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Double Allylation Reactions of (2-Azaallyl)stannanes: Synthesis of *N,N*-Bis(3-butenyl)amines and Their Conversion to 2,3,6,7-Tetrahydroazepines via Ring-Closing Metathesis

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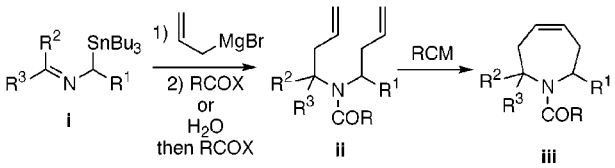
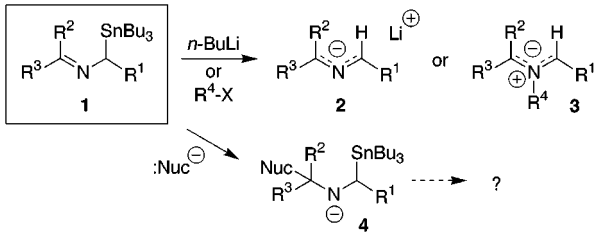
ABSTRACT



Treatment of (2-azaallyl)stannanes (i) with 2.2 equiv of allylmagnesium bromide afforded good yields of *N,N*-bis(3-butenyl)amines derivatives (ii), which were subjected to ring-closing metathesis to afford 2,3,6,7-tetrahydroazepines (iii). Thus, (2-azaallyl)stannanes are the synthetic equivalents of amine α,α′-dications.

We have shown that (2-azaallyl)stannanes **1** are precursors of nonstabilized 2-azaallyllithiums **2** and azomethine ylides **3** (Scheme 1), both of which undergo [3 + 2] cycloadditions

Scheme 1. Reactions of (2-Azaallyl)stannanes



with alkenes to produce pyrrolidines.[1] As part of a program to explore additional uses of (2-azaallyl)stannanes, we have examined the reactions of these compounds with nucleophiles (**1** → **4**, Scheme 1). The fate of the intermediate anion **4** was of particular interest.

One impetus for the current study was the unexpected result summarized in Scheme 2.[2] Transmetalation of stannane **5** to 2-azaallyllithium **6** using a single equivalent of *n*-butyllithium was attempted for the purpose of a [3 + 2] cycloaddition with 1-hexene. Rather than the expected pyrrolidine **7**, we obtained the acyclic material **8** in 40% yield.[2] Since nonactivated alkenes are reluctant partners in 2-azaallyl anion cycloadditions, we used 1-hexene as the solvent. However, it is known that tin−lithium exchange is slower in noncoordinating solvents;[3] thus we propose that

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(1) See the following recent papers and the earlier work cited therein: (a) Pearson, W. H.; Lovering, F. E. *J. Org. Chem.* **1998**, *63*, 3607−3617. (b) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688−689.

(2) Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329−1345.

(3) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842−853.

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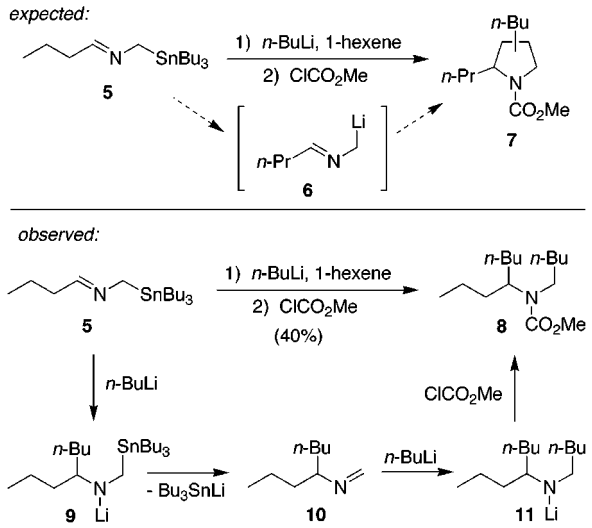
Scheme 2. An Initial Result



addition of the *n*-butyllithium to the imine is competitive with transmetalation, generating adduct **9** (cf. **4** in Scheme 1). Elimination of tributylstannyllithium from **9** generates the intermediate imine **10**, a substrate for further addition of *n*-butyllithium, resulting in the double alkylated intermediate **11** and ultimately the final product **8**. Tri-*n*-butyltin hydride was observed as a byproduct in the reaction, consistent with the loss of tributylstannyllithium as shown.

The result shown in Scheme 2 led us to examine the scope of (2-azaallyl)stannanes **1** as synthetic equivalents of amine α,α′-dications **12**, which could also be named 2-azaallyl dications from the alternative resonance form **13** (Figure 1).

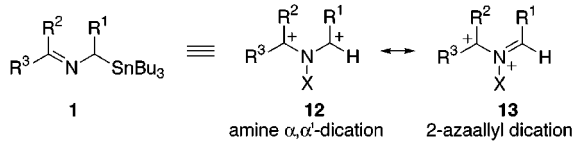
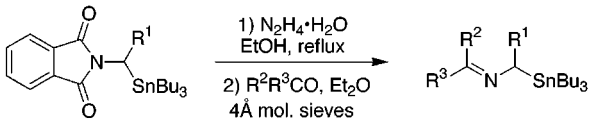


Figure 1. (2-Azaallyl)stannanes **1** are synthetic equivalents of the dication **12/13**.

The addition of nucleophiles to imines is an important route to amines and has been investigated in depth.[4] The reactions of stannanes **1** with nucleophiles may provide a new variation of this venerable chemistry. Initial studies on the combination of a simple (2-azaallyl)stannane (i.e., **1**, $R^1 = R^2 = H$, $R^3 = {}^i$Pr) with *n*-butyllithium in hexane or toluene failed to produce results similar to those shown in Scheme 2, resulting instead in the formation of tetrabutyltin and decomposition products. To avoid tin−lithium exchange, we examined other organometallic reagents as nucleophiles.[4] However, *n*-hexylmagnesium bromide, allylzinc bromide, and allyltributylstannane (with or without a Lewis acid)[5] were found to react sluggishly with the (2-azaallyl)stannane.[6] Since allylic organomagnesium reagents are of sufficient reactivity to add efficiently to imines,[4,7] we then examined the reactions of (2-azaallyl)stannanes with allylmagnesium bromide (vide infra).

First, a variety of (2-azaallyl)stannanes **16** were prepared as shown in Table 1, where hydrazinolysis of the phthalimides **14**[8] and **15**[9] was followed by condensation of the resultant α-aminostannanes with aldehydes and ketones, respectively.[8,10] Kugelrohr distillation provided pure samples of the stannanes **16a**−**f**.[11]

Table 1. Preparation of (2-Azaallyl)stannanes **16a**−**f**



Phthalimide	R^1	R^2	R^3	Product	%Yield[a]
14	H	H	iPr	**16a**	89
14	H	Me	Me	**16b**	84
14	H	$(CH_2)_5$		**16c**	88
15	Me	H	iPr	**16d**	85
15	Me	H	Me	**16e**	82
15	Me	$(CH_2)_5$		**16f**	85

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

Combination of the (2-azaallyl)stannanes **16a**−**f** with 2.2 equiv of allylmagnesium bromide in THF produced the diallylated materials **17a**−**l** following quenching with various electrophiles (Table 2).[12] The free amines **17a**, **17d**, **17f**, and **17h** (entries 1, 4, 6, and 8) were best purified by acid/base extraction, producing material of sufficient purity to obviate further purification, which otherwise leads to loss of material due to volatility. The amine **17k** could be purified by chromatography in 91% yield (entry 11). Direct quenching of the *N*-magnesio intermediates with chloroformates was

(4) Selected reviews: (a) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 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, 1991; Vol. 2, pp 975−1006. (c) Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. (d) Bloch, R. *Chem. Rev.* **1998**, *98*, 8, 1407−1438. (e) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094.

(5) Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146−147.

(6) Wright and co-workers have reported related methodology, where *N*-allyl imines were combined with allylmagnesium bromide to afford 4-aza-1,7-octadienes, which were subjected to ring-closing metathesis to afford 1,2,5,6-tetrahydropyridines. Difficulty adding other organometallics was encountered. See: Wright, D. L.; Schulte, J. P.; Page, M. A. *Org. Lett.* **2000**, *2*, 1847−1850.

(7) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 1.

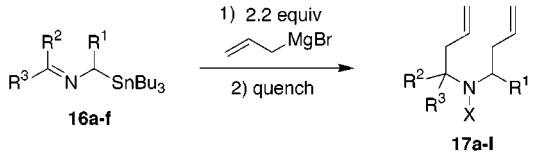
(8) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1992**, *57*, 6354−6357.

(9) Pearson, W. H.; Clark, R. B. *Tetrahedron Lett.* **1999**, *40*, 4467−4471.

(10) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220−2222.

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

Table 2. Double Allylation of (2-Azaallyl)stannanes **16a−f**



Entry	Imine	Quench	X	R^1	R^2	R^3	Product	%Yield[a]
1	**16a**	H_2O	H	H	H	iPr	**17a**	78[b]
2	**16a**	$ClCO_2Ph$	CO_2Ph	H	H	iPr	**17b**	80
3	**16a**	$ClCO_2Bn$	CO_2Bn	H	H	iPr	**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]
7	**16c**	HCO_2Ac[c]	CHO	H	-$(CH_2)_5$-		**17g**	60
8	**16d**	H_2O	H	Me	H	iPr	**17h**	52[b,d]
9	**16d**	HCO_2Ac[c]	CHO	Me	H	iPr	**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

[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 (see Table 3). [e] Ratio of diastereomers = 1.3:1. The relative configurations were not assigned.

possible in unhindered systems, leading to the carbamates **17b**, **17c**, **17e**, and **17j** (entries 2, 3, 5, and 10). Quenching with water followed by a separate acylation reaction was found to produce **17l** (entry 12) in higher yield than the direct acylation method, although the yield of **17l** was still only moderate. Comparison of entry 12 with entry 11 shows that the allylation reaction was highly efficient in both cases, but the acylation step in entry 12 is the difficult one, presumably due to steric hindrance. *N*-Formylation was also best accomplished by quenching with water first (entries 7 and 9).[1b] Entries 8−10 involve allylations that produce mixtures of diastereomers in modest (2.5:1 in entries 8 and 9) to low stereoselectivity (entry 10).

Recently, there has been much interest in the use of ring-closing methathesis[13] for the construction of nitrogen heterocycles.[6,14,15] The dienes **17** were found to be well-suited for such cyclizations, producing 2,3,6,7-tetrahydroazepines **18** in an efficient manner (Table 3). The assembly of the relatively crowded tetrahydroazepine **18g** is successful. The relative configurations of the two diastereomers of **18e** were

Table 3. Tetrahydroazepines via Ring-Closing Metathesis

Diene	Conditions	Product(s)[a]
17b: X=CO_2Ph **17c**: X=CO_2Bn	$PhCH{=}RuCl_2(PCy_3)_2$ CH_2Cl_2, reflux	**18a**: X=CO_2Ph (98%) **18b**: X=CO_2Bn (87%)
17e	"	**18c** (65%)
17g	"	**18d** (95%)
17i (2.5:1 βMe:αMe)	"	**18e** (75%) (2.5:1 βMe:αMe)[b]
17j (1.3:1)	"	**18f** (96%) (1.3:1)
17l	"	**18g** (89%)

[a] All yields are of purified material. [b] The relative configurations were assigned after reduction of **18e** with $LiAlH_4$ and analysis of the *N*-methyl derivatives by ^1H NMR/NOE spectroscopy.

(12) **Representative Procedure: Preparation of Diene 17b.** Allylmagnesium bromide (2.2 mL of a 1.0 M solution in ether, 2.2 mmol) was added in a dropwise fashion to a solution of the imine **16a** (0.374 g, 1.00 mmol) in THF (5 mL) at −78 °C. After 30 min, phenyl chloroformate (0.344 g, 2.20 mmol) was added and the mixture was allowed to warm slowly to room temperature, then diluted with water and ether. The organic layer was separated, and the aqueous layer was extracted 3× with ether. The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (0−3% ethyl acetate/hexanes gradient) gave 0.230 g (80%) of diene **17b** as a clear colorless oil. ^1H NMR ($CDCl_3$, 400 MHz, room temperature, rotomers present) δ 7.44-7.07 [m, 5 H containing 7.36 (app t, J = 6.6 Hz), 7.18 (app t, J = 7.2 Hz), 7.09 (app t, J = 7.2 Hz)], 5.89−5.73 (m, 2 H), 5.16−5.01 (m, 4 H), 3.69 (app br s, 1 H), 3.27−3.17 (m, 2 H), 2.53−2.33 (m, 4 H), 1.90 (app br s, 1 H), 1.02 (app t, J = 6.4 Hz), 1.00 (app d, J = 3.2 Hz), 0.98 (app d, J = 3.2 Hz), 1.04−0.98 (total 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.22, 151.59, 151.47, 135.94, 135.57, 135.41, 129.56, 129.20, 125.11, 125.02, 121.75, 121.70, 117.15, 116.78, 116.55, 116.41, 64.48 (br), 45.02 (br), 35.31, 34.95, 34.34, 32.98, 31.49, 31.00, 20.49, 20.41, 20.34.

(13) Recent reviews: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037−2056. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (d) *Alkene Metathesis in Organic Synthesis*; Fürstner, A., Ed.; Springer-Verlag: Heidelberg, 1998. (e) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141−8153. (f) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (g) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519−529.

(14) For a review focusing on ring-closing metathesis of nitrogen-containing compounds, see: (a) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75−89. For recent references in this general area, see: (b) Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3193−3195. (c) Varray, S.; Gauzy, C.; Lamaty, F.; Lazaro, R.; Martinez, J. *J. Org. Chem.* **2000**, *65*, 6787−6790. (d) Cossy, J.; Willis, C.; Bellosta, V.; Bouzbouz, S. *Synlett* **2000**, 1461−1463. (e) Felpin, F.-X.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *Synlett* **2000**, 1646−1648. (f) Groaning, M. D.; Meyers, A. I. *Chem. Commun.* **2000**, 1027−1028.

assigned by NOE/NMR spectroscopy and thus allowed assignment of the precursor diene **17i**.

(15) Osipov 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**, 1031−1033. For other imine allylation/RCM work, see: (b) Kumareswaran, R.; Balasubramanian, T.; Hassner, A. *Tetrahedron Lett.* **2000**, *41*, 8157−8162. For iminium ion allylation/RCM to produce tetrahydropiperidines and 2,3,6,7-tetrahydroazepines, see: (c) 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*, 3716−3721. For RCMs of *N*,*N*-bis(3-butenyl)amine derivatives to 2,3,6,7-tetrahydroazepines, see the following: (d) Paquette, L. A.; Leit, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 8126−8127. (e) Pernerstorfer, J.; Schuster, M.; Blechert, S. *Synthesis* **1999**, 138−144. (f) Schürer, S. C.; Gessler, S.; Buschmann, N.; Blechert, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3898−3901. For another RCM approach to tetrahydroazepines, see: (g) Vo-Thanh, G.; Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Synlett* **2001**, 37−40.

The double allylation of (2-azaallyl)stannanes illustrates a new use of these imines and provides a useful route to *N*,*N*-bis(3-butenyl)amines (or 5-aza-1,8-nonadienes), which in turn are precursors of 2,3,6,7-tetrahydroazepines via ring-closing metathesis. We are currently examining the addition of other organometallics to these stannanes and are especially interested in adding two different organometallics in a sequential fashion.

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