

## Catalytic Sulfur Ylide Reactions: Use of Diazoacetamides for the Diastereoselective Synthesis of Glycidic Amides.

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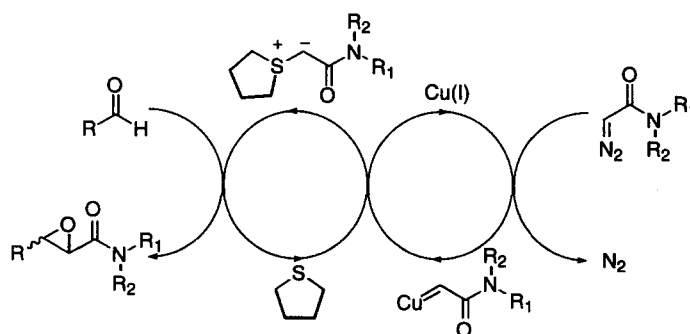
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Diazoacetamides react with aldehydes in the presence of catalytic quantities of  $\text{Cu}(\text{acac})_2$  (5 mol%) and tetrahydrothiophene (20 mol%) to give glycidic amides in good yields and high diastereoselectivity.

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Epoxides are important intermediates in organic synthesis. Glycidic esters and amides are particularly useful as they can be further elaborated with a high degree of regio- and stereocontrol and as a result are key intermediates in the synthesis of several pharmaceutical products.<sup>1,2</sup> They are usually prepared by oxidation of an appropriate alkene.<sup>1,3-11</sup> However, the alkenes employed are often derived from Wittig type reactions of the corresponding aldehyde and hence the epoxidation is a two step process from the aldehyde. Alternatively, the aldehyde can be converted to the glycidic compounds directly by employing either a Darzens<sup>12</sup> reaction or a sulfur ylide mediated approach.<sup>13</sup> It should be noted that the Darzens reaction often occurs with relatively low diastereoselectivity.

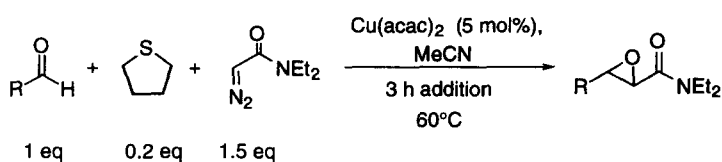
The sulfur ylide mediated synthesis of glycidic amides was first reported by Ratts<sup>14</sup> and has recently been extended by Fernández.<sup>15-18</sup> In these reported procedures the sulfur ylides were generated by deprotonation of the corresponding sulfonium salts with base. However, it is also possible to generate a sulfur ylide from a sulfide and a diazocompound, a process which occurs under neutral conditions.<sup>19</sup> Within our group we have developed a catalytic sulfur ylide cycle for the synthesis of epoxides,<sup>20,21</sup> cyclopropanes<sup>22</sup> and



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aziridines<sup>23</sup> using phenyl diazomethane to generate the sulfur ylide *in situ*. Use of a suitable chiral sulfide within these cycles allows these processes to occur with high enantioselectivity. We wish to report that we have now extended the scope of this catalytic cycle to the synthesis of glycidic amides with high diastereoselectivity by employing diazoacetamides<sup>24</sup> within the catalytic cycle, as outlined in the above scheme.

It was found that upon changing from phenyl diazomethane and benzyl ylides (reported previously) to the less reactive diazoacetamides and corresponding ylides that the reaction temperature needed to be elevated to increase the efficiency of both the formation of the metal carbenoid and turnover of the sulfide. Further optimisation revealed that tetrahydrothiophene was superior to dimethyl sulfide, Cu(acac)<sub>2</sub> was better than Rh<sub>2</sub>(OAc)<sub>4</sub>, and that reactions were best conducted in acetonitrile at relatively high concentration. Under these optimised conditions and employing *N,N*-diethyl diazoacetamide good yields of epoxides were obtained with a range of aldehydes (Table 1).<sup>25</sup>



Entry	Aldehyde	Yield (%)	<i>Trans:cis</i> <sup>a</sup>	Product
1	<i>p</i> Cl-C <sub>6</sub> H <sub>4</sub> CHO	79	>95:5	<b>1a</b>
2	PhCHO	79	>95:5	<b>1b</b>
3	<i>p</i> NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> CHO	71	>95:5	<b>1c</b>
4	<i>p</i> Me-C <sub>6</sub> H <sub>4</sub> CHO	63	>95:5	<b>1d</b>
5	<i>p</i> MeO-C <sub>6</sub> H <sub>4</sub> CHO	44	>95:5	<b>1e</b>
6	Valeraldehyde	64	>90:10 <sup>b</sup>	<b>1f</b>
7	<i>c</i> -C <sub>6</sub> H <sub>11</sub> -CHO	64	>90:10 <sup>b</sup>	<b>1g</b>

<sup>a</sup> Determined by <sup>1</sup>H NMR of products.

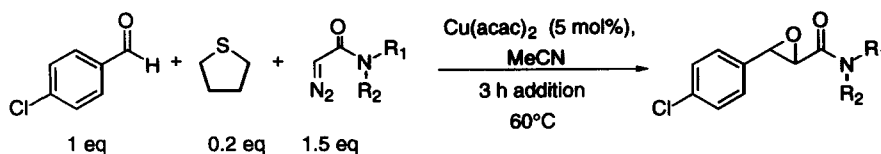
<sup>b</sup> Due to overlapping signals, it was not possible to determine the ratio of isomers to greater accuracy.

**Table 1.**

In all cases the *trans* epoxides were obtained with high diastereoselectivity which is in an agreement with the results of Ratts and Fernández, despite the higher temperatures at which the reactions are being performed. This suggests that the barrier to the formation of the *cis* epoxide is significant and this route provides a highly diastereoselective method to the *trans* glycidic amides.

Having established the scope of the process with a variety of aldehydes, we further examined the effect of varying the structure of the diazoacetamide on the reaction and the results are summarised in Table 2.

Good yields were obtained with alkyl substituted diazoacetamides (entries 1-3) but significantly lower yields were obtained with *N*-methoxy-*N*-methyl diazoacetamide (entry 4), although utilising *p*-nitrobenzaldehyde furnished the corresponding epoxide in 80 % yield. As can be clearly seen the same high diastereoselectivity can be achieved upon changing the amide substituents, suggesting that they are not important in the control of the diastereoselectivity.



Entry	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	Trans:cis	Product
1	Et	Et	79	>95:5	<b>1a</b>
2	Me	Me	78	>95:5	<b>2a</b>
3	-C <sub>4</sub> H <sub>9</sub> -		75	>95:5	<b>3a</b>
4	Me	OMe	40	>95:5	<b>4a</b>

Table 2.

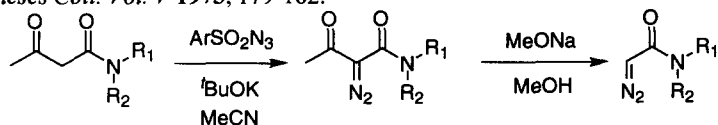
In summary, we have found conditions under which diazoacetamides can be employed in our catalytic cycle for the preparation of glycidic amides and currently work is underway to render this process asymmetric.

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- 25) Typical procedure. A mixture of aldehyde (1 mmol), tetrahydrothiophene (18  $\mu$ L, 0.2 mmol) and  $\text{Cu}(\text{acac})_2$  (13 mg, 5 mol%) were placed in MeCN (0.2 mL) and warmed to 60  $^{\circ}\text{C}$ . The diazoacetamide (1.5 mmol) was dissolved in MeCN (0.5 mL) and added over 3 hours *via* a syringe pump. After complete addition the reaction was stirred for 1 hour before purification by flash column chromatography.