Cycloaddition

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A Masked 1,3-Dipole Revealed from Aziridines**

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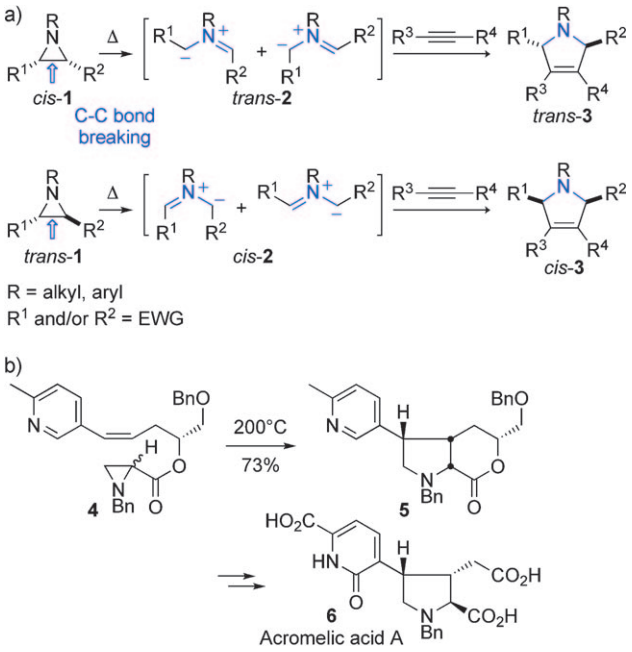
aziridines · cycloaddition · heterocycles · Lewis acids

In memory of Philippe Klotz

Heterocycles are thought to be part of more than half of the known organic compounds. A large number of them are natural products and many synthetic derivatives are used as drugs, agrochemicals, dyes, or materials. A recent review has highlighted that the heterocyclic chemical space is far from having been fully explored and hundreds of simple structures, predicted to be tractable, still remain to be conquered.[1] Needless to say the search for innovative routes towards their formation is still a field of intense investigation. Among the several strategies available, cycloadditions offer unequaled opportunities since multiple bonds can be created in one step with high degrees of efficiency, selectivity, and atom economy.[2] Of particular significance is the 1,3-dipolar cycloaddition which has been claimed to be "the single most important method for the construction of heterocyclic five-membered rings in organic chemistry".[2b]

Azomethine ylides are common 1,3-dipoles especially useful for the preparation of five-membered nitrogen heterocycles, *N*-alkyl- or *N*-arylaziridines being one of their most widely used synthetic precursors.[3] Heine and Peavy,[4a] Padwa and Hamilton,[4b] and Huisgen et al.[4c] first reported azomethine ylide formation by thermal aziridine ring-opening, which proceeds through a conrotatory C–C bond-breaking process according to the Woodward–Hoffmann rules. The *cis*- and *trans*-aziridines **1** therefore lead to *trans*- and *cis*-azomethine ylides **2**, respectively, which can then be trapped by various dipolarophiles (e.g., alkynes) in concerted 1,3-dipolar cycloadditions to give nitrogen heterocycles (e.g., **3**; Scheme 1 a). A noteworthy application of this reaction is the concise enantioselective synthesis of acromelic acid A (**6**) which was successfully developed by Takano et al. (Scheme 1 b).[5]

The chemistry of aziridines is centered on ring-opening reactions with a wide range of nucleophiles as a consequence of their ring strain.[6] These reactions have led to the formation of various important 1,2-difunctionalized scaffolds such as amino acids, amino sugars, and β-lactams. Interestingly, this reactivity has been elegantly applied to the formation of five-membered nitrogen heterocycles through



Scheme 1. a) Aziridines in 1,3-dipolar cycloadditions involving azomethine ylides. b) Application of methodology to natural product synthesis. EWG = electron-withdrawing group, Bn = benzyl.

a formal [3+2] cycloaddition involving C–N bond breaking. Hiyama and co-workers, and then Zwanenburg and co-workers described the reaction of aziridines (**7**) with nitriles in the presence of boron trifluoride etherate for the preparation of imidazolidines.[7] Scheme 2 a shows as an example the reaction of **7** with acetonitrile to **9**. These Lewis acid mediated transformations have been proposed to proceed in a Ritter fashion by an initial S_N2-type aziridine ring-opening to give intermediates such as **8**. The use of π nucleophiles such as allylsilanes (e.g., **10**; Scheme 2 b), alkenes, and alkynyltungsten complexes in the presence of a Lewis acid has also been shown to induce similar stepwise cycloadditions thereby suggesting that aziridines may behave as masked 1,3-dipoles.[8,9] The synthetic potential of this methodology is demonstrated by its application to the total synthesis of physostigmine (**15**; Scheme 2 c).[10]

This formal [3+2] cycloaddition is generally observed with simple aliphatic aziridines. In contrast, the introduction of substituents, likely to stabilize a positive charge, onto one of the carbon atoms of an N-sulfonylated aziridine generates a very different reactivity. Mann and co-workers have been the first to investigate the formation of the uncommon zwitter-

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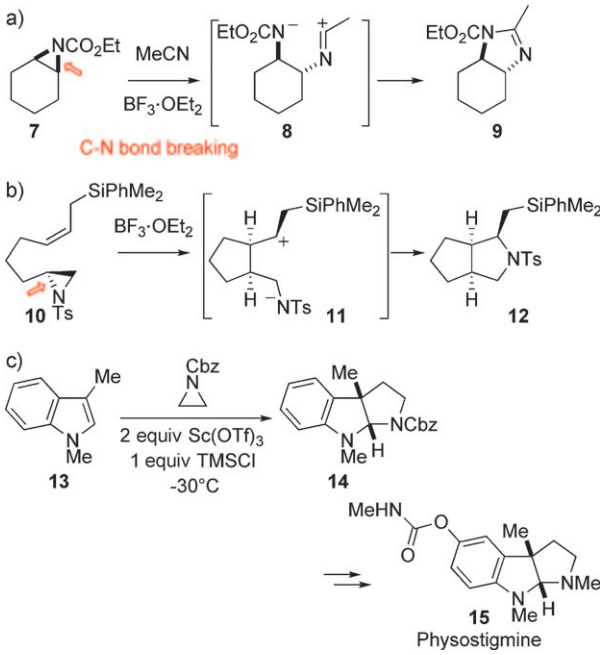
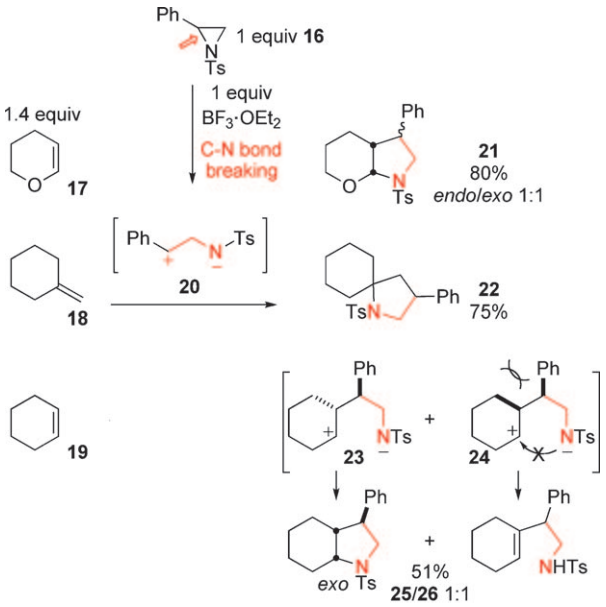


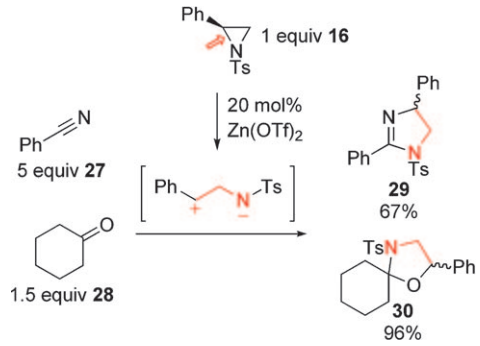
Scheme 2. Aziridines in formal [3+2] cycloadditions involving S_N2-type nucleophilic ring-opening. Cbz = benzyloxycarbonyl, Tf = trifluorosulfonyl, TMS = trimethylsilyl.

ionic 1,3-dipole **20** generated from 2-phenyl-*N*-tosylaziridine (**16**) by C–N bond cleavage,[11] a process induced by the addition of a stoichiometric amount of boron trifluoride etherate or a catalytic quantity of scandium(III) triflate (Scheme 3).[12] The resulting electron-deficient intermediate was then shown to efficiently react under kinetic control with non-activated alkenes to give the corresponding pyrrolidines. Moreover, starting from dihydropyran **17** or *gem*-disubstituted olefin **18**, the formation of only one regioisomer, **21** or **22**,



Scheme 3. 2-Phenyl-*N*-tosylaziridine (**16**) in 1,3-dipolar cycloaddition reactions with alkenes. Ts = 4-toluenesulfonyl.

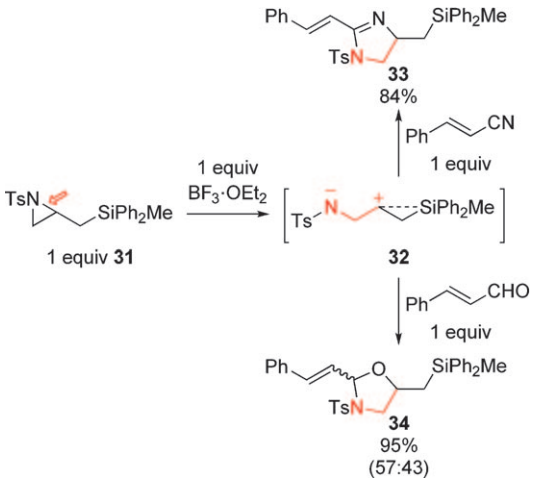
respectively, is observed in good yield. Singh and co-workers have since then demonstrated that such Lewis acid mediated [3+2] cycloadditions also occur with nitriles (e.g., **27**) and ketones (e.g., **28**) to afford imidazolines **29** and oxazolidines **30**, respectively (Scheme 4).[13]



Scheme 4. 2-Phenyl-*N*-tosylaziridine (**16**) in 1,3-dipolar cycloaddition reactions with nitriles and ketones.

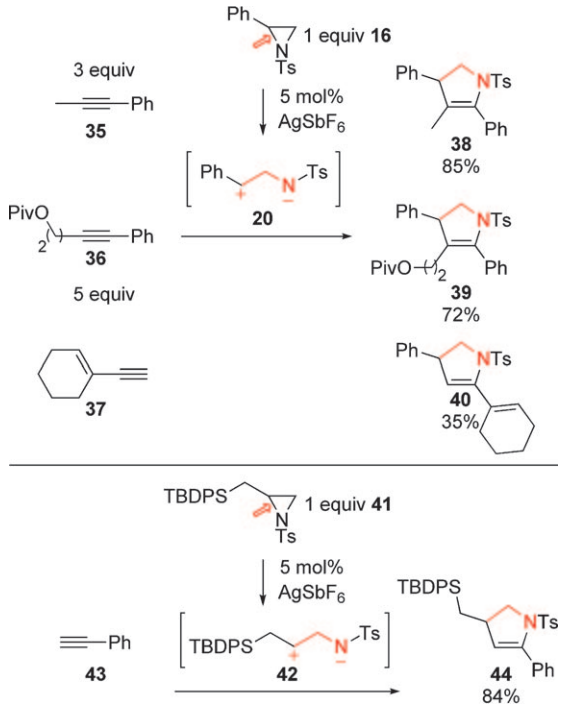
In contrast to azomethine ylides **2**, which are internally stabilized by delocalization, the two charges of the new 1,3-dipole **20** are stabilized in an *exo* fashion, simultaneously by both the tosyl and phenyl groups. Formation of this zwitterionic intermediate is suggested by the isolation of racemic imidazolidines and oxazolidines starting from optically pure aziridines.[13b] The complexation of the Lewis acid to one of the sulfonyl oxygen atoms probably induces the generation of a discrete stable benzylic carbocation. Moreover, the cycloaddition is presumed to occur by a stepwise pathway as indicated by the reaction with cyclohexene (**19**; see Scheme 3).[11b] In contrast to the case of dihydropyran, only the corresponding *exo*-cycloadduct **25** is isolated together with the noncyclized derivative **26**. Both products would arise from the initial reaction between cyclohexene and dipole **20** to afford intermediates **23** and **24**. Whereas the former leads to the expected cycloadduct, the latter would preferentially undergo elimination since *gauche* interactions would disfavor cyclization. It is suggested that stabilization of the cation in the case of dihydropyran **17** is responsible for the formation of a 1:1 ratio of the *endo*/*exo*-compounds **21**. It is also probable that, as with *gem*-disubstituted alkenes, such a stabilizing effect strongly influences the regioselectivity of the cycloaddition.

Importantly, recent studies have appeared that greatly improve the scope and synthetic value of this new type of [3+2] cycloaddition compared to a cyclic carboamination. A clever application of the β-silicon effect has allowed the generation of a similar 1,3-dipole **32** from silylmethyl-substituted aziridine **31** (Scheme 5).[14] Use of a nitrile or a carbonyl compound in the presence of a stoichiometric amount of boron trifluoride etherate leads to the corresponding imidazoline **33** and oxazolidine **34**, respectively, in very good yields. The silylmethyl moiety then offers the opportunity to carry out subsequent functional group transformations since it can be considered as a masked hydroxymethyl substituent.



Scheme 5. The formation of a 1,3-dipole from a 2-silylmethyl-*N*-tosylaziridine.

Even more interestingly, alkynes have been shown to act as highly efficient dipolarophiles in these cycloadditions in the presence of a catalytic quantity of various Lewis acids such as $FeCl_3$ (10 mol%)[15] or $AgSbF_6$ (5 mol%).[16] Brønsted acids, for example TfOH (5 mol%), have also proven to be compatible.[16] A wide range of nonsymmetrical alkyl- and arylalkynes, though introduced in slight excess, can be used in combination with 2-phenyl- (**16**) or 2-silylmethyl-*N*-tosylaziridine (**41**) to afford various substituted 2-pyrrolines with complete regioselectivity (Scheme 6). The reaction tolerates the presence of a methyl ether unit, a pivaloic ester group (**36**), and a cyclopropyl ring, and excellent chemoselectivity is



Scheme 6. Aziridines in 1,3-dipolar cycloaddition reactions with alkynes. TBDPS = *tert*-butyldiphenylsilyl.

observed in the case of 1-ethynylcyclohex-1-ene (**37**). Test experiments starting from an optically pure aziridine, as well as using electronically differentiated phenylacetylenes, once again support the hypothesis of a stepwise process via the zwitterionic 1,3-dipoles **20** and **42**.

Comparison of the transformations involving aziridine-derived azomethine ylides with those described above clearly demonstrates that the formation of the type of 1,3-dipole is controlled by the aziridine substitution. Changing the electronic nature of the functions located on the nitrogen atom as well as on the carbon atoms of the ring allows the induction of a distinct bond cleavage. Breaking of the C–N (C–C) bond specifically occurs in the presence of an electron-withdrawing (donating) group on the nitrogen atom and a substituent on the carbon atom which stabilizes the generated carbocation (anion). Fundamentally, since two C–N bonds are theoretically in competition, this substituent directs the regioselectivity of the ring-opening thereby favoring the formation of a single dipole.

In conclusion, these zwitterionic intermediates (C^+–C–N^- versus the former C^+–N–C^-) open new avenues to discover cycloadditions likely to produce novel heterocyclic scaffolds. Additionally, Mann and co-workers successfully demonstrated that analogous 1,4-dipoles can be generated from azetidines.[17] However, much work remains to be done to improve both the efficiency and the stereoselectivity of these formal [3+2] cycloadditions. In this context, particular attention should be paid to the development of conditions allowing conservation of the geometry of the starting materials. The *cis* and *trans* aziridines indeed generally afford a mixture of cycloadducts whereas *E* or *Z* alkenes have never been studied thus far. Moreover, this strategy has been applied only starting from *N*-arenesulfonylaziridines. Since removal of an *N*-sulfonyl group sometimes proves to be troublesome, it would be useful to determine whether the reaction could be extended to amides or carbamates. Finally, these recent works tend to support the idea that heterocycles, even the simplest of them, have not unveiled all their secrets.

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