ORGANIC LETTERS

2001
Vol. 3, No. 5
711−714

Asymmetric Syntheses of Fused Bicyclic Compounds by Conjugate Additions of Allylic Organolithium Species to Activated Olefins and Subsequent Cyclizations

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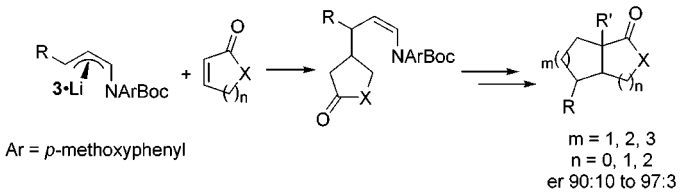
Received December 18, 2000

ABSTRACT



Addition of the configurationally stable organolithium species produced by enantioselective deprotonation of *N*-Boc-*N*-(*p*-methoxyphenyl) allylamines to α,β-unsaturated carbonyl compounds affords 1,4-addition products in good yields with high diastereomeric and enantiomeric ratios. Further transformations of these compounds provide [3.3.0]-, [4.3.0]-, [5.3.0]-, and [5.4.0]-carbocycles and heterocycles with high stereoselectivities.

The stereoselective synthesis of bicyclic ring compounds is of particular interest as a result of the high occurrence of its core skeletal framework in numerous biologically important compounds, namely, steroids. As a result several stereoselective strategies have been developed and utilized to access these ring systems, including [3 + 2] annulations,[1] Robinson annulations,[2] and Michael addition techniques.[3] Of the several strategies available to solve this problem, stereoselective Michael additions have the capacity to allow fusion of differently sized carbocyclic and heterocyclic rings onto the Michael acceptor.

We have developed an asymmetric organolithium-based conjugate addition methodology mediated by the chiral ligand (−)-sparteine.[4] The products obtained from the conjugate addition reactions are precursors to a number of synthetically useful compounds, including 3,4- and 3,4,5-substituted piperidines.[5] The focus of this report is further exploration of the synthetic utility to prepare bicyclic ring compounds.

The organolithium species employed in these conjugate addition reactions are generated by treatment of *N*-Boc allylamines **1** or **2** with *n*-BuLi and (−)-sparteine at −78 °C in toluene.[6,7] Addition of the lithiated intermediate **4** to

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(1) Peng, Z. H.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 1379.

(2) (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 1. (b) Gawley, R. E. *Synthesis* **1976**, 777.

(3) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (b) Feringa, B. L. *Acc. Chem. Res*. **2000**, *33*, 346. (c) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc*. **1999**, *121*, 1104 and references therein.

(4) (a) Park, Y. S.; Weisenberger, G. A. *J. Am. Chem. Soc.* **1997**, *119*, 10537. (b) Curtis, M. D.; Beak, P. *J. Org. Chem.* **1999**, *64*, 2996.

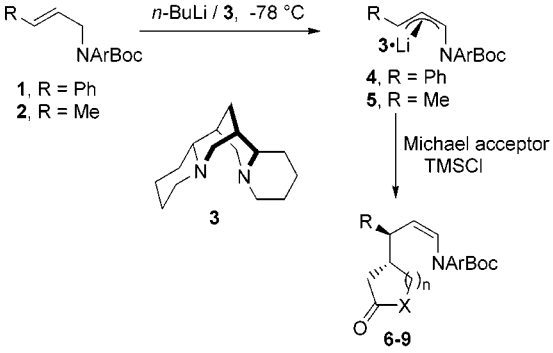
(5) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.*, in press.

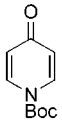
(6) (a) Pippel, D. J.; Weisenberger, G. A.; Wilson, S. R.; Beak, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2522. (b) Pippel, D. J.; Weisenburger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.*, in press. The configuration of **4** has been established by X-ray crystallography. The configuration of **5** is assumed to be analogous to a cyclohexyl derivative, a η^1 coordinated monomer, but it may be η^1 or η^3.

10.1021/ol007012+ CCC: $20.00
Published on Web 02/02/2001

both five- and six-membered α,β-unsaturated lactones provides the corresponding conjugate addition products **6** and **7** in 71% and 85% yields, respectively, with high enantioselectivities and diastereoselectivities as shown in Table 1

Table 1. Allylic Organolithium Conjugate Addition Reactions



entry	amine	acceptor	product	% yield	dr	er
1	**1**		**6**, n = 1	71%	>95:5	97:3
2	**1**		**7**, n = 2	85%	89:11	96:4[a]
3[b]	**2**		**8**	62%	83:17	98:2[a]
4	**1**		**9**	80%	93:7	90:10[a]

[a] For the major diastereomer. [b] TMSCI was not required in this reaction.

(entries 1 and 2). In the absence of trimethylsilyl chloride (TMSCl), the yield of the reaction decreased significantly. The rate of addition of electrophile also affected the yield, suggesting that the enolate formed upon addition is reactive under these conditions and that the TMSCl prevents side reactions.

The absolute configuration of **7** has been determined by X-ray crystallographic analysis of an (*S*)-(−)-1-(1-naphthyl)-ethylamine derivative.[6a] The allylic organolithium species **5** derived from the crotyl allylamine **2** reacts with 2-cyclohexenone to give highly enantioenriched **8** (entry 3). Reaction of the organolithium species **4** with *N*-Boc-pyridin-4-one gives **9** in 80% yield as a 93:7 mixture of diastereomers with an enantiomeric ratio (er) of 90:10 for the major diastereomer (entry 4).[8,9]

(7) Toulene was used for the standard reaction conditions since it provided product with the highest enantiomeric ratio. Although the standard time for the deprotonation step is 1 h, recent kinetic studies has shown that the deprotonation step requires only few minutes.[6b]

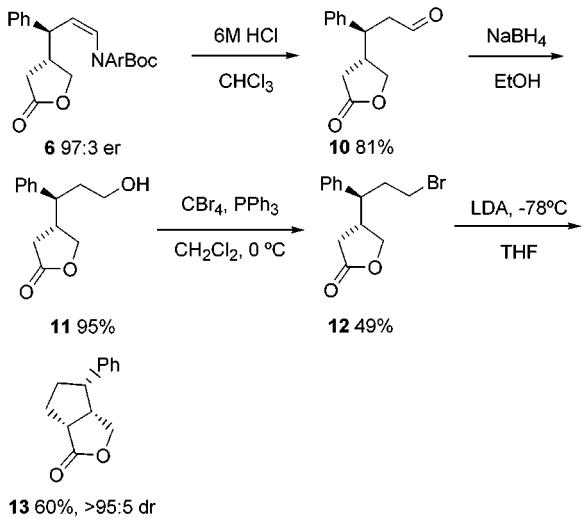
(8) The absolute configuration of **9** was assigned by derivatization and X-ray crystallography using anomalous dispersion. The determination of the absolute configuration is detailed in Supporting Information.

(9) The crystallographic data for derivative of **9**, **16**, and **37** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 154907, 154565, and 154566, 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; email: deposit@ccdc.cam.ac.uk).

The functionalized conjugate addition products **6**−**9** can be efficiently elaborated to [3.3.0]-, [4.3.0]-, [5.3.0]-, and [5.4.0]-carbocyclic and heterocyclic compounds. Our approach provides bicyclic ring constructions of five-, six-, and seven-membered rings to an existing ring scaffold with control of diastereoselectivity and enantioselectivity at the new stereogenic centers.

Closure to Five-Membered Rings. The formation of five-membered rings can be effected with the carbon skeleton of the initial conjugate addition products. The elaboration of Michael adducts **6** and **7** to bicarbocyclic compounds utilizes the ability to unmask an enecarbamate to a corresponding β-substituted aldehyde. As demonstrated in Scheme 1, acid

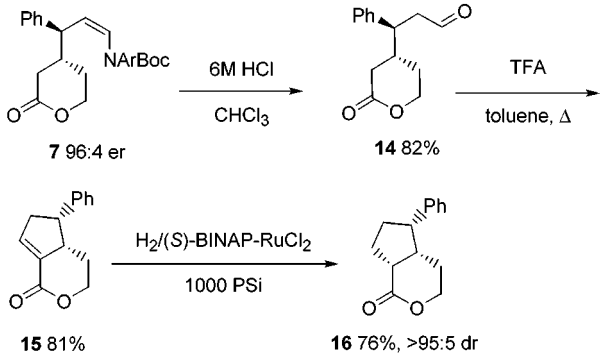
Scheme 1



hydrolysis of **6** provides aldehyde **10**, which on reduction with $NaBH_4$ gives alcohol **11**. Subsequent bromination and cyclization of **12** with LDA in THF at −78 °C affords [3.3.0] bicyclic compound **13** in 60% yield with >95:5 dr.

Cyclization of **7** to the [4.3.0] bicarbocyclic compound **16** was accomplished through a modified route as shown in Scheme 2. Hydrolysis of the major diastereomer of **7** provided the β-substituted aldehyde **14** in 82% yield.

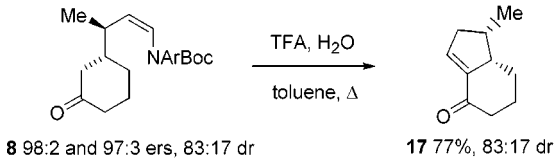
Scheme 2



Subsequent reflux in trifluoroacetic acid and toluene afforded the product **15** in 81% yield. Hydrogenation of **15** with (*S*)-BINAP-$RuCl_2$ provided the [4.3.0] bicyclic compound **16** in 76% yield as a single diastereomer. The relative stereochemistry of **16** has been established from X-ray crystallography, which indicates the hydrogenation of **15** affords *cis*-fused carbocycles (Scheme 2).[9]

With cyclohexenone as the electrophile, asymmetric lithiation−substitution of **1** resulted in mixtures of 1,2- and 1,4-addition products in low yields with poor diastereoselectivity. However, the reaction sequence is more selective with *N*-Boc-*N*-(*p*-methoxyphenyl) crotylamine **2**. Conjugate addition of the organolithium **5** to cyclohexenone in *tert*-butyl methyl ether (MTBE) afforded **8** in 62% yield with enantiomeric ratios of 98:2 and 97:3 for the major and minor diastereomers, respectively.[4a] The Michael adduct **8** was cyclized with solution of TFA/H_2O in toluene in a single step to afford the [4.3.0] bicyclic compound **17** in 77% yield as a mixture of diastereomers (Scheme 3).

Scheme 3

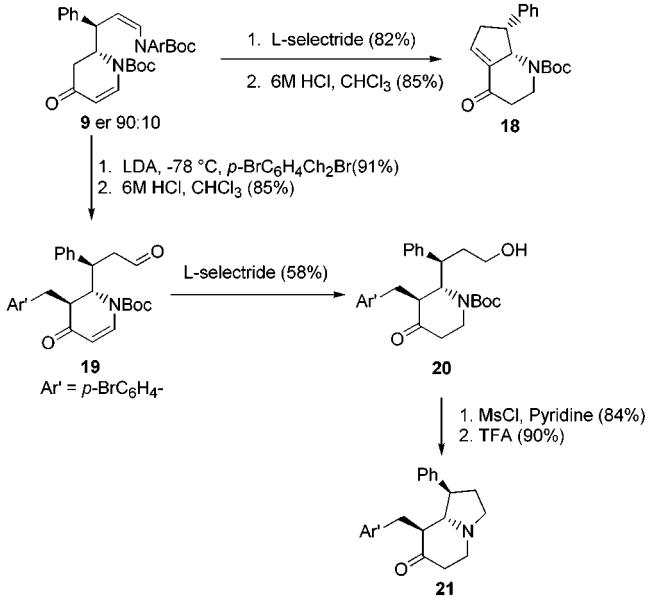


8 98:2 and 97:3 ers, 83:17 dr — **17** 77%, 83:17 dr

The conjugate addition product **9** was reduced with L-selectride prior to subsequent hydrolysis of the enecarbamate provided the [4.3.0] product **18** in 85% yield as shown in Scheme 4.

To effect cyclization onto nitrogen, the carbon α to the carbonyl was blocked prior to hydrolysis using conventional

Scheme 4

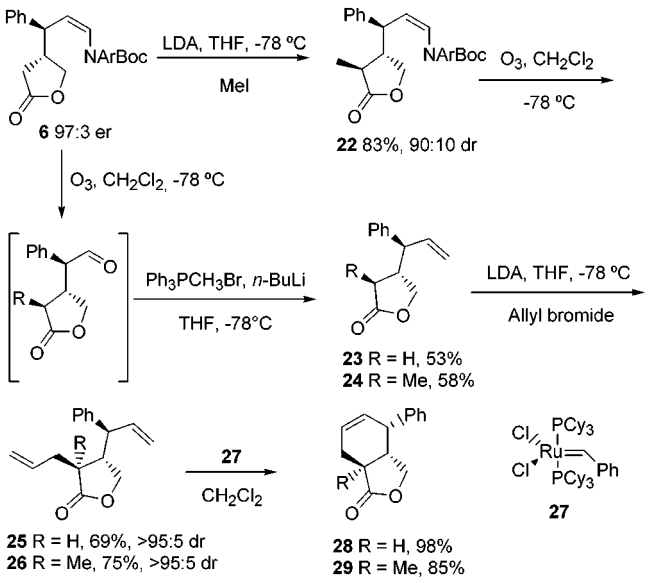


enolate chemistry with *p*-bromobenzyl bromide as the alkylating agent. Hydrolysis of the *trans*-alkylated product provided the aldehyde **19** in 85%. Reduction of both the aldehyde and ring double bond with L-selectride provided the corresponding alcohol, which was converted to the mesylate in 84% yield. Deprotection of the ring nitrogen followed by cyclization gave **21** with the [4.3.0] skeletal structure of an indolizidine alkaloid.

Closure to Six-Membered Rings. Construction of rings with more than three carbon atoms requires alteration of the carbon skeleton of the initial enecarbamate adduct. The strategy we have implemented involves using the Grubbs ring closing metathesis (RCM) reaction as the key step in the formation of the new six- or seven-membered ring, after incorporation of two olefinic groups by oxidation, olefination, and allylation.[10] This strategy allows also efficient and highly enantioselective formation of a quaternary center.

A Wittig reaction of the aldehyde formed by ozonolysis of the enecarbamate functionality provided one olefin, and the other was incorporated using enolate chemistry with allyl bromide as the electrophile. The ozonolysis of **6** or **22** followed by a reductive workup with Me_2S gave the corresponding aldehydes as shown in Scheme 5. Each of

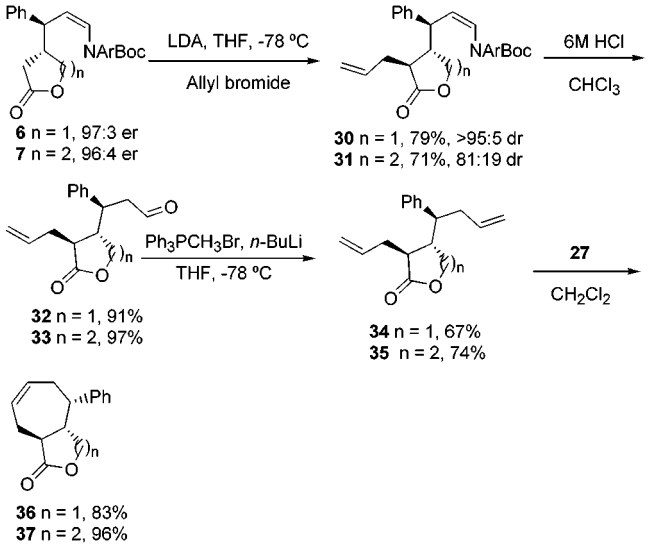
Scheme 5



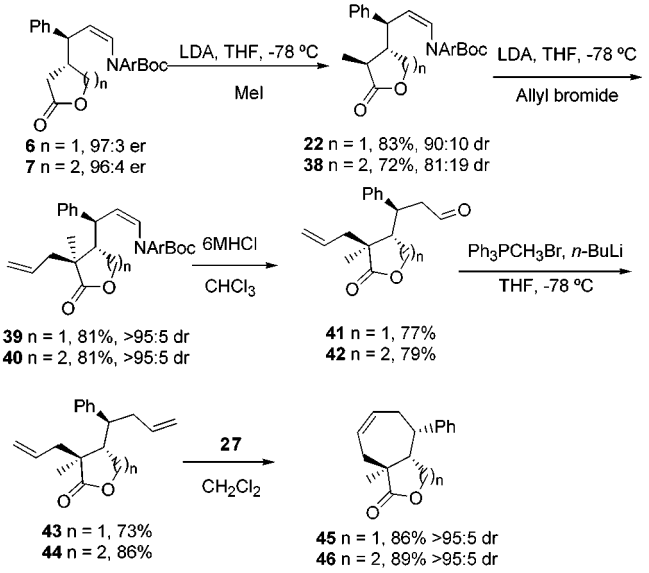
the aldehydes was used directly in the Wittig reaction to give the alkenes **23** and **24**. ^1H NMR analysis indicated no epimerization had occurred at the benzylic position. Alkylation of the enolate derived from the lactone **23** or **24** with allyl bromide provided the corresponding dienes **25** and **26,** which were cyclized with the Grubbs catalyst **27**, bis-(tricyclohexylphosphine) benzylidene ruthenium dichloride.

(10) (a) Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192. (b) Martin, S. F.; Chen, H. J.; Courtney, A. K.; Liao, Y.; Patzel, M.; Rmser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251. (c) Houri, A. F.; Xu, Z.; Cogan, D.; Hoveyda, A. H.; *J. Am. Chem. Soc.* **1995**, *36*, 1621. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

Scheme 6



Scheme 7



The [4.3.0]-bicyclic compounds **28** and **29**, with three contiguous stereogenic centers, were isolated in 98% and 85% yields, respectively. The synthesis of **29** demonstrates control of a quaternary center by this approach.

Closure to Seven-Membered Rings. We have applied a similar RCM strategy to the construction of seven-membered rings as shown in Scheme 6. Treatment of the Michael adducts **6** or **7** with LDA at −78 °C followed by addition of allyl bromide affords **30** and **31** in good yields and moderate to high diastereoselectivities. Hydrolysis of **30** or the major diastereomer from **31** leads to the corresponding aldehydes **32** and **33** in 91% and 97% yields, respectively. Wittig olefination provided the dienes **34** and **35**, which undergo RCM to give the highly enantioenriched [5.3.0] and [5.4.0] carbocyclic compounds **36** and **37** in good yields. The relative stereochemistry at the ring junction for **37** has been established from X-ray crystallography, which indicates the alkylation and subsequent RCM strategy affords *trans*-fused bicarbocyclic products as shown in Scheme 6.[9]

The enecarbamate **38** was prepared from **7** by a reaction analogous to that used for **22** as shown in Scheme 7. A second enolate−alkylation reaction of **22** or **38** with allyl bromide selectively incorporates the quaternary stereogenic center, providing **39** and **40** both in 81% yield. Hydrolysis and subsequent olefination provides the required dienes **43** and **44** for RCM. Ring closure reactions provided the [5.3.0] and [5.4.0] carbocyclic compounds **45** and **46** with three contiguous stereogenic centers, including one quaternary center.

In summary, the transformations described herein proceed with high enantioselectivity and diastereoselectivity in the construction of both carbocycles and heterocycles. On the basis of the high diastereoselectivies observed with several other Michael acceptors,[4] we expect that this approach will be widely applicable.

Acknowledgment. This work was supported by a grant from the National Institute of Health (GM-18874). We are grateful for this support. We thank Timothy A. Johnson for determining the absolute configuration of **9**.

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

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