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Asymmetric Carbon−Carbon Bond Formations in Conjugate Additions of Lithiated *N*-Boc Allylic and Benzylic Amines to Nitroalkenes: Enantioselective Synthesis of Substituted Piperidines, Pyrrolidines, and Pyrimidinones

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Abstract: (−)-Sparteine mediated lithiations of *N*-Boc-allylic and benzylic amines provide configurationally stable intermediates which on conjugate additions to nitroalkenes provide highly enantioenriched enecarbamate products in good yields, and with high diastereoselectivities. Straightforward transformations of these adducts offer general routes to substituted 3,4-substituted piperidines, 3,4-substituted pyrrolidines, and 4,5-substituted pyrimidinones. Diastereoselective substitutions of intermediate lactams followed by reduction provide 3,4,5-substituted piperidines and 3,4-trisubstituted pyrrolidines. Lithiation adjacent to nitrogen of 3,4-substituted piperidines and pyrrolidines followed by diastereoselective substitution opens a route to 2,4,5- and 2,4,5,6-substituted piperidines as well as 2,3,4- and 2,3,4,5-substituted pyrrolidines. The enantiomers of the enecarbamate and 3,4-substituted piperidine products may be accessed by stannylation/transmetalation sequences as well as by further manipulation of 4-substituted piperidones. The methodology is used to synthesize both enantiomers of an aspartic peptidase inhibitor intermediate, 3-hydroxy-4-phenylpiperidine, as well as the antidepressant (+)-femoxetine.

Introduction

Carbon−carbon bond formations which are diastereoselective and enantioselective at both bond termini can be of exceptional value for asymmetric synthesis. Although such dual stereocontrol is unusual for conjugate additions, a few cases generalized by (1) have been described.[1,2]

(1)

We have reported 1,4-additions to form carbon−carbon bonds which are highly diastereoselective and enantioselective. The additions of the organolithium species formed by (−)-sparteine mediated lithiations of *N*-Boc-*N*-(*p*-methoxyphenyl) allylic and benzylic amines to activated olefins (Scheme 1) provide products in most cases with >90:10 diastereomeric ratio (dr) and >95:5 enantiomeric ratio (er).[2,3] The functional groups in these conjugate addition products have a 1,5- or 1,4-relationship which has allowed their use as chiral building blocks for desirable synthetic targets including carbocyclic and heterocyclic rings.[3]

Asymmetric conjugate additions to nitroalkenes have been a useful approach to substituted nitrogen heterocycles by subsequent reductions and cyclizations. Most of the reactions reported have focused on conjugate additions of enolates and have been limited to the synthesis pyrrolidine derivatives.[1d,4] We have communicated the conjugate addition of lithiated *N*-Boc-*N*-(*p*-methoxyphenyl) allylic amines to nitroalkenes to provide enecarbamate products which are readily converted to substituted piperidines including the antidepressant (−)-paroxetine.[5] We now report further development of this methodology with allylic and benzylic organolithium intermediates to allow access to enantioenriched 3,4- and 3,4,5-substituted piperidines, 3- and 4-substituted pyrrolidines, and 2,3-substituted pyrimidinones.[6] In conjunction with our earlier work this lithiation/substitution approach allows asymmetric carbon−carbon bond formation for each position of the piperidine and pyrrolidine rings.

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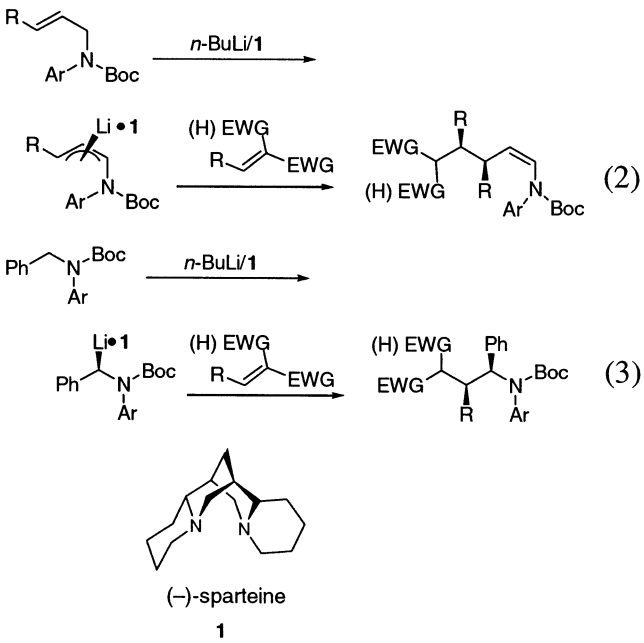
(6) For syntheses of enantioenriched substituted pyrimidinones see: (a) Chan, A. W.-Y.; Ganem, B. *Tetrahedron Lett.* **1995**, *36*, 811. (b) De Lucca, G. V.; Liang, J.; Aldrich, P. E.; Calabrese, J.; Cordova, B.; Klabe, R. M.; Rayner, M. M.; Chang, C.-H. *J. Med. Chem.* **1997**, *40*, 1707. (c) Kaiser, A.; Balbi, M. *Tetrahedron: Asymmetry.* **1999**, *10*, 1001.

Scheme 1

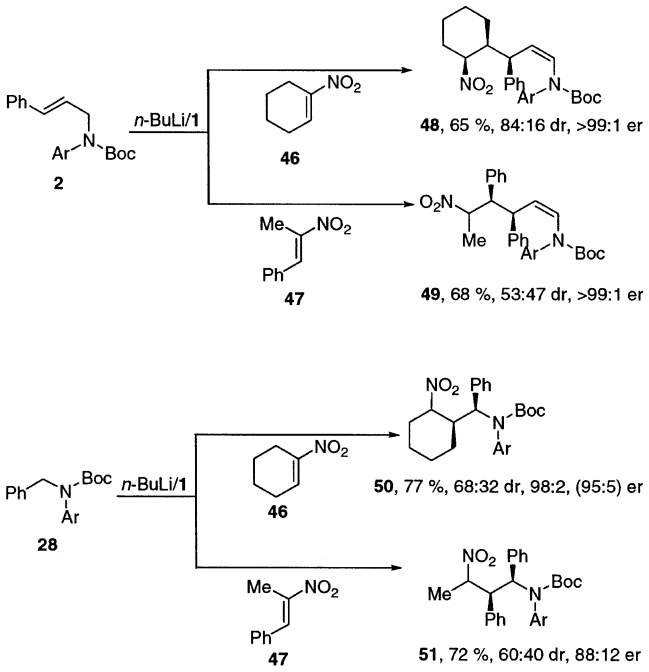


Results and Discussion

Conjugate Additions to Nitroalkenes. Treatment of the *N*-Boc-*N*-(*p*-methoxyphenyl) allylic amines **2**−**5** with *n*-BuLi/**1** at −78 °C provides the configurationally stable organolithiums **6**−**9** which on conjugate additions to nitroalkenes **10**−**16** provide the enecarbamates **17**−**27** in good yields with high diastereomeric and enantiomeric ratios (Table 1). A valuable feature of these conjugate additions is the ability to incorporate aryl, alkyl, and heterocyclic substituents at both ends of the new bond in achieving good yields and high selectivities. The enantioselectivity remains high when the nitroalkene is unsubstituted (entry 7) but declines considerably when the allylic organolithium is unsubstituted (entry 11). In most cases, enantiomeric ratios were determined to be >97:3 following derivatization to diastereomeric derivatives.[7] While the diastereomers of **18**−**27** were inseparable by chromatography or prep-HPLC, the diasteromers can be easily separated after subsequent conversion to derivatives followed by recrystallization or column chromatography. The absolute configurations of **17**, **19**, **23**, **25,** and **27** were determined by derivatization and X-ray crystallographic analysis or comparison to known compounds.[8] The configurations are consistent with reaction of **6** (R_1 = Ph) with the nitroalkenes with inversion based on the known structure of **6** (vide infra).[9] The absolute configurations of **18**, **20**−**22**, **24**, and **26** are assigned by analogy.

The benzylic organolithiums **34** and **35** generated from **28** and **29** undergo highly diastereoselective and enantioselective addition to aryl and alkyl substituted nitroalkenes (Table 2). However, when substituents containing heteroatoms were utilized, there was a reduction of dr and/or er (entries 6, 8, and 9). It was also observed that the geometry of the nitroalkene plays a significant role in the diastereoselectivity. Reaction of **34** with *cis*-*β*-nitrostyrene provided the adduct with a 68:32 dr, whereas *trans*-*β*-nitrostyrene provided the same adduct with a 92:8 dr. The absolute configurations of **39** and a derivative of **36**[7] were determined by X-ray crystallographic analysis and are consistent with a reaction pathway for **34** (R_1 = Ph) with inversion. All other configurations are assigned by analogy to **36** and **39**. In all cases, the diastereomers were separable by either prep-HPLC, column chromatography, or recrystallization.

Two disubstituted nitroalkenes have been investigated and provide products containing three contiguous stereogenic centers. Addition of organolithium intermediates derived from **2** and **28** to *β*-methyl-*β*-nitrostyrene (**47**) provides **49** and **51** in good yields. The low diastereomeric ratio is attributed to an unselective protonation of the nitronate generated from the addition. When nitrocyclohexene (**46**) is utilized as the electrophile, an increase in the dr is observed with protonation being favored from the least hindered face of the nitronate. This geometry for the newly formed bond was established by ^{1}H NMR and is consistent with that observed in other conjugate additions to 1-nitrocyclohexene.[10] The diastereomers in these additions were separable by column chromatography or prep-HPLC.



Synthesis of Disubstituted Piperidines, Pyrrolidines, and Pyrimidinones. The enecarbamates derived from these conjugate additions are useful precursors to 3,4-substituted piperidines and pyrrolidines.

The piperidine syntheses are summarized in Table 3. Hydrolysis of the enecarbamates **17**−**20**, **22**−**23**, **25** with HCl in $CHCl_3$ provides the crude nitroaldehydes. Oxidation with $NaClO_2$, esterification, hydrogenation of the nitro group, and concomitant cyclization provides piperidones **52**−**58**. In most cases these lactams could be recrystallized to >99:1 dr in good yields. Reduction with LAH and Boc-protection provided piperidines **59**−**61** in good yields. The enecarbamates **21** and **24** containing a furan ring are not compatible with this oxidative

(7) Provided in Supporting Information.
(8) Crystallographic data for compounds have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 190127−190133. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
(9) Pippel, D. J.; Weisenburger, G. A.; Wilson, S. R.; Beak, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2522.
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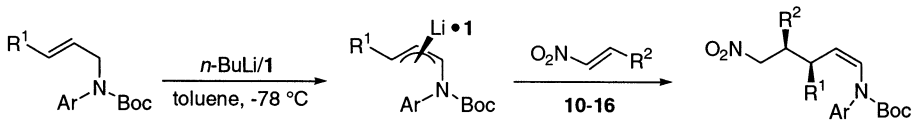
Table 1. Conjugate Addition of *N*-Boc-*N*-(*p*-methoxyphenyl)allylamines **2**−**5** to Nitroalkenes **10**−**16**

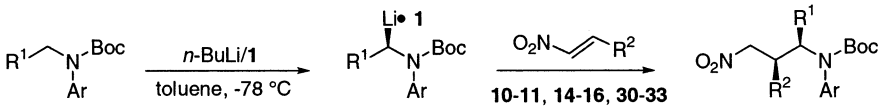


2-5 **6-9** **17-27**

entry	allylamine	R^1	nitroalkene	R^2	product	yield (%)	dr[a]	er[b]
1	**2**	Ph	**10**	Ph	**17**	90	94:6	94:4[c]
2	**2**	Ph	**11**	Cy[d]	**18**	83	95:5	>97:3
3	**2**	Ph	**12**	*i*-Bu	**19**	73	98:2	>97:3
4	**2**	Ph	**13**	*o*-MeOPh	**20**	82	93:7	>97:3
5	**2**	Ph	**14**	2-furyl	**21**	82	94:6	>97:3
6	**2**	Ph	**15**	OTIPS	**22**	83	92:8	>97:3
7	**2**	Ph	**16**	H[e]	**23**	82	−	>97:3
8	**3**	2-furyl	**10**	Ph	**24**	90	93:7	>97:3
9	**4**	Me	**10**	Ph	**25**	74	90:10	>97:3
10	**4**	Me	**12**	*i*-Bu	**26**	74	84:16	>97:3
11	**5**	H	**10**	Ph	**27**	74	−	75:25

[a] Diastereomeric ratios were determined by ^{1}HNMR integration. [b] Enantiomeric ratios of diastereopure derivatives. [c] Enantiomeric ratios determined by CSP−HPLC. [d] Cy = cyclothexy. [e] Nitroethylene was premixed with (TMS)Cl.

Table 2. Conjugate Addition of *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamines **28** and **29** to Nitroalkenes **10**, **11**, **14**−**16**, and **30**−**33**

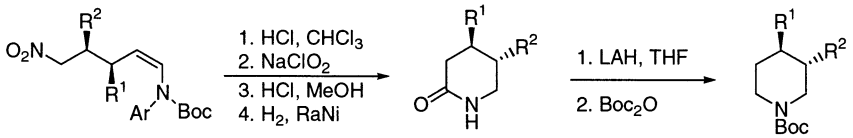


28-29 **34-35** **36-45**

entry	allylamine	R^1	nitroalkene	R^2	product	yield (%)	dr[a]	er[b,c]
1	**28**	Ph	**10**	Ph	**36**	93	92:8	>99:1
2	**28**	Ph	**30**	Ph[d]	**37e**	81	68:32	96:4
3	**28**	Ph	**31**	*i*-Pr	**38**	90	99:1	97:3
4	**28**	Ph	**32**	Me	**39**	95	90:10	>99:1
5	**28**	Ph	**11**	Cy	**40**	92	92:8	94:6
6	**28**	Ph	**15**	OTIPS	**41**	82	77:23	88:12
7	**28**	Ph	**16**	H	**42**	71	−	96:4
8	**28**	Ph	**14**	2-furyl	**43**	84	63:27	(96:4)
9	**28**	Ph	**33**	2-thiophene	**44**	89	89:11	97:3
10	**29**	2-furyl	**10**	Ph	**45**	98	>99:1	>99:1

[a] Diastereomeric ratios were determined by ^{1}HNMR intergration. [b] Enantiomeric ratios determined by CSP−HPLC. [c] er of minor diastereomer in parentheses. [d] *cis*-β-Nitrostyrene was used. [e] The major diastereomer is **36**.

Table 3. Conversion of Enecarbamates **17**−**20**, **22**, **23**, and **25** to Lactams **52**−**58** and Piperidines **59**−**61**



17-20, 22-23, 25 **52-58** **59-61**

entry	substrate	er	R^1	R^2	lactam	yield[b] (%)	dr[c]	piperidine	yield (%)
1	**17**	96:4	Ph	Ph	**52**	59	>99:1	**59**	79
2	**18**	>97:3	Ph	Ph[d]	**53**	57	>99:1	−	−
3	**19**	>97:3	Ph	i-Pr	**54**	71	>99:1	**60**	82
4	**20**	>97:3	Ph	Me	**55**	61	>99:1	**61**	82
5	**21**	>97:3	Ph	Cy	**56**	58	>99:1	−	−
6	**22**	>97:3	Ph	OTIPS	**57a**	55	>99:1[d]	−	−
7	**23**	>97:3	Ph	H	**58**	79	−	−	−

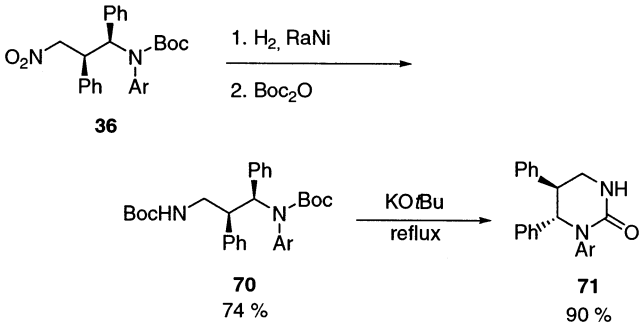
[a] Esterification with CH_2N_2. [b] Yields from enecarbamate. [c] dr following recrystallization. [d] dr following chromatography.

approach, but we have reported an alternative approach allowing for their conversion to the corresponding 3,4-substituted piperidines.[5]

Pyrrolidines rings can be accessed by a sequence which begins with ozonolysis of the enecarbamate double bond. The reactions are summarized in Table 4. The ozonolysis of **17** and **25**−**27** is followed by reductive workup with dimethyl sulfide to provide the requisite aldehyde which is subjected to oxidation, esterification, reduction, and cyclization to provide pyrrolidinones **62**−**65**. Conversion to the pyrrolidines **66**−**69** is achieved in good yields by LAH reduction and treatment with Boc_2O. In all cases the minor diastereomer was removed by chromatography of an intermediate ester or lactam.

The products derived from addition of the benzylic organolithiums can also serve as useful precursors to 3,4-substituted pyrimidinones as demonstrated by the conversion of **36** to **71**.

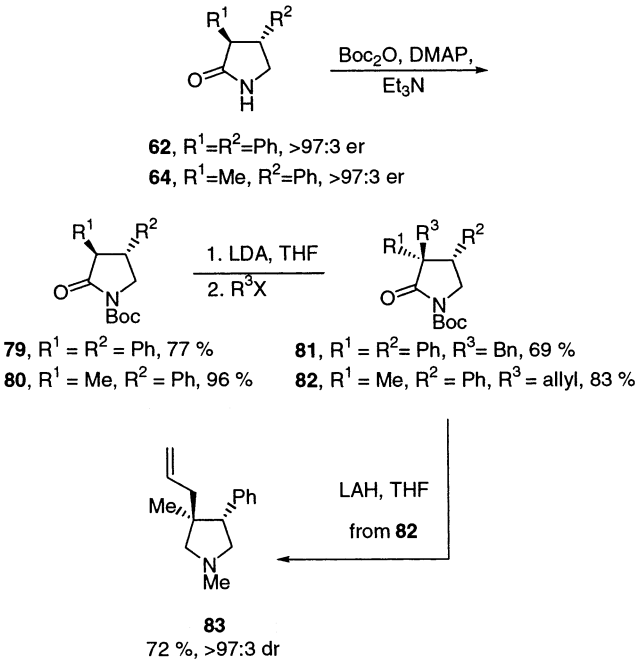
Hydrogenation of **36** and treatment with Boc_2O provides the *N*-Boc diamine **70,** which on reflux in KOtBu provides the pyrimidinone **71**.



Elaboration of the Cyclic *N*-Boc Amines. The disubstituted piperidones and pyrrolidinones can be used to provide more highly substituted enantioenriched piperidines and pyrrolidines; the illustrative cases reported here exhibit high diastereocontrol.

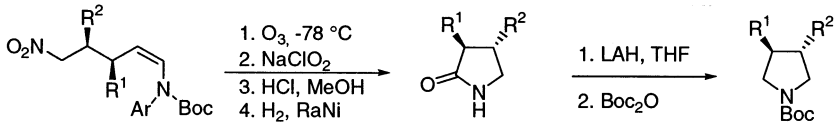
Enolate formation of the benzyl protected, 4,5-substituted piperidones **72**−**74** followed by reaction with electrophiles provided 3,4,5-substituted piperidones with high diastereoselectivities (Table 5). Optimal results were obtained when *t*-BuLi was used as the base for enolate formation. Alternative protecting groups such as Boc and amide bases gave inferior results. Reduction of the trisubstituted lactams with LAH provided the trisubstituted piperidines **75**−**78** in good yield and with high diastereomeric ratios.

Further substitution of the 3,4-substituted pyrrolidinones provides access to quaternary centers. In the case of **62** and **64**, Boc protection to give **79** and **80** followed by treatment with LDA and alkylations provides good yields of the trisubstituted products **81** and **82**. The relative configuration of **81** was determined by X-ray crystallographic analysis which reveals the electrophile prefers approach from the opposite face of the 4-substituent in the alkylation.[8] Reduction of **82** with LAH provides *N*-methyl pyrrolidine **83** containing a stereogenic quaternary center.



Stereocontrolled substitutions adjacent to nitrogen can be achieved by lithiation of the substituted *N*-Boc piperidines and pyrrolidines.[11] Treatment of **59** with 2.4 equiv of *sec*-BuLi/

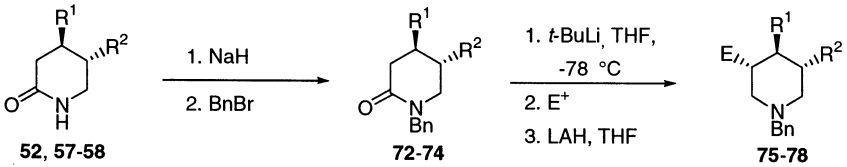
Table 4. Conversion of Enecarbamates **17**, **25**−**27** to Lactams **62**−**65** and Pyrrolidines **66**−**69**



entry	substrate	er	R^1	R^2	lactam	yield (%)	dr	pyrrolidine	yield (%)
1	**17**	96:4	Ph	Ph	**62**	61	>99:1[a]	**66**	52
2	**25**	>97:3	Me	Ph	**63**	48	>99:1[a]	**67**	82
3	**26**	>97:3	Me	*i*-Bu	**64**	65	>99:1[b]	**68**	79
4	**27**	>75:25	H	Ph	**65**	76	−	**69**	79

[a] Ester diastereomers are separable by chromatography. [b] Diastereomers separated by conversion to *N*−Boc derivative, chromatography, and deprotection.

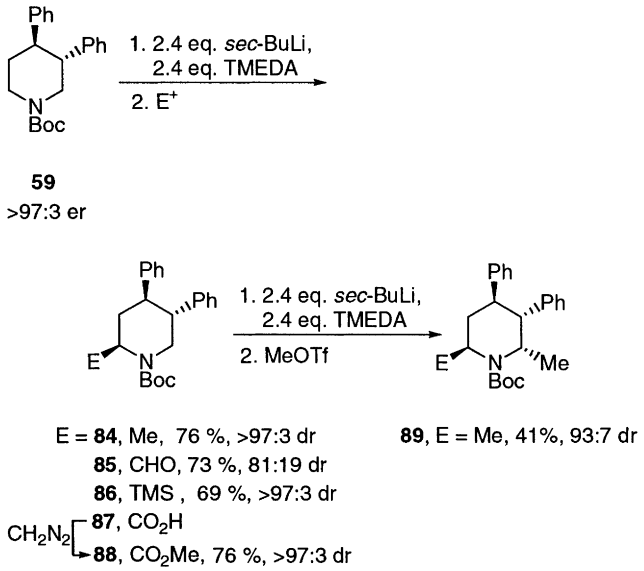
Table 5. Conversion of Lactams **52**, **57**, **58** to Trisubstituted Piperidines **75**−**78**



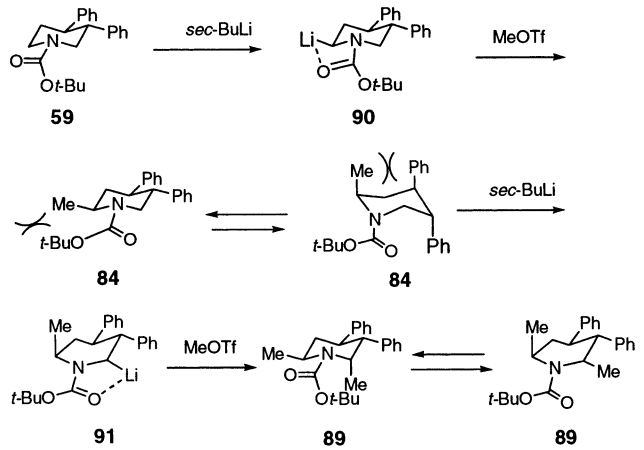
entry	substrate	er	R^1	R^2	benzylated	yield (%)	electrophile	E	piperidine	yield (%)	dr
1	**52**	>97:3	Ph	Ph	**72**	90	MeI	Me	**75**	76	>97:3
2	**52**	>97:3	Ph	Ph	**72**	90	BnBr	Bn	**76**	52[a]	>97:3
3	**58**	>97:3	Ph	Ph	**73**	85	BnBr	Bn	**77**	77	>97:3
4	**57**	>97:3	Ph	OTIPS	**74**	90	allylBr	allyl	**78**	77	>97:3

[a] LDA used base.

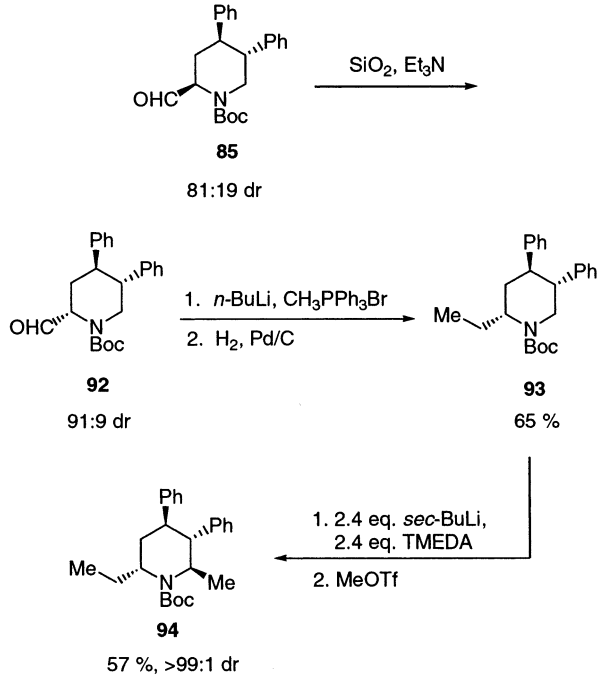
TMEDA followed by reaction with electrophiles provides 2,4,5-substituted piperidines **84**−**88** as single regioisomers in good yields and with high diastereoselectivities. Significantly less conversion to the desired product was observed using 1.2 equiv of *sec*-BuLi/TMEDA. The absolute configuration of **86**, verified by X-ray crystallographic analysis, confirms that the substituents are in equatorial orientations.[8] When the trisubsubstituted piperidine **84** is subjected to the same conditions followed by reaction with MeOTf, the tetrasubstituted piperidine **89** is obtained in 41% yield and 93:7 dr with a trans orientation of the substituents at the 2- and 6-positions.[11]



The stereochemistry and yields in the piperidine lithiations can be rationalized by analysis of the reaction pathways of the intermediate organolithium species. The lithiation of **59** is preferentially equatorial to provide intermediate **90**.[11] Substitution by MeOTf with retention provides the triequatorial substituted product **84**. For the second complex induced deprotonation to occur, rotation of the Boc group is necessary and would lead to an $A_{1,3}$ interaction between the 2-methyl substituent and the Boc group.[11] Although this strain can be relieved by a conformation which places the 2-substituent in the axial orientation, this would result in a 1,3-diaxial interaction with the 4-phenyl substituent. These interactions may force the intermediate in the second lithiation to adopt the twist boat illustrated by **91**, providing the trans stereochemistry observed at the 2- and 6-positions.



The $A_{1,3}$ interaction between the 2-substituent and the Boc group can control access to additional diastereomers of the substituted piperidines. The aldehyde **85** can be equilibrated with SiO_2 and Et_3N to provide the thermodynamically favored 2-axially substituted aldehyde **92**.[11] Olefination and hydrogenation provide the axial 2-ethyl substituted **93**, which on lithiation and substitution with MeOTf provides **94** as a single diastereomer.[12]

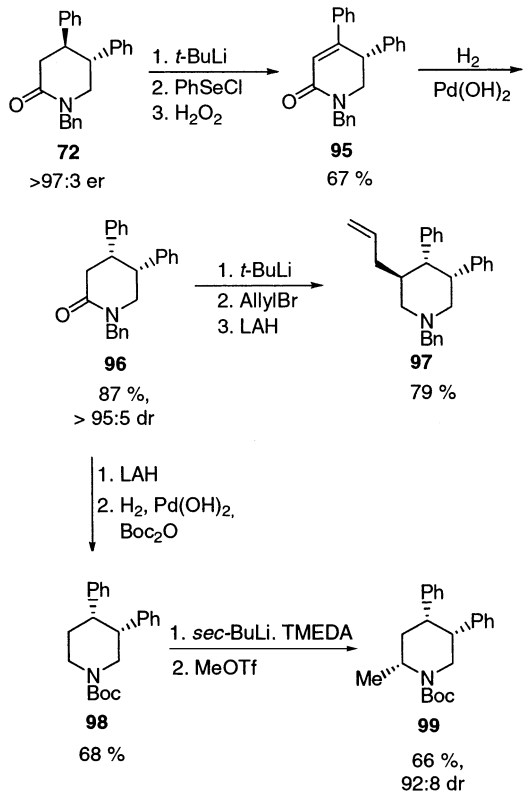


Although the stereochemistry of the piperidines **75**−**78** prepared from the conjugate addition products is trans 3,4-substituted, cis 3,4-substitution can be accessed through straightforward transformations and elaborated to trisubstituted piperidines. Enolate formation and substitution of **72** with *t*-BuLi and PhSeCl gives the selenide which on oxidation and elimination provides the unsaturated piperidone **95** in 67% yield. Catalytic hydrogenation from the least hindered face of **95** provides the *cis*-piperidone **96**. Further alkylation and reduction of **96** provides the 3,4,5-substituted piperidine **97** in 79% yield. The synthesis of a 2,4,5-substituted piperidine can be initiated by LAH reduction of **96** followed by exchange of the benzyl group for the Boc to provide the cis 3,4-substituted Boc piperidine **98**. Further α-lithiation and substitution with MeOTf provides 2,4,5-substituted **99** in 66% yield with 92:8 dr. The relative configuration of **99** was assigned by X-ray crystallographic analysis (Scheme 2).[8]

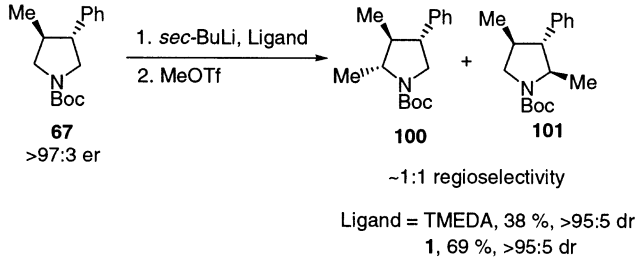
Substitution at the 2- and 5-positions of the 3,4-disubstituted pyrrolidine ring can also be achieved using lithiation/substitution methodology. Treatment of **67** with *sec*-BuLi/TMEDA and substitution with MeOTf provides **100** and **101** in a 1:1 ratio in

(11) (a) Lee, W. K.; Beak, P. *J. Org. Chem.* **1993**, *58*, 1109−1117. (b) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2001**, *3*, 3737.
(12) The higher diastereoselectivity of **94** relative to **89** may be associated with relief of the $A_{1,3}$ strain in the equatorially lithiated intermediate, resulting in **93** being more reactive toward equatorial lithiation.

Scheme 2



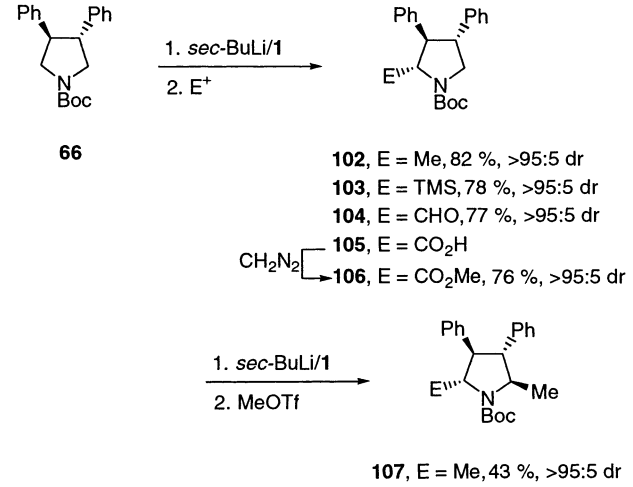
38% yield with >95:5 dr. A higher 69% yield was observed when using **1** as the ligand with the same product distribution.[13]



Lithiation of the C_2-symmetric *N*-Boc pyrrolidine **66** with *sec*-BuLi/**1** and substitution with a variety of electrophiles proceeds in good yields with high diastereoselectivities to give **102**−**105**. The absolute configuration of **102** was determined by conversion to the *N*-tosylate and X-ray crystallographic analysis.[8] Further lithiation of **102** and reaction with MeOTf provides **107** in 43% yield and >95:5 dr. The stereochemistry of **102** and **107** is consistent with asymmetric deprotonation of the *pro*-R proton of **66** with *sec*-BuLi/**1**, followed by substitution by MeOTf with retention (Scheme 3).

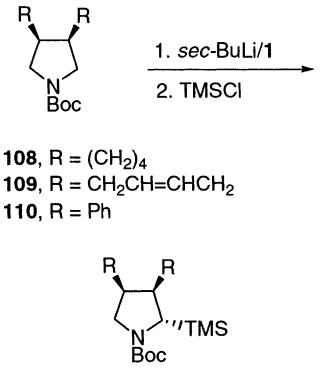
Although the geometry of the pyrrolidines **66**−**69** obtained from the sequences beginning with the conjugate addition is trans 3,4-substituted, an alternative route to the enantioenriched cis 3,4-substituted pyrrolidines is available by the asymmetric deprotonation of meso 3,4-substituted pyrrolidines. Treatment of **108**−**110** with *sec*-BuLi/**1** followed by substitution with (TMS)Cl provides the trisubstituted pyrrolidines **111**−**113**.

Scheme 3



However, no more than 50% conversion to the product is obtained with good diastereoselectivities and variable enantioselectivities. The absolute configuration of **111** was determined by conversion to the *N*-tosylate followed by X-ray crystallographic analysis.[8]

Deprotonation of the pro-*S* proton of *N*-Boc pyrrolidine is supported by calculations which reveal steric effects to be important in the transition state for proton removal.[13,14] Removal of the pro-*S* with *sec*-BuLi/**1** for **108**−**110** is consistent with the results with *N*-Boc pyrrolidine and does not appear to be sterically disfavored. However the selectivity with **66** is for deprotonation of the *pro*-R proton. Removal of the pro-*S* from **66** apparently would require approach of *sec*-BuLi/**1** from the same face as the phenyl substuent; thus, the steric effect of the phenyl substituent reverses the selectivity.



Synthesis of Enantiomeric Compounds. Because (−)-sparteine is the only readily available enantiomer, alternative approaches are required to access the enantiomeric products of reactions under control of this chiral ligand. Two approaches are demonstrated by the present work.

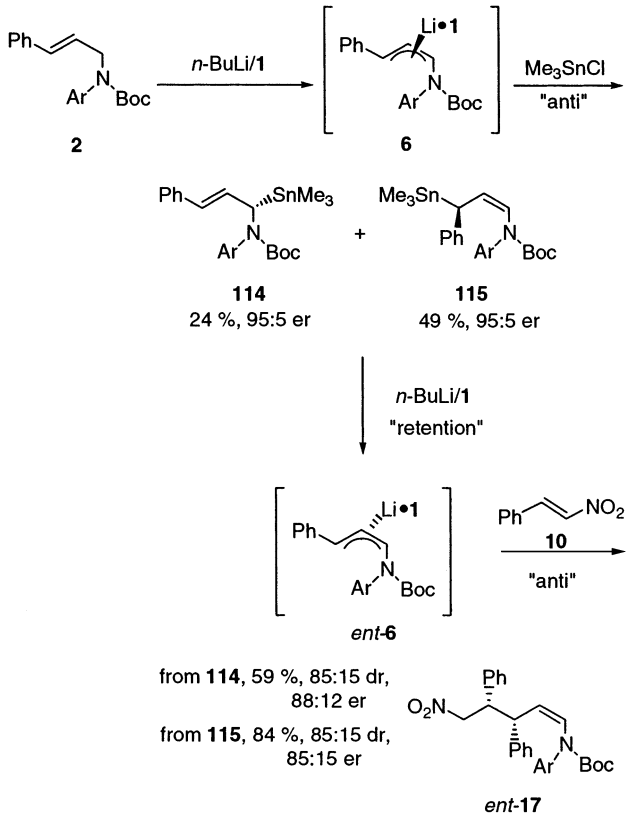
Epimeric structures of the diastereomeric organolithiums **6** and **34** can be generated by lithiation/stannylation followed by transmetalation.[15,16] The reversal in configuration is attributed

(13) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.

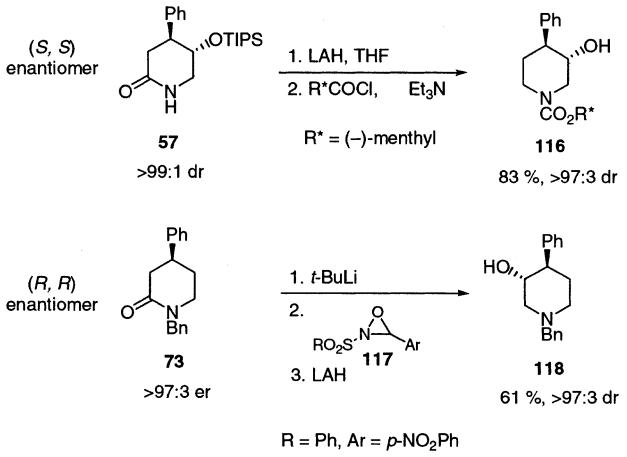
(14) (a) Wiberg, K. B.; Bailey, W. F. *J. Am. Chem. Soc.* **2001**, *123*, 8231. (b) Wiberg, K. B.; Bailey, W. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2127.

(15) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757.

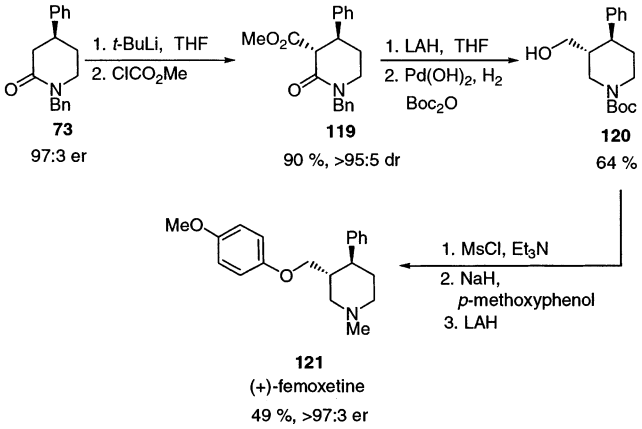
to stannylation by trimethylstannyl chloride with inversion, followed by transmetalation of the enantioenriched trimethylstannane with *n*-BuLi with retention. This approach is shown for the synthesis of *ent*-**17**. Transmetalation of stannanes **114** and **115**, which were generated by treatment of **6** with Me_3SnCl, provides *ent*-**6**.[16] Subsequent addition of **10** provides *ent*-**17** with reduced diastereoselectivities and enantioselectivities. The transmetalation step requires **1** as the ligand to maintain the configurational stability of *ent*-**6**.[17] The structure of *ent*-**17** was established by comparison of chiral HPLC retention times with those known for **17**.[2b]



The synthesis of both enantiomers of 3-hydroxy-4-phenyl piperidine, an intermediate in the synthesis of aspartic peptidase inhibitors,[18] is illustrative of another approach to enantiomeric compounds. Reduction of lactam **57**, which was synthesized by the conventional conjugate addition−cyclization route, by LAH followed by acylation provides the less active aspartic peptidase inhibitor intermediate **116** in high enantiomeric ratio. The LAH reduction also resulted in complete removal of the triisopropylsilyl protecting group. The (*R*,*R*)-enantiomer of 3-hydroxy-4-phenylpiperidine is accessed by elaboration of piperidone **73**. Enolization of **73** with *t*-BuLi followed by hydroxylation with oxaziridine **117** provides the opposite configuration of the 3,4-substituents. Further LAH reduction provides **118**, the more active enantiomer of the aspartic peptidase inhibitor intermediate.



We have previously reported the synthesis of the antidepressant (−)-paroxetine by this conjugate addition methodology. The antidepressant (+)-femoxetine **121**, which has the enantiomeric configuration to (−)-paroxetine, can be accessed by the enolization and substitution approach.[19] Treatment of **73** with *t*-BuLi and substitution with $ClCO_2Me$ provides **119** in 90% yield and >95:5 er. Reduction of both the amide and ester functionality by LAH, followed by exchange of the benzyl group with the Boc, provides intermediate **120** in 64%.[19] Conversion to the mesylate, displacement with the sodium salt of *p*-methoxyphenol, and LAH reduction of the Boc group provided (+)-femoxetine in 49% yield.

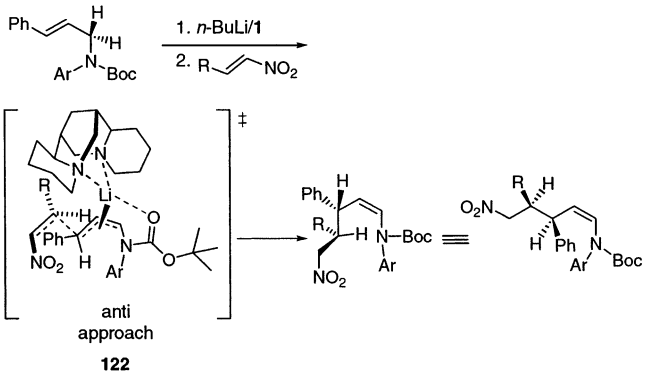


Reaction Pathway. Knowledge of the absolute configurations of the lithiated intermediates and products in the conjugate additions allows rationalization of the stereochemical course of the reactions. The formation of organolithiums **6** and **34** has been established to occur by asymmetric deprotonation of **2** and **28** with *n*-BuLi/**1**.[15,16a] The absolute configuration of **6** has been established by X-ray crystallographic analysis.[9] The known configurations of the enecarbamates **17**, **19**, **23**, **25,** and **27** (vide supra) reveals substitution of **6** with nitroalkenes occurs with inversion by anti approach of the nitroalkene. This is represented by **122**.

Assignment of the configuration to **34** from the X-ray structure of a tin precursor and an assumption of retentive tin lithium exchange as well as analogy to **6** in conjunction with

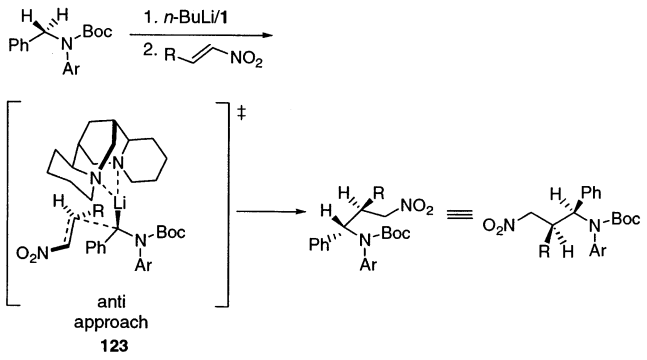
(16) (a) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218. (b) Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522.
(17) The erosion of the enantiomeric ratio of *ent*-**17** may indicate the transmetalation of **114** and **115** is not completely stereoselective.
(18) Bursavich, M. G.; Rich, D. H. *Org. Lett.* **2001**, *3*, 2625, and references therein.
(19) For previous syntheses see: Amat, M.; Bosch, J.; Hidalgo, J.; Canto, M.; Perez, M.; Llor, N.; Molins, E.; Miravitales, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074, and references therein.

the known absolute configurations of **36** and **39** shows an anti reaction pathway to also be operative in the conjugate additions of **34**. This leads to a transition-state representation as **123**.



122

Comparison of **122** and **123** shows differences with respect to the preferred reacting face of the nitroalkene. To the extent this simple analysis is credible, it suggests there is no dominant steric interaction that leads to a common transition structure for the allylic and benzylic additions. The preferred diastereomers may be a result of the sum of several steric interactions in the transition state, a result which has been found by computational analysis for a (−)-sparteine/*n*-BuLi deprotonation.[14]



123

Summary

Asymmetric syntheses of 3,4- and 3,4,5-substituted piperidines, 3,4-substituted pyrrolidnes, and 2,3-substituted pyrimidinones can be achieved by (−)-sparteine mediated lithiation of *N*-Boc-*N*-(*p*-methoxyphenyl) allylic and benzylic amines and conjugate addition to nitroalkenes. The 1,4-addition products serve as useful synthetic intermediates in the synthesis of highly enantioenriched products in high yields and diastereoselectivities. Access to a wide range of substitution patterns and diastereomers of these substituted ring systems is possible by further elaboration of intermediates. The stereochemical course of the conjugate addition has been established to involve substitution of the intermediate organolithiums with the nitroalkenes with inversion of configuration. The high selectivities and substituent compatability in the conjugate addition should render this methodology useful for the solution of future synthetic challenges.

Experimental Section

General Procedures. All lithiation reactions were performed in oven dried or flame dried glassware under a positive pressure of nitrogen with freshly distilled solvents. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone. Toluene and dichloromethane were distilled from CaH_2. (−)-Sparteine was distilled from the commercially available (Aldrich) compound and stored under nitrogen. Commercial *t*-BuLi (solution in pentane), *sec*-BuLi (solution in cyclohexane), and *n*-BuLi (solution in hexanes) were titrated prior to use against *N*-pivaloyl-*o*-toluidine according to literature procedure.[20] Nitroalkenes were either obtained from Aldrich or synthesized according to literature procedure.[21]

Representative Procedure for Lithiation and Conjugate Addition of *N*-Boc-*N*-(*p*-methoxyphenyl) Benzylic and Allylic to Nitroalkenes: (4-Methoxyphenyl)(5-nitro-3-phenyl-4-triisopropylsilanyloxypent-1-enyl)carbamic Acid *tert*-Butyl Ester (22). To a stirring solution of **2** (0.200 g, 0.588 mmol) in toluene (13 mL) under N_2 was added **1** (0.138 mL, 0.647 mmol). The solution was cooled to −78 °C, and *n*-BuLi (0.431 mL of a 1.50 M solution in hexanes, 0.452 mmol) was added. The yellow solution was stirred for 1 h at −78 °C, and *E*-2-triisopropylsilanoxy-1-nitroethylene[21a] (**15**; 0.202 g, 0.823 mmol) in toluene (2 mL) was added dropwise over 1 h by syringe pump. After complete addition, the solution was stirred for an additional 10 min at −78 °C, quenched with MeOH (1 mL) and warmed to room temperature. The solution was poured into water (10 mL) and brine (5 mL) and extracted with ether (3 × 15 mL). The combined organics were dried over $MgSO_4$ and concentrated to an orange oil. Purification by silica gel column chromatography (10:1 pet ether/EtOAc) gave **22** (0.286 g, 83%, 92:8 dr) as a colorless oil. Major diastereomer: ^{1}H NMR (acetone-d_6, 500 MHz) δ 0.95 (m, 3H, C*H*CH$_3$), 1.03 (m, 18H, C*H*CH$_3$), 1.39 (s, 9H, C(C*H*$_3$)$_3$, 3.35 (dd, 1H, J = 7.8, 5.3 Hz, C*H*Ph), 3.76 (s, 3H, OC*H*$_3$), 4.23 (dd, J = 12.6, 3.2 Hz, 1H, O$_2$NC*H*$_2$CH), 4.50 (dd, J = 12.6, 8.3 Hz, 1H, O$_2$NC*H*$_2$CH), 4.64 (ddd, J = 8.9, 6.8, 3.4 Hz, 1H, OC*H*), 5.32 (t, J = 9.0 Hz, 1H, C*H*═CHN), 6.70 (m, 2H, Ph*H*), 6.82 (m, 2H, Ph*H*), 6.83 (dd, J = 9.2, 1.5 Hz, 1H, CH═C*H*N), 6.79 (d, J = 9.2 Hz, 1H, CH═C*H*N), 6.96 (m, 2H, Ph*H*), 7.21 (m, 3H, Ph*H*); ^{13}C NMR (acetone-d_6, 125.6 MHz) δ 12.9 (CH), 17.9 (CH$_3$), 27.6 (CH$_3$), 47.3 (CH), 55.0 (CH$_3$), 74.8 (CH), 74.8 (C), 80.7 (CH$_2$), 113.6 (CH), 127.0 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 133.9 (C), 139.2 (C), 153.0 (C), 158.9 (C). Anal. Calcd for $C_{32}H_{48}N_2O_6Si$: C, 65.72; H, 8.27; N, 4.79. Found: C, 65.51; H, 8.12; N, 4.99.

Representative Procedure for Conversion of Enecarbamates to 5-Nitropentanoic Acid Methyl Esters. Conversion of 22 to 57, Part 1: 5-Nitro-3-phenyl-4-triisopropylsilanoxypentanoic Acid Methyl Ester. To a stirred solution of **22** (3.15 g, 5.39 mmol) in $CHCl_3$ (127 mL) was added 6 N HCl (9.74 mL). After 2 h, thin layer chromatography (TLC) indicated no remaining starting material and the mixture was poured into H_2O (100 mL) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organics were dried over $MgSO_4$ and concentrated. The residue was dissolved in *t*-BuOH (130 mL) and 2-methyl-2-butene (26.0 mL). A solution of $NaClO_2$ (4.45 g, 48.7 mmol) and NaH_2PO_4 (4.45, 36.9 mmol) in H_2O (44.0 mL) was added, and the resulting yellow solution was stirred for 10 min. The solution was poured into CH_2Cl_2 (180 mL) and acidified with 2.5% HCl (180 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 150 mL). The combined organics were dried over $MgSO_4$ and concentrated. Chromatography of the residue with 7:3 pet ether/EtOAc gave the crude acid which was esterified with an ethereal solution of diazomethane (3 equiv). Purification by column chromatography (10:1 pet ether/EtOAc) gave the title compound (1.56 g, 71%, 92:8 dr) as a colorless oil. Major diastereomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.13 (m, 21 H, ((C*H*$_3$)$_2$C*H*)$_3$Si), 2.77 (dd, J = 16.1, 10.9 Hz, 1H, C*H*$_2$CO$_2$Me), 3.07 (dd, J = 16.1, 4.5 Hz, 1H, C*H*$_2$CO$_2$Me), 3.61 (s, 3H, OC*H*$_3$), 3.63 (m, 1H, C*H*Ph), 4.18 (dd, J = 12.2, 4.3 Hz, 1H, C*H*$_2$NO$_2$), 4.31 (dd, J = 12.4, 8.0 Hz, 1H, C*H*$_2$NO$_2$), 4.88 (dt, J = 8.1, 4.1 Hz, 1H, C*H*OTIPS),

(20) Suffert, J. *J. Org. Chem.* **1989**, *54*, 510.
(21) (a) Denmark, S. E.; Juhl, M. *Helv. Chim. Acta*, submitted for publication. (b) Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185. (c) Denmark, S. E.; Marcin, L. *J. Org. Chem.* **1993**, *58*, 3850.

7.27 (m, 3H, Ph*H*), 7.35 (m, 2H, Ph*H*); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 12.7 (CH), 18.0 (CH_3), 18.0 (CH_3), 32.8 (CH_2), 46.0 (CH), 51.7 (CH_3), 73.1 (CH), 77.7 (CH_2), 127.6 (CH), 128.2 (CH), 128.8 (CH), 137.7 (C), 172.1 (C). Anal. Calcd for $C_{21}H_{35}NO_5Si$: C, 61.58; H, 8.61; N, 3.42. Found: C, 61.72; H, 8.54; N, 3.52.

Representative Procedure for Catalytic Hydrogenation and Cyclization to Lactams. Conversion of 22 to 57, Part 2: 4-Phenyl-5-triisopropylsilanyloxypiperidin-2-one (57). To a solution of the methyl ester (1.34 g, 3.27 mmol) in MeOH (50 mL) was added RaNi (~1.0 mL). The mixture was hydrogenated at 250 psi for 72 h. The catalyst was filtered, and the filtrate was concentrated to an opaque oil. Purification by column chromatography (3:2 pet ether/EtOAc) gave the title compound (0.886 g, 78%, >99:1 dr) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00 (m, 21 H, ($(CH_3)_2CH)_3Si$), 2.59 (dd, J = 17.8, 4.7 Hz, 1H, CHC*H*$_2$CON), 2.95 (dd, J = 17.8, 6.4 Hz, 1H, CHC*H*$_2$CON), 3.24 (m, 3H, C*H*Ph, NC*H*$_2$), 4.16 (dt, J = 5.6, 3.6 Hz, 1H, C*H*OTIPS), 7.21 (m, 3H, Ph*H*), 7.30 (m, 2H, Ph*H*), 7.37 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 12.2 (CH), 17.8 (CH_3), 17.9 (CH_3), 32.6 (CH_2), 45.2 (CH), 46.3 (CH_2), 69.3 (CH), 127.0 (CH), 127.3 (CH), 128.6 (CH), 140.9 (C), 172.2 (C). HRMS−FAB (M + 1). Calcd for $C_{20}H_{34}NO_2Si$: 348.2359. Found: 348.2359. $[\alpha]_D^{20}$: +7.1° (c = 1.95, $CHCl_3$).

Representative Procedure for Reduction to Piperidines: 3-(2-Methoxyphenyl)-4-phenylpiperidine-1-carboxylic Acid *tert*-Butyl Ester (61). To a solution of **55** (0.060 g, 0.213 mmol) in THF (1.5 mL) was added LAH (0.642 mL of a 1 M solution in THF, 0.642 mmol), and the solution was stirred at reflux for 4 h. The reaction was cooled to room temperature, quenched carefully with saturated Na_2SO_4, filtered, and concentrated. The crude residue was redissolved in CH_2Cl_2 (4 mL), and Boc_2O (0.073 mL, 0.319 mmol) was added. The solution was stirred for 1 h and concentrated. Purification by column chromatography (8:1 pet ether/EtOAc) **61** (0.064 g, 82%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.51 (s, 9H, O*t-Bu*), 1.81 (td, J = 12.6, 3.9 Hz, 1H, CHC*H*$_2$CH), 1.92 (m, 1H, CHC*H*$_2$CH), 2.90 (m, 2H, NC*H*$_2$), 3.06 (m, 1H, C*H*Ph), 3.47 (m 1H, C*H*Ph), 3.72 (s, 3H, C*H*$_3$-OPh), 4.29 (m 2H, NC*H*$_2$), 6.71 (d, J = 8.4 Hz, 1H, Ph*H*), 6.77 (t, J = 7.3 Hz, 1H, Ph*H*), 7.01−7.14 (m, 7H, Ph*H*); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 28.4 (CH_3), 34.7 (CH_2), 47.2 (CH), 55.3 (CH_3), 56.2 (CH_2), 60.3 (CH_2), 79.3 (C), 110.5 (CH), 120.3 (CH), 125.9 (CH), 127.2 (CH), 127.4 (CH), 127.9 (CH), 141.7 (C), 129.5 (C), 144.1 (C), 154.8 (C), 157.2 (C). HRMS−FAB (M + 1). Calcd for $C_{23}H_{30}NO_3$: 368.2226. Found: 368.2225. $[\alpha]_D^{20}$: −5.6° (c = 0.25, $CHCl_3$).

Representative Procedure for Conversion of Enecarbamates to 4-Nitrobutyric Acid Methyl Esters. Conversion of 17 to 62, Part 1: 4-Nitro-2,3-diphenylbutyric Acid Methyl Ester. A solution of **17** (3.15 g, 6.44 mmol) in CH_2Cl_2 (90 mL) was cooled to −78 °C. O_3 was bubbled through the solution until a purple solution persisted (~30 min). O_2 was then bubbled through the solution for 15 min at −78 °C followed by the addition of dimethyl sulfide (5 mL). The solution was slowly warmed to room temperature, stirred overnight, and concentrated. The residue was dissolved in *t*-BuOH (140 mL) and 2-methyl-2-butene (32.6 mL). A solution of $NaClO_2$ (5.43 g, 59.4 mmol) and NaH_2PO_4 (5.43 g, 45.0 mmol) in H_2O (54.0 mL) was added, and the resulting yellow solution was stirred for 10 min. The solution was poured into CH_2Cl_2 (220 mL) and acidified with 2.5% HCl (220 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 180 mL). The combined organics were dried over $MgSO_4$ and concentrated. Chromatography of the residue with 7:3 pet ether/EtOAc and then 5% AcOH gave the crude acid, which was redissolved in MeOH (90 mL) and treated with HCl (16.3 mL of a 2 N solution in Et_2O, 32.6 mmol). The solution was stirred for 72 h and concentrated. Purification of the residue by column chromatography (6:1 pet ether/EtOAc) gave the title compound (1.39 g, 72%, >99:1 dr) as a white solid: mp 84−86 °C (lit.[22] 100−136 °C; mixture of diastereomers) The ^{1}H NMR spectrum was consistent with reported literature values.[22]

Representative Procedure for Benzyl Protection of Piperidones: 1-Benzyl-4-phenylpiperidin-2-one (73). To a solution of **58** (0.400 g, 2.28 mmol) in THF (5 mL) under an N_2 atmosphere at room temperature was added NaH (0.164 g, 6.84 mmol), followed by benzyl bromide (1.36 mL, 11.4 mmol). The mixture was stirred overnight and carefully quenched with H_2O (10 mL). The aqueous layer was extracted with ether (3 × 15 mL), dried over $MgSO_4$, and concentrated. Purification by column chromatography (1:1 pet ether/EtOAc) gave **73** (0.514 g, 85%) as a white solid: mp 88−90 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.94 (m, 1 H, C*H*$_2$CHPh), 2.08 (m, 1 H, C*H*$_2$CHPh), 2.60 (dd, J = 17.6, 10.9 Hz, 1H, CHC*H*$_2$CO), 2.68 (ddd, J = 17.4, 5.1, 1.9 Hz, 1H, CHC*H*$_2$CO), 3.11 (tdd, J = 11.2, 5.2, 3.0 Hz, 1H, C*H*Ph), 3.29 (m, 2H, CHC*H*$_2$N), 4.58 (d, J = 14.5 Hz, 1H, PhC*H*$_2$N), 4.75 (d, J = 14.5 Hz, 1H, PhC*H*$_2$N), 7.19−7.37 (m, 10 H, Ph*H*); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 30.0 (CH_2), 38.5 (CH), 39.3 (CH_2), 46.2 (CH_2), 49.8 (CH_2), 126.4 (CH), 126.7 (CH), 127.3 (CH), 128.1 (CH), 128.5 (CH), 128.6 (CH), 137.0 (C), 143.3 (C), 169.1 (C). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.36; H, 7.24; N, 5.42. $[\alpha]_D^{20}$: −35.9° (c = 1.1, $CHCl_3$), >97:3 er lit.[23] $[\alpha]_D^{20}$: +35.0° (c = 1.1, $CHCl_3$), 96:4 er.

Representative Procedure for Enolization and Substitution of 2-Piperidones with *t*-BuLi. Conversion of 73 to 77, Part 1: 1,3-Dibenzyl-4-phenylpiperidin-2-one. To a solution of **73** (0.250 g, 0.942 mmol) in THF (19 mL) at −78 °C was added *t*-BuLi (0.606 mL of a 1.7 M solution in pentane, 1.03 mmol). After stirring 20 min, BnBr (0.224 mL, 1.88 mmol) was added, and the solution was stirred at −78 °C for 1.5 h and slowly warmed to room temperature. H_2O (20 mL) was added, and the aqueous was extracted with ether (3 × 20 mL). The combined ether extracts were dried over $MgSO_4$ and concentrated. Purification of the residue by column chromatography (7:3 pet ether/EtOAc) gave the title compound (0.285 g, 85%, >97:3 dr) as a colorless oil. Major diastereomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.89 (m, 2H, C*H*$_2$CHPh), 2.73 (dd, J = 13.9, 4.9 Hz, 1H, CHC*H*$_2$Ph), 2.84 (td, J = 9.6, 6.6 Hz, 1H, C*H*Ph), 3.09 (m, 2H, C*H*$_2$N, C*H*CH$_2$Ph), 3.48 (dd, J = 13.8, 4.9 Hz, 1H, CHC*H*$_2$Ph), 4.48 (d, J = 14.6 Hz, 1H, NC*H*$_2$Ph), 4.89 (d, J = 14.4 Hz, 1H, NC*H*$_2$Ph), 7.13−7.38 (m, 15H, Ph*H*); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 30.7 (CH_2), 34.8 (CH_2), 41.8 (CH), 46.2 (CH_2), 48.4 (CH), 50.7 (CH_2), 126.1 (CH), 126.8 (CH), 127.3 (CH), 127.3 (CH), 128.1 (CH), 128.5 (CH), 128.7 (CH), 130.0 (CH), 136.9 (C), 139.1 (C), 143.4 (C), 171.3 (C). HRMS−FAB (M + 1). Calcd for $C_{25}H_{26}NO$: 356.2014. Found: 356.2016.

Representative Procedure for Reduction of Benzyl Lactams to Benzyl Piperidines. Conversion of 73 to 77, Part 2: 1,3-Dibenzyl-4-phenylpiperidine (77). To a solution of 1,3-dibenzyl-4-phenylpiperidin-2-one (0.160 g, 0.450 mmol) in THF (9 mL) was added LAH (1.35 mL of a 1 M solution in THF, 0.1.35 mmol), and the solution was stirred at reflux for 4 h. The reaction was cooled to room temperature, quenched carefully with saturated Na_2SO_4, filtered, and concentrated. Purification by column chromatography (7:3 pet ether/EtOAc) gave **77** (0.137 g, 90%) as a colorless oil. Major diastereomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.85 (m, 3H, C*H*$_2$CHPh, CHC*H*$_2$Ph), 1.97 (td, J = 10.9, 4.1 Hz, 1H, C*H*$_2$N), 2.11 (m, 1H, C*H*CH$_2$Ph), 2.27 (m, 2H, C*H*Ph, C*H*CH$_2$Ph), 2.62 (d, J = 12.8 Hz, 1H, NC*H*$_2$), 2.94 (d, J = 11.2 Hz, 1H, NC*H*$_2$), 2.99 (d, J = 11.1 Hz, 1H, NC*H*$_2$), 3.35 (d, J = 13.1 Hz, 1H, NC*H*$_2$Ph), 3.68 (d, J = 13.1 Hz, 1H, NC*H*$_2$Ph), 7.03 (m, 2H, Ph*H*), 7.14−7.40 (m, 13H, Ph*H*); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 35.0 (CH_2), 38.3 (CH_2), 43.0 (CH), 49.3 (CH), 53.3 (CH_2), 59.8 (CH_2), 63.3 (CH_2), 125.7 (CH), 126.3 (CH), 126.9 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.6 (CH), 128.9 (CH), 129.2 (CH), 138.1 (C), 140.4 (C), 145.1 (C). HRMS−FAB (M + 1). Calcd for $C_{25}H_{28}N$: 342.2222. Found: 342.2223. $[\alpha]_D^{20}$: +26.7° (c = 1.25, $CHCl_3$).

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Representative Procedure for Boc-Protection of Pyrrolidinones: 4-Isobutyl-3-methyl-2-oxopyrrolidine-1-carboxylic Acid *tert*-Butyl Ester. To a solution of **64** (0.590 g, 3.80 mmol) in CH_2Cl_2 (25 mL) was added DMAP (0.464 g, 3.80 mmol), Et_3N (0.530 mL, 3.80 mL), and Boc_2O (1.75 mL, 7.60 mmol). The solution was stirred for 2 h at room temperature and concentrated. Purification of the residue by column chromatography (7:1 pet ether/EtOAc) provided the title compound (0.702 g, 72%, >99:1 dr) as a colorless oil. Major diastereomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (d, J = 6.6 Hz, 3H, CH_2CHMe_2), 0.92 (d, J = 6.7 Hz, 3H, CH_2CHMe_2), 1.18 (d, J = 6.9 Hz, 3H, $CHMe$), 1.26 (ddd, J = 13.5 9.4, 5.1 Hz, 1H, CH_2CHMe_2), 1.43 (ddd, J = 13.7, 9.2, 4.7 Hz, 1H, CH_2CHMe_2), 1.52 (m, 9H, $C(CH_3)_3$) 1.63 (m, 1H, CH_2CHMe_2), 1.88 (m, 1H, NCH_2CH), 2.12 (dq, J = 10.7, 7.1 Hz, 1H, CHMe), 3.13 (dd, J = 10.7, 9.7 Hz, 1H, NCH_2), 3.86 (dd, J = 10.7, 7.9 Hz, 1H, NCH_2); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 13.8 (CH_3), 21.8 (CH_3), 23.5 (CH_3), 25.7 (CH), 28.0 (CH_3), 37.4 (CH), 42.3 (CH_2), 45.1 (CH), 50.3 (CH_2), 82.7 (C), 150.3 (C), 176.2 (C). Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.77; H, 10.24; N, 5.63. $[\alpha]_D^{20}$: −55.4° (c = 1.3, $CHCl_3$).

Representative Procedure for Enolization and Substitution of 2-Pyrrolidinones with LDA: 3-Benzyl-2-oxo-3,4-diphenylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (81). To a solution of **79** (0.038 g, 0.112 mmol) in THF (2 mL) at −78 °C was added LDA (0.073 mL of a 2.0 M solution in THF, 0.145 mmol). After stirring 90 min, BnBr (0.04 mL, 0.336 mmol) was added and the solution slowly warmed to room temperature. The solution poured into saturated NH_4Cl (10 mL), and the aqueous layer was extracted with ether (3 × 10 mL). The combined ether extracts were dried over $MgSO_4$ and concentrated. Purification of the residue by column chromatography (9:1 pet ether/EtOAc) gave **81** (0.033 g, 69%, >97:3 dr) as a colorless oil. Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation from benzene/hexane: mp 136−138 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.55 (s, 9H, O*t-Bu*), 3.24 (d, J = 13.9 Hz, 1H, CH_2Ph), 3.57−3.70 (m, 4H, CH_2Ph, CHPh, CH_2N), 6.77 (m, 2H, Ph*H*), 6.93 (m, 2H, Ph*H*), 7.10−7.20 (m, 6H, Ph*H*), 7.31 (m, 1H, Ph*H*), 7.39 (m, 2H, Ph*H*), 7.47 (m, 2H, Ph*H*); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 28.0 (CH_3), 41.8 (CH_2), 44.2 (CH), 48.8 (CH_2), 61.4 (CH_2), 83.1 (C), 127.0 (CH), 127.1 (CH), 127.2 (CH), 127.9 (CH), 128.0 (CH), 128.0 (CH), 128.5 (CH), 129.3 (CH), 131.4 (CH), 136.9 (C), 136.9 (C), 139.3 (C), 149.7 (C), 175.6 (C). HRMS−FAB (M + 1). Calcd for $C_{28}H_{30}NO_3$: 428.2226. Found: 428.2226. $[\alpha]_D^{20}$: +34.3° (c = 1.0, $CHCl_3$).

Representative Procedure for Lithiation of Boc-3,4-Disubstituted Piperidines: 2-Methyl-4,5-diphenylpiperidine-1-carboxylic Acid *tert*-Butyl Ester (84). To a stirring solution of **59** (0.150 g, 0.444 mmol) in ether (4.6 mL) under N_2 was added TMEDA (0.161 mL, 1.07 mmol). The solution was cooled to −78 °C and *sec*-BuLi (0.730 mL of a 1.46 M solution in cyclohexane, 1.07 mmol) was added. The solution was stirred for 10 min at −78 °C, warmed to −25 °C for 1 h, and cooled back to −78 °C for 1 h. MeOTf (0.161 mL, 1.42 mmol) was added, and the solution was stirred for an additional 15 min at −78 °C, warmed to room temperature, and quenched with saturated NH_4Cl (5 mL). The aqueous layer was extracted with ether (4 × 10 mL) and dried over $MgSO_4$. Purification by column chromatography (25:1 pet ether/EtOAc) gave **84** (0.119 g, 76%, >97:3 dr) as a colorless oil. Major diastereomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (d, J = 6.1 Hz, 3 H, CH_3-CH), 1.46 (s, 9H, O*t-Bu*), 1.80 (q, J = 12.7 Hz, 1H, CH_3CHCH_2CH), 2.00 (ddd, J = 13.4, 6.1, 2.4 Hz, 1H, CH_3CHCH_2CH), 2.89 (m, 2H, CHPh), 3.64 (dd, J = 14.2, 6.2 Hz, 1H, NCH_2), 3.93 (dd, J = 14.2, 2.2 Hz, 1H, NCH_2), 4.12 (dquint, J = 12.3, 6.1 Hz, 1H, $NCHCH_3$), 7.02 (m, 4H, Ph*H*), 7.17 (m, 6H, Ph*H*); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.4 (CH_3), 28.5 (CH_3), 37.5 (CH_2), 44.6 (CH_2), 46.6 (CH), 49.6 (CH), 50.4 (CH), 79.4 (Cq), 126.2 (CH), 127.4 (CH), 127.6 (CH), 128.1 (CH), 128.2 (CH), 144.3 (C), 144.7 (C), 155.0 (C). Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.59; H, 8.34; N, 3.66. $[\alpha]_D^{20}$: +1.2° (c = 1.25, $CHCl_3$).

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Supporting Information Available: Experimental procedures for the preparation of compounds including data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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