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Experimental Demonstration of Base-Catalyzed Interconversion of Isomeric Betaine Intermediates in the Corey–Chaykovsky Epoxidation

David R. Edwards,* Jenny Du, and Cathleen M. Crudden*

Department of Chemistry, Queen's University, 90 Bader Lane, Kingston, Ontario, Canada, K7M 3N6

cruddenc@chem.queensu.ca

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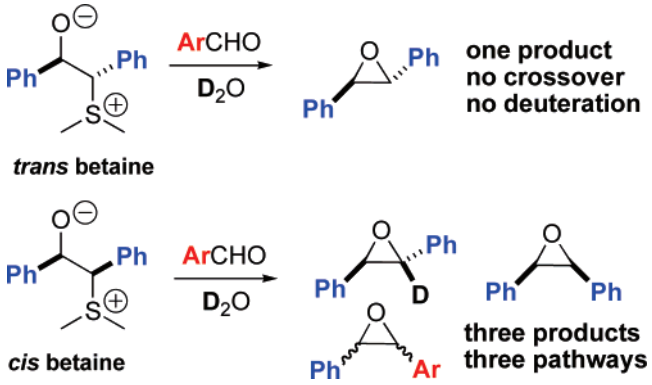
ABSTRACT



The collapse of hydroxysulfonium salts has been examined as a model for the epoxidation of aldehydes. The anti diastereomer reacted with retention of stereochemistry and no crossover, while the syn diastereomer gave crossover products along with cis and trans epoxides. Deprotonation and reprotonation on the carbon of the α-hydroxy sulfonium ylide is presumed responsible for production of the trans epoxide. This reaction pathway has been proposed to explain losses of enantioselectivity but never directly observed.

The Corey−Chaykovsky reaction, in which an aldehyde and an ylide are coupled to yield an epoxide has proven to be a versatile and valuable method for the production of epoxides.[1] Since the initial discovery of this reaction,[2] catalytic enantioselective variants have been reported which have permitted the synthesis of a broad range of products including epoxides, cyclopropanes, aziridines, glycidic amides, and acids.[1] From a variety of mechanistic probes, in addition to theoretical calculations,[3] a general consensus on the mechanism of the reaction has been reached. In broad strokes, the mechanism entails deprotonation of the sulfonium salt to generate an ylide, attack on the aldehyde partner generating a betaine (**1**, Scheme 1), and expulsion of the sulfide leaving group to generate the epoxide.

The critical questions then surround identification of the rate-determining step and the reversibility of the remaining individual steps, both of which can have a significant impact

(1) (a) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611. (b) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433. (c) Aggarwal, V. K.; Charmant, J. P. H.; Fuentes, D.; Harvey, J. N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R. I.; Smith, C.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 2105. (d) Aggarwal, V. K; Hebach, C. *Org. Biomol. Chem.* **2005**, *3*, 1419. (e) Aggarwal, V. K.; Richardson, J. *Chem. Commun.* **2003**, 2644.

(2) (a) Johnson, A. W.; LaCount, R. B. *Chem. Ind. (London)* **1958**, 1440. (b) Johnson, A. W.; LaCount, R. B. *J. Am. Chem. Soc.* **1961**, 417.

(3) (a) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747. (b) Volatron, F.; Eisentein, O. *J. Am. Chem. Soc.* **1987**, *109*, 1. (c) Lindvall, M. K.; Koskinen, A. M. P. *J. Org. Chem.* **1999**, *64*, 4595. (d) Lindvall, M. K.; Koskinen, A. M. P. *Tetrahedron* **2001**, *57*, 4629.

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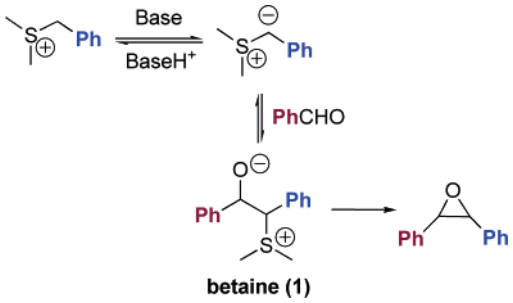
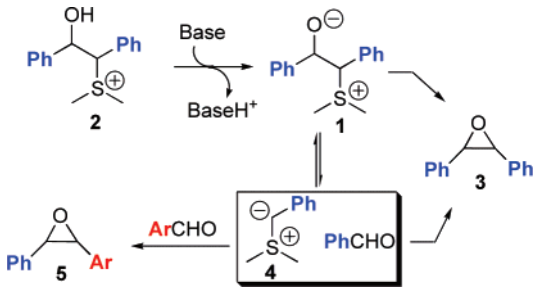
Scheme 1. General Mechanism for the Corey—Chaykovsky Epoxidation Reaction



on the control of relative stereochemistry and the introduction of chirality. Answers to these questions often hinge upon betaine crossover experiments.[1c,d,4]

In a typical crossover experiment, an independently generated α-hydroxy sulfonium salt (**2**) is treated with base to generate the corresponding betaine **1**, Scheme 2. The

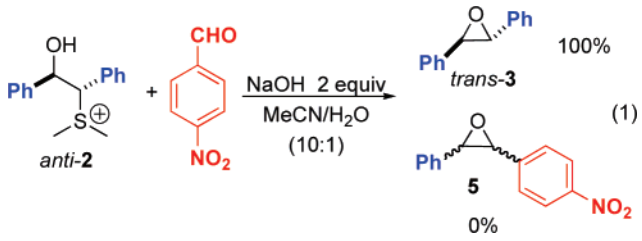
Scheme 2. Probing the Reactivity of Betaine **1** with an Intermolecular Competition Experiment



deprotonation is conducted in the presence of a second aldehyde, ArCHO, which is *more* reactive than PhCHO to ascertain the preferred pathway for reaction of **1**, that is, collapse to **3** or reversion to **4** and aldehyde. Since any free ylide (**4**) generated from **1** will react preferentially with ArCHO, the observation of unsymmetrical arylepoxides (**5**) in the experiment is interpreted as evidence for generation of free ylide **4** in the reaction. In addition, since it is possible to independently generate syn and anti sulfonium salts, this experiment permits information to be obtained about the reactivity of both syn and anti betaines under controlled conditions.

Using this method, we have uncovered a previously unknown and significant difference in reactivity of the two diastereomers of **2**. These results, which can have an impact on the introduction of chirality in this system, are presented herein.

The *syn*- and *anti*-α hydroxy sulfonium salts (**2**) were generated by the method of Aggarwal which involves treatment of cis or trans stilbene oxide with MeSNa, followed by methylation with methyl iodide.[4a] Deprotonation of the anti diastereomer of **2** with NaOH in a mixed solvent system of CH_3CN/H_2O (10:1) was carried out using *p*-NO_2-benzaldehyde as the trapping agent (2 equiv), eq 1.



The reactivity of *p*-NO_2-benzaldehyde relative to benzaldehyde itself was determined by reacting both aldehydes with ylide **4** under similar reaction conditions.[5] *p*-NO_2-benzaldehyde reacted faster than benzaldehyde by a factor of 62. Owing to the increased reactivity of *p*-NO_2-benzaldehyde, and the fact that it is used in excess, it is reasonable to assume that it will efficiently trap any free ylide that is generated. Despite this fact, when *anti*-betaine **2** was treated with base in the presence of excess *p*-NO_2-benzaldehyde, the only observable product is *trans*-stilbene oxide. This is consistent with direct collapse of the *anti*-betaine to form the expected *trans*-epoxide product. The absence of any crossover products (**5**) indicates that the *anti*-betaine is formed irreversibly in the typical epoxidation reaction, in line with previous reports by Aggarwal.[4a]

Remarkably, reaction of the *syn*-betaine (**2**) under identical conditions resulted in a vastly different outcome, eq 2. In this case, significant amounts of the crossover products were obtained; *cis*-NO_2-stilbene oxide (*cis*-**5**) 10% and *trans*-NO_2-stilbene oxide (*trans*-**5**) 50%. The expected *cis*-stilbene oxide (*cis*-**3**) was also obtained (31%) and *trans*-stilbene oxide (*trans*-**3**) made up the remainder of the epoxide products at 9%, (Table 1, entry 1). The observation of crossover products *cis*- and *trans*-**5** is expected and indicates that the formation of the *syn*-betaine is reversible. The appearance of *trans*-stilbene oxide, albeit in minor amounts, is more difficult to explain.

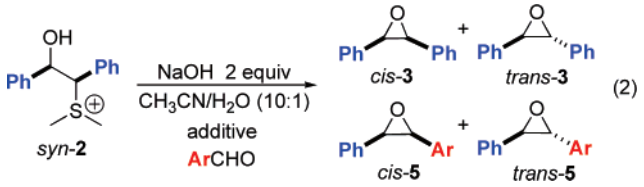
As noted previously, the k_{rel} for the reaction of **4** with *para*-NO_2-benzaldehyde and benzaldehyde is 62:1 under the reaction conditions described. Despite this fact, the ratio of *trans*-**3** to *trans*-**5** obtained in the experiment is closer to 5:1. This is an order of magnitude lower than expected if both species are being produced via the free ylide, which undergoes competitive trapping with both *para*-NO_2-benzaldehyde and benzaldehyde present in solution (Scheme 1).

Repeating the experiment with 10 equiv of *para*-NO_2-benzaldehyde in an attempt to further bias formation of **5** gave the same result as with 2 equiv (entry 2). This indicates

(4) (a) Aggarwal, V. K.; Calamai, S.; Ford, J. G. *J. Chem. Soc., Perkins Trans. 1* **1997**, 593. (b) Aggarwal, V. K.; Charmant, J. P. H.; Ciampi, C.; Hornby, J. M.; O'Brien, C. J.; Hynd, G.; Parsons, R. *J. Chem. Soc., Perkins Trans. 1* **2001**, 3159. (c) Yoshimine, M.; Hatch, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5831.

(5) k_{rel} determined by competition experiment between excess benzaldehyde and *p*-nitrobenzaldehyde reacting with a limiting amount of sulfonium salt **4** (see Supporting Information for full details).

Table 1. Crossover Studies with *syn*-**2**[a]



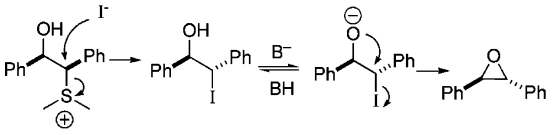
entry	ArCHO	NaI	*cis*-**3**	*trans*-**3**	*cis*-**5**	*trans*-**5**
1	2 equiv		31	9	10	50
2	10 equiv		31	8	6	55
3	2 equiv	1.5 equiv	33	9	11	47

[a] Ar = *p*-nitrophenyl

that all the free ylide generated in the experiment is being efficiently trapped by *para*-NO_2-benzaldehyde to form *cis*- and *trans*-**5**.

To rule out the possibility that the *trans*-stilbene oxide was generated by a counterion promoted inversion of the betaine, the reaction was repeated in the presence of excess iodide (entry 3). In this scenario, the iodide counterion would first displace the sulfonium substituent with inversion at carbon in an S_N2-type process.[6] The intermediate so generated would then undergo direct ring closure to provide stilbene oxide with trans geometry, and regenerate the iodide catalyst, Scheme 3.

Scheme 3. Possible Invertive Process Yielding *trans*-**3** from *cis*-**1**



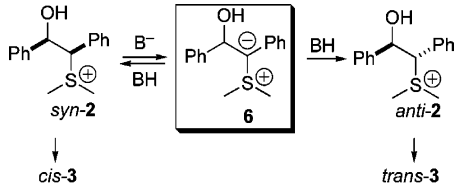
If this pathway were responsible for production of *trans*-stilbene oxide, the addition of exogenous iodide would be expected to alter the product distribution in the crossover experiment in favor of *trans*-stilbene oxide. As shown in Table 1, entry 3 the addition of 1.5 equiv of NaI resulted in essentially no change in the product distribution. Consequently a double inversion process can be discounted.

Having firmly ruled out (a) free ylide trapping with benzaldehyde and (b) counterion catalyzed isomerization of *syn*-betaine as sources of *trans*-stilbene oxide, we next turned to a third potential source for this product. Specifically, base catalyzed isomerization of *syn*-betaine-**2** to *anti*-**2**, which could then undergo ring closure to afford *trans*-stilbene oxide. In this process, the *syn*-betaine would undergo deprotonation to furnish a new ylide species **6**, Scheme 4. Betaines such as **6** have previously been shown to be sp^2 hybridized[7] and therefore reprotonation of **6** could occur from

(6) Ratts, K. W.; Yao, A. N. *J. Org. Chem.* **1966**, *31*, 1689.

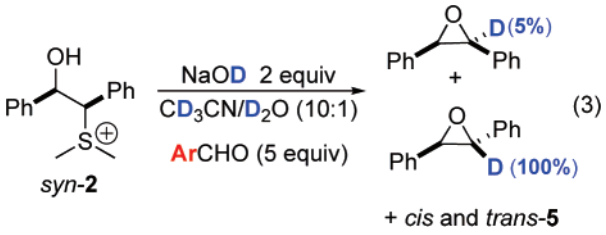
(7) Aggarwal, V. K.; Schade, S.; Taylor, B. *J. Chem. Soc., Perkins Trans. 1* **1997**, 2811.

Scheme 4. Isomerization of *syn*-**2** via C−H Deprotonation

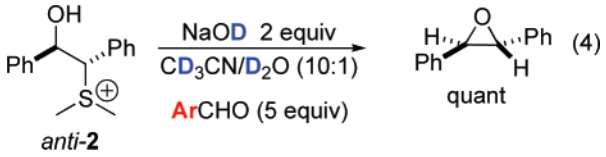


either face producing *anti*-**2**. Ring closure of *anti*-**2** would then be responsible for the production of *trans*-stilbene oxide.

Evidence for the base catalyzed isomerization of betaines was obtained from a deuterium labeling study. The crossover experiment was carried out with *syn*-**2** as in eq 3, but this time using CH_3CN/D_2O/NaOD. In addition to the expected crossover products *cis*- and *trans*-**5**, *trans*-stilbene oxide was obtained with quantitative deuteration at one of the benzylic carbons, eq 3. In contrast, only 5% deuteration was observed in the cis product.



These results indicate that *syn*-**2** reacts via three pathways: (1) direct collapse to epoxide *cis*-**3**, (2) reversion to benzaldehyde and free ylide and (3) deprotonation to **6**, which is converted into *trans*-**3**.[8] On the other hand, the *anti*-betaine generated from *anti*-**2** reacted cleanly with no crossover products and no deuterium incorporation, consistent with the facile ring closure from the *anti*-betaine (eq 4).



These findings support Aggarwal's suggestion that the diastereoselectivity in epoxidations of this type results from a fast collapse of the *anti*-betaine to the corresponding *trans*-epoxide, compared with the slow collapse of *syn*-betaines.[3a,4a]

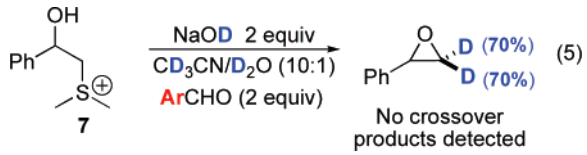
It should be noted that the base catalyzed isomerization of betaines has precedent in the elegant work of Vedejs and co-workers with phosphonium betaine analogues.[9] Furthermore, Aggarwal has proposed that the near identical product distribution obtained in crossover experiments with *anti*- and

(8) Note that the low deuteration observed in *cis*-**3** implies that once **6** is generated, deuteration occurs with high stereoselectivity to yield *anti*-betaine **2** which collapses to yield *trans*-**3**.

(9) (a) Vedejs, E.; Fleck, T.; Hara, S. *J. Org. Chem.* **1987**, *52*, 4637. (b) Vedejs, E.; Fleck, T. *J. Am. Chem. Soc.* **1989**, *111*, 5861.

syn-betaines of ester and amide stabilized *N*-tosyl-protected imines may result from base-catalyzed equilibration of betaines.[4b] However, since incomplete trapping of free ylide in these experiments could also account for the product distributions obtained, a definitive demonstration of interconversion of *syn* and *anti* betaines is important.[10] Considering that ester and amide stabilized betaines represent even more activated substrates for base catalyzed isomerization, it is entirely likely that a similar process is operative with these substrates.

To probe the effect of the stabilizing group, substrate **7** which would generate an *unstabilized* betaine was subjected to the combined crossover/labeling experiment, eq 5. No crossover products were obtained indicating irreversible formation of the betaine. However, significant deuteration did occur, indicating that the betaine is sufficiently persistent to allow proton transfer to occur, even when reversion to free ylide does not occur.[11]



(5)

The present study convincingly demonstrates for the first time that betaine intermediates in the Corey−Chaykovsky reaction can be subject to base catalyzed isomerization. All classes of betaine; stabilized, semistabilized and unstabilized classes, are capable of undergoing proton abstraction and, if structurally feasible, isomerization. Understanding of this process is critical since it is likely to *increase diastereoselectivity* in favor of the preferred trans isomer, but *decrease enantioselectivity*. A similar effect was observed during cyclopropanation studies.[12] It should be noted that although only 25% of the *syn*-betaine underwent isomerization in the current system, variations in substrate structure and reaction conditions could have a significant effect on the extent of deprotonation observed.[13] In particular, this possibility should be considered for cases which exhibit low enantioselectivity.

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Supporting Information Available: Experimental procedures, proton and deuterium NMR spectra for deuterium labeling experiments, crossover experiments, and competition experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Relative rate data for the two competing substrates were not available.

(11) It is not clear if this results from a relatively slow ring closure or faster H^+ abstraction from the secondary carbon α to the sulfonium group.

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

(13) For example, less than 5% isomerization is observed using DBU in pure CH_3CN.