# A highly efficient methodology of asymmetric epoxidation based on a novel chiral sulfur ylide†‡

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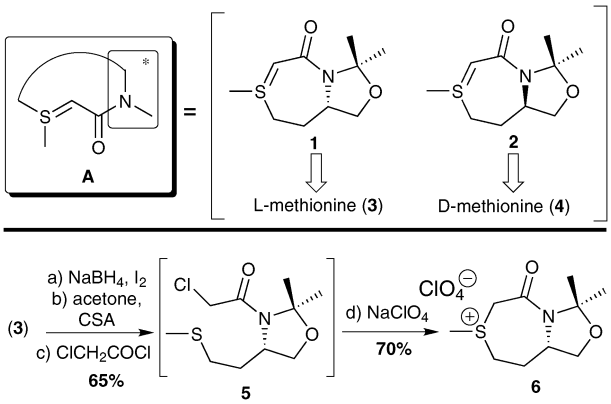
*Received (in Cambridge, UK) 19th June 2009, Accepted 22nd July 2009*
*First published as an Advance Article on the web 7th August 2009*
**DOI: 10.1039/b912070j**



**A new type of chiral sulfur ylides has been synthesized and their reactivities against carbonyl compounds tested, showing a high degree of stereoselectivity in the formation of *trans* epoxy amides under very mild reaction conditions.**

The myriad of asymmetric methods for epoxidation of olefins reflects the importance of the oxirane ring in organic synthesis.[1] Less exploited have been the epoxidation methods based on reactions of carbonyl compounds with chiral sulfur ylides. Nevertheless, numerous research groups have contributed to this area,[2] with the Aggarwal group being one of the most prolific.[3] Our experience with the synthesis of glycidic amides *via* amide-stabilized sulfur ylides[4] prompted us to consider the asymmetric version of this reaction. For this type of sulfur ylides, the introduction of chirality may be achieved either at the amide residue[5] or at the sulfide fragment,[6] the latter being more efficient in terms of enantiomeric efficiency. We propose a third type of chiral sulfur ylide, unreported so far,[7] as depicted generically as a cyclic sulfur ylide type **A**. For this new class of ylide, the bicyclic sulfur ylides **1** and **2** were identified as potential candidates, which can be prepared from the corresponding commercially available α-amino acids L- and D-methionines (**3** and **4**). Thus, we synthesized the corresponding sulfonium salt precursor from **3** according to the sequence described in Scheme 1, through the 2-chloroacetamide intermediate **5**, which was readily cyclized in the presence of sodium perchlorate to the sulfonium salt **6** in 70% overall yield after crystallization (Scheme 1). In a similar way, the enantiomeric sulfonium salt **7** was prepared from D-methionine (**4**).

With both enantiomerically pure sulfonium salts in hand, the next step was to explore the reactivity of the corresponding ylides towards carbonyl compounds and stringently test their scope and limitations in asymmetric synthesis. To this end, we began our study with the *in situ* preparation of the corresponding ylide **1** from sulfonium salt **6** and its reaction with simple aldehydes (Table 1). Initially, the *in situ* generation of the sulfur ylide and subsequent reaction with an aldehyde was carried out according to the Aggarwal's conditions. Thus, treatment of the sulfonium salt with a potassium hydroxide




**Scheme 1** The design and synthesis of new chiral sulfur ylides.

solution in ethanol, followed by addition of the aldehyde, afforded in moderate to good yields (except for aldehyde **8k**) the corresponding epoxy amides **9a–j**, which were isolated as single diastereoisomers. Investigating other reaction conditions, we found that using *tert*-butanol as solvent and an aqueous sodium hydroxide solution as base, the yields were remarkably improved compared to those obtained under Aggarwal's conditions (see Table 1).

The detection of only one diastereoisomer by NMR spectroscopy indicated an excellent level of stereochemical control that was confirmed by determination of the absolute stereochemistry and measurement of the enantiomeric purities of the corresponding epoxy alcohols **10**, obtained by sequential reduction with Red-Al and sodium borohydride,[8] or alternatively, by treatment with Super-hydride®.[9] A measure of their specific rotations and comparison with literature data allowed us to establish the absolute stereochemistry for **10** as (2*R*,3*R*). On the other hand, the formation of the Mosher ester[10] and subsequent GC-MS analysis revealed an enantiomeric excess greater than 98% for all cases, demonstrating the synthetic value of this new chiral reagent. In a similar way as for **6**, treatment of sulfonium salt **7** with base, followed by reaction with aldehydes of the resulting sulfur ylide **2**, afforded the corresponding epoxy amides **11a–i** in similar yields and diastereomeric excesses as with ylide **1**, and transformed into their corresponding epoxy alcohols **12** (Table 1). Nevertheless, it was disappointing to find that for aldehyde **8k** (entry 20) the corresponding epoxy amide **11k** was not formed, the result being a complex mixture of decomposition products. This discouraging, although not surprising, result was ascribed to the basic conditions in which the reactions were conducted, favoring the elimination of the alkoxy group at the β-position of the starting aldehyde. To circumvent this important barrier

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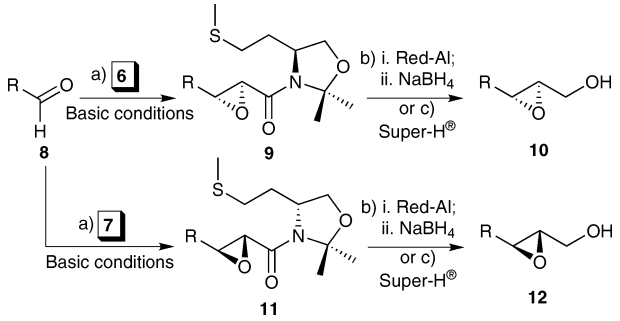
† We would like to dedicate this article to Prof. A. Vasella on the occasion of his 65th birthday.

‡ Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all new compounds. See DOI: 10.1039/b912070j

**Table 1** Reaction of sulfur ylides **1** and **2** with simple aldehydes




8 9 10 11 12

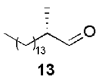
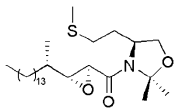
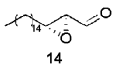
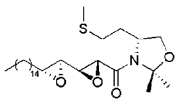
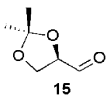
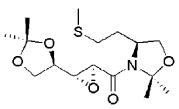
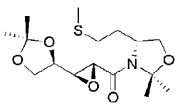
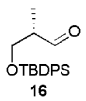
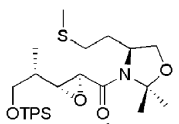
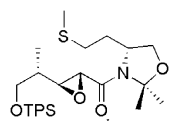
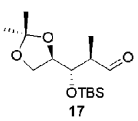
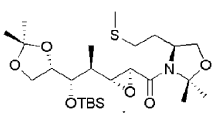
| Entry | R | Epoxy amide[a] (yield (%); *de* (%))[b] | Epoxy alcohol[c] (%) |
|---|---|---|---|
| 1 | Ph-(**8a**) | **9a** (75; >98) | **10a** (67) |
| 2 | | **11a** (82; >98) | **12a** (75) |
| 3 | 4-$MeC_6H_4$-(**8b**) | **9b** (80; >98) | **10b** (80) |
| 4 | | **11b** (80; >98) | — |
| 5 | 2-$MeC_6H_4$-(**8c**) | **9c** (79; >98) | **10c** (73) |
| 6 | | **11c** (70; >98) | — |
| 7 | 4-$MeOC_6H_4$-(**8d**) | **9d** (70; >98) | — |
| 8 | | **11d** (75; >98) | **12d** (80) |
| 9 | 4-$ClC_6H_4$-(**8e**) | **9e** (85; >98) | — |
| 10 | | **11e** (85; >98) | **12e** (69) |
| 11 | 4-$O_2NC_6H_4$-(**8f**) | **9f** (84; >98) | — |
| 12 | | **11f** (85; >98) | **12f** (59) |
| 13 | $CH_3CH_2$-(**8g**) | **9g** (61; >98) | — |
| 14 | | **11g** (63; >98) | **12g** (56) |
| 15 | $(CH_3)_2CH$-(**8h**) | **9h** (95; >98) | — |
| 16 | | **11h** (61; >98) | — |
| 17 | Cyclohexyl (**8i**) | **9i** (44; >98) | **10i** (98) |
| 18 | | **11i** (45; >98) | — |
| 19 | $PhCH_2$-(**8j**) | **9j** (74; >98) | — |
| 20 | $TPSOCH_2CH_2$-(**8k**) | **11k** (71; >98) | **12k** (75) |

[a] Reaction conditions: 1.0 equiv. sulfonium salt, 1.0 equiv. 3.0 M NaOH, *t*BuOH, 3 h, 0 °C, then addition of 1.0 equiv. of aldehyde, 6–8 h, 25 °C except for entry 20 in which was the following: 1.0 equiv. of aldehyde, 1.0 equiv. of sulfonium salt, 1.0 equiv. 3.0 M NaOH, $CH_2Cl_2$–$H_2O$ (1 : 1). [b] Diastereoisomeric excess was determined by direct analysis of the resulting epoxy amide by NMR spectroscopy and also by transformation into the epoxy alcohol, formation of the Mosher ester and analyses by NMR and GC/MS. [c] The reductions to epoxy alcohols only were carried out for the indicated cases by use of condition c, except for entry 14, in which was used condition b.

we attempted the two-phase method, developed by our group,[11] to obtain the coveted epoxy amide in 71% yield (Table 1, entry 20).

Having extensively explored the reaction of these chiral sulfonium salts with simple aldehydes and outlining the stereochemical differentiation exerted by the sulfur ylides **1** and **2**, we next sought to employ more complex chiral aldehydes to test whether the methodology could be applied to the synthesis of complex molecules. Thus, we proceeded to study the reactions of sulfonium salts **6** or **7** with a collection of chiral aldehydes carefully selected based upon their utilization in total synthesis. The results from these studies are summarized in Table 2. Notable problems arose due to the presence of alkoxy groups in the β-position of starting aldehydes (*e.g.* aldehydes **16** and **17**), as was anticipated for aldehyde **8k**. In these cases, the yields of the desired epoxy amides (**22–24**) were remarkably improved by use of the

**Table 2** Reaction of sulfur ylides **1** and **2** with complex aldehydes

| Sulfur ylide | Aldehyde | Epoxy amide (yield (%); *de* (%)) | Epoxy alcohol[c] (%) |
|---|---|---|---|
| 1 |  13 |  **18** (60; >98)[a] | **25** (79) |
| 2 |  14 |  **19** (72; >98)[a] | — |
| 1 |  15 |  **20** (62; >98)[a] | **26** (75) |
| 2 | |  **21** (50; >98)[a] | **27** (71) |
| 1 |  OTBDPS 16 |  OTPS **22** (71; >98)[b] | **28** (75) |
| 2 | |  OTPS **23** (62; >98)[b] | **29** (75) |
| 1 |  OTBS 17 |  OTBS **24** (48; >98)[b] | — |

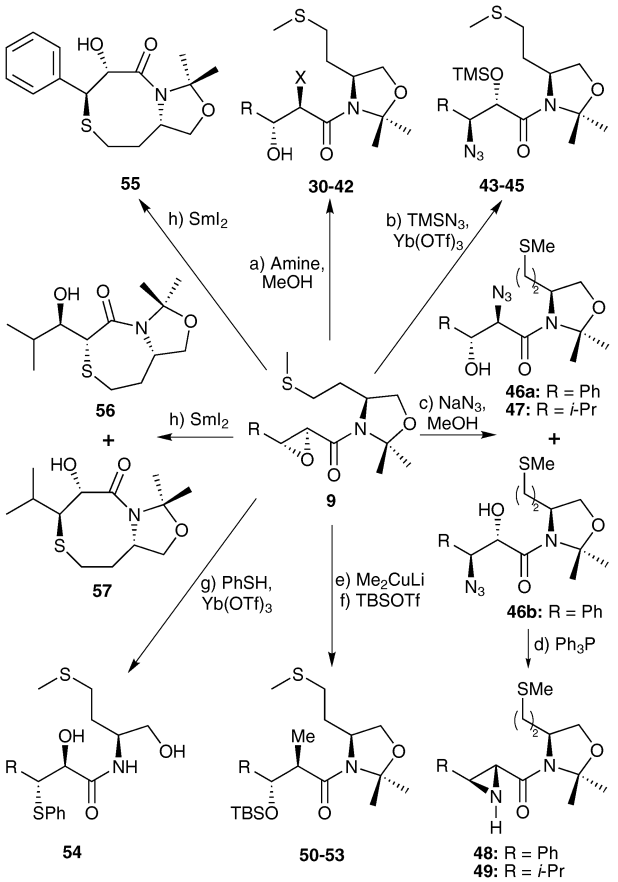
[a] 1.0 equiv. sulfonium salt, 1.0 equiv. 3.0 M NaOH, *t*BuOH, 3 h, 0 °C, then addition of 1.0 equiv. of aldehyde, 6–8 h, 25 °C. [b] 1.0 equiv. of aldehyde, 1.0 equiv. of sulfonium salt, 1.0 equiv. 3.0 M NaOH, $CH_2Cl_2$–$H_2O$ (1 : 1). [c] 3.0 equiv. Super-H®, THF, 0 °C, 0.5 h.

two-phase method, despite the difficulties of reacting sterically hindered aldehydes under these conditions. With all these epoxy amides in hand (Table 2), the synthetic possibilities for the synthesis of natural or designed products are diverse. Especially noteworthy are the epoxy amides **22–24**, which may present applications in the synthesis of the macrolide type natural products.[12] On the other hand, the epoxy amides **18** and **19** represent advanced intermediates for the synthesis of the stevastelins.[13]

Finally, as part of these preliminary studies concerning the reactivity of the described sulfur ylides, we explored the synthetic possibilities that the resulting epoxy amides may provide in the field of asymmetric synthesis by the study of their reactivity towards nucleophilic reagents of differing nature including nitrogen, sulfur and alkyl-type

nucleophiles. Thus we selected simple epoxy amides, described in Table 1, to be subjected to the action of the aforementioned nucleophiles, such as amines, $TMSN_3$ in the presence of a Lewis acid, sodium azide, organocuprate reagents and thiols.




**Scheme 2** Opening reactions of epoxy amides with nucleophiles. *Reagents and conditions*: (a) 5.0 equiv. of amine or $NH_3$ in $H_2O$, MeOH, 70 °C, 6–8 h, 69% for **30** (R = Ph, X = $NH_2$), 72% for **31** (R = Ph, X = NHMe), 75% for **32** (R = Ph, X = NHBn), 93% for **33** (R = Ph, X = NHallyl), 54% for **34** (R = Ph, X = NHPh), 68% for **35** (R = Ph, X = $NMe_2$), 65% for **36** (R = *p*-$MeOC_6H_4$, X = $NH_2$), 83% for **37** (R = *p*-$MeOC_6H_4$, X = NHMe), 71% for **38** (R = *p*$MeC_6H_4$, X = NHMe), 74% for **39** (R = *p*-$ClC_6H_4$, X = NHMe), 62% for **40** (R = *n*-Pr, X = NHMe), 84% for **41** (R = *i*-Pr, X = NHMe), 65% for **42** (R = Bn, X = NHMe). (b) 2.5 equiv. of $TMSN_3$, 0.2 equiv. of $Yb(OTf)_3$, $CH_2Cl_2$, 25 °C, 8 h, 85% for **43** (R = *p*-$MeOC_6H_4$), 12% for **44** (R = Ph), 15% for **45** (R = *p*-$MeC_6H_4$). (c) 10.0 equiv. of $NaN_3$, MeOH, 70 °C, 8 h, 87% for **46a**/**46b** (R = Ph, 2 : 1 mixture), 76% for **47** (R = *i*-Pr). (d) 1.5 equiv. $Ph_3P$, THF, 25 °C, 6 h, 62% for **48**, 89% for **49**. (e) 5.0 equiv. $Me_2CuLi$, THF, 0 °C, 8 h. (f) 1.5 equiv. TBSOTf, 2.0 equiv. 2,6-lutidine, $CH_2Cl_2$, 0 °C, 0.5 h, 56% for **50** (R = Ph), 64% for **51** (R = *i*-Pr), 60% for **52** (R = Chx), 52% for **53** (R = Bn). (g) 2.5 equiv. of PhSH, 0.3 equiv. of $Yb(OTf)_3$, $CH_2Cl_2$, 25 °C, 1–2 days, 77% for **54** (R = *p*-$MeOC_6H_4$). (h) 2.0 equiv. of $SmI_2$, THF, 25 °C, 2 h, 37% for **55** (R = Ph), 80% for **56** + **57** (R = *i*-Pr, 1 : 1 mixture).

In general, all epoxy amides showed very good reactivity and complete regioselectivity in the opening process at C-2 or at C-3 positions depending on the reaction conditions. The exceptions were found in aliphatic epoxy amides which against $TMSN_3$ and thiols, respectively, did not react, or for the reactions of aromatic epoxy amides with sodium azide in which there was a lack of regioselectivity, obtaining a mixture of regioisomers. For this particular case, interestingly, the mixture of azido alcohols **46a** and **46b** was transformed into one aziridine, **48**, by treatment with $Ph_3P$.[14] Finally, we decided to check the chemical behavior of these epoxy amides against other types of reagents such as $SmI_2$ which has proven to be a useful reagent for the transformation of simple epoxy amides into 2-hydroxy amides.[15] In our case, when the epoxy amides were reacted with a freshly prepared solution of $SmI_2$ in THF, we found that the pendant methyl sulfide interfered with the reaction producing thiocane derivative **55** with epoxy amide **9a**, and a mixture of thiepane **56** and thiocane **57** when aliphatic epoxy amide **9h** was used. Together with these compounds, α,β-unsaturated amides were also detected as minor products (<10%) (Scheme 2).

We thank Ministerio de Educación y Ciencia (CTQ07-66518) and Junta de Andalucía (FQM-03329) for financial support.

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