Highly enantioselective synthesis of dialkyl and alkyl aryl *N*-tosylsulfimides

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Enantiomerically pure *S*-alkyl-*S*-[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-*N*-tosylsulfimides react with Grignard reagents affording dialkyl and alkyl aryl sulfimides in high chemical yield and enantiomeric excess.

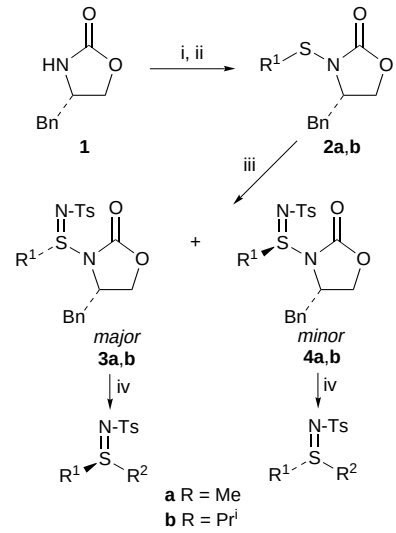
Sulfimides are a class of compounds potentially of interest in the field of medicine,[1] because of their different pharmacological properties: several families of structurally related sulfimides have shown antimicrobial, diuretic and hypotensive properties, inhibitor effects on tumor growth and activity as antidepressants and stimulants of the central nervous system.

In organic synthesis sulfimides are versatile reagents due to the presence of an S^{IV}=N moiety which provides two reaction sites susceptible to attack by both nucleophilic and electrophilic reagents. Moreover, like sulfoxides, sulfimides form stable α-carbanions. This property has recently been exploited in asymmetric methylidene transfer from the sodium salt of (*S*)-*S*-methyl-*S*-*p*-tolyl-*N*-tosylsulfimide to prochiral carbonyl groups yielding epoxides with ees of up to 70%.[2] Wider applications of sulfimides are limited, however, because of the dearth of general synthetic methodologies affording high ees. The first procedure for the preparation of optically active sulfimides took advantage of the stereospecific reaction of chiral sulfoxides with various iminating species, such as bis(*N*-tosylsulfur diimine), *N*-sulfinyltoluene-*p*-sulfonamide and toluene-*p*-sulfinyl nitrene.[3] More recently Uemura[4] reported the asymmetric synthesis of alkyl aryl sulfimides by imidation of the corresponding prochiral sulfides with [*N*-(toluene-*p*-sulfonyl)imino]phenyliodinane (PhI=NTs) in the presence of a catalytic amount of Cu^{I} salts and chiral 4,4′-disubstituted bis(oxazoline) ligands, the ee being in the range 10–71%.

N-Functionalized chiral oxazolidinones are commonly employed auxiliaries which afford excellent degrees of asymmetric induction in reactions ranging from alkylations to aldol condensations and Diels–Alder additions.[5] Their use has been highly successful in the stereoselective construction of a number of natural products, antibiotics, macrolides and other pharmacologically important compounds. Recently chiral *N*-sulfinyloxazolidinones were used by Evans[6] as sulfinylating agents of a series of organometallic nucleophiles for the synthesis of sulfoxides, sulfinate esters and sulfinamides with up to 100% ee.

Now we report a new enantioselective synthesis of dialkyl and alkyl aryl *N*-tosyl sulfimides *via S*-alkyl-*S*-[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-*N*-tosylsulfimides **3** and **4** prepared from the corresponding *N*-(alkylthio)oxazolidinones[6] by reaction with chloramine T (Scheme 1).

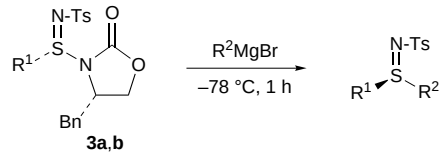
Reagents **3** and **4**, separated by flash chromatography, reacted with a series of Grignard reagents to give the corresponding sulfimides (Tables 1 and 2).‡ The displacement reaction occurred with good chemical yields even with bulky organometallic reagents such as cyclohexylmagnesium bromide (Table 1, entry 7; Table 2, entry 7) and 2-naphthylmagnesium bromide (Table 1, entry 4; Table 2, entry 4). However, *tert*-butylmagnesium bromide did not react, even when used in a large excess (four-fold excess) and for longer reaction time. In all the cases examined, no racemization of the recovered chiral auxiliary was observed.



Scheme 1 *Reagents and conditions:* i, $Bu^{n}Li$ (1 equiv.), THF, 0 °C, 0.5 h; ii, R′S–SO_2Me (1.2 equiv.), room temp., 1 h; iii, Chloramine T (1.1 equiv.), toluene, $C_{16}H_{33}Bu_3PBr$ (0.05 equiv.), room temp., 4 h; iv, R^2MgBr (2 equiv.), THF, −78 °C, 1 h

The enantioselectivity in the formation of sulfimides was almost unaffected by the reaction temperature, indeed the ee of *S*-methyl-*S*-phenyl-*N*-tosylsulfimides obtained from diastereoisomers **3a** and **4a** with phenylmagnesium bromide was unchanged at both −78 and 0 °C. Therefore, intermediates **3a** and **4a** did not undergo epimerization, unlike *N*-sulfinyloxaz-

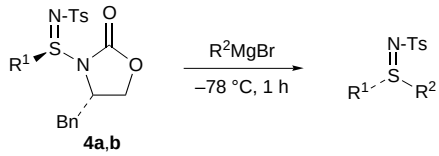
Table 1 Chemical yields and ees for nucleophilic displacement reactions on diastereoisomers **3a** and **3b**



Entry	R^1	R^2	Yield (%)	Ee (%)[a]
1	Me	Ph	91	94
2[b]	Me	Ph	72	81
3	Me	*p*-tolyl	89	87 (*R*)
4	Me	2-naphthyl	75	> 98
5	Me	Bn	86	84
6	Me	vinyl	89	98
7	Me	Cy	85	98
8	Me	Pr^{i}	80	85
9[c]	Me	Bu^{t}	—	—
10[c]	Pr^{i}	Ph	39	96

[a] Determined by HPLC using a Chiralcel OD (entries 5, 6, 7, 8), Chiralcel OJ (entries 1, 2, 10) or Chiralpack AS column (entry 3) with different mixtures of *n*-hexane–EtOH as the mobile phase. The optical purity of *S*-methyl-*S*-naphthyl-*N*-tosylsulfimide (entry 4) was obtained by ^{1}H NMR analysis using $Eu(tfc)_3$. [b] For 1 h at 0 °C. [c] For 8 h at 25 °C.

Table 2 Chemical yields and ees for nucleophilic displacement reactions on diastereoisomers **4a** and **4b**



4a,**b**

Entry	R^1	R^2	Yield (%)	Ee (%)[a]
1	Me	Ph	88	85
2[b]	Me	Ph	69	83
3	Me	*p*-tolyl	91	94 (*S*)
4	Me	2-naphthyl	72	> 98
5	Me	Bn	87	92
6	Me	vinyl	92	98
7	Me	Cy	84	96
8	Me	Pr^i	84	88
9[c]	Me	Bu^t	—	—
10[c]	Pr^i	Ph	40	78

[a] Determined by HPLC using a Chiralcel OD (entries 5, 6, 7, 8), Chiralcel OJ (entries 1, 2, 10) or Chiralpack AS columns (entry 3) with different mixtures of *n*-hexane–EtOH as the mobile phase. The optical purity of *S*-methyl-*S*-naphthyl-*N*-tosylsulfimide (entry 4) was obtained by ^{1}H NMR analysis using $Eu(tfc)_3$. [b] For 1 h at 0 °C. [c] For 8 h at 25 °C.

olidinones, which are configurationally unstable at the sulfur atom.[6] This could explain the high imidation stereoselectivity with respect to overall chemical yield.

Increasing the steric hindrance at the sulfur atom in diastereoisomers **3b** and **4b** affected the yield but not the ee of the sulfimides formed (Table 1, entries 1, 10; Table 2, entries 1, 10), thus extending this methodology to *S*-alkyl-*S*-[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-*N*-tosylsulfimides having *S*-alkyl substituents other than methyl.

Diastereoisomer **3a** yielded *S*-methyl-*S*-*p*-tolyl-*N*-tosylsulfimide (Table 1, entry 2) with 87% ee and (*R*) absolute configuration according to the literature,[3] the opposite enantiomer [94% ee, (*S*)] being obtained from diastereoisomer **4a**. If we assume that the nucleophilic displacement occurred with inversion of configuration, as in the case of the *N*-sulfinyloxazolidinones,[6] the absolute configuration at the sulfur atom should be (*R*) for the diastereoisomer **3a** and (*S*) for the diastereoisomer **4a**.

In summary, this study represents a further example of the synthetic versatility of chiral oxazolidinones and describes a new approach to optically active sulfimides with good chemical yields and high ees.

Notes and References

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‡ *Experimental procedure*: *S*-Methyl-*S*-[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-*N*-tosylsulfimides **3a** and **4a** were prepared by adding chloramine T (1.1 equiv.) to *N*-(methylthio)oxazolidinone (ref. 6) (1 equiv.) and hexadecyltributylphosphonium bromide (0.05 equiv.) in toluene as solvent. After 4 h at room temperature, normal work-up afforded the diastereoisomers **3a** and **4a**. Purification by flash silica gel column chromatography (hexane–ethyl acetate 3 : 7) gave pure **3a** and **4a** in the ratio 2.3 : 1 (yield 80%.) Sulfimides were obtained by reacting diastereoisomers **3a** and **4a** (1 equiv.) with the Grignard reagents (2 equiv.) at −78 °C for 1 h in THF as solvent (ref. 6) and purification by flash silica gel column chromatography (Et_2O–MeOH 9 : 1). Diastereoisomers **3b** and **4b** were prepared in an analogous way and obtained in the ratio 1.3 : 1 (yield 72%). MeS–SO_2Me was purchased from Aldrich, and Pr^iS–SO_2Me was prepared according to the literature (ref. 7).

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