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Synthesis of *N*,*N*-Bis(3-butenyl)amines from 2-Azaallyl Dication Synthetic Equivalents and Conversion to 2,3,6,7-Tetrahydroazepines by Ring-Closing Metathesis

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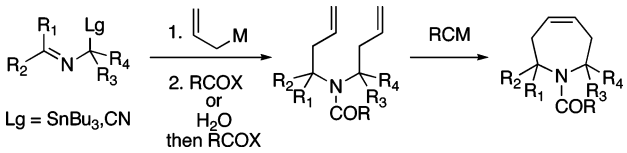
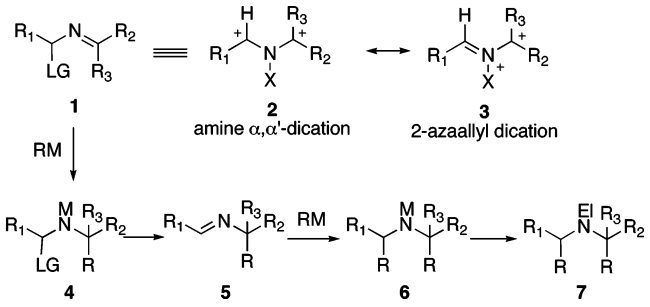


N,*N*-Bis(3-butenyl)amines can be prepared by the double allylation of either (2-azaallyl)stannanes or (2-azaallyl)nitriles, both of which thereby act as synthetic equivalents to amine α,α′-dications (2-azaallyl dications). Allylmagnesium bromide is the reagent of choice for the double allylation of both substrates, although allyllithium also effects the double allylation of (2-azaallyl)nitriles. Ring-closing metathesis can be performed on the *N*-protected amines, or with in situ protonation, on the free amines to provide 2,3,6,7-tetrahydroazepines. (2-Azaallyl)nitriles can also be monoallylated to provide *N*-(3-butenyl)-aminonitriles, whereas the double allylation of (2-azaallyl)stannanes cannot be stopped at monoallylation. (2-Azaallyl)silanes undergo monoallylation to give *N*-(3-butenyl)aminosilanes but do not undergo double allylation.

Introduction

The addition of nucleophiles to imines as an important route to amines has been investigated in depth, largly due to the synthetic utility of the products in forming amino acids and heterocycles and in syntheses of natural products.[1] These reactions differ in a number of ways from the analogous reactions of aldehydes and ketones, not the least of which is the presence of an additional substituent on the heteroatom. We surmised that by the inclusion of a leaving group adjacent to the imino nitrogen that we may be able to take advantage of the intermediate anion in a subsequent cascade of reactions. In this manner, a double addition reaction can be envisioned in which a nucleophile initially adds to the imine **1**, generating adduct **4** (Scheme 1). Upon elimination of the leaving group, **4** can give rise to intermediate imine **5**, a suitable substrate for further nucleophilic addition, resulting in adduct **6** and ultimately in the double addition product **7**. As an extension of our long-standing interest in the chemistry of organostannanes, we began an exploration of synthetic equivalents of amine α,α′-dications **2**, which could also be named 2-azaallyl dications from the alternative resonance form **3** (vide infra).

SCHEME 1



Our interest in this area was sparked by the unexpected result summarized in Scheme 2.[2] Previously, we have shown that (2-azaallyl)stannane **8** is a precursor of the 2-azaallyllithium **9**, which undergoes [3 + 2] cycloadditions with alkenes to produce pyrrolidines.[2,3] Attempted cycloaddition of stannane **8** with

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(1) Selected reviews: (a) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 1, pp 355−396. (b) Kleinman, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 2, pp 975−1006. (c) Enders, D.; Reinhold: U. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1895. (d) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (e) Steinig, A. G.; Spero, D. M. *Org. Prep. Proc. Int.* **2000**, *32*, 205.

(2) Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, *4*, 1329.

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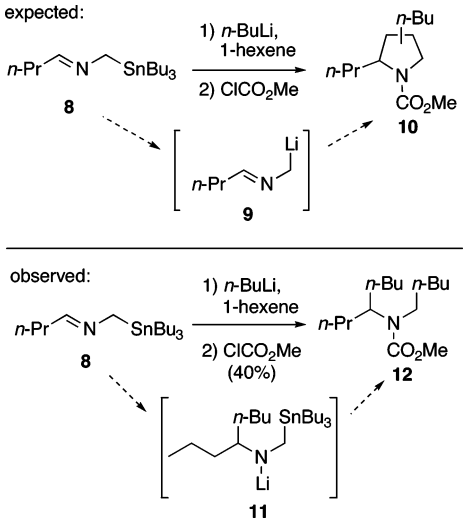
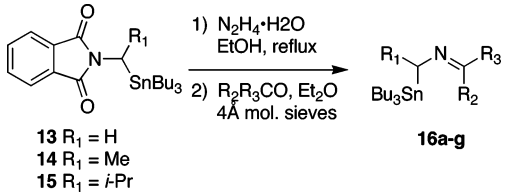
SCHEME 2



1-hexene, however, yielded the double addition product **12** in 40% yield (80% based on *n*-butyllithium as the limiting reagent), and none of the expected pyrrolidine **10**. As transmetalation is known to be slower in noncoordinating solvents such as 1-hexene,[4] addition of *n*-butyllithium to the imine in this case is competitive with transmetalation, leading to adduct **11**, which ultimately gives rise to the observed product **12** after trapping with methyl chloroformate.

In an earlier communication,[5] we reported our initial results of the double allylation reaction of a variety of (2-azaallyl)-stannanes with allylmagnesium bromide; however, we were also interested in examining other synthetic equivalents of 2-azaallyl dications. Katritzky and co-workers have also reported a variation of this double allylation methodology using a benzotriazole group as the leaving group.[6] In the presence of organometallic reagents, α-aminonitriles have been shown to undergo elimination of cyanide to generate intermediate imines, followed by nucleophilic addition to yield substituted amines.[7] Thus, we decided to explore the reactivity of (2-azaallyl)nitriles toward double nucleophilic addition since α-aminonitriles would be generated from the initial addition and could undergo the established elimination/addition chemistry to ultimately provide bisaddition products. Previously, (2-azaallyl)nitriles have been used as precursors of 2-azaallyllithiums and azomethine ylides for [3 + 2] cycloadditions and alkylation reactions.[8] In this paper, we report the reactivity of (2-azaallyl)nitriles toward double nucleophilic addition and report in full the double allylation reactions of (2-azaallyl)stannanes. We also report the conversion of the *N*,*N*-bis(3-butenyl)amines obtained as products from the double allylation reactions to 2,3,6,7-tetrahydroazepines through ring-closing metathesis.

TABLE 1. Preparation of (2-Azaallyl)Stannanes 16a−g[5]



phthalimide	R^1	R^2	R^3	product	% yield[a]
13	H	H	*i*-Pr	**16a**	89
13	H	Me	Me	**16b**	84
13	H	−(CH$_2$)$_5$−		**16c**	88
14	Me	H	*i*-Pr	**16d**	85
14	Me	H	Me	**16e**	82
14	Me	−(CH$_2$)$_5$−		**16f**	85
15	*i*-Pr	H	*i*-Pr	**16g**	67

[a] Yield of pure, Kügelrohr-distilled material.

Results and Discussion

For our initial studies, a variety of (2-azaallyl)stannanes **16** were prepared as shown in Table 1, where hydrazinolysis of the phthalimides **13**−**15**[5,9] was followed by condensation of the resultant α-aminostannanes with aldehydes and ketones. Kügelrohr distillation provided pure samples of the stannanes **16**.[5,10]

Combination of the (2-azaallyl)stannanes **16** with 2.2 equiv of allylmagnesium bromide in THF produced the bisallylated materials **17** after quenching with various electrophiles (Table 2). In many cases, direct quenching of the *N*-magnesio intermediates with chloroformates was possible, leading to the carbamates **17b**, **17c**, **17e**, and **17j** (entries 2, 3, 5, and 10). However, for the derivatization of sterically hindered amines, it was found that quenching the reaction with water followed by a separate acylation step was superior. This procedure worked well for *N*-formylation (entries 7 and 9) and for the formation of carbamate **17*l***, although the yield of **17*l*** was only modest in comparison to the yield of the free amine **17k** (entries 11 and 12). The free amine **17m** was found to be too hindered to undergo acylation at all. Entries 8−10 and 13 involve allylations that produce mixtures of diastereomers in modest (5.3:1 in entry 13) to low (entry 10) diastereoselectivity.

The double addition reactions of (2-azaallyl)stannanes were attempted with other organometallics. Reaction of stannane **16a** with *n*-butyllithium in either hexane or toluene resulted mainly in tin−lithium exchange, while *n*-hexylmagnesium bromide, allylzinc bromide, and allyltributylstannane (with or without a Lewis acid)[11] reacted sluggishly.

We briefly examined the viability of a double addition reaction with (2-azaallyl)silane **19**, prepared by condensation of isobutyraldehyde with amine **18** (Scheme 3). Upon reaction

(3) For a review, see: Pearson, W. H.; Stoy, P. *Synlett* **2003**, 903.

(4) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.

(5) Pearson, W. H.; Aponick, A. *Org. Lett.* **2001**, *3*, 1327.

(6) Katritzky, A. R.; Nair, S. K.; Silina, A. *J. Org. Chem.* **2002**, *67*, 7530.

(7) (a) Böshagen, H.; Geiger, W.; Junge, B. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 806. (b) Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 1635.

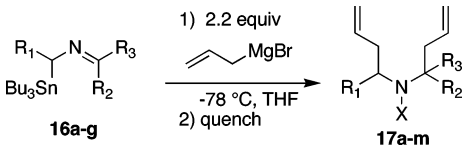
(8) (a) Tsuge, O.; Ueno, K.; Kanemasa, S.; Yorozu, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1809. (b) Tsuge, O.; Ueno, K.; Kanemasa, S.; Yorozu, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3347. (c) Tsuge, O.; Kanemasa, S.; Yorozu, K.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3359. (d) Opio, J. O.; Labidalle, H. G.; Miocque, M. *Synth. Commun.* **1991**, *21*, 1743. (e) Gaucher, A.; Ollivier, J.; Marguerite, J.; Paugam, R.; Salaün, J. *Can. J. Chem.* **1994**, *72*, 1312. (f) Gaucher, A.; Dorizon, P.; Ollivier, J.; Salaün, J. *Tetrahedron Lett.* **1995**, *36*, 2979. (g) Perosa, A.; Selva, M.; Tundo, P. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2485. (h) De Kimpe, N.; Sulmon, P.; Stevens, C. *Tetrahedron* **1991**, *47*, 4726.

(9) (a) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1992**, *57*, 6354. (b) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220. (c) Pearson, W. H.; Clark, R. B. *Tetrahedron Lett.* **1999**, *40*, 4467.

(10) All are new compounds with the exception of imine **16a**, which was previously prepared in lower yield by a more difficult method,[2] and **16d**, which had been made[9c] but not isolated prior to the current work. We have also previously reported the preparation of **16g**.[9a]

(11) (a) Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 147. (b) Wang, D.-K.; Dai, L.-X.; Hou, X.-L. *Tetrahedron Lett.* **1995**, *36*, 8649.

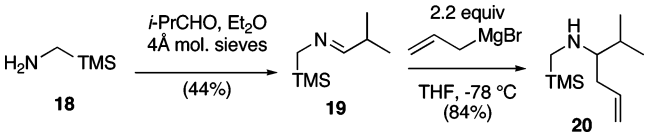
TABLE 2. Double Allylation of (2-Azaallyl)Stannanes 16a−g



entry	imine	quench	X	R^1	R^2	R^3	product	% yield[a]
1	**16a**	H_2O	H	H	H	*i*-Pr	**17a**	78[b]
2	**16a**	$ClCO_2Ph$	CO_2Ph	H	H	*i*-Pr	**17b**	80
3	**16a**	$ClCO_2Bn$	CO_2Bn	H	H	*i*-Pr	**17c**	81
4	**16b**	H_2O	H	H	Me	Me	**17d**	75[b]
5	**16b**	$ClCO_2Bn$	CO_2Bn	H	Me	Me	**17e**	47
6	**16c**	H_2O	H	H	$-(CH_2)_5-$		**17f**	48[b]
8	**16d**	H_2O	H	Me	H	*i*-Pr	**17h**	52[b]
9	**16d**	HCO_2Ac[c]	CHO	Me	H	*i*-Pr	**17i**	72[d]
10	**16e**	$ClCO_2Me$	CO_2Me	Me	H	Me	**17j**	72[e]
11	**16f**	H_2O	H	Me	$-(CH_2)_5-$		**17k**	91
12	**16f**	$ClCO_2Me$[c]	CO_2Me	Me	$-(CH_2)_5-$		**17l**	47
13	**16g**	H_2O	H	*i*-Pr	H	*i*-Pr	**17m**	67[f,g]

[a] Yield of chromatographically purified material unless otherwise noted. [b] Acid−base extraction gave pure material that was not purified further. [c] Quenched first with water. [d] Ratio of (*R**,*R**):(*R**,*S**) diastereomers = 2.5:1. The relative configuration was assigned after ring-closing metathesis and reduction of the formyl group to a methyl (see Table 7). [e] Ratio of diastereomers = 1.3:1. The relative configurations were not assigned. [f] Ratio of diastereomers = 5.3:1. The relative configurations were not assigned. [g] Reaction temperature was −20 °C.

SCHEME 3

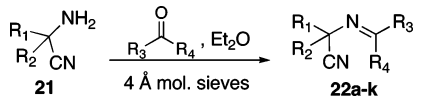


of **19** with allylmagnesium bromide in THF at −78 °C only monoallylated product **20** was obtained. While only monoallylation was possible with the silane, even in the presence of excess reagent, subjection of the corresponding stannane **16a** to 1 molar equiv of allylmagnesium bromide led to a mixture of the starting stannane and the double allylation product without a trace of the monoallylation product, as observed by GC/MS. The reactivity of (2-azaallyl)silanes with allylmagnesium bromide thus appears to differ drastically from the reactivity of (2-azaallyl)stannanes due to the differing leaving group abilities of the tributyltin anion versus the trimethylsilyl anion.

Next we set out to explore the reactivity of (2-azaallyl)nitriles **22**, which were readily available by condensation of the modified Strecker adducts **21**[8h,12] with aldehydes or ketones (Table 3). In contrast to the stannane chemistry, we were able to prepare tetrasubstituted (2-azaallyl)nitriles (cf. **22k**) as the addition of HCN to ketimines is a facile process. Condensation of the Strecker adduct with a ketone, however, did require more forcing conditions (Me_3Al activation[13]) than the aldimines. Preparation of an analogous tetrasubstituted (2-azaallyl)stannane has not yet been achieved.

With a good source of (2-azaallyl)nitriles established, the nitrile **22f** was chosen as the initial system and subjected to double allylation with allylmagnesium bromide under various conditions (Table 4). Surprisingly, in this reaction, use of the typical ethereal solvents resulted in low yields of the desired

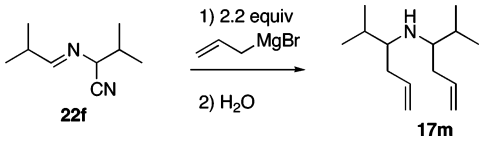
TABLE 3. Preparation of (2-Azaallyl)nitriles



entry	R^1	R^2	R^3	R^4	product	% yield[a]
1	H	H	*i*-Pr	H	**22a**	80
2	Me	H	Me	H	**22b**	64
3	Me	H	*i*-Pr	H	**22c**	52
4	*i*-Pr	H	Me	H	**22d**	81
5	*i*-Pr	H	*c*-Pr	H	**22e**	92
6	*i*-Pr	H	*i*-Pr	H	**22f**	86
7	Me	Me	Me	H	**22g**	80[b]
8	Me	Me	*i*-Pr	H	**22h**	54
9	$-(CH_2)_5-$		Me	H	**22i**	89
10	$-(CH_2)_5-$		*i*-Pr	H	**22j**	85
11	$-(CH_2)_5-$		Me	Me	**22k**	75[c]

[a] Yield of pure, Kügelrohr-distilled material unless otherwise noted. [b] Crude material was of sufficient purity without Kügelrohr distillation. [c] Alternate reaction conditions: Me_3Al premixed with aminonitrile in toluene, then acetone added with stirring for 4 h at room temperature.

TABLE 4. Optimization of Double Allylation Reaction



entry	solvent	temp (°C)	time	% yield	dr[a]
1	THF	0	30 min	20	2.9:1
2	Et_2O	0	5 min	46	1:2.0
3	$PhCH_3$	rt	2 d	35	1:1.8
4	CH_2Cl_2	0	30 min	58	1:3.2
5	CH_2Cl_2	−78	4 h	67	≥25:1[b]
6	CH_2Cl_2[c]	−78 → rt	8 h	67	1:1.5

[a] The relative configurations were not assigned. [b] Minor diastereomer not detected by ^1H NMR. [c] Et_2O was removed from allylmagnesium bromide prior to reaction.

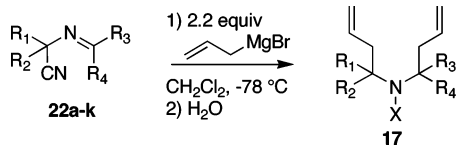
bisallylation product **17m** (entries 1 and 2). The use of nonethereal solvents such as dichloromethane and toluene has been reported to increase the yields of various Grignard reactions.[14] While the use of toluene failed to improve the yield (entry 3), a significant yield increase was observed when the noncoordinating solvent dichloromethane was employed (entry 4). In fact, the highest yield and best diastereoselectivity was obtained with dichloromethane at −78 °C (entry 5). When the Et_2O was removed from the allylmagnesium bromide in vacuo, then replaced with dichloromethane as the sole solvent, the reaction required warming to room temperature and a longer reaction time to go to completion (entry 6). This change did not detract from the yield, but higher reaction temperature adversely affected the diastereoselectivity of the reaction. While there is clearly a significant solvent effect (entries 1−3) on the diastereoselectivity as well as on the yield, we are unable to offer a rationale for this effect as we could not assign the relative

(12) For methods of preparation of the modified Strecker adducts see: (a) Paventi, M.; Edward, J. T. *Can. J. Chem.* **1987**, *65*, 282.

(13) Eisch, J. J.; Sanchez, R. *J. Org. Chem.* **1986**, *51*, 1848.

(14) (a) Tamai, Y.; Hattori, T.; Date, M.; Koike, S.; Kamikubo, Y.; Akiyama, M.; Seino, K.; Takayama, H.; Oyama, T.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1685. (b) Shawe, T. T.; Hansen, D.; Peet, K. A.; Prokopowicz, A. S.; Robinson, P. M.; Cannon, A.; Dougherty, K. E.; Ross, A. A.; Landino, L. M. *Tetrahedron* **1997**, *53*, 1547. (c) Xu, L.; Trudell, M. L. *J. Heterocycl. Chem.* **1996**, *33*, 2037. (d) Meyers, A. I.; Shawe, T. T.; Gottlieb, L. *Tetrahedron Lett.* **1992**, *33*, 867. (e) Ohno, M.; Shimizu, K.; Ishizaki, K.; Sasaki, T.; Eguchi, S. *J. Org. Chem.* **1988**, *53*, 729.

TABLE 5. Double Allylation of (2-Azaallyl)nitriles 22a−k



entry	imine	X	R^1	R^2	R^3	R^4	product	% yield[a](dr)
1	**22a**	H	H	H	*i*-Pr	H	**17a**	80[b,c]
2	**22b**	CO_2Me[d]	Me	H	Me	H	**17j**	65 (1.7:1)[e]
3	**22c**	CHO[f]	Me	H	*i*-Pr	H	**17i**	49 (1:1.5)[c,g]
4	**22d**	CHO[f]	*i*-Pr	H	Me	H	**17i**	66 (2.9:1)[g]
5	**22e**	H	*i*-Pr	H	*c*-Pr	H	**17n**	57 (1.7:1)[h]
6	**22f**	H	*i*-Pr	H	*i*-Pr	H	**17m**	67[i]
7	**22g**	H	Me	Me	Me	H	**17o**	74[b]
8	**22h**	H	Me	Me	*i*-Pr	H	**17p**	53[c]
9	**22i**	H	$-(CH_2)_5-$		Me	H	**17k**	73
10	**22j**	H	$-(CH_2)_5-$		*i*-Pr	H	**17q**	52[c]
11	**22k**	H	$-(CH_2)_5-$		Me	Me	**17r**	48[c]

[a] Yield of chromatographically purified material unless otherwise noted. [b] Acid−base extraction gave pure material that was not purified further. [c] Alternate conditions employed: Et_2O removed from allylmagnesium bromide and reaction slowly warmed from −78 °C to room temperature. [d] Reaction quenched with $ClCO_2Me$. [e] Relative configurations not assigned. [f] Separate formylation step with HCO_2Ac. [g] Ratio of (*R**,*S**):(*R**,*R**) diastereomers. The relative configuration was assigned after ring-closing metathesis and reduction of the formyl group to a methyl (see Table 7). [h] Ratio of (*R**,*S**):(*R**,*R**) diastereomers. The relative configuration was assigned after ring-closing metathesis (see Table 8). [i] Single diastereomer by ^1H NMR.

configurations of the diastereomers.[1,15] Of important note, however, is that the sole diastereomer obtained in the optimized reaction of (2-azaallyl)nitrile **22f** (entry 5) was obtained as the major diastereomer in the double allylation of (2-azaallyl)-stannane **16g** (Table 2, entry 13).

Upon subjection of (2-azaallyl)nitriles **22** to the optimized reaction conditions, moderate to good yields of bisallylated products **17** were obtained for some of the substrates (Table 5). However, for imines **22c**, **22h**, **22j**, and **22k**, only trace amounts of the desired products were obtained under the standard conditions. Fortunately, the reaction yields for these substrates could be greatly improved by employing alternative conditions in which the ether was completely removed from the allylmagnesium bromide prior to the reaction. With regard to selectivity, the diastereoselectivities obtained in the reactions of imines **22b−e** were markedly lower than the diastereoselectivity observed in the initially examined reaction of imine **22f** (entries 2−5 vs entry 6) likely due to the reduced steric demand present in these substrates. In the formation of **17j** (entry 2), the major diastereomer obtained was the same as that in the double allylation of (2-azaallyl)stannane **16e** (entry 10, Table 2).

We next examined the addition of other Grignard reagents. No double addition products could be detected from reaction of the imines **22** with vinylmagnesium bromide, benzylmagnesium chloride, or ethylmagnesium bromide; however, reaction with allenylmagnesium bromide produced small amounts of an inseparable mixture of propargylated and allenylated double addition products. Other organometallics were also screened.

SCHEME 4

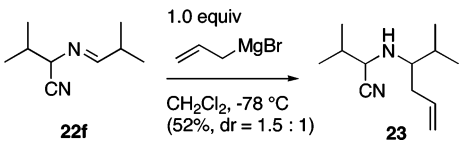
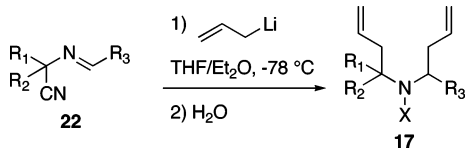


TABLE 6. Double Allylation with Allyllithium



entry	imine	X	R^1	R^2	R^3	product	% yield
1	**22f**	H	*i*-Pr	H	*i*-Pr	**17m**	69[a]
2	**22d**	CHO	*i*-Pr	H	Me	**17i**	55[b]
3	**22a**	H	H	H	*i*-Pr	**17a**	51
4	**22g**	H	Me	Me	Me	**17o**	42
5	**22i**	H	$-(CH_2)_5-$		Me	**17k**	33
6	**22b**	CO_2Me	Me	H	Me	**17j**	trace

[a] Ratio of diastereomers = 25:1. The relative configurations were not assigned. [b] Ratio of (*R**,*S**):(*R**,*R**) diastereomers = 2.6:1. The relative configuration was assigned after ring-closing metathesis and reduction of the formyl group to a methyl (see Table 7).

Reaction with allyltributylstannane in the presence of a Lewis acid ($TiCl_4$ or TMSCN) produced the monoallylated aminonitrile (**23**, Scheme 4) in low yield (∼20%), but no conditions could be found to improve the yield.[11] *B*-Allyl-9-BBN failed to undergo either the double or mono-addition reaction with (2-azaallyl)nitriles.[16] Allyllithium[17] added to (2-azaallyl)nitrile **22f** in high yield and high diastereoselectivity to give the same major diastereomer as in the reaction with allylmagnesium bromide, but this initial result was not readily extended to other (2-azaallyl)nitriles (Table 6). While the yields in entries 2−5 are moderate, they are significantly lower than the yields obtained with allylmagnesium bromide, and the reaction with **22b** (entry 6) shows that the double allylation with allyllithium is more limited in scope than that with the Grignard reaction. After these investigations, it was determined that the double addition reaction of (2-azaallyl)nitriles is limited to double allylation, which is best accomplished with allylmagnesium bromide.

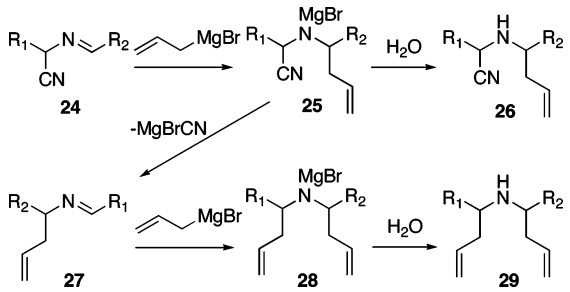
In contrast to the allylation of (2-azaallyl)stannanes, in which the formation of an intermediate monoaddition product could not be observed during the reactions, using both GC/MS and TLC to monitor reaction progress, the formation of a long-lived intermediate during the double allylation reactions of (2-azaallyl)nitriles with allylmagnesium bromide was observed. By quenching the reaction of imine **22f** before conversion was complete, this intermediate was isolated and subsequently identified as aminonitrile **23**. We found that **23** could be prepared efficiently by subjecting **22f** with a single equivalent of allylmagnesium bromide in the complete absence of Et_2O (Scheme 4).

Several mechanisms can be invoked to explain the double allylation reaction of (2-azaallyl)nitriles. On the basis of the mechanistic insights detailed below, we propose the reaction mechanism depicted in Scheme 5, in which the initial step is

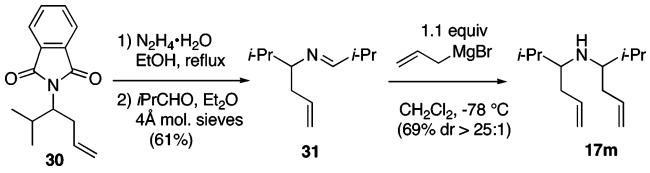
(15) For a recent review of diastereoselectivity in addition to imines bearing stereogenic *N*-substituents, see: (a) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651. For recent references in this area see: (b) Ghosh, S. N.; Singh, N.; Nanda, G. K.; Venugopalan, P.; Bharatam, P. V.; Trehan, S. *Chem. Commun.* **2003**, 1420. (c) Alexakis, A.; Gille, S.; Prian, F.; Rosset, S.; Ditrich, K. *Tetrahedron Lett.* **2004**, *45*, 1449.

(16) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9.
(17) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161.

SCHEME 5



SCHEME 6



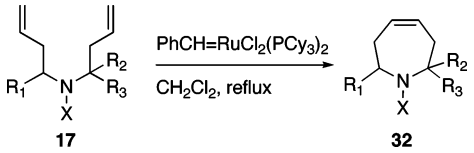
nucleophilic addition of allylmagnesium bromide to imine **24** to generate *N*-magnesio aminonitrile **25**. Quenching with water at this point yields the aminonitrile **26**, while cyanide elimination provides the intermediate imine **27**, which can undergo a second nucleophilic attack by allylmagnesium bromide to provide the *N*-magnesio intermediate **28** and the bisallylated product **29** upon aqueous quench.

As mentioned above, the amine **23**, which is derived by protonation of **25**, had been isolated. In an effort to further elucidate the mechanism, we hoped to establish whether the imines **27** could form the double addition products **29**. The proposed intermediate **31** was prepared from phthalimide **30** and subjected to the standard reaction conditions (Scheme 6). The reaction proceeded to give **17m** with nearly the same yield and diastereoselectivity observed in the double allylation of the corresponding (2-azaallyl)nitrile, making it reasonable to propose the formation of **27** by elimination of cyanide from **25** during the double allylation reaction.

Grignard reagents can react by either a polar mechanism or a single electron-transfer mechanism.[18] To evaluate the possibility that radical intermediates were involved in the double allylation reaction, we prepared the cyclopropylimine **22e** and subjected it to the standard reaction conditions (entry 5, Table 5). If radical intermediates were formed, we expected to observe rapid ring opening of the cyclopropane ring. Instead, the amine **17n** resulting from simple double allylation was isolated with the cyclopropyl ring intact and no ring-opened product could be detected. This result suggests that the mechanism of the reaction involves nucleophilic attack to generate anionic, not radical, intermediates.

The double allylation products obtained from the reactions of both (2-azaallyl)nitriles and (2-azaallyl)stannanes were found to be well suited substrates for ring-closing metathesis reactions.[19] Recently, there has been tremendous interest in the use of ring-closing metathesis for the construction of nitrogen heterocycles.[20,21] In our initial communication,[5] we reported the results summarized in Table 7, in which the dienes **17** were converted in an efficient manner to 2,3,6,7-tetrahydroazepines **32**.

TABLE 7. Tetrahydroazepines via Ring-Closing Metathesis



entry	diene	X	R^1	R^2	R^3	product	% yield[a]
1	**17b**	CO_2Ph	H	*i*-Pr	H	**32a**	98
2	**17c**	CO_2Bn	H	*i*-Pr	H	**32b**	87
3	**17e**	CO_2Bn	H	Me	Me	**32c**	65
4	**17g**	CHO	H	$-(CH_2)_5-$		**32d**	95
5	**17i**[b]	CHO	Me	*i*-Pr	H	**32e**	75[b]
6	**17j**[c]	CO_2Me	Me	Me	H	**32f**	96[c]
7	**17*l***	CO_2Me	Me	$-(CH_2)_5-$		**32g**	89

[a] All yields are of purified material. [b] Ratio of (*R**,*R**):(*R**,*S**) diastereomers = 2.5:1. The relative configurations were assigned after reduction of **32e** with $LiAlH_4$ and analysis of the *N*-methyl derivatives by ^1H NMR/NOE spectroscopy. [c] Ratio of diastereomers = 1.3:1. The relative configurations were not assigned.

Since the more hindered amines were resistant to acylation, we needed to find conditions to perform the ring-closing metathesis (RCM) without first acylating the amine. Olefin metathesis, however, is known to be incompatible with free amines due to catalyst inhibition by the basic nitrogen, although the ammonium salts have been shown to undergo metathesis.[22] Furthermore, there have been reports of ring-closing metathesis of secondary and tertiary free amines protonated in situ to form six-membered heterocycles,[23a−c] as well as a report of RCM of a tertiary free amine to form a seven-membered ring under acidic

(18) (a) *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996. (b) Hoffmann, R. W. *Chem. Soc. Rev.* **2003**, *32*, 225 and references therein.

(19) Recent reviews: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (d) *Alkene Metathesis in Organic Synthesis*; Fürstner, A., Ed.; Springer-Verlag: Heidelberg, Germany, 1998. (e) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141. (f) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (g) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519. (h) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.

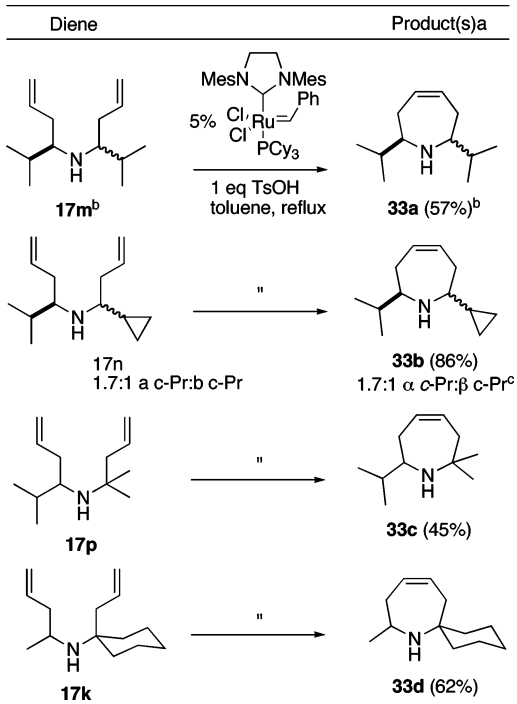
(20) Recent reviews focusing on ring-closing metathesis of nitrogen-containing compounds: (a) Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693.

(21) Dixneuf and co-workers have reported related methodology, where *N*-Cbz imines were combined with allylmagnesium bromide or 3-butenylmagnesium bromide followed by *N*-allylation to afford 4-aza-1,7-octadienes or 4-aza-1,8-nonadienes, respectively, which were subjected to RCM to afford 1,2,5,6-tetrahydropiperidines or 2,5,6,7-tetrahydroazepines, isomers of the tetrahydroazepines reported herein. See: (a) Osipov, S. N.; Artyushin, O. I.; Kolomiets, A. F.; Bruneau, C.; Dixneuf, P. H. *Synlett* **2000**, 1031. For other imine allylation/RCM work, see: (b) Kumareswaran, R.; Balasubramanian, T.; Hassner, A. *Tetrahedron Lett.* **2000**, *41*, 8157. (c) Felpin, F.-X.; Lebreton, J. *Tetrahedron Lett.* **2003**, *44*, 527. For iminium ion allylation/RCM to produce tetrahydropiperidines and 2,3,6,7-tetrahydroazepines, see: (d) Barrett, A. G. M.; Ahmed, M.; Baker, S. P.; Baugh, S. P. D.; Braddock, D. C.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 3716. (e) Chevallier, F.; Beaudet, I.; Le Grognec, E.; Toupet, L.; Quintard, J.-P. *Tetrahedron Lett.* **2004**, *45*, 761. For RCMs of *N*,*N*-bis(3-butenyl)amine derivatives to 2,3,6,7-tetrahydroazepines, see the following: (f) Paquette, L. A.; Leit, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 8126. (g) Pernerstorfer, J.; Schuster, M.; Blechert, S. *Synthesis* **1999**, 138. (h) Schürer, S. C.; Gessler, S.; Buschman, N.; Blechert, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3898. For another RCM approach to tetrahydroazepines, see: (i) Vo-Thanh, G.; Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Synlett*, **2001**, 37.

(22) Fu, G. C.; Nguyen, S. B. T.; Grubbs, R. B. *J. Am. Chem. Soc.* **1993**, *115*, 9856.

(23) (a) Wright, D.; Schulte, J.; Page, M. *Org. Lett.* **2000**, *2*, 1847. (b) Edwards, A. S.; Wybrow, R. A. J.; Johnstone, C.; Adams, H.; Harrity, J. P. A. *Chem. Commun.* **2002**, 1542. (c) Verhelst, S. H. L.; Martinez, B. P.; Timmer, M. S. M.; Lodder, G.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Org. Chem.* **2003**, *68*, 9598. (d) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848.

TABLE 8. Ring-Closing Metathesis of Free Amines



[a] All yields are of purified material. [b] Minor diastereomer not detected by ^{1}H NMR. [c] Diastereomers assigned by ^{1}H NMR/NOE experiments.

conditions.[23d] We were delighted to find that this methodology was applicable to the formation of seven-membered rings from secondary amines, thus allowing the formation of 2,3,6,7-tetrahydroazepines **33** from the unacylated *N*,*N*-bis(3-butenyl)-amines **17** (Table 8). In these reactions, it was found that the use of acid to protonate the free amine was necessary, as the reaction did not proceed at all under neutral conditions. It was also found that conducting the reaction with the original Grubbs catalyst required a higher catalyst loading (~20 mol %), and the yields were much lower and the reaction more sluggish than that with the second generation catalyst.[23a]

Conclusion

We have illustrated a new use of (2-azaallyl)stannanes and (2-azaallyl)nitriles as synthetic equivalents of α,α′-dications (2-azaallyl dications), both of which can undergo double allylation reactions with allylmagnesium bromide. These reactions provide an efficient route to *N*,*N*-bis(3-butenyl)amines, which in turn are precursors of 2,3,6,7-tetrahydroazepines via ring-closing metathesis. The observation of the monoallylated intermediate during the double allylation of (2-azaallyl)nitriles made it reasonable to propose a mechanism involving initial nucleophilic addition followed by loss of the cyanide to provide an intermediate imine that can undergo a second nucleophilic attack. This insight suggests that the stepwise addition of two different organometallic reagents to a (2-azaallyl)nitrile would be possible. Given the ease of preparation of (2-azaallyl)nitriles and the potential for stepwise addition, this methodology could present an efficient route to a wide variety of secondary *N*-(3-butenyl)amines.

Representative Experimental Section

Cyclohexylidenetributylstannanylmethylamine (16c). The title compound was prepared following the literature procedure.[9a] Hydrazine hydrate (15.00 g, 300 mmol) was added slowly, in one portion, to a solution of the phthalimide **13** (2.69 g, 6.00 mmol) in ethanol (12 mL). A preheated heating mantle was put in place, the solution was brought to reflux, and the temperature was maintained for 30 min, then the reaction was cooled to room temperature and worked up in the following manner. The solution was diluted with ether, washed successively with 4 portions of H_2O and 2 portions of brine then dried over Na_2SO_4 and the solvent was removed in vacuo. For evaporation of the volatile compounds, a rotary evaporator was employed, using a water bath at room temperature (not heated) to aid the process. A crude yellow oil was obtained and used in the ensuing reaction without further purification. The oil was dissolved in ether (3.5 mL) and dry 4 Å molecular sieves added to the solution. A solution of cyclohexanone (0.5889 g, 6.000 mmol) in ether (2 mL) was added, and the resulting solution was stirred overnight. The reaction mixture was filtered over Celite with ether to remove the sieves, and the solvent was removed in vacuo. A colorless oil, 2.1061 g (88%), was obtained after Kugelrohr distillation: bp 125−128 °C (air bath) (0.025 mmHg); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.54 (s, 2H, ^2J [$^{117/119}$Sn−^{1}H] = 23.6 Hz), 2.25−2.20 (m, 4H), 1.69−1.60 (m, 6H), 1.56−1.46 (m, 6H), 1.30 (app sextet, 6H, J = 7.2 Hz), 0.91−0.86 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 39.5, 37.8, 29.2, 27.6, 27.4, 26.5, 26.2, 13.7, 9.6 (J [$^{117/119}$Sn−^{13}C] = 156.3 Hz); IR (neat) 1643 (m) cm^{-1}; LRMS (CI with NH_3) *m*/*z* (rel intensity) 402 (79), 344 (15), 286 (21), 210 (18), 110 (100), 98 (67); HRMS (CI with NH_3) calcd for $C_{19}H_{40}N^{120}Sn$ $(M + H)^+$ 402.2183, found 402.2167. Anal. Calcd for $C_{19}H_{39}NSn$: C, 57.02; H, 9.82; N, 3.50. Found: C, 56.79; H, 9.92; N, 3.22.

***N*-(1-Allyl-cyclohexyl)-*N*-(but-3-enyl)formamide (17g).** Allylmagnesium bromide (2.2 mL of a 1.0 M solution in ether, 2.2 mmol) was added in a dropwise fashion to a −78 °C solution of the imine **16c** (0.4000 g, 1.000 mmol) in THF (5.0 mL), and the resulting solution was stirred for 45 min. H_2O (1.0 mL) was then added, and the mixture was allowed to warm to room temperature. The THF was removed in vacuo and the resulting residue was dissolved in water. The solution was then extracted with ether, the combined extract was dried over Na_2SO_4, and the solvent was removed in vacuo to afford an oil that was used without further purification.

Acetic formic anhydride (0.18 g, 2.0 mmol) was added to a 0 °C solution of the crude amine in CH_2Cl_2. Triethylamine (0.7 mL, 5.0 mmol) was cautiously added in a dropwise fashion and the evoluion of gas was observed. After 1 h, the reaction was diluted with $NaHCO_3$ (saturated aqueous solution) and extracted with CH_2Cl_2. The combined extracts were washed with 2 portions of $NaHCO_3$ (saturated aqueous solution) and dried over $MgSO_4$, and the solvent was removed in vacuo. Flash chromatography (3−15% EtOAc/hexanes gradient) afforded 0.1315 g (60%) of a pale yellow oil: R_f 0.14 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.28 (s, 1H), 5.81 (dddd, 1H, J = 17.0, 10.25, 6.8, 6.8 Hz), 5.60 (dddd, 1H, J = 17.5, 10.3, 7.3, 7.3 Hz), 5.14−5.02 (m, 4H), 3.28−3.25 (m, 2H), 2.30 (d, 2H, J = 7.5 Hz), 1.90−1.87 (m, 2H), 1.70−1.66 (m, 2H), 1.54−1.49 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.0, 135.6, 132.0, 119.6, 116.3, 60.3, 42.0, 40.6, 34.9, 33.3, 25.6, 21.8; IR (neat) 1656 (s) cm^{-1}; LRMS (CI with NH_3) *m*/*z* (rel intensity) 288 (14), 260 (7), 206 (26), 181 (16), 108 (16), 91 (100); HRMS (CI with NH_3) calcd for $C_{18}H_{26}NO_2$ $(M + H)^+$ 288.1964, found 288.1973.

7-Azaspiro[5.6]dodec-10-ene-7-carbaldehyde (32d). Benzylidenebis(tricyclohexylphosphine)dichlororuthenium (0.0210 g, 0.0250 mmol), Grubb's catalyst, was added to a refluxing solution of the diene **17g** (0.1126 g, 0.5000 mmol) in CH_2Cl_2 (25 mL). After 45 min, analysis of the reaction mixture by GCMS showed that the reaction was complete. The solution was cooled to room temperature then allowed to stir open to air for 16 h, and the solvent was then removed in vacuo. Flash chromatography (20% EtOAc/hexanes) afforded 0.0916 g (95%) of a clear colorless oil: R_f 0.12 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz containing rotomers) δ 8.51 (s, 0.92H), 8.17 (s, 0.08H), 5.71−5.53 (m, 2H),

3.73 (t, 1.84H, $J = 5.5$ Hz), 3.62 (t, 0.16H, $J = 5.5$ Hz), 2.88−2.81 (m, 0.16H), 2.55 (d, 0.16H, $J = 4.0$ Hz), 2.43 (d, 1.84H, $J = 7.0$ Hz), 2.34 (d, 1.84H, $J = 5.5$ Hz), 1.92−1.87 (m, 2H), 1.78−1.75 (m, 2H), 1.58−1.53 (m, 2H), 1.51−1.44 (m, 2H), 1.41−1.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.1, 131.0, 124.2, 61.7, 37.0, 36.1, 35.8, 30.4, 25.5, 22.3; IR (neat) 1655 (s) cm^{-1}; LRMS (EI, 70 eV) *m*/*z* (rel intensity) 193 (83), 164 (53), 150 (71), 110 (100), 81 (50), 67 (60); HRMS (EI, 70 eV) calcd for $C_{12}H_{19}NO$ $(M)^+$ 193.1467, found 193.1458.

2-Isobutylideneamino-3-methylbutyronitrile (22f). Isobutyraldehyde (1.91 mL, 21 mmol) was added to a mixture of 2-amino-3-methylbutyronitrile[11] (2.09 g, 21 mmol) and 4Å molecular sieves (5 g) in Et_2O (20 mL). After 16 h, the mixture was vacuum-filtered through a pad of Celite and concentrated. Kügelrohr distillation (68 °C/0.04 mmHg) yielded 2.74 g (86%) of **22f** as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, 1 H, $J = 4.8$, 1.5 Hz), 4.27 (dt, 1 H, $J = 5.1$, 1.5 Hz), 2.17 (d sept, 1 H, $J = 6.8$, 5.1 Hz), 2.50−2.58 (m, 1 H), 1.11 (d, 6 H, $J = 7.0$ Hz), 1.07 (d, 3 H, $J = 6.6$ Hz), 0.98 (d, 3 H, $J = 6.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 117.1, 64.7, 34.2, 32.3, 19.0, 17.6; IR (neat) 2242 (w), 1668 (s) cm^{-1}; MS (EI, 70 eV) *m*/*z* (rel intensity) 153 (5, $[M + H]^+$), 137 (13, $[M - CH_3]^+$), 109 (100, $[M - i\text{-Pr}]^+$); HRMS (CI, CH_4) calcd for $C_9H_{16}N_2$ $[M + H]^+$ 153.1392, found 153.1388.

Bis(1-isopropyl-but-3-enyl)amine (17m). Imine **22f** (152 mg, 1.0 mmol) was added dropwise to allylmagnesium bromide (2.69 mL of a 0.82 M solution in Et_2O, 2.2 mmol) in CH_2Cl_2 (5 mL) at −78 °C. After 6 h, the reaction was quenched with water and warmed to room temperature. The mixture was diluted with water, extracted (CH_2Cl_2), washed (saturated $NaHCO_3$), dried ($MgSO_4$), and concentrated. The residue was chromatographed (5% ethyl acetate/hexanes) to give 139 mg (67%) of **17m** as a pale yellow oil. The minor diastereomer could not be detected by ^{1}H NMR or GC/MS. R_f 0.55 (5% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (tdd, 2 H, $J = 17.2$, 10.2, 7.1 Hz), 5.05 (ddd, 2 H, $J = 17.2$, 3.3, 1.4 Hz), 5.09−5.00 (m, 2 H), 2.39 (td, 2 H, $J = 7.4$, 4.4 Hz), 2.18−2.09 (m, 2 H), 2.02−1.92 (m, 2 H), 1.76 (d sept, 2 H, $J = 6.9$, 4.1 Hz), 1.07 (br s, 1 H), 0.87 (d, 6 H, $J = 6.9$ Hz), 0.85 (d, 6 H, $J = 6.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 116.7, 59.6, 35.1, 30.2, 18.5, 17.8; IR (neat) 3337 (br) cm^{-1}; MS (EI, 70 eV) *m*/*z* (rel intensity) 168 (100, $[M - CH_2CHCH_2]^+$), 166 (48, $[M - i\text{-Pr}]^+$); HRMS (CI, CH_4) calcd for $C_{14}H_{28}N$ $[M + H]^+$ 210.2222, found 210.2224.

2,7-Diisopropyl-2,3,6,7-tetrahydro-1*H*-azepine (33a). *p*-Toluenesulfonic acid (69 mg, 0.4 mmol) was added to diene **17m** (83 mg, 0.4 mmol) in toluene (4 mL). After 30 min, Grubbs second generation catalyst ([1,3-bis(2,3,4-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylphosphine)-ruthenium) (17 mg, 0.02 mmol) was added, and the solution was heated to reflux for 3 h. After being cooled to room temperature, the mixture was diluted with saturated K_2CO_3, extracted (Et_2O), dried ($MgSO_4$), and concentrated. The residue was chromatographed (10% ethyl acetate/hexanes) to give 41.2 mg (57%) of **33a**. R_f 0.21 (10% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (dd, 2 H, $J = 5.0$, 2.5 Hz), 2.28 (ddd, 2 H, $J = 10.1$, 4.7, 2.2 Hz), 2.18 (tdd, 2 H, $J = 15.0$, 5.0, 2.5 Hz), 2.04 (dd, 2 H, $J = 15.0$, 9.6 Hz), 1.62 (d sept, 2 H, $J = 6.9$, 4.7 Hz), 1.25 (br s, 1 H), 0.93 (d, 6 H, $J = 6.9$ Hz), 0.92 (d, 6 H, $J = 6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.9, 64.0, 34.5, 32.3, 19.1, 18.9; IR (neat) 3582 (br) cm^{-1}; MS (EI, 70 eV) *m*/*z* (rel intensity) 181 (2, $[M]^+$), 138 (100, $[M - i\text{-Pr}]^+$); HRMS (EI, 70 eV) calcd for $C_{12}H_{23}N$ $[M]^+$ 181.1830, found 181.1835.

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Supporting Information Available: Full experimental procedures and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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