SCIENCES & BIOENGINEERING SCIENCES

The Research Group

Organic Chemistry

has the honor to invite you to the public defense of the PhD thesis of

Sudip Guria

to obtain the degree of Doctor of Sciences

Title of the PhD thesis:
Chiral Brønsted Acid-Catalyzed Enantioselective Hetero-Cyclization of Non-Activated Alkenes

Promotor:
Prof. dr. Ulrich Hennecke (VUB)

The defense will take place on
Friday, May 12, 2023 at 16 h in auditorium I.2.02

Members of the jury

Prof. dr. ir. Ken Broeckhoven (VUB, chair)
Prof. dr. Charlotte Martin (VUB, secretary)
Prof. dr. Steven Ballet (VUB)
Prof. dr. Mercedes Alonso Giner (VUB)
Prof. dr. Meike Niggemann (RWTH Aachen)
Prof. dr. Johan Winne (Universiteit Gent)

Curriculum vitae

Sudip Guria obtained his MSc degree in chemistry from the Indian Institute of Technology, Kharagpur, India, in 2018. In summer 2018, he joined the Hennecke group for his PhD studies in organic chemistry, first at the University of Münster (WWU), Germany, and since April 2019 at the Vrije Universiteit Brussel (VUB), Belgium. During his doctoral studies, he worked on enantioselective iodocycloetherification and hydro-amination of non-activated alkenes using chiral Brønsted acid catalysts. During PhD, Sudip has three international peer-reviewed articles (one will be submitted soon). He has presented his work in three conferences and has supervised two MSc thesis students.

Abstract of the PhD research

Chiral heterocycles are prevalent structures commonly present in natural products as well as active pharmaceutical ingredients. Therefore, their enantioselective synthesis is of high relevance for efficient and sustainable organic chemistry. Organocatalysis (Nobel Prize 2021) has emerged as a premier, environmentally-friendly method for enantioselective synthesis. Therefore, this PhD thesis describes investigations into enantioselective heterocyclization of non-activated alkenes catalyzed by a modern class of organocatalysts: chiral Brønsted acids. The first part of this thesis describes enantioselective iodocycloetherifications of a broad range of alkenols to prepare chiral tetrahydrofurans using BINOL-based chiral phosphoric acid (CPA) catalysts. It was found that it is required to add triphenylphosphine selenide as cocatalyst to achieve consistently high enantioselectivity. This method provided high yields and enantioselectivity for a wide range of 1,1-disubstituted as well as 1,2-disubstituted alkenols as long as the alkenes were (*Z*)-configured. (*E*)-alkenols afforded only racemic products suggesting that (*E*)-alkene derivatives do not fit into the catalytic pocket.

The second part of this thesis reports the enantioselective synthesis of chiral pyrrolidines via intramolecular hydroamination of non-activated alkenes using highly acidic, confined imidodiphosphorimidate (IDPi) catalysts. Hydroamination of alkenes is a very important organic transformations with high degree of atom economy and has been mostly carried out by metal catalysis. To overcome the limited reactivity of traditional organic Brønsted acids in this transformation, highly acidic, confined IDPi catalysts were used in combination with electron- deficient protecting groups on nitrogen atoms. This strategy enabled highly enantioselective intramolecular hydroaminations providing chiral pyrrolines via 5-*exo* cyclization on a broad range of substrates. Trisubstituted alkenes also furnished chiral pyrrolidines in high yield and enantioselectivity via 5-*endo* cyclization. Deuterium labelling experiments using trisubstituted alkenes showed highly diastereoselective (>20:1 *dr*) *anti*-addition reactions indicating that the reactions proceed via a concerted mechanism also supported by DFT calculations. A kinetic study demonstrated that the reaction follows a Michaelis-Menten kinetic suggesting that the IDPi catalyst behaves like an artificial enzyme in this transformation.

The third part of the thesis describes initial experiments into the chiral Brønsted acid-catalysed synthesis of cyclic amides via Beckmann rearrangement. These experiments indicate that an enantioselective transoximation/*in situ* Beckmann rearrangement sequence is possible and can deliver chiral cyclic amides in enantio-enriched form, however, further optimisation will be necessary.