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Effective tuning of the arene and alkanesulfinamides for highly enantioselective synthesis of (*S*)-4-chlorophenylphenylmethylamine, a key intermediate for antihistamic (*S*)-cetirizine

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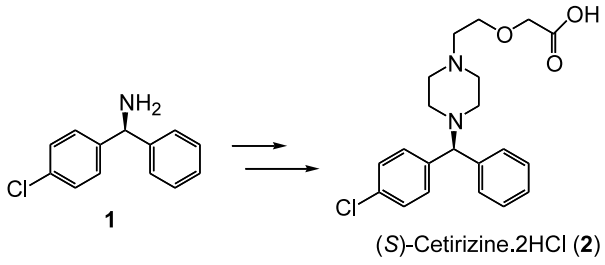
Abstract—High diastereoselectivity (>94%) has been achieved in the phenylMgBr addition process to chlorophenyl aldimine derived from the new and sterically hindered triisopropylbenzene sulfinamide (TIPBSA) in the synthesis of a key intermediate of (*S*)-Cetirizine. Surprisingly, under the same reaction conditions, toluenesulfinamide derived chlorophenyl aldimine provided only 10% ee.

Enantioselective synthesis of diarylmethylamines has drawn much interest recently due to their importance as intermediates in the synthesis of biologically active compounds.[1,2] (*S*)-4-chlorophenylphenylmethylamine (*S*)-**1**, for example, is the key intermediate for the asymmetric synthesis of enantiomerically pure (*S*)-cetirizine·2HCl (**2**) (Scheme 1), a non-sedating histamine H1-receptor antagonist used for the treatment of allergy, and is currently marketed as Xyzal™ in Europe. The (*S*)-enantiomer displays a better pharmacological profile than the racemate.[3] Several methods have been reported for the synthesis of enantiomeric pure (*S*)-cetirizine employing resolution techniques,[4] a stoichiometric heavy metal,[5] or chromatography.[6] A process for efficient asymmetric synthesis of enantiomeric pure (*S*)-cetirizine, however, is rather limited. Recent literature revealed that *tert*-butanesulfinamide and toluenesulfinamide have been applied to many important asymmetric processes.[7–9] Herein, we disclose an efficient design of the arenesulfinamide for the asymmetric synthesis of (*S*)-cetirizine intermediate **1** with high diastereoselectivity (94% de).



Scheme 1.

Identification of an effective asymmetric method for the synthesis of enantiopure (*S*)-**1** plays a major role in the practical synthesis of (*S*)-cetirizine. Recently, Bolm et al.[2a] developed a remarkably effective catalytic enantioselective process for the asymmetric addition of phenylzinc reagent to *N*-formylimine derived from *N*-[4-chlorophenylmethyl-(toluene-4-sulfonyl)]formamide to generate diarylamine **1** in excellent enantioselectivity (94% ee). We also disclosed our initial results for rapid assembly of (*S*)-cetirizine using (*S*)-diarylamine, (*S*)-**1**, that was constructed employing readily available and pharmaceutically acceptable reagents.[3] Thus, addition of PhMgBr to *N*-*tert*-butanesulfinyl-*p*-chloro-benzaldimine (*R*)-**3a** (R = *tert*-butyl) derived from the condensation of (*R*)-*tert*-butanesulfinamide and *p*-chlorobenzaldehyde gave, after mild acidic hydrolysis, (*S*)-**1** as the major enantiomer with only moderate enantiopurity of 75% ee at 0°C in toluene (Scheme 2). Further optimization of reaction conditions to improve

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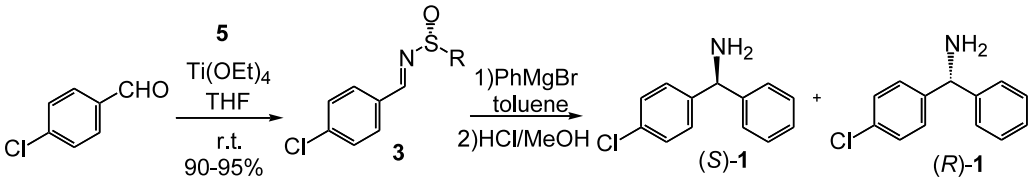


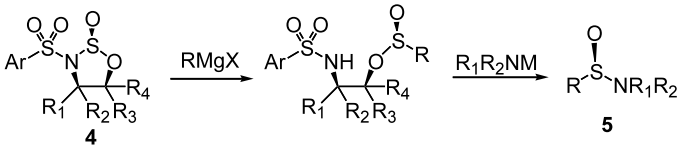
Scheme 2.

the selectivity was unsuccessful. Toluene was found to be the solvent of choice for this process. We, therefore, turned our attention toward tuning the structure of the chiral sulfinamides to moderate the diastereoselectivity of the adduct.[3]

To tune the diastereoselectivity of the organometallic addition process, a wide range of structurally diverse arene- and alkanesulfinamides was required. This ultimately led us to discover and develop a new technology for modular synthesis of enantiopure tertiary alkane and arene sulfinamides from arane *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide (**4**, **ASOO**) (Scheme 3, Fig. 1).[10] With the new technology for the preparation of chiral sulfinamides, our focus centered on the finding of new sulfinamide for achieving high selectivity in the asymmetric synthesis of (*S*)-**1**.

Initial attempts were focused on the asymmetric addition of PhMgBr to imine derived from tertiary alkanesulfinamides. We envisioned that introduction of a more bulky group to alkanesulfinamides might increase the diastereoselectivity for organometallic addition to **3**. Thus, a variety of (*R*)-alkanesulfinamides were synthesized as shown in Figure 1 (**5a**–**d**).[11] As outlined in Scheme 2, condensation of *p*-chlorobenzaldehyde with the sulfinamides using Ellman's method provides the desired imines.[7b] The diastereoselectivity for PhMgBr asymmetric addition was investigated in toluene at 0°C and the results are outlined in Table 1. Surprisingly, when bulky admantylsulfinamide (**5b**, AdSA, entry 2) was used as an auxiliary, the ee decreased from 75 to 68% as compared to *tert*-butanesulfinamide (TBSA, entry 1). Increasing the steric bulk of branched alkyl sulfinamide provided comparable selectivity. Using 2-methylbutanesulfinamide (DMESA) (**5c**) gave 76% ee for (*S*)-**1** (entry 3). More bulky 3-ethylpentanesulfinamide (TESA) **5d** increased the ee from 75 to 79% (entry 4).[12] It was noted that modification of alkyl groups imparted little change in selectivity and performed similar to the use of TBSA.

At this point, we turned our efforts to evaluate the use of arene sulfinamide for the synthesis of (*S*)-**1** with



Scheme 3.

optimal selectivity. First, Davis' toluenesulfinamide (pTSA) (**5e**) was used as chiral auxiliary for the study. Surprisingly, **5e** gave very low selectivity with only 10% ee for (*S*)-**1** (Table 1, entry 5). It is interesting to note that by increased the bulk of the aromatic ring to 2,4,6-mesityl (TMPSA) (**5f**), the selectivity increased dramatically to provide the amine (*S*)-**1** in 50% ee (Table 1, entry 6).

With this result, we envisioned that further increases in the steric bulk on the aromatic ring of the sulfinamide might give high diastereoselectivity for PhMgBr addition to imine **3**. Thus, a new sulfinamide was designed by substituting the 2, 4 and 6 positions of the phenyl ring with isopropyl groups to give sulfinamide (TIPPSA) **5g**,[11] which was prepared according to

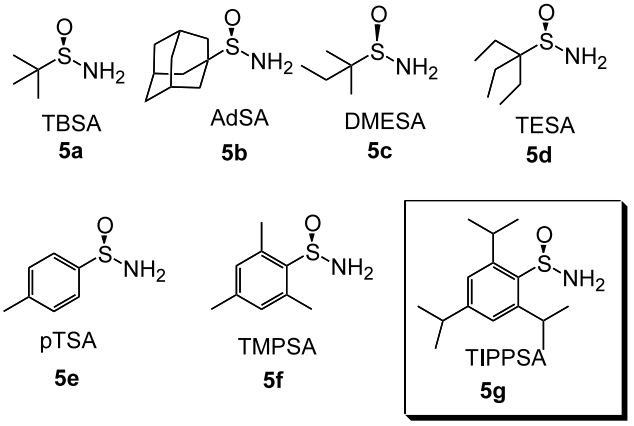


Figure 1. Structure of alkane and arene sulfinamides.

Table 1. Results for the PhMgBr addition to the sulfinyl imine for the asymmetric synthesis of (*S*)-**1** at 0°C in toluene

Entry	**5**	% Yield[a]	% Ee[b]
1	**5a**	81	75
2	**5b**	85	68
3	**5c**	79	76
4	**5d**	88	79
5	**5e**	77	10
6	**5f**	83	50
7	**5g**	84	91
8	**5a**	83	82 (–20 to 0°C)
9	**5g**	80	94 (–20 to 0°C)

[a] Yield was based on wt% assay by HPLC analysis.

[b] Enantiomeric excess (ee) was based on chiral HPLC analysis on chiralcel OD column, 250×5 mm, 10 μm; 220 nm; eluted with hexane/IPA/DEA (90:10:0.1).

Scheme 3. We are pleased to find that when PhMgBr is added to **3g** in toluene at 0°C for 5 h, after acidic hydrolysis with HCl/MeOH, (*S*)-**1** is obtained in 84% yield with 91% ee. The selectivity for this reaction was further improved by lowering the reaction temperature. A 94% ee of (*S*)-**1** was obtained when PhMgBr is added to **3g** at −20°C and aged for 4 h, followed by warming the reaction mixture to 0°C. However, only 82% ee of the final product was observed when *tert*-butanesulfinamide was used under the same reaction condition. To the best of our knowledge, this disclosure reports the first systematic evaluation of the structure sulfinyl chiral auxiliary for the asymmetric synthesis of diarylmethylamines with high selectivity. After achieving a higher selectivity for the asymmetric synthesis of (*S*)-**1**, the synthesis of (*S*)-cetirizine was efficiently accomplished as reported.[3]

In conclusion, we have systematically studied the effect of arene- and trialkylmethyl sulfinamides for the asymmetric synthesis of (*S*)-diarylmethylamine-**1**. From this study, we identified a novel and hindered arenesulfinamide, **TIPPSA (triisopropylphenylsulfinamide)**, as an optimal sulfinamide for highest diastereoselectivity in the addition of PhMgBr to chlorophenyl aldamine **3g**. Applications of the steric outcome for TIPPSA to other important asymmetric processes are under investigation and will be reported in due course.

References

1. (a) Sakurail, S.; Ogawa, N.; Suzuki, T.; Kato, K.; Ohashi, T.; Yasuda, S.; Kato, H.; Ito, Y. *Chem. Pharm. Bull.* **1996**, *44*, 765; (b) Bishop, M. J.; MaNutt, R. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1331.
2. (a) Hermanns, N.; Dahmen, S.; Bolm, C.; Braese, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692 and references cited therein; (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895; (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407; (d) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651; (e) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976.
3. Pflum, D. A.; Krishnamurthy, D.; Han, Z.; Wald, S. A.; Senanayake, C. H. *Tetrahetron Lett.* **2002**, *43*, 923 and references cited therein.
4. (a) Clemo, G. R.; Gardner, C.; Raper, R. J. *J. Chem. Soc.* **1939**, 1958; (b) Opalka, C. J.; D'Ambra, T. E.; Faccone, J. J.; Bodson, G.; Cossement, E. *Synthesis* **1995**, 766.
5. Corey, E. J.; Halal, C. J. *Tetrahedron Lett.* **1996**, *37*, 4837.
6. Pflum, D. A.; Wilkinson, H. S.; Tanoury, G. J.; Kessler, D. W.; Kraus, H. B.; Senanayake, C. H.; Wlad, S. A. *Org. Process Res. Dev.* **2001**, *5*, 110.
7. For the use of Ellman's *tert*-butanesulfinamide as auxiliary in the synthesis of chiral nitrogen containing compounds, see: (a) Owens, D. T.; Hollander, J. F.; Oliver, A. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 1539 and references cited therein; (b) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913; (c) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron Lett.* **1999**, *40*, 6709; (d) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396; (e) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772; (f) Lee, Y.; Silverman, R. B. *Org. Lett.* 2000, *2*, 303; (g) Borg, G.; Chino, M.; Elmann, J. A. *Tetrahedron Lett.* **2001**, *42*, 1433; (h) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847; (i) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589; (j) Lee, A.; Elman, J. A. *Org. Lett.* **2001**, *3*, 3707; (k) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051.
8. For the use of Davis' *p*-toluenesulfinamide as auxiliary in the synthesis of chiral nitrogen containing compounds, see: (a) Davis, F. A.; Reddy, R. E.; Szewezyk, 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, 2000, Vol. 2, p. 249; (e) Davis, F. A.; Lee, S.; Zhang, H.; Fanelli, D. L. *J. Org. Chem.* **2000**, *2*, 8704.
9. For the first evaluation of the effect of the structure of chiral sulfinamides in asymmetric synthesis of chiral amines, see: Han, Z.; Krishnamurthy, D.; Pflum, D.; Grover, P.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2002**, *4*, 4025.
10. Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, K. Q.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880.
11. Synthesis of enantiopure sulfinamides **5a**–**f** and their analytical data were reported in Ref. 10. Same method was applied for the synthesis of **5g**. Triisopropylphenylmagnesium bromide (TIPPMgBr) was prepared in situ by reaction of TIPPBr in ether with magnesium in the presence of dibromoethane. *N*-Mesityl-aminoindanol derived oxathiazolidine-2-oxide was used in the preparation of TIPPSA according Scheme 3 to give a 87% overall yield and >99% ee. Chiral HPLC analysis: Chiralcel OD, 250× 4.6 mm, Hex/IPA 9:1, 222 nm, 1 mL/min. (H^1 $CDCl_3$): 1.24 (d, $J=6.96$ Hz, 6H), 1.27 (d, $J=6.71$, 6H), 1.33 (d, $J=6.96$, 6H), 2.88 (septet, $J=6.9$ Hz, 1H), 4.04 (septet, $J=6.78$ Hz, 2H), 458 (s, 2H), 7.08 (s, 2H). ^{13}C (δ $CDCl_3$): 23.9, 24.3, 24.5, 28.4, 34.4, 123.1, 138.9, 147.9, 152.0.
12. Typical experiment procedure for the asymmetric synthesis of (*S*)-**1** using **5g**. **Preparation of 3g**: To a mixture of **5g** (0.45 g, 1.68 mmol) and 4-chlorobenzaldehyde (0.25g, 1.82 mmol) in THF (10 mL) was added $Ti(OEt)_4$ (4.0 g), the mixture was stirred at 50°C for 4 h and reaction was monitored by TLC analysis. The reaction mixture was worked up and final compound was purified on chromatography to afford **3g** (0.62 g) in 95% yield. ^1H NMR ($CDCl_3$): δ 1.14 (d, $J=6.84$ Hz, 6H), 1.25 (d, $J=6.95$ Hz, 6H), 1.28 (d, $J=6.71$ Hz, 6H), 2.89 (m, 1H), 3.82 (m, 2H), 7.09 (s, 2H), 7.40–7.46 (m, 2H), 7.76–7.82 (m, 2H), 8.81 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.9, 24.2, 24.5, 24.9, 28.2, 34.6, 123.2, 129.5, 130.7, 132.9, 134.5, 138.7, 149.9, 153.1, 160. Anal calcd for $C_{22}H_{28}ClNOS$: C, 67.76; H, 7.24; N, 3.59. Found: C, 68.15; H, 7.45; N, 3.14. **Preparation of 1**: To a **3g** (0.11 g, 0.28 mmol) solution in toluene (3 mL) under argon at −20°C was PhMgBr (0.19 mL, 3 M in ether) slowly. After stirring at −20°C for 5 h, the reaction mixture was warmed to 0°C, stirred, and the reaction was monitored by TLC analysis. The reaction was quenched with 4 M HCl in methanol and worked up to furnish **1** in 80% yield and 94% ee based on HPLC analysis.[3]