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Mechanistic and stereochemical aspects of the Lewis acid mediated cleavage of α-aminoacetals

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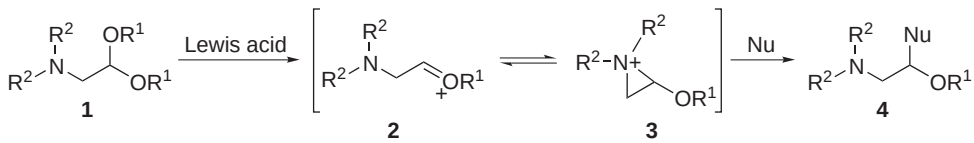
Abstract—The TMSOTf mediated nucleophilic cleavage of α-aminoacetals can be used to prepare a variety of substituted amines, with variable levels of stereocontrol depending on the substitution patterns. The reaction most likely proceeds via either an α-alkoxy aziridinium ion or an α-oxocarbenium ion depending on the type of nucleophile.

The Lewis acid mediated nucleophilic cleavage of acetals is a reaction of considerable mechanistic and synthetic interest. In particular, the nature of the reactive species involved is determined by an intricate balance of electronic and steric effects, and reaction conditions.[1] Our interest in acetal chemistry stems from its potential for stereocontrolled synthesis, as demonstrated by our synthesis of the unusual but very important nucleoside analogue Lamivudine, which is currently used for the treatment of HIV and hepatitis B.[2] We also have an interest in the chemistry of aziridinium ions, and we, and other groups, have shown them to be versatile, yet underused intermediates in synthetic organic chemistry.[3] In an extension of this work, and analogous to our recent α-thiothiiranium ion chemistry,[4] is the potential for the formation of the little studied α-alkoxy aziridinium ions[5] such as **3**, which would be expected to be in equilibrium with open chain α-oxocarbenium ions **2** and various intermediate forms, generated by Lewis acid mediated cleavage of α-aminoacetals[6] **1** (Scheme 1).

We believed this work to be of mechanistic interest, particularly if reaction pathways involving either **2** or **3** could be distinguished, but it was also important synthetically due to the potential for the formation of a variety of highly functionalised amines, which often show interesting biological activity. We thus embarked on a research programme to investigate the reactivities of intermediates such as **2** and **3**, and to exploit them in the area of stereocontrolled synthesis.

Synthesis of the appropriate acetal precursors was readily accomplished by reacting the required secondary amine (diallylamine, dibenzylamine) with bromoacetaldehyde diethyl acetal in DMF at 90°C in the presence of catalytic potassium iodide (71–74% yield). Substituents on nitrogen were chosen such that they would allow subsequent deprotection to the corre-



Scheme 1.

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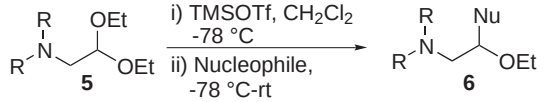
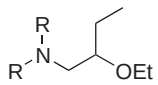
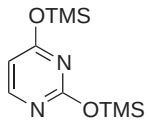
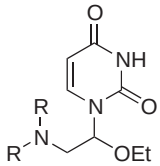
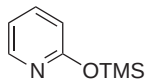
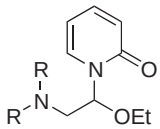
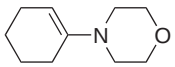
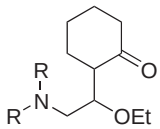
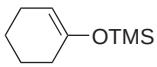
Table 1. TMSOTf mediated nucleophilic cleavage of α-aminoacetals



5 **6**

Entry	R	Nucleophile	Product	Yield (%)
1	allyl	Et_2Zn		72
2	Bn	Et_2Zn		86
3	Bn	EtMgBr		71
4	allyl			75
5	Bn			77
6	allyl			64
7	Bn			84
8	Bn			86[a]
9	Bn			13[a,b]

[a]78:22 mixture of isomers; [b]Major product (57%) is enone from further loss of EtOH.

sponding primary amine if required.[7] We then investigated the Lewis acid mediated nucleophilic cleavage of these simple acetals.

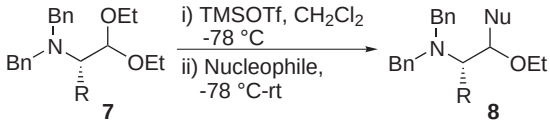
Treatment of the substrates with trimethylsilyl trifluoromethanesulfonate (TMSOTf) at –78°C followed by addition of the nucleophile and slowly warming to room temperature gave good yields of the acetal substitution products **6** (Table 1).

Reaction with organometallic species such as dialkyl zinc and Grignard reagents proceeded efficiently, for both the *N*-allyl and *N*-benzyl substrates. Similarly, introduction of the uracil group and 2-pyridone was also efficient. Enamines reacted smoothly to introduce carbonyl functionality, but with silyl enol ethers, the Lewis acidic reaction conditions led to further loss of ethanol to give the α,β-unsaturated ketone as the major product.

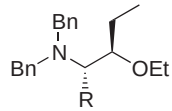
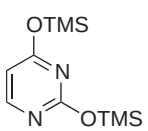
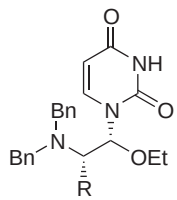
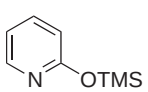
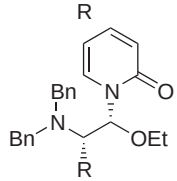
These encouraging preliminary results led us to consider investigating more complex systems, which had greater potential for stereocontrolled synthesis, but would also provide more revealing mechanistic data to help determine the dominant reactive species. The substrates were synthesised from the corresponding optically active amino alcohols by *N*-dibenzylation (BnBr, KI, DMF, 80°C), Swern oxidation, and acetal formation (EtOH, $(EtO)_3CH$, H_2SO_4). They were then subjected to the same reaction conditions as before. The results of these reactions are shown in Table 2.

Table 2 shows a number of interesting trends. Firstly, the use of diethyl zinc as nucleophile gives high levels of diastereoselectivity, irrespective of size of the substituent R. Secondly, when R is large (Bn, ^{i}Pr) high levels of selectivity are obtained, irrespective of the nucleophile. Thirdly, low selectivity is observed with the

Table 2. TMSOTf mediated nucleophilic cleavage of chiral α-aminoacetals



7 **8**

Entry	R	Nucleophile	Major product	diast. ratio	Yield (%)
1	Bn	Et_2Zn		95:5[a]	64
2	^{i}Pr	Et_2Zn		93:7	61
3	Me	Et_2Zn		94:6	77
4	Bn			95:5[b]	70
5	^{i}Pr			89:11	78
6	Me			55:45	71
7	Bn			95:5	89
8	Me			54:46	87

[a]Sterechemical assignment confirmed by comparison with literature;[8] [b]Stereochemical assignment confirmed by X-ray crystallography, *vide infra*.[9]

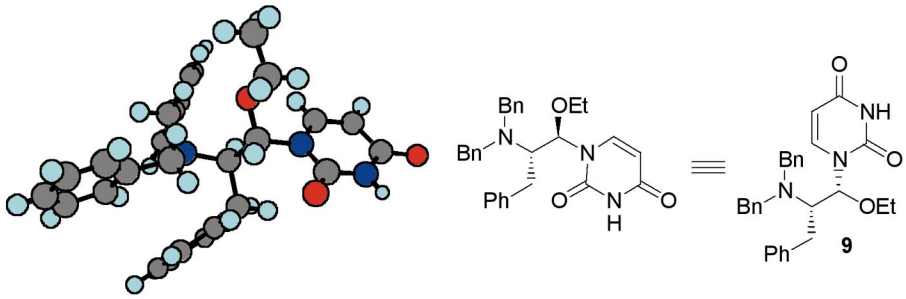
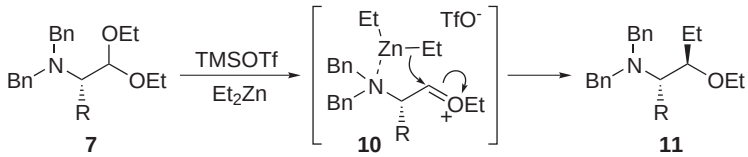


Figure 1. X-Ray crystal structure of **9**.



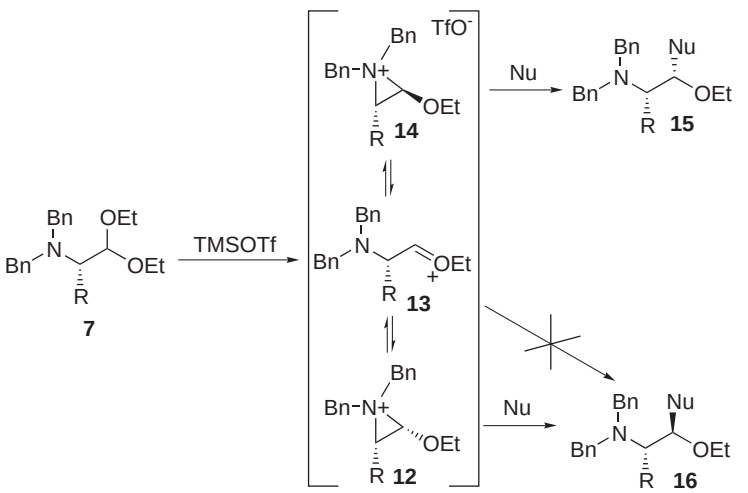
Scheme 2.

nitrogen heterocycles with a small R group in the substrate (Me). Finally, the sense of stereoselection is reversed when switching from diethyl zinc to the nitrogen heterocycles. These intriguing observations allow considerable insight into the nature of the reactive intermediates involved.

Of crucial importance to our arguments, are the stereochemical assignments for the major products of the reaction. In the case of the diethyl zinc additions, this was assigned by comparison with the literature. The addition of diethyl zinc to the analogous aldehyde gives the *syn* diastereomer as the major product.[8] Subsequent *O*-ethylation shows this product to be the minor isomer of our reactions, and hence confirms our *anti* assignment (entries 1–3). The stereochemistry of the uracil derivative **9** (Table 2, entry 4) was determined by X-ray crystallography (Fig. 1), which clearly shows the *syn* stereochemistry.[9] There is also a very good correlation between ^{1}H NMR chemical shifts in the *syn* and *anti* diastereomeric series.[10]

Let us first consider the high levels of stereocontrol observed when using diethyl zinc as the nucleophile. It is likely that the reaction proceeds via pre-coordination of the diethyl zinc to the tertiary amine group within the substrate (e.g. **10**), as is usually required to activate such organometallic reagents.[8,11] Subsequent intramolecular delivery of the ethyl group exaggerates the effect of the R-substituent, leading to high levels of *anti* selectivity in each case (Scheme 2). Note that because the nitrogen atom is now coordinated to the zinc, it is no longer able to stabilise the adjacent cationic centre, and so it would not be expected to be able to form an α-alkoxy aziridinium ion intermediate.

The addition of nitrogen heterocycles is more complex. Although variable levels of selectivity observed may be



Scheme 3.

expected and are consistent with the size of the substituents R, the predominant *syn* stereoselectivity is unlikely to originate by addition to the α-oxocarbenium ion **2**. Instead, the intermediacy of an α-alkoxy aziridinium ion can be invoked to explain the observations (Scheme 3). There are two possible isomeric α-alkoxy aziridinium intermediates we can form, the *cis* **12** and *trans* **14** isomers, which may be in equilibrium via a small concentration of the α-oxocarbenium ion. Extensive broadening observed during variable temperature NMR experiments on intermediates derived from **7** (R = Bn) suggest this, but other equilibrium processes such as acetal exchange cannot be discounted at this time.[10]

Stereocontrolled S_N2 nucleophilic ring opening of the *trans* isomer **14** would give the observed *syn* product, whereas the *cis* isomer **12** would give the *anti* product. For large substituents (R = Bn, ^{i}Pr), the *trans* aziridinium ion **14** would be expected to be significantly more stable than the *cis* **12** due to steric effects, hence the high *syn* selectivity observed with these substituents. The fact that little or no *anti* product is formed suggests that direct addition to the α-oxocarbenium ion **13** does not occur, and this also provides additional evidence for the importance of the coordinated diethyl zinc intermediate in the previous case. With small substituents (R = Me) there would be much less difference in energy between the *cis* and *trans* isomeric aziridinium ions, and hence both would be present in similar concentrations leading to the mixture of products observed.

In summary, we have shown that the TMSOTf mediated nucleophilic cleavage of α-aminoacetals, can be used to introduce efficiently a variety of groups, with variable levels of stereocontrol depending on the substitution patterns. The reaction most likely proceeds via a novel α-alkoxy aziridinium ion, but an α-oxocarbenium ion is a likely intermediate in the presence of nucleophiles capable of coordinating to the tertiary amine group.

Acknowledgements

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