The Synthesis of Homoallylic Amines Utilizing a Cuprate-Based 1,2-Metalate Rearrangement

Christopher E. Neipp, John M. Humphrey, and Stephen F. Martin*

Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712

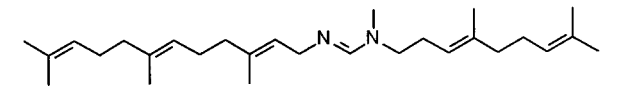
sfmartin@mail.utexas.edu

Received September 18, 2000

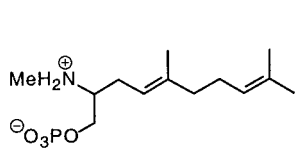
Lithiation of the *N*-2,4,6-triisopropylbenzenesulfonyl-2-pyrroline (**16**) and treatment of the resulting cyclic vinyllithium reagent with $R_2CuCNLi_2$ produced an acyclic vinyl organometallic species that, when treated with an electrophile (H_2O or RX), gave the homoallylic sulfonamides **18a**−**k** in 37−93% yields and in >95% diastereoselectivity. The deprotection of a representative homoallylic sulfonamide **18d** was achieved in 83% yield by sonication in the presence of lithium wire and catalytic 4,4′-di-*tert*-butylbiphenyl (DBB). The efficacy of this general procedure for the production of homoallylic amine derivatives is demonstrated by the preparation of the diene amine **25**, a key intermediate in the synthesis of a squalene synthetase inhibitor.

Introduction

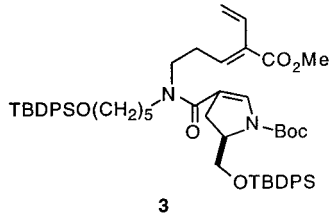
The homoallylic amine functional array is an important structural subunit found in biologically active compounds as well as in key intermediates in the synthesis of alkaloid natural products and nitrogen heterocycles. For example, the homoallylic amines **1** and **2** have been shown to inhibit squalene synthetase.[1] We have used homoallylic amines and homoallylic diene amines, respectively, as dienophiles and dienes in intramolecular Diels−Alder reactions that led to the formation of nitrogen heterocycles found in different families of alkaloids.[2] Indeed, the amine **3** was an intermediate in the total, enantioselective synthesis of manzamine A.[3] Owing to their obvious importance, the development of general and efficient methods for the synthesis of homoallylic amines and their derivatives has been a topic of considerable interest.



1



2



3

A number of methods for the synthesis of homoallylic amines have been reported,[4−6] but the most commonly used reactions leading to their preparation involve additions of allylic organometallics or allyl silanes to imines or nitriles.[7,8] Unfortunately, none of these methods allow for a significant degree of stereochemical control in forming homoallylic amines having either a di- or trisubstituted olefin. Indeed, none of the methods that have been reported for the synthesis of trisubstituted olefins have been adapted to the direct formation of homoallylic amines.[9,10] Thus, the challenge before us was to develop a general and stereoselective entry to homoallylic amines having di- and trisubstituted carbon−carbon double bonds. From the standpoint of flexibility, a method that employed a common starting material as a precursor would have obvious advantages.

(1) (a) Steiger, A.; Pyun, H.-J.; Coates, R. M. *J. Org. Chem.* **1992**, *57*, 3444−3449. (b) Prashad, M. *J. Med. Chem.* **1993**, *36*, 631−632.

(2) (a) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *47*, 5170−5180. (b) Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124−6134. (c) Martin, S. F.; Geraci, L. S. *Tetrahedron Lett.* **1988**, *29*, 6725−6728. (d) Martin, S. F.; Liao, Y.; Rein, T.; Wong, Y. *Tetrahedron Lett.* **1994**, *35*, 691−694.

(3) Martin, S. F.; Humphrey, J. H.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866−867.

(4) Anderson, J.; Dupau, P.; Siddons, D.; Smith, S.; Swarbrick, M. *Tetrahedron Lett.* **1998**, *39*, 2649−2650.

(5) Vankar, Y. D.; Kumaravel, G.; Rao, C. T. *Synth. Commun.* **1989**, *19*, 2181−2198.

(6) (a) de Castro Dantas, T. N.; Laval, J. P.; Lattes, A. *Tetrahedron* **1983**, *39*, 3337−3344. (b) DeShong, P.; Leginus, J. M.; Lander, S. W., Jr. *J. Org. Chem.* **1986**, *51*, 574−576. (c) Armstrong, S. K.; Warren, S.; Collington, E. W.; Naylor, A. *Tetrahedron Lett.* **1991**, *32*, 4171−4174. (d) Berry, M. B.; Craig, D.; Jones, P. S. *Synlett* **1993**, 513−514.

(7) (a) Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1004−1005. (b) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *106*, 5031−5033. (c) Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146−147. (d) Tanaka, H.; Inoue, K.; Pokorski, U.; Taniguchi, M.; Torii, S. *Tetrahedron Lett.* **1990**, *31*, 3023−3026. (e) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4−6. (f) Veenstra, S. J.; Schmid, P. *Tetrahedron Lett.* **1997**, *38*, 997−1000. (g) Loh, T.-P.; Ho, D. S.-C.; Xu, K.-C.; Sim, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 865−868. (h) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242−4243. (i) Meester, W. J. N.; Rutjes, F. P. J. T.; Hermkens, P. H. H.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 1601−1604.

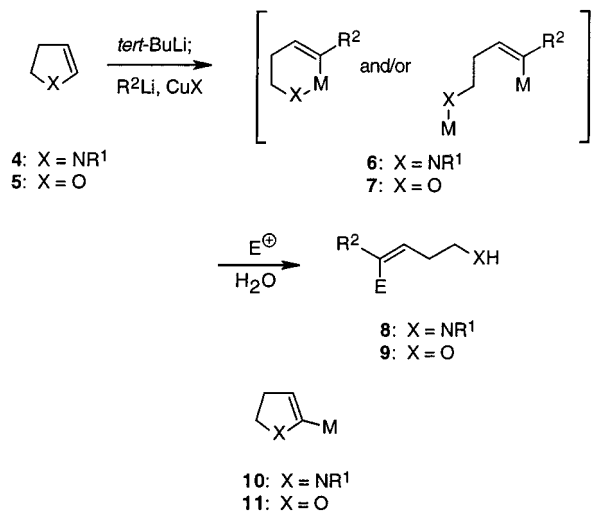
(8) Yu, M.; Zhang, Y.; Guo, H. *Synth. Commun.* **1997**, *27*, 1495−1500.

(9) For reviews on the synthesis of substituted olefins, see: (a) Faulkner, D. J. *Synthesis* **1971**, 175−189. (b) Reucroft, J.; Sammes, P. G. *Quart. Rev. Chem. Soc.* **1971**, *25*, 135−169.

(10) (a) Martin, S. F.; Daniel, D.; Cherney, R. J.; Liras, S. *J. Org. Chem.* **1992,** *57*, 2523−2525 (and references therein). (b) Quayle, P.; Wang, J.; Xu, Jie; Urch, C. J. *Tetrahedron Lett.* **1998**, *39*, 485−488. (c) Kawasaki, To.; Ichige, T.; Kitazume, T. *J. Org. Chem.* **1998**, *63*, 7525−7528. (d) Beller, M.; Riermeier, T. H. *Eur. J. Inorg. Chem.* **1998**, 29−35. (e) Cristau, H. J.; Taillefer, M. *Tetrahedron* **1998**, *54*, 1507−1522. (f) Breit, B.; Zahn, S. K. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 8, 969−971. (g) de Meijere, A.; Brase, S. *J. Organomet. Chem.* **1999**, *576*(1−2), 88−110.

10.1021/jo001386z CCC: $20.00
Published on Web 12/28/2000

Scheme 1

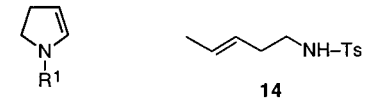


A search of the literature led us to consider the possibility that α-lithiation of a suitably protected pyrroline such as **4** followed by reaction with an organocuprate reagent would generate an intermediate of the general type **10** (M = CuR^2Li). We anticipated that **10** (M = CuR^2Li) would undergo a 1,2-metalate rearrangement to deliver a vinyl organometallic intermediate **6** that could be trapped in situ with an electrophile to furnish the homoallylic amine **8** (Scheme 1). This novel strategy was inspired by Fujisawa's intriguing discovery that ortho lithiation of 2,3-dihydrofuran (**5**) to give **11** (M = Li), followed by an organocuprate-induced 1,2-metalate rearrangement via an intermediate of the general form **7,** afforded disubstituted, (*E*)-homoallylic alcohols **9** (E = H).[11] This methodology was subsequently developed extensively by Kocienski, who found that the reaction could be applied to the stereoselective synthesis of homoallylic alcohols **9** with di- and trisubstituted olefins;[12] bis-homoallylic alcohols were also accessible by a variant of this protocol.

Despite the obvious appeal of a nitrogen variant of the Fujisawa−Kocienski reaction for the synthesis of homoallylic amines **8**, a survey of the literature revealed no precedent for the ring opening of an α-metalated dihydropyrrole **10** to give an intermediate such as **6**. On the contrary, a recent review by Braun suggests that α-nitrogen-substituted alkenyllithium compounds such as **10** (M = Li) exhibit exclusive carbanion-like activity,[13] not the electrophilic carbenoid behavior of the analogous oxygen-substituted alkenyllithiums **11** that is ostensibly necessary for the metalate rearrangement to form **6**. Inasmuch as the poor leaving group ability of R_2N-M is at least partly responsible for the noncarbenoid nature of α-lithiated amines,[14] it occurred to us that placement of more strongly electron-withdrawing groups on nitrogen might give metalated derivatives of **10** that would rearrange to give **6**, thereby leading to homoallylic amines **8**. Toward this end, we examined the candidacy of several *N*-substituted pyrrolines **4** as potential starting materials for the stereoselective synthesis of homoallylic amines and report herein the results of these studies.

Results and Discussion

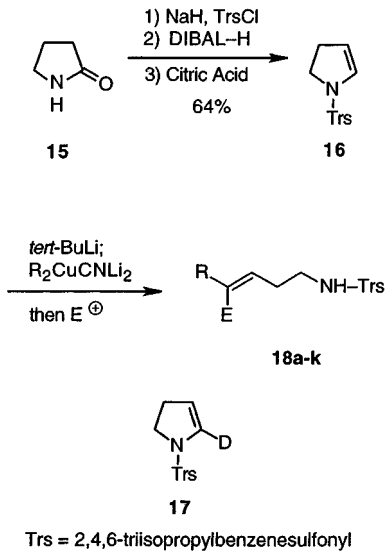
We initially examined whether the N-protected pyrrolines **12** and **13** could be used as substrates for the synthesis of protected homoallylic amines. The initial deprotonation of **12** seemed well precedented by the work of Beak and Meyers, who reported that *N*-Boc and *N*-formamidino piperidines and pyrrolidines undergo facile deprotonation with *t*-BuLi to give the corresponding α−amino carbanions.[15] However, we found in preliminary experiments that the *N*-substituted pyrroline **12** did not cleanly undergo α-metalation with *s*-BuLi or *t*-BuLi under several conditions, and a number of unidentified products were produced in these experiments. Although we found that the *N*-tosyl pyrroline **13** could be metalated, the reaction of the resulting α-lithio enesulfonamide with Me_3CuLi_2·LiBr followed by aqueous workup gave **14**, albeit in only about 10% yield. Because **14** was accompanied with a number of other unidentified products including unreacted **13**, we queried whether a modified sulfonamide derivative might provide superior results. In this context, it is relevant that 2,4,6-triisopropylbenzenesulfonyl (trisyl) hydrazones are superior to *p*-toluenesulfonyl hydrazones in the Shapiro olefin synthesis.[16]



12: R^1 = Boc
13: R^1 = Ts
14

In the event, the *N*-trisyl pyrroline **16** was first prepared in 64% yield and three steps from 2-pyrrolidinone (**15**) (Scheme 2). Metalation of **16** with *t*-BuLi at

Scheme 2



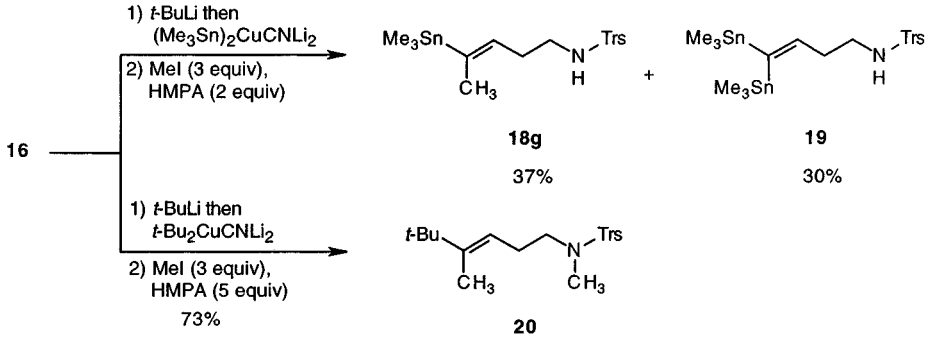
(11) Fujisawa, T.; Kurita, Y.; Kawashima, M.; Sato, T. *Chem. Lett.* **1982**, 1641−1642.
(12) (a) Kocienski, P.; Wadman, S.; Cooper, K. *J. Am. Chem. Soc.* **1989**, *111*, 2363−2365. (b) Kocienski, P.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933−1940.
(13) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 430−451.
(14) Boche, G.; Marsch, M.; Harback, J.; Harms, K.; Ledig, B.; Schubert, F.; Lohrenz, J.; Ahlbrecht, H. *Chem. Ber.* **1993**, *126*, 1887−1894.
(15) (a) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109−1117. (b) Meyers, A. I.; Edwards, P. D.; Bailey, T. R.; Jagdmann, G. E., Jr. *J. Org. Chem.* **1985**, *50*, 1019−1026.
(16) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147−154.

Table 1.

entry	cuprate	electrophile	product (**18**) R	product (**18**) E	% yield[a,b]
a	$Me_2CuCNLi_2$	H_2O	Me	H	71
b	$(CH_2{=}CH)_2CuCNLi_2$	H_2O	$H_2C{=}CH-$	H	66
c	$Ph_2CuCNLi_2$	H_2O	Ph	H	75
d	*n*-$Bu_2CuCNLi_2$	H_2O	*n*-Bu	H	77
e	*sec*-$Bu_2CuCNLi_2$	H_2O	*s*-Bu	H	68
f	*tert*-$Bu_2CuCNLi_2$	H_2O	*t*-Bu	H	93
g	$(Me)_3Sn_2CuCNLi_2$	MeI	Me_{3Sn}	Me	37
h	*tert*-$Bu_2CuCNLi_2$	MeI	*t*-Bu	Me	92
i	*tert*-$Bu_2CuCNLi_2$	allyl bromide	*t*-Bu	allyl	88
j	*tert*-$Bu_2CuCNLi_2$	I_2	*t*-Bu	I	92
k	*tert*-$Bu_2CuCNLi_2$	Me_3SnCl	*t*-Bu	Me_3Sn	80
l	$Me_2CuCNLi_2$	Me_3SnCl	Me	Me_3Sn	75

[a] Yields are based upon products isolated by column chromatography on silica gel. [b] Isomeric purity was established as >95:5 on the basis of ^1H NMR spectroscopy on a 300 MHz instrument.

Scheme 3



−78 °C in Et_2O proceeded cleanly as evidenced by a preliminary experiment in which the anion was quenched with CD_3OD to provide **17** with >95% deuterium incorporation. After some experimentation, we discovered that **16** could be converted to homoallylic amines **18a**−**k** in good overall yields and stereoselectivity by sequential metalation with *t*-BuLi (−78 °C), reaction with a higher order cyanocuprate ($R_2CuCNLi_2$) (0 °C → rt), followed by the addition of an electrophile, E^+ (see Table 1). The best results were obtained when a slight excess of $R_2CuCNLi_2$ was used; lower yields of homoallylic amines were obtained when a catalytic quantity (10%) of CuCN was employed. Those cuprates generated by treatment of $CuBr{\cdot}SMe_2$ with 3 equiv of RLi could also be used successfully, but the yields of homoallylic amine were not reproducible. In several control experiments, we found that simply treating lithiated **16** with another organolithium reagent in the absence of CuCN failed to yield any homoallylic amine; lithiation of **16** prior to treatment with a cuprate was necessary for the reaction to proceed. The ring-opening reaction did not occur when THF was used as the solvent, and the reaction proceeded slowly and incompletely when Et_2O/THF mixtures were used. The observation of this solvent effect is consistent with observations of Fujisawa who screened diethyl ether, dimethoxyethane, THF, and dioxane as solvents for the transformation **5** → **9** and found that using diethyl ether led to higher yields of ring-opened products.[11] THF presumably inhibits metal-assisted ionization of the intermediate vinyl organometallic agents **10** and **11** to give the putative electrophilic carbenoid that then undergoes 1,2-metalate rearrangement.[17] In this context, it may also be relevant that such carbenoids are more stable in THF than in diethyl ether.[18]

Examination of the results summarized in Table 1 reveals that with the exception of entry g, the yields of stereochemically pure homoallylic amines are normally in the range of 70−90%. With respect to entry g there are several observations that are noteworthy: When a solution of Me_3SnLi that was prepared in THF was used, none of the homoallylic amine **18g** (R = Me_3Sn, E = Me) was obtained upon quenching with MeI. This is perhaps not surprising, because the presence of THF had already been shown to impede the metalate rearrangement. Consequently, it was necessary to prepare Me_3SnLi from $(Me_3Sn)_2$ in Et_2O.[19] Because the distannylated product **19** was isolated in 30% yield in addition to the desired product **18g** (Scheme 3), it is conceivable that the formation of Me_3SnLi, which is normally generated in THF,[20] was incomplete in Et_2O, and that the $(Me_3Sn)_2$ remaining may have reacted with some of the vinyl organometallic intermediate to produce **19** as a byproduct. No effort was made to optimize this reaction as the primary purpose for preparing **18g** was for NOE studies.

The number of equivalents of the electrophile (other than H_2O) that was used to react with the intermediate vinyl anion (Table 1, entries g−l) also deserves comment. In general, we found that optimal yields were obtained

(17) (a) Duraisamy, M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1984**, *106*, 5035−5037. (b) Topolski, M.; Duraisamy, M.; Rachon, J.; Gawronski, J.; Gawronska, K.; Goedken, V.; Walborsky, H. M. *J. Org. Chem.* **1993**, *58*, 546−555.

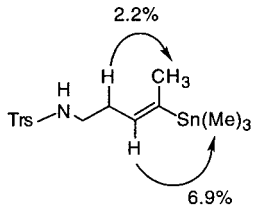
(18) (a) Köbrich, G.; Akhtar, A.; Ansari, F.; Breckoff, W. E.; Büttner, H.; Drischel, W.; Fischer, R. H.; Flory, K.; Fröhlich, H.; Goyert, W.; Heinemann, H.; Hornke, I.; Merkle, H. R.; Trapp, H.; Zündorf, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 41−52. (b) Boche, G.; Marsch, M.; Müller, A.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1032−1033.

(19) The Me_3SnLi used to prepared **11f** was made according to the procedure in ref 18b, except diethyl ether was used as a solvent.

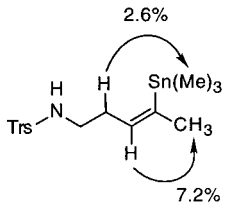
(20) (a) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4836−4838. (b) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481−1486. (c) Kitching, W.; Olszowy, H. A.; Drew, G. M. *Organometallics* **1982**, *1*, 1244−1246. (d) Reimann, W.; Kuivila, H. G.; Farah, D.; Apoussidis, T. *Organometallics* **1987**, *6*, 557−565.

when 3 equiv of electrophile and 2 equiv of HMPA were used, as when lesser quantities were employed, the desired product was obtained in reduced yields. However, use of a larger excess of electrophile and/or HMPA led to the formation of C-, N-dialkylated products as illustrated by the formation of **20** (Scheme 3). Of course, it is recognized that, in some situations, it may be desirable to alkylate the nitrogen (vide infra).

The stereochemistry assigned to the homoallylic sulfonamides was supported by NOE studies performed with **18g** and **18l**. Specifically, irradiation of the allylic methylene group in **18g** gave a small enhancement to the vinyl methyl group and none to the trimethylstannyl group, whereas irradiation of the vinyl hydrogen significantly enhanced the signal from the trimethylstannyl group and none to the vinyl methyl group. Similarly, irradiation of the allylic methylene group in **18l** gave a small enhancement to the trimethylstannyl group and none to the vinyl methyl group, whereas irradiation of the vinyl hydrogen significantly enhanced the signal from the vinyl methyl group and none to the trimethylstannyl group.

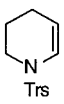


15g

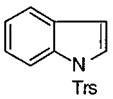


15l

Inasmuch as 2-lithiated 3,4-dihydro-2*H*-pyran and benzofuran were known to undergo 1,2-metalate rearrangements of the general type shown in Scheme 1,[12,21] we were intrigued by the possibility that the analogous trisyl-protected 1,2,3,4-tetrahydro-pyridine **21** and indole **22** might also undergo metalation with *tert*-BuLi followed by ring opening upon treatment with higher order cyanocuprates. However, while **21** and **22** each underwent clean α-deprotonation, reaction of the intermediate α−lithio enamides with *tert*-$Bu_2CuCNLi_2$ did not furnish the expected ring opened products under the usual reaction conditions, and multiple products were obtained when the reactions were conducted at higher temperatures. The increased stability of α-metalated **21** relative to **10** is consistent with Kocienski's observation that the α-cuprate derived from dihydropyran is more stable than that of dihydrofuran.[12] We did not subject the cuprates derived from **21** and **22** to extensive scrutiny, so it remains possible that they might be induced to undergo ring opening reactions under specifically defined conditions.[22]

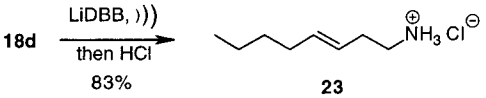


21



22

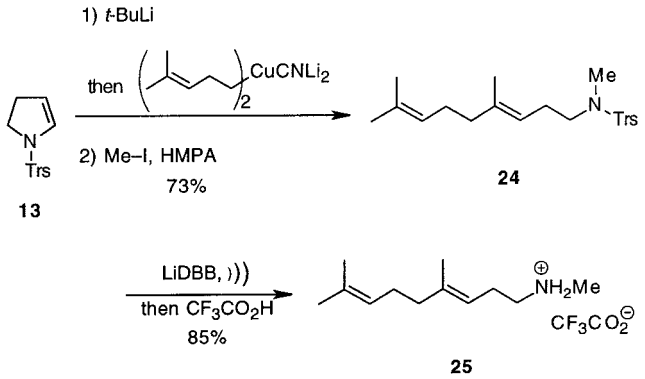
Having established the efficacy of this novel approach to protected homoallylic amines, the task of removing the *N*-trisyl group remained. Sulfonamide deprotections are traditionally performed under dissolving metal conditions,[23] and there are also several recent reports which address this issue.[24,25] We have found that sonication of **18d** with lithium wire (10 equiv) and catalytic 4,4′-di-*tert*-butylbiphenyl (DBB) in anhydrous THF at room temperature led to the rapid removal of the trisyl group, and the desired homoallylic amine **23** was readily isolated in good yield as its HCl salt.



23

The practical utility of this methodology for the synthesis of homoallylic amines is illustrated by the preparation of the homoallylic diene amine **25**, which is a precursor of the squalene synthetase inhibitor **1**. Thus, reaction of the α-lithio derivative of **16** with the cuprate derived from 5-lithio-2-methyl-2-pentene and CuCN gave an intermediate ring-opened vinyl cuprate reagent that was methylated with excess methyl iodide and HMPA to give **24** in 73% yield. Deprotection of **24** by the action of lithium wire and catalytic DBB then furnished **25** in 85% yield. Because of the convergent nature of this approach to **25**, it should be possible to rapidly prepare a variety of squalene synthetase inhibitors related to **1** simply by varying the cuprate and the electrophile (Scheme 4).

Scheme 4



13 **24** **25**

Conclusion

We have invented and developed a convergent and stereoselective route to homoallylic sulfonamides based upon a 1,2-metalate rearrangement. Owing to the availability of a variety of organocuprates and the versatility offered by the ability to prepare vinyl stannanes and iodides, it is now possible to rapidly assemble protected homoallylic amines having a broad range of substitution

(21) Nguyen, T.; Negishi, E. *Tetrahedron Lett.* **1991**, *32*, 5903−5906.

(22) 1,2-Metalate rearrangements of various cyclic enol ethers must be executed under specifically defined reaction conditions. See: Ashworth, P.; Broadbelt, B.; Jankowski, P.; Kocienski, P.; Pimm, A.; Bell, R. *Synthesis* **1995**, 199−206.

(23) (a) Kovacs, J.; Ghatak, U. R. *J. Org. Chem.* **1966**, *31*, 119−121. (b) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311−5312. (c) D'Souza, L.; Day, R. A. *Science* **1968**, *160*, 882−883. (d) Cottrell, P. T.; Mann, C. K. *J. Am. Chem. Soc.* **1971**, *93*, 3579−3583. (e) Gold, E. H.; Babad, E. *J. Org. Chem.* **1972**, *37*, 2208−2210. (f) Quaal, K. S.; Ji, S.; Kim, Y. M.; Closson, W. D.; Zubieta, J. A. *J. Org. Chem.* **1978**, *43*, 1311−1316. (g) Art, J. F.; Kestemont J. P.; Soumillion, J. Ph. *Tetrahedron Lett.* **1991**, *32*, 1425−1428. (h) Fleming, I.; Frackenpohl, J.; Ila, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1229−1235. (i) Dalko, P. I.; Brun, V.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 8979−8982.

(24) Sabitha, G.; Reddy, B. V. S.; Abraham, S.; Yadav, J. S. *Tetrahedron Lett.* **1999**, *40*, 1569−1570.

(25) Nyasse, B.; Grehn, L.; Ragnarsson, U. *Chem. Commun.* **1997**, 1017−1018.

patterns from a common intermediate. As such this methodology could find application in combinatorial synthesis. The removal of the trisyl group may be readily achieved under mild conditions to give the parent homoallylic amines. The practical utility of this method has been illustrated by the facile synthesis of **25**, a key intermediate in the synthesis of a known inhibitor of squalene synthetase. Applications of this methodology to the synthesis of a diverse array of homoallylic amines by combinatorial and related tactics are the subjects of current investigations, the results of which will be reported in due course.

Experimental Section

General Methods. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from potassium/benzophenone ketyl, and diethyl ether (Et_2O) was distilled from sodium/benzophenone ketyl immediately prior to use. HMPA was distilled from CaH_2 and stored under argon in a flame dried round-bottom flask. Flash chromatography was conducted according to the Still protocol[26] using ICN Biomedicals ICN-SILITech 32−63d silica gel with the indicated solvents. Melting points are uncorrected. All NMR spectra were taken on a 300 MHz instrument in deuterated chloroform ($CDCl_3$) unless otherwise indicated; ^{13}C spectra were taken at 75 MHz. Chemical shifts (δ) are expressed as ppm relative to tetramethylsilane ($\delta = 0.00$ ppm) referenced to the residual protic solvent. Splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; hep, heptet; m, multiplet; comp, complex multiplet; br, broad; app, apparent. High-resolution mass spectra were taken on VG Analytical ZAB2-E instrument. IR spectra were recorded as films on sodium chloride plates on a Perkin-Elmer 1600 series FTIR.

***N*-2′,4′,6′-Triisopropylbenzenesulfonyl-2-pyrrolidinone (15).** A mixture of a 60% dispersion of NaH in mineral oil (1.98 g, 24.0 mmol) and 2-pyrrolidinone (2.5 mL, 32.9 mmol) in THF/Et_2O (350 mL, 2.5:1) was stirred for 2 h under argon at 0 °C (bath temperature). 2,4,6-Triisopropylbenzenesulfonyl chloride (1.24 g, 4.11 mmol) was then added in one portion, and the reaction was stirred at 0 °C for 2 h and then at room temperature for 4 h. Water (200 mL) and saturated NaCl (50 mL) were slowly added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated NaCl (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Hexanes (300 mL) were added to the residue, and this resulting mixture was stored at room temperature overnight. The resulting white precipitate was collected by filtration and washed with hexanes (20 mL). The filtrate was concentrated under reduced pressure, and hexane (100 mL) was added. The resulting second crop of white precipitate was filtered and triturated with hexanes (5 mL). The combined precipitates were dried under vacuum to give 11.1 g (96%) of *N*-2′,4′,6′-triisopropylbenzenesulfonyl-2-pyrrolidinone as a white solid: mp 111−112 °C; ^1H NMR δ 7.15 (s, 2 H), 4.06 (hep, J = 6.8 Hz, 2 H), 3.93 (t, J = 6.9 Hz, 2 H), 2.88 (hep, J = 6.9 Hz, 1 H), 2.45 (t, J = 8.0, 2 H), 2.11 (app p, J = 7.6 Hz, 2 H), 1.21−1.26 (comp, 18 H); ^{13}C NMR δ 173.6, 153.9, 151.6, 131.3, 123.9, 46.1, 34.2, 32.2, 29.3, 24.5, 23.5, 18.7; IR ($CHCl_3$) 1732 cm^{-1}; mass spectrum (CI) m/z 352.1942 [$C_{19}H_{29}NO_3S$ (M + 1) requires 352.1946], 352 (base), 310, 244, 203.

***N*-2′,4′,6′-Triisopropylbenzenesulfonyl-2-pyrrolidinol.** A solution of 1 M DIBAL-H in CH_2Cl_2 (24 mL, 24 mmol) was added dropwise with stirring over 30 min to a solution of *N*-2′,4′,6′-triisopropylbenzenesulfonyl-2-pyrrolidinone (4.2 g, 12 mmol) in THF (100 mL) at 0 °C (bath temperature) under argon. Stirring was continued for 10 min, whereupon saturated aqueous NH_4Cl (25 mL) was added dropwise. The ice bath was removed, and the resulting white slurry was stirred for 1.5 h. This slurry was filtered through a plug of cotton, and the precipitate was rinsed with EtOAc (4 × 5 mL). The filtrate was concentrated under reduced pressure, and the resulting white solid was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to give 3.13 g (74%) of *N*-2′,4′,6′-triisopropylbenzenesulfonyl-2-pyrrolidinol as a white solid: mp 95−97 °C; ^1H NMR δ 7.15 (s, 2 H), 5.53−5.55 (m, 1 H), 4.19 (hep, J = 6.7 Hz, 2 H), 3.46−3.52 (m, 1 H), 3.13−3.22 (m, 1 H), 3.01−3.07 (br s, 1 H), 2.88 (hep, J = 6.9 Hz, 1 H), 1.81−2.19 (comp, 4 H), 1.23−1.26 (comp, 18 H); ^{13}C NMR δ 153.2, 151.1, 131.6, 123.9, 83.1, 46.2, 34.1, 34.06, 29.3, 24.8, 23.5, 22.6; IR ($CHCl_3$) 3448, 2962, 2930, 2870, 1600 cm^{-1}; mass spectrum (CI) m/z 354.2103 [$C_{19}H_{31}NO_3S$ (M + 1) requires 354.2103], 354, 336 (base), 267.

***N*-2′,4′,6′-Triisopropylbenzenesulfonyl-2-pyrroline (16).** A mixture of citric acid monohydrate (460 mg, 2.2 mmol) and *N*-2′,4′,6′-triisopropylbenzenesulfonyl-2-pyrrolidinol (3.13 g, 8.9 mmol) in toluene (30 mL) was heated under reflux with constant removal of H_2O (Dean Stark) for 3 h, whereupon saturated $NaHCO_3$ (30 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with saturated NaCl (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting white solid was purified by flash chromatography eluting with hexanes/EtOAc (9:1) to give 2.7 g (90%) of **16** as a white solid: mp 76−78 °C; ^1H NMR (CD_3OD) δ 7.27 (s, 2 H), 6.36−6.38 (m, 1 H), 5.18−5.21 (m 1 H), 4.16 (hep, J = 6.8 Hz, 2 H), 3.52 (t, J = 9.1 Hz, 2 H), 2.93 (hep, J = 7.1 Hz, 1 H), 2.59−2.67 (m, 2 H), 1.22−1.28 (comp, 18 H); ^{13}C NMR (CD_3OD) δ 155.0, 152.7, 131.8, 130.5, 125.2, 110.3, 47.5, 35.4, 30.7, 25.1, 24.0; IR ($CHCl_3$) 3019, 2963, 2930, 1600 cm^{-1}; mass spectrum (CI) m/z 336.1989 [$C_{19}H_{29}NO_2S$ (M + 1) requires 336.1997], 336 (base), 294.

General Procedure for Converting 16 to Homoallylic Sulfonamides 18a−l. A solution of RLi (3.6 mmol; 1.5 M MeLi in Et_2O; 0.4 M CH_2=CHLi in Et_2O/pentane;[27] 1.4 M PhLi in cyclohexane/Et_2O; 1.2 M *n*-BuLi in hexanes; 1.1 M *sec*-BuLi in cyclohexane; 1.3 M *t*-BuLi in pentane) was added dropwise to a slurry of CuCN (160 mg, 1.8 mmol) in dry, degassed (freeze/pump/thaw, 3×) Et_2O (5 mL) at −78 °C under argon. The resulting slurry was then stirred at 0 °C, whereupon it became homogeneous. Into a separate flask containing a slurry of **16** (0.5 g, 1.5 mmol) in dry, degassed (freeze/pump/thaw, 3×) Et_2O (2.5 mL) at −78 °C (bath temp) under argon was added a solution of 1.3 M *t*-BuLi in pentane (1.2 mL, 1.5 mmol). The resulting yellow slurry of lithiated **16** was stirred at −78 °C and then at 0 °C for an additional 20 min. To this solution of **16** was added $R_2CuCNLi_2$ in one portion via cannula. The reaction mixture was then stirred at room temperature until the ring opening was complete as judged by TLC. (The time depended upon the cuprate as follows: *tert*-butyl, *sec*-butyl, and trimethylstannyl cuprate required 1 h; butyl cuprate required 3 h; methyl and phenyl cuprate required 6 h; vinyl cuprate required 12 h). The resulting mixture was then either subjected directly to an aqueous work up to give **18a−f** (procedure A) or treated with a suitable electrophile prior to aqueous work up to give **18g−l** (procedure B).

Procedure A. The reaction mixture was then cooled to 0 °C (bath temperature), and a solution of saturated NH_4Cl/NH_4OH (10 mL, 9:1) was added in one portion. The resulting gray/pale blue mixture was transferred to a separatory funnel, and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure at 35 °C. The crude product was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (9:1) to give the homoallylic sulfonamides **18a−f**.

Procedure B. The reaction mixture was cooled to −78 °C (bath temperature), and the appropriate electrophile (3 equiv) was added in one portion; HMPA (0.52 mL, 3 mmol) was then added. The cooling bath was removed, and the resulting

(26) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(27) Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609−5617.

suspension was stirred at room temperature until the reaction was complete as judged by TLC. (Typical reaction times varied with the electrophile as follows: MeI, 2 h; allyl bromide, 30 min; I_2, 30 min; Me_3SnCl, 30 min.) The reaction was then subjected to an aqueous workup as described in procedure A to give the homoallylic sulfonamides **18g**−**l**.

***N*-2′,4′,6′-Triisopropylbenzenesulfonyl-3(*E*)-pentenamine (18a):** mp 49−51 °C; ^{1}H NMR δ 7.14 (s, 2 H), 5.43−5.52 (m, 1 H), 5.18−5.28 (m, 1 H), 4.32 (br t, J = 5.9 Hz, 1 H), 4.12 (hep, J = 6.6 Hz, 2 H), 2.83−2.99 (comp, 3 H), 2.17 (dt, J = 6.6, 6.6 Hz, 2 H), 1.56−1.65 (m, 3 H), 1.21−1.28 (comp, 18 H); ^{13}C NMR δ 152.6, 150.2, 132.1, 129.2, 126.8, 123.7, 42.0, 34.1, 32.4, 29.6, 24.8, 23.6, 17.9; IR ($CHCl_3$) 3023, 2962, 2871 cm^{-1}; mass spectrum (CI) m/z 352.2315 [$C_{20}H_{33}NSO_2$ (M + 1) requires 352.2310], 352 (base), 336, 283, 254.

***N*-2′,4′,6′-Triisopropylbenzenesulfonyl-3(*E*)-3,5-hexadienamine (18b):** mp 83−85 °C; ^{1}H NMR δ 7.14 (s, 2 H), 6.22 (dt, J = 16.7, 10.1 Hz, 1 H), 6.06 (dd, J = 15.0, 10.1 Hz, 1 H), 5.49 (dt, J = 15.0, 6.8 Hz, 1 H), 5.11 (d, J = 16.7 Hz, 1 H), 5.01 (d, J = 10.1 Hz, 1 H), 4.30 (br t, J = 6.8 Hz, 1 H), 4.12 (hep, J = 6.7 Hz, 2 H), 3.02 (app q, J = 6.8 Hz, 2 H), 2.88 (hep, J = 7 Hz, 1 H), 2.29 (app q, J = 6.8 Hz, 2 H), 1.23−1.25 (comp, 18 H); ^{13}C NMR δ 152.7, 150.2, 136.3, 134.2, 132.1, 129.8, 123.8, 116.8, 41.9, 34.1, 32.5, 29.6, 24.8, 23.6; IR ($CHCl_3$) 3327, 2961, 2929, 2870, 1150 cm^{-1}; mass spectrum (CI) m/z 364.2307 [$C_{20}H_{33}NSO_2$ (M + 1) requires 364.2310], 364 (base), 296.

***N*-2′,4′,6′-Triisopropylbenzenesulfonyl-4-phenyl-3(*E*)-butenamine (18c):** mp 134−136 °C; ^{1}H NMR δ 7.20−7.28 (comp, 5 H), 7.14 (s, 2 H), 6.41 (d, J = 15.7 Hz, 1 H), 6.03 (dt, J = 15.7, 6.6 Hz, 1 H), 4.43 (br t, J = 6.6 Hz, 1 H), 4.14 (hep, J = 6.8 Hz, 2 H), 3.10 (app q, J = 6.6 Hz, 2 H), 2.89 (hep, J = 6.9 Hz, 1 H), 2.43 (app q, J = 6.6 Hz, 2 H), 1.22−1.25 (comp, 18 H); ^{13}C NMR δ 152.7, 150.3, 136.7, 133.3, 132.2, 128.6, 127.5, 126.1, 125.6, 123.8, 42.1, 34.1, 33.1, 29.7, 29.6, 24.8, 23.6; IR ($CHCl_3$) 3019, 2964, 1213 cm^{-1}; mass spectrum (CI) m/z 414.2466 [$C_{25}H_{35}NO_2S$ (M + 1) requires 414.2467], 414 (base), 372.

***N*-2′,4′,6′-Triisopropylbenzenesulfonyl-3(*E*)-octenamine (18d):** mp 54−55 °C; ^{1}H NMR δ 7.14 (s, 2 H), 5.48 (dt, J = 15.3, 6.7 Hz, 1 H), 5.21 (dt, J = 15.3, 6.7 Hz, 1 H), 4.31 (br t, J = 6.7 Hz, 1 H), 4.13 (hep, J = 6.8 Hz, 2 H), 2.83−3.00 (comp, 3 H), 2.18 (app q, J = 6.7 Hz, 2 H), 1.95 (app q, J = 6.7 Hz, 2 H), 1.22−1.30 (comp, 22 H), 0.86 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 152.6, 150.3, 134.8, 132.1, 125.4, 123.7, 42.1, 34.1, 32.5, 32.2, 31.4, 29.6, 24.8, 23.6, 22.2, 13.9; IR ($CHCl_3$) 3019, 2962, 1213 cm^{-1}; mass spectrum (CI) m/z 394.2775 [$C_{23}H_{39}NO_2S$ (M + 1) requires 394.2780], 394 (base), 338.

(±)-*N*-2′,4′,6′-Triisopropylbenzenesulfonyl-5-methyl-3(*E*)-heptenamine (18e): mp 76−78 °C; ^{1}H NMR δ 7.14 (s, 2 H), 5.37 (dd, J = 15.4, 6.8 Hz, 1 H), 5.18 (dt, J = 15.4, 6.8 Hz, 1 H), 4.30 (br t, J = 6.8 Hz, 1 H), 4.13 (hep, J = 6.7 Hz, 2 H), 2.83−3.00 (comp, 3 H), 2.18 (app q, J = 6.8 Hz, 2 H), 1.94 (app hep, J = 6.8 Hz, 1 H), 1.22−1.26 (comp, 20 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.80 (t, J = 7.4 Hz, 2 H); ^{13}C NMR δ 152.6, 150.3, 140.5, 132.2, 123.8, 123.7, 42.2, 38.3, 34.1, 32.6, 29.6, 29.6, 24.9, 23.6, 20.0, 11.7; IR ($CHCl_3$) 3019, 2965, 1213 cm^{-1}; mass spectrum (CI) m/z 394.2782 [$C_{23}H_{39}NO_2S$ (M + 1) requires 394.2780], 394 (base), 283, 267.

***N*-2′,4′,6′-Triisopropylbenzenesulfonyl-5,5-dimethyl-3(*E*)-hexenamine (18f):** mp 133−134 °C; ^{1}H NMR δ 7.14 (s, 2 H), 5.52 (dt, J = 15.7, 1.0 Hz, 1 H), 5.14 (dt, J = 15.7, 6.5 Hz, 1 H), 4.29 (t, J = 6.5 Hz, 1 H), 4.13 (hep, J = 6.8 Hz, 2 H), 2.83−3.00 (comp, 3 H), 2.18 (dddd, J = 6.5, 6.5, 6.5, 1.0 Hz, 2 H), 1.22−1.25 (comp, 18 H), 0.94 (s, 9 H); ^{13}C NMR δ 152.6, 150.2, 145.6, 132.2, 123.7, 120.0, 42.3, 34.1, 33.0, 32.7, 29.58, 29.55, 24.9, 23.6; IR ($CHCl_3$) 3018, 2965, 1211 cm^{-1}; mass spectrum (CI) m/z 394.2788 [$C_{23}H_{39}NO_2S$ (M + 1) requires 394.2780], 394 (base), 352, 296.

***N*-2′,4′,6′-Triisopropylbenzenesulfonyl-4-trimethylstannyl-3(*E*)-pentenamine (18g):** mp 83−86 °C; ^{1}H NMR δ 7.14 (s, 2 H), 5.38−5.41 (m, 1 H), 4.26−4.30 (m, 1 H), 4.09−4.18 (m, 2 H), 3.00 (app q, J = 6.6 Hz, 3 H), 2.88 (hep, J = 7 Hz, 1 H), 2.32 (app q, J = 6.6 Hz, 2 H), 1.69−1.86 (m, 3 H), 1.22−1.25 (comp, 18 H), −0.032−0.19 (m, 9 H); ^{13}C NMR δ 152.7, 150.3, 143.3, 134.9, 132.1, 123.8, 42.2, 34.1, 29.6, 28.2, 24.9, 23.5, 18.5, −10.2; IR ($CHCl_3$) 2018, 2961, 2869, 1462, 1321 cm^{-1}; mass spectrum (CI) m/z 516.1950 [$C_{23}H_{41}NO_2SSn$ (M + 1) requires 516.1958], 516 (base), 500, 352.

***N*-2′,4′,6′-Triisopropylbenzenesulfonyl-4,5,5-trimethyl-3(*E*)-hexenamine (18h):** mp 100−102 °C; ^{1}H NMR δ 7.14 (s, 2 H), 5.03 (br t, J = 7.1 Hz, 1 H), 4.34 (br s, 1 H) 4.15 (hep, J = 6.7 Hz, 2 H), 2.83−2.97 (comp, 3 H), 2.19 (app q, J = 7.1 Hz, 2 H), 1.55 (s, 3 H), 1.17−1.26 (comp, 18 H), 0.97 (s, 9 H); ^{13}C NMR δ 152.6, 150.2, 147.2, 132.2, 123.7, 116.1, 42.6, 36.2, 34.1, 29.6, 28.9, 28.4, 24.9, 23.6, 12.9; IR ($CHCl_3$) 3019, 2963, 1221 cm^{-1}; mass spectrum (CI) m/z 408.2930 [$C_{24}H_{41}NO_2S$ (M + 1) requires 408.2936], 408 (base), 296, 267, 205.

4-*tert*-Butyl-*N*-2′,4′,6′-triisoproprylbenzenesulfonyl-3(*E*),6-heptadienamine (18i): mp 81−83 °C; ^{1}H NMR δ 7.14 (s, 2 H), 5.71−5.58 (m, 1 H), 5.16 (t, J = 6.9 Hz, 1 H), 4.85−4.92 (m, 2 H), 4.34 (br t, J = 6.7 Hz, 1 H), 4.15 (hep, J = 6.7 Hz, 2 H), 2.83−3.01 (comp, 3 H), 2.77 (dt, J = 5.9, 1.6 Hz, 2 H), 2.17 (app q, J = 6.7 Hz, 2 H), 1.18−1.26 (comp, 18 H), 0.97 (s, 9 H); ^{13}C NMR δ 152.6, 150.2, 148.0, 137.0, 132.2, 123.7, 119.0, 114.8, 42.6, 36.7, 34.1, 32.1, 29.6, 29.1, 28.4, 24.9, 23.6; IR ($CHCl_3$) 3019, 2965, 1213, 1151 cm^{-1}, mass spectrum (CI) m/z 434.3084 [$C_{26}H_{43}NO_2S$ (M + 1) requires 434.3093], 434 (base), 269, 205, 186.

4-Iodo-*N*-2′,4′,6′-triisopropylbenzenesulfonyl-5,5-dimethyl-3(*Z*)-hexenamine (18j): mp 106−108 °C; ^{1}H NMR δ 7.15 (s, 2 H), 5.45 (t, J = 6.7 Hz, 1 H), 4.44 (br t, J = 6.3 Hz, 1 H), 4.15 (hep, J = 6.7 Hz, 2 H), 3.05 (q, J = 6.7 Hz, 2 H), 2.88 (hep, J = 6.9 Hz, 1 H), 2.34 (q, J = 6.7 Hz, 2 H), 1.14−1.27 (comp, 18 H), 1.11 (s, 9 H); ^{13}C NMR δ 152.7, 150.2, 132.2, 129.9, 126.9, 123.8, 41.4, 40.5, 37.7, 34.1, 30.5, 29.6, 24.9, 23.6; IR ($CHCl_3$) 3019, 2968, 1425 cm^{-1}; mass spectrum (CI) m/z 520.1741 [$C_{23}H_{38}INO_2S$ (M + 1) requires 520.1746], 520 (base), 462, 394.

***N*-2′,4′,6′-Triisopropylbenzenesulfonyl-5,5-dimethyl-4-trimethylstannyl-3(*Z*)-hexenamine (18k):** mp 103−104 °C; ^{1}H NMR δ 7.14 (s, 2H), 5.76 (t, J = 7.1 Hz, 1 H), 4.25−4.37 (m, 1 H), 4.15 (hep, J = 6.7 Hz, 2 H), 2.99 (app q, J = 6.8 Hz, 2 H), 2.88 (hep, J = 7 Hz, 1 H), 2.19−2.28 (m, 2 H), 1.22−1.26 (comp, 18 H), 0.98 (s, 9 H), 0.25−0.07 (m, 9 H); ^{13}C NMR δ 160.0, 152.6, 150.2, 132.1, 129.7, 123.8, 42.8, 38.7, 34.1, 33.8, 30.4, 29.6, 24.9, 23.6, −5.2; IR ($CHCl_3$) 3018, 2965, 1522 cm^{-1}; mass spectrum (CI) m/z 558.2429 [$C_{26}H_{48}NO_2SSn$ (M + 1) requires 558.2428], 556 (base), 542, 394. **(*Z*)-*N*-2′,4′,6′-Triisopropylbenzenesulfonyl-4-trimethylstannyl-3-pentenamine (18l).** mp 84−86 °C; ^{1}H NMR δ 7.14 (s, 2 H), 5.76−5.84 (m, 2 H), 4.29 (br t, J = 6.2 Hz, 1 H), 4.12 (hep, J = 6.8 Hz, 2 H), 2.80−3.02 (comp, 3 H), 2.15−2.26 (m, 2 H), 1.76−1.92 (m, 3 H), 1.22−1.25 (comp, 18 H), 0.035−0.22 (m, 9 H); ^{13}C NMR δ 152.6, 150.3, 143.7, 135.7, 131.9, 123.7, 42.5, 34.1, 34.0, 29.6, 26.5, 24.9, 23.6, −8.8; IR ($CHCl_3$) 3018, 1522, 1424, 1211 cm^{-1}; mass spectrum (CI) m/z 516.1966 [$C_{23}H_{41}NO_2SSn$ (M + 1) requires 516.1958], 516 (base), 514, 500, 394, 352.

3(*E*)-Octenamine Hydrochloride (23). Li (0) wire (∼45 mg, 6.5 mmol) that had been freshly cut into several small pieces was added to a solution of 4,4′-di-*tert*-butylbiphenyl (34 mg, 0.13 mmol) and **18d** (500 mg, 1.3 mmol) in THF (12 mL) under argon at room temperature. The reaction flask was placed in a sonication bath and sonicated for 20 min. The excess Li metal was removed, and EtOH (0.5 mL) was added. The mixture was concentrated under vacuum, and the residue was dissolved in 10% aqueous HCl (5 mL). The aqueous solution was extracted with Et_2O (2 × 2 mL). A 3 M solution of NaOH saturated with NaCl (5 mL) was carefully added to the aqueous layer, and the resulting mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and acidified with 4 M HCl in dioxane (1 mL). This solution was then concentrated under vacuum, and the solid residue was dried overnight under high vacuum to give 173 mg (83%) of **23**: ^{1}H NMR δ 5.53−5.63 (m, 1 H), 5.26−5.36 (m, 1H), 2.98 (br s, 2 H), 2.40−2.45 (m, 2 H), 1.95−2.02 (m, 2 H), 1.20−1.35 (comp, 4 H), 0.85 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 135.3, 123.5, 39.8, 32.2, 31.3, 30.6, 22.2, 13.9; IR ($CHCl_3$) 3409, 3048, 2974, 1606 cm^{-1}; mass spectrum (CI) m/z 128.1438 [$C_8H_{17}N$ (M + 1) requires 128.1439], 128 (base).

***N*-2′,4′,6′-Triisopropylbenzenesulfonyl-*N*,4,9-trimethyl-3(*E*),7-nonadienamine (24).** Li(0) wire (90 mg, 13 mmol) was cut up into several small pieces and added to a solution of 5-bromo-2-methyl-2-pentene (0.48 mL, 3.6 mmol) in dry, degassed (freeze/pump/thaw, 3×) Et_2O (4 mL) under argon at 0 °C. This mixture was stirred (using a glass coated stirring bar) for 1 h at 0 °C. A solution of 1.4 M *t*-BuLi in pentane (0.91 mL, 1.3 mmoL) was added to a separate flask containing a solution of **16** (430 mg, 1.3 mmol) in dry, degassed (freeze/pump/thaw, 3×) Et_2O (2 mL) at −78 °C under argon. The resulting yellow slurry was stirred at −78 °C for 30 min and then at 0 °C for 20 min. The solution of 5-lithio-2-methyl-2-pentene was then added in one portion via cannula to a slurry of CuCN (140 mg, 1.5 mmol) in dry, degassed (freeze/pump/thaw, 3×) Et_2O (4 mL) at −78 °C under argon. The organocuprate was then stirred at 0 °C for 20 min. The cuprate (a green solution) was then added in one portion via cannula to the slurry of lithiated **16** at 0 °C. The reaction was then stirred at room temperature for 3 h. The reaction was cooled to −78 °C, whereupon HMPA (2.2 mL, 13 mmol) and MeI (0.46 mL, 7.7 mmol) were added. The resulting slurry was stirred for 1 h at room temperature. A solution of saturated NH_4Cl/NH_4OH (10 mL, 9:1) was added and the mixture transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. The crude was then purified by flash chromatography eluting with hexanes/EtOAc (9:1) to give 420 mg (73%) of **21** as a white solid: mp 46−48 °C; ^{1}H NMR δ 7.13 (s, 2 H), 4.98−5.07 (comp, 2 H), 4.15 (hep, J = 6.8 Hz, 2 H), 3.08−3.13 (m, 2 H), 2.87 (hep, J = 6.9 Hz, 1 H), 2.73 (s, 3 H), 2.26 (app q, J = 7.7 Hz, 2 H), 1.92−2.03 (comp, 4 H), 1.64 (s, 3 H), 1.56 (s, 3 H), 1.54 (s, 3 H), 1.21−1.24 (comp, 18 H); ^{13}C NMR δ 152.9, 151.4, 137.8, 131.5, 130.9, 124.1, 123.8, 120.0, 48.1, 39.6, 34.1, 33.2, 29.2, 26.5, 26.3, 25.6, 24.8, 23.6, 17.7, 16.0; IR ($CHCl_3$) 3019, 2962, 2928, 1215, 1149 cm^{-1}; mass spectrum (CI) *m*/*z* 448.3244 [$C_{27}H_{43}NO_2S$ (M + 1) requires 448.3249], 448 (base), 310.

***N*,4,9-Trimethyl-3(*E*),7-nonadienamine Trifluoroacetate (25).** Li(0) wire (∼20 mg, 2.9 mmol) that had been freshly cut into several small pieces was added to a solution of DBB (3 mg, 0.011 mmol) and **18d** (50 mg, 0.11 mmol) in THF (1 mL) under argon at room temperature. The reaction flask was placed in a sonication bath and sonicated for 10 min. The excess Li metal was removed, and 1 M HCl (0.5 mL) and Et_2O (1 mL) were added. The layers were separated, and the organic layer was extracted with 1 M HCl (3 × 0.5 mL). The aqueous layers were combined, and 6 M NaOH (0.5 mL) was added. This mixture was then saturated with NaCl and extracted with Et_2O (5 × 1 mL). The organic layers were combined, dried (Na_2SO_4), and acidified with trifluoroacetic acid (0.5 mL). This solution was then concentrated under vacuum, and the oily residue was dried overnight under high vacuum to give 28 mg (85%) of **25**: ^{1}H NMR δ 9.30 (br s, 2H), 4.98−5.06 (br m, 2 H), 2.82−2.96 (br m, 2 H), 2.65 (br s, 3 H), 2.34−2.46 (br m, 2 H), 1.94−2.03 (comp, 4 H), 1.64 (s, 3 H), 1.58 (s, 3 H), 1.56 (s, 3 H); ^{13}C NMR δ 140.2, 131.7, 123.8, 117.3, 49.0, 39.5, 32.8, 26.4, 25.6, 24.7, 17.6, 15.9; IR ($CHCl_3$) 3563, 3015, 2974, 1678, 1431, 1214 cm^{-1} mass spectrum (CI) *m*/*z* 296.1833 [$C_{14}H_{24}FNO_2$ (M + 1) requires 296.1837], 296, 182 (base), 115.

Acknowledgment. We thank the National Institutes of Health (GM 25439), the Robert A. Welch Foundation, Pfizer, Inc., and Merck Research Laboratories for their generous support of this research.

Supporting Information Available: Copies of ^{1}H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001386Z