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A One-pot Aza-Payne Rearrangement-Epoxide Ring Opening Reaction of 2-Aziridinemethanols: A Regio- and Stereoselective Synthetic Route to Diastereomerically Pure 1,2-Amino Alcohols

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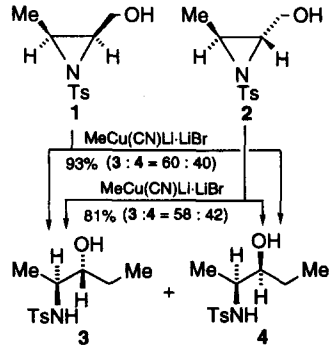
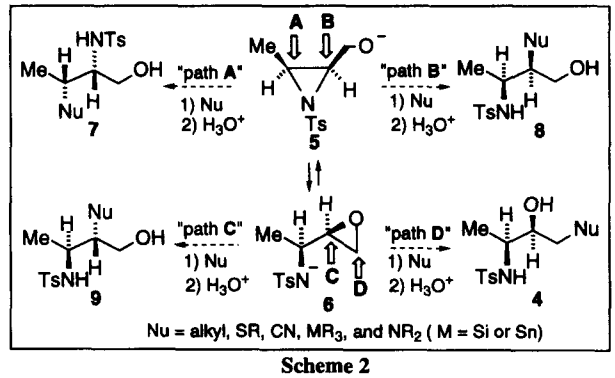
Abstract: A regio- and stereoselective synthetic route to diastereomerically pure 1,2-amino alcohols via *a one-pot* aza-Payne rearrangement - epoxide ring opening reaction of 2-aziridinemethanols is reported. Satisfactory yields are obtained in excellent diastereoisomeric excesses by successive exposure of 2-aziridinemethanols to potassium hydride and nucleophilic reagents in a one-pot manner.

N-Activated aziridines have been utilized as substrates in a number of important synthetic transformations.[1] On account of the ring strain present in aziridines,[2] the potential utility of *N*-activated aziridines as building blocks for synthesis of biologically active compounds reflects their ability to undergo regioselective ring-opening reactions with a wide range of nucleophilic reagents.[3] One very important aspect of aziridine ring-opening reactions is that they are usually stereospecific, producing secondary amines with inversion of configuration at the site of the ring opening via an S_N2 mechanism.[4] We have been interested in the synthetically useful ring-opening reaction of aziridine-ring bearing compounds with organocopper reagents in connection with synthetic studies on bioactive compounds of stereochemically well defined structure.[5] Unexpectedly, when both 2-aziridinemethanols **1** and **2** were treated with MeCu(CN)Li·LiBr, 60:40 and 58:42 mixtures of protected 1,2-amino alcohols **3** and **4** were obtained as shown in Scheme 1.[5a,c,e] Although these transformations with a lower order cuprate were interesting from the viewpoint of the reaction mechanism, the low stereoselectivity precludes their use for synthetic applications.



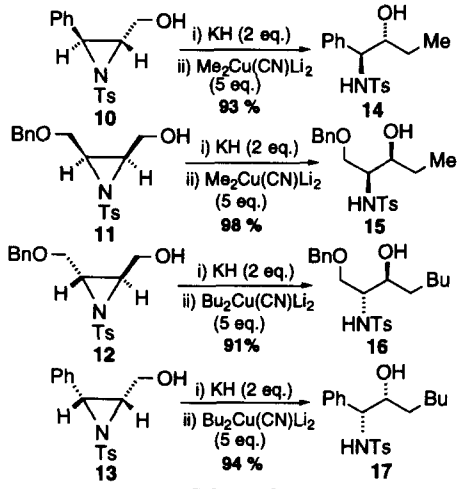
Scheme 1



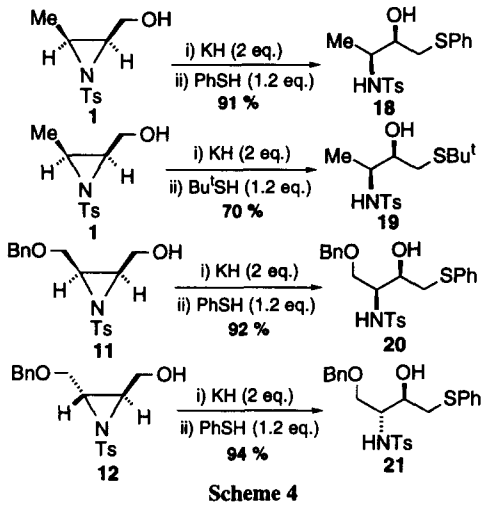
Scheme 2

It was our expectation to be able to synthesize stereochemically pure amino alcohols in a stereo- and regioselective manner in a one-pot sequence from readily available 2-aziridinemethanols by successive treatment with potassium hydride and various nucleophilic reagents as shown in Scheme 2. In principle, reaction of 2-aziridinemethanol **1** with bases such as KH followed by nucleophilic reagents in a one-pot manner could afford

one or a mixture of four amino alcohols **4**, **7**, **8**, and **9** *via* the anionic intermediates **5** and **6**. Thus, it is not an easy matter to predict whether **A**, **B**, **C**, or **D** is the major reaction pathway. In order to make such reactions practically useful, it is inevitable to know the favored reaction pathway before an evaluation regarding the relative merits of aza-Payne rearrangement - epoxide ring opening reaction. In a preliminary experiment, the rearrangement-epoxide ring opening reaction scenario does in fact lead to the stereochemically pure amino alcohols *via* the path D in Scheme 2. We now report that this approach is a viable and potentially useful route to stereodefined 1,2-amino alcohols from readily available chiral 2-aziridinemethanols.



Scheme 3



Scheme 4

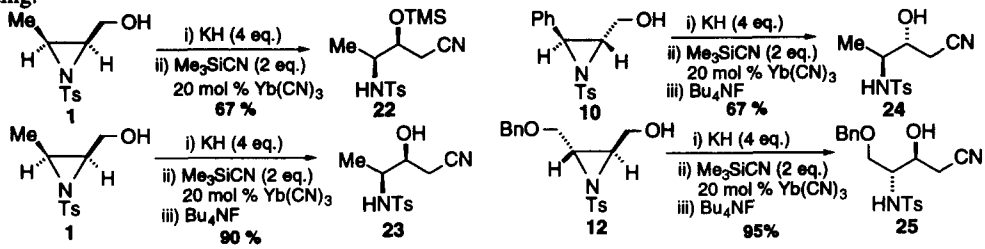
Exposure of **10**[5c] and **11**[5c] to potassium hydride (2 equiv.) in THF at 0 °C for 1 h, followed by the addition of $Me_2Cu(CN)Li_2 \cdot 2LiBr$ (5 equiv.) by syringe, and the whole mixture was stirred for 1 h at 0 °C to give the single products **14** and **15** in 93% and 98% yield, respectively (Scheme 3). This contrasted with our previous work [5a,e] where the reaction of **1**[5c] and **2**[5c] with MeCu(CN)Li·LiBr gave a mixture of 1,2-amino alcohols **3** and **4**. In a series of bases, KH[5e] gave the best results in combination with 1.2~5 equivalents of nucleophilic reagents. It should be clearly noted that the use of MeMgBr instead of MeCu(CN)Li·LiBr or $Me_2Cu(CN)Li_2 \cdot 2LiBr$ was not successful for a clean transformation. In a similar manner, reaction of the anionic equilibrium mixture derived from **12**[5c] with $Bu_2Cu(CN)Li_2$ afforded the single product **16** in 91% isolated yield. We were unable to detect any regio- or stereoisomeric compounds in these reactions.

This one-pot regio- and stereoselective method would be truly useful if it could be successfully extended to other nucleophiles. As shown in Scheme 4, the reaction of **1** with KH followed by PhSH and ^{t}BuSH gave the diastereomerically pure phenylthio- and *tert*-butylthio amino alcohols **18** and **19** in 91% and 70% yields, respectively.[7] Similarly, 2-aziridinemethanols **11**[5c] and **12**[5c] could easily converted into the phenylthio amino alcohols **20** and **21**, respectively, in high yields (Scheme 4).

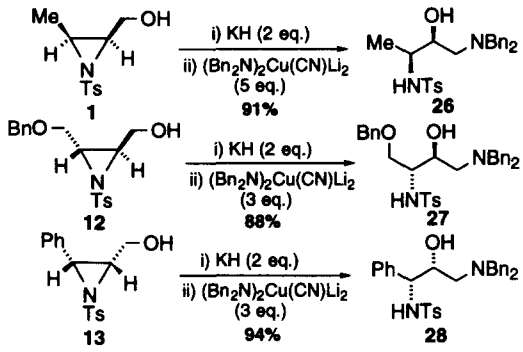
Likewise, the reaction of **1** with KH followed by the sequential addition of Me_3SiCN and $Yb(CN)_3$ [8] yielded the nitrile **22** in 67% yield after flash chromatographic purification. The low yield of **22** may be attributed to the rather low stability of the siloxy group in **22**. In the event, sequential treatment of **1** with KH, Me_3SiCN (3 equiv.) in the presence of $Yb(CN)_3$ (0.2 equiv.), and Bu_4NF (1.5 equiv.) yielded the cyano amino alcohol **23** in 90% isolated yield. By a procedure identical with that described for the reaction of **1**, 2-aziridinemethanols **10** and **12** afforded cyano amino alcohols **24** and **25**, respectively, in high yields (Scheme 5).

Attempts to use either dibenzylamine or lithium dibenzylamide to effect the epoxy ring opening of anionic intermedates derived from 2-aziridinemethanols **1**, **12**, and **13** were unsuccessful. Fortunately, use of a higher

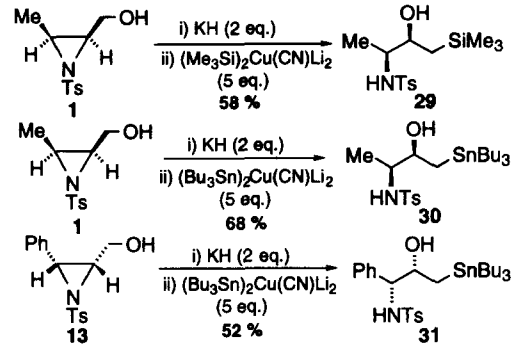
order amide cuprate,[9] $(Bn_2N)_2Cu(CN)Li_2$,[9a] had overcome the problem to yield diastereomerically pure diamino alcohols **26**, **27**, and **28** in high yields as shown in Scheme 6 and had placed the method on a synthetic footing.[10]



Scheme 5

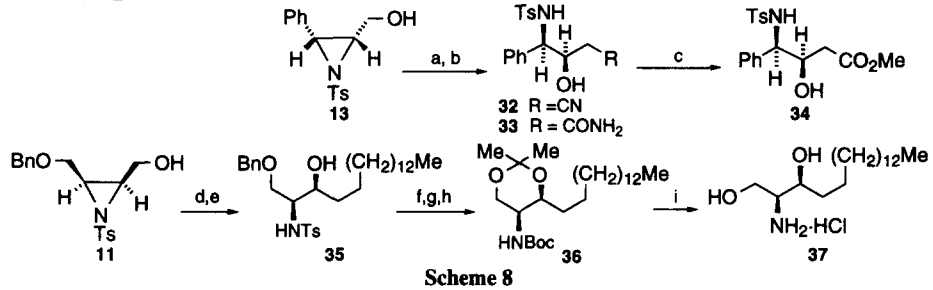


Scheme 6



Scheme 7

As can be seen from Scheme 7, acceptable chemical yields of compounds **29**, **30**, and **31** were obtained from the treatment of 2-azridinemethanols **1** and **13** with KH followed by $(Me_3Si)_2Cu(CN)Li_2$ or $(Bu_3Sn)_2Cu(CN)Li_2$.



Scheme 8

Reagents: a) i. KH (2 eq.), ii. TMSCN - 20 mol % $Yb(CN)_3$, iii. Bu_4NF (85%); b) 30% H_2O_2 - K_2CO_3 - MeOH (54%); c) i. 2*N*-KOH - MeOH, ii. etherial CH_2N_2 (80%); d) KH (2 eq.); e)$[Me(CH_2)_{13}]_2Cu(CN)(MgCl)_2$ (5 eq.) (89.5%); f) H_2 - PtO_2 - MeOH (91%); g) 2,2-dimethoxypropane - Me_2CO (1:2), $BF_3{\cdot}Et_2O$ (94.2%); h) i. Na - NH_3, ii. $(Boc)_2O$ (75.5%); i) 3N-HCl in THF (98.7%)

Having established useful reaction conditions for the synthesis of various amino alcohols with very high optical purity, the utility of aziridinemethanols **13** and **11**[5c] was briefly investigated. As shown in Scheme 8, the nitrile **32**, derived from **13** in 85% yield by the same procedure described above, was treated with an alkaline hydrogen peroxide to yield an amide **33**, which upon successive treatment with 2N-KOH in MeOH, 5% hydrochloric acid, and ethereal diazomethane yielded an amino acid methyl ester **34**, m.p. 106 °C, $[\alpha]_D$ - 33° (in CHCl3), in 80% yield. L-*threo*-C18-dihydrosphingosine **37** {hydrochloride: m.p. 75~77 °C, $[\alpha]^{20}_D$

- 10.4° (in MeOH)} can be readily synthesized from 2-aziridinemethanol **11** as shown in Scheme 8 via a sequence of reactions.[11]

In conclusion, an attractive one-pot regio- and stereoselective synthetic route to 1,2-amino alcohols from readily available 2-aziridinemethanols has been developed. Isolation or purification of the intermediate resulting from the aza-Payne rearrangement is not necessary. This methodology leads to a series of useful diastereomerically pure amino alcohols to be utilized in the synthesis of more complex molecules.

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