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Aziridine Synthesis via Nucleophilic Attack of Carbene Equivalents on Imines: the Aza-Darzens Reaction

Joseph Sweeney*[a]

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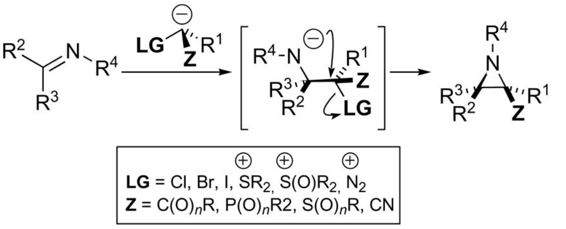
The development of new methods for the efficient synthesis of aziridines has been of considerable interest to researchers for more than 60 years, but no single method has yet emerged as uniformly applicable, especially for asymmetric synthesis of chiral aziridines. One method which has been intensely examined and expanded of late involves the nucleophilic addition to imines by anions bearing α-leaving groups; by analogy with the glycidate epoxide synthesis, these processes are often described as "aza-Darzens reactions". This Microreview gives a summary of the area, with a focus on contemporary developments.

Introduction

Aziridines are versatile and powerful synthetic intermediates,[1] but their use in academic and industrial chemistry is much less widespread than that of the corresponding oxygen analogues, epoxides. This under-exploitation is perhaps due to the relative dearth of methods available for the preparation of aziridines. The aza-Darzens reaction is one of the oldest and most flexible methods for preparation of functional aziridines: the process involves the reaction of imines with stabilized anions bearing α-leaving groups. The aza-Darzens reaction has been used to prepare a diverse range of mono-, di- and trisubstituted aziridines (Referring to substitution at carbon); the reaction has not been widely applied to the preparation of tetra-substituted aziridines. The mechanism has two distinct steps: initial (potentially reversible) nucleophilic attack upon the C=N bond followed by favoured (and normally irreversible) 3-*exo*-*tet* cyclization of the intermediate amide anions [Equation (1)]. Overall, therefore, the nucleophile is acting as a *carbene equivalent*; however, notwithstanding this, relatively few reactions of carbenes or carbenoids with imines proceed by a Darzens-like mechanism (for instance, reacting via formation and in situ cyclization of azomethine ylides[2]) and these reactions are, therefore, outside the scope of this review.[3]



(1)

Aza-Darzens Reaction: General Features[1a–1c,1f–1i,4]

A broad range of stabilizing groups is tolerated in the anionic component of the aza-Darzens reaction; carbonyl and sulfur functionalities dominate the literature reports, but many other substituents mediate the transformation. A narrower range of leaving groups has been used, and reactions normally involve α-halogeno and α-sulfonio anions.

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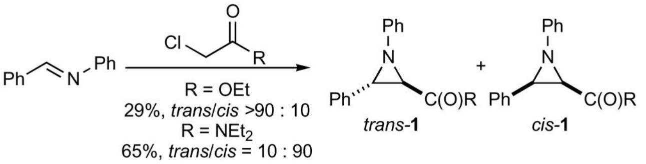
[a] Department of Chemistry, University of Reading,
Reading RG6 6AD, United Kingdom
Fax: +44-118-378-6331
E-mail: j.b.sweeney@rdg.ac.uk

A native of Liverpool, Joe Sweeney studied at Imperial College (B. Sc. 1984) before obtaining a doctorate in Jack Baldwin's group at Oxford, working on new synthetic methods using allylstannanes and aziridines. During these studies, the first reactions of serine-derived aziridines with organocuprates were established. After finishing his D. Phil. in 1987, Joe was a Royal Society of Chemistry Fellow in Steve Benner's group (ETH, Zürich), and started his academic career as an organic chemist at the University of Leicester in 1989; in 1990, he moved to the University of Bristol. Since 1996 Joe has been a faculty member at the University of Reading, where he is currently Professor of Synthesis and Chemical Biology. His principal research interests are asymmetric and catalytic synthesis and useful mimicry of bioactive macromolecules. His principal diversions are his family and Liverpool Football Club.

Aza-Darzens Reaction Using α-Halogeno Anions

The first true aza-Darzens reaction was reported by Deyrup, in 1969.[5] Thus, ethyl chloroacetate reacted with *N*-phenylbenzaldimine in the presence of KO*t*Bu to give *trans*-aziridine **1**, in mediocre yield [Equation (2)]. The yield of the reaction was improved when the corresponding chlorodiethylamide was used, and the diastereoselectivity of the reaction was inverted. This observation was rationalized as arising from a change in the relative rates of the two steps in the mechanism (aldol-like reaction and ring closure) in the reaction of the less-stable amide enolate.



trans-**1** *cis*-**1**

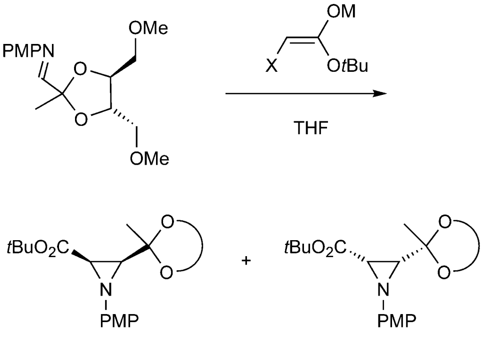
(2)

This single example was subsequently developed into a general method in the 1970s, when Wartski described the reaction of a range of esters and nitriles with *N*-phenylarylimines to give aziridines, in good yields.[6] Once again, the diastereomer ratios obtained were variable, with *trans*-isomers usually predominating but with unpredictable stereoselectivity being observed for certain substrates (Table 1). The method was subsequently extrapolated to dichloroacetates, which reacted with arylaldimines to give chloroaziridines, as single diastereoisomers (of undetermined configuration).[7] The use of halo esters in aza-Darzens processes has been developed and a broad range of aziridines may be prepared using the method.[8]

Since the original reports, many other halogenated anions have been reported as useful in aza-Darzens processes. Thus, sulfone-stabilized anions undergo efficient aza-Darzens reactions with imines, giving 2-(phenylsulfonyl)-aziridines (Table 2).[9–11]

(Chloromethyl)dihydrooxazoles have also functioned as useful reagents in aza-Darzens reactions, giving aziridines in good yields.[13]

The first reports of asymmetric aza-Darzens reactions of α-halogeno anions were facilitated using reagent control in the imine component: chiral acetals of 2-keto imines react with excellent, cation-dependent diastereoselectivity.[14] Thus, lithium enolates prefer to add to the imine *si*-face, and zinc enolates have the opposite predilection [Equation (3)].

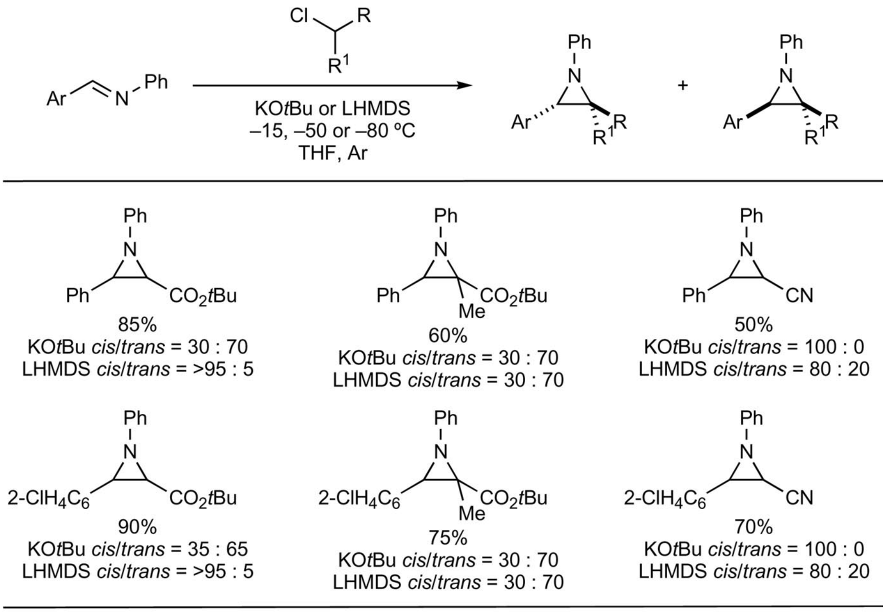


44%, 91 : 9, M = Li, X = Cl, –78 °C → r.t.
35%,100 : 0, M = Li, X = Cl, –78 → 50 °C
59%, 0 : 100, M = ZnBr, X = Br, –78 °C → r.t.

(3)

Chiral non-racemic sulfinimines have been shown to undergo a diverse range of aza-Darzens reaction with α-

Table 1. Aza-Darzens reaction of α-chloro esters and nitriles with *N*-phenylimines.



85%
KO*t*Bu *cis*/*trans* = 30 : 70
LHMDS *cis*/*trans* = >95 : 5

60%
KO*t*Bu *cis*/*trans* = 30 : 70
LHMDS *cis*/*trans* = 30 : 70

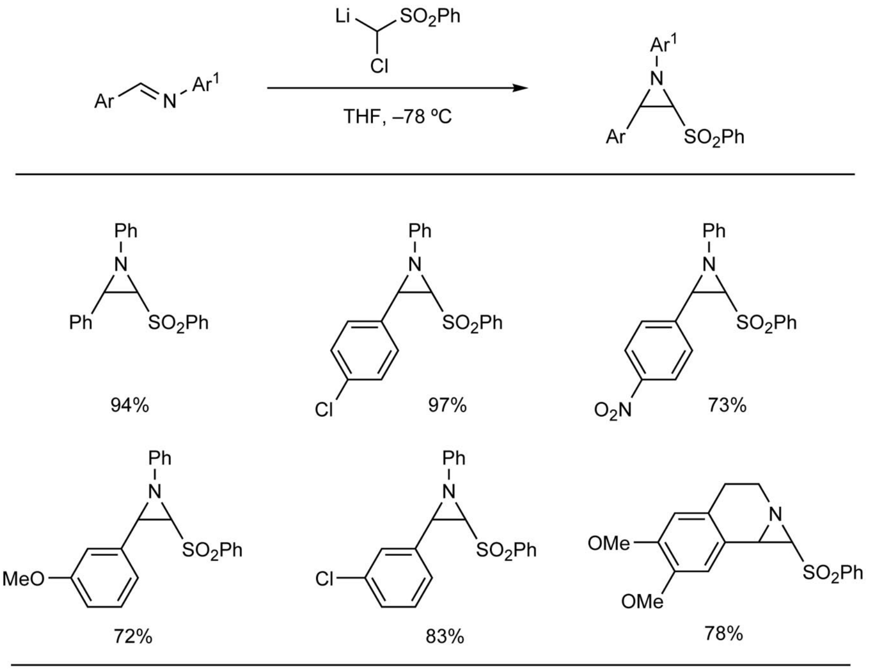
50%
KO*t*Bu *cis*/*trans* = 100 : 0
LHMDS *cis*/*trans* = 80 : 20

90%
KO*t*Bu *cis*/*trans* = 35 : 65
LHMDS *cis*/*trans* = >95 : 5

75%
KO*t*Bu *cis*/*trans* = 30 : 70
LHMDS *cis*/*trans* = 30 : 70

70%
KO*t*Bu *cis*/*trans* = 100 : 0
LHMDS *cis*/*trans* = 80 : 20

Table 2. Aza-Darzens reaction of α-chloro sulfones.[12]



bromo-,[15,16] and chloro enolates to give *cis*-*N*-(*p*-tolylsulfinyl)aziridine-2-carboxylates and -phosphonates,[17,18] with excellent diastereoselectivity (Table 3). Again, the nature of the enolate cation plays a crucial role, both in controlling the topology of the process, and suppressing imine isomerisation.[19] This methodology has been employed to excellent effect in a wide range of target-oriented syntheses.[20,21]

Asymmetric aza-Darzens synthesis using reagent control in the anionic component has also been reported. *N*-Diphenylphosphinyl-("*N*-Dpp")benzaldimines react with chiral α-bromoacylsultams to give diastereomerically pure aziridines in good yield (Table 4).[23] The reaction generally gives *cis*-aziridines as single isomers, but steric and electronic effects are important: where *ortho*-substituents are present in the aryl unit, *trans*-aziridines often dominate the

Table 3. Asymmetric aza-Darzens by reagent control: using chiral sulfimines.[22]

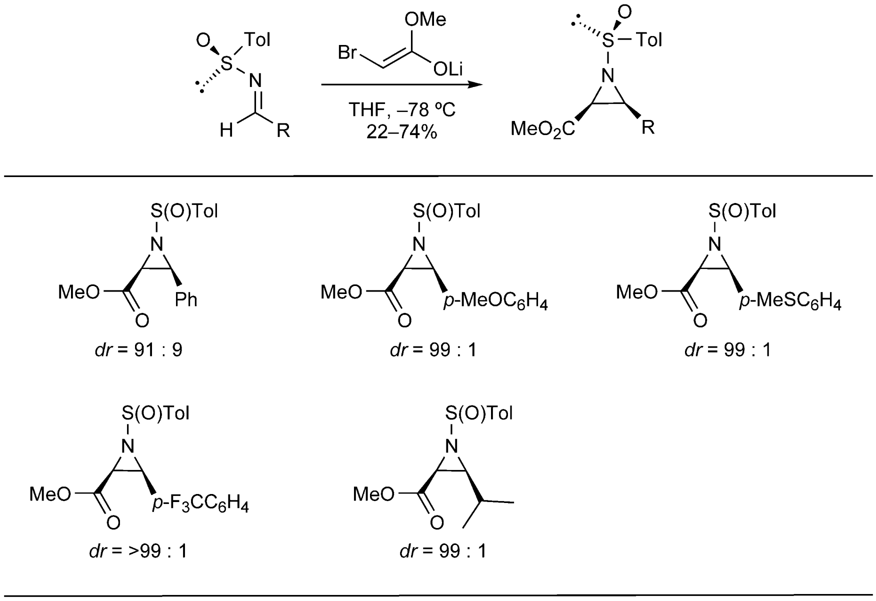
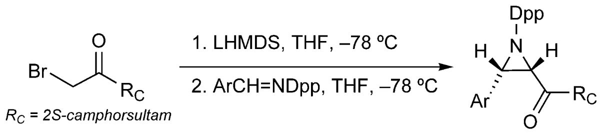
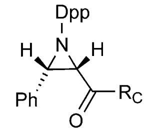
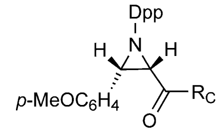
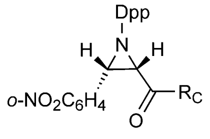
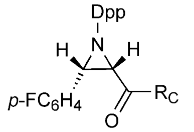
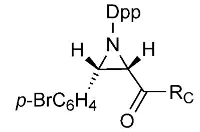
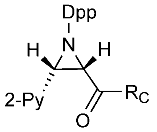


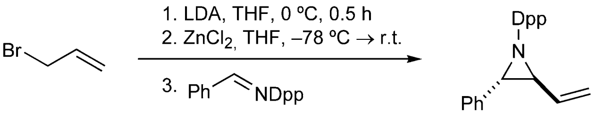
Table 4. Asymmetric aza-Darzens by reagent control: using chiral sultamoyl enolates.



 71% *cis/trans* = 100 : 0 *dr* = >95 : 5	 60% *cis/trans* = 100 : 0 *dr* = >95 : 5	 72% *cis/trans* = 100 : 0 *dr* = >95 : 5
 60% *cis/trans* = 100 : 0 *dr* = >95 : 5	 65% *cis/trans* = 100 : 0 *dr* = >95 : 5	 71% *cis/trans* = 100 : 0 *dr* = >95 : 5

reaction [for instance (2-halo)arylimines give only *trans*-aziridines[24] whereas 3- and 4-substituted arylimines give exclusively *cis*-isomers].[25] A single analogous reaction of a menthyl ester of bromoacetate was lower-yielding and less stereoselective.[26]

Carbonyl stabilization of anions is not a pre-requisite for aza-Darzens reactions, and adjacent alkenyl or benzylic substitution can facilitate the processes. Thus, vinylaziridines are frequently made in this way, for instance by α-deprotonation of allyl halides, and reaction of the anions with imines. By such a method, *N*-alkyl-vinylaziridines were first obtained by reaction of *gem*-chloro(methyl)allyllithium with aldimines and ketimines.[27] The lithio anions were originally obtained by transmetallation,[28] but direct deprotonation is straightforward: *N*-Dpp-benzaldimines react with 2-lithioallyl bromide with good diastereocontrol, to give mainly *trans*-ethenyl-*N*-Dpp-aziridines [Equation (4)].[29]



58%
cis/trans = 90 : 10 (4)

A similar type of halogenated allyl anion is involved in the reaction of cyclopropene-1,1-dicarboxylic acids with imines, which gives *cis*-vinylaziridines by means of a formal [1+2] cycloaddition reaction (Table 5).[30] The reaction is catalyzed by a sub-stoichiometric amount of NaI, and involves halide ring-opening of the cyclopropene, nucleophilic attack of the intermediate (2-iodo)vinylenolate upon the sulfonylimine, followed by iodide displacement from the intermediate alkenyl malonate.

3-Chloroallenylzinc compounds react with sulfinimines via initial nucleophilic attack at the imine moiety, followed by bromide displacement, with high levels of diastereocontrol. Racemic zinc reagents undergo reaction with single enantiomers of sulfinimine with excellent stereoselectivity, by means of a closed transition state (Table 6).[31]

Anion stabilization by adjacent multiple bonds is not an absolute requirement for efficient aza-Darzens reaction; for instance, [dibromo(silyl)methyl]lithium reacts with *N*-arylimines to give polyfunctionalized aziridines, useful for preparation of a range of highly substituted aziridines.[32] Thus, trisubstituted aziridines can be obtained by reaction with Grignard reagents, with high *trans*-stereoselectivity (Table 7).

Aza-Darzens Reaction Using Sulfonium and Sulfoxonium Ylides

The use of sulfur substituents to stabilize adjacent anionic character *and* subsequently act as leaving groups has been widely exploited in aziridine syntheses. Although the first descriptions of a "true" (i.e., using α-halogeno anions) aza-Darzens process was not reported until the end of the 1960s [vide supra, Equation (2)],[5] the reactions of 2-sulfonium and 2-sulfoxonium anions with imines were first described in the early 1960s; these processes were the first syntheses of aziridines by aza-Darzens like reaction. Corey and Chaykovsky first reported the use of sulfoxonium and sulfonium methylides to aziridinate imines,[33] with roughly contemporaneous description of similar sulfonium aziridination reported by Franzen and Driessen.[34]

Aza-Darzens Reaction Using Unsaturated Sulfonium Ylides

Aziridinations using unstabilized sulfonium ylides can be inefficient, due to the instability of the sulfur reagents.

Table 5. Aza-Darzens synthesis of vinylaziridines via 1,1-dicarboxylic acids.[30]

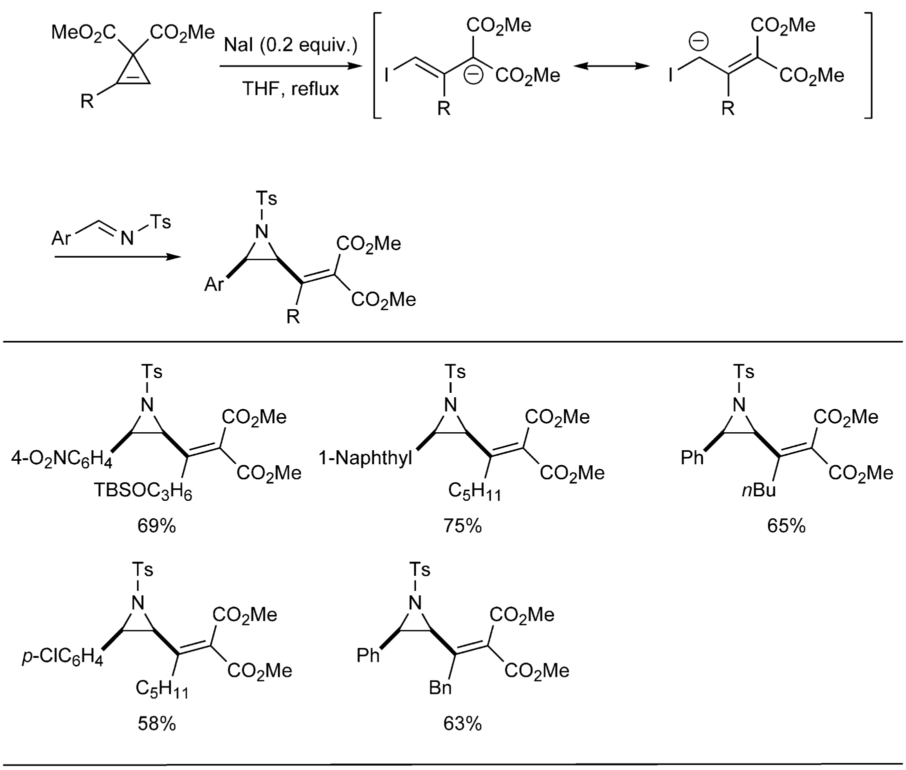


Table 6. Aza-Darzens synthesis of 2-ethenylaziridines via chiral sulfoximines.[31]

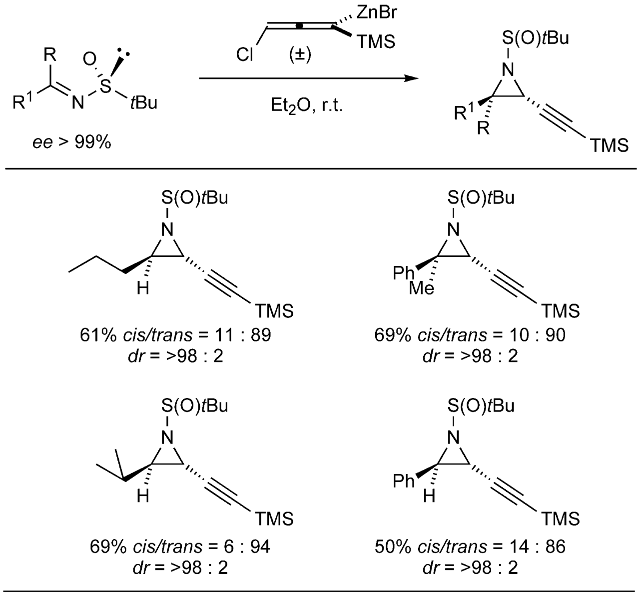
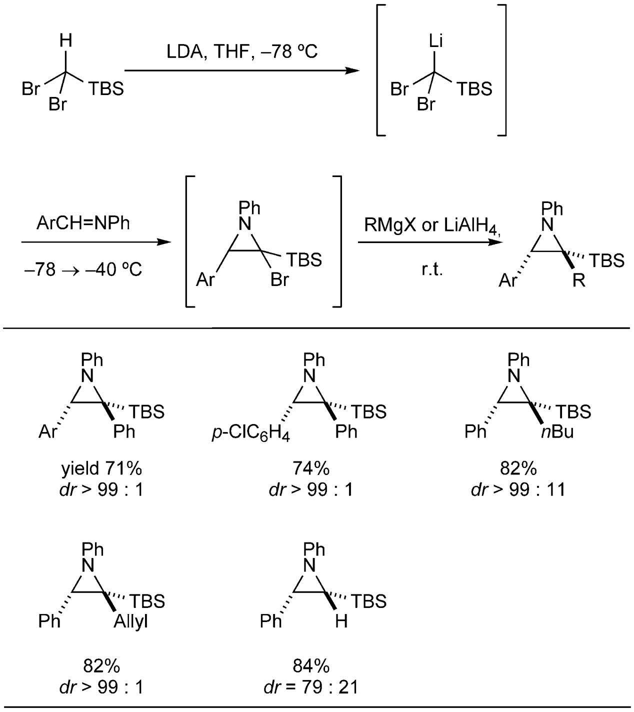
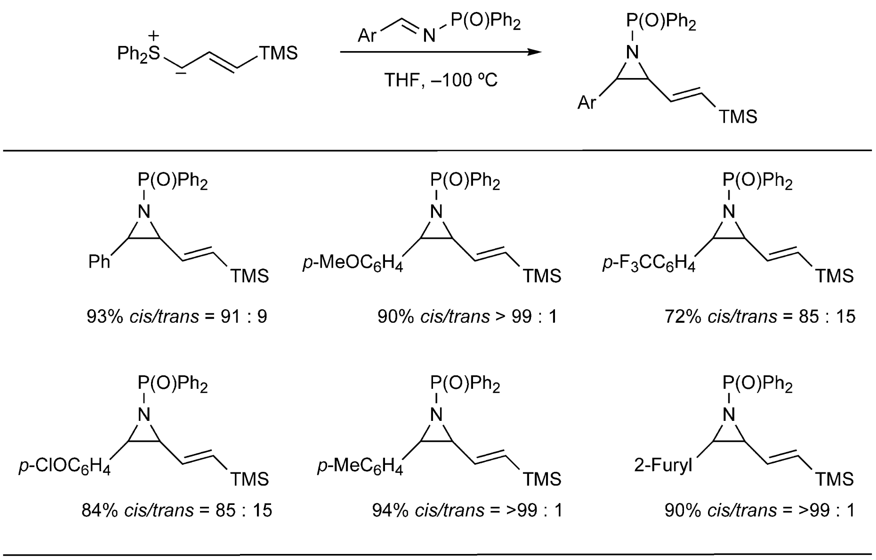


Table 7. Aza-Darzens synthesis of tetra-substituted aziridines using [dibromo(silyl)methyl]lithium.[32]



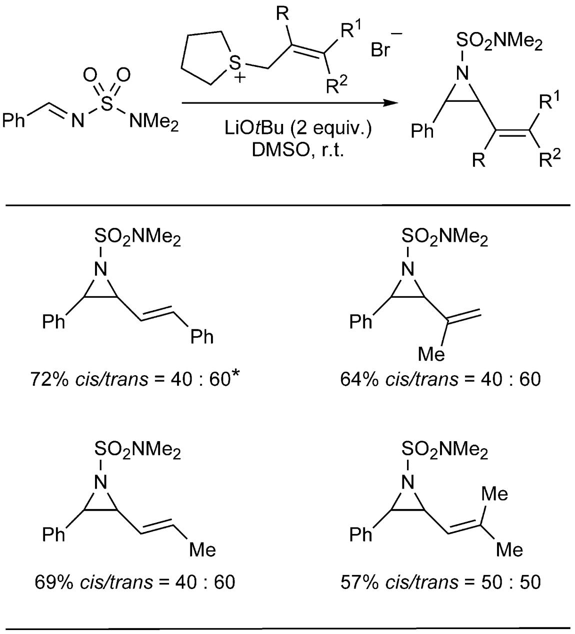
More stable ylides, derived from allylsulfonium salts,[35] react in considerably better yields with tosyl-[36] and phosphanyl-imines, and with broader scope, but only if reactions are carried out at very low temperature (typically –100 °C) (Table 8).[37] These stringent conditions are essential if one is to obtain high diastereoselectivity; the *cis*/*trans* ratio is also dependent upon the precise structure of the ylide, with diphenylsulfonium ylides leading predominantly to *cis*-vinylaziridines, and dimethylsulfonium salts lead to *trans*-aziridines.

Table 8. Aza-Darzens reaction of dpp-imines with allylsulfonium ylides.[37]



N-Sulfamoylimines react efficiently with allyl sulfonium ylides, to give substituted vinylaziridines bearing a more practical *N*-substituent than the ubiquitous sulfonamido group (Table 9).[38] However, although the reactions proceed in acceptable yield, they are poorly stereoselective.

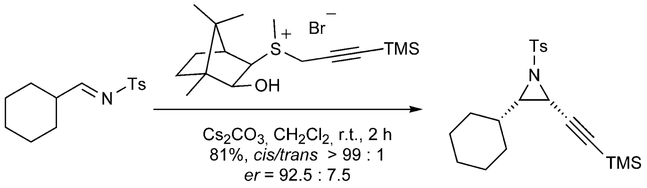
Table 9. Aza-Darzens reaction of *N*-(sulfamido)imines.[38]



* Chloride salt used

Asymmetric Aza-Darzens Reaction Using Chiral Sulfonium Ylides

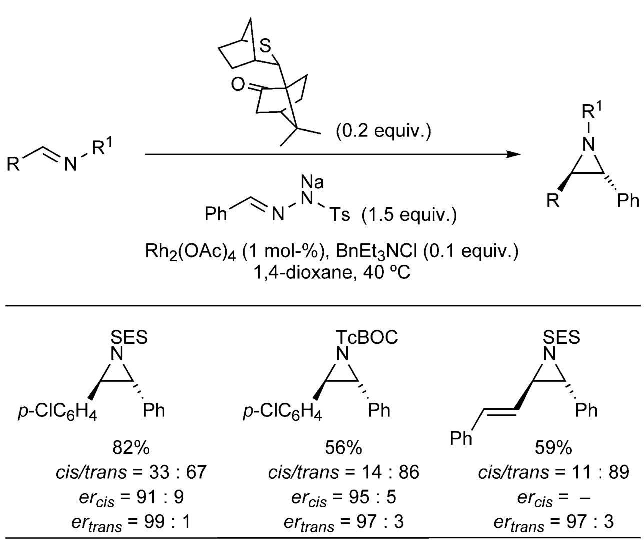
Chiral alkynyl sulfonium ylides react with *N*-tosylimines to give 3-aryl- and 3-alkyl-2-[2′-(trimethylsilyl)ethynyl]aziridines in high yield and with excellent diastereoselectivity, and though the enantiocontrol is moderate, a single recrystallization provides highly enantiomerically enriched products [Equation (5)].[39,40] In addition, the reaction conditions are mild and the procedure operationally simple.



(5)

Chiral sulfonium ylides (formed in situ from diazo compounds and a metal catalyst) react with a range of imines

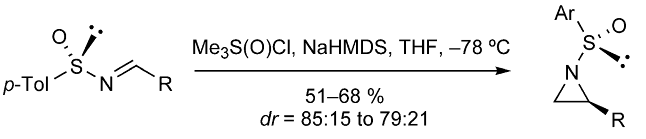
Table 10. Catalytic asymmetric aza-Darzens reaction using chiral sulfur ylides.[43]



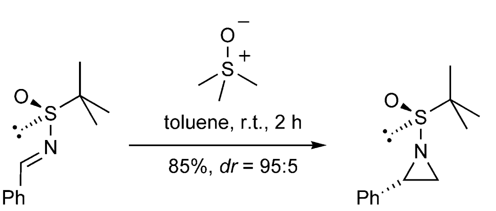
(tosyl, SES, Dpp and carbamoyl) to give aziridines with acceptable diastereo- and enantiocontrol (Table 10).[41] This method offers several significant advantages over other process, especially given that, although sulfonamides can sometimes be cleaved under mild conditions,[42] the tolylsulfonamide moiety in particular is normally rather obdurate and is often difficult to remove under mild conditions. The ability to routinely access non-sulfonylated aziridines makes this method of real utility.

Asymmetric Aza-Darzens Reaction by Addition of Sulfur Ylides to Chiral Imines

Because the original reports of the utility of sulfur ylides in aza-Darzens processes, the use of chiral imines has been intensely studied as an asymmetric aziridination method.[44] Sulfoxonium methylene ylides aziridinate enantiomerically pure tolylsulfinimines at low temperature, with moderate diastereoselectivity [Equation (6)].[45,46] When *tert*-butylsulfinimines are employed, diastereoselectivities are improved [Equation (7)];[47] these substrates also allow aziridination of aliphatic imines, using a modified solvent system (Table 11),[48] with high levels of stereoselectivity ($dr > 90:10$). The method is very practical, because the diastereomeric products are often chromatographically separable. The stability of the ylide is crucial to the stereoselectivity of the aziridination: when (less-stabilized) dimethylsulfonium methylides are used in the reactions, the diastereoselectivity is often diminished or even reversed.

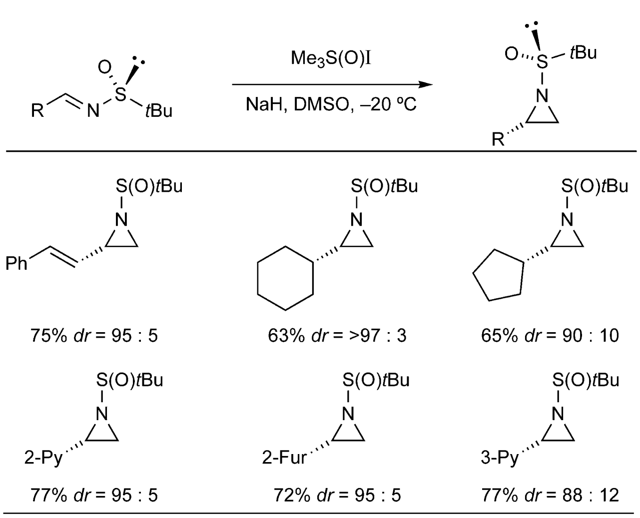


(6)[45]



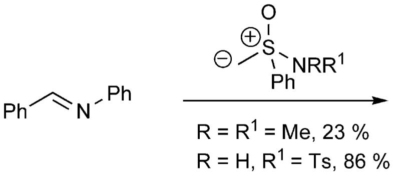
(7)

Table 11. Asymmetric aza-Darzens aziridination of aliphatic chiral *tert*-butylsulfinimines.[48]

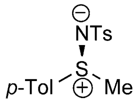


Vinylaziridines can also be obtained using this methodology (by the application of allylsulfonium ylides), but the *cis*/*trans* ratio is variable.[49] However, the (usually dominant) *trans*-isomers are obtained with excellent diastereoselectivity (Table 12).

Anions of *N*-(*p*-tolylsulfonyl)sulfoximines undergo aza-Darzens reaction with *N*-arylimines; the nature of the *N*-substituent is extremely influential. Thus, the first reports of these reactions record that (dimethylamino)phenyloxosulfonium methylide reacts with *N*-phenylbenzaldimine in low yield,[50] whereas *N*-tosylsulfoximines react with the same substrate in excellent yield [Equation (8)].[51] Asymmetric reagents execute stereoselective aziridination, but generally with low enantioselectivity ($er \approx 75:25$ for reaction with *N*-phenylbenzaldimine).[52] Allylic sulfoximine ylides react with higher enantioselectivity (Table 13).[53] Chiral sulfimides (such as **2**) have also been used for asymmetric aziridination; again the reactions proceed with low enantioselectivity ($er \leq 80:20$).[54]



(8)



2

Asymmetric Aza-Darzens Reaction Using Other Ylides

Iodonium ylides also react with imines to form aziridines in a Darzens-like reaction, via 2-iodonium amide anions, and the method has been widely used for the synthesis of vinylaziridines. Monocarbonyl iodonium ylides react with imines, to give 2-acylaziridines, with the diastereoselectivity strongly controlled by the imine activating group and the solvent: both *cis*- (using trimethylbenzenesulfonylimines, in THF) and *trans*-aziridines (from *N*-benzoylimines, in THF/DMSO or THF) can be obtained with good stereoselectivity.[55] The analogous monocarbonyl bismuthonium ylides give 2,3-aziridino ketones, with no solvent effect reported.[56]

Table 12. Vinylaziridines from S-chiral sulfimines.[49]

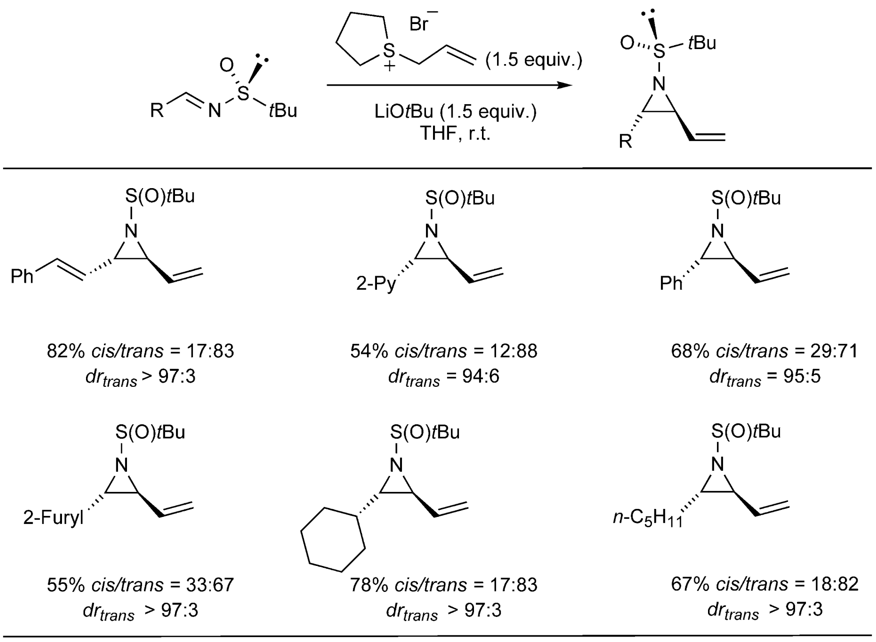
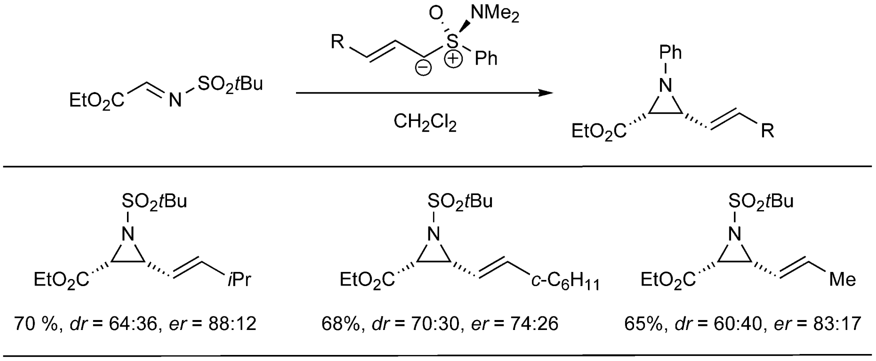


Table 13. Vinylaziridines from chiral allylsulfoximines.[49]



Summary and Outlook

Aza-Darzens reactions are amongst the oldest methodologies used to prepare aziridines and, as this review has hopefully demonstrated, the rich diversity of modern variations on the original reactions has developed the general process into a powerful tool for preparation of heterocycles of real synthetic utility. The continuing development of (especially) catalytic methodologies and the amelioration of current problem in these processes will render aza-Darzens chemistry a valuable asset to modern chemists for the foreseeable future.

Acknowledgments

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[1] a) P. E. Fanta, in: *Heterocyclic Compounds with Three- and Four-membered Rings*, part 1 (Ed.: A. Weissberger), Wiley Interscience, New York, **1964**, p. 528; b) O. C. Dermer, G. E. Ham, *Ethylenimine and Other Aziridines*, Academic Press, New York, **1969**; c) J. A. Deyrup, in: *The Chemistry of Heterocyclic Compounds* (Ed.: A. Hassner), Wiley, New York **1983**, vol. 42, part 1, p. 1; d) D. Tanner, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599; e) W. McCoull, F. A. Davis, *Synthesis* **2000**, 1347; f) J. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247; g) X. E. Hu, *Tetrahedron* **2004**, *60*, 2701; h) A. Padwa, S. S. Murphree, *ARKIVOC* **2006**, 6; i) J. B. Sweeney, *Science of Synthesis* (Eds.: E. Schaumann, D. Enders), Georg Thieme Verlag, Stuttgart, New York **2008**, vol. 40a, p. 643.

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