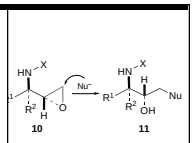
The aza-Payne rearrangement: a synthetically valuable equilibration



CHEMICAL SOCIETY REVIEWS

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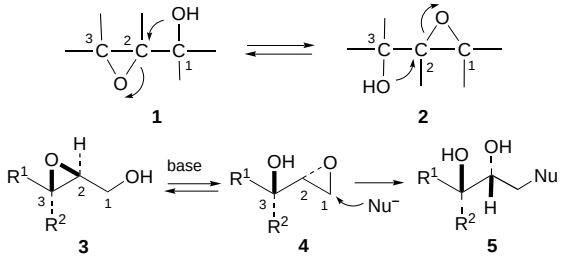
An aza-Payne rearrangement of *N*-activated 2-aziridinemethanols, synthesized in an optically active form, with potassium *tert*-butoxide (Bu^{t}OK), potassium hydride (KH), or sodium hydride (NaH) at near 0 °C in common aprotic solvents such as tetrahydrofuran (THF), toluene, or a mixed solvent of THF–HMPA followed by quenching at low temperature gives the corresponding epoxy sulfonamides in high yields. The anionic reaction intermediates, generated by treatment of 2-aziridinemethanols with a base, react readily in a one-pot manner with a variety of nucleophiles such as organocopper reagents, thiols, and trimethylsilyl cyanide to yield the optically active corresponding functionalized 1,2-amino alcohols in good yields. Upon exposure of 2,3-epoxy amines to an equimolar mixture of Bu^{t}OK and BuLi (super base) in a mixed solvent of THF and *n*-hexane at −78 °C, the equilibrium lies exclusively toward the hydroxyaziridine forming direction.

1 Introduction

Historically, the first documented report of a possible Payne rearrangement in carbohydrate chemistry was probably that of British chemists, Lake and Peat, who reported around 60 years ago the isomerization of one epoxy alcohol into another under basic conditions.[1] The next major advance in terms of this type of isomerization, however, came in 1957 when Angyal and Gilham demonstrated unambiguously that the hydroxy group on the C-1 carbon atom adjacent to the epoxide ring in **1** could carry out an intramolecular nucleophilic displacement, yielding the more stable epoxy alcohol **2**, and this process was referred to as 'epoxide migration' (Scheme 1).[2] This epoxide migration has become a well-known reaction in the area of carbohydrate chemistry.[3]



Scheme 1

The most influential paper on this type of reaction, however, was Payne's 1962 publication describing the equilibration (epoxide migration) of racemic simple 2,3-epoxy alcohols under basic conditions.[4] In the case of the intramolecular nucleophilic displacement of simple 2,3-epoxy alcohols such as **3**, the term 'Payne rearrangement'[5,6] has been widely adopted in honor of this pioneering work rather than the wording 'epoxide migration'. One important aspect of the rearrangement is that the reaction is usually stereospecific, proceeding with inversion of configuration at the C-2 carbon of the epoxide-ring *via* an S_N2 type mechanism.

Payne also reported the considerable synthetic potential of the rearrangement, although this potential was apparently overlooked by the chemists of the time. In addition, because the relative proportions of epoxy alcohols **3** and their isomeric *terminal* epoxides **4** at equilibrium are highly structure dependent,[4] the preparative value of the Payne rearrangement under aqueous alkaline conditions has long been rather limited.

Since the discovery of the Sharpless asymmetric epoxidation of allylic alcohols to prepare chiral 2,3-epoxy alcohols **3**,[7] the regioselective nucleophilic ring-opening at the C-1 position of more reactive *terminal* epoxides **4** resulting from the Payne rearrangement of 2,3-epoxy alcohols **3** in basic media has become an important tool for the synthesis of polyfunctional synthetic building blocks **5** (Scheme 1). Such a one-pot transformation has been termed a 'Payne rearrangement–ring opening reaction' by Sharpless.[5]

On the other hand, aziridines are often vital structural units of biologically active molecules and are frequently employed as synthetic building blocks of natural compounds and elsewhere.[8] Recently, by using Lewis acids such as TMSOTf, *N*,*N*-dibenzylated or *N*,*N*-diallylated 2,3-epoxy amines, compounds of type **6** have been reported by Rayner and co-workers to rearrange to the aziridinium salts **7** which open at the more reactive C-1 position with various nucleophiles to yield the rearrangement–opening products **8**.[9–11] For example, the 2,3-epoxy-*N*,*N*-diallylamine derivative **6** (R^1 = Pr^n, R^2 = H) was treated with TMSOTf to yield the aziridinium salt **7** in quantitative yield. Removal of the trimethylsilyl group of **7** with potassium carbonate in methanol and subsequent intramolecular rearrangement regenerated the original epoxy amine starting material **6** in a high yield. It should also be stressed that the rearrangement of the epoxy amines **6** to the aziridinium salts **7** is irreversible (Scheme 2). For a more complete overview of

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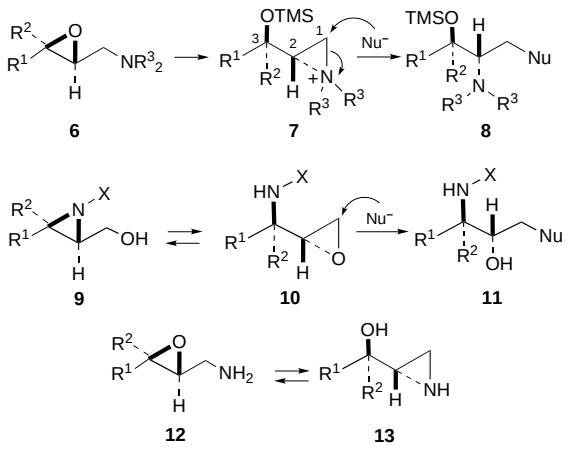
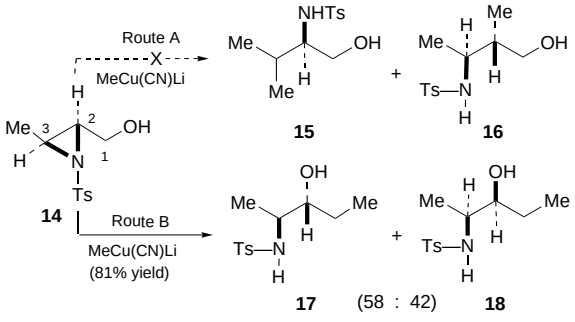


Scheme 2 R^1, R^2 = alkyl or aryl; R^3 = allyl or benzyl X = CO_2R, mesyl, or tosyl, *etc*.

the above described methods developed by Rayner to obtain enantiomerically pure compounds, the reader may refer to a recent and excellent review.[11]

Until recently, due to its reversible nature, the aza-Payne rearrangement of 2-aziridinemethanols **9** and 2,3-epoxy amines of type **12** has been much less extensively examined (Scheme 2).[12–19] Although the relative proportions of the 2-aziridinemethanols **9** and the epoxy amines **10** would be substrate as well as reaction condition dependent, conflicting experimental evidence for the direction of the aza-Payne rearrangement has been reported. Some reactions of epoxy sulfonamides **10** (X = Ts) have been shown to produce 2-aziridinemethanols of type **9** under basic conditions.[12] In contrast, with some *N*-tosyl 2-aziridinemethanols **9**, the equilibrium favours the epoxy *N*-tosylamides **10**.[13] Furthermore, epoxy amines of type **12** provide access to hydroxyaziridines **13** in the presence of Lewis acids such as BF_3,[14] Bu^{n}Li–Me_3Al,[15] Ti(OPr^i)$_4$,[16] and SiO_2.[17]

During a study of organocopper reactions (Scheme 3),[18] we found that the reaction of 2-aziridinemethanol **14** with methylcyanocuprate [MeCu(CN)Li·LiBr] afforded two products. To our surprise, the products were neither the expected primary alcohol **15** nor the isomeric primary alcohol **16** (Route A), but the secondary alcohols **17** and **18**. The formation of the secondary alcohol **17** suggested a reaction path proceeding *via* the aza-Payne rearrangement–ring opening (Route B).[19]



Scheme 3

There has been no systematic investigation of the above-described phenomena, and the issue of delineating the factors which are responsible for controlling the direction of the aza-Payne rearrangement remains a topic of much attention. We therefore examined the equilibrium of the aza-Payne rearrangement by chemical and theoretical studies in simple systems.[19]

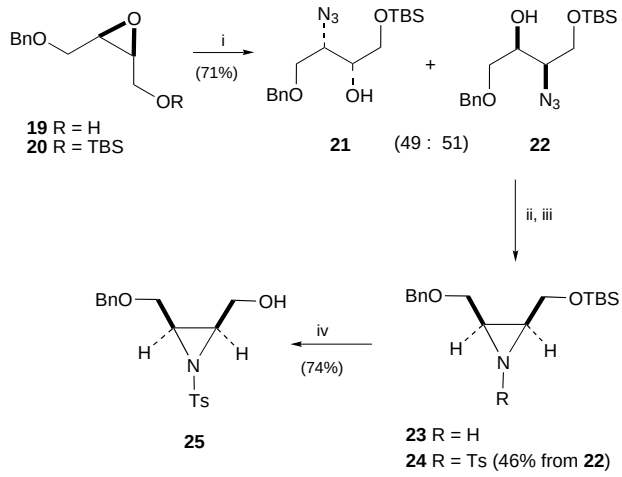
It is not the purpose of this review to present detailed information of all available preparative methods for the requisite substrates, nor to give an encyclopaedic discussion of the aza-Payne rearrangement. Rather, I wish to present an overview of recent advances made by our team and other groups that may be important in the understanding of this chemical reaction and to fill some of the voids described above by studying the potential of the aza-Payne rearrangement reaction.

2 Synthesis of 2-aziridinemethanols

Various *N*-substituted or unsubstituted enantiomerically pure (or enriched) 2-aziridinemethanols may be prepared by two broadly applicable methods, *viz*. by starting from enantiomerically pure 2,3-epoxy alcohols[20,21] which, in turn, could be readily prepared from allylic alcohols by the use of the Sharpless asymmetric epoxidation,[7] or by starting from synthetic or natural amino acids.[20,22] Because the reactivity of NH-aziridines towards nucleophiles is low, activation by the introduction of an electron-withdrawing group on the ring nitrogen atom is required. The term 'activated aziridines' has been introduced by Ham for aziridines that easily undergo nucleophilic S_N2-type ring-opening *in the absence of a formal positive charge* on the nitrogen atom.[23] The arenesulfonyl, methanesulfonyl, acyl and alkoxycarbonyl moieties serve as good activating groups, while nucleophilic ring-opening reactions of aziridines involving a positively charged nitrogen have been extensively studied by Rayner.[11]

2.1 Synthesis from 2,3-epoxy alcohols

In terms of availability and cost of synthetic precursors, chiral 2,3-epoxy alcohols, which are readily prepared from suitable allylic alcohols by the use of Sharpless asymmetric epoxidation,[7] are by far the most common starting materials for the synthesis of various types of 2-aziridinemethanols. The example shown in Scheme 4 illustrates a synthetic route to the 2-aziridinemethanol **25** starting from the chiral 2,3-epoxy alcohol **19** (Scheme 4).[20]



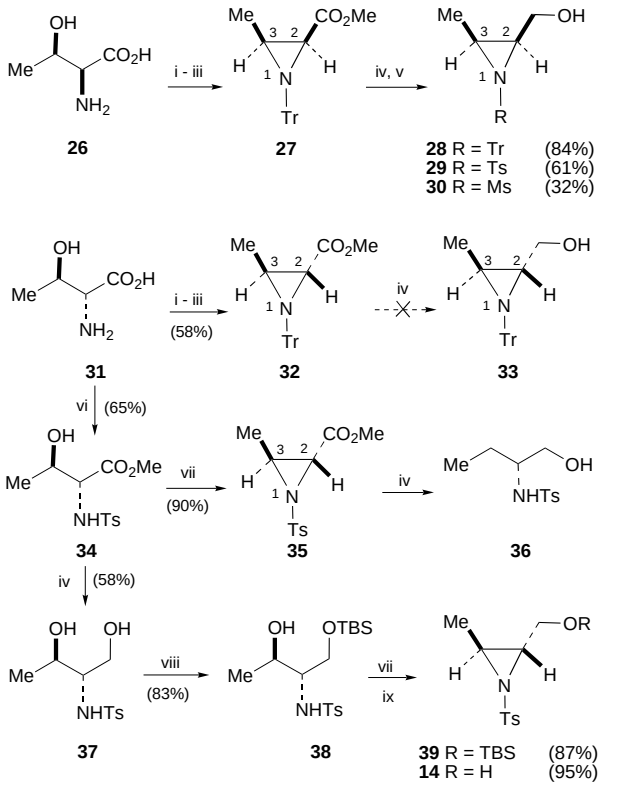
Scheme 4 *Abbreviations*: Bn = benzyl; TBS = Bu^t(Me)$_2$Si; Ts = 4-methylphenylsulfonyl. *Reagents*: i, NaN_3–NH_4Cl refluxing H_2O–2-methoxyethanol; ii, PPh_3 in refluxing THF; iii, Et_3N–TsCl in THF; iv, Bu_4NF in THF.

The silyloxy epoxide **20** prepared from 2,3-epoxy alcohol **19**[7] (86% ee) was reacted with sodium azide in the presence of ammonium chloride[24] to yield a *ca.* 1:1 mixture of two products **21** and **22**.[20] Although the separation of these two isomers could be conveniently accomplished by flash silica gel chromatography, the reaction of a mixture of **21** and **22** with triphenylphosphine followed by tosylation yielded the *N*-tosyl aziridine **24** *via* **23** as the sole isolable product, which upon exposure to tetrabutylammonium fluoride, yielded the target *N*-activated 2-aziridinemethanol **25**. Although the enantiomeric excess (ee) of the starting epoxy alcohol **19** was only 86%, essentially enantiopure 2-aziridinemethanol **25** (> 98% ee) was obtained by recrystallization of the crude product[20] and many

other 2-aziridinemethanols could be prepared in a similar way.

2.2 Synthesis from amino acids

Synthesis of *N*-activated 2-aziridinemethanols can also be achieved starting from chiral natural or synthetic amino acids, such as L-threonine **26** and D-*allo*-threonine **31** as outlined in Scheme 5. *N*-Trityl 2,3-*cis*-aziridine **27**,[25] readily prepared in



Scheme 5 *Abbreviations*: Tr = triphenylmethyl; Ts = 4-methylphenylsulfonyl; Ms = methanesulfonyl; TBS = *tert*-buthyldimethylsilyl. *Reagents*: i, $SOCl_2$–MeOH; ii, TrCl–Et_3N in DMF iii, MsCl–pyridine then reflux; iv, DIBAL-H; v, TFA then TsCl–Et_3N or TFA then MsCl–Pr^i_2NEt; vi, $SOCl_2$–MeOH then TsCl–Et_3N; vii, PPh_3–diethyl azodicarboxylate; viii, TBSCL–imidazole–4-DMAP; ix, Bu_4NF.

high yields from L-threonine **26**, was then reduced with diisobutylaluminum hydride (DIBAL) to yield the 2-aziridinemethanol **28** (> 99% ee) in high yield. Removal of the trityl group followed by tosylation (or mesylation) gave *N*-tosyl (or *N*-mesyl) 2-aziridinemethanol **29** (> 98% ee) or **30** (> 98% ee).[20]

Synthesis of the isomeric aziridine, 2,3-*trans* **14**, proved considerably more troublesome and various standard routes were attempted unsuccessfully. Thus, D-*allo*-threonine **31**, while readily converting into *N*-tritylaziridine ester **32**, failed to give the desired 2-aziridinemethanol **33** on reduction with DIBAL, a surprising observation in view of the successful reduction of the isomeric ester **27** under the same conditions.

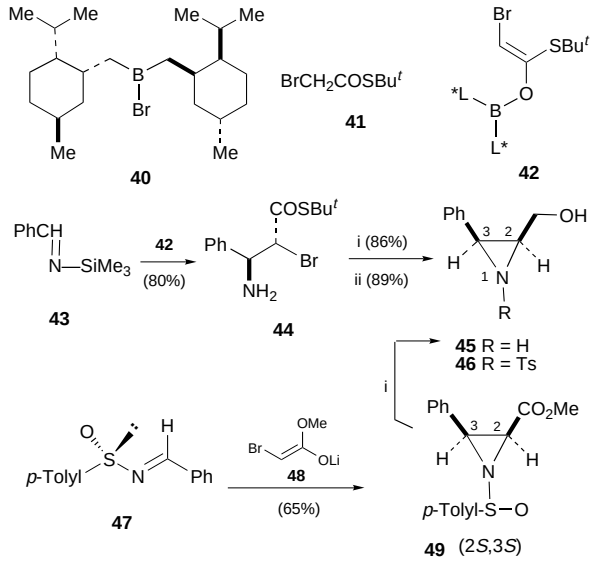
Next, reduction of the readily available *N*-tosyl aziridine **35** was examined. The aziridine methyl ester **35**, derived from D-*allo*-threonine **31** *via* the *N*-tosyl methyl ester **34** in the usual way, was treated with DIBAL to yield a mixture of products from which the undesired ring-opened product **36** was isolated as the major product. Other reducing agents were tried but without success.

Finally, the silyloxyaziridine **39** was easily synthesized from the *N*-tosyl ester **34**. Selective silylation of diol **37** which, in turn, was derived from **34** by reduction with DIBAL, and the subsequent aziridine-ring formation yielded the 2-aziridinemethanol silyl ether **39**, which upon desilylation with tetrabutylammonium fluoride afforded the desired *N*-tosyl 2-aziridinemethanol **14** (> 98% de).[20]

Synthetic methods for the preparation of some *N*-activated 2-aziridinemethanols from appropriate amino acids, such as L-serine, D-serine, D-threonine, and L-methionine, have also appeared recently.[20,22]

2.3 Asymmetric synthesis

Recently, elegant asymmetric syntheses of *N*-activated 2-aziridinemethanols have been described[26,27] and these two methods can be applied to the synthesis of various types of synthetically important 2-aziridinemethanols bearing a phenyl group. The major limitation of these methods is that only non-enolizable *N*-trimethylsilyl imines, like **43** or sulfinimines **47**, can be prepared from aromatic aldehydes efficiently.



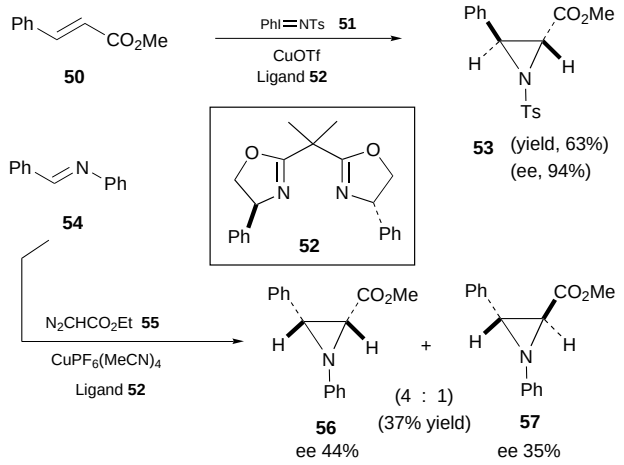
Scheme 6 *Reagents*: i, $LiAlH_4$; ii, TsCl–Et_3N

Treatment of the chiral bromoborane **40** and *tert*-butyl bromothioacetate **41** in the presence of triethylamine yields the boron enolate **42** which, on reaction with the trimethylsilyl imine **43**, yields α-bromo-β-amino thioester **44** in a very high diastereo- and enantio-selective manner. Reduction of **44** with lithium aluminum hydride then affords the 2-aziridinemethanol **45** which can easily be converted into the *N*-activated 2-aziridinemethanol **46**.[26]

Another highly diastereoselective one-pot synthesis of *N*-activated 2,3-*cis*-2-aziridinemethanols has been accomplished by the use of a Darzens-type reaction.[27] Thus, exposure of the lithium enolate **48** of methyl bromoacetate to optically pure sulfinimine **47** yields 2,3-*cis*-aziridine ester **49** in high yield, with the added advantage that the *N*-sulfinyl can be removed under mild conditions. Interestingly, both removal of the *N*-sulfinimine group and reduction of the ester group in **49** could be carried out by treatment with $LiAlH_4$ to yield directly chiral 2-aziridinemethanol **45**.[27]

Evans and co-workers have developed an efficient asymmetric aziridination reaction (Scheme 7).[28] Reaction of methyl cinnamate **50** with [*N*-(*p*-tolylsulfonyl)imino]iodobenzene **51** in the presence of 5 mol% of a catalyst derived from copper(I) triflate and chiral 4,4′-disubstituted bis(oxazoline) **52** afffords the aziridine ester **53** with high enantioselectivity. Both CuOTf and $Cu(OTf)_2$ can be employed in the formation of competent catalysts, and similar enantioselectivities were observed in each case.

The transition metal-catalyzed transfer of diazocarbonyl-derived carbenes to imines has been studied by using the *N*-benzylidene aniline **54** by Jacobsen and his co-workers.[29] Jacobsen found that the copper(I) complex, $[CuPF_6(MeCN)_4]$, in the presence of the ligand **52** was most effective in catalyzing

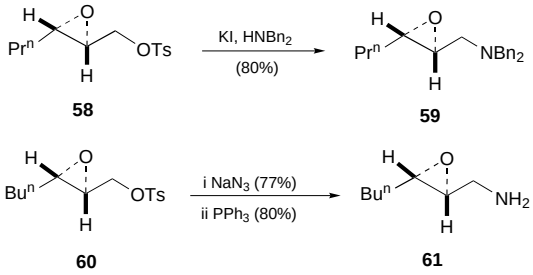


Scheme 7

the aziridination reaction to yield aziridines **56** and **57**, which like esters **53**, could be transformed into the corresponding 2-aziridinemethanols by reduction. Although more than a dozen other attractive and excellent methods for the synthesis of chiral 2-aziridinemethanols and their analogues have been developed,[30] detailed descriptions of all synthetic methods for the requisite 2-aziridinemethanols are beyond the scope of this article.

3 Synthesis of 2,3-epoxy amine substrates

Although there are many methods available for the synthesis of epoxides possessing internal secondary or tertiary amino groups, Rayner synthesized several *terminal N,N*-diallyl- or -dibenzyl-2,3-epoxy amines from the corresponding tosylates of 2,3-epoxy alcohols by sodium iodide-catalyzed displacement using *N,N*-diallylamine or *N,N*-dibenzylamine.[9–11] A typical example is illustrated by the transformation of the tosylate **58** into the *N,N*-disubstituted terminal amine **59** (Scheme 8).

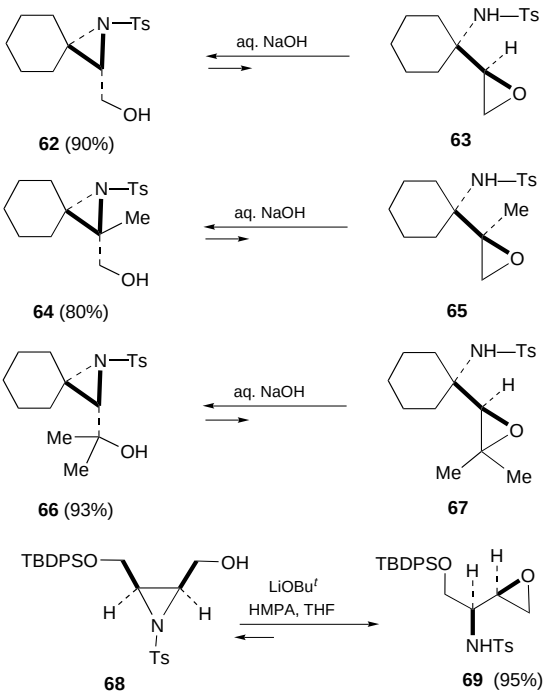


Scheme 8

Epoxides like **61** which possess a primary amino group at the terminal position can easily be synthesized from the corresponding 2,3-epoxy alcohol tosylates like **60** according to a two-step sequence of reactions.[15] This involves (1) substitution of the tosyloxy group by treatment with sodium azide and (2) reduction of the azide group with triphenylphosphine.[31] However one should appreciate that low molecular weight epoxy amines, such as **61**, pose serious problems with respect to isolation as the usual extractive workup leads to considerable loss of the water-soluble product. Consequently, after the reduction of azides with triphenylphosphine is complete, the reaction mixture is usually concentrated and then the product may be distilled using a bulb-to-bulb distillation apparatus under reduced pressure. In this way, 2,3-epoxy amines are easily obtained in pure form.

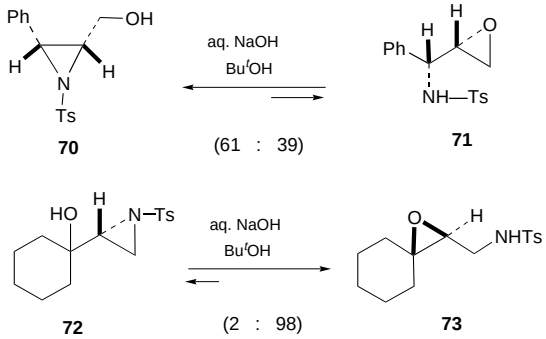
4 Aza-Payne rearrangement reaction of *N*-activated 2-aziridinemethanols

As has been mentioned earlier in this article, the Payne rearrangement of 2,3-epoxy alcohols is usually carried out in aqueous sodium hydroxide and results in an equilibrium mixture of the starting 2,3-epoxy alcohol and the isomeric 3-hydroxy-1,2-epoxide.[4–6] However, there have been conflicting publications about the favoured direction of the corresponding aza-Payne reaction. Whereas reaction of *N*-tosyl epoxy sulfonamides **63**, **65** and **67** has been reported to yield 2-aziridinemethanols **62**, **64** and **66**, respectively, by brief heating in aqueous basic conditions,[12] with 2-aziridinemethanol **68** the equilibrium lies exclusively toward the opposite direction to yield *N*-tosyl epoxy sulfonamide **69**[13] (Scheme 9).



Scheme 9 *Abbrevations*: TBDPS = *tert*-butyldiphenylsilyl

In the case of *N*-Boc or *N*-trityl aziridines, poor yields of rearrangement products were also obtained from base-catalyzed isomerization reactions and consequently, we initiated our study on the aza-Payne rearrangement to determine the scope of the reaction with respect to reaction conditions. Not unexpectedly, exposure of *N*-tosyl-2-aziridinemethanol **70** to an aqueous sodium hydroxide solution in the presence of *tert*-butyl alcohol as co-solvent at 0 °C for 18 h produced a 61 : 39 equilibrium mixture of **70** and a rearranged product **71** (Scheme 10). Much higher selectivity (**72** : **73** = 2 : 98) is found with

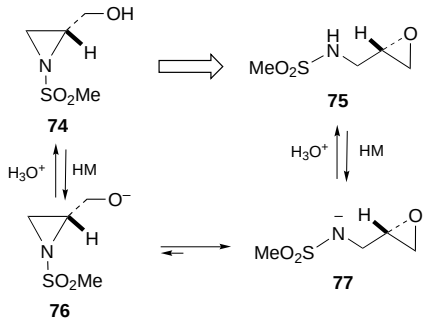


Scheme 10

activated aziridine **72** in which there is branching at the hydroxy-bearing carbon. From the results shown in Scheme 10, it is apparent that the relative proportions of the 2-aziridinemethanols (**70**, **72**) and epoxy sulfonamides (**71**, **73**) at equilibrium are highly structure dependent. Consequently, the preparative value of the aza-Payne rearrangement under

aqueous alkaline conditions is limited. In addition, the aqueous conditions employed preclude the use of many synthetically important organometallic nucleophiles, such as organocopper reagents, for subsequent reactions in a one-pot manner. The present review also illustrates how this problem can be overcome.

Because knowledge of the relative thermodynamic stability of *N*-activated 2-aziridinemethanols and 2,3-epoxy amines is the key to an understanding of the isomerization phenomenon, we have also undertaken *ab initio* molecular orbital calculations in simple compounds. The energy minimum of *N*-mesyl-2-aziridinemethanol **74** was predicted to be only 1.7 kcal mol^{-1} higher than the energy minimum of epoxy sulfonamide **75** (Scheme 11).[19]



Scheme 11

Next, under basic conditions in an *aprotic solvent*, would the oxa-anion **76** of *N*-mesyl-2-aziridinemethanol **74** or the aza-anion **77** of epoxy sulfonamide **75** be expected to be the more stable species? Both theoretical and experimental aspects of this study were carried out with *N*-mesyl-2-aziridinemethanol **74** and epoxy sulfonamide **75** and the geometries of optimized reactant oxa-anion **76**-**A**, the transition state **TS** involved in the rearrangement step, and the product aza-anion **77**-**A** as well as relative energies are shown in Fig. 1.

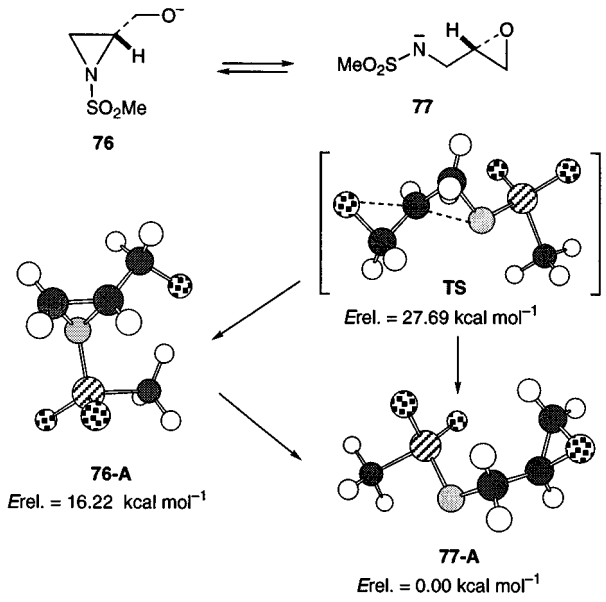
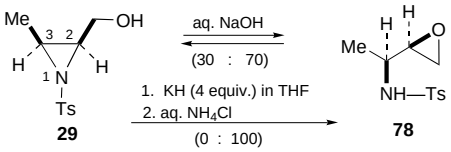


Fig. 1 RHF/3-21+G* optimized geometries and their relative energies for the aza-Payne rearrangement: **TS**, the transition structure; **76**-**A**, the reactant oxa anionic energy minimum; **77**-**A**, the product aza anionic energy minimum.

We found that the reactant oxa-anionic energy minimum **76**-**A** was predicted to be *ca*. 16.22 kcal mol^{-1} higher in energy than the product aza-anionic energy minimum **77**-**A**. Consequently, exclusive formation of the epoxy sulfonamide **75** could be expected by treatment of **74** with a base, such as Bu^{t}OK, potassium hydride (KH), sodium hydride (NaH), or lithium diisopropylamide (LDA) followed by quenching at low temperature (Scheme 11). In fact, the *N*-mesyl-2-aziridinemethanol **74** did give only the rearranged product **75** upon exposure to NaH (1.3 equiv.) in a mixed solvent of THF–HMPA (12 : 1) followed by quenching at −78 °C and we were unable to detect unreacted starting **74** by ^{1}H NMR analysis.[19]



Scheme 12

As can be seen from Scheme 12, exposure of 2-aziridinemethanol **29** to aqueous NaOH provides a 30 : 70 equilibrium mixture of the aziridine **29** and the rearranged product **78**. In order to identify suitable reaction conditions for this rearrangement, the influence of base, solvent, and reaction temperature were studied in more detail using the readily available *N*-tosyl-2-aziridinemethanol **29** as the test starting material (Table 1). Based on this study, we can offer some general comments on factors that influence the successful outcome of the aza-Payne reaction.[19]

Table 1 Aza-Payne rearrangement of (2*S*,3*S*)-3-methyl-*N*-tosyl-2-aziridinemethanol **29** to yield epoxy sulfonamide **78**[a]

Entry	Base	Solvent	Conditions	Yield of **78** (%)
1	DBU (5 equiv.)	THF–HMPA[b]	RT (3 h)	0
2	Bu^{n}Li (1.2 equiv.)	THF–HMPA[b]	0 °C (18 h)	17
3	LDA (4 equiv.)	THF	RT (1 h)	0[c]
4	KH (4 equiv.)	THF	−78 °C (5 h)	< 1
5	NaH (4 equiv.)	THF	−20 °C (4 h)	< 1
6	NaH (4 equiv.)	THF	0 °C (5 h)	77
7	NaH (4 equiv.)	THF	RT (2 h)	82
8	NaH (4 equiv.)	THF–HMPA[d]	RT (2 h)	92
9	Bu^{t}OK (1.2 equiv.)	THF–HMPA[b]	0 °C (2 h)	99
10	KH (4 equiv.)	THF	−20 °C (2 h)	96
11	KH (4 equiv.)	THF	0 °C (30 min)	96
12	KH (4 equiv.)	toluene	0 °C (1 h)	99
13	KH (4 equiv.)	CH_2Cl_2	0 °C (1 h)	99
14	KH (4 equiv.)	DME	0 °C (2 h)	99
15	KH (4 equiv.)	1,4-dioxane	RT (30 min)	99

[a] Isolated and unoptimized yields of epoxy sulfonamide **78**. [b] THF–HMPA = 10 : 1. [c] A complex mixture of products was obtained. [d] THF–HMPA = 12 : 1.

(1) In the case of *N*-Boc or *N*-trityl aziridines, poor yields were obtained from base-catalyzed isomerization reactions, however, this problem can be overcome by the use of *N*-alkyl- or *N*-aryl-sulfonylated aziridines.

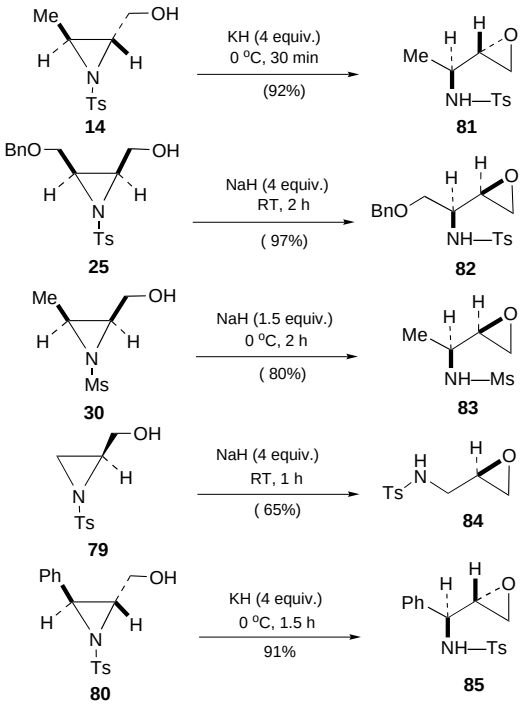
(2) Although DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), BuLi, and LDA were inappropriate for clean and efficient rearrangements (Entries 1–3, Table 1), bases such as NaH, Bu^{t}OK, and KH gave satisfactory results (Entries 8–15, Table 1). Using KH as a base, the rate of rearrangement of activated aziridinemethanols was much faster than that observed using NaH under otherwise identical conditions. For example, treatment of **29** with NaH at 0 °C for 5 h yields the epoxy sulfonamide **78** in 77% yield, while exposure of the same substrate to KH at 0 °C for 30 min affords **78** in 96% isolated yield (entries 6 and 11, Table 1).

(3) The reaction temperature is an important factor and hence the temperature should be carefully controlled. For example, while **29** reacted with KH at −20 °C after 2 h to afford only the rearranged product **78** in 96% isolated yield (entry 10), treatment of the same substrate **29** at −78 °C for 5 h led to complete recovery of the unchanged starting material (entry 4).

Although the rearrangement rates are dependent upon the base used, the reaction normally proceeds completely in the direction of the epoxy sulfonamide **78** at either 0 °C or RT (*ca.* 25 °C).

(4) THF or a mixture of THF and HMPA is the solvent of choice. Although rearrangement of **29** with NaH in THF alone is rather slow (entries 5, 6, and 7), acceleration of the rearrangement is accomplished by the addition of HMPA (entry 8). Other common solvents such as toluene, dichloromethane, dimethoxyethane, and 1,4-dioxane can be used equally well for the reaction of **29** with KH (entries 12–15).

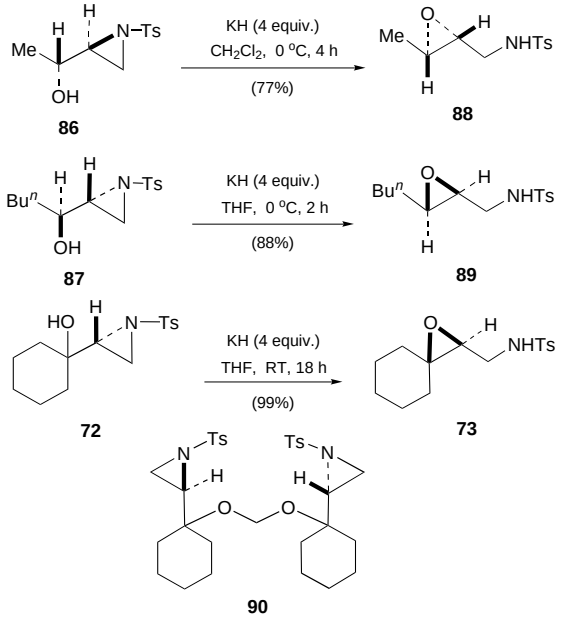
The bases NaH and KH were found to be the best among those tested for the rearrangement. As can be seen from Scheme 12, although exposure of the aziridine **29** to an aqueous sodium hydroxide solution gave a 30 : 70 mixture of **29** and **78**, treatment of **29** in THF with KH gave exclusively **78**. Thus, we have used these two bases for the reaction of some representative 2-aziridinemethanols. Satisfactory results obtained for 5 different activated aziridines (**14**, **25**, **30**, **79**, and **80**) bearing a primary hydroxymethyl group at the C-2 position of the aziridine-ring are summarized in Scheme 13. By exposure to either NaH or KH followed by quenching, all aziridinemethanols yielded the corresponding rearranged epoxy sulfonamides **81**–**85** in high isolated yields.[19]



Scheme 13 All reactions were carried out in THF–HMPA (10 ~ 12 : 1). *Abbreviations*: Ts = 4-methylphenylsulfonyl; Ms = methanesulfulfonyl; Bn = benzyl.

In a similar manner, as shown in Scheme 14, activated aziridines (**86**, **87** and **72**) having a secondary or tertiary hydroxy group react equally well to yield the respective epoxy sulfonamides (**88**, **89** and **73**) in high yields. In all the rearrangements listed in Schemes 13 and 14, no evidence for unrearranged starting material was detected by HPLC analysis of the crude reaction product(s). Thus, the reaction appears to be quite general for activated aziridines possessing wide structural variety, giving isolated yields which are good to excellent. In addition, the reversible nature of the reaction in protic solvents, as shown in Scheme 10, can be altered to an essentially irreversible process in aprotic solvents.[19]

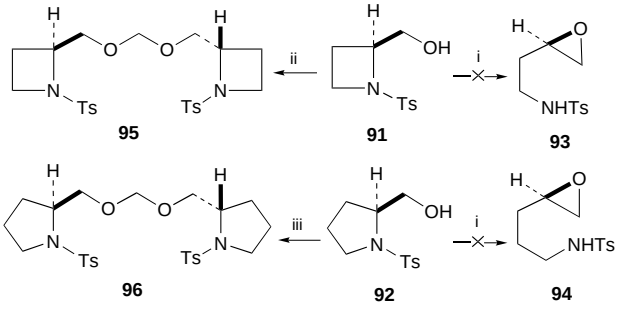
It should be clearly noted that the aziridine **72** (Scheme 14), possessing a tertiary hydroxy group, rearranged slowly in THF in the presence of KH to give solely the epoxy sulfonamide **73**. On the other hand, similar treatment with KH (4 equiv.) but in CH_2Cl_2 at room temperature for 18 h unexpectedly provided a



Scheme 14

mixture of **73** (85% yield) and an undesired compound **90** (*ca.* 5% yield) rather than pure **73**. Consequently, despite the slow rate of rearrangement in THF, this is the solvent of choice for the reaction of compounds of type **72** bearing a tertiary hydroxy group.[19] Formation of the minor product **90** could be explained in the following manner. In the first step, reaction between CH_2Cl_2 and KH will produce a carbene species (:CHCl). Trapping of the carbene by an alkoxide, generated by exposure of the alcohol **72** to KH, will produce a chloromethyl ether, which will react with another alkoxide under typical S_N2 conditions to yield the product **90**. Formation of the major product **73** is an example of an intramolecular S_N2 reaction and, presumably, would be much faster than the side reaction to form **90**.

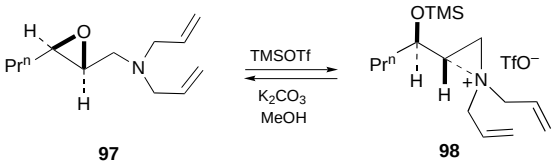
Not unexpectedly, the attempted rearrangement reaction of *N*-tosyl-(*S*)-azetidinemethanol **91** or *N*-tosyl-(*S*)-prolinol **92** with NaH or KH in THF led to recovery of the starting material. The reaction in CH_2Cl_2 under otherwise identical conditions gave solely the corresponding adducts **95** and **96** in high yields (Scheme 15). This demonstrates that the rearrangement reactions are specific to three-membered aza-cycles possessing a large strain energy.[19]



Scheme 15 *Reagents and conditions*: i, KH in THF, 0 °C, 0%; ii, KH in CH_2Cl_2, 0 °C, 3 h, 84%; iii, KH in CH_2Cl_2, 0 °C, 3 h, 95%

5 Aza-Payne rearrangement reaction of 2,3-epoxy amines

The direction of the equilibrium of the aza-Payne rearrangement of epoxy amines has been investigated by many research groups.[9–17,19] It is well established by Rayner[9–11] that quantitative generation of quaternary aziridinium salt **98** could be accomplished by exposure of 2,3-epoxy *N*,*N*-diallylamine **97** to trimethysilyl triflate (Scheme 16); a process that is essentially



97 **98**

Scheme 16

irreversible. However, desilylation of the aziridinium salt **98** by treatment with potassium carbonate in methanol regenerates the original 2,3-epoxy diallylamine **97** and it would appear that, at least in this present case, desilylation and subsequent aziridinium ion ring-opening to yield original 2,3-epoxy amine **97** is a more favourable process. In other words, 2,3-epoxy amine **97** is thermodynamically more stable than the corresponding aziridinium ion.

Would a 2,3-epoxy amine or its isomeric 2-aziridinemethanol be expected to be the more thermodynamically stable compound? In order to reduce the size of the problem such that *ab initio* calculations could be employed, model systems of 2,3-epoxy amine **99** and 2-aziridinemethanol **100** were chosen for study. We found that the energy minimum **99**-**A** of 2,3-epoxy amine **99** was predicted to be *ca.* 4.77 kcal mol^{-1} lower in energy than the energy minimum **100**-**A** of 2-aziridinemethanol **100** at the RHF/3-21G level (Fig. 2).[19] Thus, calculations predict that the 2,3-epoxy amine **99** is more stable rather than the 2-aziridinemethanol **100** and based on these calculations, we were apprehensive as to the possibility of successfully isomerizing 2,3-epoxy amines, such as **99**, into 2-aziridinemethanols of type **100**.

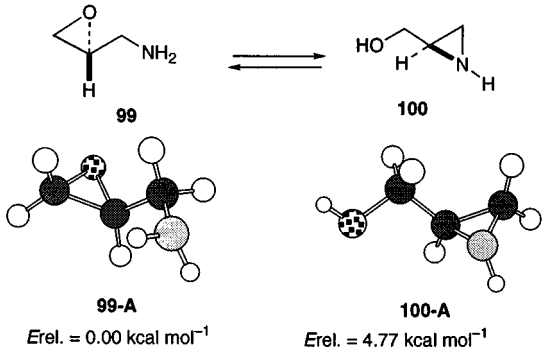
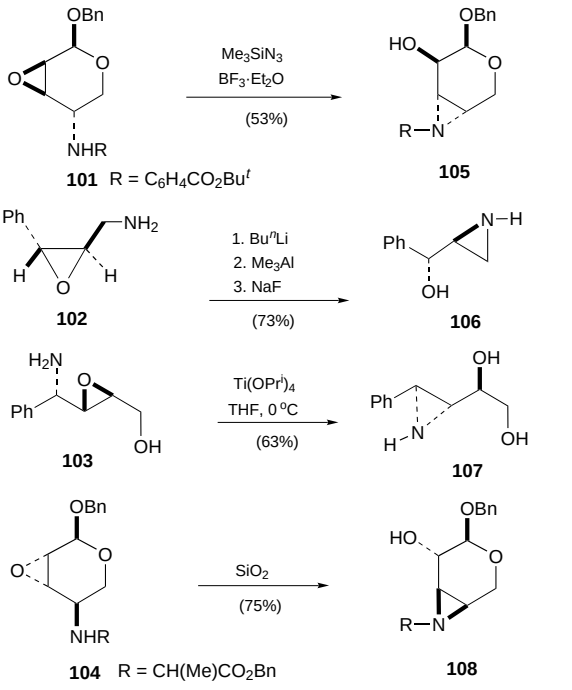


Fig. 2 RHF/3-21G optimized structures **99**-**A** of **99** and **100**-**A** of **100**

Several research groups[14–17] studied the aza-Payne rearrangement on various types of 2,3-epoxy amines, including amino sugars and typical examples are listed in Scheme 17. It is apparent that all reactions were carried out in the presence of a Lewis acid, such as $BF_3{\cdot}Et_2O$, Bu^nLi–Me_3Al, $Ti(OPr^i)_4$ or silica gel. Voelter reported that the reaction of the amino sugar **101** in Et_2O with $BF_3{\cdot}Et_2O$ in the presence of trimethylsilyl azide produced the sugar **105** involving an aziridine ring group.[14] Vaultier and co-workers found that the exposure of 2,3-epoxy amine **102** to a mixture of Bu^nLi and Me_3Al in THF furnished the 2-aziridinemethanol **106**. Both Bu^nLi and Me_3Al are essential for a clean transformation.[15] Sato and co-workers discovered that $Ti(OPr^i)_4$ is an effective catalyst for the aza-Payne rearrangement of 2,3-epoxy amine **103** into the aziridine alcohol **107**.[16] Interestingly, Voelter and co-workers reported that epoxy amines like **104** afforded the corresponding aziridine alcohols of type **108** merely by exposure to silica gel in a mixed solvent of *n*-hexane and EtOAc.[17]

Thus, under Lewis acidic conditions, the direction of the rearrangement of epoxy amines **101**–**104** to yield the corresponding aziridine alcohols **105**–**108** has to be considered as a general rule.

We have also studied the rearrangement of 2,3-epoxy amines, but under basic conditions. A number of common bases, such as metal hydrides (NaH, KH, *etc.*) and metal alkoxides (Bu^tOK, EtONa, *etc.*), were reacted, unsuccessfully, with epoxy amines **109** and **110**. The rearrangement of epoxy amines with MeLi and Bu^nLi proceeds very slowly but this reaction does not go to completion. For example, although the epoxy amine **110** reacted with MeLi and Bu^nLi to yield the hydroxyaziridine **115**, the reaction never proceeded beyond 83% and 71% completion, respectively (Scheme 18).



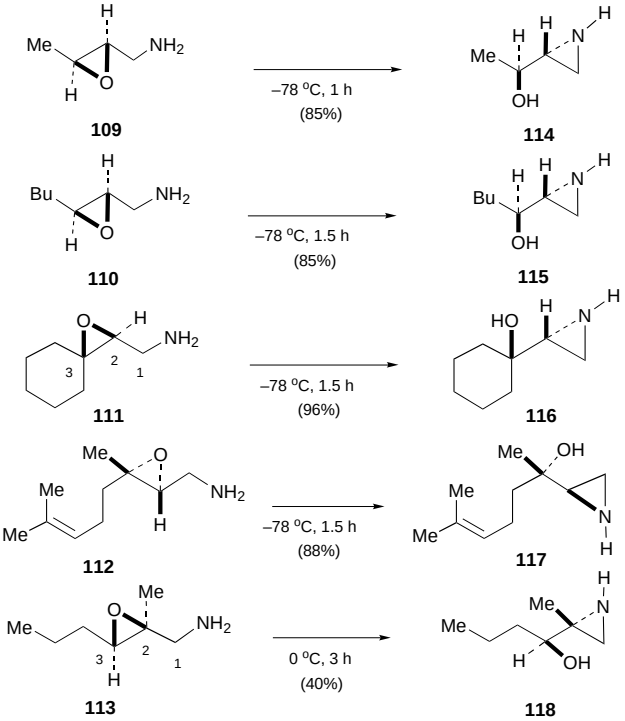
101 R = $C_6H_4CO_2Bu^t$ **105**

102 **106**

103 **107**

104 R = $CH(Me)CO_2Bn$ **108**

Scheme 17 *Abbreviation*: Bn = benzyl



109 **114**

110 **115**

111 **116**

112 **117**

113 **118**

Scheme 18 All reactions were carried out in *n*-hexane–THF (1 : 2 ~ 1 : 5) with a mixed reagent of Bu^nLi/Bu^tOK (1 : 1), (1.5 ~ 2.0 equiv.)

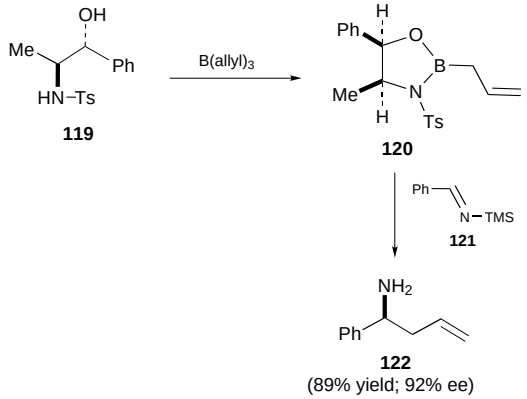
After further study, we did find that treatment of the 2,3-epoxy amines **109** and **110** with a mixture of 1.5 equiv. of Bu^nLi and 1.5 equiv. of Bu^tOK ('super base')[32] at −78 °C to yield only the corresponding rearranged hydroxyaziridines **114** and **115** respectively, in high yields, with no detectable traces of

the corresponding reactants **109** and **110**. It should be noted that these low molecular weight, water-soluble hydroxyaziridines such as **114** also pose a problem with respect to product isolation (see above). Consequently, following the reaction of the epoxy amine **109** with the super base, the reaction was quenched at −78 °C with saturated aqueous ammonium chloride. The mixture was allowed to warm to 0 °C, then filtered through a short Celite pad. Concentration, followed by recrystallization or distillation using a bulb-to-bulb distillation apparatus under reduced pressure, yielded the pure material **114**.

Disubstitution at the C-3 position of 2,3-epoxy amines such as **111** and **112** does not exert any influence on the rearrangement giving aziridines **116** and **117** respectively. As anticipated, increasing the steric bulk at the C-2 carbon in **113** does decrease the relative reaction rate for the aza-Payne rearrangement and yields the expected aziridine alcohol **118** in rather low yield (compare the reaction of **111** and **112** with **113**, Scheme 18). The study demonstrates that the aza-Payne reaction of 2,3-epoxy amines with Bu^{t}OK/Bu^{n}Li proceeds at −78 °C in high isolated yields, except for the less reactive substrate **113**.

6 One-pot aza-Payne rearrangement-epoxide ring opening reaction of 2-aziridinemethanols. Simple stereoselective synthetic route to synthetically important 1,2-amino alcohols

Acyclic 1,2-amino alcohols play an important role as chiral auxiliaries and chiral building blocks in the preparation of biologically active compounds.[33] For example, enantiomerically pure *N*-tosyl-1,2-amino alcohol **119** was treated with triallylborane to yield *B*-allyloxazaborolidine **120** which, upon reaction with trimethylsilylimine **121**, yielded homoallylamine **122** (89% chemical yield, 92% ee) as shown in Scheme 19. This



Scheme 19

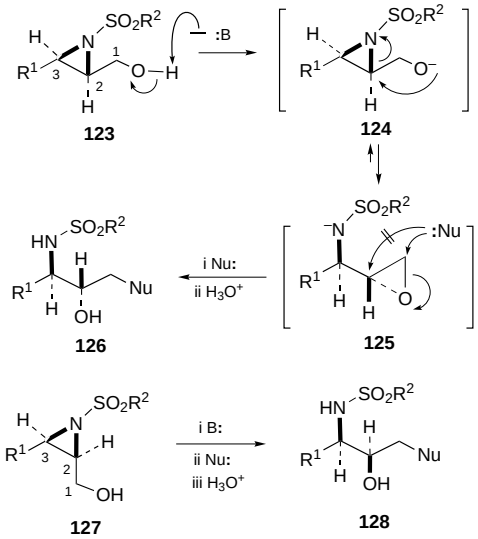
represents the highest selectivity realized in the enantioselective allylation of various types of imines.[34]

Acyclic chiral 1,2-amino alcohols can be prepared by several fundamental routes: (i) reduction of chiral amino acids; (ii) epoxide-opening reaction by the use of nitrogen nucleophiles, such as amines and azides; (iii) selective ring opening reaction of 1,2-cyclic sulfates with a wide variety of amines and azides; (iv) stereoselective addition of nucleophiles to α-amino aldehydes and ketones, and osmium-catalyzed asymmetric aminohydroxylation of olefins in the presence of chiral ligands.

As described in section 2, methods for the synthesis of *N*-activated 2-aziridinemethanols are well established; however, except for a few cases,[13,27] there have been no systematic investigations toward a simple and effective method for synthesizing chiral *N*-protected 1,2-amino alcohols from readily available chiral 2-aziridinemethanols. Aza-Payne rearrangement of 2-aziridinemethanols followed by reacting with appropriate nucleophiles seems to meet this demand in terms of the stereoselectivity and efficiency.

The Payne rearrangement of a 2,3-epoxy alcohol to an isomeric 1,2-epoxy alcohol, except for the recent protocol developed by Page, Rayner and Sutherland,[6] usually requires a basic aqueous medium, a requirement that places a serious restriction on the types of nucleophilic agents which may be used in the subsequent epoxide-ring opening reaction in a one-pot manner.

We anticipated being able to synthesize stereochemically well defined functionalized enantiomerically pure *N*-protected 1,2-amino alcohols **126** in a stereo- and regio-selective sense starting from 2-aziridinemethanols, such as **123**, *via* anionic intermediates **124** and **125** by successive treatment with base and various nucleophilic reagents (epoxide ring-opening of the intermediate **125** at the less substituted carbon of the epoxide has been well documented). Thus, whereas stereospecific synthesis of the *anti*-amino alcohol **126** could be expected starting from 2,3-*trans*-aziridino alcohol **123**, *syn*-amino alcohol **128** could be stereospecifically synthesized from 2,3-*cis*-aziridino alcohol **127** in a one-flask manner (Scheme 20). The rearrangement-epoxide ring opening reaction scenario does, in fact, lead to the stereochemically pure 1,2-amino alcohols.

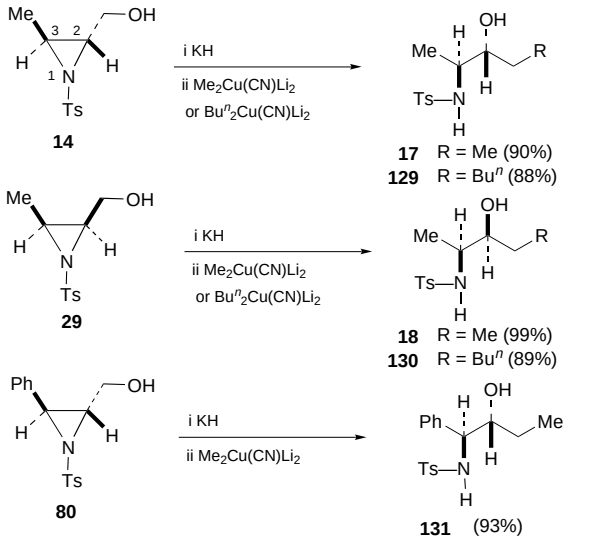


Scheme 20

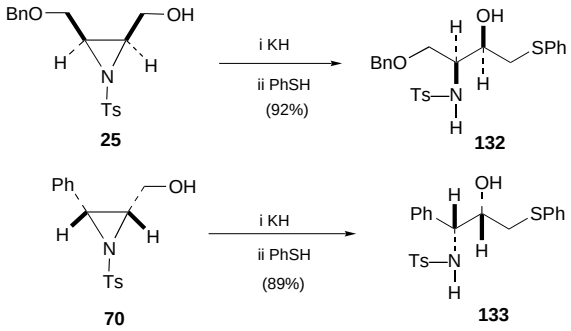
Initial experiments with 2-aziridinemethanol **14** revealed that KH was superior to either NaH or LDA as a base, and KH was therefore used for all experiments. Reaction of **14**, **29** and **80** with KH (2 equiv.) in THF at 0 °C for 1 h, was followed by the addition of $Me_2Cu(CN)Li_2$·2LiBr (5 equiv.) or Bu^{n}Cu(CN)Li_2 in a one-pot manner, and the mixture was then stirred for 1 h to yield the corresponding *N*-protected 1,2-amino alcohols in high yields as shown in Scheme 21. The presence of an excess of KH does not exert any influence on the organocopper reactions of intermediate epoxy aza-anions of type **125** in Scheme 20. It should be clearly noted that the use of MeLi·LiBr or MeMgBr instead of $Me_2Cu(CN)Li_2$·2LiBr did not result in clean transformations.[35]

The usefulness of this one-flask reaction would be enhanced if it could be successfully extended to other nucleophiles. Alkylthio and arylthio groups are important functional groups in various types of chemical transformations and, as shown in Scheme 22, the reactions of **25** and **70** with KH followed by PhSH in a one-pot manner gave the diastereomerically pure phenylthio amino alcohols **132** and **133** in 92 and 89% yields, respectively. Although similar treatment with KH and Bu^{t}SH yielded only the corresponding *tert*-butylthio amino alcohols, the overall yields of products were considerably lower (60–70%).[35]

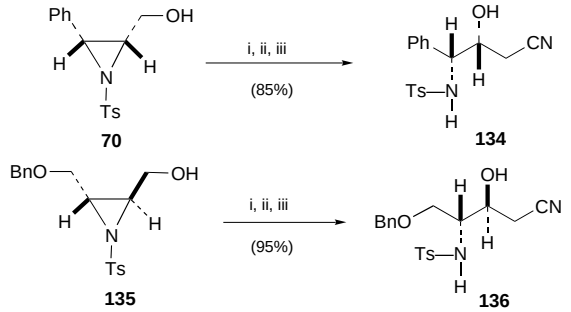
N-Protected 1,2-amino alcohols bearing a nitrile group could also be prepared in a one-pot manner as shown in Scheme 23. The reaction of **70** and **135** with KH followed by the sequential



Scheme 21 All reactions were carried out with 2 mol equiv. of KH and 5 mol equiv. of organocopper reagents



Scheme 22 All reactions were carried out with 2 mol equiv. of KH and 1.2 mol equiv. of PhSH

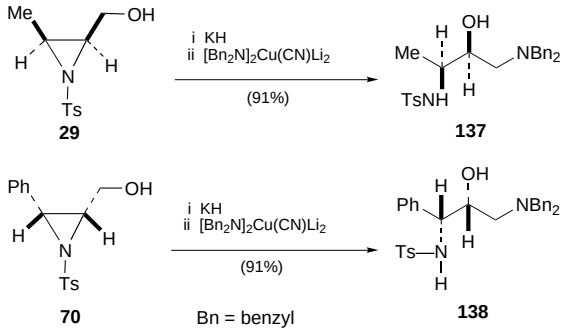


Scheme 23 *Reagents*: i, KH (2 equiv.); ii, Me_3SiCN (3 equiv.), $Yb(CN)_3$ (0.2 equiv.); iii, Bu_4^nNF

addition of Me_3SiCN (3 equiv.) in the presence of $Yb(CN)_3$ (0.2 equiv.) and Bu_4NF (1.5 equiv.) yielded the nitriles **134** and **136**, respectively, in high yields after flash chromatographic purification. This reaction also appears to be quite general, giving yields which are good to excellent.[35]

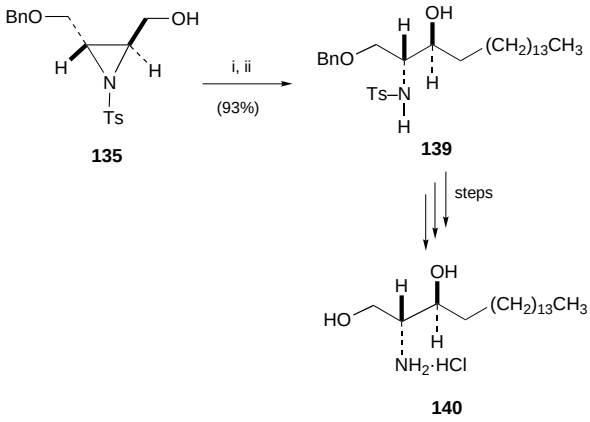
As shown in Scheme 24, synthesis of diamino alcohols **137** and **138** from aziridines **29** and **70** was also investigated. All attempts to use either dibenzylamine or lithium dibenzylamide to effect the epoxide ring opening of an anionic intermediate derived from 2-aziridinemethanol **29** were unsuccessful. Fortunately, use of the higher order amide cuprate, $(Bn_2N)_2Cu(CN)Li_2$, overcame the problem and yielded diastereomerically pure diamino alcohols **137** and **138** in high yields from aziridinemethanols **29** and **70**.

In view of the synthetic utility of the above described reactions, it was of interest to examine whether these trans-



Scheme 24 Reactions were carried out with 2 mol equiv. of KH and 5 mol equiv. of organocopper reagents

formation products could be useful as synthetic intermediates. For example, (2*R*,3*S*)-C18-dihydrosphingosine **140** can be readily synthesized in good overall yields from 2-aziridinemethanol **135** as shown in Scheme 25 *via* a sequence of reactions.[35]



Scheme 25 *Reagents*: i, KH (2 equiv.); ii, $[Me(CH_2)_{13}]_2Cu(CN)Li_2$ (5 equiv.)

7 Concluding remarks

The aza-Payne rearrangement of activated 2-aziridinemethanols with bases such as KH and NaH in most common solvents such as THF, toluene, or a mixed solvent of THF–HMPA, followed by quenching at low temperature gives the corresponding epoxy sulfonamides. Upon exposure of 2,3-epoxy amines to an equimolar mixture of Bu^tOK–Bu^nLi in a mixed solvent of THF and *n*-hexane at −78 °C, the equilibrium lies exclusively toward the hydroxy aziridine forming direction. Although yields were not necessarily optimized, an attractive one-pot regio- and stereo-selective synthetic route to chiral 1,2-amino alcohols from readily available 2-aziridinemethanols *via* the aza-Payne rearranged intermediates has been described. Isolation or purification of intermediates resulting from the aza-Payne rearrangement is not necessary. This methodology leads to a series of useful diastereomerically pure 1,2-amino alcohols which can be utilized as chiral auxiliaries for asymmetric synthesis. In addition, the amino alcohols could be used for the synthesis of more complex molecules. The chemistry of the aza-Payne rearrangement reported herein increases our understanding of this relatively unexplored class of reactions.

Many of the examples presented here have been developed with a view to large-scale laboratory synthesis in a simple manner. It is clearly evident, even from the selective results described in this review, that the aza-Payne rearrangement of 2-aziridinemethanols and 2,3-epoxy amines offer enormous potential for the synthesis of useful materials in enantiomerically pure form. The use of the aza-Payne reaction seems to be increasing and it would be apparent that researchers are

considering this strategy as a valuable alternative to the well-established routine, but lengthy, routes.

8 Acknowledgements

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