Asymmetric Synthesis of Epoxides using Chiral Sulfimides

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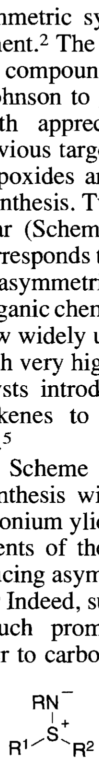
The sodium salt of (*S*)-sulfimide **8** reacts with carbonyl compounds to yield (*R*)-epoxides in 60–64% yield and 21–70% e.e.

Sulfimides **1** (Chemical Abstracts name sulfilimines) are the nitrogen analogues of sulfoxides **2**.[1] Despite the fact that they are easy to prepare and that their chemistry parallels closely that of sulfoxides, which have many synthetic applications, sulfimides remain a relatively poorly studied class of compounds. Our particular interest is in the application of sulfimides to problems in asymmetric synthesis where, again, chiral sulfoxides are prominent.[2] The reaction of the anion of sulfimides **3** with carbonyl compounds was shown by the groups of Tamura and of Johnson to give reasonable yields of epoxides (Scheme 1), with appreciable *trans* selectivity.[3] Hence, epoxides were obvious targets for our programme.

Non-racemic epoxides are prominent among intermediates for asymmetric synthesis. Two very different disconnections of epoxides are clear (Scheme 2). The functional group interconversion (*a*) corresponds to the epoxidation of an alkene. The realisation of the asymmetric version of this reaction is one of the triumphs of organic chemistry in recent years. The Sharpless epoxidation is now widely used to convert allylic alcohols into their epoxides with very high enantioselectivity[4] and the chiral manganese catalysts introduced by Jacobsen now allow unfunctionalised alkenes to be epoxidised, again with high enantioselectivity.[5]

Option (*b*) in Scheme 2 is a true disconnection, as a corresponding synthesis will require formation of a carbon–carbon bond. Sulfonium ylides **4**, which are commonly used as synthetic equivalents of the alkylidene fragment **5**, offer the possibility of inducing asymmetry in this reaction, as remarked by Trost in 1973.[6] Indeed, sulfonium ylides derived from chiral sulfides hold much promise as reagents for asymmetric alkylidene transfer to carbonyl groups (Scheme 3), as demonstrated by the groups of Furukawa, Durst and Solladié-Cavallo.[7,8] As enantiomerically pure sulfides are not particularly readily available, the need for a stoichiometric amount of the reagents is a serious drawback of these procedures, although the sulfide can be recovered. In response to this, Aggarwal's group have devised an ingenious catalytic version of the reaction (Scheme 4) and we eagerly await a report of high enantioselectivity in this process.[9]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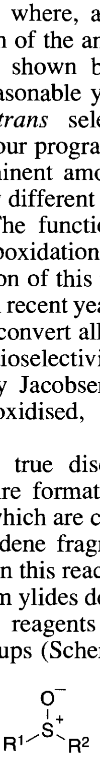
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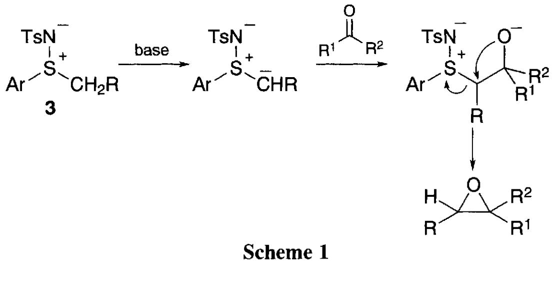
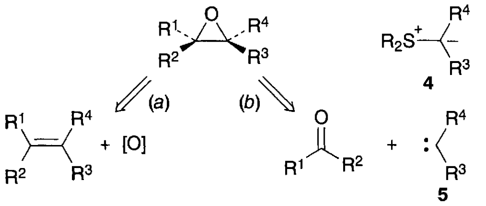
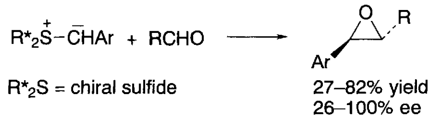

Scheme 1


Scheme 2


Scheme 3

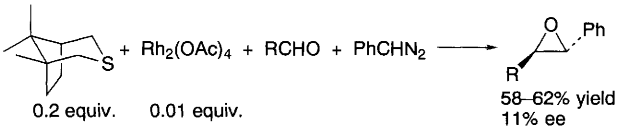
Notably, asymmetric transfer of the simplest alkylidene group, *viz*. methylidene, from chiral sulfonium ylides has not yet been realised.[6,8] Other chiral sulfur reagents, where the sulfur is the sole chiral centre, have been investigated in this respect. Epoxides produced from chiral imidosulfoxonium ylide **6** were reported with up to 20% e.e.[10] and from the sodium salt of sulfoximide **7** with around 10% e.e.[11]

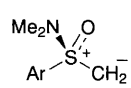
This study thus aimed to assess the potential of sulfimides as reagents for asymmetric synthesis by addressing the problem of asymmetric methylidene transfer to carbonyl groups. The ready availability of the necessary sulfimide **8** in enantiomerically enriched form made this area particularly attractive.

Enantiomerically pure (*R*)-sulfoxide **9** was converted to (*S*)-sulfimide **8** by the procedure of Cram (Scheme 5).[12] The (*S*)-sulfimide used in this study was always >90% enantiomerically pure, as judged by both its optical rotation and ^{1}H NMR spectrum with a chiral shift reagent.

Before attempting the asymmetric methylidene transfer reactions we reinvestigated the work from the groups of Tamura and of Johnson.[3] We felt sodium hydride in THF at room temperature to be the most promising reaction conditions, as both reasonable yields and high diastereoselectivities had been reported with this system. As, on repetition of the literature procedure, we found yields to be rather variable, we decided to attempt the reactions with inverse addition, *i.e.* carbonyl compound before sodium hydride. Under these conditions the reaction is highly repeatable, with yields of 60–64% in all successful cases. The reaction only failed with highly conjugated or sterically hindered carbonyls **10f** and **10g**.

The asymmetric reactions were carried out using (*S*)-**8** at the lowest temperature which could be attained without reducing the yield. A representative range of carbonyl compounds **10** were used, including dialkyl and alkylaryl aldehydes and


Scheme 4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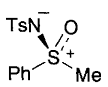
Ar = 4-MeC$_6$H$_4$-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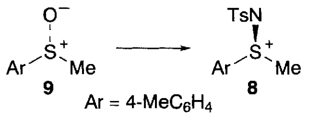
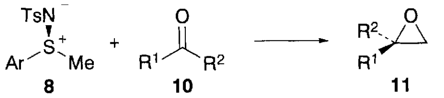

Scheme 5 *Reagents and conditions*: TsNSO, pyridine, 0 °C (Ts = toluene-*p*-sulfonyl)

Table 1 Reaction conditions, yields and e.e.s for syntheses of epoxides **11**

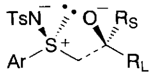
11	R^1	R^2	T/°C	t/h	Yield (%)	E.e. (%)	$[\alpha]_D$ (589 nm)
a	Ph	H	−5	24	63	70	+31 (26 °C, benzene)
b	Ph	Me	20	160	60	45	+31.4 (26 °C, acetone)
c	cyclohexyl	H	20	160	62	[a]	+36.7 (26 °C, acetone)
d	$PhCH_2CH_2$	Me	66	140	64	21	+8.3 (29 °C, acetone)
e	(E)-PhCH=CH	H	20	90	62	42	+11.2 (29 °C, acetone)
f	(E)-PhCH=CH	Ph	—	—	0	—	—
g	Bu^t	Me	—	—	0	—	—

[a] Not yet determined, see text.



8 **10** **11**

Scheme 6 *Reagents and conditions*: NaH, THF, 1–7 d, −5 °C to reflux



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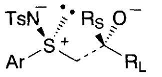

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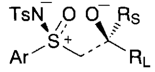
R_S = small group, R_L = large group



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ketones as well as an α,β-unsaturated aldehyde (Scheme 6).† The results are summarised in Table. 1.

Enantiomeric excesses were measured either by chiral HPLC or by ^1H NMR with a chiral shift reagent. Epoxide **11c** has no chromophore for HPLC analysis and we have not yet been able to resolve the enantiomers by NMR. All epoxides **11** produced from (S)-sulfimide **8** have positive optical rotations which, where literature comparison is possible, corresponds to the (R)-epoxide. We therefore assume that all the product epoxides **11** have the (R)-configuration, but this remains to be confirmed.

The predictable sense of the asymmetric induction can be rationalised by means of an open chain model, similar to one proposed by Pearson for reaction of a sulfoximide analogue,[13] which is appropriate in the case of a sodium counterion. The model assumes that the largest groups in both the sulfimide and the carbonyl component will prefer an antiperiplanar relationship with respect to the newly forming chain, *i.e.* Ar antiperiplanar to the forming carbon–carbon bond and R_L antiperiplanar to the CH_2–S bond. This assumption generates two transition states **12** and **13**. We propose that the unfavourable electrostatic interaction between the highly negatively charged oxygen and nitrogen centres in **12** will lead to a preference for **13** in all cases. Increasing the size of the small group R_S will raise the energy of **13** more than the energy of **12**, as in **13** there are unfavourable steric interactions between R_S and TsN. The model thus predicts that (S)-sulfimide **8** will lead to (R)-epoxide **11** (*via* **13**) and that the enantiomeric excess will increase as the size of group R_S decreases, as observed.

This model can also be applied to the analogous reaction of sulfoximide **7** with acetophenone. In this case, we assume that the more unfavourable electrostatic interaction will be between the two oxygen atoms and thus (R)-sulfoximide will lead to (S)-epoxide *via* transition state **14**, as observed.[11] As steric factors would also favour this transition state it would be expected that the enantiomeric excess would increase with increasing size of group R_S (until R_S and R_L are of similar sizes), but no data is available to confirm this. It should also be noted that Johnson proposed that addition of the sulfoximide anion is reversible,[14] in which case our model would be irrelevant.

In summary, the sodium salt of sulfimide **8** can be used as an asymmetric methylidene transfer reagent to carbonyl groups. Epoxides are produced in 60–64% yield and 21–70% e.e., with (S)-sulfimide giving (R)-epoxide. The sense of the asymmetric induction can be rationalised by employing an open chain model which minimises both the gauche effects between the largest groups and the electrostatic interactions between the most electronegative groups.

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Footnote

† To a solution of **8** (0.33 mmol) in dry THF (15 ml) was added first carbonyl compound (0.33 mmol) then hexane-washed sodium hydride (2.3 mmol) and the mixture was stirred under dry nitrogen as in Table 1. The THF was removed by evaporation and water (15 ml) was added to the residue. The product was then extracted into pentane.

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