Cycloadditions

A Lewis Acid Catalyzed Intramolecular [4+3] Cycloaddition Route to Polycyclic Systems That Contain a Seven-Membered Ring**

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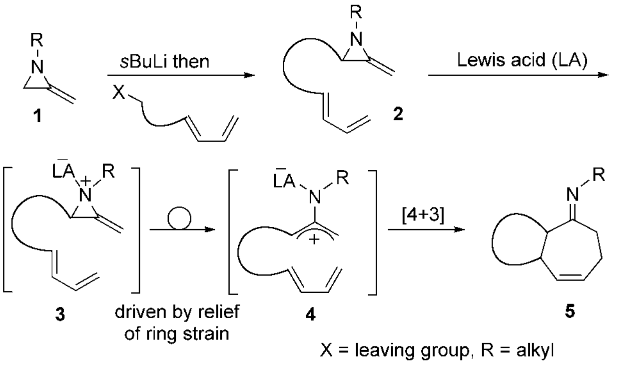
Oxyallyl cations are important intermediates in the synthesis of seven-membered rings by way of [4+3] cycloadditions with 1,3-dienes.[1] The products commonly serve as useful templates in organic synthesis.[2] Intramolecular cycloadditions of oxyallyl cations are especially useful for the construction of complex polycyclic systems.[1e,f,3] For example, Harmata and co-workers have used this approach to make aphanamol I, widdrol, and (+)-dactylol.[1e] Less well-studied are 2-aminoallyl cations, which also participate in [4+3] cycloadditions.[4] Interestingly, these *N*-substituted cations appear to have some advantages over the more extensively studied oxyallyl cations. For example, Cha and co-workers have shown that in some situations cycloadditions that involve 2-aminoallyl cations proceed in higher yields and/or with enhanced stereocontrol.[4g] Furthermore, Kende and Huang have shown that asymmetric induction (up to 60% *ee*) is possible in [4+3] cycloadditions that involve 2-aminoallyl cations by incorporating a chiral, nonracemic element into the cation.[4h] Despite these potential benefits, 2-aminoallyl cations are not widely used because methods for their generation are rather limited. Typically, they involve the solvolysis of unstable α-chloroenamines[4a,d–g] or 2-chloroimines[4c,h] with stoichiometric amounts of silver(I) salts.

As part of a program aimed at exploring the scope and utility of 2-methyleneaziridines **1** in organic synthesis,[5] we realised that these heterocycles might serve as alternative precursors to 2-aminoallyl cations. As methyleneaziridines can be functionalised readily at C3,[5c] we felt that this methodology might be especially useful for the development of intramolecular [4+3] cycloadditions. The general strategy is depicted in Scheme 1. Lithiation and alkylation of **1** with an appropriately functionalized 1,3-diene is expected to provide direct entry to cycloaddition precursor **2**. Complexation of the nitrogen atom of **2** to a suitable Lewis acid might then generate the highly strained and reactive aziridinium ion **3**,[6] which could be expected to undergo fragmentation to Lewis acid complexed 2-aminoallyl cation **4**. Further intramolecular reaction with the appended 1,3-diene would lead to cycloheptenone imine **5**. Thus, in just two synthetic operations, polycyclic systems might be produced from the readily accessible methyleneaziridine **1**. Herein we report our initial studies, which demonstrate the validity of this new approach to seven-membered rings.



Scheme 1. Proposed Lewis acid catalyzed intramolecular [4+3] cycloaddition of 2-methyleneaziridines.

A variety of cycloaddition precursors **6**–**12** were made to probe this chemistry in detail with respect to changes in the 1,3-diene and aziridine components as well as in the nature of the linking tether (Table 1). Lithiation of *N*-benzyl-2-isopropylideneaziridine (*s*BuLi, TMEDA, −78 °C, THF, 5 h) and further reaction with 2-(3-iodopropyl)furan (**13**), 2-(4-iodobutyl)furan (**14**), and 7-iodo-hepta-1,3-diene provided **6** (67%), **7** (71%) and **8** (83%), respectively, after column chromatography. Similarly, reaction of *N*-benzyl-2-cyclohexylideneaziridine with **13**, and separately **14**, gave **9** (61%) and **10** (62%), respectively. We used geometrically pure (*Z*)- and (*E*)-*N*-benzyl-2-ethyleneaziridine,[5d] to produce (*Z*)-**11** (59%) and (*E*)-**11** (71%), respectively, by lithiation and reaction with **13**. Finally, deprotonation and diastereocontrolled alkylation of (*S*)-*N*-(1-phenylethyl)-2-isopropylidene-aziridine gave **12** (63%) as a single diastereomer whose relative configuration was assigned by correlation with literature data.[5c]

Initial cycloaddition studies were conducted on furan-tethered aziridine **6**, which bears a three-carbon linking chain between the reaction partners. After some experimentation, it was determined that treatment of **6** with excess $BF_3{\cdot}OEt_2$ (150 mol%) in dichloromethane at room temperature for 16 h yielded tricyclic imine **15** in 67% yield as a single stereoisomer after silica-gel chromatography (Table 1, entry 1). The structure and stereochemistry of **15** were unambiguously confirmed by X-ray crystallography after reduction of the imine from the *Si* face with sodium cyanoborohydride and conversion of the resulting amine

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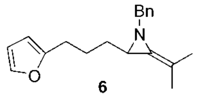
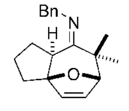
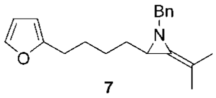
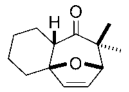
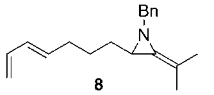
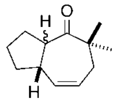
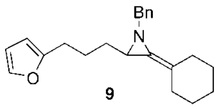
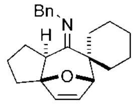
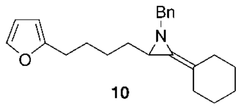
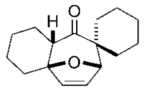
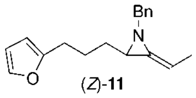
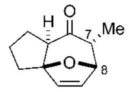
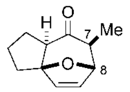
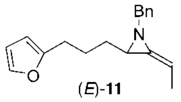
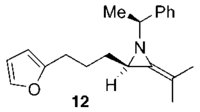
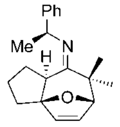
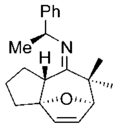
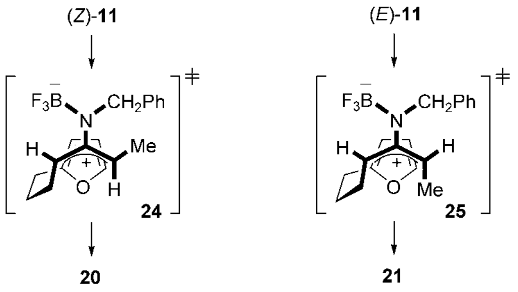
Table 1: Lewis acid catalyzed intramolecular [4+3] cycloaddition of 2-methyleneaziridines **6**–**12**.

Entry	Aziridine	Lewis acid (method)[a]	Cycloadducts	Yield [%][b]	Ratio
1	 **6**	$BF_3{\cdot}OEt_2$ (A)	 **15**	67[d]	–
2		$Sc(OTf)_3$ (B)		57	–
3	 **7**	$BF_3{\cdot}OEt_2$ (C)	 **16**	70[e]	–
4		$Sc(OTf)_3$ (D)		60	–
5	 **8**	$BF_3{\cdot}OEt_2$ (E)	 **17**	53	56:44
6	 **9**	$BF_3{\cdot}OEt_2$ (A)	 **18**	67[f]	–
7	 **10**	$BF_3{\cdot}OEt_2$ (C)	 **19**	65[e]	–
8	 (*Z*)-**11**	$BF_3{\cdot}OEt_2$ (C)[c]	 **20**  **21**	56[f]	**20/21** 80:20
9	 (*E*)-**11**	$BF_3{\cdot}OEt_2$ (C)[c]		45[f]	**20/21** 32:68
10	 **12**	$BF_3{\cdot}OEt_2$ (A)	 **22**  **23**	72	45:55

[a] Method A: $BF_3{\cdot}OEt_2$ (150 mol%), CH_2Cl_2, −30°C, 1 h; then room temperature, 16 h; method B: $Sc(OTf)_3$ (10 mol%), CH_2Cl_2, −30°C, 1 h; then room temperature, 16 h; method C: same as method A; then aqueous H_2SO_4 (10%), MeOH, 16 h, room temperature; method D: same as method B; then aqueous H_2SO_4 (10%), MeOH, 16 h, room temperature; method E: $BF_3{\cdot}OEt_2$ (150 mol%), $ClCH_2CH_2Cl$, −60°C to reflux, 48 h; then aqueous H_2SO_4 (10%), MeOH, 16 h. [b] Yield of isolated product. [c] Cycloaddition and hydrolysis conducted at 50°C. [d] Structure determined by X-ray crystallography after reduction of the imine and formation of the HCl salt (see text). [e] Structure determined by X-ray crystallography. [f] Ring junction stereochemistry confirmed by NOE difference experiments.

into its crystalline hydrochloride salt (data not shown). Significantly, **6** could also be converted into **15** by using just a catalytic amount (10 mol%) of scandium(III) triflate (Table 1, entry 2).[7] Representative procedures are provided in the Supporting Information. Ketone products can be isolated from these reactions by inclusion of an acidic workup step. For example, reaction of aziridine **7** with either $BF_3{\cdot}OEt_2$ or $Sc(OTf)_3$ provided tricyclic ketone **16**, again as a single diastereomer, after workup with aqueous H_2SO_4 in methanol (Table 1, entries 3 and 4). The reaction is not limited to electron-rich dienes such as furan. For example, aziridine **8**, which incorporates a simple monosubstituted 1,3-diene, reacts to give **17** as a mixture of diastereomers. In this case, better yields were obtained by heating **8** and $BF_3{\cdot}Et_2O$ in 1,2-dichloroethane at reflux for 48 h prior to acidic hydrolysis (Table 1, entry 5). The reaction also accommodates changes in the nature of the structure of the methyleneaziridine component (Table 1, entries 6–10). However, we have been unable to determine if intramolecular cycloadditions proceed with methyleneaziridines that do not bear carbon substituents on the alkene terminus.[8] Interestingly some stereochemical "memory" is apparent in the cycloaddition of (*Z*)- and (*E*)-**11**. Both produce **20** and **21**, but the relative amounts of these two diastereomers is dependent on the alkene geometry in the starting material (Table 1, entries 8 and 9). The assignment of the relative stereochemistry within **20** and **21** was made on the basis of the vicinal coupling constant between 7-H and 8-H (**20**: $J_{7,8} = 5.3$ Hz; **21**: $J_{7,8} = 0.0$ Hz).[9] The conversion of diastereomerically pure **12** into near equal quantities of tricycles **22** and **23** is mechanistically significant as it reveals that the stereochemical homogeneity at C3 of **12** is almost completely lost during the cycloaddition (Table 1, entry 10).

We propose that the cycloadditions of **6**, **8**, **9**, **11**, and **12** proceed via a compact transition state, with the tethering arm orientating itself *anti* to the bulky Lewis acid complexed amino substituent. This is illustrated for the conversion of (*Z*)- and (*E*)-**11** into the major products **20** and **21** via **24** and **25**, respectively (Scheme 2). In support of this hypothesis, it is known that cyclic 2-aminoallyl cations favor compact transition states.[4a] Furthermore, the loss of stereochemical integrity in the conversion of **12** into **22** and **23** is consistent with the formation of a planar 2-aminoallyl cation. To account for the switch in stereochemical outcome in the preparation of **16** (and **19**), an extended transition state may prevail with a longer linking tether.[10] However, in considering the analysis of these reactions, it is important to bear in mind that other mechanistic alternatives cannot be ruled out. For example, the formation of **15**–**23** might proceed in a stepwise manner by direct nucleophilic attack of the 1,3-diene unit onto the aziridinium cation **3**, followed by subsequent ring closure of the resulting enamine onto the allylic cation derived from the diene.[11] Efforts to obtain direct evidence



Scheme 2. Postulated transition states for the formation of **20** and **21**.

for the involvement of allylic cation **4** have thus far proved unsuccessful.[12]

To conclude, a very concise new entry into a range of polycyclic systems that contain seven membered rings has been devised based on an intramolecular Lewis acid catalyzed [4+3] cycloaddition of methyleneaziridines. Efforts to develop asymmetric variants of this chemistry by using chiral Lewis acid catalysts or chiral, nonracemic methyleneaziridines are currently ongoing in our laboratory.

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[1] For reviews, see: a) R. Noyori, Y. Hayakawa, *Org. React.* **1983**, *29*, 163; b) H. M. R. Hoffmann, *Angew. Chem.* **1984**, *96*, 29; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 1; c) J. Mann, *Tetrahedron* **1986**, *42*, 4611; d) J. H. Rigby, F. C. Pigge, *Org. React.* **1997**, *51*, 351; e) M. Harmata, *Acc. Chem. Res.* **2001**, *34*, 595; f) M. Harmata, P. Rashatasakhon, *Tetrahedron* **2003**, *59*, 2371.

[2] M. Lautens, *Synlett* **1993**, 177; I. V. Hartung, H. M. R. Hoffmann, *Angew. Chem.* **2004**, *116*, 1968; *Angew. Chem. Int. Ed.* **2004**, *43*, 1934.

[3] For a recent example, see: C. Rameshkumar, R. P. Hsung, *Angew. Chem.* **2004**, *116*, 625; *Angew. Chem. Int. Ed.* **2004**, *43*, 615.

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[5] a) N. Prévost, M. Shipman, *Org. Lett.* **2001**, *3*, 2383; b) J. F. Hayes, M. Shipman, H. Twin, *J. Org. Chem.* **2002**, *67*, 935; c) J. F. Hayes, N. Prévost, I. Prokes, M. Shipman, A. M. Z. Slawin, H. Twin, *Chem. Commun.* **2003**, 1344; d) J. J. Shiers, M. Shipman, J. F. Hayes, A. M. Z. Slawin, *J. Am. Chem. Soc.* **2004**, *126*, 6868, and references therein.

[6] Protonation and methylation of *N*-substituted methyleneaziridines with $HFSO_3/SbF_5$ and $[Me_2Cl]^+[SbF_5Cl]^-$, respectively, are known to produce the corresponding methyleneaziridinium cations; see: E. Jongejan, H. Steinberg, T. J. de Boer, *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 145.

[7] Examples of catalytic [4+3] cycloadditions of allyl cations are uncommon; for a recent example with scandium(III) triflate, see: M. Harmata, U. Sharma, *Org. Lett.* **2000**, *2*, 2703.

[8] Attempts to make substrates that bear two hydrogen atoms on the exocyclic double bond of the methyleneaziridine have been hampered by their lack of stability during silica-gel chromatography. However, preliminary experiments establish that 2-methyleneaziridines do participate in *intermolecular* [4+3] cycloadditions. For example, the reaction of 1-(1-phenylethyl)-2-methyleneaziridine with excess furan ($BF_3{\cdot}Et_2O$ (1.5 equiv), CH_2Cl_2, room temperature, 16 h; then aqueous AcOH (1M), 2 h) yields 8-oxabicyclo[3.2.1]octan-3-one in 24% yield (unoptimized).

[9] A. M. Montaña, S. Ribes, P. M. Grima, F. Garcia, *Magn. Reson. Chem.* **1998**, *36*, 174.

[10] In the case of **16** (and **19**), it is conceivable that the switch in the preferred diastereomer is not due to a change in the cycloaddition transition state but results from thermodynamic equilibration of the α stereocenter of the ketone during hydrolysis. From labeling experiments, we know that hydrolysis (D_2SO_4/D_2O in CD_3OD) leads to some deuterium incorporation (≈36% D) into **16** at the center α to the ketone.

[11] For recent theoretical studies on [4+3] cycloadditions that support stepwise mechanisms, see: M. Harmata, P. R. Schreiner, *Org. Lett.* **2001**, *3*, 3663; J. A. Sáez, M. Arnó, L. R. Domingo, *Org. Lett.* **2003**, *5*, 4117.

[12] A large downfield shift of the signal for the aziridine methylene group is observed in the ^1H NMR spectrum (400 MHz, CD_2Cl_2) of *N*-benzyl-2-isopropylideneaziridine upon addition of $BF_3{\cdot}Et_2O$ (150 mol%) which suggests coordination of the nitrogen atom of the aziridine to the Lewis acid. Selected data: uncomplexed: $\delta = 2.37$ ppm (2H, s); complexed: $\delta = 3.09$ (1H, s), 2.52 ppm (1H, s). However, signals for the allylic cation were not observed.