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A New Protocol for the In Situ Generation of Aromatic, Heteroaromatic, and Unsaturated Diazo Compounds and Its Application in Catalytic and Asymmetric Epoxidation of Carbonyl Compounds. Extensive Studies To Map Out Scope and Limitations, and Rationalization of Diastereo- and Enantioselectivities

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Abstract: A variety of metalated tosylhydrazone salts derived from benzaldehyde have been prepared and were reacted with benzaldehyde in the presence of tetrahydrothiophene (THT) (20 mol %) and $Rh_2(OAc)_4$ (1 mol %) to give stilbene oxide. Of the lithium, sodium, and potassium salts tested, the sodium salt was found to give the highest yield and selectivity. This study was extended to a wide variety of aromatic, heteroaromatic, aliphatic, α,β-unsaturated, and acetylenic aldehydes and to ketones. On the whole, high yields of epoxides with moderate to very high diastereoselectivities were observed. A broad range of tosylhydrazone salts derived from aromatic, heteroaromatic, and α,β-unsaturated aldehydes was also examined using the same protocol in reactions with benzaldehyde, and again, good yields and high diastereoselectivities were observed in most cases. Thus, a general process for the in situ generation of diazo compounds from tosylhydrazone sodium salts has been established and applied in sulfur-ylide mediated epoxidation reactions. The chiral, camphor-derived, [2.2.1] bicyclic sulfide **7** was employed (at 5−20 mol % loading) to render the above processes asymmetric with a range of carbonyl compounds and tosylhydrazone sodium salts. Benzaldehyde tosylhydrazone sodium salt gave enantioselectivities of 91 ± 3% ee and high levels of diastereoselectivity with a range of aldehydes. However, tosylhydrazone salts derived from a range of carbonyl compounds gave more variable selectivities. Although those salts derived from electron-rich or neutral aldehydes gave high enantioselectivities, those derived from electron-deficient or hindered aromatic aldehydes gave somewhat reduced enantioselectivities. Using α,β-unsaturated hydrazones, chiral sulfide **7** gave epoxides with high diastereoselectivities, but only moderate yields were achieved (12−56%) with varying degrees of enantioselectivity. A study of solvent effects showed that, while the impact on enantioselectivity was small, the efficiency of diazo compound generation was influenced, and CH_3CN and 1,4-dioxane emerged as the optimum solvents. A general rationalization of the factors that influence both relative and absolute stereochemistry for all of the different substrates is provided. Reversibility in formation of the betaine intermediate is an important issue in the control of diastereoselectivity. Hence, where low diastereocontrol was observed, the results have been rationalized in terms of the factors that contribute to the reduced reversion of the syn betaine back to the original starting materials. The enantioselectivity is governed by ylide conformation, facial selectivity in the ylide reaction, and, again, the degree of reversibility in betaine formation. From experimental evidence and calculations, it has been shown that sulfide **7** gives almost complete control of facial selectivity, and, hence, it is the ylide conformation and degree of reversibility that are responsible for the enantioselectivity observed. A simple test has been developed to ascertain whether the reduced enantioselectivity observed in particular cases is due to poor control in ylide conformation or due to partial reversibility in the formation of the betaine.

Introduction

The reaction of sulfur ylides with carbonyl compounds to give epoxides[1] provides a complementary method to oxidation of alkenes[2] for the preparation of these valuable synthetic intermediates. Although sulfur ylide reactions have traditionally operated with stoichiometric amounts of sulfonium salts, we have recently reported a catalytic and asymmetric process for carbonyl epoxidation that operated under neutral conditions and employed substoichiometric amounts of a sulfide and metal catalyst (Scheme 1).[3] To achieve good yields, slow addition of the diazo compound was required to avoid reaction of the metal carbene with the diazo compound, which, in this case, would furnish stilbenes.

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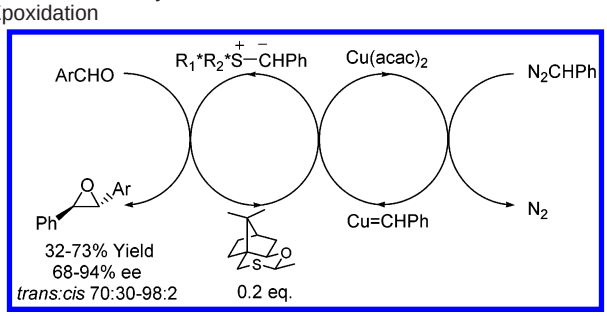
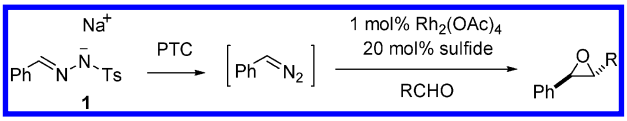
Scheme 1. Catalytic Process for Sulfur Ylide Mediated Epoxidation



However, a limitation of this methodology was the need to synthesize and handle diazo compounds, which, because they are invariably toxic and unstable,[4] limited the practicality of the process. We therefore considered the possibility of generating the diazo compound in situ[5] and coupling this reaction to our established epoxidation process (Scheme 2).

Scheme 2. In Situ Generation of Diazo Compounds and Subsequent Use in Epoxidation



Diazo compounds can be generated from their corresponding tosylhydrazone salts, for example, **1**, by photolysis,[6] vacuum pyrolysis,[7] thermolysis of a suspension in a suitable solvent,[8] or thermolysis in a biphasic medium (organic/aqueous) in the presence of a phase transfer catalyst (PTC).[9] Although none of these conditions could be coupled to our established epoxidation process, we discovered that a combination of certain elements from the latter two processes was ultimately successful. Specifically, warming a suspension of the tosylhydrazone salt **1** in the presence of a PTC (to aid passage from the solid to liquid phase) allowed generation of the diazo compound at moderate temperature, and this process was compatible with our established epoxidation procedure.[10] Furthermore, the necessity for slow addition of the diazo compound, which had previously required syringe pumps, now needed nothing more sophisticated than a thermostat: to generate the diazo compound very slowly, reactions were performed at 30 °C and required 2 days to reach completion, while generation could be carried more rapidly at 40 °C over a shorter period of time (between 3 and 24 h). An additional advantage of this in situ process is that it is much more efficient than the ex situ process: less diazo precursor is required, and higher yields and higher trans selectivities were obtained. Indeed, considering the number of steps and the potential for unwanted side reactions in the cascade process,[11] the efficiency is remarkable. This improvement in efficiency is a consequence of adding the diazo compound a molecule at a time instead of a drop at a time and results in even lower concentrations of the diazo compound. Thus, the previously dominant side reaction between the metal carbene and diazo compound to furnish stilbenes is minimized.

In this paper, we describe our extensive studies to map out the scope and limitations of the process. We were interested in determining which classes of carbonyl compounds and which classes of diazo precursors could be employed for the preparation of epoxides. Having established this, we were then keen to determine which coupling partners could be used with chiral sulfides for asymmetric epoxidation. Furthermore, determining the scope of the diazo precursors for epoxidation has considerably greater ramifications because we have shown that the in situ generation of diazo compounds can also be applied to other reactions: aziridination of imines,[12a] cyclopropanation of both electron-deficient[12a] and electron-rich alkenes,[12b] [3+2] cycloadditions with alkenes and alkynes to give pyrazoles,[13] Wittig reactions,[14] and aldehyde homologation.[15] Thus, diazo precursors that can be employed in epoxidation reactions are also likely to succeed in these other processes.

Results and Discussion

Effect of the Counterion and Metal Catalyst. Initial investigations centered around the nature of the counterion of the tosylhydrazone salt and the metal catalyst (Table 1). This study showed that all counterions could be employed, although the diastereoselectivity was significantly lower with lithium (factors influencing diastereoselectivity are discussed later). Rhodium acetate was found to be more efficient than copper acetylacetonate, and so the combination of rhodium acetate and a sodium counterion was employed in subsequent studies.

Reaction of Benzaldehyde-Derived Tosylhydrazone Salt with a Variety of Carbonyl Compounds. The reaction of

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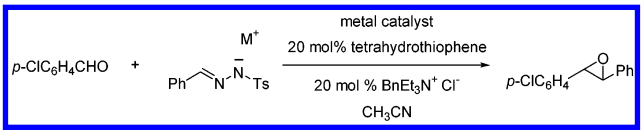
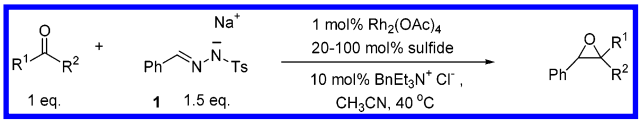
Table 1. Effect of Counterion on the Epoxidation Process



entry	metal catalyst (mol %)	*T*/°C	M^+	yield/%[a]	trans:cis
1	$Cu(acac)_2$ (5)	40	Na	73	>98:2
2	$Cu(acac)_2$ (5)	40	Li	54	74:26
3	$Cu(acac)_2$ (5)	40	K	62	>98:2
4	$Cu(acac)_2$ (5)	40	NBu_4	57[b]	>98:2
5	$Rh_2(OAc)_4$ (1)	40	Na	86	>98:2
6	$Rh_2(OAc)_4$ (1)	40	NBu_4	55[b]	>98:2

[a] Isolated yield of epoxide. [b] No PTC was used.

Table 2. Yields and Diastereomeric Ratios of Epoxides Formed from Carbonyl Compounds and Tosylhydrazone Salt **1** Using Tetrahydrothiophene or Pentamethylene Sulfide



entry	carbonyl compound	sulfide[a]/ mol %	*t*/h	yield/%[b]	trans:cis
1	benzaldehyde	THT/20	24	95	>98:2
2	*p*-nitrobenzaldehyde	THT/20	24	94	>98:2
3	*p*-chlorobenzaldehyde	THT/20	24	86	>98:2
4	*p*-methylbenzaldehyde	THT/20	24	97	>98:2
5	*p*-methoxybenzaldehyde	THT/20	24	98	>98:2
6	mesitaldehyde	THT/20	24	87	>98:2
7	2-thiophenecarboxaldehyde	THT/20	24	90[c]	>98:2
8	2-furaldehyde	THT/20	24	80[c]	>98:2
9	3-furaldehyde	THT/20	24	85	90:10
10	2-pyridinecarboxaldehyde	THT/20	24	62	87:13
11	3-pyridinecarboxaldehyde	THT/20	24	71	>98:2
12	4-pyridinecarboxaldehyde	THT/20	24	33[d]	>98:2
13	*N*-Ts-indole-3-carboxaldehyde	THT/20	24	50	>98:2
14	valeraldehyde	THT/20	24	53	70:30
15	phenylacetaldehyde	THT/20	24	60	>98:2
16	cyclopropanecarboxaldehyde	THT/20	24	69	94:6
17	cyclohexanecarboxaldehyde	THT/20	24	70	65:35
18	pivaldehyde	THT/100	24	49 (10[e])	>98:2
19	acrolein	THT/100	24	0	
20	methacrolein	THT/100	24	39[c](16[c,e])	>98:2
21	crotonaldehyde	THT/20	24	33[c]	>98:2
22	3-trimethylsilylacrolein	THT/100	24	55 (30[e])	>98:2
23	3-methyl-2-butenal	THT/100	24	73[c](39[c,e])	>98:2
24	*trans*-cinnamaldehyde	THT/20	24	97[c]	>98:2
25	triisopropylsilylpropargyl-aldehyde	THT/20	24	60	50:50
26	formaldehyde	THT/13	42	25[f]	NA
27	cyclohexanone	THT/20	24	32	NA
28	acetophenone	THT/20	24	15	<2:98
29	*p*-nitroacetophenone	THT/20	24	traces	
30	cyclohexanone	PMS/20	24	54	NA
31	acetophenone	PMS/20	24	15	<2:98
32	*p*-nitroacetophenone	PMS/20	24	69	<2:98

[a] THT = tetrahydrothiophene, PMS = pentamethylene sulfide. [b] Isolated yield of product. [c] Crude yield determined by ^1H NMR spectroscopy with an internal standard (epoxide is unstable on silica gel and alumina). [d] Using phenyldiazomethane instead of hydrazone salt gave >90% yield epoxide. [e] Yields obtained using 20 mol % THT. [f] One equivalent of tosylhydrazone salt was used with 1.03 equivalents of CH_2O, 13 mol % THT, 13 mol % PTC, and 0.7 mol % $Rh_2(OAc)_4$.

benzaldehyde-derived tosylhydrazone sodium salt **1** was then studied with a broad range of carbonyl compounds (Table 2). Simple aromatic aldehydes (electron-rich/neutral/poor, entries 1−6), including the hindered aromatic aldehyde, mesitaldehyde (entry 6), all worked well, furnishing the epoxides in high yields and high diastereoselectivities. Heteroaromatic (furyl, thiophenyl, pyridyl, and indolyl) aldehydes were also examined, and moderate to good yields were obtained with variable diastereoselectivities (entries 7−13). Although 4-pyridinecarboxaldehyde gave a low yield of epoxide when the tosylhydrazone salt was employed, the yield was >90% when phenyl diazomethane was used, indicating that the ylide reaction was highly efficient. We do not have an explanation for the low yield, and further optimization was not carried out. A broad range of aliphatic aldehydes was tested with primary, secondary, and tertiary substitution α- to the carbonyl, and they were all found to be effective, although, to obtain reasonable yields in the case of the hindered substrate pivaldehyde, a stoichiometric amount of sulfide was required. However, the yields for the aliphatic aldehydes were lower than with aromatic aldehydes, and diastereoselectivities were more variable (entries 14−18). A noteworthy example is phenylacetaldehyde (entry 15), which is especially prone to enolization. Its success (60% yield and 98:2 diastereoselectivity) indicates that the intermediate ylide is more nucleophilic than it is basic toward this substrate.

Until recent work by Shi et al.,[16] unsaturated epoxides had been difficult to prepare in a regiocontrolled manner by oxidation of a diene, so α,β-unsaturated aldehydes were also examined as possible substrates because our method is inherently regiospecific. Although acrolein was unsuccessful (entry 19) and methacrolein and crotonaldehyde were low yielding (entries 20 and 21), other β-substituted unsaturated aldehydes worked more effectively (entries 22−24). Acrolein bearing the readily cleavable TMS substituent in the 3-position (entry 22) was a good substrate, thus allowing acrolein-derived epoxides to be synthesized. The yields obtained with unsaturated aldehydes were more sensitive to the amount of sulfide employed, and, except for the cases of crotonaldehyde and cinnamaldehyde (entries 21 and 24), higher yields were obtained with 1 equiv of sulfide.

Acetylenic aldehydes could also be used, although TIPS- rather than TMS-substituted propargyl aldehyde was required (entry 25). The latter substrate rapidly decomposed under the reaction conditions, and no epoxide was observed.

Paraformaldehyde gave only traces of styrene oxide. However, a low yield of the desired product was obtained when a freshly prepared solution of monomeric formaldehyde was used (entry 26). Attempts to increase the yield by employing greater amounts of aldehyde were unsuccessful.

The application of ketones as the carbonyl coupling partner to afford trisubstituted epoxides was less successful (entries 27−29). These reactions furnished a substantial amount of the byproduct 2-tolyltetrahydrothiophene **2**, which was presumably formed by Sommelet−Hauser rearrangement[17] of ylide **3** (Scheme 3). We assume that the slower reacting ketones provide time for ylide equilibration and rearrangement to occur. Similar rearrangement products were observed in reactions with other, less electrophilic substrates, for example, reaction with pivaldehyde (entry 18) and cyclopropanation with α,β-unsaturated

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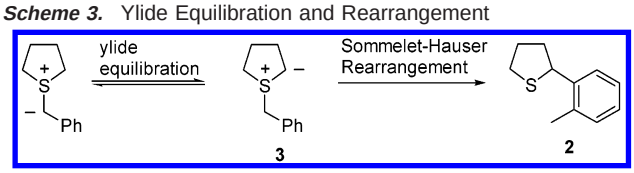
Scheme 3. Ylide Equilibration and Rearrangement



carbonyl compounds.[18] In an effort to reduce the extent of this side reaction, we sought sulfides that had a lower propensity for ylide equilibration and were guided by Fava's studies on the rate of deuterium exchange of the α-protons of cyclic sulfonium salts.[19] He showed that the rate of exchange of the α-protons in a five-membered ring was an order of magnitude faster than that for the corresponding six-membered ring. Therefore, we replaced tetrahydrothiophene with pentamethylene sulfide (PMS) and observed a significant increase in yield of ketone-derived epoxides ranging from 15% to 69% (entries 30−32).

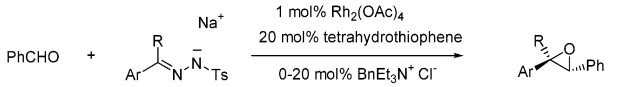
Reaction of a Variety of Aromatic, Heteroaromatic, and Ketone-Derived Hydrazone Salts with Benzaldehyde. Having established the scope of the carbonyl compounds that could be employed, we sought to determine the range of hydrazone salts which might be effective in epoxidation. These salts were readily prepared from the corresponding tosylhydrazone by deprotonation with sodium methoxide, and most were found to be stable and suitable for prolonged storage (see Supporting Information for tables on hydrazones and hydrazone salt formation, including comments on synthesis and stability).

In optimizing the different tosylhydrazone salts, we varied the amount of PTC (0−20%), temperature (30−40 °C), and solvent as each of these variables affects the rate and efficiency of diazo formation. Although only the optimum solvent is shown in Table 3, other solvents have been examined, and the results are presented in the Supporting Information.

We found that the reproducibility of the reaction depended on the quality of the tosylhydrazone salt employed. Provided the tosylhydrazone salt had been prepared from the corresponding tosylhydrazone with 1.03−1.08 equiv of base, and the salt was devoid of methanol, good yields in the epoxidation process were achieved. The salts could easily be titrated against acid to determine the excess base content, and, in general, those that required between 1 and 1.1 equiv of acid to reach the end point were superior to those that required greater amounts of acid (see Supporting Information).

When the salt was prepared correctly, good yields were generally obtained with both electron-rich (entries 1−6) and electron-deficient (entries 7−13) aryldiazo precursors. The tosylhydrazone salt derived from mesitaldehyde gave a very low yield of epoxide (entry 3), indicating that 2,6-di-*ortho*-substituted aryldiazo precursors were not suitable substrates. The *p*-methoxy derivative (entry 5) provides a notable example of the ease and simplicity of the current method, as its use in our process was uneventful and high yielding. In contrast, it has been reported that the corresponding diazo compound decomposes even at −80 °C and can detonate when isolated.[20] We would, therefore, never have contemplated handling this diazo compound, but no problems were encountered with the diazo precursor. Electron-deficient aryldiazo precursors furnished the corresponding diazo compounds more readily, and, as such, lower temperatures could

Table 3. Yields and Diastereomeric Ratios of Epoxides Formed from Benzaldehyde and Substituted Tosylhydrazone Salts, Using 0.2 equiv of Tetrahydrothiophene



entry	Ar	R	solvent	*T*/°C	PTC/%	yield/%[a]	trans:cis
1	*p*-MeC_6H_4	H	CH_3CN	40	5	87	87:13
2	*o*-MeC_6H_4	H	$CF_3C_6H_5$	40	5	84	>98:2
3	2,4,6-$Me_3C_6H_2$	H	CH_3CN	40	20	17	>98:2
4	*m*-TBSOC_6H_4	H	CH_3CN	30	5	77	>98:2
5	*p*-$MeOC_6H_4$	H	CH_3CN	40	10	73	71:29
6	*o*-$MeOC_6H_4$	H	$CF_3C_6H_5$	40	5	92	>98:2
7	*p*-ClC_6H_4	H	CH_3CN	40	20	95	>98:2
8	*p*-FC_6H_4	H	toluene	30	10	0−96[b]	>98:2
9	*o*-FC_6H_4	H	1,4-dioxane	30	5	86	>98:2
10	*p*-$NO_2C_6H_4$	H	unstable product				
11	*m*-$NO_2C_6H_4$	H	CH_3CN	40	20	74	>98:2
12	*p*-CNC_6H_4	H	1,4-dioxane	40	0	90	>98:2
13	*p*-$CO_2MeC_6H_4$	H	CH_3CN	30	0	81	>98:2
14	2-furyl	H	$CF_3C_6H_5$	40	5	96[c]	80:20
15	3-furyl	H	CH_3CN	40	5	52	58:42
16	3-pyridyl	H	1,4-dioxane	40	10	51[d]	>98:2
17	C_6H_5	Me	1,4-dioxane	30	20	74[e]	>98:2

[a] Isolated yield of product. [b] Capricious substrate (see text). [c] Crude yield determined by ^1H NMR spectroscopy with an internal standard (epoxide is unstable on silica gel and alumina). [d] 100 mol % THT is used. [e] In situ salt formation from 2,4,6-triisopropylbenzenesulfonyl hydrazone using NaHMDS as the base (HMDS = 1,1,1,3,3,3-hexamethyldisilazane).

be employed. Although good yields were obtained with most of these substrates, the *p*-fluoro compound was found to be capricious, giving highly variable yields of epoxide from the same batch of starting materials (entry 8). In contrast, the *o*-fluoro isomer performed well and consistently in the epoxidation process (entry 9). The *p*-nitrobenzaldehyde tosylhydrazone sodium salt was unstable and decomposed immediately upon formation, giving a deep red solution (entry 10). In contrast, the *m*-nitro derivative was a stable salt and afforded the epoxide in high yield (entry 11). Heteroaromatic diazo precursors could also be employed, and moderate to good yields were achieved with 2-furyl, 3-furyl, and 3-pyridyl substrates (entries 14−16). Both the 2-furyl- and the 3-furyl-derived diazomethanes are reportedly unstable and decompose readily on isolation.[21] However, with our "user-friendly" in situ protocol for generating the diazo compound, smooth epoxidation reactions ensued in moderate to high yield. The epoxide derived from the 2-furaldehyde tosylhydrazone salt was especially sensitive, and so a crude yield based on NMR with an internal standard is provided. The 3-pyridyl tosylhydrazone salt required a stoichiometric amount of tetrahydrothiophene to achieve reasonable yields (entry 16, 51% yield as compared to a 33% yield obtained when 20 mol % sulfide was used). The pyridine nitrogen can potentially compete with the sulfide to form a nonproductive ylide, and it appears that this process can only be overcome at high sulfide concentrations. The 2-pyridyl tosylhydrazone salt failed to give any epoxide: [1,2,3]-triazolo-[1,5-α]pyridine was isolated instead, and this was presumably formed from cyclization of the diazo intermediate or from the tosylhydrazone salt itself.[22]

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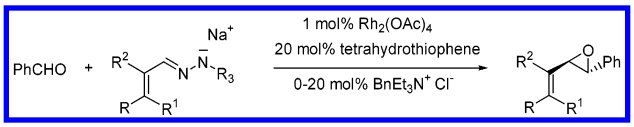
Table 4. Yields and Diastereomeric Ratios of Epoxides Formed from Benzaldehyde and Substituted Unsaturated Sulfonyl Hydrazones Using 20 mol % Tetrahydrothiophene



entry	R	R^1	R^2	R^3	solvent	*T*/°C	PTC/%	yield/%[a]	trans:cis
1	H	H	H	Ts	$CF_3C_6H_5$	40	10	20[b]	65:35
2	H	H	H	2,4,6-^{i}Pr$_3$C$_6$H$_2$ SO$_2$	toluene	20	10	40[c,d]	58:42
3	H	H	Me	Ts	$CF_3C_6H_5$	40	10	46[b]	96:4
4	H	H	Me	2,4,6-^{i}Pr$_3$C$_6$H$_2$ SO$_2$	1,4-dioxane	40	10	51[d](60)[e]	82:18
5	Me	H	H	Ts	1,4-dioxane	40	10	30[b,e]	50:50
6	Me	H	H	2,4,6-^{i}Pr$_3$C$_6$H$_2$ SO$_2$	1,4-dioxane	20	5	37[c,d](45)[e]	50:50
7	Me	H	H	*p*-$NO_2C_6H_4SO_2$	THF	40	20	59[c,e]	50:50
8	Ph	H	H	Ts	1,4-dioxane	40	10	69[d](88)[e]	58:42
9	$SiMe_3$	H	H	Ts	1,4-dioxane	40	10	88[f]	62:38
10	Ph	H	Me	Ts	1,4-dioxane	30	10	76[g]	>98:2
11	Me	Me	H	Ts	$CF_3C_6H_5$	40	5	24[e]	58:42
12	Me	Me	H	2,4,6-^{i}Pr$_3$C$_6$H$_2$ SO$_2$	1,4-dioxane	20	0	70[c,e]	50:50
13	Ph	Ph	H	Ts	toluene	40	5	71[d](98)[e]	67:33

[a] Isolated yield of product. [b] 100 mol % THT was used. [c] In situ salt formation from 2,4,6-triisopropylbenzenesulfonyl hydrazone using NaHMDS (HMDS = 1,1,1,3,3,3-hexamethyldisilazane) as the base. [d] Epoxide was purified on basic Al_2O_3 (grade 5). [e] Crude yield determined by ^{1}H NMR spectroscopy with an internal standard (epoxide is unstable to silica gel and alumina). [f] In situ salt formation from the corresponding hydrazone using LiHMDS as the base. [g] Epoxide was purified on basic Al_2O_3 (grade 2).

We were also able to achieve epoxidation from a ketone-derived hydrazone salt, although this required the employment of the 2,4,6-triisopropylbenzenesulfonylhydrazone[23] (entry 17): the corresponding tosylhydrazone gave only 15% of the desired epoxide. The hydrazone salt of this more hindered sulfonylhydrazone cannot be isolated as it decomposes much more readily to the diazo compound. Indeed, whenever the triisopropylsulfonyl or *p*-nitroarylsulfonyl salts (vide infra) were used, the salts were always generated and used in situ. Although good yields were usually achieved for the acetophenone-derived hydrazone salt, we found that this substrate was somewhat capricious.

Reaction of α,β-Unsaturated Hydrazone Salts with Benzaldehyde. Unsaturated diazo precursors could also be employed, although yields and diastereoselectivities showed considerable structure-dependent variation (Table 4). The use of unsaturated sulfonium salts to give α,β-unsaturated epoxides is well established,[24] although, in some cases, ylide equilibration and subsequent [2,3] sigmatropic rearrangement compete with epoxidation.[25] Several of the α,β-unsaturated precursors led to hydrolytically sensitive epoxides, and crude NMR yields were significantly higher than isolated yields (entries 5, 7, 11, and 12). However, decomposition during purification could be limited by using basic alumina (see Supporting Information for preparation), instead of silica gel, for chromatography.

The acrolein-derived tosylhydrazone salt gave a low yield and low diastereoselectivity of the unsaturated epoxides, but the yield could be improved using the triisopropylbenzenesulfonylhydrazone salt (entries 1 and 2). The methacrolein-derived substrate gave a moderate yield of epoxide but high diastereoselectivity (entry 3). A slightly higher yield was obtained with the triisopropylbenzenesulfonylhydrazone (entry 4), but lower diastereoselectivity was observed in this case. Substitution at the β-position gave improved yields of epoxide when a phenyl or trimethylsilyl group was present (entries 5−9). When a trimethylsilyl group was present in the β-position (entry 9), LiHMDS was used as the base as there were solubility problems when either NaHMDS or KHMDS were used. The crotonaldehyde derivative gave low yields with both the tosylhydrazone and the triisopropylbenzenesulfonylhydrazone (entries 5 and 6), but a significant improvement in yield (entry 7, 59%) was achieved using the *p*-nitrobenzenesulfonylhydrazone derivative.

The combination of both an α- and a β-substituent was particularly effective, giving both high yield and high diastereoselectivity (entry 10). Two β-substituents could also be employed, and, again, moderate to good yields were achieved (entries 11−13).

Unsaturated diazo compounds are known to cyclize rapidly to give pyrazoles. In fact, this unimolecular cycloaddition reaction is extremely fast with rate constants ranging from 4−78 $\times 10^5$ s^{-1} depending on substitution.[26] Although pyrazoles were indeed observed as byproducts in many of the above cases, the small amount isolated indicates that decomposition of the tosylhydrazone salt and metal carbene formation are even faster. Of course, in our case, both the diazo compound and the hydrazone salt itself can cyclize to give the same pyrazole.[27]

Application of Chiral Sulfide 7 to Asymmetric Epoxidation. Having established the scope and limitations of epoxidation using tetrahydrothiophene, we sought to render the process asymmetric using chiral sulfide **7** (Figure 1). From our previous studies using a broad range of chiral sulfides,[28] conformationally locked sulfide **7** was found to be optimal as it gave high yield, high enantioselectivity, and high diastereoselectivity in the formation of stilbene oxide.[10a] Furthermore, it was completely stable to the reaction conditions and could be reisolated in essentially quantitative yield. Details of the synthesis of sulfide

(22) Wentrop, C. *Tetrahedron* **1974**, *30*, 1301.
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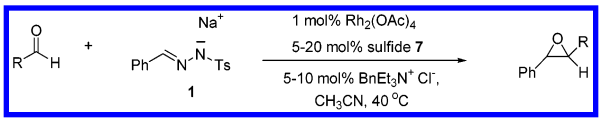
(26) Brewbaker, J. L.; Hart, H. *J. Am. Chem. Soc.* **1969**, *91*, 711.

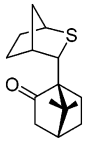
Table 5. Yields, Enantioselectivities, and Diastereoselectivities of Epoxides Formed from Aldehydes and Tosylhydrazone Salt **1** Using 5−20 mol % Sulfide **7**



entry	aldehyde	sulfide/mol %	*t*/h	PTC/%	yield/%[a]	trans:cis	ee/%[b,c] trans (cis)
1	benzaldehyde	5	48	5	82	>98:2	94
2	*p*-nitrobenzaldehyde	5	48	5	75	>98:2	92
3	*p*-chlorobenzaldehyde	5	48	5	80	>98:2	91
4	*p*-methylbenzaldehyde	5	48	5	84	>98:2	90
5	*p*-methoxybenzaldehyde	5	48	5	68	>98:2	92
6	mesitaldehyde	5	48	5	55	>98:2	94
7	2-thiophenecarboxaldehyde	20	48	10	100[d]	>98:2	93[f]
8	2-furaldehyde	5	48	5	60[d]	>98:2	91[f]
9	3-furaldehyde	5	48	5	77	>98:2	92
10	*N*-Ts-indole-3-carboxaldehyde	20	24	10	30[d]	>98:2	89
11	valeraldehyde	20	48	10	46	75:25	89
12	cyclopropanecarboxaldehyde	20	24	10	50	>98:2	94
13	cyclohexanecarboxaldehyde	5	48	5	58	88:12	90 (74)
14	3-methyl-2-butenal	20	24	10	21[e]	>98:2	87
15	3-trimethylsilylacrolein	20	24	10	35	>98:2	88
16	*trans*-cinnamaldehyde	5	48	5	70[d]	>98:2	87

[a] Isolated yield of product. [b] Determined by chiral HPLC. [c] The absolute configuration of the major enantiomer is 1*R*,2*R*. This has been proven in many cases by comparison of either retention times on chiral HPLC columns, or optical rotations, with literature values. The remaining few are assumed by analogy (see Supporting Information). [d] Crude yield determined by ^{1}H NMR spectroscopy with an internal standard (epoxide is unstable on silica gel and alumina). [e] Epoxide was purified on basic Al_2O_3 (grade 5). [f] The absolute configuration of the major enantiomer is 1*R*,2*S*. This has been proven by comparison of chiral HPLC retention times with literature values.

7 have been previously reported[10a] and are reproduced in the Supporting Information.



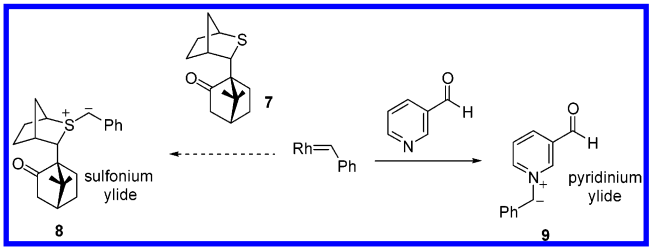
7

Figure 1. Optimum chiral sulfide for catalytic epoxidation procedure.

Asymmetric Epoxidation of a Range of Aldehydes with Benzyl Tosylhydrazone Salts. The reactions were performed using 5 mol % chiral sulfide **7**, except in the cases where the yields using tetrahydrothiophene were low, in which case 20 mol % chiral sulfide was employed (Table 5). We found that aromatic aldehydes furnished epoxides in high yield with high diastereoselectivity and enantioselectivity (entries 1−6). Mesitaldehyde gave a moderate yield of epoxide, presumably because of its steric hindrance. Heteroaromatic aldehydes worked well (entries 7−10), affording moderate to good yields of epoxides with high diastereo- and enantioselectivities. Interestingly, the sulfur atom of thiophenecarboxaldehyde did not compete with sulfide **7** in ylide formation; high yield and enantioselectivity was also observed for this substrate.

Epoxides were also prepared in good yields and high selectivities when 2- and 3-furaldehydes were employed as substrates (entries 8 and 9). However, in contrast to our studies with tetrahydrothiophene, epoxide formation was not observed when 2- and 3-pyridinecarboxaldehydes were used with sulfide **7**. We believe that formation of the sulfonium ylide **8** competes with the formation of the pyridinium ylide **9**, and the latter reaction dominates because of the higher nucleophilicity of the pyridine nitrogen as compared to that of the hindered sulfide **7**, which is present in the reaction mixture in smaller amounts (Scheme 4). The nonbasic, heteroaromatic, *N*-Ts-indolecarboxaldehyde (entry 10) was an effective substrate, although, in this case, the sensitive epoxide was obtained in rather low yield.

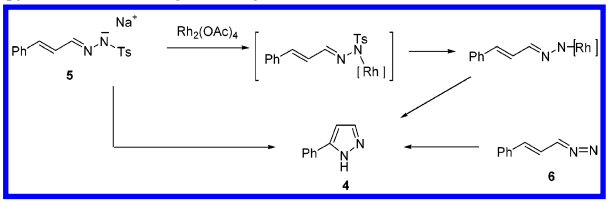
Scheme 4. Competitive Interception of Metal Carbenoid by Pyridyl Substrates



Aliphatic aldehydes gave moderate yields (entries 11−13), moderate to good diastereoselectivities, and high enantioselectivities. Hindered aliphatic aldehydes, for example, pivaldehyde, did not afford any epoxide but gave a range of decomposition products instead. Phenylacetaldehyde, which performed well with tetrahydrothiophene, afforded no epoxide when chiral sulfide **7** was employed perhaps because the more hindered ylide was now less nucleophilic and acted as a base instead.

A limited number of α,β-unsaturated aldehydes could also be employed: cinnamaldehyde was an excellent substrate (entry

(27) Doyle, M. P.; Yan, M. *J. Org. Chem.* **2002**, *67*, 602. Doyle has observed formation of pyrazole **4** during reaction of the tosylhydrazone salt **5** with $Rh_2(OAc)_4$ and proposed rhodium coordination to explain the fact that pyrazole formation is faster in this route as compared to cyclization of the corresponding diazo compound **6**. It is, however, also possible that the pyrazole is formed by direct cyclization of salt **5**.



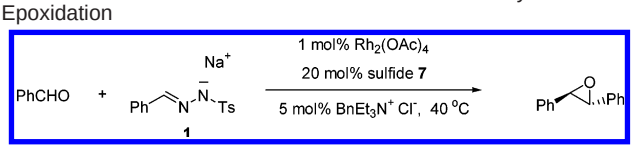
(28) Aggarwal, V. K.; Angelaud, R.; Bihan, D.; Blackburn, P.; Fieldhouse, R.; Fonquerna, S. J.; Ford, G. D.; Hynd, G.; Jones, E.; Jones, R. V. H.; Jubault, P.; Palmer, M. J.; Ratcliffe, P. D.; Adams, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2604.

16), but the other substrates were low yielding (entries 14 and 15), and crotonaldehyde did not furnish any epoxide. We are currently investigating the origin of the low yields with the alkyl substituted α,β-unsaturated aldehydes. Nevertheless, the enantioselectivities in all cases were excellent.

When the epoxidation of benzaldehyde using chiral sulfide **7** was performed on a 50 mmol scale, a similar yield (78%) and enantioselectivity (92% ee) were obtained (compare to result obtained on a 0.33 mmol scale in Table 5, entry 1). On this scale, it was found that further reductions in catalyst loading were possible: $Rh_2(OAc)_4$ was reduced from 1.0 to 0.5 mol %, and the phase transfer catalyst was reduced from 5 to 3 mol %. We also found it easier to stir the reaction mixture if the diazo precursor was added in two batch portions.

Effect of Solvent on Asymmetric Induction. Our next goal was to carry out the epoxidation of benzaldehyde with different hydrazone salts in the presence of chiral sulfide **7**, and, as we were going to investigate solvent effects on the efficiency of the process, we needed to determine which solvents gave high enantioselectivities in the epoxidation process (Table 6).

Table 6. Effect of the Solvent on the Enantioselectivity of the Epoxidation



entry	solvent	yield/%[a]	trans:cis	ee/%[b,c]
1	^{t}BuOMe	62	>98:2	89
2	$CF_3C_6H_5$	70	>98:2	87
3	1,4-dioxane	82	>98:2	85
4	toluene	69	>98:2	86
5	CH_3CH_2CN	48	97:3	70
6	CH_3CN	87	>98:2	94
7	THF	81	>98:2	81
8	CH_2Cl_2	70	>98:2	88

[a] Isolated yield of product. [b] Determined by chiral HPLC. [c] In all cases, the absolute configuration of the major enantiomer is 1*R*,2*R*. This has been proved in many cases by comparison of either retention times on chiral HPLC columns, or optical rotations, with literature values. The remaining few are assumed by analogy (see Supporting Information).

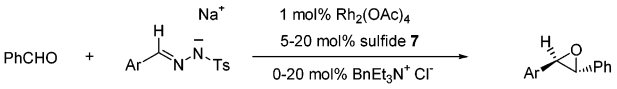
From a variety of solvents, we found that, with the exception of tetrahydrofuran (entry 7) and propionitrile (entry 5), all of them performed well in terms of enantioselectivity. The best yields and enantioselectivities were achieved with toluene, α,α,α-trifluorotoluene, 1,4-dioxane, and acetonitrile (entries 2, 3, 4, and 6, respectively). Dichloromethane (entry 8) also performed well, but as there are concerns about using chlorinated solvents on a large scale, we decided to carry out optimization of the reactions between the various hydrazone salts and benzaldehyde with the four solvents mentioned above.

Asymmetric Epoxidation Using Different Hydrazone Salts and Benzaldehyde. With electron-rich diazo precursors, good yields and high enantioselectivities were generally obtained (Table 7, entries 1−6). Diastereoselectivities were also high except in the case of the *p*-methoxydiazo precursor (Table 7, entry 5). As we expected, the mesitaldehyde derivative afforded the epoxide in very low yield, even when 1 equiv of chiral sulfide was used (entry 3). This is presumably due to the steric problems associated with the use of a hindered carbene (vide supra), which are amplified by the use of a hindered sulfide. Electron-deficient diazo precursors furnished the epoxides in high yields and high diastereoselectivities, but the enantioselectivities were more variable and solvent-dependent (see Supporting Information). Moderate yields and enantioselectivities were obtained with heteroaromatic precursors. The results presented in Table 7 are the optimized conditions for each individual substrate; all results employing other solvents, temperatures, and changing the sulfide loading are given in the Supporting Information.

Asymmetric Epoxidation Using α,β-Unsaturated Hydrazone Salts. The use of α,β-unsaturated hydrazones for asymmetric epoxidations was less successful as yields were often low (Table 8). Diastereoselectivity was also low except in the cases where there was a substituent in the β-position (entries 2 and 5), when complete trans selectivity was observed. Similar observations have recently been reported by Metzner, employing 2,5-dimethylthiolane in stoichiometric epoxidation reactions.[24f]

Moderate to good enantioselectivities were observed for β-unsubstituted or β-monosubstituted substrates (entries 1−5).

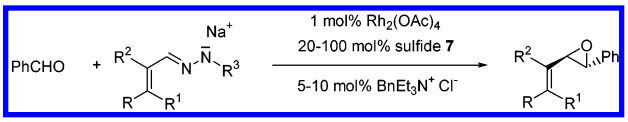
Table 7. Yields, Enantioselectivities, and Diastereoselectivities of Epoxides Formed from Benzaldehyde and Tosylhydrazone Salts Using Sulfide **7**



entry	Ar	solvent	*T*/°C	**7**/mol %	PTC/%	yield/%[a]	trans:cis	ee/%[b,c] trans (cis)
1	*p*-MeC_6H_4	CH_3CN	40	5	5	74	95:5	93
2	*o*-MeC_6H_4	CH_3CN	30	5	5	64	>98:2	83
3	2,4,6-$Me_3C_6H_2$	CH_3CN	40	100	5	10	>98:2	94
4	*m*-$TBSOC_6H_4$	1,4-dioxane	30	20	10	67	>98:2	92
5	*p*-$MeOC_6H_4$	CH_3CN	30	20	5	95	80:20	93
6	*o*-$MeOC_6H_4$	CH_3CN	30	5	5	70	>98:2	93
7	*o*-FC_6H_4	CH_3CN	30	20	5	76	>98:2	82
8	*p*-ClC_6H_4	CH_3CN	40	20	10	81	>98:2	93
9	*p*-CNC_6H_4	1,4-dioxane	40	20	0	70	>98:2	64
10	*p*-$CO_2MeC_6H_4$	CH_3CN	30	20	0	80	>98:2	73
11	2-furyl	CH_3CN	40	20	10	53[d]	90:10	61[f]
12	3-furyl	toluene	40	20	5	46	63:37	63 (31)

[a] Isolated yield of product. [b] Determined by chiral HPLC. [c] The absolute configuration of the major enantiomer is 1*R*,2*R*. This has been proven in many cases by comparison of either retention times on chiral HPLC columns, or optical rotations, with literature values. The remaining few are assumed by analogy (see Supporting Information). [d] Crude yield determined by ^{1}H NMR spectroscopy with an internal standard (epoxide is unstable on silica gel and alumina). [f] The absolute configuration of the major enantiomer is 1*S*,2*R*. This has been proven by comparison of chiral HPLC retention times with literature values.

Table 8. Yields, Enantioselectivities, and Diastereoselectivities of Epoxides Formed from Benzaldehyde and Tosylhydrazone Salts Using 0.05−0.2 equiv of Sulfide **7**



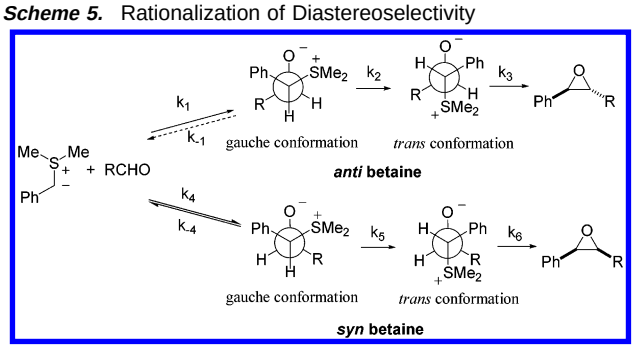
entry	R	R^1	R^2	R^3	% **7**	solvent	*T*/°C	PTC/%	yield/%[a]	trans:cis	ee/%[b,c] trans
1	H	H	H	2,4,6-^{i}Pr$_3$C$_6$H$_2$SO$_2$	20	1,4-dioxane	20	10	15[d]	50:50	79
2	H	H	Me	Ts	100	$CF_3C_6H_5$	40	10	12	>98:2	88
3	Ph	H	H	Ts	20	$CF_3C_6H_5$	40	10	27[d]	72:28	78
4	SiMe$_3$	H	H	Ts	20	1,4-dioxane	40	10	46[e]	62:38	70
5	Ph	H	Me	Ts	20	1,4-dioxane	30	5	41	>98:2	67
6	Me	Me	H	2,4,6-^{i}Pr$_3$C$_6$H$_2$SO$_2$	20	1,4-dioxane	30	10	45	50:50	48
7	Ph	Ph	H	Ts	20	$CF_3C_6H_5$	40	5	56[f]	67:33	20

[a] Isolated yield of product. [b] Determined by chiral HPLC. [c] In all cases, the absolute configuration of the major enantiomer is 1*R*,2*R*. This has been proven in many cases by comparison of either retention times on chiral HPLC columns, or optical rotations, with literature values. The remaining few are assumed by analogy (see Supporting Information). [d] In situ salt formation from 2,4,6-triisopropylbenzenesulfonylhydrazone using NaHMDS as the base. [e] Crude yield determined by ^{1}H NMR spectroscopy with an internal standard (epoxide is unstable on silica gel and alumina). [f] In situ salt formation from the tosylhydrazone using LiHMDS as the base (HMDS = 1,1,1,3,3,3-hexamethyldisilazane).

However, β,β-disubstituted substrates only furnished epoxides with low enantioselectivity (entries 6 and 7).

Origin of Diastereoselectivity. Sulfur ylides react with carbonyl compounds via betaine intermediates to give epoxides. From simple crossover experiments, we have previously reported that the reaction of a benzyl sulfonium ylide with an aldehyde or ketone was remarkably finely balanced.[29] In reactions with benzaldehyde, the trans epoxide was derived from nonreversible formation of the anti betaine, indicating that bond rotation and ring closure have lower activation barriers than reversion to starting materials (relative rates: $k_2 > k_{-1}$) (Scheme 5).

Scheme 5. Rationalization of Diastereoselectivity



In contrast, crossover experiments showed that the syn betaine, which would lead to the cis epoxide, was formed reversibly.[29] DFT calculations underpinned these experimental observations, producing the same relative activation barriers (relative rates: $k_2 > k_{-1}$; $k_{-4} > k_5$).[30] It was found that the highest activation barrier along the two reaction pathways was for the torsional rotation step from the gauche to the trans conformation of the betaines. Thus, the formation of the syn betaine is nonproductive; it is formed but reverts back to the aldehyde and ylide, as subsequent rotation from the gauche to the trans conformation has a higher activation barrier. Hence, the high trans selectivity observed with benzaldehyde is a result of nonproductive formation of the syn betaine and productive formation of the anti betaine. In general, providing syn betaine formation is reversible and nonproductive, high diastereoselectivity should result. The degree of reversibility in syn betaine formation is influenced in the following ways: (i) an increase in the thermodynamic stability of the starting materials (ylide and aldehyde) will lead to greater reversibility in betaine formation (increase in k_{-4}) and thus higher diastereoselectivity; (ii) increasing the steric hindrance of the ylide or aldehyde will give rise to an increase in the torsional rotation barrier (increase in k_5) and thus render betaine formation more reversible, resulting in increased diastereoselectivity; and (iii) increased solvation of the alkoxide by metals or a protic solvent will result in the lowering of the torsional rotation barrier (decrease in k_5) and thus reduced reversibility leading to reduced diastereoselectivity.

Of course, the factors which increase the reversibility in the syn betaine formation have the same effect on the anti betaine formation, and this process may, therefore, also be partially reversible. Although this does not have any effect on the diastereoselectivity, it does have important consequences for the enantioselectivity (vide infra).

These principal factors that are responsible for diastereoselectivity are substantiated by the many examples provided and are discussed below.

(1) Stability of Carbonyl Group. Aromatic aldehydes give high trans selectivity because reversion of the syn betaine yields a carbonyl group that is in conjugation with an aromatic ring. Such conjugation is not available to aliphatic aldehydes, thus resulting in reduced reversibility, because reversion back to starting materials is less favorable. This leads to an overall decrease in diastereocontrol. On the basis of this analysis, the results in Table 2 can be broadly understood. Aromatic (entries 1−6), heteroaromatic (entries 7−13), and unsaturated aldehydes (entries 19−25) gave high diastereocontrol as expected. In some cases, aliphatic aldehydes (entries 14−18) gave lower diastereoselectivities as expected (entries 14 and 17), but phenylacetaldehyde and cyclopropanecarboxaldehyde (entries 15 and 16) gave very high selectivities (>98:2 and 96:4), and, at this stage, these two examples are difficult to rationalize.

(2) Steric Hindrance of the Ylide/Aldehyde. Reduced steric hindrance of the ylide/aldehyde allows more facile bond rotation from the gauche to the trans conformation of the betaine, leading to reduced reversibility in betaine formation, thereby resulting in a decrease in diastereoselectivity. Conversely, an increase in

(29) Aggarwal, V. K.; Calamai, S.; Ford, J. G., *J. Chem. Soc., Perkin Trans. 1* **1997**, 593.
(30) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747.

steric hindrance of the ylide/aldehyde leads to an increase in diastereoselectivity.

Thus, the acetylenic aldehyde (Table 2, entry 25) gave low diastereoselectivity, while aliphatic aldehydes of increasing steric hindrance showed increasing levels of diastereocontrol (Figure 2). Furthermore, increased trans selectivity was observed with the more hindered chiral sulfide **7** as compared to tetrahydrothiophene.

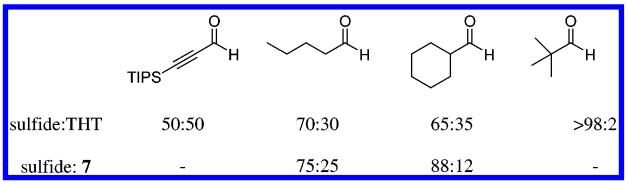


Figure 2. Trans:cis ratios of epoxides formed from benzyl tosylhydrazone salts and aliphatic and acetylenic aldehydes.

Additional data supporting the general principle that more hindered substrates give higher trans selectivities can be found in Table 4 and are portrayed in Figure 3. The smaller unsaturated ylides bearing an α-hydrogen (Table 4, entries 1, 2, 5−9, and 11−13) showed low diastereocontrol (betaine formation is essentially nonreversible), whereas those bearing an α-methyl group (Table 4, entries 3, 4, and 10) showed higher diastereocontrol (syn betaine formation is more reversible).

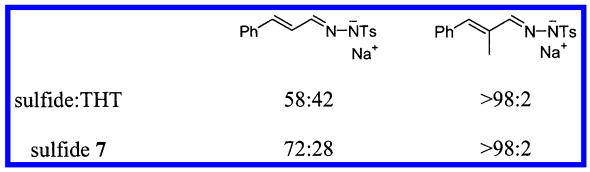


Figure 3. Trans:cis ratios of epoxides formed from unsaturated tosylhydrazone salts and benzaldehyde.

(3) Reduced Stability of the Ylide. On the basis of the principles described above, the selectivity with different aryldiazomethanes can also be rationalized. Clearly, syn betaine formation will be more reversible with more stable ylides, resulting in increased trans selectivity. Indeed, electron-deficient aromatics all gave very high selectivities (Table 3, entries 7−13). Conversely, betaine formation is less reversible with less stable ylides (electron-rich aromatics), and, again, this was observed in practice (Table 3, entries 1 and 5, and Figure 4).

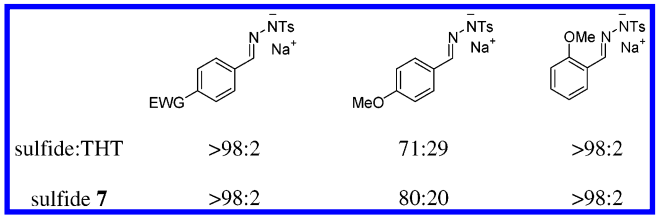


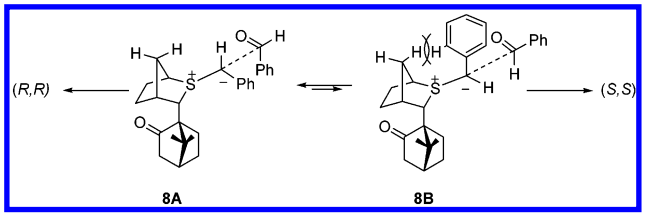
Figure 4. Trans:cis ratios of epoxides formed from tosylhydrazone salts and PhCHO.

It was indicated above that steric hindrance of the ylide resulted in greater reversibility in betaine formation and therefore greater diastereoselectivity. Hence, as shown in Figure 4, use of the more hindered sulfide **7** invariably resulted in an increase in diastereoselectivity. Interestingly, electron-rich substrates bearing an *ortho* substituent also showed high stereocontrol, indicating that reversibility due to steric hindrance outweighed the expected nonreversibility due to the intermediacy of a less stable ylide (Table 3, compare entries 1/2 and 5/6). Clearly, the selectivity will be dependent upon the nature and position of the substituents attached to the aromatic ring.

(4) Increased Solvation of Charges. Finally, the diastereoselectivity will also be influenced by the reaction conditions. If the charges can be more effectively solvated, either by metal complexation or by use of a protic solvent, the barrier to bond rotation of the initially formed betaine should be reduced, thereby resulting in reduced reversibility and a corresponding decrease in diastereoselectivity. This accounts for the reduced diastereoselectivity observed when the Li hydrazone salt was employed as compared to the Na hydrazone salt (74:26 vs >98:2, respectively, Table 1).[31] Reduced diastereoselectivity was also observed in CH_3CN/H_2O, as compared to neat CH_3CN (74:26 vs >98:2, respectively).[32] Again, this was a result of improved solvation of the alkoxide resulting in a reduction of the barrier to bond rotation, leading to a reduced reversibility and, hence, lower trans:cis selectivity.

Origin of Enantioselectivity. The model for the origin of enantioselectivity is shown in Scheme 6. We believe that a single ylide diastereomer is formed, and, as a result of electronic repulsions, this can exist in either of the two conformations **A** and **B** where the lone pairs of electrons on carbon and sulfur are orthogonal.[33]

Scheme 6. Rationale for Enantioselectivity



Once a single diastereomeric sulfonium ylide is formed, enantioselectivity is governed by three main factors: (i) ylide conformation, (ii) facial selectivity of the ylide reaction, and (iii) the degree of reversibility in betaine formation.

Space filling models for sulfonium ylide **8A** optimized at the B3LYP 6-31G* level show that complete facial selectivity is expected as a result of the bulky camphor group effectively blocking reaction from one face (Figure 5).

The enantioselectivity observed with different ylides is therefore influenced by factors (i) and (iii), and these are discussed, according to ylide type, in more detail below.

(1) Unhindered, Electron-Rich/Neutral Aryl-Stabilized Ylides. The phenyl stabilized sulfonium ylide has been the most extensively studied ylide, and high and uniform enantioselectivity was observed, not only with different aldehydes (Table

(31) The increase in cis selectivity with metals of increasing ability to bind to oxygen is also observed in the Wittig reaction. However, although the sulfur and phosphorus ylides show similar trends, they do so for very different reasons. In the sulfur ylide reactions, the trends in diastereoselectivity correlate with increased complexation of the metal (Li > Na > K) with the alkoxide intermediate which results in reduced barriers to bond rotation leading to lower *E* selectivity. In the related phosphorus ylide reactions, it is believed that lithium salts act as Lewis acids, leading to an earlier transition state, which favors formation of the *Z* alkene. See: Ward, W. J., Jr.; McEwen, W. E. *J. Org. Chem.* **1990**, *55*, 493.

(32) These observations were made using 0.33 mmol of *p*-chlorobenzaldehyde, 5 mol % $Cu(acac)_2$, 1 equiv of THT, 20 mol % benzyltriethylammonium chloride in 0.5 mL of CH_3CN + 0.5 mL of H_2O, and 1 mL of CH_3CN, respectively.

(33) Aggarwal, V. K.; Schade, S.; Taylor, B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2811.

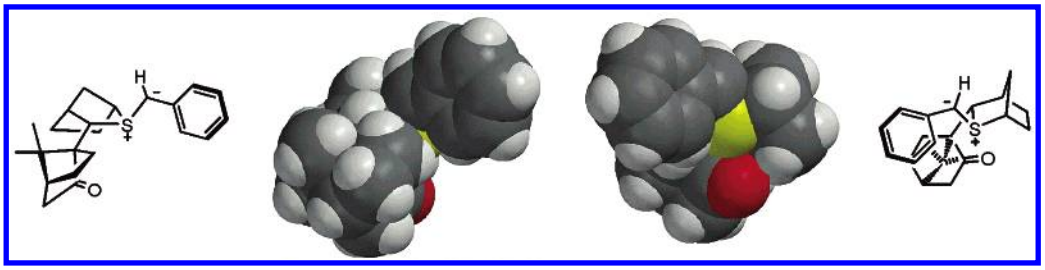
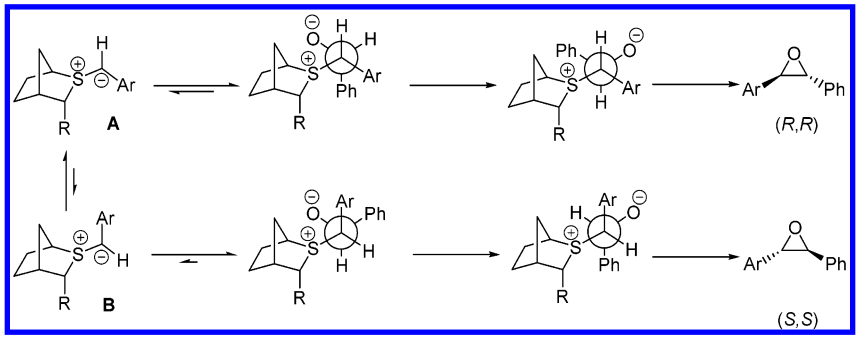


Figure 5. Space filling models derived from DFT calculations of **8A** showing how the camphor group effectively blocks one face of the ylide from aldehyde attack. Related ChemDraw diagrams of the same view are given (for clarity).

Scheme 7. Consequences for Enantioselectivity Due to Partial Reversibility in Anti Betaine Formation



5, 87−94% ee), but also with other electrophiles (e.g., aziridination of imines: 89−98% ee; cyclopropanation of acrylate derivatives: 89−92% ee).[12a] This suggests that the dominant factor responsible for enantioselectivity with all of these substrates is ylide conformation (**8A**:**8B** ratio) because reactions with *N*-toluenesulfonyl imines[34] are also essentially nonreversible and give similar enantioselectivities to aldehydes. As stated above, the ylide can adopt conformations **8A** or **8B**, but **8A** should be strongly favored as **8B** suffers from nonbonded 1,4 steric interactions. However, the ratio of ylide conformers **8A**:**8B** does not directly correlate with enantioselectivity as the minor conformer **8B** is likely to be much more reactive than conformer **8A**.[35] This is because steric interactions between the methylene bridge and the phenyl group result in rotation of the phenyl group by ca. 42° out of conjugation (determined by DFT calculations; see Figure 6), resulting in reduced overlap with the carbanion and therefore reduced stabilization of the ylide. The calculations not only reveal the twist of the phenyl ring in conformer **8B** which is absent in **8A**, but also greater pyramidalization of the carbon atom of ylide **8B** as compared to **8A** due to reduced overlap of the carbanion with the aromatic ring. Nevertheless, the major enantiomer of the epoxide correlates with reaction of the major conformer of the ylide (**8A**) on its less hindered face (i.e., for this class of ylide with sulfide **7**, the *R*,*R* epoxide was always the major product).

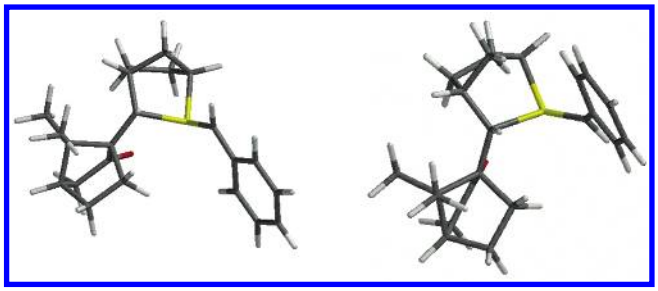


Figure 6. Models derived from DFT calculations showing the ylide conformations **8A** and **8B**, respectively.

Other electron-rich aryl-stabilized ylides all gave high enantioselectivity as factors (i) and (iii) were effectively controlled (Table 7, entries 1, 3−6, 91−94% ee).

(2) Hindered, Electron-Deficient Aryl-Stabilized Ylides. Lower enantioselectivity was observed with electron-deficient aryl-stabilized ylides as well as those that were sterically hindered [Table 7; entry 2, *o*-Me (83% ee); entry 9, *p*-CN (64% ee); entry 10, *p*-CO_2Me (73% ee)]. As with the neutral/electron-rich substrates, ylide conformation with this class of ylide should also be well, if not better, controlled in favor of conformer **A**. In these cases, as discussed above (see section on diastereoselectivity), formation of the syn betaine is reversible and nonproductive, but formation of the anti betaine is also likely to be partially reversible. This has consequences for enantioselectivity because the degree of reversibility in anti betaine formation is likely to be different for conformers **A** and **B** (Scheme 7). As ylide conformer **B** is higher in energy (less stable) than conformer **A**, it will react less reversibly (ylides of increasing stability react with increasing reversibility in betaine formation) with aldehydes to give the intermediate betaine, resulting in conformer **B** being "overexpressed" in the product distribution. Thus, a small degree of reversibility in the anti betaine formation, which occurs with stabilized/hindered ylides, results in a reduction in enantioselectivity as conformer **B** reacts less reversibly than conformer **A** and is therefore converted to epoxide more rapidly.[36]

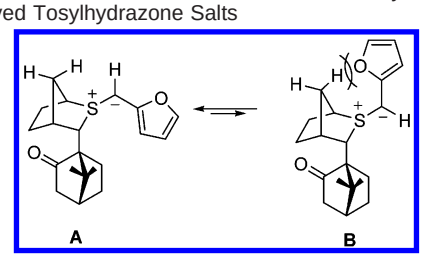
Very hindered substrates gave high enantioselectivity [e.g., 2,4,6-trimethylphenyl-stabilized ylide, Table 7, entry 3 (94% ee)], and this can also be rationalized using the same model. Presumably, in this case, even though betaine formation is partially reversible, conformer **B** is even more disfavored due

(34) Aggarwal, V. K.; Charmant, J. P. H.; Ciampi, C.; Hornby, J. M.; O'Brien, C. J.; Hynd, G.; Parsons, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3159.
(35) DFT calculations indicate that the energy difference between conformers **A** and **B** is 18.3 kJ mol^{-1}, which, according to the Boltzmann equation, correlates to a ratio of 1129:1 at 40 °C. If these were both equally reactive, this would correspond to 99.8% ee.
(36) For a full discussion, see: Aggarwal, V. K.; Richardson, J. *Chem. Commun.* **2003**, in press.

to severe steric hindrance, so the reaction occurs largely via conformer **A**, leading to high enantioselectivity.

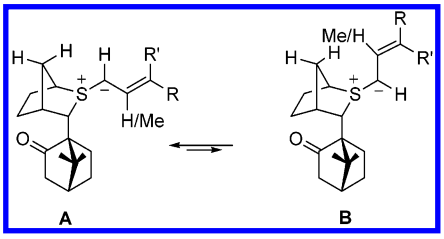
(3) Five-Membered Ring Heteroaromatic-Stabilized Ylides. Furyl-stabilized ylides gave lower enantioselectivities than six-membered ring aromatic substrates (Table 7, entries 11 and 12, 61% ee and 63% ee, respectively), presumably because the **A**:**B** ratio is lower as a result of reduced steric hindrance in conformer **B** (Scheme 8). As these substrates give rise to less stabilized ylides relative to a phenyl-stabilized ylide, they will be expected to react nonreversibly with aldehydes [i.e., factor (iii) is well controlled], and so it is factor (i) (ylide conformation) that is responsible for the reduction in enantioselectivity.

Scheme 8. Rationale for Reduced Enantioselectivity for Furyl-Derived Tosylhydrazone Salts



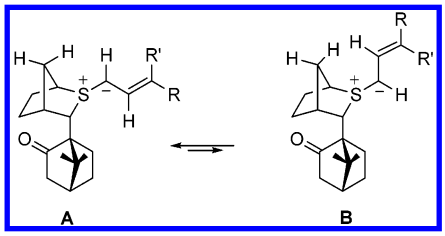
(4) α,*β*-Unsaturated Sulfonium Ylides. α-Methyl substituted α,*β*-unsaturated substrates showed higher enantioselectivity (Table 8, entries 2 and 5, 67−88% ee) than unsaturated substrates bearing only an α−H (20−78% ee). These results can also be rationalized by considering the ratio of the ylide conformers **A** and **B** (Scheme 9).

Scheme 9. Possible Conformers of α,*β*-Unsaturated Sulfonium Ylides



For substrates bearing an α-methyl group, conformer **B** will be strongly disfavored due to steric hindrance, and high selectivity results from reaction via the dominant conformer **A**. Without the α-methyl group, conformer **B** is not disfavored to such a great extent as this ylide conformation suffers from less steric hindrance. As a result of the smaller energy difference between conformers **A** and **B**, lower enantioselectivity is observed. The *β*-dimethyl and *β*-diphenyl unsaturated substrates showed lower enantioselectivity than the mono *β*-substituted derivatives, presumably due to destabilizing interactions present in **A** which resulted in the ratio of conformers **A**:**B** being more finely balanced. As it was not obvious why this should be the case, we performed DFT calculations on a series of substrates and calculated the **A**:**B** ratio of conformers (Table 9). Although the ratios did not correlate exactly with the enantiomeric excesses observed, the trends did fit with the observed selectivities; the presence of two *β*-substituents resulted in a significant change in the ratio of conformers as compared to a single *β*-substituent. While conformer **A** was strongly favored with a single *β*-phenyl group (91:9), it was only marginally favored with two *β*-phenyl groups (61:39).

Table 9. Calculated Ratios of Conformers **A** and **B** for Various Unsaturated Ylides and the Corresponding Enantiomeric Excesses Observed

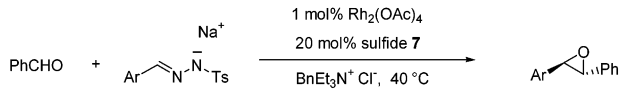


entry	R	R′	ee/%[a] trans	**A**:**B** calculated ratios[b]
1	Ph	H	78	91:9
2	Me	Me	48	79:21
3	Ph	Ph	20	61:39

[a] Enantiomeric excess of major trans epoxide, determined by chiral HPLC. [b] Ratios calculated using the Boltzmann equation with energies obtained at the B3LYP/6-31G* (acetonitrile) level.

A Test for Reversibility in Betaine Formation. As discussed above, the reduced enantioselectivity observed with certain ylides derived from sulfide **7** is mainly due to either poor control in ylide conformation [factor (i)] or reversibility in betaine formation [factor (iii)]. If low enantiocontrol is observed, it would be useful to know which of the two factors was responsible. We have devised a simple test to determine this. As discussed in the section on diastereoselectivity, the degree of reversibility in betaine formation can be influenced by the electrophile employed or by the reaction conditions. Reduced reversibility can be achieved by (i) use of an aliphatic aldehyde (reduction in k_{-4}, Scheme 5), (ii) use of protic solvents (e.g., MeCN/H_2O mixture) which solvate the alkoxide (reduction in k_5), or (iii) use of lithium salts which again solvate the alkoxide (reduction in k_5). Three classes of substrates that gave reduced enantioselectivity [Table 7: hindered, *o*-MeC_6H_4 (83% ee); electron deficient, *p*-$CO_2MeC_6H_4$ (73% ee); and 2-furyl (63% ee)] were tested for reversibility by performing reactions in MeCN/H_2O and comparing them to those carried out in MeCN. If the primary factor for lower levels enantioselectivity with these substrates was reversibility, higher enantioselectivity should be observed in MeCN/H_2O as compared to MeCN itself. Indeed, higher enantioselectivities were observed with the hindered and electron-deficient aromatic substrates in MeCN/H_2O (Table 10), indicating that the lower enantioselectivities

Table 10. Effect of the Addition of Protic Solvent on the Enantiomeric Excess of Epoxides Formed with Selected Tosylhydrazone Salts and Benzaldehyde

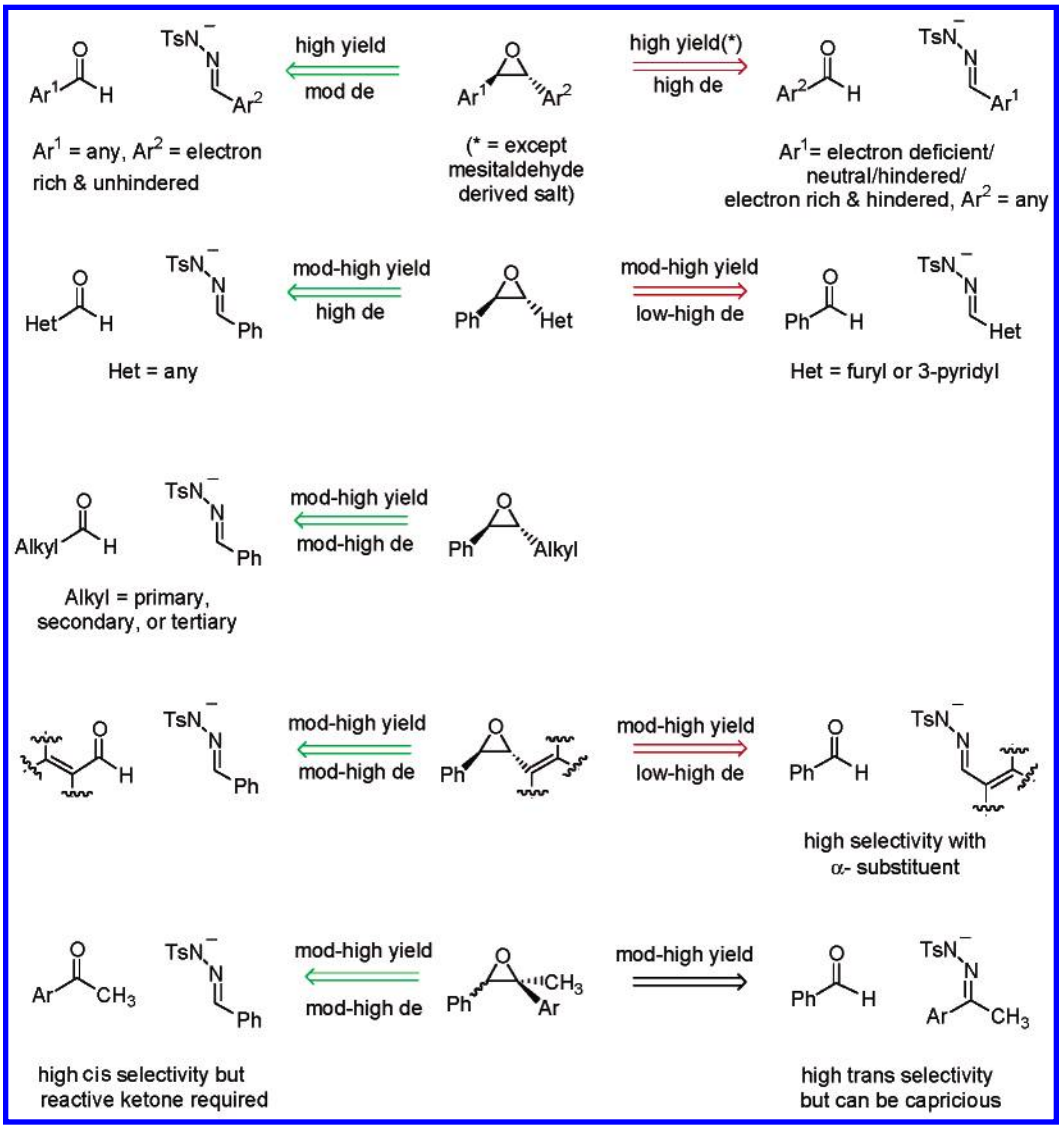


entry	Ar	solvent	PTC (%)	ee (%)[a]	trans:cis
1	*p*-$CO_2MeC_6H_4$	CH_3CN	0	73	100:0
2	*p*-$CO_2MeC_6H_4$	CH_3CN/H_2O(9:1)	0	86	100:0
3	*o*-MeC_6H_4	CH_3CN	5	83	100:0
4	*o*-MeC_6H_4	CH_3CN/H_2O(9:1)	5	89	100:0
5	2-furyl	CH_3CN	10	61	91:9
6	2-furyl	CH_3CN/H_2O(9:1)	10	61	95:5

[a] Determined by chiral HPLC.

observed in MeCN were due to partial reversibility in the formation of the anti betaines. In contrast, no change in

Scheme 10. Retrosynthetic Analysis of Epoxide Formation Using Achiral Unhindered Sulfides (Such as Tetrahydrothiophene)[a]



[a] Green arrows indicate good disconnections; red arrows indicate poor disconnections.

enantioselectivity was observed for the furyl substrate in MeCN/H_2O, indicating that, in this case, reversibility was not responsible for the reduced enantioselectivity, and therefore it must have been due to the poorer control over the conformation of the ylide (factor (i), **A**:**B** ratio).

Thus, conducting reactions in MeCN/H_2O and comparing the results with MeCN provides a very simple test for reversibility in betaine formation. Although these studies validate our model for enantioselectivity, they did not provide a practical solution for improving the enantiomeric excess, as the yields in MeCN/H_2O were substantially lower than those in MeCN alone.[37]

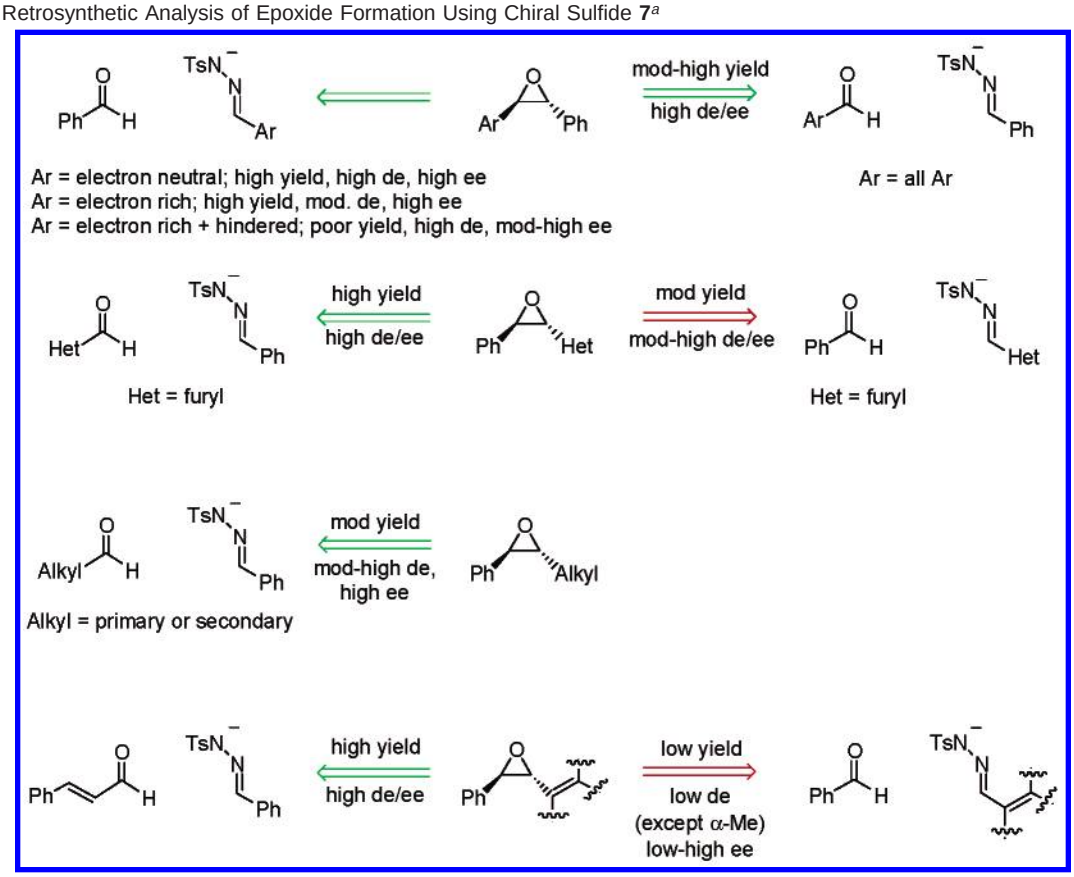
Conclusions

In this paper, we have shown that reactions of tosylhydrazone sodium salts with carbonyl compounds catalyzed by sulfides and $Rh_2(OAc)_4$ is an efficient method for the synthesis of epoxides and has broad applicability with respect to both the carbonyl compounds and the hydrazone salts that can be employed. The tosylhydrazone salt derived from benzaldehyde was tested with 29 different carbonyl compounds covering both aldehydes and ketones. All aromatic and heteroaromatic aldehydes gave good yields of epoxides, and most showed very high diastereoselectivity in favor of the trans epoxide (>87:13, most >98:2). Aliphatic aldehydes were also explored, and all (primary, secondary, and tertiary substituted) performed well, furnishing epoxides in good yield and with moderate to high diastereoselectivity (65:35 to 98:2). α,β-Unsaturated aldehydes could also be used (except for acrolein), and good yields were achieved with both β-alkyl (73%) and β-aryl (97%) substituents. The product epoxides derived from unsaturated aldehydes were especially sensitive to hydrolysis on silica gel during purification. Acetylenic aldehydes were also effective substrates, although epoxides were obtained as a 1:1 ratio of cis:trans isomers. Ketones demonstrated the limits of the reactivity of phenyl stabilized sulfonium ylides; activated ketones were effective substrates, but unactivated ketones were not.

A range of tosylhydrazone salts was tested in reactions with benzaldehyde. High yields of epoxides were obtained with all

(37) Yields are <10% for each of these substrates. Preliminary results suggest that using LiBr as an additive also results in higher enantioselectivity (reduced reversibility in betaine formation) without reducing yields. Full details will be published in due course.

Scheme 11. Retrosynthetic Analysis of Epoxide Formation Using Chiral Sulfide **7**[a]



[a] Green arrows indicate good disconnections; red arrows indicate poor disconnections.

aromatic aldehyde-derived tosylhydrazone salts except those bearing two *ortho* substituents. Electron-deficient substrates gave epoxides with a high degree of stereocontrol, but electron-rich substrates gave lower stereocontrol unless the substrate possessed an *ortho* substituent (i.e., it possessed increased steric hindrance), in which case high selectivity was restored. Unsaturated hydrazones could also be employed, but low diastereoselectivity was commonly observed unless the substrate possessed an α-substituent, in which case high diastereocontrol was achieved. A hydrazone salt derived from an aryl alkyl ketone was also tested, and a good yield, with complete trans selectivity, was achieved.

While this summary details how different classes of nucleophiles and electrophiles behaved, we believe it is even more helpful to consider a retrosynthetic analysis of the different classes of product epoxides that can be prepared by this strategy. In each case, the disconnection leads to two possible pairs of carbonyl compound and hydrazone, and Scheme 10 details which combination is likely to lead to good yields and high diastereoselectivities.

The same analysis can be done replacing tetrahydrothiophene with chiral sulfide **7** (Scheme 11). This scheme shows different classes of epoxides that we have made, indicating which is the optimum pair of hydrazone and carbonyl compound coupling partners, that lead to epoxides in good yields and with useful levels of stereocontrol.

This analysis shows that diaryl and aryl−alkyl epoxides can be prepared with good levels of selectivity. Heteroaryl−aryl epoxides bearing furyl groups can be prepared, but heteroaryl groups bearing a basic nitrogen (e.g., pyridyl) are not compatible with the catalytic, asymmetric process. The range of unsaturated epoxides that can be prepared is limited to those derived from cinnamaldehyde; other unsaturated aldehydes were low yielding. The use of tosylhydrazone salts bearing unsaturated substituents was generally low yielding.

Factors that influence both diastereo- and enantiocontrol have been analyzed. High diastereocontrol in favor of the trans epoxide was observed in the coupling of most partners and was due to reversible, nonproductive formation of the syn betaine (which would have given the cis epoxide) and nonreversible (and therefore productive) formation of the anti betaine. The occasions where low diastereocontrol was observed were due to nonreversible or only partially reversible formation of the syn betaine. There are four factors that contribute to reduced reversibility of the betaine back to the original starting materials: (i) reduced steric hindrance of the ylide/aldehyde that allows more facile bond rotation from the gauche to the trans conformation of the betaine (e.g., low diastereocontrol with acetylenic aldehydes, and α,*β*-unsaturated hydrazones with only an α-H substituent); (ii) lower stability of the carbonyl group which reduces the tendency for the betaine to revert back to the ylide and carbonyl group (e.g., with aliphatic aldehydes); (iii) reduced stability of the ylide which reduces the tendency for the betaine to revert back to the ylide and carbonyl group (e.g., tosylhydrazones derived from electron-rich aromatic aldehydes); and (iv) increased solvation of the betaine by Li salts or protic solvent leads to a reduction in the barrier to bond rotation of the intermediate betaine which results in reduced reversibility and, therefore, reduced diastereoselectivity.

The enantioselectivity is governed by the ylide conformation, facial selectivity in the ylide reaction, and again the degree of reversibility in betaine formation. We believe that, with sulfide **7**, facial selectivity is essentially complete, and it is ylide conformation and the degree of reversibility that largely control the outcome of the reaction. All aldehydes employed with the tosylhydrazone salt derived from benzaldehyde gave uniform enantioselectivity (91 ± 3% ee), showing that the nature and structure of the ylide, rather than the electrophile, dominate the stereochemical outcome of the reaction.

Lower enantioselectivity was observed with the following: (i) less hindered ylides, because ylide conformation was less well controlled (e.g., furyl, α,β-unsaturated substrates with α-H); (ii) more stable ylides, because formation of the anti betaine was also reversible/partially reversible (in addition to syn betaine formation being reversible) (e.g., *p*-$CNC_6H_4CHNNTs$ salt); and (iii) hindered ylides because anti betaine formation was reversible/partially reversible (in addition to syn betaine formation being reversible) (e.g., *o*-$MeC_6H_4CHNNTs$ salt).

Although points (i) and (iii) suggest that there is only a narrow window of opportunity for obtaining high enantioselectivities, Tables 5−8 show a large number of examples where high enantioselectivity is achieved.

This paper maps out the range of epoxides that can be prepared in racemic and enantiomerically enriched form using our novel sulfur ylide mediated process. As the catalytic, racemic process shows a broader substrate scope than the asymmetric one, a stoichiometric asymmetric process has been developed to fill the gaps.[38] It is likely that, in those cases where carbonyl compounds are first converted to alkenes and then oxidized to epoxides, this one step alternative process should be advantageous and, therefore, be the method of choice. The process is user-friendly as diazo compounds are generated in situ from the corresponding hydrazone salts and are consumed as they are formed, so there is never any buildup of these potentially explosive intermediates. Indeed, the process has been carried out on a 50 mmol scale. The broad range of tosylhydrazone salts that we have demonstrated in epoxidation reactions shows that the in situ generation of diazo compounds from their hydrazone salts is a general method which will, no doubt, find application in many other transformations. We have already begun to explore some of these transformations in our own labs such as aziridination of imines,[12a] cyclopropanation of electron-rich[12a] and electron-deficient alkenes,[12b] cycloadditions with alkynes to give pyrazoles,[13] Wittig olefination reactions of aldehydes,[14] and homologation of aldehydes.[15]

Experimental Section

General Procedure for the Preparation of Aldehyde[7]- and Ketone[8a]-Derived Sulfonyl Hydrazones (For Example, Benzaldehyde Tosylhydrazone). To a rapidly stirred suspension of sulfonylhydrazide (5.0 g, 26.8 mmol) in methanol (10 mL) was added aldehyde or ketone (24.0 mmol) dropwise (solid reagents were added as a methanol solution or portionwise). A mildly exothermic reaction ensued, and the hydrazide dissolved. Within 5−10 min, the tosylhydrazone began to precipitate. After approximately 30 min, the mixture was cooled to 0 °C, and the product was removed by filtration, washed with a small quantity of methanol, and purified according to the procedure described in Table 2 in the Supporting Information. See table notes in the Supporting Information for exceptions to the general procedure.

Benzaldehyde Tosylhydrazone. White needles (5.40 g, 82%), mp 127−128 °C (lit.,[39] 128−129 °C); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.37 (3H, s, C*H*$_3$), 7.26−7.37 (5H, m, Ar*H*), 7.52−7.61 (2H, m, Ar*H*), 7.80 (1H, s, C*H*), 7.89 (2 H, d, J = 9.0 Hz, Ar*H*), 8.44 (1 H, br s, N*H*).

General Procedure for the Preparation of Tosylhydrazone Sodium Salts.[7] A 1 M sodium methoxide solution was prepared by adding sodium (288 mg, 12.5 mmol) to anhydrous methanol (12.5 mL) with external cooling. Once all of the metal had dissolved, the tosylhydrazone (12.35 mmol) was added, and the mixture was stirred until the solid had dissolved. After the mixture was stirred for a further 15 min, the methanol was removed under reduced pressure, at room temperature, to yield the hydrazone salts in quantitative yield. The solid hydrazone salt was then ground using a pestle and mortar to give a free flowing powder. All salts were stored at −20 °C, and exposure to direct light was avoided. See the Supporting Information for notes on stability.

Benzaldehyde Tosylhydrazone Sodium Salt. White solid (Found: C, 56.8; H, 4.3; N, 9.2. $C_{14}H_{13}N_2SO_2Na$ requires C, 56.8; H, 4.4; N, 9.5); υ_{max} (KBr disk)/cm^{-1} 3056, 1245, 1129, 1088; ^{1}H NMR (250 MHz, D_2O) δ 2.26 (3H, s, C*H*$_3$), 7.29 (5H, m, Ar*H*), 7.49 (2H, d, J = 10.0 Hz, Ar*H*), 7.71 (2H, d, J = 10.0 Hz, Ar*H*), 7.96 (1H, s, C*H*); ^{13}C NMR (63 MHz, D_2O) δ 20.4, 126.2, 126.5, 128.5, 129.2, 135.6, 139.2, 142.3, 145.5; *m*/*z* (FAB) 297 (M^+ + 1, 84%).

General Procedure for the Epoxidation of Aldehydes and Ketones (Tables 2−4). To a 5 mL round-bottomed flask fitted with a nitrogen balloon were added sequentially tetrahydrothiophene (in the case of ketones, pentamethyl sulfide was used) (20 mol %), anhydrous acetonitrile (1.0 mL), rhodium(II) acetate dimer (1.5 mg, 1 mol %), benzyl triethylammonium chloride (7.5 mg, 10 mol %), aldehyde or ketone (0.33 mmol, 1.0 equiv), and tosylhydrazone sodium salt (0.50 mmol, 1.5 equiv). The reaction mixture was stirred vigorously at room temperature for 10 min, and then at 40 °C for 3−24 h. The reaction was quenched by the addition of water (0.5 mL) and ethyl acetate (0.5 mL). The aqueous layer was washed with ethyl acetate (2 × 0.5 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was analyzed by ^{1}H NMR to determine the diastereomeric ratio and then purified by flash column chromatography to afford the corresponding epoxide. For asymmetric epoxidations (Tables 5−7), tetrahydrothiophene was replaced by chiral sulfide **7**.

Stilbene Oxide.[40] White solid; R_f = 0.70 (10% EtOAc/petrol), mp 65−67 °C (lit.,[40] 67−68 °C); ^{1}H NMR (250 MHz, $CDCl_3$) δ trans 3.85 (2H, s, 2 × C*H*), 7.16−7.37 (10H, m, Ar*H*); cis δ 4.28 (2H, s, 2 × C*H*), 7.01−7.15 (10H, m, Ar*H*).

General Procedure for Epoxidation of Alkenyl Aryl Sulfonylhydrazones, Ketone Sulfonylhydrazones, and Trimethylsilylacrolein Sulfonylhydrazone via in Situ Salt Generation. To a 5 mL round-bottomed flask fitted with a nitrogen balloon was added hydrazone (0.45 mmol) with 1 mL of THF. The solution was cooled to −78 °C, and a 1 M solution of NaHMDS (0.45 mmol, 1.5 equiv) in THF was added and stirred for 1 h at this temperature. The solvent was removed under reduced pressure at −20 °C, after which the flask was loaded with solvent (0.8 mL), tetrahydrothiophene (0.06 mmol, 5.5 μL), rhodium(II) acetate dimer (0.003 mmol, 0.9 mg), benzyl triethylammonium chloride (0.03 mmol, 6.8 mg), and benzaldehyde (0.3 mmol, 30.5 μL).

In all cases, the reaction was quenched after the given time by cooling to room temperature and then adding water (0.5 mL) and ethyl acetate (0.5 mL). The aqueous layer was washed with ethyl acetate (2 × 0.5 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was analyzed by ^{1}H NMR

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to determine the diastereomeric ratio and then purified by flash column chromatography to afford the corresponding epoxide.

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Supporting Information Available: Experimental details including spectral data for the preparation of all compounds, tables containing HPLC data, optimization of solvent conditions, preparation and stability of diazo compounds, hydrazones, and their corresponding salts, summary of literature data on the formation of diazo compounds, notes on the epoxidation procedures, and details of DFT calculations (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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