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Overview of Carbanion Dynamics and Electrophilic Substitutions in Chiral Organolithium Compounds

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Introduction

It has been noted that “organolithiums are the most widely used organometallics in contemporary organic chemistry”.¹ The undeniable truth of this statement derives partly from the widespread use of commercially available butyllithium isomers as bases, but it is not an exaggeration to state that functionalized organolithiums in more complex molecules are important species in their own right, as evidenced by the large number of reviews and monographs that have appeared since 1990.^{1–7} Lithium, atomic number 3, is the smallest of the metals, but the structure of organolithium compounds and their reaction chemistry can be diabolically complex. This complexity is in part due to the electrostatic nature of bonding between lithium and carbon, and the tendency of organolithium compounds to aggregate.^{8,9} The possibility of homochiral and heterochiral aggregates is usually not addressed in studies of the steric course of chiral organolithium reagents. In this review, the aggregation state of the various organolithiums will not normally be considered, and for simplicity, they will be drawn as monomers.

The focus of this chapter is the dynamics, mechanism, and steric course of substitution reactions of aliphatic organolithiums whose metal-bearing carbon is stereogenic. There are four comprehensive treatises on organolithium chemistry that have been published since 2002.⁷ Several topics covered briefly in this chapter are elaborated more thoroughly in accompanying chapters of this volume. Examples have been chosen to illustrate particular points, and the original literature or one of the monographs should be consulted for details on scope.

The Carbon-Lithium Bond

What might be called the “degree of covalency” of the carbon-lithium bond varies with temperature, solvent, and structure of the organic component. Collins and Streitwieser have asserted that methyllithium is 79.7% ionic.¹⁰ The situation is considerably more complex than that statement implies, but the view among theoreticians appears to be that the C–Li bond is best described as being ionic.¹¹ A recent review discusses the nature of the C–Li bond, and concludes that “the nature of the C–Li bond varies from compound to compound”, [but] “the covalent components cannot be neglected”.¹²

Some authors prefer to denote the carbon lithium bond as an ion pair in which the lithium and carbon are either in van der Waals contact (a contact ion pair) or separated by solvent (a solvent-separated ion pair). In such instances, scalar coupling between the lithium and carbon atoms can reveal details about structure – especially aggregation state.¹³ Unless the carbanion is considerably stabilized by factors such as delocalization and the lithium ion by solvation, it is unlikely that the lithium cation strays far from the carbanion, so these are the two most relevant representations. The distinction between a polar covalent bond and a contact ion pair is irrelevant to the stereochemical issues under discussion in this chapter,

since the species under consideration are chiral as a result of association with the lithium. Therefore for simplicity, and because it implies a specific configuration, the carbon-lithium bond will normally be drawn as covalent in the chapters of this volume.

Chiral Organolithiums

There are two types of chiral organolithiums commonly encountered, as illustrated in Figure 1: η^1 carbanion ligands associated with the lithium, and having a chirality center at the metal bearing carbon, and unsymmetric η^3 allyl carbanion ligands giving the organolithium compound planar chirality. Such species are enantiomers (isoenergetic) in the absence of any other chirality element, but become diastereomers in the presence of, for example, a ligand on lithium that is also chiral, or another chirality element in the carbanion fragment. A complicating factor in the chemistry of allylic and benzylic organolithiums is that they may be either η^1 or η^3 , or equilibrating mixtures of the two. Often, the solution structure of synthetically useful organolithiums has not been determined, and it is not safe to extrapolate from similar structures.

Methods of Generation of Organolithiums

Several strategies may be used to generate an organolithium, including deprotonation, reductive lithiation, and transmetalation (Figure 2). Deprotonation is only useful if the conjugate acid of the carbanion is activated in some way. Protons α to a carbonyl to form enolates are the obvious example. The chapter in this volume by Simpkins and Weller reviews chiral lithium amide bases in the deprotonation of enantiotopic protons for the formation of enolates, and in several other enantioselective processes.

For deprotonation to form a lithium-carbanion pair, a proximal directing group on a heteroatom, a double bond, or an aromatic ring is usually necessary to activate the proton(s) toward removal by a strong base such as butyllithium. Recent years have seen numerous examples of butyllithium (BuLi) or *sec*-butyllithium (*s*-BuLi) complexed with a chiral ligand, to create a chiral base that is able to effect enantioselective deprotonations by distinguishing enantiotopic protons.^{1,4,5,14,15} The chapter by Kizirian in this volume details the use of organolithium bases such as the alkylolithiums that are coordinated to chiral diamine ligands.

Reductive lithiations include reductions of sulfides, selenides, tellurides, or halides with lithium metal or lithium arenes.^{8,16} Tertiary α -aminoorganolithiums can be made by reductive decyanation.¹⁷ The metal most commonly exchanged for lithium is tin, via the reaction of organostannane compounds with BuLi.^{18,19}

Of these, some are suitable for asymmetric synthesis of configurationally stable organolithiums. Later sections of this chapter deal with organolithiums that can interconvert due to a low inversion barrier, or be dynamically resolved with chiral ligands. More complete coverage of these issues are discussed in the chapters by Hoffmann (the Hoffmann Test for configurational stability) and Coldham and Sheikh (dynamic resolutions of chiral organolithiums). Here, two of the more common methods for preparing configurationally stable organolithiums are summarized briefly.

Asymmetric deprotonations

When chiral ligands such as sparteine are complexed to *sec*-butyllithium, a chiral base is formed. The first highly selective application to stereoselective deprotonation is illustrated in Figure 3a.^{5,20} In this example, there is no mesomeric stabilization which might lower the kinetic barrier to deprotonation, and the α -alkoxy organolithiums are configurationally

stable for hours at low temperature. Shortly after this work on α -alkoxy deprotonations was disclosed, it was applied to enantioselective deprotonation of pyrrolidines, as illustrated in Figure 3b.^{21,22} Note, however, that this deprotonation is much less successful with *N*-Boc piperidines.^{23,24} Possible rationales for the steric course of the deprotonations are shown in the brackets, which assumes that the *s*-BuLi-sparteine complex is monomeric.^{5,20,22,25} In both cases, the H_{Si} proton (*i.e.*, the proton that sits on the *Si* face of the triangle formed by the other 3 ligands on carbon) is removed selectively from a complex formed by coordination of the carbamate carbonyl to the lithium-sparteine chelate.²³

Tin-lithium exchange

Virtually all tin-lithium exchange reactions occur with net retention of configuration at the metal-bearing carbon.²⁶ The challenge of producing enantiopure, configurationally stable organolithiums by tin-lithium exchange therefore reduces to the preparation of enantiopure organostannanes.

Enantiomerically enriched α -alkoxy stannanes can be made by the methods outlined in Figure 4. Asymmetric reduction of acyl stannanes can be accomplished with BINAL-H with excellent enantioselectivity (Figure 4a).¹⁹ The α -hydroxystannanes are stable to isolation and can be derivatized with either benzyloxymethyl chloride or methoxymethyl chloride easily. As shown in Figure 4b, chloroboronates can be treated with tributyltin lithium with inversion; subsequent oxidation affords essentially enantiopure α -hydroxystannanes.²⁷ Figure 4c illustrates the ring opening of stannyl dioxolanes with excellent diastereocontrol. Oxidation and elimination furnish the scalemic α -hydroxystannanes.²⁸

Enantiopure α -aminoorganostannanes are available by the methods shown in Figure 5. Acyclic α -aminoorganostannanes can be prepared by diastereoselective addition of tributyltin lithium to *tert*-butyl sulfinimines, in which the tributyltin nucleophile adds to the *Si* face of the imine, when the sulfoxide has the (*R*) configuration.²⁹ If the R group is unbranched, the sulfoxide can be replaced by an *N*-Boc group by the two step sequence shown. If the R group is branched, a slightly longer route is necessary. Addition of tributyltin lithium to cyclic *N*-acyl iminium ions having the trans-cumylcyclohexyl chiral auxiliary is only modestly selective. The reaction proceeds through a conformationally mobile iminium ion, which probably accounts for the low selectivity. Nevertheless, the diastereomers are separable. Reduction affords enantiopure *N*-methyl-2-(tributylstannyl)-pyrrolidines and -piperidines.³⁰

Of course, one obvious method for making organostannanes is to treat an organolithium with a trialkylstannyl chloride. While apparently redundant, this method has advantages in certain circumstances. For example, it provides the opportunity to prepare an organolithium, by tin-lithium exchange, that is free of diamine ligands such as TMEDA or sparteine, or in a solvent different from that used for the deprotonation, or to swap the activating/directing group for another functional group.

Because the reaction of a mesomerically stabilized organolithium with tributylstannyl chloride often proceeds with inversion, while tin-lithium exchange proceeds with retention, sequential electrophilic substitutions of Li to Sn, then Sn back to Li, can invert the carbanion configuration. Two examples of this lithium-tin-lithium exchange sequence are shown in Figure 6. In the first example, the (*R*)-organolithium is obtained by deprotonation of the conjugate acid with *s*-BuLi-TMEDA. Electrophilic substitution proceeds with inversion to give the (*R*)-stannane. Tin-lithium exchange then affords (*S*)-organolithium.³¹ The laterally lithiated pivanilides shown in Figure 6b are prepared by dynamic resolution of the racemic organolithium with sparteine (see later section for details).^{32,33} Here again, stannylation

occurs with inversion to give the (*R*)-stannane from the (*S*)-lithiopivanilide. Tin lithium exchange from the (*R*)-stannane then yields the (*R*)-organolithium.

Carbanion Dynamics

First of all, note the distinction between enantiomerization and racemization. Enantiomerization is the conversion of one enantiomer to another, whereas racemization describes the conversion of an enantioenriched substance to a racemate. The rate constants for interconversion of two enantiomers are k_{RS} and k_{SR} , whereas the rate constant for racemization is the sum of the two: $k_{rac} = k_{RS} + k_{SR}$.

Questions of configurational stability are critical to the use of chiral organolithium compounds in asymmetric synthesis. The pertinent issue is the *time frame* of configurational stability. Some organolithium compounds are configurationally stable for hours, others for only seconds. The general equation for half-life toward equilibrium for two species (such as stereoisomers) is given by

$$\frac{1}{t_{1/2}} = \left(\frac{k_B T}{h \ln 2} \right) \left(e^{\frac{-\Delta G^\ddagger}{RT}} \right) \left(e^{\frac{-\Delta G^\ddagger}{RT}} + 1 \right),$$

where k_B is Boltzmann's constant, h is Planck's constant, and R is the universal gas constant. When $\Delta G^\circ = 0$ (as in conversion of enantiomers), the relationship simplifies, and can be expressed as

$$\Delta G^\ddagger = RT \ln \left(\frac{2k_B T t_{1/2}}{h \ln 2} \right).$$

This relationship is plotted in Figure 7 for three temperatures (0, -40, and -80 °C). While recognizing that free energy is, itself, a function of enthalpy, entropy, and temperature, Figure 6 illustrates that, at a given temperature, very small differences in $\Delta G^\ddagger$ can have a profound effect on the lifetime of chiral carbanions. This relationship is important, not only to the types of organolithiums discussed in this chapter, but also to the configurationally labile enolates discussed in the chapter by Carlier, Hsu, and Bryson in this volume.

Relative Rates: Inversion vs Substitution

Unlike S_N2 reactions, in which only invertive substitution is allowed by a concerted pathway, S_E2 reactions are allowed for both retentive and invertive concerted (polar) pathways.³⁴ Because both are observed, the steric course is distinguished by adding the suffixes “ret” and “inv” for retentive and invertive substitutions, respectively.³⁵ Thus, electrophilic, aliphatic, bimolecular substitutions, abbreviated S_E2 in the Hughes-Ingold terminology,³⁶ may be categorized as S_E2ret or S_E2inv ,³⁵ depending on the steric course. Single electron transfer (SET) can occur by oxidation of the carbanion to a radical, which opens new reaction manifolds that can be problematic to a synthesis plan.

The two limits for the rate of carbanion inversion are very fast and very slow - relative to the rate of reaction with an electrophile. These are considered first; subsequently, situations in which inversion and substitution compete are discussed.

Fast Inversion

When the rate of organolithium epimerization is fast relative to reaction with an electrophile, Curtin-Hammett kinetics^{37,38} ensue. The energy profile is as shown in Figure 8. The relative energies of the organolithiums, (*R*)-RLi and (*S*)-RLi, are not relevant; that is, they may be enantiomers or diastereomers. In Figure 8, the barrier to inversion, $\Delta G_{im}^\ddagger$, is low compared to the energy of activation for any substitution manifold, $\Delta G_{sub}^\ddagger$, by whichever pathway is favored. Under these conditions, evaluating the steric course of the reaction is not a trivial matter.

Slow Inversion

At the other extreme are compounds that are configurationally stable for relatively long periods of time. The reaction profile for this situation is illustrated in Figure 9. If the configuration of the organolithium is known, then the configuration of the product(s) allows determination of the steric course. A mixture of stereoisomeric products could imply competing S_E2inv/S_E2ret reaction pathways, or competition between such polar pathways and SET. If the latter can be ruled out (*vide infra*), for example by using radical clock electrophiles,³⁹ the product ratio can be used to evaluate the relative rates of invertive vs retentive substitution using transition state theory ($\Delta\Delta G^\ddagger$ in Figure 9).

Benzylic Systems

Benzylic organolithium compounds usually have low configurational stability, and enantiomerization can be studied by dynamic NMR spectroscopy (DNMR). Several examples, whose thermodynamic parameters have been established, are given in Figure 10. The benzylic lithiohydrocarbon shown in Figure 10a enantiomerizes through a solvent-separated ion pair.⁴⁰ The α -thio and α -seleno compounds in Figure 10b/c also involve a solvent separated ion pair, but the rate determining step in these cases is rotation around the carbanion C–S or C–Se bond, as influenced by the hyperconjugation between the Li–C bond and the σ^* orbital of the C–S or C–Se bond.^{41–43} Enantiomerization in the examples in Figure 10a–c involve formation of a solvent-separated ion pair from the contact ion pair. This ion separation probably involves coordination of an additional solvent molecule to the lithium, consistent with the negative entropies of activation for these examples. Alternatively, the negative entropy of activation may be attributable to the formation of a larger dipole resulting in electrostatic restriction of the solvent.⁴³ The chelated α -silylbenzylic organolithium illustrated in Figure 10d enantiomerizes by a conducted tour mechanism,⁴⁴ that is, the lithium remains chelated by the tertiary amine as it moves from one face of the carbanion to the other.⁴⁵ Very similar dynamics were observed in an analogous allylic system in which the phenyl ring is replaced by a double bond.⁴⁶ Here again, the negative enthalpy of activation is consistent with additional solvation of the transition state. The α -aminobenzylic lithium illustrated in Figure 10e, which is monomeric in THF, equilibrates between η^1 and η^3 isomers. Enthalpic and entropic enantiomerization barriers were not determined for this compound, but the free energies of enantiomerization at the coalescence point were determined in THF alone, and with *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDTA, Figure 10, inset).⁴³ Interestingly, the addition of amine additives that coordinate lithium raise the barrier slightly. Most probably, the rate determining step in this case is the formation of a solvent-separated ion pair, and the authors note that additives clearly affect the nature of the contact ion pair, but do not necessarily facilitate the formation of the solvent-separated ion pair.⁴³ For the examples in Figure 10a–d, the free energies are plotted as a function of temperature. Note the profound effect that the negative entropy has on the free energy barriers of the examples in Figure 10a,b, and d. Since these compounds have

$\Delta G^\ddagger \leq 12.5$ kcal/mol at temperatures from -80 to $+25$ °C, and with reference to Figure 7, it is clear that all of these are organolithiums configurationally labile.

Nonbenzylic systems

In the absence of mesomeric delocalization, the carbanion is η^1 coordinated to the lithium, but enantiomerization parameters have only been determined for a few systems. The meso organolithium shown in Figure 11 is an example of an organolithium which is configurational stable for only a few minutes at -78 °C.⁴⁷ The rate of epimerization of this lithiohydrocarbon was accelerated by lithium iodide and was strongly dependent on the total organolithium concentration, suggesting that the inversion involves a dimeric (or possibly higher) aggregate in the transition state. Consistent with this hypothesis is the fact that the tridentate ligand, PMDTA, which would be expected to inhibit aggregation, retards the rate of epimerization by a factor of 20, and increases the half life from 9 minutes to greater than two hours at -78 °C.

Heteroatom Stabilized Systems

The dynamics of enantiomerization of heteroatom-stabilized organolithiums can vary widely, as shown by the examples in Figure 12. The lithiated *S,N* acetal shown in Figure 12a⁴⁸ is related to several acyl anion equivalents that have been developed (see below).⁴⁸⁻⁵¹ This organolithium is a monomer in solution, and the barrier to inversion is similar in magnitude to the examples in Figure 10. Two pairs of examples illustrate the difficulty in predicting the effect of chelation on enantiomerization barriers.⁵² Figure 12b-c illustrate organolithiums stabilized by two silane groups; in the latter instance, chelation by a tertiary amine lowers the free energy barrier slightly. The authors found that the enantiomerization is unimolecular and suggest that the chelated example may invert by a concerted tour mechanism.^{44-46,53} In this context, the “concerted tour” refers to a mechanism whereby the cation is “escorted” from one face of the carbanion to the other by a pendant heteroatom, to which it remains coordinated.

The effect of chelation in the two examples in Figure 12d-e, having one α -thio and one α -silyl group, is the opposite of that in the examples of Figure 12b-c.⁵² Even though the enantiomerization is also unimolecular, chelation raises the free energy of activation. The small entropies of activation in these examples suggest minimal additional solvation in the transition state. Since these compounds all have $\Delta G^\ddagger \leq 12$ kcal/mol below $+25$ °C, and with reference to Figure 7, it is clear that none will have appreciable configurational stability.

The lithiated pyrrolidines shown in Figure 13a-c are much more stable, and could not be evaluated by DNMR.⁵⁴ The dynamics were evaluated in a 4:1 hexane:ether solvent mixture because similar compounds can be resolved dynamically in the presence of a chiral ligand in this solvent system.⁵⁵ All show first order kinetics for enantiomerization, but this would be observed for a monomer to monomer or a dimer to dimer inversion. The solution structures are complex,^{54,56} and hypotheses about the mechanism of enantiomerization are tentative. Computational studies indicate that the lowest energy transition structures for solvated enantiomerization of all three lithiopyrrolidines are monomeric.^{54,57} The *N*-methoxyethylpyrrolidine and the *N*-ethylpyrrolidine in Figure 13a-b have significantly larger enthalpies of activation than any of the previous examples, and negligible entropies of activation. The enantiomerization of the *N*-ethyl compound, which exists as a mixture of monomer and dimer, was accelerated by PMDTA, consistent with a lower barrier in a monomeric transition state. The enantiomerization of the *N*-methoxyethyl compound was found to be zero order in THF (*i.e.*, $[\text{THF}]^0$), consistent with little additional solvation in the transition state. The *N*-ethyl and the *N*-Boc pyrrolidines in Figure 13b-c were also studied in ether because of decomposition above -80 °C in THF. The *N*-Boc pyrrolidine offered a big

surprise: the very large entropy of activation, along with an enormous *positive* entropy of activation, which is in stark contrast to all the previous examples. This large, positive entropy of activation persists when the measurements were conducted in hexane ether mixtures. The authors calculated a transition structure in which the lithium is intimately bound to the carbonyl oxygen of the *N*-Boc, and concluded that the enantiomerization occurs by a concerted four-membered ring mechanism. In this scenario, the authors speculated that the bulky *O*-*tert*-butyl group must move through the solvent cage and force significant solvent reorganization.⁵⁴ An additional contribution to the positive entropy could be increased pseudorotation in the 5-membered ring as the C–Li bond is broken.⁵⁸ Later work showed that the diamines TMEDA and sparteine change the mechanism of carbanion inversion, whereas the diamine diisopropylbispidine (DIB), does not.⁵⁸ Sparteine and TMEDA have the interesting effect of reducing both the enthalpy of activation (C–Li bond breaking) and entropy of activation (the transition state is more organized, consistent with coordination of the additional ligand). Diisopropylbispidine does not appear to bind the lithiums nearly as strongly, since the inversion barriers across the temperature range –80 to +25 °C is essentially the same as the barriers in hexane/ether.

Diastereomeric Bias

In all of the above examples, there is only one chirality element to consider. In cases of high configurational lability in a parent system, stereoelectronic factors and additional chirality elements can impart a diastereomeric bias to a system that results in a configurationally stable organolithium. An early example of presumed diastereomeric bias, inferred from the products of electrophilic substitution (and assumed to be S_E2_{ret}), is shown in Figure 14a. The organolithium is formed by deprotonation, then quenched with methyl iodide to afford the substitution product in 98:2 dr. In this example, the more stable (*R*) organolithium diastereomer has the phenyl and the isopropyl groups *trans* in the bicyclic chelate.⁵⁹ Although α -thioorganolithiums are usually not configurationally stable, the (*S*) organolithium shown in Figure 14b, which is formed by a diastereoselective deprotonation, is configurationally stable at low temperature.⁶⁰ A particularly well-characterized organolithium, also formed by deprotonation, is shown in Figure 14c.^{48,51,61} This lithiated *S,N*-acetal is structurally related to the achiral species depicted in Figure 12a. Detailed NMR and IR spectroscopic studies, and computational studies revealed the stereochemical features.⁴⁸ The geminal phenyl groups (in particular the phenyl group *cis* to the isopropyl group) restrict the conformational space of the adjacent isopropyl group, forcing the isopropyl methyls into a conformation that is *anti* to the two phenyl groups.⁶² Stereoelectronic factors place the S–CH₃ bond antiperiplanar to the C–Li bond. The lithium is probably coordinated to the carbonyl oxygen,⁶³ (the Li–O bond is calculated to be 2.044 Å, while the Li–C bond is 2.221 Å), so the (*S*) configuration at the metal bearing carbon places the –SCH₃ group *anti* to the isopropyl group, or on opposite faces of the bicyclic system. Calculations at the B3LYP/6-31+G(d)//PM3 level of theory place this structure 4.3 kcal/mol lower in energy than the diastereomeric organolithium having the (*R*) configuration at the metal-bearing carbon. Similar factors control the configuration and conformation of the related organolithium in Figure 14d.⁵⁰ The chiral acyl anion equivalents in Figure 14c–d react with several electrophiles with retention at the metal-bearing carbon. Figure 14e illustrates the generation of each of a diastereomeric pair of organolithiums, which equilibrate rapidly at –78 °C (even more rapidly in the presence of TMEDA) to afford the less crowded diastereomer of the bicyclic chelate.⁶⁴ Figure 14f illustrates a similar experiment in a sterically constrained bicyclic system. In this case, the epimerization is considerably slower, but is driven by the fact that only the diastereomer having the (*R*) configuration at the metal-bearing carbon can be easily coordinated by the carbonyl oxygen in this tricyclic system.⁶⁵

Metalated amides and amidines of tetrahydroisoquinolines are useful intermediates in alkaloid synthesis,^{3,66,67} and the details of the stereoselective lithiation and electrophilic substitution are instructive. When the α -deuteriotetrahydroisoquinoline shown in Figure 15a was lithiated and alkylated with methyl iodide, the product was obtained with 98% diastereoselectivity (*S*), and less than 5% of the deuterium label.⁶⁸ To account for the lack of a primary deuterium isotope effect, the authors postulated a mechanism whereby the organization of a bidentate chelate of the butyllithium as the rate determining step in the metalation. In the chelate, the butyl group is trans to the isopropyl, placing it proximal to the H $_{\alpha}$ proton (or deuterium), resulting in a stereoselective deprotonation. The authors postulated that the intermediate organolithium has the (*R*) configuration (*i.e.*, that the organolithium does not equilibrate to a mixture of diastereomers) and that alkylation with methyl iodide occurs with inversion. Deuteration with DMSO-*d*₆ afforded the (*R*) deuterated product. If the assumption of the configuration is correct, alkylation occurs with inversion and deuteration with retention. The chiral auxiliary is necessary to maintain configurational stability, as shown by the example in Figure 15b.⁶⁹ In this case, a formamidine lacking a stereocenter was used to mediate the deprotonation of an enantioenriched 1-methyltetrahydroisoquinoline at -78 °C. Quenching with benzyl chloride at -100 °C gave racemic product. These results are consistent with an inherently labile organolithium that can be stabilized in a single configuration by a chiral auxiliary. In the absence of the chiral auxiliary, enantiomerization probably occurs through a concerted tour.

Dynamic Resolutions

When the ratio of a mixture of stereoisomers in solution changes for some reason, the phenomenon is called an asymmetric transformation of the first kind. Asymmetric transformations of the second kind involve a similar equilibration of stereoisomers, with concomitant separation of one of them by crystallization or chemical reaction. A subset of asymmetric transformations are called dynamic thermodynamic^{1,70,71} and dynamic kinetic^{1,72,73} resolutions. In organolithium chemistry, dynamic resolutions involve an external, chiral ligand on lithium. Depending on the barrier for interconversion between the two diastereomeric organolithium complexes, and the magnitude of the inversion barrier relative to the rate of reaction, the resolutions may be classified as follows:

Dynamic thermodynamic, if the barrier to organolithium inversion is relatively high compared to the rate of subsequent reaction; or

Dynamic kinetic, if the barrier to organolithium inversion is low relative to the rate of subsequent reaction (*i.e.*, Curtin-Hammett³⁸ conditions).

The chapter in this volume by Coldham and Sheikh cover these two topics thoroughly. The following discussion is therefore selective.

Dynamic Thermodynamic Resolutions

Dynamic thermodynamic resolution is distinct from classical kinetic resolutions and from dynamic kinetic resolutions (see below) in that equilibration of organolithiums and resolution by selective reaction can often be accomplished in separate steps. The energy profile for a dynamic thermodynamic resolution is shown in Figure 16. Enantiomeric organolithium compounds, (*R*)-RLi and (*S*)-RLi, interconvert with rate constant k_{ent} and enantiomerization barrier ΔG_{ent}^a . Complexation with a chiral ligand, L*, affords a diastereomeric mixture of organolithium complexes, (*R*)-RLi·L* and (*S*)-RLi·L*, having an energy difference of ΔG° , and which invert with rate constant k_{inv}/k_{-inv} and epimerization barrier $\Delta G_{invl-inv}^a$. Reaction with an electrophile then affords products (*R*)-RE and (*S*)-RE. The important feature of this scheme is that (*R*)-RLi·L* and (*S*)-RLi·L* can interconvert; it

does not matter whether this happens by direct epimerization (rate constant $k_{\text{inv}/-\text{inv}}$) or by dissociation from L^* and enantiomerization (rate constant k_{ent} , see Figure 16, inset). In dynamic thermodynamic resolutions, $k_R, k_S > k_{\text{inv}}$, but the relative rates, $k_{\text{inv}}, k_{\text{ent}}, k_R, k_S$, and the percent conversion to products can all influence the product ratio.⁷⁰ If the reaction with electrophile E^+ is taken to complete conversion, the product ratio will reflect the thermodynamic ratio of the two diastereomeric complexes, $(R)\text{-RLi}\cdot\text{L}^*$ and $(S)\text{-RLi}\cdot\text{L}^*$. However, if $k_R, k_S \gg k_{\text{inv}}$, the relative rates of reaction, k_R/k_S , and the relative population of the two species determine the product ratio at partial conversion, just as in classical kinetic resolutions.⁷⁰ Note that the rates of product formation depends on the quantities $k_R[(R)\text{-RLi}\cdot\text{L}^*]$ and $k_S[(S)\text{-RLi}\cdot\text{L}^*]$, respectively, not just k_R/k_S . Thus, for the less stable diastereomer ($(S)\text{-RLi}\cdot\text{L}^*$ in this example) to provide the major product, the quantity $k_S[(S)\text{-RLi}\cdot\text{L}^*]$ must be greater than $k_R[(R)\text{-RLi}\cdot\text{L}^*]$. In Figure 16, the more stable diastereomer has the faster rate of reaction to product, but the opposite situation can also occur.

A clear picture of a dynamic thermodynamic resolution can be found in an example where the organolithium is configurationally stable at low temperature, but labile at higher temperatures. Figure 17 illustrates such an example, in which the results of several experiments were used to produce an energy profile for the entire system.⁷⁴ The racemic dilithiated *ortho*-ethyl pivaniide was generated by double deprotonation at $-25\text{ }^\circ\text{C}$ in methyl *tert*-butyl ether (MTBE), then cooled to $-78\text{ }^\circ\text{C}$ for 15 minutes. A solution of sparteine in MTBE, precooled to $-78\text{ }^\circ\text{C}$, was then added. This procedure should afford a 50:50 mixture of the (S) and (R) organolithium-sparteine complexes. Consistent with this is the nearly equal ($56:44 \pm 2\%$) ratio of silylated products obtained when quenched with trimethylsilyl chloride (entry 1 in Figure 17). In contrast, quenching with 10 mol% electrophile afforded a 91:9 ratio ($R:S$), which was taken to indicate the difference in activation energies, $\Delta G_R - \Delta G_S = 0.81\text{ kcal/mol}$, for reaction of the diastereomeric complexes with TMS-Cl at $-78\text{ }^\circ\text{C}$ (entry 2). Entry 3 describes an experiment in which the (R) and (S) organolithium complexes were allowed to equilibrate at $-25\text{ }^\circ\text{C}$, before being re-cooled to $-78\text{ }^\circ\text{C}$ and quenched. The 92:8 ratio of enantiomers (63% yield) reflects the relative population of the two organolithium diastereomers. After correcting for the unequal ratio of enantiomers obtained in entry 1, a free energy difference, ΔG° , of 0.97 kcal/mol was calculated for the organolithium diastereomers. If the 92:8 thermodynamic ratio of diastereomeric organolithiums is treated with 10 mol% electrophile, the product is obtained in a 99:1 er (entry 4). This product ratio (see above) is due both to the difference in energies of activation for the two organolithium diastereomers, and to their 92:8 relative population. Since in this case, the more highly populated (more stable) diastereomer is also the most reactive ($\Delta G_R^a > \Delta G_S^a$), the er of the product can be improved by diastereomeric recycling in the same pot, as illustrated by entry 5. After equilibration at $-25\text{ }^\circ\text{C}$ and cooling to $-78\text{ }^\circ\text{C}$, the 92:8 ratio of organolithium diastereomers is treated with 45 mol% electrophile. In a control experiment, workup at this point afforded a 98:2 er of product. Warming the reaction mixture to $-25\text{ }^\circ\text{C}$, cooling again to $-78\text{ }^\circ\text{C}$, then treating with another 45 mol% electrophile, afforded silylated product in a 97:3 er and a yield of 72%.

Dynamic Kinetic Resolutions

A dynamic kinetic resolution^{1,72,73} occurs in organolithium chemistry when diastereomeric organolithium complexes, $(R)\text{-RLi}\cdot\text{L}^*$ and $(S)\text{-RLi}\cdot\text{L}^*$ (L^* is a chiral ligand), which epimerize with rate constant k_{inv} , are allowed to react with an electrophile (Figure 18). The electrophilic substitution proceeds with rate constants k_R and k_S , acting on the $(R)\text{-RLi}\cdot\text{L}^*$ and $(S)\text{-RLi}\cdot\text{L}^*$ complexes, respectively, to give products $(R)\text{-RE}$ and $(S)\text{-RE}$. If $k_{\text{inv}} \gg k_R, k_S$, the process follows Curtin-Hammett kinetics,³⁸ and the $(R)\text{-RE}/(S)\text{-RE}$ product ratio depends on the difference in transition state energies, $\Delta G_{\text{TS}}^\ddagger$. Figure 18 illustrates this limiting

case, in which $k_{\text{inv}} \gg k_R, k_S$. Note that the product ratio depends on both ratio of rates k_R/k_S and k_{inv}/k_R since, assuming that (*R*)-RLi·L* is the faster reacting enantiomer, k_{inv} and k_R compete.^{73,75} In the absence of kinetic studies on the rates of inversion vs. substitution, one can use deuterium labelling to deconvolute the deprotonation step from the substitution step. Alternatively, one can use the Hoffmann test. Each of these methods are discussed, in turn, below.

An example that obeys Curtin-Hammett kinetics in organolithium substitutions is found in the chemistry of tetrahydroisoquinolyl oxazolines shown in Figure 19.⁷⁶ This is not an example of a dynamic resolution, since it involves a chiral auxiliary in the organolithium, but it illustrates a method for determining the source of stereoselectivity in an electrophilic substitution. In these oxazolines the deprotonation is stereoselective, but the stereoselectivity in the deprotonation is not the source of the diastereoselectivity of the overall sequence. This was shown by a pair of deprotonations using diastereomeric deuterium labelled compounds. With H_{Si} replaced by deuterium, the methylated product is obtained with 50% deuterium incorporation and 92:8 dr. With deuterium in place of H_{Re} , the methylated product is obtained with 97% deuterium incorporation and 91:9 dr. From this data, the relative rate for removal of H_{Si} over H_{Re} was calculated to be 5.8:1. Prior coordination of the butyllithium to the oxazoline nitrogen was postulated to account for the selectivity in the deprotonation, similar to the coordination complex postulated for the formamidines in Figure 15a. However in the case of the oxazolines, there is an isotope effect of approximately 5.9, indicating that deprotonation is rate-determining in this system. The variable deuterium content in the products, coupled with the consistent diastereoselectivity in the two experiments, clearly implicate equilibration of the organolithium diastereomers shown. The initial conclusion in 1987⁷⁶ was that the stereoselectivity in the alkylation was due to a thermodynamic preference for one organolithium diastereomer, as in the formamidines of Figure 15,⁶⁸ but subsequent studies were less conclusive and Curtin-Hammett kinetics were also considered.⁷⁷ Later, DNMR studies placed an upper limit of 8.2 kcal/mol on the barrier to inversion, suggesting that Curtin-Hammett kinetics were the most likely explanation for the stereoselectivity in the alkylation.⁶⁷

Competing Inversion and Substitution: the Hoffmann Test

It is often less obvious than in the above examples, that a dynamic kinetic resolution is operative. In between these two limiting situations are instances where the rates of inversion and substitution are similar. The energy profile is shown in Figure 20. The critical aspect of this situation is the configurational stability of the organolithium on the time scale of its reaction with an electrophile. In the continuum of relative rates, when k_{inv} , k_R , and k_S are close in value, the mathematical treatment is complex,⁷⁰ and product ratio is a function of both relative rates and percent conversion. The chapter by Hoffmann in this volume discusses the theory behind the Test that was discovered in his group, and also relates the interesting story of its development. Variations on the Test are also discussed in the chapter by Kizirian in this volume.

Under some circumstances, it is possible to use mutual kinetic resolutions to evaluate relative rates of inversion and electrophilic substitution.^{78,79} The Hoffmann test is based on the reaction of a chiral organolithium with a chiral electrophile, and analysis of the diastereomer ratio of the products. Two experiments are run (Figure 21). In experiment 1, racemic organolithium is allowed to react with racemic electrophile (*rac*-E*); the kinetic resolution selectivity factor, *s*, is evaluated by determining the diastereomer ratio of the products, which reflects the relative rates k_{RR}/k_{RS} for formation of the two products.⁸⁰ For obvious reasons, the ratio must not be unity; for practical reasons, it is best if the kinetic resolution has a low selectivity factor, $1.2 < s < 3.0$ (see below). In experiment 2, the same

reaction is carried out with enantiopure electrophile, and the reaction carried to 100% conversion. If the organolithium is configurationally stable, the product in experiment 2 will have a 50:50 dr. If the dr of the products of the two experiments is the same (and not 50:50), the organolithium is configurationally labile on the time scale of the reaction, and the organolithium has been kinetically resolved. If the diastereomer ratios from the two experiments are different, the organolithium is configurationally stable. In other words, comparison of the dr for the two experiments reveals the configurational stability of the organolithium on the time scale of the electrophilic substitution.

There are some limitations of the Hoffmann test that have been recognized from the beginning.⁷⁸

1. The dr in Experiment 2 depends on the percent conversion. In order to ensure complete conversion in Experiment 2, an excess of the chiral electrophile should be used. This will require longer reaction times than were required in Experiment 1, and the extra length of time depends on the selectivity factor, *s*. For this reason, it is prudent to employ reactions in which *s* is small (≤ 3.0).
2. If the rate of reaction in Experiment 2 is faster than the rate of the addition of the organolithium to the electrophile, inverse addition should be employed.
3. A 50:50 dr in Experiment 2 can only be reached if the electrophile is enantiopure. Good results are still possible if a moderate excess (1 – 5 equivalents) of electrophile having $\geq 98.5:1.5$ er are used.
4. If there are side reactions that consume the organolithium, they should not exceed ten percent.

Additionally, in light of several pieces of evidence presented in this chapter, one should bear in mind some further issues that could complicate matters:

- 5 It is assumed that the steric course of the reaction of the chiral organometal is 100% selective, *i.e.*, that the electrophilic substitution is 100% S_E2_{ret} or 100% S_E2_{inv} , and that SET is not a competing mechanism.
- 6 It is possible that the rate of racemization changes as a reaction proceeds. Many electrophilic substitutions accumulate lithium halide or lithium alkoxide salts as the reaction proceeds. Lithium salts sometimes facilitate inversion of organolithiums.⁴⁷
- 7 An asymmetric synthesis would use an enantiopure organolithium. Since the Hoffmann test uses racemic organolithium, it assumes that the aggregation state of enantiopure and racemic organolithiums are the same, and that the kinetics of reactions of electrophiles with homochiral and heterochiral aggregates (or monomers in equilibrium with them) are the same. However, aggregation can affect the rate of inversion, in either direction – depending on the system!

Steric Course of Electrophilic Substitutions: η^1 organolithiums

Electrophilic, aliphatic, bimolecular substitutions, abbreviated S_E2 in the Hughes-Ingold terminology,³⁶ may be categorized as S_E2_{ret} or S_E2_{inv} ,³⁵ depending on the steric course. Substitution can also occur stepwise, via single electron transfer (SET) and subsequent coupling of the resultant radicals. Usually, intermolecular radical couplings are stereorandom, but advances in stereoselectivity of radical coupling reactions show significant promise.⁸¹

For η^1 organolithiums having central chirality at the metal-bearing carbon, possible mechanisms for electrophilic substitution are illustrated in Figure 22. Replacement of lithium by an electrophile can take place with inversion, designated S_E2inv ,³⁵ as illustrated in Figure 22a. The trigonal bipyramidal transition structure can be stabilized by resonance if the groups R^1 and/or R^2 are vinyl or aryl. The invertive transition state can be destabilized by steric hindrance – especially when the electrophile is an alkyl halide that must also invert in the transition state. Substitution may also occur with retention of configuration at carbon, as shown in Figure 22b, and designated S_E2ret .³⁵ Sometimes, retentive substitutions occur when the electrophile is a carbonyl compound, and coordination to the lithium is possible. However, coordination of the halogen of an alkyl halide to the lithium, and retentive substitution through a four-membered-ring transition state, is symmetry forbidden.^{34,35} The third possibility is single electron transfer, SET, shown in Figure 22c. In this instance, the carbanion is oxidized to a rapidly inverting radical by the electrophile; subsequent coupling affords racemic products. Radical disproportionation, dimerizations, and other undesired side reactions can also occur following SET. Various combinations of organolithiums and electrophiles may prefer one of the two polar pathways, but when a polar pathway is slowed, for example by steric crowding, SET can intervene. Examples illustrating these points follow.

Examples of S_E2inv

Examples of invertive electrophilic substitutions (Figure 22a) of organolithiums that are known to be configurationally stable under the reaction conditions are illustrated in Figure 23. In the first example, Figure 23a, double deprotonation of *ortho*-ethyl pivanilide affords an organolithium that can be dynamically resolved, with sparteine at $-25\text{ }^\circ\text{C}$, to the *R* enantiomer shown. Control experiments confirmed that the organolithium is configurationally stable at $-78\text{ }^\circ\text{C}$, and reaction with all electrophiles tested proceeds with inversion of configuration.³² No rationale for the steric course was given, and the solution structure of the dilithio compound is not known. Possibly, a sparteine coordinates to the lithium and blocks coordination of the cyclohexanone carbonyl. The bulky sparteine could also inhibit approach of the electrophile to the carbanion from the side bearing the complexed lithium, while the benzene ring also stabilizes an sp^2 -like transition structure during the carbanion inversion. Figure 23b shows an example of a lithiated tertiary carbamate, also configurationally stable at $-78\text{ }^\circ\text{C}$.³¹ Some electrophiles react with this same organolithium with retention (see below). The authors rationalize the invertive reaction by suggesting that electrophiles that are particularly reactive (having a low energy LUMO), and are weak Lewis bases (poor ligands for lithium), react preferentially with inversion when the carbanion is also mesomerically stabilized. Inversion is also seen in α -thio organolithiums that have appreciable *s*-character (*i.e.*, more planar carbanion) and crowding around the lithium (Figure 23c).⁸² This α -thioorganolithium exhibits surprising configurational stability, with a half-life for enantiomerization estimated at several hours at $0\text{ }^\circ\text{C}$. In the fourth example (Figure 23d), alkylation of 2-lithio-*N*-methylpiperidine with primary alkyl halides proceeds with inversion. In this case, there is no mesomeric stabilization of an invertive transition state, so the driving force for the invertive alkylation is not obvious.^{83,84} Interestingly, alkylation with tributyltin chloride proceeds with retention. NMR studies revealed that the solution structure of the organolithium is a nitrogen-bridged monomer as shown.⁸⁵ In contrast, 2-lithio-*N*-methylpyrrolidines, which are homochiral dimers in solution,⁸⁵ alkylate with 80% inversion and 20% retention by a polar (*i.e.*, nonradical) mechanism.⁸⁶ It may be that steric influences are at work here, as suggested by diversion of both lithiopyrrolidines and lithiopiperidines to SET mechanisms when the rings are substituted (see below).^{87,88} The alkyl group on nitrogen can affect the steric course. For example, in contrast to *N*-methyl-2-lithiopyrrolidine, *N*-2,3,3-trimethylallyl-

lithiopyrrolidine gives products of apparently complete retention with trimethylsilyl chloride, tributyltin chloride, and carbonyl-containing electrophiles.⁸⁹

Examples of S_E2ret

Figure 24 illustrates several examples of retentive substitution (Figure 22b) of configurationally stable organolithiums. The reaction of α -alkoxyorganolithiums lacking mesomeric stabilization, typified by the seminal example in Figure 24a, undergo retentive substitution exclusively, independent of the electrophile.^{14,90} Figure 24b shows the same organolithium illustrated previously in Figure 23b. However in this case, acylation with an ester proceeds with retention of configuration.³¹ The rationale offered for the difference in behavior is that the ester is less reactive and is a stronger Lewis base than the acid chloride, making it a better ligand for lithium, and leading to retentive substitution. In α -alkoxyorganolithiums, when coordination of a carbonyl electrophile to the lithium is likely, retentive substitution follows. Figure 24c illustrates the retentive substitution of 2-lithio-*N*-methylpiperidine with cyclohexanone.^{83,84} In contrast to the alkylation illustrated in Figure 23c, reaction of this organolithium with all carbonyl compounds tested (carbon dioxide, dimethyl carbonate, methyl chloroformate, ketones, and aldehydes), proceeded with retention of configuration (except benzophenone - see below). The dipole-stabilized lithiopyrrolidine shown in Figure 24d reacts with trimethylsilyl chloride, tributylstannyl chloride, and carbonyl electrophiles such as ketones with complete retention.^{21,22,91} These compounds do not react well with alkyl halides, probably due to the intervention of SET (see below).

Examples of SET

When does SET complicate synthetic schemes? For α -alkoxyorganolithiums and α -thioorganolithiums, rarely – if ever. In the case of α -aminoorganolithiums, two factors seem to be important. One is steric hindrance of an invertive electrophilic substitution, and the other is the reduction potential of the electrophile vs the oxidation potential of the organolithium. Ebersson has extended Marcus theory to organic processes,⁹³ and postulated that the partitioning of SET and polar pathways is dependent in part upon the difference in oxidation potential of the nucleophile and the reduction potential of the electrophile. According to this theory, reactions whose free energies of electron transfer, ΔG_{ET} , are more endothermic than +23 kcal/mol at room temperature are unlikely to occur by SET because the rate would be too slow. Conversely, if $\Delta G_{ET} < -20$ kcal/mol, then SET will be fast. In between these extremes, other factors may come into play. Pross has suggested that both SET and polar pathways involve an initial single electron shift,⁹⁴ and if coupling of the two spins is feasible following the single electron shift, a polar pathway is followed. Moreover, Pross asserted that any factor (steric, electronic, or geometric) that operates to inhibit or hinder the coupling process will tend to favor a SET pathway over a polar one.

Invertive electrophilic substitutions involving sp³ nucleophiles and sp³ electrophiles are sterically demanding reactions, since both require inversion at both carbons, as shown in Figure 25. Tell-tale signs of SET are stereorandom couplings at the metal-bearing carbon, appearance of dimers, and formation of products of radical disproportionation. Radical probe electrophiles can be used to confirm the presence of radicals on the reaction coordinate.^{39,86,88} EPR spectroscopy has been used to detect radicals in additions of α -aminoorganolithiums to benzophenone,^{84,86} but the presence of a radical in a reaction mixture does not place it on the reaction coordinate.

Figure 26 illustrates an example of an SET reaction that is most likely the result of steric inhibition of a preferred S_E2inv reaction pathway. Compare Figure 26 with Figure 23d. In the absence of the *tert*-butyl group (Figure 23d), the piperidine ring can adopt a

conformation that allows invertive substitution to proceed in a relatively unhindered fashion (Figure 23d). On the other hand, when a *tert*-butyl group locks the ring, the axial C–H bond obstructs approach of the electrophile to the back side of the C–Li bond (Figure 26 inset). With invertive substitution hindered, oxidation of the carbanion to a radical ensues, producing coupling product stereorandomly and in low yield, along with a dimer and the two products of radical disproportionation.

By examining the steric course of reactions of nonracemic α -aminoorganolithiums with benzaldehyde and benzophenone, an estimate of relative oxidation potentials can be made, as shown in Figure 27.⁶ The effect of oxidation potential of the organolithium can be seen by comparing the example in Figure 27a with that of Figure 24d, which illustrate reactions with benzophenone as electrophile.^{83,84} In contrast to the *N*-Boc 2-lithiopyrrolidine, the *N*-methyl analog adds benzophenone stereorandomly. Similar comparisons of the steric course of electrophilic substitutions suggest that lithiated amidines are more prone to oxidation than lithiated *N*-methyl heterocycles, which are in turn more prone to oxidation than *N*-Boc compounds. It has also been noted that transmetalation from Li to MgX moves the oxidation potential to more positive values and renders SET less likely.^{6,95}

Implicating or Eliminating SET as a mechanism

How does one determine whether SET is operative or not? Since you can *disprove* a hypothesis, but not *prove* one, it can be a challenge. One of the more famous axioms of the fictional detective, Sherlock Holmes, states: “Eliminate all other factors, and the one which remains must be the truth.”⁹⁶ Consider the reaction in Figure 27a;⁸⁶ racemic product is formed in good yield, and three mechanistic possibilities could be responsible:

1. S_E2ret and S_E2inv pathways compete;
2. The electrophile catalyzes the racemization of the organolithium; and
3. Radical pairs couple after SET.

The first possibility was deemed unlikely because all other carbonyl electrophiles that were examined in this system react with exclusive retention, as illustrated in Figure 28a.^{83,84} The second possibility, catalytic racemization of the organolithium, was disproved by stirring the enantioenriched organolithium shown in Figure 28b with substoichiometric amounts of benzophenone. After 1h, the reaction was quenched with cyclohexanone, and analysis of the product mixture revealed that the benzophenone adduct was racemic, but the cyclohexanone adduct had the same *er* (within experimental error) as the starting organolithium.⁸⁶ Thus, by the Holmes axiom, SET is the most likely explanation for the stereorandom coupling.

Radical clocks can also be used to probe for single electron transfer reactions. For example, as shown in Figure 29a, benzyl bromide was found to couple stereorandomly with *N*-methyl-2-lithiopyrrolidine and *N*-methyl-2-lithiopiperidine.^{83,84} This activated alkyl halide is more easily reduced than an unactivated alkyl halide, so the possibility of SET was investigated using the activated halide cyclopropylmethyl bromide. Reduction of this electrophile to cyclopropylmethyl radical would be followed by fast ring opening to the butenyl radical (Figure 29b, inset). In the event, both pyrrolidine dimers and racemic 3-butenyl coupling products were detected. These products are consistent with an SET mechanism.

Lithiated *N*-methylpyrrolidines couple with unactivated alkyl halides to give products of lower *er* than the starting organolithium, as shown in Figure 30a.^{83,84} This result could be explained by SET competing with a polar mechanism, by catalytic racemization of the organolithium, or by competing invertive and retentive pathways. The experiment illustrated in Figure 30b showed that radical processes are not major players in this process, since

mainly hexenyl-substituted pyrrolidine was observed, with only small amounts of cyclopentylmethyl-substituted product detected.⁸⁶ This experiment does not, however, completely rule out SET, since the rates of polar and radical couplings were not measured. Nevertheless, hexenyl bromide had previously been used to detect SET processes in two other types of α -aminoorganolithiums,⁹⁷ so SET seemed unlikely as a possible explanation. The possibility of catalytic racemization of the organolithium by the electrophile was disproven by the experiment shown in Figure 30c.⁸⁶ The conclusion was that the low er in the examples of Figure 30 are the result of competing S_E2_{inv} and S_E2_{ret} polar mechanisms. As was true of rigid 2-lithiopiperidines (Figure 26),^{87,88} rigid 2-lithiopyrrolidines tend to suffer SET upon reaction with alkyl halide electrophiles.⁸⁸

Steric Course of Electrophilic Substitutions: η^3 organolithiums

Allylic organolithiums, either η^3 allyls or equilibrating η^1 regioisomers can add additional complications due to double bond geometry, and the site of electrophilic substitution. As shown in Figure 31a, invertive substitution can occur α to substituent **a** or **b** to provide two constitutional isomers. It is apparent that conjugation will stabilize the transition structure in Figure 31a more so than when the carbanion is not allylic. Retentive substitution can occur at either terminus of the allyl anion, as shown in Figure 31b. Finally, it is possible for the electrophile to oxidize the organolithium to a radical. Stereorandom coupling following such SET would then afford the two racemic substitution products, as shown in Figure 31c. In all three cases, if the organolithium equilibrates between the two η^1 regioisomers in acyclic systems, the possibility of double bond isomerization arises, complicating matters further.

Examples of S_E2_{inv}

Amine-substituted allyllithium compounds can serve as homoenolate equivalents, as shown in Figure 32. Tin-lithium exchange of a mixture of diastereomeric allyl stannanes yields an allylic organolithium which, upon alkylation affords only *Z*-configured enamines. This result was explained by equilibration to a thermodynamic mixture containing predominantly the *Z*-allylic organolithium. It is not clear whether the organolithium is η^1 or η^3 , but the transition structure that is proposed to account for the steric course is shown in the inset. This transition structure features an enamine in which the pyrrolidine ring is twisted orthogonal to the π -system to allow coordination of the methoxy group (and perhaps the nitrogen) to coordinate the lithium, and substitution takes place with inversion. Hydrolysis gives β -substituted ketones in high enantiopurity.⁹⁸

Lithiated *N*-Boc-*N*-aryl cinnamyl amines have been extensively studied, and several modes of substitution have been determined that depend on the conditions of the reaction.⁹⁹ The steric course of the example in Figure 33 is based on the solid state structure of the intermediate organolithium.¹⁰⁰ Stereoselective deprotonation is responsible for the enantioselective formation of the illustrated organolithium. In the solid state, the cinnamyl group is bound in an η^3 fashion, but is bound more closely to C^3 than to C^1 . The Boc carbonyl oxygen is also coordinated to the lithium, and the amide bond is twisted 68° from the allyl plane to facilitate this coordination and to relieve electron repulsion between the amide π -system and the allylic anion π -system. Solution NMR studies confirmed that the η^3 structure exists as a monomer in solution.⁹⁹ Quenching the anion with benzyl bromide affords the (*S,Z*) enamide in 84% yield and 98:2 er, the product of invertive substitution. The (*R,E*) diastereomer is also formed in 5% yield and 88:12 er. If the crystals are dissolved in ether at -78°C and quenched at that temperature with benzyl bromide, the (*S,Z*) product is obtained in 99:1 er.¹⁰⁰

Examples of S_E2ret

The organolithium illustrated in Figure 33 adds to ketones with retention of configuration at the metal-bearing carbon, as shown in Figure 34.⁹⁹⁻¹⁰¹ In this instance, coordination of the cyclohexanone carbonyl oxygen to the lithium cation is postulated to precede electrophilic substitution. Since the organolithium is monomeric, the carbonyl addition probably proceeds through a 4-membered transition structure.

Deprotonation of indenides with butyllithium-sparteine affords η^3 organolithiums, as illustrated in Figure 35. The organolithium having the (*S*) configuration at C¹ is the more stable diastereomer, and crystallizes preferentially. The 1-butyindenide-Li-sparteine complex was analyzed by X-ray crystallography, and revealed a shorter bond from Li to C³ than to C¹. The products of the reaction indicate that the electrophile inserts into the longer C–Li bond, and substitutes for lithium with retention of configuration. The authors note a significant solvent effect in this system. If ether is replaced by THF, the 3-substituted indene is obtained as the major product, having a 50:50 er. X-ray crystallographic analysis of the organolithium intermediate revealed a η^1 organolithium species having the lithium bound to C³, and coordinated to 3 THF molecules, but not sparteine.¹⁰²

Summary and Conclusions

The examples of stereoselectivity in this chapter reveal a broad array of chemical reactivity, inversion dynamics, and stereoselectivity in synthesis. Chiral, nonracemic organolithium compounds are available by a number of means, including enantioselective deprotonation, metal-exchange reactions, and asymmetric transformations such as dynamic resolutions. Particularly intriguing to the field of asymmetric synthesis is the notion that dynamic resolutions permit resolution of racemic organolithiums *in situ* by the addition of chiral ligands. It now appears that both enantioselective deprotonations and dynamic resolutions can be accomplished using sub-stoichiometric amounts of chiral ligands. As of this writing, the discovery of such processes is empirical, but it is anticipated that, as knowledge of organolithium dynamics is acquired, such processes will become predictable by prior design.

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Figure 2.
Possible sources of organolithium compounds.

Figure 3. Sparteine-mediated deprotonation of carbamates: (a) α to oxygen in carbamates;^{5,20} (b) α to nitrogen in pyrrolidines.^{21,22}

Figure 5. Synthesis of α -aminoorganostannanes: (a) by addition to acyclic sulfinimines;²⁹ (b) addition to cyclic N -acyliminium ions.³⁰

Figure 6. The lithium-tin-lithium exchange sequence: (a) α -oxyorganolithiums,³¹ (b) laterally lithiated pivanilides.^{32,33}

Figure 7.

The relationship between the free energy inversion barrier and the half-life for racemization of enantiomers at three temperatures (top to bottom, 0, -40, and -80 °C).

Figure 8.
Substitution of configurationally labile organolithiums.

Figure 9.
Substitution of configurationally stable organolithiums.

Figure 10.

Enantiomerization barriers for representative benzylic and allylic organolithiums (ΔG and ΔH (kcal/mol); ΔS (cal/mol·K)): (a) benzylic lithiohydrocarbon;⁴⁰ (b) α -thio benzylic organolithium;⁴³ (c) α -seleno benzylic organolithium;⁴² (d) chelated α -silyl benzylic organolithium that enantiomerizes by a conducted tour;⁴⁵ (e) α -amino benzylic organolithium.⁴³

Figure 11.
A lithiohydrocarbon that epimerizes through an aggregate.⁴⁷

Figure 12. Enantiomerization barriers for nonbenzylic organolithiums: (a) Dipole-stabilized *S,N*-acetal;⁴⁸ (b-e) α -disilyl and α -thio- α -silyl organolithiums, with and without chelation;⁵²

Figure 13.
 (a-c) Lithiated pyrrolidines.⁵⁴

Figure 14.

Organolithiums that are configurationally stable due to a diastereomeric bias. (a) α -lithio-*N*-benzyloxazolidinone;⁵⁹ (b) α -thioorganolithium;⁶⁰ (c-d) Lithiated *S,N*-acetals;^{48,50} (e) Fast equilibration of diastereomeric organolithiums;⁶⁴ (f) Slow equilibration of diastereomeric organolithiums.⁶⁵

Figure 15. Formamidines: (a) Configurational stability imparted by a chiral auxiliary;⁶⁸ (b) Configurational lability in the absence of a chiral auxiliary.⁶⁹

Figure 16.

Energy profile and reaction scheme for a dynamic thermodynamic resolution.^{1,70}

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Figure 18.
General scheme of a dynamic kinetic resolution in organolithium chemistry.¹

Figure 19.
Lithiation/alkylation of tetrahydroisoquinolyloxazolines.^{67,76,77}

Figure 20.

Energy profile of system where k_{inv} , k_R , and k_S are comparable.

Experiment 1
racemic RLi and racemic E*

Experiment 2
racemic RLi, enantiopure E*

Figure 21.

The Hoffmann test for configurational stability on the time scale of the reaction with an electrophile.^{78,79}

Figure 22.

Figure 23.

$\text{S}_{\text{E}2\text{inv}}$ electrophilic substitutions of configurationally stable organolithiums. (a) laterally lithiated pivanilide;³² (b) dipole and mesomerically stabilized α -oxyorganolithium;³¹ (c) dipole and mesomerically stabilized α -thioorganolithium;⁸² (d) unstabilized α -aminoorganolithium.^{83,84}

Figure 24.

$\text{S}_{\text{E}}2_{\text{ret}}$ electrophilic substitutions for configurationally stable organolithiums. (a) unstabilized α -alkoxyorganolithium;⁹⁰ (b) dipole and mesomerically stabilized α -alkoxyorganolithium;³¹ (c) unstabilized α -aminoorganolithium;^{83,84} (d) dipole stabilized α -aminoorganolithium.^{21,22,91,92}

Figure 25.

Severe crowding can result when S_E2inv and S_N2inv at sp^3 carbons are coupled.

Figure 26. Single electron transfer can preempt electrophilic substitution when the $\text{S}_{\text{E}2\text{inv}}$ transition state is crowded.^{87,88}

Figure 27.

(a) Stereorandom addition to benzophenone attributed to SET;⁸⁶ (b) Approximate order of susceptibility to SET: organolithiums having less positive oxidation potentials are more easily oxidized to radicals.⁶

Figure 28.

(a) Retentive substitution with carbonyl electrophiles;^{83,84} (b) Evidence that benzophenone does not catalyze racemization of the organolithium.⁸⁶

Figure 29.

(a) Stereorandom coupling of benzyl bromide;^{83,84} (b) Coupling with cyclopropylmethyl bromide affords racemic products resulting from coupling with butenyl radical, as well as dimer.⁸⁶

Figure 30.

(a) Invertive coupling of lithiopyrrolidine with an alkyl halide, ~80% inversion and ~20% retention;^{83,84} (b) Invertive coupling with a radical clock, giving approximately the same percentage inversion;⁸⁶ (c) Evidence that the electrophile is not catalyzing the racemization of the organolithium.⁸⁶

Figure 31. General schemes for electrophilic substitutions of η^3 organolithiums (or equilibrating η^1 regioisomers).

Figure 32.
An η^3 allyllithium reagent as a homoenolate equivalent.⁹⁸

Figure 33. Deprotonation to a planar chiral, η^3 complexed organolithium, and invertive S_E2' inv substitution.^{99,100}

Figure 35.
Asymmetric substitution of η^3 indenide-sparteine complexes.¹⁰²