3010, 2940, 1500, 1470, 1330, 1020, 860, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (9 H, s), 2.45 (3 H, s), 2.83–3.00 (2 H, s), 7.14 (2 H, s), 7.55 (2 H, s); MS, *m/e* 321 (M^+). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.32; H, 7.24; N, 4.63.

Nitration with Mixed Acid. To a solution of 0.5 mmol of **28e–g** in 150 mL of AcOH was added gradually at room temperature a solution of 2.2 mL of fuming HNO_3 and 1 mL of concentrated sulfuric acid. After the reaction mixture was stirred for 1 h, it was poured into a large amount of ice water. The organic layer was washed with water, dried over $MgSO_4$, and evaporated in vacuo to leave a residue that was recrystallized to give **33d–f**.

2-Nitro-7-bromo-4,5,9,10-tetrahydropyrene (33e): yellow prisms (hexane/benzene, 1:2), mp 248–250 °C; IR (KBr) 2940, 1605, 1575, 1510, 1440, 1420, 1340, 1310, 1250, 1225, 1080, 985, 910, 890, 855, 810, 870, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.80–3.05 (8 H, m), 7.30 (2 H, s), 7.96 (2 H, s); MS, *m/e* 329, 331 (M^+). Anal. Calcd for $C_{16}H_{12}BrO_2N$: C, 58.20; H, 3.66; N, 4.24. Found: C, 58.31; H, 3.74; N, 4.39.

2-Nitro-7-cyano-4,5,9,10-tetrahydropyrene (33f): pale brown prisms (benzene), mp >300 °C; IR (KBr) 3060, 2940, 2210, 1580, 1505, 1440, 1430, 1335, 1085, 920, 900, 775, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.92–3.08 (8 H, m), 7.43 (2 H, s), 8.00 (2 H, s); MS, *m/e* 276 (M^+). Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.68; H, 4.52; N, 10.12.

2,7-Dinitro-4,5,9,10-tetrahydropyrene (33q): yellow prisms (hexane/benzene, 1:3), mp >300 °C; IR (KBr) 3100, 2950, 1590, 1445, 1425, 1335, 1100, 920, 900, 765, 745, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.05 (8 H, s), 8.02 (4 H, s); MS, *m/e* 296 (M^+). Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.84; H, 4.16; N, 9.53.

Nitration of 2-Methyl-7-*tert*-butyl-4,5,9,10-tetrahydropyrene (36a) with Fuming HNO_3. To a solution of 138 mg (0.5 mmol) of **36a** in 150 mL of AcOH was added gradually a solution of 2.7 mL of fuming HNO_3 and 6 mL of AcOH. After the reaction mixture was stirred at room temperature for 1 h, it was treated and worked up as described above to give 112.6 mg (85%) of **33b**.

Nitration of 36a with 63% HNO_3. To a solution of 138 mg (0.5 mmol) of **36a** in 150 mL of AcOH was added gradually a solution of 2.7 mL of 63% HNO_3 and 6 mL of AcOH. After the reaction mixture was stirred at room temperature for 1 h, it was treated and worked up as described above to give 136 mg of starting compound (**36a**).

Nitration of 2,7-Di-*tert*-butyl-4,5,9,10-tetrahydropyrene (36b) with Fuming HNO_3. To a solution of 153 mg (0.5 mmol) of **38a** in 150 mL of AcOH was added gradually a solution of 2.7 mL of fuming HNO_3 and 6 mL of AcOH. After the reaction mixture was stirred at room temperature for 1 h, it was treated and worked up as described above to give 138.3 mg (90%) of **33c**.

Nitration of 36b with 63% of HNO_3. To a solution of 153 mg (0.5 mmol) of **36b** in 150 mL of AcOH was added gradually a solution of 2.7 mL of 63% HNO_3 and 6 mL of AcOH. After the reaction mixture was stirred at room temperature for 1 h, it was treated and worked up as described above to give 150 mg of starting compound (**36b**).

Preparation of 1-Methoxy-2-amino-7-*tert*-butyl-4,5,9,10-tetrahydropyrene (39) by Reduction of 37b. After hydrogen gas was introduced into a solution of 150 mg (0.445 mmol) of **37b** in 20 mL of ethanol in the presence of 40 mg of 10% Pd/C under stirring for 3 h at room temperature, the Pd/C was filtered off. The filtrate was evaporated in vacuo to leave the residue, which was recrystallized from hexane to give 130 mg (95%) of **39** as pale yellow prisms, mp 84–87 °C: IR (KBr) 3200, 3010, 2940, 1580, 1460, 1430, 1410, 1325, 1210, 980, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (9 H, s), 2.60–3.20 (8 H, m), 3.74 (3 H, s), 6.48 (1 H, s), 7.07 (2 H, s); MS, *m/e* 307 (M^+). Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.75; H, 8.26; N, 4.51.

Preparation of 1-Methoxy-7-butyl-4,5,9,10-tetrahydropyrene (40) by Deamination of 39. To a solution of 100 mg (0.325 mmol) of **39** in 2 mL of concentrated hydrochloric acid was added gradually at 10–13 °C a solution of 61 mg (0.78 mmol) of sodium nitrite in 1 mL of water. The reaction mixture was stirred for 15–20 min at 5–10 °C and poured rapidly into 2 mL of ice-cold 30% hydrophosphorous acid solution and then allowed to stand at room temperature for 12 h. The reaction mixture was extracted with dichloromethane. The dichloromethane extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo to leave a residue, which was column chromatographed on silica gel by using a mixture of hexane and benzene (1:1) to give 30 mg (31.6%) of **40** as a colorless oil: IR (Nujol) 2940, 1610, 1480, 1380, 1360, 1100, 1025, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (9 H, s), 2.80–3.00 (8 H, m), 3.83 (3 H, s), 6.69 (1 H, d, J = 8.1 Hz), 6.99 (1 H, d, J = 8.1 Hz), 7.10 (2 H, s); MS, *m/e* 292 (M^+). Anal. Calcd for $C_{21}H_{24}O$: C, 86.25; H, 8.27. Found: C, 86.48; H, 8.31.

Reaction of 8,11-Dimethoxy-5-*tert*-butyl[2.2]metacyclophane (42) with Iodine To Give 40. A solution of 336 mg (1.04 mmol) of **42** and 524 mg (2.08 mmol) of iodine in 6 mL of benzene was stirred for 12 h at 60 °C. The reaction mixture was washed with 10% sodium thiosulfate solution and then with water. The benzene solution was dried over $MgSO_4$ and evaporated in vacuo to leave the residue, which was column chromatographed on silica gel by using hexane as eluent to give 241 mg (79.3%) of **40**.

Oxidation of 8,16-Dimethyl-5,13-dimethoxy[2.2]metacyclophane (25) with $FeCl_3$. After a mixture of 50 mg (0.17 mmol) of **25** and 1.75 mg of $FeCl_3$ in 5 mL of $CHCl_3$ was stirred at room temperature for 3 h, the formed precipitate was filtered. To the filtrate was added 3 mL of 3 N HCl, and the extract was washed with water, dried over Mg_2SO_4, and evaporated in vacuo to leave a residue that was recrystallized from 23 mg (51%) of **24**.

Formation, Structures, and Reactions of Selected α′-Lithioallyl Amides

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Lithiations of the selected allyl amides **6**, **10**, **14**, and **17** give the α′-lithioallyl amides **7**, **11**, **15**, and **18**. The structures of **7**, **11**, and **18** are characterized by their NMR spectra. Electrophilic substitutions of these reagents are usually regioselective at the γ′-position, but there are exceptions. In situ lithiation–electrophilic substitutions are effective for **10** and **17** with LiTMP–$(CH_3)_3SiCl$, *n*-BuLi–$C_6H_5CH_2Cl$, and *n*-BuLi–$Cl(CH_2)_4Cl$. Hydrogen–deuterium isotope effects are consistent with diastereoselective removal of a pseudoequatorial proton from **17**. The lithiations are suggested to occur in an amide–organolithium complex and most readily in systems that can achieve a *Z* conformation.

Allyl organolithium reagents bearing a terminal nitrogen have proven to be of synthetic value, and the chemistry of such species is of continuing interest.[1,2] A number of tertiary allyl amide analogues have been found to undergo

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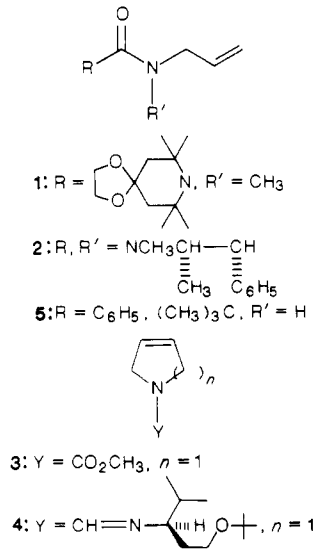
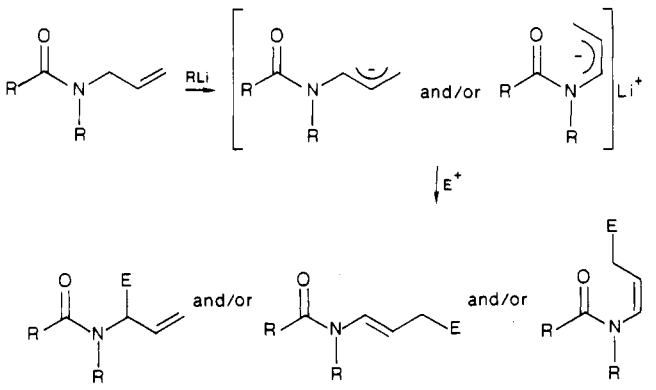
α′-lithiation to give dipole-stabilized carbanions. Seebach provided an early and clever example with the lithiation–electrophilic substitution sequence of the urea **1** to give γ′-substituted products which are readily converted to β-substituted aldehydes by treatment with acid.[3] Helmchen generated an α′-lithioallyl amide reagent from the urea **2** and used it, after trans metalation, for additions to carbonyl electrophiles which showed high diastereoselectivities.[4] Pandit and Macdonald have found that the Δ³-pyrrolidine carbamate **3** gives products of α′-substitution in the lithiation–electrophilic substitution sequence.[5] Meyers has used the chiral formamidines of Δ³-pyrrolidine and Δ³-piperidine **4** for α′-lithiation and electrophilic substitutions in elegant asymmetric syntheses. These reports illustrate the advantages of this approach to amine elaboration.[6] Secondary allyl amides have been shown by Tishler to undergo dilithiation to give *N*-lithio α′-lithioallyl amide reagents which react with electrophiles at the γ′-position.[7]

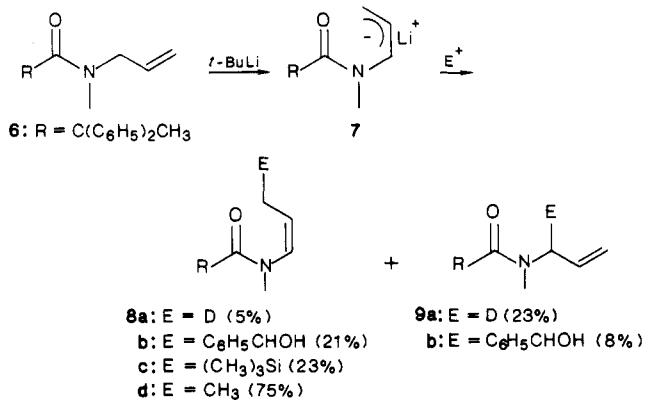


We have carried out α′-lithiation of selected allyl amides, determined the structure of the resulting substituted allyl lithium reagents by NMR, and investigated the course of the reaction of these organometallics with electrophiles. Scheme I illustrates the possible chemistry of the simplest of these species. Lithiation is expected to occur when the allyl group is syn to the carbonyl oxygen and to provide a terminally nitrogen substituted allyl anion which could exist in the *Z* and/or *E* conformations.[1,2] Reaction of this allyl lithium reagent with electrophiles could occur to give the α′- or γ′-substituted isomeric products.

Scheme I



Scheme II



The allyl amides we have investigated were chosen to provide systems in which the allyl lithium reagents would be free to rotate, as for **7** from **6**, or constrained to cis, **11** from **10**, or trans, **15** from **14**, geometries. In addition, **17** provides a system that has diastereotopic α′-protons. We find that α′-lithioallyl amide reagents, which have the expected planar structure, can be produced by these lithiations and that these reagents react with electrophiles, usually preferentially at the γ′-position. However, the yields from this sequence are modest. Hydrogen–deuterium isotope effects are consistent with slow deprotonation and low stereoselectivity.

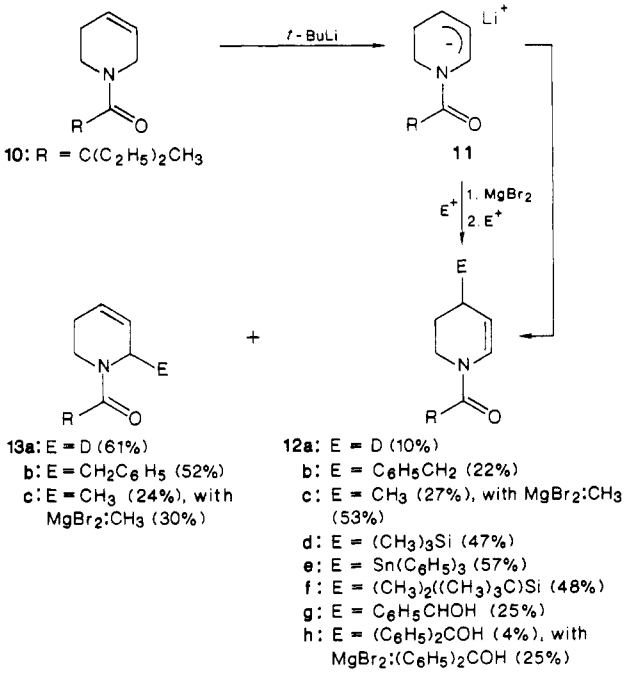
Results

Syntheses of the Allyl Amides. The allyl amides **6**, **10**, **14**, and **17** were prepared by straightforward syntheses, which are summarized in the Experimental Section and the supplementary material.

Lithiations of the Allyl Amides. Lithiation with *tert*-butyllithium, −78 °C, in 4:1 diethyl ether/tetrahydrofuran for 15 min was found to be satisfactory for most cases.[8,9] Scheme II provides the results for the lithiation–electrophilic substitution sequence of **6** with methanol-*d*, methyl iodide, trimethylsilyl chloride, and

(1) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471.
(2) In particular, amino allyl lithium reagents have been useful as homoenolate equivalents. For summaries, see: (a) Biellman, J.; Ducep, J. *Org. React. (N.Y.)* **1982**, *27*, 1. (b) Ahlbrecht, H. *Chimia* **1977**, 391. (c) Stowell, J. C. *Chem. Rev.* **1984**, *84*, 409. Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. In acyclic systems, the double-bond geometry in the product is usually trans and the regiochemistry of the reaction is affected by the metal. For representative cases, see: Ahlbrecht, H.; Bonnet, G.; Enders, D.; Zimmermann, G. *Tetrahedron Lett.* **1980**, *21*, 3175. Yamamoto, Y.; Yatagai, H.; Saito, Y.; Maruyama, K. *J. Org. Chem.* **1984**, *49*, 1096. Martin, S. F.; DuPriest, M. T. *Tetrahedron Lett.* **1977**, 3925. Julia, M.; Schouteetan, A.; Baillarge, M. *Tetrahedron Lett.* **1974**, 3433. Schouteetan, A.; Julia, M. *Tetrahedron Lett.* **1975**, 607. Ahlbrecht, H.; Eichler, J. *Synthesis* **1974**, 672. Rauchschwalbe, G.; Ahlbrecht, H. *Synthesis* **1974**, 663.
(3) Hassel, T.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 399.
(4) Roder, H.; Helmchen, G.; Peters, E.-M.; Peters, K.; Schnering, H.-S. v. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 898.
(5) Armande, J. C. L.; Pandit, U. K. *Tetrahedron Lett.* **1977**, 897. Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1984**, *37*, 1503. Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193.
(6) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270. Meyers, A. I.; Bailey, T. R. *J. Org. Chem.* **1986**, *51*, 872.
(7) Tischler, A. N.; Tischler, M. H. *Tetrahedron Lett.* **1978**, 3407.
(8) The diethylbutanoyl group has been used previously. Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010. Other conditions could be used for the lithiation, but these were most suitable for comparison with the allyl amides of the present study.
(9) For details, see: Lee, B. Ph.D. Thesis, University of Illinois, 1987. Available from University Microfilms, Ann Arbor, MI.

Scheme III

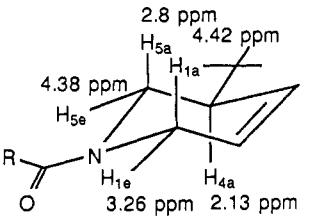


benzaldehyde as electrophiles. The predominant γ'-substitution and Z geometry in the products **8** are assigned on the basis of the ^1H NMR spectra of the products. This stereochemistry and regiochemistry are consistent with that of most related allyl lithium reagents.[2,10] We estimate that 5% of the E isomers of **8** would have been detected in the cases of methylation and silylation but note that yields and material balances are not high. The α'-substituted products **9** are obtained as minor products with methanol-*d* and benzaldehyde. The sequence is shown to involve **7** with the Z conformation as an intermediate (vide infra).

The Δ^3-piperidinyl amide **10** has been lithiated and electrophilically substituted to give **12** and **13** as shown in Scheme III. The intermediate allyl lithium reagent **11** necessarily has a cis conformation in this case. In addition to deuteriation, methylation, and silylation, **11** has been treated with benzyl chloride, triphenyltin chloride, *tert*-butyldimethylsilyl chloride and benzophenone and with magnesium bromide prior to reaction with methyl iodide and benzophenone. The results of these experiments show predominant γ'-substitution with carbonyl compounds and silyl chlorides and a mixture of α'- and γ'-substitution with alkyl halides. The latter results contrast with those of Meyers et al., who observed predominantly γ-substitution with the corresponding formamidine.[6]

Lithiation of the allyl amide **14** in which the allyl lithium reagent **15** is necessarily in the E geometry was the most difficult of the series studied. We had to use hexane as solvent and *tert*-butyllithium or lithium tetramethylpiperidide to achieve metalation. Before the reactions with trimethylsilyl chloride and methyl iodide to give the products **16**, a precipitate, presumably **15**, appears in the reaction. The sequence is shown in Scheme IV.

The conformationally fixed system **17** was investigated to provide information about the stereochemistry of the lithiation and substitution steps. The ^1H NMR assignments of Figure 1 for structure **17** provide chemical shift and coupling values which were used as standards to assign

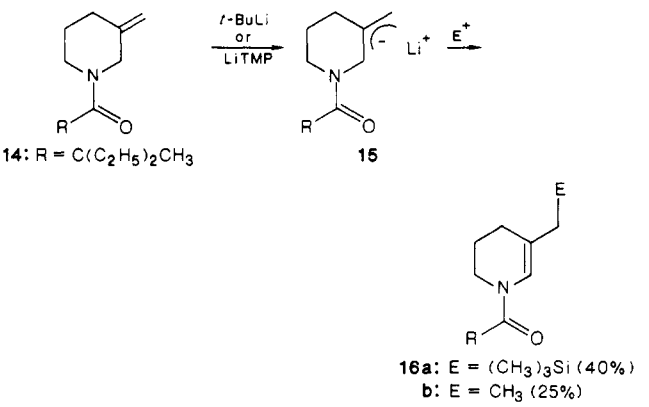


17

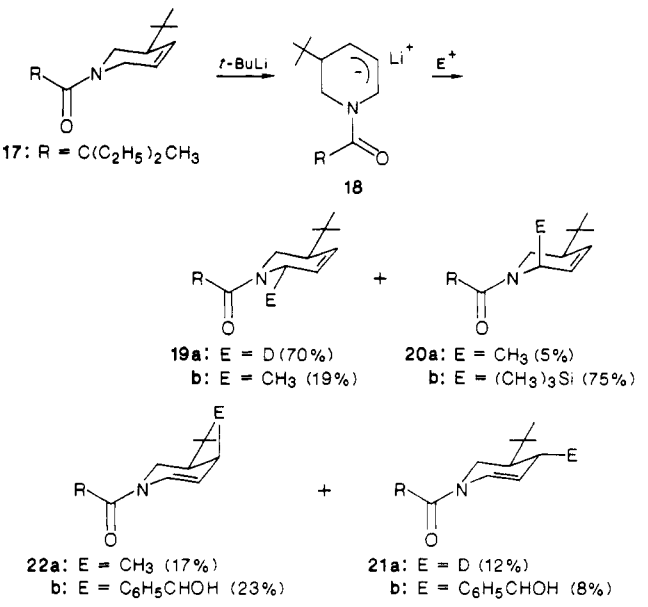
$JH_4H_5ax = 10.5$ Hz
$JH_4H_5eq = 4.5$ Hz

Figure 1.

Scheme IV



Scheme V

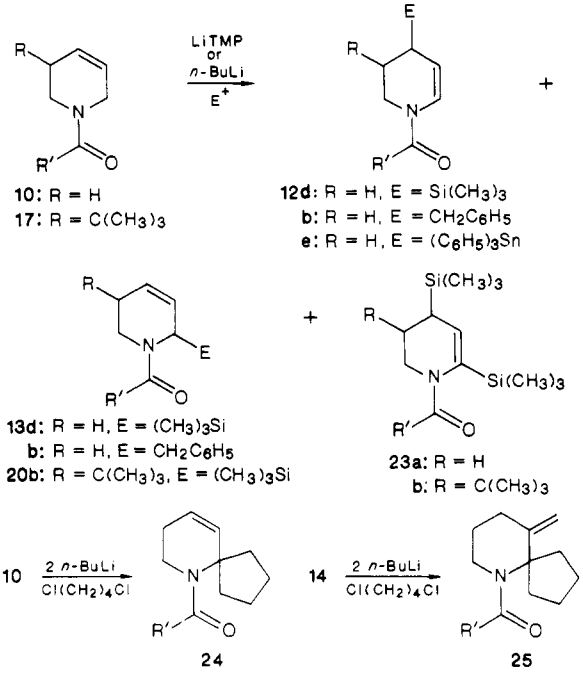


stereochemistry to the products **19–22** shown for the sequence in Scheme V.[9] The distinction between the axial and equatorial protons and the magnitudes of the couplings are consistent with precedent and a half-chair conformation of the piperidine ring.[9,11]

(10) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932 and references cited therein.

(11) Siddall, T. H., III; Stewart, W. E. *J. Mol. Spectrosc.* **1967**, *24*, 290. Palasy, P. D.; Utley, J. H. P.; Hardsone, J. D. *J. Chem. Soc., Perkin Trans. 2* **1984**, *No. 2*, 807. Lambert, J. B.; Shurvell, H. F.; Verbit, L.; Cooks, R. G.; Stout, G. H. *Organic Structural Analysis*; Macmillan: New York, 1967; Chapters 4 and 6. Lambert, J. B.; Keske, R. G.; Carhart, R. E.; Jovanovich, A. P. *J. Am. Chem. Soc.* **1967**, *89*, 3761. A barrier of ca. 12 kcal/mol for amide rotation was obtained from a coalescence temperature of −27 °C.

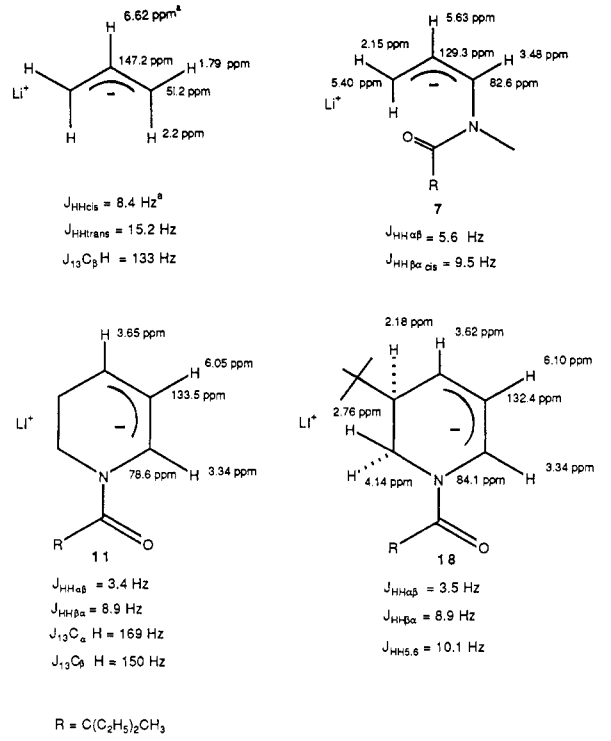
Scheme VI[a]



[a] R′ = $C(C_2H_5)_2CH_3$.

The reaction sequence proceeds via **18** and was carried out with the electrophiles methanol-*d*, methyl iodide, trimethylsilyl chloride, and benzaldehyde. Deuteriation gives mainly the α′-substituted product **19** with largely equatorial substitution. The α′-substitution products obtained with methyl iodide and trimethylsilyl chloride are axial. Deuteriation also gives some γ′-substituted products, and that regiochemistry, with axial stereochemistry, is observed for the major isolated products of methylation and of reaction with benzaldehyde. The yields are low.

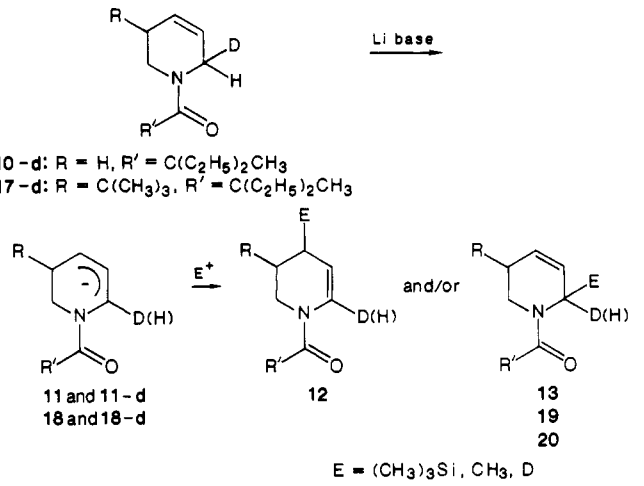
In an effort to obtain better yields, we investigated a number of in situ lithiation–substitutions as summarized in Scheme VI for **10** and **17**.[12] With **10**, 1 equiv of lithium tetramethylpiperidide, and 2 equiv of trimethylsilyl chloride, the products are **12d** and **13d** in 59% and 13% yields. With 3 equiv of base and 6 equiv of the electrophile, the disilylated product **23** is obtained in 86% yield.[13] Under the former conditions, **17** gives **20b** in 31% yield, while the latter conditions give **23** in 83% yield. Reaction of **14** with lithium tetramethylpiperidide and trimethylsilyl chloride gives **16a** in 64% yield. Other electrophiles are also compatible with in situ reactions. Treatment of **10** with lithium tetramethylpiperidide and triphenyltin chloride gives **12e** in 64% yield. The use of *n*-butyllithium with **10** in the presence of benzyl chloride gives **12b** and **13b** in 73% yield in a 40:60 ratio. Treatment of **10** and **14**, respectively, with 2 equiv of *n*-butyllithium and 1,4-dichlorobutane provides **24** and **25** in 10% and 31% yields. Although the yields are low, the convenience of this reaction for forming spiro rings is interesting.



[a] all values from ref 14

Figure 2. ^1H and ^{13}C NMR values.

Scheme VII



Structures of the α′-Lithioallyl Amides. Allyl lithium reagents are known to be aggregated species and have been represented as both localized and delocalized structures.[14] We have measured the ^1H and ^{13}C NMR spectra of the α′-lithioallyl organolithium amides **7**, **11**, and **18**. The pertinent chemical shifts and coupling constants are shown in Figure 2 along with the values for allyllithium. The α′,β′ coupling constant of 5.6 Hz for **7** is consistent with the precedent *Z* geometry.[14] The spectrum for **18**,

(12) For a number of in situ trapping reactions in lithiations, see: Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1984**, *37*, 1503. Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193. Ahlbrecht, H.; Eichler, J. *Synthesis* **1974**, 672. Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155. Taylor, S. L.; Lee, D. Y.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. Eaton, P. E.; Castaldi, G. *J. Am. Chem. Soc.* **1985**, *107*, 724. Goronowicz, G. A.; West, R. *J. Am. Chem. Soc.* **1968**, *90*, 4478.

(13) Both **12a** and **13a** can provide **22** under these reaction conditions, with **13a** reacting faster. Use of *n*-butyllithium as the in situ base provides **12a** and **22** in 71% and 9% yields. Reaction of **10** with 1 equiv of lithium tetramethylpiperidide and *tert*-butyldimethylsilyl chloride gives **12f** in 53% yield.

(14) O'Brien, D. H. *Comprehensive Carbanion Chemistry*; Buncel, T., Durst, E., Eds.; Elsevier: New York, 1980; Vol. 5, Chapter 6. Chandrasekhai, J.; Andrade, J. G.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5609. Bartmess, J. E.; Hehre, W. J.; McIver, R. T.; Overman, L. E. *J. Am. Chem. Soc.* **1977**, *99*, 1976. Boche, G.; Mortens, D.; Wagner, H.-U. *J. Am. Chem. Soc.* **1976**, *98*, 2668. Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. Ahlbrecht has shown that J_{HHcis} is 9.1 Hz and $J_{HHtrans}$ is 14.8 Hz in an α-amino allyl lithium.[2] The values for the allyl lithium in Table 1 (supplementary material) are from the following: Frankel, G.; Halasa, A. F.; Mochel, V.; Stumpe, R.; Tate, D. *J. Org. Chem.* **1985**, *50*, 4563 and references cited therein.

which has a large axial–axial coupling for the protons at the 5- and 6-positions, is consistent with a conformationally fixed structure. The other values for **7**, **11**, and **18** are consistent with literature assignments for related systems and with the planar structures shown. Although delocalized monomeric representations are used for convenience, these species are likely aggregated and could be rapidly equilibrating.

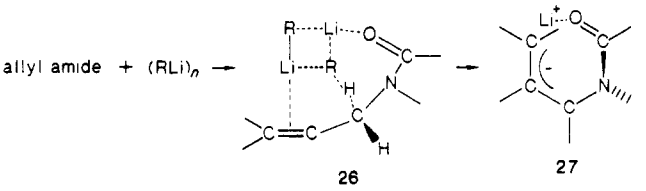
Isotope Effects in the Formations of 11 and 18. We have determined the intramolecular hydrogen deuterium isotope effects for deprotonations of **10** and **17** providing **11** and **18**, respectively, by the experiments shown in Scheme VII. The ratio of the products for the reaction of **10**-*d* with *t*-BuLi or LiTMP at −78 °C gives an isotope effect of 15.4 ± 2.0 for the formation of **11**. Distinction between the diastereotopic α' axial and equatorial protons is provided by the lithiation of 17-d_e and 17-d_a in which the stereochemistry of the deuterium if >95% in the pseudoequatorial and pseudoxial positions, respectively. Analysis of the product ratio under the protocol of Eliel provides a ratio of pseudoequatorial to pseudoaxial hydrogen removal of 2.4 and an average isotope effect for these deprotonations of 9.3 ± 5.0.[15] The large isotope effects are in the range expected for rate-limiting proton removal. The 2.4 diastereoselectivity difference between the axial and equatorial hydrogen removals is interesting. Efforts to obtain kinetic (intermolecular) isotope effects with **10**-d_2 and **10** provided values that covered a wide range in accord with the sensitivity of such experiments to large isotope effects and the extent of reaction.[10,16]

Discussion

The above data show that lithiation of the allyl amides **6**, **10**, **14**, and **17** proceeds by removal of the α'-allyl proton to give planar allyl lithium species and that the *Z* configuration is preferred in an acyclic system. It also appears that systems that can achieve a *Z* conformation metalate more readily and may be more stable than one with an enforced *E* conformation. The allyl lithium reagents investigated herein react with most electrophiles regioselectively at the γ'-position. These observations are consistent with previous studies of related systems.[14,17]

The isotope effects are consistent with formation of a complex and removal of the α'-proton within that complex.[18] The demonstration of a relatively small difference in rate of removal of the axial and equatorial protons from **17** might seem surprising since the allyl portion of the product is planar and loss of the pseudoaxial proton could be viewed as promoted by impending delocalization. However, removal of an axial proton could be inhibited by the electron repulsions between the anion and the amide π electrons which Bach has calculated to be an important effect in directing the lithiations of the corresponding saturated systems to be orthogonal to the π bonds of the amide.[19–22] Indeed, if the carbonyl oxygen is bound to the organolithium which effects the proton removal, the planes of the amide and the allyl group may be twisted with respect to each other in the transition structure and in the product.

A possible transition structure for these lithiations is shown as **26**. In this structure, the bridging of the oxygen and double bond by the lithium of the aggregate rationalizes the preference for removal of the allyl proton and for *Z* geometries in the product since alternatives that would give *E* products position the base away from the α'-protons. In the case of a conformationally free allyl group, this leads to structure **27**. By twisting the nitrogen so that the amide and allyl systems are not coplanar, the oxygen of the carbonyl group can be bonded to a lithium which is associated with both ends of the allyl system. The suggestion that deprotonation is activated by multiple associations of the organolithium base is consistent with the kinetics of related reactions.[18] It should also be noted that the relationships of ground-state structures of intermediates to transition structures for the deprotonation or electrophilic substitution are inferential and that kinetic control is assumed as for related directed lithiations.[23]



Experimental Section[24]

***N*-Allyl-*N*-methyl-2-ethyl-2-methylbutanamide (6).** To a stirring solution of 0.304 g (2.12 mmol) of *N*-methyl-2-ethyl-2-methylbutanamide in 20 mL of THF at −78 °C under Ar was added 1.98 mL (1.18 M, 2.33 mmol) of *sec*-butyllithium. This step was followed by warming to −14 °C for 10 min and cooling to −78 °C before addition of 0.37 mL (4.24 mmol) of allyl bromide.

(15) For analysis of diastereotopic proton removals, see: Eliel, E. L.; Hartmann, A. A.; Abatjoglou, A. G. *J. Am. Chem. Soc.* **1974**, *96*, 1807.

(16) Melander, R. C.; Sanders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1980; Chapter 4.

(17) Beak, P.; Becker, P. D. *J. Org. Chem.* **1982**, *47*, 3855; Beak, P.; Carter, L. *J. Org. Chem.* **1981**, *46*, 2363.

(18) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* In Press.

(19) Bach, R. D.; Braden, M. L.; Wolber, G. J. *J. Org. Chem.* **1983**, *48*, 1509.

(20) The stabilization resonance energy of the allyl anion of 10–18 kcal/mol (Thompson, T. B.; Ford, W. T. *J. Am. Chem. Soc.* **1979**, *101*, 5459) and the destabilization of the α anion and the amide π system of 15–18 kcal/mol could be accommodated by a structure in which the amide is twisted with respect to the allyl system, as shown for **27**.

(21) Meyers and Gawley have reported investigations of diastereoselectivity in the α' deprotonations of isoquinoline derivatives of chiral amino oxazolines and formamidines. While Gawley (Gawley, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1265) observed a selectivity of 5.8 for removal of diastereotopic protons and an isotope effect of 5.9, Meyers and Dickman (Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263) found that the removal of one of the diastereomeric protons was specific and therefore greater than the isotope effect. Meyers also observed an equal extent of reaction of d_1 and d_0 reactant, consistent with a rate-determining step other than deprotonation.

(22) We have found the isotope effect for removal of the equatorial proton in *N*-(2-ethyl-2-methylbutanoyl)-4-*tert*-butylpiperidine-2-*d* at −78 °C to be 23 ± 4, consistent with the values for **10**.

(23) Beak, P.; Hunter, J. E.; Jun, Y. H.; Wallin, A. P. *J. Am. Chem. Soc.* **1987**, *109*, 5403.

(24) NMR spectra were taken in deuteriochloroform unless otherwise indicated. Infrared spectra were in CCl_4 solution. Mass spectra were obtained on a Varian MAT Ch-5 spectrometer with an ionization voltage of 10 or 70 eV or a Finnigan MAT 731 spectrometer. Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory. Analytical gas chromatography was performed on a Hewlett-Packard 5970A gas chromatograph equipped with programmable temperature control and a flame-ionization detector. The column used was a SE-52, 0.25 mm × 25 mm capillary column; column head pressure 9 psi, injector temperature 250 °C, detector temperature 300 °C, and programs as indicated. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Bulb-to-bulb distillations were performed on an Aldrich Kugelrohr; boiling points refer to air-bath temperatures and are uncorrected. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium/benzophenone. Dichloromethane (CH_2Cl_2), hexane, and benzene were distilled from calcium hydride. Alkyllithium reagents were purchased from Aldrich Inc. and titrated by the method of Ronald or Tischler.[25] All other chemicals were used as obtained or purified by distillation or recrystallization as needed. All glassware was oven-dried prior to use, and all reactions were done under a dry nitrogen or argon atmosphere. Brine refers to a saturated solution of sodium chloride. The experimental data for **8a–d**, **9a,b**, **12a–c,e–h**, **13a–c**, **16a,b**, **19a,b**, **20a–c**, **21a,b**, **22a,b**, **23a,b**, **24**, and **28–33** is in the supplementary material.

The reaction mixture was then stirred at room temperature overnight before addition of 30 mL of ether, sequential washings with 20 mL of 2% HCl, 5% $NaHCO_3$, and brine, and drying with $MgSO_4$. Removal of solvent in vacuo gave 0.346 g of yellow oil. This oil was purified by MPLC using silica gel and 10% (v/v) EtOAc/hexane to give 0.194 g of light yellow oil. Distillation at 90 °C (3 Torr) returned 0.194 g (50%) of **6** as a clear oil: ^1H NMR (300 MHz) δ 5.81–5.72 (m, 1 H, J = 5.6, 10, 17 Hz, CH_2CH), 5.19 (s, 1 H, J = 10 Hz, $CHCH_2$), 5.14 (d, 1 H, J = 17 Hz, $CHCH_2$), 4.01 (d, 1 H, J = 5.6 Hz, NCH_2), 2.99 (s, 3 H, NCH_3), 1.78 (m, 2 H, $C(CH_2CH_3)$), 1.49 (m, 2 H, $C(CH_2CH_3)$), 1.20 (s, 3 H, CCH_3), 0.89 (t, 6 H, $(CH_2CH_3)_2$); IR (film) 2966 (s), 2938 (s), 2880 (m), 1624 (s), 1458 (m), 1383 (s), 1267 (m), 1082 (m), 920 (m) cm^{-1}.

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.76; H, 11.62; N, 7.76.

Procedure A. General Procedure for the Lithiation and Electrophilic Substitution of Amide 6. To a stirring solution of 1.3 equiv of *tert*-butyllithium in 4:1 ether/THF solvent to make an ca. 0.13 M solution under Ar in −78 °C was added 1 equiv of **6** as an ca. 1.0 M solution in 4:1 ether/THF at room temperature via cannula. The reaction mixture was stirred at −78 °C for 15 min before addition of 2 equiv of electrophile. This was followed by addition of an equal volume of ether, sequential washings with 2% HCl, 5% $NaHCO_3$, and brine, and drying with $MgSO_4$. Removal of solvent in vacuo gave crude reaction products, which were generally purified by MPLC.

***N*-[(1-Ethyl-1-methylpropyl)carbonyl]-1,2,5,6-tetrahydropyridine (10).** To a stirring solution of 3.5 mL (38 mmol) of 1,2,5,6-tetrahydropyridine and 2.30 g (57 mmol) of sodium hydroxide in 15 mL of water at 0 °C was added 5.70 g (38.4 mmol) of 2-ethyl-2-methylbutanoyl chloride dropwise. The reaction mixture was then stirred at room temperature for 1 h before addition of 75 mL of ether, sequential washings with saturated NH_4Cl/2% HCl, 5% $NaHCO_3$, and brine, and drying with $MgSO_4$. Removal of solvent in vacuo gave a clear oil, which was distilled at 120 °C (1 Torr) to give 6.44 g (86%) of **10** as a clear oil: ^1H NMR (90 MHz) δ 5.75 (m, 2 H, CH=CH), 4.08 (m, 2 H, NCH_2CH), 3.70 (t, 2 H, NCH_2CH_2), 2.19 (m, 2 H, $C(CH_2CH_3)$), 2.0–0.90 (m, 16 H, $C(CH_2CH_3)_2$, NCH_2CH_2, CCH_3); IR (film) 2900 (s), 1620 (s), 1405 (s) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 195 (M^+, 12), 110 (18), 85 (55), 67 (30), 43 (100).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80;, H, 10.84; N, 7.17. Found: C, 73.98; H, 10.68; N, 7.30.

Procedure B. General Procedure for the Lithiation and Electrophilic Substitution of Amides 10 and 17. To a stirring solution of 1.3 equiv of *tert*-butyllithium in 4:1 ether/THF solvent to make an ca. 0.13 M solution under Ar at −78 °C was added 1 equiv of **10** and **17** as an ca. 1.0 M solution in 4:1 ether/THF also at −78 °C via cannula. The reaction mixture was stirred at −78 °C for 15 min before addition of 2 equiv of electrophile and stirring at room temperature for 1–2 h. This was followed by workup as described in procedure A to give crude products, which were further purified as described.

***N*-[(1-Ethyl-1-methylpropyl)carbonyl]-4-(trimethylsilyl)-1,4,5,6-tetrahydropyridine (12d).** According to procedure B, 2.19 mL (1.38 M, 3.03 mmol) of *tert*-butyllithium, 0.394 g (2.02 mmol) of **10**, and 0.51 mL (4.03 mmol) of TMSCl gave 0.688 g of an oil. Purification by MPLC using silica gel and 10% (v/v) EtOAc/hexane gave 0.688 g of an oil. Distillation at 100 °C (0.5 Torr) returned 0.306 g (47%) of **12d** as a clear oil: ^1H NMR (200 MHz, relative to $CHCl_3$ at 7.24 ppm) δ 6.87 (d, 1 H, J = 8 Hz, NCH), 4.87 (d, 1 H, J = 8 Hz, NCH=CH), 4.19 (dm, 1 H, J = 16 Hz, $NCH_{eq}H$), 3.14 (overlapping dd, 1 H, J = 16 Hz, $NCHH_{ax}$), 2.08–1.68 (m, 4 H, NCH_2CHH, CH=$CHCH$, $C(CH_2CH_3)$), 1.68–1.37 (m, 5 H, NCH_2CHH, $C(CH_2CH_3)$), 1.19 (s, 3 H, CCH_3), 0.84 (dt, 6 H, $C(CH_2CH_3)_2$), 0.10 (s, 9 H, $Si(CH_3)_3$); IR (film) 2968 (s), 1635 (s), 1477 (w), 1240 (m), 1175 (w), 1003 (w), 880 (w), 837 (s) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 281 (M^+, 16), 127 (19), 96 (65), 85 (100), 73 (35).

Anal. Calcd for $C_{15}H_{29}NOSi$: C, 67.35; H, 10.93; N, 5.24. Found: C, 67.70; H, 10.59; N, 5.26.

***N*-[(1-Ethyl-1-methylpropyl)carbonyl]-3-oxopiperidine (29)** was synthesized from 3-hydroxypiperidine as shown in Scheme VIII.

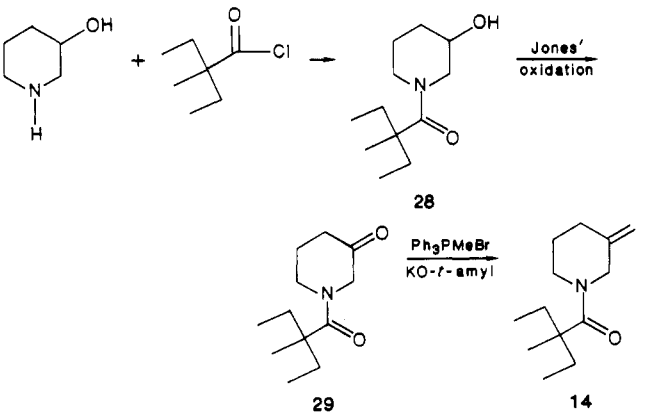
***N*-[(1-Ethyl-1-methylpropyl)carbonyl]-3-methylenepiperidine (14).** To a flask containing 59.41 g (166.3 mmol) of triphenylmethylphosphonium bromide was added 109 mL (1.52 M, 166.3 mmol) of potassium *tert*-amyloxide in benzene followed by reflux for 40 min.[26] while maintaining reflux, a solution of 4.973 g (23.7 mmol) of **29** was added dropwise over 20 min. After being treated at reflux for 2 h, the solution was cooled and added to 300 mL of water before addition of 100 mL of ether and sequential washings with 2% HCl and 5% $NaHCO_3$. The organic solvent was then removed in vacuo to give 20 g of a solid, which was taken up again in ether. Hexane was added to precipitate impurities, and the mixture was filtered. The filtrate was sequentially washed with water and brine and dried with $MgSO_4$. The distillations at 120 °C (1 Torr) gave 3.36 g (68%) of **14** as a clear oil: ^1H NMR (90 MHz) δ 4.77 (d, 2 H, C=CH_2), 4.07 (s, 2 H, NCH_2), 3.63 (t, 2 H, NCH_2), 2.30 (t, 2 H, CH_2C=C), 2.0–1.3 (m, 6 H, NCH_2CH_2, $C(CH_2CH_3)_2$), 1.23 (s, 3 H, CCH_3), 0.88 (t, 6 H, $C(CH_2CH_3)_2$); IR (film) 2976 (s), 2945 (s), 1625 (s) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 209 (M^+, 31), 124 (42), 85 (65), 81 (57), 43 (100).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.64; H, 11.00; N, 6.70. Found: C, 74.30; H, 11.23; N, 6.82.

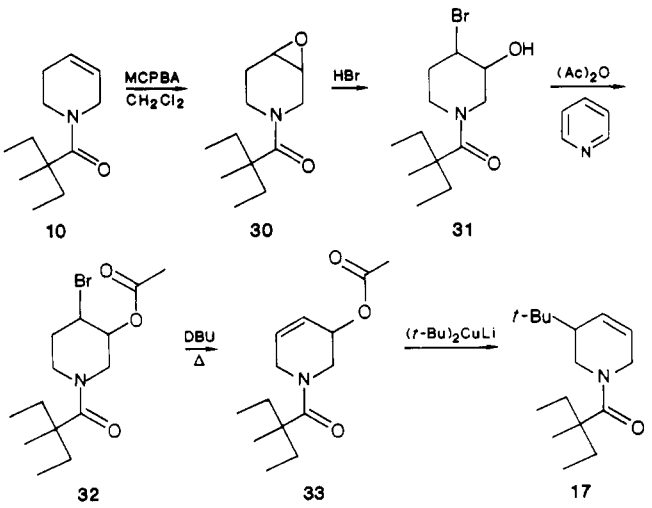
Procedure C. General Procedure for the Formation of LiTMP. To a stirring solution of the desired amount of 2,2,6,6-tetramethylpiperidine (TMP) as a 1.0 M solution in THF at 0 °C under Ar was added 1.1 equiv of *n*-butyllithium. The reaction mixture was then stirred at room temperature for 15 min before cooling to the desired reaction temperature.

***N*-[(1-Ethyl-1-methylpropyl)carbonyl]-5-*tert*-butyl-1,2,5,6-tetrahydropyridine (17) was** synthesized from **33** according to Scheme IX. To a stirring heterogeneous solution of 0.799 g (3.89 mmol) of CuBr·Me_2S in 15 mL of Me_2S and 10 mL

Scheme VIII



Scheme IX



(25) Lansinger, J. M.; Winkle, M. R.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87. Tischler, A. N.; Tischler, M. H. *Aldrichimica Acta* **1978**, *11*, 20.

(26) Schaw, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760.

of THF at −100 °C was added 4.57 mL (1.70 M, 7.78 mmol) of *tert*-butyllithium dropwise via syringe to give an orange solution. This solution was then warmed to −14 °C and stirred for 5 min before addition of 0.985 g (3.89 mmol) of **33** in 2 mL of THF at room temperature via cannula. Stirring was continued for 2 h at −14 °C. After warming to room temperature and stirring for 1 h, 50 mL of ether was added, followed by washing with 30 mL of pH 8 NH_4OH/NH_4Cl. The organic layer was then filtered through Celite, washed two times with 30 mL of the pH 8 solution and brine, and dried with $MgSO_4$. Removal of the solvent in vacuo gave 0.947 g of a light yellow oil. Purification by MPLC using silica gel and 5% (v/v) EtOAc/hexane gave 0.476 g of **17** and 0.214 g (28%) of **10**.

17. Distillation at 120 °C (1 Torr) gave 0.435 g (44%) of **17** as a clear oil: ^{1}H NMR (200 MHz) δ 5.85 (br d, 1 H, J = 10.3 Hz, NCH_2CH=C), 5.75 (dm, 1 H, J = 10.3, 3.7, 2.5, 1.9 Hz, CH=C*H*), 4.40 (m, 2 H, J = 17.9, 12.5, 3.7 Hz, $NCH_{eq}HCH_2$, $NCH_{eq}HCH$), 3.62 (br d, 1 H, J = 17.9, 1.9 Hz, $NCH_{ax}HCH$), 2.81 (dd, 1 H, J = 12.5, 10.5 Hz, $HCH_{ax}HCH_2$), 2.13 (m, 1 H, J = 10.5, 2.5 Hz, C*H*-*t*-Bu), 1.74 (m, 2.5 H, $C(CH_2CH_3)$), 1.46 (m, 2 H, $C(CH_2CH_3)$), 1.17 (s, 3 H, CCH_3), 0.91 (s, 10 H, $C(CH_3)_3$), 0.83 (dt, 7.5 H, $C(CH_2CH_3)_2$). Decoupling: irradiation of the signal at 5.85 ppm decoupled the signal at 5.75, leaving a broad singlet; irradiation of the signal at 5.75 ppm decoupled the signal at 5.85 ppm, leaving a singlet; irradiation of the signal at 4.40 ppm decoupled the signals at 5.75, 3.62, 2.81, and 2.13 ppm, leaving a doublet, broad singlet, doublet, and doublet of multiplets, respectively; irradiation of the signal at 3.62 ppm decoupled the signals at 4.40 and 2.13 ppm, leaving a multiplet and doublet of triplets, respectively; irradiation of the signal at 2.81 ppm decoupled the peaks at 4.40 and 2.13 ppm, leaving a multiplet and broad singlet, respectively; irradiation of the signal at 2.13 ppm decoupled the signals at 4.40, 3.62, and 2.81 ppm, leaving a multiplet, sharpened doublet, and doublet, respectively. IR (film): 3045 (w), 2975 (s), 2958 (s), 2880 (m), 1623 (s), 1460 (m), 1415 (s), 1368 (m), 1225 (m), 1178 (m), 1053 (w), 752 (w) cm^{-1}. Mass spectrum (70 eV): m/e (relative intensity) 252 (21), 251 (M^+, 96), 195 (20), 194 (20), 194 (100), 110 (21), 85 (28).

Anal. Calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.31; H, 11.66; N, 5.72.

Procedure D. General Procedure for the in Situ Reaction of Amides 10 and 17 Using LiTMP and TMSCl. To a stirring solution of the required equivalents of LiTMP in THF at −78 °C under Ar were added the desired equivalents of amide and TMSCl (2 equiv relative to LiTMP) as a mixture in THF at room temperature via cannula. The reaction mixture was then stirred at room temperature for a minimum of 2 h before addition of an equal volume of ether, sequential washing with saturated NH_4Cl/2% HCl, 5% $NaHCO_3$, and brine, and drying with $MgSO_4$. Removal of solvent in vacuo gave crude products, which were purified as described.

In Situ Formation of 12d and *N*-[(1-Ethyl-1-methylpropyl)carbonyl]-2-(trimethylsilyl)-1,2,5,6-tetrahydropyridine (13d) Using LiTMP/TMSCl. According to procedure D, 0.94 mmol of LiTMP in 18 mL of THF, 0.183 g (0.94 mmol) of **10**, and 0.36 mL of TMSCl (2.891 mmol) in 2 mL of THF gave 0.253 g of a yellow oil. Purification by MPLC using silica gel and 2% (v/v) EtOAc/hexane gave 0.182 g (72%) of a mixture of **12d** and **13d** as determined by ^{1}H NMR comparison with authentic materials: GC analysis using standard conditions and an oven temperature of 200 °C shows the yield of **12d** to be 53% and that of **13d** to be 13%.

12d and **13d**: ^{1}H NMR (200 MHz) δ 6.87 (d, 0.37 H, **13d**, NC*H*), 5.64, (m, 2 H, **12d**, C*H*=C*H*), 4.87 (dd, 0.4 H, **13d**, NCH=C*H*), 4.81 (br s, 1 H, **12d**, NC*H*TMS), 4.22 (m, 1 H, **12d** and **13d**, $NCH_{eq2}H$), 3.15 (br t, 1 H, **12d** and **13d**, $NCH_{ax}H$), 2.25 (m, 1 H, **12d**, NCH_2CHH), 2.08–1.40 (m, 12 H, **12d** and **13d**, NCH_2CH_2, $C(CH_2CH_3)_2$), 1.18 (s, 4.1 H, CCH_3), 0.87 (m, 8.7 H, $C(CH_2CH_3)_2$), 0.08 (s, 8.5 H, **12d**, $Si(CH_3)_3$), 0.1 (s, 3 H, **13d**, $Si(CH_3)_3$); GC analysis of this mixture using standard conditions and an oven temperature of 200 °C showed the ratio of **12d**:**13d** to be 70:30, respectively.

Anal. Calcd for $C_{15}H_{29}NOSi$: C, 67.35; H, 10.93; N, 5.24. Found: C, 67.40; H, 10.96; N, 5.17.

***N*-[(1-Ethyl-1-methylpropyl)carbonyl]-10-methylene-6-azaspiro[4.5]decane (25).** To a stirring solution of 0.179 g (0.86 mmol) of **14** and 0.09 mL (0.86 mmol) of 1,4-dichlorobutane in 18 mL of THF at −78 °C under Ar was added 1.47 mL (1.22 M, 1.80 mmol) of *n*-butyllithium dropwise via syringe. The reaction mixture was warmed to room temperature and stirred for 1 h before addition of 20 mL of ether, sequential washings with 2% HCl, 5% $NaHCO_3$, and brine, and drying with $MgSO_4$. Removal of solvent in vacuo gave 0.182 g of a light yellow oil. Purification by MPLC using silica gel and 2% (v/v) EtOAc/hexane gave 0.071 g (31%) of **25** as a clear oil: ^{1}H NMR (200 MHz) δ 4.82 (s, 1 H, C=C*H*H), 4.76 (s, 1 H, C=CH*H*), 3.47 (t, 2 H, J = 6.4 Hz, NCH_2), 2.34 (t, overlapping m, 4 H, J = 6.4 Hz, $NCH_2CH_2CH_2$, $CHHCH_2CH_2CHH$), 2.05–1.35 (m, 14 H, NCH_2CH_2, $CHHCH_2CH_2CHH$, $C(CH_2CH_3)_2$), 1.17 (s, 3 H, CCH_3), 0.88 (t, 6 H, $C(CH_2CH_3)_2$); IR (film) 3084 (w), 2961 (s), 2874 (m), 1632 (s), 1456 (m), 1392 (m), 1358 (m), 1167 (m), 1151 (m), 895 (m) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 264 (2), 263 (M^+, 12), 171 (36), 143 (82), 85 (100), 69 (46), 43 (83), 41 (42).

Anal. Calcd for $C_{17}H_{29}NO$: C, 77.51; H, 11.10; N, 5.32. Found: C, 78.19; H, 10.97; N, 5.09.

Acknowledgment. We are grateful to the National Institutes of Health Institute of General Medicine for support of this work.

Supplementary Material Available: Experimental details of procedure E for the NMR examination of α'-allyl amide anions, Tables 1 and 2 giving data for ^{1}H and ^{13}C NMR experiments with **7**, **11**, and **18**, Table 3 giving intramolecular isotope effect determination data for **10**-*d* **17**-*d*, and experimental details for **8a–d**, **9a,b**, **12a–c,e–h**, **13a–c**, **16a,b**, **19a,b**, **20a–c**, **21a,b**, **22a,b**, **23a,b**, **24**, and **28–33** (28 pages). Ordering information is given on any current masthead page.