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Recycling the *tert*-Butanesulfinyl Group in the Synthesis of Amines Using *tert*-Butanesulfinamide

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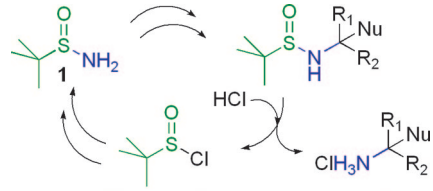

A practical process for recycling the *tert*-butanesulfinyl group upon deprotection of *N*-*tert*-butanesulfinyl amines has been achieved. Treatment of *N*-*tert*-butanesulfinyl amines with HCl in cyclopentyl methyl ether results in complete conversion to *tert*-butanesulfinyl chloride and the corresponding amine hydrochloride salt, which is isolated by filtration in analytically pure form and in quantitative yield. Treatment of the resulting sulfinyl chloride solution with aqueous ammonia then provides analytically pure *tert*-butanesulfinamide in 97% yield. Alternatively, the *tert*-butanesulfinyl chloride solution can be treated with ethanol and catalytic quinidine as a sulfinyl transfer catalyst to provide a cyclopentyl methyl ether solution of ethyl *tert*-butanesulfinate with 88% ee. Addition of $NaNH_2$ in ammonia followed by simple trituration of the product with octane provides *tert*-butanesulfinamide with 99% ee and in 67% overall isolated yield based upon the starting *N*-*tert*-butanesulfinyl amine.

Introduction

tert-Butanesulfinamide (**1**) is an extremely versatile chiral amine reagent that is now used in a number of the most popular approaches for the asymmetric synthesis of amine-containing compounds.[1] Key features of these methods include (a) the direct condensation of **1** with a wide range of aldehydes and ketones in high yields under mild conditions to give stable *N*-sulfinyl imines **2**, (b) the electrophilicity of imines **2** that enables diverse nucleophiles to be added cleanly and, when stereocenters are introduced, with high diastereoselectivity, and (c) the convenient and high-yielding cleavage of the *N*-sulfinyl group to provide the desired amine products **4** (Scheme 1).

The removal of the sulfinyl group is typically performed with an acid such as hydrogen chloride in a protic solvent such as methanol, ethanol, or water[2] to produce sulfinate ester or sulfinic acid byproducts ±**5** as undesired waste. The recovery of the sulfinyl group with recycling back to the *tert*-butanesulfinamide starting material has the potential to significantly enhance the utility and practicality of sulfinamide chemistry, particularly for large-scale applications for which it would result in significant waste reduction and reduced starting material costs. Herein, we report an extremely straightforward single-step recycling of the sulfinyl group to provide racemic **1** with near quantitative recovery, as well as a practical two-step procedure that proceeds via dynamic kinetic resolution to provide (*R*)-**1** in 99% ee and 67% overall yield.

Results and Discussion

Racemic rather than enantiomerically pure *tert*-butanesulfinamide has been used in the synthesis of a large number of different amines because either the desired amine product is achiral,[3] the racemic rather than enantiomerically pure product is desired,[4] or the sulfinyl group is not the stereocontrolling element in the addition step.[5] For these applications, we

(1) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39. (c) Kochi, T.; Mukade, T.; Ellman, J. A. *J. Syn. Org. Chem. Jpn.* **2004**, *62*, 128. (d) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869.

(2) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883.

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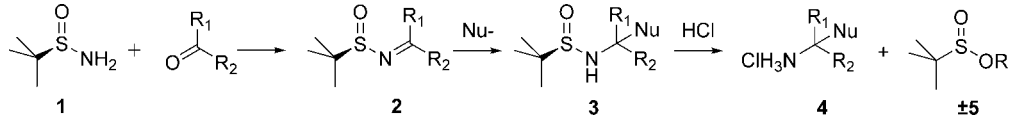
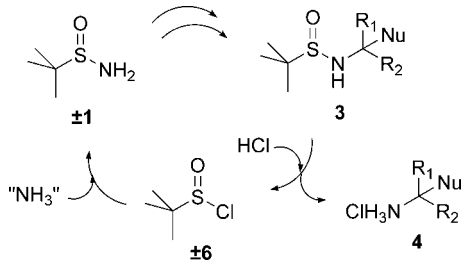
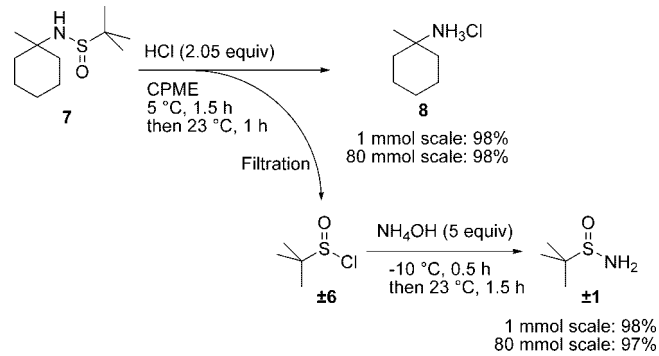
SCHEME 1. Asymmetric Synthesis of Amines Using *tert*-Butanesulfinamide



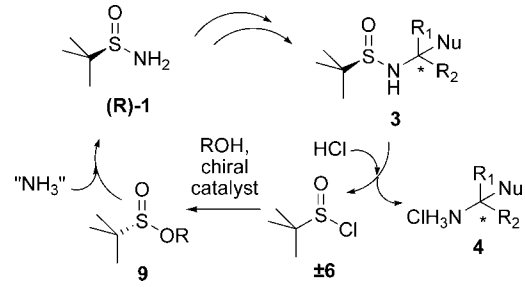
SCHEME 2. Recovery of Racemic *tert*-Butanesulfinamide



SCHEME 3. Recovery of Racemic *tert*-Butanesulfinamide



SCHEME 4. Recovery of Enantiomerically Pure *tert*-Butanesulfinamide



envisioned that a highly practical and efficient method for the recovery of the sulfinyl group with recycling to racemic **1** could be achieved by performing the HCl-mediated cleavage step in an aprotic solvent to provide the desired amine hydrochloride **4** and sulfinyl chloride **6**, which is not configurationally stable and rapidly racemizes (Scheme 2). Assuming that sulfinyl chloride **6** could indeed be formed cleanly and in high yield, separation from the amine hydrochloride **4** followed by addition of an ammonia source should then enable the complete recycling of racemic **1**.

An acid-stable aprotic solvent is required not only to enable the preparation of the sulfinyl chloride but also to effect efficient precipitation of the desired amine hydrochloride salt **4** and, consequently, separation from the sulfinyl chloride solution. Cyclopentyl methyl ether (CPME) was selected because it is an inexpensive and safe nonpolar solvent that has seen increasing use in industrial applications.[6] Alternative nonpolar ethereal solvents that would also efficiently precipitate amine hydrochloride **4**, such as diethyl ether and *tert*-butyl methyl ether, were rejected due to high flammability and instability to HCl, respectively.

Tertiary carbinamine derivative **7** (Scheme 3) was selected as a model substrate due to the large number of instances where pharmaceutical companies have employed racemic **1** for the preparation of cyclic tertiary carbinamines.[3] Sulfinyl group cleavage from compound **7** was carried out using a slight excess (2.05 equiv) of hydrogen chloride in CPME for 1 h at 0 °C followed by 1 h at 23 °C. Simple filtration through a glass filter using positive nitrogen pressure then provided analytically pure amine hydrochloride **8** in very high yield along with a solution of sulfinyl chloride **6** in CPME. Addition of the solution of sulfinyl chloride to ammonium hydroxide at −10 °C resulted in the formation of racemic **1**, which was isolated with virtually complete recovery from **7** in analytically pure form simply by concentration, dilution with 1/9 EtOAc/hexanes, followed by filtration to remove the NH_4Cl byproduct, and reconcentration. The scale independence of this procedure from 1 to 80 mmol of **7** indicates that this process should be successful on considerably larger scales. This straightforward procedure enables the recovery of the sulfinyl group with conversion back to *tert*-butanesulfinamide (**1**) with almost no material loss.

With the successful recovery of the sulfinyl group with recycling to racemic **1** achieved, we next directed our efforts to the more challenging recovery of highly enantiomerically enriched material.[7] As illustrated in Scheme 4, we envisioned that this could be accomplished by dynamic kinetic resolution of **6** to provide enantiomerically enriched sulfinate ester **9** followed by conversion back to sulfinamide (*R*)-**1**.[8]

Several quite selective methods for the dynamic kinetic resolution of configurationally unstable *tert*-butanesulfinyl chlo-

(3) (a) Velazquez, F.; Bogen, S. L.; Arasappan, A.; Venkatraman, S.; Njoroge, F. G.; Shih, N.-Y. PCT Patent Appl. WO 2008124148, 2008. (b) Baeschlin, D. K.; Sedrani, R.; Flohr, S.; Namoto, K.; Sirockin, F.; Gessier, F.; Fenton, G.; Beswik, M. C.; Clark, D. E.; Waszkowycz, B. PCT Int. Appl. WO 2008077597, 2008. (c) Plettenburg, O.; Lorenz, K.; Goerlitzer, J.; Loehn, M.; Biscarrat, S.; Jeannot, F.; Duclot, O. PCT Int. Appl. WO 2008077556, 2008. (d) John, V.; Maillard, M.; Tucker, J.; Aquino, J.; Hom, R.; Tung, J.; Dressen, D.; Shah, N.; Neitz, R. J. PCT Int. Appl. WO 2005087215, 2005. (e) Fujii, H.; Nishimura, Y.; Nitta, A.; Sakami, S.; Nakaki, J.; Kozono, H. PCT Int. Appl. WO 2007063928, 2007. (f) John, V.; Maillard, M.; Tucker, J. PCT Int. Appl. WO 2005087752, 2005. (g) Davies, T. G.; Garrett, M. D.; Boyle, R. G.; Collins, I. PCT Int. Appl. WO 2007125321, 2007. (h) Caldwell, J. J.; Collins, I. *Synlett* **2006**, 2565. (i) Nitta, A.; Fujii, H.; Sakami, S.; Nishimura, Y.; Ohyama, T.; Satoh, M.; Nakaki, J.; Satoh, S.; Inada, C.; Kozono, H.; Kumagai, H.; Shimamura, M.; Fukazawa, T.; Kawai, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5435.

(4) Naskar, D.; Roy, A.; Seibel, W. L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 8865.

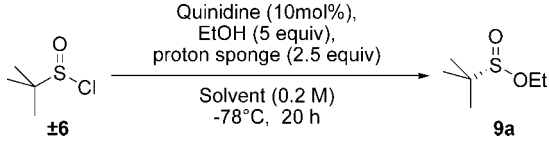
(5) McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1645.

(6) Watanabe, K.; Yamigiwa, N.; Torisawa, Y. *Org. Process Res. Dev.* **2007**, *11*, 251.

(7) We also tried the direct conversion of *tert*-butanesulfinyl chloride to *tert*-butanesulfinamide by using ammonia or ammonium hydroxide with sulfinyl transfer catalysts, but so far, this procedure has not been rendered enantioselective.

(8) For leading references demonstrating complete inversion of stereochemistry in the addition of amide anions as well as carbanions to *tert*-butanesulfinate esters, see: (a) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880. (b) Khiar, N.; Fernandez, I.; Alcudia, F. *Tetrahedron Lett.* **1994**, *35*, 5719. (c) Drabowicz, J.; Dudzinski, B.; Mikolajczyk, M.; Wieczorek, M. W.; Majzner, W. R. *Tetrahedron: Asymmetry* **1998**, *9*, 1171.

TABLE 1. Solvent Screen Using Ethanol and Quinidine



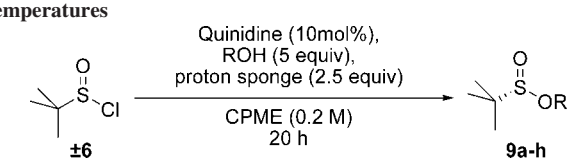
entry	solvent	yield (%)[a]	ee (%)[b]
1	CH_2Cl_2	57	26
2	AcOEt	-[c]	70
3	toluene	23	77
4	THF	30	79
5	CPME	36 (69)[d]	91 (90)[d]

[a] Yields determined by NMR with 2,6-dimethoxytoluene as an internal standard. [b] Enantiomeric excess determined by chiral HPLC. [c] Yield could not be determined due to overlapping of ethyl acetate and ethyl sulfinate NMR peaks. [d] Reaction time was 40 h.

ride using an alcohol nucleophile and a chiral sulfinyl transfer catalyst have been reported.[9] However, these procedures are not practical and cost-effective from an industrial standpoint due to the necessity of relatively high molecular weight alcohols or multistep catalyst preparation. We consequently focused on quinidine as a commercially available and inexpensive sulfinyl transfer catalyst and ethanol as a practical and low molecular weight nucleophile (Table 1). Proton sponge (1,8-bis(dimethylamino)naphthalene) was employed as the HCl scavenger because we had previously determined that other common amine bases catalyze nonselective sulfinate ester formation.[9a] We began by examining various solvents at −78 °C (Table 1). Using dichloromethane resulted in a moderate yield and low enantiomeric purity of the ethyl sulfinate **9a** (entry 1), with the low selectivity due to a competitive background reaction. Ethyl acetate, toluene, and THF resulted in slightly lower yields but improved selectivities (entries 2−4). By using cyclopentyl methyl ether (CPME) as the solvent, the sulfinate ester **9a** was obtained with high enantiomeric purity (entry 5). Longer reaction times resulted in increased yields; however, the reaction did not proceed to completion even after 40 h (entry 5).

We next evaluated higher reaction temperatures using several simple alcohol nucleophiles with CPME as solvent in order to improve the yield while maintaining high product enantiomeric purity (Table 2). When EtOH was employed, the temperature could be raised to −50 and even −40 °C to provide the ethyl sulfinate **9a** in a quantitative yield with only minimal reduction in selectivity (entries 1 and 2). The reaction performed at −20 °C also resulted in an excellent yield, but a more significant drop in selectivity was observed (entry 3). Use of PrOH and BuOH at −50 °C (entries 4 and 7) provided slightly higher selectivity (88−89% ee) than was observed for EtOH (entry 1), but the yields were a bit lower. Moreover, when these longer chain alcohols were employed at or above −40 °C, a more significant drop in the enantiomeric purity of the sulfinate ester products was observed (entries 5, 6, 8, and 9). Thus, we chose −50 °C as the optimal reaction temperature and evaluated additional alcohol nucleophiles with varying steric properties and acidities. Increasing the steric bulk of the alcohol resulted in lower yields and did not increase the enantiomeric purity of

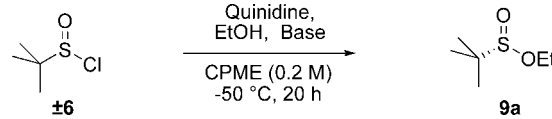
TABLE 2. Alcohol Screen Using Quinidine at Various Temperatures



entry	alcohol	temperature (°C)	sulfinate ester	yield (%)[a]	ee (%)[b]
1	EtOH	−50	**9a**	>99	87
2		−40	**9a**	>99	87
3		−20	**9a**	>99	79
4	PrOH	−50	**9b**	98	89
5		−40	**9b**	97	86
6		−20	**9b**	99	76
7	BuOH	−50	**9c**	95	88
8		−40	**9c**	97	85
9		−20	**9c**	91	66
10	*i*-BuOH	−50	**9e**	<85	88
11	*i*-PrOH	−50	**9e**	<2	70
12	$(CF_3)_2CHOH$	−50	**9f**	>99	2
13	FCH_2CH_2OH	−50	**9g**	>99	89
14	CF_3CH_2OH	−50	**9h**	98	79

[a] Yields determined by NMR with 2,6-dimethoxytoluene as an internal standard. [b] Enantiomeric excess determined by chiral HPLC.

TABLE 3. Optimization of Reaction Conditions



entry	base	base (equiv)	catalyst (mol %)	EtOH (equiv)	yield (%)[a]	ee (%)[b]
1	$NaHCO_3$	2.5	10	5	19	58
2	K_2CO_3	2.5	10	5	18	70
3	Na_2CO_3	2.5	10	5	17	74
4	proton sponge	2.5	10	5	>99	87
5	proton sponge	2.5	20	5	>99	87
6	proton sponge	2.5	5	5	>99	86
7	proton sponge	2.5	1	5	84	84
8	proton sponge	1.5	10	5	>99	88
9	proton sponge	1.2	10	2	45	87

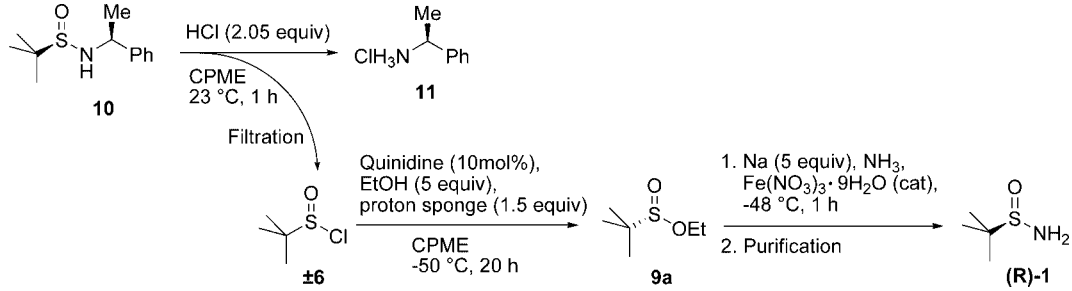
[a] Yields determined by NMR with 2,6-dimethoxytoluene as an internal standard. [b] Enantiomeric excess determined by chiral HPLC.

the sulfinate ester products (entries 10 and 11). More acidic alcohols provided excellent reaction conversion (entries 12−14), and 2-fluoroethanol (entry 13) gave comparable selectivity to the sterically similar primary unbranched alcohols ethanol, propanol, and butanol (entries 1, 4, and 7).

To further optimize the reaction, a final evaluation of the reaction parameters was performed (Table 3). As anticipated, inorganic bases were not beneficial for this reaction (entries 1−3). Increasing the catalyst loading to 20 mol % or decreasing to 5 mol % did not result in any change in the yield or enantiomeric purity of the product. However, the use of 1 mol % of catalyst resulted in a slight reduction in selectivity and a lower yield (entries 4−7). The stoichiometry of proton sponge could be reduced to 1.5 equiv without any detrimental effects (entry 8), but when the stoichiometry of the alcohol was dropped to 2 equiv, a significant reduction in yield was observed (entry 9). A variety of cinchona-derived catalysts were also evaluated with EtOH as the nucleophile and CPME as the solvent at −50 °C, but none provided comparable selectivity to quinidine. Notably, quinine provided the opposite sense of induction (72%

(9) (a) Evans, J. W.; Fierman, M. B.; Miller, S. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 8134. (b) Shibata, N.; Matsunaga, M.; Nakagawa, M.; Fukuzumi, T.; Nakamura, S.; Toru, T. *J. Am. Chem. Soc.* **2005**, *127*, 1374. (c) Peltier, H. M.; Evans, J. W.; Ellman, J. A. *Org. Lett.* **2005**, *7*, 1733. (d) Shibata, N.; Matsunaga, M.; Fukuzumi, T.; Nakamura, S.; Toru, T. *Synlett* **2005**, *11*, 1699.

TABLE 4. Recovery and Recycling of Enantiomerically Pure *tert*-Butanesulfinamide



		11	**9a**	**1** (crude)	**1**		**1** (mother liquors)	
entry	scale of **10**	yield (%)	ee (%)[a]	ee (%)[a]	yield (%)	ee (%)[a]	yield (%)	ee (%)[a]
1	0.9 g	98	87	86	63	98 (*R*)	17	33 (*R*)
2	18 g	98	87	86	67	99 (*R*)	19	19 (*R*)
3[b]	0.9 g	99	86	85	65	98 (*R*)	21	40 (*R*)

[a] Enantiomeric excess determined by chiral HPLC. [b] Recycled proton sponge and quinidine were used.

ee), indicating that this method could potentially access both enantiomers of *tert*-butanesulfinamide (see Supporting Information).

Enantiomerically pure *N*-sulfinyl-protected α-branched amine **10**[10] was selected as a model substrate for developing appropriate conditions for the recovery of the sulfinyl group to provide **1** with high enantiomeric purity (Table 4). Initially, the reaction was conducted on gram scale (entry 1). Treatment of *N*-sulfinyl amine **10** with 2.05 equiv of hydrogen chloride in CPME at room temperature resulted in complete sulfinyl group removal to provide the benzyl amine hydrochloride **11**, which was removed by pressure filtration through a glass filter under an inert atmosphere. The filtered *tert*-butanesulfinyl chloride solution was used directly for dynamic kinetic resolution under the optimized conditions. An extractive workup then provided the CPME solution of ethyl *tert*-butanesulfinate (**9a**) with 87% ee. Notably, the extractive workup in addition to removing the excess ethanol enables the recovery of the quinidine and proton sponge mixture (vide infra). The CPME solution of *tert*-butanesulfinate ester **9a** was then directly added to 5 equiv of sodium amide in NH_3 at −48 °C.[11] Simply removing the ammonia gas by gradual warming to ambient temperature under a gentle nitrogen flush followed by filtration provided a CPME solution of *tert*-butanesulfinamide (**1**) with 86% ee. The enantiomeric purity of the *tert*-butanesulfinamide product could easily be enhanced by stirring the product in hydrocarbon solvents, and thus, after solvent replacement from CPME to octane, the analytically pure *tert*-butanesulfinamide (**1**) was obtained by stirring the resulting suspension and filtration in 63% yield and 98% ee. Increasing the reaction scale 20-fold resulted in an improved 67% overall yield of **1**, which was obtained with 99% ee (entry 2). The high yield and enantiomeric purity of **1** obtained upon increasing the scale over an order of magnitude bodes well for effectively performing the reaction at even larger scales. Moreover, concentration of the mother liquors provided **1** in approximately 19% yield and with 19% ee. The good overall mass recovery of **1** (86%) suggests that an even higher overall recovery to (*R*)-**1** can be expected upon identification of an even more highly selective sulfinyl transfer catalyst.

Reuse of the quinidine and proton sponge mixture obtained upon extraction during the dynamic kinetic resolution step was also investigated. When the reaction was performed using recovered quinidine and proton sponge on gram scale, the same yield and % ee were observed (entry 3, Table 4) when compared to the reaction performed with new quinidine and proton sponge (entry 1). Therefore, not only has a procedure been established for the recovery of the *tert*-butanesulfinyl group to provide *tert*-butanesulfinamide (**1**) with high enantiomeric purity, but recovery and reuse of the sulfinyl transfer catalyst and acid scavenger employed in the dynamic resolution step can also be accomplished by simple extractive isolation.

Conclusions

In conclusion, a practical process for recycling the *tert*-butanesulfinyl group upon deprotection of *N*-*tert*-butanesulfinyl amines **3** has been achieved. Treatment of *N*-*tert*-butanesulfinyl amines **3** with HCl in cyclopentyl methyl ether results in complete conversion to *tert*-butanesulfinyl chloride **6** and the corresponding amine hydrochloride salt **4**, which is isolated by filtration in analytically pure form and in quantitative yield. Treatment of the sulfinyl chloride solution with aqueous ammonia then provides analytically pure *tert*-butanesulfinamide with virtually complete recovery (97% yield). Alternatively, the *tert*-butanesulfinyl chloride solution can be treated with ethanol and catalytic quinidine as a sulfinyl transfer catalyst to provide a cyclopentyl methyl ether solution of ethyl *tert*-butanesulfinate (**9a**) in 88% ee. Addition of $NaNH_2$ in ammonia followed by simple trituration of the product with octane provides analytically pure *tert*-butanesulfinamide (**1**) with 99% ee and in 67% overall isolated yield based upon the starting *N*-*tert*-butanesulfinyl amine **3**. The reported protocols should greatly enhance the practicality and utility of large-scale applications of *tert*-butanesulfinamide-based amine synthesis methods.

Experimental Section

Large-Scale Procedure for the Recovery of Racemic *tert*-Butanesulfinamide 1. To a solution of **7** (17.39 g, 80.00 mmol) in CPME (156 mL) was added 43.9 mL of 3.74 M HCl in CPME (0.164 mol, 2.05 equiv) at 5 °C, the first 8.60 mL over a period of

(10) *tert*-Butanesulfinamide derivative **10** was prepared from (*R*)-*tert*-butanesulfinamide (**1**) in good yield according to literature procedures. (a) Liu, G.; Cogan, D. A.; Owens, T. D.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278. (b) Reference 2. (c) Reference 5.

(11) The use of sodium amide eliminated the troublesome multi-extractive workup when using lithium amide. Weix, D. J.; Ellman, J. A. *Org. Synth.* **2005**, *82*, 157.

5 min, and then after 10 min, the remaining 35.3 mL over a period of 25 min. After 1 h at 5 °C, the reaction mixture was allowed to warm to 23 °C. After 1 h at 23 °C, crystals were removed by pressure filtration through a glass filter and were washed with CPME (100 mL) under an inert atmosphere to provide **8** (11.75 g, 98%) as a white solid and the CPME solution of **6**.

The filtered solution of **6** was slowly added to 14.8 M ammonium hydroxide (27 mL, 0.40 mol, 5 equiv) to keep the internal temperature at −10 °C (ca. 35 min), and the reaction mixture was stirred for 30 min at −10 °C and then for 1.5 h at 23 °C. The solvent was removed, and EtOAc/hexanes (1/9, 350 mL) was added. After 3 h, the resulting inorganic salt was removed by filtration and washed with EtOAc/hexanes (1/9, 50 mL). The solvent was removed in vacuo, and hexanes (200 mL) was added. Concentration then provided **1** (9.37 g, 97%) as a white solid.

8:[12] mp 270−275 °C (decomp.); ^{1}H NMR (D_2O, 400 MHz) δ 1.29 (s, 3H), 1.23−1.35 (m, 1H), 1.40−1.70 (m, 9H); ^{13}C NMR (D_2O, 100 MHz) δ 21.2, 22.7, 24.3, 35.3, 54.5; MS (ESI) *m*/*z* 114 (MH^+). The data corresponded to that reported in the literature.

1: mp 98−102 °C; ^{1}H NMR (400 MHz) δ 1.23 (s, 9H), 3.82 (br s, 2H); ^{13}C NMR (100 MHz) δ 22.1, 55.3; MS (ESI) *m*/*z* 122 (MH^+). Anal. Calcd for $C_4H_{11}NOS$: C, 39.64; H, 9.15; N, 11.56; S, 26.46. Found: C, 39.30; H, 9.51; N, 11.48; S, 26.56.

Large-Scale Procedure for the Recovery of *tert*-Butanesulfinamide (*R*)-1. To a solution of **10** (18.03 g, 80.00 mmol) in CPME (181.9 mL) was added 38.1 mL of 4.30 M HCl in CPME (0.164 mol, 2.05 equiv) at 23 °C, 6.50 mL over a period of 4 min, and after 10 min,[13] the remaining 31.6 mL over a period of 35 min. After 1 h, the crystals were removed by pressure filtration through a glass filter and washed with CPME (140 mL) under an inert atmosphere to provide **11** (12.37 g, 98%, 99% ee) as a white solid and the CPME solution of **6**.

(a) Preparation of Ethyl Sulfinate 9a: To the filtered solution of **6** was added proton sponge (25.71 g, 0.1200 mol, 1.5 equiv) at −50 °C, and then a solution of quinidine (2.60 g, 8.00 mmol, 0.10 equiv) and EtOH (23.4 mL, 0.400 mol, 5.0 equiv) in CPME (40 mL) was slowly added to keep the internal temperature at −50 °C (ca. 45 min). After 20 h at −50 °C, the reaction mixture was allowed to warm to 10 °C over 20 min. The reaction mixture was washed with 1 M HCl twice (160 mL, 80 mL), saturated $NaHCO_3$ (80 mL), and brine (80 mL) to provide the CPME solution of **9a** with 87% ee.

(b) Recovery of Proton Sponge and Quinidine: The separated acidic water layers were combined (ca. 250 mL), and sufficient 5 M NaOH was added to make alkaline (pH 14). The aqueous phase was then extracted three times with 30 mL of ether. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to recover the mixture of quinidine and proton sponge as a pale pink solid (28.19 g, 100%).

(c) Conversion of Ethyl Sulfinate 9a to *tert*-Butanesulfinamide (*R*)-1: To an ammonia solution (ca. 400 mL) at −40 °C was added $Fe(NO_3)_3 \cdot 9H_2O$ (162 mg, 0.400 mmol, 0.005 equiv) followed by addition of small pieces of sodium (9.20 g, 0.400 mol, 5 equiv) over 3 h. After the solution turned into a dark gray suspension, the reaction mixture was cooled to −48 °C. The CPME solution of **9a** was slowly added to the freshly prepared sodium amide in NH_3 to keep the internal temperature at −48 °C (ca. 1 h). After 1 h, solid ammonium chloride (23.5 g, 0.440 mol) was added in eight portions over 8 min, and the mixture was allowed to slowly warm to room temperature overnight under a gentle stream of nitrogen. CPME (100 mL) was added to the resulting mixture, and the mixture was concentrated under a reduced pressure until the total volume was ca. 300 mL. After stirring at room temperature for 30 min, the resulting inorganic salt was removed by filtration and was washed with CPME (30 mL) to give the CPME solution of **1** with 86% ee. The filtered solution was concentrated until the total volume was ca. 80 mL. Octane (200 mL) was added to the resulting solution, and the mixture was concentrated until the total volume was ca. 80 mL. More octane (200 mL) was added, and the same operation was repeated. The resulting suspension was stirred at room temperature for 20 h and then at 0 °C for 4 h. The crystals were collected by filtration and washed with cold hexanes (60 mL, precooled to 0 °C) and suction-dried to provide (*R*)-**1** (6.47 g, 67%, 99% ee) as a white solid.

11:[14] $[\alpha]^{20}_D$ −4.3 (*c* 0.37, MeOH); mp 168−171 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.63 (d, 3H, J = 6.9 Hz), 4.46 (q, 1H, J = 6.9 Hz), 7.36−7.49 (m, 5H); ^{13}C NMR (CD_3OD, 100 MHz) δ 19.3, 50.9, 126.3, 128.7, 128.8, 138.2; MS (ESI) *m*/*z* 122 (MH^+). The enantiomeric ratio of **11** was determined by conversion to *N*-benzoyl-1-phenylethylamine followed by HPLC analysis (Diacel Chiralpak IB column, 90:10 hexanes/IPA; 1.0 mL/min), t_1 = 15.5 min, t_2 = 18.9 min. The data corresponded to that reported in the literature.[14]

(*R*)-**1**: $[\alpha]^{20}_D$ +4.7 (*c* 0.81, $CHCl_3$); mp 104−106 °C; ^{1}H NMR (400 MHz) δ 1.23 (s, 9H), 3.75 (br s, 2H); ^{13}C NMR (100 MHz) δ 22.2, 55.3; MS (ESI) *m*/*z* 122 (MH^+). Anal. Calcd for $C_4H_{11}NOS$: C, 39.64; H, 9.15; N, 11.56; S, 26.46. Found: C, 39.61; H, 9.33; N, 11.48; S, 26.08. The enantiomeric ratio of (*R*)-**1** was determined by HPLC analysis (Diacel Chiralpak AS column, 90:10 hexanes/EtOH; 1.2 mL/min; 220 nm; (*R*) rt = 7.8 min, (*S*) rt = 11.0 min).

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Supporting Information Available: Complete experimental details and spectral data for all compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) A separate addition of the HCl solution enabled stirring of the reaction mixture to be easily performed. If all of the HCl solution is added continuously, the stirring becomes difficult due to the high viscosity of the slurry.

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