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Improved Synthesis of *tert*-Butanesulfinamide Suitable for Large-Scale Production

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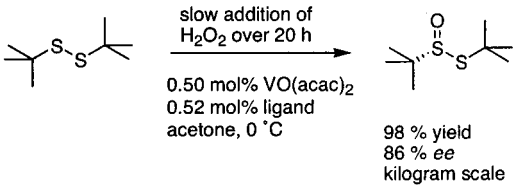
ABSTRACT

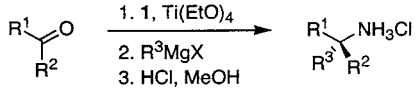


An improved synthesis of *tert*-butanesulfinamide that overcomes the scalability problems of the previous syntheses is described. The key step is the catalytic asymmetric oxidation of the inexpensive di-*tert*-butyl disulfide starting material. The new homogeneous reaction conditions utilize an inexpensive chiral ligand prepared in a single step from commercially available *cis*-1-amino-indan-2-ol. The reaction is performed at a 2.3 M concentration in the practical solvent acetone and can readily be run on a kilogram scale.

Chiral amines are key components of many pharmaceutical agents, materials, and catalysts. Since its introduction in 1997,[1] *tert*-butanesulfinamide (**1**) has proven to be an extremely versatile chiral ammonia equivalent for the asymmetric synthesis of amines. Condensation of **1** with a wide variety of ketones and aldehydes provides *N*-sulfinyl imines in high yields. The *tert*-butanesulfinyl group both activates these imines to attack by nucleophiles and serves as a chiral directing group to provide *N*-*tert*-butanesulfinyl amine products in high yields and with high diastereoselectivity. Removal of the *tert*-butanesulfinyl group under mild conditions cleanly provides the amine products. Due to these desirable characteristics, **1** has found extensive use both in academics and industry.[2] Applications include the asymmetric synthesis of tertiary carbinamines[3] (Scheme 1), α-branched amines,[4] highly substituted *β*-amino acids,[5,6] α-amino acids,[7] α-trifluoromethylamines,[8] 1,2-amino alcohols,[9] 1,3-amino alcohols,[10] and ethylenediamines.[11] In addition, *tert*-butanesulfinamide has been employed in a number of drug discovery and development efforts[12] and is the key chirality-bearing component of new classes of ligands for asymmetric catalysis.[13]

Enantiomerically pure **1** was first synthesized in two steps from the inexpensive petroleum byproduct di-*tert*-butyl disulfide (**2**) in 68% overall yield (Scheme 2).[14] Asymmetric oxidation of **2** proceeded with high enantioselectivity and conversion using only 0.25 mol % catalyst and with 30% hydrogen peroxide as an inexpensive, easy to handle oxidant. After bulb-to-bulb distillation of the thiosulfinate ester **3**, displacement with $LiNH_2$ provided *tert*-butanesulfinamide (**1**) in analytically and enantiomerically pure form by simple crystallization.

Scheme 1. Synthesis of Tertiary Carbinamines Using **1**



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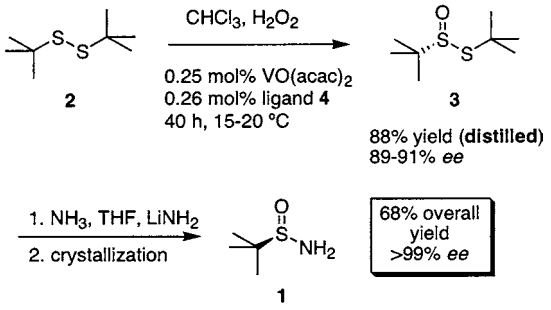
Scheme 2. Original *tert*-Butanesulfinamide Synthesis



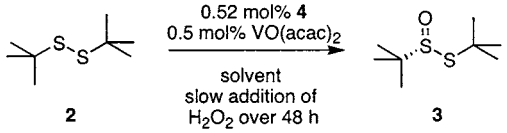
Although the reaction sequence is short and efficient and has enabled extensive use of the reagent, several improvements in the oxidation of **2** to **3** are necessary to enable large-scale production of **1**. First, ligand **4** is derived from *tert*-butyl glycinol, for which the (*S*)-enantiomer is quite expensive[15] and the (*R*)-enantiomer is currently not commercially available. In addition, the expensive and toxic solvent chloroform is required to achieve high conversion and enantioselectivity. Also, to achieve high yield in the conversion of **3** to **1**, the thiosulfinate ester must be purified away from the starting material by bulb-to-bulb distillation. Most seriously, the oxidation reaction does not scale well beyond 1 mole. The oxidation reaction is biphasic (chloroform/water) with the hydrogen peroxide dissolved in the aqueous layer and the substrate and catalyst dissolved in the chloroform layer. Consequently, the reaction is inefficient with slow stirring. However, if stirring is too vigorous the catalyst is exposed to excess hydrogen peroxide and is destroyed.[16] This biphasic reaction is therefore very sensitive to the vessel shape and the rate of stirring and does not proceed with high conversion or selectivity on a large scale (>1 mole).

Researchers at Sepracor encountered sufficient difficulty scaling the oxidation reaction of **2** that they developed an alternative route to **1**.[17] While their novel route provides access not only to **1** but also to a range of other sulfinamides, the sequence is not suitable for large-scale production. It requires stoichiometric use of *cis*-1-amino-indan-2-ol as a chiral auxiliary, four transformations, and four purification steps, including chromatography on silica gel.

Herein we report a new homogeneous oxidation procedure that proceeds efficiently, independent of the reaction scale, and is performed at high concentrations using the inexpensive and relatively nontoxic solvent acetone. In addition, the procedure utilizes an inexpensive ligand that can be prepared as either enantiomer in a single step from commercially available materials. Indeed, the new oxidation procedure proceeds with sufficiently high conversion and fidelity that *tert*-butanesulfinamide **1** may be prepared by direct addition of lithium amide to the oxidation product **3** without purification of **3**.

Investigations on the mechanism of the asymmetric oxidation of **2** showed that, under homogeneous conditions, addition of stoichiometric H_2O_2 destroyed the oxidation catalyst, resulting in very poor conversions and enantioselectivities. As shown in Table 1, good conversions, albeit with modest selectivity, could be accomplished by slow addition of hydrogen peroxide using a syringe pump (entries 1−3). A more thorough investigation of the reaction solvent and temperature has resulted in conditions that provide significant improvement in the reaction selectivity (entries 7 and 9). Use of acetonitrile as a solvent at 0 °C provides the highest conversion and selectivity (entry 9). Further

Table 1. Solvent and Temperature Screen with Ligand **4**



entry	solvent[a]	*T* (°C)	conversion (%)[b]	ee (%)[c]
1	*i*PrOH	23	96	51
2	THF	23	80	44
3[d]	CF_3CH_2OH	23	nd	74
4	acetone	23	94	53
5	acetone	0	59	68
6	CH_3NO_2	23	89	80
7	CH_3NO_2	0	93	83
8	CH_3CN	23	100	75
9	CH_3CN	0	100	83
10	CH_3CN	−20	97	81

[a] Reactions were carried out with 0.1 mol of disulfide (1.4 M). H_2O_2 (0.11 mol) was then added via syringe pump. [b] Conversion determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by HPLC analysis using a chiral column (see Supporting Information). [d] Results from ref 16.

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(11) See ref 7b.
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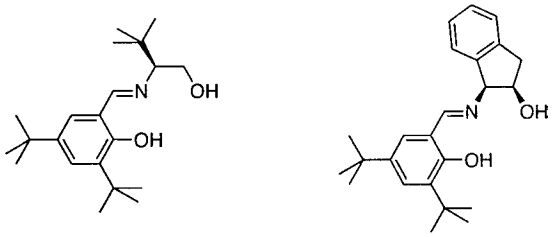
cooling to −20 °C does not result in an increase in enantioselectivity (entry 10).

Having found homogeneous conditions that give excellent conversion, we set out to improve the enantioselectivity of the oxidation. In the development of the initial procedure for the asymmetric oxidation of **2**, the *tert*-butyl glycinol-derived ligand **4** (Scheme 3) was determined to be more

Scheme 3. Ligands for Oxidation of Di-*tert*-butyl Disulfide

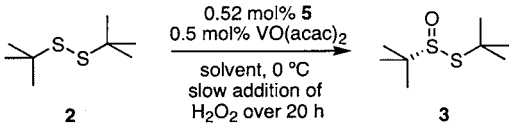


4 **5**

selective than all of the other amino-alcohol-derived ligands that were investigated.[14] However, we chose to reevaluate the previously investigated ligand **5** under the new oxidation procedure since this ligand can be prepared in one step from commercially available, enantiomerically pure *cis*-1-amino-indan-2-ol[18] and 3,5-di-*tert*-butylsalicylaldehyde.[19]

Ligand **5** provides oxidation product **3** in only 80% ee in the solvent CH_3CN (Table 2, entry 1), which was previously

Table 2. Solvent and Concentration Screen with Ligand **5**



2 **3**

entry	solvent[a]	concentrated (M)	conversion (%)[b]	ee (%)[c]
1	CH_3CN	1.4	97	80
2	acetone	1.4	98	86
3	2-butanone[d]	1.4	97	84
4	acetone	2.3	96	87
5	acetone	3.1	95	87
6	acetone	3.8	48	78

[a] Reactions were carried out with 0.1 mol of disulfide. H_2O_2 (0.11 mol) was then added via syringe pump. [b] Conversion determined by ^1H NMR of the crude reaction mixture. [c] Determined by chiral HPLC analysis (see Supporting Information). [d] Reaction was run at 8 °C.

determined to be the optimal solvent for ligand **4** (Table 1, entry 9). In contrast, ligand **5** provides **3** with 98% conversion and 86% ee when acetone is used as the solvent (Table 2, entry 2), even though acetone is a less effective solvent for ligand **4** (Table 1, entries 4 and 5). The reaction proceeded equally well in the analogous solvent 2-butanone (entry 3).

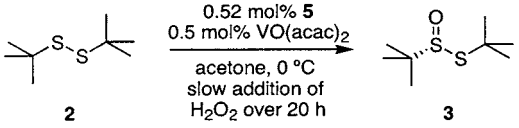
(18) Both enantiomers are commercially available for ~$15/g.

(19) Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882−2883. See Supporting Information.

The oxidation reaction is very tolerant of concentration changes (Table 2, entries 2, 4, and 5). Increasing the concentration from 1.4 to 2.3 M and even to 3.1 M does not affect yield or selectivity (entries 4 and 5). Only at 3.8 M does the yield and enantioselectivity drop significantly (entry 6). The efficiency of the reaction at high concentrations has clear practical ramifications for large-scale production. At a concentration of 2.3 M, the disulfide starting material constitutes 35% of the reaction mixture's volume.

Most importantly, under the optimized conditions, the oxidation reaction is completely scale independent (Table 3). As expected for a homogeneous reaction, no reduction

Table 3. Scalability of Oxidation Reaction



2 **3**

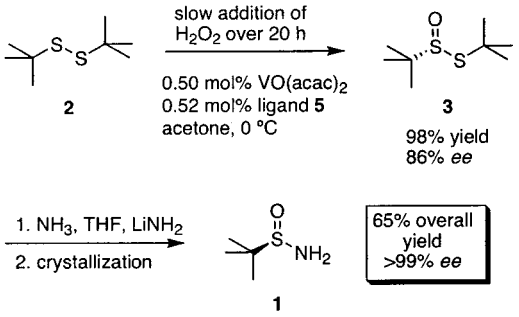
entry[a]	scale (**2**)	conversion (%)[b]	ee (%)[c]
1	0.1 mol	96	85.9−87.2
2	1.0 mol	98	85.5−86.0
3	5.6 mol (1 kg)	99	85.4−86.1

[a] Reactions were carried out in acetone (2.3 M) by the slow addition of 30% H_2O_2 (1.1 equiv) via syringe pump. [b] Conversion determined by ^1H NMR of the crude reaction mixture. [c] Determined by chiral HPLC analysis (see Supporting Information).

in reaction rate, conversion, or enantioselectivity is observed in scaling the reaction over 50-fold from 0.1 mole (entry 1) to >5 mole (1 kg) (entry 3). Kilogram-scale reactions using either distilled or undistilled **2** gave identical conversions and enantiomeric excesses within 0.7%.

Due to the high reaction conversion, lithium amide displacement upon **3** can be accomplished without purification of **3**. This eliminates the tedious bulb-to-bulb distillation of **3** that was required in the initial procedure to remove the residual starting material **2** (Scheme 1). As shown in Scheme 4, a simple trituration of crude **1** with hexanes provides the product in 95% ee and in 75% overall yield from **2**. A single recrystallization[20] then provides **1** in >99% ee and in 65% overall yield.[21]

Scheme 4. New Sulfinamide Synthesis



2 **3** **1**

In summary, we have reported an improved procedure for the asymmetric oxidation of di-*tert*-butyl disulfide **2**, which serves as the key step in the synthesis of enantiopure *tert*-butanesulfinamide **1**. The significant improvements to the oxidation procedure are the use of the inexpensive and readily available ligand **5**, the use of the cheap and relatively nontoxic solvent acetone, and the use of only a single purification step. Most importantly, the use of homogeneous reaction conditions eliminates any scale dependence for conversion or enantioselectivity. This new, more efficient route to **3** enables easier, lower cost access to large quantities of *tert*-butanesulfinamide.

(20) Crystallized from 5 mL of hexanes/g of sulfinamide.

(21) Crystallization from 10 mL of hexanes/g of sulfinamide provides enantiopure material (minor enantiomer not detectable) in 60% overall yield.

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Note Added after ASAP Posting. In the version posted ASAP March 15, 2003, the concentration of the starting material was reported incorrectly in all instances. The corrected version was posted March 21, 2003.

Supporting Information Available: Detailed experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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