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One-pot asymmetric synthesis of *tert*-butanesulfinyl-protected amines from ketones by the in situ reduction of *tert*-butanesulfinyl ketimines

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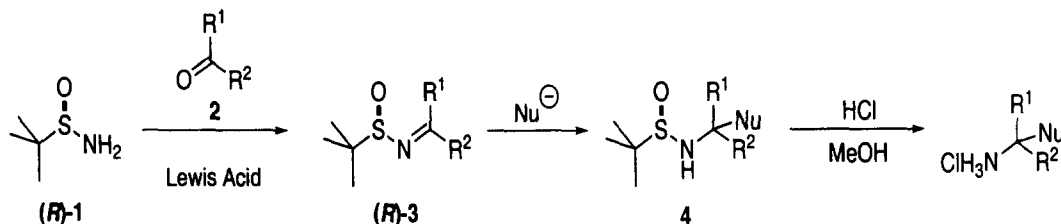
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Abstract

A one-pot method for the asymmetric synthesis of *tert*-butanesulfinyl-protected amines is described. The ketones **2** are condensed with (*R*)-*tert*-butanesulfinamide **1** and the *tert*-butanesulfinyl imine intermediates reduced in situ with NaBH₄ to afford the sulfinamides **4** in 66–86% yield and with drs from 90:10 to 97:3 for both aryl alkyl and dialkyl ketones. Ti(OEt)₄ serves as both a water scavenger and catalyst for imine condensation, and as a Lewis acid that provides enhanced reduction rates and dr. © 1999 Elsevier Science Ltd. All rights reserved.

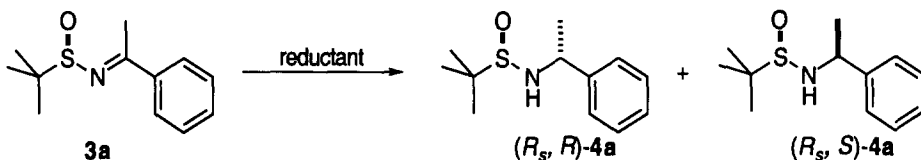
α -Branched amines are key elements of many potent and selective pharmaceuticals, asymmetric catalysts and materials such as unnatural biopolymers. One of the most versatile approaches towards the synthesis of α -branched amines is the reductive amination of ketones. However, with few exceptions,¹ the methods that have been reported for the asymmetric reduction of ketimines provide access to only a limited set of α -branched amine products.^{2,3} Furthermore, these methods generally require isolation of the ketimine intermediate prior to the reduction step. Herein we report the first general one-pot method for the asymmetric synthesis of pre-protected α -branched amines by the Ti(OEt)₄-mediated NaBH₄ reduction of *N*-*tert*-butanesulfinyl ketimines, which are generated in situ from *tert*-butanesulfinamide **1** and the corresponding ketones.



Scheme 1.

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Table 1
Reductions of sulfinyl ketimine **3a**



reductant	solvent	additive	temperature	yield	dr
Na(OAc) ₃ BH	THF	---	rt	42	95:5 ^a
Na(CN)BH ₃	THF	CH ₃ CO ₂ H	rt	77	87:13 ^b
	Toluene	Ti(OEt) ₄	rt	34	75:25 ^b
NaBH ₄	THF	---	rt	83	91:9 ^b
	THF	---	-48 °C	83	92:8 ^a
	THF	Ti(OEt) ₄	-48 °C	97	96:4 ^a
LiBH ₄	THF	Ti(OEt) ₄	-48 °C	75	86:14 ^a

^a Diastereoselection determined by GC analysis of (*R*)- and (*S*)-MTPA derivatives formed after sulfinyl cleavage of the crude product (ref. 7). ^b Diastereoselection determined by HPLC analysis of the sulfinamide product.

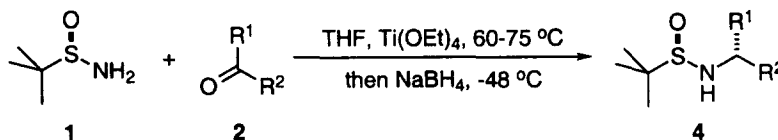
Enantiopure sulfinamide **1** is easily and inexpensively prepared in two steps and in 71–75% overall yield from *tert*-butyl disulfide.⁴ Direct condensation of *tert*-butanesulfinamide **1** with a wide array of aldehydes and ketones provides *tert*-butanesulfinyl imines **3**⁵ to which nucleophiles^{6,7} add in high yields and with excellent diastereocontrol (Scheme 1). Significantly, primary amines can be easily liberated from the sulfinamide products **4** by treatment with methanolic acid.⁸

While highly enantioenriched α -substituted amines can be prepared by the 1,2-addition of Grignard reagents to *tert*-butanesulfinyl aldimines (**3**, R¹=H), the reduction of *tert*-butanesulfinyl ketimines (**3**, R¹=alkyl) is clearly a complementary and useful method. First, for many synthetic targets a ketone precursor is more readily accessible than the aldehyde and Grignard precursors. Second, the sulfinyl moiety should activate the C=N bond towards the 1,2-addition of mild reducing agents, which would allow for the synthesis of amines with functionality that is incompatible with Grignard reagents. Although the asymmetric reduction of sulfinyl imines has previously been explored,⁹ the small number of sulfinyl ketimines that were previously synthetically accessible limited these studies. Moreover, the reductants (DIBAL, 9-BBN, LiAlH₄) that were observed to provide the highest stereoselectivities are not compatible with a variety of functionalities, such as nitriles, esters, or certain alkenes. Previous to our work, the reduction of *tert*-butanesulfinyl ketimines had not been investigated.

We began by evaluating the reduction of sulfinyl imine **3a** with several mild and inexpensive reducing agents (Table 1). At room temperature, NaBH₄ provided the best yield and diastereoselectivity. It was found that the addition of Ti(OEt)₄ improved the dr and greatly enhanced the rate of reduction. As a result, when the reaction was performed at -48 °C, in the presence of Ti(OEt)₄, the sulfinamide product was isolated in 97% yield with a 96:4 dr.

Our interest in incorporating Ti(OEt)₄ in the reduction of imine **3a** stemmed from its role as Lewis acid and water scavenger in the condensation of ketones with **1** (Scheme 1). The reduction could therefore potentially be performed without the isolation of the ketimine intermediate. Indeed, condensation of **1** with acetophenone (1.2 equiv., 65 °C), followed by in situ reduction with NaBH₄ at -48 °C afforded the sulfinamide **4a** in 78% yield and with 96:4 dr, identical to the dr for the reduction of pure sulfinyl imine **3a** (Table 2, entry **2a**).

Table 2
Reductive amination of ketones with sulfinamide 1



ketone 2	R ¹	R ²	<i>E/Z</i> ^a	time ^b (h)	product ^{c,d}	yield	dr ^e
2a	Me	Ph	---	10	4a	78	96:4
2b	Me	<i>i</i> -Pr	---	3	4b	66	97:3
2c	Me	Bu	5:1	3	4c	82	83:17
2d	Me	<i>i</i> -Bu	6:1	14	4d	74	92:8
2e	Bu	<i>i</i> -Pr	---	5 ^f	4e	77 ^f	92:8 ^f
2f	Me	Bn	5:1	6	4f	86	90:10
2g	Me	<i>p</i> -NCPH	---	7	4g	82	96:4
2h	Me	(<i>E</i>)-CH=CHPh	3:1	24	4h	76	90:10

^a Refers to the *E/Z* ratio of isolated *tert*-butanesulfinyl imine intermediates as determined by ¹H NMR. ^b Time for reduction to go to completion. ^c Sample characterization of sulfinamides 4c and 4g is provided (ref. 10). ^d Absolute configuration determined by correlation with known amines. ^e Diastereoselection determined by GC analysis of (*R*)- and (*S*)-MTPA derivatives formed after sulfinyl cleavage of the crude product (ref. 7). ^f Obtained with 3 equiv of Ti(OEt)₄ and reduction at -20 °C.

The generality of the Ti(OEt)₄-mediated one-pot reductive amination was then investigated.¹⁰ Ketones **2b–2h** were condensed with *tert*-butanesulfinamide **1** by heating in THF and Ti(OEt)₄ (2 equiv.). Upon completion, the reaction mixture was cooled to -48 °C and added to a solution of NaBH₄ in THF, also at -48 °C. This method was found to be general for both alkyl aryl and dialkyl ketones. The sulfinamides **4b–4h** were obtained in yields ranging from 66 to 86%. The diastereoselectivity was also high, ranging from 90:10 to 97:3, except for the reductive amination of the most demanding substrate, methyl butyl ketone (**2c**), which still proceeded with 83:17 dr despite the similar steric size of the methyl and butyl substituents.

The rate of reduction is highly substrate-dependent, but most reductions went to completion in 3–24 h. One exception was the reductive amination of isopropyl butyl ketone **2e**. Under the standard conditions, the reduction did not proceed to completion even after 48 hours. By using 3 equiv. of Ti(OEt)₄ and performing the reduction at -20 °C, sulfinamide **4e** was isolated after 5 h in 77% yield and with 92:8 dr (Table 2).

Interestingly, the diastereoselectivities for the reductive aminations of ketones **2d**, **2f**, and **2h** were higher than the *E/Z* ratio of the isolated sulfinyl ketimine intermediates. For example, the sulfinamide **4h** was obtained in a 90:10 diastereomeric ratio, whereas the sulfinyl imine intermediate was isolated as a 3:1 mixture of *E/Z* isomers (¹H NMR in CDCl₃). This enhancement of the dr of the sulfinamide over the *E/Z* ratio of the sulfinimine has also been observed in the 1,2-addition of organolithiums to *tert*-butanesulfinyl ketimines.

Notably, the reductive amination of the highly enolizable ketone **2f** afforded sulfinamide **4f** in 86% yield with 90:10 dr. Moreover, the reduction is quite chemoselective under these conditions. The reductive amination of the (*E*)- α,β -unsaturated ketone **2h** gave only the 1,2-adduct, in 76% yield. This is significant, as NaBH₄ has been observed to reduce α,β -unsaturated ketones to give a mixture of 1,2- and 1,4-adducts¹¹ and Grignard additions to α,β -unsaturated *tert*-butanesulfinyl aldimines proceeds with

competing 1,2- and 1,4-addition.¹² Also, no reduction of the nitrile functionality was detected in the reductive amination of 4-acetyl benzonitrile **2g**, which proceeded in 82% yield.

This protocol represents the first general one-pot method for the asymmetric synthesis of pre-protected α -substituted amines from ketones. A wide variety of ketones can be condensed with *tert*-butanesulfinamide **1** in the presence of $\text{Ti}(\text{OEt})_4$, and the resulting *tert*-butanesulfinyl ketimines were reduced in situ with NaBH_4 to afford *tert*-butanesulfinyl-protected amines. The $\text{Ti}(\text{OEt})_4$ serves as a water scavenger and catalyst for imine condensation, and as a Lewis acid that provides enhanced reduction rates and drs. Not only aromatic but also aliphatic, acyclic ketones can be reductively aminated in good yields and with high diastereoselectivity. In addition, this procedure is compatible with other functionalities present in the molecule, such as nitriles and double bonds conjugated to the imine.

Acknowledgements

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References

- Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1103–1107.
- Johansson, A. *Contemp. Org. Synth.* **1995**, *2*, 393–408.
- Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094.
- Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011–8019.
- Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.
- Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12–13.
- Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883–8904.
- For a review of asymmetric synthesis using sulfinyl imines, see: Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Reddy, G. V.; Zhou, P. *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *120*, 291–303.
- (a) Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 341–343. (b) Hua, D. H.; Lagneau, N.; Wang, H.; Chen, J. *Tetrahedron: Asymmetry* **1995**, *6*, 349–352. (c) Hose, D. R. J.; Mahon, M. F.; Molloy, K. C.; Raynham, T.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 691–703.
- General Procedure: To a 0.5 M solution of freshly distilled $\text{Ti}(\text{OEt})_4$ (2 equiv.) and ketone (1.2 equiv.) in THF under an N_2 atmosphere was added **1** (1 equiv.) and the flask was heated (60–75°C). Upon completion, as determined by TLC, the mixture was cooled to room temperature first and then to –48°C before it was cannulated dropwise into a –48°C solution of NaBH_4 (4 equiv.) suspended in a minimal volume of THF, followed by a THF rinse. The mixture was stirred at –48°C until the reduction was complete, and then MeOH was added dropwise until gas was no longer evolved. The resulting mixture was poured into an equal volume of brine with rapid stirring. The resulting suspension was filtered through a plug of Celite and the filter cake was washed with EtOAc. The filtrate was washed with brine, and the brine layer was extracted with EtOAc (3×). The combined organic portions were dried (Na_2SO_4), filtered, and concentrated. The sulfinamides **4** were purified by silica gel chromatography (hexanes/EtOAc). Pure amine hydrochlorides were isolated by the published procedure [Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914]. Product characterization for sulfinamides **4c** and **4g**: (*R,S*, *R*)-**4c**. ^1H NMR (300 MHz) δ 0.89 (m, 3H), 1.15 (d, $J=8.2$, 3H), 1.19 (s, 9H), 1.31–1.33 (m, 4H), 1.40–1.59 (m, 2H), 3.03 (s, 1H), 3.32–3.40 (m, 1H). ^{13}C NMR (101 MHz) δ 13.89, 21.35, 22.43, 22.48, 27.88, 38.04, 51.20, 55.09. Anal. calcd for $\text{C}_{10}\text{H}_{23}\text{NOS}$: C, 58.47; H, 11.31; N, 6.82. Found: C, 58.36; H, 11.10; N, 6.81. (*R,S*, *R*)-**4g**. ^1H NMR (300 MHz) δ 1.14 (s, 9H), 1.43 (d, $J=6.7$, 3H), 3.67 (d, 1H), 4.45–4.53 (m, 1H), 7.40 (d, $J=8.2$, 2H), 7.53 (d, $J=8.3$, 2H). ^{13}C NMR (101 MHz) δ 22.55, 22.96, 54.14, 55.80, 111.36, 118.64, 127.45, 132.51, 149.42. Anal. calcd for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{OS}$: C, 62.35; H, 7.26; N, 11.19. Found: C, 62.46; H, 7.12; N, 11.04.
- Meyer, G. R. *J. Chem. Educ.* **1981**, *58*, 628–630.
- Liu, G. Unpublished results.