Catalytic Asymmetric Synthesis of *tert*-Butanesulfinamide. Application to the Asymmetric Synthesis of Amines

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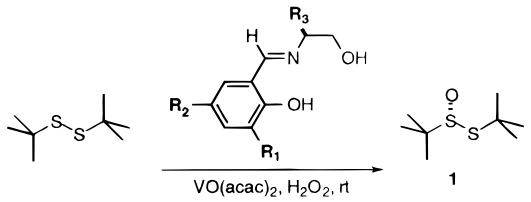
Greater than 75% of drugs and drug candidates incorporate amine functionality.[1] Nonetheless, the asymmetric synthesis of amines,[2] excluding α-amino acids, is much less developed than the asymmetric synthesis of other common functional groups. *p*-Toluenesulfinamide and the corresponding sulfinimines have become the focus of increasing attention for the asymmetric synthesis of aziridines, α- and *β*-amino acids, and, in very limited studies, α-branched amines.[3,4] Davis, who pioneered efforts on the study of *p*-toluenesulfinimines, demonstrated that the sulfinyl group serves as an ideal auxiliary because it activates the imine for nucleophilic addition, provides diastereofacial selectivity, and is easy to remove simply by treatment with mild acid. In our own efforts to develop *N*-acylsulfinamides for diastereoselective enolate alkylation chemistry,[5] we found *tert*-butanesulfinamide to be superior to *p*-toluenesulfinamide due to the lower molecular weight, enhanced diastereofacial selectivity,[6] and enhanced nucleophilicity of the amine functionality. Unfortunately, expedient methods have not been reported for the preparation of optically pure *tert*-butanesulfinamide.[6] Herein we report a highly practical two-step procedure to prepare large quantities of optically pure *tert*-butanesulfinamide with the key step being the catalytic asymmetric oxidation of *tert*-butyl disulfide, which serves as an extremely inexpensive starting material (<2 cents/g). We further describe the utility of *tert*-butanesulfinamide for the general and expedient asymmetric synthesis of α-branched amines.

We envisaged that *tert*-butanesulfinamide could be derived from a *tert*-butyl *tert*-butanethiosulfinate intermediate (**1**, eq 1). The chemistry of scalemic thiosulfinates has not been explored extensively, but limited precedent did indicate that addition of metal amides[7] and carbanion[8] nucleophiles to enantioenriched thiosulfinates occurs stereospecifically to provide sulfinamide and sulfoxide products, respectively. The most expedient method for the preparation of the thiosulfinate would be catalytic asymmetric oxidation of *tert*-butyl disulfide, although previous oxidative approaches toward optically pure thiosulfinates have resulted in disappointing selectivities.[9] We considered a number of different oxidation catalysts but were most attracted to a recent report by Bolm on the asymmetric oxidation of thioethers.[10] The vanadium catalysts employed are highly catalytic (as little as 0.01% catalyst) and are compatible with the inexpensive stoichiometric oxidant hydrogen peroxide. The only detraction was the generally modest reported enantioselectivities (53−70% for thioethers and 85% ee for 2-phenyl-1,3-dithiane).

Table 1. Optimization of Catalytic Asymmetric Oxidation of *tert*-Butyl Disulfide (Eq 1)[a]

	ligand				
entry	R_1	R_2	R_3	conversion (%)[b]	ee (%)[c]
1	*t*-Bu	*t*-Bu	*t*-Bu	94	82
2	*t*-Bu	NO_2	*t*-Bu	18	45
3	*t*-Bu	OMe	*t*-Bu	85	79
4	*t*-Bu	H	*t*-Bu	88	83
5	H	H	*t*-Bu	50	46
6	OMe	H	*t*-Bu	17	>10
7	NO_2	Br	*t*-Bu	15	>10
8	Br	Br	*t*-Bu	23	50
9	*t*-Bu	*t*-Bu	*i*-Pr	16	45
10	*t*-Bu	*t*-Bu	Bn	69	53
11	*t*-Bu	*t*-Bu	Ph	47	25
12	*t*-Bu	*t*-Bu	*t*-Bu	98	91[d]

[a] All reactions were performed at room temperature and unless otherwise noted in CH_2Cl_2 with 2% $VO(acac)_2$ and 3% ligand. [b] Conversions determined by GC analysis with tridecane as an internal standard. [c] Enantioselectivity determined by chiral HPLC analysis. [d] Reaction performed in $CHCl_3$ with 1% $VO(acac)_2$ and 1.1% ligand.



(1)

We first explored a number of different ligands at 2% catalyst loading using the general reaction conditions reported by Bolm, room temperature with CH_2Cl_2 as the solvent. Data for selected ligands are provided in Table 1. Steric effects at the 5-position of the aryl ring are not important, but electronic effects play a critical role in both catalyst turnover and selectivity (entries 1−4, Table 1). Both electronic and steric factors were found to be important for substituents at the 3-position of the aryl ring (entries 5−8). Finally, steric effects play an important role at R_3, with the *tert*-butyl group providing significantly higher selectivity than other substituents. On the basis of these studies, the optimal ligand is prepared by condensation of 3,5-di-*tert*-butylsalicylaldehyde with *tert*-leucinol, both of which are commercially available (entries 1 and 12, Table 1).

Solvent was also found to have a dramatic effect upon catalyst selectivity. In particular, while 1,2-dichloroethane provides comparable selectivities to CH_2Cl_2 (82% ee), $CHCl_3$ provides much higher enantioselectivity (91% ee). The reaction did not proceed in CCl_4 due to the poor solubility of the catalyst. Other solvents including acetonitrile, toluene, nitromethane, *tert*-butyl alcohol, and THF resulted in much poorer selectivities. Employing the optimized conditions, the reaction has been performed reproducibly on half mole scale at 1.5 M concentrations with 1% catalyst to provide a 96−98% yield of pure product in

(1) MDL Drug Data Report, MDL Information Systems, Inc., San Leandro, CA.

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(3) For a recent comprehensive compilation of research in this area, see: 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*, 2555−2563.

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(5) Backes, B. A.; Ellman, J. A. 213th American Chemical Society National Meeting, San Francisco, CA, April 1997; ORGN 066.

(6) *tert*-Butanesulfinimines have also been observed to provide enhanced diastereoselectivity relative to *p*-toluenesulfinimines in aziridine synthesis. Ruano, J. L. G.; Fernández, I.; Catalina, M. P.; Cruz, A. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407−3414.

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(8) Sagramora, L.; Koch, P.; Garbesi, A.; Fava, A. *J. Chem. Soc., Chem. Commun.* **1967**, 985−986.

(9) (a) Davis, F. A.; Jenkins, R. H.; Awad, S. B.; Stringer, O. D.; Watson, W. H.; Galloy, J. *J. Am. Chem. Soc.* **1982**, *104*, 5412−5418. (b) Nemecek, C.; Duñach, E.; Kagan, H. B. *New J. Chem.* **1986**, *10*, 761−764.

(10) Bolm, C.; Bienewald, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2640−2642.

(11) The *tert*-butanesulfinamide has been stored over 6 months at room temperature without decomposition or loss of optical purity.

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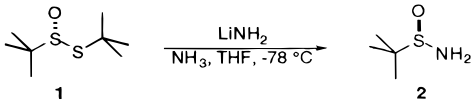
91% ee, after bulb-to-bulb distillation. We have increased the reaction concentration to 2 M and have decreased the catalyst loading to 0.5% with little loss in conversion or enantioselectivity and suspect that further reductions in catalyst loading are possible.

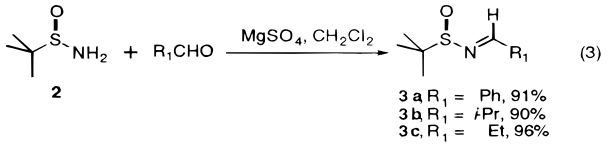
Addition of lithium amide in ammonia to thiosulfinate **1** provides *tert*-butanesulfinamide **2** (eq 2). This transformation has been performed on half mole scale, and a single crystallization provides optically pure *tert*-butanesulfinamide **2** in 75% overall yield from *tert*-butyl disulfide.[11] It is important that



1 2 (2)

ammonia be used as solvent in the lithium amide addition step, since the poor solubility of lithium amide in other solvents results in extensive racemization. Carbanion nucleophiles also add to thiosulfinate **1** in high yields and stereospecifically, with inversion, as demonstrated by the addition of methyl Grignard (91% yield). Because *tert*-butyl *tert*-butanethiosulfinate can be crystallized to optical purity, *tert*-butyl disulfide oxidation and Grignard addition also provide an extremely practical two-step preparation of *tert*-butyl sulfoxides, which have advantages over the commonly used *p*-tolyl sulfoxides for some applications.[12]

The straightforward preparation of *tert*-butanesulfinimines **3** (eq 3) from *tert*-butanesulfinamide is central to the preparation of chiral amines. Direct condensation of *tert*-butanesulfinamide with aldehydes in the presence of $MgSO_4$ provides *tert*-butanesulfinimines **3** in high yield. No racemization is observed



2 (3)

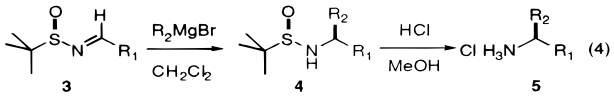
in the condensation step as determined by chiral HPLC analysis. In contrast to *tert*-butanesulfinamide, *p*-toluenesulfinamide is a poorer nucleophile and does not cleanly condense with aldehydes.[3] The sulfinimines are instead prepared by addition of lithium bis(trimethylsilyl)amide to optically pure *p*-toluenesulfinate esters followed by treatment with CsF and aldehyde, or by reaction of the *p*-toluenesulfinate esters with imine anions prepared by DIBAL reduction of the corresponding nitrile followed by addition of methyllithium. Both routes proceed in modest yields, particularly for the preparation of sulfinimines from aliphatic aldehydes, and require the separation of the chiral alcohol byproduct.

The utility of *tert*-butanesulfinimines was demonstrated by the preparation of α-branched amines **5** (eq 4, Table 2).[13] In all cases addition of Grignard reagents to the sulfinimines proceeds from the same face with high diastereoselectivity as determined by GC analysis of the Mosher amides, which are prepared upon removal of the *tert*-butanesulfinyl group (vide infra). The addition reactions are exceptionally clean, often

Table 2. Asymmetric Synthesis of α-Branched Amines (Eq 4)[a]

			sulfinamide **4**		amine **5**	
entry	R_1	R_2	yield (%)[b]	dr (%)[c]	yield (%)[b]	configuration
1	Et	Me	96	93:07	97	*S*
2	Et	*i*-Pr	97	92:08	92	*R*
3	Et	Ph	100	96:04	90	*R*
4	*i*-Pr	Me	99	98:02	97	*S*
5	*i*-Pr	Et	100	97:03	93 (85)[d]	*S*
6	*i*-Pr	Ph	98	89:11	91 (76)[d]	*R*
7	Ph	Me	96	97:03	88	*S*
8	Ph	Et	98	92:08	94	*S*
9	Ph	*i*-Pr	29	97:03		*S*

[a] All reactions were performed with CH_2Cl_2 as solvent and the magnesium bromide derivative as 3 M in Et_2O. [b] Yields are determined by mass balance of analytically pure material. [c] Diastereoselectivity (dr = diastereomer ratio) is determined by preparation of the Mosher amides from the crude amine product after treatment of the sulfinamide **4** with HCl in MeOH. [d] Yield of optically pure material after a single crystallization.



3 4 5 (4)

providing analytically pure material after extractive workup, and proceed in near quantitative yields with the exception of the addition of isopropyl Grignard to the sulfinimine of benzaldehyde. Only for this reaction does reduction compete with Grignard addition (entry 9, Table 2). The highest diastereoselectivities are observed when CH_2Cl_2 is used as the solvent. Final isolation of the amine is extremely straightforward and proceeds in high yield by treatment of the sulfinamide with HCl in methanol, followed by precipitation of the amine hydrochloride with ether. As demonstrated for entries 5 and 6 (Table 2), recrystallization readily provides the optically pure amine hydrochlorides.

A highly practical and efficient two-step synthesis of optically pure *tert*-butanesulfinamide in 75% overall yield is described. The key step is asymmetric catalytic oxidation of *tert*-butyl disulfide to provide *tert*-butyl *tert*-butanethiosulfinate. The direct preparation of *tert*-butanesulfinimines is also described, and a general and expedient synthesis of scalemic α-branched amines from these intermediates is demonstrated. Further applications of *tert*-butanesulfinimines, *tert*-butanesulfinamide, and the *tert*-butyl *tert*-butanethiosulfinate intermediate are under investigation.

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Supporting Information Available: All experimental procedures and analytical data (7 pages). See any current masthead page for ordering and Internet access instructions.

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(13) To our knowledge, the only study reporting Grignard additions to *p*-toluenesulfinimines prepared from aldehydes explores the addition of benzyl Grignard reagents to sulfinimines of aryl aldehydes (60−74% de). Addition of the more basic MeMgBr occurred exclusively at sulfur. Moreau, P.; Essiz, M; Merour, J.-Y.; Bouzard, D. *Tetrahedron: Asymmetry* **1997**, *8*, 591−598.