Asymmetric Synthesis of Epoxides

Sulfur-Ylide-Mediated Synthesis of Functionalized and Trisubstituted Epoxides with High Enantioselectivity; Application to the Synthesis of CDP-840**

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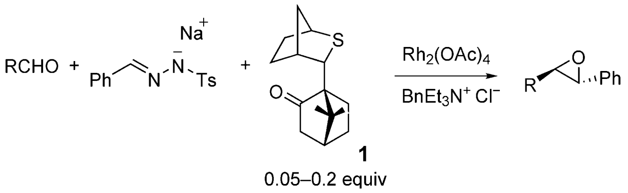
The carbonyl group occupies a position of central importance in organic synthesis as it allows ready functionalization, for example, in the α, β, and γ positions. Direct transformations into other versatile functional groups, such as alkenes and epoxides, further increase the importance of carbonyl groups in synthesis. The ability to conduct such transformations enantioselectively would be extremely useful, and toward this goal we recently reported a practical, catalytic, and asymmetric conversion of aldehydes into epoxides by using the sulfide **1** (Scheme 1).[1] The sulfide **1**, which is readily available in both enantiomeric forms, was obtained in four steps in 48 % overall yield from camphorsulfonyl chloride.



Scheme 1. Catalytic and asymmetric epoxidation of aldehydes; conditions: $Rh_2(OAc)_4$ (1 mol%), $BnEt_3N^+Cl^-$ (10 mol%), CH_3CN, 40°C.

However, attempts to apply our catalytic process to the synthesis of CDP-840, through an epoxidation reaction with 4-pyridinecarboxaldehyde, were unsuccessful. In mapping out the scope of the catalytic process we discovered that, as well as the reactions of heteroaromatic aldehydes that bear basic groups, those of *n*-alkyl aliphatic aldehydes, α,β-unsaturated aldehydes, acetylenic aldehydes, and ketones gave either low yields, low diastereomeric ratios, or low enantioselectivities.[2] A further limitation of the catalytic process emerged when we attempted to use α,β-unsaturated hydrazones with the chiral sulfide **1**, as only low yields were observed. As unsaturated epoxides[3] and epoxides that contain a basic nitrogen functionality are difficult to prepare by oxidative methods, we were keen to find a solution to this problem. Indeed, a common limitation in catalytic asymmetric synthesis is substrate specificity and one solution to the problem is to devise a stoichiometric process with good recovery of the chirality-transfer agent. An outstanding example is the Evans auxiliary, which, even though it is used in stoichiometric amounts, is widely employed as a result of its broad applicability, reliability, and recyclability. Although enantioselective epoxidations with stoichiometric quantities of sulfide have been described, their scope is limited. Solladié-Cavallo et al. have only described the reaction of Eliel's oxathiane benzyl sulfonium salt with aromatic,[4] heteroaromatic,[5] and α,β-unsaturated aldehydes.[6] Metzner and coworkers have reported moderate to high enantioselectivities in reactions of *trans*-2,5-dimethylthiolane benzyl sulfonium salt with aromatic and heteroaromatic aldehydes[7] and moderate enantioselectivities in related allyl sulfonium salt reactions.[8] Furthermore, it is not possible to access both enantiomers of these sulfides easily, which further limits their practical applications.

Herein we describe a process for the epoxidation of a very broad range of carbonyl compounds, including ketones, in high yields and with high selectivities. Although stoichiometric quantities of sulfide were required, the resulting high

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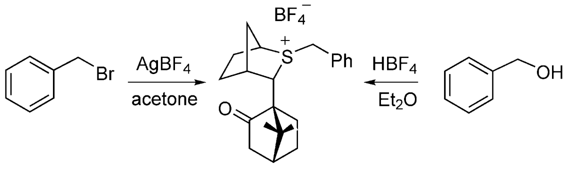
enantioselectivities, diastereoselectivities, and yields, together with the increase in scope, now allow this process to be employed in the synthesis of complex and challenging targets, which is also exemplified herein.

Initial studies were carried out with the benzyl sulfonium salt **2a**. This salt was originally prepared from the sulfide **1**, BnBr, and $AgBF_4$, but we have since found that the reaction of **1** with BnOH in the presence of HBF_4 in Et_2O is also effective. Although the use of ROH/HX has been reported previously for the synthesis of sulfonium salts, a large excess of the sulfide is invariably required.[9] We have found conditions under which the sulfonium salt is formed in high yield in the presence of just 1 equivalent of the sulfide. This process is more economical and gives cleaner products, as the salt simply precipitates from the solution in diethyl ether (Scheme 2).



2a

Scheme 2. Preparation of the chiral sulfonium salt.

Subsequent treatment of the salt with a carbonyl compound and either a phosphazene base[5,10] at low temperature or KOH[11] at room temperature furnished the corresponding epoxides (Table 1). Following an initial reaction with benzaldehyde, in which the corresponding epoxide was produced with very high selectivity (Table 1, entry 1), only substrates that performed poorly in the catalytic reaction were examined. The reactions of pyridine carboxaldehydes (Table 1, entries 2 and 3) gave the desired epoxides in high yields and with high diastereoselectivities and almost perfect ($>99\%$) enantioselectivities under both sets of conditions. A series of unsaturated aldehydes were tested (Table 1, entries 5–7) and although reactions with acrolein proceeded in low yields, the use of methacrolein and crotonaldehyde both led to yields of up to 90%. In all cases the selectivities were exceptionally high. High enantioselectivities were also observed with acetylenic aldehydes (e.g. Table 1, entry 8), although diastereoselectivities were poor. In the cases in which the epoxide was stable to chromatography, the sulfide was recovered in essentially quantitative yield.

Ketones,[12] which have never been employed previously in asymmetric sulfur-ylide-mediated epoxidations, performed remarkably well in this system to furnish epoxides with high enantioselectivities. Cyclohexanone and 4-*tert*-butylcyclohexanone (Table 1, entries 9 and 10) provide dramatic examples of the effectiveness of the epoxidation process. In the latter case the epoxide was obtained as a single diastereomer and a single enantiomer in high yield (Scheme 3). Furthermore, the method was found to be applicable to nonsymmetrical ketones, although in these cases the *cis* diastereomer was formed preferentially (exclusively in the case of *p*-nitroacetophenone) with moderate to high enantioselectivity. The full scope of the reaction with ketones is currently being investigated. These are the first examples of both the desymmetrization of a carbonyl group and the asymmetric synthesis of trisubstituted epoxides with chiral sulfur ylides.

The process was also extended to α,β-unsaturated sulfonium salts, which were prepared either by the reaction of the sulfide with the corresponding alcohol and HBF_4, or by alkylation with the appropriate unsaturated bromide. Although the use of allyl and methallyl sulfonium salts led to moderate yields of the epoxides (perhaps because of competing γ attack), high diastereoselectivities and high enantioselectivities were nevertheless observed. However, with the more substituted substrates **2d** and **2e** high yields were once again observed and the high selectivities maintained. Interestingly, considerably higher diastereoselectivities are observed with α-substituted (d.r. $>99{:}1$) than with α-unsubstituted (d.r. $=91{:}9$) α,β-unsaturated sulfonium salts. Metzner and co-workers made a similar observation.[8] Although α,β-unsaturated sulfonium salts have been employed in epoxidation reactions,[13] it has been reported that [2,3] sigmatropic rearrangements often compete.[14] No such rearrangements were observed in our case, thus indicating that ylide equilibration did not occur.

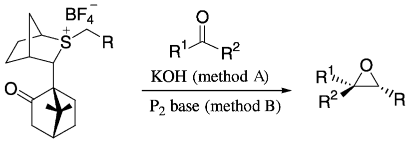
Although in all cases the use of the phosphazene base at low temperature (method B) provided superior results to KOH at room temperature (method A), the fact that high enantioselectivities were also observed under the latter conditions will render this the method of choice for industrial applications in many cases. However, high selectivities could only be obtained by using the phosphazene base at low temperature in some cases (Table 1, entries 4 and 13). As the use of this phosphazene base is undesirable for large-scale operations, a lower cost, lower-molecular-weight base that would perform as effectively was sought. A number of cheap and readily available bases were tested and we discovered that potassium hexamethyldisilazide (KHMDS) was indeed equally effective (method C).

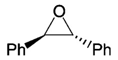
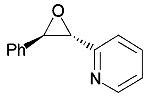
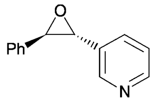
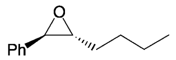
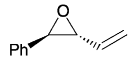
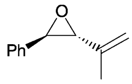
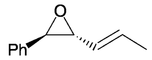
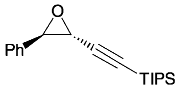
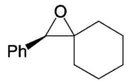
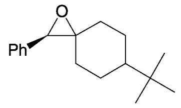
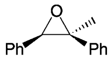
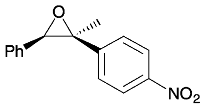
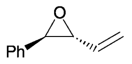
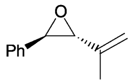
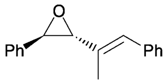
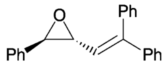
The high yields and selectivities observed, coupled with the recyclable nature of the sulfide, render this process practical for these especially difficult substrates. This feature was demonstrated in a short synthesis of the anti-inflammatory agent CDP-840.[15] We envisaged that CDP-840 could be obtained from the alcohol **3**, which could itself be prepared by a copper-catalyzed regioselective ring opening of the diaryl epoxide **4** with a Grignard reagent (Scheme 4).

As the alcohol was to be removed in the final step, we could tolerate a mixture of *cis* and *trans* epoxides, provided that both were obtained with high enantioselectivity and with the same configuration (*S*) at C3. These requirements led us to consider the coupling of the sulfonium salt **5** with 4-pyridinecarboxaldehyde. The sulfonium salt **5** was prepared by treating the aryl alcohol **6** and *ent*-**1** with HBF_4 in Et_2O. Again, this direct method for sulfonium salt formation was found to be cleaner, higher yielding, and more economical than the standard two-step procedure involving formation of the bromide followed by alkylation in the presence of $AgBF_4$. Subsequent treatment of the salt with the phosphazene base and the aldehyde furnished the epoxide in high yield with

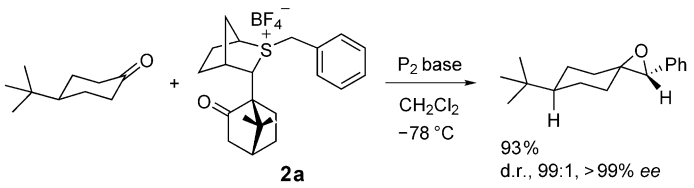
Table 1: Reactions of sulfonium salts with various electrophiles

2a R = Ph
2b R = CHCH$_2$
2c R = C(Me)CH$_2$
2d R = C(Me)CHPh
2e R = CHCPh$_2$

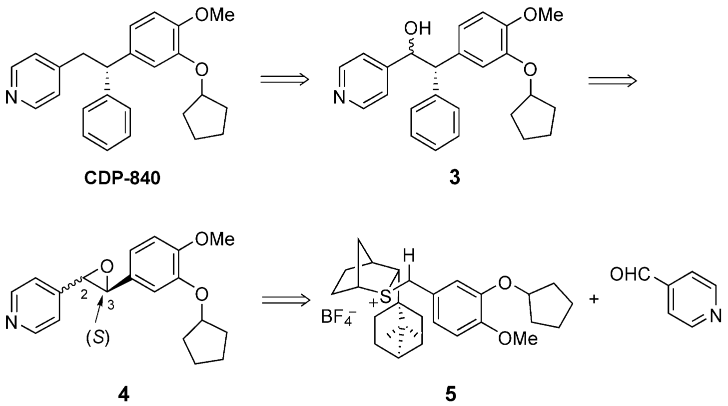


Entry	Salt	Electrophile	Major product	Method[a]	Yield [%][b]	d.r.[c]	*ee*[d]
1	**2a**[e]	benzaldehyde		A	75	98:2	98
2	**2a**	2-pyridine-carboxaldehyde		A B	91 88	91:9 98:2	95 (80[f]) 99
3	**2a**	3-pyridine-carboxaldehyde		A B	74 59	97:3 >99:1	98 >99
4	**2a**	valeraldehyde		A B C	58 64 87	60:40 92:8 90:10	91 97 >99
5	**2a**	acrolein		A B	30[g],[h] 19[g],[h]	90:10 >99:1	97 >99
6	**2a**	methacrolein		A B	51[g] 52[g]	96:4 >99:1	96 99
7	**2a**	crotonaldehyde		A B	72[g] 90[g]	98:2 >99:1	90 95
8	**2a**	TIPS-propargyl aldehyde		A B	50 51	60:40 63:37	95 99
9	**2a**	cyclohexanone		B	85	–	92
10	**2a**	4-*tert*-butyl-cyclohexanone		B	93	99:1	>99
11	**2a**	acetophenone		B	77	33:67	93 (50[f])
12	**2a**	*p*-nitro-acetophenone		B	73	>1:99	71
13	**2b**[e]	benzaldehyde		A B C	33[g] 43[g] 28[g]	71:29 91:9 82:18	84 89 90
14	**2c**[e]	benzaldehyde		A B	37[g] 26[g]	97:3 >99:1	97 97
15	**2d**[i]	benzaldehyde		A B	96[g] 93[g]	96:4 >99:1	90 93
16	**2e**[i],[j]	benzaldehyde		B	69[g]	91:9	90

[a] Method A: carbonyl compound, KOH, MeCN/H$_2$O (9:1), room temperature; method B: P$_2$ base, CH$_2$Cl$_2$, −78 °C, 10 min, followed by addition of the carbonyl compound; method C: KHMDS (0.5 M in toluene), THF, −78 °C, 2 h, followed by addition of the carbonyl compound. [b] Yield of isolated product. [c] *Trans*/*cis*. [d] In all cases the major enantiomer has the *R* configuration at the benzylic position. [e] Prepared from the alkyl bromide followed by counterion exchange. [f] The *ee* value for the *cis* isomer. [g] The yield was determined by ^{1}H NMR spectroscopy against an internal standard (the epoxide is unstable on silica gel). [h] Aldehyde: 5 equiv. [i] Prepared from the alcohol and HBF$_4$. [j] We thank Mamta Patel for carrying out this experiment.



Scheme 3. Desymmetrization of 4-*tert*-butylcyclohexanone. P_2 base = *N*,*N*,*N'*,*N'*-tetramethyl-*N''*-(tris(dimethylamino)phosphoranylidene)phosphoric triamide ethylimine.

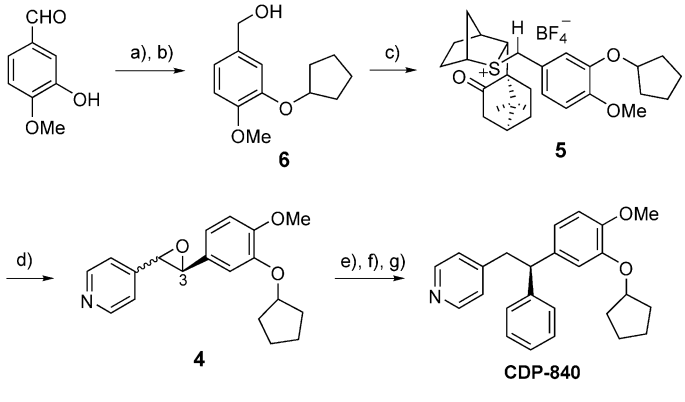


Scheme 4. Retrosynthetic analysis of CDP-840.

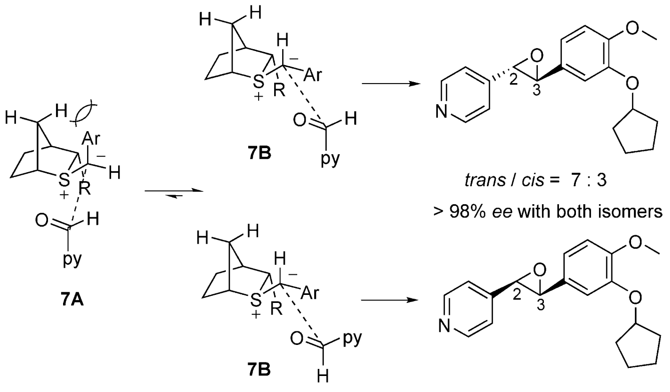
essentially complete control of enantioselectivity (Scheme 5). Furthermore, the sulfide was recovered in quantitative yield.

The diastereoselectivity of the epoxidation was low, but as expected this proved inconsequential for our total synthesis. The origin of the enantioselectivity for both diastereomers is explained in Scheme 6.[16] The reaction of the ylide **7** with 4-pyridinecarboxaldehyde to give the intermediate betaine is not reversible as the ylide is destabilized by the *p*-methoxy substituent. The enantioselectivity is therefore determined by the ylide conformation and its face selectivity.[17] The high enantioselectivity observed is a consequence of ylide conformer **7B** being strongly favored over conformer **7A** owing to 1,4-steric interactions and essentially complete preference for *Si*-face attack, as the *Re* face of the ylide is hindered by the bulky camphor moiety. As the aldehyde can approach in different orientations, both betaine diastereomers and thereby the two epoxide diastereomers are formed. The ylide is less stable than a benzyl-substituted ylide and the betaines are formed non-reversibly, which accounts for the low diastereoselectivity observed. Crucially, the epoxide stereocenter at C3 has the *S* configuration in both isomers. To preserve the integrity of the C3 stereogenic center the method of purification of the epoxide turned out to be critical. Purification on silica gel resulted in some decomposition but also changed the diastereomeric ratio from 7:3 to 9:1. Furthermore, the enantiomeric excess of the purified *trans* epoxide was much lower. Presumably silica-gel-promoted ring opening at C3 of the acid-sensitive *cis* epoxide, and following bond rotation and ring closure the *trans* epoxide was obtained with the opposite stereochemistry at C3, thus eroding the enantiomeric excess. However, purification on basic alumina gave the epoxide in high yield and high enantioselectivity, and in the same diastereomeric ratio as observed in the crude reaction mixture, thus indicating that no equilibration had occurred. Ring opening of the epoxide with PhMgBr occurred with complete regioselectivity and with clean inversion of stereochemistry at C3. Finally, removal of the hydroxy group furnished CDP-840 in enantiomerically pure form. Comparison of the optical rotation of our sample of CDP-840 with the literature value[18] not only confirmed its absolute configuration but also lent further weight to our model for the source of the enantioselectivity.

In summary, we have described the highly enantio- and diastereoselective reaction of aldehydes and ketones with chiral sulfonium ylides to generate di- and trisubstituted epoxides. The scope of the epoxidation reaction was further



Scheme 5. Synthesis of CDP-840. Reagents and conditions: a) K_2CO_3, cyclopentyl bromide, DMF, 60 °C, 12 h, 97%; b) $NaBH_4$, MeOH, room temperature, 1 h, 99%; c) *ent*-**1**, HBF_4, Et_2O, room temperature, 4 h, 80%; d) P_2 base, CH_2Cl_2, −78 °C, 15 min, then 4-pyridinecarboxaldehyde, −78 °C, 1 h, 89% (*trans*/*cis* = 7:3), > 98% *ee*; e) PhMgBr (2.5 equiv), CuI (0.25 equiv), THF, −40 °C, 15 h, 85%; f) Et_3N, MsCl, CH_2Cl_2, 0 °C, 30 min; g) Zn, AcOH, room temperature, 5 h, 80% (2 steps). DMF = *N*,*N*-dimethylformamide; Ms = methanesulfonyl.



Scheme 6. The origin of the enantioselectivity. py = pyridyl.

demonstrated by its application to the synthesis of a target compound (CDP-840) with significant functionality.

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[16] This model also applies to the substrates shown in Table 1.

[17] For a full discussion of factors that govern the enantioselectivity, see V. K. Aggarwal, J. Richardson, *Chem. Commun.* **2003**, in press.

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