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PAPER

# Identification of the best-suited leaving group for the diastereoselective synthesis of glycidic amides from stabilised ammonium ylides and aldehydes†

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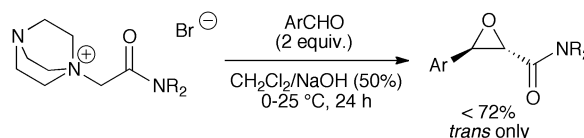
In comparison to the use of sulfur ylides, the use of ammonium ylides for the synthesis of epoxides is significantly less developed. As a part of our systematic investigations concerning the use of amide-stabilised ammonium ylides for the synthesis of glycidic amides we have focused on the identification of the best-suited amino leaving group for this purpose. Whereas tertiary amines like quinuclidine or cinchona alkaloids were found to be not suited for epoxide formation, trimethylamine was found to be the leaving group of choice, yielding *trans*-glycidic amides in excellent yields of > 90%.

## Introduction

The use of ylides for the (dia-)stereoselective synthesis of epoxides starting from carbonyl compounds has attracted considerable interest over the last decades.<sup>1–8</sup> The straightforward use of easily available carbonyl electrophiles in combination with ylide nucleophiles makes this method a highly useful alternative to other epoxide forming reactions like oxidations of double bonds<sup>9</sup> or the classical Darzens reaction.<sup>10</sup>

The synthesis of an oxirane ring by addition of a sulfur ylide to an aldehyde or ketone was introduced in the 1960s<sup>1</sup> and a variety of applications using chiral sulfonium ylides either as auxiliaries or in a catalytic fashion have been reported so far.<sup>2–4</sup> Besides the use of sulfur ylides, ammonium ylides have also been successfully employed in different (dia-)stereoselective C–C bond forming reactions over the last years.<sup>5–8,11–15</sup> Gaunt *et al.* showed that the addition of  $\alpha$ -halo carbonyl compounds to  $\alpha,\beta$ -unsaturated Michael acceptors in the presence of catalytic amounts of cinchona alkaloids gives access to almost enantiopure cyclopropanes *via in situ* formation of a chiral ammonium ylide.<sup>11</sup> However, with respect to the syntheses of epoxides or aziridines only a few examples have been reported so far. Whilst the diastereoselective synthesis of aziridines can be accomplished using DABCO-derived stabilised ammonium ylides,<sup>14</sup> the synthesis of epoxides has so far mainly been limited to semi-stabilised benzylic ammonium ylides<sup>7</sup> and cyano-stabilised<sup>5</sup> ammonium ylides. In addition, it was shown that more stabilised ester-derived ammonium ylides do not undergo epoxide formation.<sup>15</sup>

We have recently developed a highly *trans*-selective protocol for the synthesis of glycidic amides by reacting aromatic aldehydes with stabilised amide-derived ammonium ylides.<sup>8</sup> Key to success in this approach was the use of biphasic conditions together with a two-fold excess of aldehyde to give the corresponding glycidic amides in moderate to good yields (Scheme 1).



**Scheme 1** Amide-based ammonium ylides for epoxide formation.<sup>8</sup>

However, although it was shown for the first time that ammonium ylides bearing an  $\alpha$ -carbonyl group can successfully be employed in oxirane syntheses, it must be clearly pointed out that this reaction is very close to the limit of what is possible with ammonium ylides. This can be illustrated by the fact that the yields were strongly dependent on the electronic properties of the aldehydes.<sup>8</sup> Whereas electron neutral aldehydes reacted in moderate to good yields (up to 72%), more electron rich aldehydes reacted much more slowly. On the other hand, electron deficient aldehydes were prone to rapid Cannizzaro decomposition under the highly basic reaction conditions.

Due to the high potential of this type of reaction for the diastereoselective synthesis of glycidic amides we therefore decided to carry out additional investigations to get a clearer picture about the potential and the limitations of this methodology.

## Results and discussion

Recent studies by Aggarwal *et al.* clearly showed that a key factor in ylide-based epoxide formation reactions is the leaving group quality of the onium group, which decreases in the order O > S > N > P.<sup>13</sup> Accordingly, ammonium ylides are less reactive in epoxide forming reactions than sulfur ylides. Furthermore, the

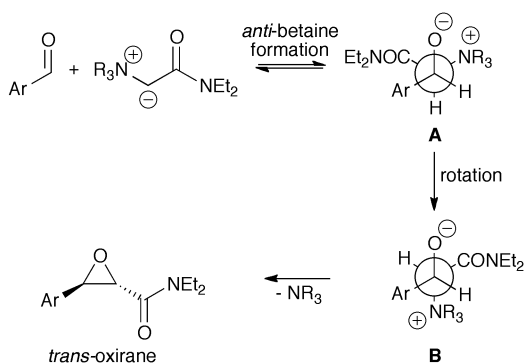
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presence of a carbonyl group  $\alpha$  to the leaving group (stabilised ylides) significantly increases the barrier to ring closure.

It is noteworthy that the high *trans*-selectivity observed in the reaction of amide-stabilised ammonium ylides with aldehydes (Scheme 1)<sup>8</sup> is in full accordance with results published for epoxidations using amide-stabilised sulfur ylides.<sup>4</sup> Thus, in analogy to studies by Aggarwal *et al.*,<sup>3d</sup> it can be assumed that addition of the ylide to the aldehyde gives the *synclinal anti*-betaine **A** first (Scheme 2). Bond rotation then leads to the *antiperiplanar anti*-betaine **B**, which, upon ring closure, yields the *trans*-oxirane. Systematic investigations by Aggarwal *et al.* revealed that for stabilised sulfonium ylides formation of *syn*- and *anti*-betaines is reversible, but bond rotation towards *antiperiplanar* betaines **B** is more hindered for *syn*-betaines (which would give *cis*-oxiranes) than for *anti*-betaines, thus favouring *trans*-epoxide formation.<sup>3d,13</sup> Although we have no direct experimental or computational evidence yet, it seems reasonable that the high *trans*-selectivity using amide-derived ammonium ylides might be due to similar reasons.



**Scheme 2** Formation of *trans*-oxiranes via the *anti*-betaines **A** and **B**.

During our initial investigations, the biphasic combination of  $\text{CH}_2\text{Cl}_2$  and aqueous  $\text{NaOH}$  (50%) (100 equiv.) was found to be superior over monophasic or liquid/solid conditions.<sup>8</sup> During these investigations, aldehyde- and ylide-derived by- or decomposition products were observed. Whereas activated aldehydes (*e.g.* *p*-nitro) mainly gave Cannizzaro disproportionation byproducts, more electron neutral or electron rich aldehydes were found to be more stable under the chosen conditions.<sup>16</sup> With respect to the ylide, a reasonable consumption was observed in all experiments, even if no product was formed. Although the formed by-products could not be clearly identified, it seems reasonable that not only the ylides themselves decompose, but also the intermediate betaines (**A** and **B**) undergo some decomposition. This is also supported by the fact that it was never possible to quantitatively re-isolate the aldehyde (respectively benzyl alcohol and benzoic acid), even if no epoxide product was formed. It can therefore be rationalized that some betaine is always formed but the reduced leaving group ability of the amino group makes ring closure be the limiting step in this reaction.

Therefore, we decided to investigate the influence of the leaving group on the reaction outcome and to determine the best-suited amino group for our approach. As summarised in Table 1, several tertiary amines were used to synthesise the corresponding quaternary ammonium ylides **3–7** and tested in the reaction with benzaldehyde (**1**) under biphasic conditions.

**Table 1** Identification of the best-suited amine leaving group

Entry	Amine ( $\text{R}_3\text{N}$ )	Salt	Yield <sup>a</sup> (%)
1	DABCO	<b>3</b>	67
2	Quinuclidine	<b>4</b>	32
3	Quinine-OMe	<b>5</b>	0
4	$\text{Et}_3\text{N}$	<b>6</b>	41
5	$\text{Me}_3\text{N}$	<b>7</b>	92

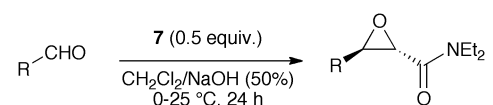
<sup>a</sup> Isolated yields.

Entry 1 represents the recently developed standard reaction using DABCO-derived ammonium salt **3** as the nucleophile (67% yield).<sup>8</sup> Replacing DABCO for quinuclidine (salt **4**), the yield dropped significantly (32%). This significant decrease in yield is in contrast to recent reports by Aggarwal *et al.*<sup>7c</sup> and Kimachi *et al.*<sup>7a</sup> describing either similar or only slightly reduced yields in the syntheses of stilbene oxides using DABCO- or quinuclidine-derived benzylic ammonium ylides. Furthermore, using cinchona alkaloid based ylides (*e.g.* *O*-methyl protected quinine based salt **5**, entry 3) absolutely no product formation was observed.

Employing triethylamine as the amine component (entry 4) the yield was still significantly lower compared to DABCO. Of note, in all these lower yielding experiments (entries 2–4), NMR spectra of the crude products showed significant amounts of unidentified decomposition products. However, when we changed to trimethylamine ( $\text{Me}_3\text{N}$ ) (salt **7**, entry 5) almost quantitative conversion of **7** to the epoxide product **2** was observed. Using just 1.2 equiv. of **1** the yield decreased to 58% illustrating that decomposition of **1** is the limiting factor hereby.

The striking differences in reactivity should mainly be due to the different leaving group abilities of the different amines and less due to different nucleophilicities as all ammonium ylides are supposed to be highly nucleophilic.<sup>7,13</sup> As species with lower basicity are supposed to have a higher leaving group ability<sup>17</sup> it is obvious why quinuclidine ( $\text{p}K_{\text{a}} = 11.4$ )<sup>18a</sup> and triethylamine ( $\text{p}K_{\text{a}} = 10.7$ )<sup>18b</sup> are not as good leaving groups as DABCO ( $\text{p}K_{\text{a}} = 8.9$ )<sup>18a</sup> and trimethylamine ( $\text{p}K_{\text{a}} = 9.8$ ).<sup>18b</sup> However, this fact alone does not explain why  $\text{Me}_3\text{N}$  is by far the best leaving group whereas cinchona alkaloids ( $\text{p}K_{\text{a}}$  of quinine = 8.7)<sup>18c</sup> do not yield any product at all. The missing reactivity of the cinchona-derived salt **5** is not fully understood yet as these compounds should be good nucleophiles as demonstrated by Gaunt *et al.*<sup>11</sup> However, one might reason that bond rotation towards the required *antiperiplanar* betaine **B** has a much higher activation barrier than in the case of small amine groups due to repulsion between the large quinoline group of quinine and the phenyl group of the benzaldehyde,<sup>19</sup> which would explain why we just observed formation of decomposition products. On the other hand, the high yields using **7** may therefore be attributed to the smallest steric hindrance among the employed amino groups, thus facilitating bond rotation towards the required *antiperiplanar* betaine **B**.

It is noteworthy that even less stabilised cinchona-derived benzylic ammonium ylides, which should be more reactive, did not yield any epoxides under the biphasic conditions. This is

**Table 2** Reaction of different aldehydes with **7**


Entry	R	Aldehyde	Product	Yield <sup>a, b</sup> (%)
1	Ph-	<b>1</b>	<b>2</b>	92 (67) <sup>b</sup>
2	4-MeC <sub>6</sub> H <sub>4</sub> -	<b>8</b>	<b>9</b>	95 (68) <sup>b</sup>
3	2-MeC <sub>6</sub> H <sub>4</sub> -	<b>10</b>	<b>11</b>	90
4	4-ClC <sub>6</sub> H <sub>4</sub> -	<b>12</b>	<b>13</b>	90 (72) <sup>b</sup>
5	4-BrC <sub>6</sub> H <sub>4</sub> -	<b>14</b>	<b>15</b>	97
6	4-Biphenyl-	<b>16</b>	<b>17</b>	93
7	4-MeOC <sub>6</sub> H <sub>4</sub> -	<b>18</b>	<b>19</b>	83 (47) <sup>b</sup>
8	2-MeOC <sub>6</sub> H <sub>4</sub> -	<b>20</b>	<b>21</b>	98
9	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> -	<b>22</b>	<b>23</b>	<5 <sup>c</sup>
10	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -	<b>24</b>	<b>25</b>	17 <sup>d</sup> (<10) <sup>b</sup>
11	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -	<b>26</b>	<b>27</b>	12 <sup>d</sup>
12	3-Pyridyl-	<b>28</b>	<b>29</b>	<10 <sup>c, d</sup>
13	n-Undecyl-	<b>30</b>	<b>31</b>	0 <sup>c</sup>
14	Cyclohexyl-	<b>32</b>	<b>33</b>	54

<sup>a</sup> Isolated yields. <sup>b</sup> Yields obtained using DABCO salt **3** are given in brackets (taken from Ref. 8) <sup>c</sup> Determined by <sup>1</sup>H NMR of the crude product. <sup>d</sup> Large amounts of Cannizzaro decomposition products. <sup>e</sup> Decomposition of aldehyde.

in full accordance with a recent report by Kimachi *et al.* on the syntheses of stilbene oxides using cinchona-derived benzylic ammonium ylides in THF (*t*-BuOK as a base).<sup>7b</sup> Surprisingly, this group identified brucine as a suitable chiral amine for the syntheses of enantioenriched stilbene oxides.<sup>7b</sup>

Accordingly, these results clearly point out the high importance of the appropriate leaving group for this reaction.

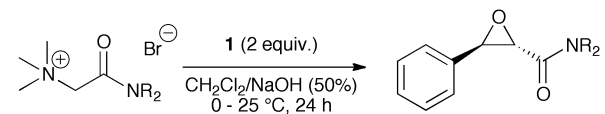
Having identified trimethylamine as the amino group of choice, we next screened the reaction of **7** with several aldehydes (2 equiv.)<sup>16</sup> under standard conditions (Table 2).

Reactions with a variety of different aromatic aldehydes (entries 1–8) gave the corresponding *trans*-configured glycidic amides in good to excellent yields. In average the yields were about 20 to 30% higher compared to the DABCO-based epoxidations.<sup>8</sup> In addition, it was found that the Me<sub>3</sub>N-derived salt **7** is also superior upon reaction with electron rich aldehydes like the anisaldehydes **18** and **20** (entries 7 and 8). Whereas the DABCO salt **3** gave the *p*-methoxy substituted glycidic amide **19** in 47% only under standard conditions,<sup>8</sup> reaction of salt **7** with aldehyde **18** gave the oxirane **19** in 83% isolated yield (entry 7). Furthermore, the *o*-methoxy aldehyde **20** was found to be even more reactive furnishing epoxide **21** almost quantitatively. However, using the even more electron rich aldehyde **22** as an electrophile, only traces of product were observed in the NMR spectrum of the crude product. Also carrying out the reaction at higher temperature did not improve the conversion significantly (<10% *in situ*). Furthermore, the starting aldehyde was reisolated almost quantitatively. This is absolutely identical to our recent result using DABCO-derived salts and therefore suggests that the electron rich aldehyde **22** is not electrophilic enough for betaine formation. As the results for DABCO- and Me<sub>3</sub>N-derived ylides are the same it can be reasoned that both ylides are similarly nucleophilic. This also implies that the higher reactivity of **7** with more electron neutral aldehydes (entries 1–8, Table 2) is really due to an enhanced leaving group ability of Me<sub>3</sub>N.

On the other hand, using more electron deficient aldehydes like the nitro aldehydes **24** and **26** or the pyridyl carbaldehyde **28**, mainly Cannizzaro decomposition products were observed (entries 10–12). Although the nitroaldehydes **24** and **26** could be converted into the corresponding epoxides **25** and **27** in rather low yields only (entries 10, 11), a beneficial effect of the leaving group was observed as reaction of **24** with **3** was found to give epoxide **25** in trace amounts only.<sup>8</sup> Nevertheless, these highly activated aldehydes (the same counts for **28**) are too unstable under the highly basic reaction conditions and neither carrying out these reactions at lower temperatures nor using less base did improve the result.

Using the lauric aldehyde **30**, full consumption of the aldehyde was observed but no epoxide **31** could be obtained. As an NMR spectrum of the crude product showed signals in the olefinic region, a self-aldol condensation under the highly basic conditions seems to be the dominant reaction of **30**. In contrast, the reaction of **7** with cyclohexanecarboxaldehyde (**32**) gave the targeted *trans*-epoxide **33** in 54%. Although the yield was lower than for most aromatic aldehydes, it was clearly shown that  $\alpha$ -branched aliphatic aldehydes, which cannot undergo self-condensation reactions, are suitable electrophiles for ylide-based epoxidations. Accordingly, despite the highly basic conditions, the scope of this reaction is not just limited to aldehydes without  $\alpha$ -H only.

Next, a screening of other trimethylamine-derived amide-based ylides in the reaction with **1** (2 equiv.) was undertaken (Table 3).

**Table 3** Reaction of different trimethylamine-derived ylides with **1**


Entry	Amide	Salt	Product	Yield <sup>a</sup> (%)
1		<b>7</b>	<b>3</b>	92
2		<b>34</b>	<b>35</b>	74
3		<b>36</b>	<b>37</b>	49
4		<b>38</b>	<b>39</b>	93
5		<b>40</b>	<b>41</b>	86
6		<b>42</b>	<b>43</b>	0

<sup>a</sup> Isolated yields.

Other tertiary amides (entries 2, 4, and 5) gave yields comparable to the test reaction between **1** and **7**. Using the secondary amide **36**, the corresponding glycidic amide **37** could be isolated in 49% (entry 3). This lower yield for secondary amides is in accordance with our recent results using DABCO-derived ammonium salts where a low yield of 24% only was obtained in the synthesis of **37**.<sup>8</sup> As an increased amount of Cannizzaro products was formed, the lower yield seems to be due to a significantly reduced reactivity of the secondary amide-derived salt **36** (similar results for sulfur ylides were reported by Aggarwal *et al.*<sup>4b</sup>). Unfortunately, the use of Weinreb amide **42** did not yield any epoxide **43**. Hereby, the aldehyde **1** (besides Cannizzaro products) was almost fully recovered whereas the ammonium salt **42** totally decomposed.

Finally, we were also interested whether the scope of this methodology can be expanded to even more stabilised ester-derived ammonium ylides. However, the reaction of trimethylamine-derived ester-based ammonium ylides with benzaldehyde totally failed and not even traces of the epoxides could be obtained. Accordingly, although we have identified the best-suited leaving group and reaction conditions with respect to the synthesis of glycidic amides, the corresponding glycidic esters are still not accessible.

## Conclusions

It was shown that the use of ammonium ylides bearing an  $\alpha$ -carbonyl group for the syntheses of epoxides is highly dependent on the choice of the employed leaving group. Whereas trimethylamine and DABCO were found to be suitable amino groups giving access to *trans*-configured glycidic amides in good to excellent yields, other tertiary amines were found to be less suited. Especially cinchona alkaloid-derived ammonium ylides were found to be absolutely unreactive in the syntheses of glycidic amides as well as in the syntheses of stilbene oxides. The scope of the reaction was found to be rather broad for several aromatic aldehydes and different amides and excellent yields of >90% could be obtained. Only highly electron rich as well as highly electron deficient aldehydes were found to be less suited. Whereas electron rich aldehydes are not electrophilic enough for this reaction, more activated aldehydes were found to mainly undergo Cannizzaro decomposition mainly. On the other hand, it was also shown that enolisable  $\alpha$ -branched aldehydes do undergo epoxide formation under the highly basic reaction conditions whereas unbranched ones do not yield any epoxides due to self-aldol condensation. On the other hand, ester-derived ammonium ylides were not reactive under the developed conditions.

## Experimental section

### General

Melting points were measured on a Kofler melting point microscope (Reichert, Vienna). <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded on a Bruker Avance DRX 500 MHz spectrometer using a TXI cryoprobe with z-gradient coil and on a Bruker Avance DPX 200 MHz spectrometer. All NMR spectra were referenced on the solvent peak. High resolution mass spectra were obtained using an Agilent 6520 Q-TOF mass spectrometer with an ESI source and an Agilent G1607A coaxial sprayer. IR spectra were recorded on a

Shimadzu IR Affinity-1 Fourier transform infrared spectrometer. All chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. All reactions were performed under an Ar-atmosphere.

### General procedure for the syntheses of Me<sub>3</sub>N-ammonium salts

One equivalent of Me<sub>3</sub>N (33% solution in EtOH) was added to a solution of one equivalent of the  $\alpha$ -bromo amide in THF (10 mL g<sup>-1</sup> amide) and stirred for 24 h at room temperature. The resulting solid was filtered off, washed with EtOAc (3 $\times$ ), and dried *in vacuo* to give the product in sufficient purity for the epoxide formation reaction.

### Ammonium salt 7

Prepared from 2-bromo-*N,N*-diethylacetamide<sup>20</sup> (8.92 g, 45.9 mmol) in 88% (10.27 g, 40.5 mmol). White solid. M.p.: 186–188 °C; <sup>1</sup>H NMR (500 MHz,  $\delta$ , CDCl<sub>3</sub>, 298 K): 1.14 (t, *J* = 7.3 Hz, 3H), 1.27 (t, *J* = 7.3 Hz, 3H), 3.36 (q, *J* = 7.3 Hz, 2H), 3.47 (q, *J* = 7.3 Hz, 2H), 3.63 (s, 9H), 5.00 (s, 2H) ppm; <sup>13</sup>C NMR (125 MHz,  $\delta$ , CDCl<sub>3</sub>, 298 K): 12.9 (CH<sub>3</sub>-), 14.5 (CH<sub>3</sub>-), 41.0 (-CH<sub>2</sub>-), 42.0 (-CH<sub>2</sub>-), 54.7 (-N<sup>+</sup>(CH<sub>3</sub>)<sub>3</sub>), 63.2 (-CH<sub>2</sub>CO-), 162.4 (-CO-) ppm; IR (film):  $\tilde{\nu}$  = 3003, 2978, 2945, 1639, 1483, 1467, 1446, 1433, 1384, 1357, 1278, 1238, 1215, 1139, 1097, 1078, 1022, 975, 954, 927, 894 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd for C<sub>9</sub>H<sub>21</sub>N<sub>2</sub>O<sup>+</sup>: 173.1654 [M<sup>+</sup>]; found: 173.1651.

### General procedure for the preparation of epoxides

A vigorously stirred solution of ammonium salt (1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was cooled to 0 °C, followed by addition of 50% NaOH (5 mL). After 5 min the aldehyde (2 mmol) was added in one portion. The biphasic mixture was warmed to 25 °C over 1 h and vigorously stirred for 23 h. After extraction with EtOAc, the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. Column chromatography (silica gel, heptanes/EtOAc = 7 : 3) gave the glycidic amides in the reported yields.

### *trans*-*N,N*-Diethyl-3-phenyloxirane-2-carboxamide (**2**)

Obtained in 92% as a white to yellow solid. Analytical data are in full accordance with those reported in literature.<sup>4a</sup> <sup>1</sup>H NMR (500 MHz,  $\delta$ , CDCl<sub>3</sub>, 298 K): 1.16 (t, *J* = 7.3 Hz, 3H), 1.20 (t, *J* = 7.3 Hz, 3H), 3.40–3.51 (m, 4H), 3.58 (d, *J* = 1.4 Hz, 1H), 4.09 (d, *J* = 1.4 Hz, 1H), 7.32–7.39 (m, 5H) ppm; <sup>13</sup>C NMR (125 MHz,  $\delta$ , CDCl<sub>3</sub>, 298 K): 13.1, 15.0, 41.0, 41.6, 57.3, 57.7, 125.8, 128.6, 128.7, 135.9, 165.8 ppm; IR (film):  $\tilde{\nu}$  = 2972, 2933, 2873, 1643, 1487, 1450, 1409, 1365, 1271, 1217, 1145, 1095, 1076, 893, 754, 698, 617 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd for C<sub>13</sub>H<sub>17</sub>NO<sub>2</sub>: 220.1332 [M + H]<sup>+</sup>; found: 220.1329.

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## Notes and references

- (a) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, **84**, 867–868; (b) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353–1364; (c) A. W. Johnson and R. B. Laccount, *Chem. Ind.*, 1958, 1440–1441.
- (a) V. K. Aggarwal, in *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, New York, 1999, vol. 2, 679; (b) E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches and V. K. Aggarwal, *Chem. Rev.*, 2007, **107**, 5841–5883.
- (a) O. Illa, M. Arshad, A. Ros, E. M. McGarrigle and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2010, **132**, 1828–1830; (b) J. Zanardi, C. Lriverend, D. Aubert, K. Julienne and P. Metzner, *J. Org. Chem.*, 2001, **66**, 5620–5623; (c) M. Davoust, J.-F. Briere, P.-A. Jaffres and P. Metzner, *J. Org. Chem.*, 2005, **70**, 4166–4169; (d) V. K. Aggarwal and J. Richardson, *Chem. Commun.*, 2003, 2644–2651.
- For glycidic amides from sulfur ylides see: (a) Y.-G. Zhou, X.-L. Hou, L.-X. Dai, L.-J. Xia and M.-H. Tang, *J. Chem. Soc., Perkin Trans. 1*, 1999, 77–80; (b) V. K. Aggarwal, J. P. H. Charmant, 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**, 2105–2114; (c) V. K. Aggarwal, G. Hynd, W. Picoul and J.-L. Vasse, *J. Am. Chem. Soc.*, 2002, **124**, 9964–9965.
- For the use of cyano-stabilised ammonium ylides see: (a) A. Kowalkowska, D. Sucholbiak and A. Jonczyk, *Eur. J. Org. Chem.*, 2005, 925–933; (b) A. Jonczyk and A. Konarska, *Synlett*, 1999, 1085–1087.
- A. Alex, B. Larmanjat, J. Marrot, F. Couty and O. David, *Chem. Commun.*, 2007, 2500–2502.
- For benzylic ammonium ylides see: (a) T. Kimachi, H. Kinoshita, K. Kusaka, Y. Takeuchi, M. Aoe and M. Ju-ichi, *Synlett*, 2005, 842–844; (b) H. Kinoshita, A. Ihoriya, M. Ju-ichi and T. Kimachi, *Synlett*, 2010, 2330–2334; (c) R. Robiette, M. Conza and V. K. Aggarwal, *Org. Biomol. Chem.*, 2006, **4**, 621–623.
- M. Waser, R. Herchl and N. Müller, *Chem. Commun.*, 2011, **47**, 2170–2172.
- For selected examples see: (a) M. J. Porter and J. Skidmore, *Chem. Commun.*, 2000, 1215–1225; (b) T. Nemoto, H. Kakei, V. Gnanadesikan, S.-Y. Tosaki, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.*, 2002, **124**, 14544–14545; (c) S. Matsunaga, T. Kinoshita, S. Okada, S. Harada and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **126**, 7559–7570.
- For stereoselective Darzens approaches see: (a) S. Arai, K. Tokumaru and T. Aoyama, *Tetrahedron Lett.*, 2004, **45**, 1845–1848; (b) E. J. Corey and S. Choi, *Tetrahedron Lett.*, 1991, **32**, 2857–2860; (c) P. Bakó, Z. Rapi, G. Keglevich, T. Szabó, P. Sóti, T. Vigh, A. Grün and T. Holczbauer, *Tetrahedron Lett.*, 2011, **52**, 1473–1476.
- For the syntheses of cyclopropanes see: (a) M. J. Gaunt and C. C. C. Johansson, *Chem. Rev.*, 2007, **107**, 5596–5605; (b) C. C. C. Johansson, N. Bremeyer, S. V. Ley, D. R. Owen, S. C. Smith and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2006, **45**, 6024–6028; (c) C. D. Papageorgiou, M. A. Cubillo de Dios, S. V. Ley and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2004, **43**, 4641–4644; (d) N. Bremeyer, S. C. Smith, S. V. Ley and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2004, **43**, 2681–2684; (e) C. D. Papageorgiou, S. V. Ley and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2003, **42**, 828–831.
- C.-Y. Zhu, X.-M. Deng, X.-L. Sun, J.-C. Zheng and Y. Tang, *Chem. Commun.*, 2008, 738–740.
- V. K. Aggarwal, J. N. Harvey and R. Robiette, *Angew. Chem., Int. Ed.*, 2005, **44**, 5468–5471.
- For aziridination see: L. D. S. Yadav, R. Kapoor and Garima, *Synlett*, 2009, 3123–3126.
- Y. Wang, Z. Chen, A. Mi and W. Hu, *Chem. Commun.*, 2004, 2486–2487.
- Although all reactions were carried out under inert conditions, varying amounts of benzoic acids were observed in several cases presumably due to autoxidation of the aldehydes. Thus 2 equiv. of aldehyde were used to obtain a reasonable compromise between yield and required amount of starting material.
- This means correlating a kinetic property (leaving group ability) with a thermodynamic property (basicity): K. P. C. Vollhardt and N. E. Schore, *Organic Chemistry*, W. H. Freeman, New York, 1998.
- $pK_a$  values in  $H_2O$ : (a) E. A. Castro, M. Aliaga, P. R. Campodonico, J. R. Leis, L. Garcia-Rio and J. G. Santos, *J. Phys. Org. Chem.*, 2008, **21**, 102–107; (b) D. R. Lide, *Handbook of Chemistry and Physics*, 76th Ed. CRC Press, Boca Raton, 1995–1996; (c) M. Srinivas, M. G. Hopperstad and D. C. Spray, *Proc. Natl. Acad. Sci. U. S. A.*, 2001, **98**, 10942–10947.
- It has been shown that bond rotation towards betaines B is the crucial step in epoxidations using stabilised ylides (see Ref [3d]).
- T. Hama, X. Liu, D. A. Culkin and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 11176–11177.