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Ammonium ylides for the diastereoselective synthesis of glycidic amides†

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A highly *trans*-selective protocol for the synthesis of glycidic amides was developed. This approach gave access to oxiranes by reacting stabilised ammonium ylides bearing an α -carbonyl group and aromatic aldehydes in moderate to good yields.

The (dia-)stereoselective synthesis of glycidic amides and esters has attracted considerable interest over the last few decades mainly due to the high potential of these compounds as synthetically useful intermediates in a variety of organic syntheses. Ylides have proven to be very powerful synthons for the formation of epoxides^{1–4} providing alternatives to the oxidation of α,β -unsaturated carbonyl compounds^{5,6} or the Darzens reaction between α -halo esters or amides and carbonyl groups.⁷ The synthesis of oxirane rings by reacting a sulfur ylide with an aldehyde or ketone was introduced around 50 years ago¹ and a variety of applications using chiral sulfonium ylides either in stoichiometric or even in catalytic quantities have been reported.^{2–4} Next to sulfur ylides the use of ammonium ylides for C–C bond formation has attracted considerable interest over the last few years.^{8–14} Gaunt *et al.* showed that cinchona alkaloid catalysts are highly useful for stereoselective cyclopropanations proceeding *via* an ammonium ylide mechanism.⁸ Besides the syntheses of cyclopropanes the diastereoselective formation of epoxides in analogy to the Corey–Chaykovsky reaction has been described.^{11–13} However, this synthetically useful transformation has so far been limited to benzylic ammonium ylides¹³ and cyano-stabilised ammonium ylides^{11,12} giving the corresponding oxiranes in moderate yields only, whereas ester-stabilised ylides did not yield the epoxides.¹⁴ Previous 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.⁹ Furthermore, the presence of a carbonyl group α to the leaving group (stabilised ylides) significantly increases the barrier to ring closure. Altogether, these investigations clearly demonstrate why ammonium ylides are less suited for epoxide formation than sulfur ylides and rationalize why no oxirane

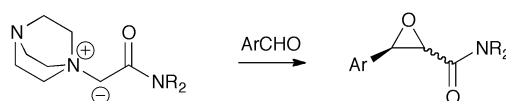
syntheses with ammonium ylides bearing an α -carbonyl group have been reported so far.⁹

However, from the few reported examples it was clearly proven by Jonczyk *et al.*¹¹ that cyano-stabilised ylides (being less stabilised than esters)¹⁵ undergo such reactions under biphasic conditions in moderate yield. Furthermore, less stabilised benzylic ylides give access to *trans*-selective formation of stilbene oxides in moderate to good yields.¹³ Thus, it seems reasonable that similarly stabilised ammonium ylides might be successfully employed for epoxide formation.

Based on a recent investigation of the stability of ylides,¹⁵ we reasoned that amide based ammonium ylides (being less stabilised than cyano-based ylides, but higher stabilised than benzylic), might undergo oxirane formation when reacted with aldehydes since they should be sufficiently balanced with respect to nucleophilicity and leaving group ability. Due to the high interest in glycidic amides,⁴ an ammonium ylide based synthetic approach would thus significantly broaden the scope of this methodology.

We therefore focused on the development of reactions between DABCO-derived amide-based ammonium ylides and aromatic aldehydes (Scheme 1).

Initial attempts were carried out reacting a small excess of benzaldehyde (**1**) with the diethylamide-derived ammonium salt **2** in dry THF using *t*-BuOK (1.2 equiv.) as the base at room temperature (Table 1, entry 1). After 24 h, full conversion of **1** was observed and the *trans*-configured glycidic amide **3** could be isolated in 32% yield. Noteworthy, not even trace amounts of the *cis*-diastereomer were obtained (judged by ¹H NMR). As we had observed a significant decrease in yield (<20%) using lower quality THF, addition of molecular sieves (4 Å) to the reaction mixture was tested, resulting in an improved yield of 47% (entry 2). However, besides the target product, large amounts of benzyl alcohol and benzoic acid resulting from base mediated Cannizzaro disproportionation of **1** accompanied by unidentified decomposition products of **2** were obtained. Unfortunately, neither addition of tetrabutylammonium bromide,¹⁶ nor reducing the reaction temperature improved suppression of these side reactions. Also using other



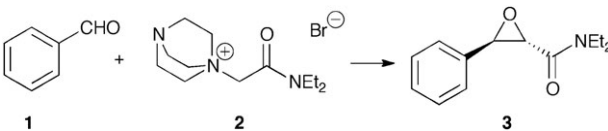
Scheme 1 Targeted use of amide-based ammonium ylides for epoxide formation.

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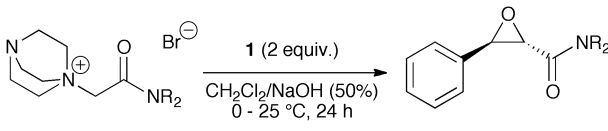
Table 1 Screening of conditions for the reaction of **1** and **2**


Entry	Solvent	Base	<i>T</i> (°C)	<i>t</i> (h)	1 : 2	Yield ^a (%)	<i>trans</i> ^b (%)
1	THF	<i>t</i> -BuOK	0 → 25	24	1.2	32	>99
2	THF (4 Å)	<i>t</i> -BuOK	0 → 25	24	1.2	47	>99
3	THF	KOH	0 → 25	24	1.2	23	>99
4	EtOH	KOH	0 → 25	24	1.2	0	>99
5	CH ₃ CN	Cs ₂ CO ₃	0 → 25	24	1.2	0	>99
6	CH ₃ CN (aq)	KOH	0 → 25	24	1.2	0	>99
7	DMSO	<i>t</i> -BuOK	0 → 25	24	1.2	45	>99
8	THF (4 Å)	<i>t</i> -BuOK	0 → 25	24	2	55	>99
9	CH ₂ Cl ₂	50% NaOH	0 → 25	24	1.2	55	>99
10	CH ₂ Cl ₂	50% NaOH	0 → 25	24	2	67	>99
11	CH ₂ Cl ₂	50% NaOH	0 → 25	24	3	77	>99
12	CH ₂ Cl ₂	50% NaOH	0 → 25	24	0.5	50	>99
13	CH ₂ Cl ₂	50% NaOH	40	8	3	76	>99
14	CH ₂ Cl ₂	50% KOH	0 → 25	24	3	62	>99

^a Isolated yields. ^b Determined by ¹H NMR of the crude product.

solvent/base combinations (entries 3–7 in Table 1 give a representative overview of only a few of the tested conditions), no improvement could be achieved. Noteworthy, some of the conditions which were reported to be very successful in sulfur ylide transformations (e.g. entry 6)¹⁷ gave absolutely no conversion in our case. The only significant product formation was observed when using *t*-BuOK in DMSO (45%, entry 7). As disproportionation of **1** was found to be the major limiting factor, 2 equiv. of aldehyde were used next (entry 8), but the yield could only be improved slightly (55%), and large amounts of the Cannizzaro products were formed.

Accordingly, even with only equimolar amounts of base the disproportionation of the aldehyde limited the yield in all these homogeneous or liquid/solid experiments (entries 1–8). Therefore we investigated biphasic conditions in analogy to those reported by Jonczyk *et al.*¹¹ Carrying out the reaction in a 2 : 1 mixture of CH₂Cl₂ and 50% NaOH (aq) at ambient temperature (25 °C), full conversion of **1** was observed within 24 h. The oxirane **3** was obtained in 55% yield with excellent *trans*-selectivity (entry 9). Although a big excess of base (~100 equiv.) was necessary to achieve a reliable performance, the Cannizzaro reaction was well suppressed and only negligible amounts of benzyl alcohol could be detected. However, although all reactions were performed under inert conditions (Ar-atmosphere), considerable amounts of benzoic acid were formed presumably by autoxidation of **1**. To overcome this limitation, the relative amount of **1** was doubled (entry 10). This increased the yield to 67% after a 24 h reaction time (longer reaction times did not improve the yield anymore). With 3 equiv. of **1** the yield was 77% (entry 11), while using an excess of ammonium salt **2**, the yield dropped to 50% (entry 12). This clearly underscores that indeed the decomposition of **1** is the yield-limiting factor. Running the reaction at elevated temperature (40 °C, with excess **1**) resulted in good conversion after 8 h, giving **3** in 76% (entry 13). Noteworthy, carrying out the reaction at 40 °C for a longer

Table 2 Reaction of different amide derived ylides with **1**


Entry	Amide	Salt	Product	Yield ^a (%)	<i>trans</i> ^b (%)
1		2	3	67	>99
2		4	5	72	>99
3		6	7	24	>99
4		8	9	58	>99

^a Isolated yields. ^b Determined by ¹H NMR of the crude product.

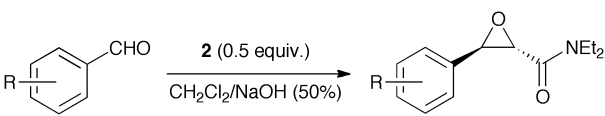
time (>24 h) resulted in a significant decomposition of the epoxide product. Using 50% KOH (aq) as the base resulted in a reduced yield of 62% only (entry 14). Neither lower temperature, nor varying the amount of base or solvent ratios (e.g. less H₂O) and concentrations improved the yield any more.

Using quinuclidine-based ammonium salts instead of DABCO-derived ones gave **3** in 15% yield only, whereas quinine as the amine part did not give any product, indicating the importance of leaving group ability for this reaction.

Having developed a reliable biphasic procedure for the highly *trans*-selective synthesis of **3** in a reasonable yield, we next investigated the use of other amide-derived ylides in the reaction with **1** (2 equiv.)¹⁸ under these conditions (Table 2).

It was clearly shown that all other amides give the products in high *trans*-selectivity too. Furthermore, other tertiary amides (entries 2 and 4, Table 2) give yields comparable to the test reaction between **1** and **2**. However, using the secondary amide **6**, the corresponding glycidic amide **7** could only be isolated in a reduced yield of 24% (entry 3). In this case, an increased amount of benzoic acid was obtained, due to autoxidation of unreacted **1**. Accordingly, this lower yield is due to a significantly reduced reactivity of the secondary amide-derived salt **6** (a similar tendency for sulfur ylides was reported by Aggarwal *et al.*^{4b}).

Finally, reaction of **2** with other aromatic aldehydes was investigated (Table 3). All reactions were first carried out under the standard conditions using 2 equiv. of the aldehyde (cond. A) to get a clear picture about the influence of the different substituents on the reactivity (entries 1–3, 5, 7, 9). All aldehydes reacted to the *trans*-epoxides exclusively. However, whereas the similarly activated aldehydes **10** and **12** gave the glycidic amides **11** and **13** in good yields (entries 2–4), the conversion of the more electron-rich anisaldehyde **14** was significantly lower resulting in a reduced yield of 47% after 24 h. As expected, Cannizzaro reaction was no problem in this case but high amounts of unreacted **14** were found. The even

Table 3 Reaction of different aromatic aldehydes with **2**


Entry	Ar	Aldehyde	Product	Cond. ^a	Yield ^b (%)	trans ^c (%)
1	Ph-	1	3	A	67	>99
2	4-MeC ₆ H ₄ -	10	11	A	68	>99
3	4-ClC ₆ H ₄ -	12	13	A	72	>99
4	4-ClC ₆ H ₄ -	12	13	A ^d	82	>99
5	4-MeOC ₆ H ₄ -	14	15	A	47	>99
6	4-MeOC ₆ H ₄ -	14	15	B	50	>99
7	4-Me ₂ NC ₆ H ₄ -	16	17	A	<5 ^e	>99
8	4-Me ₂ NC ₆ H ₄ -	16	17	B	<20 ^{e,f}	>99
9	4-NO ₂ C ₆ H ₄ -	18	19	A	<10 ^{e,g}	>99
10	4-NO ₂ C ₆ H ₄ -	18	19	C	<10 ^{e,g}	>99

^a A: 0 → 25 °C, 24 h; 100 equiv. NaOH; B: 40 °C, 24 h, 100 equiv. NaOH; C: 0 °C, 24 h, 50 equiv. NaOH ^b Isolated yields. ^c Determined by ¹H NMR of the crude product. ^d 3 equiv. of **12** were used. ^e Judged by ¹H NMR of the crude product. ^f The product decomposed during column chromatography. ^g Complete Cannizzaro decomposition of **18**.

more electron rich dimethylaminobenzaldehyde **16** showed only minor conversion, giving just traces of product under standard conditions. By contrast, the highly electron-deficient nitrobenzaldehyde **18** was fully consumed within 24 h, but giving mainly the corresponding Cannizzaro products and less than 10% of the product **19** even at reduced temperature and using less base (entries 9 and 10). Reaction of the deactivated **14** at elevated temperature (40 °C, entry 6) resulted in almost full conversion of **14** after 24 h, giving **15** in 50% accompanied with unidentified by-products. This can be rationalized by decomposition of the aldehyde **14** as well as the oxirane **15** under these harsher basic conditions. On the other hand, even under these conditions, **16** was found to be rather unreactive yielding less than 20% of **17** (entry 8).

Accordingly, the aptitude of different aldehydes for this type of reaction strongly depends on their electronic properties. Whereas similarly activated aldehydes like **1**, **10**, and **12** give the glycidic amides in good yields, the electron poor **18** is prone to rapid Cannizzaro decomposition under the highly basic conditions. On the other hand, electron rich aldehydes like **14** and **16** are significantly less reactive.

In conclusion, although ammonium ylides bearing an α-carbonyl group are less reactive in oxirane synthesis than sulfur ylides, excellent *trans*-selectivity and acceptable yields could be achieved by reacting amide-derived ammonium ylides with aromatic aldehydes. Key to success is the use of biphasic conditions together with a two-fold excess of aldehyde. The reaction is tolerant to different tertiary amide groups whereas secondary amides are less reactive. Using differently activated aldehydes, the outcome was strongly dependent on the electronic properties of the electrophile. Thus, it seems reasonable that this reaction is very close to the limit of what is possible with ammonium ylides. Nevertheless, to the best of our knowledge, this is the first time that stabilised ammonium

ylides possessing an α-carbonyl group have been successfully employed in oxirane formation.

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