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First Application of Tunable Alkyl or Aryl Sulfinamides to the Stereoselective Synthesis of a Chiral Amine: Asymmetric Synthesis of (*R*)-Didesmethylsibutramine ((*R*)-DDMS) Using (*R*)-Triethylmethylsulfinamide ((*R*)-TESA)†

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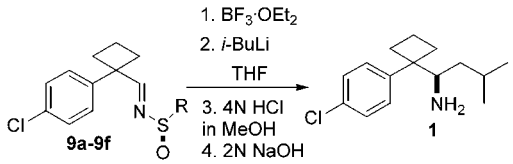
ABSTRACT



R = *t*-Bu, $C(C_2H_5)_3$, $C(CH_3)_2C_2H_5$, 2-mesityl, 1-adamantyl

A highly diastereoselective addition of *i*-BuLi to a triethylmethylsulfinamide derived aldimine was used as the key step in the first asymmetric synthesis of (*R*)-didesmethylsibutramine, a metabolite of sibutramine for the potential treatment of CNS disorders.

Among nitrogen-containing biologically active organic compounds, chiral amines represent an important class for the development of active pharmaceutical ingredients and other pharmaceutical intermediates. Despite their prime importance in the pharmaceutical industry, the economically viable and practical asymmetric synthesis of chiral amines poses significant challenges to organic chemists.[1] One such chiral amine of interest to Sepracor is (*R*)-didesmethylsibutramine (DDMS, **1**), a single enantiomeric version of a pharmacologically active metabolite of sibutramine **2**.[2] Preliminary preclinical studies indicate that (*R*)-DDMS is a potent serotonin, norepinephrine, and dopamine re-uptake inhibitor that can be potentially used in the treatment of CNS disorders.[3] To evaluate this unique triple mechanism of action, process research efforts were directed toward the synthesis of optically pure (*R*)-DDMS. We recently reported the synthesis of optically pure (*R*)-DDMS using a novel resolution process with 20% overall yield.[4] To identify an efficient high- yielding synthesis for (*R*)-DDMS, we have focused our research efforts in the development of an asymmetric synthesis of DDMS. Herein, we disclose the first

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† Dedicated to Professor Carol Johnson on the occasion of his retirement.

(1) (a) Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, 8, 1895. (b) Kobayashi, S.; Ishitani. H. *Chem. Rev.* **1999**, *99*, 1069. (c) Senanayake, C. H.; Krishnamurthy, D. *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 590.

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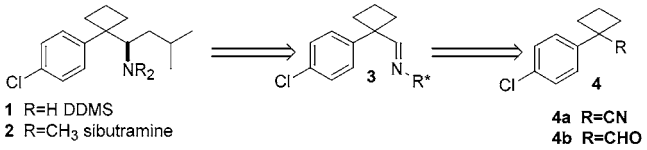
practical asymmetric synthesis of (*R*)-DDMS using the novel (*R*)-triethylmethylsulfinamide ((*R*)-TESA).

We envisioned that application of an enantio- or diastereoselective addition to imine **3** (asymmetric C−C bond forming reaction) would provide a straightforward route to a high-yielding synthesis for optically pure DDMS. Imine **3** could be obtained from the corresponding hindered aldehyde **4b**, which in turn can be readily accessed from known nitrile **4a** (Scheme 1).[5]

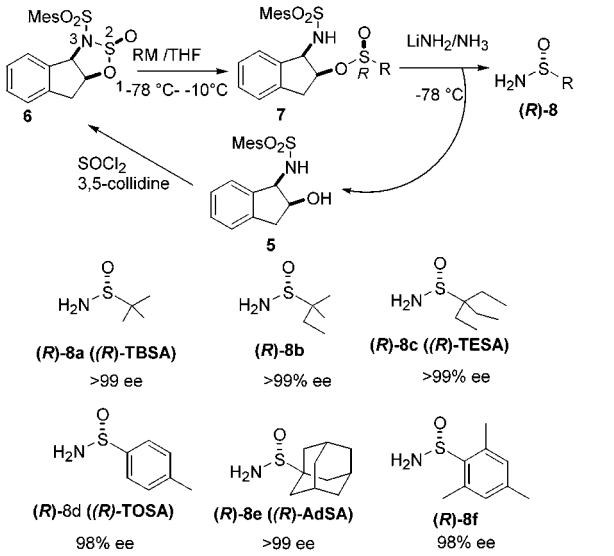
Scheme 1. Retro-Synthetic Analysis for DDMS



We thought that application of enantiopure sulfinamide[6,7] as a chiral auxiliary for preparation of optically pure DDMS was a viable alternative method, provided a range of chiral sulfinamides with both antipodes can be accessed in large quantities with a reasonable price.[8] In this context, we recently reported the first, practical, and modular approach for production of several enantiopure sulfinamides using a key chemoselective ring opening of a recyclable, aminoindanol based *endo*-1,2,3-oxathiazolidine-2-oxide (**6**, Scheme 2).[9]

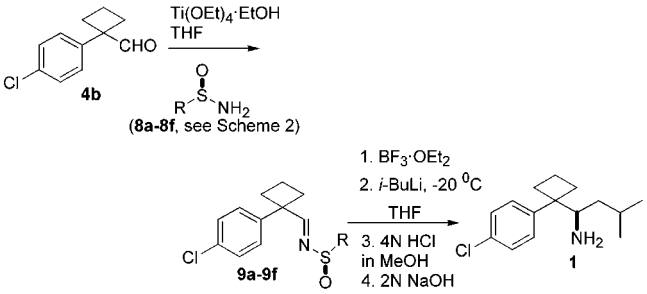
With these optically pure chiral sulfinamides in hand, our initial effort in the asymmetric synthesis of (*R*)-DDMS was focused on the identification of an efficient and scalable chiral sulfinamide auxiliary for the diastereoselective addition to imine **3**. To begin our investigations, a variety of chiral

Scheme 2. Modular Asymmetric Synthesis of Chiral Sulfinamides



alkyl or aryl sulfinyl aldimines **9a**−**f** were prepared from aldehyde **4b** and the corresponding sulfinamides **8a**−**f** in excellent yields using known method.[10] Additions of *i*-BuLi to imines were conducted at −20 °C in the presence of BF_3·OEt_2,[11a] and the results are summarized in Table 1.

Table 1. Addition of *i*-BuLi to Sulfinyl Aldimines **9**[a]



entry	**9**, R	% yield[b]	% ee[c]
1	$C(CH_3)_3$ (**9a**)	85	88
2	$C(C_2H_5)_3$ (**9c**)	82	88
3	$C(CH_3)_2C_2H_5$ (**9b**)	77	80
4	Ad (**9e**)	75	80
5	4-methylphenyl (**9d**)[d]	–	–
6	2-mesityl (**9f**)	60	50

[a] See Supporting Information for detailed experimental procedures. [b] Except for entry 1, yields are based on the HPLC analysis. [c] % ee values are determined by chiral HPLC analysis. [d] No desired product was formed.

Treatment of *i*-BuLi with aldimine **9a** followed by acidic removal of the *tert*-butylsulfinyl group provided 88% ee of

(5) Krishnamurthy, D.; Han, Z.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett*. **2002**, *43*, 2331.

(6) For the use of *p*-toluenesulfinamide as auxiliary in the synthesis of chiral nitrogen containing compounds see: (a) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. S. *Tetrahedron Lett*. **1993**, *34*, 6229. (b) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev*. **1998**, *27*, 13. (c) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem*. **1997**, *62*, 2555. (d) Zhou, P.; Chen, B.-C.; Davis, F. A. *Advances in Sulfur Chemistry*; Rayner, C. M., Ed.; JAL Press: Greenwich, CT, 2000; Vol. 2, p 249. (e) Davis, F. A.; Lee, S.; Zhang, H.; Fanelli, D. L. *J. Org. Chem*. **2000**, *65*, 8704.

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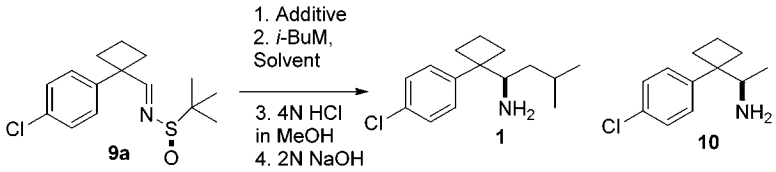
(8) (*R*)-TBSA is available from Aldrich Chemical Co. only in gram quantities ($130/g).

(9) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc*. **2002**, *124*, 7880.

(10) (a) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem*. **1999**, *64*, 1278. (b) All new sulfinyl aldimine gave satisfactory analytical data.

(11) (a) Preliminary studies showed the use of BF_3·OEt_2 minimizes the formation of byproducts. (b) Observed stereochemistry is consistent with previously proposed nonchelation controlled models.[7n]

Table 2. Stereoselective Addition of *i*-BuM to Aldimine **9a**[a]



entry	nucleophile	additive	solvent	temp, °C	% yield[b]	% ee[c] (*R*/*S*)	chemical purity[d]
1	*i*-BuMgBr	–	THF or toluene	−78 to 100	–	–	–
2	*i*-BuMgBr	$BF_3{\cdot}OEt_2$	THF or toluene	−78 to 100	–	–	–
3	*i*-BuMgBr	Me_3Al	THF	−20 to 25	90[e]	40[e] (*R*)	–
4	*i*-BuLi	–	MTBE	−78 to 25	–	–	–
5	*i*-BuLi	$BF_3{\cdot}OEt_2$	MTBE	−78 to 25	–	–	–
6	*i*-BuLi	$BF_3{\cdot}OEt_2$	toluene	−78	78	98 (*R*)	99.0
7	*i*-BuLi	$BF_3{\cdot}OEt_2$	THF	−78	90	99 (*R*)	99.2
8	*i*-BuLi	Me_3Al	THF	−78	90	99 (*R*)	98.7
9	*i*-BuLi	Me_3Al	toluene	−45	36	38 (*S*)	62.0
10	*i*-BuLi	Oct_3Al	THF	−78	85	98 (*R*)	96.5
11	*i*-BuLi	Oct_3Al	toluene	−20	37	76 (*S*)	55.0
12	*i*-BuLi	TMEDA	THF	−78	84	99 (*R*)	99.7
13	*i*-BuLi	TMEDA	toluene	−78	85	95 (*R*)	98.4

[a] For detailed experimental procedures see the Supporting Information. [b] Yields are determined by HPLC quantification. [c] Ee values are determined using the chiral HPLC method. [d] Chemical purity was determined by HPLC area %. [e] Yield and ee refers to methyl transfer product **10**.

(*R*)-DDMS with 85% yield.[11b] Surprisingly, change of trimethylmethylsulfinyl aldimine **9a** to triethylmethylsulfinyl aldimine **9c** provided no further increase in the ee (entry 2). Interestingly, use of dimethylethylmethylsulfinyl aldimine **9b** decreased the ee from 88% to 80%. Introduction of a more hindered adamantyl group in imine **9** (**9e**) also decreased the ee to 80%. The attempted use of *p*-tolylsulfinamide was not fruitful, as it provided many byproducts. 2-Mesitylsulfinamide **9f** provided 60% yield and 50% ee, and proved to be less effective in this diastereoselective process. It should be noted that in most cases reaction yields are not affected by modification of sulfinyl aldimine structures. Among the various chiral sulfinamides, only the triethyl derivative performed similar to *tert*-butyl sulfinamide, and none gave >88% ee at −20 °C.

On the basis of the above results, imines **9a** and **9c** proved to be better than other imines, and hence, further optimization studies to obtain (*R*)-DDMS in high yield with excellent % ee and high chemical purity were centered on these imines. Since imines **9a** and **9c** gave identical results, *tert*-butylsulfinyl aldimine **9a** was used as the representative substrate for further experimentation. Thus, after obtaining large quantities of imine **9a**, our attention focused on the systematic screening studies on the organometallic addition process, as depicted in Table 2. These studies included an examination of various additives, solvents, and nucleophiles for the addition process to produce (*R*)-DDMS in high yield, excellent enantioselectivity, and high purity. The use of *i*-BuMgBr was not effective in this reaction and gave no desired product in any of the cases (entries 1−3).

Interestingly, the use of *i*-BuMgBr in the presence of Me_3Al gave a methyl transfer product **10**.[12] Utilization of the more reactive *i*-BuLi in MTBE with or without $BF_3{\cdot}OEt_2$ gave disappointing results (entry 4 and 5). However, when toluene or THF is used as the solvent, *i*-BuLi added to imine **9a** in the presence of $BF_3{\cdot}OEt_2$ to provide (*R*)-DDMS in >75% yield and >98% ee (entries 6 and 7). The use of Al based Lewis acids provided similar results, as compared to $BF_3{\cdot}OEt_2$ when THF is used as solvent (entry 8 and 10). Interestingly, when THF is replaced with toluene, Al-based Lewis acids provided the (*S*)-enantiomer albeit in low % ee (entries 9 and 11). Use of the Lewis base TMEDA provided comparable results with $BF_3{\cdot}OEt_2$ either in THF or in toluene.[13] It is important to mention that the decrease of % ee with increase in temperature is more pronounced when toluene is used as solvent (Figure 1). However, a minor fluctuation in % ee with respect to temperature is observed when THF is used as the solvent (Figure 1).[14] Thus, optimal conditions were established in THF at −78 °C, using $BF_3{\cdot}OEt_2$ as additive and *i*-BuLi as nucleophile, to provide (*R*)-DDMS in excellent yield with >98% ee and >99% chemical purity.

Although (*R*)-DDMS can be prepared in high yield and excellent enantiomeric purity using (*R*)-TBSA, during the acidic removal of the *tert*-butylsulfinyl group to form (*R*)-DDMS, a malodorous odor was generated, which limited the large-scale operation of TBSA. Therefore, we turned our attention to other sulfinamide auxiliaries which can effectively provide outstanding induction compared to (*R*)-

(12) For a similar methyl transfer process in ketimine see ref 7f.

(13) Isolation of DDMS as the DDMS·D-TA salt may not be effective in the presence of TMEDA. Therefore the use of TMEDA was not considered for further optimization.

(14) Use of 1:1 THF:toluene as solvent has the same effect of temperature on % ee as THF alone.

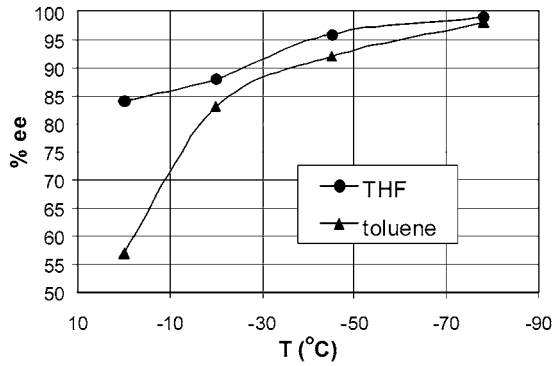


Figure 1. Effect of temperature on percent ee of (*R*)-DDMS.

TBSA without evolution of an unpleasant odor[15] during the removal of the sulfinyl group. It is gratifying to mention that use of (*R*)-TESA derived imine **9c** retained the excellent induction and did not evolve any odor during the acidic removal of the sulfinyl group.

After identifying (*R*)-TSEA as the practical chiral auxiliary and optimal condition for the diastereoselective addition process, a chromatography free asymmetric synthesis of (*R*)-DDMS was demonstrated in a single vessel using imine **9c**, as depicted in Scheme 3.

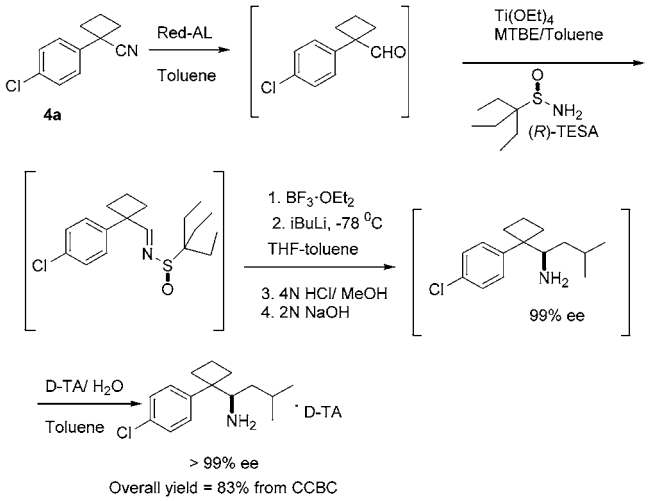
Thus, treatment of Red-Al with nitrile **4a** in toluene provided aldehyde **4b**,[16] which was then subjected to Ellman's condition with (*R*)-TESA to provide imine **9c**. Diastereoselective addition of *i*-BuLi in the presence of BF_3·OEt_2 at −78 °C was followed by cleavage of the chiral auxiliary to afford (*R*)-DDMS in 99% ee. Isolation of (*R*)-DDMS is accomplished by treating crude DDMS solution in toluene with an aqueous solution of D-TA. The overall yield for this process from nitrile **4a** is 83% with >99% ee and >99.5% chemical purity.

In summary, for the first time, the effect of the structure of various chiral sulfinamides on the stereoselectivity of

(15) In the production environment **9c** is preferred over **9a** due to low volatility of byproducts from hydrolysis reaction.

(16) Red-Al is less expensive and more efficient in the large-scale reduction of **4a** to **4b**.

Scheme 3. Single Vessel Asymmetric Synthesis of (*R*)-DDMS·D-TA



i-BuLi addition has been evaluated. Application of *tert*-butyl and triethylmethylsulfinamide at −20 °C gave DDMS in 88% ee; on the other hand, use of aryl sulfinamides such as 2,4,6-mesitylsulfinamide gave only 50% ee. Due to practical limitation in the use of (*R*)-TBSA, (*R*)-TESA was developed as a practical auxiliary for the asymmetric synthesis of (*R*)-DDMS. Using (*R*)-TESA as an auxiliary, a single vessel protocol was developed for the asymmetric synthesis of (*R*)-DDMS that provided an overall yield of 83% and >99% ee. Further insight into the role of the sulfinamide structure in sulfinyl imines toward the outcome of nucleophillic addition processes, and further evaluation of structurally unique sulfinamide auxiliaries, such as (*R*)-TESA, for the preparation of challenging chiral amines are being pursued, and will be reported in due course.

Supporting Information Available: ^{1}H and ^{13}C NMR and MS data and description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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