Acc. Chem. Res. **2000,** *33,* 715−727

Dynamic Thermodynamic Resolution: Control of Enantioselectivity through Diastereomeric Equilibration

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Received April 25, 2000

ABSTRACT

A theoretical foundation, tools for recognition and control, and recent examples of a class of asymmetric transformation termed dynamic thermodynamic resolution are presented. Enantioselective reaction pathways that involve an induced diastereomeric equilibration to intermediates, which are configurationally stable on the time scale of a subsequent reaction, are illustrated. Dynamic thermodynamic resolution differs from the classic, well-documented pathways of kinetic resolution and dynamic kinetic resolution in that equilibration and resolution can be operative on one system in separate controllable steps. This approach offers a high level of flexibility and provides multiple opportunities for optimization of enantioselectivity.

Introduction

Asymmetric synthesis has become a major focal point of synthetic chemistry in the past two decades. Reactions which provide highly enantioenriched products from racemic substrates offer many advantages for asymmetric syntheses but require a step in which significant resolution is achieved. Differences in the chemical or physical properties of diastereomers are at the heart of resolutions of chiral molecules.[1]

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A conceptual basis for a reaction in which the enantiomers **A** and *epi*-**A** are converted to resolved **D** is illustrated in Figure 1. In the most general case, **A** and *epi*-**A** engage in a chemical reaction or physical interaction with **B***, a chiral, nonracemic species, to form **A•B*** and *epi*-**A•B***. The species **B*** can be a chiral ligand, a chiral auxiliary, or even a chiral solvent.

The two diastereomeric complexes may or may not equilibrate once formed (k_1, k_{-1}). Subsequently, **C** reacts with **A•B*** (k_2) and *epi*-**A•B*** (k_3) to provide **D** and *epi*-**D,** respectively, with concomitant release of **B***. Three limiting cases may be envisioned depending on the relative magnitudes of k_1, k_{-1}, k_2, and k_3.

If the diastereomeric complexes **A•B*** and *epi*-**A•B*** do not interconvert and one reacts more rapidly with **C** ($k_1 = k_{-1} = 0$ and $k_2 \neq k_3$), then a kinetic resolution may be effected.[2,3] Such processes are well documented, and many occur by selective reaction of **A•B*** and *epi*-**A•B*** with **C** wherein the chiral reagent **B*** provides the requisite differences in molecular interactions in diastereomeric transition states. In classic resolutions by selective crystallization, a physical process occurs with the diastereomeric energy difference provided by crystal lattice energies. In chiral chromatography, the differences in diastereomeric adsorption/desorbtion energies are amplified by repetitive events. The chemical process is represented by the energy diagram in Figure 2a, and the final product ratio, **D**/*epi*-**D**, will depend on the relative rates of reaction (k_2/k_3), the percent conversion, and the populations of **A•B*** and *epi*-**A•B***.

If the diastereomers **A•B*** and *epi*-**A•B*** equilibrate more rapidly than they react with **C** (k_1, $k_{-1} \gg k_2$, k_3), the product ratio is determined by the difference in energies for the two diastereomeric transition states ($\Delta\Delta G^{\ddagger}$), as shown in Figure 2b. Such dynamic kinetic resolutions follow Curtin−Hammett kinetics, and the product ratios do not show a dependence on conversion.[4−8]

In a third scenario, **A•B*** and *epi*-**A•B*** can interconvert but do not equilibrate in the presence of the reagent **C** (k_1, $k_{-1} \neq 0$, k_2, $k_3 \gg k_1$, k_{-1}), as represented in Figure 2c. In this case, the thermodynamic ratio of **A•B***/*epi*-**A•B*** determines the final product ratio **D**/*epi*-**D** for reactions carried to complete conversion, but the relative rates of reaction, k_2 and k_3, affect product ratios at lower conversions. We have coined the term "dynamic thermodynamic resolution" to describe these processes and believe a number of reactions are best understood in terms of this reaction pathway.[9,10] These reactions always involve an induced diastereomeric equilibration which may or may not also be coupled with a kinetic resolution in the product-forming step to maximize stereoselectivity (vide infra). Dynamic thermodynamic resolution differs from kinetic resolution and dynamic kinetic resolution in that equilibration and resolution can be operative on one system in separate controllable steps.

An essential feature of dynamic thermodynamic resolution is that the resolution is not dependent on the

10.1021/ar000077s CCC: $19.00
Published on Web 07/29/2000

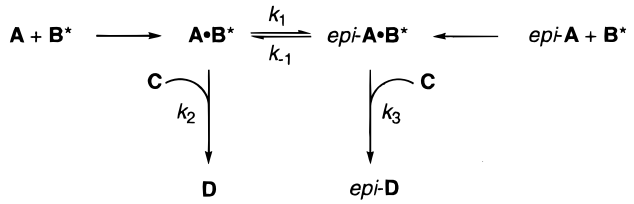


FIGURE 1. Reaction of enantiomers **A** and *epi*-**A** with **C** mediated by **B*** to provide resolved **D**.

reactions used to form the complexes. Hence, different methodologies and many systems are, in principle, amenable to this approach. Recognition and exploitation of this phenomenon can allow resolutions of systems not susceptible to kinetic or dynamic kinetic resolution.

In this Account we introduce a seminal example of a dynamic thermodynamic resolution, provide a theoretical background for the reaction pathway, and offer insights for recognition and control of this mode of asymmetric induction. Examples of diastereomeric equilibration that are not themselves dynamic thermodynamic resolutions, but that are important from a pedagogical standpoint, precede summaries of selected reports of dynamic thermodynamic resolution. The cases herein have been chosen from a number of laboratories and often involve organolithium chemistry. However, the phenomenon and the analysis are widely applicable.[11]

An illustrative example of a dynamic thermodynamic resolution is the complexation−substitution of the dilithio species **1** shown in Figure 3. When **1**, formed by deprotonation or tin−lithium exchange, is exposed to the chiral ligand (−)-sparteine (**2**), diastereomeric complexes **1•2** and *epi*-**1•2** are formed. Reaction with excess chlorotrimethylsilane provides **3** with enantiomeric ratios (er's) that vary significantly depending on the reactions conditions.[12−14] If the reaction is executed entirely at −78 °C, (*R*)-**3** is produced with an er of 56:44. If the reaction is carried out initially at −78 °C but warmed to −25 °C and then cooled to −78 °C before addition of the chlorotrimethylsilane, (*R*)-**3** is obtained with an er of 92:8. These results are best understood in terms of diastereomeric equilibration.[15]

The populations of the states **1•2**and *epi*-**1•2** can be established under either kinetic or thermodynamic control. In the first experiment, equal amounts of (*R*)-**1** and *epi*-**1** coordinate with (−)-sparteine to provide a kinetic ratio of **1•2**and *epi*-**1•2**. At −78 °C these species do not equilibrate, and the product ratio after reaction with an excess of electrophile reflects the approximately equal populations of **1•2** and *epi*-**1•2**. In the second experiment, a thermodynamic ratio of **1•2**and *epi*-**1•2** is produced by warming the reaction mixture to −25 °C. Cooling to −78 °C then halts the equilibration process. Subsequent reaction with an excess of electrophile provides a product ratio that reflects the thermodynamic populations of **1•2** and *epi*-**1•2,** and significant enantioenrichment is observed. The reaction pathways at both −78 °C and with warming to −25 °C are represented by the energy diagrams shown in Figure 3.[16]

Theory

Analyses of prototypical reactions in terms of the relative populations of the diastereomeric complexes, **A•B***and *epi*-**A•B***, and the rates of their reactions with **C** illustrate the possibilities for enantioenrichment under dynamic thermodynamic resolution. In the case of **1•2** and *epi*-**1•2** (Figure 3), the relative magnitudes of k_2 and k_3 do not affect the product ratio because the diastereomers are configurationally stable on the time scale of the reaction, and an excess of electrophile converts the entire populations of the diastereomers to products. The rate constants k_2 and k_3 are associated with diastereomeric transition states of unequal energy, and therefore the er of the product varies with extent of reaction.

A more complete description of the dynamic thermodynamic resolution mode of asymmetric induction is provided by the three hypothetical scenarios in Figure 4. In each case, the initial populations of **A•B*** and *epi*-**A•B*** are set according to their ratios at thermodynamic equilibrium, a distinctive feature of dynamic thermodynamic resolution. These diastereomers do not equilibrate on the time scale of the reaction with **C**, and once the reaction partner **C** is added, the ratios **A•B*** to *epi*-**A•B*** can deviate from equilibrium values.

For the graphs shown in Figure 4a-1, 4b-1, and 4c-1, calculation of product ratios (**D**/*epi*-**D**) as a function of percent conversion was performed by defining the kinetic expressions for the reactions that produce each of **D** and *epi*-**D** as shown in eq 1.

$$\frac{\mathrm{d}[\mathbf{D}]}{\mathrm{d}t} = k_2[\mathbf{C}][\mathbf{A{\bullet}B^*}]$$

$$\frac{\mathrm{d}[epi\text{-}\mathbf{D}]}{\mathrm{d}t} = k_3[\mathbf{C}][epi\text{-}\mathbf{A{\bullet}B^*}] \qquad (1)$$

Assuming the reaction partner **C** is present in large excess validates a pseudo-first-order approximation and permits solving the differential equations in eq 1 to give the expressions shown in eq 2. Here, $[\mathbf{A{\bullet}B^*}]_0$ and $[epi\text{-}\mathbf{A{\bullet}B^*}]_0$ are the thermodynamically determined initial amounts of **A•B*** and *epi*-**A•B***, and $k_{\mathbf{D}}$ and $k_{epi-\mathbf{D}}$ are the pseudo-first-order rate constants.

$$[\mathbf{D}] = [\mathbf{A{\bullet}B^*}]_0 - [\mathbf{A{\bullet}B^*}]_0\, \mathrm{e}^{-k_{\mathrm{D}}t}$$

$$[epi\text{-}\mathbf{D}] = [epi\text{-}\mathbf{A{\bullet}B^*}]_0 - [epi\text{-}\mathbf{A{\bullet}B^*}]_0\, \mathrm{e}^{-k_{epi\text{-}\mathbf{D}}t} \qquad (2)$$

The results can be plotted to show the change in enantiomeric ratio as a function of the percent conversion.[17] Figure 4a-1 shows the er of the product obtained from equal amounts of **A•B*** and *epi*-**A•B*** reacting with **C**, with the different relative rates (k_2/k_3) specified on the graph. At complete conversion, a racemic product is necessarily obtained, but high enantiomeric ratios could be realized if one diastereomer reacts considerably faster and the reaction is terminated before complete conversion. This reaction profile is similar to a classical kinetic resolution but differs in that the 1:1 ratio of intermediates may be reestablished at any point in the reaction through

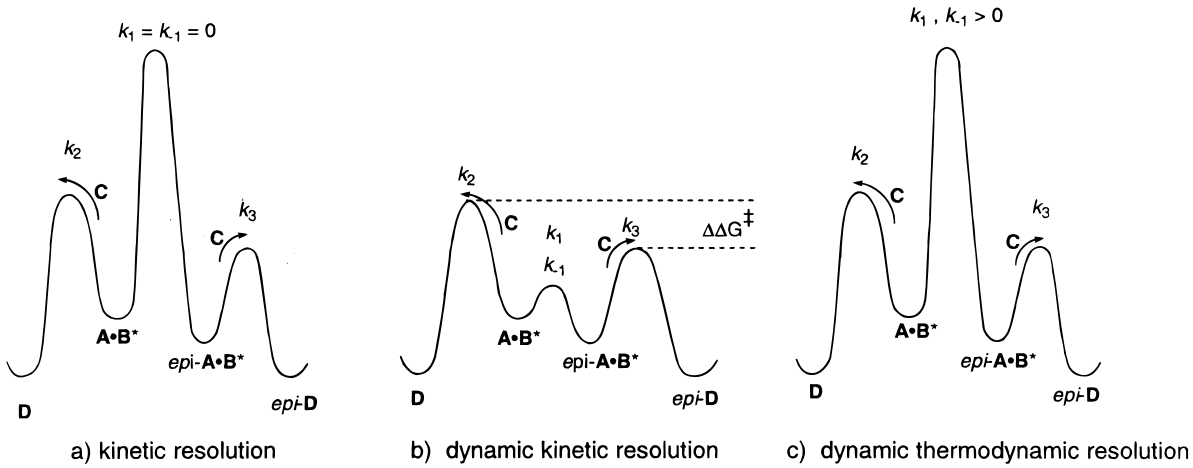


FIGURE 2. Energy diagrams for resolution of enantiomers **A** and *epi*-**A** through reaction with an achiral component **C** mediated by a chiral reagent **B*** by (a) kinetic resolution, (b) dynamic kinetic resolution, or (c) dynamic thermodynamic resolution.

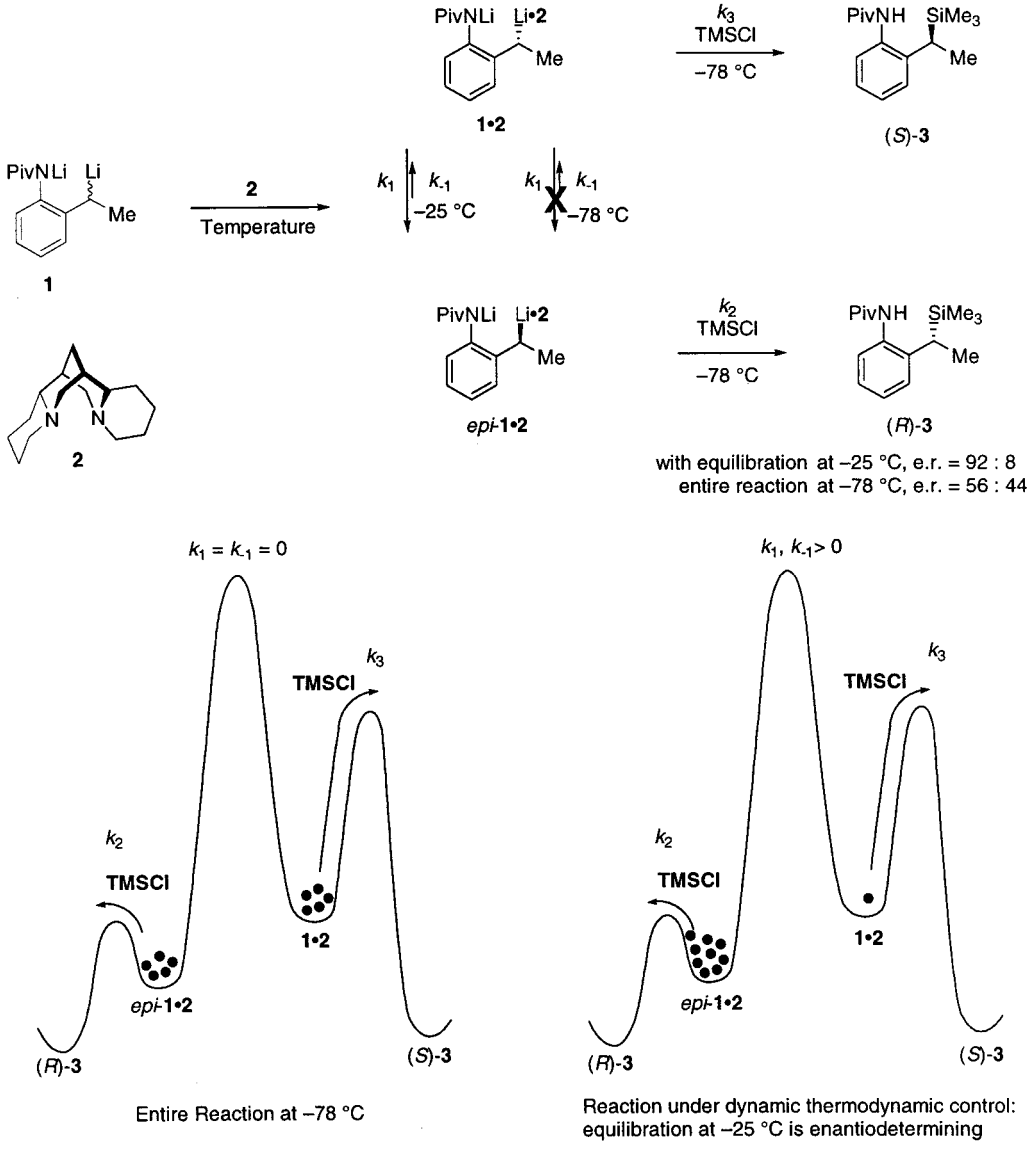


FIGURE 3. Results and energy diagrams for reaction between diastereomeric organolithium species **1•2**and *epi*-**1•2** and TMSCl under isothermal and variable temperature protocols.[16]

manipulation of experimental conditions. Figures 4b-1 and 4c-1 show cases when the initial populations of **A•B*** and *epi*-**A•B*** are unequal. For these hypothetical examples the initial ratio of **A•B*** and *epi*-**A•B*** is set as 4:1. The more

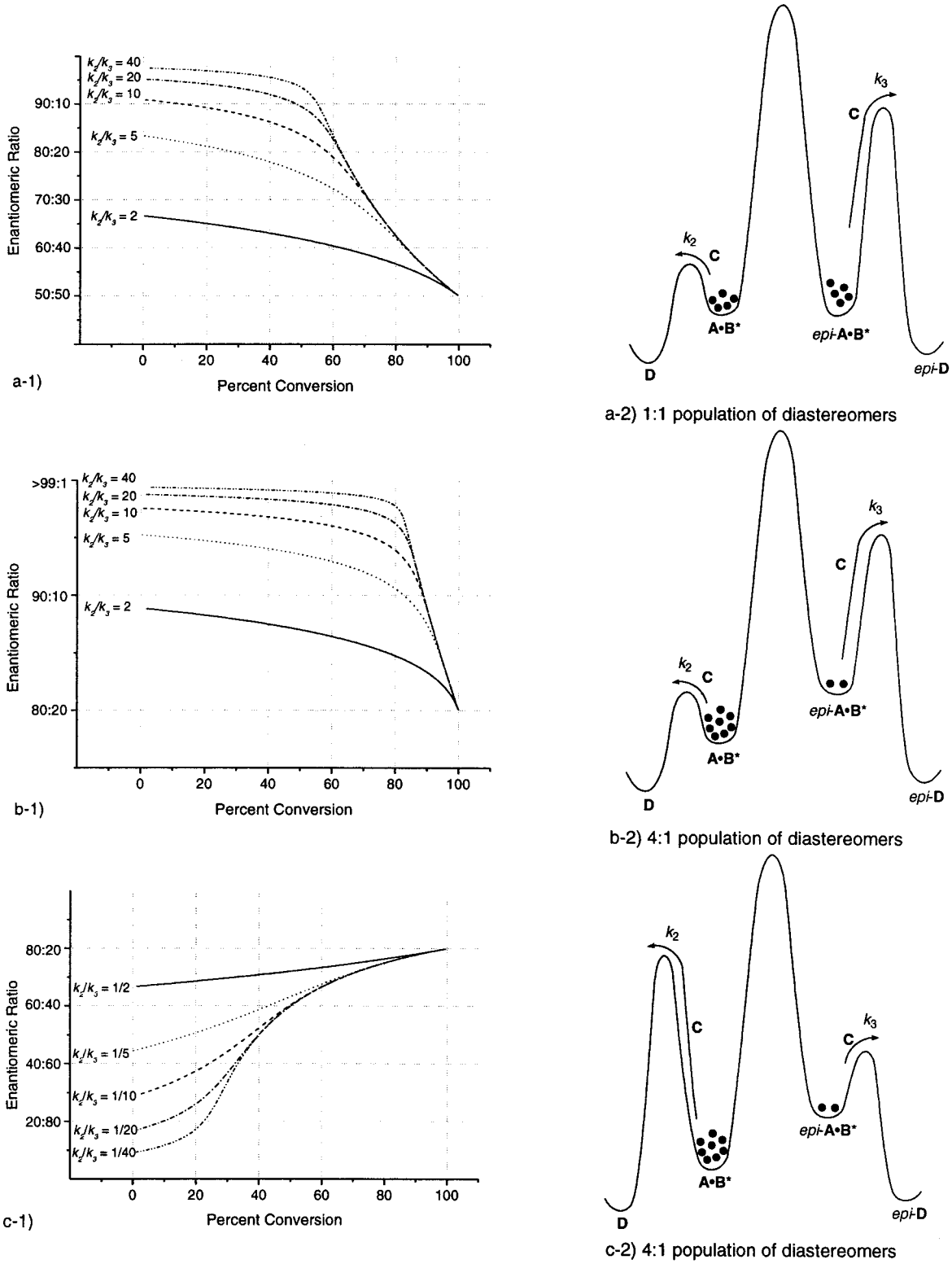
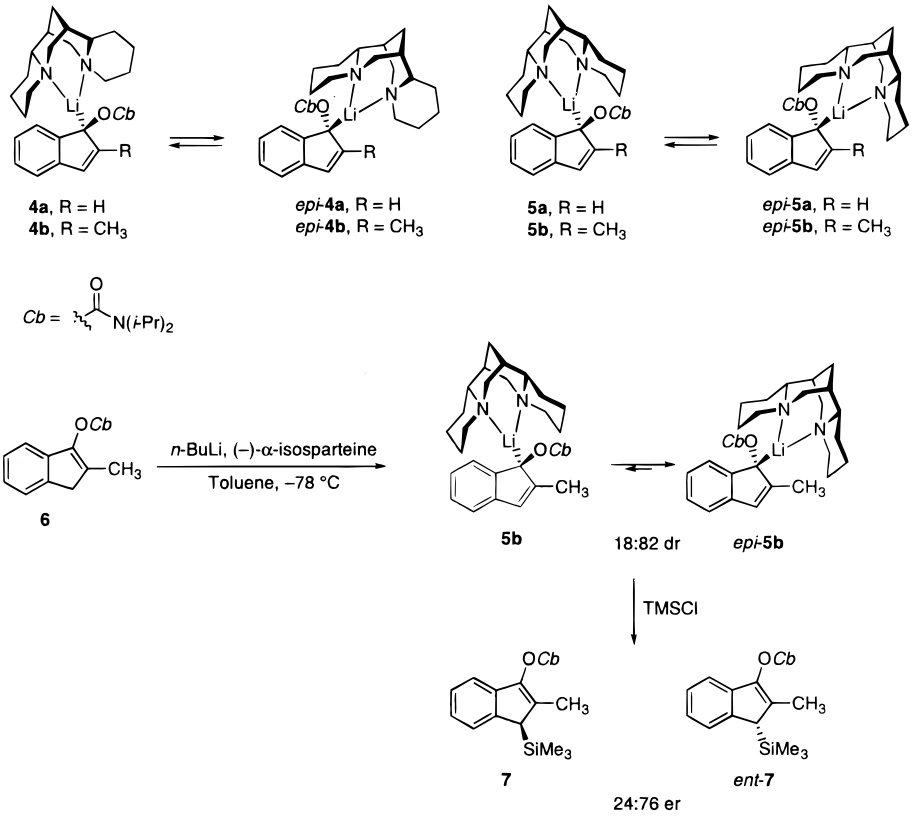


FIGURE 4. Graphs of product enantiomeric ratios as a function of percent conversion for (a) 1:1 mixture of diastereomers, (b) 4:1 mixture of diastereomers with the major diastereomer more reactive, and (c) 4:1 mixture of diastereomers with the minor diastereomer more reactive.

populated species can be either more (Figure 4b-1) or less (Figure 4c-1) reactive than the minor species.

The qualitative energy diagrams of Figure 4a-2 through 4c-2 illustrate each possibility. Figure 4a-2 shows the two diastereomeric intermediates that are coincidentally of equal energy. The diastereomers will react with **C** with different rates, but the product ratio at complete conversion will reflect the original ratio. In Figure 4b-2, the population is determined by the thermodynamic stability of each state, and the more populated state reacts more rapidly. Figure 4c-2 depicts the case when the less stable species is the more reactive toward **C**. In the case shown in Figure 4b-2, an increase in selectivity occurs at low conversion, whereas in the case shown in Figure 4c-2 a

Scheme 1



reversal in selectivity is expected at low conversions. It is noted that for the reaction of the less populated state to be faster than that of the more populated state, k_3[**C**][*epi*-**A**•**B***] must be greater than k_2[**C**][**A**•**B***]. It is insufficient that $k_3 > k_2$ because the relative velocities of the two reactions also depend on the relative populations of each state as well as the rate constants.

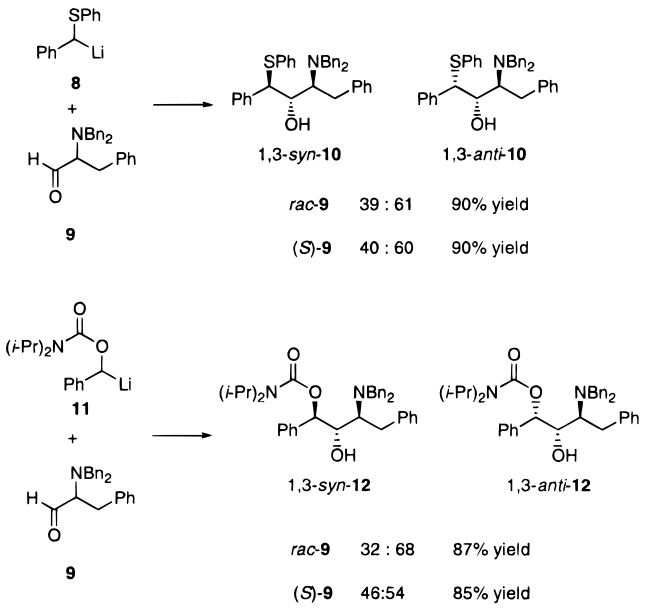
The fact that the product ratio can change as the reaction proceeds is an important aspect of dynamic thermodynamic resolution processes. By controlling the reaction conditions, highly selective protocols can be developed which can provide for the formation of significantly enantioenriched products even when the reaction may seem to be unselective prima facie.

Recognition and Control

Of central importance in both recognition and control of dynamic thermodynamic resolution processes is the interplay between rates of isomerization of the diastereomers and forward velocity of reactions of the diastereomers to provide products. In this context, spectroscopic and chemical methods for the determination of configurational stability are very useful.

Techniques that provide direct observation of the diastereomeric intermediates are of particular value. In a recent collaboration, Hoppe and Fraenkel determined the diastereomeric ratios and the interconversion activation parameters for the epimers of indenide•(−)-sparteine **4** and indenide•(−)-α-isosparteine **5** by comparing calculated and experimental ^{1}H NMR line shapes at various temperatures.[18] For **5a**, $\Delta H^{\ddagger} < 5$ kcal/mol; for **5b**, $\Delta H^{\ddagger} =$ 8.0−8.5 kcal/mol; for **4a**, $\Delta H^{\ddagger} = 13.5$ kcal/mol; and for **4b**, $\Delta H^{\ddagger} > 25$ kcal/mol. A typical reaction is shown for the conversion of **6** to **7** via **5b** (Scheme 1). Since the product ratio after reaction with chlorotrimethylsilane is consistent with the ratio of diastereomeric intermediates, it is likely that a dynamic thermodynamic resolution is the operative reaction pathway for asymmetric lithiation−substitution of these indenides.

In an ingenious chemical approach, Hoffmann has developed a technique for determining configurational stability of diastereomers relative to the time scale of reaction with an electrophile.[19] The Hoffmann test involves the execution of two separate reactions and comparison of the diastereomeric products from each reaction. In the first, a racemic organolithium intermediate such as **8** or **11** is allowed to react with the racemate of a chiral electrophile illustrated by **9**. The diastereomeric ratios of the products from these reactions reveal any preference for formation of the 1,3-*anti* versus the 1,3-*syn* products **10** and **12**. In a second reaction, the racemic organolithium intermediate is allowed to react with the a single enantiomer of the same chiral electrophile.[20] If the intermediate is configurationally labile, as in the case of **8**, the 1,3 diastereomeric ratio will be identical to that observed in the reaction with racemic electrophile. Alternatively, if the intermediate is configurationally stable, as in the case of **11**, a 1,3 diastereomeric ratio of ∼50:50 will be observed at high conversion.



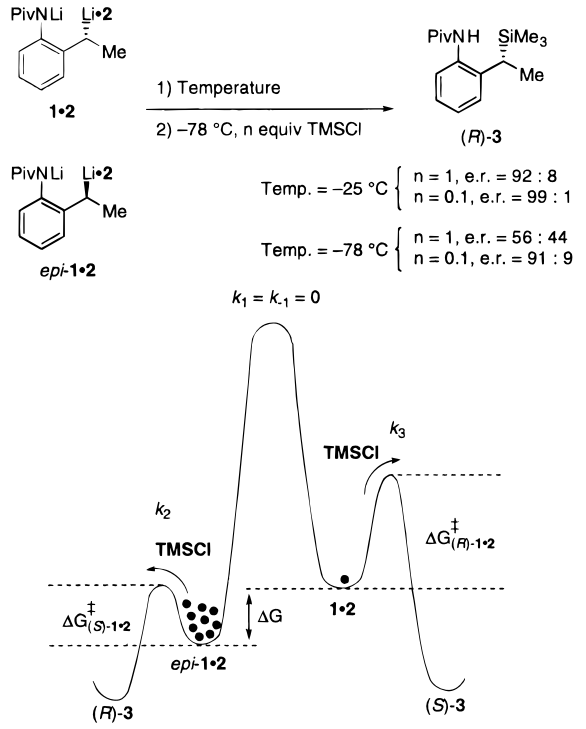
Other experiments which provide evidence for and allow control of dynamic thermodynamic resolution processes may be divided into three general groups: (1) reactions which are not taken to completion; (2) reactions which are designed to induce diastereomeric equilibration; and (3) reactions which combine both of these control elements.

As shown in Figure 4, if the rates of the two product-forming reactions are not equal, the er or dr of products will depend on the percent conversion. Thus, variation of enantiomeric ratio as a function of the time may indicate a dynamic thermodynamic resolution. Moreover, in such cases, control of the extent of reaction through the addition of deficient electrophile or quenching prior to its completion can offer an approach to improve enantiomeric ratios.

A modified Hoffmann test for configurational stability confirmed an energy profile analogous to Figure 4b-2 for reaction of equilibrated **1•2** with chlorotrimethylsilane at −78 °C, to give **3** (Scheme 2).[13] When 0.1 equiv of chlorotrimethylsilane is used, an enantiomeric ratio of 99:1 is obtained, as compared to an er of 92:8 with 1.0 equiv of the electrophile under the same conditions. Enrichment in the enantiomer of **3** that results from the faster reaction is apparent. Moreover, if the diastereomeric complexes are assumed to react with the same stereoselectivities, albeit at different rates, the experimental results can be used to estimate the thermodynamic parameters for the reaction. The difference in thermodynamic stabilities of *epi*-**1•2** and **1•2** is 0.97 kcal/mol, and the difference in the activation barriers for reactions of the diastereomers with chlorotrimethylsilane is 0.8 kcal/mol with the more stable complex, *epi*-**1•2**, being the more reactive.

Evidence for the operation of dynamic thermodynamic resolution pathways may also be provided by changes in reaction selectivities after the diastereomers have been equilibrated to a thermodynamic ratio from an initial kinetic ratio. The effect is often observed only by cooling the reaction after thermodynamic equilibrium is achieved,

Scheme 2



Energy diagram for reaction of **1•2** and *epi*-**1•2** with TMSCl at −78 °C

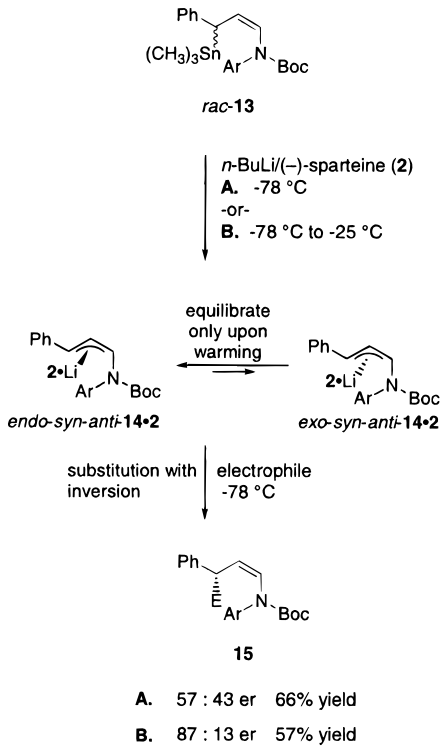
epi-**1•2** : **1•2** = 92 : 8, set by equilibration at −25 °C

$\Delta G = 0.97$ kcal/mol

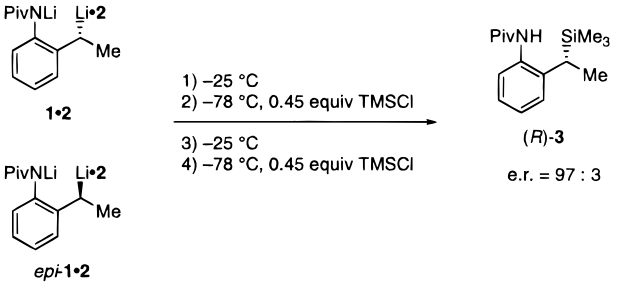
$\Delta G^{\ddagger}_{\mathbf{1•2}} - \Delta G^{\ddagger}_{epi\text{-}\mathbf{1•2}} = 0.81$ kcal/mol at −78 °C

effectively freezing out a given ratio of intermediates, as demonstrated for **1•2** to **3** (vide supra). The transformation of *rac*-**13** to **15** via **14•2**, which gives products with high enantiomeric ratios only if the intermediate is warmed prior to reaction with electrophile at −78 °C, also demonstrates management of product enantioselectivity by control of the reaction conditions.[21] Execution of the reaction at a constant temperature of −78 °C affords **15** that is essentially racemic, with a 57:43 er. However, at thermodynamic equilibrium, which is achieved through warming to −25 °C, the complexes *endo-syn-anti*-**14•2** and *exo-syn-anti*-**14•2** are present in a ratio of 87:13; this ratio is reflected in the products of invertive reactions with electrophiles at −78 °C to give **15**.

Reactions for which either the minor or the major diastereomeric species is significantly more reactive present additional possibilities for recognition and control of resolutions through sequential reaction sequences. If the thermodynamically less populated diastereomer reacts more rapidly (Figure 4c-2), a useful protocol could involve the addition of two electrophiles. The first could be considered a sacrificial electrophile that would selectively reduce the population of the minor, more reactive diastereomeric intermediate. The second electrophile could then react with the major diastereomeric intermediate to provide a product with higher enantioenrichment than would be obtained directly (vide infra).



Alternatively, if the major diastereomeric species is the more reactive (Figure 4b-2), an improved enantiomeric ratio could be achieved at incomplete conversion by addition of deficient electrophile. Subsequent reequilibration of the diastereomeric intermediates prior to a second addition of electrophile could provide high overall yield and selectivity. For example, in the reactions of **1•2** and *epi*-**1•2**, addition of 0.45 equiv of electrophile, followed

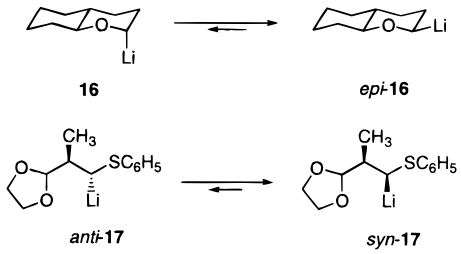


by warming (−25 °C), cooling (−78 °C), and then addition of a second 0.45 equiv of electrophile gave (*R*)-**3** with an increased er of 97:3.[13] The warming allows repopulation of the depleted more stable but more reactive complex and subsequent improvement of the er. This result illustrates diastereomeric recycling as a viable technique for improvement of enantiomeric ratios.

Diastereomeric Equilibrations

An essential feature of all dynamic thermodynamic resolutions is diastereomeric equilibration. Changes in time and temperature that affect diastereomeric ratios of products have been recognized by a number of workers and provide important precedents for the cases we have selected for this account. We emphasize, however, that these reactions are not themselves dynamic thermodynamic resolutions as they do not provide enantioenriched products.

Early investigations of reactions of α-heteroatom organolithium species revealed that equilibrations of diastereomeric intermediates could influence product ratios. In 1984, Cohen showed that the equilibrium between **16** and *epi*-**16** could be controlled by temperature to afford different ratios of axial and equatorial products on reaction with benzaldehyde.[22] In 1988, McDougal established



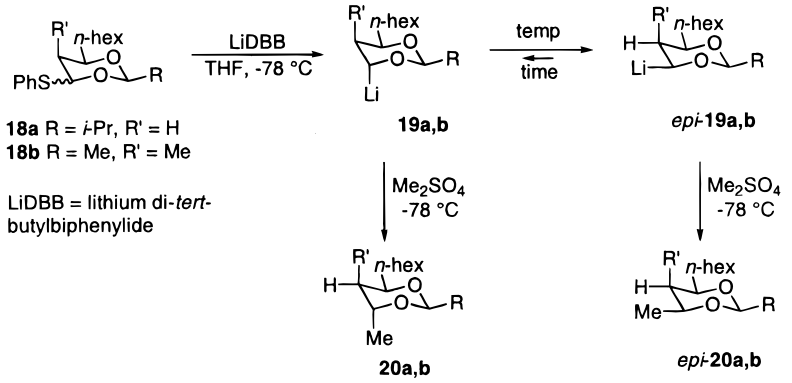
that equilibration between *syn*-**17** and *anti*-**17** occurs by showing that product ratios were a function of the equilibration time.[23] Many subsequent examples of diastereomeric equilibration have also involved α-heteroatom organolithium intermediates.

The stereoselective reductive lithiation substitution of 4-(phenylthio)-1,3-dioxanes reported by Rychnovsky provides a recent demonstration of the effect of time and temperature on equilibration of intermediates to control ratios of diastereomeric products.[24] The initial reduction product from **18a** is the kinetically favored axial species **19a** that is stable at −78 °C (Scheme 3). Reaction of **19a** with dimethyl sulfate provides **20a** and *epi*-**20a** in a ratio of 99:1 (entry 1). However, when the reaction temperature is raised to −20 °C for 30 min, virtually complete equilibration to the thermodynamically more stable equatorial isomer *epi*-**19a** occurs. Reaction of *epi*-**19a** with dimethyl sulfate affords **20a** and *epi*-**20a** in a ratio of 1:99 (entry 2). In the reaction of the 5-methyl substituted **18b**, the diastereomers interconvert more slowly and react with dimethyl sulfate to provide a 52:48 ratio of **20b** to *epi*-**20b** after exposure of **19b** and *epi*-**19b** to -20 °C for 60 min (entries 3−6).

These results are consistent with a lack of equilibration for all intermediates at −78 °C. The equatorial intermediates *epi*-**19a** and *epi*-**19b** are thermodynamically favored at higher temperatures, but the equilibration of **19a** to *epi*-**19a** proceeds more rapidly than that of **19b** to *epi*-**19b**.

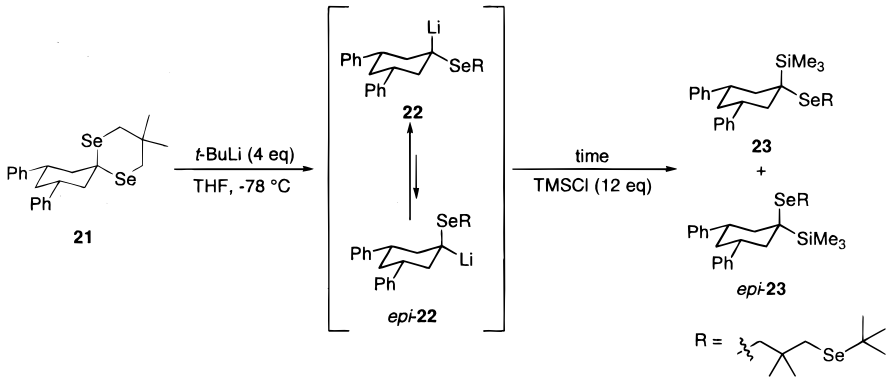
Reich and co-workers have demonstrated how manipulation of reaction times can affect equilibration of an intermediate and enhance the diastereomeric ratio of the products. For the lithium−selenium exchange of **21** followed by reaction with chlorotrimethylsilane, the kinetic intermediate formed was the equatorial lithio species *epi*-**22**, as shown by an in situ reaction with chlorotrimethylsilane affording **23** and *epi*-**23** in a 7:93 ratio, respectively (Scheme 4).[25] However, on longer reaction times *epi*-**22** equilibrated to the thermodynamically preferred axial

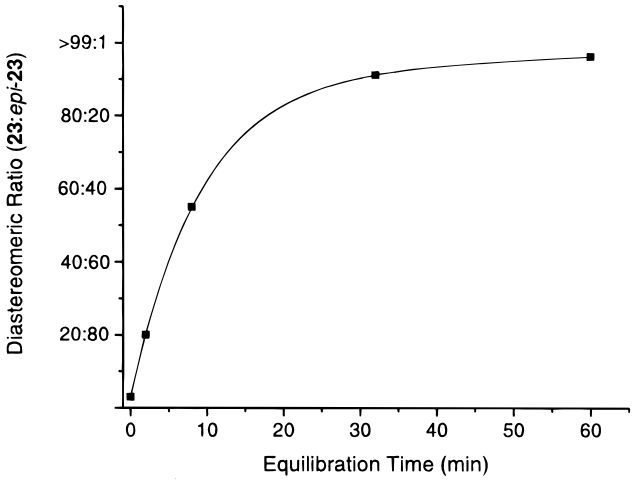
Scheme 3



entry	equil temp	equil time	Starting Material	**20**:*epi*-**20**
1	-78 °C	30 min	**18a**	99:1
2	-20 °C	30 min	**18a**	1:99
3	-78 °C	30 min	**18b**	99:1
4	-20 °C	10 min	**18b**	88:12
5	-20 °C	30 min	**18b**	67:33
6	-20 °C	60 min	**18b**	52:48

Scheme 4

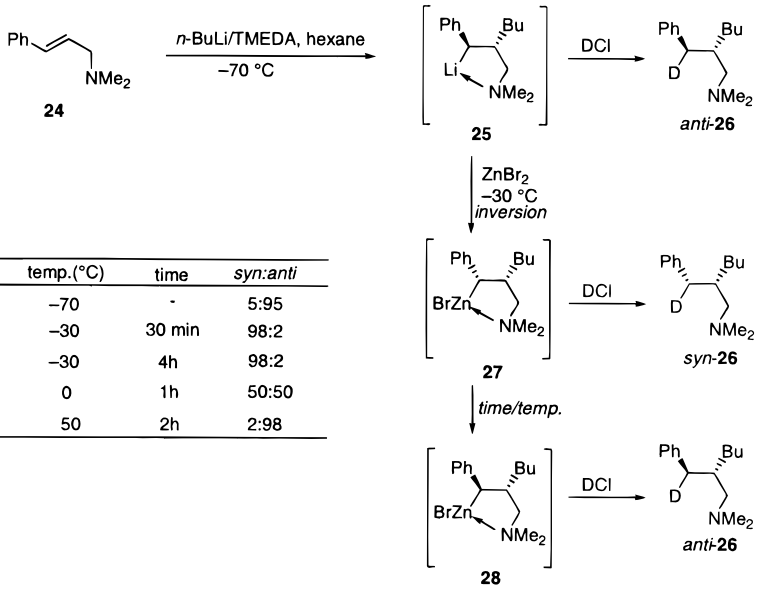




lithio species **22**. The equilibration was complete after 1 h at −78 °C with products **23** and *epi*-**23** formed in a 96:4 ratio.

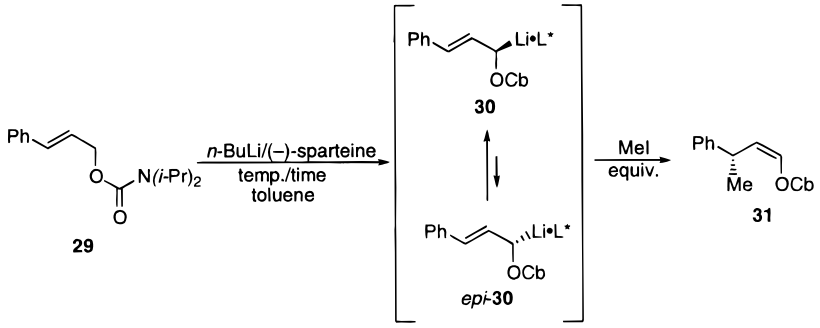
Product control through equilibration of diastereomeric intermediates is also known for organometallic species that do not bear an α-heteroatom. Normant and co-workers have been able to control the diastereoselectivity of the carbolithiation−electrophilic substitutions of cinnamyl alcohols and amines through manipulation of time and temperature.[26] Carbolithiation of the cinnamylamine **24** with *n*-BuLi/TMEDA provides the thermodynamically favored *anti* intermediate **25** (Scheme 5). Reaction of **25** with DCl proceeded with retention of configuration to give predominantly *anti*-**26** in a dr of 95:5 (entry 1). On the other hand, transmetalation of **25** with $ZnBr_2$ occurred with inversion to give **27,** which is configurationally stable at and below −30 °C. This configurational stability is evidenced by reaction with DCl after 30 min and after 4 h to provide *syn*-**26** with a dr of 98:2 in both cases (entries 2 and 3). However, the zincated intermediate **27** can be thermally equilibrated to the favored *anti* intermediate and subsequently reacted with DCl to give predominantly *anti*-**26** (entries 4 and 5). An asymmetric variant of this protocol was realized by employing a catalytic amount of (−)-sparteine in place of TMEDA for the carbolithiation of cinnamyl alcohol. In this case, the absolute configuration at the homobenzylic center is set upon addition to

Scheme 5



entry	*via*	temp.(°C)	time	*syn:anti*
1	**25**	−70	-	5:95
2	**27**	−30	30 min	98:2
3	**27**	−30	4h	98:2
4	**27**	0	1h	50:50
5	**27**	50	2h	2:98

Scheme 6



entry	Temp.(°C)	Time(h)	Equiv. MeI	Yield(%)	er
1	−110	0.5	3	80	58:42
2	−96	0.5	3	73	64:36
3	−78→ −25→ −78	3.5	3	77	78:22
4	−78	0.5	3	85	75:25
5	−78	0.5	0.2	16	53:47

the olefin, but diastereomeric equilibration was employed to control the benzylic stereogenic center.

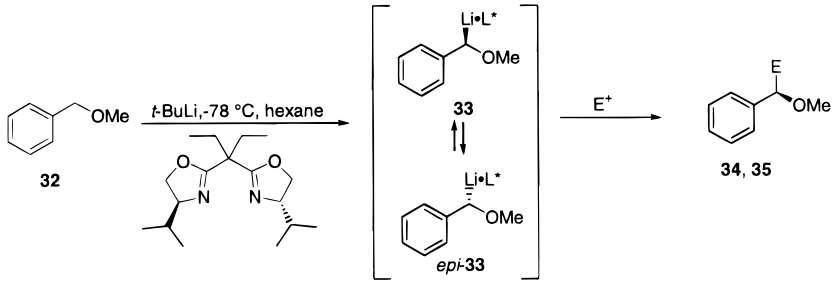
Dynamic Thermodynamic Resolution

Induced diastereomeric equilibrations under the influence of a chiral nonracemic species through rational modifications of experimental variables provide a basis for asymmetric synthesis by means of dynamic thermodynamic resolution, as presented in Figures 1 and 2c. The reactions of **1** in the presence of **2** to afford (*R*)-**3** provide a prototypical example. That case also demonstrates the use of stoichiometry as a diagnostic and control element. For example, the enantiomeric ratio of the product **3** was improved from 92:8 to 97:3 by consecutive additions of 0.45 equiv of electrophile that were separated by a diastereoselective equilibration. Enantioselective synthesis through dynamic thermodynamic resolution has been realized in other laboratories.

In the stereoselective lithiation−substitution of the cinnamyl carbamate **29**, Hoppe and co-workers demonstrated that a dynamic thermodynamic resolution is the operative reaction course.[27] Time, temperature, and quantity of electrophile were used to probe and elucidate the reaction pathway. Lithiation of **29** with *n*-BuLi/(−)-sparteine provides the diastereomeric lithiated intermediates **30** and *epi*-**30**, which equilibrate very slowly below −90 °C, but are fully equilibrated after a half hour at −78 °C (Scheme 6, entries 1−4). Reaction with iodomethane provided the γ-substituted (*Z*)-enecarbamates **31** in good yields with moderate er's.

The details of the reaction pathway were further resolved by employment of a modified Hoffmann test for configurational stability. In two separate reactions, excess

Scheme 7



Electrophile (pdt)	CO_2 (**34**)			PhCHO (**35**)		
Equiv. of E^+	4.0	0.5	0.1	4.0	0.5	0.1
% Yield[a]	59	26	10	78	15	3
er[a]	87:13	74:26	72:28	85:15	78:22	68:32

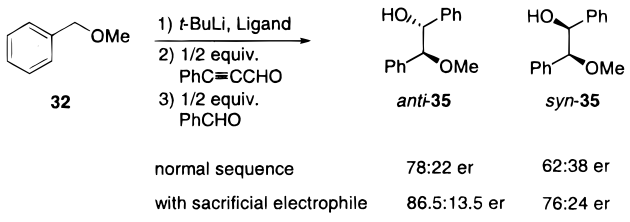
[a]Yields and er's for products derived from aldehyde electrophiles are reported for the *anti* diastereomers. The same trend was also observed for the corresponding *syn* diastereomer.

and deficient amounts of iodomethane were added to **30**/*epi*-**30** mixtures (entries 4 and 5). An erosion in the er of the product from 75:25 with 3 equiv of electrophile to 53:47 with 0.2 equiv was observed. This indicates that the reaction is controlled by dynamic thermodynamic resolution and that the thermodynamically less stable diastereomeric complex, *epi*-**30**, reacts more rapidly with electrophile. These results suggest that the reaction pathway depicted in Figure 4c-2 is the operative course of reaction.

Nakai and co-workers have observed a dynamic thermodynamic resolution in the stereoselective lithiation−substitution of benzyl methyl ether (**32**) to provide highly enantioenriched 1,2-diols and α-methoxy carboxylic acids **34** and **35** (Scheme 7).[28,29] The stereochemical determining step for these reactions was demonstrated to occur after deprotonation because lithiation of *rac*-**32**-d^1 followed by reaction with CO_2 provided the carboxylated product **34**-d^1 with high deuterium incorporation (>96%). In this experiment, both yield (73%) and selectivity (87:13 er) were comparable to results obtained with **32**.

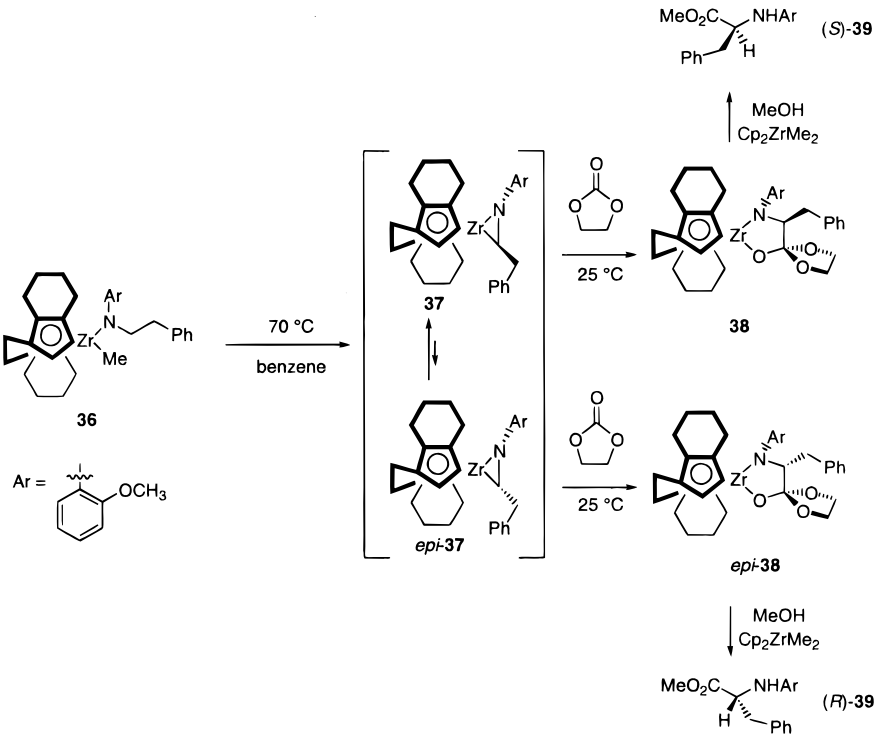
Additional experiments employing variable amounts of electrophile determined the resolution pathway. For both carboxylate and aldehydic electrophiles, a decrease in the product er was observed as the equivalents of electrophile were decreased from 4.0 to 0.1, a result inconsistent with dynamic kinetic resolution. A dynamic thermodynamic resolution is the operative pathway. The minor, thermodynamically less stable diastereomeric Li−ligand complex reacts more rapidly with the electrophiles, leading to erosion of the product er as the equivalents of electrophile are decreased (Figure 4c-2).

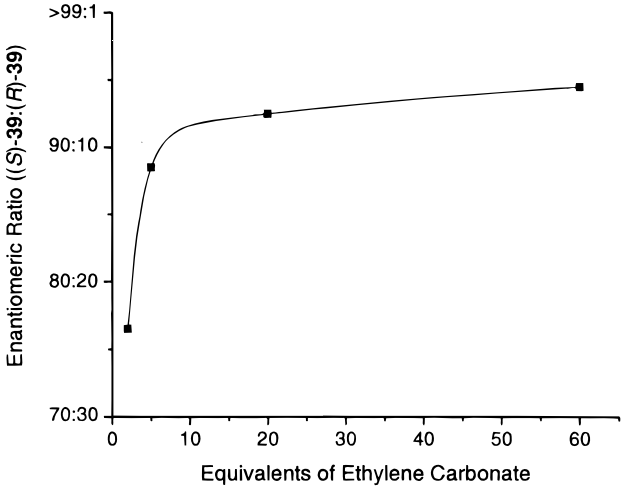
Because the minor diastereomeric complex is the more reactive, this reaction is well-suited to optimization through a sacrificial electrophile approach. In fact, when the lithiated intermediated was treated with 0.5 equiv of propargyl aldehyde followed by 0.5 equiv of benzaldehyde, the er of both benzaldehyde derived diastereomeric products *anti*-**35** and *syn*-**35** was enhanced relative to the normal protocol. Presumably, the propargyl aldehyde selectively removes the thermodynamically less favored but more reactive intermediate, increasing the concentration of the major diastereomeric complex. This improved ratio of diastereomeric intermediates is then reflected in the final product ratios of **35**.

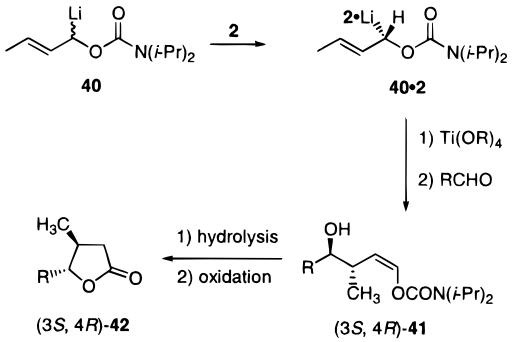


A thorough investigation of dynamic thermodynamic resolution has been reported by Norton for the synthesis of α-amino acid esters using chiral zirconaaziridine complexes.[30] In these reactions, the diastereomeric zirconaaziridines **37** and *epi*-**37** are generated from zirconium amide **36** with concomitant elimination of methane at high temperatures (Scheme 8). This mixture of intermediates is then cooled to room temperature. Upon addition of ethylene carbonate, irreversible C−O insertion into the zirconium−carbon bond occurs to yield intermediates **38** and *epi*-**38**, which can undergo zirconium-assisted methanolysis to give amino acids **39**. The stereochemical determining step of the reaction was probed by varying the number of equivalents of ethylene carbonate. Upon increasing the equivalents of ethylene carbonate from 2 to 60, the product er increased from 77:23 to 95:5, favoring (*S*)-**39**. To explain this result, Norton proposes that when 60 equiv of ethylene carbonate are used, the rate of equilibration of the diastereomeric zirconaaziridine intermediates **37** and *epi*-**37**, a first-order process, is no longer competitive with the rate of reaction with electrophile, a second-order process which is affected by the concentration of ethylene carbonate. Thus, the 95:5 product ratio is representative of the thermodynamic ratio of **37** and *epi*-**37**. However, as fewer equivalents of ethylene carbonate are used, the rate of equilibration of

Scheme 8



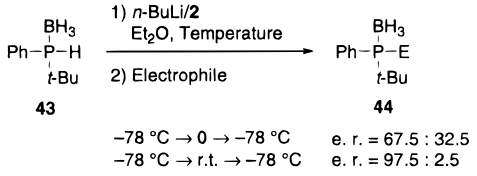




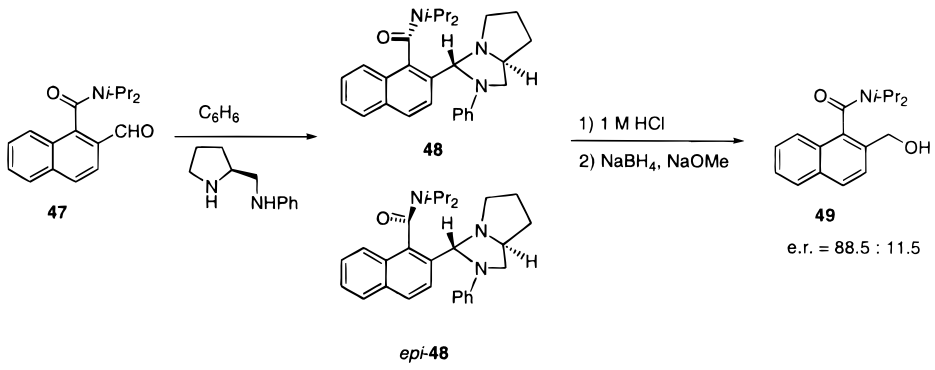
37 and *epi*-**37** becomes greater than the rate of reaction with electrophile. Therefore, at high concentration of ethylene carbonate, the high enantiomeric ratios result from a dynamic thermodynamic resolution reaction pathway.

The driving force for resolutions by formation of the more stable diastereoisomer is not limited to soluble complexes. Hoppe has shown that complexation of racemic **40** with **2** provides **40•2** by selective crystallization.[31,32] Subsequent rapid invertive transmetalation with titanium isopropoxide followed by reactions with aldehydes gives single diastereomers (3*S*, 4*R*)-**41** with er's greater than 90:10. Hydrolysis and oxidation provided efficient syntheses of highly enantioenriched γ-lactones **42** and illustrated the use of **40•2** as an asymmetric homoenolate synthetic equivalent.[33] Vedejs has recently provided cases, which he terms crystallization-induced asymmetric transformations.[34] We also classify these reaction sequences as a dynamic thermodynamic resolutions.[35]

The synthesis of chiral nonracemic phosphine ligands reported by Livinghouse is also a process for which the stereoselectivity results from a dynamic thermodynamic resolution.[36] In this sequence, deprotonation of **43** in the presence of (−)-sparteine (**2**) and subsequent reaction with an electrophile gave the substituted products **44** in good yield. The enantiomeric ratio of the product depended on the temperature and time of the metalation reaction. If the reaction is warmed from −78 °C to 0 °C for 30 min, a poor er (68:32) is observed upon reaction with electrophile at −78 °C. However, if the equilibration period involves warming to 25 °C for 1 h, the product is obtained with an enantiomeric ratio of 98:2.

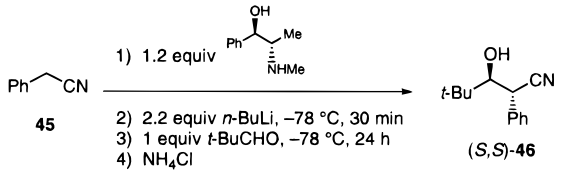


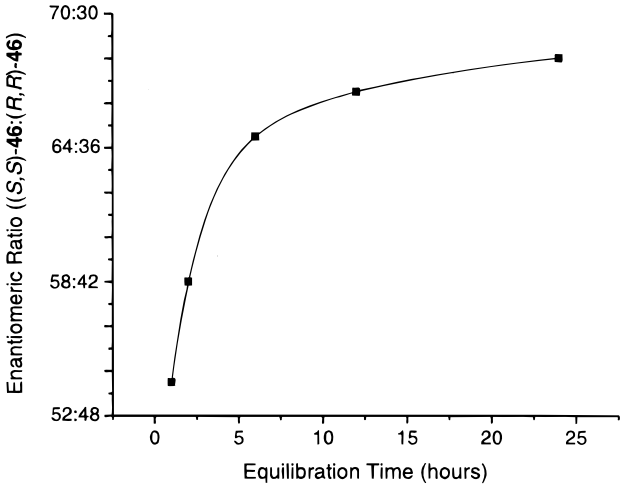
Scheme 9



at room temp, **48**:*epi*-**48** = 1:3
at reflux, 24 h, **48**:*epi*-**48** = >90:10

A recent report of lithium ephedrinate mediated aldol reactions of arylacetonitriles to aldehydes by Carlier also illustrates dynamic thermodynamic resolution.[37] When **45** is sequentially exposed to (1*R*,2*S*)−(−)-ephedrine, *n*-BuLi, *t*-BuCHO, and NH_4Cl, the pure anti aldol product **46** is obtained with enantioselectivities which depend on reaction time. The authors note that the enantiomeric ratio, but not yield, changes with time and propose that the enantiomeric products are initially formed in a kinetic ratio. However, because the enantiomeric products are part of diasteromeric mixed aggregates with the lithium ephedrinate ligand, their thermodynamic stabilities are unequal. Thus, an equilibration pathway is available through a retro-aldol reaction and the thermodynamic ratio is reached over 24 h.





Dynamic thermodynamic resolution is widely applicable. Clayden has recently reported an enantioselective synthesis of atropisomers that proceeds through a controllable equilibration from an initially formed kinetic product to a thermodynamically favored isomer.[38] In this case, formation of aminals **48** and *epi*-**48** results from reaction between chiral, racemic **47** and a proline-derived diamine (Scheme 9). If the reaction is conducted at room temperature and assayed prior to completion, a 3:1 kinetic ratio of *epi*-**48** to **48** is found. However, if the reaction mixture is heated at reflux for 24 h, a thermodynamic ratio of >90:10 in favor of the opposite epimer is observed. Acid-catalyzed aminal hydrolysis completes the synthesis of enantiomerically enriched **47**, which was assayed for stereochemical purity following conversion to alcohol **49**.

Conclusions

Classical kinetic resolutions and dynamic kinetic resolutions have long been recognized as important methods for the preparation of enantioenriched compounds. Dynamic thermodynamic resolution pathways have also been recognized but have been much less utilized. Significant enantioselectivities may be achieved by an induced equilibration of diastereomeric intermediates and control of reaction conditions often for cases which initially give low levels of resolution.

A very important feature of reactions controlled by dynamic thermodynamic resolutions is their adaptability for optimization. Significantly enhanced resolutions may be achieved by (1) equilibrating intermediates by control of reaction time and/or temperature; (2) controlling the extent of conversion either with stoichiometry of the electrophile or the reaction time; (3) increasing the rate of a second-order reaction relative to that of a first-order reaction by concentration; (4) employing a sacrificial electrophile; or (5) using a diastereomeric recycling protocol. The opportunity for control of enantioslectivity through rational changes in reaction conditions combined with potential wide applicability render dynamic thermodynamic resolutions an important class of asymmetric transformation. This approach is at an early stage of development, and future applications should be forthcoming.

We are grateful to our colleagues for their outstanding intellectual and experimental contributions. We appreciate support for the work in our laboratories from the National Institutes of Health-

General Medical Sciences (NIH-GM-18874) and the National Science Foundation (NSF-98-19422).

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(3) In a classic kinetic resolution, the resolution is acheived through, "...unequal reaction rates of the enantiomers with a chiral, nonracemic agent (reagent, catalyst, or enzyme)...." [1] As shown in Figure 2, both enantiomers form complexes with the chiral reagent, and the actual resolution occurs in the unequal rates of reaction between **A•B*** and **C** and between *epi*-**A•B*** and **C**; we believe this type of reaction is still best classified as a kinetic resolution.

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(7) The dynamic kinetic resolution phenomenon defined by Noyori[6] relates to a reaction in which enantiomers are interconverting under the reaction conditions. In Figure 2 we show an extension in which the diastereomers **A•B*** and *epi*-**A•B*** are interconverting under the reaction conditions.[8]

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(10) We believe the descriptor "dynamic" to be appropriate as dynamic events are operative in dynamic thermodynamic resolution in two ways; the initial equilibration of complexes is dynamic, as is a resolution process which can provide improved selectivities at less than complete conversion.

(11) By our definition, a process which fits the description dynamic thermodynamic resolution is necessarily an enantioselective synthesis.

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(15) The current protocol in which **1•2** is generated by addition of (−)-sparteine to **1** evolved from an earlier approach in which **1•2** was generated through reaction of *o*-ethyl pivanilide with *n*-BuLi/(−)-sparteine. The fact that the deprotonation in that case was not enantiodetermining is supported by the results shown in Figure 3.

(16) The energy diagrams in Figure 3 represent the major diastereomeric complex, (*S*)-**1•2**, as being the more reactive. This assignment is supported by data which are presented in the Recognition and Control section of this article.

(17) The curves in Figure 4 were derived assuming an excess of electrophile and pseudo-first order conditions, and the predictions at various % conversions are only valid for examples wherein the % conversion is controlled by stopping the reaction prior to completion. Reactions which limit % conversion through employment of deficient electrophile will behave differently. The actual curves were produced by the strictly numerical approach of solving the differential equations for enantiomeric ratios at different % conversions.

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