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Highly Enantioselective Synthesis of Glycidic Amides Using Camphor-Derived Sulfonium Salts. Mechanism and Applications in Synthesis

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Abstract: The reactions of a range of amide-stabilized sulfur ylides derived from readily available camphor-derived sulfonium salts for the synthesis of glycidic amides have been studied. Primary, secondary, and tertiary amides were tested, and it was found that the highest enantioselectivities were observed with tertiary amides, which provided glycidic amides in good to excellent yields, exclusive trans selectivity, and excellent enantioselectivities. The reaction was general for aromatic aldehydes, but aliphatic aldehydes gave more variable enantioselectivities. The epoxy amides could be converted cleanly into epoxy ketones by treatment with organolithium reagents. We were also able to effect selective ring opening of the epoxy amides with a variety of nucleophiles, followed by hydrolysis of the amide to yield the corresponding carboxylic acid. This methodology was applied to the total synthesis of the target compound SK&F 104353. A combination of crossover experiments and theoretical calculations has revealed that the rate- and selectivity-determining step is ring closure, not betaine formation as was the case for phenyl-stabilized ylides.

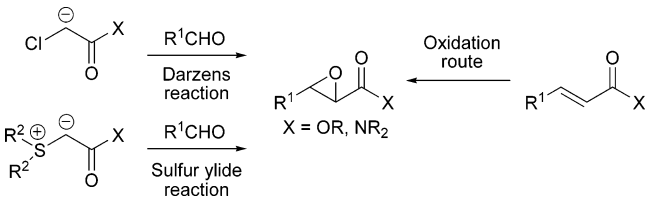
Introduction

Glycidic esters and amides are important and versatile intermediates in organic synthesis, and a number of methods exist for their preparation (Scheme 1).

One such route involves oxidation of the corresponding α,β-unsaturated esters or amides.[1] Most of the work in this area involves asymmetric variations of the Weitz−Scheffer epoxidation[2] in which a variety of metals have been used.[1]

Some particularly elegant work has been carried out in this area by Shibasaki et al.,[3] using lanthanide-derived catalysts. Epoxidation of α,β-unsaturated ketones employed a La−BINOL−$Ph_3As{=}O$ complex generated in situ from $La(O^iPr)_3$, BINOL, and $Ph_3As{=}O$ in a 1:1:1 ratio, and when enantiopure BINOL was used, epoxides were generated in moderate to excellent yield (72−99%) with high enantiomeric excess (89−99% ee).[4] Although the methodology could not be directly applied to the formation of glycidic esters, carboxylic acid imidazolides[4] and α,β-unsaturated-*N*-acyl-pyrroles,[5] which act as ester surrogates, underwent epoxidation in a highly selective manner. In addition, α,β-unsaturated amides were also amenable to epoxidation, yielding glycidic amides with excellent levels of enantiocontrol.[6]

Scheme 1. Possible Routes toward the Synthesis of Epoxy Amides and Esters



There are also examples in which chiral phase-transfer catalysts derived from Cinchona alkaloids have been used to induce asymmetry in the epoxidation of electron-deficient alkenes,[7−9] although unfortunately, this methodology has not yet been applied to the synthesis of glycidic amides and esters.

In the early 1980s, Juliá et al. reported the use of a triphasic epoxidation system involving an aqueous solution of NaOH and H_2O_2, a solution of chalcone in an organic solvent, and an insoluble poly-(L)-alanine catalyst.[10] A wide range of chalcone derivatives were investigated, giving products with good to excellent levels of enantioselectivity (50−99% ee). Recent modifications by Roberts involved the use of a biphasic system

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that utilized the much cheaper sodium percarbonate as both oxidant and base, while retaining a high level of enantiocontrol.[11] This methodology is currently restricted to the epoxidation of enones.

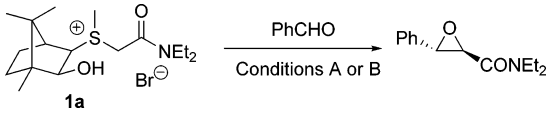
Chiral dioxiranes have been developed by a number of groups as asymmetric oxidants,[12] most notably by Shi and co-workers.[13] Shi et al. employed ketones derived from (−)-quinic acid that were oxidized by Oxone to form dioxiranes in situ, which could carry out highly enantioselective epoxidation on a range of enones (82−96% ee).[14] α,β-Unsaturated esters have also been employed as substrates using a fructose-derived ketone. Again, high enantioselectivities (82−98%) were obtained for a number of trans and trisubstituted substrates.[15]

Another metal-free approach has been reported by Jørgensen et al. in which α,β-unsaturated aldehydes underwent epoxidation using an organocatalyst.[16] Using a proline-derived chiral amine with hydrogen peroxide as the oxidant, epoxidation occurred in good yield and high diastereoselectivity with excellent levels of enantiomeric excess (>94% ee) for a range of substrates.

An alternative to the oxidative method for the formation of glycidic amides and esters is a Darzens reaction.[17] Although chiral phase-transfer catalysts have been explored in reactions of α-haloketones (and α-halosulfones), the enantioselectivities observed were only moderate (53−86% ee).[18,19] Superior results have been achieved using chiral reagents and chiral auxiliaries, but in these cases, a two-step process (C−C bond formation followed in a separate step by ring closure) is required. Corey et al. have developed a highly enantioselective version of the Darzens reaction in which an achiral aldehyde and *t*-butyl bromoacetate in the presence of a chiral borane were converted into an intermediate chiral α-bromo-β-hydroxy ester, which was subsequently transformed into the corresponding epoxy ester in up to 98% ee.[20]

Sulfur ylide methodology has also been applied to the synthesis of glycidic esters and amides. The reactivity of the ester-stabilized ylides is too low to react with simple aldehydes to form 2,3-substituted epoxy esters;[21,22] they react only with 1,2-dicarbonyl compounds. However, Delmas has shown that ester-stabilized ylides can react under specific conditions.[23] Using either the solid base $Ba(OH)_2 \cdot 8H_2O$ (C−O) or $K_2CO_3 \cdot 1.5H_2O$, ester-stabilized ylides underwent reaction with very electrophilic aldehydes, whereas use of the strong base KOH or a more hydrated barium hydroxide base (C-200) did not yield any epoxide. It was proposed that a lattice of specific dimensions and basic properties was required to complex the ester-stabilized ylide on the solid surface and provide it with appropriate reactivity.

Scheme 2. Dai et al.'s Asymmetric Synthesis of Epoxy Amides Using Chiral Sulfonium Salt **1a**[29]



Recent work in our own laboratory has shown that carboxylate-substituted sulfur ylides (thetin salts) can be used in asymmetric epoxidation to yield glycidic acids,[24] but unfortunately, the enantioselectivities observed to date are modest (up to 67% ee).

Amide-stabilized sulfonium ylides, however, have attracted more attention and have been shown to react with both aldehydes and ketones to afford glycidic amides with a high degree of trans selectivity.[25] It has been demonstrated by López-Herrera et al. that good diastereoselectivity can also be achieved when chiral aldehydes are employed (>92% de for a single trans isomer).[26]

We previously reported the preparation of glycidic amides in good yields and high diastereoselectivity (>95:5) using an achiral sulfonium ylide that was prepared in situ via the reaction between a sulfide and diazoacetamide in the presence of a copper catalyst.[27] More recently, Seki has shown that it is possible to prepare glycidic amides with a moderate degree of enantioselectivity (64% ee) using chiral sulfur ylides that were generated in situ from diazoacetamide in the presence of catalytic amounts of chiral binaphthylsulfide and copper(II) acetylacetone.[28]

Dai et al. also reported the preparation of enantiomerically enriched glycidic amides using chiral sulfonium salt **1a** with a range of aromatic aldehydes (Scheme 2).[29] The camphor-derived sulfide[30] that was employed had previously been used in the formation of enantiomerically enriched 2,3-diarylepoxides, with enantioselectivities reaching up to 74% when a stoichiometric quantity of sulfide was employed.[31]

The glycidic amide products were obtained under either solid−liquid phase-transfer conditions (conditions A: acetonitrile and KOH at room temperature) or liquid−liquid phase-transfer conditions (conditions B: dichloromethane and aqueous NaOH at 0 °C) for a range of aldehydes. Moderate to excellent yields (49−94%) with moderate levels of asymmetric induction (up to 72% ee) were achieved.[29] It is interesting to note that, although the sulfonium bromide salts were prepared and isolated prior to the reaction, their diastereomeric purity was not discussed. Indeed, we believe that the enantiomeric excesses observed in this and related work by the same group could have been improved by using a single diastereomer of sulfonium salt (vide infra).

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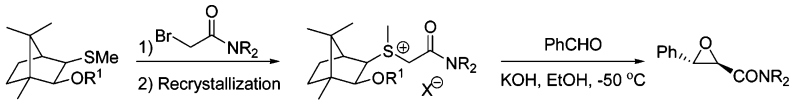
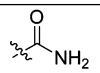
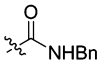
Table 1. Asymmetric Synthesis of (2*R*,3*S*)-2,3-Epoxy Amides via Camphor-Derived Sulfonium Salts **1**−**3**



2a R^1 = H
2b R^1 = Me

Entry	Amide	Salt	Sulfonium salt			Epoxy-amide	
			R^1	X	Salt ratio	Yield	ee[a]
1		**3a**	H	Br	100:0	-	13[b,c]
2		**4a**	H	Br	100:0	56	2[b]
3		**1a**	H	Br	100:0	85	92
4		**1b**	Me	Br	100:0	93	97

[a] The enantiomeric excess was determined by chiral HPLC, and the absolute configuration of the product in entries 3 and 4 was determined by comparison of HPLC elution orders and by comparison of $[\alpha_D]$ values with the literature. All others are given by analogy. [b] These reactions were carried out using *p*-Cl−PhCHO as the substrate. [c] Epoxidation was carried out at room temperature.

The same chiral sulfide was employed by Tang et al. for the preparation of vinyl cyclopropanes which involved the addition of an allylic sulfur ylide to α,*β*-unsaturated esters, amides, and ketones.[32] It was noted that the sulfonium salts employed on this occasion were diastereomerically pure by NMR spectroscopy, and enantioselectivities of >94% were achieved for a range of substrates.

Dai et al.[29] had reported that the hydroxyl group in **1a** was responsible for controlling the conformation of the ylide thereby enhancing enantioselectivity. If this were correct, replacing the OH group for OMe would be expected to lower the selectivity. We elected to test this hypothesis, but instead of observing a decrease in enantiomeric excess, we obtained much improved enantioselectivity.[33] In this article, we describe the features of the ylide required to give high enantioselectivity, the application of the products in synthesis, and mechanistic and computational studies that have now established the rate- and therefore enantio-determining step of the reaction.

Results and Discussion

Sulfide **2a** was synthesized in high yield and only two steps from D-camphor[30] and was readily methylated to give sulfide **2b**.[31] With the desired hydroxy- and methoxy-substituted chiral sulfides (**2a** and **2b**) in hand, the corresponding sulfonium salts were prepared in excellent yield using a variety of α-bromoamides, including primary, secondary, and tertiary amides. In some cases, a diastereomeric mixture of sulfonium salts, varying by their stereochemistry at the sulfur atom, was obtained that was recrystallized prior to use to furnish the diastereomerically pure salt. Brief optimization of the reaction conditions showed that high enantioselectivities could be obtained using KOH in EtOH at −50 °C (for a discussion of base effects, see ref 33).

It should be noted that enantioselectivities were determined by chiral HPLC, and the absolute configuration of the major product from the addition of the sulfonium salt **1a** to benzaldehyde was determined by $[\alpha_D]$ and comparison with literature values.[29] The absolute stereochemistry of this product was found to be (2*R*,3*S*), and the epoxide had a negative $[\alpha_D]$ value. It was assumed, by analogy, that all other epoxides prepared during this study also had the absolute configuration (2*R*,3*S*).

Using the hydroxy-substituted sulfide **2a** (R^1 = H, Table 1, entries 1−3), a very poor yield was observed for the reaction involving the primary amide (**3a**, entry 1), and the enantioselectivity was also low. The secondary amide (**4a**) also gave very low enantiomeric excess (entry 2). However, upon changing the substrate to a tertiary amide, excellent yields and enantioselectivities were observed (entry 3). In addition, it can be seen that changing from the hydroxy sulfonium salt **1a** to the methoxy-substituted salt **1b** led to a slightly higher yield and an increase in enantioselectivity (entry 4).

Using methoxy-substituted sulfonium salt **1b**, which gave the best results in the original study, an investigation into substrate scope was undertaken using a variety of aldehydes (Table 2).

The reaction was found to be general for a range of aromatic and heteroaromatic aldehydes with equally high levels of enantiomeric excess (see Supporting Information for full details). Aliphatic aldehydes, however, were found to be more unpredictable. Whereas tertiary and monosubstituted aliphatic aldehydes resulted in products with high enantioselectivity (93% and 63% ee, respectively; entries 4 and 2), secondary aldehydes, rather inexplicably, gave very low selectivity. In all cases, the trans epoxide was formed exclusively.

Further functionalization of the glycidic amide products was then carried out.[33] It was possible to convert the epoxy amide into the corresponding epoxy ketone with complete chemoselectivity using an organolithium reagent (Scheme 3). Subjecting the epoxy ketone to *m*-CBPA gave the corresponding ester in good yield, which could then be hydrolyzed to the corresponding carboxylic acid (vide infra). Direct hydrolysis of the tertiary amide to the acid in the presence of the sensitive epoxide moiety was not possible.

In addition, it was possible to carry out a regioselective nucleophilic ring-opening of the epoxides. It was initially assumed that ring-opening would occur preferentially at the benzylic position, but addition of thiophenol in a range of

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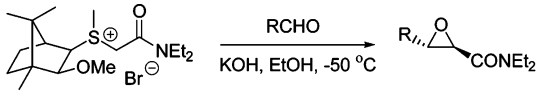
Table 2. Asymmetric Synthesis of (2*R*,3*S*)-2,3-Epoxy Amides Using Camphor-Derived Sulfonium Salt **1b** and a Variety of Aldehydes



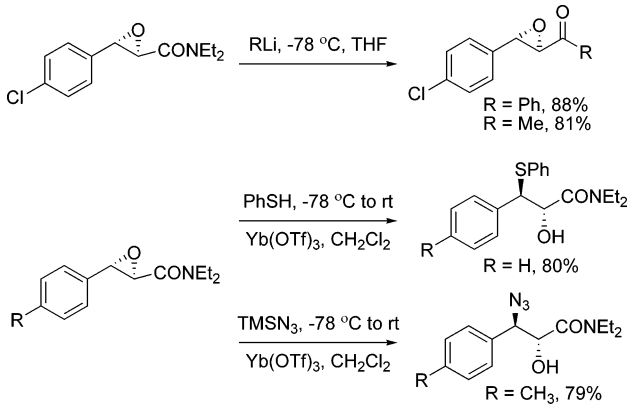
1b **5**

Entry	R	% Yield of **5**	% ee[a]
1	Ar	85-93	92-97
2[b]	dodecyl	84	63
3[c]	*i*-propyl	79	10
4[c]	*t*-butyl	87	93

[a] The enantiomeric excess was determined by chiral HPLC, and the absolute configuration of the product was determined by comparison of HPLC elution orders and [α_D] values with the literature (see Supporting Information for further details and an expanded table of results). [b] Epoxidation was carried out at −30 °C. [c] Epoxidation was carried out at −20 °C.

solvents with different bases furnished a 1:1 mixture of regioisomers. Reports by Berhens and Sharpless[34] of regioselective C_3-ring opening of glycidic esters and secondary amides[35] using $Ti(OiPr)_4$ were also tested, but they also gave a 1:1 mixture of regioisomers. Finally, it was discovered that $Yb(OTf)_3$ catalyzed the ring-opening with complete regioselectivity at the C_3 position for both S and N nucleophiles (Scheme 3).

Scheme 3. Further Functionalization of Epoxy Amides



Although epoxidation had been shown to work well with the *N*,*N*-diethyl amide derivatives, the limitations that had been observed, in terms of transformation into the corresponding carboxylic acid, as well as our interest in the effect of the amide functionality in the epoxidation reaction, prompted us to investigate other amide functionalities (Table 3). We hoped that this would help us identify the features required for selectivity, but it was also thought that the synthesis of enantiopure epoxides containing more versatile amide functionalities would improve the applicability of this method in the synthesis of complex target compounds. Because we had observed that primary and secondary amides did not give useful levels of enantioselectivity, our attention was focused on the use of a range of other tertiary amide substrates that could be readily prepared, would give high enantioselectivity in the epoxidation step, and might be more easily hydrolyzed. In our efforts to understand the features responsible for high enantioselectivity, we tested both the −OH- and −OMe-substituted sulfonium salts. In most cases, the enantioselectivities observed for the OMe derivative were superior.

Initially, salts with bromide as the counteranion were employed, but investigations were also made into the use of other counterions including $^-BPh_4$ and $^-ClO_4$. The respective salts had different solubilities and, therefore, in some cases, facilitated the recrystallization process. These salts could be prepared via an ion-exchange method that involved stirring the bromide sulfonium salt with, for example, $NaBPh_4$ overnight in a minimum volume of acetone. Complete ion exchange could be observed by NMR studies. It was observed, however, that a change in counteranion did not have much influence on the observed enantioselectivity (see entries 2, 4, and 5). In general, as previously observed, we saw slight increases in enantioselectivity on going from the hydroxy sulfide to the methoxy-derived sulfide (compare entries 5 and 6 and entries 12 and 13).

It is interesting to note that, in some cases, temperature does not appear to have an effect on the enantioselectivity of the reaction. Comparing entries 2 and 3 (which were carried out at RT and −50 °C, respectively), it can be seen that decreasing the temperature from RT to −50 °C gave only a 2% increase in enantiomeric excess. However, there is a much larger effect for salt **7a** (entries 7 and 8). In this case, there was an increase from 81% to 97% ee when the temperature was lowered. It is not clear why some amides are more sensitive to temperature effects than others.

From Tables 1 and 3, we can conclude that, whereas dialkyl and cyclic amides are good substrates for our epoxidation process, primary and secondary amides and morpholine-substituted amides are not useful substrates for this reaction.

Although formation of the desired sulfonium salts occurred uneventfully and generally in high yield, in each case, a diastereomeric mixture of sulfonium salts was obtained (ratio was established by ^1H NMR spectroscopy), ranging from 3:2 to 16:1 (except for **7a**, which was obtained as a single diastereomer after alkylation). In the design and synthesis of chiral sulfides for use in asymmetric epoxidation reactions, the diastereomeric purity of the intermediate sulfonium salt is usually a major consideration.[36,37] It is for this reason that the sulfides employed often either are C_2-symmetric,[36,38,39] in which alkylation of either lone pair of the sulfur leads to the same diastereomeric product, or have a conformationally rigid structure in which only one of the lone pairs of the sulfur is available for alkylation.[36,40] In the specific case of this work, the importance of using a single diastereomer of sulfonium salt was realized at an early stage of the investigation (Table 4).

Through analysis of the stereochemical outcomes of different diastereomeric mixtures of sulfonium salts, it was shown that the higher the diastereomeric purity of the salt, the higher the enantioselectivity of the epoxide (entries 5 and 6). It is also interesting to note that the pure minor diastereomer of salt **1b**

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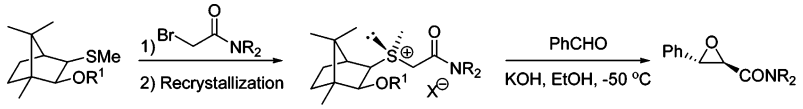
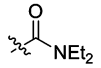
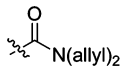
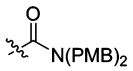
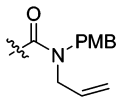
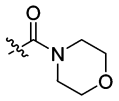
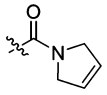
Table 3. Asymmetric Synthesis of (2*R*,3*S*)-2,3-Epoxy Amides Using a Range of Camphor-Derived Sulfonium Salts



Entry	Amide	Salt	Sulfonium salt			Epoxy-amide	
			R^1	X	Salt ratio	Yield	ee[a]
1		**1b**	Me	Br	100:0	93	97
2		**6a**	H	Br	100:0	92[b,c]	87[b,c]
3		**6a**	H	Br	100:0	100[b]	89[b]
4		**6a**	H	BPh_4	100:0	n/d	87[b,c]
5		**6a**	H	ClO_4	100:0	90[b,c]	85[b,c]
6		**6b**	Me	ClO_4	100:0	98[b,c]	90[b,c]
7		**7a**	H	ClO_4	100:0	61	97
8		**7a**	H	ClO_4	100:0	n/d	81[c]
9		**8a**	H	ClO_4	100:0	71	92
10		**9a**	Me	BF_4	3:1	76[b,d]	39[b,d]
11		**10a**	H	Br	100:0	68	81
12		**10a**	H	Br	100:0	82[b]	85[b]
13		**10b**	Me	Br	100:0	74	90

[a] The enantiomeric excess was determined by chiral HPLC, and the absolute configuration of the product in entry 1 was determined by comparison of HPLC elution order with the literature. All others are given by analogy. [b] These reactions were carried out using *p*-Cl−PhCHO as the substrate. [c] Epoxidation was carried out at room temperature. [d] Epoxidation was carried out at 0 °C. [e] Pure minor diastereoisomer was used. n/d = yield not determined.

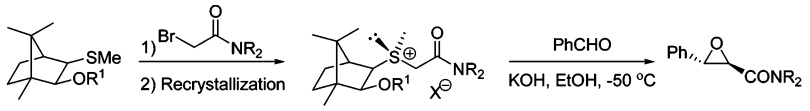
yielded the same major enantiomer of epoxide but with lower enantioselectivity (54% ee as opposed to 97% ee; compare entries 2 and 4).[33] Keeping this in mind and comparing our results with those obtained by Dai et al. under very similar reaction conditions (entry 3),[41] we believe that our superior enantioselectivity is due to the use of a single diastereomer of sulfonium salt. Fortunately, in most cases, the major diastereomer of the sulfonium salt could be isolated either by recrystallization (this was aided in some cases by counteranion exchange, vide supra) or by column chromatography. The stereochemistry at sulfur for the major isomer of sulfonium salt **6b** was determined by X-ray analysis to be *R* (see Figure 1), and thus, the stereochemistry at sulfur of the major diastereomer of the rest of the sulfonium salts has been assigned by analogy.

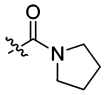
Ring Opening of Epoxides and Applications. Whereas diallyl amide was resistant to hydrolysis to the corresponding glycidic acid, the epoxide could be opened by thiophenol. As in the case of the diethyl amide, a mixture of regioisomers in a 1:1 ratio was obtained in the presence of $Ti(O^iPr)_4$.[34] However, use of $Yb(OTf)_3$ led to ring opening of amide **12** with complete regioselectivity at the C_3 position with both sulfur and nitrogen nucleophiles (Scheme 4). According to the literature, cleavage of *N*-allyl substituents of amide groups can be effected using either rhodium,[42,43] ruthenium,[44] or nickel[45] catalysts, but in our hands, all attempts to prepare either the primary or secondary

(41) Although our reaction was carried out at −50 °C rather than room temperature, we believe that temperature does not have a great effect on the enantioselectivity. Indeed, we have shown that, whereas epoxidation at −50 °C gives a product with 92% ee, the corresponding reaction at room temparture resulted in an epoxide with 87% ee (see Table 3 and ref 33).

(42) Lessen, T. A.; Demko, D. M.; Weinreb, S. M. *Tetrahedron Lett.* **1990**, *31*, 2105−2108.
(43) Moreau, B.; Lavielle, S.; Marquet, A. *Tetrahedron Lett.* **1977**, *18*, 2591−2594.
(44) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781−3784.
(45) Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **1998**, *39*, 4679−4682.

Table 4. Investigation into Importance of Diastereomeric Purity of Sulfonium Salt



Entry	Amide	Salt	Sulfonium salt			Epoxy-amide	
			R^1	X	Salt ratio	Yield	ee[a]
1		**1a**	H	Br	100:0	85	92
2		**1b**	Me	Br	100:0	93	97
3[b]		**1a**	H	Br	Unknown	61	71.5
4[c]		**1b**	Me	Br	0:100	nd	54
5		**11b**	Me	Br	2:1	72[d,e]	73[d,e]
6		**11b**	Me	Br	14:1	84[d,e]	90[d,e]

[a] The enantiomeric excess was determined by chiral HPLC, and the absolute configuration of the product in entry 1 was determined by comparison of HPLC elution order with the literature. All others are given by analogy. [b] Results from ref 29; reaction carried out in CH_3CN at room temperature. [c] Pure minor diastereoisomer was used. [d] These reactions were carried out using *p*-Cl−PhCHO as the substrate. [e] Epoxidation was carried out at 0 °C.

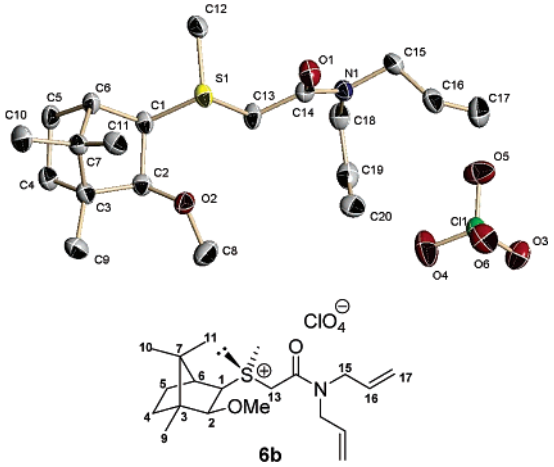
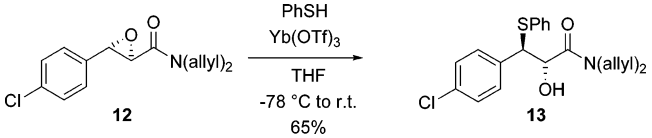


Figure 1. X-ray structure of sulfonium salt **6b**.

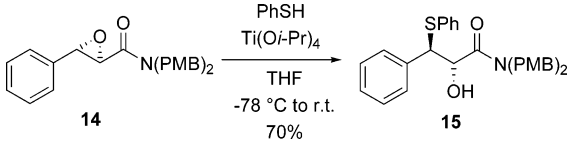
amide proved to be fruitless both in the presence of the sensitive epoxide functionality (**12**) and even after ring opening had occurred (**13**).

Scheme 4. Ring Opening of Diallyl-Substituted Epoxy Amide **12**



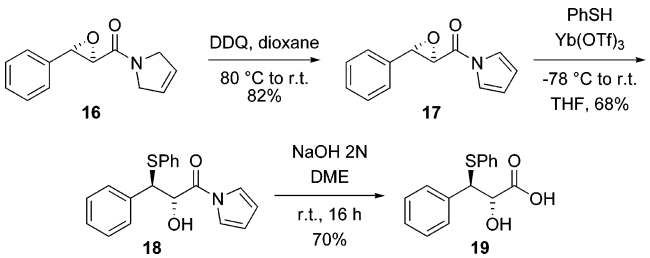
Efforts then focused on the bis-PMB-protected amide, as it was anticipated that this could be cleaved by use of CAN[46] or DDQ.[47] Again, good yields and excellent selectivities were observed for the formation of the desired glycidic amide **14**, and this time, ring-opening of the epoxide with a sulfur nucleophile in the presence of $Ti(O\text{-}^iPr)_4$ yielded a single regioisomeric product (ring opened in the C_3 position) according to the method of Berhens and Sharpless (Scheme 5).[34] The selectivity for ring opening at C_3 in this case was probably facilitated by the much bulkier amide substituents. Unfortunately, efforts to hydrolyze this amide, either before or after ring opening, also proved to be unsuccessful.

Scheme 5. Ring Opening of Bis-PMB-Protected Epoxy Amide 14



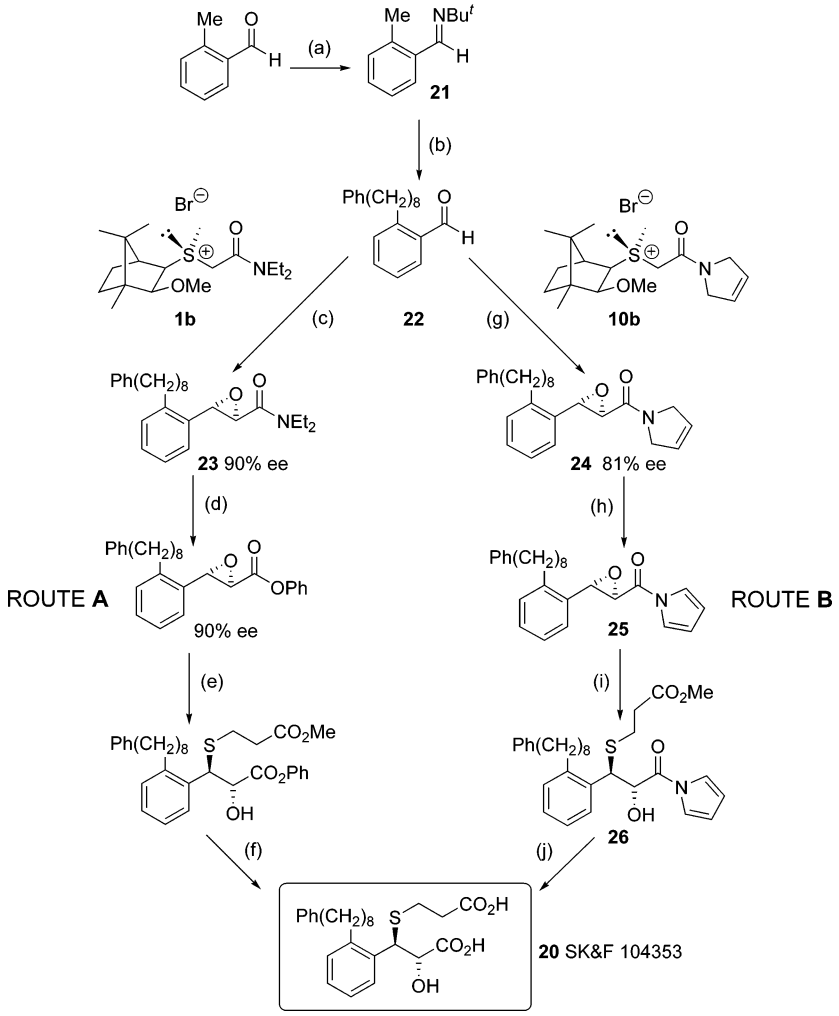
Following the work of Shibasaki et al.,[48] who successfully employed an epoxy acyl pyrrole as a versatile intermediate and glycidic ester surrogate, epoxide **16** was prepared in good yield and high enantioselectivity (entries 11 and 13, Table 3). The product was then oxidized by DDQ to give the pyrrole intermediate **17**. It was not possible to prepare the pyrrole epoxide **17** directly, as the corresponding pyrrolamido sulfonium salt was unreactive toward the aldehyde. After ring opening using PhSH in the presence of $Yb(OTf)_3$, the pyrrole was readily hydrolyzed to the corresponding acid (**19**) by treatment with NaOH in good yield (Scheme 6).

Scheme 6. Ring Opening and Hydrolysis of Epoxy Acyl Pyrrole **17**



(46) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1414.
(47) Grunder-Klotz, E.; Ehrhardt, J.-D. *Tetrahedron Lett.* **1991**, *32*, 751−752.

Scheme 7. Two Approaches to the Total Synthesis of SK&F 104353[a]



[a] Reagents and conditions. (a) *t*-BuNH$_2$, toluene, 110 °C, 93%. (b) (i) LDA, Ph(CH$_2$)$_7$Br, THF, −78 to 60 °C; (ii) HCl, 85%. (c) **22**, KOH, MeOH, −30 °C, 24 h, 77%. (d) (i) PhLi, THF, −78 °C, 84%; (ii) *m*-CPBA, CH_2Cl_2, Δ, 68%. (e) HS−$(CH_2)_2$−CO_2Me, Yb(OTf)$_3$, CH_2Cl_2, −78 °C to room temperature, 64%. (f) NaOH, MeOH, H_2O, room temperature, 16 h, 81%. (g) **22**, KOH, EtOH, −50 °C, 48 h, 62%. (h) DDQ, dioxane, 85 °C, 8 h, 81%. (i) HS−$(CH_2)_2$−CO_2Me, Yb(OTf)$_3$, CH_2Cl_2, −78 °C to room temperature, 58%. (j) NaOH, DME, H_2O, room temperature, 16 h, 85%.

In summary, we have shown that it is possible to prepare epoxy amides in good yield, complete diastereoselectivity, and excellent enantioselectivity when secondary alkyl and cyclic amides are employed as substrates. The importance of using a diastereomerically pure sulfonium salt to obtain epoxides in high enantioselectivity has been illustrated, and we have shown that, although low temperature is an important consideration for some amides, in other cases, equally high selectivities can also obtained at room temperature. In addition, we have demonstrated that the epoxy amide products can be further functionalized by nucleophilic ring opening under Lewis acidic conditions. The corresponding carboxylic acids can be obtained either by the addition of organolithium reagents followed by Baeyer−Villiger oxidation and subsequent hydrolysis or by use of an epoxy acyl dihydropyrrole that can be oxidized and then subsequently hydrolyzed to the carboxylic acid.

Asymmetric Synthesis of SK&F 104353. The synthetic applicability of our new methodology for the enantioselective synthesis of glycidic amides was showcased in the synthesis of SK&F 104353 (**20**), a leukotriene D_4 inhibitor for the potential treatment of bronchial asthma.[49] The shortest synthesis of SK&F 104353 to date was reported by Lantos et al.[50] In their synthesis, the desired epoxide was formed in 95% ee using the Juliá−Collona epoxidation[10] on an α,β-unsatutated ketone with a polyleucine catalyst. The target compound was obtained in a 35% overall yield in eight steps.

We were able to prepare this molecule by two complementary routes, both of which involved the sulfur ylide methodology discussed above as the key step (Scheme 7). Route A involving the diethylamide sulfonium salt **1b**, was reported in a communication[33] and is also described in the Supporting Information.

Route B involved the reaction of the diastereomerically pure sulfonium salt **10b**, instead of **1b**, with the known aldehyde **22**[51] (Scheme 7, route B), and in this case, the glycidic amide was obtained in 81% ee. In both routes A and B, the chiral sulfide **2b** was reisolated by column chromatography in >90%

(48) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9474−9475.

(49) Mong, S.; Wu, H. L.; Miller, J.; Hall, R. F.; Gleason, J. G.; Crooke, S. T. *Mol. Pharmacol.* **1988**, *32*, 223.

(50) Flisak, J. R.; Gombatz, K. J.; Holmes, M. M.; Jarmas, A. A.; Lantos, I.; Mendelson, W. L.; Novack, V. J.; Renich, J. J.; Schneider, L. *J. Org. Chem.* **1993**, *58*, 6247.

(51) Firth, M. A.; Mitchell, M. B.; Smith, S. A. C. *J. Org. Chem.* **1995**, *59*, 2616.

yield. Oxidation of **24** using DDQ afforded the pyrrole derivative **25** in high yield, and this epoxy acyl pyrrole was then opened with 3-mercaptopropionate in the presence of $Yb(OTf)_3$. The ring-opened derivative **26** was formed as a 14:1 mixture of regioisomers that were separable by silica gel chromatography. The major isomer was obtained in moderate yield and was subsequently hydrolyzed to give the target compound **20**. Thus, the target compound was formed via this complementary route in a sequence of five linear steps with an overall yield of 23%.

Origins of Diastereoselectivity and Enantioselectivity. The mechanism of the sulfur-ylide-mediated epoxidation reaction involves two key steps along each of the diastereoisomeric pathways leading to cis and trans epoxides (see Figure 2 for semistabilized ylide epoxidations).[52] The first is addition of the ylide onto the aldehyde to form a betaine intermediate. This initial addition step occurs via a quasi-[2 + 2] mode of addition (i.e., where the sulfonium and oxy groups are gauche with respect to each other), which makes favorable Coulombic interactions between the dipoles of the polar reactants possible.[52] The betaine formed initially is therefore in a cisoid conformation. In order for the second key step to occur, this betaine needs to undergo rotation around the newly formed carbon−carbon bond to give the corresponding transoid conformer. This latter betaine can then ring close to yield the desired epoxide.

Two isomeric betaines can be formed during the addition step: an anti and a syn diastereomer. After torsional rotation and ring closure, these betaines lead, respectively, to a trans and a cis epoxide. Through experimental[53,54] and computational[52] investigations, we recently showed that, in the reaction of semistabilized ylides (R_2SCHPh), the high trans selectivity is a result of similar rates of formation for both syn and anti betaines, where formation of the syn betaine is reversible but the anti betaine does not reverse and leads directly to the trans epoxide (Figure 2). This difference in reactivity between the two diastereomeric pathways was found to be mainly due to the high barrier for the torsional rotation step for the syn betaine.

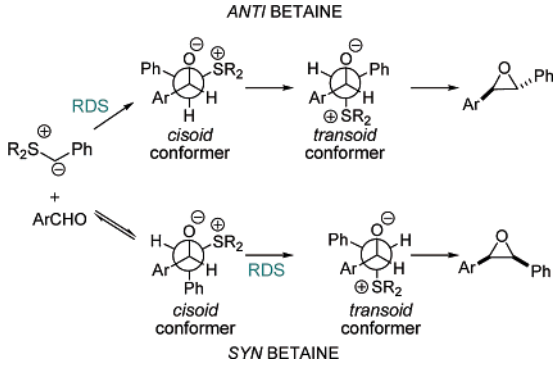
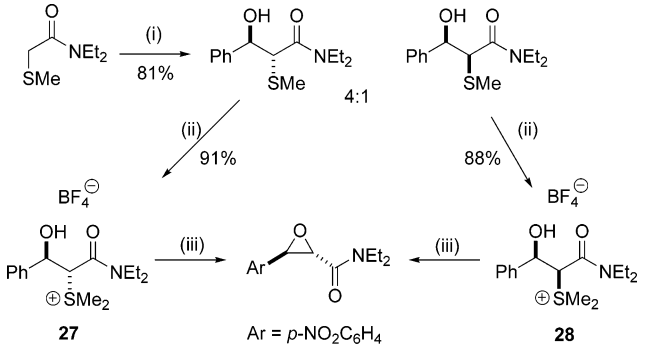


Figure 2. Mechanism of semistabilized ylide epoxidation.

In the case of amide-stabilized ylides, one might expect greater reversibility in betaine formation because the ylide is more stable than in the case of phenyl-stabilized ylides. To test whether betaine formation is reversible, a crossover experiment was conducted in which the two diastereomeric betaines were independently generated by another route in the presence of a more reactive aldehyde. If betaine formation were nonreversible, direct ring closure would occur without incorporation of the more reactive aldehyde and ring closure would be a stereospecific process, whereas if betaine formation were reversible, the more reactive aldehyde would be trapped and trans epoxide would be preferentially obtained even in the case of the syn betaine.

The substrates for the crossover experiments, **27** and **28**, were prepared by an aldol reaction, followed by separation of the diastereoisomers and subsequent alkylation with Meerwein's salt (Scheme 8). Treatment of either the anti or syn β-hydroxy sulfonium salt (**27** or **28**, respectively) with a base in the presence of a more reactive aldehyde (p-$NO_2C_6H_4CHO$) gave only trans epoxide in which the more reactive aldehyde had been incorporated (Scheme 8).

Scheme 8. Crossover Experiments Indicating that the Betaine Formation Is Reversible[a]



[a] Reagents and conditions. (i) LDA. −78 °C, LiCl, PhCHO; (ii) Me_3OBF_4, CH_2Cl_2; (iii) 3 equiv of p-$NO_2C_6H_4CHO$, 1.5 equiv of NaOH, CH_2Cl_2, H_2O, room temperature.

This indicates that, in the case of amide-stabilized ylides, both diastereomeric betaines reverse to reactants, which means that the rate- and selectivity-determining step must lie after the addition step in both cases. The exclusive trans selectivity observed in these reactions must therefore result from a significant barrier in either the bond rotation or ring-closure step of the syn betaine, which results in reversal back to the ylide and aldehyde. But which of the two steps (bond rotation or ring closure) is rate-determining? Is it the same in both diastereomeric pathways? What is the origin of the exclusive trans epoxide formation? To answer these questions, we investigated the energy profile of the reaction of ylide **29** with benzaldehyde computationally (Figure 3). Calculations[55] were carried out at the B3LYP/6-311+G**//B3LYP/6-31G* level, including a continuum description of ethanol as the solvent (see the Supporting Information for computational details). Such methods have already been shown to describe accurately energy profiles of similar systems.[52,56]

As previously observed for reaction of semistabilized ylides,[52] the addition of the stabilized ylide **29** to benzaldehyde occurs via a quasi-[2 + 2] approach of the reactants, leading to the betaines in their cisoid conformation. Given the stabilization

(52) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747−5756.
(53) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926−10940.
(54) Aggarwal, V. K.; Richardson, J. *Chem. Commun.* **2003**, 2644−2651.
(55) Calculations were carried out using the Jaguar 4.0 pseudospectral program package (*Jaguar 4.0*; Schrödinger, Inc.: Portland, OR, 1991−2000). Relative energies correspond to electronic energies at the indicated level of theory. See Supporting Information for computational details.
(56) Aggarwal, V. K.; Harvey, J. N.; Robiette, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 5468−5471.

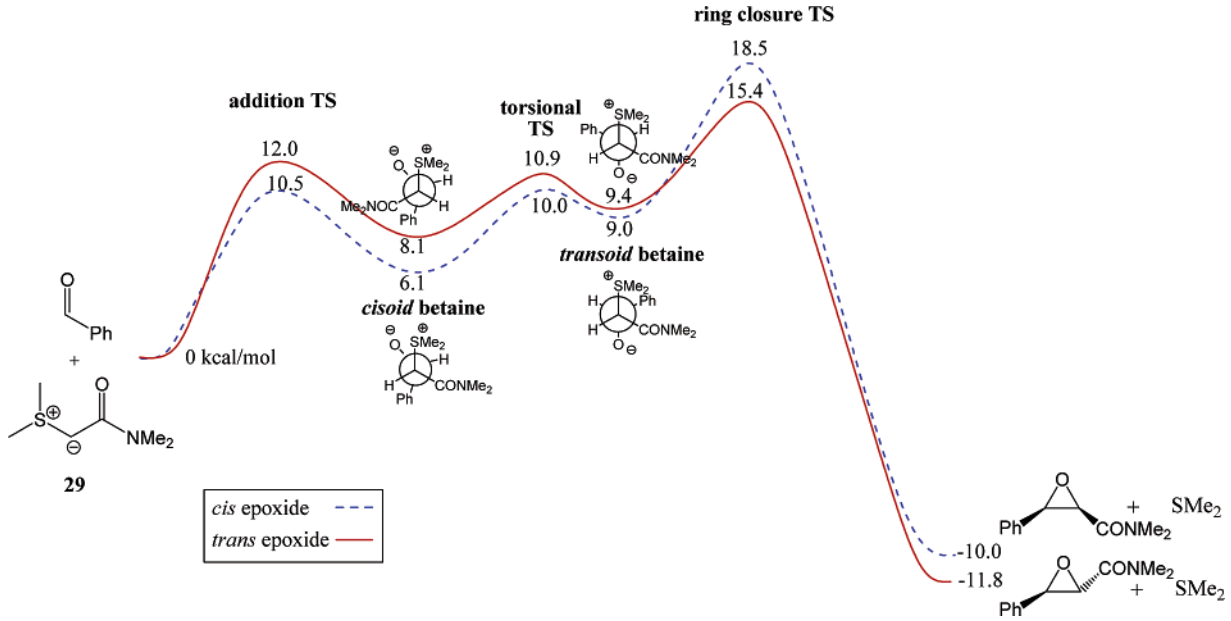


Figure 3. Computed potential energy profile for the epoxidation reaction between benzaldehyde and ylide 29. Energies were obtained at the B3LYP/6-311+G**(ethanol)//B3LYP/6-31G*(ethanol) level and are given in kcal/mol relative to reactants.

of the reactants, this step is endothermic (6−8 kcal/mol; for comparison, the energy of this step was between −2 and −3 kcal/mol for the semistabilized Me_2SCHPh ylide[52]) and, consequently, occurs with a significant energy barrier (10−12 kcal/mol; the barrier is ∼4 kcal/mol for Me_2SCHPh ylide[52]). The syn diastereomer of the betaine is found to be more stable and formed through a lower barrier than the anti one. However, for both diastereomeric cisoid betaines, the energy barrier to torsional rotation is close to the barrier to reverse to reactants. Moreover, compared to a phenyl substituent, the amide group imposed a higher barrier to ring closure,[57] and the highest point on the potential energy surface was found to be, in both cases, the transition state of the ring-closure step. Therefore, the addition and the rotation steps should be entirely reversible for both diastereomeric pathways. In other words, the rate-determining, and thus diastereoselectivity-determining, step is ring closure (Figure 4).

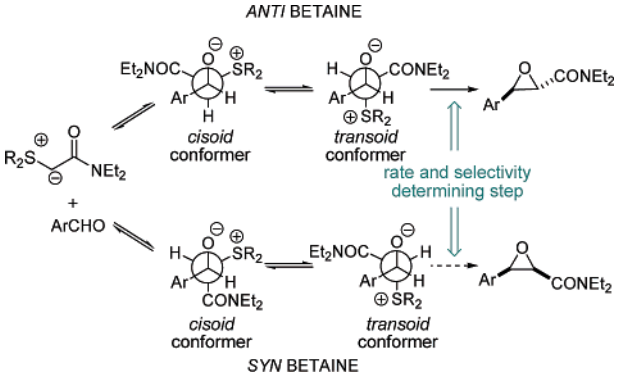
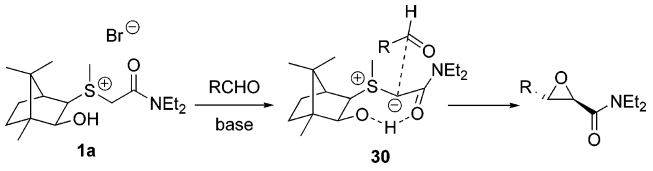


Figure 4. Origin of diastereo- and enantioselectivity in stabilized ylide reactions.

The exclusive formation of trans epoxide in reactions of stabilized ylides can thus be explained as follows: Initial addition to form the syn betaine is faster than formation of the anti betaine. However, ring closure of the syn betaine to the cis epoxide is highly disfavored because of developing steric interactions between the phenyl and amide substituents, so that syn betaine formation is unproductive. Reversion to reactants is followed by addition to form the anti betaine, which undergoes ring closure much more rapidly, leading to the observed preferential formation of trans epoxide. It is harder to account for the high enantioselectivity that is observed.

Scheme 9. Transition State Proposed by Dai et al.[29] to Explain the Enantioselectivity



Dai et al. proposed that sulfonium salt **1a** reacts with aldehydes via transition state **30** (Scheme 9), in which hydrogen bonding controls the conformation of the ylide and nonbonding interactions between the ylide and aldehyde are responsible for the enantioselectivities observed.[29] However, our calculations and crossover experiments indicate that selectivity in the addition step is unimportant in determining the enantioselectivity of the overall process. If we assume similar energy profiles for the reaction of the chiral ylide **1a** and for **29**, the enantioselectivity must be determined by the relative energy of enantiogenic transition states in the ring-closure step. The exact nature of the interactions in these transition states that are responsible for the high enantioselectivity observed is, however, very difficult to identify because of the flexibility of the system.

Conclusions

We have described a completely diastereoselective, highly enantioselective, and practical process for the synthesis of epoxy amides. To achieve high diastereoselectivity, single

(57) The high barrier to ring closure seems to be due to the substitution of the electrophilic carbon by an electron-withdrawing group (an amide). This is in contradiction to the high reactivity usually observed for α-halogenated carbonyl compounds in S_N2 reactions. Studies aiming at understanding this dissimilarity are currently underway in our laboratories.

diastereomers of sulfonium salts bearing tertiary amides are required. The epoxy amide products were further transformed by ring opening with a variety of nucleophiles, followed by hydrolysis of the amide to yield the corresponding carboxylic acid. In addition, we have demonstrated how this methodology can be applied to two complementary syntheses of SK&F 104353.

Moreover, we have enhanced our mechanistic understanding of this process. Crossover experiments indicated that the formation of both the syn and anti betaines is reversible, and a computational study allowed us to identify the rate- and selectivity-determining step as being ring closure, not bond rotation as was the case with phenyl-stabilized ylides.

Supporting Information Available: Full experimental details, compound characterization data, X-ray structures, computational details, and tables with optimized Cartesian coordinates and corresponding energies for all species discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0568345