SYNTHETIC APPLICATIONS OF THE VERSATILE NEW CHIRAL N-SULFINIMINE: N-2,2-DIMETHYL-1,3-DIOXOLAN-4-YL METHYLENE)-2-METHYL PROPANE-2-SULFINAMIDE

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ABSTRACT
We report an asymmetric synthesis of chiral amines (4S,5S)-Cytoxzone, Taxol side chain moiety and (S)-Levetiracetam starting from versatile new chiral N-sulfinimine. The key step, stereo selective 1,2-addition of Grignard reagent to chiral N-sulfinimine derived from (R)-glyceraldehyde acetonide and (S)-t-BSA gave the corresponding sulfonamide in high diastereo selectivity. Subsequent reactions yielded the targeted biological active and pharmaceutical important compounds with high purity (>99%) and yield.

KEYWORD: N-Sulfinimine, 1,2 addition of organo metallics, 4S,5S)- Cytoxzone, Taxol side chain moiety, (S)-Levetiracetam.

INTRODUCTION
The amine group is one of the fundamental structures in organic chemistry and α-branched amines play a crucial role as characteristic structural features in bioactive natural products and pharmaceutically important compounds.[1]

Sulfinimines (N-sulfinyl imines) are a special class of imines that display unique reactivity and stereoselectivity.[2a] Moreover, unlike other imine N- auxiliaries, the sulfinyl group in the product sulfamid is easily removed under mild conditions.[2b] The preparations and reactions of sulfinimines including their applications in asymmetric synthesis have been the subject of several reviews that cover the literature from their first preparation through 1999.[3]

![](Fig-1_Synthesis_of_tern-butanesulfinamide.png)

This report is intended to update the most recent advances in asymmetric transformations using enantiopure sulfinimines and application in enantioselective synthesis of targeted biological active compounds like (4S,5S)- Cytoxzone, Taxol side chain moiety, (S)-Levetiracetam and several other molecules using versatile new chiral N-Sulfinimine(N-2,2-dimethyl-1,3-dioxolan-4-y)methylene)-2-methylpropane-2-sulfamid with high purity.[4]

Enantiopure 2-methyl-2-propanesulfinamide (tert-butane sulfamid) was introduced by Ellman in 1997.[5] As a chiral ammonia equivalent (Fig-1), it can easily condense with aldehydes and ketones to afford tert-butane sulfinil imines in high yields (Fig-2).[6]
The tert-butane sulfinyl 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 diastero selectivity. Subsequent removal of the tert-butane sulfinyl group under mild conditions cleanly provides the amine products. Many versatile building blocks have been identified including syn- and anti-1,2- or 1,3-amino alcohols, α-branched and α-α-dibranched amines, 6 α- or β-amino acids and esters 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. Furthermore, tert-butane sulfinamide has been used in the synthesis of asymmetric ligands or catalysts and in a few cases, appears as the chirality-bearing component.

Fig-2 General sequence for the synthesis of amines from N-tert-Butanesulfinyl imines

Fig-3: 1,2 addition of organ metallic reagents to tert-butylsulfinyl ketimines & aldimines via six-member ring transition state

For the additions of Grignard reagents to imine, a six-membered ring transition state with Mg Coordinated to the oxygen of the sulfinyl group can be proposed (Fig-3). In this transition state, the bulky ten-butyl group occupies the less hindered equatorial position resulting in preferential attack from the same face for all additions. This transition state is consistent with the observed asymmetric induction for all of the reactions performed and is consistent with the observed solvent effects. The non-coordinating solvent, CH₂Cl₂, provides the highest selectivity’s, while more strongly coordinating solvents like Et₂O and especially THF likely interfere with the formation of the proposed six-membered ring transition state resulting in reduced selectivity’s.

Fig-4: synthetic applications of versatile N-sulfinimine (N-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide) towards biological active molecules
The versatility of 2-Methyl-2-propanesulfinamide (Ellman’s Sulfinamide) as chiral auxiliary discouresed in various review articles.[13] The Applications of tert-butane sulfinamide in the Asymmetric synthesis of amines as well documented in the literature.[12] Recent applications of chiral N-tert-butanesulfinylimine, chiral diene ligands and chiral sulfur olefin ligands in asymmetric synthesis.[15]

The present review covers the application of new versatile chiral methylpropane-2,2-dioxolan sulfinamide for the preparation of biological active molecules tetra fluorinated amino sugars, N-Boc-Norloline (insect anti feedant & insecticidal activities), Cytoxazone (cytokine modulator), Hydroxyl ethylamine inhibitors, Levetiracetam (Anti epileptic), Taxol side chain (Anti cancer), N-sulfonyl aziridines (chiral amine source).

The aldehyde, Glyceraldehyde acetonide, on reaction with t-butylsulfinamide ((S,R)-t-BSA) using CuSO₄ in dichloromethane at room temperature yielded the (S,R,E)-N-((S,S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide 1 with more than 99% de (Scheme-1). No epimisation at α-centre was detected by high performance liquid chromatography (HPLC) analysis of chiral sulfinimine, 1 which provides an access to generate a diverse range of substituted imines by 1,2-addition of Grignard reagents.

Example:1
Asymmetric synthesis of 4S,5S)-2-oxo-4-phenyloxazolidine-5-carboxylic acid using a 1,2-addition of PhMgBr to an N-sulfinimine derived from (R)-glyceraldehyde acetonide and (S)-t-BSA Babu, K. Chandra et al reported the synthesis of taxol side chain using versatile N-sulfinimine (S,E)-N-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide.[19]

Chiral 3-Amino-3-phenylpropane-1,2-diol is a key chiral structural component in a variety of therapeutically active molecules such as side chain of Taxol[16] and its 2-oxazolidinone derivatives like Cytoxazone, epi-Cytoxazone[17] The syn-β-amino alcohols such as 1,2-aminoindanols serve as biological active molecules as well as chiral ligands.[18]

Herein, Babu, K. Chandra et al reported an asymmetric synthesis of taxol side chain via stereoselective 1,2-addition of phenylmagnesium bromide (PhMgBr) to new N-sulfinimine,1 derived from (R)-glyceraldehyde acetonide.

Scheme-1: Synthesis of (S,E)-N-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide

Scheme-2: Mechanistic pathway for the addition of PhMgBr to convert sulfinimine,1 into sulfinamine, 2

It is apparent that the 1,2-addition of PhMgBr to chiral sulfinimine, 1 proceeds via transition state 1a (Scheme-2).[20]
Chiral sulfinimine, 1 on treatment with PhMgBr in ether at -70°C gave the (S)-N-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)(phenyl)methyl)-2-methylpropene-2-sulfinamide, 2 with high diastero selectivity (95.24% de by HPLC). Deprotection of the t-butylsulfonyl group and 1,3-dimethyl acetal in 3 was performed in acidic media (methanolic HCl) to give the syn-β-aminoalcohol 3. The amine functionality in 3 was protected as N-Boc derivative 4. Compound 4, on exposure to NaH in THF cyclosis regioselectively to 5. Alcohol 5 has been confirmed to exist in threo configuration (syn product) To oxidise primary alcohol of compound 5, into respective acid 6 in non-racemisation way using CrO3 (Jone’s method) to oxidize compound 5 into corresponding carboxylic acid 1 in moderate yields ~55% (Scheme 5) Ester of 6 (syn) can be epimerised to respective anti-isomer, but it is not vice-versa. Earlier, from our research group ethyl ester of 6 (syn racemize) has been epimerised to its ethyl ester of anti-isomer 7 (racemic). Thus, this strategy is diverse enough to produce both syn and anti isomers as per the requirement. Moreover, stereo centers in 7 are similar to taxol side chain.

Concussion: Babu, K. Chandra et al, reported an asymmetric synthesis of taxol side chain via stereoselective 1,2-addition of phenylmagnesium bromide (PhMgBr) to new N-sulfinimine.

Example 2: Asymmetric Synthesis of Amines by the Knoehn-Type MgCl2-Enhanced Addition of Benzyl Zinc Reagents to N-tert-Butanesulfinyl Aldimines

Jonathan, A. Ellman et al, synthesized hydroxyl ethylamine-based protease inhibitors using versatile N-sulfinimine (S,E)-N-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropene-2-sulfinamide.[21]

Previous reported methods were limited to the coupling of aryl and vinyl boron reagents to N-sulfinimine, which are sp2 hybridized. Therefore, additions of sp3 hybridized organo metallic reagents that also proceed with broad functional group compatibility would represent a significant advance. Herein Ellman et al reported the application of this new methodology for the diastereoselective addition of a variety of benzyl zinc reagents to N-tert-butanesulfinyl imine,1 substrates with excellent functional group tolerance.

Here in this the application of this new methodology for the diastereoselective addition of a variety of benzyl zinc reagents to chiral N-tert-butanesulfinyl imine, 1 substrates with excellent functional group tolerance proteases such as HIV protease and β-secretase.[22] Benzyl zinc reagent added to imine,1 in high yield and with exceptionally high selectivity. Importantly, the stereo chemistry obtained is that most commonly found in hydroxyl ethylamine-based protease inhibitors. Diastereomer, 8 was converted to N-Boc amino diol, 9 by simultaneous deprotection of the sulfinyl and
isopropylidene protecting groups followed by Boc-protection of the amine functionality (Scheme-4). N-Boc-3-amino-1,2-diols with the stereochemistry present in 9 provide direct access to hydroxyl ethylamine inhibitors.\(^{23}\)

**Conclusion:** Jonathan, A. Ellman et al. reported synthesis of hydroxyl ethylamine-based protease inhibitors using versatile N-sulfinimine by stereo selective 1,2-addition of Benzyl Zinc Reagent to imine.

**Example:3**

**New, efficient, and high-yielding asymmetric synthesis of (4S,5S)-cytoxazone**

Babu, Kollapudi Chandra et al. synthesized (4S,5S)-cytoxazone (A microbial metabolite) using versatile N-sulfinimine \((S,E)-N-(((S)-2,2\text{-dimethyl-1,3-dioxolan-4-yl})\text{methylene})\text{-2-methylpropane-2-sulfamid})^{[24]}\).

Here in this Babu, Kollapudi Chandra et al reported a new approach for the asymmetric synthesis of (4S,5S)-Cytoxazone. 13 in five steps and in 48% overall yield starting from versatile N-sulfinimine.

The key step includes stereo selective 1,2-addition of p-methoxy phenyl magnesium bromide (p-OMePhMgBr) to chiral N-sulfinimine with high diastereo selectivity. Deprotection of t-butyldimethyl sulfonyl group and 1,3-dimethyl acetal in single step followed by N-Boc protection and subsequent carbonylation yields the targeted (4S,5S)-Cytoxazone, 13.

**SCHEME-5: Asymmetric synthesis of (4S,5S)-Cytoxazone using versatile N-sulfinimine (S,E)-N-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide**

**Conclusion:** Babu, Kollapudi Chandra et al, synthesized (4S,5S)-cytoxazone (A microbial metabolite) using versatile N-sulfinimine, 1 by stereo selective 1,2-addition of p-methoxy phenyl magnesium bromide to imine.

**Example:4**

**Enantio selective synthesis of antiepileptic drug, (-)-Levetiracetam. Synthetic applications of the versatile new chiral N-sulfamine**

Chandra Babu, K. et al, synthesized (-)-Levetiracetam (antiepileptic drug)using versatile N-sulfamine \((S,E)-N-(((S)-2,2\text{-dimethyl-1,3-dioxolan-4-yl})\text{methylene})\text{-2-methylpropane-2-sulfamid})^{[25]}\).

Here in this Chandra Babu, K. et al reported an asymmetric synthesis of (-) – Levetiracetam, 19 in six steps starting from versatile new chiral N-sulfamine, 1. The key step, stereoselective 1,2-addition of Ethylmagnesium bromide (EtMgBr) to chiral N-sulfamine to give the corresponding sulfonamide, 14 in high diastereoselectivity. Simultaneous deprotection & deacetylation followed by NaIO\(_2\) cleavage and reduction gave \(\beta\)-amino alcohol, 16. Subsequent reactions yielded the targeted compound levetiracetam, 19.
SCHEME-6: Enantioselective synthesis of antiepileptic drug, (-)-Levetiracetam using versatile N-sulfinimine (S,E)-N-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylprop-2-sulfamid

Conclusion: Chandra Babu, K. et al, synthesized (-)-Levetiracetam (antiepileptic drug) using versatile N-sulfinimine, by stereo selective 1,2-addition of Ethyl magnesium bromide to imine.

Example:5  
Stereo selective Synthesis of Carbohydrate-Derived N-Sulfonyl Aziridines  
Rodriguez-Solla, Humberto et al, synthesized carbohydrate and biological active aziridines, sugar aziridines, sugar amino acids, aza sugars using versatile N-sulfinimine (R,E)-N-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylprop-2-sulfamid.[26]

Here in Humberto et al, reported synthesis of N-Sulfonyl Aziridines which is useful intermediate for chiral amines, aza sugars, sugar amino acids. versatile N-sulfinimine Initial attempts to prepare aziridines were performed starting from imine, Iodo methyl lithium was generated in situ by treatment of diodo methane with methyl lithium in the presence of imine at −78°C using tetrahydrofuran (THF) as solvent and followed by oxidation of N-sulfinil aziridines was carried out in the presence of MCPBA and N-sulfonyl aziridine being isolated as a single stereoisomer in 86% yield (scheme 7). Aziridination reactions on other sugar-based imines gives good yields (>70%) and in stereoisomeric ratios ranging from 72:28 to >98:2.

Conclusion: In conclusion, Here described the reaction of iodo methyl lithium with a variety of imines to afford, in high yields, sugar-based N-sulfonyl aziridines.

Example:6  
Stereo selectivity of the Honda-Reformatsky Reaction in Reactions with Ethyl Bromo difluoro acetate with α-Oxynenated Sulfinylimines  
Fontenelle, Clement Q. et al, reported the synthesis of α,α-difluoro-β-amino acids (Biological active pharma and agro products) using versatile N-sulfinimine (S,E)-N-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylprop-2-sulfamid[27] by Honda-Reformatsky reaction.

The fluorine and related compounds shows relatively more pharmaceutical and agrochemical biological activities, around 20% of the commercially available pharmaceuticals and 30% of agrochemicals are fluorinated and performance materials, such as liquid crystals. Given the abundance of amine-containing bioactive compounds, their fluorination has received great attention. The β-position of amino groups is often considered for fluorination given the resulting effect on their pKa(H) value and lipophilicity. Fluorination will also have an impact on the amine hydrogen-bonding properties and will induce potentially strong conformational effects.

A mixture of sulfinyl imine and RhCl(PPh3)3 (3 mo %) in THF at −20°C react with Ethyl Bromo difluoro acetate and Et2Zn followed by Purification gives desired α,α-difluoro-β-amino acids by Honda-Reformatsky Reaction.
The conformational properties and biological activities of β-amino acids have received great attention, including the corresponding α,α-difluoro-β-amino acids. Their synthesis using direct C–C bond formations with fluorinated building blocks usually involve Reformatsky reaction of BrCF₂COOEt to imine derivatives (Scheme 8). The synthesis of enantio enriched α,α-difluoro-β-amino acid derivatives using the Reformatsky reaction has been reported with imines derived from chiral amines. Excellent diastereoselictivity’s are obtained with imines derived from aromatic aldehydes, while imines derived from aliphatic substrates generally give lower selectivity’s.

**Conclusion:** successfully synthesized (3R,4S,SS)-ethyl 4,5-isopropylidenedi oxy-3-(tert butyl sulfinyl amino)-2,2-difluoropentanoate (α,α-difluoro-β-amino acids and esters) by Honda-Reformatsky Reaction using Ethyl Bromo difluoro acetate and versatile N-sulfinimine, I (α-Oxygenated Sulfinylimines)

**Example:7**

The synthesis of tetra-fluorinated amino-sugars

Fontenelle, Clement Q. et. al., reported the synthesis of tetra-fluorinated amino-sugars synthesized carbohydrate and biological active aziridines, sugar arridines, sugar amino acids, azo sugars using versatile N-sulfinimine (S,E)-N-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide. (28)

The amino group in α-position of a CF₂(CF₃) group is proposed as a mimic for the hydrogen bond accepting capacity of an alcohol group. Fluorination of carbohydrates is a popular strategy to investigate carbohydrate binding epitopes and enzymes mechanism or to stabilize glycosidic bonds and indeed a vast number of fluorinated carbohydrate and their glycosides have been synthesized for these purpose.

**Example:8**

Studies on the Second-Generation Approach to Loline Alkaloids: Synthesis of N-Bus-norloline through N-tert-Butanesulfinyl Imine Based Asymmetric Vinylogous Mannich Reaction

Ye, Jian-Liang, et. al., reported the synthesis of N-Bus-norloline through N-tert-Butanesulfinyl Imine Based Asymmetric Vinylogous Mannich Reaction (Loline alkaloids).

Loline alkaloids are a group of saturated pyrrolizidine alkaloids. Loline alkaloids show a broad spectrum of bioactivities including insect antifeedant and insecticidal activities. Significantly, although the insecticidal activities of loline alkaloids are approximately as potent as nicotine, these alkaloids exhibit low mammalian toxicity.
SCHEME 10: Synthesis of N-Bus-norloline (Loline Alkaloids) through N-tert-Butanesulfinyl Imine Based Asymmetric Vinylogous Mannich Reaction

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