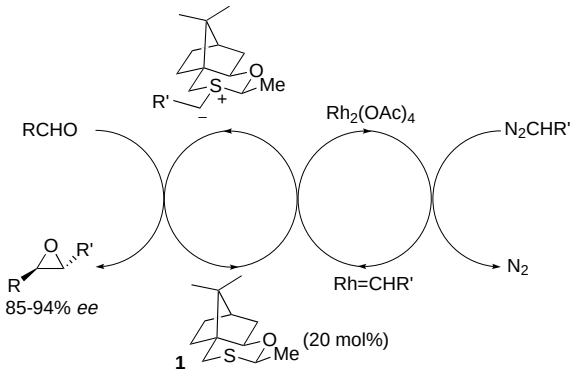
Catalytic Asymmetric Synthesis of Epoxides from Aldehydes Using Sulfur Ylides with In Situ Generation of Diazocompounds**

Varinder K. Aggarwal,* Emma Alonso, George Hynd, Kevin M. Lydon, Matthew J. Palmer, Marina Porcelloni, and John R. Studley

The development of new methods for catalytic epoxidation continues to attract considerable attention. Whilst most methods have concentrated on alkene oxidation,[1] we have focused our efforts on the epoxidation of carbonyl compounds.[2] Recently, we reported a catalytic and asymmetric process for converting carbonyl compounds directly into epoxides which operated under neutral conditions and employed sub-stoichiometric amounts of sulfide **1** and metal catalyst (Scheme 1).[3]

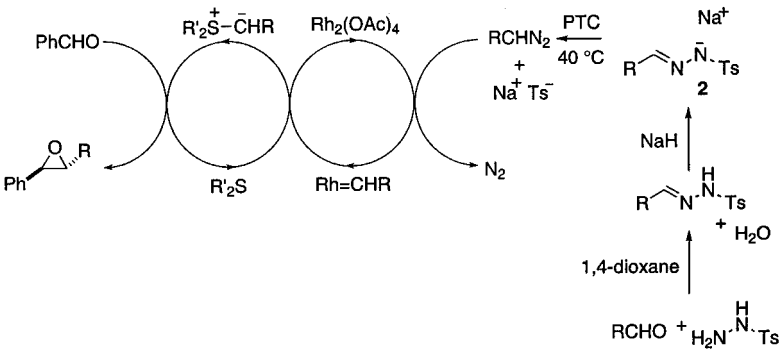


Scheme 1. Catalytic cycle for epoxidation.

However, a limitation of the original protocol was the need to synthesize and handle diazocompounds, which, since they are potentially explosive,[4] severely limits the practicality of the process. We therefore considered the possibility of generating the diazo compound in situ and coupling this reaction to our established epoxidation process. Herein we describe our success in achieving this aim and beyond—to the development of a unique process for the direct coupling of two different aldehydes to form epoxides with control over the relative and absolute stereochemistry.

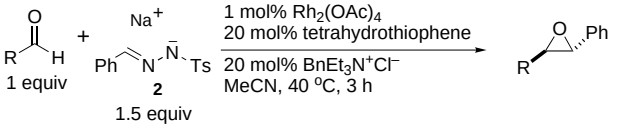
We focused our efforts on the use of the Bamford–Stevens reaction for generating the diazo compound,[5] and after some experimentation found that warming a suspension of the tosylhydrazone salt **2** (tosyl = Ts = toluene-4-sulfonyl) in the presence of a phase-transfer catalyst[6] (PTC; to aid the passage from the solid to the liquid phase), allowed the generation of the diazo compound at moderate temperature.[7] This modified protocol was also compatible with our established epoxidation process and was remarkably efficient (Scheme 2, Table 1, entry 1). Furthermore, these new conditions were found to be general (Table 1). All the aromatic, heteroaromatic, and unsaturated aldehydes investigated furnished the corresponding epoxide in high yields and with high *trans* selectivities (entries 1–7). Aliphatic aldehydes also worked well, although they gave lower yields and selectivities (entries 8 and 9).

Following this success we decided to investigate a more diverse range of tosylhydrazone salts in the epoxidation process. Initially, we utilized a variety of substituted aryl tosylhydrazone salts (**2a**–**g**, Table 2). The yields of the epoxides obtained were excellent, except where a sterically hindered reagent was employed (Table 2, entry 6). In general *trans* epoxides were obtained exclusively, but tosylhydrazone



Scheme 2. One-pot coupling of a carbonyl compound with either a tosylhydrazone salt or a second carbonyl compound. Ts = toluene-4-sulfonyl.

Table 1. Yields and ratios of epoxides formed from aldehydes and tosylhydrazone salt **2** using 0.2 equivalents of tetrahydrothiophene.



Entry	Aldehyde	Yield [%][a]	*trans*:*cis*[b]
1	benzaldehyde	95	> 98:2
2	*p*-nitrobenzaldehyde	94	> 98:2
3	*p*-chlorobenzaldehyde	86	> 98:2
4	*p*-methoxybenzaldehyde	98	> 98:2
5	3-pyridinecarboxaldehyde	71	> 98:2
6	*trans*-cinnamaldehyde	97[c]	> 98:2
7	*trans*-crotonaldehyde	78[c]	91:9
8	cyclohexanecarboxaldehyde	69	65:35
9	valeraldehyde	59	70:30

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Crude yield determined by ^{1}H NMR spectroscopy (epoxides are unstable to silica gel). Bn = benzyl.

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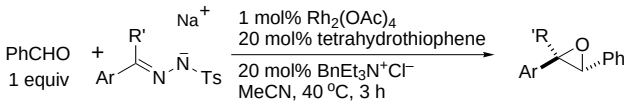
Table 2. Yields and ratios of epoxides formed from benzaldehyde and tosylhydrazone salts using 0.2 equivalents of tetrahydrothiophene.

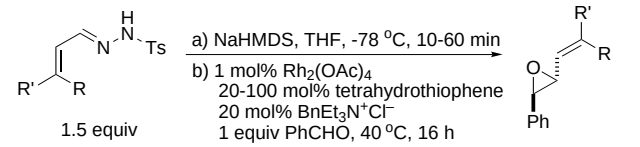


Entry	Ar	R′	Salt	Yield [%][a]	*trans*:*cis*[b]
1	*p*-ClC_6H_4	H	**2a**	95	>98:2
2	*p*-$MeOC_6H_4$	H	**2b**	96	67:33
3	*p*-MeC_6H_4	H	**2c**	73	80:20
4	*o*-MeC_6H_4	H	**2d**	86	>98:2
5	*p*-CNC_6H_4	H	**2e**	89	>98:2
6	2,4,6-$Me_3C_6H_2$	H	**2f**	17	>98:2
7	C_6H_5	Me	**2g**[c]	86	>98:2

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] In situ salt formation from 2,4,6-triisopropylbenzenesulfonyl hydrazone using NaHMDS (HMDS = 1,1,1,3,3,3,-hexamethyldisilazane) as the base.

salts bearing electron-donating substituents led to lower diastereoselectivity (Table 2, entries 2 and 3). Tosylhydrazone salts derived from aryl ketones were also successfully employed in the process (Table 2, entry 7). We were also able to couple alkenylhydrazones **3**–**5** with benzaldehyde to furnish vinyl epoxides (Table 3). Although high yields were obtained, the diastereoselectivity was poor and this problem is currently being addressed.

Table 3. Yields and ratios of epoxides formed from benzaldehyde and alkenyl-substituted sulfonylhydrazones using 1.0 equivalents of tetrahydrothiophene.



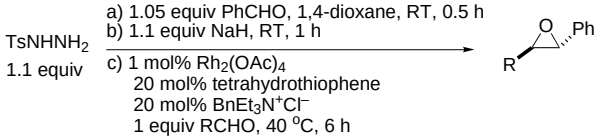
Entry	R	R′	Hydrazone	Yield [%][a]	*trans*:*cis*[b]
1	CH_3	CH_3	**3**	>90	50:50
2[c]	Ph	Ph	**4**	>90	67:33
3	H	$SiMe_3$	**5**	76[d]	50:50

[a] Crude yield determined by ^{1}H NMR spectroscopy (epoxides are unstable to silica gel). [b] Determined by ^{1}H NMR spectroscopy. [c] Using 0.2 equiv of tetrahydrothiophene. [d] Yield of isolated pure epoxide (stable to silica gel).

Having demonstrated that we could generate a diazo compound in situ, we considered the possibility of generating the hydrazone itself in situ. Remarkably, this worked (Table 4) and provided a one-pot, atom-economical method for coupling two different aldehydes to give epoxides. Thus, we have developed a general, user-friendly catalytic process for preparing epoxides by coupling together a carbonyl compound with either a tosylhydrazone salt or a second carbonyl compound (Scheme 2).

Our efforts to render these processes asymmetric using thioacetal **1**, which had worked well in the epoxidation process when preformed phenyldiazomethane was used,[3] were not successful: only low yields of the corresponding

Table 4. Yields and ratios of epoxides formed from aldehydes and tosylhydrazone salt **2** (generated in situ) using 0.2 equivalents of tetrahydrothiophene.

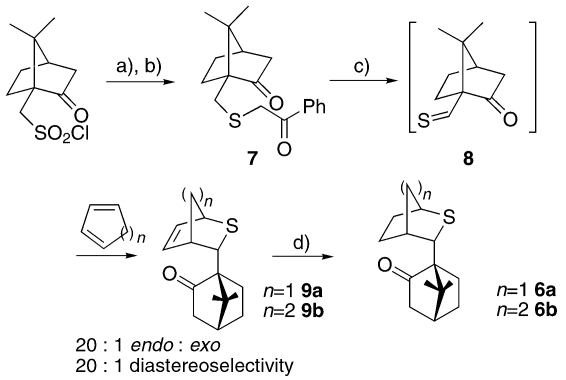


Entry	Aldehyde (RCHO)	Yield [%][a]	*trans*:*cis*[b]
1	benzaldehyde	70	>98:2
2	*p*-nitrobenzaldehyde	81	>98:2
3	*p*-methoxybenzaldehyde	70	>98:2
4	pyridine 3-carboxaldehyde	40	>98:2
5	cyclohexanecarboxaldehyde	30	70:30
6	valeraldehyde	43	80:20

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy.

epoxides were obtained. We therefore embarked on the synthesis of a range of stable, mono and bicyclic chiral sulfides based on thiolanes, thianes, and 1,4-oxathianes, and from this extensive study we found that the bridged bicyclic sulfides **6a**, **b** performed exceptionally well.

The [2.2.1] bicyclic sulfide **6a** was prepared in four steps from camphorsulfonyl chloride in 48% overall yield (Scheme 3). The key step in the synthesis was the cyclo-



Scheme 3. Reagents and conditions: a) PPh_3, 1,4-dioxane:H_2O (4:1), 1 h, reflux, 92%; b) $PhCOCH_2Cl$, K_2CO_3, THF, RT, 20 h, 82%; c) sun lamp (*hν*), CH_2Cl_2, 20 °C, 6 h, cyclopentadiene →**9a**, 76% or cyclohexadiene →**9b**, 40%; d) H_2, Pd-S/C EtOH, RT, 3 h, **6a**, 84%; **6b**, 82%.

addition of thioaldehyde **8** (generated photochemically from phenacyl sulfide **7**) with cyclopentadiene.[8] This reaction was not only highly *endo* selective, but also showed very high levels of diastereoselectivity. A single diastereomeric cycloadduct was obtained in 76% yield. Hydrogenation and recrystallization gave analytically pure sulfide **6a** whose structure was confirmed by X-ray analysis. The [2.2.2] bicyclic sulfide **6b** was prepared in an analogous manner (Scheme 3).

The conditions for epoxidation were optimized with sulfide **6a** and it was found that the sulfide loading could be reduced from 20 mol% to just 5 mol% without significantly affecting the yield or *ee* value (Table 5, entry 1). Furthermore we were also able to recover and reuse the sulfide without any loss of

Table 5. Yields, enantioselectivities, and diastereoselectivities of epoxides formed from aldehydes and tosylhydrazone salt **2** using 0.05 equivalents of sulfide **6a**.[a]

Entry	Aldehyde	Yield [%][b]	d.r.[c]	*ee* [%]
1	benzaldehyde	82	> 98:2	94
2	benzaldehyde[d]	82	> 98:2	92
3	*p*-nitrobenzaldehyde	75	> 98:2	92
4	*p*-chlorobenzaldehyde	80	> 98:2	91
5	*p*-methoxybenzaldehyde	68	> 98:2	92
6	*p*-tolualdehyde	84	> 98:2	90
7	*o*-tolualdehyde	68	> 98:2	90
8	*trans*-cinnamaldehyde	70[c]	98:2	87
9	cyclohexanecarboxaldehyde	58	88:12	90
10	2-furylaldehyde	60[c]	98:2	91
11	3-furylaldehyde	77	98:2	92

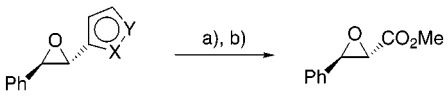
[a] Aldehyde (1.0 mmol), tosylhydrazone sodium salt **2** (2.0 mmol), sulfide **6a** (0.05 mmol), phase-transfer catalyst (0.05 mmol), $Rh_2(OAc)_4$ (0.01 mmol), and CH_3CN (0.8 mL). [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy (epoxides are unstable to silica gel). [d] Using **6b** in place of **6a**.

asymmetric induction. Sulfide **6b** gave a similarly high yield and enantioselectivity (Table 5, entry 2), but as its synthesis was lower yielding further studies were conducted with **6a**.

The new procedure was applied to a range of aromatic, heteroaromatic, unsaturated, and aliphatic aldehydes and was found to be general (Table 5) and gave high yields, high diastereoselectivities, and high enantioselectivities in all cases.

The process shown in Table 5, entry 1 has been scaled up to a 50-mmol scale and found to give similar yields and enantioselectivities (78 and 92%, respectively). Further reductions in catalyst loading of $Rh_2(OAc)_4$ and the phase-transfer catalyst have been achieved upon scale-up. Conducting work on this scale would not have been contemplated using the ex situ process.[4]

Finally, the synthetic utility of the process is demonstrated by the conversion of the furaldehyde-derived epoxides into glycidic esters with high enantiomeric excess values (Scheme 4). Glycidic esters are versatile intermediates and



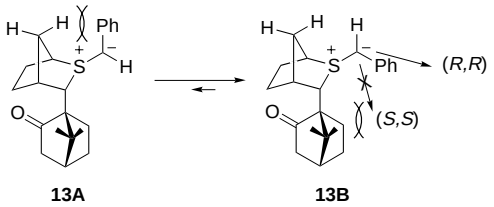
10, X = O, Y = CH
11, X = CH, Y = O

12, 60% yield, 91% *ee*
12, 67% yield, 93% *ee*
$[\alpha]_D^{25} = +160.3$ ($c = 0.56$ in $CHCl_3$)
ref. [10]: $[\alpha]_D^{25} = +179.4$ ($c = 1$ in $CHCl_3$)

Scheme 4. Reagents and conditions: a) $RuCl_3$ (2 mol%), $NaIO_4$ (4 equiv), $MeCN:CCl_4:H_2O$, RT, 3 h; b) CH_2N_2, Et_2O, RT.

have found widespread use in synthesis. Thus, oxidation of **10**/**11** with $RuCl_3/NaIO_4$ followed by esterification[9] furnished the glycidic esters in good yields. The absolute stereochemistry of the glycidic ester was determined by comparison of the $[\alpha]_D$ value with the literature value,[10] and this provided additional proof of the stereochemical assignment of the furaldehyde-derived epoxides.

The following model is proposed to account for the high enantioselectivity.[11] Of the two lone pairs only the *exo* lone pair reacts to form a single sulfonium ylide **13**.[12] The ylide can adopt conformations **13A** or **13B**, but **13B** should be strongly favored because of the 1,4-steric interactions present in **13A** (Scheme 5). The face selectivity of the ylide is then controlled



13A **13B**

Scheme 5. Model to account for the enantioselectivity.

by the bulky camphor group which blocks attack from the *Si* face, thus leading to the *R*,*R* epoxide. To achieve *high* enantioselectivity requires control of the conformation and high face selectivity of the ylide. The control in the ylide conformation arises from the conformational rigidity of sulfides **6a**, **b**, which means that ylide conformer **13A** cannot be easily accommodated through small changes in bond angles around the sulfur atom. This effect leads to a significant difference in the energy between the two ylide conformers **13A**, **B**, which in conjunction with the high face selectivity imposed by the bulky camphor moiety results in the high enantioselectivity observed.

In summary, we have developed a new class of sulfides which, at 5 mol% loading, gives high diastereoselectivities, high enantioselectivities, and high yields in the coupling of a range of different aldehydes with tosylhydrazone salts. The process has been scaled up and now represents a practical way of converting carbonyl compounds directly into epoxides with control of relative and absolute stereochemistry.

Experimental Section

Epoxidation of benzaldehyde (50-mmol scale): Compound **6a** (62.5 mg, 2.5 mmol), anhydrous acetonitrile (50 mL), rhodium(II) acetate dimer (110 mg, 0.25 mmol), benzyl triethylammonium chloride (228 mg, 1.0 mmol), benzaldehyde (5.1 mL, 50 mmol), and tosylhydrazone sodium salt **2** (22.3 g, 75 mmol) were added sequentially to a 100-mL 2-neck flask. The reaction mixture was stirred at 40 °C under a static nitrogen pressure for 2 d using an overhead stirrer. The reaction was quenched by the addition of water (25 mL) and ethyl acetate (25 mL), and the phases were separated. The aqueous layer was washed with ethyl acetate (2×25 mL) and the combined organic phases dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was analyzed by ^1H NMR spectroscopy to determine the diastereomeric ratio and then purified by flash column chromatography to afford stilbene oxide (7.6 g, 78%).

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[12] Alkylation of sulfide **6** with benzyl bromide gave a single sulfonium salt whose stereochemistry was determined by X-ray analysis. Full details will be published elsewhere.

Application of Chiral Sulfides to Catalytic Asymmetric Aziridination and Cyclopropanation with In Situ Generation of the Diazo Compound**

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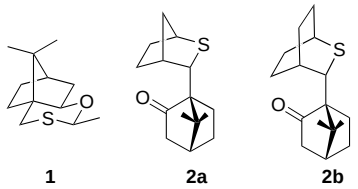
In the preceding paper we described a highly efficient catalytic process for converting carbonyl compounds into epoxides with high enantioselectivity. Herein we describe the extension of this work to the asymmetric aziridination of imines[1] and to the asymmetric cyclopropanation of electron-deficient alkenes.[2]

We previously reported that 1,3-oxathiane **1** gave good yields and high enantioselectivity in aziridination[3] and cyclopropanation[4] reactions. However, these processes are

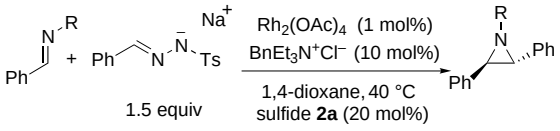


1 **2a** **2b**

potentially hazardous, cannot be easily scaled up, and the sulfide cannot be fully recovered. We successfully solved these problems in the epoxidation reaction by generating the diazo compound in situ and by developing a new class of chiral sulfides **2**,[5] which were completely stable to the reaction conditions. We were keen to examine whether these new conditions and new sulfides were compatible with the aziridination and cyclopropanation processes.

Optimization of the conditions for aziridination of the *N*-SES-activated imine derived from benzaldehyde[6] (this imine is easily prepared and provides a readily cleavable group) with sulfide **2a** revealed that 1,4-dioxane was the best solvent. A broad study of different activating groups on the nitrogen atom showed that sulfonylimines[7] led to aziridines in good yield, high enantioselectivities, but low diastereoselectivities (Table 1, entries 1 – 3). A notable example is the naphthylsulfonylimine, which gave excellent results and this group is considerably easier to deprotect[8] than the toluene-4-sulfonyl (tosyl) group. Improved diastereoselectivity was observed

Table 1. Effect of the nitrogen substituent on the yield, diastereoselectivity, and enantioselectivity.[a]



Entry	R	Yield [%][b]	d.r.[c] (*trans*:*cis*)	*ee* [%][d]
1	SES	75	2.5:1	94
2	Ts	68	2.5:1	98
3	$SO_2C_{10}H_7$	70	3:1	97
4	Boc	33[e,f]	8:1	89
5	TcBoc	71	6:1	90
6[g]	SES	66	2.5:1	95

[a] Tosylhydrazone salt (1.5 equiv), imine (1.0 equiv), phase-transfer catalyst (PTC, 0.1 equiv), $Rh_2(OAc)_4$ (0.01 equiv), 1,4-dioxane (0.33 M), chiral sulfide **2a** (0.2 equiv), 40 °C. [b] Yield of isolated product. [c] The *trans*:*cis* ratio was determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess values were determined on a Chiralcel OD column; the absolute configuration was 1*R*,2*R*. [e] 0.05 equiv of PTC were used. [f] *trans*-stilbene oxide was obtained as the main side product. [g] 5 mol % of sulfide was used. Ts = tosyl = toluene-sulfonyl.

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