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On the utility of *S*-mesitylsulfinimines for the stereoselective synthesis of chiral amines and aziridines†

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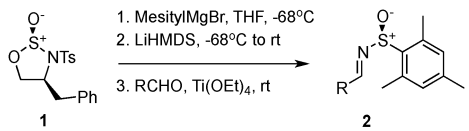
The synthetic utility of *S*-mesitylsulfinimines for the synthesis of chiral amines and aziridines was examined through their reactions with Grignard reagents, with the ylides derived from trimethylsulfonium iodide and *S*-allyl-tetrahydrothiophenium bromide and through an aza-Darzens manifold, affording convenient access to a diverse range of highly substituted chiral amines and aziridines in high yields and excellent stereoselectivities.

Chiral amines are key structural functionalities found in a wide range of natural products, drug candidates and active pharmaceutical ingredients. The most direct method the synthesis of functionalised amines is through 1,2-nucleophilic addition to imines. This approach is particularly attractive due to the ready availability of aldehydes and ketones which can be easily transformed into imines. However, the relatively low electrophilicity of imines is such that an electron withdrawing *N*-substituent is usually required to enhance their reactivity.[1] In this role the *N*-sulfinyl substituent has come to the fore as an excellent imine activating group, whilst also serving as a chiral auxiliary.[2] Both the *p*-tolyl[3] and *tert*-butyl[4] chiral sulfinyl moieties have been demonstrated to be successful directing/activating groups for a large variety of transformations.[2] More recently, the *S*-mesitylsulfinyl protecting/directing group was introduced by Davies,[5] which promises the advantages of the *p*-tolylsulfinimines (UV active, removal with either acidic conditions or by Grignard addition), with the superior stereo-directing effect of the more bulky *tert*-butylsulfinyl group pioneered by Ellman.

Whilst the utility of *tert*-butylsulfinimines and *p*-tolyl sulfinimines is well documented, no reports on the relative reactivity and stereodirecting ability of *S*-mesitylsulfinimines has been reported. Indeed, the only reactions of *S*-mesitylsulfinimines to date has been their use in the synthesis of phosphonyl-aziridines using an aza-Darzens-type approach,[5] where they gave excellent levels of diastereocontrol and high yields. One potential reason for this low uptake is the lack of a simple access to these sulfinimines. Recently we published a convenient one-pot multicomponent protocol for the high yielding and highly enantioselective synthesis of a range of sulfinimines,[6] including *S*-mesitylsulfinimines,[7] using cheap commercially available reagents (Scheme 1). With this new and cost-effective access to these substrates, we herein present our investigations into the utility of these useful chiral building blocks for the synthesis of chiral amines and aziridines, and compare their reactivity with *tert*-butylsulfinimines. Our first investigations looked into the addition of Grignard reagents to *S*-mesitylsulfinimines (Table 1).

The optimum solvent for reaction of *S*-*tert*-butylsulfinimines with Grignard reagents was shown to be dichloromethane (DCM) by Ellman,[4] who investigated a range of examples which gave very good diastereomeric ratios (88 : 12 to 99 : 1) and yields in the range of 29–100% using *S*-*tert*-butylbenzylidenesulfinimine as the substrate. In the work of Guijarro and Yus[8] they estimated a 21% yield with 60 : 40 d.r. in the reaction of *iso*-propylmagnesium bromide with *S*-*tert*-butylbenzylidenesulfinimine in DCM—showing that hindered nucleophiles can be problematic with this directing group. They found that the use of dimethylzinc co-promotor in THF was able to enhance the yields and diastereoselectivities in the addition of *iso*-propylmagnesium bromide with *S*-*tert*-butylbenzylidene-sulfinimine, giving the product in 81% yield and 94 : 6 d.r. As a comparison to these results, we found that reactions of *S*-mesitylbenzylidenesulfinimine **2a** with n-propylmagnesium chloride and *iso*-propylmagnesium chloride in DCM (Table 1, entries 1 and 2) gave only moderate yields and poor selectivity, thus other solvents were invesigated. Using THF as a solvent improved matters considerably (in contrast to Ellman's studies),[9] for example n-propyl magnesium chloride reacted with **2a** to give **3a** in 90% yield and 86 : 14 d.r. (entry 3). However, we found that use of 2-methyl THF (MeTHF) was optimal, giving 82% yield and 92 : 8 d.r. (entry 5) with these substrates. The reaction of *iso*-propyl magnesium chloride with **2a** in MeTHF gave **3b**



Scheme 1 Synthesis of *S*-mesitylsulfinimines.

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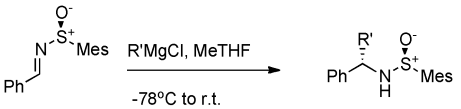
Table 1 Nucleophilic addition to *S*-mesitylsulfinimines



2a **3a-i**

Entry	Solvent	Nucleophile	3	Yield (%)	dr
1	DCM	^{n}PrMgCl	**3a**	54	53 : 47
2	DCM	^{i}PrMgCl	**3b**	52	69 : 31
3	THF	^{n}PrMgCl	**3a**	90	86 : 14
4	THF	Me_3Al, ^{i}PrLi	**3b**	80	87 : 13
5	MeTHF	^{n}PrMgCl	**3a**	82	92 : 8
6	MeTHF	^{i}PrMgCl	**3b**	69	98 : 2
7	MeTHF	EtMgCl	**3c**	92	91 : 9
8	MeTHF	^{i}BuMgCl	**3d**	78	95 : 5
9	MeTHF	^{n}HexylMgCl	**3e**	74	74 : 26
10	MeTHF	CyMgCl	**3f**	88	99 : 1
11	MeTHF	BnMgCl	**3g**	93	70 : 30
12	MeTHF	AllylMgBr	**3h**	89	83 : 17
13	THF	*p*TolMgBr/CuI	**3i**	64	83 : 17

in 69% yield and 98 : 2 d.r., which contrasts significantly with Ellman's result with *S*-*tert*-butylbenzylidenesulfinimine, which gave just 29% yield with this substrate, and avoids the requirement for addition of the pyrophoric additive dimethyl zinc. Also interesting to note is that our reactions in MeTHF gave the opposite diastereomer to that noted by Ellman, suggesting an open-transition state is in operation, rather than the chelating transition state Ellman invokes with *S*-*tert*-butylsulfinimines when reacting with Grignard reagents in DCM.[9] Our diastereomeric ratios were determined from the ^{1}H NMR of the crude reaction mixture and by chiral HPLC. The absolute configuration of the major diastereoisomer was deduced by the removal of the *N*-sulfinyl group and comparison of the sign of the specific rotation of the free primary amines with the reported data, where these are known. The reaction of **2a** with *iso*-propyllithium and trimethylaluminium in THF gave **3b** in 80% yield and 87 : 13 d.r., thus the Grignard reagent was the preferred nucleophile for higher diastereoselectivity and for simplicity of the reaction. It is also worthwhile to note that we did not observe attack at sulfur in these reactions, which can be a problem with the *p*-tolylsulfinimines.[10]

Spurred on by these results, we investigated a wide range of Grignard additions to *S*-mesitylsulfinimines (Tables 1 and 2), and found that, with a few exceptions, additions were high yielding and stereoselective. The yield was found to be effected by the size of the nucleophile, as the additions of *iso*-propyl Grignard were often lower yielding, and in some cases gave poor stereoselectivity (*e.g.* Table 2, entries 7, 8). It is important to note, however, that in many cases these larger nucleophiles fail to react with *tert*-butylsulfinimines.[9]

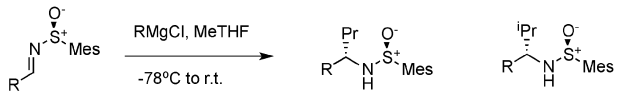
It was found that the *S*-mesitylsulfinyl group could be removed under a variety of conditions (Scheme 2). Furthermore, oxidation to the sulfonamide was also found to be facile.

A particular class of amines that has great potential for further elaboration are chiral aziridines.[11] Our previous investigations on the synthesis of aziridines have focused on the suitability of *tert*-butylsulfinimines as substrates for aziridination *via* reaction with both dimethylsulfonium methylide[12] and allylic sulfur ylides.[13] In both cases aziridines were formed in good yields and diastereoselecivities. We therefore decided to compare these results with the *S*-mesitylsulfinimine substrates (Table 3).

Gratifyingly the *S*-mesitylsulfinimines were found to be excellent substrates for the synthesis of aziridines, either through the ylide-based methodology or the Darzens-based methodology developed by Davis for *p*-tolylsulfinimines.[14] Good to excellent yields and diastereoselectivities were observed, with only the pentylaldimine (Table 3, Entry 1) giving a mediocre diastereoselectivity (*cf.* 65% yield, 90 : 10 dr for the corresponding *tert*-butylsulfinimine aziridination).[12] *Tert*-butylsulfinyl groups can be difficult to remove from aziridines without ring-opening, requiring very careful monitoring whilst treating the aziridine with freshly prepared HCl in ether. One of the advantages of the *p*-tolylsulfinyl group is that it can be removed from aziridines by mildly acidic conditions. We were pleased to find that **6g** was deprotected cleanly by treatment with TFA in acetone/water (1 : 1), giving the deprotected aziridine in 87% yield.

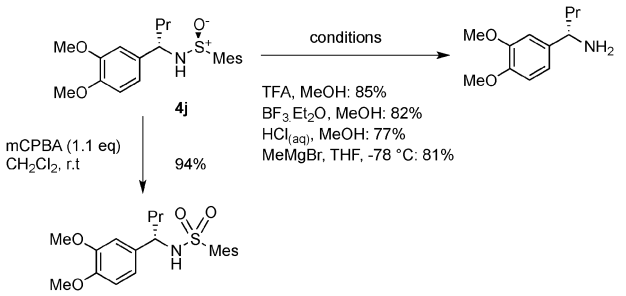
In conclusion, we have found that *S*-mesitylsulfinimines offer a useful alternative to the more commonly used *p*-tolyl

Table 2 Synthesis of *S*-mesitylsulfinamides



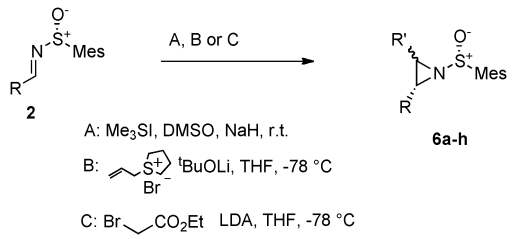
2 **4a-k** **5a-k**

Entry	*R*		Yield **4** (dr) *n*-PrMgCl	Yield **5** (dr) *i*-PrMgCl
1	Ph	**a**	82% (92 : 8)	69% (98 : 2)
2	4-MeOPh	**b**	80% (85 : 15)	79% (99 : 1)
3	Mesityl	**c**	94% (94 : 6)	82% (99 : 1)
4	4-ClPh	**d**	92% (88 : 12)	90% (96 : 4)
5	Ph(CC)-	**e**	81% (88 : 12)	61% (83 : 17)
6	Furyl	**f**	92% (87 : 13)	93% (97 : 3)
7	Pentyl	**g**	54% (57 : 43)	39% (49 : 51)
8	Ph(CHCH)-	**h**	72% (91 : 9)	34% (50 : 50)
9	Cy	**i**	73% (58 : 42)	57% (75 : 25)
10	3,4-DiMeOPh	**j**	89% (79 : 21)	92% (99 : 1)
11	Me(CHCH)-	**k**	67% (77 : 23)	60% (92 : 8)



Scheme 2 Deprotection and oxidation of the *S*-mesitylsulfinyl group.

Table 3 Synthesis of aziridines



Entry	R, R'	Method	6	Yield (%)	d.r. (*cis*/*trans*)
1	Pentyl, H	A	**6a**	93	75 : 25
2	Cy, H	A	**6b**	66	80 : 20
3	Ph, H	A	**6c**	95	89 : 11
4	2-Napth, H	A	**6d**	50	91 : 9
5	Cy, vinyl	B	**6e**	73	95 : 5 (1 : 4)
6	Cy, CO_2Et	C	**6f**	74	96 : 4 (2 : 1)
7	Ph, CO_2Et	C	**6g**	87	99 : 1 (49 : 1)
8	2-furyl, CO_2Et	C	**6h**	52	93 : 7 (12 : 1)

and *tert*-butylsulfinimines. They favour reaction *via* an open transition state, which allows larger nucleophiles to be used when compared with the *tert*-butylsulfinimines, and are therefore complementary in their reactivity to the Ellman sulfinimines. Futhermore, they are UV active, which simplifies the monitoring of reactions by TLC or HLPC, and are readily available in high enantiomeric excess.

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