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Asymmetric Synthesis of Amines using a Chiral, Non-Racemic, Cyclic Sulphinamide.

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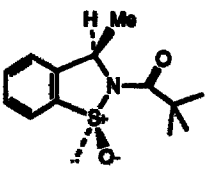
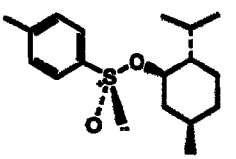
Abstract: *The homochiral cyclic sulphinamide $S_{(S)}R$-(+)-1 has been employed in the asymmetric synthesis of α-methylbenzylamine via the benzylidene sulphinamide $R_{(S)}R$-(-)-3. Following diastereoselective reduction and hydrolysis $S_{(S)}R$-(+)-1 can be recycled in one step from the sulphinic acid 6.*

In a series of recent publications we have described the preparation and synthetic applications of the homochiral cyclic sulphinamide *$S_{(S)}R$-(+)-1*.[1] This reagent may be converted into chiral sulphoxides *via* reactions with nucleophiles such as Grignard reagents or the enolates of esters or ketones. In each case inversion of configuration at sulphur is observed. Sulphinamide *$S_{(S)}R$-(+)-1* has several advantages over the more commonly used homochiral sulphoxide source 1R,2S,5R-(-)-menthyl-(S)-p-tolylsulphinate 2 (S-2).[2] It is readily available in either homochiral form from inexpensive starting materials and is not prone to epimerisation at sulphur during use or in storage however most significantly it has been demonstrated to be recyclable after use.[1c] In this paper we report the application of *$S_{(S)}R$-(+)-1* to the asymmetric synthesis of amines.



$S_{(S)}R$-(+)-1

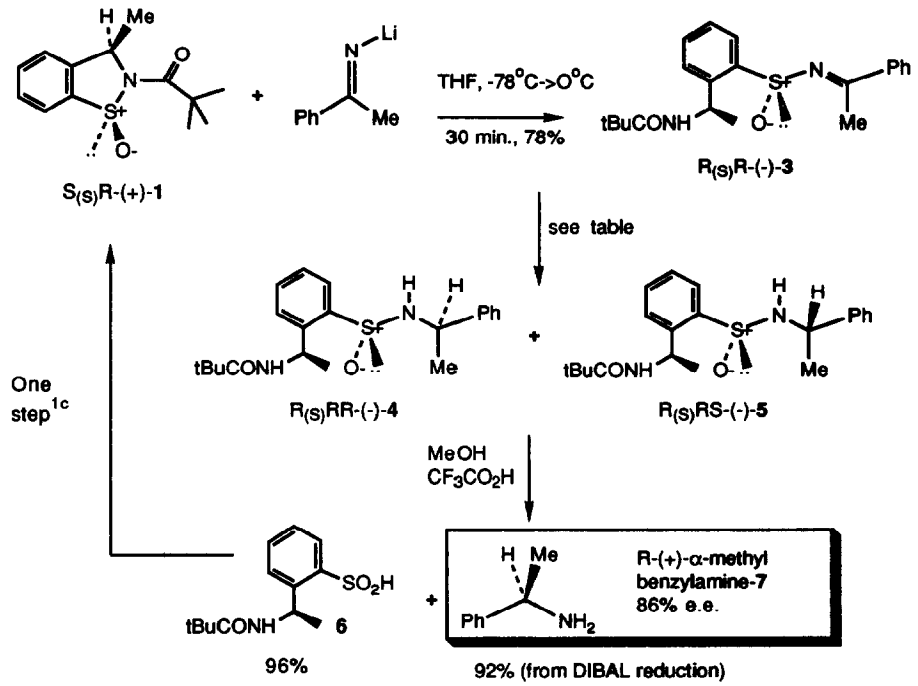


S-2

Addition of the lithiated imine generated by the reaction of methyllithium with benzonitrile to sulphinamide *$S_{(S)}R$-(+)-1* resulted in clean formation of the benzylidene sulphinamide *$R_{(S)}R$-(-)-3* as a single diastereoisomer (scheme 1). Benzylidene sulphinamides have been reported in racemic[3,4] and enantiomerically enriched form.[5-8] In the latter case, with one exception,[9] these have been prepared from the reaction of lithiated imines with S-2 in which case inversion of configuration at sulphur is observed. On this basis we have been able to assign the configuration at the sulphur atom in *$R_{(S)}R$-(-)-3*.[10,11] Reduction of *$R_{(S)}R$-(-)-3* to the diastereoisomeric products *$R_{(S)}RR$-(-)-4* and *$R_{(S)}RS$-(-)-5* with a variety of hydride transfer reagents has been examined (scheme, table). The highest selectivity was obtained using di-isobutylaluminium hydride (DIBAL) in THF or ether at -23°C[10] and was observed to decrease with the reaction temperature. The diastereoselectivity of this reaction was assessed by the use of 270 and 400 MHz ^{1}H-NMR and HPLC. Two equivalents of DIBAL are required since deprotonation of the amide side chain is observed.

In order to determine the configuration of the new stereogenic centre in the reduction products we reacted sulphinamide *S(S)R-(+)-1* with the lithio-anions of each enantiomer of α-methylbenzylamine. The product from the R- enantiomer of amine gave a product which by 270 MHz ^{1}H-NMR and TLC was identical to the major diastereoisomer of the DIBAL reduction product *R(S)RR-(-)-4* described above. The adduct from the S- amine was identical to the minor diastereoisomer *R(S)RS-(-)-5*. Amines are known to react with chiral sulphinate esters with inversion of configuration at sulphur,[12] hence this serves to confirm that our earlier assignment of the sulphur configuration in **3** was correct.

Scheme

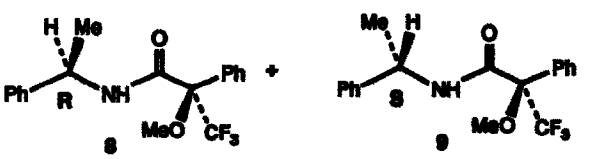


In order to complete the synthesis of amines we required a method for the hydrolysis of the imine reduction products. This was achieved simply by treating the 13:1 mixture of *R(S)RR-(-)-4* and *R(S)RS-(-)-5* with methanolic trifluoroacetic acid. The products were isolated by the addition of 2N hydrochloric acid followed by extraction with dichloromethane. This procedure gave the sulphinic acid **6**, via the methyl sulphinate ester which was hydrolysed on workup with acid. Neutralisation of the acidic aqueous layer followed by extraction with dichloromethane gave α-methylbenzylamine **7** (scheme). Conversion of the amine mixture to the (R)-MTPA amide derivatives **8** and **9**[13] revealed that the ratio of enantiomers from the hydrolysis was 13:1 and therefore confirmed that no epimerisation had taken place during the hydrolysis process. Standard samples of each (R)-MTPA amide were independently produced from reactions of R and S

α-methyl benzylamine to confirm our stereochemical assignment. The conversion of sulphinic acid **6** to diastereoisomerically pure cyclic sulphinamide *S(S)R-(+)-1* in one step has been reported.[1c]

Table; Reduction reactions of $R_{(S)}$R-(-)-3

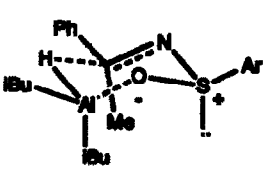
Reducing agent/conditions	Yield	d.e. (major diastereoisomer)	
$LiAlH_4$, THF, r.t., 16 hr.	80%	34%	$R_{(S)}RR$-(-)- (4)
$NaBH_4$, EtOH, 0°C, 4 hr.	87%	0%	-
L-Selectride, THF, -78°C, 4 hr.	52%	40%	$R_{(S)}RS$-(-)- (5)
L-Selectride, ether, -78°C, 3 hr.	53%	40%	$R_{(S)}RS$-(-)- (5)
LS-Selectride, THF, -78°C, 1.5 hr.	20%	60%	$R_{(S)}RS$-(-)- (5)
LS-Selectride, ether, -78°C, 3 hr.	56%	60%	$R_{(S)}RS$-(-)- (5)
REDAL, THF, -78°C, 20 hr.	63%	77%	$R_{(S)}RS$-(-)- (4)
$[(MeO)_2AlH_2]Li$, THF, -78°C, 22hr.	47%	0%	-
$[(t\text{-}BuO)_2AlH_2]Li$, THF, -78°C, 22hr.	43%	25%	$R_{(S)}RS$-(-)- (5)
DIBAL, THF, -78°C, 4hr.	22%	34%	$R_{(S)}RR$-(-)- (4)
DIBAL, CH_2Cl_2, -78°C, 17 hr.	69%	60%	$R_{(S)}RR$-(-)- (4)
DIBAL, toluene, -78°C, 4 hr.	78%	0%	-
DIBAL, THF, -40°C, 4hr.	90%	83%	$R_{(S)}RR$-(-)- (4)
DIBAL, THF, -23°C, 4hr.	98%	86%	$R_{(S)}RR$-(-)- (4)



The high diastereoselectivity of the imine reduction process achieved with DIBAL compared to the much lower selectivities with anionic hydride sources suggests that the coordination of *R(S)R-(-)-3* to the reducing agent is essential. We propose that the reduction takes place through the chelated species illustrated in the figure in which the groups on the sulphur atom and the larger group on the imine are in pseudo-equitorial positions.[11] It has been assumed that the imine exists in the configuration in which the sulphoxide group is *trans*- to the phenyl group rather than the smaller methyl group. It has further been assumed that the amide side chain (which is deprotonated), does not participate in the reaction. Reactions carried out with DIBAL at higher temperatures gave higher selectivities, which suggests that the situation may be rather more complex. We are currently in the process of investigating these transformations further.

Figure

Proposed transition state for benzylidene sulphinamide reduction by DIBAL.



In conclusion we have demonstrated that the cyclic sulphinamide *S(S)R-(+)-1* may be employed for the asymmetric synthesis of amines. Furthermore it may be recycled after use and therefore represents the first example of a reagent of this type. We are currently investigating the optimisation and synthetic scope of this process.

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10) All new compounds gave satisfactory spectroscopic and analytical data.

11) In all diagrams we have illustrated R(S)R-(-)-3 as the E- isomer with respect to the C=N bond geometry. Although we have no direct experimental evidence, it is known that the energy barrier to isomerisation about this double bond is *ca.* 20 kcal/mol[14] and have therefore assumed that the isomer with the sulphur atom and large phenyl rings opposite each other will predominate.

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