Tytuł projektu

Asymetryczna organokataliza N-heterocyklicznymi karbenami (NHC) jako efektywne narzędzie w syntezie funkcjonalizowanych związków organicznych

Project title

Asymmetric N-heterocyclic carbene (NHC) organocatalysis as an effective tool for the synthesis of functionalized organic compounds

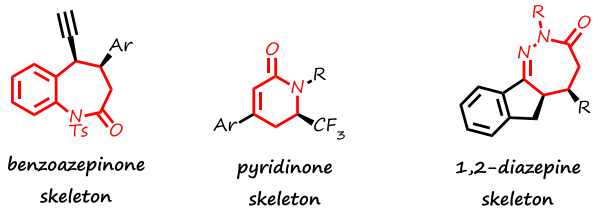
Dyscyplina /Area of science

Nauki chemiczne

PROJECT DESCRIPTION

Project goals

- The aim of this proposal is the development of methodology for the synthesis of important compounds widely occurring in many natural bioactive products, e.g. **1,2-diazepine, benzoazepinone, and pyridinone** derivatives, using NHC organocatalysts.



The project concentrates on systematic studies of the NHC-catalyzed reactions involving broad spectrum of activation of the carbonyl group, e. g. reactions proceeding *via* generation of acyl enolate, homoenolate, γ-enolate intermediates and also engaging a cooperative catalysis by using Brønsted acids and transition metals. Asymmetric NHC-catalyzed reactions enabling the generation of quaternary stereogenic centers, and other sterically demanding chemical processes will also be studied. The development of efficient strategies for the stereoselective construction of privileged heterocyclic systems is an ongoing objective in chemical synthesis. Therefore, we are interested to develop a new methodology for the rapid construction of such frameworks.

Outline and work plan

The integration of two distinct catalytic pathways in a single flask is a powerful strategy in chemical synthesis. Through independent activation of separate nucleophilic and electrophilic species, this synergistic approach makes possible previously inaccessible transformations and can improve existing chemical reactions. In particular, the fusion of transition metal and organocatalysis concepts has become a major research endeavor over the last decade. Although there has been remarkable progress in this area, the combination of N-heterocyclic carbenes with late transition metals remains

underexplored, and more importantly, quite counter intuitive given the strong propensity for NHCs to bind to transition metals with high affinity. While cooperative catalysis with NHCs and Lewis or Brønsted acids has been shown to increase reactivity and afford products with unprecedented levels of selectivity, the incorporation of NHCs with late transition metals (TMs) presents a considerable challenge. In this context, the metal−allenylidene species is a promising synthetic intermediate for organic chemists; it enables the integration of a synthetically flexible alkyne functional group.

Given the background above, we propose highly innovative strategy combining a cooperative NHC/transition metal catalysis for the formal asymmetric [4+2] and [4+3] cycloadditions of acyl enolate or acyl homoenolate with copper-allenylidene species generated from ethynyl benzoxazinonones (Scheme 1). To the best of my knowledge, a simple combination of transition metal such as copper and strong-coordinating NHC (as organocatalyst) remains challenging and elusive.

The incorporation of lipophilic trifluoromethyl groups in bioactive compounds is a popular strategy to increase their bioavailabilities by increasing their ability to cross membranes. In addition, the strength of the carbon-fluorine bond generally results in an increased metabolic stability relative to that of the parent C-H analogue. In this context, the dihydropyridone motifs are a recognized feature of numerous structurally diverse natural products and bioactive pharmaceuticals. Classical routes involve uncatalyzed Diels–Alder reactions and more recently metal-catalyzed π-olefin and π-alkynecyclizations. The current state-of-the-art methods for the production of chiral dihydropyridinones bearing trifluoromethyl moieties remains undeveloped.

Therefore, we would like to propose cooperative NHC/Brønsted acid system for simple one-pot strategy for the asymmetric synthesis of δ-lactams bearing trifluoromethyl groups. The research plan includes formal [4+2] cycloaddition of in situ formed fluorinated aldimines from corresponding N,O-acetals with NHC-activated γ-carbons. Finally, the NHC catalysis will be used in the constructing of 1,2-diazepine-fused indenes involving homoenolate intermediates with azoalkenes generated *in situ* from α-halogeno hydrazones. The application of cyclic hydrazones (derived from indenes, chromanones, tetralones) to produce polycyclic products remains a formidable challenge. Additionally, several challenges had to be overcome, such as a) tolerance of *in situ* generated azolkenes under the reaction conditions of NHC catalysis; b) diastereoselectivity; c) finding reaction conditions which afford high *ee's* and yields.

Diazepines are important heterocycles, which are present in a wide range of natural products and bioactive compounds such as ACE inhibitors, analgesic agents, platelet aggregation inhibitors, and nonsteroidal anti-inflammatory agents. The 1,2-diazepine motif is also an important scaffold in asymmetric synthesis, and intermolecular reactions have rarely been reported for the asymmetric synthesis of 1,2-diazepines. Consequently, the development of more general strategies for the construction of enantioenriched 1,2-diazepine derivatives with functional diversity is still highly desirable.

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Literature

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Rafiński Z. *ChemCatChem*, **2016**, *8*, 2599.
Dzieszkowski K., Rafiński Z. *Catalysts*, **2018**, *8*, 549.
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Required initial knowledge and skills of the PhD candidate

- ➔ Good knowledge of organic chemistry
- ➔ Predispositions and strong motivation for scientific work (regularity and timeliness)
- ➔ Independence in achieving the set research goals, at the same time the ability to work in a group.)

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