SCIENCES & BIOENGINEERING SCIENCES

The Research Group

Organic Chemistry

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

Karlijn HOLLANDERS

to obtain the degree of Doctor of Sciences

Joint PhD with Antwerp University

Title of the PhD thesis:

Transition metal-catalyzed directed amide cleavage for use in peptidomimetic research

Promotors:

Prof. Steven Ballet (promotor, VUB)
Prof. Bert Maes (promotor, UA)

The defense will take place on

Tuesday November 26 2019 at 17.00h

in Auditorium I.2.03 at the Campus Humanities, Sciences and Engineering of the Vrije Universiteit Brussel, Pleinlaan 2 - 1050 Elsene, and will be followed by a reception.

Members of the jury:

Prof. Stefan Weckx (chairman, VUB)
Prof. Pieter Van Der Veken (secretary, UA)
Prof. Ulrich Hennecke (VUB)
Prof. Christophe Vande Velde (UA)
Dr. Vincent Aucagne (Univ. d'Orléans)
Prof. Corinne Gosmini (Univ. Paris Saclay)

Curriculum vitae

Karlijn Hollanders (°1990) obtained a Bachelor in Chemistry at the Plantijn Hogeschool in Antwerp. Following a bridging program, she started her Master of Science in Chemistry at the Vrije Universiteit Brussel. After an Erasmus internship at the University of St. Andrews and a graduation in 2014, she started her doctoral research at the Research Group of Organic Chemistry (VUB) and the Organic Synthesis Department (UA). Her research focused on amide cleavages for use in peptidomimetic applications. Karlijn is the author of four peer-reviewed publications, and two manuscripts in revision.

Abstract of the PhD research

The amide bond is the key functional group in many biomolecules, such as peptides and proteins, and its selective formation was studied extensively, witnessed by a catalogue of so-called coupling reagents able to condense amines and carboxylic acids. Such direct acylations of an amine by an *in situ* activated carboxylic acid remain the commonly applied methods to form amides. Although rarely considered, the amide is herein presented as a carboxylic acid surrogate to overcome the inherent limitations associated with coupling reagents. In the framework of this PhD thesis, an in-house developed methodology involving the esterification of a primary amide through a Zn-catalyzed nicotinate-directed cleavage with alcohols was extended to transamidations. The activation mechanism can be regarded as 'biomimetic': the C^3-ester substituent of the pyridine in the directing group contributes to the abundance of the trans amide bond conformer which is suitable for Zn chelation, allowing $C{=}O_{amide}$-Zn-$N_{directing\ group}$ coordination. Additionally, the incoming nucleophile, a Zn-coordinated alcohol, is activated by hydrogen bonding with the ligand of the catalyst.

A focus was placed on primary amide cleavage by amines to make and modify peptide substrates. Accordingly, the efficient introduction of the directing group was pursued *via* Pd-catalyzed amidation of the *N*-Boc-protected amino acid amides. The consecutive amide cleavage successfully allowed the desired transamidations with amino acid esters/amides as a method for diverse applications in peptide research, exemplified by segment condensations, macrocyclizations, and solid-phase synthesis. Additionally, the amide cleavage was pursued on products of the Ugi reaction through the development of suitable 3-substituted 2-isocyanopyridines. These enabled the cleavage of the *C*-terminal amide of the Ugi product with various *O*- and *N*-nucleophiles, which eventually led to the assembly of constrained dipeptide mimetics.