PhD Proposal 2017

School: ECOLE CENTRALE MARSEILLE	
Laboratory: Institut des Sciences Moléculaires de Marseille	**Web site: http://ism2.univ-amu.fr/pages-bleues/index2.htm**
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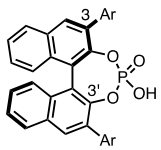
Title: Design, Synthesis and Catalytic Activity of New P-Stereogenic Brønsted Acids
Scientific field: Methodology in organic chemistry
Key words: Enantioselective organocatalysis, Brønsted acid catalysis, P-Chirogenic phosphorus compounds

Details for the subject:

Background, Context:

Organocatalysis was conceptualized in 2000 and never stopped increasing since then.[1] Different activation modes have been developed and catalysis using a chiral Brønsted acid is one of the major field of organocatalysis.[2] In 2004, the teams of Terada[3] and Akiyama[4] have pioneered the use of chiral phosphoric acids for enantioselective Mannich reactions. These species have a BINOL skeleton providing an axial chirality on their backbone. In the Mannich reaction in particular and more generally in the imine activation, an ion pair between the chiral phosphate anion and the iminium cation is formed. Thus, the nucleophilic addition is favored on one side, which explain the high enantioselectivity observed in these reactions. BINOL-phosphoric acids have been successfully used in many reactions. However, even if these catalysts are very effective, they suffer from a very low variability and a tedious synthetic access (minimum 5 steps from enantiopur BINOL). The axial chirality is relatively far away from the reactive center making necessary to introduce large groups at positions 3 and 3' to obtain a



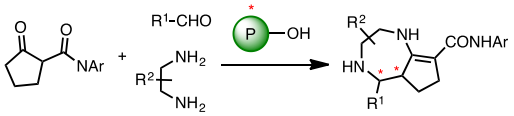
Terada, Ar = 4-phenylnaphthalen-2-yl
Akiyama, Ar = 4-nitrophenyl

strong chiral environment around the reactive center, an essential feature for good enantioselectivities. Many steps are required for the installation of these large groups which hampers the development of reactions using these catalysts for industrial development.

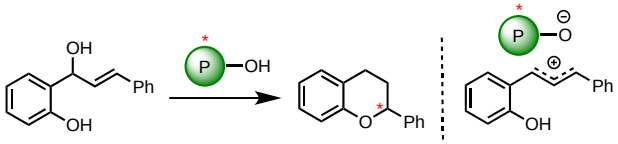
Research subject, work plan:

To overcome these drawbacks, we propose an original design for new simple and easy accessible Brønsted acids in which the chirality is centered on the phosphorus atom.[5] The stereogenic element being closer to the reactive center, high levels of enantioselectivity could be achieved, without the need of sterically demanding functional groups.
Several families of catalysts such as thiophosphonic acids with stereogenic phosphorus atom will be synthesized using the method described in our institute.[6]

They will be tested in model reactions electrophilic activation imines such as Friedel-Crafts, Mannich, Strecker, etc. If we are successful, we wish to go further and to evaluate our new catalysts in electrophilic activation of ***aliphatic imines***, which are far less studied than their aromatic counterparts because they are less reactive and easily decompose in acidic medium. These substrates generally require the use of a high catalyst loading,[7] a strong base,[8] or a structurally complex organocatalyst.[9] These catalysts will also be used to control the selectivity in reactions previously developed in the laboratory,[10] for example a MCR involving an intramolecular Mannich reaction (see adjacent scheme).



Finally, we will use of these new P-stereogenic catalysts not only as chiral Brønsted acids but also as chiral counter anion in asymmetric counteranion-directed catalysis (ACDC).[11] Conjugate bases of chiral phosphoric acids have shown their powerful catalytic activity in asymmetric ion-pairing catalysis,[12] especially for the activation of iminum and oxonium ions. However, the metal-free enantioselective addition to carbocation is much more challenging because of the increased difficulty in successfully activating carbocation systems as a close ion-pairing system.[13] In the designed catalyst, the chirality being close form the negative charge and the relative small size of the chiral counter anion (compare to classical BINOL-derived phosphates/ phosphoramidate anions) should provide for close proximity between ions, and consequently, high selectivities might be expected. The catalytic activity of chiral thiophosphinic acid will first be evaluated in model reaction such as the intramolecular allylic substitution (see scheme).



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