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A Conjunctive Approach to the Synthesis of Functionalized Piperidines from Imines

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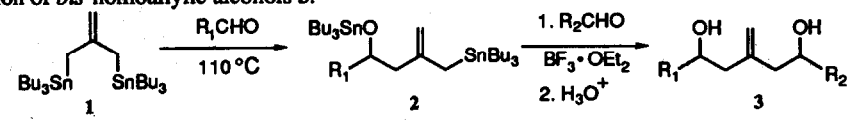
Abstract: A two-step method for the construction of 2,6 disubstituted piperidines from an imine, 3-tri-*n*-butylstannyl-2-[(tri-*n*-butylstannyl)methyl] propene, and an aldehyde is described.

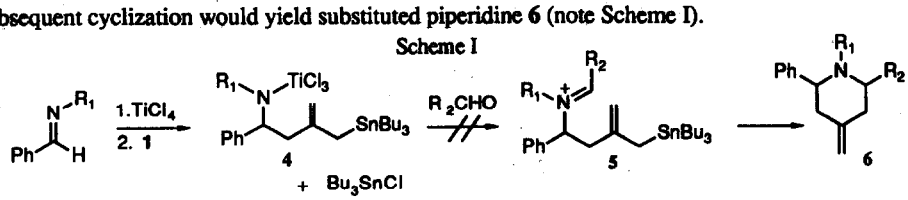
Recently, in the context of considering new synthetic approaches for the total synthesis of alkaloids, we had occasion to examine the potential of the known reagent **1**[1] as a conjunctive reagent for the synthesis of functionalized piperidines, a structural element common to many alkaloids of biological significance. The *bis*-stannane **1** is readily prepared in 70% yield from commercially available 1-chloro-(2-chloromethyl) propene by reaction with tri-*n*-butylstannyllithium and its reactivity with certain electrophiles has already been established.[2] Due to the double activation provided by the presence of two allylic stannyl substituents, **1** is considerably more reactive towards electrophiles than are simple allylstannanes, and the difference in reactivity between **1** and the monostannyl intermediate which results from reaction of **1** with an electrophile has been demonstrated by Ueno[1] (note eq 1). Thus, the *bis*-stannane **1** reacts with aldehydes under thermal conditions at considerably lower temperatures than does, *e.g.* allyltri-*n*-butylstannane; hence, the remaining allylstannane moiety is stable to the reaction conditions. Introduction of a second aldehyde and an appropriate Lewis acid then leads to the production of *bis*-homoallylic alcohols **3**.



(1)

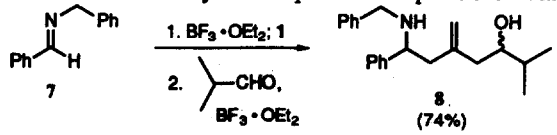
We envisioned that the differential reactivity exhibited between **1** and the monostannane resulting upon initial reaction with an electrophile might be exploited to good advantage for the synthesis of piperidines. Specifically, we expected that complexation of an imine with $TiCl_4$, followed by introduction of **1**, should afford intermediate **4**,[3] from which introduction of a second aldehyde could yield a new imminium ion species (**5**). Subsequent cyclization would yield substituted piperidine **6** (note Scheme I).

Scheme I



Unfortunately, all attempts to reduce this scheme to practice have, thus far, failed. Although the initial addition of *bis*-stannane **1** to a variety of aldimines proved successful with a number of Lewis acids, in no case did the introduction of a second aldehyde (with or without additional Lewis acid) lead to the desired piperidines:

either no reaction occurred or the products were amino alcohols derived from reaction of the allylstannane moiety in intermediates **4** with the second aldehyde.[4] A specific example is shown in equation 2 below.



These amino alcohols could subsequently be cyclized under Mitsunobu conditions as reported by Bernotas[5] to yield the desired piperidines; however, these were obtained as mixtures of *cis* and *trans* isomers (as would be expected), a feature which clearly detracts from the synthetic utility of the method. Results obtained according to the general experimental protocols provided[6] are summarized in the table below.[7,8]

Table. Reaction of **1** With Benzaldimines and Aldehydes Followed by Mitsunobu Cyclization

Entry	R_1	R_2	%yield (**8**)[a]	%yield (**6**)[a]
A	Bn	Ph	55	68
B	Bn	Et	47	60
C	Bn	^{i}Pr	74	60
D	^{i}Pr	Ph	50	57
E	^{i}Pr	Et	54	45

[a] Isolated yields after flash chromatography.

References and Notes

1. Sano, H.; Okara, M.; Ueno, Y. *Synthesis* **1983**, *11*, 933.
2. A very similar trimethyl reagent has recently been employed in a two step sequence to yield diketones from *bis* acid chlorides: Seconi, G.; Ricci, A.; Modini, A.; Dembec, P.; Deg'Innocenti, A. *Synthesis* **1991**, *4*, 267.
3. Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146.
4. This occurred even with N-silylimines. For the use of N-silylamines for the preparation of imines, see: Kruger, C.; Rochow, E. G.; Wannagat, U. *Chem. Ber.* **1963**, *96*, 2132.
5. Bernotas, R. C.; Cube, R. V. *Tetrahedron Lett.* **1991**, *32*, 161.
6. All new compounds were fully characterized by spectroscopic techniques (^{1}H NMR, ^{13}NMR, IR) and their molecular formulas established by microanalysis or high resolution mass spectrometry. Typical procedure for the preparation of **2A**: To a stirring solution of *N*-benzyl-benzaldimine (200 mg, 1.02 mmol) in methylene chloride (10 mL) was added boron trifluoride etherate (0.151 mL, 1.23 mmol) dropwise via syringe. The resulting solution was stirred for 10 min at -78 °C. To this solution was added 3-tri-*n*-butylstannyl-2-[(tri-*n*-butylstannyl)methyl]propene **1**, (0.647 mL, 1.12 mmol) dropwise via syringe. The cold bath was then allowed to expire over 2 h and the reaction mixture slowly warmed to room temperature. After 20 h, the reaction mixture was cooled to -78 °C. To this solution was added boron trifluoride etherate (0.126 mL, 1.02 mmol) followed by benzaldehyde (0.209 mL, 2.05 mmol). After 6 h, the reaction was quenched with saturated aq $NaHCO_3$ (20 mL). The mixture was then diluted with methylene chloride (10 mL) and the aqueous layer was extracted twice with methylene chloride (20 mL). The combined organic phase was dried with Na_2SO_4 and concentrated. The mixture was then chromatographed over a silica gel column (15 x 1.5 cm) eluting with hexanes through 25% EtOAc/ hexanes. The product containing fractions were combined and concentrated to give 200 mg (55%) of a colorless liquid.

   Typical procedure for cyclization of **3A** under Mitsunobu conditions: To a stirring solution of amino alcohol **8A** (100 mg, 0.280 mmol) and triphenyl phosphine (88.0 mg, 0.336 mmol) in dry THF (3 mL) was added diethyl diazodicarboxylate (58.0 mg, 0.336 mmol) dropwise via syringe. After 3 h, the reaction was quenched with water. The aqueous layer was separated and extracted with methylene chloride (3x10 mL). The combined organic phase was dried with Na_2SO_4 and concentrated. The mixture was separated by flash chromatography with a 12 x 1 cm column eluting with hexanes through 15% EtOAc/hexanes. The product containing fractions were combined and concentrated to give 64.0 mg (68%) of a colorless liquid.
7. For related reactions involving an allylsilane, see: Grieco, P. A.; Fobare, W. F. *Tetrahedron Lett.* **1986**, *27*, 5067.

8. Financial support of this research by the National Institutes of Health (Grant CA 52834) is gratefully acknowledged.

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