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The Synthesis of Optically Active 2-Phenylthio Aldehydes

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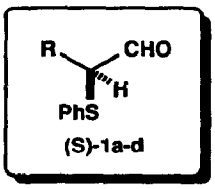
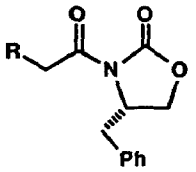
Abstract: Optically active linear and branched chain 2-phenylthio aldehydes can be made in high optical purity (up to >98% e.e.) by sulfenylation of a phenylalanine-derived oxazolidinone imide, reduction and re-oxidation with the Dess-Martin reagent even though the products enolise easily.

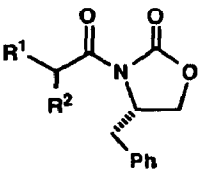
The use of racemic 2-phenylthio (PhS) aldehydes to achieve high Felkin[1] selectivity has been well demonstrated in Mukaiyama-type aldol reactions of both stereogenic and non-stereogenic silylketene acetals.[2] *Syn* or *anti*-selective aldol reactions of lithium or boron enolates with racemic 2-PhS-aldehydes also show good Felkin control.[3] However, homochiral versions of these processes in which the 2-PhS-aldehyde is the sole source of chirality have yet to be realised. This is mainly because the synthesis of optically active 2-PhS aldehydes is made difficult since these aldehydes racemise easily by enolisation unless C-2 is quaternary. Ugi[4] reported the first synthesis of enantiomerically enriched 2-PhS-aldehydes (maximum 51% e.e.), Poli and Scolastico[5] have made enantiomerically pure 2-ArS-aldehydes *via* bis-ArS-acetals, and Enders[6] has recently reported the most general synthesis to date *via* alkylation of the SAMP derivative of 2-RS-acetaldehyde. We have used asymmetric aldol reactions with prochiral 2-PhS-aldehydes as a route to β-hydroxysulfides for our rearrangement chemistry[3] and wish to use homochiral 2-PhS-aldehydes in both single and double stereodifferentiating aldol reactions as an alternative approach to the same intermediates. We now report the synthesis of highly enantiomerically enriched 2-PhS-aldehydes **1** (>98% e.e.) by diastereoselective sulfenylation of chiral enolates derived from the Evans oxazolidinone[7] **3**.



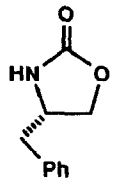
(S)-1a-d



2a-d



2e



3

There are few reports of asymmetric sulfenylation. Moderate e.e.s have been reported from chiral sulfenamides[8] and tin (II) enolates in the presence of a chiral diamine ligand.[9] Sulfenylation of O-silyl imide enolates from Evans valine-derived oxazolidinones gives reasonable diastereoselectivity[10] and sulfenylation of lithium enolates from imidazolidinones gives very high asymmetric induction.[11] We have sulfenylated lithium enolates of the Evans phenylalanine-derived oxazolidinones **2** (Scheme 1 and table 1) and report that diastereoselectivity is excellent with compounds **2a-d** (R = Et, Pr, i-Pr, t-Bu) but poor with compounds **2e** having a branched chain next to the carbonyl group. Aldehydes of type **1** are more useful than those blocked at the 2-position but to complete their synthesis we have had to solve the problem of racemisation by enolisation.

Scheme 1

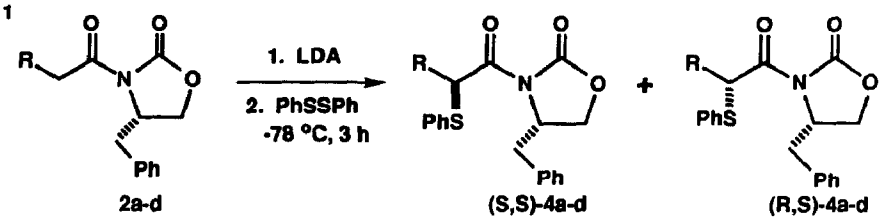


Table 1: Diastereoselective Sulfenylation of Imides 2

Imide	R	Yield (%) of 2 from 3	Ratio[a] (S,S) : (R,S)-4	Yield[b], % (S,S)-4
2a	Et	86	97:3	83
2b	n-Pr	93	>97:3	89
2c	i-Pr	84	>97:3	92
2d	t-Bu	91	>97:3	88

[a]Determined by ^{1}H NMR (250 MHz) on the crude reaction mixture. [b]Yield after column chromatography.

The reactions in scheme 1 were highly diastereoselective: the minor diastereoisomer could be detected by the ^{1}H NMR (250 MHz) of the crude reaction mixture only in the case of **4a**. The major products (S,S)-**4a-d** were obtained as highly crystalline compounds after purification by column chromatography to remove excess PhSSPh. Only (S,S)-**4b** failed to crystallise. We believe the sense of asymmetric induction with this non-chelating electrophile to be the same as that of the alkylation of the corresponding lithium enolates[7] and of the sulfenylation of related silyl enol ethers[10] and opposite to that of aldol reactions of the corresponding boron enolates.[3]

Conversion to homochiral 2-PhS-aldehydes **1** now required cleavage of the external amide bond of **4** and reduction without racemisation. The successful partial reduction of achiral *N*-acylthiazolidin-2-ones[12] and of a chiral *syn* aldol product based on the valine-derived Evans imide[13] to the respective aldehydes using DIBAL and Red-Al® [$NaAlH_2(OCH_2CH_2OMe)_2$] prompted us to investigate the direct reduction of the imides **4** to the 2-PhS-aldehydes **1**. Nucleophilic attack, especially by LiOH,[7] is usually preferred at the external amide carbonyl in compounds resembling **4**, so we also considered an alternative route *via* complete reduction of the imides **4** to the intermediate homochiral 2-phenylthio alcohols **5** using $LiBH_4/H_2O$[14] (scheme 2 and table 2) followed by oxidation. In the event reduction with Red-Al® gave some racemisation while reduction with $LiBH_4/H_2O$ preserved stereochemical integrity, but this alternative route required a careful choice of oxidant to avoid racemisation in the formation of the aldehydes **1** from the alcohols **5**.

Scheme 2

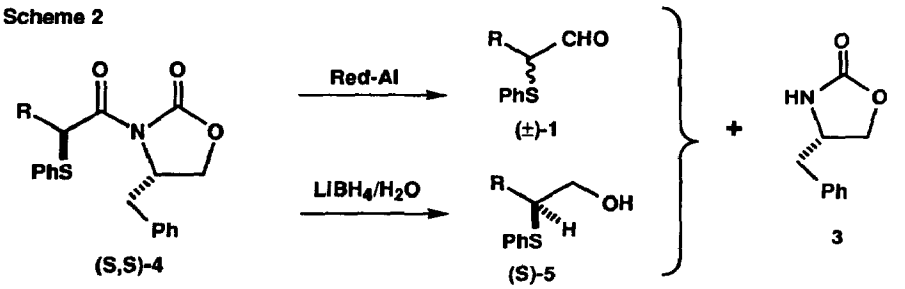


Table 2: Reduction of Sulfenylated Imides (S,S)-4 to Aldehydes 1 and Alcohols (S)-5.

Entry	R in Imide (S,S)-4	Reducing agent	Temp.	Product 1 or (S)-5	Yield[a] (%) 1 or (S)-5	e.e.[b] (%) 1 or (S)-5
1.	Et	Red-Al®	-78 °C	(±)-**1a**	-	0
2.	n-Pr	Red-Al®	-78 °C	(±)-**1b**	-	0
3.	i-Pr	Red-Al®	-78 °C	(S)-**1c**	8	45
4.	i-Pr	Red-Al®	0 °C	(S)-**1c**	23 (68)	14
5.	t-Bu	Red-Al®	-78 °C	(S)-**1d**	10 (65)	97
6.	t-Bu	Red-Al®	0 °C	(S)-**1d**	16	94
7.	Et	$LiBH_4/H_2O$	room temp.	(S)-**5a**	94	>98
8.	n-Pr	$LiBH_4/H_2O$	room temp.	(S)-**5b**	90	>98
9.	i-Pr	$LiBH_4/H_2O$	room temp.	(S)-**5c**	93	>98
10.	t-Bu	$LiBH_4/H_2O$	room temp.	(S)-**5d**	30[c] (60)	>98

[a]Yield after column chromatography on silica, yield in brackets is of recovered starting material; [b]For aldehydes: e.e. determined by ^{1}H NMR (250 MHz) in the presence of the chiral shift reagent Eu(hfc)$_3$, for alcohols: by ^{1}H NMR (250 and 400 MHz) analysis of diastereomeric Mosher esters in comparison with racemic compounds[3]; [c]Yield after 2 days.

Red-Al® reductions of the less hindered sulfenylated imides (S,S)-**4a,b** gave racemic 2-PhS-aldehydes (entries 1-2, table 2). The more hindered aldehydes **1c,d** were formed with reasonable e.e.s but the yields were poor (entries 3-6). DIBAL reduction gave more or less similar results. However, total reduction with $LiBH_4/H_2O$ gave good yields of the alcohols (S)-**5** in excellent optical purity (entries 7-10): only with the most hindered imide (S,S)-**4d** was the yield poor. The chiral auxiliary **3** was recovered in both reductions. Oxidation of the homochiral 2-PhS-alcohols (S)-**5** to the 2-PhS-aldehydes **1** required chemoselective oxidation under non-basic conditions to avoid both oxidation at sulfur and racemisation. The Swern[15]and Dess-Martin[16] methods were obvious choices. Results are presented in table 3.

Table 3: Oxidation of Homochiral 2-Phenylthio Alcohols (S)-5 to Aldehydes (S)-1.

Entry	Alcohol 5	Conditions	Product	Yield[a], %	e.e.[b], %
1.	(S)-**5a**	Swern, Et_3N	(±)-**1a**	86	0
2.	(S)-**5a**	Swern, i-Pr_2NEt	(±)-**1a**	-[c]	0
3.	(S)-**5c**	Swern, Et_3N	(±)-**1c**	94	0
4.	(S)-**5c**	Swern, i-Pr_2NEt	(S)-**1c**	74[d]	71
5.	(S)-**5d**	Swern, Et_3N	(S)-**1d**	34[d]	57
6.	(S)-**5a**	Dess-Martin	(S)-**1a**	92[e]	>98
7.	(S)-**5c**	Dess-Martin	(S)-**1c**	90[e]	93

[a]Yield after column chromatography on silica; [b]Determined by ^{1}H NMR (250 MHz) in the presence of the chiral shift reagent Eu(hfc)$_3$; [c]Yield not determined; [d]Some starting material was recovered, 22-34%; [e]Yield of crude aldehyde.

Swern oxidations gave racemic aldehydes **1a** whether Et_3N or i-Pr_2NEt was used as base. Optically active **1c** and **1d** could be formed by this method but yields and e.e.s were moderate. The Dess-Martin oxidation was far superior to the Swern (entries 1-5 vs 6-7): the Dess-Martin oxidations proceeded smoothly and were over within 0.5 hours at room temperature. The crude aldehydes were very clean by ^{1}H NMR and

could be used in crude form for other synthetic transformations. Presumably the success of the Dess-Martin procedure is due to the slightly acidic to near neutral conditions during oxidation and work-up while the limited success of the Swern procedure is due to base-catalysed racemisation of the product aldehydes (use of the more hindered base i-Pr$_2$NEt followed by a cold acid-buffered wash helps minimise racemisation, entry 3 vs entry 4, table 3). Purification of the aldehydes **1** from the Swern procedure by column chromatography did not result in complete racemisation (contrary to the previous report[5]) especially with the more sterically hindered branched chain 2-PhS-aldehydes **1c** and **1d** (table 2 entries 3-6 and table 3 entries 4-5). But the less sterically hindered open chain aldehydes (**1a**) and (**1b**) (table 2 entries 1-2 and table 3 entries 1-2) may well racemise on columning as is reported with similar aldehydes.[5] The fact that aldehyde **1a** (table 3 entry 6) was obtained in optically pure form from the Dess-Martin oxidation shows that racemisation of optically active 2-PhS-aldehydes under acidic conditions is not a serious problem.[17]

In summary we have demonstrated an alternative route to highly enantiomerically enriched enolisable 2-PhS-aldehydes which is complementary to the Enders[6] route - we sulfenylate chiral enolates while they alkylate pre-sulfenylated SAMP derivatives - and shown that such aldehydes are configurationally stable under suitable conditions and can be isolated. No doubt use of the opposite enantiomer of the chiral auxiliary **3** in the sulfenylation reaction would give the opposite enantiomer of the aldehydes **1**. Our approach also provides homochiral 2-phenylthio alcohols **5** which are important precursors for homochiral epoxides.[9,18] This approach does not permit the synthesis of blocked 2-PhS-aldehydes from **2e** and aldols from these aldehydes must be made by kinetic resolution.[3a]

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