Delineation of the factors governing reactivity and selectivity in epoxide formation from ammonium ylides and aldehydes†

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Diastereoselectivity in reactions of aryl-stabilised ammonium ylides are highly sensitive to the nature of the amine and the ylide substituent. DFT calculations are consistent with a mechanism in which reversibility in betaine formation [despite the high energy (and therefore instability) of ammonium ylides] is finely balanced due to the high barrier to ring closure.

There has been considerable interest in the development of stereoselective methods to prepare epoxides. While most methods have concentrated on alkene oxidation,[1] we have focused our efforts on the epoxidation of carbonyl compounds. In this context, we have reported an efficient catalytic and asymmetric process converting carbonyl compounds directly into epoxides using sulfur ylides.[2] We asked ourselves whether ammonium ylides could also be used to effect the same transformation.[3] The very few examples of ammonium ylide reactions with aldehydes also encouraged us to study this area further.

Wittig[4] and Sato[5] had shown that non- and phenyl-stabilsed ammonium ylides react with carbonyl compounds to give β-hydroxyammonium salts whilst Jończyk[6] had found that cyano-stabilised ylides gave the corresponding epoxides. Yields in almost all of these cases were only moderate. Only a handful of examples of the ring closure of β-hydroxyammonium salts to give epoxides has been reported.[7] Thus, it was not clear whether the dearth of literature examples of ammonium ylide epoxidations was due to ylide instability (prone to Stevens or Sommelet–Hauser rearrangements[3,8]) *versus* reactivity (ammonium ylides are expected to have high nucleophilicity, due to the low stabilisation of the negative charge[9]) or because of problems in ring closure, or both.

In considering reactivity toward aldehydes *versus* stability issues, we chose aryl-stabilised ammonium ylides and used cyclic amines derived from six membered rings to minimize the propensity for Stevens rearrangement since ring expansion to a seven membered ring should be less favourable.[2b]

If ring closure was problematic, we sought to explore this issue by investigating both quinuclidine and DABCO derivatives (respectively ylides **1** and **2**), the latter being a better leaving group.[10] Indeed, we have previously highlighted the importance of leaving group ability in all of the important reactions of onium ylides including additions to aldehydes.[11] During the course of our studies, Kimachi *et al.* reported that reactions of benzyltriethylammonium salts with base and benzaldehyde gave epoxides with moderate to high yields and diastereoselectivities depending on the electronic nature of the benzyl group.[12]

The results of our studies on the reactions of ylides **1** and **2** with benzaldehyde are given in Table 1.

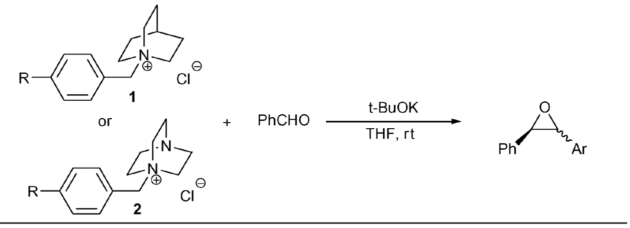
Our results show a clear general correlation between the electron rich/poor character of the ylidic aromatic ring and the observed yield and diastereoselectivity (Table 1): stabilisation of the ylide leads to good yields and diastereoselectivities while ylides bearing an electron-donating group react with generally poorer yields and much lower selectivities.

The use of DABCO (instead of quinuclidine) as the amino group did not affect yield, indicating that ring closure is not a significant problem in the reaction of aryl-stabilized ammonium ylides. However, it did affect diastereoselectivity: DABCO derivatives gave a systematically lower *trans* : *cis* ratio compared to the corresponding quinuclidine derivatives.

The lower yields in the case of substitution by an electron-donating group can be accounted for by the lower stability of the ylides and hence a larger propensity to give side reactions.[9] The origin of the changes in diastereoselectivity with substitution on the other hand is less apparent.

In epoxidation reactions of phenyl-stabilised sulfur ylides, experimental and computational studies showed that the observed high *trans* selectivity was the result of a similar rate of formation

Table 1 Influence of ylide stabilisation and the nature of ammonium group on yield and diastereoselectivity



Entry	Substrate	R	Yield (%)[a]	*trans* : *cis*[b]
1	**1a**	OMe	38	61 : 39
2	**2a**	OMe	41	50 : 50
3	**1b**	Me	60	65 : 35
4	**2b**	Me	43	56 : 44
5	**1c**	H	41	92 : 8
6	**2c**	H	42	70 : 30
7	**1d**	Cl	77	96 : 4
8	**2***d*	Cl	71	92 : 8
9	**1e**	CF_3	77	99 : 1
10	**2e**	CF_3	77	99 : 1

[a] Isolated yields. [b] Determined by ^1H NMR on the crude mixture.

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of both *syn* and *anti* betaines where formation of the *syn* betaine was reversible but the *anti* betaine was non-reversible.[2d] In the present case (ammonium ylides), the much lower stabilisation of the ylide[9] would be expected to lead to systematic non-reversibility of the initial addition step, which would therefore also be the selectivity determining step. This intuitive reasoning, however, does not explain the observed trends.

This leads to the question: what is the origin of the decrease in selectivity when using less stabilised ylides or upon changing the amine from quinuclidine to DABCO derivatives? What are the factors governing selectivity in ammonium ylide reactions with aldehydes? In order to answer these questions, we have investigated the energy profile of the reaction of ylide **3** with benzaldehyde by computational means (Fig. 1).[13] Calculations were carried out at the B3LYP/6-31 + G**//B3LYP/6-31G* level of theory including a continuum description of THF as solvent.‡

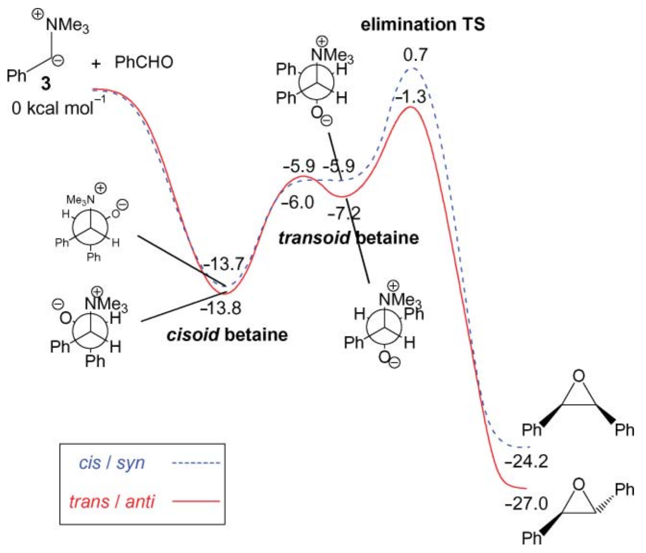


Fig. 1 Computed‡ potential energy surface (kcal mol^{-1}) for stilbene oxide formation from **3** and benzaldehyde.

The mechanistic sequence is similar to that in sulfur ylide reactions:[2d] addition of the ylide to the aldehyde generates a betaine intermediate, torsional rotation converts the *cisoid* betaine into the *transoid* conformer with the two charged groups *anti* to each other, and finally ring closure, with concomitant expulsion of the amine, gives the corresponding epoxide.

As a result of the low stabilisation of reactants,[9] the initial addition step is found to be fairly exothermic. Two isomeric betaines can be formed during this step, an *anti* and a *syn* diastereomer, with both being found to be equally stable. Due to the high nucleophilicity of the ylide, betaine formation occurs without enthalpic barrier[14] (for comparison, the corresponding barrier in the case of sulfur ylides was *ca.* 4.5 kcal mol^{-1}).[2d] This means that no (or very low) selectivity is expected for this step; *syn* and *anti* betaines should be formed in a *ca.* 50 : 50 ratio.

One of the most significant differences between the sulfur ylide and the ammonium ylide reactions is the high barrier to elimination, 12.5 and 14.4 kcal mol^{-1}, from *cisoid* betaine, for *anti* and *syn* isomers respectively (for comparison, in the sulfur ylide case these barriers are respectively 1.3 and 5.4 kcal mol^{-1}[2d]). This difference can be accounted for by the poor leaving group ability of the ammonium group. A previous study on reactivity in onium ylide reactions showed indeed that leaving group ability decreased in the order OMe_2, SMe_2, NMe_3, PMe_3.[11] Because of the poor leaving group ability of ammonium ions, the elimination step is rate determining in the reaction of ammonium ylides with aldehydes. This also accounts for the isolation of β-hydroxyammonium salts upon work-up of the reaction of ammonium ylides with aldehydes.[4,5]

Another consequence of the high barrier to ring closure is that the elimination TS is close in energy to the reactants.[15] Due to the poor leaving group ability of the ammonium group, and despite the high energy of the reactants, betaine formation is thus likely to be somewhat prone to reversibility. This is of great importance in determining selectivity. Indeed, if no reversal occurs, the selectivity determining step is the addition step, whereas if betaine formation is reversible, selectivity is determined by the relative energy of the two diastereomeric elimination TSs.

The observed influence of ylide stabilisation on selectivity can thus now be understood (Fig. 2): substitution of the ylide by an electron-withdrawing group decreases the relative energy of reactants[16] but does not affect, or if anything increases the barrier to ring closure (see below), thus rendering betaine formation more reversible. Selectivity is thereby determined at the ring closure step, which explains the observed high preference for *trans* epoxides. In contrast, when the ylide is substituted by an electron-donating group, relative energy of the reactants increases and the barrier to ring closure is, if anything, reduced. Selectivity in these cases is thereby determined at the addition step, which, due to its absence of enthalpic barrier, must occur with no (or very low) selectivity.

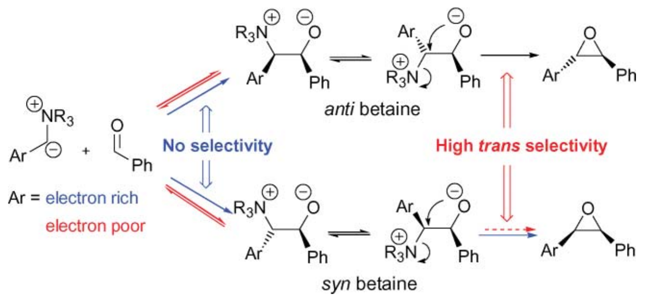
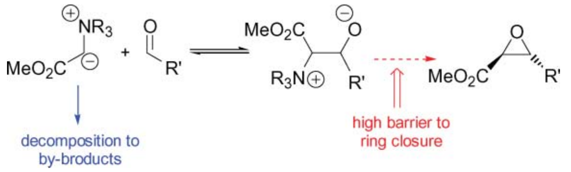


Fig. 2 Origin of observed variations in diastereoselectivity according to ylide stabilisation in reactions of ammonium ylides with aldehydes.

The observed decrease in selectivity when using DABCO derivatives (ylides from **2**) instead of quinuclidine (ylides from **1**) can be explained following the same reasoning: DABCO is a better leaving group than quinuclidine,[10] which means that the barrier to ring closure is lower in reactions of ylides **2** relative to ylides **1**. Relative energy of reactants on the other hand should not be significantly affected by the nature of the ammonium group. The use of DABCO derived ammonium ylides thus leads to a decrease in the reversal of betaine formation, and hence to a reduction in selectivity.

The above analysis has important implications for carbonyl-stabilised ammonium ylides. Although such ylides have been effective in cyclopropanation reactions,[17] we and others[18] have been unsuccessful in effecting reactions with aldehydes (Scheme 1).

Previous studies[19] showed that the presence of a carbonyl group α to the leaving group (sulfonium) leads to a substantial increase



Scheme 1 Problems with epoxide formation from ester-stabilized ammonium ylides.

in the barrier to ring closure (the barriers to ring closure, from the *anti* betaine, for Ph and $CONMe_2$ are 1.8 and 6.0 kcal mol^{-1}, respectively). In the case of the sulfonium group, this does not prevent epoxidation from occurring but the combination of this with the poor leaving group ability of the ammonium group makes this barrier too high in this case and no epoxide is formed.

In conclusion, we have shown that yield and diastereoselectiivity in reactions of aryl-stabilized ammonium ylides with aldehydes are strongly influenced by the nature of the amine and the ylide substituent. Electron-deficient aromatics, which are able to stabilise the ylide, give good yields whereas electron-rich aromatics, which destabilise the ylide, give poor yields. Perhaps the most surprising result from this study is the ease of reversal of betaine formation, despite the high energy of the ammonium ylide. This is a consequence of the high barrier to ring closure due to the poor leaving group ability of the amine. Reversibility in betaine formation is very finely balanced: groups that stabilise the ylide and/or increase the barrier to ring closure (electron-deficient aryl groups) lead to reversibility and high *trans* selectivity whilst groups that destabilise the ylide and/or reduce the barrier to ring closure (electron-rich aryl groups, better amine leaving group) lead to reduced reversibility and lower *trans* selectivity. The failure of ester-stabilised ylides to form epoxides can be accounted for by the further increase in barrier to ring closure. Thus, the success of ammonium ylide epoxidation is critically dependant on ylide stability *vs* reactivity toward aldehydes and the barrier to ring closure.

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Notes and references

‡ Calculations were carried out as stated for both the geometry optimization and the single point energy calculation using the Jaguar 4.0 pseudospectral program package.[20] This method has been selected to be the most adequate for the studied system after investigation of the model reaction of CH_2O with CH_2NMe_3 at a variety of different levels of theory (see the ESI for full details). Relative energies correspond to electronic energies at the indicated levels of theory.

1 (*a*) T. Katsuki, in *Comprehensive Asymmetric Catalysis II*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin, 1999, pp. 621–648.

2 (*a*) V. K. Aggarwal and C. L. Winn, *Acc. Chem. Res.*, 2004, **37**, 611–620; (*b*) V. K. Aggarwal, E. Alonso, I. Bae, G. Hynd, K. M. Lydon, M. J. Palmer, M. Patel, M. Porcelloni, J. Richardson, R. A. Stenson, J. R. Studley, J.-L. Vasse and C. L. Winn, *J. Am. Chem. Soc.*, 2003, **125**, 10926–10940; (*c*) V. K. Aggarwal, I. Bae, H.-Y. Lee, J. Richardson and D. T. Williams, *Angew. Chem., Int. Ed.*, 2003, **42**, 3274–3278; (*d*) V. K. Aggarwal, J. N. Harvey and J. Richardson, *J. Am. Chem. Soc.*, 2002, **124**, 5747–5756; (*e*) V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lydon, M. J. Palmer, M. Porcelloni and J. R. Studley, *Angew. Chem., Int. Ed.*, 2001, **40**, 1430–1433.

3 For reviews on ammonium ylides chemistry, see: (*a*) J. A. Vanecko, H. Wan and F. G. West, *Tetrahedron*, 2006, **62**, 1043–1062; (*b*) J. S. Clark, *Nitrogen, Oxygen and Sulfur Ylide Chemistry: A Practical Approach in Chemistry*, Oxford University Press, Oxford, UK, 2002; (*c*) I. E. Markó, *Comprehensive Organic Synthesis, vol. 3*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, p. 913.

4 G. Wittig and R. Polster, *Justus Liebigs Ann. Chem.*, 1956, **599**, 1–12.

5 Y. Maeda and Y. Sato, *J. Chem. Soc., Perkin Trans. 1*, 1997, **12**, 1491–1493.

6 (*a*) A. Jończyk and A. Konorska, *SYNLETT*, 1999, **7**, 1085–1087; (*b*) A. Kowalkowska, D. Sucholbiak and A. Jończyk, *Eur. J. Org. Chem.*, 2005, **19**, 925–933.

7 For the most recent example see: O. Cervinka and V. Struzka, *Collect. Czech. Chem. Commun.*, 1990, **55**, 2685–91.

8 (*a*) R. Brükner, *Comprehensive Organic Synthesis, vol. 6*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, p. 873; (*b*) Y. Maeda and Y. Sato, *J. Chem. Soc., Perkin Trans. 1*, 1997, **12**, 1491–1493.

9 Stabilisation of the negative charge in α of the onium group can be estimated by the pK_a of the corresponding onium salt. The pK_a values (in DMSO) of Me_3NCH_2Ph and Me_2SCH_2Ph are 31.9 and 17.8, respectively, showing a much lower stability of the ammonium ylide compared to its sulfonium analogue. For a discussion of ylide stability, see (*a*) J.-P. Cheng, B. Liu, Y. Zhao, Y. Sun, X.-M. Zhang and Y. Lu, *J. Org. Chem.*, 1999, **64**, 604–610; (*b*) T. Naito, S. Nagase and H. Yamataka, *J. Am. Chem. Soc.*, 1994, **116**, 10080–10088.

10 It has been shown previously that leaving group ability (kinetic property) correlates with the thermodynamic property of basicity for leaving groups bonded through the same atom (*e.g.* for different R_3N leaving groups); species with low basicity have high leaving group ability (see K. P. C. Vollhardt and N. E. Schore, *Organic Chemistry*, W. H. Freeman, New York, 1998). DABCO is a weaker base than quinuclidine (respective pK_a values in DMSO are 8.9 and 9.8; see D. H. Ripin and D. A. Evans' pK_a table at http://daecr1.harvard.edu/pdf/evans_pKa_table.pdf) and is thus expected to have increased leaving group ability as compared to quinuclidine.

11 V. K. Aggarwal, J. N. Harvey and R. Robiette, *Angew. Chem., Int. Ed.*, 2005, **44**, 5468–5471.

12 T. Kimachi, H. Kinoshita, K. Kusaka, Y. Takeuchi, M. Aoe and M. Ju-ichi, *SYNLETT*, 2005, **5**, 842–844.

13 For related computational studies (on sulfur ylide mediated epoxidations), see ref. 2*d* and (*a*) M. A. Silva, B. R. Bellenie and J. M. Goodman, *Org. Lett.*, 2004, **6**, 2559–2562; (*b*) M. K. Lindvall and A. M. P. Koskinen, *J. Org. Chem.*, 1999, **64**, 4596–4606.

14 A set of constrained geometry optimization at successively smaller values of the C–C distance was carried out to check that the interaction between reactants is indeed uniformly attractive.

15 The energies reported here are electronic energies, while kinetics depend on the corresponding free energies, so entropic considerations need to be taken into account. For addition of the ylide and epoxidation to occur without reversion to reactants, the elimination TS needs to lie lower in free energy than the variational TS for cleavage into reactants. As a rough estimate, the loose, variational cleavage TS may have a slightly higher entropy (hence more favourable free energy) than the tighter elimination TS, but this should not make the relative free energies drastically different to the relative potential energies. The cleavage TS will have a potential energy very close to, if a bit lower than, that of the reactants. The small difference in potential energy between the two TS shown in Fig. 1 will translate into a small difference in their free energies, so that changes in substitution could quite easily tune the system either into fully reversible behaviour or completely irreversible behaviour—as suggested by experimental evidence.

16 It is worth noting, however, that stabilisation of the ylide might lead to the emergence of a barrier to addition.

17 (*a*) C. D Papageorgiou, M. A. Cubillo de Dios, S. V. Ley and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2004, **43**, 4641–4644; (*b*) N. Bremeyer, S. C. Smith, S. V. Ley and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2004, **43**, 2681–2684; (*c*) C. D. Papageorgiou, S. V. Ley and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2003, **42**, 828–831.

18 W. Yuanhua, C. Zhiyong, M. Aiqiao; and H. Wenhao, *Chem. Commun.*, 2004, 2486–7.

19 V. K. Aggarwal, D. Fuentes, J. N. Harvey, G. Hynd, D. Ohara, W. Picoul, R. Robiette, C. Smith, J.-L. Vasse and C. L. Winn, *J. Am. Chem. Soc.*, 2006, **128**, DOI: 10.1021/ja0568345.

20 *Jaguar 4.0*, Schrödinger, Inc., Portland, OR, 1991–2000.