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ADDITION OF DIMETHYLOXOSULFONIUM METHYLIDE TO ENANTIOMERICALLY PURE SULFINIMINES: ASYMMETRIC SYNTHESIS OF 2-SUBSTITUTED AZIRIDINES

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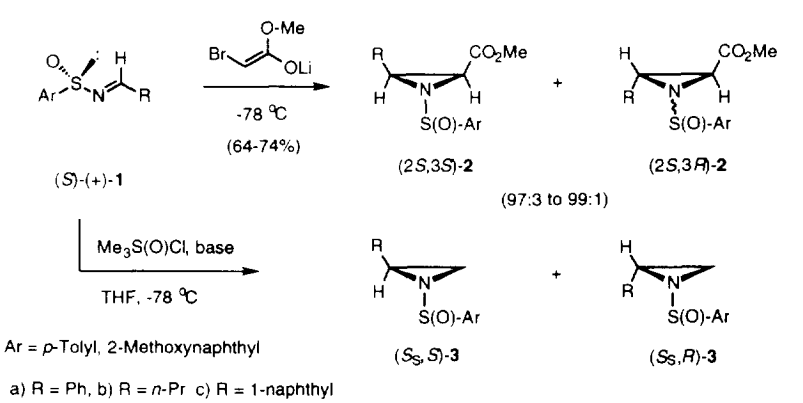
Summary: Diastereoselective addition of dimethyloxosulfonium methylide to chiral nonracemic pure sulfinimines **1** affords N-sulfinyl aziridines **3** in 58-70% de which are readily separated. The N-sulfinyl auxiliary in **3** was removed, without ring-opening, by treatment with MeLi.

Chiral nonracemic aziridines are versatile synthetic intermediates for asymmetric synthesis because of their high reactivity and ability to function as carbon electrophiles.[1,2] With carbon and heteroatom nucleophiles these compounds afford functionalized secondary amines on ring-opening. In addition, Tanner has demonstrated their utility as chiral auxiliaries and as chiral ligands.[3] While racemic aziridines are readily available, procedures for their synthesis in enantiomerically pure form are limited. Ring closure of β-amino alcohols, derived from amino acids, is one frequently used method but is limited by the availability of the starting material.[1,4] Another procedure employs optically active epoxides prepared via the Sharpless epoxidation of allylic alcohols or the asymmetric dihydroxylation of alkenes.[1] We recently described a convenient, highly diastereoselective asymmetric synthesis of *cis-N-(p*-toluenesulfinyl)-2-carbomethoxyaziridines **2** via a Darzens-type reaction of the lithium enolate of methyl bromoacetate with enantiopure sulfinimines **1** (Scheme 1).[2] These aziridines are precursors of the difficult to prepare *syn*-β-hydroxy-α-amino acid structural unit present in many bioactive materials such as the broad spectrum antibiotic thiamphenicol.[5] Enantiomerically pure sulfinimines are chiral ammonia imine building blocks. They have been used, not only in the aforementioned synthesis of aziridines,[2] but also in the asymmetric synthesis of amines,[6] α-[7] and β-amino acids,[8] the taxol side chain[8a] and its fluorinated analog.[8c]

SCHEME 1

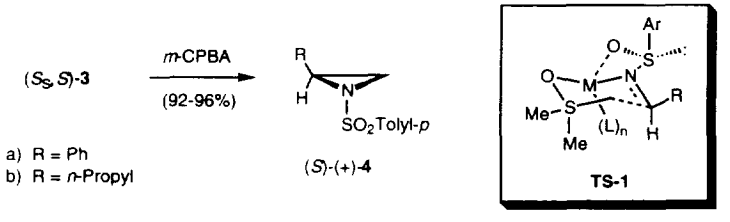


Limited attention has been given to the synthesis of aziridines by the addition of ylides to imines.[9,10] Here we describe preliminary results of new methodology for the asymmetric synthesis of 2-substituted aziridines **3** via the addition of dimethyloxosulfonium methylide to chiral nonracemic sulfinimine (*S*)-(+)-**1**. In the course of this work, Garcia Ruano et. al., independently reported similar results, but apparently incorrectly assigned the absolute configuration of the major aziridine product (see also below).[11]

Typically a THF solution of trimethylsulfoxonium chloride (2.0 mmol) was treated at 0 °C with an equivalent amount of the appropriate base and cooled to –78 °C after 30 min. The sulfinimines **1a-c** (1.0 mmol) were added to the ylide at this temperature and after completion of the reaction (3-4 h), quenched with sat. NH_4Cl solution. The enantiomerically pure sulfinimines **1** were prepared from commercially available (1,*R*,2*S*,5*R*)-(–)-menthyl (*S*)-*p*-toluenesulfinate [Andersen Reagent] or (1,*R*,2*S*,5*R*)-(–)-(*S*)-menthyl-2-methoxy-1-naphthalenesulfinate,[7,12] LiHMDS, CsF and the appropriate aldehyde as previously reported.[13] These results are summarized in the Table.

In all cases examined mixtures of the aziridine diastereoisomers (S_S,*S*)-**3** and (S_S,*R*)-**3** were obtained in good to modest yield. The de's, determined on the reaction mixtures by ^1H NMR, proved to be relatively insensitive to the reaction conditions and the structure of the **1** (58-70% de). However, solvents other than THF resulted in lower yields. Optimum conditions in terms of yield, de and convenience were found with sodium bis(trimethylsilyl)amine (NaHMDS) in THF (entry 4). Interestingly the (+)-2-methoxy-1-naphthysulfinyl auxiliary gave lower de's (50%) and yields (entry 10). Just the opposite was found in our recently reported asymmetric Strecker synthesis where this chiral auxiliary gave improved de's over that of the *p*-toluenesulfinyl group.[7]

The diastereomers were readily separated in excellent yield by preparative TLC (EtOAc/CH_2Cl_2/*n*-pentane) on silica gel.[14] The absolute configuration was established for (S_S,*S*)-(+)-**3a** by oxidation with 1.5 eq of *m*-chloroperbenzoic acid (*m*-CPBA) to give the known (+)-(*S*)-(*N*-*p*-toluenesulfonyl)-2-phenylaziridine (**4a**) in near quantitative yield.[15] In a similar manner (+)-(S_S,*S*)-**3b** was oxidized to (*S*)-**4b** in 92% yield.[17] As pointed out earlier *N*-tosyl activation often affords superior reactivity and regiospecificity in aziridine ring opening reactions.[2] This key activating group is easy installed simply by oxidizing the *N*-sulfinyl group in **3**. The absolute configuration at C-2, determined to be (*S*) in the major aziridine diastereomer **3a**, is consistent with chair-like transition state **TS-1** followed by intramolecular ring closure. By analogy the absolute configurations of the major products in **3b** and **3c** are therefore also (*S*) at C-2.



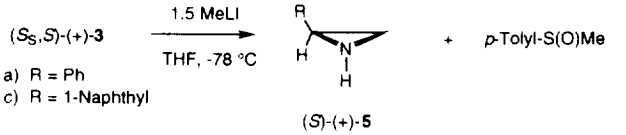
One of the advantages of the N-sulfinyl auxiliary in aziridine 2-carboxylic acids **2** is that it is easily removed without epimerization by treatment with trifluoroacetic (TFA) in MeOH.[2] By contrast removal of

Table: Reaction of Sulfinimines **1** with Dimethyloxosulfonium Methylide

entry	Sulfinimine R =	Base	Solvent/°C/time (h)	N-Sulfinyl Aziridines **3** $(S_S,S)/(S_S,R)$ [a]	% Yield[b]
1	Ph	*n*-BuLi	THF/–78 /3.5	75:25	62
2		LDA	THF/–78/4.0	75:25	15
3		NaH	THF/–78 to rt/4.0	61:39	75
4		NaHMDS	THF/–78/3.5	79:21	68
5		NaHMDS	Et_2O/–78/3.5	68:32	43
6		NaHMDS	PhMe/–78/2.0	56:44	54
7		NaHMDS	THF/–78 to rt/4.0	71:29	80[c]
8		LiHMDS	THF/–78/3.5	73:27	53
9		KHMDS	THF/–78/3.5	70:30	54
10	Ph [2-MN][d]	NaHMDS	THF/–78/3.5	75:25	51
11	*n*-Pr	NaHMDS	THF/–78 to 0/3.5	84:16	68
12	1-Naphthyl	NaHMDS	THF/–78 to –20/5.0	85:15	57

a) The ratio determined on the crude mixture by ^{1}H NMR. b) Isolated yields. c) Trimethylsulfoxonium iodide used to generate the ylide. d) (+)-2-Methoxy-1-naphthysulfinyl auxiliary used see refs. 7 and 12.

the N-sulfinyl auxiliary in **3** proved to be difficult without ring-opening. Thus treatment of **3a** with TFA/MeOH gave ring opened products in addition to methyl *p*-tolylsulfinate.[16] There was no reaction with DIBAL, but $LiAlH_4$ gave the 2-phenylaziridine (**5a**), detected by ^{1}H NMR, along with ring-opened products.[18] The propensity for ring-opening reactions in **3**, contrasts with aziridine 2-carboxylic esters **2**, and is undoubtedly due to the presence of the deactivating carboxyl group in the latter as well as other factors.[19] The best method for removal of the N-sulfinyl group was treatment of **3a** with 1.5 equiv. methyllithium at –78 °C followed by quenching with sat. NH_4Cl. The known (*S*)-(+)-2-phenylaziridine (**5a**)[19,20] was isolated in 54% yield and (*S*)-(+)-**5c** in 56% yield.[21] The former result provides additional confirmation of the absolute configuration of the major aziridine diastereoisomer (S_S,S)-**3a**. In addition to **5**, (*S*)-(–)-methyl *p*-tolylsulfoxide was isolated in 60% yield and >97% ee.[22]



In summary, new methodology is reported for the asymmetric synthesis of 2-aryl and 2-alkyl aziridines which are versatile chiral building blocks. The antipodal aziridines are readily available from the enantiomeric sulfinimines; e.g.; (*R*)-(–)-**1**.[13]

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15. (*S*)-(+)-**4a**, mp 76-78 °C; [lit.[16] mp 78-79]; $[\alpha]_D^{20}$ +65.5 (c, 1.0 benzene), [lit.[16] $[\alpha]_D^{20}$ –65.5 (c, 1.18 benzene) for the (*R*)-(-)-**4a**].
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