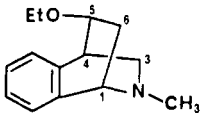
1 H), 4.21-4.19 (m, 1 H), 4.09 (br m, 3 H), 3.85-3.54 (m, 3 H), 3.50 (br s, 6 H, 2 × OCH_3), 3.47-3.21 (m, 4 H), 2.65-2.59 (m, 1 H), 2.44 (br m, 1 H), 1.46-1.43 (m, 1 H), 1.32-1.29 (m, 1 H), 1.28-1.18 (m, 6 H, 2 × $NCO_2CH_2CH_3$), 1.09, 1.02 (2 t, 3 H each, 2 × OCH_2CH_3); high resolution mass spectrum calcd for $C_{17}H_{23}NO_4$ 305.1630, found 305.1632.

In order to further confirm the structure assignment for compound **75**, it was treated with lithium aluminum hydride (LAH) as follows: A solution of **75** (36 mg, 0.118 mmol) in 1.5 mL of anhydrous ether was added dropwise to a stirred suspension of LAH (8 mg, 0.21 mmol) in 1 mL of anhydrous ether under N_2 at room temperature. The reaction mixture was then heated to reflux for 5 h. It was then cooled, and the excess LAH was carefully destroyed by adding ice-cold aqueous ethyl acetate. The reaction mixture was then extracted with ethyl acetate, and the organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. On purification using chromatotron, the residue gave **75a** (20 mg, 78%) consisting of only one isomer



75a

(TLC, ^1H 400-MHz NMR): IR ($CHCl_3$) 1600, 1450, 1370, 1350, 1340, 1240, 1090, 940, 910 cm^{-1}; ^1H NMR δ 7.36-7.18 (m, 4 H, Ar*H*), 3.94 (ddd, 1 H, J = 1.83, 3.05, 8.54 Hz, C_1-*H*), 3.90-3.88 (m, 1 H, C_5-*H*), 3.56 (dq, 1 H, J = 7.33, 9.16 Hz, $^1/_2OCH_2CH_3$), 3.44 (dd, 1 H, J = 1.83, 10.38 Hz, $^1/_2C_3$-H_2), 3.39 (dq, 1 H, J = 7.33, 9.16 Hz, $^1/_2OCH_2CH_3$), 3.35 (ddd, 1 H, J = 1.83, 1.83, 3.05 Hz, $^1/_2C_3$-H_2), 2.81 (ddd, 1 H, J = 3.66, 6.70, 14.65 Hz, $^1/_2C_6$-H_2), 2.19 (s, 3 H, NCH_3), 2.07 (dd, 1 H, J = 3.05, 10.38 Hz, C_4-*H*), 1.37 (ddd, 1 H, J = 2.46, 3.05, 14.65 Hz, $^1/_2C_6$-H_2), 1.07 (t, J = 7.33 Hz, OCH_2CH_3); high resolution mass spectrum calcd for $C_{14}H_{19}NO$ 217.1468, found 217.1468.

Reaction of 76 with Dowex and methanol: A mixture of **76** (80 mg, 0.26 mmol), Dowex-50×8 (50 mg), and methanol (1 mL) was stirred at room temperature for 5 h. The reaction was then worked up as described above for the recycling experiment. The crude product was purified by using chromatotron to give **77** (62 mg, 81%). The product **77** consisted of two rotamers in the ratio 2:1: IR ($CHCl_3$) 1695, 1630, 1570, 1450, 1400, 1375, 1350, 1330, 1290, 1120, 1100, 1075, 1055, 960, 910 cm^{-1}.

Major rotamer: ^1H NMR δ 7.21-7.06 (m, 4 H, Ar*H*), 6.79 (d, 1 H, J = 8.06 Hz, C_4-vinylic *H*), 5.86 (d, 1 H, J = 8.06 Hz, C_3-vinylic *H*), 5.52-5.48 (m, 1 H, C_1-*H*), 4.37 (dd, 1 H, J = 4.39, 4.40 Hz, *CH*-$(OMe)_2$), 4.25 (q, 2 H, J = 6.59 Hz, $NCO_2CH_2CH_3$), 3.31, 3.26 (2 s, 3 H each, $CH(OCH_3)_2$), 2.10-1.98 (m, 1 H, $^1/_2CH_2CH(OMe)_2$), 1.90-1.78 (m, 1 H, $^1/_2CH_2CH(OMe)_2$), 1.31 (t, 3 H, J = 6.59 Hz, $NCO_2CH_2CH_3$).

Minor rotamer: ^1H NMR δ 7.21-7.06 (m, 4 H, Ar*H*), 6.93 (d, 1 H, J = 8.06 Hz, C_4-vinylic *H*), 5.95 (d, 1 H, J = 8.06 Hz, C_3-vinylic *H*), 5.39-5.35 (m, 1 H, C_1-*H*), 4.29 (q, 2 H, J = 7.33 Hz, $NCO_2CH_2CH_3$), 3.30, 3.24 (2 s, 3 H each, $CH(OCH_3)_2$), 1.36 (t, 3 H, J = 7.33 Hz, $COOCH_2CH_3$).

Acknowledgment. We are indebted to the National Cancer Institute for Grant CA-39351, to the American Cancer Society for Grant CH-272, and to CUNY for PSC research awards which supported this work. The JEOL GX 400 NMR spectrometer used in the research was purchased with funds awarded by NSF-PCM 111745. We thank Professor P. A. Wender for a stimulating discussion about our tetralin work, Professor J. R. Falck for valuable information about the cycloaddition, and Professor C. K. Bradsher for furnishing some unpublished results.

Supplementary Material Available: Structure assignments for tetralins and one-bond products and experimental data for compounds **26a**, **27a**, and **27b** (9 pages). Ordering information is given on any current masthead page.

Complex-Induced Proximity Effects: Remote Lithiations of Carboxamides

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Abstract: The reactions of *sec*-butyllithium with *N,N*-diisopropyl-2-methylpent-4-enamide (**8**), *N,N*-diisopropylcyclohex-3-enecarboxamide (**9**), *N,N*-diisopropyl-2-methyl-3-phenylpropanamide (**28**), *N,N*-diisopropyl-2-methyl-3-(phenylthio)propanamide (**29**), *N,N*-diisopropyl-3-(phenylthio)-2-((phenylthio)methyl)propanamide (**30**), *N,N*-diisopropyl-3-(phenylthio)-2-((phenylthio)methyl)butanamide (**31**), and *N,N*-diisopropyl-3-(phenylthio)-2-methylbutanamide (**39**) provide organolithium reagents that are the result of β-lithiations. The direction of these metalations to the β-protons in the presence of thermodynamically more acidic α-protons is notable, and the operation of a complex-induced proximity effect that dominates over resonance and inductive effects is suggested. The regio- and stereochemistry of the reactions of the β-lithiated amides and of the corresponding Grignard and aluminum derivatives with a number of electrophilic reagents is reported. High selectivity is observed in many cases, and rationales for the course of these reactions are provided. Lithiation of *N,N*-diisopropyl-2-methyl-4-(phenylthio)-butanamide (**47**) is shown to occur at the γ position, but the corresponding γ-vinyl- or γ-phenyl-substituted amides or an amide with δ-phenylthio substitution does not undergo analogous metalations.

Substitution of a carbon-hydrogen bond by a sequence that involves deprotonation and reaction of the resulting formal carbanion with an electrophile is a general synthetic strategy for making carbon-carbon and carbon-heteroatom bonds. In most cases the intermediate carbanion is generated by removal of a proton from a carbon which bears a functional group capable of stabilizing the adjacent negative charge by resonance and/or inductive effects. We have been exploring the possibility that association between a functional group and an organolithium base can provide a complex which kinetically leads to a transition structure in which the base removes a proton from a carbon which is not adjacent to the directing functionality.[1,2]

In this report we provide information about the direct β-lithiations of α-alkyl carboxamides which are β-substituted by a vinyl, phenyl, or phenylthio group, to give the organolithium reagents **2**. These cases are notable because the complex-induced proximity effect in these lithiations must dominate the more familiar res-

(1) Beak P.; Meyers A. I. *Acc. Chem. Res.* **1986**, *19*, 356.
(2) Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1.

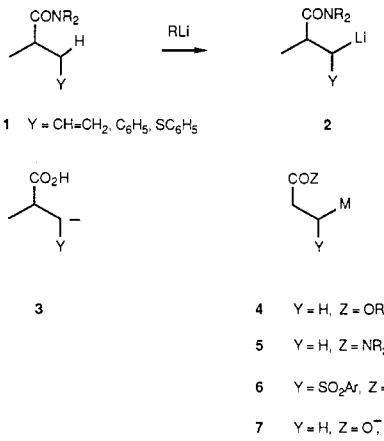
0002-7863/87/1509-5403$01.50/0

Table I. Lithiation and Electrophile Substitution of *N,N*-Diisopropyl-2-methylpent-4-enamide (**8**)

amide	metal	electrophile	product(s)	yield,[a] %	β:δ[b]
8	Li	CH_3I	**12a**	82	...:100
8	Li	$PhCH_2Cl$	**13a,b**	65	13:77
8	Mg	$PhCH_2Cl$	**13a**	56	...:100
8	Li	CH_2=$CHCH_2Br$	**14a,b**	63	28:72
8	Mg	CH_2=$CHCH_2Br$	**14a**	69	...:100
8	Li	$(CH_3)_3SiCl$	**15a**	56	...:100
8	Al	$(CH_3)_3SiCl$	**15b**	59	100:...
8	Li	DOD	**16a,b**	90[c]	42:58
8	Mg	DOD	**16a**	81[d]	...:100
8	Al	DOD	**16a,b**	45[e]	90:10
8	Mg	Ph_3SnCl	**17a**	40	...:100
8	Li	$(CH_3)_2CO$	**18a**	42	...:100
8	Li	Ph_2CO	**19a**	75	...:100
8	Al	Ph_2CO	**19a**	52	...:100

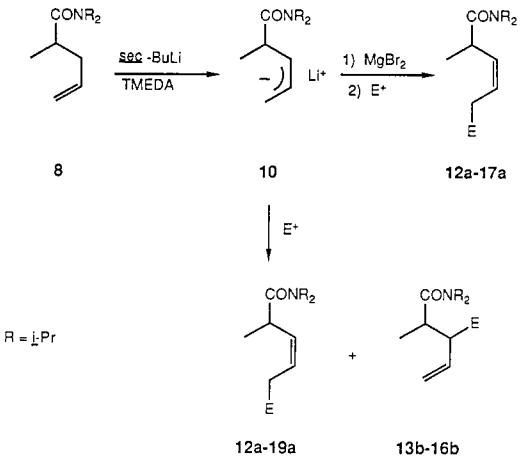
[a] Yield of analytically pure material. [b] Regioisomers, if present, were unseparated. Error is ±5%. [c] 91 ± 5% d_1. [d] 54 ± 5% d_1. [e] 96 ± 5% d_1.

onance and inductive effects involved in directing most deprotonations. The direct formation of **2** involves kinetic selection of a β-proton over an available thermodynamically more acidic α-proton. The regio- and stereochemical features of the reactions of these organolithium reagents with a number of different electrophiles are reported. We also report that a phenylthio group in the γ-position of an α-alkyl carboxamide can direct a remote metalation. The present work illustrates the synthetic potential of these readily available novel species.[3]



The reagents provided by β-lithiation of an α-alkyl carboxamide are synthetically equivalent to **3**, an α-alkyl homoenolate anion of a carboxylic acid. The homoenolate anion has been the subject of considerable work and recent reviews.[4] This synthetic equivalent also is provided by γ-substitution of heterosubstituted allyl anions,[5a] ring openings of cyclopropanol derivatives,[5b] and the use of carbonyl protected derivatives of organometallic reagents.[5c] The species that are most analogous to those reported in this work are the β-metalated esters **4** reported by Goswami,[6a] Murai,[5b] Nakamura,[5b] and Kuwajima[6b] and the dilithiated amides

Scheme I



Scheme II

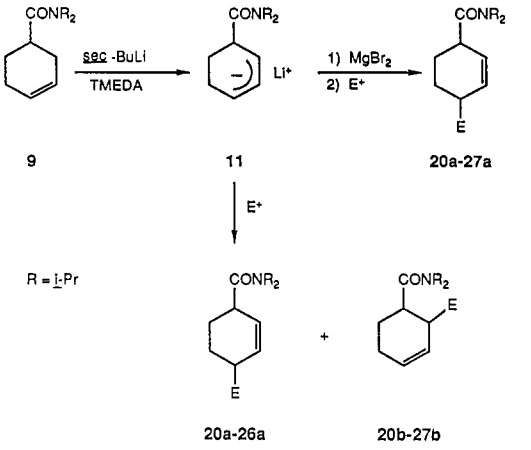


Table II. Lithiation and Electrophilic Substitution of *N,N*-Diisopropylcyclohex-3-enecarboxamide (**9**)

amide	metal	electrophile	product(s)	yield,[a] %	β:δ[b]
9	Li	CH_3I	**20a,20b**	71	75:25
9	Mg	CH_3I	**20a**	95	...:100
9	Li	$C_5H_{11}I$	**21a,21b**	92	70:30
9	Mg	$C_5H_{11}I$	**21a**	50	...:100
9	Li	CH_2=$CHCH_2Br$	**22b**	94	100:...
9	Mg	CH_2=$CHCH_2Br$	**22a**	49	...:100
9	Li	$(CH_3)_3SiCl$	**23a,23b**	47	71:29
9	Mg	$(CH_3)_3SiCl$	**23a**	58	...:100
9	Li	PhSSPh	**24a,24b**	81	60:40
9	Li	DOD	**25a,25b**	94[c]	78:28
9	Mg	DOD	**25a**	82[d]	...:100
9	Li	$(CH_3)_2CO$	**26a,26b**	72	20:80
9	Mg	$(CH_3)_2CO$	**26a**	67	...:100
9	Mg	CH_2O	**27a**	56	...:100
9	Li	CH_2O	**27b**	5[e]	100:...

[a] Yields of analytically pure material. [b] Regioisomers, if present, were unseparated. Ratio is for yield indicated; error is ±5%. [c] 96 ± 5% d_1. [d] 93 ± 5% d_1. [e] Difficulties in purification resulted in an unusually low yield of analytically pure material.

5 and **6** of Goswami[7a] and of Tanaka.[7b] Seebach also has generated dianions which can provide similar chemistry.[8] The parent system, the dilithiated carboxylic acid derivative **7**, was prepared by halogen metal exchange some years ago by Caine and Frobese.[9] Related directed β-lithiations at vinyl hydrogens of β-heteroat-

(3) For a preliminary report see Beak, P.; Hunter, J. E.; Jun, Y. M. *J. Am. Chem. Soc.* **1983**, *105*, 6350.

(4) Stowell, J. C. *Chem. Rev.* **1984**, *84*, 409. Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205. Earnshaw, C.; Torr, R. S.; Warren, S. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2893.

(5) For recent examples and leading references see: (a) Hoppe, D.; Hanko, R.; Brönneke, A.; Lichtenberg, F.; Hülsen, E. V. *Chem. Ber.* **1985**, *118*, 2822. Wilder, L.; Weber, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 1329. Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421. Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth B. *Chem. Ber.* **1985**, *118*, 1441. Hertenstein, U.; Hunig, S.; Reichlet, H.; Schaller, R. *Chem. Ber.* **1986**, *119*, 722. (b) Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745. Ryu, I.; Murai, S.; Sonoda, N. *J. Org. Chem.* **1986**, *51*, 2389. (c) Enda, J.; Kuwajima, I. *J. Am. Chem. Soc.* **1985**, *107*, 5495.

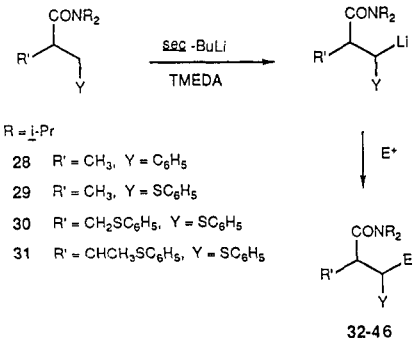
(6) (a) Goswami, R. *J. Org. Chem.* **1985**, *50*, 5907. (b) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, 83. (c) For a similar case see Baker, W. R. *J. Org. Chem.* **1985**, *50*, 3942.

(7) (a) Goswami, R.; Corcoran, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 7182. (b) Tanaka, K.; Wakita, H.; Yoda, H.; Kaji, A. *Chem. Lett.* **1984**, 1359.

(8) Seebach, D.; Pohmakotr, M.; Schregenberger, C.; Weidmann, B.; Mali, R. S.; Pohmakotr, S. *Helv. Chim. Acta* **1982**, *65*, 419; Beslin, P.; Dlubala, A. *Tetrahedron Lett.* **1986**, *27*, 1687 and references cited therein.

(9) Caine, D.; Frobese, A. S. *Tetrahedron Lett.* **1978**, 883.

Scheme III



om-substituted α,β-unsaturated system have been extensively investigated and used synthetically by Schmidt.[10] The β'-lithiations of α,β-unsaturated carboxamides also are considered to be analogous to the present cases.[11]

Results and Discussion

Lithiations at Secondary β- and γ-Positions. We report, as prototypical acyclic and cyclic cases, β-lithiations and electrophilic substitutions of the β-vinyl-substituted systems, *N,N*-diisopropyl-2-methylpent-4-enamide (**8**) and *N,N*-diisopropylcyclohex-3-enecarboxamide (**9**). The lithiations are conveniently carried out at −78 °C in tetrahydrofuran (THF) with a slight excess of *sec*-butyllithium–*N,N,N',N'*-tetramethylethylenediamine (*sec*-BuLi/TMEDA) for 10–30 min, followed by addition of the electrophile to give the products in good yields. The reactions are summarized in Schemes I and II and Tables I and II. The products were isolated by MPLC and characterized by spectroscopy and chemical analysis. As indicated in the schemes, lithiation of **8** provides the acyclic allyllithium reagent **10** and lithiation of **9** provides the cyclic allyllithium reagent **11**. Alkylation, silylation, stanylation, deuteriation and addition to carbonyl compounds of these allyllithium reagents proceeds to give **12–19** from **10** and **20–27** from **11**.

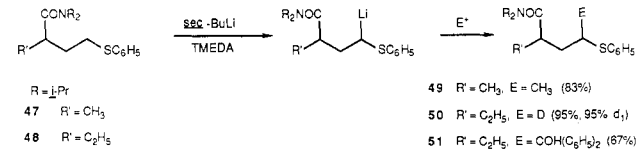
The regioselectivities of the electrophilic substitutions of the unsymmetrical allyllithium reagents **10** and **11** were determined by ^{1}H NMR decoupling experiments, and the β:δ substitution ratio was confirmed by capillary GLPC. For example, irradiation of an α-proton of a δ-substituted isomer decouples both an olefinic proton and the α-methyl group and establishes the double bond to be in the β:γ position. Formation of only δ-substitution products **12a**, **15a**, **18a**, and **19a** is observed for the reaction of **10** with methyl iodide, chlorotrimethylsilane, acetone, and benzophenone. Substitution in the δ-position provides the predominant product with benzyl chloride, allyl bromide, and deuterium oxide. The regiochemistry can be controlled, in some cases, by addition of other metals prior to reaction with the electrophile.[12] In the acylic case **10**, addition of magnesium bromide etherate prior to addition of benzyl chloride, allyl bromide, or deuterium oxide gives only the δ-substitution products **13a**, **14a**, and **16a**. Addition of triethylaluminum to **10** provides a predominance of the β-substitution product **16b** upon reaction with chlorotrimethylsilane and deuterium oxide but has no effect upon the reaction with benozphenone. The geometries for **12a** and **19a** are assigned to be *Z*-based on the olefinic hydrogen coupling constants of 10.2 and 11.2 Hz, respectively.[14] For the assignment of *Z* geometry to **16a** the *E* isomer was prepared and shown to be a different compound. This stereochemistry is assigned to other δ-substituted products based on similar values of the olefinic coupling constants, and the allyllithium reagent **10** is considered to have the cis geometry shown in Scheme I.

Table III. Lithiation and Electrophilic Substitution of Amides **28**, **29**, **30**, and **31**

amide	electrophile	product	yield,[a] %	ratio[b]
28	CH_3I	**32**	82	82:18
28	CH_3CH_2I	**33**	53	73:27
28	$PhCH_2Cl$	**34**	84	74:26
28	CH_2=$CHCH_2Br$	**35**	70	96:4
28	$(CH_3)_3SiCl$	**36**	65	98:2
28	CH_3OD	**37**	87[c]	80:20
28	Ph_2CO	**38**	63	100:...
29	CH_3I	**39**	80	
29	$PhCH_2Cl$	**40**	52	
29	CH_2=$CHCH_2Br$	**41**	46	
29	$(CH_3)_3SiCl$	**42**	80	
29	PhSSPh	**43**	48	
29	DOD	**44**	79[d]	
29	Ph_2CO	**45**	41	75:25
30	CH_3I	**31**	51	
31	CH_3I	**46**	50	

[a] Yields of analytically pure material. [b] Ratio of diastereoisomers. Diastereoisomers, if present, were unseparated and ratios were determined by capillary GPLC and NMR spectroscopy. Error is ±5%. [c] 99 ± 5% d_1. [d] 97 ± 5% d_1.

Scheme IV



The regioselectivities of the electrophilic reactions in the six-membered ring of **11** are somewhat different from those observed with the acyclic system. With most electrophiles β-substitution predominates, except for additions to acetone which provides largely the δ-substituted isomer **26a**. Treatment of **11** with magnesium bromide etherate prior to addition of the electrophile leads regioselectively to the δ-substituted products **20a**, **21a**, **22a**, **23a**, **25a**, **26a**, and **27a** for reactions with methyl iodide, *n*-pentyl iodide, chlorotrimethylsilane, deuterium oxide, acetone, and formaldehyde. It also is notable that the reactions are diastereoselective (vide infra).

Lithiations at positions β to a carboxamide group have also been achieved for β-phenyl and β-phenylthio α-alkyl carboxamides as illustrated for the reactions of **28**, **29**, **30**, and **31** in Scheme III and Table III. The structures of the products **32–46** are assigned on the basis of spectral and analytical data. High regioselectivity in the lithiation of a secondary hydrogen in preference to a tertiary hydrogen is observed for the conversion of **31** to **46**.

Phenylthio substitution is also capable of directing lithiation to a position γ with respect to the carboxamide. Such substitutions are illustrated in Scheme IV for the conversions **47** and **48** to **49**, **50**, and **51**, respectively. Attempts to achieve analogous γ deprotonations for vinyl or phenyl substitution or at an ϵ site with

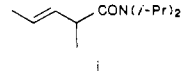
(10) Miyata, O.; Schmidt, R. R. *Tetrahedron Lett.* **1982**, *23*, 1793 and references cited therein.

(11) (a) Beak, P.; Kempf, D. J.; Wilson, K. D. *J. Am. Chem. Soc.* **1985**, *107*, 4745. (b) Tanaka, K.; Yoda, H.; Isobe, Y.; Kaji, A. *J. Org. Chem.* **1986**, *51*, 1856 and references cited therein.

(12) For examples of the effect of metals on the regiochemistry of electrophilic additions to formal allyl anions see: Hassel, T.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 399. 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.

(13) Yamamoto, Y.; Maruyama, K. *J. Org. Chem.* **1983**, *48*, 1564; Yamamoto, Y.; Yatagai, H.; Saito, Y.; Muruyama, K. *J. Org. Chem.* **1984**, *49*, 1096.

(14) Becker, E. D. *High Resolution NMR; Theory and Chemical Applications*, 2nd ed.; Academic: New York, 1980; p 96. The assignments are also consistent with those reported for an analogous vinyl group in 2,2-dimethyl-3-butenecarboxamide of J_{trans} = 17.5 Hz and J_{cis} = 10.6 Hz. Romanet, R.; Chemizart, A.; Duhoux, S.; David, S. *Bull. Soc. Chim. Fr.* **1963**, 1048. To confirm these assignemts (*E*)-*N,N*-diisopropyl-2-methylpent-3-enecarboxamide (i) was prepared and shown to have a coupling constant between the

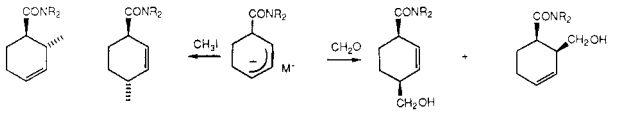


i

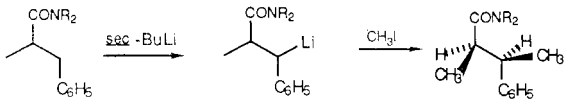
olefinic protons of 15.7 Hz. See the supplementary material for details.

phenylthio activation were not successful. The latter case is significant because it shows the phenylthio group by itself is not capable of causing the lithiation; therefore, the carboxamide must also be playing a role in directing the reaction.[15]

The diasteroselectivity of the electrophilic substitutions on the reagents resulting from these remote lithiations can be high. For example, each of the regioisomers obtained from the reaction of the cyclic system **11** with methyl iodide is a single diastereomer. The β-substituted isomer **20b** is assigned a trans relationship between the methyl and the carboxamide, based on a coupling constant of 9.5 Hz between the tertiary ring protons.[16] The δ-substituted methylated isomer **20a** is trans whether formed from **11** or via magnesium bromide as established by comparison with authentic material.[17] However, the single hydroxymethyl diastereomer **27a** obtained in 56% yield by reaction of **11** with magnesium bromide followed by formaldehyde is the cis isomer. This was established by conversion of **27a** to the corresponding hydroxymethyltosylate which was reduced to the authentic cis methyl isomer. The cis geometry of **27b** obtained, albeit in 5% yield, from reaction of the allyllithium **11** with formaldehyde was assigned on the basis of a coupling constant of less than 1 Hz between the tertiary ring protons. A search for the trans isomers of **27** suggests they are not present at detectable levels as products of these reactions.



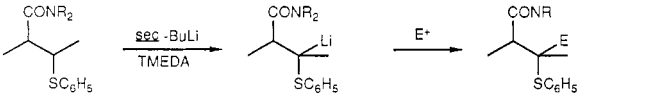
High diastereoselectivity also is observed upon addition of the organolithium reagent from the acyclic β-phenyl system **28** to alkylating and silyating agents and to benzophenone. The major diastereoisomer **32**, obtained from the metalation of **28** and reaction with methyl iodide, has the parf relative configuration established by comparison with the authentic parf and pref *N*,*N*-diisopropyl-2-methyl-3-phenylbutanamides obtained from the corresponding acids.[18] Other major products in this series are presumed to have the parf configuration. Interestingly, the diastereoselectivity for reaction of this anion with ethyl iodide at 20 °C is 90:10 and at −100 °C is 53:47. Poor diastereoselectivity is observed on reaction of the phenylthio-stabilized lithium reagents from **29**. However, in the case of the lithiation and electrophilic substitution of **48** at the γ-position providing **51**, only one diastereoisomer of **51** is found. The potential use of directed remote lithiations for diastereoselective synthesis in both cyclic and acyclic systems, which is suggested by these results, is especially interesting.[19]



28

R = i-Pr

Lithiations at Tertiary β-Positions. Lithiation of a tertiary position β to the amide can be achieved with phenylthio activation as illustrated for the lithiation of **39**. Reaction of the intermediate **52** with methyl iodide or chlorotrimethylsilane provides the substituted products **53** or **54**, respectively. Chemical proof of the position of substitution was provided by reductive cleavage of thiophenol from **53** to provide *N*,*N*-diisopropyl-2,3-methylbutanecarboxamide.

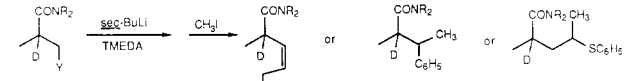


39 52 53 E = CH_3 (86%)

R = i-Pr 54 E = $Si(CH_3)_3$ (49%)

The Amide-Directed Remote Lithiations. A most interesting feature of the lithiations of **8** and **9** is that a β-proton, activated by an adjacent carbon–carbon double bond, is removed in preference to an α-proton which is activated by an adjacent carbonyl function. The differences in thermodymanic acidity of these protons can be estimated as ca. 9 pK_a units in favor of the α-proton.[3] Metalation of **9** with sodium dimesylate in Me_2SO-d_6 occurs preferentially at the α-position as expected for formation of an enolate.[3]

In order to be certain the β-deprotonations are direct reactions, we have carried out the lithiation of the deuteriated amides **8**-*d*, **28**-*d*, and **47**-*d* and allowed the lithium reagents formed to react with methyl iodide. In all cases the α-deuterium is retained in the methylated products **12**-*d*, **32a**-*d*, and the α-deuterium is retained in the methylated products **12a**-*d*, **32a**-*d*, and **49**-*d*, respectively. Thus, these reactions do not involve an initial α-deprotonation followed by an unexpected proton transfer.



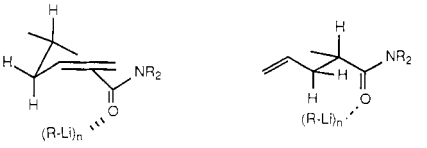
8-d Y = CH=CH2

28-d Y = C6H5

47-d Y = CH2SC6H5

12a-d 32-d 49-d

We suggest the role of the carboxamide in kinetically directing these lithiations involves bonding of the carbonyl oxygen to the lithium of the *sec*-butyllithium reagent in a preequilibrium complex.[1,3,11,20] From this complex a *sec*-butyl group can apparently achieve a transition state in which it is positioned to remove the β-proton more easily than one in which the thermodynamically more acidic α-proton is available. Suggested complexes for the reaction of **8** are **55** or **56**. In the case of the transition structure



55 56

from **55** the *cis* geometry of **10** would be obtained directly while **56** would give a trans allyllithium species, which could have a low barrier for isomerization to **10**.[20,21] Transition structures similar to these have been suggested by Weiler and Snieckus for γ-deprotonations of α,β-unsaturated esters and amides.[22]

(15) For lithiations of alkyl phenyl sulfides with *t*-butyllithium HMPA see: Dolak, T. M.; Bryson, T. A. *Tetrahedron Lett.* **1977**, 1961.

(16) Semmelhack, M. F.; Herndon, J. W.; Springer, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 2497. A trans 1,2-disubstituted cyclohex-3-enecarboxylic acid which has similar coupling constants is reported.

(17) The compounds were demonstrated to be the same by ^1H NMR and ^{13}C NMR and by coelution from capillary GLPC. The preparation of the material of established stereochemistry is described in the supplementary materials.

(18) (a) For determinations of structure see Theine, A.; Traynham, J. G. *J. Org. Chem.* **1974**, *39*, 153. Jackman, L. M.; Lown, J. W. *J. Chem. Soc.* **1962**, 3776; (b) For the parf and pref nomenclature see: Carey, F. A.; Kuehne, M. E. *J. Org. Chem.* **1982**, *47*, 3811.

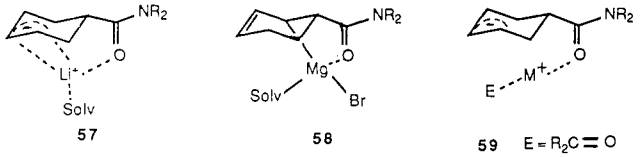
(19) P. McDougal has independently observed a diastereoselective remote lithiation in anoter phenylthio-substituted system. P. McDougal, private communication, February, 1986.

(20) (a) For direct observation of a carboxamide-lithium complex in a lithiation and leading references see: Al-Aseer, M.; Beak, P.; Hay, D.; Kempf, D. J.; Mills, S.; Smith, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 2080. (b) For suggestions of similar transition states see: Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1985**, *26*, 1939. Majewski, M.; Green, J. R.; Snieckus, V. *Ibid.* **1986**, *27*, 531.

(21) The geometry of reactants and products in the crotyl lithium and Grignard systems has been studied. The *Z* isomers are predominant but both isomers are usually observed. Bates, R. B.; Beavers, W. A. *J. Am. Chem. Soc.* **1974**, *96*, 5001. Hutchison, D. A.; Beck, K. R.; Benkeser, R. A.; Grutzer, J. B. *Ibid.* **1973**, *95*, 7075.

The carboxamide functionality may be effective in directed lithiations not only because of its strong affinity for lithium and resistance to nucleophilic addition but also because the alkyl groups on nitrogen could incline the complexed organolithium reagent toward the prospectively acidic proton. In the competitive transition structures for deprotonation the α-proton must not be readily available in the proper geometry for overlap with the carbonyl. Transition structures with appropriate frontier orbital alignments for the σ-orbital of the kinetically acidic β-proton and the π^*-orbital of the double bond must be more readily accessible. It is to be noted that the carbon–oxygen–lithium and *sec*-butyl–hydrogen–carbon bond angles which are critical to the competitive transition states are not well-defined and may be quite flexible. In comparing the β-lithiation, which could be envisioned to involve a seven-membered ring vs. the possible six-membered ring for enolate formation, a large carbon–oxygen–lithium bond angle could be involved, and the aggregated lithium reagent could be complexed to the vinyl or on the face of the amide system.

The Electrophilic Substitutions. The extent to which the observed selectivity involves the deprotonation and/or electrophilic substitution needs to be established. The present work does suggest the reactions may be highly stereoselective, even in acyclic systems. The formation of the *Z* olefins **12a–19a** from **10** is notable, and we estimate 5% of the *E* isomer would have been detected.[21] The parf selective formations of **32–38** from **28** illustrate the potential for diastereoselectivity in synthesis. Rationalizations for the reactions of **11** which are consistent with the established structures of the be reasonably represented as an η^3 ion pair **57**, and the corresponding Grignard reagent as an η^1 species. If the reaction of **57** and **58** with carbonyl compounds involves initial displacement of solvent from the metal to give **59**, subsequent additions can proceed in an endo cyclic mode to give the cis products **27a** from **58** and **27b** from **57**. On the other hand, if the electrophile is a halide, which leads to **60**, displacement in an endo cyclic ring is



57 58

59 E = $R_2C{=}O$

60 E = $R_3C{-}X$

geometrically unfavorable and the S_E2' process established by Felkin for allyl Grignard reagents would be followed.[23,24] It must be noted however that the regioselectivity of the reactions of **10** and **11**[25] is a function of the amount of *sec*-butyllithium and that the diastereoselectivity of the reactions of the organolithium from **28** is affected by temperature, suggesting that more complicated reactions involving aggregation and/or additional complexations may be involved. Related and equally speculative rationales can be constructed for the effect of other metals on these reactions.[12,13] Clearly more work is needed to develop the synthetic potential and define the nature of the reactive species in these and related reactions.

Summary. The present report documents the β- and γ-lithiations and subsequent electrophilic substitutions of appropriately substituted α-alkyl carboxamides. The mechanism of these novel lithiations may be considered to illustrate a complex-induced proximity effect in which kinetic domination over the more well-known resonance and inductive effects is operative. The synthetic use of these species is demonstrated, and rationales for the high regio- and stereochemistry of the initial lithiations and subsequent electrophilic substitutions observed in some cases are provided.

Experimental Section

All reactions involving organolithiums were performed in oven-dried glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium/benzophenone ketyl before use. *n*-Butyllithium and *sec*-butyllithium were titrated prior to use according to the procedure of Shapiro et al.[26] *N,NN',N'*-Tetramethylethylenediamine (TMEDA) was 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. Vacuum distillations were carried out in a Kugelrohr apparatus, and temperatures given are bath values.

Magnesium bromide etherate was prepared from 10.5 g (0.438 mol) of magnesium, 100 mL of dry Et_2O and 15 mL of dry benzene treated with 0.50 mL (0.006 mmol) of 1,2-dibromoethane. After the ethene evolved, the solution was heated to reflux, and an additional 19.5 mL (0.226 mol) of 1,2-dibromoethane was added dropwise at a rate sufficient to keep the solution at reflux. The solution was stirred 12 h and then filtered under a nitrogen atmosphere giving a solution of magnesium bromide etherate. The titer was calculated by using the known volume of solvents, and the difference between starting mass of magnesium and the magnesium recovered upon filtration.

Preparation of amides is presented in supplementary material.

Metalation of Amides. Typical procedures involve reactions on a scale of 1–2 mmol of amide. Variations of these procedures, the amount of reagents used, and purification methods are given with spectroscopic and analytical data of individual products.

Procedure A. To a stirred solution of the amide and TMEDA in 10–15 mL of THF cooled in a −78 °C bath was added *sec*-BuLi. After being stirred 15–30 min at −78 °C, the solution was treated with the electrophile. Liquid electrophiles were added neat; solids were dissolved in 10–15 mL of THF and cooled in a −78 °C bath prior to addition. About 1 h 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 20–30 mL of Et_2O, the organic portion was dried over $MgSO_4$ and concentrated in vacuo to give crude product.

Procedure B. To a stirred solution of the amide and TMEDA in 10–15 mL of THF cooled in a −78 °C bath was added *sec*-BuLi. After being stirred 15–30 min at −78 °C, a solution of magnesium bromide etherate in Et_2O or triethylaluminum in hexane cooled to −78 °C was added. After 15 min, the electrophile was added, and procedure A was followed.

Procedure C. To a stirred solution of the amide and TMEDA in 10–15 mL of THF cooled in a −78 °C bath was added *sec*-BuLi. After being stirred 15–30 min at −78 °C, a solution of magnesium bromide etherate cooled to −78 °C was added. The solution was warmed until it became clear, recooled, and treated with an electrophile, and procedure A was followed.

(*Z*)-*N,N*-Diisopropyl-2-methylhex-3-enamide (12a). Procedure A: 255 mg (1.29 mmol) of **8**, 0.23 mL (1.53 mmol) of TMEDA, 1.15 mL (1.47 mmol) of *sec*-BuLi, 10 mL of THF, and 0.20 mL (3.21 mmol) of methyl iodide. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent. Kugelrohr distillation (95 °C, 2.0 mmHg) gave 223 mg (82%) of pure **12a** as a colorless oil. ^1H NMR (360 MHz, C_6D_6): δ 0.85 (m, 9 H, CH_3, CH_2CH_3), 1.32 (d, J = 6.6 Hz, 3 H, $COCHCH_3$), 1.47 (d, J = 7.1 Hz, 3 H, CH_3), 1.49 (d, J = 7.1 Hz, 3 H, CH_3), 1.90 (dq, J = 7.4 Hz, J = 7.3 Hz, 3 H, $CHCH_2$), 3.08 (br, 1 H, NCH), 3.41 (dq, J = 9.6 Hz, 1 H, COCH), 3.78 (m, J = 6.5 Hz, 1 H, NCH), 5.26 (m, 1 H, CH_2CH), 5.61 (dd, J = 10.6 Hz, $CHCH{=}C$). Decoupling: irradiation of the resonance at 3.41 ppm decouples the protons at 1.32 and 5.61 ppm, leaving a singlet and doublet; irradiation at 5.26 ppm decouples the proton at 1.90 ppm, leaving a multiplet. ^{13}C NMR (360 MHz, THF, TMEDA, C_6D_6): δ 17.81, 20.73, 21.20, 37.11,

(22) (a) For allyllithium structures see: Stähle, M.; Schlosser, M. *J. Organomet. Chem.* **1981**, *220*, 277. Neugebauer, W.; Schleyer, P. v. R. *J. Organomet. Chem.* **1980**, *198*, C1. Brownstein, S.; Bywater, S.; Worsfold, D. J. *Ibid.* **1980**, *199*, 1. Fraenkel, G.; Halasa, A. F.; Mochel, V.; Stumpe, R.; Tate, D. *J. Org. Chem.* **1985**, *50*, 4563. Thompson, T. B.; Ford, W. T. *J. Am. Chem. Soc.* **1979**, *101*, 5459. West, P.; Purmort, J. I.; McKinley, S. V. *J. Am. Chem. Soc.* **1968**, *90*, 797. (b) For allyl Grignard structures see: Whitesides, G. M.; Nordlander, J. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1962**, *84*, 2010. Whitesides, G. M.; Nordlander, J. E.; Roberts, J. D. *Discuss. Faraday Soc.* **1962**, *34*, 185. Nordlander, J. E.; Young, W. G.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 494. Nordlander, J. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1959**, *81*, 1769.

(23) Felkin, H.; Frejerman, C. *Tetrahedron Lett.* **1970**, 1045. Felkin, H.; Roussi, G. *Tetrahedron Lett.* **1965**, 4153.

(24) Tenud, L.; Farouq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2059. McGarrity, M. J.; King, J. F.; Stothers, J. B. *Tetrahedron Lett.* **1982**, *23*, 4465.

(25) Reacting allyl bromide with a solution **10** and an excess *sec*-BuLi gives a β:δ ratio of 30:70. With 25 equiv of excess *sec*-BuLi present a β:δ ratio of 60:40 is obtained. In a similar fashion reaction of **11** with methyl iodide with no excess base gives a 74:26 ratio of β and δ isomers. With **11** and 25 equiv of excess base a 97:3 ratio is obtained.

(26) Lipton, M. F.; Sorenson, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155.

(27) Bossert, F. *Ann. Chim.* **1964**, *680*, 40.

(28) Beak, P.; Wilson, K. D. *J. Org. Chem.* **1986**, *518* 4627.

39.11, 47.97, 115.55, 137.50, 173.90. IR (film): 2890 (s), 1640 (s), 1445 (s), 1360 (s), 1327 (s), 1290 (m), 1211 (m), 1155 (m), 1045 (m), 1028 (m) cm^{-1}. Mass spectrum (70 eV): *m/e* (relative intensity) 211 (M^+, 3), 196 (3), 168 (7), 128 (37), 86 (100), 55 (37), 43 (100), 41 (39).

Anal. Calcd for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63. Found: C, 73.54; H, 11.88; N, 6.60.

(*Z*)-*N*,*N*-Diisopropyl-2-methyl-6-phenylhex-3-enamide (13a) and *N*,*N*-Diisopropyl-3-benzyl-2-methylpent-4-enamide (13b). Procedure A: 249 mg (1.26 mmol) of **8**, 0.20 mL (1.33 mmol) of TMEDA, 1.30 mL (1.40 mmol) of *sec*-BuLi, 10 mL of THF, and 0.40 mL (3.48 mmol) of benzyl chloride. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent. Kugelrohr distillation (125–150 °C, 2.5 mmHg) gave 236 mg (65%) of **13a** and **13b** as a colorless oil. ^1H NMR (90 MHz, relative area): δ 1.19 (m, 9 H, CH_3, $COCHCH_3$), 1.48 (d, J = 7 Hz, 6 H, CH_3), 2.00 (m), 2.45 (m), 2.65 (m), 3.00 (m), 3.45 (m), 3.95 (m, 1 H, NCH), 4.77 (dd, J = 10 Hz, 1 H, **13b**, C=CH_2), 4.91 (m, 1 H, **13b**, C=CH_2), 5.42 (m, 2 H, **13a**, CH=CH), 5.75 (m, 2 H, **13b**, CH=CH_2), 7.15 (m, 5 H, ArH). IR (film): 2940 (s), 1640 (s), 1438 (s), 1370 (s), 1335 (s), 1218 (m), 1138 (m), 1040 (m), 752 (m), 700 (s) cm^{-1}. Mass spectrum (70 eV): *m/e* (relative intensity) 287 (M^+, 9), 272 (2), 244 (5), 196 (6), 157 (6), 128 (46), 114 (15), 91 (40), 86 (100), 43 (95).

Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.57; H, 10.26; N, 4.90.

(*Z*)-*N*,*N*-Diisopropyl-2-methyl-6-phenylhex-3-enamide (13a). Procedure B: 257 mg (1.30 mmol) of **8**, 0.20 mL (1.33 mmol) of TMEDA, 1.43 mL (1.56 mmol) of *sec*-BuLi, 1.40 mL (1.34 mmol) of magnesium bromide etherate, 10 mL of THF, and 0.50 mL (3.99 mmol) of benzyl chloride. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent. Kugelrohr distillation (155 °C, 10.0 mmHg) gave 208 mg (56%) of pure **13a** as a colorless oil. ^1H NMR (360 MHz, C_6D_6): δ 0.81 (m, 6 H, CH_3), 1.22 (d, J = 6.7 Hz, 3 H, $COCHCH_3$), 1.44 (m, 6 H, CH_3), 2.22 (m, 2 H, C=$CHCH_2$), 2.48 (t, J = 7.6 Hz, 2 H, $CHCH_2CH_2$), 3.06 (br, 1 H, NCH), 3.34 (m, 1 H, COCH), 3.69 (m, 1 H, NCH), 5.29 (m, J = 10.8 Hz, 1 H, CHCH=CH), 5.61 (m, 1 H, CHCH=C), 7.04 (m, 2 H, ArH), 7.10–7.15 (m, 3 H, ArH). Decoupling: irradiation of the resonance at 3.34 ppm decouples the protons at 1.22 and 5.61 ppm, leaving a singlet and doublet; irradiation of the resonance at 2.22 ppm decouples the protons at 2.48 and 5.29 ppm, leaving a broad singlet and doublet. ^{13}C NMR (360 MHz): δ 18.26, 18.34, 20.65, 20.71, 20.98, 29.56, 35.78, 36.96, 45.69, 125.94, 128.13, 128.34, 131.33, 141.54, 173.70. IR (film): 2976 (s), 2940 (s), 1633 (s), 1439 (m), 1370 (m), 1333 (m), 1214 (m), 702 (m) cm^{-1}. Mass spectrum (70 eV): *m/e* (relative intensity) 237 (M^+, 2), 222 (1), 192 (12), 128 (53), 86 (100), 43 (62).

Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.29; H, 10.41; N, 4.96.

(*Z*)-*N*,*N*-Diisopropyl-2-methylocta-3,7-dienamide (14a) and *N*,*N*-Diisopropyl-3-ethenyl-3-methylhex-5-enamide (14b). Procedure A: 593 mg (3.01 mmol) of **8**, 0.46 mL (3.05 mmol) of TMEDA, 3.30 mL (3.60 mmol) of *sec*-BuLi, 20 mL of THF, and 0.80 mL (9.24 mmol) of allyl bromide. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent. Kugelrohr distillation (100 °C, 0.5 mmHg) gave 448 mg (63%) of**14a** and **14b** as a colorless oil. ^1H NMR (360 MHz, C_6D_6, relative area): δ 0.84 (m, 6 H, CH_3), 1.09 (d, J = 6.2 Hz, **14b**, $COCHCH_3$), 1.29 (d, J = 6.1, **14a**, $COCHCH_3$), 1.46 (m, 6 H, CH_3), 1.98 (s, 4 H, **14a**, CH_2CH_2), 2.41 (m, **14b**, allylic CH), 2.54 (m, **14b**, allylic CH), 3.07 (br, 1 H, NCH), 3.39 (m, 1 H, **14a**, COCH), 3.64 (m, **14b**, NCH), 3.76 (m, **14a**, NCH), 4.94–5.11 (m, 4 H, **14b**, C=CH_2, C=CH_2; 2 H, **14a**, C=CH_2), 5.25 (m, 1 H, **14a**, CH_2CH=CH), 5.65–5.74 (m, 2 H, **14a**, CHCH=CH_2, CH=CH_2; **14b**, CHCH=C-H_2C, CH=CH_2). ^{13}C NMR (360 MHz): δ 15.27, 18.37, 20.67, 20.98, 36.85, 37.09, 39.93, 45.63, 46.42, 47.76, 48.09, 114.92, 115.46, 115.79, 128.75, 131.03, 136.54, 137.76, 140.04, 173.21. IR (film): 3010 (m), 2975 (s), 2935 (s), 1662 (s), 1439 (s), 1371 (m), 1333 (m), 1295 (m), 1214 (m), 1134 (m), 817 (m), 735 (m) cm^{-1}. Mass spectrum (10 eV): *m/e* (relative intensity) 237 (M^+, 3), 22 (3), 194 (20), 128 (38), 86 (100), 43 (90).

Anal. Calcd for $C_{15}H_{27}NO$: C, 75.90; H, 11.46; N, 5.90. Found: C, 75.95; H, 11.29; N, 5.75.

(*Z*)-*N*,*N*-Diisopropyl-2-methyl-3,7-dienamide (14a). Procedure B: 298 mg (1.51 mmol) of **8**, 0.23 mL (1.53 mmol) of TMEDA, 1.80 mL (1.96 mmol) of *sec*-BuLi, 1.80 mL (1.73 mmol) of magnesium bromide etherate, 10 mL of THF, and 0.40 mL (4.62 mmol) of allyl bromide. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent. Kugelrohr distillation (160 °C, 1.0 mmHg) gave 248 mg (69%) of pure **14a** as a colorless oil. ^1H NMR (360 MHz, C_6D_6): δ 0.84 (d, J = 6.5 Hz, 3 H, CH_3), 0.85 (d, J = 6.4 Hz, 3 H, CH_3), 1.26 (d, J = 6.7 Hz, 3 H, $COCHCH_3$), 1.42 (d, J = 6.2 Hz, 3 H, CH_3), 1.44 (d, J = 6.2 Hz, 3 H, CH_3), 1.98 (s, 4 H, CH_2CH_2), 3.07 (br, 1 H, NCH), 3.37 (m, 1 H, COCH), 3.76 (m, J = 6.7 Hz, 1 H, NCH), 4.96 (d, J = 9.2 Hz, 1 H, (*E*)-C=CH_2), 4.99 (d, J = 16.5 Hz, 1 H, (*Z*)-C=CH_2), 5.26 (m, 1 H, CH_2CH=CH), 5.60 (dd, J = 10.8 Hz, J = 10.1 Hz, 1 H, CHCH=C), 5.70 (m, 1 H, CH=CH_2). Decoupling: irradiation of the resonance at 3.37 ppm decouples the protons at 1.26 and 5.60 ppm, leaving a singlet and doublet; irradiation of the resonance at 1.98 ppm decouples the protons at 5.26 and 5.70 ppm, leaving a doublet and a doublet of doublets. ^{13}C NMR (360 MHz): δ 18.18, 18.27, 20.37, 20.52, 26.75, 33.36, 36.72, 45.51, 47.61, 114.78, 128.61, 130.90, 137.66, 173.12. IR (film): 2976 (s), 2940 (s), 1662 (m), 1438 (m), 1371 (m), 1332 (m), 1214 (m), 1135 (m), 1035 (m), 915 (m) cm^{-1}. Mass spectrum (70 eV): *m/e* (relative intensity) 237 (M^+, 2), 222 (1), 194 (12), 128 (53), 86 (100), 43 (62).

Anal. Calcd for $C_{15}H_{27}NO$: C, 75.90; H, 11.46; N, 5.90. Found: C, 75.74; H, 11.72; N, 5.93.

(*Z*)-*N*,*N*-Diisopropyl-2-methyl-3-(trimethylsilyl)pent-3-enamide (15a). Procedure A: 258 mg (1.31 mmol) of **8**, 0.20 mL (1.33 mmol) of TMEDA, 1.35 mL (1.46 mmol) of *sec*-BuLi, 10 mL of THF, and 0.45 mL (3.55 mmol) of chlorotrimethylsilane. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent. Kugelrohr distillation (105 °C, 1.0 mmHg) gave 150 mg (56%) of pure **15a** as a white solid, mp 48–51 °C. ^1H NMR (360 MHz, C_6D_6): δ 0.02 (s, 9 H, $SiCH_3$), 0.88 (d, J = 6.7 Hz, 3 H, CH_3), 0.90 (d, J =6.6 Hz, 3 H, CH_3), 1.30 (d, J = 6.7 Hz, 3 H, $COCHCH_3$), 1.46 (m, 8 H, CH_2, CH_3), 3.09 (m, 1 H, NCH), 3.38 (m, 1 H, COCH), 3.85 (m, 1 H, NCH), 5.34 (m, 1 H, CH_2CH), 5.56 (dd, J = 10.7 Hz, J = 9.8 Hz, 1 H, CHCH=CH). Decoupling: irradiation of the resonance at 3.38 ppm decouples the protons at 1.30 and 5.56 ppm leaving a singlet and doublet. IR (KBr): 2980 (s), 1625 (s), 1430 (m), 1360 (m), 1332 (m), 1247 (m), 1036 (m), 850 (s), 842 (m), 768 (m) cm^{-1}. Mass spectrum (10 eV): *m/e* (relative intensity) 269 (M^+, 2), 254 (8), 226 (21), 128 (57), 86 (100), 73 (85), 43 (100).

Anal. Calcd for $C_{15}H_{31}NOSi$: C, 66.85; H, 11.59; N, 5.20. Found: C, 67.14; H, 11.41; N, 4.98.

***N*,*N*-Diisopropyl-2-methyl-3-(trimethylsilyl)pent-4-enamide (15b).** Procedure B: 422 mg (2.14 mmol) of **8**, 0.33 mL (2.19 mmol) of TMEDA, 2.20 mL (2.51 mmol) of *sec*-BuLi, 2.50 mL (2.50 mmol) of triethylaluminum, 15 mL of THF, and 1.00 mL (7.88 mmol) of chlorotrimethylsilane. Purification by MPLC on silica with hexane/ethyl acetate as the eluent. Two Kugelrohr distillations (123 °C, 0.4 mmHg) gave 341 mg (59%) of pure **15b** as a white solid, mp 47–49 °C. ^1H NMR (360 MHz, reference $CHCl_3$): δ –0.03 (s, 9 H, $SiCH_3$), 1.06 (d, J = 6.8 Hz, 3 H, $COCHCH_3$), 1.18 (d, J = 6.6 Hz, 3 H, CH_3), 1.20 (d, J = 6.6 Hz, 3 H, CH_3), 1.34 (d, J =6.7 Hz, 6 H, CH_3), 2.00 (dd, J = 11.0 Hz, J = 8.2 Hz, 1 H, SiCH), 2.78 (m, 1 H, COCH), 3.35 (m, 1 H, NCH), 4.86 (m, 1 H, NCH), 4.84 (dd, J = 16.8 Hz, J = 1.8 Hz, 1 H, CH_2=CH), 4.90 (dd, J = 10.0 Hz, 1 H, CH_2=CH), 5.60 (m, 1 H, CH_2=CH). ^{13}C NMR (200 MHz, reference $CDCl_3$) δ –2.11, 17.65, 20.51, 20.73, 20.92, 21.04, 36.26, 37.67, 45.58, 47.96, 113.55, 137.18, 174.45. Mass spectrum (10 eV): *m/e* (relative intensity) 269 (M^+, 3), 254 (27), 226 (100), 128 (42), 86 (43), 73 (19), 43 (13).

Anal. Calcd for $C_{19}H_{25}NOSi$: C, 66.85; H, 11.59; N, 5.20. Found: C, 67.03; H, 11.58; N, 5.01.

(*Z*)-*N*,*N*-Diisopropyl-2-methyl-5-(triphenylstannyl)pent-3-enamide (17a). According to procedure B: 401 mg (2.03 mmol) of **8**, 0.31 mL (2.06 mmol) of TMEDA, 2.40 mL (2.42 mmol) of *sec*-BuLi, 2.10 mL (2.52 mmol) of magnesium bromide etherate, 10 mL of THF, and 1.575 g (4.09 mmol) of chlorotriphenyltin. Purification on a Chromatotron using silica gel with hexane/methylene chloride as the eluent, removal of low boiling impurities by Kugelrohr distillation (160 °C, 6.0 mmHg), and a second Chromatotron chromatography gave 445 mg (40%) of pure **17a** as a white solid, mp 87–88.5 °C. ^1H NMR (200 MHz): δ 0.87 (d, J = 6.6 Hz, 3 H, $COCHCH_3$), 1.03 (d, J = 6.7 Hz, 3 H, CH_3), 1.08 (d, J = 6.6 Hz, 3 H, CH_3), 1.34 (d, J = 6.6 Hz, 6 H, CH_3), 2.40 (m, 2 H, CH_2), 3.39 (m, 2 H, COCH, NCH), 3.88 (m, 1 H, NCH), 5.31 (dd, J = 10.9 Hz, J = 9.0 Hz, 1 H, $COCHCH$), 5.73 (m, 1 H, CH_2CH), 7.23–7.72 (m, 15 H, ArH). Decoupling: irradiation of the resonance at 2.40 ppm decouples the proton at 5.73 ppm, leaving a doublet; irradiation of the resonance at 3.39 ppm decouples the protons at 0.87, 1.34, and 5.31 ppm leaving a singlet, singlet, and doublet. IR (film): 3063 (m), 2969 (m), 1640 (m), 1429 (s), 1370 (s), 1331 (s), 1262 (m), 1211 (m), 1156 (m), 1134 (m), 1075 (s), 997 (m) cm^{-1}.

Anal. Calcd for $C_{30}H_{37}NOSn$: C, 65.95; H, 6.83; N, 2.56; Sn, 21.73. Found: C, 65.81; H, 6.80; N, 2.48; Sn, 21.68.

(*Z*)-*N*,*N*-Diisopropyl-6-hydroxy-2,6-dimethylhept-3-enamide (18a). Procedure A: 261 mg (1.32 mmol) of **8**, 0.20 mL (1.33 mmol) of TMEDA, 1.10 mL (1.41 mmol) of *sec*-BuLi, 10 mL of THF, and 1.00 mL (13.64 mmol) of acetone. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent. Recrystallization from pentane gave 143 mg (42%) of pure **18a** as a white solid, mp 62–64.5 °C. ^1H NMR

(360 MHz, C_6H_6): δ 1.15 (d, J = 6.2 Hz, 3 H, CH_3), 1.17 (d, J = 6.6 Hz, 3 H, COCHCH_3), 1.19 (d, J = 6.2 Hz, 3 H, CH_3), 1.25 (s, 6 H, COHCH_3), 1.37 (d, J = 6.4 Hz, 3 H, CH_3), 1.38 (d, J = 6.4 Hz, 3 H, CH_3), 2.25 (d, J = 7.6 Hz, 2 H, CH_2), 3.41 (br, 1 H, NCH), 3.55 (m, 1 H, COCH), 4.04 (m, 1 H, NCH), 5.53 (dt, J = 10.9 Hz, J = 7.4 Hz, 1 H, CHCH$_2$), 5.68 (m, 1 H, COCHCH). Decoupling: irradiation of the signal at 3.55 ppm decouples the protons at 1.17 and 5.68 ppm, leaving a singlet and doublet. IR (KBr): 3300 (s), 2900 (s), 1610 (s), 1430 (m), 1360 (s), 1327 (m), 1290 (m), 1245 (m), 1208 (m), 1160 (m), 1033 (m), 859 (m) cm^{-1}. Mass spectrum (70 eV): m/e (relative intensity) 255 (M^+, 2), 240 (3), 128 (34), 86 (96), 59 (26), 43 (100).

Anal. Calcd for $C_{15}H_{22}NO_2$: C, 70.54; H, 11.45; N, 5.48. *Found:* C, 70.84; H, 11.49; N, 5.34.

(*Z*)-*N*,*N*-Diisopropyl-6-hydroxy-2-methyl-6,6-diphenylhex-3-enamide (19a). Procedure A: 426 mg (2.16 mmol) of **8**, 0.33 mL (2.19 mmol) of TMEDA, 2.40 mL (2.62 mmol) of *sec*-BuLi, 10 mL of THF, and 1.202 g (6.60 mmol) of benzophenone. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent giving 506 mg (75%) of pure **19a** as a white solid, mp 106.5–108.5 °C. ^{1}H NMR (360 MHz, C_6D_6): δ 0.82 (m, 6 H, CH_3), 1.18 (d, J = 6.7 Hz, 3 H, COCHCH_3), 1.41 (m, 6 H, CH_3), 2.76 (m, 1 H, CH_2), 2.88–3.12 (m, 3 H, COHCH_2, NCH), 3.38 (m, 1 H, COCH), 3.71 (m, 1 H, NCH), 5.36 (m, 1 H, CH=CH), 5.71 (dd, J = 10.7 Hz, J = 7.8 Hz, 1 H, CH_2CH=CH), 7.07 (m, 2 H, ArH), 7.10–7.20 (m, 4 H, ArH), 7.47 (d, 4 H, J = 9.6 Hz, 4 H, ArH). Decoupling: irradiation of the resonance at 3.38 ppm decouples the protons at 1.18 and 5.71 ppm, leaving a singlet and doublet. ^{13}C NMR (360 MHz): δ 18.30, 18.43, 20.64, 20.99, 21.05, 36.97, 40.22, 45.79, 48.05, 124.38, 125.93, 126.11, 126.69, 128.01, 134.75, 146.58, 146.97, 173.44. IR ($CHCl_3$): 2960 (s), 2870 (m), 1615 (s), 1438 (s), 1366 (m), 1329 (s), 1150 (m), 1128 (m), 1025 (m), 1004 (m), 886 (m), 862 (m) cm^{-1}. Mass spectrum (70 eV): m/e (relative intensity) 379 (M^+, 2), 197 (41), 183 (28), 105 (15), 86 (100) 43 (56).

Anal. Calcd for $C_{25}H_{33}NO_2$: C, 79.11; H, 8.76; N, 3.69. Found: C, 79.17; H, 8.63; N, 3.85.

(*Z*)-*N*,*N*-Diisopropyl-6-hydroxy-2-methyl-6,6-diphenylhex-3-enamide (19a). Procedure B: 379 mg (1.92 mmol) of **8**, 0.30 mL (2.00 mmol) of TMEDA, 2.00 mL (2.38 mmol) of *sec*-BuLi, 2.40 mL (2.40 mmol) of triethylaluminum, 20 mL of THF, and 1.206 g (6.62 mmol) of benzophenone. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent giving 399 mg (52%) of pure **19a** as a white solid, mp 106.5–108 °C.

***trans*-*N*,*N*-Diisopropyl-4-methylcyclohex-2-enecarboxamide (20a) and *trans*-*N*,*N*-Diisopropyl-2-methylcyclohex-3-enecarboxamide (20b).** Procedure A: 0.90 g (4.3 mmol) of **9** and excess methyl iodide. Purification of Kugelrohr distillation (126–128 °C, 2 mmHg) and column chromatography on silica gel with chloroform/ethyl acetate as the eluent gave 0.68 g (71%) of pure **20**. **20a**: ^{1}H NMR (90 MHz) δ 0.95 (d, J = 7.5, 3 H), 1.15–1.50 (m, 12 H), 1.55–2.20 (m, 5 H), 3.16 (s, 1 H), 3.45 (m, 1 H), 3.95 (m, 1 H) 5.30–5.75 (m, 2 H); mass spectrum, m/e (relative intensity) 223 (M^+, 11), 128 (54), 86 (100), 43 (57).

Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.45; H, 11.22; N, 6.23.

20b: ^{1}H NMR (360 MHz) δ 0.93 (d, J = 7.0 Hz, 3 H, CHCHCH_3), 1.21 (d, J = 6.7 Hz, 3 H, CH_3), 1.25 (d, J = 6.7 Hz, 3 H, CH_3), 1.38 (d, J = 6.1 Hz, 6 H, CH_3), 1.72 (m, 2 H, COCHCH_2), 2.07 (m, 2 H, CHCH_2), 2.25 (dt, J = 4.1 Hz, J = 10.0 Hz, 1 H, COCH), 2.69 (m, 1 H, COCHCH), 3.54 (m, 1 H, NCH), 4.03 (m, 1 H, NCH), 5.54 (d, J = 10.0 Hz, 1 H, CHCH=CH), 5.63 (m, 1 H, C=CH). Decoupling: irradiation at 2.69 ppm decoupled the protons at 2.25 ppm, leaving a singlet and doublet, J = 5.5 Hz; irradiation at 1.72 ppm decoupled the proton at 2.25 ppm, leaving a broad doublet, J = 9.5 Hz. ^{13}C NMR (360 MHz): δ 20.09 (q), 20.91 (q), 21.48 (q), 25.14 (t), 26.86 (t), 33.03 (d), 45.72 (d), 47.84 (q), 124.86 (d), 133.31 (d), 174.79 (s). IR (KBr): 3010 (m), 2970 (s), 2937 (s), 2877 (m), 1630 (s), 1440 (s), 1370 (m), 1325 (s), 1208 (m), 1130 (m), 1042 (m), 678 (m), 608 (m) cm^{-1}. Mass spectrum: m/e (relative intensity) 223 (M^+, 25), 128 (41), 86 (100), 43 (55).

Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.24; H, 11.36; N, 6.35.

***trans*-*N*,*N*-Diisopropyl-4-methyl-2-cyclohexenecarboxamide (20a).** Procedure C: 0.44 (2.1 mmol) of **9** and excess methyl iodide yielded 0.46 g (95%) of pure **20a**. The NMR spectra are identical with **20a** obtained above, and a satisfactory analysis was obtained.

***N*,*N*-Diisopropyl-4-*n*-pentylcyclohex-2-enecarboxamide (21a) and *N*,*N*-Diisopropyl-2-*n*-pentylcyclohex-3-enecarboxamide (21b).** Procedure A: 0.38 g (1.8 mmol) of **9** and excess iodopentane. Purification by Kugelrohr distillation (168–172 °C, 2 mmHg) gave 0.47 g (92%) of pure **21**. **21a**: ^{1}H NMR (90 MHz) δ 0.60–1.35 (m, 23 H), 1.60–2.30 (m, 5 H), 2.45–2.67 (s, 1 H), 3.45 (m, 1 H), 3.95 (m, 1 H), 5.40–5.80 (m, 2 H). **21b**: ^{1}H NMR (90 MHz) δ 0.60–1.35 (m, 23 H), 1.60–2.30 (m, 5 H), 2.45–2.67 (s, 1 H), 3.45 (m, 1 H), 3.95 (m, 1 H), 5.70 (s, 2 H). Mass spectrum, m/e (relative intensity) 279 (M^+, 7), 128 (66), 86 (100), 43 (31).

Anal. Calcd for $C_{18}H_{33}NO$: C, 77.36; H, 11.90; N, 5.01. Found: C, 77.36; H, 12.08; N, 4.97.

***N*,*N*-Diisopropyl-4-*n*-pentylcyclohex-2-enecarboxamide (21a).** Procedure C: 0.350 g (1.68 mmol) of **9**, 0.25 mL (1.68 mmol) of TMEDA, 1.87 mL (2.02 mmol) of *sec*-BuLi, 15 mL of THF, 1.11 mL (2.10 mmol) of magnesium bromide etherate, and 3.73 mL (28.6 mmol) of *n*-pentyl iodide. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent and Kugelrohr distillation gave 0.24 g (50%) of **21a**. The ^{1}H NMR *is consistent with* **21a** *obtained from procedure* A.

Anal. Calcd for $C_{18}H_{33}NO$: C, 77.36; H, 11.90; N, 5.01. Found: C, 76.94; H, 11.74; N, 4.91.

***N*,*N*-Diisopropyl-2-(2-propenyl)cyclohex-3-enecarboxamide (22b).** Procedure A: 0.41 g (1.96 mmol) of **9** and excess allyl bromide. Purifcation by Kugelrohr distillation (145–152 °C, 1.5 mmHg) gave 0.46 g (94%) of pure **22b**: ^{1}H NMR (90 MHz) δ 1.00–1.40 (m, 12 H), 1.50–2.45 (m, 7 H), 2.75 (s, 1 H), 3.20–3.60 (m, 1 H), 3.88–4.11 (m, 1 H), 4.87 (d, 2 H), 5.60 (s, 2 H), 5.40–6.00 (m, 1 H). Mass spectrum, m/e (relative intensity) 249 (M^+, 17), 209 (21), 206 (18), 128 (60), 86 (100), 43 (29).

Anal. Calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.62. Found: C, 77.05; H, 11.05; N, 5.44.

***N*,*N*-Diisopropyl-4-(2-propenyl)cyclohex-2-enecarboxamide (22a).** Procedure C: 312 mg (1.49 mmol) of **9**, 0.23 mL (1.49 mmol) of TMEDA, 12 mL of THF, 1.66 mL (1.79 mmol) of *sec*-BuLi, 0.99 mL (1.87 mmol) of magnesium bromide etherate, and 2.20 mL (25.40 mmol) of allyl bromide. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent and Kugelrohr distillation gave a 0.184 g (49%) of **22a**. ^{1}H NMR (200 MHz): δ 1.17 (d, 6 H, J = 6.6 Hz, CH_3), 1.32 (d, 6 H, J = 6.5, 1.7 Hz, CH_3), 1.72–2.00 (m, 4 H, CH_2CH_2), 2.01 (dd, 2 H, CHCH_2CH=CH_2), 2.28 (m, 1 H, CH=CHCHCH_2), 3.12 (m, 1 H, COCH), 3.50 (b, 1 H, NCH), 4.05 (m, 1 H, J = 6.7 Hz, NCH), 4.93–5.02 (m, 2 H, CH=CH_2), 5.49–5.81 (m, 3 H, CH=CH$_2$, CH=CH). Decoupling: irradiation of the resonance at 5.55 ppm doublet of doublets at 2.01 collapses to a doublet J = 5.2 Hz; irradiation of the resonance at 5.69 ppm multiplets at 2.01, 3.12, and 4.93–5.02 ppm collapse. IR (CCl_4): 3070 (w), 3000 (m), 2970 (s), 2935 (s), 1640 (s), 1440 (s), 1370 (s), 1320 (s), 1130 (m), 1040 (m), 915 (m) cm^{-1}.

Anal. Calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.62. Found: C, 76.61; H, 11.12; N, 5.62.

***N*,*N*-Diisopropyl-4-(trimethylsilyl)cyclohex-2-enecarboxamide (23a) and *N*,*N*-Diisopropyl-2-(trimethylsilyl)cyclohex-3-enecarboxamide (23b).** Procedure A: 0.30 g (1.4 mmol) of **9** and excess chlorotrimethylsilane. Purification by Kugelrohr distillation 166–172 °C, 2 mmHg) gave 0.19 g (47%) of pure **23**. ^{1}H NMR (90 MHz): **23a**, δ 0.05 (s, 9 H), 1.20–1.40 (m, 12 H), 1.50–2.50 (m, 6 H), 3.35 (m, 1 H), 4.05 (m, 1 H), 5.35–5.75 (m, 2 H); **23b**, δ 0.05 (s, 9 H), 1.20–1.40 (m, 12 H), 1.50–2.50 (m, 6 H), 3.35 (m, 1 H), 4.05 (m, 1 H), 5.50 (s, 2 H). Mass spectrum, m/e (relative intensity) 282 (23), 281 (M^+, 100), 238 (88), 208 (29), 128 (76), 86 (99), 43 (20).

Anal. Calcd for $C_{16}H_{31}NOS$: C, 68.26; H, 11.10; N, 4.98. Found: C, 68.38; H, 10.89; N, 4.78.

***N*,*N*-Diisopropyl-4-(trimethylsilyl)cyclohex-2-enecarboxamide (23a).** Procedure C: 0.65 g (3.2 mmol) of **9** and excess chlorotrimethylsilane gives 0.51 g (58%) of pure **23a**: ^{1}H NMR (200 MHz) δ 0.03 (s, 9 H, SiCH_3), 1.22 (d, 6 H, J = 6.8 Hz, CH_3), 1.37 (d, 6 H, J = 6.6 Hz, CH_3), 1.45–2.00 ppm (m, 5 H, CH_2CH_2CHSi), 3.22 (m, 1 H, COCH), 3.53 (br, 1 H, NCH), 4.05 (m, 1 H, J = 6.7 Hz, NCH), 5.51–5.81 (m, 2 H, CH=CH); *IR* (CCl_4) *3000* (w), *2970* (m), *2955* (m), *1645* (s), *1435* (m), *1370* (m), *1320* (m), *1250* (m) cm^{-1}.

Anal. Calcd for $C_{16}H_{31}NOS$: C, 68.26; H, 11.10; N, 4.98. Found: C, 68.38; H, 10.89; N, 4.78.

***N*,*N*-Diisopropyl-4-(phenylthio)cyclohex-2-enecarboxamide (24a) and *N*,*N*-Diisopropyl-2-(phenylthio)cyclohex-3-enecarboxamide (24b).** Procedure A: 0.7 g (3.4 mmol) of **9** and excess diphenyl disulfide. Purification of Kugelrohr distillation (182–186 °C, 2 mmHg) and flash chromatography on silica gel gave 0.86 g (81%) of pure **24**. **24a**: ^{1}H NMR (90 MHz) δ 1.10–1.50 (m, 12 H), 1.70–2.90 (m, 6 H), 3.20–4.20 (m, 2 H), 5.60–5.80 (m, 2 H), 7.05–7.70 (m, 5 H).

Anal. Calcd for $C_{19}H_{27}NOS$: C, 71.87; H, 8.57; N, 4.41; S, 10.10. Found: C, 72.15; H, 8.43; N, 4.63; S, 10.14.

24b: ^{1}H NMR (90 MHz) δ 1.10–1.50 (m, 12 H), 1.70–2.90 (m, 6 H), 3.20–4.20 (m, 2 H), 5.70 (d, 2 H), 7.05–7.70 (m, 5 H). Mass spectrum, m/e (relative intensity) 317 (M^+, 4), 128 (100), 109 (40), 77 (88).

Anal. Calcd for $C_{19}H_{27}NOS$: C, 71.87; H, 8.57; N, 4.41; S, 10.10. Found: C, 71.73; H, 8.65; N, 4.61; S, 10.15.

***N*,*N*-Diisopropyl-4-(methylhydroxyethyl)cyclohex-2-enecarboxamide (26a) and *N*,*N*-Diisopropyl-2-(methylhydroxyethyl)cyclohex-3-ene-**

carboxamide (26b). Procedure A: 0.30 g (1.4 mmol) of **9** and excess acetone. Purification by Kugelrohr distillation (128–130 °C, 0.5 mmHg) and column chromatography on silica gel with diethyl ether gave 0.27 g (72%) of pure **26**. ^{1}H NMR (90 MHz): **26a**, δ 1.10–1.40 (m, 18 H), 1.50–2.30 (m, 6 H), 3.21 (s, 1 H, OH), 3.50 (m, 1 H), 4.1 (m, 1 H), 5.70–6.10 (m, 2 H); **26b**, 1.10–1.45 (m, 18 H), 1.5–2.6 (m, 6 H), 2.30 (s, 1 H, OH), 3.20–4.20 (m, 2 H), 5.50 (d, 2 H). Mass spectrum, *m/e* (relative intensity) 261 (M^+, 3), 209 (98), 166 (30), 128 (100), 86 (80).

Anal. Calcd for $C_{16}H_{29}NO_2$: C, 71.86; H, 10.93; N, 5.24. Found: C, 71.76; H, 10.80; N, 5.17.

***N,N*-Diisopropyl-4-(methylhydroxyethyl)cyclohex-2-enecarboxamide (26a).** Procedure B: 2.07 mL (2.8 mmol) of *sec*-BuLi, 488 mg (2.33 mmol) of **9**, 0.35 mL (2.33 mmol) of TMEDA, 15 mL of THF, 1.54 mL (2.91 mmol) of magnesium bromide etherate, and 2.91 mL (39.61 mmol) of acetone. Purification by Kugelrohr distillation followed by MPLC using hexane/ethyl acetate and Kugelrohr distillation again gave 0.42 g (67%) of **26a** as a clear oil. The ^{1}H NMR is consistent with that of **26a** obtained from procedure A.

Anal. Calcd for $C_{16}H_{29}NO_2$: C, 71.86; H, 10.93; N, 5.24. Found: C, 71.83; H, 10.80; N, 5.38.

***cis*-*N,N*-Diisopropyl-4-(hydroxymethyl)cyclohex-2-enecarboxamide (27a).** Procedure B: 2.692 g (12.88 mmol) of **9**, 2.00 mL (13.27 mmol) of TMEDA, 13.00 mL (17.94 mmol) of *sec*-BuLi, 11.00 mL (13.20 mmol) of magnesium bromide etherate, 50 mL of THF, and a formaldehyde solution precooled in a −78 °C bath, prepared by passing the formaldehyde evolved from the cracking of 3.70 g (123.3 mmol) of paraformaldehyde through 50 mL of THF at ambient temperature. Purification by flash chromatography on silica gel with hexane/ethyl acetate as the eluent. Recrystallization from methylene chloride and hexane gave 1.721 g (56%) of pure **27a** as white solid, mp 85–86.5 °C. ^{1}H NMR (90 MHz): δ 1.23 (d, J =7.5 Hz, 6 H, CH_3), 1.34 (d, J = 7 Hz, 6 H, CH_3), 1.73 (m, 4 H, CH_2CH$_2$), 2.25 (m, 1 H, CHCH$_2$OH), 3.25 (m, 1 H, NCH), 3.49 (m, 1 H, COCH), 3.54 (d, J = 6 Hz, 2 H, CH_2OH), 3.62 (m, 1 H, OH), 4.03 (m, J = 7.5 Hz, 1 H, NCH), 5.72 (m, 2 H, CH=CH). ^{13}C NMR (60 MHz): δ 20.56, 20.89, 22.57, 23.78, 36.73, 39.63, 45.40, 47.81, 65.17, 65.17, 126.97, 130.03, 173.20. Mass spectrum (70 eV), *m/e* (relative intensity) 239 (M^+, 2), 209 (2), 208 (2), 128 (48), 86 (100), 43 (99).

Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.05; H, 10.82; N, 5.69.

***cis*-*N,N*-Diisopropyl-2-(hydroxymethyl)cyclohex-3-enecarboxamide (27b).** Procedure B: 500.8 mg (2.39 mmol) of **9**, 0.51 mL (3.35 mmol) of TMEDA, 2.56 mL (3.35 mmol) of *sec*-BuLi, and 50 mL of THF and a formaldehyde solution precooled in a −78 °C bath, prepared by passing the formaldehyde evolved from the cracking of 906.1 mg (30.20 mmol) of paraformaldehyde through 50 mL of THF at ambient temperature. Purification on a Chromatotron using silica gel with hexane/ethyl acetate as the eluent, MPLC on silica gel with hexane/ethyl acetate as the eluent, Kugelrohr distillation, and repeated HPLC on silica gel with hexane/ethyl acetate gave 28 mg (5%) of **27b** as a white solid, mp 99 °C. ^{1}H NMR (200 MHz): δ 1.08 (d, J = 6 Hz, 3 H, CH_3), 1.18 (d, J = 7.4 Hz, 3 H, CH_3), 1.38 (d, J = 6.6 Hz, 3 H, CH_3), 1.40 (d, J = 7.4 Hz, 3 H, CH_3), 1.72 (m, 2 H, COCHCH_2), 2.02 (m, 1 H, COCHC*H*), 2.11 (m, 2 H, CHCH_2, 2.31 (m, 1 H, COCH), 3.28 (m, J = 7.4 Hz, 1 H, NCH), 3.48 (m, 1 H, CH_2OH), 3.73 (m, 1 H, CH_2OH), 4.27 (m, 1 H, OH), 4.50 (m, J = 6.4 Hz, 1 H, NCH), 5.69 (d, 1 H, CHC*H*CH), 5.83 (m, 1 H, CHC*H*CH$_2$). Decoupling: irradiation of the resonance at 5.83 ppm decouples the protons at 2.11 ppm. Irradiation of the resonance at 1.72 ppm decouples the proton at 2.31 ppm leaving a broad singlet, J < 1 Hz.

Anal. Calcd for $C_{14}H_{25}O_2N$: C, 70.23; H, 10.53; N, 5.86. Found: C, 69.91; H, 10.68; N, 5.63.

***N,N*-Diisopropyl-2-methyl-3-phenylbutanamide (32).** Procedure A: 33 mg (1.35 mmol) of **28**, 0.21 mL (1.39 mmol) of TMEDA, 1.60 mL (1.39 mmol) of *sec*-BuLi, 10 mL of THF, and 0.25 mL (4.02 mmol) of methyl iodide. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent and Kugelrohr distillation (120–125 °C, 4.5 mmHg) gave 288 mg (82%) of pure **32** as a white solid, mp 34–35.5 °C. ^{1}H NMR (360 MHz): major isomer (relative area), δ 1.02 (m, 6 H, CH_3), 1.17 (d, J = 6.7 Hz, 3 H, COCHCH_3), 1.29 (d, J = 7.1 Hz, 9 H, CH_3, ArCHCH_3), 2.75 (m, 1 H, COCH), 3.07 (m, 1 H, ArCH), 3.17 (m, 1 H, NCH), 3.86 (m, 1 H, NCH), 7.21 (m, 5 H, ArH); minor isomer (relative area), δ 0.68 (d, J = 6.9 Hz, 3 H, CH_3), 1.21 (d, J = 6.9 Hz, 3 H, CH_3), 1.26 (d, J = 6.9 Hz, 3 H, CH_3). Mass spectrum (70 eV): *m/e* (relative intensity) 261 (M^+, 20), 246 (4), 218 (28), 204 (4), 114 (31), 105 (82), 91 (70), 86 (100), 58 (92), 43 (91).

Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 78.00; H, 10.41; N, 5.29.

***N,N*-Diisopropyl-2-methyl-3-phenylpentanamide (33).** Procedure A: 473 mg (1.91 mmol) of **28**, 0.30 mL (2.00 mmol) of TMEDA, 2.05 mL (2.30 mmol) of *sec*-BuLi, 15 mL of THF, and 0.46 mL (5.75 mmol) of ethyl iodide. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent and Kugelrohr distillation (110–112 °C, 1.2 mmHg) gave 279 mg (53%) of pure **33** as a white solid, mp 58–69.5 °C. ^{1}H NMR (360 MHz): major isomer (relative area), δ 0.70 (m, 6 H, CH_3, CH_2CH_3), 0.94 (d, J = 6.8 Hz, 3 H, CH_3), 1.04 (d, J = 6.7 Hz, 3 H, CH_3), 1.19 (d, J = 7.0 Hz, 3 H, COCHCH_3), 1.28 (d, J = 6.6 Hz, 3 H, CH_3), 1.50 (m, 1 H, CH_2), 1.91 (m, 1 H, CH_2), 2.83 (m, 2 H, CHCH), 3.13 (m, 1 H, NCH), 3.89 (m, 1 H, NCH), 7.17 (m, 5 H, ArH); minor isomer (relative area), δ 0.66 (m, CH_3), 0.80 (d, J = 6.2 Hz), 1.26 (d, J = 7.0 Hz, CH_3), 1.40 (m, CH), 4.15 (m, 1 H, NCH). IR (KBr): 2960 (s), 2925 (m), 2865 (m), 1615 (s), 1435 (m), 1362 (m), 1134 (m), 1291 (m), 761 (m), 698 (m) cm^{-1}. Mass spectrum (70 eV): *m/e* (relative intensity) 246 (M^+, 8), 246 (4), 232 (23), 157 (37), 147 (12), 128 (10), 119 (37), 114 (55), 105 (44), 91 (100), 86 (88), 58 (43), 43 (78).

Anal. Calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.23; H, 10.70; N, 4.86.

***N,N*-Diisopropyl-2-methyl-3,4-diphenylbutanamide (34).** Procedure A: 448 mg (1.81 mmol) of **28**, 0.28 mL (1.86 mmol) of TMEDA, 2.00 mL (2.20 mmol) of *sec*-BuLi, 15 mL of THF, and 0.65 mL (5.65 mmol) of benzyl chloride. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent and two Kugelrohr distillations (140 °C, 3.5 mmHg) gave 512 mg (84%) of pure **34** as white solid, mp 72–85 °C. ^{1}H NMR (360 MHz): major isomer (relative area), δ 0.78 (d, J = 6.6 Hz, 3 H, CH_3), 0.93 (d, J = 6.7 Hz, 3 H, CH_3), 1.08 (d, J = 6.5 Hz, 3 H, COCHCH_3), 1.30 (d, J = 7.0 Hz, 3 H, CH_3), 1.31 (d, J = 6.7 Hz, 3 H, CH_3), 2.78 (t, J = 13.0 Hz, 1 H), 3.02 (m, 1 H), 3.15 (m, 1 H), 3.28 (m, 2 H), 3.95 (m, 1 H, NCH), 6.95 (m, 2 H, ArH), 7.02–7.18 (m, 8 H, ArH); minor isomer (relative area), δ 0.88 (m, 3 H, CH_3), 1.14 (d, J = 6.4 Hz, 3 H), 1.25 (d, J = 7.6 Hz, 3 H), 1.38 (m, 1 H), 2.61 (m, 1 H), 2.89 (m, 1 H). IR (KBr): 3063 (m), 3030 (m), 2960 (s), 2930 (m), 2873 (m), 1615 (s), 1434 (m), 1361 (m), 1332 (m), 1290 (m), 1122 (7), 692 (s) cm^{-1}. Mass spectrum (10 eV): *m/e* (relative intensity) 337 (M^+, 1), 325 (1), 294 (1), 247 (11), 157 (100), 114 (96), 91 (9), 86 (25), 58 (15), 43 (12).

Anal. Calcd for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15. Found: C, 82.14; H, 9.40; N, 4.16.

***N,N*-Diisopropyl-2-methyl-3-phenylhex-5-enamide (35).** Procedure A: 454 mg (1.84 mmol) of **28**, 0.28 mL (1.86 mmol) of TMEDA, 2.00 mL (2.20 mmol) of *sec*-BuLi, 15 mL of THF, and 0.50 mL (5.78 mmol) of allyl bromide. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent. Kugelrohr distillation (140 °C, 3.5 mmHg) gave 369 mg (70%) of pure **35** as a colorless oil. ^{1}H NMR (360 MHz): δ 0.74 (d, J = 6.5 Hz, 3 H, CH_3), 0.96 (d, J = 6.7 Hz, 3 H, CH_3), 1.06 (d, J = 6.6 Hz, 3 H, CH_3), 1.21 (d, J = 6.6 Hz, 3 H, COCHCH_3), 1.29 (d, J = 6.6 Hz, 3 H, CH_3), 2.36 (m, 1 H, CH_2), 2.60 (m, 1 H, CH_2), 2.90 (m, J = 9.8 Hz, 1 H, COCH), 3.06 (m, 1 H, ArCH), 3.16 (br, 1 H, NCH), 3.89 (m, 1 H, NCH), 4.85 (d, J = 9.6 Hz, 1 H, (E)-C=CH_2), 4.97 (d, J = 17.0 Hz, 1 H, (Z)-C=CH_2), 5.56 (m, 1 H, C=CH), 7.18 (m, 5 H, ArH). Decoupling: irradiation of the resonance at 5.56 ppm decouples the protons at 2.36 and 2.60 ppm, leaving a doublet and doublet of doublet; irradiation of the resonance at 1.21 ppm decouples the protons at 2.90 ppm, leaving a doublet. ^{13}C NMR (360 MHz): δ 16.42, 20.11, 20.33, 20.78, 21.33, 35.92, 42.72, 45.49, 48.52, 115.81, 126.00, 127.88, 128.53, 136.68, 143.39, 174.15. IR (KBr): 2960 (s), 2922 (m), 1620 (s), 1450 (m), 1448 (m), 1365 (m), 1269 (m), 697 (m) cm^{-1}. Mass spectrum (70 eV): *m/e* (relative intensity) 287 (M^+, 6), 272 (7), 246 (30), 244 (30), 157 (51), 131 (47), 114 (98), 91 (75), 86 (85), 43 (100).

Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.42; H, 10.17; N, 5.01.

***N,N*-Diisopropyl-2-methyl-3-(trimethylsilyl)-3-phenylpropanamide (36).** Procedure A: 340 mg (1.38 mmol) of **28**, 0.21 mL (1.39 mmol) of TMEDA, 1.50 mL (1.65 mmol) of *sec*-BuLi, 10 mL of THF, and 0.60 mL (4.73 mmol) of chlorotrimethylsilane. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent gave 285 mg (65%) of pure **36** as a white solid, mp 87–90 °C. ^{1}H NMR (360 MHz): δ 0.01 (s, 9 H, $SiCH_3$), 0.92 (d, J = 6.6 Hz, 3 H, CH_3), 0.93 (d, J = 6.7 Hz, 3 H, CH_3), 1.20 (d, J = 6.6 Hz, 3 H, CH_3), 1.33 (d, J = 6.8 Hz, 3 H, COCHCH_3), 1.38 (d, J = 6.7 Hz, 3 H, CH_3), 2.72 (d, J = 11.1 Hz, 1 H, ArCH), 3.21 (m, J = 6.7 Hz, 1 H, NCH), 3.34 (dq, 1 H, COCH), 4.11 (m, J = 6.6 Hz, 1 H, NCH), 7.13 (m, 3 H, ArH), 7.25 (m, 2 H, ArH). ^{13}C NMR (360 MHz, reference $CDCl_3$): δ −0.88, 18.75, 19.70, 20.18, 20.65, 21.21, 39.62, 40.47, 45.29, 48.03, 124.37, 127.58, 128.31, 143.92, 174.59. IR (KBr): 2910 (m), 1630 (s), 1430 (m), 1365 (m), 1335 (m), 1275 (m), 1260 (m), 1248 (m), 1215 (m), 1155 (m), 1135 (m), 1115 (m), 925 (m), 870 (s), 837 (s), 760 (m), 702 (s) cm^{-1}. Mass spectrum (70 eV): *m/e* (relative intensity) 319 (M^+, 3), 304 (14), 276 (93), 73 (100), 43 (46).

Anal. Calcd for $C_{17}H_{33}NOSi$: C, 71.41; H, 10.41; N, 4.38. Found:

C, 71.40; H, 10.39; N, 4.41.

***N,N*-Diisopropyl-*3-d*-2-methyl-3-phenylpropanamide (37).** Procedure A: 253 mg (1.02 mmol) of **28**, 0.16 mL (1.06 mmol) of TMEDA, 1.11 mL (1.22 mmol) of *sec*-BuLi, 10 mL of THF, and 0.15 mL (3.60 mmol) of methyl alcohol-*d*. Purification by flash chromatography on silica gel with hexane/ethyl acetate as the eluent and Kugelrohr distillation (100–111 °C, 0.4 mmHg) gave 236 mg (87%) of pure **37** as a colorless oil. ^{1}H NMR (360 MHz): δ 0.88 (m, 3 H, CH_3), 1.09 (d, J = 6.7 Hz, 3 H, CH_3), 1.14 (d, J = 6.6 Hz, 3 H, COCHCH_3), 1.26 (d, J = 6.3 Hz, 3 H, CH_3), 1.33 (m, 3 H, CH_3), 2.60 (m, CHD), 2.88 (m, 1 H, COCH), 3.01 (m, CHD), 3.47 (br, 1 H, NCH), 3.86 (m, 1 H, NCH), 7.21 (m, 5 H, ArH). Mass spectrum (70 eV): *m/e* (relative intensity) 248 (M^+, 21), 233 (43), 205 (42), 120 (44), 92 (75), 91 (76), 86 (100), 58 (67), 43 (88); calcd % d = 99.[29]

Anal. Calcd for $C_{16}H_{24}DNO$: C, 77.37; H, 10.15; N, 5.64. Found: C, 77.33; H, 10.16; N, 5.74.

***N,N*-Diisopropyl-4-hydroxy-2-methyl-3,4,4-triphenylbutanamide (38).** Procedure A: 324 mg (1.31 mmol) of **28**, 0.21 mL (1.39 mmol) of TMEDA, 1.50 mL (1.65 mmol) of *sec*-BuLi, 10 mL of THF, and 932 mg (5.11 mmol) of benzophenone. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent and recrystallization from hexane gave 356 mg (63%) of pure **38** as a white solid, mp 195–196.5 °C. ^{1}H NMR (200 MHz): δ 0.59 (d, J = 6.5 Hz, 3 H, CH_3), 0.84 (d, J = 7.0 Hz, 3 H, CH_3), 1.02 (d, J = 6.5 Hz, 3 H, CH_3), 1.08 (d, J = 7.0 Hz, 3 H, CH_3), 1.29 (d, J = 6.7 Hz, 3 H, COCHCH_3), 3.08 (m, J = 6.8 Hz, 1 H, NCH), 3.50 (m, 1 H, COCH), 3.78 (m, J = 6.6 Hz, 1 H, NCH), 4.21 (d, J = 7.8 Hz, 1 H, ArH), 5.40 (s, 1 H, COH), 7.04 (m, 5 H, ArH), 7.15–7.43 (m, 8 H, ArH), 7.81 (d, J = 8.3 Hz, 2 H, ArH). ^{13}C NMR (360 MHz): δ 18.83, 19.98, 20.11, 20.50, 20.86, 40.22, 45.92, 48.84, 57.20, 79.97, 125.59, 125.74, 125.87, 126.14, 126.44, 127.08, 127.28, 128.14, 131.98, 139.54, 147.10, 147.74, 175.35. IR ($CHCl_3$): 3250 (m), 2970 (s), 2932 (m), 1602 (s), 1444 (s), 1371 (m), 1329 (s), 1031 (m), 691 (m), 657 (m) cm^{-1}. Mass spectrum (10 eV): *m/e* (relative intensity) 430 (M + 1$^+$, 1), 352 (1), 247 (96), 204 (100), 183 (53), 128 (11), 105 (19), 86 (30), 58 (59), 43 (11).

Anal. Calcd for $C_{29}H_{35}NO_2$: C, 81.10; H, 8.07; N, 3.26. Found: C, 81.13; H, 8.19; N, 3.26.

***N,N*-Diisopropyl-2-methyl-4-phenyl-3-(phenylthio)butanamide (40).** Procedure A: 378 mg (1.35 mmol) of **29**, 0.21 (1.39 mmol) of TMEDA, 1.60 mL (1.76 mmol) of *sec*-BuLi, 10 mL of THF, and 0.60 mL (5.21 mmol) of benzyl chloride. Purification on a Chromatotron using silica gel with hexane/ethyl acetate as the eluent. Kugelrohr distillation (160 °C, 0.4 mmHg) gave 224 mg (52%) of pure **40**, as a colorless oil. ^{1}H NMR (200 MHz): major isomer, δ 1.13 (d, J = 6.7 Hz, 6 H, CH_3), 1.31 (d, J = 6.7 Hz, 3 H, CH_3), 1.39 (d, J = 6.3 Hz, 3 H, CH_3), 1.40 (d, J = 6.7 Hz, 3 H, CH_3), 2.72 (m, 2 H, COCH, CHCH_2), 3.04 (dd, J = 3.8 Hz, J_{gem} = 14.0 Hz, 1 H, CHCH_2), 3.49 (br, 1 H, NCH), 3.61 (dt, J = 8.8 Hz, 1 H, SCH), 3.81 (m, 1 H, NCH), 7.24 (m, 10 H, ArH): minor isomer, δ 0.99 (m, CH_3), 3.20–3.40 (m). IR (film): 3060 (m), 3025 (m), 3000 (m), 2970 (s), 2930 (m), 2870 (m), 1624 (s), 1532 (m), 1438 (s), 1369 (s), 1329 (s), 1263 (m), 1208 (m), 1149 (m), 1133 (m), 1110 (m), 1045 (m), 1026 (m), 945 (m), 743 (s), 698 (s) cm^{-1}.

Anal. Calcd for $C_{23}H_{31}NOS$: C, 74.51; H, 8.46; N, 3.79; S, 8.68. Found: C, 74.81; H, 8.57; N, 3.74; S, 8.56.

***N,N*-Diisopropyl-2-methyl-3-(phenylthio)hex-5-enamide (41).** Procedure A: 364 mg (1.30 mmol) of **29**, 0.20 mL (1.33 mmol) of TMEDA, 1.40 mL (1.74 mmol) of *sec*-BuLi, 10 mL of THF, and 0.50 mL (5.74 mmol) of allyl bromide. Purification on a Chromatotron using silica gel with hexane/ethyl acetate as the eleunt. Kugelrohr distillation (148 °C, 0.6 mmHg) gave 142 mg (46%) of pure **41** as a light yellow oil. ^{1}H NMR (200 MHz): δ 1.05–1.21 (m, 15 H, CH_3), 2.12–2.90 (m, 3 H, COCH, CHCH_2), 3.32–3.74 (m, 3 H, NCH, SCH), 3.97 (m, J = 6.4 Hz, 1 H, NCH, minor isomer), 5.09 (m, 2 H, CH_2=CH), 5.96 (m, 1 H, CH_2=CH), 7.23 (m, 3 H, ArH), 7.48 (m, 2 H, ArH). IR (film): 3070 (m), 3000 (m), 2962 (s), 2930 (s), 2872 (m), 1620 (s), 1435 (s), 1367 (m), 1326 (s), 1270 (m), 1200 (m), 1148 (m), 1130 (m), 1023 (m), 912 (m), 744 (s), 690 (s) cm^{-1}. Mass spectrum (10 eV): *m/e* (relative intensity) 319 (M^+, 1), 210 (100), 86 (35), 43 (26).

Anal. Calcd for $C_{19}H_{29}NOS$: C, 71.41; H, 9.16; N, 4.38; S 10.03. Found: C, 71.41; H, 9.10; N, 4.40; S, 9.76.

***N,N*-Diisopropyl-2-methyl-3-(trimethylsilyl)-3-(phenylthio)propanamide (42).** Procedure A: 443 mg (1.59 mmol) of **29**, 0.24 mL (1.59 mmol) of TMEDA, 1.70 mL (2.11 mmol) of *sec*-BuLi, 10 mL of THF, and 0.90 mL (7.09 mmol) of chlorotrimethylsilane. Purification on a Chromatotron using silica gel with hexane/ethyl acetate as the eluent. Kugelrohr distillation (145 °C, 0.6 mmHg) gave 446 mg (80%) of pure **42** as a colorless oil. ^{1}H NMR (200 MHz): major isomer (relative area), δ 0.18 (s, 9 H, $SiCH_3$), 0.96 (d, J 6.7 Hz, 3 H, CH_3), 1.06 (d, J = 6.7 Hz, 3 H, CH_3), 1.27 (d, J = 6.6 Hz, 3 H, CH_3), 1.29 (d, J = 7.3 Hz, 3 H, CH_3), 1.33 (d, J = 7.0 Hz, 3 H, CH_3), 2.65 (d, J = 6.0 Hz, 1 H, $SiCH_3$), 2.88 (m, 1 H, COCH), 3.29 (br, 1 H, NCH), 3.56 (m, J = 6.7 Hz, 1 H, NCH), 7.25 (m, 3 H, ArH), 7.49 (d, J = 7.9 Hz, 2 H, ArH); minor isomer (relative intensity), δ 0.17 (s, 9 H, $SiCH_3$), 1.17 (m, 9 H, CH_3, COCHCH_3), 1.35 (d, J = 6.7 Hz, 3 H, CH_3), 1.37 (d, J = 6.7 Hz, 3 H, CH_3), 2.99 (m, 2 H, SiCHCH), 3.38 (m, 1 H, NCH), 4.02 (m, J = 6.7 Hz, 1 H, NCH), 7.12 (m, 1 H, ArH), 7.24 (m, 2 H, ArH), 7.38 (m, 2 H, ArH). IR (film): 3005 (m), 2970 (s), 2940 (m), 2092 (m), 1632 (s), 1440 (s), 1373 (s), 1327 (s), 1249 (s), 1216 (m), 1153 (m), 1136 (m), 1120 (m), 1046 (m), 844 (s), 748 (m), 697 (m) cm^{-1}. Mass spectrum (70 eV): *m/e* (relative intensity) 336 (21), 308 (19), 242 (100), 86 (11), 73 (86), 43 (48).

Anal. Calcd for $C_{19}H_{33}NOSSi$: C, 64.88; H, 9.47; N, 3.99; S, 9.12. Found: C, 64.79; H, 9.47; N, 4.23; S, 9.38.

***N,N*-Diisopropyl-2-methyl-3,3-bis(phenylthio)propanamide (43).** Procedure A: 644 mg (2.31 mmol) of **29**, 0.34 mL (2.26 mmol) of TMEDA, 2.60 mL (2.81 mmol) of *sec*-BuLi, 10 mL of THF, and 1.360 g (6.23 mmol) of diphenyl disulfide. Purification on a Chromatotron using a silica gel plate with hexane/ethyl acetate as the eluent gave 432 mg (48%) of pure **43** as a yellow oil. ^{1}H NMR (90 MHz): δ 1.08 (d, J = 7 Hz, 6 H, CH_3), 1.43 (m, 9 H, CH_3, COCHCH_3), 2.94 (m, 1 H, NCH), 3.38 (m, 1 H, COCH), 3.68 (m, J = 6 Hz, NCH), 4.53 (d, J = 9.0 Hz, 1 H, SCH), 6.97 (m, ArH, 10 H). IR (film): 2969 (s), 2932 (m), 1634 (s), 1581 (w), 1474 (s), 1439 (s), 1372 (s), 1330 (s), 1271 (w), 1210 (w), 1136 (w), 1045 (m), 1024 (m), 747 (s), 693 (s).

Anal. Calcd for $C_{22}H_{29}NOS_2$: C, 68.17; H, 7.54; N, 3.61; S, 16.54. Found: C, 68.01; H, 7.42; N, 3.60; S, 16.60.

***N,N*-Diisopropyl-*3-d*-2-methyl-3-(phenylthio)propanamide (44).** Procedure A: 305 mg (1.09 mmol) of **29**, 0.17 mL (1.13 mmol) of TMEDA, 1.20 mL (1.49 mmol) of *sec*-BuLi, 10 mL of THF, and 0.20 mL (11.07 mmol) of deuterium oxide. Purification on a Chromatotron using silica gel with hexane/ethyl acetate as the eluent. Kugelrohr distillation (160 °C, 1.0 mmHg) gave 242 mg (79%) of pure **44** as a light yellow oil. ^{1}H NMR (200 MHz): δ 1.10 (d, J = 6.4 Hz, 3 H, CH_3), 1.13 (d, J = 6.0 Hz, 3 H, CH_3), 1.21 (d, J = 6.7 Hz, 3 H, CH_3), 1.36 (m, 6 H, CH_3), 2.83 (m, 1 H, COCH), 2.90 (m, SCDH), 3.28 (br, SCDH), 3.52 (br, 1 H, NCH), 3.83 (m, 1 H, NCH), 7.16–7.38 (m, ArH, 5 H). Mass spectrum (10 eV): *m/e* (relative intensity) 280 (M^+, 22), 265 (2), 237 (1), 171 (100), 152 (5), 86 (41), 59 (30), 58 (50), 43 (36); calcd % d = 97.[29]

Anal. Calcd for $C_{16}H_{24}DNOS$: C, 68.85; H, 8.99; N, 4.99; S, 11.43. Found: C, 68.49; H, 8.96; N, 5.01; S, 11.48.

***N,N*-Diisopropyl-4-hydroxy-2-methyl-4,4-diphenyl-3-(phenylthio)butanamide (45).** Procedure A: 336 mg (2.79 mmol) of **29**, 1.30 mL (1.61 mmol) of *sec*-BuLi, 10 mL, of THF, and 1.068 g (5.86 mmol) of benzophenone. Purification by MPLC on silica gel with hexane/ethyl acetate as the eluent gave 229 mg (41%) of pure **45** as a white solid, mp 50–56 °C. ^{1}H NMR (200 MHz): major isomer (relative area), δ 0.69 (d, J = 6.2 Hz, 3 H, CH_3), 1.05 (d, J = 6.7 Hz, 3 H, CH_3), 1.36 (m, 9 H, CH_3), 3.17 (m, 2 H, NCH, COCH), 3.65 (m, 1 H, NCH), 4.88 (d, J = 7.0 Hz, 1 H, SCH), 6.92–7.63 (m, 15 H, ArH); minor isomer (relative area), δ 0.58 (d, J = 6.7 Hz, 3 H, CH_3), 1.45 (m, 6 H, CH_3), 3.53 (m, 1 H, NCH), 4.16 (d, J = 3.4 Hz, 1 H, SCH). IR (Nujol): 1605 (s), 1329 (s), 1275 (m), 1157 (m), 1137 (m), 1034 (m), 910 (m), 740 (s), 703 (s), 645 (m), 635 (m) cm^{-1}. Mass spectrum (10 eV): *m/e* (relative intensity) 315 (4), 279 (45), 170 (100), 128 (95), 86 (92), 58 (32), 43 (38).

Anal. Calcd for $C_{29}H_{35}NO_2S$: C, 75.45; H, 7.98; N, 2.75; S, 6.95. Found: C, 75.79; H, 7.69; N, 2.79; S, 6.82.

***N,N*-Diisopropyl-3-(phenylthio)-2-(1-(phenylthio)ethyl)butanamide (46).** Procedure A: 201 mg (0.50 mmol) of **31**, 0.08 mL (0.53 mmol) of TMEDA, 0.60 mL (0.75 mmol) of *sec*-BuLi, 5 mL of THF, and 0.15 mL (2.41 mmol) of methyl iodide. Purification on a Chromatotron using silica gel with hexane/ethyl acetate as the eluent gave 103 mg (50%) of pure **46**, as a colorless oil. ^{1}H NMR (200 MHz) δ 0.82–1.45 (m, 18 H, CH_3), 3.00–4.25 (m, 5 H, NCH, COCHCH), 7.11–7.57 (m, 10 H, ArH). IR (film): 2970 (s), 2930 (m), 1630 (s), 1583 (m), 1476 (s), 1439

(29) The amount of deuterium in a sample was determined by solving the following matrix equation

$$\begin{bmatrix} I_0 & I_{-1}\cdots & I_{-n} \\ I_1 & I_0\cdots & I_{-(n-1)} \\ \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot \\ I_n & I_{n-1}\cdots & I_0 \end{bmatrix} \begin{bmatrix} d_0 \\ d_1 \\ \cdot \\ \cdot \\ \cdot \\ d_n \end{bmatrix} = a \begin{bmatrix} I'_{-1} \\ I'_0 \\ \cdot \\ \cdot \\ \cdot \\ I'_{n-1} \end{bmatrix}$$

where d_n = fraction of material in the sample containing n deuterium atoms, I_0 = relative intensity of a peak observed by mass spectrometry of starting material; generally the molecular ion, I_n = relative intensity of peak n *m/e* units above I_0, I_{-n} = relative intensity of peak n *m/e* units below I_0, I'_0 = relative intensity of peak observed by mass spectrometry of a deuteriated sample, generally the molecular ion, and a = normalization coefficients.

(s), 1372 (s), 1306 (m), 1210 (m), 1161 (m), 1134 (m), 1040 (m), 1024 (m), 745 (s), 693 (s) cm^{-1}.

Anal. Calcd $C_{24}H_{31}NOS_2$: C, 69.35; H, 8.00; N, 3.37; S, 15.43. Found: C 69.04; H, 8.31; N, 3.44; S, 15.17.

***N,N*-Diisopropyl-2-methyl-4-(phenylthio)pentanamide (49).** A solution of 0.17 mL (1.13 mmol) of TMEDA in 10 mL of THF was cooled in a −78 °C bath and treated in a dropwise fashion with 1.30 mL (1.43 mmol) of *sec*-BuLi followed by a solution of 319 mg (1.09 mmol) of **47**, in 10 mL of THF. Purification on a Chromatotron using silica gel with hexane/ethyl acetate as the eluent gave 278 mg (83%) of pure **49** a light yellow oil as two isomers with a ratio slightly in excess of 1:1. ^1H NMR (200 MHz): δ 1.08–1.46 (m, 18 H, CH_3), 1.63 (m, 1 H, $CHCH_2$, major isomer), 1.90–2.22 (m, 1 H, $CHCH_2$, major isomer; 2 H, $CHCH_2$, minor isomer), 2.98–3.60 (m, 3 H, $CHCH_2CH$, NCH), 4.02–4.28 (m, 1 H, NCH), 7.29 (m, 5 H, ArH). IR (film): 2967 (s), 2932 (m), 1634 (s), 1439 (s), 1372 (m), 1323 (m), 747 (m), 693 (m) cm^{-1}. Mass spectrum (10 eV): *m/e* (relative intensity) 307 (M^+, 2), 198 (21), 157 (55), 114 (100), 86 (13), 58 (16), 43 (16).

Anal. Calcd for $C_{18}H_{29}NOS$: C, 70.31; H, 9.51; N, 4.56; S, 10.43. Found: C, 70.31; H, 9.73; N, 4.64; S, 10.37.

***N,N*-Diisopropyl-2-ethyl-5-hydroxy-6,6-diphenyl-4-(phenylthio)pentanamide (51).** Procedure A: 341 mg (1.11 mmol) of **48**, 0.17 mL (1.13 mmol) of TMEDA, 1.20 mL (1.45 mmol) of *sec*-BuLi, 10 mL of THF, and 364 mg (4.12 mmol) of benzophenone. Purification by MPLC on silica gel with hexane/ethyl acetate followed by chromatography on a Chromatotron using silica gel with hexane/ethyl acetate as the eluent gave 364 mg (67%) of pure **51** as a white solid, mp 111–115 °C. ^1H NMR (360 MHz): δ 0.78 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.15 (d, J = 7.1 Hz, 3 H, CH_3), 1.17 (d, J = 7.2 Hz, 3 H, CH_3), 1.35 (d, J = 5.6 Hz, 3 H, CH_3), 1.37 (d, J = 6.3 Hz, 3 H, CH_3), 1.53 (m, 1 H, CH_2CH_3), 1.64 (m, 1 H, CH_2CH_3), 1.81 (m, 1 H, $CHCH_2$), 1.92 (m, 1 H, $CHCH_2$), 2.93 (m, 1 H, COCH), 3.37 (br, 1 H, NCH), 4.21 (m, 1 H, NCH), 4.26 (dd, J = 3.0 Hz, J = 10.5 Hz, 1 H, SCH), 7.08 (m, 8 H, ArH), 7.30 (m, 5 H, ArH), 7.49 (m, 2 H, ArH). Decoupling: irradiation of resonance at 0.78 ppm decouples the protons at 1.53 and 1.64 ppm leaving multipets; irradiation of the resonance at 2.93 ppm decouples the protons at 1.53, 1.64, 1.81, and 1.92 ppm leaving multipets; decoupling of the resonance at 4.26 ppm decouples the protons at 1.81 and 1.92 ppm leaving two set of doublet of doublets. ^{13}C NMR (360 MHz, $CDCl_3$): δ 11.8, 20.4, 20.6, 20.8, 23.9, 34.3, 42.9, 45.6, 47.8, 60.3, 80.8, 125.7, 126.5, 126.6, 127.4, 128.0, 128.6, 136.6, 144.5, 145.4, 174.0. IR (KBr Nujol) 1628 (s), 1491 (m), 1341 (m), 1298 (m), 1171 (m), 1067 (m), 1038 (m), 745 (m), 702 (m) cm^{-1}. Mass spectrum (10 eV): *m/e* (relative intensity) 403 (M^+, 1) 362 (13), 306 (100), 198 (45), 171 (63), 128 (62).

Anal. Calcd for $C_{31}H_{39}NO_2S$: C, 76.03; H, 8.03; N, 2.86; S, 6.55. Found: C, 76.25; H, 7.85; N, 2.74; S, 6.29

***N,N*-Diisopropyl-2,3-dimethyl-3-(phenylthio)butanamide (53).** Procedure A: 334 mg (1.13 mmol) of **39**, 0.17 mL (1.13 mmol) of TMEDA, 1.50 mL (1.47 mmol) of *sec*-BuLi, 10 mL of THF, and 0.35 mL (5.62 mmol) of methyl iodide. Purification on a Chromatotron using silica gel with hexane/ethyl acetate as the eluent and Kugelrohr distillation (145 °C, 0.6 mmHg) gave 297 mg (86%) of pure **53** as a white solid, mp 54–60 °C. ^1H NMR (200 MHz): δ 0.93 (d, J = 6.3 Hz, 3 H, CH_3), 0.96 (d, J = 7.6 Hz, 3 H, CH_3), 1.29 (br, 9 H, $SCCH_3$, CH_3), 1.34 (d, J = 7.0 Hz, 3 H, $COCHCH_3$), 1.47 (s, 3 H, $SCCCH_3$), 2.73 (q, J = 7.0 Hz, 1 H, COCH), 3.50 (br, 1 H, NCH), 3.61 (m, J = 6.7 Hz, 1 H, NCH), 7.35 (m, 3 H, ArH), 7.53 (m, 2 H, ArH). ^{13}C NMR (200 MHz): δ 14.4 (q), 20.6 (q), 20.8 (q), 21.4 (q), 23.9 (q), 28.36 (q), 42.1 (d), 45.7 (d), 48.2 (d), 52.7 (s), 128.6 (d), 129.1 (d), 132.1 (s), 137.9 (d), 174.1 (s). Mass spectrum (10 eV): *m/e* (relative intensity) 307 (M^+, 7), 198 (41), 128 (55), 86 (100), 43 (52).

Anal. Calcd for $C_{18}H_{29}NOS$: C, 70.31; H, 9.51; N, 4.56; S, 10.43. Found: C, 70.27; H, 9.66; N, 4.46; S, 10.05.

***N,N*-Diisopropyl-2-methyl-3-(trimethylsilyl)-3-(phenylthio)butanamide (54).** Procedure A: 364 mg (1.24 mmol) of **39**, 1.50 mL (1.65 mmol) of *sec*-BuLi, 10 mL of THF, and 0.50 mL (4.03 mmol) of chlorotrimethylsilane. Purification on a Chromatotron using silica gel with hexane/ethyl acetate as the eluent. Kugelrohr distillation (160 °C, 0.7 mmHg) gave 215 mg (49%) of pure **54** a yellow oil as two isomers with a ratio slightly in excess of 1:1. ^1H NMR (200 MHz): major isomer (relative intensity), δ 0.18 (s, 9 H, $SiCH_3$), 1.18–1.46 (m, 18 H, CH_3, $CHCH_3CCH_3$), 3.07 (q, J = 7.0 Hz, 1 H, COCH), 3.37 (m, J = 6.7 Hz, 1 H, NCH), 4.19 (m, J = 6.7 Hz, 1 H, NCH), 7.30 (m, 3 H, ArH), 7.53 (m, 2 H, ArH); minor isomer (relative intensity), δ 0.26 (s, 9 H, $SiCH_3$), 0.94 (d, J = 6.4 Hz, 3 H, CH_3), 0.97 (d, J = 6.0 Hz, 3 H, CH_3), 2.73 (q, J = 6.7 Hz, 1 H, COCH), 3.62 (m, J = 6.4 Hz, NCH). IR (film): 3005 (m), 2986 (s), 2900 (m), 1639 (s), 1440 (m), 1369 (m), 1346 (m), 1244 (m), 1210 (m), 1125 (m), 1037 (m), 846 (s), 750 (m), 704 (m), 694 (m), 673 (m) cm^{-1}.

Anal. Calcd for $C_{20}H_{35}NOSSi$: C, 65.70; H, 9.65; N, 3.91; S, 8.77. Found: C, 65.39; H, 9.38; N, 3.91; S, 8.84.

***cis*-*N,N*-Diisopropyl-4-methylcyclohex-2-enecarboxamide.** To a solution of 709 mg (2.97 mmol) of **27a** in 10 mL of dry pyridine under N_2 was added 2.434 g (12.77 mmol) of *p*-toluenesulfonyl chloride. The solution was maintained at −10 °C for 7 h, then poured into ice water, and extracted with Et_2O. The combined organic phases were washed twice with 10% HCl, dried (Na_2SO_4), and reduced in vacuo giving 867 mg (74%) of **69** as a white solid, mp 77.5–78.5 °C. ^1H NMR (200 MHz): δ 1.21 (d, J = 6.7 Hz, 6 H, CH_3), 1.34 (d, J = 6.5 Hz, 6 H, CH_3), 1.68 (m, 4 H, CH_2CH_2), 2.45 (s, 3 H, $ArCH_3$), 2.46 (m, 1 H, $CHCH_2O$), 3.23 (m, 1 H, COCH), 3.47 (m, 1 H, NCH), 3.88 (m, 2 H, CH_2O), 3.98 (m, 1 H, NCH), 5.68 (m, 2 H, CH=CH), 7.34 (d, J = 8.3 Hz, 2 H, ArH), 7.78 (d, J = 8.2 Hz, 2 H, ArH). ^{13}C NMR (200 MHz): δ 20.63, 21.29, 21.64, 22.57, 22.74, 34.17, 39.82, 45.77, 48.25, 72.42, 126.99, 127.90, 129.30, 129.88, 132.93, 144.75, 172.60.

To a mixture of 133 mg (3.50 mmol) of lithium aluminum hydride in 5 mL of THF cooled in a 0 °C bath was added a solution of 459 mg (1.17 mmol) of the tosylate in 2 mL of THF. The solution was warmed to ambient temperature and stirred 20 min, recooled in a 0 °C bath, and quenched with 3 mL of ethyl acetate, followed by 10 mL of H_2O. The aqueous phase was extracted with Et_2O. The combined aqueous phases were dried ($MgSO_4$) and reduced in vacuo. Purification by MPLC on silica gel with hexane/ethyl acetate gave 31 mg (12%) of *cis*-*N,N*-diisopropyl-4-methylcyclohex-2-enecarboxamide as a colorless oil. ^1H NMR (200 MHz): δ 1.03 (d, J = 6.9 Hz, 3 H, $CHCHCH_3$), 1.23 (d, J = 6.7 Hz, 6 H, CH_3), 1.37 (d, J = 6.6 Hz, 6 H, CH_3), 1.44–1.97 (m, 4 H, CH_2), 2.17 (br, 1 H, $CHCHCH_3$), 3.20 (m, 1 H, COCH), 3.48 (br, 1 H, NCH), 4.04 (m, 1 H, NCH), 5.53 (ddd, J = 10.2 Hz, J = 2.6 Hz, J = 1.90 Hz, 1 H, CH=CH), 5.75 (dd, J = 2.2 Hz, J = 3.1 Hz, 1 H, $CH=CH_2$). ^{13}C NMR (200 MHz, reference $CDCl_3$): δ 20.64, 20.70, 20.99, 21.45, 23.38, 28.29, 29.14, 39.90, 45.64, 48.00, 124.62, 135.24, 173.35.

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Supplementary Material Available: Experimental data on the metalation of amides (22 pages). Ordering information is given on any current masthead page.