Abstract

Project title: New chiral macrocyclic bidentate ligands for Mn-catalysed asymmetric synthesis of atropisomeric biisoquinoline derivatives

Keywords: Asymmetric synthesis; chiral catalysts; chiral ligands; chiral Mn catalysts; atropisomeric biisoquinoline; oxidative cyclisation; cis-β-amino esters

Enantiopure chiral molecules are extensively used as pharmaceuticals, agrochemicals, flavors, fragrances, nutrients, and functional materials. More than 50% of today's top-selling drugs are sold as chiral molecules. Enantiomers of a chiral compound might exhibit different biological activities such as pharmacology, toxicology, pharmacokinetics, and metabolism as both the enantiomers of a chiral molecule might show different chemical and physical properties in a chiral environment. After the thalidomide tragedy, the USA FDA's 1988 guideline made the pharmaceutical companies use chiral drugs as single enantiomers, which made way for the "chiral switching" from racemic drug molecules to enantiopure molecules. This phenomenon made it necessary to develop reliable new chiral catalysts and asymmetric reactions to make enantiopure molecules.

Our HRHR collaborative research proposal focuses on synthesizing a new class of chiral atropisomeric macrocyclic bidentate binaphthyl derived diamine, diether, and diimine ligands with variable ring size (10/11/12-membered), and variable structures using cis/trans-disubstituted cyclohexane. These new enantiopure ligands, along with Mn salt, will be used as the chiral catalysts for the asymmetric synthesis of atropisomeric biisoquinoline derivatives via enantioselective homocoupling of the corresponding haloheteroarene. The impact and implications of the project are given below.

- Atropisomeric biisoquinoline is considered to be "neglected chiral ligands" as they easily racemize at room temperature. Converting the synthesised enantioenriched biisoquinoline to the corresponding metal complex at the lower temperature will be the crucial step of this research proposal, making the "neglected chiral ligands" highly useful chiral catalysts.
- This asymmetric homocoupling reaction will be utilised in enantioselective total synthesis of biaryl and biheteroaryl moiety containing natural products of biological relevance.
- Various macrocyclic sizes (10/11/12-membered) and the shape of the chiral diamine ligands will provide the required flexibility in extending the application of the new chiral ligand for the development of several essential new asymmetric synthesis.
- If successful, this HRHR proposal will provide two classes of useful chiral ligands/catalysts for the area of asymmetric synthesis.