KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY

Title (Name of Technology)

Method for Preparing Highly Optically Active 2-Sufonyloxy-1-Phenylethanol Derivatives

Executive Summary

Dr. Kee-In, Lee has finally developed efficient method for preparing higly optically active 2-sufonyloxy-1-phenylethanol derivatives. Many drugs such as Paroxetine and Salmeterol, currently available drugs such as Fluoxetin (Prozac) contain 2-amino-1-phenylethanol moeity and opticlly active 2-sulfonyloxy-1-phenylethanol derivatives are essential intermediates in producing 2-amino-1-phenylethanol derivatives. Thus, more effective methods for preparing 2-sufonyloxy-1-phenylethanol derivatives in a high yield and a high e.e. value are now required in the industries of pharmacy.

Korea Research Institute of Chemical Technology (KRICT) intends to enter into a technology transfer or licensing transaction with regard to the method for preparing optically active 2-sulfonyloxy-1-phenylethanol derivatives. Terms of the transaction are not set, and interested parties may further discuss the details if they wish to enter into an agreement.

② Industry Sector: 2. Animal health(Pharmaceutical), 3.Biotechnology (Human therapeutics), 8. Non-profit org./Government(Government), 9. Pharmaceutical (Generics)

③ Therapeutic Target: 5. Central Nervous System (Pain, acute) 6. Dermatological (Acne, Dermatitis: atopic, Dermatosis,)

④ Development phase: early stage

⑤ Type of business relationship sought (including licensing availability): development collaboration, or non-exclusive or exclusive licensing agreement

■ **IP Owner Summary**

Korea Research Institute of Chemical Technology

Ministry of Knowledge Economy Is The Competent Ministry

■ **Personal Description of Researcher**

▫ Name
Kee-In, Lee, Ph.D
▫ Present Position
Senior Research Engineer
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Key Technology Highlights

□ **Efficient Method for Preparing Optically Active 2-Sulfonyloxy-1-Phenylethanol derivatives**

Conducting asymmetrical reduction of an α–sulfonyloxy acetophenon compound in the presence of the rhodium compound having pentamethylcyclopentadienyl group as catalyst and a hydrogen donor provide optically active 2-sulfonyloxy-1-phenylethanol derivatives .

□ **High e.e.(enantiomeric exess) Value of Product**

By using the method of present invention which undergoes reduction of α-substituted acetophenone with asymmetrical rhodium catalysts, 2-suifonyloxy-1-phenylethanol derivatives of high e.e. value can be obtained.

□ **Low Cost**

The method of present invention requires low cost due to the use of unexpensive catalyst in small amounts.

□ **Safe Process.**

It is also safe because aminoketone reduced by hydrogen does not have to be disubstituted one while asymmetric reduction of aminoketone using hydrogen at high pressure can be conducted only when the amino group of aminoketone is disubstituted and it is difficult to derivatize the product thereof, and the hydrogen gas used in the reduction is danger.

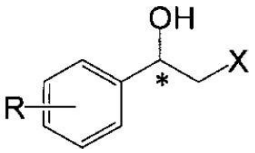
□ **Strong IP Position**

These technologies have been filed for a patent application in a multitude of countries or have been already patented in Korea. The pending patent applications are anticipated to be patented in the near future.

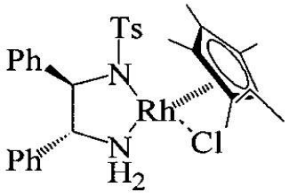
Technology Overview

- **Technology Platform**

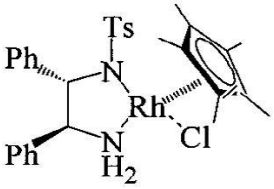
The core technology of Dr. Kee-In, Lee and Dr. Do-Min, Lee is to provide novel method for preparing higly optically active 2-sulfonyloxy-1-phenylethanol derivatives of formula 1 by using a rhodium compoud catalyst. Rhodium compound of formula 2 or 3 reduce α-sulfonyloxy acetophenone compound asymetrically in a high e.e. value.



Formula 1



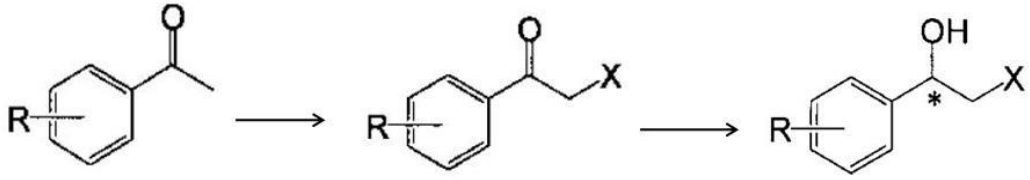
Formula 2



Formula 3

Background and unmet needs: Opticlly active 2-sulfonyloxy-1-phenylethanol derivatives of formula 1 are essential intermediate for producing 2-amino-1-phenylethanol derivatives which have been used in the preparations of several agricultural chemicals, medical supplies, fine chemicals and building blocks, and 60 biologically active substances. The asymmetric reduction of α-substituted acetophenone using oxazaborolidine catalyst and borane is mainly employed method in the preparation of 2-sulfonyloxy-1-phenylethanol derivatives. However, such method require high cost due to the use of expensive catalyst in an excess amount, and have wide fluctuation of the optical activity of the product depending on the substitution of the phenyl moiety, in addition, the reduction is highly sensitive to humidity.

Overall Reaction Scheme of Preparing 2-sulfonyloxy-1-phenylethanol derivatives : Generally, the compound of formula1 is prepared by conventional method using acetophenon as starting material and α-mesyloxy acetophenone as essential intermediate.



Wherein, X is a halogen atom such as -Cl and −Br, or a leaving group such as mesyloxy (-OMs) and tosyloxy (-OTs) ; R is one or more substituents, each independently, selected from the group of H, F, Cl, Br, OMe, OBn, NO_2, CF_3, Me, tert-Bu, CH_2OMe (Me=methyl, Bn=benzyl, Bu= Butyl).

The α-sulfonyloxy acetophenone compound used in the above process may be prepared by a conventional method ; for instance, the α-tosyloxy acetophenone compound may be prepared by reacting acetophenone with [hydroxyl(tosyloxy)iodido] benzene and similary, the α-mesyloxy acetophenone compound may be prepared by reacting acetophenone with [hydroxyl(mesyloxy)iodido] benzene.

Rhodium compound of formula 2 or 3 reduce α-acetophenone compound asymetrically to produce optically active 2-sulfonyloxy-1-phenylethanol derivatives.

Preparation of the rhodium catalyst of formula 2 and 3

the rhodium catalyst can be obtained in a yield of 70% by reacting 1 equivalent of (pentamethylcyclopentadienyl) rhodium(III) chloride dimer ($[Rh(C_5Me_5)Cl_2J_2]$), 2 equivalent of optically active l,2-diphenylethylene-N-(p-toluenesulfonyl)diamine (TsDPEN) and 4 equivalent of triethylamine in methylene chloride, and washing and recrystallizing the reaction mixture. Not only by the conventional methods above, the rhodium catalyst of formula 2 and 3 may be prepared by methods (A) and (B) described below.

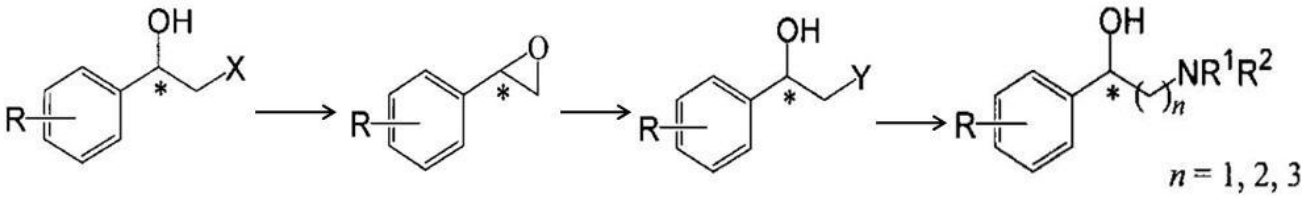
Method (A) - reacting 1 equivalent of (pentamethylcyclopentadienyl)rhodium(lll) chloride dimer, 2 equivalent of optically active 1,2-diphenylethylene-N-(p-toluenesulfonyl)diamine(TsDPEN) and 4 equivalent of triethylamine in methylene chloide as a solvent to obtain a reaction mixture, and removing the solvent from the reaction mixture ; and

Method (B) − reacting 1 equivalent of (pentamethylcyclopentadienyl)rhodium(lll) chloride dimer and 2 equivalent of optically active 1,2-diphenylethylene-N-(p-toluenesulfonyl)diamine(TsDPEN) in methylene chloide as a solvent, in the absence of triethylamine, to obtain a reaction mixture, and removing the solvent from the reaction mixture.

The compound of formula 2 and 3 can be easily and efficiently prepared by the method (A) and (B) in a higher yield than that of conventional method, and therefore, the compound of formula 1 obtained in the asymmetrical reduction of α-chloro acetophenones using the catalyst of formula 2 or 3 exhibits a higher e.e. value than that of the products obtained in the conventional methods.

Preparation of optically active 2-amino-1-phenylethanol derivatives

Generally, 2-amino-1-phenylethanol derivatives of formula 6 is prepared by a conventional method using starting material of of formula 1 and essential intermediates of formula 4 and 5.



Formula 1 **Formula 4** **Formula 5** **Formula 6**

wherein, Y is $-NH_2$, primary or secondary amine, $-N_3$, or −CN ; and R is −H, halogen, alkyl, hydroxy, amine, $-NO_2$ or $-CF_3$ substituted in ortho-, meta-, para-, position of phenyl group.

Representative examples of drug containing 2-amino-1-phenylethanol derivatives include blockbuster drugs such as Paroxetine (Paxil, anti-depression agent) and Salmeterol (Seretide, anti-asthma agent), currently available drugs such as Fluoxetin (Prozac), Sotalol (Betapace), Formotero (Foradil) and Fexofenadine (Allegra), which are derived from chiral switches in the pipeline, adrenoceptor agonists such as Tulobuterol, Metaproterenol, Fenoterol and Terbutaline; and NR1/2B subtype NMDA receptor antagonists such as Ifenprofil and Eliprodil. Further, there are several candidate drugs having 2-amino-l-phenylethanol moiety under development, which include adrenoceptor agonists such as Albuterol, Calcimimetics, Terbutaline, Ritodrine, Salmeterol. Suloctidil and Synephrine; NR1/2B subtype NMDA receptor antagonists such as CP-101,606 and Ro-25-6981.

Patents and Publications

KRICT has patents issued or filed for application in Korea and WIPO with regrad to the above technology.

TABLE. List of Patents

Country	Status	Patent, Publication or Appln. No.
PCT	-	WO 2008/054155
Korea	Granted	10-0821567