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Multicomponent Synthesis of Chiral Sulfinimines

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Abstract: Two oxathiozolidine-*S*-oxide templates have been developed and used in a four-component coupling protocol for the synthesis of a wide range of chiral sulfinimines in high enantiomeric excesses. The templates can be synthesized from cheap commodity chemicals in three steps in high yields. Furthermore the template is easily recovered in high yields for recycling.

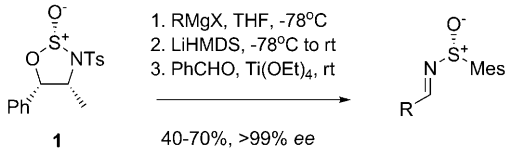
Keywords: butanesulfinimine · imines · mesitylsulfinimine · multicomponent reactions · sulfinimines

Introduction

Chiral amines are high value commodities that can be found in a large number of natural products and active pharmaceutical ingredients (e.g. Tamiflu, Plavix, Januvia). Over the past two decades chiral sulfinimines have come to the fore as versatile chiral building blocks for the synthesis of chiral amines by addition of a suitable nucleophile or by reduction with a hydride reagent.[1] First developed by Davis and co-workers[2] and subsequently by Ellman and co-workers,[3] both *p*-tolylsulfinimines (Davis)[1d] and *tert*-butylsulfinimines (Ellman)[1a] have changed the way in which chemists synthesize chiral amines. Sulfinimines are significantly more stable to hydrolysis when compared with *N*-sulfonyl and *N*-carbamoyl imines,[1a] and the stereogenic sulfur group is able to confer a high degree of stereocontrol in many cases upon reaction with a wide range of nucleophiles. Furthermore the *N*-sulfinyl group is usually cleaved easily from the formed chiral amine by simple acid treatment.[1]

Whilst the chemistry of sulfinimines has been well explored over the past three decades, the synthesis of chiral sulfinimines has seen fewer developments. The original synthesis developed by Davis and co-workers used an oxidation of sulfenimines, which gave racemic sulfinimines.[2] Subsequently both Cinquini et al.[4] and Davis et al.[5] reported on the use of the Anderson reagent for the synthesis of chiral sulfinimines by reaction with either metalloimines (Cinquini) or LiHMDS and aldehydes in a three-component reaction (Davis). These methods suffered due to the difficulty in recycling the sugar-based chiral auxiliary. The most common method, however, is the condensation of chiral sulfinamides with aldehydes, as pioneered by Ellman and co-workers for the synthesis of *tert*-butylsulfinimines.[3] This method is quite general, and various desiccants such as copper sulfate or titanium tetraethoxide can be used. The synthesis of the chiral sulfinamides can be achieved either by a catalytic asymmetric oxidation of di-*tert*-butyldisulfide followed by ammonolysis in liquid ammonia and sodium amide,[3] or by Senanayake and co-workers' adaptation of Wudl's sulfoxide synthesis, which uses a chiral amino-alcohol template for the addition of lithium amide and Grignard reagents to generate chiral sulfinamides.[6]

Recently we disclosed a convenient synthesis of chiral non-racemic *S*-mesitylsulfinimines using a four-component coupling[7] based on Senanayake's norephedrine-derived template **1** (Scheme 1). This method generated chiral sulfinimines in a single reaction procedure in excellent enantioselectivities and greater yields than the multistep route. The disadvantage to this method was that template **1** is derived from norephedrine, which is relatively expensive and on the controlled precursor list.



Scheme 1. Four-component synthesis of chiral *S*-mesitylsulfinimines.

Results and Discussion

Herein we describe a versatile multicomponent reaction (MCR) methodology for the synthesis of chiral sulfinimines using a template derived from L-phenylalanine, an inexpensive, chiral, readily available starting material. Template **3** (Scheme 2) is prepared in three steps from L-phenylalanine or in two steps from L-phenylalaninol. Since our initial preparation of **3** its formation as a diastereomeric mixture has

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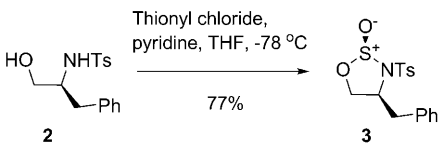
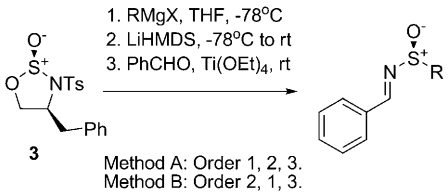


Scheme 2. Formation of chiral template **3**.

been published by Gallagher and Rujirawanich[8] using thionyl chloride and pyridine. The issue of the formation of the diastereomeric mixture was overcome by the avoidance of an aqueous workup, which we found gave rise to the partial epimerization of oxathiazolidine-*S*-oxide **3**. Thus, rather than using an aqueous quench, we found that concentration of the reaction mixture, and purification using an ISOLUTE CN cartridge[9] cleanly gave one diastereoisomer in 77% yield (Scheme 2), for which the stereochemistry was confirmed by X-ray crystallography (see the Supporting Information).

We decided to test the efficacy of the new template **3** by the synthesis of a range of *S*-functionalized benzylidenesulfinimines. The results of the synthesis of four sulfinimines (*tert*-butyl, *p*-tolyl, *iso*-propyl, mesityl) that are most commonly seen in the literature using the template **3** in the MCR (Method A) are shown in Table 1.

Table 1. Multicomponent synthesis of benzaldimines.



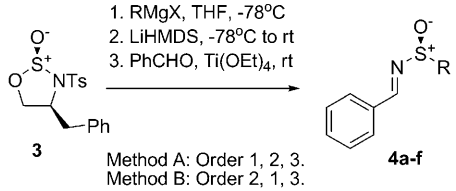
Entry	Grignard	Method A		Method B	
		yield [%]	*ee* [%]	yield [%]	*ee* [%]
1	*t*BuMgCl	20	95.2	63	0.9
2	*p*-TolMgBr	27	94.3	52	8.6
3	*i*PrMgCl	59	89.1	63	2.6
4	MesMgBr	80	97.6	56	1.3

Our initial method (Method A) involved the addition of the Grignard reagent followed by LiHMDS and finally benzaldehyde and titanium tetraethoxide. We found that *tert*-butyl magnesium chloride successfully added into the oxathiazolidine oxide but the subsequent addition of LiHMDS was extremely slow, and only a low yield of *tert*-butylsulfinimine (20%) was isolated even when a large excess (six equivalents) of LiHMDS was used. The *p*-tolylmagnesium bromide reacted to give the *p*-tolylsulfinimine in 27% yield, in this case the lower yield observed being due to double addition of the Grignard reagent to **3** giving an unwanted sulfoxide by-product. The isopropyl and mesityl Grignards gave good yields of 59% and 80%, respectively. All of these examples had high enantiomeric excess, with the mesityl sulfinimine having the highest at 97.6%. It was found in all cases to be important to add just one equivalent of the Grignard reagent—any more and double addition to give the sulfoxide would predominate. The use of two equivalents of LiHMDS and raising the temperature of the reaction to room temperature were found to be necessary to drive the second step to completion. Two equivalents of aldehyde with titanium(IV) ethoxide were found to be the optimum conditions for the third (condensation) step. Amino alcohol **2** was easily recovered from the reaction mixture by chromatography, and was found to be unchanged in optical rotation, thus allowing easy recycling (e.g. it was recovered in 94% yield in entry 4, Table 1, Method A).

In their synthesis of *S*-*tert*-butylsulfinamide, Han, Senanayake and their co-workers[6a] noted that changing the order of the first two steps using template **1** (LiHMDS and *tert*-butylmagnesium bromide) was found to give a high yield and stereoselectivity. Thus we investigated the use of template **3** with this reversal of addition (Method B). We found that only one equivalent of LiHMDS and one equivalent of Grignard reagent were necessary to obtain good yields for all four examples of sulfinimine (Table 1). This was a great improvement in yield for the *p*-tolyl and *tert*-butyl sulfinimines, but on further analysis the products were all found to be near-racemic. We also found that with the reverse addition a by-product formed that was inseparable by flash chromatography, which we identified as alcohol **2** with trimethylsilyl protection of the alcohol. This could be conveniently removed by the addition of TBAF prior to workup so as to change the R_F of the impurity and enable separation.

To explore scope of the reaction further, a range of Grignard reagents were then applied to the MCR keeping benzaldehyde as the fourth component using Method A (Table 2). The cyclopentyl and cyclohexyl examples

Table 2. Synthesis of sulfinimines.



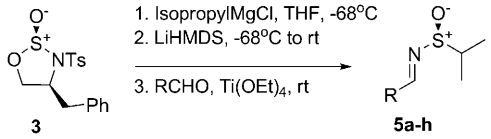
Entry	R	**4**	Yield [%]	*ee* [%]
1	2-thienyl	**4a**	43	66.3
2	cyclopentyl	**4b**	53	93.2
3	cyclohexyl	**4c**	67	93.0
4	4-chloro-3-fluorophenyl	**4d**	29[a]	96.6
5	(3,5-bis(trifluoromethyl)phenyl)	**4e**	29	81.8
6	2-biphenyl	**4f**	59	96.8

[a] The sulfinimine product had gained a trimethylsilyl group at the *ortho*-position next to the fluoro group.

(Table 2, entry 2 and 3) unsuprisingly gave similar results to the isopropyl Grignard. The main product isolated from the 4-chloro-3-fluorophenyl example (Table 2, entry 4) had gained a trimethylsilyl group on the aromatic ring in the 2-position (presumably by *ortho*-lithiation and subsequent reaction with HMDS). Although isolated in low yield, this product had a high enantiomeric excess (96.6%), and potentially leads the way to further diversification by use of other traps, although this will not be discussed here. The 2-biphenyl sulfinimine (Table 2, entry 6) was prepared in a good yield (59%) and high enantiomeric excess (96.8%). Thus template **3** gives greater stereocontrol when the Grignard used is more sterically hindered at the nucleophilic carbon.

We next investigated the synthesis of *S*-isopropylsulfinimines[10] (Table 3). It was found that the aromatic sulfinimines were formed in moderate to good yields and enantiomeric excesses in the region of 90%. However, alkylsulfinimines were isolated in significantly lower yields due to hydrolysis in the workup/purification conditions.

Table 3. Synthesis of *S*-isopropylsulfinimines.

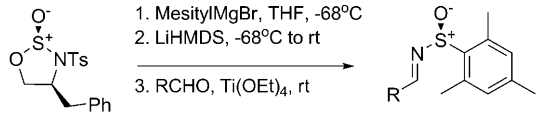


3 5a-h

Entry	Aldehyde	5	Yield [%]	*ee* [%]
1	benzaldehyde	**5a**	59	89.1
2	4-methoxybenzaldehyde	**5b**	48	92.5
3	4-nitrobenzaldehyde	**5c**	32	89.4
4	furfural	**5d**	61	89.5
5	*trans*-cinnamaldehyde	**5e**	50	92.0
6	cyclopropanecarboxaldehyde	**5f**	17	89.9
7	cyclohexanecarboxaldehyde	**5g**	12	90.4
8	hexanal	**5h**	19	91.5

With moderate success with the *S*-isopropylsulfinimines, we next turned our attention to *S*-mesitylsulfinimines (Table 4), which were introduced by Davis and co-workers in 2003[11] who found they have better stereodirecting ability than the *p*-tolylsulfinimines but, like their tolyl cousins, *S*-mesitylsilfinamide products can be deprotected with methyl magnesium chloride as well as strong acid, making their deprotection more flexible than *tert*-butylsulfinamides. In general it was found that the MCR produced *S*-mesitylsulfinimines in good to excellent yields and excellent enantiomeric excesses. The lowest yields at 33% and 46% (Table 4, entry 3 and 13) were observed with electron-withdrawing aromatic aldehydes, where the susceptibility to coordinate the titanium tetraethoxide is greatest, slowing the condensation stage and accelerating hydrolysis in the workup. Alkyl aldehydes performed well in the one-pot reaction, as long as four equivalents of aldehyde were used. In the case of the hexanal MCR (Table 4, entry 8), it was found that the aldehyde condensation step had to be shortened due to reaction of **6h** with excess hexanal.

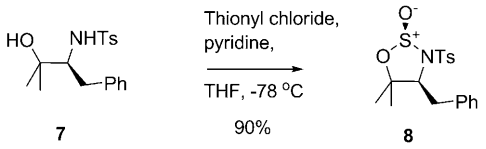
Table 4. Synthesis of *S*-mesitylsulfinimines.



3 6a-q

Entry	Aldehyde	6	Yield [%]	*ee* [%]
1	benzaldehyde	**6a**	80	97.6
2	4-methoxybenzaldehyde	**6b**	62	99.2
3	4-nitrobenzaldehyde	**6c**	46	98.3
4	furfural	**6d**	62	98.6
5	*trans*-cinnamaldehyde	**6e**	60	99.1
6	cyclopropanecarboxaldehyde	**6f**	72	88.6
7	cyclohexanecarboxaldehyde	**6g**	71	99.2
8	hexanal	**6h**	52	99.2
9	1,1-dimethylethyl 3-formyl-1*H*-indole-1-carboxylate	**6i**	50	95.0
10	1,3-oxazole-4-carboxaldehyde	**6j**	72	99.0
11	1,3-thiazole-5-carbaldehyde	**6k**	81	98.3
12	pivaldehyde	**6l**	61	99.0
13	2-pyridinecarboxaldehyde	**6m**	33	100
14	1-benzofuran-2-carbaldehyde	**6n**	84	93.8
15	6-((*tert*-butyldimethyl-silyl)oxy)hexanal	**6o**	60	98.9
16	5-bromo-2-thiophenecarbox-aldehyde	**6p**	85	96.4
17	3-chloro-4-fluorobenzaldehyde	**6q**	73	97.1

To improve the yields for the *p*-tolyl sulfinimine synthesis a more sterically hindered oxathiazolidine oxide **8** was investigated, which could also be prepared from L-phenylalanine in four steps. The formation of the oxathiazolidine oxide **8** was straightforward from **7**[12] giving only one diastereoisomer in 90% yield (Scheme 3), the structure of which was confirmed by X-ray crystallography (see the Supporting Information).

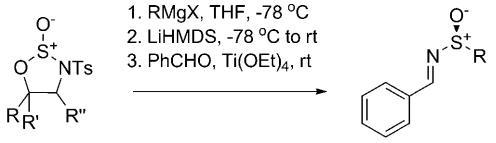


7 8

Scheme 3. Synthesis of template **8**.

Comparison of the performance of all three templates (**1**, **3**, and **8**) for the formation of *S*-functionalized benzylidenesulfinimines is set out in Table 5. The templates **1** and **3** gave comparable results for the synthesis of all sulfinimines, with low yields being observed for *S*-*p*-tolyl and *S*-*tert*-butyl benzylidenesulfinimines, the former case being due to unwanted double addition of the Grignard forming a sulfoxide. The more sterically hindered template **8** was able to overcome this issue, enabling the *S*-*p*-tolyl and *S*-isopropyl benzylidenesulfinimines to be generated in good yields and ex-

Table 5. Synthesis of *S*-isopropylsulfinimines.

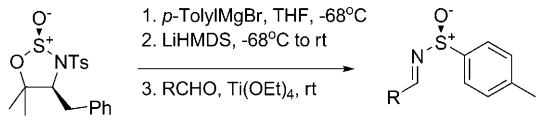


		Oxathiazolidine oxide					
		1		**3**		**8**	
Entry	RMgX	yield [%]	*ee* [%]	yield [%]	*ee* [%]	yield [%]	*ee* [%]
1	*t*BuMgCl	0	–	20	95.2	0	–
2	*p*-TolMgBr	27	98.6	27	94.3	49	99.8
3	*i*PrMgCl	49	98.7	59	89.1	71	98.9
4	MesMgBr	65	99.2	80	97.6	8	–

cellent enantiomeric excess. The *S-tert*-butyl and *S*-mesityl benzylidenesulfinimines were not formed well due to the steric bulk of the Grignard reagents used.

With an enhanced method for the formation of *S-p*-tolylsulfinimines, we investigated the scope of the MCR (Table 6). It was found that a range of *S-p*-tolylsulfinimines were produced in moderate to good yields and high stereoselectivity.

Table 6. Synthesis of *S-p*-tolylsulfinimines.

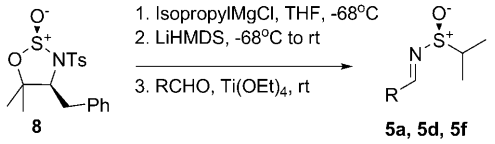


8 **9a-g**

Entry	Aldehyde	**9**	Yield [%]	*ee* [%]
1	benzaldehyde	**9a**	49	99.8
2	4-methoxybenzaldehyde	**9b**	82	99.1
3	4-nitrobenzaldehyde	**9c**	33	99.0
4	furfural	**9d**	31	98.8
5	*trans*-cinnamaldehyde	**9e**	59	99.7
6	cyclopropanecarboxaldehyde	**9f**	62	97.8
7	cyclohexanecarboxaldehyde	**9g**	19	98.8

The improvements observed in the reaction of the isopropylmagnesium chloride with template **8** in the MCR (Table 5, entry 3) was confirmed with two further examples (Table 7). The yield and enantiomeric excess were much improved compared with template **3** for the cyclopropanecarboxaldimine product **5f** (possibly due to easier separation from the template), although the yield with the furfural-derived product **5d** was comparable with an increase seen in enantiomeric excess.

Table 7. Synthesis of *S*-isopropylsulfinimines.



8 **5a, 5d, 5f**

Entry	Aldehyde	**5**	Yield [%]	*ee* [%]
1	benzaldehyde	**5a**	71	98.9
2	furfural	**5d**	61	100
3	cyclopropanecarboxaldehyde	**5f**	53	98.7

Conclusion

In conclusion, we have developed a versatile multicomponent reaction capable of generating a wide range of chiral sulfinimines from simple commercially available reagents in good yields and high enantioselectivities. We are further developing the template-directed multicomponent reaction for the versatile one-pot synthesis of chiral sulfinamides and will report our findings in due course.

Experimental Section

The entire experimental section can be found in the Supporting Information, including compound characterization data and copies of NMR spectra.

Acknowledgements

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