Strained azetidinium ylides: new reagents for epoxidation†

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Azetidinium ylides effected facile epoxidation of various carbonyl compounds furnishing tri or tetrasubstituted epoxides that were unattainable *via* classical ammonium ylide chemistry; the produced trisubstituted oxiranes gave rise to a remarkable cascade of reactions leading to some original pyrrolidin-3-ones.

The stereoselective preparation of functionalised epoxides has generated great efforts from organic chemists in several complementary directions. These versatile small molecules were synthesised from alkenes *via* oxidation routes, the Darzens reaction also proved effective starting from carbonyl compounds, and more recently sulfur and ammonium ylides showed very interesting results in aldehyde epoxidation. Notably, the work of Aggarwal *et al.*[1] allowed the asymmetric preparation of glycidic esters or amides using camphor-derived sulfonium ylides: good yields and excellent selectivities were observed by the authors. The same group generalised the discussion about the important factors playing a role in ylide reactivity,[2] and a critical parameter was circumscribed: the leaving group ability of the heteroatom. In the onium group, leaving group ability decreases in the order O > S > N > P hence drawing the following trend for the epoxidation reaction: theoretically, oxonium ylides would be the most efficient reagents, sulfonium ylides can effect the reaction at very low temperature, while the less reactive ammonium ylides require room temperature to react. Finally, phosphonium ylides rather proceed through the Wittig reaction due the oxophilicity of the heteroatom. The group of Aggarwal also pinpointed the critical nature of ammonium ylides.[3] They showed that aryl-stabilised ammonium ylides could perform the epoxidation of benzaldehyde in moderate to good yields while the less reactive ester or cyano-stabilised ammonium ylides **1** were completely inactive (Scheme 1).[4]

This absence of oxirane formation was attributed to the incapacity of alkoxide **2** to displace the ammonium, which has poor leaving group ability. The energetic barrier of subsequent ring-closure is then too high to be overcome.

Involved in azetidinium ylide chemistry, we were interested by this lack of reactivity of ammonium ylides towards epoxidation. In
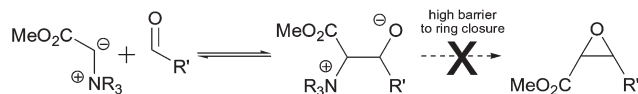
Scheme 1   Failure of epoxidation with ammonium ylides.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, spectroscopic data, ^{1}H and ^{13}C NMR spectra and ORTEP diagram of **19**. See DOI: 10.1039/b701848g
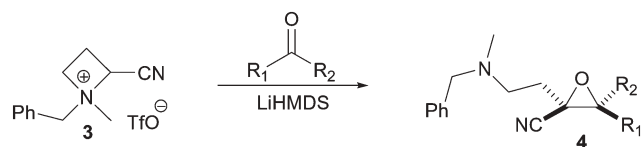
Scheme 2   Epoxidation of carbonyl compounds with azetidinium ylides.

fact, we have recently reported a cyclopropanation reaction driven by a crucial feature of azetidinium ylides:[5] these reagents include a strained four-membered ring that reinforces the leaving group character of the nitrogen thus assuring the efficiency of the process.[6] We thought that such an energetic gain would be critical to success in carbonyl group epoxidation with azetidinium ylides.

To test the feasibility of this epoxidation, we reacted ylide **5**, generated *in situ* by deprotonation of azetidinium salt **3**[5] with LiHMDS, together with benzaldehyde. To our delight, the crude mixture was exclusively constituted of the desired epoxide **4a** in nearly quantitative yield (Scheme 2).

However, upon standing at room temperature, the epoxide slowly decomposed. For this reason, chromatographic purification had to be done very quickly in order to retain an excellent yield. As

Table 1   Results of carbonyl compound epoxidation

	Carbonyl	Product **4**	Yield[a] (%)
a			98
b			77
c		—	—[b]
d		—	—[b]
e			94
f			99
g			99

[a] Crude yields were in all cases quantitative, the yield of the purified product is given. [b] The epoxide rapidly reacted at 20 °C precluding its isolation, *vide infra*.
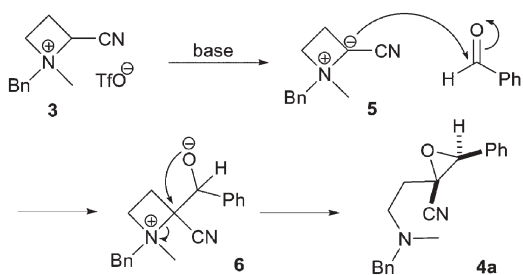
Scheme 3 Mechanism of epoxidation.

can be seen in Table 1, aromatic and aliphatic aldehydes were smoothly converted to the corresponding epoxide. Azetidinium ylide **5** was even reactive towards ketones and provided tetrasubstituted epoxides **4f,g**, all entries showing the formation of a unique diastereomer.[7] Nevertheless, in some cases (entries **c** and **d**) the epoxide was detected by TLC as the sole compound in the mixture at −78 °C, but after work-up at room temperature was totally consumed.

The mechanism of this reaction is rather simple, ammonium salt **3** is deprotonated to generate the ylide **5** and it then attacks the carbonyl compound to form alkoxide **6**. This then finally evolves to the epoxide **4** in a three-membered ring closing/four-membered ring opening process (Scheme 3).

In a second step we investigated the stereochemical outcome of this transformation. The use of enantiopure azetidinium salt **7**[8] with acetophenone led to the formation of a single isomer **8** in 61% yield after purification. Gratifyingly, in contrast with our observations of cyclopropanation reactions,[5] the replacement of the cyano group with an ester did not affect the epoxidation ability of the azetidinium ylide. Enantiopure epoxide **10** could be obtained in 85% yield from **9** (Scheme 4).[8]

The relative configurations of compounds **8** and **10** were deduced by comparison of ^{1}H NMR signals with known similar compounds.[7] Absolute configurations were assumed to be identical to those induced in cyclopropanation reactions.[5] It should be added that reactions involving ester-bearing azetidiniums were however capricious, for instance, we never succeeded in the epoxidation of acetone. This shows the complexity of the parameters governing ammonium ylide chemistry.

In order to prove the crucial role played by the ring strain present in these azetidinium ylides, the homologous pyrrolidinium salt **11** was treated with benzaldehyde or acetone under similar conditions. In both cases the reactants were recovered, but the ammonium salt was completely epimerised at the position alpha to the cyano group, indicating that deprotonation did occur, but without any formation of epoxide **12** (Scheme 5).
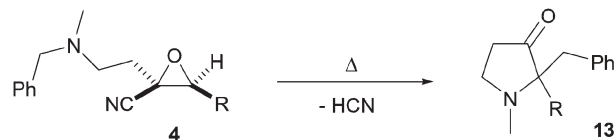
Here, in a five membered-ring, the absence of ring strain does not bring the decisive energetic "help" needed to perform the difficult ring-closure of the transient alkoxide, which unable to
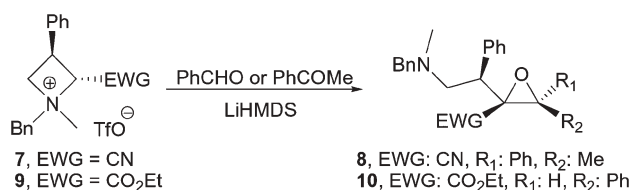
Scheme 4 Epoxidation with chiral azetidinium salts.
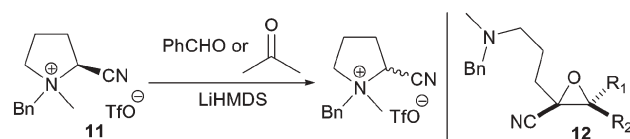
Scheme 5 Failure of epoxidation with a pyrrolidinium salt.

Scheme 6 Rearrangement of cyano epoxides.

cyclise, evolves back to the reactants.[3] This demonstrates that ring strain present in the intermediate **6** is essential to assist the departure of the ammonium and thus to allow epoxide formation.

The degradation of some epoxides remained intriguing for us; we therefore looked in detail at the nature of decomposed products obtained in entry **c**. To our surprise rather than degradation, the process cleanly converted the epoxide into a major compound. Evolution of hydrogen cyanide was evident by a characteristic odour. All analytical data (^{1}H and ^{13}C NMR, IR, mass spectrum) of the purified product **13** were consistent with a pyrrolidin-3-one disubstituted in position 2 (Scheme 6).

The generality of this rearrangement was then proven when all trisubstituted epoxides **4a–e**, showed identical reactivity when heated under vacuum for various times as detailed in Table 2.

This unexpected rearrangement can be explained by the following sequence of reactions, shown for example in Scheme 7 with compound **4a**. This latter bears a nucleophilic moiety (tertiary amine) as well as an electrophilic epoxide; these two can react in an intramolecular fashion to close into a five membered-ring, leading

Table 2 Results of epoxide rearrangement

	Carbonyl	Product **13**	Time[a]/h, yield (%)
a			4, 81
b			12, 71
c			2, 58
d			8, 20
e			3, 20

[a] Conditions: the crude epoxide was heated neat at 50 °C under vacuum for the time indicated in hours.
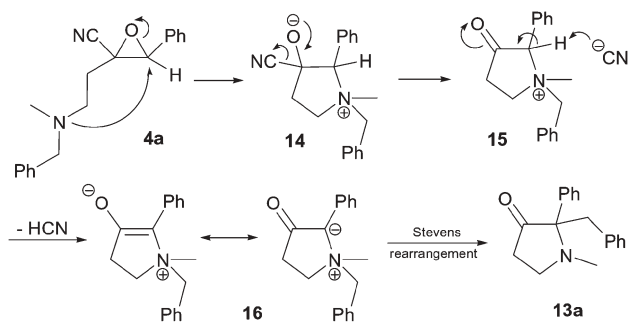
Scheme 7 Mechanism of the rearrangement.
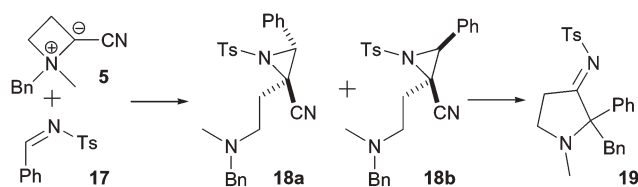
Scheme 8 Aziridination of an imine.

to zwitterion **14**. The alkoxide can evolve to a ketone upon elimination of a cyanide anion, leaving ammonium **15**. The cyanide then abstracts a proton from position 2, particularly acidic due to the concomitant presence of an ammonium, a ketone and in some cases an additional aromatic group. Hydrogen cyanide is liberated while ammonium ylide **16** is formed. This intermediate finally undergoes a classical Stevens rearrangement[9] with a [1,2]-shift of the benzyl group from the nitrogen to the carbon atom to furnish pyrrolidinone **13a**.

So the unique and fortuitously well arranged structure of epoxides **4a–e** allowed this cascade of reactions to occur,[10] providing disubstituted pyrrolidin-3-ones, rarely found in the literature.[11]

Reaction of ylide **5** with tosylimine **17** with the aim of preparing **18** led to an interesting result. After complete consumption of the reactants, TLC revealed the presence of two products that we attributed to the formation of two diastereomers **18a** and **18b** with Rf_{18a} 0.22 and Rf_{18b} 0.33. Work-up at room temperature showed the progressive disappearance of **18b**. Heating at 50 °C for 30 min led to the complete conversion of compound **18b** into a new product: **19** with Rf_{19} 0.46, while compound **18a** was left intact as indicated by the remaining spot with Rf_{18a} 0.22 (Scheme 8).

Separation of the products gave pure aziridine **18a** in 30% yield and pyrrolidine **19** also in 30% yield. The structure of crystalline compound **19** was ascertained by X-ray diffraction analysis.[12] Unfortunately the configuration of compound **18a** could not be assigned, NOE experiments being inconclusive. Although, it is reasonable to think that **18b**, which can undergo the rearrangement presents a *trans* relationship between the aminoethyl chain and the phenyl group, allowing the nitrogen atom to attack easily the aziridine. On the contrary, in **18a** a *cis* relationship between the

aminoethyl chain and the phenyl group, the latter hampers the nucleophilic attack of the nitrogen, preventing the rearrangement.

In conclusion, azetidinium ylides, easily generated by deprotonation of the corresponding azetidinium salts, are robust reagents to perform epoxidation of carbonyl compounds in a diastereo-selective manner. Epoxidation of aldehydes as well as ketones proceeded in good yields, the aliphatic or aromatic nature of these having little influence. Aziridination of a tosylimine was also possible. The ring strain inherent in azetidine heterocycles proved essential to realize this epoxidation efficiently. This is to be compared with the unstrained hydroxyammonium salts used by Jończyk *et al.*,[4] who reported the first epoxidation using cyano-stabilised ammonium ylides, which proved reactive only towards aldehydes, in moderate yields. The epoxides can be used in further reactions, but their intrinsic reactivity led us to observe an unusual rearrangement producing pyrrolidin-3-ones having a quaternary carbon centre. This cascade of reactions moreover involves the formation of a cyclic ammonium ylide which undergoes a Stevens rearrangement, exemplifying the versatile reactivity of nitrogen ylides.

We wish to thank Vincent Steinmetz whose skills in mass spectrometry provided a decisive clue to determine the structure of compounds **13** and **19**, which were at first mysterious.

Notes and references

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10 Epoxides **4f** and **4g** do not give rise to such rearrangements. However, the mass spectrum of **4g** shows a strong peak at m/z [M − CN]$^+$ = 218.2 indicating the occurrence of cyanide loss, which could correspond to the formation of cationic intermediate **15g**. The lack of an acidic proton in this intermediate prevents further reaction.
11 Similar structures in enantiopure form are found in: T. Ooi, T. Miki and K. Maruoka, *Org. Lett.*, 2005, **7**, 191–193.
12 Crystal data for **19**: $C_{25}H_{26}N_2O_2S$, $a = 9.7061(10)$, $b = 10.1783(10)$, $c = 11.4792(11)$ Å, $\alpha = 96.318(4)$, $\beta = 107.261(4)$, $\gamma = 100.935(4)°$, space group $P\bar{1}$, CCDC 633153. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b701848g.