ASYMMETRIC SYNTHESIS OF ENANTIOENRICHED TRISUBSTITUTED 4,5-DIHYDRO-1*H* - PYRROLE-3-CARBALDEHYDE COMPOUNDS

IITM Technology Available for Licensing

PROBLEM STATEMENT

- Poly-substituted dihydropyrroles, especially the 4,5-dihydropyrrole isomers, are vital nitrogen-containing heterocycles with significant biological activity. However, current synthetic routes often involve harsh conditions.
- While synthetic methods for 2,3- and 2,5-dihydropyrroles are relatively developed, efficient and selective synthesis of 4,5-dihydropyrroles remains particularly challenging due to stereochemical complexity and limited methodological advances.
- Many conventional methods rely on transition metal catalysts, which generate toxic waste, require costly purification to remove residues.
- There is a pressing need to develop a practical, cost-effective, and environmentally friendly synthetic route for chiral, poly-substituted 4,5-dihydropyrroles—particularly trisubstituted 4,5-dihydro-1H-pyrrole-3-carbaldehydes—using easily available starting materials under mild, metal-free conditions to support industrial applications.

TECHNOLOGY CATEGORY/ MARKET

Technology Category: Drugs & Pharmaceutical engineering
Industry: Pharmaceutical
Application: Drugs manufacturing
Market: The organic chemicals market size is projected to reach USD 24.25 billion by 2032.

INTELLECTUAL PROPERTY

IITM IDF Ref. - 3022
Patent No: IN 564108

TRL (Technology Readiness Level)

TRL-3: Experimental proof of concept

Research Lab

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TECHNOLOGY

Utilizes (*R*)-diphenylprolinol trimethylsilyl ether as a chiral organocatalyst to synthesize trisubstituted 4,5-dihydro-1*H*-pyrrole-3-carbaldehydes with high selectivity.

Employs commercially available α,β-unsaturated aldehydes and substituted 4-methylthiazolium salts; avoids complex or expensive reagents.

Entire process operates at 0°C in dry toluene, with no need for transition metals, ensuring safer and scalable operation.

Achieves 64–98% enantioselectivity with diastereomer ratio >20:1 in 20–30 hours; isolates a single major diastereomer.

Uses 20 mol% catalyst and 2 equivalents of DMAP base; reaction confirmed by TLC and completed via extraction and column chromatography.

Applicable to a wide range of substituted reactants without protocol changes; consistent stereoselectivity maintained across substrates.

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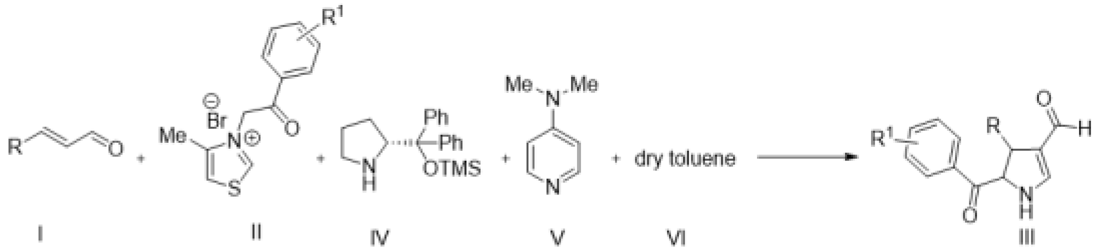
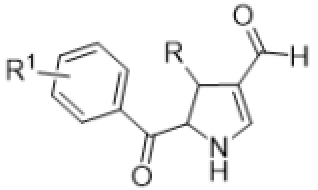


In an embodiment of the present invention, the process comprises.



Formula III

R^1 is independently selected from the group comprising of hydrogen, alkyl, alkoxy, hydroxy, and halogen, wherein the halogen is selected from Cl, Br, and F; and R is independently selected from the group comprising of substituted or unsubstituted phenyl, and 5 to 6 membered heteroaryl having heteroatom selected from O, N or S.

Key Features / Value Proposition

Produces enantioenriched products with up to 98% enantioselectivity and >20:1 diastereomeric ratio, yielding a single diastereomer out of four possible.

Utilizes a chiral organocatalyst (*R*-diphenylprolinol trimethylsilyl ether) instead of costly or toxic transition metals, making the process environmentally friendly.

Implements a one-pot asymmetric domino synthesis, reducing the number of steps and purification requirements.

Operates at low temperature (0°C) using dry toluene and DMAP as a base, enhancing reaction control and stability.

Tolerates a broad range of α,β-unsaturated aldehydes and 4-methylthiazolium salts, consistently yielding high selectivity across variants.

Uses commercially available and inexpensive starting materials, enabling cost-effective, scalable production of valuable chiral compounds.

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