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Properly Designed Modular Asymmetric Synthesis for Enantiopure Sulfinamide Auxiliaries from *N*-Sulfonyl-1,2,3-oxathiazolidine-2-oxide Agents

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Over the past few years our group has been engaged in the development of many single enantiomeric drugs. Several of these drugs contained chiral amine functionality,[1] and development of economically viable general solutions were examined. After evaluation of many asymmetric methods for the synthesis of chiral amines, we found enantiopure sulfinamide auxiliary utilization to be an ideal solution; however, a *general, practical, and economical method* for the preparation of these valuable enantiopure sulfinamides is still lacking. Literature research revealed that Davis *p*-toluenesulfinamide[2] demonstrated that the sulfinyl group served as the first widely used auxiliary for imine activation on the addition of a variety of nucleophiles for many asymmetric processes.[3] In 1997, Ellman and co-workers demonstrated that 2-methyl-2-propanesulfinamide (TBSA) was superior to *p*-toluenesulfinamide (TOSA) for some asymmetric processes.[4] They have developed an elegant method for the preparation of enantiopure (*R*)-TBSA ((*R*)-**10a**) using *tert*-butyl disulfide.[5] Recently, we disclosed a rapid assembly of (*S*)-cetirizine using (*S*)-diarylamine **2**. The (*S*)-**2** was constructed utilizing a phenyl Grignard addition to *N*-*tert*-butanesulfinyl-*p*-chlorobenzaldimine ((*R*)-**1**) in a 75% ee (Scheme 1).[6] This synthesis required structurally diverse aryl and alkyl sulfinamides for tuning the diastereoselectivity of the organometallic addition process, and in parallel, for preparing multikilogram quantities of (*R*)-TBSA to produce large quantities of (*S*)-**2**.

We began to investigate the scalability of Ellman's protocol and found that the (*R*)-TBSA procedure is scale-dependent, amenable to gram quantities, but not to kilogram quantities.[7] Therefore, we turned our attention to other methods. Herein, we disclose the first general and practical modular synthesis of enantiopure tertiary alkyl and aryl sulfinamide auxiliaries from *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide building blocks for fine-tuning the enantioselectivity of many asymmetric synthetic applications.

Three decades ago, Wudl and Lee demonstrated that carbon nucleophiles selectively cleave the more reactive S−O bond of (−)-ephedrine-derived 1,2,3-oxathiazolidine-2-oxide in the presence of the *N*-methyl S−N bond to produce *N*-methyl sulfonamide derivatives.[8] These acyclic sulfonamide derivatives were then treated with a second carbon nucleophile to give optically active sulfoxides with low enantioselectivites and yields. The major reason this method was not widely practiced was that cleavage of the S−N bond of acyclic sulfonamide with nucleophiles was extremely difficult, unlike the S−O bond of sulfinates.[9] We envisage that *activation of nitrogen of* 1,2,3-oxathiazolidine-2-oxide derivatives may reverse the bond-cleaving order (S−N vs S−O) to selectively cleave the S−N bond in the presence of appropriate nucleophiles, which may lead to a synthetic equivalent for modular synthesis of enantiopure alkyl and aryl sulfinamides (**6**).

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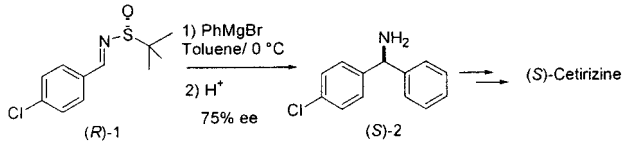
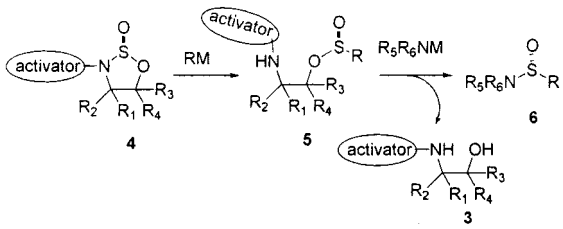
Scheme 1



Scheme 2



Our strategy is to devise conformationally constrained 1,2,3-oxathiazolidine-2-oxide **4**, bearing an activated group on nitrogen from thionyl chloride, and *N*-activated amino alcohol **3**. The N−S bond of **4** could be cleaved chemoselectively with an organometallic reagent (preferably Grignard) with inversion of configuration at the sulfur atom, followed by mild displacement of the O−S bond with a nitrogen nucleophile with inversion of configuration, which should lead to **6** (Scheme 2). To test this hypothesis, we envisaged an activation group of nitrogen as the *p*-toluenesulfonyl group, and a conformationally constrained backbone as the indane platform.

Initial efforts of the synthesis of labile indane derived *p*-toluenesulfonyl 1,2,3-oxathiazolidine-2-oxide **8a** met with difficulties. It was found that 75:25 diastereomeric ratio of *endo*/*exo*-**8a** can be obtained by simply treating (1*R*,2*S*)-1-*N*-tosyl-aminoindanol (**7a**) in THF at −45 °C with 1.5 equiv of thionyl chloride, followed by a *slow addition* of 2.5 equiv of TEA at −45 °C. Quenching with water or acidic conditions showed immediate decomposition. However, quenching with an aqueous bicarbonate at −45 °C provided a clean diastereomeric mixture of **8a** with an excellent yield (>98%).

We first explored the effect of the solvent and base on the diastereoselectivity. As depicted in Table 1, the solvent and base combination had a pronounced effect on the *endo*/*exo* ratio of **8a**. With aprotic solvents in the presence of TEA, the major isomer was *endo*-**8a**. Surprisingly, CH_2Cl_2 gave *exo*-selectivity (Table 1, entry 2). In THF/TEA, imidazole, and pyridine provided comparable selectivity. Selectivity can be further increased by the methyl substitution pattern of the pyridine ring. Thus, 2,6-lutidine and 3,5-lutidine provided increased selectivites (entries 6 and 7), while 4-picoline ascertained a similar selectivity to pyridine (entry 8). 2,4,6-collidine afforded the best *endo*-selectivity (*endo*/*exo*, 91:9). In this study, it is clear that changing the base/solvent combination can moderate the ratio of *endo*/*exo* selectivity.

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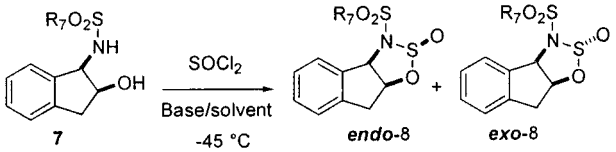
Table 1. Diastereoselective Formation of *endo*-**8**



7 *endo*-8 *exo*-8

entry	7	R_7	base(solvent)	*endo*-**8**:*exo*-**8**[a]
1	**7a**	4-tolyl	TEA(THF)	75:25
2	**7a**	4-tolyl	TEA(CH_2Cl_2)	19:81
3	**7a**	4-tolyl	TEA(EtOAc)	73:27
4	**7a**	4-tolyl	imidazole(THF)	70:30
5	**7a**	4-tolyl	py(THF)	80:20
6	**7a**	4-tolyl	2,6-lutidine(THF)	85:15
7	**7a**	4-tolyl	3,5-lutidine (THF)	87:13
8	**7a**	4-tolyl	4-picoline (THF)	78:22
9	**7a**	4-tolyl	2,4,6-collidine(THF)	91:9
10	**7b**	2,4,6-mesityl	2,4,6-collidine(THF)	93:7
11	**7b**	2,4,6-mesityl	3,5-lutidine (THF)	97:3
12	**7c**	2,4,6-isopropyl-Ph	2,4,6-collidine(THF)	95:5

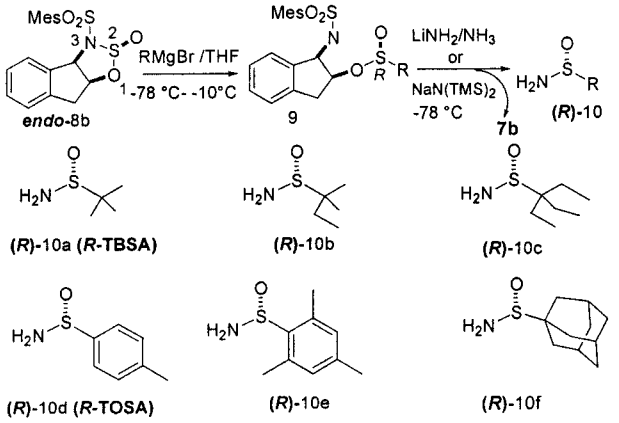
[a] *endo*/*exo* ratio is determined by ^{1}H NMR analysis.

Our attention was next focused on the optimization of the steric effect of the arylsulfonyl group on the diastereoselectivity. As illustrated in Table 1, in the THF collidine mixture, a substitution of the 2- and 6-positions of the phenyl ring of R_7 with methyl groups increased the *endo*/*exo* selectivity to 93:7. Furthermore, increasing the bulk at the 2,4,6-position of the phenyl ring with triisopropyl groups gave the highest *endo*/*exo* selectivity (95:5). Due to the higher selectivity, and the readily available and inexpensive nature of 2,4,6-mesitylenesulfonyl chloride and (1*R*,2*S*)-aminoindanol, further optimization work centered on the preparation of *endo*-**8b**. Surprisingly, when 3,5-lutidine was used as the base in THF, the *endo*/*exo* selectivity jumped to 97:3. *It is extremely gratifying to mention that the preparation of kilogram quantities of this synthetically important enantiopure, endo-**8b**, is not difficult and that the procedure is amenable to scale-up.*[10]

Having generated large quantities of (2*S*,4*R*,5*S*)-**8b** (*endo*-**8b**), our immediate attention was then focused on the production of (*R*)-TBSA, utilizing a chemoselective ring-opening (CRO) with inversion of configuration at the sulfur atom, using *tert*-butyl organometallic reagent followed by a lithium amide addition. We first evaluated the addition of *tert*-butyl Grignard to *endo*-**8b** in THF at low temperature (−78 to −10 °C). It is important to note that *tert*-butyl Grignard only cleaves the S−N bond in the presence of the S−O bond of **8b** to produce stable, and crystalline (1*R*,2*S*,*R*)-**9a** sulfinate ester in >95% yield with diastereopure form.[11] The exposure of **9a** to lithium amide in liquid ammonia at −78 °C in THF led to S−O bond breakage with inversion of configuration at the S atom, giving quantitative conversions of enantiopure (*R*)-**10a** and **7b**. This overall process is highly reproducible for the production of (*R*)-**10a** (>90%) with regeneration of auxiliary **7b**, with an excellent recovery (>96%). It is worth noting that (*S*)-TBSA can also be generated with the same procedure utilizing antipode (2*R*,4*S*,5*R*)-**8b**.

Viability of this stereospecific double inversion nucleophilic displacement process was extended to the production of other structurally diverse tertiary alkyl and aryl sulfinamides. As illustrated in Scheme 3, (*R*)-2-methylbutyl-((*R*)-**10b**), (*R*)-3-ethylpentyl-((*R*)-**10c**), (*R*)-2,4,6-mesityl-((*R*)-**10e**), and (*R*)-1-adamantyl ((*R*)-**10f**) sulfinamides were produced in >99% ee with excellent yields, without any complications.[10b] In the case of diastereopure **9d**, when exposed to $LiNH_2/NH_3$ at −78 °C, it provided only 90% ee of (*R*)-**10d**. However, upon treatment of **9d** with $NaN(TMS)_2$ in THF at −78 °C, it provided 99% ee with an 85% yield of (*R*)-**10d**.[12,10b] To the best of our knowledge, this is the first modular synthesis for production of this valuable family of enantiopure sulfinamides.

Scheme 3



In conclusion, we have developed a general and practical technology to prepare enantiopure *endo*-1,2,3-oxathiazolidine-2-oxide **8** using chiral *N*-sulfonyl amino alcohol derivatives and thionyl chloride. The importance of this new chiral reagent was exemplified by the expedient production of unique sulfinamide ligands in excellent yields and enantiopurities. The behavior of structurally diverse sulfinimines derived from these sulfinamides on the organometallic delivery processes are under active investigation. Further applications of *activated 1,2,3-oxathiazolidine 2-oxide reagents as the central chiral building block* for many asymmetric processes are under evaluation.[13]

Supporting Information Available: Experimental details and X-ray structures for *endo*-**8b**, *exo*-**8b**, and (1*R*,2*S*,*R*)-**9a** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) The absolute stereochemistry of *endo*-**8b** was unambiguously established by single-crystal X-ray analysis to be *S*-configuration at the sulfur atom. (b) For the detailed experimental procedure, see Supporting Information.

(11) The reaction proceeds with clean S_N2 at the S atom to produce a single diastereomer (1*R*,2*S*,*R*)-**9a**, which was established by single-crystal X-ray analysis.

(12) This $NaN(TMS)_2$ addition method can be applied to the synthesis of (*R*)-**10e**.[10b]

(13) Preparation of functionally diverse sulfoxides using *endo*-**8** will be reported soon.

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