Highly Diastereoselective and Enantioselective Carbon−Carbon Bond Formations in Conjugate Additions of Lithiated *N*-Boc Allylamines to Nitroalkenes: Enantioselective Synthesis of 3,4- and 3,4,5-Substituted Piperidines Including (−)-Paroxetine

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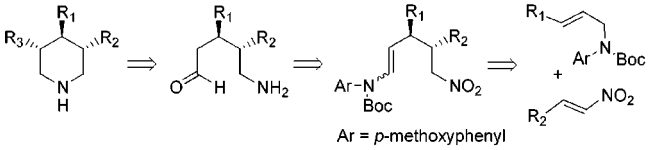
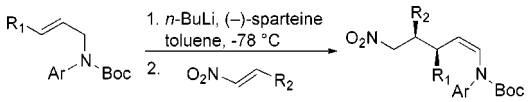
Carbon−carbon bond-forming reactions that create two stereogenic centers with high diastereo- and enantioselectivity in a single step can open new strategic approaches to valued structures. The piperidine ring is the central structure of many biologically active alkaloid natural products and pharmaceuticals.[1] General strategies which have been developed for the synthesis of enantioenriched, substituted piperidines utilize amino acids, chiral catalysts, and auxiliaries[2] and focus on asymmetric carbon substitution at the 2- and 6-positions.[2,3] Methods providing substitution at the 3-, 4-, and 5-positions of the piperidine ring are quite limited.[2,4] We now report the development of (−)-sparteine-mediated lithiation and conjugate addition of *N*-Boc-*N*-(*p*-methoxyphenyl)-allylamines to α,β-unsaturated nitro compounds. This addition occurs with high enantio- and diastereoselectivity and serves as the key step in the efficient synthesis of highly enantioenriched piperidines with substitution at the 3-, 4-, and 5-positions. The retrosynthetic analysis is shown below.



Treatment of *N*-Boc-*N*-(*p*-methoxyphenyl)allylamines **1**−**3** with *n*-BuLi in the presence of (−)-sparteine at −78 °C in toluene for 1 h generated a lithiated intermediate that underwent conjugate addition to nitroalkenes **4**−**8** and provided enecarbamates **10**−**16** in good yield and with high diastereo- and enantioselectivities as shown in Table 1.[5] The utilization of a variety of *N*-Boc allylamines and nitroalkenes allows for the incorporation of aliphatic (entries 2−3 and 7), aromatic (entries 1−7), and heterocyclic substituents (entries 5 and 6). After subsequent transformations, the enantiomeric ratios (er's) of diastereopure derivatives were determined to be >97:3 (vide infra).

Table 1. Conjugate Addition of *N*-Boc-*N*-(*p*-methoxphenyl)-allylamines **1**−**3** to Nitroalkenes **4**−**8**

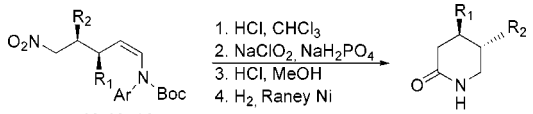


1-3 4-8 10-16

entry	substrate	R_1	nitro-alkene	R_2	product[a]	yield (%)	dr[b]
1	**1**	Ph	**4**	Ph	(*S*,*R*)−**10**[c]	90	94:6
2	**1**	Ph	**5**	Cy[d]	(*S*,*S*)−**11**	83	95:5
3	**1**	Ph	**6**	*i*-Bu	(*S*,*S*)−**12**	73	98:2
4	**1**	Ph	**7**	*o*-MeOPh	(*S*,*R*)−**13**	82	93:7
5	**1**	Ph	**8**	2-furyl	(*S*,*S*)−**14**	82	94:6
6	**2**	2-furyl	**4**	Ph	(*S*,*R*)−**15**	90	93:7
7	**3**	Me	**4**	Ph	(*S*,*R*)−**16**	74	90:10

[a] Enantiomeric ratios were assessed to be at a minimum of 90:10 by CSP-HPLC.[6] [b] Diastereomeric ratios were determined by ^{1}H NMR integration. [c] 96:4 er for major diastereomer.[5] [d] Cy = cyclohexyl.

Table 2. Conversion of Enecarbamates **10**−**13**, **16** to Lactams **17**−**21**

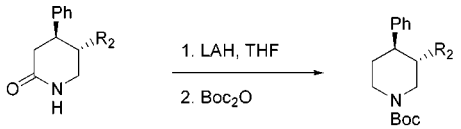


10-13, 16 17-21

entry	substrate	R_1	R_2	lactam	yield (%)	dr
1	(*S*,*R*)-**10**	Ph	Ph	(*R*,*R*)-**17**	59	>99:1
2	(*S*,*S*)-**11**	Ph	Cy	(*R*,*S*)-**18**	57	>99:1
3	(*S*,*S*)-**12**	Ph	*i*-Bu	(*R*,*S*)-**19**	71	>99:1
4	(*S*,*R*)-**13**	Ph	*o*-MeOPh	(*R*,*R*)-**20**	61	>99:1
5	(*S*,*R*)-**16**	Me	Ph	(*R*,*R*)-**21**	58	>99:1

Enecarbamates **10**−**13** and **16** were converted to the corresponding 4,5-disubstituted lactams **17**−**21** in good yields as shown in Table 2. Hydrolysis of the enecarbamates to the aldehydes, followed by oxidation and esterification,[7] provided nitroesters. Reduction and concomitant cyclization provided the lactams in good yield and as single diastereomers following recrystallization.

Lactams (*R*,*R*)-**17** and (*R*,*S*)-**19** were reduced with lithium aluminum hydride and treated with Boc_2O to provide 3,4-disubstituted piperidines (*R*,*R*)-**22** and (*S*,*R*)-**23**.



(*R*,*R*)-**17**, R_2 = Ph, (*R*,*S*)-**19**, R_2 = *i*-Bu

(*R*,*R*)-**22**, R_2 = Ph, 79 %
(*S*,*R*)-**23**, R_2 = *i*-Bu, 82 %

The enantiopurity of lactams **17**−**21** was assessed by derivatization with enantiopure (−)-menthylchloroformate directly or after reduction. In all cases, the enantiomeric ratio was assessed to be >97:3 by ^{1}H NMR, ^{13}C NMR, and GC. The absolute configurations of (*R*,*R*)-**17** and (*R*,*S*)-**19** were determined by X-ray crystallographic analysis of the *N*-*p*-bromobenzyl derivative.[8] All other configurations are assigned by analogy.

(1) (a) Elbein, A. D.; Molyneux, R. In *Alkaloids; Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley & Son: New York, 1987; Vol. 57, p 1. (b) It has been noted by Watson (Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679) that over 12 000 piperidines were in preclinical or clinical studies in a recent ten year period.

(2) For recent reviews, see: (a) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633. (b) Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3493.

(3) (a) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155. (b) Dawei Ma, D.; Sun, H. *Org. Lett.* **2000**, *2*, 2503. (c) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623. (d) Guilloteau-Bertin, B.; Compere, D.; Gil, L.; Marazano, C.; Das, B. C. *Eur. J. Org. Chem.* **2000**, 1391 and references therein.

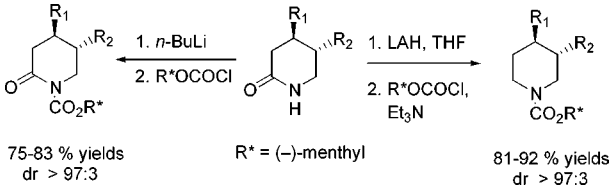
(4) For recent examples, see: (a) Amat, M.; Bosch, J.; Hidalgo, J.; Canto, M.; Perez, M.; Llor, N.; Molins, E.; Miravitales, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074. (b) Meyers, A. I.; Lamar, J. E.; Dwyer, M. P. *Tetrahedron Lett.* **1999**, *40*, 8965. (c) Ghosez, L.; Jnoff, E. *J. Am. Chem. Soc.* **1999**, *121*, 2617. (d) Schuffenhaur, A.; Borner, C.; Schneider, C. *Eur. J. Org. Chem.* **1999**, 3353.

(5) For the first report of this addition, see: Curtis, M. D.; Beak, P. *J. Org. Chem.* **1999**, *64*, 2996 and refernces therein.

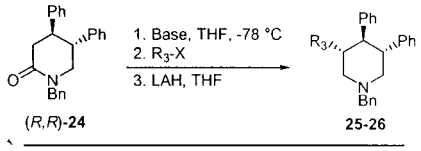
(6) Precise enantiomeric ratios could not be assessed due to low *E*/*Z* and disastereoselectivity in reactions utilizing achiral ligands. These reactions afforded chromatographically inseparable mixtures that do not allow for reliable analyses.

(7) Whisler, M. C.; Soli, E. D.; Beak, P. *Tetrahedron Lett.* **2000**, *41*, 9527.

10.1021/ja005748w CCC: $20.00
Published on Web 01/11/2001



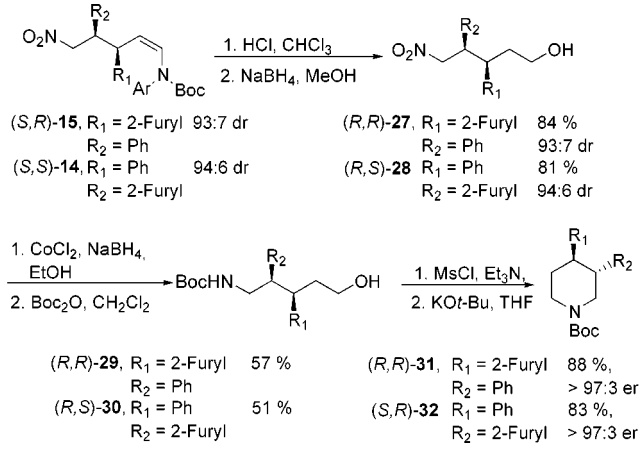
This methodology can be extended to 3,4,5-trisubstituted piperidines by substitution of 4,5-disubstituted lactams. Treatment of benzyl-protected lactam (*R*,*R*)-**24** with *t*-BuLi or LDA followed by substitution with electrophiles and subsequent lithium aluminum hydride reduction provided *N*-benzyl-3,4,5-trisubstituted piperidines (*R*,*R*,*R*)-**25** and (*R*,*R*,*R*)-**26** as single diastereomers.



base	R_3-X	R_3	product	yield (%)
t-BuLi	MeI	Me	(*R*,*R*,*R*)-**25**	76
LDA	BnBr	Bn	(*R*,*R*,*R*)-**26**	52

Because the 2-furyl substituent can be transformed to other functionalities, its location at the 3- or 4-position would be synthetically useful. The enecarbamates (*S*,*S*)-**14** and (*R*,*S*)-**15** were hydrolyzed and reduced to provide nitro alcohols (*R*,*R*)-**27** and (*R*,*S*)-**28** in good yields (Scheme 1). Further reduction[9]

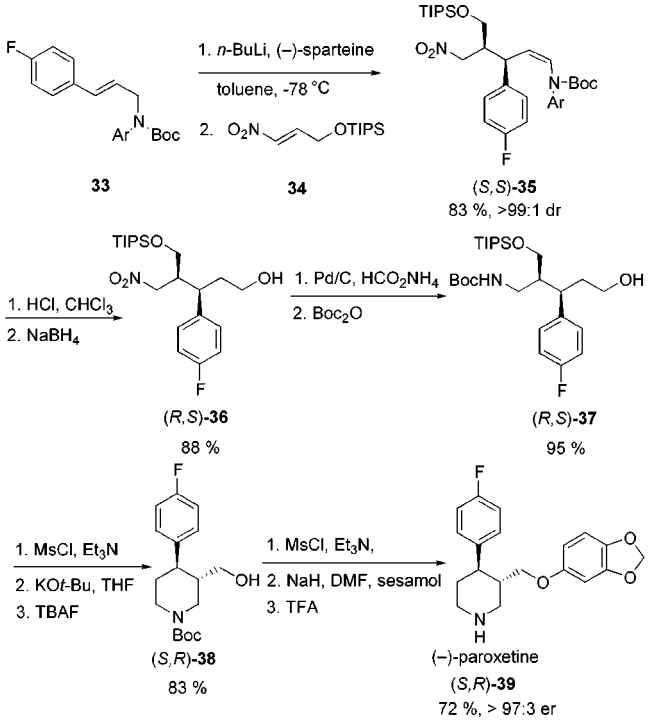
Scheme 1



followed by Boc protection provided the Boc-amino alcohols (*R*,*R*)-**29** and (*R*,*S*)-**30**. Cyclization was achieved by mesylation and treatment with KO*t*-Bu to provide Boc-piperidines (*R*,*R*)-**31** and (*S*,*R*)-**32** in good yield and with high er's.

We have demonstrated the synthetic utility of this methodology by an efficient synthesis of (−)-paroxetine ((*S*,*R*)-**39**), which is marketed as the hydrochloride, Paxil/Seroxat, a selective seratonin reuptake inhibitor.[10] Treatment of **33** with *n*-BuLi in the presence of (−)-sparteine under standard conditions followed by conjugate addition to nitroalkene **34** provided the desired enecarbamate (*S*,*S*)-**35** in 83% yield as a single diastereomer (Scheme 2).

Scheme 2



Hydrolysis and reduction of the resulting aldehyde provided nitro alcohol (*R*,*S*)-**36** in 88% yield. Reduction of the nitro functionality by transfer hydrogenation and subsequent Boc-protection afforded (*R*,*S*)-**37** in 95% yield. Cyclization and deprotection afforded (*S*,*R*)-**38** in 83% yield. Mesylation followed by displacement with sesamol and subsequent deprotection provided (*S*,*R*)-**39** in 72% yield and >97:3 er (11 steps, 41% from **33**.).

In summary, lithiation of *N*-Boc-*N*-(*p*-methoxyphenyl)allylamines in the presence of (−)-sparteine and subsequent conjugate addition to nitroalkenes provides *Z*-enecarbamates in good yields and with high enantio- and diastereoselectivity. These adducts are useful precursors to enantioenriched 3,4- and 3,4,5-substituted piperidines. In conjunction with our previous work,[3a] highly diastereo- and enantioselective substitution at every position of the piperidine ring can be achieved by lithiation/substitution methodology. Further exploration of the synthetic utility of the conjugate addition and determination of the origin of diastereoselectivity are areas of future interest.

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Supporting Information Available: Detailed experimental procedures including spectroscopic and analytical data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Crystallographic data for structures (*R*,*R*)-**17** and (*R*,*S*)-**19** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 145232 and 145233, respectively. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax (+44) 1223-336033; e-mail deposit@ccdc.cam.ac.uk).

(9) Chandler, M.; Conroy, R.; Cooper, A. W.; Lamont, R. B.; Scicinski, J. J.; Smart, J. E.; Storer, R.; Weir, N. G.; Wilson, R. D.; Wyatt, P. G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1189.

(10) Previous syntheses have utilized resolution of enantiomers, chiral auxiliaries, and most recently a porcine liver esterase catalyzed disymmetrization, see: (a) Yu, M. S.; Lantos, I.; Peng, Z.; Yu, J.; Cacchio, T. *Tetrahedron Lett.* **2000**, *41*, 5647. (b) Reference 4a and references therein.