Improved Asymmetric Hydroformylation of Therapeutics Using Novel Bisphosphines

INVENTORS • Clark Landis, Thomas Clark, Jerzy Klosin

WARF: PO4447US

The Wisconsin Alumni Research Foundation (WARF) is seeking commercial partners interested in developing a new class of bisphosphines for use in hydroformylation.

OVERVIEW

Asymmetric synthesis is important in the pharmaceutical industry because frequently only one optically active isomer, or enantiomer, is therapeutically active. Therefore, it is often desirable to selectively produce one particular enantiomer over its mirror image. One example of such a pharmaceutical product is the anti-inflammatory drug Naproxen. While the (S)-enantiomer is a potent anti-arthritic agent, the (R)-enantiomer is a liver toxin.

Special procedures must be followed to produce the desired enantiomer rather than optically inactive racemic mixtures, in which equal amounts of each mirror image enantiomer cancel each other out. To obtain the desired enantiomer from such a racemic mixture, the mixture must be separated using laborious and expensive processes that result in low yields of the desired enantiomer.

More cost-effective is the synthesis of the desired enantiomer in a catalytic, enantioselective transformation. Catalytic hydroformylation of alkenes is used widely for commodity-scale production of achiral or racemic aldehydes. In principle, catalysts that are chiral by virtue of attached chiral ligands could enable cost-effective synthesis of chiral aldehydes from alkenes by asymmetric hydroformylation. However, existing chiral ligands produce chiral catalysts that are limited in scope and predictability of performance. A wider range of chiral ligands with improved activity and selectivity is needed.

THE INVENTION

UW–Madison researchers have developed a method for using a new class of bisphosphines as ligands in catalytic transformations of alkenes. The method involves subjecting an alkene to an asymmetric reaction such as hydroformylation, which is carried out in the presence of a bisphosphine ligand catalyst. The bisphosphine ligand is synthesized according to the formula depicted in the figure, or as the opposite enantiomer of the formula. Using this process, asymmetric hydroformylation reactions resulting in 90
percent or greater of the desired enantiomer are possible. The ligand structure has a modular design, which can be varied systematically to obtain the best results for any given alkene substrate, and can be synthesized efficiently from readily available raw materials.

APPLICATIONS

- Drug production
- Hydroformylation reactions for selective production of optically active aldehydes
- Catalysts with high activity and regioselectivity

KEY BENEFITS

- Allows hydroformylation reactions to be industrially useful due to high catalyst activities and enantioselectivities
- Provides flexible structural design that can be customized for any alkene substrate
- Uses readily available raw materials for ligand synthesis

ADDITIONAL INFORMATION

Related Technologies
For information about a one-step method to synthesize a diazaphosphacycle, see WARF reference number P01419US.

Publications

Tech Fields
Materials & Chemicals - Synthesis
Drug Discovery - Drug production & design

CONTACT INFORMATION

For current licensing status, please contact Mark Staudt at mstaudt@warf.org or 608-960-9845.

FIGURES

The bis(diazaphospholane) ligand used in hydroformylation reactions for enantioselective products.