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Alkaloid synthesis via [3+2] cycloadditions*

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Abstract: Tin-lithium exchange on (2-azaallyl)stannanes affords nonstabilized 2-azaallyllithiums (2-azaallyl anions) that undergo [π4s+π2s] cycloadditions with alkenes to afford pyrrolidines. The scope of this method has been expanded to include 2-azapentadienyllithiums and heteroatom-substituted 2-azaallyllithiums. Alternatively, the (2-azaallyl)stannanes may also be used to generate nonstabilized azomethine ylides via *N*-alkylation/destannylation or *N*-protonation/destannylation, and these ylides were also found to be useful for the synthesis of pyrrolidines by [π4s+π2s] cycloadditions with alkenes. Applications of both methods to the total synthesis of alkaloids such as (+)-coccinine, lepadiformine stereoisomers, lapidilectine B, and indolizidine 239CD have been accomplished.

INTRODUCTION

The pyrrolidine ring is found in many natural compounds and may be fused to other rings in a variety of ways (Fig. 1). We have been interested in developing a pyrrolidine synthesis that would be general enough to use for making diverse pyrrolidine-containing compounds such as those shown.

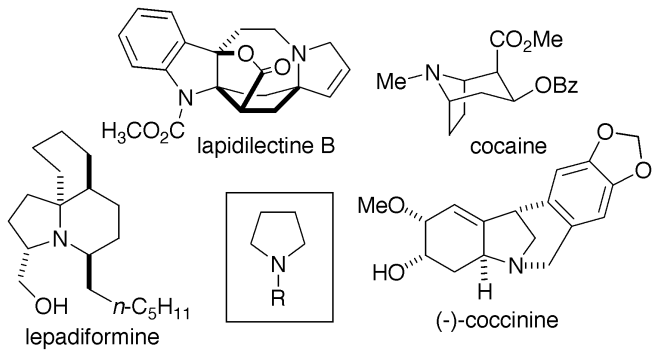

Fig. 1 Examples of pyrrolidine-containing natural products.

When considering routes to ring-containing structures, cycloadditions are of obvious significance, since they have the advantages of synthetic efficiency and potentially high stereoselectivity. Among the possible cycloaddition strategies that might be used to make a pyrrolidine ring, we have chosen to explore disconnection of the C2/C3 and C4/C5 bonds, thus requiring the use of either a 2-azaallyl anion (**1**) or an azomethine ylide (**2**) in a [π4s+π2s] cycloaddition with an alkene (Scheme 1).

Prior to our work, the anionic cycloaddition of 2-azaallyllithiums, a specific type of 2-azaallyl anion, with alkenes was limited to anions bearing two or more aryl groups, chemistry pioneered by

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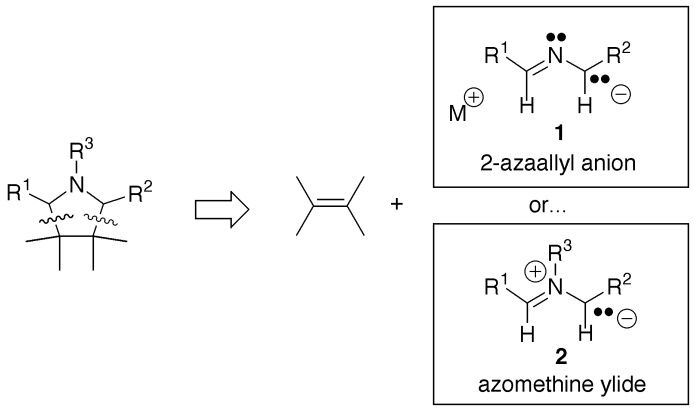
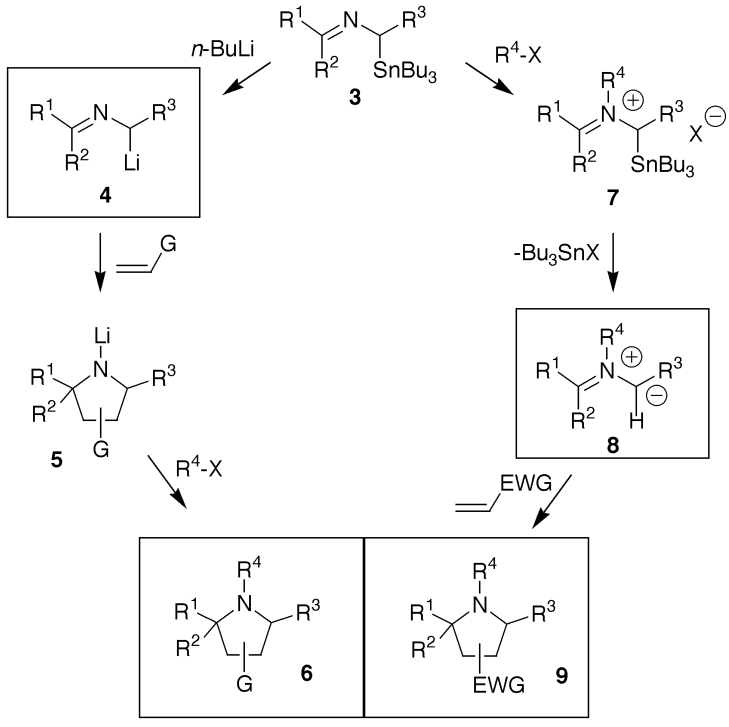


Scheme 1 [3+2] Approaches to the pyrrolidine ring.

T. Kauffmann [1]. More stabilized anions such as those derived from the deprotonation of the imines of glycine esters have been generated and found to undergo "cycloadditions" with electron-poor alkenes [2]. Such anions are best considered as enolates rather than 2-azaallyl anions. Their reactions with alkenes are related to the Michael addition reaction. The generation and cycloaddition of the first nonstabilized 2-azaallyl anions (**4**), i.e., those bearing only hydrogen or alkyl groups, was made possible in our labs by the transmetalation of (2-azaallyl)stannanes **3** with *n*-butyllithium at low temperature (Scheme 2) [3]. The cycloaddition of **4** with alkenes gave the *N*-lithiopyrrolidines **5** and ulti-



Scheme 2 Generation and cycloaddition of 2-azaallyl anions and azomethine ylides from (2-azaallyl)stannanes **3**.

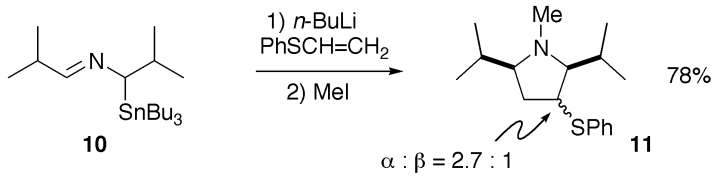
mately the pyrrolidines **6** after quenching with a variety of electrophiles. Hence, three new bonds were formed in one synthetic operation.

We also found that nonstabilized azomethine ylides **8** could be generated from (2-azaallyl)stannanes (Scheme 2). Thus, *N*-alkylation [4] or -protonation [5] of **3** generated **7**, which upon destannylation gave the ylides **8**. Cycloaddition with alkenes, especially electron-poor alkenes, gave the pyrrolidines **9**. The rarity of nonstabilized azomethine ylides, especially those that are *N*-unsubstituted (i.e., R^4 = H) makes this chemistry a welcome complement to existing methods for ylide generation. The generation of either the anions **4** or the ylides **8** from the same precursor **3** is also a useful complementarity.

An overview of the scope of these cycloadditions is presented below, along with exemplary applications to alkaloid synthesis.

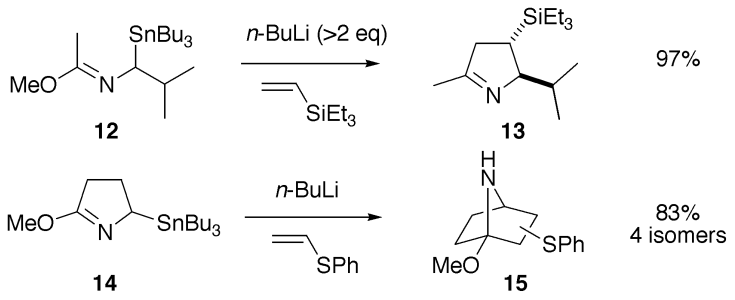
2-AZAALLYLLITHIUM CYCLOADDITIONS

A specific example of a cycloaddition of a nonstabilized 2-azaallyllithium with an alkene is shown in Scheme 3. Transmetalation of **10** in the presence of phenyl vinyl sulfide leads to the *N*-lithiopyrrolidine cycloadduct, which is quenched with iodomethane to give the pyrrolidine **11** as a mixture of stereoisomers.



Scheme 3 Example of a simple 2-azaallyl anion cycloaddition.

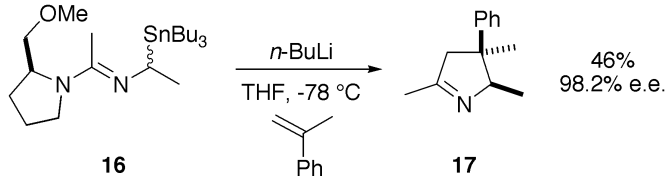
It is also possible to generate 2-azaallyllithiums bearing heteroatoms such as OR, NR_2, and SR, leading to cycloadducts of a higher oxidation state [6,7]. After the cycloaddition, the 2-heterosubstituted-*N*-lithiopyrrolidine may eliminate LiX to give a 1-pyrroline. For example, the imidates **12** and **14** lead to the formation of the pyrroline **13** and the bridged-bicyclic pyrrolidine **15**, respectively (Scheme 4). Loss of lithium methoxide in the latter case is not possible due to stereoelectronics. The use of **14** also illustrates the first use of *cyclic* 2-azaallyl anions.



Scheme 4 Generation and cycloaddition of heteroatom-substituted 2-azaallyl anions.

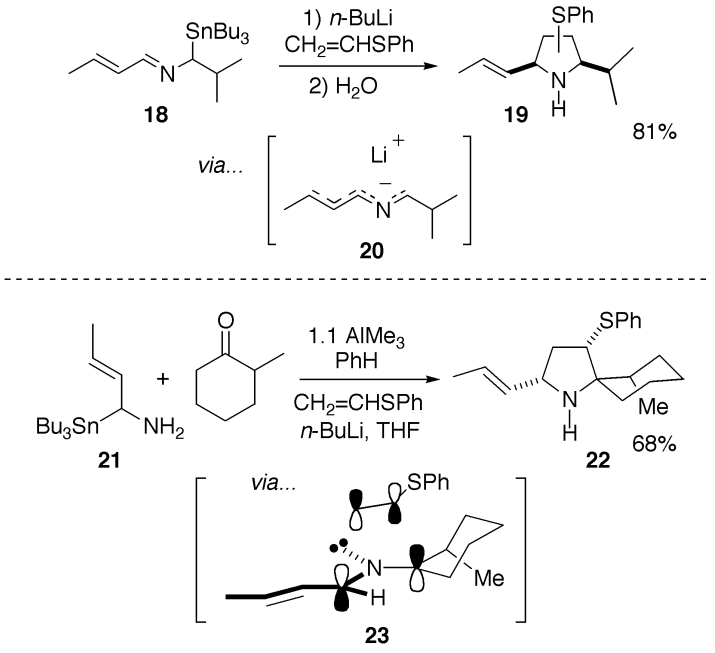
Another attractive feature of heteroatom-substituted 2-azaallyl anions is the ability to incorporate a heteroatom-linked chiral auxiliary. The first example of an asymmetric 2-azaallyl anion is shown

below (Scheme 5), where transmetalation of the chiral, nonracemic amidine **16** gives a chiral anion that reacts stereoselectivly with α-methylstyrene, producing the pyrroline **17** in high e.e. [8]. The chiral auxiliary is ejected during the reaction and may be recovered and re-used.



Scheme 5 The first asymmetric 2-azaallyl anion cycloaddition. The relative configuration of the product is as shown, but the absolute configuration is not known.

More conjugated versions of 2-azaallyllithiums have also been developed (Scheme 6). Transmetalation of the conjugated imine **18**, derived from crotonaldehyde and an amino stannane, generates the 2-azapentadienyllithium **20**, which undergoes cycloaddition with phenyl vinyl sulfide to give the 2-propenylpyrrolidine **19** [9]. Alternatively, the double bond can be placed in the amino stannane, as in **21** [10,11]. Condensation of this amine with 2-methylcyclohexanone gave the intermediate (2-azaallyl)stannane, which upon transmetalation gave the 2-azapentadienyllithium **23** and thus the spirofused alkenylpyrrolidine **22**. This reaction also illustrates the use of a one-flask method for both imine formation and anion chemistry.

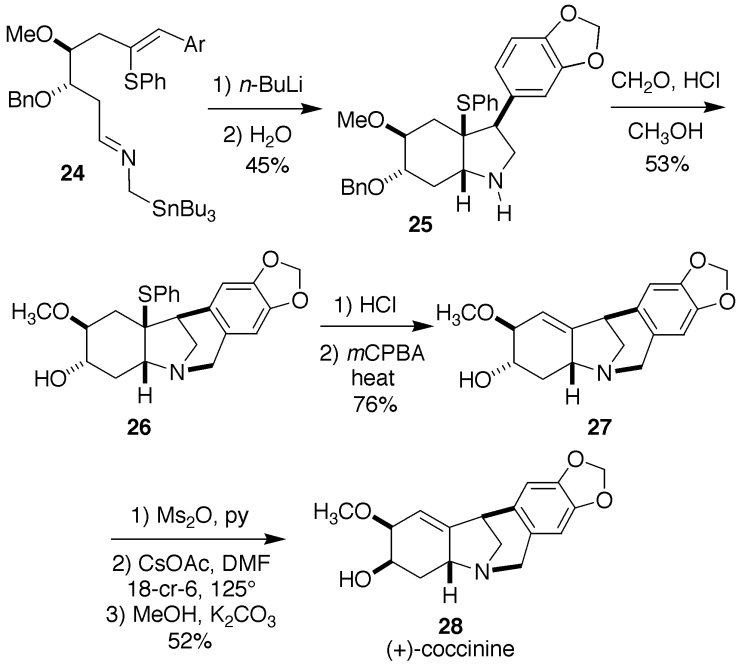


Scheme 6 Generation and cycloaddition of 2-azapentadienyl anions.

In addition to the examination of the scope of the 2-azaallyl anion method for pyrrolidine synthesis, we have been exploring the use of this chemistry for the construction of pyrrolidine-containing natural products. Examples include the total synthesis of crinine [12,13], amabiline [13,14], augusta-

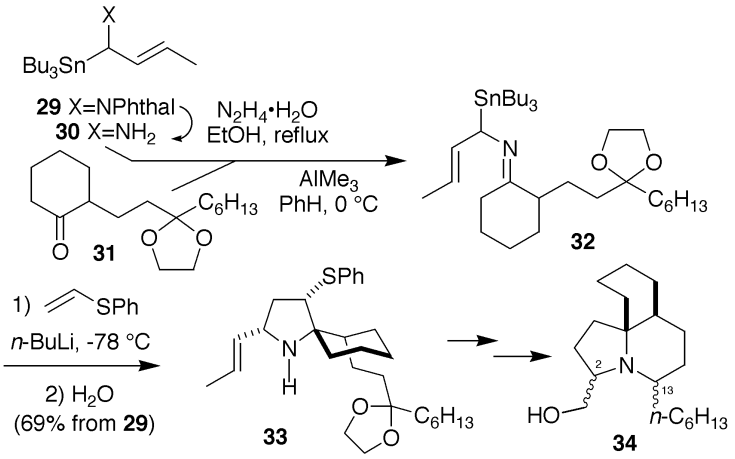
mine [13,14], and an approach to 6a-epipretazettine [15]. Three additional examples of these efforts are briefly described below.

The *Amaryllidaceae* alkaloid (–)-coccinine (see Fig. 1) is an example of the 5,11-methanomorphanthridine class of these alkaloids. We accomplished a synthesis of the enantiomer of this substance, i.e., (+)-coccinine (**28**), using an intramolecular cycloaddition of a 2-azaallyllithium with a vinyl sulfide (Scheme 7). Treatment of the (2-azaallyl)stannane **24** with *n*-butyllithium followed by an aqueous workup gave the perhydroindole **25**, which was subjected to a Pictet–Spengler cyclization to give **26**. Elimination of the sulfoxide of **26** to **27** followed by inversion of the secondary alcohol gave the desired *ent*-alkaloid **28**.



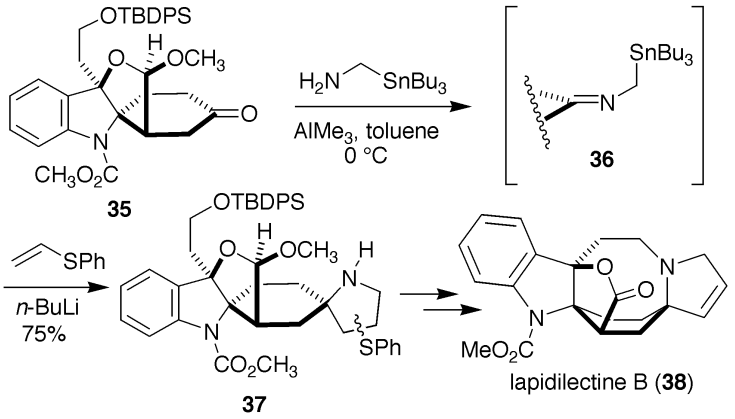
Scheme 7 Total synthesis of (+)-coccinine using the 2-azaallyl anion method.

The total synthesis of the marine alkaloid lepadiformine [16] has been complicated by the uncertainty surrounding its actual stereostructure. The correct structure of this compound has now been shown to be as depicted in Fig. 1 above. We used the 2-azapentadienyllithium cycloaddition method (Scheme 8) to synthesize the lepadiformine skeleton for the first time [10,11]. Hydrazinolysis of the phthalimide **29** gave the amine **30**, which was condensed with the ketone **31** to provide the imine **32**. Transmetalation of **32** in the presence of phenyl vinyl sulfide produced the pyrrolidine **33** in good overall yield from **29** and as a single isomer. An intramolecular reductive amination, oxidative cleavage of the propenyl side-chain, and various functional group manipulations afforded **34**, where we could make three of the possible four diastereomers of this substance at C2 and C13. Weinreb [17,18] and Kibayashi [19] synthesized the fourth possible diastereomer at those positions, but none of these compounds matched the natural product. Based on these results, we proposed that lepadiformine was epimeric to **34** at the quaternary bridgehead position [11], a hypothesis that was verified by other groups by total synthesis [20–22].



Scheme 8 Total synthesis of stereoisomers of lepadiformine using the 2-azaallyl anion method.

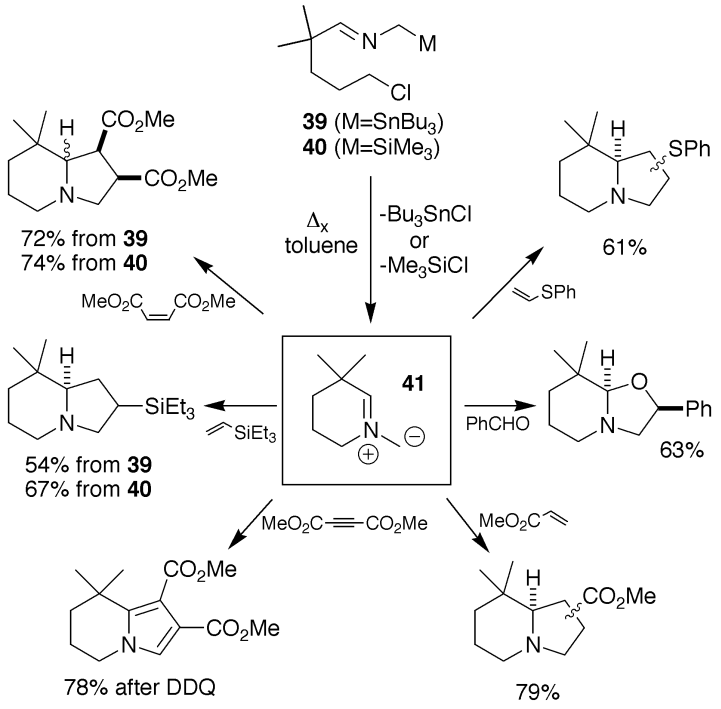
Most recently, we described the first total synthesis of lapidilectine B (**38**) [23], the first member of this class of *Kopsia lapidilecta* alkaloids (Scheme 9) [24]. A one-flask imine formation/cycloaddition procedure was effective for the conversion of the carbonyl compound **35** to the cycloadduct **37** in good yield via the stannane **36**. Functional group manipulation then afforded lapidilectine B **38**.



Scheme 9 Total synthesis of lapidilectine B using the 2-azaallyl anion method.

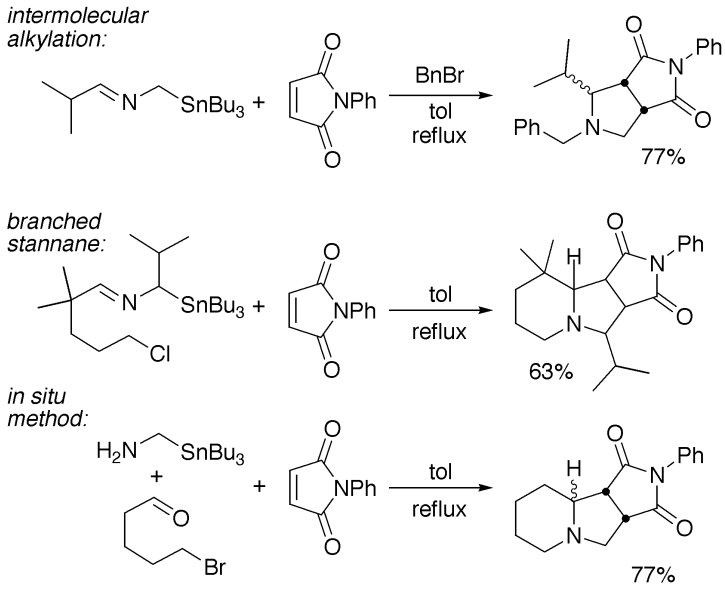
AZOMETHINE YLIDE CYCLOADDITIONS

As discussed above (see Scheme 2), we have also examined the use of (2-azaallyl)stannanes as precursors of azomethine ylides. This method may also be used with certain (2-azaallyl)silanes, reminiscent of earlier work by Vedejs, Padwa, Tsuge, Achiwa, and others [25]. For example, heating the stannane **39** or silane **40** in refluxing toluene in the presence of a variety of dipolarophiles results in the formation of the cycloadducts shown via the intermediacy of the nonstabilized azomethine ylide **41** (Scheme 10) [4]. Note the use of heterodipolarophiles (benzaldehyde) and even electron-rich dipolarophiles (phenyl vinyl sulfide and triethylsilylethene).



Scheme 10 Generation and cycloaddition of the nonstabilized azomethine ylide **41** from a (2-azaallyl)stannane (**39**) or -silane (**40**).

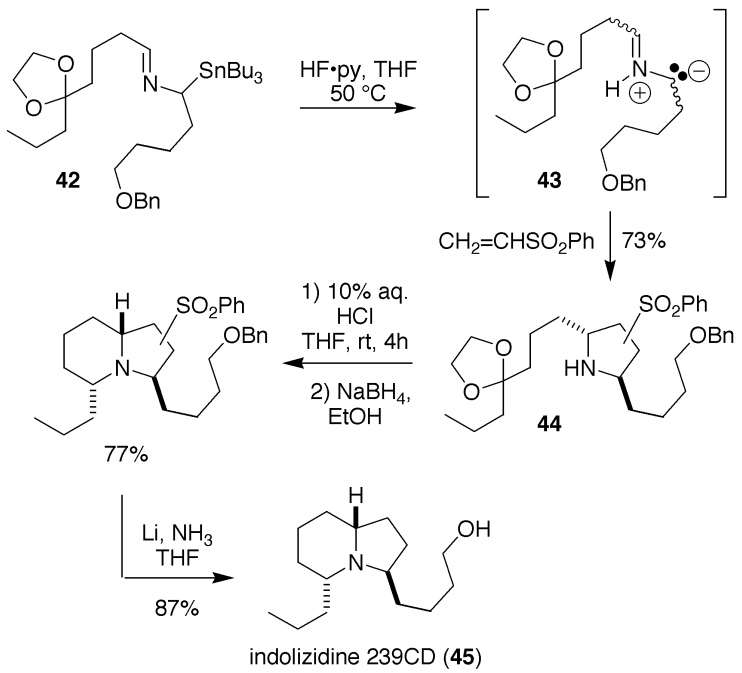
Intermolecular *N*-alkylation is also possible (Scheme 11). Branched stannanes can also be used as shown in the middle reaction in Scheme 11, resulting in more highly branched pyrrolidines. This



Scheme 11 Alternate strategies for the generation and cycloaddition of nonstabilized azomethine ylides from (2-azaallyl)stannanes.

offers an advantage over silicon chemistry, since branched α-aminosilanes are more difficult to prepare than branched α-aminostannanes. The last example in Scheme 11 shows a one-flask condensation/ylide formation/cycloaddition.

We have begun to explore the use of (2-azaallyl)stannanes to prepare ylides for natural products synthesis (Scheme 12) [26]. The (2-azaallyl)stannane **42**, upon treatment with HF•pyridine [5], produces the *N*-unsubstituted, nonstabilized ylide **43**, a very rare type of ylide. Cycloaddition with phenyl vinyl sulfone affords the pyrrolidine **44** as a mixture of regio- and stereoisomers, all of which have the 2,5-*trans* relationship on the pyrrolidine ring, a welcome result. Hydrolysis of the ketal followed by an intramolecular reductive amination afforded the penultimate indolizidine, which was subjected to a lithium-ammonia reduction to remove the sulfone and benzyl group, yielding the alkaloid indolizidine 239CD **45**.



Scheme 12 Generation of an *N*-unsubstituted, nonstabilized azomethine ylide and its use in the formation of a *trans*-2,5-disubstituted pyrrolidine.

CONCLUSIONS

Nonstabilized 2-azaallyl anions and azomethine ylides are traditionally difficult to generate, but have the most potential for the synthesis of pyrrolidine-containing natural products. The use of (2-azaallyl)stannanes to make such reactive species shows much promise as a general strategy for the synthesis of such compounds.

ACKNOWLEDGMENTS

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