

# SYNLETT Spotlight 306

## 2-Methyl-2-propanesulfinamide (Ellman's Sulfinamide): A Versatile Chiral Reagent



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

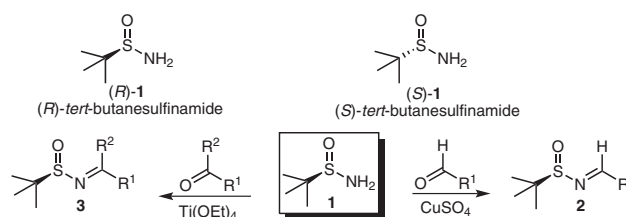
Compiled by Xiao-Yu Guan

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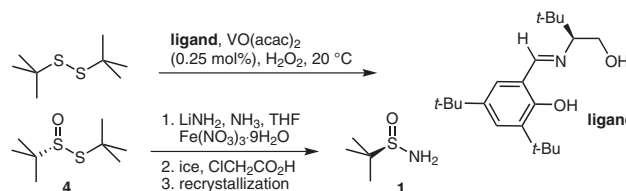
### Introduction

Enantiopure 2-methyl-2-propanesulfinamide (*tert*-butanesulfinamide) was introduced by Ellman in 1997.<sup>1</sup> As a chiral ammonia equivalent, it can easily condense with aldehydes and ketones to afford *tert*-butanesulfinyl imines in high yields (Scheme 1).<sup>2</sup> The *tert*-butanesulfinyl group activates these imines for the addition of many different classes of nucleophiles and serves as a powerful chiral directing group to provide products with generally high diastereoselectivity. Subsequent removal of the *tert*-butanesulfinyl group under mild conditions cleanly provides the amine products. Many versatile building blocks<sup>3</sup> including *syn*- and *anti*-1,2- or 1,3-amino alcohols,<sup>4,5</sup>  $\alpha$ -branched and  $\alpha,\alpha$ -dibranched amines,<sup>6</sup>  $\alpha$ - or  $\beta$ -amino acids and esters<sup>7,8</sup> can be efficiently synthesized by using this methodology. In addition, this methodology can also be used in the synthesis of antibiotics, biologically active compounds, and other complex natural products.<sup>9</sup> Furthermore, *tert*-butanesulfinamide has been used in the synthesis of asymmetric ligands<sup>10</sup> or catalysts<sup>11</sup>, and in a few cases, appears as the chirality-bearing component.<sup>12</sup>



**Scheme 1** Synthesis of sulfinyl aldimines or ketimines

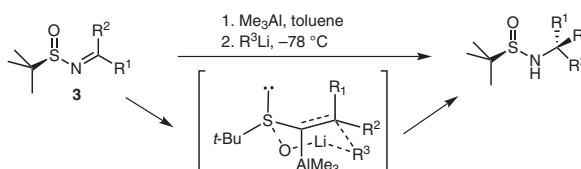
Each configuration of 2-methyl-2-propanesulfinamide is readily available in a two-step process of catalytic asymmetric oxidation of *tert*-butyl disulfide, followed by the reaction of the *tert*-butanethiosulfinate product 4 with an amide anion (Scheme 2).<sup>13</sup>



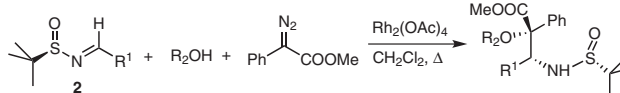
**Scheme 2** Preparation of (*R*)-*tert*-butanesulfinamide

### Abstracts

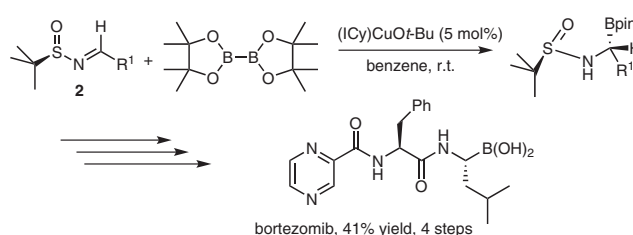
(A) Ellman and co-workers have demonstrated the facile synthesis of chiral  $\alpha,\alpha$ -dibranched amines through 1,2-addition of organolithium reagents to *N*-*tert*-butanesulfinyl ketimines, which proceeds with high yields and diastereoselectivities.<sup>6b</sup>



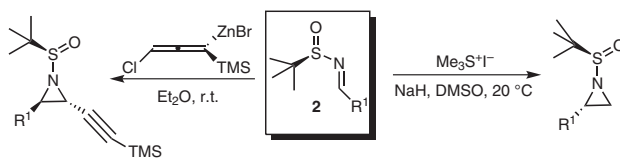
(B) *N*-*tert*-Butylsulfinyl imines have been used in a highly diastereoselective multi-component reaction of phenyldiazoacetates, alcohols, and imines, which provides readily access to  $\beta$ -amino- $\alpha$ -hydroxyesters in high optical purity.<sup>4d</sup>



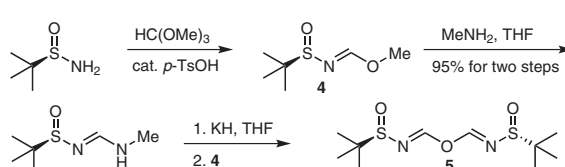
(C) Ellman and co-workers have reported the copper-catalyzed addition of bis(pinacolato)diboron to *N-tert*-butanesulfinyl aldimines with excellent diastereoselectivity for diverse chiral  $\alpha$ -amino boronic acids.<sup>14</sup> Furthermore, the *N*-sulfinyl  $\alpha$ -amino boronate ester addition products can be used as intermediates in the asymmetric synthesis of bortezomib.



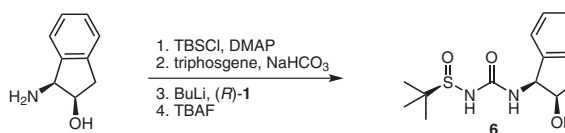
(D) Morton and co-workers synthesized chiral aziridines using trimethylsulfonium iodide with good yields and diastereoselectivities.<sup>15a</sup> Chemla and Ferreira reacted a racemic allenylzinc substrate with various *N-tert*-butanesulfinyl imines to achieve *trans*-ethynylaziridines as diastereomerically and enantiomerically pure compounds in good yields.<sup>15b</sup>



(E) Using *N-tert*-butanesulfinamide as starting material, Ellman and co-workers have synthesized a novel bis(sulfinyl)imidoamidine (siam) ligand **5** in three straightforward steps.<sup>10b</sup> The complex of bis(sulfinyl)imidoamidine **5** with copper(II) catalyzes the Diels–Alder reaction with exceptional levels of enantio- and diastereoselectivity.



(F) Ellman and co-workers have developed a new class of organo-catalysts that incorporate the *N*-sulfinyl urea substituent, which is acidifying and serves as a chiral controlling element.<sup>11</sup> The condensation of *tert*-butanesulfinamide with the appropriate isocyanate in one step provides urea **6**, which is proven to be an efficient organo-catalyst in the enantioselective aza-Henry reaction.



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