The β′ Lithiation of α,β-Unsaturated Amides

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Abstract: The sequence of β′ lithiation and electrophilic substitution of α,β-unsaturated secondary and tertiary amides is reported to provide a convenient method for selective β′ functionalization of α,β-unsaturated acid derivatives. Lithiation with *sec*-BuLi/TMEDA of *N*-methyl-1-cyclohexenecarboxamide (**19**), *N*-methyl-1-cyclopentenecarboxamide (**30**), *N*,*N*-diisopropyl-1-cyclohexenecarboxamide (**36**), *N*,*N*-diisopropyl-6-(trimethylsilyl)-1-cyclohexenecarboxamide (**47**), *N*,*N*-diisopropyl-6-(phenylthio)-1-cyclohexenecarboxamide (**48**), *N*-methyl-4-*tert*-butyl-1-cyclohexenecarboxamide (**56**), (*E*)-*N*,2-dimethylbutenamide (**87**), *N*,2-dimethyl-3-ethyl-2-pentenamide (**92**) and (*E*)-*N*,*N*-diisopropyl-2-methyl-2-butenamide (**104**) occurs at the β′ position. Displacements and addition reactions by the resulting 2-carboxamido allyllithium reagent with a wide variety of electrophiles illustrate the regiochemistry and stereochemistry of this novel β′ substitution in cyclic and acyclic systems. In unsymmetrical acyclic cases regioselective substitution can be achieved. A number of additional conversions of the substituted products are illustrated, including formation of α,β′-unsaturated butyrolactones, β′,β′-spirosubstituted products, and β,β′-disubstituted derivatives. The lithiation of **19** is shown to be kinetically controlled, and the role of the amide function is postulated to lie in its ability to coordinate *sec*-BuLi in a pre-equilibrium complex which directs deprotonation to a proximate site.

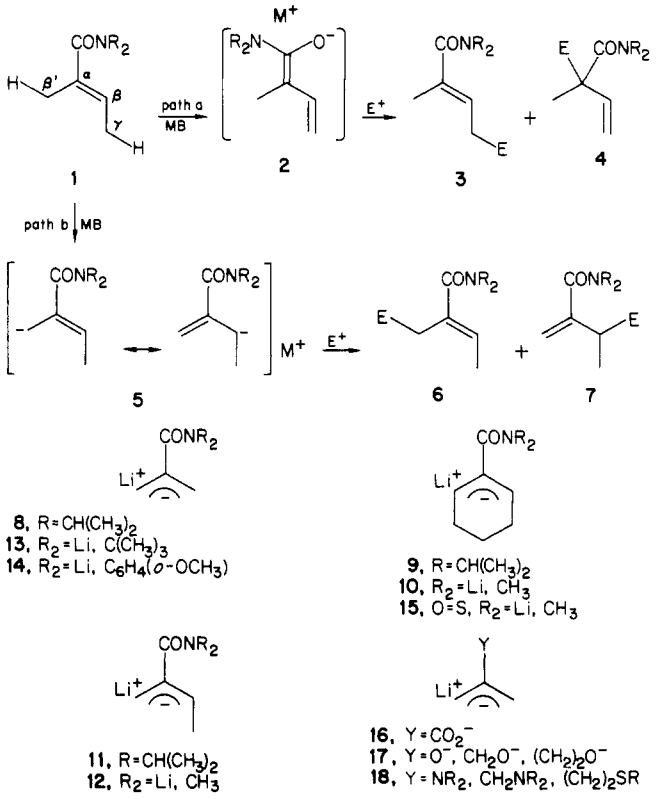
The conversion of a carbon–hydrogen bond to a carbon electrophile bond by deprotonation to give a formal carbanion which subsequently adds to an electrophile is one of the most widely used sequences for the synthesis of organic compounds. The facile formation of new organolithium reagents from readily available precursors can provide species which are uniquely useful in a variety of syntheses. In this report we describe the β′ lithiations of α,β-unsaturated amides to give 2-carboxamido allyllithium reagents and the reactions of these species with a number of different electrophiles.[1] The regio- and stereochemical features of the reactions are delineated and a variety of synthetic uses demonstrated. This novel lithiation is attributed to kinetic deprotonation due to a proximity effect in an amide–organolithium base complex.[2]

The most well precedented reaction of an α,β-unsaturated amide as a proton donor is illustrated by path a in Scheme I. Removal of the thermodynamically most acidic γ proton from **1** provides the enolate **2** which reacts with electrophiles to give the α- and γ-substituted products, **3** and **4**, respectively.[3] Snieckus and co-workers have taken elegant synthetic advantage of the formation of N,γ-dianions analogous to **2** from secondary amides.[3c-f] That work establishes that deprotonation of the γ carbon can occur even in the presence of a formal amide anion, albeit their cases do not have a β′ hydrogen.

We have been interested in the kinetic β′ lithiations of α,β-unsaturated amides with organolithium bases.[2] The reaction is illustrated by path b in Scheme I. Initial deprotonation of **1** gives the 2-carboxamido allyllithium reagent **5** which provides the β′-substituted products **6** and **7** on electrophilic substitution. Such a metalation is precedented by the work of Kauffmann, who postulated that *N*,*N*-diisopropylmethacrylamide reacts with lithium diisopropylamide to give **8** as a transient species.[4] More recently, we,[1] Gschwend,[5] Tanaka,[6] and Yoshida[7] have reported β′ lithiations of α,β unsaturated amides to give the 2-carboxamido allyllithiums **9**–**15** as stable species. Although the precursors to **13** and **14** lack competitively acidic protons, the precursors to **9**, **10**, **11**, **12**, and **15** bear γ protons and selective removal of the β′ hydrogen is notable. Lithiation at the β′ position is a particularly interesting result for the tertiary amide precursors to **9** and **11** in which the γ proton clearly should be the thermodynamically most acidic.

The β′ position of α,β-unsaturated acid derivatives has not been generally recognized as bearing an acidic hydrogen, thus, sequences

Scheme I



(1) Preliminary reports have appeared. (a) Beak, P.; Kempf, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 4550. (b) Kempf, D. J.; Wilson, K. D.; Beak, P. *J. Org. Chem.* **1982**, *47*, 1610.

(2) For other cases see: Beak, P.; Hunter, J. E.; Jung, Y. M. *J. Am. Chem. Soc.* **1983**, *105*, 6350 and references cited therein.

(3) (a) For recent examples of γ-deprotonation of α,β-unsaturated acid derivatives in the presence of β′-protons see: Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1980**, 2509. Tischler, S. A.; Weiler, L. *Ibid.* **1980**, 4303. (b) Vedejs, E.; Gapinski, D. M. *Ibid.* **1981**, 4913. (c) Majewski, M.; Mpango, G. P.; Thomas, M. T.; Wu, A.; Snieckus, V. *J. Org. Chem.* **1981**, *46*, 2029. (d) Oakleaf, J. A.; Thomas, M. T.; Wu, A.; Snieckus, V. *Tetrahedron Lett.* **1978**, 1645. (e) Wu, A.; Snieckus, V. *Ibid.* **1975**, 2057. (f) Wolfe, J. F.; Timitsis, G. B.; Morris, D. R. *J. Org. Chem.* **1969**, *34*, 3263. (g) **Note Added in Proof**: Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1985**, *26*, 1939; **1984**, *25*, 1333.

(4) Bannwarth, W.; Eidenschink, R.; Kauffmann, T. *Angew Chem., Int. Ed. Eng.* **1974**, *13*, 468.

(5) Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1980**, *45*, 4257.

(6) Tanaka, K.; Nozaki, Y.; Tamura, N.; Tanikaga, R.; Kaji, A. *Chem. Lett.* **1980**, 1567.

(7) Tamaru, Y.; Kagotani, M.; Yoshida, Z. *Tetrahedron Lett.* **1981**, 3409. Tamura, Y.; Kagotani, M.; Furukawa, Y.; Amino, Y.; Yoshida, Z. *Ibid.* **1981**, 3413.

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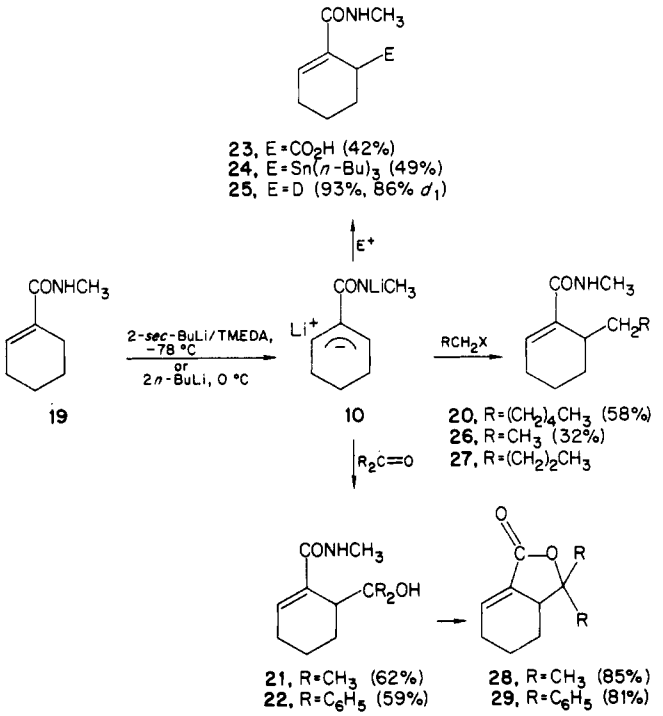
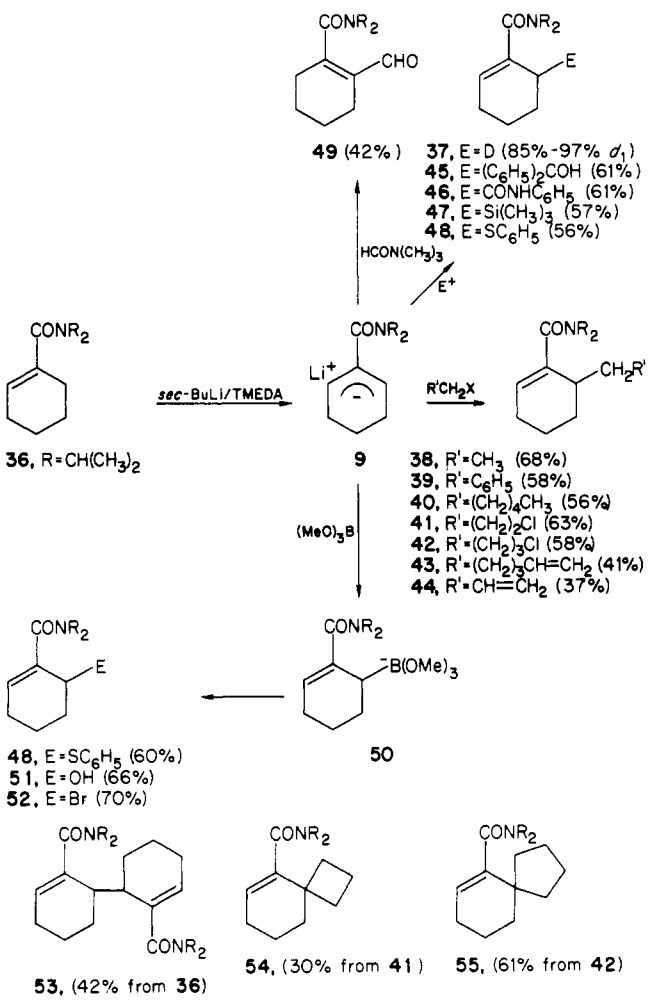
Scheme II



Scheme III



involving **5** provide a new approach to substitution at that site. The allyllithium reagents **9–15** are versatile nucleophiles, and their synthetic uses have recently been demonstrated in a number of laboratories, especially for the preparation of derivatives of α-methylene butyrolactones from symmetric 2-carboxamidoallyllithiums.[1,5-8] Formally, these organolithium reagents are equivalent to substituted methacrylic acid dianion, **16**, and are part of the larger class of 2-substituted allyl carbanions illustrated by **17** and **18**.[9,10]

Results and Discussion

Unless otherwise noted the β′ lithiations of the α,β-unsubstituted amides were accomplished at −78 °C with *sec*-butyllithium/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (*sec*-BuLi/TMEDA) in dry tetrahydrofuran for 0.1 to 2.0 h. Addition of the electrophile at −78 °C was followed by allowing the solution to warm to room temperature prior to isolation of the β′-substituted products. The products were characterized spectrally, and the yields are for analytically pure compounds unless otherwise noted.

Cyclic Symmetrical α,β-Unsaturated Amides. The dilithiation of *N*-methyl-1-cyclohexenecarboxamide (**19**) proceeds readily to provide the 2-carboxamido allyllithium **10** which can be converted to the β′-substituted products **20–26** upon reaction with 1-bromohexane, acetone, benzophenone, carbon dioxide, tri-*n*-butyltin chloride, deuterium oxide, and ethyl iodide, respectively, in the yields shown in Scheme II. Complete conversion of **19** to **10** could be achieved in 0.2 h with 2 equiv of *sec*-BuLi/TMEDA at −78 °C or in 0.25 h with *n*-BuLi at 0 °C.[11] Excess organolithium reagent is not necessary and may be detrimental. Thus, the formation of **27** observed in 18% yield if 2.9 equiv of *n*-BuLi is used as the base and ethyl iodide as the alkylating agent is attributed to halogen metal exchange of the excess lithium reagent followed by alkylation of **10** by the 1-iodobutane formed.[12]

The β′ carbons of the dianion **10** appear to be the most nucleophilic sites; alkylation at nitrogen is not observed under the reaction conditions. The position of alkylation for **20** was determined by irradiation of the unsubstituted two-proton allylic resonance at 2.0–2.1 ppm which decouples the one proton olefinic proton at 6.2 ppm while irradiation of the substituted one-proton allylic resonance at 2.6 ppm has no effect on the olefinic signal. Substitution at the β′ carbon in **21** and **22** was established unequivocally by conversions to the bicyclic lactones **28** and **29** on

(8) Ladlaw, M.; Pattenden, G. *Synth. Commun.* **1984**, 11.

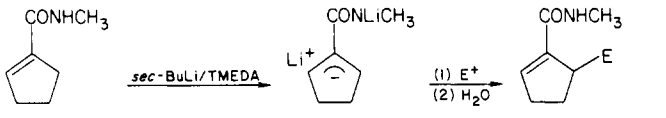
(9) Other equivalents for **16** are known. For example, reactions of (α-bromomethyl)acrylic esters with zinc and carbonyl compounds provide products resulting from nucleophilic addition by the β′ position of the acrylate to the carbonyl compound, see: Ohler, E.; Reininger, K.; Schmidt, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 457. Lee, K. H.; Wu, Y. S.; Hall, I. H. *J. Med. Chem.* **1977**, *20*, 911. Stamos, I. K.; Howie, G. A.; Manni, P. E.; Haws, W. J.; Byrn, S. R.; Cassady, J. M. *J. Org. Chem.* **1977**, *42*, 1703. For the corresponding allyl nickel derivative see: Hegedus, L. S.; Wagner, S. D.; Waterman, E. L.; Siirala-Hansen, K. *J. Org. Chem.* **1975**, *40*, 593. For approaches to **16** which do not involve a 2-substituted allylic anion, see: Adlington, R. M.; Barrett, A. G. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2848. Bond, F. T.; DiPietro, R. A. *J. Org. Chem.* **1981**, *46*, 1315. Stemke, J. E.; Chamberlin, A. R.; Bond, F. T. *Tetrahedron Lett.* **1976**, 2947.

(10) For cases in which Y = O^-: Sandifer, R. M.; Bhattacharya, A. K.; Harris, T. M. *J. Org. Chem.* **1981**, *46*, 2260 and references cited therein. Y = $N(CH_2)_4$: Thompson, H. W.; Huegi, B. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1603. Duhamel, L.; Chauvin, J.; Messier, A. *J. Chem. Res., Synp.* **1982**, *48* and references cited therein. Y = CH_2O^-: Carlson, R. M. *Tetrahedron Lett.* **1978**, 111. Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1981**, *103*, 5972. Kozikowski, A. P.; Nieduzak, T. R.; Scripko, J. *Organometallics* **1982**, *1*, 675 and references cited therein. Y = $CH_2N(CH_3)_2$: Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1981**, *46*, 3349. Y = $(CH_2)_2O^-$: Cardillo, G.; Contento, M.; Sandri, S.; Panunzio, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1729. Y = $(CH_2)_2SR$: Cazes, B.; Guittet, E.; Julia, S.; Ruel, O. *J. Organomet. Chem.* **1979**, *177*, 67. For more highly subsituted cases see: Sarkar, T. K.; Andersen, N. H. *Tetrahedron Lett.* **1978**, 3513. Ghosh, S.; Ghatak, U. R. *J. Org. Chem.* **1981**, *46*, 1486. For dimetallations of 2-methylpropene see: Bates, R. B.; Gordon, B., III; Keller, P. C.; Rund, J. V.; Mills, N. S. *J. Org. Chem.* **1980**, *45*, 168 and references cited therein. In addition a number of formal allyl anions bearing 1-substitutents which can provide additional stabilization to the anion are known.

(11) For details including optimization of metalation conditions, characterizations of other products, and details of spectroscopic experiments see: Kempf, D. J. Ph.D. Thesis, 1982; Wilson, K. D. Ph.D. Thesis, 1984 University of Illinois at Urbana—Champaign, available from University Microfilm, Ann Arbor, Michigan.

(12) The product **26** is obtained in 32% yield in this case.

heating in toluene and xylene, respectively. Similar dilithiation and electrophilic substitution of *N*-methyl-1-cyclopentenecarboxamide (**30**) provides **32–35**.

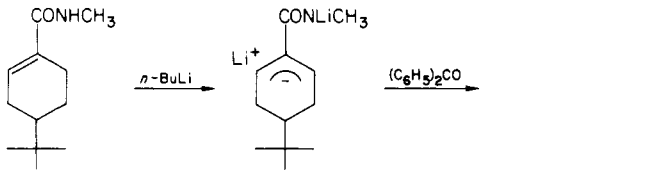


30 **31**

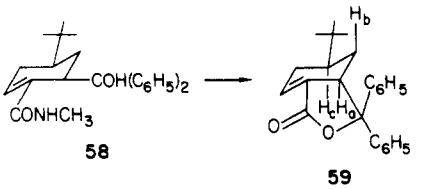
32, E=D, (71%, 96% d_1)
33, E=$(CH_2)_5CH_3$ (43%)
34, E=$(C_6H_5)_2COH$ (53%)
35, E=$(CH_3)_2COH$ (58%)

The β′ lithiations of **19** and **30** in the presence of the γ hydrogens could be attributed to deactivation of the carbonyl of the amide by initial lithiation at nitrogen. However, the tertiary amide *N*,*N*-diisopropyl-1-cyclohexenecarboxamide (**36**) undergoes β′ lithiation to provide **9**. This 2-carboxamido allyllithium intermediate can be converted to **37–48** on treatment with deuterium oxide, ethyl iodide, benzyl chloride, 1-bromohexane, 1-bromo-3-chloropropane, 1-bromo-4-chlorobutane, 5-bromo-1-pentene, allyl bromide, benzophenone, phenyl isocyanate, chlorotrimethylsilane, and diphenyl disulfide, respectively, in the yields shown in Scheme III.[13] Reaction of **9** with dimethylformamide provides the conjugated aldehyde **49**, presumably due to isomerization following formylation. Heteroatom substitution at the β′ position of **36** can be achieved by conversion of **9** to the ate complex **50**, followed by treatment with diphenyl disulfide, hydrogen peroxide, or bromine, to give **48**, **51**, and **52** respectively.[14] Attempts to prepare **52** by reaction of **9** with dibromotetrachloroethane led to **53**. Apparently this arises by reaction of **9** and **52** in situ, a possibility which was substantiated by formation of **53** in 41% yield from those precursors. Conversion of **41** and **42** to the spirocompounds **54** and **55**, respectively, on exposure to *sec*-BuLi/TMEDA in the presence of hexamethylphosphoric triamide at room temperature shows that lithiation and intramolecular alkylation at a tertiary β′ proton can be achieved. However, attempts to achieve lithiation and intermolecular substitution of tertiary β′ hydrogens of α,β-unsaturated amides, e.g., **38**, gave the desired product in only 25% yield.[11]

We have investigated the diastereoselectivity of the additions to carbonyl compounds. Reaction of *N*-methyl-4-*tert*-butyl-1-cyclohexenecarboxamide (**56**) with 2 equiv of *n*-BuLi gives **57**. Addition of benzophenone gives **58** and lactonization provides **59** in 54% overall yield. The spectral properties of both **58** and **59** indicate the presence of one isomer which is assigned equatorial substitution based on the ^1H NMR spectrum of **59**. The key

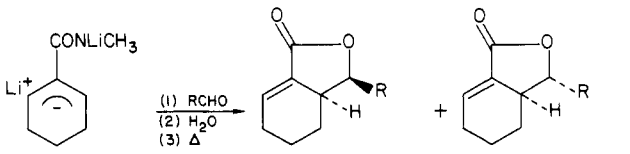


56 **57**



58 **59**

observation is the appearance of H_b at δ 0.40 with 12-Hz couplings to H_a and H_c characteristic of trans diaxial geometry in a six-membered ring.[11,15,16] The reaction of **10** with aldehydes shows little diastereoselectivity. Thus addition of benzaldehyde to **10** followed by cyclization provides the erythro isomer **60e** and the threo isomer **60t** in 67% yield in a 54:46 ratio. The assignment of stereochemistry is based on assignment of the proton at δ 0.46 in **60e** as analogous to H_b in **59**. In contrast the comparable proton in **60t** appears at δ 1.34. Reaction of **10** with valeraldehyde followed by cyclization provides **61e** and **61t** as a 58:42 mixture in 57% yield. The lactone **61t** is neocnidilide, a naturally occurring compound, and a small amount of pure material was obtained by careful chromatography.[17] The erythro diastereoselectivity could be greatly enhanced to give a 49:1 mixture of **60e**:**60t** by treatment of the ate complex **50** with valeraldehyde followed by cyclization.[14,18] However, **60e** is obtained in only 16% yield.



10 **60e**, R=C_6H_5 **60t**, R=C_6H_5
61e, R=$(CH_2)_3CH_3$ **61t**, R=$(CH_2)_3CH_3$

The β′-lithiated α,β-unsaturated amides **9–15** have been widely used for the synthesis of derivatives of α-methylene butyrolactones.[3,5–8,19] In order to demonstrate some other possibilities we have carried out a number of substitutions on derivatives of β′-lithio α,β-unsaturated amides, including systems which are also 1-heteroatom substituted allylic carbanions.[20] Lithiation of the β′-silyl-substituted α,β-unsaturated amide **47** provides **62** which reacts with benzyl chloride, ethyl iodide, 5-bromo-1-pentene, acetone, and *N*,*N*-dimethylbenzamide to give **63–68**, respectively, in the yields shown in Scheme IV. The vinylsilane products obtained from **62** are consistent with the regioselectivity observed with other 1-(trimethylsilyl)allyllithiums.[20,21]

Reaction of **62** with benzaldehyde follows a more complex course. The diene **69** is obtained in 44% yield.[22] A hydroxyamide **70**, assigned threo stereochemistry, is formed in 17% yield, along with a mixture of the erythro isomer of **70** and the hydroxysilane **71**.[23] The diene **69** is presumably formed in a Peterson syn elimination from **72**.[24] If the reaction is quenched with water

(13) The formations of **47** and **48** are also accompanied by disubstituted products formed in low yields. In the case of **47** this has synthetic advantages while **48** can be prepared more readily via the borate route (vide infra).

(14) Mikhaikov, B. M. *Organomet. Chem. Rev. Sect. A* **1972**, *8*, 1 and references cited therein. Kidwell, R. L.; Murphy, M.; Darling, S. In "Organic Synthesis"; Wiley: New York, 1973; Collect. Vol. 5, pp 918. For the photochemical coupling of a borane and disulfide see: Brown, H. C.; Midland, M. M. *J. Am. Chem. Soc.* **1971**, *93*, 3291.

(15) Lambert, J. B.; Shurvell, H. F.; Verbit, L.; Cooks, R. G.; Stout, G. H. "Organic Structural Analysis"; Streitweiser, A., Ed.; Macmillian Publishing Co.: New York, 1976; p 65–71. Coupling constants calculated for MM2 minimized structures of **59** and the corresponding isomer with axial substitution according to the procedures of Altona (Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783) were found to correspond to that of **59**.

(16) Treatment of **57** with deuterium oxide provides both equatorially and axially substituted products in ca. 1:1 ratio.[11]

(17) Mitsuhashi, H.; Muramatsu, T. *Tetrahedron*, **1964**, *20*, 1971 and references cited therein. Nagai, U.; Mitsuhashi, H. *Ibid.* **1965**, *21*, 1433.

(18) High diastereoselectivity is found with both allyl boronates and allylic borane "ate" complexes; Hoffmann, R. W.; Zeiss, H. J. *J. Org. Chem.* **1981**, *46*, 1309. Wuts, P. G. M.; Bigelow, S. S. *Ibid.* **1982**, *47*, 2498. Midland, M. M.; Preston, S. B. *J. Am. Chem. Soc.* **1982**, *104*, 2330. Fujita, K.; Schlosser, M. *Helv. Chim. Acta* **1982**, *65*, 1258. **Note Added in Proof**: Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 1969.

(19) The lactone **28** has previously been obtained by partial hydrogenation of a monoterpene lactone which is a metabolite produced by the koala bear: Southwell, I. A. *Tetrahedron Lett.* **1975**, 1885.

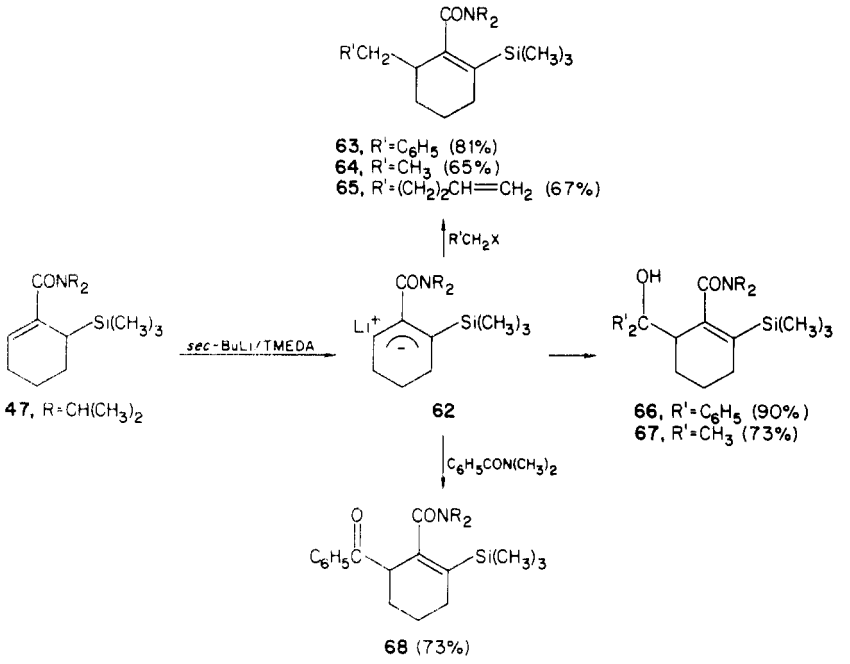
(20) α-Heterosubstituted allyl organometallics are of considerable synthetic value. Biellmann, J. F.; Ducep, J. B. *Org. React.* **1982**, *27*, 1. Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 5004. Ahlbrecht, H. *Chimia* **1977**, *31*, 391 and references cited therein.

(21) For synthetic use of vinyl silanes see: Fleming, I. In "Comprehensive Organic Chemistry"; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Elmsford, NY, 1979; Vol. 3, Part 13. Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761.

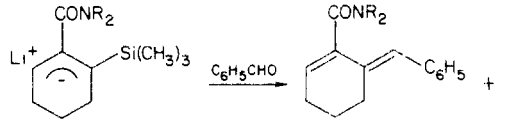
(22) The phenyl in **69** is assigned a position cis to the allylic methylene group since the latter appears at δ 2.59 to 2.70 ppm in the ^1H NMR spectrums as compared with 2.1 ppm in methylene cyclohexane.

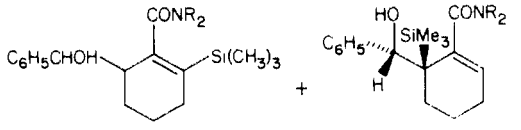
(23) The assignments of stereochemistry to **70t** and **70e** are based on couplings of the benzyl and ring protons of 8 and 3 Hz, respectively. In a conformation with intramolecular hydrogen bonding between the hydroxyl and amide groups the former would be expected to have the larger coupling.

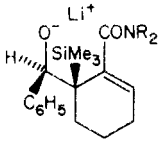
Scheme IV



after 5 min at −78 °C an alcohol corresponding to **72** can be observed in a mixture with **70** and **71**. Presumably the lithium salt of **71** does not form an olefin as readily as **72** due to repulsive steric interactions between the phenyl and amide groups in the transition state for syn elimination. The possibility that **69** results from reversible addition of **62** to benzaldehyde is discounted by the fact that **70** is recovered unchanged upon treatment with *sec*-BuLi/TMEDA at −78 °C followed by warming to ambient temperature. The regioselectivity of the reaction of **62** with benzaldehyde, which is different from that of other electrophiles (vide supra), is apparently under kinetic control.

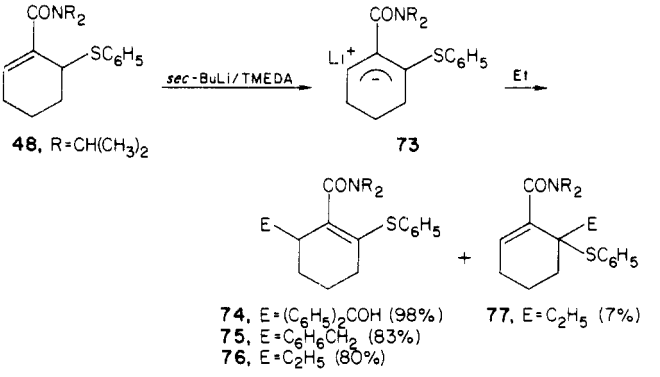




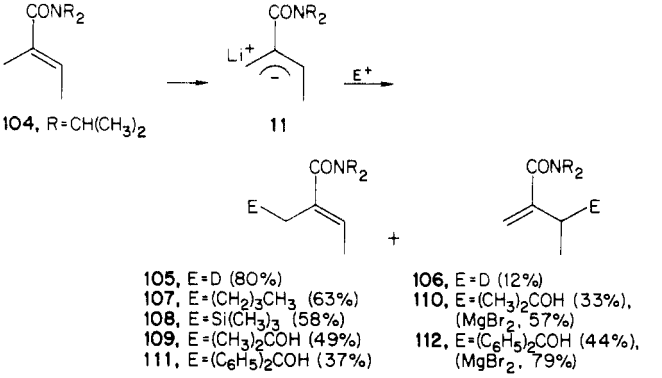


Lithiation of the β′-phenylthio α,β-unsaturated amide **48** provides **73** as shown in Scheme V. Reaction of **73** with benzophenone, benzyl chloride, or ethyl iodide gives the substituted products, **74**, **75**, and **76** respectively. The formation of **74** is consistent with the regioselectivity usually observed for addition of α-thioallyl anions to carbonyl electrophiles.[20] However, the formation of **75** and **76** displays regiochemistry opposite to that usually observed on alkylation of α-thioallyl anions, although it should be noted that the latter contains ca. 8% of **77**. It is reasonable to assume that the amide, by complexation with lithium, would affect the course of the reaction.[25]

Scheme V



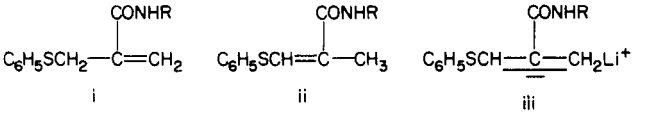
Scheme VI



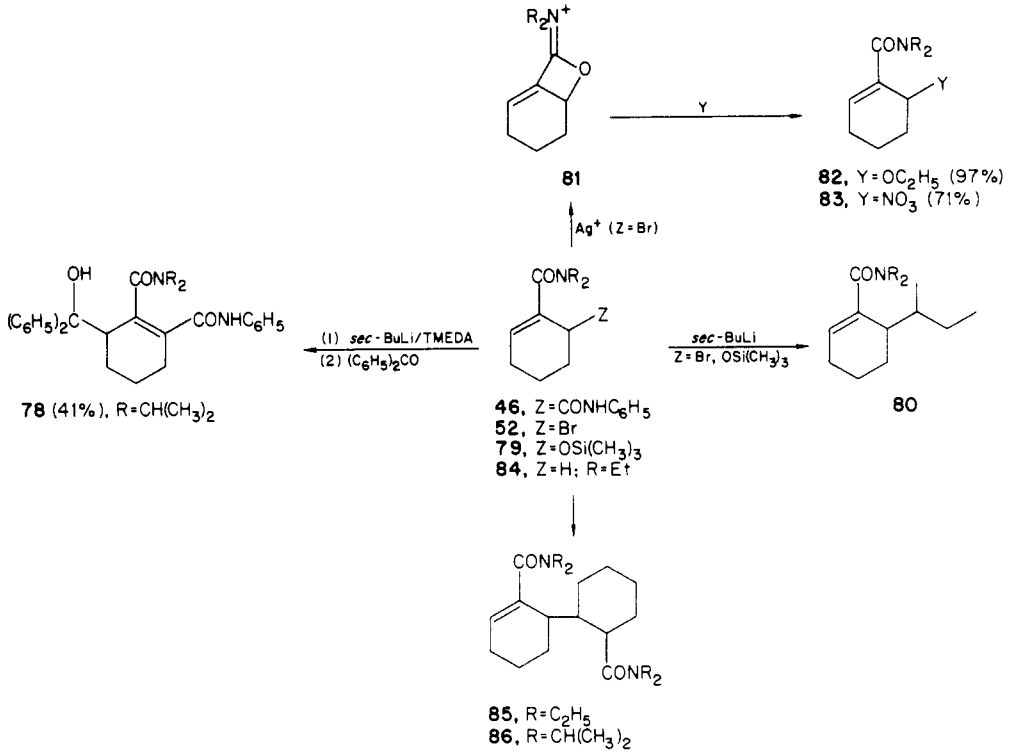
Sequential substitution of two different carbon electrophiles at the β′ and β positions of an α,β-unsaturated amide to provide

(24) Petersen, D. J. *J. Org. Chem.* **1968**, *33*, 780. Chan, T. H. *Acc. Chem. Res.* **1977**, *10*, 442 and references cited therein.

(25) Recent examples indicate that the high regioselectivity is maintained with a variety of electrophiles: Kitaoka, M.; Takahashi, Y.; Kosugi, H.; Uda, H. *Chem. Lett.* **1983**, 1065. Kitaoka et al. report dilithiation of i and ii provides iii (R = *t*-Bu) which also reacts with electrophiles at the α position. We have found that tertiary amides corresponding to i also undergo β′ lithiations. (Wilson, K.; Beak, P., unpublished work.)



Scheme VII

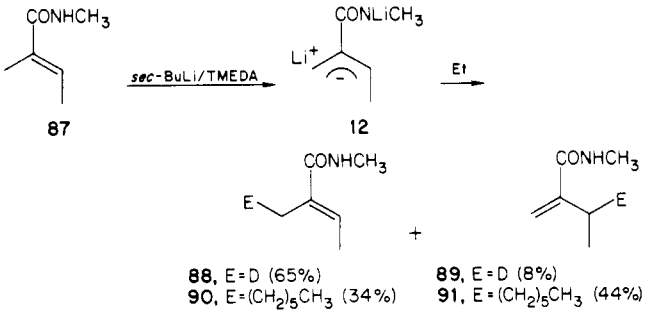


a 1,2,3-trisubstituted cyclohexene is demonstrated by the conversion of **36** via **46** (Scheme IV) to **78**. Attempts to achieve metalation of the trimethylsilyl ether **79** and the bromide **52** provide **80** in which substitution by *sec*-BuLi has occurred. Treatment of **52** with silver tetrafluoroborate gives the salt **81** which can be observed by ^{1}H NMR.[26] This compound forms the ether **82** on reaction with ethanol or the nitrate **83** if silver nitrate is used for the cyclization.

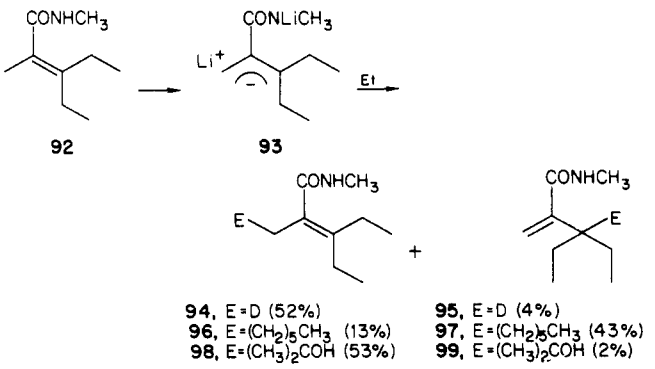
The group on the amide nitrogen plays a role in the β′-lithiation reactions. An attempt to carry out the lithiation and alkylation of *N*,*N*-diethyl-1-cyclohexenecarboxamide (**84**) led to **85** in 45% yield. The formation of **85** probably occurs via initial β′ lithiation followed by the well-precedented 1,4-addition to **84**.[27] Apparently the isopropyl groups on nitrogen in **36** provide hinderance to both 1,2- and 1,4-addition[28] (see Scheme VII).

Acyclic Unsymmetrical α,β-Unsaturated Amides. If the sequence of β′ lithiation and electrophilic substitution of α,β-unsaturated amides is to be generally synthetically useful, both steps need to be regioselective in acyclic and unsymmetric systems. We have investigated some secondary and tertiary amides which are precursors to unsymmetrical 2-amido allyllithiums.

Lithiation of (*E*)-*N*,2-dimethyl-2-butenamide (**87**) with 2 equiv of *s*-BuLi/TMEDA provides **12** which on reaction with methanol-*O*-d_1 gives a 8:1 mixture of **88** and **89**. The retention of double bond geometry in **88** suggests retention of the stereochemistry of **87** in **12**. Reaction of **12** with 1-bromohexane gives a 3:4 mixture of **90** and **91**.



Regiospecific β′ lithiation of *N*,2-dimethyl-3-ethyl-2-pentenamide (**92**) gives the 2-carboxamido allyllithium **93** as evidenced by deuteration to give **94** and **95** in a 12:1 ratio. The allyllithium **93** reacts with 1-bromohexane to afford **96** and **97** in a 1:3 ratio and with acetone to afford a 10:1 mixture of **98** and **99**. The mixture of **98** and **99** was not separated but converted to the lactone **100** in 36% overall yield. Low yields of products corresponding to **96** and **97**, but with additive alkylation on nitrogen, were also obtained and characterized spectroscopically.



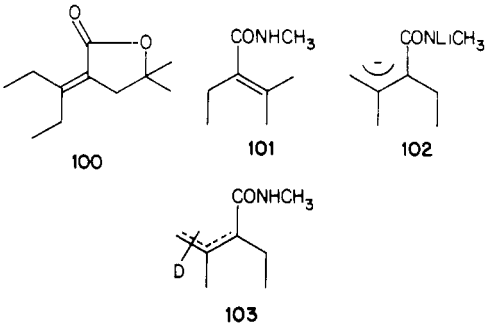
The β′ lithiation of **92** by *sec*-BuLi/TMEDA is notable because **92** contains potentially acidic γ-methylene hydrogens which are

(26) The ^{1}H NMR spectrum of **81** in CD_2Cl_2 displays four separate methyl resonances, which appear as doublets at δ 1.34, 1.38, 1.51, and 1.52 ppm. The isopropyl protons appear as heptets at δ 3.88 and 4.35 ppm. The former is coupled to the signals at δ 1.51 and 1.52 ppm while the latter is coupled to the remaining methyl signals. The spectrum also shows an olefinic resonance at δ 6.4 ppm and a multiplet at δ 4.6 ppm which is attributed to the methine proton α to oxygen.

(27) For additions to secondary and tertiary amides see: Mpango, G. B.; Mahalanabis, K. K.; Mahdavi-Damghani, Z.; Snieckus, V. *Tetrahedron Lett.* **1980**, 4823. Baldwin, J. E.; Dupont, W. A. *Ibid.* **1980**, 1881. Seebach, D.; Locher, R. *Angew Chem., Int. Ed. Engl.* **1979**, *18*, 957. Houlihan, W. J.; Parrino, V. A.; Vike, Y. *J. Org. Chem.* **1981**, *46*, 4511. For secondary and tertiary thioamides see: Tamaru, Y.; Harada, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1979**, *101*, 1316. Tamaru, Y.; Kagotani, M.; Yoshida, Z. *J. Org. Chem.* **1979**, *44*, 2816.

(28) However, reaction of **9** with vinyltriphenylphosphonium bromide did provide an unpurified product which could be assigned a structure **86**.[11]

located syn to the amide group. The amide *N*,3-dimethyl-2-ethyl-2-butenamide (**101**) also contains γ hydrogens syn to the amide group, and in this case lithiation occurs at the syn γ position to form **102** as evidenced by deuteration to give a mixture of the monodeuterated α,β- and β,γ-unsaturated isomers of **103**. On the basis of the regioselectivity observed for these lithiations of **87**, **92**, and **101**, it appears that lithiation by *sec*-BuLi/TMEDA will occur initially at hydrogens in close proximity to the amide group and that the apparent selectivity for proton removal by *sec*-BuLi/TMEDA is the following: β' methyl – syn γ methyl > syn γ methylene ≫ anti methyl.[1,2,3g]

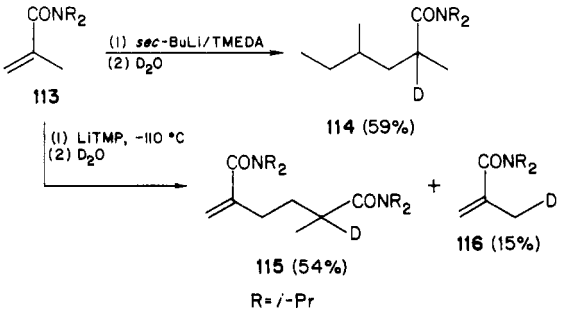


Lithiation of the tertiary amide (*E*)-*NN*-diisopropyl-2-methyl-2-butenamide (**104**) gives **11** as shown in Scheme VI. The intermediacy of **11** is shown by the formation of the substituted products **105–112** on treatment with deuterium oxide, 1-iodobutane, chlorotrimethylsilane, acetone, and benzophenone, respectively. In order to determine if the ratio of **111**:**112** is due to equilibration, each isomer separately is treated with lithium hydride in tetrahydrofuran at room temperature for 80 mn and the unrearranged amides are recovered in 93% and 81% yield, respectively, establishing that their formation is under kinetic control. In the cases of ketone addition, if **11** is treated with magnesium bromide prior to addition of the electrophile, only the regioisomers **110** and **112** are obtained. The geometry of **111** was established by NOE experiments. Irradiation of the methyl group causes an enhancement of 4.5% in the β-methylene resonance while irradiation of the vinyl hydrogen has no effect on that resonance. Retention of double bond geometry of **104** and **11** is thereby indicated.

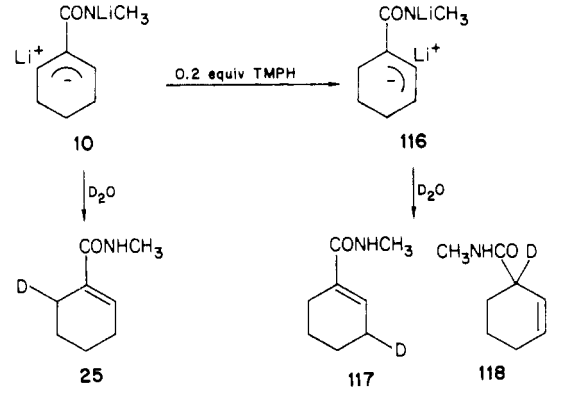
The regiochemistry of the substitutions of the organolithium reagents **11**, **12**, and **93** is somewhat different from those observed with other formal allylic carbanions in which alkylation is usually favored at the primary site while addition to carbonyl groups predominates at the more substituted center.[20,29] Although an extensive study has not been done, comparison of the regioselectivity of substitution of the unsymmetrical acyclic 2-carboxamido allyllithium reagent **11** with **12** and **93** suggests that these are complimentary. Alkylation of **12** and **93**, derivatives of the secondary amides, is regioselective for substitution at the more substituted terminus of the allylic system.[1] Addition of **93** to acetone gives high regioselectivity for the opposite isomer. On the other hand, alkylation of **11**, the 2-carboxamido allyllithium reagent from a tertiary amide, gives higher regioselectivity for alkylation at the less substituted end of the allyl system and little regioselectivity on additions to acetone and benzophenone. The addition of magnesium bromide to **11** in the latter cases enhances selectivity to favor addition at the more substituted terminus and may be synthetically useful.[2,30] In all cases, **105**, **107**, **108**, **109**, and **111**; only one geometric double bond isomer is obtained, and for **105** and **111** this isomer was shown by NOE experiments to have the same geometry as **104**.

The choice between the secondary and tertiary amides could depend on the desired regioselectivity or on the subsequent conversions. Secondary amides are more easily hydrolyzed, but tertiary amides could prove more useful if subsequent additions are desired. More information with be needed to make these distinctions more clearly.

We have also reinvestigated the lithiations of *N*,*N*-diisopropylmethacrylamide (**113**) which was suggested by Kauffmann to give **8** as a transient species.[4] We find that treatment of **113** with *sec*-BuLi/TMEDA followed by deuterium oxide provides the 1,4-addition product **114**. Treatment of **113** with LiTMP followed by deuterium oxide gives **115** and **116**. The formation of the monodeuterated amide **116** demonstrates that the allyllithium species **8** is only moderately stable under the reaction conditions, as 1,4-addition of intermediate **8** to **113** to afford **115** provides a process competitive with the lithiation.



Kinetic Regiospecificity of the Lithiation. We have suggested that these β' lithiations are kinetically determined and evidence on that point is provided by further studies of **10**. Thus, while **10** gives **25** the product of β' deuteration on treatment with deuterium oxide, if **10** is treated with 0.2 equiv of 2,2,6,6-tetramethylpiperidine and the solution is stirred at ambient temperature for 36 h prior to addition of deuterium oxide, only the α and γ deuterated products **117** and **118** are obtained in 60% yield with 58% deuterium incorporation. Equilibriation of **10** to **116** has apparently occurred by a protonation–deprotonation sequence with **116** being thermodynamically the more stable isomer. Similar γ lithiation is also observed for the reaction of **87** with LiTMP.[3]



Rationale for β' Lithiations. The carboxamide function may be considered to direct metalation to the β' position by initial association to the organolithium base with the carbonyl oxygen of the amide.[2] The kinetically acidic site is determined in part by the ring size of the transition state for removal of a proton in the vicinity of the complexed base.[1,31,32] It should be noted that more than one amide or organolithium could be part of the complex. In the absence of γ protons which are cis to the amide,

(29) Benkeser, R. A. *Synthesis*, **1971**, 347. Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1.

(30) A change in the regiochemistry of reaction of allyllithium and allylmagnesium bromide has been noted and rationalized in other cases.[20]

(31) For a case of direct observation of such association between an amide and *s*-BuLi in an equilibrium complex of a directed lithiation see: Al-Asser, M.; Beak, P.; Hay, D.; Kempf, D. J.; Mills, S.; Smith, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 2080.

(32) Precedents for β deprotonation are ortho lithiations of amides (Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *10*, 306) and β lithiation of β-heteroatom substituted α,β-unsaturated amides (Schmidt, R. R.; Talbiersky, J.; Russegger, R. *Tetrahedron Lett.* **1979**, 4273 and references cited therein).

deprotonation occurs exclusively at the β′ position as illustrated by the reactions of **19**, **29**, **36**, **47**, **48**, **56**, **67**, **87**, and **104**. If a syn γ carbon is present, however, metalation also may be directed to that position, since it is also accessible to the organolithium which is complexed to the amide. Thus, while lithiation of **92** which bears a syn γ proton occurs only at the β′ position, lithiation of **101** occurs at the γ position.

Competition with 1,4-addition also may be observed. Thus while **13** and **15** are produced by β′ lithiation of *N*-*tert*-butylmethacrylamide and *N*-methyl-1-cyclohexenethiocarboxamide, respectively, *N*-phenylmethacrylamide and *N*-phenyl α,β-unsaturated thioamides give products from 1,4-addition of the organolithium base.[5,7,27] Although more information about the mechanism of lithiation and the reactivity of organolithium substrate complexes will be needed, it appears that by proper choice of substrate, substituents, and base, β′ lithiation can be selected and the resulting species are synthetically useful.

Experimental Section[33]

All reactions involving organolithiums were performed in oven-dried glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone ketyl before use. *n*-Butyllithium and *sec*-butyllithium were titrated prior to use according to the procedure of either Watson and Eastham or Shapiro et al.[34] *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA) and diisopropylamine were distilled from calcium hydride. All other solvents and reagents were of reagent grade or higher. Unless otherwise noted, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or CCl_4 with tetramethylsilane as an internal standard.

Preparation of Amides. *N*-Methyl-1-cyclohexenecarboxamide (19). 1-Cyanocyclohexene[35] (4.15 g, 0.039 mol) in 20 mL of dichloromethane was cooled in an ice bath and treated with ca. 10 mL (0.1 mol) of methyl fluorosulfonate. After being heated at reflux under a N_2 atmosphere for 17 h, the mixture was cooled in an ice bath and excess water was added. The orange mixture was stirred at ambient temperature for 3 h and made basic with 1:1 concentrated aqueous ammonia in ethanol. The solution was extracted with three portions of dichloromethane and dried ($MgSO_4$) and the solvent removed in vacuo to give a yellow oil. Bulb-to-bulb distillation followed by recrystallization from pentane gave 2.77 g (51%) of pure **19**: mp 66–67 °C (lit.[36] mp 60 °C); ^1H NMR (90 MHz) δ 1.5–1.8 (m, 4 H, CH_2), 2.0–2.3 (m, 4 H, allylic CH_2), 2.86 (d, $J \approx 5$ Hz, 3 H, NCH_3), 5.7–6.2 (br, 1 H, NH), 6.5–6.6 (m, 1 H, C=CH); ^{13}C NMR δ 21.6, 22.2, 24.3, 25.3, 26.4, 133.2 (2 C), 169.4; IR (KBr) 3380 (s, br), 2954 (s), 1667 (s, C=O), 1635 (s), 1560 (s), 1440 (m), 1418 (m) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 139 (96, M^+), 109 (68), 81 (100), 79 (36), 53 (21); isotope ratio 140 (10.1), 139 (95.6), 138 (17.0), 111 (6.8), 110 (18.9), 109 (68.3), 108 (7.8), 82 (15.0), 81 (100), 80 (8.2).

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.82; H, 9.55; N, 10.07.

***N,N*-Diisopropyl-1-cyclohexenecarboxamide (36).** 1-Cyclohexenecarboxylic acid[35] (5.0 g, 0.040 mol) was heated at reflux in 10 mL (0.14 mol) of thionyl chloride for 2.5 h. Removal of the excess thionyl chloride and dissolution of the crude acid chloride in 20 mL of ether, followed by addition to a solution of 28 mL of diisopropylamine (0.2 mol) in 1 L of ether, stirring at ambient temperature for 4 h, and extractive workup provided a yellow oil. Two Kugelrohr distillations followed by elution through a gravity silica column with chloroform and a third distillation (60–65 °C (0.1 mm)) gave 6.49 g (78%) of pure **35** as a colorless liquid: ^1H NMR (90 MHz) δ 1.29 (d, $J = 7$ Hz, 12 H, CH_3), 1.55–1.74 (m, 4 H, CH_2), 1.97–2.27 (m, 4 H, allylic CH_2), 3.74 (heptet, $J = 7$ Hz, 2 H, NCH), 5.5–5.70 (m, 1 H, C=CH; IR (NaCl, film) 2970 (m), 2940 (m), 1623 (s, C=O), 1440 (s), 1372 (s), 1326 (s), 1220 (m), 1165 (m), 1032 (m) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 209 (24, M^+), 166 (11), 109 (100), 86 (16), 81 (44), 79 (12); isotope ratio 210 (3.4), 209 (23.8), 208 (2.2), 110 (8.0), 109 (100), 108 (2.6).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.48; H, 11.03; N, 6.61.

***N*-Methyl-4-*tert*-butyl-1-cyclohexenecarboxamide (56).** 4-*tert*-Butyl-1-cyanocyclohexene[37] (3.56 g, 0.218 mol) and 7.34 g (0.377 mol) of silver tetrafluoroborate were combined, treated with 2.4 mL (0.039 mol) of iodomethane in 200 mL of dichloromethane, and allowed to stir at ambient temperature for 12 h. Water was added and after 0.5 h of stirring, the silver iodide was removed by filtration. The organic layer was washed with 5% $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo to a colorless oil. The amide was separated from unreacted nitrile by successive elution through a gravity silica column with hexane and ethyl acetate. Pure **56**, 2.86 g (67%), was obtained by recrystallization from chloroform/hexane: mp 97.5–98.5 °C; ^1H NMR (360 MHz, benzene-d_6) δ 0.76 (s, 9 H, CH_3), 0.91–1.12 (m, 2 H, CH_2), 1.63–1.72 (m, 2 H, allylic CH_2), 1.92–2.00 (m, 1 H, CH), 2.05–2.16 (m, 1 H, β′-CH_2), 2.47–2.53 (m, 1 H, β′-CH_2), 2.74 (d, $J = 4.7$ Hz, 3 H, NCH_3), 6.17 (br, 1 H, NH), 6.61–6.63 (m, 1 H, C=CH); ^{13}C NMR δ 23.7, 25.8, 26.4, 27.1 (3 C), 32.1 43.5, 133.0 133.7, 169.1; IR (KBr) 3352 (s), 2980 (s), 1668 (s, C=O), 1627 (s), 1552 (s), 1412 (m), 1287 (s), 663 (s) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 195 (44, M^+), 180 (11), 165 (8), 138 (100), 112 (20), 108 (16), 81 (36), 58 (34), 57 (47); isotope ratio 196 (7.0), 195 (43.5), 194 (0.6), 139 (23.0), 138 (100), 137 (3.0).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.82; H, 10.87; N, 7.16.

Metalations of Amides. In general, lithiations with *sec*-butyllithium/TMEDA were performed according to procedure A and metalations with *n*-butyllithium according to procedure B. The typical procedures presented below represent reactions on a scale of 1–2 mmol of amide. The amounts of solvents used in the extractive workup of reactions of larger scale were correspondingly greater. Variations of these procedures, the amounts of reagents used, and purification methods are given with the spectroscopic and analytical data of the individual product.

Procedure A. To a stirred solution of TMEDA in 10 mL of THF under a N_2 atmosphere at −78 °C was added *sec*-butyllithium followed by a solution of the amide in 5–10 mL of THF. After being allowed to stir for the indicated time at −78 °C, the solution was treated with the electrophile. Liquid electrophiles were added neat, solids were added either neat or as solutions in 5–10 mL of THF, and gaseous carbon dioxide was introduced into the atmosphere of the reaction vessel. A few minutes after the addition was complete, the bath was removed and the solution allowed to warm to ambient temperature prior to addition of ca. 10 mL of saturated NH_4Cl in 2% HCl. Following extraction with 10–20 mL of either diethyl ether or dichloromethane, the organic portion was dried over either $CaSO_4$ or $MgSO_4$ and concentrated in vacuo to give the crude product.

Procedure B. To a stirred solution of the amide in 8–10 mL of THF cooled in a −78 °C bath was added *n*-butyllithium dropwise. The resulting solution was placed in an ice water bath for the indicated time. After recooling to −78 °C, the electrophile was added, and the solution was allowed to warm to ambient temperature prior to quenching with saturated NH_4Cl. The reaction mixture was worked up in the manner described in procedure A to afford the crude product.

Procedure C. To a stirred solution of TMEDA in 30–60 mL of THF under a N_2 atmosphere at −100 °C was added *sec*-butyllithium followed by a solution of the amide in 5–10 mL of THF. After the mixture was stirred for the indicated time, the electrophile was added and the solution allowed to warm to ambient temperature prior to quenching with saturated NH_4Cl. The reaction mixture was worked up in the manner described in procedure A to afford the crude product.

***N*-Methyl-6-hexyl-1-cyclohexenecarboxamide (20).** Procedure A: 102 mg (0.73 mmol) of **19**, 1.16 mL (1.54 mmol) of *sec*-BuLi, 0.23 mL (1.5 mmol) of TMEDA, 20 mL of THF, 0.5 h, 0.10 mL (0.73 mmol) of 1-bromohexane. Separation of MPLC on silica by elution with hexane/ethyl acetate afforded, after removal of the solvent in vacuo, 94 mg (58%) of pure **20** as a white solid: mp 55–55.5 °C; ^1H NMR (90 MHz) δ 0.85 (t, $J = 5$ Hz, 3 H, CH_3), 1.27 (br s, 10 H, acyclic CH_2), 1.5–1.65 (m, 4 H, cyclic CH_2), 2.0–2.1 (m, 2 H, allylic CH_2), 2.5–2.6 (m, 1 H, allylic CH), 2.82 (d, $J = 5$ Hz, 3 H, NCH_3), 5.6–5.8 (br, 1 H, NH), 6.2 (m, 1 H, C=CH). Decoupling: irradiation at 2.0 ppm decoupled the proton at 6.2 ppm; saturation of the peak at 2.6 ppm had no observable effect on the signal at 6.2 ppm. IR (KBr) 3358 (s), 2967 (s), 1661 (s, C=O), 1636 (s), 1554 (s), 1471 (m), 1413 (m), 714 (m) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 223 (85, M^+), 166 (50), 152 (100), 139 (82), 138 (89), 95 (35), 81 (63), 79 (36), 67 (29), 58 (61).

Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28, H, 11.28; N, 6.27. Found: C, 75.35; H, 11.46; N, 6.18.

***N*-Methyl-6-(1-hydroxy-1-methylethyl)-1-cyclohexenecarboxamide (21).** Procedure A: 95 mg (0.68 mmol) of **19**, 1.1 mL (1.5 mmol) of

(33) Mass spectra were recorded by Mr. Carter Cook and associates on Varian MAT CH-5 and 731 mass spectrometers. Elemental analyses were performed by Mr. J. Nemeth and associates. Melting points are uncorrected. The temperatures reported for bulb-to-bulb distillations in a Kugelrohr apparatus represent the temperature of the hot air bath and are not necessarily an accurate measure of the boiling points. Vapor pressure chromatography (VPC) was performed on a 12.5-m Hewlett-Packard cross-linked dimethyl silicone capillary column (0.2 mm in diameter).

(34) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165. Lipton, M. F.; Sorensen, C. M.; Sadler, A. C.; Shapiro, R. H. *Ibid.* **1980**, *186*, 155.

(35) Wheeler, O. H.; Lerner, I. *J. Am. Chem. Soc.* **1956**, *78*, 63.

(36) Klein, J. *Tetrahedron* **1964**, *20*, 465.

sec-BuLi, 0.22 mL (1.5 mmol) of TMEDA, 10 mL of THF, 1 h, 0.4 mL (5 mmol) of acetone. Two Kuglrohr distillations (120–125 °C (0.2 mm)) gave 83 mg (62%) of pure **21** as a white solid: mp 68–70 °C; ^{1}H NMR (90 MHz) δ 1.07 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 1.5–1.7 (m, 4 H, CH_2), 2.0–2.2 (m, 2 H, allylic CH_2), 2.5–2.8 (m, 1 H, allylic CH), 2.77 d, J = 5 Hz, 3 H, NCH_3), 3.8 (br, 1 H, OH), 6.2–6.4 (br, 1 H, NH), 6.35 (t, J = 4 Hz, 1 H, C=CH); mass spectrum (70 eV), *m/e* (relative intensity) 151 (7), 139 (100), 109 (38), 81 (26), 79 (19), 58 (24).

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.81; H, 9.85; N, 7.10.

2-(*N*-Methylcarbamoyl)-2-cyclohexenecarboxylic Acid (23). Procedure A: 155 mg (1.11 mmol) of **19**, 2.1 mL (2.9 mmol) of *sec*-BuLi, 0.80 mL (5.3 mmol) of TMEDA, 25 mL of THF, 0.5 h. Dry, gaseous CO_2 was passed through the solution for several minutes, water was added, followed by 5% NaOH, and the reaction was worked up extractively with dichloromethane for the acidic product. The crude acid was recrystallized from acetone to give 81 mg (42%) of pure **23** as a white solid: mp 139–140 °C; ^{1}H NMR (90 MHz, Me_2SO-d_6/$CDCl_3$) δ 1.5–1.8 (m, 4 H, CH_2), 2.0–2.2 (m, 2 H, allylic CH_2), 2.62 (d, J = 5 Hz, 3 H, NCH_3), 3.3–3.5 (m, 1 H, allylic CH), 6.4–6.5 (m, 1 H, C=CH), 7.7–7.9 (br, 1 H, NH), 12.0–12.2 (br, 1 H, OH); IR (KBr) 3435 (s, br), 2930 (s, br), 1742 (m, C=O), 1670 (m, C=O), 1621 (s), 1422 (m), 1327 (m), 1227 (s), 903 (w), 630 (w) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 183 (8, M^+), 165 (56), 139 (60), 125 (34), 109 (34), 108 (50), 81 (62), 79 (100), 77 (32), 58 (58).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.10; H, 6.96; N, 7.45.

***N*-Methyl-6-(tri-*n*-butylstannyl)-1-cyclohexenecarboxamide (24).** Procedure A: 112 mg (0.80 mmol) of **19**, 1.28 mL (1.7 mmol) of *sec*-BuLi, 0.26 mL (1.7 mmol) of TMEDA, 10 mL of THF, 35 min, 0.22 mL (0.81 mmol) of tri-*n*-butyltin chloride. Bulb-to-bulb distillaton (140–150 °C (0.3 mm)) gave 166 mg (49%) of pure **24** as a colorless oil: ^{1}H NMR (90 MHz) δ 0.7–0.95 (br, 9 H, CH_3), 1.1–1.5 (m, 18 H, acyclic CH_2), 1.6–2.0 (m, 4 H, cyclic CH_2), 2.0–2.2 (m, 2 H, allylic CH_2), 2.4–2.5 (m, 1 H, allylic CH), 2.78 (d, J = 5 Hz, 3 H, NCH_3), 5.5–5.7 (br, 1 H, NH), 5.8–6.0 (m, 1 H, C=CH; IR (NaCl, film) 3300 (m), 2895 (s), 1646 (m, C=O), 1620 (s), 1532 (m), 1459 (m), 1409 (m) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 429 (0.8, M^+), 376 (16), 374 (14), 373 (17), 372 (100), 371 (37), 370 (74), 369 (30), 368 (42).

Anal. Calcd for $C_{20}H_{39}NOSn$: C, 56.10; H, 9.18; N, 3.27; Sn, 27.72. Found: C, 55.87; H, 9.14; N, 3.27; Sn, 27.64.

3,3-Dimethyl-3a,4,5,6-tetrahydro-1(3*H*)-isobenzofuranone (28). A solution of 56 mg (0.28 mmol) of **21** in toluene was heated at reflux for 40 h. After removal of the solvent in vacuo, the crude product was eluted through a short column of silica to provide 38 mg (85%) of pure **28** as a colorless liquid: ^{1}H NMR (90 MHz) δ 1.18 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.3–1.7 (m, 2 H, CH_2), 1.8–2.0 (m, 2 H, CH_2), 2.2–2.3 (m, 2 H, allylic CH_2), 2.5–2.7 (m, 1 H, allylic CH), 6.78 (q, J = 4 Hz, 1 H, C=H); IR ($CHCl_3$) 2995 (s), 2960 (s), 1761 (s, C=O), 1393 (m), 1380 (m), 1311 (m), 1286 (s), 1131 (m), 1041 (s) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 166 (8, M^+), 108 (100), 80 (46), 79 (65), 43 (30); ^{1}H NMR and mass spectral data correspond to published values.[19]

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.02; H, 8.48.

***N*,*N*-Diisopropyl-6-ethyl-1-cyclohexenecarboxamide (38).** Procedure A: 2.54 g (12.2 mmol) of **36**, 10.0 mL (13.4 mmol) of *sec*-BuLi, 2.0 mL (13 mmol) of TMEDA, 130 mL of THF, 15 min, 1.2 mL (15 mmol) of iodoethane. Separation by MPLC on silica by elution with hexane/ethyl acetate followed by Kugelrohr distillation (75–80 °C (0.2 mm)) afforded 1.95 g (68%) of pure **38** as a colorless liquid: ^{1}H NMR (360 MHz) δ 0.93 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.05–1.2 (m, 6 H, CH_3), 1.3–1.6 (m, 10 H, CH_2, CH_3), 1.65–1.75 (m, 1 H, CH_2), 1.85–1.95 (m, 1 H, CH_2), 2.03–2.07 (m, 2 H, allylic CH_2), 2.35–2.45 (m, 1 H, allylic CH), 3.3–3.45 (br, 1 H, NCH), 4.2–4.35 (br, 1 H, NCH), 5.65 (m, 1 H, C=CH); IR (NaCl, film) 2950 (s), 2920 (s), 1620 (s, C=O), 1432 (s), 1369 (s), 1322 (s), 1218 (m), 1165 (m), 1032 (m) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 237 (9, M^+), 208 (65), 194 (12), 137 (100), 109 (45), 81 (20), 79 (16), 43 (29), 41 (27).

Anal. Calcd for $C_{15}H_{27}NO$: C, 75.90; H, 5.90; N, 11.46. Found: C, 76.17; H, 6.02; N, 11.53.

***N*,*N*-Diisopropyl-6-(3-chloropropyl)-1-cyclohexenecarboxamide (41).** Procedure A: 1.26 g (6.06 mmol) of **36**, 4.50 mL (6.35 mmol) of *sec*-BuLi, 0.90 mL (6.0 mmol) of TMEDA, 35 mL of THF, 15 min, 0.80 mL (7.5 mmol) of 1-bromo-3-chloropropane. After treatment with the bromide, the solution was allowed to stir at ambient temperature for 12 h. Separation by MPLC on silica with hexane/ethyl acetate as an eluent followed by two Kugelrohr distillations (135–140 °C (0.4 mm)) afforded 1.091 g (63%) of pure **41** as a colorless liquid: ^{1}H NMR (90 MHz) δ 1.30 (d, J = 7 Hz, 12 H, CH_3), 1.41–2.1 (m, 10 H, CH_2) 2.4–2.6 (m, 1 H, allylic CH), 3.50 (t, J = 6 Hz, 2 H, $ClCH_2$), 3.3–4.1 (br, 2 H, NCH), 5.6–5.7 (m, 1 H, C=CH); IR (NaCl, film) 2900 (s), 1623 (s, C=O), 1435 (s), 1367 (s), 1327 (s), 1215 (m), 1162 (m) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 287 (2.4, M^+), 285 (7.6, M^+), 250 (13), 208 (100), 187 (24), 185 (75), 109 (19), 81 (33), 79 (23).

Anal. Calcd for $C_{16}H_{28}ClNO$: C, 67.23; H, 9.87; N, 4.90; Cl, 12.40. Found: C, 67.20; H, 9.81; N, 4.81; Cl, 12.59.

***N*,*N*-Diisopropyl-6-(4-chlorobutyl)-1-cyclohexenecarboxamide (42).** Procedure A: 423 mg (2.02 mmol) of **36**, 2.0 mL (2.2 mmol) of *sec*-BuLi, 0.33 mL (2.2 mmol) of TMEDA, 10 mL of THF, 15 min, 0.28 mL (2.4 mmol) of 1-bromo-4-chlorobutane. After addition of the bromide, the solution was allowed to stir at ambient temperature for 9 h. Separation by MPLC on silica with hexane/ethyl acetate as an eluent followed by Kugelrohr distillation (145–155 °C (0.2 mm)) afforded 351 mg (58%) of pure **42** as a colorless liquid: ^{1}H NMR (90 MHz) δ 1.30 (d, J = 7 Hz, 12 H, CH_3), 1.3–1.9 (m, 10 H, CH_2), 1.9–2.2 (m, 2 H, allylic CH_2), 2.3–2.6 (m, 1 H, allylic CH), 3.50 (t, J = 7 Hz, 2 H, $ClCH_2$), 3.3–4.2 (br, 2 H, NCH), 5.65 (td, J_1 = 4 Hz, J_2 = 2 Hz, 1 H, C = CH); IR (NaCl film) 2890 (s), 1622 (s, C=O), 1433 (s), 1370 (s), 1312 (s), 1215 (m), 1158 (m), 1025 (m) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 301 (1.7, M^+), 229 (7.0, M^+), 209 (22), 208 (100), 201 (24), 199 (75), 81 (72), 79 (29), 67 (27), 43 (32), 41 (30).

Anal. Calcd for $C_{17}H_{30}ClNO$: C, 68.09; H, 10.08; Cl, 11.82; N, 4.67. Found: C, 68.23; H, 9.98; Cl, 11.87; N, 4.87.

***N*,*N*-Diisopropyl-6-(hydroxydiphenylmethyl)-1-cyclohexenecarboxamide (45).** Procedure A: 238 mg (1.08 mmol) of **36**, 1.0 mL (1.2 mmol) of *sec*-BuLi, 0.19 mL (1.2 mmol) of TMEDA, 10 mL of THF, 5 min, 225 mg (1.23 mmol) of benzophenone in 5 mL of THF. Separation by MPLC on silica by elution with hexane/ethyl acetate gave 271 mg (61%) of pure **45** as a white solid: mp 175–176 °C; ^{1}H NMR (360 MHz) δ 0.48 (m, 3 H, CH_3), 106 (m, 3 H, CH_3), 1.19–2.1 (m, 6 H, CH_3), 1.28–1.31 (m, 1 H, CH_2), 1.47–1.52 (m, 2 H, CH_2), 1.73–1.75 (m, 1 H, CH_2), 2.08–2.12 (m, 2 H, allylic CH_2), 3.06–3.10 (m, 1 H, NCH), 3.57–3.58 (m, 1 H, allylic CH), 4.12–4.16 (m, 1 H, NCH), 5.78 (m, 1 H, C=CH), 6.67 (br, 1 H, OH), 7.05–7.09 (m, 2 H, ArH), 7.18–7.25 (m, 4 H, ArH), 7.44–7.47 (m, 2 H, ArH), 7.59–7.62 (m, 2 H, ArH). Decoupling: irradiation at 0.48 and 1.06 ppm partially decoupled the multiplets at 3.08 and 4.14 ppm, respectively, leaving quartets. Irradiation at 1.20 ppm partially decoupled the multiplets at both 3.08 and 4.14 ppm, again leaving quartets. IR (KBr) 3450 (m, br), 2940 (m), 1598 (s, C=O), 1450 (s), 1370 (s), 1325 (m), 761 (s), 705 (s) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 373 (1), 247 (7), 209 (100), 194 (15), 166 (19); field desorption mass spectrum 393 (17), 392 (58), 391 (100), 210 (8), 209 (71).

Anal. Calcd for $C_{26}H_{33}NO_2$: C, 79.76; H, 8.50; N, 3.58. Found: C, 79.79; H, 8.46; N, 3.58.

***N*,*N*-Diisopropyl-6-(*N*'-phenylcarbamoyl)-1-cyclohexenecarboxamide (46).** Procedure A: 1.563 g (7.48 mmol) of **36**, 6.0 mL (8.5 mmol) of *sec*-BuLi, 1.0 mL (6.6 mmol) of TMEDA, 125 mL of THF, 15 min, 1.0 mL (9.2 mmol) of phenyl isocyanate. The product was purified by MPLC on silica with hexane/ethyl acetate as an eluent. Recrystallization from chloroform/hexane gave 1.496 g (61%) of pure **46** as a white solid: mp 191–195 °C; ^{1}H NMR (360 MHz) δ 1.0–1.5 (br m, 12 H, CH_3), 1.6–1.8 (m, 3 H, CH_2), 2.1–2.3 (m, 2 H, allylic CH_2), 2.3–2.4 (m, 1 H, CH_2), 3.2–3.7 (br, 1 H, NCH), 3.4 (br s, 1 H, allylic CH), 4.0–4.4 (br, 1 H, NCH), 5.9–5.95 (m, 1 H, C=CH), 7.03–7.08 (m, 1 H, ArH), 7.26–7.3 (m, 2 H, ArH), 7.6–7.62 (m, 2 H, ArH), 9.2–9.4 (br, 1 H, NH); IR (KBr) 3440 (s), 2935 (w), 1707 (s, C=O), 1597 (m, C=O), 1492 (m), 1425 (s), 761 (m), 695 (w) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 328 (6, M^+), 236 (100), 209 (28), 166 (31), 109 (40), 81 (32), 79 (25), 77 (22).

Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 73.10; H, 8.54; N, 8.75.

***N*,*N*-Diisopropyl-6-(trimethylsilyl)-1-cyclohexenecarboxamide (47).** Procedure A: 2.56 g (12.2 mmol) of **36**, 10.5 mL (14 mmol) of *sec*-BuLi, 2.0 mL (1.3 mmol) of TMEDA, 130 mL of THF, 15 min. The solution was added dropwise to 6.8 g (63 mmol) of chlorotrimethylsilane in 100 mL of THF at −78 °C. The reaction was worked up in the usual manner, and the crude product was purified by MPLC on silica with hexane/ethyl acetate as an eluent. Pure **47** (1.97 g, 57%) was obtained as a white solid, mp 62–64 °C, along with 0.63 g (15%) of *N*,*N*-diisopropyl-2,6-bis(trimethylsilyl)-1-cyclohexenecarboxamide (**119**) which contained a small amount of *N*,*N*-diisopropyl-6,6-bis(trimethylsilyl)-1-cyclohexenecarboxamide, also as a white solid, mp 88–106 °C. **47**: ^{1}H NMR (90 MHz) δ 0.07 (s, 9 H, $Si(CH_3)_3$), 1.28 (d, J = 7 Hz, 12 H, CH_3), 1.5–1.8 (m, 5 H, CH_2, allylic CH), 1.9–2.1 (m, 2 H, allylic CH_2), 3.3–4.0 (br, 2 H, NCH), 5.63 (t, J = 4 Hz, 1 H, C=CH); IR (KBr) 2940 (s), 1623 (s, C=O), 1444 (m), 1369 (m), 1329 (m), 1247 (m), 1212 (m), 850 (s), 839 (s) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 281 (30, M^+),

266 (45), 238 (70), 109 (100), 81 (38), 73 (73).

Anal. Calcd for $C_{16}H_{31}NOSi$: C, 68.27; H, 11.10; N, 4.28. Found: C, 68.28; H, 11.27; N, 5.02.

119: ^{1}H NMR (220 MHz) δ 0.04 (s, 9 H, $Si(CH_3)_3$), 0.06 (s, 9 H, $Si(CH_3)_3$), (d, J = 7 Hz, 3 H, CH_3), 1.16 (d, J = 7 Hz, 3 H, CH_3) 1.35 (d, J = 7 Hz, 3 H, CH_3), 1.44 (d, J = 7 Hz, 3 H, CH_3), 1.5–1.7 (m, 4 H, CH_2), 1.8–1.9 (m, 1 H allylic CH), 2.05–2.15 (m, 2 H, allylic CH_2), 3.30 (heptet, J = 7 Hz, 1 H, NCH), 3.92 (heptet, J = 7 Hz, 1 H, NCH); IR (KBr) 2970 (w), 1619 (s, C=O), 1436 (s), 1370 (s), 1318 (s), 1243 (s), 1155 (m), 1039 (m), 840 (s) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 353 (3, M^+), 338 (8), 310 (9), 280 (100), 238 (6), 222 (8), 75 (11), 73 (50).

Anal. Calcd for $C_{19}H_{39}NOSi_2$: C, 64.52; H, 11.11; N, 3.96. Found: C, 64.43; H, 11.05; N, 4.00.

***N*,*N*-Diisopropyl-6-(phenylthio)-1-cyclohexenecarboxamide (48).** Procedure A: 273 mg (1.31 mmol) of **36**, 1.1 mL (1.5 mmol) of *sec*-BuLi, 0.20 mL (1.3 mmol) of TMEDA, 10 mL of THF, 10 min. The solution was added dropwise to 660 mg (3.03 mmol) of diphenyldisulfide in 5 mL of THF at −78 °C. After being worked up in the usual manner, the reaction mixture was separated by MPLC on silica by elution with hexane/ethyl acetate. Kugelrohr distillation (115–120 °C (0.1 mm)) afforded 231 mg (56%) of pure **48** as a white solid: mp 82–83.5 °C: ^{1}H NMR (360 MHz) δ 1.2 (br s, 6 H, CH_3), 1.4 (br s, 6 H, CH_3), 1.8–2.1 (m, 4 H, CH_2), 2.1–2.25 (m, 2 H, allylic CH_2), 3.3–3.5 (m, 1 H, SCH), 4.33 (br, 2 H, NCH), 5.81 (t, J = 4 Hz, 1 H, C=CH), 7.2–7.3 (m, 3 H, ArH), 7.4–7.5 (m, 2 H, ArH); IR (KBr) 2967 (m), 2937 (m), 1645 (s, C=O), 1439 (m), 1368 (m), 1315 (m), 739 (s) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 317 (49, M^+), 217 (65), 208 (65), 109 (100), 107 (49), 81 (60), 79 (48).

Anal. Calcd for $C_{19}H_{27}NOS$: C, 71.88; H, 8.57; N, 4.41; S, 10.10. Found: C, 71.74; H, 8.75; N, 4.19; S, 10.05.

Preparation of 48 via Lithium (2-(*N*,*N*-Diisopropylcarbamoyl)-2-cyclohexenyl)trimethoxyborate. Procedure A: 972 mg (4.65 mmol) of **36**, 6.0 mL (5.9 mmol) of *sec*-BuLi, 0.90 mL (5.9 mmol) of TMEDA, 30 mL of THF, 30 min. The solution was treated with trimethylborate and allowed to warm to ambient temperature. A solution of 2.5 g (11 mmol) of diphenyl disulfide in 10 mL of THF was added, and the resulting solution was heated at reflux under N_2 atmosphere for 3 days. After cooling, extractive workup, and separation by MPLC on silica with hexane/ethyl acetate as an eluent, two Kugelrohr distillations gave 882 mg (60%) of pure **48**, mp 83.5–84.5 °C.

2-(*N*,*N*-Diisopropylcarbamoyl)-1-cyclohexenecarboxaldehyde (49). Procedure A: 260 mg (1.24 mmol) of **36**, 1.0 mL (1.3 mmol) of *sec*-BuLi, 0.20 mL (1.3 mmol) of TMEDA, 10 mL of THF, 5 min, 0.15 mL (1.9 mmol) of dimethylformamide. The crude product was purified by MPLC on silica by elution with hexane/ethyl acetate. Kuglrohr distillation (80–85 °C (0.15 mm)) gave 123 mg (42%) of pure **49** as a colorless liquid: ^{1}H NMR (90 MHz) δ 1.19 (d, J = 7 Hz, 6 H, CH_3), 1.50 (d, J = 7 Hz, 6 H, CH_3), 1.65–1.85 (m, 4 H, CH_2), 2.20–2.25 (m, 4 H, allylic CH_2), 3.45 (heptet, J = 7 Hz, 1 H, NCH), 3.83 (heptet, J = 7 Hz, 1 H, NCH), 9.76 (s, 1 H, CHO); IR (NaCl, film) 2980 (m), 2930 (m), 1675 (s, C=O), 1620 (s, C=O), 1440 (s), 1370 (m), 1330 (s), 1217 (m), 1160 (m) cm^{-1}; mass spectrum (10 eV), m/e (relative intensity) 209 (2), 194 (100), 152 (65), 109 (21); field ionization mass spectrum 238 (36), 237 (100, M^+), 194 (17).

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 71.14; H, 9.88; N, 5.77.

***N*,*N*-Diisopropyl-6-hydroxyl-1-cyclohexenecarboxamide (51).** Procedure A: 2.54 g (12.2 mmol) of **36**, 10.0 mL (13.4 mmol) of *sec*-BuLi, 2.0 mL (13 mmol) of TMEDA, 100 mL of THF, 10 min. After treatment of the solution with 1.7 mL (18 mmol) of trimethylborate, the solution was allowed to warm to 0 °C for 1 h, treated with 2 mL of glacial acetic acid and 5 mL of hydrogen peroxide (30%), and stirred at ambient temperature for 22 h. After addition of 10 mL of water and 100 mL of ether, the solution was washed with three 30-mL portions of saturated $(NH_4)_2SO_4$ in 10% $Fe(NH_4)_2(SO_4)_2$ and 30 mL of brine, dried ($MgSO_4$), and reduced in vacuo to a light brown oil. Separation by MPLC on silica by elution with hexane/ethyl acetate followed by bulb-to-bulb distillation (95–105 °C (0.2 mm)) gave 1.80 g (66%) of **51**: white solid; mp 109–111 °C; ^{1}H NMR (90 MHz) δ 1.31 (d, J = 7 Hz, 12 H, CH_3), 1.7–1.9 (m, 4 H, CH_2), 2.0–2.2 (m, 2 H, allylic CH_2), 3.57 (d, J = 3 Hz, 1 H, OH), 3.5–4.1 (br, 2 H, NCH), 4.25–4.35 (m, 1 H, OCH), 5.78 (t, J = 4 Hz, 1 H, C=CH). Upon exchange with D_2O, the doublet at 3.57 ppm disappeared. ^{13}C NMR δ 17.6, 20.8 (br, 4 C), 24.9, 30.7, 48.2 (br, 2 C), 65.1, 128.0, 137.2, 172.1; IR (KBr) 3340 (m, br), 1610 (s, C=O), 1462 (s), 1358 (s), 1164 (m), 993 (m), 712 (m) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 225 (2, M^+), 192 (35), 125 (22), 107 (22), 86 (100), 79 (35), 41 (28).

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.56; H, 10.21; N, 6.08.

***N*,*N*-Diisopropyl-6-bromo-1-cyclohexenecarboxamide (52).** Procedure A: 337 mg (1.61 mmol) of **36**, 2.0 mL (1.7 mmol) of *sec*-BuLi, 0.26 mL (1.7 mmol) of TMEDA, 8 mL of THF, 20 min. The solution was treated with 0.22 mL (1.9 mmol) of trimethylborate and subsequently warmed to 0 °C for 1 h. After treatment with 94 μL (1.8 mmol) of Br_2, the solution was allowed to stir at ambient temperature for 0.5 h. Saturated brine was then added, and after being stirred for 4 h, the mixture was worked up in the usual manner. Separation by MPLC on silica by elution with hexane/ethyl acetate followed by Kugelrohr distillation (80–90 °C (0.1 mm)) gave 325 mg (70%) of pure **52** as a white crystalline solid: mp 62.0–63.5 °C: ^{1}H NMR (90 MHz) δ 1.30 (d, J = 7 Hz, 6 H, CH_3), 1.35 (d, J = 7 Hz, 6 H, CH_3), 1.8–2.4 (m, 6 H, CH_2), 3.4–4.3 (br, 2 H, NCH), 5.2–5.3 (m, 1 H, BrCH), 5.74 (t, J = 4 Hz, 1 H, C=CH); ^{13}C NMR δ 17.7, 20.6 (2 C), 21.0 (2 C), 24.5, 32.6, 47.9 (br, 2 C), 48.9, 128.0, 136.5, 169.9; IR (KBr) 2963 (m) 1621 (s, C=O), 1445 (s), 1370 (s), 1324 (s), 1212 (m), 1160 (m), 758 (m) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 289 (2.1, M^+), 287 (2.0, M^+), 274 (6), 272 (6), 208 (100), 189 (24), 187 (23), 109 (34), 107 (66), 105 (29), 86 (41), 81 (23), 79 (68), 77 (47), 43 (35), 41 (33); isotope ratio 190 (1.8), 189 (24.2), 188 (2.1), 187 (23.0).

Anal. Calcd for $C_{13}H_{22}BrNO$: C, 54.17; H, 7.69; Br, 27.72; N, 4.86. Found: C, 54.30; H, 7.83; Br, 27.56; N, 4.83.

5-(*N*,*N*-Diisopropylcarbamoyl)spiro[3.5]non-5-ene (54). A solution of 0.28 mL (0.27 mmol) of *sec*-BuLi and 0.04 mL (0.3 mmol) of TMEDA in 10 mL of THF was cooled to −78 °C and treated dropwise with a solution of 66 mg (0.23 mmol) of **41** in 5 mL of THF over a period of 35 min. After the solution was stirred at −78 °C for 15 min, 0.05 mL (0.3 mmol) of hexamethylphosphoramide was added, and the resulting solution was stirred at ambient temperature for 5 h. After being worked up in the manner described for procedure A, the mixture was separated by MPLC on silica with hexane/ethyl acetate as an eluent. Kugelrohr distillation (75–80 °C (0.15 mm)) afforded 17 mg (30%) of pure **54** as a colorless liquid: ^{1}H NMR (360 MHz) δ 1.09–1.14 (m, 6 H, CH_3), 1.46–1.52 (m, 6 H, CH_3), 1.6–2.1 (br m, 11 H, CH_2), 2.7–2.8 (m, 1 H, CH_2), 3.3–3.5 (m, 1 H, NCH), 3.8–4.0 (m, 1 H, NCH), 5.46 (t, J = 4 Hz, 1 H, C=CH); IR (NaCl, film) 2910 (s), 2880 (s), 1675 (m), 1622 (s, C=O), 1438 (s), 1367 (s), 1317 (s), 1215 (m), 1161 (m), 1032 (m), 758 (s) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 249 (10, M^+), 221 (13), 206 (27), 178 (100), 164 (14), 149 (21), 122 (26), 121 (38), 93 (27), 91 (25), 79 (17), 77 (24), 43 (25), 41 (19).

Anal. Calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.62. Found: C, 76.87; H, 10.85; N, 6.00.

6-(*N*,*N*-Diisopropylcarbamoyl)spiro[4.5]dec-6-ene (55). To a solution of 0.40 mL (0.44 mmol) of *sec*-BuLi and 0.05 mL (0.3 mmol) of TMEDA in 10 mL of THF at −78 °C was added, in a dropwise fashion, 62 mg (0.21 mmol) of **42** in 5 mL of THF over a period of 20 min. Upon completion of the addition, stirring was continued at −78 °C for 40 min, after which 0.06 mL (0.3 mmol) of hexamethylphosphoramide was added, and the solution was allowed to warm to ambient temperature for 0.5 h. After addition of 10 mL of saturated NH_4Cl in 2% HCl, the mixture was extracted with 20 mL of ether, washed with 5 mL of 6 N HCl, dried ($MgSO_4$), and reduced in vacuo to a colorless oil. Separation by MPLC on silica by elution with hexane/ethyl acetate followed by Kugelrohr distillation (85–90 °C (0.15 mm)) gave 33 mg (61%) of pure **55** as a white solid: mp 57–58 °C; ^{1}H NMR (360 MHz) δ 1.05–1.2 (br d, 6 H, CH_3), 1.25–1.4 (m, 2 H, CH_2), 1.4–1.5 (m, 6 H, CH_3), 1.65 (br s, 9 H, CH_2), 2.0–2.1 (m, 2 H, allylic CH_2), 2.3–2.4 (m, 1 H, CH_2), 3.3–3.4 (br, 1 H, NCH), 4.1–4.2 (br, 1 H, NCH), 5.57 (t, J = 4 Hz, 1 H, C=CH); IR (mull) 1626 (s, C=O), 1450 (s), 1438 (s), 1367 (s), 1320 (s), 1216 (m), 1158 (m), 1041 (m), 769 (m) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 263 (56, M^+), 248 (21), 220 (25), 206 (40), 163 (100), 93 (43), 91 (28), 79 (34), 67 (46), 43 (28), 41 (29).

Anal. Calcd for $C_{17}H_{29}NO$: C, 77.51; H, 11.10; N, 5.32. Found: C, 77.44; H, 11.05; N, 5.44.

5-*tert*-Butyl-3,3-diphenyl-3aα,4,5α,6-tetrahydro-1(3*H*)-isobenzofuranone (59). Procedure B: 214 mg (1.10 mmol) of **56**, 1.05 mL (2.5 mmol) of *n*-BuLi, 8 mL of THF, 0 °C, 15 min. After cooling the solution to −78 °C, 300 mg (1.65 mmol) of benzophenone was added dropwise as a solution in 5 mL of THF over a period of 15 min. Stirring was continued at −78 °C for 1.2 h, after which the solution was allowed to warm to ambient temperature and quenched with saturated NH_4Cl in 2% HCl. Following a workup in the manner described for procedure A, separation was effected by MPLC on silica with hexane/ethyl acetate as an eluent. The crude hydroxyamide, 268 mg (65%), was obtained upon removal of solvent: ^{1}H NMR (360 MHz) δ 0.70 (s, 9 H, CH_3), 1.1–1.2 (m, 1 H, ring CH), 1.3–1.4 (m, 1 H, ring CH), 1.55–1.65 (m, 1 H, ring CH), 1.8–1.9 (m, 1 H, ring CH), 2.1–2.2 (m, 1 H, ring CH), 2.29 (d, J = 5 Hz, 3 H, NCH_3), 3.55–3.65 (m, 1 H, allylic CH), 5.3–5.4 (br, 1 H, NH), 6.0–6.05 (m, 1 H, C=CH), 6.16 (s, 1 H, OH), 7.1–7.2 (m, 2 H, ArH), 7.2–7.3 (m, 4 H, ArH), 7.4–7.5 (m, 4 H, ArH); mass

spectrum (10 eV), *m/e* (relative intensity) 359 (3), 346 (4), 282 (4), 195 (100), 177 (19), 164 (78), 138 (60), 120 (17), 107 (60), 105 (17). The hydroxyamide, 173 mg (0.46 mmol), was treated with 7 mL of xylenes and heated at reflux for 8 h. After removal of the solvent in vacuo, the product was separated by MPLC on silica by elution with hexane/ethyl acetate to give 132 mg (83%), 54% from **56**, of pure **59** as a white crystalline solid: mp 183.5–185 °C: ^{1}H NMR (360 MHz) δ 0.40 (q, J_{1-3} = 12 Hz, 1 H, $H_{4\beta}$), 0.84 (s, 9 H, CH_3), 1.59 (dddd, J_1 = 12 Hz, J_2 = 11 Hz, J_3 = 5 Hz, J_4 = 2 Hz, 1 H, H_5), 1.84 (dddd, J_1 = 20 Hz, J_2 = 11 Hz, J_3 = 5 Hz, J_4 = 3 Hz, 1 H, $H_{6\beta}$), 2.11 (ddd, J_1 = 12 Hz, J_2 = 5 Hz, J_3 = 2 Hz, 1 H, $H_{4\alpha}$), 2.31 (br, dq, J_1 = 12 Hz, J_{2-4} = 3–5 Hz, 1 H, $H_{6\alpha}$), 3.66 (m, 1 H, H_{3a}), 6.94 (br q, J_{1-3} = ca. 4 Hz, 1 H, H_7), 6.98–7.01 (m, 2 H, ArH), 7.21–7.25 (m, 3 H, ArH), 7.34–7.42 (m, 3 H, ArH), 7.48–7.51 (m, 2 H, ArH); ^{13}C NMR δ 27.1 (3 C), 27.4, 28.0, 32.2, 43.7, 48.0, 90.9, 126.1 (2 C), 126.5 (2 C), 127.6, 127.9 (2 C), 128.2, 128.4 (2 C), 129.5, 138.1, 141.0, 143.4, 169.5; IR (KBr) 2963 (m), 1763 (s, C=O), 1687 (w), 1632 (m), 1449 (w), 1369 (w), 1248 (s), 1037 (w), 968 (m), 750 (m), 703 (s) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 346 (5, M$^+$), 183 (4), 164 (97), 107 (100), 105 (32), 93 (17), 79 (19), 77 (38), 57 (42), 41 (31).

Anal. Calcd for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56. Found: C, 83.21; H, 7.61.

3-Phenyl-3a,4,5,6-tetrahydro-1(3*H*)-isobenzofuranones (60e and 60t). Procedure B: 360 mg (2.5 mmol) of **19**, 1.8 mL (5.4 mmol) of *n*-BuLi, 8 mL of THF, 0 °C, 0.5 h, 0.35 mL (3.5 mmol) of benzaldehyde. Extractive workup in the manner described for procedure A gave the crude hydroxyamide, which was subsequently heated at reflux in 25 mL of xylenes for 20 h. The crude brown oil was separated by MPLC on silica with hexane/ethyl acetate as an eluent. Removal of the solvent in vacuo afforded 372 mg (67%) of a 54:46 mixture of **60e** and **60t**, respectively, as determined by capillary VPC. Three Kugelrohr distillations (125–130 °C (0.3 mm)) were required to obtain a sample which gave the correct combustion analysis: mp 64–102 °C; ^{1}H NMR (360 MHz, **60e**, H'; **60t**, H'') δ 0.47 (tdd, J_1 = 12 Hz, J_2 = 11 Hz, J_3 = 2 Hz, 1 H', CH_2), 1.34 (tdd, J_1 = 12 Hz, J_2 = 11 Hz, J_3 = 3 Hz, 1 H'', CH_2), 1.45–1.61 (m, 2 H, CH_2), 1.65–1.84 (m, 2 H, CH_2), 1.92–2.16 (m, 3 H, CH_2), 2.20–2.45 (m, 3 H, CH_2), 2.72–2.82 (m, 1 H'', allylic CH), 3.26–3.36 (m 1 H', allylic CH), 4.93 (d, J = 9.3 Hz, 1 H'', OCH), 5.73 (d, J = 9.0 Hz, 1 H', OCH), 6.90 (q, J = 3 Hz, 1 H'', C=CH), 6.94 (q, J = 3 Hz, 1 H', C=CH), 7.07–7.10 (m, 2 H, ArH), 7.30–7.42 (m, 8 H, ArH). Decoupling: irradiation at 3.31 ppm partially decoupled the signals at 6.94, 5.73, and 0.47 ppm; irradiation at 2.77 ppm partially decoupled the signals at 6.90, 4.93, and 1.34 ppm. IR (NaCl, film) 2940 (s), 1750 (s, C=O), 1678 (m), 1457 (m), 1315 (m), 1250 (s), 1225 (s), 1180 (s), 1020 (s) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 214 (6, M$^+$), 108 (100), 80 (29), 79 (44), 77 (15).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.33; H, 6.60.

Preparation of Isocnidilide 61e and Neocnidilide 61t. Procedure B: 739 mg (5.33 mmol) of **19**, 8.0 mL (11.2 mmol) of *n*-BuLi, 25 mL of THF, 0 °C, 0.5 h, 0.80 mL (7.5 mmol) of valeraldehyde. Extractive workup in the manner described for procedure A gave 1.545 g of the crude mixture of hydroxyamides. A portion (232 mg) of the mixture was heated at reflux in 15 mL of xylenes for 24 h. After removal of the solvent in vacuo, the mixture was separated by MPLC on silica with hexane/ethyl acetate as a eluent. Kugelrohr distillation (100–105 °C (0.25 mm)) afforded 88 mg (57%) of a mixture of **61e** and **61t** which gave the correct combustion analysis. The mixture was determined by capillary VPC to be a 58:42 ratio, respectively. Pyrolysis of another portion of the crude hydroxyamides at reflux in xylenes for 36 h gave a 62:38 mixture of **61e** and **61t**, respectively. Partial separation by MPLC on silica by elution with hexane/ethyl acetate afforded a small amount of **61t** which was free of **61e**. Prolonged contact with silica or chloroform resulted in decomposition of both isomers. The IR spectrum of **61t** was identical with the published spectrum of neocnidilide.[17] **61t**: ^{1}H NMR (360 MHz) δ 0.92 (t, J = 7 Hz, 3 H, CH_3), 1.17 (tdd, J_1 = 13 Hz, J_2 = 11 Hz, J_3 = 3 Hz, 1 H, CH_2), 1.35–1.45 (m, 3 H, CH_2), 1.5–1.6 (m, 2 H, CH_2), 1.7–1.8 (m, 2 H, CH_2), 1.94 (ddd, J_1 = 13 Hz, J_2 = 6 Hz, J_3 = 3 Hz, 1 H, CH_2), 2.06 (ddt, J_1 = 12 Hz, J_2 = 5 Hz, J_3 = 4 Hz, 1 H, CH_2), 2.15–2.25 (m, 1 H, CH_2), 2.34 (dm, J = 20 Hz, 1 H, CH_2), 2.45–2.55 (m, 1 H, CH), 3.97 (ddd, J_1 = 9 Hz, J_2 = 7 Hz, J_3 = 5 Hz, 1 H, OCH), 6.78 (q, J = 3 Hz, 1 H, C=CH); IR (NaCl, film) 2880 (s), 1755 (s, C=O), 1680 (m), 1448 (m), 1420 (m), 1343 (m), 1326 (m), 1250 (s), 1228 (s), 1185 (s), 1088 (m), 1017 (s), 933 (m), 737 (m) cm^{-1}. The mass spectrum (10 eV) was taken on the mixture, *m/e* (relative intensity) 194 (2, M$^+$), 137 (9), 108 (100), 81 (5), 80 (14), 79 (11).

Anal. (for mixture **61e,t**) Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.89; H, 9.33.

Preparation of Isocnidilide via Lithium (2-(*N*,*N*-Diisopropylcarbamoyl)-2-cyclohexenyl)trimethoxyborate. Procedure B: 186 mg (1.34 mmol) of **19**, 2.0 mL (2.8 mmol) of *n*-BuLi, 8 mL of THF, 0 °C, 40 min. After recooling the solution to −78 °C, 0.20 mL (1.8 mmol) of trimethylborate was added, and the resulting mixture was allowed to warm to 0 °C for 15 min. After again recooling to −78 °C, the solution was treated with 0.33 mL (3.1 mmol) of valeraldehyde and allowed to warm to ambient temperature. Extractive workup in the manner described for procedure A gave a nearly colorless oil which was heated at reflux at 15 mL of xylenes for 34 h. After removal of the solvent in vacuo, separation by MPLC on silica by elution with hexane/ethyl acetate followed by Kugelrohr distillation afforded 43 mg (16%) of a 98:2 mixture of **61e** and **61t**, respectively, as determined by capillary VPC: ^{1}H NMR (360 MHz) δ 0.09 (t, J = 7 Hz, 3 H, CH_3), 1.2–1.4 (m, 6 H, acyclic CH_2), 1.4–1.6 (m, 2 H, CH_2), 1.85–2.0 (m, 2 H, CH_2), 2.15–2.25 (m, 1 H, CH_2), 2.3–2.4 (m, 1 H, allylic CH_2), 3.0–3.1 (m, 1 H, allylic CH), 4.6–4.7 (m, 1 H, OCH), 6.29 (br q, J = 3 Hz, 1 H, C=CH). The IR spectrum of **61e** was identical with the spectrum published for isocnidilide.[17] IR (NaCl, film) 2880 (s), 1755 (s, C=O), 1675 (m), 1444 (m), 1328 (m), 1224 (m), 1188 (s), 1035 (s), 995 (m), 947 (s), 755 (m), 704 (m) cm^{-1}.

***N*,*N*-Diisopropyl-6-benzyl-2-(trimethylsilyl)-1-cyclohexenecarboxamide (63).** Procedure A: 166 mg (0.59 mmol) of **47**, 0.60 mL (0.80 mmol) of *s*-BuLi, 0.11 mL (0.73 mmol) of TMEDA, 8 mL of THF, 5 min., 0.30 mL (2.6 mmol) of benzyl chloride. Separation by MPLC on silica by elution with hexane/ethyl acetate followed by Kugelrohr distillation (110–120 °C (0.15 mm)) afforded 171 mg (81%) of pure **63** as a white solid: mp 104–105.5 °C; ^{1}H NMR (360 MHz) δ 0.13 (s, 9 H, $Si(CH_3)_3$), 1.20 (d, J = 7 Hz, 3 H, CH_3), 1.28 (d, J = 7 Hz, 3 H, CH_3), 1.40–1.43 (m, 2 H, CH_2), 1.49 (d, J = 7 Hz, 3 H, CH_3), 1.54 (d, J = 7 Hz, 3 H, CH_3), 1.57–1.70 (m, 2 H, CH_2), 2.07–2.13 (m, 2 H, allylic CH_2), 2.33–2.39 (m, 1 H, allylic CH), 2.48 (dd, J_1 = 14 Hz, J_2 = 12 Hz, 1 H, PhCH), 3.03 (dd, J_1 = 14 Hz, J_2 = 3 Hz, 1 H, PhCH), 3.41 (heptet, J = 7 Hz, 1 H, NCH), 4.05 (heptet, J = 7 Hz, 1 H, NCH), 7.12–7.15 (m, 2 H, ArH), 7.17–7.20 (m, 1 H, ArH), 7.22–7.29 (m, 2 H, ArH); IR (KBr) 2960 (s), 2917 (s), 1617 (s, C=O), 1440 (s), 1370 (s), 1323 (s), 1246 (s), 868 (s), 836 (s), 757 (s), 702 (s) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 371 (29, M$^+$), 356 (24), 298 (30), 280 (54), 181 (32), 179 (26), 75 (36), 73 (100).

Anal. Calcd for $C_{23}H_{37}NOSi$: C, 74.33; H, 10.04; N, 3.77. Found: C, 74.09; H, 9.85; N, 4.04.

***N*,*N*-Diisopropyl-6-(hydroxydiphenylmethyl)-2-(trimethylsilyl)-1-cyclohexenecarboxamide (66).** Procedure A: 167 mg (0.59 mmol) of **47**, 0.50 mL (0.67 mmol) of *sec*-BuLi, 0.10 mL (0.66 mmol) of TMEDA, 8 mL of THF, 5 min. 130 mg (0.71 mmol) of benzophenone. After addition of benzophenone, the mixture was stirred at −78 °C for 15 min after which it was quenched with saturated NH_4Cl in 2% HCl and allowed to warm to ambient temperature. The crude mixture was worked up in the manner described for procedure A. Separation by MPLC on silica with hexane/ethyl acetate as an eluent afforded, after removal of the solvent in vacuo, 247 mg (90%) of pure **66** as a white solid: mp 136–138 °C; ^{1}H NMR (90 MHz) δ 0.13 (s, 9 H, $Si(CH_3)_3$), 0.82 (d, J = 7 Hz, 3 H, CH_3), 1.13 (d, J = 7 Hz, 3 H, CH_3), 1.24 (d, J = 7 Hz, 3 H, CH_3), 1.30 (d, J = 7 Hz, 3 H, CH_3), 1.4–1.7 (m, 4 H, CH_2), 1.8–2.0 (m, 2 H, allylic CH_2), 3.14 (heptet, J = 7 Hz, 1 H, NCH), 3.3–3.5 (m, 1 H, allylic CH), 4.13 (heptet, J = 7 Hz, 1 H, NCH), 5.03 (s, 1 H, OH), 7.0–7.3 (m, 6 H, ArH), 7.4–7.6 (m, 4 H, ArH); IR (KBr) 3450 (m, br), 2975 (m), 1595 (s, C=O), 1447 (s), 1368 (m), 1328 (m), 1246 (m), 838 (s), 703 (s) cm^{-1}; mass spectrum (10 eV), *m/e* (relative intensity) 448 (3), 281 (95), 266 (31), 238 (51), 208 (100), 183 (35).

Anal. Calcd for $C_{29}H_{41}NO_2Si$: C, 75.11; N, 8.91; N, 3.02. Found: C, 74.99; H, 8.84; N, 3.00.

***N*,*N*-Diisopropyl-6-benzoyl-2-(trimethylsilyl)-1-cyclohexenecarboxamide (68).** Procedure A: 170 mg (0.60 mmol) of **47**, 0.55 mL (0.74 mmol) of *sec*-BuLi, 0.10 mL (0.66 mmol) of TMEDA, 8 mL of THF, 5 min, 119 mg (0.80 mmol) of dimethylbenzamide. Separation by MPLC on silica by elution with hexane/ethyl acetate gave, after removal of the solvent in vacuo, 170 mg (73%) of pure **68** as a white solid: mp 106–107 °C; ^{1}H NMR (360 MHz) δ 0.18 (s, 9 H, $Si(CH_3)_3$), 1.0–1.4 (br, 12 H, CH_3), 1.55–1.60 (m, 1 H, CH_2), 1.8–2.0 (m, 3 H, CH_2), 2.2–2.3 (m, 2 H, allylic CH_2), 3.24 (t, J = 7 Hz, 1 H, allylic CH), 4.0–4.3 (br, 2 H, NCH), 7.42 (br t, J = 7 Hz, 2 H, ArH), 7.49 (br t, J = 7 Hz, 1 H, ArH), 7.96 (br d, J = 7 Hz, 2 H, ArH); IR (KBr) 2958 (m), 1675 (s, C=O), 1615, (s, C=O), 1442 (s), 1320 (s), 1212 (s), 890 (s), 721 (s) cm^{-1}; mass spectrum (10 eV), *m/e* (relative intensity) 385 (52, M$^+$), 312 (79), 285 (15), 284 (20), 280 (100), 264 (18), 181 (41), 105 (82).

Anal. Calcd for $C_{23}H_{35}NO_2Si$: C, 71.64; H, 9.15; N, 3.63. Found: C, 71.78; H, 9.21; N, 3.66.

***N*,*N*-Diisopropyl-6-(hydroxydiphenylmethyl)-2-(phenylthio)-1-cyclohexenecarboxamide (74).** Procedure A: 182 mg (0.57 mmol) of **48**, 0.55 mL (0.74 mmol) of *sec*-BuLi, 0.10 mL (0.66 mmol) of TMEDA, 8 mL

of THF, 5 min, 138 mg (0.76 mmol) of benzophenone. The mixture was stirred at −78 °C for 30 min, before being allowed to warm to ambient temperature and worked up by the usual extractive procedures. The product was purified by MPLC on silica with hexane/ethyl acetate as an eluent. Removal of the solvent in vacuo afforded 281 mg (98%) of pure **74** as a white solid: mp 128–129 °C; ^{1}H NMR (360 MHz) δ 0.43 (d, J = 7 Hz, 3 H, CH_3), 1.25 (d, J = 7 Hz, 3 Hz, CH_3), 1.28 (d, J = 7 Hz, 3 H, CH_3), 1.30 (d, J = 7 Hz, 3 H, CH_3), 1.38–1.43 (m, 3 H, CH_2), 1.67–1.73 (m, 1 H, CH_2), 2.11–2.17 (m, 2 H, allylic CH_2), 3.14 (heptet, J = 7 Hz, 1 H, NCH), 3.69–3.72 (m, 1 H, allylic CH), 4.10 (heptet, J = 7 Hz, 1 H, NCH), 6.24 (s, 1 H, OH), 7.04–7.11 (m, 2 H, ArH), 7.20–7.32 (m, 7 H, ArH), 7.38 (d, J = 8 Hz, 2 H, ArH), 7.50 (d, J = 8 Hz, 2 H, ArH), 7.68 (d, J = 8 Hz, 2 H, ArH); IR (KBr) 3430 (s), 2972 (m), 2930 (m), 1597 (s, C=O), 1475 (m), 1447 (s), 1368 (m), 1332 (m), 745 (s), 704 (s) cm^{-1}; mass spectrum (10 eV), m/e (relative intensity) 317 (100), 217 (59), 216 (17), 208 (87), 109 (12).

Anal. Calcd for $C_{32}H_{37}NO_2S$: C, 76.91; H, 7.46; N, 2.80; S, 6.42. Found: C, 76.99; H, 7.53; N, 2.66; S, 6.19.

N,N-Diisopropyl-6-ethyl-2-(phenylthio)-1-cyclohexenecarboxamide (76) and N,N-Diisopropyl-6-ethyl-6-(phenylthio)-1-cyclohexenecarboxamide (77). Procedure A: 189 mg (0.60 mmol) of **48**, 0.60 mL (0.80 mmol) of *sec*-BuLi, 0.10 mL (0.66 mmol) of TMEDA, 8 mL of THF, 0.10 mL (1.2 mmol) of iodethane. Separation by MPLC by elution with hexane/ethyl acetate/dichloromethane followed by Kugelrohr distillation (130 °C (0.3 mm)) gave 179 mg (87%) of a ca. 92:8 mixture of **76**:**77**, respectively, as a colorless oil: ^{1}H NMR (360 MHz) δ 0.94 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.85 (d, J = 7 Hz, 3 H, CH_3), 1.21 (d, J = 7 Hz, 3 H, CH_3), 1.4–1.6 (m, 2 H, CH_2), 1.45 (d, J = 7 Hz, 3 H, CH_3), 1.50 (d, J = 7 Hz, 3 H, CH_3), 1.7–1.85 (m, 4 H, CH_2), 2.05–2.2 (m, 3 H, allylic CH_2, CH), 3.37 (heptet, J = 7 Hz, 1 H, NCH), 4.02 (heptet, J = 7 Hz, 1 H, NCH), 7.15–7.4 (m, 5 H, ArH). Additionally, the presence of a minor (ca. 20–25%) rotational isomer was indicated by the following signals: δ 1.17 (d, J = 7 Hz, 3 H′, CH_3), 1.29 (d, J = 7 Hz, 3 H′, CH_3), 1.48 (d, J = 7 Hz, 3 H′, CH_3), 2.55–2.65 (m, 1 H′, allylic CH), 3.44 (heptet, J = 7 Hz, 1 H′, NCH), 4.09 (heptet, J = 7 Hz, 1 H′, NCH). The presence of ca. 8% of **77** was shown by a small multiplet at 5.83 ppm (C=CH). IR (NaCl, film) 2930 (s), 1622 (s, C=O), 1435 (s), 1363 (s), 1320 (s), 1217 (m), 1160 (m), 1132 (m), 748 (s, br) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 345 (32, M$^+$), 245 (100), 236 (59), 218 (19), 189 (37), 109 (18), 79 (24), 43 (23).

Anal. (For the mixture **76**:**77**). Calcd for $C_{21}H_{31}NOS$: C, 73.00; H, 9.04; N, 4.05; S, 9.28. Found: C, 72.71; H, 8.97; N, 3.97; S, 9.45.

Reaction of 52 with Silver Tetrafluoroborate. Silver tetrafluoroborate (64 mg, 0.33 mmol) and **52** (39 mg, 0.14 mmol) were combined in a dark vessel and treated with 4 mL of dichloromethane. After the mixture was stirred at ambient temperature under a N_2 atmosphere for 1.5 h, H_2O was added and stirring was continued for 3 h. The resulting mixture was extracted with two portions of chloroform, dried ($MgSO_4$), and concentrated to a crude solid. Separation by MPLC on silica with hexane/ethyl acetate as an eluent followed by Kugelrohr distillation afforded 16 mg (56%) of pure **81**, mp 112–113.5 °C.

To obtain a spectrum of **81**, **52** and excess silver tetrafluoroborate were combined in CD_2Cl_2 and stirred for 2 h. After the insoluble salts were allowed to settle, the solution of **81** was transferred to a NMR tube: ^{1}H NMR (360 MHz) δ 1.34 (d, J = 7 Hz, 3 H, CH_3), 1.38 (d, J = 7 Hz, 3 H, CH_3), 1.51 (d, J = 7 Hz, 3 H, CH_3), 1.52 (d, J = 7 Hz, 3 H, CH_3), 1.65–1.75 (m, 2 H, CH_2), 1.8–1.9 (m, 2 H, CH_2), 2.05–2.15 (m, 2 H, allylic CH_2), 3.88 (heptet, J = 7 Hz, 1 H, NCH), 4.35 (heptet, J = 7 Hz, 1 H, NCH), 4.5–4.6 (m, 1 H, OCH), 6.4–6.45 (m, 1 H, C=CH). Upon addition of D_2O to the NMR tube, the spectrum changed to one which was identical with **51**. The ^{13}C NMR spectrum showed the presence of both **81** and **52**: ^{13}C NMR (CD_2Cl_2) δ 16.8, 20.1 (high intensity), 21.3, 22.4, 25.4, 27.5, 29.1, 51.4, 56.2, 56.9, 70.2, 118.3, 130.2, 137.9, 141.1, 174.0.

N,N-Diisopropyl-6-ethoxy-1-cyclohexenecarboxamide (82). A mixture of 33 mg (0.12 mmol) of **52** and 76 mg (0.39 mmol) of silver tetrafluoroborate was treated with 3 mL of ethanol and 3 mL of dichloromethane. The resulting suspension was stirred at ambient temperature in the dark under a N_2 atmosphere for 4 h. After treatment with saturated brine, stirring was continued for 1 h. The mixture was then extracted with chloroform, dried ($MgSO_4$), and reduced in vacuo to a colorless liquid. Kugelrohr distillation (90–100 °C (0.1 mm)) afforded 28 mg (97%) of pure 82: ^{1}H NMR (360 MHz) δ 1.13 (d, J = 7 Hz, 3 H, CH_3), 1.15 (d, J = 7 Hz, 3 H, CH_3), 1.2–1.5 (br, 9 H, CH_3, CH_2CH_3), 1.5–1.6 (m, 1 H, CH_2), 1.65–1.85 (m, 3 H, CH_2), 1.95–2.15 (m, 2 H, allylic CH_2), 3.3–3.5 (br, 1 H, NCH), 3.42 (dq, J_1 = 9 Hz, J_2 = 7 Hz, 1 H, OCH_2), 3.62 (dq, J_1 = 9 Hz, J_2 = 7 Hz, 1 H, OCH_2), 4.15–4.25 (m, 1 H, OCH), 4.25–4.45 (br, 1 H, NCH), 5.65–5.75 (m, 1 H, C=CH); IR (NaCl, film) 2880 (s), 1620 (s, C=O), 1433 (s), 1360 (s), 1346 (s), 1319 (s), 1212 (m), 1158 (m), 1087 (s), 1028 (m) cm^{-1}; mass spectrum (10 eV), m/e (relative intensity) 253 (1.6, M$^+$), 209 (35), 208 (31), 207 (33), 192 (100), 153 (42), 109 (37), 107 (36), 86 (26), 81 (23), 79 (49), 47 (44).

Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.06; H, 10.87; N, 5.30.

(E)-N,2-Dimethyl-2-butenamide (87). Tiglic acid was treated sequentially with thionyl chloride and aqueous methylamine to give after two Kugelrohr distillations (60–65 °C (0.3 mm)) 7.3 g (67%) of **87** (lit.[39] bp 132–134 °C (20 mm)): ^{1}H NMR (90 MHz) δ 1.71 (d, J = 7 Hz, 3 H, $CHCH_3$), 1.82 (s, 3 H, CH_3), 2.80 (d, J = 5 Hz, 3 H, NCH_3), 6.29 (q, J = 7 Hz, 1 H, C=CH), 6.35–6.65 (br, 1 H, NH); IR (NaCl, film) 3300 (s), 2930 (m), 1670 (s, C=O), 1627 (s), 1530 (s), 1408 (m) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 113 (51, M$^+$), 98 (13), 83 (41), 58 (18), 55 (100); isotope ratio 114 (4.3), 113 (51), 112 (1.6), 84 (2.8), 83 (41), 82 (3.9).

(E)-N-Methyl-2-heptyl-2-butenamide (90) and N-Methyl-2-(1-methylheptyl)propenamide (91). Procedure A: 216 mg (1.91 mmol) of **87**, 3.1 mL (4.1 mmol) of *sec*-BuLi, 1.05 mL (6.9 mmol) of TMEDA, 20 mL of THF, 45 min, 0.28 mL (1.9 mmol) of 1-bromohexane; conditions. Separation by MPLC on silica by elution with hexane/ethyl acetate afforded 128 mg (34%) of **90** and **167** mg (44%) of **91** as colorless oils after removal of solvent in vacuo. **90**: ^{1}H NMR (90 MHz) δ 0.87 (t, J = 6 Hz, 3 H, CH_2CH_3), 1.30 (br s, 10 H, CH_2), 1.72 (d, J = 7 Hz, 3 H, allylic CH_3), 2.2–2.45 (m, 2 H, allylic CH_2), 2.83 (d, J = 5 Hz, 3 H, NCH_3), 5.75–6.15 (br, 1 H, NH), 6.23 (q, J = 7 Hz, 1 H, C=CH); IR (NaCl, film) 3295 (s), 2900 (s), 1662 (s, C=O), 1622 (s), 1530 (s), 1465 (m), 1407 (m), 1308 (w), 1158 (w) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 197 (22, M$^+$), 182 (39), 140 (46), 126 (49), 113 (47), 112 (53), 69 (34), 58 (85), 55 (100), 41 (67).

Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.96; H, 11.83; N, 6.99.

91: ^{1}H NMR (90 MHz) 0.86 (t, J = 6 Hz, 3 H, CH_2CH_3), 1.05 (d, J = 7 Hz, 3 H, $CHCH_3$), 1.27 (br s, 10 H, CH_2), 2.45–2.8 (m, 1 H, CH), 2.83 (d, J = 5 Hz, 3 H, NCH_3), 5.13 (s, 1 H, C=CH), 5.44 (s, 1 H, $C=CH_2$), 5.9–6.3 (br, 1 H, NH); IR (NaCl, film) 3295 (m), 2940 (s), 1665 (s, C=O), 1628 (s), 1545 (s), 1469 (w), 1417 (w), 1161 (w), 929 (w) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 197 (17, M$^+$), 182 (86), 168 (58), 140 (48), 126 (82), 98 (41), 84 (45), 58 (100), 55 (79), 41 (79).

Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 73.08; H, 11.56; N, 7.04.

N,N-Diisopropyl-2-octene-3-carboxamide (107). Procedure A: 444 mg (2.42 mmol) of **104**, 2.67 mmol of *sec*-BuLi and 414 μL (2.75 mmol) of TMEDA, 60 mL of THF, 15 min, 304 μL (2.67 mmol) of 1-iodobutane. After the solution was stirred for 30 min at ambient temperature, 581 mg of the 763 mg of crude oil was separated by MPLC with 30% ethyl acetate/hexanes, to afford after bulb-to-bulb distillation 280 mg (63%) of **104**: bp$^{3.0}$ 95–100 °C; ^{1}H NMR (360 MHz) δ 0.88 (t, J = 6 Hz, 3 H, CH_2CH_3), 1.31 (d, J = 7 Hz, 12 H, CH_3), 0.95–1.50 (unresolved m, 6 H, CH_2), 1.65 (d, J = 7 Hz, 3 H, allylic CH_3), 2.23 (m, 2 H, allylic CH_2), 3.73 (m, 2 H, NCH), 5.40 (q, J = 7 Hz, 1 H, C = $CHCH_3$); mass spectrum (70 eV), m/e (relative intensity) 239 (11), 224 (15), 196 (16), 182 (60), 168 (11), 139 (100), 86 (26), 69 (88), 55 (81), 43 (52), 41 (50); IR (NaCl, film) 1624, 1435, 1365, 1330, 1210, 1160, 1130, 1045, 828, 758 cm^{-1}.

Anal. Calcd for $C_{15}H_{29}NO$: C, 75.57; H, 11.84; N, 5.88. Found: C, 75.52; H, 12.0; N, 5.51.

N,N-Diisopropyl-5-methyl-5-hydroxy-2-hexene-3-carboxamide (109) and N,N-Diisopropyl-3,4-dimethyl-4-hydroxypentene-2-carboxamide (110). Procedure A: 888 mg (4.85 mmol) of **104**, 5.34 mmol of *sec*-BuLi, and 804 μL (5.34 mmol) of TMEDA, 135 mL of THF, 5 min, 712 μL (9.7 mmol) of reagent grade acetone. The solution was stirred for 15 min and then worked up and separated by MPLC eluting with 25% ethyl acetate/hexanes and recrystallized from ethyl acetate/hexanes to give 578 mg (49%) of **109** and 375 mg (32%) of **110**. **109**: mp 91–92.5 °C; ^{1}H NMR (90 MHz) δ 1.28 (s, 6 H, CH_3), 1.32 (d, J = 7 Hz, 12 H, CH_3), 1.68 (d, J = 7 Hz, 3 H, allylic CH_3), 2.35 (s, 2 H, allylic CH_2), 3.77 (m, 2 H, NCH), 4.47 (s, 1 H, OH), 5.62 (q, J = 7 Hz, 1 H, C = $CHCH_3$); mass spectrum (10 eV), m/e (relative intensity) 226 (5), 183 (49), 168 (100), 140 (37), 125 (21), 123 (29), 95 (25), 86 (45), 83 (53), 55 (28), 43 (35); IR (KBr) 3360, 1654, 1600, 1339, 1135, 795 cm^{-1}.

Anal. Calcd for $C_{20}H_{27}NO_2$: C, 69.66; H, 11.28; N, 5.80. Found: C, 69.49; H, 11.22; N, 5.64.

110: mp 75–76 °C; ^{1}H NMR (90 MHz) δ 1.03 (s, 3 H, CCH_3), 1.12 (s, 3 H, CCH_3), 1.24 (d, J = 7 Hz, 12 H, CH_3), 1.42 (d, J = 7 Hz, 3 H, $CHCH_3$), 2.38 (q, J = 7 Hz, 1 H, $CHCH_3$), 3.34 (qq, J = 7 Hz, 1 H, NCH), 4.28 (m, 1 H, NCH), 4.92 (s, 1 H, C = CH), 5.05 (s, 1 H, OH), 5.10 (s, 1 H, KC = CH); mass spectrum (10 eV), m/e (relative intensity) 241 (1), 226 (5), 183 (50), 168 (100), 140 (43), 125 (13), 95 (11), 86 (39), 83 (37); IR (KBr) 3320, 1631, 1591, 1348, 1123, 935 cm^{-1}.

Anal. Calcd for $C_{20}H_{27}NO_2$: C, 69.66, H, 11.28; N, 5.80. Found: C, 69.83; H, 11.22; N, 5.77.

Preparation of 110 with $MgBr_2$-Et_2O. Procedure C: 974 mg (5.31 mmol) of **104**, 5.85 mmol of *sec*-BuLi, 8.82 μL (5.85 mmol) of TMEDA, 150 mL of THF, 5 min, 1.51 g (5.85 mmol) of $MgBr_2$-Et_2O was added with stirring at −60 °C for 15 min and then 712 μL (9.7 mmol) of acetone was added and with stirring for 20 min prior to workup. Recrystallization from dichloromethane/pentane afforded 724 mg (57%) of **110**: mp 77–79 °C, mixture mp 78–79 °C.

Metalation and Equilibration of 19. A solution of 201 mg (1.45 mmol) of **19** in 7 mL of THF was cooled to −78 °C and treated with 2.0 mL (2.8 mmol) of *n*-BuLi. The resulting solution was allowed to warm to ambient temperature for 15 min, after which 0.05 mL (0.3 mmol) of 2,2,6,6-tetramethylpiperidine was added. After 36 h, the mixture was cooled to 0 °C and treated with 0.1 mL (5 mmol) of D_2O. Extractive workup in the manner described for procedure A left a brown oil, which was distilled (Kugelrohr, 90–95 °C (0.2 mm)) to give 122 mg (60%) of a colorless liquid. Analysis of the ^1H NMR spectrum indicated a ca. 60:40 mixture of **117**:**118** respectively. The presence of **118** was indicated by the following resonances: δ 2.81 (d, J = 5 Hz, 3 H, NCH_3), 5.66 (br d, J = 10 Hz, 1 H, β-H), 5.95 (dt, J_1 = 10 Hz, J_2 = 4 Hz, γ-H); mass spectrum (70 eV), isotope ratio m/e (relative intensity) 141 (8.3), 140 (68.4), 139 (42.1), 83 (49.8), 82 (90.1), 81 (60.0); calcd % d = 68% (for the mixture **117**, **118**).[38]

(37) Abramovitch, R. A.; Struble, D. L. *Tetrahedron Lett.* **1966**, 289.

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Supplementary Material Available: Experimental details about compounds and the preparations of **22**, **25–27**, **29**, **30**, **32–35**, **37**, **39**, **40**, **43**, **44**, **47**, **53**, **64**, **65**, **67**, **70**, **71**, **75**, **78**, **79**, **83**, **84**, **88**, **89**, **92**, **94–97**, **100**, **101**, **103**, **105**, **108**, **106**, **111**, **112**, **114–116** (28 pages). Ordering information is given on any current masthead page.

(38) The amount of deuterium incorporation in a sample was determined by solving the following set of simultaneous equations: $d(I_{-1}) + (1-d)I_0 = a(I'_{-1})$; $d(I_0) + (1-d)I_{+1} = a(I'_0)$, where d = fraction of deuterated material in the sample, I_0 = relative intensity of the molecular ion peak in the starting material, I_{-1} = relative intensity of the M − 1 peak in the starting material, I_{+1} = relative intensity of the M + 1 peak in the starting material, I'_0 = relative intensity of the molecular ion peak in the deuterated sample, I'_{-1} = relative intensity of the M − 1 peak in the deuterated sample, and a = normalization coefficient. The process was repeated for another major peak in the spectrum, usually the acylium ion (M − NR_2). The results generally agreed within 1–2% with both peaks.

(39) Rekker, R. F.; Nauta, W. T. *Recl. Trav. Chim. Pays.-Bas* **1964**, *83*, 1039–1046.

(40) For a detailed description of the NOE experiment used see: Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703. Also see: Noggle, J. H.; Schirmer, R. A. "The Nuclear Overhauser Effect; Chemical Applications"; Academic Press: New York, 1971.

Synthesis, Characterization, and Properties of Hexadecyl Silica: A Novel Hydrophobic Matrix for Protein Immobilization

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Abstract: A convenient and inexpensive synthesis of an insoluble protein carrier is described. Hexadecyl silica, prepared by simple heating of hexadecanol and silica gel, has been shown to be a suitable matrix for protein immobilization with total retention of biochemical activity and the possible use of the adsorbed proteins in continuous catalytic operations. Gels with various degrees of substitution were prepared, and the maximum ligand density attainable was found to be ca. 90 mg of lipid per g of adsorbent. The degree of substitution has been observed to be an important factor in the adsorptive properties of the carrier. The extent of adsorption of three arbitrarily chosen proteins was found to increase with increasing ligand density, reaching maximum values with gels of higher hydrophobicities. Protein adsorption was also found to be a function of matrix/protein ratio in a similar manner. The pH stability of the matrix was also investigated. Although the extent of cleavage of the ligand increased with increasing pH, no deleterious effect on the adsorptive properties of the support was observed.

In recent years, wide attention has been directed toward the application of enzymes in organic synthesis.[1] In fact, laboratory scale stereospecific preparation of a number of compounds has been realized with enzymes as chiral catalysts.[2] This will clearly provide a new dimension to the use of immobilized enzyme systems, the importance of which for industrial purposes has already been recognized.[3]

During the course of our studies on immobilized enzyme systems,[4-7] it became evident that hydrophobic matrices may be used for adsorption of a variety of proteins, including enzymes. More importantly, adsorption conditions with such hydrophobic gels did not appear to have an adverse effect on the native properties of the proteins examined. For example, adsorbed glutamate dehydrogenase, used as a model allosteric enzyme, underwent its normal heterotropic allosteric conformational transitions in response to its effectors (inhibitors and activators) to a similar extent as its free form.[4-6]

On the other hand, application of such gels to large-scale enzymatic transformations is hampered by (a) the number of reactions required for the preparation of the hydrophobic ligand (i.e., hexadecyl glycidyl ether), (b) the requirement of large

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(1) (a) Takemura, T.; Jones, J. B. *J. Org. Chem.* **1983**, *48*, 791 and references therein. (b) Whitesides, G. M.; Wong, C.-H. *Aldrichimi. Acta* **1983**, *16*, 27.

(2) (a) Wong, C.-H.; Whitesides, G. M. *J. Am. Chem. Soc.* **1983**, *105*, 5012. (b) Hirschbein, B. L.; Whitesides, G. M. *Ibid.* **1982**, *104*, 4458. (c) Haslegrave, J. A.; Jones, J. B. *Ibid.* **1982**, *104*, 4666. (d) Jakova, I. J.; Goodbrand, H. B.; Lok, K. P.; Jones, J. B. *Ibid.* **1982**, *104*, 4659. (e) Gross, A.; Abril, O.; Lewis, J. M.; Geresh, S.; Whitesides, G. M. *Ibid.* **1983**, *105*, 7428. (f) Walt, D. R.; Findeis, M. A.; Rios-Mercadillo, V. M.; Augé, J.; Whitesides, G. M. *Ibid.* **1984**, *106*, 234. (g) Patterson, M. K.; Szajewki, R. P.; Whitesides, G. M. *J. Org. Chem.* **1981**, *46*, 4682. (h) Rozzel, J. D., Jr.; Benner, S. A. *Ibid.* **1983**, *48*, 1190. (i) Wong, C.-H.; Whitesides, G. M. *Ibid.* **1983**, *48*, 3199. (j) Abril, O.; Crans, D. C.; Whitesides, G. M. *Ibid.* **1984**, *49*, 1360. (k) Wilson, K. W.; Baca, S. P.; Barber, Y. J.; Scallen, T. J.; Marrow, C. J. *Ibid.* **1983**, *48*, 3960. (l) Stockigt, J.; Pfitzner, A.; Keller, P. J. *Tetrahedron Lett.* **1983**, *24*, 2485. (m) Wang, Y.-F.; Sih, C. J. *Ibid.* **1984**, *25*, 4999. (n) Ooi, Y.; Hashimoto, T.; Mitsuo, N.; Satoh, T. *Ibid.* **1984**, *25*, 2241. (o) Augé, C.; David, S.; Gautheron, C. *Ibid.* **1984**, *25*, 4663. (p) Petkov, D. D.; Stoineva, I. B. *Ibid.* **1984**, *25*, 3751. (q) Kobuyashi, S.; Kamiyama, K.; Iimori, T.; Ohno, M. *Ibid.* **1984**, *25*, 2557. (r) Contributing Authors, Section IX D: *Methods Enzymol.* **1976**, *44*, 831.

0002-7863/85/1507-4756$01.50/0