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Control of Diastereoselectivity by Solvent Effects in the Addition of Grignard Reagents to Enantiopure *t*-Butylsulfinimine: Syntheses of the Stereoisomers of the Hydroxyl Derivatives of Sibutramine

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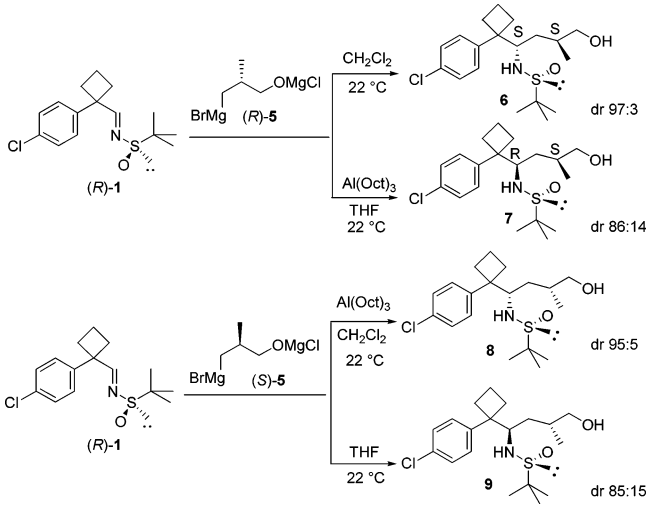
ABSTRACT



An efficient method has been developed to prepare all four isomers of the hydroxyl derivatives of sibutramine by addition of Grignard reagents (*R*)- or (*S*)-5 to a single enantiomer of sulfinyl imine (*R*)-1 simply by tuning the reaction solvent. The phenomenon of the reversed diastereoselectivity in CH_2Cl_2 and THF implied that the reaction may proceed through a chelated cyclic transition state in CH_2Cl_2 and nonchelated acyclic transition state in THF.

Organic compounds with chiral amine functionality represent an important class of active pharmaceutical ingredients, catalysts, and materials. Despite this fact, practical synthesis of enantiomerically pure chiral amines still remains a challenging task.[1] Enantiomerically pure aldimines or ketimines generated from an aldehyde or ketone with an alkyl or aryl sulfinamide are versatile building blocks in the construction of chiral amines, and their application has attracted a large amount of interest.[2] However, methods for the preparation

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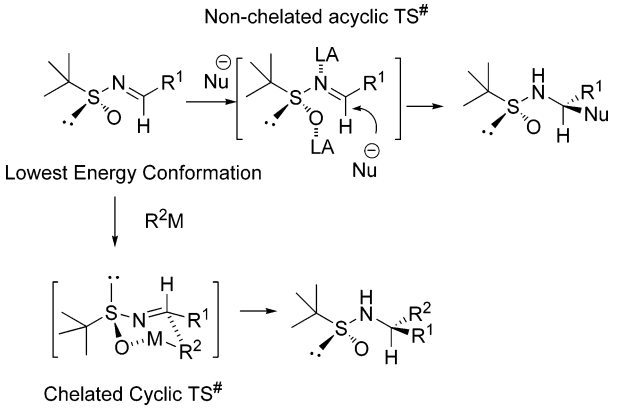
of enantiomerically pure sulfinamides are rather limited. We disclosed previously a general process for rapid access to a variety of aryl or alkyl sulfinamides in optically pure form with equal accessibility to either enantiomer. Included in this list of examples is *tert*-butanesulfinamide prepared from optically pure *N*-sulfonyl [1,2,3]-oxathiazolidine-2-oxide and its application for the syntheses of several drug candidates.[3] Recently, we reported another efficient asymmetric synthesis of enantiopure sulfinates, which are common precursors to access both sulfoxides and sulfinamides.[4] High diastereoselectivity for the addition of nucleophiles such as Grignards, lithium reagents, or enolates to sulfinimines has been demonstrated, and a chelated cyclic transition state has been proposed for the high selectivity observed in this process.[5]

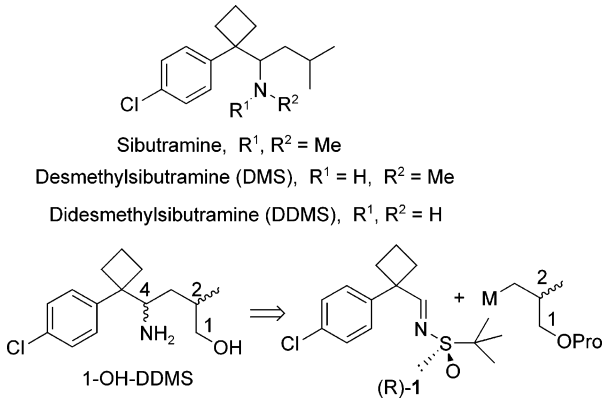
However, the concept of obtaining a reversal of diastereoselectivity while utilizing the same enantiomer of either (*R*)- or (*S*)-sulfinimines by altering the transition state has not yet been well documented for these reaction systems (Scheme 1).[6]

Scheme 1. Mechanistic Models to Predict the Stereochemical Outcomes of the Nucleophilic Additions



As part of our program to develop improved chemical entities (ICEs) from important existing drugs, we were interested in investigating each of the potential metabolites of the antiobesity drug sibutramine (Scheme 2). Preliminary preclinical studies indicated that the hydroxylated derivatives of sibutramine (1-OH-DDMS) are potent monoamine re-

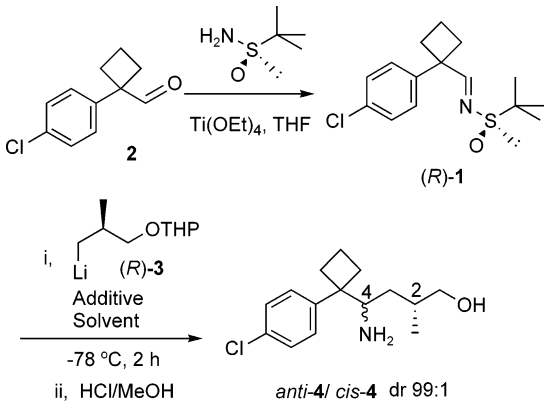
Scheme 2. Retrosynthetic Analysis for Preparation of the Hydroxyl Derivatives of Sibutramine



uptake inhibitors that can be potentially used for the treatment of CNS disorders.[7] To identify the absolute configuration of the active metabolite, as well as conduct a comparison of the biological activities of these stereoisomers, efficient synthetic methods were needed to prepare the stereoisomers. Herein, we report the first efficient stereoselective syntheses of all four isomers of 1-OH-DDMS using (*R*)-*tert*-butanesulfinamide-derived sulfinimine intermediate (**1**) as the common synthon for preparation of each stereoisomer. In this case, we demonstrated the above concept to manipulate the diastereoselectivity by taking advantage of solvent effects.

The synthesis starts with the preparation of a common single enantiomer of the key intermediate, the (*R*)-*tert*-butanesulfinyl imine **1**. Condensation of the aldehyde **2** with (*R*)-*tert*-butylsulfinamide in THF at 22 °C, catalyzed by $Ti(OEt)_4$, gave **1** in 94% yield (Scheme 3). Next, addition

Scheme 3. Diastereoselective Addition of Lithium Reagent (*R*)-**3** to (*R*)-*t*-Butanesulfinimide **1**



of the THP-protected organolithium reagent (*R*)-**3** to imine **1** was examined. In both Et_2O and THF, the addition occurred at −78 °C and gave consistently *anti*-**4** as the major

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product in high yield after cleavage of the chiral auxiliary with methanolic HCl. These results are summarized in Table 1. A diastereomeric ratio of up to 99:1 was achieved when

Table 1. Addition of Organolithium (*R*)-3 with (*R*)-*t*-butanesulfinimine **1**

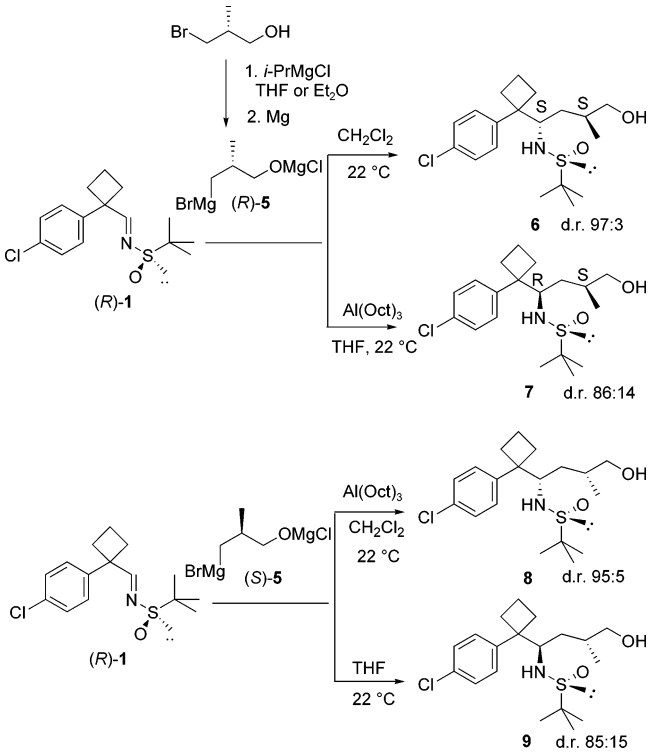
entry	solvent	Lewis acid	yield (%)	anti/cis[a]
1	Et_2O	N/A	93	95:5
2	THF−Et_2O (2:1)	N/A	88	85:15
3	THF−Et_2O (2:1)	$BF_3{\cdot}OEt_2$ (1.1 equiv)	79	96:4
4	THF−Et_2O (2:1)	$BF_3{\cdot}OEt_2$ (2.2 equiv)	85	98:2
5	Et_2O−hexane (3:1)	$Al(Oct)_3$ (1.2 equiv)	99	96:4
6	THF−Et_2O−hexane (2:1:1)	$Al(Oct)_3$ (1.2 equiv)	82	99:1

[a] Ratios were measured by HPLC.

the reaction was catalyzed with 1.2 equiv of $Al(Oct)_3$ or 2 equiv of $BF_3{\cdot}Et_2O$ (Table 1, entries 4 and 6). In these cases, it is proposed that the additions occurred predominantly through the nonchelated acyclic transition state pathway. To reverse the facial selectivity, via the chelated cyclic transition state, it was believed that a nonchelating solvent would be essential to prevent competitive coordination of the solvent to the metal cation (nonchelated acyclic TS#). Chlorinated or hydrocarbon solvents such as toluene were expected to meet this criterion. The potential incompatibility of reacting certain lithio reagents in these solvents prompted us to first study the addition with Grignard reagents.

The Grignard reagents (*S*)- and (*R*)-**5**, were derived from (*R*)- and (*S*)-3-bromo-2-methyl propanol, respectively, by a modified procedure according to literature.[8] The results of addition to (*R*)-*tert*-butylsulfinimine (**1**) are summarized in Table 2. As we anticipated, a remarkable solvent effect was observed. For instance, when (*R*)-**5** was added to **1** in CH_2Cl_2, the reaction proceeded at 22 °C to form a diastereomeric mixture of **6** and **7**, with a ratio of 97:3, favoring the chelated cyclic transition state product (Table 2, entry 1). Not surprisingly, in the case where $Al(Oct)_3$ was added, the diastereoselectivity deteriorated to 76:24 and retarded the reaction (Table 2, entry 2). This is likely due to the competitive coordination of the added Lewis acid to the sulfinyl oxygen, which would enhance the acyclic transition state pathway. On the other hand, when the reaction was carried out in THF, poor diastereoselectivity resulted, giving **6** and **7** in a ratio of 40:60, thus indicating a mismatched addition of (*R*)-**5** to (*R*)-**1** via the nonchelated pathway (Table 2, entry 3). Addition of a Lewis acid such as 1.2 equiv of $Al(Oct)_3$ improved the diastereoselectivity of the mismatched addition when run in THF from 40:60 to 14:86 (Table 2, entry 4).

Scheme 4. Diastereoselective Addition of Grignard Reagent (*R*)- or (*S*)-**7** to (*R*)-*t*-Butanesulfinimide **1**



Similarly, the addition of (*S*)-**5** to **1** afforded a higher diastereoselectivity of addition when run in CH_2Cl_2 to give **8** and **9** in a ratio of 91:9 (Table 2, entry 5) and a lower opposite selectivity in THF to afford **8** and **9** in a ratio of

Table 2. Addition of Grignard Reagents (*R*)- or (*S*)-**5** to Sulfinimide **1**

entry	**5**	solvents	Lewis acid	temp (°C)/time (h)	yield[a] (%)	dr[b]
1	*R*	CH_2Cl_2−Et_2O (2:1)	N/A	−48 to rt/24	74	**6/7** 97:3
2	*R*	CH_2Cl_2−Et_2O−hexane (4:2:1)	$Al(Oct)_3$ (1.2 equiv)	−78 to rt/36		**6/7** 76:24
3	*R*	THF	N/A	−78 to rt/2	57 (95)[c]	**6/7** 40:60
4	*R*	THF−hexane (7:1)	$Al(Oct)_3$ (1.2 equiv)	−78 to rt/48		**6/7** 14:86
5	*S*	CH_2Cl_2−Et_2O (2:1)	N/A	0 to rt/10	76.5 (84.5)	**8/9** 91:9
6	*S*	CH_2Cl_2 −Et_2O−hexane (4:2:1)	$Al(Oct)_3$ (1.2 equiv)	−78 to rt/24	65	**8/9** 95:5
7	*S*	THF	N/A	0 to rt/2	75 (88)	**8/9** 15:85
8	*S*	THF−hexane (7:1)	$Al(Oct)_3$ (1.2 equiv)	−78 to rt/2		**8/9** 19:81
9	*S*	toluene−Et_2O (2:1)	N/A	rt/24	30	**8/9** 94:6
10	*S*	CH_2Cl_2−Et_2O (2:1)	$BF_3{\cdot}OEt_2$ (2.2 equiv)	−78 to rt/24	0	

[a] Isolated yield of pure major isomer. [b] Measured by HPLC.

15:85 (Table 2, entry 7). In contrast to the addition of (*R*)-**5** to **1**, the addition of (*S*)-**5** to **1** in CH_2Cl_2, in the presence of 1.2 equiv of $Al(Oct)_3$, gave improved diastereoselectivity from 91:9 to 95:5 (Table 2, entry 6), whereas a slight decrease of selectivity (from the original 15:85 to 19:81) was observed when 1.2 equiv of $Al(Oct)_3$ was added to the mixture of (*S*)-**5** and **1** in THF (Table 2, entry 8). The addition of $BF_3{\cdot}Et_2O$ to the reaction mixture in CH_2Cl_2 resulted in no product formation, probably due to the reactivity of the Grignard reagent with $BF_3{\cdot}Et_2O$ at 22 °C (Table 2, entry 10). Although the reaction in toluene gave better selectivity, the addition was much slower (Table 2, entry 9). After separation by column chromatography, all four isomers **6**−**9** were converted into their respective target molecules by treatment with methanolic HCl to cleave the chiral auxiliary.

The absolute stereochemistry at C-4 was assigned by X-ray crystallography on intermediate **8** (Figure 1). The structures of the other isomers were deduced from **8** on the basis of comparisons of both ^1H and ^{13}C NMR data.

Figure 1. Diagram of the X-ray crystal structure of **8**.

In summary, an efficient synthetic method has been developed whereby addition of the Grignard reagents (*R*)- or (*S*)-**5** to the common synthon **1** readily allows access to each of the four stereoisomers of the hydroxyl sibutramine by proper choice of reaction conditions. The reversed diastereoselectivity observed in CH_2Cl_2 and THF implies that the reactions may undergo chelated cyclic transition state and nonchelated acyclic transition states, respectively. From these preliminary results, it is conceivable that the presence of a Lewis acid would facilitate the nonchelated pathway but disfavor the chelated one, providing that more than 2 equiv of a Lewis acid are added. When the nucleophile contains chirality, matched and mismatched additions could occur. Therefore, it is conceivable to design a kinetic resolution by reaction of enantiopure sulfinimines with a racemic nucleophile to provide one diastereomer preferentially as the major adduct. The differing aggregation states of Grignard reagents in CH_2Cl_2 or THF should have an influence on the reaction rates. Further applications of enantiomerically pure sulfinimines for the preparation of a variety of chiral amines with important therapeutic indications are under investigation and will be reported in due course.

Supporting Information Available: Experimental procedures and full spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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