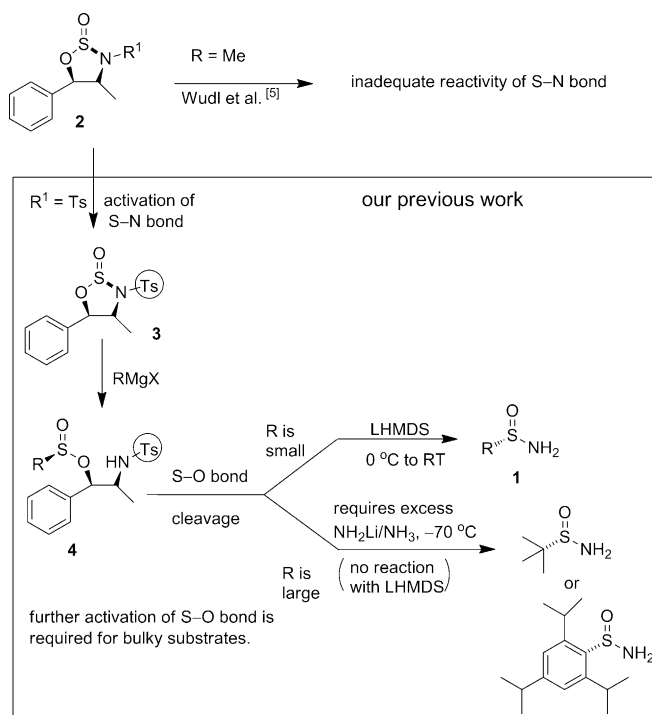


Design and Synthesis of Chiral Oxathiozinone Scaffolds: Efficient Synthesis of Hindered Enantiopure Sulfinamides and Sulfinyl Ketimines

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Chiral-sulfinamide-mediated (**1**; see Scheme 1) chemistry has become one of the most employed approaches for the synthesis of compounds containing chiral amine functionalities.^[1] Moreover, their utility has been extended to being used as chiral ligands for many catalytic asymmetric transformations.^[2] Although the potential of chiral sulfinamides has long been recognized, only a few methods have been developed for their synthesis. Among the prominent works are the method reported by Davis et al.^[3a] for the synthesis of *p*-toluenesulfinamide (*p*TSA) from Anderson's reagent, the method reported by Ellman and co-workers^[3b] for the synthesis of *tert*-butanesulfinamide (*t*BSA) from *tert*-butyl *tert*-butanethiosulfinate, and others.^[3c–e] However, these methods cannot meet the demand for accessing sulfinamides with diverse structures, which are required to fine-tune stereoselectivities in asymmetric synthesis. To meet this need, soon after the report from the group of Ellman, we designed and developed a versatile cyclic-oxathiozolidinone-based chiral sulfinyl-transfer agents which provide access to a range of sulfinamides with diverse structures (Scheme 1).^[4]

The success of this method hinged on the recognition that the reactivity of the cyclic oxathiozolidinone **2** could be activated by an electron-withdrawing substituent on the nitrogen atom (**3**), thus allowing for the facile cleavage of the S–N bond to provide the desired sulfinate intermediate **4**.^[4a] However the reaction conditions required for the cleavage of the S–O bond in **4** to liberate the desired sulfinamides relied heavily on the steric bulk of the R substituent.^[4c] While the S–O bond could be readily cleaved with LHMDS at 0 °C to room temperature to generate some



Scheme 1. Approaches for the synthesis of sulfinamides. Ts = 4-toluenesulfonyl.

sulfinamides, in the case of hindered substrates [e.g. $R = t\text{Bu}$ or triisopropylphenyl (TIPP)], the use of excess $\text{NH}_2\text{Li}/\text{NH}_3$ (Li/NH_3) was required to incorporate the amino group. Currently, $\text{NH}_2\text{Li}/\text{NH}_3$ is prepared in situ by portionwise addition of a large excess of solid Li metal to anhydrous NH_3 at reaction temperatures of less than –70 °C.^[4] These reaction conditions, in addition to the safe handling and disposal of waste generated by using $\text{NH}_2\text{Li}/\text{NH}_3$, have limited our ability to produce these important sulfinamides on large scale. Therefore, the efficient and practical synthesis of sterically hindered sulfinamides remained an unsolved problem in the field.

Considering that the steric environment provided by the bulky alkyl (e.g. *t*Bu) or aryl (e.g. TIPP) substituents of the sulfinamides is critical for obtaining high stereoselectivities,^[6,7] it was highly desirable to develop a more practical and cost-effective process for their synthesis by replacing $\text{NH}_2\text{Li}/$

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NH₃ with a safer and greener reagent such as LHMDS for the final S–O bond cleavage.^[4d,e] We envisioned that this goal could be achieved by tuning the S–O bond reactivity in our cyclic oxathiazolidinone templates. Herein, we report a new chiral sulfinyl-transfer agent containing a more activated S–O bond, from which both sterically hindered enantiopure sulfinamides and sulfinyl ketimines were prepared under mild reaction conditions.

To identify a template with a more reactive S–O bond, the reaction between the *tert*-butanesulfinates **5** and LHMDS was first investigated (Table 1). It is clear that S–OR bond

Table 1: Reactivity of the sulfinates **5** toward LHMDS.^[a]

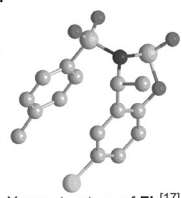
$\text{R}-\text{O}-\text{S}(=\text{O})-\text{O}-\text{C}(\text{CH}_3)_3 \xrightarrow[\text{2) H}_2\text{O}]{\text{1) LiN}(\text{SiMe}_3)_2, \text{THF}/0^\circ\text{C to RT}} \text{R}-\text{OH} + \text{H}_2\text{N}-\text{S}(=\text{O})-\text{O}-\text{C}(\text{CH}_3)_3$					
Entry	5	R	pK _a ^[b]	t [h]	Conversion [%] ^[c]
1	5a	Et	16	> 12	0
2	5b	PhCH ₂	15.4	> 12	0
3	5c	Ph	9.95	1.5	99
4	5c* (20% ee) ^[d]	Ph	9.95	1.5	99 (20% ee)
5	5d	4-ClC ₆ H ₄	9.38	< 1	99
6	5e	4-MeOC ₆ H ₄	10.2	4–5	95

[a] Reactions were conducted in THF by adding LHMDS at 0°C, stirring for 30 min, and then warming to ambient temperature. [b] See reference [8] for the pK_a values of ROH. [c] Based on HPLC analysis. [d] Based on HPLC analysis using a chiral stationary phase. THF = tetrahydrofuran.

reactivity is affected by the basicity of the leaving group or the pK_a value of the corresponding ROH (that is, the reactivity increases as the pK_a value of ROH^[8] decreases). In general, good correlation between the S–O bond strength and the electronegativity of the oxygen atom, as predicted based on the pK_a values of the selected alcohol substrates from which the sulfinates were synthesized, was observed. For example, no reaction was observed for the sulfinates derived from ethanol or benzyl alcohol (entries 1 and 2), however, the reaction of **5c**, derived from phenol, was complete in 1.5 hours, thus providing the desired product in quantitative yield (entry 3). The presence of an electron-withdrawing substituent on the phenol ring (**5d**) increased the reactivity (entry 5), whereas the reactivity was attenuated with an electron-donating group (**5e**; entry 6). The effect of sterics on the reactivity of the S–O bond was also observed.^[8f] Application of a chiral sulfinates (**5c***, 20% ee)^[9] in this transformation demonstrated that no erosion of enantiomeric purity occurred under the present reaction conditions (entry 4).

With successful identification of a more reactive S–O bond derived from a phenol-based template, the sulfinyl-transfer agent benzoxathiazine 2-oxide **7** (Table 2) was designed. It was envisioned that optically pure **7** could be efficiently accessed on large scale from the simple and commercially available chiral aminophenol **6**.^[10a] After screening several reaction conditions,^[10b] it was found that slow addition of pyridine to a solution of **6a** and SOCl₂ at

Table 2: Conditions surveyed for the synthesis of **7**.^[a]

$\text{R}'-\text{C}_6\text{H}_3(\text{OH})-\text{NH}-\text{Ts} \xrightarrow[\text{base/THF}]{\text{SOCl}_2} \text{R}'-\text{C}_6\text{H}_3(\text{O}-\text{S}(=\text{O})-\text{N}-\text{Ts})$		$\text{6a: R}' = \text{H}$ $\text{6b: R}' = \text{Cl}$		7a,b			
Entry	6	R'	Base	T [°C]	7	d.r. ^[b]	
1	6a	H	pyridine	–40	7a	98:2	
2	6a	H	pyridine	–15	7a	98:2	
3	6a	H	pyridine	0	7a	97:3	
4	6b	Cl	pyridine	–40	7b	99:1	
5	6b	Cl	pyridine	–10	7b	98:2	
6	6b	Cl	pyridine	0	7b	98:2	

[a] Reactions were performed in THF with full conversion. Refer to the Supporting Information for further details. [b] The d.r. was determined by ¹H NMR analysis.

–40°C provided the desired product with excellent selectivity (entry 1). Notably, the reaction temperature has negligible effect on the selectivity, with minimal erosion of the d.r. value noted when the reaction temperature was increased from –40°C to 0°C (entries 2 and 3). Despite the promising profile of this chiral template, crystallization of **7a** to diastereomerically pure material proved highly challenging. Modification of the sulfonyl group on the nitrogen atom did not improve the crystallinity of **7a**.^[10c] The *para*-chloro-substituted phenol derivative **6b** that has been used successfully in the synthesis of P-chiral phosphine oxides^[10a] was subsequently examined. Analogous reaction conditions afforded **7b** with equally high selectivity (entry 4). Again, raising the temperature did not adversely affect the selectivity (entries 5 and 6). In contrast to **7a**, **7b** was readily obtained by recrystallization from EtOAc/heptanes in diastereomerically pure form (> 99.5:0.5 d.r.). From a process control point of view, scale-up was conducted at –10°C to yield **7b** (2.0 kg) in 87% yield and 99.6:0.4 d.r. with an *S* configuration at the sulfur center as confirmed by a single-crystal X-ray structure.

With sufficient quantities of the chiral template **7b**, the evaluation of the synthesis of (*R*)-*t*BSA (**1a**) by cleavage of the S–N bond with *tert*-butylmagnesium chloride and subsequent cleavage of the S–O bond upon addition of LHMDS was initiated (Table 3). Addition of *t*BuMgCl to **7b** in THF at –30°C selectively cleaved the S–N bond, thus providing the diastereomerically pure, stable, and crystalline sulfinates **8a** in 91% yield. Gratifyingly, treatment of **8a** with LHMDS in THF at –10°C→0°C cleaved the S–O bond effectively in quantitative conversion. After quenching the reaction with aqueous NH₄Cl solution, enantiopure (*R*)-*t*BSA (**1a**) was isolated in 90% yield and 99.7:0.3 e.r. Temperatures up to –10°C for the Grignard addition and 0°C for the LHMDS addition did not result in any erosion of the enantiomeric purity of **1a**.

This efficient and simple method was further demonstrated in the synthesis of other sterically hindered sulfinamides (Table 3). A variety of structurally diverse and sterically hindered alkyl and aryl sulfinamides were readily

Table 3: Synthesis of sterically hindered sulfonamides.^[a]

Entry	RMgX	8 Yield [%]	1	Yield [%]	e.r. ^[b]
1		91 (8a)		90	99.7:0.3
2		85 (8b)		84	98.8:1.2
3		75 (8c)		73	98.8:1.2
4		88 (8d)		91	99:1
5		56 (8e) ^[d]		83	99.9:0.1

[a] Refer to the Supporting Information for detailed reaction conditions. [b] Enantiomeric ratios were determined by HPLC analysis using a chiral stationary phase. [c] With 0.5 equiv of $\text{MgBr}_2 \cdot \text{OEt}_2$ added. [d] Reaction conducted in CH_2Cl_2 in the presence of bis[2-(*N,N*-dimethylamino)-ethyl]ether.^[13] [e] With 0.2 equiv of $\text{MgBr}_2 \cdot \text{OEt}_2$ added.

synthesized in high yields and e.r. values. Notably, the chiral sulfonamide **1d** has never been previously prepared (entry 4).^[12] In the case of **1d** and **1e**, a slight decrease in enantiopurity was observed when the LHMDS addition was performed at higher temperature. An excellent e.r. value (99:1) was obtained if the addition was started at -78°C or by addition of 0.2 equivalents of $\text{MgBr}_2 \cdot \text{OEt}_2$ (entry 5). Additionally, it has been demonstrated that the double nucleophilic substitution can be carried out by a one-pot protocol.^[13]

To highlight the utility of this new process, the scope of this chemistry was extended to the direct synthesis of sterically hindered chiral sulfinyl ketimines (**9**) by addition of an imine nucleophile to the sulfinate ester **8** (Table 4). Sulfinyl ketimines are key intermediates in the synthesis of chiral amine compounds and their synthesis has been carried out by condensation of a ketone with sulfonamide in the presence of a Lewis acid, such as tetraalkoxytitanium.^[1c,d] However, when sterically hindered ketones are employed, the yield decreases even under forcing reaction conditions.^[14] Therefore, the synthesis of **9** from **8** would allow for an efficient and direct synthesis of sterically hindered sulfinyl ketimines.

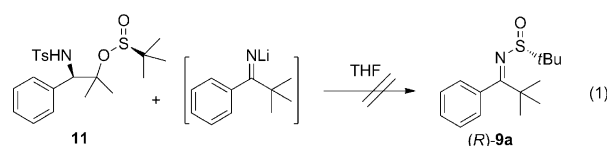
The synthesis of (*S*)-*N*-(*tert*-butyl-phenylmethylidene)-2-*tert*-butane-2-sulfonamide (**9a**) was first explored. Addition of *t*BuLi at -78°C to benzonitrile in THF generated the lithium imide, which was then slowly added to **8a** in THF at -78°C . This hindered lithiumimide readily cleaves the S–O bond to yield sulfinyl ketimine **9a** in good yield upon isolation and greater than 99:1 e.r., exclusively as one *E/Z* isomer (Table 4, entry 1). Increasing the reaction temperature led to decreased

Table 4: Synthesis of sterically hindered chiral ketimines and amines.

Entry	R	9	Yield [%]	e.r. ^[a]	10	Yield [%]	d.r. ^[b]
1		9a	85	99.1:0.9	10a	99	93:7
2		9c	91	99.5:0.5	10c	95	94:6
3		9d	78	98.4:1.6	10d	98	95:5
4		9e	71	98.4:1.6	10e	97	> 99:1 ^[c]

[a] Based on HPLC analysis using chiral stationary phase. [b] Based on ^1H NMR analysis. [c] Only one diastereomer was observed.

enantiopurity (that is, 90:10 e.r. for **9a** at -40°C). Conversely, under the same reaction conditions, the synthesis of **9a** using the sulfinate **11** failed to provide the desired product and no reaction was observed [Eq. (1)]. This result clearly demonstrates the higher reactivity of the S–O bond in the phenol backbone.

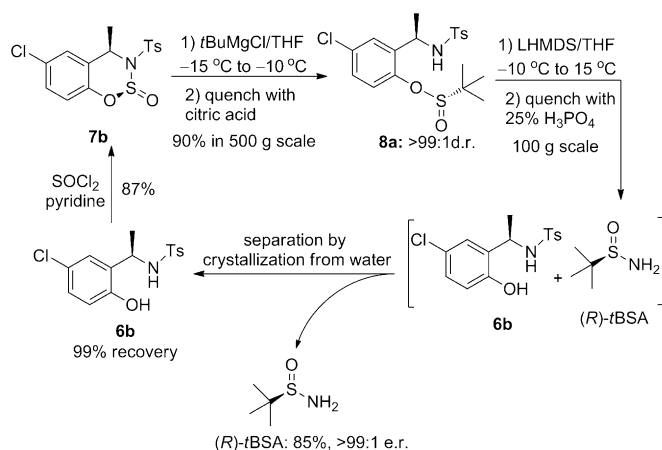


As presented in Table 4, a variety of hindered ketimines were prepared by following this sequence. Ketimines with different alkyl functionalities (**9a,c,d**) were prepared in good yields and excellent selectivities. The ketimine **9e**, containing a hindered aryl group, was also prepared in good yield and 98:2 e.r. (Table 4, entry 4). For comparison, only 20% yield was obtained from the condensation reaction between TIPP sulfonamide (TIPPSA) and the ketone. It is worth pointing out that ketimines with different sulfinyl groups would provide an avenue for fine-tuning the stereoselectivity in the synthesis of chiral amines by either reduction or nucleophilic addition. While direct synthesis of nonhindered chiral ketimines using Anderson's reagent was previously reported, our newly developed chiral template allows an efficient and direct synthesis of structurally diverse bulky chiral sulfinyl ketimines by stereoselective substitution of a chiral sulfinate.^[15]

The reduction of **9** in the synthesis of the chiral amine **10** was initially studied to understand the effect of the alkyl and arylsulfinyl groups on the stereoselectivity. Reduction of **10a** with different reducing reagents was first investigated. Among the reagents examined (e.g. NaBH_4 , L-selectride, and 9-BBN), NaBH_4 in THF gave the best selectivity, thus

providing **10a** in 93:7 d.r.^[16] and almost quantitative yield (Table 4, entry 1). The same reaction conditions were then applied to other substrates. Similar selectivities were observed when other alkylsulfinyl groups were used (**10c,d**; entries 2 and 3). However, better selectivity was observed when the TIPPS sulfinyl group was used, and only one diastereomer of **10e** was observed. The effect of the sulfinyl group on the selectivity is obvious and the application of this method in the synthesis of other chiral amines under different reactions conditions is under further exploration.

The potential of this powerful method for the large scale synthesis of (*R*)-*t*BSA was also demonstrated. The preliminary process has been conducted on 100 g scale as shown in Scheme 2. Reaction of **7b** with *t*BuMgCl at -15°C gave **8a** in up to 90% yield upon isolation. Treatment of **8a** with



Scheme 2. Practical process for large scale synthesis of (*R*)-*t*BSA.

LHMDS at $-10 \rightarrow 15^{\circ}\text{C}$ and subsequent quenching with 25% phosphoric acid resulted in a mixture of **6b** and (*R*)-*t*BSA. After switching the solvent to water, **6b** and (*R*)-*t*BSA were effectively separated by crystallizing out **6b** while leaving (*R*)-*t*BSA in the aqueous phase. The auxiliary **6b** was recovered in 99% yield and can be used in the next production cycle. The (*R*)-*t*BSA was then extracted using CH_2Cl_2 in 85% yield and 99.5:0.5 e.r. Clearly, this protocol is operationally simple, mild, and practical, and is commercially feasible for the synthesis of (*R*)-*t*BSA on large scale.

In summary, through the studies of S–O bond reactivities derived from different alcohols, we have developed a chiral amine template based on a phenol backbone (**6**), from which the optically pure chiral sulfinyl-transfer agent benzo-[1,3]oxathiazin-2-one **7** was prepared effectively. The intermediate **7** contains S–N and S–O bonds with differentiated reactivities that allow the synthesis of sterically hindered chiral sulfinamides and sulfinyl ketimines under mild reaction conditions. This method is practical, efficient, green, and has the potential to provide an economical commercial process for the synthesis of enantiopure bulky sulfinamides, such as *t*BSA and TIPPSA.

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- [1] a) C. H. Senanayake, Z. Han, D. Krishnamurthy in *Organosulfur Chemistry in Asymmetric Synthesis* (Eds.: T. Toru, C. Bolm), Wiley-VCH, Weinheim, **2008**, p. 234; b) C. H. Senanayake, D. Krishnamurthy, Z.-H. Lu, Z. Han, I. Gallou, *Aldrichimica Acta* **2005**, 38(3), 93–104; c) Z. Han, D. C. Reeves, D. Krishnamurthy, C. H. Senanayake in *Comprehensive Chirality*, Vol. 3 (Eds.: E. M. Carreira, H. Yamamoto), Elsevier, Amsterdam, **2012**, pp. 560–600; d) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, 110, 3600–3740; e) P. Zhou, B.-C. Chen, F. A. Davis, *Tetrahedron* **2004**, 60, 8003–8030.
- [2] a) K. L. Kimmel, J. D. Weaver, M. Lee, J. A. Ellman, *J. Am. Chem. Soc.* **2012**, 134, 9058–9061, and references therein; b) T.-S. Zhu, S.-S. Jin, M.-H. Xu, *Angew. Chem.* **2012**, 124, 804–807; *Angew. Chem. Int. Ed.* **2012**, 51, 780–783; c) Y. Wang, X. Feng, H. Du, *Org. Lett.* **2011**, 13, 4954–4957.
- [3] a) F. A. Davis, A. J. Friedman, E. W. Kluger, *J. Am. Chem. Soc.* **1974**, 96, 5000–5001; b) G. Liu, D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1997**, 119, 9913–9914; c) D. A. Cogan, G. Liu, K. Kim, B. J. Backes, J. A. Ellman, *J. Am. Chem. Soc.* **1998**, 120, 8011–8019; d) J. L. García Ruano, I. Fernández, M. del Prado Catalina, A. A. Cruz, *Tetrahedron: Asymmetry* **1996**, 7, 3407–3414; e) N. Khiar, I. Fernández, F. Alcudia, *Tetrahedron Lett.* **1994**, 35, 5719–5722.
- [4] a) Z. Han, D. Krishnamurthy, P. Grover, Q. K. Fang, C. H. Senanayake, *J. Am. Chem. Soc.* **2002**, 124, 7880–7881; b) Z. Han, D. Krishnamurthy, P. Grover, Q. K. Fang, X. Su, H. S. Wilkinson, Z. H. Lu, D. Magiera, C. H. Senanayake, *Tetrahedron* **2005**, 61, 6386–6408; c) Z. S. Han, A. M. Meyer, Y. Xu, Y. Zhang, R. Busch, S. Shen, N. Grinberg, B. Z. Lu, D. Krishnamurthy, C. H. Senanayake, *J. Org. Chem.* **2011**, 76, 5480–5484; d) I. Fernández, V. Valdivia, B. Gori, F. Alcudia, E. Alvarez, N. Khiar, *Org. Lett.* **2005**, 7, 1307–1310; e) I. Fernández, V. Valdivia, N. Khiar, *J. Org. Chem.* **2008**, 73, 745–748.
- [5] a) F. Wudl, T. B. K. Lee, *J. Chem. Soc. Chem. Commun.* **1972**, 61–62; b) F. Wudl, T. B. K. Lee, *J. Am. Chem. Soc.* **1973**, 95, 6349–6358.
- [6] D. A. Cogan, G. Liu, J. A. Ellman, *Tetrahedron* **1999**, 55, 8883–8904.
- [7] Z. Han, R. Busch, K. R. Fandrick, A. Meyer, Y. Xu, D. Krishnamurthy, C. H. Senanayake, *Tetrahedron* **2011**, 67, 7035–7041.
- [8] a) P. Ballinger, F. A. Long, *J. Am. Chem. Soc.* **1960**, 82, 795–798; b) G. A. Fasman, *Handbook of Biochemistry and Molecular Biology*, CRC, Cleveland, OH, **1997**; c) R. Stewart, R. Van der Linden, *Can. J. Chem.* **1960**, 38, 2237–2255; d) I. S. Chang, J. T. Price, A. J. Tomlinson, C. J. Willis, *Can. J. Chem.* **1972**, 50, 512–520; e) M. M. Fickling, A. Fischer, B. R. Mann, J. Packer, J. Vaughan, *J. Am. Chem. Soc.* **1959**, 81, 4226–4230; f) Refer to Table 1 in the Supporting Information for detailed information.
- [9] a) M. Wakayama, J. A. Ellman, *J. Org. Chem.* **2009**, 74, 2646–2650; b) H. M. Peltier, J. W. Evans, J. A. Ellman, *Org. Lett.* **2005**, 7, 1733–1736.
- [10] a) Z. S. Han, N. Goyal, M. A. Herbage, J. D. Sieber, B. Qu, Y. Xu, Z. Li, J. T. Reeves, J.-N. Desrosiers, S. Ma, N. Grinberg, H. Lee, H. P. R. Mangunuru, Y. Zhang, D. Krishnamurthy, B. Z. Lu, J. J. Song, G. Wang, C. H. Senanayake, *J. Am. Chem. Soc.* **2013**, 135, 2474–2477; and refer to the Supporting Information for the synthesis of chiral amines; b) Refer to Table 2 in the Supporting

- Information for detailed information; c) 4-chlorophenyl-, 2-mesityl-, and 2-methylphenylsulfonyl groups were investigated.
- [11] (*R*)-*t*BSA was obtained from the reaction of **7a** with *t*BuMgCl and subsequent addition of LHMDs. The *S* configuration depicted was based on double inversion at sulfur atom for nucleophilic substitution.
- [12] The reaction for the synthesis of **1d** was conducted in the presence of 0.5 equivalents of MgBr₂·OEt₂ to improve the selectivity.
- [13] See the Supporting Information for detailed experimental information. X. Wang, L. Zhang, X. Sun, Y. Xu, D. Krishnamurthy, C. H. Senanayake, *Org. Lett.* **2005**, 7, 5593–5595.
- [14] a) Z. Han, D. Krishnamurthy, C. H. Senanayake, *Org. Process Res. Dev.* **2006**, 10, 327–333; b) G. K. Datta, J. A. Ellman, *J. Org. Chem.* **2010**, 75, 6283–6285.
- [15] a) R. Annunziata, M. Cinquini, F. Cozz, *J. Chem. Soc. Perkin Trans. 1* **1982**, 339–343; b) D. H. Hua, S. W. Miao, J. S. Chen, S. Iguchi, *J. Org. Chem.* **1991**, 56, 4–6; c) L. Storace, L. Anzalone, P. N. Confalone, W. P. Davis, J. M. Fortunak, M. Giangiordano, J. J. Haley, Jr., K. Kamholz, H.-Y. Li, P. Ma, W. A. Nugent, R. L. Parsons, Jr., P. J. Sheeran, C. E. Silverman, R. E. Waltermire, C. C. Wood, *Org. Process Res. Dev.* **2002**, 6, 54–63.
- [16] The stereochemistry of the chiral amines was assigned according to: J. T. Colyer, N. G. Andersen, J. S. Tedrow, T. S. Soukup, M. M. Faul, *J. Org. Chem.* **2006**, 71, 6859–6862.
- [17] See the Supporting Information for crystallographic data of **7b**.