

# Asymmetric Carbon–Carbon Bond Formations by Conjugate Additions of Lithiated *N*-Boc Allylic Amines to Nitroalkenes: Enantioselective Synthesis of Functionalized Cyclopentanoids

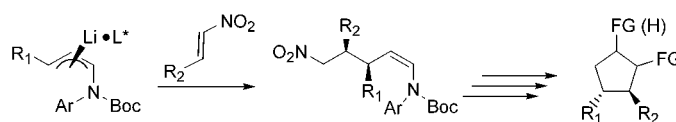
Timothy A. Johnson, Michael D. Curtis,<sup>†</sup> and Peter Beak\*

Department of Chemistry, Roger Adams Laboratory, University of Illinois at Urbana–Champaign, Urbana, Illinois 61801

beak@scs.uiuc.edu

Received June 1, 2002

## ABSTRACT



Allylic organolithiums generated by enantioselective deprotonation of *N*-Boc-*N*-(*p*-methoxyphenyl) allylic amines undergo conjugate additions with nitroalkenes to provide enecarbamates containing two contiguous stereogenic centers in good yields with high diastereoselectivities and enantioselectivities. Further elaboration of these adducts to enantioenriched substituted cyclopentanones and aminocyclopentanes is reported.

There are a number of strategies for the asymmetric synthesis of cyclopentanoids.<sup>1,2</sup> Often these are stimulated by the occurrence of the cyclopentane ring in biologically active compounds. For example, the trans-2,3-disubstituted cyclopentanone structure is found in the E series of 11-deoxyprostaglandins,<sup>3</sup> and aminocyclopentanoids have been reported to be potent glycosidase inhibitors.<sup>2a</sup>

We have recently reported the (–)-sparteine-mediated lithiations of *N*-Boc-*N*-(*p*-methoxyphenyl) allylic amines, and

subsequent conjugate additions to nitroalkenes provides enecarbamate products that contain two contiguous stereogenic centers in good yields with high diastereoselectivity and enantioselectivity. We have demonstrated that these adducts serve as useful precursors to highly substituted piperidines and pyrrolidines.<sup>4,5</sup> We now report that these asymmetric conjugate additions can be key steps in the syntheses of 2,3-disubstituted cyclopentanones and cyclopentylamines with high enantioenrichments.

Treatment of *N*-Boc-*N*-(*p*-methoxyphenyl) allylic amines **1** and **2** with *n*-BuLi and (–)-sparteine at –78 °C provides configurationally stable organolithiums **3** and **4**, which on conjugate additions to nitroalkenes **5** and **6** provide enecar-

<sup>†</sup> Present address: Procter and Gamble Pharmaceuticals, PO Box 191, Norwich, NY 13825.

(1) For general approaches to cyclopentanoids, see: Hudlicky, T.; Price, J. D.; *Chem. Rev.* **1989**, 89, 1467.

(2) For recent asymmetric syntheses of cyclopentanoids, see: (a) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1998**, 63, 6178. (b) Barluenga, J.; Tomas, M.; Ballesteros, A.; Santamaria, J.; Brillet, C.; Garcia-Granda, S.; Pinera-Nicolas, A.; Vazquez, J. T. *J. Am. Chem. Soc.* **1999**, 121, 4516. (c) Trost, B. M.; Pinkerton, A. B. *J. Org. Chem.* **2001**, 66, 7714. (d) La, D. S.; Sattely, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, 123, 7767.

(3) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, 97, 107.

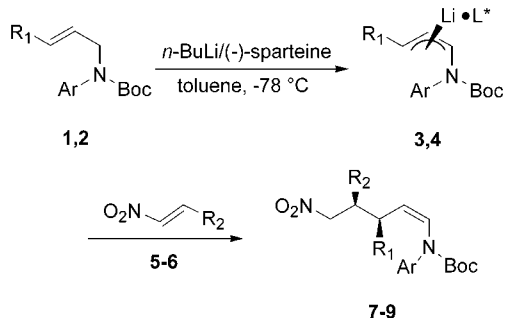
(4) (a) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, 123, 1004. (b) Johnson, T. A.; Jang, D. O.; Slafer, B. W.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.*, submitted for publication.

(5) For conjugate additions of lithiated allylic amines to other activated olefins, see: (a) Park, Y. S.; Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1997**, 119, 10537. (b) Curtis, M. D.; Beak, P. *J. Org. Chem.* **1999**, 64, 2996. (c) Lim, S. H.; Curtis, M. D.; Beak, P. *Org. Lett.* **2001**, 3, 711. (d) Lim, S. H.; Beak, P. *J. Am. Chem. Soc.*, submitted for publication.

bamates **7–9** in good yields and with good diastereomeric (dr) and enantiomeric ratios (er).<sup>4,5</sup>

Both aryl- and alkyl-substituted allylic amines and nitroalkenes can be utilized in the conjugate addition to give the conjugate addition products in good yields with high selectivities. The absolute configurations of **7** and **8** have been determined previously by X-ray crystallographic analysis of derivatives.<sup>4a</sup> The absolute configuration of **9** is assigned by analogy.

**Table 1.** Conjugate Addition of *N*-Boc-*N*-(*p*-Methoxyphenyl)allyl amines **1** and **2** to Nitroalkenes **5** and **6**

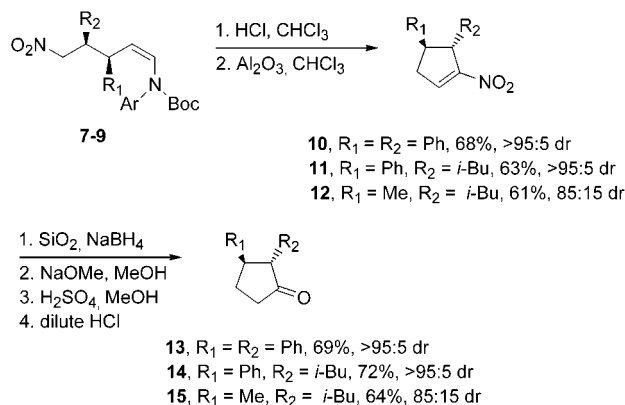


entry	amine	R <sub>1</sub>	nitroalkene	R <sub>2</sub>	product	yield (%)	dr <sup>a</sup>	er <sup>b</sup>
1	<b>1</b>	Ph	<b>5</b>	Ph	<b>7</b>	90	94:6	96:4 <sup>c</sup>
2	<b>1</b>	Ph	<b>6</b>	<i>i</i> -Bu	<b>8</b>	73	98:2	>97:3
3	<b>2</b>	Me	<b>6</b>	<i>i</i> -Bu	<b>9</b>	74	84:16	>97:3

<sup>a</sup> Diastereomeric ratios were determined by <sup>1</sup>H NMR integration.  
<sup>b</sup> Enantiomeric ratios of diastereopure derivatives. <sup>c</sup> Enantiomeric ratios were determined by CSP-HPLC.

The enecarbamates **7–9** are readily converted to 2,3-disubstituted cyclopentanones by the transformations shown in Scheme 1. Acidic treatment of **7–9** provides the nitro-

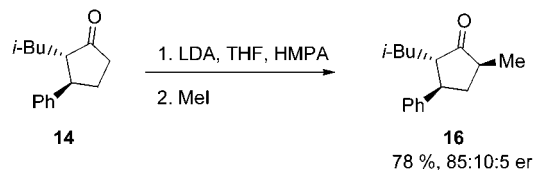
**Scheme 1**



aldehydes with the necessary 1,5-relationship between the functional groups for intramolecular cyclization to a cyclopentane ring. Subsequent heating at reflux of the crude

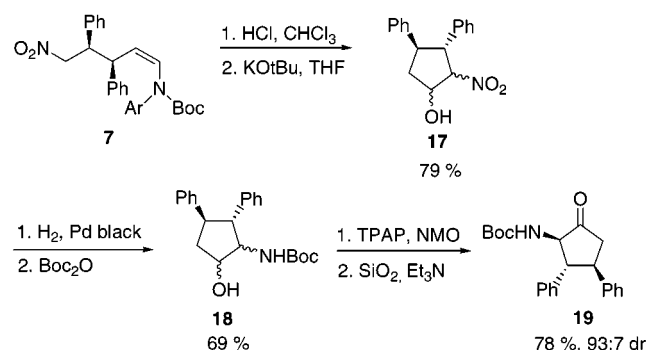
aldehydes with basic alumina results in intramolecular nitroaldol reaction and dehydration to provide the nitroalkenes **10–12**.<sup>6</sup> Reduction of nitroalkenes **10–12** with NaBH<sub>4</sub><sup>7</sup> using the conditions reported by Borchardt provides crude nitroalkanes that can be converted to trans-2,3-disubstituted cyclopentanones **13–15** in good yields by a Nef reaction.<sup>8</sup>

Elaboration of the 2,3-disubstituted cyclopentanones to 2,3,5-trisubstituted cyclopentanones can be diastereoselective. Treatment of **14** with LDA at –78 °C in THF/HPMA followed by substitution with MeI provides the trisubstituted cyclopentanone **16** in 78% yield and good diastereoselectivity.



An amine group can be introduced at the 2-position of a 3,4-disubstituted cyclopentanone from **7** by reduction of the nitro functionality and subsequent transformations. The approach is shown in Scheme 2. Hydrolysis of **7** followed

**Scheme 2**

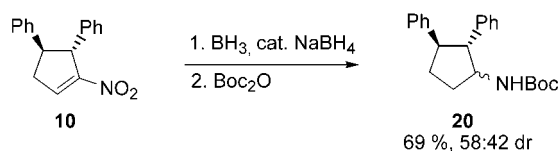


by treatment of the resulting nitroaldehyde with KO<sup>t</sup>-Bu provides nitro alcohol **17** in 79% yield as a mixture of diastereomers. Hydrogenation of the nitro group and treatment of the resulting amine with Boc<sub>2</sub>O furnishes Boc-amino alcohol **18** in 69% yield. Oxidation of the alcohol with TPAP/NMO provides ketone **19** in 79% yield and 93:7 dr. Although the diastereomeric ratio of crude **19** is 80:20, column chromatography in the presence of Et<sub>3</sub>N allows equilibration of **19** to a thermodynamic product ratio of 93:7.

The nitroalkene **10** can be an intermediate for synthesis of a 2,3-disubstituted cyclopentylamine as demonstrated by the conversion of **10** to **20**. Reduction of the double bond and nitro group, accomplished in a single step using

- (6) Ballini, R.; Castagnani, R.; Petri, M. *J. Org. Chem.* **1992**, *57*, 2160.  
 (7) Sinhababu, A. K.; Borchardt, R. T. *Tetrahedron Lett.* **1983**, *24*, 227.  
 (8) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716.

$\text{BH}_3 \cdot \text{THF}$  with a catalytic amount of  $\text{NaBH}_4$ ,<sup>9</sup> followed by Boc protection of the crude amine provided **20** in 69% yield, albeit as a 58:42 mixture of diastereomers.



In summary, we have developed a new approach for the asymmetric synthesis of functionalized substituted cyclopentanoids. The key carbon–carbon bond formation is a (–)-sparteine-mediated lithiation of *N*-Boc-*N*-(*p*-methoxyphenyl) allylic amines followed by conjugate addition to nitroalkenes. The nitro enecarbamate products of the conjugate addition

can readily be converted to a number of substituted cyclopentanone and cyclopentylamine derivatives. Since either epimer of the lithiated intermediates can be obtained, this approach can be useful to provide both enantiomers of the products.<sup>4b,10</sup> Further development of this methodology is anticipated.

**Acknowledgment.** We are grateful to the National Institutes of Health (GM-18874) for support of this work.

**Supporting Information Available:** Experimental procedures for the preparation of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL026277G

(9) Kabalka, G. W.; Guindi, L. H. M. *Tetrahedron* **1990**, *46*, 7443.

(10) The epimers of **3** and **4** can be produced by a stannylation–lithiation sequence, albeit with some loss of enantioselectivity.