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Development of Large Scale Asymmetric Process for *tert*-Butanesulfinamide

Philomen DeCroos, Zhengxu S. Han, Kanwar Sidhu, Jon Lorenz, Larry Nummy, Denis Byrne, Bo Qu, Yibo Xu, Ling Wu, Heewon Lee, Frank Roschangar, Jinhua J. Song, Chris H. Senanayake**

Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877, USA

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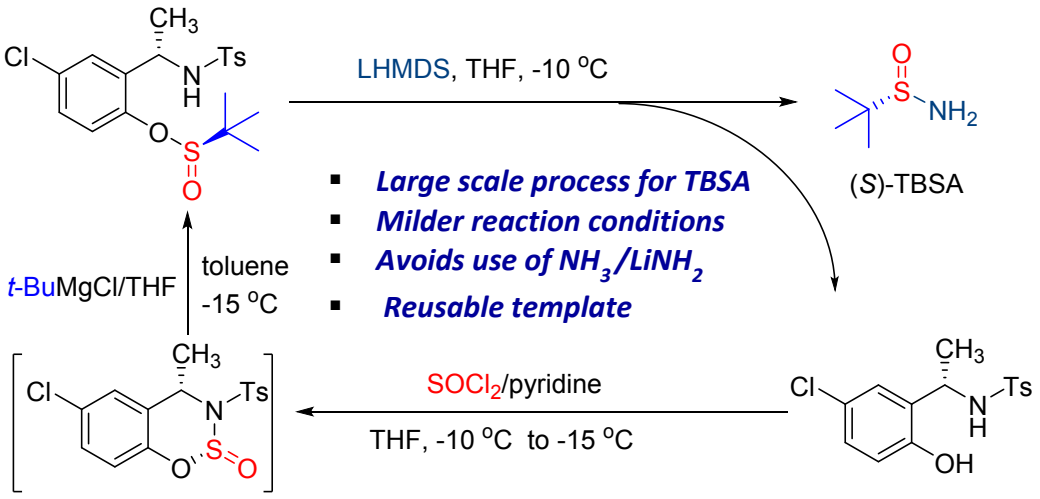
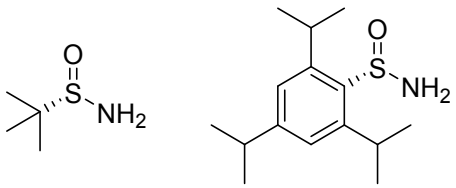


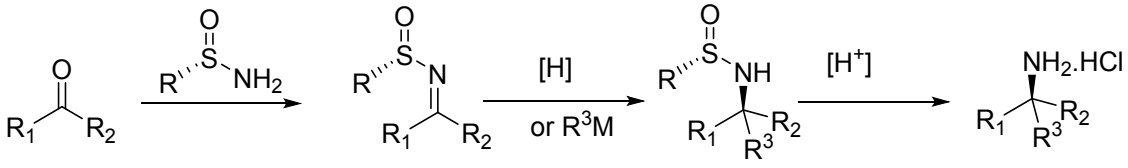
KEYWORDS: chiral sulfinamide, large scale, S-N and S-O bond strength, lithium amide

ABSTRACT: Process development for a scalable and green synthesis of chiral *tert*-butanesulfinamide (TBSA) on multi kilogram scale is reported. The process is based on the identification of a chiral sulfinyl transfer agent benzo[1,3]oxathiozin-2-one that contains active and differentiated S-N and S-O bonds, which allows the synthesis to proceed under mild reaction conditions. This method is practical and overcomes the disadvantages of earlier methods deploying harsh reaction conditions and hazardous and toxic reagents.

INTRODUCTION

Chiral sulfinamides are becoming powerful auxiliaries for the synthesis of chiral amines, which are of great interest to both academic and industry.[1-3] Sulfinamides have also found use as chiral ligands for catalytic asymmetric transformations.[4-6] It has become evident that bulky alkyl- or arylsulfinamides provide higher stereoselectivities, such as Ellman's *tert*-butanesulfinamide (**1a**, TBSA)[2a] or Han-Senanayake's triisopropylbenzenesulfinamide (**1b**, TIPPSA, Scheme 1).[7] TBSA, in particular, is frequently used in the production of drug substance on large scale and additional method for its production could enhance availability (Scheme 2).[8] Therefore, a practical and cost-effective process for the synthesis of hindered sulfinamides is highly desirable.



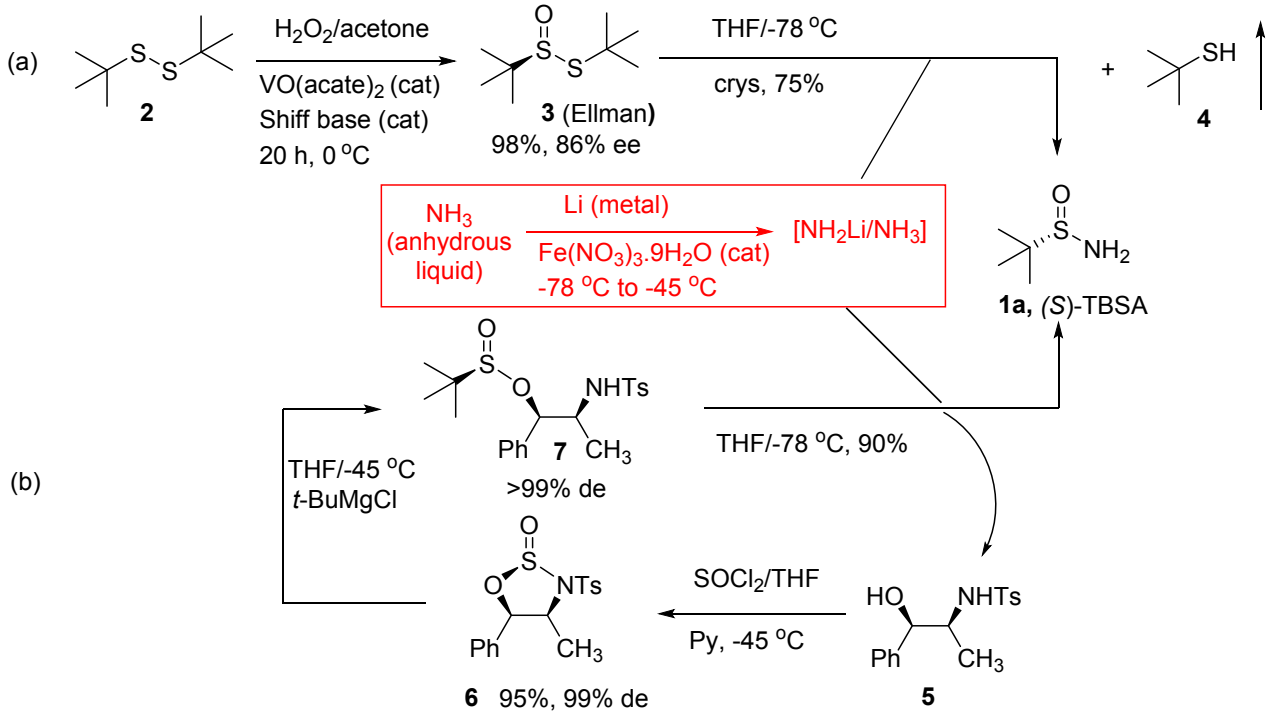


Scheme 1: General synthesis of chiral amines from chiral sulfinamides

Synthesis of bulky sulfinamides in an economical way remains a challenge. The available methods for the synthesis of TBSA include Ellman's approach using chiral sulfinothioate **3** prepared from di-*tert*-butyldisulfide **2**,[9a,b] and our method by using sulfinate **6** derived from chiral 1,2-aminoalcohol **5**[9c,d] (Scheme 2). Our initial attempt to synthesize TBSA using Ellman's method encountered the release of toxic and foul-smelling gas *tert*-butylthiol **4**. The byproduct **4** must be controlled before releasing to the environment (eq (a), Scheme 2).[9f] To provide an alternative route to **1,** we designed our first generation chiral sulfinyl transfer reagent **6** that was

applied in the synthesis of TBSA on kilogram scale successfully (eq (b), Scheme 2). This method avoids the release of toxic gas and template **5** can be recycled.

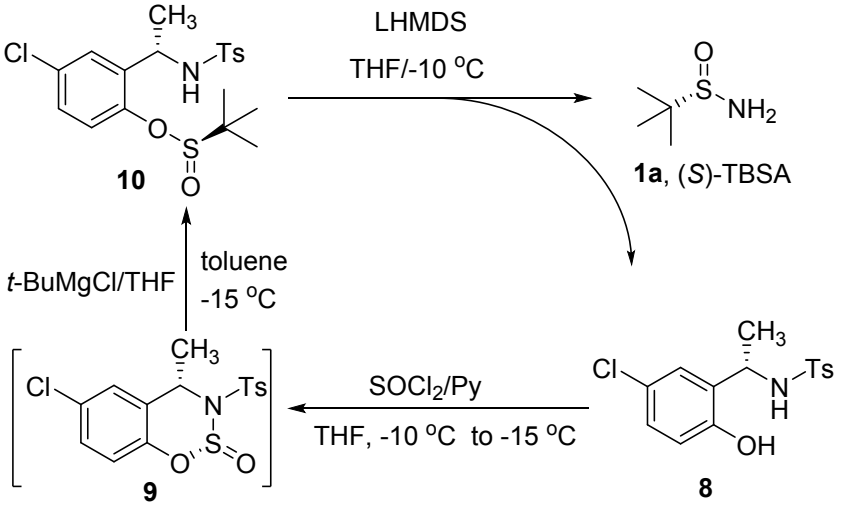
Further scale-up investigation showed that both methods (eqs (a) and (b), Scheme 2) share one common drawback in the synthesis of TBSA, which is the use of excess of $LiNH_2/NH_3$ (NH_3/Li) as a strong nucleophile in order to overcome the steric barriers in the cleavage of either S-S bond or S-O bond. *The NH_2Li/NH_3 needs to be freshly prepared in situ by portion-wise addition of a large excess of lithium metal to anhydrous NH_3 used as solvent at a reaction temperature of −78 °C.*[9] In the preparation of $LiNH_2$ on large scale, a very thick slurry was formed which causes serious agitation problems and potential safety concerns.[10] Furthermore, reaction work up is by slow evaporation of NH_3 until the reactor temperature reached from −78 °C to about room temperature. The NH_3 could also be trapped to another reactor at < −40 °C or by water. The quenching of the reaction with solid NH_4Cl is very exothermic and has to be added very slowly. Due to these drawbacks associated with the described procedure, the production of TBSA presents safety issues on large scale. The safe handling of the reaction and the treatment of the waste in an environmentally friendly manner are also concerns.



Scheme 2: Comparison of the two methods for the synthesis of chiral *tert*-butanesulfinamide

Our ultimate goal is to develop a process for the production of TBSA in a more practical and economic means by overcoming the above mentioned obstacles. The key elements to consider are avoiding low temperature reaction conditions and to replace NH_2Li/NH_3 with a milder nucleophile, such as lithium bis(trimethylsilyl)amide (LHMDS) that is an equivalent of "NH_2" functionality.[11] To achieve this, a new template with sulfinates containing an active S-O bond is needed, which can be cleaved by LHMDS. We, therefore, designed the second generation chiral template **8** that is based on a phenol backbone, from which optically pure chiral sulfinyl transfer agent benzo[1,3]oxathiozin-2-one **9** can be prepared effectively (Scheme 3).[12] Intermediate **9** contains S-N and S-O bonds with differentiated reactivity, so that *tert*-BuMgCl addition can selectively cleave the weaker S-N bond to afford the chiral sulfinate **10** in 90% yield and >99:1 dr. Subsequent treatment of **10** with LHMDS cleaves the following S-O bond to afford the desired (*S*)-TBSA in 85% yield and >99:1 er based on 100 g scale. The template **8** can be

recycled in excellent yield and can be used in the next cycle.[12] Most importantly, the entire process is performed under mild reaction conditions. In the following we describe the technical details in the process development for large scale production of TBSA.



Scheme 3: New method for the synthesis of TBSA under mild reaction conditions

Process Development

Production of chiral benzo[1,3]oxathiozin-2-one 9. Our first task was to develop a scalable process for the synthesis of **9** in good yield and high stereoselectivity, and to identify a reaction media for **9** that can facilitate the following *tert*-butylmagnesium chloride (*t*-BuMgCl) reaction in the synthesis of **10** without isolation of **9**. The established procedure[11] was first investigated on scale, in which **8** was treated with 1.3 equiv of thionyl chloride ($SOCl_2$) and 2.7 equiv of pyridine at 25 °C in THF, and the reaction afforded **9** in 98:2 dr and >95% yield. Upon completion, the reaction mixture was diluted with EtOAc and sodium bicarbonate ($NaHCO_3$) aqueous solution was added to quench the reaction. It turned out that this protocol suffers from a few issues. First, the quenching process is exothermic and produces large amount of gases from the reaction of $NaHCO_3$ with the excess $SOCl_2$. Second, the pH of the quenched mixture is about 6 and pyridine could not be efficiently removed from the organic phase with aqueous wash. The

presence of pyridine reduces the efficiency of product recovery. Third, concentration of the resulting organic phase by azeotrope distillation at 40 °C under vacuum to remove residue water causes 5-10% racemization of the title compound **9.**

Further optimization of reaction conditions led to the reduction of the stoichiometries of $SOCl_2$ and pyridine to 1.02 equiv and 2.3 equiv, respectively. The reaction was also conducted at milder temperature of 10 °C to 15 °C by slow addition of pyridine in 1 h to afford the product in a similar diastereoselectivity and yield. Under this condition, the reaction could be quenched with water instead of $NaHCO_3$. The resulting mixture has a pH of 3 to 4, which facilitates pyridine removal from the organic phase. The following organic phase concentration by distillation avoided the racemization of **9**, but decomposition of **9** to **8** occurred in this process. This issue was then solved by introducing 5% of sodium hydrogen phosphate (Na_2HPO_4) aqueous wash followed by another water wash, which gave a final pH of about 7. Under this condition, both the hydrolysis and racemization of **9** were found minimal during the distillation process.

Evaluation of solvent effect on the overall process found that toluene as co-solvent benefits the efficiency of solvent switching and the removing of water in the organic phase during the azeotrope distillation process. The selectivity and yield are not affected in the presence of toluene. Moreover, toluene can be used as solvent of **9** for next step reaction. Therefore, the optimal process was conducted by addition of $SOCl_2$ in toluene solution to a mixture of **8** in THF and pyridine at 10 °C to 15 °C. Upon work-up, the organic phase was distilled around 20 °C under vacuum to reach a KF below 0.03% affording a stable solution of **9** in a toluene solution. Three batches were carried out and the reactions in the synthesis of **9** gave a yield of up to 94% and 97.6:2.4 dr (Table 1).

Table 1: Scale up results in the production 9 and 10

Batch #	Scale of 8	Yield of 9 in toluene[a] (dr)	Yield of 10[b] (dr) isolated quantity	Purity of 10	Yield in 2 steps
1	15.0 kg	73.9%[c] (97.5:2.5)	87.0% (98.97:1.03) 12.73 kg	99.7A%	64.3%
2	15.0 kg	94.0% (97.5:2.5)	86.5% (98.39:1.61) 16.1 kg	99.7A%	81.3%
3	16.5 kg	87.9% (97.6:2.4)	85.4% (98.8:1.2) 16.35 kg	99.8A%	75.1%

[a] Assay yield based on HPLC analysis of product in toluene solution. [b] isolated yield based on the reaction from **9** to **10**. [c]Lower yield resulted from the first trial with low pH of quenched reaction mixture

Ring opening reaction for the synthesis of chiral sulfinate 10. Studies showed that the optimal temperature for the reaction of *t*-BuMgCl with **9** in toluene is around 15 °C. Initially, the reaction was performed by slow addition of 1.1 equiv of 1.0 M *t*-BuMgCl in THF to a toluene solution of **9.** The reaction completed within 10-20 min after addition as monitored by HPLC analysis. But compound **8** was found in the reaction mixture in more than 6%, which was resulted from the further addition of the extra Grignard to the product **10** by cleaving the S-O bond. To minimize this side reaction, the end point of Grignard addition was, therefore, determined by applying *in situ* React-IR to monitor the reaction.[13a] This monitoring method was found successful by avoiding overcharge of the Grignard reagents. The required amount of Grignard reagents is only 1.05 equiv, with which a clean reaction was observed with minimal formation of starting template **8.**

The quenching of the reaction is also important for a successful process. When $NaHCO_3$ solution was used to quench the reaction; it resulted in the deposition of a large mass of magnesium salts that cannot be conveniently filtered. Use of 50% aqueous ammonium acetate

was briefly evaluated; however, the pH of the quenched mixture remained at about pH 10, which caused a significantly racemization of **10** to form the undesired diastereomers of **10'** (Figure 1) at up to 18%. In order to control the pH to neutral, large amount of ammonium acetate solution was required, which significantly decreased batch volume efficiency. Alternatively, quenching with 20% of citric acid was found to provide clean phase separation, and the optimal condition was identified using 0.4 equiv of citric acid to achieve a final pH of around 6. Then the organic phase was washed with 5% of Na_2HPO_4 solution to reach the final pH to neutral, which suppressed the racemization and hydrolysis of the title product **10**.

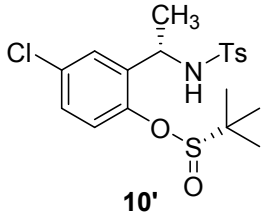
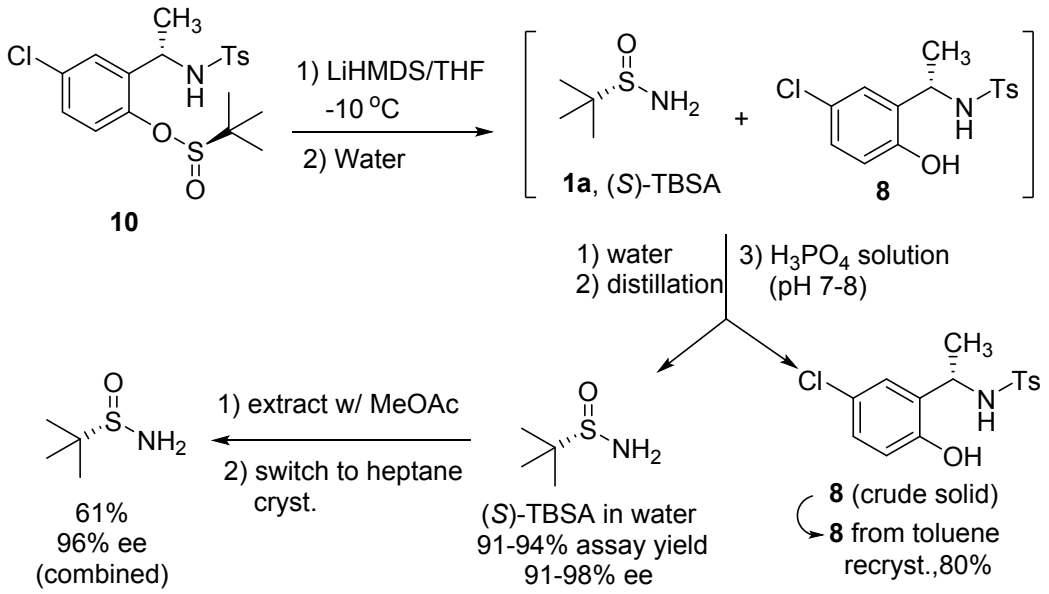


Figure 1: Structure of undesired diastereomer **10'**

Product **10** is a crystalline solid and isolation by crystallization was attempted. Heptane was found the optimal anti-solvent for the recrystallization. Therefore, the THF was first distilled off at about 40 °C to 45 °C, and the residual water was also removed under azeotrope. The crystallization of **10** in toluene was first generated by stirring the mixture for 2 h to form a slurry. To increase the yield, heptane was added. The crystallization was completed by first stirring the mixture at about 40 °C for 2 h, then cooled to 10 °C to 15 °C, and agitated for 2 h. Product **10** was collected as a white solid in 85% average yield from the Grignard reaction and up to 99: 1 dr, and >99% purity based on the results of the three executed batches (Table 1). The overall yield for the two-step reaction in the synthesis of **10** from **8** was also listed in Table 1.

Synthesis and isolation of TBSA and recovery of the template 8 (Scheme 4)



Batch #	Scale of **10**	Weight of (*S*)-TBSA aq solution	(*S*)-TBSA assay Wt.%	(*S*)-TBSA assay weight	Yield (er)
1	14.50 kg	61.90 kg	6.21 %	3.84 kg	93.9% (98.8:1.2)
2	14.24 kg	60.40 kg	6.27 %	3.79 kg	94.3 (95.5:4.5)
3	16.00 kg	76.35 kg	5.38 %	4.11 kg	91.1% (95.6:4.4)

Scheme 4: Synthesis of (*S*)-TBSA and recovery of template **8**

The synthesis of (*S*)-TBSA, its isolation, and the recovery of the template **8** is shown in Scheme 4. In contrast to earlier methods, the reaction of **10** with LHMDS was performed under mild conditions at –10 °C in THF. The reaction completed in 20-30 min after addition of LHDMS due to the active S-O bond of **10**. The reaction could be quenched by addition of water while keeping the internal temperature around –5 °C to give a reaction mixture of (*S*)-TBSA and the template **8**.[13b] Initial solubility study found that both compounds are soluble to some degree in most of organic solvents, and use of organic solvents cannot separate them efficiently. It turned out that (*S*)-TBSA has good solubility in water, but **8** is not.[13c] For better separation, both THF and trimethylsilanol formed from LHDMS need to be removed by distillation and it was

achieved at about 55 °C at 10-20 mmHg vacuums. The optimal crystallization condition was then found by adjusting the pH of the mixture at 7 to 8 by adding 25% phosphoric acid at about 10 °C, from which crude **8** was crystallized out as a nice slurry and collected by filtration. (*S*)-TBSA was collected as an aqueous solution in the filtrate in 91% to 94% assay yield and 91% to 98% ee (Scheme 4).

(*S*)-TBSA is very soluble in water and its recovery from aqueous solution was investigated. Initially, dichloromethane (DCM) was used as the extraction solvent. The aqueous phase was saturated with NaCl for efficient extraction. The recovery yield is about 75% after four extractions with equal volume of DCM to aqueous solution. Methyl acetate (MeOAc), however, was found as more efficient extraction solvent, and four extractions yielded a >98% recovery yield. For large scale production, this was accomplished by continuous extraction. The extracts was then distilled and switched to heptane, and (*S*)-TBSA was crystallized out from heptane.

The above three batches of (*S*)-TBSA in aqueous solution was combined and partial of it was extracted with MeOAc to give 137 kg extracts with 6.0 wt% of (*S*)-TBSA (8.21 kg in 93% ee).[13d] After switching the solvent to heptane, (*S*)-TBSA was isolated by crystallization in 61.4% yield (5.04 kg based on assayed amount of TBSA in MeOAc) and 96.2% ee.[12] One more recrystallization from MTBE/heptane (5.04 kg) furnishes (*S*)-TBSA (4.24 kg) in 84% yield and 99.2% ee.[13d]

The recovery of the template is straightforward. Crude **8** was first dissolved in THF and filtered to remove the inorganic salts followed by switching the solvent to toluene. The desired template **8** was recrystallized from toluene in more than 80% recovery yield and 99% ee, which was successfully used in the next cycle for the production of TBSA.

Conclusion

We have successfully developed a practical, safe and environmentally friendly process for the synthesis of enantiomerically pure *tert*-butanesulfinamide on 15 kg scale of chiral template **8**. The three-step process was conducted under mild reaction conditions in the pilot plant. Chiral TBSA was provided in about 40% overall yield and 99% ee starting from **8**. The modest overall yield is affected by the isolation of enantiomerically pure TBSA from MeOAc extract and the recrystallization, which is under further optimization. The template was recovered in 80% yield. The process employs environmentally friendly raw materials and eliminates the use of hazardous or toxic chemicals, such as liquid ammonia and lithium metal. The process is also performed under milder temperature. The current process generates about 187 kg waste/kg TBSA or 22.7 kg waste/mole of TBSA (cEF value).

Experimental

Synthesis of (2*S*,4*R*)-6-chloro-4-methyl-3-tosyl-3,4-dihydrobenzo[e][1,2,3]-oxathiazine 2-oxide 9. To a jacket reactor equipped with a nitrogen inlet and temperature probe was charged **8** (15.0 kg, 46.0 mol) under nitrogen followed by anhydrous THF (26.67 kg) and stirred to get a homogeneous solution. Pyridine (8.57 kg, 108.34 mol, 2.35 equiv) was added in one portion. After the solution was cooled to 10 °C to 15 °C, $SOCl_2$ (5.80 kg, 48.76 mol, 1.05 equiv) in toluene (54 kg) was added over 1 h while keeping the internal temperature below 10 °C. The reaction mixture was stirred at 10 °C to 15 °C for 30 min to complete the reaction. Water (30 kg) was added slowly while keeping the internal temperature around 0 °C. After phase separation, the aqueous layer was removed and the organic phase was washed with 5% sodium hydrogen phosphate (30 kg) followed by water (30 kg). The organic phase was concentrated by distillation under vacuum to get about 60.9 kg of product in toluene with a KF of 0.03%. The

content was assayed by HPLC analysis to give 16.08 kg of product in 94% yield and 97.5:2.5 dr. The mixture was then stored at 0 °C to 5 °C and used directly for next step reaction (product may precipitate out during storage).

Synthesis of 4-chloro-2-((*S*)-1-((4-methylphenyl)sulfonamido)ethyl)phenyl (*S*)-2-methylpropane-2-sulfinate 10. To the slurry of **9** (16.08 kg, 43.24 mol) in toluene from last step was added THF (20.8 kg), stirred to get a homogenous solution at ambient temperature. The mixture was cooled to –10 °C to –15 °C and *t*-BuMgCl (45.98 kg, 45.40 mol, 1.05 equiv) was added over 1.5 h while maintaining the internal temperature below –10 °C and stirred for 10-20 min to complete the reaction as monitored by *in-situ* React-IR. Toluene (13.5 kg) was added followed by 10% of aqueous citric acid solution (43.0 kg) over 30 min maintaining the internal temperature below –5 °C and then warmed to ambient temperature after addition. The phases were separated and the aqueous phase was removed. After washing with 5% of Na_2HPO_4 solution (33 kg) and water (32 kg), the organic phase was distilled under vacuum (10 to 20 mm Hg) until the internal temperature reached to about 40 °C to 45 °C to leave about 40 L of residue and stirred for 2 h to form a slurry. Heptane (13 kg) was added over 30 min and stirred for 2 h at about 40 °C. The mixture was cooled to 10 °C to 15 °C and stirred for 2 h and filtered. The wet cake was washed with toluene/heptane mixture (1:1, v/v) (13 kg) and dried to give the desired product **10** (16.10 kg) in 86.5% yield and 98.4:1.6 dr.

Synthesis of (*S*)-*tert*-butanesulfinamide (*S*)-TBSA. To a THF solution of LHMDS solution (55.10 kg, 1.3 M in THF, 77.56 mol, 2.30 equiv) at –10 °C was added **10** (14.5 kg, 33.72 mol) in THF (25.7 kg) slowly maintaining the internal temperature below –5 °C and stirred for 20 to 30 min to complete the reaction. Water (14.5 kg) was added at around –5 °C and then the reaction mixture was warmed to 20 °C to 30 °C. The content was distilled under vacuum (10-20 mm Hg)

until the internal temperature reached to about 55 °C to about 40 L left. Cooled the mixture to around 10 °C and 25% of phosphoric acid solution (4.35 kg) was added over 30 min. The mixture was warmed to 30 °C to 35 °C and stirred 2 h to form a slurry. Cooled the mixture to 20 °C and added 25 % of phosphoric acid solution (6.7 kg) until the pH of the solution was 7-8. The mixture was stirred 2 to 3 h and filtered and the wet cake was washed with water (14.5 kg) to give 61.9 kg of filtrate with 3.84 kg (6.21 wt%) of crude (*S*)-TBSA in 93.9% yield and 98.8:1.2 er. The wet cake was dried at 55 °C under vacuum to give 13.9 kg of crude **8** that was saved for later recovery process.

Recovery of (*S*)-TBSA from aqueous solution. An aqueous solution of (*S*)-TBSA (140 kg from combined three batches with 8.38 kg of *(S)*-TBSA based on assay (some aqueous solution was used for process development) was added 35 kg of NaCl and dissolved followed by extraction with methyl acetate (about 130 kg) to yield a solution of *(S)*-TBSA in methyl acetate (137 kg with about 8.21 kg of *(S)*-TBSA based on assay in 98% recovery yield and 93 % ee (Note: one batch of TBSA has low ee, which is produced during the process study). The content was distilled at about 60 °C to leave about 22 L of residue. Heptane (50 kg) was added and the mixture was continuously distilled until the internal temperature reached to about 85 °C to 90 °C to reach a volume of about 35 L. The mixture was cooled to 40 °C and stirred 2 h to form a slurry, and then cooled to 10 °C and stirred for 2 h. The slurry was filtered and the wet cake was dried at 30 °C under vacuum to give the product (6.57 kg crude with 5.04 kg of pure (*S*)-TBSA based on assay)[14] in 61.4% yield and 96.2 % ee (in one particular trial run, the ee of the resulting TBSA was only 93%. Normally, the process would provide >95% ee of (*S*)-TBSA and one crystallization is enough to get the product in >99% ee).

Recrystallization of (*S*)-TBSA if the optical purity is less than 99% ee. A reactor was charged (*S*)-TBSA (6.57 kg, 76.7wt%, 96% ee) and MTBE (24.31 kg) and the mixture was stirred at 35-45 °C to dissolve the product. Cooled the mixture to room temperature and the content was filtered and washed with MTBE (2 kg). The filtrate was concentrated to about 20 L and 8.51 kg of heptane was added while maintaining the internal temperature above 50 °C. The mixture was seeded with (S)-TBSA in >99% ee and cooled the content to 40 °C around 10 min and stirred at 40 °C for 2 h. The mixture was cooled to 10 °C, stirred for 1 h and filtered. The wet cake was washed with cooled heptane and dried at 30 °C to 35 °C overnight under vacuum to give (*S*)-TBSA as a white solid (4.26 kg) in 84.5% yield and 99.7% ee.

Recovery of template 8. To the crude template **8** (15.8 kg, 73.6%) was charged THF (25.84 kg) and stirred at 20 °C to 30 °C for about 30 min. The slurry was filtered and the cake was washed with THF (14.54 kg). The filtrate was distilled to about 26 L and toluene (41.87 kg) was added. The mixture was further distilled at about 60 °C to about 33 L and cooled to around 50 °C. The product was allowed to crystallize over 1 to 2 h. Cooled the slurry to 20 °C over 2 h and filtered and the wet cake was washed with toluene (60 mL) and dried at 60 °C for over 3 h under vacuum to give **8** (9.1 kg) in 78% recovery yield.

Supporting Information: Analytics for reaction monitoring and the analysis of enantiomeric purity.

Corresponding Authors: email: steve.han@boehringer-ingelheim.com

Notes:

Vendor's information for supplying of 8: Astatach (Chengdu) BioPhatmaceutical Corp.; 488 West Kelin Rdoad, Wenjiang Dist., Chengdu, Sichuan, 611130, P. R. China

Phone: +86-28-82666873; Fax: +86-28-82666739; Emai: sales@astatech.com.cn

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10. The synthesis of NH_2Li on large scale is a very tedious process that needs a long time to condense the ammonia under low temperature. The following addition of lithium metal is operated by slowly addition to avoid the reaction mixture heating up. The initiation for the formation of NH_2Li under $Fe(NO_3)_3$ catalyst is not consistent depending on the dryness of the ammonia solvent because ammonia tents to absorb moisture easily. With continuous addition of lithium, a very think slurry would suddenly form and lead to difficult agitation.

11. A similar strategy was report by Chelouan, A.; Recio, R.; Alcudia, A.; Khiar, N.; Fernandez, I. DMPA-Catalysed Sulfinylation of Diacetone-D-Glucose: Improved Method for the Synthesis of Enantiopure *tert*-Butyl Sulfoxides and *tert*-Butanesulfinamides, *Eur. J. Org. Chem*. **2014**, *31*, 6935-6944.

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commercially available and **8** is also available on large scale from the vendor and the process is to be published in due course (see note for vendor's information).

13. a) Refer Figure S3 for React-IR time-course spectrum; b) Refer Supporting Information for the calorimetry of the process progress. c) The solubility study was performed by dissolving a mixture of template **8** and TBSA in different solvents and then monitoring the content of them in the solution; d) Refer experimental procedures for detailed operation.

14. The crude TBSA contains some NaCl which resulted from the carry-over water from the aqueous extraction with MeOAc.