# Diastereoselective Synthesis of N-tert-Butanesulfinylamines through Addition of p-Nitrobenzyl Chloride to N-tert-Butanesulfinimines Using a TDAE Strategy

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Cédric Spitz, Omar Khoumeri, Thierry Terme, Patrice Vanelle*

Aix-Marseille Université, Institut de Chimie Radicalaire ICR, UMR CNRS 7273, Laboratoire de Pharmaco-Chimie Radicalaire, Faculté de Pharmacie, 27 Boulevard Jean Moulin – CS 30064, 13385 Marseille Cedex 05, France
Fax +33(4)91794677; E-mail: patrice.vanelle@univ-amu.fr

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**Abstract:** An easy and efficient method of diastereoselective synthesis of *N-tert*-butanesulfinylamines using a TDAE strategy was developed. Good yields and diastereoselectivities were achieved using readily available *N-tert*-butanesulfinimines and commercially available *p*-nitrobenzyl chloride.

**Key words:** *N-tert*-butanesulfinimines, diastereoselectivity, TDAE, addition, chiral auxiliary

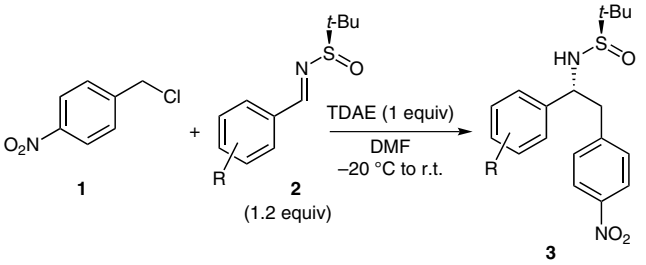
The asymmetric synthesis of amines has received much attention in recent years due to the fact that the amine functionality is present in many biologically active compounds.[1] Adding organometallic reagents to *N*-sulfinimines is one of the most commonly used methods for the asymmetric synthesis of amines.[2] When a nucleophile is added to enantiomerically pure *N-tert*-butanesulfinimines, it usually leads to amines in good yields and diastereoselectivities. Furthermore, the *tert*-butanesulfinyl chiral auxiliary can be removed easily under acidic conditions, giving the corresponding chiral primary amines. However, a disadvantage of the use of organometallic reagents such as Grignard or organolithium reagents is the poor functional-group tolerance. Recently, Ellman and co-workers reported the $MgCl_2$-enhanced addition of benzyl zinc reagents to *N-tert*-butanesulfinimines with good yields, diastereoselectivities, and better functional-group tolerance.[3]

Tetrakis(dimethylamino)ethylene (TDAE) is an organic reducing agent, which reacts with halogenated derivatives to generate a carbanion under mild conditions.[4] Since 2003, we have undertaken a program directed toward the development of original synthetic methods using TDAE methodology in medicinal chemistry.[5] In particular, we have shown that from *o*- and *p*-nitrobenzyl chlorides, TDAE was able to generate a nitrobenzyl carbanion, which can react with various electrophiles such as aromatic aldehydes, α-ketoester, ketomalonate, α-ketolactam, and sulfonimine derivatives.[6]

To the best of our knowledge, the addition of organometallic reagents bearing a nitro group to *N-tert*-butanesulfinimines has never been described, probably due to the difficulty of generating organometallic nitro compounds.[7] As part of our research program,[8] we report herein the application of our TDAE methodology for the diastereoselective addition of *p*-nitrobenzyl chloride to a variety of enantiopure (*R*)-*N-tert*-butanesulfinimines to produce chiral amines in good yields and diastereoselectivities.

The reaction between *p*-nitrobenzyl chloride (**1**) and various enantiopure aromatic *N*-sulfinimines **2a**–**j** in the presence of TDAE at –20 °C for one hour, followed by two

**Table 1** Diastereoselective Addition of *p*-Nitrobenzyl Chloride (**1**) to Aromatic Sulfinimines **2a**–**j** Using TDAE Strategy[a]




1 2 (1.2 equiv) 3

| Entry | R | Imines | Yield of **3** (%)[b] | dr[c] |
|---|---|---|---|---|
| 1 | H | **2a** | 51 | 84:16 |
| 2 | 4-$NO_2$ | **2b** | 70 | 87:13 |
| 3 | 3-$NO_2$ | **2c** | 75 | 83:17 |
| 4 | 2-$NO_2$ | **2d** | 68 | 83:17 |
| 5 | 4-Br | **2e** | 62 | 84:16 |
| 6 | 3-Br | **2f** | 64 | 85:15 |
| 7 | 2-Br | **2g** | 69 | 83:17 |
| 8 | 4-OMe | **2h** | 45[d] | 81:19 |
| 9 | 3-OMe | **2i** | 52 | 84:16 |
| 10 | 2-OMe | **2j** | 54 | 81:19 |

[a] Reactions were performed using 1 equiv of chloride **1**, 1.2 equiv of imines **2a**–**j**, and 1 equiv of TDAE in anhyd DMF stirred at –20 °C for 1 h and then maintained at r.t. for 2 h.
[b] Isolated yield of a mixture of diastereoisomers after purification by chromatography.
[c] Determined by $^1$H NMR analysis of the crude mixture.
[d] Conditions: 1 equiv of imine **2h**, 3 equiv of chloride **1**, and 3 equiv of TDAE were used.

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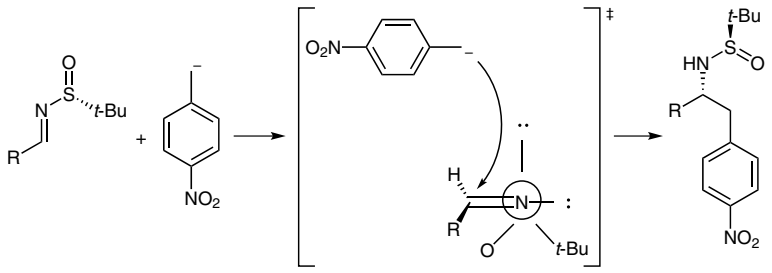


**Scheme 1** Stereochemical induction

hours at room temperature led to the corresponding amines[9] in good yields (45–75%) and diastereoselectivities (from 81:19 to 87:13) as shown in Table 1. Reactions with both electron-poor (entries 2–7) and electron-rich (entries 8–10) aromatic imines produced good yields and good diastereoselectivities. As expected, electron-rich aromatic imines resulted in a slightly diminished yield. *Para*, *meta*, and *ortho* substitution were all well tolerated and, encouragingly, did not affect the diastereoselectivity.

The absolute configuration of the major diastereoisomer of amine **3b** was assigned as *R*,*R* by X-ray structural analysis (Figure 1).[10]

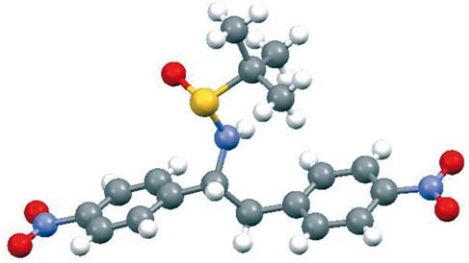
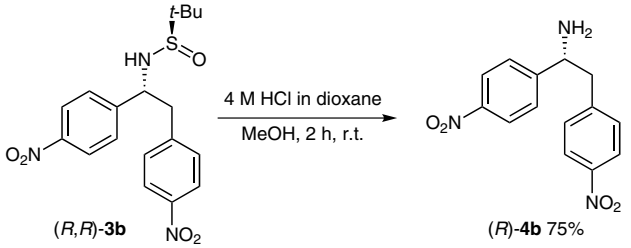


**Figure 1** X-ray crystal structure of major diastereoisomer (*R*,*R*)-**3b**

The direction of induction is consistent with an open transition state as proposed for a number of *N*-*tert*-butanesulfinimines addition reactions (Scheme 1).[2,3]

Besides the mild reaction conditions and the simplicity of the purification procedure, another advantage associated with this method is that it produces *N*-*tert*-butanesulfinyl-protected amines. Such a protecting group is easy to cleave under acidic conditions.[11] For example, when amine (*R*,*R*)-**3b** was subjected to HCl in dioxane–MeOH,[12] primary amine (*R*)-**4b** was obtained in 75% yield (Scheme 2).




**Scheme 2** Removal of *tert*-butanesulfinyl group

In conclusion, the diastereoselective addition of *p*-nitrobenzyl chloride to *N*-*tert*-butanesulfinimines using the TDAE strategy allowed the synthesis of *N*-*tert*-butanesulfinylamines in good yields and diastereoselectivities. Furthermore, the primary amines can be obtained easily by deprotection of the sulfinyl group under acidic conditions. The tolerance of nitro groups suggests this method is a good alternative to the use of organometallic reagents to prepare enantiopure primary amines containing nitro substituents. Further research is in progress to extend the scope to other type of *N*-*tert*-butanesulfinimines.

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**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) **General Procedure**
To a stirred solution of *N*-sulfinimine **2** (0.24 mmol) in DMF (1 mL) at –20 °C was added TDAE (0.2 mmol) followed by dropwise addition of a solution of *p*-nitrobenzyl chloride (**1**) in DMF (1 mL). The solution was vigorously stirred at –20 °C for 1 h and then maintained at r.t. for 2 h. $H_2O$ (5 mL) was added, and the aqueous solution was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layer was washed with $H_2O$ (20 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent furnished the crude product. Purification by silica gel chromatography (EtOAc–PE: from 6:4 to 8:2 depending on the polarity of substrates) allowed pure amine products **3** as a mixture of diastereoisomers.
***N*-[1,2-Bis(4-nitrophenyl)ethyl]-2-methylpropane-2-sulfinamide (3b)**
**Major Diastereoisomer (*R*,*R*)**
Yellow solid; mp 171–174 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.6 Hz, 2 H), 8.08 (d, *J* = 8.5 Hz, 2 H), 7.40 (d, *J* = 8.6 Hz, 2 H), 7.18 (d, *J* = 8.5 Hz, 2 H), 4.80–4.70 (m, 1 H), 3.67 (d, *J* = 4.7 Hz, 1 H), 3.48 (dd, *J* = 13.5, 6.2 Hz, 1 H), 3.13 (dd, *J* = 13.5, 7.7 Hz, 1 H), 1.17 (s, 9 H). $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 48.2, 147.8, 147.1, 144.3, 130.5, 128.3, 124.2, 123.8, 60.1, 56.6, 43.0, 22.6. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $[C_{18}H_{21}N_3O_5SNa]^+$: 414.10941; found: 414.10979.
**Minor Diastereoisomer (*R*,*S*)**
Yellow solid; mp 145–148 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.8 Hz, 2 H), 8.12 (d, *J* = 8.7 Hz, 2 H), 7.39 (d, *J* = 8.8 Hz, 2 H), 7.19 (d, *J* = 8.7 Hz, 2 H), 4.86–4.79 (m, 1 H), 3.58 (br s, 1 H), 3.24 (dd, *J* = 7.3, 3.6 Hz, 2 H), 1.19 (s, 9 H). $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 148.0, 147.7, 147.4, 143.3, 130.5, 128.7, 124.11, 124.08, 59.0, 56.3, 44.7, 22.6. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $[C_{18}H_{21}N_3O_5SNa]^+$: 414.10941; found: 414.10982.
(10) CCDC 929478 contains the supplementary crystallographic data of compound (*R*,*R*)-**3b** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.
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(12) **Deprotection of Amine (*R*,*R*)-3b**
To a stirred solution of N-protected amine (*R*,*R*)-**3b** (47 mg, 0.12 mmol) in MeOH (4 mL) was added 4 M HCl in dioxane (180 μL, 0.72 mmol), and the solution was stirred at r.t. for 2 h. The reaction mixture was then concentrated under reduced pressure, diluted with EtOAc (20 mL), and washed with sat. aq $NaHCO_3$ (20 mL). The aqueous layer was extracted twice more with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure Solvents were evaporated under vacuum. Purification by silica gel chromatography ($CH_2Cl_2$–MeOH = 95:5) allowed pure primary amine **4b** (26 mg, 75%).
**(*R*)-1,2-Bis(4-nitrophenyl)ethylamine (*R*)-(4b)**
Yellow solid; mp 141–144 °C. $^1$H NMR (200 MHz, $CD_3OD$): δ = 8.20 (d, *J* = 8.7 Hz, 2 H), 8.11 (d, *J* = 8.7 Hz, 2 H), 7.56 (d, *J* = 8.7 Hz, 2 H), 7.35 (d, *J* = 8.7 Hz, 2 H), 4.55–4.45 (m, 1 H), 3.27–3.14 (m, 2 H). $^{13}$C NMR (50 MHz, $CD_3OD$): δ = 149.0, 148.4, 146.2, 146.2, 131.7, 129.3, 124.8, 124.6, 57.7, 44.4. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $[C_{14}H_{13}N_3O_4Na]^+$: 310.07983; found: 310.07965.



 