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Synthetic Applications of Lithiated *N*-Boc Allylic Amines as Asymmetric Homoenolate Equivalents

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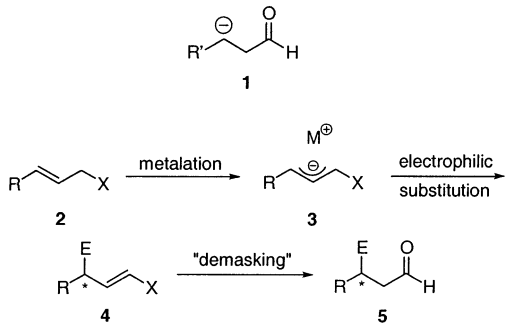
Received June 3, 2002

Lithiation of *N*-(Boc)-*N*-(*p*-methoxyphenyl) allylic amines in the presence of (−)-sparteine provides asymmetric homoenolate equivalents which react with electrophiles to provide highly enantioenriched enecarbamates. Acidic hydrolysis of the enecarbamates can provide the corresponding *β*-substituted aldehydes. A synthetic sequence that involves a stereocontrolled intramolecular nitrone−olefin dipolar cycloaddition has been developed for the preparation of enantioenriched 2-formyl-4-phenyl-1-aminocyclopentanes from one *β*-allyl-substituted aldehyde. Further manipulations allow access to an enantioenriched *β*-lactam. In another synthetic sequence, transmetalation of the lithiated intermediates and reactions with aldehyde electrophiles can be controlled to afford highly enantioenriched anti homoaldol products. Use of an anti aldehyde homoaldol product as the chiral electrophile in an iterative reaction provides a double homoaldol product containing four stereogenic centers with high diastereoselectivity and enantioselectivity. Reaction pathways are proposed to account for the observed products.

Introduction

The chemistry of homologues of aldehyde enolates, depicted by the synthetic equivalent **1**, is emerging as a useful synthetic strategy. One general approach is the metalation of a heteroatom-substituted allyl derivative **2** to provide **3**, which is the actual species represented by **1**. Reaction of **3** with an electrophile at the *γ* position affords **4**, which can be hydrolyzed to provide a *β*-substituted aldehyde **5**.[1]



The value of this methodology has been significantly enhanced by recent developments of convenient asymmetric homoenolate synthetic equivalents. The work of Hoppe and co-workers, which revealed that (−)-sparteine-controlled lithiations adjacent to the oxygen of allyl carbamates provided such synthetic equivalents, was seminal. Asymmetric homoenolate equivalents were reported from lithiation of (*E*)- and (*Z*)-2-butenyl carbamates and (*E*)-3-trimethylsilyl-2-propenyl carbamates.[2] Oxygen-based systems have been very well developed in the Hoppe laboratories for a variety of asymmetric syntheses, including deoxy sugar analogues and bicyclic tetrahydrofuran carboxaldehydes.[3]

We have developed the chemistry of (−)-sparteine-complexed lithiated intermediates of *N*-(Boc)-*N*-(*p*-methoxyphenyl) allylic amines as asymmetric homoenolate synthetic equivalents.[4] Lithiated *N*-Boc cinnamylamine substrates have been investigated and found to give products with high regio-, diastereo-, and enantioselectivities upon reaction with alkyl halide,[4] Michael acceptor,[5] and nitroalkene[6] electrophiles. Transmetalation and reaction with aldehyde electrophiles allow access to

(1) (a) For a review, see: Ahlbrecht, H.; Beyer, U. *Synthesis* **1999**, *3*, 365−390. (b) Özlügedik, M.; Kristensen, J.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Eur. J. Org. Chem.* **2002**, 414−427.

(2) (a) Zschage, O.; Schwark, J.-R.; Krämer, T.; Hoppe, D. *Tetrahedron* **1992**, *48*, 8377−8388. (b) Zschage, O.; Schwark, J.-R.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 296−298. (c) Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69−71. (d) Hoppe, D.; Hanko, R.; Brönneke, A.; Lichtenberg, F.; van Hülsen, E. *Chem. Ber.* **1985**, *118*, 2822−2851. (e) Hoppe, D.; Lichtenberg, F. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 372.

(3) (a) Peschke, B.; Lüssmann, J.; Dyrbusch, M.; Hoppe, D. *Chem. Ber.* **1992**, *125*, 1421−1430. (b) Paulsen, H.; Graeve, C.; Frölich, R.; Hoppe, D. *Synthesis* **1996**, 145−148.

(4) (a) Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522−9530. (b) Park, Y. S.; Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 10537−10538. (c) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218−12219. (d) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 9, 552−560.

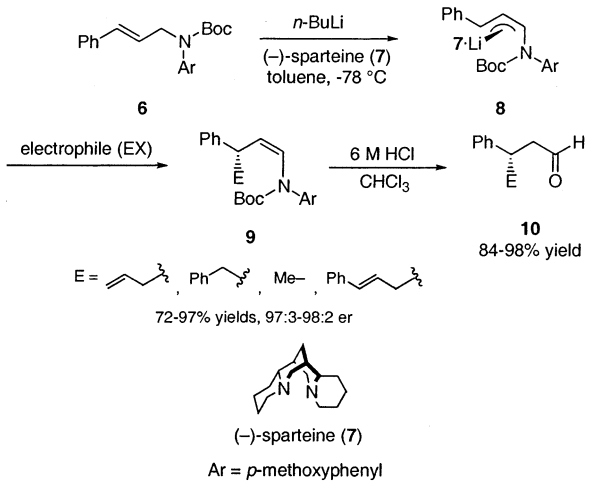
(5) Curtis, M. D.; Beak, P. *J. Org. Chem.* **1999**, *64*, 2996−2997.

(6) Johnson, T. J.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004−1005.

10.1021/jo0260084 CCC: $25.00
Published on Web 01/23/2003

highly enantioenriched homoaldol products.[7] The mechanisms of these reactions have been investigated[4a,7] and products resulting from lithiation/substitution of the *N*-Boc cinnamylamine substrates have been converted into highly enantiomerically enriched substituted piperidines, pyrrolines,[6] fused bicarbocyclic compounds,[8] and fused bicyclic lactams.[9]

We have previously established that (−)-sparteine-mediated α-lithiation of *N*-(Boc)-*N*-(*p*-methoxyphenyl)-cinnamylamine (**6**) in toluene at −78 °C provides a configurationally stable η^3-lithiated intermediate **8** of known absolute configuration.[10] The *pro-R* proton of **6** is selectively removed by the chiral base complex to provide the lithiated intermediate, which undergoes reaction with a variety of electrophiles to afford highly enantioenriched γ-substituted *Z*-enecarbamates **9**.[4a,c] Reaction of **8** with allyl bromide, benzyl bromide, methyl iodide, and cinnamyl bromide occurs with inversion of configuration at the metalated center. The enecarbamates **9** can be easily hydrolyzed to provide β-substituted aldehydes **10** in high yields without loss of enantioenrichment. In this sequence, the lithiated intermediate **8** is the asymmetric homoenolate synthetic equivalent.

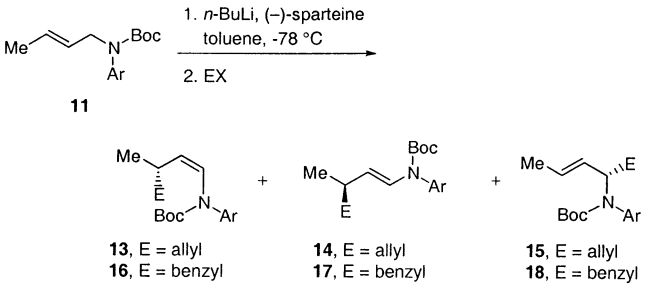


In the present report, we provide new information about the scope of the conversion of **2** to **4** for the *N*-Boc allylic amine derivatives, a sequence for the enantioselective conversion of the allyl-substituted compound to enantioenriched 2-formyl-4-phenyl-1-aminocyclopentane derivatives, including β-lactam substitution, and an iterative homoaldol reaction that is highly diastereo- and enantioselective.

Results and Discussion

(−)-Sparteine-Mediated Lithiations and Substitutions. We now report our investigation of the *N*-(Boc)-*N*-(*p*-methoxyphenyl)crotylamine (**11**) and *N*-(Boc)-*N*-(*p*-methoxyphenyl)cyclohexyl allylamine (**12**) in lithiation/substitution sequences. The lithiation of the *N*-Boc crotylamine **11** with *n*-BuLi·(−)-sparteine followed by reaction with allyl bromide provides *Z* and *E* geometrical isomers of the γ-substituted product, **13** and **14**, respectively, with the enantiomeric ratios of 94:6 and 92:8, respectively. The *Z* and *E* geometrical isomers are easily separable by column chromatography. The absolute configuration of **13** is assigned based on analogy to **9** for E = benzyl[4c] and is provisional. The configurations of **13** and **14** are assigned as opposite based on isomerization of **13** to **19** and comparison of optical rotation with **14** (vide infra). The lithiated complex of the *N*-Boc crotylamine undergoes stereoselective reaction with benzyl bromide to provide *Z* and *E* γ-substituted products **16** and **17** as well as the α-substituted product **18**. The enecarbamates **16** and **17** are obtained with enantiomeric ratios of 94:6 and 98:2, respectively. The *E* geometrical isomer **17** is easily purified by column chromatography; however, the *Z* γ-substituted product **16** was not separable from the α-substituted product **18**. The enantiomers of **18** were not completely separable by chiral HPLC, but the enantiomeric ratio was determined to be >80:20. The results of the reactions with the *N*-Boc crotylamine **11** are shown in Table 1.

TABLE 1. Results of Lithiation/Substitution of *N*-(Boc)-*N*-(*p*-methoxyphenyl)crotylamine (11)



EX	product	yield (%)	er[a]
Br	**13**	51	94:6
	14	26	92:8
	15	trace	nd
Ph Br	**16**	32	94:6
	17	14	98:2
	18	7	>80:20

[a] nd = not determined

The enantiomeric ratio of the *Z* γ-substituted product **13** was determined by chiral HPLC. The *Z* enecarbamate **13** was isomerized to the *E* enecarbamate **19** with TFA/TFAA in CH_2Cl_2. The optical activity of the *E* enecarbamate **19**, which has a known enantiomeric ratio of 94:6, was measured. Comparison of this value with the optical rotation of the *E* enecarbamate **14** allows an er of 92:8 to be assigned to **14**.[11] This procedure was also

(7) Whisler, M. C.; Vaillancourt, L.; Beak, P. *Org. Lett.* **2000**, *2*, 2655−2658. This publication contains errors in the abstract graphic and in footnote 1 of Table 2. Transmetalation with a titanium reagent provides products with *Z*:*E* ratios of 98:2, not *E*:*Z* ratios of 98:2, as reported.

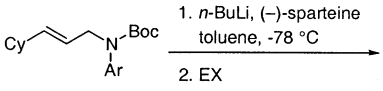
(8) Lim, S. H.; Curtis, M. D.; Beak, P. *Org. Lett.* **2001**, *3*, 711−714.

(9) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056−9062.

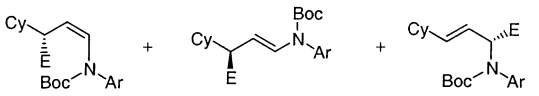
(10) Pippel, D. J.; Weisenburger, G. A.; Wilson, S. R.; Beak, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2522−2524.

(11) In most cases, enantiomeric ratios are determined by chiral HPLC comparison with racemic standards. In these cases, reaction with the achiral diamine TMEDA to prepare racemic material provides only *Z* γ-substituted product and α-substituted product.

TABLE 2. Lithiation/Substitution of *N*-(Boc)-*N*-(*p*-methoxyphenyl)cyclohexyl Allylamine (12)



12



20, E = Me
23, E = allyl
26, E = benzyl

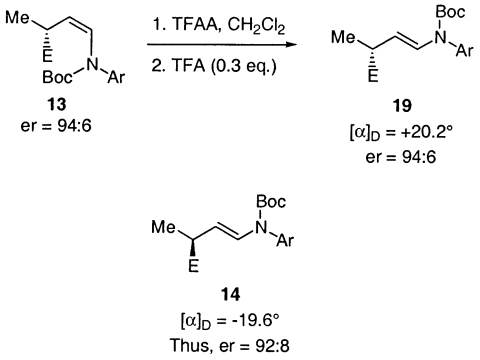
21, E = Me
24, E = allyl
27, E = benzyl

22, E = Me
25, E = allyl
28, E = benzyl

EX	product	yield (%)	er[a]
MeI	**20**	43	92:8
	21	27	96:4
	22	6	nd
	**23**	21	57:43
	24	31	67:33
	25	21	nd
	**26**	12	55:45
	27	11	nd
	28	38	72:27

[a] nd = not determined

used to determine the enantiomeric ratios of **16**, **17**, **23**, and **24** (vide infra).



13
er = 94:6

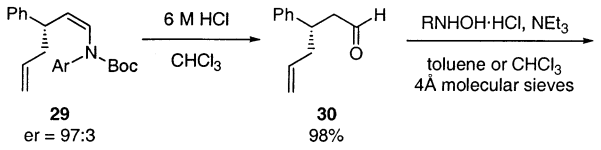
19
$[\alpha]_D$ = +20.2°
er = 94:6

14
$[\alpha]_D$ = -19.6°
Thus, er = 92:8

The (−)-sparteine-mediated lithiation and substitution of *N*-Boc cyclohexyl allylamine **12** provides the expected products with methyl iodide, allyl bromide, and benzyl bromide as electrophiles, as shown in Table 2. The products of methylation, **20** and **21**, are obtained with enantiomeric ratios of 92:8 and 96:4, respectively. However, the products obtained from the reactions with allyl bromide, **23** and **24**, and benzyl bromide, **26** and **28**, have low enantiomeric ratios. The enantiomeric ratios of **23** and **24** are 57:43 and 67:33, respectively, and the ers of **26** and **28** are 55:45 and 72:27, respectively. The α-substituted products **25** and **28** were isolated in significant yields. In these reactions, the *E* geometrical isomer was separable by column chromatography; however, the *Z* γ-substituted products **20**, **23**, and **26** were not separable from the α-substituted products **22**, **25**, and **28**.

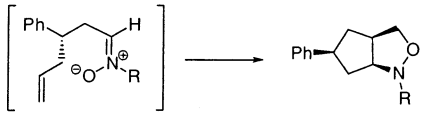
Synthesis of 2-Formyl-5-phenyl-1-aminocyclopentanes. The 1,5 relationship of the allyl group and the aldehyde functionality in the hydrolysis products of the enantioenriched allyl-substituted enecarbamates suggests that cyclopentane ring-forming reactions should be investigated. We have found that intramolecular nitrone−olefin dipolar cycloadditions,[12] which can be initiated by reaction of the aldehyde and an *N*-substituted hydroxylamine hydrochloride, proceed efficiently. As shown in Table 3, reaction of aldehyde **30**, obtained by hydrolysis of **29**, with *N*-benzylhydroxylamine hydrochloride, *N*-methylhydroxylamine hydrochloride, or *N*-isopropylhydroxylamine hydrochloride provides the expected cyclopentyl products **32**−**34** in good yields with moderate diastereoselectivities, presumably via the nitrone **31**. The reaction of **30** with *N*-benzylhydroxylamine hydrochloride proceeds at room temperature; the reactions of **30** with *N*-methylhydroxylamine hydrochloride and *N*-isopropylhydroxylamine hydrochloride require heating to reflux for product formation. The diastereomers are readily separable by column chromatography. The absolute configuration of the major diastereomer of **32**, from the reaction of aldehyde **30** with *N*-benzylhydroxylamine hydrochloride, was determined by X-ray crystallographic analysis.[13] The stereochemistry of **33** and **34** is assigned by analogy to **32**. The reaction can be carried out without isolation from *N*-Boc-anisidene, the byproduct of the hydrolysis, to provide the products in similar yields and stereoselectivities to those in Table 3.

TABLE 3. Hydrolysis and Cycloaddition of Enecarbamate 29



29
er = 97:3

30
98%



31

32-34

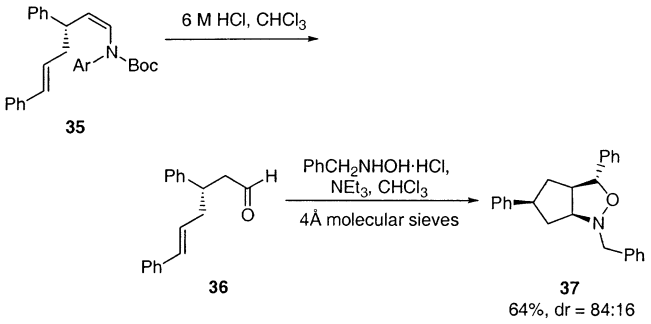
R	product	yield (%)	dr
CH_2Ph	**32**	81	80:20
Me	**33**	69	78:22
i-Pr	**34**	73	84:16

Three new stereocenters can be formed in the cycloadditon by using a more highly substituted allyl group on the enecarbamate starting material. Use of cinnamyl bromide in the lithiation/substitution reaction provided the γ-substituted enecarbamate **35**. Reaction of aldehyde **36** with *N*-benzylhydroxylamine hydrochloride under the same reaction conditions as described above led to the bicyclic product **37** in 64% yield with an 86:14 ratio of easily separable diastereomers. The absolute configura-

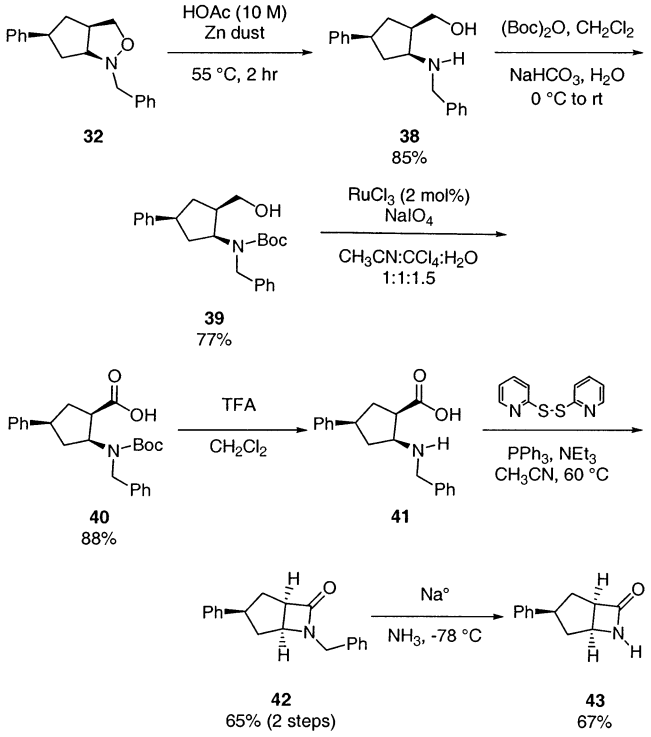
(12) LeBel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc.* **1964**, *86*, 3759−3767.

(13) The crystallographic data for **32** and **54** have been depositied with the Cambridge Crystallographic Data Centre as supplementary publication nos. 186903 and 186902, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (fax (+44) 1223−336033; e-mail deposit@ccdc.cam.ac.uk).

tion of **37** has been assigned by analogy to **32** and by a reasonable transition state model (vide infra).

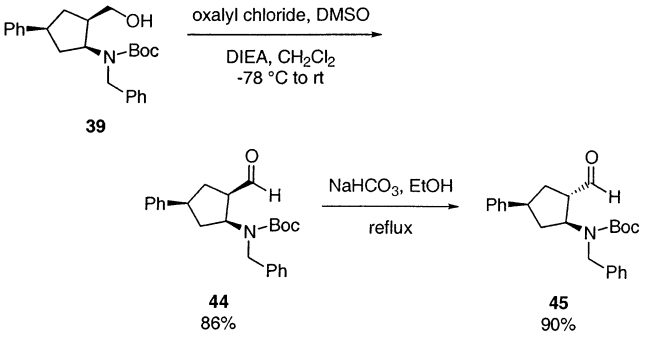


The nature and position of the functional groups in **32**−**34** offer an opportunity for the synthesis of highly enantioenriched β-lactams.[14] The reaction sequence we have developed is shown for the conversion of **32** to **43**.



In the first step toward the β-lactam synthesis, the N−O bond of isoxazoline **32** is cleaved by treatment with Zn/HOAc to provide amino alcohol **38** in 85% yield, which on Boc protection of the secondary amine provides **39** in 77% yield.[15] Oxidation of the protected amino alcohol **39** with $RuCl_3/NaIO_4$ affords the *N*-protected amino acid **40** in 88% yield. Deprotection with TFA provides the amino acid **41**, a structurally modified analogue of cispentacin.[16] Coupling of the crude amino acid **41** according to Ohno's procedure[17] with 2,2′-dipyridyl disulfide (Aldrithiol), PPh_3, and NEt_3 provides β-lactam **42** in 65% over the two steps. Benzyl deprotection is achieved with a dissolving metal reduction using sodium metal and liquid ammonia at −78 °C. The deprotected highly enantiomerically enriched β-lactam **43** was isolated in 67% yield.

A 1,2-trans-substituted chiral cyclopentane can be accessed by a two-step sequence from the chiral cis-substituted *N*-protected amino alcohol **39**. Swern oxidation of **39** provides the cis cyclopentyl aldehyde **44** in 86% yield, including approximately 10% of the epimerized product. Treatment of **44** with $NaHCO_3$ in refluxing EtOH provides the 1,2,4-trans-substituted aldehyde **45** in 90% yield.

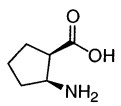


Synthesis of Masked Homoaldol Products. Reactions in which two stereogenic centers are created with high diastereo- and enantioselectivity are of exceptional value in asymmetric synthesis. Homoaldol reactions are of particular interest because of the novel addition of an aldehyde β to a carbonyl functionality.[18] A number of methods have been reported for the asymmetric synthesis of homoaldol reaction products. Hoppe and co-workers have thoroughly studied the (−)-sparteine-mediated lithiation/transmetalation/substitution sequences of *N*,*N*-diisopropylcarbamates for the synthesis of homoaldol precursors.[2] An (*S*)-2-prolinol ether chiral auxiliary approach has been developed by Ahlbrecht and co-workers for lithiation and aldehyde electrophile substitution of α-substituted allylamines.[19] Hoffmann and co-workers

(14) Chiral β-lactams are of considerable interest, as many pharmacologically active compounds contain this framework. See: *Antibiotics Containing the β-Lactam Structure*; Morin, R. B., Goldman, M., Eds.; Academic Press: New York, 1983; Vols. 1−3. Recent efforts for efficient asymmetric syntheses of azetidin-2-ones have concentrated on stereoselective ketene−imine cycloadditions and ester enolate−imine condensations. See: (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223−3225. (b) Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2000**, 563−572.

(15) A number of attempts made to simultaneously cleave the N−O bond of **32** and Boc-protect the resulting secondary amine **38** by Pd-catalyzed hydrogenation in the presence of Boc_2O were unsuccessful.

(16) Cispentacin has recently been isolated from *Bacillus cereus* and *Streptomyces setonii* and shown to have potent activity as an antifungal antibiotic in mice. See: (a) Konishi, M.; Nishio, M.; Saitoh, T.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1989**, *42*, 1749−1755. (b) Oki, T.; Hirano, M.; Tomatsu, K.; Numata, K.; Kamei, H. *J. Antibiot.* **1989**, *42*, 1756−1762. (c) Iwamoto, T.; Tsujii, E.; Ezaki, M.; Fujie, A.; Hashimoto, S.; Okuhara, M.; Kohsaka, M.; Imanaka, H. *J. Antibiot.* **1990**, *43*, 1−7. (d) Kawabata, K.; Inamoto, Y.; Sakane, K. *J. Antibiot.* **1990**, *43*, 513−518. Cispentacin is a compound of synthetic interest: (e) Fülöp, F.; Palkó, M.; Kámán, J.; Lázár, L.; Sillanpää, R. *Tetrahedron: Asymmetry* **2000**, *11*, 4179−4187. (f) Aggarwal, V. K.; Roseblade, S. J.; Barrell, J. K.; Alexander, R. *Org. Lett.* **2002**, *7*, 1227−1229.



cispentacin

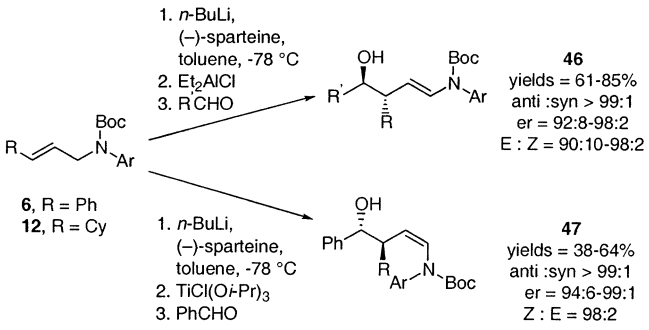
(17) Kobayashi, S.; Iimori, T.; Izawa, T.; Ohno, M. *J. Am. Chem. Soc.* **1981**, *103*, 2406−2408.

(18) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932−948.

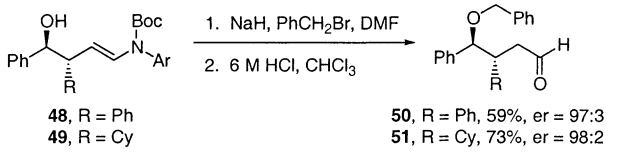
(19) Ahlbrect, H.; Kramer, A. *Chem. Ber.* **1996**, *129*, 1161−1168.

developed a series of useful allylic boron reagents for the preparation of homoallylic alcohols.[20]

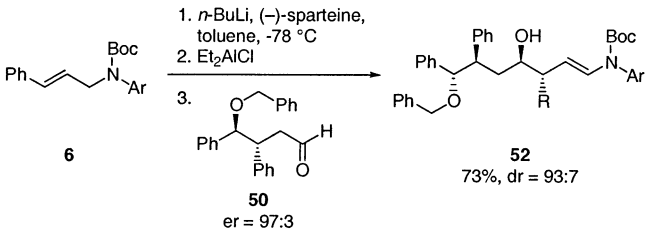
We have recently communicated the fact that lithiation of **6** or **12** upon subsequent transmetalation with Et_2AlCl or $TiCl(Oi\text{-}Pr)_3$ provides intermediates which undergo stereoselective reaction with aldehydes to give masked homoaldol products **46** and **47**.[7] This approach allows either enantiomer of a desired masked anti homoaldol product to be prepared with high stereointegrity.[21]



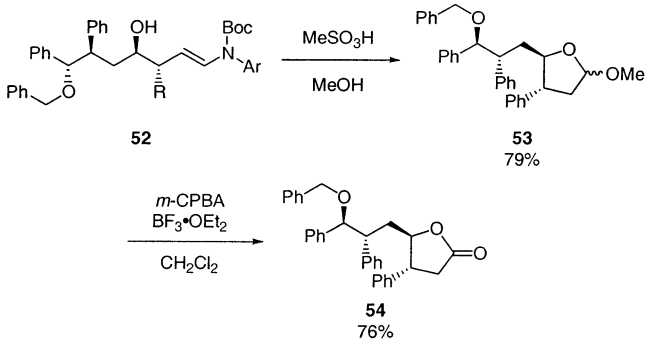
Absolute configurations were assigned by derivatization and X-ray crystallography and also by calculation of optical rotations.[22] Demasking of homoaldol products **48** and **49** by *O*-protection and subsequent hydrolysis provided the 3,4-disubstituted-4-alkoxy-aldehydes **50** and **51**.



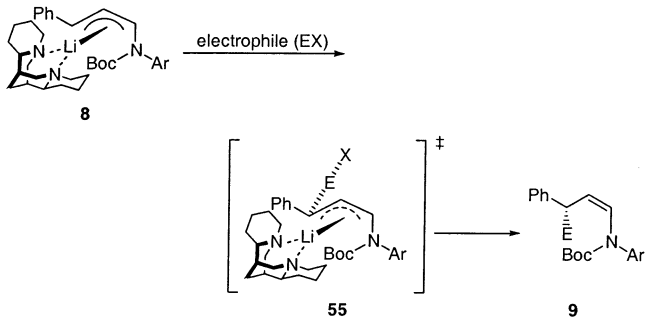
We now report that these homoaldol products can be utilized as chiral electrophiles in the homoaldol reaction. Lithiation and Et_2AlCl transmetalation of **6** followed by addition of *O*-protected homoaldol product **50** provides the iterative product **52** in 73% yield. The diastereoselectivity of the reaction is high; only two trans configured diastereomers in a ratio of 93:7 are detected.



The absolute configuration of **52** was determined by derivatization and X-ray crystallographic analysis. Methanolysis of **52** provided lactol **53** in 79% yield as a mixture of two diastereomers. Oxidation[23] of **53** with *m*-CPBA and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 gave a single diastereomer of **54** in 76% yield. A crystal suitable for X-ray crystallography was obtained by recrystallization.



Reaction Pathways. Previous work has established that the lithiated intermediate **8** is an η^3 species in the solid state and in solution with the absolute configuration shown.[4a] The absolute configurations of products from the alkylations of **8** require an invertive carbon−carbon bond formation. Our postulate is that the (−)-sparteine restricts access to the lithium ion and the sp^2 character of the allyl anion allows access to the electrophile by the si face of the nucleophile to allow the reactions to proceed with the inversion of configuration as shown for **55**.



Previous investigations of the kinetics and mechanism of the enantioselective deprotonation of **12** provide evidence that the lithiated intermediate of **12** is an enantioenriched, configurationally stable, α-lithiated η^1 species complexed to (−)-sparteine.[24] We presume this is also the case for the crotyl system **11**. The intermediates may be postulated to exist as two rotamers, **56** and **rot-56** (R = Cy) and **57** and **rot-57** (R = Me).[25] The η^1 character of the species should allow rotation for these intermediates more easily than for the η^3 intermediate **8**. The rate of rotation and the rate of reaction with electrophile were evaluated by an adapted Hoffmann's test for configurational stability.[26] The lithiated intermediate of **12** was reacted with 0.1 equiv of MeI. The resulting γ-substituted products were isolated in a 2:1 *Z*:*E* ratio, which is the same result as with excess MeI electrophile. This experi-

(20) (a) Hoffmann, R. W.; Dresely, S.; Lanz, J. *Chem. Ber.* **1988**, *121*, 1501−1507. (b) Hoffmann, R. W.; Dresely, S. *Chem. Ber.* **1989**, *122*, 903−909.

(21) It is of interest to note that the lithiation/transmetalation/substitution reactions with cyclohexyl allylamine **12** do not suffer the stereoselectivity problems observed for reaction of lithiated intermediates **56** and **rot-56** with alkyl bromides.

(22) Kondru, R. K.; Wipf, P.; Beratan, D. N. *Science* **1998**, *282*, 2247−2250. The $[\alpha]_D$ calculations were performed by Gustavo Mouro, David Beratan, and Peter Wipf at the University of Pittsburgh.

(23) Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, *18*, 419−420.

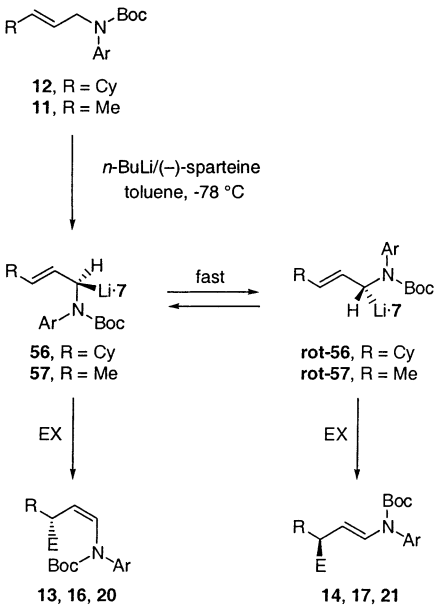
(24) Pippel, D. J.; Weisenburger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919−4927.

(25) These rotamers are indistinguishable at −78 °C by ^6Li and ^{13}C NMR. See ref 22.

(26) (a) Hoffmann, R. W.; Rühl, T.; Harbach, J. *Liebigs Ann. Chem.* **1992**, 725−730. (b) Hirsch, R.; Hoffmann, R. W. *Chem. Ber.* **1992**, *125*, 975−982. See also ref 4d.

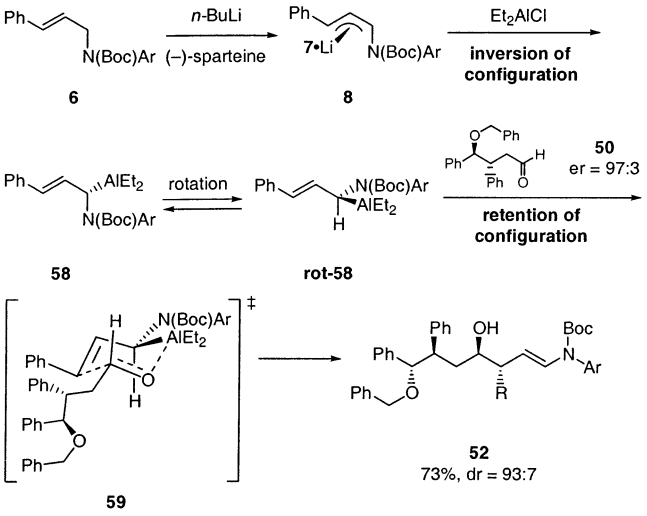
ment is consistent with the rotamers undergoing equilibration at a rate faster than reaction with electrophile, exhibiting classic Curtin−Hammett reactivity.[27]

The presence of two rotamers is consistent with olefin geometry and absolute configurations of the products obtained from the lithiation/substitution reactions. The transition states leading to the γ-substituted *E* and *Z* isomeric products may be considered to arise from reactions of the electrophile with each of the rotameric lithiated intermediates **56** and **rot-56** (R = Cy) and **57** and **rot-57** (R = Me). Since each rotamer places the lithium·(−)-sparteine complex on a different face of the substrate, the geometries and the configurations of the products are correlated and formed by invertive reactions in transition structures which are shown to resemble each allyllithium species. Products **13**, **14**, **16**, **17**, **20**, and **21** also are considered to arise by similar transition structures.



The low enantioenrichment observed for products **23**, **24**, **26**, and **28** resulting from reaction of **56** and **rot-56** with allyl bromide and benzyl bromide may be ascribed to the bulk of the cyclohexyl substituent of the allylic amine. The increased amount of α-substitution from **56** relative to **57** is consistent with a higher energy of activation for reaction at the γ position of **57**. An increase in the energy of activation for the stereoselective γ substitution may allow other facially less discriminating pathways to be competitive and lower the enantiomeric ratio of the products. Because the smaller methyl substituent does not cause as much steric congestion as the cyclohexyl group, products **13**, **14**, **16**, and **17** are obtained with high enantiomeric ratios. A single electron-transfer mechanism (SET) was discounted because of the high enantiomeric ratios observed in products obtained by lithiation and substitution of **6** and **11**. All reactions were run under the same conditions at −78 °C.

Knowledge of the absolute configurations of products allows assignment of a stereochemical course for the transmetalated homoaldol reactions. Transmetalation of **8** with Et_2AlCl is considered to proceed with inversion of configuration to give **58**, which is in equilibrium with conformation **rot-58**. Favorable coordination between the Boc group and the aluminum atom in the transition state for the carbon−carbon bond formation is shown for the six-membered transition state[28] **59**, which leads to **52**. Precoordination of the aldehyde electrophile to the metal atom leads to addition to the electrophile with retention of configuration.[29]



It has been established that transmetalation with $TiCl(O\textit{i}\text{-}Pr)_3$ provides *Z*-enecarbamate products, e.g. **47**, with the opposite absolute configuration[30] to that described for the Et_2AlCl transmetation/substitution. We suggest that transmetalation with $TiCl(O\textit{i}\text{-}Pr)_3$ also proceeds with inversion of configuration to provide a newly metalated intermediate **60**. The reaction of this intermediate with aldehyde electrophile is suggested to occur through transition state **61** to provide *Z*-configured enecarbamates **47** with absolute and geometrical configurations opposite to the products resulting from the reaction with Et_2AlCl. The difference between transition states **59** and **61** may be attributed to the ligands around the metal atoms. The two diethyl groups around aluminum do not sterically interfere with the larger −N(Boc)Ar group in **59**. Thus, the −N(Boc)Ar group adopts an energetically favorable pseudoequatorial position during reaction with the electrophile. However, upon reaction with electrophile in the titanium complex, the −N(Boc)Ar moiety may adopt a pseudoaxial position in **61** because of interference

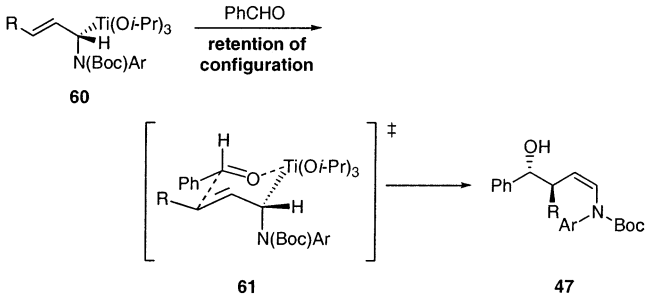
(27) A possibility exists that the rotamers do not, in fact, interconvert on the time scale of the reaction and that the energies of activation for reaction with electrophile are coincidentally the same.

(28) These allylmetal reactions are presumed to proceed through six-membered transition states. See: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, 2207−2293.

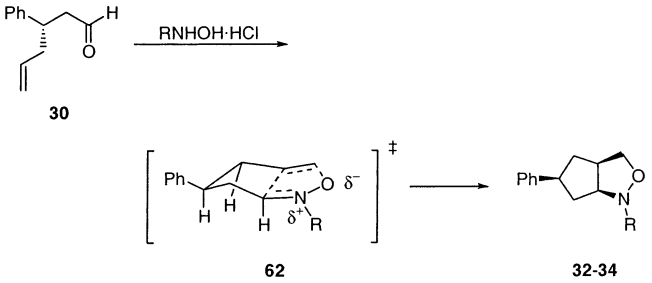
(29) Upon coordination with aldehyde, the coordination sphere around aluminum is proposed to be tetrahedral. See: Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*; John Wiley & Sons: New York, 1994; Chapters 1 and 2.

(30) The absolute configurations of the products obtained by transmetalation with $TiCl(O\textit{i}\text{-}Pr)_3$ were determined by *O*-protection and hydrolysis to the corresponding *O*-protected aldehyde (vide supra). Comparison of optical rotations was made with aldehydes **50** and **51**, whose absolute configuration was determined by X-ray crystal analysis of derivatives.

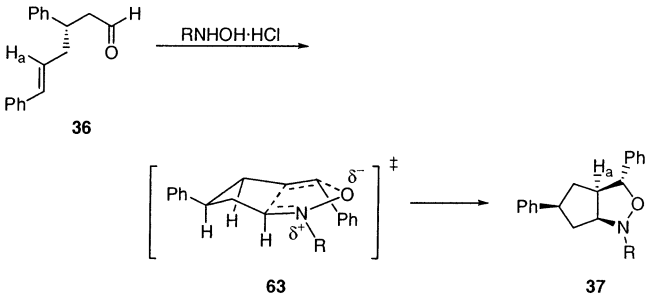
with the three sterically demanding isopropoxy groups around the titanium atom.[31]



The formation of the cyclopentyl rings by the 1,3-dipolar cycloaddition reactions is consistent with reaction via transition structure **62**.[32] The absolute configuration of the stereocenter in **32** is known; thus, transition state **62** accounts for the absolute configuration of the products **32**−**34.** The phenyl ring occupies a pseudoequatorial position in order to alleviate any unfavorable interactions.



The absolute configuration for the major diastereomer of **37** can be postulated based on the transition state for the cycloaddition. The reaction is known to be kinetically controlled,[12] allowing for retention of olefin configuration in the transition state **63** and in the resulting isoxazoline **37**.



Summary

The synthetic utility of asymmetric homoenolate equivalents has been demonstrated by syntheses from several laboratories; development of the methodology continues as new approaches to desirable target compounds are described. In this report, we demonstrate the use of lithiated *N*-Boc allylic amines for syntheses of highly enantioenriched γ-substituted enecarbamates, 2-formyl-4-phenyl-1-aminocyclopentanes, β-lactams, and iterative homoaldol products. This work demonstrates a value of the homoaldol approach for the efficient preparation of complex molecules with up to four stereogenic centers. Reasonable reaction pathways can be proposed to account for the observed products. Reactions of the lithiated intermediated with transmetalating reagents and with alkyl halide electrophiles occur with inversion of configuration, while reactions of the transmetalated titanium and aluminum species with aldehyde electrophiles are postulated to occur with retention of configuration.

Experimental Section

All glassware used in lithiation reactions was either flame-dried or oven-dried, and cooled under a nitrogen atmosphere. Solvents and reagents were used as received, unless noted. Toluene and dichloromethane were freshly distilled from CaH_2 under N_2 prior to use. Tetrahydrofuran (THF) was distilled from Na/benzophenone under N_2. *n*-BuLi in hexanes was used at a concentration determined by titration with *N*-pivaloyl-*o*-toluidine.[33] (−)-Sparteine was distilled under N_2 from CaH_2 prior to first use.

Mass spectrometric data were acquired at the University of Illinois Mass Spectrometry Laboratory by electron ionization (EI) or fast atom bombardment (FAB) technique. Elemental analyses were carried out by the University of Illinois Microanalytical Service Laboratory. Sample purity was determined to be >95% by ^{13}C NMR spectra. Diastereomeric purity was determined by ^1H NMR integration. "Standard workup" refers to dilution with ether, addition of H_2O, separation of phases, extraction of the aqueous layer with ether, combination of the organic phases, drying with $MgSO_4$, and concentration by rotary evaporation.

Representative Nitrone−Olefin Dipolar Cycloaddition: Synthesis of (5*S*)-1-Benzyl-5-phenyl-hexahydrocyclopenta[*c*]isoxazole (32). To a stirring solution of **30** (60 mg, 0.345 mmol) in toluene (3 mL, 0.12 M) was added benzylhydroxylamine hydrochloride (121 mg, 0.759 mmol), triethylamine (0.11 mL, 0.759 mmol), and molecular sieves. The mixture was allowed to stir overnight at room temperature and was monitored by TLC. When no starting material remained, the mixture was poured into water. Standard workup provided crude **32** as a light yellow oil. Column chromatography (90:10 petroleum ether:EtOAc) provided the product as a white solid (78 mg, 81%): mp 55−57 °C. A crystal suitable for X-ray crystallographic analysis was grown by recyrstallization from EtOH. The more retained minor diastereomer was characterized spectroscopically: ^1H NMR (acetone-d_6, 400 MHz) δ 1.71 (m, 1H, CH_2CHCH$_2$O), 1.82 (m, 1H, CH_2CHCH$_2$O), 1.98 (m, 2H, CH_2CHN), 3.24 (qt, 1H, J = 8.1 Hz, PhC*H*), 3.45 (sept, 1H, J = 6.1 Hz, C*H*CH$_2$O), 3.49 (m, 1H, C*H*N), 3.57 (dd, 1H, J = 8.4, 6.3 Hz, CH_2O), 3.99 (AB, 2H, J = 13.4 Hz; ν_a = 4.03 ppm; ν_b = 3.95 ppm, PhCH_2), 4.25 (t, 1H, J = 8.6 Hz, CH_2O), 7.19−7.44 (m, 10H, ArH). ^{13}C NMR (acetone-d_6, 100 MHz) δ 38.9, 42.8, 47.5, 61.1, 71.6, 72.4, 72.8, 126.2, 127.0, 127.3, 128.1, 128.4, 129.1, 138.8, 144.1. HRMS-FAB (M + 1) calcd for $C_{19}H_{22}NO$ 279.1623, found 279.1623. The less retained major diastereomer was obtained as a white solid and was characterized spectroscopically: ^1H NMR (acetone-d_6, 400 MHz) δ 1.53 (m, 1H), 1.66 (q, J = 11.5 Hz, 1H), 2.14 (m, 1H), 2.34 (m, 1H), 3.01 (sept, J = 6.1 Hz, 1H), 3.20 (m, 1H), 3.59 (dd, J = 8.5, 2.7 Hz, 1H), 3.69 (q, J = 8.1 Hz, 1H), 3.90 (AB, J = 13.4 Hz; ν_a = 3.96 ppm; ν_b = 3.84 ppm, 2H),

(31) Although unusual, a pentacoordinate titanium atom is not unprecedented. The geometry around the titanium atom is postulated as trigonal bipyramidal. For an X-ray crystal structure of a pentacoordinate titanium complex, see: Kirschbaum, K.; Conrad, O.; Giolando, D. M. *Acta Crystallogr., Sect. C* **2000**, *C56*, e541. For proposals of other reaction pathways through a pentacoordinate titanium complex, see: Adam, W.; Corma, A.; Reddy, T. I.; Renz, M. *J. Org. Chem*. **1997**, *62*, 3631−3637 and ref 2a.

(32) Confalone, P. N.; Huie, E. M. In *Organic Reactions*; Kende, A. S., Ed.; John Wiley & Sons: New York, 1988; Vol. 36, Chapter 1.

(33) Suffert, J. *J. Org. Chem*. **1989**, *54*, 509−510.

4.11 (m, 1H), 7.14−7.40 (m, 10H). ^{13}C NMR (acetone-d_6, 125 MHz) δ 40.2, 40.8, 46.3, 47.6, 59.6, 59.9, 71.5, 126.3, 127.1, 127.1, 128.3, 128.6, 129.2, 138.7, 143.9. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.27; H, 7.48; N, 5.15.

Representative Lithiation and Substitution: Synthesis of (3*S*)-*N*-(*tert*-Butoxycarbonyl)-3,6-diphenyl-*N*-(4-methoxyphenyl)-(1*Z*,5*E*)-hexadien-1-amine (35). To a stirring solution of **6** (205 mg, 0.60 mmol) in toluene (12 mL, 0.05 mmol) was added (−)-sparteine (0.19 mL, 0.84 mmol). The mixture was cooled to −78 °C and *n*-BuLi (0.962 mL, 0.52 mmol) was added dropwise. After being stirred for 1 h at −78 °C, cinnamyl bromide (0.18 mL, 1.21 mmol) was added to the mixture and the stirring was continued for 2 h. The mixture was then quenched with MeOH (1 mL) and warmed to room temperature. Standard workup and subsequent column chromatography and preparative HPLC (95:5 petroleum ether:EtOAc) provided pure **35** as a colorless oil (276 mg, 93%). ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.37 (s, 9H), 2.34 (m, 2H), 3.13 (m, 1H), 3.78 (s, 3H), 5.09 (t, J = 9.5 Hz, 1H), 5.93 (m, 1H,), 6.25 (d, J = 9.8 Hz, 1H), 6.65 (d, J = 9.1 Hz, 1H), 6.85−7.29 (m, 14H). ^{13}C NMR (acetone-d_6, 100 MHz) δ 27.7, 40.4, 42.3, 55.1, 80.5, 114.0, 121.0, 126.1, 126.2, 127.1, 127.5, 127.6, 128.3, 128.4, 128.7, 131.4, 135.2, 138.0, 144.2, 153.3, 158.2.

(1*S*,2*S*,4*S*)-1-Amino-*N*-benzyl-2-hydroxymethyl-4-phenylcyclopentane (38). To a stirring solution of **32** (153 mg, 0.548 mmol) in 10 M AcOH (10 mL, 0.06 M) was added Zn dust (717 mg, 10.97 mmol). The mixture was heated to 55 °C. After being stirred for 3 h, the mixture was cooled to room temperature, diluted with water, basified with 6 M KOH, and extracted with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), and concentrated to provide **38** as a pure colorless oil (130 mg, 85%) requiring no further purification. ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.65 (m, 2H), 2.09 (m, 1H), 2.36 (m, 2H), 2.98 (m, 1H), 3.30 (br s, 1H), 3.39 (m, 1H), 3.71 (d, J = 5.8 Hz, 2H), 3.82 (AB, J = 13.2 Hz; ν_a = 3.87 ppm; ν_b = 3.76 ppm, 2H), 7.13−7.39 (m, 10H). ^{13}C NMR (acetone-d_6, 125 MHz) δ 36.6, 41.8, 43.2, 43.2, 52.8, 60.5, 63.2, 126.0, 126.9, 127.2, 128.3, 128.4, 128.5, 141.2, 145.6. HRMS-FAB (M + 1) calcd for $C_{19}H_{24}NO$ 282.1858, found 282.1857.

(1*S*,2*S*,4*S*)-1-Amino-*N*-benzyl-*N*-(*tert*-butoxycarbonyl)-2-hydroxymethyl-4-phenylcyclopentane (39). To a stirring solution of **38** (55 mg, 0.195 mmol) in MeOH (3 mL, 0.07 M) was added $NaHCO_3$ (115 mg, 1.37 mmol). $(Boc)_2O$ (0.13 mL, 0.585 mmol) was then added and the mixture was stirred at room temperature overnight. The mixture was poured into water and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated to provide the crude product as a yellow oil. Purification by column chromatography (80:20 petroleum ether:EtOAc) provided **39** (57 mg, 77%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.45 (s, 9H), 1.78 (q, J = 11.8 Hz, 1H), 2.16 (br m, 3H), 2.55 (m, 1H), 2.92 (br s, 1H), 3.02 (m, 1H), 3.66 (m, 2H), 4.37 (m, 2H), 4.63 (br m, 1H), 7.18−7.33 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.6, 28.6, 35.9, 37.4, 42.8, 59.5, 60.7, 63.1, 80.7, 126.4, 126.6, 127.0, 127.3, 128.6, 128.7, 139.7, 144.4, 157.2. HRMS-FAB (M + 1) calcd for $C_{24}H_{31}NO_3$ 382.2382, found 382.2383.

(1*R*,2*S*,4*S*)-2-Amino-*N*-benzyl-*N*-(*tert*-butoxycarbonyl)-4-phenyl-1-cyclopentanecarboxylic Acid (40). To protected amino alcohol **39** (57 mg, 0.150 mmol) was added 1.5 mL of solvent (1:1:1.5 CH_3CN:CCl_4:H_2O) and $NaIO_4$ (128 mg, 0.598 mmol). $RuCl_3$ (0.7 mg, 0.022 mmol) was then added and the colorless solution became yellowish brown in color. The mixture was allowed to stir overnight. H_2O was then added and the solution was poured into a separatory funnel and washed with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), and concentrated. The light brown oil was dissolved in ether and filtered through a pad of Celite. Concentration of the filtered solution provided the product **40** (52 mg, 88%), which was carried directly to the subsequent deprotection reaction without further purification. ^{1}H NMR (acetone-d_6, 400 MHz) (Note: restricted rotation causes severe broadening of peaks) δ 1.45 (br s, 9H), 2.14 (br s, 1H), 2.20 (m, 1H), 2.35 (t, J = 8.5 Hz, 2H), 2.97 (m, 1H), 3.48 (m, 1H), 4.44 (m, 1H), 4.74 (br m, 2H), 7.19−7.63 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.6, 35.9, 37.8, 42.9, 46.3, 49.2, 59.8, 80.9, 126.8, 126.9, 127.4, 127.4, 128.6, 128.7, 139.8, 143.5, 156.4, 180.0. HRMS-FAB (M + 1) calcd for $C_{24}H_{30}NO_4$ 396.2175, found 396.2176.

(3*S*)-6-Aza-6-benzyl-3-phenyl-bicyclo[3.2.0]heptan-7-one (42). To a stirring solution of **40** (27 mg, 0.067 mmol) in CH_2Cl_2 (1 mL, 0.07M) was added approximately 0.25 mL of 30% TFA in CH_2Cl_2. The mixture was allowed to stir at room temperature for 12 h and was monitored by TLC. Concentrated TFA (0.25 mL) was then added and the reaction stirred until complete consumption of starting material was observed. Upon consumption of starting material, the TFA/CH_2Cl_2 mixture was removed in vacuo. Residual TFA was removed by azeotroping with $CHCl_3$ and toluene in vacuo. The crude, deprotected amino acid **41** was dissolved in CH_3CN (1.5 mL, 0.045 M) and NEt_3 (14 μL, 0.10 mmol) was added. A small amount of white precipitate immediately formed and the reaction was stirred for 10 min. PPh_3 (21 mg, 0.08 mmol) and 2,2′-dipyridyl disulfide (Aldrithiol, 18 mg, 0.08 mmol) were then added. The reaction was heated to 60 °C for 8 h. The yellow homogeneous reaction mixture was then diluted with H_2O and washed with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated to provide crude **42** as a yellow oil. Column chromatography (50:50 petroleum ether:EtOAc) provided pure **42** (12 mg, 65%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.01 (m, 2H), 2.08 (ddd, J = 16.7, 8.8, 7.7 Hz, 1H), 2.52 (ddd, J = 14.2, 5.1, 3.2 Hz, 1H), 3.58 (qt, J = 7.1 Hz, 1H), 3.62 (m, 1H), 3.88 (AB, J = 15.0 Hz; ν_a = 4.28 ppm; ν_b = 3.47 ppm, 2H), 7.12−7.36 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.3, 35.6, 44.4, 46.2, 55.6, 58.1, 126.3, 126.7, 127.8, 128.6, 128.6, 129.0, 135.8, 143.5, 169.9. IR ($CHCl_3$) 1742 cm^{-1}. HRMS-FAB (M + 1) calcd for $C_{19}H_{20}NO$ 278.1545, found 278.1546.

6-Aza-(3*S*)-phenyl-bicyclo[3.2.0]heptan-7-one (43). To approximately 5 mL of NH_3 at −78 °C was added the protected β-lactam **42** dissolved in THF (0.5 mL, 0.12 M) dropwise with a syringe. Small bits of sodium were added until the dark blue color persisted. The reaction was allowed to stir for 5 min, whereupon NH_4Cl(s) was added to quench the sodium. When the mixture was colorless, the reaction was allowed to warm to room temperature and the NH_3 evaporated. The residue was then dissolved in sat. NH_4Cl. The aqueous mixture was washed with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated to provide crude **43** as a colorless oil. The product was further purified by column chromatography (90:10 $CHCl_3$:MeOH) to provide pure **43** (8 mg, 67%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09 (ddd, J = 13.9, 6.6, 2.7 Hz, 1H), 2.16 (m, 1H), 2.26 (m, 1H), 2.44 (ddd, J = 13.9, 6.4, 4.2 Hz, 1H), 3.60 (qt, J = 7.6 Hz, 1H), 3.68 (m, 1H), 4.20 (m, 1H), 5.66 (br s, 1H), 7.18−7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.8, 38.7, 47.8, 55.0, 57.2, 126.4, 126.9, 128.6, 143.7, 171.2. HRMS-FAB (M + 1) calcd for $C_{12}H_{14}NO$ 188.1075, found 188.1075.

(1*R*,2*S*,4*S*)-2-Amino-*N*-benzyl-*N*-(*tert*-butoxycarbonyl)-4-phenyl-1-cyclopentanecarboxylic Acid (44). CH_2Cl_2 (0.5 mL) and oxalyl chloride (21 μL, 0.25 mmol) were added to a flame-dried flask and cooled to −78 °C. DMSO (32 μL, 0.45 mmol) was dissolved in CH_2Cl_2 (0.25 mL) and added to the reaction mixture. After the mixture was stirred for 30 min, the alcohol **39** (34 mg, 0.09 mmol), dissolved in CH_2Cl_2 (1 mL), was added dropwise. After this mixture was stirred at −78 °C for 1.5 h, diethylisopropylamine (0.14 mL, 0.82 mmol) was added and the reaction was warmed to room temperature. The mixture was poured into 1 M HCl (25 mL) and the layers were separated. The organic layer was washed with 1 M HCl, H_2O, and brine, dried over $MgSO_4$, and concentrated to provide crude **44** as a light yellow oil. Column chromatography (80:20 petroleum ether:EtOAc) provided the pure **44** as a colorless oil in 86% yield (29 mg). Approximately 10% of the epimerized product was observed by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz)

(Note: restricted rotation causes severe broadening of peaks) δ 1.47 (s, 9H), 2.02 (m, 1H), 2.13 (q, J = 11.5 Hz, 1H), 2.20 (m, 1H), 2.40 (m, 1H), 2.92 (sept, J = 6.3 Hz, 1H), 3.20 (br s, 1H), 4.35−4.48 (br m, 3H), 7.18−7.36 (m, 10H), 9.73 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.6, 33.3, 38.1, 42.8, 51.8, 55.1, 60.4, 80.7, 126.7, 127.1, 127.3, 127.4, 128.7, 128.8, 139.1, 143.3, 155.8, 203.2. HRMS-FAB (M + 1) calcd for $C_{24}H_{30}NO_3$ 380.2226, found 380.2226.

(1*S*,2*S*,4*S*)-2-Amino-*N*-benzyl-*N*-(*tert*-butoxycarbonyl)-4-phenyl-1-cyclopentanecarboxylic Acid (45). To a stirring solution of **44** (9 mg, 0.02 mmol) in EtOH (1 mL, 0.02M) was added $NaHCO_3$. The mixture was heated to 110 °C for 3 h. The mixture was then cooled to room temperature and filtered over Celite to afford the epimerized product **45** (8 mg, 90%), which required no further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) (Note: restricted rotation causes severe broadening of peaks) δ 1.48 (br s, 9H), 2.09 (m, 2H), 2.14 (qt, J = 11.7 Hz, 1H), 2.33 (m, 1H), 2.90 (m, 1H), 3.20 (m, 1H), 4.35−4.58 (br m, 3H), 7.18−7.36 (m, 10H), 9.65 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.6, 29.9, 32.3, 42.8, 50.4, 58.6, 61.7, 80.9, 126.7, 126.7, 127.1, 127.5, 128.7, 128.7, 128.8, 139.1, 143.3, 202.5. HRMS-FAB (M + 1) calcd for $C_{24}H_{30}NO_3$ 380.2226, found 380.2223.

Representative Lithiation/Transmetalation/Substitution: Synthesis of (3*R*,4*S*,6*S*,7*S*)-7-Benzoxy-*N*-(*tert*-butoxycarbonyl)-4-hydroxy-*N*-(4-methoxyphenyl)-3,6,7-triphenyl-(*E*)-1-hepten-1-amine (52). To a stirred solution of **6** (52 mg, 0.152 mmol) in toluene (2.5 mL, 0.06 M) under N_2 was added (−)-sparteine (49 μL, 0.212 mmol). The solution was cooled to −78 °C. *n*-BuLi (0.12 mL, 0.182 mmol) was added dropwise, ensuring that the temperature of the mixture did not exceed −76 °C. The bright yellow solution was allowed to stir for 30 min, whereupon Et_2AlCl (0.17 mL, 0.303 mmol, 1.8 M solution in toluene) was added dropwise with careful temperature control. The solution became colorless within 2 min and was allowed to stir for 1 h. A solution of aldehyde **50** (100 mg, 0.303 mmol) in 0.5 mL of toluene was then added, ensuring that the temperature of the mixture did not exceed −76 °C. The reaction was allowed to stir at −78 °C for 3 h, and was then quenched with MeOH (1 mL) and allowed to warm to room temperature. The solution was diluted with ether and poured onto 50 mL of 2 M HCl. The organic layer was removed, and the aqueous layer was washed with ether. The combined organic layers were dried ($MgSO_4$) and concentrated to provide the crude product as a yellow oil. The crude product was purified by column chromatography (80:20 petroleum ether:EtOAc) to afford **52** as a colorless oil (73 mg, 75%). The *E* geometrical isomer was obtained with a dr of 92:8. The diastereomers were separated by preparative HPLC with a solvent system of 90:10 hexanes:EtOAc. A crystal suitable for X-ray crystallographic analysis was grown by recrystallization from EtOH. ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.40 (s, 9H), 1.91 (m, 2H), 2.21 (m, 1H), 3.19 (d, J = 4.9 Hz, 1H), 3.22 (m, 1H), 3.35 (dd, J = 9.8, 4.2 Hz, 1H), 3.62 (m, 1H), 3.80 (s, 3H), 4.32 (AB, J = 11.7 Hz, ν_a = 4.39 ppm; ν_b = 4.25 ppm, 2H), 4.52 (d, J = 7.1 Hz, 1H), 4.79 (dd, J = 14.2, 9.8 Hz, 1H), 6.89−7.36 (m, 25H). ^{13}C NMR (acetone-d_6, 100 MHz) δ 27.7, 37.4, 49.4, 51.3, 55.0, 70.7, 72.9, 80.4, 86.1, 108.9, 114.4, 125.9, 126.3, 127.3, 127.4, 127.5, 127.6, 128.0, 128.0, 128.1, 128.3, 128.5, 129.2, 129.9, 131.9, 132.2, 139.2, 141.0, 142.7, 144.7, 152.5, 158.8. HRMS-FAB (M + 1) calcd for $C_{44}H_{47}NO_5$ 670.3532, found 670.3530.

(4*R*,5*S*)-5-(2*S*,3*S*-Diphenyl-3-benzoxy-propyl)-4-phenyl-butyrolactone (54). To a stirred solution of **52** (72 mg, 0.11 mmol) in MeOH (1.5 mL, 0.07 M) at room temperature was added methanesulfonic acid (3.5 μL, 0.05 mmol). The reaction was allowed to stir overnight and was then poured into a mixture of KOH and brine. Standard workup provided lactol **53**. The crude product was purified by column chromatography (90:10 petroleum ether:EtOAc) to afford colorless oil **53** as an equal mixture of two diastereomers in 79% yield (41 mg). The diastereomers were not separated and were carried directly to the subsequent *m*-CPBA/BF_3·OEt_2 oxidation reaction. To a stirring solution of **53** (41 mg, 0.09 mmol) in CH_2Cl_2 (2 mL, 0.04 M) was added *m*-CPBA (44 mg, 0.26 mmol) and BF_3·OEt_2 (3.2 μL, 0.03 mmol). The cloudy reaction mixture was allowed to stir overnight and was then poured into $NaHSO_3$ (aq). The organic layer was removed and the aqueous layer washed with CH_2Cl_2. The combined organic layers were washed with $NaHCO_3$ (aq), dried over $MgSO_4$, filtered, and concentrated to afford the crude light yellow oil. The crude product was purified by column chromatography (90:10 petroleum ether:EtOAc) to afford white solid **54** in 76% yield (30 mg): mp 155−157 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.33 (m, 1H), 2.53 (m, 1H), 2.77 (ABX, ν_a = 2.89 ppm; ν_b = 2.63 ppm; J_{AB} = 17.7 Hz; J_{AX} = 8.7 Hz; J_{BX} = 10.4 Hz, 2H), 2.94 (X of ABX, 1H), 3.24 (q, J = 8.6 Hz, 1H), 4.28 (AB, J = 11.8 Hz, ν_a = 4.41 ppm; ν_b = 4.14 ppm, 2H), 4.30 (d, J = 7.9 Hz, 1H), 4.54 (q, J = 8.1 Hz, 1H), 6.63−7.34 (m, 20H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.9, 37.6, 38.6, 48.6, 49.1, 60.6, 70.8, 85.7, 126.7, 127.5, 127.7, 127.8, 127.8, 128.0, 128.2, 128.2, 128.5, 128.6, 129.3, 138.5, 139.5, 140.3, 141.1, 175.8. HRMS-FAB (M + 1) calcd for $C_{32}H_{31}NO_3$ 463.2273, found 463.2273.

Acknowledgment. This work was supported by a grant from the National Institutes of Health (GM-18874). We are grateful for this support.

Supporting Information Available: Experimental procedures and spectral data for compounds **13**−**17**, **24**, **26**−**28**, **32**−**35**, **37**−**40**, **42**−**45**, **52**, and **54**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0260084