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Diastereoselective sulfur ylide promoted aldol/epoxidation

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Abstract—A mixture of cyclohexanone or 4-methylcyclohexanone and an aromatic aldehyde is treated with dimethylsulfoxonium methylide to effect a tandem aldol/epoxidation reaction. The resulting product contains three or four new stereocenters but only one of the possible four or eight diastereomers is formed.

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The epoxide has long been a useful functional group in organic synthesis¹ allowing for the formation of new carbon–carbon bonds and providing a pathway to a variety of other functional groups. This, together with the pharmaceutical industry's ever-growing need for methods to produce single enantiomers of chiral compounds,² has spurred much activity in the development of new stereoselective epoxidation reactions.^{3–7} Most of the work has involved oxidation of alkenes and is highlighted by the excellent methods of Sharpless/Katsuki,³ Jacobsen,⁴ Shi,⁵ and Julia⁶ Although less work has been done in the area of methylene transfer to the carbonyl group, impressive selectivities have been achieved by Aggarwal and co-workers using chiral sulfonium ylides.^{7,8}

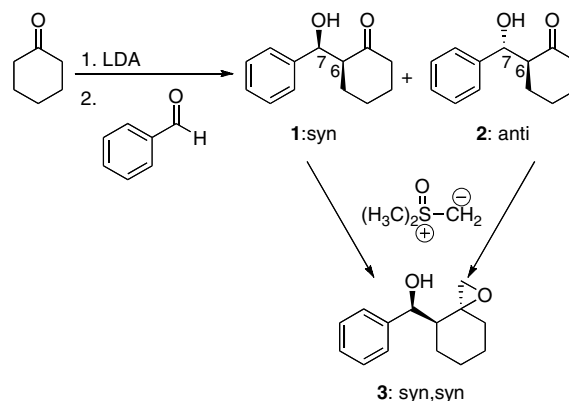
Hydroxyl group directing effects have been observed in several different reactions including peracid epoxidation of allylic alcohols⁹ and Simmons-Smith cyclopropanation of allylic alcohols.¹⁰ An interesting example of a carbon–carbon double bond exhibiting a directing effect on sulfur ylide epoxidation has also been reported.¹¹

However, none of the stereoselective epoxidation methods mentioned above take advantage of the hydroxyl directing effect save perhaps the Sharpless method. Indeed, all achieve their remarkable selectivity through careful control of the steric environment during the

reaction. While a β -hydroxyl directing effect in the sulfur ylide epoxidation is rare,¹² there are several examples of an α -alkoxy or hydroxy directing effect.¹³

We have developed an interesting and highly selective epoxidation reaction between β -hydroxy ketones and sulfoxonium ylides.¹⁴ The β -hydroxy ketones **1** and **2**¹⁵ were prepared via generation of the lithium enolate of cyclohexanone with LDA followed by addition of benzaldehyde. They were isolated as a mixture of two diastereomers (Scheme 1). When this mixture was reacted with dimethylsulfoxonium methylide a single diastereomer of the resulting epoxide was isolated. The structure of this product was assigned as **3** based on proton and carbon NMR spectra.

Upon separation of the hydroxy-ketone diastereomers by column chromatography we were surprised to find



Scheme 1.

Keywords: Stereoselective; Epoxidation; Sulfur ylide.

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that performing the epoxidation reaction on each of these isomers separately provided the same single diastereomer in approximately 50% yield (Scheme 1). Monitoring the reaction by TLC immediately after combining the reagents clearly indicated that the hydroxy ketones equilibrate under the reaction conditions. This equilibration could occur either by deprotonation/reprotonation α to the ketone or retro-aldol/aldol. Isolation of styrene oxide (formed from epoxidation of benzaldehyde) argued for the retro-aldol/aldol. Clearly, only one of the isomers reacts to form the epoxide.

X-ray crystallographic analysis of the higher R_f hydroxy-ketone diastereomer confirmed its structure as **1** (*syn*).¹⁶ The crystal structure of **3** revealed it to have a *syn*, *syn* configuration (Fig. 1).¹⁷

Our recognition that the two diastereomers of the β -hydroxy ketone equilibrated under the reaction conditions led us to investigate a one-pot aldol/epoxidation sequence. Accordingly, when a 1:1 mixture of cyclohexanone and benzaldehyde in DMF is treated with 1.75 equiv of dimethylsulfoxonium methylide, the sulfoxonium ylide catalyzes the aldol reaction and then adds to the carbonyl to form the epoxide (Scheme 2).

No diastereomeric product could be detected by NMR for any of the examples we studied. Isolated yields are typically in the range of 40–70% using cyclohexanone and a variety of aromatic aldehydes (Table 1). In all cases, small amounts of aldol product and styrene oxide (or the equivalent) are present before purification. We found that using 1.75 equiv of ylide was optimal and using a larger excess of ylide did not improve the yield. Surprisingly, replacing cyclohexanone with 4-methylcyclohexanone also produced a single diastereomer—this time with four new stereocenters. However, cyclopentanone provided only aldol product with no epoxidation. Aliphatic aldehydes provided complex mixtures.

We believe the stereoselectivity results from attraction of the positively charged sulfur of the ylide to the oxygen of the hydroxyl group and possibly from hydrogen bonding between the hydroxyl hydrogen and the ylide oxy-

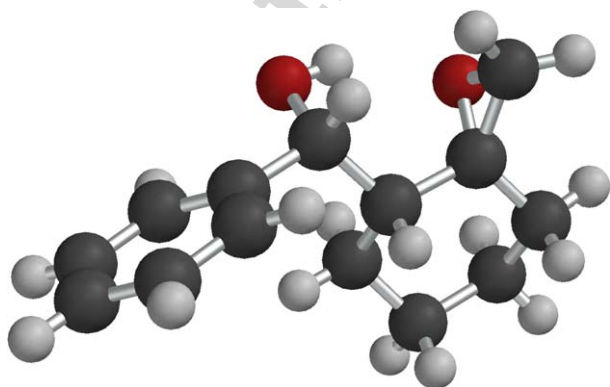
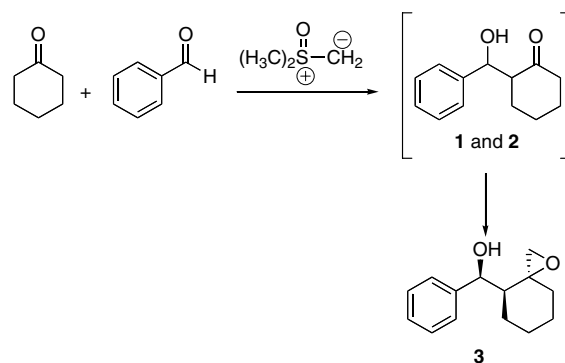


Figure 1.



Scheme 2.

Table 1. Tandem aldol/epoxidation of cyclohexanones and aromatic aldehydes

Entry	Ketone	Aldehyde	Product ^a	Yield ^b (%)
1				71
2				60
3				40
4				25
5				41
6				41

^a All products were characterized by ¹H and ¹³C NMR.¹⁹

^b Isolated yield after column chromatography.

gen. The resulting complex formed between the ylide and **1** positions the ylide for equatorial attack¹⁸ on the carbonyl which leads to epoxide **3**. However, hydroxy ketone **2** either does not easily form such a complex with the ylide or the resulting complex does not result in epoxidation. The fact that **8** and **9** are also produced as single diastereomers strongly suggests that the reaction is under thermodynamic control.

Use of sulfonium ylides in this reaction provided only small quantities of the epoxide product **3** with styrene

oxide as the predominant product. Interestingly, the stereochemistry of the sulfonium ylide reaction appears to be the same as for the sulfoxonium ylide even though sulfonium ylides typically add axially.¹⁸

In summary, a novel tandem aldol/epoxidation reaction promoted by dimethylsulfoxonium methylide has been developed. This reaction constructs three new stereocenters with complete diastereoselectivity. A variety of aromatic aldehydes can be combined with cyclohexanone or 4-methylcyclohexanone. Acyclic ketones and nonaromatic aldehydes did not participate in this reaction.

Acknowledgements

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Compound **3**: White crystalline solid (71%). Mp 73–75 °C; *R*_f = 0.33 (5:1 hexanes/EtOAc); ¹H NMR (CDCl₃): δ 7.15–7.5 (m, 5H), 4.95 (d, *J* = 1.7 Hz, 1H), 3.73 (s, 1H), 3.45 (d, *J* = 3.2 Hz, 1H), 2.71 (d, *J* = 3.2 Hz, 1H) and 1.1–2.1 (m, 9H); ¹³C NMR (CDCl₃): δ 142.2, 128.0, 126.8, 125.8, 72.2, 63.2, 51.9, 44.2, 35.2, 25.2, 23.9, and 21.8.
Compound **4**: White crystalline solid (71%). ¹H NMR (CDCl₃): δ 7.31 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 5.02 (s, 1H), 3.85 (s, 1H), 3.55 (d, *J* = 3.2 Hz, 1H), 2.75 (d, *J* = 3.2 Hz, 1H) and 1.1–2.1 (m, 9H).
Compound **5**: White crystalline solid (60%). IR 3446, 2935, 2861, 1503, 1490, 1445, 1239, 1039; ¹H NMR

(CDCl₃): δ 6.82 (s, 1H), 6.75 (s, 2H), 5.93 (s, 2H), 4.88 (d, $J = 1.7$ Hz, 1H), 3.73 (s, 1H), 3.44 (d, $J = 3.2$ Hz, 1H), 2.71 (d, $J = 3.2$ Hz, 1H) and 1.1–2.0 (m, 9H); ¹³C NMR (CDCl₃): δ 147.4, 146.3, 136.3, 118.8, 107.9, 106.7, 100.9, 72.1, 63.1, 52.0, 44.5, 35.2, 25.2, 23.9, and 22.0.

Compound **6**: White crystalline solid (40%). IR 3460, 3005, 2938, 2859, 1601, 1588, 1491, 1464, 1438, 1235, 1083, 1050, 1028, 759; ¹H NMR (CDCl₃): δ 7.49 (dd, $J_1 = 7.4$ Hz, $J_2 = 1.7$ Hz, 1H), 7.21 (td, $J_1 = 7.7$ Hz, $J_2 = 1.7$ Hz, 1H), 6.95 (t, $J = 7.7$ Hz, 1H), 6.82 (d, $J = 8.1$ Hz, 1H), 5.18 (s, 1H), 3.78 (s, 3H), 3.70 (s, 1H), 3.48 (d, $J = 3.5$ Hz, 1H), 2.69 (d, $J = 3.5$ Hz, 1H), 2.15 (m, 1H) and 1.1–2.0 (m, 8H); ¹³C NMR (CDCl₃): δ 155.5, 130.2, 127.8, 127.7, 120.3, 109.9, 67.4, 63.2, 55.3, 52.1, 41.0, 35.3, 25.3, 24.0, and 22.5.

Compound **7**: White crystalline solid (25%). ¹H NMR (CDCl₃): δ 7.34 (s, 1H), 6.34 (d, $J = 1.2$ Hz, 1H), 6.26 (d,

$J = 3.2$ Hz, 1H), 4.94 (d, $J = 1.7$ Hz, 1H), 3.50 (br s, 1H), 3.31 (d, $J = 3.2$ Hz, 1H), 2.67 (d, $J = 3.2$ Hz, 1H) and 1.2–1.9 (m, 9H).

Compound **8**: White crystalline solid (41%). IR 3453, 2926, 2868, 1494, 1451, 902, 753, 734, 702; ¹H NMR (CDCl₃): δ 7.1–7.5 (m, 5H), 4.93 (d, $J = 1.7$ Hz, 1H), 3.80 (s, 1H), 3.52 (d, $J = 3.2$ Hz, 1H), 2.75 (d, $J = 3.2$ Hz, 1H), 1.1–2.2 (m, 8H) and .86 (d, $J = 5.4$ Hz, 3H); ¹³C NMR (CDCl₃): δ 142.0, 128.0, 126.8, 125.8, 72.1, 62.9, 51.7, 43.7, 35.1, 32.2, 32.0, 29.9, and 22.4.

Compound **9**: White crystalline solid (41%). ¹H NMR (CDCl₃): δ 7.31 (d, $J = 8.7$ Hz, 2H), 7.24 (d, $J = 8.7$ Hz, 2H), 4.91 (s, 1H), 3.82 (s, 2H), 3.50 (d, $J = 3.2$ Hz, 1H), 2.78 (d, $J = 3.2$ Hz, 1H), 1.9–2.1 (m, 2H), 1.67 (m, 1H), 1.2–1.5 (m, 5H), and 0.88 (d, $J = 5.4$ Hz, 3H); ¹³C NMR (CDCl₃) 140.7, 132.3, 128.3, 127.0, 71.8, 62.9, 51.8, 43.6, 35.0, 32.1, 32.0, 29.9, and 22.6.