available chiral compound in both enantiomeric forms. A prochiral reactant and a reagent are connected through the diol as a chiral tether, and the species generated by the activation of the reagent moiety reacts with the reactant moiety placed at the other end of the tether. Due to the flexible and sufficiently long tether that causes a minimal geometrical strain all the way

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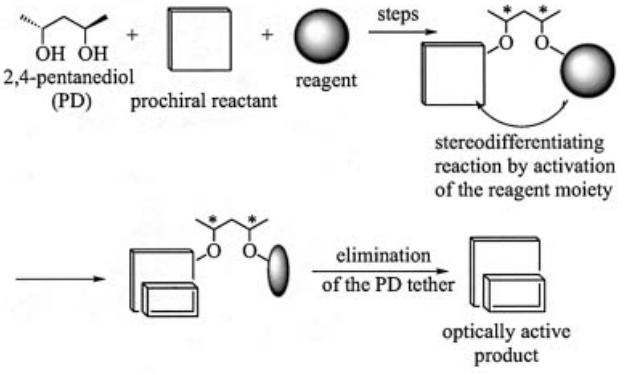
MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

through the internal reaction, the reaction field is loose and broad, and thus varied combinations of the moieties can be employed. Overall procedure of the PD-tethered reaction consists of incorporation of the two moieties, activation of the reactant part to promote the stereodifferentiating internal reaction, and then elimination of the PD tether to give an optically active product as illustrated in Scheme 1.[3] Similar asymmetric syntheses can be performed when an active species is introduced in situ at a hydroxy group of the PD carrying a reactant moiety at the other hydroxy group.



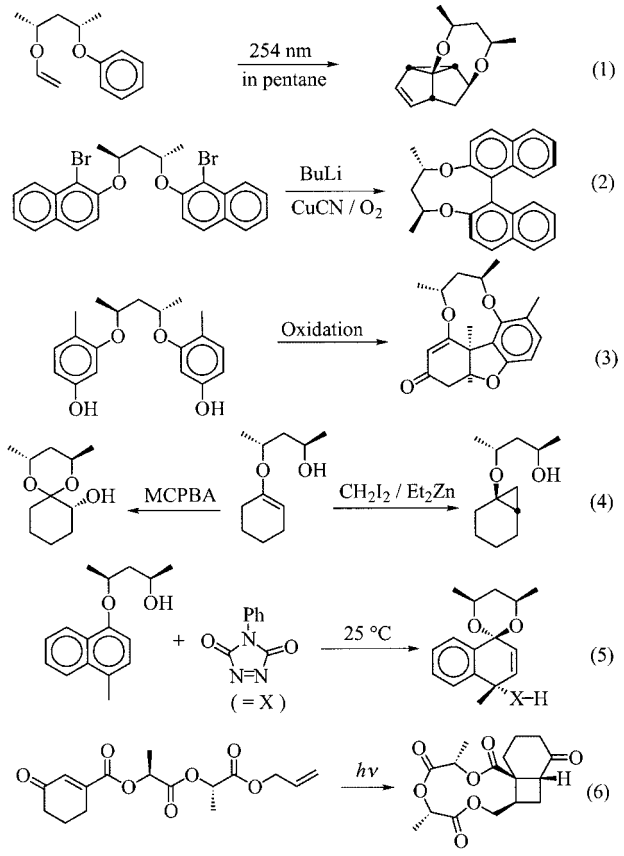
Scheme 1. Asymmetric synthesis with 2,4-pentanediol tether

Some examples of the tethered reactions are shown in Scheme 2.[4] Reactions (1)−(3) display typical examples of the PD-tethered reaction. Reactions (4)−(5) show examples tethering the active species in situ. Reaction (6) indicates an example using another chiral tether, which is designed similarly to the PD tether in the property. So far as we have studied, the PD-tethered reactions were found to produce single isomers in nine different types of reactions including (1)−(5), and it was proved that the PD tether is a reliable and diverse reaction design for asymmetric synthesis.

Stereocontrol design of the PD-tethered reaction is distinctive from Breslow's work. The stereocontrollability of the PD tether does not look high, nor is it difficult to estimate which stereoisomer is mainly produced because of the loose restriction of the relative geometry of the reaction sites induced by the tether. In general, wide applicability can be achieved by such loose reaction control, while high selectivity necessitates strict control. The PD tether is an outstanding stereocontroller because it displays a well-balanced tip between the diversity and stereocontrollability of the incompatible factors in asymmetric synthesis. The question raised here is why the PD tether can control the reaction so effectively only with the two methyl groups on the tether. In this review, our current understanding of the stereocontrol mechanism is presented.

2. Temperature-Independent Stereocontrollability

Lower temperature is, in general, required to achieve better selectivity in asymmetric synthesis. Therefore, a satisfactory result can be obtained at the lower limit of the temperature to afford the product in a reasonable reaction rate. This section produces experimentally rather uncommon but theoretically normal properties; the selectivity does not depend on the reaction temperature.

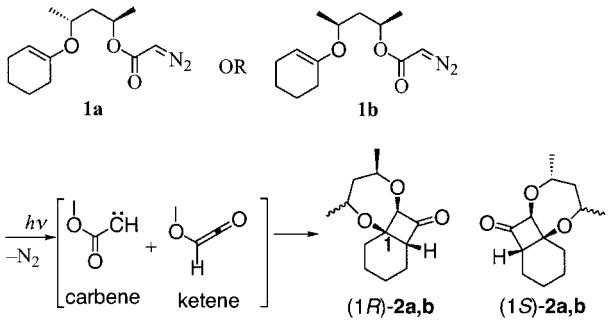


Scheme 2. Examples of asymmetric syntheses with chiral tether

2.1 Ketene-Olefin Cycloaddition by Solution Photolysis

To elucidate the stereocontrol factors of the PD-tethered reaction, the stereoselectivity was studied carefully by performing the reaction over a wide range of temperature. Cycloaddition reaction of an olefin and a ketene was selected because the ketene can be readily generated by the photolysis of a diazo ester irrespective of the temperature at which the subsequent cycloaddition takes place, though this reaction has the disadvantage of formation of the carbene (ca. two third of the diazo ester) that is trapped by the solvent. When a pentane or decane solution of a PD-tethered substrate **1a** was irradiated with a mercury lamp, **2a** produced by the addition of the generated ketene with the internal olefin was obtained in 33% yield (Scheme 3).[5] In contrast, the reaction of **1b** to **2b** was ineffective and did not give any clear product other than the solvent adducts via the carbene. In the reaction of **1a**, the stereoisomer (1*R*)-**2a** predominated as the major cycloadduct produced, and its stereoisomer (1*S*)-**2a** was not detected. The highly stereoselective formation of the cyclobutanone **2a** is not

surprising for a PD-tethered reaction but is merely an additional example. A remarkable feature of this reaction, however, is that the high stereoselectivity was maintained even at 150 °C, and in the temperature range from −78 °C to that high temperature, no sign of (1*S*)-**2a** was detected (< 0.5%). The observed performance is much more than expected from the simple structure of the PD tether.



Scheme 3. PD-tethered [2+2] ketene-olefin cycloadditions

A mechanistic study with regard to the selectivity is not possible when the minor isomer is undetectable. The key to address this issue is in the non-production of **2b** by the photolysis of **1b**, where the ketene must be generated in the same fraction as that with **1a**. The difference between the two diastereomeric substrates can be due to the stereodirections of the two methyl groups on the tether; matching in the tether of **1a** while conflicting in **1b**. In this context, singly methylated tethers in **1c** and **1d** (see Figure 1) have less stereocontrollability than the PD tether in **1a**, and association of the selectivities with **1c** and **1d** represents the results with **1a**.

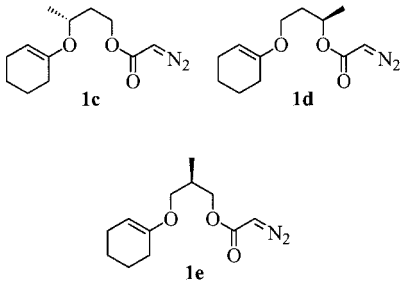


Figure 1. Substrates having singly methylated tethers

Stereoselectivity of the reactions of **1c** and **1d** and their regioisomer **1e** was studied under the same photolysis conditions as the reactions of **1a** and **1b**. With the substrate **1c**, the selectivity of the intramolecular cycloaddition was again very high resulting in > 99% diastereomeric excess (*de*) of cyclobutanone (1*R*)-**2c** in the temperature range of −78 °C to 130 °C. The strict stereocontrol with the singly methylated tether is welcome from the synthetic viewpoint, but again its level is too high to analyze the reaction selectivity with this substrate. Fortunately, the other two singly methylated tethers in **1d** and **1e** have imperfect stereocontrollability in the cycloaddition resulting in mixtures of the stereoisomers, (1*R*)-**2** and (1*S*)-**2**. The *de* values of the obtained **2d** and **2e** at room temperature were 85% and 10%, respectively. Because the major stereoisomers of both **2c** and **2d** have (1*R*)-stereochemistry, the two-methyl groups in the tether of **1a** should work cooperatively in the stereodirection of the addition, while the directing effects compete in the reaction of **1b**. The distinctive nature of these tethered reactions is that the stereoselectivity is almost independent of the temperature. Through the reaction temperatures from −78 °C to 130 °C, the *de* values observed were within the range of 84−88% for **2d** and 10−11% for **2e**. The Arrhenius plots regarding the selectivity, ln [(1*R*)-**2**/(1*S*)-**2**] vs. 1/*T*, constitute "flat" lines in the temperature range twice as wide as in Kelvin (Figure 2). This temperature independency of the stereoselectivity can be the origin of the strict stereocontrol at the high temperature in the reaction of **1a** and **1c**.

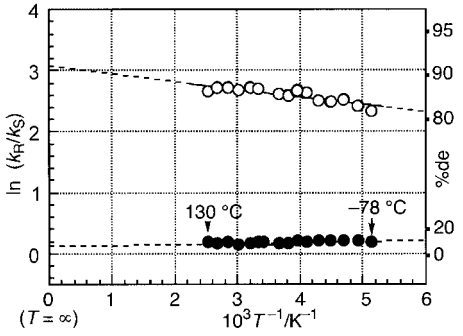
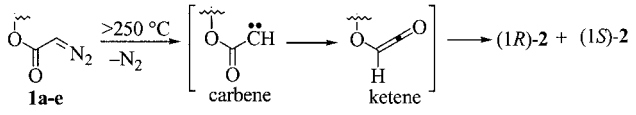


Figure 2. Plots of $\ln(k_R/k_S)$ as a function of $1/T$ for the reactions of **1d** (open circles) and **1e** (black filled circles); the abscissa is extended to $T = \infty$ to show the intercepts

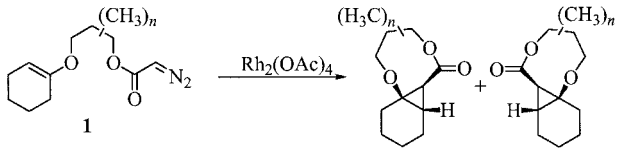
2.2 Asymmetric Synthesis in Vapor

The temperature-independent stereocontrollability of the chiral tethered reactions with **1** prompted us to perform the first vapor phase-asymmetric synthesis. Flash vacuum pyrolysis (FVP) is a flow reaction activated by short contact of a substrate with a surface heated to high temperature. For a diazo ester substrate like **1**, denitrogenation requires high reaction temperature of at least 250 °C. The generated carbene from **1** in the vapor phase has fewer molecules around it in contrast to the solution photolysis and gives the ketene through the Wolff rearrangement, unless that process is slower than the internal carbene-olefin addition (Scheme 4). The reaction of **1a** pyrolyzed at 270 °C proceeded as desired, and the product obtained collected at the cold trap was solely **2a**, and the isolated yield was as high as 70%.[6] However, the reaction over 300 °C was accompanied by a secondary reaction; decomposition of **2** to give the cyclopropane compounds, which are identical with the product shown in Scheme 5.[7] So far as we have studied, the reaction of **1a** and **1c** resulted in over 99% *de* of (1*R*)-**2** up to 350 °C, and the temperature range of the strict stereo-

control with these tethers was extended from −78 °C to 350 °C, that is from 195 to 623 Kelvin.



Scheme 4. Tethered [2+2] ketene-olefin cycloadditions in vapor



Scheme 5. Rhodium catalyzed cyclopropanation with **1**

The results with **1d** and **1e** are slightly more complicated for determining the selectivities of the cycloaddition. Their reaction at 260 °C gave 82% *de* of **2d** and 13% *de* of **2e**; both values are well consistent with the results obtained by the photolysis in solution. At 350 °C, the *de* values were decreased to 72 and 12%, respectively, and at 400 °C, the decrease became obvious affording 17 and 3% *de*. The falling of the *de* at the higher temperature was attributable to the secondary reaction of **2** because the FVP of **2d** resulted in a 5−7% decrease even at 300 °C. From the selectivity of the photochemical and the thermochemical reactions, it is concluded that the selectivity is commonly within a narrow range peculiar to each tether.

Predominant formation of **2** by the FVP at 270 °C in keeping the *de* values obtained by the solution photolysis discards the possibility that the carbene route in the solution contributed the product stereoselectivity by the kinetic resolution of the reactant conformers. The success in the FVP study can be the first step in using an industrially advantageous vapor phase reaction in asymmetric syntheses.

2.3 Rate-Determining Step and Selectivity

The stereoselectivity of an intramolecular and irreversible end-to-end reaction is classified into three modes by the rate-determining steps as the Gibbs energy profiles in Figure 3 show.[8] The PD-tethered reactions must be expressed by one of them or their combination. Mode A has the rate-determining steps at the end of the reaction coordinates near the products, and a ratio of their rates simply governs the product selectivity. In mode B, the product-forming steps are faster than the conformational change in the activated reactant molecule, and thus, the selectivity is determined by the rates of the conformational changes to yield reactive conformers for the intrinsic reactions. Mode C also has slower conformational changes, but the conformers produced from a common precursor are isolated in energy minima connected to the intrinsic reaction pathways.[9] In this case, the selectivity of the final product is independent of the rate-determining intrinsic reactions, but it depends on the composition of the kinetically quenched conformers and is predetermined.

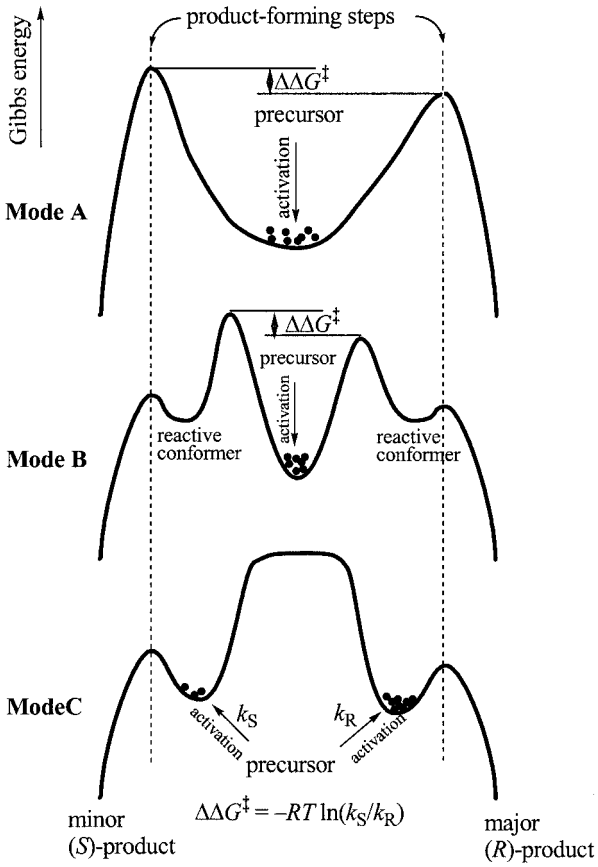


Figure 3. The three stereochemical modes of intramolecular end-to-end reaction having different rate-determining steps

Thermodynamic treatment of the selectivities in mode A and mode B leads to the differential activation free energy $\Delta\Delta G^{\ddagger}$ ($= \Delta G^{\ddagger}_{S} - \Delta G^{\ddagger}_{R}$) indicated in Figure 3. In the case of mode C, the product ratio is governed by a predetermined population ratio of the conformers, and thus, the selectivity depends on the $\Delta\Delta \cong G^{\ddagger}$ for the formation of the conformers of the activated species (Figure 3). When generation of the activated species is very fast as is the photolysis of **1**, the observed rate ratio is essentially equal to a population ratio of the corresponding conformers in the precursor. In any mode, the differential activation free energy $\Delta\Delta G^{\ddagger}$ is divided into a temperature-dependent factor, differential activation enthalpy $\Delta\Delta H^{\ddagger}$, and an independent factor, differential activation entropy $\Delta\Delta S^{\ddagger}$, as represented in Equation (1).

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

2.4. Differential Activation Parameters

The treatment of the results with **1d** in Figure 2 by Equation (1) results in −0.23 kcal·mol^{-1} of $\Delta\Delta H^{\ddagger}$, the value of which constitutes only a part of the reaction selectivity of 1.5 kcal·mol^{-1} in $\Delta\Delta G^{\ddagger}$ (20 °C). Thus, the remaining majority of the selectivity is governed by the entropy term $T\Delta\Delta S^{\ddagger}$. Because the orientation of the selectivity by the enthalpy and entropy terms are opposite, the accurate expression must be that 1.73 kcal·mol^{-1} of $T\Delta\Delta S^{\ddagger}$ is reduced in part to 1.5 in $\Delta\Delta G^{\ddagger}$ by the enthalpy term. In asymmetric syntheses, it is not uncommon that entropy control of the selectivity exceeds the enthalpy control at a high reaction temperature,[10] but in the reaction of **1d**, the entropy term contributes the major part of the selectivity even at −78 °C ($T\Delta\Delta S^{\ddagger}$ = 1.2 kcal·mol^{-1}).[11] Although the reaction selectivity with **1e** is very poor, its temperature dependency indicates the same tendency as that with **1d**; the reaction is stereocontrolled mainly by the entropy term $T\Delta\Delta S^{\ddagger}$ of 0.08 kcal·mol^{-1} at 20 °C, which is much larger than the $\Delta\Delta H^{\ddagger}$ of 0.03 kcal·mol^{-1}.

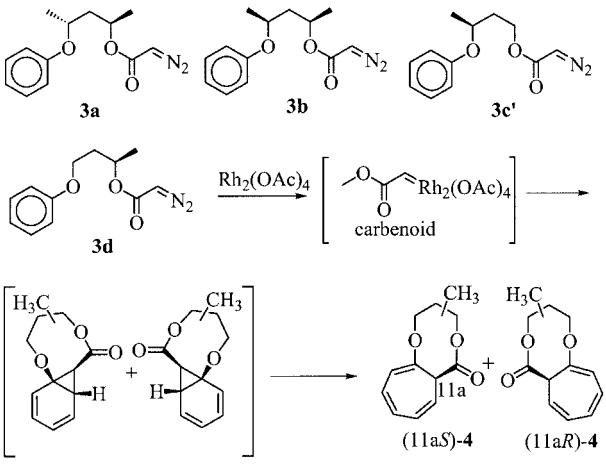
For the reaction of **1a**, the selectivity dependency on the temperature has never been known due to the low production of the stereoisomer below the detection limit, but the entropy-driven stereocontrol found in the reactions of **1d** and **1e** should also contribute to the enormous stereocontrol with the PD-tethered substrate **1a**. The mode of the selectivity with regard to the rate-determining steps is also experimentally unproved for the reactions of **1**. At this stage, mode A is the most proper model judging from the activation energy determined for the cycloaddition of ketene and ethylene (E_a = 32 kcal·mol^{-1})[12] and the expected potential barriers for rotation of the six bonds in the tether to interconvert the conformers (3−8 kcal·mol^{-1} by the MM2 calculations). Nevertheless, the activation free energy for the cycloaddition with **1** can be lower than expected,[13] and solvation may make the rotation barrier higher than expected from the simple calculation.

3. Chiral Perturbation Approach

A chiral source incorporated in any asymmetric synthesis causes formation of two stereoisomers unevenly by affecting the two parallel reaction rates differently. When the effects are small, their difference must be small, and then the product selectivity is poor. Contrarily, the large effects can result in sufficient difference to achieve the high selectivity, but this does not always happen. Dissymmetrical incorporation of a certain atom, group or reagent affects both the stereoisomeric processes, and the selectivity is the result of cancellation or cooperation of these perturbations. In this section, the origin of the selectivity due to the PD tether is investigated by the analysis of the reaction rates; how the methyl groups on the tether perturb the intramolecular reaction rates.

3.1 Buchner Reaction with Chiral Tether

Stereoselective intramolecular Buchner reaction of **3a-d** with a rhodium catalyst necessitates differentiation of the two vicinal stereotopos as shown in Scheme 6. The conformational change to move the rhodium carbenoid part from one reaction transition state to the other is smaller compared with the reaction of **1**, where inversion of the cyclohexene ring or turnaround of the reagent moiety is required to move between the two transition states. The two possible intramolecular [2+1] cycloadducts must readily isomerize to (11a*S*)-**4** and (11a*R*)-**4**, stereospecifically. The stereochemical purities of the obtained **4a-d** therefore display the selectivities of the stereotopos-differentiating carbenoid addition controlled by the chiral tether. Table 1 gives the stereoselectivity observed at 20 °C.[14]



Scheme 6. Rhodium carbenoid addition to an internal aromatic ring

In this reaction, the best result is achieved with a PD tether of different stereochemistry from that found in the reaction of **1**; **3b** gives better results of over 99.6% *de* of (11a*S*)-**4b** than those of **3a**, which performs moderately high stereocontrol to result in 92% *de* of (11a*S*)-**4a**. The substrate **3b** and its analogues can be prepared easily from (2*R*,4*R*)-PD and phenol analogues under the Mitsunobu conditions as an enantio- and diastereomerically pure form, and their reactions give essentially optically pure cycloheptatriene **4b** and its analogues in very high yields.[15] As expected from the results with **3a** and **3b**, **3c′** (antipode of **3c**) and **3d** also gave (11a*S*)-**4** as major isomers. Thus, two methyl groups in **3b** work cooperatively to give the (11a*S*)-product, while those in **3a** compete with each other for their stereodirection. Formation of **4a** in favor of the (11a*S*)-isomer from **3a** is reasonable because **3d** shows higher stereoselectivity than **3c′**.

3.2 The Effective Molarity and Its Standardization

The values of effective molarity (EM) for the formation of **4** represent the effectiveness of the intramolecular additions of the carbenoids generated from **3a-d** and were determined by the reaction in the presence of benzene in varied concentrations, where the carbenoid adds to both the

Table 1. Stereoselectivities, effective molarities (EM), and chiral perturbation factors (α) for reactions of **3a**−**d** at 20 °C

Substrate	% *de* of **4**	$k_{(11aS)}/k_{(11aR)}$	$EM_{(11aS)}$ (mol·dm^{-3})	$\alpha_{(11aS)}$	$\alpha_{(11aR)}$
3a	92	24	2.3 ± 0.3	64 ± 10	2.7 ± 0.4
3b	> 99.6	> 500	5.0 ± 0.1	140 ± 3	< 0.29 ± 0.01
3c′	62	4.2	0.42 ± 0.04	12 ± 1	2.9 ± 0.3
3d	95	41	0.32 ± 0.02	9.1 ± 0.5	0.22 ± 0.01

internal and external aromatic groups. The relative rates of formation of (11a*S*)-**4** vs. the benzene adduct were converted into the $EM_{(11aS)}$ values by the calibration with the independently determined reactivity ratio of benzene/anisole against the carbenoid and their reaction-site numbers. The $EM_{(11aS)}$ values are larger with the doubly methylated substrates, **3a** and **3b**, than those of the singly methylated ones, **3c′** and **3d** (Table 1). This acceleration of the intramolecular cyclization reaction is classically known as the Thorpe−Ingold effect.[16] Briefly, the acceleration by the methyl substitution is large in a small ring formation (e.g., a six-membered ring) mainly by a decrement in the activation enthalpy, moderate in a medium ring formation (e.g., a nine-membered ring) mainly by entropy factor, and small in a large ring (e.g., a 10-or-more-membered ring).[17] Substrates **3** formally undergo reaction through a nine-membered ring formation, where the methyl substitution can affect the entropy term.

To exhibit the role of these phenomena in the reaction selectivities with **3a-d**, a reference substrate **3f** that carries 1,3-propanediol as the non-methylated achiral tether was introduced. The reaction of **3f** gave a racemic mixture of **4f** ($k_{(11aS)}/k_{(11aR)} = 1$), and the EM value for the formation of a single enantiomer was determined to be 0.035 mol·dm^{-3}. Using this value as a standard, the relative reaction rates of **3a**−**d** to give (11a*S*)-**4a**−**d** were calculated and given in Table 1 as $\alpha_{(11aS)}$. The order of these rate enhancements is not large; therefore, the other cyclization process to give (11a*R*)-**4** must not be much accelerated to explain the observed strict stereocontrol. In fact, $\alpha_{(11aR)}$ calculated from $\alpha_{(11aS)}$ and the (11a*S*)/(11a*R*) ratio in **4** (Table 1) are small, and some values are even less than unity, which indicates deceleration of the reaction.

The values of $\alpha_{(11aS)}$ and $\alpha_{(11aR)}$ represent the effects of the methyl substitution on the intramolecular reaction rate divided into each stereoisomeric process, and the ratio of the stereoisomeric α values is certainly equal to the reaction selectivity in the ratio ($\alpha_{(11aS)}/\alpha_{(11aR)} = k_{(11aS)}/k_{(11aR)}$). Because the methyl substituents on the tether are the origin of the stereocontrol, the α values are the governing factor in the selectivity and α was named the "chiral perturbation factor". The selection of a standard reaction (or a reference substrate) involves other options and depends on which structural character of the stereocontrol one wants to extract. The selection of the presently employed reference **3f** is intended to display the role of the methyl groups and is intuitionally reasonable because of its simple structure. In fact, such standardization has been well employed for the analysis of the rate-controlling factors in cyclization reactions.[18]

3.3 Perturbation Enthalpy and Entropy

Thermodynamic treatment of the temperature dependency of the α values gives the temperature dependent factor $\delta\Delta H^{\ddagger}$ and the independent $\delta\Delta S^{\ddagger}$, the values of which are suggestive of the mechanism of how the reaction is accelerated or decelerated. Having two pairs of the energy terms corresponds to the separation of the $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values using the standard reaction, and thus, differences between diastereomeric pairs are equal to the differential activation energies (e.g., $\delta\Delta H^{\ddagger}_{(11aR)} - \delta\Delta H^{\ddagger}_{(11aS)} = \Delta\Delta H^{\ddagger}$). The $\delta\Delta H^{\ddagger}$ and $\delta\Delta S^{\ddagger}$ for **3a**−**d** obtained from the experiments under the limited temperature range (0−60 °C) are mapped in a graph indicating enthalpy vs. entropy perturbations of the reaction rate in Figure 4.[19]

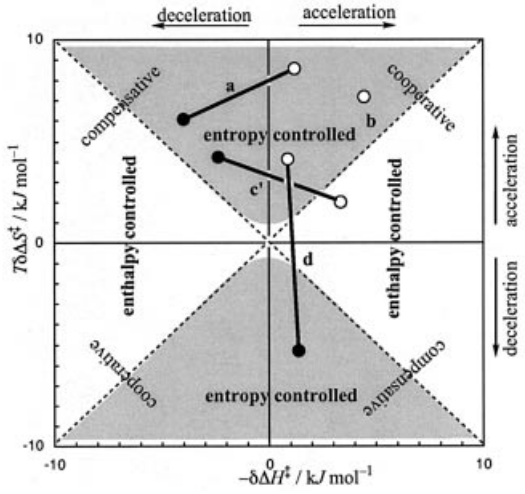


Figure 4. Enthalpy and entropy plots for chiral perturbation factors for (**11a*S***) products (open circles) and (**11a*R***) (black filled circles) of the reaction with **3a**−**d** at 20 °C

Except for the major (11a*S*)-product formation with **3c′**, the chiral perturbation factors α are governed by the entropy term by more than 50% (20 °C). Deceleration found in the process from **3d** to (11a*R*)-**4d** is shown to be mostly governed by the entropy term, and again the reaction with the tether-**d** results in a small temperature dependency of the stereoselectivity. The perturbations in enthalpy, which should be the results of different steric effects on the ground and the transition states, accelerate the formation of (11a*S*)-**4** and decelerate that of (11a*R*)-**4** for the reactions of **3a** and

3c′. The values of $\delta\Delta S^{\ddagger}$ are large especially in the doubly methylated substrates, **3a** and **3b**. The small $\Delta\Delta S^{\ddagger}$ value in the reaction of **3a** is ascribed to the cancellation of the perturbation entropies, $\delta\Delta S^{\ddagger}_{(11aR)}$ and $\delta\Delta S^{\ddagger}_{(11aS)}$. The perturbation entropies by the methyl substitution are expected to be caused by destabilization of the ground state under the conventional analysis, but the decelaration effect on the formation of (11a*R*)-**4d** clearly indicates that the determinant factor in the perturbation entropy is not so simple but the transition states are also affected by the methyl substituents in entropy term. Although the rhodium carbenoid is a very active species and the estimated activation energy for the Buchner reaction is not high,[20] reasonable changes of the EM values by the substitution to the phenyl ring in **3** and insensitivity of the *de* to the existence of competitive reactions suggest that this reaction is also classified in mode A; the reaction selectivity as well as the rate was determined at the carbenoid addition step.[21]

4. Conclusions and Further Tasks

The asymmetric syntheses with the PD tether were suggested to be driven by the entropy term. The PD tether is flexible, but regulation of the relative geometry of the reactant and reagent moieties is still unambiguous. The weak and remote interaction between the chiral source (methyl groups) and the reaction site under the moderate regulation by the tethering seems to be the key to drive the asymmetric synthesis by the entropy term. There are no universal asymmetric reaction design applicable to any reactions. Nevertheless, the chiral tethered reactions using PD or its simpler analogue have much wider applicability than regular asymmetric syntheses Entropy-driven asymmetric synthesis presented for the chiral tethered reactions is an unusual and outstanding stereocontrol concept and should show many benefits in the future in practical syntheses.

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