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Dynamic Thermodynamic Resolution: Advantage by Separation of Equilibration and Resolution

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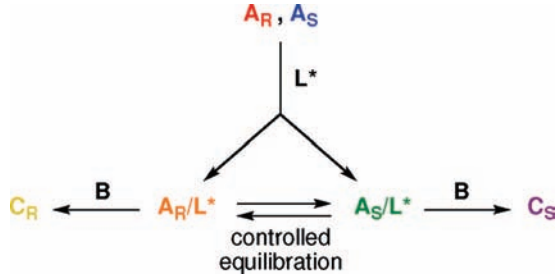
CONSPECTUS



In the investigation of a chemical reaction, researchers typically survey variables such as time, temperature, and stoichiometry to optimize yields. This Account demonstrates how control of these variables, often in nontraditional ways, can provide significant improvements in enantiomeric ratios for asymmetric reactions. Dynamic thermodynamic resolution (DTR) offers a convenient method for the resolution of enantiomeric products in the course of a reaction. This process depends on an essential requirement: the equilibration of the penultimate diastereomers must be subject to external control. As a general case, the reaction of A_R, A_S with B under the influence of the chiral species, L*, gives resolved products C_R and C_S.

In the first step of dynamic resolution under thermodynamic control, the enantiomeric reactants A_R and A_S and L* form the diastereomers A_R/L* and A_S/L*. The equilibrium between A_R and A_S can be rapid, slow, or not operative, and L* can represent a ligand, an auxiliary, or a crystallization process that provides a chiral environment. Second, the populations of the diastereomers are controlled, usually by thermal equilibration. Finally, the reaction of the diastereomers with a reagent B provides the enantiomeric products C_R and C_S. The control of the diastereomeric equilibrium distinguishes DTR from other resolution techniques. By contrast, physical resolutions separate thermodynamically stable, nonequilibrating diastereomers, and dynamic kinetic resolutions utilize kinetic control for reactions of rapidly equilibrating diastereomers.

The dynamic thermodynamic resolutions discussed in this Account illustrate cases of significantly improved enantioselectivities using this technique. Although many of the well-recognized cases come from organolithium chemistry, the principles are general, and we also present cases facilitated by other chemistries. This approach has been used to control enantioselectivities in a number of different reactions, with improvements in enantiomeric ratios up to 99% from essentially racemic reactants.

Introduction

Time, temperature, and stoichiometry are variables routinely surveyed in the investigation of a reaction. Changes in time (sometimes shorter but usually longer), in temperature (sometimes lower but usually higher), and in stoichiometry

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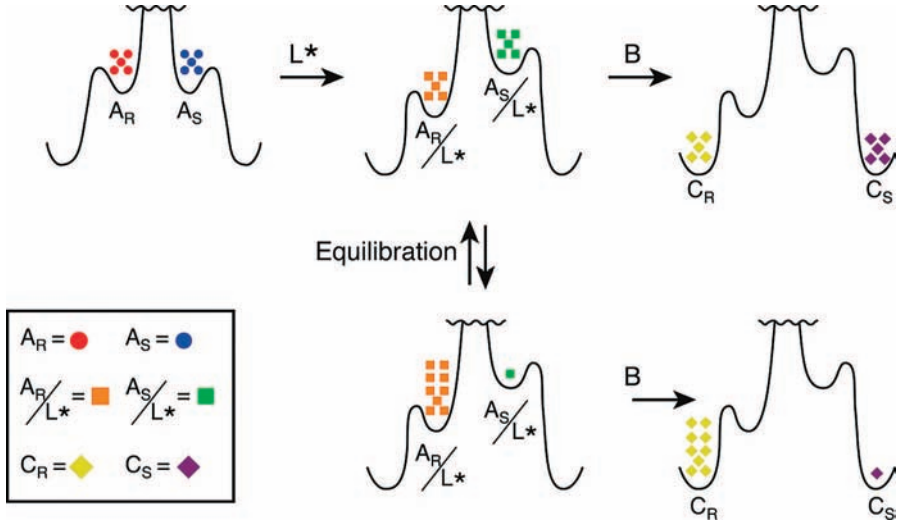


FIGURE 1. Energy and reaction diagrams for dynamic thermodynamic resolution of A to provide C.

(usually higher concentrations) are tested empirically. This Account demonstrates how control of these variables, often in nontraditional ways, can provide significant improvements in enantiomeric ratios for asymmetric reactions.[1,2]

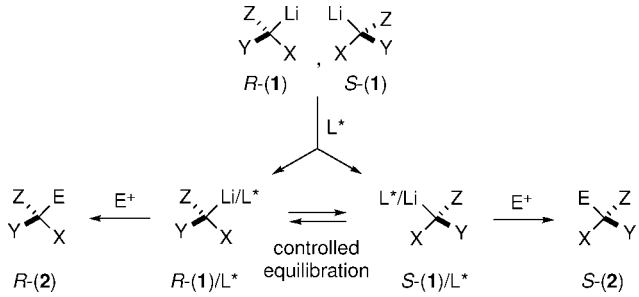
Classic resolutions from racemic mixtures require the formation and physical separation of diastereomers followed by removal of the resolving agent. The separated diastereomers can be salts, covalent compounds, or complexes. Selective crystallization and chiral chromatography, illustrative of the former and latter approaches, are considered to be thermodynamically driven.

Resolution in the course of a reaction involves diastereomeric transient complexes or transition structures that favor one enantiomer over the other. If control of the population of transient diastereomers is possible and recognized, a dynamic resolution under thermodynamic control (dynamic thermodynamic resolution, DTR) may be developed. If the diastereomeric species have significantly different thermodynamic stabilities or activation energies in a subsequent reaction, an initially racemic reactant can provide a highly enantioenriched product in a convenient one flask operation under DTR. It is control of the diastereomeric populations that makes DTR different from dynamic kinetic resolution (DKR), in which diastereomeric species are in rapid equilibrium and the extent of resolution is determined by the Curtin−Hammett principle.

The energy and reaction diagrams of Figure 1 progressively illustrate the general case of DTR from A_R, A_S to C_R and C_S. A racemic mixture of the enantiomers A_R and A_S under the influence of an enantiopure species L* followed by reaction with an achiral reagent B is shown to provide unequal amounts of the products C_R and C_S. The first diagram shows the equal populations and equal energies of A_R and A_S in an initial achiral environment. The next step of association with L* provides equal populations of the nonequilibrated diastereomers A_R/L* and A_S/L*. Direct reaction of this mixture with the reagent B then would provide equal amounts of C_R and C_S. However, if the diastereomers are allowed to equilibrate, their energy difference will lead to unequal populations of A_R/L* and A_S/L*. Subsequent reaction with B then provides resolution in the formation of unequal amounts of C_R and C_S. Each of these steps is very well-known. However, their combination with intentional control of the equilibration offers opportunities for resolutions that otherwise might not be recognized.

The profiles in Figure 1 illustrate the possibilities of DTR for a case in which the activation energies for reaction of the diastereomers are equal. In cases where these are not equal, additional enantioenrichment may be possible. For example, if the lower energy diastereomer has the lower activation energy, the use of appreciably less than one equivalent of the achiral reactant would lead to an enantiomeric ratio larger than would be observed with a full equivalent of the reagent. In this case, repeated limited amounts of the reagent followed by reequilibrations of the diastereomers would provide enantioenrichments that significantly exceed the relative populations of the equilibrated diastereomers (*vide infra*). If, alternatively, the higher energy diastereomer has the lower activation energy, reaction of the nonequilibrated diastereomers with less than one equivalent would afford an enantioenriched product. In this case, use of a sacrificial reagent, which would select the minor but more reactive diastereomer to make a different product, followed by the reaction of the original reagent with the more highly populated, less reactive diastereomer would lead to an enantioenriched product. The first profile of Figure 1 illustrates a case in which A_R and

SCHEME 1



A_S are not rapidly interconverting relative to their reaction with L*. If there is facile equilibrium between the enantiomers relative to the association with L*, the population of the resulting stable diastereomers would be determined by the difference in activation energies for the association step. That population of stable diastereomers could be subject to subsequent thermodynamic control through equilibration.

Under DTR, the enantiodetermining diastereomeric energy differences, which lie in the relative stabilities of the diastereomers or in the transition states leading to the product, are available for enantiocontrol. The source of thermodynamic energy difference between the diastereomers could be the energy differences of species in solution, on absorption, or in the solid state.

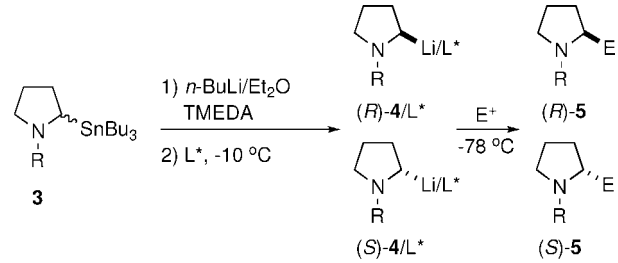
The most well-recognized examples of enantiocontrol based on DTR are in organolithium chemistry with a general case shown in Scheme 1. The generation of chiral organolithium reagents, their configurational stability, the reaction mechanisms involving chiral organolithium reagents, and the transfer of stereochemical information with enantioenriched organolithium reagents have recently been reviewed.[3] The well-known complexation, aggregation, crystallization, and sometimes slow equilibrations of organolithium species may increase the opportunities for DTR.

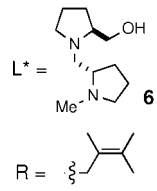
The selected examples in this Account illustrate how straightforward management of the experimental conditions can provide control of the diastereomeric equilibrations and lead to significantly improved enantioselectivities. We believe that recognition of this possibility could provide useful enantioenrichment for reactions that, absent this consideration, would not be developed.

Ligand-Based Control

A reaction sequence that clearly demonstrates the use of temperature to control a diastereomeric and subsequent enantiomeric ratio (er) was reported by Coldham and co-workers. They found that when a racemic α-lithio amine pyrrolidine derivative (*R*)-**4**/L* and (*S*)-**4**/L*, generated by tin−lithium exchange from racemic **3**, was treated with the enantioenriched chiral ligand **6** at −10 °C then stirred for 90 min prior to cooling to −78 °C for the addition of the electrophile, the products (*R*)-**5** and (*S*)-**5** were obtained with er's of 96:4 (Scheme 2).[4] This is consistent with an initial 1:1 ratio of diastereomeric complexes being converted to a higher ratio through equilibration, which ultimately provides a highly enantioenriched product.

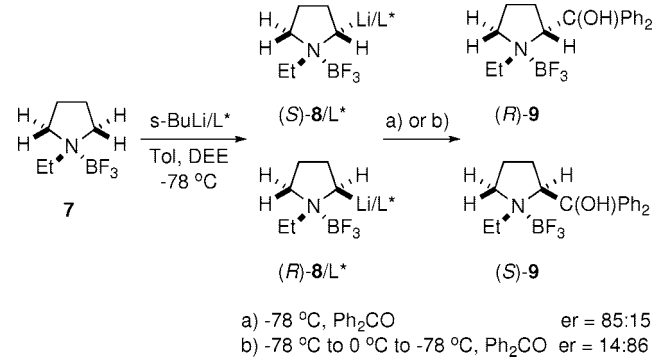
SCHEME 2





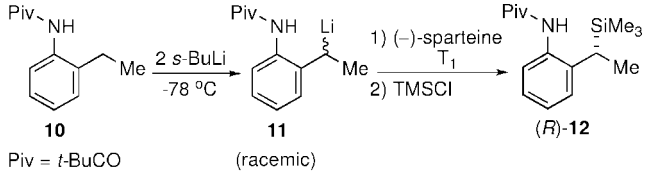
entry	E^+	yield (%)	er (*R*:*S*)
1	PhNCO	51	96:4
2	TMSCl	62	5:95
3	Me_2SO_4	59	6:94
4	$C_6H_{10}O$	48	95:5

SCHEME 3



The work of Kessar and co-workers illustrates how a warm−cool cycle can invert an enantiomeric ratio.[5] The lithiation of BF_3-complexed *N*-ethyl pyrrolidine under kinetic control provides lithiated diastereomers with (*R*)-**8**/L* as the major compound. When the reaction is kept at −78 °C followed by addition of benzophenone, (*S*)-**9** is the major product. However, if the lithiated intermediates are warmed to 0 °C and stirred for 2 h, then cooled to −78 °C before addition of benzophenone, the enantiomeric ratio is reversed and (*R*)-**9** is the major product (Scheme 3). The reaction at −78 °C occurs without equilibration and warming to 0 °C allows the diastereomeric intermediates to equilibrate.

SCHEME 4



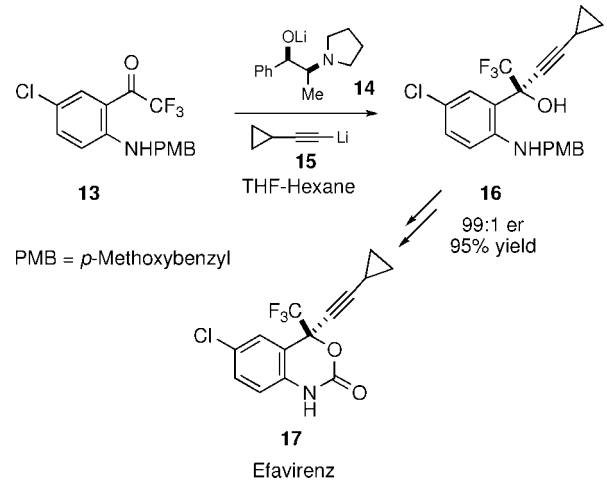
T_1 (°C)	TMSCl (equiv)	Yield (%)	er (*R*:*S*)
-78	1.0	52	56:44
-25, -78	1.0	72	90:10
-78	0.1	n/a	91:9
-25	0.1	76[a]	99:1

[a] The warm−cool cycle was repeated for a total of 10 times.

For reactions in which the activation energies for conversion of the diastereomers to product are significantly different, it is possible to achieve enantioenrichments higher than that provided by their thermodynamic ratio. An illustrative case is the dilithiation of **10** to give racemic **11**, which upon treatment with (−)-sparteine followed by reaction with tetramethylsilyl chloride (TMSCl) yields (*R*)-**12** and (*S*)-**12**.[6] The initial reaction at −78 °C gives racemic products because there is little equilibration between the diastereomers. The subsequent warm−cool cycle allows equilibration of the diastereomers, presumably to a 90:10 ratio, which leads to an er of 90:10 of the subsequent enantiomers (Scheme 4). The observation that addition of 0.1 equiv of the electrophile for a reaction entirely at −78 °C gives an er significantly different from racemic reveals that each of the diastereomers has a different energy of activation for reaction with TMSCl. The correspondence of er's from the reaction with 1.0 equiv of the equilibrated system with the 0.1 equiv with the unequilibrated system establishes that the more populated diastereomer has the lower activation energy. Hence, successive cycles of equilibration and limited amounts of reagent offer an opportunity for enrichment higher than is available from the thermodynamic ratio of the enantiomers. A ten step sequence provided a yield of 76% with an er of 99:1. In this case, a reaction that has initially an unpromising er has been converted to a reaction that provides a high er by the use of DTR.

Separation of the thermodynamic and dynamic steps in a warm−cool cycle has been used by Collum, Grabowski, and co-workers for the synthesis of the HIV reverse transcriptase inhibitor efavirenz, **17**.[7] The highly stereoselective 1,2-addition reaction of **15** to **13** requires the formation of 2:2 tetrameric complex of alkoxide **14** and lithium acetylide **15**. Generation of the alkoxide−acetylide mixture at low temperature and subsequent reaction with **13**, without establishing equilibrium, provided the addition product **16** with 93:7 er

SCHEME 5



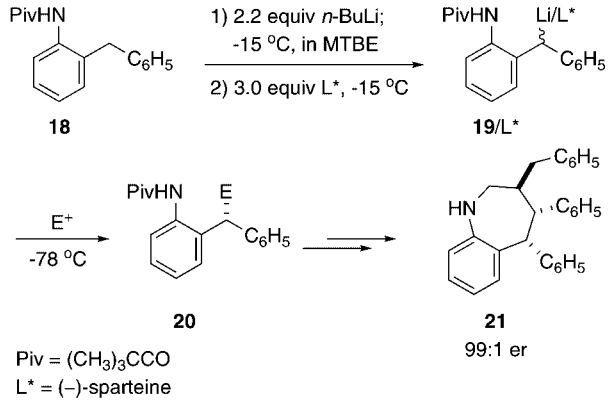
(Scheme 5). However, a higher yield and a higher enantioselectivity of 99:1 were obtained when 2.0 equiv of **14** and 2.0 equiv of **15** were allowed to equilibrate prior to reaction with the ketone **13**.

The equilibration of diastereomers can be solvent-controlled. The lithiation and substitution of the substrate **18** with *s*-BuLi in the presence of (−)-sparteine in diethyl ether was found by Wilkinson et al. to be kinetically controlled, with diastereomeric complexes in rapid equilibrium, to give er's in the range of 73:27 to 88:12. [8] However, Park and co-workers found that in methyl *t*-butyl ether (MTBE) the sequence becomes thermodynamically controlled and provided er's in the range of 88:12 to 98:2 (Scheme 6). An interesting feature of this result is that no precipitation is evident, suggesting that a soluble complex can drive the critical diastereomeric equilibration. Subsequently, the methodology was applied to the asymmetric synthesis of a 3,4,5-substituted benzazepine system **21** in high yield.[9]

O'Brien et al. studied the lithiation−substitution of *N*-pivaloyl-*o*-ethylaniline **23**, following preparation of the chiral (+)-sparteine surrogate **22**.[10] After treatment of **23** with 2.4 equiv of *s*-BuLi in diethyl ether at −25 °C for 2 h, the dianion was treated with 2.9 equiv of **22** followed by equilibration for 45 min at −25 °C and cooling to −78 °C. Addition of trimethylsilyl chloride, gave 58% of the silylated product (*S*)-**24** with 93:7 er (Scheme 7). This result is comparable to that of the (−)-sparteine process, which provided 72% yield of (*R*)-**24** with 95:5 er.[11]

Another interesting illustration of solvent control that allows the enrichment of either enantiomer from the same reactants by taking advantage of DTR has been reported by Hoppe and co-workers for the synthesis of highly enantioenriched vinylallenes.[12] The reaction of the carbamate **25** with *n*-BuLi/(−)-

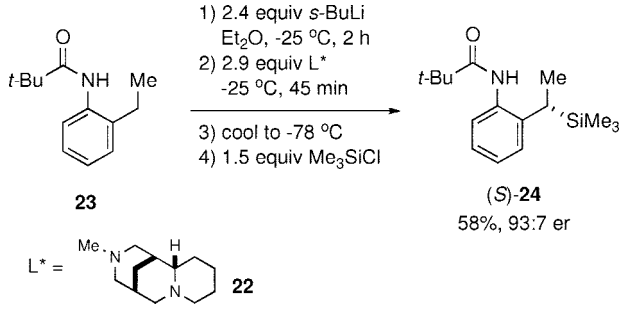
SCHEME 6



E	yield (%)	er (*R*:*S*)
$PhCH_2$	80	93:7
p-$BrC_6H_4CH_2$	85	98:2
CH_2=$CHCH_2$	80	94:6
$(CH_3)_3Sn$	85	88:12
$Ph(CH_3)_2Si$	77[a]	90:10
PhCHO	95[b]	99:1 ; 90:10
p-BrC_6H_4CHO	85[c]	98:2 ; 73:27
$(CH_3O_2C)_2CHCHCH_3$	66[d]	99:1 ; 89:11

[a] Base was *s*-BuLi. [b] dr is 81:19. [c] dr is 97:3. [d] dr is 92:8.

SCHEME 7

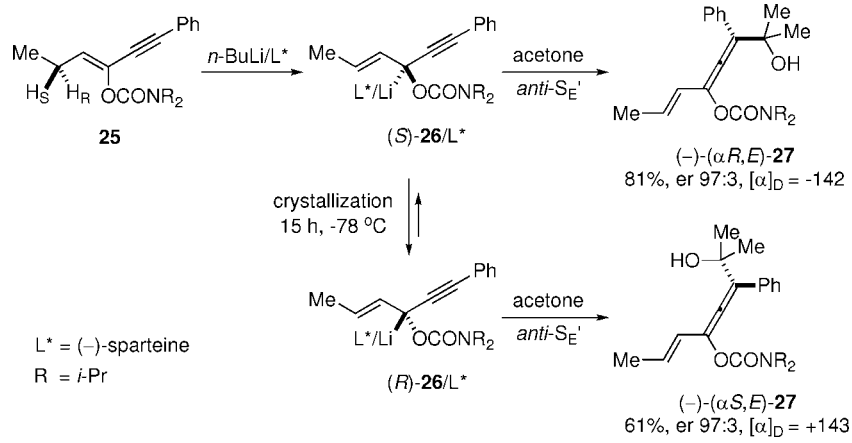


sparteine in toluene at −78 °C for 30 s formed the lithium chelate (*S*)-**26**/L*, which on reaction with acetone provided (α*R*,*E*)-**27** in 81% yield with an er of 97:3. However, when a pentane/toluene mixture was used as solvent, a brownish precipitate was formed, which upon stirring for 15 h followed by addition of acetone, provided the opposite enantiomer (α*S*, *E*)-**27** in 61% yield with an er of 97:3 (Scheme 8). The initial reaction is an asymmetric lithiation with (−)-sparteine to provide (*S*)-**26**/L*. Subsequent equilibration drives the reaction to (*R*)-**26**/L*. Each of the epimers then subsequently reacts with acetone to give, respectively, the enantiomers of **27**. The results are consistent with the formation of (*S*)-**26**/L* as the kinetic diastereomer, which is transformed to the thermodynamically stable diastereomer (*R*)-**26**/L*. The precipitation, which apparently involves selective crystallization, appears to provide the thermodynamic driving force for the equilibration.

Lete and co-workers investigated the α-oxybenzyl lithium complexes of **29**/L* generated by deprotonation of **28** with *s*-BuLi in the presence of (−)-sparteine (1.1 equiv) at −78 °C. After 5 min, reaction with imine **30** under various conditions gave the *threo* isomer of **31** as the major diastereomer (Scheme 9). The reaction provided the best diastereo- and enantioselectivity when an excess of the *s*-BuLi/(−)-sparteine (2.2 equiv) was used and the reaction was quenched at low temperature to give single diastereomers. The enantiomeric ratio was significantly improved after recrystallization to 98:2.[13] The generation and use of the α-oxybenzyllithium derived from *O*-benzyl carbamate and *s*-BuLi/(−)-sparteine in the coupling reaction with a prochiral imine provided enantioenriched *threo*-β-amino alcohol derivatives with modest to good er's. The stereochemical outcome of the reaction indicates that the organolithium intermediate with the (*S*)-configuration is favored by equilibration, and the subsequent addition reaction takes place with retention of configuration to give (1*R*,2*R*)-**31** as the major enantiomer.

The extent of equilibration of an intermediate diastereomeric complex can be controlled by a chiral ligand. The deprotonation of the thiocarbamate **32** reported by Hoppe with 1.2 equiv of *n*-BuLi in toluene is completed in 30 min at −78 °C. With (−)-sparteine in the reaction mixture, a product with moderate er (73:27) is obtained in 97% yield after addition of trimethylsilyl chloride. Changes in the reaction temperature, solvent, and deprotonation times did not lead to significant improvements in the enantiomeric ratio of the silylation product. It was shown that the configuration of the C−Li bond complexed with (−)-sparteine is not stable under the reaction conditions and that the (−)-sparteine ligand does not provide significant differentiation between the two enantiomeric protons.[14] However, the same reaction in the presence of the chiral bis(oxazoline) ligands **35** or **36** yielded the silylation product with an er of >99:1 in 87% yield. The *in situ* reactions with the same chiral ligands and trimethylsilyl chloride as an electrophile provided a product with an er of 52:48, suggesting that enantiotopic differentiation is not occurring during the deprotonation step. Longer deprotonation time or warming the reaction mixture to higher temperature (−25 °C) facilitated thermodynamic equilibration of the diastereomers (*S*)-**33**/L* and (*R*)-**33**/L* to give the enantioenriched substitution product (Scheme 10). Substitution reactions with allyl bromide, methyl triflate, triethylsilyl chloride, and pivaloyl chloride also provided high selectivities and good yields. This

SCHEME 8



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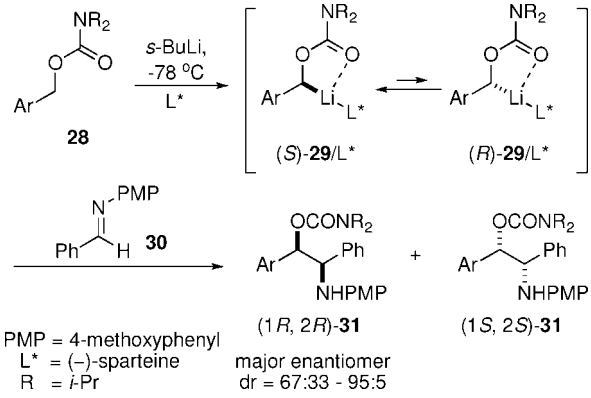
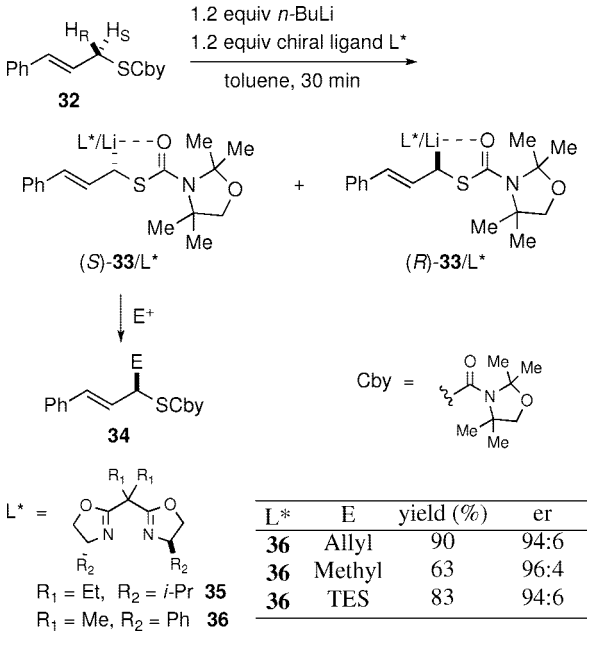


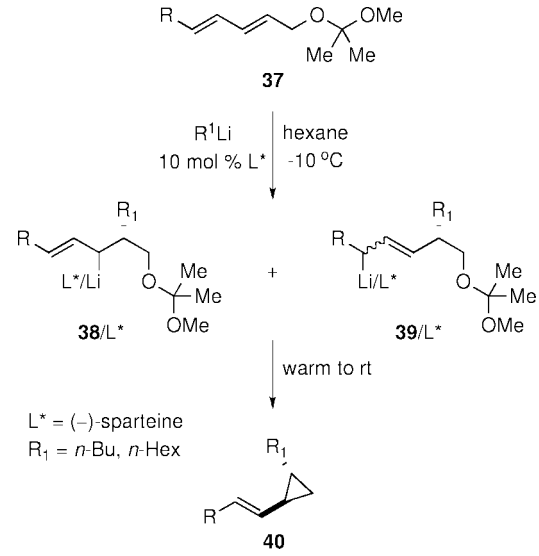
SCHEME 10



L*	E	yield (%)	er
36	Allyl	90	94:6
36	Methyl	63	96:4
36	TES	83	94:6

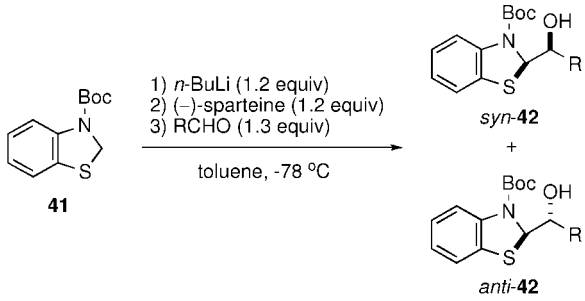
approach provides efficient access to acyclic, highly enantioenriched allylic thiol derivatives **34**.

SCHEME 11



Marek and co-workers showed that the course of a lithiation–substitution reaction involving DTR could be controlled by diastereomeric equilibration with less than 1 equiv of the chiral ligand. The formation of enantioenriched 1,2-disubstituted cyclopropanes, by carbolithiation of the mixed acetal **37** in the presence of (–)-sparteine, occurs by an intramolecular displacement. Upon warming, a 1,3-elimination gives the chiral 1,2-disubstituted cyclopropanes **40** with er's greater than 95:5 (Scheme 11). The allylic organolithium species is a mixture of *cis*- and *trans*-diastereomers. If the reaction mixture is warmed to room temperature as soon as the carbolithiation is completed, the formation of the vinyl cyclopropanes occurs in yields of 45–70% with er's up to 92:8. The configuration of the initially formed stereogenic center does not change in the 1,3-elimination reaction, but upon warming, the configuration of the allyl lithium is equilibrated

SCHEME 12



R	yield (%)	*syn*/*anti*	*syn* er	*anti* er
Ph	93	60:40	97:3	94:6
p-MeC_6H_4	92	53:47	88:12	97:3
p-$MeOC_6H_4$	92	55:45	86:14	94:6
p-ClC_6H_4	96	51:49	89:11	95:5
1-Naphthyl	89	57:43	86:14	93:7
2-Naphthyl	97	58:42	87:13	93:7

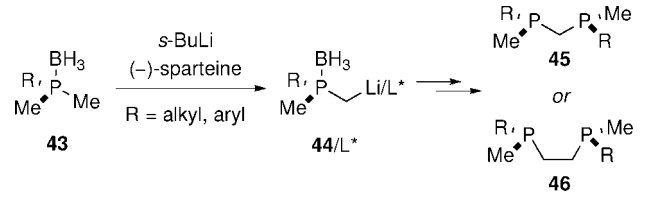
to provide the thermodynamically more stable (*E*)- and the *trans*-disubstituted vinylcyclopropanes.[15]

Toru reported that reaction of lithiated *N*-Boc-benzothiazolidine **41** with aromatic aldehydes in the presence of (−)-sparteine provided *syn*- and *anti*-**42** with high enantioselectivity and low diastereoselectivity (Scheme 12).[16] A mechanistic study revealed that the reaction proceeded by asymmetric substitution and not by asymmetric deprotonation. A test with a deficient amount of an electrophile confirmed the reaction proceeded through a DTR pathway. Each diastereomer could be converted to the corresponding chiral ethane diol by hydrolysis followed by reduction, hence the lithiated anions served as formyl anion synthetic equivalents.

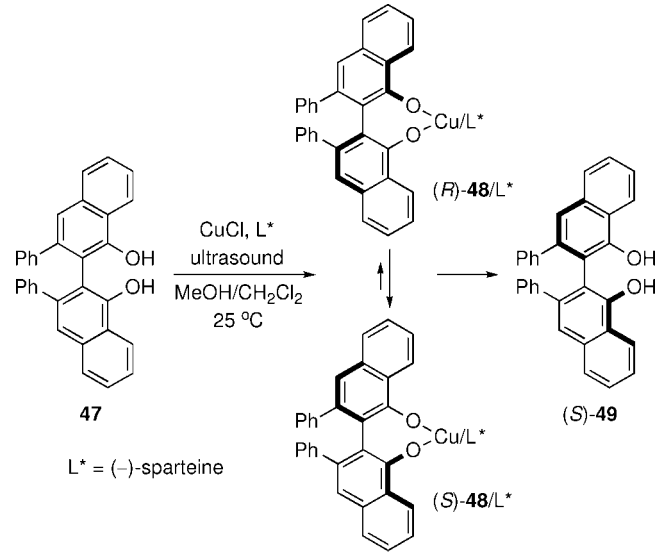
Valentine et al. developed the preparation of enantiomerically pure tertiary alkyl and aryl phosphines for asymmetric catalysis using DTR. The borane complexes of alkyldimethyl- or aryldimethylphosphines **43** were treated with *s*-BuLi in the presence of (−)-sparteine to afford the diastereomers **44**/L*. Control of the enantioselectivity was obtained by equilibrating the diastereomeric organolithium intermediates prior to their conversion to **45** and **46** (Scheme 13).[17]

Wulff and co-workers used an *in situ* generated copper(II)−(−)-sparteine species to drive the deracemization of BINOL, VAPOL, and VANOL ligands.[18] The equilibration of the VANOL complex was carried out with *in situ* generation of copper(II) chloride. The product was obtained with 61% recovery and >99:1 er. Subsequent removal of the copper and the ligand gave the (*S*)-enantiomers of BINOL, VANOL, and VAPOL (Scheme 14).

SCHEME 13



SCHEME 14

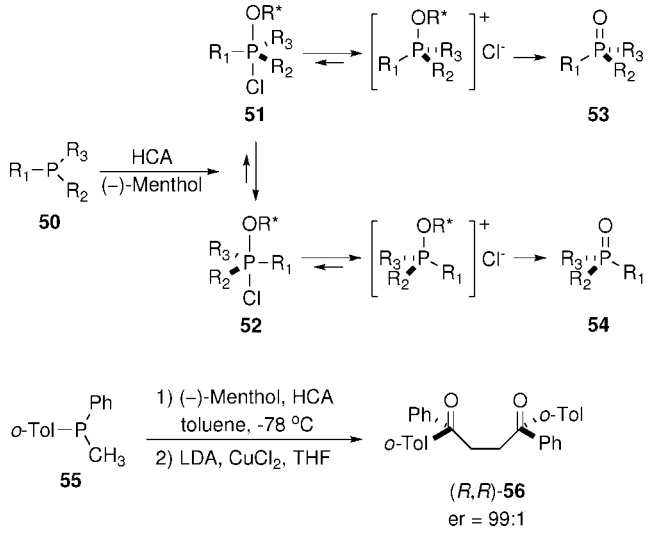


Auxiliary-Based Control

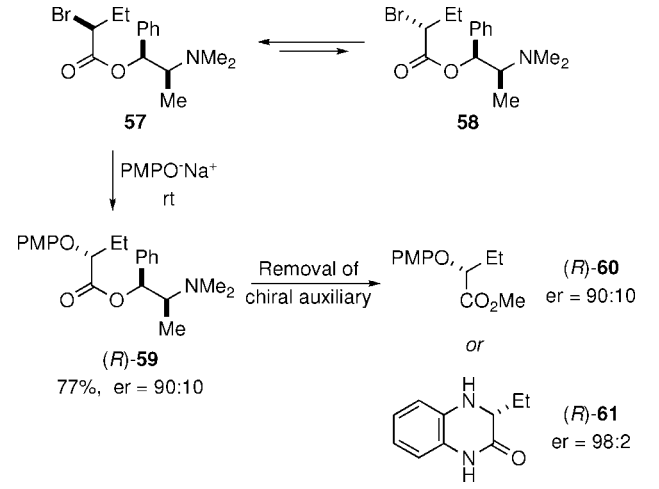
Dynamic resolutions that involve equilibrations of diastereomers have been recognized for a number of reactions that involve chiral auxiliaries. An interesting case in which a chiral auxiliary is both generated by covalent bond formation and then cleaved during the resolution is the oxidative resolution of **50** reported by Gilheany et al.[19] The reaction of a racemic phosphine **50** with hexachloroacetone (HCA) and (−)-menthol provided the corresponding phosphine oxide **54** in high yield and high er (Scheme 15). The (−)-menthol used as a transfer chiral auxiliary was converted to (+)-neomenthyl chloride in the course of the reaction. The stereoselection may be attributed to the equilibration of the intermediate diastereomers **51** and **52** or the corresponding alkoxyphosphonium salts through DTR. The use of the reaction to provide the chiral ligand (*R*,*R*)-**56** from **55** with an er of 99:1 is remarkably efficient.

Dynamic resolutions after intentional equilibrations of diastereoisomers have been recognized for a number of reactants with chiral auxiliaries. Park et al. studied the reaction of the *N*-methyl pseudoephedrine α-bromo-α-ethyl esters **57** and **58** (α*R*/α*S*=56:44) with sodium *p*-methoxyphenoxide ($PMPO^-Na^+$). They found the reaction provided (*R*)-**59** in a 75:25 er after methanolysis. However, when the starting ester

SCHEME 15



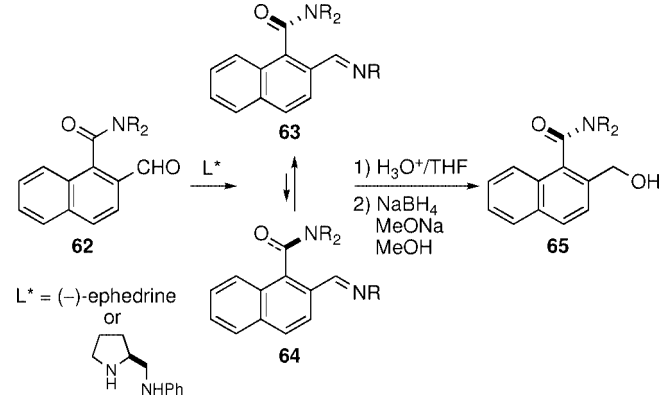
SCHEME 16



was equilibrated with triethyl amine before treatment with a nucleophile, equilibration provided an 89:11 ratio of the two diastereomers. Subsequent treatment of the equilibriated mixture with sodium *p*-methoxyphenoxide ($PMPO^{-}Na^{+}$) gave (*R*)-**59** with a 90:10 ratio in 77% yield, which was then converted to (*R*)-**60** with the same er (Scheme 16).[20] The dependence of the product ratio on the diastereomeric ratio of the α-bromo compounds shows equilibration of the α-bromo esters to be slower than the substitution reaction. With 1,2-phenylenediamine as the nucleophile, a subsequent intramolecular cyclization provided the α-substituted dihydroquinoxalinone **61** with an er of 98:2. The low nucleophilicity of the aniline amino group presumably provided time for the starting ester to equilibrate, resulting in an enhanced er.

Clayden very nicely employed auxiliary-controlled DTR for the preparation of single atropisomers of aromatic tertiary amides. Condensation of the 2-formyl naphthamide **62** with

SCHEME 17



a proline-derived 1,2-diamine or with (−)-ephedrine in refluxing toluene afforded single atropisomers of imidazolidine or oxazolidines **63** and **64**. Hydrolysis of the auxiliaries followed by immediate reduction of the corresponding aldehyde provided the enantiomerically enriched alcohols **65** (Scheme 17). The conformational preference about the atropisomeric axis accounts for the observed stereochemical thermodynamic control.[21]

In a related investigation by Clayden, the two atropdiastereoisomeric sulfoxides **67**, derived from the reaction of **66** with (−)-menthyl *p*-toluenesulfinate, were seen to be critical intermediates in an efficient and high yielding DTR. The more stable of the diastereoisomers, *anti*-**67**, was used for the sulfoxide−lithium exchange to regenerate an enantioenriched nucleophilic organolithium reagent. Its subsequent use led to **68** with high er's (Scheme 18). [22] Clayden also showed that the stereocontrolling unit is the chiral axis in tertiary amidophosphine ligands in a similar allylic alkylation.[23]

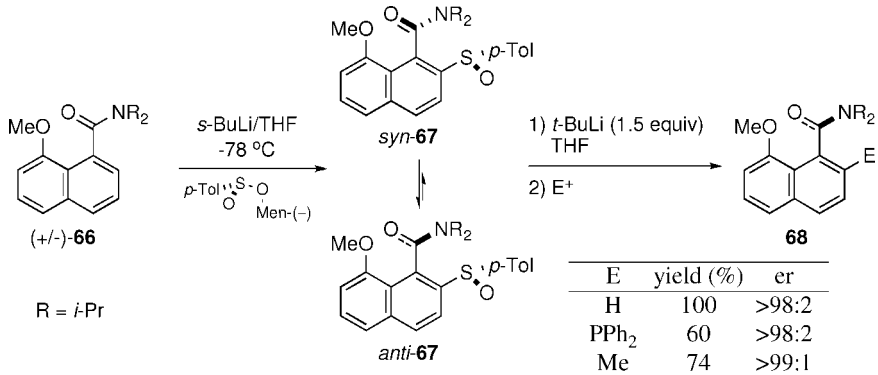
An asymmetric synthesis of bisoxazoline atropisomers by DTR was reported for a copper-mediated Ullmann reaction by Meyers in the conversion of **69** to **70** and **71** (Scheme 19). The (*S*,*S*,*R*)-**70**−Cu complex has unfavorable nonbonding interactions between the two isopropyl groups and results in the equilibrium favoring the (*S*,*S*,*S*)-**71**−Cu complex by 93:7.[24]

Crystallization-Based Control

For DTRs in which precipitates are present, the driving force is likely the well-known crystallization-induced dynamic resolution (CIDR). A review of CIDR has recently been published.[25] For CIDR, the subsequent diastereoselective reaction leading to an enantioenriched product needs to occur before loss of configuration. Both ligand-based and auxiliary-based cases are known.

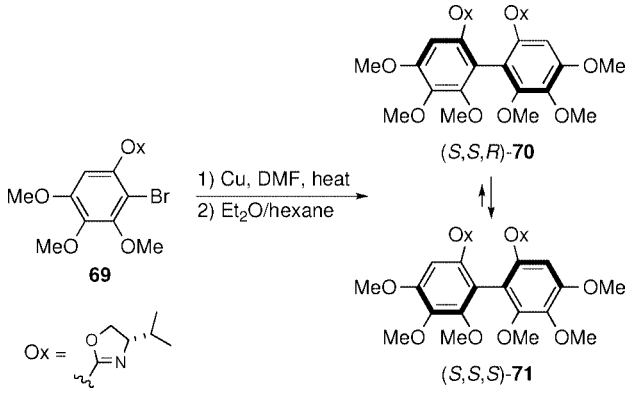
In 1995, Hoppe and Boche reported crystallization-induced dynamic resolution of (−)-sparteine-coordinated lithium indenides. Deprotonations of 1-alkylindenes **72** by *n*-butyl-

SCHEME 18

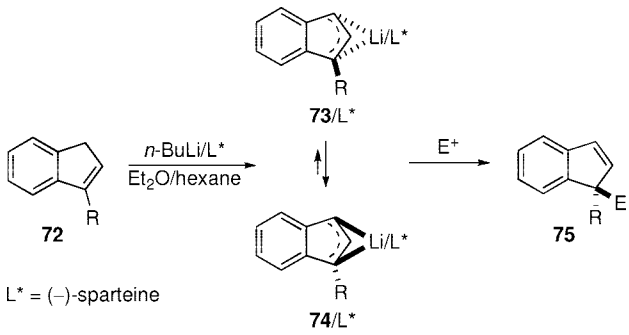


E	yield (%)	er
H	100	>98:2
PPh_2	60	>98:2
Me	74	>99:1

SCHEME 19



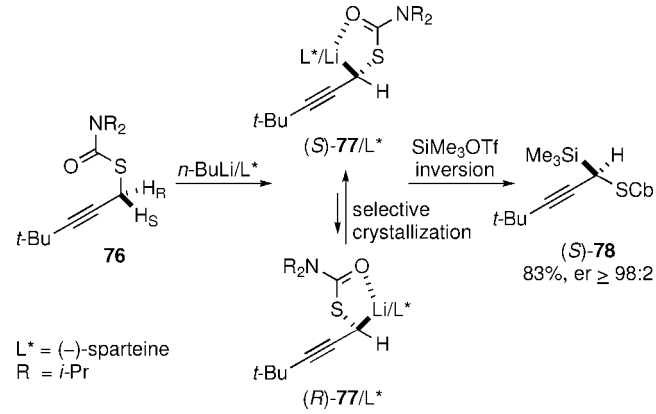
SCHEME 20



lithium/(−)-sparteine in ether/hexane with subsequent crystallization, followed by addition of electrophiles, yielded 1-substituted indenes **75** with high ers (>98:2) and retention of configuration (Scheme 20).[26]

Hoppe showed that the lithiation of the propargylic thiocarbamate **76** with *n*-BuLi in the presence of (−)-sparteine in pentane gives a mixture of (*R*)-**77**/Li and (*S*)-**77**/Li. At temperatures below −30 °C, the (*S*)-isomer selectively crystallized and its absolute configuration was established. Reaction of the precipitate with trimethylsilyl triflate (TMSOTf) provided (*S*)-propargylsilane **78** in 83% yield with an er of ≥98:2 (Scheme 21).[27] When the precipitated crystal was dissolved, kept in toluene at −78 °C for 6 h, and subsequently treated with

SCHEME 21

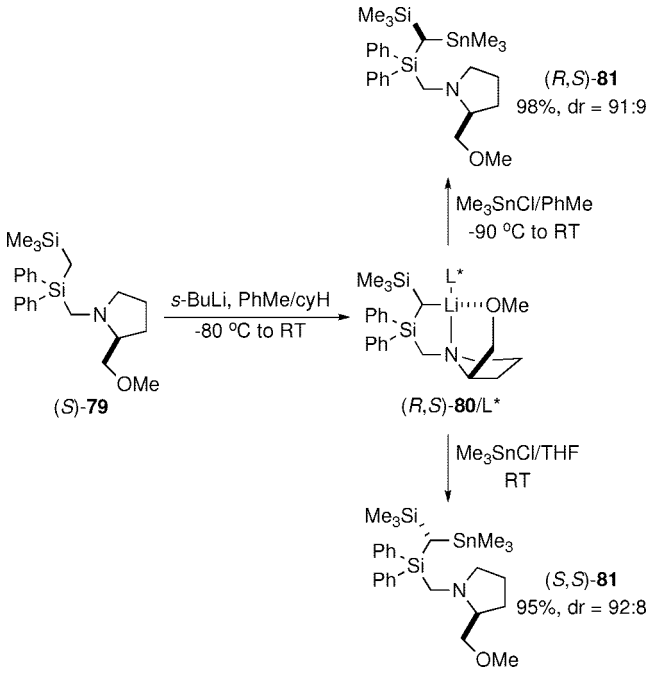


TMSOTf, an identical er was obtained, establishing the configurational stability of (*S*)-**77**/Li.

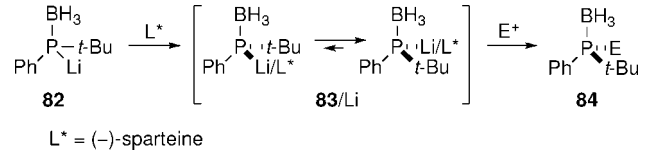
Strohmann and co-workers reported the synthesis of the highly diastereomerically enriched α-lithiated alkylsilanes **80** using (*S*)-2-(methoxymethyl)pyrrolidine (SMP) as a chiral auxiliary. The choice of the reaction solvent influences the stereochemical outcome. The lithiation of (*S*)-**79** in toluene/cyclohexane gave a precipitate, assigned as (*R,S*)-**80**/L*, which on reaction with trimethyltin chloride afforded (*R,S*)-**81** with a dr of 91:9. In THF, the same electrophile provided (*S,S*)-**81** with 92:8 dr (Scheme 22). In the presence of THF, two diastereomeric alkyllithiums **80**/L* were observed by ^{13}C NMR spectroscopy at room temperature.[28]

Livinghouse and co-workers showed that stereoselectivity in the synthesis of the phosphine derivative **84** results from a crystallization-induced dynamic resolution. The lithiated *tert*-butylphenylphosphine-borane **82** in the presence of (−)-sparteine at −78 °C furnished a nearly homogeneous solution of **83**/Li, which upon warming to 25 °C, deposited a precipitate (Scheme 23). Subsequent reaction with an electrophile gave the substituted products **84** with er's of 96:4 to >99:1. Precipitation was found to be crucial to the success of the pro-

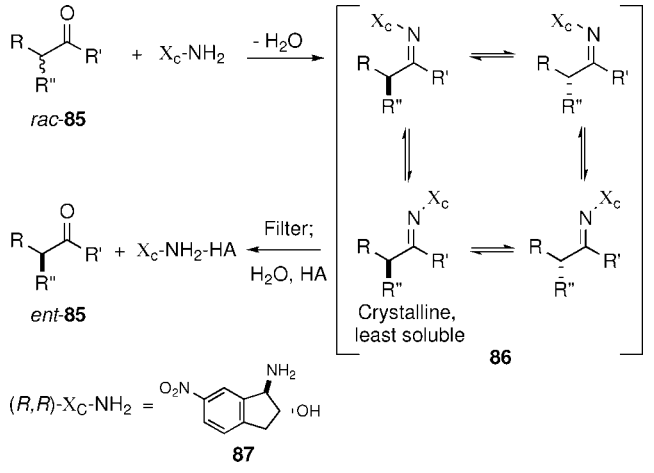
SCHEME 22



SCHEME 23



SCHEME 24



cedure.[29] If the reaction was warmed to 0 °C for 30 min prior to addition of the electrophile, an er of 68:32 was obtained.

A remarkably useful auxiliary-mediated CIDR of unfunctionalized aldehydes and ketones was developed by Evans by formation of crystalline imines **86**, using amine **87** as the resolving reagent (Scheme 24). While the dr's of all *E*/*Z* isomers of **86** were close to 1:1 in solution, crystallization of the imines resulted in improved selectivity. The best results were obtained with unpurified solid imine stirred as a solid–liquid mixture at 23 °C in polar solvents. A simple one-flash preparation of the imine followed by hydrolysis with aqueous $CuCl_2$ afforded *ent*-**85** in high yields with high er's.[30]

Summary

For many asymmetric reactions, the variables of time, temperature, solvent, and use of chiral nonracemic ligands or auxiliaries can be easily controlled. Rational management of these variables for reactions in which stable diastereomers are subject to equilibration may allow separation of thermodynamic and kinetic steps of a resolution and provide significant improvement in enantiomeric ratios. Although the most well recognized and developed examples of DTR are in organolithium chemistry, its application can be more extensive. In favorable cases, the approach is often more efficient than more global changes.

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BIOGRAPHICAL INFORMATION

Won Koo Lee received his B.S. and M.S. degrees from Sogang University, Korea, and his Ph.D. from the University of Illinois at Urbana–Champaign. After postdoctoral work at the University of California at Berkeley, he returned to Korea and joined the faculty of Sogang University in 1993. His research interests are chiral aziridine chemistry, synthesis of structurally modified amino acids, and natural product synthesis.

Yong Sun Park received his B.S. and M.S. degrees from Yonsei University, Korea, and his Ph.D. from the University of Illinois at Urbana–Champaign in 1996. Since he joined the faculty of chemistry department of Konkuk University in 1998, he has been primarily interested in the invention of new asymmetric synthetic methodologies.

Peter Beak received his B.A. from Harvard University and his Ph.D. from Iowa State University. He joined the faculty at the University of Illinois at Urbana–Champaign in 1961. His research area is synthetic methodology and reactive intermediates.

FOOTNOTES

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2 For an excellent summary of an applicable kinetics analysis, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; p 647. Andraos, J. Quantification and Optimization of Dynamic Kinetic Resolution. *J. Phys. Chem. A* **2003**, *107*, 2374–2387, and references therein. We prefer the use of enantiomeric ratios (er's) rather then enantiomeric excesses (ee's) because (1) er's are directly measured, (2) er's are directly related to the diastereomeric energy difference in intermediates or transition states, which control the product ratios, and (3) er's are a more accurate reflection of the actual improvement in the course of investigation of an asymmetric reaction. For example, improving an ee from 80 to 90 is actually an er change from 90:10 to 95:5. In order to compare to previous literature values of ee, we prefer to report er's as summing to 100. See: Gawley, R. E. Do the Terms "% ee" and "% de" Make Sense as Expressions of Stereoisomer Composition or Stereoselectivity? *J. Org. Chem.* **2006**, *71*, 2411–2416.

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