Regioselective, Diastereoselective, and Enantioselective Lithiation−Substitution Sequences: Reaction Pathways and Synthetic Applications

PETER BEAK,* AMIT BASU, DONALD J. GALLAGHER, YONG SUN PARK, AND S. THAYUMANAVAN

Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

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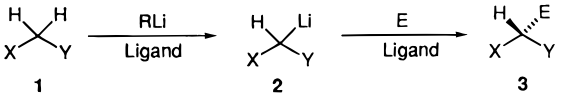
Organolithium chemistry is broadly integrated and widely applied in studies that bridge inorganic, physical, organic, and theoretical chemistry.[1] Reactions with organolithium species as reagents, reactants, or intermediates are so well established that organolithiums are the most widely used organometallics in contemporary organic chemistry.

Deprotonative lithiations are commonly used to generate enolates, ylides, and dipole-stabilized, localized sp^2 or sp or delocalized carbanions as reactive intermediates for diverse applications.[2] A sequence in which a proton on a tetrahedral carbon is replaced by a substituent begins with removal of a proton from **1** to give the formally sp^3 organolithium **2**. Reaction of **2** with an electrophile subsequently provides **3**.



Each step can be influenced by the presence of a ligand. The hydrogen which is replaced in **1** is enantiotopic, and the intermediate **2** and product **3** are chiral. With the proper choice of substrate and ligand, these reactions afford products with excellent regioselectivity, diastereoselectivity, and enantioselectivity.

In this Account we discuss work that has established reaction pathways for which **2** is a dipole-stabilized carbanion α to nitrogen or a benzylic carbanion. The mechanistic studies provide a basis for understanding and for developing synthetic applications of the sequence. We focus on work in Urbana, with an emphasis on asymmetric reactions, but the field has been developed by the efforts of many contributors.[3−5]

Peter Beak received a B.A. from Harvard University and a Ph.D. from Iowa State University where he worked with Ernest Wenkert. He is a Jubilee Professor of Liberal Arts and Sciences in the Chemistry Department at the University of Illinois at Urbana-Champaign.

Amit Basu started research in chemistry with Patrick McDougal at Reed College in Portland, OR, receiving his B.A. in 1992. He obtained his Ph.D. with Peter Beak in 1996 and is currently a postdoctoral fellow in Daniel Kahne's group at Princeton University.

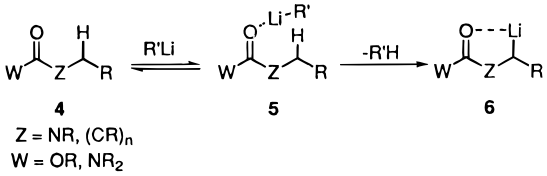
Donald J. Gallagher was born in Medford, MA, and received his B.S. degree in chemistry from Tufts University. He received a Ph.D. degree from the University of Illinois at Urbana-Champaign under the direction of Peter Beak and is currently working at G. D. Searle in Skokie, IL.

Yong Sun Park was born in Seoul, Korea, and received his B.S. and M.S. degrees in chemistry from Yonsei University. He received a Ph.D. degree from the University of Illinois at Urbana-Champaign in 1996 and is a postdoctoral fellow with Peter Beak.

S. Thayumanavan was born in Tirunelveli, India, and received his B.Sc. and M.Sc. degrees at the American College, India. He finished his Ph.D. with Peter Beak in 1996 and is a postdoctoral associate with Seth Marder at the California Institute of Technology.

Reaction Pathways

Prelithiation Complexes. Lewis base coordination with organolithium reagents is a central theme in organolithium chemistry.[1,6] The formation of a complex between an organolithium reagent and a functional group prior to a deprotonative directed lithiation has been suggested to rationalize reactions which give products different from conventional expectation.[7] This hypothesis, termed the complex-induced proximity effect (CIPE), while more broadly applicable, has been supported by kinetic studies for specific cases of deprotonations adjacent to the nitrogen of amides, carbamates, and ureas.[8] The deprotonative steps can be considered to involve complexation of **4** with an organolithium base to give **5**, which leads to **6**.



Regioselective and Diastereoselective Reactions. A sequence which demonstrates a regioselective and diastereoselective course for a lithiation−substitution at a methylene group is shown for the conversion of *N*-Boc-piperidine (**7**) to *trans*-2,6-dimethyl-*N*-Boc-piperidine (**9**) via **8**.[9]

(1) Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277−297. Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227−234. Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 354−451. Schlosser, M. Ed. *Tetrahedron* **1994**, *50*, 5845−6128.

(2) Gray, M.; Tinkl, M.; Snieckus, V. In *Comprehensive Organometallic Chemistry*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier Science Ltd.: New York, 1995; Vol. 11, Chapter 1 and references cited therein.

(3) Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Aherns, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure Appl. Chem.* **1994**, *66*, 1479−1486. Tomioka, K. *Synthesis* **1990**, 541−549. Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1−26. Koga, K.; Shindo, M. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 1021−1032.

(4) Klute, W.; Dress, R.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1409−1411. Hoffmann, R. W.; Julius, M.; Chemla, F.; Ruhland, T.; Frenzen, G. *Tetrahedron* **1994**, *50*, 6049−6060. Hoffmann, R. W.; Dress, R. K.; Ruhland, T.; Wenzel, A. *Chem. Ber.* **1995**, *128*, 861−870.

(5) Elworthy, T. R.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 6089−6096. Gawley, R. E.; Zhang, Q. *Tetrahedron* **1994**, *50*, 6077−6088.

(6) Brown, T. L. *Pure Appl. Chem.* **1970**, *23*, 447−462. *Polyamine-Chelated Alkali metal Compounds*; Langer, A. W., Jr., Ed.; American Chemical Society: Washington, DC, 1974.

(7) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356−363. Klumpp, G. *Recl. Trav. Chim. Pays.-Bas* **1986**, *105*, 1−21 and references cited therein.

(8) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145−8153. Gallagher, D. J.; Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1992**, *114*, 5872−5873. Resek, J.; Beak, P. *J. Am. Chem. Soc* **1994**, *116*, 405−406. Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1995**, *60*, 7092−7093.

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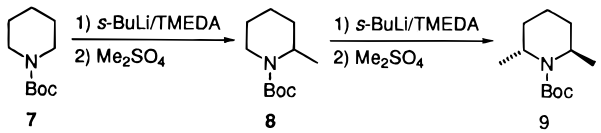
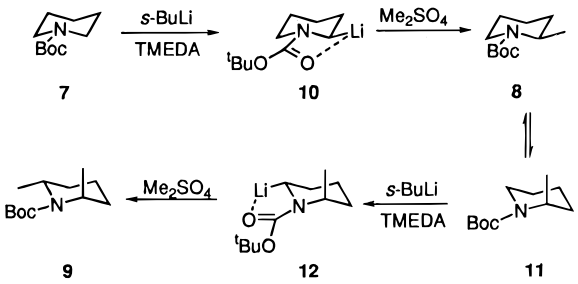


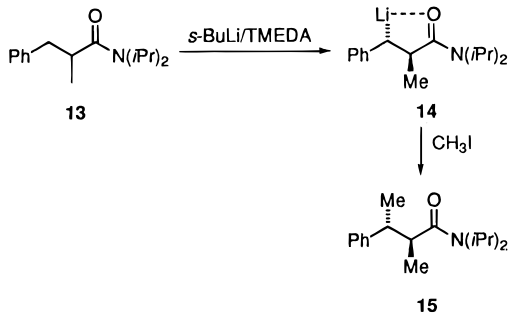
7 **8** **9**

The deprotonation of **7** with *sec*-BuLi/TMEDA provides the dipole-stabilized carbanion **10**, which undergoes methylation with retention of configuration to give **8**. The equatorial lithiation is considered to be favored because it allows effective complexation of the carbonyl oxygen with the lithium and avoids the repulsive interactions between the carbanionic lone pair and the amide π-system that would be present in an axially lithiated intermediate.[10] The 2-substituent in **8** is axial in order to relieve $A_{1,3}$ strain, and a subsequent equatorial lithiation−substitution provides the *trans* product **9** diastereoselectively. Regioselectivity in the lithiation of **11** arises from preference for lithiation at the less substituted position.



7 **10** **8** **9** **12** **11**

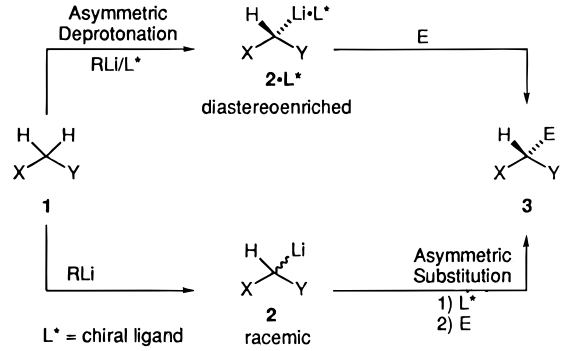
A sequence which illustrates stereoselection in lithiation−substitution at a benzylic position is the conversion of **13** to **15** via **14**. The β-lithiation is



13 **14** **15**

favored over α-lithiation by a CIPE as well as the $A_{1,3}$ strain that would result from formation of the enolate. The diastereoselectivities of the deprotonation and substitution steps were shown to be independent by studies of deuterated substrates.[11]

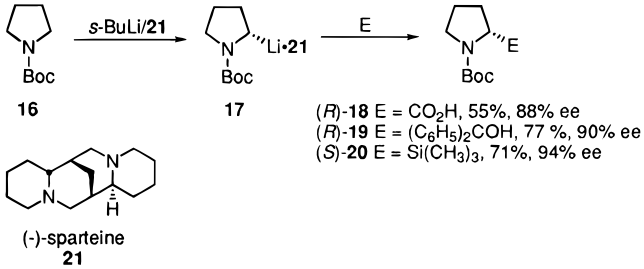
Enantioselective Reactions. The introduction of asymmetry in a chiral ligand mediated lithiation−substitution requires diastereomeric interactions in an intermediate or transition state in the sequence. The enantiodetermining step can be the lithiation, as an asymmetric deprotonation, or a postdeprotonation step, as an asymmetric substitution. A chiral ligand complexed to lithium can create the necessary diastereomeric environment in either step. In an asymmetric deprotonation, the organolithium reagent complexed to the chiral ligand is a chiral base which selectively abstracts an enantiotopic proton from the prochiral substrate **1**. The enantioenriched organolithium intermediate **2** or **2·L*** is configurationally stable and reacts stereoselectively with an electrophile, providing the enantioenriched product **3**. In an



asymmetric substitution, the enantiodetermining step occurs after deprotonation. The racemic organolithium **2** can afford enantioenriched product **3** under the influence of the chiral ligand by different pathways depending on whether **2** is slowly or rapidly epimerizing with respect to its rate of reaction with the electrophile (vide infra).

A seminal report by Nozaki and co-workers established that the naturally occurring and readily available alkaloid (−)-sparteine could be used as a useful ligand for enantioinduction at a carbanionic center in a lithiation−substitution sequence, albeit with poor selelctivity.[12] More recent investigations by Hoppe with α-oxygen dipole-stabilized carbanions have demonstrated high enantioselectivities for reactions in the presence of (−)-sparteine.[13] Hoppe's work has stimulated a number of further developments. Results from our laboratories will be used to illustrate the asymmetric reaction pathways for (−)-sparteine-mediated lithiation−substitution sequences which convert **1** to **3**.

Asymmetric Deprotonation. The reaction of *N*-Boc-pyrrolidine (**16**) with *sec*-BuLi/(−)-sparteine (**21**) gives (*R*)-**17** which reacts with electrophiles to provide enantioenriched products **18**−**20** with enantiomeric excesses (ee) of 88−94%.



Two experiments established an asymmetric deprotonation pathway for this sequence.[14,15] Addition of

(9) For early work on amide-directed lithiations of piperidines see: Beak, P.; Zajdel, W. J. J. *Am. Chem. Soc.* **1984**, *106*, 1010−1018. For introduction of the Boc group as a directing and stabilizing group see: Beak, P.; Lee, W-K. *Tetrahedron Lett.* **1989**, *30*, 1197−1200. For the Boc-piperidines see: Beak, P.; Lee, W-K. *J. Org. Chem.* **1990**, *55*, 2578−2580. Beak, P.; Lee, W-K. *J. Org. Chem.* **1993**, *58*, 1109−1117.

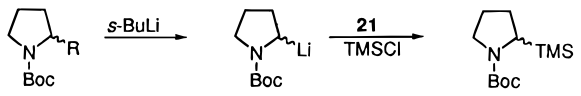
(10) Houk, K. N.; Rondan, N. G.; Beak, P.; Zajdel, W. J.; Schleyer, P. v. R.; Chandrashekhar, J. *J. Org. Chem.* **1981**, *46*, 4108−4110. Bach, R. D.; Braden, M. L.; Wolber, G. J. *J. Org. Chem.* **1983**, *48*, 1509−1514.

(11) Lutz, G. P.; Wallin, A. P.; Kerrick, S. T.; Beak, P. *J. Org. Chem.* **1991**, *56*, 4938−4943.

(12) Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905−913.

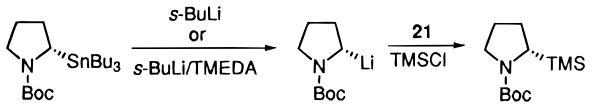
(13) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422−1424.

(−)-sparteine and (TMS)Cl to racemic 2-lithio-*N*-Boc-pyrrolidine (**17**), generated either by deprotonation of **16** with *sec*-BuLi or from tin−lithium exchange of **22**, provided essentially racemic **20**. This result rules out a postdeprotonative enantiodetermining step.



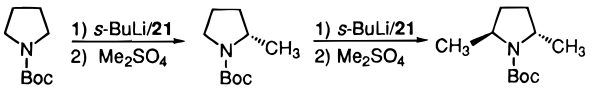
16 (R=H) or *rac*-**22** (R=$SnBu_3$) *rac*-**17** **20**

The configurational stability of the intermediate was evaluated by generation of enantioenriched (*R*)-**17** from the tin−lithium exchange reaction of (*S*)-**22** (96% ee), followed by reaction with (TMS)Cl in both the absence and presence of TMEDA. The product (*S*)-**18** was enantioenriched, consistent with substantial configurational stability under these reaction conditions.[16]



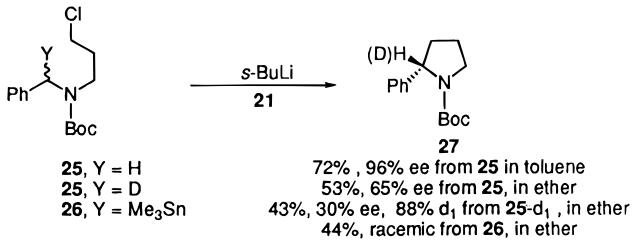
(*S*)-**22** 96% ee (*R*)-**17** (*S*)-**18** 93% ee (*s*-BuLi) 74% ee (*s*-BuLi/TMEDA)

The enantioenrichments from **16** provided an opportunity to amplify the enantioselectivity with a chiral substrate.[17,18] When the lithiation−substitution of **16** is carried out twice with *sec*-BuLi/(−)-sparteine and dimethyl sulfate, the enantiomeric excess of 94% of (*S*)-**23** increases to >99% after the second substitution to provide (*S*,*S*)-**24**. If the *pro-S* hydrogen is replaced in the second step with the same fidelity as in the first step, a calculated ee of 99.8% is expected.



16 (*S*)-**23** 88% 94% ee (*S*,*S*)-**24** 75% >99% ee, 80% de

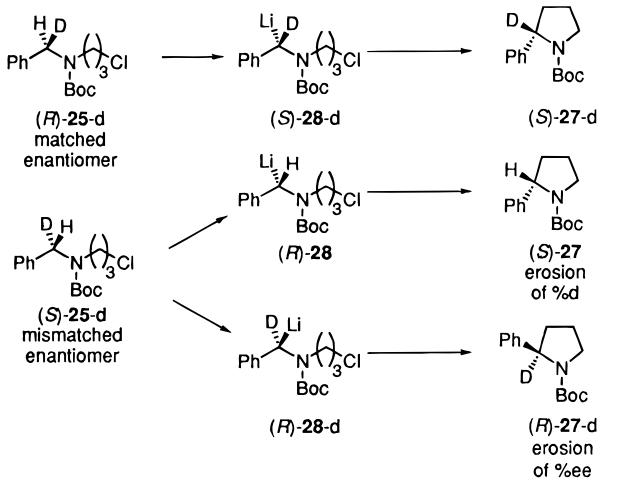
The conversion of *N*-Boc-*N*-benzyl-3-chloropropylamine (**25**) to (*S*)-*N*-Boc-2-phenylpyrrolidine (**27**) with *sec*-BuLi/(−)sparteine in toluene also proceeds via an asymmetric deprotonation.[19] The mechanism of the reaction was investigated by comparing the yields and enantioselectivities of **27** derived from **25** and *rac*-**25**-d_1 in ether. If the deprotonation were unselective, the proton should be preferentially removed from *rac*-**25**-d_1 due to the high isotope effect, affording the product with an ee and yield comparable to that from **25**. However, the product (*S*)-**27** obtained from *rac*-**25**-d_1



25, Y = H
25, Y = D
26, Y = Me_3Sn
27
72% , 96% ee from **25** in toluene
53%, 65% ee from **25**, in ether
43%, 30% ee, 88% d_1 from **25**-d_1 , in ether
44%, racemic from **26**, in ether

showed an erosion in yield and ee. Moreover, tin−lithium exchange of *rac*-**26** in the presence of (−)-sparteine gives a racemic product. Both results rule out a postdeprotonation asymmetric substitution.[20]

Since the pathway of asymmetric deprotonation is followed by **25**, the results with **25**-d_1 allow evaluation of the relative importance of the enantioselectivity of the deprotonation and the deuterium isotope effect. One of the enantiomers of **25**-d_1 is the matched enantiomer and the other the mismatched enantiomer for these two factors. The matched enantiomer, presumably (*R*)-**25**-d_1, will provide (*S*)-**28**-d_1 analogous to the diprotio compound. The mismatched enantiomer, (*S*)-**25**-d_1, can react by three pathways. If the enantioselectivity overrides the isotope effect, then the deuterium will be removed to form (*R*)-**28**, and the enantiomeric excess of the product will be invariant, while deuterium incorporation will be eroded. If the isotope effect overrides the enantioselectivity, the proton will be removed to provide (*R*)-**28**-d_1, resulting in decreased enantiomeric excess. Alternatively, if

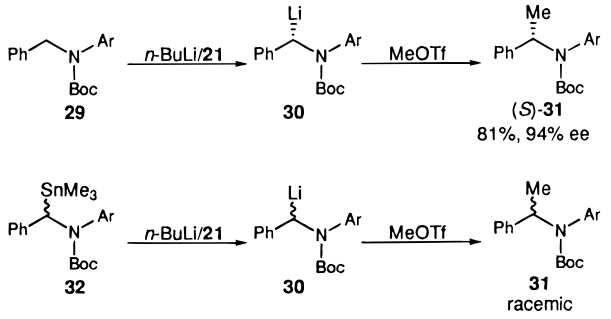


both the isotope effect and enantioselectivity are high, the mismatched enantiomer may be unreactive, resulting in a decreased yield of product. In this case, the enantiomeric excess of the product remains invariant, and the product and starting material will both have high deuterium content. The results indicate that the isotope effect overrides the enantioselectivity since the yield and ee are reduced for the reaction of **25**-d_1 relative to **25**.

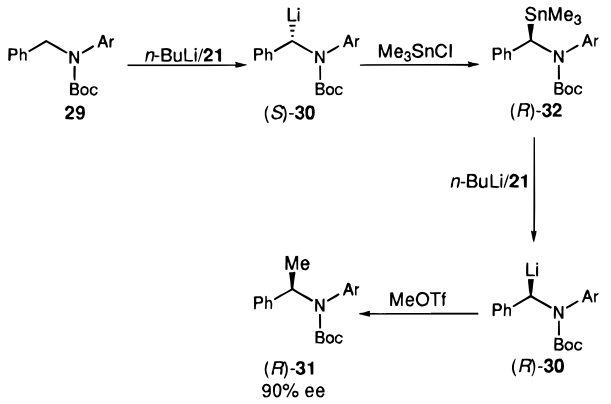
Enantioselectivity in the lithiation−substitution of *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine (**29**) also may be attributed to an asymmetric deprotonation.[21] Reaction of **29** with *n*-BuLi/(−)-sparteine followed by

(14) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708−9710.
(15) Efforts to identify other chiral ligands for the asymmetric deprotonation of *N*-Boc-pyrrolidine have been reported. Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. *J. Org. Chem.* **1995**, *60*, 8148.
(16) The organolithium (*R*)-**17** was reported to be configurationally labile in the absence of diamine in our preliminary communication (ref 14). This was found to be in error and corrected in the full paper (ref 17).
(17) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231−3239.
(18) Rauenstrach, V.; Mégard, P.; Bourdin, B.; Furrer, A. *J. Am. Chem. Soc.* **1992**, *114*, 1418−1428. The major reaction of the minor enantiomer and the minor reaction of the major enantiomer provide the *meso* diastereomer (*R*,*S*)-**24** in low yield.
(19) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715−721.
(20) High H−D isotope effects have been observed for these reactions. Hoppe, D.; Paetow, M.; Hintze. *Angew Chem., Int. Ed. Engl.* **1993**, *32*, 394−396. Kaiser, B.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 323−325. See also ref 11.
(21) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757−3758.

reaction with methyl triflate gives (*S*)-**31** with high enantioenrichment. Tin−lithium exchange of (*rac*)-**32** in the presence of (−)-sparteine gives racemic **31** on reaction with methyl triflate, ruling out a pathway of asymmetric substitution.

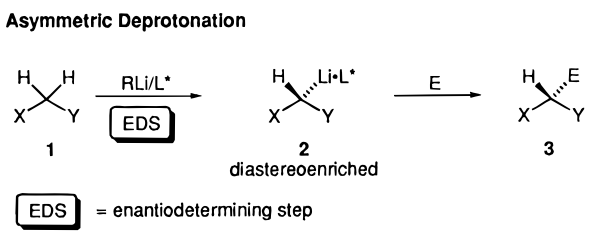


An interesting result was obtained when the configurational stability of the organolithium intermediate was investigated by the tin−lithium exchange of enantioenriched **32**. Upon treatment of **32** with *n*-BuLi/(−)-sparteine, followed by methyl triflate, (*R*)-**31**, the opposite enantiomer of the product obtained by the direct deprotonation−substitution sequence, was obtained. This result illustrates how either



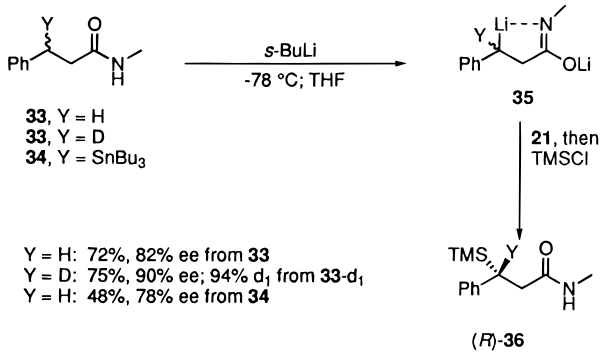
enantiomer of **31** can be obtained from **29**. We assume that stannylation of **30** proceeds with inversion of configuration to give (*R*)-**32** (vide infra).[22] These results show clearly that the asymmetric deprotonation of **29** with *n*-BuLi/(−)-sparteine produces a configurationally stable organolithium intermediate under the reaction conditions.

The above results can be generalized to conversions of **1** to **3** via **2** for aymmetric deprotonations in the presence of a chiral ligand, L*.



(22) The configuration of the organostannane **32** was assigned as *S* in the original communication (ref 21), under the assumption that the organolithium underwent an invertive substitution with all electrophiles. Greater consistency with other results is achieved by assuming retentive substitution and invertive stannylation. However, these assignments remain provisional.

Asymmetric Substitution. Although the α position of **33** might be expected to bear the most acidic proton, the effect of *N*-lithiation and the CIPE promotes *β*-lithiation to afford **35**.[23] Exposure of **35** to (−)-sparteine followed by reaction with trimethylsilyl chloride provides the enantioenriched product (*R*)-**36**.



Generation of racemic **35** from the tin precursor **34** in the presence of (−)-sparteine gives the product **36** with a comparable enantioenrichment. When *rac*-**33**-d_1 is treated with *sec*-BuLi/(−)-sparteine, **36** is formed with high ee and deuterium incorporation. This result indicates that an asymmetric deprotonation of **33** does not occur. Thus, the enantiodetermining step in the lithiation−substitution sequence from **33** to **36** occurs after deprotonation, and the pathway is an asymmetric substitution.

Two limiting pathways can be envisioned for asymmetric substitutions. In one pathway the diastereomeric complexes between the organolithium intermediate and the chiral ligand can be configurationally stable with respect to their rate of reaction with the electrophile. In this case the enantioselectivity of the products is determined by the ratio of the diastereomeric complexes that is established before the substitution step. This is termed dynamic thermodynamic resolution because the ratio of complexes is dynamically controlled prior to reaction with electrophile. The subsequent electrophilic substitution occurs with configurationally stable complexes. Figure 1 and the kinetic analysis shown illustrate the pathway.

In a different pathway, the diastereomeric complexes are configurationally labile with respect to their rate of reaction with the electrophile. This is a case of dynamic kinetic resolution, in which a stereogenic reactive center undergoes rapid epimerization and one of the diastereomeric complexes reacts preferentially under the reaction conditions.[24] In this case, the enantioselectivity is determined by the difference in the diastereomeric transition state energies for the reaction with the electrophiles. A reaction diagram for this pathway is shown in Figure 2, along with the kinetic definition.[25]

(23) Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516−2518.

(24) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−56 and references cited therein. In this paper, Noyori et al. define a dynamic kinetic resolution as a process in which *enantiomers* can interconvert under the reaction conditions and provide an elegant kinetic analysis. The definition can be extended to include situations that involve interconverting *diastereomers*. In that case, the kinetic analysis outlined by Seeman must be used. Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134. For a recent application see: Gately, D. A.; Norton, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3479−3489. For a related discussion, see: Hirsch, R.; Hoffmann, R. W. *Chem. Ber.* **1992**, *125*, 975−982.

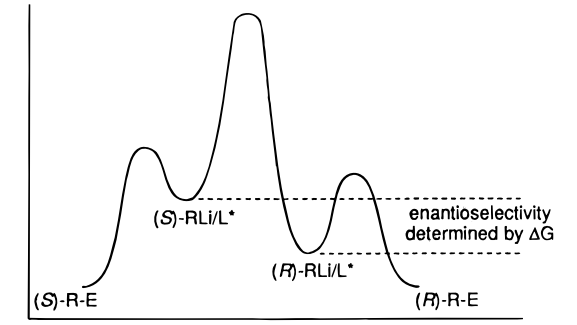
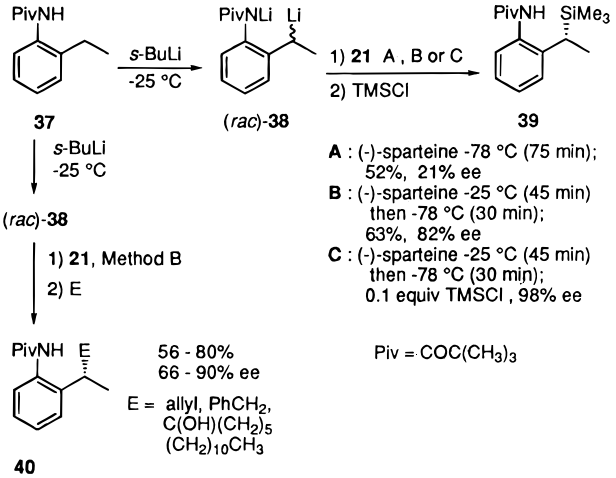
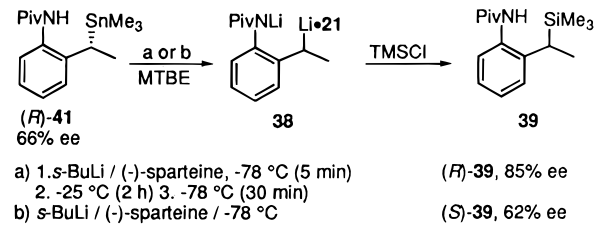


Figure 1. Energy diagram and kinetic definition for dynamic thermodynamic resolution.

Dynamic Thermodynamic Resolution. Lateral lithiation of *o*-ethyl-*N*-pivanilide (**37**) with *sec*-BuLi at −25 °C produces **38**. When **38** is cooled to −78 °C before addition of (−)-sparteine and trimethylsilyl chloride, the product (*R*)-**39** is obtained with 21% ee (method A).[26] However, if the (−)-sparteine is added at −25 °C and stirred for 45 min prior to cooling to −78 °C and reaction with trimethylsilyl chloride, (*R*)-**39** is obtained with 82% ee (method B). The use of other electrophiles with this warm−cool protocol gives enantioenriched compounds **40** in useful yields with good enantiomeric excesses.



Clarifying information about the reaction was provided by tin-lithium exchange reactions. When (*R*)-**41** (66% ee) was treated with *sec*-BuLi/(−)-sparteine, but allowed to stir at −25 °C for 2 h prior to cooling to −78 °C and addition of (TMS)Cl (method a), the product (*R*)-**39** was obtained with 85% ee. However,



treatment of (*R*)-**41** (66% ee) with *sec*-BuLi/(−)-sparteine followed by (TMS)Cl at −78 °C (method b) provided the enantiomer (*S*)-**39** with enantioenrichment similar to that of the reactant.

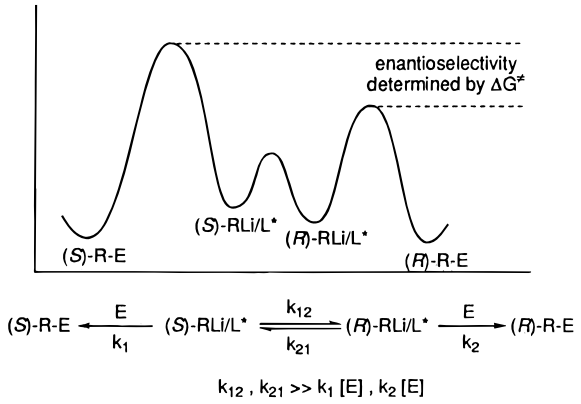


Figure 2. Energy diagram and kinetic definition for dynamic kinetic resolution.

These results are consistent with a reaction pathway in which the diastereomeric complexes formed between **38** and (−)-sparteine equilibrate to a thermodynamic ratio at −25 °C. This ratio is maintained on cooling to −78 °C, and the complexes are nonequilibrating at that temperature. Thus, the tin−lithium exchange of (*R*)-**41** at −78 °C provides fidelity in stereoinformation transfer, but a warm−cool cycle restores the thermodynamic ratio. The enantioselectivity is determined by the ratio of the nonequilibrating diastereomeric complexes at −78 °C. The asymmetric induction from **37** is an example of the dynamic thermodynamic resolution of Figure 1.

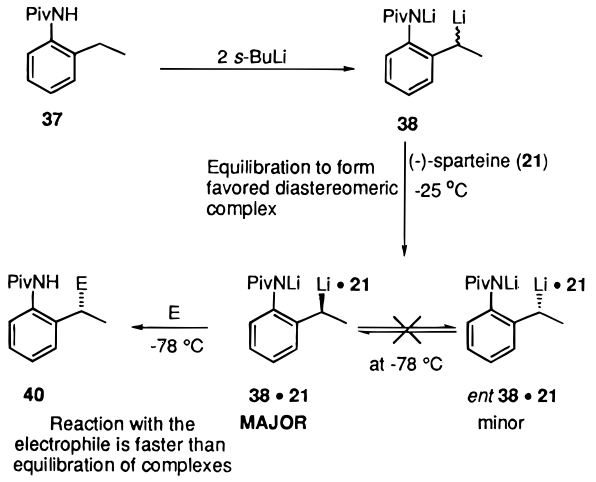
When the reaction of **37** with *sec*-BuLi/(−)-sparteine is carried out at −78 °C with 0.10 equiv of trimethylsilyl chloride as the electrophile, (*R*)-**39** is obtained with 82% ee (method C).[27] This result is different from the 21% ee observed for treatment of the same complexes with excess trimethylsilyl chloride at the same temperature (vide supra). The different ratio arises from a kinetic resolution in the reaction of the diastereomeric complexes **38·21** with the electrophile. This is a case of Figure 1 in which the activation energies for the diastereomeric substitution steps are not equal, i.e., $k_1 \neq k_2$. Comparison of the result of method C with the 98% ee obtained when 0.1 equiv of trimethylsilyl chloride is allowed to react with the equilibrated ratio of diastereomeric complexes leads to assignment of a ratio of equilibrated diastereomeric complexes of 92:8 at −25 °C, favoring (*S*)-**38·21**.[27] The sequence is shown for the conversion of **37** to **40** with an assumption of invertive substitution.

The above interpretation of the reactions of the diasteromeric complexes of **38** and **21** is a variant of the elegant Hoffman test of configurational stability of organolithiums.[4] We refer to this application of the test as the "poor man's Hoffmann test", since we are not using chiral enantioenriched electrophiles. Application of the test, i.e., observation of a difference in ee dependent on the amount of the electrophile, may

(25) Figure 2 depicts epimerization of the diastereomeric complexes proceeding directly without the intermediacy of the uncomplexed organolithium. In a recent study of α-selenoorganolithium reagents, Hoffmann has shown that epimerization occurs faster than decomplexation followed by epimerization. However, we cannot rule out a pathway involving decomplexation followed by inversion. Hoffmann, R. W.; Klute, W.; Dress, R. K.; Wenzel, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1721−1726.

(26) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575−1576.

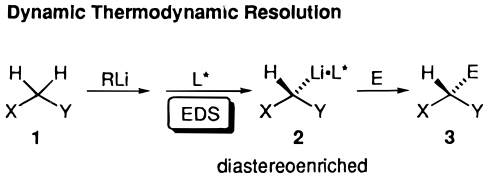
(27) Basu, A.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, 61, 5718−5719.



be used to detect configurationally stable complexes. A recent application of this test shows that the asymmetric substitution of **33** is also a case of dynamic thermodynamic resolution.[28]

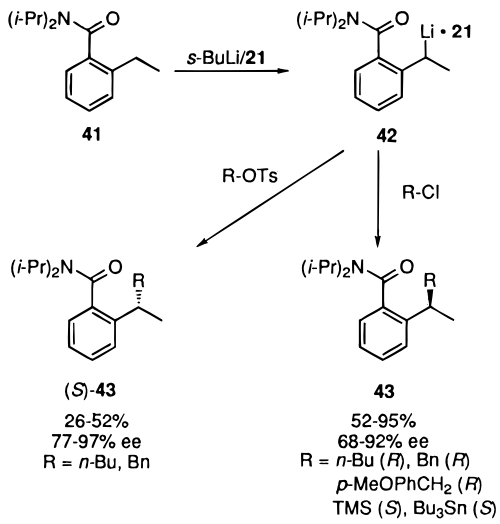
Selective diastereomeric complex formation can be driven by crystallization. Hoppe and co-workers have observed a dynamic thermodynamic resolution of diastereomeric complexes through selective crystallization with (−)-sparteine and developed this observation to provide an asymmetric homoenolate equivalent.[29]

Asymmetric substitution by a dynamic thermodynamic resolution in the presence of the chiral ligand L* is illustrated in Figure 1.

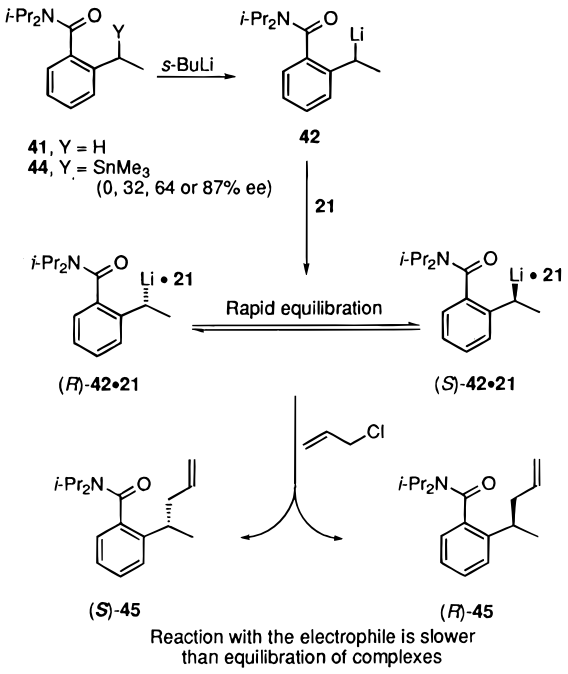


Dynamic Kinetic Resolution. Lithiation of **41** with *sec*-BuLi/(−)-sparteine generates the intermediate **42·21**, which reacts with alkyl halides and silyl and stannyl chlorides to give the products **43** in good yields and high enantioselectivities.[30] The identity of the nucleofuge has a significant effect on the enantioselectivity of the reaction. For example, *n*-BuCl, *n*-BuBr, and *n*-BuI afford the products (*R*)-**43** with 80%, 74%, and 28% ee, respectively. Remarkably, alkylation with *n*-BuOTs as electrophile affords (*S*)-**43** with 97% ee. The Cl/OTs dichotomy applies to benzyl and allyl electrophiles as well.

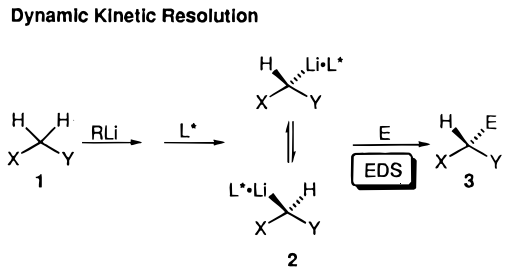
Treatment of the organostannane **44** with *sec*-BuLi/(−)sparteine at −78 °C followed by reaction with allyl chloride provides the product (*R*)-**45** with 82−87% ee irrespective of the enantioenrichment of **44**. The enantioselectivity does not change measurably in the course of the reaction, a result which disfavors, but does not absolutely exclude, a dynamic thermodynamic resolution. The results suggest that the organolithium intermediate **42·21** is configurationally labile. The enantioselectivity is determined by the



difference in the diastereomeric transition state energies of the substitution step. This pathway of dynamic kinetic resolution is shown for the equilibrating complexes (*R*)-**42·21**and (*S*)-**42·21** and represents a case of Figure 2.



Asymmetric substitution by dynamic kinetic resolution with the chiral ligand L* is illustrated in Figure 2.



It is possible for more than one pathway to be operative with a single substrate. Schlosser has shown that *N*-Boc-*N*-methyl-*N*-benzylamine under-

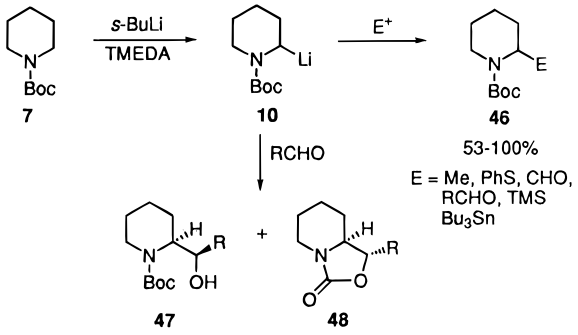
(28) Gallagher, D. J.; Du, H.; Long, S. A.; Beak, P. *J. Am. Chem. Soc.*, in press.
(29) Marsch, M.; Harms, K.; Zschage, O.; Hoppe, D.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 321−323.
(30) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755−9756.

goes an initial asymmetric deprotonation followed by equilibration of the resultant intermediate.[31] In this case, the enantioselectivity of the product is determined in a postdeprotonation step, even though an asymmetric deprotonation occurs. This result is similar to our observations for the diastereoselective deprotonation and substitution of **13** (vide supra).[11]

Absolute Configurations. The configurations assigned to the products of reactions with carbon and silyl electrophiles in our work are secured by comparisons with authentic compounds or by firm analogy. The configurations for the organolithium intermediates and stannanes in the reaction schemes are based on assumptions about reaction stereochemistry and are provisional.[32]

Synthetic Applications

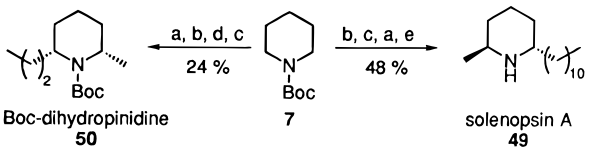
Regioselective and Diastereoselective Synthesis. The lithiation−substitution of *N*-Boc-piperidine (**7**) provides examples of synthetically useful diastereoselectivities with an α-lithioamine synthetic equivalent. Treatment of **7** with *sec*-BuLi/TMEDA at −78 °C gives the lithiated intermediate **10**, which upon treatment with a variety of electrophiles provides facile access to a wide variety of 2-substituted piperidines **46**.[9] While the reactions of **10** with aldehydes afford a mixture of diastereomers, preferential cyclization of the *syn* isomer, often under the reaction conditions, gives **47** and **48** which are readily separated.



Diastereoselectivities observed with *N*-Boc cyclic amines can be utilized for stereodivergent synthesis of *cis* and *trans* piperidine alkaloid derivatives. The sequence shown affords the 2,6 *trans* substitution of the ant venom solenopsin A (**49**). A strategy for 2,6 *cis* substitution is available as shown by the synthesis of *N*-Boc-dihydropinidine (**50**). In the latter case the *cis* stereochemistry provided by epimerization of the intermediate *trans*-2-formyl-6-methylpiperidine is driven by $A_{1,3}$ strain.

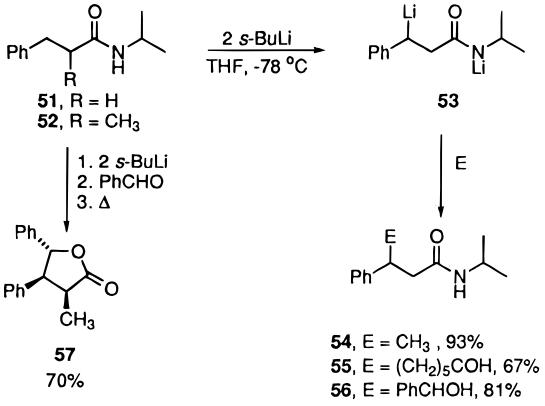
(31) Schlosser, M.; Limat, D. *J. Am. Chem. Soc.* **1995**, *117*, 12342−12343.

(32) Hoppe and Boche have determined the solid state structures of an α-lithio oxygen dipole-stabilized carbanion and a lithiated 1-butylindene which are complexed to (−)-sparteine. See ref 29 and Hoppe, I.; Marsch, M.; Harms, K.; Boche, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2158−2160. The stereochemistry of the products from the reactions of these carbanions with electrophiles does not show a highly consistent pattern. Hoppe and Gawley have reported reactions in which a single substrate undergoes substitution with similar electrophiles with both retention and inversion. Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097−6108. Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763−5769. Our assignments of absolute configuration are consistent with the stereochemical course of the majority of known reactions, but, as noted, they are not definitive.

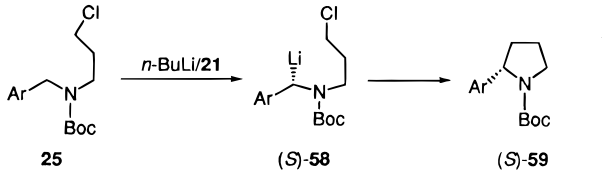


a) *s*-BuLi/TMEDA; Me_2SO_4. b) *s*-BuLi/TMEDA; DMF
c) Ph_3PCHR; H_2/Pd/C. d) silica gel e) TFA

The regioselectivity and diastereoselectivity of the lithiation−substitution of *N*-isopropyl-3-phenylpropionamide (**51**) have been studied.[33] The regioselective β-lithiation provides a homoenolate synthetic equivalent in a two-step, one-flask reaction from a readily available precursor to provide **54**−**56**. Although **56** is obtained as a diastereomeric mixture, lithiation−substitution and cyclization with *N*-isopropyl-3-phenyl-2-methylpropionamide (**52**) in the same sequence provide **57** diastereoselectively.



Asymmetric Deprotonations. The enantioselective lithiation−substitution of *N*-Boc-pyrrolidine (**16**) provides (*ent*)-proline (*S*)-**18**, the Corey−Itsuno catalyst (*S*)-**19**, and the C_2 symmetric chiral auxiliary (*S*,*S*)-**24** in good yields and high enantioselectivities. The lithiation cyclization of **25** to (*S*)-**27** has been generalized to afford highly enriched 2-aryl-*N*-Boc-pyrrolidines **59** via (*S*)-**58**.[19]

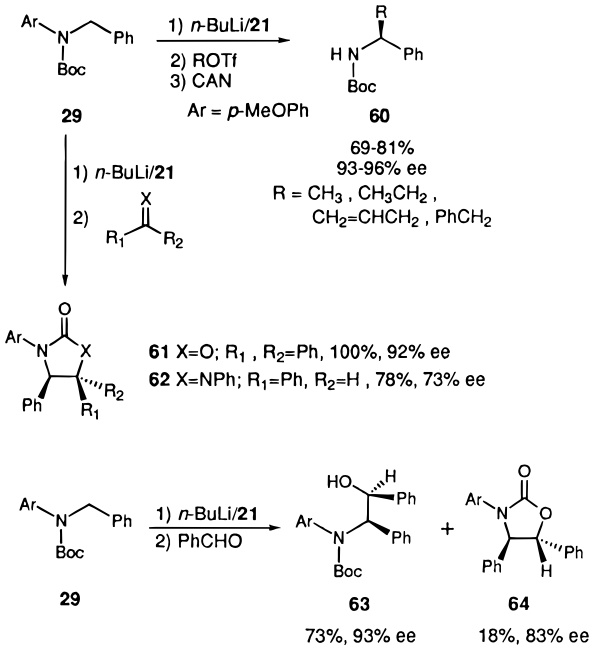


Ar = Ph, *p*-Cl-Ph, *p*-F-Ph, *p*-Me-Ph, *m*-MeO-Ph, 1-naphthyl, 2-naphthyl, 3-thienyl, 3-furyl

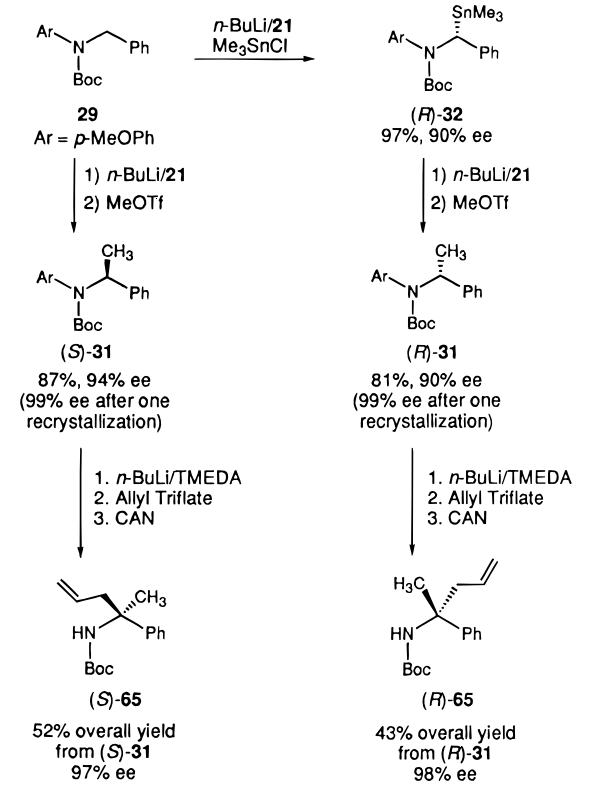
The asymmetric deprotonation of *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine (**29**) provides the basis for useful asymmetric elaborations.[21] Lithiation of **29** with *n*-BuLi/(−)-sparteine in toluene at −78 °C followed by reaction with alkyl triflates and subsequent oxidation provides the *N*-Boc-α-alkylbenzylamines **60** with excellent enantioselectivities and good yields. The use of a ketone or imine as an electrophile followed by in situ cyclization of the initial adducts affords the corresponding oxazolidinone **61** or imidazolidinone **62**. In both cases one recrystallization gives products with >95% ee. With benzaldehyde as the electrophile, the

(33) Lutz, G. P.; Du, H.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 4542−4554.

β-amino alcohol **63** and the oxazolidinone **64** are obtained with high enantioselectivities. This methodology should be useful for syntheses of highly enantioenriched amino alcohols and diamines.

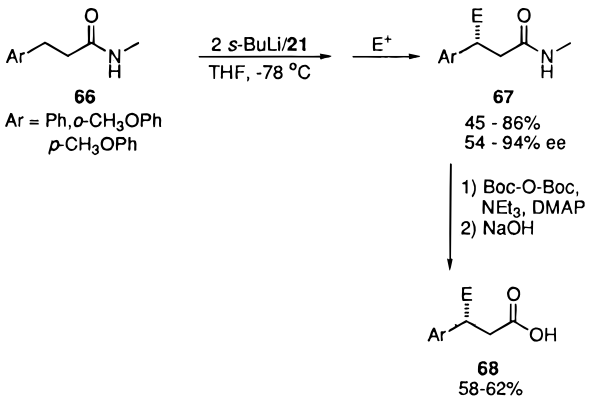


Both (*S*)-**31** and (*R*)-**31** are available from **29** by control of the method of lithiation. An important aspect of this methodology is that the tertiary anion from **31** is configurationally stable. Treatment of (*S*)-**31** with *n*-BuLi/TMEDA followed by reaction with allyl triflate provides (*S*)-α-allyl-α-methyl-*N*-Boc-benzylamine [(*S*)-**65**] with 96% ee. The enantiomer (*R*)-**65**

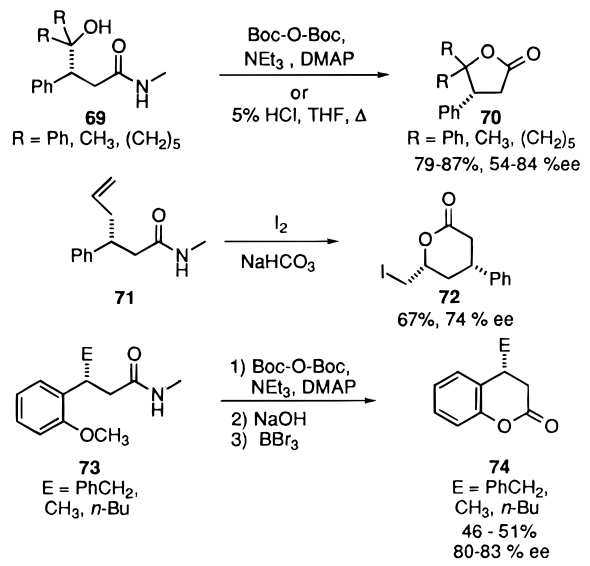


is prepared with 98% ee from (*R*)-**31** using the same reagents. The syntheses of tertiary and quaternary centers of α-substituted and α,α-disubstituted benzylic amines with control of absolute configuration should stimulate applications and extensions of the methodology.

Asymmetric Substitutions. Although the chiral ligand need not be present during the lithiation step of an asymmetric substitution, it is most convenient to carry out the lithiation in its presence as shown for the conversion of **66** to **67**. The products can be hydrolyzed under mild conditions to provide the enantioenriched acids **68**.[33]



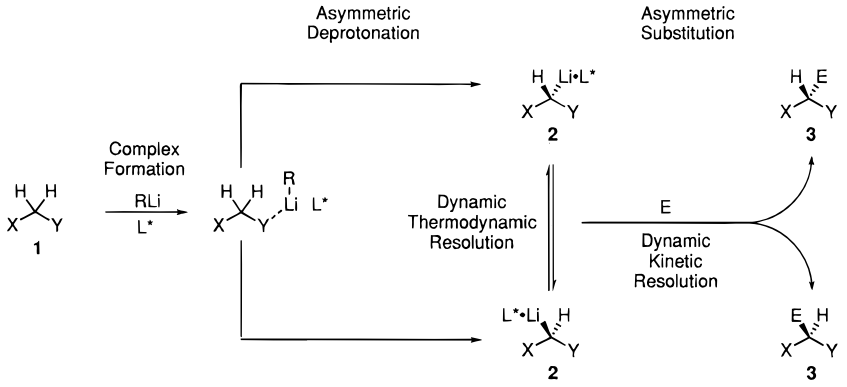
The carbinols **69**, derived from the reaction of **66** with ketones, can be cyclized to provide the enantioenriched lactones **70**. Iodolactonization of the β-allyl-substituted amide **71** gives exclusively the *syn* diastereomer of the β,δ,δ-trisubstituted δ-lactone **72**. The methodology has been extended to provide 3-(*o*-methoxyphenyl)propionamides **73**, which can be hydrolyzed, demethylated, and cyclized to provide enantioenriched dihydrocoumarins **74**.



Summary

The conversion of **1** to **2** to **3** provides a convenient and efficient synthetic strategy for regioselective, diastereoselective, and enantioselective syntheses. The processes by which selectivity is introduced in these lithiation−substitution sequences are shown in Scheme 1. After initial complexation, a regioselective or diastereoselective deprotonation can occur. In an asymmetric deprotonation, the enantioenriched **2** or

Scheme 1

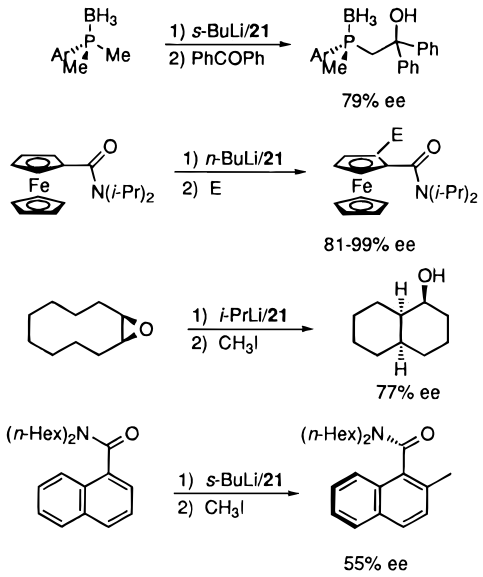


2·L* retains its configuration and reacts stereoselectively with electrophiles. If **2** is produced in racemic form, two different diastereoselective pathways for asymmetric substitution are available. The pathway which involves selective formation of one nonequilibrating complex is a dynamic thermodynamic resolution. If the diastereomeric complexes are in rapid equilibrium, a pathway of dynamic kinetic resolution is followed. While the cases we have discussed involve (−)-sparteine as the chiral ligand, the scheme applies to other ligands as well as to reactions involving chiral auxiliaries.

Future Work

The highly regioselective, diastereoselective, and enantioselective reactions which have been demonstrated should stimulate new synthetic applications which will expand the methodology. Evans and coworkers have shown that *sec*-BuLi/(−)-sparteine distinguishes between enantiotopic methyl groups in a prochiral phosphine−borane complex.[34] Snieckus has recently reported the (−)-sparteine-mediated preparation of enantioenriched ferrocene derivatives.[35] Hodgson has provided an interesting ring-opening cyclization of a *meso*-epoxide with *i*-PrLi/(−)-sparteine.[36] We have recently accomplished the enantioselective synthesis of atropisomeric compounds by this approach.[37]

Further studies are clearly needed. Information about the absolute configurations of the lithiated intermediates, the role of the ligands, and the stereochemistry of the substitutions is limited. Catalytic enantioselective lithiation−substitution sequences, whether as asymmetric deprotonations or as asymmetric substitutions, remain elusive.[38] Investigations directed at structural elucidation of diastereomeric complexes could provide insight into their reactivity as well and permit refinement of models for the transfer of stereochemical information from the ligand to the product. These efforts should provide the basis for rational development of novel synthetic strategies utilizing enantioselective lithiation−substitution sequences.



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AR950142B

(34) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075−9076.

(35) Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 685−686.

(36) Hodgson, D. M.; Lee, G. P. *J. Chem. Soc. Chem. Commun.* **1996**, 1015−1016.

(37) Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 2899−2902.

(38) In this regard the recent study by Hoffmann and co-workers demonstrating the ability to control the rate of reaction of diastereomeric complexes with electrophiles relative to the rates of reaction with uncomplexed organolithiums represents a significant advance toward catalysis. Hoffmann, R. W.; Klute, W. *Chem. Eur. J.* **1996**, *2*, 694−700.