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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)-Cytoxazone, 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, 4*S*,5*S*)- Cytoxazone, 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 sulfinamide 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]

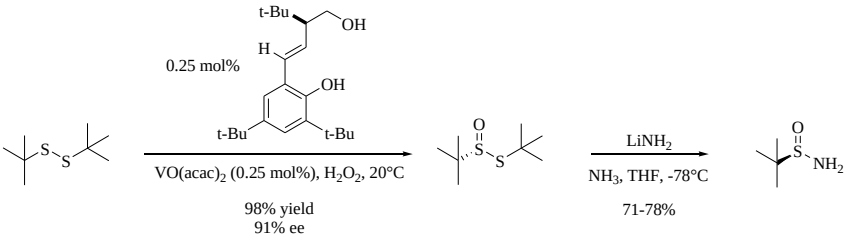


Fig-1 Synthesis of *tert*-butanesulfinamide

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 (4*S*,5*S*)- Cytoxazone, Taxol side chain moiety, (*S*)-Levetiracetam and several other molecules using versatile new chiral *N*-Sulfinimine(*N*-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide) with high purity.[4]

Enantiopure 2-methyl-2-propanesulfinamide (*tert*-butane sulfinamide) 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 sulfinyl imines in high yields (**Fig-2**).[6]

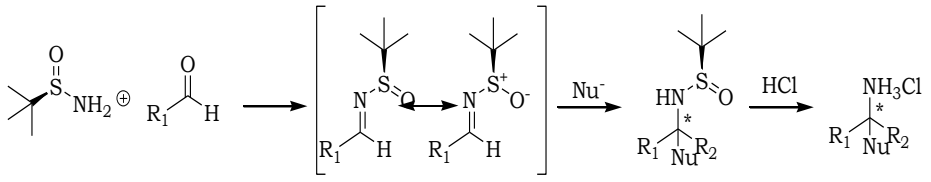


Fig-2 General sequence for the synthesis of amines from *N-tert*-Butanesulfinyl imines

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 diastereo selectivity. Subsequent removal of the *tert*-butane sulfinyl group under mild conditions cleanly provides the amine products. Many versatile building blocks[7] 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[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*-butane sulfinamide has been used in the synthesis of asymmetric ligands[10] or catalysts[11] and in a few cases, appears as the chirality-bearing component.[12]

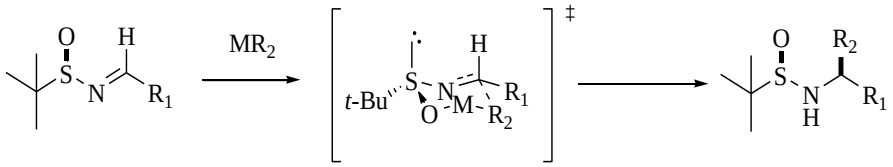


Fig-3: 1,2 addition of organ metallic reagents to *tert*-butylsulfinyl ketimines & aldemines via six-member ring transition state

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, CH_2CI_2, provides the highest selectivity's, while more strongly coordinating solvents like Et_20 and especially THF likely interfere with the formation of the proposed six-membered ring transition state resulting in reduced selectivity's.

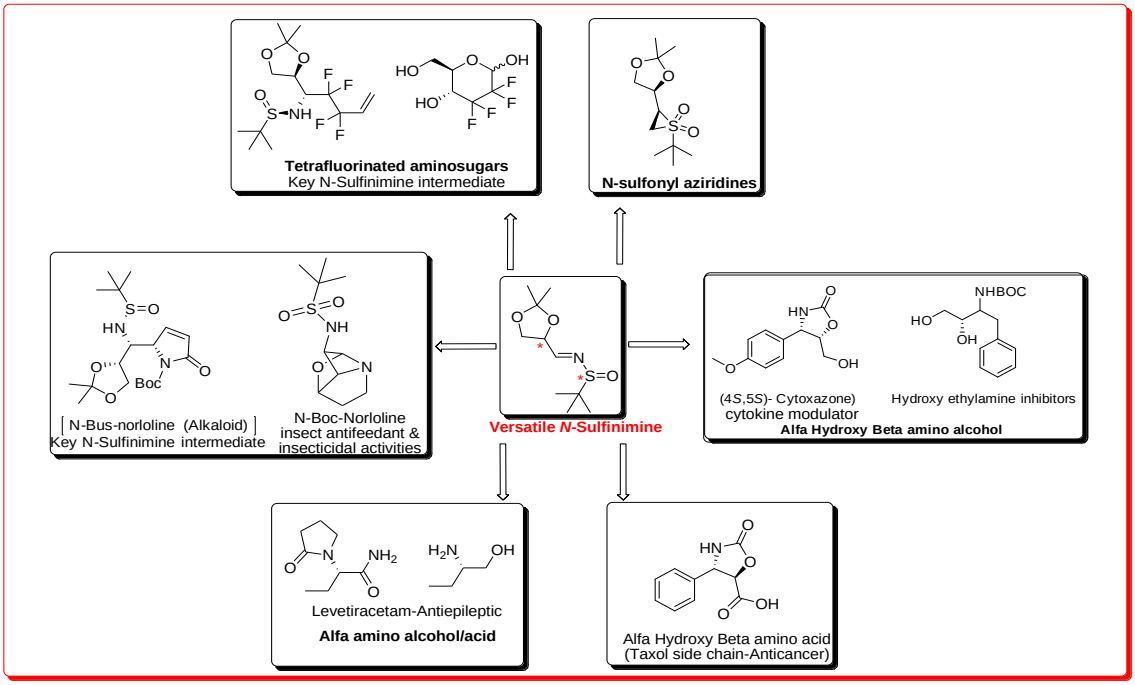
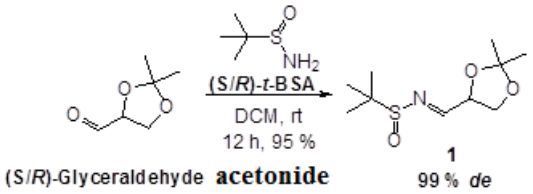


Fig-4: synthetic applications of versatile *N*-sulfinimine (*N*-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide) towards biological active molecules

The versatility of 2-Methyl-2-propanesulfinamide (Ellman's Sulfinamide) as chiral auxiliary discoursed in various review articles.[13] The Applications of tert-butane sulfinamide in the Asymmetric synthesis of amines as well documented in the literature.[14] 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 *N*-sulfinimine (*N*-2,2-dimethyl -1,3-dioxolan-4-yl) methylene)-2-methylpropane-2-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 $CuSO_4$ in dichloromethane at room temperature yielded the (*S/R,E*)-*N*-(((*S/R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide **1** with more than 99% *de* (Scheme-**1**). No epimerisation 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.



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

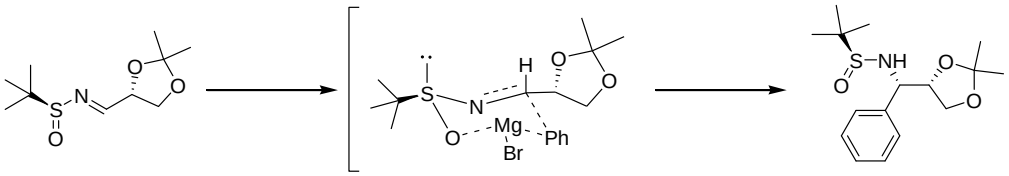
Example:1

Asymmetric synthesis of (4*S*,5*S*)-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]

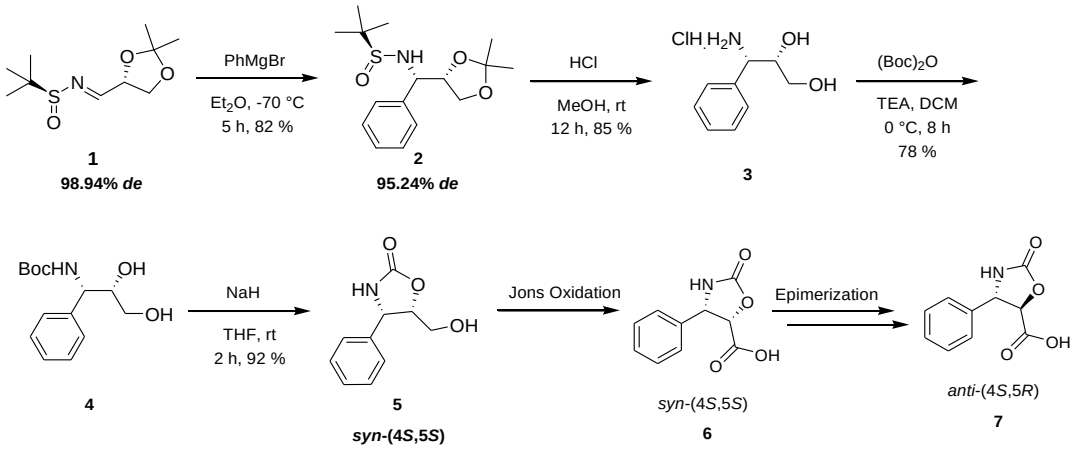
Chiral 3-Amino-3-phenylpropane-1,2-diol is a key chiral structural component in a variety of therapeutically active molecules such as side chain of Taxol[16] and its 2-oxazolidinone derivatives like Cytoxazone, *epi*-Cytoxazone.[17] The *syn*-β-amino alcohols such as 1,2-aminoindanols serve as biological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



Scheme-3: Asymmetric synthesis of (4S,5S)-2-oxo-4-phenyloxazolidine-5-carboxylic acid using versatile N-sulfinimine (S,E)-N-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide

Chiral sulfinimine, **1** on treatment with PhMgBr in ether at -70°C gave the (*S*)-*N*-((*S*)-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)(phenyl)methyl)-2-methylpropane-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 cyclised 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 CrO_3 (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* racemic) 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.

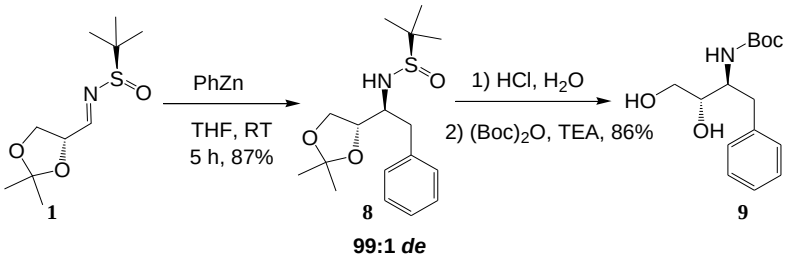
Concussion: *Babu, K. Chandra et al*, reported an asymmetric synthesis of taxol side chain *via* stereoselective 1,2-addition of phenylmagnesium bromide (PhMgBr) to new *N*-sulfinimine.

Example:2

Asymmetric Synthesis of Amines by the Knochel-Type $MgCl_2$-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-methylpropane-2-sulfinamide.[21]

Previous reported methods were limited to the coupling of aryl and vinyl boron reagents to N-sulfinimine, which are sp^2 hybridized. Therefore, additions of sp^3 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 diastereo selective addition of a variety of benzyl zinc reagents to *N*-tert-butanesulfinyl imine,**1** substrates with excellent functional group tolerance.



SCHEME-4: Asymmetric Synthesis of Amines (hydroxyl ethylamine-based protease inhibitors) using versatile N-sulfinimine (S,E)-N-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide

Here in this the application of this new methodology for the diastereo selective 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.

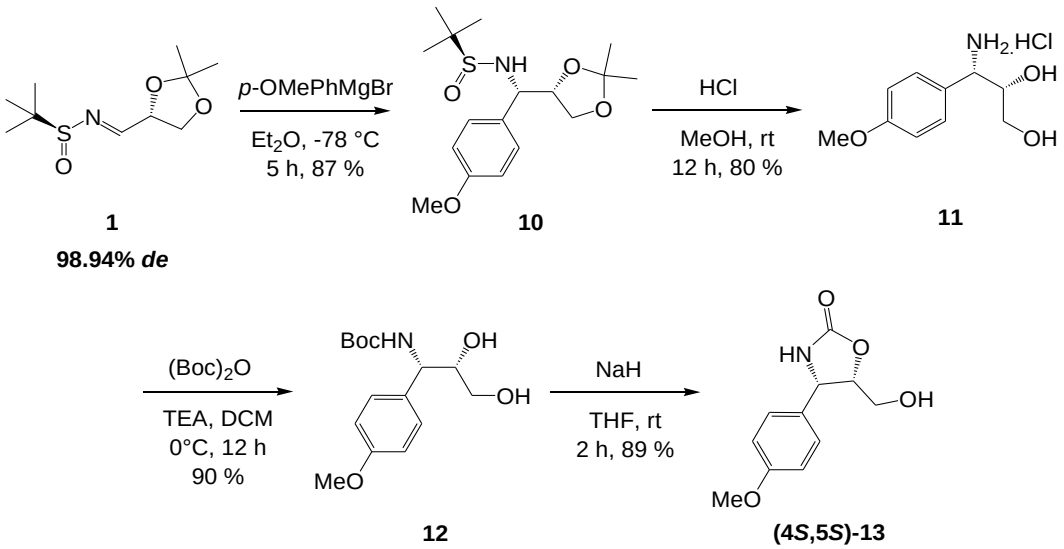
Example:3

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-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide.[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-butylsulfonyl 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

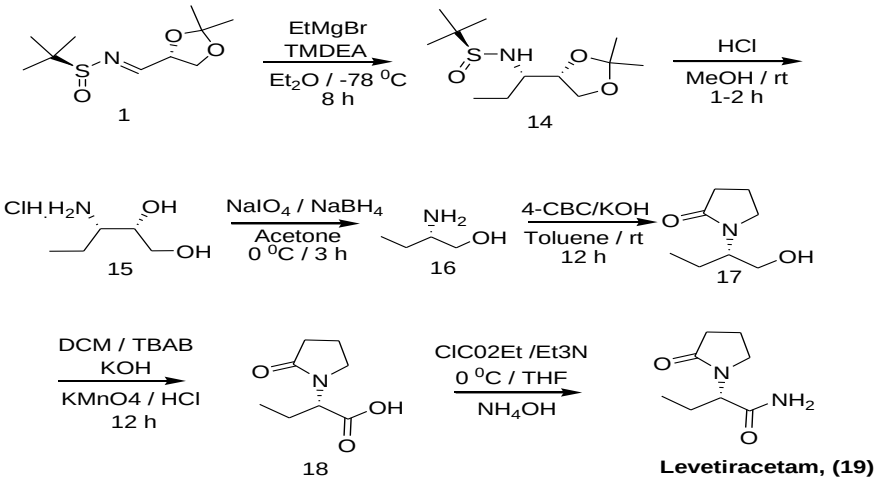
Concusion: *Babu, Kollapudi Chandra et al*, synthesized (4*S*,5*S*)-cytoxazone (A microbial metabolite) using versatile N-sulfinimine, **1** by stereo selective 1,2-addition of p-methoxy phenyl magnesium bromide to imine.

Example:4

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

Chandra Babu, K. et al, synthesized (-)-Levetiracetam (antiepileptic drug)using versatile N-sulfinimine (S,E)-N-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide.[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*- sulfinimine,**1**. The key step, stereoselective 1,2-addition of Ethylmagnesium bromide (EtMgBr) to chiral *N*-sulfinimine to give the corresponding sulfonamide,**14** in high diastereoselectivity. Simultaneous deprotection & deacetylation followed by $NaIO_4$ cleavage and reduction gave *β*-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-methylpropane-2-sulfinamide

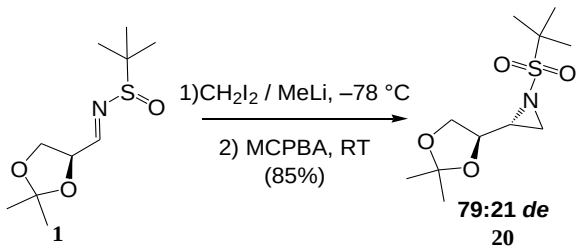
Concusion: Chandra Babu, K. et al, synthesized (-)-Levetiracetam (antiepileptic drug) using versatile N-sulfinimine,**1** by stereo selective 1,2-addition of Ethyl magnesium bromide to imine.

Example:5

Stereo selective Synthesis of Carbohydrate-Derived *N*-Sulfonyl Aziridines

Rodriguez-Solla, Humberto et al, synthesized carbohydrate and biological active aziridines, sugar ariridines, sugar amino acids, azo sugars using versatile N-sulfinimine (R,E)-N-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide.[26]

Here in ***Humberto et al,*** reported synthesis of N-Sulfonyl Aziridines which is usefull intermediate for chiral amines, azo 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 diiodo 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.



SCHEME-7: Stereo selective Synthesis of Carbohydrate-Derived *N*-Sulfonyl Aziridines

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.

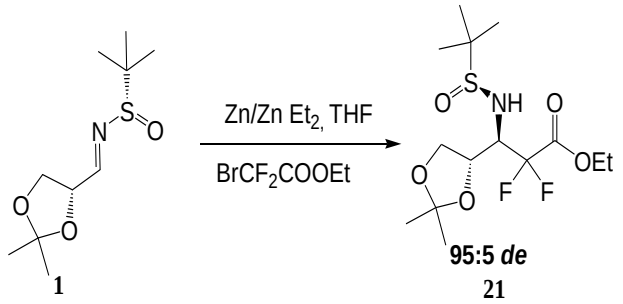
Example:6

Stereo selectivity of the Honda-Reformatsky Reaction in Reactions with Ethyl Bromo difluoro acetate with α-Oxygenated 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-methylpropane-2-sulfinamide[27] *by Honda-Reformatsky reaction.*

The fluorine and related compounds shows relatively more pharmaceutical and agrochemical biological activitys, 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 Et_2Zn followed by Purification gives desired α,α-difluoro-β-amino acids by Honda-Reformatsky Reaction.



SCHEME-8: Stereo selective Synthesis of α,α-difluoro-β-amino acids and esters by Honda-Reformatsky Reaction in Reactions with Ethyl Bromo difluoro acetate with α-Oxygenated Sulfinylimines

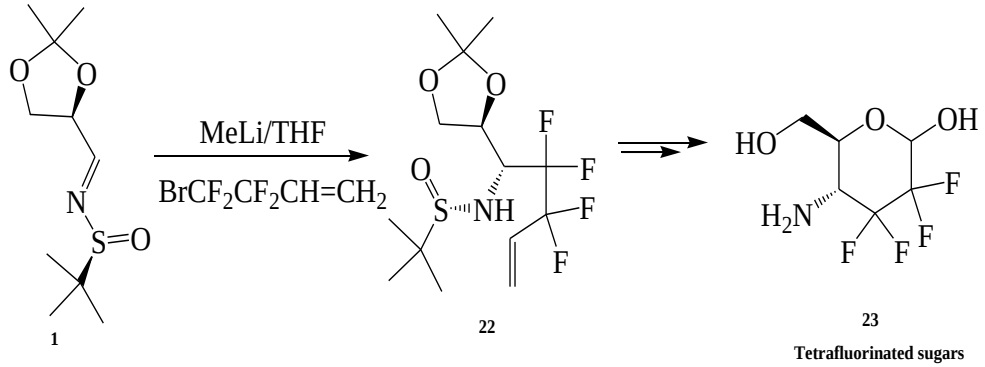
The conformational properties and biological activities of β-amino acids have received great attention, including the corresponding α,α-difluoro-β-amino acids. Their synthesis using direct C−C bond formations with fluorinated building blocks usually involve Reformatsky reaction of $BrCF_2COOEt$ to imine 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 diastereo selectivity's are obtained with imines derived from aromatic aldehydes, while imines derived from aliphatic substrates generally give lower selectivity's.

Conclusion: successfully synthesized (3*R*,4*S*,S*S*)-ethyl 4,5-isopropylidenedioxy-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, 1* (α-Oxygenated Sulfinylimines)

Example:7

The synthesis of tetra-fluorinated amino-sugars

Fontenelle, Clement Q. et al, reported the synthes of tetra-fluorinated amino-sugars *synthesized carbohydrate and biological active aziridines, sugar ariridines, 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]



SCHEME-9: *synthesis of* tetra-fluorinated amino-sugars *using versatile N-sulfinimine (S,E)-N-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide*

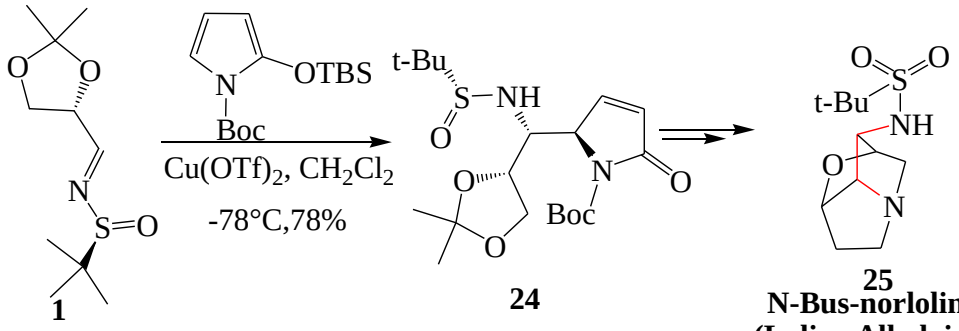
The amino group in α-position of a $CF_2(CF_2)$ group is proposed as a mimic for the hydrogen bond accepting capacity of an alcohol group. Fluorination of carbohydrates is a popular strategy to investigate carbohydrate binding epitopes and enzymes mechanism or to stabilize glycosidedic bonds and indeed a vast number of flurintted carbohydrade 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).[29]

Loline alkaloids are a group of saturated pyrrolizidine alkaloids.[30] 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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