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General One-Pot Method for the Preparation of *N-tert*-Butanesulfinylamine Diastereomer Mixtures as Standards for Stereoselectivity Determinations

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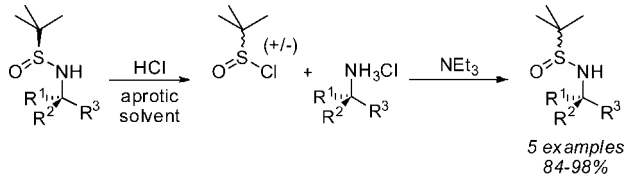
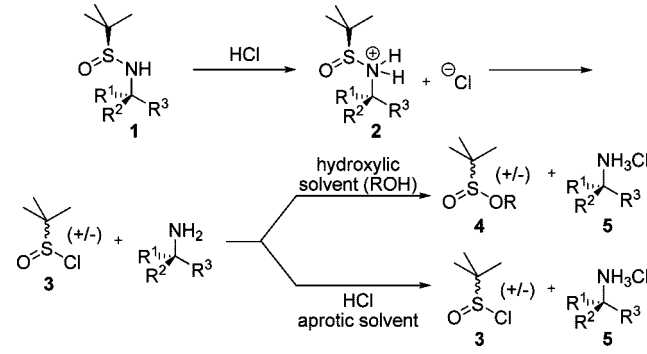


The one-pot preparation of *N*-sulfinylamine diastereomers proceeds in excellent yields (84−98%) for a diverse set of *N*-sulfinyl imine addition products. The method is operationally simple and extractive isolation provides analytically pure mixtures of diastereomers as standards for the rapid and accurate determination of *N*-sulfinylamine diastereomeric purity.

The asymmetric synthesis of chiral, α-branched amines is an important and heavily pursued endeavor due to the high frequency with which this structural motif occurs in drugs and natural products.[1] Additions of nucleophiles to enantiomerically pure *N-tert*-butanesulfinyl imines are among the most popular approaches for the asymmetric synthesis of amines.[2] However, to rigorously determine the diastereoselectivity of the nucleophilic addition step, further derivatization of the product is often necessary to obtain standards for the analysis of stereoisomeric purity. Typically, cleavage of the *tert*-butanesulfinyl group is followed by isolation and then reaction of the resulting amine with a derivatization reagent such as racemic sulfinyl chloride or both (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[3] These multistep procedures are tedious and require the use of expensive reagents of limited stability. We report herein a general and easy-to-perform one-pot method for the preparation of *N-tert*-butanesulfinylamine diastereomer mixtures.

SCHEME 1. Proposed Mechanism of Acid-Catalyzed Cleavage of 1 in Hydroxylic versus Aprotic Solvents



The HCl-mediated cleavage of the *tert*-butanesulfinyl group is thought to proceed by an acid−base reaction to provide **2**, followed by attack of chloride anion at the electrophilic sulfur to produce the configurationally unstable *tert*-butanesulfinyl chloride (**3**) (Scheme 1).[4] The deprotection of an *N*-sulfinylamine **1** to provide the amine hydrochloride **5** is generally carried out in the presence of a hydroxylic cosolvent, which reacts rapidly in situ with the sulfinyl chloride to give sulfinate ester **4** as a byproduct.[3a] However, we have recently demonstrated that by carrying out the HCl-mediated cleavage in an aprotic solvent, racemic sulfinyl chloride **3** is generated in near quantitative yield.[4] Upon the basis of this observation, we envisioned that authentic diastereomers of *N-tert*-butanesulfinylamines could readily be formed in one pot by HCl-mediated sulfinyl group cleavage in an aprotic solvent followed by addition of base to the same reaction vessel without any workup to achieve resulfinylation of the amine.

To explore this hypothesis, *N*-sulfinylamine **1a** was treated with HCl at room temperature followed by addition of triethylamine at −78 °C (Table 1, entry 1). Gratifyingly, the *N*-sulfinylamine diastereomer mixture **6a** was obtained in quantitative yield and with 65:35 dr. Furthermore, it was found that cooling the reaction mixture prior to the addition of base was unnecessary, with a high yield and an approximate 1:1 mixture of *N*-sulfinylamine diastereomers obtained at room temperature (entry 2). While the reaction proceeded in high yield (77−99%) in a range of aprotic solvents (entries 2−5), dichloromethane was chosen for subsequent reactions due to its greater ability to solubilize a wide range of amine hydrochloride salts.

A variety of bases for the resulfinylation reaction were next evaluated. Hünig's base provided a moderate yield of the sulfinyl diastereomers (entry 6). Proton sponge provided a comparably high yield relative to triethylamine (entry 7); however, its separation from the product by simple extractive techniques was

(1) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Sturmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788–824.

(2) For reviews on the asymmetric synthesis of amines via *N-tert*-butanesulfinyl imines, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (c) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162.

(3) For representative examples of diastereomer analysis after 1,2-nucleophilic additions to *N-tert*-butanesulfinyl imines, see: (a) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883. (b) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819. (c) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092. (d) Beenen, M. A.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304. (e) Beenen, M. A.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6910.

(4) (a) Wakayama, M.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 2646. (b) After submission of this manuscript another report on the formation of *tert*-butanesulfinyl chloride, **3**, by HCl-mediated deprotection of **1** in aprotic solvents appeared. Aggarwal, V. K.; Barbero, N.; McGarrigle, E. M.; Mickle, G.; Navas, R.; Ramon, J.; Unthank, M. G.; Yar, M. *Tetrahedron Lett.* **2009**, Article in Press, DOI: 10.1016/j.tetlet.2009.03.020.

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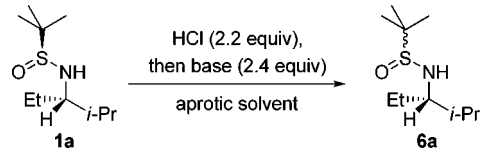
TABLE 1. Reaction Optimization



entry	solvent	base	base addition temp	yield (%)[a]	dr[b]
1	THF	triethylamine	−78 °C	99	65:35
2	THF	triethylamine	rt	90	54:46
3	EtOAc	triethylamine	rt	77	57:43
4	Dioxane	triethylamine	rt	99	58:42
5	CH_2Cl_2	triethylamine	rt	86	60:40
6	CH_2Cl_2	Hünig's base[c]	rt	50	54:46
7	CH_2Cl_2	proton sponge[d]	rt	85	58:42
8	CH_2Cl_2	pyridine	rt	0	

[a] Yields were determined by ^{1}H NMR relative to 3,5-dimethoxytoluene. [b] Diastereomeric ratio was determined by NMR analysis. [c] *N*,*N*-Diisopropylethylamine. [d] 1,2-Bis(dimethylamino)naphthalene.

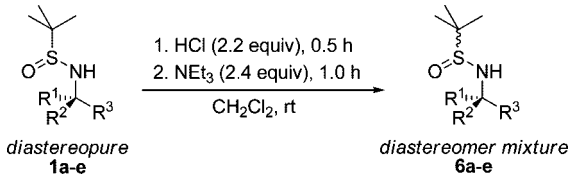
unsuccessful. As might be expected from its decreased basicity, pyridine failed to provide any product (entry 8).

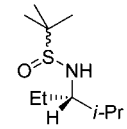
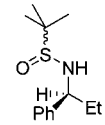
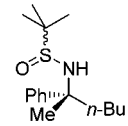
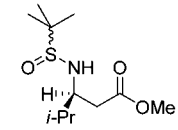
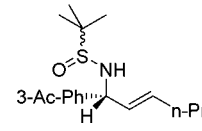
To demonstrate the generality of the method, a variety of *N*-sulfinyl imine addition products were prepared and evaluated under the optimal reaction conditions (Table 2). α-Branched benzylic amines provided an approximate 3:2 ratio of *N*-sulfinylamine diastereomers despite the structural dissimilarity of the two α-substituents (entry 2). Sterically encumbered tertiary carbinamines required slightly longer times for the deprotection of the *tert*-butanesulfinyl group (1 h versus 0.5 h), but still provided a mixture of diastereomers in high yield (entry 3). *β*-Amino esters (entry 4) and α-branched allylic amines (entry 5) are also competent substrates for the reaction sequence. Notably, a simple extractive isolation provided analytically pure material in all cases.

Diastereomerically pure *N*-sulfinylamines generally did not provide a 1:1 mixture of diastereomers upon resulfinylation with sulfinyl chloride **3** (Table 2). This could be the result of either incomplete sulfinyl chloride racemization or dynamic resolution of the sulfinyl chloride under the reaction conditions.[6] The incomplete racemization of sulfinyl chloride was ruled out by subjecting diastereomerically pure (R_S,*S*) and (R_S,*R*) *N*-sulfinylamines to the reaction conditions. As long as the *N*-sulfinylamine starting material is completely deprotected and the intermediate sulfinyl chloride **3** fully racemizes, the same diastereomeric ratio should be obtained independent of the relative configurations of the sulfinyl and α-stereocenters. Indeed, both (R_S,*S*) and (R_S,*R*) *N*-sulfinylamines provided a diastereomeric ratio of 62:38 (Table 3). As predicted, both reactions provided the same major diastereomer as opposite enantiomers: (S_S,*S*) for the (R_S,*S*) starting amine **1b** and (R_S,*R*) for the (R_S,*R*) starting amine **1f**. Therefore, the ∼3:2 ratio of diastereomers is the result of dynamic resolution of sulfinyl chloride under the reaction conditions.[6]

In conclusion, a one-pot method has been developed for the preparation of authentic diastereomers of *N*-*tert*-butanesulfinylamines. This straightforward method, which proceeds in high yields for a broad range of *N*-sulfinylamines, should be extremely useful for obtaining *N*-sulfinylamine diastereomer mixtures as standards for the rapid and accurate determination of diastereomeric purity.

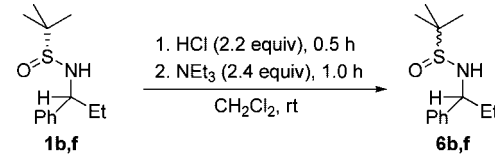
TABLE 2. Preparation of Diastereomer Mixtures from Various *N*-*tert*-Butanesulfinylamines



entry	diastereopure *N*-sulfinyl amine **1**		*N*-sulfinyl amine diastereomer mixture **6**	yield (%)[a]	dr
1	**1a** (S_S, *S*)		**6a**	86	60:40[b]
2	**1b** (R_S, *S*)		**6b**	98	62:38[c]
3[d]	**1c** (S_S, *R*)		**6c**	85	52:48[b]
4	**1d** (R_S, *S*)		**6d**	84	53:47[b]
5	**1e** (R_S, *R*)		**6e**	98	56:44[c]

[a] Yields were determined by mass balance of analytically pure material. [b] Diastereomeric ratio was determined by NMR analysis. [c] Diastereomeric ratio was determined by NMR and HPLC analysis. [d] The HCl-mediated *N*-*tert*-butanesulfinyl deprotection was performed for 1 h.

TABLE 3. Evidence for Complete Racemization of Sulfinyl Chloride 3 under the Reaction Conditions



entry	diastereopure *N*-sulfinylamine **1**	*N*-sulfinylamine diastereomer mixture **6**[a]	
1	**1b** (R_S,*S*)	**6b**	62:38 (S_S,*S*):(R_S,*S*)
2	**1f** (R_S,*R*)	**6f**	62:38 (R_S,*R*):(S_S,*R*)

[a] Diastereomeric ratio was determined by NMR and HPLC analysis.

Experimental Section

General Procedure for Preparing an Authentic Mixture of *N*-*tert*-Butanesulfinylamines. The *N*-sulfinylamine **1** (1.0 equiv) dissolved in CH_2Cl_2 (0.16 M) in an oven-dried vial equipped with

(5) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.

(6) The dynamic resolution of sulfinyl chloride with chiral amine nucleophiles has previously been reported: Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 10127.

a Teflon coated stir bar under nitrogen was placed in an ambient water bath. HCl (4.4 M) in dioxane (2.2 equiv) was added dropwise to this solution, and the reaction mixture was stirred at rt for 0.5−1 h. NEt_3 (2.4 equiv) was then added dropwise and the resulting mixture was stirred at rt for 1 h. The reaction mixture was diluted with EtOAc and washed successively with 1 N $NaHSO_4$, saturated $NaHCO_3$, and brine. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide an authentic mixture of *N*-sulfinylamine diastereomers. The extractive isolation provided analytically pure material.

***N*-(1-Ethyl-2-methylpropyl)-*tert*-butanesulfinylamine (6a).** The general procedure was followed with *N*-sulfinylamine **1a** (20 mg, 0.097 mmol), 4.4 M HCl dioxane (48 μL, 0.21 mmol), and NEt_3 (32 μL, 0.23 mmol) in CH_2Cl_2 (0.61 mL) to afford 17.2 mg (86% yield) of **6a** as a mixture of diastereomers (60:40; S_S,*S*:R_S,*S*). The reaction mixture was stirred for 0.5 h after the HCl addition and for 1 h after the NEt_3 addition. The diastereomeric ratio was determined by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82−0.98 (m, 9H), 1.208 (s, 5.4H), 1.212 (s, 3.6H), 1.33−1.44 (m, 0.6H), 1.47−1.64 (m, 1.4H), 1.75−1.83 (m, 0.4H), 1.89−1.99 (m, 0.6H), 2.84 (d, 0.4H, J = 6.9 Hz), 2.92−2.99 (m, 1H), 3.06 (d, 0.6H, J = 6.9 Hz). The ^{1}H NMR shifts of the (R_S,*S*) diastereomer correspond to the literature data and those of the (S_S,*S*) diastereomer correspond to the literature data for its (R_S,*R*) enantiomer.[5] MS (ESI) *m*/*z* 206 $[MH]^+$. Anal. Calcd for $C_{10}H_{23}NOS$: C, 58.49; H, 11.29; N, 6.82. Found: C, 58.13; H, 10.91; N, 6.50.

***N*-(1-Phenylpropyl)-*tert*-butanesulfinylamine (6b).** The general procedure was followed with *N*-sulfinylamine **1b** (40 mg, 0.17 mmol), 4.4 M HCl dioxane (85 μL, 0.37 mmol), and NEt_3 (57 μL, 0.41 mmol) in CH_2Cl_2 (1.1 mL) to afford 39.1 mg (98% yield) of **6b** as a mixture of diastereomers (62:38; S_S,*S*:R_S,*S*). The reaction mixture was stirred for 0.5 h after the HCl addition and for 1 h after the NEt_3 addition. The diastereomeric ratio was determined by both ^{1}H NMR and HPLC analysis. HPLC analysis (silica column, hexanes:EtOH 97:3, 1.0 mL/min, λ = 210 nm) t_{minor} = 10.6 min, t_{major} = 12.2 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (t, 1.9H, J = 7.3 Hz), 0.84 (t, 1.1H, J = 7.3 Hz), 1.18 (s, 3.4H), 1.23 (s, 5.6H), 1.71−1.91 (m, 1.4H), 2.00−2.11 (m, 0.62H), 3.41 (s, 1H), 4.25−4.32 (m, 1H), 7.24−7.38 (m, 5H). The ^{1}H NMR shifts of the (R_S,*S*) diastereomer correspond to the literature data and those of the (S_S,*S*) diastereomer correspond to the literature data for its (R_S,*R*) enantiomer.[5] MS (ESI) *m*/*z* 240 $[MH]^+$. Anal. Calcd for $C_{13}H_{21}NOS$: C, 65.23; H, 8.84; N, 5.85. Found: C, 64.96; H, 9.07; N, 5.70.

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Supporting Information Available: General experimental methods; specific reaction conditions for **6c**−**f**; copies of ^{1}H NMR of **6a**−**f**, ^{13}C NMR of **6d**−**e**, and HPLC traces of **6b**,**e**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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