Communications to the Editor

α-Lithiation of *N*-(*tert*-Butoxycarbonyl)-*N*-(*p*-methoxyphenyl)allylamines Mediated by (−)-Sparteine: Enantioselective Syntheses of Either Enantiomer of 3-Substituted Enecarbamates

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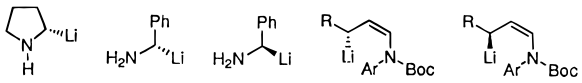
The chiral ligand approach to asymmetric synthesis with organolithium intermediates has emerged as an important synthetic transformation.[1−9] Lithiation−substitution sequences of pyrrolidine, benzylamine, and allylcarbamate derivatives afford high levels of enantioenrichment in the presence of (−)-sparteine.[1−3,5] The α-lithioamine synthetic equivalents which have been provided are shown as **1** and **2**. We now report extension of the methodology to enantioselective elaboration of allylic amines to furnish either enantiomer of a γ-allyl lithioamine synthetic equivalent represented as **3**. Facile conversions of the enecarbamate to amine and carbonyl functionalities complete a new approach to enantioenriched compounds which have a 1,3 relationship between the functional group and the asymmetric center.[10,11]



1 **2** *ent*-**2** **3** *ent*-**3**

Treatment of *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine (**5**) (Boc = *tert*-butoxycarbonyl) with 1.1 equiv of *n*-butyllithium/**4** at −78 °C in toluene for 1 h followed by addition of an electrophile affords products **7**−**11** with enantiomeric ratios (er = enantiomeric ratio) greater than 96:4 in good yields as shown in Table 1 (Scheme 1). Deprotonation α to nitrogen provides the allylic carbanion **6** which reacts with electrophiles either at the γ or α position. Carbon-carbon bond forming electrophiles react at the γ position to afford the enecarbamates **7**−**10**.[12] The *trans* isomers of **7**−**10** are obtained in 2−3% yield and can be separated by preparative HPLC. The absolute configurations of (*S*)-**9**, the product of reaction with benzyl bromide, and (*R*)-**10**, the product of reaction with cyclohexanone, were assigned

Scheme 1

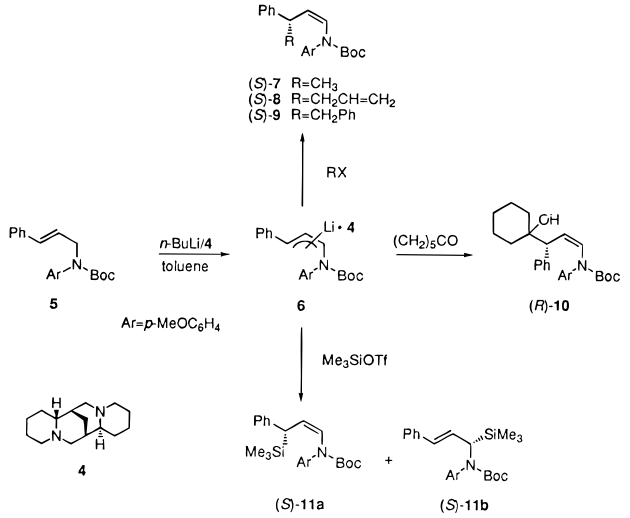


Table 1. Yields and Enantiomeric Ratios of the Products from Reactions of *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine (**5**) with *n*-BuLi/**4** in Toluene Followed by Reaction with an Electrophile

electrophile	product	yield (%)	er (% ee)[a]
CH_3OTf	(*S*)-**7**	74	96.0:4.0 (92)
CH_3I	(*S*)-**7**	73	97.5:2.5 (95)
$H_2C{=}CHCH_2Br$	(*S*)-**8**	72	97.0:3.0 (94)
$PhCH_2Br$	(*S*)-**9**	70	98.0:2.0 (96)
$(CH_2)_5C{=}O$	(*R*)-**10**	77	99.0:1.0 (98)
Me_3SiOTf	(*S*)-**11a**	34	97.0:3.0 (94)
	(*S*)-**11b**	46	98.0:2.0 (96)

[a] Enantiomeric ratios were determined by CSP-HPLC.

by independent chemical syntheses and comparison of chiral stationary phase(CSP)-HPLC retention times. The sense of electrophilic substitution of the carbonyl electrophile is opposite to that for the alkyl halide electrophiles for these reactions.[3,13−15] The absolute configurations of **7** and **8** are provisionally assigned on the basis of their correspondence to **9** as the more retained isomer on the CSP-HPLC column.[16] Use of trimethylsilyl triflate as the electrophile provides a mixture of the α isomer (*S*)-**11b** and the γ isomer (*S*)-**11a** in 46 and 34% yields, respectively. The absolute configuration of (*S*)-**11a** was assigned by independent chemical synthesis and comparison by CSP-HPLC. The absolute configuration of (*S*)-**11b** is assigned by analogy to (*S*)-**11a** and is provisional.

We investigated a transmetalation−substitution sequence as an approach to obtain either enantiomer of the products.[3,14,15] Use of trimethyltin chloride as the electrophile provides a mixture of the α isomer (*R*)-**12b** and the γ isomer (*R*)-**12a** in 24 and 49% yields with a 95:5 enantiomeric ratio.[17−19] The enantioenriched lithium intermediate **6** is prepared by tin−lithium exchange of enantioenriched (*R*)-**12a** (95:5 er) in the presence of (−)-sparteine. Addition of allyl bromide affords

(1) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.
(2) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715.
(3) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757.
(4) Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure Appl. Chem.* **1994**, *66*, 1479.
(5) Zschage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657.
(6) Paulsen, H.; Graeve, C.; Hoppe, D. *Synthesis* **1996**, 141.
(7) Klein, S.; Marek, I.; Poisson, J. F.; Normant, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 8853.
(8) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075.
(9) Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 685.
(10) Hoppe has reported an asymmetric homoenolate synthetic equivalent with 2-alkenyl esters of carbamic acid with *sec*-BuLi/(−)-sparteine which provides this relationship.[5,6]
(11) Normant has reported asymmetric carbolithiation of cinnamate derivatives in the presence of (−)-sparteine which provides this relationship.[7]
(12) The olefin geometry is assigned as *cis* by the magnitude of the coupling constant between the two olefinic protons (J = 9.5 Hz). The *cis* enecarbamates isomerize to the *trans* isomers without racemization in $CDCl_3$.
(13) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755.
(14) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575.
(15) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097.
(16) Pirkle, W. H.; Pochapsky, T. C.; Mahler, G. S.; Corey, D. E.; Reno, D. S.; Alessi, D. M. *J. Org. Chem.* **1986**, *51*, 4991.
(17) The assignment of absolute configuration to the organostannane **12** is based on the assumption of invertive stannylation.[14,15,25]
(18) Zschage, O.; Schwark, J.-R.; Krämer, T.; Hoppe, D. *Tetrahedron* **1992**, *48*, 8377.
(19) Rapid addition of Me_3SnCl (1 M solution in hexanes) is necessary in order to obtain consistent enantiomeric ratios.

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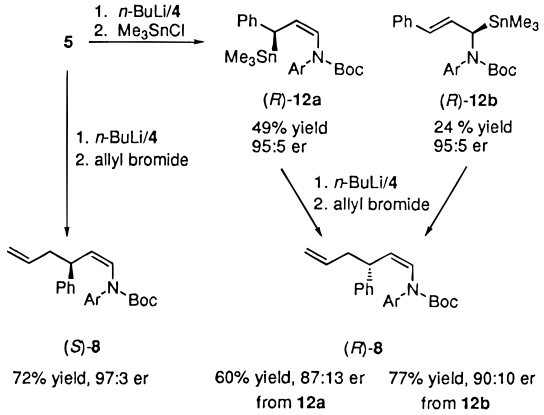
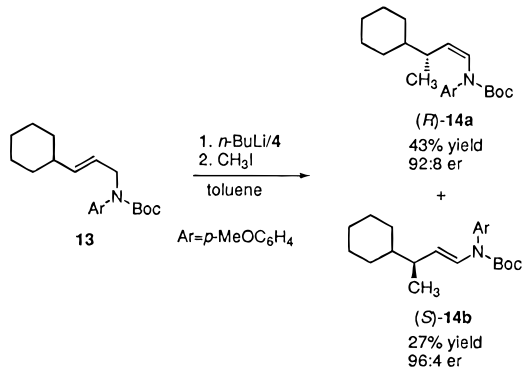
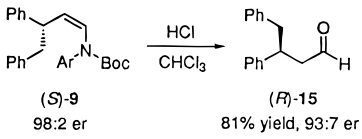
(*R*)-**8** in 60% yield with an 87:13 er. The same product, (*R*)-**8**, is obtained in 77% yield with a 90:10 er when (*R*)-**12b** (95:5 er) is submitted to the same reaction sequence.[20]



The high enantioselectivity and regioselectivity observed in this reaction is not limited to cinnamate derivatives. Treatment of *N*-Boc-*N*-(*p*-methoxyphenyl)-3-cyclohexyl-(*E*)-2-propene-1-amine (**13**) with *n*-BuLi/**4** at −78 °C in toluene for 1.5 h followed by addition of methyl iodide affords a mixture of the *cis* and *trans* γ isomers (*R*)-**14a** and (*S*)-**14b** in 43 and 27% yields with 92:8 and 96:4 er, respectively.[21] The absolute configuration of (*R*)-**14a** is assigned by analogy to the sequence with **5**. The absolute configuration of (*S*)-**14b** was assigned by isomerization to (*S*)-**14a**.[18]

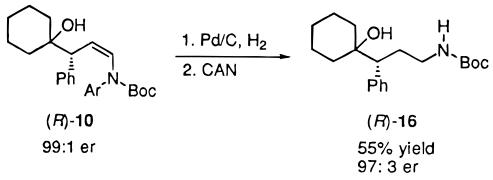


This methodology can provide either enantiomer of a homoenolate synthetic equivalent and a γ-lithioamine synthetic equivalent.[22] Hydrolysis of (*S*)-**9** with HCl affords the enantioenriched aldehyde (*R*)-**15** in 81% yield with 93:7 er.[23]

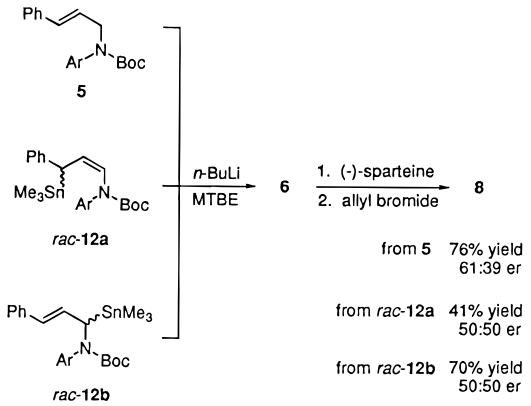


Reduction of (*R*)-**10** followed by oxidative cleavage of the *p*-methoxyphenyl group with ceric ammonium nitrate (CAN)[24] provides the highly enantioenriched protected primary amine (*R*)-**16** in 55% yield with 97:3 er.

The two limiting pathways for asymmetric replacement of a prochiral hydrogen in a lithiation−substitution sequence are an asymmetric deprotonation, in which one of the prochiral



hydrogens is selectively removed to give a configurationally stable organolithium anion, and an asymmetric substitution, in which the enantiomeric ratio is established in a post-deprotonation step.[25] Generation of the racemic lithiated intermediate **6** by reaction of **5** with *n*-BuLi followed by addition of (−)-sparteine and allyl bromide affords **8** in 76% yield with a 61:39 er. Generation of **6** by tin−lithium exchange of racemic **12a** or racemic **12b** with *n*-BuLi followed by addition of (−)-sparteine and allyl bromide affords racemic **8** in 41 and 70% yields, respectively.[26] These results suggest that the enantiodetermining step in the sequence is an asymmetric deprotonation.



The lithiated intermediate **6** must be configurationally stable if asymmetric deprotonation is the enantiodetermining step. Configurational stability is consistent with transmetalation of the enantioenriched tin derivatives (*R*)-**12a** and (*R*)-**12b** to afford enantioenriched (*R*)-**8** and the observation that lithiation−substitution of **5** provides enantioenriched (*S*)-**8** (*vide supra*). If **6** were not configurationally stable, the same enantiomer of the product (*S*)-**8** should be produced regardless of the starting material (**5**, (*R*)-**12a**, or (*R*)-**12b**) used to generate **6**. In contrast, when enantioenriched **6** is prepared by tin−lithium exchange of enantioenriched (*R*)-**12b** with *n*-BuLi or *n*-BuLi/TMEDA followed by addition of allylbromide, racemic **8** is obtained in 52 and 41% yields, respectively. These results show that while the enantioenriched organolithium intermediate **6** maintains its configuration in the presence of (−)-sparteine it does not maintain its configuration by itself or in the presence of TMEDA.[27]

Synthetic applications, determination of the structures of intermediates, and investigation of the mechanism of the reaction are matters of future interest.

Acknowledgment. We are grateful to the National Institute of Health and the National Science Foundation for support of this work.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **5**, (*S*)-**7**, (*S*)-**8**, (*S*)-**9**, (*R*)-**10**, (*S*)-**11a**, (*S*)-**11b**, (*R*)-**12a**, (*R*)-**12b**, **13**, (*R*)-**14a**, (*S*)-**14b**, (*R*)-**15**, (*R*)-**16**, transmetalation procedures for (*R*)-**12a** and (*R*)-**12b**, and absolute configuration determinations of (*S*)-**9**, (*R*)-**10**, and (*S*)-**11a** (16 pages). See any current masthead page for ordering and Internet access instructions.

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(20) The product (*R*)-**8**, derived from **12**, contains ca. 20% of the *E* isomer.

(21) The α isomer is obtained in 6% yield.

(22) Ahlbrecht, H.; Enders, D.; Santowski, L.; Zimmermann, G. *Chem. Ber.* **1989**, *122*, 1995.

(23) The erosion of er is attributed to the *trans* isomer (*R*)-**9** present in (*S*)-**9**. The isomers can be separated by preparative HPLC but were not in this case to demonstrate that high enantioenrichment is possible without this added step.

(24) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(25) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 0000.

(26) Furthur work is under way to determine the origin of the 61:39 er observed when **5** is metalated followed by addition of (−)-sparteine and allyl bromide.

(27) The influence of (−)-sparteine on the configurational stability of an anion has been previously observed.[3]