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Epoxy-Annulations by Reactions of α-Amido Ketones with Vinyl Sulfonium Salts. Reagent versus Substrate Control and Kinetic Resolution

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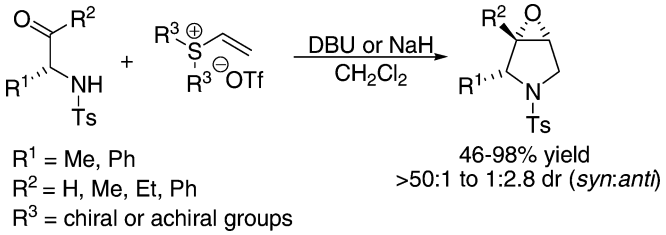
ABSTRACT

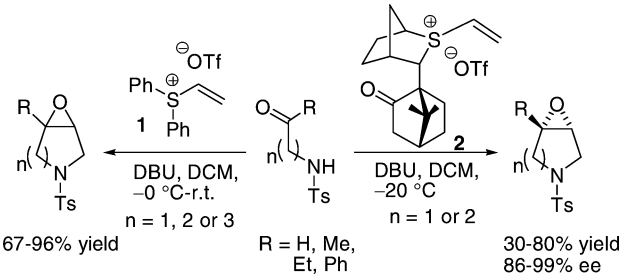


Diphenyl vinyl sulfonium salt and chiral amido-ketones undergo highly diastereoselective epoxy-annulation reactions in good yield. The use of a chiral vinyl sulfonium salt dominates the stereochemical outcome of the annulation reaction (reagent control is greater than substrate control), and this has allowed the kinetic resolution of racemic amido-ketones to be achieved.

The development of novel methods for the asymmetric synthesis of functionalized heterocycles is of great interest in synthesis as such motifs are ubiquitous in both natural products and biologically active pharmaceutical agents. We recently reported that diphenyl vinyl sulfonium salt **1** reacts with α-, *β*-, and *γ*-amido aldehydes/ketones to give 5-, 6-, and 7-membered nitrogen heterocycles containing epoxides in high yield.[1a] Furthermore, through the use of the chiral vinyl sulfonium salt **2**, high enantioselectivity could also be achieved (Scheme 1).[1a,2]

As chiral α-amido aldehydes and ketones are very readily available from the corresponding amino acids, it occurred to us that this novel annulation methodology could potentially be applied to a stereocontrolled synthesis of epoxy pyrrolidines bearing additional substituents. Issues of substrate versus reagent control would clearly affect the outcome of the reaction, and these issues are the focus of the current paper.

Scheme 1. Vinyl Sulfonium Salt Mediated Epoxy-Annulation Reaction of Achiral α-, *β*-, and *γ*-Amido Aldehydes/Ketones



We began our studies by probing the extent of substrate control in the epoxy annulation reaction using the achiral

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(1) (a) Unthank, M. G.; Hussain, N.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7066. For other applications of diphenyl vinyl sulfonium salts in the synthesis of heterocycles, see: (b) Wang, Y.; Zhang, W.; Colandrea, V. J.; Jimenez, L. S. *Tetrahedron* **1999**, *55*, 10659 and references therein. For other work describing the use of chiral vinyl sulfonium salts in synthesis, see: (c) Kim, K.; Jimenez, L. S. *Tetrahedron: Asymmetry* **2001**, *12*, 999.

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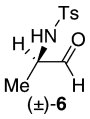
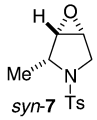
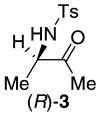
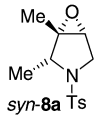
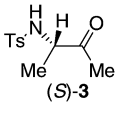
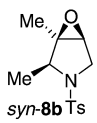
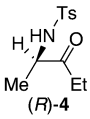
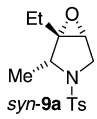
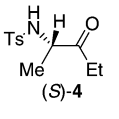
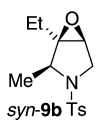
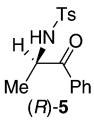
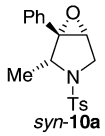
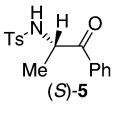
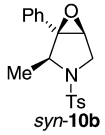
diphenyl vinyl sulfonium salt **1**. We chose alanine as our starting point because it bears the smallest possible substituent in the α position and would therefore show the minimum level of substrate control attainable. A series of α-amido ketones **3**, **4**, and **5**[3] and the corresponding aldehyde **6**[4] were therefore prepared using established Weinreb or alcohol oxidation methodology, respectively.[5] This series of substrates were then treated with DBU in the presence of the vinyl sulfonium salt **1** and gave the corresponding epoxy pyrrolidines (Table 1, method A). The ketone substrates all performed well, giving high yields of annulated products **8**, **9**, and **10**, but the amino aldehyde **6** was less effective, presumably due to its inherent instability.[6] There was a broad correlation between the size of the carbonyl substituent and the degree of selectivity observed: large substituents (Ph, Table 1, entries 6 and 7) gave high *syn* selectivity (>50:1) whereas small substituents (H, Table 1, entry 1) gave essentially no selectivity (1.2:1). No epimerisation of the stereogenic center adjacent to the ketone functionality was detected in any of the cases.

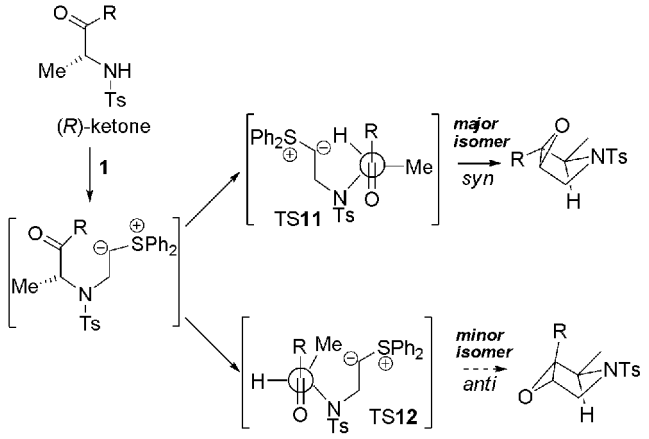
Table 1. Reactions of Alanine-Derived Amido-Ketones with Vinyl Sulfonium Salts **1** and **2**[a]

	substrate	product	method	yield (%)	dr (*syn*:*anti*)[b]
1	 (±)-**6**	 *syn*-**7**	A	46	1.2:1
2	 (*R*)-**3**	 *syn*-**8a**	A	87	4.6:1
			B	80	>50:1
3	 (*S*)-**3**	 *syn*-**8b**	A	87	4.6:1
			C	65	1:2.8
4	 (*R*)-**4**	 *syn*-**9a**	A	67	3.7:1
			B	66	>50:1
5	 (*S*)-**4**	 *syn*-**9b**	A	67	3.7:1
			C	69	1:3.5
6	 (*R*)-**5**	 *syn*-**10a**	A	96	>50:1
			B	84	>50:1
7	 (*S*)-**5**	 *syn*-**10b**	A	96	>50:1
			C	98	1:1.7

[a] Reagents and conditions. **Method A** (optimal conditions for substrate-controlled reactions): diphenyl vinyl sulfonium salt **1** (1.2 equiv), DBU (2 equiv), CH_2Cl_2 (0.09 M), 2−4 h, 0 °C. **Method B** (optimal conditions for "matched" reactions): chiral vinyl sulfonium salt **2** (1.0 equiv), NaH (1.2 equiv), CH_2Cl_2 (0.015 M), 5−18 h, 0 °C. **Method C** (optimal conditions for "mis-matched" reactions): chiral vinyl sulfonium salt **2** (1.0 equiv), DBU (2 equiv), CH_2Cl_2 (0.015 M), 18 h, 0 °C-rt [b] Major isomer (*syn*) from the substrate-controlled reactions (Method A) is shown.

The substrate-controlled selectivity observed can be rationalized by considering the two Felkin-Ahn[7] transition states that ultimately lead to the two possible epoxides. The factors that control the outcome of the reaction include (i) preferred approach of the ylide over the H substituent rather than the Me group (favors TS**11**, Scheme 2) and (ii) steric hindrance between the Me group and the carbonyl substituent R (favors TS**11**). The latter effect will increasingly favor TS**11** as the carbonyl substituent increases in size, suggesting that this factor is primarily responsible for the selectivity observed in Table 1.

Scheme 2. Proposed Model for Substrate-Controlled Annulation Reaction



These results show that very high diastereoselectivity can be observed in the substrate-controlled epoxy annulation process employing the readily available diphenyl vinyl sulfonium salt **1**. Furthermore, *syn* isomers are preferentially

(2) For the synthesis of the chiral sulfide from which **2** is derived, see: (a) Aggarwal, V. K.; Fang, G.; Kokotos, C. G.; Richardson, J.; Unthank, M. G. *Tetrahedron* **2006**, *62*, 11297. (b) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1430.

(3) For the synthesis of *N*-tosyl alanine, see: (a) Sdira, S. B.; Felix, C. P.; Giudicelli, M-B. A.; Seigle-Ferrand, P. F.; Perrin, M.; Lamartine, R. J. *J. Org. Chem.* **2003**, *68*, 6632. For the synthesis of amino-ketones from their respective Weinreb amides, see: (b) Chen, W. B.; Jin, G. Y. *Heteroatom Chem.* **2003**, *14*, 603.

(4) For the synthesis of highly epimerisable amino aldehydes, see: Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359.

(5) See Supporting Information for full details.

(6) Reaction of the amino aldehyde (±)-**6** was only carried out on the racemate. This example was done to establish the relationship between the size of the carbonyl substituent and level of substrate control. As both yield and diastereoselectivity were low with this substrate, further work on the enantioenriched material was not conducted.

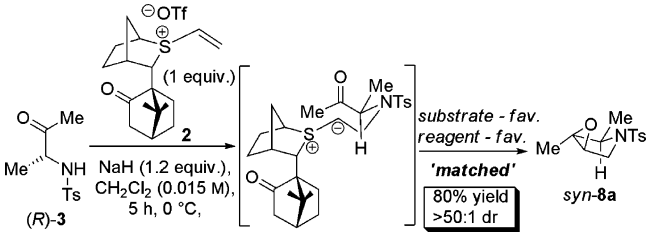
(7) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199.

formed, which are of course the more difficult isomers to access because alkene epoxidation (e.g., with mCPBA) favors the *anti* isomers.[8]

We then investigated the reactions of the enantiomerically enriched amido ketones[9] **3**, **4**, and **5** with the chiral vinyl sulfonium salt **2** to explore the balance between reagent and substrate control. We had previously shown[1a] that high levels of reagent control could be achieved in the reaction of the achiral α-amido ketones with the chiral vinyl sulfonium salt **2** (92−97% e.e.). However, when both reagent and substrate could exert control, we were interested to know which would dominate. To address this, we reacted (*R*)- and (*S*)-amido ketones **3**, **4**, and **5** with the (+)-vinyl sulfonium salt **2**, and the results are summarized in Table 1. The two enantiomers of the amido ketone required slightly different conditions to achieve acceptable yields (methods B and C).

In all cases where the substrate and reagent favored the formation of the same product (matched case), a single (*syn*) diastereomer was formed in good yield. In the mis-matched cases, the *anti* diastereomer was obtained predominantly showing that *the reagent dominated the outcome of the*

Scheme 3. Proposed Model for "Matched" Reaction of (*R*)-Amido Methyl-Ketone (*R*)-**3** with Chiral Vinyl Sulfonium Salt **2** (Method B)



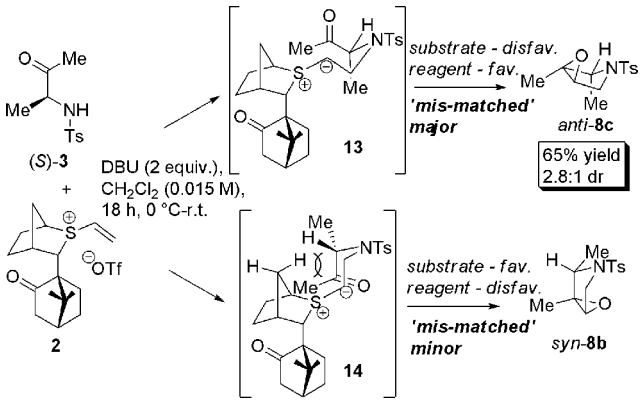
reaction. The matched and mis-matched stereochemical outcomes of amido ketone **3** are illustrated in Schemes 3 and 4, respectively. The factors affecting substrate control have already been outlined, and the factors influencing reagent control follow from our established model[10] in which ylide conformer **13** is favored over conformer **14** (see Scheme 4), and in both cases, addition of the ylide occurs on the opposite face to the bicyclic camphor moiety.

(8) For examples of epoxidation of unsaturated chiral 5-membered heterocycles to give *anti*-isomers see: (a) Quibbel, M.; Ben, A.; Flinn, N.; Monk, T.; Ramjee, M.; Ray, P.; Wang, Y.; Watts, J. *Bioorg. Med. Chem.* **2005**, *13*, 609. (b) Wang, Y.; Ben, A.; Flinn, N.; Monk, T.; Ramjee, M.; Watts, J.; Quebell, M. *Bioorg. Med. Chem. Lett.* **2002**, *15*, 1327. (c) Lazaro, A.; Garcia, L.; Correia, C. R. D. *Tetrahedron Lett.* **2003**, *44*, 1553. (d) Severino, E. A.; Correa, C. R. D. *Org. Lett*. **2000**, *2*, 3039. (e) Baldwin, J. E.; Field, R. A.; Lawrence, C. C.; Lee, V.; Robinson, J. K.; Schofield, C. J. *Tetrahedron Lett.* **1994**, *35*, 4649. (f) Wardrop, D. J.; Bowen, E. G. *Chem. Commun*. **2005**, 5106. (g) Burley, I.; Hewson, A. T. *Tetrahedron Lett.* **1994**, *35*, 7099.

(9) Only the higher yielding chiral ketone substrates were chosen to react with the valuable chiral vinyl sulfonium salt **2**. The amino-aldehyde **6** was considered unsuitable for these reactions due to its lack of substrate-controlled diastereosectivity with diphenyl vinyl sulfonium salt **1**.

(10) (a) 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. (b) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611. (c) Aggarwal, V. K.; Richardson, J. *Chem. Commun.* **2003**, 2644.

Scheme 4. Proposed Model for "Mis-Matched" Reaction of (*S*)-Amido Methyl-Ketone (*S*)-**3** with Chiral Vinyl Sulfonium Salt **2** (Method C)



The amido ketones could potentially racemize during the course of the reaction although this was not detected with the alanine-derived substrates. Racemization would be much more of a potential problem in the extreme case of phenyl glycine-derived ketone **15**, and so to explore the limit of our annulation reaction, this substrate was prepared[11] and tested. Reaction with diphenyl vinyl sulfonium salt **1** under standard conditions afforded the *syn* epoxide with the expected high diastereoselectivity (due to the bulky phenyl ketone moiety) but some degree of racemization. However, using NaH in place of DBU (method A*, Table 2), no racemisation was

Table 2. Substrate-Controlled Epoxy-Annulation Reaction with Vinyl Sulfonium Salt **1**[a]

	substrate	product	% yield (method)	dr (*syn*:*anti*)	ee (%)
1	(*R*)-**15**	*syn*-**16a**	78 (A)	>50:1	81
			73 (A*)	>50:1	>99
2	(*S*)-**15**	*syn*-**16b**	78 (A)	>50:1	81
			73 (A*)	>50:1	>99

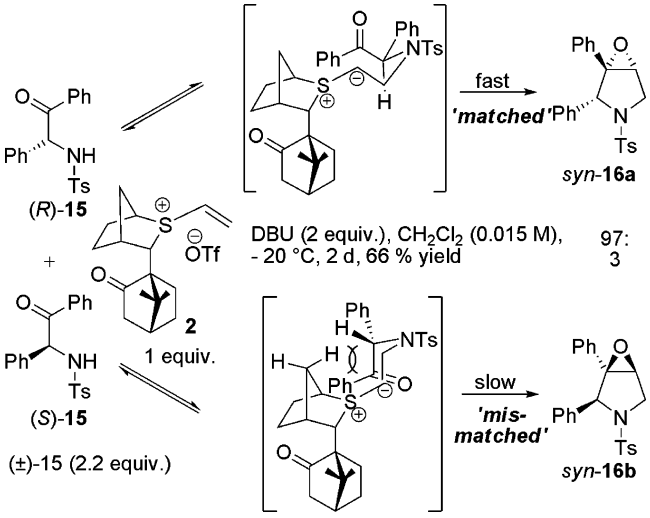
[a] Reagents and conditions. **Method A** (optimal alanine-derived substrate-controlled reaction conditions): diphenyl vinyl sulfonium salt **1** (1.2 equiv), DBU (2 equiv), CH_2Cl_2 (0.09 M), 2 h, 0 °C. **Method A*** (optimal substrate-controlled reaction conditions for highly epimerisable substrates): diphenyl vinyl sulfonium salt **1** (1.2 equiv), NaH (1.2 equiv), CH_2Cl_2 (0.09 M), 2 h, 0 °C.

detected and the product was obtained with equally high diastereoselectivity, thus demonstrating the potential of the method with sensitive substrates.

We recognized that due to the strong preference for bulky phenyl ketones to form *syn* epoxides, we would expect the

mismatched reaction between (*S*)-**15** and (+)-vinyl sulfonium salt **2** to be slow. We believed that we could exploit the difference in rates of reaction between matched and mismatched cases through a kinetic resolution of (±)-**15** with the (+)-isomer of **2**. Experimentally, it was found that by using 2.2 equiv of (±)-amido-ketone **15**, with respect to (+)-chiral vinyl sulfonium salt **2** at 0 °C a 66% yield of the *syn*-heterocycle, **16a** was obtained in 90% e.e. after 5 h. By reducing the reaction temperature from 0 to −20 °C, the *syn* epoxide was obtained in similar yield but the enantiomeric excess was increased to 94% (Scheme 5). Thus, an

Scheme 5. Kinetic Resolution of (±)-Amido-Ketone **15**



effective kinetic resolution of phenyl glycine-derived (±)-amido-ketone **15** has been achieved. It is most likely that kinetic resolution occurs in the ylide + ketone step (see Scheme 5), implying that amide addition to the vinyl sulfonium salt is reversible. Although this investigation is not the first to probe "matched" versus "mis-matched" reactions of chiral electrophiles with a chiral sulfonium ylide,[12] it does represent the first report of a chiral sulfonium ylide-mediated kinetic resolution.

In summary, a highly (*syn*) diastereoselective epoxy-annulation reaction has been developed using alanine-derived amido-ketones and the achiral diphenyl vinyl sulfonium salt **1**. The (*syn*) diastereoselectivity of the reaction can be either increased or over-turned to favor the *anti* isomer through the use of the chiral vinyl sulfonium salt **2** indicating that the reagent dominates the stereochemical outcome of the annulation reaction. The phenyl ketones **5** and **15**, in particular, resulted in a very high degree of substrate-controlled diastereoselectivity in reactions with the diphenyl vinyl sulfonium salt **1** (>50:1 *syn*:*anti*), which was further exploited in a kinetic resolution of a (±)-**15** using the chiral vinyl sulfonium salt **2**. Because both enantiomers of both the chiral vinyl sulfonium salt and the amido ketones are available, either enantiomer of either diastereomer of the epoxy pyrrolidines can be prepared using this annulation methodology.

Acknowledgment. We thank GlaxoSmithKline and the EPSRC for support of this work. We thank Mr. Saowanit Saithong and Dr. J.P.H. Charmant for X-ray analysis.

Supporting Information Available: Experimental procedures and characterisation data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For the tosylation of phenyl glycine, see (a) González-Cameno, A. M.; Badía, D.; Domínguez, E.; Urtiaga, M. K.; Arriortua, M. I.; Solans, X. *Tetrahedron* **1994**, *50*, 10971. For the synthesis of Weinreb amides of phenyl glycine, see (b) Myers, M. C.; Wang, J.; Iera, J. A.; Bang, J.; Hara, T.; Saito, S.; Zambetti, G. P.; Appella, D. H. *J. Am. Chem. Soc.* **2005**, *127*, 6152. For the temperature-controlled treatment of the Weinreb amides with PhMgBr, see (c) Chen, W. B.; Jin, G. Y.; *Heteroatom Chem.* **2003**, *14*, 603.

(12) For other examples of reactions of chiral sulfur ylides with chiral aldehydes, see (a) Aggarwal, V. K.; Bi, J. *Beilstein J. Org. Chem.* **2005**, *http://bjoc.beilstein-journals.org/content/1/1/4*. (b) Bellenie, B. R.; Goodman, J. M. *Chem. Commun.* **2004**, 1076.