ORGANIC LETTERS

2000
Vol. 2, No. 17
2655−2658

Highly Enantioselective Syntheses of *anti* Homoaldol Products by (−)-Sparteine-Mediated Lithiation/Transmetalation/Substitution of *N*-Boc Allylic Amines

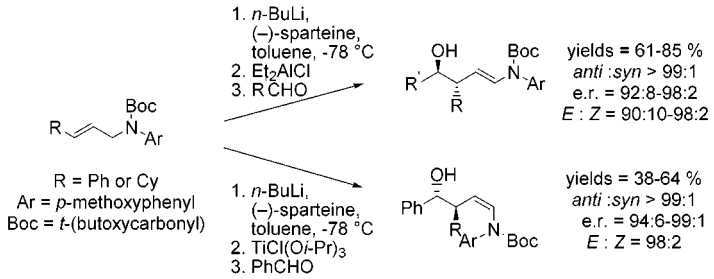
Marna C. Whisler, Louis Vaillancourt, and Peter Beak*

Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

beak@scs.uiuc.edu

Received June 9, 2000

ABSTRACT



(−)-Sparteine-mediated lithiation/transmetalation/substitution of *N*-Boc allylic amines provides *anti*-configured homoaldol precursors in yields of 38−85% and enantiomeric ratios of 83:17−99:1. Subsequent *O*-protection and hydrolysis allows access to *O*-protected homoaldol adducts in good yields. The absolute configurations of the homoaldol products have been assigned by calculation of optical rotations and by X-ray crystallography of derivatives. A stereochemical course of reaction for the lithiation/transmetalation/substitution sequence is proposed.

Homologated aldol products are an important class of organic compounds that are generally prepared by the reaction of a homoenolate synthetic equivalent with aldehydes or ketones.[1] In our laboratories, *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine[2] **1** and *N*-Boc-*N*-(*p*-methoxyphenyl)-3-cyclohexylallylamine[3] **2** have been shown to undergo metalation with *n*-BuLi/(−)-sparteine to provide chiral homoenolate equivalents. We now report that these lithiated allylamine derivatives can be transmetalated, reacted with aldehydes, and hydrolyzed to afford *anti* homoaldol adducts in good yields and enantiomeric ratios. This methodology allows entry into a class of synthetically useful compounds. Hoppe et al. have reported homoenolate synthetic equivalents from the lithiation/transmetalation/substitution of (*E*)- and (*Z*)-2-butenyl carbamates[4] and (*E*)-3-trimethylsilyl-2-propenyl carbamates.[5]

Treatment of allylic amines **1** or **2** with *n*-BuLi/(−)-sparteine results in lithiated complexes with assigned configurations.[6] Reaction of these lithiated intermediates with

(1) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. For a review of chiral homoenolate equivalents, see: Ahlbrecht, H.; Beyer, U. *Synthesis* **1999**, 365.

(2) (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.

(3) Pippel, D. J.; Weisenburger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.*, submitted for publication.

(4) Hoppe, D.; Lichtenberg, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 239. For reviews, see: (a) Hoppe, D.; Krämer, T.; Schwark, J.-R.; Zschage, O. *Pure Appl. Chem.* **1990**, *62*, 1999. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282.

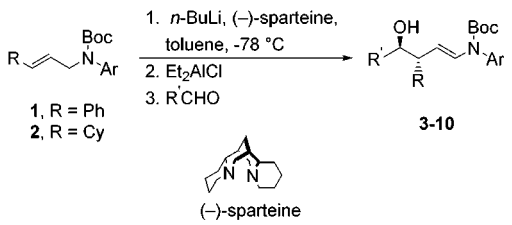
(5) (a) van Hülsen, E.; Hoppe, D. *Tetrahedron Lett.* **1985**, *26*, 411. (b) Zschage, O.; Schwark, J.-R.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657. (c) Marsch, M.; Harms, K.; Zschage, O.; Hoppe, D.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 321.

10.1021/ol006186o CCC: $19.00
Published on Web 07/28/2000

aldehydes provides a mixture of products with low diastereoselectivity. However, if the lithiated intermediate is transmetalated before addition of aldehyde electrophile, high yields of diastereomerically pure products can be obtained. Absolute configuration and *E*/*Z* selectivity in the masked homoaldol products are controlled by the transmetalating reagent. Thus, transmetalation with Et_2AlCl, $Ti(O\textit{i}\text{-}Pr)_4$, or $TiCl(O\textit{i}\text{-}Pr)_3$ allows access to the desired olefin geometry and absolute configuration.

The results of our standard protocol for these masked homoaldol reactions are shown in Table 1. The allylic amine

Table 1. Results from Lithiation/Et_2AlCl Transmetalation/Substitution Sequences



entry	R	R′	product	yield (%)[a]	er[b]	*E*:*Z*
1	Ph	Ph	**3**	85	97:3	90:10
2	Ph	Me	**4**	66	92:8	95:5
3	Ph	*i*-Pr	**5**	61	95:5	98:2
4	Ph	Cy	**6**	66	98:2	95:5
5	Cy	Ph	**7**	82	94:6	90:10
6	Cy	Me	**8**	72	93:7	97:3
7	Cy	*i*-Pr	**9**	81	94:6	98:2
8	Cy	Cy	**10**	84	95:5	98:2

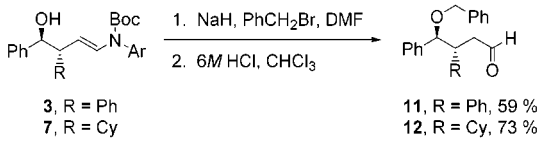
[a] The reported yield is a mixture of *E* and *Z* isomers of opposite absolute configuration. If the isomers are not separated, the er of the product would be reduced when carried through the hydrolysis sequence. Separation of the *E* and *Z* isomers of **3** was achieved by preparative HPLC. [b] In all cases, the ratio *anti*:*syn* > 99:1.

1 or **2** is treated with *n*-BuLi/(−)-sparteine at −78 °C and subsequently transmetalated with Et_2AlCl. The reaction is stirred for 45 min before addition of the aldehyde. After workup, homoaldol precursors **3**−**10** are obtained in good yields. As shown in Table 1, high *E*/*Z* selectivities and good *anti*:*syn* and enantiomeric ratios are obtained upon additions to benzaldehyde (entries 1 and 5) and three alkyl aldehydes (entries 2−4, 6−8).

In all cases, the relative configuration of the two newly formed stereogenic centers is *anti* and the *E* geometrical isomer is the primary product. Deblocking of the enamide to the aldehyde functionality is performed in two steps, as is demonstrated by two examples in Scheme 1. The alcohol functionality is protected with NaH/benzyl bromide to provide the *O*-benzyl enecarbamate. Acid hydrolysis of the crude enecarbamate affords the aldehydes **11** or **12** as *O*-protected homoaldol products.

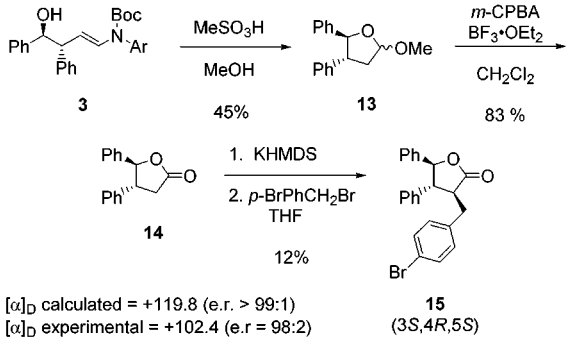
(6) The configuration of the lithiated intermediate of **2** is assigned by analogy to that of **1**, which has been established by X-ray crystallography. See: Pippel, D. J.; Weisenburger, G. A.; Wilson, S. R.; Beak, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2522.

Scheme 1



The absolute configurations of the homoaldol precursors **3** and **7** were assigned by two methods. The enamides **3** and **7** were converted to the lactones **14** and **17** respectively, and values for the signs and magnitudes of the optical rotations for **14** and **17** were calculated.[7] The $[\alpha]_D$ value calculated for **14** is +119.8 (er > 99:1), while the experimental $[\alpha]_D$ is +102.4 (er = 98:2). For **17**, the calculated $[\alpha]_D$ value is +48.1 (er > 99:1), while the experimental $[\alpha]_D$ is +23.4 (er = 94:6). The absolute configurations shown in Schemes 2 and 3 are in accord with experimental values.

Scheme 2



The absolute configuration of **3** was also established by preparation of **15**, a compound suitable for X-ray diffraction. Methanolysis of **3** and subsequent oxidation[8] of **13** provides lactone **14**. Enolization of **14** with KHMDS and *p*-bromobenzyl bromide provides crystalline (3*S*,4*R*,5*S*)-diphenylbutyrolactone (**15**), whose absolute configuration was assigned by X-ray crystallography using anomolous dispersion (Scheme 2).[9]

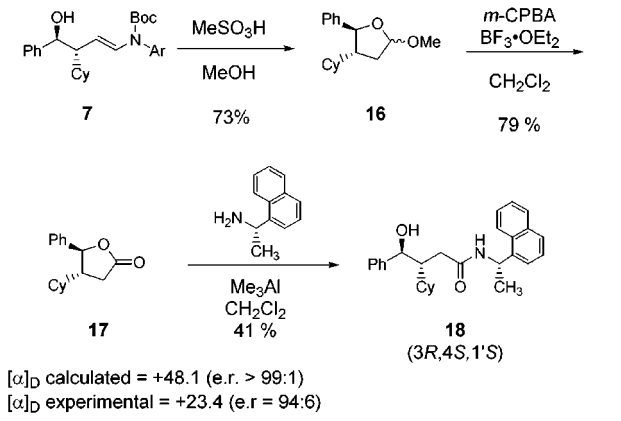
Derivatization and X-ray crystallography were carried out to establish the absolute configuration of cyclohexyl allylic amine **7**. Lactone **17** was prepared by a sequence similar to that used for the cinnamylamine derivative. Compound **17** underwent ring opening with (*S*)-(−)-1-(1-naphthyl)-ethylamine in the presence of Me_3Al[10] to give crystalline

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

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

(9) The crystallographic data for **15** and **18** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 145026 and 145027, 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).

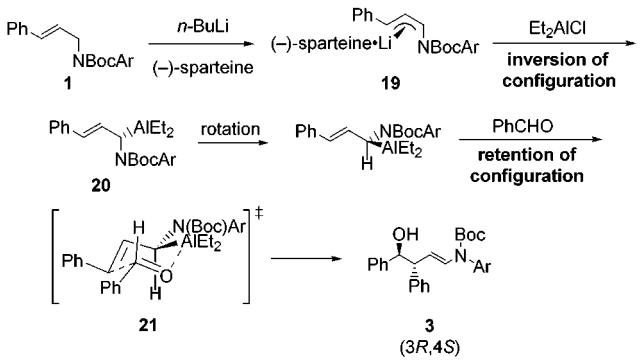
Scheme 3



(3*R*,4*S*,1′*S*)-**18**, a product with known configuration at one stereogenic center (Scheme 3).

The absolute configurations of both **3** and **7** reveal overall inversion of configuration from the organolithium intermediate. Scheme 4 illustrates the proposed stereochemical course

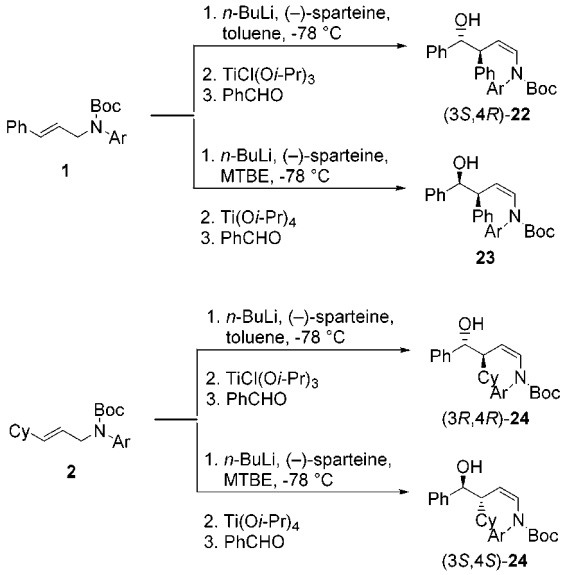
Scheme 4



of the reaction of cinnamylamine derivative **1**, *n*-BuLi/(−)-sparteine, Et_2AlCl, and benzaldehyde. Reaction of **1** with *n*-BuLi/(−)-sparteine affords the η^3 complex **19** with known configuration as shown.[6] Transmetalation with Et_2AlCl proceeds with inversion of configuration to give **20**. The reaction of **20** with benzaldehyde is proposed to occur through six-membered transition state **21**[11] with retention of configuration to provide (3*R*,4*S*)-**3**.[12] The proposed stereochemical course of reaction for the cyclohexyl allylic amine is analogous, although the Li•(−)-sparteine complex is known to be coordinated in an η^1 fashion to the cyclohexyl allylic amine.[3]

Treatment of the lithiated intermediate of **1** or **2** with a titanium reagent and subsequent reaction with electrophile

Table 2. Results from Lithiation/Titanium Transmetalation/Substitution Sequences



entry	transmetalation reagent	product	yield (%)	*anti*:*syn*[a]	er[b]
1	$TiCl(O\textit{i}\text{-}Pr)_3$	**22**	64	>99:1	>99:1
2	$Ti(O\textit{i}\text{-}Pr)_4$	**23**	63	46:54	95:5[c]
3	$TiCl(O\textit{i}\text{-}Pr)_3$	**24**	38	>99:1	94:6
4	$Ti(O\textit{i}\text{-}Pr)_4$	**ent-24**	69	>99:1	84:16

[a] In all cases, the ratio *E*:*Z* is 98:2. [b] The er reported is of the major diastereomer. [c] The er reported is of the *syn* diastereomer, the absolute configuration of which has not been assigned. The er of the major enantiomer of the *anti* diastereomer (3*S*,4*R*) is 83:17.

provides the *Z*-enecarbamates **22**−**24**, as shown in Table 2. Use of $TiCl(O\textit{i}\text{-}Pr)_3$ for transmetalation allows access to the *Z*-homoaldol precursors with absolute configurations opposite to those reported in Table 1. Transmetalation of the lithiated intermediate of **1** with $TiCl(O\textit{i}\text{-}Pr)_3$ is presumed to proceed with inversion of configuration. Subsequent reaction with PhCHO provides **22** (Table 2, entry 1). The lithiated intermediate of **1** may not undergo transmetalation with $Ti(O\textit{i}\text{-}Pr)_4$ and therefore exhibits little facial selectivity in reaction with benzaldehyde (*anti*:*syn* = 46:54, Table 2, entry 2).[13] In fact, reaction of the lithiated intermediate of **1** with isobutyraldehyde provides the homoaldol precursor **5** with an *anti*:*syn* ratio of 44:56.

Transmetalation of the lithiated intermediate of **2** with $TiCl(O\textit{i}\text{-}Pr)_3$ and reaction with PhCHO (Table 2, entry 3) provides **24**, while transmetalation with $Ti(O\textit{i}\text{-}Pr)_4$ provides **ent-24** (Table 2, entry 4).[14] For the reaction sequence with **2**, transmetalation with $TiCl(O\textit{i}\text{-}Pr)_3$ is presumed to proceed

(10) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4171.

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

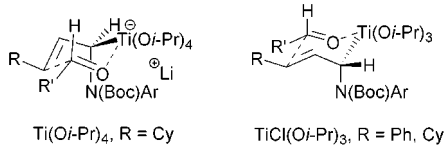
(12) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097.

(13) Hoppe, I.; Marsch, M.; Harms, K.; Boche, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2158.

(14) The absolute configurations of the products obtained by transmetalation with a titanium reagent were determined by *O*-protection and hydrolysis to the corresponding *O*-protected aldehyde (vide supra). Comparison of optical rotations was made with aldehydes **11** and **12**, whose absolute configuration was determined by X-ray crystal analysis of derivatives **15** and **18**.

with inversion of configuration, while reaction with Ti(O*i*-Pr)$_4$ is suggested to occur with retention of configuration. We propose that the lithiated intermediate of cyclohexyl derivative **2** precoordinates with the oxygen of the Ti(O*i*-Pr)$_4$ reagent, allowing transmetalation to proceed with retention of configuration.

For the titanium sequences, product selectivities are attributed to reaction via the six-membered transition states depicted in Figure 1. The R′ substituent of the aldehyde is



Ti(O*i*-Pr)$_4$, R = Cy TiCl(O*i*-Pr)$_3$, R = Ph, Cy

Figure 1. Proposed transition states for reaction of allylic amine, aldehyde, and Ti(O*i*-Pr)$_4$ or TiCl(O*i*-Pr)$_3$.

preferentially located in a pseudoequatorial position, giving rise to *anti* products. The geometrical selectivity observed upon transmetalation with a titanium reagent is opposite to that obtained upon transmetalation with Et_2AlCl. The reaction between an aldehyde and the metalated *N*-Boc allylic amine can be dissected into two steps: aldehydic oxygen complexation with the metal atom followed by carbon−carbon bond formation between the allylic double bond and the aldehyde. Depending on the transmetalating agent used, either step in the reaction sequence may be rate-limiting or stereodetermining.[15]

The present methodology entails (−)-sparteine-mediated asymmetric deprotonation, followed by stereoselective transmetalation and substitution to afford highly stereoenriched homoaldol precursors. In the cases reported by Hoppe et al., stereoselectivity is achieved by kinetic resolution[16] or preferential crystallization[5] of one diastereomeric complex. The *N*-Boc allylamine substrates **1** and **2** behave differently from similar cases investigated by Hoppe et al., where transmetalation with Ti(O*i*-Pr)$_4$ proceeds with inversion of configuration and transmetalation with TiCl(O*i*-Pr)$_3$ is nonstereoselective.[17]

The present work allows access to either enantiomer of homoaldol product from the achiral substrate **1** or **2** and the chiral diamine (−)-sparteine. The methodology of Hoppe et al. allows access to the opposite enantiomer by transmetalation and substitution of (oxybutenyl) stannanes, which in their preparation require the use of the alkyl tin halide reagents.[18]

In summary, a protocol has been developed for the transformation of *N*-Boc-*N*-aryl achiral allylic amines into homoaldol products with stereocontrolled formation of two contiguous stereogenic centers. Proper choice of transmetalating reagent in the (−)-sparteine-mediated lithiation/transmetalation/substitution/protection/hydrolysis sequence allows access to both enantiomers of the *anti*-configured *O*-protected homoaldol products, in good yields with high diastereoselectivities and enantioselectivities.

Acknowledgment. This work was supported by a grant from the National Institute of Health (GM-18874). We are grateful for this support. We thank Dr. Peter Wipf, Mr. Gustavo Mouro, and Dr. David Beratan at the University of Pittsburgh for the $[\alpha]_D$ calculations.

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.

OL006186O

(15) A possible origin of the *E* and *Z* selectivites may be as described by Hoffmann et al. See: Hoffmann, R. W.; Landmann, B. *Chem. Ber.* **1986**, *119*, 1039 for a discussion on the *E*/*Z* selectivities observed upon addition of allylboronates to aldehydes.

(16) Zschage, O.; Schwark, J.-R.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 296.

(17) See: ref 13 and Krämer, T.; Hoppe, D. *Tetrahedron* **1987**, *28*, 5149.

(18) (a) Krämer, T.; Schwark, J.-R.; Hoppe, D. *Tetrahedron Lett.* **1989**, *30*, 7037. (b) Zschage, O.; Schwark, J.-R.; Krämer, T.; Hoppe, D. *Tetrahedron* **1992**, *48*, 8377. (c) Paulsen, H.; Graeve, C.; Hoppe, D. *Synthesis* **1996**, 141.