Synthesis of diphosphine ligands with two atropisomeric axes and their application in asymmetric hydrogenation

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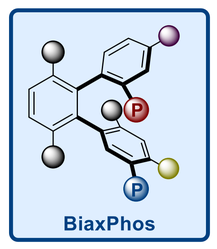
Background and objectives

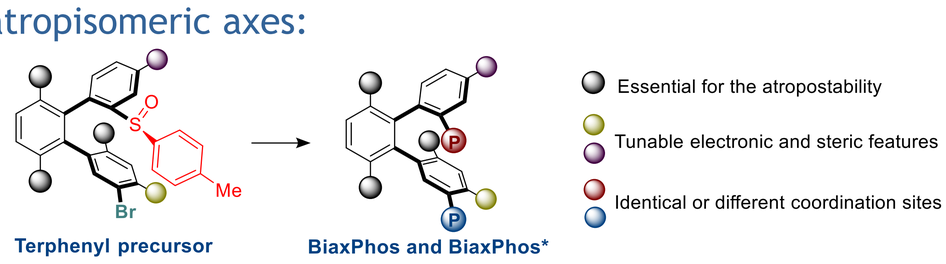
Asymmetric synthesis represents a continuously growing research field, requesting constant search for chiral ligands to achieve high selectivity and reactivity. Among these chiral ligands, diphosphines are the most commonly employed and explored. In this work, we are focusing on the synthesis of fully modulable, chiral C_1-symmetric diphosphines bearing two distinct coordinating motifs. Their synthesis through late-stage modification of a recently developed enantiopure scaffolds, featuring a unique tridimensional architecture, offers the access to a large library of ligands, starting from a single common precursor.[1]



- Double atropisomeric diphosphine ligands
- Dissymmetrical and pseudo symetrical ligands
- Highly modulable

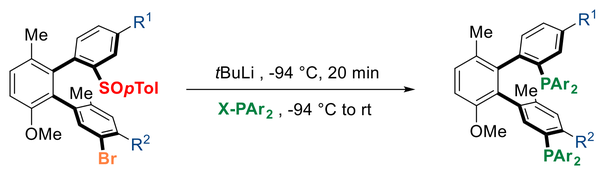
Ligand features

Single terphenyl precursor with unique chiral architecture bearing two atropisomeric axes:

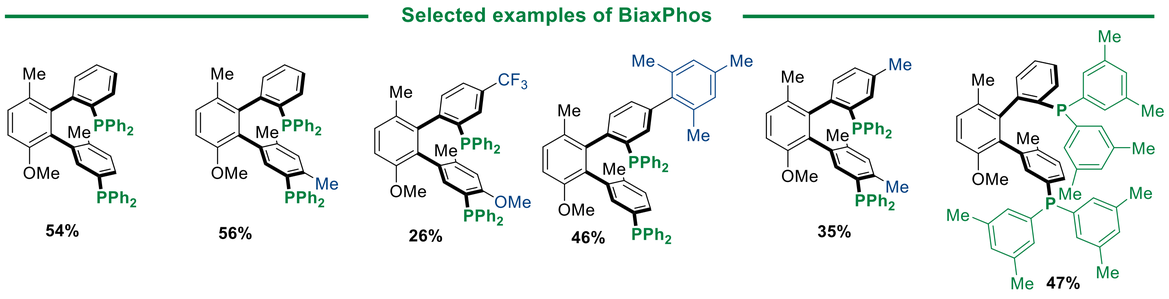


Synthesis of BiaxPhos ligands

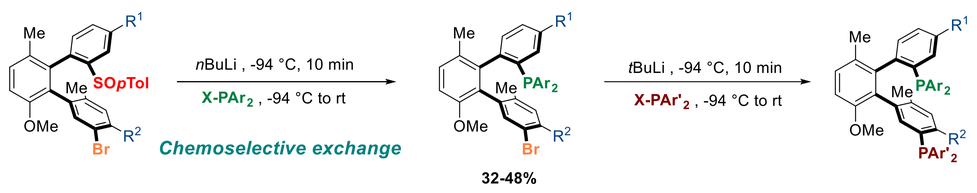
To synthesize the diphosphines ligands, two different pathways were developed.
BiaxPhos ligand bearing two identical diarylphosphine moieties: the terphenyl skeleton is subjected to a simultaneous lithiation of both sulfoxide and bromine groups using a sufficiently strong lithium base. Quenching the mixture with an excess of the phosphine electrophile leads to the pseudo-symmetric BiaxPhos ligand.



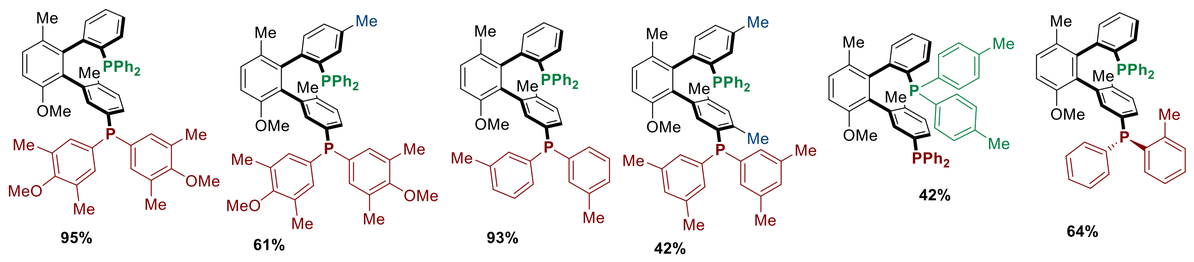
Selected examples of BiaxPhos



BiaxPhos* ligands bearing two different phosphine units: taking advantage of the weak difference in reactivity of the sulfoxide and bromine groups with lithium bases. A chemoselective lithiation and functionalization of the C-sulfoxide bond, followed by the functionalization of the C-Br motif furnishes these dissymmetrical ligands.

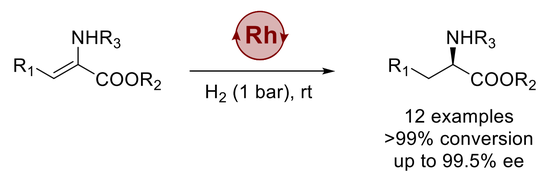


Selected examples of BiaxPhos*

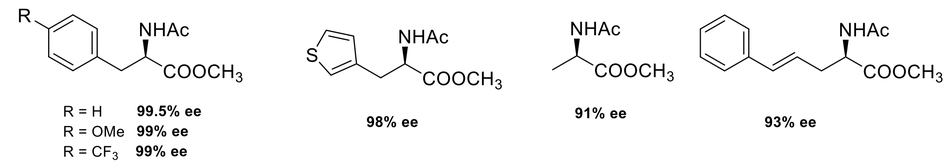


Asymmetric hydrogenation of amino acids

These novel ligands showed high reactivity in the rhodium catalyzed asymmetric hydrogenation of alkenes, affording amino acid derivatives with excellent enantioselectivities (up to 99.5%).

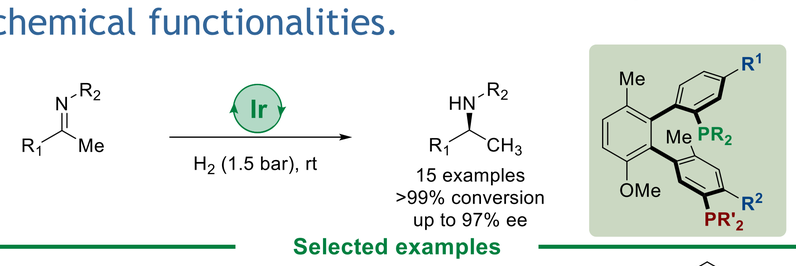


Selected examples

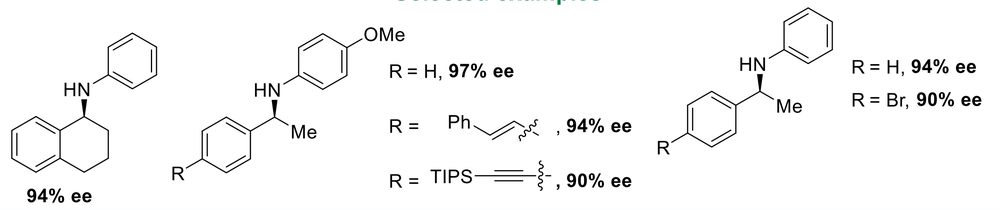


Asymmetric hydrogenation of imines

A pre-prepared complex of a BiaxPhos* Ligand and an iridium catalyst showed a high efficiency and enantioselectivity in asymmetric hydrogenation of imines, being compatible with different chemical functionalities.

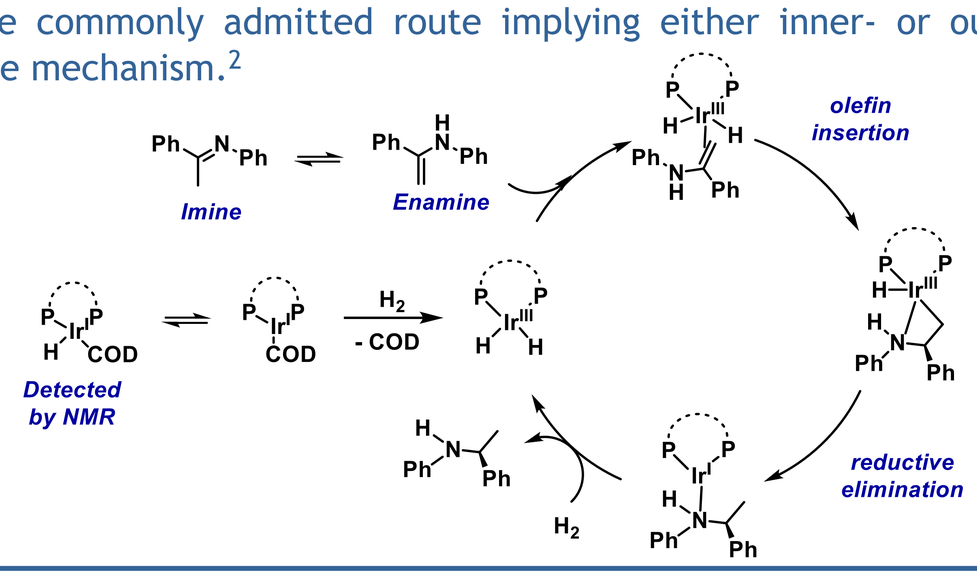


Selected examples



Mechanism

Experimental studies combined with DFT calculations suggest that the developed Ir-BiaxPhos* complex in the imine hydrogenation reactions leads to an unprecedented mechanistic scenario. These ligands promote an enantioselective enamine hydrogenation, instead of the commonly admitted route implying either inner- or outer-sphere mechanism.[2]



Conclusions & future work

We have designed a new family of ligands that have proven highly interesting for the asymmetric hydrogenation of both imines and amino acid derivatives under mild reaction conditions in terms of temperature and pressure of H_2. In our laboratory, these ligands have found many other interesting applications in asymmetric catalysis.

CNRS INC Valorization program

References

[1] Dherbassy, Q.; Djukic, J.-P.; Wencel-Delord, J.; Colobert, F. *Angew. Chem. Int. Ed.* **2018,** *57* (17), 4668.
[2] Submitted paper.