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Asymmetric Lithiation−Substitution Sequences of Substituted Allylamines

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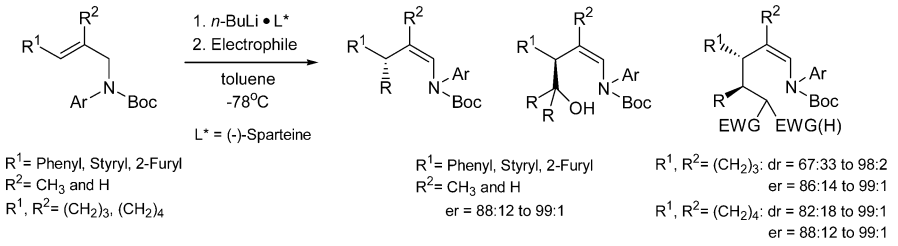

(−)-Sparteine-mediated asymmetric lithiation−substitution sequences of 2- and 3-substituted *N*-(Boc)-*N*-(*p*-methoxyphenyl) allylic amines with electrophiles have been investigated. Asymmetric lithiation−substitutions of *N*-(Boc)-*N*-(*p*-methoxyphenyl) allylic amines **11**, **12**, **13**, **14**, and **15** provide highly enantioenriched enecarbamates in good yields. Further transformations to give aldehydes, acids, ketones, and a Diels−Alder adduct are reported. The 1,4-addition products from reactions of the lithiated allylic amines from **14** and **15** with conjugated activated alkenes gives enecarbamates with two and three stereogenic centers in good yields with high diastereomeric and enantiomeric ratios. Synthetic transformation of these products by acid hydrolysis and subsequent cyclization provide stereoselective access to bicyclic compounds containing four and five stereogenic centers with high diastereoselectivity and enantioselectivity. It is suggested that allyllithium complexes generated by asymmetric deprotonation react with most electrophiles with inversion of configuration.

Introduction

Carbon−carbon bond-forming reactions of lithiated benzylic and allylic amine derivatives mediated by chiral ligands are of current interest for asymmetric amine synthesis and provide asymmetric homoenolate synthetic equivalents. Sequences which begin with deprotonation or tin−lithium exchange by alkyllithium bases at the α-carbon of amine substrates provide examples of the utility of this methodology.[1−8]

Asymmetric lithiation−substitution reactions of *N*-aryl-*N*-Boc benzylamine **1** and of *N*-aryl-*N*-Boc cinnamylamine **2**, in the presence of (−)-sparteine (**3**) have been developed in our laboratories (Scheme 1). Deprotonations with *n*-BuLi carried out at −78 °C followed by reaction with electrophiles give the highly enantioenriched products **5** and **7** in high yields with high enantiomeric ratios (ers).[9] The enecarbamate products from the *N*-Boc allylamines are synthetically useful as they can be readily converted to β-substituted carbonyl compounds, α-substituted aldehydes, and γ-substituted amine derivatives. It has been shown that these reactions usually occur with inversion of configuration at the lithiated intermediate.[10]

The lithiated intermediates **4** and **6** were characterized by ^{6}Li and ^{13}C NMR of labeled *n*-BuLi and *N*-Boc

(1) (a) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220. (b) Burchat, A. F.; Chong, J. M.; Park, S. B. *Tetrahedron Lett.* **1993**, *34*, 51.

(2) (a) Pearson, W. H.; Lindbeck, A. C.; Kempf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622. (b) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546.

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(4) (a) Elworthy, T. R.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 6089. (b) Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589.

(5) Gross, K. M.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315. (b) Gross, K. M.; Beak, P. *J. Org. Chem.* **1997**, *62*, 7679.

(6) Coldham, I.; Copley, R. C. B.; Haxell, T. F. N.; Howard, S. *Org. Lett.* **2001**, *3*, 3799.

(7) (a) Gaul, C.; Arvidsson, P. I.; Bauer, W.; Gawley, R. E.; Seebach, D. *Chem. Eur. J.* **2001**, *7*, 4117. (b) Gaul, C.; Scharer, K.; Seebach, D. *J. Org. Chem.* **2001**, *66*, 3059. (c) Gaul, C.; Seebach, D. *Org. Lett.* **2000**, *2*, 1501.

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(9) (a) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757. (b) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574. (c) Kim, B. J.; Park, Y. S.; Beak, P. *J. Org. Chem.* **1999**, *64*, 1705.

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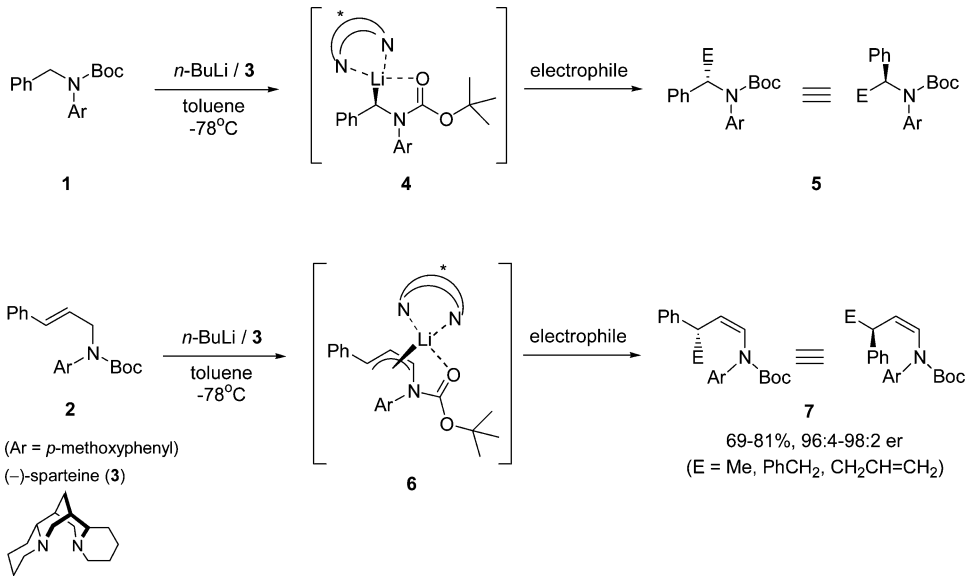
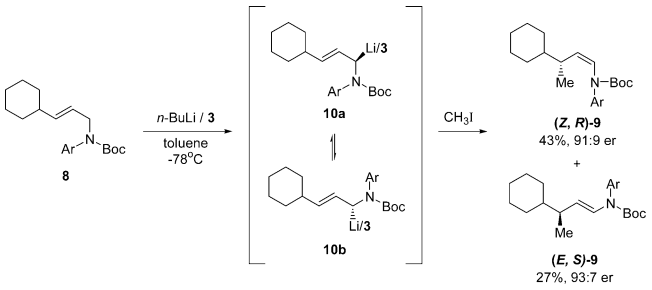
SCHEME 1



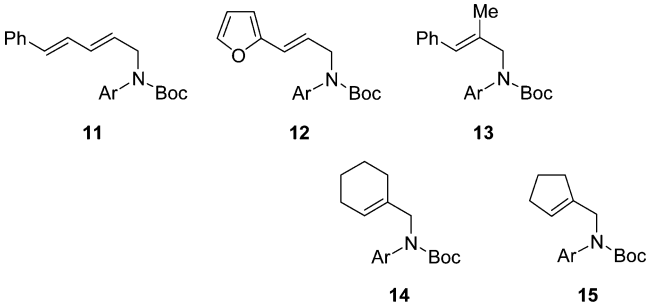
SCHEME 2



amines.[11] The NMR data support assignment of organolithiums **4** and **6** as largely monomeric, with coordination of the Boc carbonyl and **3** to the lithium. The diastereomeric ratios (drs) of **4** and **6** were found to be 91:9 and 96:4, respectively, consistent with high stereoselectivities in reactions with electrophiles. The structure of **6** was determined by X-ray crystallographic analysis. The stereochemical course of these reactions were determined to be asymmetric deprotonations to provide **4** and **6**. Asymmetric substitutions were ruled out by establishing that racemic organolithium species on exposure to (−)-sparteine followed by reactions with electrophiles did not afford racemic products.[9,11,12]

Lithiation–substitution of the cyclohexyl-substituted allylic amine derivative **8** with methyl iodide was investigated to evaluate the effects of alkyl vs aryl allylic substitution on the allylic terminus.[13] The *cis* product (*Z,R*)-**9** was obtained in 43% yield with a 91:9 er (Scheme 2). The *trans* isomer, (*E,S*)-**9**, was obtained in 27% with a 93:7 er with the opposite absolute configuration at the chiral carbon. ^{6}Li and ^{13}C NMR studies indicated monomeric species represented as **10** to be coordinated to the α-carbon. A Sn–Li exchange study confirmed asymmetric deprotonation to be the enantiodetermining event. The formation of (*Z,R*)-**9** and (*E,S*)-**9** can be rationalized if rotation about the C1–C2 axis is competitive with or faster than reaction with the electrophile and the reaction with methyl iodide proceeds with inversion of configuration.

We now report lithiation–substitution reactions of selectively substituted allylic amines. Lithiation–substitutions of **11**–**15** in the presence of (−)-sparteine establish that the asymmetry of the sequence is maintained in the presence of an additional double bond, a heteroaromatic ring, substitution on the central carbon of the allyl group, and incorporation of the double bond in a five- or six-membered ring. In addition to the alkylation and addition reactions of the lithiated intermediates, conjugate additions have been investigated.



Results

Asymmetric Lithiation–Substitution Sequence of 11. The lithiation–substitution reaction sequence with the *N*-Boc-*N*-(*p*-methoxyphenyl)pentadiene amine **11** was carried out to determine the effect of an additional conjugated double bond on product regioselectivity and enantioselectivity. An interesting issue was whether ϵ substitution, presumably more remote than γ substitution, from the site of complexation of the lithium with

(11) (a) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561. (b) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218. (c) Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522. (d) Pippel, D. J.; Weisenburger, G. A.; Wilson, S. R.; Beak, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2522.

(12) Tin–lithium exchange occurs with retention of configuration: Reich, H. J.; Borst, M. B.; Coplien, N. H.; Phillips, N. H. *J. Am. Chem. Soc.* **1992**, *114*, 6577.

(13) Pippel, D. J.; Weisenburger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919.

SCHEME 3

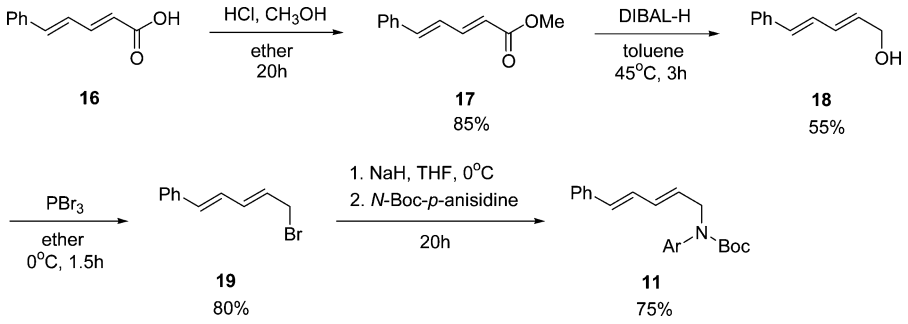
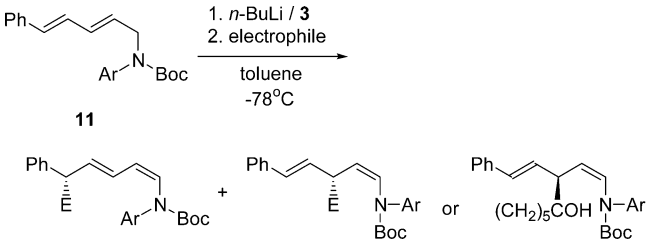


TABLE 1. Asymmetric Lithiation−Substitutions of 11



entry	electrophile	E	product	yield (%)	er
1	CH_3OTf	$-CH_3$	**20**	60	88:12
			21	10	78:22
2	$C_6H_5CH_2Br$	$-CH_2C_6H_5$	**22**	57	93:7
			23	25	91:9
3	$CH_2{=}CHCH_2Br$	$-CH_2CH{=}CH_2$	**24**	29	90:10
			25	44	89:11
4	$(CH_3)_3SiOTf$	$-Si(CH_3)_3$	**26**	75	96:4
5	$(CH_2)_5CO$	$-COH(CH_2)_5$	**27**	79	94:6 (99:1)[a]

[a] After recrystallization.

the ligand and carbonyl oxygen, would give a high enantiomeric ratio.

The synthesis of **11** was initiated by esterification of the unsaturated acid **16** under acidic conditions to afford the methyl ester **17** in high yield.[14] Reduction with DIBAL-H to the alcohol **18** was followed by conversion to bromide **19** with PBr_3. Coupling of **19** with the sodium salt of *N*-Boc-*p*-anisidine yielded the desired *N*-protected amine **11** (Scheme 3).

Treatment of **11** with 1.1 equiv of *n*-BuLi and 1.1 equiv of **3** in toluene at −78 °C for 1 h, followed by the addition of electrophiles, provides the products **20**−**27** shown in Table 1. Reaction with methyl triflate as the electrophile provided products **20** and **21** (entry 1). A solvent study was performed to determine optimal conditions with respect to yield, regioselectivity, and enantioselectivity. With toluene as the solvent, a 60% yield of **20** was obtained, although a minor amount of isomer **21** was also formed in 10% yield. The er of **20** was determined to be 88:12. Etheral solvents were surveyed and found to provide the products with lower regioisomeric and enantiomeric ratios.

Two halide electrophiles, benzyl bromide and allyl bromide, gave isomeric mixtures of C-5- and C-3-substituted products **22**, **23**, **24**, and **25**. All isomers were found to have good enantioenrichments of 89:11−93:7 (entries 2 and 3). With trimethylsilyl triflate as the electrophile (entry 4), only the α-substituted product **26** was obtained in a good yield of 75% with a 96:4 er. The absolute configurations are assigned by analogy to products obtained from **2** as (*S*). The isomers were separated by preparatory HPLC, and the enantiomeric ratios were determined by chiral stationary phase CSP-HPLC comparison to independently synthesized racemic samples.[15,16] The olefin geometry of the products was determined by the magnitude of the olefinic coupling constants, and assignment to each proton was made unambiguously by ^1H NMR spectroscopy using $\{^1H, ^1H\}$ decoupling experiments. Reaction with cyclohexanone as the electrophile resulted in the formation of the γ-substituted product **27** with a 94:6 er, which could be improved to 99:1 after recrystallization (entry 5).

Two synthetic transformations of **20** were demonstrated. The hydrolytic conversion of **20** to an enantioenriched δ-substituted α,β-unsaturated aldehyde was accomplished with hydrochloric acid. The hydrolysis proceeded smoothly to give **28** in moderate yield, demonstrating that lithiated **11** can be a homoenolate synthetic equivalent.[11]

Conversion of **20**, which has *E*,*Z* geometry, to **29**, which has *E*,*E* geometry, was carried out to provide a diene suitable for the concerted [4 + 2] cycloaddition (Scheme 4). Isomerization of **20** to **29** proceeded in good yield with dry, catalytic trifluoroacetic acid. Access to this isomer also confirmed that **29** was not detected from the lithiation−substitution sequence of **11**. Reaction of **29** with maleic anhydride and *N*-methylmaleimide in toluene resulted in the formation of the highly diastereomerically enriched products presumed to arise by favored endo addition to give **30** and **31** in moderate and good yields as 95:5 mixtures of diastereomers.[17]

Asymmetric Lithiation−Substitution Sequences of 12. To test the methodology in a system bearing a

(14) Drew, J.; Letellier, M.; Morand, P.; Szabo, A. G. *J. Org. Chem.* **1987**, *52*, 4047.

(15) Racemic samples were synthesized using TMEDA as the ligand.

(16) Compound enantiomeric ratios (er's) were determined by comparison of chiral stationary phase CSP-HPLC data to independently synthesized racemic compounds. Diastereomeric ratios (dr's), when applicable, were determined by ^1H NMR integrations. Diastereomers were separated by column chromatography or preparatory HPLC.

(17) (a) Overman, L. E.; Freerks, R. L.; Petty, C. B.; Clizbe, L. A.; Ono, R. K.; Taylor, G. F.; Jessup, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 2816. (b) Wu, T.-C.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2293. (c) Zezza, C. A.; Smith, M. B. *J. Org. Chem.* **1988**, *53*, 1161. (d) Wasserman, H. H.; Blum, C. A. *Tetrahedron Lett.* **1994**, *35*, 9787. (e) Grant-Young, K.; Smith, M. B.; Ovaska, T.; Wang, C.-J. *Synth. Commun.* **1998**, *28*, 4233.

SCHEME 4

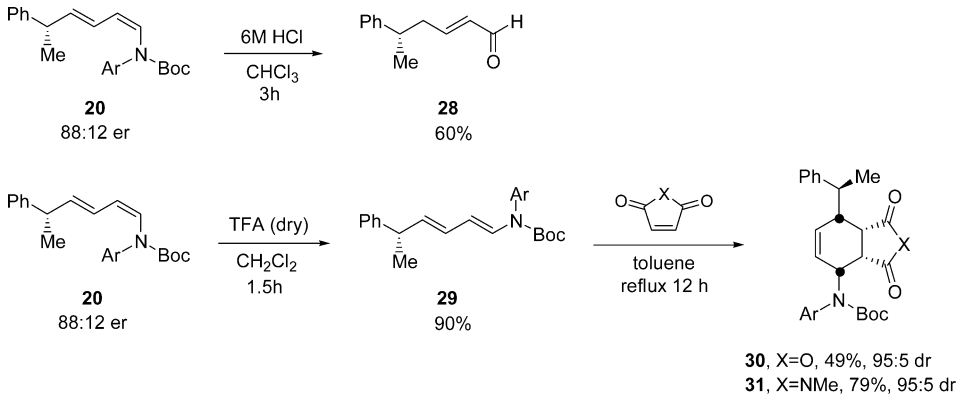
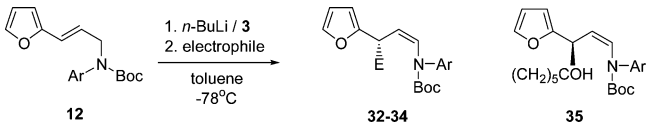


TABLE 2. Asymmetric Lithiation−Substitutions of 12[a]

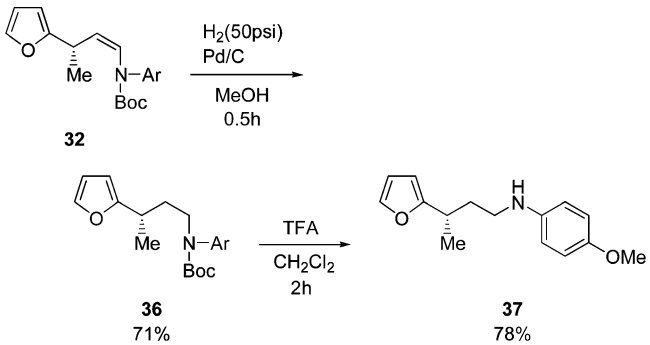


entry	electrophile	E	product	yield (%)	er
1	CH_3OTf	$-CH_3$	**32**	80	97:3
2	$C_6H_5CH_2Br$	$-CH_2C_6H_5$	**33**	70	98:2
3	$CH_2{=}CHCH_2Br$	$-CH_2CH{=}CH_2$	**34**	65	97:3
4	$(CH_2)_5CO$	$-COH(CH_2)_5$	**35**	68	98:2

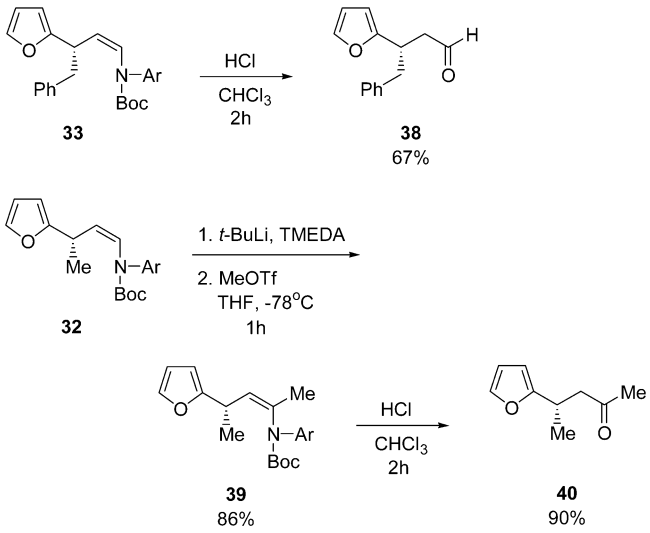
[a] Three reaction sequences were carried out to test further the durability of the furan ring.

sensitive heterocyclic ring, the effect of a furan ring on the terminus of the allylic system was investigated with the lithiation−substitution of **12**.[18] The scope of the asymmetric reaction of **12** is summarized in Table 2, with products **32**−**35** obtained in yields of 65−80%, with ers of 97:3−98:2.[16] The absolute configurations are assigned by analogy to the reactions of **2**.[11] These results are similar to those found with **2**.

Three reactions were carried out to test the durability of the furan ring to further conversions. Deprotection of the amine and reduction of the olefin of **32** demonstrated access to enantioenriched γ-substituted amines. Hydrogenation of **32** at atmospheric pressure to give **36** proceeded smoothly. Reduction at pressures higher than 50 psi or longer reaction times did result in furan ring reduction. Subsequent Boc deprotection with TFA provided **37**.



Conversion of the enecarbamates to β-substituted aldehydes and ketones was demonstrated by the formation of **38** and **40**. Compound **33** was easily converted to the corresponding aldehyde **38** by treatment with HCl. The ketone **40** was prepared by α-lithiation of **32** with *t*-BuLi and TMEDA in THF followed by addition of methyl triflate to give **39**. Subsequent hydrolysis under acidic conditions provided ketone **40**.[19]



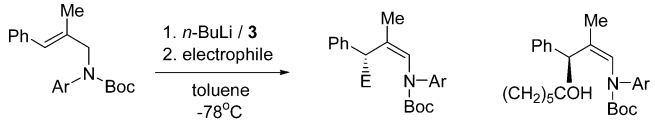
Asymmetric Lithiation−Substitution Sequences of 13. The sequence was investigated with **13** to determine if substitution on the central atom of the allyl system would affect the reaction. Treatment of **13** with 1.1 equiv of *n*-BuLi and 1.1 equiv of **3** at −78 °C for 1 h and subsequent additions of electrophiles provided the products **41**−**46** in good yields with high ers (Table 3).[16] In most cases, only the (*Z*)-enecarbamate product was obtained. The (*Z*) geometry of **41**−**44** and **46** was confirmed by ^{1}H NOE NMR experiments (+4.13% to +9.68%) which indicated through-space couplings between the β-methyl group and the olefinic proton.

The γ-substituted products with halide and triflate carbon electrophiles were obtained in good yields with er's ranging from 90:10 to 93:7 (entries 1−3). With a silyl electrophile, the product was formed from reaction in 87% yield with a 93:7 er, as shown in entry 4. This is in contrast with the lithiation−substitution of **2** with trimethylsilyl triflate which gave both the (*Z*)-enecarbamate product and the α-substituted product in nearly equal

(18) Johnson, T. A.; Jang, D. O.; Slafer, B. W.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2002**, *124*, 11689.

(19) Poirier, J.-M.; Dujardin, G. *Heterocycles* **1987**, *25*, 399.

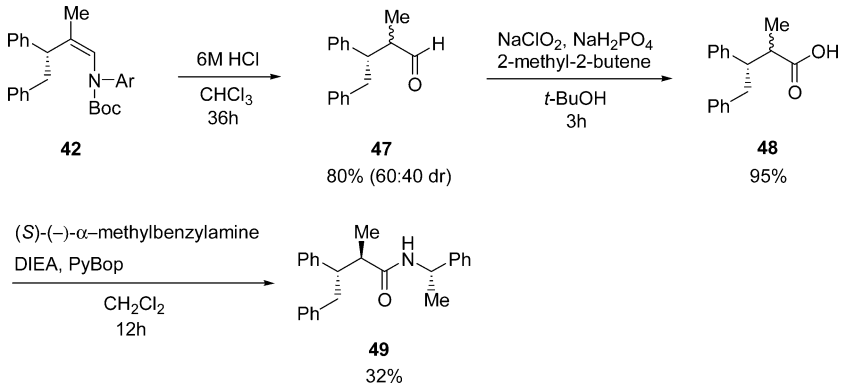
TABLE 3. Asymmetric Lithiation−Substitutions of 13



13 41-45 46

entry	electrophile	E	product	yield (%)	er
1	CH_3OTf	$-CH_3$	**41**	78	91:9
2	$C_6H_5CH_2Br$	$-CH_2C_6H_5$	**42**	86	93:7
3	$CH_2{=}CHCH_2Br$	$-CH_2CH{=}CH_2$	**43**	85	90:10
4	$(CH_3)_3SiOTf$	$-Si(CH_3)_3$	**44**	87	93:7
5	C_6H_5CHO	$-CH(OH)C_6H_5$	**45**	90 (60:40 dr)	99:1, 84:16
6	$(CH_2)_5CO$	$-COH(CH_2)_5$	**46**	77	93:7

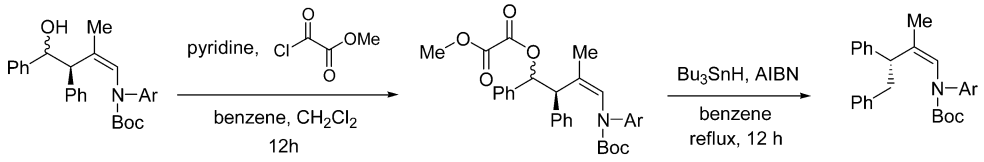
SCHEME 5



42 **47** 80% (60:40 dr) **48** 95%

49 32%

SCHEME 6



45a **45b** **50a**, 85% **50b**, 81% **42**, 51% 63%

yields.[11] With benzaldehyde as the electrophile (entry 5), low diastereoselectivity was observed even when transmetalating agents such as Et_2AlCl were employed.[20] One diastereomer was highly enantioenriched, while the other diastereomer had only moderate enantioenrichment. Cyclohexanone reacted with lithiated **13** to afford **46** with a 93:7 er with the absolute configuration is assigned by analogy to retentive addition found for the reaction of **2** with cyclohexanone.[11]

Determination of Absolute Configurations and Further Transformations. The absolute configuration of **6** has been established, and the same configuration is assigned by analogy to the lithiated intermediate in the lithiation−substitution sequence beginning with **13**. Determination of the absolute configuration of the products then allows assignments of the substitutions as retentive or invertive. The absolute configuration of **42** was determined by conversion to **49**, a crystalline compound suitable for X-ray crystallography. Acid hydrolysis of **42** provided aldehyde **47** as a 60:40 mixture of diastereomers in 80% yield. Oxidation of the diastereomeric mixture to the acid **48** was accomplished in 95% yield and followed by coupling to (*S*)-(−)-α-methylbenzylamine, a compound of known configuration. The two diastereomers of product **49** were separated by chromatography, and crystal growth of a single diastereomer of **49** was carried out by slow evaporation in a $CDCl_3$ solution in 32% yield (Scheme 5).[11,21]

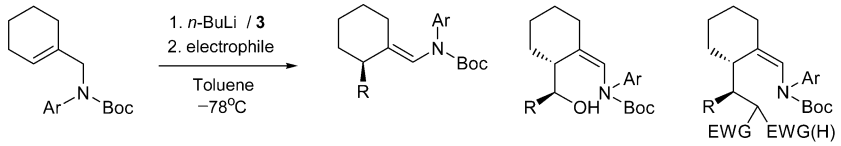
X-ray crystallographic analysis of **49** demonstrates the newly formed chiral center to be (*S*). This absolute configuration of **49** is taken to indicate that reactions between the lithiated intermediate from **13** and halide electrophiles occur with inversion of configuration.

The absolute configuration of diastereomeric products **45a** and **45b**, arising from reaction of the lithiated intermediate from **13** with benzaldehyde, was also determined. Since X-ray quality crystals of derivatives were not available, an alternative method was used. Deoxygenation of **45a** and **45b** each began with conversion to the oxalates **50a** and **50b** in good yields (Scheme 6). Deoxygenation then gave (*S*)-**42**. All samples of **42**, from lithiation−substitution using benzyl bromide and from the two diastereomers of **45**, had the same retention

(20) Whisler, M. C.; Vaillancourt, L.; Beak, P. *Org. Lett.* **2000**, *2*, 2655.

(21) Kim, D. D. Unpublished results.

TABLE 4. Asymmetric Lithiation−Substitutions of 14



14 **(*E*)-52** **(*Z*)-53,54** **(*Z*)-55-60**

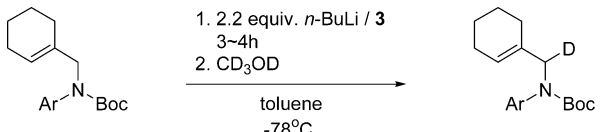
entry	electrophile	yield(%)[a]	products[b]	dr[c]	er[d]
1	*p*-BrPh⁄Br	80[e]	**(*E*,*R*)-52**	–	99:1
2	Ph⁄C(=O)H	97	**(*Z*,*S*,*R*)-53**	82:18	99:1
3	*p*-BrPh⁄C(=O)H	96	**(*Z*,*S*,*R*)-54**	82:18	99:1
4	*p*-BrPh⁄NO_2	93	**(*Z*,*S*,*R*)-55**	98:2	99:1
5	(2 Furyl)⁄NO_2	90	**(*Z*,*S*,*R*)-56**	95:5	90:10
6	*p*-BrPh⁄CO_2Et	75	**(*Z*,*S*,*R*)-57**	96:4	99:1
7	Ph⁄SO_2Ph	52	**(*Z*,*S*,*R*)-58**	99:1	90:10
8	Ph⁄CO_2Et, CN	98	**(*Z*,*S*,*S*)-59**	93:7	88:12
9	Ph⁄N=S(=O)-*p*-tolyl	90	**(*Z*,*S*,*R*,*S*)-60**	99:1	> 95:5[f]

[a] Isolated yields (%) for mixture of diastereomers. [b] Absolute configurations for entries 1, 3, 4, 6, and 9 were assigned by X-ray crystallography and that for entries 2, 5, 7, and 8 were assigned by analogy. [c] Diastereomeric ratios were determined by ^{1}H NMR integration. Drs for entries 2 and 3 were determined after separation of diastereomers by preparative HPLC, respectively. [d] Enantiomeric ratios were determined by CSP-HPLC analysis by comparison with authentic materials.[15] [e] Isolated yield for mixture (*E*/*Z* = 69:31). [f] Enantiomeric ratio was determined to be minimum >95:5 by ^{1}H NMR analysis.

times for the major enantiomer on CSP-HPLC, indicating all three compounds have the same absolute configuration at the benzylic center. Accordingly, these products are considered to be formed by invertive reactions with the lithiated intermediate from **13**.

Asymmetric Lithiation−Substitution Sequences of Cyclic Allylamines 14 and 15. Extension of the methodology to systems with endocyclic double bonds in six- and five-membered rings was investigated with **14** and **15**. Each reactant was synthesized according to previously described procedures by the established reactions of reductive amination and Boc reaction or ester reduction, bromination, and amine coupling.[22−24]

High Diastereoselective and Enantioselective Lithiation−Substitution Sequence of 14. The asymmetric lithiation−substitution sequence of **14** using the standard reaction protocol with 1.1 equiv of base and ligand resulted in poor yields and incomplete deuterium incorporation. However, the use of 2.2 equiv of *n*-BuLi and **3**, over a 3−4 h period, resulted in a 70% yield of **51** with complete deuterium incorporation.[25]



14 **51**

70%

Asymmetric lithiation of **14** by reaction of *n*-BuLi/**3** at −78 °C followed by addition of alkyl halide, aromatic aldehyde, and activated olefins with electron-withdrawing substituents as electrophiles provided the enantioenriched products **52**−**60** in good yields as shown in Table 4.

The reaction of (−)-sparteine lithiated **14** with *p*-bromobenzyl bromide afforded a mixture of isomers, (*E*,*R*)-**52** and (*Z*,*S*)-**52**, in 80% yield (*E*/*Z* = 69:31). The stereochemistry (*E*,*R*)-**52** with a 99:1 er was determined by X-ray crystallography. The diastereomeric ratio of 82:18 observed in reaction of **14** with *p*-bromobenzaldehyde showed remarkable selectivity with respect to aromatic aldehydes as compared to the poor selectivity observed with the *trans*-cinnamyl allylic amine **2**.[20]

The absolute configurations of (*Z*,*S*,*R*)-**54** and (*Z*,*R*,*R*)-**54** were directly confirmed by X-ray crystallography. Acid hydrolysis of (*Z*,*S*,*R*)-**54** to aldehyde (*S*,*R*,*R*)-**54a** followed by intramolecular cyclization afforded 3-(*p*-bromophenyl)-octahydroisobenzofuran-1-ol **61** in 73% yield and with a diastereomeric ratio of 74:26 (Scheme 7).

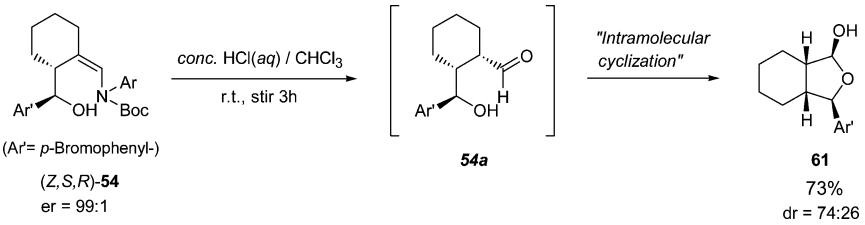
(22) For a synthesis of the prochiral amine substrate, see the Supporting Information.

(23) Concellon, J. M.; Llavona, L.; Bernad, P. L., Jr. *Tetrahedron* **1995**, *51*, 5573.

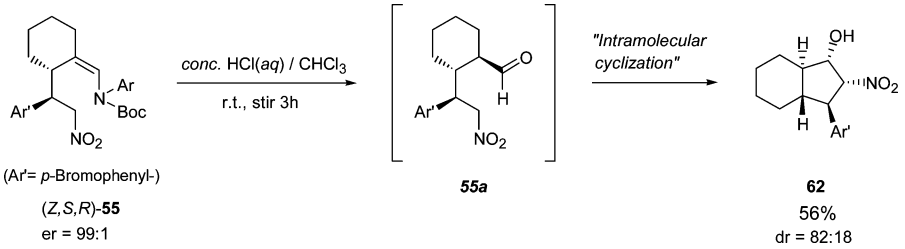
(24) Kozyrkov, Y. Y.; Kulinkovich, O. G. *Synlett* **2002**, *3*, 443.

(25) The requirement of 2 equiv of base is made by analogy to the *N*-Boc piperidine analogue. See: Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 1889.

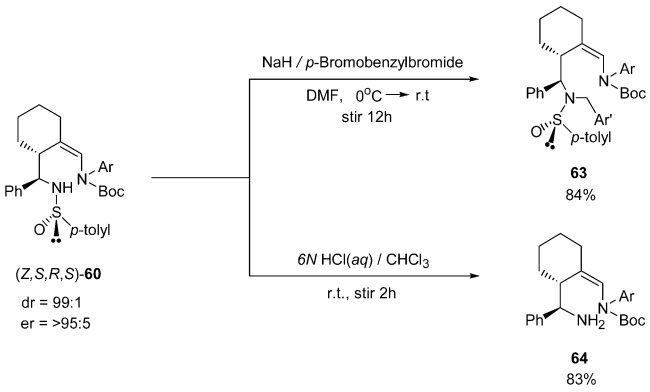
SCHEME 7



SCHEME 8



SCHEME 9



The stereochemistry of the four stereogenic centers in crystalline major diastereomer **61** was established by X-ray crystallography. Reaction of (−)-sparteine lithiated **14** with benzaldehyde also gave enantioenriched (*Z*,*S*,*R*)-**53** and (*Z*,*R*,*R*)-**53** with 99:1 and 87:13 er's and with 82:18 dr.

Lithiation−substitution sequences from **14** with *trans*-olefins activated with nitro, ester, sulfonyl, and nitrile groups provided the enecarbamates (*Z*)-**55**−**59** with the two or three newly generated stereogenic centers in good yields and with high diastereo- and enantioselectivities. The absolute configuration of (*Z*,*S*,*R*)-**57** was directly determined by X-ray crystallography and that of (*Z*,*S*,*R*)-**55** was confirmed by synthesis of crystalline **62** by acid hydrolysis (Scheme 8).

The reaction of (−)-sparteine lithiated **14** with (*S*)-(+)-*N*-benzylidene-*p*-toluenesulfinamide provided the enecarbamate (*Z*,*S*,*R*,*S*)-**60** in 90% yield and with 99:1 dr and >95:5 er. The absolute configuration of (*Z*,*S*,*R*,*S*)-**60** was established by conversion to the crystalline *N*-*p*-bromobenzyl enecarbamate (*Z*,*S*,*R*,*S*)-**63** and X-ray crystallography. Hydrolysis of (*Z*,*S*,*R*,*S*)-**60** in the presence of 6 N HCl provided the chiral amine (*Z*,*S*,*R*)-**64** in 83% yield without C−N bond cleavage of enamine moiety (Scheme 9).

The reaction of (−)-sparteine lithiated **14** with Ph_3SnCl provided a mixture of α-stannylated (*E*,*S*)-**65** and γ-stannylated (*E*,*S*)-**65** in 40% and 47% yields.[26] The absolute configurations of the other compounds reported herein are based on analogy to these assignments.

High Diastereoselective and Enantioselective Lithiation−Substitution Sequence of 15. Asymmetric lithiation of **15** with *n*-BuLi/**3** at −78 °C followed by addition to *p*-bromobenzaldehyde afforded a mixture of diastereomers, (*Z*,*S*,*R*)-**68** and (*Z*,*R*,*R*)-**68**, in 93% yield and with diastereomeric ratio 87:13 (Table 5). The absolute configuration of crystalline (*Z*,*S*,*R*)-**68** was determined by X-ray crystallography.

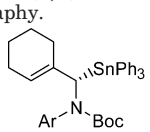
Lithiation−substitution sequences of **15** with activated *trans*-olefins provided the corresponding enecarbamates (*Z*)-**69**−**73** with the two or three newly generated stereogenic centers in good yields and with diastereo- and enantioselectivities shown in Table 5.

The absolute configuration of enantioenriched (*Z*,*S*,*R*)-**69** was assigned by suitable X-ray crystallography of crystalline (*R*,*R*,*R*)-**76**, obtained after condensation of thiosemicarbazide with the aldehyde (*R*,*R*,*R*)-**75** formed by acid hydrolysis of (*Z*,*S*,*R*)-**69** with TFA (Scheme 10).

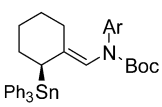
The reaction of (−)-sparteine lithiated **15** with (*S*)-(+)-*N*-benzylidene-*p*-toluenesulfinamide provided (*Z*,*S*,*R*,*S*)-**74** in excellent yield but with lower diastereo- and enantioselectivity than observed for the reaction from (−)-sparteine lithiated **14**.

Asymmetric Deprotonations. The diastereomeric enantiodetermining step in the two-step sequences of these reactions could be either the lithiation or the substitution. If the asymmetric deprotonation step is enantiodetermining, the enantioenrichment of the products is determined in the formation of a configurationally stable anion which undergoes substitution with high

(26) The absolute configuration of α-(*E*,*S*)-**65** was established by X-ray crystallography. Subsequent transmetalation of α-(*E*,*S*)-**65** with *n*-BuLi and (−)-sparteine did not give any tin−lithium exchanged product and α-(*E*,*S*)-**65** was recovered in 85(%) yield after column chromatography.

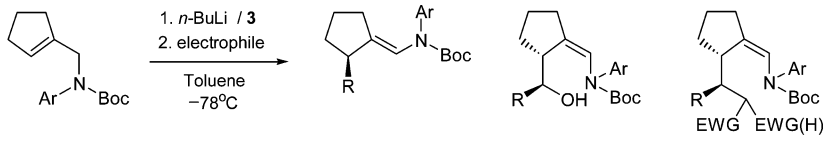


α-(*E*,*S*)-**65**



γ-(*E*,*S*)-**65**

TABLE 5. Asymmetric Lithiation−Substitutions of 15

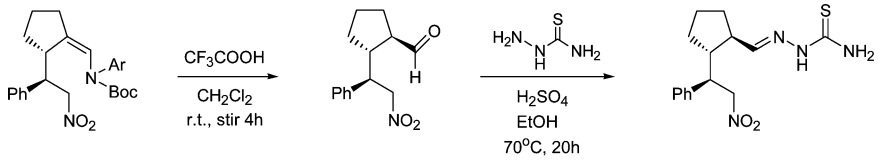


15 **(*E*)-66,67** **(*Z*)-68** **(*Z*)-69-74**

entry	electrophile	yield(%)[a]	products[b]	dr[c]	er[d]
1	CH_3OTf	78	**(*E,S*)-66**	–	89:11
2	$(CH_3)_3SiOTf$	79	**(*E,S*)-67**	–	86:14
3	*p*-BrPh(C=O)H	93	**(*Z,S,R*)-68**	87:13	99:1
4	PhNO_2	76	**(*Z,S,R*)-69**	91:9	99:1
5	*p*-BrPhNO_2	82	**(*Z,S,R*)-70**	98:2	97:3
6	Ph(CH$_3$)NO_2	93	**(*Z,S,S*)-71**	67:33	96:4
7	PhCO_2Et CO_2Et	99	**(*Z,S,S*)-72**	93:7	96:4
8	PhCO_2Et CN	99	**(*Z,S,S*)-73**	78:22	88:12
9	Ph−N=S(O)−*p*-tolyl	99	**(*Z,S,R,S*)-74**	90:10	> 86:14[e]

[a] Isolated yields (%) for mixture of diastereomer. [b] Absolute configurations for entries 1 and 2 were assigned by X-ray crystallography and those for entries 1, 2, and 5−9 were assigned by analogy. [c] Diastereomeric ratios were determined by ^{1}H NMR integration. Dr for entry 1 was determined after separation of diastereomers by preparative HPLC. [d] Enantiomeric ratios were determined by CSP-HPLC analysis by comparison with racemic materials.[15] [e] Enantiomeric ratio was determined to be minimum >86:14 by ^{1}H NMR analysis.

SCHEME 10



(*Z,S,R*)-**69** er = 99:1 → **75** dr = >98:2, 71% → **76** 73%

stereoselectivity. If an asymmetric substitution is the key step, either a dynamic kinetic resolution or dynamic thermodynamic resolution could be operative.[10,11,27]

The enantiocontrolling step with **12** was evaluated by tin−lithium exchange experiments. The racemic tin compound **77** was obtained in 60% yield by lithiation of **12** with *n*-BuLi/TMEDA and reaction with tributyltin chloride. Transmetalation of **77** with *n*-BuLi, followed by addition of (−)-sparteine and benzyl bromide, afforded racemic **33**. This lack of enantioenrichment is taken as evidence that a post-deprotonative enantioinduction is not operative and that an asymmetric deprotonation must be the enantiodetermining step for the sequences from **12** with *n*-BuLi/**3** (Scheme 11).

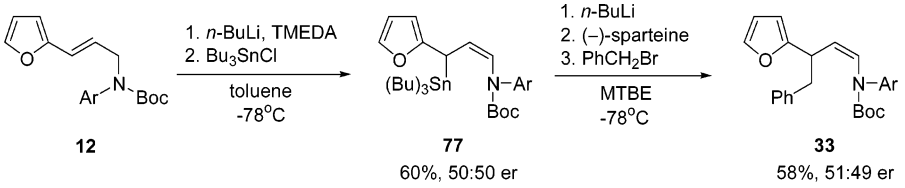
The configurational stability of the organolithium intermediate was examined and found to support an asymmetric deprotonation pathway. The enantioenriched tin compound (*S*)-**77** was prepared in 63% yield with a 97:3 er from **12**. Addition of a premixed, precooled solution of *n*-BuLi and **3**, followed by benzyl bromide, produced compound (*R*)-**33** in 60% yield with an 80:20 er (Scheme 12).

These results suggest solvent and structure can affect the course of this reaction. When the lithiation−substitution sequence is carried out in toluene, the product is (*S*)-**33** in 70% yield with a 98:2 er (Table 2).[28] The reduction

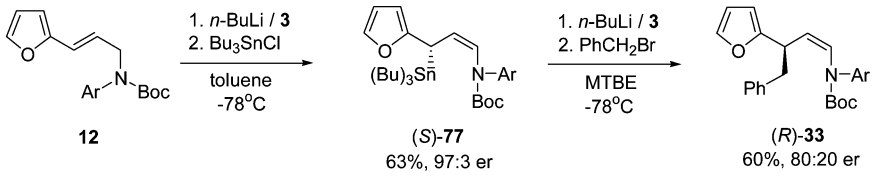
(27) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715.

(28) The net inversion in configuration of these products is consistent with the previously reported inversion-retention pathway in the tin−lithium exchange process. It is noted the sequence with (*S*)-**77** shows greater loss of enantioenrichment than with (*S*)-**33** suggesting a role for the furanyl oxygen in the epimerization process.

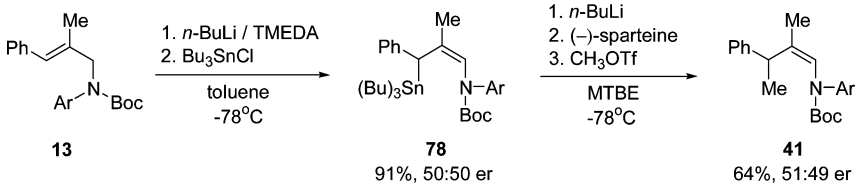
SCHEME 11



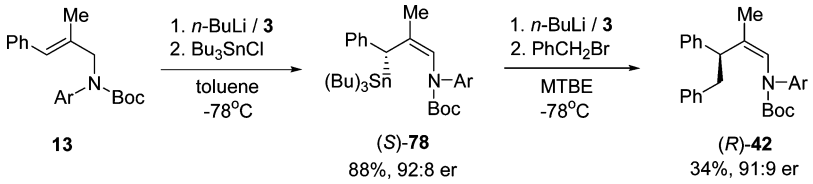
SCHEME 12



SCHEME 13



SCHEME 14



in er from 97:3 for (*S*)-**77** to 80:20 for (*R*)-**33** in the presence of MTBE could occur during or after the transmetalation process or in the reaction with the electrophile. It should be noted that the lithiated species from tin−lithium exchange of **77** and deprotonation of **12** which are epimeric at the lithiated carbon, are diasteromeric as both epimers are complexed with (−)-sparteine.

Similar studies suggest that an asymmetric deprotonation is also stereochemically determining for the sequence with **13**. The racemic tin product **78** was synthesized, and subsequent tin−lithium exchange followed by sequential addition of (−)-sparteine and methyl triflate provided racemic **41** (Scheme 13). The formation of a racemic product indicates the process is not an asymmetric substitution. An enantiodetermining deprotonation step is considered to be the enantiocontrolling step.

To assess the configurational stability of this lithiated intermediate, the tin−lithium exchange was carried out from the organotin (*S*)-**78**. The chiral tin compound was synthesized from **13** in 88% yield, with a 92:8 er. Transmetalation at −78 °C with a premixed, precooled solution of *n*-BuLi/**3**, followed by reaction with benzylbromide provided (*R*)-**42** with a 91:9 er, demonstrating configurational stability of the organolithium/**3** complex at −78 °C.[28] To eliminate the possibility of a kinetic resolution, the er of recovered (*S*)-**78** was examined and found to be 92:8. Since the product from this tin−lithium exchange sequence has the expected opposite absolute configuration found from the reaction sequence of Table 3, these results also demonstrate an approach to obtaining both enantiomers with the single chiral ligand (Scheme 14).[12]

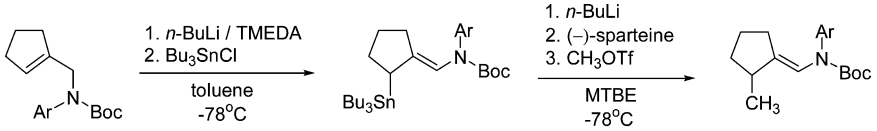
The reaction pathway for the cyclic substrate **15** was also evaluated. Synthesis of racemic **79** was accomplished in 68% yield from **15** and tributyltin chloride. Transmetalation with *n*-BuLi, addition of **3**, and reaction with methyl triflate provided **66** in 45% yield as a racemic compound (Scheme 15). This is taken as strong evidence that an asymmetric deprotonation is the enantiodetermining step in this sequence.

The configurational stability of the lithiated intermediate was examined as heretofore. Enantioenriched (*S*)-**79** was prepared with a 79:21 er. Addition of the chiral lithium reagent, followed by methyl triflate, produced (*R*)-**66** as an 80:20 mixture of enantiomers, demonstrating configurational stability of the lithiated intermediate (Scheme 16). Again a route to the opposite absolute configuration from that observed for the direct reaction is provided by this sequence.

Effects of Substitution on the Allyl System. The present work probes the effect of substitution at the 2- and 3-positions of the allyl group of the *N*-Boc allylamines on the enantioenrichment of products from (−)-sparteine-mediated lithiation−substitution sequences.[22]

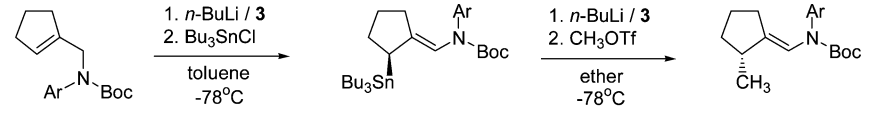
Previously, the sequence with *N*-Boc cinnamylamines with substitutions of methyl groups at the 1- and 3-posi-

SCHEME 15



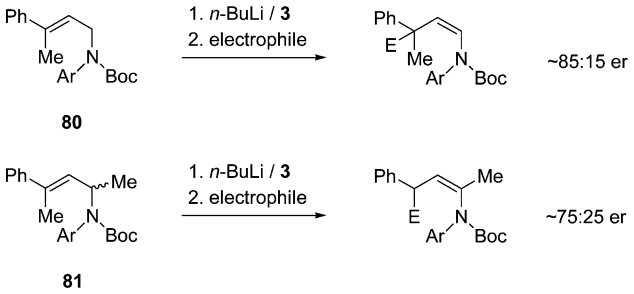
15 **79** 68%, 50:50 er **66** 45%, 52:48 er

SCHEME 16



15 (*S*)-**79** 78%, 79:21 er (*R*)-**66** 26%, 80:20 er

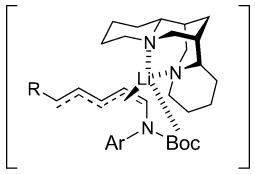
tions was found to lead to eroded enantioenrichments relative to the unsubstituted system as shown for **80** and **81**.[21,29]



80 **81**

In the present work, substitution of a methyl group at the 2-position of the cinnamyl system for **13** provides products with high enantiomeric ratios. Replacement of the phenyl group of the cinnamyl system with the vinyl phenyl of **11** or the 1-furanyl group of **12** also provides products from the lithiation-substitution sequence with high enantiomeric ratios. In the case of **12**, a possible competitive deprotonation of the furan ring does not interfere with the reaction. The products of the reactions of **14** and **15** show that this approach for asymmetric syntheses can be extended to cyclic systems.

The enantioenrichments of the ϵ-substituted products from the lithiation−substitution of **11** shows that extension of the position of substitution by two carbon atoms does not reduce stereoselectivity. The enantiomeric ratios for the isomeric pairs **20/21**, **22/23**, and **24/25** shows the C-3- and C-5-substituted products to have comparable ers (Table 1). If the structure of lithiated **11** is assumed to resemble its cinnamyl analogue **6** as an η^3-complex, coordination of lithium to the Boc carbonyl suggests favorable location of lithium over C-1 to C-3. Bond formation on alkylation can be rationalized to take place with inversion at the sterically most accessible carbon on the bottom face of the delocalized carbon anion as shown for **82** based on analogy to the reaction pathway of **2**. For the reaction of **82** with cyclohexanone, coordination of the carbonyl oxygen to lithium is considered to direct the electrophile to the 3-position with retention.



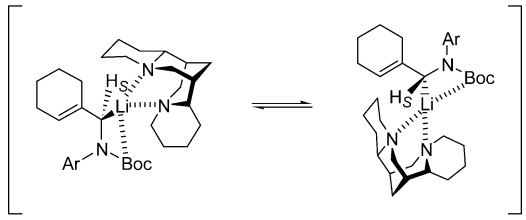
82

The enecarbamate products formed by (−)-sparteine lithiation−substitution of the *N*-Boc amines **12** and **13**, summarized in Tables 2 and 3, provide (*Z*)-enecarbamate products with good to high ers. By analogy to **2**, the base/(−)-sparteine complex is considered again to selectively remove the *pro-R* proton to give configurationally stable organolithium intermediates in both cases.

Incorporation of the electrophile with inversion or retention of configuration is highly electrophile dependent. It has been demonstrated both by X-ray crystallographic analysis of **49** and by analogy to products derived from **2**, that halide electrophiles react with inversion of configuration.[11] It has also been demonstrated that cyclohexanone reacts with retention of configuration.[11] In the case of benzaldehyde, reaction occurs with inversion of configuration, although the electrophile has a coordinating carbonyl group. Presumably benzaldehyde is more reactive than cyclohexanone and does not require precoordination to lithium prior to substitution to assist the reaction.

For reactions from **14** and **15** formation of an η^1-complex, analogous to **10**, seems likely to be generated by asymmetric deprotonation of *pro-R* proton as shown for **83**. To rationalize the absolute configurations determined by X-ray crystallographic analysis, a rotamer **84** of the initial species is considered to react with *p*-bromobenzylbromide with inversion of configuration to give enantioenriched (*E*,*R*)-**52** (er = 99:1). For *p*-bromobenzaldehyde, reaction occurs with inversion of configuration to provide high enantioenriched (*Z*,*S*,*R*)-**54** (er = 99:1) as major diastereomer (dr = 82:18). For the reaction of **83** with activated olefins with electron-withdrawing groups, the absolute configuration at the newly formed chiral carbon is consistent with inversion.

(29) Weisenburger, G. A. Ph.D. Thesis, University of Illinois at Urbana−Champaign, 1998.



83 **84**

Summary

A broad survey of asymmetric lithiation−substitution reactions has been carried out with 2 and 3 substituted *N*-Boc allylamines. Product enantioenrichments are generally high, and the enantiodetermining step is considered to be an asymmetric deprotonation. Determination of absolute configurations, along with previously known organolithium structural information, suggest reactions with inversion of configuration are the most favored pathway for reaction of these organolithium nucleophile with most electrophiles. Synthetic applications including enecarbamate manipulation, Diels−Alder sequences, and cyclizations following hydrolysis are illustrated by the present studies.

Experimental Procedures

General Information. All reactions involving air-sensitive compounds were carried out under a nitrogen atmosphere in oven or flame-dried glassware which was cooled under nitrogen. All commercial reagents were used without further purification, unless otherwise noted. Solvents were distilled immediately prior to use; diethyl ether and THF were distilled from Na/benzophenone ketyl under nitrogen, and toluene and methylene chloride were distilled over CaH_2 under nitrogen. (−)-Sparteine was distilled over CaH_2. The base *n*-BuLi was titrated according to the method of Suffert.[30]

Representative Lithiation of *N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-5-phenyl-(*E*,*E*)-2,4-pentadien-1-amine (11) and Electrophilic Substitution: Preparation of (*S*)-*N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-5-phenyl-(*Z*,*E*)-1,3-hexadien-1-amine (20) and (*R*)-*N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3-methyl-5-phenyl-(*Z*,*E*)-1,4-pentadien-1-amine (21). A solution of **11** (173 mg, 0.474 mmol) and (−)-sparteine (0.12 mL, 0.521 mmol) in toluene (10 mL) was cooled to −78 °C. *n*-BuLi (0.326 mL, 0. 521 mmol) was added, and the solution was stirred for 1h. Methyl triflate (0.107 mL, 0.948 mmol) was added and stirred for 1 h. The reaction was quenched with methanol at −78 °C, and after warming to ambient temperature, standard workup, chromatography (1:10 ethyl acetate/hexane), and preparative HPLC (3.5% ethyl acetate/hexane) afforded **20** and **21** (107 mg, 60%; 18 mg, 10%, respectively). **20**: ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.05 (d, J = 7.1, 3H), 1.40 (s, 9H), 3.20 (quint, J = 6.8, 1H), 3.81 (s, 3H), 5.30 (m, 2H), 5.58 (m, 1H), 6.55 (d, J = 8.3, 1H), 6.90−7.05 (m, 4H), 7.11−7.28 (m, 5H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 20.9, 28.2, 42.8, 55.7, 81.4, 114.9, 123.8, 126.8, 127.0, 127.9, 129.1, 129.5, 135.6, 138.4, 146.4, 153.7, 159.0; HRMS (M^+) calcd for $C_{24}H_{29}NO_3$ 379.2147, found 379.2148. The enantiomeric ratio of **20** was determined to be 88:12 by CSP-HPLC Chiralpak AD (1.0% *i*-PrOH/hexane, 1.0 mL/min). The major enantiomer had a retention time of 12.8 min, and the minor enantiomer had a retention time of 10.4 min. **21**: ^{1}H NMR (acetone-d_6, 400 MHz) δ 0.85 (d, J = 6.8, 3H), 1.40 (s, 9H), 2.73 (m, 1H), 3.79 (s, 3H), 4.75 (t, J = 9.8, 1H), 5.90 (m, 2H), 6.58 (d, J = 9.3, 1H), 6.91 (m, 2H), 7.10−7.30 (m, 7H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 19.9, 27.3, 33.6, 54.7, 80.0, 113.5, 113.7, 125.7, 126.6, 126.7, 127.6, 128.2, 133.2, 135.1, 137.6, 153.0, 157.8; HRMS (M^+) calcd for $C_{24}H_{29}NO_3$ 379.2147, found 379.2147. The enantiomeric ratio of **21** was determined to be 78:22 by CSP-HPLC Chiralpak AD (1.0% *i*-PrOH/hexane, 1.0 mL/min). The major enantiomer had a retention time of 8.6 min, and the minor enantiomer had a retention time of 7.7 min.

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Supporting Information Available: Experimental procedures, characterization data, and X-ray crystallographic structures (CIF) for **49**, **52**, **54**, **57**, **61**, **62**, **63**, **65**, **68**, and **76**. This material is available free of charge via the Internet at http://pubs.acs.org.

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