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On the Mechanism of Ylide-Mediated Cyclopropanations: Evidence for a Proton-Transfer Step and Its Effect on Stereoselectivity

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Abstract: In this paper, we describe studies on the cyclopropanation of Michael acceptors with chiral sulfur ylides. It had previously been found that semi-stabilized sulfonium ylides (e.g., Ph-stabilized) reacted with cyclic and acyclic enones and substituted acrylates with high ee and that stabilized sulfonium ylides (e.g., ester-stabilized) reacted with *cyclic* enones again with high ee. The current study has focused on the reactions of stabilized sulfonium ylides with *acyclic* enones which unexpectedly gave low ee. Furthermore, a clear correlation of ee with ylide stability was observed in reactions with methyl vinyl ketone (MVK): ketone-stabilized ylide gave 25% ee, ester-stabilized ylide gave 46% ee, and amide-stabilized ylide gave 89% ee. It is believed that following betaine formation an unusual proton transfer step intervenes which compromises the enantioselectivity of the process. Thus, following addition of a stabilized ylide to the Michael acceptor, rapid and reversible intramolecular proton transfer within the betaine intermediate, prior to ring closure, results in an erosion of ee. Proton transfer occurred to the greatest extent with the most stabilized ylide (ketone). When the same reactions were carried out with deuterium-labeled sulfonium ylides, higher ee's were observed in all cases since proton/deuteron transfer was slowed down. The competing proton transfer or direct ring-closure pathways that are open to the betaine intermediate apply not only to all sulfur ylides but potentially to all ylides. By applying this model to S-, N-, and P-ylides we have been able to rationalize the outcome of different ylide reactions bearing a variety of substituents in terms of chemo- and enantioselectivity.

Introduction

Cyclopropanes are common motifs to a large number of natural products and biologically active pharmaceutical agents.[1] They are usually prepared by addition of metal carbenoids to electron-rich/-neutral alkenes or by addition of ylides to electron-deficient alkenes.[2] We, and others, have shown that chiral semi-stabilized sulfur ylides are particularly effective at promoting asymmetric cyclopropanation of acyclic electron-deficient alkenes; with unsaturated esters, in particular, high diastereoselectivity is also observed (Scheme 1).[3] Furthermore, we have also shown that ester-stabilized sulfur ylides are effective in the cyclopropanation of cyclic enones, albeit with low diastereoselectivity in this case (Scheme 2).[4,5] In all cases, high ee's were obtained, and the absolute sense of asymmetric induction was in keeping with the model described for asymmetric epoxidation.[6] Based on these positive results, the reaction of an ester-stabilized ylide with an acyclic enone was expected to give a cyclopropane with both high dr and ee. We envisaged that such methodology could be effectively utilized in the synthesis of the cyclopropyl-containing natural products hali-

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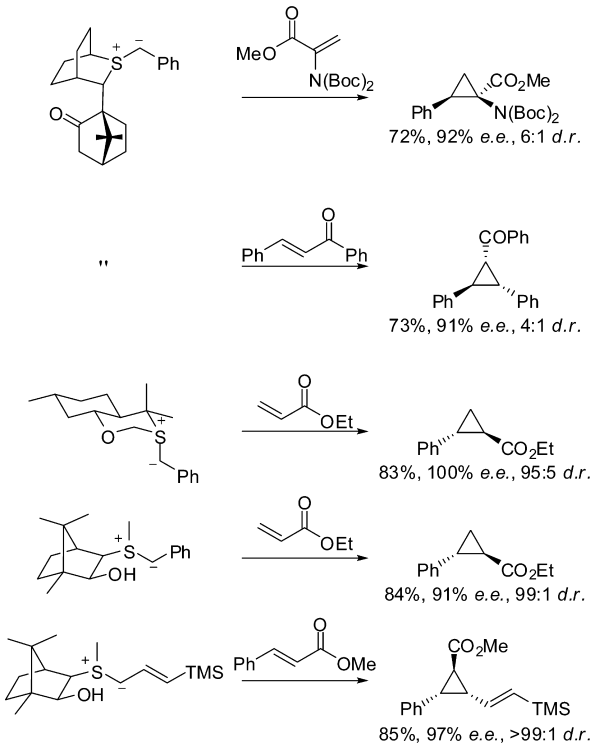
(4) Aggarwal, V. K.; Grange, E. *Chem.—Eur. J.* **2006**, *12*, 568–575.

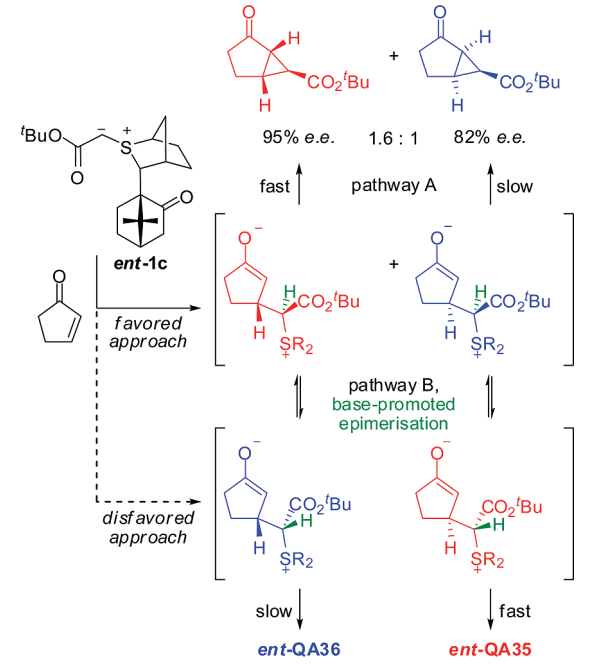
(5) For cyclopropanations using achiral, stabilized sulfur ylides, see ref 3d and references therein; see also: Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351–3355.

10.1021/ja910631u

Scheme 1. Asymmetric Cyclopropanations with Semi-stabilized Ylides[3]



Scheme 2. Asymmetric Cyclopropanation of Cyclopentenone with Ester-Stabilized Ylide ***ent*-1c**[4]



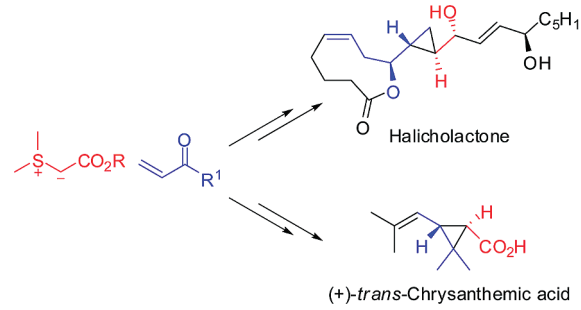
cholactone and chrysanthemic acid (Scheme 3). However, our synthetic plans were thwarted as further methodological studies produced surprisingly poor results. Through detailed analysis of the reaction, we are now able to account for the factors responsible for the chemo- and enantioselectivity in this and in fact all reactions of stabilized ylides (S, N, and P) with enones.

Results and Discussion

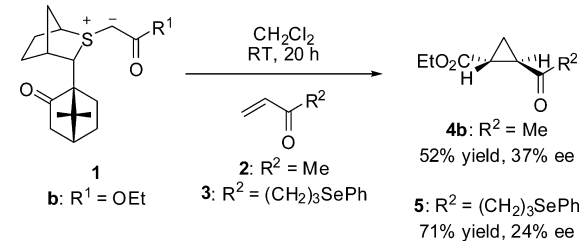
Our surprise came in reactions of the ester-stabilized ylide **1b** with the acyclic enones **2** and **3**, which gave the corresponding cyclopropanes but with alarmingly low enantioselectivity (Scheme 4).[7] The differences in enantioselectivities in reactions of the chiral ester-stabilized ylides **1b** (R^1 = OEt) and **1c** (R^1 = O-*t*-Bu) with cyclopentenone (81% and 95% ee, respectively)[4] and enone **3** (24% ee) were especially striking. Some clues to the origin of this difference in selectivity were illuminated from our earlier study on the cyclopropanation of cyclopentenone.[4] Previously, we had found that the enantioselectivity was dependent on concentration: high concentration gave low enantioselectivity, whereas low concentration gave high enantioselectivity. These observations were accounted for by considering the fate of the betaine intermediate, which can undergo either direct (unimolecular) ring closure leading to high enantioselectivity (pathway A, Scheme 2) or bimolecular deprotonation/protonation by base or ylide (pathway B), which leads to epimerization and consequently a substantial erosion in enantioselectivity. At low concentration, the bimolecular process B is slowed down considerably, and unimolecular ring-closure via pathway A dominates leading to high enantioselectivity.

However, the reaction of ylide **1b** with enone **3** did not respond to changes in concentration: the same levels of selectivity (24% ee) were observed at 1 and 0.01 M. If epimerization of the betaine intermediate was still the cause of the erosion of ee, the above experiments showed that this process was now also unimolecular. In the case of the acyclic enone reaction, the *Z*-enolate could act as the base and remove the acidic proton intramolecularly, generating an ylide intermediate **7**. Reprotonation on either face of the ylide and ring closure would lead then to racemic cyclopropane (Scheme 5). In the case of cyclic

Scheme 3. Planned Starting Point for Syntheses of Halicholactone and (+)-*trans*-Chrysanthemic Acid

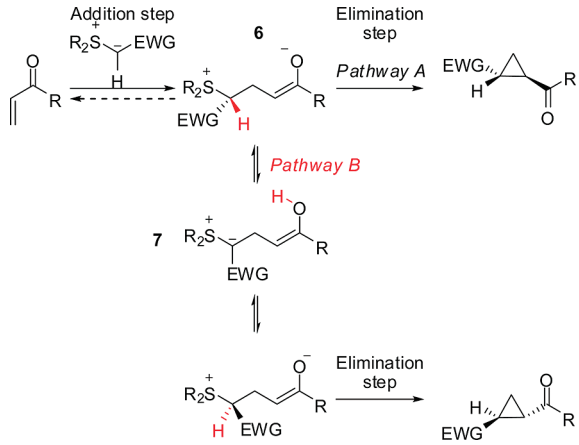


Scheme 4. Asymmetric Cyclopropanations of Acyclic Enones with Ester-Stabilized Ylide **1b**



(6) (a) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, *107*, 5841–5883. (b) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611–620. Aggarwal, V. K. In *Comprehensive Asymmetric Catalysis II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; pp 679−693. (c) Aggarwal, V. K.; Richardson, J. *Chem. Commun.* **2003**, 2644–2651. (d) 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.

Scheme 5. Proposed Pathways Leading to Cyclopropanes from Enones



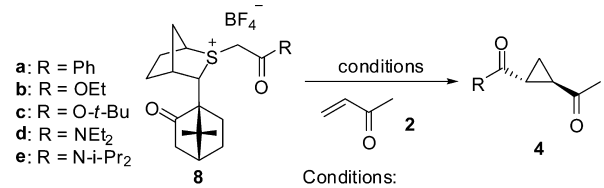
enones, the enolate is constrained to the *E* geometry and so cannot participate in intramolecular proton-transfer events.[8]

This proposed rationale could be easily tested by simply changing the nature of the ylide substituent: a more anion-stabilizing group, e.g., a ketone, should reduce the rate of direct ring closure (pathway A) and facilitate proton transfer (pathway B) leading to low enantioselectivity.[9] In contrast, a less anion-stabilizing group should slow the proton transfer (pathway B) and promote ring closure (pathway A) and thus lead to high enantioselectivity. A series of sulfonium salts bearing different carbonyl functionalities were therefore prepared and reacted with methyl vinyl ketone (MVK) **2** (Table 1). As expected, a marked increase in enantioselectivity was observed with decreasing electron-withdrawing capacity of the carbonyl group (entries 1−4).

Further confirmation that proton transfer via pathway B was responsible for the erosion in enantioselectivity came from kinetic isotope effects. Substituting a proton on the ylidic carbon for a deuteron should result in a slower rate of H/D transfer from carbon to oxygen and thus slow down pathway B. The rate of direct ring closure (pathway A) is not expected to be as significantly affected by the isotope change, and so an overall increase in ee can be expected with the change in isotope.

Unfortunately, attempts to use **D_2-8a** with NaH resulted in an unexpected loss of D during the cyclopropanation process. Since base-promoted H/D-exchange of sulfonium salts was known to be rapid,[10] we employed a two-phase system consisting of water/CH_3CN in the presence of sulfonium salt **8a**,**d**,**e**, NaOH, and MVK **2** to effect cyclopropanations. The experiments were repeated using D_2O/NaOD in place of H_2O/NaOH,

Table 1. Enantioselectivities Obtained in the Reaction of **2** with Different Stabilized Ylides under Various Conditions[a]

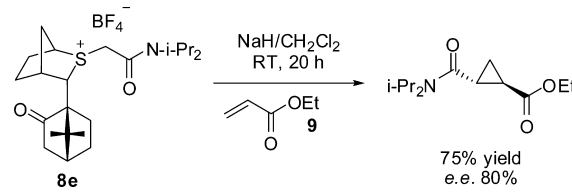


Conditions:
A: NaH/CH_2Cl_2, RT, 20 h
B: $NaOH/CH_3CN/H_2O$, RT, 22 h
C: $NaOD/CH_3CN/D_2O$, RT, 22 h

		% ee		
	R	NaH	$NaOH/H_2O$	$NaOD/D_2O$[b]
1	Ph	26	49	68
2	OEt	37	*c*	
3	O-*t*-Bu	46	*c*	
4	NEt_2	78	70[d]	85
5	N-*i*-Pr_2	85	88	92

[a] Yields were in the range 52−91%; see the Supporting Information for details. [b] Using $NaOD/D_2O$, the isolated product had deuterium incorporated on the cyclopropyl carbon α to C(O)R and on the CH_3 group; see the Supporting Information for details. [c] These standard conditions were not effective for cyclopropanations with ester-stabilized ylides. [d] Reaction time: 18 h.

Scheme 6. Asymmetric Cyclopropanation of Ethyl Acrylate **9**[11]



and the results are summarized in Table 1. Control experiments firmly established that the protons adjacent to the sulfonium ion and carbonyl group exchanged much more rapidly than formation of the cyclopropane and that no exchange of any of the cyclopropyl protons occurred under the reaction conditions (see the Supporting Information for details).

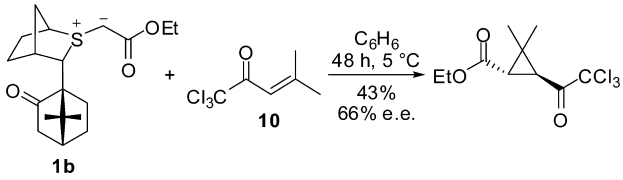
The experiments showed that in all cases the reactions of the deuterium-labeled ylides gave higher enantioselectivities than their protonated analogues. This strongly supports the proposal that deprotonation−reprotonation (probably by the enolate; pathway B, Scheme 5) is responsible for the erosion in ee observed.

Reaction of the amide-stabilized ylide **1e** with ethyl acrylate **9** was also tested (Scheme 6), and this gave slightly lower ee compared to MVK (compare entry 5 in Table 1). This result also fits with our model: in this case the ester enolate is more basic and so pathway B is enhanced.[11]

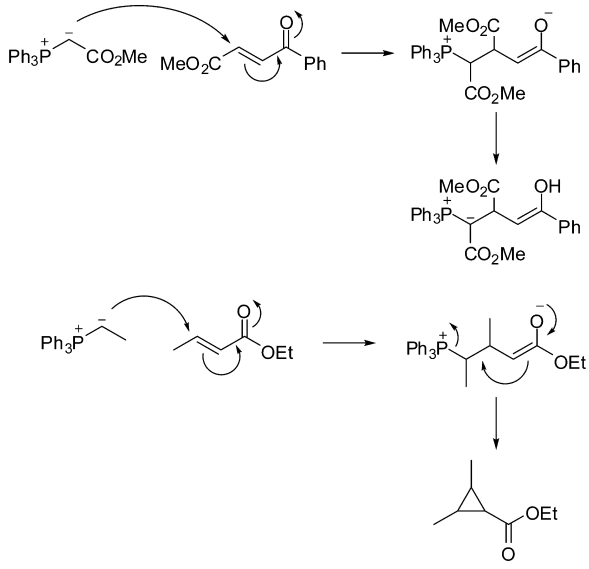
The competing pathways open to betaine **6** that we have identified here now allow us to rationalize many of the sulfur ylide reactions reported to date. Reactions of aryl-stabilized ylides give high ee because cyclization (pathway A) is enhanced, and proton transfer (pathway B) is strongly disfavored since an aryl group is not able to stabilize the ylide sufficiently. Reaction of the stabilized sulfur ylide with enone **10** gave intermediate levels of enantioselectivity compared to MVK **2** (Scheme 7). In this case, the *gem*-dimethyl group in the chain of the betaine

(7) Huang reported two examples of low ee's in cyclopropanations of acyclic substrates using a stabilized ylide: ref 3e.
(8) As part of a computational study on sulfur ylide cyclopropanations, in partial geometry optimizations of betaine intermediates, Sunoj noted the enolate oxygen could deprotonate ylidic hydrogen atoms but there was no further discussion of mechanistic possibilities: Janardanan, D.; Sunoj, R. B. *J. Org. Chem.* **2007**, *72*, 331–341.
(9) Calculations on transition states for ring-closure of betaines derived from sulfur ylides and aldehydes and for analogous intermolecular substitution reactions show a greater degree of S_N1 character in the intramolecular case, explaining the lower ring-closing reactivity with EWGs adjacent to the leaving group; see: Aggarwal, V. K.; Charmant, J. P. H.; Fuentes, D.; Harvey, J. N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R.; Smith, C.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 2105–2114.
(10) Greenberg, F. H.; Schulman, E. M. *J. Org. Chem.* **1993**, *58*, 5853–5854.
(11) Of course, the ester enolate should also be more nucleophilic than the ketone enolate, but evidently the difference in enolate reactivity is more pronounced in proton transfer than in alkylation.

Scheme 7. Cyclopropanation of Enone **10** with Ester-Stabilized Ylide **1b**



Scheme 8. Comparison of the Reactivity of Stabilized and Nonstabilized Phosphorus Ylides with α,β-Unsaturated Esters[13]

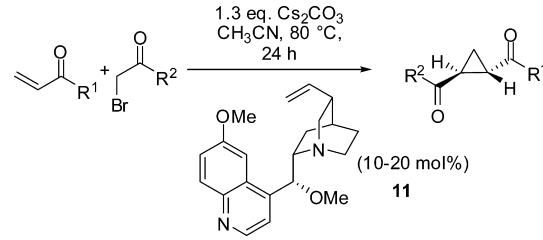


promotes ring closure (pathway A) through the Thorpe−Ingold effect, accounting for the higher levels of selectivity observed.

The analysis of the different competing pathways open to the betaine intermediate (proton transfer versus ring-closure) can be extended to other ylides and nicely accounts for the observed results. For example, stabilized phosphorus ylides do not react with Michael acceptors to give cyclopropanes (Scheme 8). Following conjugate addition, proton transfer occurs instead to give a new stabilized phosphorus ylide.[13] This observation can be rationalized according to the competing pathways open to the intermediate betaine. The extremely poor leaving group ability of the phosphonium ion[12] coupled with its ability to stabilize negative charge results in very slow ring closure (pathway A) and rapid proton transfer (pathway B). In contrast, nonstabilized phosphorus ylides do react with Michael acceptors to give cyclopropanes.[13] In this case, the absence of an EWG serves to inhibit proton transfer (pathway B) and the EDG promotes ring-closure (pathway A), thus leading to cyclization.

At the opposite end of ylide reactivity, Gaunt and Ley have shown that ammonium ylides derived from cinchona alkaloids (e.g., **11**) are highly effective in asymmetric cyclopropanations of Michael acceptors.[14] In this case, proton transfer in the betaine intermediates is expected to be much less favored than ring closure due to the lower acidity of the C−H protons as a result of the poorer ability of the ammonium ion to stabilize the ylide

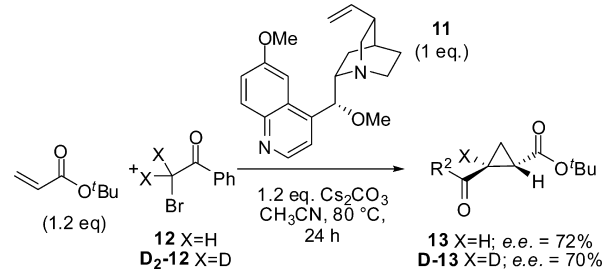
Table 2. Asymmetric Cyclopropanation with Ammonium Ylides[14c]



entry[a]	R^1	R^2	% ee
1[b]	O-*t*-Bu	Ph	71
2	OBn	O-*t*-Bu	80
3	Ph	O-*t*-Bu	86
4	Ph	NEt_2	97

[a] Yields: 75−96%. [b] 1 equiv of **11** was used.

Scheme 9. Ammonium Ylide Cyclopropanation with **12** and **D_2-12**



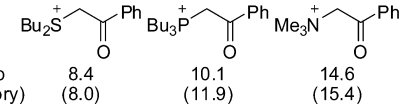
intermediate. Indeed, compared to sulfonium salts, ammonium salts are at least 6 orders of magnitude less acidic.[15] Nevertheless, a subtle effect on ee was observed according to the nature of the Michael acceptor and ylide substituent: higher ee was observed with the less anion-stabilizing group (Table 2). However, this was not due to competing proton transfer in the intermediate betaine since we have found that both **12** and **D_2-12** gave cyclopropanes **13** and **D-13** with essentially the same ee (Scheme 9). The small differences in ee observed between the different substrates (Table 2) could be due to one or more of the following: (i) the varying degrees of background cyclopropanation (Darzens-type reaction of the halocarbonyl compound with the Michael acceptor)[16] (ii) the varying degrees of competing alkylation on the quinoline nitrogen and subse-

(12) Aggarwal, V. K.; Harvey, J. N.; Robiette, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 5468–5471.

(13) (a) Bestmann, H. J.; Seng, F. *Angew. Chem., Int. Ed.* **1962**, *1*, 116. See also: (b) Redon, S.; Leleu, S.; Pannecoucke, X.; Franck, X.; Outurquin, F. *Tetrahedron* **2008**, *64*, 9293–9304. (c) Kondratov, I. S.; Gerus, I. I.; Furmanova, M. V.; Vdovenko, S. I.; Kukhar, V. P. *Tetrahedron* **2007**, *63*, 7246–7255.

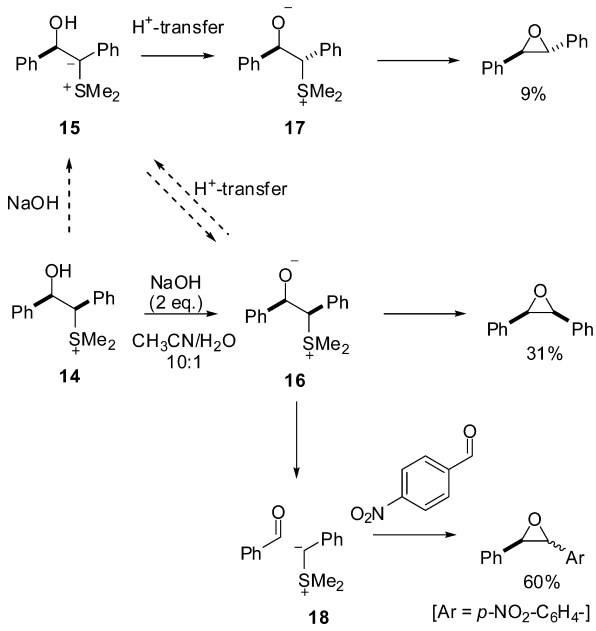
(14) (a) Papageorgiou, C. D.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 828–831. (b) Bremeyer, N.; Smith, S. C.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2681–2684. (c) Papageorgiou, C. D.; Cubillo de Dios, M. A.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4641–4644. (d) Johansson, C. C. C.; Bremeyer, N.; Ley, S. V.; Owen, D. R.; Smith, S. C.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6024–6028. (e) Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596–5605.

(15) pK_a values for stabilized ylides of nitrogen, sulfur, and phosphorus (in DMSO): (a) Cheng, J.-P.; Liu, B.; Zhao, Y.; Sun, Y.; Zhang, X.-M.; Lu, Y. *J. Org. Chem.* **1999**, *64*, 604–610. (b) Zhang, X. M.; Bordwell, F. G.; Van Der Puy, M.; Fried, H. E. *J. Org. Chem.* **1993**, *58*, 3060–3066. (c) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463. (d) For the predicted pK_a in DMSO for a range of ylides, see: Fu, Y.; Wang, H.-J.; Chong, S.-S.; Guo, Q.-X.; Liu, L. *J. Org. Chem.* **2009**, *74*, 810−819.



(16) Kojima, S.; Suzuki, M.; Watanabe, A.; Ohkata, K. *Tetrahedron Lett.* **2006**, *47*, 9061–9065.

Scheme 10. Mechanistic Investigations by Crudden Demonstrating That Proton Transfer Events Can Intervene in Sulfur Ylide-Mediated Epoxidations



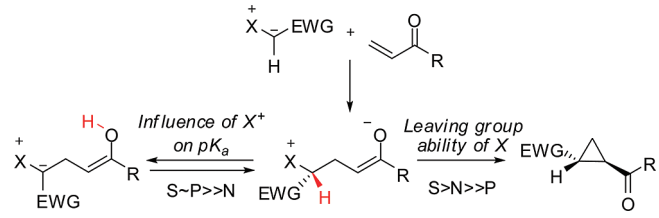
quent cyclopropanation[17] or (iii) the inherent enantioselectivities with the substrates in question.

That proton transfer events can intervene in sulfur−ylide mediated epoxidations under certain conditions has also been demonstrated by Crudden and co-workers (Scheme 10).[18] They showed that a *syn*-α-hydroxysulfonium salt **14** could be deprotonated to form the corresponding ylide **15** (as well as the *syn*-betaine **16** which led to *cis*-stilbene oxide). Reprotonation of the ylidic carbon then mostly led to the *anti*-betaine **17** (giving *trans*-epoxide) as well as giving a small amount of *syn*-betaine (giving *cis*-epoxide). The *anti*-α-hydroxysulfonium salts only gave *trans*-epoxides. Thus *syn*-betaines can lead to *trans*-epoxides without reversion to ylides (e.g., **18**) if proton-transfer processes are in operation.

Conclusions

In summary we have identified an unexpected proton transfer step in the sulfur ylide cyclopropanation reaction of acyclic Michael acceptors which compromises the enantioselectivity of the process. From ketone- to amide-stabilized ylides, the enantioselectivity varies from 25−89% ee. Thus, following addition of a ketone-stabilized ylide to the Michael acceptor, rapid and reversible intramolecular proton transfer within the betaine intermediate, prior to ring closure, results in an erosion of ee. With the less acidic amide-stabilized ylides, the rate of intramolecular proton transfer is reduced and so higher ee's are observed. The competing proton-transfer or direct ring-closure pathways that are open to the betaine intermediate apply not only to all sulfur ylides but potentially to all ylides. Phosphorus ylides suffer from considerably higher barriers to ring closure (leaving group ability of the onium ion falls in the order S > N ≫ P),[12] and as such, stabilized phosphorus ylides undergo proton transfer only. In contrast, ammonium ylides, which are least able to undergo proton transfer (ability of the onium ion to stabilize negative charge falls in the order S ∼ P ≫ N), are much better able to deliver high enantioselectivities than sulfur ylides, although their scope is more limited. Through consideration of the pathways open to the betaine intermediates and their relative rates according to the leaving group ability of the onium ion and its ability to stabilize negative charge (pK_a) allows us to rationalize and now predict the outcome of different ylide reactions in terms of chemo- and enantioselectivity (Scheme 11).

Scheme 11. Factors Affecting the Outcome of Ylide Cyclopropanation



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Supporting Information Available: Experimental procedures, full characterization, and additional experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Gaunt has found that placing a Me substituent at the 2-position of the quinoline ring enhances the enantioselectivity and yield in intramolecular cyclopropanation reactions. See ref 14d. Attempts to prepare a pure ammonium salt derived from **11** and phenacyl bromide were not successful, suggesting that competing alkylation at the quinoline ring was indeed a competing process.

(18) Edwards, D. R.; Du, J.; Crudden, C. M. *Org. Lett.* **2007**, *9*, 2397–2400.