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ASYMMETRIC SYNTHESIS OF SULFINIMINES: CHIRAL AMMONIA IMINE SYNTHONS

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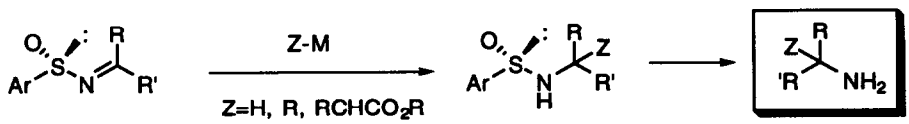
Summary: *Two Andersen-type procedures for the preparation of enantiopure sulfinimines* **1** *(R=H) in better than 95% ee from nitriles and aldehydes are described.*

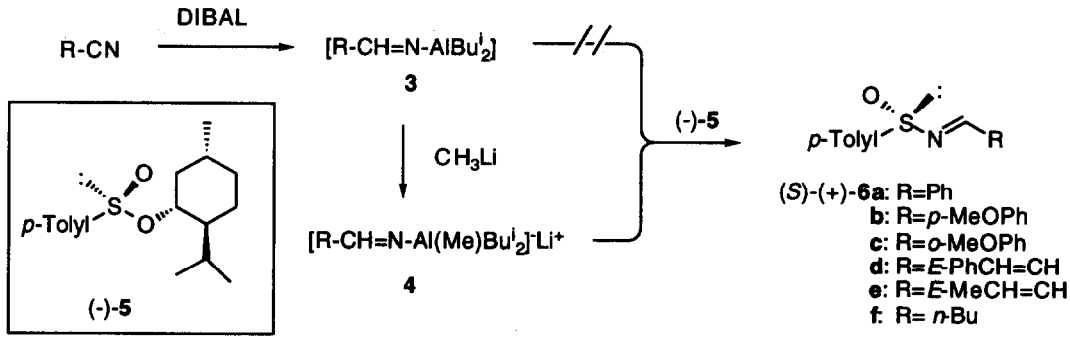
Sulfinimines **1** are ammonia imine (R'RC=NH) synthons because additions across the C-N double bond affords sulfinamides **2** in which the S-N bond is easily cleaved to amino derivatives.[1,2] Nonracemic sulfinimines **1** are therefore chiral ammonia imine synthons. They have found utility in the asymmetric synthesis of amines[3,4] and β-amino acid derivatives.[4,5] Moderate yields of enantiopure **1** are available by an Andersen-type synthesis; e.g. the reaction of a metaloketimine (ArRC=NM) with menthyl *p*-tolyl sulfinate.[3,4] However, only alkyl aryl, ketone derived sulfinimines **1** (R≠H) are available because the metaloketimines are prepared from aromatic nitriles, lithium and Grignard reagents (RM). Recently we introduced a more general approach to these materials involving the asymmetric oxidation of sulfenimines (ArS-N=CR'R, R=H, alkyl) with (+)- or (-)-N-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine an asymmetric oxidizing reagent.[5,6] Aldehyde and ketone derived sulfinimines **1** are available in >95% ee in both enantiomeric forms. In this context we describe two new procedures for the preparation of these important reagents from aromatic nitriles and aldehydes.



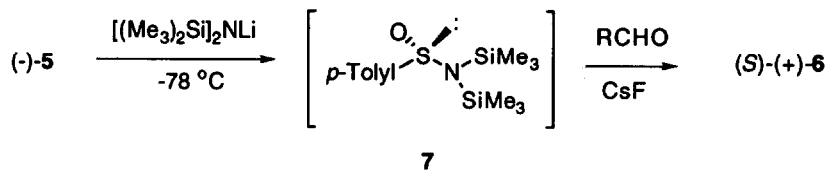
1 **2**

The reduction of nitriles by DIBAL to aldiminoaluminum compounds **3** followed by hydrolysis constitutes a useful synthesis of aldehydes.[7] However, treatment of benzonitrile at 0 °C with DIBAL followed by addition of (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate [Andersen Reagent] (**5**) under a variety of conditions gave none of the desired sulfinimine **6a**. Although hydrolysis produces benzaldehyde the aldiminoaluminum **3** is apparently not nucleophilic enough to displace the menthyl alkoxide. However, formation of the *ate* complex **4**,[8] by treatment of **3** with 1 equiv. of methyllithium, prior to reaction with **5**, gives moderate to good yields of **6**. Typically the

appropriate nitrile (3 mmol) was added to an equivalent amount of DIBAL in *n*-hexane at 0 °C followed after 2 h by 3.0 mmol of MeLi in ether. After 2 h the reaction mixture was cooled to -40 °C, 1 mmol of (-)-**5** added, the reaction mixture stirred for 8 h at r.t. and quenched by addition of ethyl acetate/H_2O. The product was purified by flash chromatography. More polar solvents such as THF, Et_2O resulted in reduced yields. These results, **Method A**, are summarized in the Table.



The second method involves a "one-pot" reaction of lithium bis(trimethylsilyl)amide (LiHMDS) with (-)-**5** to give an intermediate sulfinamide **7**,[9] which, on treatment with excess aldehyde and cesium fluoride, gives **6** in good to excellent yield.[10] At -78 °C (1 mmol) of (-)-**5** in THF was treated with 1.5 equiv. of LiHMDS and warmed to r.t. After 5 h the reaction mixture was cooled to 0 °C and 2 mmol of the appropriate aldehyde and powdered CsF (99.99%) added. Stirring at r.t. was continued for 8 h at which time a sat. solution of NH_4Cl was added. The sulfinimines were isolated by flash chromatography. These results, **Method B**, are summarized in the Table.



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With aldehydes the "one pot" procedure employing sulfinamide **7** (Method B) is more general and gave superior yields of sulfinimines compared to Method A. The exception was crotonaldehyde which gave no reaction (entry 10). In this case crotononitrile and Method A afforded sulfinimine **6e** in 33% (entry 9). Both methods generally failed with aliphatic nitriles and aldehydes (entries 12 and 13) although **6f** was detected in the latter case (entry 13). The ability of MeLi to deprotonate the α-protons of aliphatic aldiminoaluminum **3**[11] is likely responsible for the failure of Method A with butyronitrile. Contributing to the low yields of the "one-pot" (Method B) procedure are aldol type reactions caused by the bases present in solution.[12] Indeed a modification of Method B improved the yields of both **6e** and **6f** to 57 and 30 percent, respectively

Table: Asymmetric Synthesis of Sulfinimines form Nitriles and Aldehydes.

entry	Nitrile/Aldehyde	Procedure	Sulfinimine **6**[c] Ee[a] (config.)	[% Yield][b]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	mp °C
1	Ph-CN	Method A	**6a** >95% (*S*)	[36]	+119.8 (1.9)	77-8
2	PhCHO	Method B	>95% (*S*)	[82]	+117.0 (2.1)	
3	*p*-MeOPhCN	Method A	**6b** >95% (*S*)	[37]	+ 41.1° (2.0)	135-7
4	*p*-MeOPhCHO	Method B	>95% (*S*)	[90]	+ 37.9° (1.49)	
5	*o*-MeOPhCHO	Method B	**6c** >95% (*S*)	[81]	+362.9 (1.43)	71-3
6	*E*-PhCH=CH-CN	Method A	**6d** >95% (*S*)	[42]	+ 336° (2.0)	114-5
7		Method A[d]	>95% (*R*)	[38]	- 334° (2.0)	
8	*E*-PhCH=CH-CHO	Method B	>95% (*S*)	[85]	+ 337° (1.54)	
9	*E*-MeCH=CH-CN	Method A	**6e** >95% (*S*)	[33]	+ 610.7 (2.3)	39-40
10	*E*-MeCH=CH-CHO	Method B	Sulfinimine not detected			
11	*E*-MeCH=CH-CHO	Method B[e]	>95% (*S*)	[57]	+ 617.5 (1.66)	
12	*n*-Bu-CN	Method A	Sulfinimine not detected			
13	*n*-Bu-CHO	Method B	**6f**	[<10][f]		
14	*n*-Bu-CHO	Method B[e]	>95% (*S*)	[30]	+ 308.8 (1.35)	oil
15	PhC(O)Me	Method B[e]	Sulfinimine not detected			

a) The ee% were determined by use of $Eu(hfc)_3$ b) Isolated yields. c) Ref. 13. d) Prepared from (+)-**5**. e) Prepared from isolated **7** and CsF. f) Sulfinimine imino proton at δ 8.2 ppm detected by ^1H NMR.

(entries 11 and 14). This change involves the isolation of crude **7** by quickly extracting it into EtOAc, washing with water and drying prior to treating it with 2 equiv. of the aldehyde and CsF. Acetophenone failed under these conditions (entry 15).

The ee's of the new sulfinimines **6** were determined by using the chiral shift reagent $Eu(hfc)_3$ by observing the change in the methyl protons of the *p*-tolylsulfinyl group. The sulfinimines **6** have the (*S*)-configuration because the (-)-**5** Andersen reagent is used. It is noteworthy that both the (*R*)- and (*S*)-sulfinimines are readily available by use of the appropriate Andersen reagent. For example (*R*)-cinnamaldehyde sulfinimine **6d** was prepared starting from (+)-**5** (entry 7). Studies currently underway are evaluating the utility of enantiopure sulfinimines **6** for asymmetric synthesis.

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9. Attempts to isolate **7** results in hydrolysis to the sulfinamide. Its solution ^{1}H NMR is fully consistent with its structure.
10. Sulfenimines have been prepared by reaction of N,N-bis(trimethylsilyl)sulfenamides with aldehydes and ketones. Morimoto, T.; Nezu, Y.; Achiwa, K.; Sekiya, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1584.
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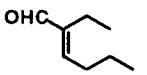
12. When *n*-Bu_4NF was used as the catalysts compounds i and ii were isolated in low yield.



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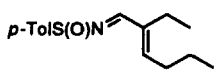

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13. All new compounds gave satisfactory elemental analysis and had spectra consistent with their structures.

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