Tryptamine Synthesis by Iron Porphyrin Catalyzed C–H Functionalization of Indoles with Diazoacetonitrile

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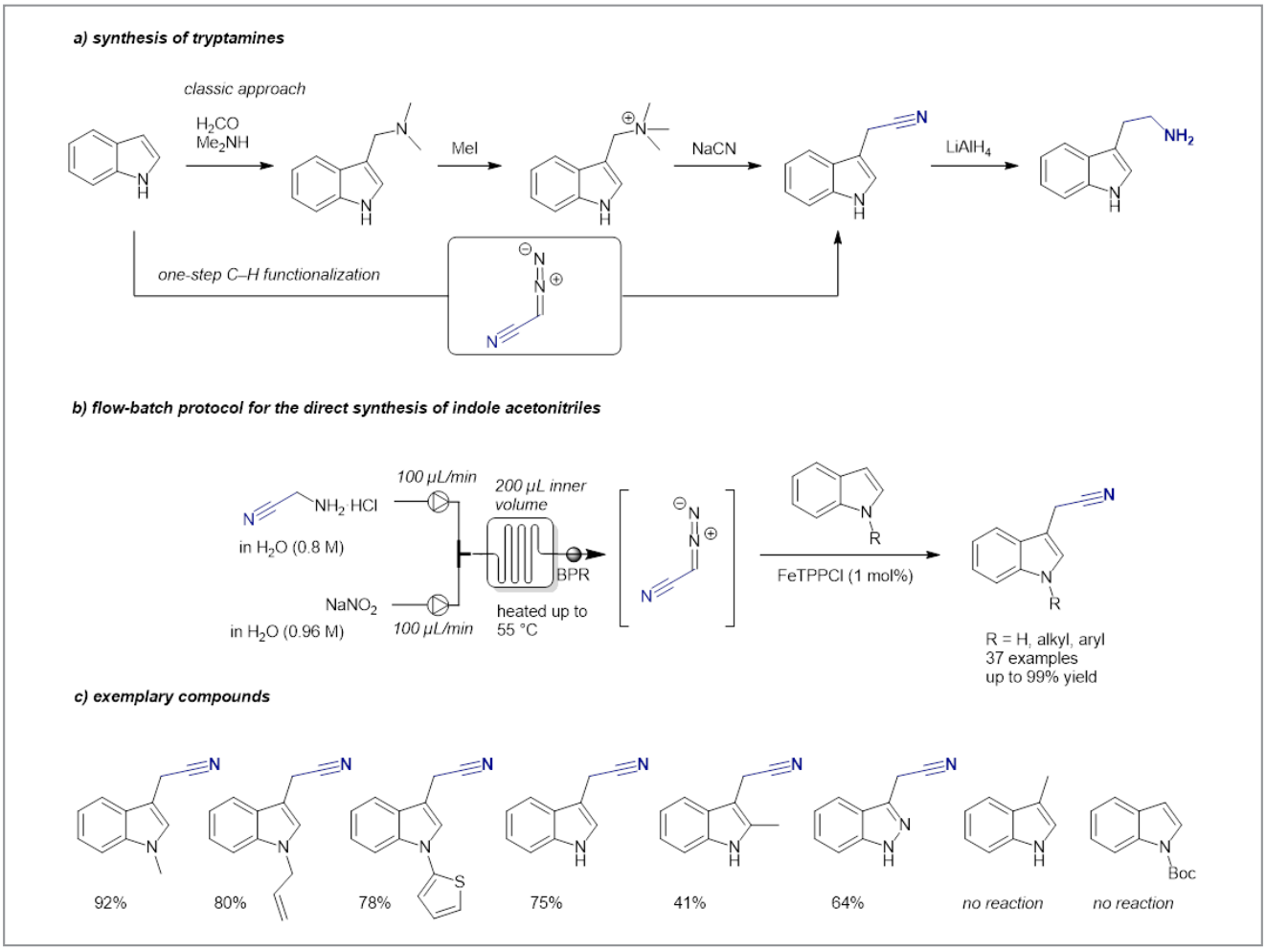
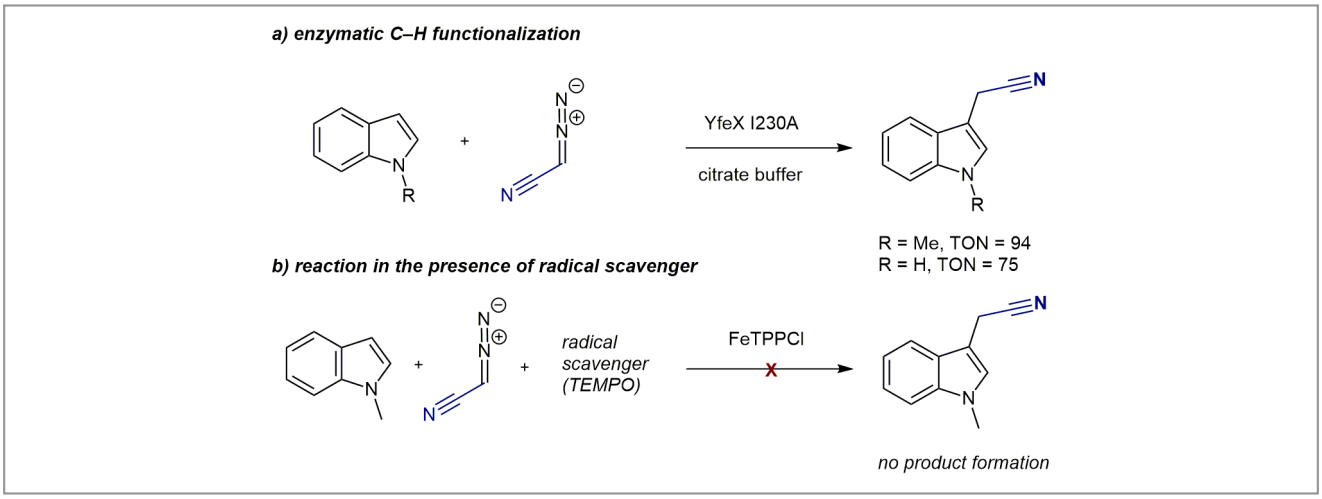
Tryptamines are important endogenous signaling molecules that play a pivotal role in biochemical processes like the regulation of the sleep–wake rhythm. The closely related serotonin possesses key regulatory functions in the cardiovascular system and organ development and plays a central role as a neurotransmitter in the central nervous system. The synthesis of tryptamines is typically conducted following a classic route starting with a Mannich reaction of an indole heterocycle, followed by quaternization of the amine, nucleophilic substitution with highly toxic cyanide and final reduction (Scheme 1a).

Professor Koenigs (RWTH Aachen University, Germany) and co-workers previously reported on carbene transfer reactions of the underexplored and explosive diazoacetonitrile reagent (*Green Chem.* **2017**, *19*, 2118–2122; *Chem. Commun.* **2017**, *53*, 6577–6580). Prof. Koenigs and Katharina J. Hock – a PhD student in the Koenigs group – explained: "We were intrigued by this small fascinating reagent and wanted to find



Scheme 1 a) Strategies for the synthesis of tryptamines. b) Realization of a flow-batch protocol for the synthesis of diazoacetonitrile and subsequent iron(III)-catalyzed direct C–H functionalization of indole heterocycles. c) Selected examples of the substrate scope.



Scheme 2 a) Enzymatic C–H functionalization reaction with the YfeX enzyme. b) Reaction in the presence of a radical scavenger.

solutions to make it commonly available for organic synthetic chemists." Building on their experience in continuous-flow chemistry and the handling of highly reactive diazolkanes (*Chem. Eur. J.* **2016**, 9542–9545), the team set up the goal of exploring C–H functionalization reactions. Prof. Koenigs hypothesized that the reaction of diazoacetonitrile with indole heterocycles should provide a streamlined and unprecedented access to tryptamines and their precursors.

Quite unexpectedly, the team identified a simple iron porphyrin catalyst to be highly efficient in the direct C–H functionalization of protected and unprotected indole heterocycles with diazoacetonitrile (Scheme 1b and 1c), and they demonstrated the applicability of this transformation even on gram-scale. Prof. Koenigs explained that the limitations of the existing methods lay with the necessity of having either expensive catalysts or cyclopropanation reactions of the indole heterocycle with acceptor-only diazo compounds. "The synthesis of diazoacetonitrile using flow technology was crucial for obtaining high yields and circumventing risks associated with handling this explosive diazoalkane, as the reactive diazoalkane is directly consumed by the catalyst after addition to the reaction mixture and only diminutive amounts are present in the flow reactor," commented Katharina J. Hock.

Prof. Koenigs teamed up with Jun.-Prof. Martin J. Weissenborn (Leibniz Institute of Plant Biochemistry and Martin-Luther University Halle-Wittenberg, Germany) who had previously shown a carbene-transfer reaction (*ChemCatChem* **2016**, *8*, 1636–1640), and Dr. Junming Ho (University of New South Wales, Sydney) to next investigate biocatalytic C–H functionalization reactions with an iron–heme-containing enzyme and to gain an understanding of the reaction mechanism of this transformation.

Jun.-Prof. Weissenborn and Anja Knorrscheidt – a PhD student in the Weissenborn group – studied the reaction of acceptor-only diazoalkanes with indole heterocycles using the enzyme YfeX. "YfeX is a remarkably stable enzyme with an impressive expression rate. The site-specific mutagenesis in the active site improved the biocatalytic C–H functionalization reaction to more than 90 turnovers (Scheme 2a)," commented Jun.-Prof. Weissenborn.

The reaction mechanism of this C–H functionalization reaction was studied by using deuterium labeling experiments, which however did not provide a clear mechanistic picture. "Maybe there is a radical pathway involved in this C–H functionalization reaction," suggested Dr. Ho. Indeed, reactions in the presence of radical scavengers did not provide the desired reaction product (Scheme 2b), thus supporting the hypothesis of a radical pathway.

Prof. Koenigs concluded: "This protocol opens up not only the possibility of pursuing safe applications of hazardous diazoacetonitrile but also provides a new, operationally simple route to important tryptamines starting from simple, commercially available reagents, also on gram-scale. Simple organometallic or enzymatic iron catalysts were identified as being highly efficient in this reaction and first experiments showed an intriguing aspect of iron-catalyzed carbene-transfer reactions. The latter are currently under further investigations from an experimental and theoretical perspective to gain a better understanding of the underlying reaction mechanism."

About the authors

K. J. Hock

Katharina J. Hock studied chemistry at the Goethe University Frankfurt am Main (Germany). She did her Masters thesis in the group of Dr. Georg Manolikakes and moved to RWTH Aachen University (Germany) in January 2016 to pursue her PhD thesis with Prof. Koenigs working on safe applications of small and reactive diazoalkanes in carbene-transfer reactions and cycloaddition reactions.

A. Knorrscheidt

Anja Knorrscheidt received her BA in chemistry from the Martin Luther University Halle-Wittenberg (Germany) in the group of Prof. Csuk in 2014. In 2016 she completed her study in chemistry with her MSc at the Leibniz Institute of Plant Biochemistry (Germany) under the supervision of Prof. Wessjohann in 2016. At the same institute she continued as a PhD student in the beginning of 2017 to work in the group of Jun.-Prof. Weissenborn, focusing her research on enzyme-catalyzed carbene-transfer reactions.

R. Hommelsheim

Renè Hommelsheim was born in 1995 in Aachen (Germany). He received his BSc in chemistry from the RWTH Aachen University in 2017. During his Bachelor and Master studies, he worked on the synthesis and applications of diazoalkanes under the supervision of Prof. Koenigs.

Dr. J. Ho

Junming Ho completed his PhD (2011) from the Australian National University under the mentorship of Prof. Michelle Coote and Prof. Christopher Easton. From 2013 to 2017, he was an A*STAR International Fellow at Yale University (USA), and research scientist in the Institute of High Performance Computing (Singapore). In 2017, he moved to the University of New South Wales (Australia), where he currently leads the computational chemistry group focusing on multi-scale simulations and physical organic chemistry.

Prof. M. J. Weissenborn

Martin J. Weissenborn completed his MSc in 2008 at the University of Lund, Sweden, and his Chemistry Diploma (Dipl.-Chem.) in 2009 at the University of Kiel, Germany. His diploma thesis was under the supervision of Prof. Thisbe Lindhorst. From 2009–2012 he did his PhD at the Manchester Institute of Biotechnology (UK) in the lab of Prof. Sabine Flitsch. In 2012 he moved to Stuttgart, Germany, and carried out postdoctoral studies in the group of Prof. Bernhard Hauer. In 2016 he had a research stay in the lab of Prof. Don Hilvert at the ETH Zürich, Switzerland. Since autumn 2016 he is jointly appointed Junior-Professor at the Martin Luther University Halle-Wittenberg, Institute of Chemistry, and the Leibniz Institute of Plant Biochemistry (Germany). His research interests focus on discovery and directed evolution of novel non-natural enzymatic reactions.

Prof. R. M. Koenigs

Rene M. Koenigs obtained his PhD in 2011 from RWTH Aachen University (Germany) under the guidance of Prof. Magnus Rueping. He subsequently moved to Grunenthal GmbH (Germany), working as a medicinal chemist on GPCR and ion channel targets. In 2015 he was appointed as Junior-Professor at RWTH Aachen University. His research interests focus on applications of carbene transfer reactions, continuous-flow chemistry and fluorine chemistry.

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