Complex-Induced Proximity Effects: The Effect of Varying Directing-Group Orientation on Carbamate-Directed Lithiation Reactions

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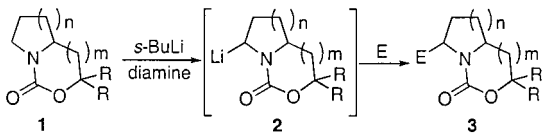
Abstract: A series of selected bicyclic carbamates in which the range of accessible angles and distances between the carbonyl group and the proton removed in an α-lithiation reaction are structurally defined have been investigated. Oxazolidinones **7**−**10** undergo stereoselective lithiation−substitution reactions to provide *cis*-**18**−**27** and *cis*-**31**−**35** as the major diastereomers. Two series of competition experiments show that the conformationally restricted carbamates **7**, **10**, **11**, and **15** undergo lithiation via complexes more efficiently than Boc amines **4**−**6**. These results along with semiempirical calculations suggest that a small dihedral angle and a calculated distance of 2.78 Å between the carbamate carbonyl oxygen and the proton to be removed are favorable for a carbamate-directed lithiation. A series of tin−lithium exchange experiments on *cis*- and *trans*-**18** and (*S*)-**39** indicate that the configurational stability of a carbamate-stabilized organolithium species may be enhanced by restrictive geometry.

Introduction

The course of many novel reactions in organolithium chemistry can be rationalized by considering the pathways available to a complex formed by association between an organolithium reagent and a Lewis basic functionality of a substrate.[1] For deprotonative lithiation reactions the geometrical constraints within a complex in the transition state for transfer of the proton to the lithiating reagent have been shown to be important for efficient reaction. For example, a systematic study of secondary and tertiary benzamides and of benzylic alcohols demonstrated that the orientation of the directing group with respect to the proton removed in *ortho* lithiations significantly affects the reaction efficiency.[2] For reactions that provide α-lithioamine derivatives of amides an orthogonal relationship between the lithio carbanion and the pi system of the amide has been established to be favorable.[3−9] Qualitatively this arrangement allows complexation of the lithium with the carbonyl oxygen and relieves the possible repulsive interaction between the electron pairs of the carbanion and the pi system in which would be present a fully planar system. Theoretical calculations and empirical observations support an orthogonal arrangement in α-lithio *N*-Boc amines as well.[6,8−12]

To experimentally evaluate the effect of geometry in the formation and on the stability of α-lithioamine derivatives of carbamates we have carried out a systematic investigation of lithiation−substitution of selected bicyclic structures **1** to give **3** via **2**. The systems we prepared constrain the position of the



carbonyl oxygen with respect to the proton removed in an α-lithiation reaction and consequently with respect to the organolithium base in the presumptive complex. We have found by competition experiments that changes in the ring sizes significantly affect the reactivities of **1** in the lithiations which provide **2**. The location of the carbonyl oxygen with respect to lithium is also found to affect the configurational stability of **2**.

Results

Syntheses of Bicyclic Carbamates. The bicyclic carbamates **7**−**11** containing a five-membered oxazolidinone ring were synthesized by directed lithiation of *N*-Boc pyrrolidine (**4**), *N*-Boc piperidine (**5**), and *N*-Boc perhydroazepine (**6**) and reaction with diisopropyl ketone or di-*tert*-butyl ketone.[9] Cyclization of the intermediate alkoxide occurred when the reaction was warmed to room temperature. The installation of the sterically bulky isopropyl and *tert*-butyl groups was necessary to prevent addition by the butyllithium lithiating reagent to the carbamate carbonyl group.

(1) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356−363; Anderson, D. R., Faibish, N.-C., Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 7553.
(2) Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10628−10636.
(3) Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010−1018.
(4) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.* **1989**, *54*, 175−181.
(5) Meyers, A. I.; Edwards, P. D.; Reiker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270.
(6) Meyers, A. I.; Milot, G. *J. Org. Chem.* **1993**, *58*, 6538−6540.
(7) Meyers, A. I.; Milot, G. *J. Am. Chem. Soc.* **1993**, *115*, 6652−6660.
(8) Kopach, M. E.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 6764−6765.
(9) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109−1117.
(10) Rondan, N. G.; Houk, K. N.; Beak, P.; Zajdel, W. J.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Org. Chem.* **1981**, *46*, 4108−4110.
(11) Bach, R. D.; Braden, M. L.; Wolber, G. J. *J. Org. Chem.* **1983**, *48*, 1509−1514.
(12) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552−560.

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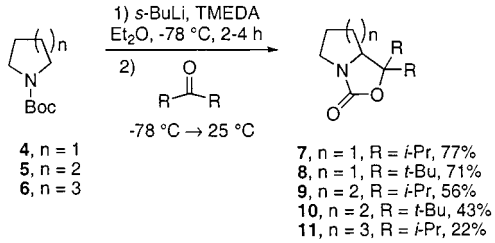
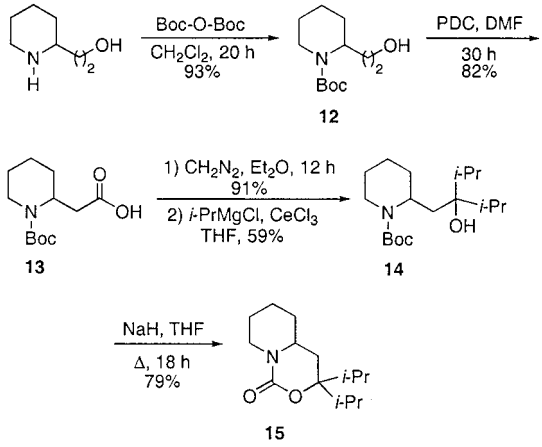


The differences in yields observed for these reactions result from differences in reactivities of the corresponding Boc amines toward metalation (vide infra). The equatorial disposition of the carbamate ring in the piperidine derivatives **9** and **10** is established by the values of ^{1}H NMR coupling constants and is consistent with previous work.[3,5,9]

The oxazinan-2-one **15** was prepared to provide a compound which, due to the carbamate in the six-membered ring changes the position of the carbamyl oxygen with respect to the proton of interest. The synthesis of carbamate **15** began with the reaction of commercially available 2-piperidine ethanol with di*tert*-butyl dicarbonate. The resulting alcohol **12** was oxidized with pyridinium dichromate to afford the carboxylic acid **13** which was treated with diazomethane[13] to form the methyl ester. Treatment of the ester with 2.2 equiv of $CeCl_3$14 and isopropylmagnesium chloride provided **14**,[15] which on treatment of **14** with sodium hydride in refluxing THF afforded the bicyclic carbamate **15**.



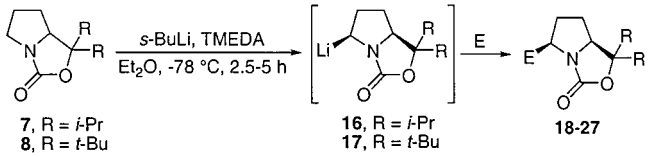
Stereoselective Lithiation−Substitutions of Bicyclic Carbamates. As shown in Table 1, the pyrrolidine-derived oxazolidinones **7** and **8** upon treatment with *sec*-butyllithium (*s*-BuLi)/TMEDA at −78 °C followed by electrophiles provide the substituted products **18**−**27** in good yields. Stannyl and silyl chlorides, dimethyl sulfate, ketones, and benzaldehyde were successfully used as electrophiles. A significant feature of this lithiation−substitution reaction is the generally high *cis* diastereoselectivity; only single diastereomers of products **18**−**21** and **23**−**27** were isolated.

The relative configuration of stannane **18** was determined to be *cis* by X-ray crystallography. An interesting feature of this structure is the near coplanarity of the carbonyl group and the carbon−tin bond. Assuming the reaction with trimethyl tin chloride proceeds with retention of configuration, this coplanar disposition in **18** may be taken to suggest that the proton in **7** that is more nearly coplanar with the carbonyl group is favored for removal.

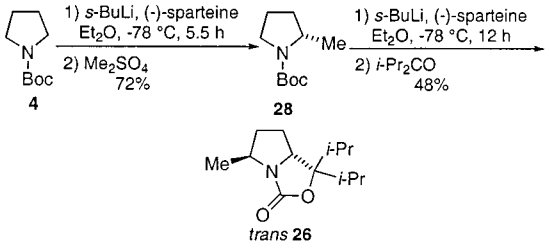
Table 1. Lithiation and Substitution of **7** and **8** to Provide **18**−**27**

product	R	electrophile	E	time (h)	yield[a] (%)
18	*i*-Pr	Me_3SnCl	$SnMe_3$	5	78
19	*i*-Pr	Bu_3SnCl	$SnBu_3$	3.5	67
20	*i*-Pr	TMSCl	$SiMe_3$	4	64
21	*i*-Pr	$PhMe_2SiCl$	$SiMe_2Ph$	4.5	43
22	*t*-Bu	$PhMe_2SiCl$	$SiMe_2Ph$	2	77, 8[a]
23	*i*-Pr	*i*-Pr_2CO	C(OH)*i*-Pr_2	2.5	68
24	*t*-Bu	Ph_2CO	$C(OH)Ph_2$	3	48[b]
25	*t*-Bu	PhCHO	CH(OH)Ph	5	66[c]
26	*i*-Pr	Me_2SO_4	Me	3	68
27	*t*-Bu	Me_2SO_4	Me	5	77

[a] A careful search for diastereomers in each case did not reveal their presence. We estimated at least 2% of any diastereomers would have been detected by GC analyses. [b] A compound tentatively identified as the *trans* diastereomer was isolated in 8% yield. [c] Additional product was present but was not separated from benzophenone. [d] Two diastereomers were formed in a 1.5:1 ratio.



The *cis* configuration of the methyl substituted oxazolidinone **26** was determined by comparison of this product to authentic *trans*-**26**, which was synthesized by sequential enantioselective metalations of pyrrolidine **4** with *s*-BuLi/(−)-sparteine.[16] Treatment of *N*-Boc pyrrolidine with *s*-BuLi/(−)-sparteine followed by dimethyl sulfate provided methyl pyrrolidine **28**, which was treated with *s*-BuLi/(−)-sparteine followed by diisopropyl ketone to yield *trans*-**26**. Physical and spectroscopic evidence confirmed that *trans*-**26** is different from *cis*-**26**, the product generated from lithiation of **7** and substitution with Me_2SO_4. By analogy to **18** and **26** the remaining products in Table 1 are assigned the *cis* configuration.



With benzaldehyde as the electrophile, alcohol **25** was isolated as a 1.5:1 mixture of two diastereomers with different configurations at the hydroxy bearing carbon. Evidence for highly diastereoselective lithiation−substitution at the ring carbon in this reaction was provided by deoxygenation[17] of **25** to provide a single diastereomer of the benzyl substituted oxazolidinone.[18,19]

The lithiation−substitutions of **9** and **10** were investigated as shown in Table 2. Treatment of **9** with *s*-BuLi/TMEDA

(13) Black, T. H. *Aldrichimica Acta* **1983**, *16*, 3−10.

(14) Dimitrov, V.; Bratovanov, S.; Simova, S.; Kostova, K *Tetrahedron Lett.* **1994**, *35*, 6713−6716.

(15) The presence of $CeCl_3$ was necessary for the success of the addition.

(16) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231−3239.

(17) Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588−1589.

(18) In addition, two diastereomers were observed when benzyl bromide was used as the electrophile, but the products were not isolated. It is likely that lithiation occurred selectively in these reactions, but substitution of **16** with these halides occurs with lower selectivity. Low facial selectivity in the substitution of α-lithioamines with alkyl halides has been reported.[19] An 8% yield of a compound tentatively identified as *trans*-**22** was isolated when chlorodimethylphenylsilane was used as an electrophile.

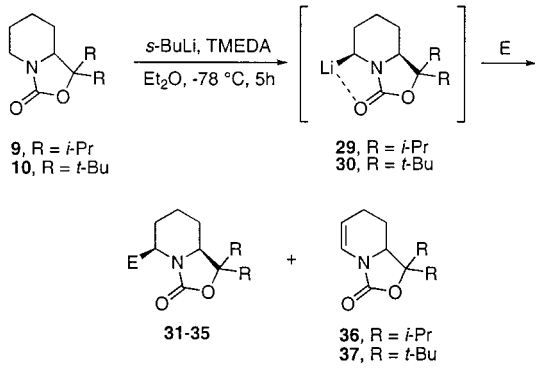
(19) Gross, K. M. B.; Jun, Y. M.; Beak, P. *J. Org. Chem.* **1997**, *62*, 7679.

Table 2. Lithiation−Substitution of Bicyclic Carbamates **9** and **10** to Give **31**−**35**

product	R	electrophile	E	yield[a] (%)
31	*t*-Bu	Me_2SO_4	Me	85
32	*i*-Pr	Ph_2CO	$C(OH)Ph_2$	59[b]
33	*t*-Bu	Ph_2CO	$C(OH)Ph_2$	62[c]
34	*i*-Pr	$PhMe_2SiCl$	$SiMe_2Ph$	47, 14[d]
35	*t*-Bu	$PhMe_2SiCl$	$SiMe_2Ph$	50, 10[d]

[a] A careful search for diastereomers in each case did not reveal their presence. We estimated at least 2% of any diastereomers would have been detected by GC analyses. [b] Olefin **36** was isolated in 8% yield. [c] Olefin **37** was isolated in 10% yield, and a compound tentatively identified as *trans*-**33** was isolated in 2% yield. [d] The yields of the *cis* and *trans* isomers are reported.

followed by dimethyl sulfate provided diastereomerically pure **31** in 85% yield. The reactions of **9** and **10** with benzophenone were also highly stereoselective, and *cis*-**32** and *cis*-**33** were obtained in 59 and 62% yields, respectively, along with small amounts of olefins **36** and **37**. The substitutions of organolithiums **29** and **30** with chlordimethylphenylsilane were not completely selective; **34** and **35** were formed as 3:1 and 5:1 *cis*:*trans* mixtures, respectively.

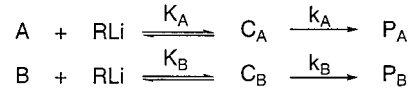


The major diastereomers isolated from the reactions of **9** and **10** with electrophiles were assigned the *cis* configuration on the basis of ^{1}H NMR coupling constants of the protons at C-2 and C-6. For each of the compounds **31**−**33** and the major diastereomers of **34** and **35**, both H-2 and H-6 have characteristic axial−axial coupling constants (8−13 Hz) and characteristic axial−equatorial coupling constants (3−6 Hz).[20] These data indicate that both H-2 and H-6 in the disubstituted piperidines **31**−**35** are axial protons and that the *cis* diequatorially substituted diastereomers are the major products obtained from diastereoselective lithiations−substitutions of **9** and **10**.[20]

In the oxazolidinones **7**−**10** the *cis* protons are more nearly planar with and in closer proximity to the carbonyl group than are the *trans* protons (vide infra). On the basis of analogy to the lithiation−substitution of Boc amines, retentive substitutions are assumed, and the organolithiums **16**, **17**, **29**, and **30** are assigned *cis* geometry. Lithiation−substitution occurs highly selectively on the more sterically encumbered concave face of the bicyclic systems. This stereochemistry suggests that there is a geometrical requirement for a carbamate-directed lithiation in which the carbamate carbonyl group complexes to *s*-BuLi to direct lithiation to the same face of the bicyclic system.[1]

Competitive Efficiency in Carbamate-Directed Lithiations: Comparison of Constrained Carbamates and Boc Amines. Oxazolidinones **7**, **10**, and **11**, oxazinan-2-one **15**, and

Scheme 1



N-Boc amines **4**, **5**, **6**, and *rac*-**23** were subjected to a series of competition experiments to determine whether they undergo directed lithiation with significantly different efficiencies.

A previous kinetic analysis of a carbamate-directed lithiation provided evidence for fast complex formation between *N*-Boc pyrrolidine and isopropyllithium/(−)-sparteine prior to the deprotonation step.[22] The equilibrium favored complexation and was followed by a rate-determining deprotonation. Under this mode, Scheme 1 can be used to describe the kinetic competition experiments carried out on two carbamates. Reactants A and B are the two carbamates used in the competition experiment, and K_A and K_B are the equilibrium constants for complexation of A and B with RLi to form C_A and C_B, the resulting complexes. The constants k_A and k_B are the rate constants for deprotonation to form lithiated products, P_A and P_B, respectively. The magnitudes of both the equilibrium constants and the rate constants can affect the competitive efficiencies of the reactions compared.

The competition experiments were carried out in two ways: under pseudo-first-order conditions with 15 equiv of *s*-BuLi or under second-order conditions with a deficient amount of *s*-BuLi. Under pseudo-first-order conditions, the equilibria shown in Scheme 1 are assumed to lie far on the side of the complexes C_A and C_B. If two carbamates have different equilibrium constants for complexation with *s*-BuLi, the presence of a large excess of *s*-BuLi may compensate for the difference by forcing the equilibria to the side of the complex. In that case, the pseudo-first-order competition experiments would reflect differences in competitive efficiencies for the deprotonation step. Comparisons of the relative extents of lithiation of two carbamates under pseudo-first-order and second order would test this assumption. The observed extents of reaction should be the same if complexation is not a determining factor and different if complexation is important. We recognize that this simplification and the discounting of possible differences in side reactions and effects of organolithium products P_A and P_B on the reaction restrict us to a semiquantitative interpretation of the results.[2]

For both sets of competition experiments shown in Table 3, two carbamates were treated with *s*-BuLi/TMEDA followed by a deuterium source. Not all the substrates were directly compared, but selected substrates were used in direct competition experiments as described in Supporting Information to determine an order of competitive efficiencies for each series. The yields for each of the products were generally above 80%. A typical competition is shown for **4** and **10**.

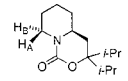
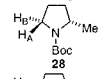
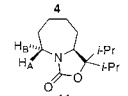
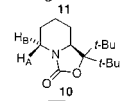
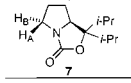
Some inconsistencies were observed in the competition experiments. A competitive efficiency of 28 for oxazolidinone **10** with respect to piperidine **5** was calculated from a direct

(20) Pretsch, E.; Siebel, J.; Clerc, T.; Bieman, K. *Tables of Spectral Data for Structure Determination of Organic Compounds*; 2nd ed.; Springer-Verlag: Berlin, 1989.

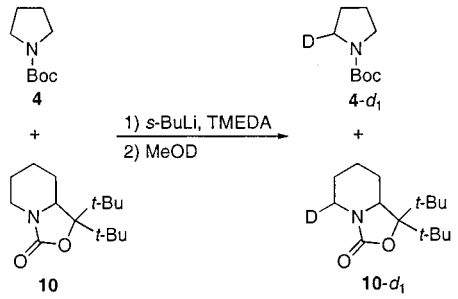
(21) The *cis*-2,6-disubstituted piperidines **31**−**35** arise from sequential equatorial lithiation−substitutions. It was reported previously that in sequential metalations of **2**, 2,6-disubstituted piperidines with *trans* geometry are obtained.[9] The equatorial lithiation and substitution of pipieridine **2** followed by trapping with Me_2SO_4 provides 2-methyl *N*-Boc piperidine. In this case, the methyl group α to the nitrogen interacts unfavorably with the Boc group through $A_{1,3}$ strain, and a ring flip occurs placing the substituent in the axial position. A second equatorial lithiation of the substituted *N*-Boc piperidine results in a product with *trans* geometry. For equatorially substituted cyclic carbamates **9** and **10**, $A_{1,3}$ strain is not a factor, and the expected second equatorial lithiation results in the *cis* diastereomers **31**−**35**.

(22) Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1995**, *60*, 7092−9093.

Table 3. Competitive Efficiencies for Selected Carbamates from the Two Series of Competition Experiments

Substrate	Pseudo-1st-Order Competitive Efficiency	Second Order Competitive Efficiency	Dihedral Angles[a,b] (H_A, H_B)	Distance[a] from carbonyl oxygen[c] (H_A, H_B) (Å)
 **6**	1	1	36°, 148°[e] 20°, 97°	2.64, 3.88[c] 2.41, 3.44
 **5**	3	4	20°, 127°	2.48, 3.78
 **15**	nd	19	18°, 124°	2.52, 3.79
 **28**	72	46	39°, 66°[e]	2.60, 3.14[d]
 **4**	235	68	36°, 70°	2.57, 3.16
 **11**	330	920	20°, 127°	2.69, 3.96
 **10**	705	4800	10°, 96°	2.66, 3.72
 **7**	fast[e]	19000	28°, 77°	2.78, 3.70

[a] The values for angles and distances of the lowest energy conformations were averaged. [b] The dihedral angle is defined as the angle between the planes containing H, C, N, and N, CO. [c] Since two distinct sets of conformers were generated, the sets were not averaged. [d] Only conformations with the carbonyl pointing away from the methyl group were considered. [e] Under pseudo-first-order conditions, the lithiation of **7** was complete in less than one minute.



comparison of these two carbamates under pseudo-first-order conditions. However, data comparisons from the other competition experiments in the series would predict a competitive efficiency of >200 for this experiment as shown in Table 3. This higher value for the competitive efficiency is more consistent with the series of experiments. Also a direct comparison of pyrrolidine **4** and oxazolidinone **11** under pseudo-first-order conditions was not highly reproducible, and the competitive efficiency for **11** is considered the least reliable data point.

A control experiment was carried out to determine if equilibration of lithiated products was occurring. Pyrrolidine **4** was treated with *s*-BuLi/TMEDA for 2 h, and a solution of oxazolidinone **7** was added. The mixture was allowed to stir for 30 min, followed by quenching with an excess of AcOD. In this experiment, carbamate **7** was recovered with 1.81% deuterium incorporation, and **4** was formed with 72.59% deuterium incorporation. This experiment shows that the deuterated products were formed from kinetic deprotonations and the competitive efficiencies calculated for the competition experiments do not reflect thermodynamic products.

The order of competitive efficiency in each set of experiments in Table 3 is the same, but there are clearly quantitative differences. In the second-order series, bicyclic carbamate **11** is lithiated greater than 1 order of magnitude faster than pyrrolidine **4**, the most efficiently lithiated Boc amine. In contrast the results of the pseudo-first-order experiments indicate that **4**, **11**, and **10** are lithiated with rather similar efficiencies. If it is presumed that under pseudo-first-order conditions the competitions involve fully complexed and equilibrated species, the competitive efficiencies in this series may be attributed only to differences in the rates of deprotonation of the substrates. The second-order experiments may then reflect differences in the extent of complex formation or other steps prior to deprotonation. The quotient of the second-order competitive efficiency and the pseudo-first-order competitive efficiency may provide an estimate of the differences in equilibrium constants for complexation for two substrates in a given competition experiment. For example, in a competition between piperidine **5** and oxazolidinone **10**, **10** may be considered to undergo lithiation 230 times faster and complexation 5 times faster than **5**. However, the data is not sufficient to allow firm interpretation. A more detailed kinetic analysis of these reactions is needed.

Nonetheless, the consistent order in differences in lithiation efficiencies for carbamates of diverse structure are consistent with a geometrical requirement for carbamate-directed lithiations. Under both pseudo-first-order and second-order conditions, the oxazolidinones **7**, **10**, and **11** are lithiated more efficiently than each of the *N*-Boc amines. The differences between lithiation efficiencies of *N*-Boc amines **4**, **5**, **6**, and **28** were observed previously and are semiquantitatively defined here.[9,16]

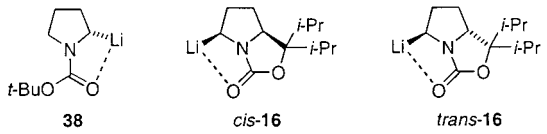
A comparison of the piperidine-based carbamates illustrates the effects of varying directing group geometry on the efficiency of lithiation. In the second-order series, the oxazinan-2-one **15**, which contains a six-membered carbamate ring, was lithiated >200 times less efficiently than the corresponding oxazolidinone **10**, which contains a five-membered carbamate ring. However, **15** was lithiated approximately 5 times more efficiently than the less restricted piperidine **5**. These results indicate that constraining the carbamate in a six-membered ring increases the efficiency of the lithiation reaction with respect to the less restricted *N*-Boc amine, but the geometry achieved by the carbamate of the oxazolidinone **10** is more favorable.[23]

Calculations of Ground-State Structures of the Carbamates. In an effort to obtain insight into the effect of the carbamate directing group orientation on competitive efficiency, semiempirical PM3 calculations were carried out to identify the lowest-energy ground state conformations of the carbamates. If the ground-state structures are reflective of constraints in the transition states for deprotonation, a correlation may be found between dihedral angles and distances between the directing group and the proton removed. The results are shown in Table 3.[24]

The Effect of the Position of the Carbonyl Group on the Configurational Stabilities of Lithiated Carbamates: A Comparison of Rigid Carbamates and *N*-Boc Amines. To evaluate the effect of restricting the position of the carbamate carbonyl group on the configurational stability of a dipole-

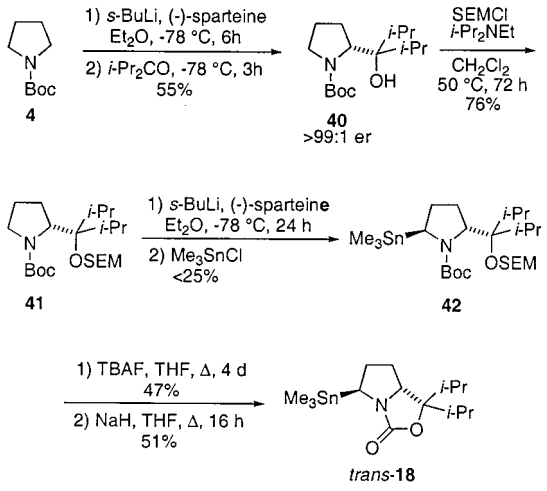
(23) Oxazinan-2-one **15**, the third entry of Table 3, was subjected to lithiation in the presence of pyrrolidine **4** under second-order conditions, and the deuterated product from **15** was obtained in 66% yield and 6% d_1, and side products were observed by GC and GC/MS. The GC/MS data for the side products were consistent with addition of *s*-BuLi to the carbamate carbonyl group. If the remaining 34% of the material generated from **15** can be attributed to addition products, it may be concluded that this carbamate undergoes addition approximately 5 times faster than metalation.

stabilized organolithium, the organolithiums **38**, *cis*-**16**, and *trans*-**16** were prepared from the corresponding organostannanes and their stabilities investigated.



38 *cis*-**16** *trans*-**16**

Syntheses of Organostannanes. The stannane (*S*)-**39** was generated in 86% yield and with 96:4 er by treatment of pyrrolidine **4** with *s*-BuLi/(−)-sparteine followed by substitution with Me_3SnCl. The stannane *cis*-**18** was synthesized as shown in Table 1. The synthesis of *trans*-**18** was accomplished in five steps using sequential asymmetric deprotonations of pyrrolidine **4** as described for the synthesis of *trans*-**26**. Pyrrolidine **4** was treated with *s*-BuLi/(−)-sparteine followed by diisopropyl ketone.[25] After recrystallization, alcohol **40** was isolated in 55% yield with >99:1 er and was protected as the 2-(trimethylsilyl)-ethoxymethyl (SEM) ether **41** in 76% yield. Ether **41** was treated with *s*-BuLi/(−)-sparteine for 24 h followed by reaction with Me_3SnCl to provide a mixture of products which contained disubstituted pyrrolidine **42**. Desilyation and cyclization provided the *trans*-disubstituted pyrrolidine **18** in 24% yield.



4 **40** >99:1 er **41** **42** *trans*-**18**

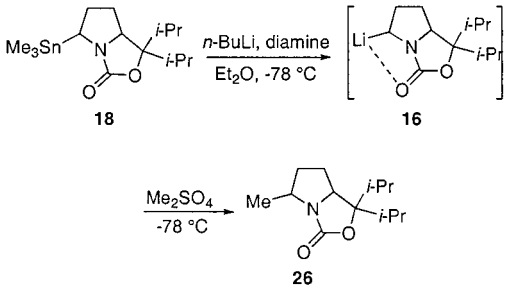
Configurational Stability of Organolithiums, 38, *cis*-16 and *trans*-16. The trimethyl tin compounds (*S*)-**39**, *cis*-**18** and *trans*-**18** were used to prepare **38**, *cis*-**16** and *trans*-**16** by tin−lithium exchanges. The results of transmetalation experiments with *cis*-**18** and *trans*-**18** are summarized in Table 4. Treatment of stannane **18** with *s*-BuLi or *n*-BuLi at −78 °C in the presence or absence of TMEDA provided the organolithiums **16**, which were treated with dimethyl sulfate to give *cis*- or *trans*-**26**. The diastereomeric ratios for **26** were determined by GC analyses and comparison to mixtures of authentic *cis*- and *trans*-**26** (vide supra).

Table 4. Tin−Lithium Exchange of **18** to Provide **26**[a]

stannane	diamine	temp (°C)	time (h)	yield **26** (%)	*cis*:*trans* **26**
cis-**18**	TMEDA	−78	4	57	>99:1
cis-**18**	TMEDA	−40	1	44	>99:1
cis-**18**	none	−78	6	69	>99:1
cis-**18**	none	−40	5	21	>99:1
trans-**18**	none	−78	5	56	<1:99
trans-**18**	none	−40	1	24	2:1
trans-**18**	TMEDA	−78	1	44	1:1
trans-**18**	TMEDA	−78	6.5	21	>99:1

[a] When aging at −40 °C was desired, the solution was maintained at −78 °C for 20 min and then placed in a −40 °C bath for the indicated time before cooling to −78 °C and adding Me_2SO_4 to provide **26**.

The results in Table 4 indicate that in the presence or absence of TMEDA and at either −78 °C or at −40 °C, a highly stereoselective transmetalation−substitution takes place and the organolithium *cis*-**16** maintains its configuration. The remainder of the material isolated from these reactions was destannylated **7**. Both transmetalation−substitution of *cis*-**18** and lithiation−substitution of **7** provide *cis* products, and the configurations of *cis*-**18** and *cis*-**26** are both known unambiguously. Transmetalation−substitution is reasonably assigned as doubly retentive.



18 **16** **26**

When *trans*-**16** was maintained at −78 °C in the absence of TMEDA for 6 h, no epimerization of the organolithium was observed by GC, and only *trans*-**26** was isolated along with destannylated **7**. The organolithium *trans*-**16** is significantly more configurationally stable than the rotationally unrestricted, diastereomerically biased, carbamate-stabilized organolithiums reported by Pearson and Lindbeck, which epimerize at −78 °C within 5 min.[26,27] However, when our reaction was warmed to −40 °C in the absence of diamine, some epimerization occurs after 1 h, and a 2:1 ratio of *cis*:*trans* **26** was observed after reaction with dimethyl sulfate. In the presence of TMEDA the epimerization occurs at −78 °C. After 1 h, a 1:1 ratio of *cis*:*trans* **26** was observed, and after 5 h at −78 °C only the *cis*-**26** diastereomer was isolated from the reaction. As in the transmetalations of *cis*-**18**, the remainder of the material isolated from these reactions was destannylated **7**.

The comparison of the transmetalations of *cis*- and *trans*-**18** indicate that *cis*-**16** is more thermodynamically stable than *trans*-**16** and the position of the carbamate functionality with respect to the lithium ion affects the stability of a dipole-stabilized carbanion. Complexation of the lithium by the carbonyl oxygen of *trans*-**16** would be expected to be more difficult than in *cis*-**16** due to the longer distance between the lithium and oxygen atoms in the former.

Semiempirical PM3 calculations indicate that *trans*-**16** to be 6.5 kcal/mol higher in energy than *cis*-**16**. In these calculations,

(24) The Spartan software was used to carry out the calculations, and conformational searches were carried out on PM3 minimized structures to find global minima. Systematic searches, in which selected bonds are rotated systematically at specified angles, were carried out on bicyclic carbamates **7**, **10**, **11**, and **15** and Boc amines **4**, **28**, and **5**. For the constrained carbamates, the isopropyl and *tert*-butyl substituents were allowed to rotate to generate possible conformations for minimization. For the Boc amines, rotation about the N−CO bond was allowed. An Osawa search, which carries out ring flips as well as systematic bond rotations, was carried out on perhydroazepine **6**.

(25) Quenching the reaction at −78 °C was necessary to prevent cyclization of the alkoxide.

(26) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546−8548.

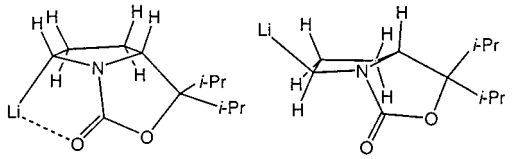
(27) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622−2636.

Table 5. Tin−Lithium Exchange of (*S*)-**39** To Give (*S*)-**28**[a]

solvent	temp (°C)	time (h)	yield **28** (%)	er **28**
THF	−78	2	65	95:5
Et_2O	−40	1	65	89:11
Et_2O	−40	2	53	82:18
Et_2O	−40	3	76	80:20
Et_2O	−40	5	33	65:35
Et_2O	−40	6.5	54	61:39
Et_2O	−40	8	20	55:45
Et_2O/TMEDA	−78	10	66	90:10
Et_2O/TMEDA	−40	1	50	46:54

[a] For reactions at −40 °C, transmetalation was carried out at −78 °C for 20 min, and the solution was warmed to −40 °C over 50 min.

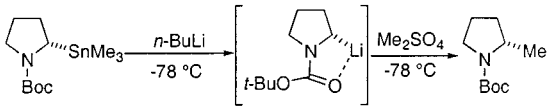
chelation between the lithium and the carbonyl oxygen was specified, and the remaining valences of the lithium were occupied by Et_2O molecules. In the absence of chelation and in the presence of an additional Et_2O molecule, *trans*-**16** was calculated to be 1.6 kcal/mol lower in energy than *cis*-**16**. These results support the possibility that *trans*-**16** has a weaker chelating interaction between the carbonyl oxygen and the lithium than *cis*-**16**. Additionally, the orthogonal relationship between pi system and the anion that is favorable in dipole-stabilized carbanions appears to be less accessible *trans*-**16** than in *cis*-**16**.



cis-**16** *trans*-**16**

The configurational stability of **38** was studied by transmetalation of stannane (*S*)-**39** and subsequent reaction with dimethyl sulfate. It was established previously that organolithium **38** is configurationally stable in Et_2O at −78 °C.[16] In the present study the configurational stability of **38** at −40 °C in Et_2O in the presence or absence of TMEDA and at −78 °C in THF was investigated. The results of the transmetalation experiments under various conditions are listed in Table 5.

The results in Table 5 indicate that the organolithium **38** is configurationally stable at −78 °C in THF for at least 2 h. At −40 °C epimerization of **38** was observed after 1 h, and **28** was isolated with 89:11 er. The amount of epimerization of organolithium **38** increased over time, and nearly racemic methyl pyrrolidine **28** was obtained after 8 h at −40 °C.



(*S*)-**39** e.r. = 95:5 (*S*)-**38** (*S*)-**28**

While a slow epimerization of organolithium **38** was observed at −40 °C, the configurational lability of **38** was much higher in the presence of TMEDA. Transmetaltion of **39** in the presence of TMEDA at −78 °C for 10 hours followed by the addition of dimethyl sulfate provided **28** with 90:10 er. This result indicates that epimerzation occurs at −78 °C in the presence of TMEDA and is consistent with a previous report.[16] The organolithium **38** is rapidly configurationally labile at −40 °C in the presence of TMEDA, and racemic **28** was provided after only 1 h.

The transmetalation−substitution of (*S*)-**39** provides (*S*)-**28**, which has the same absolute configuration as the product generated from asymmetric deprotonation of **4** and substitution with dimethyl sulfate. The absolute configuration of (*S*)-**28** was established previously by conversion to (*S*, *S*)-*N*-Boc-2,5-dimethylpyrrolidine, and the assignment of (*S*)-**39** is based on analogy to this previous work and doubly retentive reactions.[16]

Discussion

The results summarized in Tables **1**−**4** show that lithiations of the carbamates **7**−**10** and **15** proceed with removal of the proton nearest to the carbonyl oxygen in reactions which are kinetically, as well as thermodynamically favored.

The data in Table 3 do not show a clear trend between the dihedral angles available to the calculated ground state conformations of carbamates **7**, **10**, **11**, and **15** and the competitive efficiencies. In each case, however, the dihedral angle between the carbamate carbonyl group and the *cis* proton is much smaller than the angle between the carbonyl and the *trans* proton. In conjunction with the observation that **7**−**10** undergo lithiation−substitution with high *cis* stereoselectivity, these data suggest that the angle between the carbonyl group and the proton to be removed can be a controlling factor in carbamate-directed lithiations. For *N*-Boc amines **4**, **5**, and **6**, the range of possible angles between the carbamate carbonyl group and the proton removed is expected to be greater since Boc group is less restricted than in the constrained carbamates. The fact that the bicyclic carbamates are lithiated with greater efficiency than the Boc amines also suggests that constraining the position of the proton to be removed at an appropriate angle to the carbamate increases the efficiency of lithiation.

The distance between the carbamate carbonyl group and the proton removed appears to be important. The distance between the carbonyl and the proton of interest generally decreases as the amine ring size increases in the ground state. Carbamate **7** is lithiated with the greatest competitive efficiency and a distance of 2.78 Å between the carbamate carbonyl group and the proton removed as calculated by PM3 is taken to be optimal. Generally, competitive efficiency decreases as the calculated distance between the carbamate carbonyl group and the proton removed decreases from 2.78 Å.

Wilberg and Bailey have recently calculated a transition state for the enantioselective removal of the *pro*-S hydrogen of **4** with *i*-PrLi−(−)-sparteine.[28] The hydrogen oxygen distance is 2.64 Å in the ground state of the complex and 2.80 Å in the transition state. Würthwein, Behrens, and Hoppe have carried out a calculation for lithiation adjacent to oxygen in an *i*-PrLi−(−)-sparteine complex and obtain a transition state value of 2.799 Å.[29]

Our studies of the configurational stability of **38** show that epimerization is slow at −40 °C in the absence of diamine but rapid in the presence of TMEDA. The epimerization of *trans*-**16** is also greatly facilitated by the presence of TMEDA. The ligand may coordinate to the lithium and form an ion pair in which the lithium can be delivered to the opposite face of the bicyclic system. In the absence of TMEDA, the configurational stability of *trans*-**16** is greater than that of more flexible dipole-stabilized diastereomerically biased carbanions. Organolithium *cis*-**16** is more thermodynamically stable than *trans*-**16**, and chelation between the carbamate carbonyl group and the lithium is considered to provide a driving force for the epimerization of *trans*-**16**. This study suggests that rotationally restricted dipole-stabilized carbanions with a favorable geometry between

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(29) Würthwein, E. U.; Behrrens; and Hoppe, D. *Eur. J. Org. Chem.* **1999**, *5*, 3459.

the lithium and the carbonyl group may have enhanced configurational stability relative to less restricted carbanions.

The presence of TMEDA increased the rate of epimerization of both **38** and *trans*-**16**. It has been proposed that highly coordinating additives and solvents facilitate the epimerization of organolithiums by providing stabilization to charge-separated species.[30−32] It is believed that in cases where this effect is observed, the rate-determining step for epimerization is the separation of the carbon and lithium into an ion pair. The accelerating effect of highly coordinating additives was not observed for the epimerization of α-thio- and α-selenoorganolithiums.[33,34] For these organolithiums rotation about the carbanionic carbon−heteroatom bond is proposed to be the rate-determining step. The results from the configurational stability studies in Tables 4 and 5 are consistent with a mechanism in which separation of the carbon and lithium into an ion pair is the rate-determining step. The ligand TMEDA may facilitate the epimerization of *trans*-**16** by chelating to the lithium atom and delivering it to the opposite side of the molecule. Epimerization of *trans*-**16** is also observed in the absence of TMEDA at higher temperatures. It is possible that at −40 °C in the absence of diamine, the solvent may facilitate separation of the carbon and lithium to provide a pathway to the more thermodynamically stable organolithium *cis*-**16**. Alternatively, a dimerization dissociation process can be envisioned.

The results of these studies indicate that the orientation of the carbamate carbonyl group with respect to the lithium affects the configurational stability of a carbanion. The organolithium *cis*-**16**, a rigid structure in which a dipole-stabilizing group is in close proximity to the lithium atom, was found to undergo a highly stereoselective substitution reaction with dimethyl sulfate at −78 °C and −40 °C to provide *cis*-**26**. The structurally rigid *trans*-**16** is less thermodynamically stable than *cis*-**16** but maintains its configuration at −78 °C in the absence of TMEDA.

Therefore, it is more configurationally stable than rotationally flexible diastereomerically biased organolithiums studied by Pearson and co-workers.[26,27] At −40 °C, *trans*-**16** undergoes epimerization within 1 h, and this epimerization, which is facilitated by TMEDA or the solvent, may be driven by chelation of the lithium to the carbamate carbonyl oxygen. On the other hand, the organolithium **38** epimerizes at −40 °C and is therefore less configurationally stable than 2-lithio-*N*-methylpyrrolidine, which was studied by Gawley and co-workers.[35] It is possible that chelation of the carbonyl oxygen to the lithium may facilitate epimerization in **38** since a rotation which carries the lithium away from the carbanionic carbon is possible. These rationales assume the epimerization is unimolecular; a prospect which has not been established. An alternative pathway involving another lithium in a complex which assists backside epimerization is also possible.

Summary

The selectivity of proton transfer in these reactions are reasonably attributed to favorable arrangements for transfer of the proton to the lithiating reagent within a complex of the carbamates with the reagent. The competition experiments between a series of bicyclic carbamates and *N*-Boc amines show that the rigid carbamates were lithiated significantly faster than less rotationally restricted *N*-Boc amines. Differences between competition experiments carried out under second-order and pseudo-first-order conditions suggest that an additional factor favoring the rigid carbamates may be a more favorable prelithiation complex formation. The sum of these results suggest that appropriate restriction of the geometry of the substrate can increase the efficiency of the lithiation reaction and a small angle between the carbonyl group and the proton removed is favored. This work is consistent with the importance of complexation in the reactions and stabilities of lithio dipole-stabilized carbanions.

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Supporting Information Available: The experimental detail is provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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