International call for doctoral projects - Strategic partnerships

Stereoselective C–C Bond Formation Catalyzed by an NHC-Zn Complex

Context

This doctoral project proposal is developed within the framework of the doctoral programs of the Scientific Policy aimed at strengthening Sorbonne University's international partnerships. The main goal of this proposal is to initiate collaboration with the University of Tokyo (Todai), identified as a strategic partner; thus, fully meeting this objective. Specifically, this collaboration would be realized through a co-supervised doctoral program between Professors Shu Kobayashi and Yasuhiro Yamashita, School of Science / University of Tokyo, and Dr. Olivier Jackowski, Faculté des Sciences and Ingénierie / Sorbonne Université.

Professors Shu Kobayashi and Yasuhiro Yamashita, internationally renowned, belong to the Synthetic Organic Chemistry Laboratory, Department of Chemistry, School of Science at the University of Tokyo. Their research interests encompass the development of new synthetic methods, as well as the design of novel highly stereoselective organometallic catalysts. Precisely, their work focuses on the development of metal amide complexes (K, Li, Zn) as potent basic catalysts,[1] applied in the stereoselective formation of C–C bonds through 1,2-addition reactions of enolates with and imines.[2]

The Organometallic Reactivity and Catalysis for Synthesis (ROCS) group at IPCM (UMR 8232, Parisian Institute of Molecular Chemistry) at Sorbonne University (SU) works in the area of main-group metal-mediated synthesis (Mg, Zn, Si). The team is recognized for its expertise in the preparation and handling of bimetallic species, as well as in the use of Lewis bases as catalysts. Particularly, this latter theme, led by Dr. Olivier Jackowski, proposes the activation of organometallic reagents such as Grignard reagents and organozinc compounds using a non-racemic chiral Lewis base (NHC) to achieve stereoselective formation of C–C bonds in allylic alkylation reactions,[3] bypassing transition metals.

Thus, within the framework of a shared common interest in asymmetric transformations, Japanese expertise in the selective addition of enolates using metal amide catalysts intersects with the know-how of the ROCS team on the preparation and use of NHCs as Lewis base catalysts for organometallic reagents. The goal of this proposal and its innovative character lies in the prospect of combining these two complementary fields with the specific aim of developing stereoselective C–C bond formation catalyzed by an NHC-Zn complex.

Objective and Scientific Approach

Organozinc derivatives are key reagents in organic synthesis that provide carbanion equivalents with exceptional functional group tolerance. Among these, the most widely available and easy-to-handle are organozinc halides (RZnBr or RZnCl) and a wide array of functionalized reagents of such type can be prepared readily. However, a general lack of reactivity has restricted their use so far to cross-coupling chemistry. This can be ascribed to the lower Lewis acidity of the zinc atom in comparison with other more reactive organozinc species (*i.e*. R_2Zn). In a first aspect of the project, our goal is to find methods to enhance the Lewis acidity of RZnX reagents and thereby embrace a much broader reactivity profile, including for instance the application to 1,2-additions to carbonyl derivatives, not reported to date.

In this context, Lewis base activation of organometallic reagents will be considered to increase the reactivity of organozinc halides toward carbonyl substrates. Such activation mode leads Metal–R bonds more ionic and

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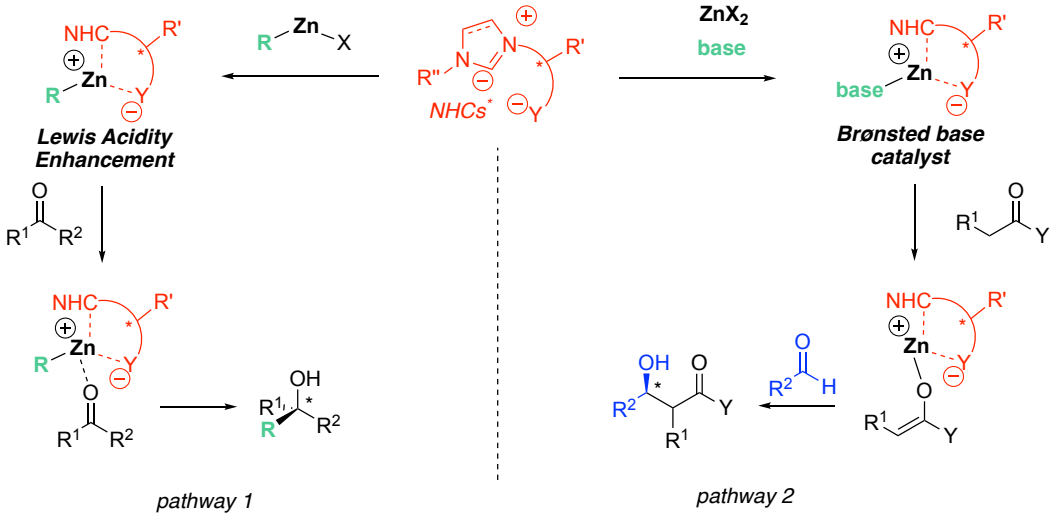
[1] a) Y. Yamashita, S. Kobayashi *Chem. Eur. J.* **2018**, *24*, 10. b) Y. Yamashita *Chem. Commun*. **2022**, *58*, 1078.

[2] a) Y.Yamashita, A. Noguchi, S. Fushimi, M. Hatanaka, S. Kobayashi *J. Am. Chem. Soc.* **2021**, *143*, 5598. b) Y. Yamashita, S. Fushimi, T. Banik, T. Kimura, S. Kobayashi *Org. Lett.* **2024**, *asap,* DOI: 10.1021/acs.orglett.3c04326.

[3] a) O. Jackowski, A. Alexakis *Angew. Chem. Int. Ed*. **2010**, *49*, 3346; b) D. Grassi, C. Dolka, O. Jackowski, A. Alexakis *Chem. Eur. J*. **2013**, *19*, 1466. c) Pérez-Sevillano, R.; Ferreira, F.; Jackowski, O**.** *Chem. Eur. J.* **2023**, *29*, e202302227.

improves Lewis acidity of metal, and the use of bidentate NHCs seems to be good candidates.[4] With these systems we expect high tunability and flexibility with a possible chirality transfer for the 1,2-addition reactions (scheme, pathway 1). This kind of activation has been advantageously applied in the case of allylic substitutions with Grignard reagents (RMgX)[3] and also using dialkylzinc reagents.[5] However, no such activation of organozinc halides has been reported yet. Additions to aldehydes, ketones and carbon monoxide will be explored.



Scheme

In another approach, the use of enolate reagents is also being considered. Indeed, the use of enolizable carbonyl derivatives offers a rapid and efficient strategy for accessing more complex molecular motifs via adolisation reactions.[6] Nevertheless, enolates have the disadvantage of having to be prepared stoichiometrically, essentially in the form of silylated enol ethers. Thus, the development of a method that generates the enolate catalytically *in situ* has attracted a great deal of interest over the last two decades. In particular, the use of zinc enolates has required the presence of Et_2Zn and a non-racemic chiral ligand, namely ProPhenol[7] or a binol derivative.[8]

In this context and in continuity with the first approach, catalytic equimolar quantities of bidentate NHCs and zinc salts in the presence of a base are therefore envisaged for the development of enantioselective catalytic 1,2-addition reactions on aldehydes and/or imines (Scheme, pathway 2). The advantage of this approach is that it uses only safe and cheap elements that are easy to handle, unlike the pyrophoric Et_2Zn.

Desired skills: Training in organic and organometallic chemistry with an interest in methodology and multi-step synthesis.

Location: Sorbonne Université – IPCM, 4 place Jussieu 75005 PARIS.

Contact: Dr Olivier Jackowski (olivier.jackowski@sorbonne-universite.fr, 01 44 27 92 64)

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[4] A. I. Poblador Bahamonde, S. Halbert *Eur. J. Org. Chem.* **2017**, 5935.

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[6] Y. Yamashita, T. Yasukawa, W-J. Yoo, T. Kitanosono, S. Kobayashi *Chem. Soc. Rev.*, **2018**, *47*, 4388.

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