# The *tert*-Butanesulfinyl Group: An Ideal Chiral Directing Group and Boc-Surrogate for the Asymmetric Synthesis and Applications of *β*-Amino Acids

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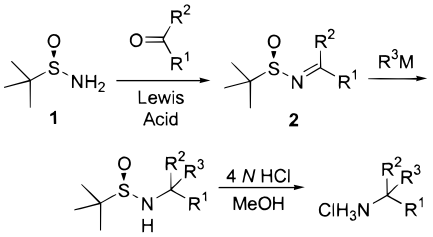
*β*-Amino acids are components of numerous natural products and therapeutic agents.[1] Recently, oligomers of *β*-amino acids have received considerable attention due to their unique structural properties.[2] Although a number of methods are available for the synthesis of *β*-substituted amino acids, highly substituted derivatives are not readily accessible.[1]

We have recently reported a practical, catalytic enantioselective synthesis of the versatile chiral ammonia synthon *tert*-butanesulfinamide **1** in two steps and 71−75% overall yield from *tert*-butyl disulfide.[3] Sulfinamide **1** condenses readily with aldehydes and ketones to give *tert*-butanesulfinyl imines **2** in high yields.[4] Additions of Grignard reagents or organolithiums to **2** proceed cleanly with high diastereoselectivities. Acidic methanolysis then provides the desired α-branched amine−hydrochloride products.[5]



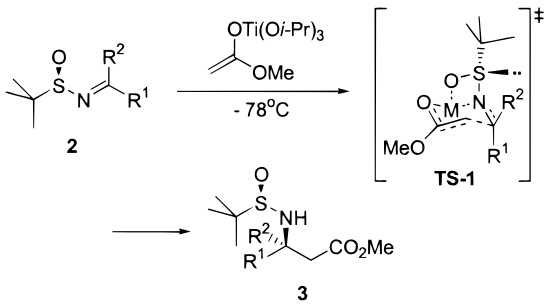

Here, we report that *tert*-butanesulfinyl imines can also serve as chiral building blocks for the asymmetric synthesis of *β*-amino acids via enolate additions to **2**. This method is extremely general, providing access not only to *β*-substituted *β*-amino acids but also to *β*,*β*- and α,*β*-disubstituted *β*-amino acids.[5,6] The latter two classes of *β*-amino acids cannot readily be prepared using standard Arndt−Eistert α-amino acid homologations, Michael addition of amines to acrylate derivatives, or hydrogenation of 3-amino acrylates.[1] Furthermore, we demonstrate that the *tert*-butanesulfinyl moiety serves not only as an imine activating and chiral directing group but also as a versatile amine protecting group for subsequent synthetic transformations.

**Table 1. Solvent and Metal Ion Effects on Diastereofacial Selectivity of Enolate Additions to 2 ($R^1$ = Ph, $R^2$ = H)**

| metal enolate (base) | solvent | yield[a] (%) | dr[b] |
|---|---|---|---|
| Li (LDA) | THF | 76 | 83:17 |
| Li (LDA) | $Et_2O$ | 91 | 67:33 |
| Na (NaHMDS) | THF | 89 | 75:25 |
| Na (NaHMDS) | $Et_2O$ | 78 | 96:4 |
| 1 equiv of $ClTi(O\text{-}i\text{-}Pr)_3$ (LDA) | THF | 90 | 87:13 |
| 2 equiv of $ClTi(O\text{-}i\text{-}Pr)_3$ (LDA) | THF | 90 | 98:2 |
| 4 equiv of $ClTi(O\text{-}i\text{-}Pr)_3$ (LDA) | THF | 90 | 99:1 |

[a] Isolated yields of analytically pure material. [b] Diastereoselectivity was determined by HPLC analysis of the corresponding MTPA derivatives, prepared after sulfinyl cleavage of unpurified product.

**Scheme 1**




To effect the synthesis of *β*-amino acids, we first explored the effect of different metal enolate species and solvents on yield and diastereofacial selectivity of the enolate addition to the *tert*-butanesulfinyl aldimine derived from benzaldehyde. Additions of lithium, sodium, and titanium enolates of methyl acetate to **2** ($R^1$ = Ph, $R^2$ = H) were carried out in THF or $Et_2O$ (Table 1).

The stereoselectivity observed for the lithium and titanium enolate addition is consistent with a proposed Zimmerman−Traxler-type six-membered transition state **TS-1** favoring approach of the enolate from the *si*-face of **2** ($R^1$ = Ph, $R^2$ = H) as shown in Scheme 1.[7] The titanium enolate is prepared by transmetalation of the corresponding lithium enolate with $ClTi(O\text{-}i\text{-}Pr)_3$ and is proposed to be in equilibrium with the lithium enolate and a lithium−titanium−ate enolate complex.[8] The effect of $ClTi(O\text{-}i\text{-}Pr)_3$ stoichiometry on diastereoselectivity was therefore evaluated. An appreciable improvement in diastereoselectivity was observed upon increasing the $ClTi(O\text{-}i\text{-}Pr)_3$ stoichiometry from 1 to 2 equiv, but no significant improvement in stereoselectivity was observed at higher stoichiometries.

Reaction generality was then evaluated by performing titanium (2 equiv) enolate additions to aryl, branched alkyl, and unbranched alkyl *tert*-butanesulfinyl aldimines. All of the substrates showed high diastereoselectivities and high yields. Even enolate additions to sulfinyl ketimines (entries **3f** and **3g**, Table 2) proceeded in high yields and stereoselectivities.[9]

We have also preliminarily evaluated the diastereoselective synthesis of α,*β*-disubstituted *β*-amino esters by reaction of the titanium enolate of methyl propionate with **2** ($R^1$ = $CH_3$, $R^2$ = H) to give 92% of the major diastereomer **4**

(1) For a review of *β*-amino acid syntheses see: Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582. For leading references on catalytic asymmetric syntheses of *β*-amino acids see: (a) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431−432. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *Ibid.* **1997**, *119*, 7153−7154.

(2) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (b) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015−2022. (c) Clark, T. D.; Buehler, L. K.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 651−656.

(3) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011−8019.

(4) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.*, submitted.

(5) For a review of *p*-toluenesulfinyl imine chemistry, see: Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13−18.

(6) Acetate enolate additions to *p*-toluenesulfinyl aldimines have been explored by others: Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. *J. Org. Chem.* **1995**, *60*, 7037−7039; Fujusawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881−3884.

(7) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387−6389.

(8) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722−5728.

(9) Only the *E* isomer of sulfinyl ketimines prepared from isopropyl methyl ketone and acetophenone are observed by $^1H$ NMR.

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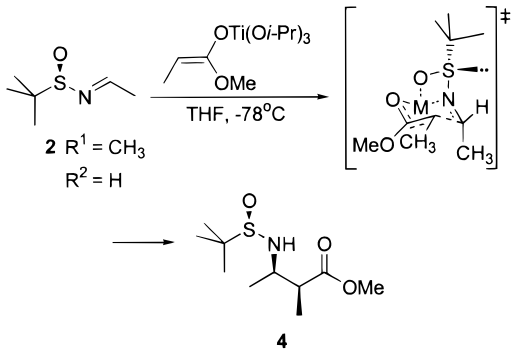
**Table 2. Effect of Sulfinyl Imine Substitution on Yield and Diastereoselectivity**

| cmpd | $R^1$ | $R^2$ | yield[a] (%) | dr[b] |
|---|---|---|---|---|
| **3a** | Me | H | 94 | 99:1 |
| **3b** | *i*-Pr | H | 85 | 98:2 |
| **3c** | *i*-Bu | H | 80 | 98:2 |
| **3d** | Ph | H | 90 | 98:2 |
| **3e** | 3-pyridine | H | 70 | 95:5[c] |
| **3f** | *i*-Pr | Me | 85 | 99:1 |
| **3g** | Ph | Me | 89 | 98:2 |

[a] Isolated yields of analytically pure material. [b] Diastereoselectivity was determined by HPLC analysis of the MTPA derivatives, prepared after sulfinyl cleavage of unpurified product. [c] Diastereoselectivity was determined by $^1$H NMR.

**Scheme 2**

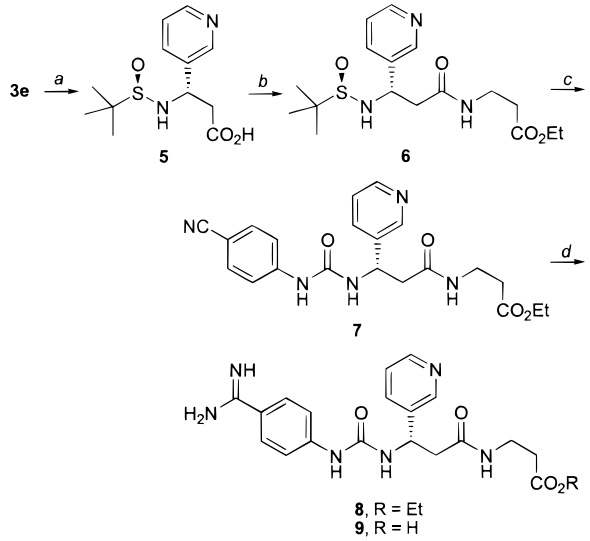



(Scheme 2). Cleavage of the *tert*-butanesulfinyl group followed by acylation with benzoyl chloride provides the benzamide product. Correlation of the spectral properties to literature values for optical rotation and $^1$H and $^{13}$C NMR spectra[10] confirmed that the reaction proceeded with *syn* selectivity, consistent with a Zimmerman−Traxler transition state.

The *tert*-butanesulfinyl group not only is an ideal auxiliary for the synthesis of *β*-amino esters but also can serve as a versatile, low molecular weight protecting group that can be readily removed by treatment with stoichiometric HCl. To demonstrate the suitability of the *tert*-butanesulfinyl group as a Boc-surrogate, we have prepared compound **8**, which constitutes a formal synthesis of **9**, investigated by Monsanto Co. (St. Louis) as a GPIIbIIIa antagonist and which incorporates *β*-(3-pyridine)-*β*-amino acid.[11] This *β*-amino acid is also a key pharmacophore in a number of other reported GPIIbIIIa antagonists.[12]

Hydrolysis of **3e** cleanly provided acid **5**, demonstrating the stability of the *tert*-butanesulfinyl group toward basic

**Scheme 3[a]**




[a] Reaction conditions: (a) LiOH, MeOH, $H_2O$; (b) *β*-Ala-OEt·HCl, DCC, HOBt, $CH_2Cl_2$; (c) HCl, EtOH, then 4-cyanophenylisocyanate, *i*-$Pr_2NEt$, DMF; (d) HCl, EtOH, then $NH_4OH$, $NH_4Cl$.

reaction conditions (Scheme 3). After filtration through silica gel, the acid was coupled to *β*-Ala-OEt using standard peptide coupling conditions in 85% yield for the two-step process. The *tert*-butanesulfinyl group was then cleaved by brief treatment with HCl/EtOH at room temperature, followed by reaction with 4-cyanophenylisocyanate to afford **7** in 92% overall yield. Conversion of the nitrile to an amidine was accomplished by treatment with HCl/EtOH and then $NH_4OH/NH_4Cl$ to afford the literature compound **8** in 65% yield, which can be converted to **9** by straightforward saponification.[11]

In conclusion, we have demonstrated the utility of *tert*-butanesulfinyl imines for the asymmetric synthesis of *β*-substituted and *β*,*β*- and α,*β*-disubstituted *β*-amino acids in high yields and diastereoselectivities. We have further demonstrated the utility of the *tert*-butanesulfinyl group as a versatile amine protecting group that is stable to basic conditions and amide bond formations but can be cleaved with stoichiometric acid treatment. The applicablity of *N*-*tert*-butanesulfinyl-*β*-amino acids to the rapid solid-phase synthesis of *β*-amino acid oligomers will be reported in due course.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for compounds **2e** and **3**−**8** (10 pages).

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