SYNLETT Spotlight 306

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

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

Introduction

Enantiopure 2-methyl-2-propanesulfinamide (*tert*-butanesulfinamide) was introduced by Ellman in 1997.¹ As a chiral ammonia equivalent, it can easily condense with aldehydes and ketones to afford *tert*-butanesulfinyl imines in high yields (Scheme 1).² 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 blocks³ including *syn*- and *anti*-1,2- or 1,3-amino alcohols,^{4,5} α -branched and α,α -dibranched amines,⁶ α - or β -amino acids and esters^{7,8} 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.⁹ Furthermore, *tert*-butanesulfinamide has been used in the synthesis of asymmetric ligands¹⁰ or catalysts¹¹, and in a few cases, appears as the chirality-bearing component.¹²

Scheme 1 Synthesis of sulfinyl aldimines or ketimines

Each configuration of 2-methyl-2-propanesulfinamid 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).¹³

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

Abstracts

(A) Ellman and co-workers have demonstrated the facile synthesis of chiral α,α -dibranched amines through 1,2-addition of organolithium reagents to *N*-*tert*-butanesulfinyl ketimines, which proceeds with high yields and diastereoselectivities.^{6b}

(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 β -amino- α -hydroxyesters in high optical purity.^{4d}

(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 α -amino boronic acids.¹⁴ Furthermore, the *N*-sulfinyl α -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.^{15a} 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.^{15b}

(E) Using *N*-*tert*-butanesulfinamide as starting material, Ellman and co-workers have synthesized a novel bis(sulfinyl)imidoamidinium (siam) ligand **5** in three straightforward steps.^{10b} The complex of bis(sulfinyl)imidoamidinium **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.¹¹ 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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